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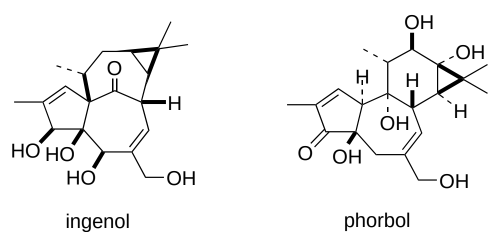
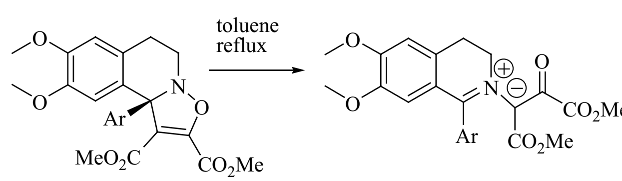
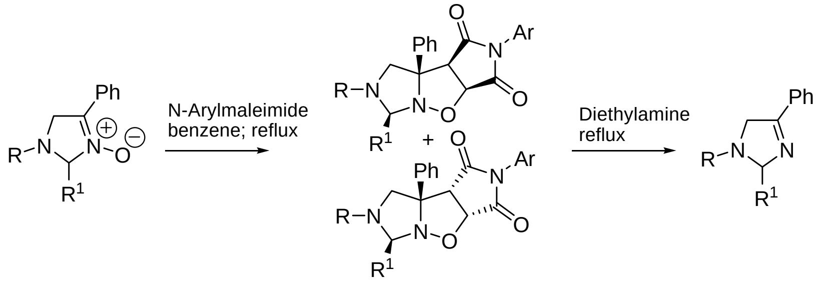
Contents

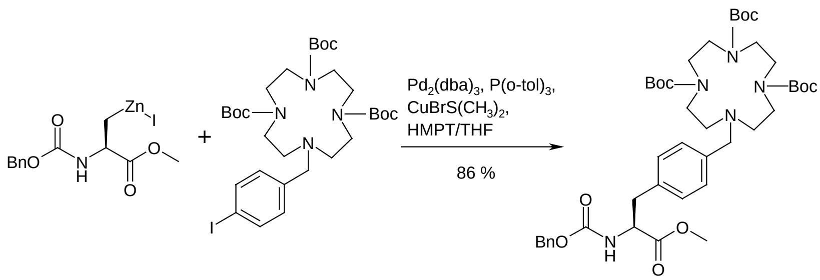
REPORT

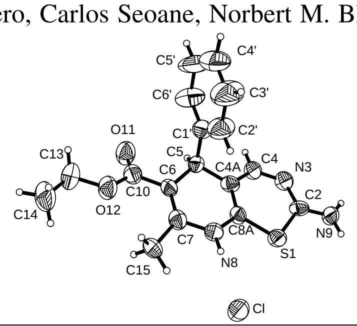


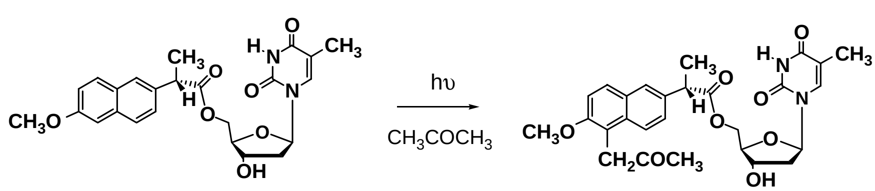
ARTICLES







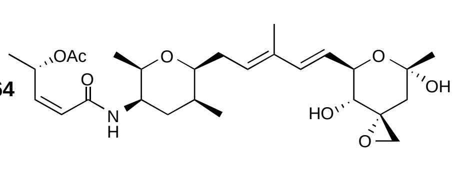


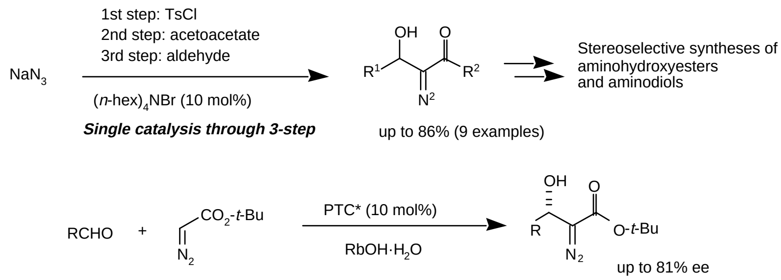


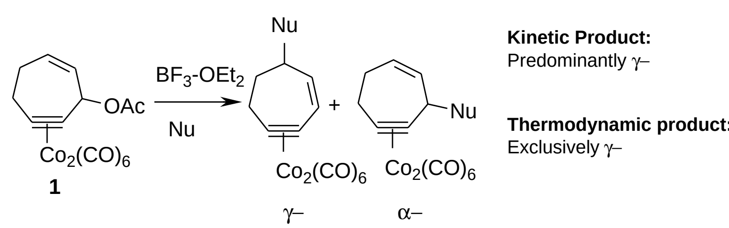
1 2

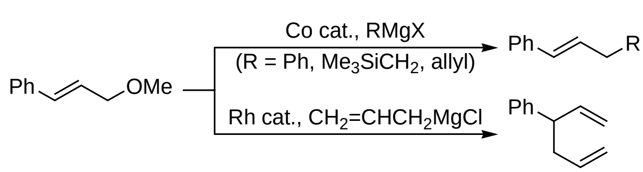
The photobehavior of **1** is dominated by the naphthalene-derived chromophore. In the presence of acetone, this was found to be the photoreactive site, and only **2** was obtained. Thymine dimers and acetone photoadducts involving the thymine ring, which would arise from the thymine triplet excited state, were not detected.

FR901464

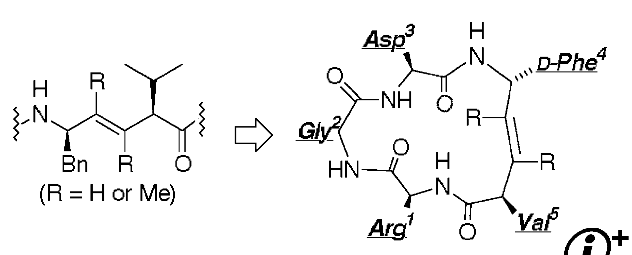


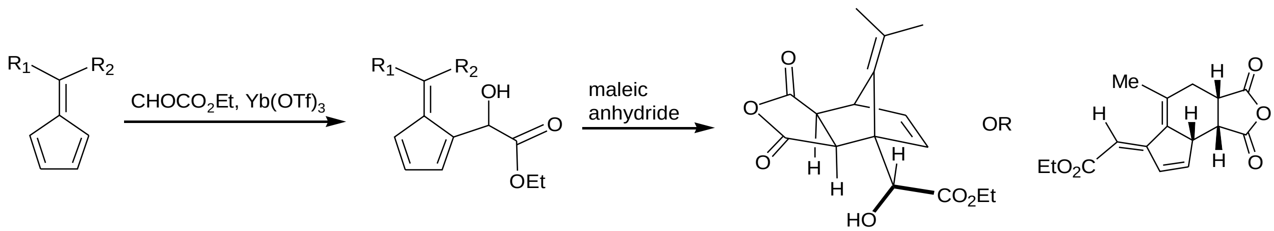


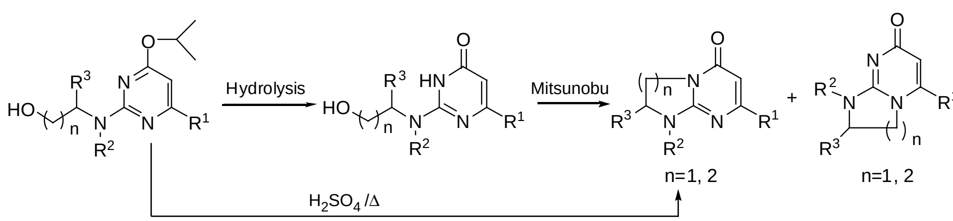


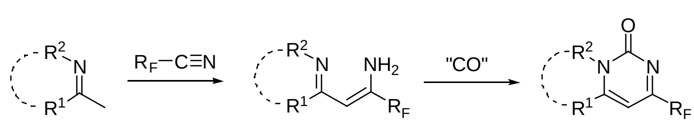


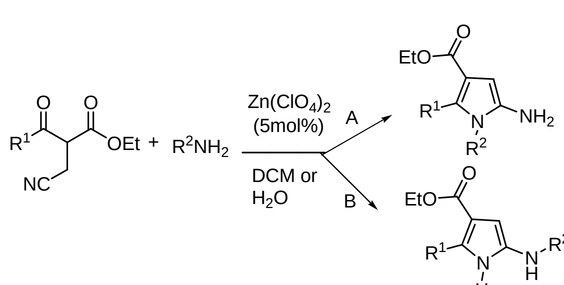
ψ[(*E*)-CMe=CH]- and ψ[(*E*)-CMe=CMe]-type alkene isosteres are potential –CO–NH- and –CO–NMe-type peptide bond mimetics, respectively. The application of these chiral isosteres to conformational studies on cyclic RGD peptides having potent integrin antagonistic activities is reported.

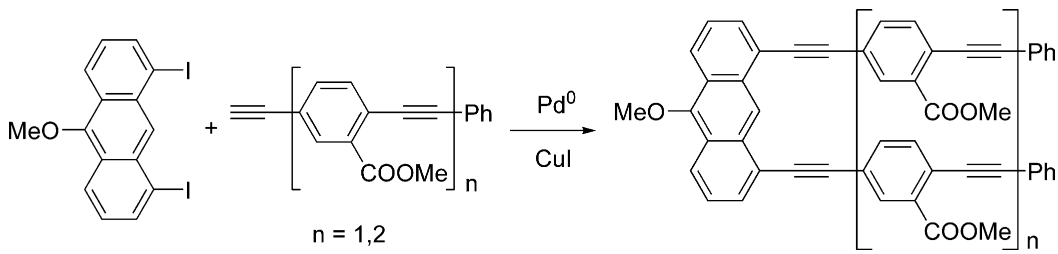


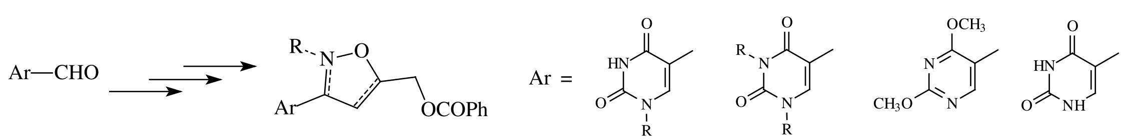

CHOCO2Et, Yb(OTf)3
maleic
anhydride
OR

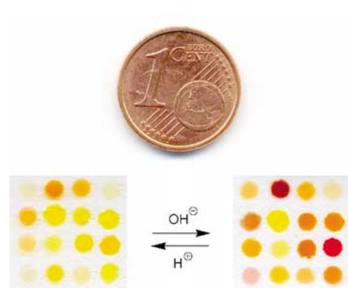

Hydrolysis
Mitsunobu
n=1, 2
n=1, 2
H2SO4 /Δ

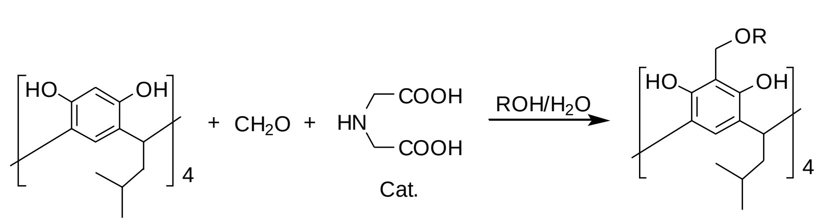

RF—C≡N
"CO"

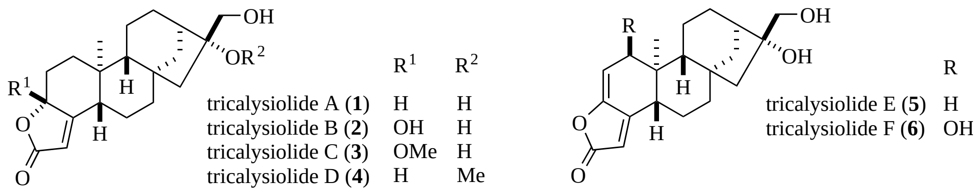

Zn(ClO4)2
(5mol%)
DCM or
H2O


MeO
I
I
+
Ph
COOMe
n
n = 1,2
Pd0
CuI
MeO
Ph
COOMe
Ph
COOMe
n

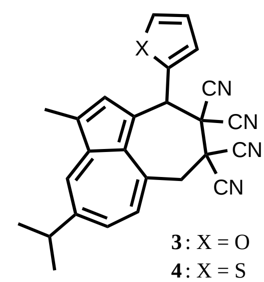

Ar—CHO
R
N—O
Ar
OCOPh
Ar =
O
HN
O
N
R
OCH3
CH3O
NH

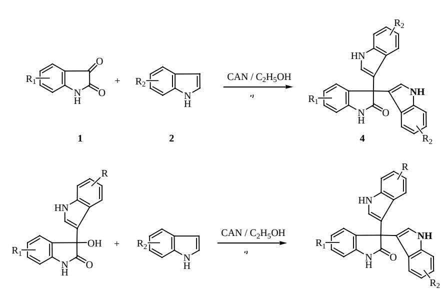

OH
H

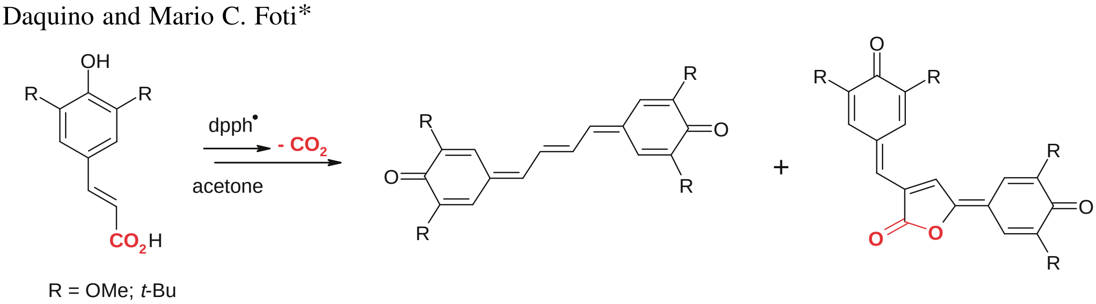

HO
OH
4
+ CH2O +
HN
COOH
COOH
Cat.
ROH/H2O
OR
HO
OH
4



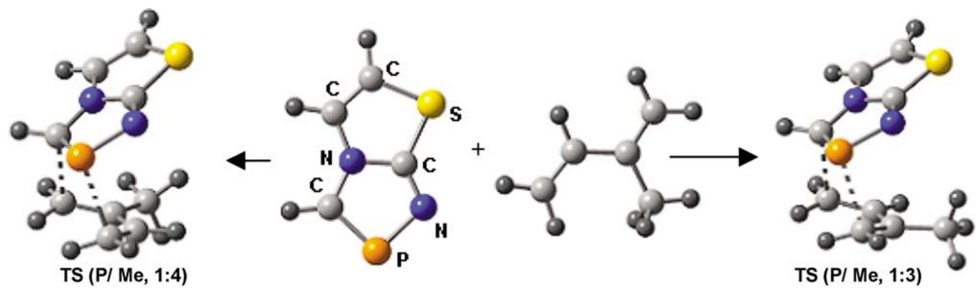
Reactions of the title *meso* forms **1** and **2** with TCNE in benzene at 25 °C for 5 h (for **1**) and 48 h (for **2**) under oxygen give new compounds **3** and **4**, respectively, in 74 and 21% isolated yields. The title studies, affording interesting molecular structures **3** and **4**, are reported.

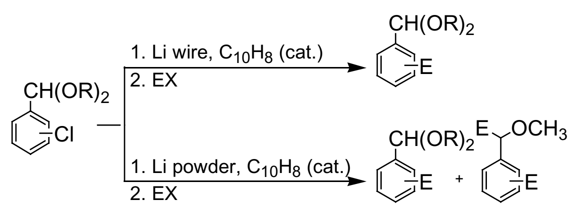


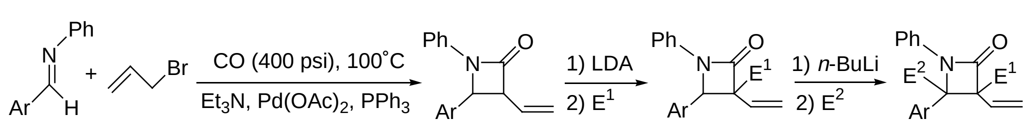


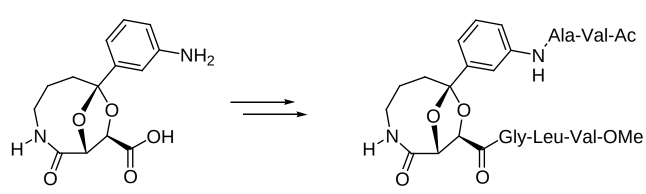


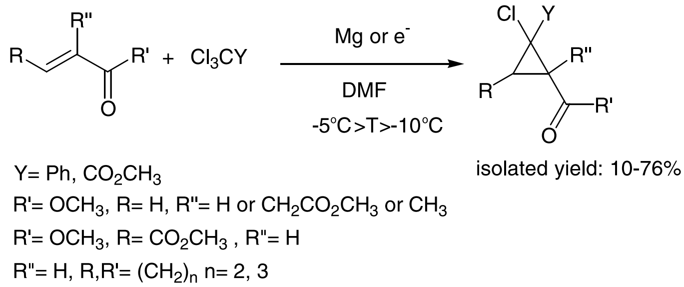
4-Hydroxy cinnamic acids are oxidized by the dpph˙ radical and yield in non-hydroxylic polar solvents *p*-quinomethanes of complex structure.

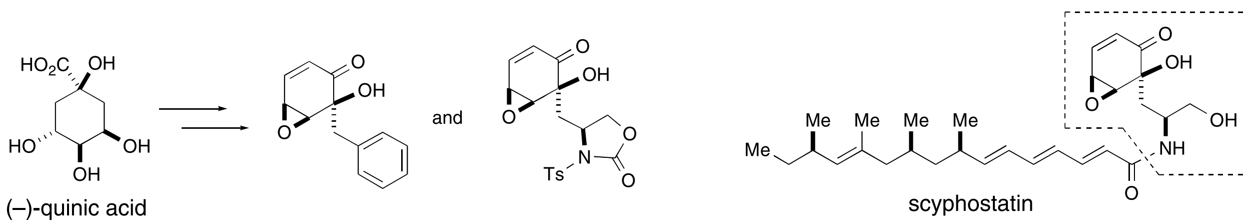

C
C
S
N
C
C
N
P
TS (P/ Me, 1:4)
TS (P/ Me, 1:3)


CH(OR)2
Cl
1. Li wire, C10H8 (cat.)
2. EX
CH(OR)2
E
1. Li powder, C10H8 (cat.)
2. EX
CH(OR)2
E
E
OCH3
E


Ph
N
Ar
H
Br
CO (400 psi), 100˚C
Et3N, Pd(OAc)2, PPh3
Ph
N
O
Ar
1) LDA
2) E1
Ph
N
O
E1
Ar
1) n-BuLi
2) E2
Ph
E2
N
O
E1
Ar


NH2
O
O
H
N
O
OH
O
Ala-Val-Ac
N
H
Gly-Leu-Val-OMe
reverse turn inducer





OTHER CONTENTS

*Corresponding author
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Synthetic approaches to ingenol

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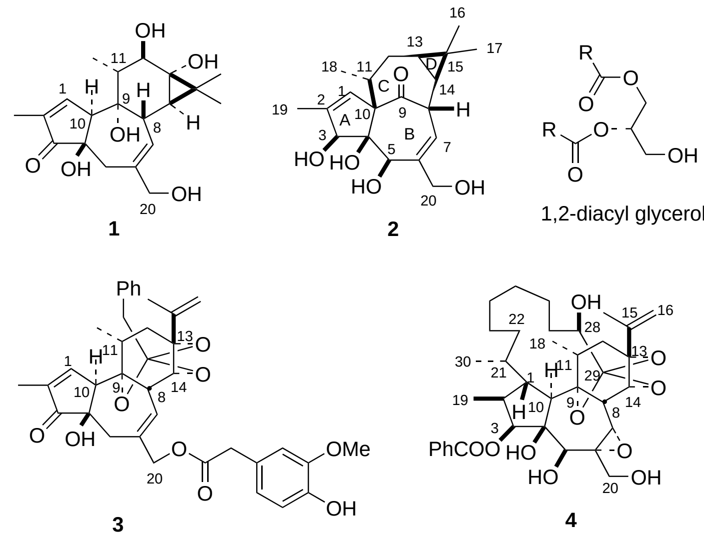
Contents

1. Introduction

Some species of the *Euphorbiaceae* plant family were known to produce milky, often toxic latex, which was blamed for the poisoning of livestock. At the same time, several species were used in folk medicine for treatment of a variety of ailments. Studies to identify the active principles of these plants led to the isolation and characterization of 12,13-diesters of the tetracyclic diterpene, phorbol (**1**), from the *E. Croton tiglium* (Scheme 1).[1] From the *E. lathyris* and *E. ingens* species was subsequently isolated the 3-hexadecanoyl ester of ingenol (**2**).[2] Certain lipophilic long chain esters of **1** and **2**, along with bryostatin, debromoaplysiatoxin, and teleocidin, are known to be highly potent tumor promoting agents. Their mode of action is putatively associated with binding to and activation of protein kinase C (PKC) by mimicking the function of 1,2-diacyl glycerol, the endogenous PKC activator.[3] However, a key pharmacophore common to a structurally diverse group of these tumor promoters has not yet been established. Two representative members of the structurally related daphnane family are resiniferatoxin (**3**) and gnidimacrin (**4**);[4] there is a conspicuous similarity of the oxygenation pattern in the lower subunit between **1** and **3** and also **2** and **4**. However, **3** and **4** are devoid of cocarcinogenic activity, but instead exhibit analgesic and antitumor activity, respectively. It is interesting to note that certain ester derivatives of **2** have recently been reported to possess anti-leukemic and anti-HIV activity.[5] Biological activity of these natural products is thus significantly altered by subtle, yet little-understood, structural modifications. A unified synthetic strategy for tiglianes, ingenanes, and daphnanes would be highly desirable to shed light on the structure–activity relationships, which in turn could lead to the development of useful

Keywords: Ingenol; In, out-configuration; Photocycloaddition; Retro-aldol; Nicholas reaction; Semi-pinacol rearrangement; Ring-closing olefin metathesis; Ireland-Claisen rearrangement; High-order cycloaddition; [1,5-Hydrogen sigmatropic rearrangement.
* Corresponding author. Fax: +1 313 577 8822; e-mail: jcha@ chem.wayne.edu

doi:10.1016/j.tet.2005.10.035



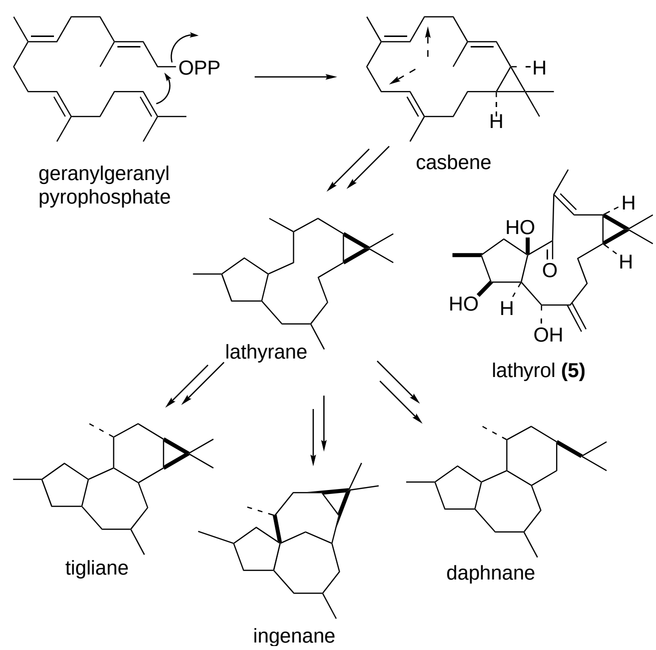
Scheme 1.

biochemical tools and new therapeutic agents, presumably by selective modulation of PKC isozymes.

The biological activity and the structural complexity of these diterpenes have attracted numerous studies directed toward total syntheses over two decades. A landmark synthesis of phorbol (**1**) was first reported by Wender and co-workers.[6] The broad applicability of the key oxidopyrylium cycloaddition approach was demonstrated by subsequent synthesis of resiniferatoxin (**3**).[7] Our laboratory achieved a formal synthesis of **1** by intersecting with Wender's advanced intermediate.[8] More recently appeared the first total synthesis of ingenol (**2**) by Winkler and co-workers who devised an ingenious application of intramolecular dioxenone photocycloaddition.[9] Soon thereafter followed three notable syntheses of **2** by the Tanino–Kuwajima, Wood, and Kigoshi groups.[10–12] This review delineates the highlights of the total syntheses of **2**. Also included is a summary of other syntheses of the ingenanes, together with our own work.[13]

2. Structural relationship between ingenanes and miglianes

A cursory look at the three diterpenoid families suggests that they are derived biosynthetically in plants from geranylgeranyl pyrophosphate, probably via macrocyclic precursors (Scheme 2). Casbene- and lathyrane-type macrocyclic diterpenes might serve as suitable biogenetic precursors.[14] For example, a transannular aldol condensation of lathyrol (**5**), a prototypical lathyrane, could result in the C8–C9 bond formation to provide the tigliane skeleton. Although no details are known, a 1,2-alkyl shift (e.g., Wagner–Meerwein rearrangment) connects tiglianes to ingenanes. During the course of structural identification studies with 3,4;5,20-di-isopropylideneingenol (**6**; structure not shown), treatment of 9(*R*)-alcohol **7** with MsCl yielded the tigliane skeleton **8** (Scheme 3).[2b] On the other hand, migration of a different C–C bond (i.e., C4–C10) was observed with 9(*S*)-alcohol **9** to furnish **10** due to the well-defined (*anti*-periplanar) stereoelectronic requirements. Similarly, treatment of ingenol (**2**) itself with aqueous $HClO_4$ in methanol triggered a vinylogous retro-pinacol rearrangement to give **11** in 49% yield (84% based on consumed starting material).[15] Particularly noteworthy are the mild conditions and good yield for the pivotal rearrangement, which might well be of biogenetic significance.

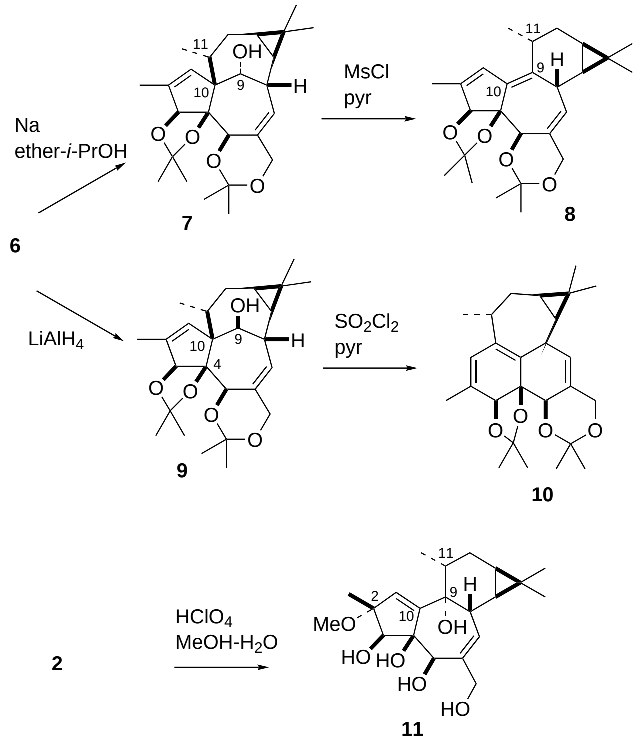


Scheme 2.

The facility of these skeletal rearrangements can be attributed to relief of sizeable strain associated with the trans intrabridgehead stereochemistry of **2**.

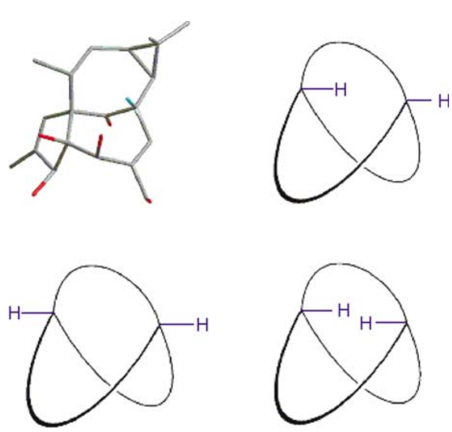
3. Inside–outside stereochemistry

The formidable challenges in synthetic studies of **2** arise primarily from the highly strained *in–out* stereochemistry, the most distinctive structural characteristic. The *in–out* nomenclature was first introduced for bridged bicyclic compounds by Simmons.[16] As denoted in simple, graphic



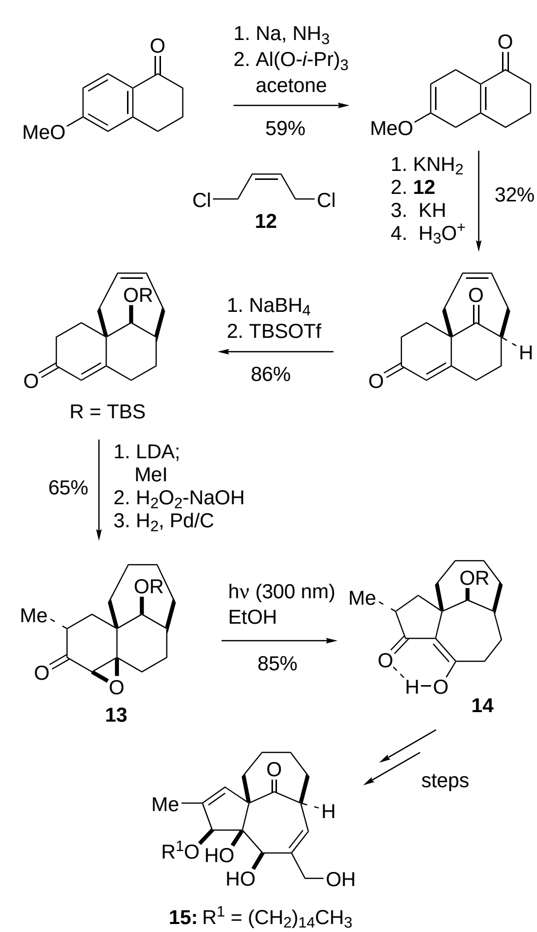
Scheme 3.

representations, the *in–out* nomenclature refers to the location of the bridgehead hydrogen atoms or other substituents (Scheme 4): typically, the *in–in* configuration is the least stable owing to the inevitable H–H repulsive interaction. The energy difference between *in–out* and *out–out* arrangements depends on ring sizes. In the case of ingenol, the natural *in–out* configuration was calculated to be more strained by 5.9 kcal/mol than the corresponding *out–out* isomer, that is, the C-8 epimer (isoingenol).[17a]



Scheme 4.

The importance of the distinctive *in–out* stereochemical facet was clearly underscored by Paquette, as a suitably functionalized isoingenol analog **15**, having the fully elaborated AB ring of **2**, was completely lacking in the biological activity related to the esters of **2** (Scheme 5): the synthesis began with Birch reduction of 6-methoxy-1-tetralone and subsequent double alkylation with **12**. Photoisomerization of α,β-epoxyketone **13** induced ring transposition to afford the isoingenol skeleton **14** with cis intrabridgehead (*out–out*) stereochemistry.[18]



Scheme 5.

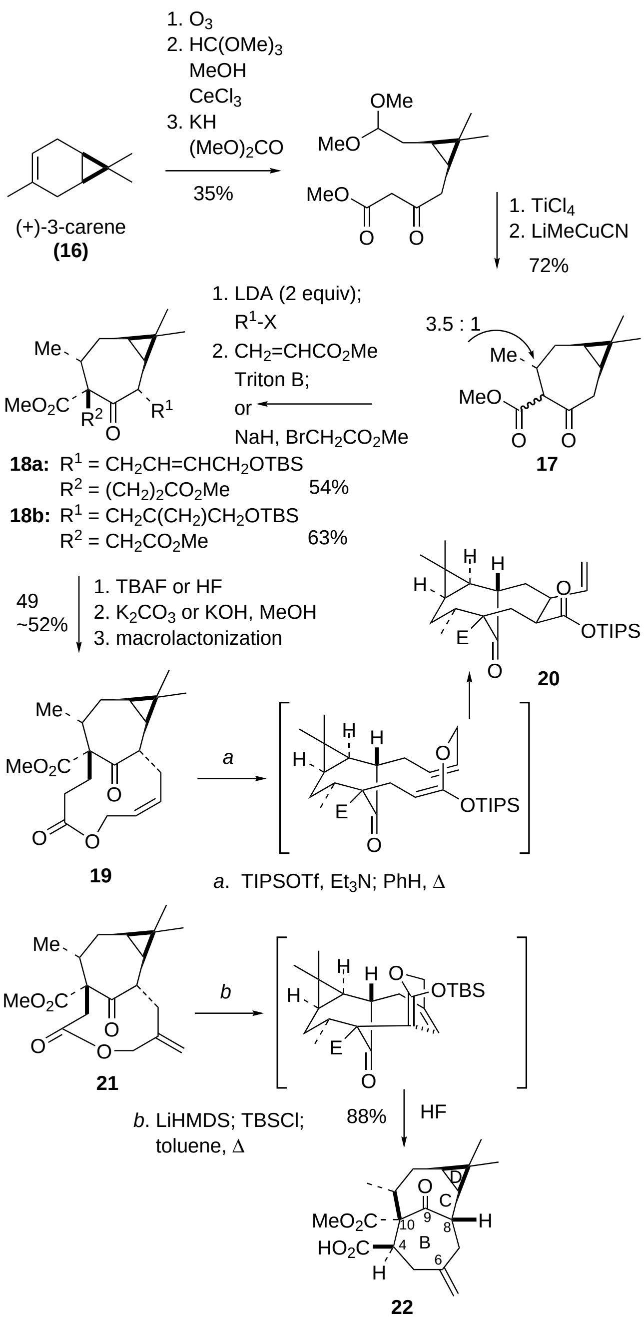
Therefore, a successful synthesis must address the rare *in–out* stereochemical issue, along with efficient installation of the densely positioned hydroxyl groups and stereoselective introduction of the methyl group at C11.

4. Synthetic approaches to 2

Inasmuch as the *in–out* stereochemistry has been shown to be indispensable to biological activity, the otherwise attractive approaches to the isoingenanes are not covered herein. Readers are instead referred to two excellent reviews on these previous studies.[13,19]

4.1. Funk's Ireland–Claisen rearrangement approach

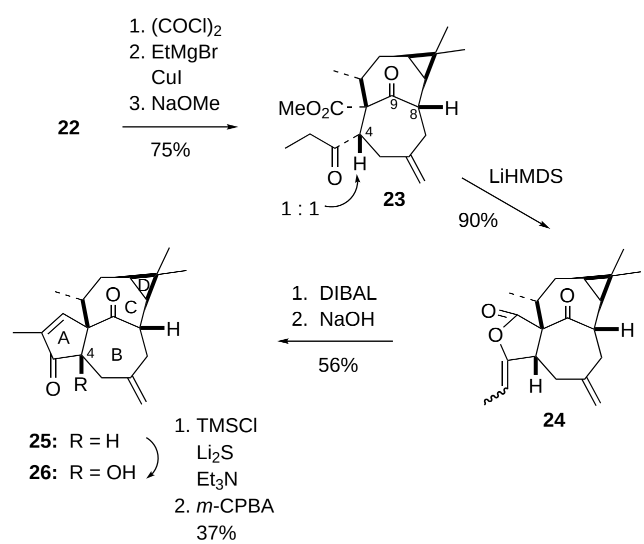
Funk found an incisive solution to the principal stereochemical issue in an Ireland–Claisen rearrangement of a considerably less strained macrobicyclic lactone, which proceeds with ring contraction to furnish a more strained *trans*-fused bicyclo [4.4.1] system.[17] In his CD→BCD→ABCD sequence, the requisite *trans* configuration at C8 and C10 was established at an early stage by sequential diastereoselective alkylation reactions of ketoester **17** to provide **18a** and **18b** (Scheme 6). Starting with (+)-3-carene (**16**), **17** was prepared by standard methods; conjugate addition of LiMeCuCN to the enone (structure not shown) took place with ∼3.5:1 diastereoselectivity at C-11. Alkylation of the dianion of **17** occurred opposite to the cyclopropane ring and subsequent Michael reaction delivered **18a** as a single isomer. The dominant stereocontrol element in the last step is believed to be the methyl group at C-11. Following straightforward functional group elaboration, macrolactone **19** was subjected to the key rearrangement that took place via a boatlike transition state to deliver **20** possessing the BCD ring skeleton of **2**. The indicated stereochemical assignment was verified by single-crystal X-ray analysis.[17a]



Scheme 6.

The Ireland–Claisen rearrangement-induced ring contraction strategy was next extended to **21** containing suitably placed functionalities so as to facilitate the A ring construction. As one of the reacting termini in the [3,3]-sigmatropic rearrangement is exocyclic to the macrocyle, a chairlike transition state was found to be operative, and single-crystal X-ray analysis (of the corresponding bromo lactone) indicated that the major rearrangement product **22** arose from the indicated transition state.[17b]

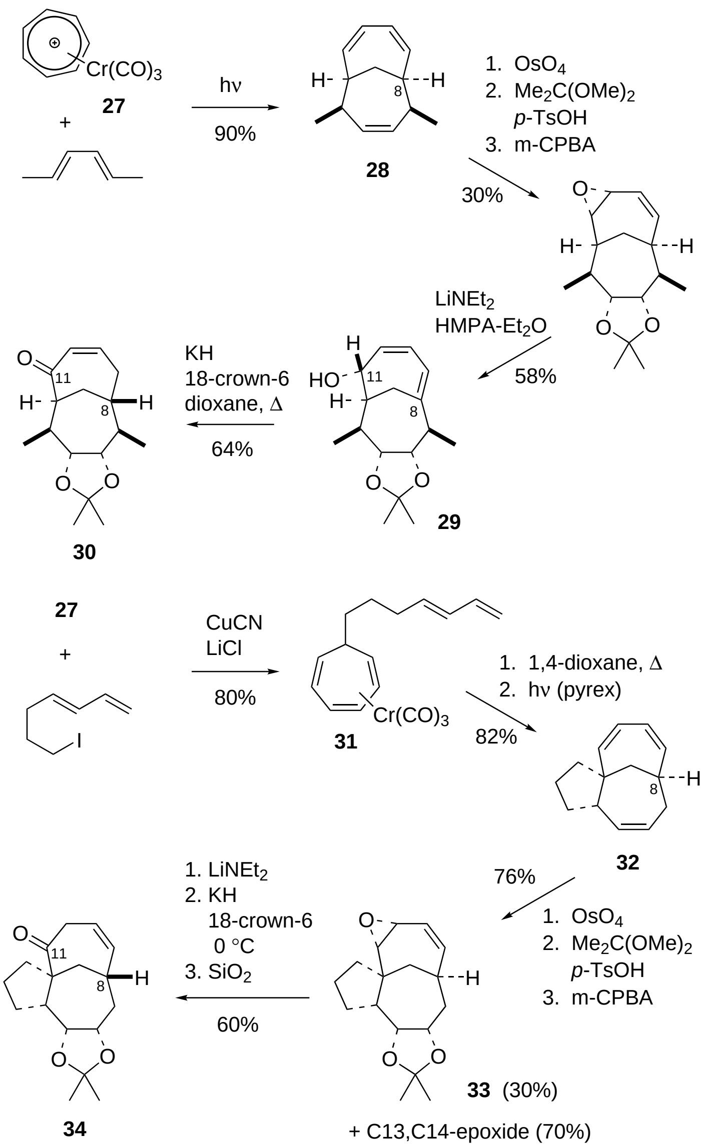
Toward completion of the ingenane tetracyclic ring system, inversion of configuration of the C4 carboxylic acid was necessary: the requisite epimerization was dealt with by base-catalyzed equilibration of the ketone intermediate to deliver **23** as a 1:1 mixture (Scheme 7). It should be noted that enolization of the C9 carbonyl is precluded by poor overlap between the inside C8 hydrogen atom and the carbonyl *p*-orbitals. The lithium enolate of ketone **23** underwent clean *O*-acylation to give enol lactone **24** as an inconsequential 2:1 mixture of the *Z*/*E* isomers. The desired aldol product **25** was then obtained by DIBAL reduction of **24** and subsequent treatment with NaOH in MeOH. Finally, the C4 hydroxyl group was introduced by the Rubottom oxidation of the trimethylsilyl enol ether of **25** to afford the fully assembled and enantiomerically pure ingenol derivative **26**.[17b]



Scheme 7.

4.2. Rigby's [1,5]-hydrogen sigmatropic rearrangement approach

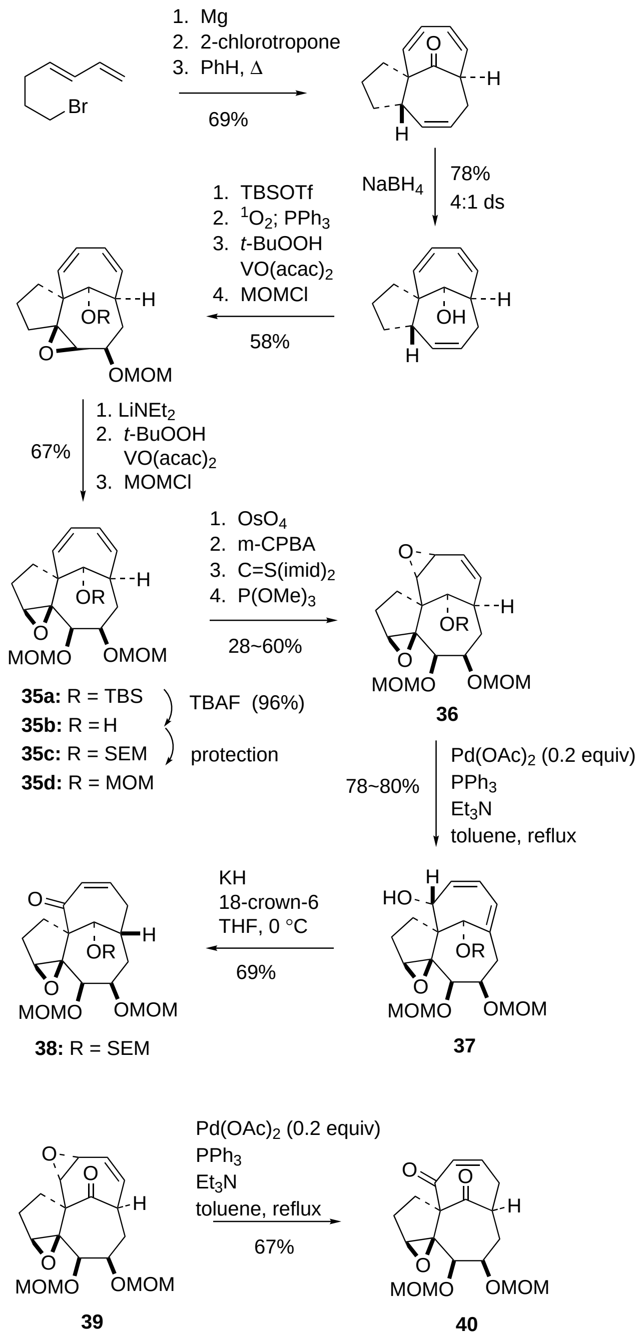
Rigby reported an ingenious solution for conversion of a readily accessible *cis*-intrabridgehead bicyclo[4.4.1]undecane compound to its highly strained trans (*in–out*) isomer: alkoxide-accelerated [1,5]-hydrogen shift was utilized to countermand the otherwise adverse thermodynamics.[20] Chromium(0)-mediated [6π+4π] cycloaddition between **27** and *E*,*E*,-2,4-hexadiene delivered **28** as a single (*endo*) diastereomer in excellent yield (Scheme 8).[21] By taking advantage of the well-defined facial bias inherent in bicyclo[4.4.1] derivatives, the necessary bridgehead double bond was introduced by straightforward elaboration to give



Scheme 8.

29. The pivotal alkoxide-mediated [1,5]-hydrogen sigmatropic rearrangement[22] of **29** yielded the *in–out* enone **30** to establish the correct C8 bridgehead stereochemistry as a consequence of a suprafacial [1,5] hydrogen shift.[20a] This useful protocol was next extended to the intramolecular cycloadduct **32** to afford a functionalized ingenane tricycle **34**.[20b] The structures of **30** and **34** (as its α,β-conjugated enone isomer) were confirmed by single crystal X-ray analysis. It is worth noting that a high level of convergency is possible by an intramolecular [6+4] cycloaddition reaction to construct the ABC ring system. In contrast, it is not feasible in intermolecular processes to directly introduce substituents at the incipient bond forming centers in the 6π component.

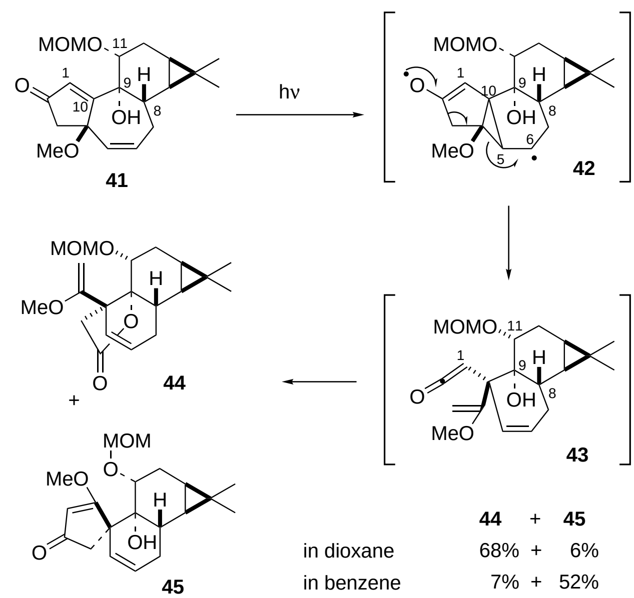
The general applicability of the key sigmatropic rearrangement, along with the compatibility with highly functionalized substrates (e.g., **35**[20d,e] including an epoxide functionality), was also demonstrated with an advanced intermediate **37** for the preparation of **38**: chemoselective epoxide ring opening was achieved by palladium-promoted isomerization of an allylic epoxide, that is, **36**→**37**, in the presence of a non-reactive C3,C4-epoxide (Scheme 9).[20c] The mechanism for this interesting dienol formation was proposed to involve *anti*-elimination by the action of a base from a π-allyl-Pd intermediate. Interestingly, the reaction was found to be sensitive to steric effects, as the bulky TBS group at C9 (i.e., **36** where R = TBS) failed to react even in the presence of a stoichiometric amount of $Pd(OAc)_2$. The requisite *trans*-intrabridgehead compound **38** (where R = SEM) was readily obtained by applying the above-mentioned conditions to **37**. It is noteworthy that the respective ketone **39**, possessing a keto group at C9, underwent a different isomerization reaction, presumably via *syn*-elimination of a π-allyl-Pd intermediate, to give **40** in 67% yield; this remarkable divergence between **36** and **39** could be attributed to conformational changes attendant to the slight, yet significant, structural or functional group changes.[20c]



Scheme 9.

4.3. Cha's semi-pinacol rearrangement approach

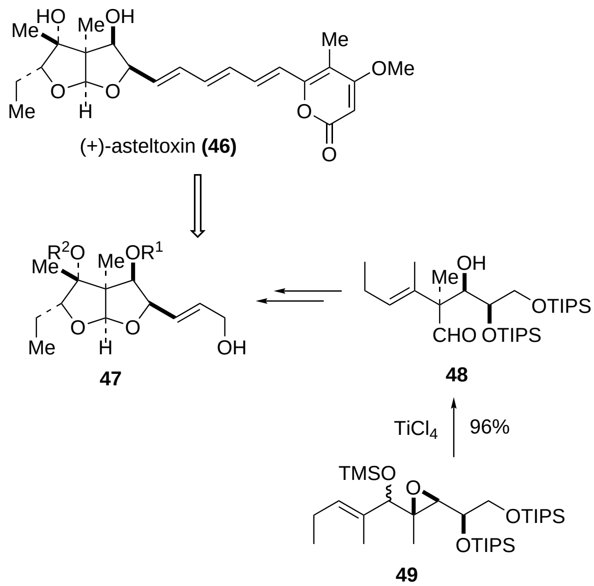
Following up on our formal, enantioselective synthesis of (+)-phorbol (**1**),[8] we were interested in the development of a unified approach to tiglianes, daphnanes, and ingenanes. As delineated in Scheme 3, a missing link between tiglianes and ingenanes could be found in an appropriate 1,2-alkyl shift, which might well be involved in their biogenesis and could also provide an efficient, integrated synthetic strategy. Other laboratories, not surprisingly, explored this simple, yet attractive, tactic. Recently, it came to our attention that several years ago the Wender group had examined the photochemical ring transposition of a C9, C10 epoxide as a logical extension of their first total synthesis of phorbol (**1**) toward the ingenanes: irradiation of a C9, C10 epoxide resulted in exclusive migration of the undesired C8–C9 bond despite the fact that the C9–C11 bond is aligned perfectly *anti*-periplanar to the C10-oxygen bond of the epoxide.[23] More recently, Paquette and co-workers explored a possible photochemical entry to **2**. Instead of the photoinduced 1,2-shift in the anticipated vinylogous α-ketol rearrangement, however, they observed a deep-seated rearrangement presumably due to the presence of the C5–C6 double bond (Scheme 10).[24] Photoexcitation of **41** likely generates the triplet state of the cyclopentenone, which next produces the cyclopropylcarbinyl biradical **42**. Subsequent formation of the ketene **43** accounts for the observed formation of **44** and **45**.



Scheme 10.

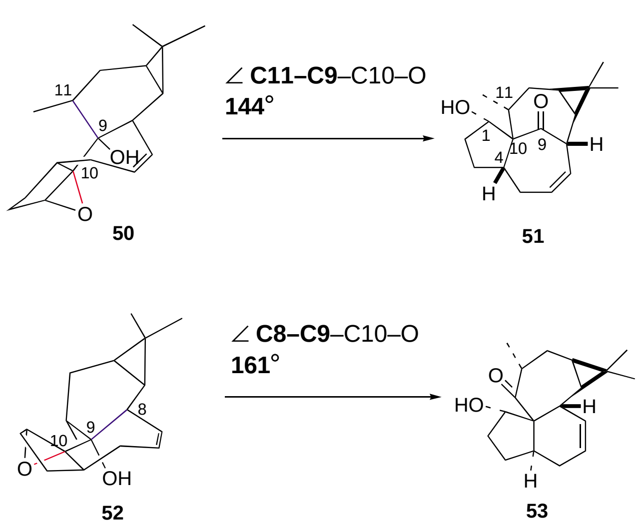
Nonetheless, a 1,2-alkyl shift was deemed by us to provide a unique solution to the challenging *in–out* stereochemistry of **2**. Additionally, we reasoned that the irreversible semi-pinacol rearrangement of an epoxy alcohol would provide the necessary driving force for the 1,2-alkyl shift in the otherwise contra-thermodynamic direction. The choice of the Tsuchihashi–Suzuki rearrangement protocol[25–27] was further reinforced by our successful synthesis of (+)-asteltoxin (**46**): a highly functionalized bis(tetrahydrofuran) **47** was readily prepared by the semi-pinacol rearrangement of an epoxy alcohol derivative **49** to enantioselectively provide the aldehyde **48** possessing the requisite quaternary center (Scheme 11).[28,29] Other benefits in the A+C′D→AB′C′D→ABCD approach are convergence and projected ease in forming a rigid, yet strain-free, seven-membered B'-ring (to set the stage for the key semi-pinacol rearrangement).[30]

Inspection of molecular models indicated that the epoxide **50** is conformationally rigid and that the desired migration of the C9–C11 bond would be most probable to deliver **51** in light of the stereoelectronic requirements: the C9–C11 bond could be aligned antiperiplanar to the C10-the epoxide



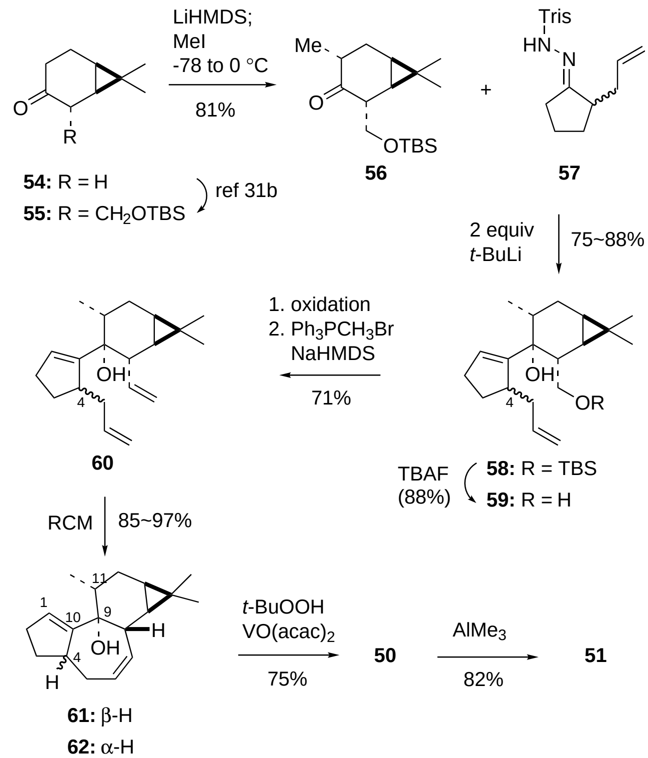
Scheme 11.

oxygen bond, whereas the C8–C9 bond is all but orthogonal (MM2 calculation results of the core skeleton are shown in Scheme 12). In the case of an isomeric epoxide **52** with the unnatural configuration at C4, it is noteworthy that migration of only the undesired C8–C9 bond could take place and that formation of **53** would be most likely.



Scheme 12.

Starting with (+)-3-carene (**16**), we first prepared the known, enantiomerically pure ketone **54**,[31a] which was then converted to **56** by adaptation of Shibasaki's method and subsequent methylation of **55** (Scheme 13).[31b] The Shapiro reaction of racemic hydrazone **57** gave convenient access to the required cyclopentenyllithium and the adduct **58** was obtained in excellent yield. In a preliminary investigation, racemic **57** was employed for convenience. The vinyl group was then installed by standard methods to set the stage for ring closing olefin metathesis of **60**,[32] which proved to be remarkably efficient (refluxing CH_2Cl_2, 5–5.5 mM concentration) to afford a separable 1:1 mixture of **61** and **62**. Hydroxyl-directed epoxidation of allylic alcohol **61** and subsequent semi-pinacol rearrangement of the resulting epoxy alcohol **50** gave the tetracyclic core **51** bearing *in–out* intrabridgehead stereochemistry.



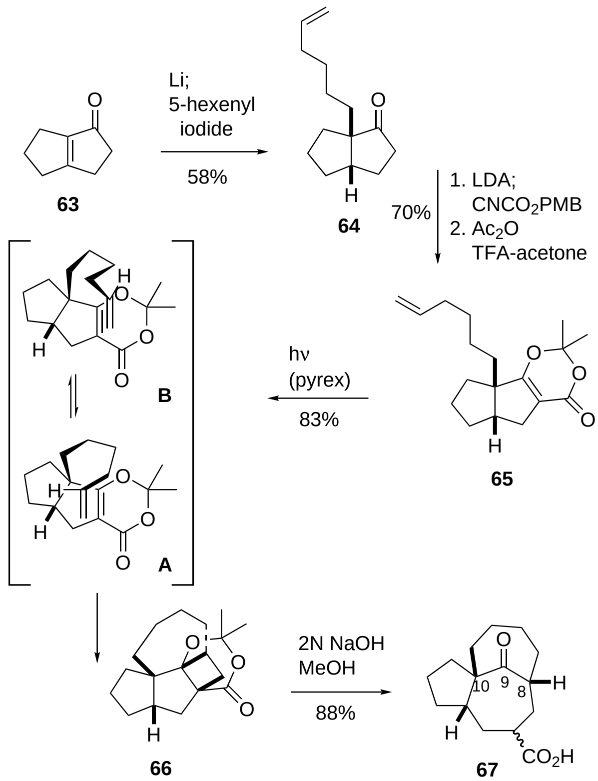
Scheme 13.

Our future plan is to complete a concise, convergent synthesis of ingenol (**2**) by pre-installation of all the necessary functionalities in fragment **57** prior to its coupling to **56**. We also hope to develop a unified approach to the syntheses of the ingenane, tigliane, and daphnane diterpenes.

5. Total syntheses of 2

5.1. Winkler's synthesis of 2

An elegant synthetic methodology to establish the *in–out* intrabridgehead stereochemistry, concurrent with rapid increase of molecular complexity, was devised by Winkler and co-workers by utilizing a modified de Mayo photocycloaddition–retroaldol fragmentation;[33,34] an intramolecular version was adapted to control the regio- and diastereoselectivity of the key photocycloaddition and provided the first preparation of a tricyclic ingenane system **67** having the correct *in–out* configuration (Scheme 14): preparation of the photocycloaddition substrate **65** began with reductive alkylation of **63**.[13,35a,b] The intramolecular dioxenone [2+2] photocycloaddition resulted in exclusive formation of the *in–out* isomer **66** in 83% yield. This attractive approach is a striking example of the diastereocontrol exerted by the preferred folding of the nascent (seven-membered) ring, in which conformer **A** would encounter the least nonbonded interactions (vis-à–vis **B**).



Scheme 14.

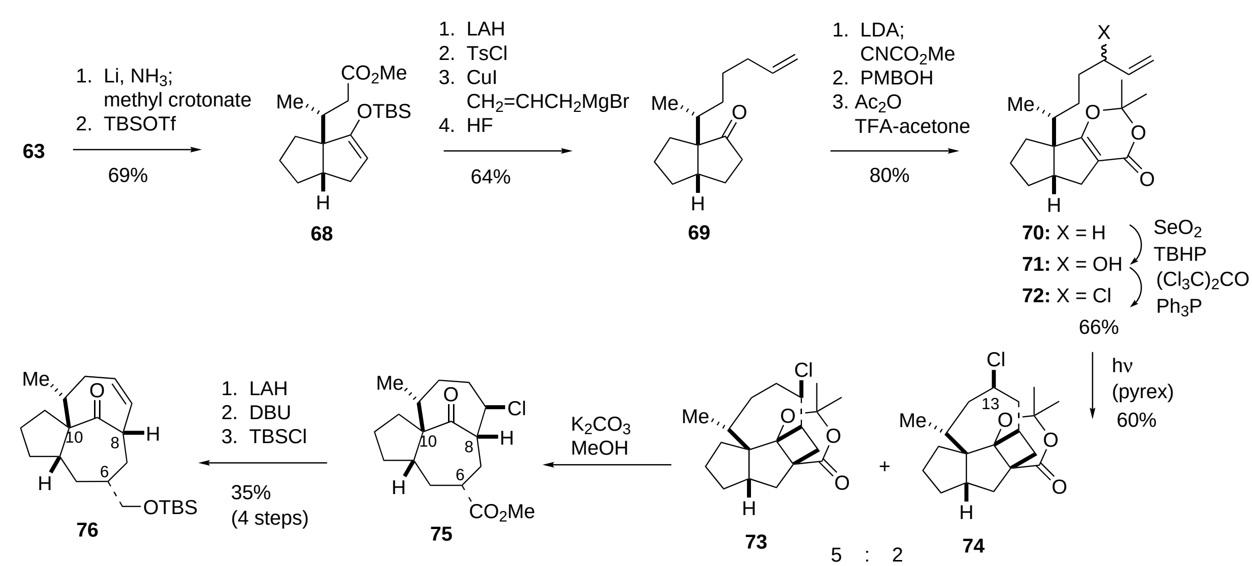
The synthetic utility of the intramolecular dioxenone photocycloaddition has been amply demonstrated by the Winkler group, including an imaginative synthesis of manzamine.[34]

Extensive investigation for the introduction of all functionalities of the ABC rings of **2** finally culminated in its first total synthesis in 2002.[9] The synthesis began with a highly diastereoselective (14:1) Michael addition of the enolate derived from enone **63** to establish the C11 methyl group at an early stage (Scheme 15). Dioxenone **70** was next prepared by following straightforward functional group elaboration of cyclopentanone **69**. To facilitate the introduction of the cyclopropane D ring via the corresponding olefin, allylic chloride **72** was then secured as a 1:1 mixture of the C14 chloro epimers. Irradiation of **72** gave a 5:2 mixture (60% yield) of the C14β chloro product **73** and the C13β chloro isomer **74**. The selective formation of the former, presumably arising from the **72**β isomer, closely mirrors clean conversion of **65** to **66**. On the other hand, the bewildering formation of **74** has been rationalized by a series of transannular hydrogen atom abstractions initiated by the dioxenone triplet from the **72**α epimer.[36] Retroaldol fragmentation of **73** with methanolic K_2CO_3 afforded **75**, as a 7:1 ratio of C6 epimers, which was then converted to **76** by standard methods.

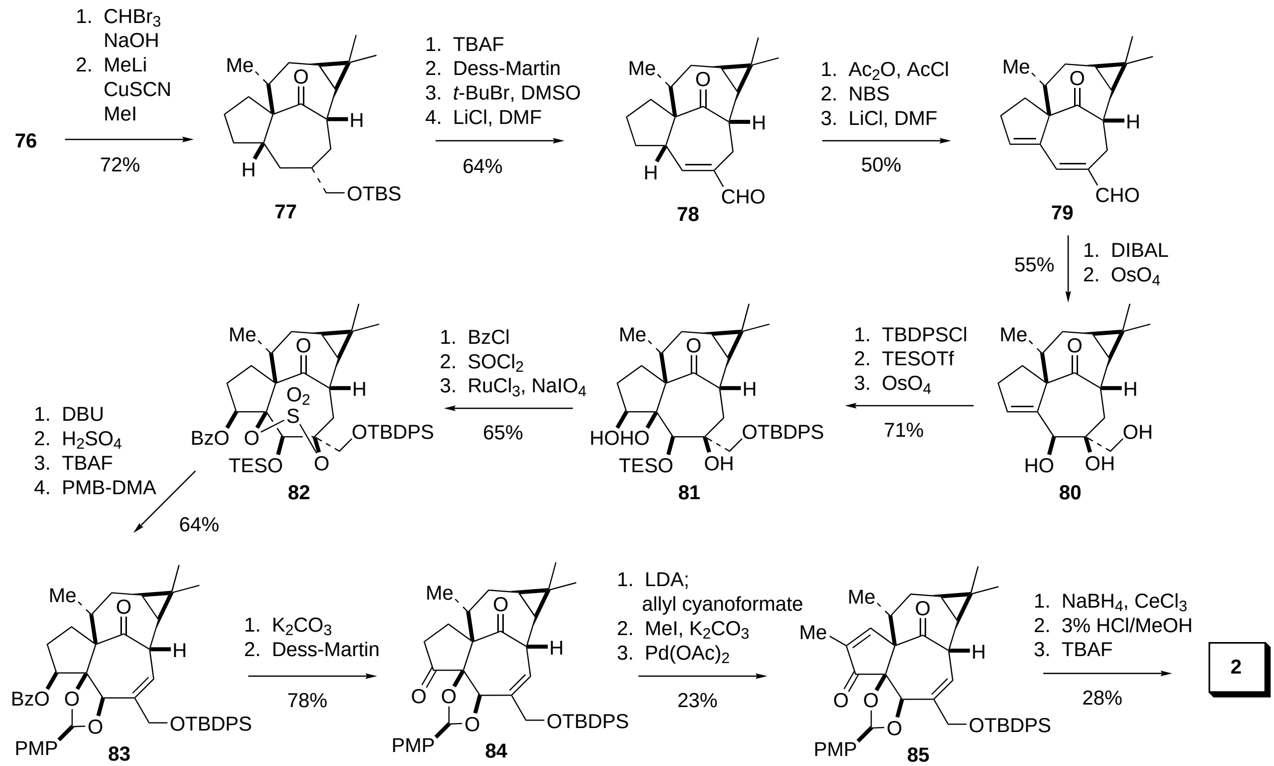
The tetracyclic core **77** was next obtained by dibromocarbene addition and reductive methylation. With **77** in hand, the remaining task for the completion of the synthesis entailed functionalization of the AB rings by relying on the C6 hydroxymethyl group as the sole linchpin. Diene aldehyde **79** was prepared via $\Delta^{5,6}$ unsaturated aldehyde **78** for the subsequent challenging introduction of the triol functionalities at C3, C4, and C5. Two consecutive dihydroxylation reactions occurred from the sterically less hindered β face to deliver **81**. The requisite elimination of the C6 tertiary alcohol was next accomplished via cyclic sulfate **82** by the action of DBU, and subsequent protection as a *p*-methoxybenzylidene acetal afforded **83**. Finally, the first total synthesis of **2** was completed through the intermediacy of ketone **84**.

5.2. Tanino–Kuwajima's synthesis of 2

The Tanino and Kuwajima group designed an efficient tandem cyclization–rearrangement approach to the *in–out* intrabridgehead stereochemistry by adaptation of the Nicholas reaction.[10,37,38] An intramolecular, Lewis-acid mediated variant of *trans*-decalin **86**, initiated by a stabilized propargyl cation, provided excellent diastereocontrol at C11 as a consequence of the *E*-ethylidene



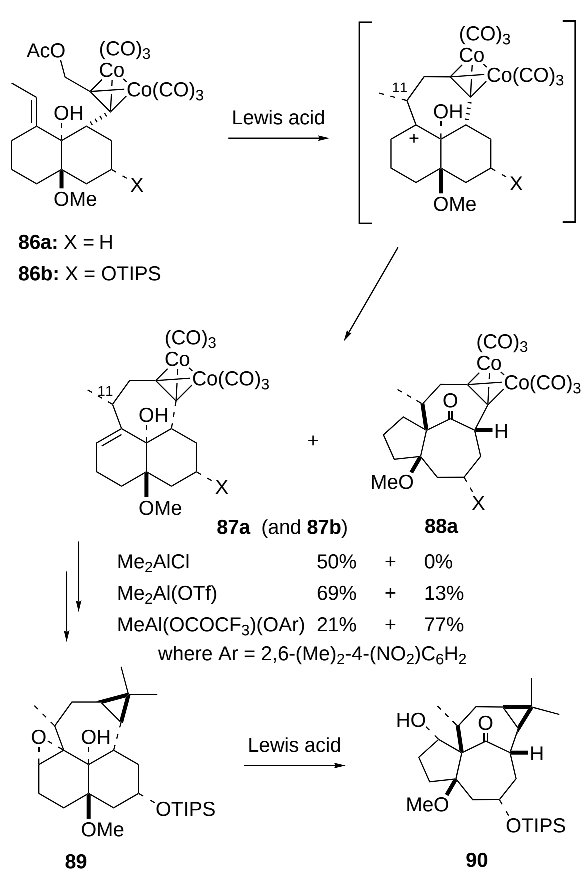
Scheme 15.



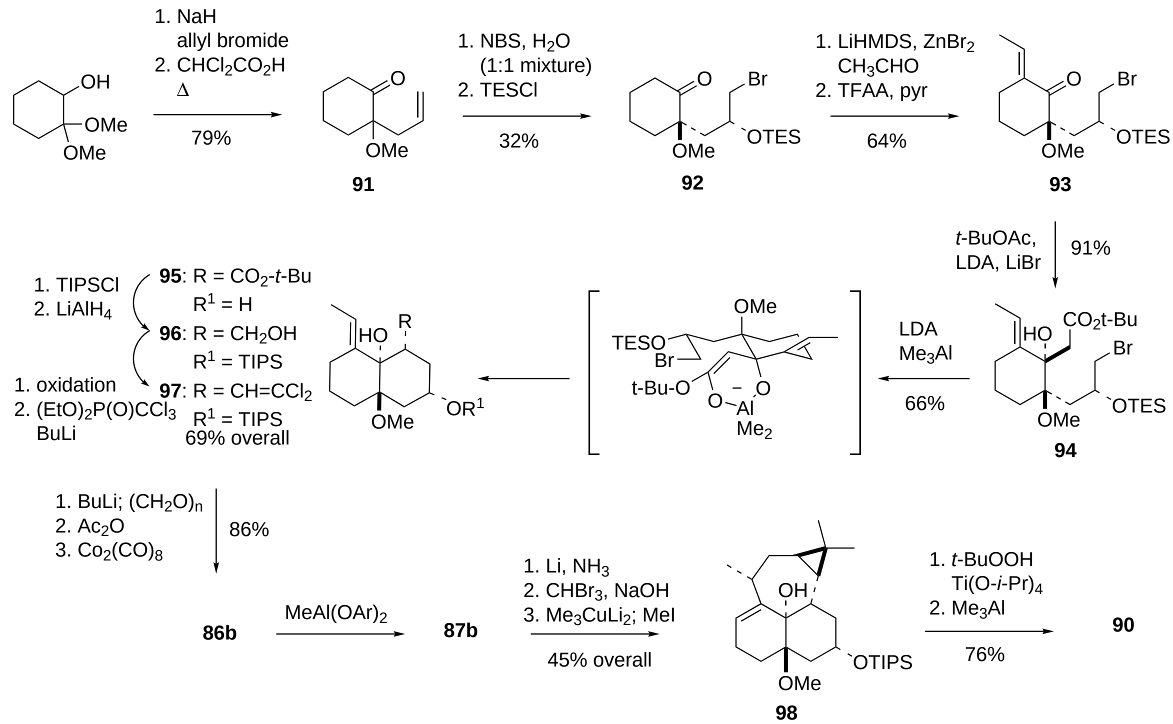
Scheme 16.

geometry (Scheme 17).[37] The final product distribution (i.e., elimination vs rearrangement leading to **87a** and **88a**, respectively) depended on the nature of aluminum-based Lewis acids, possibly due to their interaction with the tertiary hydroxyl group. Ultimately, the semi-pinacol rearrangement of the epoxy alcohol derived from **87b** was successfully utilized for a total synthesis of **2**. This rearrangement sequence (**89**→**90**) parallels the reaction pathway **9**→**10** (Scheme 3), but in the reverse direction. In the synthesis of **2** or analogs, therefore, the semi-pinacol rearrangement of epoxy alcohols could be profitably employed to reverse both transformations described in Scheme 3; the Tanino–Kuwajima synthesis of **2**, along with the above-mentioned Cha's approach (Section 4.3), underscores the synthetic power of the semi-pinacol rearrangement of epoxy alcohols.[25–28]

The isolated methoxy group in the initial study (e.g., **87a** and **88a**) proved to be insufficient for introduction of the requisite functionalities in the AB rings. The total synthesis of **2** was made possible by way of **86b** and **87b** and began with a Claisen rearrangement of 2,2-dimethoxycyclohexanol, followed by bromoetherification, to afford **92** (Scheme 18). An aldol condensation of **92** with acetaldehyde and diastereoselective addition of an acetate enolate anion in the presence of LiBr (presumably to form a five-membered chelate) delivered **94**. *Trans*-decalin **95** was then obtained by intramolecular alkylation by the action of trimethylaluminum and the observed stereochemistry is in accord with the indicated transition model. Subsequent chain elongation gave **97**, which was next converted to a dicobalt–acetylene complex **86b**. Under the influence of methylaluminum bis(2,6-dimethyl-4-nitrophenoxide), **86b** underwent exceptionally diastereoselective cyclization to afford **87b**. The dicobalt



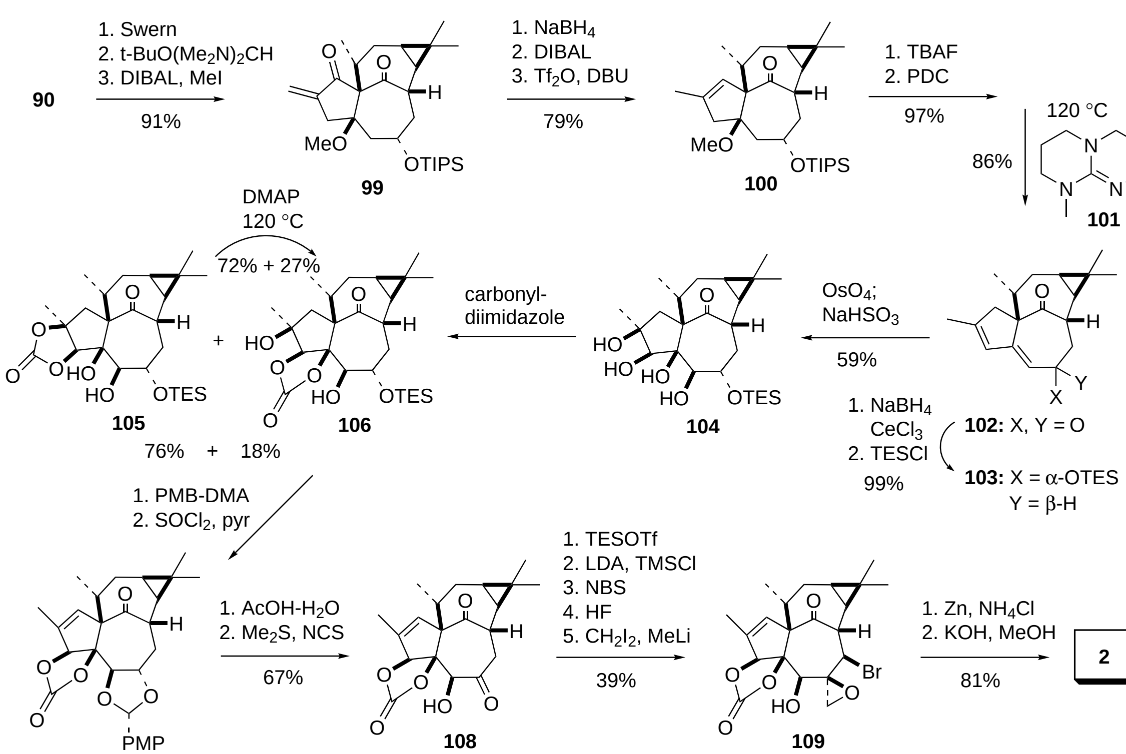
Scheme 17.



Scheme 18.

cluster was thus found useful for facile annulation of the seven-membered ring and also subsequent installation of the D ring. Hydroxy-directed epoxidation of **98** and the key semi-pinacol rearrangement of **89** by the action of Me_3Al yielded **90** possessing the ingenane skeleton with the correct stereochemistry.

The remaining steps were directed at the taxing functionalization of the AB rings: oxidation of the secondary alcohol, use of Bredereck's reagent, and subsequent elaboration afforded cyclopentene **100** (Scheme 19). The fully conjugated dienone **102** was prepared to later introduce the triol functionalities; following the Luche reduction and



Scheme 19.

silylation, dihydroxylation of **103** with an excess of osmium tetroxide gave **104** as a single isomer. Subsequent A ring functionalization was accomplished via the cyclic carbonate **106**; unfortunately, unfavorable regioselectivity in carbonate formation marred the protection sequence. As delineated in Winkler's first synthesis (Scheme 16), installation of the $\Delta^{6,7}$ double bond proved to be far from trivial. Ultimately, the allylic alcohol moiety in the B ring was introduced by reductive elimination of epoxide **109** to complete a total synthesis of **2**.

5.3. Kigoshi's formal synthesis of 2

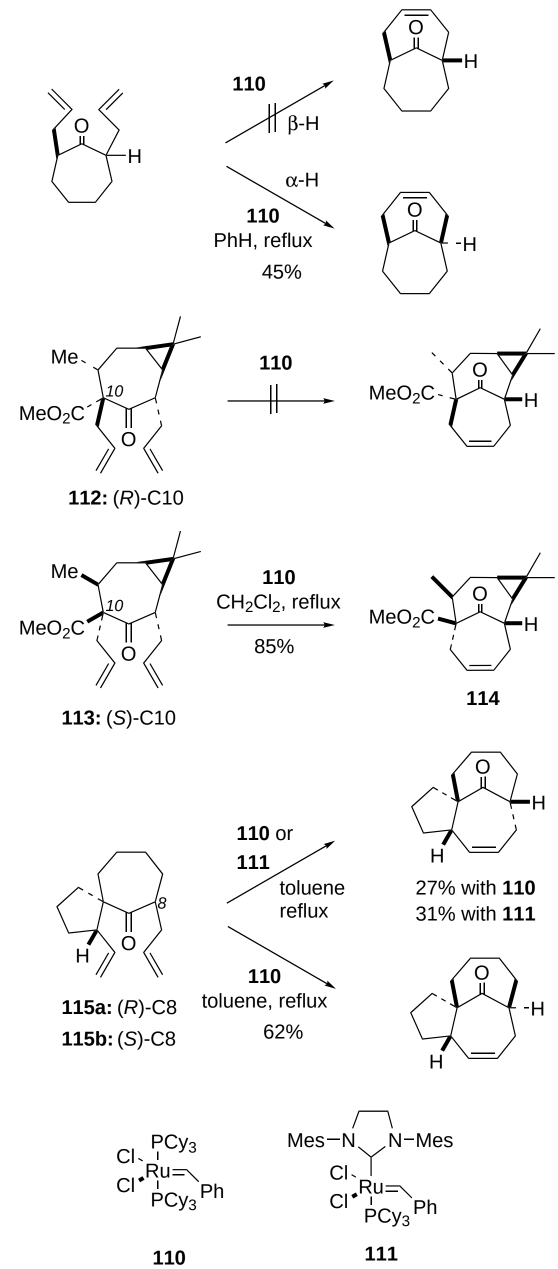
The Kigoshi group reported direct cyclization of a seven-membered ring to construct the *in*,*out*-bicyclo[4.4.1]undecane skeleton of **2** by olefin metathesis.[39] Central to successful annulation of a highly strained seven-membered ring is the presence of the A ring, which would help constrain the otherwise flexible conformation of the pendant side chain and also bring closer the terminal olefins. Without the A ring, for example, ring-closing olefin metathesis (RCM) failed to afford the desired cyclization product; instead oligomerization was observed (Scheme 20). The prerequisite of the A ring for RCM was independently demonstrated by Wood and co-workers with **112** and **113**.[40]

Starting with Funk's keto ester **17**, the A ring in **118** was first constructed by intramolecular alkylation of **117** (Scheme 21). After considerable experimentation, use of a sterically hindered base was found to be essential for high diastereoselectivity of the spirocyclization step. The key substrates **119** and **120** were then prepared by straightforward allylation; RCM investigations showed that the second-generation catalyst **111** was more efficacious than **110** to provide **121** in 53% yield under optimized conditions [refluxing toluene, shorter reaction time (30 min), 1.5 mM concentration]. Under identical conditions, **120** afforded **122** in impressive (87%) yield, which is undoubtedly attributable to the well-known stability of the trisubstituted olefin toward the catalyst **111** to thwart competing ring opening reactions. Nonetheless, it is worth mentioning that a relatively high temperature is necessary for formation of **121** and **122** (compared to **61** and **62**). Finally, allylic oxidation of **122** with SeO_2 gave **78**; since the latter had been converted to **2** by Winkler, this work constitutes a formal synthesis of **2**.

Particularly noteworthy in Kigoshi's synthesis of **122** is the facility of RCM to effect closure to strained seven-membered carbocycles. This example is another testimonial to the distinctive utility of RCM in organic synthesis.

5.4. Wood's synthesis of (+)-2

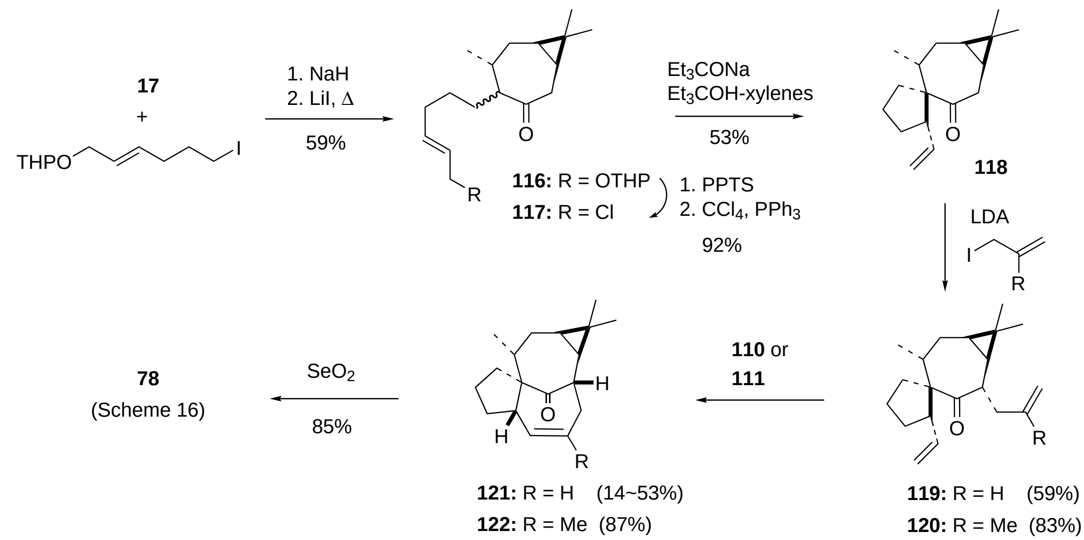
Independent of Kigoshi's work, Wood and co-workers reported a closely related RCM strategy to build the strained *in–out* ABCD ring system (A + CD → ABCD).[40] As pointed out in Scheme 20, successful cyclization is predicated on incorporation of the five-membered A ring, which was conveniently installed by a Diels–Alder reaction of cyclopentadiene (vide supra). However, tandem ring-opening and ring-closing metathesis of **123** did not occur; instead only ring-opening metathesis was observed to



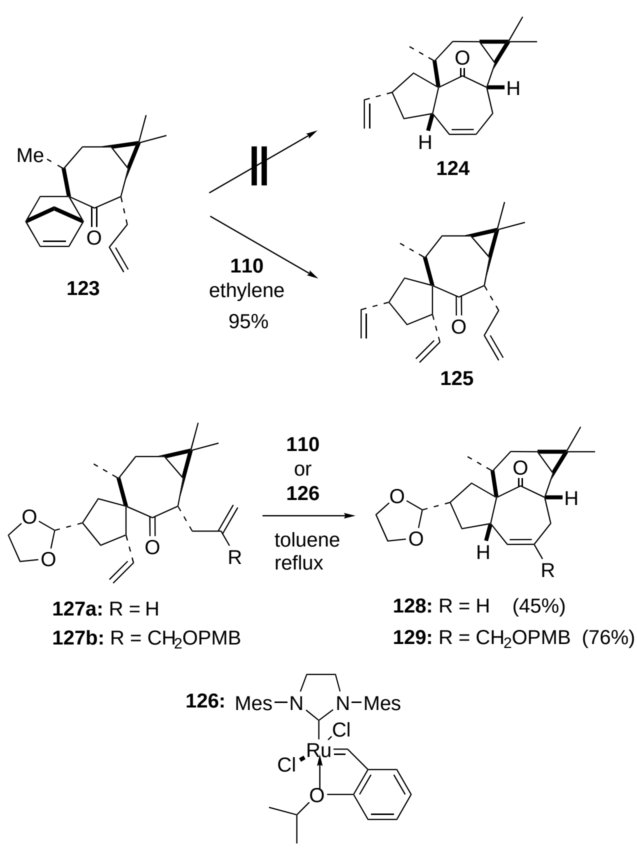
Scheme 20.

provide triene **125** in excellent yield under an atmosphere of ethylene (Scheme 22). A simple solution to circumvent competing reversion of **125** to **123** was to block the C2 olefin (e.g., in **125**) prior to the RCM step. As observed by Kigoshi,[12] the formation of a more robust trisubstituted olefin product (**129** vs **128**) benefited from improved yield (76 vs 45%) and lower catalyst loading (25 vs 80 mol%). Although the Hoveyda catalyst **126** was required for the formation of **129** in acceptable yields,[11,32e] **129** has the built-in advantage of possessing the requisite C20 hydroxymethyl group.

Making use of Funk's ketoester **17**, the Lewis acid-catalyzed Diels–Alder reaction between **131** and cyclopentadiene gave a 20:8:1 mixture of three diastereomers; the major diastereomer (*endo* cycloadduct) **132** possessed the requisite stereochemistry (Scheme 23).[11,40] Subsequent



Scheme 21.



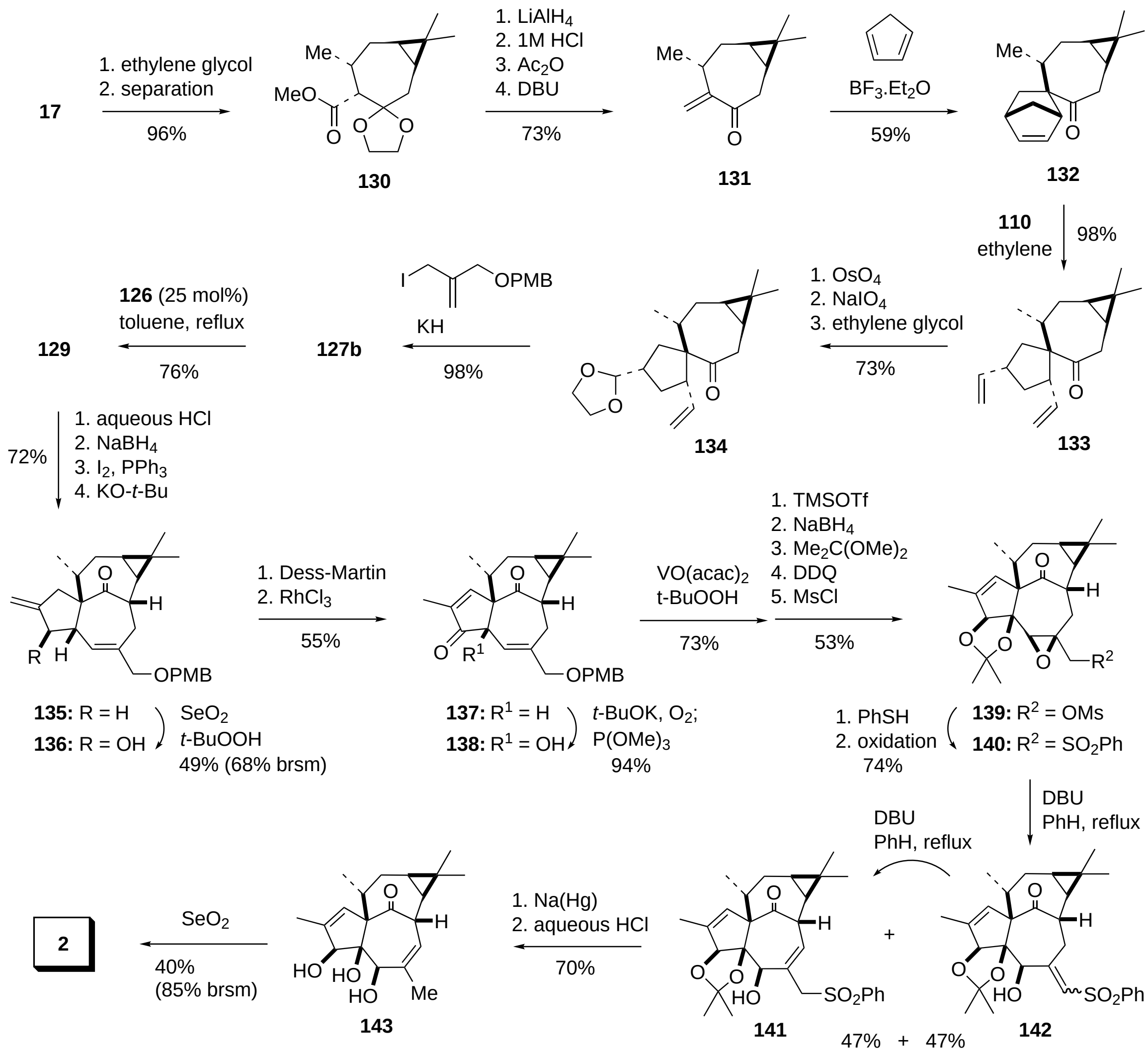
Scheme 22.

RCM of **132** with ethylene, selective functionalization of the desired olefin of **133**, and allylation of **134** then delivered **127b**. As mentioned above, RCM of **127b** gave the key tetracycle **129** in good yield. Next, straightforward elaboration, including regioselective allylic oxidation of **135**, afforded **137**, and oxidation of its enolate cleanly yielded α-hydroxy ketone **138**. Reduction of **137** or **138** proved to be futile, since it occurred from the less hindered, convex face to give the undesired *anti*-diol derivatives. The taxing reduction was, therefore, deferred to a later stage. Hydroxyl-directed epoxidation at the $\Delta^{5,6}$ double bond of **138** was then undertaken. Interestingly, protection of the C4 tertiary alcohol as the TMS ether and subsequent reduction of the C3 keto group stereoselectively afforded the desired β-alcohol. Just what subtle factors influence the preferred conformation and reactivity of the ingenane skeleton has not been determined.

The remaining task involved functionalization of the B ring. As was the case with both previous syntheses by Winkler and Tanino–Kuwajima, another obstacle had to be overcome to introduce the $\Delta^{6,7}$ double bond. For example, **138** proved to be recalcitrant toward oxidation by singlet oxygen. Ultimately, the unusually sluggish ring opening of the C5, C6 epoxide succeeded by use of DBU on the C20 sulfoxide; both β,γ and α,β-unsaturated sulfones **141** and **142** were obtained in a 1:1 ratio. The final conversion of the allylic sulfone **141** to the corresponding primary alcohol at C20 was achieved by a reductive removal–oxidation sequence in order to complete a total synthesis of **2**.

6. Conclusion

Recently emerged three ground-breaking total syntheses of ingenol (**2**) and a formal synthesis: these syntheses highlight attractive approaches to the highly strained inside, outside topography of the ingenane diterpenes, the principal synthetic challenge. Also significant are resourceful maneuvers that were deployed for elaboration of rather under-functionalized advanced intermediates to stereoselectively install the dazzling array of dense functionalities on the southern periphery. These total syntheses of **2**, while stunning feats in natural product synthesis, were somewhat hamstrung by a linear sequence of multi-step transformations to hurdle the latter challenge: the unique intricacy, posed by the high degree of oxygenation and the surprisingly difficult introduction of the $\Delta^{6,7}$ double bond, should be addressed in future studies for more convergent, step-economical syntheses to be reduced to practice. New powerful methodology (e.g., ring-closing olefin metathesis) will undoubtedly aid in streamlining the total syntheses of



Scheme 23.

structurally complex target molecules such as **2**. Also likely is the development of unified strategies for synthesizing ingenanes, tiglianes, and daphnanes.

It is hoped that synthetic studies will help shed light on the structure–activity relationships of these biologically potent natural products, elucidate the molecular basis for their biological activity, and eventually lead to the development of useful biochemical tools and new therapeutic agents.

Acknowledgements

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Biographical sketch

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Synthesis of stable azomethine ylides by the rearrangement of 1,3-dipolar cycloadducts of 3,4-dihydroisoquinoline-2-oxides with DMAD

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Abstract—1-Aryl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolines were prepared according to a one-pot procedure involving the reaction of 2-(3,4-dimethoxyphenyl)-ethylamine with aromatic aldehydes in TFA at reflux. The tetrahydroisoquinolines were treated with H_2O_2–WO_4^{2-} in methanol at room temperature to give the corresponding 3,4-dihydroisoquinoline-2-oxides. Treatment of these cyclic nitrones with DMAD in toluene at room temperature gave the corresponding isoxazolo[3,2-*a*]isoquinolines. These compounds were heated in toluene at reflux to give the corresponding ylides in high yields (Method A). The effect of the substituents on the rate of the rearrangement of such compounds prompted us to discuss a new mechanism involving consecutive C–C bond heterolysis and 1,3-sigmatropic shift. A one-pot reaction involving the treatment of the nitrones with equimolar amounts of DMAD in refluxing toluene also gave the ylides (Method B). The structures of the prepared compounds were elucidated by spectral means and elemental analyses.

1. Introduction

The synthetic utility of the 1,3-dipolar cycloaddition reaction is evident from the number and the scope of targets that can be prepared by this chemistry. Nitrones are the most useful through their ability to generate nitrogen- and oxygen based functionality from the cycloadducts.[1] The cycloadducts of di- and triarylimidazoline 3-oxides[2] with a variety of dipolarophiles[3] give bicyclic compounds with potentially interesting biological activity.[4] On the other hand, they are a source of new heterocyclic compounds via interesting ring-opening reactions.[5]

Previously, we reported the synthesis of stable adducts of Δ^3-imidazoline 3-oxides with DMAD[3d,e] and 3-phenylpropanoic acid alkyl esters.[3f] Thermally and base-induced ring-opening reactions of these adducts were demonstrated. As a continuation of our interest in the ring-opening reactions of 4-isoxazolines,[3d,e] we prepared 1-aryl-3,4-dihydroisoquinoline-2-oxides from the oxidation of 1-aryl-1,2,3,4-tetrahydroisoquinolines under the conditions recently reported[6] and their adducts with DMAD. It is known that nitrones react with alkynes to give generally unstable adducts or those, which are stable can be subjected to rearrangements under thermal conditions. Rearrangements of DMAD adducts of some heterocyclic *N*-oxides has been reviewed.[1a] 4,5-Dihydroimidazole *N*-oxides undergo 1,3-dipolar cycloaddition with alkyne dipolarophiles and the cycloadducts were shown to convert to the corresponding ene-1,1-diamines.[7] The thermal reaction of some 4-isoxazoline derivatives leading to isoquinoline-fused pyrroles has been investigated and it was found that the pathway of the rearrangement to pyrroles is consistent with a route involving an acylaziridine.[8]

2. Results and discussion

We report herein the synthesis of 1-aryltetrahydroisoquinolines **2a–e** and their oxidation with H_2O_2–WO_4^{2-} in methanol at room temperature to give cyclic nitrones **3a–e**. Isolated or in situ formed 8,9-dimethoxy-10b-aryl-6,10b-dihydro-5*H*-isoxazolo[3,2-*a*]isoquinoline-1,2-dicarboxylic acid dimethyl esters **4a–e** were shown to undergo substituent–dependent rearrangement to novel stable 3,4-dihydroisoquinolinium *N*-ylides **5a–e** (Scheme 1). The results are presented in Table 1. A new mechanism involving consecutive C–C bond heterolysis and 1,3-sigmatropic shift is discussed.

Keywords: Isoquinoline; 1-Aryl-1,2,3,4-tetrahydroisoquinoline; THI; Pictet–Spengler; Oxidation with H_2O_2–tungstate; 3,4-Dihydroisoquinoline-2-oxide; Rearrangement; Isoxazoloisoquinoline; Stable azomethine ylide; 4-Isoxazoline rearrangement mechanism; Alkyne; DMAD; Dipolar cycloaddition; Synthesis; Heterocycles.
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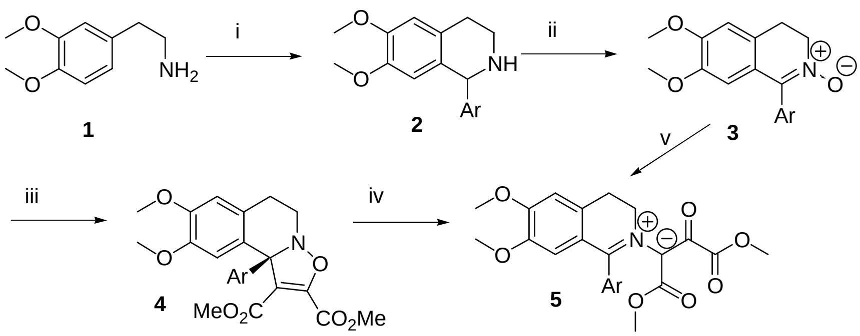
Table 1. Synthesis of compounds **2a–e**, **3a–e** and **4a–e**

1–5	Ar	Yield (%)		
		2	3	4
a	Ph	70[a]	43[b]	95[c]
b	3,4 $(MeO)_2C_6H_3$	85	50	97
c	$3\text{-}NO_2C_6H_4$	80	40	96
d	$4\text{-}ClC_6H_4$	70	69	98
e	3,4 $(OCH_2O)C_6H_3$	60	45	97

[a] The reaction times were 3, 5.5, 2.5, 5, 5.5 h for **2a**,**b**,**c**,**d**,**e**, respectively.
[b] The reaction times were 5.5, 17.5, 23, 21, 19 for **3a**,**b**,**c**,**d**,**e**, respectively.
[c] The reaction times were 18, 5.5, 24, 18, 15 for **4a**,**b**,**c**,**d**,**e**, respectively.

corresponding nitrones **3a–e** in toluene in the presence of DMAD (see Table 2, Method B). It was shown that isoxazolo[3,2-*a*]isoquinolines convert at different rates to the corresponding ylides **5a–e**. The structure of stable 3,4-dihydroisoquinolinium *N*-ylides **5a–e** was deduced from their elemental analyses and spectral data. The compounds are highly coloured and soluble in diluted acids with loss of their colours. The extraction of the acidic water solutions of ylides **5** with $CHCl_3$ again affords the free ylides **5**. Our preliminary experiments show that they react, as expected, with dipolarophiles such as phenyl isocyanate.



Scheme 1. Reagents and conditions: (i) ArCHO; TFA; reflux; (ii) H_2O_2–Na_2WO_4; MeOH; rt; (iii) DMAD; toluene; rt; (iv) toluene; reflux; (v) DMAD; toluene; reflux.

2-(3,4-Dimethoxyphenyl)-ethylamine **1** was reacted with an equimolar amount of the corresponding aromatic aldehyde in refluxing TFA to give in good yields the corresponding 1-aryl-1,2,3,4-tetrahydroisoquinolines **2a–e**.

Compounds **2** were treated with H_2O_2–WO_4^{2-} in methanol according to a method we have recently reported[6] to give 3,4-dihydroisoquinoline-2-oxides **3a–e**. The products were purified by chromatographic methods and were recrystallized from ethanol–ether (1/3).

Nitrones **3a–e** were reacted with DMAD in toluene at room temperature to give quantitatively the corresponding isoxazolo[3,2-*a*]isoquinolines **4a–e**. The products were purified by recrystallization from ethanol in the cases of **4a**,**c**,**e** and preparative TLC in the cases of **4b**,**d**. The NMR as well as the infra red spectral data for compounds **4a–e** are in good agreement with those we have previously reported for similar adducts.[3d–f] Isolated **4a–e** were refluxed in toluene for the times specified in Table 2 (Method A) to give heretofore unreported exclusively stable azomethine ylides **5a–e**. The methods available for generating azomethine ylides, were discussed in a resent review.[9] The same products resulted from the direct heating of the

Table 2. Synthesis of *N*-ylides **5a–e**

	Yield		Reaction time (h)	
	Method A[a]	Method B[b]	A	B
5a	93	75	11	12
5b	100	74	1.5	1.5
5c	82	95	7	8
5d	91	71	13	14
5e	87	96	4	4.2

[a] Yields are based on the starting **4**.
[b] Yields based on the starting **3**.

On the other hand their reactions with amines as diethylamine lead to the formation of corresponding 3,4-dihydroisoquinoline. The ^{13}C NMR spectroscopic assignments specifically for **5e** are shown in Figure 1.

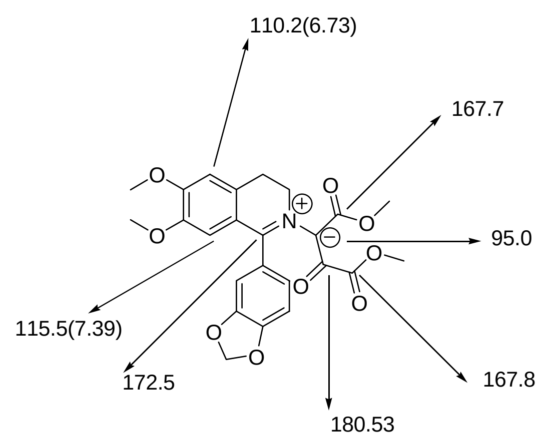
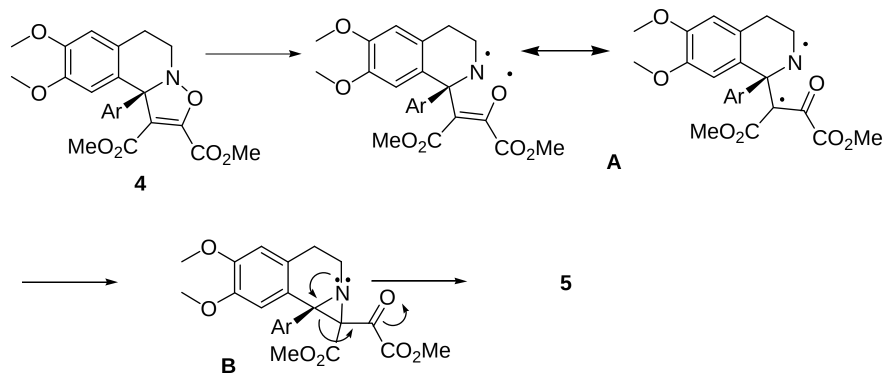


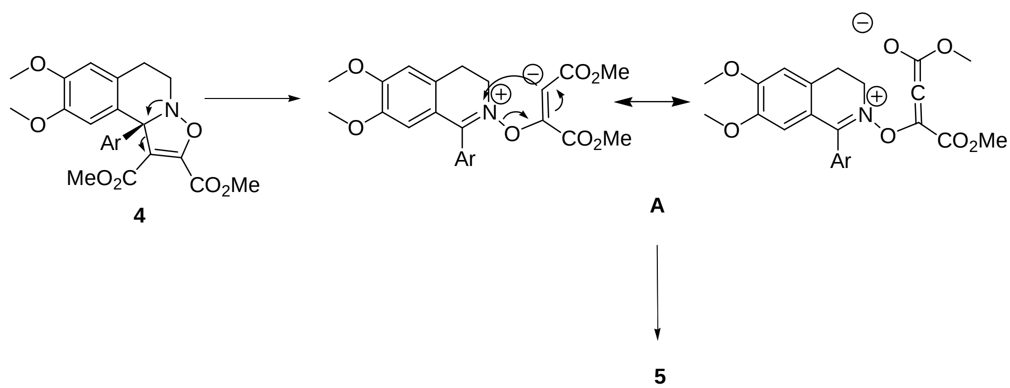
Figure 1. Some ^1H and ^{13}C NMR assignments for compound **5e**.[10]

Electron donating groups on the aromatic ring at C-10b of compounds **4** increase the rate of rearrangement to ylides **5** while electron-withdrawing groups (see Table 2 for the reaction times) decrease it.

Aziridines are generally assumed to be involved in the rearrangements of 4-isoxazolines.[9] A similar approach could be assumed for the conversion of compounds **4** to **5** as depicted in Scheme 2. The homolysis of N–O bond in compounds **4** could give diradicals **A**, which could cyclize to the corresponding aziridines **B**. Thermal ring-opening of aziridine part of **B** could give ylides **5** (see Scheme 2).



Scheme 2. Probable aziridine involving mechanism for the rearrangement of isoxazoloisoquinolines **4**.



Scheme 3. Probable C–C bond heterolysis involving mechanism for the rearrangement of isoxazoloisoquinolines **4**.

However, the pronounced substituent effects discussed above do not support the acylaziridine intermediate in the rearrangement of 4-isoxazolines. It is expected that the substituents on the 10b-phenyl will affect neither homolysis nor heterolysis of the N–O bond in the isoxazoline part of compounds **4**. This prompted us to consider an alternative mechanism outlined in Scheme 3. Electron donating groups on the aromatic ring of **4** probably favour the C-3, C-4 bond heterolysis to give zwitter ions **A** stabilised by resonance, which in turn undergo 1,3-sigmatropic rearrangement to give ylides **5a–e**. The electron donating groups on the aromatic ring at C-10b could stabilise the forming azomethine ylides by their +R effects.

Thus, 1-aryltetrahydroisoquinolines prepared according to Pictet–Spengler procedure from 2-(3,4-dimethoxyphenyl)-ethylamine and the corresponding aromatic aldehydes were oxidized to nitrones **3** the 1,3-dipolar cycloaddition products of which with DMAD were shown to afford previously unknown and stable 3,4-dihydroisoquinolinium *N*-ylides when heated in toluene. A plausible mechanism involving consecutive C–C bond heterolysis and 1,3-sigmatropic shift was discussed.

3. Experimental

Melting points were recorded on an Electrothermal Digital melting point apparatus. Infrared spectra were recorded on a Mattson 1000 FTIR. NMR spectra were recorded on a Mercury Plus 400 MHz spectrometer. UV/vis spectra of compounds **5a–e** were recorded on a Shimadzu UV-2100 spectrophotometer. TLC controls were performed using silica gel coated aluminium sheets. Chloroform, petroleum ether, methanol and acetone (45:40:10:5) solvent mixture was used as an eluent system. Visualisation was effected with UV light. The elemental analyses were performed on a EuroEA 3000 CHNS analyser.

3.1. Synthesis of 1-aryl-1,2,3,4-tetrahydroisoquinolines 2. General procedure

To a solution of 2-(3,4-dimethoxyphenyl)-ethylamine (5 mmol, 0.9062 g) in TFA (3 mL) the corresponding aldehyde (5 mmol) was added and the solution was refluxed for the time specified in Table 1. The reaction mixture was poured onto ice and basified with sodium hydroxide. The mixture was extracted with chloroform (3×10 mL) and the combined extracts were dried over anhydrous Na_2SO_4. The organic solvent was evaporated under vacuum and the residue was crystallized from ethanol.

3.1.1. 6,7-Dimethoxy-1-phenyl-1,2,3,4-tetrahydroisoquinoline 2a. $R_f=0.31$; yield 0.943 g, 70%; mp 110–111 °C; IR (KBr) ν_{NH} 3328 cm^{-1}. (400 MHz, $CDCl_3$): δ 1.87 (1H, s), 2.64–2.71 (1H, m), 2.82–2.90 (1H, m), 2.94–2.99 (1H, m), 3.11–3.17 (1H, m), 3.55 (3H, s), 3.79 (3H, s), 4.97 (1H, s), 6.17 (1H, s), 6.56 (1H, s), 7.17–7.26 (5H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ 29.7; 42.3; 56.3; 56.4; 61.9; 111.4; 111.9; 127.8; 128.1; 128.8;

129.3; 130.3; 145.3; 147.5; 148.1. Anal. Calcd for $C_{17}H_{19}NO_2$ (269.34) C, 75.81; H, 7.11; N, 5.20; Found C, 75.75; H, 7.20; N, 5.30.

3.1.2. 1-(3,4-Dimethoxyphenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline 2b. $R_f=0.23$; yield 85%; mp 88–89 °C; IR (KBr) ν_{NH} 3567 cm^{-1}. (400 MHz, $CDCl_3$): δ 1.83 (1H, s), 2.71–2.77 (1H, m), 2.92–2.99 (1H, m), 3.03–3.1 (1H, m), 3.22–3.28 (1H, m), 3.66 (3H, s), 3.84 (3H, s), 3.88 (3H, s), 3.89 (3H, s), 4.99 (1H, s), 6.28 (1H, s), 6.63 (1H, s), 6.78–6.83 (3H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ 29.3; 42.2; 55.8; 55.8; 55.9; 56.0; 61.5; 110.7; 110.9; 111.4; 111.8; 121.3; 127.6; 130.1; 137.3; 147.0; 147.6; 148.3; 149.0. Anal. Calcd for $C_{19}H_{23}NO_4$ (329.39) C, 69.28; H, 7.04; N, 4.25; Found C, 69.35; H, 6.88; N, 4.23.

3.1.3. 6,7-Dimethoxy-1-(3-nitrophenyl)-1,2,3,4-tetrahydroisoquinoline 2c. $R_f=0.15$; yield 1.257 g, 80%; mp 109–111 °C; IR (KBr) ν_{NH} 3312 and 3256 cm^{-1}. (400 MHz, $CDCl_3$): δ 1.77 (1H, s), 2.73–2.79 (1H, m), 2.91–2.98 (1H, m), 3.04–3.10 (1H, m), 3.14–3.20 (1H, m), 3.64 (3H, s), 3.89 (3H, s), 5.16 (1H, s), 6.17 (1H, s), 6.66 (1H, s), 7.49 (1H, t, $J=7.6$ Hz), 7.61 (1H, d, $J=7.6$ Hz), 8.12–8.17 (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ 29.1; 41.6; 55.8; 55.9; 60.7; 110.7; 111.8; 122.5; 123.8; 127.9; 128.2; 129.3; 135.2; 147.2; 147.3; 148.1; 148.4. Anal. Calcd for $C_{17}H_{18}N_2O_4$ (314.34) C, 64.96; H, 5.77; N, 8.91; Found C, 64.94; H, 5.75; N, 9.02.

3.1.4. 1-(4-Chlorophenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline 2d. $R_f=0.54$; yield 1.063 g, 70%; mp 103–105 °C; IR (KBr) ν_{NH} 3242 cm^{-1}. (400 MHz, $CDCl_3$): δ 1.81 (1H, s), 2.71–2.77 (1H, m), 2.88–2.96 (1H, m), 3.01–3.07 (1H, m), 3.16–3.22 (1H, m), 3.64 (3H, s), 3.87 (3H, s), 5.02 (1H, s), 6.20 (1H, s), 6.63 (1H, s), 7.20 (2H, d, $J=8.0$ Hz), 7.29 (2H, d, $J=8.0$ Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 29.2; 41.8; 55.8; 55.9; 60.8; 110.8; 111.5; 127.7; 128.5; 129.3; 130.3; 133.1; 143.4; 147.1; 147.8. Anal. Calcd for $C_{17}H_{18}ClNO_2$ (303.78) C, 67.21; H, 5.97; N, 4.61; Found C, 67.10; H, 5.97; N, 4.75.

3.1.5. 1-Benzo[1,3]dioxol-5-yl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline 2e. $R_f=0.37$; yield 0.940 g, 60%; mp 133–134 °C; IR (KBr) ν_{NH} 3252 cm^{-1}. (400 MHz, $CDCl_3$): δ 1.76 (1H, s), 2.70–2.75 (1H, m), 2.88–2.95 (1H, m), 3.0–3.06 (1H, m), 3.19–3.24 (1H, m), 3.67 (3H, s), 3.87 (3H, s), 4.97 (1H, s), 5.94 (2H, s), 6.28 (1H, s), 6.62 (1H, s), 6.71–6.77 (3H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ 29.3; 41.9; 55.8; 55.9; 61.2; 101.0; 107.9; 109.2; 110.9; 111.42; 122.2; 127.7; 129.9; 139.1; 146.8; 147.1; 147.7; 147.7. Anal. Calcd for $C_{18}H_{19}NO_4$ (313.35) C, 68.99; H, 6.11; N, 4.47; Found C, 68.90; H, 5.99; N, 4.55.

3.2. Synthesis of 1-aryl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-2-oxides 3a–e. General procedure

To a solution of tetrahydroisoquinoline **2** (0.5 mmol) in methanol (10 mL) H_2O_2 (35%, 2 mmol) was added in the presence of $Na_2WO_4\cdot H_2O$ (0.025 mmol, 8.3 mg). The reaction mixture was stirred at room temperature for the specified time. The solvent was evaporated and water (15 mL) was added to the residue and extracted with chloroform (3×10 mL). The combined extracts were dried and the solvent evaporated. The purification was performed by preparative TLC using silica gel as adsorbent and chloroform, petroleum ether, methanol and acetone (45:40:10:5) solvent mixture as an eluent.

3.2.1. 6,7-Dimethoxy-1-phenyl-1,2,3,4-tetrahydroisoquinoline-2-oxide 3a. $R_f=0.51$; yield 0.061 g, 43%; mp 156–157 °C; IR (KBr) $\nu_{C=N}$ 1590 cm^{-1}; ν_{N-O} 1286 cm^{-1}. (400 MHz, $CDCl_3$): δ 3.15 (2H, t, $J=7.6$ Hz), 3.62 (3H, s), 3.91 (3H, s), 4.26 (2H, t, $J=7.6$ Hz), 6.36 (1H, s), 6.76 (1H, s), 7.43–7.49 (3H, m), 7.56 (2H, d, $J=7.02$ Hz). (100 MHz, $CDCl_3$): δ 27.9; 56.3; 56.4; 59.8; 110.5; 110.6; 123.6; 125.7; 128.5; 129.6; 130.4; 131.4; 142.3; 147.9; 149.6. Anal. Calcd for $C_{17}H_{17}NO_3$ (283.32) C, 72.07; H, 6.05; N, 4.94; Found C, 72.05; H, 5.99; N, 4.97.

3.2.2. 1-(3,4-Dimethoxyphenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline *N*-oxide 3b. $R_f=0.28$; yield 0.086 g, 50%; mp 165–166 °C; IR (KBr) $\nu_{C=N}$ 1590 cm^{-1}; ν_{N-O} 1283 cm^{-1}. (400 MHz, $CDCl_3$): δ 3.14 (2H, t, $J=7.2$ Hz), 3.65 (3H, s), 3.87 (3H, s), 3.91 (3H, s), 3.93 (3H, s), 4.24 (2H, t, $J=7.2$ Hz), 6.45 (1H, s), 6.75 (1H, s), 6.95 (1H, d, $J=8.4$ Hz), 7.13 (1H, d, $J=8.4$ Hz) 7.20 (1H, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ 27.9; 56.1; 56.2; 56.3; 56.4; 59.8; 110.6; 110.8; 111.8; 113.5; 123.5; 123.6; 123.7; 125.9; 142.3; 147.9; 148.7; 149.6; 149.9. Anal. Calcd for $C_{19}H_{21}NO_5$ (343.37) C, 66.46; H, 6.16; N, 4.08; Found C, 66.40; H, 6.34; N, 4.06.

3.2.3. 6,7-Dimethoxy-1-(3-nitrophenyl)-1,2,3,4-tetrahydroisoquinoline *N*-oxide 3c. $R_f=0.54$; yield 0.066 g, 40%; mp 172–173 °C; IR (KBr) $\nu_{C=N}$ 1584 cm^{-1}; ν_{N-O} 1284 cm^{-1}. (400 MHz, $CDCl_3$): δ 3.20 (2H, t, $J=7.6$ Hz), 3.65 (3H, s), 3.95 (3H, s), 4.29 (2H, t, $J=7.6$ Hz), 6.31 (1H, s), 6.81 (1H, s), 7.69 (1H, t, $J=8.0$ Hz), 8.01 (1H, d, $J=8.0$ Hz), 8.30 (1H, d, $J=8.0$ Hz), 8.51 (1H, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ 27.6; 56.2; 56.3; 59.9; 109.8; 110.8; 122.2; 124.2; 125.6; 125.7; 129.3; 132.8; 136.6; 139.7; 148.0; 148.1; 149.9. Anal. Calcd for $C_{17}H_{16}N_2O_5$ (328.32) C, 62.19; H, 4.91; N, 8.53; Found C, 62.10; H, 4.95; N, 8.66.

3.2.4. 1-(4-Chlorophenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline *N*-oxide 3d. $R_f=0.56$; yield 0.110 g, 69%; mp 216–217 °C; IR (KBr) $\nu_{C=N}$ 1595 cm^{-1}; ν_{N-O} 1284 cm^{-1}. (400 MHz, $CDCl_3$): δ 3.15 (2H, t, $J=7.6$ Hz), 3.65 (3H, s), 3.92 (3H, s), 4.25 (2H, t, $J=7.6$ Hz), 6.35 (1H, s), 6.76 (1H, s), 7.45 (2H, d, $J=8.4$ Hz), 7.57 (2H, d, $J=8.4$ Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 27.9; 56.3; 56.4; 59.9; 110.3; 110.7; 123.1; 125.8; 128.8; 129.7; 132.0; 135.5; 141.3; 148.1; 149.7. Anal. Calcd for $C_{17}H_{16}ClNO_3$ (317.77) C, 64.26; H, 5.08; N, 4.41; Found C, 64.40; H, 5.03; N, 4.42.

3.2.5. 1-Benzo[1,3]dioxol-5-yl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline *N*-oxide 3e. $R_f=0.56$; yield 0.074 g, 45%; mp 169–170 °C; IR (KBr) $\nu_{C=N}$ 1590 cm^{-1}; ν_{N-O} 1288 cm^{-1}. (400 MHz, $CDCl_3$): δ 3.13 (2H, t, $J=8.0$ Hz), 3.68 (3H, s), 3.91 (3H, s), 4.23 (2H, t, $J=8$ Hz), 6.02 (2H, s), 6.44 (1H, s), 6.74 (1H, s), 6.89 (1H, d, $J=8.0$ Hz), 6.98 (1H, d, $J=8.0$ Hz), 7.16 (1H, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ 27.9; 56.3; 56.4; 59.8; 101.6; 108.4; 110.5; 110.7; 111.0; 123.6; 123.7; 124.7; 125.8; 141.9; 147.7; 147.9; 148.6; 149.6. Anal. Calcd for $C_{18}H_{17}NO_5$ (327.33) C, 66.05; H, 5.23; N, 4.28; Found C, 66.00; H, 5.20; N, 4.08.

3.3. Synthesis of isoxazolo[3,2-*a*]isoquinolines 4a–e. General procedure

To a solution of nitrone **3** (0.15 mmol) in toluene (10 mL) DMAD (0.225 mmol, 0.032 g) was added and the reaction mixture stirred for the specified time. The solvent was evaporated under vacuum and the residue crystallized from ethanol in the cases of **4a**,**c**,**e**. Compounds **4b**,**d** were purified by preparative TLC.

3.3.1. 8,9-Dimethoxy-10b-phenyl-6,10b-dihydro-5*H*-isoxazolo[3,2-*a*]isoquinoline-1,2-dicarboxylic acid dimethyl ester 4a. $R_f=0.22$; yield 0.061 g, 95%; mp 124–125 °C; IR (KBr) $\nu_{C=O}$ 1758; 1712 cm^{-1}; $\nu_{C=C}$ 1626 cm^{-1}. (400 MHz, $CDCl_3$): δ 2.64–2.70 (1H, m), 3.14–3.22 (1H, m), 3.26–3.33 (1H, m), 3.64–3.72 (1H, m), 3.66 (3H, s), 3.68 (3H, s), 3.87 (3H, s), 3.89 (3H, s), 6.63 (1H, s), 6.99 (1H, s), 7.27–7.37 (5H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.8; 47.1; 52.2; 53.4: 56.0; 56.1; 77.3; 110.8; 112.3; 114.9; 126.6; 126.8; 128.2; 128.3; 129.1; 142.8; 147.7; 148.5; 153.5; 159.8; 163.6. Anal. Calcd for $C_{23}H_{23}NO_7$ (425.43) C, 64.93; H, 5.45; N, 3.29; Found C, 65.10; H, 5.55; N, 3.40.

3.3.2. 10b-(3,4-Dimethoxyphenyl)-8,9-dimethoxy-6,10b-dihydro-5*H*-isoxazolo[3,2-*a*]isoquinoline-1,2-dicarboxylic acid dimethyl ester 4b. $R_f=0.89$; yield 0.071 g, 97%; oil; IR (KBr) $\nu_{C=O}$ 1758; 1712 cm^{-1}; $\nu_{C=C}$ 1626 cm^{-1}. (400 MHz, $CDCl_3$): δ 2.60–2.70 (1H, m), 3.15–3.22 (1H, m), 3.24–3.32 (1H, m), 3.64–3.72 (1H, m), 3.67 (3H, s), 3.71 (3H, s), 3.79 (3H, s), 3.85 (3H, s), 3.86 (3H, s), 3.89 (3H, s), 6.62 (1H, s), 6.76 (1H, d, $J=8.4$ Hz), 6.82 (1H, dd, $J=8.4$, 2.0 Hz), 6.96 (1H, d, $J=2.0$ Hz), 7.04 (1H, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.7; 46.9; 52.3; 53.3: 56.0; 56.1; 77.0; 110.4; 110.8; 112.3; 112.4; 115.7; 121.9; 126.6; 126.7; 135.0; 147.6; 148.4; 148.7; 149.0; 152.9; 159.7; 163.8. Anal. Calcd for $C_{25}H_{27}NO_9$ (485.48) C, 61.85; H, 5.61; N, 2.89; Found C, 61.80; H, 5.63; N, 2.89.

3.3.3. 8,9-Dimethoxy-10b-(3-nitrophenyl)-6,10b-dihydro-5*H*-isoxazolo[3,2-*a*]isoquinoline-1,2-dicarboxylic acid dimethyl ester 4c. $R_f=0.79$; yield 0.068 g, 96%; mp 123–124 °C; IR (KBr) $\nu_{C=O}$ 1758; 1719 cm^{-1}; $\nu_{C=C}$ 1644 cm^{-1}. (400 MHz, $CDCl_3$): δ 2.72–2.77 (1H, m), 3.15–3.24 (1H, m), 3.25–3.31 (1H, m), 3.64–3.72 (1H, m), 3.67 (3H, s), 3.70 (3H, s), 3.87 (3H, s), 3.89 (3H, s), 6.65 (1H, s), 6.89 (1H, s) 7.50 (1H, t, $J=8.2$ Hz), 7.8 (1H, d, $J=8.2$ Hz), 8.16 (1H, d, $J=8.2$ Hz), 8.25 (1H, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.9; 47.3; 52.5; 53.5: 56.1; 77.2; 111.2; 111.6; 114.1; 123.3; 124.1; 125.2; 126.8; 129.3; 135.2; 145.5; 148.1; 148.3; 148.9; 153.9; 159.5; 163.4. Anal. Calcd for $C_{23}H_{22}N_2O_9$ (470.43) C, 58.72; H, 4.71; N, 5.95; Found C, 58.80; H, 4.90; N, 6.10.

3.3.4. 10b-(4-Chlorophenyl)-8,9-dimethoxy-6,10b-dihydro-5*H*-isoxazolo[3,2-*a*]isoquinoline-1,2-dicarboxylic acid dimethyl ester 4d. $R_f=0.74$; yield 0.068 g, 98%; oil; IR (KBr) $\nu_{C=O}$ 1755; 1709 cm^{-1}; $\nu_{C=C}$ 1638 cm^{-1}. (400 MHz, $CDCl_3$): δ 2.63–2.0 (1H, m), 3.12–3.20 (1H, m), 3.23–3.30 (1H, m), 3.64–3.72 (1H, m), 3.67 (3H, s), 3.69 (3H, s), 3.87 (3H, s), 3.89 (3H, s), 6.62 (1H, s), 6.95 (1H, s), 7.28–7.32 (4H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.8; 47.2; 52.3; 53.4; 56.0; 56.1; 76.8; 110.9; 112.1; 114.6; 126.2; 126.8; 128.5; 130.5; 134.2; 141.5; 147.9; 148.7; 153.6; 159.7; 163.5. Anal. Calcd for $C_{23}H_{22}ClNO_7$ (459.88) C, 60.07; H, 4.82; N, 3.05; Found C, 60.10; H, 4.83; N, 3.10.

3.3.5. 10b-Benzo[1,3]dioxol-5-yl-8,9-dimethoxy-6,10b-dihydro-5*H*-isoxazolo[3,2-*a*]isoquinoline-1,2-dicarboxylic acid dimethyl ester 4e. $R_f=0.86$; yield 0.068 g, 97%; mp 122–123 °C; IR (KBr) $\nu_{C=O}$ 1749; 1716 cm^{-1}; $\nu_{C=C}$ 1637 cm^{-1}. (400 MHz, $CDCl_3$): δ 2.61–2.67 (1H, m), 3.12–3.18 (1H, m), 3.25–3.32 (1H, m), 3.66–3.77 (1H, m), 3.67 (3H, s), 3.71 (3H, s), 3.84 (3H, s), 3.87 (3H, s), 5.93 (2H, s), 6.60 (1H, s), 6.75 (1H, d, $J=8.4$ Hz), 6.78 (1H, d, $J=8.4$ Hz), 6.88 (1H, s) 7.02 (1H, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.7; 46.9; 52.2; 53.3: 56.0; 56.1; 77.1; 101.5; 107.8; 109.7; 110.8; 112.2; 114.9; 122.9; 126.6; 126.7; 136.8; 147.5; 147.7; 147.8; 148.5; 153.4; 159.8; 163.6. Anal. Calcd for $C_{24}H_{23}NO_9$ (469.44) C, 61.40; H, 4.94; N, 2.98; Found C, 61.50; H, 5.10; N, 3.10.

3.4. Synthesis of azomethine ylides 5a–e. Method A; General procedure

A solution of compound **4** (0.1 mmol) in toluene (5 mL) was refluxed for the specified time (see Table 2). The solvent was evaporated under vacuum and the residue subjected to a silica gel coated TLC plate and eluted with chloroform, petroleum ether, methanol and acetone (45:40:10:5) solvent mixture. The isolated product was crystallized from ethanol ether mixture (1:5).

3.5. Synthesis of azomethine ylides 5a–e. Method B; General procedure

To a solution of nitrone **3** (0.2 mmol) dissolved in toluene (10 mL) DMAD was added and the mixture refluxed for the specified time. The solvent was evaporated and the mixture was subjected on a preparative TLC plate coated with silica gel. The isolated coloured compounds were crystallized from ethanol ether mixture (1:5).

3.5.1. Azomethine ylide 5a. $R_f=0.5$; yield; Method A, 0.040 g, 93%; Method B, 0.064 g, 75%; light red coloured crystals; mp 228–229 °C; IR (KBr) $\nu_{C=O}$ 1726; 1664 cm^{-1}. UV/vis λ_{max} $CHCl_3$ nm: 256.5, 313.5, 361.5, 455.1; (400 MHz, $CDCl_3$): δ 3.25 (2H, t, $J=7.4$ Hz), 3.52 (3H, s), 3.63 (3H, s), 3.69 (3H, s), 4.16 (3H, s), 4.01–4.21 (1H, m), 4.25–4.30 (1H, m), 6.57 (1H, s), 6.86 (1H, s), 7.44–7.53 (5H, m). (100 MHz, $CDCl_3$): δ 26.9; 50.8; 52.0; 54.3; 56.3; 56.8; 95.5; 110.5; 115.5; 121.0; 128.2; 128.5; 131.8; 131.9; 134.7; 148.3; 156.1; 164.3; 168.6; 171.1; 174.9. Anal. Calcd for $C_{23}H_{23}NO_7$ (425.43) C, 64.93; H, 5.45; N, 3.29; Found C, 64.98; H, 5.60; N, 3.40.

3.5.2. Azomethine ylide 5b. $R_f=0.47$; yield; Method A, 0.049 g, 100%; Method B, 0.072 g, 74%; dark orange crystals; mp 128–129 °C; IR (KBr) $\nu_{C=O}$ 1725; 1665 cm^{-1}. UV/vis λ_{max} $CHCl_3$ nm: 255.5, 391.5; (400 MHz, $CDCl_3$): δ 3.13 (2H, t, $J=6.4$ Hz), 3.37 (3H, s), 3.71 (3H, s), 3.87 (6H, s), 3.88 (3H, s), 3.98 (3H, s), 4.16 (2H, t, $J=6.4$ Hz), 6.76 (1H, s), 6.86 (1H, d, $J=9.2$ Hz), 6.91 (1H, d, $J=9.2$ Hz), 6.98 (1H, s), 7.45 (1H, s). (100 MHz, $CDCl_3$): δ 26.6; 50.5; 51.8; 53.1; 56.0; 56.1; 56.2; 56.4; 96.1; 107.5; 109.9; 110.8; 115.3; 115.6; 121.9; 132.2; 139.1; 148.1; 148.6; 148.9; 154.8; 167.2; 167.6; 172.1; 180.3. Anal. Calcd for

$C_{25}H_{27}NO_9$ (485.48) C, 61.85; H, 5.61; N, 2.89; Found C, 61.90; H, 5.75; N, 3.00.

3.5.3. Azomethine ylide 5c. R_f = 0.59; yield; Method A, 0.039 g, 82%; Method B, 0.090 g, 95%; dark red crystals; mp 213–214 °C; IR (KBr) $\nu_{C=O}$ 1735; 1688 cm^{-1}. UV/vis λ_{max} $CHCl_3$ nm: 228.0, 233.0, 259.0, 315.5, 372.0, 469.0; (400 MHz, $CDCl_3$): δ 3.16–3.24 (1H, m), 3.31–3.40 (1H, m), 3.59 (3H, s), 3.63 (3H, s), 3.65 (3H, s), 4.03 (3H, s), 4.15–4.22 (1H, m), 4.24–4.32 (1H, m), 6.49 (1H, s), 6.89 (1H, s), 7.65 (1H, t, J = 8.0 Hz), 7.88 (1H, d, J = 8.0 Hz), 8.32 (1H, s), 8.37 (1H, d, J = 8.0 Hz). (100 MHz, $CDCl_3$): δ 26.8; 51.1; 52.1; 54.3; 56.5; 56.9; 92.1; 110.9; 114.5; 119.9; 123.9; 126.2; 129.4; 133.4; 134.3; 135.1; 147.6; 148.7; 156.9; 164.3; 168.1; 170.3; 171.5. Anal. Calcd for $C_{23}H_{22}N_2O_9$ (470.43) C, 58.72; H, 4.71; N, 5.95; Found C, 58.58; H, 4.80; N, 6.10.

3.5.4. Azomethine ylide 5d. R_f = 0.67; yield; Method A, 0.042 g, 91%; Method B, 0.066 g, 71%; dark red crystals; mp 178–179 °C; IR (KBr) $\nu_{C=O}$ 1727; 1665 cm^{-1}. UV/vis λ_{max} $CHCl_3$ nm: 258.0, 262.0, 366.5, 461.5; (400 MHz, $CDCl_3$): δ 3.22–3.29 (2H, m), 3.54 (3H, s), 3.65 (3H, s), 3.71 (3H, s), 4.01 (3H, s), 4.17–4.25 (2H, m), 6.53 (1H, s), 6.86 (1H, s), 7.42 (4H, br s). ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.8; 51.0; 52.1; 54.4; 56.4; 56.9; 96.3; 110.6; 115.1; 120.6; 128.6; 130.1; 130.3; 134.9; 138.1; 148.4; 156.4; 164.3; 168.4; 170.9; 173.7. Anal. Calcd for $C_{23}H_{22}ClNO_7$ (459.88) C, 60.07; H, 4.82; N, 3.05; Found C, 60.15; H, 5.01; N, 3.30.

3.5.5. Azomethine ylide 5e. R_f = 0.59; yield; Method A, 0.41 g, 87%; Method B, 0.090 g, 96%; dark red crystals; mp 123–124 °C; IR (KBr) $\nu_{C=O}$ 1734; 1718 cm^{-1}. UV/vis λ_{max} $CHCl_3$ nm: 255.0, 297.5, 386.0; (400 MHz, $CDCl_3$): δ 3.08 (2H, t, J = 7.0 Hz), 3.40 (3H, s), 3.70 (3H, s), 3.84 (3H, s), 3.96 (3H, s), 4.08 (2H, t, J = 7.0 Hz), 5.98 (2H, s), 6.73 (1H, s), 6.78 (1H, d, J = 8.4 Hz), 6.84 (1H, d, J = 8.4 Hz), 6.86 (1H, s), 7.40 (1H, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.9; 50.9; 52.1; 53.3; 56.43; 56.6; 95.0; 102.1; 105.5; 108.4; 110.2; 115.5; 117.7; 122.2; 132.7; 140.7; 147.3; 148.1; 148.3; 155.0; 167.7; 167.8; 172.5; 180.5. Anal. Calcd for $C_{24}H_{23}NO_9$ (469.44) C, 61.40; H, 4.94; N, 2.98; Found C, 61.50; H, 5.10; N, 3.10.

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Dipolar cycloadditions of imidazoline 3-oxides with *N*-arylmaleimides. Synthesis and diethylamine induced ring-opening of *exo* and *endo* hexahydro-7-oxa-2,5,6a-triaza-cyclopenta[*a*]pentalene-1,3-diones

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Abstract—1,4-Diarylimidazoline 3-oxides react with *N*-arylmaleimides in benzene to give predominantly the corresponding *endo* adducts. Chiral imidazoline 3-oxides react diastereospecifically (cis configuration of the tetrahydroimidazo ring) and diastereoselectively to give *cis–endo* adducts. The effects of substituents on the aromatic ring of the maleimide was investigated. The presence of electron-withdrawing or releasing groups have minor effect on the total yields but more pronounced is the effect on the ratio of *exo* and *endo* diastereomers. The adducts undergo an interesting and unprecedented ring-opening in the presence of secondary amines to give deoxygenated 3-imidazoline 3-oxides instead of the expected double cis elimination products. Tertiary amines did not induce any reaction.

1. Introduction

Nitrones are well-known 1,3-dipoles in thermal cycloaddition reactions with multiple bond systems to provide various heterocyclic five membered ring systems.[1] The cycloadducts of di- and triarylimidazoline 3-oxides[2] with a variety of dipolarophiles[3] give bicyclic compounds with potentially interesting biological activity.[4] On the other hand, they are source of new heterocyclic compounds via interesting ring-opening reactions.[5] In our previous work, the 1,3-dipolar cycloadditions of imidazoline 3-oxides was shown to proceed regio- and diastereoselectively and interesting reactions of these adducts under a variety of conditions especially the double cis elimination they undergo in the presence of dialkylamines was reported.[3d–e,5] *exo* Adducts of *N*-methyl and *N*-phenylmaleimides with chiral 1-benzyl-4-phenyl-2-imidazoline 3-oxide were reported recently.[6] As a continuation of our interest in the synthesis of imidazoisoxazolidines with potential anticancer activity and in the stereochemistry of dipolar cycloadditions of 1,4-diaryl and 1,2,4-triarylimidazoline 3-oxides with different dipolarophiles, we planned to react a series of *N*-arylmaleimides with imidazoline 3-oxides[7] **1** and to subject them to ring-opening in the presence of secondary and tertiary amines.[8] The latter reaction would serve as an important entry into the synthesis of chiral 3-hydroxypyrrolidines, which have attracted attention after the discovery of the glycosidase inhibitor activity of the natural product nojirimycin.[9] The retrosynthetic plan related to the synthesis of chiral pyrrolidin-3-ols is depicted in Scheme 1. (*S*)-Nitrone would give the *exo* and *endo* adducts; the ring-opening of the *exo* adduct would give (*S*)-pyrrolidin-2,5-diones while *endo* would give (*R*), and the reduction of both would give the corresponding chiral pyrrolidin-3-ols. The reverse will be true if we start from (*R*)-nitrone.

For the most widely studied nitrone, *C*-phenyl-*N*-methylnitrone, the frontier orbital energies indicate HOMO control for electron-deficient dipolarophiles.[10] Our observations on the cycloadditions of compounds **1** with electron deficient dipolarophiles corroborate the conclusion that the process is HOMO controlled. In this investigation we were also interested in the effect of substituents on the *N*-aryl group of the maleimide on the reaction yield and the *exo–endo* selectivity of the cycloaddition reaction with cyclic nitrones **1**. The problem of *endo–exo* selectivity in 1,3-dipolar cycloadditions is far from definitively assessed and the *endo–exo* selectivity of the cycloaddition of 3,4-dihydroisoquinoline 2-oxide with different types of dipolarophiles was reported.[11a] The *exo–endo* selectivity of 1,3-dipolar cycloaddition of *C*,*N*-diphenylnitrone to

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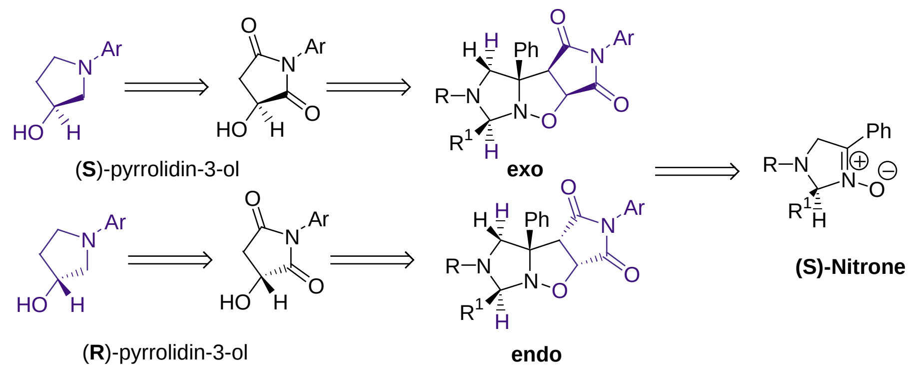


Scheme 1. Retrosynthetic analysis for the asymmetric synthesis of pyrrolidin-3-ols.

tert-butyl vinyl ether in the presence of chiral Ti(IV) species was recently reported.[11]

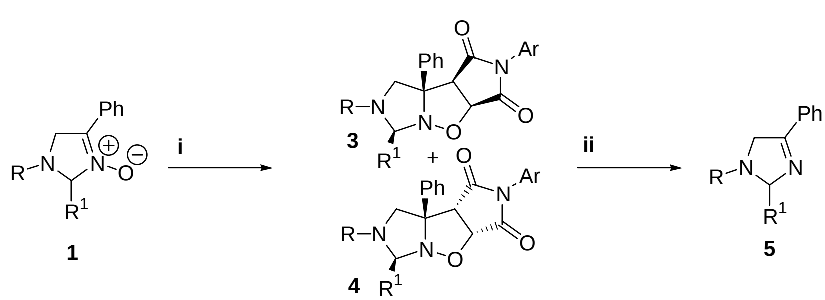
We report herein the synthesis and ring-opening reactions of a new class of compounds, namely hexahydro-7-oxa-2,5,6a-triaza-cyclopenta[*a*]pentalene-1,3-diones. The reaction of nitrones **1a–i** with *N*-arylmaleimides **2** in benzene and toluene was shown to proceed selectively to give the *endo* adducts as major products. The *exo–endo* ratio increases when electron-donating groups are present on the N-2 aryl, and decreases when the groups are electron-withdrawing. The reaction of adducts **3** and **4** separately or their mixture with diethylamine led to a so far unobserved interesting ring-opening to give di- and triaryl-3-imidazolines **5** instead of the expected double cis elimination products. The mechanism of this reaction is also briefly discussed.

2. Results and discussions

To elucidate the solvent effect on the rate and product ratio of the dipolar cycloaddition, nitrone **1a** was refluxed in different solvents in the presence of 4 equiv of *N*-phenylmaleimide (Scheme 2 and Table 1). The reaction was observed to proceed much faster in solvents such as benzene, acetonitrile and toluene. The reaction proceeds with higher *endo* selectivity in toluene while the cycloaddition in dichloromethane, THF and acetonitrile was unselective. The reaction is too slow in DCM, 39% yield was achieved after 48 h reflux.

At first we decided to develop the model reaction starting with racemic nitrones **1**. Compounds **1a–i** were reacted with maleimides **2** in benzene to give adducts **3** and **4** in high total yields (Scheme 2 and Table 2).

The cycloaddition nearly completes within 10 h in the cases where C-2 of the nitrone is unsubstituted, while in the cases of C-2 aryl substituted nitrones **1c–e** the reaction time was five times longer to achieve the same yields due to the steric hindrance of the aryl groups. The *exo–endo* ratio is approximately the same in the cycloaddition of nitrones **1a–d** with *N*-phenylmaleimide. The ratio is close to 1:1 in the case of **1e** (C-2 substituent is 3-nitrophenyl group) the steric hindrance of which probably does not support the formation of the transition state leading to the *endo* adduct. To understand the role of the substituents on the *N*-aryl group of **2** it is useful to compare the *exo–endo* ratio of cycloadditions with **1a**,**f–i** (Table 2). It is seen that the electron-donating groups favor the formation of *endo* adducts, while electron-withdrawing groups do not. Beside the steric effects contributing to the *exo–endo* ratio, secondary orbital interactions between the aryl rings at N-2 and N-5 and may be between N-5 and the carbonyls at the pyrrolidine ring are probably also responsible for the stabilization of the transition state leading to *endo* adduct. The effect of substituents on the total yields of adducts **3** and **4** are of the same magnitude independent of their nature. This means electron-donating groups somewhat increase the LUMO energy of the electron deficient maleimide and thus decelerate the *exo* adduct formation. Computations of the HOMO and LUMO energies for maleimides **2** confirmed this. On the other hand, computation of the HOMO and LUMO energies for nitrone **1a** and comparison with the corresponding HOMO and LUMO energies of maleimides **2** clearly revealed that the cycloaddition should be a HOMO controlled process. The same electron-donating substituent probably raises the energy of N-2 phenyls HOMO to give a better π interaction between the N-5 aryl. Conversely, electron-withdrawing groups decrease the LUMO energy of the electron deficient maleimide thus accelerating the *exo*



Scheme 2. Reagents and reaction conditions; (i) 4 equiv *N*-arylmaleimide **2**; benzene, reflux; (ii) Diethylamine, reflux, 23 h.

Table 1. Solvent effect on the 1,3-dipolar cycloaddition of **1a** with *N*-phenylmaleimide

Solvent	Reaction time (h)	Total yield (%)	Yield (%)	
			3a	**4a**
Benzene	10	100	35	65
Toluene	10	80	24	57
THF	10	56	23	33
DCM	48[a]	39	19	20
Acetonitrile	10	86	45	41

[a] The yield of the reaction for 10 h reaction time is 12% and the ratio of *exo* and *endo* isomers is 1:2.

adduct formation but lower the π interaction between the N-5 aryl.

Some characteristic assignments for adducts **3** and **4** based on extensive 1D and 2D NMR experiments are given in Table 3.

The *exo* stereochemistry of adducts **3a–b**,**f–i** was confirmed by NOESY1D experiments performed on compound **3a** (Fig. 1) as follows:

Irradiation of proton at C-7a enhanced the signal of 3aH (1%). Irradiation of the doublet of 6Ha enhanced the signals of 6Hb (12.72%) and *ortho* protons of *N*-tolyl group (6.66%). The irradiation of 6Hb enhances the signal of 6Ha (13.62%) and the *ortho* protons' signals of *N*-tolyl (3.92%) and 3b-phenyl (2.93%). Irradiation of 4Hb, enhanced the signals of 4Ha, and the *ortho* protons of both phenyls at N-5 and C-3b by 19.0, 6.81, and 9.13%, respectively. The irradiation of 3aH enhances the signals of 7aH (3.3%), 4Ha (3.09%) and *ortho* protons of 3b-phenyl by 0.5%. Irradiation of 4Ha enhances the signals of 4Hb (18.7%), 3aH (6.17%), 7a (1%), and *ortho* protons of *N*-tolyl group. 7aH was irradiated to give enhancement for 3aH (1.75%) and the *ortho* protons of *N*-phenyl group at 7.04 ppm (4.0%).

Table 2. Synthesis of hexahydro-7-oxa-2,5,6a-triaza-cyclopenta[*a*]pentalene-1,3-diones **3a–i** and **4a–i**

Entry	R	R^1	Ar	Total yield	Yield (%) of		*exo–endo*[a]
					3	**4**	
a	4-MeC_6H_4	H	Ph	100[b]	35	65	1:1.86
b	4-$MeOC_6H_4$	H	Ph	100[b]	38	62	1:1.63
c	4-MeC_6H_4	4-$MeOC_6H_4$	Ph	90[c]	33	57	1:1.73
d	4-$MeOC_6H_4$	4-$MeOC_6H_4$	Ph	92[c]	32	60	1:1.87
e	4-$MeOC_6H_4$	3-$NO_2C_6H_4$	Ph	74[c]	33	41	1:1.24
f	4-MeC_6H_4	H	4-$MeOC_6H_4$	93[b]	24	69	1:2.88
g	4-MeC_6H_4	H	4-$NO_2C_6H_4$	85[b]	35	50	1:1.43
h	4-MeC_6H_4	H	4-ClC_6H_4	88[b]	36	52	1:1.44
i	4-MeC_6H_4	H	4-MeC_6H_4	88[b]	28	60	1:2.14

[a] The ratio of the isolated adducts.
[b] Reaction time 10 h.
[c] Reaction time 51 h.

Table 3. Characteristic ^1H NMR spectroscopic data for *exo* and *endo* adducts **3** and **4**

	exo							*endo*					
	3aH	4Ha	4Hb	6Ha	6Hb	7aH		3a	4Ha	4Hb	6Ha	6Hb	7aH
3a	3.98	3.80	4.17	4.79	4.53	5.17	**4a**	4.02	3.11	4.60	4.49	4.66	5.15
3b	3.98	3.79	4.12	4.76	4.53	5.17	**4b**	4.01	3.05	4.56	4.44	4.63	5.15
3c	3.92	3.96	4.61	5.81		5.17	**4c**	4.04	4.77	3.87	5.64		5.16
3d	3.92	3.96	4.61	5.76		5.19	**4d**	4.04	4.71	3.85	5.63		5.17
3e	3.92	3.96	4.70	5.85		5.21	**4e**	4.06	4.69	3.95	5.76		5.22
3f	3.96	3.79	4.16	4.78	4.52	5.15	**4f**	4.01	3.10	4.58	4.49	4.65	5.15
3g	4.02	3.81	4.19	4.79	4.54	5.21	**4g**	4.05	3.08	4.62	4.47	4.59	5.19
3h	3.97	3.79	4.16	4.78	4.52	5.16	**4h**	4.01	3.08	4.59	4.48	4.63	5.15
3i	3.95	3.78	4.15	4.78	4.52	5.14	**4i**	4.01	3.10	4.59	4.49	4.65	5.14

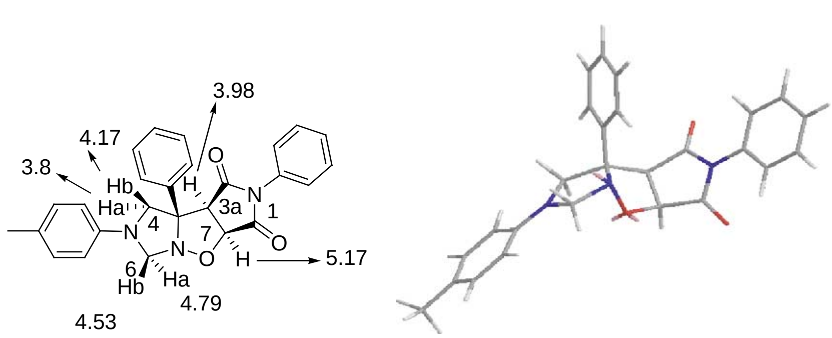


Figure 1. Some selected chemical shifts assignments for **3a** and its energy minimised 3D model (total energy 99.4078 kcal/mol).

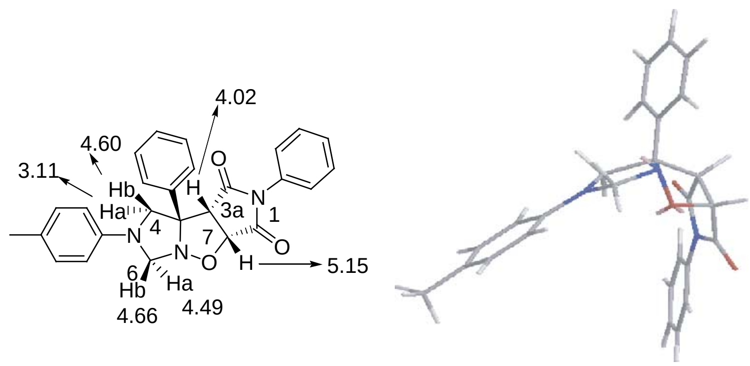


Figure 2. Some selected chemical shifts assignments for **4a** and its energy minimised 3D model (total energy 99.0050 kcal/mol).

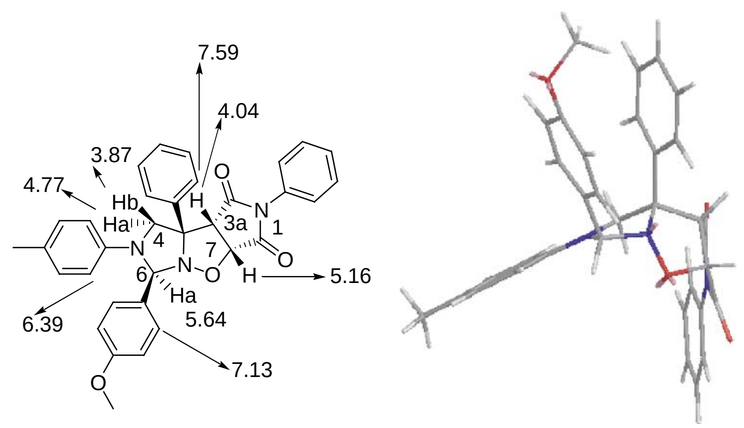


Figure 3. Some selected chemical shifts for *cis–endo* adduct **4c** and its energy minimised 3D model (total energy 27.2092 kcal/mol).[12]

Finally, the *ortho* protons of 3b-phenyl were irradiated to give enhancements for the signals of 4Hb (2.11%) and 6Hb (0.5%). The energy minimised conformations of compounds **3a**, **4a** and **4c** (see Figs. 1–3) are supporting the observed correlations by NOESY1D experiments. On the other hand, the total energy of **3a** was by 0.4028 kcal/mol higher than that of **4a**.

The NOESY1D experiment results for *endo* adduct **4a** are as follows: irradiation of 6Ha enhanced the signals of 6Hb (17.2%), the *ortho* protons of *N*-tolyl group (3.07%) and 4Ha (0.66%). The irradiation of 4Ha enhanced the signals of 4Hb (19.18%), *ortho* protons of *N*-tolyl and 3b-phenyl by 1.69 and 0.9%, respectively. Irradiation of 3aH enhanced the signals of 7aH and 3b-phenyls *ortho* protons by 3.3 and 2.66%, respectively. Irradiation of 4Hb enhances the signal of 4Ha by 17.71% and the *ortho* protons of *N*-tolyl and 3b-phenyl by 7.30 and 2.59%. Irradiation of *ortho* protons of 3b-phenyl enhances the signals of 4Hb and 3aH by 1.5 and 1%, respectively.

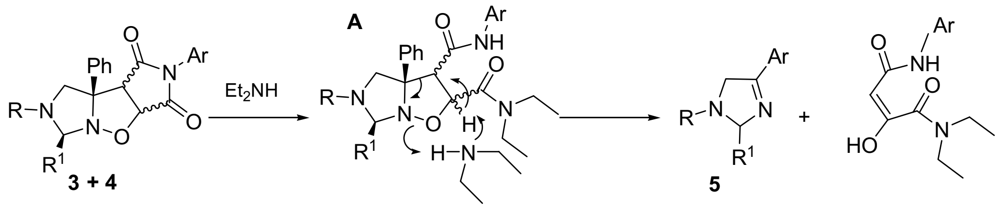
To prove the cis orientation of the phenyls at C-3b and C-6 we have irradiated the corresponding protons at the imidazolidine and isoxazolidine rings of **4c** as follows: the proton at C-3a was irradiated to give enhancements for the C-3b-phenyls' *ortho* protons (3.61%) and for the 7aH (3.98%). 4Hb was irradiated to give enhancements for 4Ha (27.0%) and the *ortho* protons of the phenyls at C-3b, N-5 and C-6 by 2.84, 2.58 and 4.13%, respectively. Irradiation of 4Ha enhanced the signals of 4Hb (27.8%) and the signals of *N*- and C-3b-phenyls' *ortho* protons by 10.0 and 2.71%, respectively. The irradiation of C-6H enhanced the signals of C-6 phenyls and N-5 phenyls *ortho* protons. This unequivocally proves the *cis–endo* configuration of compounds **4c–e**.

According to the developed procedure isolated, compounds **3** and **4** or their mixture were refluxed in diethylamine in order to prepare the racemic mixtures of pyrrolidin-3-ols as in Scheme 1, however, this treatment led to the formation of new 3-imidazolines **5a–e** (Scheme 2 and Table 4). The compounds were easily characterized by elemental analyses and spectral methods. The characteristic IR frequencies for C=N appears at ca.1630 cm^{-1}. The methylenes at C-2 and C-5 in the cases of **5a–b** appear as two proton triplets as a results of long range coupling between them. The long range

Table 4. Synthesis of 3-imidazolines **5a–e**

Starting material	Product	Yield (%)	Mp (°C)
3a+4a	**5a**	90	117–119
3b+4b	**5b**	100[a]	129–130
4c	**5c**	92	176–178
3c	**5c**	98	176–178
3d+4d	**5d**	88	152–153
3e	**5e**	92	182–184
4e	**5e**	92	182–184

[a] The reaction time was 23 h for all entries except for entry 2 where the reaction time is 39 h.



Scheme 3. Proposed mechanism for the conversion of adducts **3** and **4** into **5**.

coupling is observed between the protons at C-2 and the AB system at C-5 in the cases of **5c–d**.

The probable mechanism for the ring-opening of compounds **3** and **4** in diethylamine is depicted in Scheme 3. The nucleophilic attack of diethylamine leads to intermediate **A** (isolated in the case of **4b**), which probably undergo diethylamine assisted synchronous ring-opening to give imidazolines **5** and the corresponding oxaloacetic acid amides. The isolated and characterized **A** (5-(4-methoxyphenyl)-3a-phenyl-hexahydroimidazo[1,5-*b*]isoxazole-2,3-dicarboxylic acid 2-diethylamide 3-phenylamide **4b**′, was isolated from the reaction of **3b** and **4b** in diethylamine for 23 h) was refluxed in diethylamine for 23 h to give imidazoline **5b** in 92% yield.

To prove the structure of 5-(4-methoxyphenyl)-3a-phenylhexahydroimidazo[1,5-*b*]isoxazole-2,3-dicarboxylic acid 2-diethylamide 3-phenylamide **4b**′ we have performed NOESY1D experiments as follows: irradiation of C-4Hb proton led to enhancement of the signals of C-4Ha (18.05%), *p*-anisyl (3.58%) and C-3b phenyls (4.27%) *ortho* protons. While the irradiation of C-4Ha enhances the signals of C-4Hb (16.34%), *N*-*p*-anisyl (7.20%) and C-3b phenyls *ortho* protons (1.3%). Irradiation of C-3H enhanced the signals of C-2H (4.09%), C-3b phenyls *ortho* protons (2%) and the amide proton at 8.89 ppm. The latter correlation was indicative for the determination of the right regioisomer. Thus, all these experiments allowed us to assign the configuration shown in Figure 4.

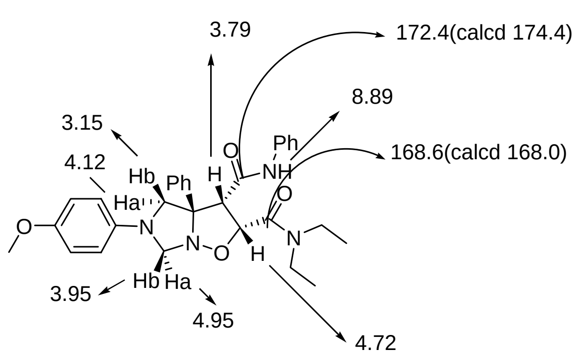


Figure 4. Some characteristic chemical shifts for intermediate bisamide **4b**′.

exo Adduct **3a** was shown to give nucleophilic addition product faster than *endo* adduct **4a**. The reaction times for the disappearance of the corresponding adducts (TLC controls) were 1.5 and 6 h, respectively.

Compounds **3a**,**c** and **4a**,**c** were refluxed in triethylamine for 48 h but no conversion was observed, the starting materials were recovered unchanged.

