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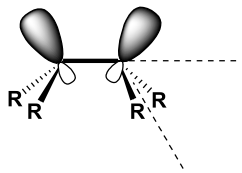
# Contents

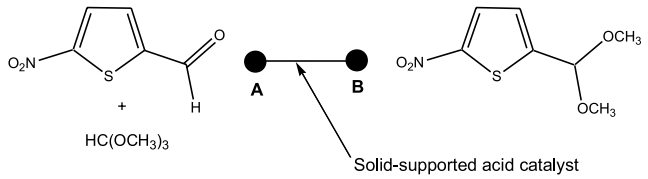
## REPORT





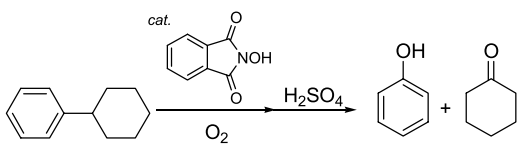

## ARTICLES

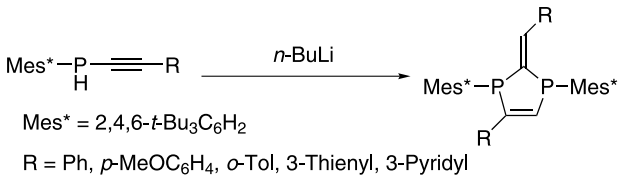





By incorporating a series of solid-supported acid catalysts into an EOF-based flow reactor, we demonstrate the synthesis and deprotection of 10 acetals in excellent yields and purity, without the need for additional product purification.

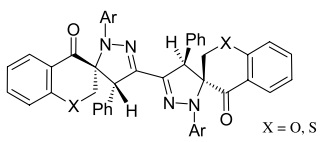




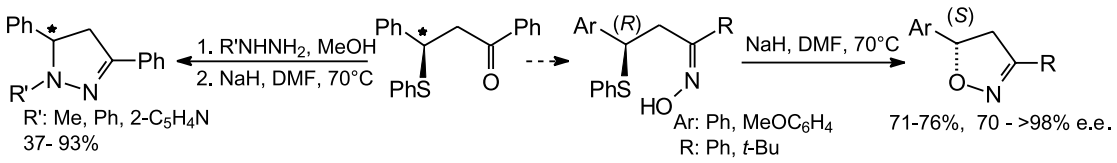



A new synthetic method for sterically protected 1,4-diphosphafulvenes has been developed starting from (arylethynyl)phosphines and ca. 0.25 molar amount of butyllithium.

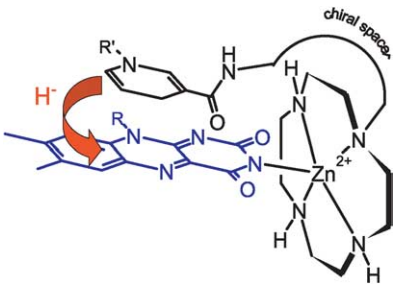




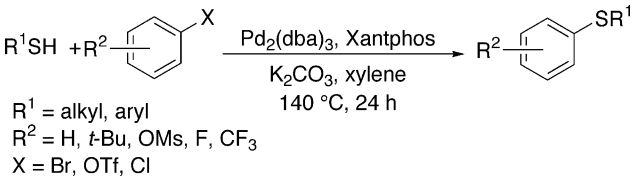


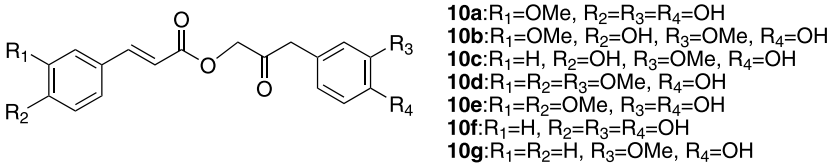


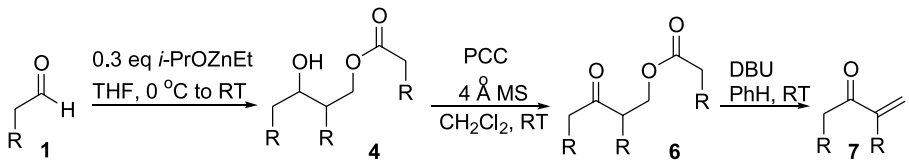

Zinc cyclen linked to 1,4-dihydronicotine amide by chiral peptides binds and reduces flavin in aqueous buffered solution, but not stereospecifically.



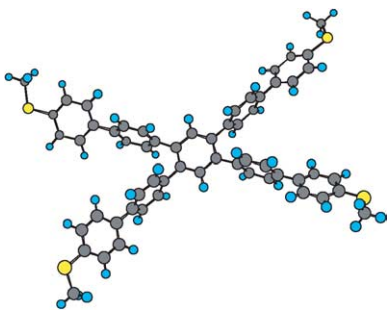


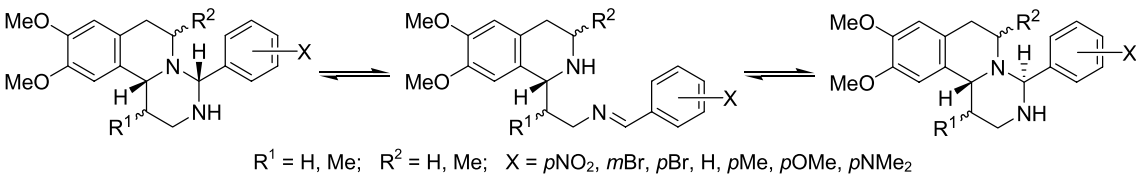


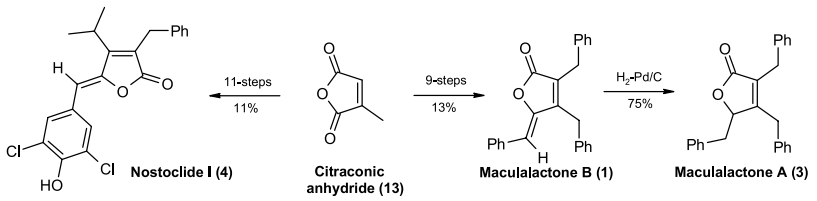


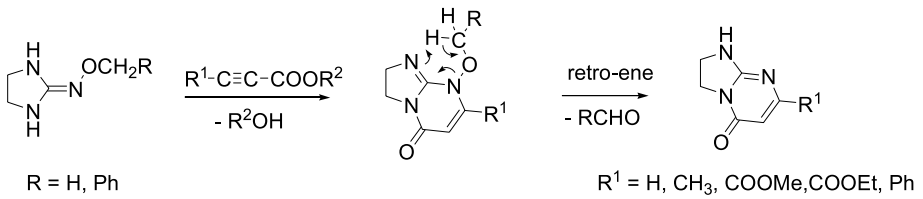
X-branched structure, due to twisting around the central core, has been shown to have enhancing morphological and thermal stabilities as well as solubility and processibility and was used as a plateform for novel luminophore.



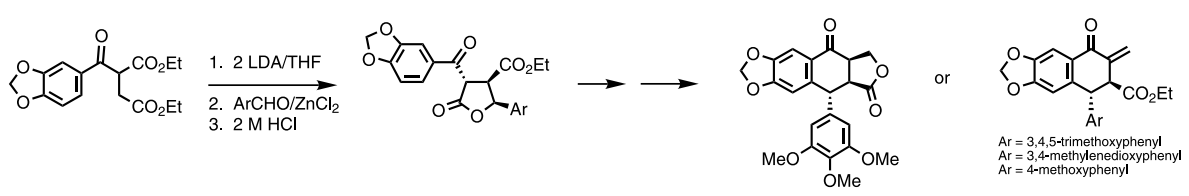


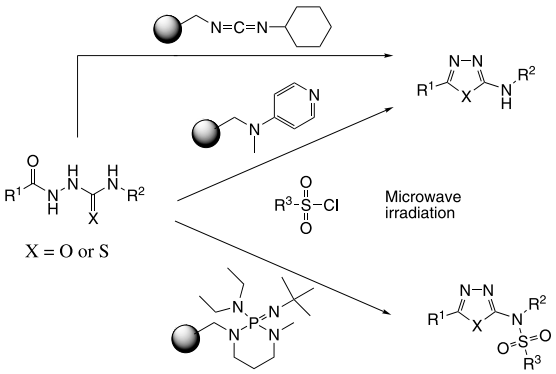





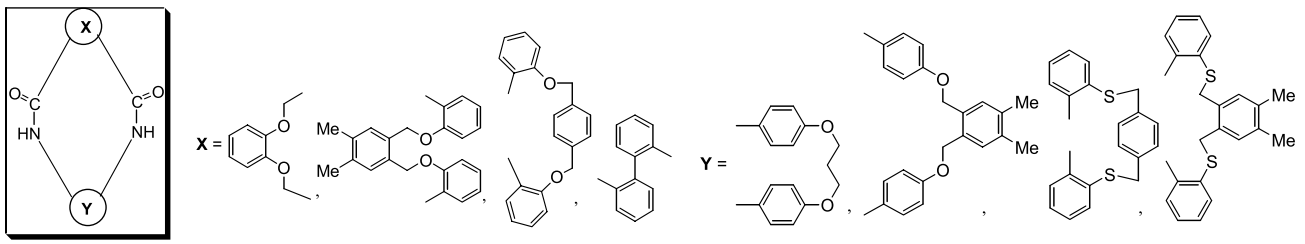





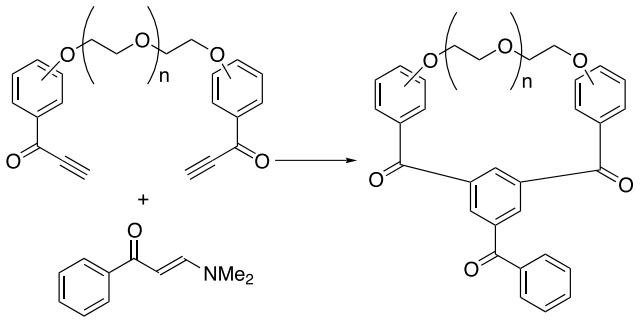





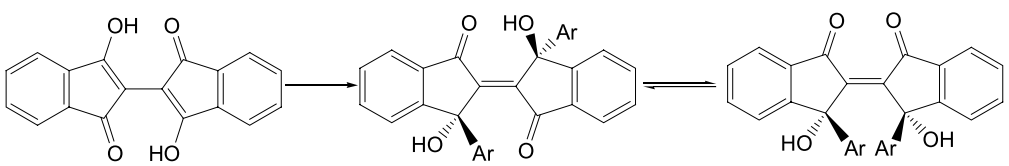


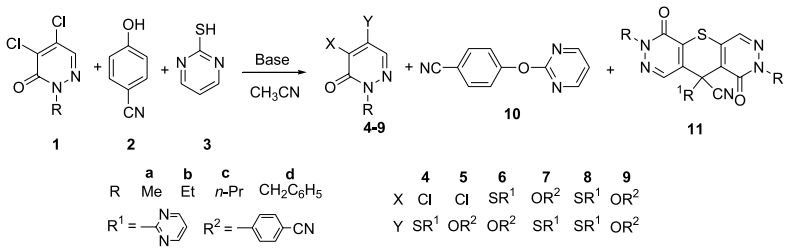







## OTHER CONTENTS



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# Chemistry of pyramidalized alkenes

Santiago Vázquez* and Pelayo Camps*

*Laboratori de Química Farmacèutica (Unitat Associada al CSIC), Facultat de Farmàcia, Universitat de Barcelona, Av. Diagonal 643, Barcelona, E-08028, Spain*

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* Corresponding authors. Tel.: +34 93 402 4536; fax: +34 94 403 5941 (S.V.); e-mail addresses: svazquez@ub.edu; camps@ub.edu


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## 1. Introduction

As mentioned in introductory organic chemistry textbooks, the ideal geometry for a double bond has the olefinic carbon atoms and the four atoms connected to them in the same plane. Thus, in the ground state of ethylene, all six atoms lie in one plane, the bond angles are near 120° and the carbon–carbon distance is 1.34 Å. However, as stressed by Mislow as early as 1965, 'planarity is not expected if the molecules does not have a plane of symmetry passing through the sp$^2$ carbon atoms and all four corresponding ligands'.[1] Cyclopentene is a good example, ab initio calculations showing that, when the molecule is allowed to adopt its equilibrium envelope conformation, the sp$^2$ carbon atoms are pyramidalized.[2] Pyramidalized alkenes are molecules containing carbon–carbon double bonds in which one or both of the doubly bonded carbon atoms do not lie in the plane defined by the three atoms attached to it. Deviations of the planarity for the vast majority of olefinic carbon atoms are small. However, when a carbon–carbon double bond is located at the bridgehead positions of a polycyclic structure, severe deviations of the usual planar geometry occur.[3]

In bridgehead alkenes, there are two different types of distortions, the out-of-plane bending and the in-plane bending. The latter is the major distortion observed in small cyclic alkenes (e.g., cyclopropene).[4] In bridgehead alkenes, the out-of-plane bending is much more important and two major modes of distortion can be distinguished: twisting and pyramidalization.[5] One extreme case is the pure twisting: the two olefinic carbon atoms stay fully sp$^2$ hybridized and thus planar (Fig. 1a). As a consequence, the two p orbitals are misaligned, which weakens the π-component of the double bond. This is visualized by the twisting angle, $\tau$, which is defined as the dihedral angle between the two p orbitals. In the other extreme situation, the *syn* pyramidalization, the carbon atoms are rehybridized by admixture of additional p character into the original sp$^2$ σ-bonds; this makes the geometry around the carbon non-planar. The π bond is now formed from two p-orbitals with some added s-character; the alignment between the two orbitals is optimal ($\tau=0$), but their orientation in the p-plane is no longer parallel and, for this reason, the distance between them increases and the net overlap is smaller. As we will discuss below, there is now an out-of-plane or flap angle, $\Psi$, defined as the dihedral angle between a plane containing two *cis*-substituents and the two olefinic carbon atoms and the plane containing the two other *cis*-substituents and the two olefinic carbon atoms and this is usually referred to as its supplementary $\zeta=180°-\Psi$, (Fig. 1b). Usually, the situation encountered in anti-Bredt alkenes is intermediate: twisting and pyramidalization occur simultaneously (Fig. 1c).

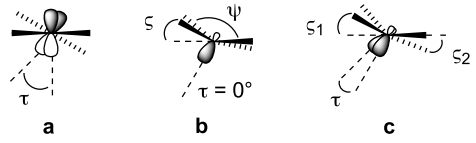



**Figure 1.** Modes of distortion of strained olefins.

Another form of pyramidalization, in which the π-type sp$^n$ orbitals are oriented towards opposite sides of the double bond, is called *anti* pyramidalization. Although calculations have shown that *anti* pyramidalization of the carbon atoms of the double bond is energetically more favorable than *syn* pyramidalization,[6] it is much less common and will only be mentioned briefly here.

Bridgehead olefins with torsionally strained double bonds ('twisted or anti-Bredt alkenes') have been studied extensively,[7] but olefins in which the carbon atoms forming the double bonds are pyramidalized ('pyramidalized alkenes') have received much less attention. In this report, we deal with the synthesis and reactivity of untwisted, but pyramidalized, bridgehead olefins. Where appropriate, a mention of the physical and chemical properties will be made. Twisted alkenes, distorted aromatic compounds, such as cyclophanes, fullerenes and fullerene-related compounds are out of the scope of this report.

Some reviews on pyramidalized alkenes have appeared,[8] the more comprehensive being the excellent survey by Borden in 1989,[8b] although more concise accounts have appeared later.[9] The present report will cover the material that has appeared since 1989 up to mid 2004, although some previous aspects covered by Borden will be mentioned here.

As discussed in more detail later, pyramidalization changes the typical chemistry of the double bond dramatically. Dimerization of highly pyramidalized alkenes occurs rapidly, and pyramidalized alkenes that do not dimerize at room temperature react with atmospheric oxygen[10] and with nucleophilic reagents.[11]

Pyramidalization allows the 2s atomic orbitals of the olefinic carbon atoms to be mixed into the π bond. The increase in 2s character stabilizes both the π and the π* molecular orbitals. However, this rehybridization also decreases the overlap of the two hybrid orbitals, as compared to the overlap of two parallel p atomic orbitals, by pointing the large lobes of the hybrid orbitals away from each other. The loss of the bonding overlap in the π molecular orbital destabilizes it. The effects of increased 2s character and reduced overlap tend to cancel, so that the energy of the π molecular orbital remains relatively constant. In contrast, a reduction of antibonding overlap in

π* stabilizes this molecular orbital further. Hence, the π* molecular orbital drops rapidly in energy upon pyramidalization. Therefore, excitation of an electron from π to π* is made energetically less costly on increasing pyramidalization.[12] The unusually low energy of π* is responsible for the ease of reduction of pyramidalized alkenes, for the ability of pyramidalized alkenes to form stable complexes with transition metals, such as Pt(0), that can donate electron density into this molecular orbital,[13] and for the deshielding observed for the olefinic carbon atoms in $^{13}C$ NMR.[14]

## 2. Measurements of pyramidalization

In studying pyramidalized alkenes, it is convenient to use a geometrical parameter to measure pyramidalization.[15] More than 20 years ago, Borden et al. introduced the pyramidalization angle, *Φ*, as a measure of pyramidalization.[12a] Strictly speaking, the *Φ* angle is applicable only to those cases having $C_{2v}$ symmetry, with a mirror plane bisecting and perpendicular to the double bond and a mirror plane containing the double bond. As shown in Figure 2a, *Φ* is the angle between the plane containing one of the doubly bonded carbon atoms and the two substituents attached to it and the extension of the double bond. From the bond angles R–C–R (*β* in Fig. 2a) and R–C–C (*α* in Fig. 2a), the pyramidalization angle, *Φ*, was obtained from the formula:

$$\cos \Phi = -\cos(\mathrm{RCC})/[\cos\tfrac{1}{2}(\mathrm{RCR})]$$

Another method to describe the distortions of double bonds is the Pi-Orbital-Axis-Vector (POAV) analysis developed by Haddon; it is based on rehybridization of non-planar olefinic carbon atoms as calculated from their bond and dihedral angles and is very useful for molecules which have non-planar conjugated olefins, for example, bridged annulenes and fullerenes.[16]

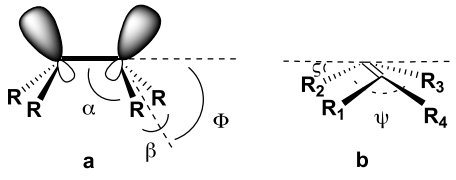



**Figure 2.** Schematic representation of a pyramidalized alkene and of the pyramidalization angle, *Φ*.

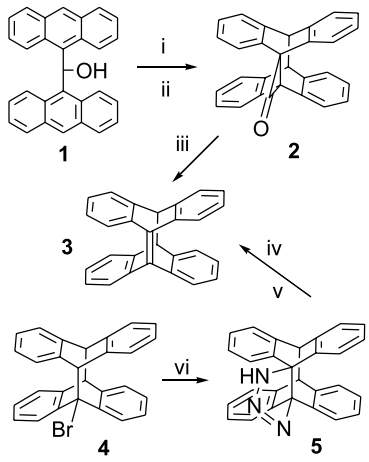
Some alternative measurements of pyramidalization have been proposed, such as the flap or hinge angle, *Ψ*,[17] defined as the dihedral angle between the planes $R_1CCR_2$ and $R_3CCR_4$ and usually referred to as its supplementary $\zeta = 180° - \Psi$ (Figs. 1b and 2b), and the butterfly angle, *ω*, orthogonal to the previously defined pyramidalization angle, *Φ*.[13e]

Taking into account that most of the literature on pyramidalized alkenes uses the pyramidalization angle, *Φ*, as the measure of the pyramidalization, we will mainly use this parameter throughout the text.

## 3. 9,9′-Didehydrodianthracene and related alkenes

### 3.1. 9,9′-Didehydrodianthracene

The title compound **3** has historic interest, because it was the first substantially pyramidalized alkene to be synthesized and it offered the first experimental evidence that pyramidalized alkenes are suceptible to nucleophilic addition reactions, as predicted by frontier orbital theory. Although Applequist et al. had suggested the formation of **3** by the reaction of 9-bromodianthracene **4** with strong bases,[18] it was not until 1968 that Weinshenker and Greene described the successful isolation of **3**.[19] Its preparation was originally carried out by the photochemical decarbonylation of the cyclopropanone **2**, which was, in turn, synthesized from carbinol **1** (Scheme 1).



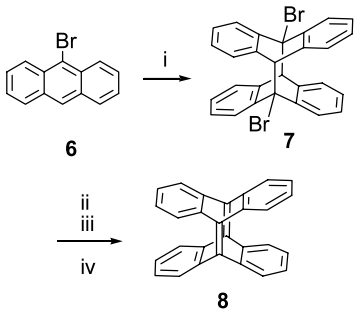

**Scheme 1.** Syntheses of 9,9′-didehydrodianthracene, **3**. (i) h*ν*, 1,4-dioxane; (ii) DCC, DMSO; (iii) h*ν*, benzene; (iv) *t*-BuOK, DME, mesityl-$SO_2$–$ONH_2$; (v) $Pb(OAc)_4$, benzene; (vi) *t*-BuOK, $NaN_3$, DMSO, rt, 2d.

Later, Greene published an alternative synthesis of **3**, starting from **4**.[20] The synthesis involved base-induced dehydrobromination of **4**, capture of the olefin by azide ion, conversion of the triazoline **5** into an *N*-aminotriazoline and oxidation with lead tetraacetate (Scheme 1). Interestingly, without azide, the base added to the olefin, demonstrating the reactivity of pyramidalized alkenes with nucleophiles.

### 3.2. 9,9′,10,10′-Tetradehydrodianthracene

The synthesis of 9,9′,10,10′-tetradehydrodianthracene **8** parallels the second preparation of **3**.[19] Thus, photodimerization of 9-bromoanthracene **6** afforded 9,10′-dibromodianthracene **7** which on treatment with potassium *t*-butoxide in the presence of sodium azide provided a bistriazoline, which was converted into a bis-*N*-aminotriazoline and oxidized with lead tetraacetate to the desired compound **8**, stable to heat, air and moisture (Scheme 2). The stability of **8** is rather surprising, owing to the lack of stability of the of 9,9′-didehydrodianthracene **3**. An X-ray analysis was carried out on **8**, establishing a pyramidalization angle of 35°.[21]

Although **8** was first synthesized in 1974, its chemistry remained unexplored for 20 years. It was not until 1994,



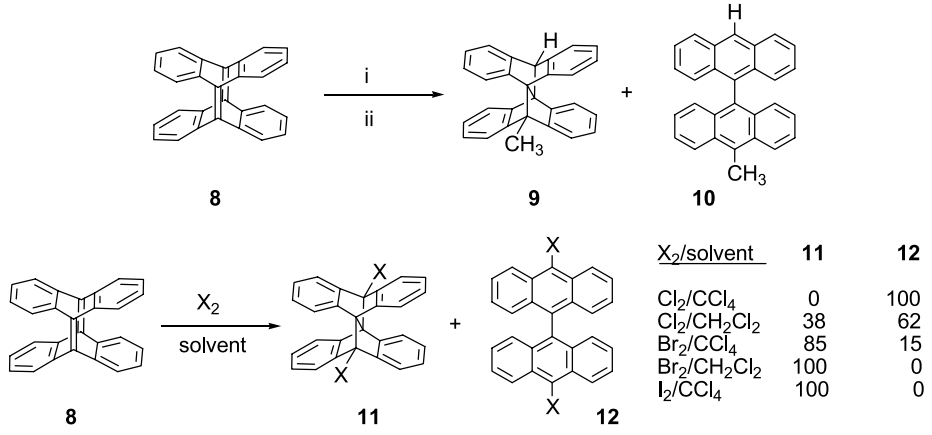

**Scheme 2.** Synthesis of 9,9′,10,10′-tetradehydrodianthracene, **8**. (i) h$\nu$; (ii) *t*-BuOK, $NaN_3$; (iii) *t*-BuOK, DME, mesityl-$SO_2$–$ONH_2$; (iv) $Pb(OAc)_4$, benzene.

when Herges and co-workers started an excellent series of papers dealing with the exciting reactivity of **8**.

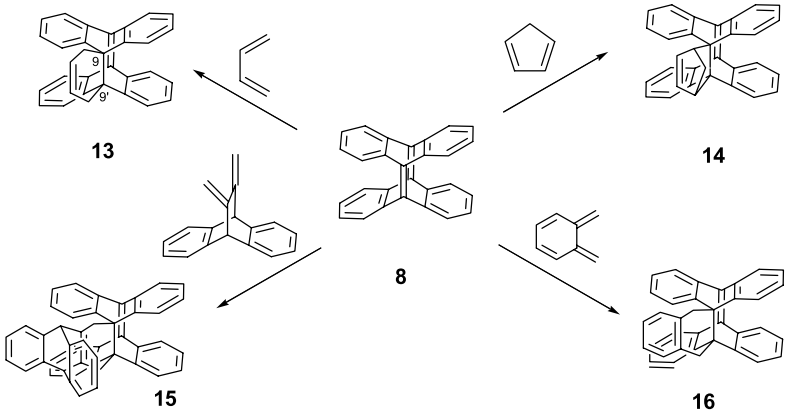
First, Herges et al. studied nucleophilic and electrophilic additions to **8** (Scheme 3). Interestingly, the addition of methyllithium led to mixtures of **9**, by the formation of a transannular bond, and **10**, through electrocyclic ring opening.[22] On the other hand, **8** also reacted with halogens to give transannular **11** (*anti* addition) and ring-opened **12** (*syn* addition) products.[23] For the electrophilic additions, the product ratio showed a remarkable solvent dependence.

These unusual transannular additions are favored by the exact coplanarity and the closeness of the π orbitals of the double bonds of **8**. The spatially close arrangement of the two double bonds in **8**, as well as their pyramidalization, lower the LUMO and raise the HOMO energy of the system. Thus, the reactivity in Diels–Alder reactions towards electron-rich, as well as electron-deficient, dienes should be enhanced in compounds such as **8**. Indeed, Herges found that **8** underwent Diels–Alder reactions with both kinds of dienes. It was noted that **8** reacted with electron-rich dienes under ambient conditions and that only 1:1 products **13**–**16** were observed, even with a large excess of the diene and under drastic conditions (Scheme 4).[24]

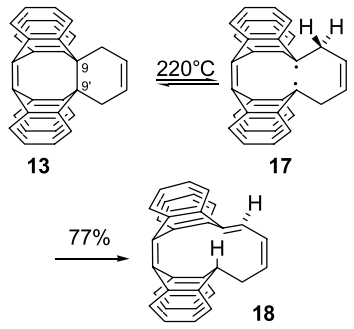
These results are remarkable, because two strained and highly pyramidalized double bond are available in **8**. Herges found that the enhanced reactivity of **8**, compared with its mono Diels–Alder adducts, was mainly due to through-bond and through-space interactions of the two pyramidalized double bonds. After reaction with one olefinic bond, the interaction between the two π systems is cancelled and the reactivity of the remaining double bond is reduced. Interestingly, the cycloaddition adducts have a very long C9–C9′ single bond (>1.65 Å). This accounts for the thermally induced isomerization of cycloadduct **13** to **18** through a formal homo 1,3-sigmatropic H shift, the usual double bond of a 1,3-sigmatropic H shift being replaced by a strained σ-bond (Scheme 5).[24]




**Scheme 3.** Transannular reactivity of diene **8**. (i) $CH_3Li$; (ii) $H_3O^+$.

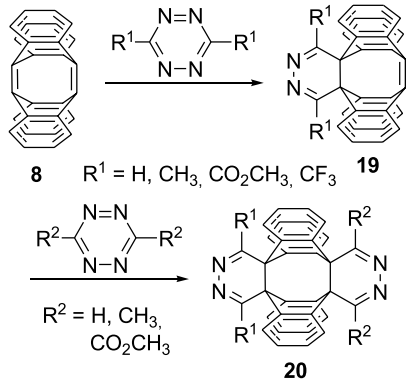



**Scheme 4.** Reactions of **8** with electron-rich dienes.




**Scheme 5.** Themal isomerization of cycloadduct **13** to **18**.

Room-temperature Diels–Alder reactions of **8** with 1 equiv of several 1,2,4,5-tetrazines, electron-deficient dienes, gave 1:1 adducts, **19**.[25] Surprisingly, the tetrazines which normally follow a Diels–Alder reaction with inverse electron demand exhibit the reverse order of reactivity than expected for such a mechanism. The parent tetrazine reacted faster than the diester- and the bis(trifluoromethyl)-substituted tetrazines. Moreover, only the parent tetrazine formed 2:1 products with the 1:1 adducts at room temperature, while the methyl- and methoxycarbonyl-substituted tetrazines required drastic conditions (heat, 4 kbar) to give the 2:1 products, **20**. This unexpected behavior is easily explained taking into account that the electronic effect of the 3,6-substituents in tetrazines is far outweighted by steric factors (Scheme 6).

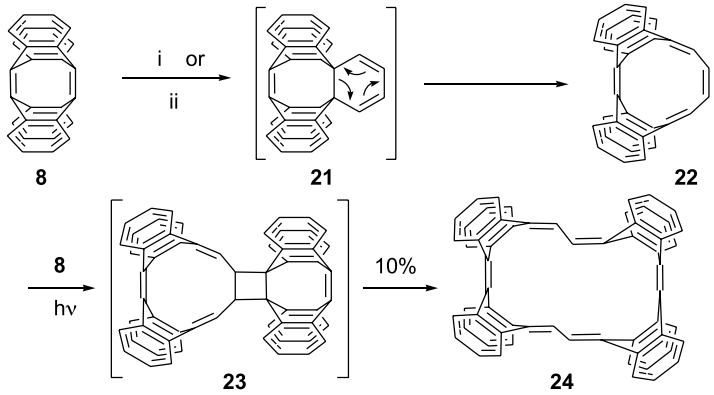



**Scheme 6.** Diels–Alder reactions of **8** with electron-deficient dienes.

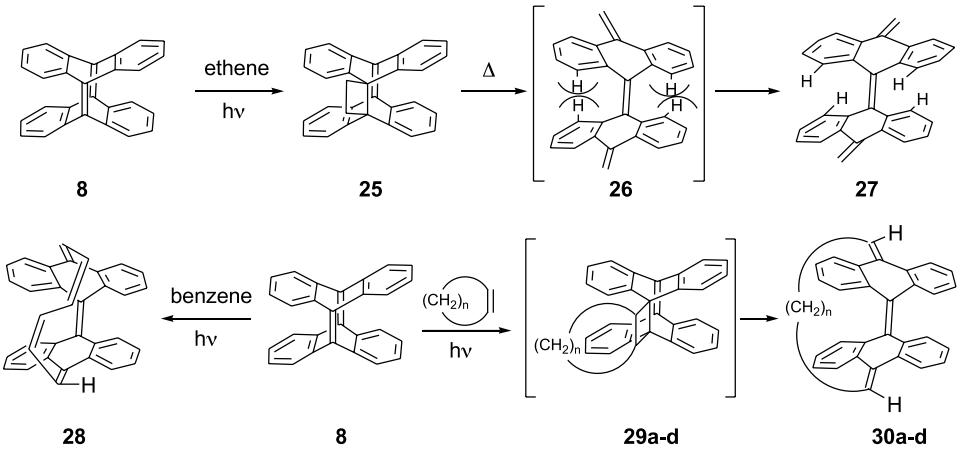
On the other hand, Diels–Alder reaction of **8** with α-pyrone or 1,2-diazine led to the corresponding Diels–Alder adducts, which extruded $CO_2$ and $N_2$, respectively.[26] Electrocyclic ring opening of **21** resulted in the conjugated, bridged bianthraquinodimethane **22**. Photochemically induced methathesis of **22** with **8** directly led to cyclophane **24**, composed of two bianthraquinodimethane units, which are connected by C–C, so that a fully conjugated belt-like system is formed (Scheme 7).[26]

Upon photolysis, ethene added to **8** forming a very strained, but isolable, cyclobutane derivative **25** in 32% yield.[27] Upon heating, a cycloreversion took place to the bianthraquinodimethane **26**. Because of the repulsion between the *peri*-hydrogen atoms, the bianthraquinoid system cannot adopt a planar conformation. Thus, the *syn*-pyramidalized bianthraquinodimethane **26**, initially formed upon ring opening of **25**, immediately changes pyramidalization to give the more stable *anti*-pyramidalized conformation, **27** (Scheme 8). Compound **8** also reacts with a number of cycloalkenes and even with benzene in photochemical [2+2] cycloadditions to give cyclobutanes, which immediately undergo [2+2] cycloreversion, yielding the product of an overall metathesis reaction. The cyclophane-like bridged bianthraquinodimethanes **30** are fixed by the alkane chain in the usually less stable *syn*-pyramidalized form (Scheme 8). The central pyramidalized double bond of **30c** in the X-ray structure has a pyramidalization angle of 12.2°.[27]

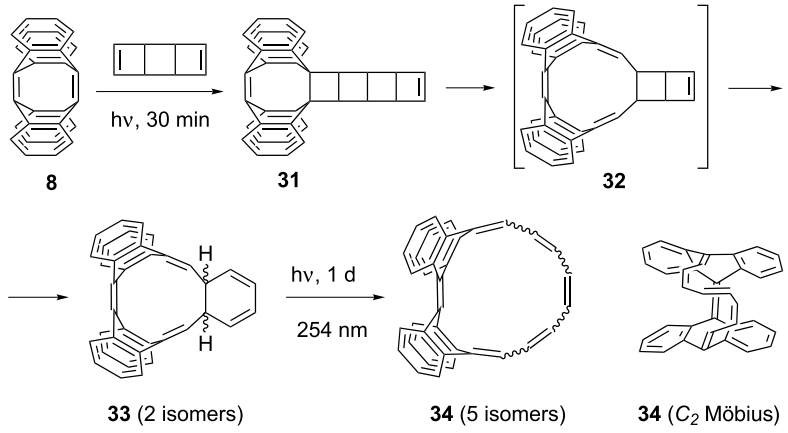
Forty years ago, Heilbronner predicted on purely theoretical grounds that cyclic molecules with the topology of a Möbius band should be aromatic if they contained $4n$ π electrons.[28] Very recently, Herges reported the synthesis of the first stable Möbius aromatic hydrocarbon, the twisted [16]annulene **34**, using **8** and *syn*-tricyclo[4.2.0.0$^{2,5}$]octa-3,7-diene, a valence isomer of cyclooctatetraene, and the aforementioned synthetic strategy. In the first step, a [2+2] cycloaddition product **31** is formed, which could be isolated. This compound, containing four fused cyclobutane rings, underwent cycloreversion to give an unstable intermediate **32** which again opened in an electrocyclic reaction to form a $C_2$ and a $C_s$ symmetric 1,3-cyclohexadiene **33**. Both isomers were isolated and characterized by X-ray structure analysis. Irradiation of this mixture led to **34** as a mixture of several isomers. [16]Annulene **34** may have 108 isomers, and five were separated by HPLC and fully characterized including crystallographic analysis. Very interestingly, one ($C_2$




**Scheme 7.** Synthesis of 'phane' **24** (i) α-pyrone, then 140 °C, –$CO_2$, 36%; (ii) 1,2-diazine, then –$N_2$, 80%.



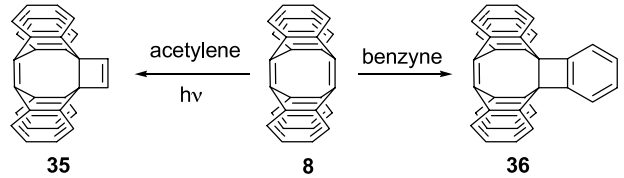

**Scheme 8.** Metathesis of tetradehydrodianthracene **8** with ethene, benzene and cycloalkenes; yields: **28** (25%), **30a** ($n=3$, 11%), **30b** ($n=5$, 29%), **30c** ($n=6$, 60%), **30d** ($n=8$, 26%).



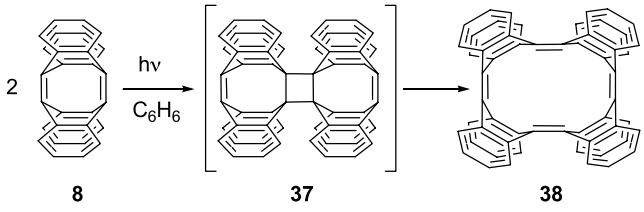

**Scheme 9.** Synthesis of first Möbius aromatic hydrocarbon from **8** and *syn*-tricyclo[4.2.0.0$^{2,5}$]octa-3,7-diene.

symmetry) of them exhibits Möbius topology and is moderately aromatic (Scheme 9).[29]

If alkynes are used as the reaction partners instead of alkenes in the cycloaddition, cyclobutene derivatives are obtained as stable products (Scheme 10).[30] Cycloaddition products of **8** with both acetylene and benzyne were




**Scheme 10.** Reactivity of tetradehydrodianthracene **8** with alkynes.



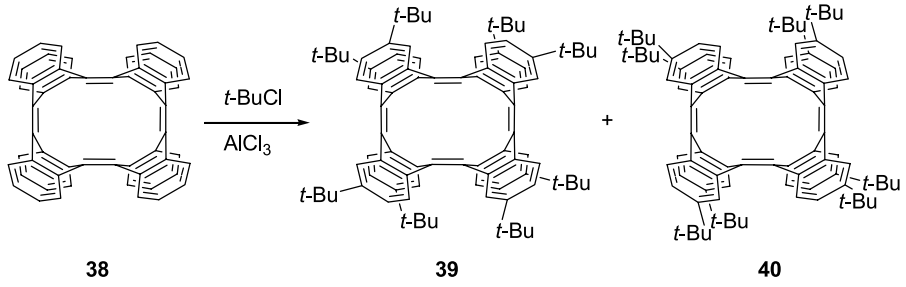

**Scheme 11.** Dimerizing metathesis of tetradehydrodianthracene **8** to the 'picotube' **38**.

characterized by X-ray structure analysis. These studies showed that the central C–C single bond in **35** is 1.677(3) Å and the corresponding bond in **36** is even longer (1.713(2) Å), being one of the longest, stable C–C bonds. Moreover, the remaining double bonds in **35** and **36** are strongly pyramidalized ($\Phi=34°$).

Herges and co-workers have also reported that photolysis of a suspension of **8** in benzene led to the dimeric, highly symmetric ($D_{4h}$) 'picotube' **38** through a photochemical [2+2] cycloaddition to **37** with subsequent [2+2] cycloreversion (Scheme 11).[31]

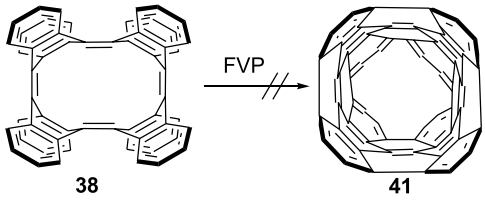
Compound **38** has four anthracene units, an approximately tubular structure with a diameter of 5.4 Å and a length of 8.2 Å, and is the first conventionally synthesized compound that shows tubular aromaticity. Although **38** is extraordinarily thermally stable and unreactive towards oxidation, Herges has succeeded in exploring its fascinating reactivity. For example, **38** reacted under Friedel–Crafts conditions with *t*-BuCl and $AlCl_3$ to give two octasubstituted products, **39** and **40**, in 15 and 14% yield, respectively (Scheme 12).[32]

While the $C_{4h}$ symmetric **40** is achiral, $D_4$ symmetric **39** is chiral and, indeed, both enantiomers of **39** were separated. On the other hand, the attempted dehydrocyclization of **38**

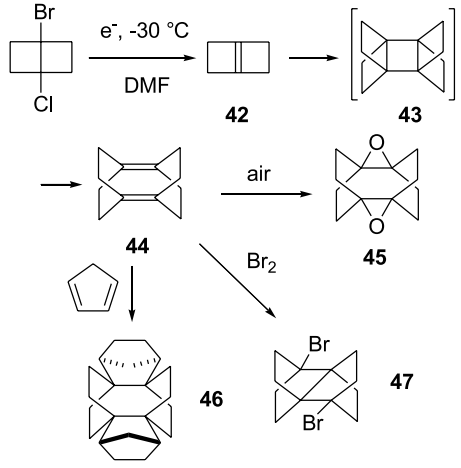



**Scheme 12.** Friedel–Crafts alkylation of 'picotube' **38**.

to 'buckytube' **41** led to a mixture of polycyclic hydrocarbons (Scheme 13).[33] Although it was expected that **38** acted as a π-spherand, since all p-orbitals point approximately towards the interior of the cavity, further studies did not meet this expectation.[34] Nevertheless, **38** reacted with lithium metal to form an unusually stable tetraanionic species that can host two $Li^+$ cations within the inner face of the molecule.[35]




**Scheme 13.** Attempted synthesis of 'buckytube' **41**.




**Scheme 14.** Synthesis and reactivity of **44**.

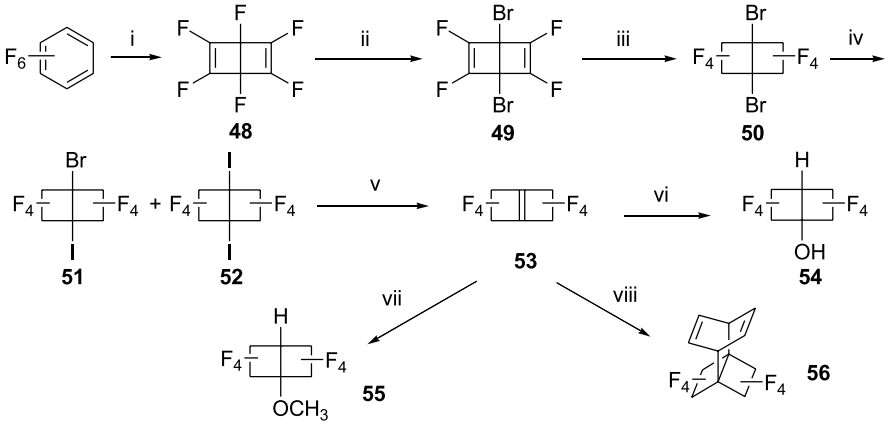
### 3.3. Tricyclo[4.2.2.2$^{2,5}$]dodeca-1,5-diene

Tricyclo[4.2.2.2$^{2,5}$]dodeca-1,5-diene **44**[10a,36] can be viewed as a simplified analog of **8**. Diene **44** was synthesized by dimerization of bicyclo[2.2.0]hex-1(4)-ene **42**, an interesting compound (Scheme 14). Although very strained, **42** is not pyramidalized. Thus, its high reactivity is due primarily to angle bending, rather than torsional strain.[12c] Wiberg has reviewed the chemistry of **42** and no further comments will be added here.[37]

An X-ray structure of **44** showed carbon–carbon double-bond lengths of 1.35 Å, as in **8**, a pyramidalization angle of 27.3° and, interestingly, a separation between the two double bonds of 2.395 Å.[38] Wiberg studied the reactivity of **44**,[10a,36] that showed all the common patterns of the reactivity of pyramidalized alkenes: epoxidation upon oxygen exposure, high reactivity in Diels–Alder reactions and silver complex formation. The short transannular distance between the π bonds and the considerable strain that is relieved accounts for the formation of **47** upon reaction of **44** with 1 equiv of $Br_2$ (Scheme 14).

Recently, Lemal et al. have reported the synthesis of octafluorobicyclo[2.2.0]hex-1(4)-ene **53** from hexafluorobenzene (Scheme 15).[39]

As mentioned earlier, **42** has a planar structure. By

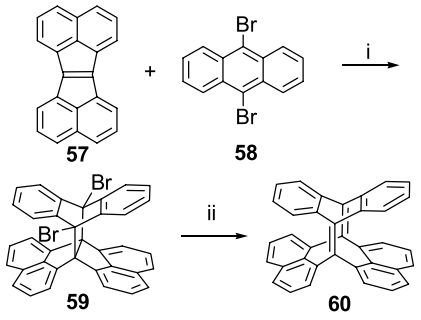



**Scheme 15.** Synthesis and reactivity of **53**. (i) hν; (ii) $AlBr_3$, pentane; (iii) $F_2$/He, −80 °C; (iv) KI, hν; (v) Hg, sonication; (vi) $H_2O$; (vii) $CH_3OH$; (viii) benzene.

demanding more p character from the central bonds, perfluoroalkyl substituents on the double bond might force pyramidalization of that bond.[40] However, electron-diffraction and theoretical studies showed a planar structure for **53**.[41] In contrast to its very labile hydrocarbon parent that dimerizes and polymerizes rapidly at sub-ambient temperatures, alkene **53** is thermally very robust. Its reactivity with nucleophiles (water, methanol) and its cycloaddition chemistry have been studied. Compound **53** is the first alkene to yield a Diels–Alder adduct with benzene and is among the most powerful dienophiles known.[42]

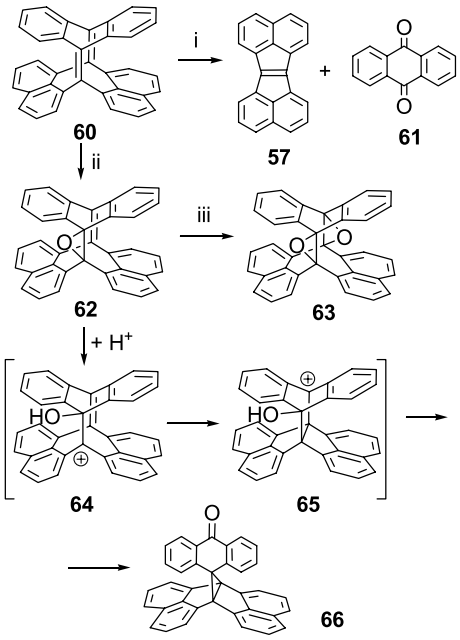
### 3.4. Related polyenes

Dyker and co-workers have synthesized polyene **60**, a compound similar to 9,9′,10,10′-tetradehydrodianthracene **8**.[43] Diels–Alder reaction of the annelated pentalene **57** with 9,10-dibromoanthracene **58** yielded the benzene-bridged [4.3.3]propellane **59**, which upon reaction with triphenylmethyllithium, underwent metalation followed by 1,4-elimination of lithium bromide with cleavage of the strained central carbon–carbon single bond of the propellane skeleton to give **60** in 79% yield (Scheme 16). The pyramidalization angle on the benzene-bridge side is 34.9°, similar to the corresponding pyramidalization angle in **8**. On the naphthaleno-bridged side, the pyramidalization angle is 16.5°. The distances between the symmetrically positioned olefinic carbon atoms are 2.47 and 2.66 Å, respectively.




**Scheme 16.** Synthesis of polyene **60**. (i) 220 °C, 3 h, 78%; (ii) THF, rt, $[(C_6H_5)_3]CLi$, 79%.

As mentioned before, on exposure to molecular oxygen, strained alkenes easily undergo oxidation to epoxides. However, **60**, in the dark, is kinetically stable towards oxygen. Sunlight irradiation of a $CDCl_3$ solution of **60** gave anthraquinone **61** and the annelated pentalene **57**. Diepoxide **63** was prepared by the stepwise oxidation of **60** with dimethyldioxirane and the monoepoxide **62** was isolated as an intermediate. Diepoxide **63** is stable, although, when heated in naphthalene at 285 °C, it decomposes into **57** and **61**. Interestingly, **62** is extremely labile on silica gel or neutral alumina and rearranges to propellane **66**, probably through acid-induced ring opening of the epoxide, transannular ring closure and migration of an alkyl group (Scheme 17).

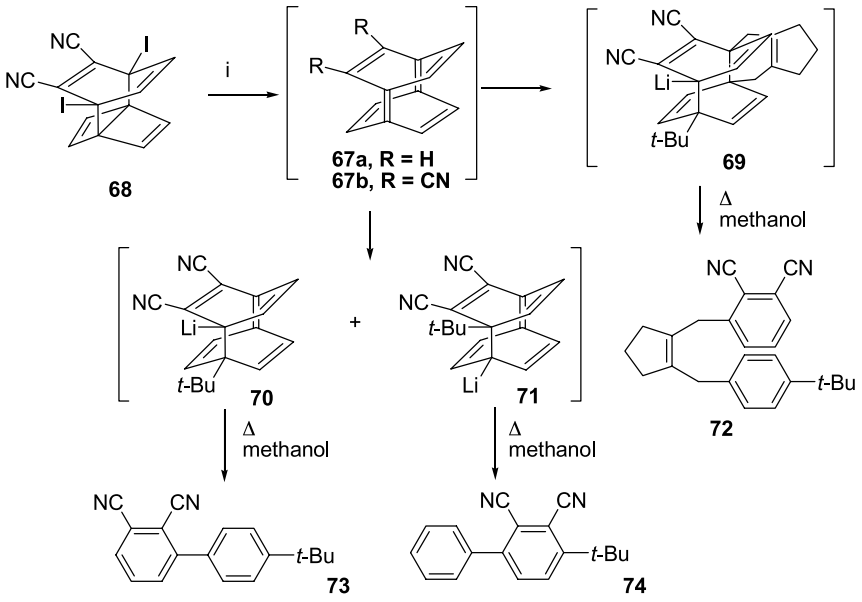



**Scheme 17.** Reactivity of polyene **60**. (i) sunlight, $O_2$, $CDCl_3$; (ii) DMD, 15 °C, 40 min, 55%; (iii) DMD, 16 h, rt, 80%.

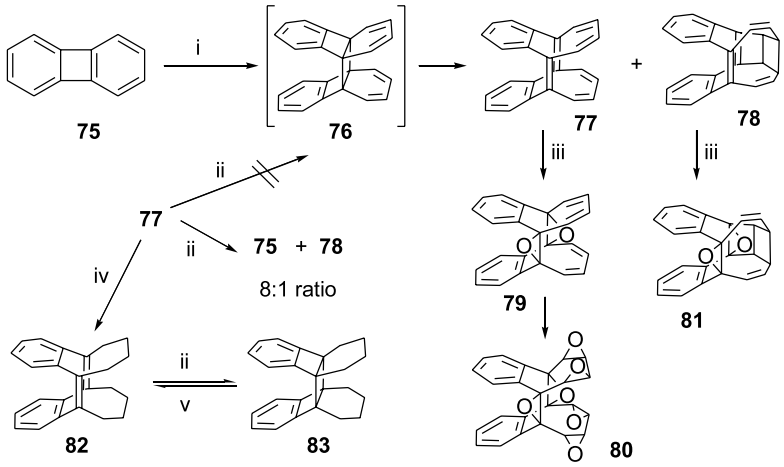
Tricyclo[4.2.2.2$^{2,5}$]dodeca-1,3,5,7,9,11-hexaene **67a** is a highly strained and symmetrical fully unsaturated hydrocarbon, a simplified analog of **8**. Although the parent compound **67a** is unknown, Tsuji and co-workers reported in 1997 the generation and trapping of the 3,4-dicyano derivative **67b**.[44]

Reaction of **68** with an excess of *t*-butyllithium in the presence of 1,2-dimethylenecyclopentane led to a mixture of products, **72**, **73** and **74**, the formation of which is consistent with the generation of **67b**. Taking into account that the calculated pyramidalization angle of **67a** is 37.0° [B3LYP/6-31G(d)] and that the more highly pyramidalized alkenes have been isolated, or, at least, neatly trapped, it seems reasonable that an alternative method of generation, not involving a strongly nucleophilic reagent, could lead to the isolation of **67a** (Scheme 18).[44]

Compounds consisting of two propellanes that share a cyclobutane ring in the center were named 'buttaflanes' by Greenberg and Liebman.[45] Related to **8**, polyenes **77** (60% yield) and **78** (10% yield), the intramolecular photocycloadducts of two peripheral double bonds of **77**, were synthesized by irradiation of biphenylene **75** in *n*-hexane, probably through the intermediacy of buttaflane **76** (Scheme 19).[46] An X-ray study showed that the two double bonds connecting the two former biphenylene units in **77** are moderately pyramidalized ($\Phi \approx 20°$).[47] The epoxidation of **77** and **78** with MCPBA took place preferentially at the two bridgehead alkenes,[46] although epoxidation of all non-aromatic double bonds in **77** to give **80** is also possible.[48] The catalytic hydrogenation of **77** with Pd/C gave an octahydrogenated compound **82** ($\Phi = 27.2°$).[46,49] Interestingly, while the direct irradiation of **77** gave no **76**, but only biphenylene and compound **78** (in a ratio of 8:1), irradiation of **82** gave the buttaflane **83**.[46]




**Scheme 18.** Generation and chemical trapping of a tricyclo[4.2.2.2$^{2,5}$]dodeca-1,3,5,7,9,11-hexaene derivative. (i) *t*-butyllithium, THF, −78 °C, 1,2-dimethylenecyclopentane.




**Scheme 19.** Synthesis of buttaflane **83** and related pyramidalized alkenes. (i) h$\nu$, 30 h, hexane, **77** (60%), **78** (10%); (ii) h$\nu$; (iii) MCPBA, **79** (77%), **81** (86%); (iv) $H_2$, Pd/C, **82** (93%); (v) Δ.

## 4. Sesquinorbornenes, oxasesquinorbornenes and related alkenes

### 4.1. Sesquinorbornenes and related alkenes

During the 1980s, the groups of Bartlett, Paquette and Watson synthesized and fully characterized several derivatives of *syn*- and *anti*-sesquinorbornene, **84** and **85**, respectively, and *syn*- and *anti*-sesquinorbornadiene, **86** and **87**, respectively (Fig. 3). Most of these derivatives are fairly stable compounds and several X-ray studies were carried out.

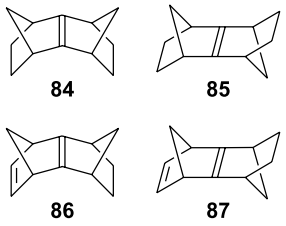



**Figure 3.** *syn*- and *anti*-Sesquinorbornenes and *syn*- and *anti*-sesquinorbornadienes.

Although there are a few exceptions, near-planar alkene geometries have been the rule in the derivatives of **85** and **87**. For the *syn*-sesquinorbornenes, pyramidalization angles ranging from 24 to 26° were found. Borden has extensively reviewed the chemistry of these compounds,[8b] and we will only add that, recently, ab initio[50] and DFT[51] calculations have been carried out on **84** and **85**.[52] Holthausen and Koch[50] found that both HF/6-31G(d) and MP2/6-31G(d) geometries were in good agreement with the available crystal structures, although electron correlation was crucial for obtaining accurate results for the out-of-plane angle. They concluded that force field calculations are not adequate for quantitatively determining pyramidalized alkenes. Nelsen and Reinhardt,[51] using UB3LYP/6-31+

G(d), also found an excellent agreement with the experimental data. For example, the calculated difference in the vertical ionization potentials for **84** and **85** is exactly the same as the experimental value. On the other hand, Eckert-Maksic et al. employed MP2/6-31G(d) and B3LYP/6-31G(d) calculations to investigate the structure of some of the carbocations and their boron analogues embedded in the *syn*-sesquinorbornene framework, hitherto not studied experimentally (Fig. 4).[53] They showed conclusively that the carbocations have a non-classical structure and exhibit homoaromatic 3-center/2-electron bonding.[54] The calculated minimum energy structures of all the species can only be understood by invoking the homoconjugative interaction between the electron-deficient center(s) and the carbon–carbon double bond. Concerning the non-planarity of the double bond in the species **88**–**90**, not surprisingly, the bending of the molecular framework is *exo*,*exo*, the opposite of that found in the neutral molecule **84**.

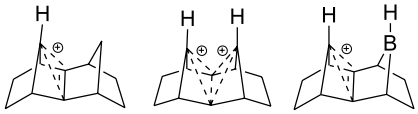
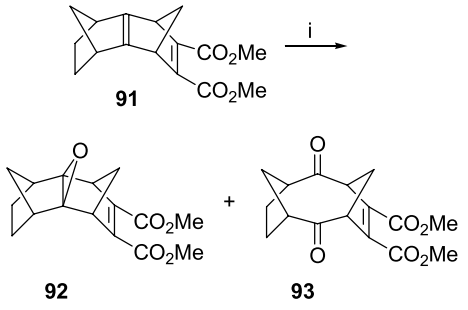



**Figure 4.** Minimum energy stationary points for *syn*-sesquinorbornenyl carbocation **88**, dication **89** and the boron analogue **90**.

The central double bonds in *syn*-sesquinorbornadiene **86** deviate from planarity slightly more than those in the comparable derivatives of *syn*-sesquinorbornene **84**, and the *syn*-sesquinorbornadienes are more reactive towards oxygen.[10b,55] For example, Barlett and Banavali found that bubbling oxygen through a methylene chloride solution of **91** at room temperature for 2 days in the dark led to its complete conversion into epoxide **92** and diketone **93** and they discussed the mechanism of these spontaneous autoxidations (Scheme 20).[10b]




**Scheme 20.** Oxidation of **91** to **92** and **93**. (i) $O_2$, rt, 2 h, $CH_2Cl_2$, 70% **92**, 30% **93**.

Paquette, De Lucchi, and co-workers prepared *syn*- and *anti*-sesquinorbornatriene, **94** and **95**, and certain of their spectral properties were determined.[56] However, the high reactivity of **94** with atmospheric oxygen at its internal unsaturated linkage precluded the experimental definition of the extent of π-pyramidalization at its central double bond. Later, Paquette et al. synthesized **96**. By virtue of its steric hindrance, the internal double bond is very difficult to approach and **96** is indeed stable (Fig. 5).[57]

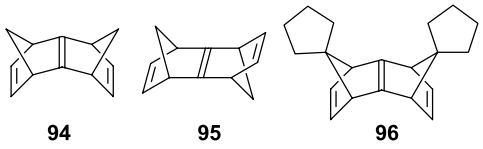
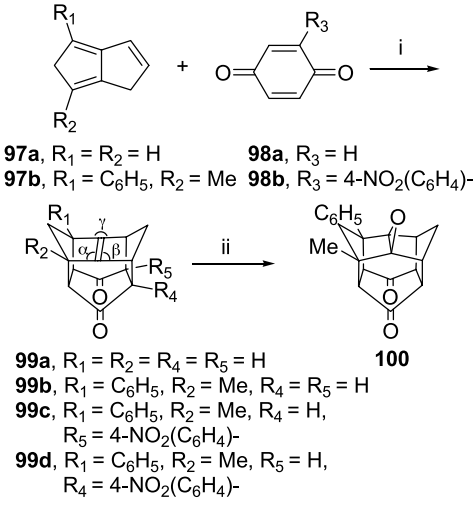



**Figure 5.** *syn*- and *anti*-Sesquinorbornatrienes, **94** and **95**, and stable derivative **96**.

While solutions of the parent triene **94** in chloroform are converted into the monoepoxide within minutes at room temperature when exposed to air, **96** exhibits no sensitivity to atmospheric oxygen and is inert, at room temperature, to *m*-chloroperbenzoic acid, phenyl azide and diazomethane. The X-ray diffraction structure of **96** indicated a pyramidalization angle of 32.4°. Worthy of note is the highly deshielded chemical shift of the central olefinic carbon atoms (172.0 ppm), within experimental error of the value recorded for the same carbon atoms in the parent **94** (172.1 ppm) and probably a world record for deshielding at an unconjugated olefinic carbon atom. The resonance due to the two central olefinic carbon atoms appears at 151.6 ppm in **84** and at 157.4 ppm in **86**. Thus, an enhancement in the level of paramagnetic contributions to the $^{13}C$ NMR shift is manifested in a non-linear fashion as the pyramidalization increases from **84** ($\Phi \sim 24°$) to **86** and, ultimately, to **94** ($\Phi \sim 32°$).[57a,58]

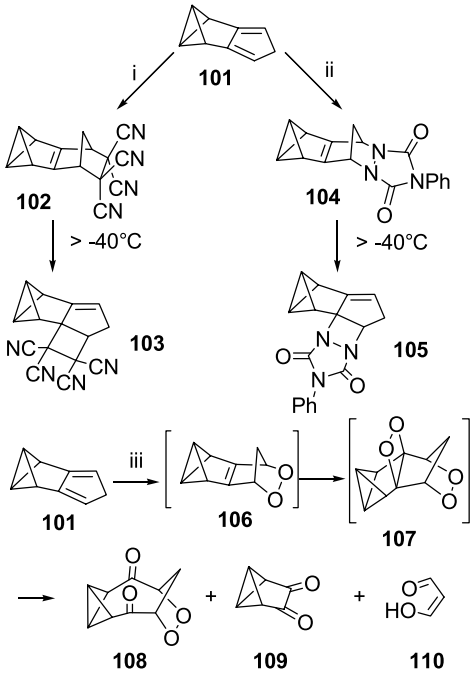
Recently, Griesbeck and co-workers have prepared the twofold-bridged sesquinorbornenes **99a–d** using sequential [4+2] cycloadditions of benzoquinones **98a–b** with 1,5-dihydropentalenes **97a–b**.[59] Unfortunately, no X-ray analysis could be performed to date, neither for the parent compound **99a**, nor for its derivatives **99b–d**. Nevertheless, B3LYP/6-31G(d) calculations found a $\Phi$ value of 46.5° for **99a**. These calculations led to the suggestion that the cage compounds **99a–d**, stable at room temperature, have a remarkably high double-bond pyramidalization. This pyramidalization results mainly from the strong compression of the $\alpha$ and $\beta$ angles, which is typical for sesquinorbornenes, not being counterbalanced by the expansion of the $\gamma$ angle. In typical *syn*-sesquinorbornenes, the $\gamma$ angle can reach values up to 144°, while B3LYP/6-31G(d) predicts a $\gamma$ value




**Scheme 21.** Synthesis and reactivity of **99**. (i) $CH_2Cl_2$, rt; (ii) DMD, −30 °C, 10 min, 71%.

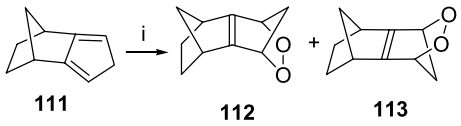
of 127.9° for **99a**. The cage compound **99b** was quantitatively epoxidized by a variety of reagents: dimethyldioxirane gave **100** after some minutes at −20 °C, and singlet oxygen likewise reacted efficiently, whereas triplet oxygen needed some days for completion.[59b] Worthy of note is that no trace of 1,2-dioxetane or the corresponding cleavage products were formed in the singlet oxygen reaction. Thus, the pyramidalization of the central double bond is described by a radical-like behavior in its reaction with triplet oxygen, as well as the unusual oxygen-atom transfer from singlet oxygen (Scheme 21).

Recently, Christl and co-workers have synthesized 1,2,3,5-tetrahydro-1,2,3-methenopentalene **101**, a valence isomer of isoindene.[60] The pentalene **101** reacts at low temperature either with tetracyanoethene or 4-phenyl-1,2,4-triazoline-3,5(4*H*)-dione to furnish the benzvalenes **102** and **104**, respectively, but, on warming (> −40 °C), these were transformed into the formal [2+2] cycloadducts **103** and **105**, respectively. The reaction of **101** with an excess of singlet oxygen at −60 °C gave a mixture of dioxoninedione **108**, diketone **109**, and the *cis*-enol of malondialdehyde **110**, in 14, 16 and 11% yields, respectively. The use of a smaller amount of oxygen allowed the observation of the Diels–Alder adduct **106**. The authors proposed that **101** reacts with singlet oxygen to give firstly the adduct **106**, which, via **107**, in competing processes, turns into **108** on the one hand, as well as **109** and **110** on the other. Compounds **102**, **104** and **106** are related to *syn*-sesquinorbornenes and theoretical calculations (UB3LYP/cc-pVDZ) showed a pyramidalization angle of 21.2° for the unknown parent benzvalene hydrocarbon (Scheme 22).




**Scheme 22.** Reactivity of 1,2,3,5-tetrahydro-1,2,3-methenopentalene **101**. (i) TCNE, −40 °C; (ii) PTAD, −40 °C; (iii) sensitizer, $^3O_2$, −60 °C, Na vap lamp.