3. Conclusions

In conclusion, we studied the reaction of imidazoline 3-oxides **1** with of *N*-arylmaleimides **2**. The reactions of nitrones **1a–b**,**f–i** with *N*-arylmaleimides **2** in benzene give predominantly the corresponding *endo* adducts **4a–b**,**f–i**. Chiral imidazoline 3-oxides **1c–e** react diastereospecifically with respect to the cis configuration in the tetrahydroimidazo ring and diastereoselectively to give *cis–endo* adducts **4c–e**.The effect of substituents on the phenyl ring of the maleimide was investigated. The presence of electron-withdrawing or releasing groups have minor effects on the total yields but the effect on the ratio of *exo* and *endo* diastereomers is more pronounced. The *exo–endo* ratio increases when electron-donating groups are present on the N-2 aryl, and decreases when the groups are electron-withdrawing. Adducts **3** and **4** undergo an interesting ring-opening in the presence of secondary amines to give the deoxygenated 3-imidazoline 3-oxides **5** instead of the expected double cis elimination products. This reaction will serve as a convenient method for the synthesis of otherwise inaccessible 3-imidazolines. Tertiary amines did not induce any reaction.

4. Experimental

4.1. General

Melting points were recorded on an Electrothermal Digital melting point apparatus. Infrared spectra were recorded on a Mattson 1000 FTIR. 1D and 2D NMR experiments were performed on a Varian Mercury Plus 400 MHz spectrometer. Visualisation was effected with UV light. Imidazoline 3-oxides **1a–e** were prepared according to the method we have recently reported.[7] The elemental analyses were performed on a EuroEA 3000 CHNS analyser. The total energies of compounds **3a**, **4a**, **4c**, *cis–exo* **3c** and the FMO energy calculations for maleimides **2** and nitrone **1a** were performed using CS MOPAC Pro in ChemOffice 6.

4.1.1. 1,2-Bis-(4-methoxyphenyl)-4-phenyl-2,5-dihydro-1*H*-imidazole 3-oxide 1d. Yield, 2.0 g, 23%; white needles; mp 200–201.5 °C; IR (KBr) $\nu_{C=N}$ 1610 cm^{-1}; ^{1}H NMR δ 3.73 (3H, s), 3.80 (3H, s), 4.81 (1H, dd, J=14.0, 3.2 Hz), 5.14 (1H, dd, J=14.0, 5.6 Hz), 6.10 (1H, dd, J=5.6, 3.2 Hz), 6.57 (2H, d, J=8.8 Hz), 6.82 (2H, d, J=8.8 Hz), 6.94 (2H, d, $J=8.4$ Hz), 7.45–7.49 (3H, m), 7.56 (2H, d, $J=8.4$ Hz), 8.34 (2H, dd, $J=7.6$, 3.6 Hz). ^{13}C NMR δ 53.4; 55.6; 55.9; 90.0; 113.9; 114.6; 115.3; 127.2; 128.9; 129.0; 129.6; 131.1; 134.5; 136.9; 138.8; 153.0; 161.2. Anal. Calcd for $C_{23}H_{22}N_2O_3$ (374.43) C, 73.78; H, 5.92; N, 7.48; found C, 73.75; H, 5.90; N, 7.45.

4.1.2. 1-(4-Methoxyphenyl)-2-(3-nitrophenyl)-4-phenyl-2,5-dihydro-1*H*-imidazole 3-oxide 1e. Yield 2.38 g, 26%; yellow needles; mp 190–191 °C; $\nu_{C=N}$ 1610 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.80 (3H, s), 4.86 (1H, dd, $J=14.0$, 3.2 Hz), 5.26 (1H, dd, $J=14.0$, 5.6 Hz), 6.25 (1H, dd, $J=5.6$, 3.2 Hz), 6.55 (2H, d, $J=9.2$ Hz), 6.84 (2H, d, $J=9.2$ Hz), 7.48–7.52 (3H, m), 7.65 (1H, t, $J=7.6$ Hz), 8.06 (1H, d, $J=8.0$ Hz), 8.29–8.33 (3H, m), 8.51 (1H, t, $J=2.0$ Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 53.9; 55.9; 89.1; 114.2; 115.5; 123.2; 123.4; 126.9; 127.2; 129.1; 130.1; 131.7; 134.9; 135.6; 138.3; 138.5; 148.0; 153.7. Anal. Calcd for $C_{22}H_{19}N_3O_4$ (389.40) C, 67.86; H, 4.92; N, 10.79; found C, 67.83; H, 4.90; N, 10.75.

The maleimides used were prepared according to a method known in the literature.[13a] Maleimide **2g** was prepared according to a modified literature procedure:[13b] to a mixture of 4-nitroaniline (5.1 mmol, 0.772 g) and maleic anhydride (6.04 mmol, 0.592 g) PPA (7 g) was added and the mixture stirred for 15 h at 80 °C on a water bath. The mixture was poured into cold water and the product precipitated was filtered and dried in a vacuum oven. Yield 0.598 g, 54%; yellow amorphous solid; mp 163–164 °C; IR (KBr) $\nu_{C=O}$ 1724 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.93 (2H, s), 7.68 (2H, d, $J=9.6$ Hz), 8.34 (2H, d, $J=9.6$ Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 124.7; 125.7; 134.9; 137.3; 146.4; 168.8.

4.2. Synthesis of hexahydro-7-oxa-2,5,6a-triaza-cyclopenta[*a*]pentalene-1,3-diones 3a–i and 4a–i. General procedure

To a solution of imidazoline 3-oxide **1** (0.12 mmol) in benzene (10 mL) maleimide (0.48 mmol) was added and the reaction mixture stirred for the specified time. The solvent was evaporated and the mixture was separated by column chromatography using silica gel as an adsorbent and petroleum ether ethyl acetate as a solvent mixture. The compounds were recrystallized from ether or ethanol.

4.2.1. *exo*-2,3b-Diphenyl-5-*p*-tolyl-hexahydro-7-oxa-2,5,6a-triaza-cyclopenta[*a*]pentalene-1,3-dione 3a. Yield 0.018 g, 35%; white needles; mp 177–178 °C; IR (KBr) $\nu_{C=O}$ 1713 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.24 (3H, s), 3.80 (1H, d, $J=8.8$ Hz), 3.98 (1H, d, $J=7.6$ Hz), 4.17 (1H, d, $J=8.8$ Hz), 4.53 (1H, d, $J=11.2$ Hz), 4.79 (1H, d, $J=11.2$ Hz), 5.17 (1H, d, $J=7.6$ Hz), 6.42 (2H, d, $J=8.0$ Hz), 7.00–7.05 (4H, m), 7.31–7.40 (6H, m), 7.57 (2H, d, $J=7.2$ Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.5; 56.7; 56.8; 71.0; 80.7; 112.3; 126.2; 126.6; 126.9; 129.0; 129.2; 129.3; 129.4; 130.1; 131.3; 136.0; 143.6; 171.2; 174.1. Anal. Calcd for $C_{26}H_{23}N_3O_3$ (425.48) C, 73.39; H, 5.45; N, 9.88; found C, 73.34; H, 5.40; N, 9.95.

4.2.2. *exo*-5-(4-Methoxyphenyl)-2,3b-diphenyl-hexahydro-7-oxa-2,5,6a-triaza-cyclopenta[*a*]pentalene-1,3-dione 3b. Yield 0.020 g, 38%; white needles; mp 120–121 °C; IR (KBr) $\nu_{C=O}$ 1716 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.74 (3H, s), 3.79 (1H, d, $J=8.4$ Hz), 3.98 (1H, d, $J=7.2$ Hz), 4.12 (1H, d, $J=8.8$ Hz), 4.53 (1H, d, $J=11.2$ Hz), 4.76 (1H, d, $J=11.2$ Hz), 5.17 (1H, d, $J=7.2$ Hz), 6.46 (2H, d, $J=8.8$ Hz), 6.83 (2H, d, $J=9.2$ Hz), 6.99 (2H, d, $J=7.6$ Hz), 7.30–7.40 (6H, m), 7.56 (2H, d, $J=7.2$ Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 56.1; 56.9; 57.2; 71.5; 77.3; 80.8; 113.3; 115.4; 126.2; 126.5; 129.0; 129.1; 129.2; 129.4; 131.3; 136.1; 140.5; 152.3; 171.2; 174.1. Anal. Calcd for $C_{26}H_{23}N_3O_4$ (441.48) C, 70.73; H, 5.25; N, 9.52; found C, 70.80; H, 5.40; N, 9.42.

4.2.3. *exo*-6-(4-Methoxyphenyl)-2,3b-diphenyl-5-*p*-tolyl-hexahydro-7-oxa-2,5,6a-triaza cyclopenta[*a*]pentalene-1,3-dione 3c. Yield 0.021 g, 33%; white needles; mp 167–168 °C; IR (KBr) $\nu_{C=O}$ 1712 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.23 (3H, s), 3.70 (3H, s), 3.92 (1H, d, $J=7.6$ Hz), 3.96 (1H, d, $J=9.2$ Hz), 4.61 (1H, d, $J=9.2$ Hz), 5.17 (1H, d, $J=7.6$ Hz), 5.81 (1H, s), 6.43 (2H, d, $J=8.8$ Hz), 6.58 (2H, d, $J=8.4$ Hz), 6.89–7.18 (10H, m), 7.18–7.51 (4H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.5; 55.5; 57.5; 57.7; 77.0; 79.7; 85.5; 113.4; 113.5; 126.1; 127.0; 127.4; 128.2; 128.6; 128.9; 129.1; 129.3; 129.9; 130.2; 131.3; 135.3; 144.0; 159.5; 171.1; 174.1. Anal. Calcd for $C_{33}H_{29}N_3O_4$ (531.60) C, 74.56; H, 5.50; N, 7.90; found C, 74.60; H, 5.60; N, 7.78.

4.2.4. *exo*-5,6-Bis-(4-methoxyphenyl)-2,3b-diphenyl-hexahydro-7-oxa-2,5,6a-triaza-cyclopenta[*a*]pentalene-1,3-dione 3d. Yield 0.021 g, 32%; white needles; mp 165–166 °C; IR (KBr) $\nu_{C=O}$ 1712 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.70 (3H, s), 3.72 (3H, s), 3.92–3.96 (2H, two overlapping d, $J=7.6$, 8.8 Hz), 4.61 (1H, d, $J=8.8$ Hz), 5.19 (1H, d, $J=7.6$ Hz), 5.76 (1H, s), 6.46 (2H, d, $J=8.4$ Hz), 6.58 (2H, d, $J=8.0$ Hz), 6.78 (2H, d, $J=8.4$ Hz), 6.95–6.99 (3H, m), 7.08–7.14 (3H, m), 7.21–7.25 (2H, m), 7.30–7.35 (4H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.5; 55.9; 57.6; 57.8; 77.0; 79.7; 85.4; 113.5; 114.4; 115.1; 126.1; 127.0; 127.4; 128.3; 128.7; 128.9; 129.1; 129.3; 129.6; 135.3; 144.7; 152.6; 159.5; 171.1; 174.1. Anal. Calcd for $C_{33}H_{29}N_3O_5$ (547.60) C, 72.38; H, 5.34; N, 7.67; found C, 72.32; H, 5.40; N, 7.60.

4.2.5. *exo*-5-(4-Methoxyphenyl)-6-(3-nitrophenyl)-2,3b-diphenyl-hexahydro-7-oxa-2,5,6a-triaza-cyclopenta[*a*]-pentalene-1,3-dione 3e. Yield 0.022 g, 33%; yellow needles; mp 173–174 °C; IR (KBr) $\nu_{C=O}$ 1715 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.73 (3H, s), 3.92 (1H, d, $J=7.1$ Hz), 3.96 (1H, d, $J=8.8$ Hz), 4.70 (1H, d, $J=8.8$ Hz), 5.21 (1H, d, $J=7.1$ Hz), 5.85 (1H, s), 6.44 (2H, d, $J=8.8$ Hz), 6.80 (2H, d, $J=8.8$ Hz), 7.01–7.09 (5H, m), 7.18–7.38 (6H, m), 7.52 (1H, d, $J=7.6$ Hz), 7.79 (1H, s), 7.96 (1H, d, $J=7.6$ Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.9; 57.2; 57.4; 77.1; 80.0; 85.3; 114.5; 115.3; 122.9; 123.2; 125.9; 126.9; 128.5; 129.0; 129.2; 129.3; 129.4; 131.2; 134.1; 134.3; 140.0; 140.2; 148.2; 153.1; 170.8; 173.8. Anal. Calcd for $C_{32}H_{26}N_4O_6$ (562.57) C, 68.32; H, 4.66; N, 9.96; found C, 68.30; H, 4.60; N, 9.98.

4.2.6. *exo*-2-(4-Methoxyphenyl)-3b-phenyl-5-*p*-tolyl-hexahydro-7-oxa-2,5,6a-triaza-cyclopenta[*a*]pentalene-1,3-dione 3f. Yield 0.013 g, 24%; white needles; mp 187–188 °C; IR (KBr) $\nu_{C=O}$ 1716 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.23 (3H, s), 3.78 (3H, s), 3.79 (1H, d, J=8.6 Hz), 3.96 (1H, d, J=7.4 Hz), 4.16 (1H, d, J=8.6 Hz), 4.52 (1H, d, J=10.9 Hz), 4.78 (1H, d, J=10.9 Hz), 5.15 (1H, d, J=7.4 Hz), 6.41 (2H, d, J=8.2 Hz), 6.87–6.94 (4H, m), 7.03 (2H, d, J=8.2 Hz), 7.31 (1H, t, J=7.2 Hz), 7.37 (2H, t, J=7.2 Hz), 7.55 (2H, t, J=7.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.5; 55.7; 56.7; 56.8; 71.0; 77.2; 80.7; 112.3; 114.7; 123.8; 126.5; 126.8; 127.4; 129.2; 129.3; 130.1; 136.0; 143.6; 159.8; 171.5; 174.4. Anal. Calcd for $C_{27}H_{25}N_3O_4$ (455.51) C, 71.19; H, 5.53; N, 9.22; found C, 71.21; H, 5.50; N, 9.27.

4.2.7. *exo*-2-(4-Nitrophenyl)-3b-phenyl-5-*p*-tolyl-hexahydro-7-oxa-2,5,6a-triaza-cyclopenta[*a*]pentalene-1,3-dione 3g. Yield 0.020 g, 35%; yellow needles; mp 175 °C; IR (KBr) $\nu_{C=O}$ 1728 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.24 (3H, s), 3.81 (1H, d, J=8.8 Hz), 4.02 (1H, d, J=7.2 Hz), 4.19 (1H, d, J=8.8 Hz), 4.54 (1H, d, J=10.8 Hz), 4.79 (1H, d, J=10.8 Hz), 5.21 (1H, d, J=7.2 Hz), 6.40 (2H, d, J=8.4 Hz), 7.04 (2H, d, J=8.4 Hz), 7.24–7.26 (3H, m), 7.35–7.41 (2H, m), 7.54 (2H, d, J=8.0 Hz), 8.23 (2H, d, J=9.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.5; 56.8; 56.9; 71.0; 77.2; 80.8; 112.4; 124.6; 126.4; 126.6; 127.1; 129.3; 129.5; 130.2; 135.8; 136.6; 143.5; 147.3; 170.5; 173.4. Anal. Calcd for $C_{26}H_{22}N_4O_5$ (470.48) C, 66.37; H, 4.71; N, 11.91; found C, 66.40; H, 4.76; N, 11.90.

4.2.8. *exo*-2-(4-Chlorophenyl)-3b-phenyl-5-*p*-tolyl-hexahydro-7-oxa-2,5,6a-triaza-cyclopenta[*a*]pentalene-1,3-dione 3h. Yield 0.020 g, 36%; white needles; mp 186–187 °C; IR (KBr) $\nu_{C=O}$ 1720 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.24 (3H, s), 3.79 (1H, d, J=8.4 Hz), 3.97 (1H, d, J=7.6 Hz), 4.16 (1H, d, J=8.4 Hz), 4.52 (1H, d, J=11.2 Hz), 4.78 (1H, d, J=11.2 Hz), 5.16 (1H, d, J=7.6 Hz), 6.41 (2H, d, J=8.6 Hz), 6.95–6.98 (2H, m), 7.04 (2H, d, J=8.6 Hz), 7.31–7.40 (5H, m), 7.54 (2H, d, J=8.6 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.5; 56.7; 56.8; 71.0; 77.2; 80.7; 112.3; 126.5; 127.0; 127.4; 129.2; 129.3; 129.6; 129.7; 130.1; 134.8; 135.9; 143.6; 171.0; 173.8. Anal. Calcd for $C_{26}H_{22}ClN_3O_3$ (459.92) C, 67.90; H, 4.82; N, 9.14; found C, 68.05; H, 4.96; N, 9.27.

4.2.9. *exo*-3b-Phenyl-2,5-di-*p*-tolyl-hexahydro-7-oxa-2,5,6a-triaza-cyclopenta[*a*]pentalene-1,3-dione 3i. Yield 0.015 g, 28%; white needles; mp 194–195 °C; IR (KBr) $\nu_{C=O}$ 1716 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.23 (3H, s), 2.30 (3H, s), 3.78 (1H, d, J=8.19 Hz), 3.95 (1H, d, J=7.4 Hz), 4.15 (1H, d, J=8.19 Hz), 4.52 (1H, d, J=10.9 Hz), 4.78 (1H, d, J=10.9 Hz), 5.14 (1H, d, J=7.4 Hz), 6.41 (2H, d, J=8.0 Hz), 6.88 (2H, d, J=8.0 Hz), 7.03 (2H, d, J=8.0 Hz), 7.17 (2H, d, J=8.0 Hz), 7.30–7.37 (3H, m), 7.55 (2H, d, J=7.6 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.5; 21.4; 55.7; 56.8; 71.0; 77.0; 80.7; 112.3; 126.0; 126.6; 126.8; 128.6; 129.1; 129.2; 130.0; 130.1; 136.0; 139.1; 143.6; 173.3; 174.2. Anal. Calcd for $C_{27}H_{25}N_3O_3$ (439.51) C, 73.78; H, 5.73; N, 9.56; found C, 73.75; H, 5.70; N, 9.50.

4.2.10. *endo*-2,3b-Diphenyl-5-*p*-tolyl-hexahydro-7-oxa-2,5,6a-triaza-cyclopenta[*a*]pentalene-1,3-dione 4a. Yield 0.033 g, 65%; white needles; mp 185–186 °C; IR (KBr) $\nu_{C=O}$ 1709 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.28 (3H, s), 3.11 (1H, d, J=10.1 Hz), 4.02 (1H, d, J=8.6 Hz), 4.49 (1H, d, J=9.4 Hz), 4.60 (1H, d, J=10.1 Hz), 4.66 (1H, d, J=9.4 Hz), 5.15 (1H, d, J=8.6 Hz), 6.52 (2H, d, J=8.6 Hz), 6.88 (2H, d, J=7.0 Hz), 7.08 (2H, d, J=8.6 Hz), 7.19–7.25 (3H, m), 7.35 (1H, t, J=7.4 Hz), 7.44 (2H, t, J=7.4 Hz), 7.66 (2H, d, J=7.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.7; 54.2; 59.8; 75.3; 80.6; 80.9; 115.0; 125.8; 126.5; 128.4; 128.9; 129.2; 129.3; 129.8; 130.2; 131.4; 141.5; 142.9; 173.0; 174.1. Anal. Calcd for $C_{26}H_{23}N_3O_3$ (425.48) C, 73.39; H, 5.45; N, 9.88; found C, 73.40; H, 5.33; N, 10.05.

4.2.11. *endo*-5-(4-Methoxyphenyl)-2,3b-diphenyl-hexahydro-7-oxa-2,5,6a-triaza-cyclopenta[*a*]pentalene-1,3-dione 4b. Yield 0.033 g, 62%; white needles; mp 182–183 °C; IR (KBr) $\nu_{C=O}$ 1712 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.05 (1H, d, J=10.4 Hz), 3.75 (3H, s), 4.01 (1H, d, J=8 Hz), 4.44 (1H, d, J=9.6 Hz), 4.56 (1H, d, J=10.0 Hz), 4.63 (1H, d, J=9.6 Hz), 5.15 (1H, d, J=8.0 Hz), 6.57 (2H, d, J=8.5 Hz), 6.81 (2H, d, J=8.5 Hz), 6.90 (2H, d, J=7.4 Hz), 7.2–7.25 (3H, m), 7.34 (1H, t, J=7.41 Hz), 7.43 (2H, t, J=7.4 Hz), 7.66 (2H, d, J=7.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 54.8; 55.9; 59.8; 75.9; 80.8; 81.0; 115.2; 116.3; 125.8; 126.6; 128.4; 128.9; 129.2; 129.3; 131.4; 139.3; 141.58; 154.1; 173.0; 174.3. Anal. Calcd for $C_{26}H_{23}N_3O_4$ (441.48) C, 70.73; H, 5.25; N, 9.52; found C, 70.85; H, 5.33; N, 9.48.

4.2.12. *endo*-6-(4-Methoxyphenyl)-2,3b-diphenyl-5-*p*-tolyl-hexahydro-7-oxa-2,5,6a-triaza-cyclopenta[*a*]pentalene-1,3-dione 4c. Yield 0.036 g, 57%; white needles; mp 189–191 °C; IR (KBr) $\nu_{C=O}$ 1720 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.22 (3H, s), 3.74 (3H, s), 3.87 (1H, d, J=10.0 Hz), 4.04 (1H, d, J=8.4 Hz), 4.77 (1H, d, J=10.0 Hz), 5.16 (1H, d, J=8.4 Hz), 5.64 (1H, s), 6.38 (2H, d, J=8.6 Hz), 6.76 (2H, d, J=8.6 Hz), 6.80 (2H, d, J=7.4 Hz), 6.93 (2H, d, J=8.2 Hz), 7.12 (2H, d, J=8.6 Hz), 7.19–7.32 (4H, m), 7.37 (2H, t, J=7.4 Hz), 7.60 (2H, d, J=7.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.5; 52.7; 55.4; 59.4; 79.9; 80.3; 84.6; 114.2; 114.3; 126.0; 126.3; 127.9; 128.3; 128.7; 128.8; 129.0; 129.2; 129.9; 131.2; 131.5; 141.3; 141.6; 159.6; 172.9; 174.0. Anal. Calcd for $C_{33}H_{29}N_3O_4$ (531.60) C, 74.56; H, 5.50; N, 7.90; found C, 74.45; H, 5.63; N, 7.85.

4.2.13. *endo*-5,6-Bis-(4-methoxyphenyl)-2,3b-diphenyl-hexahydro-7-oxa-2,5,6a-triaza-cyclopenta[*a*]pentalene-1,3-dione 4d. Yield 0.039 g, 60%; white needles; mp 159–160 °C; IR (KBr) $\nu_{C=O}$ 1716 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.70 (3H, s), 3.73 (3H, s), 3.85 (1H, d, J=10.0 Hz), 4.04 (1H, d, J=8.4 Hz), 4.71 (1H, d, J=10.0 Hz), 5.17 (1H, d, J=8.4 Hz), 5.63 (1H, s), 6.41 (2H, d, J=9.0 Hz), 6.69 (2H, d, J=9.0 Hz), 6.74 (2H, d, J=8.6 Hz), 6.85–6.87 (2H, m), 7.09 (2H, d, J=8.6 Hz), 7.21–7.33 (4H, m), 7.38 (2H, t, J=7.8 Hz), 7.60 (2H, d, J=7.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 53.0; 55.4; 55.9; 59.4; 79.9; 80.4; 85.0; 114.1; 115.0; 115.6; 126.0; 126.2; 128.3; 128.8; 128.8; 129.1; 129.2; 131.2; 131.4; 137.7; 141.7; 152.9; 159.5; 172.9; 174.1. Anal. Calcd for

$C_{33}H_{29}N_3O_5$ (547.60) C, 72.38; H, 5.34; N, 7.67; found C, 72.35; H, 5.53; N, 7.51.

4.2.14. *endo*-5-(4-Methoxyphenyl)-6-(3-nitrophenyl)-2,3b-diphenyl-hexahydro-7-oxa-2,5,6a-triaza-cyclopenta-[*a*]pentalene-1,3-dione 4e. Yield 0.028 g, 41%; yellow needles; mp 119–120 °C; IR (KBr) $\nu_{C=O}$ 1714; 1724 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.70 (3H, s), 3.95 (1H, d, J=10.0 Hz), 4.06 (1H, d, J=8.0 Hz), 4.69 (1H, d, J=10.0 Hz), 5.22 (1H, d, J=8.0 Hz), 5.76 (1H, s), 6.41 (2H, d, J=8.8 Hz), 6.71 (2H, d, J=9.2 Hz), 6.90 (2H, d, J=8.8 Hz), 7.25–7.57 (10H, m), 8.05–8.08 (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ 53.1; 55.9; 59.5; 80.0; 80.3; 84.5; 115.2; 115.7; 122.7; 123.5; 125.8; 126.1; 126.3; 129.0; 129.2; 129.3; 129.4; 131.1; 133.7; 134.4; 140.8; 141.5; 148.6; 153.4; 172.7; 173.6. Anal. Calcd for $C_{32}H_{26}N_4O_6$ (562.57) C, 68.32; H, 4.66; N, 9.96; found C, 68.43; H, 4.59; N, 9.90.

4.2.15. *endo*-2-(4-Methoxyphenyl)-3b-phenyl-5-*p*-tolyl-hexahydro-7-oxa-2,5,6a-triaza-cyclopenta[*a*]pentalene-1,3-dione 4f. Yield 0.038 g, 69%; white needles; mp 187–187.4 °C; IR (KBr) $\nu_{C=O}$ 1705 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.27 (3H, s), 3.10 (1H, d, J=10.0 Hz), 3.75 (3H, s), 4.01 (1H, d, J=8.4 Hz), 4.49 (1H, d, J=9.6 Hz), 4.58 (1H, d, J=10.0 Hz), 4.65 (1H, d, J=9.6 Hz), 5.15 (1H, d, J=8.4 Hz), 6.51 (2H, d, J=8.2 Hz), 6.71 (2H, d, J=8.9 Hz), 6.8 (2H, d, J=8.9 Hz), 7.05 (2H, d, J=8.2 Hz), 7.34 (1H, t, J=7.02 Hz), 7.43 (2H, t, J=7.4 Hz), 7.66 (2H, d, J=7.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.7; 54.2; 55.7; 59.7; 75.3; 80.5; 80.8; 114.5; 115.0; 123.9; 125.8; 127.8; 128.3; 129.3; 129.7; 130.2; 141.6; 143.0; 159.7; 173.2; 174.3. Anal. Calcd for $C_{27}H_{25}N_3O_4$ (455.51) C, 71.19; H, 5.53; N, 9.22; found C, 71.09; H, 5.70; N, 9.25.

4.2.16. *endo*-2-(4-Nitrophenyl)-3b-phenyl-5-*p*-tolyl-hexahydro-7-oxa-2,5,6a-triaza-cyclopenta[*a*]pentalene-1,3-dione 4g. Yield 0.028 g, 50%; yellow needles; mp 176–177 °C; IR (KBr) $\nu_{C=O}$ 1716 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.29 (3H, s), 3.08 (1H, d, J=10.0 Hz), 4.05 (1H, d, J=8.0 Hz), 4.47 (1H, d, J=9.6 Hz), 4.59 (1H, d, J=9.6 Hz), 4.62 (1H, d, J=10.0 Hz), 5.19 (1H, d, J=8.0 Hz), 6.50 (2H, d, J=8.2 Hz), 7.05 (2H, d, J=8.2 Hz), 7.14 (2H, d, J=9.0 Hz), 7.36 (1H, t, J=7.4 Hz), 7.43 (2H, t, J=7.4 Hz), 7.65 (2H, d, J=7.4 Hz), 7.54 (2H, d, J=9.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.7; 54.2; 59.9; 75.4; 80.7; 81.4; 115.1; 124.4; 125.8; 127.1; 128.6; 129.4; 130.4; 130.5; 136.8; 141.0; 142.6; 147.2; 172.3; 173.5. Anal. Calcd for $C_{26}H_{22}N_4O_5$ (470.48) C, 66.37; H, 4.71; N, 11.91; found C, 66.30; H, 4.65; N, 11.85.

4.2.17. *endo*-2-(4-Chlorophenyl)-3b-phenyl-5-*p*-tolyl-hexahydro-7-oxa-2,5,6a-triaza-cyclopenta[*a*]pentalene-1,3-dione 4h. Yield 0.029 g, 52%; white needles; mp 158–160 °C; IR (KBr) $\nu_{C=O}$ 1712 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.28 (3H, s), 3.08 (1H, d, J=10.0 Hz), 4.01 (1H, d, J=8.0 Hz), 4.48 (1H, d, J=9.6 Hz), 4.59 (1H, d, J=10.0 Hz), 4.63 (1H, d, J=9.6 Hz), 5.15 (1H, d, J=8.0 Hz), 6.50 (2H, d, J=8.4 Hz), 6.83 (2H, d, J=9.2 Hz), 7.05 (2H, d, J=8.4 Hz), 7.17 (2H, d, J=9.2 Hz), 7.31–7.38 (1H, m), 7.42–7.46 (2H, m), 7.64–7.67 (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.7; 54.2; 59.8; 75.3; 80.6; 81.0; 115.0; 125.8; 127.8; 128.4; 129.4; 129.4; 129.8; 130.0; 130.3; 134.7; 141.4; 142.8; 172.8; 174.0. Anal. Calcd for $C_{26}H_{22}ClN_3O_3$ (459.92) C, 67.90; H, 4.82; N, 9.14; found C, 68.00; H, 4.80; N, 9.22.

4.2.18. *endo*-3b-Phenyl-2,5-di-*p*-tolyl-hexahydro-7-oxa-2,5,6a-triaza-cyclopenta[*a*]pentalene-1,3-dione 4i. Yield 0.032 g, 60%; white needles; mp 178–179 °C; IR (KBr) $\nu_{C=O}$ 1706 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.28 (3H, s), 2.29 (3H, s), 3.10 (1H, d, J=10.0 Hz), 4.01 (1H, d, J=8.4 Hz), 4.49 (1H, d, J=9.2 Hz), 4.59 (1H, d, J=10.0 Hz), 4.65 (1H, d, J=9.2 Hz), 5.14 (1H, d, J=8.4 Hz), 6.52 (2H, d, J=8.0 Hz), 6.76 (2H, d, J=8.0 Hz), 7.02 (2H, d, J=8.0 Hz), 7.06 (2H, d, J=8.0 Hz), 7.35 (1H, t, J=7.6 Hz), 7.43 (2H, t, J=7.2 Hz), 7.66 (2H, d, J=7.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.5; 21.1; 54.0; 59.5; 75.0; 80.4; 80.6; 114.8; 125.6; 126.1; 128.1; 128.5; 129.0; 129.5; 129.6; 130.0; 138.8; 141.4; 142.8; 172.9; 174.0. Anal. Calcd for $C_{27}H_{25}N_3O_3$ (439.51) C, 73.78; H, 5.73; N, 9.56; found C, 73.70; H, 5.70; N, 9.50.

4.2.19. 5-(4-Methoxyphenyl)-3a-phenyl-hexahydro-imidazo[1,5-*b*]isoxazole-2,3-dicarboxylic acid 2-diethyl-amide 3-phenylamide 4b′. Yield 0.023 g, 18%; white needles; mp 166–167 °C; IR (KBr) ν_{NH} 3445 cm^{-1}; $\nu_{C=O}$ 1691 and 1620 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.92 (6H, t, J=7.6 Hz), 2.58 (4H, q, J=7.6 Hz), 3.17 (1H, d, J=10.0 Hz), 3.70 (3H, s), 3.79 (1H, d, J=7.2 Hz), 3.95 (1H, d, J=10.8 Hz), 4.12 (1H, d, J=10.0 Hz), 4.72 (1H, d, J=7.2 Hz), 4.95 (1H, d, J=10.8 Hz), 6.50 (2H, d, J=8.6 Hz), 6.70 (2H, d, J=8.6 Hz), 6.94 (1H, t, J=7.0 Hz), 7.09 (2H, t, J=7.0 Hz), 7.21–7.35 (6H, m), 7.59 (2H, d, J=7.8 Hz), 8.90 (1H, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.3; 42.2; 55.8; 58.3; 66.7; 72.7; 79.4; 80.5; 115.0; 116.0; 120.1; 124.1; 125.9; 127.7; 128.7; 129.0; 138.2; 140.5; 144.7; 153.2; 168.6; 172.4. Anal. Calcd for $C_{30}H_{34}N_4O_4$ (514.62) C, 70.02; H, 6.66; N, 10.89; found C, 70.10; H, 6.60; N, 10.85.

4.3. Base catalysed ring-opening of compounds 3 and 4. Synthesis of 2,5-dihydro-1*H*-imidazole 5a–e. General procedure

Method A. Compound **3** or **4** (0.25 mmol) were refluxed in diethylamine (5 mL) for 23 h. The solvent was evaporated and the product was purified by preparative TLC using petroleum ether ethyl acetate as eluent (2:1). The products were recrystallized from ethanol or ether. *Method B*. The mixture of adducts **3** and **4** from the cycloaddition of nitrones **1** (0.25 mmol) with maleimides (1 mmol) **2** was dissolved in diethylamine (5 mL) and refluxed for 23 h. The solvent was evaporated and the isolation of the product **5** is as in Method A.

4.3.1. 4-Phenyl-1-*p*-tolyl-2,5-dihydro-1*H*-imidazole 5a. Method B; yield 0.053 g, 90%; white needles; mp 117–119 °C; IR (KBr) $\nu_{C=N}$ 1631 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.28 (3H, s), 4.57 (2H, t, J=5.2 Hz), 5.43 (2H, t, J=5.2 Hz), 6.52 (2H, d, J=8.4 Hz), 7.11 (2H, d, J=8.4 Hz), 7.38–7.53 (3H, m), 7.82–7.89 (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.6; 55.3; 79.0; 112.2; 121.5; 127.6; 129.0; 130.3; 131.6; 136.0; 143.4; 169.3. Anal. Calcd for

$C_{16}H_{16}N_2$ (236.31) C, 81.32; H, 6.82; N, 11.85; found C, 81.30; H, 6.85; N, 11.90.

4.3.2. 1-(4-Methoxyphenyl)-4-phenyl-2,5-dihydro-1*H*-imidazole 5b. Method B; yield 0.063 g, 100%; white needles; mp 129–130 °C; IR (KBr) $\nu_{C=N}$ 1631 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.78 (3H, s), 4.55 (2H, t, J=5.2 Hz), 5.41 (2H, t, J=5.2 Hz), 6.56 (2H, d, J=9.2 Hz), 6.91 (2H, d, J=8.4 Hz), 7.45–7.51 (3H, m), 7.87 (2H, d, J=8.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.7; 56.1; 79.4; 113.0; 115.5; 127.6; 129.0; 131.7; 132.5; 140.4; 152.0; 169.7. Anal. Calcd for $C_{16}H_{16}N_2O$ (252.31) C, 76.16; H, 6.39; N, 11.10; found C, 76.20; H, 6.30; N, 11.05.

4.3.3. 2-(4-Methoxyphenyl)-4-phenyl-1-*p*-tolyl-2,5-dihydro-1*H*-imidazole 5c. Method B; yield 0.080 g, 93%; white needles; mp 176–178 °C; IR (KBr) $\nu_{C=N}$ 1623 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.23 (3H, s), 3.79 (3H, s), 4.72 (1H, dd, J=15.2, 3.6 Hz), 4.99 (1H, dd, J=15.2, 6.0 Hz), 6.45 (1H, dd, J=6.0, 3.6 Hz), 6.51(2H, d, J=8.8 Hz), 6.89 (2H, d, J=8.6 Hz), 7.02 (2H, d, J=8.8 Hz), 7.39–7.48 (5H, m), 7.88 (2H, d, J=7.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.5; 55.5; 57.5; 91.6; 113.0; 114.5; 126.6; 127.9; 128.3; 128.9; 130.0; 131.6; 132.4; 133.1; 143.3; 159.7; 166.8. Anal. Calcd for $C_{23}H_{22}N_2O$ (342.43) C, 80.67; H, 6.48; N, 8.18; found C, 80.60; H, 6.40; N, 8.20.

4.3.4. 1,2-Bis-(4-methoxyphenyl)-4-phenyl-2,5-dihydro-1*H*-imidazole 5d. Method B; yield 0.079 g, 88%; white needles; mp 152–153 °C; IR (KBr) $\nu_{C=N}$ 1623 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.73 (3H, s), 3.79 (3H, s), 4.69 (1H, dd, J=14.8, 4.0 Hz), 4.99 (1H, dd, J=14.4, 6.0 Hz), 6.40 (1H, dd, J=6.0, 4.0 Hz), 6.55 (2H, d, J=9.2 Hz), 6.81 (2H, d, J=9.2 Hz), 6.9 (2H, d, J=8.8 Hz), 7.4–7.5 (5H, m), 7.87–7.89 (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.5; 56.0; 57.9; 91.9; 113.8; 114.5; 115.2; 127.9; 128.3; 128.9; 131.5; 132.4; 133.2; 140.2; 152.0; 159.6; 166.9. Anal. Calcd for $C_{23}H_{22}N_2O_2$(358.43) C, 77.07; H, 6.19; N, 7.82; found C, 77.09; H, 6.10; N, 7.87.

4.3.5. 1-(4-Methoxyphenyl)-2-(3-nitrophenyl)-4-phenyl-2,5-dihydro-1*H*-imidazole 5e. Method A (from **3e**) yield 0.086 g, 92%; Method A (from **4e**) yield 0.086 g, 92%; yellow needles; mp 182–184 °C; IR (KBr) $\nu_{C=N}$ 1623 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.74 (3H, s), 4.74 (1H, dd, J=14.8, 4.0 Hz), 5.08 (1H, dd, J=14.8, 5.6 Hz), 6.49–6.54 (coincident 2H, d, J=9.0 Hz, 1H, dd, J=5.6, 4.0 Hz), 6.83 (2H, d, J=9.0 Hz), 7.44–7.57 (4H, m), 7.86–7.88 (3H, m), 8.16–8.19 (1H, m), 8.37 (1H, t, J=2.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.6; 58.5; 91.5; 114.1; 115.4; 122.44; 123.5; 127.9; 129.1; 130.1; 131.9; 132.0; 133.5; 139.7; 143.5; 149.0; 152.7; 168.4. Anal. Calcd for $C_{22}H_{19}N_3O_3$ (373.40) C, 70.76; H, 5.13; N, 11.25; found C, 70.80; H, 5.10; N, 11.14.

4.4. The treatment of compounds 3 and 4 with triethylamine

Compound **3** or **4** (0.25 mmol) was dissolved in triethylamine (5 mL) and the mixture refluxed for 48 h. The solvent was evaporated and the starting material was recovered unchanged.

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Synthesis of α-diazo-β-hydroxyesters through a one-pot protocol by phase-transfer catalysis: application to enantioselective aldol-type reaction and diastereoselective synthesis of α-amino-β-hydroxyester derivatives

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Abstract—The one-pot synthesis of α-diazo-β-hydroxyesters from sodium azide under phase-transfer-catalyzed conditions has been achieved. This protocol includes three different chemical transformations promoted by a single catalyst in each step to give products in good to excellent yields. The reaction was applied to a catalytic asymmetric aldol-type reaction using α-diazoesters with aldehydes in the presence of a chiral quaternary ammonium salt and gave products with up to 81% ee. The diastereoselective transformation of the products to chiral α-amino-β-hydroxyester derivatives is also described.

1. Introduction

Phase-transfer-catalyzed reactions are some of the most environmentally-friendly processes in synthetic organic chemistry due to their simplicity, mild conditions and high cost performance.[1] Particularly, chiral quaternary ammonium salts have been recognized as powerful asymmetric phase-transfer catalysts (PTCs) since Dolling and O'Donnell independently reported their pioneering studies.[2] In this paper, we report the PTC-promoted one-pot synthesis of α-diazo-β-hydroxyesters from sodium azide, acetoacetate and aldehydes in the presence of a single catalyst without isolation of intermediates. The application to enantioselective carbon–carbon bond-forming reactions and the diastereoselective synthesis of α-amino and α-hydrazino-β-hydroxyesters is also described in detail.[3]

2. Resullts and discussion

2.1. One-pot synthesis of α-diazo-β-hydroxyesters

α-Diazo-β-hydroxyesters are useful as a potential source of amino alcohols or acids and their facile preparation using the aldol-type reaction of α-diazoesters with aldehydes has been investigated.[4,5] Since the starting α-diazoesters and the precursor, tosyl azide are both readily available under PTC conditions,[6] we expected that all three sequences could be promoted by a single phase-transfer catalyst without isolation of any explosive intermediates.

First, we investigated a three-step protocol using tosyl chloride, *t*-butyl acetoacetate **1a** and benzaldehyde **3a** in the presence of tetrahexylammonium bromide (THAB, 10 mol%) as a PTC. The results are summarized in Table 1. The azidation of tosyl chloride (first step) in CH_2Cl_2 proceeded quantitatively (rt, 1 h), however, diazo-transfer (second step) with aqueous 11% NaOH at rt was slow (85 h). Subsequent aldol-type reaction (third step) with **3a** (5 equiv) gave the desired product **4a** in 70% yield (entry 1). Ethylester **1b** was more reactive in diazo-transfer step and the reaction was completed within 9 h, and the aldol-type reaction gave **5a** in 87% (entry 2). The solvent influenced the rate of diazo-transfer, for example, the reaction in diethyl ether enabled rapid conversion in diazo-transfer and **5a** was obtained in 82% yield through three steps (entry 3). Although a longer reaction time was required, benzylester **1c** was also transformed to **2c** in 25 h and subsequent C–C bond formation gave **6** in 51% overall yield (entry 4).

Next, we applied this three-step protocol to various aldehydes under optimized conditions (Table 2). The

Keywords: Aldol-type reaction; α-Diazo-β-hydroxyester; α-Amino-β-hydroxyester.
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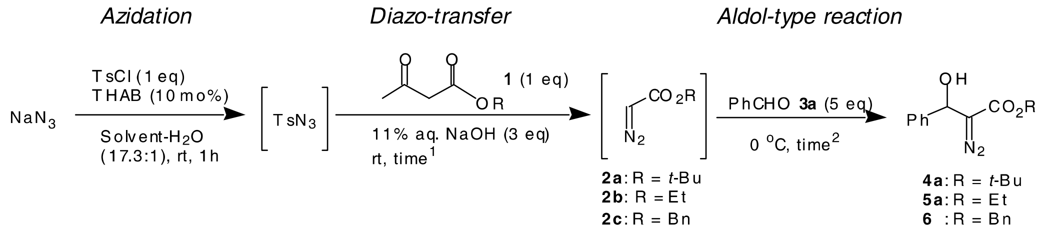
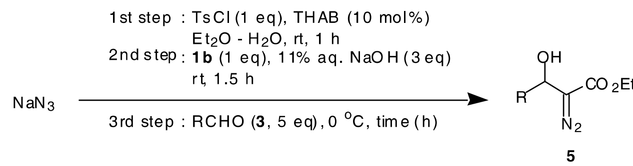
Table 1. One-pot syhthesis of α-diazo-β-hydroxyesters under PTC conditions



Entry	1	Solvent	Time[1] (h)	Time[2] (h)	Yield (%)
1	**1a**: R = *t*-Bu	CH_2Cl_2	85	3	**4a**: 70
2	**1b**: R = Et	CH_2Cl_2	9	3	**5a**: 87
3	**1b**: R = Et	Et_2O	1.5	3	**5a**: 82
4	**1c**: R = Bn	Et_2O	25	7	**6**: 51

Table 2. One-pot reaction using various aldehydes



Entry	**3**: Aldehyde	Time (h)	Yield (%)
1	**3b**: R = 4-MeO–C_6H_4	2	**5b**: 73
2	**3c**: R = 4-CF_3–C_6H_4	12	**5c**: 76
3	**3d**: R = 1-Napthyl	3	**5d**: 80
4	**3e**: R = $Ph(CH_2)_2$	3	**5e**: 86[a]
5	**3f**: R = *i*-Bu	20	**5f**: 82
6	**3g**: R = *i*-Pr	3	**5g**: 75
7	**3h**: R = *c*-Hex	4	**5h**: 75
8	**3i**: R = *t*-Bu	18	**5i**: 73

[a] Three equivalent of **3e** was used.

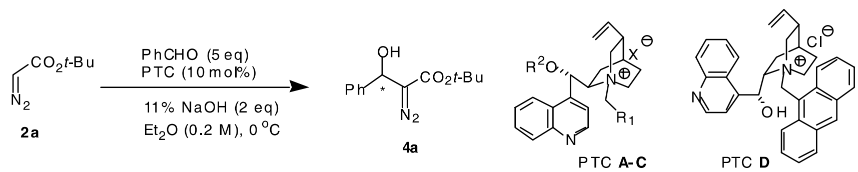
aromatic aldehydes shown in entries 1–3 were smoothly transformed into the corresponding adducts **5b–d** in yields of 73–80%. In the case of aliphatic aldehydes including sterically hindered substrate such as **3i**, the reactions also proceeded without any significant self-condensation with a range of 73–86% yield (entries 4–8).

2.2. Asymmetric aldol-type reaction using a chiral quaternary ammonium salt as a PTC

After succeeding with the one-pot synthesis of α-diazo-β-hydroxyesters, we next investigated catalytic asymmetric synthesis. Only one example of a catalytic asymmetric aldol-type reaction using α-diazoester has been reported.[7] Initially, we surveyed this reaction using cinchoninium salts (**A–C**[9e]) (Table 3). Although the enantioselectivities were poor, an *N*-anthracenyl group gave better results at 0 °C (entry 2). Moreover, a secondary hydroxy group was found to be essential in asymmetric induction, suggesting that hydrogen bonding between the catalyst and substrates is important (entry 2 vs 3). Since the cinchonidinium salt (PTC **D**) gave a slightly better result, the reaction conditions were further optimized using catalyst **D** (Table 4).

With a stronger base such as aqueous KOH, the reaction proceeded to give **4a** at lower temperature (Table 4, entries

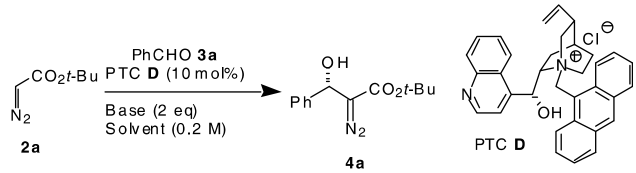
Table 3. Catalytic asymmetric aldol-type reaction of **2a** with **3a** using various PTCs



Entry	PTC	R[1]	R[2]	X	Time (h)	Yield (%)	ee (%)[a]
1	**A**	Ph	H	Br	2.5	51	6 (*S*)
2	**B**	9-Anthracenyl	H	Cl	2	84	14 (*R*)
3	**C**	9-Anthracenyl	Allyl	Br	3	96	0
4	**D**				3	76	24 (*S*)

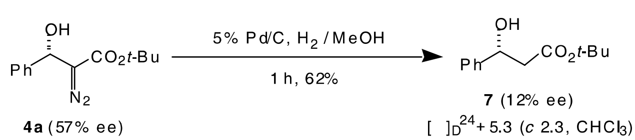
[a] Determined by chiral HPLC analysis using DAICEL CHIRALCEL OD.

Table 4. Catalytic asymmetric aldol-type reaction of **2a** with **3a** using PTC **D**



Entry	Solvent	Base	**3a** (equiv)	Conditions	Yield (%)	ee (%)
1	Et_2O	25% KOH	5	−20°C, 8 h	70	25
2	Et_2O	50% KOH	5	−40°C, 2 h	74	39
3	Et_2O	50% KOH	5	−60°C, 16 h	65	20
4	Et_2O	50% KOH	1.5	−40°C, 14 h	96	48
5	Et_2O	50% RbOH	1.5	−40°C, 10 h	72	51
6	PhMe	50% KOH	1.5	−40°C, 38 h	83	45
7	PhMe	50% RbOH	1.5	−40°C, 10 h	96	56
8	PhMe	50% CsOH	1.5	−40°C, 20 h	76	56

1–3). Under biphase conditions of 50% KOH and Et_2O at −40 °C, 1.5 equiv of **3a** was enough for the reaction to proceed in 96% yield with moderate enantioselectivity (entry 4). The best result (96% yield, 56% ee)[8] was obtained using 50% aqueous RbOH in toluene at −40 °C (entry 7). The absolute stereochemistry of **4a** was determined to be *S* by comparison with the reported optical rotation[10] after diazo decomposition to β-hydroxyester **7** (Scheme 1 and Section 3).

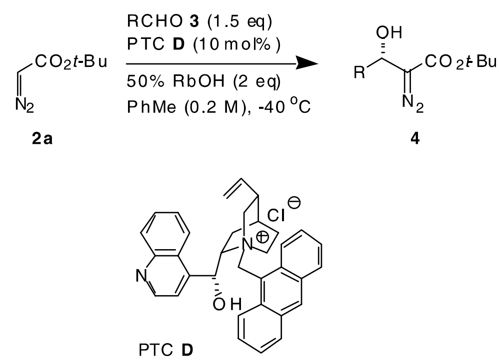


Scheme 1. Determination of the absolute stereochemistry of **4a**.

Next, various aldehydes were used in this reaction under the optimized conditions. The electron density on the aromatic rings was found to strongly influence the enantioselectivity (Table 5). For example, **3b**, which has a 4-MeO group, gave a racemate, while **3c** which has an electron-withdrawing group 4-CF_3, gave **4c** in 81% yield with 73% ee (entries 1 and 2). 4-Alkylated substrates were also converted with lower ee (entries 4 and 5). 1- and 2-Naphthaldehydes were converted to **4d** and **4l** in respective yields of 86% (79% ee) and 94% (56% ee) (entries 3 and 6). In the case of aliphatic substrates, primary and secondary aldehydes such as **3e–h** gave 22–42% ee (entries 7–10), but pivalaldehyde **3i** was transformed to **4i** in 83% yield with 81% ee (entry 11).

The aldol-type reaction of α-diazoesters under basic media has been reported to include an equilibrium process,[4f] so the time course of the chemical yield and ee of **4a** and **4i** during asymmetric reactions were investigated. As shown in Figure 1, in the case of aromatic aldehyde **3a** both the chemical yield and ee of **4a** gradually increased. The chemical yield reached equilibrium after 5 h and the ee remained at about 60% ee after 3 h. In the reaction of aliphatic aldehyde **3i**, the initial ee of **4i** was 70%, and this gradually increased to 80% ee after 5 h. The former result suggests the possibility of a retro-aldol reaction.[11] With regard to this reversible mechanism, enantioselection might occur in the differentiation of the carbonyl plane of

Table 5. Enantioselective synthesis of **4** with various aldehydes using PTC **D**



Entry	Aldehyde **3**	Time (h)	Yield (%)	ee (%)
1	**3b**: R = 4-MeO–C_6H_4	120	**4b**: 56	0
2	**3c**: R = 4-CF_3–C_6H_4	140	**4c**: 81	73
3	**3d**: R = 1-Napthyl	94	**4d**: 86	79
4	**3j**: R = 4-Me–C_6H_4	18	**4j**: 66	39
5	**3k**: R = 4-Bu–C_6H_4	120	**4k**: 63	32
6	**3l**: R = 2-Naphthyl	110	**4l**: 94	56
7	**3e**: R = Ph$(Ch_2)_2$	72	**4e**: 32	33
8	**3f**: R = *i*-Bu	72	**4f**: 85	22
9	**3g**: R = *i*-Pr	20	**4g**: 53	42
10	**3h**: R = *c*-Hex	10	**4h**: 88	33
11	**3i**: R = *t*-Bu	72	**4i**: 84	81

aldehydes in the C–C bond-forming step or the reversal retro-aldol step by kinetic resolution.

To test the latter possibility, (±)-**4a** was subjected to retro-aldol conditions with 50% RbOH in toluene (10 h) in the presence of PTC **D**, and the formation of **2a** and **3a** was observed. However, the ee of the recovered **4a** (72%) was very low (Scheme 2). This result suggests that the asymmetric induction of **4a** occurs mainly not via kinetic resolution in the retro-aldol step but rather through the carbon–carbon bond-forming step. In the case of **4i**, an alcoholic proton might be less acidic than benzyl alcoholic proton in **4a** and the retro-aldol reaction seems to be disfavored. As outlined in Scheme 3, k'_S and k'_R are considered to be equal but the rate of C–C bond formation (k_S) is greater than k_R in the reaction of **3a** with **2a**.

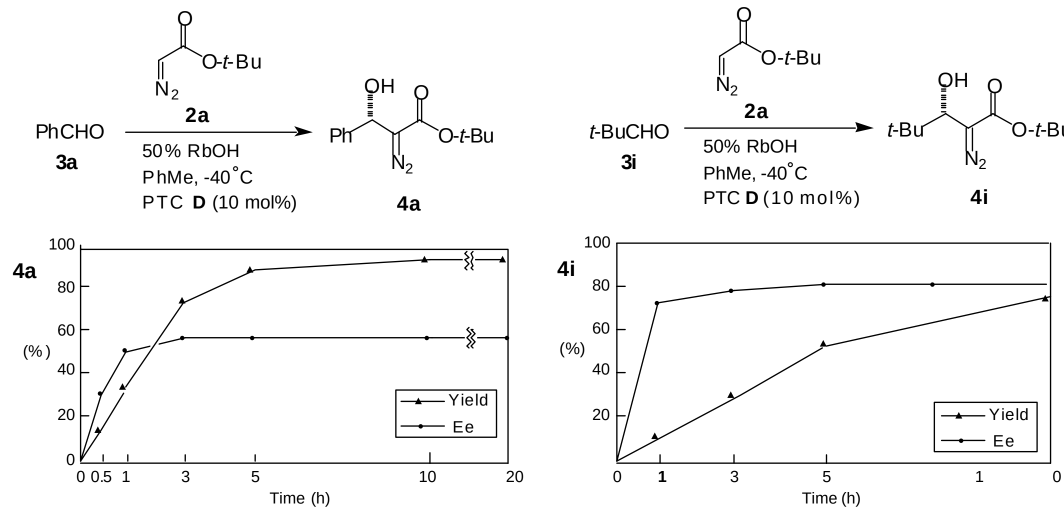
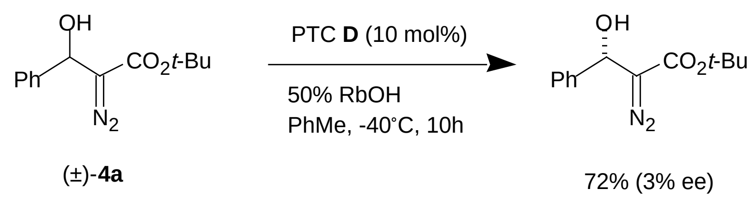
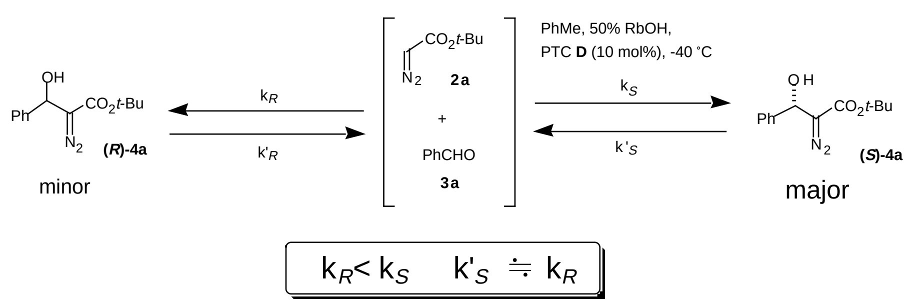


Figure 1. Time course of yield and ee in the reaction of **2a** with **3a** and **3i**.



Scheme 2. Retro aldol-type reaction of (±)-**4a** with PTC **D**.

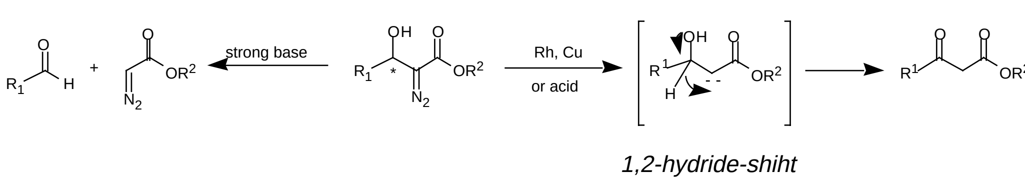


Scheme 3. Postulated reaction pathway for the catalytic asymmetric aldol-type reaction.

The presence of this retro-aldol process for racemic **4a** explains the increase in ee in the initial step of the reaction using **3a**. In the same way, a large excess of **3a** resulted in a lower ee (Table 4, entry 2 vs 4).

2.3. Transformation of optically active α-diazo-β-hydroxyesters to α-amino-β-hydroxyester derivatives

Many organic transformations using a diazo-functionality via diazo-decomposition have been reported[12] due to its high reactivity with late transition metals. However, only limited examples of transformation using α-diazo-β-hydroxyesters have been reported,[13] since they are unstable under basic (retro-aldol reaction) and acidic (diazo decomposition) media. Furthermore, they gave simple 1,3-dicarbonyl compounds via a 1,2-hydride shift by reacting with transition metals (Scheme 4). To establish a new synthetic transformation of α-diazo-β-hydroxyesters without any loss of chiral centers, we attempted the reduction of a diazo group to hydrazone or hydrazine as an amine



Scheme 4. Decomposition of α-diazo-β-hydroxyesters.

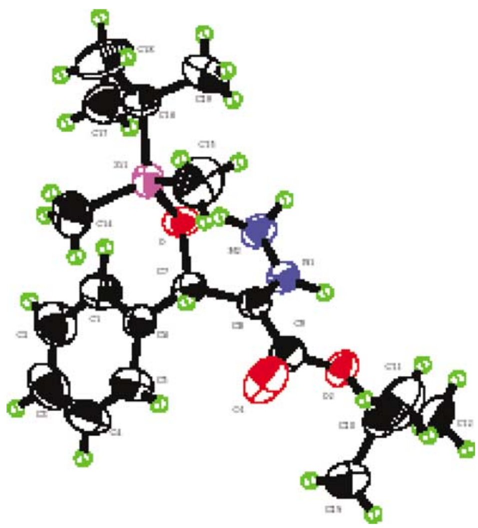


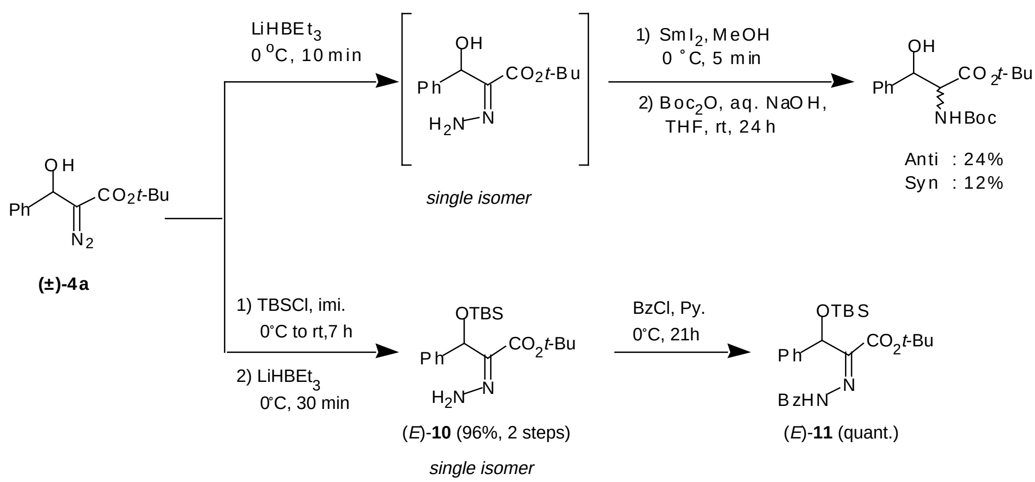
Figure 2. X-ray structure of (*E*)-**10**.

equivalent,[14,15] which are known to be useful building blocks for the synthesis of polypeptides and biologically important molecules.[16,17]

First, we attempted to convert (±)-**4a** to hydrazonoester without protection of its hydroxy group. Reduction with $LiHBEt_3$ proceeded smoothly but the stability of the product was problematic and subsequent reduction with SmI_2 and protection with Boc_2O gave amino alcohols in low yields. Next, the initial protection of (±)-**4a** with TBSCl followed by reduction of the diazo group by $LiHBEt_3$ gave hydrazone **10** as a single isomer in 96% yield. Its configuration was confirmed by X-ray crystallographic analysis to be *E* (Fig. 2). Subsequent *N*-benzoylation (BzCl with pyridine in CH_2Cl_2 at 0 °C) gave (*E*)-**11** without significant isomerization[18] (Scheme 5).

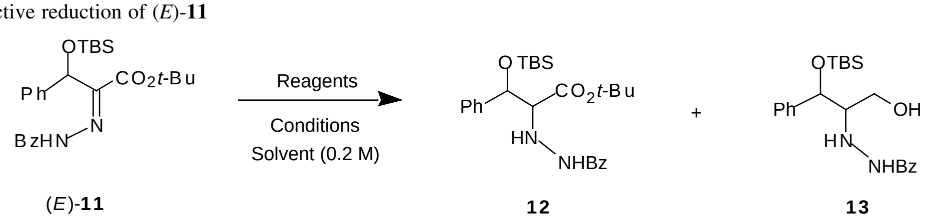
The further diastereoselective reduction of C=N bond was investigated (Table 6). The treatment of (*E*)-**11** with $NaBH_4$ at 0 °C in EtOH gave α-hydrazinoester *anti*-**12** in 92% yield, exclusively (entry 1). In the case of $LiBH_4$, a mixture of **12** and **13** was obtained with respective yields of 55 and 12%. However, no diastereoselectivities were observed in either product (entry 2). The reaction of Red-Al with **11** in toluene gave **13** as a separable diastereomixture in moderate yield, while no selectivity was observed (entry 3).

Further transformations of **12** and **13** are outlined in Scheme 6. N–N bond cleavage of *anti*-**12** with SmI_2 followed by protection with Boc_2O gave **14** (65% yield) as a mixture of *syn*- and *anti*-isomers (1:2.6) due to epimerization at the α-position.[19] In the case of *syn*-**13** and *anti*-**13**, similar transformation gave the corresponding alcohols **15**



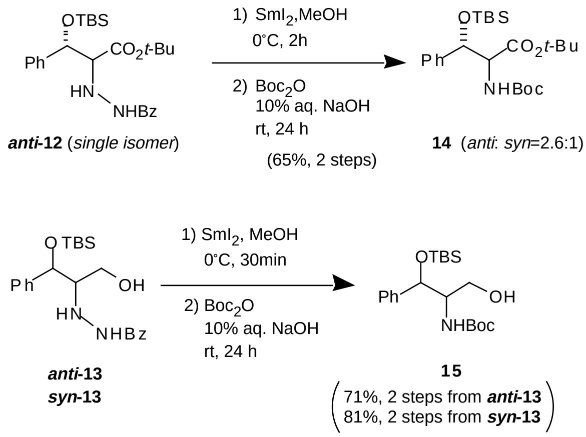
Scheme 5. Preparation of hydrazones.

Table 6. Diastereoselective reduction of (*E*)-**11**

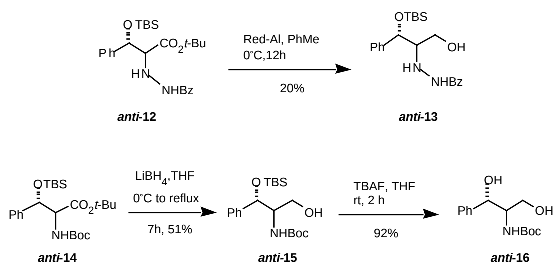


Entry	Reagents (equiv)	Solvent	Conditions	Yield (%)	
				12 (*syn*:*anti*)[a]	**13** (*syn*:*anti*)[a]
1	$NaBH_4$ (5)	EtOH	0°C, 2 h	92 (*anti* only)	0
2	$LiBH_4$ (5)	THF	0°C to rt, 19 h	55 (1:1)	12 (1:1)
3	Red-Al (5)	PhMe	0°C, 2 h	0	60 (1:1)

[a] Determined by ^{1}H MNR analysis.

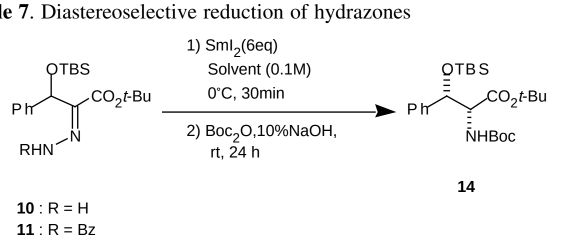


Scheme 6. N–N bond cleavage of **12** and **13** by SmI_2.



Scheme 7. Determination of relative configuration.

Table 7. Diastereoselective reduction of hydrazones



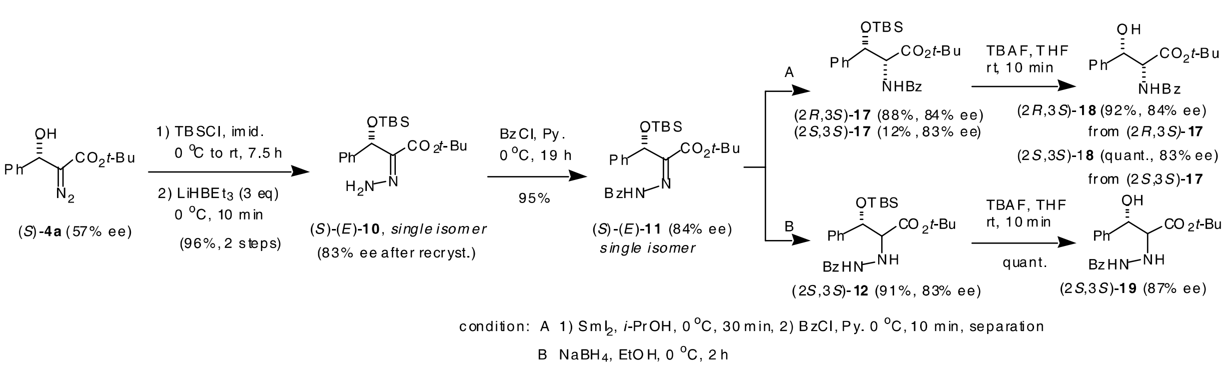
Entry	Substrate	Solvent	Yield (%)	*syn*:*anti*
1	**10**	MeOH	100	2:1
2	**10**	*i*-PrOH	100	3.3:1
3	**11**	MeOH	77	5.4:1
4	**11**	*i*-PrOH	100	6.7:1

in respective yields of 81 and 71%. The stereochemistry of *anti*-**14** was determined by conversion to *anti*-**16** (Scheme 7), the stereochemistry of which was confirmed by comparison to the literature via *anti*-**15**.[20] The relative stereochemistry of *anti*-**12** was also confirmed by conversion to *anti*-**13**.

To enhance the utility of this synthetic protocol, we next investigated the diastereoselective one-pot transformation of hydrazones to amino groups (Table 7). For example, the reaction of (*E*)-**10** with SmI_2[19] in MeOH followed by protection with Boc_2O gave the desired product **14** in quantitative yield (syn/anti = 2:1). Higher diastereoselectivity was observed when the reduction was carried out in isopropanol (entries 1 and 2). The reduction of *N*-benzoylhydrazone (*E*)-**11** in isopropanol gave **14** in quantitative yield with better selectivity (syn/anti = 6.7:1, entry 4).

After successfully developing an efficient transformation to aminoesters, we next investigated the synthesis of optically active aminoesters from (*S*)-**4a** (57% ee). Initial transformation gave siloxyhydrazone (*E*)-**10**, the ee of which was increased to 83% ee by recrystallization. Subsequent reduction of (*S*)-(*E*)-**11** with SmI_2 followed by BzCl (condition A) gave (2*R*,3*S*)-**17** and (2*S*,3*S*)-**17** in respective yields of 88 and 12% without racemization. The reduction of (*S*)-(*E*)-**11** with $NaBH_4$ (condition B) gave (2*S*,3*S*)-**12** in 91% yield, exclusively, without any loss of optical purity. Treatment of these products with TBAF gave the corresponding hydroxyesters **18** and **19** (Scheme 8).

In summary, we have developed the one-pot synthesis of α-diazo-β-hydroxyesters with a single catalyst without any isolation of explosive intermediates. A PTC-catalyzed asymmetric aldol-type reaction using α-diazoester (up to 81% ee) with unique enantio enrichment and the transformations of α-diazo-β-hydroxyesters to α-amino-β-hydroxyesters in diastereoselective fashion were also established. This synthetic protocol provides a practical synthesis of optically active α-amino-β-hydroxyester derivatives, which have been recognized as useful building blocks for biologically important compounds or pharmaceuticals. Further studies of the application of this method are currently underway.



Scheme 8. Transformation of optically active **4a**.

3. Experimental

3.1. A general procedure for the one-pot synthesis of α-diazo-β-hydroxyester, synthesis of ethyl 2-diazo-3-hydroxy-3-phenylpropionate (5a) (Table 1, entry 3)

To a solution of TsCl (200 mg, 1.05 mmol) and THAB (45.5 mg, 0.1 mmol, 10 mol%) in diethylether (5.2 mL) was added NaN_3 (68.4 mg, 1.05 mmol) and water (0.3 mL) at rt. The mixture was stirred for 1 h and **1b** (0.14 mL, 1.05 mmol) and 3 N NaOH (1.17 g, 3.15 mmol) were added with stirring for an additional 1.5 h. After α-diazoacetoacetate had diappeared, benzaldehyde **3a** (0.53 mL, 5.25 mmol) was added at 0 °C and the mixture was stirred for 3 h at 0 °C. The mixture was extracted with AcOEt (10 mL×3) and the combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated in vacuo. Subsequent flash column chromatography (hexane/AcOEt=10:1) gave the desired product **5a** as a yellow oil (189.4 mg, 0.86 mmol, 82%) (reg.# 27262-59-5), ^{1}H NMR δ: ($CDCl_3$, 400 MHz) 1.28 (t, 3H, J=6.8 Hz), 3.03 (br s, 1H), 4.29 (q, 2H, J=6.8 Hz), 5.92 (d, 1H, J=2.8 Hz), 7.31–7.49 (m, 5H).

3.1.1. *tert*-Butyl 2-diazo-3-hydroxy-3-phenylpropionate (4a). Yellow oil; IR (neat) ν: 3442, 2979, 2095, 1665 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.46 (s, 9H), 2.99 (br s, 1H), 5.87 (d, 1H, J=2.8 Hz), 7.30–7.46 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 165.7, 139.0, 128.5, 128.0, 125.6, 82.0, 68.5, 28.2; LRMS (FAB) m/z: 287 (M+K); HRMS (FAB) calcd for $C_{13}H_{16}N_2O_3K$ 287.0798, found: 287.0807.

3.1.2. Benzyl 2-diazo-3-hydroxy-3-phenyl-propionate (6). Yellow oil; IR (neat) ν: 3425, 3032, 2101, 1682 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 2.90 (br s, 1H), 5.20 (s, 2H), 5.92 (d, 1H, J=3.2 Hz), 7.29–7.43 (m, 10H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 166.1, 138.7, 135.6, 128.7, 128.5, 128.34, 128.32, 128.1, 125.6, 68.6, 66.6; LRMS (FAB) m/z: 321 (M+K); HRMS (FAB) calcd for $C_{16}H_{14}N_2O_3K$ 321.0642, found: 321.0630.

3.1.3. Ethyl 2-diazo-3-hydroxy-3-(4-methoxyphenyl)-propionate (5b) (reg.#39910-24-2). Yellow crystal; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.33 (t, 3H, J=7.2 Hz), 2.95 (br s, 1H), 3.84 (s, 3H), 4.32 (q, 2H, J=7.2 Hz), 5.90 (d, 1H, J=2.0 Hz), 6.94 (d, 2H, J=8.4 Hz), 7.38 (d, 2H, J=8.4 Hz).

3.1.4. Ethyl 2-diazo-3-hydroxy-3-(4-trifluoromethyl-phenyl)propionate (5c). Yellow crystal; mp 55–59 °C (hexane–$CHCl_3$); IR (thin film) ν: 3423, 3019, 2101, 1677 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.30 (t, 3H, J=7.2 Hz), 3.14 (br s, 1H), 4.28 (q, 2H, J=7.2 Hz), 5.97 (d, 1H, J=4.0 Hz), 7.57 (d, 2H, J=8.4 Hz), 7.65 (d, 2H, J=8.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 166.2, 142.9, 130.3 (q, J=32.0 Hz), 126.0, 125.6 (q, J=3.3 Hz), 123.9 (q, J=270.7 Hz), 68.0, 61.4, 14.4; LRMS (FAB) m/z: 327 (M+K); HRMS (FAB) calcd for $C_{12}H_{11}N_2O_3F_3K$ 327.0359, found: 327.0350. Anal. Calcd for $C_{12}H_{11}F_3N_2O_3$: C, 50.01; H, 3.85; N, 9.72. Found: C, 49.89; H, 3.80; N, 9.83.

3.1.5. Ethyl 2-diazo-3-hydroxy-(1-naphthyl)propionate (5d). Yellow oil; IR (neat) ν: 3430, 3059, 2981, 2091, 1683 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.37 (t, 3H, J=7.2 Hz), 3.09 (br s, 1H), 4.29–4.39 (m, 2H), 6.67 (d, 1H, J=4.0 Hz), 7.55–7.66 (m, 3H), 7.87–8.02 (m, 4H); ^{13}C NMR δ: ($CDCl_3$, 100 MHz) 166.3, 134.0, 133.5, 129.4, 128.86, 128.81, 126.3, 125.8, 125.2, 123.2, 122.4, 66.0, 61.2, 14.3; LRMS (FAB) m/z: 309 (M+K); HRMS (FAB) calcd for $C_{15}H_{14}O_3N_2K$ 309.0642, found: 309.0672.

3.1.6. Ethyl 2-diazo-3-hydroxy-5-phenylpentanoate (5e). Yellow oil; IR (neat) ν: 3447, 3026, 2934, 2094, 1689 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.30 (t, 3H, J=7.2 Hz), 1.89–2.12 (m, 2H), 2.59 (br s, 1H), 2.70–2.88 (m, 2H), 4.26 (q, 2H, J=7.2 Hz), 4.66–4.70 (m, 1H), 7.19–7.31 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 166.4, 140.8, 128.3, 128.2, 125.9, 65.7, 60.9, 35.6, 31.7, 14.3; LRMS (FAB) m/z: 287 (M+K); HRMS (FAB) calcd for $C_{13}H_{16}N_2O_3K$ 287.0798, found: 287.0779.

3.1.7. Ethyl 2-diazo-3-hydroxy-5-methylhexanoate (5f). Yellow oil; IR (neat) ν: 3433, 2959, 2094, 1685 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.95 (d, 6H, J=6.8 Hz), 1.28 (t, 3H, J=7.2 Hz), 1.36–1.43 (m, 1H), 1.59–1.68 (m, 1H), 1.72–1.82 (m, 1H), 2.42 (br s, 1H), 4.23 (q, 2H, J=7.2 Hz), 4.75–4.79 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 166.6, 64.8, 60.9, 42.6, 24.5, 22.8, 22.0, 14.4; LRMS (FAB) m/z: 239 (M+K); HRMS (FAB) calcd for $C_9H_{16}N_2O_3K$ 239.0798, found: 239.0780.

3.1.8. Ethyl 2-diazo-3-hydroxy-4-methylpentanoate (5g) (reg.# 38491-54-2). Yellow oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.95 (d, 3H, J=6.8 Hz), 1.07 (d, 3H, J=6.8 Hz), 1.29 (t, 3H, J=8.0 Hz), 1.85–1.94 (m, 1H), 2.48 (br s, 1H), 4.22–4.29 (m, 3H).

3.1.9. Ethyl 2-diazo-3-hydroxy-3-cyclohexylpropionate (5h) (reg.# 39910-21-9). Yellow oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.97–1.30 (m, 8H), 1.52–1.79 (m, 5H), 2.03 (d, 1H, J=12.4 Hz), 2.38 (br s, 1H), 4.24 (q, 2H, J=7.2 Hz), 4.30 (dd, 1H, J=5.2, 8.4 Hz).

3.1.10. Ethyl 2-diazo-3-hydroxy-4,4-dimethyl-valerate (5i) (reg.# 39910-22-0). Yellow oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.98 (s, 9H), 1.28 (t, 3H, J=6.8 Hz), 2.54 (br s, 1H), 4.19–4.27 (m, 3H).

3.2. Typical procedure for asymmetric synthesis of *tert*-butyl 2-diazo-3-hydroxy-3-phenylpropionate (4a) using PTC D (Table 4, entry 7)

To a solution of benzaldehyde **3a** (56 μL, 0.53 mmol), *tert*-butyl diazoacetate (50.0 mg, 0.35 mmol) and PTC **D** (18.2 mg, 0.035 mmol, 10 mol%) in toluene (1.8 mL) was added 50% RbOH (82.0 μL, 0.7 mmol) at −40 °C. The mixture was stirred for 10 h and partitioned between AcOEt and water. The aqueous layer was extracted with AcOEt (5 mL×3) and the organic layers were washed with brine, dried over Na_2SO_4 and concentrated in vacuo. Subsequent flash column chromatography (hexane/AcOEt=15:1) gave the desired product **4a** as a yellow oil (83.3 mg, 0.33 mmol, 96%). $[\alpha]_D^{23}$ −20.8 (c 1.06, $CHCl_3$, 56% ee); HPLC: DAICEL CHIRALCEL OD, 254 nm, flow rate 1.0 mL/min, hexane/*i*-PrOH = 99:1, retention time: 20.7 min (major, *S*) and 23.1 min (minor, *R*).

3.2.1. *tert*-Butyl 2-diazo-3-hydroxy-3-(4-methoxyphenyl)propionate (4b). Yellow oil; IR (neat) ν: 3449, 2978, 2095, 1729, 1667 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.50 (s, 9H), 2.97 (br s, 1H), 3.81 (s, 3H), 5.82 (d, 1H, J = 2.0 Hz), 6.89–7.36 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 165.8, 159.4, 130.9, 127.0, 114.0, 82.0, 68.4, 55.2, 28.3; LRMS (FAB) *m/z*: 317 (M + K); HRMS (FAB) calcd for $C_{14}H_{18}N_2O_4K$ 317.0904, found: 317.0875; HPLC: DAICEL CHIRALCEL OD, 254 nm, flow rate 0.5 mL/min, hexane/*i*-PrOH = 95:5, retention time: 20.8 and 24.2 min.

3.2.2. *tert*-Butyl 2-diazo-3-hydroxy-3-(4-trifluoromethylphenyl)propionate (4c). Yellow oil; IR (neat) ν: 3448, 2981, 2095, 1734, 1693 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.50 (s, 9H), 3.04 (br s, 1H), 5.91 (d, 1H, J = 3.4 Hz), 7.55 (d, 2H, J = 8.4 Hz), 7.65 (d, 2H, J = 8.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 165.5, 143.0, 130.3 (q, J = 32.1 Hz), 126.2, 125.7 (q, J = 4.1 Hz), 124.0 (q, J = 271 Hz), 82.5, 68.3, 28.3; LRMS (FAB) *m/z*: 355 (M + K); HRMS (FAB) calcd for $C_{14}H_{15}F_3N_2O_3K$ 355.0672, found: 355.0657; $[\alpha]_D^{26}$ −21.7 (*c* 1.1, $CHCl_3$, 73% ee); HPLC: DAICEL CHIRALCEL OD, 254 nm, flow rate 0.5 mL/min, hexane/*i*-PrOH = 97:3, retention time: 14.2 min (major) and 16.1 min (minor).

3.2.3. *tert*-Butyl 2-diazo-3-hydroxy-3-(1-naphthyl)propionate (4d). Yellow solid (racemate); mp: 94 °C (hexane); IR (neat) ν: 3435, 2979, 2094, 1685 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.54 (s, 9H), 3.00 (br s, 1H), 6.59 (d, 1H J = 2.4 Hz), 7.49–7.56 (m, 3H), 7.82–7.96 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 165.7, 134.1, 133.5, 129.5, 128.8, 128.7, 126.5, 125.7, 125.2, 123.2, 122.5, 82.1, 66.1, 28.5; LRMS (FAB) *m/z*: 337 (M + K); HRMS (FAB) calcd for $C_{17}H_{18}N_2O_3K$ 337.0955, found: 337.0941. Anal. Calcd for $C_{17}H_{18}N_2O_3$: C, 68.44; H, 6.08; N, 9.39. Found: C, 68.30; H, 5.92; N, 9.51; optically active form (yellow oil), $[\alpha]_D^{25}$ −68.0 (*c* 0.7, $CHCl_3$, 79% ee); HPLC: DAICEL CHIRALCEL OD, 254 nm, flow rate 0.5 mL/min, hexane/*i*-PrOH = 97:3, retention time: 24.3 min (minor) and 37.4 min (major).

3.2.4. *tert*-Butyl 2-diazo-3-hydroxy-5-phenylpentanoate (4e). Yellow oil; IR (neat) ν: 3422, 3026, 2930, 2091, 1685 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.48 (s, 9H), 1.84–1.93 (m, 1H), 1.99–2.08 (m, 1H), 2.57 (br s, 1H), 2.67–2.75 (m, 1H), 2.79–2.86 (m, 1H), 4.61–4.65 (m, 1H), 7.19–7.31 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 165.9, 140.9, 128.4, 128.3, 125.9, 81.8, 65.7, 35.6, 31.8, 28.2; LRMS (FAB) *m/z*: 315 (M + K); HRMS (FAB) calcd for $C_{15}H_{20}N_2O_3K$ 315.1111, found: 315.1100; $[\alpha]_D^{23}$ −5.68 (*c* 0.3, $CHCl_3$, 33% ee); HPLC: DAICEL CHIRALCEL OD-H, 254 nm, flow rate 0.5 mL/min, hexane/*i*-PrOH = 95:5, retention time: 16.7 min (major) and 19.0 min (minor).

3.2.5. *tert*-Butyl 2-diazo-3-hydroxy-5-methylhexanoate (4f). Yellow oil; IR (neat) ν: 3443, 2958, 2871, 2089, 1693 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 0.95 (d, 6H, J = 6.4 Hz), 1.33–1.41 (m, 1H), 1.49 (s, 9H), 1.57–1.67 (m, 1H), 1.73–1.83 (m, 1H), 2.47 (br s, 1H), 4.70–4.75 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 166.0, 81.7, 64.7, 42.6, 28.3, 24.5, 22.8, 21.9; LRMS (FAB) 267 (M + K); HRMS (FAB) calcd for $C_{11}H_{20}N_2O_3K$ 267.1111, found: 267.1097; $[\alpha]_D^{23}$ −12.0 (*c* 1.0, $CHCl_3$, 22% ee); HPLC: DAICEL CHIRALPAK AD-H, 254 nm, flow rate 0.5 mL/min, hexane/*i*-PrOH = 99:1, retention time: 22.3 min (minor) and 23.9 min (major).

3.2.6. *tert*-Butyl 2-diazo-3-hydroxy-4-methylpentanoate (4g). Yellow oil; IR (neat) ν: 3448, 2966, 2090, 1669 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 0.94 (d, 3H, J = 6.8 Hz), 1.06 (d, 3H, J = 6.8 Hz), 1.49 (s, 9H), 1.82–1.94 (m, 1H), 2.58 (br s, 1H), 4.23 (dd, 1H, J = 4.4, 8.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 166.1, 81.7, 72.3, 32.8, 28.3, 18.7, 18.6; LRMS (FAB) 253 (M + K); HRMS (FAB) calcd for $C_{10}H_{18}N_2O_3K$ 253.0955, found: 253.0935; $[\alpha]_D^{22}$ −10.3 (*c* 0.6, $CHCl_3$, 42% ee); HPLC: DAICEL CHIRALPAK AD-H, 254 nm, flow rate 0.5 mL/min, hexane/*i*-PrOH = 99:1, retention time: 32.2 min (minor) and 38.3 min (major).

3.2.7. *tert*-Butyl 2-diazo-3-hydroxy-3-cyclohexylpropionate (4h). Yellow oil; IR (neat) ν: 3440, 2927, 2088, 1666 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 0.97–1.30 (m, 5H), 1.48 (s, 9H), 1.52–1.79 (m, 5H), 2.02 (d, 1H, J = 12.8 Hz), 2.38 (br s, 1H), 4.25 (dd, 1H, J = 5.2, 8.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 166.1, 81.6, 71.2, 42.0, 29.1, 29.0, 28.3, 26.1, 25.8, 25.6; LRMS (FAB) *m/z*: 293 (M + K); HRMS (FAB) calcd for $C_{13}H_{22}N_2O_3K$ 293.1268, found 293.1284; $[\alpha]_D^{19}$ −3.4 (*c* 0.9, $CHCl_3$, 33% ee) HPLC: DAICEL CHIRALCEL OJ, 254 nm, flow rate 0.5 mL/min, hexane/*i*-PrOH = 99:1, retention time: 22.1 min (major) and 35.8 min (minor).

3.2.8. *tert*-Butyl 2-diazo-3-hydroxy-4,4-dimethylvalerate (4i). Yellow solid; mp 58–61 °C; IR (KBr) ν: 3469, 2960, 2103, 1647 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 0.97 (s, 9H), 1.47 (s, 9H), 2.75 (br s, 1H), 4.20 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 166.4, 81.6, 73.7, 38.3, 28.3, 25.6; LRMS (FAB) *m/z* 267 (M + K); HRMS (FAB) calcd for $C_{11}H_{20}N_2O_3K$ 267.1111, found: 267.1104. Anal. Calcd for $C_{11}H_{20}N_2O_3$: C, 57.87; H, 8.83; N, 12.27. Found: C, 57.92; H, 8.83; N, 12.51; $[\alpha]_D^{24}$ −20.4 (*c* 1.1, $CHCl_3$, 81% ee); HPLC: DAICEL CHIRALPAK AD-H, 254 nm, flow rate 0.5 mL/min, hexane/*i*-PrOH = 99:1, retention time: 25.7 min (minor) and 27.4 min (major).

3.2.9. *tert*-Butyl 2-diazo-3-hydroxy-3-(4-*tert* butylphenyl)propionate (4k). Yellow oil; IR (neat) ν: 3467, 2965, 2093, 1732, 1687 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.31 (s, 9H), 1.50 (s, 9H), 2.86 (br s, 1H), 5.83 (d, 1H, J = 3.6 Hz), 7.34 (d, 2H, J = 8.0 Hz), 7.40 (d, 2H, J = 8.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 165.8, 151.1, 136.0, 125.5, 125.4, 81.9, 68.5, 34.5, 31.2, 28.3; LRMS (FAB) *m/z*: 343 (M + K); HRMS (FAB) calcd for $C_{17}H_{24}N_2O_3K$ 343.1424, found: 343.1432; $[\alpha]_D^{26}$ −6.6 (*c* 0.9, $CHCl_3$, 32% ee); HPLC: DAICEL CHIRALCEL OD, 254 nm, flow rate 0.5 mL/min, hexane/*i*-PrOH = 97:3, retention time: 13.3 min (major) and 17.3 min (minor).

3.2.10. *tert*-Butyl 2-diazo-3-hydroxy-3-(2-naphthyl)propionate (4l). Yellow oil; IR (neat) ν: 3432, 2978, 2095, 1667 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.51 (s, 9H), 3.21 (br s, 1H), 6.03 (d, 1H, J = 2.4 Hz), 7.45–7.54 (m, 3H), 7.82–7.86 (m, 3H), 7.94 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 165.7, 136.2, 133.2, 133.1, 128.6, 128.1, 127.6, 126.3, 126.2, 124.7, 123.6, 82.2, 68.9, 28.3; LRMS (FAB) *m/z*: 337 (M+K); HRMS (FAB) calcd for $C_{17}H_{18}N_2O_3K$ 337.0955, found: 337.0924; $[\alpha]_D^{25}$ −28.2 (*c* 1.0, $CHCl_3$, 56% ee); HPLC: DAICEL CHIRALCEL OD, 254 nm, flow rate 0.5 mL/min, hexane/*i*-PrOH=97:3, retention time: 26.7 min (major) and 28.4 min (minor).

3.3. Determination of the absolute configuration of 4a (Scheme 1)

Using a procedure similar to that of Wang et al.,[7] **4a** was converted into the corresponding β-hydroxyester **7** by hydrogenation. To a solution of optically active **4a** (57% ee, 188.5 mg, 0.76 mmol) in MeOH (10.8 mL) was added 5% of palladium charcoal (54.0 mg) and the resulting suspension was stirred for 1 h under a hydrogen atmosphere. After being filtered through a Celite pad, the mixture was concentrated in vacuo. Purification of the crude mixture by flash column chromatography gave **7** as a colorless oil (104.3 mg, 0.47 mmol, 62%, 12% ee); $[\alpha]_D^{24}$ +5.3 (*c* 2.3, $CHCl_3$). Optical purity was determined by a chiral HPLC column using DAICEL CHIRALPAK AS, 254 nm, flow rate 0.5 mL/min, hexane/*i*-PrOH=97:3, retention time: 15.9 min (major, *R*) and 17.3 min (minor, *S*).[10]

3.3.1. *tert*-Butyl 2-hydrazono-3-(*tert*-butyldimethylsilyloxy)-3-phenylpropionate (*E*)-10 (Schemes 5 and 8). To a solution of **4a** (1.80 g, 7.25 mmol) in DMF (24 mL) was added imidazole (2.16 g, 31.7 mmol) and TBSCl (1.62 g, 10.8 mmol) at 0 °C and the mixture was stirred for 1 h under the same conditions. After being stirred for 6 h at rt, the reaction mixture was diluted with H_2O (10 mL) and extracted with AcOEt (20 mL×3). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. Subsequent flash column chromatography (hexane/AcOEt=50:1) gave TBS ether as a yellow oil (2.52 g, 6.96 mmol, 96%). IR (neat) ν: 2929, 2857, 2094, 1685 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 0.05 (s, 3H), 0.10 (s, 3H), 0.88 (s, 9H), 1.47 (s, 9H), 5.72 (s, 1H), 7.26–7.38 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 164.8, 141.6, 128.3, 127.5, 125.3, 81.4, 68.7, 28.3, 25.6, 18.1, −5.0, −5.3; LRMS (FAB) *m/z*: 401 (M+K); HRMS (FAB) calcd for $C_{19}H_{30}N_2O_3SiK$ 401.1663, found: 401.1659; $[\alpha]_D^{24}$ −15.1 (*c* 1.1, $CHCl_3$, 56% ee, for *S* isomer).

To a solution of the TBS ether (1.05 g, 2.9 mmol) in dry THF (41 mL) was added $LiHBEt_3$ (1 M solution of THF, 8.7 mL, 8.7 mmol) at 0 °C under an argon atmosphere, and the reaction mixture was stirred for 30 min. The reaction was quenched with cold water (10 mL) and the resulting organic layers were extracted with AcOEt (20 mL×3). The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. Flash column chromatography (hexane/AcOEt=5:1) gave (*E*)-**10** as a white solid (1.06 g, 2.9 mmol, quant.); mp: 55–56 °C (*n*-hexane, 83% ee); IR (neat) ν: 3411, 3286, 2926, 1689, 1052 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 0.12 (s, 3H), 0.14 (s, 3H), 0.94 (s, 9H), 1.56 (s, 9H), 6.19 (s, 1H), 7.02 (br s, 2H), 7.23–7.40 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 164.0, 139.6, 136.6, 128.2, 127.2, 125.3, 81.2, 70.5, 28.1, 25.7, 18.2, −5.2, −5.3; LRMS (FAB) *m/z*: 365 (M+H); HRMS (FAB) calcd for $C_{19}H_{33}N_2O_3Si$ 365.2260, found: 365.2262. Anal. Calcd for $C_{19}H_{32}N_2O_3Si$: C, 62.60; H, 8.85; N, 7.68. Found: C, 62.63; H, 8.82; N, 7.77; $[\alpha]_D^{23}$ −85.3 (*c* 1.0, $CHCl_3$, 83% ee); HPLC DAICEL CHIRALPAK AD-H, 254 nm, flow rate 0.5 mL/min, hexane/*i*-PrOH=97:3, retention time: 16.3 min (major, *S*) and 18.5 min (minor, *R*).

3.3.2. *tert*-Butyl 2-(*N*-benzoylhydrazono)-3-(*tert*-butyldimethylsilyloxy)-3-phenylpropionate (11) (Scheme 5). To a solution of (*E*)-**10** (298.5 mg, 0.82 mmol) in CH_2Cl_2 (8.2 mL) was added pyridine (0.40 mL, 4.9 mmol) and BzCl (0.19 mL, 1.6 mmol) at 0 °C and the reaction mixture was stirred for 21 h at 0 °C. After being diluted with water (10 mL), the mixture was extracted with CH_2Cl_2 (5 mL× 3). The resulting organic layers were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. Flash column chromatography (hexane/Et_2O=10:1, hexane/AcOEt= 5:1) gave (*E*)-**11** as a pale yellow oil (383.7 mg, 0.82 mmol, quant.). IR (neat) ν: 3288, 2930, 1740, 1698, 1680, 1253, 1155, 836 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 0.14 (s, 3H), 0.18 (s, 3H), 0.95 (s, 9H), 1.58 (s, 9H), 6.31 (s, 1H), 7.23–7.54 (m, 9H), 7.83 (br s, 1H), 11.4 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 162.9, 138.2, 132.1, 128.6, 128.4, 127.9, 127.0, 125.1, 82.7, 72.0, 27.7, 25.4, 17.9, −5.3, −5.4; LRMS (FAB) *m/z*: 469 (M+H); HRMS (FAB) calcd for $C_{26}H_{37}N_2O_4Si$ 469.2523, found 469.2482; HPLC: DAICEL CHIRALCEL OD-H, 254 nm, flow rate 0.5 mL/min, hexane/*i*-PrOH=99:1, retention time: 18.8 min (major) and 23.7 min (minor); $[\alpha]_D^{24}$ +4.60 (*c* 1.0, $CHCl_3$, 84% ee). All carbon signals were observed in DMSO at 120 °C, however, isomerization to (*Z*)-**11** was observed.

Compound (*Z*)-**11** was obtained by acidic treatment of (*E*)-**11** as a colorless oil; IR (neat) ν: 3255, 2954, 2930, 2857, 1704, 1676, 1132 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 0.10 (s, 3H), 0.12 (s, 3H), 0.97 (s, 9H), 1.29 (s, 9H), 5.75 (s, 1H), 7.21–7.59 (m, 8H), 7.95 (d, 2H, *J*=7.2 Hz), 13.4 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 163.7, 161.6, 142.5, 141.1, 132.4, 132.3, 128.6, 127.5, 126.7, 125.4, 84.0, 76.0, 27.5, 25.6, 18.0, −4.5, −5.2; LRMS (FAB) *m/z*: 469 (M+H); HRMS (FAB) calcd for $C_{26}H_{37}N_2O_4Si$ 469.2523, found: 469.2494.

3.3.3. Reduction of (*E*)-11, *tert*-butyl 2-(*N*-benzoylhydrazino)-3-*tert*-butyldimethylsilyloxy-3-phenylpropionate (12) (Table 6, entry 1). To a solution of (*E*)-**11** (210.6 mg, 0.45 mmol) in EtOH (2.2 mL) was added $NaBH_4$ (83.6 mg, 2.2 mmol) at 0 °C and the solution was stirred for 2 h under the same conditions. The reaction was quenched with water (10 mL) and the mixture was concentrated in vacuo. The resulting mixture was extracted with AcOEt (5 mL×3) and the combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. Flash column chromatography (hexane/AcOEt=5:1) gave *anti*-**12** as a white amorphous solid (193.6 mg, 0.41 mmol, 92%). *syn*-**12** was synthesized under the conditions described in Table 6.

Compound *anti*-**12**. White amorphous solid; IR (KBr) ν: 3262, 2930, 2857, 1700, 1676, 1138 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: −0.14 (s, 3H), 0.07 (s, 3H), 0.91 (s, 9H), 1.39 (s, 9H), 3.98 (t, *J*=4.4 Hz, 1H), 5.11 (d, *J*=

4.4 Hz, 1H), 5.36–5.39 (m, 1H), 7.26–7.68 (m, 11H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 169.4, 166.3, 140.3 132.9, 131.6, 128.5, 127.94, 127.90, 127.3, 126.7, 81.9, 74.9, 70.0, 27.9, 25.7, 18.1, −4.8, −5.1; LRMS (FAB) *m/z*: 471 (M+H); HRMS (FAB) calcd for $C_{26}H_{39}N_2O_4Si$ 471.2679, found: 471.2671; HPLC DAICEL CHIRAPAK AS, 254 nm, flow rate 0.5 mL/min, hexane/*i*-PrOH=95:5, retention time: 15.3 (minor: 2*R*,3*R*) and 23.9 (major: 2*S*,3*S*); $[\alpha]_D^{24}$ +10.1 (*c* 1.32, $CHCl_3$, 83% ee, (2*S*,3*S*)).

Compound *syn*-**12**. White amorphous solid; IR (neat) ν: 3306, 2923, 2853, 1717, 1669, 1097 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: −0.23 (s, 3H), 0.07 (s, 3H), 0.90 (s, 9H), 1.20 (s, 9H), 3.92 (d, *J*=7.2 Hz, 1H), 4.88 (d, *J*=7.2 Hz, 1H), 5.66 (br s, 1H), 7.26–7.81 (m, 11H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 169.8, 166.5, 140.7, 132.8, 131.7, 128.6, 128.12, 128.10, 127.5, 126.8, 81.6, 75.6, 70.9, 27.7, 25.7, 18.1, −4.5, −5.0; LRMS (FAB) *m/z*: 471 (M+H); HRMS (FAB) calcd for $C_{26}H_{39}N_2O_4Si$ 471.2679, found: 471.2639.

3.3.4. Reduction of (*E*)-11, synthesis of 2-(*N*-benzoylhydrazino)-1-*tert*-butyldimethylsilyloxy-1-phenylpropanol (13) (Table 6, entry 3). To a solution of (*E*)-**11** (56.0 mg, 0.12 mmol) in toluene was added Red-Al (65% solution in toluene, 0.14 mL, 0.48 mmol) at 0 °C under an argon atmosphere and the solution was stirred for an additional 2 h. The reaction mixture was quenched with saturated Rochelle salt solution (2 mL) and MeOH (three portions). The resulting residue was extracted with $CHCl_3$ (5 mL×3) and the combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. Flash column chromatography (hexane/AcOEt=3:1) gave a mixture of *syn*-**13** and *anti*-**13** isomers as a white amorphous solid (28.8 mg, 0.07 mmol, 60%). These isomers were separated by additional column chromatography (hexane:AcOEt).

Compound *anti*-**13**. White amorphous solid; IR (KBr) ν: 3256, 2927, 1635, 1251, 1065 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: −0.21 (s, 3H), 0.06 (s, 3H), 0.86 (s, 9H), 3.08–3.13 (m, 1H), 3.71 (dd, 1H, *J*=6.4 Hz, 11.2 Hz), 3.89 (dd, 1H, *J*=2.8 Hz, 11.2 Hz), 4.66 (d, 1H, *J*=7.6 Hz), 7.29–7.41 (m, 8H), 7.47–7.52 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 167.7, 142.5, 132.2, 131.8, 128.5, 128.3, 127.8, 127.0, 126.7, 75.0, 68.6, 59.8, 25.6, 18.0, −4.6, −5.6; LRMS (FAB) *m/z*: 401 (M+H); HRMS (FAB) calcd for $C_{22}H_{33}O_3N_2Si$ 401.2260, found: 401.2227.

Compound *syn*-**13**. White amorphous solid; IR (KBr) ν: 3301, 2929, 1635, 1061, 836, 701 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: −0.18 (s, 3H), 0.04 (s, 3H), 0.87 (s, 9H), 3.07–3.11 (m, 1H), 3.44 (dd, 1H, *J*=6.8, 11.6 Hz), 3.60 (dd, 1H, *J*=2.8, 11.6 Hz), 3.83 (br s, 1H), 4.82 (d, 1H, *J*=6.0 Hz), 5.09 (br s, 1H), 7.27–7.70 (m, 11H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 167.7, 141.8, 132.5, 131.8, 128.5, 128.3, 127.8, 126.9, 126.7, 75.1, 68.5, 59.7, 25.7, 18.0, −4.5, −5.1; LRMS (FAB) *m/z*: 401 (M+H); HRMS (FAB) calcd for $C_{22}H_{33}N_2O_3Si$ 401.2260, found: 401.2289.

3.3.5. *tert*-Butyl 2-(*tert*-buthoxycarbonylamino)-3-(*tert*-butyldimethylsilyloxy)-3-phenylpropionate (14) (Scheme 6). To a solution of *anti*-**12** (89.3 mg, 0.19 mmol) in MeOH (1.9 mL) was added SmI_2 (0.1 M solution in THF, 4.2 mL, 0.42 mmol) at 0 °C under an argon atmosphere, and the solution was stirred for 2 h at 0 °C. The reaction mixture was quenched with water (1 mL) and concentrated in vacuo. To the crude residue was added THF (1.9 mL), Boc_2O (207 mg, 0.95 mmol) and 10% aqueous NaOH (380 mg, 0.95 mmol) and the resulting solution was stirred for 24 h at rt. The reaction mixture was then diluted with water (3 mL) and extracted with AcOEt (5 mL×3). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. Flash column chromatography (hexane/AcOEt=100:1–20:1) gave *anti*-**14** (less polar) as a colorless oil (40.9 mg, 0.09 mmol 47%) and *syn*-**14** (more polar) as a colorless oil (15.6 mg, 0.03 mmol, 18%), respectively.

Compound *anti*-**14**. Colorless oil; IR (neat) ν: 3444, 2930, 2857, 1714 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: −0.08 (s, 3H), 0.08 (s, 3H), 0.93 (s, 9H), 1.25 (s, 8/9H), 1.29 (br s, 1/9H) 1.46 (s, 9H), 4.25 (br s, 1/10H), 4.42 (dd, *J*=2.8, 7.6 Hz, 0.2/1H), 5.04 (br s, 0.8/1H), 5.15 (s, 8/9H), 5.42 (d, *J*=7.6 Hz, 1H); 7.20–7.41 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 168.1, 154.9, 141.0, 127.6, 127.0, 126.1, 81.7, 79.5, 75.5, 61.4, 28.3, 27.7, 25.7, 18.2, −4.8, −5.2; LRMS (FAB) *m/z*: 452 (M+H); HRMS (FAB) calcd for $C_{24}H_{42}NO_5Si$ 452.2832, found: 452.2859.

Compound *syn*-**14**. Colorless oil; IR (neat) ν: 3452, 2931, 2857, 1727, 1706 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: −0.20 (s, 3H), 0.03 (s, 3H), 0.88 (s, 9H), 1.21 (br s, 2/9H), 1.35 (s, 7/9H) 1.45 (s, 7/9H), 1.49 (s, 2/9H), 4.07 (d, *J*=9.6 Hz, 7/9H), 4.25 (dd, *J*=2.8, 9.6 Hz, 0.8/1H), 5.01 (d, *J*=9.6 Hz, 0.2/1H), 5.15 (d, *J*=2.8 Hz, 1H), 5.19 (d, *J*=2.8 Hz, 0.8/1H), 7.22–7.30 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 169.8, 155.4, 141.0, 127.9, 127.6 126.5, 81.8, 79.3, 74.8, 61.0, 28.2 28.0, 25.7, 18.0, −4.4, −5.2; LRMS (FAB) *m/z*: 452 (M+H); HRMS (FAB) calcd for $C_{24}H_{42}NO_5Si$ 452.2832, found: 452.2815.

3.3.6. 2-*tert*-Buthoxycarbonylamino-1-*tert*-butyldimethylsilyloxy-1-phenylpropanol *anti*-15 (Scheme 6). To a solution of *anti*-**13** (55.0 mg, 0.14 mmol) in MeOH (1.4 mL) was added SmI_2 (0.1 M solution in THF, 3.0 mL, 0.3 mmol) at 0 °C under an argon atmosphere and the reaction mixture was stirred for 30 min. After being quenched with water (1 mL), the resulting mixture was concentrated in vacuo. To the crude residue was added THF (1.4 mL), Boc_2O (90 mg, 0.41 mmol) and aqueous 10% NaOH (165 mg, 0.41 mmol), and the mixture was stirred for 24 h at rt. After the mixture was diluted with water (3.0 mL), it was extracted with AcOEt (5 mL×3). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. Flash column chromatography (hexane/AcOEt=5:1) gave *anti*-**15** as a white solid (36.6 mg, 0.10 mmol, 71%). As described above, *syn*-**15** was synthesized from *syn*-**13** in 81% yield (two steps).

Compound *anti*-**15**. White solid; mp 136 °C (hexane); IR (neat) ν: 3341, 3232, 2926, 1671, 1056 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: −0.09 (s, 3H), 0.08 (s, 3H), 0.93 (s, 9H), 1.47 (s, 9H), 2.97 (d, *J*=10.8 Hz, 1H), 3.39–3.46 (m, 1H), 3.60 (br s, 1H), 3.84 (d, *J*=10.8 Hz, 1H), 5.19 (s, 1H), 5.48 (d, 1H, *J*=8.0 Hz) 7.20–7.40 (m, 5H); ^{13}C NMR

($CDCl_3$, 100 MHz) δ: 155.6, 141.0, 128.2, 127.4, 125.8, 79.5, 77.6, 61.2, 56.5, 28.4, 25.8, 18.0, −4.9, −5.3; LRMS (FAB) *m/z*: 382 (M+H); HRMS (FAB) calcd for $C_{20}H_{36}NO_4Si$ 382.2414, found: 382.2408. Anal. Calcd for $C_{20}H_{35}NO_4Si$: C, 62.95; H, 9.25; N, 3.67. Found: C, 62.74; H, 9.49; N, 3.59.

Compound *syn*-**15**. Colorless oil; IR (neat) ν: 3447, 2929 2857, 1697 1496 1167 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: −0.15 (s, 3H), 0.06 (s, 3H), 0.90 (s, 9H), 1.36 (s, 9H), 2.35 (br s, 1H), 3.60–3.77 (m, 3H), 4.90 (br s, 1H), 4.91 (d, 1H, *J*=3.6 Hz), 7.22–7.33 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 156.1, 141.5, 128.1, 127.5, 126.3, 79.5 73.7, 63.0, 58.5, 28.3, 25.8, 18.1, −4.6, −5.2; LRMS (FAB) *m/z*: 382 (M+H); HRMS (FAB) calcd for $C_{20}H_{36}NO_4Si$ 382.2414, found: 382.2448.

3.4. Direct synthesis of 14 via a one-pot procedure (Table 7, entry 4)

To a solution of (*E*)-**11** (75.0 mg, 0.16 mmol) in isopropanol (1.6 mL) was added SmI_2 (0.1 M solution in THF, 9.6 mL, 0.96 mmol) at 0 °C under an argon atmosphere and the mixture was stirred for 30 min. After being quenched with water (1.0 mL), the resulting mixture was concentrated in vacuo. To the crude residue was added THF (1.6 mL), Boc_2O (104 mg, 0.48 mmol) and 10% aqueous NaOH (192 mg, 0.48 mmol), and the mixture was stirred for 24 h at rt. After dilution with water (3.0 mL), the mixture was extracted with AcOEt (5 mL×3). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. Flash column chromatography (hexane/AcOEt=100:1–20:1) gave *anti*-**14** (less polar) as a colorless oil (9.3 mg, 0.02 mmol, 13%) and *syn*-**14** (more polar) as a colorless oil (62.7 mg, 0.14 mmol, 87%), respectively.

3.4.1. Direct synthesis of 17 via a one-pot procedure (Scheme 8, condition A). To a solution of (*S*)-(*E*)-**11** (113.0 mg, 0.24 mmol) in isopropanol (2.4 mL) was added SmI_2 (0.1 M solution in THF, 14.4 mL, 1.44 mmol) at 0 °C under an argon atmosphere and the mixture was stirred for 30 min. After being quenched with water (5.0 mL), the resulting mixture was extracted with AcOEt (10 mL×3). The combined organic layers were washed with brine dry over $MgSO_4$ and concentrated in vacuo. To the crude residue was added CH_2Cl_2 (2.4 mL), BzCl (41 μL, 0.36 mmol) and pyridine (38 μL, 0.48 mmol), and the mixture was stirred for 10 min at 0 °C. After being diluted with water (1.0 mL), the mixture was extracted with AcOEt (5 mL×3). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. Flash column chromatography (hexane/AcOEt=100:1–15:1) gave (2*S*,3*S*)-**17** (less polar) as a colorless oil (13.7 mg, 0.030 mmol, 12%) and (2*R*,3*S*)-**17** (more polar) as a white solid (95.9 mg, 0.21 mmol, 88%), respectively.

3.4.2. *tert*-Butyl 2-benzoylamino-3-(*tert*-butyldimethylsilyloxy)-3-phenylpropionate (17) (Scheme 8). Compound (2*S*,3*S*)-**17**. Colorless oil; IR (neat) ν: 3434, 2929, 2857, 1725, 1661 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: −0.10 (s, 3H), −0.01 (s, 3H), 0.93 (s, 9H), 1.30 (s, 9H), 4.88 (dd, 1H, *J*=2.4, 6.8 Hz), 5.33 (d, 1H, *J*=2.4 Hz), 7.13 (d, 1H, *J*=6.8 Hz), 7.24–7.85 (m, 10H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 168.2, 166.4, 141.1, 133.9, 131.7, 128.6, 127.7, 127.1 126.9, 126.1, 82.2, 75.3, 60.9, 27.8, 25.7, 18.2, −4.7, −5.1; LRMS (FAB) *m/z*: 456 (M+H); HRMS (FAB) calcd for $C_{26}H_{38}NO_4Si$ 456.2570, found: 456.2615; HPLC: DAICEL CHIRALCEL OD-H, 245 nm, flow rate 0.5 mL/min, hexane/*i*-PrOH=96:4, retention time: 8.0 min (minor) and 14.8 min (major); $[\alpha]_D^{25}$ +40.6 (*c* 0.9, $CHCl_3$, 84% ee).

Compound (2*R*,3*S*)-**17**. White solid; mp: 68 °C; IR (neat) ν: 3448, 2954, 2929, 2856, 1728, 1668 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: −0.15 (s, 3H), 0.09 (s, 3H), 0.94 (s, 9H), 1.47 (s, 9H), 4.76 (dd, 1H, *J*=2.8, 8.8 Hz), 5.31 (d, 1H, *J*=2.8 Hz) 6.82 (d, 1H, *J*=8.8 Hz), 7.23–7.74 (m, 10H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 169.3, 167.0, 140.8, 134.4, 131.4, 128.5, 128.0, 127.8, 126.8, 126.2, 82.2, 74.4, 60.2, 28.0, 25.7, 18.0, −4.4, −5.2; LRMS (FAB) *m/z*: 456 (M+H); HRMS (FAB) calcd for $C_{26}H_{38}NO_4Si$, 456.2570, found: 456.2572. Anal. Calcd for $C_{26}H_{37}NO_4Si$: C, 68.53; H, 8.18; N, 3.07. Found: C, 68.42; H, 8.39; N, 2.99; HPLC: DAICEL CHIRALCEL OD-H, 254 nm, flow rate 0.5 mL/min, hexane/*i*-PrOH=96:4, retention time: 9.9 min (major) and 13.2 min (minor); $[\alpha]_D^{25}$ +52.3 (*c* 1.0, $CHCl_3$, 83% ee).

3.4.3. *tert*-Butyl 2-(*N*-benzoylamino)-3-hydroxy-phenylpropionate (18) (Scheme 8). Compound (2*R*,3*S*)-**18**. To a solution of (2*R*,3*S*)-**17** (71.0 mg, 0.16 mmol) in THF (0.75 mL) was added TBAF (1 M solution of THF, 0.23 mL, 0.23 mmol) at rt under an argon atmosphere and the reaction mixture was stirred for 10 min. After being quenched with water (1.0 mL), the reaction mixture was extracted with AcOEt (5.0 mL×3). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. Flash column chromatography (hexane/AcOEt=2:1) gave (2*R*,3*S*)-**18** (49.2 mg, 0.14 mmol, 92%) as a white solid; mp: 134–138 °C (hexane–AcOEt); IR (neat) ν: 3368, 2977, 1731, 1639, 1521, 1149 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.42 (s, 9H), 3.13 (br s, 1H), 4.96 (dd, 1H, *J*=3.6, 7.6 Hz), 5.26 (br s, 1H), 6.85 (d, 1H, *J*=7.6 Hz), 7.27–7.72 (m, 10H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 169.3, 167.7, 139.8, 133.8, 131.6, 128.4, 128.3, 128.0, 127.0, 126.1, 82.8, 74.5, 59.0, 27.8; LRMS (FAB) *m/z*: 342 (M+H); HRMS (FAB) calcd for $C_{20}H_{24}NO_4$ 342.1705, found: 342.1689. Anal. Calcd for $C_{20}H_{23}NO_4$: C, 70.36; H, 6.79; N, 4.10. Found: C, 70.34; H, 6.83; N, 4.10; HPLC: DAICEL CHIRALCEL OJ-H, 254 nm, flow rate 0.5 mL/min, hexane/*i*-PrOH=93:7, retention time: 19.7 min (minor) and 22.6 min (major); $[\alpha]_D^{24}$ +36.1 (*c* 1.04, $CHCl_3$, 98.1% ee).

Compound (2*S*,3*S*)-**18**. According to the procedure described above, (2*S*,3*S*)-**18** was synthesized as a white solid from (2*S*,3*S*)-**17**. White solid; mp: 134–138 °C (hexane–AcOEt); IR (neat) ν: 3427, 3322, 2925, 1735, 1636, 1159 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.46 (s, 9H), 4.86 (br s, 1H), 5.15 (dd, 1H, *J*=2.4, 6.0 Hz), 5.39 (s, 1H), 6.95 (d, 1H, *J*=6.0 Hz), 7.24–7.63 (m, 10H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 168.7, 168.2, 139.3, 133.1, 132.1, 128.6, 128.1, 127.8, 127.1, 126.0, 83.6, 75.5, 60.2, 27.9; LRMS (FAB) *m/z*: 342 (M+H); HRMS (FAB) calcd for $C_{20}H_{24}NO_4$ 342.1705, found: 341.1676. Anal. Calcd for $C_{20}H_{23}NO_4$: C, 70.36; H, 6.79; N, 4.10. Found: C, 70.06; H,

6.82; N, 4.04; HPLC: DAICEL CHIRALCEL OJ-H, 254 nm, flow rate 0.5 mL/min, hexane/*i*-PrOH = 95:5, retention time: 24.4 min (minor) and 28.5 min (major); $[\alpha]_D^{25}$ +69.8 (*c* 0.13, $CHCl_3$, 96.5% ee).

3.4.4. (2*S*,3*S*) *tert*-Butyl 2-(*N*-benzoylhydrazino)-3-hydroxy-phenylpropionate (19), (Scheme 8). According to the procedure described above, (2*S*,3*S*)-**19** was synthesized as a white amorphous material from (2*S*,3*S*)-**12**. White amorphous; IR (neat) *ν*: 3296, 2977, 1721, 1641, 1152 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) *δ*: 1.32 (s, 9H), 3.94 (d, 1H, *J* = 4.8 Hz), 5.11 (d, 1H, *J* = 4.8 Hz), 5.25 (br s, 1H), 7.27–7.69 (m, 10H), 7.94 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) *δ*: 169.5, 167.6, 139.6, 132.2, 132.0, 128.6, 128.1, 127.7, 126.9, 126.4, 82.6, 72.6, 69.3, 27.8; LRMS (FAB) *m*/*z*: 395 (M + K); HRMS (FAB) calcd for $C_{20}H_{24}N_2O_4K$ 395.1373, found: 395.1383; HPLC: DAICEL CHIRALPAK AS-H, 254 nm, flow rate 1.0 mL/min, hexane/*i*-PrOH = 80:20, retention time: 15.2 min (minor) and 28.2 min (major); $[\alpha]_D^{23}$ +15.9 (*c* 0.65, $CHCl_3$, 87% ee).

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Lewis and protic acid mediated Nicholas reactions of 3-acetoxycyclohept-1-en-4-ynedicobalt hexacarbonyl: site selectivity of nucleophile incorporation

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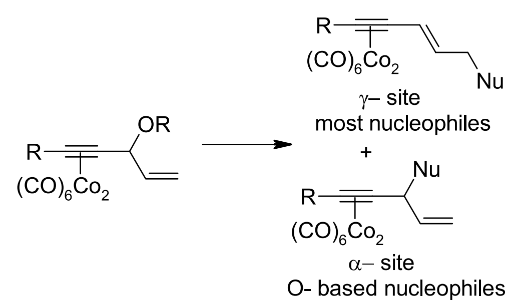
Abstract—Nicholas reactions on the cation derived from the cyclic allylic acetate alkynedicobalt complex **1** favour the γ-site kinetically for most nucleophiles, with increasing amounts of α-products in cases with greater nucleophilicity. Some regiocontrol in introduction of a specific nucleophilic fragment is possible by using different nucleophiles. Under conditions where reversibility is possible, the thermodynamically favoured site is exclusively γ-.

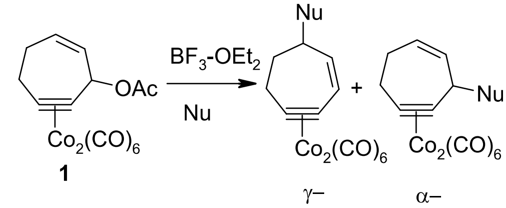
1. Introduction

Propargyl cation dicobalt hexacarbonyl complexes are one of the most widely employed transition metal stabilized reactive intermediates in organic synthesis; their chemistry is often referred to as the Nicholas reaction.[1] These cations, which may stem from alkynedicobalt complexes with propargylic leaving groups and a protic or Lewis acid, or from enyne–$Co_2(CO)_6$ complexes and an electrophile,[2] normally substitute exclusively at the propargylic site, unless the cation is also allylic. In these allylic/propargylic situations, substitution has been found to occur predominantly at the site remote to the alkyne–$Co_2(CO)_6$ unit (γ-site).[3] Exceptions exist, however, particularly where intramolecular nucleophilic attack reactions are entropically driven towards the α-site;[4] in some cases with nucleophiles, which are oxygen based, α-substitution is also observed (Scheme 1).[3a,5]



Scheme 1.

While previous studies of Nicholas reactions of allylic substrates have been focussed on acyclic cations or cyclization reactions, the analogous question for cyclic cations has not been addressed to our knowledge. We have interest in this matter from several perspectives. Our group, and other groups, have been interested in the preparation and reactivity of cycloheptynedicobalt complexes.[6,7,8] We have been able to incorporate nucleophiles γ- with respect to the alkynedicobalt unit in tandem 4+3 cycloaddition/trapping reactions, but the list of participating nucleophiles in the process is quite restricted.[6a] Substitution at the remote (γ-) position in the cycloheptenyne–$Co_2(CO)_6$ complexes (Scheme 2) would open up the ability to employ the now nucleophilic alkene function in annulation reactions with any highly electrophilic groups contained within the γ-substituent, ultimately giving fused 7,5- and 7,6- ring systems. In addition, we have an interest in clean



Scheme 2.

Keywords: Nicholas reaction; Cobalt–alkyne complexes; Cycloheptyne; Propargyl cations.

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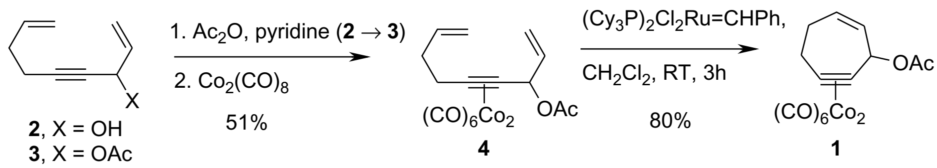


Scheme 3.

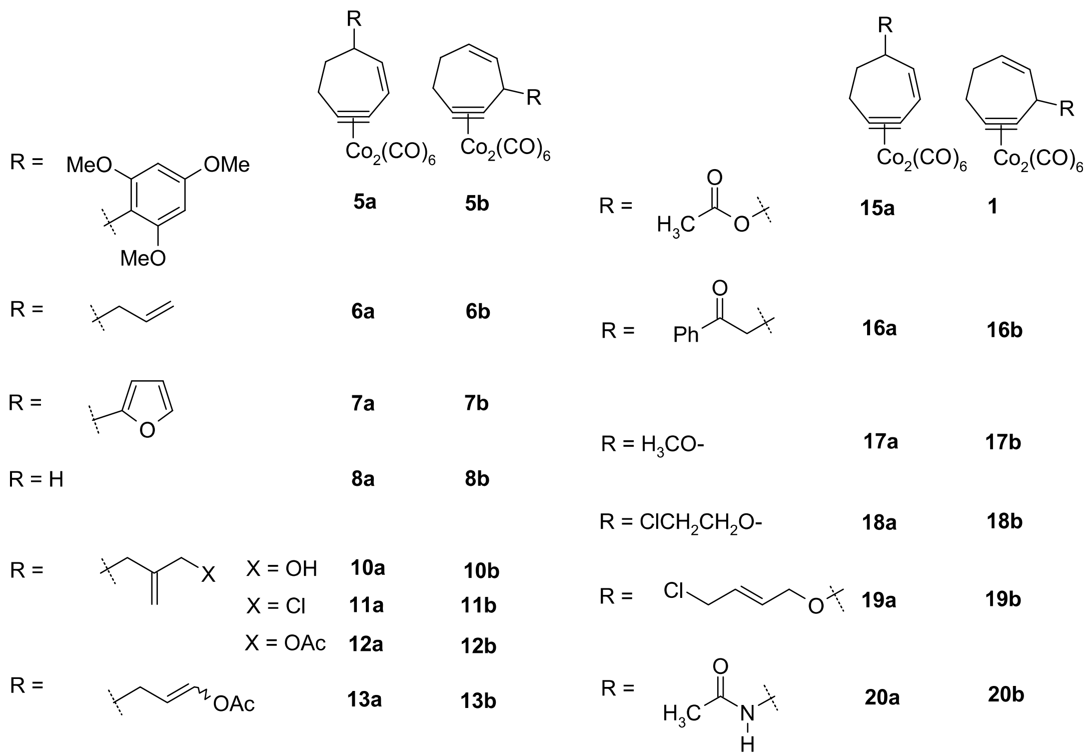


Figure 1. Nicholas reaction products of **1**.

α-substitution reactions on these complexes for facilitation of cycloaddition reactions employing the alkynedicobalt function.[9] As a result, we have deemed it of importance to study the Nicholas substitution reactions of cycloheptyne–allyl acetate complex **1**, with a range of nucleophiles.

2. Results and discussion

Cycloheptyne–allyl acetate complex **1** was prepared in straightforward fashion from the known allyl propargyl alcohol **2** (Scheme 3).[10] Standard acetylation of **2**, affording acetate **3**, followed by complexation with $Co_2(CO)_8$, gave **4** (51% yield, two steps). Ring closing metathesis, employing 10 mol% of $(Cy_3P)_2Cl_2Ru{=}CHPh$ (Grubbs' I catalyst), afforded **1** in 80% yield.[11]

With the desired substrate in hand, we chose to investigate its reaction with 1,3,5-trimethoxybenzene in order to optimize the conditions of reaction. In CH_2Cl_2 solvent (0.05 M), and with excess BF_3–OEt_2 present (10 equiv), **1** underwent reaction with 1,3,5-trimethoxybenzene at temperatures as low as −30 °C to give mixtures of the γ-substitution (C-7 substitution) product **5a** and the α-substitution (C-3 substitution) product **5b** (Fig. 1). Variation of reaction temperature revealed that the γ-substitution product predominated in all cases, with optimal yields of condensation products realized at −10 °C (Table 1) with BF_3–OEt_2 as Lewis acid. Curiously, the amount of α-substitution decreased with increasing temperature, from 41% of the products −30 °C to 14% of the product composition at 23 °C. Changing the Lewis acid from BF_3–OEt_2 to $SnCl_4$ gave similar results at −10 °C, with a marginally inferior yield. Use of Bu_2BOTf as Lewis acid, however, caused extensive unproductive decomposition, even at −30 °C. As a result, the −10 °C, BF_3–OEt_2 combination was chosen as the standard set of conditions and applied in all other cases.

Table 1. Reaction of **1** with 1,3,5-trimethoxybenzene

Conditions	Yield **5a/5b** (%)	γ-:α-Ratio
BF_3–OEt_2, −30 °C	70	59:41
BF_3–OEt_2, −10 °C	86	70:30
BF_3–OEt_2, 0 °C	73	81:19
BF_3–OEt_2, 23 °C	52	86:14
$SnCl_4$, −10 °C	77	76:24
Bu_2BOTf, −30 °C	0	—

The change in isomer ratio towards increased amounts of the major, γ-substitution product at higher reaction temperatures suggested the possibility that the results with 1,3,5-trimethoxybenzene were not the consequence of purely kinetic reactivity of the propargyl allyl cation. Past work in our group has shown evidence of reversibility in Nicholas reactions involving this nucleophile,[12] and these results would be consistent with that feature here. In fact, subjecting purified α-substitution product **5b** to the 0 °C conditions of reaction (without added 1,3,5-trimethoxybenzene) afforded a **5a/5b** mixture (23:77, 67% recovery) along with some decomposition. By contrast, subjecting **5a** to these conditions gave only recovered **5a**. Consequently, allyltrimethylsilane was also investigated as a nucleophile with **1** under varying reaction temperatures (Table 2), as reversibility in this reaction is far less likely. Under analogous concentration and stoichiometry conditions, allyltrimethylsilane afforded γ-substitution product **6a** and α-substitution product **6b**. Once again the yield reached a maximum at −10 °C, but in these cases the α-:γ-product ratios remained relatively consistent (81:19–84:16) over the temperature range investigated.

Table 2. Reaction of **1** with allyltrimethylsilane

Conditions	Yield **6a/6b** (%)	γ-:α-Ratio
BF_3–OEt_2, −30 °C	68	82:18
BF_3–OEt_2, −10 °C	83	84:16
BF_3–OEt_2, 0 °C	77	81:19
BF_3–OEt_2, 23 °C	56	83:17

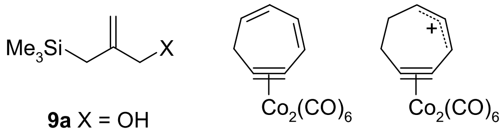
Several other carbon and hydride based nucleophiles were investigated (Table 3). Allyltributylstannane gave **6a** and **6b** in good yield (74%), but with minimal γ-:α-selectivity (**6a**:**6b** = 50:50). Conversely, furan gave condensation product **7a** through its C-2 site, with almost none of α-condensation product **7b** in evidence (62% yield, **7a**:**7b** = >96:<4).[13] The overall reduction products **8a** and **8b** could be obtained in fair yield using triethylsilane (54%, **8a**:**8b** = 63:37) or triisopropylsilane (62% yield, **8a**:**8b** = 84:16). The 2-hydroxymethyl-, 2-chloromethyl-, and 2-acetoxymethyl-substituted allylsilanes (**9a**, **9b**, and **9c**, respectively) (Fig. 2) afforded analogous products **10a/b**, **11a/b**, and **12a/b**, respectively, with somewhat lower γ-:α-ratios (59:41–72:28) relative to allyltrimethylsilane itself. Homoenolate equivalent 1-trimethylsilylallyl acetate gave the enol acetate products **13a** and **13b** (as *Z*-/*E*-isomeric mixtures) with relatively high γ-selectivity (65% yield, **13a**:**13b** = 89:11), along with small amounts of elimination product **14** (7%) and γ-acetoxy substitution product **15a** (7%). To our knowledge, this is the first example of a discrete homoenolate equivalent participating directly in a Nicholas reaction, although the cyclization-rearrangement processes of Tanino[14] and Magnus' cyclization–dyotropic rearrangements[15] may be considered specialized cases of homoenolate equivalent reactivity. In addition, complexes with analogous functional group connectivity have been made by radical reactions on enyne complexes.[16] Finally, two acetophenone enolate equivalents were introduced. The trimethylsilyl enol ether of acetophenone underwent reaction with **1** to give **16a** and **16b** in good yield (74%), but the α-condensation product actually predominated slightly with this nucleophile (**16a**:**16b** = 44:56). The enol acetate of acetophenone gave somewhat lower yields (61%, with 19% of **15a**), with the γ-product once again as the major regioisomer (**16a**:**16b** = 72:28).

Investigation of heteroatom based nucleophiles was also warranted due to the likelihood of reversibility in the substitution process (Table 4). Under standard conditions, acetic acid could be incorporated with great facility to give **15a** in good yield (79%) exclusively as the γ-substitution product. In this case, abandonment of the standard conditions in favour of neat acetic acid and H_2SO_4 gave superior results (97% yield) for **15a**. Under the standard conditions, methanol, 2-chloroethanol, and 4-chloro-2-buten-1-ol gave **17a** (65%), **18a** (59%), and **19a** (68%), each exclusively as the γ-substitution products. The latter two cases also gave modest amounts of elimination product **14** and γ-acetoxy substitution product **15a**. Again, use of a large excess of nucleophile and H_2SO_4 gave yield improvement for each of the commercially available alcohols (**17a**, 87%; **18a**, 76%). Attempts to incorporate a nitrogen based nucleophile, acetamide, met with little success under the standard reaction conditions. While a small amount of γ-substitution product **20a** could be obtained (12% yield), the major resulting product was γ-acetoxy substituted **15a** (83% yield); a small amount of elimination product **14** (5% yield) also could be isolated. Conversely, good yields of **20a** (85%) could be realized by resorting to the addition of H_2SO_4 to a solution of **1** in CH_3CN. In no cases have we observed even traces of the heteroatom based α-condensation products **1**, **17b**–**20b** as a result of these protic- or Lewis acid mediated reactions.

Table 3. Reaction of **1** with carbon and hydrogen nucleophiles[a]

Nucleophile	Product	Yield (%)	γ-:α-Ratio	**15a** (%)	**14** (%)
1,3,5-Trimethoxybenzene	**5a/5b**	86	70:30		
Allyltrimethylsilane	**6a/6b**	83	84:16		
Allyltributylstannane	**6a/6b**	74	50:50		
Furan	**7a/7b**	62	>96:4		
Et_3SiH	**8a/8b**	54	72:28		
$^iPr_3SiH$	**8a/8b**	62	84:16	3.5	
9a	**10a/10b**	76	59:41		
9b	**11a/11b**	70	72:28		
9c	**12a/12b**	76	64:36		
1-Trimethylsilylallyl acetate	**13a/13b**	65	89[b]:11[c]	7	7
$H_2C{=}C(OSiMe_3)Ph$	**16a/16b**	74	44:56		
$H_2C{=}C(OAc)Ph$	**16a/16b**	61	72:28	19	

[a] Reaction conditions: nucleophile, 1.5–2.0 equiv; solvent, CH_2Cl_2 (0.05 M); temperature, −10 °C; Lewis acid, BF_3–OEt_2 (10 equiv); reaction time, 1 h.
[b] Compound **13a** (*E*-:*Z*-) = 38:62.
[c] Compound **13b** (*E*-:*Z*-) = 51:49.



9a X = OH
9b X = Cl
9c X = OAc
14
21

Figure 2.

Table 4. Reaction of **1** with heteroatom nucleophiles[a]

Nucleophile	Product	Yield (%)	**15a** (%)	**14** (%)
CH_3CO_2H	**15a**	79		
CH_3CO_2H	**15a**	97[b]		
CH_3OH	**17a**	65		
CH_3OH	**17a**	87[b]		
2-Chloroethanol	**18a**	59	15	15
2-Chloroethanol	**18a**	76[b]		
4-Chloro-2-buten-1-ol	**19a**	68	13	4
$CH_3C(O)NH_2$	**20a**	12	83	5
CH_3CN	**20a**	85[b]		

[a] Reaction conditions, unless otherwise stated: nucleophile, 1.5–2.0 equiv; solvent, CH_2Cl_2 (0.05 M); temperature, −10 °C; Lewis acid, BF_3–OEt_2 (10 equiv); reaction time, 1 h.
[b] Using H_2SO_4 in place of BF_3–OEt_2 and excess nucleophile.

With the ready availability of γ-acetoxy substitution product **15a**, and the belief that the same cation could be generated from this compound as from **1**, we briefly explored its BF_3–OEt_2 induced Nicholas reactions. Under the otherwise standard conditions, allyltrimethylsilane reacted with **15a** to give **6a** and **6b** (81% yield) in the same ratio as from **1** (**6a**:**6b** = 84:16), strongly suggesting an identical reactive intermediate from the two allyl acetate complexes. Compound **15a** also reacted with 1,3,5-trimethoxybenzene, affording **5a** and **5b** in 80% yield (**5a**:**5b** = 76:24).

The distinction of γ- from α-adducts was readily apparent from the ^{1}H NMR spectra. Noteworthy in this respect were the resonances attributable to the vinyl proton adjacent to the alkyne–$Co_2(CO)_6$ unit in the γ-regioisomer, which appeared as a doublet ($J \cong 10$ Hz) at 6.5–6.7 ppm, deshielded by ≥0.5 ppm relative to the other alkene protons. The most distinctive features of the analogous spectra of the α-isomers were the allylic and propargylic methine protons (or methylene in **8b**), which resonated at 3.7–4.0 ppm (excepting **5b**). The ^{1}H NMR spectrum of **5b** was also noteworthy in that the resonances for two of the methoxy CH_3's appeared as a broadened signal, which sharpened upon warming and decoalesced to two singlets at −20 °C. Variable temperature ^{1}H NMR studies established a coalescence T_c of 25 °C for these methyl group resonances, and a barrier at coalescence of $\Delta G_c = 15.2$ kcal/mol. This process was attributed to restricted rotation about the Cα- aryl C bond, which interchanged the two aryl *ortho* methoxy functions.

Our analysis of the reactivity patterns in this system is as follows. The allyl propargyldicobalt cation **21** generated from either **1** or **15a** reacts in a kinetic fashion with nucleophiles predominantly, but not exclusively, at the site γ- with respect to the alkynedicobalt unit (C-7). We find it particularly instructive that a comparison the γ-: α-selectivities with Mayr's published *N* (nucleophilicity) values[17] reveals that greater nucleophilicity results in greater amounts of α- attack (Table 5). While the exact correlation between *N* and γ-:α-ratios probably involves some coincidence and other factors likely contribute,[18] a comparison between similar nucleophiles particularly supports this trend. For example, the less nucleophilic allyltrimethylsilane ($N = 1.79$, γ-:α- = 84:16) has a much greater preference for the γ-site than allyltributylstannane ($N = 5.46$, γ-:α- = 50:50). In addition, the less nucleophilic acetophenone enol acetate[19] reacts with greater γ-selectivity (γ-:α- = 72:28) than the more nucleophilic trimethylsilyl enol ether ($N = 6.22$, γ-:α- = 44:56). This is consistent with earlier work of Nicholas and Isobe on acyclic systems; low temperature reactions with alcohols and (to a small extent) enol acetates give α- attack kinetically, and these are the most reactive nucleophiles examined by these authors. The comparison of Et_3SiH and $^iPr_3SiH$ suggests that increased γ-selectivity is encouraged by larger nucleophiles, likely as a consequence of the significant steric size of the alkyne–$Co_2(CO)_6$ unit.

Table 5. Nucleophile *N* values versus γ-:α-ratios

Nucleophile[a]	*N* value	γ-:α-Ratio
$H_2C{=}C(OSiMe_3)Ph$	6.22	44:56
Allyltributylstannane	5.46	50:50
Et_3SiH	3.64	72:28
Allyltrimethylsilane	1.79	84:16
Furan	1.36	>96:4

[a] 1,3,5-Trimethoxybenzene ($N = 3.40$) is excluded as it is likely not reacting at the kinetic limit.

Conversely, the product of thermodynamic reaction, as with the heteroatom based nucleophiles, is clearly exclusively γ-. This is supported by the results of reaction of **5b** and BF_3–OEt_2, and also by the fact that methyl ether **17a** underwent reaction with nucleophile **9a** (66%, 59:41 **10a**:**10b**) under the standard conditions. The conjugation between the alkene function and the complexed alkyne unit in the γ-products, and the assertion that the γ-products are more stable than the α-adducts, are also reflected by a shortened C-3/C-4 single bond length (1.450 Å) in **17a** and a 6.7 kcal/mol (28.0 kJ/mol) energy difference between **17a** and **17b** in DFT calculations (DFT B88-PW91, CAChe®).[20] The reaction of **1** with 1,3,5-trimethoxybenzene itself is neither at the kinetic nor thermodynamic limit.

In summary, the Nicholas reactions on the cation derived from the cyclic allylic acetate alkynedicobalt complex **1** kinetically favour the γ-site for most nucleophiles, with increasing amounts of α-products in cases with greater nucleophilicity. In the introduction of a specific nucleophilic fragment, some regiocontrol is possible through variation of the nucleophile. The thermodynamically favoured site is exclusively γ-. Work on employing some of the γ-adducts for access to 7,5- and 7,6- ring systems containing the alkynedicobalt unit, by way of cyclization reactions using the alkene function, is in progress and will be reported in due course.

3. Experimental

3.1. General methods

All reaction solvents were used after passage through a solvent purification system from Innovative Technologies.

Commercial BF_3–OEt_2 was distilled and stored under nitrogen. All reactions were conducted under a nitrogen atmosphere unless otherwise noted. Flash chromatography was performed as described by Still using silica gel 60 (230–400 mesh).[21]

All new compounds are >95% purity as determined by ^{1}H and ^{13}C NMR spectroscopy. Reported regioisomeric ratios are on based on the ^{1}H NMR spectra of crude reaction products. NMR spectra were run at 500 or 300 MHz for ^{1}H and 125 or 75 MHz for ^{13}C in $CDCl_3$; chemical shifts are given in ppm and coupling constants (J) are given in Hz. High resolution mass spectra were run at the McMaster Regional Centre for Mass Spectrometry and the Ohio State Chemistry Mass Spectrometry Facility.

3.1.1. Hexacarbonyl[μ-η^4-(3-acetoxynona-1,8-dien-4-yne)]dicobalt (4). To a mixture of alcohol **2** (0.3031 g, 2.23 mmol) and acetic anhydride (1 mL) at 0 °C was added pyridine (1 mL). The solution was stirred over a 6 h period and allowed to come to room temperature. The volatiles were removed under reduced pressure, and the resulting residue containing **3** was dissolved in Et_2O (15 mL). An excess amount of $Co_2(CO)_8$ was added and the solution stirred 12 h at room temperature. The removal of volatiles under reduced pressure followed by flash chromatography (100% petroleum ether—10:1 petroleum ether/Et_2O) gave acetate complex **4** (0.5239 g, 51% yield) as a red-brown oil. IR (neat, KBr, cm^{-1}): 3085, 2958, 2093, 2050, 2020, 1746; ^{1}H NMR δ: 6.48 (d, J=6.5 Hz, 1H), 5.92 (m, 2H), 5.42 (d, J=17.0 Hz, 1H), 5.28 (d, J=10.3 Hz, 1H), 5.16 (d, J=17.1 Hz, 1H), 5.09 (d, J=10.3 Hz, 1H), 2.89 (m, 2H), 2.40 (m, 2H), 2.13 (s, 3H); ^{13}C NMR δ: 199.5, 169.8, 137.0, 135.3, 117.3, 115.9, 97.8, 94.5, 74.7, 35.5, 33.0, 20.6. MS EI *m/e* 408 (M^+-2CO). HRMS *m/e* for $C_{17}H_{14}Co_2O_8$ calcd (M^+-2CO) 407.9454, found 407.9455.

3.1.2. Hexacarbonyl[μ-η^4-(3-acetoxycyclohept-1-en-4-yne)]dicobalt (1). To a solution of **4** (0.0577 g, 0.124 mmol) in CH_2Cl_2 (5 mL) was added dichloro(phenylmethylene)bis(tricyclohexylphosphine)ruthenium (1st generation Grubbs' catalyst, 0.0102 g, 10.0 mol%) in CH_2Cl_2 (1 mL). The solution was stirred for 3 h, and subsequently concentrated under reduced pressure. Flash chromatography (20:1 petroleum ether:Et_2O) gave **1** (0.0436 g, 80%) as a red-brown oil. IR (neat, KBr, cm^{-1}) 3035, 2940, 2093, 2051, 2021, 1747; ^{1}H NMR δ: 6.70 (br s, 1H), 5.94 (m, 1H), 5.78 (dt, J=11.2, 2.2 Hz, 1H), 3.18 (dt, J=17.1, 4.3 Hz, 1H), 3.00 (ddd, J=3.7, 11.4, 17.1 Hz, 1H), 2.25–2.33 (m, 2H), 2.30 (s, 3H); ^{13}C NMR δ: 199.3, 170.4, 134.3, 130.4, 98.0, 93.0, 73.9, 33.2, 27.2, 20.6. MS *m/e* 408 (M^+-1CO), 380 (M^+-2CO), 352 (M^+-3CO), 324 (M^+-4CO), 296 (M^+-5CO), 268 (M^+-6CO). HRMS *m/e* for $C_{15}H_{10}Co_2O_8$ calcd (M^+-1CO) 407.9090, found 407.9103.

3.2. General procedure: reactions of the cycloheptenyne dicobalt complex with carbon- and heteroatom-based nucleophiles

To a solution of the nucleophile (1.5–2.0 equiv) and cycloheptenyne **1** in CH_2Cl_2 (0.05 M) at −10 °C was added BF_3–OEt_2 (10 equiv) over 30 min as a solution in CH_2Cl_2 (1.0 M). The solution was stirred for 1 h and followed by addition of aqueous sodium bicarbonate. A typical workup was performed. The crude product was purified by flash chromatography.

3.2.1. Hexacarbonyl[μ-η^4-(7-(2,4,6-trimethoxyphenyl)-cyclohept-1-en-3-yne)]dicobalt (5a) and hexacarbonyl [μ-η^4-(3-(2,4,6-trimethoxyphenyl)cyclohept-1-en-4-yne)]dicobalt (5b). A solution of cycloheptenyne **1** (0.0385 g, 0.0883 mmol) and 1,3,5-trimethoxybenzene (0.0297 g, 0.1766 mmol) in CH_2Cl_2 (2 mL) at −10 °C was subjected to BF_3–OEt_2 (0.11 mL, 0.88 mmol) via the general procedure. The product was purified by flash chromatography (25:1 petroleum ether/Et_2O) gave **5a** and **5b** (0.0412 g, 86%, **5a**:**5b**=70:30) as a red-brown oil. Careful repeated TLC afforded (in order of elution) **5b** followed by **5a**. Compound **5a**. IR (neat, KBr, cm^{-1}): 2925, 2851, 2087, 2017, 1609, 1385; ^{1}H NMR δ: 6.46 (d, J=9.8 Hz, 1H), 6.14 (s, 2H), 5.97 (dd, J=2.7, 9.9 Hz, 1H), 4.03 (m, 1H), 3.79 (s, 9H), 3.35 (m, 1H), 3.16 (m, 1H), 2.19 (m, 1H), 1.82 (m, 1H); ^{13}C δ: 200.0, 159.0, 143.1, 123.7, 116.0, 99.3, 91.5, 89.7, 55.8, 55.5, 38.0, 35.9, 31.4, 24.3. MS EI *m/e*: 544 (M^+), 516 (M^+-1CO), 488 (M^+-2CO), 460 (M^+-3CO), 432 (M^+-4CO), 404 (M^+-5CO), 376 (M^+-6CO). HRMS *m/e* for $C_{22}H_{18}Co_2O_9$ calcd (M^+) 543.9615, found 543.9609. Compound **5b**. IR (neat, KBr, cm^{-1}): 2926, 2085, 2043, 2014, 1733, 1609; ^{1}H NMR δ: 6.22 (m, 1H), 6.17 (s, 2H), 5.88 (m, 1H), 5.63 (s, 1H), 3.83 (s, 3H), 3.79 (br s, 6H), 3.24 (m, 1H), 3.03 (m, 1H), 2.41 (m, 2H); ^{13}C NMR δ: 200.3, 160.4, 137.4, 128.4, 111.0, 101.0, 100.2, 91.2, 90.2, 55.5, 54.3, 38.5, 34.5, 27.3. MS EI *m/e*: 544 (M^+), 516 (M^+-1CO), 488 (M^+-2CO), 460 (M^+-3CO), 432 (M^+-4CO), 404 (M^+-5CO), 376 (M^+-6CO). HRMS *m/e* for $C_{22}H_{18}Co_2O_9$ calcd (M^+-CO) 515.9666, found 515.9666.

Reaction of **5b** *with* BF_3–OEt_2.

To a 0 °C solution of **5b** (0.0281 g, 0.0517 mmol) in CH_2Cl_2 (4 mL) was added BF_3–OEt_2 (65 μL, 0.52 mmol). After stirring for 1 h at 0 °C, $NH_4Cl_{(aq)}$ was added and the reaction was subjected to a conventional workup. Flash chromatography (20:1 petroleum ether/Et_2O) gave **5a** and **5b** (0.0189, 67% recovery, **5a**:**5b**=23:77).

3.2.2. Hexacarbonyl[μ-η^4-(7-allylcyclohept-1-en-3-yne)] dicobalt (6a) and hexacarbonyl[μ-η^4-(3-allylcyclohept-1-en-4-yne)]dicobalt (6b). A solution if cycloheptenyne **1** (0.0817 g, 0.187 mmol) and allyltrimethylsilane (45 μL, 0.28 mmol) in CH_2Cl_2 (3.7 mL) at −10 °C was subjected to BF_3–OEt_2 (0.24 mL, 1.9 mmol) via the general procedure. Flash chromatography (25:1 petroleum ether/Et_2O) resulted in the co-elution of **6a** and **6b** (0.0650 g, 83%, **6a**:**6b**=84:16) as a red-brown oil. IR (neat, KBr, cm^{-1}): 3015, 2926, 2854, 2089, 2046, 2017, 1641, 1582; ^{1}H NMR **6a** δ: 6.52 (d, J=9.9 Hz, 1H), 5.95 (dd, J=4.3, 9.9 Hz, 1H), 5.78 (m, 1H), 5.08 (m, 2H), 3.25 (m, 1H), 3.10 (m, 1H), 2.46 (m, 1H), 2.26 (m, 2H), 2.21 (m, 1H), 1.88 (m, 1H); resonances for **6b** could be observed at δ: 5.94 (m, 1H), 5.65 (m, 1H), 5.13 (m, 2H), 3.75 (m, 1H), 3.20 (m, 1H), 2.95 (m, 1H), 2.65 (m, 1H), 2.40 (m, 1H); ^{13}C NMR δ: 200.1, 139.7, 136.3, 126.4, 117.2, 98.1, 87.5, 41.0, 40.6, 33.4, 30.3; resonances for **6b** could be observed at 136.1, 131.5, 41.8, 34.3, 30.1, 27.1. MS EI *m/e*: 418 (M^+), 390 (M^+-1CO), 362 (M^+-2CO), 334 (M^+-3CO), 306 (M^+-4CO), 278 (M^+-5CO), 250 (M^+-6CO). HRMS *m/e* for $C_{16}H_{12}Co_2O_6$ calcd (M^+) 417.9298, found 417.9287.

3.2.3. Hexacarbonyl[μ-η^4-(2-cyclohept-2-en-4-ynyl-furan)]dicobalt (7a). A solution of cycloheptenyne **1** (0.0540 g, 0.124 mmol) and furan (0.136 g, 0.186 mmol) in CH_2Cl_2 (2.5 mL) at −10 °C was subjected to BF_3–OEt_2 (0.16 mL, 1.2 mmol) via the general procedure. The crude product was purified by flash chromatography (100% petroleum ether) to yield **7a** (0.0341 g, 62%) as a red-brown oil. IR (neat, KBr, cm^{-1}): 2927, 2089, 2048, 2017, 1622, 1428; ^{1}H NMR δ: 7.35 (d, $J=1.8$ Hz, 1H), 6.71 (d, $J=9.9$ Hz, 1H), 6.28 (dd, $J=1.8$, 3.1 Hz, 1H), 6.15 (dd, $J=3.1$, 9.9 Hz, 1H), 6.03 (d, $J=3.2$ Hz, 1H), 3.89 (m, 1H), 3.17 (m, 1H), 2.98 (m, 1H), 2.23 (m, 1H), 2.08 (m, 1H); ^{13}C NMR δ: 199.9, 155.8, 141.7, 133.7, 127.8, 110.1, 106.3, 98.1, 86.8, 41.1, 32.2, 30.1. MS EI *m/e*: 444 (M^+), 416 (M^+-1CO), 388 (M^+-2CO), 360 (M^+-3CO), 332 (M^+-4CO), 304 (M^+-5CO), 276 (M^+-6CO). HRMS *m/e* for $C_{17}H_{10}Co_2O_7$ calcd (M^+) 443.9091, found 443.9082.

3.2.4. Hexacarbonyl[μ-η^4-(cyclohept-1-en-3-yne)]-dicobalt (8a) and hexacarbonyl[μ-η^4-(cyclohept-1-en-4-yne)]dicobalt (8b). A solution of cycloheptenyne **1** (0.0500 g, 0.115 mmol) and triethylsilane (0.0200 g, 0.173 mmol) in CH_2Cl_2 (2.3 mL) at −10 °C was subjected to BF_3–OEt_2 (0.15 mL, 1.1 mmol) via the general procedure. After flash chromatography (100% petroleum ether), an inseparable mixture of **8a** and **8b** (0.0235 g, 54%, **8a**:**8b**=72:28) was isolated. IR (neat, KBr, cm^{-1}): 2928, 2089, 2046, 2016, 1581, 1385; ^{1}H NMR δ: 6.54 (d, $J=9.7$ Hz, 1H), 6.10 (m, 1H), 3.20 (t, $J=5.6$ Hz, 2H), 2.41 (m, 2H), 1.87 (m, 2H); peaks for **8b** could be observed at δ: 5.97 (m, 1H), 5.88 (m, 1H), 3.10 (m, 2H), 2.41 (m, 2H), 2.33 (m, 2H); ^{13}C δ: 199.5, 135.1, 127.1, 97.9, 89.4, 35.7, 30.9, 24.9; resonances for **8b** could be observed at δ: 199.5, 132.4, 130.2, 98.1, 89.6, 34.5, 33.6, 27.2. MS EI *m/e*: 378 (M^+), 350 (M^+-1CO), 322 (M^+-2CO), 294 (M^+-3CO), 266 (M^+-4CO), 238 (M^+-5CO), 210 (M^+-6CO). HRMS *m/e* for $C_{13}H_8Co_2O_6$ calcd (M^+-CO) 349.9030, found 349.9008.

3.2.5. Hexacarbonyl[μ-η^4-(2-cyclohept-2-en-4-ynyl-methyl-prop-2-en-1-ol)]dicobalt (10a) and hexacarbonyl [μ-η^4-(2-cyclohept-2-ynyl-methyl-prop-2-en-1-ol)]dicobalt (10b). A solution of cycloheptenyne **1** (0.0776 g, 0.178 mmol) and 2-(trimethylsilylmethyl)-2-propen-1-ol (**9a**) (0.0384 g, 0.266 mmol) in CH_2Cl_2 (3.6 mL) at −10 °C was subjected to BF_3–OEt_2 (0.23 mL, 1.8 mmol) via the general procedure. Flash chromatography (3:1 petroleum ether/Et_2O) resulted in the isolation of **10a** and **10b** (0.0607 g, 76%, **10a**:**10b**=59:41) as a red-brown oil. Careful repeated TLC afforded (in order of elution) **10b** followed by **10a**. Compound **10a**. IR (neat, KBr, cm^{-1}) 3354, 2923, 2086, 2047, 2021, 1608, 1435, 1384; ^{1}H NMR δ: 6.54 (d, $J=9.9$ Hz, 1H), 5.96 (dd, $J=3.8$, 9.9 Hz, 1H), 5.17 (s, 1H), 4.94 (s, 1H), 4.09 (s, 2H), 3.28 (m, 1H), 3.12 (m, 1H), 2.61 (m, 1H), 2.28 (m, 2H), 1.91 (m, 1H), 1.75 (m, 1H), 1.51 (br s, 1H); ^{13}C NMR δ: 200.0, 146.1, 139.2, 126.3, 112.3, 98.0, 87.5, 65.6, 39.5, 38.7, 33.3, 30.3. MS EI *m/e*: 448 (M^+), 420 (M^+-1CO), 392 (M^+-2CO), 364 (M^+-3CO), 336 (M^+-4CO), 308 (M^+-5CO), 280 (M^+-6CO). HRMS *m/e* for $C_{17}H_{14}Co_2O_7$ calcd (M^+-2CO) 391.9500, found 391.9513. Compound **10b**. IR (neat, KBr, cm^{-1}) 3385, 2925, 2088, 2046, 2016, 1608, 1506, 1093; ^{1}H NMR for the δ: 5.95 (m, 1H), 5.67 (m, 1H), 5.23 (s, 1H), 5.05 (s, 1H), 4.18 (s, 2H), 3.92 (m, 1H), 3.24 (m, 1H), 3.01 (m, 1H), 2.35 (m, 4H), 1.59 (br s, 1H); ^{13}C NMR δ: 199.9, 146.1, 135.9, 131.4, 112.2, 100.9, 99.9, 65.9, 40.4, 39.3, 34.2, 26.9. MS EI *m/e*: 448 (M^+), 420 (M^+-1CO), 392 (M^+-2CO), 364 (M^+-3CO), 336 (M^+-4CO), 308 (M^+-5CO), 280 (M^+-6CO). HRMS *m/e* for $C_{17}H_{14}Co_2O_7$ calcd (M^+) 447.9403, found 447.9376.

3.2.6. Hexacarbonyl[μ-η^4-(7-(2-chloromethylallyl)cyclo-hept-1-en-3-yne)]dicobalt (11a) and hexacarbonyl[μ-η^4-(3-(2-chloromethylallyl)cyclohept-1-en-4-yne)]dicobalt (11b). A solution of cycloheptenyne **1** (0.0477 g, 0.109 mmol) and 2-chloromethyl-3-trimethylsilyl-1-propene (**9b**) (0.030 mL, 0.17 mmol) in CH_2Cl_2 (2.5 mL) at −10 °C was subjected to BF_3–OEt_2 (0.14 mL, 1.1 mmol) via the general procedure. Flash chromatography (25:1 petroleum ether/Et_2O) resulted in the co-elution of **11a** and **11b** (0.0358 g, 70%, **11a**:**11b**=72:28) as a red-brown oil. IR (neat, KBr, cm^{-1}): 2927, 2090, 2047, 2016, 2017, 1506, 1430; ^{1}H NMR δ: 6.55 (dd, $J=1.6$, 9.9 Hz, 1H), 5.97 (dd, $J=4.1$, 9.9 Hz, 1H), 5.27 (s, 1H), 5.02 (s, 1H), 4.05 (s, 2H), 3.28 (m, 1H), 3.18 (m, 1H), 2.68 (m, 1H), 2.37 (m, 2H), 1.89 (m, 1H), 1.87 (m, 1H); resonances for **11b** could be observed at δ: 5.97 (m, 1H), 5.68 (dd, $J=3.3$, 10.5 Hz, 1H), 5.31 (s, 1H), 5.14 (s, 1H), 4.13 (s, 2H), 3.26 (m, 2H), 3.14 (m, 1H), 2.45 (m, 1H), 2.33 (m, 2H), 1.71 (m, 1H); ^{13}C NMR δ: 199.9, 142.5, 138.8, 126.7, 117.1, 96.3, 86.2, 47.8, 39.6, 38.5, 33.3, 30.3; resonances for **11b** could be observed at δ: 135.7, 133.0, 116.9, 96.3, 86.2, 48.0, 40.1, 39.1, 34.1, 27.2. MS EI *m/e*: 466 (M^+), 438 (M^+-1CO), 410 (M^+-2CO), 382 (M^+-3CO), 354 (M^+-4CO), 326 (M^+-5CO), 298 (M^+-6CO). HRMS *m/e* for $C_{17}H_{13}ClCo_2O_6$ calcd (M^+) 465.9065, found 465.9038.