Finally, it should be noted that the *syn*- and *anti*-dioxasesquinorbornenes, **112** and **113**, respectively, were synthesized by the addition of singlet oxygen to




**Scheme 23.** Synthesis of dioxasesquinorbornenes **112** and **113**. (i) $O_2$, −78 °C, rose Bengal; ratio **112**:**113**=1:2.

isodicyclopentadiene **111** under irradiation at −78 °C in the presence of rose Bengal (Scheme 23).[61a]

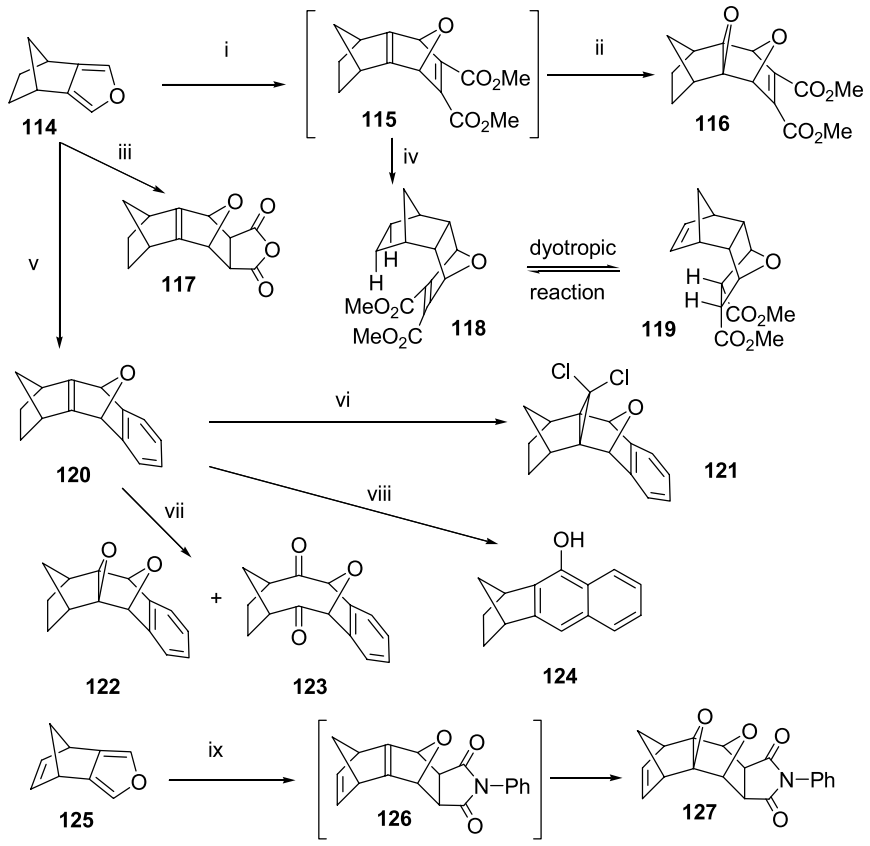
$^1H$ and $^{13}C$ NMR of the mixture of **112** and **113** were recorded at −80 °C and, upon completion of the reaction, at −25 °C, **113** disappeared more rapidly than **112**. This experiment points toward **112** being more stable than **113**, as is the case for the parent hydrocarbons. Indeed, DFT calculations [B3LYP/6-31G(d)] carried out on these compounds predict that isomer **112** is 4.9 kcal/mol more stable than **113**. On the other hand, these calculations predict an out-of-plane angle of 22.7° for **112** and 9.4° for **113**.[61b]

### 4.2. Oxasesquinorbornenes and related alkenes

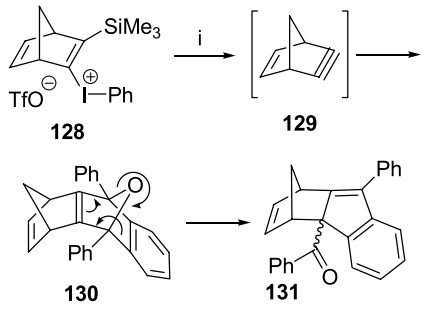
An interesting question related to pyramidalization concerns the influence of heteroatoms on the extent of double bond pyramidalization, which has consequences regarding the chemical reactivity.[62] While sesquinorbornenes are relatively stable, the introduction of an oxygen atom at the bridge causes almost all oxa-derivatives to be unstable species, readily undergoing air oxidation or molecular transformations. Despite this, some X-ray diffraction studies have been carried out. For example, Vogel and co-workers found that the Diels–Alder reaction of (2-norborneno)[*c*]-furan **114** with maleic anhydride and methyl acetylenedicarboxylate led, with very high *endo*-stereoselectivity (>98%), to *syn*-oxasesquinorbornene anhydride **117** and *syn*-oxasesquinorbornadiene **115**, respectively (Scheme 24).[63a] While **117** showed enough air stability to be crystallographically studied, **115** could not be isolated, as it was readily oxidized in the presence of air to the corresponding epoxide **116**. From the X-ray diffraction analysis of **117**, an out-of-plane angle of 16.8° for its carbon–carbon double bond was deduced.[63a]

Diene **115** could be hydrogenated selectively to **118**.[63a] Interestingly, when heated in benzene-$d_6$ at 130–160 °C, **118** rearranged reversibly to **119**, through a $[_\sigma2_s+_\sigma2_s+_\pi2_s]$ dyotropic transfer of hydrogen.[63b] The compressed structures of **118** and **119** are probably the driving force of this rearrangement, because the epoxide **116** did not rearrange. The enhanced reactivity of the oxa derivatives was pointed out by Bartlett's group. They found that the reaction of norbornenofuran **114** with a single equivalent of benzyne led to *syn*-oxabenzosesquinorbornene **120** (with an out-of-plane angle of 22.1°). Reaction of the parent *syn*-benzosesquinorbornene with dichlorocarbene for 24 h led to no reaction, whereas treatment of **120** under similar conditions resulted in complete reaction within 12 h, with formation of the dichlorocarbene adduct **121** (Scheme 24).[64]

Later, they studied the autoxidation of **120**,[10b] that proceeded smoothly at room temperature with oxygen bubbling to give, in quantitative yield, a mixture of the



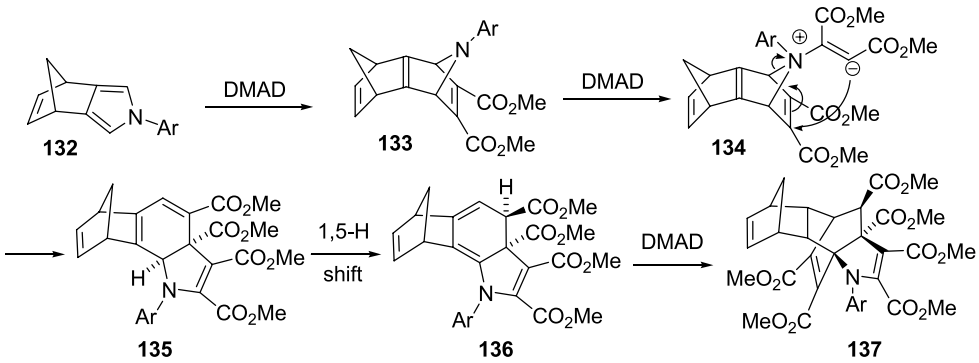

**Scheme 24.** Synthesis and reactivity of oxasesquinorbornane derivatives. (i) dimethyl acetylenedicarboxylate, $CH_2Cl_2$, 25 °C, 12 h; (ii) air, 40–50% from **114**. (iii) maleic anhydride, $CH_2Cl_2$, 25 °C, 12 h, 83%; (iv) $H_2$, Pd-C, 73%; (v) 1 equiv benzyne; (vi) $HCCl_3$, KOH, rt, 74%; (vii) $O_2$, rt, 60% **122** and 40% **123**; (viii) UV or HCl, △, 80%; (ix) *N*-phenylmaleimide, $CH_2Cl_2$, rt, 2 w, then air, 18%.




**Scheme 25.** Generation of alkyne **129** and oxasesquinorbornatriene **130**. (i) $Bu_4NF$, THF, $CH_2Cl_2$, 0 °C, 1,3-DPIBF; 43% yield.

epoxide **122** and diketone **123** in a 60:40 ratio, and also found that **120** rearranges in the presence of either UV irradiation or strong acid to 1,2,3,4-tetrahydro-1,4-methano-9-anthracenol **124**.[65]

In line with the aforementioned observations, Kobayashi and co-workers found that, when the methanoisobenzofuran **125** was left at room temperature for 2 weeks in the presence of *N*-phenylmaleimide, the epoxide **127** was isolated, albeit in low yield. Probably, as before, the formation of the epoxide **127** proceeded via air oxidation of the oxasesquinorbornadiene **126** on the central pyramidalized double bond (Scheme 24).[66]



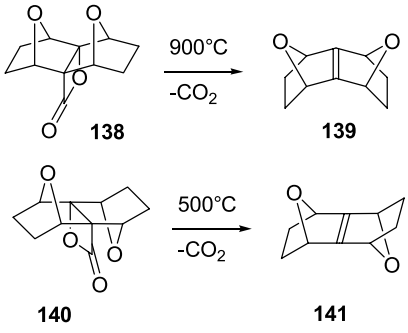

**Scheme 26.** Generation of azasesquinorbornatriene **133**. Ar=*p*-$CH_3C_6H_4$-; DMAD=dimethyl acetylenedicarboxylate.

To date, no hetero derivatives of sesquinorbornatriene have been described. However, oxasesquinorbornatriene **130** (Scheme 25) and azasesquinorbornatriene, **133** (Scheme 26) have been claimed as very reactive intermediates.

Very interestingly, the reaction of phenyl [3-(trimethylsilyl)bicyclo[2.2.1]hepta-2,5-diene-2-yl]iodonium triflate **128** with $Bu_4NF$ in the presence of 1,3-diphenylisobenzofuran (1,3-DPIBF) gave the carbonyl-containing adduct **131** in 43% yield. According to classical cyclopentyne studies by Wittig,[67] Kitamura and co-workers explained the isolation of **131** through the generation of bicyclo[2.2.1]-hept-2-en-5-yne, **129**, a Diels–Alder trapping reaction and isomerization of the primary cycloadduct **130**, an oxasesquinorbornatriene, to **131**.[68]

On the other hand, Kobayashi reported that treatment of the methanoisoindole **132** with a 4-fold excess of dimethyl acetylenedicarboxylate in refluxing benzene afforded the 1:3 adduct **137** (40%). The use of a 2-fold excess of dimethyl acetylenedicarboxylate led to a mixture of **137**, in 30% yield, along with the recovery of **132**. Scheme 26 shows the proposed mechanism for the formation of **137**. An approach of dimethyl acetylenedicarboxylate from the *endo* face of **132** provides an initial Diels–Alder adduct **133**, an azasesquinorbornatriene, which undergoes the zwitterionic aza-Cope rearrangement via **134** to give a dihydroindole intermediate **135**. A 1,5-H shift leading to **136** and a subsequent Diels–Alder reaction with dimethyl acetylenedicarboxylate provides the cycloadduct **137**.[66]

Photoelectron spectroscopic evidence for the formation of




**Scheme 27.** Pyrolytic generation of dioxasesquinorbornenes **139** and **141**.

*syn*- and *anti*-7,7′-dioxasesquinorbornene, **139** and **141**, respectively, upon pyrolytic decomposition of the corresponding β-lactones has been presented (Scheme 27).[69]

Recently, the B3LYP/6-31G(d) method has become very popular for studying pyramidalized alkenes, because it has been repeatedly shown that density functional theory (DFT) using the B3LYP/6-31G(d) method gives results in excellent agreement with the experimentally determined geometries and properties for polycyclic systems with pyramidalized double bonds.[14,51,69b,70–73] Very recently, Margetić et al. have carried out DFT calculations on several 7-oxa and 7,7′-dioxa derivatives of *syn*-sesquinorbornenes (Fig. 6) and their corresponding *anti* isomers.[69b,74] An inspection of the energy differences between the *syn*- and *anti*-isomers revealed that, although more bent, in all cases the *syn*-isomers are thermodynamically more stable by 1.4–3.8 kcal/mol.[74] This trend is in accordance with the calculated energy difference between the *syn*- and *anti*-sesquinorbornenes [2.5 kcal/mol, B3LYP/6-31G(d)] and with several experimental results.[63a] B3LYP calculations indicate that all the investigated structures showed significant non-planarity of the central double bond, with the exception of those *anti*-derivatives possessing symmetrical structures. The energy gap between the *syn*- and *anti*-isomers does not correlate well with the extent of the out-of-plane deviation.[74]

In a series of compounds with the same degree of unsaturation, the out-of-plane deviations for the central double bonds in the *syn*-dioxa derivatives are slightly larger than those of the *syn*-oxa derivatives, that, in turn, are slightly larger than the values of the corresponding hydrocarbons.[75] However, the differences are very small. For example, the out-of-plane deviation for the central double bond in **139** [17.3 and 15.8°, as calculated by the MP2/6-31G(d) and B3LYP/6-31G(d) approaches, respectively] does not differ significantly from that in *syn*-sesquinorbornene, **84** [16.3 and 15.1°, MP2/6-31G(d) and B3LYP/6-31G(d), respectively]. The small increase in these angles on going from **84** to **139** can be explained by: (i) involvement of the repulsive interaction between the non-bonding oxygen lone pairs and the π system of the double bond, and (ii) differences in the hyperconjugative interaction between the σ orbitals associated with the bridge C–O bonds and the double bond π orbital.[62,69b]

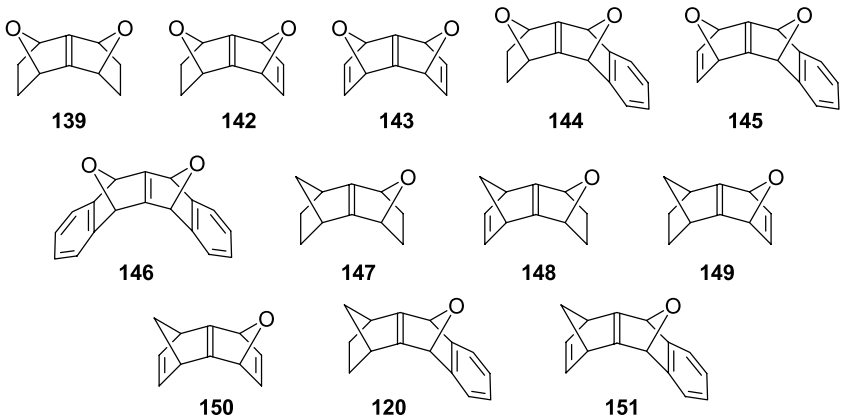
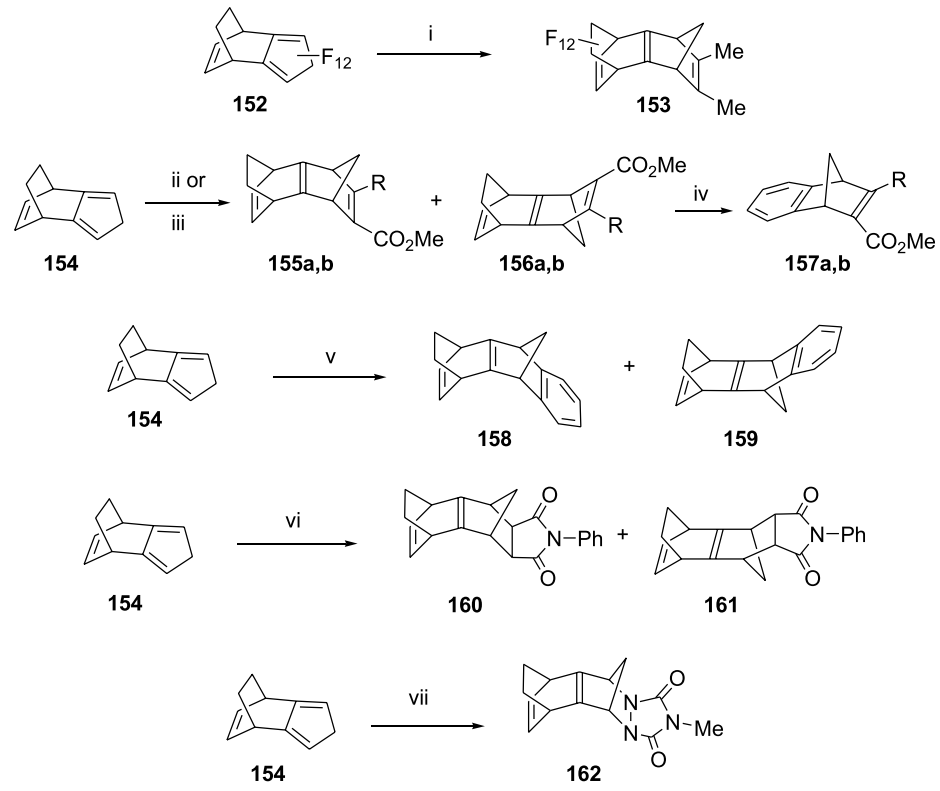



**Figure 6.** Some oxasesquinorbornenes and related alkenes studied theoretically.



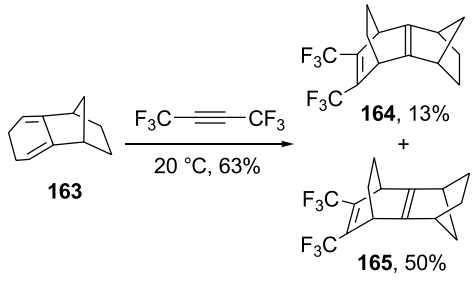

**Scheme 28.** Synthesis and reactivity of homosesquinorbornenes, homosesquinorbornadienes and homosesquinorbornatrienes. (i) 2-butyne, 120 °C, 77%; (ii) dimethyl acetylenedicarboxylate, 25 °C, **155a** (R=$CO_2Me$, 14%) and **156a** (R=$CO_2Me$, 86%); (iii) methyl propiolate, 42 °C, **155b** (R=H, 21%) and **156b** (R=H, 79%); (iv) 50 °C, **157a** (R=$CO_2Me$, 80%) or **157b** (R=H, 69%); (v) benzyne, **158** (19%) and **159** (81%); (vi) *N*-phenylmaleimide, 55%, **160**:**161** ratio 4:1; (vii) 4-methyl-1,2,4-triazoline-3,5(4*H*)-dione, 96%.

Rehybridization does not contribute to the observed feature because the olefinic carbon atoms in **84** and **139** have practically the same *s* character as calculated by NBO analysis from the B3LYP/6-31G* wavefunction.[69b]

### 4.3. Homosesquinorbornenes, sesquibicyclo[2.2.2]-octenes and related alkenes

In comparison with the sesquinorbornenes, there are few structural studies of compounds with a bicyclo[2.2.2]octyl unit fused to the bicyclo[2.2.2]octane nucleus, sesquibicyclo[2.2.2]octenes, or to the norbornene nucleus, homosesquinorbornenes.

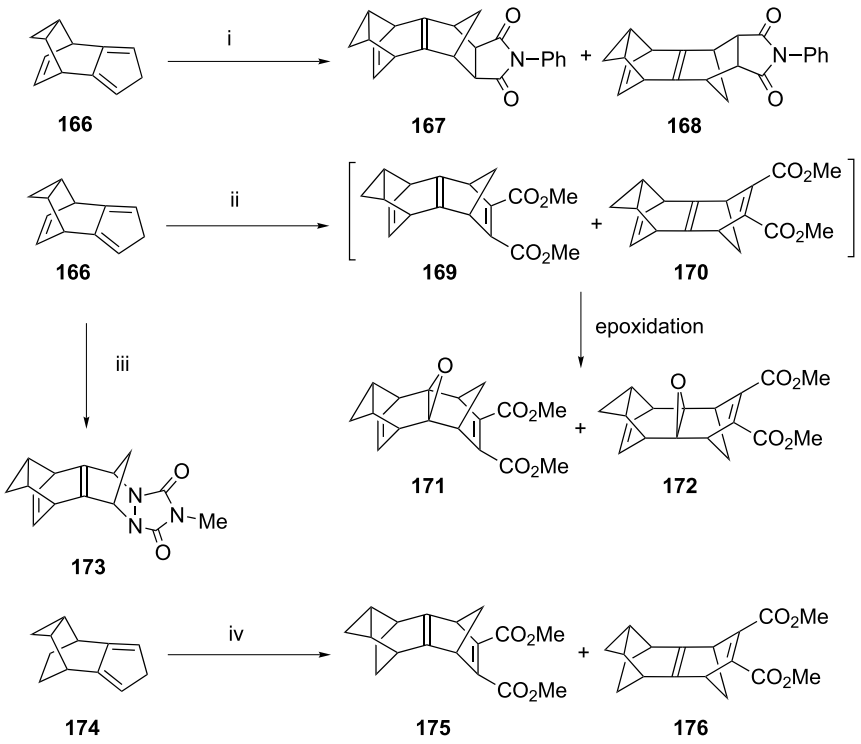
In 1972, Feast and co-workers described the condensation of perfluorotricyclo[5.2.2.$0^{2,6}$]undeca-2,5,8-triene **152** with 2-butyne to give the adduct **153** in 77% yield.[76] Afterwards, Paquette reported the synthesis of several homosesquinorbornenes, homosesquinorbornadienes and homosesquinorbornatrienes by Diels–Alder reactions of the diene **154** with dienophiles such as methyl propiolate, dimethyl acetylenedicarboxylate, maleic anhydride, *N*-phenylmaleimide and benzyne (Scheme 28).[77] Interestingly, on heating the mixture of trienes **155** and **156** clean aromatization occurred to give **157**. Similarly, Diels–Alder reaction of **154** with *N*-methyl-1,2,4-triazoline-3,5(4*H*)-dione led to the diaza derivative **162** in 96% yield.[77b]



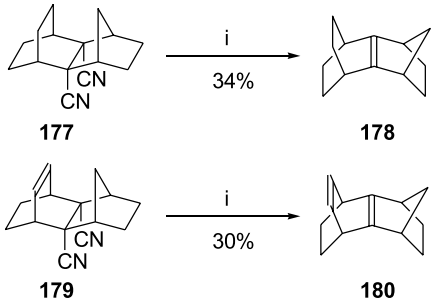

**Scheme 29.** Synthesis of homosesquinorbornadienes with diene **163**.

An alternative, rather limited, approach to homosesquinorbornenes involves Diels–Alder reactions of the diene **163**, less reactive than its cyclopentadiene counterpart, with some highly reactive dienophiles such as perfluoro-2-butyne (Scheme 29).[63d] Paquette's group also synthesized both *syn*- and *anti*-cyclopropannelated derivatives of homosesquinorbornenes related to these compounds.[77c] Representative examples are collected in Scheme 30. In 1986, De Lucchi and co-workers published the synthesis of the parent homosesquinorbornene **178** and homosesquinorbornadiene **180** via reductive elimination of the respective, readily available, β-dicyano derivatives.[78] In line with Paquette's previous observations,[77a] the diene **180** underwent thermal retro Diels–Alder elimination of ethylene to give a benzonorbornene (Scheme 31).

Most of these studies were carried out in order to examine the electronic control of stereoselectivity in Diels–Alder reactions and neither a structural analysis nor a reactivity study were carried out.[77] Only the X-ray diffraction analysis of **162**, with an out-of-plane angle of 11.7°, was obtained.[77b] An excellent agreement with this experimental value was




**Scheme 30.** Some examples of cyclopropannelated homosesquinorbornenes and related compounds. (i) *N*-phenylmaleimide, **167**:**168** ratio 4:1; (ii) dimethyl acetylenedicarboxylate; (iii) 4-methyl-1,2,4-triazoline-3,5(4*H*)-dione, 100%; (iv) dimethyl acetylenedicarboxylate, 98%, **175**:**176** ratio 3:2.




**Scheme 31.** Synthesis of the parent homosesquinorbornene **178** and the homosesquinorbornadiene **180**. (i) Na, THF, sonication.

found later by using B3LYP/6-31G(d) calculations (11.6°).[73a] B3LYP/6-31+G(d) calculations on the parent homosesquinorbornene **178** by Nelsen and Reinhardt revealed a bending angle of 11.2°,[51] similar to that calculated by Margetić et al. at the B3LYP/6-31G(d) level (10.5°).[73a] The B3LYP/6-31G(d) predicted value for the out-of-plane angle of **180** is 12.4°.[73a]

Very recently, Margetić et al. performed B3LYP/6-31G(d) calculations on a series of homosesquinorbornenes and sesquibicyclo[2.2.2]octenes, including oxa-homosesquinorbornenes.[73a] The compounds in which the two faces of the double bond are different are predicted to have a pyramidalized double bond with out-of-plane angles ranging from 1.8 to 17.9°.[75] The trend in the pyramidalization found in these series of fused polycycles is sesquinorbornenes > homosesquinorbornenes > sesquibicyclo[2.2.2]-octenes. This trend is entirely consistent with a reduction in strain in going from the [2.2.1] to the [2.2.2] systems. In line with previous reports,[62,74] the pyramidalization of the homosesquinorbornenes is slightly smaller than that of the corresponding oxa-bridged homosesquinorbornenes.[73a]

Several sesquibicyclo[2.2.2]octene derivatives have been synthesized.[79] For example, Marchand and co-workers reported the synthesis of the parent sesquibicyclo[2.2.2]-octene **181** and a tetradecacyclic-caged derivative **182**. X-ray crystallographic analysis of both compounds revealed that each alkene, as expected, is planar (Fig. 7).[79b]

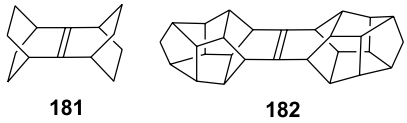



**Figure 7.** Sesquibicyclo[2.2.2]octane, **181** and derivative **182**.

Balci and co-workers carried out detailed investigations on both the *syn*- and *anti*-cyclopropannelated derivatives of **181**, along with some peroxy analogues, and reported experimental and calculated structural parameters for the compounds **183–194** (Fig. 8).[80–85] However, the parent compounds **185b** and **186b** have not yet been synthesized.

Compounds **185b**, **186b** and their known derivatives are bisnorcaranes and their syntheses took advantage of the cycloheptatriene–norcaradiene equilibrium. It is well known that cycloheptatriene is in equilibrium with its valence isomer, norcaradiene, and π-electron-withdrawing substituents at C-7 shift the equilibrium in favor of norcaradiene.[80] Therefore, a Diels–Alder reaction of excess benzyne with *trans*- and *cis*-**195** gave the bis-adducts **183a** and **184a**, respectively (Scheme 32).

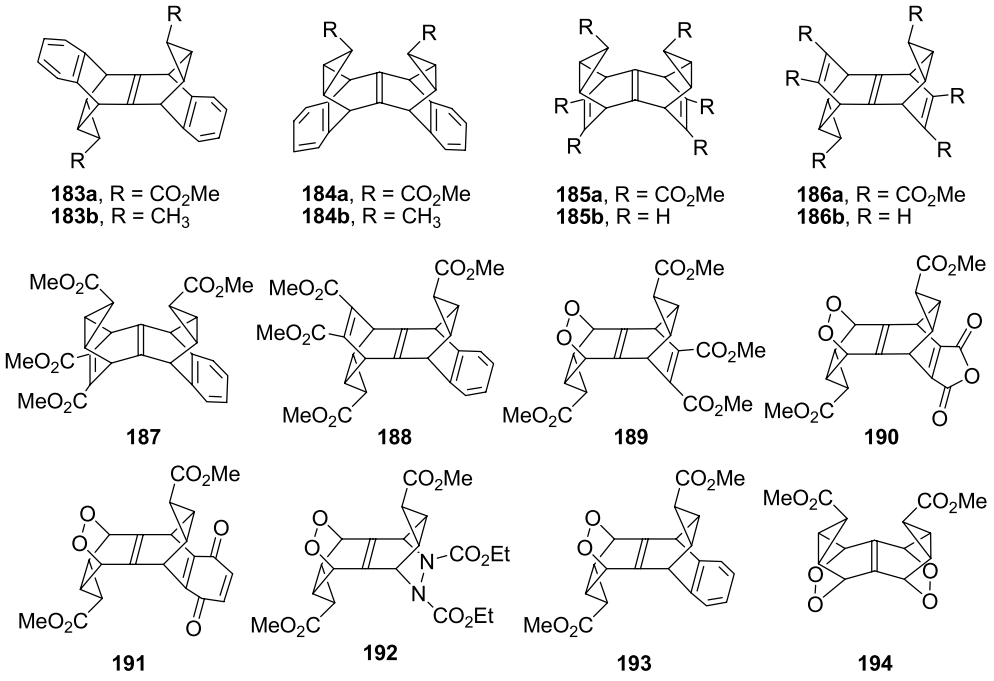
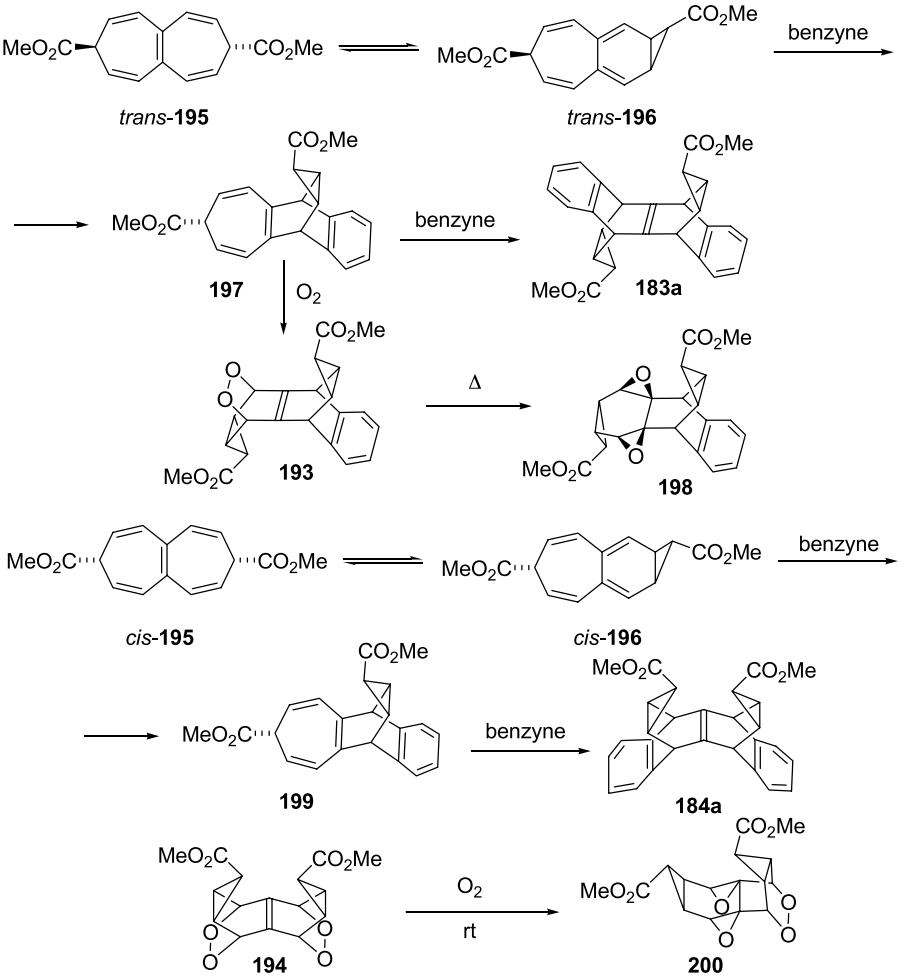



**Figure 8.** *syn*- and *anti*-Cyclopropannelated sesquibicyclo[2.2.2]octanes.[80–85]




**Scheme 32.** Synthesis and reactivity of **183a**, **184a** and related compounds.

The X-ray crystal structures of **183a** and **184a** were determined. While **183a** has a planar double bond,[80] **184a**, as expected, has a pyramidalization angle $\Phi = 16.8°$.[81] Interestingly, although pyramidalized alkenes are usually highly reactive species, when epoxidation, bromination and hydrogenation of **184a** were attempted, in all cases only the unreacted starting material was recovered. According to the authors, this lack of reactivity indicates that **184a** is so heavily congested that the pyramidalized alkene is not accessible to any reactant.[81,85]

More recently, Balci and co-workers have synthesized **183b** and **184b** starting from **183a** and **184a**, respectively, and have recorded their photoelectron spectra. The measured ionization potential of **184b** indicates that this compound and its precursor **184a** should be at least as reactive as the sesquinorbornene and sesquinorbornatriene systems, but steric shielding of the carbon–carbon double bond prevents any reaction.[85]

Similarly to the synthesis of **183a** and **184a**, cycloaddition of *cis*- and *trans*-**196** (Scheme 32) with 1 equiv of dimethyl acetylenedicarboxylate, followed by cycloaddition of the initially formed adduct with benzyne, gave **187** and **188**, respectively (Fig. 8). The symmetrical compounds **185a** and **186a** were prepared by the addition of 2 equiv of dimethyl acetylenedicarboxylate to *cis*- and *trans*-**196**.[83] The X-ray crystal structures of compounds **185a**, **187** and **188** were determined.[82] The experimental $\Phi$ values for **185a** and **187** averaged 19.9 and 16.5°, while the values for **188** averaged 8°. Replacement of the benzene rings in **184a** ($\Phi = 16.8°$) with dimethyl acetylenedicarboxylate gave rise to a bending of 19.9° in the central double bond. The rise on going from **184a** to **185a** can be explained on the grounds of the aromatic carbon–carbon bonds being longer than those of the olefinic carbon–carbon double bonds.[84]

Finally, the same group has reported the synthesis of the bis(endoperoxide) **194** upon addition of 2 equiv of singlet oxygen to *cis*-**196**. Compound **194** rearranges to the corresponding bis-epoxide **200** in nearly quantitative yield upon standing at room temperature (Scheme 32).[83] The related compounds **189–193** also underwent the rearrangement to the corresponding bis-epoxides (e.g., conversion of **193** into **198** in Scheme 32). Although all efforts to obtain suitable crystals of **194** failed, Balci and co-workers have gathered spectral and theoretical evidence of **194** being more pyramidalized than the previously synthesized cyclopropannelated compounds. Electronic structure analysis suggests that the increased pyramidalization of **194** results from: (i) hyperconjugation between the central π-bond and the four adjacent C–O bonds which weakens the double bond; the weaker double bond is more susceptible to bending; and (ii) rehybridization at the allylic carbon atoms.[83b]

## 5. Bicyclo[3.3.0]oct-1(5)-ene derivatives

In the 1980s, Houk[12b,17e,86] and Burkert,[87] independently, proposed that pyramidalization occurs to relieve unfavorable torsional interactions, favoring staggering of the bonds at adjacent carbon atoms.[9b–c] Consistent with this proposal,


**Figure 9.** *syn*- and *anti*-Bicyclo[3.3.0]oct-1(5)-ene, **201**.

a pyramidalized, $C_{2v}$ *syn* geometry of bicyclo[3.3.0]oct-1(5)-ene **201** was calculated to be lower in energy than a planar, $C_{2h}$ *anti* geometry (Fig. 9).[9c,12c]

Ab initio calculations (HF/3-21G) carried out by Hrovat and Borden predicted a pyramidalization angle of 3.6° for *syn*-**201**.[12c] High-level ab initio [MP2/6-31G(d)] and DFT [B3LYP/6-31G(d)] calculations predicted pyramidalization angles of 7.9 and 5.9°, respectively, for *syn*-**201**.[70]

### 5.1. Tricyclo[3.3.*n*.0$^{3,7}$]alk-3(7)-enes and related compounds

Borden and the present authors, independently, synthesized and studied several members of a series of highly pyramidalized alkenes containing the skeleton of tricyclo-[3.3.*n*.0$^{3,7}$]alk-3(7)-ene (Fig. 10). Bicyclo[3.3.0]oct-1(5)-ene **201** can be viewed as a member of this series with $n = \infty$. It should be noted that the direction of enforced pyramidalization of the double bond in this series of tricyclic compounds is the opposite of that found in the bicyclo[3.3.0]oct-1(5)-ene moiety of *syn*-sesquinorbornene and related compounds and also opposite to that computed to be favored in bicyclo[3.3.0]oct-1(5)-ene.

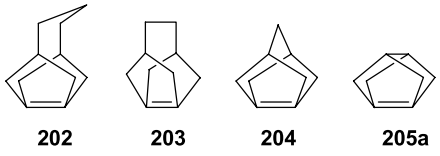



**Figure 10.** Pyramidalized alkenes containing skeleton of tricyclo-[3.3.*n*.0$^{3,7}$]alk-3(7)-ene.

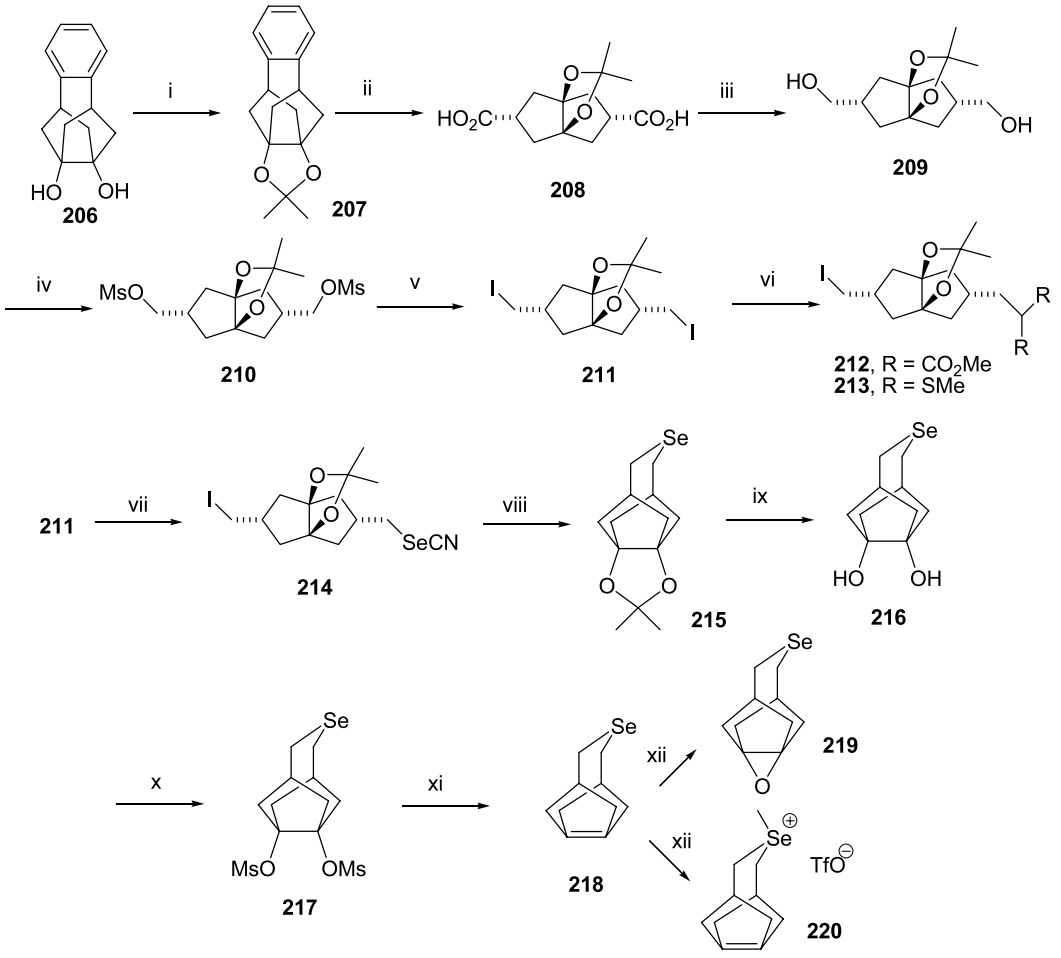
The series of tricyclo[3.3.*n*.0$^{3,7}$]alk-3(7)-enes has been revealed as an excellent benchmark for studying the effects of increasing pyramidalization in a similar framework. Several theoretical and experimental studies have been carried out in order to compare the effects of increasing pyramidalization on going from tricyclo[3.3.3.0$^{3,7}$]undec-3(7)-ene **202** to tricyclo[3.3.0.0$^{3,7}$]oct-1(5)-ene **205a**.[12c,14,70] From the results collected in Table 1, some general trends can be deduced. Theoretical calculations predict that, on going from **202** to **205a**, the pyramidalization angle increases from 28.1 to 61.9° and the carbon–carbon double bond elongates from 1.342 to 1.380 Å. On the other hand, a higher pyramidalization leads to an increase in the heat of hydrogenation and in the olefin strain energy (OSE; the amount of strain energy exceeding that of the corresponding alkane). More interestingly, as mentioned briefly in the introduction, as a consequence of the rehybridization, pyramidalized alkenes show an important decrease of the LUMO and a small increase of the HOMO energies on increasing pyramidalization, leading to smaller HOMO–LUMO gaps. As the 2p orbitals become hybridized, their overlap decreases. This probably accounts for

**Table 1**. Tricyclo[3.3.*n*.0$^{3,7}$]alk-3(7)-enes and related compounds

| | **201** | **202** | **203** | **204** | **205a** |
|---|---|---|---|---|---|
| Pyramidalization angle ($\Phi$)[a] | 5.9° | 28.1° | 42.0° | 53.7° | 61.9° |
| Carbon–carbon double bond length (Å)[a] | 1.337 | 1.342 | 1.348 | 1.362 | 1.380 |
| Heat of hydrogenation (kcal/mol)[a] | −24.8 | −40.9 | −59.4 | −75.8 | −99.1 |
| OSE (kcal/mol)[a,b] | 0.0 | 16.7 | 35.4 | 52.2 | 74.7 |
| $\Delta E_{HOMO-LUMO}$ (eV)[a] | 6.90 | 6.00 | 5.42 | 4.79 | 4.17 |
| $^{13}$C NMR chemical shift[c] | 143.9[c] (146.0)[d] | 156.1[c] (157.3)[d] | 168.6[c] | 178.2[c] | 201.2[c] |
| UV[d] | 190 nm | 217±5 nm | 245±15 nm | — | — |
| IR[d] | 1685 cm$^{-1}$ | 1611±5 cm$^{-1}$ | 1557 cm$^{-1}$ | 1496 cm$^{-1}$ | — |

[a] Calculated by B3LYP/6-31G(d).
[b] Calculated as the difference between the hydrogenation energy of each alkene and that of the reference compound bicyclo[3.3.0]oct-1(5)-ene **201**.
[c] Calculated by GIAO-MPW1PW91/6-31G(d)//B3LYP/6-31G(d).
[d] Experimental value.

some of the lengthening of the bond between these carbon atoms along the series on going from **202** to **205**. The decrease in overlap between the atomic orbitals raises the energy of the HOMO, but, since the atomic orbitals in the LUMO are out of phase, its energy is lowered, and the magnitude of the change in energy is greater than that in the HOMO. In addition, as the 2p π atomic orbitals acquire 2s character on pyramidalization, the energy of the hybrid atomic orbitals decreases, since 2s orbitals are lower in energy than 2p orbitals. This effect stabilizes both the HOMO and the LUMO. In the case of the HOMO, this latter effect works in the opposite direction of the decreased overlap between the atomic orbitals, thus accounting for the calculated behavior of the HOMO energies. In the case of the LUMO, the two effects are additive, thus explaining the large decrease in the computed LUMO energies on going along the series from **202** to **205**. This behaviour may explain the bathochromic shift and the deshielding observed in the UV and the $^{13}$C NMR spectra, respectively. Noteworthy is that Borden and co-workers have observed that the $(Ph_3P)_2Pt$ complexes of pyramidalized alkenes **202**, **203** and **204** show the opposite




**Scheme 33.** Synthesis of 10-selenatricyclo[3.3.3.0$^{3,7}$]undec-3(7)-ene **218**. (i) acetone, HCl, △, 22 h, 98%; (ii) $RuO_2$, $NaIO_4$, $CH_3CN/H_2O/CCl_4$, 24 h, 80%; (iii) $LiAlH_4$, THF, △, 24 h, 87%; (iv) MsCl, $Et_3N$, −10 °C, $CH_2Cl_2$, 76%; (v) NaI, acetone, △, 96 h, 95%; (vi) $CH_2R_2$, base; (vii) KSeCN, acetone, △, 2 h, 60%; (viii) $NaBH_4$, THF/ethanol, 40 °C, 65 h, 70%; (ix) 20% aq. acetic acid, △, 24 h, 94%; (x) MsCl, $Et_3N$, −10 °C, $CH_2Cl_2$, 30 min; (xi) Na, naphthalene, −50 °C, 90%; (xii) air; (xiii) methyl triflate.

trend, the olefinic $^{13}C$ chemical shifts moving towards higher field on increasing pyramidalization as a consequence of the increased back-donation of electron density from the HOMO of the Pt into the $\pi^*$ LUMO of the olefin.[13]

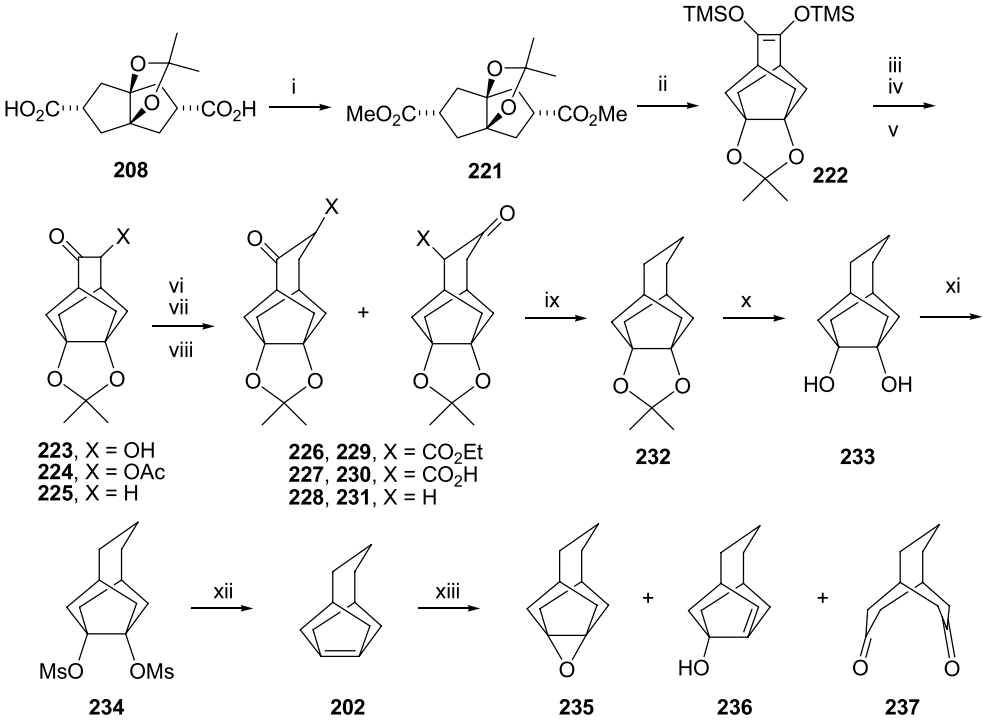
**5.1.1. Tricyclo[3.3.3.0$^{3,7}$]undec-3(7)-ene and its 10-selena derivative.** In order to synthesize the pyramidalized alkene tricyclo[3.3.0.0$^{3,7}$]undec-3(7)-ene **202**, and its heteroanalogs, Borden and co-workers prepared the diacid **208** by oxidation of the ketal **207**, easily available from pinacol **206**.[88] Conventional manipulations of **208** led to the diiodide **211**.

Reaction of **211** with the malonate ester anion and dithianyl anion gave **212** and **213**, respectively. Unfortunately, all attempts to effect ring closure in both compounds failed.[10c] Nevertheless, reaction of the diiodide **211** with sodium selenacyanate gave selenacyanate **214**, which could be transformed into **215** by reaction with $NaBH_4$. Hydrolysis of the acetonide protecting group, formation of the dimesylate **217** and reduction with sodium naphthalide gave the olefin 10-selenatricyclo[3.3.3.0$^{3,7}$]undec-3(7)-ene **218**.[88] This solid compound was stable enough to be spectroscopically investigated, but all attempts to grow crystals suitable for structure determination were thwarted by air oxidation to the corresponding epoxide **219** (Scheme 33). Notwithstanding, alkylation of **218** with methyl triflate gave the methylselenonium salt **220** that was suitable for study by X-ray crystallography.

Interestingly, the pyramidalization angles at the two double bonded carbon atoms of **220** were found to be quite different (20.3 and 12.3°), the olefinic carbon atom that is proximate to the selenium atom being less pyramidalized, probably as a consequence of the attraction between the positively charged selenium atom and the $\pi$ electrons of the double bond.[89] On the other hand, the pyramidalization angle in the parent alkene **202** is 28.1° (see below and Table 1).[10c] The higher pyramidalization found in **202** may be a reflection of the Se–C bonds in **220** being about 0.4 Å longer than the corresponding C–C bonds in **202**.

After much synthetic effort, an acyloin ring closure on the dimethyl ester **221**, followed by reductive removal of the hydroxyl group from **223**, ring expansion, hydrolysis, decarboxylation, Wolff–Kishner reduction and ketal hydrolysis gave diol **233** in 9.6% overall yield from the diacid **208**.[10c] Diol **233** was converted into dimesylate **234**, which was reduced to **202** using either sodium naphthalide or, more conveniently, sodium amalgam in ether.[10c] Unlike its lower homologues, **203**, **204** and **205**, **202** is stable to dimerization at room temperature. Although careful exclusion of air from samples of the olefin allowed it to be characterized spectroscopically, it is highly reactive towards oxygen, giving a mixture of three products, epoxide **235**, allylic alcohol **236** and diketone **237** (Scheme 34). Worthy of note is that the bridgehead double bond in **236** is torsionally strained, since it may be viewed as being *trans* in an eight-membered ring.

Both the $^1H$ and $^{13}C$ NMR spectra of **202** are temperature dependent as a consequence of the flipping of the trimethylene bridge.[90] Interestingly, the carbon–carbon double bond stretching frequency in the IR spectrum of **202** is 10 cm$^{-1}$ lower than that in its 10-selena analog **218** and the $^{13}C$ NMR chemical shift for the olefinic carbon atoms in **202** is shifted about 6.5 ppm downfield from that in **218**, consistent with the fact that the doubly bonded carbon



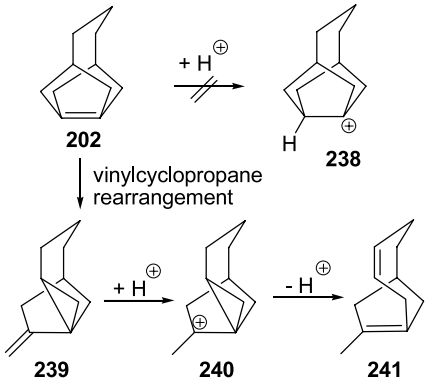

**Scheme 34.** Synthesis of tricyclo[3.3.3.0$^{3,7}$]undec-3(7)-ene **202**. (i) $CH_2N_2$, ether, 96%; (ii) Na, TMSCl, toluene, $\triangle$, 67%; (iii) methanol, $\triangle$, 84%; (iv) AcCl, dimethyl azodicarboxylate, $CH_2Cl_2$, 82%; (v) $SmI_2$, THF, 91%; (vi) $N_2CHCO_2Et$, $Et_3OBF_4$, $CH_2Cl_2$, 45%; (vii) NaOH, 98%; (viii) 1,4-dioxane, $\triangle$, 82%; (ix) $N_2H_4$, NaOH, $\triangle$, diethyleneglycol; (x) 20% aq AcOH, 24 h, $\triangle$, 81%; (xi) methyllithium, THF; then MsCl, 85%; (xii) Na(Hg), ether; (xiii) air.

atoms in **202** are calculated to have larger pyramidalization angles [28.1°, B3LYP/6-31G(d)] than those found in the salt of the selenonium analog **220** (20.3 and 12.3°) and reflected in the enhanced reactivity of **202** towards oxygen.

The photoelectron and electron transmission spectra of **202** confirmed the computational prediction that the long-wavelength UV absorptions found in pyramidalized alkenes (see Table 1, $\lambda = 217 \pm 5$ nm for **202**) are primarily due to lowering the energy of the LUMO, rather than to raising the energy of the HOMO.[10c,12c]

Cooks, Borden and co-workers have investigated the effects of alkene pyramidalization on proton affinity, using the pyramidalized olefin **202** and bicyclo[3.3.0]oct-1(5)-ene **201** as a reference compound.[91] The expectation that the relief of olefin strain energy associated with the protonation of **202** would result in a substantially greater proton affinity for **202**, compared with **201**, was confirmed by ab initio calculations and was also evident from experiments made by the kinetic method.

Interestingly, although theory and experiment agree that the strained olefin has a much higher proton affinity than **201**, the calculated difference of the proton affinity between **202** and **201** is only one half of the experimentally measured value ($23.2 \pm 2$ kcal/mol). The authors proposed that this disagreement is a consequence of the experiments involving **202** not generating carbocation **238**, but the rearranged carbocation **240**, that has been calculated to be considerably lower in energy than **238** (Scheme 35). The most stable alkene that can be formed by deprotonation of **240** is **241**. The calculated [MP4SDQ/6-31G(d)//HF/6-31G(d)] difference of 20.7 kcal/mol between the proton affinities of **241** and **201** is within the error limits of the experimental value for the difference of proton affinities ($23.2 \pm 2$ kcal/mol). This good agreement provides evidence that it is the enthalpy corresponding to formation of the cation **240**, not **238**, that is measured in the experiments starting with **202**. The rearrangement of **202** to the vinylcyclopropane **239** will be discussed in detail in the next section.




**Scheme 35.** Vinylcyclopropane rearrangement of **202** to **239** and conversion into **241**.

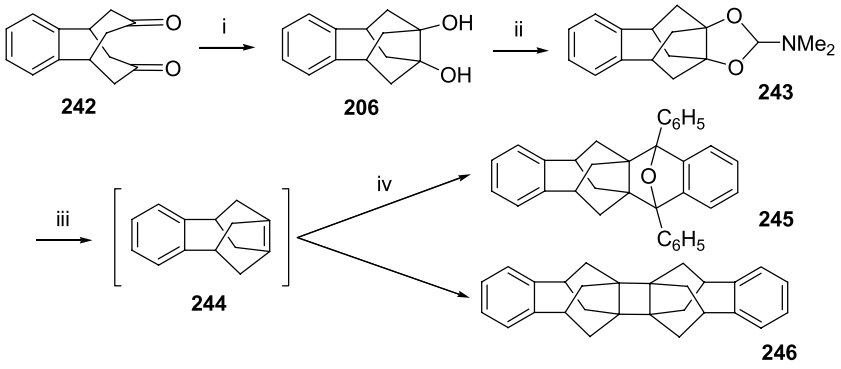
Worthy of note is that, recently, electron-energy-loss spectroscopy was applied to determine both triplet and singlet transition energies of **201** and **202** in order to investigate the effects of double bond pyramidalization on the excited states of **202**.[92]

**5.1.2. Tricyclo[3.3.2.0$^{3,7}$]dec-3(7)-ene and its benzo derivative.** The highly pyramidalized alkene **244** was the fist member of the series of tricyclo[3.3.*n*.0$^{3,7}$]alk-3(7)-enes to be prepared (Scheme 36).

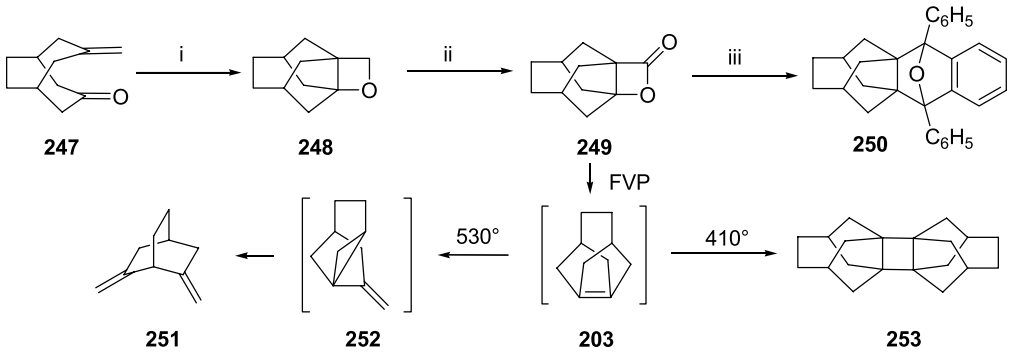
Borden, Clardy and co-workers found that the readily available diketone **242** underwent transannular ring closure to the diol **206** on reduction with zinc amalgam in aqueous HCl.[93] Pyrolysis of the dimethylaminodioxolane **243** in refluxing tetraglyme, containing 1 equiv of acetic acid and diphenylisobenzofuran gave, in 45–55% yield, the crystalline Diels–Alder adduct of **244**. In the absence of the trapping agent, the major product of the pyrolysis was the crystalline dimer **246** that could be isolated in up to 40% yield. The X-ray diffraction analysis of **246** revealed that the cyclobutane bonds joining the two halves are 1.589 Å and the other two cyclobutane bonds are 1.579 Å.[93a]

Although this synthesis was successful in demonstrating that the alkene **203** could be made, it failed to provide any useful information about the properties of this molecule. Later, Borden and co-workers synthesized β-lactone **249** from the known bicyclic ketone **247** by photochemical ring closure, followed by oxetane oxidation with catalytic $RuO_4$.

Decarboxylation of **249**, both in the gas phase and in solution, gave strong evidence for the formation of the olefin **203**. Thus, pyrolysis of **249** in refluxing tetraglyme in the




**Scheme 36.** Synthesis, chemical trapping and dimerization of 9,10-benzotricyclo[3.3.2.0$^{3,7}$]deca-3(7),9-diene **244**. (i) Zn(Hg), HCl, 92%; (ii) $(CH_3)_2NCH(OCH_3)_2$, *p*-TsOH, benzene; (iii) tetraglyme, 1 equiv acetic acid, △; (iv) 1,3-DPIBF.




**Scheme 37.** Synthesis, chemical trapping and dimerization of tricyclo[3.3.2.0$^{3,7}$]dec-3(7)-ene, **203** and rearrangement to 2,6-dimethylenebicyclo[2.2.2]octane **251**. (i) h$\nu$, benzene, 62%; (ii) $RuO_2$, $NaIO_4$, $H_2O$, $CCl_4$, 48%; (iii) tetraglyme, $\triangle$, 1,3-DPIBF, 50%.

presence of 1,3-diphenylisobenzofuran gave a crystalline Diels–Alder adduct, isolated in 50% yield (Scheme 37).[94]

FVP of **249** at 410 °C led to the isolation of a dimer of **203**. At this pyrolysis temperature, IR analysis of the pyrolysate, trapped in an argon matrix at 10 K, showed the sole products to be **203** and $CO_2$. The only product detected after warm-up was the cyclobutane dimer **253**.[95] However, as the pyrolysis temperature was raised, the formation of an isomer of **203**, spectroscopically identified as 8-methylenetricyclo-[4.2.1.0$^{1,3}$]nonane **252**, was observed. Thus, while at 440 °C the dimer constituted about 90% by weight of the product mixture and the new hydrocarbon 10%, at 530 °C the new hydrocarbon was the major product and **253** comprised only about 10% of the mixture. Interestingly, this isomer of **203** is thermally labile, undergoing rearrangement to 2,6-dimethylenebicyclo[2.2.2]octane **251**. When **249** was pyrolyzed, small amounts of **251** could be detected at 480 °C and, at 530 °C, **251** comprises about 40% of the product mixture. That **252** can act as the direct precursor of **251** was shown by partial rearrangement of the former to the latter on FVP at 500 °C. This second rearrangement relieves the substantial strain present in **252**.[95]

The reaction by which **252** is formed from the pyramidalized olefin **203** may be viewed as the reverse of the well-known vinylcyclopropane rearrangement. Usually, the equilibrium in this reaction lies far on the side of the cyclopentene product, but, in this case, as a consequence of the pyramidalization, the cyclopropane derivative is more stable. A reasonable mechanism for the rearrangement from **252** to **251** could involve cleavage of the cyclopropane ring, followed by a 1,2-vinylidene shift.[95]

Spectroscopic studies on **203** revealed a band at 1557 cm$^{-1}$ in the carbon–carbon double bond region, relatively weak in the IR, but the strongest of all the Raman bands. The shift relative to **201** (1685 cm$^{-1}$) is compatible with strong double bond pyramidalization of **203**. In addition, a broad UV band peaking at 245$\pm$5 nm, compatible with the expected lowering of the HOMO–LUMO excitation energy, was observed.[96]

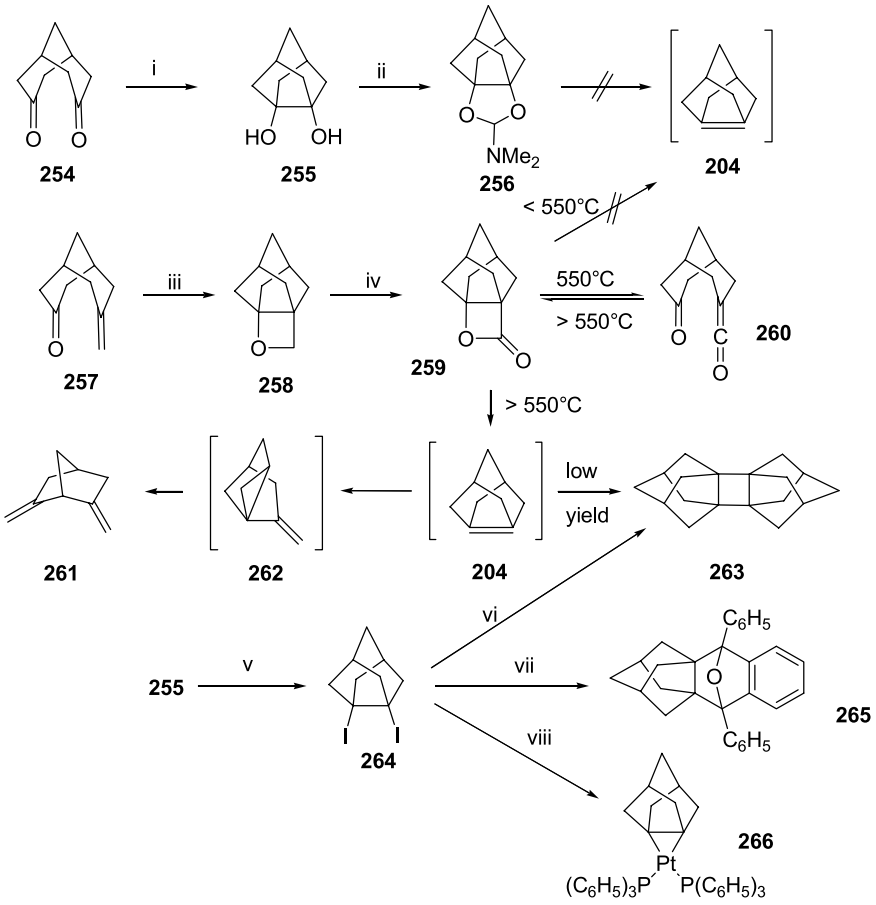
**5.1.3. Tricyclo[3.3.1.0$^{3,7}$]non-3(7)-ene.** In order to tackle the synthesis of the highly pyramidalized alkene tricyclo[3.3.1.0$^{3,7}$]non-3(7)-ene **204**, Borden and co-workers evaluated several possibilities taking into account the preceding experiences with the alkenes **202**, **203** and **244**. As previously studied in the preparation of the alkene **244**, transannular reductive ring closure of the diketone **254** yielded the pinacol **255**.[97] However, all of the known methods for the formation of olefins from diols (Corey–Winter reaction, etc.) failed to give any evidence of the formation of **204**.[98]

In a second approach, parallel to the synthesis of the alkene **203**, β-lactone **259** was prepared from the easily available methyleneketone **257**.[94] However, on pyrolysis of β-lactone **259**, once again, no evidence for the generation of **204** was found. The β-lactone survived unchanged at pyrolysis temperatures above 500 °C and, at temperatures around 550 °C, cleavage of the β-lactone did occur, but not in the desired sense, the product formed being a ketoketene **260**, rather than the alkene **204**.[99]

Since β-lactones can be prepared by cycloaddition between ketones and ketenes, Borden reasoned that the cleavage of **259** to **260** was probably reversible and that, at sufficiently high temperatures, the entropically more favorable fragmentation of the β-lactone to **204** and $CO_2$ should occur. Indeed, this did appear to happen, but, from pyrolysis at temperatures above 550 °C, only a trace amount of the dimer of **204** was isolated.[99] The major product was identified as 2,6-dimethylenenorbornane **261**, analogous to the previously isolated **251**.[95]

Finally, Borden and co-workers succeeded in preparing the highly pyramidalized alkene **204** from the diiodide **264**, in turn available from the known pinacol **255**. When the diiodide **264** was treated with butyllithium in the presence of 1,3-diphenylisobenzofuran, the Diels–Alder adduct **265** was isolated in 90% yield. When the diene was omitted from the reaction, the [2+2] dimer of **204**, **263**, was isolated in almost quantitative yield (Scheme 38).[99]

Reductive dehalogenation in the gas phase of **264** with potassium vapor allowed the matrix isolation of the olefin. A weak band at 1496 cm$^{-1}$ in the recorded IR spectrum of **204** was assigned to the stretching mode of the highly pyramidalized double bond in **204**. This absorption is about 60 cm$^{-1}$ lower than that of the corresponding stretching frequency in **203** and about 185 cm$^{-1}$ lower than the frequencies for the double bond stretch in **201** and in tetramethylethylene. Thus, pyramidalization leads to a

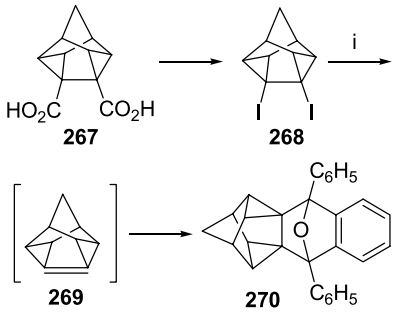



**Scheme 38.** Synthesis, chemical trapping and dimerization of tricyclo[3.3.1.0$^{3,7}$]non-3(7)-ene **204** and its rearrangement to 2,6-dimethylenebicyclo[2.2.1]-heptane **261**. (i) Zn(Hg), HCl; (ii) $(CH_3)_2NCH(OCH_3)_2$; (iii) h$\nu$, benzene, 45%; (iv) $RuO_2$, $NaIO_4$, $H_2O$, $CCl_4$, 50%; (v) $H_3PO_4$, NaI, 40%; (vi) *n*-butyllithium, −78 °C, THF, quantitative yield; (vii) *n*-butyllithium, −78 °C, 1,3-DPIBF, 90%; (viii) Na(Hg), $[(C_6H_5)_3P]_2Pt(CH_2CH_2)$.

lowering of the double bond stretching frequency. Unfortunately, the presence of metal atoms in the matrix prevented the UV spectrum of **204** from being obtained.[100]

On the other hand, reductive dehalogenation with sodium amalgam in the presence of the $[(C_6H_5)_3P]_2Pt$ complex of ethylene resulted in the formation of **266**, the stable $[(C_6H_5)_3P]_2Pt$ complex of **204**.[13a,c]

Very interestingly, Forman and co-workers have communicated the generation and trapping of pentacyclo-[4.3.0.0$^{2,4}$.0$^{3,8}$.0$^{5,7}$]non-4(5)-ene **269**, a compound related to **204** (Scheme 39).[101] Iododecarboxylation of diacid **267** led to the diiodide **268** that, upon dehalogenation with




**Scheme 39.** Generation and trapping of highly pyramidalized alkene **269**. (i) *n*-butyllithium, 1,3-DPIBF.

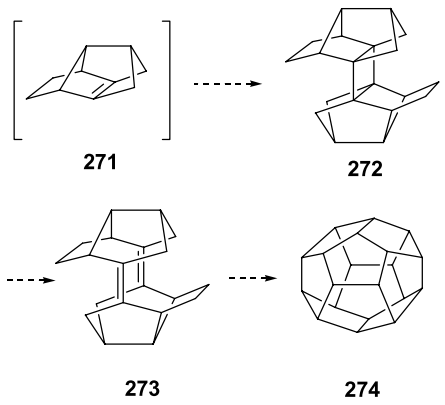
*n*-butyllithium, generated **269** that, in the presence of 1,3-DPIBF, underwent Diels–Alder reaction to the adduct **270**.[101]

We have carried out B3LYP/6-31G(d) calculations on **269** and found a pyramidalization angle, $\Phi = 64.2°$, higher than calculated for **204** ($\Phi = 53.7°$), and even greater than that for **205a** ($\Phi = 61.9°$).[61b] Taking into account that **205a** has been dimerized, it seems reasonable that suitable experimental conditions could lead to the dimerization of **269**.