3.2.7. Hexacarbonyl[μ-η^4-(acetic acid 2-cyclohept-2-en-4-ynylmethylallyl ester)]dicobalt (12a) and hexacarbonyl [μ-η^4-(acetic acid 2-cyclohept-2-en-6-ynylmethylallyl ester)]dicobalt (12b). A solution of cycloheptenyne **1** (0.0706 g, 0.162 mmol) and 2-(acetoxymethyl)allyltrimethylsilane (**9c**) (0.0509 g, 0.274 mmol) in CH_2Cl_2 (3.5 mL) at −10 °C was subjected to BF_3–OEt_2 (0.205 mL, 1.62 mmol) via the general procedure. Flash chromatography (25:1 petroleum ether/Et_2O) resulted in the co-elution of **12a** and **12b** (0.0606 g, 76%, **12a**:**12b**=64:36) as a red-brown oil. Compound **12a**. IR (neat, KBr, cm^{-1}): 2927, 2089, 2048, 2018, 1747, 1053; ^{1}H NMR δ: 6.54 (dd, $J=1.9$, 9.8 Hz, 1H), 5.94 (dd, $J=4.3$, 9.8 Hz, 1H), 5.18 (s, 1H), 5.01 (s, 1H), 4.55 (1/2 ABq, $J=13.5$ Hz, 1H), 4.51 (1/2 ABq, $J=13.5$ Hz, 1H), 3.28 (m, 1H), 3.13 (m, 1H), 2.61 (m, 1H), 2.27 (m, 2H), 2.22 (s, 3H), 2.09 (m, 1H), 2.06 (m, 1H); resonances for **12b** could be observed at ^{1}H NMR δ: 5.94 (m, 1H), 5.65 (br d, $J=10.5$ Hz, 1H), 5.23 (s, 1H), 5.12 (s, 1H), 4.68 (1/2 ABq, $J=13.2$ Hz, 1H), 4.59 (1/2 ABq, $J=13.2$ Hz, 1H), 3.87 (m, 1H), 3.22 (m, 1H), 2.98 (m, 1H), 2.71 (dd, $J=4.1$, 14.9 Hz, 1H), 2.33 (m, 2H), 2.28 (m, 1H), 2.11 (s, 3H); ^{13}C NMR δ: 199.9, 170.7, 156.1, 141.2, 138.9, 126.5, 115.35, 97.9, 87.4, 66.6, 39.7, 38.6, 33.2, 30.1;

resonances for **12b** could be observed at δ: 170.7, 141.2, 135.40, 131.5, 115.4, 100.8, 99.8, 66.6, 40.1, 39.1, 34.1, 30.3, 27.0, 20.8. MS EI *m/e*: 434 ($M^+ - 2CO$), 406 ($M^+ - 3CO$), 378 ($M^+ - 4CO$), 350 ($M^+ - 5CO$), 322 ($M^+ - 6CO$). HRMS *m/e* for $C_{19}H_{16}Co_2O_8$ calcd ($M^+ - 2CO$) 433.9605, found 433.9636.

3.2.8. Hexacarbonyl[μ-η^4-(7-(3-acetoxypropen-2-yl)-cyclohept-1-en-3-yne)]dicobalt (13a) and hexacarbonyl [μ-η^4-(3-(3-acetoxypropen-2-yl)cyclohept-1-en-4-yne)]-dicobalt (13b). A solution of cycloheptenyne **1** (0.0524 g, 0.120 mmol) and 1-trimethylsilylallyl acetate (0.0384 g, 0.223 mmol) in CH_2Cl_2 (2.4 mL) at −10 °C was subjected to BF_3–OEt_2 (0.15 mL, 1.2 mmol) via the general procedure. The crude product was purified by flash chromatography (25:1 petroleum ether/Et_2O) to yield of **13a** and **13b** (0.0369 g, 65%) as *Z*/*E*-isomeric mixtures as a red-brown oil. IR (neat, KBr, cm^{-1}): 2926, 2089, 2047, 2016, 1760, 1673, 1217; **13a** ^1H NMR δ: 7.13 (d, J=6.8 Hz, 1H, *Z*-isomer) and 7.14 (d, J=12.3 Hz, 1H, *E*-isomer), 6.55 (d, J=9.9 Hz, 1H), 5.97 (dd, J=4.4, 10.0 Hz, 1H, *Z*-isomer) and 5.95 (dd, J=4.1, 9.9 Hz, 1H, *E*-isomer), 4.89 (apparent q, J=6.8 Hz, 1H, *Z*-isomer) and 5.41 (dt, J=12.3, 7.8 Hz, 1H, *E*-isomer), 3.28 (m, 1H), 3.12 (m, 1H), 2.40–2.50 (m, 1H), 2.34 (m, 1H), 2.19 (m, 1H), 2.15 (s, 3H, *Z*-isomer) and 2.13 (s, 3H, *E*-isomer), 1.86 (m, 1H), 1.73 (m, 1H); absorptions for **13b** could be observed at 5.67 (m, 1H), 5.56 (dt, J=12.5, 7.5 Hz, 1H, *E*-isomer) and 5.08 (apparent q, J=7.0 Hz, 1H, *Z*-isomer), 3.22 (m, 1H), 3.00 (m, 1H); ^{13}C NMR δ: 200.1, 168.4, 168.2, 139.3, 139.1, 137.2, 135.8, 126.9, 126.7, 112.3, 111.4, 98.3, 87.0, 41.3, 41.2, 34.1, 33.2, 30.9, 30.3, 30.1, 29.9, 20.9. MS EI *m/e*: 476 (M^+), 448 ($M^+ - 1CO$), 420 ($M^+ - 2CO$), 392 ($M^+ - 3CO$), 364 ($M^+ - 4CO$), 336 ($M^+ - 5CO$), 308 ($M^+ - 6CO$). HRMS *m/e* for $C_{18}H_{14}Co_2O_8$ calcd ($M^+ - 2CO$) 419.9449, found 419.9455.

3.2.9. Hexacarbonyl[μ-η^4-(2-cyclohep-2-en-4-ynyl-1-phenylethanone)]dicobalt (16a) and hexacarbonyl-[μ-η^4-(2-cyclohept-2-en-6-ynyl-1-phenylethanone)]-dicobalt (16b). A solution of cycloheptenyne **1** (0.0592 g, 0.135 mmol) and 1-phenyl-1-(trimethylsiloxy)ethane (0.0519 g, 0.270 mmol) in CH_2Cl_2 (6 mL) at −10 °C was subjected to BF_3–OEt_2 (0.17 mL, 1.3 mmol) via the general procedure. The crude product was purified by flash chromatography (25:1 petroleum ether/Et_2O) to yield **16a**+**16b** (0.0496 g, 74%, 44:56 ratio) as a red-brown oil. Repeated TLC (10:1 petroleum ether/Et_2O) allowed sequential isolation of α-**16b** and γ-**16a**. Compound **16a**. IR (neat, KBr, cm^{-1}): 3018, 2927, 2089, 2047, 2017, 1683; ^1H NMR δ: 8.03 (d, J=7.8 Hz, 2H), 7.40–7.60 (m, 3H), 6.57 (dd, J=1.4, 9.8, Hz, 1H), 6.02 (dd, J=4.5, 9.8, Hz, 1H), 3.10–3.30 (m, 5H), 1.80–1.96 (m, 2H); ^{13}C NMR 199.8, 198.3, 138.7, 136.9, 133.3, 128.7, 128.0, 126.7, 97.8, 87.2, 44.0, 36.7, 32.9, 30.3. MS EI *m/e*: 468 ($M^+ - 1CO$), 440 ($M^+ - 2CO$), 412 ($M^+ - 3CO$), 384 ($M^+ - 4CO$), 356 ($M^+ - 5CO$), 328 ($M^+ - 6CO$). HRMS *m/e* for calcd ($M^+ - CO$) 467.9454, found 467.9445. Compound **16b**. IR (neat, KBr, cm^{-1}): 3022, 2930, 2089, 2046, 2014, 1688; ^1H NMR δ: 7.96 (d, J=7.8 Hz, 2H), 7.40–7.60 (m, 3H), 5.94 (m, 1H), 5.65 (dd, J=3.6, 9.8 Hz, 1H), 4.46 (m, 1H), 3.56 (dd, J=5.4, 17.3 Hz, 1H), 3.32 (dd, J=8.4, 17.3 Hz, 1H), 3.21 (m, 1H), 3.03 (m, 1H), 2.35–2.50 (m, 2H); ^{13}C NMR 199.9, 197.9, 136.7, 135.8, 133.3, 131.5, 128.7, 128.1, 100.3, 100.1, 45.7, 37.8, 34.0, 27.0. MS EI *m/e*: 496 (M^+), 468 ($M^+ - 1CO$), 440 ($M^+ - 2CO$), 412 ($M^+ - 3CO$), 384 ($M^+ - 4CO$), 356 ($M^+ - 5CO$), 328 ($M^+ - 6CO$). HRMS *m/e* for $C_{21}H_{14}Co_2O_7$ calcd (M^+) 495.9403, found 495.9401.

3.2.10. Hexacarbonyl[μ-η^4-(7-acetoxycyclohept-1-en-3-yne)]dicobalt (15a). A solution of cycloheptenyne **1** (0.0540 g, 0.124 mmol) and glacial acetic acid (0.0149 g, 0.248 mmol) in CH_2Cl_2 (2.5 mL) at −10 °C was subjected to BF_3–OEt_2 (0.16 mL, 1.3 mmol) via the general procedure. The crude product was purified by flash chromatography (10:1 petroleum ether/Et_2O) to yield the **15a** (0.0427 g, 79%) as a red-brown oil. IR (neat, KBr, cm^{-1}): 2923, 2850, 2092, 2051, 2021, 1740, 1238; ^1H NMR δ: 6.68 (d, J=10.0 Hz, 1H), 6.06 (dd, J=4.6, 10.0 Hz, 1H), 5.48 (m, 1H), 3.30 (m, 1H), 3.22 (m, 1H), 2.12 (m, 1H), 2.09 (s, 3H), 2.00 (m, 1H); ^{13}C NMR δ: 199.4, 170.0, 133.2, 128.6, 96.6, 85.0, 72.4, 30.3, 30.1, 21.0. MS EI *m/e*: 436 (M^+), 408 ($M^+ - 1CO$), 380 ($M^+ - 2CO$), 352 ($M^+ - 3CO$), 324 ($M^+ - 4CO$), 296 ($M^+ - 5CO$), 268 ($M^+ - 6CO$). HRMS *m/e* for $C_{15}H_{10}Co_2O_8$ calcd (M^+) 435.9040, found 435.9012.

H_2SO_4 conditions. To a solution of cycloheptyne **1** (0.1681 g, 0.386 mmol) in acetic acid (5 mL) was added H_2SO_4 (5 drops). The solution was stirred 1 h, at which point $NH_4Cl_{(aq)}$ was added and the mixture subjected to a conventional extractive workup. Flash chromatography as described above afforded **15a** (0.1631 g, 97%).

3.2.11. Hexacarbonyl[μ-η^4-(7-methoxy-cyclohept-1-en-3-yne)]dicobalt (Co–Co) (17a). A solution of cycloheptenyne **1** (0.0623 g, 0.143 mmol) and methanol (7.0 μL, 0.17 mmol) in CH_2Cl_2 (2.9 mL) at −10 °C was subjected to BF_3–OEt_2 (0.18 mL, 1.4 mmol) via the general procedure. The crude product was purified by flash chromatography (10:1 petroleum ether/Et_2O) to yield the **17a** (0.0379 g, 65%) as a red-brown oil. IR (neat, KBr, cm^{-1}): 2923, 2090, 2048, 2017, 1615, 1430; ^1H NMR δ: 6.61 (d, J=10.0 Hz, 1H), 6.17 (dd, J=3.9, 10.0 Hz, 1H), 3.95 (m, 1H), 3.37 (s, 3H), 3.34 (m, 1H), 3.12 (m, 1H), 2.04 (m, 2H); ^{13}C NMR δ: 199.5, 136.6, 127.3, 97.2, 86.1, 79.8, 56.3, 30.8, 30.1. MS EI *m/e*: 408 (M^+), 380 ($M^+ - 1CO$), 352 ($M^+ - 2CO$), 324 ($M^+ - 3CO$), 296 ($M^+ - 4CO$), 268 ($M^+ - 5CO$), 240 ($M^+ - 6CO$). HRMS *m/e* for $C_{14}H_{10}Co_2O_7$ calcd (M^+) 407.9091, found 407.9080.

H_2SO_4 conditions. To a solution of cycloheptyne **1** (0.0540, 0.124 mmol) in MeOH (2 mL) and CH_2Cl_2 (2 mL) at 0 °C was added H_2SO_4 (2 drops). The ice bath was removed and the reaction stirred for 1 h. $NH_4Cl_{(aq)}$ was added and the reaction was subjected to a conventional workup. Flash chromatography as described above afforded **17a** (0.0442 g, 87%).

3.2.12. Hexacarbonyl[μ-η^4-(7-(2-chloroethoxy)-cyclohept-1-en-3-yne)]dicobalt (18a). A solution of cycloheptenyne **1** (0.0510 g, 0.117 mmol) and 2-chloroethanol (10.0 μL, 0.150 mmol) in CH_2Cl_2 (2.3 mL) at −10 °C was subjected to BF_3–OEt_2 (0.15 mL, 1.2 mmol) via the general procedure. The crude product was purified by flash chromatography (20:1 petroleum ether/Et_2O) to yield the **18a** (0.0315 g, 59%) as a red-brown oil. IR (neat, KBr, cm^{-1}): 2927, 2856, 2091, 2050, 2021, 1612; ^1H NMR δ: 6.63 (d, $J=9.9$ Hz, 1H), 6.16 (dd, $J=4.0$, 10.0 Hz, 1H), 4.13 (m, 1H), 3.78 (m, 2H), 3.62 (t, $J=5.9$ Hz, 2H), 3.36 (m, 1H), 3.14 (m, 1H), 2.06 (m, 2H); ^{13}C NMR δ: 199.6, 136.0, 127.8, 97.1, 85.8, 78.8, 68.9, 43.0, 30.6, 30.4. MS EI *m/e*: 456 (M^+), 400 (M^+-2CO), 372 (M^+-3CO), 344 (M^+-4CO), 316 (M^+-5CO), 288 (M^+-6CO). HRMS *m/e* for $C_{15}H_{11}ClCo_2O_7$ calcd (M^+) 455.8857, found 455.8841.

H_2SO_4 conditions. To a solution of cycloheptyne **1** (0.0858 g, 0.197 mmol) and 2-chloroethanol (1 mL) in CH_2Cl_2 (5 mL) at 0 °C was added H_2SO_4 (3 drops). The solution was stirred for 1 h, at which point $NH_4Cl_{(aq)}$ was added and a standard workup performed. Flash chromatography as above afforded **18a** (0.0679 g, 76%).

3.2.13. Hexacarbonyl[μ-η^4-(7-(4-chlorobut-2-enyloxy)-cyclohept-1-en-3-yne)]dicobalt (19a). A solution of cycloheptenyne **1** (0.0589 g, 0.135 mmol) and 4-chloro-2-buten-1-ol (0.022 g, 0.21 mmol) in CH_2Cl_2 (2.7 mL) at −10 °C was subjected to BF_3–OEt_2 (0.17 mL, 1.3 mmol) via the general procedure. The crude product was purified by flash chromatography (25:1 petroleum ether/Et_2O) to yield the **19a** (0.0440 g, 68%) as a red-brown oil. IR (neat, KBr, cm^{-1}): 2925, 2091, 2051, 2021, 1457, 1054; ^1H NMR δ: 6.65 (d, $J=10.0$ Hz, 1H), 6.15 (dd, $J=4.0$, 10.0 Hz, 1H), 5.76 (m, 2H), 4.18 (d, $J=5.7$ Hz, 2H), 4.12 (d, $J=7.4$ Hz, 2H), 4.10 (m, 1H), 3.34 (m, 1H), 3.12 (m, 1H), 2.04 (m, 2H); ^{13}C NMR δ: 199.7, 136.1, 131.0, 128.1, 127.9, 97.1, 85.9, 63.7, 48.6, 39.1, 30.6, 30.4. MS EI *m/e*: 482 (M^+), 454 (M^+-1CO), 426 (M^+-2CO), 398 (M^+-3CO), 370 (M^+-4CO), 342 (M^+-5CO), 314 (M^+-6CO). HRMS *m/e* for $C_{17}H_{13}ClCo_2O_7$ calcd (M^+) 481.9014, found 481.9001.

3.2.14. Hexacarbonyl[μ-η^4-(cyclohept-2-en-4-ynylacetamide)]dicobalt (20a). *H_2SO_4 conditions*. Concentrated sulfuric acid was added dropwise (3 drops) to a solution of cycloheptenyne **1** (0.0645 g, 0.148 mmol) in acetonitrile (5 mL). After 10 min aqueous sodium bicarbonate was added and a typical workup proceeded. The crude reaction product was purified by flash chromatography (1:2 petroleum ether/ethyl acetate) to yield **20a** (0.0546 g, 85%) as a red-brown oil. IR (neat, KBr, cm^{-1}) 2927, 2091, 2048, 2021, 1651, 1548, 1431; ^1H NMR δ: 6.66 (dd, $J=1.6$, 9.9 Hz, 1H), 6.17 (dd, $J=4.7$, 9.9 Hz, 1H), 5.48 (br d, $J=7.2$ Hz, 1H), 4.75 (m, 1H) 3.15–3.25 (m, 2H), 2.05 (m, 1H), 1.99 (s, 3H), 1.96 (m, 1H); ^{13}C NMR δ: 199.4, 168.9, 135.1, 128.1, 97.1, 85.5, 50.6, 31.1, 23.2. MS EI *m/e*: 435 (M^+), 407 (M^+-1CO), 379 (M^+-2CO), 351 (M^+-3CO), 323 (M^+-4CO), 295 (M^+-5CO), 267 (M^+-6CO). HRMS *m/e* for $C_{15}H_{11}Co_2NO_7$ calcd (M^+-CO) 406.9250, found 406.9242.

Acknowledgements

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Cobalt- and rhodium-catalyzed cross-coupling reaction of allylic ethers and halides with organometallic reagents

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Abstract—Reactions of 2-alkenyl methyl ether with phenyl, trimethylsilylmethyl, and allyl Grignard reagents in the presence of cobalt(II) complexes are discussed. The success of the reactions heavily depends on the combination of the substrate, ligand, and Grignard reagent. In the reaction of cinnamyl methyl ether, the formation of the linear coupling products predominates over that of the relevant branched products. In the cobalt-catalyzed allylation of allylic ethers, addition of a diphosphine ligand can change the regioselectivity, mainly providing the corresponding branched products. Rhodium complexes catalyze the reactions of allylic ethers and halides with allylmagnesium chloride and allylzinc bromide, respectively, in which the branched coupling product is the major product.

1. Introduction

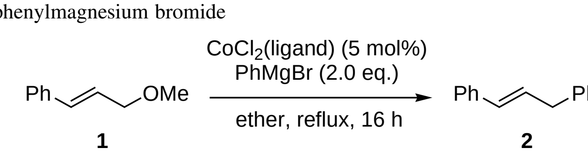
Palladium-, nickel-, and copper-catalyzed cross-coupling reactions of allylic substrates with organometallic reagents are recognized as one of the most useful reactions catalyzed by transition metals.[1] On the other hand, cobalt-catalyzed cross-coupling reactions of allylic substrates are quite rare.[2] We have been interested in cobalt-catalyzed cross-coupling reactions.[3] Here we report the reactions of allylic ethers with phenyl, trimethylsilylmethyl, and allyl Grignard reagents in the presence of cobalt complexes.[4] Rhodium-catalyzed coupling reactions are also disclosed herein.[5]

2. Results and discussions

2.1. Cobalt-catalyzed phenylation reaction of allylic ethers

The coupling reaction of cinnamyl methyl ether (**1**) with phenylmagnesium bromide was first performed (Table 1). A number of ligands were screened, and 1,5-bis(diphenylphosphino)pentane (DPPPEN) proved to be most effective for the phenylation reaction. 3,3-Diphenyl-1-propene was not detected at all. A small amount of β-methylstyrene was the only byproduct in each experiment, along with untouched **1**. The reaction of branched ether **3** with phenylmagnesium reagent under $CoCl_2$(dpppen) catalysis provided linear **2** selectively in good yield (Eq. 1). The regioselectivity of the phenylations suggests that the reactions proceed via a π-allylcobalt intermediate. The phenylation reaction of **1** at 25 °C decreased the yield of **2**. The choice of the solvent was essential to obtain **2** in satisfactory yield. A similar reaction in THF resulted in very low conversion of **1**.

Table 1. Cobalt-catalyzed reaction of cinnamyl methyl ether (**1**) with phenylmagnesium bromide



Entry	Ligand	Yield (%)
1	None	29
2	PPh_3 (10 mol%)	30
3	DPPM	24
4	DPPE	15
5	DPPP	27
6	DPPB	50
7	DPPPEN	72
8	DPPH	58

Ligands DPPM–DPPH represent $Ph_2P(CH_2)_nPPh_2$, $n=1$: DPPM; $n=2$: DPPE; $n=3$: DPPP; $n=4$: DPPB; $n=5$: DPPPEN; $n=6$: DPPH.

Keywords: Cross-coupling reaction; Cobalt; Grignard reagent; Rhodium; Allylzinc reagent.
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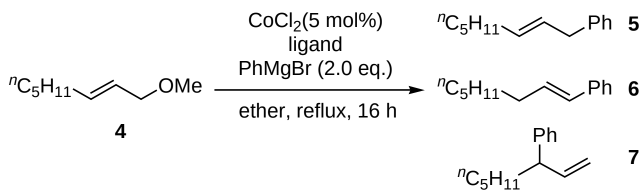
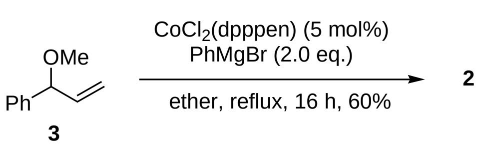
doi:10.1016/j.tet.2005.11.032

Table 2. Cobalt-catalyzed phenylation reaction of *trans*-2-octenyl methyl ether (**4**)

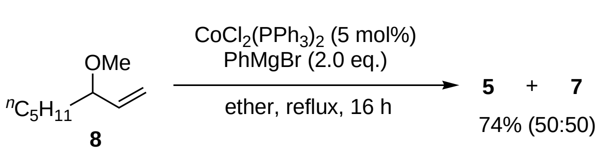


Entry	Ligand (amount)	Combined yield (%)	**5/6/7**
1	DPPPEN (5 mol%)	12	Not determined
2	None	47	58:10:32
3	DPPE (5 mol%)	32	10:53:37
4	PPh_3 (10 mol%)	78	36:7:57
5	$P(2\text{-}MeC_6H_4)_3$ (10 mol%)	39	66:<1:33
6	$P(4\text{-}MeC_6H_4)_3$ (10 mol%)	49	42:6:52
7	$P[3,5\text{-}(CF_3)_2C_6H_3]_3$ (10 mol%)	Trace	Not determined
8	$P(4\text{-}MeOC_6H_4)_3$ (10 mol%)	41	31:16:53

It is worth noting that treatment of cinnamyl bromide under similar conditions furnished a mixture of dimeric compounds such as 1,6-diphenyl-1,5-hexadiene and 3,4-diphenyl-1,5-hexadiene, in addition to a trace of **2**. The formation of the dimeric products implies that single electron transfer from a cobalt complex would yield cinnamyl radical that is destined to dimerize.[2a,c,d]

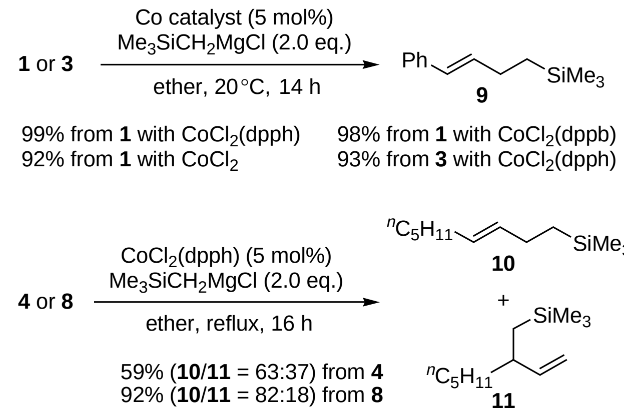

(1)

The cobalt-catalyzed phenylation reaction of *trans*-2-octenyl methyl ether (**4**) required triphenylphosphine as a ligand (Table 2, entry 4). A mixture of the corresponding coupling products **5**, **6**, and **7** was obtained. Under the reaction conditions, a part of **5** was transformed into **6**. In contrast to the reaction of **1**, the use of $CoCl_2$(dpppen) led to very poor conversion (entry 1). Without any phosphine ligand, coupling products were obtained in moderate combined yield (entry 2). Other monodentate phosphine ligands were inferior to triphenylphosphine (entries 5–8). Under $CoCl_2(PPh_3)_2$ catalysis, branched ether **8** was also converted into **5** and **7** (Eq. 2), in which no isomerization from **5** to **6** was observed.


(2)

2.2. Cobalt-catalyzed trimethylsilylmethylation reaction of allylic ethers

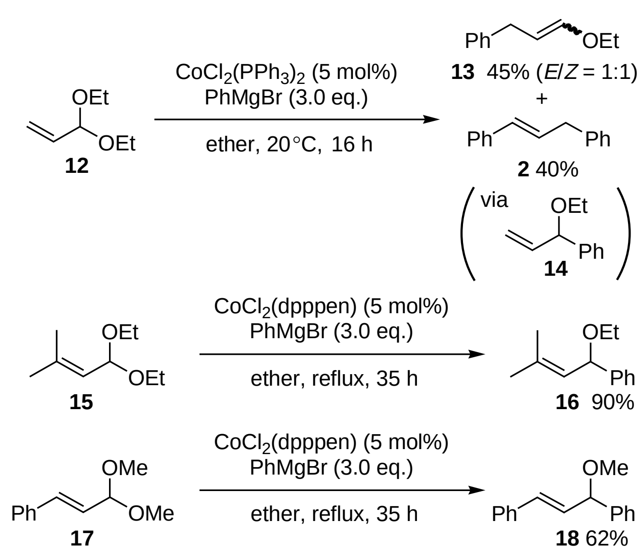
Cross-coupling reaction with Me_3SiCH_2MgCl proceeded much more smoothly than that with PhMgBr (Scheme 1). Treatment of **1** with Me_3SiCH_2MgCl in the presence of $CoCl_2$(dpph) for 14 h at 20 °C afforded the corresponding linear product **9** in 99% yield. Whereas the choice of the ligand was crucial to establish the phenylation, ligandless $CoCl_2$ and $CoCl_2$(dppb) also effected the allylation to afford **9** in 92 and 98% yields, respectively. Reactions of branched **3** with Me_3SiCH_2MgCl afforded **9** in excellent yield. On the other hand, alkyl-substituted allylic ethers **4** and **8** were converted into mixtures of regioisomers **10** and **11**. The reaction required a higher temperature to complete the reaction within a satisfactory reaction time. Trimethylsilylmethylation of branched ether **8** afforded a higher yield of **10** and **11** than that of **4**.



Scheme 1.

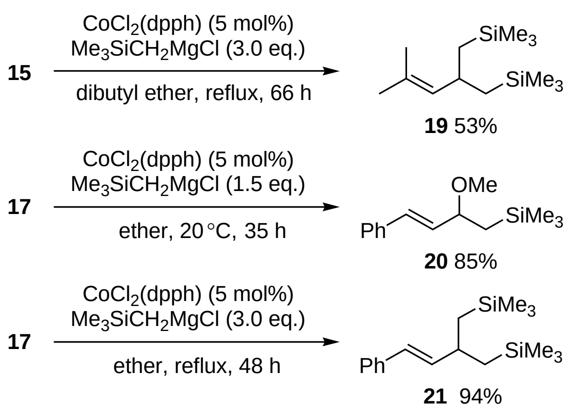
2.3. Cobalt-catalyzed reaction of α,β-unsaturated aldehyde dialkyl acetal

Treatment of acrolein diethyl acetal (**12**) with phenylmagnesium bromide in the presence of $CoCl_2(PPh_3)_2$ afforded a mixture of **2** and vinyl ether **13** (Scheme 2) Formation of doubly phenylated **2** would indicate a reaction path via the intermediate **14**. Monophenylation of acetals **15** and **17** having substituents at the terminal olefinic positions was successful under $CoCl_2$(dpppen) catalysis. The dimethyl and phenyl groups of **16** and **18** would interfere with further phenylation.



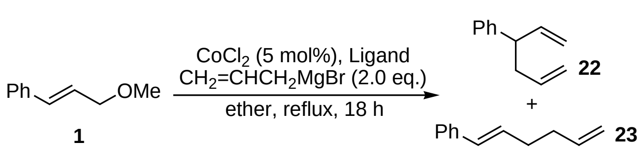
Scheme 2.

In contrast to the reaction with phenylmagnesium bromide, bis(trimethylsilylmethylation) occurred in the reaction of **15** with 3 equimolar amounts of Me_3SiCH_2MgCl in refluxing dibutyl ether (Scheme 3). Intriguingly, in the reaction of **17**, we could completely control the distribution of the product by changing the amount of the Grignard reagent and reaction time. The reaction with 1.5 equimolar amounts of Me_3SiCH_2MgCl at ambient temperature for 35 h afforded monosubstituted product **20** exclusively in 85% yield. On the other hand, treatment of **17** with 3 equimolar amounts of the Grignard reagent in refluxing ether for 48 h furnished doubly substituted product **21** in 94% yield.



Scheme 3.

Table 3. Cobalt-catalyzed coupling reaction of **1** with allylmagnesium bromide



Entry	Ligand	Yield (%)	**22/23**
1	None	78	<1:99
2	NBu_3	79	<1:99
3	TMEDA	75	<1:99
4	DPPE	57	51:49
5	DPPP	70	70:30
6	DPPB	54	19:81
7	DPPF	32	54:46

TMEDA and DPPF denote *N*,*N*,*N*′,*N*′-tetramethylethylenediamine and 1,1′-bis(diphenylphosphino)ferrocene, respectively.

2.4. Cobalt-catalyzed cross-coupling reaction of cinnamyl methyl ether with allyl Grignard reagent

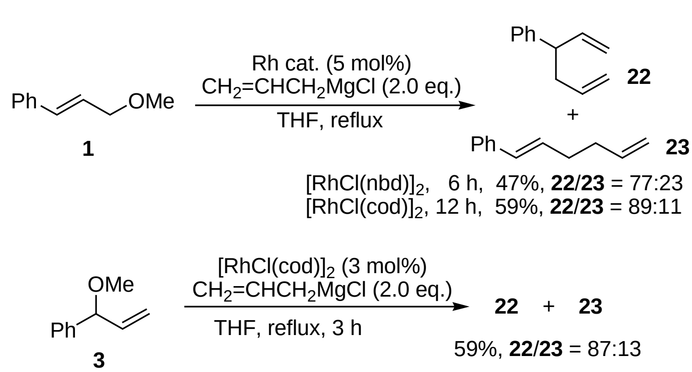
To extend the scope of the cobalt-catalyzed cross-coupling reactions, the allylation reaction of cinnamyl methyl ether was examined. The regioselectivity of the title reaction heavily depended on the ligand used (Table 3). Cobalt(II) chloride by itself catalyzed the cross-coupling to yield linear **23** exclusively (entry 1). Addition of amines as a ligand did not influence the regioselectivity (entries 2 and 3). Phosphine ligands allowed us to obtain significant amounts of branched **22**. Among them, DPPP exhibited the highest **22/23** selectivity, 70:30.

Judging from the results of Table 1, Scheme 1, and Table 3, trimethylsilylmethylmagnesium reagent proved to be the most reactive, and phenyl- and allylmagnesium reagents have similar reactivity. The low reactivity of allylmagnesium reagent may be due to the formation of π-allylcobalt that has less vacant coordination sites than phenyl- or trimethylsilylmethylcobalt has and that hence interacts weakly with the substrates at the initial oxidative addition stage.

The reactions of **1** and **3** with other Grignard reagents including vinylmagnesium bromide, methylmagnesium iodide, and alkynylmagnesium bromide failed to yield satisfactory amounts of the cross-coupling products.

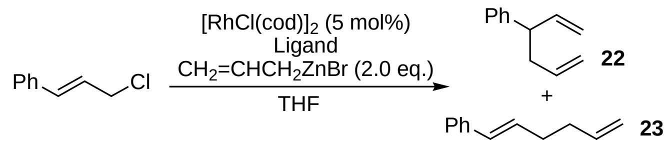
2.5. Rhodium-catalyzed cross-coupling reaction of allylic ethers with allylmagnesium reagents

Although the catalytic activity of rhodium is lower than that of cobalt, rhodium complexes also catalyzed allylation of **1** (Scheme 4). Treatment of **1** with allylmagnesium chloride in the presence of $[RhCl(nbd)]_2$ (NBD = norbornadiene) in refluxing THF yielded the corresponding dienes in 47% combined yield. The branched form **22** was mainly obtained, and the selectivity is opposite to that of cobalt-catalyzed allylation. The use of $[RhCl(cod)]_2$ (COD = 1,5-cyclooctadiene) instead of $[RhCl(nbd)]_2$ slightly improved the efficiency and selectivity of the reaction. Other rhodium complexes such as Wilkinson's catalyst and rhodium(III) acetylacetonate as well as an iridium complex $[IrCl(cod)]_2$ exhibited no catalytic activity. Branched ether **3** yielded **22** and **23** in good yield in a similar ratio under the $[RhCl(cod)]_2$ catalysis.



Scheme 4.

Table 4. Rhodium-catalyzed coupling reaction of cinnamyl chloride with allylzinc chloride



Entry	Ligand	Temperature (°C)	Time (h)	Yield (%)	**22/23**
1	None	−80	2	No reaction	—
2	None	−40	0.5	75	77:23
3	DPPB (10 mol%)	−40	2	Trace	—
4	PBu_3 (20 mol%)	−40	3	57	86:14
5	NEt_3 (20 mol%)	−40	2	70	83:17
6	NBu_3 (20 mol%)	−40	3.5	54	81:19
7	TMEDA (10 mol%)	−40	6.5	53	85:15
8	TMEDA (10 mol%)	−20	1.5	87	83:17
9	TMEDA (2.0 equiv to substrate)	−20	1.5	No reaction	—
10	$Me_2NCH_2NMe_2$ (10 mol%)	−20	1.5	73	87:13
11	$Me_2N(CH_2)_3NMe_2$ (10 mol%)	−20	1	62	84:16
12	2,2′-Bipyridyl (10 mol%)	−20	1	68	84:16
13	None, $CoCl_2$	−20	3	66	<1:99

2.6. Rhodium-catalyzed cross-coupling reaction of cinnamyl chloride with allylzinc reagents

Rhodium complexes also mediated the reaction of cinnamyl chloride with allylzinc bromide (Table 4). The reaction at −40 °C in the presence of $[RhCl(cod)]_2$ for 30 min furnished **22** and **23** in 75% yield in a ratio of 77:33 (entry 2). We screened many ligands to find that TMEDA is the best ligand with respect to the regioselectivity as well as the efficiency (entry 8). It is worth noting that a catalytic amount of diphosphine ligands such as DPPB (entry 3) and a stoichiometric amount of TMEDA (entry 9) completely inhibited the reaction. Interestingly, ligandless $CoCl_2$ effected the allylation to yield linear **23** exclusively (entry 13). An iridium complex $[IrCl(cod)]_2$ exhibited no catalytic activity.

3. Conclusion

The cobalt-catalyzed cross-coupling reaction with phenyl Grignard reagent proved to be a function of a substrate as well as of solvent and ligand. To attain high yields in the phenylation reaction, intensive tunings of variants are needed. In contrast, introduction of trimethylsilylmethyl group was facile and clean under cobalt catalysis. The reactions of cinnamyl methyl ether with both phenyl and trimethylsilylmethyl Grignard reagents yielded the corresponding linear products, irrespective of reaction conditions. The cross-coupling reactions of allylic ethers with allyl Grignard reagent with the aid of ligandless cobalt(II) chloride afforded the corresponding linear dienes. Interestingly, addition of DPPP could reverse the regioselectivity, leading to predominant formation of the branched dienes. Rhodium complexes catalyzed the reactions of allylic ethers and halides with allylmagnesium chloride and allylzinc bromide, respectively. Under rhodium catalysis, the branched coupling product was primarily formed. In both cobalt- and rhodium-catalyzed systems, π-allylmetal intermediates would be the key intermediates. The regioselectivity would depend on the ways how the carbon–carbon bonds are formed, that is, via the outer-sphere mechanism or the inner-sphere mechanism. The exact mechanism is not clear at this stage.

4. Experimental

4.1. Instrumental

^1H NMR (500 MHz) and ^{13}C NMR (125.7 MHz) spectra were taken on Varian UNITY INOVA 500 spectrometers unless otherwise noted. ^1H and ^{13}C NMR spectra were obtained in $CDCl_3$ with tetramethylsilane as an internal standard. Chemical shifts (δ) are in parts per million relative to tetramethylsilane at 0.00 ppm for ^1H and relative to $CDCl_3$ at 77.2 ppm for ^{13}C unless otherwise noted. IR spectra were determined on a SHIMADZU FTIR-8200PC spectrometer. Mass spectra were determined on a JEOL Mstation 700 spectrometer. TLC analyses were performed on commercial glass plates bearing 0.25-mm layer of Merck Silica gel $60F_{254}$. Silica gel (Wakogel 200 mesh) was used for column chromatography. The analyses were carried out at the Elemental Analysis Center of Kyoto University.

4.2. Material

Unless otherwise noted, materials obtained from commercial suppliers were used without further purification. THF and ether were purchased from Kanto Chemical Co., stored under nitrogen, and used as they are. The starting materials **1**, **3**, **4**, and **8** are prepared by the conventional Williamson ether synthesis.

4.3. General procedure for the cross-coupling reactions with Grignard reagents

The reaction of **1a** with trimethylsilylmethyl Grignard reagent is representative. Anhydrous $CoCl_2$ (7 mg, 0.05 mmol) was placed in a 50-mL two-necked flask and heated with a hair dryer in vacuo for 3 min. DPPH (27 mg, 0.06 mmol) and ether (1 mL) were sequentially added under argon. After the mixture was stirred for 30 min to obtain blue suspension, cinnamyl methyl ether (**1a**, 0.15 g, 1.0 mmol) and Me_3SiCH_2MgCl (1.0 M in ether, 2.0 mL, 2.0 mmol) were successively added to the reaction mixture at 0 °C. After being stirred for 14 h at 20 °C, the reaction mixture was poured into saturated NH_4Cl solution. The products were extracted with ethyl acetate (20 mL×3) and the combined organic layer was dried over sodium sulfate and concentrated. Silica gel column purification of the crude product provided **9** (0.20 g, 0.99 mmol) in 99% yield as colorless oil.

4.4. Rhodium-catalyzed cross-coupling reactions of cinnamyl chloride with allylzinc bromide

Zinc powder (2.94 g, 45 mmol) was placed in a 50-mL reaction flask under argon. THF (3.4 mL) was added. Chlorotrimethylsilane (0.1 mL, 0.8 mmol) and dibromoethane (0.1 mL, 2 mmol) were sequentially added at ambient temperature to activate zinc. After the mixture was stirred for 5 min, allyl bromide (2.6 mL, 30 mmol) in THF (24 mL) was added dropwise to the suspension with vigorous stirring over 15 min at 0 °C. The mixture was stirred for an additional 1 h at 25 °C. The gray supernatant liquid obtained was transferred to another flask filled with argon. The concentration of allylzinc bromide was determined by quantitative allylation reaction of an excess of benzaldehyde with allylzinc bromide prepared. The concentration was 0.87 M. $[RhCl(cod)]_2$ (25 mg, 0.05 mmol) was placed in another 50-mL two-necked flask under argon. THF (5 mL) and TMEDA (15 μL, 0.10 mmol) were successively added. The resulting solution was stirred for 5 min. Cinnamyl chloride (153 mg, 1.0 mmol, dissolved in 5 mL of THF) was added. The solution was cooled at −20 °C, and allylzinc bromide (0.87 M in THF, 2.3 mL, 2.0 mmol) was added. After being stirred for 1.5 h at −20 °C, the reaction mixture was poured into 1 M hydrochloric acid. The product was extracted with ethyl acetate (2×20 mL). The combined organic phase was dried over sodium sulfate. Evaporation followed by silica gel column purification afforded a mixture of **22** and **23** (137 mg, 0.87 mmol, 87% combined yield) in a ratio of 83:17.

4.5. Characterization data

The spectral data of the products **5**,[6] **6**,[6] **7**,[7] **13**,[8] **18**,[9] **22**,[10] and **23**[10] are found in the literature.

4.5.1. (*E*)-4-Trimethylsilyl-1-phenyl-1-butene (9). IR (neat) 3061, 2953, 2903, 1497, 1248, 962, 862, 837, 692 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.27–7.35 (m, 4H), 7.17–7.20 (m, 1H), 6.37 (d, J=16.0 Hz, 1H), 6.27 (dt, J=16.0, 6.5 Hz, 1H), 2.23 (ddt, J=10.0, 1.0, 6.5 Hz, 2H), 0.68–0.71 (m, 2H), −0.10 to 0.16 (m, 9H); ^{13}C NMR ($CDCl_3$) δ 137.98, 133.83, 128.45, 128.26, 126.66, 125.87, 27.39, 16.27, −1.59. Found: C, 76.27; H, 9.73%. Calcd for $C_{13}H_{20}Si$: C, 76.40; H, 9.86%.

4.5.2. (*E*)-1-(Trimethylsilyl)-3-nonene/3-(trimethylsilylmethyl)-1-octene (10/11=82:18). IR (neat) 2955, 2926, 1460, 1248, 968, 862, 835, 756, 691 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.52–5.59 (m, 0.18×1H), 5.35–5.46 (m, 0.82×2H), 4.91 (ddd, J=17.0, 2.0, 0.5 Hz, 0.18×1H), 4.87 (ddd, J=10.0, 2.0, 0.5 Hz, 0.18×1H), 2.05–2.13 (m, 0.18×1H), 1.95–2.02 (m, 0.82×4H), 1.23–1.37 (m, 0.82×6H+0.18×8H), 0.88 (t, J=7.0 Hz, 3H), 0.55–0.59 (m, 2H), −0.01 (s, 9H); ^{13}C NMR ($CDCl_3$). For major isomer, δ 113.03, 128.87, 32.48, 31.44, 29.35, 26.85, 22.57, 16.58, 14.08, −1.58. For minor isomer, δ 145.53, 112.56, 40.38, 38.55, 31.93, 23.26, 22.69, 14.12, −0.58. One of the sp^3-hybridized carbons of **11** could not been observed, probably due to overlapping. Found: C, 72.34; H, 12.94%. Calcd for $C_{12}H_{26}Si$: C, 72.69; H, 13.21%.

4.5.3. 1-Ethoxy-3-methyl-1-phenyl-2-butene (16). IR (neat) 2974, 2930, 1425, 1086, 756, 698 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.31–7.35 (m, 4H), 7.26–7.23 (m, 1H), 5.35 (d, J=9.0 Hz, 1H), 5.01 (d, J=9.0 Hz, 1H), 3.45–3.51 (m, 1H), 3.35–3.42 (m, 1H), 1.79 (s, 3H), 1.74 (s, 3H), 1.22 (t, J=6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 142.81, 134.99, 128.40, 127.19, 126.59, 126.43, 78.13, 63.39, 25.91, 18.40, 15.36. Found: C, 81.84; H, 9.54%. Calcd for $C_{13}H_{18}O$: C, 82.06; H, 9.54%.

4.5.4. 2-Methyl-5-trimethylsilyl-4-(trimethylsilylmethyl)-2-pentene (19). IR (neat) 2953, 2909, 1248, 837, 692 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.86 (d, J=10.0 Hz, 1H), 2.51–2.58 (m, 1H), 1.62 (s, 3H), 1.59 (s, 3H), 0.67 (dd, J=14.7, 5.3 Hz, 2H), 0.57 (dd, J=14.7, 8.5 Hz, 2H), −0.17 to 0.07 (m, 18H); ^{13}C NMR ($CDCl_3$) δ 134.73, 126.19, 30.41, 28.54, 25.63, 18.19, −0.72. Found: C, 64.59; H, 12.24%. Calcd for $C_{13}H_{30}Si_2$: C, 64.38; H, 12.47%.

4.5.5. (*E*)-3-Methoxy-4-trimethylsilyl-1-phenyl-1-butene (20). ^1H NMR (300 MHz, $CDCl_3$) δ 7.30–7.41 (m, 4H), 7.22–7.25 (m, 1H), 6.48 (d, J=15.9 Hz, 1H), 6.01 (dd, J=15.9, 8.4 Hz, 1H), 3.81 (q, J=7.8 Hz, 1H), 3.27 (s, 3H), 1.14 (dd, J=14.3, 6.8 Hz, 1H), 0.94 (dd, J=14.3, 7.7 Hz, 1H), 0.03 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 132.04, 131.15, 128.49, 127.51, 126.34, 106.68, 80.60, 55.72, 25.05, −0.62. Found: C, 71.79; H, 9.45%. Calcd for $C_{14}H_{22}OSi$: C, 71.73; H, 9.46%.

4.5.6. (*E*)-1-Phenyl-4-trimethylsilyl-3-(trimethylsilylmethyl)-1-butene (21). ^1H NMR (300 MHz, $CDCl_3$) δ 7.28–7.33 (m, 4H), 7.15–7.21 (m, 1H), 6.27 (d, J=15.6 Hz, 1H), 5.98 (dd, J=15.6, 9.0 Hz, 1H), 2.47–2.59 (m, 1H), 0.70–0.84 (m, 4H), −0.02 (s, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.22, 128.37, 126.61, 126.54, 125.82, 106.68, 36.42, 28.13, −0.41. Found: C, 70.21; H, 10.28%. Calcd for $C_{17}H_{30}Si_2$: C, 70.26; H, 10.41%.

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Application of tri- and tetrasubstituted alkene dipeptide mimetics to conformational studies of cyclic RGD peptides

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Abstract—The first application of a combination of novel ψ[(*E*)-CX=CX]-type alkene dipeptide isosteres to conformation studies of cyclic bioactive peptides was carried out (X = H or Me). For exploration of bioactive conformations of Kessler's cyclic RGD peptides, cyclo(-Arg-Gly-Asp-D-Phe-Val-) **1** and cyclo(-Arg-Gly-Asp-D-Phe-*N*-MeVal-) **2**, D-Phe-ψ[(*E*)-CX=CX]-L-Val-type dipeptide isosteres were utilized having di-, tri- and tetrasubstituted alkenes containing the γ-methylated isosteres that have been reported to be potential type II′ β-turn promoters. All of the (*E*)-alkene pseudopeptides **3–6** exhibited higher antagonistic potency against $\alpha_v\beta_3$ integrin than **1**, although potencies were slightly lower than **2**. Detailed structural analysis using ^{1}H NMR spectroscopy revealed that representative type II′ β/γ backbone arrangements proposed for **1**, were not observed in peptides **3–6**. Rather on the basis of ^{1}H NMR data, the conformations of peptides **3–6** were estimated to be more analogous to those of the *N*-methylated peptide **2**.

1. Introduction

Use of both natural and artificial modifications of bioactive peptides and proteins provides opportunities to better understand the basis for bioactivities of the parent structures and to find novel functionality that may be applied for new purposes.[1] Application of unnatural amino acids and peptidomimetics constitutes one of the most powerful methodologies in such chemical approaches to understanding ligand–protein interactions.[2] Among large numbers of mimetics, (*E*)-alkene dipeptide isosteres that are designed as nonpolar alkene replacements of planar amide moieties within dipeptides, have been widely applied to bio- and chemoactive peptides by us and others (Fig. 1).[3] Gellman et al. reported that Gly-ψ[(*E*)-CMe=CMe]-Gly-type isostere **D** is a potential β-hairpin promoter.[4] In addition, Wipf et al. have characterized D-Ala-ψ[(*E*)-CMe=CH]-L-Ala- and L-Ala-ψ[(*E*)-CCF_3=CH]-D-Ala-type isosteres such as **C** as promoting β-turn formation in the solid state due to $A^{1,2}$- and $A^{1,3}$-strain as opposed to L-Ala-ψ[(*E*)-CH=CH]-D-Ala-type motifs exemplified by **A** that have a disubstituted alkene.[5] These γ-methylated and γ-trifluoromethylated isosteres, which possess a carbon atom corresponding to a peptide bond carbonyl oxygen, are thought to be reasonable amide mimetics. Recent development of organocopper-mediated stereoselective synthesis of multi-substituted (*E*)-alkene isosteres[6] allowed us to utilize a combination of these isosteres for practical structure–activity relationship (SAR) studies on bioactive peptides.[5,6]

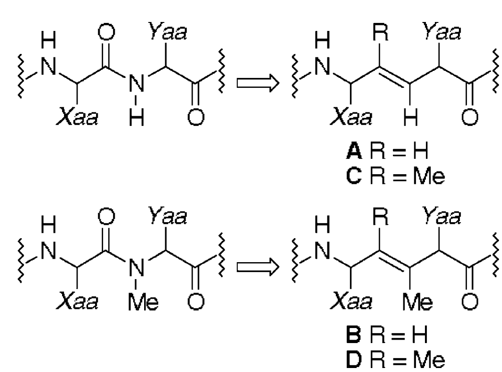

Figure 1. (*E*)-Alkene dipeptide isosteres having di-, tri- and tetrasubstituted alkenes; Xaa, Yaa = amino acid side chains.

As an exemplary application, we chose cyclic RGD peptides, cyclo(-Arg-Gly-Asp-D-Phe-Val-) **1**[7] and cyclo(-Arg-Gly-Asp-D-Phe-*N*-MeVal-) **2**,[8] which have

Keywords: (*E*)-Alkene dipeptide isostere; Cyclic RGD peptide; Integrin; Structure–activity relationship study.
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been shown to be highly potent and selective $\alpha_v\beta_3$ integrin antagonists (Fig. 2). It is well-known that $\alpha_v\beta_3$ integrin receptor and its ligands participate in many biological processes including tumor-induced angiogenesis and adhesion of osteoclasts to bone matrix and so on.[9] Peptide **1** was originally reported to adopt two distinctive secondary structures in DMSO solution; a type II′ β-turn with D-Phe at the $i+1$ position and a γ-turn with Gly at the $i+1$ position.[10,11] These structures allow two principal pharmacophores consisting of an Arg guanidino group and an Asp carboxylic acid to be located in close proximity. Among cyclic peptides, **2** is the most potent $\alpha_v\beta_3$ antagonist reported so far. It has been found to exhibit considerable conformational flexibility in water, including interconversion of two inverse γ turns (γ_i turns) and a γ turn, that do not afford identical topology of two closely located pharmacophores as observed in **1**.[8] On the other hand, the binding structure of **2** with $\alpha_v\beta_3$ integrin, which was recently disclosed by a crystal structure analysis of the ligand–receptor complex, is somewhat different from that proposed by Kessler et al.[12] The ligand binding seems to induce a structural change of the ligand binding domains of $\alpha_v\beta_3$ intergin, as well as a conformation change of ligand itself. As a result, peptide **2** exhibits distorted backbone conformations in the binding state to some extent, as compared with its calculated free-state conformations. Meanwhile, addition of an *N*-methyl group to the Val residue apparently improves $\alpha_v\beta_3$ antagonistic activity and $\alpha_v\beta_3/\alpha_{IIb}\beta_3$ selectivity, while the effect of *N*-methylation on the conformation of peptides as a whole as well as on the topology of the pharmacophores, especially in the neighbourhood of the D-Phe-Val/MeVal peptide bond, have not been discussed in detail. As such, it is difficult to rationalize structural and biological effects of certain characteristic functional groups in spite of such extensive research.

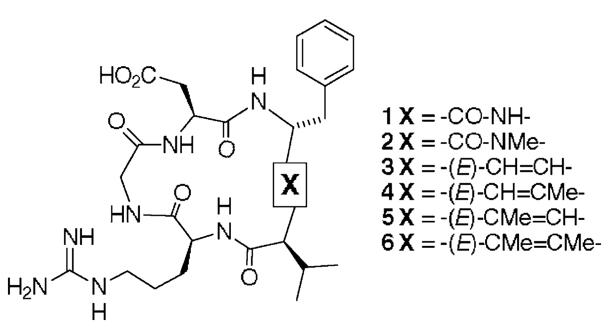


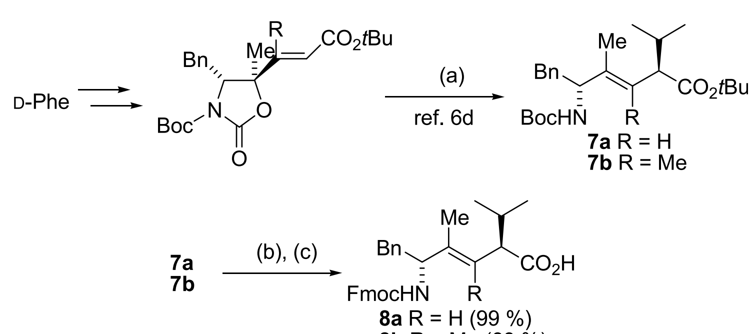
Figure 2. Structures of cyclic RGD peptides and peptidomimetics.

We recently reported the diastereoselective synthesis of γ-unmethylated D-Phe-ψ[(*E*)-CH=CX]-L-Val- and D-Phe-ψ[(*Z*)-CH=CMe]-L-Val-type alkene dipeptide isosteres (X=H or Me) with application to D-Phe-L-Val/*N*-MeVal moieties in peptides **1** and **2**.[6b] Both peptides **3** and **4** contain ψ[(*E*)-CH=CH]- and ψ[(*E*)-CH=CMe]-type isosteres, respectively, and exhibit potent antagonistic activity against $\alpha_v\beta_3$ integrin. In contrast, (*Z*)-congeners show extremely low $\alpha_v\beta_3$ and $\alpha_{IIb}\beta_3$ antagonist potency. This indicated that cis-conformation within the D-Phe-L-Val/*N*-MeVal peptide bond distorted the peptide bioactive conformations. On the other hand, slight differences between the potencies of **3** and **4**, which are independent of the presence of a β-methyl group in **4** that corresponds to an *N*-methyl group of **2**, support a conformational role for the *N*-methyl group of **2** beyond a simple steric one. To facilitate a deeper understanding of structure–activity relationships of cyclic RGD peptides, it was thought that utilization of highly functional β-turn promoters such as γ-methylated (*E*)-alkene isosteres, could be of value. Moreover, a D-Phe-ψ[(*E*)-CMe=CMe]-L-Val-type analogue could also be regarded as a D-Phe-L-*N*-MeVal dipeptide equivalent having reduced polarity, wherein the β- and γ-methyl groups could replicate allylic strain across peptide bonds between the D-Phe carbonyl oxygen and the *N*-MeVal side chain, as well as between the *N*-methyl group and the D-Phe side chain.[13] With this in mind, the synthesis and bio-evaluation of isostere-containing cyclic peptides **5** and **6** was undertaken, along with ^{1}H NMR conformational analysis and comparison with the previous peptides **1**–**4**. Reported herein are results of our application of γ-methylated alkene dipeptide isosteres to proposed type II′ β-turn motifs in bioactive peptides. We also examined the structure–activity effects of *N*-methylation of Val in cyclic RGD peptides using (*E*)-alkene isosteres having differential substitution motifs.

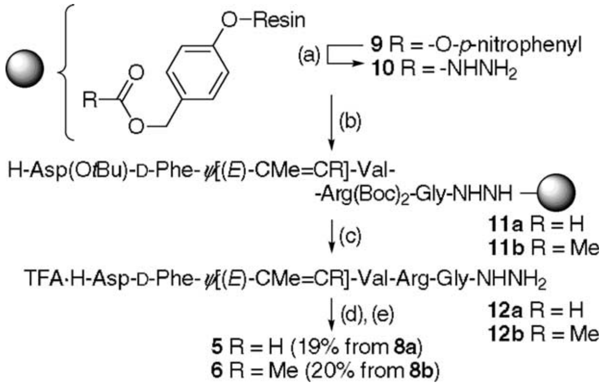
2. Results and discussion

2.1. Synthesis

Preparation of cyclic RGD peptides **5** and **6** that contain D-Phe-ψ[(*E*)-CMe=CH]-L-Val- and D-Phe-ψ[(*E*)-CMe=CMe]-L-Val-type alkene dipeptide isosteres, respectively, was performed according to the synthetic scheme utilized for the synthesis of peptide **4** (Schemes 1 and 2).[6b] In this process, a combination of Fmoc-based solid phase peptide synthesis (SPPS) and cyclization of linear peptide



Scheme 1. (a) Organocopper reagents; (b) TFA; (c) Fmoc-OSu, Et_3N.



Scheme 2. (a) $NH_2NH_2 \cdot H_2O$; (b) Fmoc-based SPPS; (c) TFA; (d) HCl, isoamyl nitrite; (e) iPr$_2$NEt.

hydrazides **12a**,**b** without side-chain protecting groups was employed by an adapted azide method in order to avoid olefinic isomerization, which would otherwise be possible during final deprotection by strong acid treatment in Boc-based synthesis. For side-chain protection, *tert*-butyl ester for Asp and (Boc)$_2$ for Arg were employed, both of which are amenable to mild acidic deprotection. TFA-treatment of the *N*-Boc-protected isosteres **7a**,**b**, which were obtained by regio- and stereoselective alkylation of β-(1,3-oxazolidin-2-one)-5-yl-α,β-enoates by organocopper reagents,[14] followed by Fmoc-reprotection, provided building blocks **8a**,**b** that were suitable for SPPS. Following the preparation of hydrazide linker **10** by treatment of *p*-nitrophenyl carbonate resin **9** with hydrazine hydrate in DMF, peptide chain elongation by Fmoc-based SPPS gave the expected protected peptide resins **11a**,**b**. Side chain deprotection and TFA-mediated cleavage from resins **11a**,**b** provided peptide hydrazides **12a**,**b**, which were subjected to successive azide formation and cyclization in highly diluted DMF solution.[15] The crude peptides were readily purified by reverse-phase HPLC to yield the expected cyclic peptides **5** and **6** in 19 and 20% yield, respectively, which were fully characterized by ^{1}H NMR and mass spectra.

2.2. Structure–activity relationships of cyclic RGD peptides and peptidomimetics

Integrin antagonistic activities of the resulting peptides **5** and **6** against $\alpha_v\beta_3$ and $\alpha_{IIb}\beta_3$ integrins were comparatively evaluated along with Kessler's RGD peptides **1** and **2**, and peptides **3** and **4** having γ-unmethylated D-Phe-ψ[(*E*)-CH=CX]-L-Val-type isosteres (X = H or Me). ELISA assays were performed using immobilized $\alpha_v\beta_3$ or $\alpha_{IIb}\beta_3$ integrin, according to the modified method of Kouns et al.[16] The results are shown in Table 1 as inhibition by peptides **1–6** of vitronectin or fibrinogen binding to the respective integrins ($n = 8$). Each of the isostere-containing peptides **3–6** showed strong $\alpha_v\beta_3$ integrin antagonistic activity within the range from $IC_{50} = 6.8$ nM for **1** to $IC_{50} = 1.4$ nM for **2**. It appeared that the amide or olefinic moiety in the D-Phe-Val/*N*-MeVal dipeptide portion of peptides **1–6** was not directly involved in recognition and binding to $\alpha_v\beta_3$ integrin. These data also support that *trans*-amide conformation within the D-Phe-Val/*N*-MeVal dipeptide was predominant in the bioactive conformations. This is consistent with a crystal structure analysis of an $\alpha_v\beta_3$ integrin–ligand complex[12] and our previous research using a combination of (*E*)- and (*Z*)-alkene dipeptide isosteres.[6b] Structure–activity relationship studies on cyclic RGD peptides investigating effects due to the *N*-methyl group of **2** using novel alkene dipeptide isosteres seemed to be highly appropriate.

It is noteworthy that only minimal differences were observed between the activities of peptides **3** and **5** having β-unmethylated isosteres and the respective β-methylated isostere-containing congeners **4** and **6**. In contrast, peptide **2**, having *N*-methyl valine, exhibited approximately five times higher potency than peptide **1**, similar to a previous report.[8] If *N*-methylation is potency-enhancing in **2**, then either peptide **4** or **6**, which possesses β-methyl group isosteric to the *N*-methyl group of **2**, could also show potencies superior to **3** or **5**, respectively. This unexpected result demonstrated that a conformational transformation from **1** to **2** and the resulting improvement of $\alpha_v\beta_3$ integrin antagonism depend on factors other than simple steric properties of the *N*-methyl group.

It was also found that peptides **5** and **6**, containing an isostere γ-methyl group, had slightly higher potency against $\alpha_v\beta_3$ integrin than the γ-unmethylated congeners **3** and **4**, respectively. Interestingly, in a crystal structure of peptide **2** complexed to $\alpha_v\beta_3$ integrin, the carbonyl oxygen of D-Phe, to which the isostere γ-methyl group corresponds, is not directly associated with any polar interactions with integrin, such as hydrogen bonding.[12] In light of this, the improved potencies of **5** and **6** may potentially be derived from steric interactions, including allylic strain induced by the γ-methyl group. Similarly, it could be surmised that D-Phe carbonyl oxygens of **1** and **2** could partially contribute to

Table 1. Integrin antagonistic activities of cyclic RGD peptides and peptidomimetics

Peptide	X	$\alpha_v\beta_3$		$\alpha_{IIb}\beta_3$		SI[a]
		IC_{50} (nM)[b]	Q[c]	IC_{50} (nM)[b]	Q[c]	
RGDS[d]	—	98 ± 29	14	270 ± 41	0.35	2.7
1	–CO–NH–	6.8 ± 2.7	1	770 ± 120	1	110
2	–CO–NMe–	1.4 ± 0.31	0.20	280 ± 42	0.36	200
3	–CH=CH–	3.6 ± 1.3	0.53	140 ± 18	0.19	40
4	–CH=CMe–	3.3 ± 0.93	0.48	100 ± 42	0.13	30
5	–CMe=CH–	2.4 ± 0.33	0.35	81 ± 18	0.11	34
6	–CMe=CMe–	1.8 ± 0.51	0.27	48 ± 11	0.06	26

[a] SI values were calculated as $SI = IC_{50}(\alpha_{IIb}\beta_3)/IC_{50}(\alpha_v\beta_3)$.
[b] The data for peptides **1–6** were obtained in comparative experiments using the same conditions.
[c] Q values were calculated as $Q = IC_{50}(\text{peptide})/IC_{50}(\mathbf{1})$.
[d] A linear peptide RGDS (H-Arg-Gly-Asp-Ser-OH) was used as a standard peptide.

appropriate dispositions of close functional groups, resulting in enhanced potencies.

In contrast, isostere-containing peptides **3–6** were less selective $\alpha_v\beta_3$ integrin antagonists than **1** or **2**, due to their relatively high potency against $\alpha_{IIb}\beta_3$ integrin. These increased potencies against $\alpha_{IIb}\beta_3$ integrin resulted from substituting the amide bonds of **1** and **2** with alkene isosteres, indicated that distinct functional groups derived from the olefinic moieties may be compatible with structural features of $\alpha_{IIb}\beta_3$ integrin. Other independent factors of RGD motifs displayed by the ligands may contribute to selectivity in interaction with the two integrins. However, we failed to ascertain what characteristics could be associated with selective recognition by the respective integrins. Locardi et al. revealed that the conformations of $\alpha_{IIb}\beta_3$ antagonists are different in the presence and absence of the receptor.[17] It is conceivable that the cyclic peptides may vary their shape by distinctive interactions in the binding state, even if the isostere moieties in **3–6** do not affect peptide conformations in the absence of the receptor.

2.3. Conformational aspects of cyclic peptidomimetics derived from ^{1}H NMR spectroscopy

Conformations of cyclic peptides have been intensively investigated using NMR spectroscopy and molecular dynamics calculations.[18] In structure–activity relationship studies on cyclic RGD peptides under 'conformational control', Kessler et al. reported that replacement at either the D-Phe or Val positions did not induce changes in backbone conformations.[10a] ^{1}H NMR parameters such as chemical shifts, temperature dependence of amide protons and ^3J-coupling constants support homogeneous families of cyclic peptide conformations. Based on similar concepts using alkene isosteres, we attempted to understand effects of the *N*-methyl groups or isostere β-methyl groups on conformations and their relationship to $\alpha_v\beta_3$ integrin antagonistic activity.[19]

In chemical shift data of peptides **1–6** in DMSO solution, downfield shifts of Arg H^N, Asp H^N, one Gly H^α (high field) and D-Phe H^α of peptides **2**, **4** and **6** that possess *N*-MeVal *N*-methyl groups or corresponding β-methyl groups, were comparable to those of **1**, **3** and **5**, respectively, (see the Supporting information). On the other hand, Gly H^N, Arg H^α, the other Gly H^α (low field) and Asp H^α of **2**, **4** and **6** were located at higher fields than those of **1**, **3** and **5**, respectively. For D-Phe H^N, no significant differences were found between **1** and **2**, while similar upfield shift correlations were observed among the isostere-containing peptides **3–6**. As such, the addition of a methyl group to the α-amino group of Val or to the isostere β-position, induced nearly equal chemical shift changes, although this may not necessarily indicate similar changes in peptide backbone conformation. These observations are in contrast to the fact that among peptides **2**, **4** and **6**, an increase in $\alpha_v\beta_3$ integrin antagonistic activity was observed only in **2**.

In a sharp contrast to effects on the chemical shifts of amide and α-protons, the vicinal coupling constants between amide protons and α-protons of each residue of peptides **1–6** displayed no common tendency due to *N*-methylation or β-methylation. If anything, the values of each residue were similar among all the peptides **1–6**. This revealed that methylation did not result in drastic ϕ angle changes.

Temperature coefficients often indicate solvent accessibility of amide protons.[18a] Kessler et al. previously reported that the temperature dependence of Arg H^N in cyclo(-Arg-Gly-Asp-D-Xaa^4-Val-) and cyclo(-Arg-Gly-Asp-D-Phe-Yaa^5-) is typically small, except in cases where cyclic amino acids such as proline are utilized for D-Xaa^4 and Yaa^5.[10a] This data supports solvent shielding of Arg H^N and indicates the presence of a hydrogen bond corresponding to a type II′ β-turn substructure. On the other hand, only a small coefficient for Gly H^N is observed in peptide **2**, although it has been reported that this has no relation to hydrogen bonding.[8] If anything, peptide **2** appeared to exhibit conformational flexibility around the Gly residues. We examined this parameter comparatively in peptides **1–6**, based on chemical shifts of amide protons in the range of 300–340 K (Table 2). Interestingly, among peptides **1–6**, a small coefficient for Arg H^N was observed in peptide **1** only, while the Gly H^N coefficients were small in the remaining peptides **2–6**. Coefficients of other residues in **2–6** were over 2.0 ppb/K, although these varied somewhat for residue among the peptides. Thus, temperature dependence tendencies of amide protons in isostere-containing peptides **3–6** appeared to be nearly identical with **2**, but different from **1**. These observations implied that the conformations of **3–6** may resemble one another in DMSO, and that these peptides may adopt flexible structures similar to **2**, rather than the representative type II′ β/γ arrangements seen with **1**.

Table 2. Temperature dependence of amide proton chemical shifts, $-\Delta\delta/\Delta T$ (ppb/K) of cyclic peptides **1–6**[a]

Peptide	Arg	Gly	Asp	D-Phe	Val
1	1.8	5.5	5.1	3.1	3.0
2	5.5	1.0	4.7	5.1	—
3	5.4	2.2	3.0	3.5	—
4	4.8	0.9	5.5	3.3	—
5	5.7	2.5	5.5	2.7	—
6	6.8	−1.4	7.4	2.5	—

[a] The data for peptides **1–6** were obtained in comparative experiments using the same conditions.

Taking into account combined biological and ^{1}H NMR data, it is evident that the lack of a Val amide hydrogen incurred by *N*-methylation in **2**, may have contributed to conformational changes that increased $\alpha_v\beta_3$ antagonistic activity. This was also observed with peptides **3–6** having alkene isosteres as well. In other words, the Val amide proton in **1** may contribute unfavorably to bioactive conformations likely through intramolecular interactions, although such an amide proton originating from the $i+2$ residue of a β-turn would be indispensable for the distinctive type II′ β/γ arrangement of cyclic pentapeptides. In contrast, it can be supposed that the carbonyl oxygen of D-Phe in **1** and **2** may be unrelated to significant interactions, since it has little apparent effect on conformation and bioactivity as compared to the amide proton of Val.

2.4. Structural calculations on cyclic peptidomimetics

To promote a better understanding of conformational aspects derived from ^{1}H NMR parameters, structural calculations of the cyclic peptides **1–6** were carried out by simulated annealing molecular dynamics/energy minimization using dihedral constraints derived from ^{1}H NMR vicinal coupling constants and NOE distance constraints.[20] These calculations afforded well-converged conformations. Interestingly, calculated low-energy backbone structures of **1–6** are highly similar to each other (see Supporting information). Backbone structures based on the five α-carbons showed nearly symmetrical pentagonal shapes. In all cases, the olefinic moieties and peptide bonds were found to be vertical to the cyclic peptide plane, although some exhibited slightly differential rotations. Of note, the proposed type II′ β/γ arrangement of **1** was not observed in either **2–6** or in **1** itself. This apparently reflects the fact that similar averaged parameters were used for structural calculations, as reported results by Nikiforovich et al.[11] This may indicate that it could be difficult to rationalize SAR studies on cyclic RGD peptides solely using structural calculation, unless the receptor-binding structures of ligands could be discussed. In practice, the presence of β- and/or γ-methyl groups in the isostere moiety appear to have little effect on the global backbone structures of the cyclic peptidomimetics, in spite of the fact that peptides **3–6** exhibited somewhat different bioactivities, respectively.

Ten superimposed low-energy structures of peptide **6** having the D-Phe-ψ[(*E*)-CMe=CMe]-L-Val-type isostere are depicted in Figure 3 as representative of the isostere-containing peptides **3–6**. Peptide **6** was the most potent $\alpha_v\beta_3$ integrin antagonist among **3–6**. The root mean square deviation (RMSD) value for all backbone heavy atoms of **6** was below 0.22 Å, and the total energy values of the refined structures were in the range of 102–108 kcal/mol. The olefinic plane of the isostere was perpendicular to the plane of the cyclic peptide. This is an ideal substructural component for a type II′ β-turn. In practice, the averaged dihedral ψ angle of D-Phe (−103.5°) and ϕ angle of Val (−92.9°), were highly consistent with theoretical β-turn values. However, the expected β-turn hydrogen bond between the amide hydrogen of Arg and the α-carbonyl oxygen of Asp could not be identified, since the peptide bonds of Asp-D-Phe and Val-Arg were also oriented perpendicular to the cyclic peptide plane. The torsional angles, D-Phe ϕ and Val ψ, were apparently different from

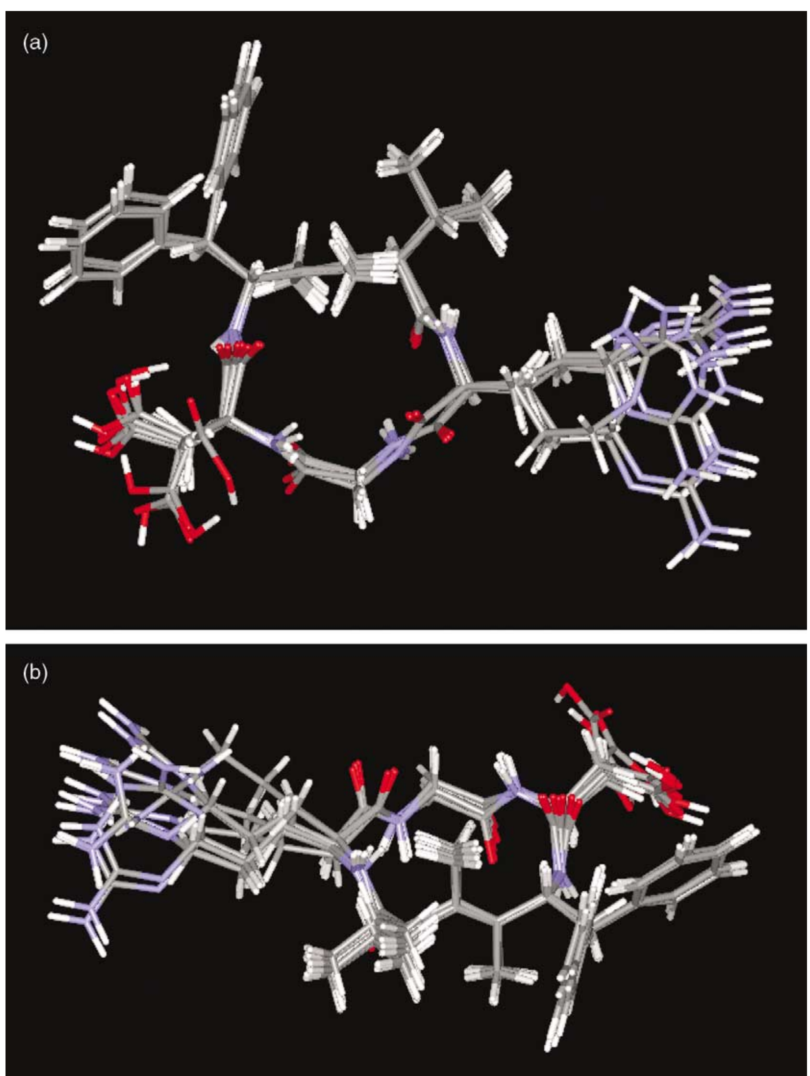


Figure 3. Overlay of ten low-energy structures of peptide **6**. (a) Top view. (b) Side view.

those typically associated with a β-turn. This allows the side chains of all residues to exhibit pseudoequatorial conformations as derived from the conformational analysis of the peptide **2**.[8] Additionally, all isostere carbonyl oxygens and γ-methyl groups were commonly directed away from side chains of neighboring residues, most probably to avoid 1,3-allylic strain across the peptide bonds. Similarly, isostere β-methyl groups were oriented upward so as to reduce steric interactions with D-Phe side chains. The averaged distance between the β-carbons of Arg and Asp of **6**, which provides topological orientation for two significant pharmacophores needed for bioactivity, was 9.0 Å. This distance was slightly longer than observed in **2**, which had previously been determined in aqueous solution.[8] These results indicated that the calculated conformation of **6** is more similar to that of the most potent peptide **2** having an *N*-methylvaline, rather than the proposed kinked conformation of **1**, which is based on a type II′ β/γ conformation.[21]

In $\alpha_v\beta_3$ integrin–ligand complexes, ligand **2** was reported to adopt a more distorted conformation as compared with structures in the absence of integrin.[12] In addition, it has been shown recently that cyclic RGD peptide ligands vary in conformations in the presence of integrins.[17,23] Thus, it may be of significance to discuss the effects of the D-Phe-L-Val/*N*-MeVal moieties in **1–6** from the viewpoint of receptor-binding conformations, even if these moieties do not interact directly with the $\alpha_v\beta_3$ integrin in the crystal structure. Analyses of binding modes of **3–6** were not carried out. However, analogous conformations in the receptor-free state and the presence of common functional groups required for binding interactions, with the exception of the olefinic moiety, could enable an estimation of conformations of the most potent isostere-containing peptide **6** in the bound state. This presupposes that **6** can adhere to $\alpha_v\beta_3$ integrin in a manner conformationally similar to **2**.

3. Conclusion

In conclusion, SAR studies on cyclic RGD peptides were conducted using novel alkene dipeptide isosteres. Cyclic peptides **5** and **6**, having D-Phe-ψ[(*E*)-CMe=CH]-L-Val- and D-Phe-ψ[(*E*)-CMe=CMe]-L-Val-type isosteres were designed and synthesized in order to investigate effects of the type II′ β/γ arrangement found in **1** as well as the role of the *N*-methyl group of *N*-MeVal in **2** on conformation and biological activity. Evaluation of the biological activities of **1–6** against $\alpha_v\beta_3$ and $\alpha_{IIb}\beta_3$ integrin demonstrated that loss of the amide proton of Val in **1** by *N*-methylation led to a remarkable increase in $\alpha_v\beta_3$ antagonistic activity of **2**, though this was not apparently due to steric factors arising from the methyl group. Structural analysis showed that γ-methylated isostere moieties would not be expected to serve as β-turn promoters, at least in these cyclic pentapeptides. Nevertheless, the calculated conformations of isostere-containing peptides **3–6** appeared to be analogous to those reported for the most potent peptide **2** rather than for **1**. Taken together, these results indicate that influences of the *N*-methyl group on conformation and biological activity of **2** could be attributed mainly to loss of the amide hydrogen functionality in the D-Phe-*N*-MeVal moiety, as opposed to steric factors such as allylic strain induced by the methyl group.

With advances in genome science, development of efficient methodologies for the rational design of therapeutically relevant agents from natural ligands is an area of increasing importance. As presented herein, alkene isosteres having differential methyl-substitutions could serve as practical tools to derive information concerning pharmacophores and bioactive conformations of bio- and chemoactive peptides and proteins.

4. Experimental

4.1. General synthetic

^{1}H NMR spectra were recorded using a Bruker AC 300 or a Bruker AM 600 spectrometer at 300 or 600 MHz. Chemical shifts of the compounds measured in $CDCl_3$ are reported in parts per million downfield from internal Me_4Si (s= singlet, d= doublet, dd = double doublet, t= triplet, m= multiplet). Those of the compounds measured in DMSO-d_6 are calibrated to the solvent signal (2.50 ppm). Nominal (LRMS) and exact mass (HRMS) spectra were recorded on a JEOL JMS-01SG-2 or JMS-HX/HX 110A mass spectrometer. Optical rotations were measured with a Horiba high-sensitive polarimeter SEPA-200 (Kyoto, Japan). For flash chromatographies, silica gel 60H (silica gel for thin-layer chromatography, Merck) and Wakogel C-200 (silica gel for column chromatography) were employed. For HPLC separations, a Cosmosil 5C18-ARII analytical (4.6× 250 mm, flow rate 1 mL/min) column or a Cosmosil 5C18-ARII preparative (20×250 mm, flow rate 11 mL/min) column was employed, and eluting products were detected by UV at 220 nm. A solvent system consisting of 0.1% TFA solution (v/v, solvent A) and 0.1% TFA in MeCN (v/v, solvent B) were used for HPLC elution.

4.1.1. (2*R*,5*R*,3*E*)-5-(9-Fluorenylmethoxycarbonyl)-amino-2-isopropyl-4-methyl-6-phenylhex-3-enoic acid (Fmoc-D-Phe-ψ[(*E*)-CMe=CH]-L-Val-OH, 8a). After treatment of the ester **7a** (108 mg, 0.258 mmol) with TFA (5 mL) for 1.5 h at room temperature, concentration under reduced pressure gave an oily residue. To a stirred solution of the above residue in MeCN–H_2O (2/1, 2.25 mL) were added Et_3N (0.072 mL, 0.517 mmol) and a solution of Fmoc-OSu (91 mg, 0.271 mmol) in MeCN (1.5 mL) at 0 °C. After being stirred for 3 h, the mixture was acidified with 0.1 N HCl and was extracted with EtOAc. The extract was washed with 0.1 N HCl and brine, and dried over $MgSO_4$. Concentration under reduced presssure followed by flash chromatography over silica gel with *n*-hexane–EtOAc (2/1) gave the title compound **8a** (123 mg, 99% yield) as a colorless oil: $[\alpha]_D^{20}$ −16.6 (*c* 0.542 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 55 °C, TMS): δ 0.70 (d, *J*=6.7 Hz, 3H), 0.87 (d, *J*=6.6 Hz, 3H), 1.67 (s, 3H), 1.92 (m, 1H), 2.77–2.99 (m, 3H), 4.14 (t, *J*=6.6 Hz, 1H), 4.25–4.41 (m, 3H), 4.91 (m, 1H), 5.26 (d, *J*=10.1 Hz, 1H), 7.08 (d, *J*=6.9 Hz, 2H), 7.12–7.30 (m, 5H), 7.35 (t, *J*=7.4 Hz, 2H), 7.49 (m, 2H), 7.72 (d, *J*=7.5 Hz, 2H). LRMS (FAB), *m/z* 484 (MH^+), 392, 260, 191, 179, 164, 154, 149, 143, 136, 91, 57, 43. HRMS (FAB), *m/z* calcd for $C_{31}H_{34}NO_4$ (MH^+) 484.2488, found: 484.2477.

4.1.2. (2*R*,5*R*,3*E*)-5-(9-Fluorenylmethoxycarbonyl)-amino-2-isopropyl-3,4-dimethyl-6-phenylhex-3-enoic acid (Fmoc-D-Phe-ψ[(*E*)-CMe=CMe]-L-Val-OH, 8b). By use of a procedure similar to that described for the preparation of the Fmoc-amino acid **8a** from **7a**, the ester **7b** (138 mg, 0.319 mmol) was converted into the title compound **8b** (131 mg, 83% yield) as a colorless oil: $[\alpha]_D^{24}$ −70.9 (*c* 1.00 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 50 °C, TMS) δ 0.36 (m, 3H), 0.91 (d, *J*=6.4 Hz, 3H), 1.49 (m, 3H), 1.71 (d, *J*=1.4 Hz, 3H), 1.96 (m, 1H), 2.66 (m, 1H), 2.81 (m, 1H), 3.98 (m, 1H), 4.15 (t, *J*=6.4 Hz, 1H), 4.41 (m, 2H), 4.81 (br, 1H), 7.06 (br, 2H), 7.10–7.30 (m, 5H), 7.31–7.39 (m, 2H), 7.51 (m, 2H), 7.72 (m, 2H). LRMS (FAB), *m/z* 498 (MH^+, base peak), 452, 406, 391, 274, 191, 179, 149, 136, 91, 69, 57, 43. HRMS (FAB), *m/z* calcd for $C_{32}H_{36}NO_4$ (MH^+) 498.2644, found: 498.2641.

4.2. General procedure for assembly of the peptide chain

Protected peptide resins were manually constructed by Fmoc-based solid phase peptide synthesis. *t*Bu ester for Asp and $(Boc)_2$ for Arg were employed for side-chain protection. Fmoc-amino acids except for Fmoc-D-Phe-ψ[(*E*)-CMe=CX]-Val-OH (X=H or Me) were coupled using 5 equiv of reagents [Fmoc-amino acid, *N*,*N*′-diisopropylcarbodiimide (DIPCDI), and HOBt·H_2O] to free amino group (or hydrazino group) in DMF for 1.5 h. Fmoc deprotection was performed by 20% piperidine in DMF (2×1 min, 1×20 min).

4.2.1. H-Asp(O*t*Bu)-D-Phe-ψ[(*E*)-CMe=CH]-Val-Arg(Boc)$_2$-Gly-NHNHCO-Wang resin (11a). After treatment of *p*-nitrophenyl carbonate Wang resin **9** (0.93 mmol g^{-1}, 161 mg, 0.15 mmol) with NH_2NH_2·H_2O (0.046 mL, 0.75 mmol) in DMF (2 mL) at room temperature for 2 h, Gly and Arg$(Boc)_2$ residues were coupled by general coupling protocol. Fmoc-D-Phe-ψ[(*E*)-CMe=CH]-Val-OH **8a** (48.3 mg, 0.100 mmol) was incorporated by double treatment with DIPCDI (0.018 mL, 0.120 mmol) and HOBt·H_2O (0.015 mg, 0.100 mmol) for 1.5 h each. After capping of the remaining free amino group with Ac_2O–pyridine, Asp(O*t*Bu) residue was coupled by general coupling protocol to provide the title peptide resin **11a**.

4.2.2. H-Asp(O*t*Bu)-D-Phe-ψ[(*E*)-CMe=CMe]-Val-Arg(Boc)$_2$-Gly-NHNHCO-Wang resin (11b). By use of a procedure similar to that described for the preparation of the resin **11a**, the title resin **11b** was synthesized from *p*-nitrophenyl carbonate Wang resin **9** (0.15 mmol) and Fmoc-amino acid **8b** (60 mg, 0.121 mmol).

4.2.3. Cyclo[-Arg-Gly-Asp-D-Phe-ψ[(*E*)-CMe=CH]-Val-]·TFA (5). The protected peptide resin **11a** was treated with TFA for 1.5 h at room temperature. Removal of the resin followed by concentration under reduced pressure gave the colorless residue, which was purified by preparative HPLC (linear gradient of B in A, 15–20% over 45 min) to provide a peptide hydrazide **12a**. To a stirred solution of **12a** in DMF (12 mL) were added a solution of 4 M HCl in DMF (0.075 mL, 0.300 mmol) and isoamyl nitrite (0.013 mL, 0.100 mmol) at −40 °C, and the mixture was stirred for 30 min at −20 °C. After dilution of the mixture with precooled DMF (68 mL), *i*Pr_2NEt (0.174 mL, 1.00 mmol) was added at −40 °C, and the mixture was stirred for 24 h at −20 °C. Concentration under reduced pressure and purification by preparative HPLC (linear gradient of B in A, 20–25% over 30 min) to give the cyclic pseudopeptide **5** (13.1 mg, 19% yield from **8a**) as freeze-dried powder: $[\alpha]_D^{20}$ −59.4 (*c* 0.656 in H_2O); t_R= 33.4 min (linear gradient of B in A, 20–40% over 40 min); ^{1}H NMR (600 MHz, DMSO-d_6, 25 °C) δ 0.46 (d, *J*=6.6 Hz, 3H), 0.66 (d, *J*=6.6 Hz, 3H), 1.32–1.46 (m, 2H), 1.53 (m, 1H), 1.58 (s, 3H), 1.69 (m, 1H), 1.84 (m, 1H), 2.40 (dd, *J*=16.2, 6.7 Hz, 1H), 2.56 (t, *J*=9.1 Hz, 1H), 2.66 (dd, *J*=16.2, 7.8 Hz, 1H), 2.74 (dd, *J*=13.5, 9.7 Hz, 1H), 2.84 (dd, *J*=13.5, 5.8 Hz, 1H), 3.07 (m, 2H), 3.26 (dd, *J*=14.4, 4.2 Hz, 1H), 3.98 (dd, *J*=14.4, 6.8 Hz, 1H), 4.17 (m, 1H), 4.29 (m, 1H), 4.55 (m, 1H), 5.05 (d, *J*=9.4 Hz, 1H), 7.12–7.25 (m, 5H), 7.36 (d, *J*=8.3 Hz, 1H), 7.46 (m, 1H), 7.93–7.99 (m, 2H), 8.11 (d, *J*=8.3 Hz, 1H), 12.28 (br, 1H). LRMS (FAB), *m/z* 572 (MH^+), 185, 154, 137, 93. HRMS (FAB), *m/z* calcd for $C_{28}H_{42}N_7O_6$ (MH^+) 572.3197, found: 572.3208.

4.2.4. Cyclo[-Arg-Gly-Asp-D-Phe-ψ[(*E*)-CMe=CMe]-Val-]·TFA (6). By use of a procedure similar to that described for the preparation of the peptide **5** from the resin **11a**, the resin **11b** was converted into the title peptide **6** (16.9 mg, 20% yield): $[\alpha]_D^{22}$ −62.6 (*c* 0.846 in H_2O); t_R= 36.3 min (linear gradient of B in A, 20–40% over 40 min); ^{1}H NMR (600 MHz, DMSO-d_6, 25 °C) δ 0.26 (d, *J*=6.5 Hz, 3H), 0.80 (d, *J*=6.4 Hz, 3H), 1.33–1.49 (m, 5H), 1.71 (s, 3H), 1.72–1.81 (m, 2H), 1.86 (m, 1H), 2.43 (dd, *J*=16.5, 6.8 Hz, 1H), 2.70–2.79 (m, 3H), 2.84 (dd, *J*=13.3, 5.1 Hz, 1H), 3.07 (m, 2H), 3.27–3.32 (m, 1H), 3.86 (m, 1H), 3.91 (dd, *J*=14.4, 6.7 Hz, 1H), 4.52 (m, 1H), 4.92 (m, 1H), 7.10–7.22 (m, 5H), 7.29 (m, 1H), 7.50 (br, 1H), 7.56 (d, *J*= 6.9 Hz, 1H), 7.74 (d, *J*=7.4 Hz, 1H), 8.54 (d, *J*=8.2 Hz, 1H), 12.30 (br, 1H). LRMS (FAB), *m/z* 586 (MH^+), 154 (base peak), 93, 91, 87, 70. HRMS (FAB), *m/z* calcd for $C_{29}H_{44}N_7O_6$ (MH^+) 586.3353, found: 586.3368.

4.3. Integrin-binding assays

Compounds were evaluated for their inhibitory activities in $\alpha_v\beta_3$ and $\alpha_{IIb}\beta_3$-ELISA (enzyme linked immunosorbent assay). $\alpha_v\beta_3$ was purified from human placenta, using RGDSPK-sepharose CL-4B affinity chromatography, followed by mono Q ion exchange chromatography, according to Pytela's protocol.[24] $\alpha_{IIb}\beta_3$ was purified from human platelet by RGDSPK-sepharose CL-4B as well.[24] $\alpha_v\beta_3$ and $\alpha_{IIb}\beta_3$ binding assays were performed according to the modified method of Kouns et al.[16] EIA plates were coated with $\alpha_v\beta_3$ or $\alpha_{IIb}\beta_3$, and blocked with bovine serum albumin. In each reaction, a test sample in the reaction mixture (20 mM Tris–HCl, 150 mM NaCl, 1 mM $CaCl_2$, 1 mM $MgCl_2$, pH 7.4, 0.100 mL) including vitronectin or fibrinogen, was added to the receptor-coated plate and incubated for 4 h at 25 °C. Thereafter the ligand binding was measured using anti-vitronectin rabbit antibody and peroxidase-conjugated anti-rabbit IgG antibody for $\alpha_v\beta_3$, or peroxidase-conjugated anti-fibrinogen antibody for

$\alpha_{IIb}\beta_3$, and 2,2′-azino-bis(3-ethylbenzthiazoline-6-sulfonic acid) as the substrate of peroxidase. The IC_{50} values were determined from measurement of absorbance at 415 nm.

4.4. NMR spectroscopy

The peptide sample was dissolved in DMSO-d_6 at concentration of 5 mM. ^{1}H NMR spectra of the peptides were recorded at 300 K using a Bruker AM 600 spectrometer at 600 MHz ^{1}H frequency. The chemical shifts were referenced to the residual DMSO (2.50 ppm). The assignments of the proton resonances were completely achieved by use of ^{1}H–^{1}H COSY spectra. $^3J(H^N,H^\alpha)$ coupling constants were measured from one-dimensional spectra. The mixing time for the NOESY experiments was set at 200, 300 and 400 ms. NOESY spectra were composed of 2048 real points in the F2 dimension and 512 real points, which were zero-filled to 1024 points in the F1 dimension, with 32 scans per t1 increment. The cross-peak intensities were evaluated by relative build-up rates of the cross-peaks. For the examination of the temperature dependence of the amide protons, the spectra of all peptides were also recorded at the every 10 K in the range of 300–340 K.

4.5. Calculation of structures

The structure calculations were performed on a Silicon Graphics Origin 2000 workstation with the NMR-refine program within the Insight II/Discover package using the consistent valence force field (CVFF). The prochiralities of two γ-methyl protons of Val were assigned based on the $^3J(H^\alpha,H^\beta)$ and the different NOE intensities in the NOESY spectra. On the other hand, the pseudoatoms were defined for the methylene protons of Arg, Asp and D-Phe, prochiralities of which were not identified by ^{1}H NMR data. The restraints, in which the Gly α-methylene participated, were defined for the separate protons without definition of the prochiralities. The dihedral ϕ angle constraints were calculated based on the Karplus equation: $^3J(H^N,H^\alpha)=6.7\cos^2(\theta-60)-1.3\cos(\theta-60)+1.5$.[25] Lower and upper angle errors were set to 15°. The NOESY spectra with a mixing time of 200 ms were used for the estimation of the distance restraints between protons. The NOE intensities were classified into three categories (strong, medium and weak) based on the number of contour lines in the cross-peaks to define the upper-limit distance restraints (2.7, 3.5 and 5.0 Å, respectively). The upper-limit restraints were increased by 1.0 Å for the involved pseudoatoms. Lower bounds between nonbonded atoms were set to their van der Walls radii (1.8 Å). These restraints were included with force constants of 25–100 kcal mol^{-1} Å^{-2} for the distances and of 25–100 kcal mol^{-1} rad^{-2} for the dihedral angles. The 50 initial structures generated by the NMR refine program randomly were subjected to the simulated annealing calculations. Detailed protocols for the calculation are found in the Supporting information. The final minimization stage was achieved until the maximum derivative became less than 0.01 kcal mol^{-1} Å^{-2} by the steepest descents and conjugate gradients methods without any solvent matrix. The families of the preferred conformations were selected from the structures with energies not higher than 8 kcal mol^{-1} compared with the lowest energy.

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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.2005.11.033. ^{1}H NMR spectra for all new compounds; ^{1}H NMR data of **3–6**; protocols of structural calculations; calculated structures and averaged dihedral angles of **3–5**; and overlay of the representative structures of **3–6**.

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Regioselective electrophilic substitutions of fulvenes with ethyl glyoxylate and subsequent Diels–Alder reactions

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Abstract—Highly regioselective electrophilic substitution of fulvenes with ethyl glyoxylate, catalyzed by $EtAlCl_2$ or $Yb(OTf)_3$ was achieved. Subsequent Diels–Alder reaction of the adduct with various dienophiles provides an efficient protocol toward highly functionalized indane and tricyclo[5.2.1.0^{2,6}]dec-8-ene systems.

1. Introduction

For decades, Friedel–Crafts reactions of aromatic compounds have played important roles in organic synthesis.[1] Recent studies of electrophilic aromatic substitution with glyoxylate, catalyzed by $Yb(OTf)_3$ or chiral bisoxazoline–copper (II) complexes, expand the applications in chemical synthesis.[2] Fulvenes, the benzene counterpart with non-benzenoid aromaticity and high polarizability, usually have different reaction patterns with benzenes. Accordingly, very few examples of the Friedel–Crafts reactions of fulvenes with acyl chlorides have been reported.[3] Yet, to the best of our knowledge, there are no reports of the direct Friedel–Crafts (or Alder–ene) reactions of fulvenes with aldehydes. In conjunction with our continuing efforts in fulvene chemistry,[4] we reported herein a simple method for the direct Friedel–Craft reaction of fulvenes with glyoxylate and the subsequent regio- and stereoselective Diels–Alder cycloaddition. The sequence provides an efficient protocol toward the highly functional indane and tricyclo[5.2.1.0^{2,6}]-dec-8-ene system.

2. Results and discussion

2.1. Regioselective electrophilic substitutions of fulvenes with ethyl glyoxylate

Initially, a solution of 6,6-dimethylfulvene (**1a**) and ethyl glyoxylate in toluene was heated to reflux for 12 h, the reaction affording trace amounts of the hydroxyester (**2a**) with complex mixtures and decomposition materials (Table 1, entry 1). Although reaction under microwave condition was accelerated (3 vs 12 h), decomposition with complex mixtures was still observed. Reaction under ultrasonic conditions did not proceed for 2 days, and the starting compounds were recovered (Table 1, entry 3). In recent studies, Lewis acid-catalyzed Friedel–Crafts reaction of aromatic compounds and ethyl glyoxylate have been shown to accelerate the reaction and improve yield.[5] Accordingly, various Lewis acid catalysts were tested in the system (Table 1, entries 4–13). Among them, reaction with catalytic amounts of $EtAlCl_2$ in benzene gave the best result: 77% yield (Table 1, entry 12).[6] A series of fulvenes (**1b–1g**) were reacted with ethyl glyoxylate to give the corresponding hydroxyesters (**2b–2g**) (Table 1, entries 14–21). In most cases, $EtAlCl_2$ was the best catalyst. However, $Yb(OTf)_3$ was more efficient than $EtAlCl_2$ in the reaction of dimethylamino fulvene (**1b** or **1c**) and ethyl glyoxylate (Table 1, entries 14–17); the reaction afforded the two regioisomers **2b** and **2b′** in ca. 5:4 ratio. Interestingly, **2c** was obtained as one regioisomer. The regio-chemistry of these adducts was determined by NOE experiment, as depicted in the scheme, Table 2.

2.2. Diels–Alder reactions of adduct 2a

In order to expand the synthetic application of these hydroxyesterfulevenes, **2a** was used as a representative example for the Diels–Alder reaction with dienophiles, such as maleic anhydride and maleic imide.[7] Reaction of **2a** with maleic anhydride in refluxing benzene yielded 85% of **3a** and **3b** in a 6:1 isomeric ratio (Table 2, entry 1). In contrast

Keywords: Diels–Alder; Friedel–Craft; Fulvene; Cycloaddition; Catalysis.
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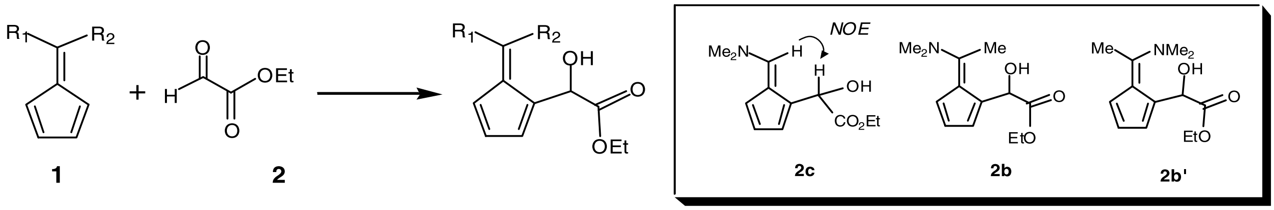
Table 1. Reactions of alkylfulvenes with ethyl glyoxylate



Entry	Fulvene	Condition	Temperature (°C)	Time (h)	Yield (%)[a]
1	**1a**. $R_1 = R_2 = Me$	Toluene	110	12	5
2	**1a**. $R_1 = R_2 = Me$	Toluene, µwave[b]	100	3	5
3	**1a**. $R_1 = R_2 = Me$	Toluene, ultrasound[c]	25	48	NR
4	**1a**. $R_1 = R_2 = Me$	Cat. BF_3–OEt_2, toluene	−78	0.2	2
5	**1a**. $R_1 = R_2 = Me$	Cat. $Yb(OTf)_3$, THF	25	1	0[d]
6	**1a**. $R_1 = R_2 = Me$	Cat. $Sc(OTf)_3$, toluene	25–60	0.5	18
7	**1a**. $R_1 = R_2 = Me$	Cat. $Sc(OTf)_3$, toluene, µwave[b]	110	0.5	48
8	**1a**. $R_1 = R_2 = Me$	Cat. $ZnCl_2$, THF	25	0.5	0[d]
9	**1a**. $R_1 = R_2 = Me$	Cat. $AlCl_3$, toluene	−30	0.5	0[d]
10	**1a**. $R_1 = R_2 = Me$	Cat. Me_2AlCl, toluene	25	8	20
11	**1a**. $R_1 = R_2 = Me$	Cat. $EtAlCl_2$, toluene	0–25	3	40
12	**1a**. $R_1 = R_2 = Me$	Cat. $EtAlCl_2$, benzene	0–25	1.5	77
13	**1a**. $R_1 = R_2 = Me$	Cat. $EtAlCl_2$, CH_2Cl_2	0–25	1.5	62
14	**1b**. $R_1 = NMe_2$; $R_2 = Me$	Cat. $EtAlCl_2$, benzene	0–25	3	22[e]
15	**1b**. $R_1 = NMe_2$; $R_2 = Me$	Cat. $Yb(OTf)_3$, THF	25	3	73[e]
16	**1c**. $R_1 = NMe_2$; $R_2 = H$	Cat. $EtAlCl_2$, benzene	0–25	3	5
17	**1c**. $R_1 = NMe_2$; $R_2 = H$	Cat. $Yb(OTf)_3$, THF	25	3	75
18	**1d**. $R_1 = R_2 = Et$	Cat. $EtAlCl_2$, benzene	0–25	1.5	72
19	**1e**. $R_1 = R_2 = n$-Pr	Cat. $EtAlCl_2$, benzene	0–25	1.5	75
20	**1f**. $R_1 = R_2 = -(CH_2)_4-$	Cat. $EtAlCl_2$, benzene	0–25	1.5	60
21	**1g**. $R_1 = R_2 = Ph$	Cat. $EtAlCl_2$, benzene	0–25	1.5	73

[a] Isolated yield of **2**.
[b] Performed using a Synthewave S402 Prolabo microwave reactor (300 W; monomode system; 10-mL reactors) operated at 60% power.
[c] Performed using an Elma Transsonic TP690-A operated at 35 kHz.
[d] Decomposed into a complicated mixture.
[e] Mixture of regioisomers (5:4).

Table 2. Reaction of fulvene **2a** with dienophiles

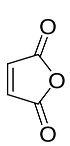
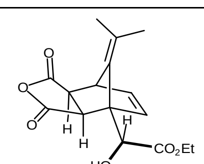
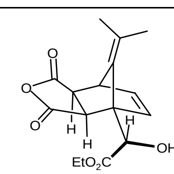
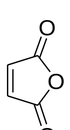
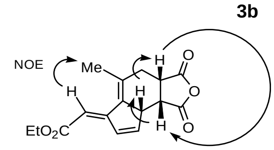
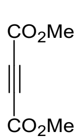
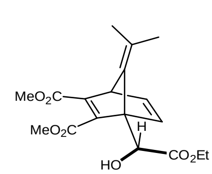
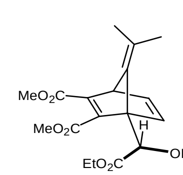
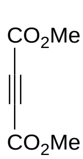
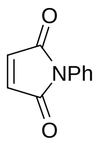
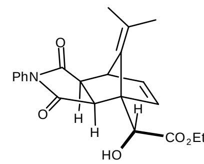
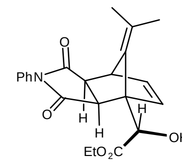
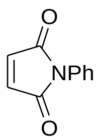
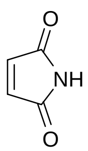
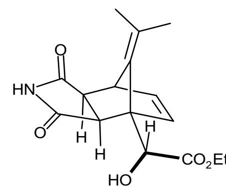
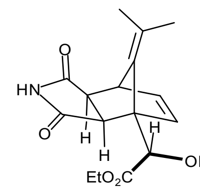
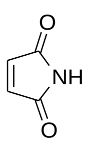
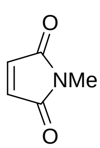
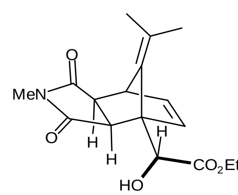
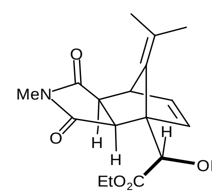
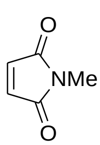
Entry	Dienophile	Reaction conditions	Temperature (°C)	Time (h)	Products	Yield (%)[a]
1		Benzene	80	8	 **3a**  **3b**	85 (6:1)[b]
2		Microwave, DMF[c]	130	0.5	 **5**	77[d]
3		Benzene	80	8	 **6a**  **6b**	83 (1.6:1)[b]
4		Microwave, toluene[c]	130	0.66		84 (2.1:1)[b]

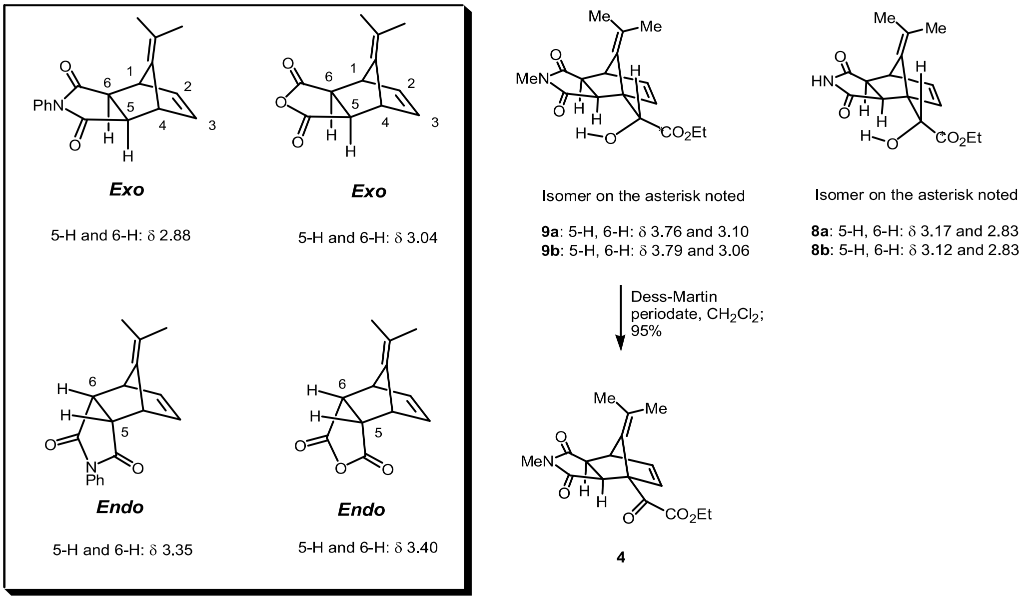
Table 2 (*continued*)

Entry	Dienophile	Reaction conditions	Temperature (°C)	Time (h)	Products	Yield (%)[a]
5		Benzene	80	8	 **7a**  **7b**	95 (1.7:1)[b]
6		Microwave, toluene[c]	130	0.66		93 (2.2:1)[b]
7		Benzene	80	5	 **8a**  **8b**	87 (1.3:1)[b]
8		Microwave, toluene[c]	130	0.66		92 (1.7:1)[b]
9		Benzene	80	5	 **9a**  **9b**	93 (1.9:1)[b]
10		Microwave, toluene[c]	130	1		85 (5:1)[b]

[a] Isolated yield.
[b] Ratio of isomers **a** and **b**.
[c] Performed using a Synthewave S402 Prolabo microwave reactor (300 W; monomode system; 10-mL reactors) operated at 60% power.
[d] Only one isomer observed.

to the *endo*-selectivity for the reaction of cyclopentadiene with maleic anhydride, reactions of 6,6-dimethylfulvene with *N*-phenylmaleic imide, maleic imide or maleic anhydride in toluene under reflux conditions have been reported to afford predominately the *exo*-adduct.[8] Thus, we suspected that the two diastereoisomers are both *exo* adducts that differ in the stereochemistry of their CH(OH)CO_2Et units. Our hypothesis is consistent with the results provided by ^{1}H NMR spectroscopy. In general, the *exo* and *endo* 6,6-dimethylfulvene adducts exhibit very different chemical shifts for their 5-H and 6-H protons (Scheme 1),[9] but our pair of isomers display very similar chemical shifts for these protons. We confirmed the epimeric nature of **9a** and **9b** unambiguously through their oxidation with the Dess–Martin periodate; both diastereoisomers gave the same ketoester (**4**) as a single isomer.

Reaction of **2a** with maleic anhydride under microwave conditions, however, afforded a different type of Diels–Alder adduct (**5**) (Table 2, entry 2). Maleic anhydride appears to add across the C-1 methyl and C-6 atom of fulvenes. The formation of **5** involves microwave-inducing isomerization of **2a** to 2-isopropenyl-cyclopenta-1,3-diene, followed by trapping with maleic anhydride via [4+2] cycloaddition.[10] The stereo- and regio-chemistry of **5** was determinate by NOE experiment, and the structure was concluded as depicted in entry 2 of Table 2. Reaction of **2a** with other dienophiles gave the corresponding Diels–Alder adduct (Table 2, entries 3–10). It is noted that reactions under microwave conditions not only facilitate the reaction rate but also increase the diastereoselectivity, especially in entry 10 of Table 2. The structure and stereochemistry of compound **7b**, the minor adduct, was



Scheme 1.

unambiguously assigned based on single crystal analysis (Fig. 1).[11]

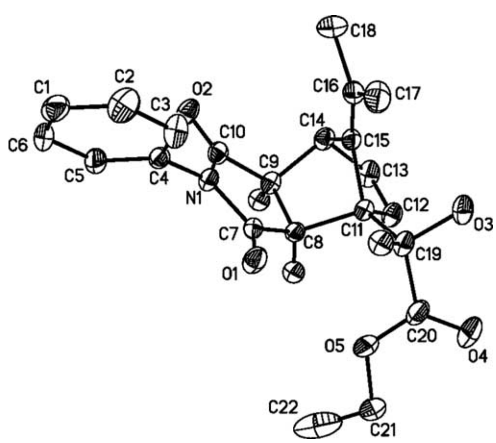
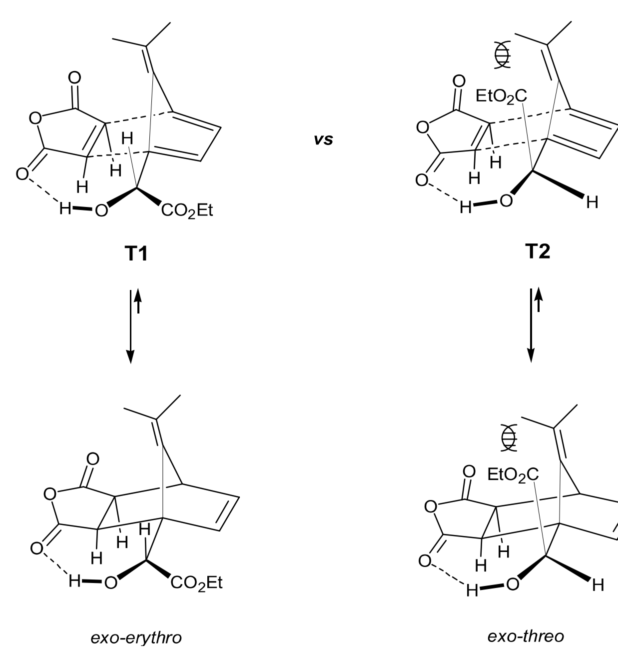


Figure 1. ORTEP plot for X-ray crystal structural of **7b**.

The Diels–Alder reaction of fulvene (**1a**) with maleic anhydride usually requires a few days to reach completion. In comparison, the reaction of **2a** with maleic anhydride is facile, presumably because of catalysis through intermolecular hydrogen bonding (Scheme 2). Such intermolecular hydrogen bonding not only facilitates the Diels–Alder reaction—acting as a Lewis acidic catalyst—but also plays a role in controlling the π-facial selectivity.[12] The observed periselectivity of the Diels–Alder reaction of **2a** with dienophiles may arise from the fact that the reaction favors the transition state T1 over T2 because of its lesser degree of steric hindrance (Scheme 2), that is, the α-ester group in transition state T2 is eclipsed with the bridging carbon–carbon bond.

3. Conclusion

In summary, we have demonstrated that the Friedel–Crafts reactions of fulvenes with ethyl glyoxylate occur with excellent regioselectivity when performed in the presence of catalytic amounts of either $EtAlCl_2$ or $Yb(OTf)_3$. In addition, the adducts obtained may be utilized in the construction of the frameworks of a number of natural products, such as those of the illudanes and FR182877. Further application of this methodology toward total synthesis of natural compounds is currently under investigation in our laboratory.



Scheme 2.

4. Experimental

4.1. General

All solvents were reagent grade. All chemicals were purchased from Aldrich Chemical Co. Reactions were normally carried out under argon atmosphere in flame-dried glassware. Merck silica gel 60 (particle size 0.04–0.063 mm) was employed for flash chromatography. HPLC was equipped with the ultraviolet and refractive index detectors. The sample was analyzed and/or separated on a Spherisorb-Si column (25 cm×10 mm, particle size 8 μ, pore size 60 Å) or a μ-Porasil column (25 cm×1.0 cm) using a flow rate of 5 mL/min and ultraviolet and refractive index detectors (ethyl acetate and hexane eluents). The flow rate of the indicated elution solvent is maintained at 5 or 1 mL/min, and the retention time of a compound is recorded accordingly. Melting points are uncorrected. Most compounds were characterized by full spectroscopic (^{1}H, ^{13}C, DEPT, HMQC, COSY, and NOESY) data. ^{1}H NMR, COSY and NOESY spectra were obtained in $CDCl_3$ unless otherwise noted at 400 MHz (Bruker DPX-400) or 500 MHz (Varian-Unity INOVA-500). ^{13}C NMR spectra, HMBC, HMQC and DEPT experiments were obtained at 100 or 125 MHz.

4.1.1. Representative procedure for the synthesis of hydroxyesterfulvene, hydroxy-(5-isopropylidene-cyclopenta-1,3-dienyl)-acetic acid ethyl ester (2a). To a solution of dimethylfulvene **1a** (27 mg, 0.25 mol) and ethyl glyoxylate (102 mg, 1.0 mmol) in dry benzene (1 mL) was added slowly a solution of ethylaluminum dichloride in C_6H_6 (0.05 mL, 1 M, 0.05 mmol) at 0 °C. The solution was stirred at 0 °C for 30 min and warm up slowly to 25 °C for 1.5 h. The reaction was quenched by the addition of H_2O (1.0 mL). The solution was extracted with EtOAc (25 mL), washed with brine, dried over Na_2SO_4 and concentrated in vacuo to give the crude product. The residue was purified by flash column chromatography with 25% EtOAc–hexane to give adduct **2a** (40 mg, 77% yield; R_f= 0.33 in 33% EtOAc–hexane) as a yellow oil. IR (neat): 3436, 2917, 1735, 1622, 1448, 1368, 1182, 1076, 829, 751 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.60 (dd, J=5.5, 1.5 Hz, 1H), 6.36 (s, 1H), 6.29 (dd, J=5.5, 2.5 Hz, 1H), 5.28 (s, 1H), 4.26–4.32 (m 2H), 2.37 (s, 3H), 2.28 (s, 3H), 1.30 (t, J=7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 173.9 (C), 152.6 (C), 139.6 (C), 132.5 (CH), 131.9 (C), 126.8 (CH), 124.2 (CH), 68.6 (CH), 61.7 (CH_2), 25.7 (CH_3), 22.9 (CH_3), 14.1 (CH_3); MS (m/z, relative intensity): 209 (M^++1, 12), 192 (13), 191 (100), 115 (75), 106 (21), 102 (42); exact mass calculate for $C_{12}H_{16}O_3$ (M^+): 208.1100; found 208.1091.

4.1.2. 5-(1-Dimethylamino-ethylidene)-cyclopenta-1,3-dienyl]-hydroxy-acetic acid ethyl ester (2b and 2b′). Prepared from **1b** according to procedure in Section 4.1.1. R_f=0.42 in 85% EtOAc–hexane, 73% yield, yellow oil; IR (neat): 3460, 2926, 1730, 1565, 1453, 1368, 1300, 1192, 1058, 1020, 916, 862, 803, 750 cm^{-1}; ^{1}H NMR (C_6D_6, 500 MHz): δ 6.90–6.54 (m, 3H), 5.49 (s, 1H), 4.02–3.89 (m, 2H), 2.32 (s, 6H), 1.74 (s, 3H), 0.87 (t, J=7.0 Hz, 3H); ^{13}C NMR (C_6D_6, 125 MHz, 5:4 ratio, *note minor product): δ 175.0 (C and C*), 157.5 (C and C*), 135.2 (C and C*), 132.3 (C and C*), 122.0 (CH), 121.1 (CH*), 119.0 (CH*), 118.5 (CH), 118.2 (CH*), 115.5 (CH), 71.0 (CH), 70.8 (CH*), 61.04 (CH_2), 61.01 (CH_2*), 42.73 ($2CH_3$), 42.70 ($2CH_3$*), 20.2 (CH_3*), 20.0 (CH_3), 14.2 (CH_3*), 14.1 (CH_3); MS (m/z, relative intensity): 237 (M^+, 1), 71 (15), 70 (10), 69 (16), 57 (43), 44 (31), 43 (100), 32 (17); exact mass calculate for $C_{13}H_{19}NO_3$ (M^+): 237.1366; found: 237.1362.

4.1.3. (5-Dimethylaminomethylene-cyclopenta-1,3-dienyl)-hydroxy-acetic acid ethyl ester (2c). Prepared from **1c** according to procedure in Section 4.1.1. R_f=0.47 in 60% EtOAc–hexane, 75% yield, yellow oil; IR (neat): 3433, 2922, 2857, 1728, 1621, 1452, 1387, 1323, 1197, 1101, 799, 735 cm^{-1}; ^{1}H NMR (C_6D_6, 500 MHz): δ 7.52 (s, 1H), 6.67 (dd, J=4.0, 2.5 Hz, 1H), 6.63 (s, 1H), 6.59 (dd, J=4.5, 1.5 Hz, 1H), 5.49 (s, 1H), 4.08–3.84 (m, 1H), 3.96–3.89 (m, 1H), 2.31 (s, 6H), 0.88 (t, J=7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 174.3 (C), 147.8 (CH), 130.7 (C), 121.6 (CH), 119.4 (CH), 116.6 (CH), 113.0 (C), 68.2 (CH), 61.5 (CH_2), 47.5 (CH_3), 40.3 (CH_3), 14.1 (CH_3); MS (m/z, relative intensity): 223 (M^+, 45), 150 (86), 149 (45), 122 (57), 121 (49), 77 (33), 44 (45) 43 (55), 42 (100), 32 (72); exact mass calculate for $C_{12}H_{17}NO_3$ (M^+): 223.1209; found: 223.1206.

4.1.4. [5-(1-Ethyl-propylidene)-cyclopenta-1,3-dienyl]-hydroxy-acetic acid ethyl ester (2d). Prepared from **1d** according to procedure in Section 4.1.1. R_f=0.51 in 33% EtOAc–hexane, 72% yield, yellow oil; IR (neat): 3473, 2971, 2936, 1735, 1616, 1368, 1182, 1463, 1371, 1300, 1201, 1063, 862, 764 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.55 (d, J=5.0 Hz, 1H), 6.32 (s, 1H), 6.27 (dd, J=5.0, 2.0 Hz, 1H), 5.20 (s, 1H), 4.29–4.21 (m, 2H), 2.90–2.85 (m, 1H), 2.64–2.60 (m, 1H), 2.55–2.49 (m, 2H), 1.27 (t, J= 7.0 Hz, 3H), 1.23–1.16 (m, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 173.9 (C), 163.9 (C), 138.5 (C), 132.5 (CH), 131.9 (C), 127.1 (CH), 124.2 (CH), 68.6 (CH), 61.6 (CH_2), 29.1 (CH_2), 26.4 (CH_2), 15.4 (CH_3), 14.09 (CH_3), 14.06 (CH_3); MS (m/z, relative intensity): 236 (M^+, 24), 218 (100), 164 (90), 163 (88), 145 (63), 144 (83), 107 (42), 77 (41), 43 (45), 41 (44); exact mass calculate for $C_{14}H_{20}O_3$ (M^+): 236.1413; found: 236.1411.

4.1.5. Hydroxy-[5-(1-propyl-butylidene)-cyclopenta-1,3-dienyl]-acetic acid ethyl ester (2e). Prepared from **1e** according to procedure in Section 4.1.1. R_f=0.67 in 33% EtOAc–hexane, 75% yield, yellow oil; IR (neat): 3503, 2960, 2932, 2871, 1733, 1613, 1456, 1368, 1206, 1058, 785, 758, 668 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.54 (dd, J=5.5, 1.5 Hz, 1H), 6.33 (s, 1H), 6.26 (dd, J=5.5, 2.5 Hz, 1H), 5.19 (s, 1H), 4.27–4.23 (m, 2H), 2.82–2.78 (m, 1H), 2.56–2.48 (m, 1H), 2.47–2.43 (m, 2H), 1.66–1.56 (m, 4H), 1.27 (t, J=7.0 Hz, 3H), 1.01 (t, J=7.5 Hz, 3H), 0.96 (t, J= 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 173.9 (C), 161.2 (C), 139.4 (C), 132.5 (CH), 132.0 (C), 126.9 (CH), 124.4 (CH), 68.6 (CH), 61.6 (CH_2), 38.7 (CH_2), 36.0 (CH_2), 24.2 (CH_2), 23.5 (CH_2), 14.6 (CH_3), 14.3 (CH_3), 14.1 (CH_3); MS (m/z, relative intensity): 264 (M^+, 24), 246 (62), 192 (100), 174 (60), 172 (74), 107 (45), 91 (45), 79 (35), 55 (41); exact mass calculate for $C_{16}H_{24}O_3$ (M^+): 264.1725; found: 264.1716.

4.1.6. Bicyclopentylidene-2,4-dien-2-yl-hydroxy-acetic acid ethyl ester (2f). Prepared from **1f** according to procedure in Section 4.1.1. R_f=0.47 in 33% EtOAc–hexane, 60% yield, yellow oil; IR (neat): 3462, 2932, 2857, 1735, 1447, 1372, 1213, 1025, 859, 754 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.48 (dd, J=5.5, 1.5 Hz, 1H), 6.39 (s, 1H), 6.28 (dd, J=5.5, 2.5 Hz, 1H), 5.26 (d, J=7.5 Hz, 1H), 4.28–4.23 (m, 2H), 2.78–2.76 (m, 2H), 2.69–2.64 (m, 2H), 1.79–1.74 (m, 4H), 1.68–1.65 (m, 2H), 1.28 (t, $J=7.0$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 173.9 (C), 161.4 (C), 136.4 (C), 133.5 (CH), 131.8 (C), 126.7 (CH), 123.8 (CH), 69.0 (CH), 61.7 (CH_2), 35.6 (CH_2), 33.3 (CH_2), 29.7 (CH_2), 28.8 (CH_2), 26.4 (CH_2), 14.2 (CH_3); MS (*m/z*, relative intensity): 248 (M^+, 26), 230 (36), 176 (93), 174 (100), 158 (47), 145 (57), 107 (33), 91 (48), 79 (39), 67 (31); exact mass calculate for $C_{15}H_{20}O_3$ (M^+): 248.1412; found: 248.1411.

4.1.7. (5-Benzhydrylidene-cyclopenta-1,3-dienyl)-hydroxy-acetic acid ethyl ester (2g). Prepared from **1g** according to procedure in Section 4.1.1. $R_f=0.46$ in 33% EtOAc–hexane, 73% yield, yellow oil; IR (neat): 3502, 3056, 2980, 1713, 1583, 1491, 1443, 1198, 1053, 700 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.43–7.32 (m, 8H), 7.29–7.22 (m, 2H), 6.66 (s, 1H), 6.41 (dd, $J=5.0$, 2.5 Hz, 1H), 6.17 (dd, $J=5.5$, 2.0 Hz, 1H), 4.26 (s, 1H), 4.12 (q, $J=7.0$ Hz, 2H), 2.73 (br s, 1H), 1.21 (t, $J=7.0$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 173.8 (C), 154.0 (C), 142.2 (C), 141.8 (C), 140.4 (C), 133.8 (2CH), 132.3 (2CH), 131.6 (C and CH), 129.2 (CH), 129.03 (CH), 128.96 (CH), 128.1 (CH), 127.9 (2CH), 127.6 (2CH), 66.5 (CH), 61.4 (CH_2), 14.0 (CH_3); MS (*m/z*, relative intensity): 332 (M^+, 13), 259 (100), 239 (11), 215 (24), 151 (10); exact mass calculate for $C_{22}H_{20}O_3$ (M^+): 332.1413; found: 332.1409.

4.1.8. Representative procedure for the conventional Diels–Alder reaction for the synthesis of hydroxy-(10-isopropylidene-3,5-dioxo-4-oxa-tricyclo[5.2.1.0^{2,6}]dec-8-en-1-yl)-acetic acid ethyl ester (3a and 3b). A solution of fulvene **2a** (30 mg, 0.14 mmol) and maleic anhydride (16 mg, 0.17 mmol) in benzene (2 mL) was heated to reflux for 8 h. The solution was concentrated in vacuo to give the residue as brown oil. The crude product was purified by flash column chromatography with 25% EtOAc–hexane (for **3a**: $R_f=0.38$ in 33% EtOAc–hexane; for **3b**: $R_f=0.37$ in 33% EtOAc–hexane) to give adduct **3a** (30 mg; 71%) and **3b** (6 mg; 14%) as the yellow oils. For **3a**: IR (neat): 3448, 2923, 1780, 1731, 1636, 1373, 1227, 1075, 1016, 926, 754 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.53 (dd, $J=6.0$, 3.5 Hz, 1H), 6.16 (d, $J=6.0$ Hz, 1H), 5.13 (s, 1H), 4.39–4.36 (m, 2H), 3.92 (dd, $J=2.0$, 1.0 Hz, 1H), 3.44 (d, $J=8.0$ Hz, 1H), 3.22 (br s, 1-OH), 3.10 (d, $J=8.0$ Hz, 1H), 1.74 (s, 3H), 1.64 (s, 3H), 1.35 (t, $J=7.0$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 173.1 (C), 170.6 (C), 169.4 (C), 138.9 (C), 138.3 (CH), 137.6 (CH), 119.5 (C), 67.6 (CH), 62.7 (CH_2), 59.7 (C), 51.0 (CH), 50.5 (CH), 48.5 (CH), 22.0 (CH_3), 18.9 (CH_3), 14.2 (CH_3). For **3b**: ^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.42 (d, $J=3.0$ Hz, 1H), 6.31 (d, $J=5.5$ Hz, 1H), 5.20 (s, 1H), 4.26–4.22 (m, 2H), 3.92 (s, 1H), 3.38 (d, $J=8.0$ Hz, 1H), 3.22 (br s, 1-OH), 3.08 (d, $J=9.0$ Hz, 1H), 1.74 (s, 3H), 1.63 (s, 3H), 1.35 (t, $J=7.0$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 172.3 (C), 170.1 (C), 169.4 (C), 138.6 (C), 138.0 (CH), 136.5 (CH), 119.3 (C), 68.1 (CH), 62.3 (CH_2), 60.7 (C), 50.5 (CH), 50.1 (CH), 49.1 (CH), 20.6 (CH_3), 18.9 (CH_3), 14.0 (CH_3); MS (*m/z*, relative intensity): 306 (M^+, 2), 191 (17), 190 (21), 136 (56), 135 (100); exact mass calculate for $C_{16}H_{18}O_6$ (M^+): 306.1103; found: 306.1108.

4.1.9. Representative procedure for the microwave condition for the synthesis of (5-methyl-1,3-dioxo-1,3,3a,4,8a,8b-hexahydro-indeno[4,5-*c*]furan-6-ylidene)-acetic acid ethyl ester (5). A mixture of fulvene **2** (30 mg, 0.14 mol) and maleic anhydride (16 mg, 0.17 mmol) in DMF (1 mL) were placed in a 10 mL quartz vial and subjected to programmed microwave irradiation at 180 W for 30 min. After a period of 2–3 min, the temperature reached a plateau of 130 °C where it remained throughout the reaction. After irradiation for 30 min and cooling, the solution was concentrated and the residue was purified by flash column chromatography with 45% EtOAc–hexane ($R_f=0.16$ in 33% EtOAc–hexane) to give adduct **5** as a yellow liquid (33 mg, 77% yield). IR (neat): 3416, 2926, 1777, 1701, 1603, 1378, 1237, 1209, 1150, 1016, 987, 930, 786, 757 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.65 (dd, $J=6.0$, 1.5 Hz, 1H), 6.61–6.64 (m, 1H), 5.91 (s, 1H), 4.20–4.14 (m, 2H), 3.65 (dd, $J=10.0$, 7.5 Hz, 1H), 3.54–3.49 (m, 1H), 3.35 (d, $J=7.5$ Hz, 1H), 2.77 (dd, $J=15.0$, 1.5 Hz, 1H), 2.56 (dd, $J=15.5$, 6.0 Hz, 1H), 2.13 (s, 3H), 1.28 (t, $J=7.0$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 173.4 (C), 169.7 (C), 166.8 (C), 153.5 (C), 139.3 (CH), 135.7 (C),134.3 (CH), 134.0 (C), 111.2 (CH), 60.00 (CH_2), 44.9 (CH), 42.5 (CH), 41.8 (CH), 34.3 (CH_2), 21.5 (CH_3), 14.3 (CH_3); MS (*m/z*, relative intensity): 288 (M^+, 4), 131 (20), 69 (36), 44 (100), 43 (64); exact mass calculate for $C_{16}H_{16}O_5$ (M^+): 288.0998; found: 288.1007.

4.1.10. *threo*-1-(Ethoxycarbonyl-hydroxy-methyl)-7-isopropylidene-bicyclo[2.2.1]hepta-2,5-diene-2,3-dicarboxylic acid diethyl ester (6a) and *erythro*-1-(ethoxycarbonyl-hydroxy-methyl)-7-isopropylidene-bicyclo-[2.2.1]hepta-2,5-diene-2,3-dicarboxylic acid diethyl ester (6b). Prepared from **2a** and dimethylacetylenedicarboxylate according to procedure in Section 4.1.8. For **6a**. $R_f=0.39$ in 33% EtOAc–hexane, 51% yield, yellow oil; IR (neat): 3472, 2952, 2920, 1717, 1626, 1435, 1371, 1285, 1214, 1123, 1097, 745 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.03–7.05 (m, 2H), 4.83 (d, $J=5.0$ Hz, 1H), 4.43 (s, 1H), 4.37 (d, $J=6.0$ Hz, 1H), 4.27 (q, $J=7.0$ Hz, 2H), 3.76 (s, 3H), 3.72 (s, 3H), 1.65 (s, 3H), 1.52 (s, 3H), 1.25 (t, $J=7.0$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 172.5 (C), 168.0 (C), 163.5 (C), 161.8 (C), 153.9 (C), 148.9 (C), 144.0 (CH), 142.2 (CH), 101.4 (C), 69.3 (C), 68.6 (CH), 62.0 (CH_2), 52.4 (2CH), 51.9 (CH_3), 21.0 (CH_3), 17.9 (CH_3), 13.9 (CH_3); MS (*m/z*, relative intensity): 350 (M^+, 15), 245 (100), 217 (81), 185 (44), 157 (51), 128 (59), 115 (56), 32 (30); exact mass calculate for $C_{18}H_{22}O_7$ (M^+): 350.1366; found: 350.1360. For **6b**: $R_f=0.31$ in 33% EtOAc–hexane, 32% yield, yellow oil; IR (neat): 3504, 2923, 1723, 1625, 1567, 1435, 1372, 1283, 1120, 1058, 940, 738 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.04–7.05 (m, 1H), 6.98 (d, $J=4.0$, 2.0 Hz, 1H), 5.05 (br s, 1H), 4.46 (d, $J=3.5$ Hz, 1H), 4.24 (q, $J=7.0$ Hz, 2H), 3.78 (s, 3H), 3.75 (s, 3H), 1.53 (s, 3H), 1.44 (s, 3H), 1.27 (t, $J=7.0$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 172.2 (C), 167.1 (C), 164.2 (C), 160.00 (C), 153.4 (C), 150.4 (C), 143.8 (CH), 141.3 (CH), 101.7 (C), 68.6 (CH), 68.1 (C), 61.9 (CH_2), 53.5 (CH), 52.3 (CH_3), 52.0 (CH_3), 20.8 (CH_3), 19.0 (CH_3), 14.0 (CH_3); MS (*m/z*, relative intensity): 350 (M^+, 15), 245 (100) 217 (81), 185 (44), 157 (51), 128 (59), 115 (56), 32 (30); exact mass calculate for $C_{18}H_{22}O_7$ (M^+): 350.1366; found: 350.1361.

4.1.11. *threo*-Hydroxy-(10-isopropylidene-3,5-dioxo-4-phenyl-4-aza-tricyclo[5.2.1.02,6]dec-8-en-1-yl)-acetic acid ethyl ester (7a) and *erythro*-hydroxy-(10-isopropylidene-3,5-dioxo-4-phenyl-4-aza-tricyclo[5.2.1.$0^{2,6}$]dec-8-en-1-yl)-acetic acid ethyl ester (7b). Prepared from **2a** and *N*-phenyl-maleimide according to procedure in Section 4.1.8. For **7a**: R_f=0.53 in 33% EtOAc–hexane, 60% yield, white solid; mp=130–134 °C; IR (neat): 3472, 2924, 1709, 1597, 1497, 1455, 1379, 1185, 740, 691 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.32–7.50 (m, 2H), 7.24 (s, 1H), 7.06 (d, J=7.5 Hz, 2H), 6.83 (d, J=6.0 Hz, 1H), 6.43 (s, 1H), 4.91 (s, 1H), 4.31–4.33 (m, 2H), 4.23 (s, 1H), 4.00 (s, 1H), 3.84 (d, J=8.0 Hz, 1H), 3.43–3.45 (m, 1H), 1.70 (s, 3H), 1.64 (s, 3H), 1.27 (t, J=7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 176.4 (C), 176.3 (C), 172.9 (C), 146.7 (C), 137.1 (CH), 133.9 (CH), 131.4 (C), 129.2 (2CH), 128.8 (CH), 126.5 (2CH), 113.2 (C), 68.3 (CH), 62.7 (CH_2), 59.9 (C), 46.7 (CH), 44.9 (CH), 44.8 (CH), 22.6 (CH_3), 18.5 (CH_3), 14.0 (CH_3); MS (*m/z*, relative intensity): 381 (M^+, 13), 317 (20), 308 (45), 191 (20), 135 (100), 91 (37), 77 (13), 32 (10); exact mass calculate for $C_{22}H_{23}NO_5$ (M^+): 381.1583; found: 381.1585. For **7b**: R_f=0.41 in 33% EtOAc–hexane, 35% yield, white solid; mp =132–136; IR (neat): 3491, 2924, 1707, 1497, 1379, 1186, 754 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.45–7.47 (m, 2H), 7.38 (d, J=7.5 Hz, 1H), 7.13 (d, J=7.5 Hz, 2H), 6.54 (dd, J=6.0, 3.5 Hz, 1H), 6.22 (d, J=6.0 Hz, 1H), 6.21 (d, J=2.0 Hz, 1H), 4.35–4.39 (m, 2H), 3.90 (d, J=3.0 Hz, 1H), 3.30 (d, J=7.5 Hz, 1H), 3.20 (s, 1H), 2.96 (d, J=7.5 Hz, 1H), 1.75 (s, 3H), 1.66 (s, 3H), 1.35 (t, J=7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 176.0 (C), 175.0 (C), 173.5 (C), 139.9 (C), 138.0 (CH), 137.6 (CH), 131.9 (C), 129.2 (CH), 128.9 (CH), 128.6 (CH), 126.9 (CH), 126.3 (CH), 117.9 (C), 68.1 (CH), 62.4 (CH_2), 59.5 (C), 50.0 (CH), 49.1 (CH), 48.1 (CH), 22.2 (CH_3), 19.2 (CH_3), 14.2 (CH_3); MS (*m/z*, relative intensity): 381 (M^+, 10), 317 (20), 308 (45), 135 (100), 117 (17), 91 (37); exact mass calculate for $C_{22}H_{23}NO_5$ (M^+): 381.1577; found: 381.1585.

4.1.12. *threo*-Hydroxy-(10-isopropylidene-3,5-dioxo-4-aza-tricyclo[5.2.1.$0^{2,6}$]dec-8-en-1-yl)- acetic acid ethyl ester (8a) and *erythro*-hydroxy-(10-isopropylidene-3,5-dioxo-4-aza-tricyclo[5.2.1.$0^{2,6}$]dec-8-en-1-yl)- acetic acid ethyl ester (8b). Prepared from **2a** and maleimide according to procedure in Section 4.1.8. For **8a**: R_f=0.36 in 60% EtOAc–hexane, 50% yield, yellow oil; IR (neat): 3306, 1709, 1186, 788, 756 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.77 (s, 1H), 6.49 (dd, J=6.0, 3.5 Hz, 1H), 6.13 (d, J=6.0 Hz, 1H), 5.17 (s, 1H), 4.31–4.41 (m, 2H), 3.80 (d, J=2.5 Hz, 1H), 3.20 (br s, 1-OH), 3.17 (d, J=7.5 Hz, 1H), 2.83 (d, J=7.0 Hz, 1H), 1.75 (s, 3H), 1.58 (s, 3H), 1.27 (t, J=7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 176.4 (C), 175.7 (C), 173.5 (C), 139.5 (C), 138.0 (CH), 137.4 (CH), 118.4 (C), 68.0 (CH), 62.4 (CH_2), 59.2 (C), 51.3 (CH), 50.2 (CH), 47.6 (CH), 22.1 (CH_3), 19.0 (CH_3), 14.2 (CH_3); MS (*m/z*, relative intensity): 305 (M^+, 2), 43 (100), 117 (16), 105 (13), 91 (40), 79 (12); exact mass calculate for $C_{16}H_{19}NO_5$ (M^+): 305.1264; found: 305.1255. For **8b**: R_f=0.33 in 60% EtOAc–hexane, 37% yield, yellow oil; IR (neat): 3208, 1710, 1186, 783, 761 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.82 (s, 1H), 6.39 (dd, J=9.0, 3.5 Hz, 1H), 6.32 (d, J=6.0 Hz, 1H), 5.20 (s, 1H), 4.22–4.26 (m, 2H), 3.82 (d, J=3.0 Hz, 1H), 3.12 (d, J=7.5 Hz, 1H), 2.83 (d, J=7.5 Hz, 1H), 1.62 (s, 3H), 1.61 (s, 3H), 1.25 (t, J=7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 177.0 (C), 176.4 (C), 172.1 (C), 139.1 (C), 138.2 (CH), 136.2 (CH), 118.3 (C), 68.8 (CH), 61.8 (CH_2), 60.2 (C), 50.5 (CH), 50.1 (CH), 47.9 (CH), 22.2 (CH_3), 20.4 (CH_3), 14.0 (CH_3); MS (*m/z*, relative intensity): 305 (M^+, 6), 198 (21), 191 (25), 149 (23), 135 (100), 117 (13), 91 (36), 57 (45), 43 (47), 41 (37), 32 (38), 31 (43) exact mass calculate for $C_{16}H_{19}NO_5$ (M^+): 305.1264; found: 305.1271.

4.1.13. *threo*-Hydroxy-(10-isopropylidene-4-methyl-3,5-dioxo-4-aza-tricyclo[5.2.1.02,6]dec-8-en-1-yl)-acetic acid ethyl ester (9a) and *erythro*-hydroxy-(10-isopropylidene-4-methyl-3,5-dioxo-4-aza-tricyclo[5.2.1.$0^{2,6}$]dec-8-en-1-yl)-acetic acid ethyl ester (9b). Prepared from **2a** and *N*-methyl-maleimide according to procedure in Section 4.1.8. For **9a**: R_f=0.36 in 50% EtOAc–hexane, 33% yield, yellow oil; IR (neat): 3460, 2924, 1696, 1343, 1379, 1292, 1132, 783 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.48 (dd, J=6.0, 3.0 Hz, 1H), 6.14 (d, J=6.0 Hz, 1H), 5.17 (s, 1H), 4.32–4.40 (m, 2H), 3.76 (d, J=3.0 Hz, 1H), 3.20 (br s, 1H), 3.10 (d, J=7.0 Hz, 1H), 2.90 (s, 3H), 2.79 (d, J=7.5 Hz, 1H), 1.65 (s, 3H), 1.54 (s, 3H), 1.35 (t, J=7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 177.0 (C), 176.2 (C), 173.6 (C), 139.6 (C), 137.8 (CH), 137.2 (CH), 118.1 (C), 68.1 (CH), 62.4 (CH_2), 59.3 (C), 50.00 (CH), 49.00 (CH), 47.7 (CH), 24.5 (CH_3), 21.9 (CH_3), 18.9 (CH_3); 14.2 (CH_3) MS (*m/z*, relative intensity): 319 (M^+, 7), 246 (22), 190 (44), 135 (100), 117 (18), 91 (36), 79 (10); exact mass calculate for $C_{17}H_{21}NO_5$ (M^+): 319.1420; found: 319.1418. For **9b**: R_f= 0.24 in 50% EtOAc–hexane, 63% yield, yellow oil; IR (neat): 3477, 2925, 1691, 1436, 1380, 1290, 1189, 1134, 794, 755 cm^{-1}; δ 6.38 (dd, J=6.0, 3.5 Hz, 1H), 6.32 (d, J=6.0 Hz, 1H), 5.19 (s, 1H), 4.21–4.25 (m, 2H), 3.79 (dd, J=2.5, 1.0 Hz, 1H), 3.06 (d, J=7.0 Hz, 1H), 2.91 (s, 3H), 2.78 (d, J=7.0 Hz, 1H), 1.56 (s, 3H), 1.54 (s, 3H), 1.24 (t, J=7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 177.5 (C), 177.1 (C), 172.1 (C), 139.3 (C), 138.1 (CH), 136.0 (CH), 118.0 (C), 68.8 (CH), 61.7 (CH_2), 60.3 (C), 49.3 (CH), 48.9 (CH), 48.0 (CH), 24.6 (CH_3), 22.1 (CH_3), 20.2 (CH_3), 14.0 (CH_3); MS (*m/z*, relative intensity): 319 (M^+, 7), 246 (24), 190 (27), 135 (100), 117 (14), 91 (22), 41 (13) exact mass calculate for $C_{17}H_{21}NO_5$ (M^+): 319.1420; found: 319.1414.

4.1.14. (10-Isopropylidene-3,5-dioxo-4-oxa-tricyclo[5.2.1.$0^{2,6}$]dec-8-en-1-yl)-oxo-acetic acid ethyl ester (4). To a solution of **9a** and **9b** mixture (4 mg, 0.012 mmol) in CH_2Cl_2 (2 mL) was added Dess–Martin periodinate (6 mg, 0.014 mmol) under Ar. The solution was stirred at room temperature for 20 min and diluted with EtOAc (20 mL). The mixture was washed with aqueous $NaHCO_3$ (1.0 mL), dried over Na_2SO_4 and concentrated in vacuo to give a yellow oil. The crude product was purified by flash column chromatography with 30% EtOAc–hexane (R_f= 0.56 in 50% EtOAc–hexane) to give adduct **4** as a yellow oil (3.6 mg, 95% yield). IR (neat): 2923, 1697, 1434, 1378, 1292, 1292, 1187, 749 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.57 (dd, J=6.0, 3.5 Hz, 1H), 6.28 (d, J=6.0 Hz, 1H), 4.40 (q, J=7.5 Hz, 2H), 3.82 (s, 1H), 3.59 (d, J=7.0 Hz, 1H), 2.86 (s, 3H), 2.85 (s, 1H), 1.58 (s, 1H), 1.54 (s, 3H), 1.41 (t, J=7.5 Hz, 3H), 1.39 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 193.0 (C), 176.5 (C), 176.5 (C), 162.1 (C), 138.9 (C), 138.5 (CH), 137.1 (CH), 119.6 (C), 64.5 (C), 62.7 (CH_2), 49.4 (CH), 48.3 (CH), 47.6 (CH), 24.6 (CH_3), 21.4 (CH_3), 20.9 (CH_3), 14.0 (CH_3); MS (*m/z*, relative intensity): 317 (M^+, 3), 244 (9), 133 (100), 77 (6), 58 (9), 55 (8), exact mass calculate for $C_{17}H_{19}NO_5$ (M^+): 317.1264; found: 317.1264.

5. Supplementary material

Experimental procedures and characterization data for the new compounds (**2–9**); and X-ray crystallographic cif file for compound **7b**. The X-ray cif file of compound **7b** was deposited with Cambridge Crystallographic Data Centre, CCDC No. 288537.

Acknowledgements

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A simple approach for the regioselective synthesis of imidazo[1,2-*a*]pyrimidiones and pyrimido[1,2-*a*]pyrimidinones

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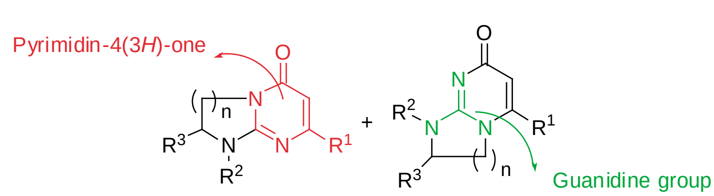
Abstract—Several imidazo and pyrimido[1,2-*a*]pyrimidinones of type **1** and **2** were synthesized through intramolecular cyclization of pyrimidines **9** or pyrimidinones **10** bearing a variety of β and γ-aminoalcohols at the 2-position. Ring closure of the pyrimidinones of type **10** under Mitsunobu conditions lead to mixtures of both bicyclic regioisomers **1** and **2**. Treatment of pyrimidines of type **9** with H_2SO_4 provided an efficient and operationally simple one-pot hydrolysis–cyclization procedure for obtaining imidazo and pyrimido[1,2-*a*]pyrimidinones **1** in good yields as the sole regioisomeric bicyclic product.

1. Introduction

The imidazo[1,2-*a*]pyrimidinones **1** ($n=1$) and **2** ($n=1$) and the pyrimido[1,2-*a*]pyrimidinones **1** ($n=2$) and **2** ($n=2$) (Fig. 1) constitute an important class of natural and non-natural products, many of which exhibit useful biological activities. The imidazo[1,2-*a*]pyrimidinone structure **1** ($n=1$) has been found in the Y base of yeast as a component of phenylalanine transfer ribonucleic acid,[1] and new acyclovir analogs possessing this ring system have exhibited antiherpetic activity on HIV-1,2.[2] Other members of this family of compounds also have pharmacological interest for their hypnotic,[3] anesthetic[4] and antiallergic[5] properties. Imidazo[1,2-*a*]pyrimidinone derivatives type **2** ($n=1$) are of considerable interest because of their activities as phosphodiesterase (PDE) inhibitors,[6] and antihypertensives.[7] Furthermore, some derivatives of pyrimido[1,2-*a*]pyrimidinones **1** ($n=2$) and **2** ($n=2$) have some utility for preventive and/or therapeutic treatment of a neurodegenerative disease caused by abnormal activity of GSK3β, such as Alzheimer's disease.[8]

The imidazo and pyrimido[1,2-*a*]pyrimidinones **1** and **2** incorporate both the guanidine and pyrimidinone functionalities (Fig. 1). It is well known that pyrimidin-4(3*H*)-ones are valuable scaffolds in different areas of research. For example, this class of compounds displays potent and selective activity as non-nucleoside HIV-1 reverse transcriptase inhibitors.[9] Other members of this family of compounds have found utility as herbicides,[10] antidepressants[11] and leishmanicides.[12] In addition, when pyrimidin-4(3*H*)-ones are substituted at the



1 n=1, 2 **2** n=1, 2

Figure 1. Imidazo and pyrimido[1,2-*a*]pyrimidinones **1** and **2**.

Keywords: Imidazo[1,2-*a*]pyrimidinone; Pyrimido[1,2-*b*]pyrimidinone; Mitsunobu reaction; *ipso*-Substitution; Acidic hydrolysis.
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2-position by an amino group, it can be considered to be a cyclic guanidine. Due to the hydrogen-bonding acceptor and donor abilities of the guanidine group,[13] 2-aminopyrimidin-4(3*H*)-ones have also served as suitable models for studies conducted on self-association[14] and the subsequent application of those studies to supramolecular chemistry.[15]

Numerous methods for the synthesis of the imidazo and pyrimido[1,2-*a*]pyrimidinones involve approaches based on either (i) cyclocondensation between 2-substituted pyrimidinone ring systems with appropriate 1,2 or 1,3-difunctionalized synthons, such as α or β-halocarbonyl compounds,[2,16] 1,2-dihaloalkanes,[17] acrolein,[18] glyoxal,[19] glycidaldehyde,[20] and α or β-aminoalcohols,[6,7,21] or (ii) cyclocondensation between 2-substituted imidazole or pyrimidine ring systems with appropriate 1,3-difunctionalized synthons, such as β-aminoesters[22] and α-acetylenic esters.[23] However, both routes can give mixtures of regioisomers. Other useful routes to these type of heterocycles involve the fusion of two heterocycles in one single step[24] or the ring contraction of other heterocyclic systems.[25]

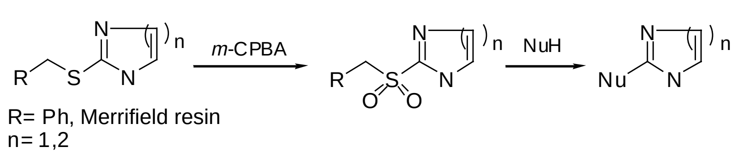
During the last few years, we have been engaged in a research program focused on the development of efficient methodologies that could be adapted readily for combinatorial and/or parallel synthesis of relevant core structures with potential therapeutic interest. We have described the synthesis of novel 2,3-dihydroimidazo[2,1-*b*][1,3]oxazoles[26] and multiple substituted pyrimidines.[27] The method has a nucleophilic *ipso*-substitution of the corresponding activated sulfones as one of the key steps, not only for introducing molecular diversity but also as cleavage reaction on solid phase synthesis (Scheme 1). In this way, several purines,[28] aminopyridazines[29] and pteridines[30] have also been prepared using an activatable sulfur linkage. Within this context, we recently reported on the synthesis of novel 2,6-disubstituted 3,4-dihydropyrimidin-4(3*H*)-ones[31] **7** starting from 2-alkylsulfanylpyrimidinones **3**. The methodology is based on a selective *O*-alkylation reaction with *i*-PrOH under Mitsunobu conditions, followed by a nucleophilic displacement of the corresponding activated sulfones with a wide variety of nucleophiles (phenoxides, Grignard reagents, and primary and secondary amines). Finally, the acidic hydrolysis of the 4-isopropoxy group under standard conditions afforded pyrimidinones **7** in good yields (Scheme 2).

As an extension of this work, an investigation was undertaken to expand the scope of this methodology and its potential application in the synthesis of more elaborate heterocyclic scaffolds based on the pyrimidin-4(3*H*)-one nucleus. Specifically, we focused our attention on imidazo[1,2-*a*]pyrimidinones and pyrimido[1,2-*a*]pyrimidinones **1** and **2**. The results of this investigation are disclosed herein.

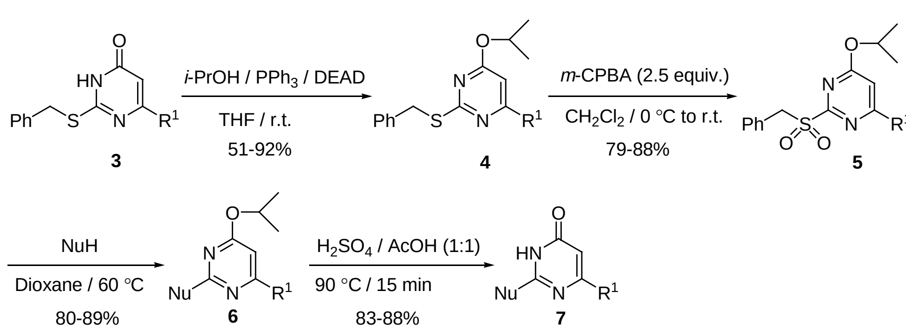
2. Results and discussion

Consistent with the goal of synthesizing more elaborate heterocyclic scaffolds based on the pyrimidin-4(3*H*)-one nucleus, and in complete analogy with the above-mentioned results, we reasoned that nucleophilic *ipso*-substitution of the sulfones **5** with a wide variety of β and γ-aminoalcohols[32] **8**, followed by subsequent acidic hydrolysis and a final cyclization step under Mitsunobu conditions would lead to the formation of a collection of imidazo and pyrimido[1,2-*a*]pyrimidin-5-ones **1** and imidazo and pyrimido[1,2-*a*]pyrimidin-7-ones **2** (Scheme 3). From these intermediates **10** the cyclization could, in principle, take place onto *N*(1) or *N*(3) to afford the regioisomers **2** and **1**, respectively.

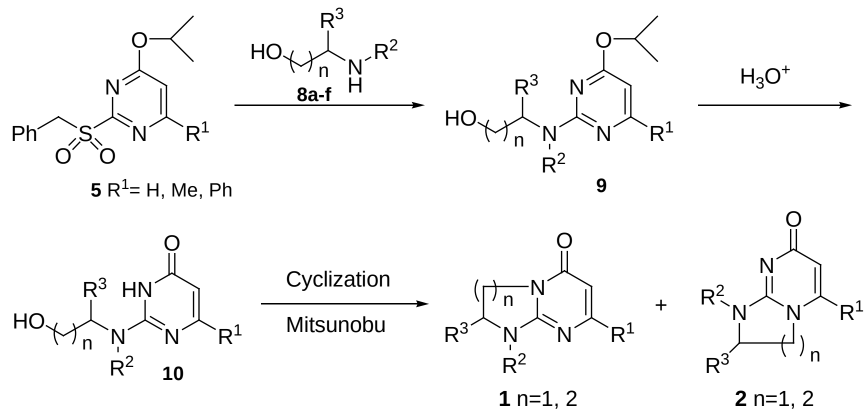
Thus, when pyrimidinyl sulfone derivatives **5** were allowed to react in 1,4-dioxane at reflux with several β and γ-aminoalcohols **8a–f** (Fig. 2), which are readily available from commercial sources and/or from the reduction of the corresponding amino acids,[33] the corresponding pyrimidines **9a–j** were obtained generally in good yields (Scheme 3, Table 1).



Scheme 1. Nucleophilic *ipso*-substitution of activated sulfones.



Scheme 2. Synthesis of 2,6-disubstituted 3,4-dihydropyrimidin-4(3*H*)-ones **7**.



Scheme 3. Preparation of imidazo and pyrimido[1,2-*a*]pyrimidinones.

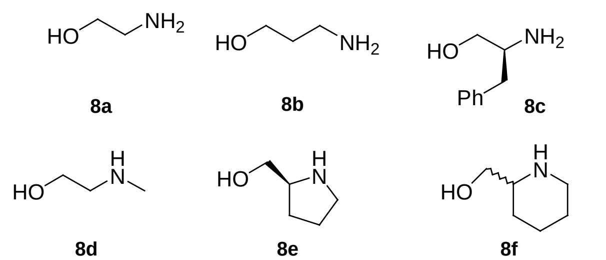


Figure 2. The employed β and γ-aminoalcohols **8**.

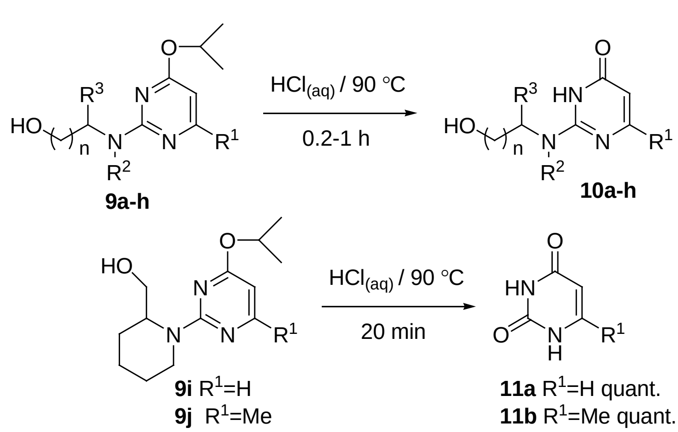
Table 1. Yields of compounds **9a**–**j**

Entry	Compound	R^1	Aminoalcohol	Yield (%)[a]
1	**9a**	H	**8a**	79
2	**9b**	Me	**8a**	76
3	**9c**	H	**8b**	65
4	**9d**	Me	**8b**	94
5	**9e**	Me	**8c**	79
6	**9f**	Ph	**8d**	85
7	**9g**	Me	**8d**	80
8	**9h**	Me	**8e**	95
9	**9i**	H	**8f**	79
10	**9j**	Me	**8f**	90

[a] Yields of isolated pure products.

Acidic hydrolysis of the pyrimidines **9** with concd HCl at 90 °C, followed by simple chromatographic filtration, yielded the corresponding target pyrimidinones **10** also in good yields (71–97%), except with the pyrimidines **9i** and **9j**, which led to the formation of the uracils **11** in quantitative yields (Scheme 4, Table 2). These results clearly indicate that the piperidinyl group in the 2-position of the pyrimidine ring is labile under these acidic conditions. We then focused our attention on the search for other acidic hydrolysis conditions that could selectively cleave the 4-alkoxy group in these two compounds, **9i** and **9j**.

When derivatives **9i** and **9j** were allowed to react with H_2SO_4 at 90 °C, compounds **1i** and **1j** were isolated in near quantitative yields (Scheme 5). The formation of products **1** could be rationalized in terms of a one-pot procedure simply by hydrolysis of the 4-isopropoxy group, followed by complete regioselective cyclization onto *N*(3) of the pyrimidinone ring to afford the corresponding imidazopyrimidinones **1**. In good agreement with this procedure, when pyrimidine **9f** was treated with H_2SO_4 at room temperature for 24 h, a mixture of pyrimidinone **10f** and imidazopyrimidinone **1f** was observed. After heating to 90 °C, the ring closure was completed in only 20 min and compound **1f** was isolated in good yield (Scheme 5). This one-pot hydrolysis–cyclization reaction was successfully extended to other pyrimidines to afford the corresponding

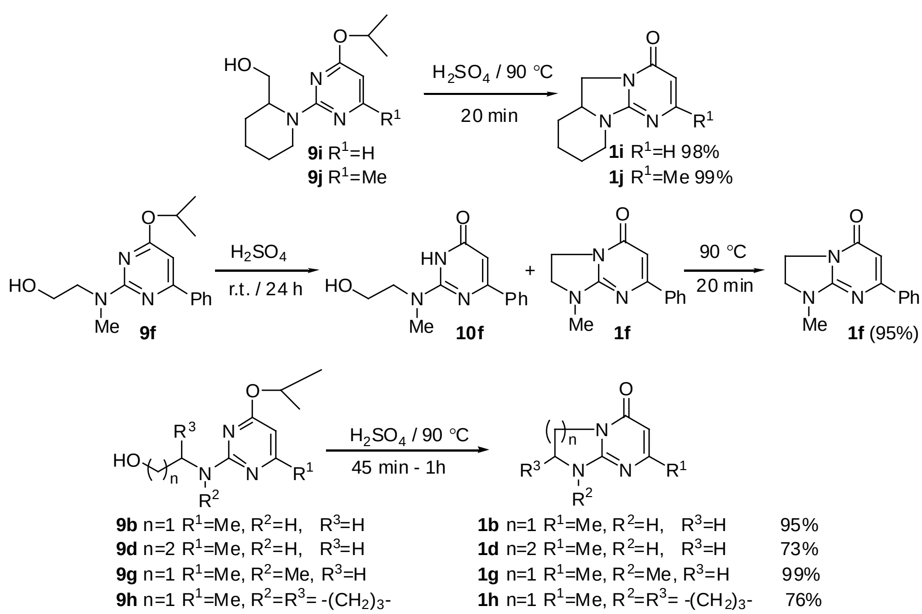


Scheme 4. Acidic hydrolysis of pyrimidines **9**.

Table 2. Yields of compounds **10a–j**

Entry	Compound	R^1	R^2	R^3	*n*	Yield (%)[a]
1	**10a**	H	H	H	1	86
2	**10b**	Me	H	H	1	97
3	**10c**	H	H	H	2	97
4	**10d**	Me	H	H	2	87
5	**10e**	H	H	Bn	1	71
6	**10f**	Ph	Me	H	1	95
7	**10g**	Me	Me	H	1	85
8	**10h**	Me	$-(CH_2)_3-$		1	94
9	**10i**	H	$-(CH_2)_4-$		1	—
10	**10j**	Me	$-(CH_2)_4-$		1	—

[a] Yields of isolated pure products.

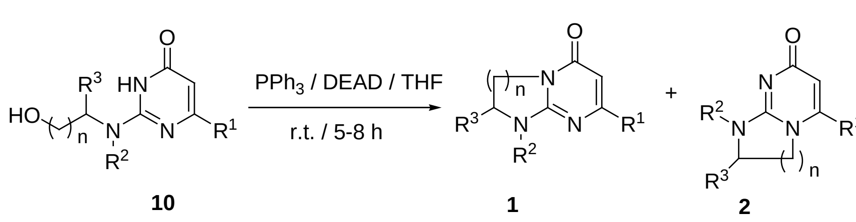


Scheme 5. Regioselective synthesis of imidazo and pyrimido[1,2-*a*]pyrimidinones **1**.

imidazopyrimidinones **1** ($n=1$) and pyrimidopyrimidinone **1** ($n=2$) with an absolute regioselectivity and in good yields (Scheme 5).

Following our initial plans we decided to investigate the feasibility of an intramolecular cyclization of the 4(3*H*)-pyrimidinones **10**, under Mitsunobu conditions. Thus, when pyrimidinones **10** were treated with PPh_3 and DEAD in anhydrous THF at room temperature for 5–8 h, a separable mixture of the regioisomeric bicyclic compounds **1** and **2** were isolated by flash chromatography in good yields (Scheme 6, Table 3). The cyclization reaction took place predominantly onto *N*(1) affording compounds of type **2** as the major regioisomer (Table 3, entries 1–4). However, when the *N*-atom at the 2-position on the pyrimidinone ring had an alkyl substituent ($R^2=Me$), the Mitsunobu reaction proceeded in high yield and with a high degree of selectivity. Only the isomer **1g** from cyclization onto *N*(3) of the pyrimidinone ring was obtained (Table 3, entry 5).

Generally, the intramolecular cyclization reaction of 2-substituted pyrimidinone ring systems takes place onto *N*(3), except when *N*(3) has an alkyl substituent,[5b,c] which blocks this nitrogen, and cyclization is only possible onto *N*(1) or when the 2-position on the pyrimidinone ring has a substituent prone to tautomerize, such as an amino[16b–c] group, with the cyclization then taking place onto both *N*(1) and *N*(3) to afford mixtures of the regioisomers **1** and **2**. This last case can explain the results in the Mitsunobu reaction. Thus, when the reaction was carried out by employing pyrimidinones **10** with a secondary amine in the 2-position ($R^2=H$), both regioisomers **1** and **2** were obtained (Table 3,



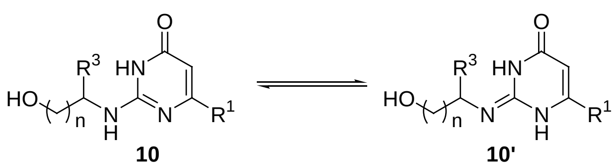
Scheme 6. Intramolecular cyclization of pyrimidinones **10** under Mitsunobu conditions.

Table 3. Yields of compounds **1** and **2**

Entry	R^1	R^2	R^3	*n*	Regioisomer **1**	Regioisomer **2**	**1**:**2**[a]	Yield (%)[b]
1	H	H	H	1	**1a**	**2a**	12:88	91
2	H	H	H	2	**1c**	**2c**	23:77	95
3	Me	H	H	2	**1d**	**2d**	27:73	91
4	Me	H	Bn	1	**1e**	**2e**	42:58	78
5	Me	Me	H	2	**1g**	—	100:0	96

[a] Ratios were calculated by yields of isolated compounds.
[b] Yields of isolated pure products.

entries 1–4). The cyclization reaction onto *N*(1) probably proceeded via its tautomeric form **10′** (Scheme 7). However, when pyrimidinone **10e** with a tertiary amine in the 2-position (R^2=Me) was employed, the tautomeric form **10′** was not possible and the cyclization reaction was completely regioselective in favor of the isomer **1** (Table 3, entry 5).



Scheme 7. Tautomerism of compounds **10**.

On the other hand, the absolute regioselectivity obtained during the synthesis of compounds **1**, regardless of the R^2 group (H, Me), when intramolecular cyclization was carried out with H_2SO_4, are in good agreement with the literature. To the best of our knowledge, intramolecular cyclization of 2-subtituted pyrimidin-4(3*H*)-ones always took place exclusively onto *N*(3) under acid reaction conditions.[34]

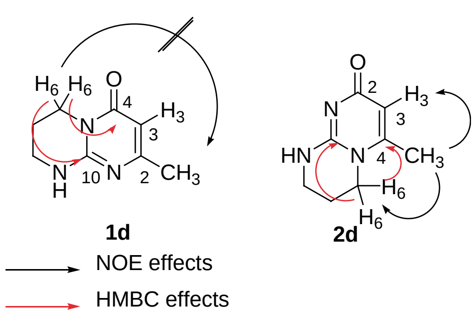


Figure 3. HMBC and NOE experiments of compounds **1d** and **2d**.

All products and intermediates were characterized by the usual spectroscopic methods, such as ^{1}H and ^{13}C spectroscopy, mass spectrometry, IR, and elemental analysis. The ^{1}H and ^{13}C NMR spectra for **1** and **2** were assigned by means of DEPT and HMQC experiments and the regiochemistry of both of these isomers **1** and **2** was established unequivocally by NOE and heteronuclear multiple bond correlation (HMBC) experiments. A NOE effect was observed between methyl protons and proton H_3, as well as between methyl protons and protons H_6 in isomers **1d**, while in isomers **2d**, a NOE effect was not observed between protons H_6 and methyl protons (Fig. 3). In addition, the HMBC experiments gave supplementary information: for isomer **1**, long range ^{1}H–^{13}C correlations are observed between protons H_6 and both carbons 4 (C=O) and 10 (C=N) (Fig. 3), while isomer **2** presented correlations between protons H_6 and carbon 2 (C=O) and carbon 4 (Fig. 3). Moreover, the structures of compounds **2e** and **1h** were established unambiguously by X-ray crystallography (Fig. 4).

3. Conclusion

In summary, we have shown that 2-substituted pyrimidinones **10** with a variety of β and γ-aminoalcohols, which are easily available from pyrimidinyl sulfone derivatives **5**, are good synthetic precursors for the preparation of imidazo and pyrimido[1,2-*a*]pyrimidinones **1** and **2** via an intramolecular ring closure. When cyclization was carried out under Mitsunobu conditions by employing pyrimidinones **10** with a secondary amine

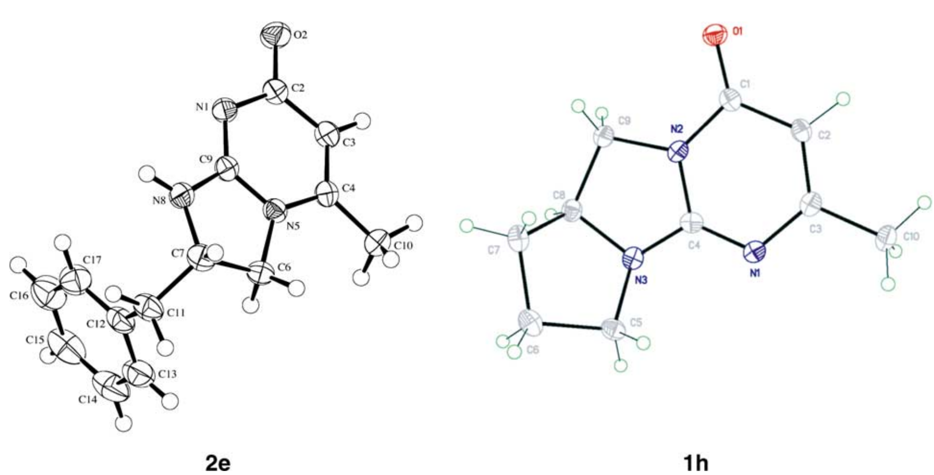


Figure 4. The molecular structures of **2e** and **1h** (Ortep-plot with ellipsoids at the 50% probability levels).

in the 2-position ($R^2=H$), both regioisomers **1** and **2** were obtained. In contrast, when the *N* atom in the 2-position on the pyrimidinone ring has an alkyl substituent ($R^2=Me$), the Mitsunobu reaction yielded the regioisomer **1** as the only product. On the other hand, treatment of the pyrimidines **9** with H_2SO_4 afforded, with an absolute regioselectivity, the imidazo and pyrimido[1,2-*a*]pyrimidinones **1** through a one-pot hydrolysis–cyclization procedure. Considering the easily available starting materials, generality of the reaction, simplicity of the procedure and good yields, this provides a straightforward method to construct a diverse array of imidazo and pyrimido[1,2-*a*]pyrimidinones **1** and **2**. However, we are aware that the orientation of the cyclization reaction could change when pyrimidinone ring would be substituted with strong electron-withdrawing or electron-donating groups. In this way, further investigation on regioselective cyclization of the pyrimidinones substituted at 6-position with nitro, amino, alkylamino or alkoxy groups are currently in progress in our laboratories.

4. Experimental

4.1. General remarks

4-Isopropoxy-2-phenylmethanesulfonyl-pyrimidine **5a**, 4-isopropoxy-6-methyl-2-phenylmethanesulfonyl-pyrimidine **5b** and 4-isopropoxy-6-phenyl-2-phenylmethanesulfonyl-pyrimidine **5c**, were prepared as previously reported by us.[28] All commercially available chemicals were used as purchased without further purification. DMF and dioxane were dried over activated molecular sieves (4 Å). THF was dried over Na/benzophenone prior use. Melting points (capillary tube) were measured with an Electrothermal digital melting point apparatus IA 91000 and are uncorrected. IR spectra were recorded on a Mattson-Galaxy Satellite FT-IR using a single reflection ATR system as a sampling accessory. ^1H and ^{13}C NMR spectra were recorded at 200 and 50 MHz, respectively, on a Brucker DPX200 Advance instrument. Spectra recorded in $CDCl_3$ were referenced to residual $CHCl_3$ at 7.26 ppm for ^1H or 77.0 ppm for ^{13}C. Spectra recorded in DMSO-d_6 were referenced to residual DMSO at 2.49 ppm for ^1H or 39.5 ppm for ^{13}C. Coupling constants (*J*) are given in Hertz (Hz). The terms s, d, t, q, sept, m, dd, refer to singlet, doublet, triplet, quartet, septet, multiplet; double doublet, br implies the signal is broad. Mass spectra were recorded by electron impact (EI, 70 eV) on a Thermo Quest 2000 series apparatus or by fast-atom bombardment (FAB) on a VG Quattro instrument or by electrospray ionitzation (ESI) using a quadrupole mass spectrometer equipped with an electrospray ion source. Elemental analyses were performed on an apparatus from Thermo Instruments, model EA1110-CHNS. Analytical thin-layer chromatography (TLC) was performed on glass plates precoated with silica gel 60 F_{254} (Merck). Visualitzation was accomplished by UV light (254 nm) and potassium permanganate. Flash-chromatography (FC) purifications were performed on silica gel 60 (230–400 mesh, Merck).

4.2. General procedure for the *ipso*-substitution reaction of pyrimidinyl sulfone derivatives 5 with amino alcohols 8. Synthesis of pyrimidines 9

Under a nitrogen atmosphere, to a solution of pyrimidinyl sulfones **5a–c** (1 equiv) in dry dioxane (3 mL/mmol), the corresponding amino alcohol **8a–f** (1.5–2 equiv) was added. The resulting mixture was refluxed for 5–24 h until the reaction was completed (TLC monitoring). The solvent was removed under reduced pressure and the resulting residue was purified by flash-chromatography (*n*-hexane/ethyl acetate 4:1 gradually increasing to pure ethyl acetate) to afford pyrimidines **9**.

4.2.1. 2-(4-Isopropoxy-pyrimidin-2-ylamino)-ethanol (9a). From 1.61 g (5.51 mmol) of sulfone **5a** and 0.50 mL (8.1 mmol) of 2-amino-ethanol **8a**, 857 mg (79%) of compound **9a** was obtained as a colorless solid. Mp: 100–101 °C. R_f 0.23 (dichloromethane/methanol 10:1). IR (neat): 3298, 3259, 1574 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.33 (d, 6H, $J=6.2$ Hz), 3.56 (t, 2H, $J=4.4$ Hz), 3.81 (t, 2H, $J=4.4$ Hz), 4.55 (br, 1H), 5.28 (sept, 1H, $J=6.2$ Hz), 5.75 (br, 1H), 5.95 (d, 1H, $J=5.6$ Hz), 7.94 (d, 1H, $J=5.6$ Hz); ^{13}C NMR ($CDCl_3$): δ 21.8 (q, 2 CH_3), 44.4, 62.6 (2t, 2 CH_2), 68.5 (d, *C*H), 98.1, 157.3 (2d, 2 CH_{pyrim}), 169.4, 162.7 (2s, 2 C_{pyrim}); MS (EI) *m/z*: 197 ($[M]^{\cdot+}$, 13). Anal. Calcd for $C_9H_{15}N_3O_2$: C, 54.81; H, 7.67; N, 21.30. Found: C, 54.60; H, 7.78; N, 21.11.

4.2.2. 2-(4-Isopropoxy-6-methyl-pyrimidin-2-ylamino)-ethanol (9b). From 1.00 g (3.27 mmol) of sulfone **5b** and 0.30 mL (4.85 mmol) of 2-amino-ethanol **8a**, 524 mg (76%) of compound **9b** was obtained as a colorless solid. Mp: 109–110 °C. R_f 0.79 (dichloromethane/methanol 3:1). IR (neat): 3265, 3190, 1568 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.33 (d, 6H, $J=6.2$ Hz), 2.25 (s, 3H), 3.56 (t, 2H, $J=4.4$ Hz), 3.83 (t, 2H, $J=4.4$ Hz), 4.65 (br, 1H), 5.25 (sept, 1H, $J=6.2$ Hz), 5.45 (br, 1H), 5.86 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 21.9, 23.4 (2q, 3 CH_3), 44.7, 63.5 (2t, 2 CH_2), 68.4 (d, *C*H), 96.9 (d, CH_{pyrim}), 162.7, 167.4, 170.0 (3s, 3 C_{pyrim}); MS (EI) *m/z*: 211 ($[M]^{\cdot+}$, 14). Anal. Calcd for $C_{10}H_{17}N_3O_2$: C, 56.85; H, 8.11; N, 19.89. Found: C, 56.96; H, 8.29; N, 19.70.

4.2.3. 3-(4-Isopropoxy-pyrimidin-2-ylamino)-propan-1-ol (9c). From 1.03 g (3.5 mmol) of sulfone **5a** and 0.4 mL (5.42 mmol) of 3-amino-propan-1-ol **8b**, 487 mg (65%) of compound **9c** was obtained as a colorless solid. Mp: 82–83 °C. R_f 0.33 (dichloromethane/methanol 10:1). IR (neat): 3280, 3219, 1560 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.33 (d, 6H, $J=6.2$ Hz), 1.77 (m, 2H), 3.57 (q, 2H, $J=6.0$ Hz), 3.67 (t, 2H, $J=5.7$ Hz), 4.15 (br, 1H), 5.26 (sept, 1H, $J=6.2$ Hz), 5.30 (br, 1H), 5.96 (d, 1H, $J=5.8$ Hz), 7.96 (d, 1H, $J=5.8$ Hz); ^{13}C NMR ($CDCl_3$): δ 22.5 (q, 2 CH_3), 33.8, 38.4, 59.4 (3t, 3 CH_2), 69.2 (d, *C*H), 98.8, 158.1 (2d, CH_{pyrim}), 163.6, 170.1 (2s, 2 C_{pyrim}); MS (EI) *m/z*: 211 ($[M]^{\cdot+}$, 9). Anal. Calcd for $C_{10}H_{17}N_3O_2$: C, 56.85; H, 8.11; N, 19.89. Found: C, 56.74; H, 8.32; N, 19.86.

4.2.4. 3-(4-Isopropoxy-6-methyl-pyrimidin-2-ylamino)-propan-1-ol (9d). From 1.23 g (4.02 mmol) of sulfone **5b** 0.46 mL (6.24 mmol) of and 3-amino-propan-1-ol **8b**, 847 mg (94%) of compound **9d** was obtained as a colorless oil. R_f 0.12 (*n*-hexane/ethyl acetate 1:1). IR (neat): 3305, 3106, 1578 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.33 (d, 6H, J=6.2 Hz), 1.81 (q, 2H, J=5.8 Hz), 2.33 (s, 3H), 3.56 (q, 2H, J=6.0 Hz), 3.70 (t, 2H, J=5.6 Hz), 5.30 (sept, 1H, J=6.2 Hz), 5.55 (br, 2H), 5.83 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 21.8, 22.6 (2q, 3 CH_3), 32.5, 38.7, 59.9 (3t, 3 CH_2), 71.4 (d, *C*H), 98.4 (d, CH_{pyrim}), 158.3, 167.0, 171.3 (3s, 3 C_{pyrim}); MS (EI) *m/z*: 225 ($[M]^{\cdot+}$, 64). Anal. Calcd for $C_{11}H_{19}N_3O_2$: C, 58.64; H, 8.50; N, 18.65. Found: C, 58.87; H, 8.62; N, 18.84.

4.2.5. 2-(4-Isopropoxy-6-methyl-pyrimidin-2-ylamino)-3-phenyl-propan-1-ol (9e). From 785 mg (2.56 mmol) of sulfone **5b** and 774 mg (5.13 mmol) of phenylalaninol **8c**, 612 mg (79%) of compound **9e** was obtained as a colorless oil. R_f 0.12 (chloroform/methanol 6:1). IR (neat): 3400, 3028, 1577 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.34 (d, 6H, J=6.2 Hz), 2.97 (d, 2H, J=7.4 Hz), 3.67 (dd, 1H, J=10.8 Hz, J'=5.6 Hz), 3.82 (dd, 1H, J=10.8 Hz, J'=2.8 Hz), 4.20 (m, 1H), 4.30 (br, 1H), 5.27 (sept, 1H, J=6.2 Hz), 5.40 (br, 1H), 5.86 (s, 1H), 7.20–7.40 (m, 5H); ^{13}C NMR ($CDCl_3$): δ 22.6, 23.8 (2q, 3 CH_3), 38.4 (t, CH_2), 55.6 (d, *C*H), 65.4 (t, CH_2), 69.3 (d, *C*H), 97.5 (d, CH_{pyrim}), 127.1, 129.2, 129.9 (3d, 5 CH_{arom}), 139.0 (s, C_{arom}), 162.2, 167.3, 170.8 (3s, 3 C_{pyrim}); MS (EI) *m/z*: 301 ($[M]^{\cdot+}$, 4). Anal. Calcd for $C_{17}H_{23}N_3O_2$: C, 67.75; H, 7.69; N, 13.94. Found: C, 67.56; H, 7.52; N, 14.12.

4.2.6. 2-[(4-Isopropoxy-6-phenyl-pyrimidin-2-yl)-methyl-amino]-ethanol (9f). From 1.00 g (2.72 mmol) of sulfone **5c** and 0.38 mL (5.4 mmol) of 2-methylamino-ethanol **8d**, 667 mg (85%) of compound **9f** was obtained as a colorless oil. R_f 0.23 (*n*-hexane/ethyl acetate 1:1). IR (neat): 3400–3200, 1534 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.42 (d, 6H, J=6.2 Hz), 3.30 (s, 3H), 3.85–4.00 (m, 4H), 5.40 (sept, 1H, J=6.2 Hz), 6.40 (s, 1H), 7.40, 7.50 (m, 3H), 7.95–8.00 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 22.6, 37.3 (2q, 3 CH_3), 53.5, 63.7 (2t, 2 CH_2), 69.3 (d, *C*H), 93.7 (d, CH_{pyrim}), 127.5, 129.2, 130.8 (3d, 5 CH_{arom}), 138.4 (s, C_{arom}), 163.6, 165.7, 170.9 (3s, 3 C_{pyrim}); MS (EI) *m/z*: 287 ($[M]^{\cdot+}$, 11). Anal. Calcd for $C_{16}H_{21}N_3O_2$: C, 66.88; H, 7.37; N, 14.62. Found: C, 67.15; H, 7.45; N, 14.35.

4.2.7. 2-[(4-Isopropoxy-6-methyl-pyrimidin-2-yl)-methyl-amino]-ethanol (9g). From 1.23 g (4.02 mmol) of sulfone **5b** and 0.48 mL (6.83 mmol) of 2-methylamino-ethanol **8d**, 721 mg (80%) of compound **9g** was obtained as a colorless oil. R_f 0.38 (*n*-hexane/ethyl acetate 1:1). IR (neat): 3450–3250, 1576 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.34 (d, 6H, J=6.2 Hz), 2.24 (s, 3H), 3.20 (s, 3H), 3.74 (t, 2H, J=4.0 Hz), 3.89 (t, 2H, J=4.0 Hz), 5.30 (sept, 1H, J=6.2 Hz), 5.81 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 21.9, 23.5, 36.6 (3q, 4 CH_3), 53.2, 63.3 (2t, 2 CH_2), 68.2 (d, *C*H), 95.7 (d, CH_{pyrim}), 162.6, 167.0, 169.6 (3s, 3 C_{pyrim}); MS (EI) *m/z*: 225 ($[M]^{\cdot+}$, 29). Anal. Calcd for $C_{11}H_{19}N_3O_2$: C, 58.64; H, 8.50; N, 18.65. Found: C, 58.66; H, 8.62; N, 18.56.

4.2.8. [1-(4-Isopropoxy-6-methyl-pyrimidin-2-yl)-pyrrolidin-2-yl]-methanol (9h). From 1.00 g (3.27 mmol) of sulfone **5b** and 0.58 mL (5.6 mmol) of prolinol **8e**, 825 mg (95%) of compound **9h** was obtained as a colorless oil. R_f 0.34 (*n*-hexane/ethyl acetate 1:1). IR (neat): 3400–3300, 1574 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.33 (d, 6H, J=6.2 Hz), 1.70–2.20 (m, 4H), 2.23 (s, 3H), 3.50–3.80 (m, 4H), 4.25 (m, 1H), 5.30 (sept, 1H, J=6.2 Hz), 5.81 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 21.9, 23.3 (2q, 3 CH_3), 23.9, 29.9, 48.2 (3t, 3 CH_2), 61.1 (d, *C*H), 68.3 (t, CH_2), 68.8 (d, *C*H), 95.7 (d, CH_{pyrim}), 161.1, 166.5, 169.6 (3s, 3 C_{pyrim}); MS (EI) *m/z*: 251 ($[M]^{\cdot+}$, 3). Anal. Calcd for $C_{13}H_{21}N_3O_2$: C, 62.13; H, 8.42; N, 16.72. Found: C, 62.19; H, 8.64; N, 16.44.

4.2.9. [1-(4-Isopropoxypyrimidin-2-yl)piperidin-2-yl]-methanol (9i). From 875 mg (3.0 mmol) of sulfone **5a** and 618 mg (5.37 mmol) of piperidin-2-yl-methanol **8f**, 596 mg (79%) of compound **9i** was obtanied as a colorless oil. R_f 0.40 (*n*-hexane/ethyl acetate 1:1). IR (neat): 3405, 1587 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.37 (d, 6H, J=6.2 Hz), 1.65–1.80 (m, 6H), 3.05 (m, 1H), 3.40 (br, 1H), 3.73 (dd, 1H, J=10.7 Hz, J'=5, 5 Hz), 3.96 (dd, 1H, J=10.7 Hz, J'=8.8 Hz, CH_2N), 4.60 (m, 1H), 4.90 (m, 1H), 5.28 (sept, 1H, J=6.2 Hz), 5.90 (d, 1H, J=6.0 Hz), 7.98 (d, 1H, J=6.0 Hz); ^{13}C NMR ($CDCl_3$): δ 19.8 (t, CH_2), 21.8 (q, 2 CH_3), 24.9, 25.6, 39.6 (3t, 3 CH_2), 52.7 (d, *C*H), 62.7 (t, CH_2), 68.2 (d, *C*H), 97.1, 157.4 (2d, 2 CH_{pyrim}), 162.6, 169.0 (2s, 2 C_{pyrim}); MS (EI) *m/z*: 251 ($[M]^{\cdot+}$, 6). Anal. Calcd for $C_{13}H_{21}N_3O_2$: C, 62.13; H, 8.42; N, 16.72. Found: C, 62.22; H, 8.34; N, 16.54.

4.2.10. [1-(4-Isopropoxy-6-methylpyrimidin-2-yl)-piperidin-2-yl]-methanol (9j). From 900 mg (2.94 mmol) of sulfone **5b** and 672 mg (5.84 mmol) piperidin-2-yl-methanol **8f**, 716 mg (90%) of compound **9j** was obtained as a colorless oil. R_f 0.44 (*n*-hexane/ethyl acetate 1:1). IR (neat): 3400, 1573 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.31 (d, 6H, J=6.2 Hz), 1.50–1.70 (m, 6H), 2.20 (s, 3H), 3.05 (m, 1H), 3.71 (dd, 1H, J=10.7 Hz, J'=4.7 Hz, CH_2N), 4.00 (dd, 1H, J=10.7 Hz, J'=9.0 Hz), 4.15 (br, 1H), 4.60 (m, 1H), 4.90 (m, 1H), 5.25 (sept, 1H, J=6.2 Hz), 5.77 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 20.6 (t, CH_2), 21.5, 24.4 (2q, 3 CH_3), 25.6, 26.5, 40.3 (3t, 3 CH_2), 53.6 (d, *C*H), 64.1 (t, CH_2), 68.7 (d, *C*H), 96.3 (d, CH_{pyrim}), 163.4, 167.9, 170.2 (3s, 3 C_{pyrim}); MS (EI) *m/z*: 265 ($[M]^{\cdot+}$, 3). Anal. Calcd for $C_{14}H_{23}N_3O_2$: C, 63.37; H, 8.74; N, 15.84. Found: C, 63.09; H, 8.83; N, 15.66.

4.3. General procedure for the hydrolysis of compounds 9 with HCl. Synthesis of pyrimidinones 10

A suspension of the corresponding 4-isopropoxypyrimidine **9** (1 equiv) in concd HCl (2 mL/mmol) was heated at 90 °C for 30 min. After cooling, the mixture was neutralized with aq 5 N NaOH and extracted with CH_2Cl_2 (3×10 mL/mmol). The combined organic layers were washed with brine (1×10 mL/mmol) and the organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting crude product was purified by flash-chromatography (ethyl acetate/methanol 10:1) to afford pyrimidinones **10**.

4.3.1. 2-(2-Hydroxy-ethylamino)-3*H*-pyrimidin-4-one (10a). From 336 mg (1.7 mmol) of 4-isopropoxipyrimidine **9a**, 226 mg (86%) of compound **10a** was obtained as a colorless solid. Mp: 176–177 °C. R_f 0.17 (dichloromethane/methanol 10:1). IR (neat): 3220–2880, 1681, 1621 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 3.30 (m, 2H), 3.51 (t, 2H, J=5.6 Hz), 4.90 (br, 1H), 5.53 (d, 1H, J=6.6 Hz), 6.55 (br, 1H), 7.57 (d, 1H, J=6.6 Hz), 10.60 (br, 1H); ^{13}C NMR (DMSO-d_6): δ 43.4, 59.2 (2t, 2 CH_2), 103.2, 149.2 (2d, 2

CH_{pyrim}), 153.9, 162.0 (2s, 2 C_{pyrim}); MS (ESI) *m/z*: 178 $[M+23]^+$, 156 $[M+1]^+$. Anal. Calcd for $C_6H_9N_3O_2$: C, 46.45; H, 5.85; N, 27.08. Found: C, 46.43; H, 5.96; N, 27.10.

4.3.2. 2-(2-Hydroxyethylamino)-6-methylpyrimidin-4(3*H*)-one (10b). From 446 mg (2.11 mmol) of 4-isopropoxipyrimidine **9b**, 346 mg (97%) of compound **10b** was obtained as a colorless solid. Mp: 192–193 °C. R_f 0.51 (dichloromethane/methanol 3:1). IR (neat): 3250, 1612 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.10 (s, 3H), 3.30 (m, 2H), 3.40 (t, 2H, $J=6.0$ Hz), 3.59 (t, 2H, $J=6.0$ Hz), 4.95 (br, 1H), 5.50 (s, 1H), 6.70 (br, 1H), 10.65 (br, 1H); ^{13}C NMR (DMSO-d_6): δ 24.4 (q, CH_3), 43.1, 60.0 (2t, 2 CH_2), 100.8 (d, CH_{pyrim}), 154.7, 163.0, 166.0 (3s, 3 C_{pyrim}); MS (ESI) *m/z*: 192 $[M+23]^+$, 170 $[M+1]^+$. Anal. Calcd for $C_7H_{11}N_3O_2$: C, 49.70; H, 6.55; N, 24.84. Found: C, 49.91; H, 6.68; N, 24.56.

4.3.3. 2-(3-Hydroxy-propylamino)-3*H*-pyrimidin-4-one (10c). From 344 mg (1.63 mmol) of 4-isopropoxipyrimidine **9c**, 268 mg (97%) of compound **10c** was obtained as a colorless solid. Mp: 141–142 °C. R_f 0.20 (dichloromethane/methanol 10:1). IR (neat): 3210–2873, 1676, 1609 cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.73 (m, 2H), 3.39 (m, 2H), 3.54 (m, 2H), 4.65 (br, 1H), 5.62 (d, 1H, $J=6.6$ Hz), 6.62 (br, 1H), 7.66 (d, 1H, $J=6.6$ Hz), 10.85 (br, 1H); ^{13}C NMR (DMSO-d_6): δ 31.9, 37.6, 58.3 (3t, 3 CH_2), 102.7, 154.4 (2d, 2 CH_{pyrim}), 155.2 162.9 (2s, 2 C_{pyrim}); MS (ESI) *m/z*: 192 $[M+23]^+$, 170 $[M+1]^+$. Anal. Calcd for $C_7H_{11}N_3O_2$: C, 49.70; H, 6.55; N, 24.84. Found: C, 49.57; H, 6.80; N, 25.05.

4.3.4. 2-(3-Hydroxy-propylamino)-6-methyl-3*H*-pyrimidin-4-one (10d). From 570 mg (2.53 mmol) of 4-isopropoxipyrimidine **9d**, 403 mg (87%) of compound **10d** was obtained as a colorless solid. Mp: 160–161 °C. R_f 0.60 (dichloromethane/methanol 3:1). IR (neat): 3215–2890, 1675, 1611 cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.71 (m, 2H), 2.10 (s, 3H), 3.40 (t, 2H, $J=6.0$ Hz), 3.54 (t, 2H, $J=6.0$ Hz), 4.70 (br, 1H), 5.47 (s, 1H), 6.90 (br, 1H), 10.75 (br, 1H); ^{13}C NMR (DMSO-d_6): δ 23.9 (q, CH_3), 32.0, 37.3, 58.3 (3t, 3 CH_2), 100.2 (d, CH_{pyrim}), 154.4, 162.7, 165.5 (3s, 3 C_{pyrim}); MS (ESI) *m/z*: 206 $[M+23]^+$, 184 $[M+1]^+$. Anal. Calcd for $C_8H_{13}N_3O_2$: C, 52.45; H, 7.15; N, 22.94. Found: C, 52.70; H, 7.13; N, 23.11.

4.3.5. 2-(1-Benzyl-2-hydroxy-ethylamino)-6-methyl-3*H*-pyrimidin-4-one (10e). From 410 mg (1.36 mmol) of 4-isopropoxipyrimidine **9e**, 251 mg (71%) of compound **10e** was obtained as a colorless solid. Mp: 145–146 °C. R_f 0.61 (dichloromethane/methanol 6:1). IR (neat): 3215–2890, 1675, 1611 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.10 (s, 3H), 2.90 (m, 2H), 3.51 (d, 2H, $J=4.2$ Hz), 4.15 (m, 1H), 5.48 (s, 1H), 6.57 (d, 1H, $J=7.6$ Hz), 7.25–7.40 (m, 5H); ^{13}C NMR (DMSO-d_6): δ 24.3 (q, CH_3), 37.2 (t, CH_2), 53.8 (d, *C*H), 61.9 (t, CH_2), 100.8 (d, CH_{pyrim}), 126.5, 128.6, 129.7 (3d, 5 CH_{arom}), 139.3 (s, C_{arom}), 154.4, 163.4, 165.8 (3s, 3 C_{pyrim}); MS (FAB^+) *m/z*: 260 ($[M+1]^+$, 100). Anal. Calcd for $C_{14}H_{17}N_3O_2$: C, 64.85; H, 6.61; N, 16.21. Found: C, 65.06; H, 6.74; N, 15.93.

4.3.6. 2-(*N*-(2-Hydroxyethyl)-*N*-methylamino)-6-phenylpyrimidin-4(3*H*)-one (10f). From 53 mg (0.18 mmol) of 4-isopropoxipyrimidine **9f**, 39 mg (95%) of compound **10f** was obtained as a colorless solid. Mp: 197–198 °C. R_f 0.40 (dichloromethane/methanol 10:1). IR (neat): 3350, 1639 cm^{-1}; ^1H NMR (DMSO-d_6): δ 3.26 (s, 3H), 3.75 (m, 4H), 5.00 (br, 1H), 6.26 (s, 1H), 7.50–7.60 (m, 3H), 8.05–8.10 (m, 2H); ^{13}C NMR (DMSO-d_6): δ 36.5 (q, CH_3), 51.8, 58.9 (2t, 2 CH_2), 95.3 (d, CH_{pyrim}), 126.6, 128.4, 130.0 (3d, 5 CH_{arom}), 137.4 (s, C_{arom}), 155.5, 161.9, 165.1 (3s, 3 C_{pyrim}); MS (FAB^+) *m/z*: 246 ($[M+1]^+$, 100). Anal. Calcd for $C_{13}H_{15}N_3O_2$: C, 63.66; H, 6.16; N, 17.13. Found: C, 63.72; H, 6.03; N, 17.30.

4.3.7. 2-[(2-Hydroxy-ethyl)-methyl-amino]-6-methyl-3*H*-pyrimidin-4-one (10g). From 560 mg (2.49 mmol) of 4-isopropoxipyrimidine **9g**, 387 mg (85%) of compound **10g** was obtained as a colorless solid. Mp: 118–119 °C. R_f 0.26 (dichloromethane/methanol 10:1). IR (neat): 3363–2851, 1647, 1565 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.13 (s, 3H), 3.15 (s, 3H), 3.65 (m, 4H), 4.90 (br, 1H), 5.55 (s, 1H), 10.85 (br, 1H); ^{13}C NMR (DMSO-d_6): δ 23.0, 35.4 (2q, 2 CH_3), 58.0, 50.6, (2t, 2 CH_2), 97.5 (d, CH_{pyrim}), 154.2, 163.6, 164.8 (3s, 3 C_{pyrim}); MS (FAB^+) *m/z*: 206 $[M+23]^+$, 184 $[M+1]^+$. Anal. Calcd for $C_8H_{13}N_3O_2$: C, 52.45; H, 7.15; N, 22.94. Found: C, 52.31; H, 7.23; N, 22.81.

4.3.8. 2-(2-(Hydroxymethyl)pyrrolidin-1-yl)-6-methylpyrimidin-4(3*H*)-one (10h). From 630 mg (2.51 mmol) of 4-isopropoxipyrimidine **9h**, 490 mg (94%) of compound **10h** was obtained as a colorless solid. Mp: 110–111 °C. R_f 0.73 (dichloromethane/methanol 6:1). IR (neat): 3380, 1686 cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.95 (m, 4H), 2.38 (s, 3H), 3.40–3.65 (m, 4H), 4.45 (br, 1H), 5.99 (s, 1H); ^{13}C NMR (DMSO-d_6): δ 19.6, (q, CH_3), 23.2, 27.9, 49.8 (3q, 3 CH_2), 61.6 (d, *C*H), 61.9 (t, CH_2), 100.6 (d, CH_{pyrim}), 151.2, 156.4, 165.6 (3s, 3 C_{pyrim}); MS (FAB^+) *m/z*: 210 $[M+1]^+$. Anal. Calcd for $C_{10}H_{15}N_3O_2$: C, 57.40; H, 7.23; N, 20.08. Found: C, 57.51; H, 7.04; N, 20.11.

4.4. General procedure for the sequential hydrolysis–cyclization of compounds 9. Synthesis of compounds 1

A suspension of the corresponding 4-isopropoxypyrimidine **9** (1 equiv) in concd H_2SO_4 (3 mL/mmol) was heated at 90 °C for 20 min–1 h until the reaction was completed (TLC monitoring). After cooling, the mixture was neutralized with aq 5 N NaOH and extracted with CH_2Cl_2 (3×10 mL/mmol). The combined organic layers were washed with brine (1×10 mL/mmol) and the organic layer was dried over $MgSO_4$, filtered and evaporated under reduced pressure to afford imidazo[1,2-*a*]pyrimidinones **1** ($n=1$) or pyrimido[1,2-*a*]pyrimidinones **1** ($n=2$).

4.4.1. 5,6,7,8,8a,9-Hexahydro-4,4b,9a-triaza-fluoren-1-one (1i). From 123 mg (0.49 mmol) of 4-isopropoxipyrimidine **9i**, 92 mg (98%) of compound **1i** was obtained as a colorless solid. Mp: 93–94 °C. R_f 0.38 (dichloromethane/methanol 10:1). IR (neat): 1659, 1579, 1545 cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.40–1.90 (m, 6H), 3.00 (m, 1H), 3.60–4.25 (m, 4H), 5.68 (d, 1H, $J=6.4$ Hz), 7.66 (d, 1H, $J=6.4$ Hz); ^{13}C NMR (DMSO-d_6): δ 22.5, 23.9, 41.0, 46.4 (5t, 5 CH_2), 54.6 (d, *C*H), 102.9, 155.3 (2d, 2 CH_{pyrim}), 155.6, 160.5 (2s, 2 C_{pyrim}); MS (ESI) *m/z*: 192 $[M+1]^+$. Anal. Calcd for $C_{10}H_{13}N_3O$: C, 62.81; H, 6.85; N, 21.97. Found: C, 62.92; H, 6.66; N, 22.00.

4.4.2. 3-Methyl-5,6,7,8,8a,9-hexahydro-4,4b,9a-triaza-fluoren-1-one (1j). From 103 mg (0.39 mmol) of 4-isopropoxipyrimidine **9j**, 79 mg (99%) of compound **1j** was obtained as a colorless solid. Mp: 121–123 °C. R_f 0.34 (dichloromethane/methanol 10:1). IR (neat): 1657, 1584, 1553 cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.40–1.95 (m, 6H), 2.13 (s, 3H), 2.95 (m, 1H), 3.55–4.20 (m, 4H), 5.58 (s, 1H); ^{13}C NMR (DMSO-d_6): δ 22.6 (t, CH_2), 23.7 (q, CH_3), 23.9, 30.1, 41.0, 46.3 (4t, 4 CH_2), 54.8 (d, CH), 100.6 (d, CH_{pyrim}), 154.7, 160.7, 165.3 (3s, 3 C_{pyrim}); MS (ESI) *m/z*: 206 $[M+1]^+$. Anal. Calcd for $C_{11}H_{15}N_3O$: C, 64.37; H, 7.37; N, 20.47. Found: C, 64.15; H, 7.46; N, 20.32.

4.4.3. 1-Methyl-7-phenyl-2,3-dihydro-1*H*-imidazo[1,2-*a*]pyrimidin-5-one (1f). From 527 mg (1.84 mmol) of 4-isopropoxipyrimidine **9f**, 394 mg (95%) of compound **1f** was obtained as a colorless solid. Mp: 130–131 °C. R_f 0.54 (dichloromethane/methanol 10:1). IR (neat): 1665, 1590, 1553 cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.12 (s, 3H), 3.69 (t, 2H, $J=8.8$ Hz), 4.16 (t, 2H, $J=8.7$ Hz), 6.29 (s, 1H), 7.40–7.50 (m, 3H), 7.95–8.00 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 32.3 (q, CH_3), 41.0, 47.8 (2t, 2 CH_2), 99.8 (d, CH_{pyrim}), 127.8, 129.1, 130.7 (3d, 5 CH_{arom}), 138.1 (s, C_{arom}), 157.3, 163.2, 164.1 (3s, 3 C_{pyrim}); MS (ESI) *m/z*: 228 $[M+1]^+$. Anal. Calcd for $C_{13}H_{13}N_3O$: C, 68.70; H, 5.77; N, 18.49. Found: C, 68.49; H, 5.93; N, 18.54.

4.4.4. 7-Methyl-2,3-dihydro-1*H*-imidazo[1,2-a]pyrimidin-5-one (1b). From 50 mg (0.24 mmol) of 4-isopropoxipyrimidine **9b**, 34 mg (95%) of compound **1b** was obtained as a colorless solid. Mp: 233–234 °C. R_f 0.54 (dichloromethane/methanol 6:1). IR (neat): 1658, 1617, 1567 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.09 (s, 3H), 3.69 (t, 2H, $J=8.8$ Hz), 4.05 (t, 2H, $J=8.8$ Hz), 5.53 (s, 1H), 7.90 (br, 1H); ^{13}C NMR (DMSO-d_6): δ 42.9, 62.1 (2t, 2 CH_2), 105.4 (d, CH_{pyrim}), 150.1, 160.0, 164.8 (3s, 3 C_{pyrim}); MS (ESI) *m/z*: 152 $[M+1]^+$. Anal. Calcd for $C_7H_9N_3O$: C, 55.62; H, 6.00; N, 27.80. Found: C, 55.70; H, 5.77; N, 27.82.

4.4.5. 2-Methyl-6,7,8,9-tetrahydro-pyrimido[1,2-*a*]pyrimidin-4-one (1d). From 420 mg (1.87 mmol) of 4-isopropoxipyrimidine **9d**, 223 mg (73%) of compound **1d** was obtained as a colorless solid. Mp: 204–205 °C. R_f 0.71 (dichloromethane/methanol 6:1). IR (neat): 3262, 1661, 1600, 1580 cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.98 (t, 2H, $J=5.6$ Hz), 2.06 (s, 3H), 3.34 (t, 2H, $J=5.4$ Hz), 3.86 (t, 2H, $J=5.7$ Hz), 5.51 (s, 1H), 7.90 (br, 1H); ^{13}C NMR (DMSO-d_6): δ 19.5 (t, CH_2), 23.4 (q, CH_3), 38.3, 38.4 (2t, 2 CH_2), 98.0 (d, CH_{pyrim}), 153.0, 161.5, 164.0 (3s, 3 C_{pyrim}); MS (ESI) *m/z*: 166 $[M+1]^+$. Anal. Calcd for $C_8H_{11}N_3O$: C, 58.17; H, 6.71; N, 25.44. Found: C, 58.34; H, 6.60; N, 25.66.

4.4.6. 1,7-Dimethyl-2,3-dihydro-1*H*-imidazo[1,2-*a*]pyrimidin-5-one (1g). From 55 mg (2.44 mmol) of 4-isopropoxipyrimidine **9g**, 39 mg (99%) of compound **1g** was obtained as a colorless solid. Mp: 132–133 °C. R_f 0.40 (dichloromethane/methanol 10:1). IR (neat): 1661, 1591, 1567 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.13 (s, 3H), 2.97 (s, 3H), 3.64 (t, 2H, $J=8.9$ Hz), 4.02 (t, 2H, $J=8.9$ Hz), 5.60 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 24.7, 32.2 (2q, 2 CH_3), 40.8, 47.7 (2t, 2 CH_2), 102.3 (d, CH_{pyrim}), 157.0, 162.5, 168.8 (3s, 3 C_{pyrim}); MS (ESI) *m/z*: 188 $[M+23]^+$, 166 $[M+1]^+$. Anal. Calcd for $C_8H_{11}N_3O$: C, 58.17; H, 6.71; N, 25.44. Found: C, 58.27; H, 6.71; N, 25.23.

4.4.7. 5-Methyl-2,3,8,8a-tetrahydro-1*H*-3a,4,7a-triaza-cyclopenta[*a*]inden-7-one (1h). From 300 mg (1.19 mmol) of 4-isopropoxipyrimidine **9h**, 174 mg (76%) of compound **1h** was obtained as a colorless solid. Mp: 77–78 °C. R_f 0.35 (dichloromethane/methanol 10:1). IR (neat): 1661, 1582, 1536 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.30–1.50 (m, 1H), 1.85–2.10 (m, 3H), 2.17 (s, 3H), 3.30–3.40 (m, 1H), 3.65–3.75 (m, 1H), 3.90–4.15 (m, 3H), 5.74 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 24.0 (q, CH_3), 25.0, 30.9, 45.6, 47.1 (4t, 4 CH_2), 59.1 (d, CH), 103.4 (d, CH_{pyrim}), 159.0, 161.8, 166.1 (3s, 3 C_{pyrim}); MS (ESI) *m/z*: 192 $[M+1]^+$. Anal. Calcd for $C_{10}H_{13}N_3O$: C, 62.81; H, 6.85; N, 21.97. Found: C, 63.08; H, 6.96; N, 22.01.

4.5. General procedure for the intramolecular Mitsunobu cyclization. Synthesis of compounds 1 and 2

Under nitrogen atmosphere, a solution of DEAD (1.1 equiv) in dry THF (5 mL/mmol) was added dropwise to a solution of Ph_3P (1.1 equiv) and the appropriate pyrimidinone **10** (1 equiv) in dry THF (10 mL/mmol) at 0 °C. The resulting mixture was warmed to room temperature and stirred for 5–8 h until the reaction was completed (TLC monitoring). The solvent was removed under reduced pressure and the crude product was purified by flash chromatography (ethyl acetate/methanol 10:1) to afford compounds **1** and **2**.

4.5.1. Intramolecular cyclization of pyrimdinone 10a. From 197 mg (1.27 mmol) of pyrimidinone **10a**, 19 mg (11%) of compound **1a** and 140 mg (80%) of compound **2a** were obtained.

4.5.1.1. 2,3-Dihydro-1*H*-imidazo[1,2-*a*]pyrimidin-5-one (1a). Isolated as a colorless solid. Mp: 151–153 °C. R_f 0.54 (dichloromethane/methanol 6:1). IR (neat): 3216, 1661, 1605, 1530 cm^{-1}; ^1H NMR (DMSO-d_6): δ 3.80 (t, 2H, $J=8.9$ Hz), 4.27 (t, 2H, $J=8.8$ Hz), 5.81 (d, 1H, $J=6.8$ Hz), 7.10 (br, 1H), 7.55 (d, 1H, $J=6.6$ Hz); ^{13}C NMR (DMSO-d_6): δ 42.8, 59.5 (2t, 2 CH_2), 102.7, 155.3 (2d, 2 CH_{pyrim}), 155.7, 162.6 (2s, 2 C_{pyrim}); MS (ESI) *m/z*: 138 $[M+1]^+$. Anal. Calcd for $C_6H_7N_3O$: C, 52.55; H, 5.14; N, 30.64. Found: C, 52.36; H, 5.23; N, 30.71.

4.5.1.2. 2,3-Dihydro-1*H*-imidazo[1,2-*a*]pyrimidin-7-one (2a). Isolated as a colorless solid. Mp: 195–196 °C. R_f 0.14 (dichloromethane/methanol 6:1). IR (neat): 3080, 1649, 1604 cm^{-1}; ^1H NMR (DMSO-d_6): δ 3.67 (t, 2H, $J=8.5$ Hz), 4.14 (t, 2H, $J=8.6$ Hz), 5.57 (d, 1H, $J=7.4$ Hz), 7.56 (d, 1H, $J=7.4$ Hz), 7.75 (br, 1H); ^{13}C NMR (DMSO-d_6): δ 40.2, 46.3 (2t, 2 CH_2), 105.1, 138.3 (2d, 2 CH_{pyrim}), 159.2, 171.2 (2s, 2 C_{pyrim}); MS (ESI) *m/z*: 160 $[M+23]^+$, 138 $[M+1]^+$. Anal. Calcd for $C_6H_7N_3O$: C, 52.55; H, 5.14; N, 30.64. Found: C, 52.67; H, 5.22; N, 30.76.

4.5.2. Intramolecular cyclization of pyrimdinone 10e. From 130 mg (0.50 mmol) of pyrimidinone **10e**, 39 mg (33%) of compound **1e** and 54 mg (45%) of compound **2e** were obtained.

4.5.2.1. 2-Benzyl-7-methyl-2,3-dihydro-1*H*-imidazo-[1,2-*a*]pyrimidin-5-one (1e). Isolated as a colorless solid. Mp: 182–183 °C. R_f 0.51 (dichloromethane/methanol 3:1). IR (neat): 3128, 1659, 1564 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.10 (s, 3H), 2.90 (m, 2H), 3.50 (br, 2H), 4.15 (m, 1H), 5.48 (s, 1H), 7.30–7.40 (m, 5H), 7.95 (br, 1H); ^{13}C NMR (DMSO-d_6): δ 19.2 (q, CH_3), 45.6, 49.0 (2t, 2 CH_2), 50.9, (d, *C*H), 99.1 (d, CH_{pyrim}), 126.9, 128.6, 129.5 (3d, 5 CH_{arom}), 138.1 (s, C_{arom}), 155.4, 160.1, 163.2 (3s, 3 C_{pyrim}); MS (FAB^+) *m*/*z*: 242 ([M+1]$^+$, 100). Anal. Calcd for $C_{14}H_{15}N_3O$: C, 69.69; H, 6.27; N, 17.41. Found: C, 69.82; H, 6.12; N, 17.63.

4.5.2.2. 2-Benzyl-5-methyl-2,3-dihydro-1*H*-imidazo[1,2-*a*]pyrimidin-7-one (2e). Isolated as a colorless solid. Mp: 227–228 °C. R_f 0.12 (dichloromethane/methanol 3:1). IR (neat): 3104, 1673, 1620, 1552 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.03 (s, 3H), 2.97 (dd, 1H, $J=13.8$ Hz, $J'=8.2$ Hz), 3.35 (dd, 1H, $J=13.7$ Hz, $J'=4.4$ Hz), 3.71 (dd, 1H, $J=10.1$ Hz, $J'=6.4$ Hz), 3.99 (dd, 1H, $J=10.1$ Hz, $J'=9.4$ Hz), 4.50 (m, 1H), 5.51 (s, 1H), 7.25–7.35 (m, 5H), 9.50 (br, 1H); ^{13}C NMR (DMSO-d_6): δ 17.4 (q, CH_3), 41.0, 48.9 (2t, 2 CH_2), 53.0, (d, *C*H), 103.7 (d, CH_{pyrim}), 127.1, 128.9, 129.8 (3d, 5 CH_{arom}), 137.0 (s, C_{arom}), 148.1, 158.9, 171.9 (3s, 3 C_{pyrim}); MS (FAB^+) *m*/*z*: 242 ([M+1]$^+$, 100). Anal. Calcd for $C_{14}H_{15}N_3O$: C, 69.69; H, 6.27; N, 17.41. Found: C, 69.84; H, 6.24; N, 17.54.

4.5.3. Intramolecular cyclization of pyrimdinone 10d. From 350 mg (1.91 mmol) of pyrimidinone **10d**, 73 mg (25%) of **1d** and 187 mg (66%) of **2d** were obtained. The spectroscopic features of **1d** was identical to those reported above.

4.5.3.1. Spectroscopic data for 4-methyl-6,7,8,9-tetrahydro-pyrimido[1,2-*a*]pyrimidin-2-one (2d). Isolated as a colorless solid. Mp: >300 °C. R_f 0.10 (dichloromethane/methanol 10:1). IR (neat): 3099, 1668, 1618, 1555 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.05 (m, 2H), 2.22 (s, 3H), 3.32 (t, 2H, $J=5.6$ Hz), 3.88 (t, 2H, $J=5.8$ Hz), 5.55 (s, 1H), 7.90 (br, 1H); ^{13}C NMR (DMSO-d_6): δ 18.1 (q, CH_3), 20.3, 38.0, 43.0 (t, CH_2), 106.2 (d, CH_{pyrim}), 149.5, 153.5, 169.2 (s, C_{pyrim}); MS (ESI) *m*/*z*: 166 [M+1]$^+$. Anal. Calcd for $C_8H_{11}N_3O$: C, 52.55; H, 5.14; N, 30.64. Found: C, 52.74; H, 5.35; N, 30.41.

4.5.4. Intramolecular cyclization of pyrimdinone 10c. From 182 mg (1.08 mmol) of pyrimidinone **10c**, 36 mg (22%) of **1c** and 119 mg (73%) of **2c** were obtained.

4.5.4.1. 6,7,8,9-Tetrahydro-pyrimido[1,2-*a*]pyrimidin-4-one (1c). Isolated as a colorless solid. Mp: 178–179 °C. R_f 0.60 (dichloromethane/methanol 3:1). IR (neat): 3219, 1660, 1603, 1555 cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.99 (m, 2H), 3.36 (t, 2H, $J=5.7$ Hz), 3.90 (t, 2H, $J=5.9$ Hz), 5.62 (d, 1H, $J=6.2$ Hz), 7.59 (d, 1H, $J=6.2$ Hz), 7.95 (br, 1H, N*H*); ^{13}C NMR (DMSO-d_6): δ 19.3, 38.3, 38.6 (3t, 3 CH_2), 99.9 (d, CH_{pyrim}), 154.1 (s, C_{pyrim}), 154.6 (d, CH_{pyrim}), 161.3 (s, C_{pyrim}); MS (ESI) *m*/*z*: 152 [M+1]$^+$. Anal. Calcd for $C_7H_9N_3O$: C, 55.62; H, 6.00; N, 27.80. Found: C, 55.49; H, 6.22; N, 27.86.

4.5.4.2. 6,7,8,9-Tetrahydro-pyrimido[1,2-*a*]pyrimidin-2-one (2c). Isolated as a colorless solid. Mp: 235–236 °C. R_f 0.22 (dichloromethane/methanol 3:1). IR (neat): 3170, 1673, 1621, 1553 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.01 (m, 2H), 3.34 (t, 2H, $J=5.3$ Hz), 3.88 (t, 2H, $J=5.3$ Hz), 5.60 (d, 1H, $J=7.4$ Hz), 7.36 (d, 1H, $J=7.4$ Hz), 8.10 (br, 1H); ^{13}C NMR (DMSO-d_6): δ 20.0, 37.8, 47.5 (3t, 3 CH_2), 106.2, 142.3 (2d, 2 CH_{pyrim}), 152.8, 169.8 (2s, 2 C_{pyrim}); MS (ESI) *m*/*z*: 174 [M+23]$^+$, 152 [M+1]$^+$. Anal. Calcd for $C_7H_9N_3O$: C, 55.62; H, 6.00; N, 27.80. Found: C, 55.45; H, 6.03; N, 27.75.

4.5.5. Intramolecular cyclization of pyrimdinone 10g. From 230 mg (1.26 mmol) of pyrimidinone **10g**, 197 mg (96%) of **1g** was obtained. The spectroscopic features of this product were identical to those reported above.

4.6. X-ray crystallographic details

4.6.1. Compound 1h. $C_{10}H_{13}N_3O\cdot 3H_2O$, $M_r=245.28$, trigonal, space group $P3_1$, $a=10.185(3)$ Å, $c=10.217(6)$ Å, $V=917.9(7)$ Å^3, $Z=3$, $D_x=1.331$ g cm^{-3}, $T=-173$ °C, crystal dimensions: $0.01\times0.05\times0.30$ mm, BRUKER SMART APEX-CCD area-detector diffractometer, Mo Kα radiation, $\lambda=0.71073$ Å, $\mu=0.103$ mm^{-1}, $\theta_{max}=28°$, 13947 measured reflections, 1489 symmetry-independent reflections, 1459 reflections with $I>2\sigma(I)$, refinement on F^2 with SHELXL-97,[35] 173 parameters, 1 restraint, $R(F)$ [$I>2\sigma(I)$ reflections]$=0.043$, $wR(F^2)$ [all reflections]$=0.101$, $S(F^2)=1.144$, $\Delta\rho_{max}=0.40$ e Å^{-3}. The asymmetric unit contains one molecule of **1h** plus three molecules of water. The enantiomer used in the refinement model was chosen arbitrarily.

4.6.2. Compound 2e. $2C_{14}H_{15}N_3O\cdot 3H_2O$, $M_r=536.63$, monoclinic, space group $P2_1$, $a=11.6063(2)$ Å, $b=10.0751(2)$ Å, $c=12.4411(2)$ Å, $\beta=108.5550(7)°$, $V=1319.17(4)$ Å^3, $Z=2$, $D_x=1.292$ g cm^{-3}, $T=-113$ °C, crystal dimensions: $0.15\times0.25\times0.27$ mm, Nonius KappaCCD area-detector diffractometer, Mo Kα radiation, $\lambda=0.71073$ Å, $\mu=0.0905$ mm^{-1}, $\theta_{max}=30°$, 36998 measured reflections, 4254 symmetry-independent reflections, 3502 reflections with $I>2\sigma(I)$, refinement on F^2 with SHELXL-97, 387 parameters, 1 restraint, $R(F)$ [$I>2\sigma(I)$ reflections]$=0.038$, $wR(F^2)$ [all reflections]$=0.092$, $S(F^2)=1.037$, $\Delta\rho_{max}=0.15$ e Å^{-3}. The asymmetric unit contains two molecules of **2e** plus three molecules of water. The chosen enantiomer was based on the assumption that the chiral centre in the molecule has the *S*-configuration as a result of the known configuration of the reagents used in the reaction.

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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.2005.11.014. CCDC-276097 and CCDC-287052 contain the supplementary crystallographic data for compounds **1h** and **2e**, respectively. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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New fluorinated 1,3-vinylogous amidines as versatile intermediates: synthesis of fluorinated pyrimidin-2(1*H*)-ones

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Abstract—The condensation of the azaenolates derived from readily available ketimines with fluorinated nitriles offers an efficient and straightforward entry to new fluorinated 1,3-vinylogous amidines. These versatile compounds, in turn, react with triphosgene to yield new fluorinated pyrimidin-2(1*H*)-ones in high yields.

1. Introduction

The introduction of fluorine atoms into organic molecules leads to important changes in the biological activities of the latter.[1] Particularly appealing as synthetic targets are fluorine-containing pyrimidine derivatives, which have been shown to have a wide variety of biological effects. For example, these derivatives are currently being used as insecticides (e.g., Flufenerim),[2a] herbicides (e.g., Primsulfuron-methyl),[2b] fungicides (e.g., Diflumetorim),[2c] and plant growth regulators in crop protection and optimization (e.g., Flurprimidol).[2d,3] They also have numerous important applications as pharmaceuticals,[2e] with one example being 5-fluorouracil, 5-(trifluoromethyl)uracil and their analogs, which have been shown to display potent antitumoral activities.[2f,g] Of the various fluorinated pyrimidine derivatives, however, pyrimidin-2(1*H*)-ones have perhaps received the greatest amount of attention in the past few years; indeed, several have been patented as suitable treatments for neurological,[4a] immunological,[4b] and viral[4c] diseases, as well as for cancer,[4a] CNS,[4d] metabolic[4e] disorders, asthma,[4f] and even as herbicides.[4g]

Among several possible precursors of pyrimidine derivatives, 1,3-vinylogous amidines are particularly interesting, as they can be used for the preparation of both acyclic and heterocyclic compounds with potential biological activity.[5] The two main methods for preparing these compounds include either the condensation of amines with 1,3-dicarbonylic compounds,[6] or the addition of azaenolates to either imidoyl halides,[7] nitriles,[8] or, as was very recently shown, imidoyl alkyl thioethers.[9] However, up until now these methodologies have not been useful for producing the fluorinated counterparts of 1,3-vinylogous amidines. Thus, Butler et al. found that while the condensation of 5-aminolevulinic acid with 1,3-diketones gives pyrroles in non-fluorinated systems, with fluorinated 1,3-diketones the condensation either stops at the intermediate enaminoketone stage when there is only a CF_3 group on the 1,3-diketone, or does not proceed at all when the diketone is fluorinated at both C_α positions.[10] Soloshonok et al. experienced similar problems in their attempts to condense fluorinated 1,3-diketones with benzylamine.[11] As for the second approach, our group has successfully managed to carry out the condensation of azaenolates with fluorinated imidoyl chlorides, a method that is, to the best of our knowledge, the only available strategy for the preparation of fluorinated *N*,*N*′-disubstituted vinylogous amidines.[12] This method allows the use of both cyclic and acyclic ketimines as starting

Keywords: Fluorinated compounds; 1,3-Vinylogous amidines; Pyrimidin-2(1*H*)-ones; Imines; Fluorinated nitriles.

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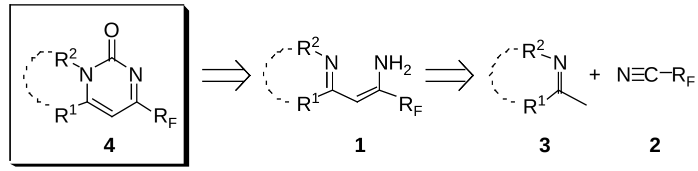


Scheme 1. Retrosynthetic analysis for compounds **1** and **4**.

material, and either aliphatic or aromatic substituents on the N atoms. Finally, Barluenga et al. have used the addition of azaenolates to non-fluorinated nitriles to furnish 1,3-vinylogous amidines,[5] which have subsequently been used in the preparation of acyclic as well as heterocyclic compounds.[13] Regarding the preparation of pyrimidin-2(1*H*)-ones, two main strategies have been used thus far: (i) the reaction between 1,3-dicarbonylic compounds or suitable derivatives with a urea,[14] and (ii) the condensation of 1,3-diimines with a carbonic acid derivative.[13,15,16]

We have now been able to devise an efficient synthesis of new fluorinated 1,3-vinylogous amidines **1** by reacting fluorinated nitriles **2** with ketimines **3** to furnish the corresponding compounds **1** (Scheme 1, retrosynthetic analysis). As an example of the usefulness of these compounds as synthetic intermediates, they were reacted with a suitable carbonic acid derivative to furnish new *C*4-fluoroalkylated *N*1,*C*6-disubstituted pyrimidin-2(1*H*)-ones **4**.

2. Results and discussion

In our synthesis, one aliphatic (**2c**) and two aromatic (**2a**, **2b**) fluorinated nitriles were used as starting materials.

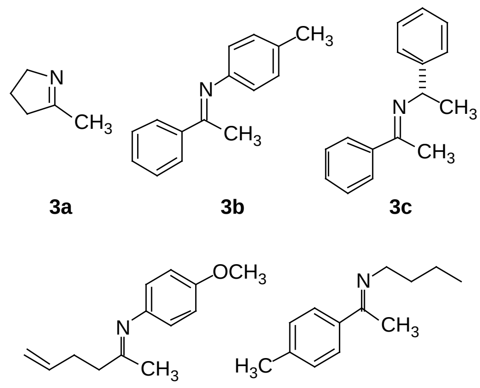


Figure 1. Imines **3** used in the condensation reactions with fluorinated nitriles **2**.

While perfluorooctanenitrile (**2c**) is commercially available, **2a** (2,2-difluoro-2-phenylacetonitrile)[17,18] and **2b** (2,2-difluoro-2-α-naphtylacetonitrile)[18] were prepared with slightly modified[19] procedures previously described in the literature.

We chose five representative *N*-substituted imines for our synthetic study: 2-methyl-1-pyrroline (**3a**), which is commercially available, and four acyclic imines derived from acetophenone (**3b** and **3c**), 5-hexen-2-one (**3d**), and *p*-methylacetophenone (**3e**), respectively. Compounds **3a** and **3d** have two different enolizable positions, while **3c** bears a chiral substituent on the N atom (Fig. 1).[20]

Thus, imines **3** were treated with 1.2 equiv of LDA in THF at −78 °C for 1 h in order to generate their aza-enolates. The temperature was then lowered to −90 °C and a solution of the fluorinated nitrile **2** (1.0 equiv) in THF was added slowly. The reaction was monitored by means of TLC (up to 2 h) and after quenching with aqueous NH_4Cl solution and standard work-up, the resulting crude reaction product was purified through column chromatography on deactivated silica gel (2% Et_3N in hexane) to afford pure fluorinated 1,3-vinylogous amidines **1a–h** in good yields (69–87%, Table 1). The results show that this condensation can be applied to any combination of fluorinated nitrile **2** with an imine **3**, thus allowing for the easy preparation of a variety of fluorinated 1,3-vinylogous amidines **1** (Scheme 2 and Table 1).

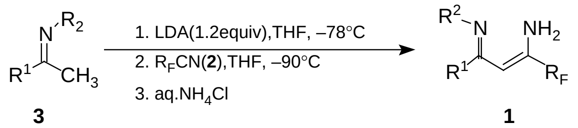
Although in principle compounds **1** might appear in three tautomeric forms (**1**α–γ in Scheme 3), only the corresponding β-imino enaminic tautomer **1**β was present, as confirmed by the ^1H NMR spectra of compounds **1** in $CDCl_3$ at 300 MHz, which showed the presence of a single tautomer in all cases.[12]

While all attempts to prepare suitable monocrystals of compounds **1a–h** failed, it was possible to prepare a complex of compound **1a** and ZnI_2 in CH_2Cl_2, which, in turn, did allow the preparation of suitable monocrystals for X-ray diffraction analysis. The X-ray diffraction structure for the complex **1a·ZnI₂** clearly shows a 1,3-diimine

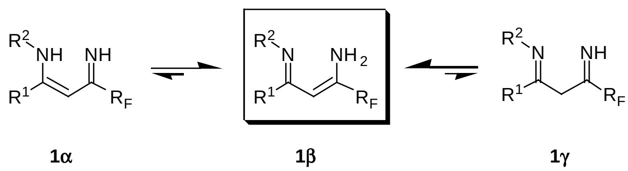
Table 1. Results for the preparation of the fluorinated 1,3-vinylogous amidines **1** (Scheme 2)

Entry	R_F	R^1	R^2	1	Yield (%)[a]
1	$CF_2C_6H_5$	–$CH_2CH_2CH_2$–		**1a**	87
2	$CF_2C_6H_5$	C_6H_5	(*S*)-(+)-C_6H_5(Me)CH	**1b**	81
3	$CF_2C_6H_5$	C_6H_5	*p*-MeC_6H_4	**1c**	83
4	$CF_2C_6H_5$	CH_2=$CH_2CH_2CH_2$	*p*-$MeOC_6H_4$	**1d**	70
5	CF_2(α-$C_{10}H_7$)	–$CH_2CH_2CH_2$–		**1e**	75
6	$CF_3(CF_2)_6$	–$CH_2CH_2CH_2$–		**1f**	71
7	$CF_3(CF_2)_6$	C_6H_5	*p*-MeC_6H_4	**1g**	79
8	$CF_2C_6H_5$	*p*-MeC_6H_4	$CH_3CH_2CH_2CH_2$	**1h**	69

[a] Yield for purified product.



Scheme 2. The synthesis of 1,3-vinylogous amidines **1** from imines **3** and fluorinated nitriles **2**.



Scheme 3. The tautomeric equilibrium in compounds **1**.

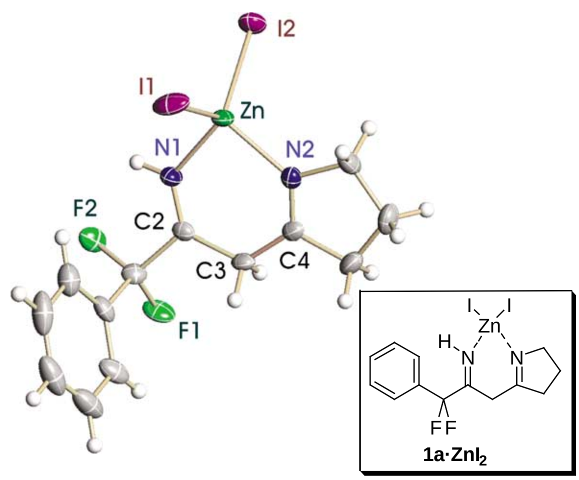


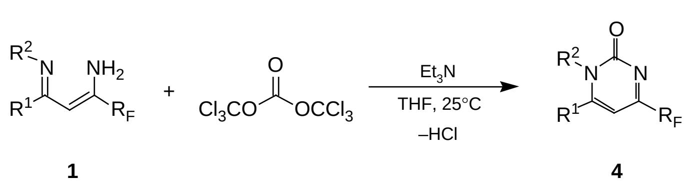
Figure 2. X-ray Structure of complex **1a**·**ZnI$_2$**. Arbitrary numbering is used in the ORTEP diagram.

structure that coordinates to the Zn atom with both N atoms (Fig. 2).[21,22] Thus, the formation of the Zn complex favors the presence of the diiminic form, in contrast with the situation observed in solution (see above). In the crystal structure, compound **1a** is *N*,*N*-chelated to the Zn atom, which is also coordinated to two iodine atoms. The geometry around the Zn atom is tetrahedral. The *N*,*N*-**1a** chelated ligand forms a quasiplanar six-member metallacycle (mean deviation 0.030 Å), with the metallacycle and the dihydropirrole ring being coplanar [N(1)–Zn–N(2)–C(4)–1.3(5) Å]. In the crystal, intermolecular N–H–I hydrogen bonds form infinite zigzag chains.[21]

The synthetic usefulness of amidines **1** was proven by their transformation into the newly described fluorinated pyrimidin-2(1*H*)-ones **4** through reaction with a suitable carbonic acid derivative. We chose triphosgene [bis(trichloromethyl)carbonate (BTC)][23] for this purpose because of its ease of handling and high reactivity towards *N*,*N'*-binucleophilic compounds. Thus, a solution of triphosgene (1.0 equiv) in THF was added to a solution of compound **1** (1.0 equiv) and Et_3N (2.0 equiv) in THF at room temperature. The reaction mixture was stirred until the starting material was no longer present (0.5–3 h, TLC analysis). Standard work-up furnished crude derivatives **4**, which were then purified by means of flash chromatography to afford fluorinated pyrimidin-2(1*H*)-ones **4a–h** in yields that ranged from 70 to 94% (Scheme 4 and Table 2).

3. Conclusion

In conclusion, fluorinated nitriles have once again proven to be versatile starting materials for the preparation of fluorinated heterocycles. In this case, the condensation of the azaenolates derived from readily available ketimines with fluorinated nitriles affords fluorinated 1,3-vinylogous amidines **1** in good yields. These compounds, in turn, easily react with triphosgene to yield fluorinated pyrimidin-2(1*H*)-ones **4** in high yields. Further studies on the reactivity of fluorinated derivatives **1** are currently under way in our laboratories and will be published in due course.



Scheme 4. The reaction of compounds **1** with triphosgene affords compounds **4**.

Table 2. Pyrimidin-2(1*H*)-ones **1** synthesized from derivatives **4** and triphosgene (Scheme 4)

Entry	1	R^1	R^2	R_F	4	Yield (%)[a]
1	**1a**	$-CH_2CH_2CH_2-$		$CF_2C_6H_5$	**4a**	94
2	**1b**	C_6H_5	(*S*)-(+)-C_6H_5(Me)CH	$CF_2C_6H_5$	**4b**	90
3	**1c**	C_6H_5	*p*-MeC_6H_4	$CF_2C_6H_5$	**4c**	87
4	**1d**	$CH_2CH_2CH{=}CH_2$	*p*-$MeOC_6H_4$	$CF_2C_6H_5$	**4d**	84
5	**1e**	$-CH_2CH_2CH_2-$		$CF_2(\alpha\text{-}C_{10}H_7)$	**4e**	77
6	**1f**	$-CH_2CH_2CH_2-$		$CF_3(CF_2)_6$	**4f**	93
7	**1g**	C_6H_5	*p*-MeC_6H_4	$CF_3(CF_2)_6$	**4g**	90
8	**1h**	*p*-MeC_6H_4	$CH_3CH_2CH_2CH_2$	$CF_2C_6H_5$	**4h**	70

[a] Yield for purified product.

4. Experimental

4.1. General

All reactions were performed with magnetic stirring in flamedried glassware under an argon atmosphere using dry, distilled solvents. Tetrahydrofuran (THF) was distilled over Na–K alloy while dichloromethane (CH_2Cl_2) was distilled over CaH_2. All other commercially obtained reagents were used as received. All reactions were monitored with thin-layer chromatography (TLC) in which precoated 250 micron softlayer silica gel GF uniplates (Merck) were used. TLC plates were visualized with UV light (254 nm), vanillin, or ammonium molybdate sprays. Flash chromatography was performed with the indicated solvent system on 60 Å (230–400 mesh, particle size 0.040–0.063 mm) normal phase silica gel. In several cases, all of which are clearly identified in the text, the silica gel for column chromatography was deactivated prior to the actual separation through treatment overnight with a 2% solution of triethylamine in hexane, followed by equilibration with the solvent mixture finally employed. 'Concentrated' refers to the removal of solvent with a rotary evaporator at normal water aspirator pressure followed by further evacuation with a two-stage mechanical pump. Yields refer to chromatographically and spectroscopically pure compounds, except where otherwise noted. All new compounds were determined to be at least 95% pure by means of NMR or GC. All melting points were determined with an open capillary. Chemical shifts were reported in δ values relative to tetramethylsilane in ^{1}H NMR standard, fluorotrichloromethane in ^{19}F NMR, and the solvent peak in ^{13}C NMR. Peak splitting patterns in the NMR are reported as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad.

4.2. Preparation of imines 3b–e

A standard method was used for the preparation of imines **3b–e**:[20,24] the ketone and the primary amine were refluxed with *p*-toluenesulfonic acid catalysis in refluxing toluene in a Dean–Stark apparatus until water formation was no longer observed. After standard work-up, the desired imines were purified through vacuum distillation. Yields for the purified imines were 93% for **3b**, 80% for **3c**, 65% for **3d**, and 72% for **3e**.

4.2.1. (4-Methoxyphenyl)-[1-methylpent-4-(*E*)-enylidene]-amine (3d). Yellowish oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.79 (s, 3H), 2.46 (m, 4H), 3.78 (s, 3H), 5.02 (dd, J_1=10.2 Hz, J_2=1.7 Hz, 1H), 5.09 (dd, J_1=17.3 Hz, J_2=1.7 Hz, 1H), 5.91 (m, 1H), 6.63 (d, J=8.7 Hz, 2H), 6.84 (d, J=8.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.6 (q), 30.5 (t), 40.7 (t), 55.4 (q), 114.1 (d), 115.0 (t), 120.6 (d), 137.7 (d), 144.7 (s), 155.7 (s), 171.4 (s). HRMS (EI$^+$) calcd for $C_{13}H_{17}NO$ (M$^+$): 203.1310, found: 203.1313.

4.2.2. (*E*)-Butyl-[1-*p*-tolylethylidene]-amine (3e). Yellowish oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.01 (t, J=7.5 Hz, 3H), 1.49 (m, 2H), 1.76 (m, 2H), 2.23 (s, 3H), 2.39 (s, 3H), 3.50 (t, J=7.2 Hz, 2H), 7.20 (d, J=8.1 Hz, 2H), 7.70 (d, J=8.1 Hz, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.5 (q), 15.6 (q), 21.3 (t), 21.6 (q), 33.6 (t), 52.3 (t), 126.9 (d), 129.3 (d), 139.2 (s), 139.6 (s), 164.9 (s). HRMS (EI$^+$) calcd for $C_{13}H_{19}N$ (M$^+$): 189.1517, found: 189.1522.

4.3. General procedure for the preparation of 1,3-vinylogous amidines 1a–h

n-Butyllithium (3.0 mmol, 2.5 M in hexane) was slowly added to a solution of diisopropylamine (3.0 mmol) in THF (3 mL) at −30 °C. The mixture was stirred for 30 min, after which the temperature was lowered to −90 °C. A solution of the imine **3** (2.5 mmol) in THF (5 mL) was then added dropwise and the reaction mixture was stirred for 1 h at that temperature to allow azaenolate formation, after which a solution of the nitrile **2** (2.5 mmol) in THF (5 mL) was slowly added. The progress of the reaction was monitored with TLC, and after ca. 1–2 h the reaction was quenched with saturated aqueous NH_4Cl solution and extracted with AcOEt (3×10 mL). The organic layers were pooled together, washed with brine, dried over anhydrous Na_2SO_4, and concentrated to give crude product **1**, which was purified as described below in each case.

4.3.1. (*Z*)-1-(Difluorophenylmethyl)-2-(4,5-dihydro-3*H*-pyrrol-2-yl)vinylamine (1a). Flash chromatography of the crude reaction product [*n*-hexane/EtOAc (3:1)] on deactivated silica gel (2% Et_3N in hexane overnight) gave a yellowish solid (87% yield): mp 82–84 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.69–1.79 (m, 2H), 2.48 (t, J=8.2 Hz, 2H), 3.85 (t, J=7.2 Hz, 2H), 4.96 (s, 1H), 6.60 (br s, 2H), 7.35–7.37 (m, 3H), 7.50–7.53 (m, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 20.9 (t), 37.0 (t), 59.0 (t), 88.4 (t, $^3J_{CF}$=6.0 Hz), 117.2 (t, $^1J_{CF}$=243.7 Hz), 124.6 (t, $^3J_{CF}$=5.7 Hz), 127.4 (d), 129.3 (t, $^4J_{CF}$=1.7 Hz), 134.2 (t, $^2J_{CF}$=27.3 Hz), 148.2 (t, $^2J_{CF}$=28.1 Hz), 172.2 (s); ^{19}F NMR (282.4 MHz, $CDCl_3$) δ −98.5 (s). HRMS (EI$^+$) calcd for $C_{13}H_{14}F_2N_2$ (M$^+$): 236.1125, found: 236.1136.

4.3.2. (+)-(*Z*)-1-(Difluorophenylmethyl)-3-[(*Z*)-(*S*)-1-phenylethylimino]-3-phenylpropenylamine (1b). Flash chromatography of the crude reaction product [*n*-hexane/EtOAc (10:1)] on deactivated silica gel (2% Et_3N in hexane overnight) gave a yellowish oil (81% yield). $[\alpha]_D^{25}$ +233.8 (*c* 1.11, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.37 (d, J=6.6 Hz, 3H), 4.43 (q, J=6.6 Hz, 1H), 4.81 (s, 1H), 7.04–7.11 (m, 4H), 7.13–7.22 (m, 6H), 7.23–7.32 (m, 3H), 7.33–7.49 (m, 2H), 8.95 (br, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 25.9 (q), 57.2 (d), 92.9 (t, $^3J_{CF}$=3.5 Hz), 117.9 (t, $^1J_{CF}$=245.5 Hz), 126.0 (t, $^3J_{CF}$=6.0 Hz), 126.4 (d), 127.1 (d), 127.8 (d), 128.5 (d), 128.8 (d), 128.9 (d), 130.6 (d), 136.0 (t, $^2J_{CF}$=27.6 Hz), 138.2 (s), 146.2 (s), 161.5 (t, $^2J_{CF}$=28.2 Hz), 164.2 (s); ^{19}F NMR (282.4 MHz, $CDCl_3$) δ −100.1 (s). HRMS (EI$^+$) calcd for $C_{24}H_{22}F_2N_2$ (M$^+$): 376.1751, found: 376.1768.

4.3.3. [(*Z*)-3-Amino-4,4-difluoro-1,4-diphenyl-but-2-en-(*Z*)-ylidene]-*p*-tolylamine (1c). Flash chromatography of the crude reaction product [*n*-hexane/EtOAc (10:1)] on deactivated silica gel (2% Et_3N in hexane overnight) gave a yellow oil (83% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.13 (s, 3H), 5.18 (s, 1H), 6.49 (d, J=8.3 Hz, 2H), 6.81 (d, J=8.1 Hz, 2H), 7.06–7.13 (m, 5H), 7.35–7.38 (m, 3H), 7.52–7.55 (m, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 21.1 (q), 95.5 (t, $^3J_{CF}$=4.9 Hz), 118.2 (t, $^1J_{CF}$=245.1 Hz), 122.5

(d), 126.0 (t, $^3J_{CF}$=5.7 Hz), 128.4 (d), 128.7 (d), 128.7 (d), 128.9 (d), 129.4 (d), 130.8 (d), 132.6 (s), 135.5 (t, $^2J_{CF}$=27.3 Hz), 138.8 (s), 145.6 (s), 155.0 (t, $^2J_{CF}$=28.4 Hz), 165.3 (s); ^{19}F NMR (282.4 MHz, $CDCl_3$) δ −99.2 (s). HRMS (EI^+) calcd for $C_{23}H_{20}F_2N_2$ (M^+): 362.1594, found: 362.1557.

4.3.4. [1-((*Z*)-2-Amino-3,3-difluoro-3-phenylpropenyl)-pent-4-en-(*E*)-ylidene]-(4-methoxyphenyl)amine (1d). Flash chromatography of the crude reaction product [*n*-hexane/EtOAc (4:1)] on deactivated silica gel (2% Et_3N in hexane overnight) gave a brownish oil (70% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.04–2.12 (m, 2H), 2.18–2.22 (m, 2H), 3.68 (s, 3H), 4.77–4.84 (m, 2H), 5.02 (s, 1H), 5.48–5.61 (m, 1H), 6.62 (d, *J*=8.8 Hz, 2H), 6.75 (d, *J*=8.8 Hz, 2H), 7.34–7.37 (m, 3H), 7.51–7.54 (m, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 31.1 (t), 32.2 (t), 54.3 (c), 92.5 (t, $^3J_{CF}$=5.7 Hz), 113.0 (d), 114.0 (t), 117.1 (t, $^1J_{CF}$=243.9 Hz), 120.7 (d), 124.6 (t, $^3J_{CF}$=5.7 Hz), 127.4 (d), 129.4 (d), 134.2 (t, $^2J_{CF}$=27.3 Hz), 136.1 (d), 142.1 (s), 149.1 (t, $^2J_{CF}$=27.9 Hz), 154.6 (s), 168.9 (s); ^{19}F NMR (282.4 MHz, $CDCl_3$) δ −98.6 (s). HRMS (EI^+) calcd for $C_{21}H_{22}F_2N_2O$ (M^+) 356.1700, found: 356.1661.

4.3.5. (*Z*)-1-(Difluoronaphthalen-1-yl-methyl)-2-(4,5-dihydro-3*H*-pyrrol-2-yl)vinylamine (1e). Flash chromatography of the crude reaction product [*n*-hexane/EtOAc (4:1)] on deactivated silica gel (2% Et_3N in hexane overnight) gave a yellowish solid (75% yield): mp 163–165 °C. ^{1}H NMR (300 , $CDCl_3$) δ 1.55–1.65 (m, 2H), 2.29 (t, *J*=8.2 Hz, 2H), 3.77 (t, *J*=7.2 Hz, 2H), 4.85 (s, 1H), 6.99 (br s, 2H), 7.29–7.37 (m, 3H), 7.69–7.79 (m, 3H), 8.04–8.07 (m, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 20.8 (t), 36.9 (t), 58.9 (t), 89.0 (t, $^3J_{CF}$=6.0 Hz), 118.4 (t, $^1J_{CF}$=243.1 Hz), 123.2 (d), 124.1 (t, $^4J_{CF}$=2.6 Hz), 124.5 (t, $^3J_{CF}$=8.6 Hz), 125.0 (d), 125.8 (d), 127.5 (d), 128.9 (t, $^3J_{CF}$=1.7 Hz), 129.0 (t, $^2J_{CF}$=24.9 Hz), 130.5 (d), 132.8 (s), 148.1 (t, $^2J_{CF}$=27.0 Hz), 172.2 (s); ^{19}F NMR (282.4 MHz, $CDCl_3$) δ −93.2 (s). HRMS (EI^+) calcd for $C_{17}H_{16}F_2N_2$ (M^+): 286.1281, found: 286.1311.

4.3.6. 1-[1-(4,5-Dihydro-3*H*-pyrrol-2-yl)-meth-(*Z*)-ylidene]-2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-pentadecafluorooctylamine (1f). Flash chromatography of the crude reaction product [*n*-hexane/EtOAc (10:1)] on deactivated silica gel (2% Et_3N in hexane overnight) gave a white solid (71% yield): mp 140–142 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.74–1.85 (m, 2H), 2.55 (t, *J*=8.2 Hz, 2H), 3.88 (t, *J*=7.2 Hz, 2H), 5.14 (s, 1H), 7.02 (br s, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 20.8 (t), 36.8 (t), 58.7 (t), 90.3 (t, $^3J_{CF}$=6.6 Hz), 107–130 (signals for the C_7F_{15} group were obscured because of their low intensity), 140.9 (t, $^2J_{CF}$=24.1 Hz), 171.5 (s); ^{19}F NMR (282.4 MHz, $CDCl_3$) δ −81.1 (m, 3F), −118.4 (m, 2F), −122.0 (m, 2F), −122.4 (m, 2F), −122.8 (m, 2F), −123.1 (m, 2F), −126.5 (m, 2F). HRMS (EI^+) calcd for $C_{13}H_9F_{15}N_2$ (M^+): 478.0526, found: 478.0527.

4.3.7. [(*Z*)-3-Amino-4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-pentadecafluoro-1-phenyldec-2-en-(*Z*)-ylidene]-*p*-tolylamine (1g). Recrystallization from *n*-hexane/CH_2Cl_2 (20:1) gave a yellowish solid (79% yield): mp 63–65 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.16 (s, 3H), 5.34 (s, 1H), 6.56 (d, *J*=8.1 Hz, 2H), 6.86 (d, *J*=8.1 Hz, 2H), 7.10–7.20 (m, 3H), 7.49–7.57 (m, 2H), 8.12–8.18 (m, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 21.1 (t), 96.9 (d), 107–130 (signals for the C_7F_{15} group were obscured because of their low intensity), 138.2 (s), 145.0 (s), 165.1 (s); ^{19}F NMR (282.4 MHz, $CDCl_3$) δ −81.2 (m, 3F), −118.7 (m, 2F), −121.9 (m, 2F), −122.3 (m, 2F), −122.3 (m, 2F), −123.1 (m, 2F), −126.6 (m, 2F). HRMS (EI^+) calcd for $C_{23}H_{15}F_{15}N_2$ (M^+): 604.0995, found: 604.0978.

4.3.8. (*Z*)-3-[(*Z*)-Butylimino]-1-(difluorophenylmethyl)-3-*p*-tolylpropenylamine (1h). Flash chromatography of the crude reaction product [*n*-hexane/EtOAc (10:1)] on deactivated silica gel (2% Et_3N in hexane overnight) gave a yellow oil (69% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.78 (t, *J*=7.1 Hz, 3H), 1.19–1.31 (m, 2H), 1.38–1.47 (m, 2H), 2.29 (s, 3H), 3.09 (t, *J*=6.8 Hz, 2H), 4.72 (s, 1H), 7.10 (s, 4H), 7.31–7.35 (m, 3H), 7.44–7.47 (m, 2H), 9.17 (br s, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.2 (q), 20.5 (t), 21.7 (q), 33.7 (t), 46.4 (t), 90.6 (d), 125.9 (t, $^3J_{C-F}$=5.5 Hz), 128.1 (d), 128.8 (d), 129.2 (d), 130.5 (d), 134.7 (s), 139.0 (s), 163.8 (s), 165.7 (s); ^{19}F NMR (282.4 MHz, $CDCl_3$) δ −100.58 (s). HRMS (EI^+) calcd for $C_{21}H_{24}F_2N_2$ (M^+): 342.1907, found: 342.1897.

4.4. General procedure for the preparation of pyrimidin-2(1*H*)-ones 4a–h

A solution of triphosgene (2.0 mmol) in THF (5 mL) was slowly added to a solution of compound **1** (2.0 mmol) and triethylamine (4 mmol) in THF (10 mL) and the resulting mixture was stirred at room temperature. When TLC monitoring indicated that the reaction was complete, it was quenched with aqueous 2 M KOH solution (5 mL) and extracted with AcOEt (3×5 mL). The organic layers were pooled together, washed with brine, dried over anhydrous Na_2SO_4, and the solvent was removed under vacuum to give a solid, which was purified as indicated below in each case.

4.4.1. 3-[Difluoro(phenyl)methyl]-6,7-dihydropyrrolo-[1,2-*f*]pyrimidin-1(5*H*)-one (4a). Flash chromatography [*n*-hexane/EtOAc (2:1)] gave a colorless oil (94% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.09–2.19 (m, 2H), 3.07 (t, *J*=7.9 Hz, 2H), 4.02 (t, *J*=7.4 Hz, 2H), 6.51 (s, 1H), 7.30–7.34 (m, 3H), 7.52–7.56 (m, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 18.9 (t), 31.6 (t), 49.0 (t), 95.1 (t, $^3J_{CF}$=4.3 Hz), 116.0 (t, $^1J_{CF}$=247.1 Hz), 124.6 (t, $^3J_{CF}$=6.3 Hz), 127.4 (d), 129.4 (d), 133.8 (t, $^2J_{CF}$=26.7 Hz), 154.4 (s), 163.9 (s), 169.3 (t, $^2J_{CF}$=31.9 Hz); ^{19}F NMR (282.4 MHz, $CDCl_3$) δ −100.7 (s). HRMS (EI^+) calcd for $C_{14}H_{12}F_2N_2O$ (M^+): 262.0917, found: 262.0925.

4.4.2. 4-(Difluoro(phenyl)methyl)-6-phenyl-1-((*S*)-1-phenylethyl)pyrimidin-2(1*H*)-one (4b). Flash chromatography [*n*-hexane/EtOAc (4:1)] gave a white solid (90% yield): mp 193–195 °C. $[\alpha]_D^{25}$ −5.79 (*c* 0.91, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.82 (d, *J*=7.1 Hz, 3H), 5.46 (q, *J*=7.1 Hz, 1H), 6.44 (s, 1H), 7.04–7.18 (m, 7H), 7.34–7.41 (m, 6H), 7.59 (dd, J_1=7.5 Hz, J_2=4.9 Hz, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 17.2 (q), 58.9 (q), 102.1 (t, $^3J_{CF}$=4.0 Hz), 117.2 (s), 126.3 (t, $^3J_{CF}$=6.3 Hz), 127.1 (d), 127.8 (d), 127.9 (d), 128.7 (d), 128.9 (d), 129.4 (d), 130.9 (d), 134.1 (s), 134.9 (s), 139.1 (s), 155.6 (s), 163.4 (s), 169.7 (s);

^{19}F NMR (282.4 MHz, $CDCl_3$) δ −100.5 (d, $^3J_{HF}$= 3.4 Hz). HRMS (EI^+) calcd for $C_{25}H_{20}F_2N_2O$ (M^+): 402.1544, found: 402.1546.

4.4.3. 4-[Difluoro(phenyl)methyl]-6-phenyl-1-*p*-tolylpyrimidin-2(1*H*)-one (4c). Recrystallization from *n*-hexane/AcOEt (10:1) gave a white solid (87% yield): mp 204–206 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 2.19 (s, 3H), 6.64 (s, 1H), 6.89 (d, J=8.3 Hz, 2H), 6.99 (d, J=8.1 Hz, 2H), 7.03–7.16 (m, 2H), 7.13–7.23 (m, 3H), 7.37–7.40 (m, 3H), 7.65–7.68 (m, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 20.1 (q), 100.0 (t, $^3J_{CF}$=4.0 Hz), 115.8 (t, $^1J_{CF}$=247.4 Hz), 124.8 (t, $^3J_{CF}$=6.0 Hz), 126.9 (d), 127.3 (d), 127.4 (d), 127.5 (d), 128.7 (d), 129.0 (d), 129.5 (d), 132.1 (s), 133.5 (t, $^2J_{CF}$=26.7 Hz), 133.8 (s), 137.8 (s), 155.3 (s), 161.1 (s), 169.7 (t, $^2J_{CF}$=32.4 Hz); ^{19}F NMR (282.4 MHz, $CDCl_3$) δ −100.9 (s). HRMS (EI^+) calcd for $C_{24}H_{18}F_2N_2O$ (M^+): 388.1387, found: 388.1298.

4.4.4. 6-(But-3-enyl)-4-[difluoro(phenyl)methyl]-1-(4-methoxyphenyl)pyrimidin-2(1*H*)-one (4d). Flash chromatography [*n*-hexane/EtOAc (4:1)] gave a white solid (84% yield): mp 115–117 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 2.13–2.20 (m, 2H), 2.30–2.35 (m, 2H), 3.75 (s, 3H), 4.84–4.93 (m, 2H), 5.46–5.60 (m, 1H), 6.53 (s, 1H), 6.93 (d, J=9.0 Hz, 2H), 7.01 (d, J=9.0 Hz, 2H), 7.35–7.38 (m, 3H), 7.60–7.63 (m, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 30.0 (t), 32.1 (t), 54.5 (q), 97.9 (t, $^3J_{CF}$=4.0 Hz), 114.3 (d), 115.8 (t, $^1J_{CF}$=247.1 Hz), 115.9 (t), 124.7 (t, $^3J_{CF}$= 6.3 Hz), 127.3 (d), 127.5 (d), 128.3 (s), 129.5 (d), 133.6 (t, $^2J_{CF}$=26.7 Hz), 134.0 (d), 155.9 (s), 159.1 (s), 163.3 (s), 169.4 (t, $^2J_{CF}$=32.2 Hz); ^{19}F NMR (282.4 MHz, $CDCl_3$) δ −101.0 (s). HRMS (EI^+) calcd for $C_{22}H_{20}F_2N_2O_2$ (M^+): 382.1492, found: 382.1493.

4.4.5. 3-[Difluoro(naphthalen-1-yl)methyl]-6,7-dihydropyrrolo[1,2-*f*]pyrimidin-1(5*H*)-one (4e). Recrystallization from *n*-hexane/CH_2Cl_2 (20:1) gave a white solid (77% yield): mp 228–230 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 2.05–2.15 (m, 2H), 3.03 (t, J=7.9 Hz, 2H), 4.01 (t, J= 7.4 Hz, 2H), 6.53 (s, 1H), 7.37–7.46 (m, 3H), 7.75–7.79 (m, 1H), 7.82–7.87 (m, 2H), 8.04–8.07 (m, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 20.4 (t), 32.9 (t), 50.3 (t), 97.2 (t, $^3J_{CF}$=3.1 Hz), 118.7 (t, $^1J_{CF}$=247.1 Hz), 125.0 (d), 125.3 (t, $^4J_{CF}$=3.1 Hz), 125.5 (t, $^3J_{CF}$=9.4 Hz), 126.4 (d), 127.4 (d), 129.1 (d), 129.7 (t, $^3J_{CF}$=2.3 Hz), 130.5 (t, $^2J_{CF}$= 24.4 Hz), 132.0 (d), 134.3 (s), 155.8 (s), 164.8 (s), 170.7 (t, $^2J_{CF}$=31.3 Hz); ^{19}F NMR (282.4 MHz, $CDCl_3$) δ −95.8 (s). HRMS (EI^+) calcd for $C_{18}H_{14}F_2N_2O$ (M^+): 312.1074, found: 312.1053.

4.4.6. 6,7-Dihydro-3-(perfluoroheptyl)pyrrolo[1,2-*f*]-pyrimidin-1(5*H*)-one (4f). Recrystallization from *n*-hexane/$CHCl_3$ (20:1) gave a reddish solid (93% yield): mp 129–131 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 2.21–2.31 (m, 2H), 3.17 (t, J=7.8 Hz, 2H), 4.17 (t, J=7.5 Hz, 2H), 6.52 (s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 20.3 (t), 33.2 (t), 50.7 (t), 97.7 (t, $^3J_{CF}$=4.3 Hz), 104–134 (signals for the C_7F_{15} group were obscured because of their low intensity), 163.5 (t, $^2J_{CF}$=25.8 Hz), 166.1 (s); ^{19}F NMR (282.4 MHz, $CDCl_3$) δ −81.2 (m, 3F), −116.4 (m, 2F), −121.7 (m, 4F), −122.4 (m, 2F), −123.1 (m, 2F), −126.5 (m, 2F). HRMS (EI^+) calcd for $C_{14}H_7F_{15}N_2O$ (M^+): 504.0318, found: 504.0327.

4.4.7. 4-(Perfluoroheptyl)-6-phenyl-1-*p*-tolylpyrimidin-2(1*H*)-one (4g). Flash chromatography [*n*-hexane/EtOAc (4:1)] gave a colorless oil (90% yield). ^1H NMR (300 MHz, $CDCl_3$) δ 2.21 (s, 3H), 6.59 (s, 1H), 6.94 (d, J=8.3 Hz, 2H), 7.02–7.09 (m, 4H), 7.17–7.27 (m, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 21.5 (q), 102.5 (d), 110–135 (signals for the C_7F_{15} group were obscured because of their low intensity), 128.2 (d), 128.8 (d), 128.9 (d), 130.3 (d), 130.9 (d), 132.9 (s), 134.8 (s), 139.6 (s), 155.8 (s), 163.6 (s), 163.7 (s); ^{19}F NMR (282.4 MHz, $CDCl_3$) δ −81.2 (m, 3F), −117.0 (m, 2F), −121.5 (m, 4F), −122.3 (m, 2F), −123.0 (m, 2F), −126.5 (m, 2F). HRMS (EI^+) calcd for $C_{24}H_{14}F_{15}N_2O$ (M+H^+): 631.0886, found: 631.0862.

4.4.8. 1-Butyl-4-(difluoro(phenyl)methyl)-6-*p*-tolylpyrimidin-2(1*H*)-one (4h). Flash chromatography [*n*-hexane/ EtOAc (4:1)] gave a colorless oil (70% yield). ^1H NMR (300 MHz, $CDCl_3$) δ 0.65 (t, J=7.2 Hz, 3H), 0.98–1.11 (m, 2H), 1.47–1.57 (m, 2H), 2.35 (s, 3H), 3.80 (t, J= 7.9 Hz, 2H), 6.42 (s, 1H), 7.13–7.15 (m, 2H), 7.22–7.25 (m, 2H), 7.33–7.35 (m, 3H), 7.58 (dd, J_1=6.4 Hz, J_2=1.5 Hz, 2H); ^{13}C NMR (75.5 Hz, $CDCl_3$) δ 13.8 (q), 20.2 (t), 21.8 (q), 30.5 (t), 47.8 (t), 101.9 (t, $^3J_{CF}$=4.0 Hz), 117.2 (t, $^1J_{CF}$=272.6 Hz), 126.2 (t, $^3J_{CF}$=6.3 Hz), 127.9 (d), 128.9 (d), 130.0 (d), 130.6 (d), 130.8 (d), 135.1 (t, $^2J_{CF}$=26.4 Hz), 141.4 (s), 156.7 (s), 163.3 (s), 169.4 (t, $^2J_{CF}$=32.2 Hz); ^{19}F NMR (282.4 MHz, $CDCl_3$) δ −100.8 (s). HRMS (EI^+) calcd for $C_{22}H_{22}F_2N_2O$ (M^+): 368.1700, found: 368.1677.

4.5. Preparation of compound 1a·ZnI_2

A solution of **1a** (243 mg; 1.03 mmol) in CH_2Cl_2 (3 mL) was slowly added to a solution of ZnI_2 (330 mg; 1.03 mmol) in CH_2Cl_2 (4 mL) at 0 °C. The mixture was stirred for 1 h, after which the solvent was removed under vacuum to give a solid, which was then purified by means of recrystallization from *n*-hexane/CH_2Cl_2. Mp 158–159 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 2.01 (m, 2H), 2.74 (t, J=8.0 Hz, 2H), 3.71 (s, 2H), 4.14 (t, J=7.5 Hz, 2H), 7.51 (m, 5H), 10.22 (s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 20.1 (t), 32.0 (t), 41.2 (t), 60.6 (t), 116.3 (s), 125.9 (t, $^3J_{CF}$=5.8 Hz), 129.3 (s), 130.3 (d), 133.0 (d), 174.3 (s), 177.4 (s); ^{19}F NMR (282.4 MHz, $CDCl_3$) δ −104.8 (s, 2F).

The crystal structure of compound **1a·ZnI₂** was determined through X-ray diffraction of a single crystal obtained by slow evaporation of a dichloromethane/*n*-hexane solution (Fig. 2).

X-ray data for compound **1a**·**ZnI_2**. Colorless lath, 0.18× 0.05×0.02 mm size, monoclinic, $P2_1/c$, a=8.2737(8), b=21.343(2), c=9.6901(14) Å, β=93.965(9), V= 1707.0(3) Å^3, Z=4, ρ_{calcd}=2.161 g cm^{-3}, θ_{max}=25.00, Mo Kα, λ=0.71073 Å, ω-scan, diffractometer Siemens P4, T=173(2) K, 3254 reflections collected of which 2992 were independent (R_{int}=0.071), absorption correction based on Psi-scans, T_{min}/T_{max} 0.174/0.328, direct primary solution and refinement on F^2 (Sheldrick, G. M. SHELXS-97 and SHELXL-97, University of Göttingen, 1997), 181 refined parameters, hydrogen atoms refined as riding, the largest difference peaks near the iodine atoms are probably due to absorption, $R_1[I>2\sigma(I)]=0.0410$, wR_2(all data)$=0.1024$.

Selected bond lengths (Å) and angles (°) Zn–N2 2.017(5), Zn–N1 2.041(5), Zn–I2 2.5393(7), Zn–I1 2.5601(8), N1–C2 1.265(8), N2–C4 1.272(8), C1–C2 1.527(8), C2–C3 1.510(8), C3–C4 1.493(8), I2–Zn–I1 117.04(3), N2–Zn–N1 92.1(2), N2–Zn–I2 112.13(13), N1–Zn–I2 113.98(13), N2–Zn–I1 111.36(13), N1–Zn–I1 107.46(14), C2–N1–Zn 126.6(4), C4–N2–Zn 127.4(4), N1–C2–C3 125.5(5), C4–C3–C2 121.7(5), N2–C4–C3 125.9(5).

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Zinc perchlorate catalyzed one-pot amination–annulation of α-cyanomethyl-β-ketoesters in water. Regioselective synthesis of 2-aminopyrrole-4-carboxylates

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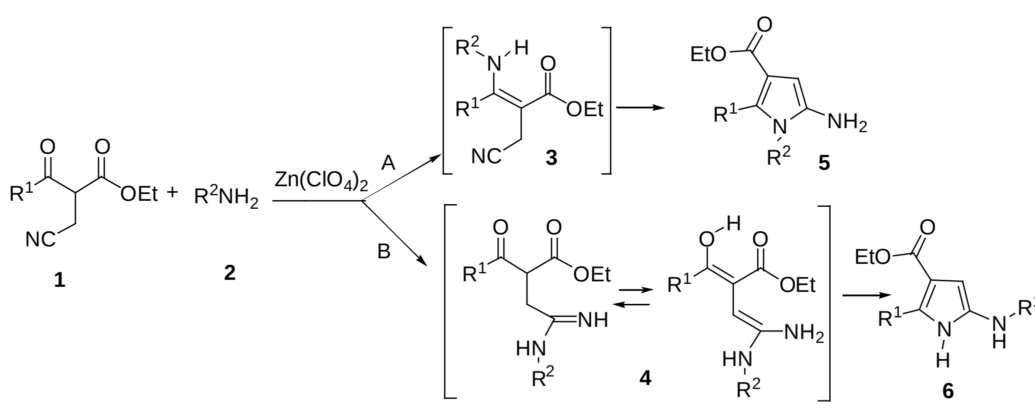
Abstract—In this paper, we report the efficient and regioselective synthesis of 2-aminopyrrole-4-carboxylates as derivatives of conformationally restricted analogues of γ-amino butyrates (GABA) via a zinc perchlorate catalyzed amination–annulation of α-cyanomethyl-β-ketoesters under mild reaction conditions in water.

1. Introduction

Pyrroles are one of the important classes of heterocyclic compounds and are used widely in both synthetic organic chemistry and material science.[1,2] Pyrroles are often seen as building blocks in naturally occurring and biologically active compounds. Aminopyrroles have been found to show interesting biological properties[3,4] or have been used as precursors for known drugs[5] and they are used as synthetic precursors for acyclic nucleoside analogues of the pyrrolo[2,3-*d*]pyrimidine ring system.[6] Aminopyrroles are not readily available through general pyrrole ring-formation methods. Many excellent methodologies have been developed for constructing pyrrole rings, in which relatively few examples have been reported for the preparation of simple 2-amino derivatives.[7]

As we have described in previous paper, the condensation reaction of α-cyanomethyl-β-dicarbonyl compounds with amines catalyzed by *p*-TsOH affords the corresponding enamines in good yields. Base catalyzed cyclization via the addition of an amine moiety to the carbon–nitrogen triple bond of nitrile furnished 2-aminopyrroles in high yields (Scheme 1, route A).[8]



Scheme 1.

Keywords: Aminopyrroles; Amination; Hetero annulation; GABA analogs; 1,3-Dicarbonyls.
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The addition of nitrogen nucleophiles to CN triple bonds of nitriles is one of the most attractive transformations of nitriles. However, the reported methods are limited because of the low reactivity of nitriles. Development of a catalytic method, which proceeds under neutral and mild conditions is desired in view of the synthetic and environmental aspects. As a line of our study on the development of a synthetic methodology for exploring enviromentally friendly processes, and to continue our investigations that are directed towards the synthesis of substituted pyrroles and related compounds,[10] we were especially interested in obtaining 2-amino-4-carboxyl- derivatives of pyrroles, which are conformationally restricted GABA structure analogous. We have found that perchlorate salts are effective catalysts for the activation of both C=O bond and the CN triple bond. These principles have led us to find a novel catalytic one-pot synthesis of 2-aminopyrroles starting from α-cyanomethyl-β-ketoesters.

Herein, we report the novel chemo- and regioselective metalperchlorate-catalyzed amination and annulation of α-cyanomethyl-β-ketoesters.

2. Result and discussion

Metal-coordinated dicarbonyl compound **1** undergoes either C=O activation to react with amines to form enamines **3**, or CN triple bond activation of nitriles to have a direct reaction with amines to afford **4** as shown in Scheme 1. This step determines the selective formation of pyrrole isomers **5** and **6** (Scheme 1).

In an initial reaction, we attempted to synthesize the enamine **3a**[8] starting with β-dicarbonyl compound **1a** and aniline by using 5 mol% of $Zn(ClO_4)_2$ in DCM in which the reaction was monitored by TLC. The isolated product was identified as a pyrrole derivative **6a** in excellent yield. The structure of the product showed that pyrrole nitrogen was not from the aniline as expected but from nitrile.

We continued our study by comparing the catalytic activity of zinc perchlorate with other metallic derivatives. Among all of the catalysts tested zinc perchlorate proved to be the most efficient, and 5 mol% of zinc perchlorate showed the highest efficiency. Moreover, the effects of other zinc salts were also tested (Table 1).

This reaction is carried out in different solvents by using 5 mol% $Zn(ClO_4)_2$ as a catalyst and as shown in Table 2 in which most of the solvents gave comparable yields. The highest yield was obtained with DCM and surprisingly water as a solvent gave comparable yields of DCM. The addition of α-cyanomethyl-β-ketoester and amine into water furnished a heterogen solution, which was heated at 80 °C and the reaction monitored by TLC. The product formation took longer than the DCM but with a comparable yield.

Various α-cyanomethyl-β-ketoesters and amines reacted under the above described conditions and the corresponding pyrroles were obtained in high yields as summarized in Table 2.

Table 1. Metal salts catalyzed formation of **6a**[a]

Entry	Catalyst (5 mol%)	Time (h)	Yield (%)
1	$Zn(ClO_4)_2$	3	91
2	$Mg(ClO_4)_2$	4	78
3	$Cu(ClO_4)_2$	4	No product
4	$LiClO_4$	5	No product
5	$Co(ClO_4)_2$	5	52
6	$NaClO_4$	4	No product
7	$Mn(ClO_4)_2$	4	No product
8	Zinctriflate	3	75
9	$ZnCl_2$	4	27
10	$Zn(OAc)_2$	4	45

[a] Commercially available metal salts are used without further purification or drying.

The above described selective amination and annulation reaction shows substrate dependent selectivity by the formation of aminopyrroles. As shown in Table 2 all representative α-cyanomethyl-β-ketoesters furnished with aromatic amines of the pyrrole products **6a–m** gave high yields (Scheme 1, path B). Only one exception was observed when we started with aliphatic α-cyanomethyl-β-ketoesters **2a–c** and aliphatic amines **2f**,**g**. In this case (Scheme 1, path A) metal-coordinated α-cyanomethyl-β-ketoester undergo C=O activation to give a dehydrative coupling between ketones and amines to form enamines **3**. The addition of a amine moiety to the carbon–nitrogen triple bond furnished 2-aminopyrroles **5a–c** (Table 3).

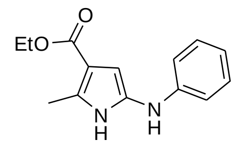
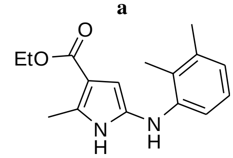
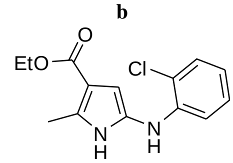
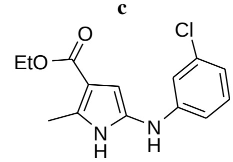
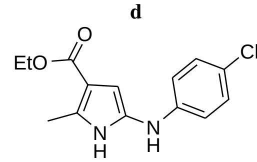
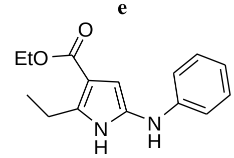
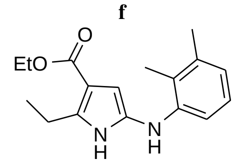
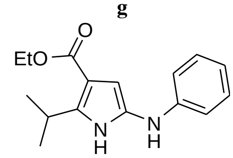
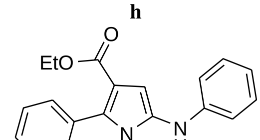
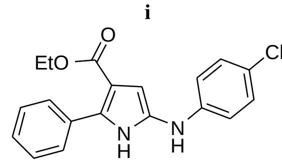
Many attempts were made for the direct- one-pot synthesis of pyrroles starting with a β-dicarbonyl compound. The reaction of bromoacetonitrile and amine in the presence of catalytical amount of $Zn(ClO_4)_2 \cdot 6H_2O$ and $Mg(ClO_4)_2$ by refluxing in DCE and H_2O furnished *N*-substituted β-enamino esters via the condensation of β-ketoesters with amines in a 25–32% yields.[9]

The present reaction can be rationalized by assuming the mechanisms depicted in Scheme 1. The catalytically active species, which would be formed by either the activation of C=O bond or CN bond from α-cyanomethyl-β-ketoesters. Coordination of nitriles to the Zn followed by the addition of the amine into the CN bonds would occur to afford α-cyanomethyl-β-ketoesters metal complex. Coordination of Zn to C=O followed by a dehydrative coupling between ketones and amines would give enamines **3**. Annulation of **3** and **4** would afford product pyrroles **5** and **6** to complete the catalytic cycle. For the chemo- and regioselective processes sterical and electronic factors of the substituents and the enamine–imine tautomeric ratio certainly play an important role. A detailed search for the mechanism of the reaction is under investigation.

3. Conclusions

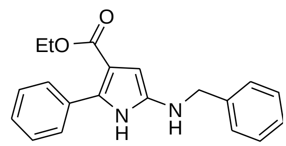
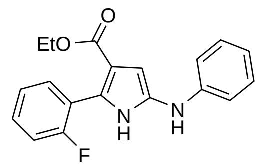
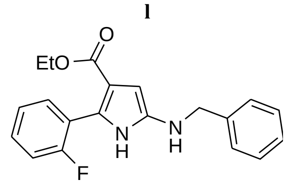
Typically, when α-cyanomethyl-β-ketoesters was allowed to react with amine in the presence of $Zn(ClO_4)_2$, in addition to the CN triple bond of **1** and subsequent to cyclocondensation took place to afford 2-aminopyrrole. The reactions can be applied to the synthesis of various multifunctionalized

Table 2. Synthesis of aminopyrroles

Entry	Ketoester **1**, R_1 =	Amine **2**, R_2 =	Product **6**	Solvent	Yield (%)[a]	Reaction time (h)
1	CH_3 **a**	C_6H_5 **a**	 **a**	DCE H_2O Benzene DMF/H_2O	91 80 85 40	3 5 4 5
2	**a**	2,3-$(CH_3)_2C_6H_3$ **b**	 **b**	DCE H_2O	78 73	5 7
3	**a**	2-Cl–C_6H_4 **c**	 **c**	DCE H_2O	79 77	3 6
4	**a**	3-Cl–C_6H_4 **d**	 **d**	DCE H_2O	93 81	3 6
5	**a**	4-Cl–C_6H_4 **e**	 **e**	DCE H_2O	94 83	3 7
6	C_2H_5 **b**	**a**	 **f**	DCE H_2O	93 77	3 6
7	**b**	**b**	 **g**	DCE H_2O	87 75	5 7
8	$(CH_3)_2CH$ **c**	**a**	 **h**	DCE H_2O	95 81	4 7
9	C_6H_5 **d**	**a**	 **i**	DCE H_2O	89 77	3 6
10	**d**	**e**	 **j**	DCE H_2O	85 74	4 7

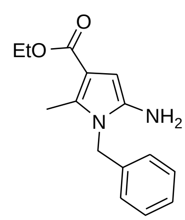
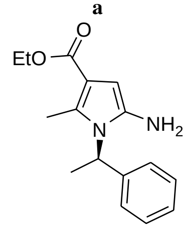
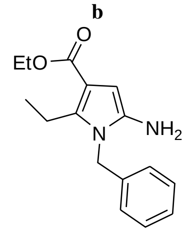
(*continued on next page*)

Table 2 (*continued*)

Entry	Ketoester **1**, R_1 =	Amine **2**, R_2 =	Product **6**	Solvent	Yield (%)[a]	Reaction time (h)
11	**d**	$C_6H_5CH_2$ **f**	 **k**	DCE H_2O	89 70	5 7
12	2F-C_6H_4 **e**	**a**	 **l**	DCE H_2O	87 74	4 6
13	**e**	**f**	 **m**	DCE H_2O	85 73	4 6

[a] Isolated yields.

Table 3. Synthesis of aminopyrroles with aliphatic amines in DCE and water

Entry	Ketoester **1**	Amine **2**	Product **5**[a]	Yield (%) DCE/H_2O	Reaction time (h) DCE/H_2O
14	**a**	**f**	 **a**	76/71	4/7
15	**a**	$C_6H_5CHCH_3$ **g**	 **b**	72/73	5/6
16	**b**	**f**	 **c**	73/76	6/7

[a] The compounds are known and have been identified by comparison of spectral data with those reported in the literature.[8]

aminopyrroles. The present $Zn(ClO_4)_2$ catalyzed nitrogen–carbon bond formation will provide a wide scope of selective transformations of nitriles and even other substrates under neutral conditions in water. The key point of the present reaction is the selective activation of both C=O bonds of 2-cyanomethyl-β-ketoesters as electrophiles and nitriles as pronucleophiles.

4. Experimental

4.1. Materials and methods

NMR spectra were recorded on a Bruker DPX 400. Chemical shifts δ are reported in ppm relative to $CHCl_3$ (^1H: $\delta = 7.27$), $CDCl_3$ (^{13}C: $\delta = 77.0$) and CCl_4 (^{13}C: $\delta =$

96.4) as internal standards. IR spectra were recorded on a Perkin Elmer 1600 FTIR series instrument.

Column chromatography was conducted on silica gel 60 (40–63 μm). TLC was carried out on aluminum sheets precoated with silica gel $60F_{254}$ (Merck), and the spots were visualized with UV light ($\lambda = 254$ nm). Optical rotations were measured with a Krüss P3002RS automatic polarimeter. Cyanomethylation of β-ketoesters and data for known compounds **5a**,**b**,**c**: See Ref.8

4.2. General procedure for the synthesis of pyrroles

a. β-Ketoester (1 mmol) was dissolved in DCE (5 ml). Corresponding amine (1.2 mmol) together with catalytic amount of $Zn(ClO_4)_2$ (5 mol%) was added to the stirring mixture and refluxed for 3–6 h. Reaction was monitored by TLC. The reaction mixture was extracted with ethyl acetate. The extract was dried over $MgSO_4$ and the solvent evaporated under reduced pressure and the crude pruduct was purified by column chromotography (hexane–ethyl acetate (4/1)).

b. β-Ketoester (1 mmol) was dissolved in water (5 ml). Corresponding amine (1.2 mmol) together with catalytic amount of $Zn(ClO_4)_2$ (5 mol%). was added to the stirring mixture. The resulting heterogeneous mixture was heated at 80 °C for 5–7 h. Reaction was monitored by TLC. The reaction mixture was extracted with ethyl acetate. The extract was dried over $MgSO_4$ and the solvent evaporated under reduced pressure and the crude pruduct was purified by column chromotography (hexane–ethyl acetate (4/1)).

4.2.1. Ethyl 2-methyl-5-(phenylamino)-1*H*-pyrrole-3-carboxylate (6a). Yield: (222 mg, 91%), white solid (mp = 123–125 °C), IR ($CHCl_3$): 3426, 3295, 3043, 2982, 2930, 2369, 2326, 1682, 1595 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.24 (3H, t, $J = 7.1$ Hz), 2.40 (3H, s), 4.16 (2H, q, $J = 7.1$ Hz), 5.06 (1H, br s, N*H*), 6.14 (1H, d, $J = 2.6$ Hz), 6.52–7.12 (5H, m), 7.98 (1H, br s, N*H*); ^{13}C NMR (100 MHz, $CDCl_3$): 13.1, 14.5, 59.1, 104.1, 111.4, 113.8, 119.3, 127.5, 129.2, 131.9, 146.4, 165.0. Anal. Calcd for $C_{14}H_{16}N_2O_2$ (244.12): C, 68.83; H, 6.60; N, 11.47. Found: C, 68.61; H, 6.42; N, 11.28.

4.2.2. Ethyl 5-(2,3-dimethylphenylamino)-2-methyl-1*H*-pyrrole-3-carboxylate (6b). Yield: (212 mg, 78%), white solid (mp = 130–132 °C), IR ($CHCl_3$): 3414, 3217, 2991, 2978, 2856, 2356, 2330, 1721, 1669 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.36 (3H, t, $J = 7.1$ Hz), 2.15 (3H, s), 2.32 (3H, s), 2.51 (3H, s), 4.29 (2H, q, $J = 7.1$ Hz), 5.02 (1H, br s, N*H*), 6.21 (1H, d, $J = 2.6$ Hz), 6.49–6.93 (3H, m), 8.04 (1H, br s, N*H*); ^{13}C NMR (100 MHz, $CDCl_3$): 13.4, 14.0, 15.4, 21.4, 60.0, 97.0, 104.6, 112.3, 121.7, 122.4, 127.1, 129.1, 132.8, 137.7, 145.4, 166.0. Anal. Calcd for $C_{16}H_{20}N_2O_2$ (272.15): C, 70.56; H, 7.40; N, 10.29. Found: C, 70.38; H, 7.21; N, 10.06.

4.2.3. Ethyl 5-(2-chlorophenylamino)-2-methyl-1*H*-pyrrole-3-carboxylate (6c). Yield: (219 mg, 79%), white solid (mp = 149–150 °C), IR ($CHCl_3$): 3673, 3304, 3052, 2930, 2895, 2353, 2326, 1682, 1591 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.24 (3H, t, $J = 7.1$ Hz), 2.44 (3H, s), 4.11 (2H, q, $J = 7.1$ Hz), 5.63 (1H, br s, N*H*), 6.24 (1H, d, $J = 2.9$ Hz), 6.62–7.21 (4H, m), 7.84 (1H, br s, N*H*); ^{13}C NMR (100 MHz, $CDCl_3$): 13.1, 14.5, 59.2, 105.6, 111.8, 113.6, 118.8, 119.4, 125.7, 127.7, 129.2, 132.4, 142.7, 164.8. Anal. Calcd for $C_{14}H_{15}ClN_2O_2$ (278.7): C, 60.33; H, 5.42; N, 10.05. Found: C, 60.12; H, 5.22; N, 9.83.

4.2.4. Ethyl 5-(3-chlorophenylamino)-2-methyl-1*H*-pyrrole-3-carboxylate (6d). Yield: (258 mg, 93%), white solid (mp = 137–139 °C), IR ($CHCl_3$): 3523, 3387, 3022, 2894, 2336, 2229, 2136, 1732, 1681 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.20 (3H, t, $J = 7.1$ Hz), 2.44 (3H, s), 4.18 (2H, q, $J = 7.1$ Hz), 5.15 (1H, br s, N*H*), 6.15 (1H, d, $J = 2.6$ Hz), 6.46–7.01 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$): 13.2, 14.4, 59.4, 105.1, 111.6, 111.9, 113.6, 119.2, 126.3, 130.3, 132.6, 135.1, 147.9, 165.2. Anal. Calcd for $C_{14}H_{15}ClN_2O_2$ (278.7): C, 60.33; H, 5.42; N, 10.05. Found: C, 60.15; H, 5.21; N, 9.84.

4.2.5. Ethyl 5-(4-chlorophenylamino)-2-methyl-1*H*-pyrrole-3-carboxylate (6e). Yield: (261 mg, 94%), white solid (mp = 136–137 °C), IR ($CHCl_3$): 3443, 3391, 3052, 2943, 2336, 2356, 2326, 1739, 1682 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.27 (3H, t, $J = 7.1$ Hz), 2.40 (3H, s), 4.16 (2H, q, $J = 7.1$ Hz), 5.13 (1H, br s, N*H*), 6.13 (1H, d, $J = 2.6$ Hz), 6.50 (2H, d, $J = 8.7$ Hz, Ph-H), 7.01 (2H, d, $J = 8.7$ Hz), 8.12 (1H, br s, N*H*); ^{13}C NMR (100 MHz, $CDCl_3$): 13.1, 14.5, 59.3, 104.3, 111.4, 114.9, 124.0, 127.1, 129.1, 132.2, 145.1, 165.2. Anal. Calcd for $C_{14}H_{15}ClN_2O_2$ (278.7): C, 60.33; H, 5.42; N, 10.05. Found: C, 60.18; H, 5.33; N, 10.22.

4.2.6. Ethyl 2-ethyl-5-(phenylamino)-1*H*-pyrrole-3-carboxylate (6f). Yield: (239 mg, 93%), white solid (mp = 125 °C), IR ($CHCl_3$): 3316, 3275, 3047, 2962, 2839, 2329, 2316, 1785, 1621 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.14 (3H, t, $J = 7.5$ Hz), 1.23 (3H, t, $J = 7.2$ Hz), 2.89 (2H, q, $J = 7.5$ Hz), 4.19 (2H, q, $J = 7.2$ Hz), 5.13 (1H, br s, N*H*), 6.21 (1H, d, $J = 2.9$ Hz), 6.61–7.13 (5H, m), 7.98 (1H, br s, N*H*); ^{13}C NMR (100 MHz, $CDCl_3$): 13.4, 14.4, 20.5, 59.3, 104.1, 110.4, 113.8, 119.3, 127.6, 129.3, 138.1, 146.5, 165.3. Anal. Calcd for $C_{15}H_{18}N_2O_2$ (258.32): C, 69.74; H, 7.02; N, 10.84. Found: C, 69.53; H, 7.11; N, 10.63.

4.2.7. Ethyl 5-(2,3-dimethylphenylamino)-2-ethyl-1*H*-pyrrole-3-carboxylate (6g). Yield: (248 mg, 87%), semisolid, IR ($CHCl_3$): 3512, 3312, 2871, 2934, 2867, 2312, 2336, 1678, 1678 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.14 (3H, t, $J = 7.5$ Hz), 1.24 (3H, t, $J = 7.1$ Hz), 2.03 (3H, s), 2.23 (3H, s), 2.85 (2H, q, $J = 7.5$ Hz), 4.13 (2H, q, $J = 7.1$ Hz), 4.94 (1H, br s, N*H*), 6.09 (1H, d, $J = 2.8$ Hz), 6.39–6.71 (3H, m), 8.06 (1H, br s, N*H*); ^{13}C NMR (100 MHz, $CDCl_3$): 12.5, 13.6, 14.5, 20.3, 20.5, 59.1, 103.5, 110.4, 111.3, 120.8, 121.4, 126.2, 128.3, 136.8, 137.8, 144.5, 165.0. Anal. Calcd for $C_{17}H_{22}N_2O_2$ (286.37): C, 71.30; H, 7.74; N, 9.78. Found: C, 71.12; H, 7.51; N, 9.48.

4.2.8. Ethyl 2-isopropyl-5-(phenylamino)-1*H*-pyrrole-3-carboxylate (6h). Yield: (187 mg, 95%), semisolid, IR ($CHCl_3$): 3523, 3285, 3061, 2979, 2922, 2345, 2313, 1672, 1612 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.26 (6H, d, $J =$

7.0 Hz), 1.34 (3H, t, $J=7.1$ Hz), 3.79–3.83 (1H, m), 4.27 (2H, q, $J=7.1$ Hz), 5.21 (1H, br s, N*H*), 6.24 (1H, d, $J=2.8$ Hz), 6.63–7.31 (5H, m), 8.07 (1H, br s, N*H*); ^{13}C NMR (100 MHz, $CDCl_3$): 14.5, 22.1, 25.8, 59.2, 104.1, 109.9, 113.7, 119.3, 127.4, 129.3, 142.0, 146.5, 164.9. Anal. Calcd for $C_{16}H_{20}N_2O_2$ (272.15): C, 70.56; H, 7.40; N, 10.29. Found: C, 70.41; H, 7.38; N, 10.15.

4.2.9. Ethyl 2-phenyl-5-(phenylamino)-1*H*-pyrrole-3-carboxylate (6i). Yield: (272 mg, 89%), white solid (mp=141–142 °C), IR ($CHCl_3$): 3421, 3065, 2982, 2934, 2904, 1695, 1591 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.17 (3H, t, $J=7.1$ Hz), 4.10 (2H, q, $J=7.1$ Hz), 5.2 (1H, br s, N*H*), 6.31 (1H, d, $J=2.3$ Hz), 6.53–7.55 (10H, m), 8.15 (1H, br s, N*H*); ^{13}C NMR (100 MHz, $CDCl_3$): 14.3, 30.7, 59.4, 105.4, 111.9, 114.1, 119.7, 128.0, 128.8, 129.4, 129.6, 131.8, 133.6, 145.9, 164.1. Anal. Calcd for $C_{19}H_{18}N_2O_2$ (306.14): C, 74.49; H, 5.92; N, 9.14. Found: C, 74.28; H, 5.83; N, 8.91.

4.2.10. Ethyl 5-(4-chlorophenylamino)-2-phenyl-1*H*-pyrrole-3-carboxylate (6j). Yield: (289 mg, 85%), white solid (mp=132–133 °C), IR ($CHCl_3$): 3513, 3372, 3153, 2897, 2239, 2450, 2389, 1732, 1679 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.14 (3H, t, $J=7.1$ Hz), 4.04 (2H, q, $J=7.1$ Hz), 5.27 (1H, br s, N*H*), 6.25 (1H, s), 6.53–7.44 (9H, m), 8.29 (1H, br s, N*H*); ^{13}C NMR (100 MHz, $CDCl_3$): 15.1, 60.6, 105.4, 112.5, 116.1, 125.2, 128.9, 128.9, 129.7, 130.1, 130.5, 132.6, 145.2, 165.6. Anal. Calcd for $C_{19}H_{17}ClN_2O_2$ (340.8): C, 66.96; H, 5.03; N, 8.22. Found: C, 66.85; H, 5.13; N, 8.02.

4.2.11. Ethyl 5-(benzylamino)-2-phenyl-1*H*-pyrrole-3-carboxylate (6k). Yield: (284 mg, 89%), yellow oil, IR (neat): 3413, 3272, 3142, 2787, 2199, 2421, 2298, 1752, 1685 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.10 (3H, t, $J=7.1$ Hz), 4.04 (3H, q, $J=7.1$ Hz), 4.07 (2H, br s), 5.68 (1H, d, $J=2.8$ Hz), 7.11–7.39 (10H, m), 8.04 (1H, br s, N*H*); ^{13}C NMR (100 MHz, $CDCl_3$): 14.3, 50.6, 59.3, 92.4, 111.1, 127.3, 127.4, 127.7, 127.8, 128.1, 128.5, 128.6, 128.9, 130.8, 132.3, 139.0, 139.3, 165.1. Anal. Calcd for $C_{20}H_{20}N_2O_2$ (320.38): C, 74.98; H, 6.29; N, 8.74. Found: C, 74.81; H, 6.14; N, 8.51.

4.2.12. Ethyl 2-(2-fluorophenyl)-5-(phenylamino)-1*H*-pyrrole-3-carboxylate (6l). Yield: (281 mg, 87%), white solid (mp=113 °C), IR ($CHCl_3$): 3525, 3266, 2987, 2921, 2964, 1699, 1601 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.16 (3H, t, $J=7.2$ Hz), 4.15 (2H, q, $J=7.2$ Hz), 5.25 (1H, br s, N*H*), 6.39 (1H, s), 6.71–7.61 (9H, m), 8.31 (1H, br s, N*H*); ^{13}C NMR (100 MHz, $CDCl_3$): 11.1, 56.6, 99.9, 110.3, 111.1, 112.3 ($J=22$ Hz), 116.4, 120.4, 122.8, 126.2, 126.5, 126.7, 127.6, 128.8, 142.2, 156.9 (d, $J=246$ Hz), 161.6. Anal. Calcd for $C_{19}H_{17}FN_2O_2$ (324.35): C, 70.36; H, 5.28; N, 8.64. Found: C, 70.32; H, 5.22; N, 8.41.

4.2.13. Ethyl 5-(benzylamino)-2-(2-fluorophenyl)-1*H*-pyrrole-3-carboxylate (6m). Yield: (287 mg, 85%), yellow oil, IR (neat): 3523, 3472, 3347, 2687, 2231, 2521, 2342, 1749, 1699 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.12 (3H, t, $J=7.0$ Hz), 4.04 (2H, q, $J=7.0$ Hz), 4.07 (2H, br s), 5.73 (1H, s), 6.91–7.48 (9H, m), 8.14 (1H, br s, N*H*); ^{13}C NMR (100 MHz, $CDCl_3$): 14.2, 50.5, 59.5, 92.0, 113.2, 115.4 (d, $J=22$ Hz), 120.3 (d, $J=13$ Hz), 123.6 (d, $J=8$ Hz), 127.4, 127.7, 128.1, 128.6, 129.0, 131.9, 138.9, 139.6, 159.1 (d, $J=245$ Hz), 164.9. Anal. Calcd for $C_{20}H_{19}FN_2O_2$ (338.38): C, 70.99; H, 5.66; N, 8.28. Found: C, 70.82; H, 5.45; N, 8.02.

4.2.14. Ethyl 2-(cyanomethyl)-4-methyl-3-oxopentanoate (1c). Yield: (155 mg, 79%), yellow oil, IR (neat): 2978, 2249, 1736, 1689 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.14 (3H, d, $J=6.7$ Hz), 1.20 (3H, d, $J=7.1$ Hz), 1.31 (3H, t, $J=7.2$ Hz), 2.83 (2H, d, $J=7.3$ Hz), 2.91 (1H, m), 3.98 (1H, t, $J=7.3$ Hz), 4.27 (2H, q, $J=7.2$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 13.9, 15.9, 18.4, 19.2, 40.5, 52.5, 62.3, 116.9, 166.3, 204.7. Anal. Calcd for $C_{10}H_{15}NO_3$ (197.23): C, 60.90; H, 7.67; N, 7.10. Found: C, 60.81; H, 7.48; N, 7.33.

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Stable chiral spirocyclic [5,5]-ammonium ylides using a metallo carbenoid approach

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Abstract—Enantiomerically pure spiro[5,5]-ammonium ylides were obtained by Rh(II)-catalyzed decomposition of α-diazo-β-carbonylesters. In the crude decomposition mixtures, variable quantities of enamino-α,β-keto esters were detected as secondary products.

1. Introduction

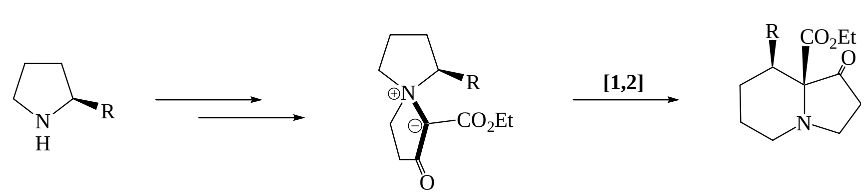
Recently, we prepared enantiopure indolizidinone alkaloids **2** by a carbenoid/spiro[5,5]-ammonium ylide/Stevens [1,2]-shift with ring-expansion tandem sequence[1] (Scheme 1). In this contest, isolation and characterization of ylide intermediates **1** in a stable and enantiopure form, enabled us, by studying their reactivity, to probe unambiguously the complete reaction cascade pathway previously proposed for similar processes, including the stereochemical reaction course.[2] We proved high chirality transfer from the original proline template to a second temporary spirocyclic ammonium nitrogen through its stereoselective quaternarization. The second one permitted the preservation of the original stereocenter during its [1,2]-shift to the newly formed neighbour quaternary indolizidinone stereocenter, a synthetic application of the SRS (self-regeneration of stereocenters) Seebach principle.[3]

In some related studies involving metallo carbenoid generation and Stevens [1,2]-rearrangement of similar non-isolable ylide intermediates, a high degree of chirality transfer from the ammonium N atom was previously observed.[2]

This stereoselectivity is in line with the extensive investigations of Ollis that demonstrate a solvent caged radical pair Stevens [1,2]-rearrangement reaction mechanism[4] or with an alternative recently proposed ion pair mediated mechanism.[5]

Concerning the Stevens [1,2]-rearrangement, notwithstanding the considerable examples performed in related studies, there are few synthetic applications. One limitation of this methodology is the need for activating groups on the migrating carbons, such as allyl, aryl, carbonyl[6] and silyl;[2c] consequently, no examples of a primary carbon migration have been reported, except for a few cases.[7]

In view of the mild conditions, the carbenoid route seems most suitable for intramolecular ylide trapping, and given the rarity of stable spirocyclic ammonium ylides obtained



R=COOR' **1** **2**

Scheme 1.

Keywords: Diazocompounds; Catalytic decomposition; Cascade process; Rearrangement.
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by this protocol,[8] we were interested in increasing their number and in studying their reactivity, including rearrangement and cycloaddition reactions.

For our purposes, the synthesis of diazoketones **4a**, **4b**, **4c**, **4d** and **4e** was planned (Figs. 1 and 2). Due to the proper diazo group position on the chain tethered to pyrrolidine or isoindoline nitrogen atom, [5,5]-spirocyclic ammonium ylides **5a**, **5b**, **5c**, **5d** and **5e** (Fig. 3) were expected to form predominantly as intermediates, by nitrogen trapping of the metallocarbene precursors, over competitive C–H insertion processes.

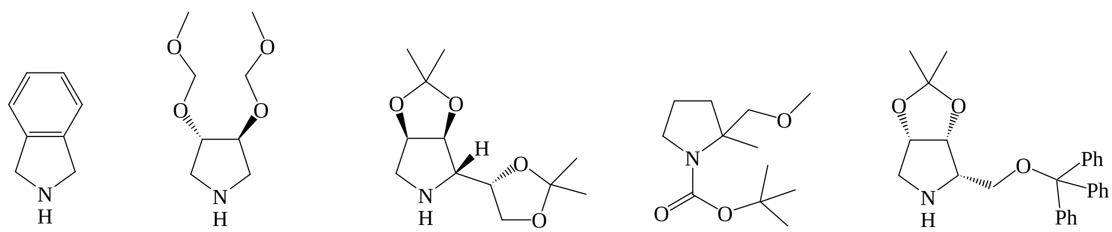
Moreover, for evaluating the enantioselectivity in generating quaternary ammonium stereocenters, the chiral diazo-substrates **4b**, **4c** and **4e** were prepared as single enantiomers.

Finally, the diazocompound **4d** synthesis was suggested by our interest in evaluating the possibility of the Stevens [1,2]-rearrangement of the corresponding ylide **5d**; to our knowledge, no examples of tertiary carbon Stevens-type migration are reported.

2. Results and discussion

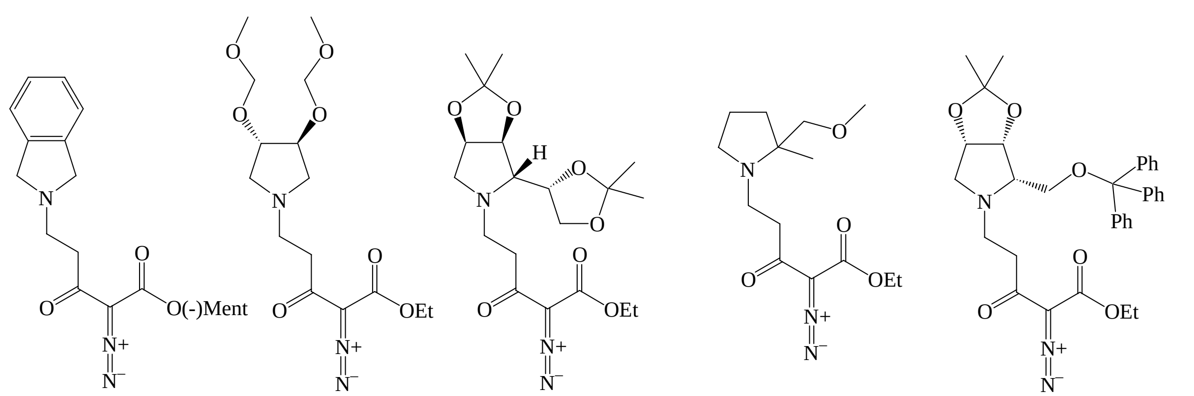
All the diazoketoesters **4a–e**, were conveniently prepared in two steps. First step was the conjugate addition of isoindoline **3a** to (−)-menthyl-3-keto-pent-4-enoate,[9] and 3,4-bis-methoxymethoxy-pyrrolidine **3b**,[10] 1,4-dideoxy-2,3,5,6-*O*-isopropylidene-1,4-imino-D-talitol **3c**,[11] 2-methoxymethyl-2-methyl-pyrrolidine **3d**,[12] and 1,4-dideoxy-2,3-di-*O*-isopropylidene-1,4-imino-5-*O*-trityl-L-lyxitol **3e**[13] to ethyl-3-keto-pent-4-enoate.[14] Then the *N*-alkyl-isoindoline and the *N*-alkyl-pyrrolidines obtained were submitted to diazo-transfer reaction with tosylazide.

^{1}H NMR analysis of diazoketoesters **4b** and **4c** and **4e** indicated their enantiomeric purity.



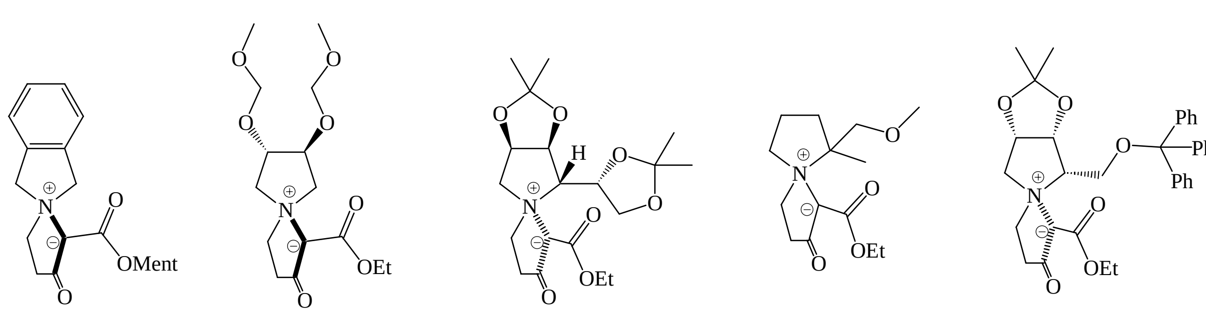
3a 3b 3c 3d 3e

Figure 1.



4a 4b 4c 4d 4e

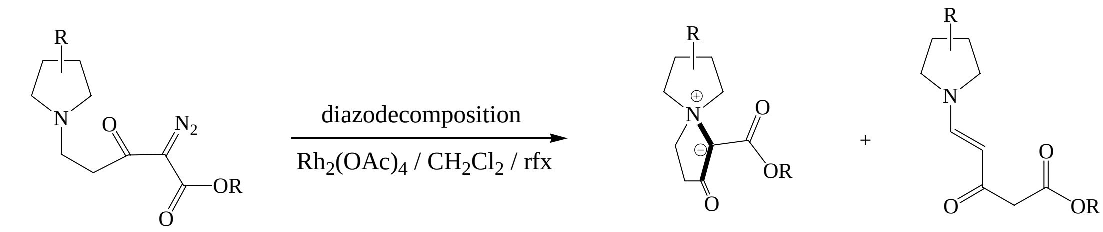
Figure 2.



5a 5b 5c 5d 5e

Figure 3.

Table 1.



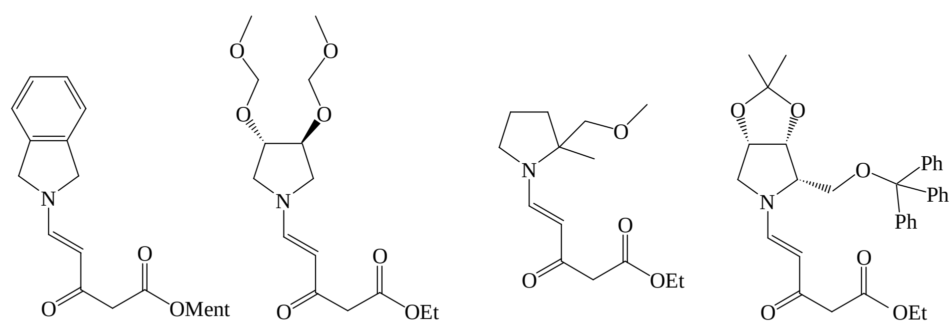
4 **5** **6**

Substrate	Yield (%)[a]	**5**:**6**[b]
4a	92	80:20
4b	89	75:25
4c	76	100:—
4d	87	70:30
4e	81	—:100

[a] Isolated yield after column chromatography.
[b] Reflects percent conversion (measured by ^{1}H NMR of crude mixture after removal of solvents).

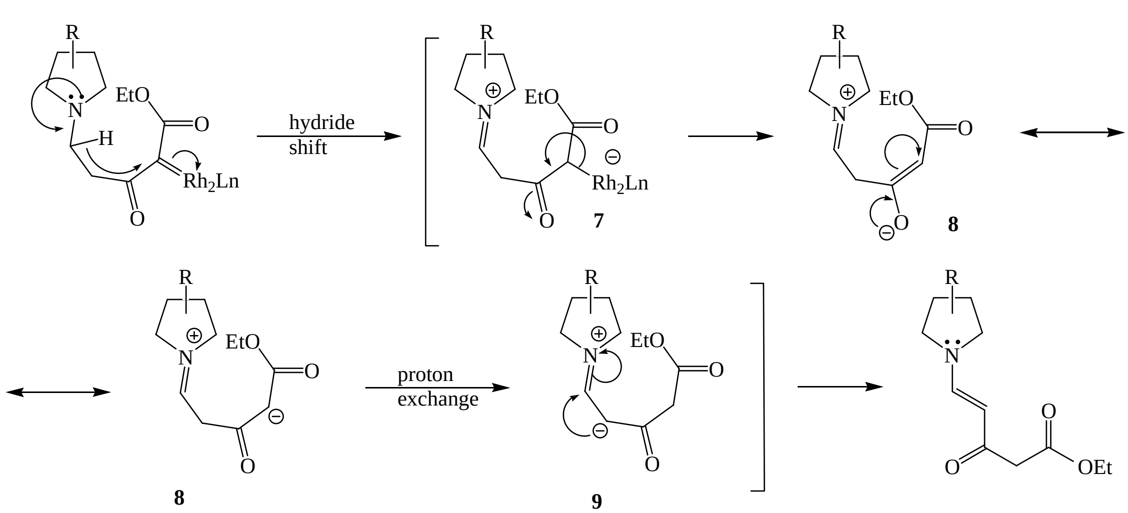
When the diazocompounds **4a**, **4b**, **4c** and **4d** were refluxed in CH_2Cl_2 solution, in the presence of rhodium(II) acetate, the corresponding ylides **5a**, **5b**, **5c** and **5d** were obtained[15] (Fig. 3 and Table 1).

Ylide **5d** was obtained as a 44:56 diastereomeric mixture. In the crude decomposition mixtures, variable quantities of enamino-α,β-keto esters **6a**, **6b** and **6c** were detected as secondary products (Fig. 4). No detectable amount of ylide



6a **6b** **6d** **6e**

Figure 4.



Scheme 2.

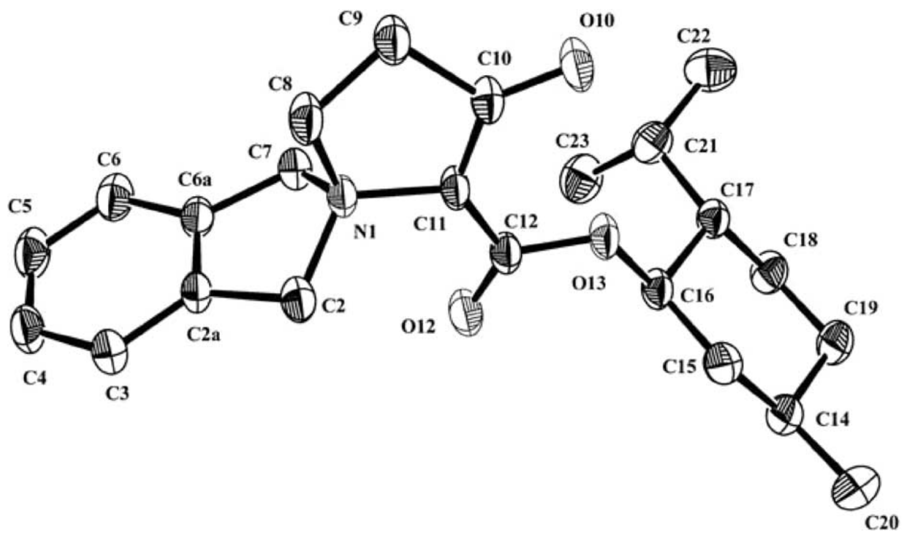
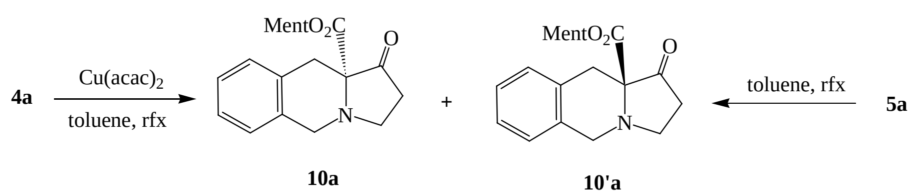


Figure 5. ORTEP view of compound **5a**.



Scheme 3.

was found in the crude reaction mixture of the dirhodium tetraacetate decomposition of diazoketone **4e** in boiling CH_2Cl_2 solution. In this case, ketopentenoic ester **6e** was obtained as the exclusive product in 81% isolated yield.

The formation of unsaturated compounds can be rationalized by a mechanism (Scheme 2), which involves an initial intramolecular metal–carbene hydride-abstraction,[16] to give a transient zwitterion intermediate **7**, which then produces the zwitterion enolate/ketone **8**. This seemingly undergoes proton exchange[17] with an adjacent α-hydrogen to give a new zwitterionic intermediate **9**. A subsequent dissipation of the charges then occurs to furnish enamine **6** with trans configuration (^{1}H NMR spectroscopy).

Isolation of ylide **5a** crystals enabled the single crystal X-ray analysis[18] to be performed (Fig. 5).

The absolute configuration of ylide **5c** was deduced from 2D NOESY correlation studies. Thus, the NOESY trace of ethyl ester methylene protons shows a positive NOE effect for the acetonide methylene protons.

The ^{1}H NMR analysis of ylides **5b** and **5c** indicated their enantiomeric purity.

Decomposition of the diazocompound **4a** in boiling toluene in the presence of $Cu(acac)_2$ provided an inseparable 1:1 diastereomeric mixture of indolizidinone alkaloids **10a** and **10′a**; surprisingly no enantioselection was obtained. By heating of ylide **5a** in toluene at reflux, without catalyst, the same diastereomeric mixture was obtained (Scheme 3).

No Stevens rearrangement products but undetectable decomposition mixtures were obtained by heating of ylides **5b** and **5c** and **5d** under the above reaction conditions.

3. Conclusion

These preliminary studies have shown that stable ammonium ylides may also be obtained using the mild and concise metallo carbenoid protocol. The ready isolation of these intermediates could be attributed to the stabilizing effect exerted on the charged ylide carbon atom by the presence of both carbonyl and ester groups. The lack of ylide formation in the catalytic decomposition of diazocompound **4e** can be rationalized in terms of steric factors.

Moreover, the thermal decomposition of ylide **5a**, affording the same mixture of alkaloids **10a** and **10′a** as obtained by catalytic decomposition of the starting diazoketone **4a**, provides a further clear confirmation of a carbenoid/spiro[5,5]-ammonium ylide/Stevens [1,2]-shift with ring-expansion tandem sequence. In this case, the [1,2]-shift is assisted by the presence of the aryl group on the migrating carbon.

No Stevens-type rearrangement products were detected in the crude reaction mixtures of the attempted thermal decomposition of ylides **5b** and **5c**: this is presumably due to the absence of activating groups on the potential migrating carbons.

No rearrangement products were also observed by heating of ylide **5d**; in our opinion, this result rules out the radical pair reaction mechanism. Due to its stability, a putative migrating tertiary radical intermediate would favour the rearrangement process.

4. Experimental

4.1. General

^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on a Varian VXR-300 spectrometer with TMS as internal standard. COSY, NOESY, HSQC and USQC-TOSCY spectra were recorded with a Bruker Avance 600 NMR spectrometer equipped with inverse detection probe. Infrared (IR) spectra were performed on a FT/IR-480plus JASKO spectrophotometer. The optical rotations were measured by a polarimeter P-1010 JASKO in a 1 dm tube. All reagents and solvents employed were reagent grade materials purified by standard methods and redistilled before use.

4.1.1. 2-Diazo-3-oxo-5-[1,3-dihydroisoindol-yl]-pentanoic acid (−)-menthyl ester 4a. To a stirred solution of isoindoline **3a** (0.5 g, 0.0042 mol) and 3-oxo-pent-4-enoic acid (−)-menthyl ester (1.1 g, 0.004 mol) in CH_2Cl_2 (15 mL), a solution of Et_3N (0.76 mL, 0.0055 mol) in CH_2Cl_2 (10 mL) was added dropwise and stirred for 30 min. To the reaction mixture, tosyl azide (1.1 g, 0.0055 mol) and a solution of Et_3N (1.1 mL, 0.015 mol) in CH_2Cl_2 (10 mL) were added dropwise at 0 °C. After the addition was complete, the solution was stirred at room temperature overnight. The solvent was evaporated and the residue was purified by flash chromatography (petroleum ether/Et_2O, 8:2) affording the title compound **4a** (0.995 g, 60% yield) as a yellow-brown oil: $[\alpha]_D^{25}$ −53 (*c* 0.7, $CHCl_3$); ^{1}H NMR: δ 0.80 (d, 3H, J=6.9 Hz), 0.92 (two overlapping doublets, 6H, J=6.9 Hz), 0.99–1.12 (m, 2H), 1.39–1.53 (m, 2H), 1.69–1.73 (m, 3H), 1.80–1.90 (m, 1H), 2.04–2.17 (m, 1H), 3.07–3.20 (m, 4H), 3.98 (s, 4H), 4.84 (dt, 1H, d: J=4.5 Hz, t: J=10.8 Hz), 7.18 (s, 4H); ^{13}C NMR ($CDCl_3$): δ 16.4, 20.6, 21.9, 23.5, 26.5, 31.4, 34.0, 39.1, 41.0, 46.9, 50.6, 58.9, 75.7, 76.5, 122.2, 126.7, 139.8, 160.9, 191.4; IR (neat): 2955, 2870, 2765, 2368, 2131, 1710, 1656, 1455, 1368, 1209, 1039, 1014, 913, 873 and 742 cm^{-1}. Anal. Calcd for $C_{23}H_{31}N_3O_3$: C, 69.49; H, 7.86; N, 10.57. Found: C, 69.61; H, 7.58; N, 10.75.

4.1.2. Diazo-decomposition of 4a. A solution of diazoketoester **4a** (0.5 g, 0.00126 mol) in CH_2Cl_2 (5 mL) was refluxed for 30 min in the presence of $Rh_2(OAc)_4$ (0.007 g, 2 mol%). The solvent was evaporated and the residue gave a 80:20 mixture of **5a** and **6a**. After flash chromatography (Et_2O/MeOH/Et_3N, 5:5:0.1) **5a** was obtained as a white solid (0.336 g, 74% yield) and **6a** as impure brown oil (0.081 g, 18% yield).