**5.1.4. Tricyclo[3.3.0.0$^{3,7}$]oct-1(5)-ene and related compounds.** Tricyclo[3.3.0.0$^{3,7}$]oct-1(5)-ene, **205**, the consummate member of the homologous series of tricyclo-[3.3.*n*.0$^{3,7}$]alk-1(5)-enes, was synthesized by our group in 1996.

While Borden's work in this area was mainly conceived from the very beginning with the purpose of experimentally and theoretically studying pyramidalization,[9a] our entry into this area of research, that has now spanned two decades, started from a very different point of view.

More than 20 years ago, the senior author of this review conceived a convergent approach to dodecahedrane that relied on the dimerization of the highly pyramidalized alkene **271**, an ethano derivative of **205**. It was believed that the dimerization of **271** would lead, mainly, to the less




**Scheme 40.** Dimerization of highly pyramidalized alkene **271** as a possible convergent approach to dodecahedrane.

crowded *anti*-dimer **272**. Thermal retrocycloaddition of **272** would give tetrasecododecahedradiene **273**, with the hope that it might be converted into dodecahedrane **274** by catalyzed hydrogenation/dehydrogenation procedures (Scheme 40).[102,103]

Since our first synthetic approaches to a precursor of **271** were not fully successful[103] and, taking into account that ab initio and DFT calculations showed (Table 2) that **271** has very similar structural and energetic parameters to **205**,[70] we first decided to tackle the synthesis of tricyclo-[3.3.0.0$^{3,7}$]oct-1(5)-ene **205a** and its 3,7-dimethyl derivative **205b** as model compounds for studying the best dimerization conditions.

After some unsuccessful attempts to develop new routes to the tricyclo[3.3.0.0$^{3,7}$]octane (bisnoradamantane) skeleton,[104] in 1988 we finally accomplished a new entry into this system (Scheme 41).

Starting from the very readily available *cis*-bicyclo-[3.3.0]octane-3,7-diones **275a** and **275b**, a short sequence furnished dimethyl tricyclo[3.3.0.0$^{3,7}$]octane-1,5-dicarboxylate **279a** and its 3,7-dimethyl derivative **279b** (Scheme 41).

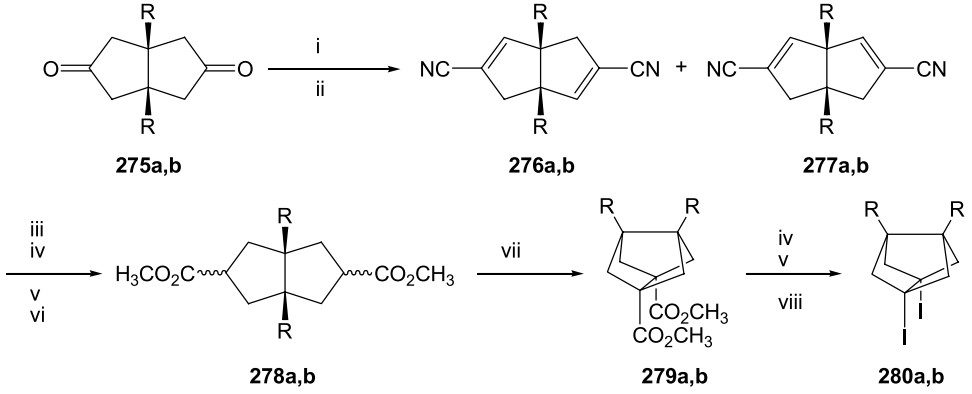
The key step of these syntheses implies the iodine oxidation of the bis-enolate derived from the corresponding dimethyl *cis*-bicyclo[3.3.0]octane-3,7-dicarboxylates **278a**,**b**.[105] From the diesters **279a**,**b**, saponification and iododecarboxylation led to the diiodides **280a**,**b**.

Reaction of **280b** with *t*-butyllithium in THF at −78 °C in the presence of 1,3-diphenylisobenzofuran allowed us to isolate the corresponding Diels–Alder adduct **281b** in 75% yield. Similarly, when the reaction was carried out in the presence of the diene **282**, the adduct **283** was obtained in 67% yield, for which an X-ray diffraction analysis was performed.

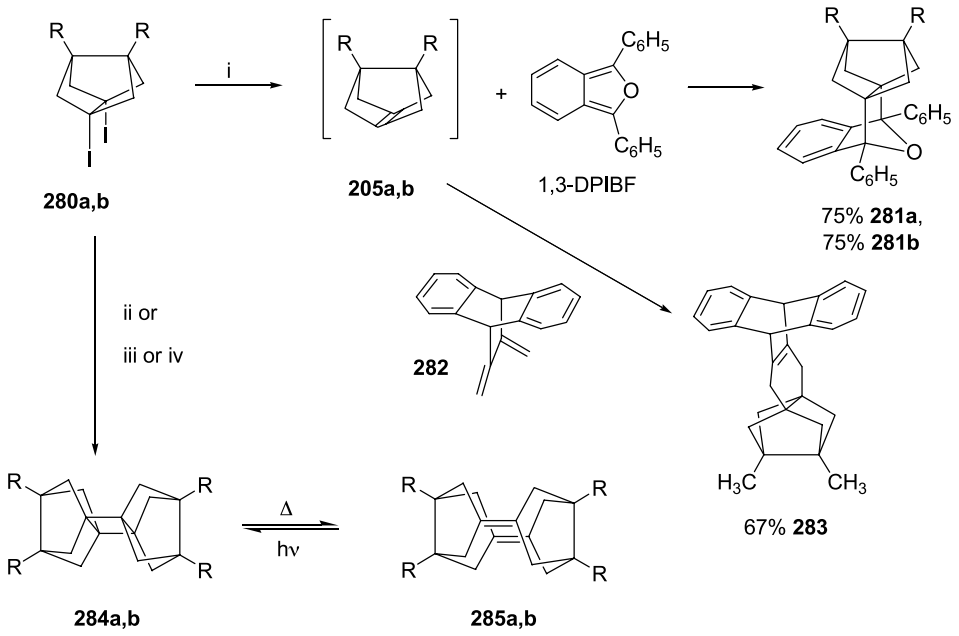
**Table 2**. Tricyclo[3.3.0.0$^{3,7}$]oct-1(5)-ene **205a** and related compounds.

| | **205a**[a] | **205b**[a] | **205c**[b] | **205d**[b] | **205e**[b] | **271**[c] | **343**[d] | **356**[e] | **368**[f] |
|---|---|---|---|---|---|---|---|---|---|
| Pyramidalization angle ($\Phi$)[g] | 61.9° | 61.7° | 62.6° | 61.7° | 60.4° | 62.3° | 62.4° | 62.4° | 62.6° |
| Carbon–carbon double bond length (Å)[g] | 1.380 | 1.380 | 1.394 | 1.381 | 1.393 | 1.381 | 1.382 | 1.381 | 1.336 |
| Heat of hydrogenation (kcal/mol)[g] | −99.1 | −96.5 | −86.1 | −96.8 | −88.8 | −97.8 | −96.3 | −96.1 | −96.1 |
| OSE (kcal/mol)[g,h] | 74.7 | 72.2 | 62.4 | 72.9 | 64.6 | 73.4 | 73.4 | 72.3 | 72.5 |
| $\Delta E_{HOMO-LUMO}$ (eV)[g] | 4.17 | 4.21 | 4.74 | 3.79 | 4.64 | 4.18 | 4.19 | 4.07 | 4.18 |
| $^{13}$C NMR chemical shift[i] | 201.2 | 192.5 | 176.9/177.9 | 191.4 | 180.2/186.9 | 205.7 | 209.6 | 198.2 | 206.1 |

[a] See Scheme 42.
[b] See Fig. 11.
[c] See Scheme 40.
[d] See Scheme 50.
[e] See Scheme 52.
[f] See Scheme 54.
[g] Calculated by B3LYP/6-31G(d).
[h] Calculated as the difference between the hydrogenation energy of each alkene and that of the reference compound bicyclo[3.3.0]oct-1(5)-ene **201**.
[i] Calculated by GIAO-MPW1PW91/6-31G(d)//B3LYP/6-31G(d).

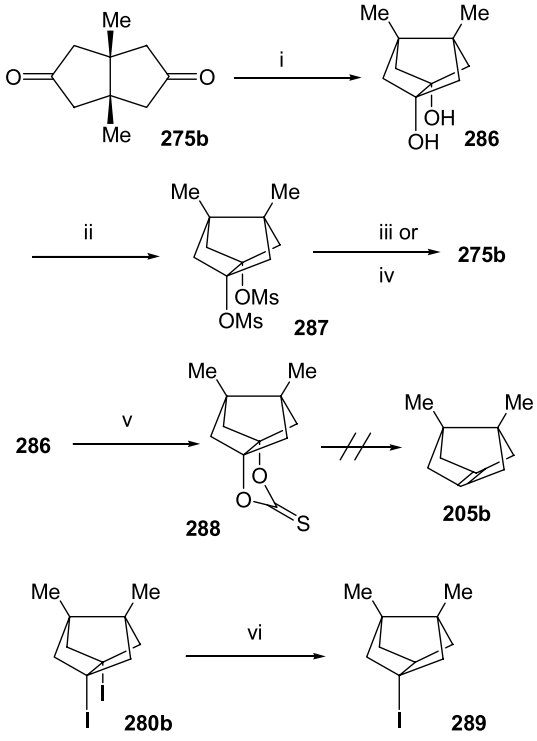



**Scheme 41.** Synthesis of diiodides **280a**,**b**. a, R=H; b, R=$CH_3$. (i) KCN, $H_2SO_4$; (ii) $POCl_3$ or $SOCl_2$, pyridine, △, 36% for **276a** and **277a**; 47% for **276b** and **277b**; (iii) $H_2$, Pd/C; (iv) KOH, methanol; (v) $H_3O^+$; (vi) methanol, $H_2SO_4$, △, 64% overall for **278a**; 72% overall for **278b**; (vii) LDA, THF, −10 °C, then $I_2$, −78 °C, 36% for **279a**, 47% for **279b**; (viii) IBDA, $I_2$, h$\nu$, benzene, 35% overall for **280a**, 78% overall for **280b**.




**Scheme 42.** Synthesis, chemical trapping and dimerization of highly pyramidalized alkenes **205a**,**b**. a, R=H; b, R=$CH_3$. (i) *t*-butyllithium, THF, −78 °C, 1,3-DPIBF or **282**; (ii) *t*-butyllithium, THF, −78 °C; (iii) Na–K, THF, rt; (iv) molten Na, 1,4-dioxane, △.

While the reaction of **280b** with *t*-butyllithium in THF at −78 °C, in the absence of a trapping agent, led to a complex mixture containing minor amounts of the cyclobutane dimer **284b**, reaction of **280b** with a large excess of molten sodium in boiling 1,4-dioxane gave the diene **285b** in 77% yield. Probably, the initially formed dimer **284b** was completely transformed into **285b** under these reaction conditions.[106]




**Scheme 43.** Unsuccessful attempts to generate **205b** and formation of **289** under laser flash photolysis experiments. (i) $TiCl_4$, Zn, pyridine, 1,4-dioxane, △, 18 h, 96%; (ii) MsCl, $Et_3N$, $CH_2Cl_2$, 65%; (iii) Na(Hg), THF, rt; (iv) molten Na, 1,4-dioxane, △; (v) $CSCl_2$, DMAP, $CH_2Cl_2$, 52%; (vi) laser flash photolysis.

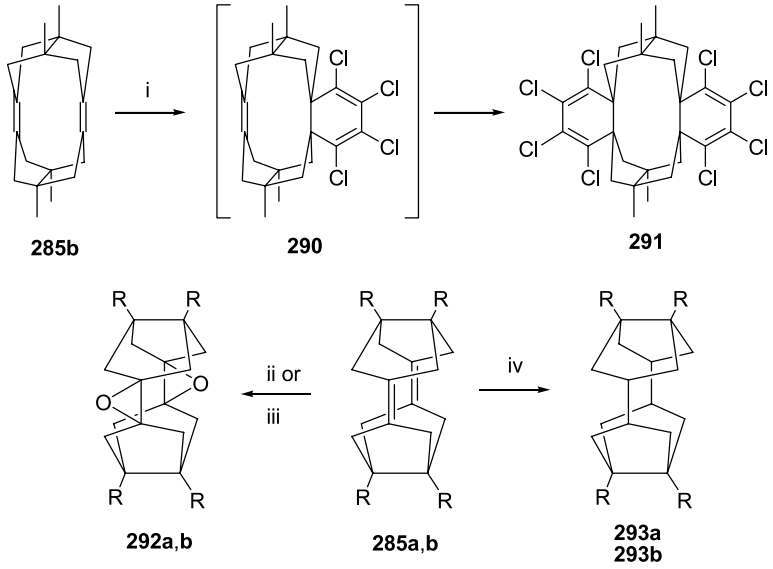
The intermediacy of **284b** was further corroborated when it was obtained by the deiodination of **280b** with sodium–potassium alloy at room temperature or, alternatively, by [2+2] photocyclization of the diene **285b** (Scheme 42).[107]

Not surprisingly, alternative approaches to generate the highly pyramidalized alkene **205b** met with failure (Scheme 43). Reaction of the dimesylate **287**, synthesized from the easily available pinacol **286**,[93b] with sodium amalgam at room temperature or with molten sodium in boiling 1,4-dioxane gave the diketone **275b** as the sole identified product. In addition, the Corey–Winter attempted reaction on **288** gave only **286**.[108]

Although we successfully generated the highly pyramidalized alkene **205b**, all our efforts directed towards the direct observation of this alkene were futile. For example, laser flash photolysis experiments directed towards the UV characterization of alkene **205b** led to compound **289**, the alkene not being observed (Scheme 43).[109] On the other hand, several attempts to isolate the $[(C_6H_5)_3P]_2Pt$ complex of **205b** by reductive dehalogenation of **280b** with sodium amalgam in the presence of the $[(C_6H_5)_3P]_2Pt$ complex of ethylene were fruitless.[108]

As for its 3,7-dimethyl derivative, the reaction of **280a** with *t*-butyllithium in the presence of 1,3-diphenylisobenzofuran gave the Diels–Alder adduct **281a**, and the reaction of **280a** with sodium in boiling dioxane gave the diene **285a** in good yield. However, irradiation of a sample of **285a** did not give pure **284a**, and an 8:2 mixture of **284a** and **285a** was spectroscopically observed instead.[110]

The X-ray diffraction analysis of the thermally unstable **284b** at −30 °C showed the cyclobutane ring to be highly rectangular, with large central and short lateral bonds. Additionally, the C4–C5 and C10–C11 bonds in **284b** and




**Scheme 44.** Reactivity of dienes **285a**,**b**. a, R=H; b, R=$CH_3$. (i) tetrachlorothiophene-*S*,*S*-dioxide, toluene, △, 12 h, 81%; (ii) *m*-CPBA, >95%; (iii) dimethyldioxirane, >95%; (iv) hydrazine, $H_2O_2$, $H_2O$, ethanol, THF, rt, 95% **293a**, 88% **293b**.

diene **285b** are very large (1.649 and 1.622 Å, for **284b** and **285b**, respectively).[107]

The thermal retrocycloaddition of **284a**,**b** to **285a**,**b** was theoretically (MM2 and ab initio methods) and, in the case of **284b**, experimentally (DSC and $^1$H NMR spectroscopy) studied. The calculated enthalpy differences for the opening of the unsubstituted cyclobutane derivative **284a** to the diene **285a** are irrespective of the method, consistently 3–4 kcal/mol larger in absolute value than that calculated for the conversion of **284b** into **285b**. This is likely to be related to the relative destabilization of diene **285b**, due to overcrowding around the C4–C5 (C10–C11) bonds. The relative destabilization of **284b** in passing to **285b**, as compared with the corresponding conversion of **284a** into **285a**, must also be apparent in their transition states, which could explain the greater kinetic stability of **284b**, as compared with **284a**.[107,110] The UV spectrum of dienes **285a**,**b** show maximum absorption bands at $\lambda$=207 and 205 nm, respectively, that allows their conversion into the corresponding cyclobutane isomers by direct irradiation with UV light in the absence of any photosensitizer.[107,110,111] This might be due to the pyramidalization of the double bonds, as observed in the X-ray diffraction analysis of diene **285b** ($\Phi$=13.0°) and in theoretical calculations on both **285a** ($\Phi$=10.6, 11.7 and 12.4° values for MM2, MM3 and HF/3-21G, respectively) and **285b** ($\Phi$=9.8, 11.2 and 11.6° values for MM2, MM3 and HF/3-21G, respectively), and to through-bond and/or through-space π–π interactions, as was later found by Gleiter and co-workers.[112]

Although pyramidalized alkenes react easily with electron-rich dienes (see, for example, Section 3.2), the slightly pyramidalized diene **285b** failed to react with cyclopentadiene and 11,12-dimethylene-9,10-dihydro-9,10-ethanoanthracene **282**, even under drastic conditions, although it did react with the electron-poor diene, tetrachlorothiophene-*S*,*S*-dioxide, to give **291** in 81% yield, probably through the intermediacy of **290**.[111]

It is well known that, in general, the strain energy (SE) of a cycloalkene is higher than that of the corresponding cycloalkane, that is, a cycloalkene usually has a positive olefin strain energy (OSE). However, Schleyer and, later, other authors, found that several cycloalkenes showed negative OSE values due to an increase in vicinal and transannular hydrogen interactions in the cycloalkane.[113] These alkenes, dubbed 'hyperstable alkenes', are characterized by their heats of hydrogenation, lower than usual, and their reluctance to be hydrogenated, even under drastic conditions, although they can be reduced with diimide or epoxidized.

Theoretical (MM2) and experimental studies showed that the dienes **285a**,**b** and their monohydrogenation products are hyperstable alkenes. Both dienes were reduced with diimide to **293a**,**b** and epoxidized with MCPBA or dimethyldioxirane to **292a**,**b** in very high yields (Scheme 44).

Reaction of **285b** with some electrophilic reagents, such as bromine or iodine, gave complex mixture of compounds, from which no transannular reaction products were found,[111] as had been observed in related examples.[10a,24]

While our work on **205a**,**b** was mainly a consequence of our interest in studying model compounds for the dimerization of **271**, our much more recent interest in **205c**,**d**,**e** originated from a very different perspective (Fig. 11).[114]

We planned the synthesis of **205c**,**d**,**e** in order to investigate the compatibility of some functional groups with the harsh conditions needed for highly pyramidalized alkene generation. On the other hand, the hypothetical dimers of these new alkenes could be interesting starting compounds for the synthesis of other polycyclic hydrocarbons, such as **294**. Tetraene **294**, with its four pyramidalized carbon–carbon double bonds, is a very interesting target. In addition to the pyramidalization-related issues ($\Phi$=26.3° and $\Phi'$=34.1°, as calculated by B3LYP/6-31G(d)), **294** has two pairs of

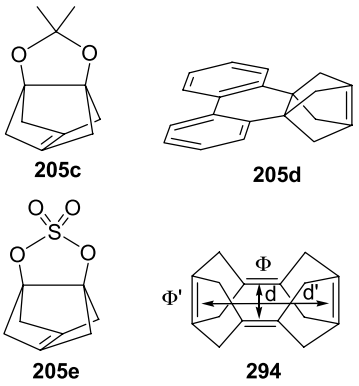
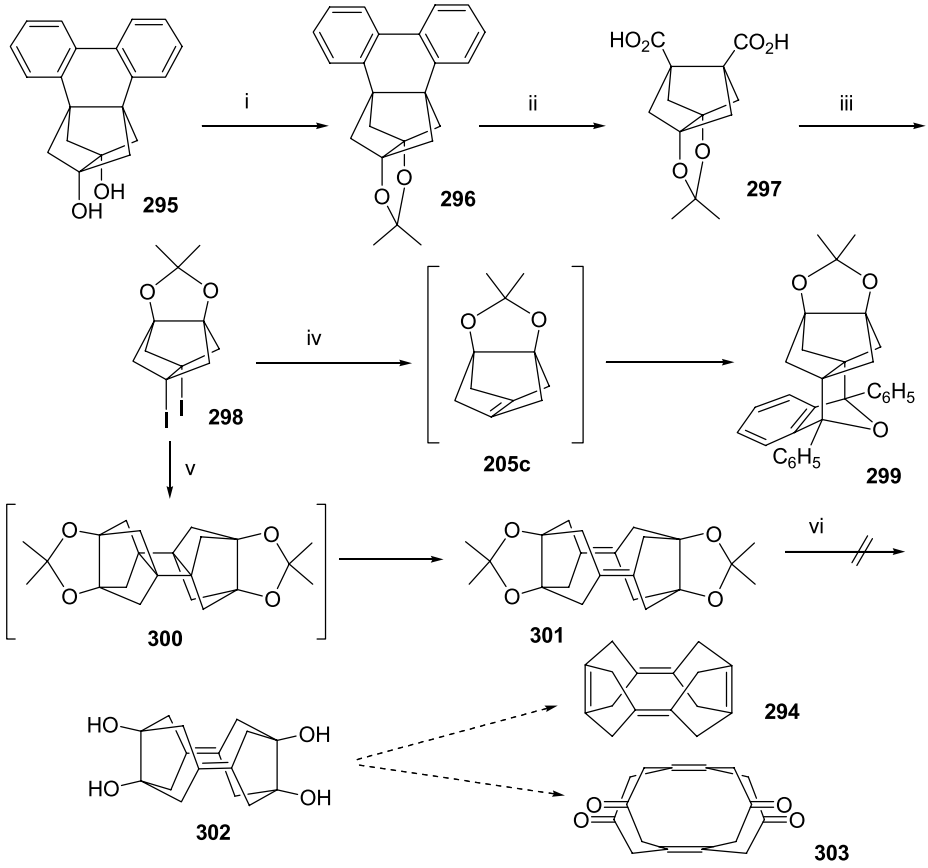



**Figure 11.** Pyramidalized alkenes **205c**,**d**,**e** and tetraene **294**.

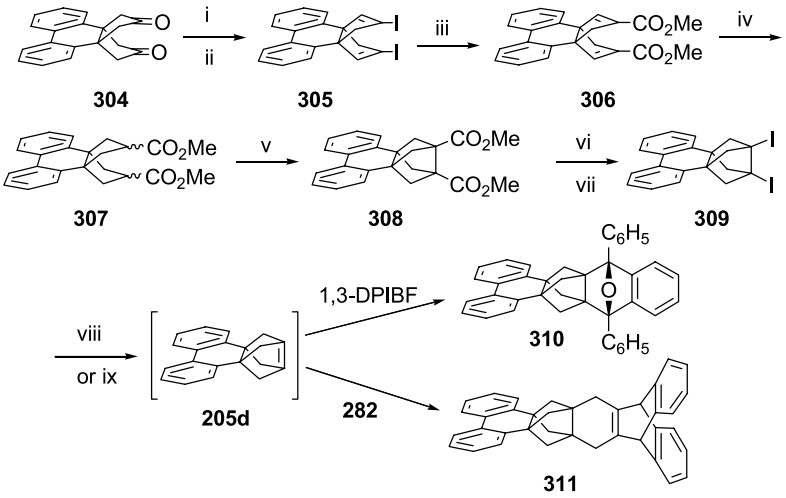
proximal ($d=3.619$ Å, $d'=3.789$ Å), parallel double bonds, and π–π orbital interactions are therefore expected to occur.[61b]

In 2002, we reported a new functionalized highly pyramidalized alkene **205c**.[114a] Alkene **205c** was generated as usual from the corresponding diiodo derivative **298**, which was prepared from the known[93b] pinacol **295** by an interesting sequence which makes use of a 2,2′-biphenylene substructure as two latent carboxyl groups (Scheme 45). Pinacol **295** was transformed into the corresponding acetonide by standard procedures and conversion into the diacid **297** was carried out in 50–60% yield by $RuO_4$ oxidation using a catalytic amount of $RuCl_3\cdot 3H_2O$ as the ruthenium-source and bleach (NaOCl) as the stoichiometric oxidant in a two-phase system working in a closed vessel. Iododecarboxylation of **297** by the standard procedure gave **298** in 49% yield. Reaction of **298** with *t*-BuLi in the presence of 1,3-diphenylisobenzofuran (1,3-DPIBF) gave the corresponding Diels–Alder adduct **299** in 61% yield.

As expected, reaction of the diiodide **298** with molten sodium in boiling 1,4-dioxane gave diene **301** in 63% yield. No cyclobutane dimer **300** was detected. Neither was **300** detected after irradiating **301** in cyclohexane, as was the case for the dienes **285a**,**b**. MM2 calculations gave an enthalpy of reaction for the transformation of **300** to **301** of −57 kcal/mol. This value is clearly higher than the corresponding values for the conversions of the parent **285a** (−46 kcal/mol) and the tetramethyl derivative **285b** (−43.2 kcal/mol). As before, the greater relative thermal stability of diene **301** must be apparent in the corresponding transition state, thus making faster the conversion of **300** into **301**. Diene **301**, like the related **285a**,**b**, is hyperstable. Hydrolysis of **301** should give the tetrol **302**, from which very interesting compounds such as the tetraene **294** or diene tetrone **303** could be obtained. However, we were not able to hydrolyze **301**. Probably, the formation of carbocations combined with the presence of the diene system, make compounds **301** and **302** very acid sensitive. Currently, we are working on the synthesis of analogues of



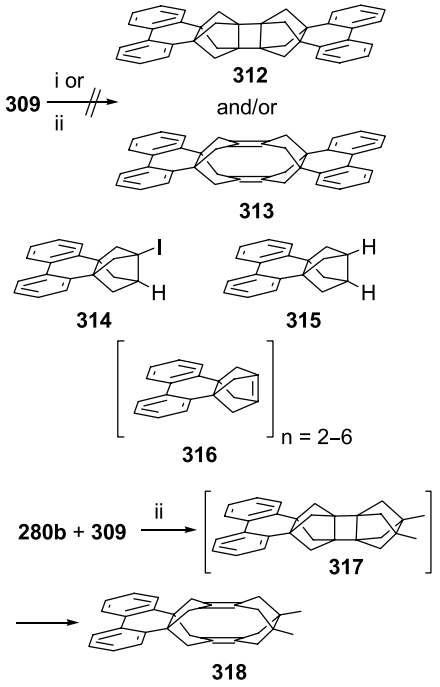

**Scheme 45.** Synthesis, chemical trapping and dimerization of highly pyramidalized alkene **205c**. (i) 2,2-Dimethoxypropane, *p*-TsOH, 4 Å MS, $CHCl_3$, reflux, 3 h, 69%; (ii) $RuCl_3\cdot H_2O$, NaOCl, $CH_3CN/CH_2Cl_2/H_2O$, rt, 60 h, 68%; (iii) $I_2$, iodosobenzene diacetate, $CH_2Cl_2$, hν, 4 h, 49%; (iv) *t*-BuLi, 1,3-diphenylisobenzofuran, −78 °C, 30 min, 61%; (v) Na, 1,4-dioxane, reflux, 4 h, 63%; (vi) $H_3O^+$.




**Scheme 46.** Synthesis and chemical trapping of highly pyramidalized alkene **205d**. (i) $NH_2NH_2 \cdot H_2O$, $Et_3N$, ethanol, 70 °C; (ii) tetramethylguanidine, $I_2$, ether, −10 °C; (iii) $Pd(OAc)_2$, $P(C_6H_5)_3$, $Et_3N$, CO, MeOH, 70 °C; (iv) $H_2$, Pd/C, ethyl acetate, MeOH; (v) hexamethyldisilazane (HMDS), *n*-butyllithium, THF; then $I_2$, −78 °C; (vi) KOH/MeOH, then 10% HCl; (vii) IBDA, $I_2$, $CH_3CN$, h$\nu$; (viii) *t*-butyllithium, THF, −78 °C; (ix) Na(Hg) 0.45%, 1,4-dioxane, rt.

**301**, having more labile protecting groups in order to provide access to the tetrol **302**.[114a]

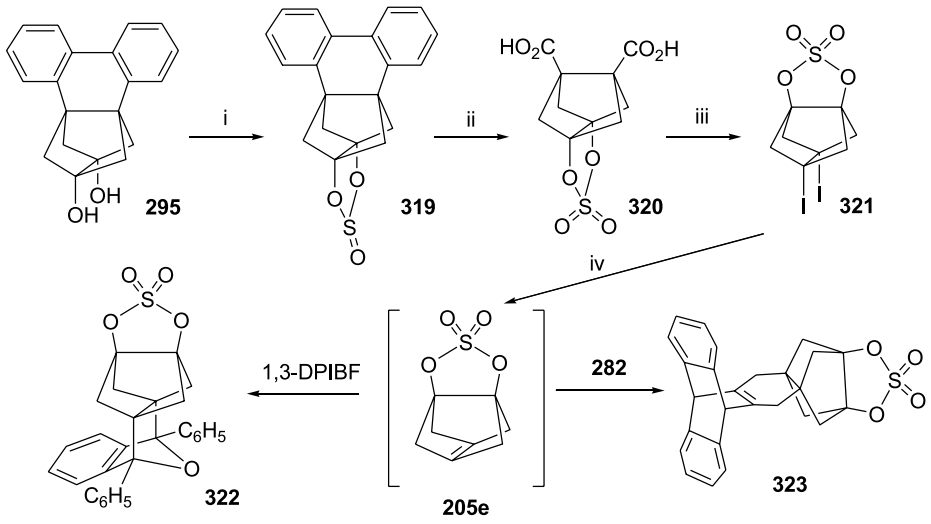
Very recently, we have prepared the highly pyramidalized alkene **205d**, that contains a 2,2′-biphenylene unit (Scheme 46).[114b,c] The synthesis of the diester **308** involves conversion of diketone **304** into bis-vinyl iodide **305** using Barton's procedure, followed by palladium-mediated methoxycarbonylation, hydrogenation and cyclization to **308** using our standard procedure. Hydrolysis of **308**, followed by iododecarboxylation, gave the diiodide **309** in 18% overall yield from diketone **304**. As expected, the reaction of **309** with *t*-BuLi in the presence of 1,3-diphenylisobenzofuran (DPIBF) or 11,12-dimethylene-9,10-dihydro-9,10-ethanoanthracene **282** gave the corresponding Diels–Alder adducts **310** and **311** in 68 and 75% yield, respectively. Worthy of note is that these adducts could also be synthesized, in very similar yields, through reaction of diiodide **309** with 0.45% Na(Hg) at room temperature, conditions that we had not used before for the trapping of highly pyramidalized alkenes (Scheme 46).