2′-[(−)-Menthoxycarbonyl]-3′-oxo-1,3-dihydrospiro [isoindole-2,1′-pyrrolidine]-2′-ylide **5a** colourless needles (ethyl acetate/Et_2O, 10:1), mp 185–187 °C; $[\alpha]_D^{25}$ −45 (*c* 0.4, $CHCl_3$); ^{1}H NMR: δ 0.76 (d, 3H, J=6.9 Hz), 0.88 (two overlapping doublets, 6H, J=6.9 Hz), 1.02–1.06 (m, 1H), 1.07–1.25 (m, 1H), 1.36–1.65 (m. 4H), 2.06–2.24 (m, 3H), 2.45–2.73 (m, 2H), 3.65–3.69 (m, 2H), 4.27–4.50 (m, 2H), 4.74 (dt, 1H, d: J=4.5 Hz, t: J=10.8 Hz), 5.74–5.86 (m, 2H), 7.26–7.41 (m, 4H); ^{13}C NMR ($CDCl_3$): δ 16.1, 20.9, 22.1, 23.3, 25.7, 32.6, 32.8, 34.3, 41.5, 46.8, 63.3, 68.6, 72.9, 123.0, 128.9, 133.8, 163.2, 178.3; IR (Nujol): 2924, 2854, 1640, 1606, 1460, 1413, 1376, 1200, 1112, 1013, 973, 767and 723 cm^{-1}. Anal. Calcd for $C_{23}H_{31}NO_3$: C, 74.46; H, 8.46; N, 3.79. Found: C, 74.20; H, 8.76; N, 3.55.

3-Oxo-5-[1,3dihydroisoindol-yl]-pent-3,4-enoic acid (−)-menthyl ester **6a**, brown oil; $[\alpha]_D^{25}$ −34 (*c* 0.11, $CHCl_3$); ^{1}H NMR: δ 0.76 (d, 3H, J=6.9 Hz), 0.86–0.91 (m, 6H), 0.98–1.10 (m, 2H), 1.25 (s, 2H), 1.32–1.51 (m, 2H), 1.63–1.70 (m, 3H), 1.83–2.06 (m, 2H), 3.42 (s, 2H), 4.75 (dt, 1H, d: J=4.5 Hz, t: J=10.8 Hz), 4.87 (s, 2H), 5.21 (d, 1H, J=12.6 Hz), 7.26–7.34 (m, 4H), 7.90 (d, 1H, J=12.6 Hz); ^{13}C NMR ($CDCl_3$): δ 16.2, 20.7, 22.0, 23.2, 26.0, 29.7, 31.4, 34.2, 40.7, 46.8, 53.3, 57.1, 74.9, 122.5, 122.7, 127.9, 128.0, 135.7, 149.1, 168.5, 188.7; IR (neat): 2955, 2869, 1715, 1650, 1571, 1463, 1361, 1271, 1143, 1097, 989 and 741 cm^{-1}. Anal. Calcd for $C_{23}H_{31}NO_3$: C, 74.46; H, 8.46; N, 3.79. Found: C, 74.54; H, 8.31; N, 3.40.

4.1.3. (10a*R*,*S*)-1-Oxo-2,3,4,5,10-tetrahydro-1*H*-pyrrolo[1,2-*b*]-isoquinoline-10a-carboxylic acid (−)-menthyl esters 10a and 10′a. A solution of diazoketoester **4a** (0.44 g, 0.00110 mol) in toluene (5 mL) was refluxed for 30 min in the presence of $Cu(acac)_2$ (0.005 g, 2 mol%). The solvent was evaporated and the residue gave, after flash chromatography (petroleum ether/ethyl acetate, 9:1) the title compounds **10a** and **10′a** as a 1:1 mixture of diastereoisomers (0.21 g, 52% yield). ^{1}H NMR: δ 0.62 (0.41) (d, 3H, J=6.9 Hz), 0.76–0.92 (m, 9H), 1.19–1.37 (m, 5H), 1.56–1.74 (m, 4H), 2.48–2.67 (m, 2H), 2.87 (2.82) (d, 1H, J=15.6 Hz), 3.24–3.38 (m, 2H), 3.52 (q, 1H, J=7.8 Hz), 4.02–4.23 (m, 2H), 4.60 (4.56) (dt, 1H, d: J=4.5 Hz, t: J=10.8 Hz), 7.07–7.17 (m, 4H). Anal. Calcd for $C_{23}H_{31}NO_3$: C, 74.46; H, 8.46; N, 3.79. Found: C, 74.31; H, 8.18; N, 3.98.

4.1.4. 5-[(3*S*,4*S*)-3,4-Bis(methoxymethoxy)pyrrolidin-1-yl]-2-diazo-3-oxo-pentanoic acid ethyl ester 4b. To a stirred solution of 3,4-bis-methoxymethoxy-pyrrolidine **3b** (1.6 g, 0.008 mol) in CH_2Cl_2 (15 mL) a solution of 3-oxo-pent-4-enoic acid ethyl ester (1.1 g, 0.008 mol) in CH_2Cl_2 (10 mL) was added dropwise and stirred for 30 min. To the reaction mixture tosyl azide (1.6 g, 0.008 mol) and a solution of Et_3N (2.8 mL, 0.02 mol) in CH_2Cl_2 (10 mL) were added dropwise at 0 °C. After the addition was complete, the solution was warmed to room temperature and stirred overnight. The solvent was evaporated and the residue was purified by flash chromatography (Et_2O/petroleum ether/Et_3N, 8:2:0.1) to give the title compound **4b** (1.8 g, 70% yield) as a yellow oil; $[\alpha]_D^{25}$ +3 (*c* 0.6, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 1.33 (t, 3H, J=7.2 Hz), 2.58 (dd, 2H, J=4.2, 10.5 Hz); 2.70–2.90 (m, 2H), (dd, 2H, J=6.0, 9.9 Hz), 3.09 (dd, 2H, J=6.9, 8.1 Hz), 3.37 (s, 6H), 4.13 (dd, 2H, J=4.2, 5.1 Hz), 4.29 (q, 2H, J=7.2 Hz), 4.67 (AB system, 4H); ^{13}C NMR ($CDCl_3$): δ 14.2, 38.6. 50.4, 55.3, 58.6, 61.2, 76.0, 81.1, 95.4, 161.0, 191.1; IR (neat): 2945, 2822, 2136, 1718 and 1655 cm^{-1}. Anal. Calcd for $C_{15}H_{25}N_3O_7$: C, 50.13; H, 7.01; N, 11.69. Found C, 50.24; H, 7.03; N, 11.65.

4.1.5. Diazo-decomposition of 4b. To a refluxing solution of $Rh_2(OAc)_4$ (0.013 g, 3 mol%) in 30 mL of dry CH_2Cl_2, a solution of **4b** (0.360 g, 0.001 mol) in dry CH_2Cl_2 (20 mL) was added dropwise over 30 min. After stirring for another 30 min at reflux, the reaction mixture was cooled and evaporated to give a 75:25 mixture of **5b** and **6b**. Purification by flash chromatography (Et_2O/ethyl acetate/Et_3N, 5:5:0.1; Et_2O/MeOH/Et_3N, 5:5:0.1) gave 0.22 g (67% yield) of **5b** as a yellow amorphous solid and 0.074 g (22% yield) of **6b** as yellow oil.

(7S,8S)-1-Ethoxycarbonyl-7,8-bis-methoxymethoxy-2-oxo-5-azonia-spiro[4.4] nonane-1-ylide **5b** $[\alpha]_D^{25}$ −3 (*c* 0.15, $CHCl_3$); ^{1}H NMR: δ 1.35 (t, 3H, J=7.2 Hz), 2.60 (t, 2H, J=7.8 Hz), 3.25 (d, 1H, J=12.9 Hz), 3.39 (d, 6H, J=6.6 Hz), 3.55–3.64 (m, 2H), 3.70–3.90 (m, 1H), 4.26 (q, 2H, J=7.2 Hz), 4.37–4.58 (m, 3H), 4.68 (dd, 2H, J=6.9, 10.2 Hz), 4.75 (dd, 2H, J=3.3, 6.9 Hz), 4.88 (dd, 1H, J=6.9, 12.9 Hz); ^{13}C NMR ($CDCl_3$): δ 14.7, 32.8, 55.9, 59.0, 63.3, 66.0, 80.0, 80.2, 96.3, 96.4, 102.3, 162.3, 178.3; IR (neat): 2933, 2826, 1735, 1653, 1609 and 1567 cm^{-1}. Anal. Calcd for $C_{15}H_{25}NO_7$: C, 54.37; H, 7.60; N, 4.23. Found: C, 54.17; H, 7.58; N, 4.21.

(4E)-5-[(3*S*,4*S*)-3,4-bis(Methoxymethoxy)pyrrolidin-1-yl]-3-oxo-pentenoic acid ethyl ester **6b** $[\alpha]_D^{25}$ +5 (*c* 0.10, $CHCl_3$); ^{1}H NMR: δ 1.27 (t, 3H, J=7.1 Hz), 3.23 (d, 1H, J=12.6 Hz), 3.36 (s, 6H), 3.38 (s, 2H), 3.44 (d, 1H, J=11.8 Hz), 3.53 (d, 1H, J=11.7 Hz), 4.14–4.21 (m, 1H), 4.17 (q, 2H, J=7.1 Hz), 4.26 (broad s, 1H), 4.60–4.75 (m, 4H), 5.09 (d, 1H, J=12.6 Hz), 7.74 (d, 1H, J=12.6 Hz); ^{13}C NMR ($CDCl_3$): δ 14.13, 48.2, 51.5, 55.6, 55.7, 60.9, 78.3, 78.7, 95.8, 96.4, 149.5, 168.9, 188.3; IR (neat): 3031, 2948, 2853, 2829, 1730, 1655 and 1593 cm^{-1}. Anal. Calcd for $C_{15}H_{25}NO_7$: C, 54.37; H, 7.60; N, 4.23. Found: C, 54.25; H, 7.63; N, 4.24.

4.1.6. 2-Diazo-5-[(3a*S*,4a*S*,6a*R*)-4-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-2,2-dimethyltetrahydro-3a*H*-[1,3]-dioxolo[4,5-*c*]pyrrol-5-yl]-3-oxo-pentanoic acid ethyl ester 4c. To a stirred solution of 1,4-dideoxy-2,3,5,6-*O*-isopropylidene-1,4-imino-D-talitol **3c** (0.679 g, 0.00279 mol) and 3-oxo-pent-4-enoic acid ethyl ester (0.397 g, 0.00279 mol), in CH_2Cl_2 (15 mL), a solution of Et_3N (0.60 mL, 0.0042 mol) in CH_2Cl_2 (10 mL) was added dropwise and stirred for 30 min. Tosyl azide (0.840 g, 0.0042 mol) and a solution of Et_3N (0.60 mL, 0.0042 mol) in CH_2Cl_2 (10 mL) were then added dropwise at 0 °C. After the addition was complete, the solution was stirred at room temperature overnight. The solvent was evaporated and the residue gave, after flash chromatography (petroleum ether/Et_2O, 8:2), the title compound **4c** (0.580 g, 84% yield) as a yellow-brown oil: $[\alpha]_D^{25}$ +81.6 (*c* 0.32, $CHCl_3$); ^{1}H NMR: δ 1.29 (s, 3H); 1.33 (t, 3H, J=6.6 Hz), 1.34 (s, 3H), 1.42 (s, 3H), 1.50 (s, 3H), 2.58 (dd, 1H, J=5.7, 10.2 Hz), 2.83–2.89 (m, 2H), 2.95–3.13 (m, 2H), 3.30–3.39 (m, 2H), 3.76 (dd, 1H, J=1.2, 8.1 Hz), 4.01 (dd, 1H, J=1.8, 8.1 Hz), 4.20 (q, 1H, J=6.6 Hz), 4.31 (AB system, 2H), 4.36 (dd, 1H, J=3.9, 6.9 Hz), 4.57–4.63 (m, 1H); ^{13}C NMR ($CDCl_3$): δ 24.8, 25.1, 26.3, 27.1, 38.5, 49.5, 58.9, 61.2, 66.1, 70.6, 76.0, 78.6, 81.8, 109.3, 112.7, 161.1, 191.5; IR (neat): 2985, 2936, 2134, 1715, 1654, 1455, 1372, 1300, 1211, 1078, 1159, 1053, 856 and 747 cm^{-1}. Anal. Calcd for $C_{19}H_{29}N_3O_7$: C, 55.46; H, 7.10; N, 10.21. Found: C, 55.71; H, 6.96; N, 10.44.

4.1.7. (6*R*,7*S*,8*S*)-1-Ethoxy carbonyl-6a-[(6a*S*)-2,2-dimethyl-1,3-dioxolan-6a-yl]-2,2-dimethyl tetrahydro-7*H*-[1,3]-dioxolo 2-oxo-5-azonia-spiro[4,4]nonane-1-ylide 5c. A solution of the diazoketoester **4c** (0.517 g, 0.00126 mol) in CH_2Cl_2 (10 mL) was refluxed for 30' in the presence of $Rh_2(OAc)_4$ (0.015 g, 3 mol%). The solvent was evaporated and the residue gave, after flash chromatography (Et_2O/MeOH/Et_3N, 5:5:0.1) the title compound **5c** as amorphous grey solid (0.365 g, 76% yield). $[\alpha]_D^{25}$ −47 (*c* 0.37, $CHCl_3$); ^{1}H NMR: δ 1.32 (s, 3H), 1.34 (t, 3H, J=6.9 Hz), 1.35 (s, 3H), 1.42 (s, 3H), 1.56 (s, 3H), 2.05–2.60 (m, 1H), 2.86 (quintet, 1H, J=4 Hz), 3.61 (t, 1H, J=7.8 Hz), 3.83 (dt, 1H, J=2.4, 8.7 Hz), 3.94–4.37 (m, 7H), 4.41 (dd, 1H, J=7.2, 12.8 Hz), 4.96 (t, 1H, J=6.6 Hz), 5.09 (dt, 1H, J=0.6, 6.6 Hz); ^{13}C NMR ($CDCl_3$): δ 14.6, 24.8, 26.6, 27.3, 33.4, 59.3, 65.2, 68.6, 76.7, 77.9, 80.8, 86.5, 105.8, 110.4, 113.7, 163.4, 179.4; IR (neat): 2926, 2854, 1652, 1607, 1460, 1419, 1376, 1263, 1210, 1078, 1055, 861and 844 cm^{-1}. Anal. Calcd for $C_{19}H_{29}NO_7$: C, 59.52; H, 7.62; N, 3.65. Found: C, 59.40; H, 7.83; N, 3.43.

4.1.8. *rac*-2-Diazo-5-(2-methoxymethyl-2-methyl-pyrrolidin-1-yl)-3-oxo-pentanoic acid ethyl ester 4d. TFA (0.48 mL, 0.006 mol) was added dropwise under nitrogen atmosphere to *rac*-*N*-Boc-2-methoxymethyl-2-methyl-pyrrolidine **3d** (0.31 g, 0.0016 mol) at 0 °C. The mixture was stirred at room temperature until the disappearance of the substrate (^{1}H NMR) and formation of trifluoroacetate of the amine (about 1 h) and then the excess of TFA was evaporated in vacuum at room temperature. To a stirred solution of the residue and 3-oxo-pent-4-enoic acid ethyl ester (0.35 g, 0.0025 mol) in CH_2Cl_2 (10 mL), a solution of Et_3N (0.35 mL, 0.0025 mol) in CH_2Cl_2 (10 mL) was added dropwise and stirred for 30 min. To the reaction mixture, tosyl azide (0.36 g, 0.0025 mol) and a solution of Et_3N (1.0 mL, 0.0075 mol) in CH_2Cl_2 (10 mL) were added dropwise at 0 °C. After the addition was complete, the solution was stirred at room temperature overnight. The solvent was evaporated and the residue was purified by flash chromatography (Et_2O/petroleum ether/Et_3N, 6:4:0.1) to give the title compound **4d** (0.30 g, 70% yield) as a yellow oil: ^{1}H NMR ($CDCl_3$): δ 0.96 (s, 3H), 1.33 (t, 3H, J=7.2 Hz), 1.48–1.59 (m, 1H), 1.74 (quintet, 2H, J=7.2 Hz), 1.84–1.96 (m, 2H), 2.61 (q, 1H, J=7.8 Hz), 2.67–2.77 (m, 1H), 2.93–3.07 (m, 2H), 3.20 (s, 3H), 3.33 (s, 3H), 4.30 (q, 2H, J=7.2 Hz); ^{13}C NMR ($CDCl_3$): δ 14.3, 17.9, 21.2, 35.9, 40.3, 44.3, 51.6, 59.2, 61.3, 62.8, 76.1, 78.7, 161.3, 192.0; IR (neat): 2965, 2928, 2132, 1718 and 1656 cm^{-1}. Anal. Calcd for $C_{14}H_{23}N_3O_4$: C, 56.55; H, 7.80; N, 14.13. Found: C, 56.73; H, 7.77; N, 14.05.

4.1.9. Diazo-decomposition of 4d. To a refluxing solution of $Rh_2(OAc)_4$ (0.013 g, 3 mol%) in 30 mL of dry CH_2Cl_2, a solution of **4d** (0.297 g, 0.001 mol) in dry CH_2Cl_2 (20 mL) was added dropwise over 30 min. After stirring for another 30 min at reflux, the reaction mixture was cooled and concentrated to give a 69:31 mixture of **5d** and **6d** (^{1}H

NMR). Purification by flash chromatography (Et_2O/ethyl acetate/Et_3N, 5:5:0.1; MeOH) gave 0.081 g of **6d** as a yellow oil and 0.180 g of inseparable mixture of ylides **5d** in the ratio of 44:56 (^1H NMR).

(4E)-5-(2-Methoxymethyl-2-methyl-pyrrolidin-1-yl)-3-oxo-pent-4-enoic acid ethyl ester **6d** ^1H NMR ($CDCl_3$): δ 1.27 (t, 3H, $J=7.2$ Hz), 1.29 (s, 3H), 1.66–1.78 (m, 1H), 1.87–2.01 (m, 2H), 2.01–2.15 (m, 1H), 3.22–3.34 (m, 4H), 3.34 (s, 3H), 3.39 (s, 2H), 2.61 (q, 1H, $J=7.8$ Hz), 2.67–2.77 (m, 1H), 2.93–3.07 (m, 2H), 3.20 (s, 3H), 3.33 (s, 3H), 4.18 (q, 2H, $J=7.2$ Hz) 5.06 (d, 1H, $J=$ 12.6 Hz), 7.78 (d, 1H, $J=12.6$ Hz); ^{13}C NMR ($CDCl_3$): δ 14.2, 21.7. 23.7, 35.9, 48.6, 48.7, 59.4, 60.9, 65.1, 78.3, 98.0, 146.9, 169.1, 188.0; IR (neat): 2977, 2934, 2874, 1735, 1651, 1600 and 1556 cm^{-1}. Anal. Calcd for $C_{14}H_{23}NO_4$: C, 62.43; H, 8.61; N, 5.20. Found: C, 62.51; H, 8.60; N, 5.18.

4.1.10. 2-Diazo-5-[(3a*R*,4*S*,6a*S*)-(2,2-dimethyl-4-trityloxymethyl-tetrahydro[1,3] dioxolo[4,5-*c*]-pyrrol-5-yl)]-3-oxo-pentanoic acid ethyl ester 4e. To a stirred solution of 1,4-dideoxy-2,3-di-*O*-isopropylidene-1,4-imino-5-*O*-trityl-L-lyx-itol **3e** (2.57 g, 0.0062 mol), and 3-oxo-pent-4-enoic acid ethyl ester (0.88 g, 0.0062 mol), in CH_2Cl_2 (15 mL), a solution of Et_3N (1.35 mL, 0.0096 mol) in CH_2Cl_2 (10 mL) was added dropwise and stirred for 30 min. The solvent was evaporated and to the residue a solution tosyl azide (1.21 g, 0.0062 mol) and Et_3N (1.35. mL, 0.0096 mol) in CH_3CN (15 mL) were added dropwise at 0 °C. After the addition was complete, the solution was stirred at room temperature overnight. The solvent was evaporated and the residue gave, after flash chromatography (petroleum ether/Et_2O, 8:2), the title compound **4e** (1.83 g, 50% yield) as a yellow oil: $[\alpha]_D^{25}$ +52.2 (*c* 0.52, $CHCl_3$); ^1H NMR: δ 1.27 (s, 3H), 1.28 (t, 3H, $J=7.2$ Hz), 1.29 (s, 3H), 2.07 (dd, 1H, $J=4.5$, 10.8 Hz), 2.30 (q, 1H, $J=5.4$ Hz), 2.40 (AB system, 1H), 2.92–2.99 (m, 2H), 3.13–3.22 (m, 2H), 3.26 (dd, 1H, $J=3.9$, 9.9 Hz), 3.56 (dd, 1H, $J=3.9$, 9.9 Hz), 4.22 (dq, 2H, $J=1.2$, 7.2 Hz), 4.58 (dt, 2H, $J=9.1$, 10.8 Hz), 7.21–7.48 (m, 15H); ^{13}C NMR ($CDCl_3$): δ 14.2, 25.5, 25.9, 37.9, 48.4, 59.4, 61.3, 62.3, 67.5, 75.9, 78.0, 80.8, 86.9, 110.9, 126.8, 127.6, 128.8, 144.2, 161.2, 191.5; IR (neat): 3085, 3057, 2982, 2936, 2800, 2132, 1714, 1654, 1490, 1448, 1371, 1299, 1209, 1172, 1152, 1117, 1068, 862, 763, 747, 706 and 633 cm^{-1}. Anal. Calcd for $C_{34}H_{37}N_3O_6$: C, 69.96; H, 6.39; N, 7.20. Found: C, 70.11; H, 6.25; N, 7.17.

4.1.11. Diazo-decomposition of 4e. A solution of the diazoketoester **4e** (1.105 g, 0.00110 mol) in CH_2Cl_2 (10 mL) was refluxed for 30 min in the presence of $Rh_2(OAc)_4$ (0.015 g, 3 mol%). The solvent was evaporated and the residue gave, after flash chromatography (petroleum ether/Et_2O, 8:2), the unsaturated compound *(4E)*-5-[(3a*R*,4*S*,6a*S*)-(2,2-dimethyl-4-trityloxymethyl-tetrahydro-[1,3]dioxolo[4,5-*c*]pyrrol-5-yl)]-3-oxo-pent-4-enoic acid ethyl ester **6e** (0.852 g, 81% yield), brown oil. $[\alpha]_D^{25}$ +47.2 (*c* 0.25, $CHCl_3$); ^1H NMR: δ 1.19 (s, 3H), 1.22 (t, 3H, $J=7.2$ Hz), 1.24 (s, 3H), 3.23–3.42 (m, 5H), (dd, 1H, $J=3.9$, 10.8 Hz), 3.70–3.78 (m, 1H), 4.13 (q, 1H, $J=$ 7.2 Hz), 4.69 (t, 1H, $J=6.3$ Hz), 4.75 (dt, 1H, $J=2.4$, 6.3 Hz), 5.01 (d, 1H, $J=13.2$ Hz), 7.20–7.45 (m, 15H), 7.91 (d, 1H, $J=13.2$ Hz); ^{13}C NMR ($CDCl_3$): δ 14.0, 24.7, 25.8, 60.8, 62.6, 63.9, 77.6, 79.0, 87.5, 112.7, 127.2, 127.8, 128.5, 143.4, 149.7, 168.7, 188.7; IR (neat): 3057, 3032, 2984, 2938, 1731, 1659, 1556, 1490, 1448, 1372, 1211, 1155, 1082, 982, 861, 764, 748, 706 and 648 cm^{-1}. Anal. Calcd for $C_{34}H_{37}NO_6$: C, 73.49; H, 6.71; N, 2.52. Found: C, 73.22; H, 6.50; N, 2.51.

Acknowledgements

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18. Crystal data and structure refinement for ylide **5a**: single crystals were obtained by recrystallization from ethyl acetate/Et_2O, 10:1. The substance ($C_{23}H_{31}NO_3$, $M_r=369.49$) crystallized in the monoclinic space group $P2_1$, $a=11.022(1)$ Å, $b=7.793(1)$ Å, $c=12.104(1)$ Å; $\alpha=90°$, $\beta=90.46(1)°$, $\gamma=90°$; $V=1039.63(18)$ Å^3, $Z=2$, $D_{calcd}=1.180$ Mg/m^3, F (000)=400, $T=295(2)$ K, crystal size $0.33\times0.27\times0.010$ mm^3, $\theta=1.85$–25.36°, limiting indices $=-12<=h<=13$, $-9<=k<=9$, $-15<=l<=14$, reflections collected=11503, independent reflections=3602 [$R_{int}=0.0244$], completness to $\theta=25.36°$: 97%, max. and min. transmission: 0.9923 and 0.9750, refinement method: full-matrix least-squares on F^2, data=3602, restrains=32, parameters=369, goodness-of-fit on $F^2=1.075$, final R indices [$I>2\sigma(I)$]: $R^1=0.0348$, $wR^2=0.0774$, R indices (all data): $R^1=0.0504$, $wR^2=0.0846$, absolute structure parameter $=-1.0(3)$, extinction coefficient=0.018(3), largest diff. peak and hole=0.109 and -0.116 e Å^{-3}. Crystallografic data have been deposited with the Cambridge Crystallografic Data Center (Deposition number: CCDC 279550).

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Photooxygenations of 1-naphthols: an environmentally friendly access to 1,4-naphthoquinones

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Abstract—Dye sensitized photooxygenations of 1-naphthols were investigated with soluble and solid-supported sensitizers and moderate to excellent yields of the corresponding 1,4-naphthoquinones were achieved in relatively short irradiation times. The mild and environmentally friendly reaction conditions made this application particularly attractive for 'Green Photochemistry'. Consequently, the photooxygenation of 1,5-dihydroxynaphthalene was studied with non-concentrated and moderately concentrated sunlight and 5-hydroxy-1,4-naphthoquinone (Juglone) was obtained in yields up to 71%.

1. Introduction

Naphthoquinone derivatives based on 5-hydroxy-1,4-naphthoquinone (Juglone, **1**) represent an important class of natural products.[1] Additionally, Juglone serves as a valuable building block for the synthesis of biologically active quinonoid compounds (Chart 1),[2] and was thus selected by us as starting material for our ongoing photoacylation study.[3] Most commonly, Juglone is synthesized from the cheap and commercially available 1,5-dihydroxynaphthalene by oxidation, but many of these thermal pathways suffer from severe disadvantages concerning yield, selectivity, sustainability, scale-up or reproducibility, respectively.[4] Dye sensitized photooxygenations can serve as a versatile alternative and various examples involving 1-naphthols have been reported in the literature.[5–7]

Due to the favorable absorption of most dyes within the visible spectrum, photooxygenation reactions have been subjected to concentrated sunlight and served as model systems for environmentally friendly and benign 'Green Photochemistry'.[8–10] Recently, we have briefly reported on solar photooxygenations to Juglone using novel holographic mirror elements.[8b] In this publication, we would like to present a comprehensive study on solar and artificial light induced photooxygenations of 1-naphthols and 1,5-dihydroxynaphthalene in particular.

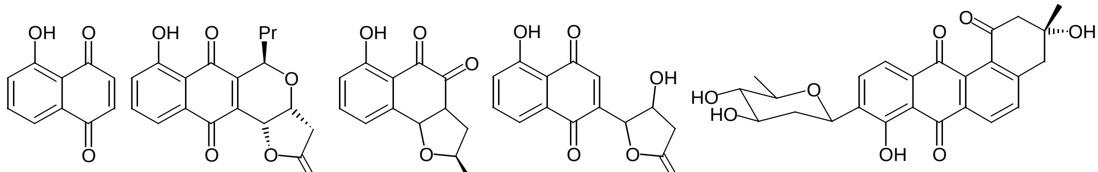

Chart 1. Quinonoid natural products synthesized from Juglone **1** (for more examples see Ref. 2).

Keywords: Quinones; Photochemistry; Photooxygenations; Green chemistry.
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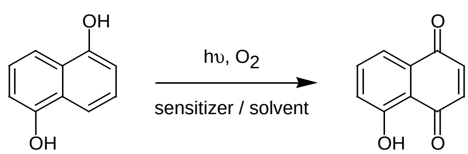
2. Results and discussion

2.1. Experiments with artificial light

To find suitable reaction conditions for the solar chemical campaign, we have launched a detailed laboratory study with artificial light and selected the photooxygenation of 1,5-dihydroxynaphthalene **2** to Juglone **1** as model system (Scheme 1). A major disadvantage of the literature procedures was the usage of the hazardous solvents dichloromethane, acetonitrile or methanol, respectively,[5] which needed to be replaced for a solar 'outdoor' application. In order to simplify the work-up procedure, we furthermore examined the usage of solid-supported sensitizers, in particular Sensitox® (rose bengal on Merryfield resin; RB_{MF})[11] and methylene blue on ion exchange resin (MB_{IE}).[12] Both materials can be easily removed by filtration and are, in principal, reusable.



Scheme 1. Photooxygenation of 1,5-dihydroxynaphthalene **2**.

Following a standardized procedure, a 0.01 M solution of 1,5-dihydroxynaphthalene **2** was irradiated with a 150 W medium-pressure mercury lamp in the presence of a sensitizer while a gentle stream of oxygen was passed through the solution (Table 1). The progress of the reaction was followed by GC or TLC analysis. After 5 h, Juglone was isolated via column chromatography using chloroform as eluent or, more conveniently, via continuous extraction with *n*-hexane in a Soxhlet extractor.

Table 1. Experimental data for the photooxygenations of **2** with artificial light (150 W medium-pressure mercury lamp)

Entry	Sens.[a]	Solvent	Time (h)	**1** (%)
1	MB	MeOH	5	51
2	RB	MeOH	5	34
3	MB_{IE}	MeOH	5	43
4	RB_{MF}	MeOH	5	32
5	—[b]	MeOH	5	2
6	MB	EtOH	5	54
7	RB	EtOH	5	37
8	MB_{IE}	EtOH	5	47
9	RB_{MF}	EtOH	5	32
10	—[b]	EtOH	5	2
11	MB	*i*-PrOH	5	58
12	RB	*i*-PrOH	5	38
13	MB_{IE}	*i*-PrOH	5	46
14	RB_{MF}	*i*-PrOH	5	33
15	—[b]	*i*-PrOH	5	2
16	MB	Acetone	5	48
17	RB	Acetone	5	71
18	MB_{IE}	Acetone	5	41
19	RB_{MF}	Acetone	5	68
20	—[b]	Acetone	5	8
21	MB	CH_2Cl_2/MeOH[c]	5	51
22	RB	CH_2Cl_2/MeOH[c]	5	34
23	MB_{IE}	CH_2Cl_2/MeOH[c]	5	43
24	RB_{MF}	CH_2Cl_2/MeOH[c]	5	28
25	—[b]	CH_2Cl_2/MeOH[c]	5	3

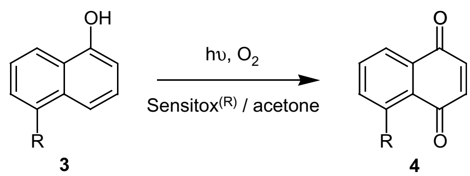
[a] Sensitizers: methylene blue (MB), rose bengal (RB), methylene blue on ion exchange resin (MB_{IE}), rose bengal on Merryfield resin (Sensitox®, RB_{MF}).
[b] Without sensitizer.
[c] CH_2Cl_2/MeOH (9:1).

In methanol, methylene blue was found to be the most effective sensitizer and the desired **1** was isolated in a reasonable yield of 51%. As would be expected for heterogeneous conditions, the yields for the solid-supported sensitizers were slightly lower with 43% (MB_{IE}) and 32% (RB_{MF}), respectively. With Sensitox®, the characteristic orange color of Juglone became clearly visible after a relatively short irradiation time. After 5 h, TLC analysis showed no sign of sensitizer leaching. In contrast to the literature,[12] significant leaching was, however, observed for methylene blue on ion exchange resin as noticeable from the green color of the final reaction mixture. Similar preferences and yields were obtained when ethanol was used as solvent. Likewise, the photooxygenation proceeded satisfactory in isopropanol and **2** was isolated in yields of 33–58%. The best Juglone yields of 71 and 68% were obtained using acetone as solvent and rose bengal or Sensitox® as sensitizer (entries 17 and 19), respectively. In comparison to the irradiations in alcohols, methylene blue gave a somewhat lower yield of 48%. Due to the limited solubility of the diol **2** in pure dichloromethane, photosensitized oxygenations were conducted alternatively in a 9:1 mixture with methanol, and Juglone was formed in yields of 28–51%. Surprisingly, the product yields did not improve as would be expected from the longer $^1O_2$ lifetime in this solvent mixture.[13] Enhanced photobleaching of the dye and photodecomposition of **1** due to the rather harsh radiation emitted from the medium-pressure mercury lamp,[5b] in combination with the formation of acid from the halogenated solvent, might explain this unexpected drop.

In the absence of sensitizer, **1** was formed in only small amounts of 2–3% in all alcoholic solvents and in the dichloromethane/methanol mixture. Solely the irradiation of **2** in pure acetone furnished Juglone in a significant yield of 8% (entry 20),[14] and we tentatively postulate a type-I photooxidation for its formation as known for phenols.[5d]

A scale-up of the photooxygenation to **1** was furthermore examined in acetone with Sensitox®, and the concentration of **2** was stepwise increased in 0.01 mol/l intervals. Up to a concentration of **2** of 0.05 mol/l, complete conversions were achieved within 5 h and **1** was isolated in yields of 65–70%. At higher concentrations, prolonged irradiation times up to 10 h were required but **1** was still isolated in good yields of 63–68%. At a diol concentration of 0.1 mol/l, the reaction was stopped after 10 h. At this stage, GC analysis showed a conversion of ca. 80%. After work-up, Juglone was obtained in 55% yield (69% based on conversion).

The photooxygenation protocol was additionally applied to 1-naphthol **3a**, 1-acetoxy-5-hydroxynaphthalene **3b** and 5-acetamido-1-hydroxynaphthalene **3c** (Scheme 2; Table 2), respectively. 1-Naphthol **3a** readily gave 53% of 1,4-naphthoquinone **4a** when irradiated with a medium-pressure mercury lamp in acetone and in the presence of Sensitox®. In line with the literature,[15b] irradiation of **3b** under identical conditions furnished Juglone **1** in 68% yield. Obviously, the acetate-group is cleaved during the course of the reaction. In contrast, the related amide-linked compound **3c** readily gave the corresponding quinone **4c** in a good yield of 61%.[15a]



Scheme 2. Photooxygenations of **3**.

Table 2. Experimental data for the photooxygenations of **3** with artificial light (150 W medium-pressure mercury lamp)

Entry	R	Sens.[a]	Solvent	Time (h)	**4** (%)
1	H (**3a**)	RB_{MF}	Acetone	5	53 (**4a**)
2	OAc (**3b**)	RB_{MF}	Acetone	5	68 (**1**)
3	NHAc (**3c**)	RB_{MF}	Acetone	5	61 (**4c**)

[a] Sensitizer: rose bengal on Merryfield resin (Sensitox®, RB_{MF}).

Due to the absorption of Juglone within the emission spectra of the medium-pressure mercury lamp,[16] we have conducted a series of experiments using a pair of 500 W halogen lamps (Table 3). Since solution purging with pure oxygen is furthermore problematic for industrial applications, we have examined its replacement with compressed air. Almost all experiments were run in non-hazardous isopropanol. Irradiations with pure oxygen readily furnished Juglone in yields of 25–70% after 5 h. Since the given set-up did not allow an even distribution of the solid-supported sensitizers within the reaction mixture, the experiments involving Sensitox® and methylene blue on ion exchanger resin (MB_{IE}) showed significantly lower conversions and yields. With compressed air, prolonged irradiation times of 10 h were required but the desired **1** was still obtained in fair to high yields of 21–71%. For laboratory purposes, we have furthermore modified the conditions reported by Cossy and Belotti for photooxygenations of 8-hydroxyquinolines.[7b] Irradiation in a 9:1 mixture of dichloromethane and methanol for 2 h and in the presence of TTP as sensitizer yielded **1** in an excellent yield of 88% (entry 5). The yield was somewhat lower with 78% when air was used as oxygen source (entry 10). Noteworthy, this procedure represents the so far best synthetic pathway to Juglone.[4]

Table 3. Experimental data for the photooxygenations of **2** with artificial light (2×500 W halogen lamps)

Entry	Sens.[a]	Solvent	Gas	Time (h)	**1** (%)
1	MB	*i*-PrOH	O_2	5	69
2	RB	*i*-PrOH	O_2	5	70
3	MB_{IE}	*i*-PrOH	O_2	5	34
4	RB_{MF}	*i*-PrOH	O_2	5	25
5	TPP[b]	CH_2Cl_2/MeOH[c]	O_2	2	88
6	MB	*i*-PrOH	Air	10	71
7	RB	*i*-PrOH	Air	10	55
8	MB_{IE}	*i*-PrOH	Air	10	45
9	RB_{MF}	*i*-PrOH	Air	10	21
10	TPP[b]	CH_2Cl_2/MeOH[c]	Air	3	78

[a] Sensitizers: methylene blue (MB), rose bengal (RB), methylene blue on ion exchange resin (MB_{IE}), rose bengal on Merryfield resin (Sensitox®, RB_{MF}), tetraphenylporphine (TPP).
[b] TPP insoluble in *i*-PrOH.
[c] CH_2Cl_2/MeOH (9:1).

2.2. Solar chemical experiments

In July and August 2005, we have conducted a series of solar chemical experiments at Dublin City University (latitude 53°23′N, 6°15′W, 50 m above sea level). Due to the volatility and flammability of the solvent acetone, we have selected the less hazardous isopropanol for our campaign. Following this strategy, various solutions of **2** were exposed in a Schlenck-flask equipped with a cold finger and a reflux condenser to direct sunlight while the solution was purged with a gentle stream of air. All experiments went smoothly and gave satisfactory results in reasonable periods of time without any noticeable side-products (Table 4). The first run (**I**) was performed with soluble rose bengal under ideal solar conditions and Juglone was isolated in a moderate yield of 39% after 3.5 h of illumination. A somewhat lower yield of 30% of **1** was obtained when the reaction was repeated for 6.5 h during a partly sunny period (**II**). With soluble methylene blue as sensitizer (**III**), Juglone became available in 44% yield after 5.5 h of partly sunny weather. Likewise, Sensitox® was tested as a heterogeneous sensitizer (**IV**). Within ½ h, the orange color of **1** became clearly visible and further intensified with progressing illumination. Due to the limited distribution of the solid sensitizer within the reaction mixture, **1** was obtained in just 19% yield after 6.5 h of perfect weather conditions. Noteworthy, all reactions described above could have been driven easily to high conversions with longer illumination times. Thus, the preliminary results obtained clearly indicate that the solar photosensitized oxygenation of 1,5-dihydroxynaphthalene opens a promising and environmentally friendly pathway to Juglone.

Table 4. Experimental data for the solar photooxygenation reactions of **2** with non-concentrated sunlight

	Experiment			
	I	**II**	**III**	**IV**
Date	12.07.2005	13.07.2005	25.07.2005	08.08.2005
Scale				
2 (g)	0.56	0.56	0.56	0.56
Sens. (g)[a]	0.05 (RB)	0.05 (RB)	0.05 (MB)	0.4 (RB_{MF})
Solvent	*i*-PrOH	*i*-PrOH	*i*-PrOH	*i*-PrOH
V (ml)	350	350	350	350
Time				
IST[b]	14:15–17:45	11:45–18:15	10:45–16:15	10:15–16:45
Total (h)	3.5	6.5	5.5	6.5
Weather	Sunny	Partly sunny	Partly sunny	Sunny
Yield **1** (%)	39	30	44	19

[a] Sensitizers: rose bengal (RB), methylene blue (MB), rose bengal on Merryfield resin (Sensitox®, RB_{MF}).
[b] Irish summer time.

Further solar chemical experiments were performed with moderately concentrated sunlight at the solar chemical facility of the German Aerospace Center (DLR) close to Cologne/Germany (latitude 50°51′N, 7°07′E, 70 m above sea level).[17] A parabolic trough collector designed for laboratory-scale (<500 ml) applications and equipped with an aluminum mirror (aperture: 41×36 cm) was selected (Fig. 1).[18] The reactor offers a geometric concentration factor of about 18 suns, but its efficiency is reduced in practice due to optical losses. Tracking of the sun is performed manually for the elevation and the azimuth every 15 min. The reaction mixture is pumped through the jacket of a Liebig condenser (diameter: 2.4 cm), which is placed in the focal line of the concentrator. Cooling water is passed through the inner tube of the condenser. Oxygen is added via a simple Y-connector, which limited its homogeneous distribution within the absorber tube.

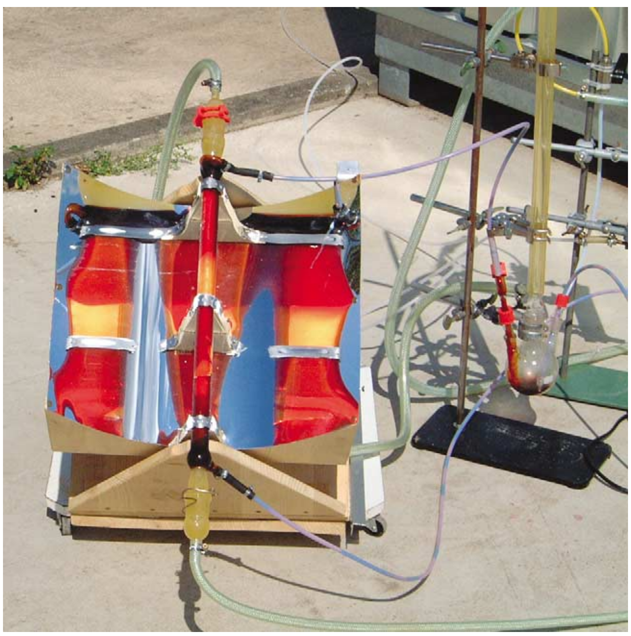


Figure 1. Laboratory-scale parabolic trough reactor during the solar photooxygenation of 1,5-dihydroxynaphthalene **2** (the red color of the sensitizer rose bengal can be clearly seen).

In August and September 2003, three laboratory-scale experiments were conducted, and the progress of each reaction was followed by GC analysis versus tetradecane as internal standard. Due to its favorable solar sensitization efficiency and overall stability,[8d] rose bengal was chosen as sensitizer. The experimental details and results from the solar chemical studies are summarized in Table 5.

The first run (**V**) was performed during a sunny period with 0.5 g of diol **2** and 0.05 g of rose bengal in 100 ml of isopropanol. The starting material was readily consumed and already after 40 min, GC analysis revealed complete conversion (>95%). During that time the reactor collected 0.07 mol of photons in the important absorption range of rose bengal between 500–600 nm.[19] After work-up, the desired product **1** was obtained in 71% yield. For the second experiment (**VI**) under mostly sunny conditions, the amount of diol **2** was doubled to 1.0 g and after 2.5 h, GC analysis showed a constant value for Juglone **1** of 74% (Fig. 2). The collector received 0.16 mol of photons in the range of 500–600 nm,[19] slightly more than double the amount as during the first experiment. After a total illumination period of 3.5 h, Juglone was obtained in a good yield of 69% (78% based on conversion). For the final experiment (**VII**), the solvent was replaced by methanol. Due to the less

Table 5. Experimental data for the solar photooxygenation reactions of **2** with moderately concentrated sunlight

	Experiment		
	V	**VI**	**VII**
Date	15.08.2003	09.09.2003	11.09.2003
Scale			
2 (g)	0.5	1.0	1.0
Rose bengal (g)	0.05	0.01	0.1
Solvent	*i*-PrOH	*i*-PrOH	MeOH
V (ml)	100	100	100
Time			
CEST[a]	14:20–16:50	13:45–17:15	10:15–14:45
Total (h)	2.5	3.5	4.5[b]
Effective (h)[c]	⅔	2.5	—
Weather	Sunny	Mostly sunny	Partly sunny
Photons (mol)[d]			
Total	0.26	0.21	0.16
Effective[e]	0.07	0.16	—
Conversion (%)[f]	>95	88	86
Yield **1** (%)	71 (75)[g]	69 (78)[g]	46 (54)[g]

[a] Central European summer time.
[b] Stopped due to rainfall.
[c] Time until conversion reaches an almost constant value.
[d] Estimated amount of photons collected between 500–600 nm.[18]
[e] Estimated amount of photons (500–600 nm) for effective illumination time.
[f] Conversion of **2** as determined by GC analysis (vs tetradecane).
[g] Yield based on conversion of **2**.

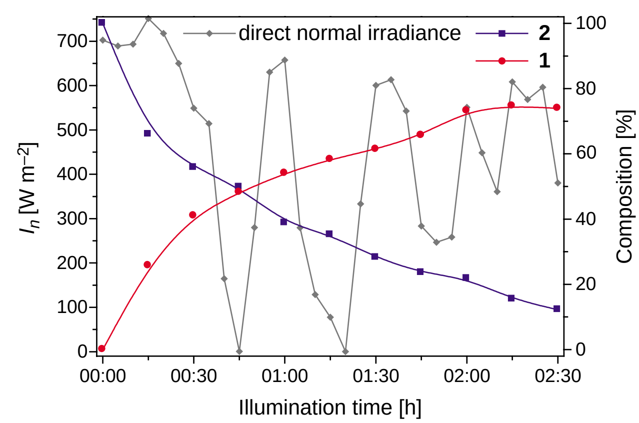


Figure 2. Direct normal irradiance (I_n) and product composition versus illumination time for the photooxygenation of 1,5-dihydroxynaphthalene **2** (Experiment VI).

favorable weather, the illumination time needed to be extended. After 4.5 h of partly sunny conditions, the reaction was stopped at 86% conversion due to beginning rainfall. At this stage the reactor had collected 0.16 mol of photons between 500–600 nm.[19] After work-up, Juglone was isolated in a moderate yield of 46% (54% based on conversion).

3. Conclusion

In conclusion, photooxygenations of 1-naphthols to the corresponding 1,4-naphthoquinones can serve as a useful and environmentally friendly alternative to existing thermal processes. The solar chemical reaction of the cheap and commercially available 1,5-dihydroxynaphthalene can be easily performed with non-concentrated or concentrated sunlight, and yields the valuable intermediate Juglone. Thus, a realization of Giacomo Ciamician's spectacular vision of 'the photochemistry of the future' (presented at the International Congress of Applied Chemistry in New York in 1912)[20] seems feasible.

4. Experimental

4.1. General methods

Melting points were measured on a Büchi B-540 apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance 400 spectrometer (400 and 100 MHz, respectively) using the solvent residual peak as internal standard. Chemical shifts (δ) are given in ppm, coupling constants (J) in Hz. MS spectra were recorded on a Finnigan MAT 8230 (EI) spectrometer. IR spectra were recorded as KBr discs on a Perkin-Elmer 298 infrared spectrophotometer, UV/vis spectra on a Perkin-Elmer Lambda 7 spectrophotometer using *n*-hexane (Janssen Chimica, spectrophotometric grade) as solvent. For combustion analysis a Heraeus CHN-O-Rapid Elemental Analyzer was used. GC analysis was performed on a Shimadzu GC-14A or a Hewlett-Packard GC 5890 Series II. A Hanau TQ-150 medium-pressure mercury lamp (150 W) or Armley 500 W halogen lamps (2×500 W) and immersion well reactors ($\lambda > 280$ nm) were used for irradiation experiments. TLC was carried out on Merck Kieselgel 60 F_{254}, column chromatography on silica gel (Macherey and Nagel) 230–240 mesh using chloroform or a 19:1 mixture of chloroform and methanol. 1,5-Dihydroxynaphthalene **2** was purified according to a modified procedure of Johnson and co-workers.[21] 1-Acetoxy-5-hydroxynaphthalene **3b** was synthesized as reported by Becher et al.,[22] 5-acetamido-1-hydroxynaphthalene **3c** via a method described by Jindal and co-workers.[23] Sensitox® was prepared with chloromethylated styrene–divinylbenzene copolymer (50–100 mesh, 1% cross-linked) according to Schapp et al.,[11] methylene blue on ion exchange resin (Lewatit SC 104 or MonoPlus SP 112) according to Williams and co-workers.[12] Solvents and reagents were commercially available and were used without further purification.

4.2. Irradiation and illumination experiments

4.2.1. Irradiations with artificial light. General procedure (medium-pressure mercury lamp). The naphthol (1.5 mmol) was dissolved in 150 ml of solvent. The sensitizer was added (MB: 10 mg; RB: 20 mg; MB_{IE}: 400 mg; RB_{MF}: 100 mg) and the solution was irradiated with a Hanau TQ-150 medium-pressure mercury lamp (150 W) for 5 h at room temperature while purging with a gentle stream of oxygen. Evaporated solvent was frequently refilled. The progress of the reaction was monitored by TLC or GC analysis. The reaction mixture was filtrated, the solvent removed in vacuum, and the residue was purified by column chromatography on silica or by extraction in a Soxhlet extractor with *n*-hexane. Experimental details are given in Tables 1 and 2.

4.2.1.1. 5-Hydroxy-1,4-naphthoquinone (Juglone, 1). Isolated by Soxhlet extraction with *n*-hexane. Orange solid, mp: 152 °C (lit.:[5a] 151–154 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.94 (s, 2H), 7.27 (dd, 1H, J = 2.2, 7.5 Hz), 7.60–7.65 (m, 2H), 11.90 ppm (s, 1H, OH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 114.0, 118.1, 123.5, 130.8, 135.5, 137.6, 138.6, 160.6, 183.2, 189.3 ppm. MS (EI, 70 eV): m/z = 174 (M^+, 100%), 146, 118, 90, 63, 39. IR (KBr): ν = 3400, 3058, 1662, 1641, 1590, 1448, 1289, 1225, 1151, 1098, 1081, 863, 827, 762, 703 cm^{-1}. UV/vis (*n*-hexane): λ_{max} = 247.8, 318.0, 427.8 nm. Anal. Calcd for $C_{10}H_6O_3$: C 68.97, H 3.47. Found: C 68.25, H 3.70.

4.2.1.2. 1,4-Naphthoquinone (4a). Isolated by column chromatography using chloroform as eluent. Yellow-brownish solid, mp: 128 °C (lit.:[24] 128.5 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.96 (s, 2H), 7.74 (m, 2H), 8.06 ppm (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 126.5, 132.0, 134.1, 138.8, 185.2 ppm. MS (EI, 70 eV): m/z = 158 (M^+, 100%), 130, 102, 76, 62, 50, 40. IR (KBr): ν = 1660, 1587, 1331, 1302, 1146, 1115, 1059, 863, 771 cm^{-1}. UV/vis (*n*-hexane): λ_{max} = 240.2, 245.3, 328.3 nm. Anal. Calcd for $C_{10}H_6O_2$: C 75.94, H 3.82. Found: C 75.55, H 3.91.

4.2.1.3. 5-Acetamido-1,4-naphthoquinone (4c). Isolated by column chromatography using chloroform as eluent. Yellow solid, mp: 170 °C (lit.:[14a] 172 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.29 (s, 3H), 6.90 (d, 1H, J = 10 Hz), 6.94 (d, 1H, J = 10 Hz), 7.72 (dd, 1H, J = 8.4 Hz), 7.81 (dd, 1H, J = 1.2, 8.4 Hz), 9.07 (dd, 1H, J = 1.2, 8.4 Hz), 11.85 (s, 1H, NH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.8, 116.1, 122.1, 126.2, 132.3, 135.9, 138.1, 140.1, 141.5, 170.1, 184.7, 189.3 ppm. MS (EI, 70 eV): m/z = 215 (M^+), 173 (100%), 145, 117, 101, 91, 63, 43. IR (KBr): ν = 3477, 3211, 1707, 1666, 1646, 1609, 1580, 1496, 1408, 1302, 1264, 1159, 833, 766, 723 cm^{-1}. Anal. Calcd for $C_{12}H_9N_1O_3$: C 66.97, H 4.22, N 6.51. Found: C 66.51, H 4.39, N 6.70.

4.2.2. General procedure (halogen lamps). Five hundred and forty milligrams (3.5 mmol) of 1,5-dihydroxynaphthalene **2** were dissolved in 350 ml of solvent. The sensitizer was added (MB: 50 mg; RB: 50 mg; MB_{IE}: 400 mg; RB_{MF}: 400 mg; TPP: 20 mg) and the solution was irradiated (2×500 W halogen lamps) in a Schlenck-flask equipped with a cold finger and a reflux condenser for 2–10 h at room temperature while purging with a gentle stream of oxygen or air. Evaporated solvent was frequently refilled. The progress of the reaction was monitored by TLC analysis. The reaction mixture was filtrated the solvent removed in vacuum, and the residue was purified by column chromatography (SiO_2, $CHCl_3$) or by extraction in a Soxhlet extractor with *n*-hexane. Experimental details are given in Table 3.

4.2.3. Illuminations with sunlight. General procedure (non-concentrated sunlight). Five hundred and forty milligrams (3.5 mmol) of 1,5-dihydroxynaphthalene **2** were dissolved in 350 ml of isopropanol. The sensitizer was added (RB: 50 mg; MB: 50 mg; RB_{MF}: 400 mg) and the solution was exposed to direct sunlight in a Schlenck-flask equipped with a cold finger and a reflux condenser for 3.5–6.5 h while purging with a gentle stream of air. Evaporated isopropanol was frequently refilled and the progress of the reaction was monitored by TLC analysis. The reaction mixture was filtrated, the solvent removed in vacuum, and the residue was purified by column chromatography (SiO_2, $CHCl_3$) or by extraction in a Soxhlet extractor with *n*-hexane. Experimental details are given in Table 4.

4.2.4. General procedure (concentrated sunlight). 1,5-Dihydroxynaphthalene **2** was dissolved in 100 ml of solvent. Rose bengal was added and the solution was exposed to moderately concentrated sunlight in a parabolic trough reactor for 2.5–4.5 h while purging with a gentle stream of oxygen. The progress of each reaction was monitored by GC analysis versus tetradecane as internal standard. The solvent was removed in vacuum, and the residue was purified by column chromatography (SiO_2, $CHCl_3$/MeOH = 19:1). Experimental details are given in Table 5.

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Investigation of the active species in a Michael addition promoted by chirally modified tetrahydroborate

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Dedicated to Professor Robert Moss on the occasion of his 65th birthday

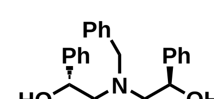
Abstract—For the first time, asymmetric 1,4-addition of various malonates to enones has been carried out using tetrabutylammoniumtetrahydroborate (TBATB) in the presence of a chiral ligand. The Michael adducts were formed in reasonably good yields (61–67%) with moderate ee's at 0 °C. ^{11}B NMR spectroscopic studies explain this unexpected reactivity through the predominant formation of an aminodiol modified borate complex in the presence of a hydride acceptor.

1. Introduction

The Michael addition, being one of the most important C–C bond-forming reactions, has attracted much attention toward the development of enantioselective catalytic procedures in recent years.[1] The current literature abounds with many reports on enantioselective Michael addition catalyzed by chiral complexes of Ru,[2a] Co,[2b] Rh,[2c] Ni,[2d] Cu,[2e] Zn,[2f] Cd,[2g] Al[2h] and other heterobimetallics.[3] Thus far, however, there are not many reports on boron catalyzed asymmetric Michael reactions.[4]

We have earlier shown that chiral aminodiol, (*R*,*R*)-**1**, in combination with $LiAlH_4$ or lanthanum–sodium, can be effectively used for asymmetric Michael additions.[5] As an extrapolation of these findings, we decided to investigate the application of chirally modified borohydrides in promoting the Michael reaction of α,β-unsaturated ketones. Although chirally modified boron has been employed to promote many asymmetric processes[6a] such as Diels–Alder,[6b] allylation[6c] and aldol[6d] reactions, little has been reported on the chirally modified tetrabutylammoniumtetrahydroborate (TBATB) system in such reactions. However, it is known that chirally modified borohydrides are effective in asymmetric reduction processes[7] but, in contrast, to chiral auxiliaries of lithium aluminum hydrides that promote asymmetric Michael addition,[3c,5] chirally modified borohydrides are not known to assist such reactions.[3c]

Herein, we give a brief report on the results of Michael additions promoted by a mixture of TBATB/(*R*,*R*)-**1** in THF and attempts to rationalize our observations.



(*R*, *R*)-**1**

2. Results and discussion

The required ligand (*R*,*R*)-**1** was prepared from the reaction of (*R*)-styrene oxide with benzylamine.[5c] First, a control reaction was performed to study the reduction pattern of cyclic enone with TBATB in the presence of (*R*,*R*)-**1**. As expected the products were alcohol and ketone resulting from an initial 1,4-addition of hydride across the enone to give the enolate, that converts into the ketone (via the enol) and gets reduced further. These findings are in agreement with other literature reports.[8]

Subsequently, (*R*,*R*)-**1** in combination with TBATB was used as a promoter in the Michael addition of cyclic enones with diethyl malonate[9] (Eq. 1). The corresponding Michael adducts from cyclohexenone and cyclopentenone were formed in good yields and with moderate enantioselectivities. The reduced products of cyclic enone were also obtained in minor amounts along with the Michael adduct. In all these cases the yields of Michael adducts remained fairly constant. The results are summarized in Table 1.

Keywords: Borohydride; Michael addition; Malonates.

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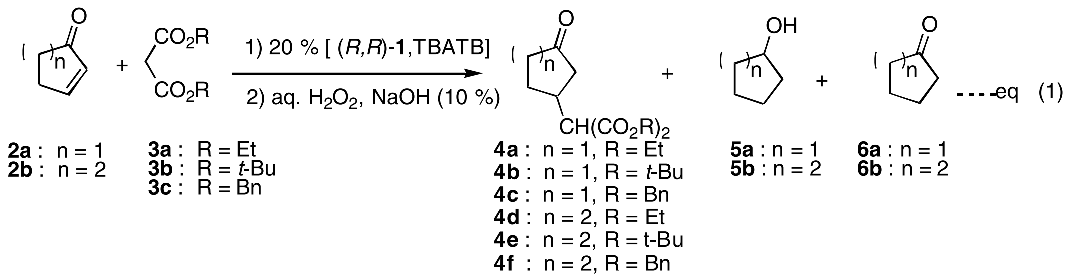
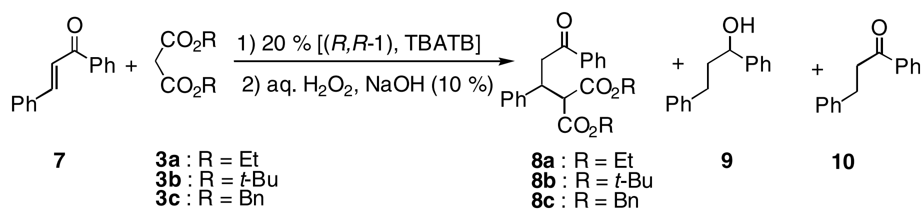
Table 1. Michael addition of various malonates to cyclic enones



Entry	Enone	Michael donor	Time (h)	Product distribution (%)[a]			%ee of **4**[b]
				4	**5**	**6**	
1	**2a**	**3a**	7	**4a**=62	**5a**=24	**6a**=14	**4a**=35
2	**2a**	**3b**	7	**4b**=64	**5a**=22	**6a**=14	**4b**=40
3	**2a**	**3c**	7	**4c**=61	**5a**=25	**6a**=12	**4c**=31
5	**2b**	**3a**	7	**4d**=67	**5b**=22	**6b**=11	**4d**=42
6	**2b**	**3b**	7	**4e**=65	**5b**=25	**6b**=10	**4e**=45
7	**2b**	**3c**	7	**4f**=63	**5b**=22	**6b**=15	**4f**=39

[a] Determined by HPLC.
[b] %ee was determined by HPLC connected to a Chiracel OD. The absolute configuration in all cases were determined by comparison of optical rotation and was found to be *R*.

Table 2. Michael addition of benzylidineacetophenone with malonates



Entry	Enone	Michael donor	Time (h)	Product distribution (%)[a]		
				8	**9**	**10**
1		**3a**	7	**8a**=62	22	16
2	**7**	**3b**	7	**8b**=64	22	14
3		**3c**	7	**8c**=61	23	16

[a] Isolated yields.

In a similar manner benzylidineacetophenone reacts with malonates to give 1,4-adducts with moderate enantioselectivity, along with minor amounts of reduced products. The results are summarized in Table 2.

Thus, in the presence of (*R*,*R*)-**1** and TBATB a mixture of enone and malonate gives reasonable yields of the Michael adducts in moderate enantiomeric excess, suggesting the formation of a chirally modified borohydride, an observation that warranted further scrutiny.

To gain better insight into these findings, we chose to study the reaction by ^{11}B NMR spectroscopy. The ^{11}B NMR spectrum of a solution containing (*R*,*R*)-**1** and TBATB in a 2:1 ratio gave a quintet centered at −57.4 ppm indicating the presence of free borohydride.[10] To this mixture, the addition of cyclohexenone in portions of 0.5 equiv, promoted the formation of a singlet centered at −15.7 ppm alongside the quintet that could be attributed to a free tetraborate anion having a tetrahedral structure,[11,6b] and with 2.1 equiv of cyclohexenone the quintet disappeared completely leaving a sharp singlet at −15.7 ppm (Fig. 1). In the absence of cyclohexenone, a mixture of **1** and TBATB, showed the quintet persisting in the ^{11}B NMR spectrum even after an overnight reflux. Thus, the need for a hydride acceptor to initiate the formation of the tetraalkoxyborate becomes clear.

When the same experiment was performed with cyclohexanone, the quintet did not disappear completely, even after addition of many equivalents of the ketone, indicative of a relatively slow hydride transfer to cyclohexanone. Nevertheless, the appearance of a sharp singlet at −15.9 ppm could be seen here as well. Also as expected, the ^{11}B NMR spectrum of a solution containing (*R*,*R*)-**1**, TBATB and diethyl malonate in the absence of cyclohexenone gave no other signal than the quintet. Not so surprising also was the sudden appearance of the singlet at −15.5 ppm beside the quintet when a small amount of cyclohexenone was added to this solution at

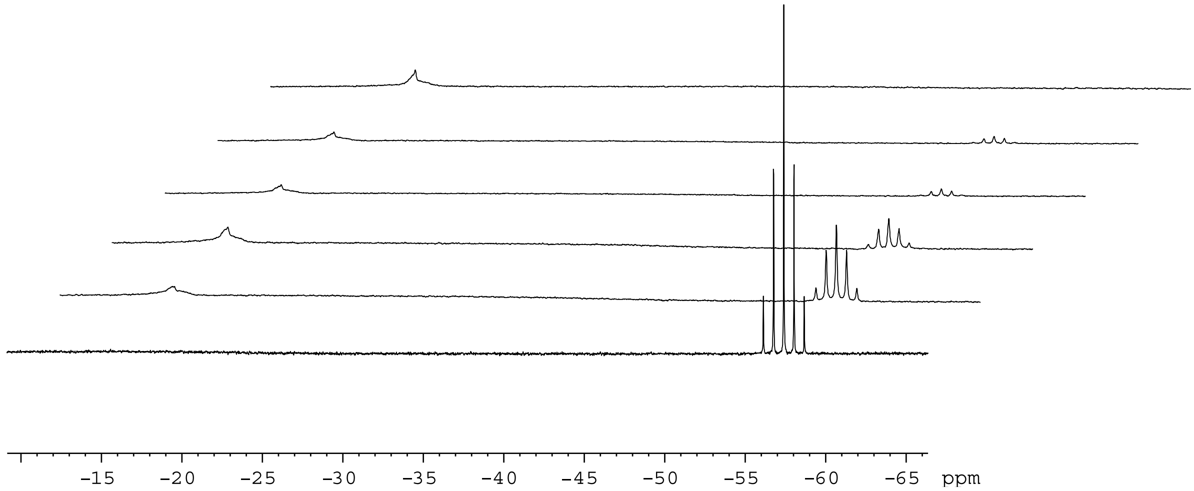
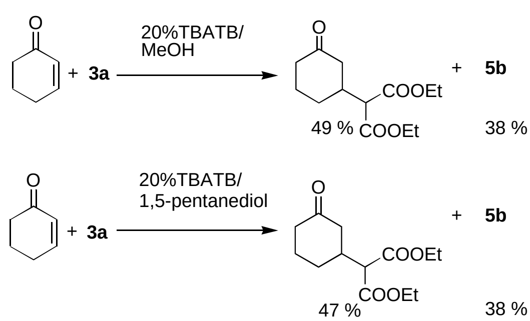


Figure 1. ^{11}B NMR spectra of **1**-TBATB and varying equivalents of cyclohexenone (a) 0 equiv (b) 0.5 equiv (c) 1.0 equiv (d) 1.5 equiv (e) 2.0 equiv (f) 2.1 equiv.

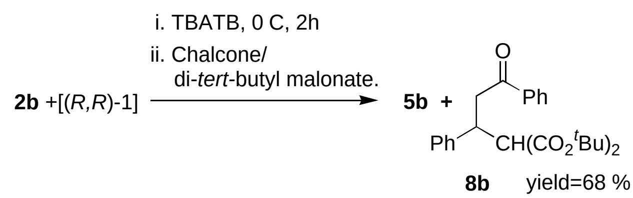
ambient conditions. Thus, the combined role of **1** and cyclohexenone in the generation of the singlet around −15 ppm in ^{11}B NMR needs to be appreciated.

To probe the effect of any interaction of the nitrogen atom in the backbone of (*R*,*R*)-**1** with the boron, the corresponding borate complex was generated from methanol or pentanediol by reacting with TBATB in the presence of the cyclic enone (Scheme 1). The borate complexes generated here, were effective in the Michael addition with product yields hovering around 47–49%, comparable to the earlier observations with (*R*,*R*)-**1** as the chelating ligand, pointing to an unlikely role for the nitrogen atom in the scaffold of **1**. Predictably, the ^{11}B NMR spectral studies of these systems were highly reminiscent of the earlier results.



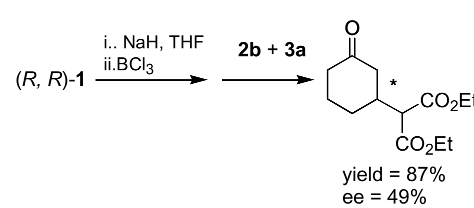
Scheme 1. Michael addition in the presence of achiral alcohols without any ligating atom in the backbone.

In order to confirm the need for a hydride acceptor in the formation of the active catalyst, we deliberately added cyclohexenone as a sacrificial hydride acceptor to the (*R*,*R*)-**1**-TBATB mixture prior to the addition of chalcone as the actual Michael acceptor. Thus, a solution of TBATB, (*R*,*R*)-**1** and cyclohexenone in the ratio 1:2:2 was stirred for a period of 2 h, to which a mixture of chalcone and malonate was added. As expected, we could get the Michael adduct corresponding to chalcone and di-*tert*-butyl malonate as the major product along with the reduction products of cyclohexenone (Scheme 2).



Scheme 2. Use of cyclohexenone as a sacrificial hydride acceptor.

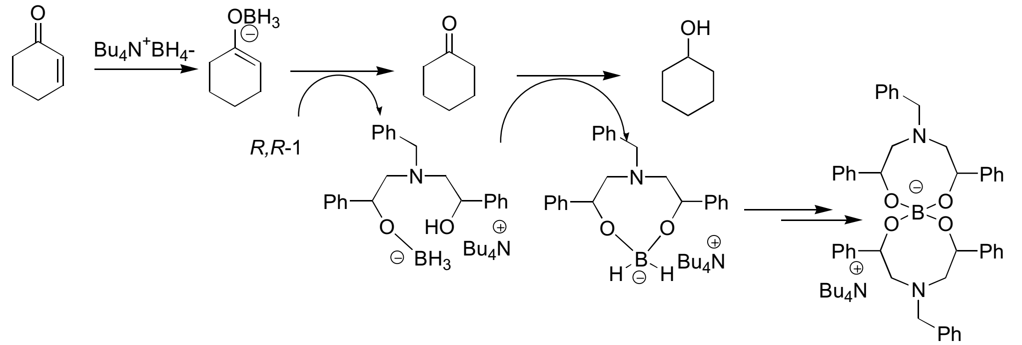
We also examined an alternate possibility for generating the borate, by reacting the disodiated (*R*,*R*)-**1** with BCl_3, to promote the Michael reaction involving cyclohexenone and diethyl malonate which, as expected, gave the Michael adduct in 87% yield with 49% ee (Scheme 3). It was also not surprising that the ^{11}B NMR spectrum of sodium aminodiolate and BCl_3 gave a peak at −16 ppm, implicating strongly the formation of a tetraborate species as in earlier cases.



Scheme 3. Asymmetric Michael addition with chiral borate generated from *R*,*R*-1 and BCl_3.

2.1. Suggested mechanism for the chirally modified borate promoted asymmetric Michael addition

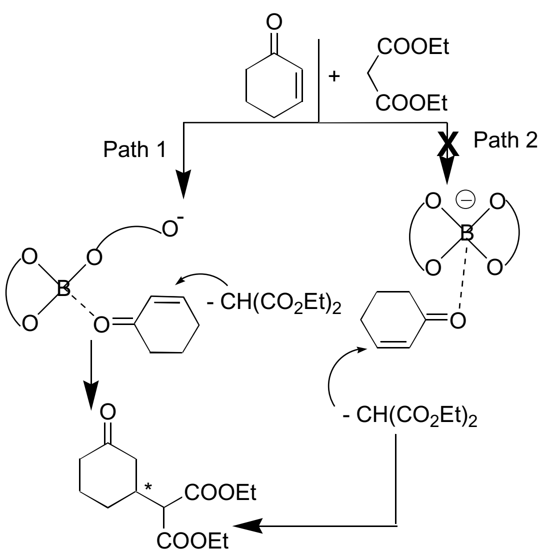
On viewing the above observations collectively, a plausible mechanism for the enantioselective Michael addition emerges (Scheme 4). The less acidic (*R*,*R*)-**1** does not react with TBATB to form the borate complex upon simple



Scheme 4. Suggested mechanism for the formation of the chirally modified borate in the asymmetric Michael addition.

mixing. However, when the enone is added, an initial hydride transfer from TBATB takes place; the enolate so generated undergoes a protic quench with (*R*,*R*)-**1** that converts it to the ketone. Stepwise mediation of boron leads to the eventual formation of the bischelate complex, the catalytically active species in the Michael reaction.

Clearly, the moderate (but tangible!) enantioselectivities observed in all these cases suggest probable coordination of cyclohexenone to a chirally modified borate complex. The possibilities could then be, either a tetracoordinate boron with one arm of the aminodiol acting as a detachable tether or a pentacoordinate hypervalent boron, the half life of which is very short on the NMR timescale[12] (vide Scheme 5). Further NMR spectroscopic investigations performed to detect the catalytically active species involved did not offer positive clues even at low temperatures (−60 °C) when only signals at −57 and −15 ppm could be observed. Since we have no clear proof by boron NMR spectroscopy or otherwise for the occurrence of pentacoordinate boron, we tend to support the former mechanism. The mechanism also explains the fact that the combined yields of the reduced products in the reaction equal a stoichiometric transfer of four hydrides from the borate (Table 1).



Scheme 5. Possible modes of activation of enone.

3. Conclusion

In conclusion, we have shown for the first time that chirally modified TBATB–aminodiol is effective in the Michael addition of α,β-unsaturated ketones with various Michael donors with moderate enantioselectivity. Evidence from ^{11}B NMR spectroscopic studies and other experiments support the formation of chiral tetrahedral borate from aminodiol and borohydride in the presence of a hydride acceptor.

4. Experimental

4.1. General experimental procedures

All operations were carried out under an atmosphere of dry, oxygen-free nitrogen employing vacuum or Schlenk line techniques, unless otherwise noted. Nitrogen was purified by passage through columns of MnO anchored on silica gel catalyst and 4 Å molecular sieves. Solid organometallic compounds were transferred in an argon-filled glove bag. All glassware, syringes and needles were oven dried at 140 °C and cooled to room temperature under nitrogen before use. Tetrahydrofuran was freshly distilled from sodium/benzophenone ketyl under nitrogen atmosphere. Cyclohexenone, di-*tert*-butylmalonate, di-ethylmalonate, di-benzylmalonate and (*R*)-styreneoxide were purchased from Lancaster synthesis and cyclopentenone was purchased from Aldrich and used as received. Tetrabutylammoniumtetrahydroborate (TBATB) was prepared from tetrabutylammonium-hydrogensulphate according to the literature procedure. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded in $CDCl_3$ at ambient temperature with TMS as the internal standard and ^{11}B NMR (135 MHz) spectra were recorded with boric acid as an external standard using AV400 Bruker spectrometer ($BF_3\cdot Et_2O$ signal appeared at −19.38 ppm). Analytical HPLC was performed with Shimadzu LC-8A HPLC instrument equipped with RI detector and chiralcel OD column. Optical rotations were measured on a JASCO DIP-370 Polarimeter. Melting points were determined in a capillary and are uncorrected. Mass spectra were recorded on a Q-TOF mass spectrometer.

4.2. General reaction procedure of malonate addition on conjugate alkenones

To a solution of TBATB (56 mg, 0.214 mmol) in dry THF (3 mL) was added a solution of aminodiol (150 mg, 0.432 mmol) in THF (3 mL). The mixture was stirred under moisture free nitrogen atmosphere for 30 min at 0 °C, then a mixture of α,β-unsaturated ketone (1.06 mmol) and Michael donor (1.06 mmol) were added. The mixture was stirred for 7 h. The reaction was then quenched by the addition of 3% aqueous hydrogen peroxide (2 mL) and 10% aqueous sodium hydroxide (1 mL). The mixture was stirred for 2 h, the layers were separated and the aqueous phase was extracted with CH_2Cl_2 (2×20 mL). The combined organic layer was dried over anhydrous sodium sulfate, concentrated and the crude product was purified by column chromatography (silica gel 60–120, acetone/hexane 10:90). NMR spectra are identical to those previously reported.[5]

%ee's were determined by HPLC (Daicel Chiralcel OD, 2.0:98.0, 2-propanol/hexane, flow rate = 0.5 mL/min, 254 nm; For example, **4e** had retention times of $t_1 = 28.6$ (*S*), $t_2 = 36.5$ (*R*)). The absolute configuration was established by comparison to the literature.[13]

Acknowledgements

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Tetrahedron

Fluorinated alcohol directed formation of dispiro-1,2,4,5-tetraoxanes by hydrogen peroxide under acid conditions

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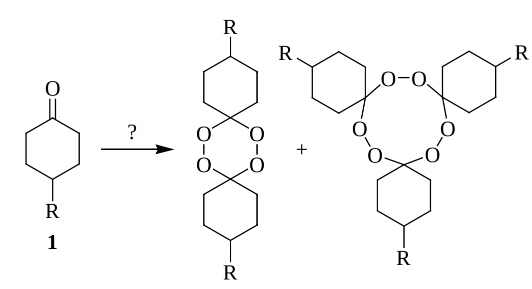
Abstract—The oxidative system MTO/30%H_2O_2/HBF_4/fluorous alcohol is promising for the selective synthesis of biologically important antimalarial dispiro-1,2,4,5-tetraoxanes by direct acid-catalysed cyclisation of various 4-substituted cyclohexanones (**1**, R = Me, Et, *t*Bu, Ph, COOEt, CF_3). The role of the substitutent at the 4-position was important in the selectivity of formation of tetraoxane (**2**, TO) with respect to hexaoxonane (**3**, HO). By the use of fluorinated alcohols and under the right reaction conditions, tetraoxanes **2** were selectively formed and synthesised in 46–86% isolated yield from 4-substituted cyclohexanones **1**.

1. Introduction

Malaria is a major communicable disease that causes or contributes to approximately 3 million deaths per year.[1] Malaria mortality has increased in recent years, mainly due to the parasites growing resistance to classical alkaloidal drugs.[2] Artemisinin and its semi synthetic derivatives as well as synthetic endoperoxides have emerged as potent non-alkaloid compounds that are active against chloroquine-resistant seves of Plasmodium.[3] Dispiro-1,2,4,5-tetraoxanes, having two endoperoxide bonds, are effective and inexpensive antimalarial agents.[4,5] The easiest path for their synthesis is the acid-catalysed peroxidation of a carbonyl compound with hydrogen peroxide. However, this method can be employed only for selected substrates, since it results in a mixture of compounds with dispiro-1,2,4,5-tetraoxane (TO) being only one among many.[6] For example, acid-catalysed cyclisation of 4-methylcyclohexanone with H_2O_2 gave only 1,2,4,5,7,8-hexaoxonane (HO), while the 4-*tert*-butyl analogue gave a mixture of both cyclic peroxides (Scheme 1).[7] An alternative route for the selective synthesis of tetraoxanes is ozonolysis of cycloalkylidenecycloalkanes,[8] enol ethers,[9] and *O*-methyl oximes,[7,10] but yields are generally low.

Improving the selectivity of the cyclisation by using H_2O_2 and acid would be particularly advantageous due to its simplicity. Fluorinated alcohols (hexafluoro-2-propanol—HFIP and trifluoroethanol—TFE)[11] are known activators of hydrogen peroxide in various oxidation reactions: oxidations of sulfides,[12] epoxidations[13] and Baeyer–Villiger oxidations.[14] This activation is attributed to the high hydrogen bond donor strength of TFE and HFIP.[15] We have already applied fluorinated alcohols in the methyltrioxorhenium-catalyzed oxidation of 4-methylcyclohexanone with 30% H_2O_2 and the reaction led to the formation of gem-dihydroperoxide. Based on this result, we were able to report the first one-pot synthesis of non-symmetric TO from simple ketones and 30% H_2O_2.[16] During this study, we selectively transformed 4-methylcyclohexanone into the corresponding TO without the formation of



Scheme 1.

Keywords: Hydrogen peroxide; Fluorinated alcohols; Cyclic peroxides; Tetraoxane; Antimalarials; Oxidation.

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HO. It was already known from the literature that the selectivity of the cyclisation is very dependent on the structure of the ketone and on reaction conditions.

Presented herein is our investigation into the factors that govern the formation of the two cyclic peroxides—tetraoxanes and hexaoxonanes from 4-substituted cyclohexanones **1** (Fig. 1) and our results on the selective direct formation of dispiro-1,2,4,5-tetraoxanes **2**.

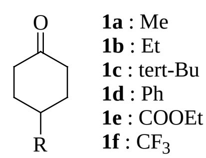
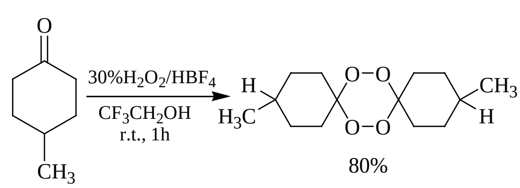


Figure 1.

2. Results and discussion

Initially, we studied the role of reaction conditions (fluorinated alcohol, acid…) on the conversion of 4-methylcyclohexanone **1a** to TO **2** and HO **3**. In the first experiment, we mixed equimolar amounts of **1a**, 30% H_2O_2 and HBF_4 in TFE for 1 h at room temperature. A white precipitate formed immediately and after a filtration, the main product formed was dispiro-1,2,4,5-tetraoxane **2a**, which was further isolated in 80% yield (Scheme 2). We did not observe the formation of hexaoxonane **3a** but we were able to show the presence of trace amounts of ε-caprolactone. Selective formation of TO **2a** in TFE was surprising, since in previous study using acetonitrile as a solvent,[7] only HO was isolated. The NMR spectrum of **2a** shows dynamic properties with a characteristic broad signal at 3.05 ppm for two protons (C1–H and C9–H), which agrees with previously published data.[17] Although two possible signals were expected for the CH_3 group there was only one sharp doublet at 0.92 ppm, indicating that the methyl groups are either in the equatorial or axial position.



1a **2a**

Scheme 2.

To gain greater insight into the role of acid in acid-catalysed peroxidation, different acids were tested. In acid-catalysed reactions of **1a** with H_2O_2 in TFE, strong acids (H_2SO_4, HCl, *p*-toluenesulfonic acid) acted as HBF_4 and the only cyclic peroxide formed was TO **2a**. Peroxidation catalysed with a weaker acid (acetic acid) did not yield any cyclic peroxide, whereas with intermediate acids, trifluoroacetic and phosphoric acid, a mixture of both cyclic peroxides was formed (**2a**:**3a** = 3:1 and 1:3.7, respectively).

Next, we took 4-ethyl- **1b** and 4-*tert*-butyl cyclohexanone **1c**. Using reaction conditions with HBF_4 in TFE as for **1a**, the 4-ethyl derivative **1b** was transformed to TO **2b**, (isolated in 69% yield, Table 1, entry 2). Surprisingly, with the *tert*-butyl derivative **1c** selectivity was lost and cyclisation afforded both cyclic peroxides—TO **2c** and HO **3c** (Table 1, entry 3). Due to the similar solubility of the two cyclic peroxides, we could only separate a mixture of both **2c** and **3c** in a ratio of 55/23 by column chromatography (63% yield). To obtain only tetraoxane **2c**, we looked for selective conditions that avoid the formation of the trimeric peroxide. First, we applied methyltrioxorhenium—MTO,[18] one of the catalysts with the broadest range of action and the one that has already been applied in the synthesis of non-symmetric TOs.[16] The use of MTO (0.1 mol%) brought some advantage (Table 1, entry 4), but further improvement was obtained by the use of a more diluted solution (0.5 M solution of **1c** instead of 1 M) that gave TO **2c** as the only cyclic peroxide formed (entry 6), isolated by column chromatography in 64% yield. Reaction at 0 °C produced a complex reaction mixture with HO **3c** being the major reaction product (entry 7). Hexafluoro-2-propanol (HFIP) is a better hydrogen bond donor than TFE and is therefore a more activating solvent for oxidation reactions.[11] The reaction of **2c** in HFIP at 0 °C was stopped after 5 min and TO **2c** was the only cyclic peroxide formed and was accompanied by ε-caprolactone **4c** (entry 8). Column chromatography gave 40% isolated yield of TO **2c**. This reaction performed at room temperature yielded only ε-caprolactone **4c** (96% isolated yield, Scheme 3).

4-Phenylcyclohexanone **1d** was the next substrate on which we investigated the effect of reaction conditions on the selectivity of acid-catalysed peroxidation. As in the case of **1c**, phenyl-derivative **1d** gave mixture of TO **2d** and HO **3d** in the MTO-catalysed reaction in TFE at standard room temperature. The isolated reaction mixture was separated by column chromatography and resulted in a mixture of a TO **2d** and HO **3d** (25% yield) in a ratio 1:1.8 as determined by NMR spectroscopy (Table 2, entry 10). HFIP had a beneficial effect on the selective formation of TO as exclusive formation of TO **2d** was observed at room temperature (46% isolated yield, entry 12). We also found a similar reactivity pattern for ethyl 4-oxocyclohexane-carboxylate **1e** (entries 13–15) where again the use of more activated conditions (HFIP, room temperature) was needed to achieve selective cyclisation to TO **2e** (50% isolated yield; entry 15). The important role of the hydrogen bond donor strength of the solvent is evident in the case of 4-trifluoromethylcyclohexanone **1f**. In TFE, the reaction was directed towards the formation of the trimeric-HO **3f** (entry 16), while the use of HFIP as a solvent resulted in the exclusive formation of TO **2f** (entry 17). After work-up, the isolated yield was 54% for HO and 86% for TO. We could conclude from the preceding experiments that the structure of ketone had a profound effect on the formation of cyclic ketones (TO vs HO). However, only TO can be selectively formed by tuning of the reaction conditions, where the presence of MTO, room temperature and more activating solvent (HFIP) plays an important role.

The sensitivity of this reaction on the type of acid and the substituent on the position 4 of the cyclohexanone ring pose the question whether TO and HO are formed independently or whether they could be inter-converted during the reaction

Table 1. The effect of reaction conditions on the MTO-catalysed oxidative cyclisation of 4-substituted cyclohexanones **1c**–**f** in fluorinated alcohols[a]

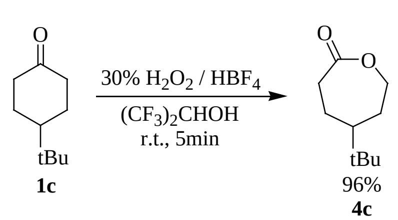
Entry	Substrate	Reaction conditions	Relative ratio (%)[b]					
			1	**2**	**3**	Other	**2/3**	Yield of **2/3** (%)[c]
1	**1a** (4-Me)	TFE, 1 M, rt, 1 h[d]	6	85		9[e]	>100	80
2	**1b** (4-Et)	TFE, 1 M, rt, 1 h[d]	4	87		9[e]	>100	69
3	**1c** (4-*t*Bu)	TFE, 1 M, rt, 1 h[d]	13	55	23	9[e]	2.39	63
4		TFE, 1 M, rt, 1 h	11	73	16	—	4.56	63
5		TFE, 1 M,, rt, 1 h[f]	44	Trace	47	9	<0.05	30
6		TFE, 0.5 M, rt, 1 h	9	77	—	14[e]	>100	64
7		TFE, 0.5 M, 0 °C, 15 min	16	23	35	26[g]	0.66	48
8		HFIP, 0.5 M, 0 °C, 5 min	—	52	—	48[e]	>100	40
9		HFIP, 0.5 M, rt, 5 min	—	—	—	100[e]	—	
10	**1d** (4-Ph)	TFE, 1 M, rt, 1 h	—	12	23	65[g]	0.52	25
11		HFIP, 0.5 M, 0 °C, 1 h	12	25	13	50[g]	1.92	26
12		HFIP, 0.5 M, rt, 5 min	—	69	—	31[e]	>100	46
13	**1e** (4-COOEt)	TFE, 1 M, rt, 1 h	—	32	38	30 [g]	0.84	17
14		HFIP, 1 M, 0 °C, 1 h	—	41	43	16[g]	0.95	14
15		HFIP, 0.5 M, rt, 5 min	5	86	—	9[e]	>100	50
16	**1f** (4-CF_3)	TFE, 1 M, rt, 1 h	23	—	61	16[g]	<0.01	54
17		HFIP, 0.5 M, rt, 5 min	3	90	—	7[g]	>100	86

[a] Reaction conditions: **1c**, 1 equiv 30% H_2O_2, 1 equiv HBF_4, 0.1 mol% MTO.
[b] Ratio determined by NMR spectroscopy.
[c] Isolated yield of the mixture **2/3** or pure compounds **2** or **3** after column chromatography.
[d] Reaction without MTO.
[e] 4-Substituted-ε-caprolactone **4**.
[f] H_3PO_4 used as acid.
[g] Mixture of hydroperoxides.

process. This subject was already debated in the seventies where it was argued that HOs are kinetically controlled products that can be converted to TOs.[19] Further studies show that TOs are thermodynamically more stable, but which of them is the kinetically preferred product depends on several reaction rates.[20]

Using both cyclic peroxides **2c** and **3c**, we made crosscheck experiments to determine their stability under the reaction conditions imposed on the synthesis of TO (with HBF_4 in TFE) and HO (with H_3PO_4 in TFE). The isolated TO **2c** was stable in the presence of weak and strong acid in TFE, while HO **3c** was stable only in the presence of a weaker acid (Table 2). In contrast, in the presence of a strong acid (HBF_4), HO **3c** decomposes into a mixture of hydroperoxide products with a small amount of ketone **1c** and lactone **4c** as determined by ^1H NMR spectra of the crude product mixture.

Further, we made experiments under conditions as reported in the literature for conversion of HO into TO with perchloric acid in acetic acid.[14] The result was that only 5% of TO **2c** together with 10% of lactone **4c** were formed. Similarly, when using CF_3-substituted HO **3f** we did not detect any conversion of HO to TO; instead **3f** was decomposed into different products. These results indicate that HO is not directly converted in high yield into TO with



Scheme 3.

acid in fluorous alcohol and furthermore, it decomposes under the reported reaction conditions. This implies that the point of decision on the reaction path for the formation of tetraoxane versus hexaoxonane should be made prior to the cyclisation step and as noted by McCullough et al., is dependent on the relative rates of several equilibria between the ketone and precursors of cyclic peroxides.[20]

3. Conclusion

We have investigated what effect the reaction parameters have on the selectivity of the cyclisation of ketones to tetraoxanes with H_2O_2 under acid conditions. By choosing the appropriate reaction conditions we found that it is possible to select for the formation of dispiro-1,2,4,5-tetraoxane over its trimer analogue—hexaoxonane. In particular, we found the role of fluorinated alcohols (TFE and HFIP) to be essential. We conclude that for the preferred formation of dispiro-1,2,4,5-tetraoxane, a higher temperature, a more activating solvent (HFIP>TFE), the presence of a catalyst (MTO) and substrate concentration have a profound influence. Also the effect of the structure of the ketone should not be overlooked. Table 3 gives a summary of the results and reaction conditions needed for selective formation of tetraoxanes **2**.

Furthermore, formation of TO and HO is competitive and it is unlikely that they could be directly inter-converted under

Table 2. Stability of TO and HO under reaction conditions

Substrate	Acid	Reaction conditions	
TO **2c**	HBF_4	H_2O_2, MTO, TFE, rt, 15 min	No conversion
TO **2c**	H_3PO_4	H_2O_2, MTO, TFE, rt, 1 h	No conversion
HO **3c**	HBF_4	H_2O_2, MTO, TFE, rt, 15 min	Decomposition
HO **3c**	H_3PO_4	H_2O_2, MTO, TFE, rt, 1 h	No conversion

Table 3. Overview of reaction conditions needed for selective formation of tetraoxane **2** by acid-catalysed peroxidation of cyclohexanones **1** with 30% H_2O_2 in fluorinated alcohols

Cyclohexanone	Reaction conditions[a]	Yield of **2** (%)[b]
4-Me **1a**	TFE, rt, 1 h	80
4-Et **1b**	TFE, rt, 1 h	69
4-*t*-Bu **1c**	0.1 mol% MTO, TFE (0.5 M), rt, 15 min	64
4-Ph **1d**	0.1 mol% MTO, HFIP, rt, 5 min	46
4-COOEt **1e**	0.1 mol% MTO, HFIP, rt, 5 min	50
4-CF_3 **1f**	0.1 mol% MTO, HFIP, rt, 5 min	86

[a] Reaction conditions: **1**: H_2O_2:$HB8_4$=1:1:1(1M).
[b] Isolated yield of TO **2** after column chromatography.

the reaction conditions employed in this synthesis. This study opens the way for the selective preparation of TOs by acid-catalysed oxidative cyclisation directly from ketones and 30% hydrogen peroxide. TOs thus obtained will be evaluated as antimalarials.

4. Experimental

4.1. General

Cyclohexanones **1** and methyltrioxorhenium were obtained from commercial sources and were used as received. Trifluoroethanol (TFE), 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) and other solvents were distilled before use. ^1H and ^{13}C spectra were obtained using a Varian Unity-300 spectrometer with TMS and $CDCl_3$ as standards. Melting points were determined on a Büchi 535 apparatus and were not corrected. Electron-spray mass spectra (8 kV spray needles, CsI or NH_4OAc) were acquired on an AutoSpec hybrid spectrometer. Elemental analyses were performed at the Microanalytisches Labor Pascher (Germany).

Caution! Although we have encountered no difficulties in working with these tetraoxanes, we advise routine precautions (shields, fume hoods, avoidance of transition metal salts) since organic peroxides are potentially hazardous.

4.1.1. Reaction procedure for synthesis of tetraoxanes 2a and 2b. First, 30% H_2O_2 (0.23 mL) and 54% HBF_4 solution in Et_2O (0.28 mL) were dissolved in TFE (2 mL). Substrate **1a** or **1b** (2 mmol) was then added and stirred at room temperature for 1 h. Reaction mixture was filtered and precipitate purified by column chromatography (SiO_2, CH_2Cl_2/petroleum ether=4:1) and obtained:

3,12-Dimethyl-7,8,15,16-tetraoxadispiro[5.2.5.2]-hexadecane (**2a**) (205 mg, 80%); white solid, mp 70–71 °C (lit.,[7] 71–72 °C); ν_{max}(KBr) 1433, 1253, 1095, 1040, 970, 890 cm^{-1}; δ_H ($CDCl_3$) 0.92 (6H, d, J=6.3 Hz), 1.06–1.34 (4H, m), 1.38–1.85 (12H, m), 3.05 (2H, br s); δ_C ($CDCl_3$) 21.35, 21.44, 29.02 (br), 30.00 (br), 30.41 (br), 31.43 (br), 31.64, 31.73, 108.12, 108.16; *m/z* (ESI) 389 ($M+Cs^+$).

3,12-Diethyl-7,8,15,16-tetraoxadispiro[5.2.5.2]-hexadecane (**2b**) (197 mg, 69%) (Found: C, 67.59; H, 9.89. $C_{16}H_{28}O_4$ requires C, 67.57; H, 9.92%); white solid, mp 111–113 °C; ν_{max}(KBr) 1420, 1325, 1145, 1030, 910, 880 cm^{-1}; δ_H ($CDCl_3$) 0.88 (6H, t, J=7.1 Hz), 1.05–1.35 (10H, m), 1.35–1.90 (10H, m), 3.05 (2H, br s); δ_C ($CDCl_3$) 11.58, 27.55 (br), 28.14 (br), 28.63, 28.75, 29.00 (br), 31.35 (br), 38.34, 38.42, 108.41, 108.47; *m/z* (ESI) 417 ($M+Cs^+$).

4.1.2. Reaction procedure for the synthesis of tetraoxane 2c. MTO (0.5 mg), 30% H_2O_2 (0.23 mL) and 54% HBF_4 solution in Et_2O (0.28 mL) were dissolved in TFE (2 mL). Substrate **1c** (2 mmol) was added and stirred at room temperature for 15 min. A typical isolation procedure followed by purification by column chromatography (SiO_2, CH_2Cl_2/petroleum ether=4:1) yielded:

3,12-Di-tert-butyl-7,8,15,16-tetraoxadispiro[5.2.5.2]-hexadecane (**2c**) (219 mg, 64%); white solid, mp 190–192 °C decomp. (lit.,[7] 196–198 °C); ν_{max}(KBr) 1435, 1365, 1190, 1063, 1055, 935, 905 cm^{-1}; δ_H ($CDCl_3$) 0.86 (18H, s), 1.03–1.52 (10H, m), 1.58–1.95 (6H, m), 3.17 (2H, br s); δ_C ($CDCl_3$) 22.81 (br), 23.09 (br), 27.57, 27.61, 29.66 (br), 31.95 (br), 32.32, 47.40, 47.54, 108.11; *m/z* (ESI) 358 ($M+NH_4^+$).

4.1.3. Reaction procedure for the synthesis of hexaoxonane 3c. MTO (0.5 mg) and 30% H_2O_2 (0.23 mL) and H_3PO_4 (0.14 mL) were dissolved in TFE (2 mL). Substrate **1c** (2 mmol) was added and stirred at 23 °C for 1 h. After typical isolation procedure and purification by column chromatography (SiO_2, CH_2Cl_2) was obtained *3,12,20-tri-tert-butyl-7,8,15,16,23,24-hexaoxatrispiro[5.2.5.2.5.2]-tetracosane* (**3c**) (102 mg, 30%); white solid, mp 194–196 °C decomp. (lit.,[7] 195–196 °C); ν_{max}(KBr) 1440, 1365, 1195, 1125, 1080, 1065, 930, 910 cm^{-1}; δ_H ($CDCl_3$) 0.86 (27H, 2 s), 1.05–1.80 (21H, m), 2.18–2.42 (6H, m); δ_C ($CDCl_3$) 23.23, 23.52, 23.64, 23.67, 23.70, 27.57, 27.60, 27.65, 29.07, 32.32, 32.52, 32.55, 47.23, 47.29, 47.52, 107.48, 107.55, 107.84; *m/z* ESI 528 ($M+NH_4^+$).

4.1.4. Reaction procedure for the synthesis of lactone 4c. MTO (0.5 mg), 30% H_2O_2 (0.23 mL) and 54% HBF_4 solution in Et_2O (0.28 mL) were dissolved in HFIP (4 mL). Substrate **1c** (2 mmol) was added and stirred at room temperature for 5 min. After a typical isolation procedure pure *4-tert-butyl-ε-caprolactone* **4c** was obtained as colorless oil (326 mg, 96%) and identified by comparison with literature data:[21]: δ_H ($CDCl_3$) 0.89 (9H, s), 1.26–1.56 (3H, m), 1.96–2.12 (2H, m), 2.51–2.62 (1H, m), 2.70 (1H, ddd, J=1.3, 7.3, 14.0 Hz), 4.17 (1H, dd, J=10.1, 12.8 Hz), 4.34 (1H, ddd, J=1.9, 5.9, 12.8 Hz); δ_C ($CDCl_3$) 23.59, 27.29, 30.08, 32.88, 33.26, 50.60, 69.02, 177.76.

4.1.5. Reaction procedure for the synthesis of tetraoxanes 2d, 2e and 2f. MTO (0.5 mg), 30% H_2O_2 (0.23 mL) and 54% HBF_4 solution in Et_2O (0.28 mL) were dissolved in HFIP (4 mL). Substrate **1d** or **1e** (2 mmol) was added and stirred at room temperature for 5 min. After typical isolation procedure, tetraoxane **2** was purified by column chromatography (SiO_2, CH_2Cl_2/petroleum ether=9:1) and obtained:

3,12-Diphenyl-7,8,15,16-tetraoxadispiro[5.2.5.2]-hexadecane (**2d**) (176 mg, 46%) (Found: C, 74.51; H, 7.30. $C_{24}H_{28}O_4\times 1/4H_2O$ requires C, 74.59; H, 7.48%); white solid, mp 209 210.5 °C decomp.; ν_{max}(KBr) 1470, 1420, 1230, 1050, 1040, 930, 920, 910 cm^{-1}; δ_H ($CDCl_3$) 1.46–2.02 (14H, m), 2.63 (2H, m), 3.31 (2H, br s), 7.30 (10H, m);

δ_C ($CDCl_3$) 29.66 (br), 31.88 (br), 43.54, 107.85, 126.28, 126.81, 128.45, 145.78; *m/z* ESI 398 ($M+NH_4^+$).

Diethyl 7,8,15,16-tetraoxadispiro[5.2.5.2]-hexadecane-3,12-dicarboxylate (**2e**) (185 mg, 50%) (Found: C, 57.76; H, 7.64. $C_{18}H_{28}O_8$ requires C 58.05, H 7.58%); white solid, mp 125–129 °C; ν_{max}(KBr) 1705, 1430, 1305, 1245, 1180, 1165, 1120, 1050, 930, 910 cm^{-1}; δ_H ($CDCl_3$) 1.26 (6H, t, $J=7.1$ Hz), 1.40–2.05 (14H, m), 2.35–2.48 (2H, m), 2.85 (2H, br s), 4.1 (4H, q, $J=7.1$ Hz); δ_C ($CDCl_3$) 14.16, 23.71 (br), 24.60 (br), 28.06 (br), 30.28 (br), 41.43, 41.58, 60.39, 107.48, 174.49; *m/z* ESI 390 ($M+NH_4^+$).

3,12-Bis(trifluoromethyl)-7,8,15,16-tetraoxadispiro[5.2.5.2]-hexadecane (**2f**) (245 mg, 86%) (Found: C, 45.88; H, 5.18. $C_{14}H_{18}F_6O_4$ requires C, 46.16; H, 4.98); white solid, mp 102.5–105 °C; ν_{max}(KBr) 1440, 1350, 1330, 1265, 1240, 1190, 1155, 1120, 1080, 1055, 1020, 975, 930, 920, 880 cm^{-1}; δ_H ($CDCl_3$) 1.43–1.75 (8H, m), 1.75–2.02 (6H, m), 2.02–2.21 (2H, m), 3.20 (2H, br s); δ_C ($CDCl_3$) 20.48 (br), 20.97 (br), 27.72 (br), 30.02 (br), 40.93 (q, J(C,F)=27 Hz), 41.00 (q, J(C,F)=27 Hz), 107.30, 127.23 (q, J(C,F)=278 Hz).

4.1.6. Reaction procedure for the synthesis of hexaoxonane 3f. MTO (0.5 mg), 30% H_2O_2 (0.23 mL) and 54% HBF_4 solution in Et_2O (0.28 mL) were dissolved in TFE (2 mL). Substrate **1c** (2 mmol) was added and stirred at room temperature for 1 h. After a typical isolation procedure and column chromatography (SiO_2, CH_2Cl_2/petroleum ether=4:1) was obtained *3,12,20-tris(trifluoromethyl)-7,8,15,16,23,24-hexaoxatrispiro[5.2.5.2.5.2]-tetracosane* (**3f**) (196 mg, 54%) (Found: C, 45.75; H, 4.79. $C_{21}H_{27}F_9O_6$ requires C, 46.16; H, 4.98%); white solid, mp 128–132 °C; ν_{max}(KBr) 1460, 1400, 1370, 1340, 1290, 1270, 1195, 1165, 1130, 1100, 1070, 960, 940, 890 cm^{-1}; δ_H ($CDCl_3$) 1.3–1.5 (3H, m), 1.5–1.8 (9H, m), 1.8–2.2 (9H, m), 2.2–2.5 (6H, m); δ_C ($CDCl_3$) 21.21 (br), 21.54 (br), 27.19 (br), 27.27 (br), 30.42 (br), 40.55 (q, J(C,F)=27 Hz), 106.84, 106.87, 106.91, 127.45 (q, J(C,F)=277 Hz).

4.1.7. Stability of peroxide 2c. Compound **2c** (51 mg, 0.15 mmol), 54% HBF_4 solution in Et_2O (41 μL, 0.3 mmol) (85% H_3PO_4 (20 μL, 0.3 mmol), respectively), 30% H_2O_2 (34 μL, 0.3 mmol) and MTO (0.08 mg, 0.3 μmol) were mixed with TFE (0.6 mL) and stirred for 15 min (1 h, respectively). CH_2Cl_2 (10 mL) was added and washed with H_2O (10 mL) and saturated solution of $NaHCO_3$ (10 mL). Organic phase was dried with Na_2SO_4, solvent was evaporated and crude product was obtained (49 mg, 48 mg, respectively). The product was analyzed by ^{1}H and ^{13}C NMR spectroscopy with $PhCF_3$ as internal standard and only signals of TO **2c** were observed.

4.1.8. Stability of peroxide 3c in the presence of H_3PO_4. Compound **3c** (51 mg, 0.1 mmol), 85% H_3PO_4 (20 μL, 0.3 mmol), 30% H_2O_2 (34 μL, 0.3 mmol), MTO (0.08 mg, 0.3 μmol) were mixed with TFE (0.6 mL) and stirred for 1 h. CH_2Cl_2 (10 mL) was added and washed with H_2O (10 mL) and saturated solution of $NaHCO_3$ (10 mL). Organic phase was dried with Na_2SO_4, solvent evaporated and 46 mg of product was obtained. The product was analyzed by ^{1}H and ^{13}C NMR spectroscopy with $PhCF_3$ as internal standard and only signals of HO **3c** were observed.

4.1.9. Stability of peroxide 3c in the presence of HBF_4. Compound **3c** (51 mg, 0.1 mmol), 54% HBF_4 solution in Et_2O (41 μL, 0.3 mmol), 30% H_2O_2 (34 μL, 0.3 mmol), MTO (0.08 mg, 0.3 μmol) were mixed with TFE (0.6 mL) and stirred for 15 min. CH_2Cl_2 (10 mL) was added and washed with H_2O (10 mL) and saturated solution of $NaHCO_3$ (10 mL). The organic phase was dried with Na_2SO_4, solvent evaporated and 51 mg of product was isolated. A crude product was analyzed by ^{1}H and ^{13}C NMR spectroscopy with $PhCF_3$ as internal standard and by comparison with spectra of known compounds. The product was composed of HO **3c** (27%), ketone **1c** (3%), lactone **4c** (7%) and mixture of hydroperoxides (69%) with singlets at 9.4 ppm in ^{1}H NMR spectra.

Acknowledgements

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The synthesis of bis(oligophenyleneethynylenes): novel potential nonlinear optical materials

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Abstract—Various functionalised phenyleneethynylene dimers **10** and trimers **12** were synthesised by palladium-catalyzed Sonogashira methodology. These dimers and trimers were coupled to 1,8-diido-10-methoxyanthracene to generate bis(oligophenyleneethynylenes) **17** and **18**. Preliminary results towards the construction of both phenyleneethynylene and phenylenevinylene hybrid motifs are presented.

1. Introduction

The effects produced by a nonlinear optical (NLO) response in a bulk material have applications in optical switching, modulation, amplification, beam steering, wavelength filters and image processing.[1] The most important contributions to this activity come from the second and third order optical susceptibilities, $\chi^{(2)}$ and $\chi^{(3)}$, and can be described on the molecular level by the first and second order hyperpolarizabilities β and γ. In order to achieve large $\chi^{(2)}$ and $\chi^{(3)}$, high values of β and γ and a high density of nonlinear optical chromophores is desired, and since the polarization of a molecule is a vector quantity, the alignment of molecular dipoles which reinforce each other is also important.

The design of NLO materials continues to present a significant challenge to organic chemists.[2] It is recognized that attributes which enhance β include high polarizability, large anharmonicity and extensive electron delocalization.[1] In order to exhibit high $\chi^{(2)}$, the molecules must also be non-centrosymmetric, and generally, the organic compounds which have shown the most promise are donor–acceptor molecules possessing conjugated spacers with a low HOMO–LUMO band-gap. However, the structural requirements for materials having significant γ and $\chi^{(3)}$ are less well understood; although a high degree of conjugation is again desirable, a non-centrosymmetric geometry is unimportant.[3]

Oligo- and poly(phenylenevinylene) molecules (OPVs and PPVs) are a well-known class of organic NLO materials, and have some of the highest $\chi^{(2)}$ and $\chi^{(3)}$ values recorded.[4] However, their alkynyl analogues, oligo(phenyleneethynylene)s (OPEs), have not been as thoroughly assessed for NLO activity, partly because of their poor solubility. Due to the absence of *E*–*Z* photoisomerization, OPEs offer the potential advantage of durability over their double bond counterparts,[5] but those previously studied have generally shown a lower NLO response in comparison,[6] which has usually been ascribed to a less effective electron delocalization along the OPE chain.[5]

Since the extent of conjugation is dependant on orbital overlap, coplanarity of the aryl moieties of the chain is an important factor for high β and γ.[7] Arylacetylenes are known to have a very low barrier (<1 kcal mol^{-1}) for rotation around their sp–sp^2 bonds,[8] hence OPEs exist in a conformational equilibrium of planar and various twisted forms.[9] It has been shown that properties such as fluorescence emission and $\chi^{(3)}$ can be altered or enhanced through coplanarity enforced by π-stacking[10] and hydrophobic/hydrophilic interactions[11] in Langmuir films, and by metal–metal bridging in related systems.[12] It is our aim to explore this theme by restricting the rotation of OPEs by covalent linking,[13] hydrogen bonding or steric bulk.

Earlier we reported the synthesis of the thiacyclophane **1** (Fig. 1) as well as some cyclophane precursors[14] and compared their absorption and emission spectra. However, the X-ray crystal structure of **1** and subsequent molecular modelling revealed that a consequence of the length of the 'arms' of the cyclophane was to induce some twisting of the OPE chains and this made the synthesis of

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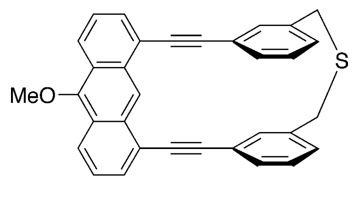

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Figure 1. A previously studied thiacyclophane.

dithiacyclophanes extremely challenging. We wished to prepare extended analogues of the precursors to thiacyclophane **1** with a view to exploring the effects of hydrogen bonding and steric bulk in the aryl spacer 'arms' on inducing coplanarity of the arylacetylene spacers. Herein we report the preparation of two bis(OPEs), after investigating various approaches for extension of OPE chains.

2. Results and discussion

The arylacetylene building blocks **2** (Fig. 2) required to generate the OPEs have been reported previously, or are commercially available.[15] In general, they were synthesized by palladium-catalyzed coupling of trimethylsilylacetylene (TMSA) with the corresponding aryl iodides, followed by protodesilylation under mild conditions.[16] The basic repeating unit of the OPE chains, the iodide **3a**,[17] was obtained in 65% overall yield from methyl *o*-anthranilate[18] by following established procedures for similar monomers[19] (Scheme 1). Alternatively, the triflate **3b** could be used.[20]

The OPE segments could be constructed in one of two ways: (a) the suitably functionalized monomers could be sequentially added to the anthracene template, extending the bis(OPE) one unit at a time; or (b) OPEs could be synthesized independently, then attached to the anthracene template. The ester side-arm acts as a handle that allows for further elaboration to groups, which may restrict the rotation of the aryl rings through hydrogen bonding or steric bulk, as well as to increase the solubility of the bis(OPE) products.[21] Monomer units containing only one ester side-arm were utilized for the development of OPE and bis(OPE) synthesis since the precursors were readily available.

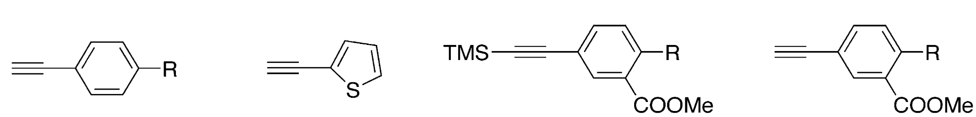
Based on previous reports, route (a) was initially investigated.[14] Protodesilylation of **3b** with potassium fluoride in methanol gave the terminal alkyne **4a** in quantitative yield; these conditions proved more efficient than either potassium carbonate–methanol or TBAF. Coupling of **4a** with **5**[22] using piperidine as a base, even when diluted with DMF, afforded the unexpected product **7**, which represents an example of an unusually facile Pd-catalyzed aryl amination reaction[23] (Scheme 2). It was believed that the formation of **7** was a consequence of the extended conjugation of the desired intermediate **6**. However, further experiments with different primary and secondary amines revealed that this reaction was specific for piperidine. The ditriflate **6** was isolated in 47% yield when the base was changed to triethylamine.

Disappointingly, the reaction of **5** with the phenolic alkyne **4b**[24] gave a complex mixture of products, which were not separable by chromatography, either directly or after attempted derivatization of the phenolic groups.[25]

A longer route for chain extension involving alternating addition of the alkynyl and aryl moieties was then explored. Reaction of **6** with an excess of TMSA afforded the disilane **8** in 74% yield; however, deprotection of **8** gave low yields of the corresponding unstable terminal bis-alkyne (Scheme 2).

The alternative route (b) to bis(OPE) formation proved to be more efficient. Sonogashira coupling of the arylacetylenes **2a**–**2g** with **3a** afforded the dimers **9a**–**9g** in 58–100% yields (Scheme 3).[26] Removal of the TMS groups was readily achieved with potassium carbonate–methanol to yield the terminal alkynes **10a**–**10g** without need for purification.[27]

Further coupling of **10a**–**10e** with **3a** gave the trimers **11a**–**11e** in good yields (Scheme 4), which again were



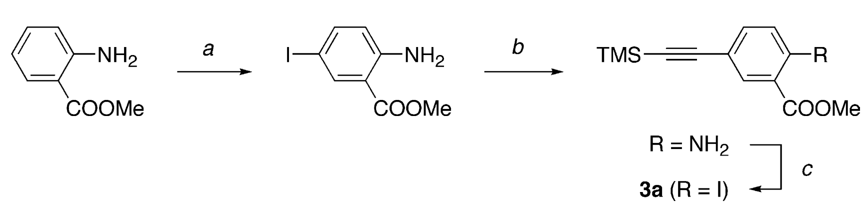
2a (R = H)
2b (R = NO_2)
2c (R = OMe)
2d (R = NHBoc)
2f (R = Br)
2g (R = SCH_2CH_2TMS)

2e

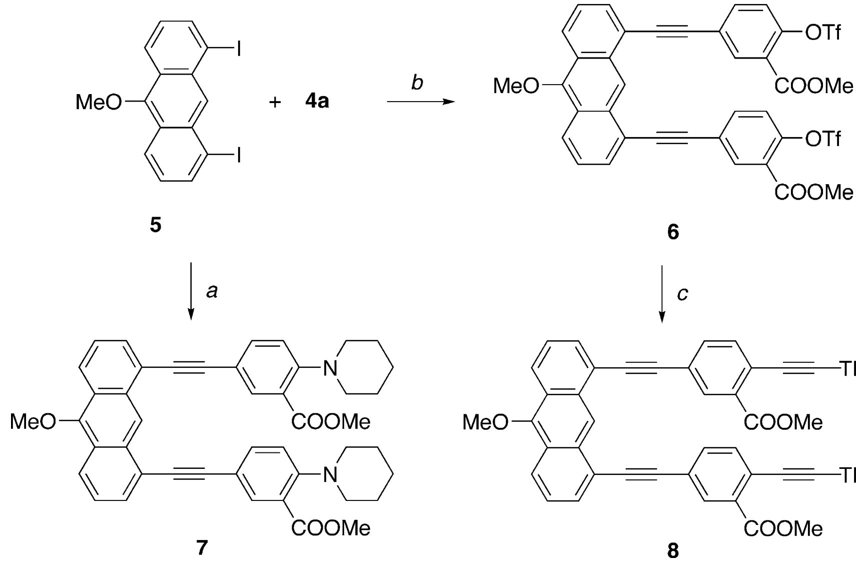
3a (R = I)
3b (R = OTf)

4a (R = OTf)
4b (R = OH)

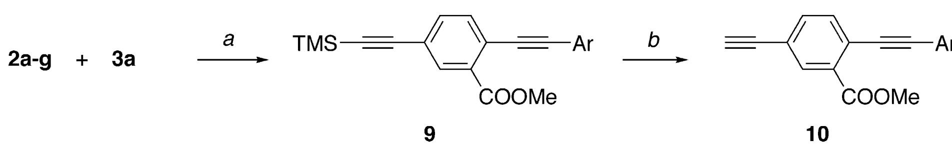
Figure 2. Monomeric building blocks for constructing OPEs.



Scheme 1. Conditions: (a) $BnMe_3NICl_2$, $NaHCO_3$, 100%; (b) TMSA, $Pd(PPh_3)_2Cl_2$, CuI, 88%; (c) (i) $BF_3 \cdot OEt_2$, *t*-BuONO; (ii) NaI, I_2, 74%.

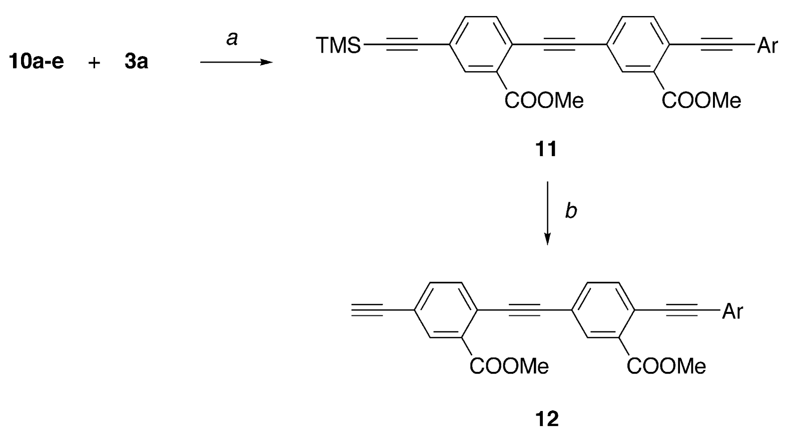


Scheme 2. Conditions: (a) $Pd(PPh_3)_4$, CuI, piperidine, DMF, 83% (**7**); (b) $Pd(PPh_3)_4$, CuI, Et_3N, DMF, 47% (**6**); (c) TMSA, $Pd(PPh_3)_4$, CuI, 74%.



a: Ar = Ph, **b**: Ar = 4-$NO_2C_6H_4$, **c**: Ar = 4-$MeOC_6H_4$, **d**: Ar = 4-$BocNHC_6H_4$
e: Ar = 2-thienyl, **f**: Ar = 4-BrC_6H_4, **g**: Ar = 4-$(TMSCH_2CH_2S)C_6H_4$

Scheme 3. Conditions: (a) $Pd(PPh_3)_2Cl_2$, CuI, 89% (**9a**); 77% (**9b**); 99% (**9c**); 58% (**9d**); 80% (**9e**); 92% (**9f**); 100% (**9g**); 54% (**9h**); (b) K_2CO_3, MeOH, 100% (**10a**); 78% (**9b**); 86% (**10c**); 95% (**10d**); 97% (**10e**); 91% (**10f**); 93% (**10g**).

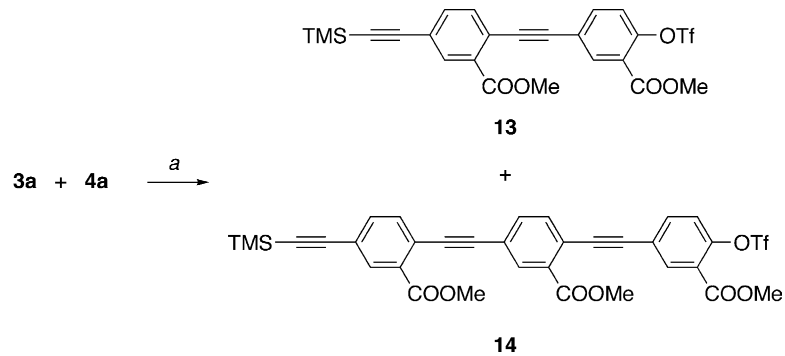


a: Ar = Ph, **b**: Ar = 4-$NO_2C_6H_4$, **c**: Ar = 4-$MeOC_6H_4$,
d: Ar = 4-$BocNHC_6H_4$, **e**: Ar = 2-thienyl

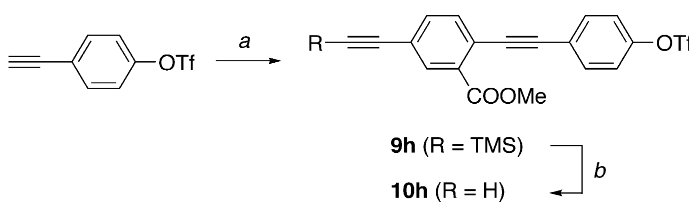
Scheme 4. Conditions: (a) $Pd(PPh_3)_2Cl_2$, CuI, 74% (**11a**); 76% (**11b**); 59% (**11c**); 63% (**11d**); 61% (**11e**); (b) K_2CO_3, MeOH, 100% (**12a**); 76% (**12b**); 95% (**12c**); 87% (**12d**); 87% (**12e**).

deprotected under mild conditions. In principle, this iterative method could be employed to generate even longer OPEs. It was found that this approach to OPE synthesis, where the chains were elaborated from the functionalized end group,[18,26a] was more facile than when the direction of chain growth was reversed.

The dimer **13** was formed by the coupling of monomeric units **3a** and **4a** (Scheme 5), which also generated a significant amount of trimer **14**. The dimer was treated with potassium carbonate–methanol, but partial hydrolysis of the triflate was observed along with deprotection of the alkyne. Dimer **13** and trimer **14** are potentially useful building



Scheme 5. Conditions: (a) $Pd(PPh_3)_2Cl_2$, CuI, 32% (**13**); 18% (**14**).



Scheme 6. Conditions: (a) **3a**, $Pd(PPh_3)_2Cl_2$, CuI, 54%; (b) KF, MeOH, 76%.

blocks for the rapid construction of soluble long chain OPEs.

It was believed that the presence of an ester in the *ortho*-position may have contributed to the unusually facile hydrolysis of the triflate.[28] This hypothesis was tested by the synthesis and deprotection of the dimer **9h** (Scheme 6), which lacks the ester in close proximity. Removal of the TMS group could be performed with potassium fluoride–methanol without concomitant sulfonate cleavage.

The synthesis of hybrid compounds containing both OPE and OPV motifs, such as **15** (Fig. 3), would provide an interesting new class of potential NLO materials. However, many of the procedures widely used for the preparation of stilbenes[29] require strongly basic conditions, which could cause unwanted silyl deprotection of the arylalkyne building blocks. Thus, mild methods for the selective preparation of *E*-stilbenes were explored.

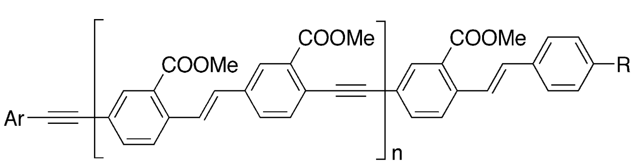


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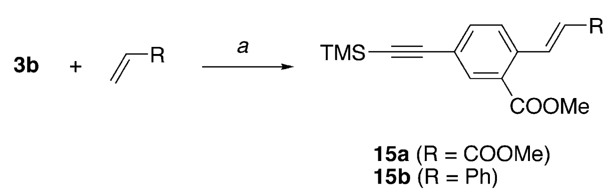
Figure 3. A hypothetical hybrid OPE-OPV structure.

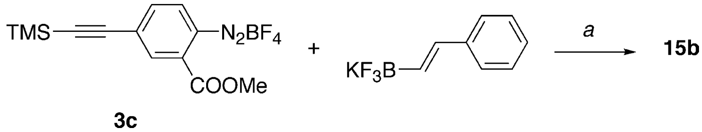
The Heck reaction[30] has been utilized for the formation of a new bond between two sp^2-carbon atoms under mild conditions. The triflate **3b** was reacted with methyl acrylate under the conditions described by Cabri[31] to afford the alkynylcinnamate **16a** (Scheme 7); only the *E*-isomer was detected by ^{1}H NMR. Next, **3b** was reacted with styrene under identical conditions to give a mixture of compounds from which the *E*-stilbene **16b** was isolated in 29% yield. Finally, 4-nitrostyrene[32] was treated with **3b**; however, in this case, an inseparable 3:1 mixture of regioisomers was obtained where the major component was the desired *E*-stilbene, and the minor component was the corresponding 1,1-disubstituted alkene.



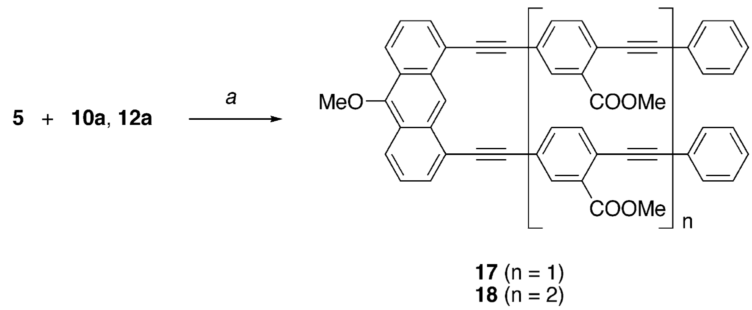
Scheme 7. Conditions: (a) $Pd(OAc)_2$, dppp, Et_3N, 47% (**15a**); 29% (**15b**).

The Suzuki–Miyaura coupling of organic halides and triflates with boronic acids or esters[33] usually requires the presence of a base. Recently Genêt et al. have demonstrated that aryldiazonium salts undergo a rapid palladium-catalyzed coupling reaction with potassium alkenyltrifluoroborates under neutral conditions.[34] Hence, the aryldiazonium tetrafluoroborate **3c**, an intermediate in the synthesis of **3a**, was treated with potassium *E*-styryltrifluoroborate[34b,35] to give the stilbene **16b** in 58% yield (Scheme 8). Attempts to extend this methodology to synthesize nitro- and methoxy-substituted stilbenes were unsuccessful, although it was suspected the problems lay with the conversion of the corresponding styrylboronic acids into their trifluoroborate salts.

The parent bis(dimer) (**17**) and bis(trimer) (**18**) were generated in 35 and 75% yields, respectively, through the palladium-catalyzed coupling of **5** with **10a** and **12a** (Scheme 9). Dimer **10a** reacted at room temperature, but the reaction of **12a** was warmed to 60 °C to increase the solubility of the intermediate monoalkynylated anthracene and ensure completion. The preparation of the more functionalized bis(OPEs), and an examination of their properties, will be discussed in a separate article.[36]



Scheme 8. Conditions: (a) $Pd(OAc)_2$, 58%.



Scheme 9. Conditions: (a) $Pd(PPh_3)_2Cl_2$, CuI, 35% (**17**); 75% (**18**).

3. Conclusions

In summary, an efficient method for the construction of trimethylsilylethynyl-terminated OPEs bearing different functional groups was elucidated, which allows access to a wide range of potential new NLO materials. Removal of the silyl protecting groups and subsequent attachment to the anthracene scaffold **5** generated bis(OPEs) **17** and **18** in which the OPE strands are held in close proximity, which could encourage coplanarity of the aryl rings and thereby increase the effective NLO response of the materials relative to their parent compounds. Preliminary results aimed at possibly further fine tuning the NLO properties by the combination of OPE and OPV elements were also discussed.

4. Experimental

4.1. General

4.1.1. Methyl 2-iodo-5-(trimethylsilylethynyl)benzoate 3a. $BF_3\cdot OEt_2$ (6.15 mL, 48.5 mmol) was cooled to −20 °C under N_2, then a solution of methyl 5-(trimethylsilylethynyl)anthranilate[23] (3.00 g, 12.1 mmol) in dry ether (30 mL) was added dropwise over 5 min. The dropping funnel was rinsed with dry ether (5 mL), then a solution of *tert*-butyl nitrite (5.05 mL, 42.4 mmol) in dry ether (15 mL) was added dropwise over 0.5 h. The resulting suspension was stirred at −20 °C for a further 10 min, then allowed to warm to 0 °C over 20 min. Dry ether (150 mL) was added and the suspension was kept at 0 °C for 15 min, filtered, and the solid collected was rinsed with ice-cold dry ether (20 mL) and briefly air dried. The crude diazonium salt **3c** (3.65 g, 10.5 mmol) was dissolved in dry MeCN (39 mL) and added dropwise to a solution of NaI (1.90 g, 12.6 mmol) and I_2 (0.27 g, 1.05 mmol) in dry MeCN (80 mL) at room temperature under N_2. The dark solution was stirred at room temperature for 1 h, 20% $Na_2S_2O_3$ (90 mL) was added and the mixture was stirred vigorously for 5 min. The mixture was extracted with CH_2Cl_2 (3×120 mL), the combined extracts were washed with brine (120 mL), dried (Na_2SO_4), filtered and concentrated under vacuum. Squat column chromatography of the residue (1:2 CH_2Cl_2/hexane) afforded **3a**[17] (3.20 g, 74% from anthranilate) as a pale yellow oil (R_f 0.28); $C_{13}H_{15}IO_2SiNa$ requires 380.9784, found $(M+Na)^+$ 380.9773; δ_H (300 MHz, $CDCl_3$) 7.93 (1H, d, $J=8.2$ Hz), 7.88 (1H, d, $J=1.9$ Hz), 7.20 (1H, dd, $J=2.2$, 8.2 Hz), 3.93 (3H, s), 0.25 (9H, s); EI-MS *m*/*z* 358 $(M^{+\cdot})$, 343.

4.1.2. Methyl 5-ethynyl-2-*O*-(trifluoromethanesulfonyl)-salicylate 4a. A mixture of **3b** (0.79 g, 2.08 mmol), anhydrous KF (116 mg, 2.00 mmol) and MeOH (20 mL) was stirred at room temperature for 18 h, then concentrated under vacuum to afford **4a** (0.64 g, 100%) as a colourless oil;[27] δ_H (200 MHz, $CDCl_3$) 8.19 (1H, d, $J=2.2$ Hz), 7.70 (1H, dd, $J=2.4$, 8.6 Hz), 7.27 (1H, d, $J=8.6$ Hz), 3.97 (3H, s), 3.21 (1H, s).

Sonogashira coupling of terminal alkynes to **5**. A mixture of **5**[22] (1.0 mmol), alkyne (2.2 mmol) and 1:2 Et_3N/DMF (6 mL) was degassed with a stream of N_2. $Pd(PPh_3)_4$ or $Pd(PPh_3)_2Cl_2$ (0.1 mmol) and CuI (0.1 mmol) were added and the mixture was stirred at room temperature under N_2 for 18 h, then poured into saturated NH_4Cl (40 mL). The resulting suspension was extracted with a suitable solvent (3×30 mL), and the combined extracts were washed with water (5×30 mL) and brine (30 mL), dried (Na_2SO_4), filtered and concentrated under vacuum.

4.1.3. 1,8-Bis[4-(trifluoromethanesulfonyloxy)-3-(methoxycarbonyl)phenylethynyl]-10-methoxyanthracene 6. The general procedure was followed using **5** (1.00 g, 2.18 mmol), **4a** (1.48 g, 4.79 mmol), CuI (41 mg, 0.22 mmol) and $Pd(PPh_3)_4$ (0.25 g, 0.22 mmol). After extraction with CH_2Cl_2, flash chromatography of the residue (1:4 EtOAc/hexane) afforded **6** (0.84 g, 47%) as a yellow solid (R_f 0.18), mp 140–145 °C (dec); $C_{37}H_{22}F_6O_{11}S_2Na$ requires 843.0405, found $(M+Na)^+$ 843.0412; δ_H (200 MHz, $CDCl_3$) 9.20 (1H, s), 8.36 (2H, dt, $J=0.9$, 8.8 Hz), 8.30 (2H, d, $J=2.2$ Hz), 7.89 (2H, dd, $J=0.9$, 6.8 Hz), 7.68 (2H, dd, $J=2.2$, 8.4 Hz), 7.51 (2H, dd, $J=7.0$, 8.8 Hz), 7.13 (2H, d, $J=8.6$ Hz), 4.17 (3H, s), 3.95 (6H, s); δ_C (50 MHz, $CDCl_3$) 163.5, 153.8, 147.6, 136.7, 136.5, 135.8, 132.0, 131.9, 125.1, 125.0, 124.9, 124.6, 124.4, 124.2, 123.3, 121.4, 120.7, 119.3, 118.8 (q, $J_{CF}=320.5$ Hz), 92.1, 90.8, 63.9, 52.9, ν_{max} 1731, 1643, 1429, 1212, 1186, 1062, 1036, 987 cm^{-1}; EI-MS *m/z* 820 ($M^{+\cdot}$), 73; UV λ_{max} (log ε) 435 (3.91), 411 (3.98), 390 (3.81), 287 (4.49), 268 (4.82) nm; fluorescence λ_{em} 455, 481 nm.

4.1.4. 1,8-Bis[3-(methoxycarbonyl)-4-(piperidin-1-yl)-phenylethynyl]-10-methoxyanthracene 7. A mixture of **5** (0.24 g, 0.53 mmol), **4a** (0.36 g, 1.17 mmol) and 1:1 piperidine/DMF (4 mL) was degassed with a stream of N_2. $Pd(PPh_3)_4$ (62 mg, 0.05 mmol) and CuI (10 mg, 0.05 mmol) were added and the mixture was stirred at room temperature under N_2 for 23 h, then poured into saturated NH_4Cl (20 mL). The mixture was extracted with CH_2Cl_2 (3×15 mL), the combined extracts were dried (Na_2SO_4), filtered and concentrated under vacuum. Flash chromatography of the residue (3:7 EtOAc/hexane) afforded **7** (0.30 g, 83%) as a yellow solid (R_f 0.37), mp 142–144 °C; δ_H (200 MHz, $CDCl_3$) 9.41 (1H, s), 8.28 (2H, d, $J=8.8$ Hz), 8.01 (2H, d, $J=2.0$ Hz), 7.76 (2H, d, $J=6.6$ Hz), 7.44–7.52 (4H, m), 6.70 (2H, d, $J=8.6$ Hz), 4.14 (3H, s), 3.85 (6H, s), 3.00–3.05 (8H, m), 1.59–1.73 (12H, m); δ_C (75 MHz, $CDCl_3$) 167.8, 153.1, 152.8, 135.8, 135.1, 131.9, 130.3, 124.9, 124.4, 122.7, 121.9, 119.8, 118.3, 114.5, 94.7, 87.0, 63.5, 53.4, 52.0, 25.9, 24.1; ν_{max} 2201, 1725, 1599, 1497, 1450, 1435, 1246, 1231, 1208, 1129, 1079, 1017, 920, 822, 732 cm^{-1}; EI-MS *m/z* 690 ($M^{+\cdot}$), 45.

4.1.5. 1,8-Bis[3-(methoxycarbonyl)-4-(trimethylsilylethynyl)phenylethynyl]-10-methoxyanthracene 8. A mixture of **6** (0.44 g, 0.53 mmol), CuI (10 mg, 0.05 mmol) and 1:2 Et_3N/NMP (6 mL) was degassed with a stream of N_2. $Pd(PPh_3)_4$ (62 mg, 0.05 mmol) and TMSA (0.30 mL, 2.13 mmol) were added and the mixture was stirred at room temperature for 19 h. The mixture was poured into saturated NH_4Cl (30 mL) and extracted with CH_2Cl_2 (3×20 mL). The combined extracts were washed with water (20 mL) and brine (20 mL), dried (Na_2SO_4), filtered and concentrated under vacuum. The residue was applied to a short column of silica, eluted with 1:1 EtOAc/hexane (100 mL) and the eluant was concentrated under vacuum. Flash chromatography of the residue (1:4 EtOAc/hexane) afforded **8** (0.28 g, 74%) as a yellow oil (R_f 0.40); $C_{45}H_{40}O_5Si_2Na$ requires 739.2312, found $(M+Na)^+$ 739.2316; δ_H (300 MHz, $CDCl_3$) 9.29 (1H, s), 8.33 (2H, d, $J=8.5$ Hz), 8.17 (2H, d, $J=1.6$ Hz), 7.83 (2H, dd, $J=0.8$, 6.9 Hz), 7.61 (2H, dd, $J=1.6$, 8.0 Hz), 7.51 (2H, dd, $J=6.7$, 8.8 Hz), 7.45 (2H, d, $J=8.0$ Hz), 4.16 (3H, s), 3.89 (6H, s), 0.31 (18H, s); δ_C (75 MHz, $CDCl_3$) 165.9, 153.4, 134.5, 134.4, 134.0, 133.3, 132.9, 131.7, 131.6, 124.9, 124.4, 123.6, 122.9, 121.1, 119.4, 103.0, 101.9, 93.7, 90.6, 63.6, 52.1, −0.1; ν_{max} 2157, 1732, 1677, 1601, 1491, 1437, 1286, 1249, 1079, 845, 760, 739 cm^{-1}; EI-MS *m/z* 716 ($M^{+\cdot}$); UV λ_{max} (log ε) 308 (4.85), 289 (4.88), 231 (5.10) nm; fluorescence λ_{em} 377 nm.

4.1.6. Methyl 5-(trimethylsilylethynyl)-2-(phenylethynyl)-benzoate 9a. A mixture of **3b** (1.00 g, 2.79 mmol), **2a** (0.33 mL, 3.07 mmol) and 1:2 Et_3N/DMF (12 mL) was degassed with a stream of N_2. CuI (27 mg, 0.14 mmol) and $Pd(PPh_3)_2Cl_2$ (98 mg, 0.14 mmol) were added and the mixture was stirred at room temperature under N_2 for 18 h. The mixture was poured into saturated NH_4Cl (50 mL) and extracted with ether (3×50 mL). The extracts were washed with water (5×50 mL) and brine (50 mL), dried ($MgSO_4$), filtered and concentrated under vacuum. Flash chromatography of the residue (3:7 CH_2Cl_2/hexane) afforded **9a** (0.83 g, 89%) as a yellow oil (R_f 0.28); $C_{21}H_{21}O_2Si$ requires 333.1311, found $(M+H)^+$ 333.1307; δ_H (200 MHz, $CDCl_3$) 8.08 (1H, dd, $J=0.9$, 1.3 Hz), 7.55–7.60 (4H, m), 7.34–7.39 (3H, m), 3.96 (3H, s), 0.26 (9H, s); δ_C (50 MHz, $CDCl_3$) 165.9, 134.6, 134.1, 133.8, 131.9, 131.8, 128.7, 128.4, 123.6, 123.1, 122.9, 103.6, 97.3, 96.2, 88.0, 52.3, −0.2; ν_{max} 2157, 1729, 1250, 1185, 1071, 1036, 848 cm^{-1}; EI-MS *m/z* 332 ($M^{+\cdot}$), 317; UV λ_{max} (log ε) 340 (4.61), 330 (4.62), 306 (4.64), 296 (4.54), 288 (4.50), 267 (4.45), 247 (4.57), 236 (4.63) nm; fluorescence λ_{em} 367 nm.

4.1.7. Methyl 5-ethynyl-2-(phenylethynyl)benzoate 10a. A mixture of **9a** (0.26 g, 0.78 mmol), anhydrous K_2CO_3 (65 mg, 0.47 mmol) and 1:1 $MeOH/CH_2Cl_2$ (8 mL) was stirred at room temperature for 3 h, then diluted with CH_2Cl_2 (20 mL), washed with water (15 mL) and brine (15 mL), dried (Na_2SO_4), filtered and concentrated under vacuum to afford **10a** (0.21 g, 100%) as a pale yellow oil;[27] δ_H (200 MHz, $CDCl_3$) 8.10 (1H, t, $J=1.1$ Hz), 7.55–7.60 (4H, m), 7.37 (3H, m), 3.97 (3H, s), 3.21 (1H, s).

4.1.8. Methyl 5-ethynyl-2-[4-(trifluoromethanesulfonyloxy)phenylethynyl]benzoate 10h. A mixture of **9h** (0.53 g, 1.10 mmol), anhydrous KF (64 mg, 1.10 mmol) and MeOH (10 mL) was stirred at room temperature for 18 h, then diluted with CH_2Cl_2 (25 mL), washed with water (15 mL) and brine (15 mL), dried (Na_2SO_4), filtered and concentrated under vacuum to afford **10h** (0.34 g, 76%) as a yellow oil;[27] δ_H (200 MHz, $CDCl_3$) 8.12 (1H, t, $J=1.1$ Hz), 7.65 (2H, m), 7.60 (2H, d, $J=1.1$ Hz), 7.28 (2H, m), 3.96 (3H, s), 3.23 (1H, s).

4.1.9. Methyl 2-[3-(methoxycarbonyl)-4-(phenylethynyl)-phenylethynyl]-5-(trimethylsilylethynyl)benzoate 11a. The procedure for **9a** was followed using **3a** (0.34 g, 0.94 mmol), **10a** (0.27 g, 1.03 mmol), CuI (9 mg, 0.05 mmol) and $Pd(PPh_3)_2Cl_2$ (33 mg, 0.05 mmol). After extraction with CH_2Cl_2, flash chromatography of the residue (3:17 EtOAc/hexane) afforded **11a** (0.34 g, 74%) as a pale yellow solid (R_f 0.12, 1:1 CH_2Cl_2/hexane), mp 118–121 °C; $C_{31}H_{26}O_4SiNa$ requires 513.1498, found $(M+Na)^+$ 513.1485; δ_H (300 MHz, $CDCl_3$) 8.17 (1H, dd, $J=0.6$, 1.6 Hz), 8.10 (1H, t, $J=0.8$ Hz), 7.66 (1H, d, $J=1.6$ Hz), 7.64 (1H, br s), 7.57–7.61 (4H, m), 7.35–7.39 (3H, m), 3.98 (3H, s), 3.97 (3H, s), 0.27 (9H, s); δ_C (75 MHz, $CDCl_3$) 165.9, 165.7, 134.6, 134.4, 134.1, 134.0, 133.9, 133.8, 132.1, 131.9, 131.8, 128.7, 128.4, 123.8, 123.4, 123.1, 122.9, 103.4, 97.7, 97.3, 96.5, 94.8, 90.6, 88.1, 52.32, 52.28, −0.2; ν_{max} 1731, 1647, 1503, 1293, 1248, 1189, 1072, 1036, 847 cm^{-1}; EI-MS *m/z* 490 ($M^{+\cdot}$), 475; UV λ_{max} (log ε) 351 (4.78), 249 (4.34) nm; fluorescence λ_{em} 388 nm.

4.1.10. Methyl 5-ethynyl-2-[3-(methoxycarbonyl)-4-(phenylethynyl)phenylethynyl]benzoate 12a. The procedure for **10a** was followed using **11a** (0.41 g, 0.83 mmol) and anhydrous K_2CO_3 (0.11 g, 0.83 mmol) to afford **12a** (0.34 g, 100%) as a yellow-orange solid;[27] δ_H (300 MHz, $CDCl_3$) 8.18 (1H, dd, $J=0.4$, 1.5 Hz), 8.13 (1H, t, $J=1.1$ Hz), 7.68 (1H, dd, $J=1.6$, 8.0 Hz), 7.65 (1H, d,

$J=0.4$ Hz), 7.57–7.61 (4H, m), 7.37 (3H, m), 3.984 (3H, s), 3.981 (3H, s), 3.23 (1H, s).

4.1.11. Methyl 2-*O*-trifluoromethanesulfonyl-5-[2-(methoxycarbonyl)-4-(trimethylsilylethynyl)phenylethynyl]-salicylate 13, and methyl 2-{4-[4-(trifluoromethanesulfonyloxy)-3-(methoxycarbonyl)phenylethynyl]-3-[methoxycarbonyl]phenylethynyl}-5-(trimethylsilylethynyl)benzoate 14. The procedure for **9a** was followed using **3a** (0.40 g, 1.10 mmol), **4a** (0.37 g, 1.21 mmol), CuI (11 mg, 0.06 mmol) and $Pd(PPh_3)_2Cl_2$ (39 mg, 0.06 mmol). After extraction with CH_2Cl_2, flash chromatography of the residue (1:1 CH_2Cl_2/hexane, then 2:1) afforded **13** (0.36 g, 32%) as a pale yellow oil (R_f 0.54, 2:1 CH_2Cl_2/hexane); $C_{24}H_{22}F_3O_7SSi$ requires 539.0808, found $(M+H)^+$ 539.0808; δ_H (200 MHz, $CDCl_3$) 8.25 (1H, d, $J=2.2$ Hz), 8.10 (1H, t, $J=1.3$ Hz), 7.79 (1H, dd, $J=2.2$, 8.4 Hz), 7.58 (2H, d, $J=1.1$ Hz), 7.30 (1H, d, $J=8.6$ Hz), 3.98 (3H, s), 3.96 (3H, s), 0.27 (9H, s); δ_C (50 MHz, $CDCl_3$) 165.5, 163.5, 147.7, 136.9, 135.8, 134.7, 134.2, 134.0, 132.1, 124.8, 124.2, 123.9, 123.1, 122.4, 118.7 (q, $J_{CF}=319.1$ Hz), 103.3, 98.1, 92.8, 90.8, 52.8, 52.4, −0.2; EI-MS *m/z* 538 ($M^{+\cdot}$), 523, 405, 375, 332. Further elution afforded **14** (0.14 g, 18%) as a yellow solid (R_f 0.22), mp 129–132 °C; $C_{34}H_{27}F_3O_9SSiNa$ requires 719.0995, found $(M+Na)^+$ 719.1000; δ_H (200 MHz, $CDCl_3$) 8.26 (1H, d, $J=2.2$ Hz), 8.20 (1H, d, $J=1.1$ Hz), 8.10 (1H, t, $J=1.1$ Hz), 7.80 (1H, dd, $J=2.2$, 8.4 Hz), 7.70 (1H, dd, $J=1.6$, 8.1 Hz), 7.63 (1H, d, $J=7.9$ Hz), 7.58 (2H, d, $J=1.3$ Hz), 7.30 (1H, d, $J=8.4$ Hz), 3.99 (3H, s), 3.98 (3H, s), 3.97 (3H, s), 0.26 (9H, s); δ_C (50 MHz, $CDCl_3$) 165.6, 165.5, 163.5, 147.7, 136.9, 135.8, 134.7, 134.6, 134.2, 134.0, 133.9, 132.3, 131.9, 128.6, 124.8, 124.2, 123.9, 123.6, 123.1, 122.8, 122.6, 125.1 (q, $J_{CF}=322.7$ Hz), 103.4, 97.9, 94.5, 93.0, 91.1, 90.9, 52.8, 52.44, 52.37, −0.2; ν_{max} 2157, 1734, 1501, 1291, 1249, 1210, 1140, 1072, 985, 845 cm^{-1}; EI-MS *m/z* 696 ($M^{+\cdot}$), 563, 274, 259, 237, 77; UV λ_{max} (log ε) 348 (4.52), 318 (4.32); fluorescence λ_{em} 386, 405 nm.

4.1.12. Methyl 2-methoxycarbonyl-4-(trimethylsilylethynyl)cinnamate 15a. To a solution of **3b** (0.50 g, 1.31 mmol) in DMF (3 mL) were added Et_3N (0.20 mL, 1.45 mmol), methyl acrylate (0.24 mL, 2.63 mmol), dppp (15 mg, 0.04 mmol) and $Pd(OAc)_2$ (7 mg, 0.03 mmol), and the mixture was stirred at 80 °C under N_2 for 6.5 h. After cooling, the mixture was diluted with CH_2Cl_2 (30 mL), washed with 5% HCl (2×20 mL), water (3×20 mL) and brine (20 mL), dried (Na_2SO_4), filtered and concentrated under vacuum. Flash chromatography of the residue (7:3 CH_2Cl_2/hexane) afforded **15a** (0.20 g, 47%) as a colourless oil (R_f 0.38); $C_{17}H_{20}O_4Si$ requires 316.1131, found ($M^{+\cdot}$) 316.1134; δ_H (300 MHz, $CDCl_3$) 8.41 (1H, d, $J=16.2$ Hz), 8.04 (1H, d, $J=1.6$ Hz), 7.59 (1H, dd, $J=1.6$, 8.2 Hz), 7.54 (1H, d, $J=8.0$ Hz), 6.31 (1H, d, $J=15.9$ Hz), 3.93 (3H, s), 3.81 (3H, s), 0.26 (9H, s); δ_C (75 MHz, $CDCl_3$) 166.8, 166.5, 142.9, 136.0, 135.2, 134.3, 129.9, 129.6, 127.8, 121.2, 103.3, 97.5, 52.5, 51.8, −0.2; EI-MS *m/z* 316 ($M^{+\cdot}$), 301.

4.1.13. Methyl 5-(trimethylsilylethynyl)-2-*E*-(2-phenylethenyl)benzoate 15b. 1,4-Dioxane (4 mL) was degassed with a stream of N_2. Crude **3c** (0.35 g, 1.00 mmol), potassium *E*-styryltrifluoroborate[34a,35] (0.25 g, 1.20 mmol) and $Pd(OAc)_2$ (11 mg, 0.05 mmol) were added and the mixture was stirred at room temperature under N_2 in the dark for 19 h. The solution was diluted with CH_2Cl_2 (40 mL), washed with water (5×25 mL) and brine (25 mL), dried (Na_2SO_4), filtered and concentrated under vacuum. Flash chromatography of the residue (2:3 CH_2Cl_2/hexane) afforded **15b** (0.19 g, 58%) as a colourless oil (R_f 0.22, 1:2 CH_2Cl_2/hexane); $C_{21}H_{22}O_2Si$ requires 334.1389, found ($M^{+\cdot}$) 334.1385; δ_H (200 MHz, $CDCl_3$) 8.04 (1H, dd, $J=0.5$, 1.8 Hz), 7.99 (1H, d, $J=16.3$ Hz), 7.68 (1H, d, $J=8.2$ Hz), 7.51–7.59 (3H, m), 7.27–7.41 (3H, m), 7.04 (1H, d, $J=16.3$ Hz), 3.93 (3H, s), 0.27 (9H, s); δ_C (50 MHz, $CDCl_3$) 167.1, 139.0, 137.2, 135.0, 134.3, 132.3, 128.7, 128.3, 128.1, 126.9, 126.7, 126.5, 122.0, 104.0, 96.0, 52.2, −0.1; ν_{max} 2159, 1722, 1492, 1295, 1248, 1208, 1073, 845 cm^{-1}; EI-MS *m/z* 334 ($M^{+\cdot}$), 319; UV λ_{max} (log ε) 327 (4.15), 269 (4.14), 259 (4.21) nm; fluorescence λ_{em} 398 nm.

4.1.14. 1,8-Bis[3-(methoxycarbonyl)-4-(phenylethynyl)-phenylethynyl]-10-methoxyanthracene 17. The general procedure was followed using **5** (0.17 g, 0.37 mmol), **10a** (0.21 g, 0.82 mmol), CuI (7 mg, 0.04 mmol) and $Pd(PPh_3)_2Cl_2$ (26 mg, 0.04 mmol). After extraction with CH_2Cl_2, flash chromatography of the residue (gradient elution 1:9 EtOAc/hexane to 1:3) afforded **17** (94 mg, 35%) as a yellow solid (R_f 0.29, 1:4 EtOAc/hexane), mp 95–105 °C (dec); $C_{51}H_{32}O_5$ requires 724.2250, found ($M^{+\cdot}$) 724.2246; δ_H (200 MHz, $CDCl_3$) 9.37 (1H, br s), 8.35 (2H, dt, $J=1.1$, 8.8 Hz), 8.24 (2H, dd, $J=0.5$, 1.8 Hz), 7.85 (2H, dd, $J=0.7$, 6.8 Hz), 7.49–7.62 (8H, m), 7.42 (2H, dd, $J=0.5$, 8.1 Hz), 7.18–7.31 (6H, m), 4.18 (3H, s), 3.93 (6H, s); δ_C (75 MHz) 165.8, 153.6, 134.3, 134.1, 133.6, 132.1, 132.0, 131.9, 131.2, 128.6, 128.4, 128.3, 125.0, 124.5, 123.6, 123.2, 122.9, 121.3, 119.6, 96.5, 93.9, 90.3, 88.1, 63.7, 52.3; ν_{max} 1723, 1500, 1281, 1184, 1074, 1036, 992 cm^{-1}; EI-MS *m/z* 724 ($M^{+\cdot}$), 709, 694, 634, 588; UV λ_{max} (log ε) 438 (4.26), 414 (4.31), 391 (4.19), 331 (4.66), 307 (4.72), 267 (4.87), 247 (4.70) nm; fluorescence λ_{em} 457, 484 nm.

4.1.15. 1,8-Bis{3-[methoxycarbonyl]-4-[3-(methoxycarbonyl)-4-(phenylethynyl)phenylethynyl]phenylethynyl}-10-methoxyanthracene 18. The general procedure was followed using **5** (0.17 g, 0.38 mmol), **12a** (0.35 g, 0.83 mmol), CuI (7 mg, 0.04 mmol) and $Pd(PPh_3)_2Cl_2$ (26 mg, 0.04 mmol), except that the reaction was stirred at 60 °C. After extraction with CH_2Cl_2, flash chromatography of the residue (9:1 CH_2Cl_2/hexane then CH_2Cl_2) afforded **18** (0.30 g, 75%) as a dark yellow solid (R_f 0.18, CH_2Cl_2), mp 158–165 °C (dec); $C_{71}H_{44}O_9Na$ requires 1063.2883, found $(M+Na)^+$ 1063.2866; δ_H (300 MHz, $CDCl_3$) 9.36 (1H, br s), 8.36 (2H, dt, $J=1.0$, 8.8 Hz), 8.22 (2H, dd, $J=0.3$, 1.5 Hz), 8.07 (2H, dd, $J=0.4$, 1.8 Hz), 7.83 (2H, dd, $J=1.0$, 7.0 Hz), 7.50–7.59 (10H, m), 7.43 (2H, dd, $J=0.4$, 8.0 Hz), 7.37 (2H, dd, $J=0.4$, 7.8 Hz), 7.22–7.34 (6H, m), 4.18 (3H, s), 3.95 (6H, s), 3.94 (6H, s); δ_C (75 MHz, $CDCl_3$) 96.5, 95.1, 93.9, 90.63, 90.60, 88.2, 63.7, 52.3, 52.2; ν_{max} 1771, 1734, 1505, 1287, 1244, 1184, 1074, 1037, 991 cm^{-1}; ESI-MS *m/z* 1063 $(M+Na)^+$; UV λ_{max} (log ε) 440 (4.48), 416 (4.57), 396 (4.55), 351 (5.01), 321 (4.85), 266 (4.95), 248 (4.85); fluorescence λ_{em} 465, 488.

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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.2005.11.015. General experimental methods and compound characterization data for **9b–g**, **10b–g**, **11b–e**, and **12b–e**.

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1,3-Dipolar cycloaddition approach to isoxazole, isoxazoline and isoxazolidine analogues of *C*-nucleosides related to pseudouridine

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Abstract—Isoxazole, isoxazoline and isoxazolidine analogues of *C*-nucleosides related to pseudouridine have been synthesized by 1,3-dipolar cycloaddition reactions of nitrile oxides and nitrones derived from mono and disubstituted uracil-5-carbaldehydes and 2,4-dimethoxypyrimidine-5-carbaldehyde. The dimethoxy derivatives have been easily deprotected to the corresponding uracils bearing the heterocyclic ring instead of a sugar moiety. The regio and stereoselectivity of the reactions are discussed.

1. Introduction

Since the latter part of the 1980s unnatural nucleoside analogues have played an important role as anticancer and antiviral agents.[1] Consequently, several variations have been made to both the heterocyclic base and the sugar moiety in the search for effective and selective derivatives. Due to the need for the base moiety to preserve the base-pairing functionalities, only minor modifications of the base are usually found in biologically active nucleosides analogues. The C-5 position is usually the position of choice for the introduction of substituents in pyrimidine nucleosides since it is not involved in the Watson–Crick base-pairing.[2] On the contrary, a lot of variations have been made in the sugar part replacing it by acyclic moieties or carbo or other heterocyclic rings. Among them, isoxazoline and isoxazolidine nucleosides have emerged as an important class of nucleoside analogues and several approaches for their synthesis have been reported.[3]

Besides the variations in the sugar and base moieties a crucial modification results from varying their connection, as in the *C*-nucleosides, which have a carbon–carbon linkage instead of an hydrolyzable carbon–nitrogen bond between the sugar and the aglycon. The most abundant natural *C*-nucleoside is pseudouridine a C-5 linked uridine. Pseudouridine is the first *C*-nucleoside found in nature and has attracted the interest of organic chemists and biochemists since its discovery in 1957.[4] The occurrence of pseudouridine in highly conserved regions of RNA indicates that certain physicochemical properties of pseudouridine are critical to the biological function of RNA molecules.

Thus the biological significance of pseudouridine has resulted in studies aimed at the incorporation of synthetic pseudouridine analogues with modified sugar moieties.[5] Recently, the synthesis of isoxazoline analogues of pseudouridine by 1,3-dipolar cycloaddition reactions of 5-uracil nitrones has been described.[6]

During recent years and in connection with our interests to induce nucleoside modifications,[7] we have also attempted to apply the convenience and diversity of 1,3-dipolar cycloaddition reactions to the synthesis of pseudouridine analogues. However, our initial attempts to isolate cycloaddition products via the in situ formation of nitrile oxides from 5-uracilcarbaldehyde oxime or 1-monosubstituted 5-uracilcarbaldehyde oximes were unsuccessful even in the presence of very active dipolarophiles such as methyl acrylate. On the contrary these oximes gave mixtures of isoxazolidines from the reaction of intermediate nitrones.[8a] Nitrone generation from oximes via a 1,2-prototropic process or an 1,3-azaprotiocyclotransfer is a well known reaction established by Grigg,[8b,c] and it has been also described by us for other oximes.[8d] The last findings indicated that nitrone cycloaddition can work with uracil nitrones barrying free NH bonds. This has been also shown recently by the work of Chiacchio et al.[6]

Keywords: Pyrimidine; Pseudouridine; Cycloaddition.
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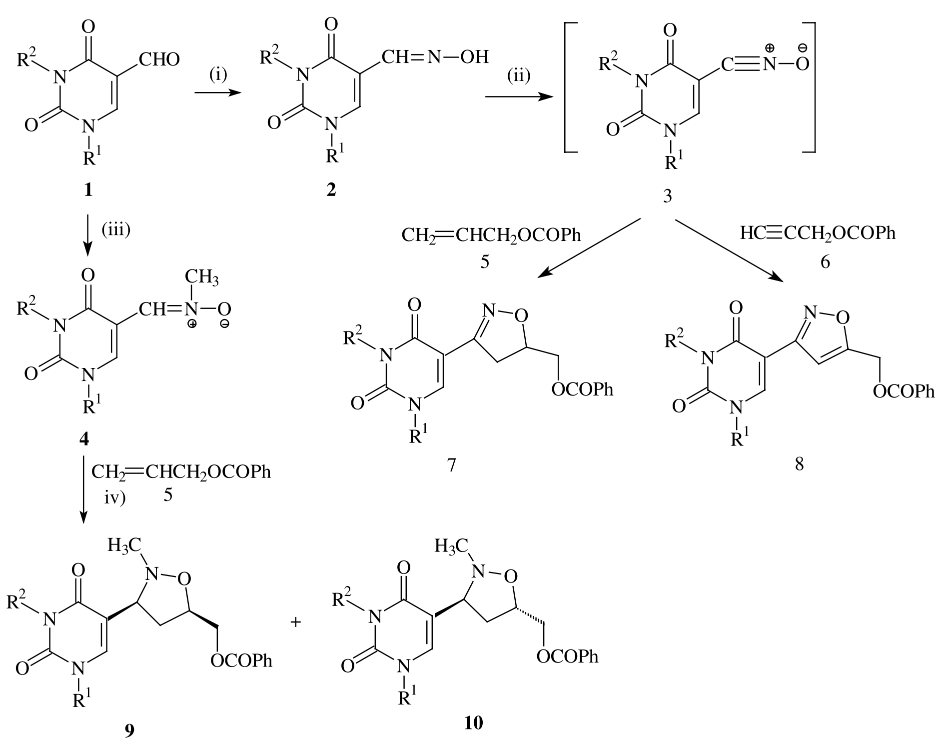
However, nucleoside analogues with restricted conformational flexibility induced by a second ring or by unsaturation are the target compounds in many cases, since they are potent inhibitors of HIV-1 reverse transcriptase.[3k,o,9] Thus, in order to expand the use of 5-uracil dipoles for the formation of both saturated and unsaturated rings, we report in this paper, the application of cycloaddition reactions of both nitrile oxides and nitrone uracil dipoles by applying monosubsituted, disubstituted and protected uracil derivatives.

2. Results and discussion

As starting materials for the formation of the dipoles we have chosen the mono and disubstituted aldehydes **1a** and **1b** and the dimethoxy-5-formyl pyrimidine **11** (Schemes 1 and 2). The octyl derivatives **1a** and **1b** have been chosen for purposes of higher solubility and enhanced hydrophobicity, whereas aldehyde **11** is a protected form of 5-formyluracil. The above aldehydes were prepared according to the procedures we have previously described.[10] The oximes **2a**, **2b**, **12** as well as the nitrones **4a**, **4b** and **14** were prepared from the corresponding aldehydes applying conventional procedures. As dipolarophiles, we have used allylic or propargylic alcohol derivatives in order to ensure the presence of a 5′-hydroxymethyl group in the final product, which potentially allows enzymatic phosphorylation for antiviral expression or incorporation into automatic solid phase synthesis.

Nitrile oxide **3b** was generated in situ from the corresponding oxime in the presence of the dipolarophile in a biphasic methylene chloride/aqueous bleach system. Generation of nitrile oxide **3a** following the same procedure was unsuccessful. As we have already mentioned, in our initial attempts we failed to isolate nitrile oxide cycloaddition products from 1-substituted uracil aldoximes. Thus, as well as the above standard procedure for the generation of the nitrile oxide **3a** from the oxime **2a**, several other alternative procedures using *N*-chlorosuccinimide, and several variations in the reaction time, temperatures and work up were also tested without success. Nitrile oxide **3b** reacted with both allylic benzoate (**5**) and propargylic benzoate (**6**) to give the isoxazoline **7b** and the isoxazole **8b**, respectively, in good yields (70–80%). The reactions were regioselective and only 5-substituted cycloadducts were isolated. The reactions of nitrones **4** with the alkene **5** took place under reflux in xylene to give isoxazolidines **9** as the main products in satisfactory yields (70–72%). The reactions were regio and stereoselective. In both cases only 5-substituted derivatives with a cis arrangement of the 3′ and 5′ substituents (structure **9**) were isolated, although in the crude reaction mixture, traces of compounds with structure **10** were also detected on the basis of some ^1H NMR chemical shifts (Table 1).

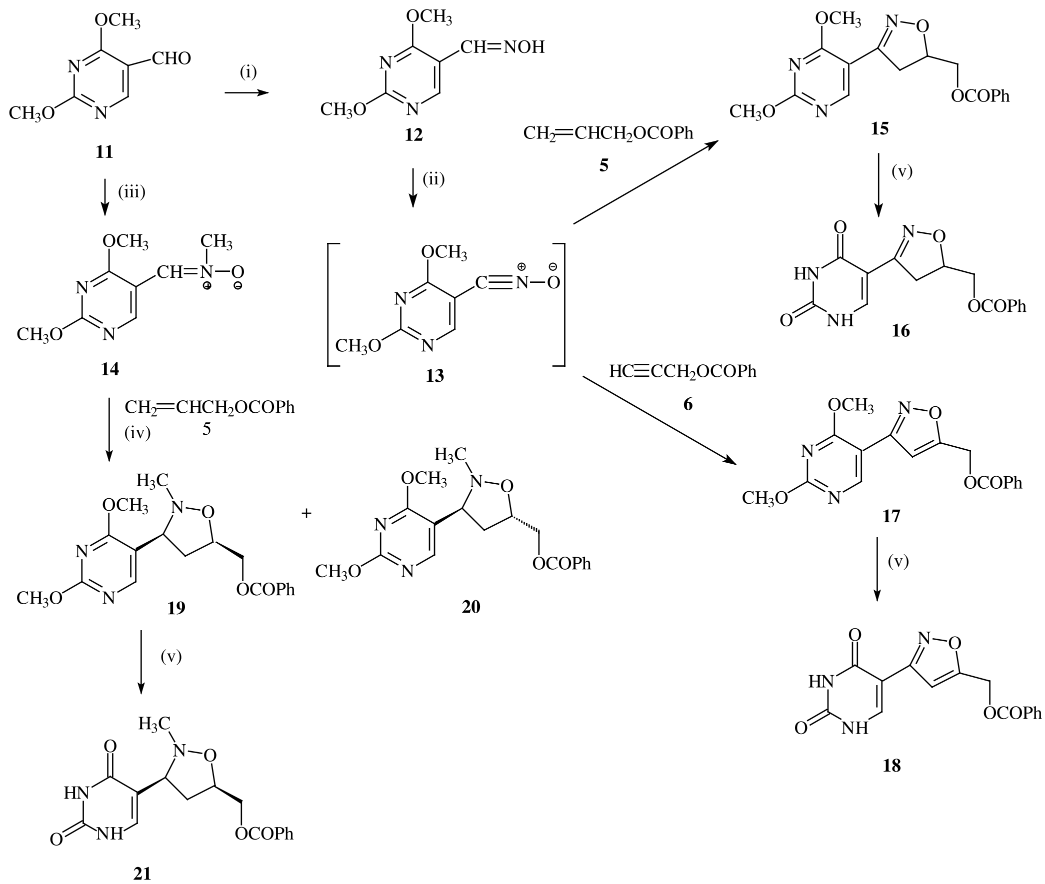
Dimethoxypyridine dipoles **13** and **14** showed analogous behaviour. Nitrile oxide **13** generated in situ from the oxime **12** reacted regioselectively with **5** to give the isoxazoline derivative **15**. The reaction of **13** with the alkyne derivative



1a, **2a**, **4a**, **9a**, **10a** $R^1 = CH_3(CH_2)_6CH_2$, $R^2 = H$

1b, **2b**,**3b**, **4b**, **7b**, **8b**, **9b**, **10b** $R^1 = R^2 = CH_3(CH_2)_6CH_2$

Scheme 1. Reagents and conditions: (i) $NH_2OH\cdot HCl$, Na_2CO_3, $EtOH/H_2O$, 20 °C, 24 h; (ii) NaOCl, CH_2Cl_2/H_2O, 0–20 °C, 24 h; (iii) $CH_3NHOH\cdot HCl$, Na_2CO_3, $EtOH/H_2O$, 20 °C, 24 h; (iv) Xylene, reflux, 48 h.



Scheme 2. Reagents and conditions: (i) $NH_2OH\cdot HCl$, Na_2CO_3, $EtOH/H_2O$, 20 °C, 24 h; (ii) NaOCl, CH_2Cl_2/H_2O, 0–20 °C, 24 h; (iii) $CH_3NHOH\cdot HCl$, Na_2CO_3, $EtOH/H_2O$, 20 °C, 24 h; (iv) Xylene, reflux, 48 h; (v) CH_3COOH, NaI, 90 °C, 1 h.

Table 1. Selected values for proton chemical shifts and coupling constants of compounds **9**, **10**, **19**, **20**

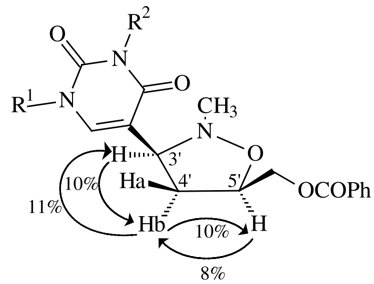
Compound	4′-Ha	4′-Hb	3′-H
9a	2.10 (dt, $J_{4'a,4'b}$=12.2 Hz, $J_{3',4'a}$=$J_{4'a,5'}$=5.1 Hz)	3.02 (ddd, $J_{4'a,4'b}$=12.2 Hz, $J_{3',4'b}$=7.3 Hz, $J_{4'b,5'}$=8.4 Hz)	4.03 (dd, $J_{3',4'a}$=5.1 Hz, $J_{3',4'b}$=7.3 Hz)
9b	2.05 (dt, $J_{4'a,4'b}$=13.6 Hz, $J_{3',4'a}$=$J_{4'a,5'}$=5.1 Hz)	3.02 (ddd, $J_{4'a,4'b}$=13.6 Hz, $J_{3',4'b}$=7.8 Hz, $J_{4'b,5'}$=8.4 Hz)	3.99 (dd, $J_{3',4'a}$=5.1 Hz, $J_{3',4'b}$=7.8 Hz)
19	2.05 (dt, $J_{4'a,4'b}$=12.8 Hz, $J_{3',4'a}$=$J_{4'a,5'}$=6.4 Hz)	2.89 (ddd, $J_{4'a,4'b}$=12.8 Hz, $J_{3',4'b}$=8.4 Hz, $J_{4'b,5'}$=7.7 Hz)	3.85 (dd, $J_{3',4'a}$=6.4 Hz, $J_{3',4'b}$=8.4 Hz)
20	2.41 (ddd, $J_{4'a,4'b}$=14.2 Hz, $J_{3',4'a}$=5.7 Hz, $J_{4'a,5'}$=7.7 Hz)	2.55 (ddd, $J_{4'a,4'b}$=14.2 Hz, $J_{3',4'b}$=3.9 Hz, $J_{4'b,5'}$=8.9 Hz)	4.24 (dd, $J_{3',4'a}$=5.7 Hz, $J_{3',4'b}$=3.9 Hz)
10a	2.29–2.37 (m)	2.60–2.69 (m)	4.22 (dd, $J_{3',4'a}$=6.0 Hz, $J_{3',4'b}$=4.1 Hz)
10b	2.25–2.35 (m)	2.60–2.69 (m)	4.22 (dd, $J_{3',4'a}$=5.2 Hz, $J_{3',4'b}$=3.8 Hz)

6 was also regioselective affording the 5′-substituted isomer **17**. The reaction of the nitrone **14** with the alkene **5** was also regioselective, but less stereospecific than that of nitrones **4** resulting in the formation of the two 5′-substituted stereoisomes **19** and **20** in a ratio 1.5:1.

The structure elucidation of the obtained cycloadducts was made on the basis of their elemental analysis and their spectral data. All the compounds give molecular ion peaks in the mass spectra and the expected chemical shifts in the ^{1}H and ^{13}C NMR spectra. The differentiation between stereoisomers **9** and **10** and between **19** and **20** was less obvious and was based on observed coupling constants and NOE measurements carried out on compound **9b**. The protons assignment was confirmed by decoupling experiments and selected chemical shifts and coupling constants of diagnostic value for compounds **9**, **10**, **19** and **20** are given in Table 1.

In **9a**, **9b**, and **19**, the one of 4′-H (4a′-H) appears at a higher field, and exhibits smaller coupling constants with both 3′-H and 5′-H than the other 4′-H (4b′-H), indicating a trans topological relationship with both of them. On the contrary, in compound **20** each of the 4′-H exhibits one large and one small coupling constant indicative that is trans to one and cis to the other. An interesting feature also in the ^{1}H NMR spectra is the difference in the chemical shifts of the two 4′-H protons, which is remarkably larger in the stereoisomers **9a**, **9b**, and **19** with a cis arrangement of the 3′ and 5′ substituents than in **20** with a trans arrangement probably as a result of the shielding effect of both substituents to the same proton. Also, the chemical shift of 3′-H is higher in the trans isomer than in the cis. Thus the presence of multipets in the ^{1}H NMR of the crude reaction mixtures at the regions 2.25–2.37 and 2.60–269 as well as a dd at δ 4.22 are indicative for isomers **10a** and **10b**.

The proposed stereochemistry for the isolated cycloadducts was further supported by NOE measurements carried out on compound **9b**. As depicted in Figure 1, the mutual large NOE enhancements observed upon saturation of 3′-H, 5′-H and 4b′-H are in accordance with their cis arrangement.



9b

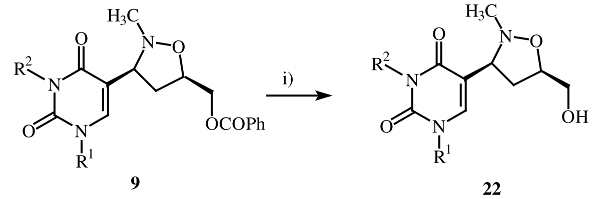
Figure 1.

It should be mentioned that the stereoselectivity of the reactions leading preferentially to cycloadducts with a cis arrangement of 3′ and 5′ substituents is favorable, since cis cycloaadducts match more the natural analogues. On the contrary, trans cycloadducts were referred as the main products of the reactions of unsubstituted uracil nitrones.[6] The observed stereoselectivity of the reactions can be explained via an *endo* approach of the dipolarophile assuming *Z*-configuration of the nitrone as it has been proved for aldonitrones.[6,11] Secondary interactions that favor an *endo* approach obviously prevail in the reactions of octyl and dioctyl substituted nitrones **4**, leading almost exclusively to the formation of cis cycloadducts **9**. In the reaction of the dimethoxy nitrone **14**, competition between steric factors and secondary interactions leads to the formation of a substantial amount of the minor trans isomer **20** as a product of the *exo* approach of the dipolarophile.

The dimethoxy derivatives **15**, **17** and **19** were readily transformed to uracil derivatives **16**, **18** and **21**, respectively, in satisfactory yields (67–72%) and without loss of the heterocyclic ring moiety, by heating in acetic acid in the presence of sodium iodide. The obtained uracils, besides the disappearance of the methoxy chemical shifts and the presence of NH resonances, exhibits in their NMR almost the same characteristics with their precursors.

The removal of the benzoyl group from the obtained cycloadducts can be also done easily by alkaline hydrolysis. In a representative experiment compounds **9a** and **9b** were transformed quantitatively to the corresponding hydroxy derivatives **22a** and **22b** with potassium hydroxide in aqueous methanol solution (Scheme 3).

In conclusion, cycloaddition reactions of nitrones or nitrile oxides derived from suitably substituted uracils or dimethoxy pyrimidines can be used as versatile procedures for the synthesis of modified pseudouridine analogues bearing isoxazole, isoxazoline or isoxazolidine rings instead of a sugar unit. The case of dimethoxy pyrimidine derivatives is significant in the sense that they could be deprotected without affecting the heterocyclic ring moiety. The presence of substituents differentiates the stereoselectivity of the reactions favoring those more close related to the natural products (cis cycloadducts) as a result of enhanced secondary interactions.



9a, **22a** $R^1 = CH_3(CH_2)_6CH_2$, $R^2 = H$

9b, **22b** $R^1 = R^2 = CH_3(CH_2)_6CH_2$

Scheme 3. Reagents and conditions: (i) KOH, MeOH/H_2O, 20 °C, 24 h.

3. Experimental

3.1. General

Mps are uncorrected and were determined on a Kofler hot-stage microscope. IR spectra were recorded on a Perkin-Elmer 297 spectrometer. ^{1}H NMR spectra were recorded at 300 MHz on a Bruker 300 AM spectrometer and ^{13}C NMR spectra at 75.5 MHz on the same spectrometer, and are quoted relative to tetramethylsilane as internal reference, in deuteriochloroform solutions, unless otherwise stated. Mass spectra (EI) were performed on a VG-250 spectrometer with ionization energy maintained at 70 eV. High resolution mass spectra (HRESI) were obtained with a 7 T APEX II spectrometer. Microanalyses were performed on a Perkin-Elmer 2400-II element analyser. Column chromatography was carried out on Merck Kieselgel (particle size 0.063–0.200 mm) and solvents were distilled before use. The preparation of the aldehydes **1** and **11** was made according to previously described procedures.[10]

3.2. Synthesis of oximes 2 and 12

General procedure. An aqueous solution (2.5 ml) of hydroxylamine hydrochloride (2.25 mmol) and sodium carbonate (1.5 mmol) were added to an ethanolic solution (5 ml) of the aldehyde **1** or **11** (1 mmol) and the reaction mixture was stirred at room temperature for 24 h. After that the ethanol was evaporated, water was added and the mixture was extracted with methylene chloride. The organic layer was dried over sodium sulfate and after evaporation of the solvent the oximes were obtained as white solids and they were used without further purification.

3.2.1. 1-Octyl-5-uracilcarbaldehyde oxime (2a). This compound was obtained in 90% yield as a white solid, mp 173–176 °C; IR (Nujol): ν_{max} 3300, 3150, 3040, 1680, 1600 cm^{-1}; ^{1}H NMR (DMSO-d_6+$CDCl_3$)): δ 0.87 (t, J= 7.2 Hz, 3H, CH_3), 1.27–1.31 (m, 10H, $CH_2CH_2(CH_2)_5CH_3$), 1.68 (br t, 2H, $CH_2CH_2(CH_2)_5CH_3$), 3.74 (t, J=7.2 Hz, 2H,

$CH_2CH_2(CH_2)_5CH_3$), 7.82 and 7.95 (two s, 2H, CH=N and 6-H), 10.79 and 11.45 (two br s, 2H, NH and OH); ^{13}C NMR (DMSO-d_6+$CDCl_3$): δ 12.9 (CH_3), 21.2, 25.0, 27.7, 27.8 and 30.3 ($CH_2(CH_2)_6CH_3$), 47.6 ($CH_2(CH_2)_6CH_3$), 105.8 (C-5), 139.6 and 140.1 (C=N and C-6), 149.3 (C-2), 161.2 (C-4); MS (EI): m/z (%) 267 (M^+, 84). Anal. Calcd for $C_{13}H_{21}N_3O_3$: C, 58.41; H, 7.92; N, 15.72. Found: C, 58.41; H, 7.86; N, 15.35.

3.2.2. 1,3-Dioctyl-5-uracilcarbaldehyde oxime (2b). This compound was obtained in 87% yield as a white solid, mp 128–130 °C; IR (Nujol): ν_{max} 3290, 3040, 1685, 1620, 1590 cm^{-1}; ^{1}H NMR: δ 0.83–0.87 (m, 6H, CH_3), 1.27–1.32 (m, 20H, $CH_2CH_2(CH_2)_5CH_3$), 1.62–1.71 (m, 4H, $CH_2CH_2(CH_2)_5CH_3$), 3.78 (t, J=7.3 Hz, 2H, $CH_2CH_2(CH_2)_5CH_3$), 3.95 (t, J=7.1 Hz, 2H, $CH_2CH_2(CH_2)_5CH_3$), 7.66 and 8.13 (two s, 2H, CH=N and 6-H), 8.80 (br s, 1H, OH); ^{13}C NMR: δ 14.0 (CH_3), 22.6, 26.4, 26.9, 27.5, 29.0, 29.2, 31.7 and 31.8 ($CH_2(CH_2)_6CH_3$), 41.8 and 50.4 ($CH_2(CH_2)_6CH_3$), 106.1 (C-5), 139.6 (C=N), 143.8 (C-6), 150.7 (C-2), 161.2 (C-4); MS (EI): m/z (%) 379 (M^+, 11). Anal. Calcd for $C_{21}H_{37}N_3O_3$: C, 66.46; H, 9.83; N, 11.07. Found: C, 66.45; H, 9.42; N, 10.79.

3.2.3. 2,4-Dimethoxy-5-pyrimidinecarbaldehyde oxime (12). This compound was obtained in 87% yield as a white solid, mp 150–154 °C; IR (Nujol): ν_{max} 3200, 3010, 1580, 1550 cm^{-1}; ^{1}H NMR: δ 4.04 (s, 3H, OCH_3), 4.06 (s, 3H, OCH_3), 8.19 and 8.56 (two s, 2H, 6-H and CH=N), 8.85 (br s, 1H, OH); ^{13}C NMR: δ 54.3 and 55.1 (OCH_3), 107.7 (C-5), 143.2 (C=N), 156.9 (C-6), 161.7 and 168.3 (C-2 and C-4); HRESIMS for $C_7H_9N_3O_3$ $(M+Na)^+$: calcd 206.0536, found 206.0536.

3.3. Synthesis of nitrones 4 and 14

General procedure. An aqueous solution (2.5 ml) of methylhydroxylamine hydrochloride (2 mmol) and sodium carbonate (1.5 mmol) were added to an ethanolic solution (5 ml) of the aldehyde **1** or **11** (1 mmol) and the reaction mixture was stirred at room temperature for 24 h. After that the ethanol was evaporated, water was added and the mixture was extracted with methylene chloride. After drying and evaporation of the solvent from the organic layer the residue nitrones were used without further purification.

3.3.1. *N*-Methyl-*C*-(1-octyl-5-uracil) nitrone (4a). This compound was obtained in 84% yield as a white solid, mp 190–193 °C; IR (Nujol): ν_{max} 3180, 3110, 3040, 1670, 1590 cm^{-1}; ^{1}H NMR (45 °C): δ 0.89 (br, 3H, CH_3), 1.29–1.34 (m, 10H, $CH_2CH_2(CH_2)_5CH_3$), 1.75 (br t, 2H, $CH_2CH_2(CH_2)_5CH_3$), 3.76–3.80 (m, 5H, $CH_2CH_2(CH_2)_5CH_3$ and N–CH_3), 7.56 (s, 1H, 6-H), 8.81 (br s, 1H, NH), 9.90 (s, 1H, CH=N(O)); ^{13}C NMR (45 °C): δ 13.8 (CH_3), 22.5, 26.5, 29.0 and 31.7 ($CH_2(CH_2)_6CH_3$), 47.6 (CH_2 $(CH_2)_6CH_3$), 53.5 (N–CH_3), 106.5 (C-5), 127.6 (CH=N(O)), 144.3 (C-6), 149.8 (C-2), 161.8 (C-4); MS (EI): m/z (%) 281 (M^+, 86). Anal. Calcd for $C_{14}H_{23}N_3O_3$: C, 59.77; H, 8.24; N, 14.93. Found: C, 59.87; H, 8.07; N, 14.89.

3.3.2. *N*-Methyl-*C*-(1,3-dioctyl-5-uracil) nitrone (4b). This compound was obtained in 87% yield as a white solid, mp 70–72 °C; IR (Nujol): ν_{max} 3070, 3030, 1695, 1630, 1590 cm^{-1}; ^{1}H NMR: δ 0.85–0.89 (m, 6H, CH_3), 1.26–1.32 (m, 20H, $CH_2CH_2(CH_2)_5CH_3$), 1.58–1.67 (m, 4H, $CH_2CH_2(CH_2)_5CH_3$), 3.79 (t, J=7.3 Hz, 2H, $CH_2CH_2(CH_2)_5CH_3$), 3.81 (s, 3H, N–CH_3), 3.96 (t, J=7.4 Hz, 2H, $CH_2CH_2(CH_2)_5CH_3$), 7.62 (s, 1H, 6-H), 9.83 (s, 1H, CH=N(O)); ^{13}C NMR: δ 14.0 (CH_3), 22.5, 26.4, 26.9, 27.5, 29.0, 29.1, 29.2, 31.7 and 31.8 ($CH_2(CH_2)_6CH_3$), 41.8, 50.6 and 53.5 ($CH_2(CH_2)_6CH_3$ and N–CH_3), 105.6 (C-5), 128.5 (CH=N(O)), 142.5 (C-6), 150.1 (C-2), 161.4 (C-4); MS (EI): m/z (%) 393 (M^+, 26). Anal. Calcd for $C_{22}H_{39}N_3O_3$: C, 67.14; H, 9.99; N, 10.68. Found: C, 67.50; H, 9.58; N, 10.53.

3.3.3. *N*-Methyl-*C*-(1,3-dimethoxy-5-pyrimidine) nitrone (14). This compound was obtained in 75% yield as a white solid, mp 168–170 °C; IR (Nujol): ν_{max} 3040, 1585, 1570, 1540 cm^{-1}; ^{1}H NMR: δ 4.04, 4.05 and 4.12 (three s, 9H, OCH_3 and N–CH_3), 7.57 (s, 1H, 6-H), 10.19 (s, 1H, CH=N(O)); ^{13}C NMR: δ 53.9, 54.2 and 54.9 (OCH_3 and N–CH_3), 107.2 (C-5), 126.4 (CH=N(O)), 157.5 (C-6), 164.8 and 167.6 (C-2 and C-4); MS (EI): m/z (%) 197 (M^+, 100). Anal. Calcd for $C_8H_{11}N_3O_3$: C, 48.73; H, 5.62; N, 21.31. Found: C, 48.62; H, 5.53; N, 21.71.

3.4. Formation of nitrile oxides 3 and 13 and reactions with the dipolarophiles 5 and 6

General procedure. A solution of the aldoxime **2** or **12** (0.5 mmol) and the dipolarophile **5** or **6** (1 mmol) in methylene chloride (5 ml) was cooled to 0 °C and commercial bleach (4 ml) was added. The reaction mixture was warmed to room temperature and allowed to react overnight with stirring. The reaction mixture was extracted with methylene chloride and the organic layer was dried over sodium sulfate. After evaporation of the solvent the residue was chromatographed on a silica gel column with hexane–ethyl acetate (3/1 for the reactions of **2b**, 2/1 for reactions of **12**) as the eluent.

3.4.1. 5-(5′-Benzoyloxymethyl-isoxazolin-3′-yl)-1,3-dioctyluracil (7b). This compound was obtained in 70% yield as an oil; IR (liquid film): ν_{max} 3060, 1710–1640, 1595, 1575 cm^{-1}; ^{1}H NMR: δ 0.87–0.89 (m, 6H, CH_3), 1.26–1.31 (m, 20H, $CH_2CH_2(CH_2)_5CH_3$), 1.61–1.70 (m, 4H, $CH_2CH_2(CH_2)_5CH_3$), 3.44 (dd, J=18.0, 7.1 Hz, 1H, 4′-H), 3.65 (dd, J=18.0, 10.9 Hz, 1H, 4′-H), 3.78 (t, J=7.4 Hz, 2H, $CH_2CH_2(CH_2)_5CH_3$), 3.93 (t, J=7.4 Hz, 2H, $CH_2CH_2(CH_2)_5CH_3$), 4.38–4.49 (m, 2H, CH_2OCOPh), 4.98–5.10 (m, 1H, 5′-H), 7.42 (t, J=7.6 Hz, 2H, Ph-H), 7.56 (t, J=7.6 Hz, 1H, Ph-H), 7.88 (s, 1H, 6-H), 8.04 (d, J=7.6 Hz, 2H, Ph-H); ^{13}C NMR: δ 14.1 (CH_3), 22.7, 26.5, 26.9, 27.1, 27.2, 27.3, 27.5, 29.1, 29.2, 29.3, 31.7 and 31.8 ($CH_2(CH_2)_6CH_3$), 39.0 (C-4′), 41.9 and 50.5 ($CH_2(CH_2)_6CH_3$), 65.4 (CH_2OCOPh), 78.5 (C-5′), 103.5 (C-5), 128.4, 129.7, 129.8 and 133.2 (C-Ph), 141.7 (C-6), 150.6 and 152.8 (C-2 and C=N), 161.0 (C-4), 166.3 (C=O); MS (EI): m/z (%) 539 (M^+, 8). Anal. Calcd for $C_{31}H_{45}N_3O_5$: C, 68.99; H, 8.40; N, 7.79. Found: C, 69.27; H, 8.57; N, 7.99.

3.4.2. 5-(5′-Benzoyloxymethyl-isoxazol-3′-yl)-1,3-dioctyluracil (8b). This compound was obtained in 80% yield as a white solid, mp 47–49 °C; IR (Nujol): ν_{max} 3050, 1710, 1650, 1595 cm^{-1}; ^{1}H NMR: δ 0.85–0.89 (m, 6H, CH_3), 1.26–1.32 (m, 20H, $CH_2CH_2(CH_2)_5CH_3$), 1.62–1.78 (m, 4H, $CH_2CH_2(CH_2)_5CH_3$), 3.83 (t, J=7.4 Hz, 2H, $CH_2CH_2(CH_2)_5CH_3$), 3.99 (t, J=7.4 Hz, 2H, $CH_2CH_2(CH_2)_5CH_3$), 5.46 (s, 2H, CH_2OCOPh), 7.13 (s, 1H, 4′-H), 7.46 (t, J=7.4 Hz, 2H, Ph-H), 7.60 (t, J=7.4 Hz, 1H, Ph-H), 8.05 (s, 1H, 6-H), 8.07 (d, J=7.4 Hz, 2H, Ph-H); ^{13}C NMR: δ 14.0 (CH_3), 22.5, 26.4, 26.8, 26.9, 27.5, 29.0, 29.1, 29.2, 31.7 and 31.8 ($CH_2(CH_2)_6CH_3$), 41.9 and 50.5 ($CH_2(CH_2)_6CH_3$), 56.9 (CH_2OCOPh), 102.4 (C-5), 104.5 (C-4′), 128.4, 129.1, 129.9 and 133.5 (C-Ph), 141.6 (C-6), 150.6 (C-2), 156.8 (C═N), 161.9 (C-4), 165.7 and 166.3 (C═O and C-5′); HRESIMS for $C_{31}H_{43}N_3O_5$ $(M+Na)^+$: calcd 560.3095, found 560.3098.

3.4.3. 5-(5′-Benzoyloxymethyl-isoxazolin-3′-yl)-2,4-dimethoxypyrimidine (15). This compound was obtained in 65% yield as a white solid, mp 132–133 °C; IR (Nujol): ν_{max} 3030, 1710, 1595, 1535 cm^{-1}; ^{1}H NMR: δ 3.32 (dd, J=17.4, 6.8 Hz, 1H, 4′-H), 3.57 (dd, J=17.4, 10.9 Hz, 1H, 4′-H), 4.01 (s, 3H, OCH_3), 4.04 (s, 3H, OCH_3), 4.43–4.56 (m, 2H, CH_2OCOPh), 5.08–5.17 (m, 1H, 5′-H), 7.41 (t, J=7.6 Hz, 2H, Ph-H), 7.55 (t, J=7.6 Hz, 1H, Ph-H), 8.02 (d, J=7.6 Hz, 2H, Ph-H), 8.65 (s, 1H, 6-H); ^{13}C NMR: δ 39.0 (C-4′), 54.2 and 54.4 (OCH_3), 65.4 (CH_2OCOPh), 78.0 (C-5′), 105.2 (C-5), 128.3, 129.4, 129.5 and 133.1 (C-Ph), 151.5 (C═N), 158.1 (C-6), 165.7, 166.1 and 167.9 (C-2, C-4 and C═O); MS (EI): m/z (%) 343 (M^+, 9%). Anal. Calcd for $C_{17}H_{17}N_3O_5$: C, 59.47; H, 4.99; N, 12.44. Found: C, 59.34; H, 4.89; N, 12.39.

3.4.4. 5-(5′-Benzoyloxymethyl-isoxazol-3′-yl)-2,4-dimethoxypyrimidine (17). This compound was obtained in 90% yield as a white solid, mp 98–100 °C; IR (Nujol): ν_{max} 3050, 1715, 1590, 1550 cm^{-1}; ^{1}H NMR: δ 4.07 (s, 3H, OCH_3), 4.11 (s, 3H, OCH_3), 5.48 (s, 2H, CH_2OCOPh), 6.82 (s, 1H, 4′-H), 7.47 (t, J=7.4 Hz, 2H, Ph-H), 7.58 (t, J=7.4 Hz, 1H, Ph-H), 8.09 (d, J=7.4 Hz, 2H, Ph-H), 8.85 (s, 1H, 6-H); ^{13}C NMR: δ 54.4 and 55.2 (OCH_3), 56.7 (CH_2OCOPh), 104.7 (C-5), 104.9 (C-4′), 128.5, 129.5, 129.9 and 133.6 (C-Ph), 156.6 (C═N), 158.1 (C-6), 163.5, 165.8, 166.7 and 168.1 (C-2, C-4, C-5′ and C═O); MS (EI): m/z (%) 341 (M^+, 23). Anal. Calcd for $C_{17}H_{15}N_3O_5$: C, 59.82; H, 4.43; N, 12.31. Found: C, 59.60; H, 4.53; N, 12.51.

3.5. Reactions of nitrones 4 and 14 with the dipolarophile 5

General procedure. A solution of the nitrone **4** or **14** (0.5 mmol) and the dipolarophile **5** (1 mmol) in xylene (5 ml) was heated to reflux and the reaction was monitored by TLC until the consumption of the nitrone. After 2 days only traces of the nitrone were detected in the TLC. The heating was stopped and after evaporation of the solvent the residue was chromatographed on a silica gel column with hexane–ethyl acetate (1/1 for the reaction of **4a**, 3/1 for the reaction of **4b**, 2/1 for the reaction of **14**) as the eluent.

3.5.1. (3′*RS*,5′*SR*)-5-(5′-Benzoyloxymethyl-isoxazolidin-3′-yl)-1-octyluracil (9a). This compound was obtained in 72% yield as an oil; IR (liquid film): ν_{max} 3190, 3060, 1715–1650, 1595, 1575 cm^{-1}; ^{1}H NMR: δ 0.87 (t, J=8.5 Hz, 3H, CH_3), 1.15–1.40 (m, 10H, $CH_2CH_2(CH_2)_5CH_3$), 1.50–1.65 (m, 2H, $CH_2CH_2(CH_2)_5CH_3$), 2.10 (dt, J=12.2, 5.1 Hz, 1H, 4′-H), 2.73 (s, 3H, *N*–CH_3), 3.02 (ddd, J=12.2, 8.4, 7.3 Hz, 1H, 4′-H), 3.48–3.76 (m, 2H, $CH_2CH_2(CH_2)_5CH_3$), 4.03 (dd, J=7.3, 5.1 Hz, 1H, 3′-H), 4.31 (dd, J=12.0, 6.0 Hz, 1H, CH_2OCOPh), 4.47 (dd, J=12.0, 3.3 Hz, 1H, CH_2OCOPh), 4.67 (dddd, J=8.4, 6.0, 5.1, 3.3 Hz, 1H, 5′-H), 7.41 (t, J=7.4 Hz, 2H, Ph-H), 7.43 (s, 1H, 6-H) 7.55 (t, J=7.4 Hz, 1H, Ph-H), 7.98 (d, J=7.4 Hz, 2H, Ph-H), 9.81 (s, 1H, NH); ^{13}C NMR: δ 13.9 (CH_3), 22.5, 26.3, 28.9, 29.0 and 31.6 ($CH_2(CH_2)_6CH_3$), 37.5 (C-4′), 44.1 and 48.7 ($CH_2(CH_2)_6CH_3$ and *N*–CH_3), 63.1 and 64.9 (C-3′ and CH_2OCOPh), 74.6 (C-5′), 113.6 (C-5), 128.3, 129.4, 129.6 and 133.1 (C-Ph), 141.7 (C-6), 150.5 (C-2), 163.5 (C-4), 166.1 (C═O); MS (EI): m/z (%) 443 (M^+, 10). Anal. Calcd for $C_{24}H_{33}N_3O_5$: C, 64.99; H, 7.50; N, 9.57. Found: C, 65.11; H, 7.50; N, 9.24.

3.5.2. (3′*RS*,5′*SR*)-5-(5′-Benzoyloxymethyl-isoxazolidin-3′-yl)-1,3-dioctyluracil (9b). This compound was obtained in 70% yield as an oil; IR (liquid film): ν_{max} 3060, 1720–1690, 1660–1630, 1590 cm^{-1}; ^{1}H NMR: δ 0.85–0.92 (m, 6H, CH_3), 1.15–1.40 (m, 20H, $CH_2CH_2(CH_2)_5CH_3$), 1.50–1.70 (m, 4H, $CH_2CH_2(CH_2)_5CH_3$), 2.05 (dt, J=13.6, 5.1 Hz, 1H, 4′-H), 2.73 (s, 3H, *N*–CH_3), 3.02 (ddd, J=13.6, 8.4, 7.8 Hz, 1H, 4′-H), 3.49–3.75 (m, 2H, $CH_2CH_2(CH_2)_5CH_3$), 3.90 (t, J=9.3 Hz, 2H, $CH_2CH_2(CH_2)_5CH_3$), 3.99 (dd, J=7.8, 5.1 Hz, 1H, 3′-H), 4.32 (dd, J=11.9, 6.1 Hz, 1H, CH_2OCOPh), 4.43 (dd, J=11.9, 3.1 Hz, 1H, CH_2OCOPh), 4.67 (dddd, J=8.4, 6.1, 5.1, 3.1 Hz, 1H, 5′-H), 7.37 (s, 1H, 6-H), 7.41 (t, J=7.6 Hz, 2H, Ph-H), 7.56 (t, J=7.6 Hz, 1H, Ph-H), 7.97 (d, J=7.6 Hz, 2H, Ph-H); ^{13}C NMR: δ 14.0 (CH_3), 22.5, 26.4, 26.9, 27.5, 28.9, 29.0, 29.1, 31.6 and 31.7 ($CH_2(CH_2)_6CH_3$), 37.7 (C-4′), 41.4, 44.2 and 49.7 ($CH_2(CH_2)_6CH_3$ and N–CH_3), 63.7 and 65.1 (C-3′ and CH_2OCOPh), 74.5 (C-5′), 112.9 (C-5), 128.3, 129.5, 129.7 and 133.1 (C-Ph), 139.3 (C-6), 150.8 (C-2), 162.6 (C-4), 166.2 (C═O); MS (EI): m/z (%) 555 (M^+, 16). Anal. Calcd for $C_{32}H_{49}N_3O_5$: C, 69.16; H, 8.89; N, 7.56. Found: C, 69.46; H, 8.81; N, 7.25.

3.5.3. (3′*RS*,5′*SR*)-5-(5′-Benzoyloxymethyl-isoxazolidin-3′-yl)-2,4-dimethoxypyrimidine (19). This compound was obtained in 52% yield as an oil; IR (liquid film): ν_{max} 3060, 1715, 1595, 1565 cm^{-1}; ^{1}H NMR: δ 2.05 (dt, J=12.8, 6.4 Hz, 1H, 4′-H), 2.68 (s, 3H, *N*–CH_3), 2.89 (ddd, J=12.8, 8.4, 7.7 Hz, 1H, 4′-H), 3.85 (dd, J=8.4, 6.4 Hz, 1H, 3′-H), 3.97 (s, 3H, OCH_3), 4.00 (s, 3H, OCH_3), 4.37 (dd, J=11.5, 3.9 Hz, 1H, CH_2OCOPh), 4.45 (dd, J=11.5, 7.1 Hz, 1H, CH_2OCOPh), 4.61 (dddd, J=7.7, 7.1, 6.4, 3.9 Hz, 1H, 5′-H), 7.37 (s, 1H, 6-H), 7.42 (t, J=7.6 Hz, 2H, Ph-H), 7.54 (t, J=7.6 Hz, 1H, Ph-H), 8.01 (d, J=7.6 Hz, 2H, Ph-H); ^{13}C NMR: δ 38.9 (C-4′), 43.5 (*N*–CH_3), 53.9 (OCH_3), 54.7 (OCH_3), 64.1 and 66.0 (C-3′ and CH_2OCOPh), 74.3 (C-5′), 113.1 (C-5), 128.2, 129.6, 129.8 and 132.9 (C-Ph), 156.4 (C-6), 164.6, 166.4 and 168.7 (C-2, C-4 and C═O); MS (EI): m/z (%) 359 (M^+, 17). Anal. Calcd for $C_{18}H_{21}N_3O_5$: C, 60.16; H, 5.89; N, 11.69. Found: C, 60.28; H, 6.10; N, 11.39.

3.5.4. (3′*RR*,5′*SS*)-5-(5′-Benzoyloxymethyl-isoxazolidin-3′-yl)-2,4-dimethoxy-pyrimidine (20). This compound was obtained in 26% yield as an oil; IR (liquid film): ν_{max} 3060, 1710, 1660, 1600–1560 cm^{-1}; ^{1}H NMR: δ 2.41 (ddd, J=14.2, 7.7, 5.7 Hz, 1H, 4′-H), 2.55 (ddd, J=14.2, 8.9, 3.9 Hz, 1H, 4′-H), 2.69 (s, 3H, *N*–CH_3), 4.00 (s, 3H, OCH_3), 4.02 (s, 3H, OCH_3), 4.24 (dd, J=5.7, 3.9 Hz, 1H, 3′-H), 4.41 (dd, J=12.2, 6.4 Hz, 1H, C*H*$_2$OCOPh), 4.50–4.61 (m, 2H, C*H*$_2$OCOPh and 5′-H), 7.47 (t, J=7.4 Hz, 2H, Ph-H), 7.57 (t, J=7.4 Hz, 1H, Ph-H), 8.11 (d, J=7.4 Hz, 2H, Ph-H), 8.35 (s, 1H, 6-H); ^{13}C NMR: δ 38.7 (C-4′), 43.8 (*N*–CH_3), 54.0 (OCH_3), 54.7 (OCH_3), 64.0 and 65.4 (C-3′ and *C*H_2OCOPh), 74.8 (C-5′), 112.6 (C-5), 128.3, 129.6, 129.9 and 133.0 (C-Ph), 156.6 (C-6), 164.6, 167.6 and 169.3 (C-2, C-4 and C=O); MS (EI): *m*/*z* (%) 359 (M^+, 14). Anal. Calcd for $C_{18}H_{21}N_3O_5$: C, 60.16; H, 5.89; N, 11.69. Found: C, 60.26; H, 5.99; N, 11.30.

3.6. Demethylation of compounds 15, 17 and 19

General procedure. The dimethoxy derivative **15** or **17** or **19** (0.2 mmol) was heated with sodium iodide (0.1 g) in glacial acetic acid (3 ml) at 90 °C for 1 h. The solvent was removed under reduced pressure and the residue was chromatographed on a silica gel column with 3% methanol in methylene chloride as the eluent.

3.6.1. 5-(5′-Benzoyloxymethyl-isoxazolin-3′-yl)-uracil (16). This compound was obtained in 72% yield as a white solid, mp 253–257 °C; IR (Nujol): ν_{max} 3210, 3080, 3040, 1710, 1640 cm^{-1}; ^{1}H NMR ($CDCl_3$/DMSO-d_6): δ 3.35 (dd, J=17.8, 6.9 Hz, 1H, 4′-H), 3.52 (dd, J= 17.8, 11.0 Hz, 1H, 4′-H), 4.33 (dd, J=12.3, 5.5 Hz, 1H, C*H*$_2$OCOPh), 4.42 (dd, J=12.3, 3.5 Hz, 1H, C*H*$_2$OCOPh), 4.96 (dddd, J=11.0, 6.9, 5.5, 3.5 Hz, 1H, 5′-H), 7.48 (t, J= 7.7 Hz, 2H, Ph-H), 7.63 (t, J=7.7 Hz, 1H, Ph-H), 7.77 (s, 1H, 6-H), 7.96 (d, J=7.7 Hz, 2H, Ph-H), 10.12 (br s, 2H, NH); ^{13}C NMR ($CDCl_3$/DMSO-d_6): δ 36.5 (C-4′), 63.7 (*C*H_2OCOPh), 75.5 (C-5′), 101.1 (C-5), 126.7, 127.4, 127.7 and 131.4 (C-Ph), 139.6 (C-6), 148.9 (C-2), 150.4 (C=N), 160.1 (C-4), 163.4 (C=O); HRESIMS for $C_{15}H_{13}N_3O_5$ $(M+Na)^+$: calcd 338.0747, found 338.0748.

3.6.2. 5-(5′-Benzoyloxymethyl-isoxazol-3′-yl)-uracil (18). This compound was obtained in 67% yield as a white solid, mp 217–220 °C; IR (Nujol): ν_{max} 3210, 3080, 3050, 1715, 1590 cm^{-1}; ^{1}H NMR ($CDCl_3$/DMSO-d_6): δ 5.47 (s, 2H, C*H*$_2$OCOPh), 7.02 (s, 1H, 4′-H), 7.51 (t, J=7.4 Hz, 2H, Ph-H), 7.64 (t, J=7.4 Hz, 1H, Ph-H), 8.01–8.07 (overlapped d and s, 3H, Ph-H and 6-H), 11.34–11.52 (overlapped br s, 2H, NH); ^{13}C NMR ($CDCl_3$/DMSO-d_6): δ 55.1 (*C*H_2OCOPh), 100.0 (C-5), 102.7 (C-4′), 126.9, 127.7, 128.0 and 131.9 (C-Ph), 139.5 (C-6), 149.3, 155.1, 160.6 163.5 and 164.6 (C-2, C-4, C=N C-5′and C=O); HRESIMS for $C_{15}H_{11}N_3O_5$ $(M+Na)^+$: calcd 336.0591, found 336.0591.

3.6.3. (3′*RS*,5′*SR*)-5-(5′-Benzoyloxymethyl-isoxazolidin-3′-yl)-uracil (21). This compound was obtained in 76% yield as a white solid, mp 210–212 °C; IR (Nujol): ν_{max} 3190, 3150, 3060, 1710, 1660 cm^{-1}; ^{1}H NMR ($CDCl_3$/CD_3OD): δ 2.03 (dt, J=12.9, 6.1 Hz, 1H, 4′-H), 2.72 (s, 3H, *N*–CH_3), 2.98 (ddd, J=12.9, 9.2, 7.4 Hz, 1H, 4′-H), 3.85 (dd, J=7.4, 6.1 Hz, 1H, 3′-H), 4.33–4.42 (m, 2H, C*H*$_2$OCOPh), 4.61–4.70 (m, 1H, 5′-H), 7.42 (s, 1H, 6-H), 7.43 (t, J= 7.4 Hz, 2H, Ph-H), 7.56 (t, J=7.4 Hz, 1H, Ph-H), 8.00 (d, J=7.4 Hz, 2H, Ph-H); ^{13}C NMR ($CDCl_3$/CD_3OD): δ 37.7 (C-4′), 43.9 (*N*–CH_3), 63.2 and 65.3 (C-3′ and *C*H_2OCOPh), 74.6 (C-5′), 113.0 (C-5), 128.3, 129.5 and 133.2 (C-Ph), 138.2 (C-6), 151.6 (C-2), 163.9 (C-4), 166.5 (C=O); MS: *m*/*z* (%) 331 (M^+, 10). Anal. Calcd for $C_{16}H_{17}N_3O_5$: C, 58.00; H, 5.17; N, 12.68. Found: C, 57.98; H, 5.01; N, 12.82.

3.7. Hydrolysis of compounds 9

General procedure. An aqueous solution (1 ml) of KOH (10%) was added to a methanolic solution (5 ml) of the compound **9a** or **9b** (0.1 mmol) and the reaction mixture was stirred at room temperature for 24 h. After that the methanol was evaporated, water was added, neutralized with ammonium chloride and the mixture was extracted with methylene chloride. The organic layer was dried over sodium sulfate and after evaporation of the solvent compounds **22** were obtained quantitatively as oils. For analytical purposes, they were further purified by column chromatography on a silica gel column with ethyl acetate as the eluent.

3.7.1. (3′*RS*,5′*SR*)-5-(5′-Hydroxymethyl-isoxazolidin-3′-yl)-1-octyluracil (22a). This compound was obtained in 100% yield as an oil; IR (liquid film): ν_{max} 3400, 3180, 3050, 1690–1640 cm^{-1}; ^{1}H NMR: δ 0.87 (t, J=6.6 Hz, 3H, CH_3), 1.19–1.40 (m, 10H, $CH_2CH_2(CH_2)_5CH_3$), 1.59–1.73 (m, 2H, $CH_2CH_2(CH_2)_5CH_3$), 2.01 (dt, J=12.9, 5.9 Hz, 1H, 4′-H), 2.50 (br s, 1H, OH), 2.69 (s, 3H, *N*–CH_3), 2.91 (dt, J=12.9, 7.9 Hz, 1H, 4′-H), 3.59 (dd, J=12.8, 5.3 Hz, 1H, C*H*$_2$OH), 3.64–3.79 (m, 3H, $CH_2CH_2(CH_2)_5CH_3$ and C*H*$_2$OH), 3.90 (dd, J=7.9, 5.9 Hz, 1H, 3′-H), 4.36–4.46 (m, 1H, 5′-H), 7.48 (s, 1H, 6-H), 9.62 (br s, 1H, NH); ^{13}C NMR: δ 14.0 (CH_3), 22.5, 26.4, 29.1, 29.7 and 31.6 ($CH_2(CH_2)_6CH_3$), 37.7 (C-4′), 44.0 and 49.1 ($CH_2(CH_2)_6CH_3$ and *N*–CH_3), 63.6 and 64.5 (C-3′ and *C*H_2OH), 76.6 (C-5′), 112.9 (C-5), 141.7 (C-6), 150.5 (C-2), 163.5 (C-4); MS (EI): *m*/*z* (%) 339 (M^+, 8). Anal. Calcd for $C_{17}H_{29}N_3O_4$: C, 60.15; H, 8.61; N,12.38. Found: C, 60.01; H, 8.90; N, 12.14.

3.7.2. (3′*RS*,5′*SR*)-5-(5′-Hydroxymethyl-isoxazolidin-3′-yl)-1,3-dioctyluracil (22b). This compound was obtained in 100% yield as an oil; IR (liquid film): ν_{max} 3400, 3060, 1690, 1660–1630 cm^{-1}; ^{1}H NMR: δ 0.85–0.92 (m, 6H, CH_3), 1.14–1.41 (m, 20H, $CH_2CH_2(CH_2)_5CH_3$), 1.50–1.75 (m, 4H, $CH_2CH_2(CH_2)_5CH_3$), 1.97 (dt, J=12.6, 6.4 Hz, 1H, 4′-H), 2.30 (br s, 1H, OH), 2.68 (s, 3H, *N*–CH_3), 2.87 (dt, J=12.6, 8.3 Hz, 1H, 4′-H), 3.59 (dd, J=11.9, 5.2 Hz, 1H, C*H*$_2$OH), 3.69–3.80 (m, 3H, $CH_2CH_2(CH_2)_5CH_3$ and C*H*$_2$OH), 3.85–3.96 (m, 3H, $CH_2CH_2(CH_2)_5CH_3$ and 3′-H), 4.34–4.43 (m, 1H, 5′-H), 7.35 (s, 1H, 6-H); ^{13}C NMR: δ 14.0 (CH_3), 22.6, 26.5, 27.0, 27.5, 29.1, 29.2, 29.7, 31.7 and 31.8 ($CH_2(CH_2)_6CH_3$), 38.0 (C-4′), 41.6, 44.0 and 50.0 ($CH_2(CH_2)_6CH_3$ and N–CH_3), 64.1 and 64.9 (C-3′ and *C*H_2OH), 76.9 (C-5′), 112.1 (C-5), 139.2 (C-6), 150.8 (C-2), 162.7 (C-4); MS (EI): *m*/*z* (%) 451 (M^+, 9). Anal. Calcd for $C_{25}H_{45}N_3O_4$: C, 66.48; H, 10.04; N, 9.30. Found: C, 66.26; H, 10.21; N, 9.25.

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Facile synthesis of 3,3-di(heteroaryl)indolin-2-one derivatives catalyzed by ceric ammonium nitrate (CAN) under ultrasound irradiation

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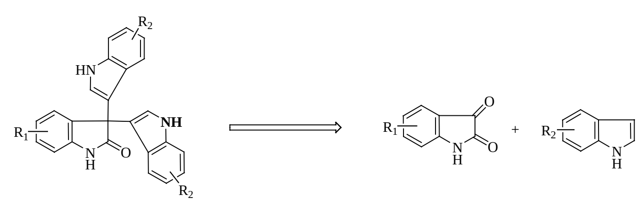
Abstract—Ceric ammonium nitrate efficiently catalyzes the reaction of isatin with indoles under sonic waves to afford symmetrical 3,3-di(indolyl)indolin-2-ones in excellent yields, as well as the reaction of 3-hydroxy-3-indolylindolin-2-ones with indoles, pyrrole to afford the corresponding adducts in excellent yields, which provides an efficient route to the synthesis of symmetrical and unsymmetrical 3,3-di(indolyl)indolin-2-one derivatives, respectively.

1. Introduction

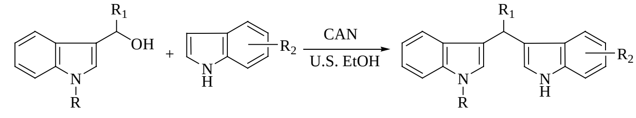
Indole fragment is featured widely in a wide variety of pharmacologically and biologically active compounds.[1] Oxindole derivatives are known to possess a variety of biological activity.[2] The 3,3-diaryloxindoles have been shown to possess mechanism-specific antiproliferative, antibacterial, antiprotozoal, and antiinflammatory activities.[3] These compounds have also been used as laxatives[4] and lead compounds for Ca^{2+}-depletion-mediated inhibition of translation initiation.[5] The 3,3-di(indolyl)indolin-2-ones can be formed by the reaction of isatin and indoles in acid conditions for long reaction times or promoted by $KAl(SO_4)_2$ under microwave conditions (Scheme 1).[6] Few methods have been developed for the synthesis of this class of compounds.[4,7] Especially, 3,3-diheteroaryloxindoles have not been widely explored. And the use of Lewis acid as a catalyst in the synthesis of 3,3-di(indolyl)oxindoles under mild conditions has not been reported.



Scheme 1.

In recent years, ceric ammonium nitrate (CAN) has been attracted much attention as an inexpensive and easily available catalyst for effecting various organic reactions.[8] The reaction of indoles with carbonyl catalyzed by CAN afford the symmetrical bisindolymethane derivatives, which has been reported recently.[9] However, the reaction must be performed using the toxic CH_3CN as the solvent under the protection of N_2 atmosphere and was only limited to the synthesis of symmetrical BIAs.

More recently, we described an ultrasound-accelerated reaction of indoles with (1*H*-indol-3-yl)alkylmethanol using a catalytic amount of CAN, which provided an efficient route to the synthesis of unsymmetrical BIAs (Scheme 2).[10] There was no previous report, which had indicated that two different indole or pyrrole residues could be so incorporated onto an indolin-2-ones derivative.



Scheme 2.

As a continue of our work on the synthesis of indole derivatives[10–12] we describe an ultrasound-accelerated reaction of isatin **1** with indoles **2** or 3-hydroxy-3-

Keywords: 3,3-Di(heteroaryl)indolin-2-one; CAN; Indole; Isatin.
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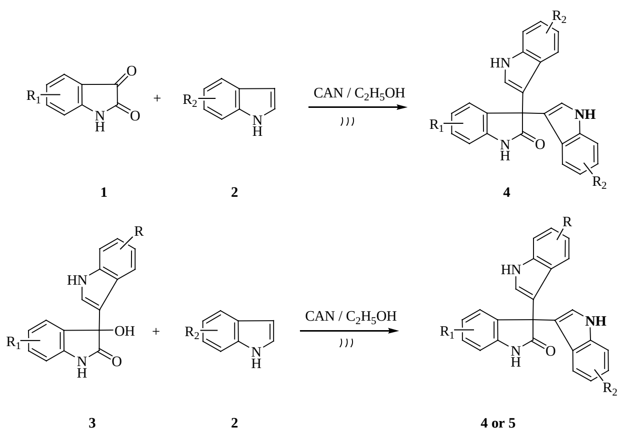
indolylindolin-2-ones **3** with indoles **2** using a catalytic amount of CAN, which provide an efficient route to the synthesis of symmetrical and unsymmetrical 3,3-bis(indolyl)oxindole derivatives, respectively (Scheme 3).



Scheme 3.

2. Results and discussion

In our initial research, we carried out the reaction of isatin **1a** with indole **2a** in the presence of CAN at room temperature using different solvents. The results were listed in Table 1. The reaction of **1a** with **2a** in the presence of CAN (10 mol%) and anhydrous C_2H_5OH (2 ml) proceeded smoothly at room temperature, giving 3,3-di(indolyl)indo-

Table 1. The solvent effect of the reaction between isatin **1a** and indole **2a**[a]

Entry	Solvent	Time (h)	Yield (%)[b]
1	Anhydrous C_2H_5OH	3	95
2		10[c]	90[c]
3	Anhydrous CH_3OH	3	96
4	CH_2Cl_2	3	80
5	CH_3CN	3	75

[a] All reactions were carried out using catalytic amount of CAN (10 mol%) at room temperature.
[b] Isolated yields.
[c] The reaction was carried out under stir condition at room temperature.

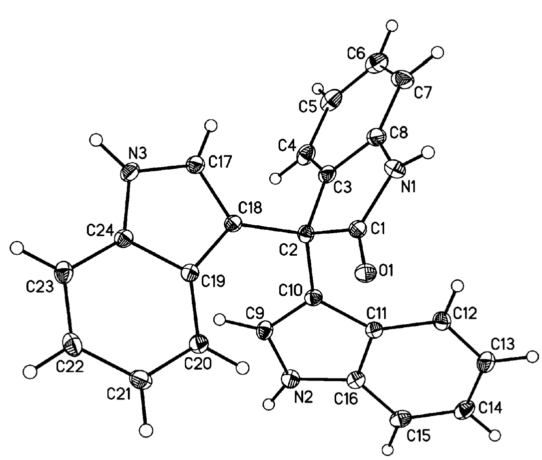
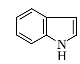
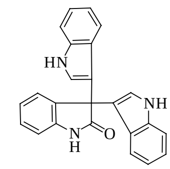
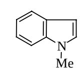
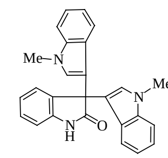
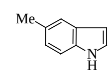
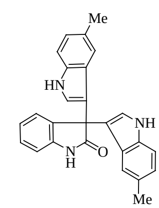
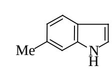
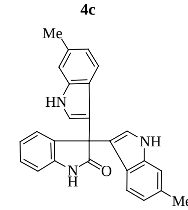
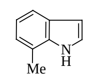
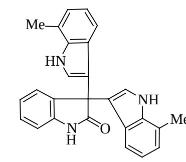
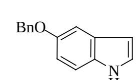
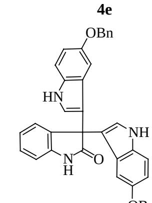
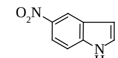
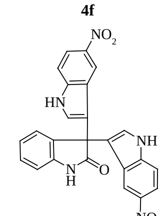
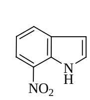
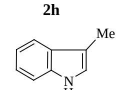


Figure 1. The crystal structure of **4a**.

Table 2. The reaction of isatin with indoles catalyzed by CAN under ultrasound irradiation condition[a]

Entry	Indoles	Products	Time (h)	Yield (%)[b]
1	 **2a**	 **4a**	3	95
2	 **2b**	 **4b**	7	83
3	 **2c**	 **4c**	8	85
4	 **2d**	 **4d**	8	86
5	 **2e**	 **4e**	8	91
6	 **2f**	 **4f**	8	82
7	 **2g**	 **4g**	10	90
8	 **2h**	—	10	nr[c]
9	 **2i**	—	10	nr[c]

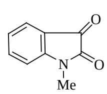
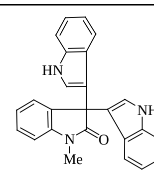
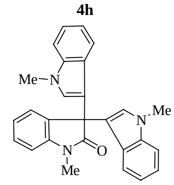
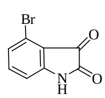
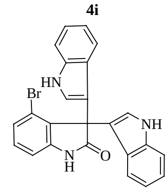
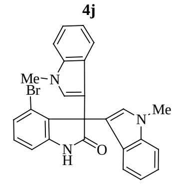
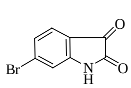
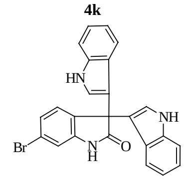
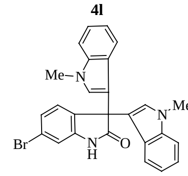
[a] All reactions were carried out under sonic conditions.
[b] Isolation yields.
[c] nr = no reaction was detected.

lin-2-one **4a** in 95% yield (Table 1, entry 1) under sonic waves for 3 h, while 90% yield was found by stiring for 10 h (Table 1, entry 2). Compound **4a** was additionally confirmed by X-ray crystal structure analysis (Fig. 1).[13] It was found that ultrasound could enhance the reaction rates. This reaction can also work well in anhydrous CH_3OH (Table 1, entry 3). However, the reaction did not progress well in CH_2Cl_2, CH_3CN during 3 h (Table 1, entries 4–5). Considering the toxicity of the methanol, study was continued using CAN/C_2H_5OH system.

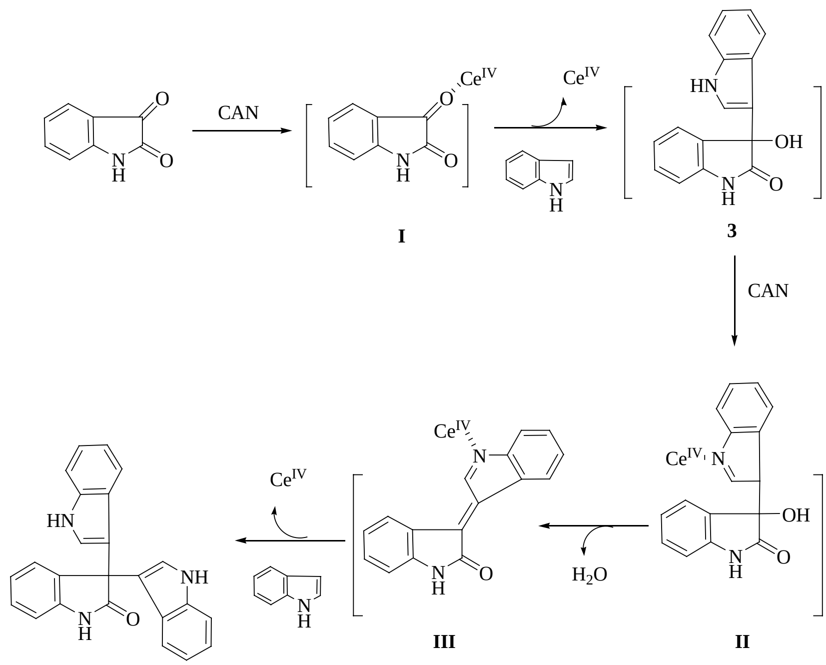
CAN was found to be an efficient catalyst in the view of handling, temperature, yields and reaction times as indicated in comparison to the reported methods. This was because of the mild Lewis acidity of CAN and a small quantity of the solvent needed. As shown in Table 2, this method worked with a wide variety of substrates. In most cases, the reaction proceeded smoothly to produce the corresponding 3-(3-oxoalkyl)indole **3** in good yield. The treatment of **1a** with indole **2e** afforded **4e** in 91% yield under identical condition (Table 2, entry 5). The substituents of the indole ring showed some effect on this conversion. When unactivated indoles such as **2h**, **2i** were used, there were no reaction under the same reaction conditions even for 10 h (Table 2, entries 8–9). Indole-2,3-diones **1**(**b–d**) could also react well with indoles **2a**, **2b**, respectively, which afforded the corresponding symmetrical 3,3-di(indolyl)indolin-2-ones **4**(**i–m**) in good to excellent yields. The results were summarized in Table 3.

The reaction was probably proceeded through the activation of carbonyl group **I** as well as the indole moiety by CAN as shown in Scheme 4. 3-Hydroxy-3-(1*H*-indol-3-yl)indolin-2-one **3** may be formed in situ as a key intermediate, which can not be obtained in this CAN–methanol system. In the following step, the N–H bond of **3** was activated by CAN to

Table 3. The reaction of **1b–1c** with indoles catalyzed by CAN under ultrasound irradiation condition[a]

Entry	Isatin	Indoles	Products	Time (h)	Yield (%)[b]
1	 **1b**	**2a**	 **4h**	2	85
2		**2b**	 **4i**	2	80
3	 **1c**	**2a**	 **4j**	3	90
4		**2b**	 **4k**	3	91
5	 **1d**	**2a**	 **4l**	3	88
6		**2b**	 **4m**	3	87

[a] All reactions were carried out under sonic conditions.
[b] Isolation yields.



Scheme 4.

give intermediate **II**, which lost of H_2O to afford **III**. The indole or pyrrole attacked **III** to give the TM and Ce^{IV}, which could be recycled to catalyze the reaction.

In order to prove the mechanism, intermediates 3-hydroxy-3-(1*H*-indol-3-yl)indolin-2-one **3**(**a–f**) were synthesized according to the reported methods.[14] We were pleased to find that the reaction of 3-hydroxy-3-(1*H*-indol-3-yl)indolin-2-one **3a** with indole **2a** in the presence of CAN (10 mol%) and anhydrous C_2H_5OH (2 ml) proceeded smoothly giving the 3,3-di(1*H*-indol-3-yl)indolin-2-one (**4a**) in 85% yield (Table 4, entry 1). This reaction can also be performed well by stirring to afford **4a** in 82% yield at room temperature.

Encouraged by this result, a number of other indoles were applied to this reaction (Scheme 5). The results were listed in Table 4. To our delight, **3a** smoothly reacted with substituted indole (**2b–e**) in the presence of CAN under sonic waves to afford the unsymmetrical 3,3-di(indolyl)indolin-2-ones (**5a–d**) in high yields (Table 4, entries 2–5) as expected. The reactions of **3a** with **2b** and **1b** with **2a** afforded the same product **5a** in 95, 84% yields under identical conditions, respectively.

It is well known that indole undergoes electrophilic substitution preferentially at their β-positions, which hold true for indoles but not for 3-substituted indoles such as 3-methyl-1*H*-indole.[15] The reaction of **3**(**a–f**) with 3-methylindole **2i** proceeded smoothly at 2-position giving the 3-indolyl-3-(3-methyl-1*H*-indol-2-yl)indolin-2-ones **6**(**a–f**) in good to excellent yields under identical conditions (Table 5, entries 1–6).

To further demonstrate the efficiency and scope of the reaction, pyrrole **7** was investigated. The reaction occurred at 2-position of pyrrole **7** predominantly while 3-substituted adducts could hardly be detected by analysis of the reaction mixture by ^{1}H NMR. A variety of (**3a–f**) and pyrrole **7** were examined to generate the desired products (**8a–f**) under sonic conditions. The results were summarized in Table 6. It should be noted that pyrrole **7** (3 mmol) and **3** (1 mmol) were used in this reaction.

In addition, the structures of the product **8c** was ascertained by spectroscopic methods, and the final proofs for the assigned structures were obtained by single-crystal X-ray analysis, respectively (Fig. 2).[13]

3. Conclusion

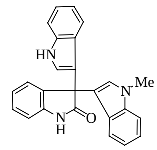
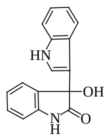
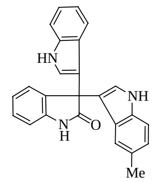
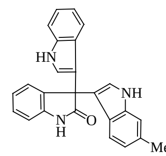
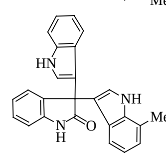
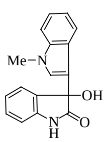
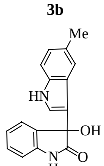
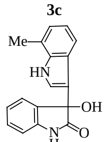
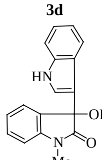
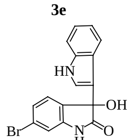
In conclusion, we have developed a simple, convenient and efficient protocol for **4**, **5**, **6**, **8** using catalytic amount of CAN under sonic conditions. At the same time, we proposed a plausible mechanism. In addition, using commercially available, easy to handle, inexpensive indole, pyrrole and the very mild conditions make this process a simple and convenient approach to obtain these compounds. It also makes it possible to design and synthesize of appropriately substituted symmetrical 3,3-di(indolyl)indolin-2-one derivatives and unsymmetrical 3-(indolyl)-3-(pyrrolyl)indolin-2-one derivatives as well as 3-(1*H*-pyrrol-2-yl)-3(1*H*-indol-3-yl)indolin-2-one derivatives, which are in progress in our laboratories.

4. Experimental

4.1. General

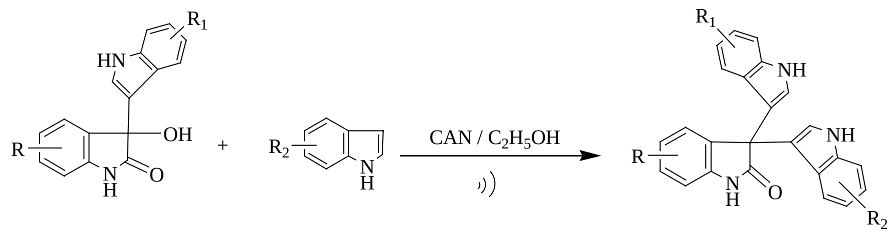
Melting points were recorded on an Electrothermal digital melting point apparatus and uncorrected. ^{1}H NMR (400 MHz)

Table 4. The reaction of **3a–f** with indoles **2** catalyzed by CAN[a]

Entry	1	Indole	Product	Time (h)	Yield (%)[b]	
1	**3a**	**2a**		**4a**	1 6[c]	85 82
2		**2b**		**5a**	5	95
3	 **3a**	**2c**		**5b**	3	80
4		**2d**		**5c**	5	95
5		**2e**		**5d**	5	84
6	 **3b**	**2a**		**5a**	1.5	84
7	 **3c**	**2a**		**5b**	1	90
8	 **3d**	**2a**		**5d**	3	90
9	 **3e**	**2a**		**4b**	1	92
10	 **3f**	**2a**		**4c**	1	92

[a] All reactions were carried out under sonication conditions.
[b] Isolated yields.
[c] The reaction was carried out under stir condition at room temperature.

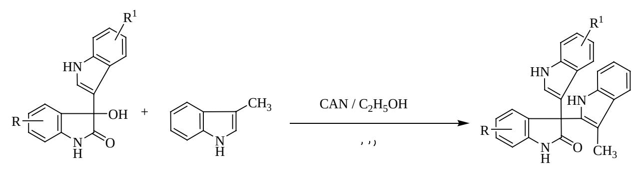
and ^{13}C NMR (100 MHz) spectra were recorded on a Varian Mercury MHz spectrometer in $CDCl_3$ or DMSO-d_6. IR Spectra were obtained on a Nicolet FT-IR500 spectrophotometer using KBr pellets. Elemental analysis was performed by a Carlo-Erba EA1110 CNNO-S analyzer. High-resolution mass spectra were obtained using GCT-TOF instrument. Ultrasound irradiation was performed in a KQ-250E ultrasonic cleaner with a frequency of 40 KHz and a normal power of 250 W. The reaction flask was located in the water bath of the ultrasonic cleaner, and the temperature of the water



3 **2a-e** R_1=R_2, **4** or R_1¡ÙR_2, **5**

Scheme 5.

Table 5. The reaction of **3**(**a**–**f**)with 3-methyl-1*H*-indole **2i**[a]

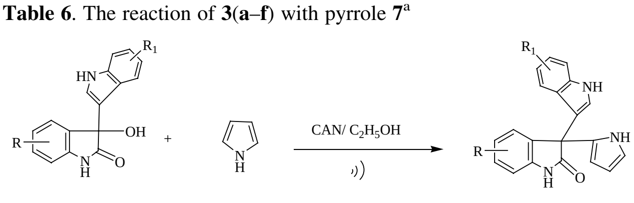


3 **2i** **6**

Entry	Sub.	Product	Time (h)	Yield (%)[b]
1	**3a**	**6a**	5	82
2	**3b**	**6b**	4	86
3	**3c**	**6c**	1	77
4	**3d**	**6d**	3	84
5	**3e**	**6e**	1	85
6	**3f**	**6f**	2	60

[a] All reactions were carried out under sonication conditions.
[b] Isolated yields.

Table 6. The reaction of **3**(**a**–**f**) with pyrrole **7**[a]



3 **7** **8**

Entry	Sub.	Product	Time (h)	Yield (%)[b]
1	**3a**	**8a**	1	88
2	**3b**	**8b**	1	85
3	**3c**	**8c**	1	85
4	**3d**	**8d**	1	83
5	**3e**	**8e**	1	82
6	**3f**	**8f**	1	80

[a] Compound **3** (1 mmol) and pyrrole **7** (3 mmol) were used, and all reactions were performed under sonication conditions.
[b] Isolated yields.

bath was controlled by 21circulative water. 3-Hydroxy-3-(1*H*-indol-3-yl)indolin-2-one derivatives **3**(**a**–**f**) [14] were prepared according to the literature methods.

4.2. Typical experimental procedure

A mixture of **1d** (0.225 g, 1 mmol), indole **2a** (0.117 g, 1 mmol), CAN (0.056 g, 0.1 mmol) and anhydrous C_2H_5OH (2 ml) was irradiated by ultrasound in a vessel until the disappearance of the starting isatin (1 h, monitored by TLC). After standing 1 h, the reaction mixture was washed by cool water (3×15 mL), warm water (2×10 mL) and cool ethanol (3×0.5 mL). The crude mixture was purified by flash chromatography to afford the pure product **4m** (0.39 g, yield: 88%).

4.2.1. 3,3-Di(1*H*-indol-3-yl)indolin-2-one, 4a. White solid; mp: >300 °C; IR (KBr): *ν* 743, 1099, 1467, 1617, 1690, 3056, 3123, 3399 (NH), 3440 (NH) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): *δ* 6.93–6.99 (m, 6H), 7.12–7.24 (m, 3H), 7.34–7.40 (m, 5H), 7.74 (br, s, 1H, NH), 8.10 (br, s, 2H, NH); HRMS [Found: *m/z* 363.1359 (M^+), calcd for $C_{24}H_{17}N_3O$: M, 363.1372].

4.2.2. 3,3-Bis(1-methyl-1*H*-indol-3-yl)indolin-2-one, 4b. White solid; mp: >300 °C (lit.,[6] 330–332 °C); IR (KBr): *ν* 1209, 1243, 1455, 1616, 1693, 2878, 2939, 3057, 3319 (NH) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): *δ* 3.71 (s, 6H, CH_3), 6.86 (s, 2H), 6.93–7.42 (m, 12H), 7.81 (br, s, 1H, NH); HRMS [Found: *m/z* 391.1686 (M^+), calcd for $C_{26}H_{21}N_3O$: M, 391.1685].

4.2.3. 3,3-Bis(5-methyl-1*H*-indol-3-yl)indolin-2-one, 4c. White solid; mp: >300 °C; IR (KBr): *ν* 751, 1107, 1235, 1466, 1614, 1712, 2853, 2914, 3386 (NH), 3413 (NH) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): *δ* 2.40 (s, 6H, CH_3), 6.78 (d, 2H, *J*=7.6 Hz), 6.93–7.00 (m, 5H), 7.14–7.40 (m, 5H), 7.54 (br, s, 1H, NH), 7.94 (br, s, 2H, NH); HRMS [Found: *m/z* 391.1667 (M^+), calcd for $C_{26}H_{21}N_3O$: M, 391.1685].

4.2.4. 3,3-Bis(6-methyl-1*H*-indol-3-yl)indolin-2-one, 4d. White solid; mp: 297–298 °C; IR (KBr): *ν* 754, 1102, 1235, 1471, 1620, 1698, 2853, 2913, 3172, 3319 (NH), 3433 (NH) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): *δ* 2.30 (s, 6H, CH_3), 6.94–7.02 (m, 7H), 7.17–7.35 (m, 5H), 7.49 (br, s, 1H, NH), 7.97 (br, s, 2H, NH); HRMS [Found: *m/z* 391.1681 (M^+), calcd for $C_{26}H_{21}N_3O$: M, 391.1685].

4.2.5. 3,3-Bis(7-methyl-1*H*-indol-3-yl)indolin-2-one, 4e. White solid; mp: 196–198 °C; IR (KBr): *ν* 747, 1101, 1343, 1470, 1089, 1455, 1487, 1617, 1699, 3054, 3410 (NH) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): *δ* 2.46 (s, 6H, CH_3), 6.85–7.00 (m, 8H), 7.18–7.24 (m, 3H), 7.40 (d, 1H, *J*=7.2 Hz), 7.73 (br, s, 1H, NH), 8.00 (br, s, 2H, NH); HRMS [Found: *m/z* 391.1671 (M^+), calcd for $C_{26}H_{21}N_3O$: M, 391.1685].

4.2.6. 3,3-Bis(5-(benzyloxy)-1*H*-indol-3-yl)indolin-2-one, 4f. White solid; mp: 198–200 °C; IR (KBr): *ν* 743, 1101, 1383, 1469, 1481, 1699, 2863, 2914, 3027, 3381 (NH), 3421 (NH) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): *δ* 6.85–7.00 (m, 8H), 7.15–7.49 (m, 19H), 7.91 (br, s, 2H, NH); HRMS

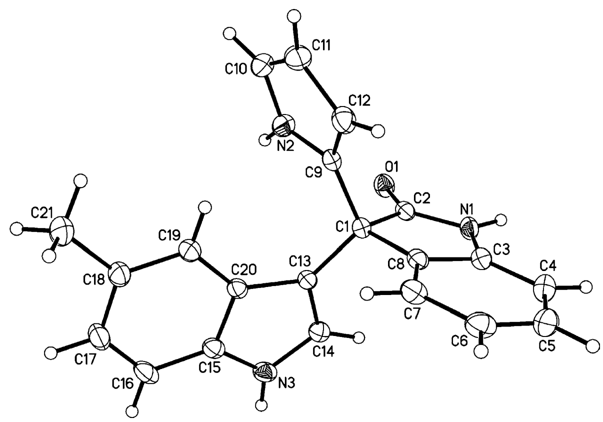


Figure 2. The crystal structure of **8c**.

[Found: *m/z* 575.2178 (M^+), calcd for $C_{38}H_{29}N_3O_3$: M, 575.2209].

4.2.7. 3,3-Bis(5-nitro-1*H*-indol-3-yl)indolin-2-one, 4g. Yellow solid; mp: >300 °C; IR (KBr): *ν* 739, 1090, 1250, 1260, 1470, 1620, 1709, 3346 (NH) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): *δ* 7.02–7.09 (m, 2H), 7.20–7.32 (m, 4H), 7.57 (d, 2H, *J*=8.4 Hz), 7.96 (d, 2H, *J*=8.4 Hz), 8.23 (s, 2H), 10.96 (br, s, 1H, NH), 11.81 (br, s, 2H, NH); HRMS [Found: *m/z* 453.1052 (M^+), calcd for $C_{24}H_{15}N_5O_5$: M, 453.1073].

4.2.8. 3,3-Di(1*H*-indol-3-yl)-1-methylindolin-2-one, 4h. White solid; mp: >300 °C (lit., 310 °C); IR (KBr): *ν* 742, 1091, 1351, 1610, 1668, 2929, 3051, 3116, 3357 (NH), 3440 (NH) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): *δ* 3.35 (s, 3H, CH_3), 6.91–7.03 (m, 6H), 7.12 (t, 3H, *J*=7.2 Hz), 7.32 (t, 4H, *J*=6.8 Hz), 7.41 (d, 1H, *J*=7.2 Hz), 8.04 (br, s, 2H, NH); HRMS [Found: *m/z* 377.1527 (M^+), calcd for $C_{25}H_{19}N_3O$: M, 377.1528].

4.2.9. 1-Methyl-3,3-bis(1-methyl-1*H*-indol-3-yl)indolin-2-one, 4i. White solid; mp: 233–235 °C (lit.,[6] 232–234 °C); IR (KBr): *ν* 746, 1087, 1469, 1606, 1722, 2924, 3049 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): *δ* 3.35 (s, 3H, CH_3), 3.70 (s, 6H, CH_3), 6.84 (d, 2H, *J*=8.0 Hz), 6.91–7.18 (m, 7H), 7.26–7.46 (m, 5H); HRMS [Found: *m/z* 405.1826 (M^+), calcd for $C_{27}H_{23}N_3O$: M, 405.1841].

4.2.10. 4-Bromo-3,3-di(1*H*-indol-3-yl)indolin-2-one, 4j. White solid; mp: >300 °C; IR (KBr): *ν* 733, 1106, 1615, 1702, 3047, 3330 (NH), 3378 (NH) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): *δ* 6.95 (d, 1H, *J*=7.0 Hz), 6.99–7.04 (m, 4H), 7.12–7.19 (m, 4H), 7.38 (d, 2H, *J*=8.0 Hz), 7.52 (d, 2H, *J*=9.2 Hz), 7.98 (br, s, 1H, NH), 8.12 (br, s, 2H, NH); HRMS [Found: *m/z* 443.0438 (M^+), calcd for $C_{24}H_{16}^{81}BrN_3O$: M, 443.0456].

4.2.11. 4-Bromo-3,3-bis(1-methyl-1*H*-indol-3-yl)indolin-2-one, 4k. White solid; mp: 281–283 °C; IR (KBr): *ν* 734, 1135, 1429, 1612, 1704, 2934, 3054, 3104, 3351 (NH) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): *δ* 3.74 (s, 6H, CH_3), 6.92 (s, 1H), 6.96–7.32 (m, 10H), 7.47 (d, 2H, *J*=8.0 Hz), 7.61 (br, s, 1H, NH); HRMS [Found: *m/z* 469.0768 (M^+), calcd for $C_{26}H_{20}^{79}BrN_3O$: M, 469.0790].

4.2.12. 6-Bromo-3,3-di(1*H*-indol-3-yl)indolin-2-one, 4l. White solid; mp: >300 °C; IR (KBr): *ν* 743, 1114, 1451, 1607, 1709, 3029, 3110, 3400 (NH), 3442 (NH) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): *δ* 6.81 (t, 2H, *J*=7.6 Hz), 6.85 (d, 2H, *J*=2.4 Hz), 7.02 (t, 2H, *J*=7.6 Hz), 7.10–7.16 (m, 3H), 7.21 (d, 2H, *J*=8.0 Hz), 7.35 (d, 2H, *J*=8.0 Hz), 10.74 (br, s, 1H, NH), 11.00 (br, s, 2H, NH); ^{13}C NMR (100.57 MHz, DMSO-d_6): 52.3, 111.7, 112.4, 113.6, 118.4, 120.3, 120.6, 121.0, 124.1, 124.4, 125.5, 126.7, 133.8, 136.9 143.0, 178.5; HRMS [Found: *m/z* 443.0450 (M^+), calcd for $C_{24}H_{16}^{81}BrN_3O$: M, 443.0456].

4.2.13. 6-Bromo-3,3-bis(1-methyl-1*H*-indol-3-yl)indolin-2-one, 4m. White solid; mp: 248–250 °C; IR (KBr): *ν* 734, 1337, 1612, 1690, 3049, 3169, 3359 (NH) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): *δ* 3.70 (s, 6H, CH_3), 6.84 (d, 2H, *J*=8.0 Hz), 6.95–7.34 (m, 11H), 8.39 (br, s, 1H, NH); HRMS [Found: *m/z* 471.0746 (M^+), calcd for $C_{26}H_{20}^{81}BrN_3O$: M, 471.0769].

A mixture of **3a** (0.225 g, 1 mmol), indole **2b** (0.117 g, 1 mmol), CAN (0.056 g, 0.1 mmol) and C_2H_5OH (2 ml) was irradiated by ultrasound in a vessel until the disappearance of the starting isatin (1 h, monitored by TLC). After standing 1 h, the reaction mixture was washed by cool water (3×15 mL), warm water (2×10 mL) and cool ethanol (3×0.5 mL). The crude mixture was purified by flash chromatography to afford the pure product **5a** (0.388 g, yield: 95%).

4.2.14. 3-(1*H*-Indol-3-yl)-3-(1-methyl-1*H*-indol-3-yl)indolin-2-one, 5a. White solid; mp: 298–300 °C; IR (KBr): *ν* 743, 1099, 1467, 1617, 1690, 3056, 3123, 3399 (NH), 3440 (NH) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): *δ* 1.99 (s, 3H), 6.77–6.86 (m, 4H), 6.90–7.03 (m, 3H), 7.06 (s, 1H), 7.17–7.25 (m, 4H), 7.35 (d, 1H, *J*=8.4 Hz), 10.60 (s, 1H), 10.83 (br, s, 1H, NH), 10.94 (br, s, 1H, NH); HRMS [Found: *m/z* 377.1523 (M^+), calcd for $C_{25}H_{19}N_3O$: M, 377.1528].

4.2.15. 3-(1*H*-Indol-3-yl)-3-(5-methyl-1*H*-indol-3-yl)indolin-2-one, 5b. White solid; mp: 281–283 °C; IR (KBr): *ν* 751, 1099, 1468, 1615, 1711, 3047, 2842, 2909, 3123, 3322 (NH), 3392 (NH) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): *δ* 2.31 (s, 3H), 6.94–7.38 (m, 13H), 7.55 (br, s, 1H, NH), 7.98 (br, s, 1H, NH), 8.07 (br, s, 1H, NH); HRMS [Found: *m/z* 377.1412 (M^+), calcd for $C_{25}H_{19}N_3O$: M, 377.1528].

4.2.16. 3-(1*H*-Indol-3-yl)-3-(6-methyl-1*H*-indol-3-yl)indolin-2-one, 5c. White solid; mp: 210–212 °C; IR (KBr): *ν* 743, 1100, 1470, 1616, 1712, 2858, 2914, 3055, 3405 (NH), 3440 (NH) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): *δ* 2.41 (s, 3H), 6.79 (d, 1H, *J*=7.6 Hz), 6.92–7.00 (m, 5H), 7.12–7.25 (m, 4H), 7.34–7.40 (m, 3H), 7.68 (br, s, 1H, NH), 7.94 (br, s, 1H, NH), 8.07 (br, s, 1H, NH); HRMS [Found: *m/z* 377.1523 (M^+), calcd for $C_{25}H_{19}N_3O$: M, 377.1528].

4.2.17. 3-(1*H*-Indol-3-yl)-3-(7-methyl-1*H*-indol-3-yl)indolin-2-one, 5d. Solid; mp: 240–242 °C; IR (KBr): *ν* 744, 1101, 1470, 1616, 1712, 2858, 2915, 3053, 3123, 3409 (NH) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): *δ* 2.47 (s, 3H), 6.87 (t, 1H, *J*=7.6 Hz), 6.94–7.40 (m, 12H), 7.70 (br, s, 1H, NH), 7.99 (br, s, 1H, NH), 8.07 (br, s, 1H, NH); HRMS

[Found: *m/z* 377.1518 (M^+), calcd for $C_{25}H_{19}N_3O$: M, 377.1528].

4.2.18. 3-(1*H*-Indol-3-yl)-3-(3-methyl-1*H*-indol-2-yl)indolin-2-one, 6a. Colorless needles; mp: 196–198 °C; IR (KBr): *ν* 738, 1107, 1471, 1615, 1724, 2852, 2970, 3052, 3365 (NH), 3441 (NH) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): *δ* 1.95 (s, 3H), 6.97–7.29 (m, 9H), 7.38 (t, 2H, *J*=7.6 Hz), 7.50 (t, 2H, *J*=8.4 Hz), 7.95 (br, s, 1H, NH), 8.12 (br, s, 1H, NH), 8.18 (br, s, 1H, NH); HRMS [Found: *m/z* 377.1494 (M^+), calcd for $C_{25}H_{19}N_3O$: M, 377.1528].

4.2.19. 3-(3-Methyl-1*H*-indol-2-yl)-3-(1-methyl-1*H*-indol-3-yl)indolin-2-one, 6b. Colorless needles; mp: 153–155 °C; IR (KBr): *ν* 742, 1470, 1615, 1714, 2852, 2914, 3047, 3350 (NH), 3395 (NH) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): *δ* 1.94 (s, 3H), 2.32 (s, 3H), 6.90 (d, 1H, *J*=2.4 Hz), 6.94 (d, 1H, *J*=7.6 Hz), 7.02 (t, 2H, *J*=7.6 Hz), 7.07–7.13 (m, 2H), 7.18 (d, 1H, *J*=7.2 Hz), 7.24 (d, 2H, *J*=8.0 Hz), 7.32 (d, 2H, *J*=7.6 Hz), 7.51 (d, 1H, *J*=7.2 Hz), 8.09 (s, 2H), 8.16 (br, s, 1H, NH); ^{13}C NMR (100.57 MHz, $CDCl_3$):9.2, 22.1, 54.2, 109.0, 110.0, 111.4, 111.6, 113.6, 118.8, 119.5, 121.6, 122.0, 123.3, 124.9, 126.1, 126.6, 128.9, 130.0, 130.4, 131.2, 133.4, 135.1, 135.9, 140.4, 178.4 (C=O); HRMS [Found: *m/z* 391.1673 (M^+), calcd for $C_{26}H_{21}N_3O$: M, 391.1685].

4.2.20. 3-(3-Methyl-1*H*-indol-2-yl)-3-(5-methyl-1*H*-indol-3-yl)indolin-2-one, 6c. Colorless needles; mp: 191–193 °C; IR (KBr): *ν* 743, 1099, 1470, 1616, 1715, 2852, 3914, 3057, 3407 (NH) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): *δ* 1.94 (s, 3H), 2.32 (s, 3H), 6.90 (d, 1H, *J*=2.4 Hz), 6.94 (d, 1H, *J*=7.6 Hz), 7.02 (t, 2H, *J*=7.6 Hz), 7.07–7.13 (m, 2H), 7.18 (d, 1H, *J*=7.2 Hz), 7.24–7.29 (m, 3H), 7.33 (d, 1H, *J*=6.4 Hz), 7.51 (d, 1H, *J*=7.6 Hz), 7.85 (br, s, 1H, NH), 8.10 (br, s, 1H, NH), 8.14 (br, s, 1H, NH); HRMS [Found: *m/z* 391.1681 (M^+), calcd for $C_{26}H_{21}N_3O$: M, 391.1685].

4.2.21. 3-(3-Methyl-1*H*-indol-2-yl)-3-(7-methyl-1*H*-indol-3-yl)indolin-2-one, 6d. Colorless needles; mp: 232–234 °C; IR (KBr): *ν* 737, 1470, 1614, 1716, 2858, 2975, 3057, 3123, 3289 (NH), 3359 (NH), 3439 (NH) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): *δ* 1.95 (s, 3H), 2.50 (s, 3H), 6.92–7.19 (m, 6H), 7.20 (d, 1H, *J*=8.4 Hz), 7.39 (d, 1H, *J*=7.2 Hz), 7.51 d, 1H, *J*=6.8 Hz), 7.18 (d, 1H, *J*=7.2 Hz), 7.24 (d, 1H, *J*=8.0 Hz), 7.32 (d, 1H, *J*=7.6 Hz), 7.71 (br, s, 1H, NH), 8.10 (br, s, 1H, NH), 8.12 (br, s, 1H, NH); HRMS [Found: *m/z* 391.1696 (M^+), calcd for $C_{26}H_{21}N_3O$: M, 391.1685].

4.2.22. 3-(1*H*-Indol-3-yl)-1-methyl-3-(3-methyl-1*H*-indol-2-yl)indolin-2-one, 6e. Colorless needles; mp: 161–163 °C; IR (KBr): *ν* 743, 1090, 1469, 1609, 1703, 2858, 2921, 3054, 3324 (NH), 3407 (NH) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): *δ* 1.90 (s, 3H), 3.33 (s, 3H), 6.93 (d, 1H, *J*=2.0 Hz), 6.96–7.21 (m, 7H), 7.34–7.40 (m, 3H), 7.48 (t, 2H, *J*=8.0 Hz), 8.10 (br, s, 1H, NH), 8.18 (br, s, 1H, NH); HRMS [Found: *m/z* 391.1670 (M^+), calcd for $C_{26}H_{21}N_3O$: M, 391.1685].

4.2.23. 6-Bromo-3-(1*H*-indol-3-yl)-3-(3-methyl-1*H*-indol-2-yl)indolin-2-one, 6f. White solid; mp: 208–210 °C; IR (KBr): *ν* 741, 1443, 1607, 1744, 3052, 3123, 3399 (NH), 3440 (NH) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): *δ* 1.90 (s, 3H), 6.78–7.39 (m, 13H), 10.33 (br, s, 1H, NH), 10.81 (br, s, 1H, NH); HRMS [Found: *m/z* 457.0590 (M^+), calcd for $C_{25}H_{18}^{81}BrN_3O$: M, 457.0613].

4.2.24. 3-(1*H*-Pyrrol-2-yl)-3(1*H*-indol-3-yl)indolin-2-one, 8a. White solid; mp: 175–177 °C; IR (KBr): *ν* 737, 759, 1106, 1469, 1614, 1708, 3326 (NH), 3430 (NH) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): *δ* 6.78 (t, 2H, *J*=8.0 Hz), 6.85 (s, 2H), 6.92 (t, 2H, *J*=8.0 Hz), 6.97–7.03 (m, 3H), 7.20 (d, 4H, *J*=8.4 Hz), 7.34 (d, 2H, *J*=8.4 Hz), 10.54 (br, s, 1H, NH), 10.92 (br, s, 2H, NH); HRMS [Found: *m/z* 313.1200 (M^+), calcd for $C_{20}H_{15}N_3O$: M, 313.1215].

4.2.25. 3-(1-Methyl-1*H*-indol-3-yl)-3-(1*H*-pyrrol-2-yl)indolin-2-one, 8b. White solid; mp: 266–268 °C (dec); IR (KBr): *ν* 743, 799, 1102, 1471, 1621, 1689, 2842, 2919, 3282 (NH), 3368 (NH) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): *δ* 2.17 (s, 3H, CH_3), 5.77 (s, 1H), 5.93 (d, 1H, *J*=2.8 Hz), 6.62 (s, 1H), 6.69–6.72 (m, 2H), 6.83 (d, 1H, *J*=8.4 Hz), 6.95 (t, 2H, *J*=7.6 Hz), 7.20–7.24 (m, 2H), 7.31 (d, 1H, *J*=8.0 Hz), 10.59 (br, s, 2H), 10.83 (br, s, 1H, NH); HRMS [Found: *m/z* 327.1363 (M^+), calcd for $C_{21}H_{17}N_3O$: M, 327.1372].

4.2.26. 3-(5-Methyl-1*H*-Indol-3-yl)-3-(1*H*-pyrrol-2-yl)indolin-2-one, 8c. White solid; mp: 253–255 °C (dec); IR (KBr): *ν* 732, 796, 1101, 1619, 1680, 2914, 3279 (NH), 3367 (NH), 3456 (NH) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): *δ* 2.17 (s, 3H, CH_3), 5.78 (s, 1H), 5.93 (d, 1H, *J*=2.4 Hz), 6.62 (s, 1H), 6.69–6.72 (m, 2H), 6.83 (d, 1H, *J*=8.4 Hz), 6.95 (t, 2H, *J*=7.2 Hz), 7.20–7.22 (m, 2H), 7.31 (d, 1H, *J*=7.2 Hz), 10.60 (br, s, 2H), 10.84 (br, s, 1H, NH); HRMS [Found: *m/z* 327.1360 (M^+), calcd for $C_{21}H_{17}N_3O$: M, 327.1372].

4.2.27. 3-(7-Methyl-1*H*-indol-3-yl)-3-(1*H*-pyrrol-2-yl)indolin-2-one, 8d. White solid; mp: 154–156 °C; IR (KBr): *ν* 742, 1101, 1470, 1619, 1689, 2975, 3055, 3296 (NH), 3388 (NH) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): *δ* 2.40 (s, 3H, CH_3), 5.78 (s, 1H), 5.93 (dd, 1H, *J*=2.8, 2.4 Hz), 6.62 (s, 1H), 6.65–6.70 (m, 3H), 6.74 (d, 1H, *J*=2.4 Hz), 6.80 (d, 1H, *J*=6.0 Hz), 7.22 (t, 2H, *J*=7.2 Hz), 7.31 (d, 1H, *J*=7.2 Hz), 10.60 (br, s, 2H), 10.94 (br, s, 1H, NH); HRMS [Found: *m/z* 327.1359 (M^+), calcd for $C_{21}H_{17}N_3O$: M, 327.1372].

4.2.28. 3-(1*H*-Indol-3-yl)-1-methyl-3-(1*H*-pyrrol-2-yl)indolin-2-one, 8e. White solid; mp: 138–140 °C (dec); IR (KBr): *ν* 742, 1088, 1470, 1610, 1698, 3054, 3410 (NH) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): *δ* 3.25 (s, 3H, CH_3), 5.76 (s, 1H), 5.92 (s, 1H), 6.69 (s, 1H), 6.78–6.83 (m, 3H), 7.00–7.04 (m, 2H), 7.14 (d, 1H, *J*=7.6 Hz), 7.31–7.39 (m, 3H), 10.69 (br, s, 1H), 11.00 (br, s, 1H, NH); HRMS [Found: *m/z* 327.1358 (M^+), calcd for $C_{21}H_{17}N_3O$: M, 327.1372].

4.2.29. 6-Bromo-3-(1*H*-indol-3-yl)-3-(1*H*-pyrrol-2-yl)indolin-2-one, 8f. White solid; mp: 184–186 °C (dec); IR (KBr): *ν* 742, 1110, 1479, 1610, 1712, 3374 (NH) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): *δ* 5.70 (s, 1H), 5.94 (s, 1H), 6.70 (s, 1H), 6.80–6.89 (m, 3H), 7.01 (t, 2H, *J*=7.4 Hz), 7.11–7.15 (m, 2H), 7.24 (d, 1H, $J=6.4$ Hz), 7.31 (d, 1H, $J=8.4$ Hz), 10.63 (br, s, 1H), 10.73 (br, s, 1H), 11.00 (br, s, 1H, NH); HRMS [Found: m/z 391.0320 (M^+), calcd for $C_{20}H_{14}^{79}BrN_3O$: M, 391.0320].

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Coupling and fast decarboxylation of aryloxyl radicals of 4-hydroxycinnamic acids with formation of stable *p*-quinomethanes

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This paper is dedicated to Keith Usherwood Ingold.

Abstract—The reaction at room temperature of 3,5-di-*tert*-butyl- and 3,5-di-methoxy-4-hydroxycinnamic acids **1** and **2** with the dpph˙ radical in acetone or other *non-hydroxylic* polar solvents yields interesting dimeric *p*-quinomethanes **10–16** characterized by a broad and strong absorption in the visible region. Although the yields appear to be low to moderate (10–40%), this simple synthesis affords quinones not otherwise obtainable, which contain an unsaturated γ-lactone ring (**14–16**). The structures have been elucidated by interpretation of ESI-MS, FT-IR and NMR spectral data. In particular, FT-IR spectra in a KBr matrix demonstrate the quinone nature of these compounds because of the presence of strong absorption bands at 1604–1640 cm^{-1} and allows excluding the presence of carboxylic acid groups in the molecules. Kinetic evidence and molecular structures suggest that the formation of these *p*-quinomethanes is best explained through an 8–8 C–C coupling of the aryloxyl radicals derived from **1** and **2** and a subsequent fast mono- or di-decarboxylation of the initial dimer by an S_E1-type mechanism. Further oxidation of the phenolic intermediates by dpph˙ yields the final quinones.

1. Introduction

Phenols (ArOH) are effective antioxidants because of their ability to react with peroxyl radicals, $RO_2^{\cdot}$, responsible for the autoxidation processes of organic materials.[1] Considerable information as to the antioxidant properties of phenols can be gained from the kinetic parameters and stoichiometry of reactions with the stable and commercially available nitrogen-centered radical, 2,2-diphenyl-1-picrylhydrazyl (dpph˙), because these parameters are correlated to those of ArOH/$RO_2^{\cdot}$.[2] This has justified an intense proliferation of studies on ArOH/dpph˙ reactions.

The mechanism and rate of ArOH/dpph˙ reactions depend largely upon the nature of phenol (vide infra) and the solvent in which these reactions occur. Recently, Litwinienko and Ingold[3] and, independently, Foti et al.[4] have demonstrated that in *alcohols* these reactions essentially proceed via an electron transfer (ET) step from the phenoxide anion ArO^- to dpph˙ (Reactions 1 and 2). 4-Hydroxycinnamic acids (HCA) are demonstrated to be ideal models to disclose this mechanism since the presence of the carboxylic acid groups strongly influences the ionization of phenolic OH and modulate the contribution of Reaction 2 over the direct H-atom transfer (Reaction 3).[4] In non-hydroxylic polar solvents, phenols are poorly ionized[5] and the reaction occurs through the direct and *slow* (since ArOH are hydrogen bonded to the solvent molecules)[6] transfer of the hydrogen atom from ArOH to dpph˙ (Reaction 3).

$$ArOH \rightleftarrows ArO^- + H^+ \tag{1}$$

$$ArO^- + dpph^{\bullet} \xrightarrow{H^+} ArO^{\bullet} + dpph-H \tag{2}$$

$$ArOH + dpph^{\bullet} \xrightarrow{slow} ArO^{\bullet} + dpph-H \tag{3}$$

$$2ArO^{\bullet} \xrightarrow{solvents} \text{various products} \tag{4}$$

Afterwards, additional work has revealed that the solvent effect plays another intriguing role in the products of the self-coupling reaction of aryloxyl radicals of HCA's, Reaction 4. For instance, in the case of sinapic acid **1**/dpph˙, Reaction 4 yielded in *methanol or ethanol* products that were totally transparent to the electromagnetic waves of the spectral region 400–800 nm. However, when this reaction was carried out in *acetone* successive scans of the UV–vis spectrum showed that the course of Reaction 4 was

Keywords: Sinapic acid; Cinnamic acids; dpph˙ radical; Decarboxylation; Free radical; *p*-Quinomethane; γ-Lactone.
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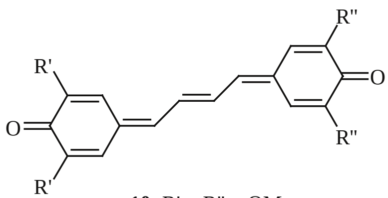
different since an intensely coloured product was formed. Chromatographic purification on silica gel of the reaction mixture gave a reasonable amount of this compound (yield 37%), which surprisingly proved to be nearly NMR-silent in many deuterated polar solvents (acetone, methanol, DMSO) (vide infra). In two solvents (CD_2Cl_2 and $CDCl_3$), however, we succeeded in obtaining excellent ^{1}H and ^{13}C NMR spectra, which revealed that this compound was the ethylene bis(*p*-quinomethane) **10**.



10: R' = R'' = OMe
11: R' = R'' = *tert*-Bu
12: R' = OMe; R'' = *tert*-Bu

The undoubted importance of this compound[7] and the peculiar mechanism by which it is formed (vide infra) led us to explore the behaviour of other HCA's (**1**–**8**, see Chart 1) with dpph$^\cdot$ (or MnO_2) in various non-hydroxylic polar solvents. We found that HCA **2** gave the corresponding dimeric *p*-quinomethane **11** as well, whereas the others did not except for 3,5-di-bromo-*p*-coumaric acid **3** and ferulic acid **6**, which gave traces of their corresponding *p*-quinomethanes. Using HCA's **1** and **2** in a 1:2 ratio (mol/mol) it was also possible to prepare the asymmetrical *p*-quinomethane **12**.

These reactions also afforded other oxidation products, which were isolated and characterized as another interesting group of stable quinones bearing an unsaturated γ-lactone ring (**14**–**16**).

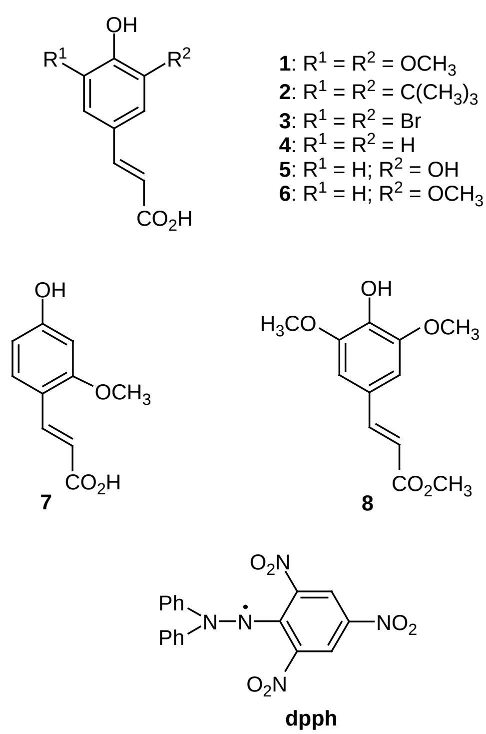
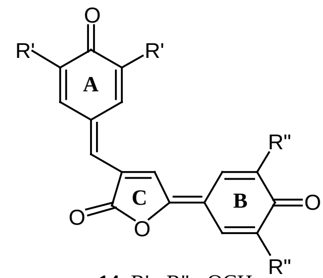


Chart 1. 4-Hydroxy cinnamic acids and relative derivatives employed in the present study.



14: R'= R''= OCH_3
15: R'= R''= $C(CH_3)_3$
16: R'= $C(CH_3)_3$
R''= OCH_3

Formation of C–C coupled dimers is not surprising in view of the fact that aryloxyl radicals undergo many of the reactions typical of oxygen and carbon radicals, such as C–C and/or C–O dimerization, isomerization, disproportionation, hydrogen abstraction and addition.[8] In fact, the chemistry of aryloxyl radicals has been investigated intensely during 1960s and early 1970s.[8,9] Various products of C–C and C–O coupling of the aryloxyl radicals derived from **1** and its methyl ester **8** have already been isolated[10,11] among which thomasidioic acid[12] (a phenolic lignan) is one of the major products. However, to the best of our knowledge in no case has formation of decarboxylated dimers been reported in mild oxidative reactions of cinnamic acids. Therefore, the *p*-quinomethanes **10**–**16** formed under our experimental conditions are even more interesting because they show that a process of mono- or di-decarboxylation has occurred spontaneously at room temperature at some stage of the reaction sequence (vide infra).

We therefore, report herein on the synthesis and spectral characterization of all these new compounds and propose a mechanistic rationale for their formation compatible with our kinetic data.

2. Results and discussion

2.1. Isolation and structure determination

In Figure 1 is reported the time evolution at 25 °C of the UV–vis spectrum of an acetone solution of dpph$^\cdot$ (0.12 mM) in which sinapic acid **1** was added to a final concentration of 1.28 mM. For comparison, the evolution of this reaction in *methanol* is also shown in the Inset (Fig. 1). The spectra in acetone show the formation of a compound with broad absorption bands in the visible region (λ_{max} at 508 nm) and which is responsible for the purplish colour of the solution. The UV–vis spectrum of this compound, isolated from the reaction mixture (see Section 4), is shown in Figure 2a. The large values of the molar extinction coefficient and λ_{max} (see Table 1) suggested a highly conjugated structure for **10**. The FT-IR spectrum in a KBr matrix also showed the presence of α,β-unsaturated carbonyl groups (1621.9, 1563.4 and 1548.5 cm^{-1})[13] and *unexpectedly the absence of carboxylic acid groups*. HPLC-ESI-MS spectrum of this compound in the positive ion-mode showed three peaks at *m/z*: 357, 379 (base peak) and 735. Since many compounds form adducts with adventitious alkali metals[14] and some of the above peaks could be due to such adducts, we deliberately used water/acetonitrile containing 0.1 mM LiCl as eluents in the HPLC-

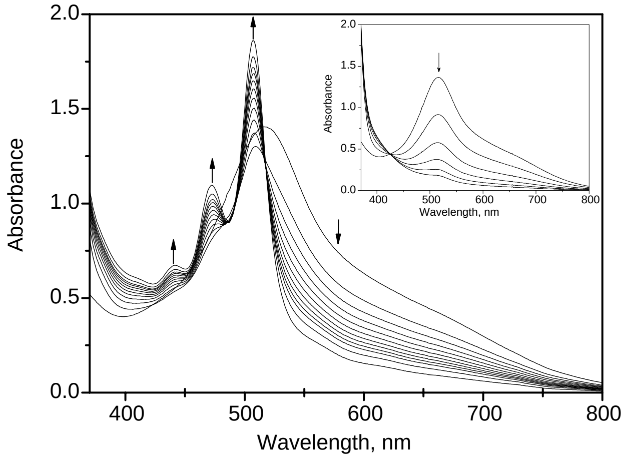


Figure 1. Spectral evolution of the reaction between sinapic acid **1** (1.28×10^{-3} M) and dpph$^{\cdot}$ (1.20×10^{-4} M) in acetone at 25 °C. Spectra were recorded at: 0; 6; 11; 21; 31; 46; and 76 s. Inset: spectral evolution of sinapic acid **1** (1.28×10^{-3} M) + dpph$^{\cdot}$ (1.25×10^{-4} M) in methanol at 25 °C at: 0; 1; 2; 3; 4; and 5 s.

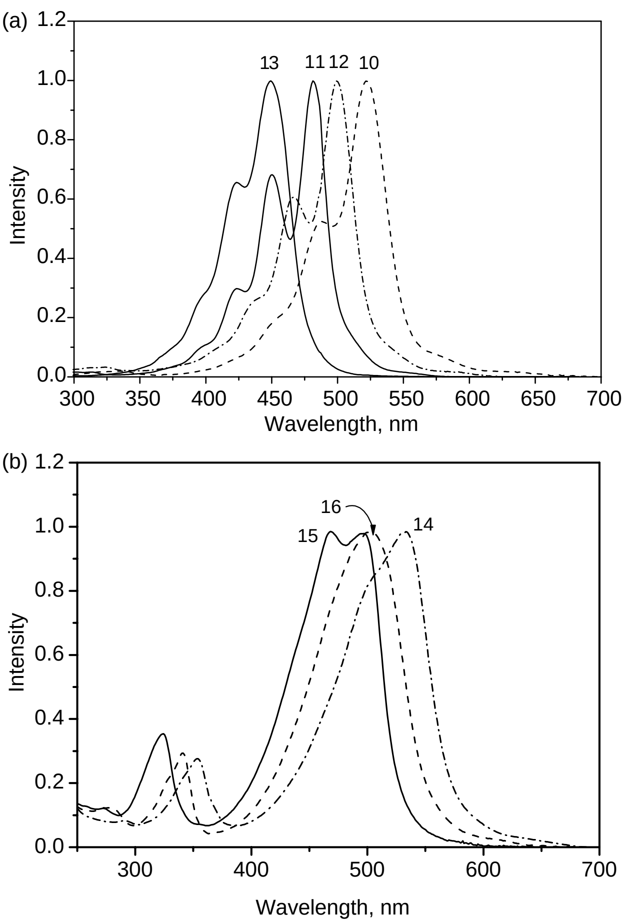


Figure 2. (a) Normalized UV–vis spectra of **10–13** obtained from the HPLC UV–DAD. The eluent composition during the readings was 20:80 water/acetonitrile for **10**; 15:85 water/acetonitrile for **12**; 100% acetonitrile for **11** and **13**. The values of λ_{max} and ε in CH_2Cl_2 are reported in Table 1. (b) Normalized UV–vis spectra of **14–16** obtained from the HPLC UV–DAD. The eluent composition during the readings was 15:85 water/acetonitrile for **14**; 10:90 water/acetonitrile for **16**; 100% acetonitrile for **15**. The values of λ_{max} and ε in CH_2Cl_2 are reported in Table 1.

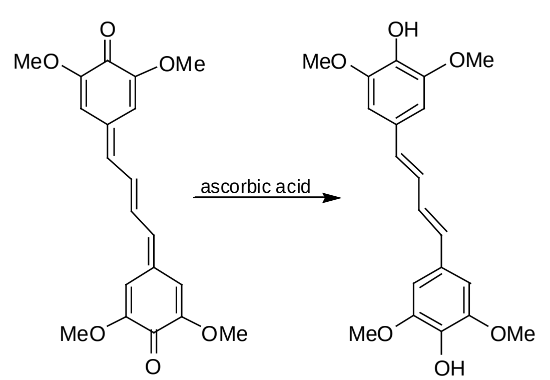
MS analyses. In the presence of LiCl, the spectrum essentially consisted of two peaks at *m/z*: 363 (base peak) and 719. Since

Table 1. FT-IR spectra in KBr and UV–vis spectra in CH_2Cl_2 of quinones **10–16**

Quinone	ν_{CO} (cm^{-1})	$\nu_{C=C}$ (cm^{-1})	λ_{max} (nm) ($\varepsilon/10^3$ M^{-1} cm^{-1})
10	1621.9	1563.4 1548.5	519 (110); 484 (56); 453 (21)
11	1605.3	1570.9 1557.6	486 (110); 454 (72); 427 (31)
12	1629.9 1607.7	1567.7 1551.7	502 (98); 468 (57); 440 (26)
13	1602.9		455 (54); 428 (36)
14	1782.6 1639.4 1621.6	1565.1	531 (40); 355 (13)
15	1781.2 1612.0	1572.6	507 (45); 477 (41); 324 (19)
16	1768.7 1640.7 1614.0	1566.2	503 (41); 344 (13)

the difference, 379−363=735−719=16 was equal to the difference in the masses of Na^+ and Li^+, the above signals were given by the following pseudo-molecular ions: $[M+H]^+$ (*m/z* 357); $[M+Na]^+$ (*m/z* 379); $[M+Li]^+$ (*m/z* 363); $[2M+Na]^+$ (*m/z* 735) and $[2M+Li]^+$ (*m/z* 719) and hence, we determined that the molecular weight of **10** was 356 ($C_{20}H_{20}O_6$ 356.38).

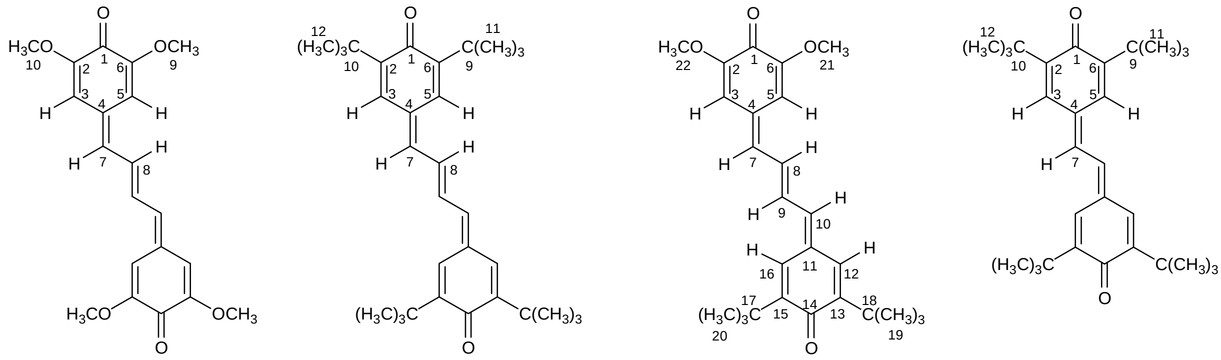
When we tried to record the NMR spectra of **10** for the final structure elucidation we unexpectedly observed that the ^{1}H NMR spectrum showed little information in many solvents (acetone, methanol, DMSO), that is, this quinone was demonstrated to be NMR-silent.[15] Addition of ascorbic acid into the NMR tube caused the bleaching of the solution and the appearance of the ^{1}H and ^{13}C NMR spectra reported in Section 4. These spectra, the pseudo-molecular peak $[M-H]^-$ at *m/z* 357, the appearance in the FT-IR spectrum in CH_2Cl_2 of a fairly sharp band at ca. 3529 cm^{-1} attributable to intramolecular H-bonded OH's[16] and finally the UV-spectrum, which was similar to that of 1,4-diphenyl-1,3-butadiene[17–19] prompted us to assign structure **10a** to this compound and, consequently, structure **10** to the oxidized form (Reaction 5). Contrary to the behaviour described above, we successively observed that in CD_2Cl_2 and $CDCl_3$ the *p*-quinomethane **10** gave both the ^{1}H and ^{13}C NMR spectra (see Table 2), which provided a further evidence of its structure.



10 **10a** (5)

One interesting aspect of the ^{1}H NMR spectrum of **10** in CD_2Cl_2 was represented by the splitting of the signals corresponding to the methoxy groups (δ_H 3.80 and 3.86) and

Table 2. ^1H and ^{13}C NMR spectra of quinones **10–12** in CD_2Cl_2 and quinone **13** in $(CD_3)_2CO$ at room temperature with respect to TMS



10 **11** **12** **13**

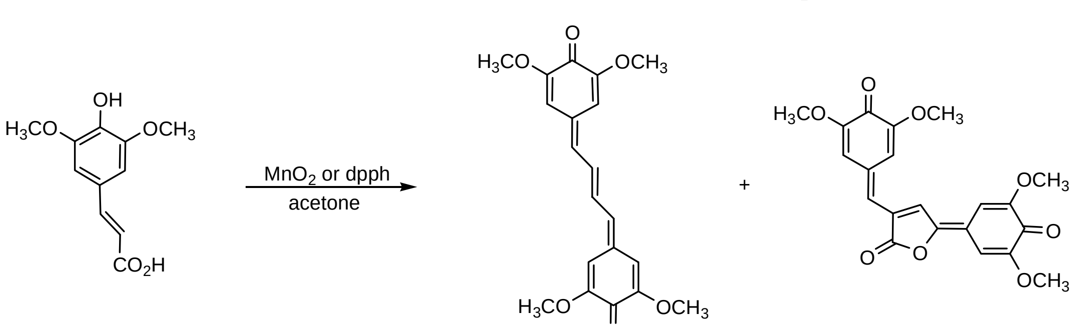
No.	δ_C	δ_H[a]	δ_C	δ_H[a]	δ_C	δ_H[a]	δ_C	δ_H[a]
1	174.4		186.6		174.4		186.6	
2	152.7		149.2		152.6		149.3	
3	111.3	6.38d 1.8	134.3	6.99d 2.3	111.2	6.37d 1.8	135.0	7.29d 2.4
4	132.8		134.6		132.9		136.9	
5	102.5	6.81d 1.8	125.3	7.50d 2.3	102.5	6.79d 1.8	125.5	7.80d 2.4
6	152.8		149.4		152.8		149.8	
7	138.0	6.90dd 2.6, 8.6	140.3	6.93dd 2.8, 8.4	137.8	6.93m	135.4	7.86s
8	133.6	7.33dd 2.6, 8.6	134.8	7.37dd 2.9, 8.4	133.4	7.35m		
9	55.6	3.91	35.4		134.4	7.35m	35.4	
10	55.6	3.85	35.9		139.9	6.93m	35.8	
11			29.6	1.36	133.9		[b]	1.34s
12			29.7	1.32	133.7	6.99d 2.4	[b]	1.31s
13					148.6			
14					186.0			
15					148.7			
16					124.7	7.50d 2.4		
17					34.9			
18					35.3			
19					29.0	1.32		
20					29.0	1.36		
21					55.5	3.90		
22					55.5	3.84		

[a] The values of δ_H are followed by multiplicity and coupling constants (Hz).
[b] The methyl carbon signals of the *tert*-butyl groups fall into the solvent signal (acetone).

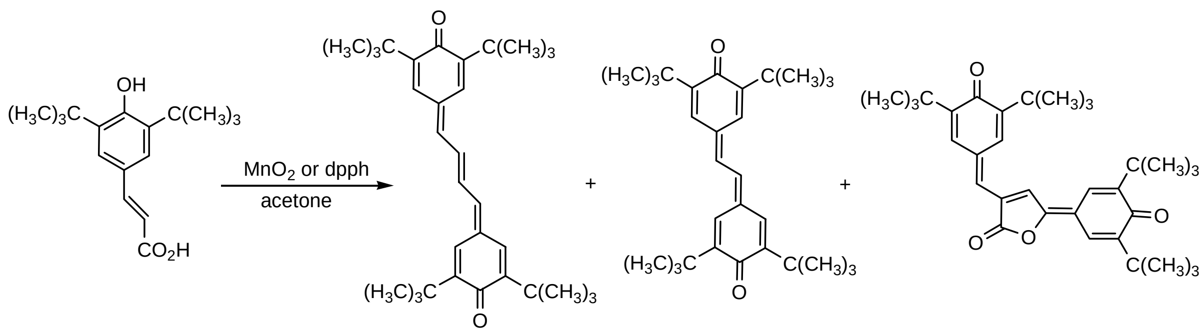
the ring protons (δ_H 6.33 and 6.76). A less pronounced splitting was also observed in the ^{13}C NMR spectrum for the pertinent carbon atoms (see Table 2). Similarly, the ^1H and ^{13}C NMR spectra of the other three *p*-quinomethanes **11–13** showed an analogous splitting (see Table 2).

This molecular asymmetry has previously been observed[20] with compound **13** and rationalized.[21] It is worth mentioning that in the case of **10a** the ^1H NMR spectrum showed one signal only for the four ring protons at about 6.67 ppm and only one for the four methoxy groups at about 3.88 ppm down to a temperature of 190 K.

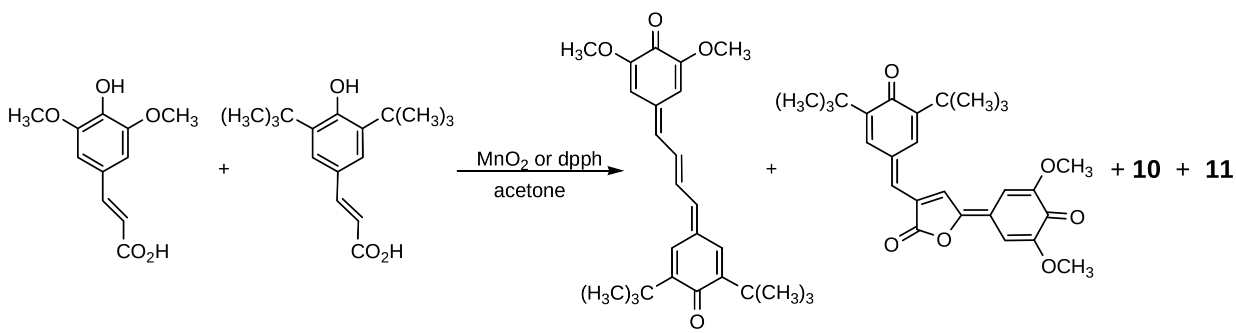
All *p*-quinomethanes **10–12** can also be prepared (yields 30–40%) by oxidation of HCA's at room temperature with activated MnO_2 in various solvents (see Section 4). The oxidation pattern with MnO_2 (evaluated by TLC analysis) was similar to that of dpph$^\bullet$ but the slightly higher yields allowed an easier isolation and characterization of the major reaction products (Reactions 6–8).



1 **10** (37%) **14** (10%) (6)



2 **11** (40%) **13** (<5%) **15** (20%) (7)



1 **2** **12** (22%) **16** (10%) (8)

The resemblance of the UV–vis and NMR spectra of quinone **11** to those of **10** (see Figure 2a and Table 2) allowed a straightforward recognition of its structure. In agreement, the ESI-MS spectrum in the positive ion-mode and in the presence of 1 mM LiCl in the acetonitrile phase showed the following peaks at *m/z* 483 $[M+Na]^+$; 467 $[M+Li]^+$ and 461 $[M+H]^+$ ($C_{32}H_{44}O_2$ 460.71).

The ^1H NMR spectrum of the asymmetric *p*-quinomethane **12** in CD_2Cl_2 solution revealed resonances of two non-equivalent MeO groups at 3.89 and 3.84 ppm and two non-equivalent *tert*-butyl groups at 1.36 and 1.32 ppm. Additional proton signals were observed at δ 6.93 (2H, m) and at 7.35 (2H, m), which could be assigned to the couples of protons H-7/H-10 and H-8/H-9, respectively, (see Table 2), on the basis of the correspondence with the resonance frequencies of H-7 and H-8 in the symmetrical quinones **10** and **11** (Table 2). The ring protons resonated as doublets at δ 6.37 (1H, $J=1.8$ Hz), 6.79 (1H, 1.8 Hz), 6.99 (1H, 2.4 Hz) and 7.50 (1H, 2.4 Hz). In this case, the correspondence in terms of coupling constants and chemical shifts with the ring protons of quinones **10** and **11** (see Table 2) allowed to assign the upfield signals, that is, 6.37 and 6.79 ppm, to the protons of the ring bearing the MeO groups and the downfield signals, that is, 6.99 and 7.50 ppm, to the ring with the *tert*-butyl groups.

The two carbonyl groups of **12** at positions 1 and 14 resonated in the ^{13}C NMR spectrum in CD_2Cl_2 at 174.4 and 186.0 ppm, respectively, as in the symmetric quinones **10** (174.4 ppm) and **11** (186.6 ppm) (see Table 2). This correspondence was also observed in the FT-IR spectra as the frequencies of CO stretching of the three quinones were 1621.9 cm^{-1} in **10**, 1606.3 cm^{-1} in **11**, and 1629.9 and 1607.7 cm^{-1} in **12** (see Table 1). Aside from the carbon signals of the *tert*-butyl and methoxyl groups, the ^{13}C NMR spectrum of **12** in CD_2Cl_2 showed 16 distinct carbon atoms versus the 8 carbon signals of the symmetric quinones **10** and **11**. HMQC, HMBC and NOESY 2D experiments (see Fig. 3) were done to establish the direct C–H bonds and the C–C connectivity.

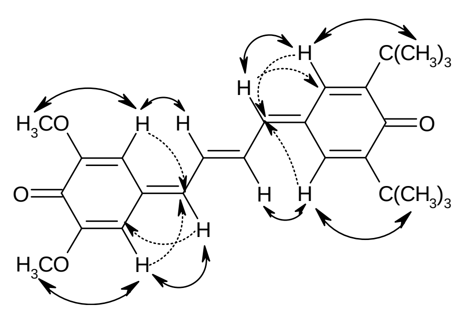


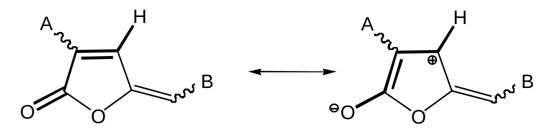
Figure 3. Selected HMBC (dotted line) and NOESY (solid line) correlations observed in the asymmetric quinone **12**.

Finally, the ESI-MS spectrum of **12** in the positive ion-mode and in the presence of 0.1 mM LiCl confirmed the structure assignment because of the presence of peaks at *m/z* 431 $[M+Na]^+$; 415 $[M+Li]^+$ and 409 $[M+H]^+$ ($C_{26}H_{32}O_4$ 408.54).

Quinones **14–16** were isolated from the reaction mixtures of **1**, **2** and **1**+**2** (1:2 mol/mol) with either $dpph^{\cdot}$ or MnO_2 in acetone at room temperature (yields ca. 10–20%, Reactions 6–8). Their UV–vis spectra are reported in Figure 2b and Table 1. The ^1H and ^{13}C NMR spectra reported in Table 3 indicated that compounds **14–16** shared the same gross molecular structure. Indeed, the proton spectrum of **14** in

CD_2Cl_2 showed the presence of four distinct signals in the range 3.86–3.94 ppm corresponding to four non-equivalent methoxy groups. In the case of compound **15**, three upfield signals at 1.33, 1.36 and 1.38 ppm (ratio 1:2:1, respectively) were observed and assigned to four *tert*-butyl groups. Two distinct signals of methoxy groups at 3.91 and 3.92 ppm and two distinct signals for two *tert*-butyl groups at 1.33 and 1.38 ppm were present in the spectrum of **16**. These spectral data therefore indicated the presence of two di-substituted benzene rings in each molecule. In addition, all ^1H NMR spectra in CD_2Cl_2 exhibited 4 sharp doublets (4H, $J\sim 1.8$–2.4 Hz), suggestive of two couples of *meta* benzene protons, and 2 sharp singlets (2H) in the spectral region 6.42–8.07 ppm, see Table 3.

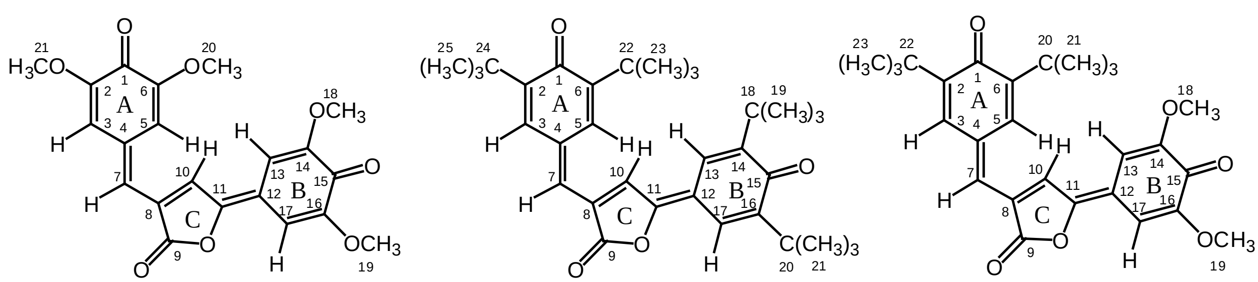
The presence of the γ-lactone moiety in **14–16** was deduced by a combination of NMR and IR spectroscopy. The FT-IR spectra in KBr suggested the presence of two different carbonyl groups ($\nu_{CO}\sim 1640$–1612 and $\nu_{CO}\sim 1780$–1770 cm^{-1}) one of which could be attributed to a quinone moiety (1640–1612 cm^{-1}) and the other one to a γ-lactone (1780–1770 cm^{-1}).[22] Resonance peaks at about 167 ppm in the ^{13}C NMR spectra in CD_2Cl_2 of **14–16** confirmed the presence of a γ-lactone moiety (see Table 3). Further, the presence of a considerably deshielded proton at about 8 ppm in the ^1H NMR spectra in CD_2Cl_2 and the extended π-electron system of these molecules, which were intensely coloured suggested an unsaturation α to the C=O and an additional exocyclic double bond on the carbon α to the O.



The above spectral data allowed the partial structures, that is, two *p*-quinomethane units and the γ-lactone unit, to be assembled into the structures given for **14–16**. The number of quaternary and C–H carbons observed in the ^{13}C NMR and DEPT spectra of **14–16** (i.e., 11 and 6, respectively) was consistent with the proposed structures as well as the HMQC, HMBC and NOESY 2D spectra. Figure 4 shows a few selected correlations observed in the HMBC and NOESY spectra of **15** and **16**.

In the case of **16**, the specific substitution of the rings A and B was deduced from the observed identity of the chemical shifts of the carbons and protons 3 and 5 with those of **15**, and 13 and 17 with those of **14**, see Table 3. This supported the conclusion

Table 3. ^1H and ^{13}C NMR spectra of quinones **14–16** in CD_2Cl_2 with respect to TMS



14 **15** **16**

No.	δ_C	δ_H[a]	δ_C	δ_H[a]	δ_C	δ_H[a]
1	174.6		186.2		186.2	
2	151.2		149.5		149.3	
3	111.7	6.42d 1.8	134.0	7.06d 2.2	134.1	7.06d 2.3
4	129.4		129.6		128.7	
5	104.4	7.14d 1.8	126.0	7.67d 2.2	126.1	7.68d 2.3
6	152.6		150.8		150.6	
7	129.0	6.80s	126.2	6.86s	126.7	6.87s
8	136.3		138.4		137.8	
9	167.1		167.2		167.1	
10	129.7	7.92s	131.1	8.07s	130.4	8.00s
11	153.6		152.9		151.1	
12	118.7		118.9		118.9	
13	102.4	6.58d 1.8	124.6	7.29d 2.4	102.2	6.56d 1.8
14	153.7		151.5		153.7	
15	174.6		185.9		174.6	
16	153.5		150.5		153.4	
17	102.6	6.97d 1.8	124.6	7.61d 2.4	102.5	6.95d 1.8
18	56.3	3.93s	35.4		56.2	3.91s
19	56.3	3.94s	29.0	1.36s	56.1	3.92s
20	56.1	3.86s	35.6		35.0	
21	55.6	3.92s	29.0	1.36s	29.0	1.38s
22			35.0		35.5	
23			28.9	1.38s	29.1	1.33s
24			35.7			
25			29.1	1.33s		

[a] The values of δ_H are followed by multiplicity and coupling constants (Hz).

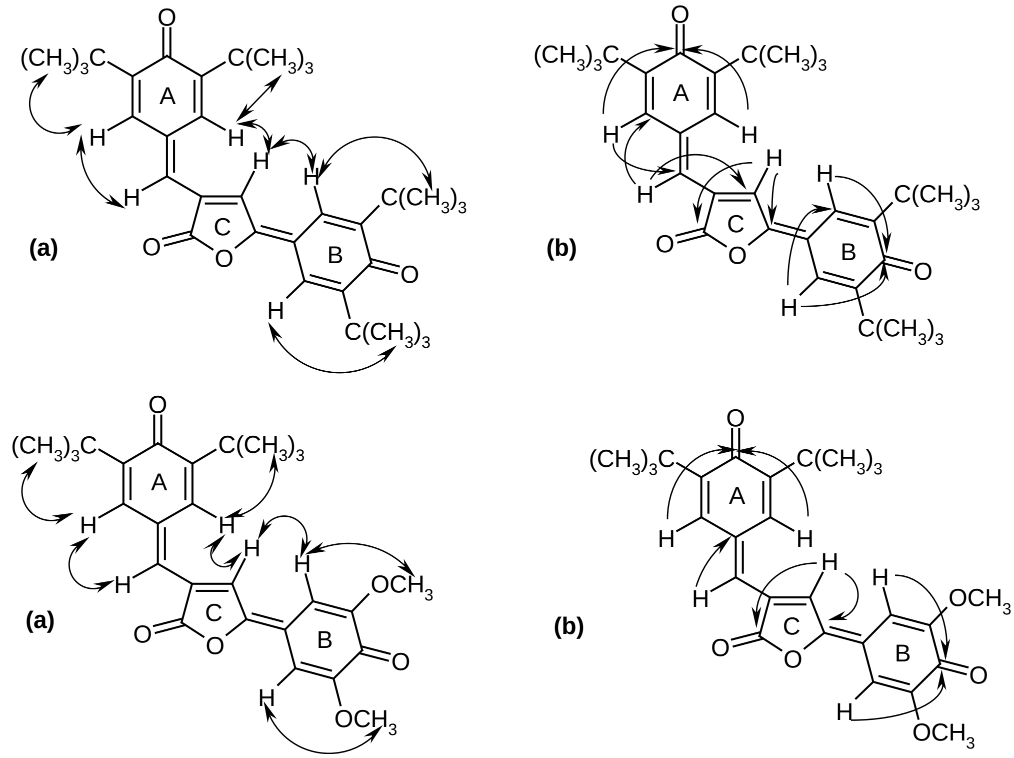


Figure 4. (a) Selected NOESY correlations observed in **15** and **16**; (b) selected HMBC correlations observed in **15** and **16**.

that the *t*-Bu groups were located on the ring A whereas ring B contained two MeO groups. Consistently, the NOESY spectrum of **16** (see Fig. 4) showed a correlation of H-7 (δ_H=6.87) with the nearest proton of the ring bearing the *t*-Bu groups, that is, H-3, δ_H=7.06. The transoid geometry of the protons 7 and 10 was deduced from the NOESY spectrum, which showed a marked correlation of H-10 with H-5 whereas there was no noticeable correlation between H-7 and H-10.

The ESI-MS spectra of quinones **14–16** were done in the positive ion-mode. For the analyses of **14** and **16** the eluents (water/acetonitrile) were added of 0.1 mM LiCl whereas in the case of **15**, which ionized with difficulty the LiCl concentration in the acetonitrile phase was increased to 1 mM. The MS spectrum of **14** showed peaks at *m/z* 437 $[M+K]^+$; 421 $[M+Na]^+$; 405 $[M+Li]^+$ and 399 $[M+H]^+$, which confirmed the structure assignment ($C_{21}H_{18}O_8$ 398.37). Analogously, the main peaks in the MS spectra of quinones **15** and **16** were at *m/z* 525 $[M+Na]^+$; 509 $[M+Li]^+$, 503 $[M+H]^+$ ($C_{33}H_{42}O_4$ 502.70) and 473 $[M+Na]^+$; 457 $[M+Li]^+$ and 451 $[M+H]^+$ ($C_{27}H_{30}O_6$ 450.54), respectively.

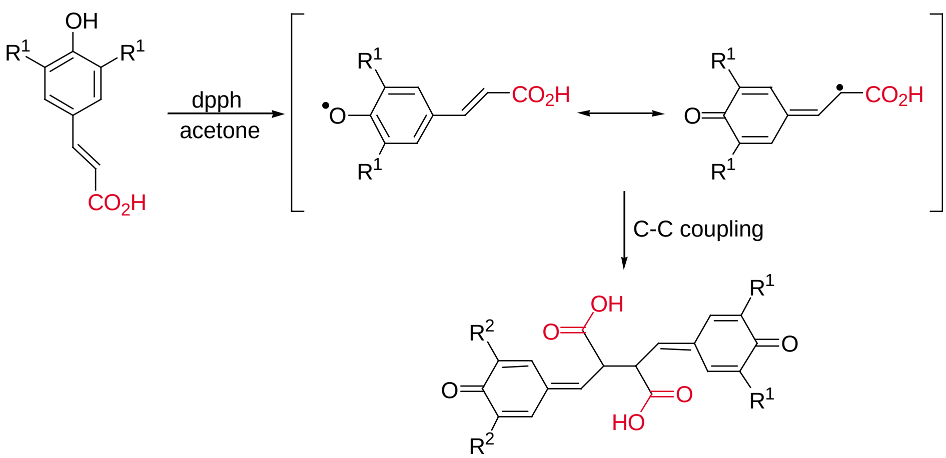
2.2. Kinetic aspects and mechanism

The molecular structures of **10–16** suggest that the formation of these *p*-quinomethanes proceeds through a C–C coupling of ArO˙ radicals at the positions 8 of the side chains (one exception is represented by **13**). The ArO˙ radicals are produced by H-atom abstraction from the phenolic OH of **1** and **2** by dpph˙ (or MnO_2), Reaction 3. The absence in the final products of one (**14–16**) or two (**10–12**) carboxylic groups is particularly surprising because of the mild conditions employed in our experiments. Decarboxylation of α,β-unsaturated carboxylic acids is known to take place with difficulty and usually requires vigorous experimental conditions[23] although for cinnamic acids the presence of *p*-OH seems to accelerate the process, which in any case requires comparatively high temperatures.[24] On the contrary, the intermediates involved in our reactions apparently undergo decarboxylation fairly readily. Under our experimental conditions, we observed that the free carboxylic acid group in the reacting HCA's **1** and **2** is of pivotal importance. Indeed, when the methyl ester **8** of sinapic acid **1** was allowed to react with dpph˙ in acetone at room temperature no traces of **10** or **14** were detected in solution.[25] The spectral changes observed during the reaction corresponded exclusively to the occurrence of Reaction 3 with a rate constant of $16\pm2\ M^{-1}\ s^{-1}$ and a stoichiometric factor[26] of ca. 1.0. The latter value demonstrates that once the aryloxyl radicals from **8** were formed in Reaction 3 they exclusively self-quenched (Reaction 4) without reacting further with dpph˙. It is interesting to observe that in the case of the reactions **1**+dpph˙ or **2**+dpph˙ carried out in acetone the stoichiometry was 1:2.

Very recently, Bietti and Capone[27] have provided spectroscopic evidence that arylethanoic acids, in the presence of $SO_4^{\cdot-}$ radicals (the oxidizing agent), lose CO_2 in water via an aromatic radical-cation formed after an ET process to $SO_4^{\cdot-}$ (with formation of SO_4^{2-} ions). Subsequently, the aromatic radical-cation undergoes fast intramolecular ET from the carboxylate anion to the ring followed by decarboxylation with formation of a resonance-stabilized benzyl radical either by a concerted or stepwise mechanism.[28]

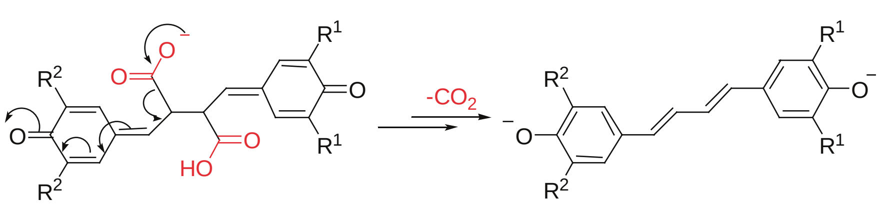
Unlike arylethanoic acids, in our case similar reactions cannot be invoked for the process of decarboxylation of the precursors of quinones **10–16** for at least two reasons. Firstly, once the radical-cations $\mathbf{1}^{\cdot+}$ or $\mathbf{2}^{\cdot+}$ were formed by ET from **1** or **2** to dpph$^{\cdot}$ they would rapidly lose a proton from the phenolic OH, affording the aryloxyl radical ArO$^{\cdot}$, long before the process of ionization of the carboxylic acid group since phenol radical-cations are strong acids[30] (in any case, the methyl ether of **1** demonstrated to be inert to dpph$^{\cdot}$ or MnO_2). Secondly, if a fraction of $\mathbf{1}^{\cdot+}$ or $\mathbf{2}^{\cdot+}$ were able to give the acyloxyl radical, that is, Ar–CH=CH–$CO_2^{\cdot}$, by ET from the carboxylate anion to the aromatic ring, this would likely react with the H-atom donors present in our system, (i.e., **1** or **2**, dpph-H and acetone) thus regenerating the parent phenol[31] since the process of decarboxylation of such a vinylacyloxyl radical is expected to be comparatively slow (lifetime of the order of microseconds).[31b–e]

In connection with the above arguments, it is important to point out that experiments carried out with dioxygen did not highlight formation of carbon-centered radicals, that is, Ar–CH=CH$^{\cdot}$, in our system. Generally, carbon radicals are known to react very quickly with the dioxygen dissolved in solution ($k \sim 10^9\ M^{-1} \times s^{-1}$).[32] If the actual mechanism of formation of **10–16** involved coupling of Ar–CH=CH$^{\cdot}$ in the presence of dioxygen there would not be any formation of C–C dimers.[33] Actually, the experiment showed that the yields of quinones **10** and **11** were unaffected by the presence or absence of oxygen in solution. Thereby, we can conclude that decarboxylation must occur after the 8–8 C–C dimerization of aryloxyls (Reaction 9).[35]

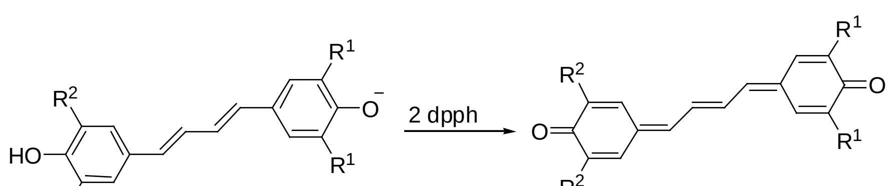


(9)

The initial C–C dimer formed in Reaction 9 may lose CO_2 via an S_E1 mechanism[36,24] (Reaction 10) followed by a fast oxidation of the phenolic intermediates (Reaction 11).



(10)



(11)

$R^1 = R^2$ = OMe; *tert*-Bu
R^1 = OMe
R^2 = *tert*-Bu

Reaction 9 is the rate-determining step for the formation of the quinones **10–16** in aprotic solvents and its rate is proportional to $[ArO^{\cdot}]^2$ (the rate constant can be close to the diffusion limit[37]). The steady-state concentration of ArO$^{\cdot}$ is essentially determined by the rates of Reaction 3 and of the overall processes of ArO$^{\cdot}$ quenching. The substituents present on phenols exert strong effects on the rate constant of Reaction 3. Electron-donating (ED) groups in the *ortho* and *para* positions of the phenol ring decrease the bond dissociation enthalpy (BDE) of OH and *increase* the rate of Reaction 3.[2,38] On the contrary, electron-withdrawing groups increase the OH BDE and *decrease* the rate of

ArO$^{\cdot}$ formation.[2,38] Therefore, the low yields observed in the reactions of HCA's **3** (bromine present in the *ortho* positions), **4** (no ED groups in the *ortho* positions), **6** (one only *ortho* ED group and intramolecular hydrogen-bond)[6] and **7** (one ED group in *meta* position) with dpph$^{\cdot}$ are readily explained. In the case of caffeic acid **5**, the rate constant of Reaction 3 is comparatively large because of the presence of two *ortho* OHs.[2] However, the main stabilization pathway of the semiquinone radical of **5** consists of an additional H-atom transfer to the dpph$^{\cdot}$ radical with formation of *ortho*-quinone therefore precluding the dimerization and subsequent reactions.

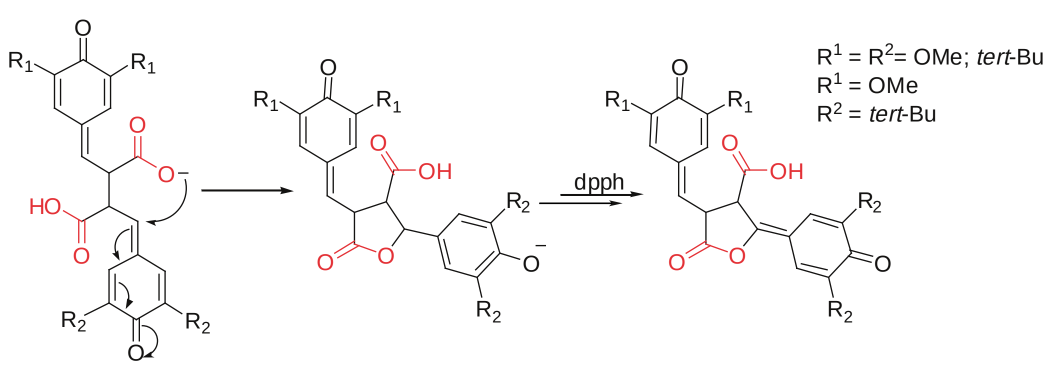
The reaction mechanism suggested above for the formation of quinones **10–12** justifies the presence of a few minor compounds found in solution. Traces of phenol **10a** were detected, for instance, during the oxidation of **1** with dpph$^{\cdot}$ or MnO_2 in acetone at room temperature although this phenol reacts quickly with dpph$^{\cdot}$, being $k_3(\mathbf{10a})=1130\pm 80\ M^{-1}\ s^{-1}$ and $n=2.0$. The presence of **10a** can be considered a convincing evidence of the occurrence of Reaction 10. Other minor compounds include quinones **14–16** bearing the γ-lactone moiety, which may originate from an intramolecular nucleophilic addition of the carboxylate anion to the opposite terminal methylene of the quinone system (Reaction 12). A subsequent S_E1 mechanism[36] of decarboxylation of the intermediate carboxylated γ-lactone and a stepwise oxidation by dpph radicals may lead to the final quinones bearing the unsaturated γ-lactone ring (Reaction 13).

that hydroxylic solvents support the ionization of Brønsted acids better than non-hydroxylic solvents of similar dielectric constant.[3–5,40] It seems likely, therefore, that the solvent plays an important role in the process of decarboxylation of the initial dimer (Reaction 10). In fact, similar solvent effects were reported for the unimolecular decarboxylation of substituted benzisoxazole-3-carboxylate anion.[41] Dramatic rate accelerations resulted if protic solvents (water, methanol or ethanol) were replaced by aprotic solvents. For instance, the rate of decarboxylation at 30 °C of 6-nitrobenzisoxazole-3-carboxylate ion in acetone resulted to be ca. 100,000 times larger than in methanol and ca. 3,300,000 times larger than in water![41]

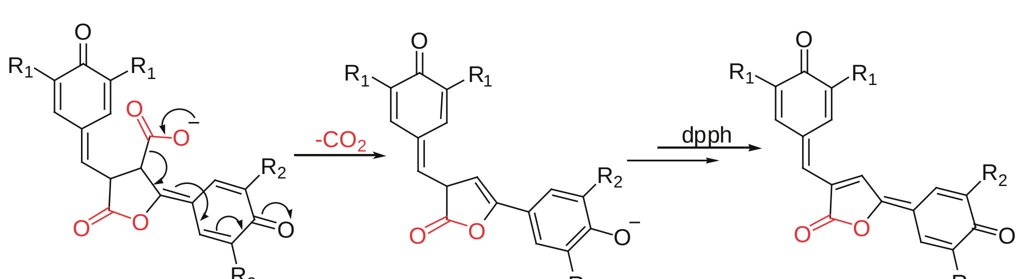
There are a number of potential explanations[42] for the inhibitory effect of alcohols but we consider it most probable that in these media the strong solvation of negative ions by hydrogen bonding is retarding decarboxylation of the initial dimer (Reaction 10) by stabilizing the carboxylate ion.[41]

3. Conclusion

We have described the synthesis and spectral identification of highly conjugated dimeric quinones **10–16** some of which bearing a peculiar unsaturated γ-lactone ring (**14–16**). The synthesis of these quinones consists of oxidizing 4-hydroxy cinnamic acids with dpph$^{\cdot}$ (or with MnO_2) in an appropriate solvent at room temperature, the process being most successful when: (i) the solvent is non-



(12)



(13)

Finally, the polar nature of the intermediates involved in the mechanisms outlined above may also explain the solvent effects observed on the yields and course of Reactions 6–8. We found that non-hydroxylic polar solvents with higher dielectric constants generally promoted the formation of quinones better than solvents with low dielectric constants.[39] In alcohols, however, no formation of quinones **10–16** was observed[39] at room temperature despite the fact

hydroxylic and of high dielectric constant; and (ii) the *ortho* positions to the phenolic OH of HCA are both occupied by bulky electron-donating groups.

The yields are low to moderate (10–40%) because of the many side reactions, however, the complex structure of these compounds makes these yields acceptable.

Kinetic data along with molecular structures and the presence in solution of a few intermediates suggest that the mechanism of formation of **10–16** with dpph˙ proceeds through four different steps: (1) formation of ArO˙ by H-atom transfer from HCA to dpph˙; (2) dimerization by 8–8 C–C coupling of two ArO˙ radicals; (3) fast decarboxylation at room temperature of the intermediate dimer by an S_E1-type mechanism; and finally, (4) oxidation of the intermediate phenolate anions by dpph˙.

4. Experimental

4.1. General

Cinnamic acids **1**, **4**, **6** were purchased from Fluka; ascorbic acid, dpph˙, cinnamic acid **2** were obtained from Aldrich and cinnamic acids **5** and **7** from Extrasynthèse. All compounds were used as received. The methyl ester **8** of sinapic acid was available from a previous work, its synthesis is described in Ref. 4. 3,5-Di-bromo-4-hydroxycinnamic acid **3** was donated by Dr. Paolo Bovicelli (ICB-CNR, Università La Sapienza, Roma) and its synthesis and spectral characterization will be reported in a separate paper. All solvents (Carlo Erba and Merck) were of the highest commercially available quality and were used without further purification (except for diethyl ether and THF, which were distilled prior to their use). NMR spectra were recorded at 400.13 MHz (^{1}H) and 100.62 MHz (^{13}C) in CD_2Cl_2 solutions at 298 K on a Bruker Avance^{TM} 400 spectrometer. Chemical shifts were referenced to the residual signal of CD_2Cl_2. HPLC analyses were done on an instrument (Waters 1525) equipped with ESI-MS (Waters Micromass ZQ) and UV–DAD (Waters 996) detectors (column: Phenomenex® Luna, C18, 250×4.6 mm (5 μm) at 20 °C using as eluent system H_2O/CH_3CN containing 0.1 or 1 mM LiCl). A double-ray Perkin Elmer Lambda 25 spectrophotometer was used for the kinetics and to record the UV–vis spectra whereas the FT-IR spectra were obtained with a Perkin Elmer Spectrum BX FT-IR System spectrophotometer. Analytical and preparative (silica gel, 20×20 cm, 0.5–1 mm thick) TLC plates and silica gel (63–200 μm) were purchased from Merck. The syntheses and purification reported in the following paragraphs for **10** and **14** with dpph˙ and **12** and **16** with MnO_2 are general and apply to all quinones. The purity of quinones **10–16** determined by HPLC analysis was not inferior to 95%.

4.2. Preparation of activated MnO_2

$MnSO_4\cdot 4H_2O$ (11 g) were dissolved in 15 ml of distilled water and the solution treated with 11.7 ml of 40% NaOH (solution A); 9.6 g of $KMnO_4$ were dissolved in 60 ml of hot distilled water (solution B). Then, the two solutions A and B were slowly mixed together in about 1 h under vigorous stirring. The final solution was centrifuged and the precipitate of MnO_2 washed with distilled water until the wash waters were colourless. The solid was then dried at 100–120 °C.

4.2.1. Preparation of 4,4′-(2-butene-1,4-diylidene)-bis(2,6-dimethoxy-2,5-cyclohexadien-1-one) 10 and 5-(3,5-dimethoxy-4-oxocyclohexa-2,5-dienylidene)-3-[(3,5-dimethoxy-4-oxocyclohexa-2,5-dienylidene)methyl]-furan-2(5*H*)-one 14 by using dpph˙. Sinapic acid **1** (200 mg, ca. 0.9 mmol) were allowed to react with 1.06 g of dpph˙ (2.69 mmol) in 300 ml of acetone at 25 °C in the dark for 2 h. After solvent removal, the crude product was purified by column chromatography on silica gel using ethyl acetate–hexane (80/20, v/v), acetone and methanol as eluents to give ca. 60 mg of **10** (final yield 37%) and ca. 20 mg of **14** (final yield 10%) as a dark violet powder. ^{1}H and ^{13}C NMR spectra were performed in dilute CD_2Cl_2 solutions and are reported in Tables 2 and 3. The UV–vis spectra are shown in Figures 2a and b whereas the FT-IR spectra are given in Table 1. The ESI-MS spectrum is discussed in Section 2.

4.2.2. Preparation of 4-[(3,5-di-*tert*-butyl-4-oxocyclohexa-2,5-dienylidene)but-2-enylidene]-2,6-dimethoxycyclohexa-2,5-dienone 12 and 3-[(3,5-di-*tert*-butyl-4-oxocyclohexa-2,5-dienylidene)methyl]-5-(3,5-dimethoxy-4-oxocyclohexa-2,5-dienylidene)furan-2(5*H*)-one 16 by using MnO_2. 3,5-Di-*tert*-butyl-4-hydroxycinnamic acid **2** (180 mg, 0.65 mmol) and sinapic acid **1** (75 mg, 0.33 mmol) were solubilized in 10 ml of acetone. The solution was then added with a syringe-pump (200 μl/min) to an initial suspension of 200 mg of MnO_2 in 1 ml of acetone (in the dark and under stirring) to which aliquots of 100 mg each of MnO_2 per 2 ml of phenol solution pumped were successively added (700 mg in total corresponding to 8 mmol). After 2 h the suspension was filtered and the solvent removed. The crude residue was then purified on a preparative TLC plate (20×20 silica gel, 1 mm thick) using hexane–acetone (90/10) as eluent to give 30 mg of **12** (yield 22%) and 12 mg of **16** (yield 10%). The UV–vis and FT-IR spectra are reported in Figures 2a and b and in Table 1. ^{1}H and ^{13}C NMR spectra performed in dilute CD_2Cl_2 solutions are reported in Tables 2 and 3. The ESI-MS spectra are reported in Section 2.