**Scheme 47.** Synthesis and chemical trapping of highly pyramidalized alkene **205d**. (i) *t*-butyllithium, THF, −78 °C; (ii) Na, 1,4-dioxane, △, 17% yield of **318**.

Contrary to our expectations, the reaction of **309** with *t*-BuLi at low temperature did not lead to the expected dimers **312** or **313**. The reaction of **309** with Na(Hg) at room temperature or with molten sodium led to complex mixtures of products, where no dimers **312** or **313** were observed. From these mixtures, the reduction products **314** and **315** were isolated and fully characterized. Additionally, in the reaction with molten sodium, some oligomers of **205d** were observed (MALDI-TOF), but the structure of **316** for $n=2$ does not seem ($^1H$ and $^{13}C$ NMR) to be **312** or **313**. So far, we do not have an explanation for the failure in the dimerization of **205d**, because, as proven by the isolation of Diels–Alder adducts **312** and **313**, it seems that the formation of the highly pyramidalized **205d** does indeed occur. The formation of **205d** was further corroborated when a mixture of the diiodides **280b** and **309** was reacted with molten sodium in boiling 1,4-dioxane, the diene **318** being isolated in low yield (Scheme 47). B3LYP/6-31G(d) calculations showed that the HOMO/LUMO energy gap on alkene **205d** is lower than in the related alkenes **205a** and **205b** (see Table 2). This could facilitate the transfer of one electron from the sodium to the alkene to give a radical anion unable to dimerize, although able to give the reduction product **315** or to polymerize.[114b]

We have also succeeded in generating **205e**. Reaction of **295** with thionyl chloride, followed by oxidation of the aromatic rings with concomitant transformation of the sulfite to sulfate, led to **320**. Iododecarboxylation of **320** in refluxing acetonitrile gave **321** (Scheme 48).[114b] Unfortunately, although we were able to generate and trap the highly pyramidalized alkene **205e** in low yields (29 and 16% for **322** and **323**, respectively), all our efforts directed to the dimerization of **205e** have been futile. Reaction of **321** with




**Scheme 48.** Synthesis and chemical trapping of highly pyramidalized alkene **205e**. (i) $Cl_2SO/Et_3N$, $CH_2Cl_2$; (ii) $RuCl_3 \cdot H_2O$, NaClO, $CH_3CN/CH_2Cl_2/H_2O$, 38% from **295**; (iii) IBDA, $I_2$, h$\nu$, $CH_3CN$, 34%; (iv) diene, *t*-BuLi, THF, −78 °C; 29% **322**; 16% **323**.

an excess of molten sodium in boiling 1,4-dioxane, with Na(Hg) at room temperature or with *t*-butyllithium at −78 °C always gave very complex mixtures of products, where no dimers were found. The formation of these mixtures and the low yields of the trapping products seem to indicate that the sulfate group is not compatible with the harsh conditions employed. On the other hand, a 1,3-elimination instead of the expected 1,2-elimination can not be ruled out (Scheme 48).

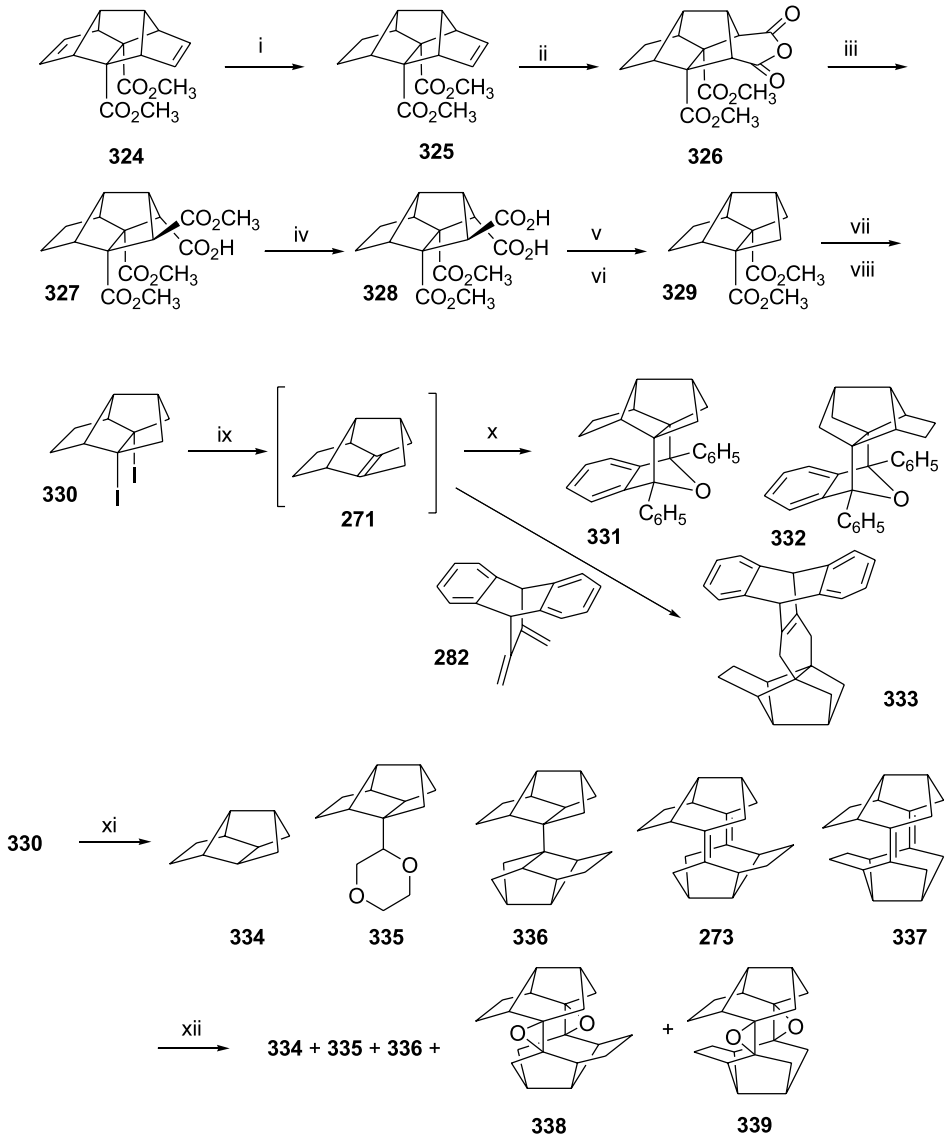
As we have already pointed out, our interest in this area arose from our aforementioned convergent approach to dodecahedrane (Scheme 40). With a reliable method to generate highly pyramidalized alkenes in hand, in 1998, we synthesized 7,8-diiodotetracyclo[5.2.1.$0^{2,6}$.$0^{3,8}$]decane **329** from the easily available diester **324**.[115] Monohydrogenation of the diene **324**, oxidation, conversion of **326** into the triester-acid **327**, selective hydrolysis of the less hindered ester, Barton's decarboxylation, hydrolysis and iododecarboxylation afforded the diiodide **330** (Scheme 49).[116]

Reaction of **330** with *t*-butyllithium at −78 °C in the presence of **282** gave the expected Diels–Alder adduct **333** in 48% yield. When a similar reaction was carried out in the presence of 1,3-diphenylisobenzofuran, a nearly 1:1 mixture of the two stereoisomeric adducts **331** and **332**, was obtained in 77% yield. To our dismay, the long-awaited dimerization of alkene **271** was not as clean as the dimerization of the 'model' compounds, **205a**,**b**. Thus, the reaction of **330** with molten sodium in boiling dioxane gave a mixture of **334**, **335**, **336** and two products, in a ratio close to 1:1, the molecular mass of which corresponded to dimers of **271**. These two isomers, probably dienes **273** and **337**, could not be separated. Epoxidation of the above mixture led to a new mixture of compounds from which a mixture of epoxides **338** and **339** was isolated in a very low overall yield (14%).[70]

For a long time, we considered that dimerization of alkene **271** would give mainly the *anti*-dimer **272**, from which the diene dimer **273**, a tetrasecododecahedradiene, could be formed (Scheme 40). Our experimental results showed that this hypothesis was not true, probably because the highly strained compound **271** is so reactive that it does not discriminate among the transition states leading to the *syn*- and *anti*-cyclobutane dimers, in spite of the great expected steric differences. Another possible explanation, according to Eaton,[117] may be that dimerization of highly pyramidalized alkenes takes place via diradical intermediates, which may explain not only the lack of selectivity, but also the formation of partially hydrogenated dimers. In addition, according to the low-energy LUMO predicted by ab initio calculations on highly pyramidalized alkenes, under the conditions used the formation of radical anions by electron transfer from sodium to the alkene **271** has to be taken into account. This may explain the formation of the dihydrodimer **336** and the reduction product **334**. Finally, the formation of **335** can be easily explained taking into account the diradical character of **271**, which was calculated to be about 11%.[70]

In 1992, previous to our work with **205a**,**b**, Borden and Paquette succeeded in generating and trapping **343**, a bis(ethano) derivative of tricyclo[3.3.0.$0^{3,7}$]oct-1(5)-ene.[118] In addition to being a derivative of **205a**, alkene **343** is very interesting because it can be regarded as a dehydro derivative of *syn*-sesquinorbornene, in which the additional carbon–carbon bond in **343** enforces pyramidalization in the opposite sense to that found in the latter hydrocarbon (see Section 4.1). Theoretical calculations on this compound predicted very similar geometries for the double bonds in **205** and **343** and OSEs and heats of hydrogenation that differ by only 3 kcal/mol (see Table 2).[70]

Starting from the diester **324**,[115] double bond hydrogenation, hydrolysis and halodecarboxylation led to the dibromide **341** and diiodide **342**. Reaction of **342** with an excess of *n*-butyllithium in THF at −78 °C in the presence of 1,3-diphenylisobenzofuran led to the Diels–Alder adduct **344**, providing evidence for the formation of **343**. Treatment of either **341** or **342** with excess *t*-butyllithium afforded two volatile products, the reduced hydrocarbon **345** and the




**Scheme 49.** Synthesis, chemical trapping and dimerization of **271**. (i) $H_2$, Pd/C, methanol; (ii) $KMnO_4$, 0 °C, $Bu_4NBr$, water/benzene; (iii) MeONa, methanol; (iv) KOH, methanol, −40 °C; (v) 2,2′-dithiobispyridine-1,1′-dioxide, *n*-$Bu_3P$; (vi) thiophenol, h$\nu$; (vii) KOH, water, methanol; (viii) IBDA, $I_2$, benzene, h$\nu$; (ix) *t*-BuLi, −78 °C, THF; (x) 1,3-DPIBF; (xi) Na, 1,4-dioxane, reflux; (xii) DMD, acetone, rt.

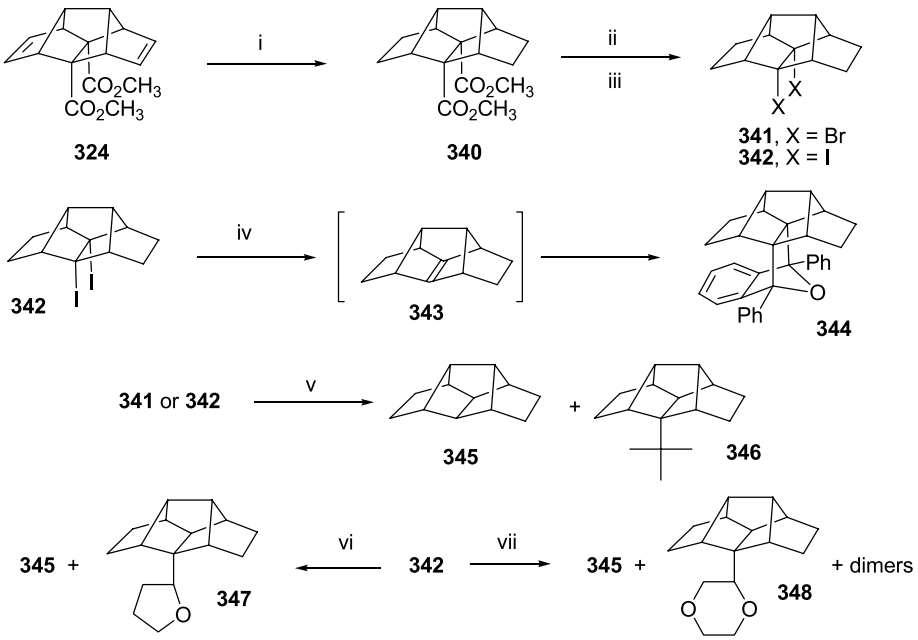
*t*-butyl adduct **346** in different ratios, depending on the experimental conditions (Scheme 50).[118,119]

When the reaction of **342** with *t*-butyllithium was repeated and $D_2O$ used to quench the reaction mixture, one deuterium was incorporated into both **345** and **346**. The observation that **345** incorporates just one deuterium atom suggests that this product may be formed by the reduction of alkene **343**, probably by electron transfer from *t*-butyllithium into its very low-lying LUMO, followed by hydrogen atom abstraction.[118]

Interestingly, [2+2] dimerization products were not observed. Probably, dimerization of alkene **343** to a cyclobutane product, as in the case of alkenes **205a**,**b**, is very difficult, due to the great steric interaction between the ethylene bridges of both approaching halves. Soon after, our group carried out the reaction of diiodide **342** with sodium–potassium alloy in THF at room temperature and with molten sodium in boiling 1,4-dioxane. While using the first experimental conditions, we obtained mainly a mixture of the reduced compound **345** and the THF-derived compound **347** and, in the second experiment, a very complex mixture of products was obtained. GC/MS analysis of this mixture suggested the presence of **345**, **348** and several products, the molecular masses of which corresponded to dimers of **343**. However, these dimers did not show (NMR) the expected $C_{2v}$ symmetry of the usual [2+2] dimers.[70]

Taking into account the results shown in Scheme 50, we thought that the steric hindrance for the dimerization of **343** could favour its cross-coupling reaction with unhindered pyramidalized alkenes such as **205a**,**b**, thus providing an alternative approach to tetrasecododecahedradienes.

Reaction of a mixture of the diiodides **342** and **280b** in a molar ratio **342**/**280b** of 1:5 with an excess of sodium in refluxing dioxane gave a mixture containing the dimer of **205b**, diene **285b**, as the main component and minor amounts of the desired cross-coupling diene **351b**. An

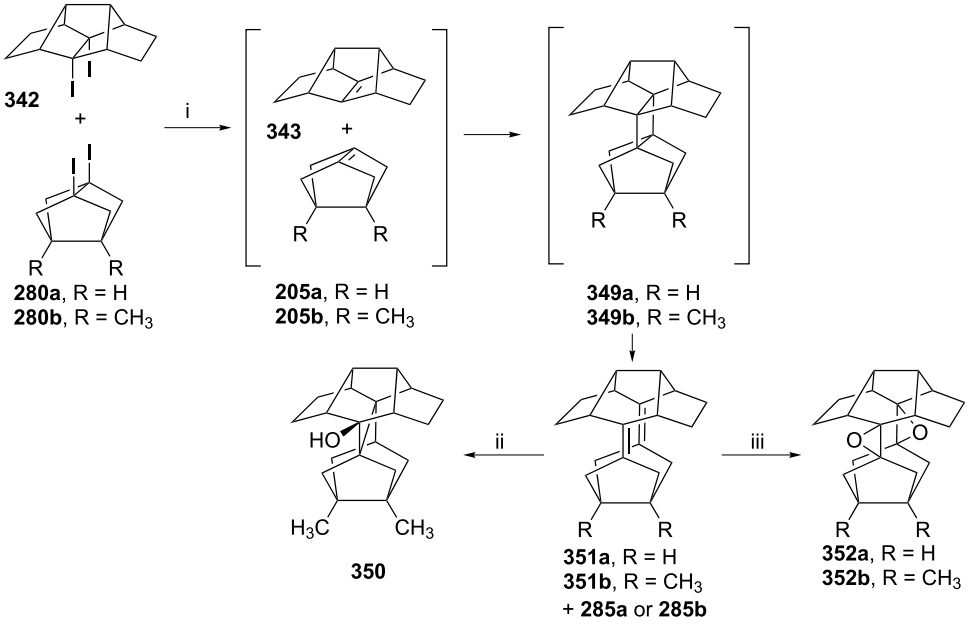



**Scheme 50.** Synthesis and reactivity of the highly pyramidalized alkene **343**. (i) $H_2$, Pd/C, methanol; (ii) hydrolysis; (iii) Hunsdiecker (X=Br) or HgO, $I_2$, h$\nu$ (X=I), (iv) *t*-BuLi, 1,3-DPIBF; (v) *t*-BuLi, THF or ether, 0 °C or −78 °C; (vi) Na(Hg), THF, rt; (vii) Na, 1,4-dioxane, reflux.

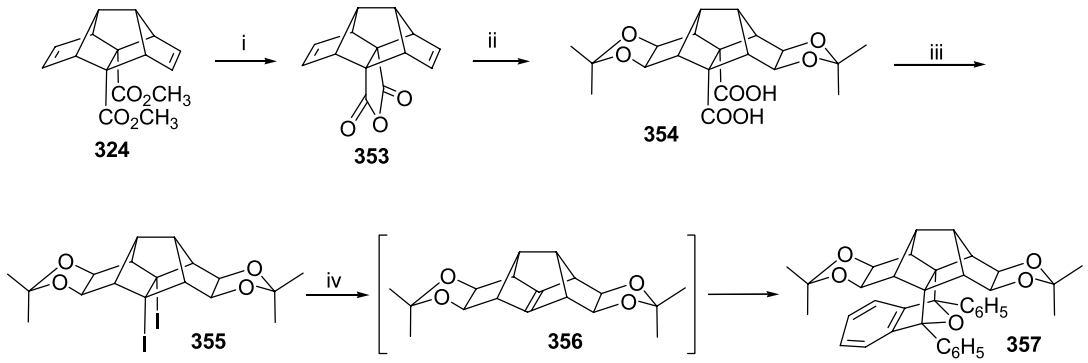
attempt to isolate **351b** from this mixture by silica gel chromatography led to its disappearance, isolating instead a small amount of a compound for which the structure of the alcohol **350** was proposed. The formation of this alcohol can be easily explained from diene **351b** through a transannular hydration.[70] To improve the yield of the cross-coupled product, these reactions were better carried out by using an excess of the more readily available diiodide **342**. Reaction of a mixture of **342** and **280b** in a molar ratio **342/280b** of 4:1 with an excess of sodium in refluxing 1,4-dioxane gave a mixture in which diene **285b** was present in only minute amounts. Similarly, when a mixture of **342** and **280a** in a molar ratio **342/280a** of 5:1 was reacted under similar reaction conditions, no diene dimer **285a** was observed.

To avoid hydration of dienes **351a**,**b** during isolation, these mixtures were treated with an excess of dimethyldioxirane (DMD) and the new mixtures were submitted to silica gel column chromatography, which allowed the isolation of the diepoxides **352a** and **352b**, in 64 and 59% yields, respectively, confirming the formation of tetrasecododecahedradienes **351a**,**b**, probably via the corresponding cyclobutane derivatives **349a**,**b** (Scheme 51).[70]

In addition, using diester **324** as a starting material, we




**Scheme 51.** Cross-coupling of highly pyramidalized alkene **343** with **205a** and **205b**. (i) Na, 1,4-dioxane, reflux; (ii) $SiO_2$; (iii) DMD.



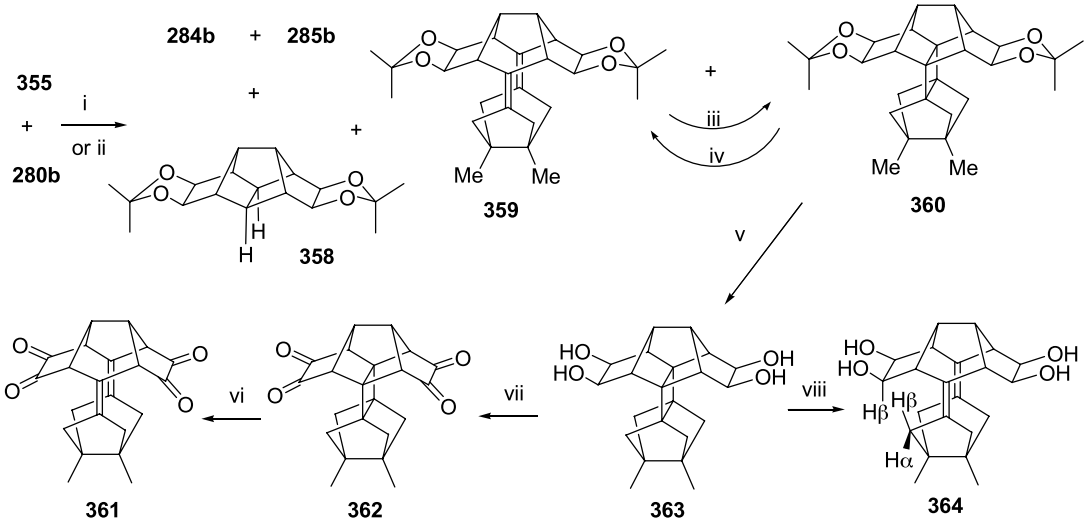

**Scheme 52.** Generation and trapping of highly pyramidalized alkene **356**. (i) (a) KOH, MeOH, $H_2O$, $\triangle$, (b) $Ac_2O$, reflux, 1 h, 86% overall; (ii) (a) *N*-methylmorpholine *N*-oxide, $K_2OsO_4 \cdot 2H_2O$, *t*-BuOH/$H_2O$/acetone 1:1:1, rt, 23 h, (b) acetone, concentrated $H_2SO_4$, $\triangle$, 18 h, 84% overall; (iii) Iodosobenzene diacetate, $I_2$, $CH_2Cl_2$, h$\nu$, 4+18 h, **355**: 42%, recovered **354**: 49%; (iv) 1,3-diphenylisobenzofuran, *t*-BuLi, THF, −78 °C, 30 min, 63%.

prepared the diiodide **355**, following the sequence shown in Scheme 52. Reaction of **355** with *t*-butyllithium in anhydrous THF at −78 °C in the presence of 1,3-diphenylisobenzofuran furnished the expected Diels–Alder adduct **357**, in 63% isolated yield.[120]

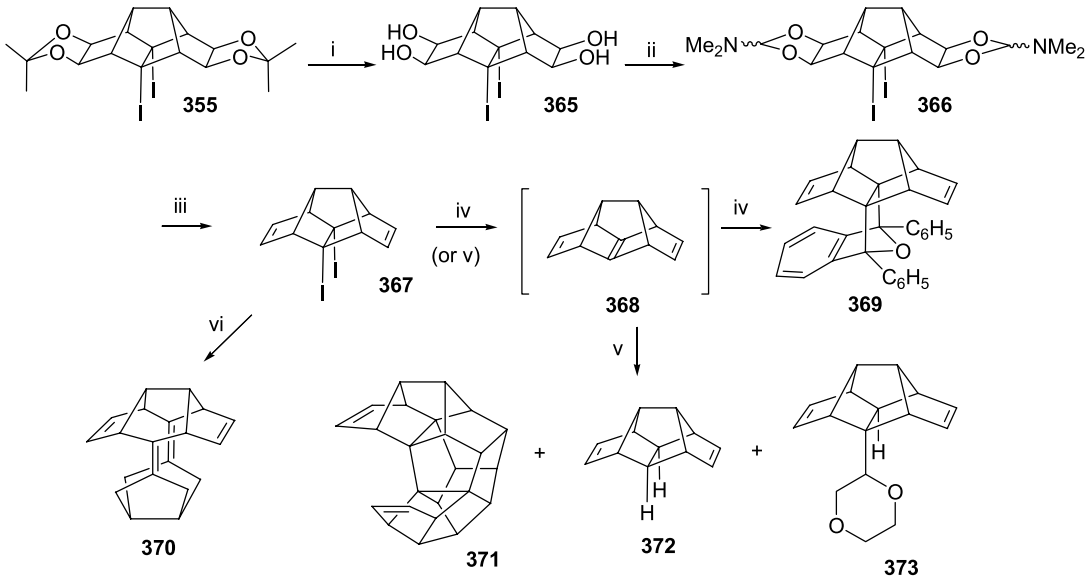
Reaction of a mixture of the diiodides **355** and **280b** in a molar ratio **355/280b** of 1:3 with an excess of molten sodium in refluxing 1,4-dioxane for 4 h gave a mixture of products which could be separated by column chromatography. The main components of this mixture were a mixture of the cross-coupled diene **359** and its isomeric cyclobutane precursor **360** in an approximate ratio of 4:1 (55% combined yield), diene dimer **285b** (37% yield), and the reduction product **358** (19% yield). Under these conditions, dimers of alkene **356** were not observed. Contrary to our previous experience in the cross-coupling of alkenes **343** and **205a** or **205b**, in these reactions we managed to separate **359** and **360** from the byproducts.[120]

Irradiation of the mixture of **359** and **360** gave pure **359** in quantitative yield. Compound **360** was shown to be stable for extended periods of time at room temperature, but was completely converted into **359** after heating in boiling 1,4-dioxane for 24 h. Alternatively, cyclobutane derivative **360** was isolated in 52% yield when the cross-coupling reaction of **355** and **280b** was carried out by using sodium amalgam at room temperature.[120] Acid hydrolysis of **360** gave quantitatively **363** which also proved to be stable for extended periods of time at room temperature, although it was thermally converted into the corresponding diene isomer **364**. Swern oxidation of **363** led to tetrone **362** in 60% isolated yield. At room temperature, **362** underwent slow [2+2] retrocycloaddition to tetrasecododecahedradiene **361**, with complete conversion of **362** into **361** being observed after heating in 1,4-dioxane under reflux for 3 h (Scheme 53).[120]

As was the case for dienes derived from pyramidalized alkenes **205a**,**b**, MM2 calculations showed that the tetrasecododecahedradienes **351b**, **359**, **361** and **364** are hyperstable and slightly pyramidalized alkenes ($\Phi \sim 10°$).




**Scheme 53.** Cross coupling of highly pyramidalized alkenes **356** and **205b**: a straightforward access to functionalized tetrasecododecahedradienes. (i) Na, 1,4-dioxane, reflux, 4 h: **285b** (37% from **280b**) and **358** (19%), **359** and **360** (55–64%, from **355**); (ii) Na (Hg), 1,4-dioxane, rt, overnight, **284b** and **285b** (41.5%, from **280b**) and **358** (48%) and **359** (52%); (iii) h$\nu$, cyclohexane, 6 h, quantitative yield; (iv) 1,4-dioxane, reflux, 24 h, quantitative yield; (v) 2 N aq. HCl, methanol, 75 °C, 16 h, 99%; (vi) 1,4-dioxane, $\triangle$, 3 h, quantitative yield; (vii) DMSO, trifluoroacetic anhydride, $CH_2Cl_2$, −60 °C, 2 h, then, $Et_3N$, −60 °C, 90 min, 60%; (viii) neat, 180 °C/0.7 Torr, 30 min, quantitative yield.

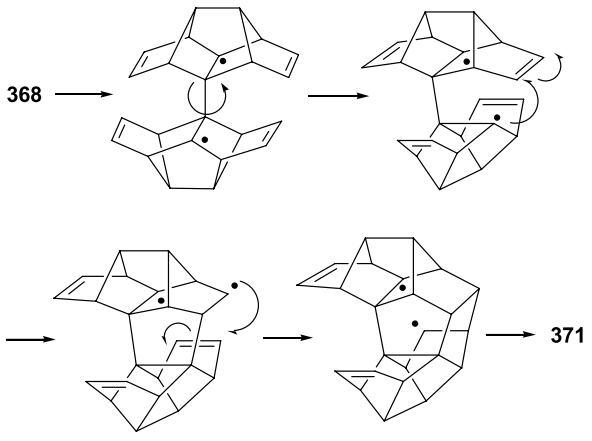



**Scheme 54.** Generation, trapping, dimerization and cross-coupling of triene **368**. (i) 2 N aq. HCl, methanol, 75 °C, 16 h, 99%; (ii) $(MeO)_2CHNMe_2$, △; (iii) $Ac_2O$, reflux, 1 h, 83% of **367** from **365**; (iv) *t*-BuLi, THF, 1,3-diphenylisobenzofuran, −67 °C, 63% of **369**. (v) Na, 1,4-dioxane, reflux, 4 h, 24% yield of pure **371**. (vi) **280b**, Na, 1,4-dioxane, reflux, 4 h, 25% yield of pure **370**.

We also studied by DSC, $^1$H NMR and theoretical methods (MM2 and ab initio) the neat conversion of **362** and **363** into **361** and **364**, respectively.[120b]

Very recently, we have reported the generation of pentacyclo[6.4.0.0$^{2,10}$.0$^{3,7}$.0$^{4,9}$]dodeca-5,8,11-triene **368**, its trapping with 1,3-diphenylisobenzofuran and its very unusual dimerization to the polycyclic compound **371** by an uncatalyzed thermal [2+2+2+2] cycloaddition process, with the formation of four new carbon–carbon bonds.[121]

Interestingly, the triene **368** can be regarded as a dehydro derivative of *syn*-sesquinorbornatriene, in which the additional carbon–carbon bond in **368** enforces pyramidalization in the oppositee sense to that found in *syn*-sesquinorbornatriene (see Section 4.1). As collected in Table 2, B3LYP/6-31G(d) calculations on highly pyramidalized alkene **368** ($\Phi$=62.6°) showed that the carbon–carbon double bond length, the OSE and the heat of hydrogenation of the pyramidalized double bond of **368** are very similar to those previously calculated for the related alkenes **205a**,**b**, **271**, **343** and **356**.[70,120b,121]




**Scheme 55.** Possible pathway for the dimerization of **368**.

Acid hydrolysis of **355**, followed by bisdehydroxylation of **365**, led to the diiodide **367**. As expected, reaction of **367** with *t*-butyllithium in THF at −67 °C in the presence of 1,3-DPIBF gave the Diels–Alder adduct **369** in 63% yield. Reaction of **367** with molten sodium gave three products, the known reduction product **372**, **373** and a dimer of **368**, the structure of which was unequivocally established by X-ray diffraction analysis (Scheme 54).

A possible mechanism for the dimerization of **368** to **371** is shown in Scheme 55. Two units of **368** are first connected by forming a carbon–carbon single bond and, after rotation around the new bond, a cascade radical process would give **371** with the formation of four new carbon–carbon bonds and three new rings.[121]

As expected, the cross-coupling reaction of **368** with **205b** led to a tetrasecododecahedratetraene **370**, but in lower yield (25%) than the previous examples shown in Schemes 51 and 53, as a consequence of the dimerization of both **368** and **205b**.[119]

### 5.2. Dodecahedrenes and related compounds

Dodecahedrene **374a** also contains a bicyclo[3.3.0]oct-1(5)-ene moiety in which the sense of pyramidalization is the same as that in the series of tricyclo[3.3.*n*.0$^{3,7}$]alk-3(7)-enes. In his monumental work on dodecahedrane,[102d,e] Prinzbach has studied several unsaturated derivatives, ranging from dodecahedrenes **374** to the smallest fullerene **378** (Fig. 12).[122]

In addition to several unsaturated dodecahedranes, Prinzbach's team has also succeeded in synthesizing several related compounds such as unsaturated seco- and diseco-dodecahedranes and homologous dodecahedrenes (Fig. 13).

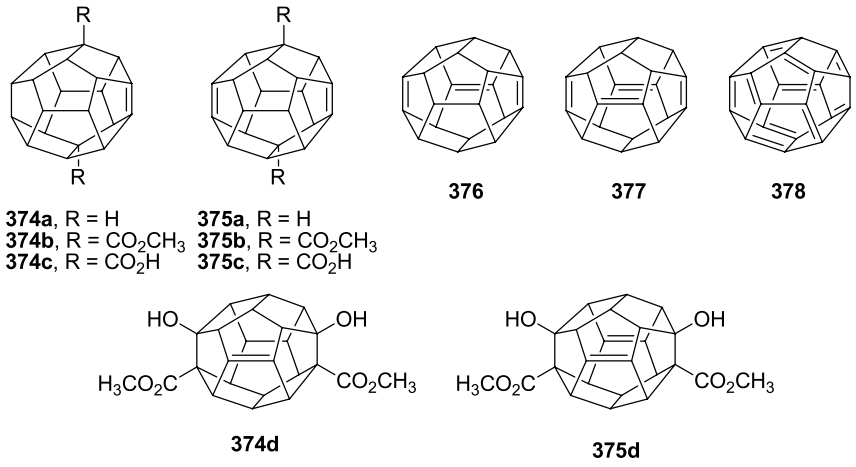



**Figure 12.** Unsaturated derivatives of dodecahedrane, including fullerene $C_{20}$ **378**.

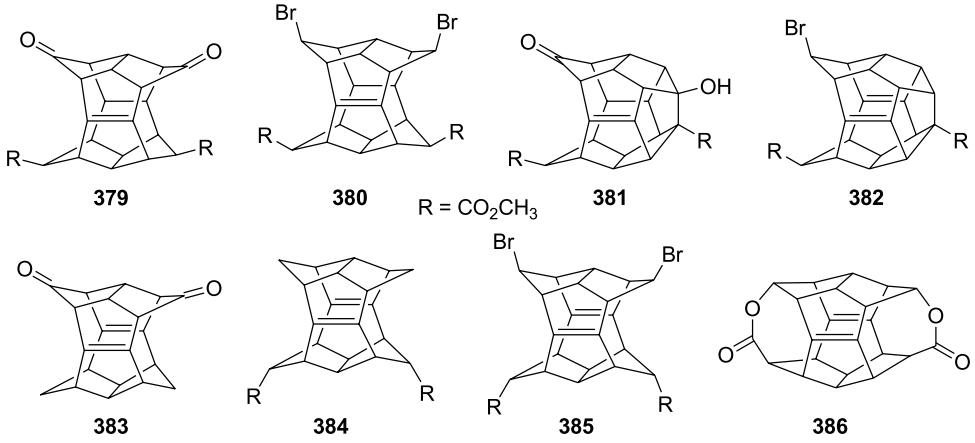


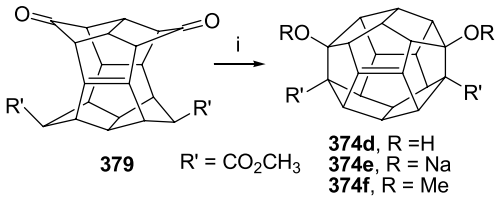

**Figure 13.** Disecododecahedrenes **379** and **380**, secododecahedrene **381**, secododecahedradiene **382**, disecododecahedradienes **383**, **384** and **385** and homologous dodecahedradiene **386**.

Prinzbach published a comprehensive review on his colossal work in this area in 1994,[102e] and some extensive papers have been published more recently,[122] so only some representative examples of this family of pyramidalized alkenes will be discussed here.

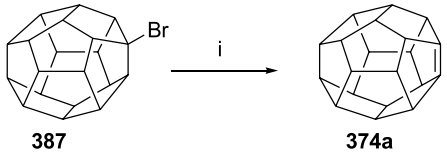
The first unsaturated dodecahedrane to be synthesized was the tetrasubstituted dodecahedrene **374d** ($\Phi \approx 46°$, MM2). Reaction of **379**, a slightly pyramidalized alkene, with NaH in anhydrous THF with the exclusion of oxygen led quantitatively to the disodium salt **374e**, while stirring over NaH/$CH_3I$ led to the dimethyl ether **374f**. With not absolutely water-free THF, diol **374d** was isolated. THF solutions of **374d** remained unchanged for days at room temperature, although it is sensitive towards oxygen. No dimers were found from the thermal activation of **374d** (Scheme 56).[123]

Although the first indirect evidence for the formation of the parent dodecahedrene in a gas-phase reaction was reported in 1989 by Marshall, Paquette and co-workers,[124] it was not until much later that Prinzbach reported the synthesis and isolation of dodecahedrene **374a** [$\Phi = 40.1$, MM2, $\Phi = 39.8$ B3LYP/6-31G(d)].

Prinzbach evaluated many approaches to dodecahedrene and found that the synthesis of choice revolves around the base-catalyzed *cis*-β-elimination in **387**.[122a] Interestingly, the base of choice is a Schwesinger's phosphoniminium fluoride which combines the high potency for *cis*-elimination with the low nucleophilicity demanded by the



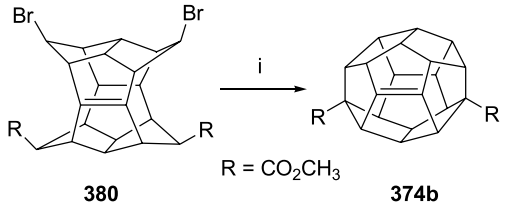

**Scheme 56.** Synthesis of dodecahedrenes **374d–f**. (i) NaH, THF.




**Scheme 57.** Prinzbach's synthesis of dodecahedrene **374a**. (i) $(Me_2N)_3P{=}N{=}P(NMe_2)_3F$.

product.[125] Compared with its derivatives carrying esters or alkoxy groups, the parent dodecahedrene proved more reactive with oxygen and somewhat more prone to dimerization (Scheme 57).

The diester **374b** was prepared by a double intramolecular $S_N2$ reaction of **380** with excess base at room temperature. Solid **374b**, with $\Phi = 46.5°$, rapidly polymerizes in contact with oxygen and could not be crystallized (Scheme 58).[126]




**Scheme 58.** Synthesis of dodecahedrene diester **374b**. (i) Base, rt, 100%.

Reaction of the strongly pyramidalized secododecahedradiene **382** ($\Phi = 35.3°$, X-ray diffraction analysis) with Schwesinger's base in degassed THF led to the colorless, crystalline, dodecahedradiene **375b** ($\Phi \approx 45°$).[125–127] The parent 1,16-dodecahedradiene **375a** [$\Phi = 46.6$, MM2, $\Phi = 39.3$, B3LYP/6-31G(d)] was obtained from the diester **375b**, through a sequence that involved a Diels–Alder reaction of **375b** with furan, saponification, decarboxylation and pyrolysis.[122a] Like alkene **374a**, the significantly more strained diene **375a** only slowly dimerizes upon heating to 100 °C and is even more prone than **374a** to react with oxygen to give epoxides.[122a] Alternatively, thermolysis of the bis-β-lactone **390** in the gas phase afforded up to 70% yield of the crystalline diene **375a** (Scheme 59).[127b]

The main feature of these unsaturated derivatives is that, although the pyramidalization of the unsaturated dodecahedranes is of a degree which normally prohibits the isolation of the respective alkene (compare with alkene **203**), surprisingly, dodecahedrene and several substituted and more unsaturated derivatives are thermally stable. This is a consequence of the close-to-parallel alignment of the four allylic hydrogen atoms and outer π-orbitals, which confers steric protection towards dimerization.[128]

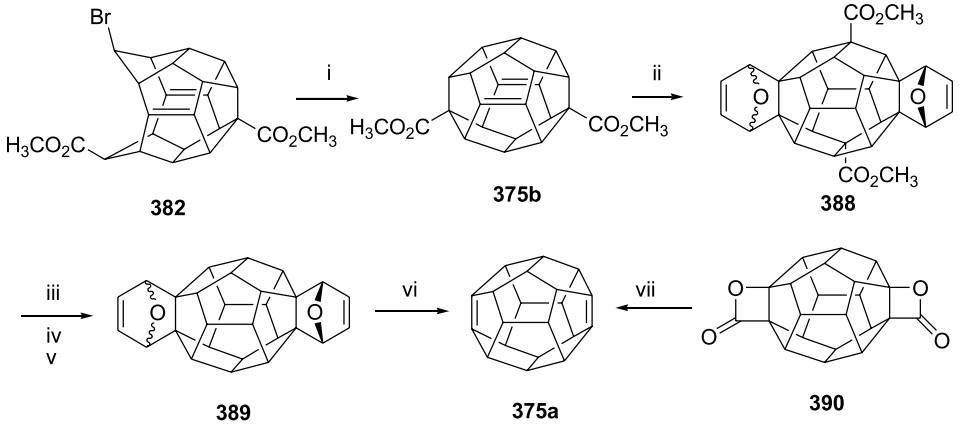
Common to several unsaturated dodecahedranes is the ease of reduction (catalytic hydrogenation and/or diimide reduction), their rapid epoxidation with peroxyacids and the addition of diazomethane to give dihydropyrazoles, the photolysis of which led to cyclopropanedodecahedranes.

Several unsaturated dodecahedranes have been spectroscopically studied. For example, the IR band for the double bond stretching vibration of dodecahedrene **374a** appears at 1658 $cm^{-1}$, practically identical with that of **374b** (1660 $cm^{-1}$). As expected, highly pyramidalized dodecahedrenes showed a long-wavelength absorption in the UV spectra (e.g., 254 nm for **374a**).[122a]

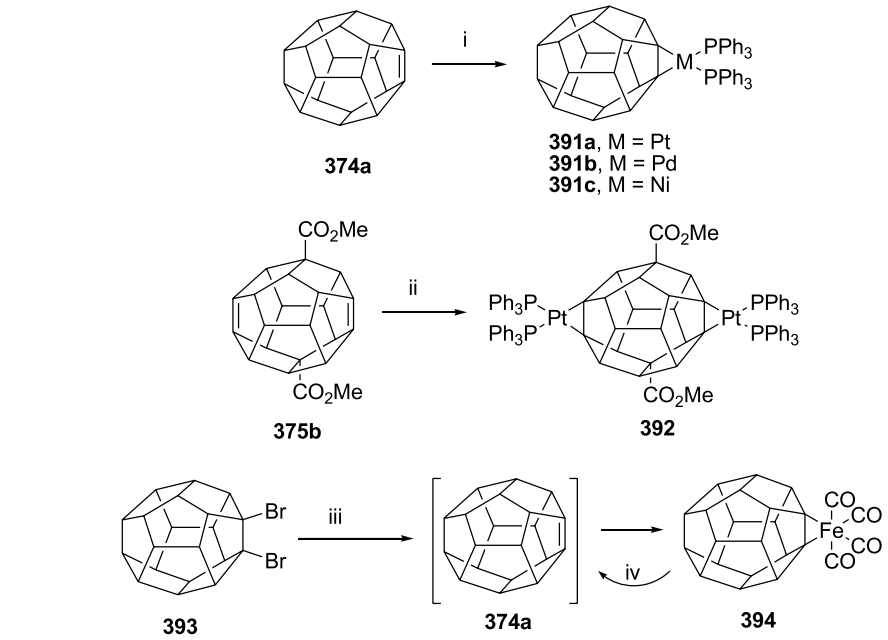
Interestingly, many of the less pyramidalized di-unsaturated derivatives also showed a long-wavelength absorption (compare 254 nm for **364a** and 255 nm for **386**, in spite of much less pyramidalization in the latter). This long-wavelength absorption of the dienes is a consequence of the transannular π–π interaction associated with short transannular distances (e.g., 2.81 in **386**). In addition, not unexpectedly, significant deshielding of the olefin carbon atom in the $^{13}C$ NMR spectra was observed ($\delta = 164.4$ ppm for **374a** and $\delta = 170.5$ ppm for **375a**; also compare $\delta =$ 151.8 ppm for **379** with $\delta = 163.1$ ppm for **374d**).[14,122a,123b]

We have already mentioned that pyramidalized alkenes are, in principle, good ligands for $d^{10}$ metals, as was elegantly confirmed by Borden.[13] Prinzbach has studied the metal complexation of several unsaturated dodecahedranes with Pt, Pd and Ni. For example, the reaction of **374a** with $Pt(PPh_3)_2(C_2H_4)$, $Pd(PPh_3)_4$ and $Ni(PPh_3)_4$ led to the complexes **391a–c**, respectively. Reaction of an excess of $Pt(PPh_3)_2(C_2H_4)$ with **375b** yielded the crystalline 1:2 complex **392**. In situ complexation of dodecahedrene **374a** was accomplished when treatment of 1,2-dibromide **393** with $Fe_2(CO)_9$ caused debromination and instantaneous complexation with in situ generated $[Fe(CO)_4]$ to yield complex **394** in very high yield. From the latter, under mild oxidative conditions, alkene **374a** was conveniently regenerated (Scheme 60).[129]

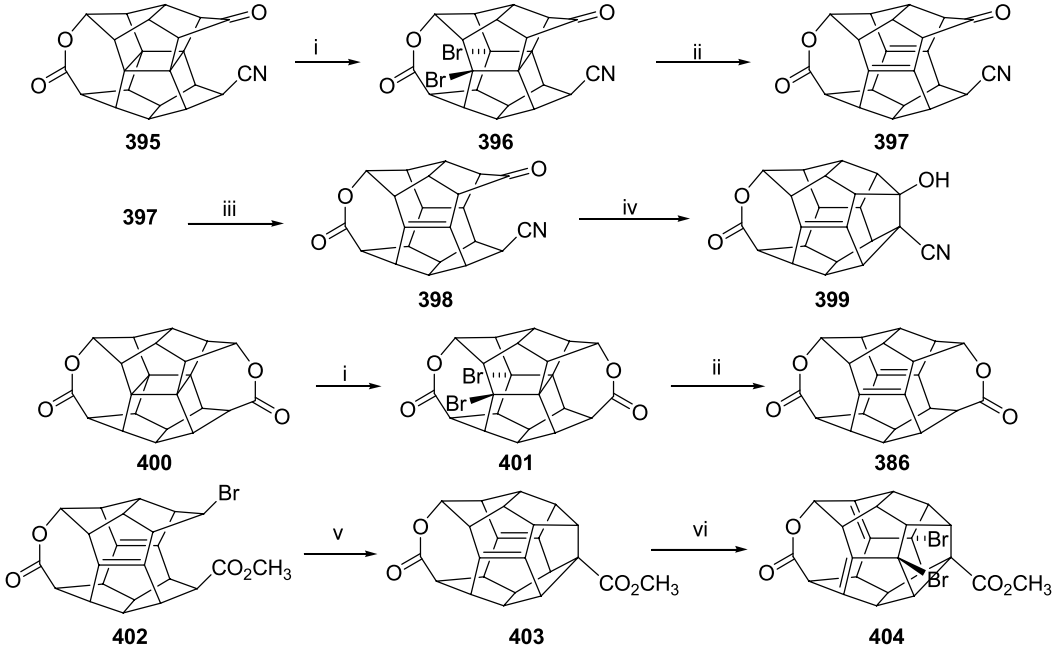
Prinzbach and his group have also synthesized several unsaturated homologous dodecahedranes and homologous secododecahedranes, such as the slightly pyramidalized




**Scheme 59.** Synthesis of dodecahedradienes **375a** and **375b**. (i) Schwesinger's base, THF; (ii) furan, 91% from **382**; (iii) methanol, aq. KOH, 2 h, △; then HCl, 92%; (iv) oxalyl chloride, benzene, △; (v) *t*-butylthiol, *N*-hydroxypyridine-2-thione, DMAP, △, 38% from **388**; (vi) pyrolysis, 55–60%; (vii) FVP, 70%.




**Scheme 60.** Metal complexation of unsaturated dodecahedranes. (i) $Pt[P(C_6H_5)_3]_2(C_2H_4)$, or $Pd[P(C_6H_5)_3]_4$, or $Ni[P(C_6H_5)_3]_4$; (ii) $Pt[P(C_6H_5)_3]_2(C_2H_4)$, excess; (iii) $Fe_2(CO)_9$; (iv) cerium ammonium nitrate (CAN).




**Scheme 61.** Homologous unsaturated dodecahedranes and related compounds. (i) $Br_2$, h$\nu$; (ii) Zn, NaI, $Na_2SO_3$; (iii) diimide; (iv) *t*-BuOK, *t*-BuOH; (v) NaOMe, methanol; (vi) $Br_2$, benzene.

derivative **386** ($\Phi = 18.2°$, X-ray diffraction analysis), the more pyramidalized **399**, that, however, is virtually insensitive to oxygen and can be isolated in the crystalline state, or the homododecahedradiene **403** ($\Phi_1 = 32°$ and $\Phi_2 = 20°$) that is oxygen sensitive, but showed no propensity for dimerization (Scheme 61). Interestingly, treatment of a benzene solution of **403** with bromine gas led to the unsymmetrically substituted, air-sensitive diene **404** ($\Phi$ between 21.8 and 26.7° in the parent dienelactone, MM2). Dienes **386** and **397**, but not **403**, underwent [2+2] cycloaddition to give, quantitatively, pagodanes **395** and **400**, respectively.[130]

More recently, Prinzbach and co-workers have collected evidence for triene **376**, tetraene **377** and even fullerene **378** (Fig. 12).[122b,c] Attempts to prepare **376** and **377** through thermal retro [2+2] and/or retro [4+2] cycloaddition strategies proved unsuccessful. However, both cage cations

and anions were liberated upon electron-impact or gas-discharge ionization of their thermally stable tris- and tetrakisanthraceno-annelated derivatives.[122c]

Finally, fullerene **378** was generated by the gas-phase debromination of a mixture of a multitude of isomeric $C_{20}H_{0-3}Br_{14-11}$ dodecahedratrienes obtained by bromination of dodecahedrane under drastic conditions (reflux of dodecahedrane in bromine under visible light irradiation for 3 days in a pressure flask). Fullerene $C_{20}$ was characterized using mass-selective anion photoelectron spectroscopy.[122b,131]

### 5.3. Acepentalene and related compounds

The highly strained acepentalene **405**, a fully unsaturated triquinane, and its 4,7-dihydroderivative **406** also contain a bicyclo[3.3.0]oct-1(5)-ene moiety (Fig. 14). Acepentalene is the smallest curved subunit of the aforementioned $C_{20}$ fullerene. We have already mentioned that, in spite of high pyramidalization, dodecahedrene does not dimerize as a consequence of the steric protection provided by the four allylic hydrogen atoms. Dihydroacepentalene is related to dodecahedrene, yet, in **406**, the pyramidalized alkene is not protected by allylic hydrogen atoms at one end.

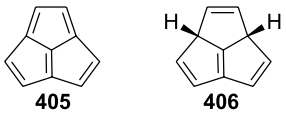


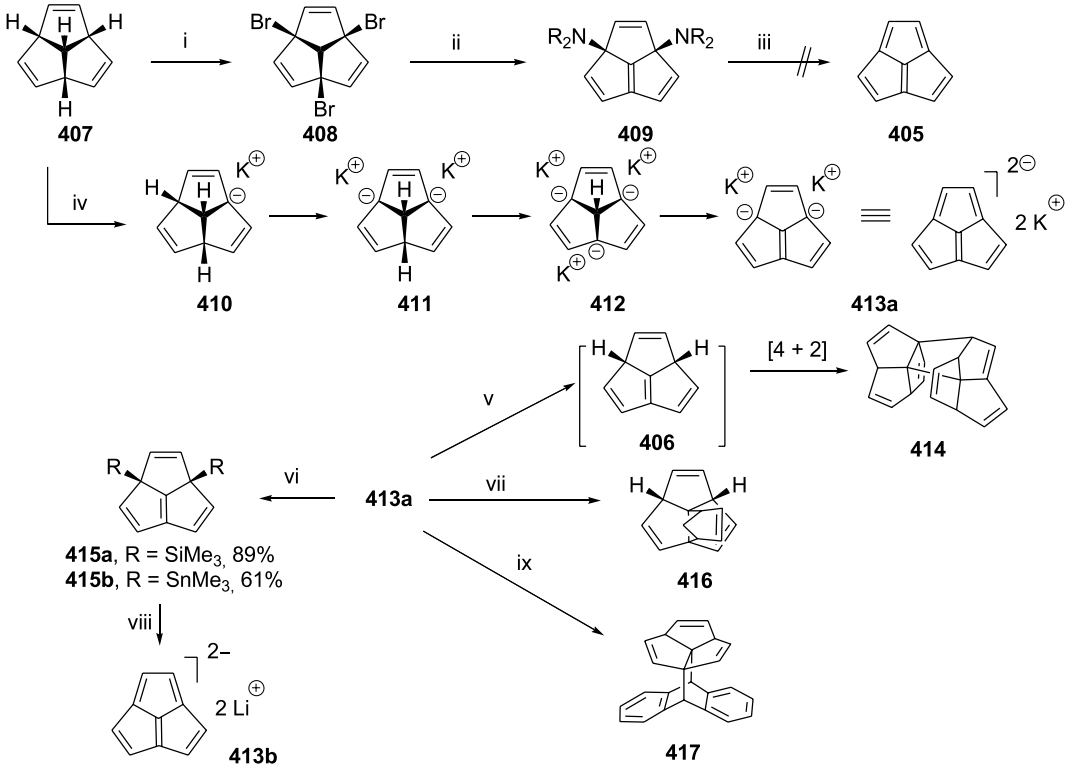

**Figure 14.** Acepentalene **405** and its 4,7-dihydroderivative **406**.

De Meijere and Kuck have reported, in a collaborative effort, the synthesis of several acepentalenes and dihydroacepentalenes.[132]

In the 1980s, de Meijere reported that stable dihydroacepentalenes of the type **409** could be obtained by the 3-fold bromination of triquinacene **407**, to form the tribromide **408**, followed by treatment with a secondary amine which, in a sequence of two consecutive substitution and elimination reactions and a third elimination, gave the tetraenes **409**. However, attempts to generate acepentalene from **409** were unsuccessful (Scheme 62).[133]

More recently, de Meijere reported the syntheses of some more versatile 4,7-disubstituted dihydroacepentalenes via stable acepentalenediides such as **413a**. Three deprotonations and one hydride elimination led from triquinacene to dipotassium acepentalenediide **413a** in a one-pot procedure that had been previously studied on a tribenzotriquinacene (see below). In contrast to acepentalene, its dianion is a closed-shell system and thereby electronically more favourable than the uncharged acepentalene. Treatment of **413a** with moist ether gave **414**, a [4+2] dimer of 4,7-dihydroacepentalene, **406**. The smooth and rapid formation of dimer **414** implies that the highly strained central double bond in **406** is not sufficiently shielded by the two hydrogens on the other bridgehead positions. Although it was not possible to observe **406**, even at −80 °C, its formation was proved by trapping reactions with various reactive dienes.[134]

4,7-Disubstituted dihydroacepentalenes are readily obtained




**Scheme 62.** Attempted synthesis of acepentalene **405**, synthesis of the dipotassium acepentalenediide **413a** and its reactivity. (i) NBS, $CCl_4$; (ii) $HNR_2$, rt, 47–86%; (iii) $CH_3I$, AgO; (iv) excess of base; (v) $H_2O$, ether, 93%; (vi) RCl; (vii) moist cyclopentadiene, 63% **416**+21% **414**; (viii) 3 equiv $CH_3Li$, DME, −60 °C; (ix) moist anthracene, 15% **417**+18% **414**.

by the reaction of **413a** with electrophiles. The bulky substituents on **415a**,**b** provided sufficient steric congestion to protect the highly reactive central double bond and prevent the molecules from undergoing dimerization. Although **415b** is highly air- and moisture-sensitive, its structure was determined by X-ray crystallography. Since the double bond in **415b** is unsymmetrically tetrasubstituted, there are two different pyramidalization angles ($\Phi_{(C1)}=34.6°$, $\Phi_{(C10)}=43.5°$), the pyramidalization angle for C1 being similar to those reported for some unsaturated dodecahedrenes (see preceding section). Attempts to homolytically cleave the trimethylstannyl residues from **415b**, either by irradiation or heating, and subsequent matrix isolation of acepentalene **405**, were unsuccessful. Nevertheless, the trimethylstannyl residues of **415b** were cleaved upon chemical ionization in the mass spectrometer to generate the anion radical of acepentalene.[133]

In a more rewarding study, **415b** was transmetallated with methyllithium to give pure **413b** in high yield. This lithium derivative was crystallized at low temperature and its low-temperature crystal structure analysis revealed an interesting dimer-sandwich structure. In solution, **415b** is essentially $C_3$ symmetric and $^1$H NMR spectroscopy and ab initio calculations suggested that both **413a** and **413b** are aromatic systems with a fast bowl-to-bowl inversion at room temperature, so that the average geometry appears as a planar aromatic π-system (Fig. 15).[134]

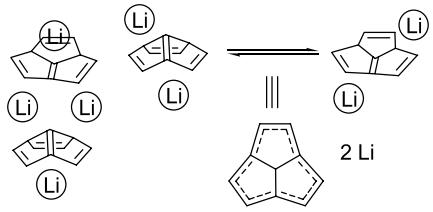
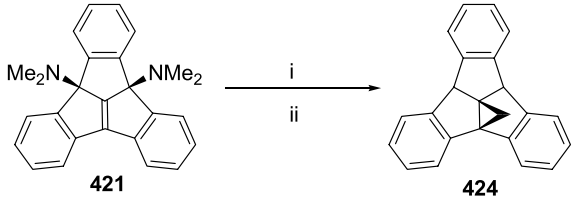



**Figure 15.** Sandwich structure of **413b** and its bowl-to-bowl inversion.

The synthesis of the particularly stable tribenzodihydroacepentalene **421**, readily accessible in very high yield from tribenzotriquinacene **418** through bromination and aminolysis with dimethylamine, has also been reported. By way of contrast with oily diamines **409**, that are oxygen sensitive, diamine **421** is a crystalline and air-stable compound, a remarkable property in view of the two strongly pyramidalized olefinic carbon atoms C1 and C10 ($\Phi_{(C1)}=39.3°$, $\Phi_{(C10)}=40.6°$, MM2). Surprisingly, when ammonia was used instead of dimethylamine, the triamino compound **420** was obtained in good yield, presumably through the intermediacy of a less kinetically stabilized analogue of **421** (Scheme 63).[135]

A number of 4-fold hetero-substituted tribenzotriquinacenes were prepared from olefin **421**. For example, **421** reacted at low temperature with bromine to give the dibromide **422**, that was converted with dimethylamine into the $C_{3v}$ symmetric **423** (Scheme 63).

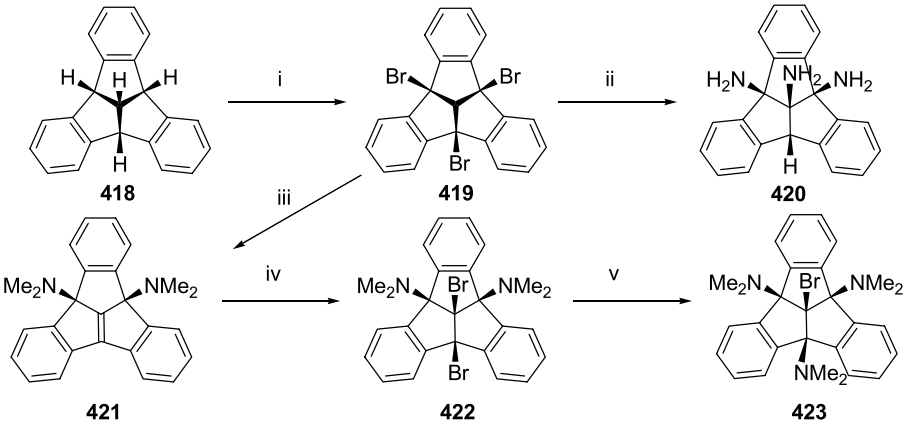
On the other hand, olefin **421** added diazomethane to give a dihydropyrazole, the irradiation of which led with complete deamination to the tetracycle **424** in low overall yield (Scheme 64).[135]



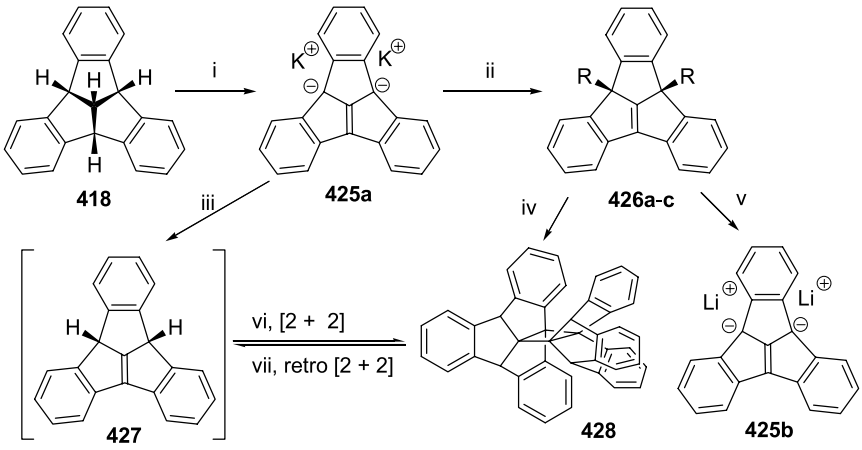

**Scheme 64.** Synthesis of cyclopropatribenzotriquinacene **424**. (i) $CH_2N_2$; (ii) h$\nu$, cyclohexane, 18% overall.

Reaction of **418** with excess of Lochmann–Schlosser base (LSB, an equimolecular mixture of *n*-butyllithium and potassium *t*-pentoxide) led to tribenzodihydroacepentalenediide **425a**, following a sequence parallel to that shown in Scheme 65. Compound **425a** could also be prepared from centro-substituted tribenzotriquinacenes with 3 equiv of LSB.[136]

The fact that **418** is more readily and efficiently transformed into **425a** than the parent triquinacene **407** into **413a** is in line with the common stabilization of conjugated non-aromatic hydrocarbons and their ions by benzo-annelation.[137] Therefore, tribenzoacepentalene should be easier to isolate than acepentalene.[136c,d]




**Scheme 63.** Synthesis of tribenzotriquinacenes through highly pyramidalized **421**. (i) $Br_2$, $CCl_4$, h$\nu$, 94%; (ii) $NH_3$, benzene, 100 °C, 82%; (iii) $HNMe_2$, benzene, 100 °C, 84%; (iv) $Br_2$, $CH_2Cl_2$, −60 °C, 6 h, 85%; (v) $HNMe_2$, benzene, 100 °C, 1 d, 54%.




**Scheme 65.** Synthesis of tribenzodihydroacepentalene **427** and its dimer **428**. (i) Excess of Lochmann–Schlosser base; (ii) RX, THF; 96% **426a**, R=$SiMe_3$; 58% **426b**, R=$CO_2Me$; 42% **426c**, R=$SnMe_3$; (iii) $H_2O$, THF; (iv) h$\nu$, 0 °C, *t*-BuSH; (v) MeLi, −60 °C; (vi) −78 °C to rt; (vii) >210 °C.

Dianion **425a** was trapped with various electrophiles to yield 4,7-disubstituted tribenzodihydroacepentalenes such as **426a–c**. The derivatives **426a–c** are unstable at room temperature or easily add electrophiles across the central pyramidalized C1–C10 double bond. In spite of difficulties in handling, suitable crystals of **426a** and **426b** were prepared and their structures studied by X-ray crystallography. The pyramidalization angles were very similar to those found in the triquinacene series (see above).

After protonation of **425a** with aqueous THF, a dimer of **427** was isolated in up to 97% yield (Scheme 65). Dimer **428** is a head-to-head ($C_s$ symmetry) dimer of **427**, the structure of which was determined by X-ray diffraction analysis. The behaviour of **427** is different to that of the parent **406** that dimerizes through a [4+2] reaction.