4.2.3. Purification of 4,4′-(2-butene-1,4-diylidene)-bis(2,6-di-*tert*-butyl-2,5-cyclohexadien-1-one) 11, 4,4′-(1,2-ethanediylidene)-bis(2,6-di-*tert*-butyl-2,5-cyclohexadien-1-one) 13 and 5-(3,5-di-*tert*-butyl-4-oxocyclohexa-2,5-dienylidene)-3-[(3,5-di-*tert*-butyl-4-oxocyclohexa-2,5-dienylidene)methyl]furan-2(5*H*)-one 15. These quinones can be obtained with both methods reported above. Their purification can be accomplished by column chromatography on silica gel or preparative TLC (silica gel) using hexane–THF (95/5) (final yields, 40% for **11** and 20% for **15**). Quinone **13** was obtained in very low yield (<5%); however, it was possible to characterize this molecule and its UV–vis and FT-IR spectra are reported in Figure 2a and Table 1. The NMR spectra are reported in Table 2; the ESI-MS spectrum obtained in the presence of 1 mM LiCl in the acetonitrile phase showed the following peaks at *m*/*z* 441 $[M+Li]^+$ and 435 $[M+H]^+$ ($C_{30}H_{42}O_2$ 434.67).

4.2.4. Synthesis of 1,4-di(4-hydroxy-3,5-dimethoxyphenyl)-1,3-butadiene 10a. This phenol was obtained by reduction of **10** with ascorbic acid using the following procedure: 4 mg of **10** (0.011 mmol) were dissolved in 2 ml of CH_2Cl_2–CH_3OH (1/1 v/v) then 3.9 mg of ascorbic acid (0.022 mmol) were added. The solution was shaken at 35–45 °C for ca. 1 h in the dark. After solvent removal, compound **10a** was extracted from the residue with CH_2Cl_2 (3×1 ml). The evaporation of the solvent yielded **10a** as a pale yellow solid in a quantitative yield. ^{1}H NMR (CD_2Cl_2) (numbering system: OH on C-1 and C-7 and C-8 on the butadiene chain), $\delta = 3.88$ (s, 12H, OCH_3), 5.54 (s, 2H, OH), 6.54 (dd, $J = 11.6$, 2.4 Hz, 2H, H_7), 6.67 (s, 4H, $H_{3,5}$), 6.83 (dd, $J = 11.6$, 2.4 Hz, 2H, H_8). ^{13}C NMR ($CDCl_3$) $\delta = 56.08$ (OCH_3), 103.14 ($C_{3,5}$), 127.31 (C_8), 128.88 (C_4), 131.80 (C_7), 134.78 (C_1), 147.13 ($C_{2,6}$). FT-IR (CH_2Cl_2, cm^{-1}) 3528.97 (m, OH), 1616.10 (m), 1601.0 (m), 1511.79 (s). The UV–vis spectrum in methanol shows a maximum at 354 nm $\varepsilon = (5.4 \pm 0.2) \times 10^4$ M^{-1} cm^{-1}. The HPLC-ESI-MS (water/acetonitrile) spectrum of **10a** in the negative ion-mode showed peaks at *m/z* 737 $[2M-H]^-$; 357 $[M-H]^-$ (base peak); 342 and 327 ($C_{20}H_{22}O_6$ 358.39).

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33. Dimerization of carbon-centered radicals, $R^{\cdot}$, is a diffusion-controlled process as well, that is, $k \sim 10^9\ M^{-1}\ s^{-1}$.[34] However, the rate of reaction of $R^{\cdot}$ with O_2 would largely be predominant because the concentration of oxygen in solution is exceedingly high ($\sim 10^{-3}$ M).
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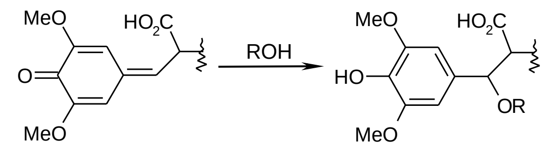
42. For instance, it is possible that in the alcohols the following addition reaction to the dimer takes place:



This reaction is, however, evaluated to be comparatively slow. In the case of a methyl *p*-quinomethane, the rate constant relative to the addition of neutral methanol has been reported to be 0.031 s^{-1} at 23 °C and ca. 500 times lower for the addition to a more stable *p*-quinomethane.[21] Other evidence in support of the poor importance of this reaction is given by the fact that the yield of formation of **10** is not significantly enhanced in the sterically hindered *tert*-butyl alcohol.[39]

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Stereoselective synthesis and functionalization of 4-heterosubstituted β-lactams

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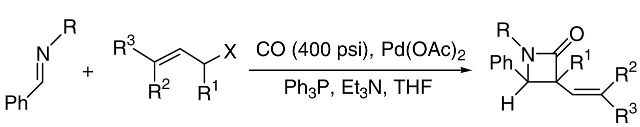
Abstract—Polyfunctionalized β-lactams were prepared with high stereoselectivity in an efficient manner. A palladium-catalyzed [2+2] carbonylative cycloaddition of allyl bromide with heteroaryliden-anilines afforded 2-azetidinones *N*-phenyl substituted, with an heteroaryl moiety linked at the C-4 carbon, and an alkenyl group at the C-3 carbon. The C-3 and the C-4 positions could be further functionalized inserting alkyl and hydroxyl groups in the azetidinone ring, through the generation of a stable azetidinyl anion then captured by various electrophiles.

1. Introduction

After the discovery of the penicillins and the cephalosporins, the past few decades have witnessed a remarkable growth in the field of β-lactam chemistry, as this heterocycle is a strategic component of various antibacterial agents.[1,2] The need for potent and effective β-lactam antibiotics, as well as more effective enzyme inhibitors, has motivated synthetic organic chemists to design new functionalized 2-azetidinones.[3,4] Applications of β-lactams in medicinal chemistry include their use as therapeutic agents for lowering the cholesterol level in plasma,[5,6] as *anti*-cancer agents,[4,7–9] and as enzyme inhibitors (for examples inhibitors of HLE[10] and cysteine proteases).[11]

Among the numerous synthetic protocols reported, a versatile and effective approach to the β-lactams preparation is the transition metal-catalyzed carbonylation of imines with allyl phosphate.[12,13] Recently, we reported the syntheses of alkenyl β-lactams in good yields and high selectivity by Pd-catalyzed [2+2] cycloaddition of allyl halides and simple imines under CO pressure[14] (Scheme 1).



Scheme 1.

In our opinion, the presence of an heterocycle as an additional substituent of the azetidinone ring should increase the solubility of these structures in polar medium. Moreover, the resulting greater susceptibility to synthetic elaborations should favour an increased and various biological activity. To our knowledge, only few examples of 4-heterosubstituted β-lactams are reported in the literature, such as the preparation of *N*-unsubstituted β-lactams bearing 2-furyl substituent at the C-4 carbon.[15] Therefore, in this paper we report the synthesis of novel alkenyl *N*-phenyl-4-heterosubstituted β-lactams, following the synthetic protocol described above, and especially the further and various functionalization of the β-lactam ring.

2. Results and discussion

The heteroaryl imines used in these reactions were prepared, in good yields, by coupling reactions of aniline with the appropriate aldehydes, according to Taguchi's method.[16] The results are collected in Table 1. The compound with a phenyl substituent was prepared and is reported for comparison with the heteroaryl groups (entry 6).

The imines **1–6** (1 mmol) were reacted with allyl bromide (1.5 mmol) by [2+2] cycloaddition, under CO pressure (400 psi), in the presence of Et_3N (2 mmol) and 2 mol% of $Pd(OAc)_2$ complexed by 8 mol% of Ph_3P, for 30–35 h. The catalytic species involved in the process is Pd(0), according to the mechanism previously reported.[17] The cycloaddition results are collected in Table 2.

The alkenyl 4-heterosubstituted β-lactams were isolated with high stereoselectivity: the obtained trans/cis ratios

Keywords: Alkenyl β-lactams; Electrophiles; Cabonylative cycloaddition; Stereoselectivity.
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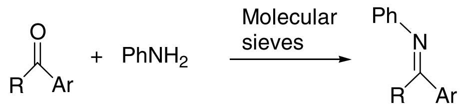
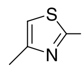
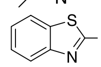
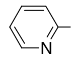
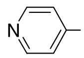
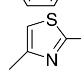
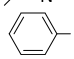
Table 1. Synthesis of imines **1–6**



1-6

Entry	R	Ar	Imine	Yield (%)[a]
1	H		**1**	70
2	H		**2**	86
3	H		**3**	72
4	H		**4**	84
5	CH_3		**5**	60
6	CH_3		**6**	78

[a] Isolated yields.

were always high, except for entries 5 and 6 (Table 2). In these cases, the presence of two groups (methyl and aryl) on the starting imines reduced the stereoselectivity of the cycloaddition reaction. Moreover, when the heterocycle was benzothiazole (entry 2), two new products **2c** and **2d** were observed, together with the expected compounds **2a** and **2b**. The **2c** and **2d** amounts were small, but they increased for longer reaction times. Their formation should be due to the isomerization of **2a** and **2b** to the more stable α-β-unsaturated carbonyl structures. For instance, when **2a** and **2b** were warmed up with Et_3N in THF, an analogous transformation was observed.

The trans and cis configurations of the β-lactam ring, have been assigned on the basis of the $^3J_{H-H}$ coupling constants between the two protons at the C-3 and the C-4 carbon atoms, ($J_{cis} > J_{trans}$).[18,19] Moreover, the spectroscopic data have been compared to those obtained for similar β-lactams previously characterized by X-ray crystallography.[17] For compounds showing a methyl group linked at C-4 or C-3, the relative configuration was assigned from the coupled ^{13}C NMR spectra. A very small or negligible $^3J_{CH_3-H}$ coupling constant corresponded to a trans configuration, while a larger $^3J_{CH_3-H}$ ($\sim 0.5 \div 1.7$ Hz) corresponded to a cis configuration.[20] These latter configurations were confirmed also by the 400 MHz-NOESY spectra. The differentiation between the two isomers **2c** and **2d** was made from the ^1H NMR spectra: the *Z* isomer displayed its vinylic proton with an upfield chemical shift, whereas the *E* compound showed a downfield chemical shift as this proton is in the deshielding region of the neighbouring carbonyl group.[21–23]

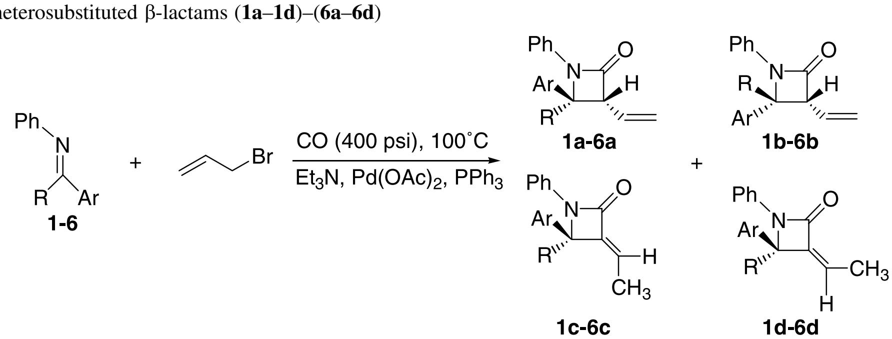
The 2-azetidinones **1a–4a** and **1b–4b** show two types of acidic protons, linked to the C-3 and the C-4 carbon atoms. The deprotonation of either of them would lead to the formation of an azetidinyl anion stabilized by a large conjugation: by structures A, B, and C in the deprotonation of the C-3 carbon, by structures D, E and by an additional inductive effect of the β-lactam nitrogen, in the deprotonation of the C-4 (Scheme 2).

However, when the *trans*-(**1a–3a**) β-lactams (1 mmol) were treated with LDA (1.2 mmol) in THF, at −78 °C, we noticed that the deprotonation occurred exclusively at the C-3 allylic carbon. Then, adding an electrophile (E^+, 1 mmol), the carbanion was trapped affording four different quenching products, resulting from A and/or C anions, according to the suggested mechanism of Scheme 2.

The results of the functionalization of **1a–3a** with various electrophiles are collected in Table 3.

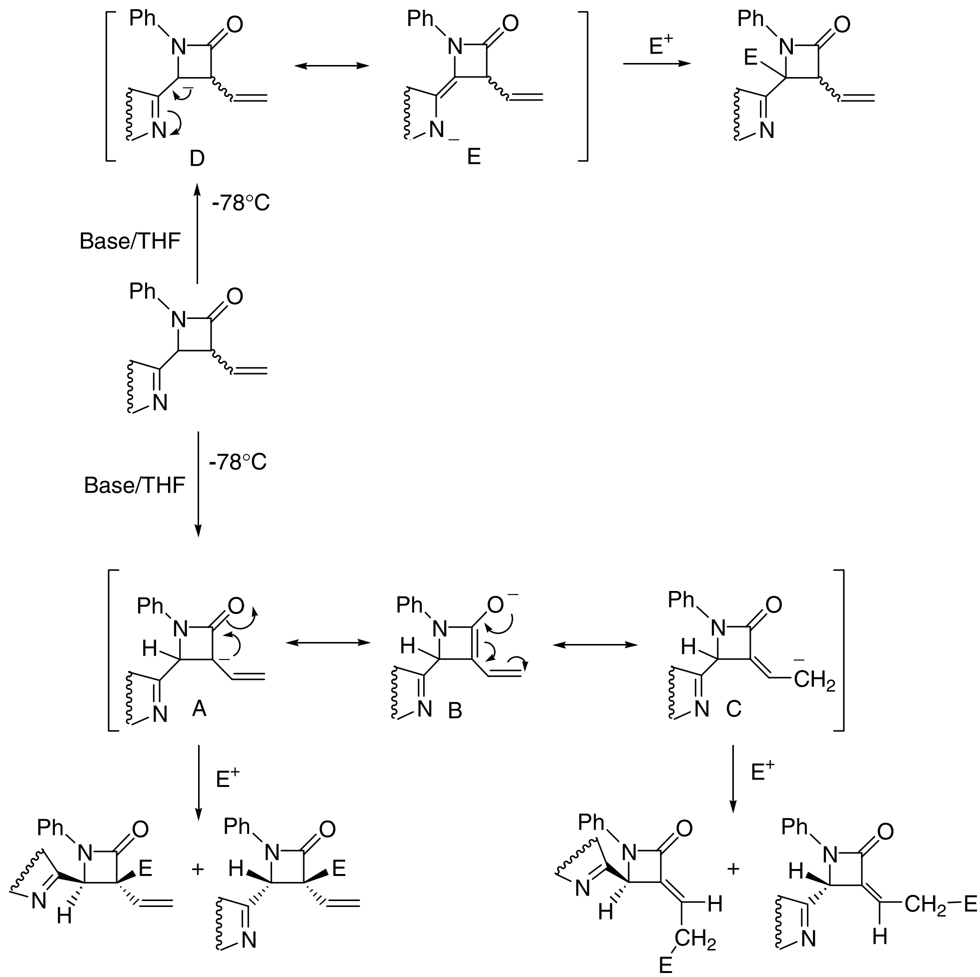
All the reactions performed with **1a** showed high yields. Using small electrophiles such as H^+ or D^+, equimolecular mixtures of cis and trans diastereomers were observed (entries 1 and 2). When alkyl halides were used, the reaction became highly diastereoselective, the cis isomer being the major reaction product (entries 3 and 5). With benzyl chloride (entry 4), in addition to the expected cis product **9b**,

Table 2. Synthesis of 4-heterosubstituted β-lactams (**1a–1d**)–(**6a–6d**)



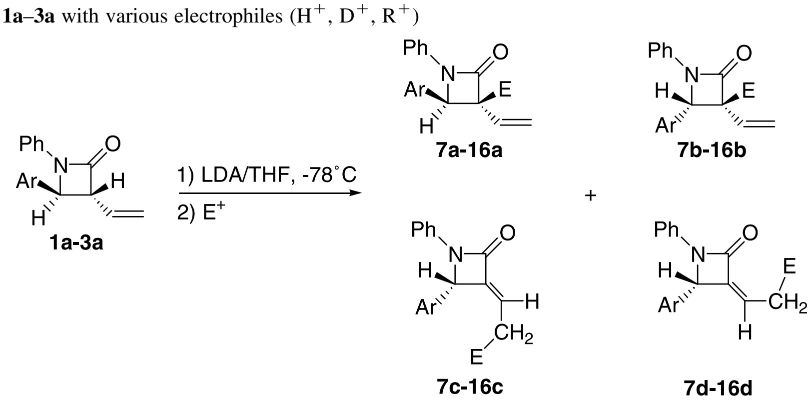
Entry	Imine	Total yield (%)[a]	Product distributions (%)[b]			
1	**1**	90	**1a** (86)	**1b** (14)	**1c** (–)	**1d** (–)
2	**2**	60	**2a** (78)	**2b** (12)	**2c** (5)	**2d** (5)
3	**3**	75	**3a** (86)	**3b** (14)	**3c** (–)	**3d** (–)
4	**4**	50	**4a** (85)	**4b** (15)	**4c** (–)	**4d** (–)
5	**5**	40	**5a** (47)	**5b** (53)	**5c** (–)	**5d** (–)
6	**6**	80	**6a** (65)	**6b** (35)	**6c** (–)	**6d** (–)

[a] Isolated yields.
[b] Diasteromeric ratios evaluated by GC and ^1H NMR spectroscopy.



Scheme 2.

Table 3. Functionalization of **1a**–**3a** with various electrophiles (H^+, D^+, R^+)



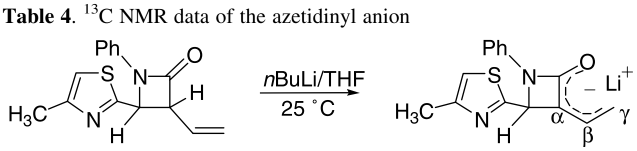
Entry	β-Lactam	E	Total yield (%)[a]	Product distributions (%)[b]							
1	**1a**	H_2O	90	**1a** (50)	**1b** (50)	**1c** (–)	**1d** (–)	—	—	—	—
2	**1a**	D_2O	90	**1a** (–)	**1b** (–)	**1c** (–)	**1d** (–)	**7a** (42)	**7b** (58)	**7c** (–)	**7d** (–)
3	**1a**	CH_3I	99	**1a** (16)	**1b** (8)	**1c** (–)	**1d** (–)	**8a** (–)	**8b** (76)	**8c** (–)	**8d** (–)
4	**1a**	$PhCH_2Cl$	85	**1a** (40)	**1b** (24)	**1c** (5)	**1d** (5)	**9a** (–)	**9b** (26)	**9c** (–)	**9d** (–)
5	**1a**	CH_2CHCH_2Br	95	**1a** (13)	**1b** (6)	**1c** (–)	**1d** (–)	**10a** (–)	**10b** (81)	**10c** (–)	**10d** (–)
6	**1a**	$(CH_3)_2CO$	87	**1a** (50)	**1b** (26)	**1c** (–)	**1d** (–)	**11a** (–)	**11b** (–)	**11c** (12)	**11d** (12)
7	**1a**	PhCHO	86	**1a** (50)	**1b** (25)	**1c** (–)	**1d** (–)	**12a** (–)	**12b** (–)	**12c** (3)	**12d** (22)
8	**2a**	D_2O	85	**2a** (–)	**2b** (–)	**2c** (–)	**2d** (–)	**13a** (50)	**13b** (50)	**13c** (–)	**13d** (–)
9	**2a**	CH_3I	90	**2a** (15)	**2b** (5)	**2c** (–)	**2d** (–)	**14a** (–)	**14b** (80)	**14c** (–)	**14d** (–)
10	**3a**	D_2O	85	**3a** (–)	**3b** (–)	**3c** (–)	**3d** (–)	**15a** (50)	**15b** (50)	**15c** (–)	**15d** (–)
11	**3a**	CH_3I	90	**3a** (–)	**3b** (–)	**3c** (–)	**3d** (–)	**16a** (10)	**16b** (90)	**16c** (–)	**16d** (–)

[a] Isolated yields.
[b] Diasteromeric ratios evaluated by GC and ^1H NMR spectroscopy.

two more isomers were also generated, **1c** and **1d**, showing an unsaturation at the C-3 carbon. These latter α-β-unsaturated β-lactams should result from water quenching the resonance structure C (Scheme 2). With carbonyl compounds as electrophiles (acetone or benzaldehyde), the quenching occurred at the terminal carbon atom of the vinylic chain, on the γ position (structure C, Scheme 2) affording products **11c**, **12c** and **11d**, **12d**, respectively (entries 6 and 7, Table 3).

The diastereomeric mixtures of **1a**,**1b** and **2a**,**2b** isolated in almost every reaction performed with **1a** (entries 1–7) and **2a** (entry 9), could be formed from quenching of any carbanion not captured by the electrophile. The results confirm a planar structure for the carbanion generated by the deprotonation at C-3 (Scheme 2). While a small electrophile such as H^+ or D^+, can bind indifferently from both sides of the molecule, bulkier electrophiles, such as alkyl halides prefer an *anti* type attack with respect to the heterocycle bonded at the C-4, leading stereoselectively to the *cis* 2-azetidinones. Moreover, the tridentate nature of the reacting anion could influence the regioselectivity of the electrophilic attack, which may be directed to the α or the γ position of the allylic moiety.[24–26] Thus α attack predominates in the irreversible reaction with alkyl halides, while γ-adducts are obtained with carbonyl compounds. The lower conversion yields observed for ketone and aldehyde with respect to alkyl halides could be due to the reversible nature of these latter addition reactions.[25,27–31] Furthemore, in order to verify if the regioselectivity was influenced by electronic effects, the ^{13}C NMR spectra of the azetidinyl anion in THF, generated deprotonating **1a** with *n*-BuLi, were recorded and data are summarized in Table 4. As recently reported for dienediolates,[32] ^{13}C NMR chemical shifts can be related with the π-electron density. The chemical shift displacements to higher fields, listed in Table 4, reveal higher π-electron density at the Cα with respect to the Cγ carbon atom, which may account for a preferential electrophilic attack to the α position of the allylic moiety, even if sterically more hindered than the γ position.

Table 4. ^{13}C NMR data of the azetidinyl anion



1a

Carbon atom	δ (ppm)		Δ (ppm)
	2-Azetidinone **1a**	Azetidinyl anion	
Cα	62.13	56.47	5.66
Cβ	136.51	136.45	0.06
Cγ	115.39	115.10	0.29

Bulky electrophiles such as ketone and aldehyde, however, seem to prefer the less hindered γ position, affording products functionalized at the Cγ carbon atom (entries 6 and 7, Table 3). ^{13}C NMR investigations of the azetidinyl anion generated with *n*-BuLi from **1b** in THF, afforded similar results observed for **1a**. For instance, for **1b** we noticed chemical shift displacements towards the same values of the azetidinyl anion reported in Table 4. This behaviour strongly supports the generation of a unique planar anion either starting from the 2-azetidinone **1a** or **1b**. Similarly, **2a** and **3a** deprotonated with LDA, at −78 °C in THF, produced the azetidinyl anion after losing the proton at the C-3. Then, quenching with D_2O led in both cases to an equimolecular mixture of trans and cis isomers (entries 8 and 10). A large stereoselectivity was instead found when the carbanion was quenched with CH_3I, having isolated only the *cis*-**14b** isomer and a cis/trans mixture in the 9:1 ratio, respectively (entries 9 and 11).

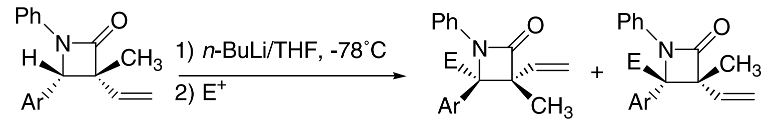
None of the reactions carried out with these substrates showed formation of products derived from deprotonation of the C-4 carbon atom, even using stronger bases like *sec*-BuLi or *n*-BuLi. The deprotonation, therefore, seems to depend on the strong difference of acidity between the hydrogens linked to the C-3 and the C-4 carbons. Deprotonation of the C-4 does not occur after treating the substrates **2c** and **2d** with LDA, which do not have protons at the C-3. For instance, quenching with D_2O produced compounds **13a** and **13b** arising from the same planar carbanion in the form A, B, and C (Scheme 2). Finally, it is worth noting that the same isomeric ratios and transformation yields were obtained deprotonating β-lactams **1b**, **2b**, and **3b** of cis configuration and trapping them with D_2O or CH_3I. This behaviour provides further support to the hypothesis of a planar structure of the carbanion stabilized by the resonance structures A, B, and C of Scheme 2.

The functionalization of the C-4 carbon atom was achievable only with β-lactams doubly functionalized at C-3, as those isolated from the above reported reactions. In particular, when **16b**, **14b**, and **8b** were treated with *n*-BuLi, in THF at −78 °C, the carbanion was formed at the C-4 with planar or configurationally unstable tetrahedral structure (structures D and E, Scheme 2), since subsequent quenching with electrophiles, such as D_2O or CH_3I, led to products functionalized exclusively at C-4 (entries 1–4, Table 5). No relevant diastereoselectivity was noticed, probably due to the two groups linked at the nearby C-3, which did not allow the electrophile to distinguish between the two sides of the carbanion.

3. Conclusion

In summary, we have synthesised novel β-lactams functionalized with several heterocycles. We exploited the possibility of inserting more functions and groups at the C-3 and C-4 carbon atoms, without performing new cyclizations, but through the generation of stable carbanions and subsequent trapping with electrophiles. The presence on the β-lactam ring of various functionalities susceptible to further synthetic elaborations, such as heterocycles, unsaturated fragments, alkyl and hydroxyl groups make this class of compounds particularly interesting for the study of their potential biological and pharmacological activities.

Table 5. Functionalization of **16b**, **14b**, and **8b** with D_2O and CH_3I



Entry	β-Lactam	E	Total yield (%)[a]	Product distributions (%)[b]	
1	**16b**	D_2O	90	**17a** (49)	**17b** (51)
2	**16b**	CH_3I	85	**18a** (48)	**18b** (52)
3	**14b**	CH_3I	90	**19a** (55)	**19b** (45)
4	**8b**	CH_3I	99	**20a** (40)	**20b** (60)

[a] Isolated yields.
[b] Diasteromeric ratios evaluated by GC and ^{1}H NMR spectroscopy.

4. Experimental

4.1. General

n-BuLi was a commercial solution in hexanes (Aldrich) and was titrated with *N*-pivaloyl-*o*-toluidine prior to use.[33] THF, triethylamine, palladium(II) acetate, triphenylphosphine, allyl bromide, 2-pyridinecarboxaldehyde, 4-pyridine-carboxaldehyde, acetophenone, 4-methyl-thiazole, 2-amino-thiophenol, glycolic acid, lithium diisopropylamide (LDA), deuterium oxide and all other chemicals were of commercial grade (Aldrich) and were used without further purification. Acetaldehyde, benzaldehyde, methyl iodide, allyl bromide, benzyl chloride, and acetone of commercial grade (Aldrich), were purified by distillation prior to use. Petroleum ether refers to the 40–60 °C boiling fraction. The ^{1}H and the ^{13}C NMR spectra were recorded on a Bruker Avance 400 apparatus (400.13 and 100.62 MHz, for ^{1}H and ^{13}C, respectively) with $CDCl_3$ as solvent and TMS as internal standard ($\delta=7.24$ for ^{1}H spectra; $\delta=77.0$ for ^{13}C spectra). The IR spectra were recorded on a Perkin Elmer spectrometer Model 283. GC–MS analyses were performed with Hewlett-Packard HP-5890 series II gas chromatograph (5% diphenyl/95% dimethylpolysiloxane capillary column, 30 m, 0.25 mm i.d.), equipped with an HP-5971 mass-selective detector operating at 70 eV (EI). The electrospray ionisation (HR-ESI-MS) experiments were carried out in a hybrid Q*q*TOF mass spectrometer (PE SCIEX-QSTAR) equipped with an ion spray ionisation source. MS (+) spectra were acquired by direct infusion (5 µL/min) of a solution containing the appropriate sample (10 pmol/µL), dissolved in a solution 0.1% acetic acid, methanol/water 50:50 at the optimum ion voltage of 4800 V. The nitrogen gas flow was set at 30 psi (pounds per square inch) and the potentials of the orifice, the focusing ring and the skimmer were kept at 30, 50, and 25 V relative to ground, respectively. Elemental analyses were performed on a Carlo Erba C, H, N analyzer. Melting points were determined using an Electrothermal melting point apparatus and are uncorrected. TLC were performed on Merck silica gel plates with F-254 indicator; viewing was by UV light (254 nm). Column chromatographies were performed on silica gel (63–200 µm) using petroleum ether/diethyl ether (Et_2O) mixtures as eluents. All reactions involving air-sensitive reagents were performed under nitrogen, in oven-dried glassware using syringe/septum cap techniques.

4.2. General procedure for the preparation of heteroaryliden-anilines 1–6

The heteroaryliden-anilines were prepared by coupling reactions of 1 mmol of aniline with the appropriate aldehydes (1 mmol) according to Taguchi's method.[16]

4.2.1. (4-Methyl-thiazol-2-yl-methylene)-phenyl-amine 1. Yield 141 mg (70%), oil. ^{1}H NMR (400.13 MHz): δ 2.53 (s, 3H), 7.07 (s, 1H), 7.26–7.43 (m, 5H), 8.65 (s, 1H). ^{13}C NMR (100.62 MHz): δ 17.0, 117.0, 121.2, 127.2, 129.3, 150.0, 152.8, 154.7, 166.3. GC–MS (70 eV) *m*/*z* (rel int.): 202 (90, M^+), 201 (94), 174 (84), 125 (14), 104 (78), 77 (100). IR ($CHCl_3$): 3060, 2960, 1620, 1590, 1500, 1440, 1200 cm^{-1}. HR-ESI-MS: *m*/*z* calcd for $C_{11}H_{11}N_2S$: 203.0644, $[M+H]^+$; found: 203.0644.

4.2.2. Benzothiazol-2-ylmethylene-phenyl-amine 2. Yield 205 mg (86%), yellow solid, mp 99.0–101.0 °C (*n*-hexane). ^{1}H NMR (400.13 MHz): δ 7.33–7.56 (m, 7H), 7.96 (d, $J=7.7$ Hz, 1H), 8.12 (d, $J=8.2$ Hz, 1H), 8.80 (s, 1H). ^{13}C NMR (100.62 MHz): δ 121.4, 122.1, 124.3, 126.6, 126.8, 127.8, 129.4, 135.4, 149.6, 153.4, 153.8, 167.4. GC–MS (70 eV) *m*/*z* (rel int.): 238 (69, M^+), 237 (94), 210 (43), 135 (23), 104 (30), 77 (100). IR ($CHCl_3$): 3050, 2960, 1620, 1590, 1430, 1310, 1200 cm^{-1}. Anal. Calcd for $C_{14}H_{10}N_2S$: C, 70.56; H, 4.23; N, 11.75. Found: C, 70.36; H, 4.18; N, 11.80.

4.2.3. Phenyl-pyridin-2-ylmethylene-amine 3. Yield 127 mg (72%), oil. ^{1}H NMR (400.13 MHz): δ 7.23–7.41 (m, 6H), 7.74 (dd, $J=7.8$, 1.2 Hz, 1H), 8.17 (d, $J=7.8$ Hz, 1H), 8.60 (s, 1H), 8.68 (d, $J=4.7$ Hz, 1H). ^{13}C NMR (100.62 MHz): δ 120.9, 121.6, 124.9, 126.5, 129.0, 136.4, 149.4, 150.8, 154.4, 160.4. GC–MS (70 eV) *m*/*z* (rel int.): 182 (79, M^+), 181 (100), 155 (67), 154 (77), 105 (53), 77 (86). IR (film): 3050, 2900, 1630, 1590, 1430, 1200, 780, 690 cm^{-1}. HR-ESI-MS: *m*/*z* calcd for $C_{12}H_{11}N_2$: 183.0923, $[M+H]^+$; found: 183.0924.

4.2.4. Phenyl-pyridin-4-ylmethylene-amine 4. Yield 153 mg (84%), yellow solid, mp 71.8–72.3 °C (*n*-hexane). ^{1}H NMR (400.13 MHz): δ 7.24–7.45 (m, 5H), 7.76 (d, $J=5.8$ Hz, 2H), 8.46 (s, 1H), 8.76 (d, $J=5.8$ Hz, 2H). ^{13}C NMR (100.62 MHz): δ 120.9, 122.3, 126.9, 129.3, 142.8, 150.6, 151.0, 157.9. GC–MS (70 eV) *m*/*z* (rel int.): 182 (94, M^+), 181 (78), 104 (73), 79 (61), 77 (100). IR ($CHCl_3$): 3060, 2960, 1630, 1600, 1480, 1410 cm^{-1}. Anal. Calcd for $C_{12}H_{10}N_2$: C, 79.10; H, 5.53; N, 15.37. Found: C, 78.98; H, 5.48; N, 15.35.

4.2.5. [1-(4-Methyl-thiazol-2-yl)-ethylidene)]-phenyl-amine 5. Yield 130 mg (60%), oil. ^{1}H NMR (400.13 MHz): δ 2.36 (s, 3H), 2.51 (s, 3H), 7.02 (s, 1H), 7.13–7.19 (m, 3H), 7.36 (t, $J=8.2$ Hz, 2H). ^{13}C NMR (100.62 MHz): δ 16.8, 17.3, 115.0, 119.6, 124.1, 128.9, 149.7, 153.8, 155.0, 169.4. GC–MS (70 eV) *m/z* (rel int.): 216 (35, M$^+$), 201 (19), 174 (23), 118 (30), 77 (100), 51 (48). IR ($CHCl_3$): 3060, 2960, 1620, 1590, 1500, 1440, 1200 cm^{-1}. HR-ESI-MS: *m/z* calcd for $C_{12}H_{13}N_2S$: 217.0801, [M+H]$^+$; found: 217.0802.

4.2.6. Phenyl-(1-phenyl-ethylidene)-amine 6. Known compound previously reported.[14]

4.3. General procedure for the preparation of alkenyl β-lactams 4-heterosubstituted (1a–1d)–(6a–6d)

A mixture of 1.0 mmol of **1–6**, 1.5 mmol of allyl bromide, 0.08 mmol of PPh_3, 0.02 mmol of Pd(AcO)$_2$, and 2 mmol of Et_3N were dissolved in 10 mL of solvent (THF) and placed in a 45 mL autoclave. The autoclave was purged, pressurized (400 psi CO), and then heated to 100 °C for 30–35 h. The reaction was then cooled to room temperature, and worked up by addition of water (15 mL) and extraction with Et_2O (3×5 mL). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. The crude products were purified by column chromatography (silica gel, petroleum ether/Et_2O=7:3) to afford the pure β-lactams (**1a–1d**)–(**6a–6d**); yields: 40–90%.

4.3.1. 4-(4-Methyl-thiazol-2yl)-1-phenyl-3-vinyl-azetidin-2-one 1a,1b. Overall yield 243 mg (90%). *Compound* **1a**. Yield 208 mg (77%), yellow solid, mp 62.0–63.6 °C (petroleum ether). ^{1}H NMR (400.13 MHz): δ 2.46 (s, 3H), 4.01 (dd, $J=7.4$, 2.3 Hz, 1H), 5.20 (d, $J=2.3$ Hz, 1H), 5.35 (d, $J=10.3$ Hz, 1H), 5.45 (d, $J=17.1$ Hz, 1H), 6.00–6.08 (m, 1H), 6.89 (s, 1H), 7.07 (t, $J=7.3$ Hz, 1H), 7.25–7.36 (m, 4H). ^{13}C NMR (100.62 MHz): δ 16.9, 58.4, 63.3, 114.6, 116.9, 120.4, 124.3, 129.1, 129.5, 137.0, 153.3, 164.5, 166.9. GC–MS (70 eV) *m/z* (rel int.): 270 (59, M$^+$), 202 (55), 201 (60), 174 (34), 150 (100), 77 (72). IR ($CHCl_3$): 3040, 2920, 1750, 1595, 1495, 1370 cm^{-1}. Anal. Calcd for $C_{15}H_{14}N_2OS$: C, 66.64; H, 5.22; N, 10.36. Found: C, 66.72; H, 5.24; N, 10.34. *Compound* **1b**. Yield 35 mg (13%), yellow solid, mp 90.5–91.5 °C (petroleum ether). ^{1}H NMR (400.13 MHz): δ 2.47 (s, 3H), 4.41 (dd, $J=6.2$, 6.1 Hz, 1H), 5.23 (dd, $J=8.6$, 1.8 Hz, 1H), 5.43–5.57 (m, 2H), 5.62 (d, $J=6.1$ Hz, 1H), 6.87 (s, 1H), 7.10 (t, $J=7.3$ Hz, 1H), 7.29–7.39 (m, 4H). ^{13}C NMR (100.62 MHz): δ 17.0, 56.9, 58.5, 114.6, 117.1, 121.9, 124.4, 127.4, 129.1, 136.9, 153.5, 164.8, 165.4. GC–MS (70 eV) *m/z* (rel int.): 270 (60, M$^+$), 202 (57), 201 (62), 174 (33), 150 (100), 77 (79). IR ($CHCl_3$): 3040, 2920, 1750, 1595, 1495, 1370 cm^{-1}. Anal. Calcd for $C_{15}H_{14}N_2OS$: C, 66.64; H, 5.22; N, 10.36. Found: C, 66.40; H, 5.21; N, 10.33.

4.3.2. 4-Benzothiazol-2-yl-1-phenyl-3-vinyl-azetidin-2-one 2a–2d. Overall yield 184 mg (60%). *Compound* **2a**. Yield 144 mg (47%), yellow solid, mp 100.0–102.0 °C (*n*-hexane). ^{1}H NMR (400.13 MHz): δ 4.10 (dd, $J=6.5$, 2.2 Hz, 1H), 5.33 (d, $J=2.2$ Hz, 1H), 5.40 (d, $J=10.4$ Hz, 1H), 5.49 (d, $J=17.1$ Hz, 1H), 6.04–6.12 (m, 1H), 7.08 (t, $J=7.4$ Hz, 1H), 7.25–7.43 (m, 5H), 7.85 (t, $J=8.0$ Hz, 1H), 7.85 (d, $J=8.0$ Hz, 1H), 8.05 (d, $J=8.2$ Hz, 1H). ^{13}C NMR (100.62 MHz): δ 59.0, 63.2, 116.9, 120.9, 122.0, 123.4, 124.6, 125.8, 126.5, 129.2, 129.3, 134.9, 137.0, 153.0, 164.2, 168.9. GC–MS (70 eV) *m/z* (rel int.): 306 (30, M$^+$), 237 (25), 186 (100), 77 (29). IR ($CHCl_3$): 3050, 2970, 1760, 1600, 1490, 1370, 1310 cm^{-1}. Anal. Calcd for $C_{18}H_{14}N_2OS$: C, 70.57; H, 4.61; N, 9.14. Found: C, 70.55; H, 4.59; N, 9.17. *Compound* **2b**. Yield 22 mg (7%), oil. ^{1}H NMR (400.13 MHz): δ 4.52 (dd, $J=6.9$, 6.2 Hz, 1H), 5.19 (dd, $J=9.4$, 1.0 Hz, 1H), 5.48–5.64 (m, 2H), 5.73 (d, $J=6.2$ Hz, 1H), 7.10 (t, $J=6.5$ Hz, 1H), 7.27–7.43 (m, 5H), 7.52 (t, $J=7.4$ Hz, 1H), 7.83 (d, $J=8.0$ Hz, 1H), 8.05 (d, $J=8.2$ Hz, 1H). ^{13}C NMR (100.62 MHz): δ 57.3, 58.7, 117.1, 121.9, 122.4, 123.3, 124.6, 125.6, 126.4, 127.0, 129.2, 134.9, 137.0, 153.3, 164.5, 167.5. GC–MS (70 eV) *m/z* (rel int.): 306 (20, M$^+$), 237 (26), 186 (100), 77 (31). IR ($CHCl_3$): 3050, 2970, 1760, 1600, 1490, 1370, 1310 cm^{-1}. HR-ESI-MS: *m/z* calcd for $C_{18}H_{15}N_2OS$: 307.0906, [M+H]$^+$; found: 307.0907. *4-Benzothiazol-2-yl-3-ethylidene-1-phenyl-azetidin-2-one* **2c**. Yield 9 mg (3%), yellow solid, mp 103.0–105.0 °C (petroleum ether). ^{1}H NMR (400.13 MHz): δ 1.77 (d, $J=7.1$ Hz, 3H), 5.97 (s, 1H), 6.49 (q, $J=7.1$ Hz, 1H), 7.06 (t, $J=7.5$ Hz, 1H), 7.26–7.45 (m, 5H), 7.53 (t, $J=8.0$ Hz, 1H), 7.84 (d, $J=8.0$ Hz, 1H), 8.08 (d, $J=8.1$ Hz, 1H). ^{13}C NMR (100.62 MHz): δ 29.7, 60.5, 116.7, 122.1, 123.4, 124.3, 125.8, 126.3, 126.7, 129.3, 135.3, 137.4, 140.3, 152.9, 160.5, 169.2. GC–MS (70 eV) *m/z* (rel int.): 306 (100, M$^+$), 277 (70), 263 (15), 186 (94), 77 (85). IR ($CHCl_3$): 3080, 2009, 1740, 1600, 1450, 1360, 1090 cm^{-1}. Anal. Calcd for $C_{18}H_{14}N_2OS$: C, 70.57; H, 4.61; N, 9.14. Found: C, 70.50; H, 4.60; N, 9.11. *Compound* **2d**. Yield 9 mg (3%), yellow solid, mp 113.0–115.0 °C (petroleum ether). ^{1}H NMR (400.13 MHz): δ 2.13 (d, $J=7.2$ Hz, 3H), 5.81 (s, 1H), 5.95 (q, $J=7.2$ Hz, 1H), 7.07 (t, $J=7.5$ Hz, 1H), 7.26–7.46 (m, 5H), 7.52 (t, $J=7.3$ Hz, 1H), 7.83 (d, $J=8.0$ Hz, 1H), 8.05 (d, $J=8.1$ Hz, 1H). ^{13}C NMR (100.62 MHz): δ 29.7, 60.6, 116.2, 122.0, 123.3, 124.3, 125.7, 126.3, 129.3, 129.8, 135.2, 137.4, 139.4, 153.0, 160.9, 169.5. GC–MS (70 eV) *m/z* (rel int.): 306 (100, M$^+$), 277 (65), 263 (15), 186 (86), 77 (75). IR ($CHCl_3$): 3080, 2009, 1740, 1600, 1450, 1360, 1090 cm^{-1}. Anal. Calcd for $C_{18}H_{14}N_2OS$: C, 70.57; H, 4.61; N, 9.14. Found: C, 70.55; H, 4.62; N, 9.18.

4.3.3. 1-Phenyl-4-pyridin-2-yl-3-vinyl-azetidin-2-one 3a,3b. Overall yield 187 mg (75%). *Compound* **3a**. Yield 161 mg (64%), white solid, mp 107.0–109.0 °C (*n*-hexane). ^{1}H NMR (400.13 MHz): δ 3.88 (dd, $J=7.5$, 2.4 Hz, 1H), 4.98 (d, $J=2.4$ Hz, 1H), 5.35 (d, $J=10.4$ Hz, 1H), 5.44 (d, $J=17.1$ Hz, 1H), 6.06–6.13 (m, 1H), 7.05 (t, $J=7.0$ Hz, 1H), 7.23–7.34 (m, 6H), 7.70 (t, $J=7.6$ Hz, 1H), 8.64 (d, $J=4.3$ Hz, 1H). ^{13}C NMR (100.62 MHz): δ 61.9, 62.4, 116.9, 120.0, 120.4, 123.3, 124.0, 129.1, 130.3, 137.2, 137.5, 150.1, 157.1, 165.1. GC–MS (70 eV) *m/z* (rel int.): 250 (13, M$^+$), 181 (22), 155 (6), 130 (100), 77 (30). IR ($CHCl_3$): 3025, 2930, 1750, 1590, 1490, 1370 cm^{-1}. Anal. Calcd for $C_{16}H_{14}N_2O$: C, 76.78; H, 5.64; N, 11.19. Found: C, 76.55; H, 5.65; N, 11.22. *Compound* **3b**. Yield 26 mg (10%), white solid, mp 101.0–103.0 °C (*n*-hexane). ^{1}H

NMR (400.13 MHz): δ 4.41 (dd, J=6.6, 6.4 Hz, 1H), 5.09 (d, J=9.5 Hz, 1H), 5.26–5.45 (m, 3H), 7.08 (t, J=7.2 Hz, 1H), 7.20–7.45 (m, 6H), 7.65 (t, J=7.5 Hz, 1H), 8.63 (d, J=4.6 Hz, 1H). ^{13}C NMR (100.62 MHz): δ 58.0, 59.8, 117.1, 121.1, 121.7, 123.0, 124.1, 128.1, 129.2, 136.7, 140.9, 149.8, 155.3, 165.2. GC–MS (70 eV) m/z (rel int.): 250 (18, M$^+$), 181 (37), 155 (10), 130 (100), 77 (46). IR ($CHCl_3$): 3025, 2930, 1750, 1590, 1490, 1370 cm^{-1}. Anal. Calcd for $C_{16}H_{14}N_2O$: C, 76.78; H, 5.64; N, 11.19. Found: C, 76.48; H, 5.62; N, 11.15.

4.3.4. 1-Phenyl-4-pyridin-4-yl-3-vinyl-azetidin-2-one 4a,4b. Overall yield 125 mg (50%). *Compound* **4a**. Yield 106 mg (42%), oil. ^{1}H NMR (400.13 MHz): δ 3.72 (dd, J= 7.9, 2.5 Hz, 1H), 4.82 (d, J=2.5 Hz, 1H), 5.37 (d, J= 10.2 Hz, 1H), 5.41 (d, J=16.6 Hz, 1H), 6.00–6.10 (m, 1H), 7.03–7.12 (m, 1H), 7.24–7.34 (m, 6H), 8.64 (d, J=5.5 Hz, 2H). ^{13}C NMR (100.62 MHz): δ 59.8, 63.7, 116.9, 120.7, 124.5, 129.3, 129.8, 137.1, 146.3, 146.8, 150.4, 164.4. GC–MS (70 eV) m/z (rel int.): 250 (5, M$^+$), 181 (10), 130 (100), 104 (25), 77 (70). IR ($CHCl_3$): 3030, 2920, 1750, 1600, 1495, 1375 cm^{-1}. HR-ESI-MS: m/z calcd for $C_{16}H_{15}N_2O$: 251.1185, [M+H]$^+$; found: 251.1184. *Compound* **4b**. Yield 19 mg (7%, measured by GC), oil. ^{1}H NMR (400.13 MHz): δ 4.44 (dd, J=6.8, 6.4 Hz, 1H), 5.21–5.51 (m, 4H), 7.03–7.40 (m, 5H), 7.52 (d, J=5.5 Hz, 2H), 8.65 (d, J=5.5 Hz, 2H). GC–MS (70 eV) m/z (rel int.): 250 (5, M$^+$), 181 (12), 130 (100), 104 (25), 77 (70). IR ($CHCl_3$): 3030, 2920, 1750, 1600, 1495, 1375 cm^{-1}. HR-ESI-MS: m/z calcd for $C_{16}H_{15}N_2O$: 251.1185, [M+H]$^+$; found: 251.1185.

4.3.5. 4-Methyl-4-(4-methyl-thiazol-2yl)-1-phenyl-3-vinyl-azetidin-2-one 5a,5b. Overall yield 114 mg (40%). *Compound* **5a**. Yield 54 mg (19%), oil. ^{1}H NMR (400.13 MHz): δ 1.99 (s, 3H), 2.46 (s, 3H), 4.09 (d, J= 7.7 Hz, 1H), 5.43 (d, J=10.5 Hz, 1H), 5.47 (d, J=17.4 Hz, 1H), 5.89–5.98 (m, 1H), 6.89 (s, 1H), 7.06 (t, J=7.3 Hz, 1H), 7.24–7.44 (m, 4H). ^{13}C NMR (100.62 MHz): δ 17.2, 19.0, 63.9, 67.1, 114.6, 117.7, 122.4, 124.4, 127.6, 129.0, 136.6, 153.4, 166.0, 171.8. GC–MS (70 eV) m/z (rel int.): 284 (7, M$^+$), 216 (11), 164 (100), 118 (13), 77 (60). IR ($CHCl_3$): 3060, 2925, 1740, 1600, 1490, 1365 cm^{-1}. HR-ESI-MS: m/z calcd for $C_{16}H_{17}N_2OS$: 285.1063, [M+H]$^+$; found: 285.1063. *Compound* **5b**. Yield 60 mg (21%), oil. ^{1}H NMR (400.13 MHz): δ 2.18 (s, 3H), 2.46 (s, 3H), 4.00 (d, J=6.9 Hz, 1H), 5.11–5.14 (m, 1H), 5.34–5.47 (m, 2H), 6.86 (s, 1H), 7.08 (t, J=7.4 Hz, 1H), 7.29 (t, J=7.4 Hz, 2H), 7.39 (t, J=7.6 Hz, 2H). ^{13}C NMR (100.62 MHz): δ 17.2, 23.0, 65.6, 67.1, 114.6, 117.9, 121.5, 124.1, 127.5, 128.9, 136.5, 153.6, 164.7, 168.7. GC–MS (70 eV) m/z (rel int.): 284 (14, M$^+$), 216 (18), 164 (100), 118 (18), 77 (62). IR ($CHCl_3$): 3060, 2925, 1740, 1600, 1490, 1365 cm^{-1}. HR-ESI-MS: m/z calcd for $C_{16}H_{17}N_2OS$: 285.1063, [M+H]$^+$; found: 285.1064.

4.3.6. 4-Methyl-1,4-diphenyl-3-vinyl-azetidin-2-one 6a,6b. Overall yield 211 mg (80%). *Compound* **6a**. Yield 137 mg (52%), oil. ^{1}H NMR (400.13 MHz): δ 1.91 (s, 3H), 3.80 (d, J=8.2 Hz, 1H), 5.36–5.43 (m, 2H), 5.90–5.99 (m, 1H), 7.04 (t, J=7.4 Hz, 1H), 7.22–7.39 (m, 9H). ^{13}C NMR (100.62 MHz): δ 19.5, 64.2, 67.8, 117.7, 122.0, 123.7, 124.8, 127.8, 128.2, 129.0, 129.1, 137.0, 141.0, 165.7. GC–MS (70 eV) m/z (rel int.): 263 (8, M$^+$), 196 (5), 195 (23), 180 (48), 144 (60), 129 (100), 77 (85). IR ($CHCl_3$): 3030, 2990, 2920, 1735, 1600, 1590, 1370 cm^{-1}. HR-ESI-MS: m/z calcd for $C_{18}H_{18}NO$: 264.1389, [M+H]$^+$; found: 264.1390. *Compound* **6b**. Yield 74 mg (28%), oil. ^{1}H NMR (400.13 MHz): δ 2.09 (s, 3H), 3.87 (d, J=7.9 Hz, 1H), 5.01 (d, J=10.4 Hz, 1H), 5.09–5.17 (m, 1H), 5.25 (d, J= 16.0 Hz, 1H), 7.06 (t, J=7.5 Hz, 1H), 7.24–7.45 (m, 9H). ^{13}C NMR (100.62 MHz): δ 23.6, 65.7, 66.9, 117.8, 120.4, 123.7, 126.5, 127.7, 128.6, 129.0, 129.2, 137.1, 138.7, 165.2. GC–MS (70 eV) m/z (rel int.): 263 (8, M$^+$), 196 (7), 195 (33), 180 (63), 144 (63), 129 (100), 77 (90). IR ($CHCl_3$): 3030, 2990, 2920, 1735, 1600, 1590, 1370 cm^{-1}. HR-ESI-MS: m/z calcd for $C_{18}H_{18}NO$: 264.1389, [M+H]$^+$; found: 264.1390.

4.4. General procedure for the functionalization of alkenyl β-lactams 4-heterosubstituted 1a–3a

To a stirred solution of 1 mmol of **1a–3a** in THF (30 mL) at −78 °C, LDA (2.0 M in hexanes, 0.6 mL, 1.2 mmol) was added dropwise under nitrogen. The resulting mixture was stirred at −78 °C for 5 min, and then the electrophile was added (1.5 mmol). The reaction was warmed up to room temperature and quenched with saturated aq NH_4Cl. The aqueous layer was extracted with Et_2O (3×20 mL) and the combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo. The crude products were purified by column chromatography (silica gel, petroleum ether/Et_2O, 1:1) to afford the pure functionalized β-lactams (**7a–7d**)–(**16a–16d**); yields: 85–99%.

4.4.1. 3-Deutero-4-(4-methyl-thiazol-2-yl)-1-phenyl-3-vinyl-azetidin-2-one 7a. Yield 103 mg (38%), (>80%D), yellow solid, mp 60.0–62.0 °C (n-hexane). The IR, ^{1}H and ^{13}C NMR data are the same of those reported for **1a**. In the ^{1}H NMR spectrum the double doublet at 4.01 ppm almost disappears, while the doublet at 5.20 becomes a singlet. GC–MS (70 eV) m/z (rel int.): 271 (72, M$^+$), 202 (70), 201 (75), 174 (51), 151 (100) 77 (85). IR ($CHCl_3$): 3020, 2910, 2850, 2220, 1750, 1595, 1500, 1370 cm^{-1}. HR-ESI-MS: m/z calcd for $C_{15}H_{14}DN_2OS$: 272.0969, [M+H]$^+$; found: 272.0970.*Compound* **7b**. Yield 141 mg (52%), (>80%D), yellow solid, mp 90.0–92.0 °C (n-hexane). The IR, ^{1}H and ^{13}C NMR data are the same of those reported for **1b**. In the ^{1}H NMR spectrum the double doublet at 4.41 ppm almost disappears, while the doublet at 5.23 becomes a singlet. GC–MS (70 eV) m/z (rel int.): 271 (57, M$^+$), 202 (65), 201 (76), 174 (40), 151 (100) 77 (90). IR ($CHCl_3$): 3020, 2910, 2850, 2220, 1750, 1595, 1500, 1370 cm^{-1}. HR-ESI-MS: m/z calcd for $C_{15}H_{14}DN_2OS$: 272.0969, [M+H]$^+$; found: 272.0970.

4.4.2. 3-Methyl-4-(4-methyl-thiazol-2yl)-1-phenyl-3-vinyl-azetidin-2-one 8b. Yield 213 mg (75%), yellow solid, mp 99.4–100.9 °C (n-hexane). ^{1}H NMR (400.13 MHz): δ 1.69 (s, 3H), 2.47 (s, 3H), 5.12 (dd, J= 9.3, 2.4 Hz, 1H), 5.24 (s, 1H), 5.42–5.49 (m, 2H), 6.86 (s, 1H), 7.09 (t, J=7.2 Hz, 1H), 7.26–7.35 (m, 4H). ^{13}C NMR (100.62 MHz): δ 17.0, 21.0, 62.9, 64.8, 114.6, 117.3, 118.4, 124.3, 129.1, 133.1, 137.1, 153.3, 165.8, 168.2. GC–MS (70 eV) m/z (rel int.): 284 (58, M$^+$), 269 (13), 202 (66), 201 (76), 174 (50), 165 (73), 164 (100) 77 (82). IR ($CHCl_3$):

3020, 2970, 2920, 1750, 1600, 1590, 1360, 1310 cm^{-1}. Anal. Calcd for $C_{16}H_{16}N_2OS$: C, 67.58; H, 5.67; N, 9.85. Found: C, 67.24; H, 5.71; N, 9.84.

4.4.3. 3-Benzyl-4-(4-methyl-thiazol-2yl)-1-phenyl-3-vinyl-azetidin-2-one 9b. Yield 79 mg (22%), yellow solid, mp 109.8–110.7 °C (*n*-hexane). ^{1}H NMR (400.13 MHz): δ 2.46 (s, 3H), 3.21 (d, J=14.1 Hz, 1H), 3.37 (d, J=14.1 Hz, 1H), 5.15 (d, J=10.4 Hz, 1H), 5.30 (s, 1H), 5.39–5.47 (m, 1H), 5.12 (d, J=17.3 Hz, 1H), 6.82 (s, 1H), 7.02 (t, J=7.1 Hz, 1H), 7.15–7.38 (m, 9H). ^{13}C NMR (100.62 MHz): δ 17.1, 41.1, 61.4, 67.3, 114.7, 117.4, 119.1, 124.3, 127.1, 128.4, 128.9, 130.3, 132.5, 135.2, 136.5, 153.2, 166.0, 167.2. GC–MS (70 eV) *m/z* (rel int.): 360 (17, M^+), 269 (27), 241 (78), 240 (100), 202 (26), 201 (36) 91 (40), 77 (62). IR ($CHCl_3$): 3020, 2950, 1750, 1600, 1490, 1370 cm^{-1}. Anal. Calcd for $C_{22}H_{20}N_2OS$: C, 73.30; H, 5.59; N, 7.77. Found: C, 73.35; H, 5.58; N, 7.79.

4.4.4. 3-Ethylidene-4-(4-methyl-thiazol-2yl)-1-phenyl-3-vinyl-azetidin-2-one 1c. Yield 11 mg (4%), oil. ^{1}H NMR (400.13 MHz): δ 1.74 (d, J=7.2 Hz, 3H), 2.48 (s, 3H), 5.85 (s, 1H), 6.42 (q, J=7.2 Hz, 1H), 6.90 (s, 1H), 7.06 (t, J=7.2 Hz, 1H), 7.26–7.31 (m, 2H), 7.43 (d, J=7.2 Hz, 2H). ^{13}C NMR (100.62 MHz): δ 17.0, 29.7, 59.9, 115.2, 116.8, 124.1, 125.9, 129.2, 133.9, 140.0, 153.0, 160.7, 176.5. GC–MS (70 eV) *m/z* (rel int.): 270 (93, M^+), 241 (45), 227 (14), 178 (47), 150 (100), 77 (56). IR ($CHCl_3$): 3020, 2930, 1740, 1595, 1500, 1360 cm^{-1}. HR-ESI-MS: *m/z* calcd for $C_{15}H_{15}N_2OS$: 271.0906, $[M+H]^+$; found: 271.0907. *Compound* **1d**. Yield 11 mg (4%), oil. ^{1}H NMR (400.13 MHz): δ 2.13 (d, J=7.2 Hz, 3H), 2.48 (s, 3H), 5.69 (s, 1H), 5.90 (q, J=7.2 Hz, 1H), 6.89 (s, 1H), 7.07 (t, J=7.4 Hz, 1H), 7.30 (t, J=7.4 Hz, 2H), 7.41 (d, J=7.4 Hz, 2H). ^{13}C NMR (100.62 MHz): δ 16.9, 29.7, 59.9, 115.0, 116.8, 124.2, 125.7, 129.2, 129.3, 137.4, 152.9, 160.7, 177.0. GC–MS (70 eV) *m/z* (rel int.): 270 (31, M^+), 241 (26), 227 (7), 178 (38), 150 (100), 77 (98). IR ($CHCl_3$): 3020, 2930, 1740, 1595, 1500, 1360 cm^{-1}. HR-ESI-MS: *m/z* calcd for $C_{15}H_{15}N_2OS$: 271.0906, $[M+H]^+$; found: 271.0907.

4.4.5. 3-Allyl-4-(4-methyl-thiazol-2yl)-1-phenyl-3-vinyl-azetidin-2-one 10b. Yield 239 mg (77%), oil. ^{1}H NMR (400.13 MHz): δ 2.47 (s, 3H), 2.74–2.77 (m, 2H), 5.15–5.54 (m, 6H), 5.87–.93 (m, 1H), 6.86 (s, 1H), 7.09 (t, J=7.0 Hz, 1H), 7.26–7.34 (m, 4H). ^{13}C NMR (100.62 MHz): δ 17.0, 39.4, 61.4, 66.2, 114.7, 117.3, 119.0, 120.1, 124.3, 129.1, 131.7, 132.1, 136.7, 153.2, 165.9, 167.0. GC–MS (70 eV) *m/z* (rel int.): 310 (15, M^+), 269 (36), 202 (40), 201 (59), 191 (69), 190 (100) 77 (85). IR ($CHCl_3$): 3060, 2920, 1750, 1695, 1490, 1360 cm^{-1}. HR-ESI-MS: *m/z* calcd for $C_{18}H_{19}N_2OS$: 311.1220, $[M+H]^+$; found: 311.1220.

4.4.6. 3-(3-Hydroxy-3-methyl-butylidene)-4-(4-methyl-thiazol-2yl)-1-phenyl-3-vinyl-azetidin-2-one 11c+11d. Overall yield 69 mg (21%), oil. Inseparable mixture of two trans and cis-configurated diasteromers (dr=1/1 by ^{1}H NMR). ^{1}H NMR, ^{13}C NMR, GC–MS, HR-ESI-MS and IR data were measured on the mixture. ^{1}H NMR (400.13 MHz): δ 1.09 (s, 3H), 1.17 (s, 3H), 1.27 (s, 3H), 1.30 (s, 3H), 1.85 (s, 1H+1H, broad), 2.28–2.33 (m, 2H), 2.48 (s, 3H+3H), 2.74–2.77 (m, 2H), 5.77 (s, 1H), 5.87 (s, 1H), 6.03 (t, J=7.4 Hz, 1H), 6.51 (t, J=7.0 Hz, 1H), 6.89 (s, 1H+1H), 7.07 (t, J=7.4 Hz, 1H+1H), 7.27–7.43 (m, 4H+4H). ^{13}C NMR (100.62 MHz): δ 15.3, 16.9, 29.0, 29.1, 29.5, 29.7, 41.9, 42.5, 60.1, 60.2, 70.7, 71.3, 115.1, 115.2, 116.8, 116.9, 124.3, 126.7, 129.1, 129.2, 130.0, 137.2, 137.3, 141.6, 141.9, 152.9, 153.0, 160.5, 161.2, 167.29, 167.3. IR ($CHCl_3$): 3400 (broad), 3020, 2960, 2920, 1735, 1600, 1490, 1370, 1100 cm^{-1}. HR-ESI-MS: *m/z* calcd for $C_{18}H_{21}N_2O_2S$: 329.1325, $[M+H]^+$; found: 329.1326. Isomer I: GC–MS (70 eV) *m/z* (rel int.): 328 (22, M^+), 310 (3), 269 (83), 236 (6), 178 (100), 150 (90), 77 (75), 59 (90). Isomer II: GC–MS (70 eV) *m/z* (rel int.): 328 (27, M^+), 310 (3), 269 (100), 236 (75), 178 (95), 150 (85), 77 (73), 59 (90).

4.4.7. 3-(3-Hydroxy-3-phenyl-propylidene)-4-(4-methyl-thiazol-2yl)-1-phenyl-3-vinyl-azetidin-2-one 12c+12d. Overall yield 79 mg (21%), oil. Inseparable mixture of two trans and cis-configurated diasteromers (dr=1/7 by ^{1}H NMR). Compound **12c**. ^{1}H NMR (400.13 MHz): δ 2.45 (s, 3H), 2.50?2.51 (m, 2H), 2.80 (s, 1H, broad), 4.62–4.68 (m, 1H), 5.77 (s, 1H), 6.32–6.38 (m, 1H), 6.88 (s, 1H), 7.06 (t, J=7.3 Hz, 1H), 7.23–7.39 (m, 9H). Compound **12d**. ^{1}H NMR (400.13 MHz): δ 2.43 (s, 3H), 2.80 (s, 1H, broad), 2.93–3.08 (m, 2H), 4.85–4.93 (m, 1H), 5.68 (s, 1H), 5.90–5.93 (m, 1H), 6.86 (s, 1H), 7.06 (t, J=7.3 Hz, 1H), 7.23–7.39 (m, 9H). *Compound* **12c+12d**. ^{13}C NMR (100.62 MHz): δ 15.2, 16.9, 37.7, 38.2, 60.1, 62.1, 73.1, 73.3, 115.1, 115.3, 116.8, 120.2, 120.7, 124.2, 124.3, 125.5, 125.7, 125.8, 126.6, 127.6, 127.7, 128.4, 128.5, 129.1, 129.3, 129.7, 137.2, 141.1, 141.2, 141.8, 143.2, 143.3, 152.9, 153.0, 160.5, 161.0, 167.1, 169.4. GC–MS (70 eV) *m/z* (rel int.): 376 (3, M^+), 358 (3), 270 (41), 269 (45), 178 (100), 150 (60), 77 (70). IR ($CHCl_3$): 3370 (broad), 2950, 1730, 1600, 1490, 1360, 1100 cm^{-1}. HR-ESI-MS: *m/z* calcd for $C_{22}H_{21}N_2O_2S$: 377.1325, $[M+H]^+$; found: 377.1326.

4.4.8. 4-Benzothiazol-2-yl-3-deutero-1-phenyl-3-vinyl-azetidin-2-one 13a. Yield 129 mg (42%), (>90%D), yellow solid, mp 100.6–102.1 °C (*n*-hexane). The IR, ^{1}H and ^{13}C NMR data are the same of those reported for **2a**. In the ^{1}H NMR spectrum the double doublet at 4.10 ppm almost disappears, while the doublet at 5.33 becomes a singlet. GC–MS (70 eV) *m/z* (rel int.): 307 (25, M^+), 237 (30), 187 (100), 77 (85). IR ($CHCl_3$): 3050, 2970, 2220, 1760, 1600, 1490, 1370, 1310 cm^{-1}. HR-ESI-MS: *m/z* calcd for $C_{18}H_{14}DN_2OS$: 308.0969, $[M+H]^+$; found: 308.0970. *Compound* **13b**. Yield 129 mg (42%), (>90%D), oil. The IR, ^{1}H and ^{13}C NMR data are the same of those reported for **2b**. In the ^{1}H NMR spectrum the double doublet at 4.52 ppm almost disappears, while the doublet at 5.73 becomes a singlet. GC–MS (70 eV) *m/z* (rel int.): 307 (25, M^+), 237 (30), 187 (100), 77 (85). IR ($CHCl_3$): 3050, 2970, 2220, 1760, 1600, 1490, 1370, 1310 cm^{-1}. HR-ESI-MS: *m/z* calcd for $C_{18}H_{14}DN_2OS$: 308.0969, $[M+H]^+$; found: 308.0969.

4.4.9. 4-Benzothiazol-2-yl-3-methyl-1-phenyl-3-vinyl-azetidin-2-one 14b. Yield 230 mg (72%), yellow solid, mp 142.4–143.6 °C (*n*-hexane). ^{1}H NMR (400.13 MHz): δ 1.75 (s, 3H), 5.10 (dd, J=10.0, 1.7 Hz, 1H), 5.35 (s, 1H), 5.45–5.60 (m, 2H), 7.10 (t, J=7.4 Hz, 1H), 7.24–7.52

(m, 6H), 7.81 (d, $J=8.0$ Hz, 1H), 8.05 (d, $J=8.0$ Hz, 1H). ^{13}C NMR (100.62 MHz): δ 21.1, 63.2, 65.0, 117.2, 118.8, 121.9, 123.2, 124.5, 125.5, 126.3, 129.2, 130.0, 132.6, 134.9, 137.1, 153.0, 167.9. GC–MS (70 eV) *m/z* (rel int.): 320 (12, M^+), 237 (22), 200 (100), 77 (60). IR ($CHCl_3$): 3050, 2970, 1760, 1600, 1490, 1370, 1310 cm^{-1}. Anal. Calcd for $C_{19}H_{16}N_2OS$: C, 71.22; H, 5.03; N, 8.74. Found: C, 71.08; H, 5.05; N, 8.71.

4.4.10. 3-Deutero-1-phenyl-4-pyridin-2-yl-3-vinyl-azetidin-2-one 15a. Yield 105 mg (42%), (>90%D), white solid, mp 107.0–109.0 °C (*n*-hexane). The IR, ^{1}H and ^{13}C NMR data are the same of those reported for **3a**. In the ^{1}H NMR spectrum the double doublet at 3.88 ppm almost disappears, while the doublet at 4.98 becomes a singlet. GC–MS (70 eV) *m/z* (rel int.): 251 (19, M^+), 182 (15), 181 (37), 131 (100), 77 (54). IR ($CHCl_3$): 3025, 2930, 2220, 1750, 1590, 1490, 1370 cm^{-1}. HR-ESI-MS: *m/z* calcd for $C_{16}H_{14}DN_2O$: 252.1248, $[M+H]^+$; found: 252.1248. *Compound* **15b**. Yield 105 mg (42%), (>90%D), white solid, mp 101.0–103.0 °C (*n*-hexane). The IR, ^{1}H and ^{13}C NMR data are the same those reported for **3b**. In the ^{1}H NMR spectrum the double doublet at 4.41 ppm almost disappears, while the doublet at 5.40 becomes a singlet. GC–MS (70 eV) *m/z* (rel int.): 251 (25, M^+), 182 (12), 181 (43), 131 (100), 77 (51). IR ($CHCl_3$): 3025, 2930, 2220, 1750, 1590, 1490, 1370 cm^{-1}. HR-ESI-MS: *m/z* calcd for $C_{16}H_{14}DN_2O$: 252.1248, $[M+H]^+$; found: 252.1249.

4.4.11. 3-Methyl-1-phenyl-4-pyridin-2-yl-3-vinyl-azetidin- 2-one 16a. Yield 24 mg (9%), white solid, mp 105.0–106.0 °C (*n*-hexane). ^{1}H NMR (400.13 MHz): δ 1.00 (s, 3H), 5.15 (s, 1H), 5.31 (d, $J=10.6$ Hz, 1H) 5.47 (d, $J=17.3$ Hz, 1H), 6.20 (dd, $J=17.3$, 10.6 Hz, 1H), 7.05 (t, $J=7.1$ Hz, 1H), 7.25–7.35 (m, 6H), 7.66 (t, $J=7.6$ Hz, 1H), 8.64 (d, $J=4.3$ Hz, 1H). ^{13}C NMR (100.62 MHz): δ 15.6, 61.7, 67.0, 116.3, 117.2, 121.4, 122.8, 124.0, 129.1, 136.6, 137.3, 137.5, 149.7, 155.5, 168.7. GC–MS (70 eV) *m/z* (rel int.): 264 (15, M^+), 181 (36), 154 (9), 144 (100), 77 (45). IR ($CHCl_3$): 3020, 2940, 2870, 1740, 1590, 1480, 1440, 1370 cm^{-1}. Anal. Calcd for $C_{17}H_{16}N_2O$: C, 82.22; H, 6.49; N, 11.28. Found: C, 82.17; H, 6.46; N, 11.30. *Compound* **16b**. Yield 214 mg (81%), white solid, mp 100.0–101.1 °C (*n*-hexane). ^{1}H NMR (400.13 MHz): δ 1.71 (s, 3H), 4.97–4.99 (m, 1H), 5.04 (s, 1H), 5.25–5.32 (m, 2H), 7.07 (t, $J=7.0$ Hz, 1H), 7.20–7.35 (m, 6H), 7.63 (t, $J=7.1$ Hz, 1H), 8.63 (d, $J=4.5$ Hz, 1H). ^{13}C NMR (100.62 MHz): δ 21.1, 62.1, 67.8, 117.2, 117.5, 121.6, 122.9, 129.09, 130.5, 133.8, 136.5, 137.2, 149.7, 155.6, 168.6. GC–MS (70 eV) *m/z* (rel int.): 264 (15, M^+), 181 (33), 154 (10), 144 (100), 77 (48). IR ($CHCl_3$): 3020, 2940, 2870, 1740, 1590, 1480, 1440, 1370 cm^{-1}. Anal. Calcd for $C_{17}H_{16}N_2O$: C, 82.22; H, 6.49; N, 11.28. Found: C, 82.20; H, 6.48; N, 11.29.

4.5. General procedure for the preparation of the azetidinyl anion

For the NMR measurements compound **1a** or **1b** (0.1 mmol) was dissolved in 0.5 ml of a mixture of THF/$CDCl_3$ in a ratio of 8:2. A ^{13}C NMR experiment was performed on these solvent mixture. The NMR tube containing the mixture was cooled to −78 °C and then *n*-BuLi (2.5 M in hexane, 40 mL, 0.1 mmol) was added to the tube. Then mixture was vigorously stirred and placed into the instrument probe wich is at the constant temperature of 25 °C. The ^{13}C NMR spectra was then acquired.

4.6. General procedure for the functionalization of 16b,14b, and 8b

To a stirred solution of 1 mmol of the 2-azetidinone in THF (30 mL) at −78 °C, *n*-BuLi (2.5 M in hexanes, 0.5 mL, 1.2 mmol) was added dropwise under nitrogen. The resulting mixture was stirred at −78 °C for 30 min, and then the electrophile was added (1.5 mmol). The reaction was warmed up to room temperature and quenched with saturated aq NH_4Cl. The mixture was worked up and purified as reported in the Section 4.4. The pure functionalized β-lactams **17a–20a** and **17b–20b** were isolated with yields of 85–99%.

4.6.1. 4-Deutero-3-methyl-1-phenyl-4-pyridin-2-yl-3-vinyl-azetidin-2-one 17a,17b. Overall yield 238 mg (90%). *Compound* **17a**. Yield 117 mg (44%), (>90%D), white solid, mp 105.0–106.5 °C (*n*-hexane). The IR, ^{1}H and ^{13}C NMR data are the same of those reported for **16a**. In the ^{1}H NMR spectrum the singlet at 5.15 ppm almost disappears. GC–MS (70 eV) *m/z* (rel int.): 265 (21, M^+), 183 (15), 182 (34), 145 (100), 77 (32). IR ($CHCl_3$): 3020, 2940, 2870, 2220, 1740, 1590, 1480, 1440, 1370 cm^{-1}. HR-ESI-MS: *m/z* calcd for $C_{17}H_{16}DN_2O$: 266.1405, $[M+H]^+$; found: 266.1405. *Compound* **17b**. Yield 122 mg (46%), (>90%D), white solid, mp 100.1–101.4 °C (*n*-hexane). The IR, ^{1}H and ^{13}C NMR data are the same of those reported for **16b**. In the ^{1}H NMR spectrum the singlet at 5.04 ppm almost disappears. GC–MS (70 eV) *m/z* (rel int.): 265 (15, M^+), 183 (11), 182 (31), 145 (100), 77 (43). IR ($CHCl_3$): 3020, 2940, 2870, 2220, 1740, 1590, 1480, 1440, 1370 cm^{-1}. HR-ESI-MS: *m/z* calcd for $C_{17}H_{16}DN_2O$: 266.1405, $[M+H]^+$; found: 266.1405.

4.6.2. 3,4-Dimethyl-1-phenyl-4-pyridin-2-yl-3-vinyl-azetidin-2-one 18a+18b. Overall yield 236 mg (85%), oil. Inseparable mixture of two trans and cis-configurated diasteromers (dr=1/1 by ^{1}H NMR and GC–MS). ^{1}H NMR, ^{13}C NMR, GC–MS, HR-ESI-MS and IR data were measured on the mixture. ^{1}H NMR (400.13 MHz): δ 0.87 (s, 3H), 1.55 (s, 3H), 1.96 (s, 3H), 2.04 (s, 3H), 4.80 (dd, $J=10.3$, 1.5 Hz, 1H), 5.11–5.29 (m, 2H), 5.34 (d, $J=10.8$ Hz, 1H), 5.50 (d, $J=17.4$ Hz, 1H), 6.07 (dd, $J=17.4$, 10.8 Hz, 1H), 7.10–7.65 (m, 16H), 8.64 (d, $J=4.7$ Hz, 1H), 8.67 (d, $J=4.7$ Hz, 1H). ^{13}C NMR (100.62 MHz): δ 17.2, 18.0, 19.1, 20.5, 64.6, 64.8, 70.1, 70.2, 115.9, 117.5, 118.0, 118.1, 121.6, 121.9, 122.1, 122.2, 123.7, 123.8, 129.0, 135.1, 135.4, 136.0, 136.1, 137.1, 137.2, 149.3, 149.5, 159.8, 159.9, 169.1, 169.2. GC–MS (70 eV) *m/z* (rel int.): 278 (22, M^+), 196 (60), 195 (70), 181 (20), 158 (80), 118 (44), 77 (100). IR ($CHCl_3$): 3040, 2920, 1750, 1590, 1500, 1365 cm^{-1}. HR-ESI-MS: *m/z* calcd for $C_{18}H_{19}N_2O$: 279.1499, [M+H]+; found: 279.1499.

4.6.3. 4-Benzothiazol-2-yl-3,4-dimethyl-1-phenyl-3-vinyl-azetidin-2-one 19a,19b. Overall yield 301 mg (90%). *Compound* **19a**. Yield 166 mg (49%), oil. ^{1}H

NMR (400.13 MHz): δ 1.22 (s, 3H), 2.08 (s, 3H), 5.39 (d, J=10.7 Hz, 1H), 5.54 (d, J=17.4 Hz, 1H), 6.02 (dd, J=10.7, 17.4 Hz, 1H), 7.11 (t, J=7.4 Hz, 1H), 7.26–7.51 (m, 6H), 7.84 (d, J=8.1 Hz, 1H), 8.05 (d, J=8.1 Hz, 1H). ^{13}C NMR (100.62 MHz): δ 17.4, 21.5, 65.9, 68.8, 117.5, 118.9, 122.1, 123.4, 124.5, 125.7, 126.5, 129.7, 130.2, 132.8, 137.3, 153.2, 167.8, 168.1. GC–MS (70 eV) *m/z* (rel int.): 334 (51, M^+), 252 (75), 251 (89), 237 (24), 214 (100), 118 (49), 77 (57). IR ($CHCl_3$): 3050, 2970, 1760, 1600, 1490, 1370, 1310 cm^{-1}. HR-ESI-MS: *m/z* calcd for $C_{20}H_{19}N_2OS$: 335.1220, $[M+H]^+$; found: 335.1220. *Compound* **19b**. Yield 134 mg (40%), oil. ^{1}H NMR (400.13 MHz): δ 1.60 (s, 3H), 2.17 (s, 3H), 4.91 (dd, J=2.9, 9.0 Hz, 1H), 5.34–5.40 (m, 2H), 7.15 (t, J=7.4 Hz, 1H), 7.25–7.50 (m, 6H), 7.82 (d, J=8.0 Hz, 1H), 8.06 (d, J=8.0 Hz, 1H). ^{13}C NMR (100.62 MHz): δ 18.5, 21.6, 66.0, 69.1, 117.3, 119.5, 122.3, 123.3, 124.5, 125.7, 126.7, 129.8, 130.8, 132.9, 137.5, 153.5, 168.0, 168.5. GC–MS (70 eV) *m/z* (rel int.): 334 (30, M^+), 252 (52), 251 (63), 237 (16), 214 (100), 118 (43), 77 (49). IR ($CHCl_3$): 3050, 2970, 1760, 1600, 1490, 1370, 1310 cm^{-1}. HR-ESI-MS: *m/z* calcd for $C_{20}H_{19}N_2OS$: 335.1220, $[M+H]^+$; found: 335.1219.

4.6.4. 3,4-Dimethyl-4-(4-methylthiazolyl)-1-phenyl-3-vinyl-azetidin-2-one 20a,20b. Overall yield 295 mg (99%). *Compound* **20a**. Yield 119 mg (40%), oil. ^{1}H NMR (400.13 MHz): δ 1.08 (s, 3H), 1.99 (s, 3H), 2.46 (s, 3H), 5.33 (d, J=10.7 Hz, 1H), 5.50 (d, J=17.5 Hz, 1H), 5.98 (dd, J=10.7, 17.5 Hz, 1H), 6.85 (s, 1H), 7.09 (t, J=7.4 Hz, 1H), 7.27–7.31 (m, 2H), 7.47–7.49 (m, 2H). ^{13}C NMR (100.62 MHz): δ 17.2, 17.3, 21.2, 65.8, 68.9, 113.9, 117.9, 118.5, 124.1, 128.2, 134.8, 136.7, 153.5, 168.6, 169.9. GC–MS (70 eV) *m/z* (rel int.): 298 (33, M^+), 216 (100), 215 (55), 201 (29), 178 (91), 174 (45), 118 (31), 77 (43). IR ($CHCl_3$): 3066, 2980, 2930, 1750, 1600, 1500, 1362 cm^{-1}. HR-ESI-MS: *m/z* calcd for $C_{17}H_{19}N_2OS$: 299.1220, $[M+H]^+$; found: 299.1219. *Compound* **20b**. Yield 176 mg (59%), oil. ^{1}H NMR (400.13 MHz): δ 1.55 (s, 3H), 2.08 (s, 3H), 2.45 (s, 3H), 4.95 (dd, J=3.7, 8.1 Hz, 1H), 5.35–5.38 (m, 2H), 6.81 (s, 1H), 7.09 (t, J=7.4 Hz, 1H), 7.27–7.31 (m, 2H), 7.46–7.48 (m, 2H). ^{13}C NMR (100.62 MHz): δ 17.2, 17.3, 19.5, 65.7, 68.8, 114.17, 119.9, 118.4, 124.1, 128.9, 134.1, 136.6, 153.2, 168.8, 170.6. GC–MS (70 eV) *m/z* (rel int.): GC–MS (70 eV) *m/z* (rel int.): 298 (30, M^+), 216 (76), 215 (44), 201 (35), 178 (100), 174 (37), 118 (25), 77 (34). IR ($CHCl_3$): 3066, 2980, 2930, 1750, 1600, 1500, 1362 cm^{-1}. HR-ESI-MS: *m/z* calcd for $C_{17}H_{19}N_2OS$: 299.1220, $[M+H]^+$; found: 299.1220.

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3-Aza-8,10-dioxa-bicyclo[5.2.1]decane (9-*exo* BTKa) carboxylic acid as a new reverse turn inducer: synthesis and conformational analysis of a model peptide

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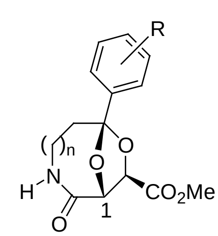
Abstract—Dipeptide isostere **5**, belonging to the class of 9-*exo* BTKa, was synthesised starting from *R*,*R*-tartaric acid and 4-nitro-1-(3-nitrophenyl)butan-1-one. The nine-membered lactam showed interesting structural features and was inserted in a 5-residue model peptide. The conformational properties of this modified peptide have been studied by NMR and molecular modelling, indicating that compound **5** acted as a reverse turn inducer.

1. Introduction

Reverse turns are structural motifs commonly found in proteins and bioactive peptides that play a central role as molecular recognition elements for many biological processes, by virtue of presenting up to four side chains in a well defined spatial arrangement.[1] In particular, β-turns consist of a tetrapeptide sequence (defined as i–$i+1$–$i+2$–$i+3$) in a non-helical region in which the peptide chain direction is reversed. These turns are often stabilised by an intramolecular hydrogen bond between the carbonyl oxygen of the first residue (i) and the amide proton of the fourth one ($i+3$)[2] thus being a key template for the design of the so-called 'turn-mimetics' in the drug discovery area.[3] During the last decade many efforts have been dedicated to synthesise new reverse turn inducers and to study the conformational preferences of turn-analogues within protein secondary structure models.[4] In recent years, we have been developing a new class of aza-dioxa[3.2.1]bicyclic compounds named BTAa[5] or BTKa,[6] the synthesis of which is based on the combination of a tartaric acid derivative and either α-amino aldehydes or α-amino ketones.[7] We have previously described the applications of these scaffolds as dipeptide isosteres when inserted in both cyclic[8] and linear[9] peptide sequences, acting as mimetics of $i+1$–$i+2$ central dipeptidic sequence of a typical β-turn motif. Moreover, bicyclic proline mimetics have been explored as reverse turn inducers in model peptides.[10]

In a recent paper,[11] we described the synthesis of two classes of enantiopure molecular scaffolds, whose lactam structure formally derives from the coupling between tartaric acid and β- or γ-ketoamines. By analogy with the previously reported 7-*exo* BTKa,[7c] we named these compounds as 8-*exo* and 9-*exo* BTKa, indicating the lactam size (eight- and nine-membered ring, respectively). The general structure is reported in Figure 1.



7-*exo* BTKa n = 0
8-*exo* BTKa n = 1
9-*exo* BTKa n = 2

Figure 1. General structure of BTKa.

The ring enlargement of the rigid 7-*exo* BTKa scaffolds afforded, as expected, more flexible compounds that represent a new class of dipeptide isosteres, prone to take different conformations and potentially useful as turn inducers. Preliminary molecular modelling calculations[11] explained the experimental upfield shift of the carbomethoxy group observed in the ^{1}H NMR when passing from

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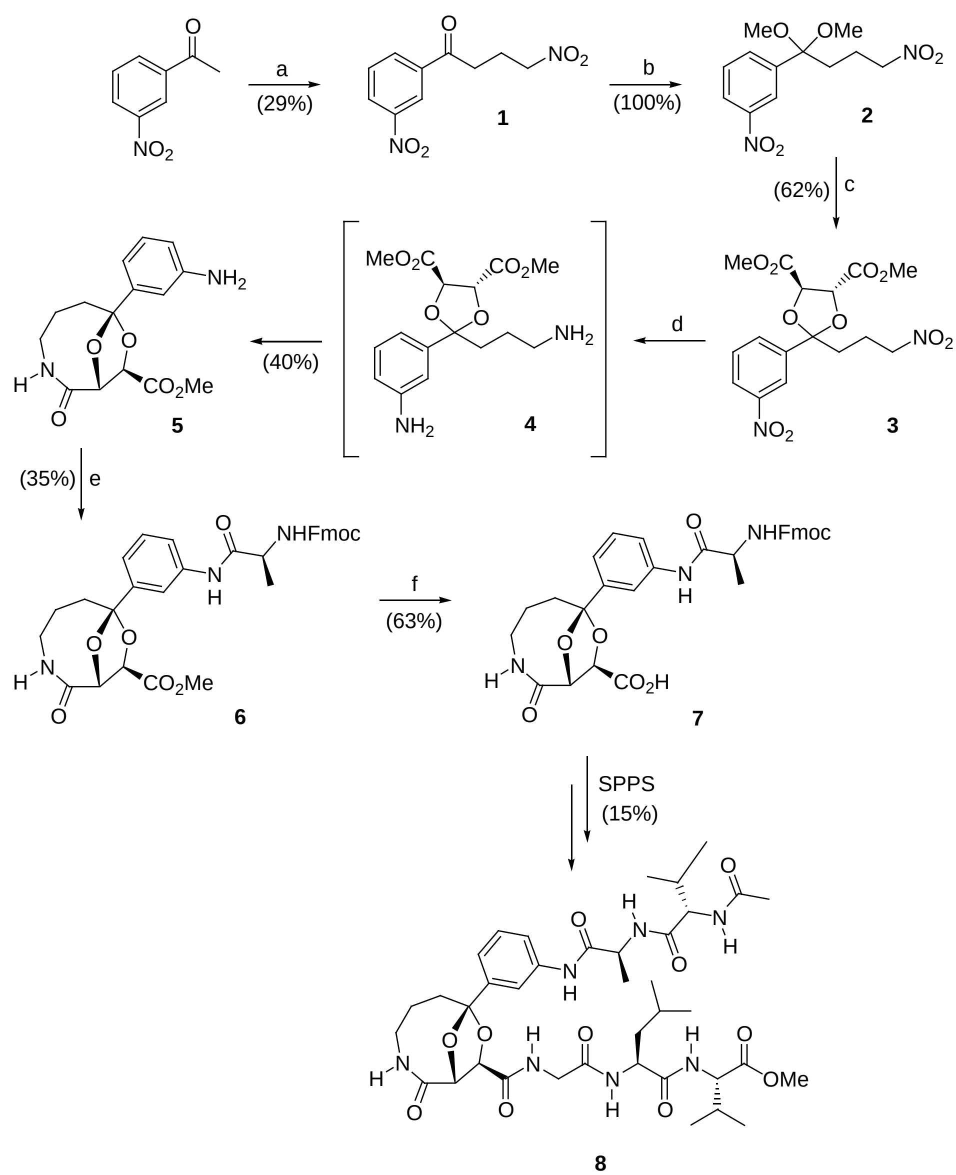
the 7-*exo* BTKa to the 8- and 9-*exo* ones[12] on the basis of the change of the average distance between this group and the aromatic ring on the bridgehead carbon, that decreases from 3.8 to 3.0 Å as the ring enlarges. This interesting structural characteristic prompted us to further investigate these molecules and their application as peptide turn inducers. In particular, we concentrated our attention on the 9-*exo* BTKa class (Fig. 1, $n=2$), that, as a consequence of the above-mentioned shortest distance of 3.0 Å between two easily functionalisable groups, could force two peptidic fragments to face each other, allowing the formation of a hydrogen bond network between them. We envisaged the ideal candidate for peptide modification in the compound bearing a *m*-NH_2 substituent on the aromatic ring. The 9-*exo* BTKa was inserted in the model sequence Ac-VA-BTKa-GLV-OMe and its effect on the peptide conformation is reported in detail in the next section.

2. Results and discussion

2.1. Synthesis

The synthesis of the target 9-*exo* BTKa (Scheme 1) started from γ-nitroketone **1**, that was obtained from commercially available 3′-nitroacetophenone in 29% yield over three steps. Compounds **2** and **3** were straightforwardly obtained in quantitative and 62% yield, respectively, following the previously reported experimental procedures.[11] Reduction of the nitro groups was first performed by the reported method, that is, hydrogenation on Raney-Ni in methanol at room temperature. By analogy to the synthesis of other 9-*exo* BTKa, a high yield of the reaction was not expected; however, reduction took place but neither lactam **5** nor diamine **4** were recovered. After a few more experiments, lactam **5** was obtained by hydrogenation with ammonium



Scheme 1. (a) (i) $(HCHO)_n$, $Me_2NH\cdot HCl$, EtOH, H^+, reflux, 2 h; (ii) NaOH aq; (iii) CH_3NO_2, TRITON B, reflux, 2 h; (b) $HC(OMe)_3$, *p*-TsOH cat., MeOH, reflux, 16 h; (c) $BF_3\cdot Et_2O$, EtOAc, 0 °C, 4 h; (d) NH_4HCO_2, Pd/C 10%, MeOH, reflux, 16 h; (e) Fmoc-Ala-OH (1 equiv), PyBROP (1 equiv), DIEA (1 equiv), $CHCl_3$, rt, 24 h; (f) LiOH aq (1.0 equiv), 1,4-dioxane/H_2O 1:1, 0 °C, 30′.

Table 1. Temperature dependence of amide proton chemical shifts for **8**

NH	$CDCl_3$		CD_3CN		DMSO-d_6	
	δ	$\Delta\delta/\Delta T$	δ	$\Delta\delta/\Delta T$	δ	$\Delta\delta/\Delta T$
Val-1	7.27	−6.83	6.82	−5.54	7.95	−4.61
Ala	6.92	−1.48	7.08	−6.07	8.25	−6.38
NH-3′	9.54	−5.64	8.81	−3.44	9.99	−5.17
Gly	7.10	−2.90	6.99	−2.27	7.78	−4.45
Leu	7.12	−5.64	6.69	−3.26	8.01	−4.64
Val-2	7.95	−5.64	7.08	−4.00	8.19	−7.21

δ are expressed in ppm and $\Delta\delta/\Delta T$ values in ppb/K.

formate over 10% Pd/C in refluxing methanol for 16 h (40% yield after purification). Compound **5** was then coupled with Fmoc-Ala-OH using PyBrop† as the activating agent and the resultant ester **6** was hydrolysed by LiOH in 1,4-dioxane/water at 0 °C to afford the Fmoc-amino acid **7**.

Peptide Ac-Val-Ala-BTKa-Gly-Leu-Val-OMe (**8**) was prepared by means of solid-phase techniques using Fmoc protocol and a HMBA-AM polystyrene resin, that afforded the title peptide with the C-terminus protected as methyl ester by a nucleophilic cleavage. Fmoc-Ala-BTKa **7** was incorporated into the growing peptide in the third coupling step. All amide couplings were monitored with bromophenol blue as internal colorimetric indicator. Nucleophilic cleavage from the resin was achieved by trans-esterification, heating a suspension of the resin at 50 °C overnight in a 9:1 MeOH/triethylamine mixture. The crude peptide was purified by semi-preparative HPLC, giving pure **8** in 15% yield.

2.2. NMR studies in $CDCl_3$

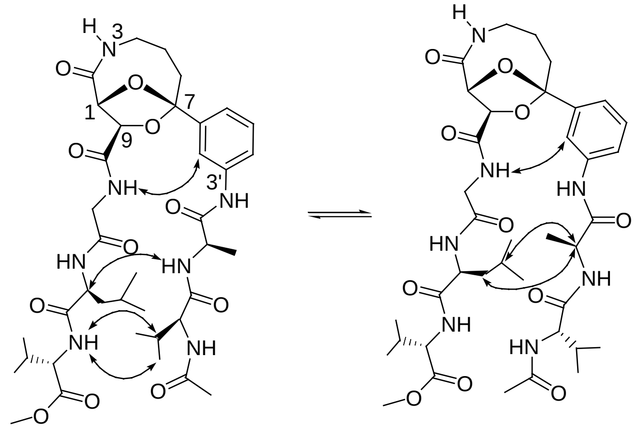
Conformational studies on peptide **8** were performed by NMR, using firstly a relatively non-polar solvent (i.e., $CDCl_3$), and successively more competitive solvents such as CD_3CN and DMSO-d_6, to investigate the solvent effect on the conformational preference of **8**. Solutions (4.2 mM) of **8** were used to achieve sufficient dilution to prevent aggregation. TOCSY and ROESY spectra were recorded to assign proton resonances and investigate both sequential and long-range NOE's that provide evidences of preferred conformations and give insight into stable reverse turn and sheet conformations.[13] Temperature dependence experiments were carried out, since the amide proton chemical shifts are sensitive to temperature and dilution variations, thus giving further insight into the conformational preferences of peptides.[14] The combination of chemical shift and $\Delta\delta/\Delta T$ coefficient of the amide protons provides information on the extent of hydrogen bonding.[2]

^{1}H NMR analysis of compound **8** in $CDCl_3$ solution was complicated by the flexibility and size of the peptidomimetic, and the attempted structural determination of **8** turned out to be complex, as spectral data of sufficient quality for structure determination were not obtained in $CDCl_3$. Moreover, signals in the ROESY spectrum indicated slow to intermediate exchange rates between several conformers. All amide values except NH-3′ were found between 7 and 8 ppm, with Val-2 NH being the most deshielded (Table 1). A temperature dependent NMR experiment indicated the presence of an equilibrium between hydrogen bonded and non-hydrogen bonded states, as many amide protons showed large $\Delta\delta/\Delta T$ values. The low $\Delta\delta/\Delta T$ coefficient of Ala NH, compared with the other amide protons, indicated the presence of a hydrogen bonded environment for this amide proton in $CDCl_3$ solutions. The glycine amide coefficient also showed a relatively temperature stable chemical shift. In this case, the low coefficient may be due to the *anti* O-8 orientation of carbonyl group at C-9 of the scaffold rather than to the existence of a hydrogen bond. The high chemical shift of Val-2 NH in conjunction with the corresponding $\Delta\delta/\Delta T$ value suggested an equilibrium of conformers in which this amide proton experienced both non-hydrogen bonded states and hydrogen bonds with different carbonyl groups.

2.3. NMR studies in CD_3CN

Experiments carried out in CD_3CN showed marked differences, suggesting that a more competitive solvent induces peptide **8** to become more organised. As a consequence of the greater solvating effect of CD_3CN, though still remaining non-competitive relatively to hydrogen bonding, the chemical shift values of the amide protons experienced significant changes, except for glycine and alanine, that appeared slightly upfield and downfield relative to signals recorded in $CDCl_3$, respectively. Moreover, the same trend of temperature coefficients as observed for $CDCl_3$ solutions was followed, with the glycine amide proton showing the lowest $\Delta\delta/\Delta T$. In contrast the alanine NH signal increased significantly, confirming the poor hydrogen bonding character of this proton in CD_3CN, which is itself a moderate hydrogen bond acceptor. The amide NH-3′ coefficient also suggested the presence of an equilibrium between hydrogen bonded and non-hydrogen bonded structures. NOE experiments suggested the existence of β-strand organisation of the main chain, as all the amino acids showed strong $\alpha,N(i,\ i+1)$ sequential peaks. Moreover, ROESY spectra of **8** showed some cross-peaks between protons on non-adjacent residues. These NOE's were indicative of an equilibrium between more equivalent conformations (Fig. 2). A strong cross-strand ROESY peak between glycine NH and H-2′ clearly demonstrated the reverse turn inducing role of the scaffold. Moreover, other cross-strand ROESY peaks between Ala NH and Leu α-H, and between Val-2 NH and both Val-1 β- and γ-H confirmed the existence of a well-ordered reverse turn structure (Fig. 2, left). Interestingly, the presence of cross-strand ROESY peaks experienced by Ala α-H with Leu β- and γ-H indicated the existence of a second conformer

† Bromotripyrrolidinophosphonium hexafluorophosphate.



8 8
Conformer I *Conformer II*

Figure 2. Peptide **8**: the arrows indicate significant cross-strand ROESY correlations in CD_3CN.

(Fig. 2, right), in which the N-terminal half was found to be flipped, thus orienting Ala NH or Ala α-H inside the turn structure, respectively. These NOE interactions demonstrated that the scaffold **5** acts as a mimetic of the central dipeptidic unit of a β-turn, thus generating an unusual reverse turn. The existence of these two highly ordered structures was in agreement with $\Delta\delta/\Delta T$ data, indicating the presence of equilibrating weak hydrogen bonds. The absence of stable hydrogen bonds characteristic of reverse turn structures indicated that the principal driving force for reverse turn formation is a consequence of the structure of the scaffold. Further stabilisation is provided by intramolecular hydrogen bonding and hydrophobic interactions that contribute to the overall organisation of the peptide into β-strands conformations.

2.4. NMR studies in DMSO-d_6

Experiments carried out in DMSO-d_6 showed all the amide protons deshielded with respect to $CDCl_3$ solutions, as expected. Nevertheless, Val-2 NH only showed a small chemical shift variation, changing from 7.96 to 8.19. Thus, the high chemical shift observed in $CDCl_3$ solution, in conjunction with low influence of solvent composition on chemical shift, indicated the Val-2 amide bond to be engaged in different hydrogen bonds, although its high temperature coefficients in both solvents were indicative of the presence of non-hydrogen bonded states, and of the absence of a specific hydrogen bond of significant strength. Gly NH showed a small temperature coefficient compared to the other protons, confirming the hypothesis that the role of the scaffold was to control the position of the adjacent species. Moreover, Val-1 NH proved to lower its coefficient on moving to a more competitive solvent, probably due to the presence of more structured conformations in the more highly solvating system. The existence of a large temperature coefficient did not prevent the hypothesis of multiple hydrogen bonds, and was in agreement with the presence of two or more equilibrating structures (due in particular to flipping of the N-terminal chain), which in turn generated different patterns of hydrogen bonds. This conformational equilibrium was particularly evident when CD_3CN and DMSO-d_6 were used as solvents. ROESY experiments in DMSO-d_6 confirmed the β-strand organisation of the reverse turn peptide, as suggested by strong $\alpha,N(i, i+1)$ sequential peaks experienced by all the amino acids. Moreover, cross-strand ROESY peaks between Val-2 NH and both Val-1 β- and γ-H were also maintained in this solvent, confirming the turn structure.

2.5. Molecular modelling

Molecular modelling using AMBER* as a force field[15] was carried out to gain further insight into the conformational preferences of peptide **8**. Full unconstrained Monte Carlo conformational search[16] using $CHCl_3$ as explicit solvent resulted in all the conformers having a marked tendency of adopting a reverse turn conformation, in which the scaffold occupies the central turn position.

The distance d and the virtual torsion angle β were computed to investigate the turn propensity The distance d between the C-α of the first and fourth residue of a β-turn is diagnostic of the presence of a reverse turn when its value is lower than 7 Å,[1a] and the virtual torsion angle β is indicative of a reverse turn when it assumes a value within the range of $0\pm30°$.[17] For peptide **8**, the chain reversing property of this unusual turn structure was assessed computing parameter d as the distance between Gly C-α and C-3′, and considering β as the dihedral angle formed by C-3′–C-5–C-9-Gly C-α. In all the conformers, d and β values fell within the diagnostic range for a turn structure, confirming the hypothesis of the scaffold acting as a nucleator of tight reverse turns. All the conformers produced by the Monte Carlo calculation showed that the turn structure of **8** was stabilised by two or more hydrogen bonds in a different fashion, producing two main groups of conformers, in agreement with the NMR data (Fig. 3). The first group of conformers included structures A, C and D, all having in common the same orientation of the two peptidic halves. The second group, represented by structure B, showed the N-terminal main chain flipped with respect to the former one. Specifically, the first group of conformers encompassing the global minimum conformer ($E=-545.2$ kJ/mol) were found in 8% abundance, and showed two hydrogen bonds, between Val-2 NH and Ala CO, and between Ala NH and Val-2 CO, thus giving a bent turn structure stabilised by a distorted β-sheet structure (Fig. 3, structure A). An additional set of structures belonging to this group were found in 36% abundance (Fig. 3, structure C), and displayed a twisted turn conformation stabilised by Ala NH and Gly CO, and Val-2 NH and Ala CO hydrogen bonds. A higher energy conformer was present in 15% abundance (Fig. 3, structure D), and showed a distorted β-strand structure of peptide halves stabilised by three hydrogen bonds formed by Gly NH and Ala CO, Ala NH and Gly CO, and between Val-2 NH and acetyl CO.

The second group of structures (18%) was represented by the second conformer in order of increasing energy ($E=-542.5$ kJ/mol), which showed a well-organised sheet structure stabilised by three hydrogen bonds: NH-3′ and Gly CO, Val-2 NH and Val-1 CO, Val-1 NH and Val-2 CO (Fig. 3, structure B). In this structure, NH-3′ was found to be engaged in a hydrogen bond with Gly CO, in agreement

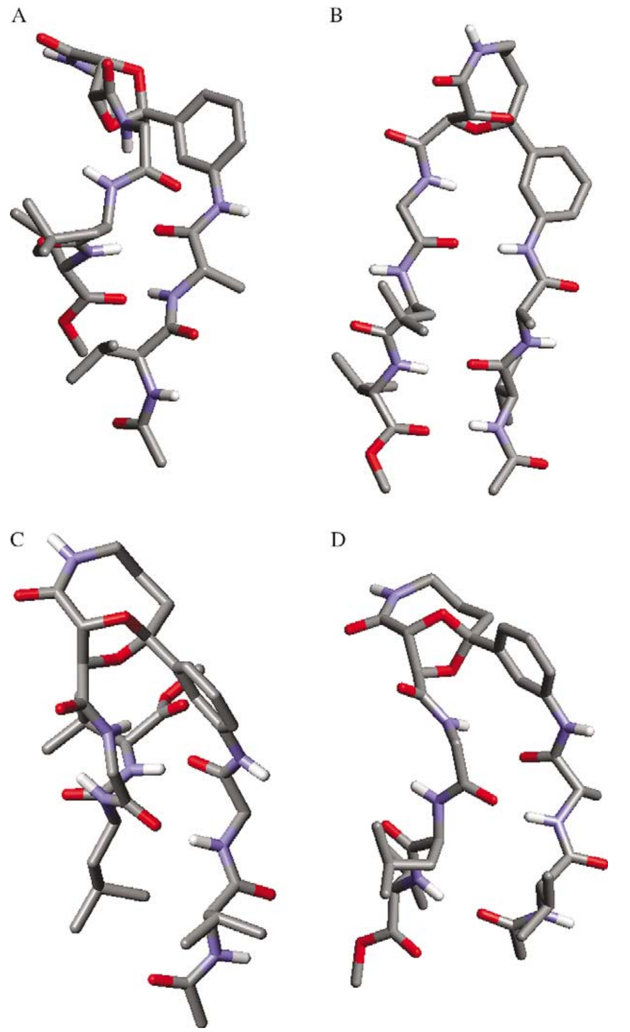


Figure 3. Low energy conformers obtained by Monte Carlo calculation.

with the lower $\Delta\delta/\Delta T$ coefficient in CD_3CN, confirming the hypothesis that such a structure was particularly relevant in this solvent (see also ROESY correlations as in Fig. 2, right). All the low energy conformers displayed a β-sheet structure with the scaffold acting as external reverse turn inducer. The presence of different hydrogen bonds experienced by Ala and Val-2 amide protons were in agreement with NMR data. In particular, the low $\Delta\delta/\Delta T$ value found in $CDCl_3$ for Ala NH was compatible with its hydrogen bonding character in a non-competitive solvent like chloroform. In the case of Val-2 NH, however, the high chemical shift and $\Delta\delta/\Delta T$ value of Val-2 amide proton in $CDCl_3$ and the slight chemical shift variation from $CDCl_3$ to DMSO-d_6 suggested an equilibrium between hydrogen bonded and non-hydrogen bonded states in all the solvents considered.

Molecular dynamic calculations over 1 ns were carried out on all of the four structures found by Monte Carlo calculations to gain information on the vicinity of local minima of found structures, and to verify the flexibility of the structures found in the conformational search. The global minimum conformer showed poor stability under MD calculations, as the hydrogen bond percentages dropped to 4.5%, giving an open turn structure, in agreement with the hypothesis of equilibrating structures, as suggested by NMR data. The population of hydrogen bonded structures was found at a lower percentage with respect to Monte Carlo calculation, confirming the high flexibility of peptide **8** and agreeing with the presence of more structures, though *d* and β values lowered only to about 60%, demonstrating the strong reverse turn propensity of model peptide **8**.

3. Conclusions

In this work, we realised the synthesis of a new dipeptide isostere belonging to the class of 9-*exo* BTKa, starting from a suitable aromatic γ-nitroketone. The title compound (**5**) was inserted in a linear peptide chain and the structural effects on the conformation of the model were studied.

We verified that compound **5** generated a tight reverse turn stabilised by its rigid structure and by the preferred *anti* orientation of carbonyl group at C-9 position. Moreover, the ring size allowed the aromatic ring to bend towards the carbonyl at C-9, thus producing an unusual reverse turn inducer. Conformational analysis by NMR in different solvent systems showed the existence of equilibrating structures, stabilised by different patterns of hydrogen bonds or simply by hydrophobic interactions. Sequential and cross-strand ROESY peaks revealed well-ordered turn structures, especially in more competitive solvents such as CD_3CN and DMSO-d_6. Moreover, when moving to a more competitive solvent, although the labile hydrogen bonds were disrupted, the β-sheet organisation of the reverse turn peptide was further stabilised, as was particularly evident in ROESY spectra in CD_3CN. The absence of stable hydrogen bonds, characteristic of reverse turn structures, indicated that the principal driving force for reverse turn formation is due to the particular structural form of the scaffold. Further stabilisation is provided by weak intramolecular hydrogen bonding and hydrophobic interactions that contribute to the overall organisation of peptide into β-strand conformations. Molecular modelling confirmed the existence of equilibrating structures, specifically due to a flip of N-terminal chain, which allowed the arrangement of the amide proton NH-3′ to the inside or outside of the turn. Finally, molecular dynamic calculations confirmed the low stability of hydrogen bond networks present in the low energy conformers, in accordance with NMR data. Introduction of chemical functionalities on amide at position 3 of the scaffold and on the aromatic ring might allow side chains isosteres to be appended at the $i+1$ and $i+2$ positions of the turn.

4. Experimental

4.1. General

Melting points are uncorrected. Chromatographic separations were performed under pressure on silica gel by flash-column techniques; R_f values refer to TLC carried out on 25-mm silica gel plates (Merck F254), with the same eluent as indicated for the column chromatography. IR spectra were recorded with a Perkin-Elmer 881 spectrophotometer in $CDCl_3$ solution.

Apart from peptide **8**, ^{1}H NMR (200 MHz) and ^{13}C NMR (50.33 MHz) spectra were recorded with a Varian XL 200 instrument in $CDCl_3$ solution. NMR spectra of peptide **8** were performed on a Varian MercuryPlus 400 spectrometer operating at 400 MHz for ^{1}H. The spectra were obtained in 4.2 mM $CDCl_3$ or CD_3CN solution where aggregation was not significant. One-dimensional ^{1}H NMR spectra for determining temperature coefficients were obtained at 298–328 K with increments of 5 K. Sample temperatures were controlled with the variable-temperature unit of the instrument. Complete proton resonance assignments were made with the aid of gCOSY, TOCSY, HSQC and ROESY experiments.

Mass spectra were carried out by EI at 70 eV, unless otherwise stated, on 5790A-5970A Hewlett-Packard and QMD 1000 Carlo Erba instruments. Microanalyses were carried out with a Perkin-Elmer 2400/2 elemental analyser. Optical rotations were determined with a JASCO DIP-370 instrument.

All the solid-phase reactions were carried out on a shaker, using solvents of HPLC quality. HPLC purification was performed with an HPLC system equipped with semi-preparative C-18 10 μm, 250×10 mm, reverse-phase column using H_2O–CH_3CN eluent buffered with 0.1% TFA. Peptide **8** was characterised by ESI-MS, 2D-NMR and HPLC system equipped with an analytical C-18 10 μm, 250×4.6 mm, reverse-phase column.

4-Nitro-1-(3-nitrophenyl)butan-1-one (**1**) was synthesised as already reported.[18]

4.1.1. 1-(1,1-Dimethoxy-4-nitrobutyl)-3-nitrobenzene (2). Synthesised using the procedure previously reported for closely related compounds,[11] starting from **1** (1.56 g, 6.55 mmol) an refluxing for 16 h. After filtration and evaporation of the solvent, crude **2** was obtained in quantitative yield and used in the next step without further purification.

Compound **2**. Yellow oil. ^{1}H NMR δ (ppm): 8.36 (s, 1H), 8.20 (d, $J=8.0$ Hz, 1H), 7.79 (d, $J=7.8$ Hz, 1H), 7.57 (t, $J=7.8$ Hz, 1H), 4.25 (t, $J=6.6$ Hz, 2H), 3.17 (s, 6H), 2.05–1.97 (m, 2H), 1.74–1.57 (m, 2H). ^{13}C NMR δ (ppm): 148.4 (s), 142.5 (s), 132.9 (d), 129.4 (d), 123.2 (d), 122.2 (d), 102.1 (s), 74.8 (t), 48.9 (q, 2C), 33.6 (t), 21.5 (t). MS *m/z* (%): 284 (M^+, 1).

4.1.2. (4*R*,5*R*)2-(3-Nitrophenyl)-2-(3-nitropropyl)-[1,3]dioxolane-4,5-dicarboxylic acid dimethyl ester (3). Synthesised using the procedure previously reported for closely related compounds,[11] starting from **2** (1.8 g, 6.33 mmol). After purification by chromatography (eluent: EtOAc/petroleum ether, 1:4, $R_f=0.25$), pure **3** was obtained as pale yellow oil (1.56 g, 62%).

Compound **3**. $[\alpha]_D^{25}$ +81.9 (*c* 1.0, $CHCl_3$). ^{1}H NMR δ (ppm): 8.36 (s, 1H), 8.20 (d, $J=8.0$ Hz, 1H), 7.83 (d, $J=8.0$ Hz, 1H), 7.55 (t, $J=8.0$ Hz, 1H), 4.81 (AB system, $J_{AB}=5.6$ Hz, 2H) 4.48 (t, $J=6.6$ Hz, 2H), 3.86 (s, 3H), 3.58 (s, 3H), 2.24–2.04 (m, 4H). ^{13}C NMR δ (ppm): 168.6 (s), 168.5 (s), 148.1 (s), 142.6 (d), 132.0 (d), 129.4 (d), 123.8 (d), 120.9 (d), 113.0 (s), 77.7 (d), 76.5 (d), 74.9 (t), 53.0 (q), 52.7 (q), 36.9 (t), 21.2 (t). MS *m/z* (%): 399 ($M^+ + 1$, 1), 310 ($M^+ - (CH_2)_3NO_2$, 100). Anal. Calcd for $C_{16}H_{18}N_2O_{10}$: C, 48.25; H, 4.55; N, 7.03. Found: C, 48.36; H, 4.52; N, 6.96.

4.1.3. (1*R*,7*R*,9*R*)7-(3-Aminophenyl)-2-oxo-8,10-dioxa-3-azabicyclo[5.2.1]decane-9-carboxylic acid methyl ester (5). Ammonium formate (1.58 g, 25.1 mmol) and Pd/C 10% (150 mg) were added to a solution of **3** (500 mg, 1.26 mmol) in MeOH (300 mL). The mixture was heated under reflux for 16 h and, after cooling, filtered through a Celite layer and finally evaporated to give crude **5**, that was purified by chromatography (eluent: EtOAc/petroleum ether 0.1% Et_3N, 3:1, $R_f=0.17$) affording pure **5** (154 mg, 40%) as a white solid.

Compound **5**. $[\alpha]_D^{25}$ −12.3 (*c* 1.0, $CHCl_3$). ^{1}H NMR δ (ppm): 7.11 (t, $J=8.0$ Hz, 1H), 6.87 (s, 1H), 6.82 (d, $J=2.2$ Hz, 1H), 6.61 (dd, $J=8.0$, 1.4 Hz, 1H), 6.52 (br s, 1H), 5.30 (d, $J=1.8$ Hz, 1H), 4.94 (d, $J=1.8$ Hz, 1H), 4.15–4.05 (m, 1H), 3.46 (s, 3H), 3.40–3.20 (m, 1H), 2.21–2.13 (m, 1H), 2.07–1.84 (m, 3H). ^{13}C NMR δ (ppm): 174.0 (s), 169.4 (s), 146.0 (s), 142.5 (s), 128.9 (d), 115.5 (d), 115.0 (d), 114.9 (s), 112.0 (d), 79.5 (d), 78.7 (d), 52.4 (q), 42.1 (t), 36.2 (t), 25.6 (t). MS *m/z* (%): 306 (M^+, 30), 247 ($M^+ - CO_2CH_3$, 9), 137 (82), 120 (100). Anal. Calcd for $C_{15}H_{18}N_2O_5 \cdot 2H_2O$: C, 52.63; H, 6.48; N, 8.18. Found: C, 52.87; H, 6.50; N, 8.29.

4.1.4. (1*R*,2*S*,7*R*,9*R*)7-{3-[2-(9*H*-Fluoren-9-ylmethoxy-carbonylamino)propionylamino]phenyl}-2-oxo-8,10-dioxa-3-azabicyclo[5.2.1]decane-9-carboxylic acid methyl ester (6). Fmoc-Ala-OH (312 mg, 1.08 mmol), PyBrop (468 mg, 1.08 mmol) and DIEA (344 μL, 2.16 mmol) were added to a solution of **5** (300 mg, 1.08 mmol) in anhydrous $CHCl_3$ (5 mL). The mixture was left at room temperature, under stirring and nitrogen atmosphere. After 24 h AcOEt (20 mL) was added and the organic phase was washed with water (2×10 mL), satd $NaHCO_3$ (2×10 mL), and dried over Na_2SO_4. After filtration and evaporation of the solvent, the obtained crude **6** was purified by flash chromatography (eluent: AcOEt/petroleum ether, 3:1; $R_f=0.22$), affording pure **6** (230 mg, 36%) as a yellowish solid.

Compound **6**. Mp 154–155 °C. $[\alpha]_D^{25}$ −44.3 (*c* 0.25, CH_3OH). ^{1}H NMR δ (ppm): 8.46 (s, 1H), 7.78–7.74 (m, 12H), 6.58 (br s, 1H), 5.47 (br s, 1H), 5.39 (s, 1H), 4.96 (s, 1H), 4.46–4.40 (m, 3H), 4.22 (t, $J=7.0$ Hz, 1H), 4.19–4.00 (m, 1H), 3.39 (s, 3H), 3.20–3.09 (m, 1H), 2.17–2.06 (m, 1H), 1.95–1.83 (m, 3H), 1.48 (d, $J=7.0$ Hz, 3H). ^{13}C NMR δ (ppm): 173.9 (s), 170.7 (s), 169.2 (s), 156.4 (s), 143.6 (s, 2C), 142.5 (s), 141.3 (s, 2C), 137.5 (d), 128.7 (d), 127.8 (d, 2C), 127.1 (d, 2C), 125.0 (d, 2C), 121.2 (d), 120.0 (d, 2C), 119.9 (d), 116.8 (d), 114.5 (s), 79.6 (d), 78.8 (d), 67.3 (t), 52.3 (q), 51.2 (d), 47.0 (t), 42.1 (d), 36.9 (t), 29.7 (t), 25.7 (q). MS *m/z* (%): 599 (M^+, 20). Anal. Calcd for $C_{33}H_{33}N_3O_8 \cdot 2H_2O$: C, 62.35; H, 5.87; N, 6.61. Found: C, 62.62; H, 5.86; N, 6.69.

4.1.5. (1*R*,2*S*,7*R*,9*R*)7-{3-[2-(9*H*-Fluoren-9-ylmethoxy-carbonylamino)propionylamino]phenyl}-2-oxo-8,10-dioxa-3-azabicyclo[5.2.1]decane-9-carboxylic acid (7). A 0.40 M solution of LiOH in H_2O (0.25 mL) was added dropwise to a solution of **6** (62 mg, 0.10 mmol) in 1,4-dioxane (0.5 mL) and water (0.5 mL) cooled at 0 °C. The resulting mixture was stirred at 0 °C for 30 min and then 5% $KHSO_4$ was added reducing the pH to 5. After concentration to a small volume, the product was extracted with $CHCl_3$ (4×10 mL), adjusting the pH to 5 after every extraction. The combined organic phases were dried over Na_2SO_4. After filtration and evaporation of the solvent, pure **7** (38 mg, 63%) was obtained as a yellowish solid.

Compound **7**. $[\alpha]_D^{25}$ −48.8 (*c* 0.3, $CHCl_3$). ^1H NMR δ (ppm): 9.13 (s, 1H), 7.76–7.67 (m, 2H), 7.57–7.40 (m, 3H), 7.40–7.14 (m, 7H), 6.25 (m, 1H), 5.23 (s, 1H), 4.89 (s, 1H), 4.42 (m, 1H), 4.29–4.11 (m, 4H), 3.17–2.74 (m, 1H), 2.03–1.45 (m, 4H), 1.37 (m, 3H). ^{13}C NMR δ (ppm): 175.1 (s), 172.0 (s), 171.7 (s), 156.4 (s), 143.8 (s), 143.5 (s, 2C), 141.2 (s, 2C), 137.7 (s), 128.7 (d), 127.7 (d, 2C), 127.0 (d, 2C), 125.1 (d, 2C), 121.2 (d), 120.1 (d), 119.9 (d, 2C), 117.0 (d), 114.5 (s), 79.2 (d), 78.7 (d), 67.0 (t), 51.3 (d), 46.9 (t), 41.4 (d), 35.7 (t), 29.6 (t), 24.8 (q). MS *m/z* (%): 586 (M^+, 10). Anal. Calcd for $C_{32}H_{31}N_3O_8\cdot 2H_2O$: C, 61.83; H, 5.67; N, 6.76. Found: C, 61.98; H, 5.72; N, 6.58.

4.2. Peptide synthesis

Peptide **8** was prepared by means of solid-phase techniques using a HMBA-AM polystyrene resin (100 mg, 0.08 mmol). A five equivalent excess of Fmoc amino acids and DIPC/HOBt carboxylic-activating mixture were used throughout the synthesis, and DMF was used as solvent. Compound **7** was used in 2 equiv excess. Final acetylation was performed with Ac_2O in DMF using catalytic 4-dimethylamino-pyridine. All amide couplings were monitored with bromophenol blue as an internal colorimetric indicator.[19] Nucleophilic cleavage from the resin was achieved by trans-esterification, heating at 50 °C overnight a suspension of the resin in a 9:1 MeOH/triethylamine mixture. Crude peptide was purified by semi-preparative HPLC using 10–90% ACN/55 min as gradient, giving pure **8** as a white solid (9.5 mg, 15%).

Compound **8**. t_R = 20.8 min (91% HPLC purity) using 0% ACN/5 min, 0–10% ACN/5 min, then 10–90% ACN/20 min as gradient. ESI-MS *m/z* (%): 788.27 (M^++1, 35), 810.46 (M^++Na, 100), 826.40 (M^++K, 45). ^1H and ^{13}C NMR data are shown in Table 2.

4.3. Computational methods

Molecular mechanics calculations were carried out on a SGI IRIX 6.5 workstation, using MacroModel (v6.5) molecular modelling software,[20] with AMBER* as a force field[15] and the implicit chloroform GB/SA solvating system.[21] Monte Carlo conformational search[16] was carried out without imposing any constraint and including amide bonds among all rotatable bonds. Two thousand structures were generated and minimised until the gradient was less than 0.05 kJ/Å/mol using the TNCG gradient implemented in Macro-Model.[22] All the conformers having an energy of 6 kcal/mol above the global minimum conformer were discarded. Molecular dynamic (MD) hybrid simulation algorithm was used to assess stability of low energy conformers. AMBER*

Table 2. Proton and carbon chemical shifts of peptide **8** (δ values are expressed in ppm, and in parentheses are reported *J* values in Hz)

	^1H (DMSO-d_6)	^1H (CD_3CN)	^1H ($CDCl_3$)	^{13}C ($CDCl_3$)
Ac	1.92	1.99	2.08	22.9
Val-1 NH	7.95 (d, 8.2)	6.82 (d, 6.8)	7.27	—
Val-1H-α	4.20 (t, 6.8)	3.99 (dd, 6.1; 6.1)	4.33	58.9
Val-1H-β	2.00	2.02	2.04	31.4
Val-1H-γ	0.90	0.87 (d, 6.9)	0.95	19.4
Ala NH	8.25 (d, 7.0)	7.08 (d, 6.2)	6.79	—
Ala α-H	4.42	4.39 (dq, 7.1; 6.2)	4.82	49.8
Ala β-H	1.34 (d, 7.0)	1.31 (d, 7.1)	1.46 (d, 6.6)	19.3
BTK H-1	4.99 (d, 2.7)	4.99 (d, 2.7)	5.31	80.0
BTK H-3	7.91	6.37 (t, 7.1)	6.20	—
BTK H-4	4.02, 3.09	4.00 and 3.07	4.20 and 3.19	40.9
BTK H-5	1.60, 2.07	1.65 and 2.03	2.13 and 1.88	25.3
BTK H-6	2.0, 2.07	2.05	2.46 and 2.13	22.2
BTK H-9	4.88 (d, 2.8)	4.80 (d, 2.7)	5.01	79.8
BTK H-2′	7.74	7.71	7.62	118.5
BTK NH-3′	9.99	8.81	9.49	—
BTK H-4′	7.70 (d, 8.0)	7.19 (d, 8.0)	7.26	121.0
BTK H-5′	7.33 (t, 7.8)	7.26 (t, 7.8)	7.36 (dd, 8.0; 7.6)	129.0
BTK H-6′	7.24 (d, 7.9)	7.73 (d, 8.0)	8.22	104.3
Gly NH	7.78 (t, 5.6)	6.99 (t, 5.9)	7.10	—
Gly α-H	3.73 (dd, 16.6, 6.0) 3.53 (dd, 16.8, 4.9)	3.54 (t, 5.9)	4.33 and 3.73	42.4
Leu NH	8.01 (d, 8.2)	6.69 (d, 8.0)	7.10	—
Leu α-H	4.43	4.35	4.84	52.1
Leu β-H	1.36, 1.60	1.45	1.50 and 1.35	42.1
Leu γ-H	1.60	1.65	1.58	24.7
Leu δ-H	0.90	0.79 (d, 7.1)	0.89 (d, 5.9)	22.8 and 19.1
Val-2 NH	8.19 (d, 8.0)	7.08 (d, 6.2)	8.02	—
Val-2H-α	4.14 (t, 7.8)	4.19 (dd, 8.3; 6.2)	4.55 (dd, 8.7; 5.8)	57.4
Val-2H-β	2.07	2.01	2.10	31.7
Val-2H-γ	0.91	0.79 (d, 7.1)	0.89 (d, 5.9)	18.9
OMe	3.64	3.58	3.75	52.2

Experiments in $CDCl_3$ solution have been carried out at 303 K, and at 298 K for DMSO-d_6 and CD_3CN solutions.

was used as force field, as implemented in Macromodel (v6.5). A time step of 0.75 fs was used and the total simulation was 2000 ps; samples were taken at 1 ps intervals, yielding 2000 conformations for analysis.

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Formation of polysubstituted chlorocyclopropanes from electrophilic olefins and activated trichloromethyl compounds

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Abstract—Chlorocyclopropanes and bicyclic chlorocyclopropanes are prepared in non basic conditions by electroreductive or Mg-promoted Barbier activation of $PhCCl_3$ or Cl_3CCO_2Me in the presence of acyclic or cyclic α,β-unsaturated carbonyl compounds.

1. Introduction

Cyclopropane containing molecules usually display interesting specific structural and physico-chemical properties. The presence of substituents on the C3 ring enables further transformations such as functional group interconversions or couplings with other molecules. Thus, 1-chlorocyclopropanecarboxylic acids are precursors of various aminocyclopropanecarboxylic acids[1a,b] known for their biological activity[2] whereas 2-chlorocyclopropanecarboxylic acids are precursors of agrochemicals,[3] and have also been used recently in the synthesis of Callipeltoside A, a novel antitumor agent, with the aim of elucidating its structure and notably the C-20 and C-21 configurations.[4]

The formation of polysubstituted chlorocyclopropanes from the coupling of acyclic α,β-unsaturated esters or cyclic α,β-unsaturated ketones with α,α-dichlorocarbanions, or equivalent nucleophilic organometallic species stabilized by an electron withdrawing group such as CO_2R or Ph, has already been reported in the literature. These nucleophilic intermediates are generated either by basic treatments (i.e., sodium hydride,[5] LDA,[6] electrogenerated bases,[7] two-phase-solid–liquid system[8] or LiHMDS-DBU[9]) of alkyl dichloroacetates and α,α-dichlorotoluene, or by an oxidative addition of a carbon–chlorine bond of the corresponding trichloromethyl compounds (Cl_3C–Y: Y = CO_2R, Ph) onto a soluble Cu(0)–isonitrile complex.[10] These preparations of chlorocylopropanes involve either a conjugate nucleophilic addition followed by subsequent ring closure (MIRC reaction[11a,b]) or carbenoid intermediates. Cyclocondensation to olefins is also mentioned with the ambiphilic chloroaryl carbenes photolytically generated from 3-chloro-3-aryldiazirines.[12] Moreover it must be noted that substituted 1-chlorocyclopropanecarboxaldehydes, precursors of methyl 1-chlorocyclopropanecarboxylates are synthesized via a semi-benzilic Favorski rearrangement of substituted 2,2-dichlorocyclobutanols obtained by reduction of the corresponding cyclobutanones.[13]

We have already investigated the synthesis of methyl 2,2-diphenylcyclopropanecarboxylates and of 2-acyl-1,1-diphenylcyclopropanes.[14a–c] We have notably reported two methods: one is an indirect electroreductive coupling between dichlorodiphenylmethane and cyclic or acyclic α,β-unsaturated carbonyl compounds (referred to below as process A),[14a,b] whereas the other one is a Mg-mediated Barbier type reaction in DMF (referred to below as process B).[14c] This last route uses the same couples of reagents as those involved in process A, but it does not apply to α,β-unsaturated methyl ketones.

2. Results and discussion

In this paper, we report the preparation of polysubstituted chlorocyclopropanes from α,β-unsaturated acyclic esters or

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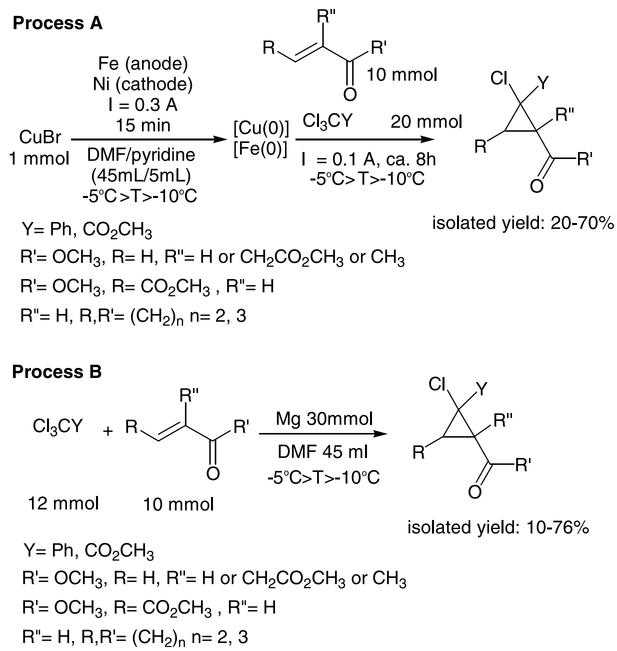


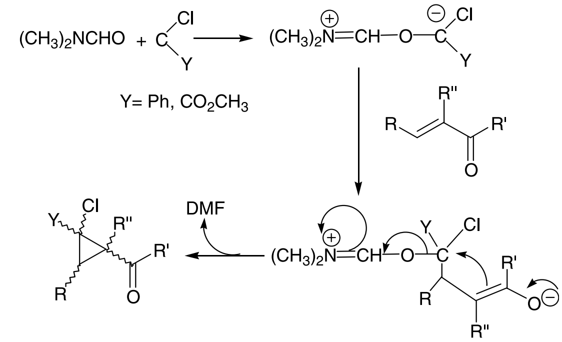
Scheme 1.

from cyclic α,β-unsaturated ketones and methyl trichloroacetate or α,α,α-trichlorotoluene (Scheme 1). It offers the opportunity to use and study both methods (processes A and B) and to compare their respective advantages and limitations, which proved to be rather complementary. The results are listed in Table 1.

These results first show that both methods generate nucleophilic intermediates, which add more or less efficiently to the olefin depending on its nature. More interestingly, these two methods are complementary. Thus, methacrylic acid esters show low reactivity in the electrochemical process (A) while yields obtained from the chemical method (B) are high (Table 1, entries 5 and 6). Such behaviour has already been observed with crotonic and methacrylic acids esters in other electrochemical reactions.[16] On the contrary, yields are higher from the electrochemical method than from the chemical one when maleic or fumaric acid esters are involved (Table 1, entries 7–10). This may indicate the occurrence, in process B, of side reactions at the olefins due to their reducibility, whereas in the electrochemical process, the cathode potential is self-controlled according to the most easily reduced species, in this case the copper salts. All the other cases studied gave similar results from both methods.

The mechanisms involved in either process have not been fully elucidated so far. The occurrence of a non complexed carbene species can, however, be ruled out in both cases, due notably to the absence of stereocontrol in the ring formation (Table 1, entries 7, 9 and 8, 10). In addition, would the carben be formed (chlorophenylcarbene and chloromethoxycarbonylcarbene) it would be rather electrophilic, as described in the literature,[12a,b,17,18] and should therefore react with electron-rich olefins like tetramethylethylene, or cyclohexene, which has never been observed.

In the Mg-Barbier type process (B), a route via α,α-dichloromagnesium compounds, which are known to lose



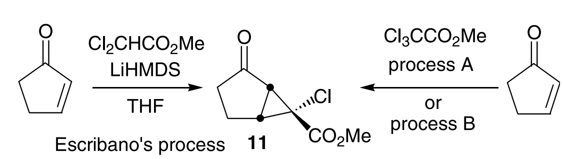
Scheme 2.

rapidly MgX_2 to form carbene intermediates,[19] is not likely since no reaction was observed in the presence of nucleophilic olefins. So, we think that a first formed carben species reacts with DMF to form a nucleophilic intermediate in a process similar to the formation of the DMF–$SOCl_2$ complex described by Newman[20] (Scheme 2). The role of DMF is even crucial in this process. Indeed, very surprisingly, no reaction occurred in diethylether or in THF instead of DMF as solvent. On the contrary, addition of an equal amount of DMF to an ether solution of $PhCCl_3$ and methyl acrylate induced the cyclopropanation to start.

With reference to the complementarity of both processes (A and B), it is clear that they do not involve the same type of nucleophilic species derived from the trichloromethyl compounds. In the electrochemical process (A), the reactive intermediate could be a copper–iron bi-metallic nucleophilic complex, which is not yet identified.

In the presence of acyclic α,β-unsaturated esters, chlorocyclopropanes are prepared, according to both methods, with a low to moderate diastereoselectivity (Table 1, entries 1–6) but, when cyclic enones are used as electrophilic olefins, the diastereoselectivity of the cyclopropanation becomes very high (Table 1, entries 11–14): only one of the two possible structures (*endo*-chlorine or *exo*-chlorine adduct) is obtained.

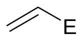
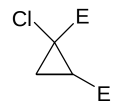
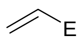
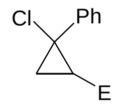
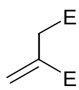
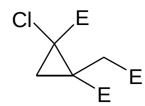
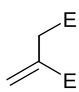
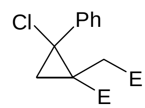
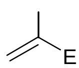
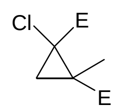
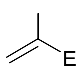
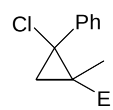
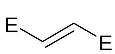
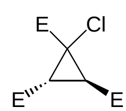
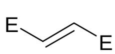
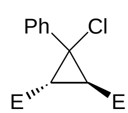
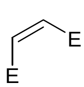
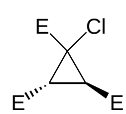
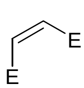
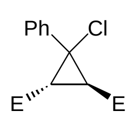
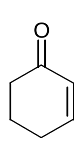
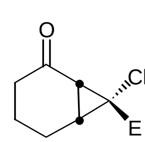
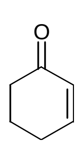
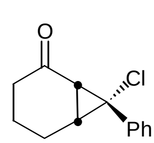
We have assigned to the compound **11** an *endo*-chlorine structure by comparison with the results obtained by Escribano et al.[9] Actually, whatever the route used (process A or B, or Escribano's process[9]) (Scheme 3), the same bicyclic compound is formed, as determined by GC-analysis, and from the ^1H and ^{13}C NMR spectra.



Scheme 3.

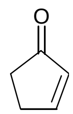
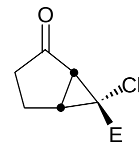
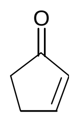
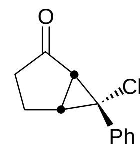
The *endo*-chlorine structure was established by Escribano[9] from X-ray diffraction experiments. Our 1D ^1H NOE-Difference NMR experiments, using selective excitation with a shaped pulse (gradient version) on the methoxy group, are consistent with the assignment given by Escribano. Indeed, the NOE effect (Fig. 1) is mainly seen at the H-1 and H-5 bridge-head protons. However, our measurement of the ^3J (^1H–^{13}C) coupling constant between

Table 1. Formation of polysubstituted chlorocyclopropanes by electroreductive or Mg-promoted coupling of α,β-unsaturated carbonyl compounds and α,α,α-trichloromethyl derivatives ($Cl_3C–Y$)

Entry	α,β-Unsaturated carbonyl compound[a] E_{red} (V/sce)[b]	Cl_3CY	Polysubstituted chlorocyclopropane[a]	*n*	Process A electrochemical process isolated yield (%)	Process B chemical process isolated yield (%)
1	 (−2.15)	$Cl_3CCO_2CH_3$		**1**	70 *R***S**/*R***R** 17/83	76 *R***S**/*R***R** 7/93
2	 (−2.15)	$PhCCl_3$		**2**	35 *R***S**/*R***R** 60/40	68 *R***S**/*R***R** 57/43
3	 (−2.05)	$Cl_3CCO_2CH_3$		**3**	57 *R***S**/*R***R** 30/70	65 *R***S**/*R***R** 28/72
4	 (−2.05)	$PhCCl_3$		**4**	41 *R***S**/*R***R** 35/65	57 *R***S**/*R***R** 36/64
5	 (−2.30)	$Cl_3CCO_2CH_3$		**5**	<10[c]	70 *R***S**/*R***R** 45/55
6	 (−2.30)	$PhCCl_3$		**6**	<10[c]	73 *R***S**/*R***R** 25/75
7	 (−1.60)	$Cl_3CCO_2CH_3$		**7**	67 *R***R**	33 *R***R**
8	 (−1.60)	$PhCCl_3$		**8**	52 *R***R**	23 *R***R**
9	 (−1.45)	$Cl_3CCO_2CH_3$		**7**	40 *R***R**	24 *R***R**
10	 (−1.45)	$PhCCl_3$		**8**	46 *R***R**	10 *R***R**
11	 (−2.15)	$Cl_3CCO_2CH_3$		**9**	58 1*RS*,6*RS*,7*RS*	53 1*RS*,6*RS*,7*RS*
12	 (−2.15)	$PhCCl_3$		**10**	30 1*RS*,6*RS*,7*RS*	50[d] 1*RS*,6*RS*,7*RS*

(*continued on next page*)

Table 1 (*continued*)

Entry	α,β-Unsaturated carbonyl compound[a] E_{red} (V/sce)[b]	Cl_3CY	Polysubstituted chlorocyclopropane[a]	*n*	Process A electrochemical process isolated yield (%)	Process B chemical process isolated yield (%)
13	 (−2.20)	$Cl_3CCO_2CH_3$		**11**	30 1*RS*,5*RS*,6*RS*	40[d] 1*RS*,5*RS*,6*RS*
14	 (−2.20)	$PhCCl_3$		**12**	20 1*RS*,5*RS*,6*RS*	40[d] 1*RS*,5*RS*,6*RS*

[a] $E=CO_2CH_3$.
[b] See Ref. 15.
[c] Determined by GC without internal standart.
[d] Reagents ratio: activated olefin/α,α,α-trichlorotoluene, 20 mmol/10 mmol.

the bridge-head protons and the carbon of the carbonyl of the C-6 methyl ester substituent gives a value of 3.7 Hz, and not 7.2 Hz as reported by Escribano.[9] This result was obtained by using a simple pulse sequence, which selectively decouples protons from the CH_3 of the methyl ester (Fig. 2), and was confirmed by 2D ^{13}C/JCH NMR experiment (Fig. 3). Our idea on the discrepancy between Escribano's work and our NMR measurements is that the Karplus relationship used by Escribano is convenient for a ^3J (^1H–Csp^3–Csp^3–$^{13}Csp^3$) like in the propane[19] but not for a ^3J (^1H–Csp^3–Csp^3–$^{13}Csp^2$) like in the compound **11**. So, we agree with the structure proposed by Escribano, but not with the NMR data. Now, regarding the other bicyclic compounds **9**, **10**, and **12** (see Table 1) we prepared, they all have ^3J (^1H–Csp^3–Csp^3–$^{13}Csp^2$) values close to 4 Hz, as for the compound **11** and by using the same NMR methods. So we think that we can reasonably assign an *endo*-Cl structure to these four bicyclic compounds.

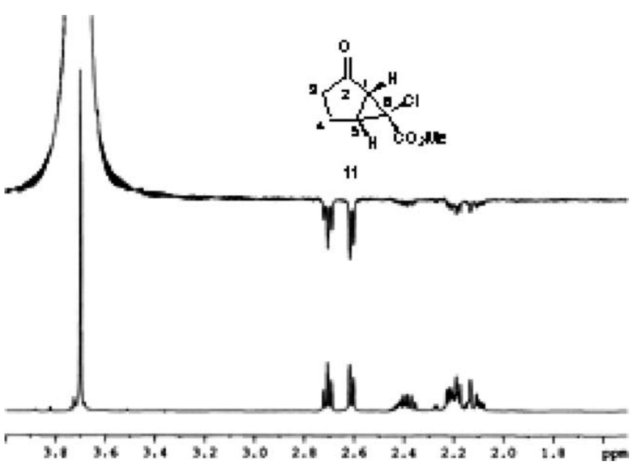


Figure 1. 1D ^1H NOE-Difference NMR of **11**.

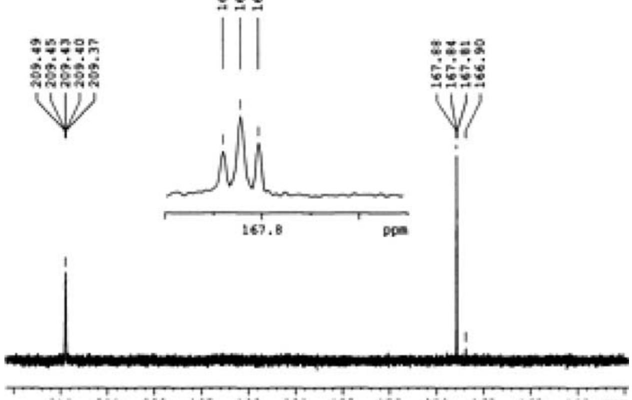


Figure 2. ^{13}C NMR decoupled $-OCH_3$ of **11**,^3J ^1H–^{13}C: H-1 and H-5/ $CO_2R=3.7$ Hz.

The cyclopropanations described here are regiospecific. Indeed, no addition onto the carbonyls of the activated olefins

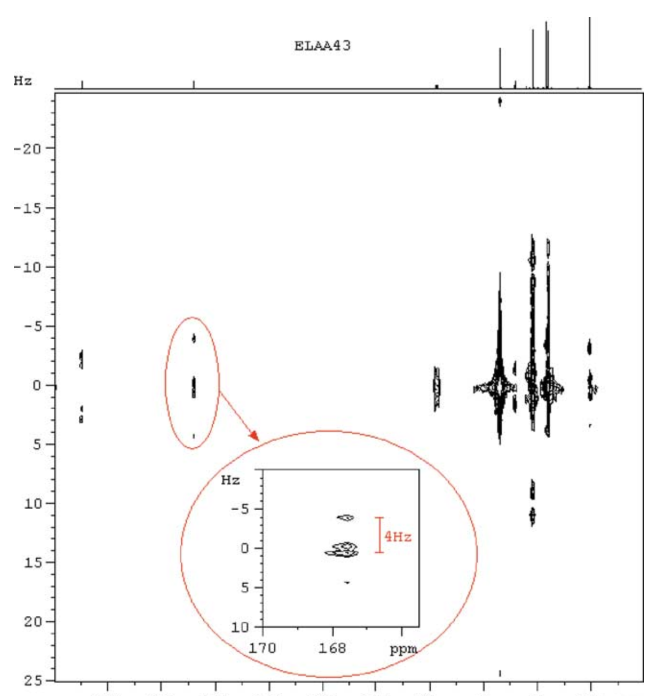
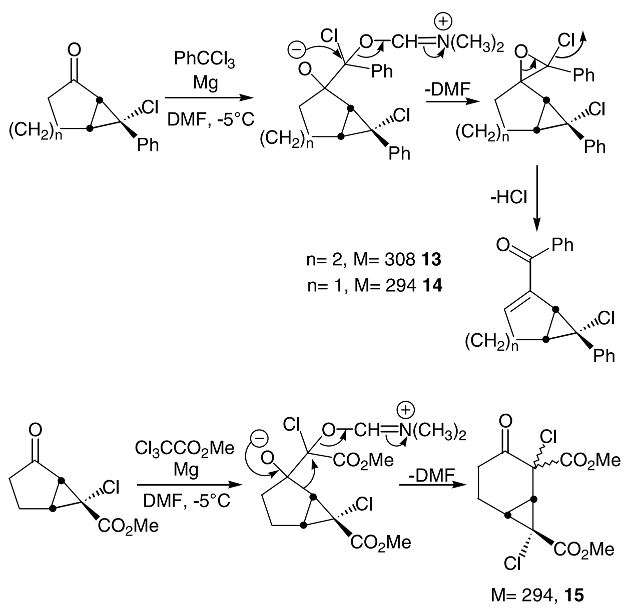


Figure 3. 2D ^{13}C/JCH NMR of **11**: ^3J ^1H–^{13}C: H-1 and H-5/$CO_2R\sim4$ Hz.

was observed during or at the near end of the reaction, though the trichloromethyl compound is used in excess. Side products coming from the halocompounds are their reduced forms and traces of the dimers (YCCl=CClY). However, with process B, and in the case of cyclic enones and Cl_3C–Y (Table 1, entries 12, 13 and 14), we could observe, at the near end of the reaction, the formation of three by-products showing parent ions at *m*/*e* = 308, 294, 294, respectively, in their mass spectra. We thus made the assumption that the nucleophilic species generated in situ could react on the carbonyl of the bicyclic products, according to reactions described by Larson[6] and by Schäfer.[21,22] The structures **13**, **14**, **15** have been postulated for these by-products (Scheme 4). To prevent this side reaction in the preparation of the compounds **10**, **11**, **12** (see Table 1), we modified process B in a way to keep the electrophilic olefins in excess vs the *gem*-polyhalocompound all over the reaction. However, surprisingly, in the preparation of the bicyclic compound **9** (Table 1, entry 11), no 1,2-addition was observed. Up to now, we have no explanation for this result.



Scheme 4.

3. Conclusions

We have described in this paper two simple, efficient and complementary methods (processes A and B) for the preparation of polysubstituted chlorocyclopropanes using electrophilic olefins and activated trichloromethyl compounds as starting materials. These new routes do not make use of strong bases or very expensive copper carbenoid *tert*-butyl isocyanides. Also, we have noticed that, in DMF, the nucleophilic species resulting from the Mg reduction of α,α,α-trichlorotoluene were able to react with ketones leading to benzoylated olefins. So far, the only other reductive route reported involves an electrochemical reduction of α,α,α-trichlorotoluene in a double-walled glass cell with a mercury pool cathode.[22a,c] We are now extending this Mg-Barbier reaction in DMF to the preparation of cycloalk-1-en-1-yl and alk-1-en-1-ylphenyl ketones.

4. Experimental

Melting points were determined with an Electrothermal IA 9100 digital melting point apparatus. ^1H, ^{13}C NMR spectra were recorded on a Bruker AC-200 (200, 50 MHz, respectively) or Bruker Avance 300 (300, 75 MHz, respectively) or Bruker DRX-400 (400, 100 MHz, respectively) spectrometers. Mass spectra (electron impact) were obtained on a GCQ Thermoquest spectrometer equipped with a DB 5MS capillary column. Infrared spectra were recorded on a Perkin Elmer Spectrum BX FT-IR spectrometer. High-resolution mass spectral analyses and elemental analyses were carried out at 'Service Central d'Analyse du CNRS', Vernaison, France. Gas chromatography was performed on a Varian 3300 chromatograph fitted with a SIL-5 CP capillary column. Solvents and chemicals were used as received. The XC10 Fe rod (iron with 0.1% of carbon) and Mg grits (50–150 mesh) were purchased, respectively, from Weber Métaux and Fluka.

4.1. General procedure

Process A, indirect electrochemical process with Fe anode in the presence of CuBr. The reactions are conducted in an undivided cell fitted with an Fe rod as the anode and a nickel foam as the cathode (area: ca. 40 cm^2). A solution of CuBr (144 mg, 1 mmol) and Bu_4NBr (300 mg) in DMF (45 mL) and pyridine (5 mL) is electrolysed at constant current intensity (0.3 A) during 15 min at $-5\,°C > T > -10\,°C$. Then, the activated olefin (10 mmol) and the α,α,α-trichloromethyl compound (20 mmol) are added and electrolysed (0.1 A) until the complete consumption of the olefin (about 8 h). The DMF is evaporated under reduced pressure. The reaction mixture is poured into a cold mixture of 1 M HCl (50 mL) and diethyl ether (50 mL). The layers are separated and extracted with diethyl ether (three portions of 25 mL). The combined ethereal extracts are washed with a saturated solution of ammonium chloride and brine, dried over $MgSO_4$. Products are isolated either by column chromatography on silica gel (230–400 mesh) or aluminium oxide (70–230 mesh) using pentane–ether as eluent.

Process B, Mg-promoted Barbier type reaction in the presence of DMF. Magnesium grits (50–100 mesh) (30 mmol) are suspended in DMF (40 mL) in a three-neck flask fitted with a thermometer and a dropping funnel, and cooled at −5 °C. Half of the solution containing olefin (10 mmol), α,α,α-trichloromethyl compound (12 mmol) and DMF (5 mL) is rapidly introduced in the flask. The beginning of the reaction is clearly indicated by the temperature rising up to +5 °C, and the mixture turning yellow. The remaining of the reactants was then added within 5 min, and the reaction is allowed to proceed up to complete consumption of the olefin. After the usual workup, the product is isolated by column chromatography on silica gel (230–400 mesh) using pentane–ether as eluent.

4.2. Isolated products

4.2.1. Dimethyl 1-chlorocyclopropane-1,2-dicarboxylate (1).[14a] CAS RN: 39822-02-1 (*R**,*S**), 39822-01-0 (*R**,*R**).

4.2.2. Methyl 2-chloro-2-phenylcyclopropane-1-carboxylate (2).[14a] CAS RN: 39822-09-8 (*R**,*S**), 39822-10-1 (*R**,*R**).

4.2.3. Dimethyl 2-chloro-1-methoxycarbonylmethylcyclopropane-1,2-dicarboxylate (3).[14a] CAS RN: 424790-89-6 (*R**,*S**), 424790-88-5 (*R**,*R**).

4.2.4. Methyl 2-chloro-1-methoxycarbonylmethyl-2-phenylcyclopropane-1-carboxylate (4) (new compound). ($C_{14}H_{15}ClO_4$); MW: 282.723. Anal. Calcd for $C_{14}H_{15}ClO_4$: C, 59.48; H, 5.35; O, 22.63; Cl, 12.54. Found: C, 59.28; H, 5.33; O, 22.63; Cl, 12.66. Pentane–ether (95/5) to (90/10); obtained: 1.16 g (yield: 41%, (*R**,*S**)/(*R**,*R**): 35:65, process A), 1.61 g (yield: 57%, (*R**,*S**)/(*R**,*R**): 36:64, process B); (*R**,*S**): oil, (*R**,*R**): mp=76–78 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ (*R**,*S**): 7.3–7.2 (Ph, 5H, m); 3.75 (OCH_3, 3H, s); 3.5 (OCH_3, 3H, s); 3.1 (CH_2, 1H, d, $J=17.6$ Hz); 2.35 (H-3 or H-3′, 1H, d, $J=7.4$ Hz); 1.65 (H-3 or H-3′, 1H, d, $J=7.4$ Hz); 1.3 (CH_2, 1H, d, $J=17.6$ Hz); for the couple H-3/H-3′ ($\Delta\nu/J=19.0$ AX system); for the methylene group ($\Delta\nu/J=21.0$ AX system). (*R**,*R**): 7.4–7.2 (Ph, 5H, m); 3.7 (OCH_3, 3H, s); 3.4 (CH_2, 1H, d, $J=17.6$ Hz); 3.2 (OCH_3, 3H, s); 2.9 (CH_2, 1H, d, $J=17.6$ Hz); 2.5 (H-3 or H-3′, 1H, d, $J=6.9$ Hz); 1.5 (H-3 or H-3′, 1H, d, $J=6.9$ Hz); for the couple H-3/H-3′ ($\Delta\nu/J=29.0$ AX system); for the methylene group ($\Delta\nu/J=5.5$ AB system). ^{13}C NMR (50 MHz, $CDCl_3$) δ (*R**,*S**): CO: 170.9, 169.9; C(Ph): 138.5, 128.5; C-2: 53.3; OCH_3: 52.0, 51.9; CH_2: 37.3; C-1: 33.3; C-3: 25.6. (*R**,*R**): CO: 171.7, 169.7; C(Ph): 137.8, 128.7; C-2: 53.4; OCH_3: 51.7, 49.7; CH_2: 37.5; C-1: 34.3; C-3: 23.7. EI-MS *m/z* (*R**,*S**): 282 (M, 1), 220 (32), 219 (13), 218 (base peak), 192 (14), 191 (20), 190 (46), 187 (13), 165 (26), 164 (16), 163 (78), 162 (17), 159 (20), 155 (11), 149 (24), 145 (20), 129 (17), 128 (56), 127 (30), 115 (11). (*R**,*R**): 282 (M, 1), 220 (30), 219 (12), 218 (base peak), 192 (16), 191 (19), 190 (41), 187 (14), 165 (26), 164 (13), 163 (71), 162 (15), 159 (21), 155 (10), 149 (22), 145 (20), 129 (20), 128 (64), 127 (30), 115 (11). IR ν (cm^{-1}) ($CDCl_3$) 3080, 3030, 2990, 2970, 2900, 1735, 1600, 1570, 1470.

4.2.5. Dimethyl 1-chloro-2-methylcyclopropane-1,2-dicarboxylate (5). ($C_8H_{11}ClO_4$); MW: 206.625; CAS RN: 42392-04-1 (*R**,*S**), 132785-43-4 (*R**,*R**). Pentane (100) to pentane–ether (95/5); obtained: 1.45 g (yield: 70%, (*R**,*S**)/(*R**,*R**): 45:55, process B; (*R**,*S**) and (*R**,*R**): oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ (*R**,*S**): 3.5 (OCH_3, 3H, s); 3.4 (OCH_3, 3H, s); 2.0 (H-3 or H-3′, 1H, d, $J=6.5$ Hz); 1.3 (CH_3, 3H, s); 1.0 (H-3 or H-3′, 1H, d, $J_{gem}=6.5$ Hz); for the couple H-3/H-3′ ($\Delta\nu/J=31.4$ AX system). (*R**,*R**): 3.65 (OCH_3, 3H, s); 3.6 (OCH_3, 3H, s); 1.85 (H-3 or H-3′, 1H, d, $J=6.6$ Hz); 1.7 (H-3 or H-3′, 1H, d, $J=6.6$ Hz); 1.2 (CH_3, 3H, s); for the couple H-3/H-3′ ($\Delta\nu/J=5.6$ AB system). ^{13}C NMR (50 MHz, $CDCl_3$) δ (*R**,*S**): CO: 170.8, 167.8; OCH_3: 53.1, 52.4; C-1: 48.5; C-2: 33.7; C-3: 27.9; CH_3: 17.3. (*R**,*R**): CO: 169.0, 166.9; OCH_3: 53.0, 52.1; C-1: 45.2; C-2: 35.1; C-3: 25.5; CH_3: 14.8. EI-MS *m/z* (*R**,*S**): 206 (M, <1), 177 (13), 176 (15), 175 (37), 174 (32), 171 (22), 170 (51), 148 (35), 147 (17), 146 (base peak), 139 (16), 133 (12), 131 (31), 127 (11), 119 (18), 115 (20), 111 (12), 87 (15), 83 (15). (*R**,*R**): 206 (M, 1), 176 (11), 175 (22), 174 (26), 171 (13), 170 (36), 148 (34), 147 (17), 146 (base peak), 139 (18), 131 (26), 119 (18), 115 (15), 111 (15), 83 (13), 55 (10). IR ν (cm^{-1}) (film) 3100, 2990, 2970, 1750, 1730, 1440.

4.2.6. Methyl 2-chloro-1-methyl-2-phenylcyclopropane-1-carboxylate (6). ($C_{12}H_{13}ClO_2$); MW: 224.687; CAS RN: 91433-96-4 (*R**,*S**), 91434-02-5 (*R**,*R**). Pentane (100) to pentane–ether (95/5); obtained: 1.64 g (yield: 73%, (*R**,*S**)/(*R**,*R**): 25:75, process B; (*R**,*S**) and (*R**,*R**): oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ (*R**,*S**): 7.4–7.6 (Ph, 5H, m); 4.0 (OCH_3, 3H, s); 2.4 (H-3 or H-3′, 1H, d, $J=6.8$ Hz); 1.7 (H-3 or H-3′, 1H, d, $J=6.8$ Hz); 1.2 (CH_3, 3H, s); for the couple H-3/H-3′ ($\Delta\nu/J=20.0$ AX system). (*R**,*R**): 7.5–7.45 (Ph, 5H, m); 3.5 (OCH_3, 3H, s); 2.6 (H-3 ou H-3′, 1H, d, $J=6.5$ Hz); 1.95 (CH_3, 3H, s); 1.6 (H-3 or H-3′, 1H, d, $J=6.5$ Hz); for the couple H-3/H-3′ ($\Delta\nu/J=32.3$ AX system). ^{13}C NMR (50 MHz, $CDCl_3$) δ (*R**,*S**): CO: 171.0; C(Ph): 137.9, 128.8, C-2: 52.1; OCH_3: 49.9; C-1: 33.1; C-3: 24.5; CH_3: 17.6. (*R**,*R**): C-4: 171.4; C-7: 139.6; other aromatic C: 128.4; C-2: 53.9; C-5: 51.8; C-1: 32.4; C-3: 26.0; C-6: 18.0. EI-MS *m/z* (*R**,*S**): 225 (M, 6), 189 (35), 167 (12), 165 (34), 161 (8), 157 (8), 131 (15), 130 (12), 129 (base peak), 128 (28), 105 (10). (*R**,*R**): 225 (M, 9), 189 (35), 167 (10), 165 (35), 161 (10), 157 (10), 131 (16), 130 (15), 129 (base peak), 128 (27), 105 (10). IR ν (cm^{-1}) (film) 3030, 2920, 1720, 1580, 1500, 1450.

4.2.7. *trans*-Trimethyl 1-chlorocyclopropane-1,2,3-tricarboxylate (7).[14d] CAS RN: 205320-46-3.

4.2.8. *trans*-Dimethyl 3-chloro-3-phenylcyclopropane-1,2-dicarboxylate (8).[14d] CAS RN: 205320-44-1.

4.2.9. (1*RS*,6*RS*,7*RS*)-Methyl 7-chloro-2-oxobicyclo[4.1.0]heptane-7-carboxylate (9). ($C_9H_{11}ClO_3$); MW: 202.637; CAS RN: 406217-16-1. Pentane–ether (90/10) to (80/20); obtained: 1.17 g (yield: 58%, process A), 1.07 g (yield: 53%, process B); oil. ^{1}H NMR (200 MHz, $CDCl_3$) 3.5 (OCH_3, 3H, s); 2.3–2.1 (2H, m); 2.1–1.8 (3H, m); 1.7–1.5 (3H, m). ^{13}C NMR (50 MHz, $CDCl_3$) δ COR: 202.5; COOR: 168.7; OCH_3: 53.5; C-7: 48.7; C-3: 38.9; C-1: 34.1; C-6: 30.1; C-4 and C-5: 23.9, 17.6. EI-MS *m/z* 202 (M, 10), 176 (23), 174 (73), 172 (28), 171 (13), 170 (88), 148 (10), 147 (31), 146 (14), 145 (34), 144 (36), 143 (51), 142 (base peak), 139 (13), 135 (32), 117 (12), 116 (10), 115 (21), 111 (11), 107 (41), 106 (10), 87 (13), 81 (14), 80 (11), 79 (99), 78 (15), 77 (43), 53 (11), 51 (40). IR ν (cm^{-1}) ($CDCl_3$) 1750, 1720.

4.2.10. (1*RS*,6*RS*,7*RS*)-7-Chloro-7-phenylbicyclo[4.1.0]-heptane-2-one (10). ($C_{13}H_{13}ClO$); MW: 220.699; CAS RN: 126252-39-9. Pentane (100) to pentane–ether (95/5); obtained: 0.662 g (yield: 30%, process A), 1.10 g (yield: 50%, process B); mp=69–70 °C. ^{1}H NMR (200 MHz, $CDCl_3$) 7.6–7.2 (Ph, 5H, m); 2.3–1.6 (H-1 to H-6, 8H, m). ^{13}C NMR (50 MHz, $CDCl_3$) δ CO: 204.9; C(Ph): 141.9, 128.3, 127.5; C-7: 54.9; C-3: 39.1; C-1: 33.6; C-6: 29.0; C-4 and C-5: 24.9, 18.6. EI-MS *m/z* 220 (M, 8), 192 (15), 185 (10), 157 (28), 141 (8), 130 (12), 129 (base peak), 128 (27), 127 (9), 115 (15). IR ν (cm^{-1}) ($CDCl_3$) 3080, 3020, 2980, 1700, 1600, 1580, 1500.

4.2.11. (1*RS*,5*RS*,6*RS*)-Methyl 6-chloro-2-oxobicyclo[3.1.0]hexane-6-carboxylate (11). ($C_8H_9ClO_3$); MW:

188.610; CAS RN: 2158-08-1. Pentane (100) to pentane–ether (85/15); obtained: 0.566 g (yield: 30%, process A), 0.754 g (yield: 40%, process B); mp = 41–42 °C. ^1H NMR (300 MHz, $CDCl_3$) 3.7 (OCH_3, 3H, s); 2.7 (H-5, 1H, t, $^3J = 6.3$ Hz); 2.6 (H-1, 1H, d, $^3J = 6.3$ Hz); 2.5–2.05 (H-3 and H-4, 4H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ COR: 209.4; CO_2R: 167.8; OCH_3: 53.8; C-6: 48.3; C-1: 41.6; C-3: 36.6; C-5: 36.0; C-4: 20.4. EI-MS *m/z* 162 (15), 160 (38), 156 (37), 149 (11), 148 (23), 147 (48), 146 (65), 145 (44), 134 (35), 133 (20), 132 (base peak), 131 (49), 129 (13), 128 (11), 125 (31), 124 (12), 118 (14), 117 (25), 116 (26), 115 (19), 111 (23), 109 (11), 101 (15), 100 (13), 93 (30), 87 (14), 80 (14), 79 (17), 73 (11), 69 (14), 65 (61), 51 (16). IR ν (cm^{-1}) ($CDCl_3$) 3068, 3050, 3010, 2956, 2873, 1730, 1703, 1440.

4.2.12. (1*RS*,5*RS*,6*RS*)-6-Chloro-6-phenylbicyclo[3.1.0]hexane-2-one (12) (new compound). ($C_{12}H_{11}ClO$); MW: 206.672. ES-HR-MS calcd for $C_{12}H_{11}ONaCl$ *m/z* 229.0396, found 229.0399. Pentane (100) to pentane–ether (95/5); obtained: 0.413 g (yield: 20%, process A), 0.811 g (yield: 40%, process B); mp = 86–87 °C. ^1H NMR (200 MHz, $CDCl_3$) 7.4–7.15 (Ph, 5H, m); 2.6–2.15 (H-1 to H-5, 6H, m). ^{13}C NMR (50 MHz, $CDCl_3$) δ O: 211.1; C(Ph): 140.8, 128.9, 128.6, 127.6; C-6: 54.5; C-1: 41.4; C-3: 37.4; C-5: 34.7; C-4: 21.1. EI-MS *m/z* 164 (20), 143 (10), 130 (11), 129 (base peak), 128 (31), 127 (8), 115 (15). IR ν (cm^{-1}) ($CDCl_3$) 3150, 3040, 2980, 2940, 1730, 1600, 1580, 1500.

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Enantiocontrolled synthesis of the epoxycyclohexenone moieties of scyphostatin, a potent and specific inhibitor of neutral sphingomyelinase

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Abstract—The epoxycyclohexenone moieties **2** and **3b** of scyphostatin (**1**), a potent and specific inhibitor of neutral sphingomyelinase, were synthesized in enantiomerically pure forms starting from (−)-quinic acid (**11**). The synthetic method features (i) the preparation of the olefin masked enones **25** and **29**, the precursors for the key aldol-type coupling reaction, (ii) the efficient and stereocontrolled aldol-type coupling reactions between **25** (or **29**) and benzaldehyde (**8**) and Garner's aldehyde analogue **9** to deliver alcohols **23** and **24**, respectively, both of which possess the requisite asymmetric quaternary carbon center at the C6 position, and (iii) the stereospecific S_N2-type epoxide ring formation of the mesylates **35** and **47** under mild basic conditions to produce the targeted compounds **2** and **3b**, respectively.

1. Introduction

Recently, sphingomyelinase (SMase) inhibitors have received considerable attention from the biological and pharmacuetical standpoints.[1] SMase is the enzyme that specifically hydrolyzes the phosphoester linkage of sphingomyelin (SM), one of the most abundant sphingolipid species, to generate ceramide and phoshocholine.[2,3] The SM-derived ceramide is believed to be an intracellular lipid second messenger in cell membranes and to play important roles in the regulation of cell proliferation, differentiation, and apoptosis.[2,3] SMase inhibitors, therefore, are considered as valuable tools for the investigation of the biological function of the enzyme and the catabolite ceramide in signal transduction.[3] In addition, selective SMase inhibitors are highly anticipated to be promising candidates for the treatment of ceramide-mediated pathogenic states such as AIDS,[4] inflammation,[5] and immunological and neurological disorders.[6]

In 1997, Ogita et al. at the Sankyo research group reported the isolation and structure elucidation of a novel natural product, scyphostatin (**1**, Fig. 1), from the mycelial extract of *Trichopeziza mollissima* SANK 13892.[7,8] This natural product was found to be a powerful and specific inhibitor of membrane-bound neutral sphingomyelinase (N-SMase).[8] It has been reported that **1** inhibits N-SMase and acidic SMase (A-SMase) with IC_{50} values of 1.0 and 49.3 μM, respectively.[7,8] Remarkably, scyphostatin is the most potent and specific one among the many low molecular weight N-SMase inhibitors of natural sources[9] or of synthetic substances[10] known to date.

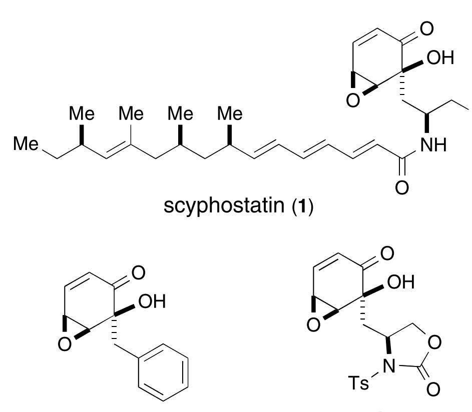

Figure 1. Structures of scyphostatin (**1**) and the epoxycyclohexeone moieties **2** and **3b**.

Keywords: Sphingomyelinase; Aldol-type coupling; Diels–Alder reaction.
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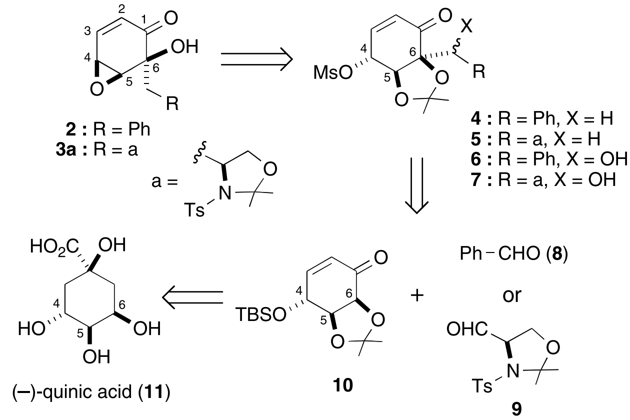
The gross structure of scyphostatin (**1**) was revealed by extensive and incisive spectroscopic studies.[7] It consists of a novel, highly oxygenated cyclohexenone ring incorporated with a C-20 unsaturated fatty acid-substituted aminopropanol side chain. This initial structure elucidation only established the relative and absolute stereochemistry of the cyclohexenone moiety of **1**.[7] In 2001, Kogen et al. at the Sankyo research group determined the relative and absolute configurations of the three stereogenic centers present in the fatty acid side chain.[11] At the almost same time, Hoye et al. disclosed an enantioselective synthesis of the C-20 unsaturated fatty acid moiety and provided alternative proof of its stereostructure including the absolute configuration.[12]

The remarkable biological properties and unique structural features make **1** an exceptionally intriguing and timely target for total synthesis. So far, a number of synthetic approaches toward scyphostatin (**1**) have been reported by Gurujar's group,[13] Taylor's group,[14] Ohkata's group,[15] Kita's group,[16] Maier's group,[17] Negishi's group,[18] and Pitsino's group.[19] We have already reported our own preliminary results concerning the enantioselective synthesis of the epoxycylohexenone substructures **2** and **3b**[20] (Fig. 1). Additionally, we have also disclosed an efficient method for the introduction of a fatty acid side chain at the amino propanol moiety.[21] In 2004, our assiduous endeavors culminated in the completion of the first total synthesis of (+)-**1**.[22] In this paper, we wish to disclose the full details of our first-generation synthesis of the epoxycyclohexenone moieties **2** and **3b** of scyphostatin (**1**).

2. Results and discussion

2.1. Primary synthetic plan for the epoxycyclohexenone moieties 2 and 3a

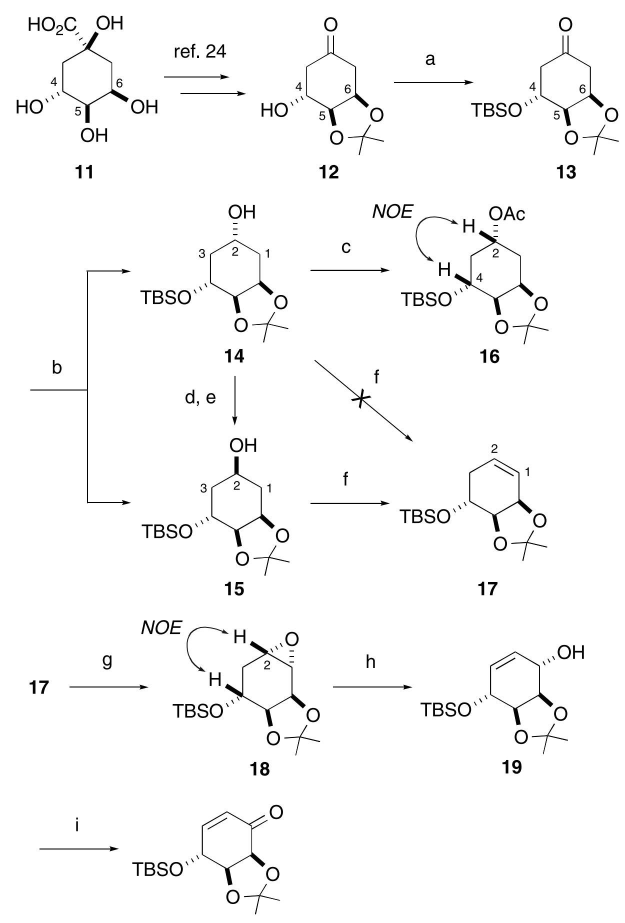
Our primary synthetic plan for the epoxycyclohexenone moieties **2** and **3a** is outlined in Scheme 1. The key feature of this plan is aldol-type coupling reactions between the cyclohexenone **10** and the aldehydes **8** and **9** to form the coupling products **6** and **7**, respectively (**10**+**8**→**6** and **10**+**9**→**7**). In these reactions, we envisioned that electrophiles **8** and **9** would approach exclusively from the less hindered α-face of the enolate, generated in situ from **10**, under the influence of the β-oriented *O*-isopropylidenedioxy moiety, thus leading to establishment of the requisite asymmetric quaternary carbon center at the C6 position (cyclohexeneone numbering)[23] in **6** and **7**. This type of coupling reaction is considerably challenging at the synthetic chemistry level, because the substrate **10** possesses unusual trihydroxy functionalities at the C4, C5, and C6 positions, and in addition, an electrophilic enone system. The coupling products **6** and **7** would be converted to the target molecules **2** and **3a** through the advanced key intermediates **4** and **5**, respectively, by sequential functional group manipulation and deprotection, or vice versa; the sequence involves deoxygenation of the secondary hydroxy group in the side chain and stereospecific S_N2-type epoxide ring formation as the crucial steps. The cyclohexenone **10** having three contiguous oxygen functionalities at the C4, C5, and C6 positions with correct stereochemistries would be derived from commercially available (−)-quinic acid (**11**).



Scheme 1. Primary synthetic plan for the epoxycyclohexeone moieties **2** and **3a**.

2.2. Synthesis of the intermediate 10

At first, as shown in Scheme 2, we pursued the synthesis of the intermediate **10**, a substrate for the key aldol-type coupling reaction, starting from commercially available (−)- quinic acid (**11**). The known cyclohexanone **12**[24] was



Scheme 2. Synthesis of the intermediate **10**. (a) TBSCL, imidazole, DMF, rt, 98%; (b) $NaBH_4$, THF–H_2O, −5 °C→rt, 53% for **14**, 44% for **15**; (c) Ac_2O, pyridine, DMAP, 0 °C→rt, 98%; (d) DEAD, Ph_3P, benzonic acid, THF, 0 °C→98%; (e) 2 M KOH–MeOH, rt, quant.; (f) DEAD, Ph_3P, THF, rt, 67% for **15**→**17**, 0% for **14**→**17**; (g) *m*CPBA, $NaHCO_3$, CH_2Cl_2, 0 °C→rt, 92%; (h) Se_2Ph_2, $NaBH_4$, EtOH, 0 °C→reflux; H_2O_2, THF, 0 °C→reflux, 78%; (i) Dess–Martin periodinane, CH_2Cl_2, rt, 95%.

readily and sufficiently prepared from **11** in three steps [(1) dimethoxypropane/*p*-TsOH/acetone, reflux, 80%; (2) $LiAlH_4$/THF, reflux, quant.; (3) $NaIO_4$/*t*-BuOH–THF–AcOH, room temperature, quant.] according to the reported procedure.[24] After protection of the hydroxy group in **12** as its *t*-butyldimethylsilyl (TBS) ether, the carbonyl function of the resulting TBS ether **13** was subjected to reduction with sodium borohydride to furnish an epimeric mixture of the alcohols **14** (53%) and **15** (44%) that were separated by silica gel column chromatography. The newly formed C2 stereochemistry of the two isomers was assigned on the basis of spectroscopic studies. The NOESY experiment of the acetate **16** derived from **14** showed a clear interaction between C2–H and C4–H.

We next examined installation of an olefinic double bond by dehydration of **14** and **15**. Thus, reaction of **15** with diethyl azodicarboxylate (DEAD) and triphenylphosphine provided the desired olefin **17** in 67% yield with complete regioselectivity at the C1–C2 position. On the contrary, treatment of the C2 epimeric alcohol **14** under the same dehydration conditions afforded none of the desired olefinic product **17**, and the unreacted starting material **14** was recovered unchanged. Therefore, the alcohol **14** was converted to **15** by employing the Mitsunobu inversion procedure[25] (98% overall yield). The difference of the reactivity between **14** and **15** under the dehydration conditions can be rationalized by conformational analyses of both **14** and **15** (Fig. 2). Thus, the NOESY experiment of **15** indicated that the cyclohexane ring takes a boat-form, which places the C2 hydroxy group in an axial position; this conformation may facilitate E2 elimination to afford the desired $\Delta^{1,2}$ olefin **17**. On the other hand, the NOESY experiment of **14** indicated that the C2 hydroxy group is in equatorial orientation within the boat-formed cyclohexane ring; this conformation would preclude any possibility of E2 elimination.

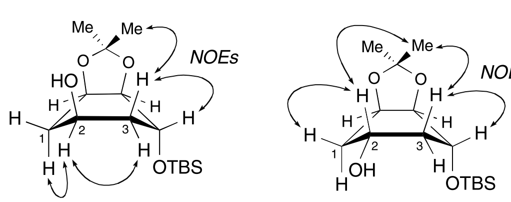
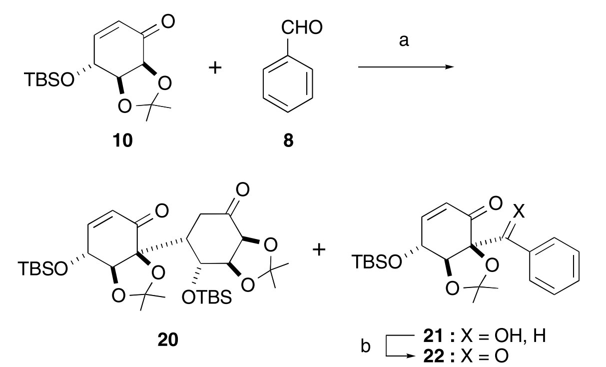


Figure 2. Conformational analyses of the alchohols **14** and **15**.

To continue the synthesis, the olefin **17** was oxidized with *m*-chloroperbenzoic acid (*m*CPBA) to give the epoxide **18** as a single diastereomer in 92% yield, whose stereochemistry was assigned based on the NOE experiment. The stereoselectivity can be explained by the consideration that the oxidizing reagent (*m*CPBA) accessed exclusively from the less hindered α-face of the molecule under the influence of the β-oriented *O*-isopropylidenedioxy moiety. Conversion of the epoxide **18** to the allyl alcohol **19** was successfully achieved by employing a reliable Sharpless protocol.[26] Thus, treatment of **18** with the phenylselenyl anion, generated in situ from diphenyl diselenide and sodium borohydride, caused the regioselective epoxide ring opening at the sterically and electrostatically favored C2 position to form the corresponding phenylselenide, which was then oxidized by excess 30% aqueous hydrogen peroxide to provide the allyl alcohol **19** in 95% overall yield via elimination of the intermediary phenylselenoxide. Finally, Dess–Martin oxidation[27] of **19** furnished the requisite intermediate **10** in 95% yield.

2.3. Initial attempts to achieve the coupling reaction of the cyclohexenone 10 with benzaldehyde (8)

Having obtained the intermediate **10**, we next investigated the crucial aldol-type coupling reaction between **10** and benzaldehyde (**8**) as shown in Scheme 3. Initial attempts to achieve this coupling reaction, unfortunately, turned out to be fruitless. Thus, reaction of the lithium enolate of **10**, generated in situ by reaction with $LiN(SiMe_3)_2$, with **8** in THF at −78 °C resulted in the predominant formation of the unexpected dimerized product **20** (38%) as a single stereo isomer and the desired coupling product **21** (12%) as an epimeric mixture with respect to the benzilic hydroxy group. Since the coupling product **21** was very unstable during isolation and purification by silica gel column chromatography, assignment of the structure and stereochemistry of **21** was performed by spectroscopic analyses (COSY, HMBC, and NOESY experiments) of the corresponding carbonyl compound **22**, readily prepared by Dess–Martin oxidation (78%).

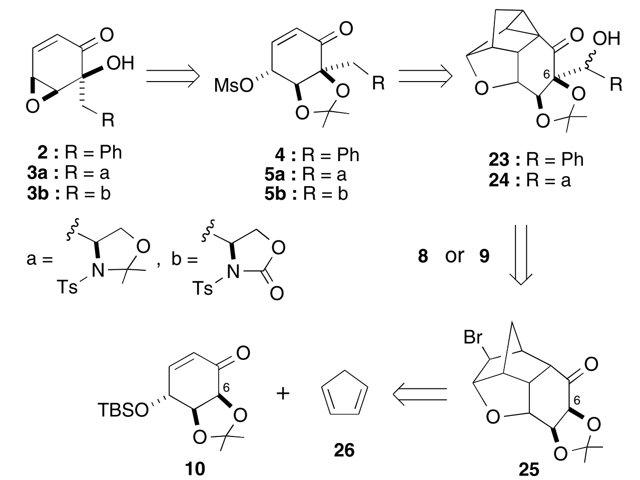


Scheme 3. Aldol-type coupling reaction of the cyclohexenone **10** and benzaldehyde (**8**). (a) $LiN(SiMe_3)_2$, THF, −78 °C, 38% for **20**, 12% for **21**; (b) Dess–Martin periodinane, CH_2Cl_2, rt, 78%.

These preliminary studies demonstrated that the enone olefin function present in **10** was extremely susceptible to nucleophilic attack of the enolate generated from **10** itself. In order to circumvent this problem, we decided to mask the highly reactive enone system of **10** in the form of the bromo ether **25** (cf. Scheme 4) during the aldol-type coupling reaction. We anticipated that **25** would behave as a promising substrate for the designed coupling reaction. Further investigations concerning the synthesis of **25** and subsequent coupling reaction with the aldehydes **8** and **9** are the subject of the following sections.

2.4. Modified synthetic plan for the epoxycyclohexenone moieties 2 and 3a

Our initial attempts to achieve the direct coupling between the cyclohexenone **10** and benzaldehyde (**8**) met with failure; therefore, we settled on modifying our original synthetic plan. Thus, as shown in Scheme 4, the bromo ether

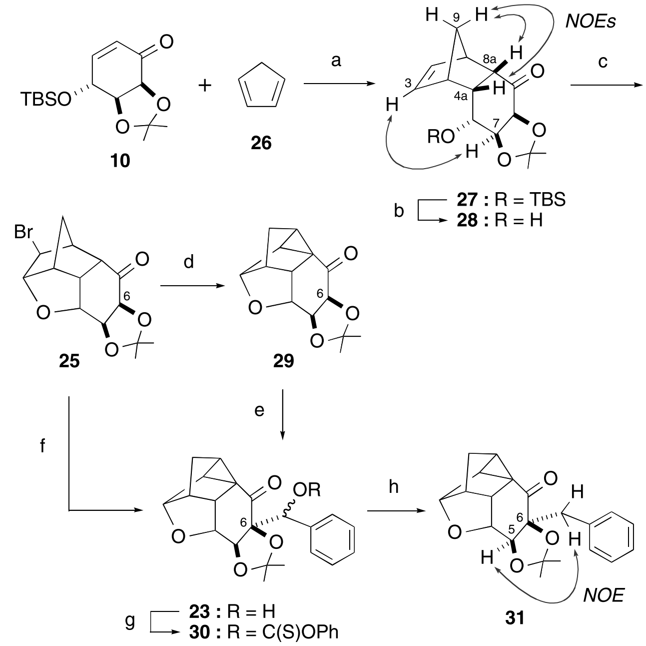


Scheme 4. Modified synthetic plan for the epoxycyclohexenone moieties **2** and **3**.

25, a synthetically equivalent of the cyclohexenone **10**, was envisaged to be prepared by Diels–Alder reaction of **10** with cyclopentadiene (**26**) followed by desilylation and bromo etherification. The crucial aldol-type reaction of **25** with the aldehydes **8** and **9** would produce the coupling products **23** and **24**, respectively, with correct stereochemistry at the C6 position. The intermediates **23** and **24** would be converted to the cyclohexenones **4** and **5**, the potential key intermediates of the target molecules **2** and **3**, via sequential functional group manipulation. As will be mentioned later (cf. Sections 2.7 and 2.8), the *N*,*O*-isopropylidene group at the C6 side chain in **24** turned out to be labile during the regeneration of the enone olefin moiety (cf. **24**→**5a**); therefore, the *N*,*O*-isopropylidene group was replaced with a sturdy cyclic carbamate group (cf. **5b**).

2.5. Synthesis of the intermediate 31 for the epoxycyclohexenone moiety 2: preparation of the masked enone 25 and subsequent aldol-type coupling reaction with benzaldehyde (8)

As shown in Scheme 5, we next carried out the synthesis of the intermediate **31** for the first target compound **2**; the sequence involved the preparation of the olefin masked cyclohexenone **25** and subsequent coupling reaction with benzaldehyde (**8**) as the crucial steps. Diels–Alder reaction of **10** with cyclopentadiene (**26**) in the presence of diethylaluminium chloride proceeded smoothly and cleanly in a completely diastereofacial- and *endo*-selective manner to provide the corresponding cycloadduct **27** as a single isomer in almost quantitative yield (97%). The structure and stereochemistry of the Diels–Alder adduct **27** was assigned based on the NMR spectral analysis including NOESY experiments; thus, clear NOE interactions between C9–H and C8a–H, C4a–H and between C3–H and C7–H were observed, respectively. After deprotection of the TBS group of **27** with tetrabutylammonium fluoride (TBAF) (75%), the resulting alcohol **28** was subjected to bromo etherification using *N*-bromosuccinimide (NBS)[28] to provide the desired tetracyclic bromo ether **25** in 86% yield.



Scheme 5. Aldol-type coupling reaction of the masked enone **25** with benzaldehyde (**8**) and the synthesis of the intermediate **31**. (a) Et_2AlCl, CH_2Cl_2, −78→0 °C, 97%; (b) TBAF, THF, 0 °C→rt, 75%; (c) NBS, CH_2Cl_2, 0 °C→rt, 86%; (d) $LiN(SiMe_3)_2$, THF, 98%; (e) $LiN(SiMe_3)_2$, THF, −78 °C; at −78 °C add. benzaldehyde (**8**), 98%; (f) $LiN(SiMe_3)_2$, THF, −78 °C; at −78 °C add. benzaldehyde (**8**), 98%; (g) phenyl chlorothionoformate, DMAP, MeCN, rt, 92%; (h) *n*-Bu_3SnH, AIBN, toluene, 110 °C, 79%.

The crucial aldol-type coupling reaction between **25**[29] and benzaldehyde (**8**) was next conducted to establish the requisite C6 asymmetric quaternary carbon center. During the optimization of the reaction conditions, we found that the bromo ether **25** exhibited an interesting and unprecedented reactivity. Thus, treatment of **25** with 1.1 equiv of $LiN(SiMe_3)_2$ in THF at −78 °C for 30 min resulted in the formation of the unexpected cyclopropane derivative **29** in almost quantitative yield (98%), whose structure was confirmed by extensive spectroscopic studies including COSY, HMBC, and NOESY experiments in the 500 MHz NMR spectra. Subsequent treatment of **29** with 1.1 equiv of $LiN(SiMe_3)_2$ in THF at −78 °C followed by addition of benzaldehyde (**8**) (2.2 equiv) afforded the desired coupling product **30** in excellent yield (98%) as a hardly separable mixture of the epimeric alcohols (6:1 by 500 MHz ^1H NMR). The C6 stereochemistry of the product **23** turned out to be completely controlled as we expected; the assignment was later confirmed by NOE study of the transformed compound **31** (vide infra).

Encouraged by these successful results, we next examined a more efficient one-pot procedure for the direct coupling of **25** and **8**. Thus, treatment of **25** with 2.2 equiv of $LiN(SiMe_3)_2$ followed by reaction with 2.2 equiv of **8** furnished the requisite coupling product **23** in 98% yield. The secondary hydroxy group in **23** was deleted by using Robin's modification[30] of the Barton method.[31] Thus, treatment of **23** with phenyl thionochloroformate in acetonitrile in the presence of 4-dimethylaminopyridine (DMAP) at ambient temperature afforded the corresponding phenoxythionocarbonate **30** in 92% yield. Compound **30** was then allowed to react with tri-*n*-butyltin hydride in toluene in the presence of a catalytic amount of 2,2′-azobisisobutyronitrile (AIBN) at 110 °C, giving rise to the desired deoxygenated product **31** in 79% yield. At this stage, the C6 stereochemistry could be unambiguously confirmed by NOESY experiments in the 500 MHz ^{1}H NMR spectrum of **31**, in which a clear NOE interaction between C5–H and the benzylic proton was observed.

2.6. Synthesis of the epoxycyclohexenone moiety 2

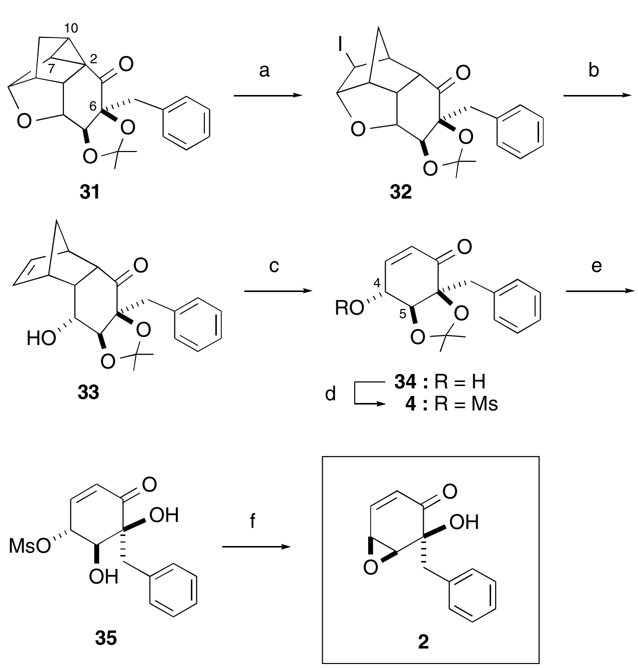
Having succeeded in introduction of the benzyl substituent at the C6 position with the correct stereochemistry, we next executed conversion of **31** into the epoxycyclohexenone moiety **2** (Scheme 6); the sequence involved regeneration of the enone system and subsequent epoxide ring formation as the pivotal steps. Regioselective cleavage of the cyclopropane ring in **31** was successfully achieved by treatment with trimethylsilyl iodide (TMSI)[32] in carbon tetrachloride at −20→−10 °C to give the desired γ-iodo ketone **32** in 89% yield as the sole product. The regioselectivitiy observed for this ring opening reaction can be explained by the so-called stereoelectronic effect. Thus, the σ_{C2-C7} orbital efficiently overlaps with the $\pi_{C=O}$ orbital, while the overlap between the σ_{C2-C10} orbital and the $\pi_{C=O}$ orbital is insufficient due to the geometrical factor. An attack of the iodo anion, therefore, occurred predominantly at the C7 position in **31**. Conversion of the γ-iodo ketone **32** to the requisite cyclohexenone **34** was effectively achieved by applying the Ogasawara procedure.[28] Thus, treatment of **32** with zinc powder in methanol containing a small amount of acetic acid gave the tricyclic compound **33** in 91% yield, which was then subjected to retro-Diels–Alder reaction by heating at 230 °C in diphenyl ether to produce **34** in 81% yield.

The remaining task to complete the synthesis of the first target compound **2** involved the critical epoxide ring formation utilizing the two oxygen functionalities at the C4 and C5 positions in **34**. Toward this end, mesylation of the hydroxy group in **34** under the standard conditions (MsCl, Et_3N, DMAP, CH_2Cl_2, 0 °C→room temperature) (85%) followed by hydrolysis of the acetonide moiety of the resulting mesylate **4** by treatment with aqueous trifluoroacetic acid (TFA), furnished the desired diol **35** in 85% yield. Finally, the expected epoxide ring formation was successfully achieved by brief exposure of **35** to 0.2 M sodium hydroxide in ether at 0 °C for 10 min, providing the epoxycyclohexenone moiety **2** in 90% yield.

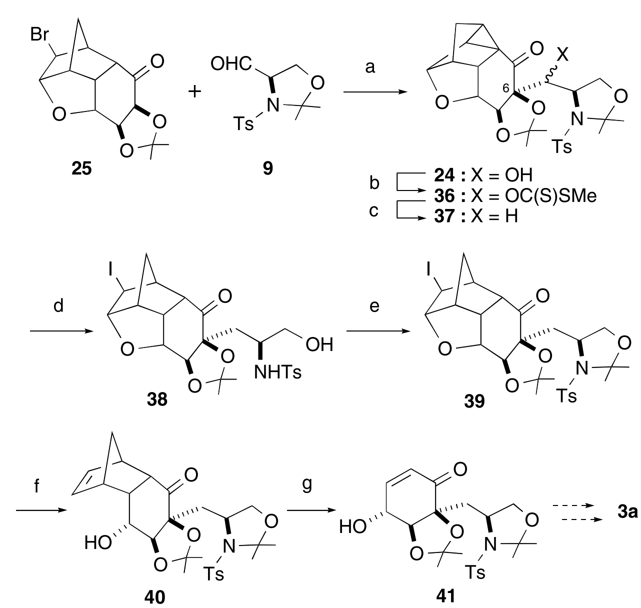
2.7. Initial attempts on the synthesis of the fully functionalized epoxycyclohexenone moiety 3a

Having established the synthetic route to the epoxycyclohexenone moiety **2**, we next undertook the synthesis of the fully functionalized epoxycyclohexenone moiety **3a** (cf. Scheme 4), which possesses the *N*,*O*-protected amino propanol side chain and the requisite asymmetric carbon centers. We envisaged that the targeted compound **3a** would be elaborated starting from the bromo ether **25** and D-serinal derivative **9**[33] [(*R*)-*N*-(*p*-toluenesulfonyl)-*N*,*O*-isopropylidene serinal], readily accessible from D-serine, based on the explored synthetic route to the epoxycyclohexenone moiety **2**.

As shown in Scheme 7, the synthesis started with the crucial aldol coupling reaction between **25** and **9**. The enolate anion, generated in situ by treatment of **25** with $LiN(SiMe_3)_2$ (2.2 equiv) in THF at −78 °C, was allowed to react with **9** (2.5 equiv) to furnish an excellent yield



Scheme 6. Synthesis of the epoxycyclohexenone moiety **2**. (a) TMSI, CCl_4, −20→−10 °C, 89%; (b) Zn, AcOH, MeOH, 60 °C, 91%; (c) Ph_2O, 230 °C, 81%; (d) MsCl, Et_3N, DMAP, CH_2Cl_2, 0 °C→rt, 85%; (e) TFA, H_2O, 0 °C, 85%; (f) 0.2 M NaOH, Et_2O, 0 °C, 90%.



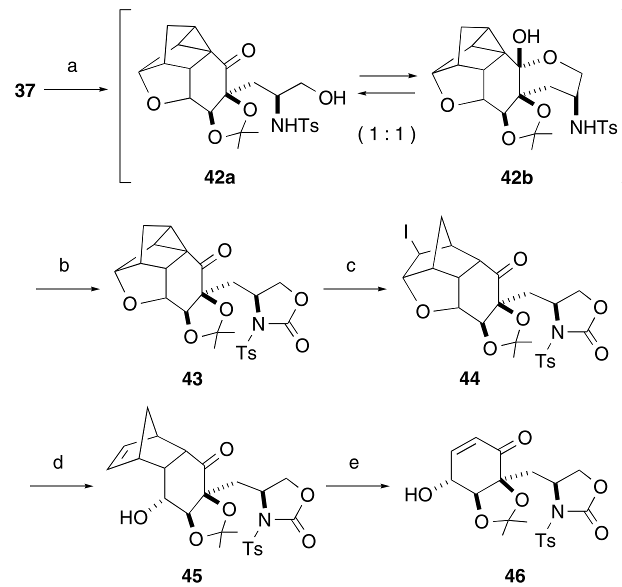
Scheme 7. Initial attempts on the synthesis of the intermediate **41** for the epoxycyclohexenone moiety **3a**. (a) $LiN(SiMe_3)_2$, THF, −78 °C; at −78 °C, add. (*R*)-*N*-(*p*-toluenesulfonyl)-*N*,*O*-isopropylidene serinal (**9**), 98%; (b) $NaN(SiMe_3)_2$, THF, −78 °C; CS_2, −78→−50 °C; MeI, −78→−50 °C, 88%; (c) *n*-Bu_3SnH, Et_3B, toluene, rt, 95%; (d) TMSI, CCl_4, −10 °C, 91%; (e) 2,2-dimethoxypropane, *p*-TsOH, benzene, 60 °C, 83%; (f) Zn, AcOH, MeOH, 60 °C, 98%; (g) Ph_2O, 230 °C, 25%.

(98%) of the desired coupling product **24** as an inseparable mixture of the epimeric alcohols (9:1 by 500 MHz ^{1}H NMR). Removal of the hydroxy group in **24** was initially attempted by employing the same reaction conditions [ClC(S)OPh, DMAP, MeCN] described for the preparation of **30** from **23** (cf. Scheme 5), which, unfortunately, ended in failure and the starting material **24** was recovered unchanged even under heating conditions. This is presumably due to the steric hindrance around the hydroxy group in **24**. Therefore, we looked at the Barton procedure[31] to achieve the requisite deoxygenation of the sterically hindered hydroxy group. Employing the original Barton conditions (NaH, CS_2, THF; MeI, 0 °C→room temperature), the reaction gave a poor yield (∼30%) of the desired methyl xanthate **36**. In order to improve the yield, some modifications were made of the reaction conditions. After several trials, to our delight, we found that treatment of **24** with $NaN(SiMe_3)_2$ (1.2 equiv) in THF at −78 °C followed by addition of carbon disulfide (10 equiv) and iodomethane (10 equiv) at the same temperature furnished the methyl xanthate **36** in 88% yield. The resulting methyl xanthate **36** was further treated with tri-*n*-butyltinhydride and triethylborane[34] in toluene at ambient temperature to afford the requisite deoxygenated product **37** in 95% yield.

With the intermediate **37** possessing the requisite *N*,*O*-protected amino propanol side chain and the correct stereochemistry in hand, our next efforts were devoted to regeneration of the cyclohexenone olefin moiety. Toward this end, regioselective cleavage of the cyclopropane ring in **37** was conducted by treatment with TMSI to give the iodo ether **38** in 91% yield. In this reaction, the *N*,*O*-isopropylidene group was simultaneously hydrolyzed; therefore, regeneration of the *N*,*O*-isopropylidene moiety of the resulting aminopropanol **38** was carried out under conventional conditions (2,2-dimethoxypropane, *p*-TsOH, benzene, 60 °C) to furnish the acetonide **39** in 83% yield. Further treatment of **39** with zinc powder in methanol containing acetic acid at 60 °C furnished the tricyclic compound **40** in 98% yield. Retro-Diels–Alder reaction of **40** by the thermolysis at 230 °C in diphenyl ether, to our disappointment, provided a poor yield (25%) of the cyclohexenone derivative **41**. This is presumably due to the instability of the *N*,*O*-isopropylidene group under the harsh reaction conditions. Fortunately, this problem was solved by replacement of the *N*,*O*-isopropylidene group with a robust cyclic carbamate group prior to subjection to the retro-Diels–Alder reaction (cf. Scheme 8). This is the subject of the following section.

2.8. Successful synthesis of the fully functionalized epoxycyclohexenone moiety 3b

The synthesis of the fully functionalized epoxycyclohexenone moiety **3b** was successfully achieved by exchanging the *N*,*O*-isopropylidene moiety in **37** with the corresponding cyclic carbamate functionality. Thus, as shown in Scheme 8, the *N*,*O*-isopropylidene moiety in **37** was selectively deprotected by exposure to aqueous hydrogen chloride in THF at 55 °C, which furnished an equilibrium mixture of the *N*-Ts-β-amino alcohol **42a** and the cyclic hemiacetal **42b** (ca. 1:1 by ^{1}H NMR). This equilibrium mixture was then treated with phosgene dimer

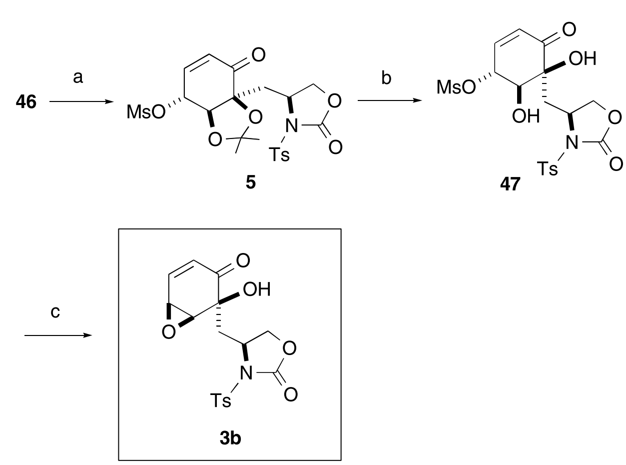


Scheme 8. Synthesis of the intermediate **46** for the epoxycyclohexenone **3**. (a) 1.0 M HCl, THF, 55 °C; (b) phosgen dimer, pyridine, THF, rt, 67% (two steps); (c) TMSI, CCl_4, −20 °C, 74%; (d) Zn, AcOH, MeOH, 60 °C, 95%; (e) Ph_2O, 230 °C, 59%.

(trichloromethyl chloroformate) in the presence of pyridine in THF, providing the desired cyclic carbamate **43** in 67% yield for the two steps.

To forward the synthesis, regeneration of the cyclohexenone olefin moiety was next investigated. Thus, regioselective cleavage of the cyclopropane ring in **43** by reaction with TMSI afforded the expected iodide **44** in 74% yield. Further treatment of **44** with zinc powder in methanol containing acetic acid furnished the alcohol **45** in 95% yield. Retro-Diels–Alder reaction of **45** proceeded effectively by thermolysis at 230 °C in diphenyl ether. The desired cyclohexenone **46** was obtained in an acceptable 59% yield.

The final route that led to completion of the synthesis of the targeted molecule **3** is summarized in Scheme 9. The hydroxy group in **46** was mesylated under standard conditions (MsCl, Et_3N, DMAP, CH_2Cl_2, 0 °C→room



Scheme 9. Synthesis of the intermediate **3b**. (a) MsCl, Et_3N, DMAP, CH_2Cl_2, 0 °C→rt, 83%; (b) TFA, H_2O, 0 °C, quant.; (c) 0.2 M NaOH, Et_2O, 0 °C, 75%.

temperature) to give the corresponding mesylate **5** in 83% yield. The *O*-isopropylidene moiety of **5** was then hydrolyzed by reaction with aqueous trifluoroacetic acid at 0 °C to provide the requisite diol **47** in quantitative yield. Finally, brief exposure of **47** to aqueous sodium hydroxide in ether at 0 °C, led to the formation of **3b** in 75% yield. The structure and stereochemistry of **3b** were unambiguously confirmed by single X-ray crystallographic analysis as depicted in Figure 3.[35]

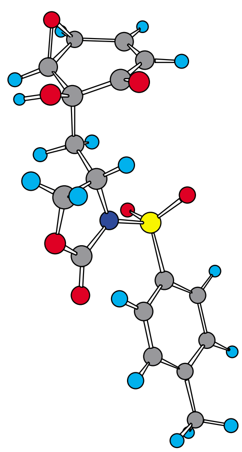


Figure 3. X-ray structure of the epoxycyclohexenone moiety **3b**. Red, O; navy, N; yellow, S; blue, H.

3. Conclusion

In conclusion, we have succeeded in developing an efficient and enantioselective synthetic pathway to the epoxycyclohexenone moieties **2** and **3b** of scyphostatin (**1**). The explored method features (i) the preparation of the key intermediate cyclohexene **10** and its olefin masked enone **25** starting from commercially available (−)-quinic acid (**11**), (ii) the aldol-type coupling reaction of the ketone **25** with benzaldehyde (**8**) or Garner's aldehyde analogue **9** to install the requisite asymmetric quaternary carbon center at the C6 position with complete stereoselectivity (**25**+**8**→**23** and **25**+**9**→**24**), and (iii) the facile epoxide ring formation of the β-hydroxymesylates **35** and **47** under mild basic conditions (**35**→**2** and **47**→**3b**). Further investigation toward the synthesis of scyphostatin analogues based on the present study is now in progress and will be reported in due course.

4. Experimental

4.1. General methods

All reactions involving air- and moisture-sensitive reagent were carried out using oven-dried glassware and standard syringe-septum cap techniques. Routine monitorings of reaction were carried out using glass-supported Merck silica gel 60 F_{254} TLC plates. Flash column chromatography was performed on Kanto Chemical Silica Gel 60N (spherical, neutral 40–50 μm) with the solvents indicated.

All solvents and reagents were used as supplied with the following exceptions. Tetrahydrofuran (THF) and ether were freshly distilled from sodium/benzophenone under argon. Dichloromethane, acetonitrile, and *N*,*N*-dimethylformamide (DMF) were distilled from calcium hydride under argon.

Melting points were taken on a Yanaco MP-3 micro melting point apparatus and are uncorrected. Measurements of optical rotations were performed with a JASCO P-1020 automatic digital polarimeter. ^{1}H and ^{13}C NMR spectra were measured with a Brucker DRX-500 (500 MHz) spectrometer or a Brucker DRX-250 (250 MHz). Chemical shifts were expressed in ppm using tetramethylsilane (δ=0) as an internal standard. The following abbreviations are used: singlet (s), doublet (d), triplet (t), multiplet (m), and broad (br). Infrared (IR) spectral measurements were carried out with a JASCO FT/IR-5300 spectrometer. Low-resolution mass (MS) spectra was measured on Shimadzu GCMS-QP2010. High-resolution mass (HRMS) spectra was measured on JEOL MStation JMS-700 mass spectrometer. Elemental analyses were performed with a Perkin Elmer 2400II apparatus.

4.1.1. (1*R*,2*R*,3*R*)-3-*tert*-Butyldimethylsiloxy-1,2-(*O*-isopropylidenedioxy)cyclohexan-5-one (13). *tert*-Butyldimethylsilyl chloride (24.4 g, 0.16 mol) was added to a stirred solution of **12**[24] (10.0 g, 54 mmol) in dry DMF (120 ml) containing imidazole (14.7 g, 0.22 mol) at room temperature. After 15 h, the mixture was diluted with ethyl acetate (800 ml). The organic layer was successively washed with 3% aqueous hydrochloric acid (2×250 ml), saturated aqueous sodium hydrogen carbonate (2×250 ml), and brine (2×250 ml), then dried over Na_2SO_4. Concentration of the solvent in vacuo afforded a residue, which was purified by column chromatography (hexane/ethyl acetate, 14:1) to give **13** (16.2 g, 98%) as a colorless oil. $[\alpha]_D^{20}$ +105.3 (*c* 1.00, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.05 (3H, s, Si-Me), 0.09 (3H, s, Si-Me), 0.83 (9H, s, Si-*t*-Bu), 1.35 (3H, s, C-Me), 1.42 (3H, s, C-Me), 2.37 (1H, ddd, *J*=1.9, 3.5, 17.5 Hz, C4–H), 2.64 (1H, dd, *J*=2.2, 17.4 Hz, C4–H), 2.65 (1H, dd, *J*=2.5, 17.5 Hz, C6–H), 2.75 (1H, dd, *J*=3.5, 17.5 Hz, C6–H), 4.16 (1H, m, C3–H), 4.22 (1H, dt, *J*=2.2, 7.2 Hz, C2–H), 4.69 (1H, m, C1–H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −5.06, −5.04, 17.9, 23.9, 25.6 (3 carbons), 26.3, 40.1, 41.9, 68.7, 72.4, 75.1, 108.7, 207.7; IR (neat) 440, 520, 690, 780, 810, 840, 870, 910, 980, 1010, 1060, 1090, 1140, 1180, 1210, 1250, 1380, 1470, 1720, 2860, 2930, 2960 cm^{-1}; HREIMS (*m/z*) calcd for $C_{14}H_{25}O_4Si$ [(M−Me)$^+$]: 285.1522, found 285.1253.

4.1.2. (1*R*,2*R*,3*R*,5*R*)- and (1*R*,2*R*,3*R*,5*S*)-3-*tert*-Butyldimethylsiloxy-5-hydroxy-1,2-(*O*-isopropylidenedioxy)cyclohexane (14) and (15). Sodium borohydride (1.30 g, 34 mmol) in water (15 ml) was added dropwise to a stirred solution of **13** (9.40 g, 31 mmol) in THF (400 ml) at −5 °C, and stirring was continued for 1 h at room temperature. The reaction was quenched with saturated aqueous ammonium chloride (30 ml) at 0 °C, and then the mixture was diluted with ethyl acetate (1000 ml). The organic layer was washed with saturated aqueous ammonium chloride (2×300 ml) and brine (2×300 ml), then dried over Na_2SO_4. Concentration of the solvent in vacuo gave a residue, which was separated by column chromatography (hexane/ethyl acetate, 5:1 → 3:1) to give **14** (5.02 g, 53%) as a more polar product and **15** (4.16 g, 44%) as a less polar product.

Compound **14**. Colorless prism, mp 47–48 °C; $[\alpha]_D^{20}$ −41.7 (*c* 1.01, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 0.10 (3H, s, Si-Me), 0.11 (3H, s, Si-Me), 0.89 (9H, s, *t*-Bu), 1.34 (3H, s, C-Me), 1.46 (3H, s, C-Me), 1.60 (1H, m, C4–H), 1.83 (1H, m, C6–H), 2.00 (1H, m, C4–H), 2.20 (1H, m, C6–H), 2.26 (1H, d, *J* = 6.8 Hz, OH), 3.89–3.97 (2H, m, C2–H, C3–H), 4.02 (1H, br, C5–H), 4.40 (1H, dd, *J* = 4.8, 9.8 Hz, C1–H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.81, −4.72, 18.0, 25.8 (3 carbons), 25.9, 28.1, 35.5, 37.7, 65.1, 71.1, 72.7, 78.87, 108.5; IR (KBr) 510, 550, 630, 660, 690, 780, 840, 870, 920, 940, 960, 1020, 1040, 1060, 1120, 1190, 1220, 1240, 1260, 1370, 1380, 1460, 2860, 2890, 2930, 2990, 3420 cm^{-1}; CIMS (*m/z*) 303 $[(M+H)^+]$; HREIMS (*m/z*) calcd for $C_{14}H_{27}O_4Si$ $[(M-Me)^+]$: 287.1679, found 287.1682.

Compound **15**. Colorless oil. $[\alpha]_D^{20}$ −33.7 (*c* 1.02, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 0.08 (3H, s, Si-Me), 0.10 (3H, s, Si-Me), 0.88 (9H, s, *t*-Bu), 1.35 (3H, s, C-Me), 1.52 (3H, s, C-Me), 1.73 (1H, m, C4–H), 1.90 (1H, ddd, *J* = 3.9, 6.3, 13.7 Hz, C4–H), 2.04 (2H, t, *J* = 4.4 Hz, C6–H), 2.27 (1H, d, *J* = 8.2 Hz, OH), 3.90 (1H, t, *J* = 5.2 Hz, C2–H), 4.04 (1H, dd, br, *J* = 7.7, 10.7 Hz, C5–H), 4.09 (1H, m, C3–H), 4.41 (1H, dd, *J* = 4.6, 9.7 Hz, C1–H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.81, −4.72, 18.0, 25.7, 25.8 (3 carbons), 28.2, 33.8, 37.9, 65.3, 68.7, 74.1, 78.9, 108.6; IR (neat) 520, 660, 780, 840, 910, 940, 960, 1000, 1050, 1070, 1120, 1150, 1220, 1250, 1380, 1460, 2860, 2890, 2930, 2960, 2990, 3440 cm^{-1}; HREIMS (*m/z*) calcd for $C_{14}H_{27}O_4Si$ $[(M-Me)^+]$: 287.1679, found 287.1680.

4.1.3. (1*R*,2*R*,3*R*,5*R*)-5-Acetoxy-3-*tert*-butyldimethylsiloxy-1,2-(*O*-isopropylidenedioxy)cyclohexane (16). Acetic anhydride (0.1 ml, 1.1 mmol) was added to a stirred solution of **14** (27 mg, 89 μmol) in pyridine (1.0 ml) containing 4-dimethylaminopyridine (1.0 mg, 8 μmol) at 0 °C, and stirring was continued for 3 h at room temperature. The reaction was quenched with saturated aqueous sodium hydrogen carbonate (1 ml) at 0 °C, and the mixture was diluted with ether (30 ml). The organic layer was successively washed with 3% aqueous hydrochloric acid (2×15 ml), saturated aqueous sodium hydrogen carbonate (2×15 ml), and brine (2×10 ml), then dried over Na_2SO_4. Concentration of the solvent in vacuo afforded a residue, which was purified by column chromatography (hexane/ethyl acetate, 7:1) to give **16** (30 mg, 98%) as a colorless oil. $[\alpha]_D^{20}$ −29.6 (*c* 1.01, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 0.07 (3H, s, Si-Me), 0.09 (3H, s, Si-Me), 0.89 (9H, s, Si-*t*-Bu), 1.34 (3H, s, C-Me), 1.45 (1H, m, C4–H), 1.46 (3H, s, C-Me), 1.82 (1H, m, C6–H), 2.03 (3H, s, Ac), 2.12 (1H, m, C4–H), 2.35 (1H, m, C6–H), 3.80 (1H, m, C3–H), 3.87 (1H, t, *J* = 5.9 Hz, C2–H), 4.39 (1H, m, C1–H), 5.04 (1H, m, C5–H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.85, −4.86, 18.0, 21.3, 25.4, 25.7 (3 carbons), 27.8, 31.2, 36.1, 66.8, 70.6, 73.0, 79.4, 108.5, 170.4; IR (neat) 410, 510, 610, 660, 700, 780, 840, 870, 900, 920, 940, 990, 1060, 1120, 1150, 1220, 1240, 1370, 1460, 1740, 2860, 2890, 2930, 2960, 2990 cm^{-1}; HREIMS (*m/z*) calcd for $C_{16}H_{29}O_5Si$ $[(M-Me)^+]$: 329.1784, found 329.1796.

4.1.4. Conversion of 14 to 15. Diethyl azodicarboxylate in toluene (40% solution, 14.5 ml, 34 mmol) was added dropwise to a stirred solution of **14** (5.00 g, 17 mmol) in dry THF (150 ml) containing triphenylphosphine (8.68 g, 34 mmol) and benzoic acid (4.15 g, 34 mmol) at 0 °C under argon. The mixture was stirred for 3 h at room temperature. Concentration of the mixture in vacuo afforded a residue, which was purified by column chromatography (hexane/ethyl acetate, 13:1) to give the corresponding benzoate (6.61 g, 98%) as a colorless oil. $[\alpha]_D^{20}$ +15.9 (*c* 1.06, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 0.09 (3H, s, Si-Me), 0.10 (3H, s, Si-Me), 0.90 (9H, s, Si-*t*-Bu), 1.37 (3H, s, C-Me), 1.55 (3H, s, C-Me), 1.92–2.10 (3H, m, C4–H, C4–H, C6–H), 2.24 (1H, dt, *J* = 5.1, 14.5 Hz, C6–H), 3.96 (1H, t, *J* = 4.9 Hz, C2–H), 4.20 (1H, m, C3–H), 4.43 (1H, q, *J* = 5.5 Hz, C1–H), 5.33 (1H, m, C5–H), 7.43 (2H, t, *J* = 7.8 Hz, Ar-H), 7.55 (1H, t, *J* = 7.4 Hz, Ar-H), 8.05 (2H, d, *J* = 7.1 Hz, Ar-H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −5.02, −4.84, 17.9, 25.7 (4 carbons), 30.9, 33.95, 33.99, 67.5, 68.8, 69.6, 72.8, 128.3 (2 carbons), 129.6 (2 carbons), 130.5, 132.9, 165.8, 207.1; IR (neat) 520, 710, 780, 840, 920, 940, 970, 1010, 1030, 1070, 1110, 1220, 1280, 1320, 1370, 1380, 1450, 1540, 1600, 1720, 1780, 2860, 2890, 2930 cm^{-1}; HREIMS (*m/z*) calcd for $C_{21}H_{31}O_5Si$ $[(M-Me)^+]$: 391.1941, found 391.1910.

2.0 M Potassium hydroxide solution (22.4 ml, 45 mmol) was added dropwise to a stirred solution of the above benzoate (6.50 g, 16 mmol) in methanol (280 ml) at 0 °C, and stirring was continued for 3 h at room temperature. The mixture was concentrated in vacuo to give a residue, which was diluted with ethyl acetate (800 ml). The organic layer was washed with brine (2×300 ml) and then dried over Na_2SO_4. Concentration of the solvent in vacuo afforded a residue, which was purified by column chromatography (hexane/ethyl acetate, 3:1) to give **15** (4.82 g, quant.) as a colorless oil. The IR, ^1H NMR, and mass spectra of this material were identical with those recorded for preparation of **15** (see, Section 4.1.2).

4.1.5. (3*R*,4*R*,5*R*)-5-*tert*-Butyldimethylsiloxy-3,4-*O*-isopropylidenedioxy-1-cyclohexene (17). Diethyl azodicarboxylate in toluene (40% solution, 21.6 ml, 50 mmol) was added dropwise to a stirred solution of **15** (5.00 g, 17 mmol) in dry THF (150 ml) containing triphenylphosphine (13.1 g, 51 mmol) at room temperature. After 3 h, the mixture was concentrated in vacuo to afford a residue, which was purified by column chromatography (hexane/ethyl acetate, 13:1) to give **17** (3.15 g, 67%) as a colorless oil. $[\alpha]_D^{20}$ −87.1 (*c* 1.05, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 0.07 (3H, s, Si-Me), 0.10 (3H, s, Si-Me), 0.89 (9H, s, Si-*t*-Bu), 1.38 (3H, s, C-Me), 1.46 (3H, s, C-Me), 2.01 (1H, m, C6–H), 2.28 (1H, m, C6–H), 3.83 (1H, m, C5–H), 3.98 (1H, t, *J* = 6.8 Hz, C4–H), 4.60 (1H, d, *J* = 6.2 Hz, C3–H), 5.80 (2H, m, C1–H, C2–H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.8, −4.5, 18.1, 25.8 (3 carbons), 26.1, 28.3, 31.9, 69.6, 72.8, 78.7, 108.6, 124.6, 128.5; IR (neat) 670, 780, 840, 910, 1010, 1060, 1120, 1220, 1250, 1380, 1460, 1690, 1730, 2860, 2930, 2960 cm^{-1}; HREIMS (*m/z*) calcd for $C_{14}H_{25}O_3Si$ $[(M-Me)^+]$: 269.1573, found 269.1570.

4.1.6. (1*S*,2*S*,3*R*,4*R*,5*R*)-5-*tert*-Butyldimethylsiloxy-1,2-epoxy-3,4-(*O*-isopropylidenedioxy)cyclohexane (18). 3-Chloroperoxybenzoic acid (*m*CPBA) (7.53 g, 45 mmol) was added in small portions to a stirred solution of **17** (4.95 g, 17 mmol) in dry dichloromethane (180 ml) containing sodium hydrogen carbonate (7.53 g, 45 mmol) at 0 °C, and stirring was continued for 24 h at room temperature. The reaction was diluted with ethyl acetate (400 ml). The organic layer was washed with saturated aqueous sodium hydrogen carbonate (2×200 ml) and brine (2×200 ml), then dried over Na_2SO_4. Concentration of the solvent in vacuo affoded a residue, which was purified by column chromatography (hexane/ethyl acetate, 13:1) to give **18** (4.81 g, 92%) as a colorless oil. $[\alpha]_D^{20}$ −29.1 (*c* 1.04, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 0.06 (3H, s, Si-Me), 0.07 (3H, s, Si-Me), 0.88 (9H, s, Si-*t*-Bu), 1.38 (3H, s, C-Me), 1.46 (3H, s, C-Me), 1.90 (1H, ddd, *J*=1.6, 6.1, 15.6 Hz, C6–H), 2.18 (1H, ddd, *J*=4.0, 5.1, 15.4 Hz, C6–H), 3.14 (1H, d, *J*=3.6 Hz, C2–H), 3.23 (1H, s, C1–H), 3.87 (1H, dd, *J*=5.8, 11.2 Hz, C5–H), 3.94 (1H, m, C4–H), 4.53 (1H, d, *J*=5.6 Hz, C3–H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.77, −4.75, 18.0, 25.7 (3 carbons), 26.0, 28.0, 29.4, 51.3, 51.7, 66.3, 71.8, 76.8, 109.2; IR (neat) 510, 710, 780, 840, 870, 910, 940, 1000, 1110, 1220, 1250, 1380, 1470, 2860, 2890, 2930, 2990 cm^{-1}; HREIMS (*m/z*) calcd for $C_{14}H_{25}O_4Si$ $[(M-Me)^+]$: 285.1522, found 285.1508.

4.1.7. (1*S*,4*R*,5*R*,6*R*)-4-*tert*-Butyldimethylsiloxy-1-hydroxy-5,6-*O*-isopropylidenedioxy-2-cyclohexene (19). Sodium borohydride (663 mg, 18 mmol) was added in small portions to a stirred suspension of diphenyl diselenide (2.74 g, 8.8 mmol) in dry ethanol (30 ml) at 0 °C under argon. After 30 min, a solution of **18** (4.80 g, 16 mmol) in dry ethanol (30 ml) was added dropwise to the mixture at room temperature. The mixture was heated at reflux for 1 h. After cooling, the mixture was diluted with dry THF (24 ml). Hydrogen peroxide in water (30% solution, 19.5 ml, 0.17 mol) was added dropwise to the mixture at 0 °C. The resulting mixture was further stirred for 5 min at 0 °C and slowly heated at reflux for 1 h. After cooling, the mixture was diluted with ether (300 ml). The organic layer was washed with saturated aqueous sodium hydrogen carbonate (2×150 ml) and brine (2×100 ml), then dried over Na_2SO_4. Concentration of the solvent in vacuo gave a residue, which was purified by column chromatography (hexane/ethyl acetate, 3:1) to give **19** (3.74 g, 78%) as a colorless oil. $[\alpha]_D^{20}$ −42.4 (*c* 1.03, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 0.11 (3H, s, Si-Me), 0.13 (3H, s, Si-Me), 0.90 (9H, s, Si-*t*-Bu), 1.34 (3H, s, C-Me), 1.40 (3H, s, C-Me), 2.90 (1H, d, *J*=8.3 Hz, OH), 4.12 (1H, m, C1–H), 4.21 (1H, t, *J*=3.7 Hz, C4–H), 4.29 (1H, dd, *J*=4.1, 7.5 Hz, C5–H), 4.33 (1H, dd, *J*=4.1, 7.5 Hz, C6–H), 5.95 (1H, dd, *J*=4.2, 9.8 Hz, C3–H), 6.07 (1H, dd, *J*=4.2, 9.8 Hz, C2–H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.81, −4.75, 18.0, 24.6, 25.8 (3 carbons), 26.6, 67.9, 68.7, 78.8, 79.0, 108.7, 132.3, 132.3; IR (neat) 410, 480, 520, 640, 660, 690, 780, 840, 890, 940, 960, 990, 1010, 1060, 1120, 1160, 1210, 1250, 1380, 1460, 1640, 2860, 2900, 2930, 2960, 2990, 3050, 3450 cm^{-1}; HREIMS (*m/z*) calcd for $C_{14}H_{25}O_4Si$ $[(M-Me)^+]$: 285.1522, found 285.1534.

4.1.8. (4*R*,5*R*,6*S*)-4-*tert*-Butyldimethylsiloxy-5,6-*O*-isopropylidenedioxy-2-cyclohexen-1-one (10). Dess–Martin periodinane (14.5 g, 34 mmol) was added in small portions to a stirred solution of **19** (5.15 g, 17 mmol) in dry dichloromethane (200 ml) at room temperature. After 2 h, the mixture was diluted with ethyl acetate (500 ml). The organic layer was washed successively with 20% aqueous sodium thiosulfate (2×200 ml), saturated aqueous sodium hydrogen carbonate (2×200 ml), and brine (2×200 ml), then dried over Na_2SO_4. Concentration of the solvent in vacuo afforded a residue, which was purified by column chromatography (hexane/ethyl acetate, 7:1) to give **10** (4.86 g, 95%) as a white solid. Recrystallization from hexane/dichloromethane (5:1) afforded colorless prisms, mp 55–56 °C; $[\alpha]_D^{20}$ −84.7 (*c* 1.02, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 0.14 (3H, s, Si-Me), 0.17 (3H, s, Si-Me), 0.92 (9H, s, Si-*t*-Bu), 1.40 (3H, s, C-Me), 1.42 (3H, s, C-Me), 4.41 (1H, m, C5–H), 4.44 (1H, d, *J*=5.9 Hz, C6–H), 4.54 (1H, m, C4–H), 6.08 (1H, d, *J*=10.3 Hz, C2–H), 6.76 (1H, ddd, *J*=1.0, 3.8, 10.3 Hz, C3–H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.74 (Si-Me), −4.73 (Si-Me), 18.1 (*C*-Me$_3$), 25.7 (3 carbons, C-*Me*$_3$), 25.9 (Me of *O*-isopropylidene), 27.4 (Me of *O*-isopropylidene), 67.1 (C4), 74.4 (C5), 79.6 (C6), 110.2 (*C*-Me$_2$ of *O*-isopropylidene), 127.9 (C2), 148.5 (C3), 194.5 (C1); IR (KBr) 470, 520, 630, 670, 730, 780, 840, 890, 940, 980, 1010, 1080, 1170, 1250, 1330, 1380, 1460, 1630, 1700, 2710, 2740, 2860, 2900, 2930, 2990, 3040, 3370, 3550 cm^{-1}; EIMS (*m/z*) 298 (M^+), 283 $[(M-Me)^+]$, 241 $[(M-t\text{-Bu})^+]$. Anal. Calcd for $C_{15}H_{26}O_4Si$: C, 60.37; H, 8.78. Found C, 60.03; H, 8.56.

4.1.9. (1*S*,5*R*,6*S*,1′*R*,2′*R*,3′*R*,4′*S*)-5,2′-Bis(*tert*-butyldimethylsiloxy)-1,6:3′,4′-bis(*O*-isopropylidenedioxy)bicyclohexyl-3-ene-2,5′-dione (20) and (4*R*,5*S*,6*S*)-6-benzoyl-4-*tert*-butyldimethylsiloxy-5,6-*O*-isopropylidenedioxy-2-cyclohexen-1-one (22). Lithium bis(trimethylsilyl)amide in THF (1.0 M solution, 1.7 ml, 1.7 mmol) was added dropwise to a stirred solution of **10** (50 mg, 0.17 mmol) and benzaldehyde (**8**) (82 μl, 0.77 mmol) in dry THF (4 ml) at −78 °C under argon, and the stirring was continued for 30 min at the same temperature. The reaction was quenched with saturated aqueous ammonium chloride (1 ml) at 0 °C, and the mixture was diluted with ether (50 ml). The organic layer was washed successively with saturated aqueous ammonium chloride (2×20 ml), saturated aqueous sodium hydrogen carbonate (2×20 ml), and brine (2×20 ml), then dried over Na_2SO_4. Concentration of the solvent in vacuo afforded a residue, which was purified by column chromatography (hexane/ethylacetate, 7:1) to give **20** (19 mg, 38%) as a white amorphous solid and **21** (7.4 mg, 12%) as colorless oil. Since compound **21** was unstable, this was immediately subjected to the following oxidation reaction.

Compound **21** (7.4 mg, 18 μmol) was treated with Dess–Martin periodinane (23.0 mg, 54 μmol) in dichloromethane (0.5 ml) at room temperature for 1 h. The reaction mixture was diluted with ethyl acetate (30 ml). The organic layer was washed successively with 20% aqueous sodium thiosulfate (2×10 ml), saturated aqueous sodium hydrogen carbonate (2×10 ml), and brine (2×10 ml), then dried over Na_2SO_4. Concentration of the solvent in vacuo afforded a residue, which was purified by column chromatography (hexane/ethyl acetate, 7:1) to give **22** (5.7 mg, 78%) as a colorless viscous oil.

Compound **20**. $[\alpha]_D^{20}$ −30.0 (*c* 1.10, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.10 (3H, s, Si-Me of C6′–OTBS), 0.15 (3H, s, Si-Me of C5–OTBS), 0.17 (3H, s, Si-Me of C5–OTBS), 0.22 (3H, s, Si-Me of C6′–OTBS), 0.84 (9H, s, *t*-Bu of C6′–OTBS), 0.92 (9H, s, *t*-Bu of C5–OTBS), 1.27 (3H, s, Me of *O*-isopropylidene), 1.30 (3H, s, Me of *O*-isopropylidene), 1.35 (3H, s, Me of *O*-isopropylidene), 1.45 (3H, s, Me of *O*-isopropylidene), 2.58 (1H, dd, *J*=7.0, 16.8 Hz, C2′–H), 2.70 (1H, dd, *J*=10.5, 17.8 Hz, C2′–H), 2.98 (1H, dd, *J*=7.1, 10.3 Hz, C1′–H), 4.05 (1H, br s, C6′–H), 4.10 (1H, t, *J*=1.7 Hz, C6–H), 4.26 (2H, br, C4′–H, C5′–H), 4.61 (1H, dd, *J*=1.0, 4.3 Hz, C5–H), 6.01 (1H, d, *J*=10.2 Hz, C3–H) 6.58 (1H, br, C4–H); ^{13}C NMR (125 MHz, CD_2Cl_2) δ −4.89, −4.80, −4.44, −4.30, 18.3, 18.4, 24.5, 25.9 (6 carbons), 26.5, 26.6, 27.1 (2 carbons), 30.1, 65.9, 78.2 (2 carbons), 79.3, 80.2, 83.5, 109.2, 111.9, 127.7, 143.5, 198.8, 204.5; IR (neat) 520, 670, 780, 810, 840, 940, 960, 980, 1010, 1040, 1070, 1100, 1130, 1180, 1210, 1230, 1260, 1380, 1470, 1700, 1730, 2860, 2930, 2950, 2990 cm^{-1}; HREIMS (*m/z*) calcd for $C_{29}H_{49}O_8Si_2$ $[(M-Me)^+]$, 581.2966, found 581.2949.

Compound **22**. $[\alpha]_D^{20}$ −3.27 (*c* 1.00, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.14 (3H, s, Si-Me), 0.15 (3H, s, Si-Me), 0.92 (9H, s, *t*-Bu), 1.27 (3H, s, C-Me), 1.46 (3H, s, C-Me), 4.58 (1H, dt, *J*=1.6, 2.2 Hz, C4–H), 4.79 (1H, dd, *J*=1.2, 3.0 Hz, C5–H), 6.13 (1H, dd, *J*=1.6, 10.3 Hz, C2–H), 6.79 (1H, ddd, *J*=1.2, 3.4, 10.3 Hz, C3–H), 7.42 (2H, t, *J*=7.8 Hz, Ph-H), 7.55 (1H, d, *J*=7.8 Hz, Ph-H), 8.22 (2H, d, *J*=7.3 Hz, Ph-H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.82, −4.72, 18.1, 25.7 (3 carbons), 26.3, 27.4, 68.1, 82.8, 89.7, 111.3, 127.1, 128.1 (2 carbons), 130.8 (2 carbons), 133.3, 134.9, 148.8, 192.8, 196.9; IR (neat) 690, 780, 840, 870, 900, 1050, 1100, 1180, 1260, 1380, 1450, 1460, 1580, 1600, 1680, 1700, 2860, 2890, 2930, 2960, 2990 cm^{-1}; HREIMS (*m/z*) calcd for $C_{22}H_{30}O_5Si$ (M^+): 402.1863, found 402.1835.

4.1.10. (1*R*,4*S*,4a*R*,5*R*,6*S*,7*S*,8a*S*)-5-*tert*-Butyldimethylsiloxy-6,7-*O*-isopropylidenedioxy-1,4,4a,5,6,7,8,8a-octahydro-*endo*-1,4-methanonaphthalen-8-one (27). Diethylaluminum chloride in hexane (1.0 M solution, 2.68 ml, 0.27 mmol) was added dropwise to a stirred solution of **10** (4.00 g, 13 mmol) and cyclopentadiene (11.1 ml, 0.13 mol) in dry dichloromethane (140 ml) at −78 °C under argon. The mixture was gradually warmed up to 0 °C over 1 h, and stirring was continued for 1 h at 0 °C. The mixture was diluted with ether (400 ml). The organic layer was washed with saturated aqueous sodium hydrogen carbonate (2×200 ml) and brine (2×200 ml), then dried over Na_2SO_4. Concentration of the solvent in vacuo afforded a residue, which was purified by column chromatography (hexane/ethyl acetate, 6:1) to give **27** (4.74 g, 97%) as a white solid. Recrystallization from hexane/dichloromethane (10:1) afforded colorless prisms, mp 92–93 °C; $[\alpha]_D^{20}$ +46.7 (*c* 1.01, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.08 (3H, s, Si-Me), 0.09 (3H, s, Si-Me), 0.89 (9H, s, Si-*t*-Bu), 1.30 (3H, s, C-Me), 1.37 (1H, d, *J*=8.4 Hz, C9–H), 1.47 (3H, s, C-Me), 1.54 (1H, d, *J*=8.4 Hz, C9–H), 2.90 (1H, ddd, *J*=3.3, 5.6, 10.2 Hz, C4a–H), 3.08 (1H, s, C1–H), 3.11 (1H, s, C4–H), 3.18 (1H, dd, *J*=3.8, 10.2 Hz, C8a–H), 3.99 (1H, t, *J*=6.2 Hz, C5–H), 4.12 (1H, d, *J*=8.4 Hz, C7–H), 4.22 (1H, dd, *J*=7.0, 8.3 Hz, C6–H), 6.12 (1H, dd, *J*=3.0, 5.6 Hz, C2–H), 6.20 (1H, dd, *J*=3.0, 5.4 Hz, C3–H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.93, −4.53, 18.0, 24.0, 25.8 (3 carbons), 26.5, 45.2, 45.7, 46.6, 49.6, 51.6, 71.6, 78.1, 79.7, 109.9, 133.1, 137.0, 208.7; IR (KBr) 560, 680, 730, 780, 840, 850, 900, 940, 970, 1010, 1040, 1080, 1110, 1160, 1210, 1260, 1380, 1460, 1720, 2860, 2900, 2930, 2960 cm^{-1}; EIMS (*m/z*) 349 $[(M-Me)^+]$, 307 $[(M-t\text{-}Bu)^+]$, 249 $[(M-TBS)^+]$; CIMS (*m/z*) 365 $[(M+H)^+]$; HREIMS (*m/z*) calcd for $C_{19}H_{29}O_4Si$ $[(M-Me)^+]$: 349.1835, found 349.1825.

4.1.11. (1*R*,4*S*,4a*R*,5*R*,6*S*,7*S*,8a*S*)-5-Trihydroxy-6,7-*O*-isopropylidenedioxy-1,4,4a,5,6,7,8,8a-octahydro-*endo*-1,4-methanonaphthalen-8-one (28). Tetrabutylammonium fluoride in THF (1.0 M solution, 15.0 ml, 15 mmol) was added to a stirred solution of **27** (3.51 g, 9.6 mmol) in dry THF (100 ml) at 0 °C, and stirring was continued for 2 h at room temperature. The mixture was diluted with ether (400 ml). The organic layer was successively washed with saturated aqueous ammonium chloride (2×150 ml), saturated aqueous sodium hydrogen carbonate (2×150 ml), and brine (2×150 ml), then dried over Na_2SO_4. Concentration of the solvent in vacuo afforded a residue, which was purified by column chromatography (hexane/ethyl acetate, 5:3) to give **24** (1.81 g, 75%) as a white solid. Recrystallization from hexane/dichloromethane (10:1) afforded colorless needles, mp 137–138 °C; $[\alpha]_D^{20}$ +112.9 (*c* 1.00, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.34 (3H, s, C-Me), 1.42 (1H, d, *J*=8.4 Hz, C9–H), 1.53 (3H, s, C-Me), 1.58 (1H, d, *J*=8.4 Hz, C9–H), 2.16 (1H, s, OH), 3.08–3.16 (3H, m, C1–H, C4–H, C5–H), 3.38 (1H, dd, *J*=3.3, 10.5 Hz, C8a–H), 4.15 (1H, t, *J*=4.1 Hz, C4a–H), 4.20 (1H, d, *J*=8.0 Hz, C7–H), 4.43 (1H, dd, *J*=5.9, 8.0 Hz, C6–H), 6.25 (1H, dd, *J*=2.6, 5.5 Hz, C3–H), 6.37 (1H, dd, *J*=3.0, 5.5 Hz, C2–H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 23.9, 26.4, 44.6 (2 carbons), 45.3, 48.4, 51.7, 70.2, 78.1, 79.7, 111.0, 134.9, 137.4, 208.6; IR (KBr) 550, 740, 860, 890, 1040, 1060, 1160, 1210, 1260, 1380, 1630, 1710, 2940, 2980, 3440 cm^{-1}; EIMS (*m/z*) 250 (M^+), 235 $[(M-Me)^+]$. Anal. Calcd for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25. Found: C, 67.35, H, 7.24.

4.1.12. (1*S*,2*S*,3*S*,4*R*,4a*R*,5*R*,6*S*,7*S*,8a*R*)-2-Bromo-3,5-epoxy-6,7-(*O*-isopropylidenedioxy)perhydro-*endo*-1,4-methanonaphthalen-8-one (25). *N*-Bromosuccinimide (2.78 g, 16 mmol) was added in small portions to a stirred solution of **28** (3.02 g, 12 mmol) in dry dichloromethane (180 ml) at 0 °C, and stirring was continued for 1 h at room temperature. The mixture was diluted with ether (400 ml). The organic layer was washed successively with 20% aqueous sodium thiosulfate (2×150 ml), saturated aqueous sodium hydrogen carbonate (2×150 ml), and brine (2×150 ml), then dried over Na_2SO_4. Concentration of the solvent in vacuo afforded a residue, which was purified by column chromatography (hexane/ethyl acetate, 4:1) to give **25** (3.41 g, 86%) as a white solid. Recrystallization from hexane/ether (5:1) afforded pale yellow prisms, mp 121–122 °C; $[\alpha]_D^{20}$ +65.9 (*c* 1.00, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.33 (3H, s, C-Me), 1.52 (3H, s, C-Me), 1.67 (1H, d, *J*=11.2 Hz, C9–H), 1.22 (1H, d, *J*=11.2 Hz, C9–H), 2.82 (1H, br, C1–H), 2.97 (1H, br, C4–H), 3.00–3.10 (2H, m, C4a–H, C8a–H), 3.82 (1H, d, $J=1.2$ Hz, C2–H), 3.88 (1H, t, $J=1.9$ Hz, C5–H), 4.28 (1H, d, $J=6.3$ Hz, C7–H), 4.44 (1H, dd, $J=0.8$, 5.3 Hz, C3–H), 4.54 (1H, dd, $J=1.7$, 6.3 Hz, C6–H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.7, 26.6, 33.7, 41.4, 42.7, 46.1, 47.5, 55.0, 77.5, 77.7, 78.1, 87.3, 111.2, 207.0; IR (KBr) 540, 710, 750, 770, 810, 840, 860, 890, 940, 970, 1060, 1090, 1160, 1210, 1270, 1310, 1380, 1460, 1720, 1790, 2890, 2940, 2990 cm^{-1}; EIMS (*m/z*) 330 [(M+2)$^+$, ^{81}Br], 328 (M$^+$, ^{79}Br), 315 [(M−Me+2)$^+$, ^{81}Br], 313 [(M−Me)$^+$, ^{79}Br]. Anal. calcd for $C_{14}H_{17}BrO_4$: C, 51.08; H, 5.21; Br, 24.27. Found: C, 51.33; H, 5.23; Br, 24.50.

4.1.13. (1*R*,2*S*,4*S*,5*S*,6*R*,7*R*,8*R*,9*S*,10*S*)-6,9-Epoxy-4,5-(*O*-isopropylidenedioxy)tetracyclo[6.2.1.0^{2,7}.0^{2,10}]undecan-3-one (29). Lithium bis(trimethylsilyl)amide in THF (1.0 M solution, 67 μl, 67 μmol) was added dropwise to a stirred solution of **25** (20 mg, 61 μmol) in dry THF (1.5 ml) at −78 °C under argon, and the stirring was continued for 30 min at the same temperature. The reaction was quenched with saturated aqueous ammonium chloride (1 ml) at −78 °C, and the mixture was diluted with ether (40 ml). The organic layer was washed successively with saturated aqueous ammonium chloride (2×15 ml), saturated aqueous sodium hydrogen carbonate (2×15 ml), and brine (2×15 ml), then dried over Na_2SO_4. Concentration of the solvent in vacuo afforded a residue, which was purified by column chromatography (hexane/ethyl acetate, 2:1) to give **29** (15 mg, 98%) as a white solid. Recrystallization from hexane/dichloromethane (10:1) afforded colorless prisms, mp 77–78 °C; $[\alpha]_D^{20}$ −61.6 (*c* 1.05, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.39 (3H, s, C-Me); 1.45 (3H, s, C-Me); 1.67 (1H, dd, $J=1.3$, 5.0 Hz, C10–H); 1.80 (1H, d, $J=11.4$ Hz, C11–H); 1.86 (1H, d, $J=11.4$ Hz, C11–H); 2.42 (1H, d, $J=4.3$ Hz, C1–H); 2.46 (1H, s, C8–H); 2.87 (1H, t, $J=2.4$ Hz, C7–H); 4.40–4.45 (3H, m, C4–H, C6–H, C9–H); 4.66 (1H, dd, $J=1.3$, 5.7 Hz, C5–H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.5, 25.0, 27.2, 30.4, 32.5, 34.3, 41.7, 44.7, 77.6, 77.9, 79.4, 82.5, 110.1, 201.7; IR (KBr) 520, 580, 630, 830, 860, 880, 920, 940, 960, 990, 1020, 1040, 1070, 1160, 1210, 1270, 1300, 1330, 1380, 1700, 2880, 2900, 2940, 2990 cm^{-1}; EIMS (*m/z*) 248 (M$^+$), 233 [(M−Me)$^+$], 190 [(M−Me_2CO)$^+$]. Anal. Calcd for $C_{14}H_{16}O_4$: C, 67.73; H, 6.50. Found: C, 67.51; H, 6.57.

4.1.14. (1*R*,2*S*,4*S*,5*S*,6*R*,7*R*,8*R*,9*S*,10*S*)-6,9-Epoxy-4-[hydroxy(phenyl)methy]-4,5-(*O*-isopropylidenedioxy)-tetracyclo[6.2.1.0^{2,7}.0^{2,10}]undecan-3-one (23). Lithium bis(trimethylsilyl)amide in THF (1.0 M solution, 94 μl, 94 μmol) was added dropwise to a stirred solution of **29** (21.0 mg, 85 μmol) in dry THF (1.0 ml) at −78 °C under argon. After 30 min, a solution of benzaldehyde (**8**) (18 μl, 0.17 mmol) in dry THF (0.5 ml) was added slowly at −78 °C, and the stirring was continued for 1 h at the same temperature. The reaction was quenched with saturated aqueous ammonium chloride (1 ml) at 0 °C, and the mixture was diluted with ether (15 ml). The organic layer was washed successively with saturated aqueous ammonium chloride (2×7 ml), saturated aqueous sodium hydrogen carbonate (2×7 ml), and brine (2×7 ml), then dried over Na_2SO_4. Concentration of the solvent in vacuo afforded a residue, which was purified by column chromatography (hexane/ethyl acetate, 2:1→1:1) to give **23** (29.3 mg, 98%) as a hardly separable epimeric mixture (6:1 by 500 MHz ^{1}H NMR). In order to obtain analytical samples, a small amount of the epimeric mixture **23** was further subjected to column chromatography (hexane/ethyl acetate, 2:1→1:1) to provide pure samples of **23a** (major, more polar) and **23b** (minor, less polar).

Compound **23a**. Colorless prisms; mp 181–182 °C; $[\alpha]_D^{20}$ −68.9 (*c* 1.17, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.98 (3H, s, C-Me), 1.38 (3H, s, C-Me), 1.61 (1H, d, $J=5.2$ Hz, OH), 1.78 (1H, d, $J=11.5$ Hz, C11–H), 1.84 (1H, d, $J=11.5$ Hz, C11–H), 2.30 (1H, d, $J=5.2$ Hz), 2.45 (1H, s), 2.90 (1H, t, $J=2.3$ Hz), 3.13 (1H, d, $J=4.1$ Hz), 4.44 (1H, d, $J=3.0$ Hz), 4.51 (1H, t, $J=2.3$ Hz), 4.52 (1H, t, $J=2.8$ Hz), 5.05 (1H, d, $J=8.5$ Hz), 7.28–7.36 (3H, m, Ph), 7.42–7.46 (2H, m, Ph); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.9, 26.2, 28.0, 30.3, 30.4, 32.4, 41.1, 46.6, 76.4, 77.7, 79.6, 83.2, 88.1, 110.1, 127.8 (2 carbons), 128.4, 129.2 (2 carbons), 138.0, 205.6; IR (KBr) 510, 600, 700, 730, 830, 880, 920, 1020, 1060, 1110, 1170, 1250, 1290, 1380, 1450, 1720, 2940, 2990, 3380 cm^{-1}; EIMS (*m/z*) 337 [(M−OH)$^+$]; CIMS (*m/z*) 355 [(M+H)$^+$]. Anal. Calcd for $C_{21}H_{22}O_6$: C, 71.17; H, 6.26. Found: C, 71.24; H 6.35.

Compound **23b**. Colorless viscous oil. $[\alpha]_D^{20}$ −85.2 (*c* 1.20, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.91 (3H, s, C-Me), 1.38 (3H, s, C-Me), 1.78 (1H, d, $J=11.5$ Hz, C11–H), 1.84 (1H, d, $J=11.5$ Hz, C11–H), 1.92 (1H, dd, $J=1.5$, 5.1 Hz, OH), 2.41 (1H, d, $J=5.1$ Hz), 2.46 (1H, s), 2.89 (1H, t, $J=2.3$ Hz), 3.23 (1H, d, $J=8.6$ Hz), 4.51 (2H, m), 4.69 (1H, d, $J=2.7$ Hz), 5.06 (1H, d, $J=8.5$ Hz), 7.27–7.31 (1H, m, Ph), 7.34 (2H, t, $J=7.4$ Hz, Ph), 7.44 (2H, d, $J=7.2$ Hz, Ph); ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.4, 26.5, 28.5, 30.3, 33.3, 33.3, 41.0, 45.2, 75.3, 77.0, 78.6, 83.3, 86.9, 110.5, 127.8 (2 carbons), 128.1, 128.5 (2 carbons), 139.2, 204.2; IR (neat) 510, 590, 710, 730, 830, 880, 920, 1060, 1170, 1240, 1290, 1380, 1450, 1700, 2940, 2990, 3470 cm^{-1}; EIMS (*m/z*) 337 [(M−OH)$^+$], 248 [(M−PhCHO)$^+$] CIMS (*m/z*) 355 [(M+H)$^+$]; HREIMS (*m/z*) calcd for $C_{14}H_{16}O_4$ [(M−PhCHO)$^+$]: 248.1049, found 248.1057.

4.1.15. One-pot procedure for the preparation of 23 from 25. Lithium bis(trimethylsilyl)amide in THF (1.0 M solution, 1.43 ml, 1.4 mmol) was added dropwise to a stirred solution of **25** (213 mg, 0.65 mmol) in dry THF (8 ml) at −78 °C under argon. After 30 min, a solution of benzaldehyde (**8**) (0.20 ml, 2.0 mmol) in dry THF (1 ml) was added slowly to the mixture at −78 °C, and the stirring was continued for 1 h at the same temperature. The reaction was quenched with saturated aqueous ammonium chloride (2 ml) at 0 °C, and the mixture was diluted with ether (50 ml). The organic layer was washed successively with saturated aqueous ammonium chloride (2×20 ml), saturated aqueous sodium hydrogen carbonate (2×20 ml), and brine (2×20 ml), then dried over Na_2SO_4. Concentration of the solvent in vacuo afforded a residue, which was purified by column chromatography (hexane/ethyl acetate, 2:1→1:1) to give **23** (225 mg, 98%) as an epimeric mixture (6:1 by 500 MHz ^{1}H NMR). The IR, ^{1}H NMR, and mass spectra of this material were identical with those recorded for the preparation of **23** (see, Section 4.1.14).

4.1.16. [(1*R*,2*S*,4*S*,5*S*,6*R*,7*R*,8*R*,9*S*,10*S*)-6,9-Epoxy-4,5-(*O*-isopropylidenedioxy)tetracyclo[6.2.1.0^{2,7}.0^{2,10}]undecan-3-one-4-yl](phenyl)methyl *O*-phenyl carbonothioate (30). Phenyl thionochloroformate (0.18 ml, 1.3 mmol) was added to a stirred solution of **23** (6:1 epimeric mixture) (230 mg, 0.65 mmol) in dry acetonitrile (10 ml) containing 4-dimethylaminopyridine (DMAP) (316 mg, 2.6 mmol) at room temperature. After 12 h, the mixture was diluted with diethyl ether (100 ml). The organic layer was successively washed with 3% aqueous hydrochloric acid (2×50 ml), saturated aqueous sodium hydrogen carbonate (2×50 ml), and brine (2×50 ml), then dried over Na_2SO_4. Concentration of the solvent in vacuo afforded a residue, which was purified by column chromatography (hexane/ethyl acetate, 5:2) to give **30** (292 mg, 92%) as a hardly separable epimeric mixture (6:1 by 500 MHz ^{1}H NMR), as a colorless oil. In order to obtain analytical samples, a small amount of the epimeric mixture **30** was further subjected to column chromatography (hexane/ethyl acetate, 4:1→3:1) to provide pure samples of **30a** (major, more polar) and **30b** (minor, less polar).

Compound **30a**. Colorless viscous oil. $[\alpha]_D^{20}$ −33.4 (*c* 1.05, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.09 (3H, s, C-Me), 1.44 (3H, s, C-Me), 1.68 (1H, br), 1.75 (1H, d, *J*=11.5 Hz), 1.83 (1H, d, *J*=11.5 Hz), 2.23 (1H, d, *J*=5.2 Hz), 2.44 (1H, s), 2.90 (1H, t, *J*=2.4 Hz), 4.50 (1H, br), 4.53 (1H, t, *J*=2.7 Hz), 4.60 (1H, br d, *J*=2.2 Hz), 6.70 (1H, s), 6.99–7.03 (2H, m), 7.22–7.27 (1H, m), 7.32–7.41 (5H, m), 7.51–7.55 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.5, 26.2, 28.1, 30.1, 30.3, 32.2, 41.2, 46.9, 76.5, 80.0, 83.2, 86.2, 87.1, 110.8, 121.9 (2 carbons), 126.5, 128.0 (2 carbons), 129.2, 129.4 (2 carbons), 130.2 (2 carbons), 133.8, 153.5, 194.1, 202.2; IR (neat) 510, 690, 750, 850, 880, 940, 1030, 1070, 1120, 1200, 1270, 1380, 1460, 1490, 1590, 1710, 2940, 2990 cm^{-1}; HREIMS (*m*/*z*) calcd for $C_{28}H_{26}O_6S$ (M^+): 490.1450, found 490.1428.

Compound **30b**. Colorless viscous oil. $[\alpha]_D^{20}$ −64.7 (*c* 1.14, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.90 (3H, s, C-Me), 1.39 (3H, s, C-Me), 1.82 (1H, d, *J*=11.4 Hz), 1.88 (1H, d, *J*=11.4 Hz), 2.15 (1H, dd, *J*=1.8, 5.1 Hz), 2.46 (1H, d, *J*=5.0 Hz), 2.50 (1H, s), 2.94 (1H, t, *J*=2.4 Hz), 4.55 (1H, t, *J*=2.5 Hz), 4.58 (1H, t, *J*=2.3 Hz), 4.90 (1H, d, *J*=2.5 Hz), 6.55 (1H, s), 6.98–7.03 (2H, m, Ph), 7.22–7.27 (1H, m, Ph), 7.32–7.46 (5H, m, Ph), 7.49–7.55 (2H, m, Ph); ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.2, 26.5, 28.7, 30.3, 33.5, 33.6, 41.3, 45.2, 77.2, 79.1, 83.1, 83.9, 85.8, 110.5, 121.9 (2 carbons), 126.6, 128.1 (2 carbons), 128.9, 129.3 (2 carbons), 129.5 (2 carbons), 134.2, 153.4, 192.9, 202.7; IR (neat) 690, 750, 880, 1020, 1070, 1200, 1270, 1380, 1460, 1490, 1590, 1700, 2940, 2990 cm^{-1}; HREIMS (*m*/*z*) calcd for $C_{28}H_{26}O_6S$ (M^+): 490.1450, found 490.1476.

4.1.17. (1*R*,2*S*,4*S*,5*S*,6*R*,7*R*,8*R*,9*S*,10*S*)-4-Benzyl-6,9-epoxy-4,5-(*O*-isopropylidenedioxy)tetracyclo[6.2.1.0^{2,7}.0^{2,10}]undecan-3-one (31). Tri-*n*-butyltin hydride (0.35 ml, 1.3 mmol) and azobisisobutyronitrile (AIBN) (21 mg, 0.13 mmol) were added to a solution of **30** (6:1 epimeric mixture) (213 mg, 0.43 mmol) in dry toluene (7.5 ml). For the deaeration of the reaction mixture, it was frozen using liquid nitrogen, and the reaction vessel was evacuated in vacuo for 30 min and then filled with dry argon. The mixture was heated at reflux for 2 h. After cooling, the mixture was concentrated in vacuo to afford a residue, which was purified by column chromatography (hexane/ethyl acetate, 1:0→3:1) to give **31** (116 mg, 79%) as a white solid. Recrystallization from hexane/ether (5:1) afforded colorless prisms, mp 107–108 °C; $[\alpha]_D^{20}$ −69.6 (*c* 0.97, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.91 (3H, s, C-Me), 1.36 (3H, s, C-Me), 1.67 (1H, dd, *J*=1.6, 5.1 Hz, C10–H), 1.80 (1H, d, *J*=11.4 Hz, C11–H), 1.85 (1H, d, *J*=11.4 Hz, C11–H), 2.33 (1H, d, *J*=4.9 Hz, C1–H), 2.46 (1H, s, C8–H), 2.90 (1H, t, *J*=2.3 Hz, C7–H), 2.99 (1H, d, *J*=13.7 Hz, C*H*$_a$H$_b$Ph), 3.22 (1H, d, *J*=13.7 Hz, CH$_a$*H*$_b$Ph), 4.39 (1H, d, *J*=3.0 Hz, C5–H), 4.54 (1H, t, *J*=2.8 Hz, C6–H), 4.57 (1H, t, *J*=2.3 Hz, C9–H), 7.22–7.34 (5H, m, Ph); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.6, 26.3, 28.1, 30.3, 31.9, 31.9, 41.2, 43.3, 46.1, 76.8, 78.5, 83.2, 85.7, 109.2, 127.0, 127.9 (2 carbons), 131.9 (2 carbons), 135.2, 207.5; IR (KBr) 510, 620, 700, 770, 830, 880, 920, 940, 990, 1030, 1060, 1080, 1100, 1120, 1140, 1170, 1240, 1300, 1330, 1380, 1450, 1490, 1710, 2870, 2930, 2990 cm^{-1}; EIMS (*m*/*z*) 338 (M^+), 280 [$(M-Me_2CO)^+$], 247 [$(M-PhCH_2)^+$]. Anal. Calcd for $C_{21}H_{22}O_4$: C, 74.54; H 6.55. Found: C, 74.65; H, 6.61.

4.1.18. (1*S*,2*S*,3*S*,4*R*,4a*R*,5*R*,6*S*,7*S*,8a*R*)-7-Benzyl-3,5-epoxy-2-iodo-6,7-*O*-isopropylidenedioxy-1,2,3,4,4a,5,6,8a-octahydro-*endo*-1,4-methanonaphthalen-8-one (32). Iodotrimethylsilane (0.10 ml, 0.70 mmol) was added dropwise to a stirred solution of **31** (120 mg, 0.36 mmol) in carbon tetrachloride (4 ml) at −20 °C under argon, and stirring was continued for 3 h at −10 °C. The reaction was quenched with 20% aqueous sodium thiosulfate (2 ml) at −10 °C, and then the mixture was diluted with ether (40 ml). The organic layer was washed successively with 20% aqueous sodium thiosulfate (2×20 ml), saturated aqueous sodium hydrogen carbonate (2×20 ml), and brine (2×20 ml), then dried over Na_2SO_4. Concentration of the solvent in vacuo afforded a residue, which was purified by column chromatography (hexane/ethyl acetate, 4:1) to give **32** (147 mg, 89%) as a colorless viscous oil. $[\alpha]_D^{20}$ +62.7 (*c* 0.96, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.89 (3H, s, C-Me), 1.32 (3H, s, C-Me), 1.84 (1H, d, *J*=11.3 Hz, C9–H), 2.24 (1H, d, *J*=11.3 Hz, C9–H), 2.88–2.97 (4H, m, C1–H, C4–H, C4a–H, C*H*$_a$H$_b$Ph), 3.07 (1H, dd, *J*=4.9, 10.1 Hz, C8a–H), 3.35 (1H, d, *J*=14.1 Hz, CH$_a$*H*$_b$Ph), 3.61 (1H, d, *J*=2.4 Hz, C2–H), 4.25 (1H, t, *J*=3.7 Hz, C5–H), 4.36 (1H, d, *J*=4.3 Hz, C6–H), 4.80 (1H, d, *J*=5.4 Hz, C3–H), 7.22–7.32 (5H, m, Ph); ^{13}C NMR (125 MHz, $CDCl_3$) δ 26.5, 28.3, 33.0, 36.5, 38.7, 39.7, 47.0, 47.7, 48.2, 75.7, 76.1, 82.1, 89.4, 110.3, 126.8, 127.9 (2 carbons), 132.0 (2 carbons), 135.3, 210.6; IR (neat) 520, 610, 660, 700, 730, 770, 850, 890, 910, 940, 970, 1050, 1060, 1120, 1160, 1220, 1230, 1260, 1380, 1450, 1490, 1710, 2890, 2930, 2990 cm^{-1}; EIMS (*m*/*z*) 466 (M^+), 451 [$(M-Me)^+$], 408 [$(M-Me_2CO)^+$], 375 [$(M-PhCH_2)^+$]; HREIMS (*m*/*z*) calcd for $C_{21}H_{23}IO_4$ (M^+): 466.0641, found 466.0636.

4.1.19. (1*R*,4*S*,4a*R*,5*R*,6*S*,7*S*,8a*S*)-7-Benzyl-5-hydroxy-6,7-*O*-isopropylidenedioxy-1,4,4a,5,6,7,8,8a-octahydro-*endo*-1,4-methanonaphthalen-8-one (33). Zinc powder (272 mg, 4.2 mmol) and acetic acid (0.24 ml, 4.2 mmol) were successively added to a stirred solution of **32** (130 mg, 0.28 mmol) in methanol (5 ml) at room temperature.

The mixture was gradually warmed to 60 °C and stirred for 1 h at the same temperature. After cooling, the mixture was diluted with ether (80 ml) and filtrated. The filtrate was washed with saturated aqueous sodium hydrogen carbonate (2×30 ml), and brine (2×30 ml), then dried over Na_2SO_4. Concentration of the solvent in vacuo afforded a residue, which was purified by column chromatography (hexane/ethyl acetate, 4:1) to give **33** (86 mg, 91%) as a white solid. Recrystallization from hexane/dichloromethane (10:1) afforded colorless prisms, mp 169–170 °C; $[\alpha]_D^{20}$ +161.0 (*c* 0.99, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 0.79 (3H, s, C-Me), 1.41 (1H, d, *J*=8.4 Hz, C9–H), 1.47 (3H, s, C-Me), 1.54 (1H, d, *J*=8.4 Hz, C9–H), 1.58 (1H, d, *J*=3.2 Hz, OH), 2.73 (1H, d, *J*=14.4 Hz, CH_aH_bPh), 2.99 (1H, s, C1–H), 3.21 (2H, m, C4–H, C8a–H), 3.41 (1H, d, *J*=14.4 Hz, CH_aH_bPh), 3.46 (1H, dd, *J*=3.7, 11.6 Hz, C4a–H), 4.40 (1H, d, *J*=4.6 Hz, C6–H), 4.45 (1H, q, *J*=3.9 Hz, C5–H), 6.20 (1H, dd, *J*=2.9, 5.4 Hz, C2–H), 6.48 (1H, dd, *J*=3.1, 5.4 Hz, C3–H), 7.20 (1H, m, Ph), 7.28–7.26 (4H, m, Ph); ^{13}C NMR (125 MHz, $CDCl_3$) δ 26.5, 27.5, 38.8, 43.3, 43.5, 45.3, 47.2, 51.0, 68.1, 80.1, 83.2, 111.4, 126.3, 127.7 (2 carbons), 132.0 (2 carbons), 133.0, 136.6, 139.1, 207.6; IR (KBr) 540, 620, 660, 700, 730, 750, 820, 850, 910, 980, 1060, 1080, 1150, 1170, 1220, 1240, 1260, 1340, 1380, 1450, 1500, 1710, 2940, 2990, 3520 cm^{-1}; EIMS (*m/z*) 340 (M^+), 325 [$(M-Me)^+$], 282 [$(M-Me_2CO)^+$], 249 [$(M-PhCH_2)^+$]. Anal. Calcd for $C_{21}H_{24}O_4$: C, 74.09, H, 7.11. Found: C, 74.01, H, 7.17.

4.1.20. (4*R*,5*S*,6*S*)-6-Benzyl-4-hydroxy-5,6-*O*-isopropylidenedioxy-2-cyclohexen-1-one (34). A stirred solution of **33** (60 mg, 0.18 mmol) in diphenyl ether (4 ml) was heated at 230 °C for 4 h. After cooling, the mixture was concentrated in vacuo to afford a residue, which was purified by column chromatography (hexane/ethyl acetate, 1:0→2:1) to give **34** (39.5 mg, 81%) as a colorless viscous oil. $[\alpha]_D^{20}$ −0.7 (*c* 0.97, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 1.08 (3H, s, C-Me), 1.29 (3H, s, C-Me), 1.70 (1H, d, *J*=6.2 Hz, OH), 3.04 (1H, d, *J*=14.1 Hz, CH_aH_bPh), 3.17 (1H, d, *J*=14.1 Hz, CH_aH_bPh), 4.13 (1H, t, *J*=1.8 Hz, C5–H), 4.61 (1H, m, C4–H), 6.16 (1H, d, *J*=10.1 Hz, C2–H), 6.81 (1H, ddd, *J*=2.0, 4.9, 10.1 Hz, C3–H), 7.25–7.34 (5H, m, Ph); ^{13}C NMR (125 MHz, $CDCl_3$) δ 26.1, 27.4, 38.9, 64.6, 78.5, 81.8, 108.6, 127.1, 127.8 (2 carbons), 128.3, 131.5 (2 carbons), 134.7, 144.4, 199.6; IR (neat) 530, 590, 620, 670, 700, 730, 760, 800, 830, 860, 900, 920, 970, 1030, 1060, 1080, 1110, 1140, 1170, 1230, 1240, 1380, 1440, 1450, 1500, 1680, 2930, 2990, 3030, 3060, 3450 cm^{-1}; EIMS (*m/z*) 274 (M^+), 259 [$(M-Me)^+$]; HREIMS (*m/z*) calcd for $C_{15}H_{15}O_4$ [$(M-Me)^+$]: 259.0970, found 259.0992.

4.1.21. (1*R*,5*S*,6*S*)-5-Benzyl-5,6-*O*-isopropylidenedioxy-4-oxo-2-cyclohexenyl methanesulfonate (4). Methanesulfonyl chloride (0.17 ml, 2.1 mmol) was added to a stirred solution of **34** (58.8 mg, 0.21 mmol) in dichloromethane (5 ml) containing triethylamine (0.42 ml, 3.0 mmol) and 4-dimethylaminopyridine (DMAP) (24 mg, 0.21 mmol) at 0 °C, and stirring was continued for 3 h at room temperature. The reaction was quenched with saturated aqueous sodium hydrogen carbonate (2 ml) at 0 °C, and the mixture was diluted with ether (80 ml). The organic layer was successively washed with 3% aqueous hydrochloric acid (2×30 ml), saturated aqueous sodium hydrogen carbonate (2×30 ml), and brine (2×30 ml), then dried over Na_2SO_4. Concentration of the solvent in vacuo afforded a residue, which was purified by column chromatography (hexane/ethyl acetate, 1:1) to give **4** (63 mg, 85%) as a colorless viscous oil. $[\alpha]_D^{20}$ −62.6 (*c* 1.19, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 1.08 (3H, s, C-Me), 1.30 (3H, s, C-Me), 2.86 (1H, d, *J*=14.5 Hz, CH_aH_bPh), 3.10 (3H, s, Ms), 3.27 (1H, d, *J*=14.5 Hz, CH_aH_bPh), 4.14 (1H, t, *J*=1.7 Hz, C5–H), 5.45 (1H, dd, *J*=1.8, 4.8 Hz, C4–H), 6.30 (1H, d, *J*=10.1 Hz, C2–H), 6.85 (1H, ddd, *J*=1.8, 4.8, 10.1 Hz, C3–H), 7.25–7.34 (5H, m, Ph); ^{13}C NMR (125 MHz, $CDCl_3$) δ 26.3, 27.4, 38.1, 38.8, 71.2, 76.3, 81.6, 109.7, 127.3, 128.1 (2 carbons), 130.8, 131.4 (2 carbons), 134.1, 138.9, 197.8; IR (KBr) 530, 620, 700, 760, 790, 850, 900, 950, 980, 1070, 1090, 1120, 1150, 1180, 1230, 1370, 1450, 1500, 1690, 1740, 2940, 2990, 3030 cm^{-1}; EIMS (*m/z*) 352 (M^+), 337 [$(M-Me)^+$], 294 [$(M-Me_2CO)^+$]; HREIMS (*m/z*) calcd for $C_{17}H_{20}O_6S$ (M^+): 352.0981, found 352.0982.

4.1.22. (1*R*,5*S*,6*S*)-5-Benzyl-5,6-dihydroxy-4-oxo-2-cyclohexenyl methanesulfonate (35). A solution of **4** (60 mg, 0.17 mmol) in trifluoroacetic acid/water (6:1) (1 ml) was stirred at 0 °C for 30 min. The mixture was concentrated in vacuo to afford a residue, which was purified by column chromatography (hexane/ethyl acetate, 1:1) to give **35** (45 mg, 85%) as a colorless viscous oil. $[\alpha]_D^{20}$ −49.8 (*c* 0.95, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 2.99 (1H, d, *J*=3.6 Hz, C3–OH), 3.16 (3H, s, Ms), 3.18 (2H, s, CH_2Ph), 3.35 (1H, s, C6–OH), 4.14 (1H, dt, *J*=1.1, 3.7 Hz, C5–H), 5.47 (1H, dt, *J*=1.1, 3.9 Hz, C4–H), 6.24 (1H, dd, *J*=1.1, 10.2 Hz, C2–H), 6.85 (1H, ddd, *J*=1.1, 3.7, 10.2 Hz, C3–H), 7.14–7.19 (2H, m, Ph), 7.22–7.31 (3H, m, Ph); ^{13}C NMR (125 MHz, $CDCl_3$) δ 38.6, 40.9, 73.3, 75.7, 78.1, 127.3, 128.4 (2 carbons), 129.0, 130.6 (2 carbons), 134.1, 141.7, 197.1; IR (neat) 530, 700, 730, 780, 850, 880, 940, 980, 1060, 1110, 1170, 1360, 1440, 1450, 1490, 1690, 2930, 3030, 3480 cm^{-1}; EIMS (*m/z*) 312 (M^+), 294 [$(M-H_2O)^+$]; HREIMS (*m/z*) calcd for $C_{14}H_{16}O_6S$ (M^+): 312.0668, found 312.0656.

4.1.23. (4*S*,5*S*,6*S*)-6-Benzyl-4,5-epoxy-6-hydroxy-2-cyclohexen-1-one (2). 0.2 M Sodium hydroxide (0.7 ml, 0.14 mmol) was added dropwise to a stirred solution of **35** (30 mg, 96 μmol) in ether (8 ml) at 0 °C. After 10 min, the mixture was extracted with ether (2×30 ml). The combined extracts were washed with brine (3×20 ml) and dried over Na_2SO_4. Concentration of the solvent in vacuo afforded a residue, which was purified by column chromatography (hexane/ethyl acetate, 2:1) to give **2** (19 mg, 90%) as a white solid. Recrystallization from hexane/ether (5:1) afforded colorless prisms, mp 96–97 °C; $[\alpha]_D^{20}$ +45.6 (*c* 0.80, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 2.93 (1H, d, *J*=13.6 Hz, CH_aH_bPh), 3.01 (1H, d, *J*=13.6 Hz, CH_aH_bPh), 3.60 (1H, dt, *J*=1.6, 3.9 Hz, C4–H), 3.65 (1H, s, OH), 3.77 (1H, d, *J*=3.9 Hz, C5–H), 6.16 (1H, dd, *J*=1.5, 9.9 Hz, C2–H), 7.09–7.15 (3H, m, Ph, C3–H), 7.22–7.32 (3H, m, Ph); ^{13}C NMR (125 MHz, $CDCl_3$) δ 44.4 (CH_2Ph), 47.9 (C4 or C5), 56.0 (C4 or C5), 77.7 (C6), 127.3 (Ph or C3), 128.4 (2 carbons, Ph), 130.2 (Ph or C3), 130.3 (2 carbons, Ph), 133.6 (Ph), 145.1 (C2), 197.5 (C1); IR (KBr) 500, 540, 580, 630, 670, 700, 750, 790, 840, 860, 900, 960, 1030, 1090, 1130, 1150, 1200, 1240, 1250, 1300, 1380, 1450, 1490, 1600, 1690, 2850, 2920, 3030, 3060, 3480 cm^{-1}; HREIMS (*m/z*) calcd for $C_{13}H_{12}O_3$ (M^+): 216.0786, found 216.0806. Anal. Calcd for $C_{13}H_{12}O_3$: C, 72.21; H, 5.59. Found: C, 71.81; H, 5.58.

4.1.24. (1*R*,2*S*,4*S*,5*S*,6*R*,7*R*,8*R*,9*S*,10*S*)-6,9-Epoxy-4,5-*O*-isopropylidenedioxy-4-[[(4*R*)-2,2-dimethyl-3-(*p*-toluenesulfonyl)oxazolidin-4-yl]hydroxymethyl]tetracyclo[6.2.1.0^{2,7}.0^{2,10}]undecan-3-one (24). Lithium bis(trimethylsilyl)amide in THF (1.0 M solution, 5.30 ml, 5.3 mmol) was added dropwise to a stirred solution of **25** (800 mg, 2.4 mmol) in dry THF (40 ml) at −78 °C under argon. After 30 min, a solution of (*R*)-*N*-(*p*-toluenesulfonyl)-*N*,*O*-isopropylidene serinal (**9**) (1.72 g, 6.0 mmol) in dry THF (20 ml) was added slowly at −78 °C, and the resulting mixture was further stirred for 1 h at the same temperature. The reaction was quenched with saturated aqueous ammonium chloride (3 ml) at −78 °C, and the mixture was diluted with ether (300 ml). The organic layer was washed successively with saturated aqueous ammonium chloride (2×100 ml), saturated aqueous sodium hydrogen carbonate (2×100 ml), and brine (2×100 ml), then dried over Na_2SO_4. Concentration of the solvent in vacuo afforded a residue, which was purified by column chromatography (hexane/ethyl acetate, 2:1→1:1) to give **24** (1.27 g, 98%) (inseparable mixture, major/minor=9:1) as a colorless viscous oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.38 (3H, s, C-Me), 1.39 (3H, s, C-Me), 1.44 (3H, s, C-Me), 1.68 (3H, s, C-Me), 1.79 (1H, d, *J*=11.3 Hz, C11–H), 1.85 (1H, d, *J*=11.3 Hz, C11–H), 2.25 (1H, d, *J*=5.2 Hz, C1–H), 2.35 (1H, dd, *J*=1.8, 5.2 Hz, C2–H), 2.41 (3H, s, Me of Ts), 2.45 (1H, s, C8–H), 2.70 (1H, d, *J*=6.8 Hz, OH), 2.90 (1H, t, *J*=2.3 Hz, C7–H), 3.76 (1H, d, *J*=6.4, 9.8 Hz, C4′–H), 4.20 (1H, d, *J*=6.5 Hz, C5′–H), 4.39 (1H, d, *J*=7.0 Hz, CH-OH), 4.51 (1H, dd, *J*=1.3, 9.8 Hz, C5′–H), 4.55 (1H, t, *J*=2.3 Hz, C9–H), 4.59 (1H, t, *J*=2.8 Hz, C7–H), 5.05 (1H, d, *J*=3.1 Hz, C6–H), 7.30 (2H, d, *J*=8.2 Hz, Ar), 7.68 (2H, d, *J*=8.2 Hz, Ar); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.6, 21.5, 24.4, 26.1, 27.8, 28.8, 29.2, 30.5, 32.6, 41.2, 47.2, 59.6, 64.7, 73.0, 76.2, 78.9, 83.2, 88.1, 96.9, 109.6, 127.8 (2 carbons), 129.7 (2 carbons), 137.8, 143.5, 206.7; IR (neat) 550, 590, 680, 730, 820, 830, 880, 940, 1030, 1100, 1150, 1230, 1250, 1340, 1370, 1380, 1460, 1710, 2880, 2940, 2990, 3440 cm^{-1}; HREIMS (*m/z*) calcd for $C_{27}H_{33}NO_8S$ (M^+): 531.1927, found 531.1903.

4.1.25. (1*R*,2*S*,4*S*,5*S*,6*R*,7*R*,8*R*,9*S*,10*S*)-6,9-Epoxy-4,5-*O*-isopropylidenedioxy-4-[[(4*R*)-2,2-dimethyl-3-(*p*-toluenesulfonyl)oxazolidin-4-yl](methyldithiocarbonyloxy)methyl]tetracyclo[6.2.1.0^{2,7}.0^{2,10}]undecan-3-one (36). Sodium bis(trimethylsilyl)amide in THF (1.0 M solution, 0.85 ml, 0.85 mmol) was added dropwise to a stirred solution of **24** (378 mg, 0.71 mmol) in dry THF (20 ml) at −78 °C under argon. After 30 min, carbon disulfide (0.43 ml, 7.1 mmol) was added slowly to the mixture at −78 °C, and stirring was continued for 1 h at the same temperature. The resulting mixture was gradually warmed to −50 °C over 1 h, and then iodomethane (0.54 ml, 7.1 mmol) was added slowly to the above mixture at −78 °C. After 1 h, the mixture was gradually warmed to −50 °C over 1 h. The reaction was quenched with saturated aqueous ammonium chloride (3 ml) at 0 °C, and then the mixture was diluted with ether (200 ml). The organic layer was washed successively with saturated aqueous sodium thiosulfate (2×80 ml), saturated aqueous sodium hydrogen carbonate (2×80 ml), and brine (2×80 ml), then dried over Na_2SO_4. Concentration of the solvent in vacuo afforded a residue, which was purified by column chromatography (hexane/ethyl acetate, 2:1) to give **36** (389 mg, 88%) as a white solid. Recrystallization from hexane/ether (5:1) afforded colorless prisms, mp 252–253 °C; $[\alpha]_D^{20}$ −2.0 (*c* 1.12, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.19 (3H, s, C-Me), 1.41 (3H, s, C-Me), 1.47 (3H, s, C-Me), 1.51 (3H, s, C-Me), 1.79 (1H, d, *J*=11.4 Hz, C11–H), 1.84 (1H, d, *J*=11.4 Hz, C11–H), 2.25 (1H, d, *J*=5.2 Hz, C1–H), 2.42 (4H, s, Me of Ts, C8–H), 2.65 (3H, s, S-Me), 2.72 (1H, dd, *J*=1.9, 5.2 Hz, C10–H), 2.88 (1H, t, *J*=2.4 Hz, C7–H), 3.77 (1H, dd, *J*=7.0, 9.5 Hz, C4′–H), 4.46 (1H, dd, *J*=1.4, 9.6 Hz, C5′–H), 4.50 (1H, t, *J*=2.7 Hz, C6–H), 4.52 (1H, t, *J*=2.2 Hz, C9–H), 4.57 (1H, d, *J*=2.8 Hz, C5–H), 4.65 (1H, d, *J*=5.9 Hz, C5′–H), 6.88 (1H, s, C*H*–OCS$_2$Me), 7.31 (2H, d, *J*=8.2 Hz, Ar), 7.69 (2H, d, *J*=8.3 Hz, Ar); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.3, 20.3, 21.5, 24.1, 25.8, 27.7, 28.7, 29.3, 30.5, 32.5, 41.4, 47.5, 58.6, 64.7, 75.6, 79.5, 80.9, 82.9, 87.4, 96.8, 109.4, 128.2 (2 carbons), 129.6 (2 carbons), 137.5, 143.4, 205.6, 214.0; IR (neat) 520, 550, 590, 650, 680, 730, 820, 880, 910, 940, 1060, 1100, 1150, 1180, 1210, 1250, 1350, 1370, 1460, 1710, 2880, 2940, 2990 cm^{-1}; EIMS (*m/z*) 621 (M^+), 606 [$(M-Me)^+$]. Anal. Calcd for $C_{29}H_{35}NO_8S_3$: C, 56.02; H, 5.67; N, 2.25; S, 15.47. Found: C, 55.85; H, 5.69; N, 2.29; S, 15.31.

4.1.26. (1*R*,2*S*,4*S*,5*S*,6*R*,7*R*,8*R*,9*S*,10*S*)-6,9-Epoxy-4,5-*O*-isopropylidenedioxy-4-[[(4*R*)-2,2-dimethyl-3-(*p*-toluenesulfonyl)oxazolidin-4-yl]methyl]tetracyclo[6.2.1.0^{2,7}.0^{2,10}]-undecan-3-one (37). Tri-*n*-butyltin hydride (0.33 ml, 1.2 mmol) and triethylborane in hexane (1.0 M solution, 0.63 ml, 0.63 mmol) were added successively to a stirred solution of **36** (384 mg, 0.62 mmol) in dry toluene (24 ml) at room temperature. After 1 h, the mixture was concentrated in vacuo to afford a residue, which was purified by column chromatography (hexane/ethyl acetate, 1:0→2:1) to give **37** (303 mg, 95%) as a white solid. Recrystallization from hexane/ether (5:1) afforded colorless prisms, mp 207–208 °C; $[\alpha]_D^{20}$ +49.1 (*c* 1.04, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.34 (3H, s, C2′-Me), 1.37 (3H, s, C-Me), 1.40 (3H, s, C-Me), 1.67 (3H, s, C2′-Me), 1.79 (1H, d, *J*=11.4 Hz, C11–H), 1.84 (1H, d, *J*=11.4 Hz, C11–H), 2.20 (1H, dd, *J*=10.9, 14.7 Hz, C4–CH_aH$_b$–C4′), 2.29 (1H, d, *J*=5.3 Hz, C1–H), 2.41 (3H, s, Me of Ts), 2.46 (1H, s, C8–H), 2.51 (1H, dd, *J*=1.8, 5.2 Hz, C10–H), 2.57 (1H, d, *J*=14.6 Hz, C4–CH$_a$$H_b$–C4′), 2.89 (1H, t, *J*=2.3 Hz, C7–H), 3.67 (1H, m, C5′–H), 4.12–4.18 (2H, m, C4′–H, C5′–H), 4.34 (1H, d, *J*=2.9 Hz, C5–H), 4.57 (2H, d, *J*=2.6 Hz, C6–H, C9–H), 7.28 (2H, d, *J*=8.1 Hz, Ar), 7.65 (2H, d, *J*=8.3 Hz, Ar); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.0, 21.5, 24.0, 26.8, 27.8, 30.3, 30.5, 31.7, 41.4, 44.5, 47.0, 55.7, 69.2, 76.30, 77.2, 83.5, 84.9, 84.9, 96.6, 109.7, 127.5 (2 carbons), 129.6 (2 carbons), 138.0, 143.2, 207.2; IR (neat) 520, 550, 600, 650, 680, 710, 840, 880, 920, 940, 1030, 1060, 1240, 1300, 1340, 1370, 1450, 1710, 2880, 2940, 2990 cm^{-1}; EIMS (*m/z*) 500 [$(M-Me)^+$]; CIMS (*m/z*) 516 [$(M+H)^+$]. Anal. Calcd for $C_{27}H_{33}NO_7S$: C, 62.89; H, 6.45; N, 2.72; S, 6.22. Found: C, 62.59; H, 6.49; N, 2.74; S, 6.25.

4.1.27. (1*S*,2*S*,3*S*,4*R*,4a*R*,5*R*,6*S*,7*S*,8a*R*)-3,5-Epoxy-2-iodo-6,7-*O*-isopropylidenedioxy-7-[(2*S*)-2-*p*-toluenesulfonylamino-3-hydroxypropyl]-1,2,3,4,4a,5,6,8a-octahydro-*endo*-1,4-methanonaphthalen-8-one (38). Iodotrimethylsilane (82 μl, 0.46 mmol) was added dropwise to a stirred solution of **37** (98 mg, 0.15 mmol) in carbon tetrachloride (10 ml) at −20 °C under argon, and stirring was continued at −10 °C for 3 h. The reaction mixture was quenched with saturated aqueous sodium thiosulfate (2 ml) at 0 °C, and then the mixture was diluted with chloroform (80 ml). The organic layer was washed successively with 20% aqueous sodium thiosulfate (2×30 ml), saturated aqueous sodium hydrogen carbonate (2×30 ml), and brine (2×30 ml), then dried over Na_2SO_4. Concentration of the solvent in vacuo afforded a residue, which was purified by column chromatography (hexane/ethyl acetate, 1:1) to give **38** (104 mg, 91%) as a white amorphous solid. $[\alpha]_D^{20}$ +44.3 (*c* 1.09, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.31 (6H, s, C-Me), 1.74 (1H, d, *J*=11.2 Hz, C9–H), 1.86 (1H, dd, *J*=3.5, 15.5 Hz, C1′–H), 2.20–2.32 (3H, m, C9–H, C1′–H, OH), 2.42 (3H, s, Me of Ts), 2.61 (1H, dd, *J*=4.8, 10.5 Hz, C8a–H), 2.75 (1H, br, C1–H), 2.87 (1H, br, C4–H), 2.91 (1H, dt, *J*=3.8, 10.5 Hz, C4a–H), 3.43 (1H, m, C2′–H), 3.67 (2H, t, *J*=4.7 Hz, C3′*H*$_2$OH), 3.75 (1H, d, *J*=1.9 Hz, C2–H), 3.80 (1H, t, *J*=2.6 Hz, C5–H), 4.17 (1H, d, *J*=2.4 Hz, C6–H), 4.60 (1H, d, *J*=11.2 Hz, C3–H), 5.84 (1H, d, *J*=4.6 Hz, N–H), 7.27 (2H, d, *J*=8.0 Hz, Ar), 7.70 (2H, d, *J*=8.2 Hz, Ar); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.5, 28.2, 28.5, 32.4, 35.8, 36.5, 42.0, 44.3, 46.6, 48.1, 51.4, 66.3, 77.0, 82.8, 85.5, 88.2, 112.8, 127.6 (2 carbons), 129.3 (2 carbons), 137.42, 143.0, 210.6; IR (neat) 550, 670, 730, 810, 850, 920, 940, 1050, 1090, 1130, 1160, 1220, 1230, 1330, 1380, 1420, 1600, 1710, 2890, 2930, 2980, 3280, 3510 cm^{-1}; HREIMS *m/z* for $C_{23}H_{27}INO_6S$ [(M−CH_2OH)$^+$]: 572.0604, found 572.0604.

4.1.28. (1*S*,2*S*,3*S*,4*R*,4a*R*,5*R*,6*S*,7*S*,8a*R*)-3,5-Epoxy-2-iodo-6,7-*O*-isopropylidenedioxy-7-[(4*S*)-2,2-dimethyl-3-(*p*-toluenesulfonyl)oxazolidin-4-yl]methyl-1,2,3,4,4a,5,6,8a-octahydro-*endo*-1,4-methanonaphthalen-8-one (39). *p*-Toluenesulfonic acid (6 mg, 34 μmol) was added to a stirred solution of **38** (100 mg, 0.17 mmol) in benzene (6 ml) containing 2,2-dimethoxypropane (0.20 ml, 1.7 mmol) at room temperature. The mixture was gradually warmed to 60 °C and stirred for 1 h at the same temperature. After cooling, the mixture was diluted with ether (80 ml). The organic layer was washed with saturated aqueous sodium hydrogen carbonate (2×30 ml) and brine (2×30 ml), then dried over Na_2SO_4. Concentration of the solvent in vacuo gave a residue, which was purified by column chromatography (hexane/ethyl acetate, 2:1) to give **39** (88 mg, 83%) as a colorless viscous oil. $[\alpha]_D^{20}$ +138.4 (*c* 0.97, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.37 (3H, s, C-Me), 1.43 (3H, s, C-Me), 1.44 (3H, s, C-Me), 1.70 (3H, s, C-Me), 1.83 (1H, d, *J*=11.2 Hz, C9–H), 2.13 (1H, dd, *J*=10.7,14.8 Hz, C7–C*H*$_2$–C4′), 2.27 (1H, d, *J*=11.2 Hz, C9–H), 2.43 (3H, s, Me of Ts), 2.48 (1H, d, *J*=4.6 Hz, C7–C*H*$_2$–C4′), 2.89–2.98 (3H, m, C1–H, C4–H, C4a–H), 3.02 (1H, dd, *J*=4.9, 10.2 Hz, C8a–H), 3.67 (1H, dd, *J*=5.5, 8.1 Hz, C5′–H), 3.93 (1H, d, *J*=2.1 Hz, C2–H), 4.16–4.22 (2H, m, C5–H, C5′–H), 4.40–4.46 (2H, m, C4′–H, C6–H), 4.80 (1H, d, *J*=5.1 Hz, C3–H), 7.32 (2H, d, *J*=8.0 Hz, Ar), 7.83 (2H, d, *J*=8.3 Hz, Ar); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.5, 24.2, 27.3, 28.2, 30.5, 33.0, 36.8, 40.2, 41.0, 46.6, 47.7, 48.3, 55.6, 68.7, 75.9, 81.4, 81.9, 89.2, 96.9, 111.3, 127.8 (2 carbons), 129.5 (2 carbons), 138.0, 143.2, 209.9; IR (neat) 510, 550, 590, 650, 680, 710, 730, 820, 840, 920, 940, 1100, 1160, 1230, 1340, 1370, 1460, 1600, 1710, 1890, 2930, 2990 cm^{-1}; HREIMS (*m/z*) calcd for $C_{26}H_{31}INO_7S$ [(M−Me)$^+$]: 628.0866, found 628.0853.

4.1.29. (1*R*,4*S*,4a*R*,5*R*,6*S*,7*S*,8a*S*)-5-Hydroxy-6,7-*O*-isopropylidenedioxy-7-[(4*S*)-2,2-dimethyl-3-(*p*-toluenesulfonyl)oxazolidin-4-yl]methyl-1,4,4a,5,6,7,8,8a-octahydro-*endo*-1,4-methanonaphthalen-8-one (40). Zinc powder (123 mg, 1.9 mmol) and acetic acid (0.11 ml, 1.9 mmol) were successively added to a stirred solution of **39** (81 mg, 0.13 mmol) in methanol (6 ml) at room temperature. The mixture was gradually warmed to 60 °C and stirred for 1 h at the same temperature. After cooling, the mixture was diluted with ether (50 ml) and filtrated. The filtrate was washed with saturated aqueous sodium hydrogen carbonate (2×20 ml), and brine (2×20 ml), then dried over Na_2SO_4. Concentration of the solvent in vacuo afforded a residue, which was purified by column chromatography (hexane/ethyl acetate, 2:1) to give **40** (64 mg, 98%) as a colorless viscous oil. $[\alpha]_D^{20}$ +127.1 (*c* 1.14, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.39 (1H, m, C9–H), 1.45 (3H, s, C-Me), 1.47 (3H, s, C-Me), 1.53 (4H, s, C-Me, C9–H), 1.67 (3H, s, C-Me), 1.81 (1H, d, *J*=2.3 Hz, OH), 2.17 (1H, dd, *J*=10.5, 14.0 Hz, C7–C*H*$_a$H$_b$–C4′), 2.25 (1H, dd, *J*=1.8, 14.4 Hz, C7–CH$_a$*H*$_b$–C4′), 2.41 (3H, s, Me of Ts), 2.98 (1H, s, C4–H), 3.13 (1H, s, C1–H), 3.21 (1H, dt, *J*=3.4, 11.7 Hz, C4a–H), 3.43 (1H, dd, *J*=3.6, 11.7 Hz, C8a–H), 3.60 (1H, dd, *J*=5.5, 9.0 Hz, C5′–H), 4.12 (1H, dd, *J*=1.8, 9.0 Hz, C5′–H), 4.37 (1H, br, C5–H), 4.43 (1H, d, *J*=4.3 Hz, C6–H), 4.45 (1H, m, C4′–H), 6.19 (1H, dd, *J*=3.0, 5.5 Hz, C3–H), 6.50 (1H, dd, *J*=3.1, 5.6 Hz, C2–H), 7.27 (2H, d, *J*=8.2 Hz, Ar), 7.85 (2H, d, *J*=8.3 Hz, Ar); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.5, 24.4, 26.5, 27.3, 30.1, 41.8, 43.1, 43.6, 45.5, 46.4, 51.2, 56.4, 68.1, 68.7, 83.0, 85.2, 96.9, 112.2, 127.7 (2 carbons), 129.4 (2 carbons), 132.7, 138.5, 140.0, 142.9, 207.6; IR (neat) 550, 600, 650, 680, 710, 730, 780, 830, 920, 1050, 1100, 1160, 1210, 1240, 1340, 1380, 1450, 1600, 1720, 1880, 2940, 2990, 3530 cm^{-1}; HREIMS (*m/z*) calcd for $C_{26}H_{32}NO_7S$ [(M−Me)$^+$]: 502.1900, found 502.1869.

4.1.30. (4*R*,5*S*,6*S*)-4-Hydroxy-5,6-*O*-isopropylidenedioxy-7-[(4*S*)-2,2-dimethyl-3-(*p*-toluenesulfonyl)oxazolidin-4-yl]methyl-2-cyclohexen-1-one (41). A stirred solution of **40** (23.0 mg, 44 μmol) in diphenyl ether (5 ml) was heated at 230 °C for 2 h. After cooling, the mixture was concentrated in vacuo to afford a residue, which was purified by column chromatography (hexane/ethyl acetate, 1:0→1:1) to give **41** (5.0 mg, 25%) as a colorless viscous oil. $[\alpha]_D^{20}$ +58.1 (*c* 0.46, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.27 (3H, s, C-Me), 1.39 (6H, s, C-Me, C-Me), 1.68 (3H, s, C-Me), 2.13 (1H, dd, *J*=10.8, 14.5 Hz, C6–C*H*$_a$H$_b$–C4′), 2.42 (3H, s, Me of Ts), 2.43 (1H, d, *J*=14.5 Hz, C6–CH$_a$*H*$_b$–C4′), 2.52 (1H, br, OH), 3.74 (1H, ddd, *J*=1.3, 5.4, 9.2 Hz, C5′–H), 4.07 (1H, dd, *J*=5.3, 10.7 Hz, C4′–H), 4.09 (1H, d, *J*=9.0 Hz, C5′–H), 4.16 (1H, t, *J*=1.7 Hz, C5–H), 4.66 (1H, br, C4–H), 6.17 (1H, d, *J*=10.2 Hz, C2–H), 6.84 (1H, ddd, *J*=2.0, 4.6, 10.1 Hz, C3–H), 7.29 (2H, d, $J=8.0$ Hz, Ar), 7.69 (2H, d, $J=8.3$ Hz, Ar); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.5, 24.1, 26.7, 27.2, 30.3, 39.5, 55.3, 64.7, 69.2, 80.7, 83.8, 97.0, 109.5, 127.6 (2 carbons), 128.2, 129.6 (2 carbons), 137.7, 143.4, 143.6, 198.8; IR (neat) 550, 590, 650, 680, 710, 750, 830, 880, 910, 1040, 1100, 1160, 1230, 1340, 1370, 1460, 1490, 1600, 1680, 2880, 2940, 2990, 3470 cm^{-1}; HREIMS (*m/z*) calcd for $C_{21}H_{26}NO_7S$ $[(M-Me)^+]$: 436.1430, found 436.1403.

4.1.31. (1*R*,2*S*,4*S*,5*S*,6*R*,7*R*,8*R*,9*S*,10*S*)-6,9-Epoxy-4,5-*O*-isopropylidenedioxy-4-[[(4*S*)-2-oxo-3-(*p*-toluenesulfonyl)oxazolidin-4-yl]methyl]tetracyclo[6.2.1.0^{2,7}.0^{2,10}]undecan-3-one (43). 1.0 M Hydrochloric acid (1.36 ml, 1.4 mmol) was added to a stirred solution of **37** (320 mg, 0.62 mmol) in THF (15 ml) at room temperature, and the mixture was heated at 55 °C for 6 h. After cooling, the mixture was neutralized with saturated aqueous sodium hydrogen carbonate (ca. 20 ml), and the resulting mixture was extracted with ether (3×50 ml). The combined extracts were washed with brine (2×50 ml), then dried over Na_2SO_4. Concentration of the solvent in vacuo afforded a residue, which was purified by column chromatography (hexane/ethyl acetate, 2:1) to give an equilibrium mixture (290 mg) of **42a** and **42b** (1:1 by 500 MHz ^{1}H NMR) as a colorless viscous oil. This equilibrium mixture was directly used for the following reaction without separation.

Trichloromethyl chloroformate (1.23 ml, 6.2 mmol) was added dropwise to a stirred solution of the above equilibrium mixture of **42a** and **42b** (290 mg, 0.61 mmol) in dry THF (30 ml) containing pyridine (1.96 ml, 24 mmol) at 0 °C, and the mixture was gradually warmed to room temperature. After 2 h, the reaction was quenched with saturated aqueous sodium hydrogen carbonate (5 ml) at 0 °C, and the mixture was diluted with ether (200 ml). The organic layer was washed successively with 3% aqueous hydrochloric acid (2×80 ml), saturated aqueous sodium hydrogen carbonate (2×80 ml), and brine (2×80 ml), then dried over Na_2SO_4. Concentration of the solvent in vacuo afforded a residue, which was purified by column chromatography (hexane/ethyl acetate, 3:2) to give **43** (209 mg, 67% in two steps) as a white solid. Recrystallization from hexane/ether (5:1) afforded colorless needles, mp 174–175 °C; $[\alpha]_D^{20}$ +27.5 (*c* 1.16, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.36 (3H, s, C-Me), 1.39 (3H, s, C-Me), 1.82 (1H, d, $J=11.6$ Hz, C11–H), 1.87 (1H, d, $J=11.6$ Hz, C11–H), 2.02–2.09 (1H, m, C4–CH_aH$_b$–C4′), 2.25 (1H, dd, $J=1.8$, 5.2 Hz, C10–H), 2.34 (1H, d, $J=5.1$ Hz, C1–H), 2.45 (3H, s, Me of Ts), 2.50 (1H, s, C8–H), 2.90 (1H, t, $J=2.2$ Hz, C7–H), 2.92 (1H, d, $J=14.6$ Hz, C4–CH$_a$$H_b$–C4′), 4.33 (1H, d, $J=3.0$ Hz, C5–H), 4.37–4.44 (2H, m, C4′=H, C5′=H), 4.57 (1H, d, $J=5.4$ Hz, C5′=H), 4.60 (1H, t, $J=2.8$ Hz, C6–H), 4.62 (1H, t, $J=2.2$ Hz, C9–H), 7.33 (2H, d, $J=8.4$ Hz, Ar), 7.86 (2H, d, $J=8.4$ Hz, Ar); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.6, 21.7, 26.8, 27.8, 30.3, 30.5, 32.1, 41.3, 43.3, 46.6, 54.6, 68.6, 76.2, 83.3, 83.9, 84.1, 110.3, 128.5 (2 carbons), 129.8 (2 carbons), 134.7, 145.7, 152.3, 205.8; IR (KBr) 540, 580, 620, 670, 750, 810, 840, 880, 920, 940, 990, 1030, 1070, 1090, 1140, 1170, 1220, 1250, 1300, 1370, 1600, 1710, 1790, 2880, 2940, 2990 cm^{-1}; EIMS (*m/z*) 501 (M^+), 486 $[(M-Me)^+]$; HREIMS (*m/z*) calcd for $C_{25}H_{27}NO_8S$ (M^+): 501.1457, found 501.1481.

4.1.32. (1*S*,2*S*,3*S*,4*R*,4a*R*,5*R*,6*S*,7*S*,8a*R*)-3,5-Epoxy-2-iodo-6,7-*O*-isopropylidenedioxy-7-[(4*S*)-2-oxo-3-(*p*-toluenesulfonyl)oxazolidin-4-yl]methyl-1,2,3,4,4a,5,6,8a-octahydro-*endo*-1,4-methanonaphthalen-8-one (44). Iodotrimethylsilane (68 µl, 0.48 mmol) was added dropwise to a stirred solution of **43** (210 mg, 0.42 mmol) in carbon tetrachloride (20 ml) at −20 °C under argon. After 1 h, the reaction was quenched with saturated aqueous sodium thiosulfate (2 ml) at −20 °C, and then the mixture was diluted with ether (150 ml). The organic layer was washed successively with 20% aqueous sodium thiosulfate (2×80 ml), saturated aqueous sodium hydrogen carbonate (2×80 ml), and brine (2×80 ml), then dried over Na_2SO_4. Concentration of the solvent in vacuo afforded a residue, which was purified by column chromatography (hexane/ethyl acetate, 3:2) to give **44** (195 mg, 74%) as a white solid. Recrystallization from hexane/ether (5:1) afforded colorless needles, mp 233–234 °C; $[\alpha]_D^{20}$ +152.8 (*c* 1.04, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.35 (3H, s, C-Me), 1.41 (3H, s, C-Me), 1.85 (1H, d, $J=11.3$ Hz, C9–H$_a$), 2.05 (1H, dd, $J=10.7$, 14.6 Hz, C7–CH_aH$_b$–C4′), 2.29 (1H, d, $J=11.1$ Hz, C9–H$_b$), 2.45 (3H, s, Me of Ts), 2.89–2.95 (3H, m, C1–H, C4a-H, C7–CH$_a$$H_b$–C4′), 2.97–3.04 (2H, m, C4–H, C8a-H), 3.80 (1H, d, $J=2.4$ Hz, C2–H), 4.29 (1H, t, $J=3.7$ Hz, C5–H), 4.42 (1H, t, $J=9.0$ Hz, C5′–H), 4.45 (1H, d, $J=4.1$ Hz, C6–H), 4.56 (1H, dd, $J=4.4$, 9.3 Hz, C5′–H), 4.80 (1H, m, C4′–H), 4.85 (1H, d, $J=5.3$ Hz, C3–H), 7.37 (2H, d, $J=8.3$ Hz, Ar), 7.96 (2H, d, $J=8.3$ Hz, Ar); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.7, 27.1, 28.0, 32.2, 36.7, 39.9, 40.7, 46.9, 47.9, 48.3, 54.5, 68.8, 75.6, 80.8, 81.0, 89.3, 111.5, 128.5 (2 carbons), 129.8 (2 carbons), 134.8, 145.5, 152.5, 210.3; IR (KBr) 540, 570, 610, 670, 760, 820, 920, 1050, 1090, 1130, 1170, 1310, 1370, 1450, 1600, 1700, 1790, 2990 cm^{-1}; EIMS (*m/z*) 629 (M^+), 614 $[(M-Me)^+]$; HRCIMS (*m/z*) calcd for $C_{25}H_{29}INO_8S$ $[(M+H)^+]$: 630.0659, found 630.0693. Anal. Calcd for $C_{25}H_{28}INO_8S$: C, 47.70; H, 4.48; N, 2.23; S, 5.09. Found: C, 47.78; H, 4.47; N, 2.30; S, 4.82.

4.1.33. (1*R*,4*S*,4a*S*,5*R*,6*S*,7*S*,8a*S*)-5-Hydroxy-6,7-*O*-isopropylidenedioxy-7-[(4*S*)-2-oxo-3-(*p*-toluenesulfonyl)oxazolidin-4-yl]methyl-1,4,4a,5,6,7,8,8a-octahydro-*endo*-1,4-methanonaphthalen-8-one (45). Zinc powder (300 mg, 4.6 mmol) and acetic acid (0.26 ml, 4.6 mmol) were successively added to a stirred solution of **44** (194 mg, 0.31 mmol) in THF/methanol (1:1) (20 ml) at room temperature. The mixture was gradually warmed to 60 °C and stirred for 1 h at the same temperature. After cooling, the mixture was diluted with ether (150 ml) and filtrated. The filtrate was washed with saturated aqueous sodium hydrogen carbonate (2×70 ml), and brine (2×70 ml), then dried over Na_2SO_4. Concentration of the solvent in vacuo afforded a residue, which was purified by column chromatography (hexane/ethyl acetate, 3:2) to give **45** (148 mg, 95%) as a colorless viscous oil. $[\alpha]_D^{20}$ +155.9 (*c* 1.00, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.41 (1H, d, $J=8.4$ Hz, C9–H), 1.50 (3H, s, C-Me), 1.53 (3H, s, C-Me), 1.56 (1H, d, $J=8.4$ Hz, C9–H), 1.94 (1H, s, OH), 2.30 (1H, dd, $J=10.5$, 14.2 Hz, C7–CH_aH$_b$–C4′), 2.44 (3H, s, Me of Ts), 2.72 (1H, dd, $J=2.1$, 14.1 Hz, C7–CH$_a$$H_b$–C4′), 3.01 (1H, s, C4–H), 3.14 (1H, s, C1–H), 3.25 (1H, dt, $J=3.2$, 11.6 Hz, C4a–H), 3.44 (1H, dd, $J=3.6$, 11.6 Hz, C8a–H), 4.17 (1H, t, $J=8.5$ Hz, C5′–H), 4.36 (1H, dd, $J=5.1$, 9.3 Hz, C5′–H), 4.44 (1H, s, C5–H), 4.59 (1H, d, $J=4.3$ Hz, C6–H), 4.92 (1H, m, C4′–H), 6.20 (1H, dd, $J=3.0$, 5.3 Hz, C3–H), 6.49 (1H, dd, $J=3.1$, 5.5 Hz, C2–H), 7.34 (2H, d, $J=8.3$ Hz, Ar), 7.95 (2H, d, $J=8.3$ Hz, Ar); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.7, 26.3, 27.2, 41.1, 43.1, 43.7, 45.5, 46.1, 51.2, 54.8, 67.9, 69.2, 82.9, 84.0, 112.5, 128.5 (2 carbons), 129.8 (2 carbons), 132.9, 134.9, 139.6, 145.5, 152.8, 207.7; IR (neat) 540, 580, 610, 670, 700, 760, 820, 850, 920, 1050, 1090, 1120, 1170, 1210, 1250, 1310, 1380, 1450, 1600, 1720, 1780, 2940, 2990, 3540 cm^{-1}; HREIMS (*m/z*) calcd for $C_{25}H_{29}NO_8S$ (M^+): 503.1614, found 503.1595.

4.1.34. (4*R*,5*S*,6*S*)-4-Hydroxy-5,6-*O*-isopropylidenedioxy-6-[(4*S*)-2-oxo-3-(*p*-toluenesulfonyl)oxazolidin-4-yl]methyl-2-cyclohexen-1-one (46). A stirred solution of **45** (148 mg, 0.29 mmol) in diphenyl ether (15 ml) was heated at 230 °C for 2 h. After cooling, the mixture was concentrated in vacuo to afford a residue, which was purified by column chromatography (hexane/ethyl acetate, 1:0→1:1) to give **46** (75.9 mg, 59%) as a colorless viscous oil. $[\alpha]_D^{20}$ +80.9 (*c* 1.05, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.26 (3H, s, C-Me), 1.40 (3H, s, C-Me), 2.09 (1H, dd, $J=11.0$, 14.5 Hz, C6–CH_aH$_b$–C4′), 2.20 (1H, d, $J=5.3$ Hz, OH), 2.44 (3H, s, Me of Ts), 2.92 (1H, dd, $J=2.2$, 14.4 Hz, C6–CH$_a$$H_b$–C4′), 4.19 (1H, t, $J=1.7$ Hz, C5–H), 4.45 (2H, d, $J=6.2$ Hz, C5′–H_2), 4.59 (1H, m, C4′–H), 4.72 (1H, t, $J=4.7$ Hz, C4–H), 6.19 (1H, d, $J=10.2$ Hz, C2–H), 6.90 (1H, ddd, $J=1.9$, 4.8, 10.1 Hz, C3–H), 7.34 (2H, d, $J=8.2$ Hz, Ar), 7.87 (2H, d, $J=8.2$ Hz, Ar); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.7, 26.6, 27.2, 39.0, 54.3, 64.1, 69.2, 80.0, 83.2, 109.9, 128.0, 128.4 (2 carbons), 129.9 (2 carbons), 134.5, 144.7, 145.8, 152.5, 198.0; IR (neat) 540, 570, 600, 670, 760, 820, 910, 1040, 1090, 1130, 1170, 1230, 1380, 1490, 1600, 1680, 1790, 2930, 3480 cm^{-1}; CIMS (*m/z*) 438 [(M+H)$^+$]; HREIMS (*m/z*) calcd for $C_{19}H_{20}NO_8S$ [(M−Me)$^+$]: 422.0910, found 422.0926.

4.1.35. (1*R*,5*S*,6*S*)-5,6-*O*-Isopropylidenedioxy-4-oxo-5-[(4*S*)-2-oxo-3-(*p*-toluenesulfonyl)oxazolidin-4-yl]methyl-2-cyclohexenyl methanesulfonate (5). Methanesulfonyl chloride (73 μl, 0.93 mmol) was added to a stirred solution of **46** (68.3 mg, 0.16 mmol) in dichloromethane (7 ml) containing triethylamine (0.17 ml, 1.2 mmol) and 4-dimethylaminopyridine (38.0 mg, 0.31 mmol) at 0 °C, and stirring was continued for 4 h at room temperature. The reaction was quenched with saturated aqueous sodium hydrogen carbonate (1 ml) at 0 °C, and the mixture was diluted with ether (70 ml). The organic layer was successively washed with 3% aqueous hydrochloric acid (2×30 ml), saturated aqueous sodium hydrogen carbonate (2×30 ml), and brine (2×30 ml), then dried over Na_2SO_4. Concentration of the solvent in vacuo afforded a residue, which was purified by column chromatography (hexane/ethyl acetate, 1:1) to give **5** (66.8 mg, 83%) as a colorless viscous oil. $[\alpha]_D^{20}$ +47.3 (*c* 1.07, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.27 (3H, s, C-Me), 1.42 (3H, s, C-Me), 2.10 (1H, dd, $J=10.8$, 14.3 Hz, C6–CH_aH$_b$–C4′), 2.45 (3H, s, Me of Ts), 2.91 (1H, dd, $J=2.2$, 14.3 Hz, C6–CH$_a$$H_b$–C4′), 3.19 (3H, s, Me of Ms), 4.34 (1H, t, $J=1.8$ Hz, C5–H), 4.43 (1H, dd, $J=4.8$, 9.4 Hz, C5′–H), 4.46 (1H, t, $J=9.3$ Hz, C5′–H), 4.58 (1H, m, C4′–H), 5.58 (1H, dd, $J=1.7$ Hz, C4–H), 6.34 (1H, d, $J=10.1$ Hz, C2–H), 6.89 (1H, ddd, $J=1.9$, 5.0, 10.2 Hz, C3–H), 7.36 (2H, d, $J=8.2$ Hz, Ar), 7.88 (2H, d, $J=8.3$ Hz, Ar); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.7, 26.8, 27.1, 38.5, 39.1, 54.0, 69.0, 69.7, 79.8, 80.9, 111.0, 128.4 (2 carbons), 129.9 (2 carbons), 130.9, 134.4, 138.9, 145.8, 152.2, 196.5; IR (neat) 540, 570, 600, 620, 670, 730, 760, 820, 860, 950, 990, 1060, 1090, 1130, 1170, 1230, 1370, 1600, 1690, 1790, 2930, 2990 cm^{-1}; CIMS (*m/z*) 516 [(M+H)$^+$]; HREIMS (*m/z*) calcd for $C_{20}H_{22}NO_{10}S_2$ [(M−Me)$^+$]: 500.0685, found 500.0696.

4.1.36. (1*R*,5*S*,6*S*)-5,6-Dihydroxy-4-oxo-5-[(4*S*)-2-oxo-3-(*p*-toluenesulfonyl)oxazolidin-4-yl]methyl-2-cyclohexenyl methanesulfonate (47). A solution of **5** (59.2 mg, 0.11 mmol) in trifluoroacetic acid/water (6:1) (3 ml) was stirred at 0 °C for 30 min. The mixture was concentrated in vacuo to give **47** (54.6 mg, quant.) as a colorless viscous oil. $[\alpha]_D^{20}$ +25.9 (*c* 1.22, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.25 (1H, dd, $J=10.0$, 14.7 Hz, C6–CH_aH$_b$–C4′), 2.30–2.40 (1H, br, OH), 2.45 (3H, s, Me of Ts), 2.50–2.90 (1H, br, OH), 2.98 (1H, d, $J=14.6$ Hz, C6–CH$_a$$H_b$–C4′), 3.18 (3H, s, Me of Ms), 4.20–4.27 (2H, m, C5–H, C4′–H), 4.30 (1H, dd, $J=4.4$, 9.3 Hz, C5′–H), 4.45 (1H, t, $J=8.8$ Hz, C5′–H), 5.47 (1H, t, $J=3.5$ Hz, C4–H), 6.38 (1H, d, $J=10.2$ Hz, C2–H), 6.89 (1H, ddd, $J=1.3$, 4.1, 10.2 Hz, C3–H), 7.37 (2H, d, $J=8.2$ Hz, Ar), 7.87 (2H, d, $J=8.3$ Hz, Ar); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.7, 38.8, 40.2, 53.6, 70.4, 74.8, 75.0, 77.0, 128.5 (2 carbons), 129.3, 130.0 (2 carbons), 134.2, 140.6, 146.1, 152.4, 198.0; IR (neat) 540, 570, 670, 730, 760, 820, 850, 940, 1090, 1170, 1360, 1600, 1700, 1780, 2360, 2930, 3480 cm^{-1}; HRCIMS (*m/z*) calcd for $C_{18}H_{22}NO_{10}S_2$ [(M+H)$^+$]: 476.0685, found 476.0658.

4.1.37. (4*S*,5*S*,6*S*)-4,5-Epoxy-6-hydroxy-6-[(4*S*)-2-oxo-3-(*p*-toluenesulfonyl)oxazolidin-4-yl]methy-2-cyclohexen-1-one (3b). 0.2 M Sodium hydroxide (1.5 ml, 0.30 mmol) was added dropwise to a stirred solution of **47** (54.5 mg, 0.11 mmol) in ether (5 ml) at 0 °C. After 20 min, the mixture was extracted with ether (3×30 ml). The combined extracts were washed with brine (3×30 ml) and dried over Na_2SO_4. Concentration of the solvent in vacuo afforded a residue, which was purified by column chromatography (hexane/ethyl acetate, 1:1) to give **3b** (32.3 mg, 75%) as a white solid. Recrystallization from hexane/dichloromethane (3:1) afforded colorless prisms, mp 224–225 °C; $[\alpha]_D^{20}$ +153.3 (*c* 0.99, $CHCl_3$); ^{1}H NMR (500 MHz, CD_2Cl_2) δ 2.34 (1H, dd, $J=10.5$, 14.2 Hz, C6–CH_aH$_b$–C4′), 2.45 (3H, s, Me of Ts), 2.51 (1H, dd, $J=1.1$, 14.2 Hz, C6–CH$_a$$H_b$–C4′), 3.49 (1H, br, OH), 3.67 (2H, m, C4–H, C5–H), 4.16 (1H, m, C4′–H), 4.34 (1H, dd, $J=4.6$, 9.4 Hz, C5′–H), 4.44 (1H, t, $J=9.1$ Hz, C5′–H), 6.35 (1H, m, C2–H), 7.27 (1H, m, C3–H), 7.38 (2H, m, Ar), 7.80 (2H, m, Ar); ^{13}C NMR (125 MHz, CD_2Cl_2) δ 21.9 (Me of Ts), 40.7 (C6–CH_2–C4′), 48.6 (C4′), 53.7 (C4), 56.5 (C5), 70.5 (C5′), 77.3 (C6), 128.7 (2 carbons, Ar), 130.3 (3 carbons, Ar, C2), 134.7 (C3), 145.9 (Ar), 146.6 (Ar), 152.4 (C2′), 197.9 (C1); IR (KBr) 540, 570, 600, 670, 760, 840, 990, 1090, 1170, 1370, 1690, 1780, 2360, 2930, 3460 cm^{-1}; HRCIMS (*m/z*) calcd for $C_{17}H_{17}NO_7S$ [(M+H)$^+$]: 380.0804, found 380.0786.

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Erratum

Erratum to "A general strategy for the synthesis of azapeptidomimetic lactams" [Tetrahedron 61 (2005) 10277]

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The publisher apologises for the following error:

'room temperature' that followed the gas chromatography (GC) and high-pressure liquid chromatography (HPLC) information in the experimental section should have read 'retention time'. This error occurred on p 10282, sections 4.1.12, 4.1.13, 4.1.16 and p 10283, sections 4.1.17, 4.1.18, 4.1.19, 4.1.20, and 4.1.21.

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Corrigendum

Corrigendum to "5-Hydroxy-3-phenyl-5-vinyl-2-isoxazoline and 3-phenyl-5-vinylisoxazole: synthesis and reactivity" [Tetrahedron 61 (2005) 11270]

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At the end of the Abstract '..3-hydroxy-5-phenyl-5-vinyl-2-isoxazoline' should read '5-hydroxy-3-phenyl-5-vinyl-2-isoxazoline'.

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