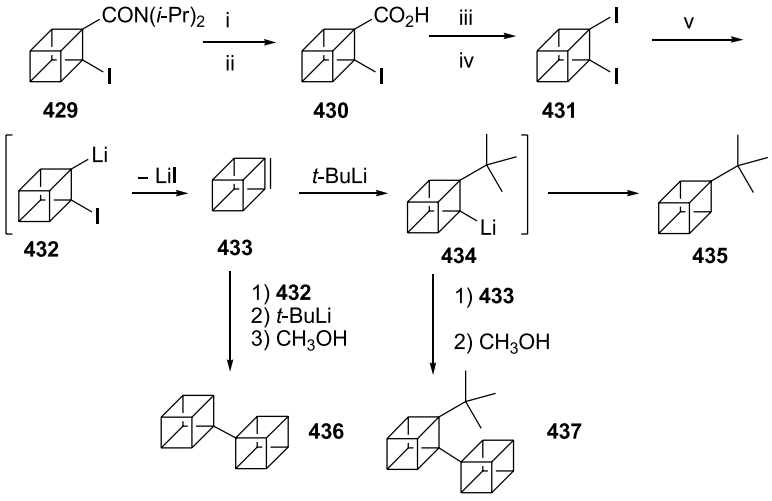
In contrast to the parent **406**, that could not be detected by NMR, even at −80 °C, the $^1$H NMR spectrum of **427** was recorded at −60 °C and its dimerization to **428** could be monitored by $^1$H NMR. Cycloaddition across the highly pyramidalized alkene in **427** with 1,3-diphenylisobenzofuran led to the corresponding Diels–Alder cycloadduct in moderate yield. Interestingly, this cycloaddition is reversible above 170 °C, as is the [2+2] dimerization above 210 °C. Thus, when heated together with anthracene or tetraphenylcyclopentadiene at 220 °C, dimer **428** gave the corresponding Diels–Alder adducts of **427** in good yields.[136] Alternatively, dimer **428** was also obtained when **426c** was irradiated with a high-pressure mercury lamp in the presence of *t*-butyl mercaptan.[136d] Finally, treatment of **426c** with methyllithium at −60 °C led to **425b** that crystallized at −30 °C. This fact allowed the single-crystal structure analysis of **425b** at low temperature.

## 6. Cubene, homocubenes and bishomocubenes

### 6.1. Cubene

Cubane, pentacyclo[4.2.0.0$^{2,5}$.0$^{3,8}$.0$^{4,7}$]octane, is one of the most exciting and extensively studied cage compounds.[138] Eaton and co-workers have worked for years on the synthesis of a myriad of cubane derivatives, including the highly pyramidalized 1,2-dehydrocubane ('cubene') **433**.[11a,117]

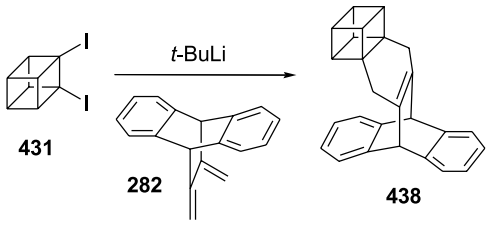
According to ab initio calculations, cubene, with a




**Scheme 66.** Generation of 1,2-dehydrocubane, 'cubene' **433**. (i) $BH_3$, THF; (ii) $KMnO_4$; (iii) $SOCl_2$; (iv) *N*-hydroxypyridine-2-thione, $CH_2ICF_3$, h$\nu$; (v) *t*-BuLi, then methanol.

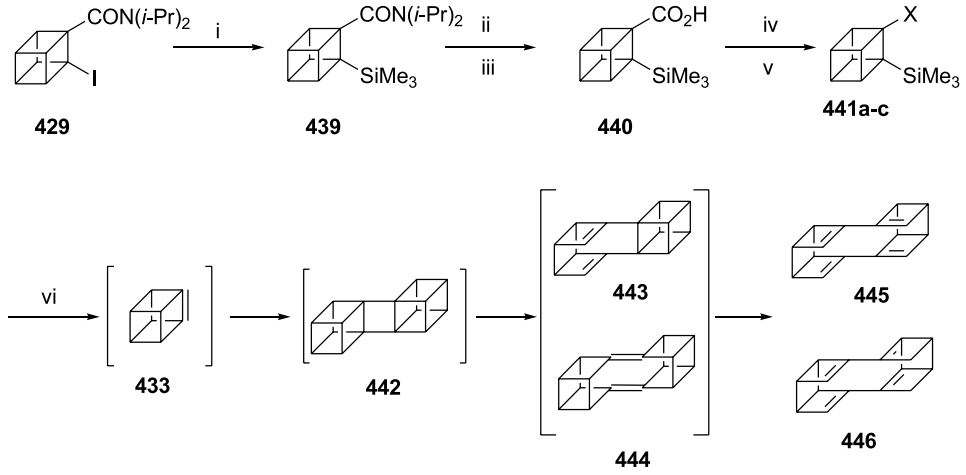
pyramidalization angle of $\Phi = 84.1°$ (HF/3-21G), is the most highly pyramidalized alkene yet known.[12c] Calculations also indicate that sufficient overlap exists between the p-orbitals of cubene for it to behave as an olefin, rather than a biradical.[12c,139] In 1988, Hrovat and Borden predicted that, despite the presence of the highly pyramidalized double bond in **433**, the compound should be preparable.[12c] Indeed, shortly thereafter, Eaton and Maggini confirmed experimentally this prediction.[11a]

Reduction of the amido group in **429** with borane, followed by oxidation of the resulting amine with $KMnO_4$, led to the carboxylic acid **430**. Barton iododecarboxylation of **430** led to 1,2-diiodocubane **431** in high yield. Treatment of **431** with excess *t*-butyllithium in THF at −70 °C, followed by quenching with methanol, gave *t*-butylcubane **435** and 2-*t*-butylcubylcubane **437** in a ratio of about 1:2, along with a trace of cubylcubane **436**. In order to account for the formation of these compounds, Eaton invoked the intermediacy of cubene, as shown in Scheme 66. Worthy of note is that, under these conditions, no dimer of cubene was found. Further evidence for the formation of cubene was provided by trapping with the diene **282**. Reaction of **431** with *t*-butyllithium at room temperature, in the presence of the diene **282**, led to the corresponding Diels–Alder adduct **438** in 64% isolated yield (Scheme 67).[11a] Interestingly, the X-ray crystal analyses of **436** and **437** revealed that the intercage bond lengths in both compounds (1.458 and 1.464 Å for **437** and **436**, respectively) are significantly shorter than usual.[140]

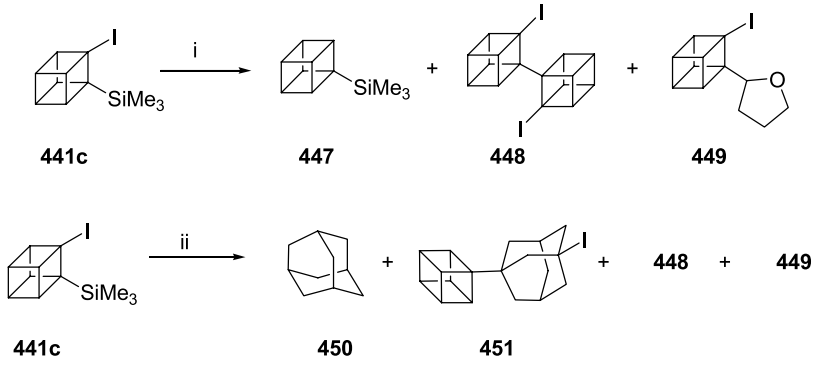



**Scheme 67.** Trapping of cubene with diene **282**.

In order to avoid the addition of *t*-butyllithium to cubene, Eaton and Lukin later developed a new approach to highly pyramidalized alkenes that involves generation of the olefin by fluoride ion-induced elimination from 1-halo-2-(trimethylsilyl)cubanes.[117] Metalation of **429** with *t*-butyllithium, followed by quenching with chlorotrimethylsilane, gave **439** in 85% yield. As the amido group in **439** is extremely resistant to any kind of hydrolysis, conversion of **439** into **440** was carried out by a reduction–oxidation sequence. Barton halodecarboxylation of **440** in the presence of the appropriate halogen-atom donors led to




**Scheme 68.** Generation and dimerization of cubene **433**. (i) *t*-BuLi, then TMSCl; (ii) $LiAlH_4$; (iii) $KMnO_4$; (iv) oxalyl chloride; (v) Barton's halodecarboxylation, **441a**, X=Cl; **441b**, X=Br; **441c**, X=I; (vi) tetrabutylammonium fluoride or hexakis(dimethylamino)phosphazenium fluoride, 0 °C, THF.




**Scheme 69.** Reactions of **441c** with fluoride anion with and without 1-iodoadamantane. (i) Fluoride anion, THF, −35 °C; (ii) 1-iodoadamantane, fluoride anion, THF, −35 °C.

the vicinal halo(trimethylsilyl)cubanes **441a–c** in an average 70% yield. While **441a** failed to give any evidence of cubene on reaction with anhydrous fluoride anion, the reaction of **441b** with tetrabutylammonium fluoride or hexakis(dimethylamino)phosphazenium fluoride at 0 °C in THF gave a mixture of two isomeric olefins **445** and **446**, very unstable thermally and sensitive to air oxidation. The formation of compounds **445** and **446** can be rationalized through dimerization of cubene to the extremely strained **442**, followed by ring opening that could occur in a variety of ways, via **443** and/or **444** (Scheme 68).[117]

The intermediacy of biradicals had been previously suggested to account for the dimerization of highly pyramidalized alkenes.[10a] In an effort to find experimental evidence for the intermediates **442**, **443** and **444**, Eaton carried out the first experimental demonstration that biradicals are involved in the dimerization of strained olefins (Schemes 69 and 70).

Thus, while reaction of fluoride anion with **441b** at lower temperatures led to the recovery of **441b**, the more reactive **441c** reacted at −35 °C. However, in this case, only traces of tetraenes **445** and **446** were found. Instead, a mixture of **447**, **448** and **449** was identified.

Reaction of **441c** with active fluoride in the presence of diene **282** led to the adduct **438** in 70% yield. Thus, it seemed that cubene is also an intermediary in the reaction of **441c** with fluoride anion. When the reaction of **441c** with fluoride anion was carried out in the presence of 1-iodoadamantane as an iodine atom donor, none of the tetraenes **445** and **446** was found (Scheme 69). Instead, the major product was 1-adamantyl-2-iodocubane **451**, isolated in 50% yield, along with 2,2′-diidobicubyl (**448**, 8% yield) and 1-iodo-2-(α-tetrahydrofuryl)cubane (**449**, 25% yield). This result supports the idea that radical processes are occurring during cubene chemistry.

The lack of iodocubane and/or 1,2-diiodocubane in the reaction mixture led to the conclusion that the origin of the compounds **447–449** in the absence of 1-iodoadamantane and **448–451** in its presence is not cubene, but the biradical **452**, as rationalized in Schemes 70 and 71.[117]

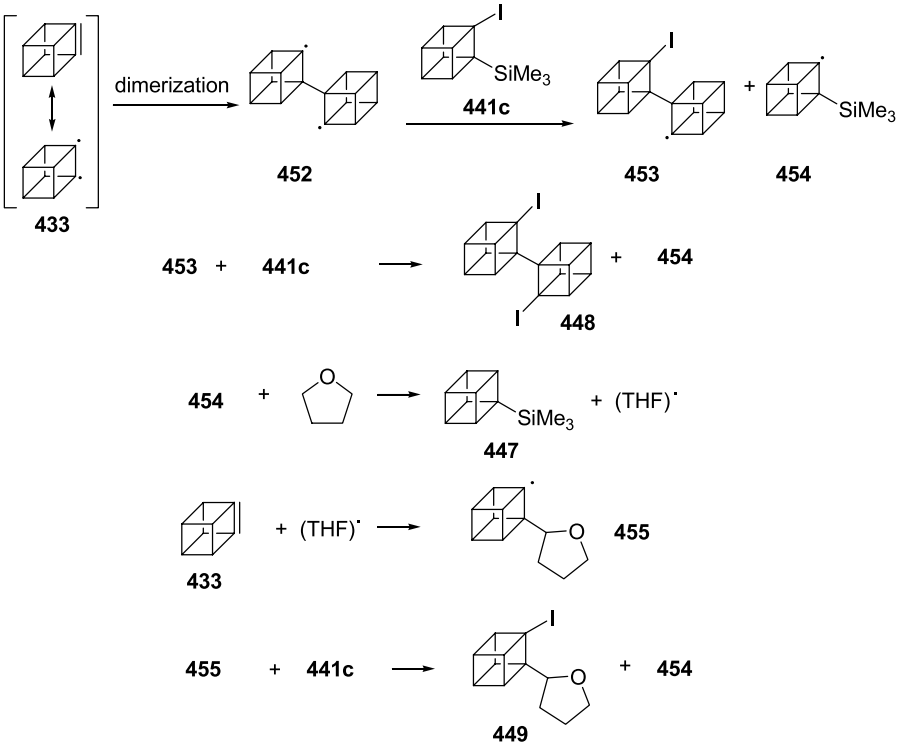
The heat of formation (238±4 kcal/mol), heat of hydrogenation (90±4 kcal/mol) and olefin strain energy (63±4 kcal/mol) of cubene have been determined by way of an ion cyclotron resonance study of its radical anion.[141]

These experimental values are in good agreement with the ab initio calculations previously reported by Hrovat and Borden [heat of hydrogenation 82.5 kcal/mol; olefin strain energy 58.9 kcal/mol; TCSCF/6-31G(d)//HF/3-21G].[12c]

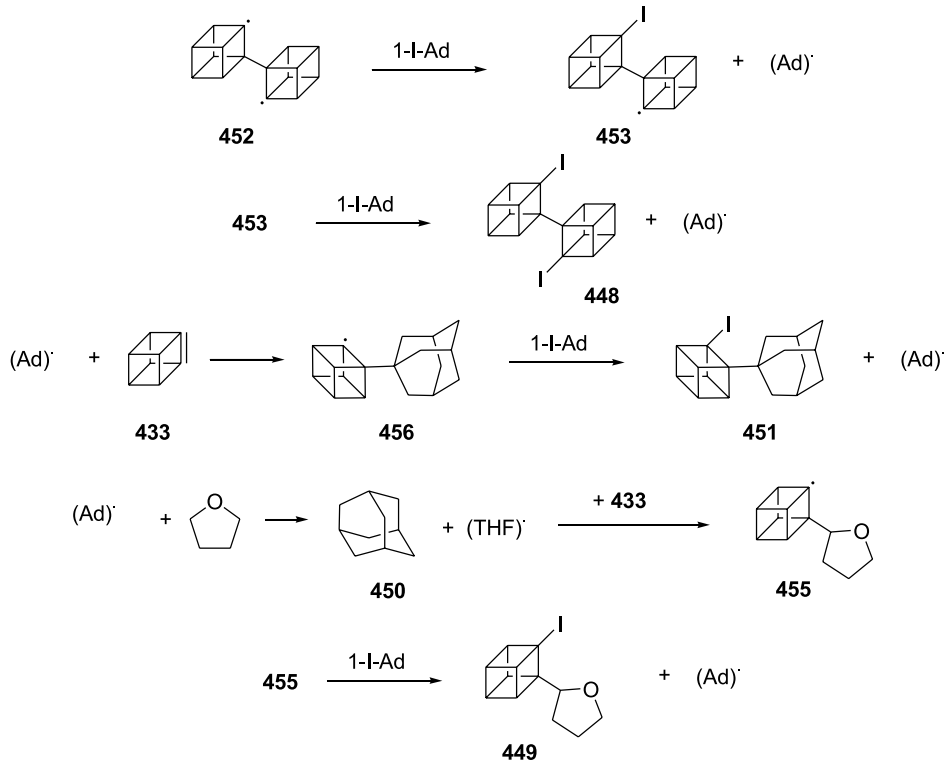
### 6.2. Homocubenes

As with cubane, homocubane (pentacyclo[4.3.0.0$^{2,5}$.0$^{3,8}$.0$^{4,7}$]nonane) **457** has held a special fascination for organic chemists.[142] Some of the unsaturated derivatives of homocubane have been synthesized and ab initio calculations have been performed for several homocubenes **458–462** (Fig. 16).

In 1988, Borden and Szeimies, independently, reported evidence for the formation of 4(5)-homocubene **458**.[11b,143] Schäfer and Szeimies found that treatment of 4-bromo-5-chlorohomocubane **463** with 5 equiv of *t*-butyllithium in pentane/ether at 0 °C, followed by aqueous work-up, afforded 4-*t*-butylhomocubane **465a** (38% yield).




**Scheme 70.** Reaction of **441c** with fluoride anion: formation of **447**, **448** and **449**.




**Scheme 71.** Reaction of **441c** with fluoride anion in the presence of 1-iodoadamantane: formation of **448**, **449** and **451**. (Ad)· = adamantyl radical; (THF)· = tetrahydrofuryl radical; 1-I-Ad = 1-iodoadamantane.

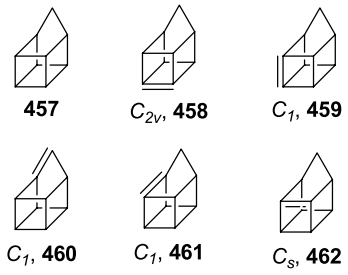
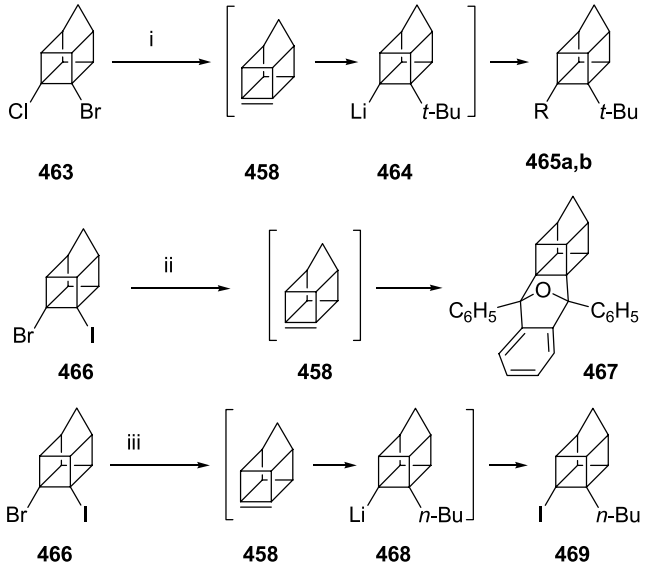



**Figure 16.** Homocubane and homocubenes.

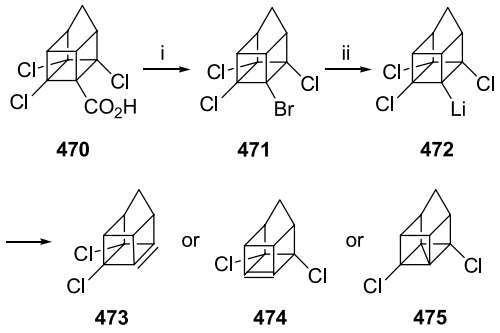



**Scheme 72.** Evidence for homocubene **458**. (i) Excess of *t*-BuLi, then $H_2O$ (**465a**, R = H) or $D_2O$ (**465b**, R = D); (ii) *n*-BuLi, 1,3-DPIBF, THF, −78 °C; (iii) excess *n*-BuLi.

Quenching the reaction with $D_2O$ instead of water led to the corresponding deuterated derivative **465b** in 34% yield (Scheme 72). When **463** was reacted with phenyllithium, results were obtained which also implied the intermediacy of **458**.[11b]

Independently, Hrovat and Borden found that the reaction of the bromoiodide **466** with 1.1 equiv of *n*-butyllithium in THF at −78 °C in the presence of 1,3-DPIBF led to the corresponding Diels–Alder adduct of 4(5)-homocubene in 50% yield (Scheme 72). Without 1,3-DPIBF, the reaction of **466** with an excess of *n*-butyllithium led mainly to **469**, the product of formal replacement of the bromine in **466** with an *n*-butyl group. The formation of **469** presumably involves the formation of **458**, addition of *n*-butyllithium to **458**, and reaction of the resulting alkyllithium with either the *n*-butyliodide produced or with unreacted **466**.[143]

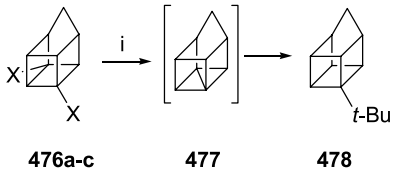
More recently, Szeimies et al. have also collected evidence for **473**, a derivative of **459**. Starting from the known acid **470**, a modified Hunsdiecker reaction afforded the tetrahalide **471**. This compound is particularly interesting, because its reductive dehalogenation with an organolithium reagent to accomplish lithium/bromide exchange to give homocubyllithium **472** could lead through 1,2-elimination to **473** (a derivative of **459**) or **474** (a derivative of **458**) and, alternatively, a 1,3-elimination would give the elusive didehydrohomocubane **475**. In the event, reaction of **471** with methyllithium in THF at −78 °C in the presence of dienes such as anthracene, 1,3-DPIBF, 9,10-dimethoxyanthracene, 1,2,3-trimethylisoindole or 2,5-dimethylfuran led to Diels–Alder adducts from homocubene **473** with different stereoselectivity, depending on the diene. In all trapping




**Scheme 73.** Alternative pathways for the reaction of **471** with MeLi. (i) HgO, $Br_2$, 1,2-dibromoethane, h$\nu$, 56%; (ii) MeLi, ether, −78 °C.

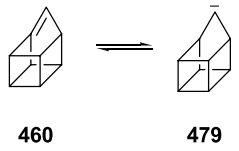
experiments there was no evidence for the intermediacy of **474** (Scheme 73).[144]

On the other hand, Schäfer and Szeimies have found evidence for didehydrohomocubane **477**. Reaction of the dihalo derivatives **476a–c** with an excess of *t*-butyllithium led to **478** in up to 78% yield (Scheme 74).[145]




**Scheme 74.** Synthesis and trapping of **477**. (i) 5.0 equiv *t*-BuLi, ether, −78 °C. **476a**, X=Cl, **476b**; X=Br, **476c**; X=I.

Taking into account these experimental results, it may be assumed that **473** is considerably more stable than **474** or **475**. Szeimies checked this supposition by ab initio calculations. Indeed, TCSCF/6-31G(d)//HF76-31G(d) calculations showed that **459** is lower in energy than **458** and **477**.[144] According to these calculations, the yet unknown homocubene **462** is the most stable isomer, and its formation should therefore be accomplished. The strongly twisted homocubene **460** is the highest in energy of all homocubenes.[144] In fact, 1(9)-homocubene **460**, the most investigated unsaturated homocubane, is not a pyramidalized alkene, but an anti-Bredt olefin. Jones and Eaton have independently synthesized the parent compound and its 9-phenyl derivative, respectively. Both compounds undergo a reversible rearrangement to the corresponding carbene, 9-homocubylidene **479** and 1-phenyl-9-homocubylidene, respectively (Scheme 75). This topic has been the subject of much work.[146]




**Scheme 75.** Anti-Bredt 1(9)-homocubene **460** and its rearrangement to carbene, 9-homocubylidene **479**.

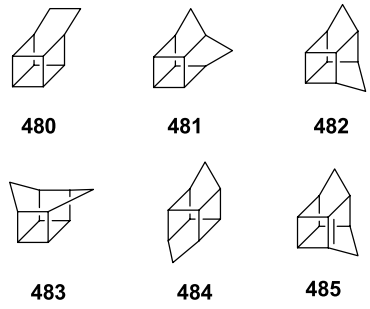
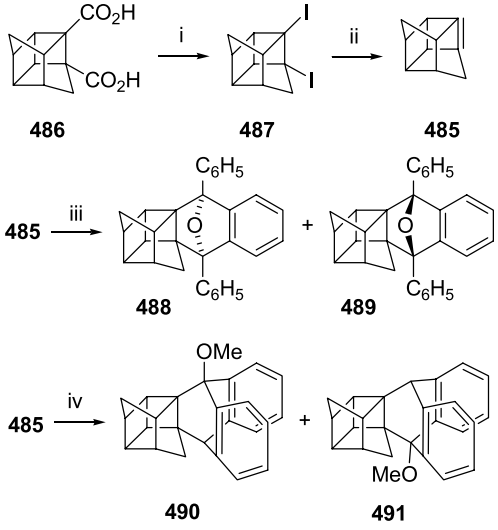



**Figure 17.** Bishomocubanes **480**-**484** and bishomocubene **485**.

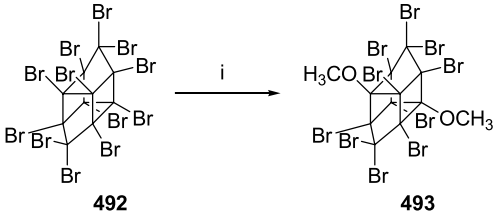
### 6.3. Bishomocubenes

There are many isomeric bishomocubanes **480**–**484** and evidence for bishomocubene **485** and an unsaturated perbromoderivative of **484** have been reported (Fig. 17).[142]

In 1999, Marchand found that the reaction of the diiodide **487** with methyllithium at −78 °C generated a 1,3-bishomocub-2(5)-ene, pentacyclo[5.3.0.$0^{2,5}$.$0^{3,9}$.$0^{4,8}$]dec-2(5)-ene **485**. In the presence of dienes, the corresponding Diels–Alder adducts were isolated (Scheme 76). Worthy of note is that trapping with 1,3-DPIBF is highly stereoselective and led only to stereoisomer **488**, the other stereoisomer **489** not being isolated, while trapping with 9-methoxyanthracene led to a 6:4 mixture of both cycloadducts **490** and **491**. Ab initio calculations carried out on **485** predicted




**Scheme 76.** Synthesis and trapping of bishomocubene **485**. (i) $PhI(OAc)_2$, benzene, h$\nu$, 86%; (ii) MeLi, THF, −78 °C; (iii) 1,3-DPIBF, 60%; (iv) 9-methoxyanthracene, 45%.




**Scheme 77.** Conversion of **492** into **493**. (i) NaOMe, THF.

pyramidalization angles at C2 and C5 of 45.7 and 46.4°, respectively.[147]

More recently, Eaton reported that the reaction of a perbromo $D_{2h}$-bishomocubane **492** with sodium methoxide led to **493** (Scheme 77). The formation of **493** can be explained by methoxide ion attack on one or other bridgehead bromine of **492**, resulting in the formation of methoxyhypobromite, bromide ion, and one or other bishomocubene, which could then subsequently add methoxyhypobromite. However, attempts to trap the bishomocubene with excesses of reactive dienes failed.[148]

## 7. Pyramidalized cyclopropene derivatives

### 7.1. Unsaturated quadricyclanes

The facile access to tetracyclo[3.2.0.0$^{2,7}$.0$^{4,6}$]heptane (quadricyclane) through a photochemically induced [2+2] cycloaddition of the commercially available 2,5-norbornadiene[149] made this framework very attractive for the installation of unusual double bonds (Fig. 18).[150] As a result of some impressive work, Szeimies and co-workers have found evidence for three unsaturated quadricyclanes, 1(7)-quadricyclene **494**,[151] 1(5)-quadricyclene **495**,[152] and 1(2)-quadricyclene, **496**.[153] The elusive anti-Bredt 2(3)-quadricyclene **497** remains unsynthesized.[150,154] Szeimies have performed ab initio calculations [TCSCF/6-31G(d)] on these compounds.[153b] As was the case for the highly strained 1(9)-homocubene **460** that is higher in energy than the other homocubenes (see preceding section), anti-Bredt 2(3)-quadricyclene **497** is less stable than **494**, **495** and **496** by 14.5, 2.7 and 10.5 kcal/mol, respectively. The OSEs for **494**, **495**, **496** and **497** are 67, 79, 71 and 81 kcal/mol, respectively. The value of 79 kcal/mol for the OSE of **495** is the highest computed for a pyramidalized alkene for which at least some experimental evidence for its existence has been provided (calculated value for the OSE of cubene **433** is 58.9 kcal/mol; the experimental value is 63±4 kcal/mol; the calculated value for the OSE of tricyclo[3.3.0.0$^{3,7}$]-oct-1(5)-ene **205a** is 74.7 kcal/mol).[155] While the diradical character of **494**, **495** and **496** is small (9, 11 and 10%, respectively), similar to that calculated for **205a** (11%),[68] the diradical character of **497** is 60%.[153b] Worthy of note is that, while **497** is a local energy minimum at the TCSCF/6-31G(d)//TCSCF/6-31G(d) level of theory, B3LYP/6-31G(d) and MP2/6-31G(d) calculations on **497** did not lead to a local energy minimum, but to a rearranged framework of carbene structure **499**.[150b] Szeimies et al. have also carried out some experiments towards the formation of 1,6-dehydroquadricyclane **498**, a very challenging compound containing four condensed cyclopropane units. Although ab initio calculations showed that **498** is a local energy minimum, it yet remains unsynthesized.[156]

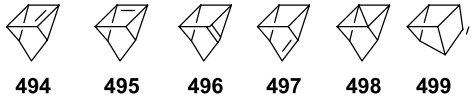
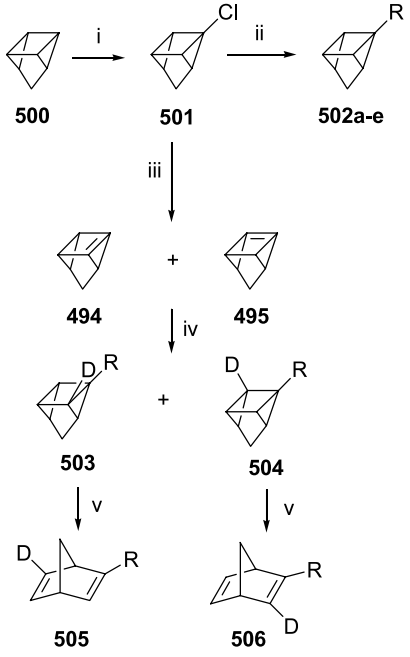
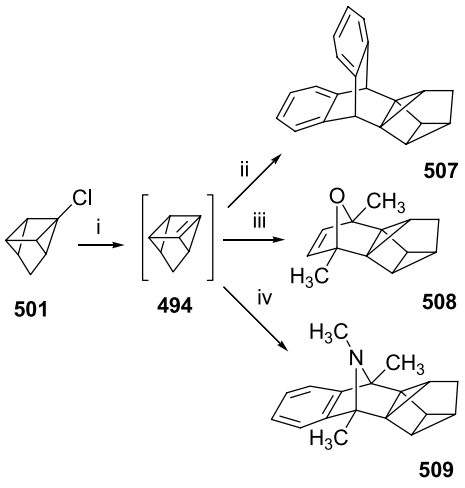



**Figure 18.** Quadricyclenes **494**-**497**, 1,6-dehydroquadricyclane **498** and carbene **499**.

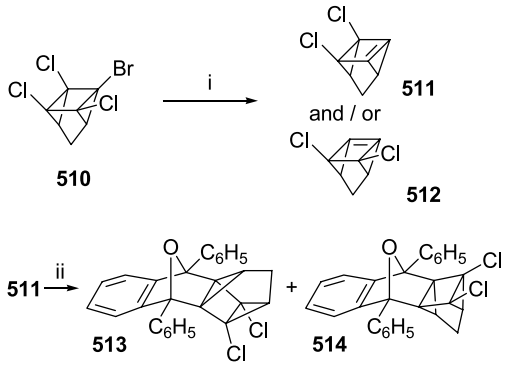
**7.1.1. 1(7)-Quadricyclene.** Metalation of quadricyclane **500** with *n*-butyllithium, followed by chlorination with *p*-toluenesulfonyl chloride, afforded 1-chloroquadricyclane **501** in 44% yield. Treatment of **501** with an excess of organolithium compounds (methyllithium, phenyllithium, *n*-, *s*- and *t*-butyllithium) led to exchange of chlorine for the organic group of the base, probably through an elimination–addition process. In principle, compounds **502a–e** could be generated from **494**, **495** and/or **496**. In order to clarify the correct structure of the intermediate, compound **501** was treated with an excess of *n*-butyllithium, followed by quenching with $D_2O$ and isomerization to the corresponding norbornadiene. $^1$H NMR analysis of the crude residue revealed an 83:17 mixture of **505** and **506**. These results



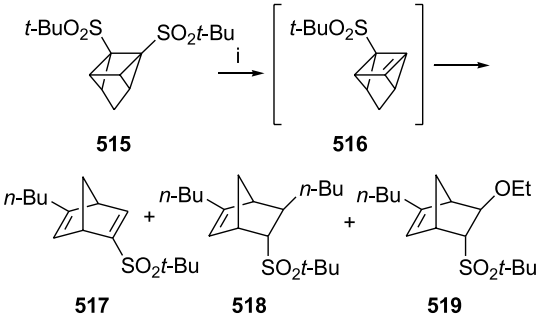

**Scheme 78.** Generation of quadricyclenes **494** and **495**. (i) *n*-BuLi, *n*-hexane, 24 h, 20 °C; then *p*-toluenesulfonyl chloride, 44%; (ii) RLi, $H_2O$, **502a**, R=Me, 36%; **502b**, R=Ph, 32%; **502c**, R=*n*-Bu, 62%; **502d**, R=*s*-Bu, 39%; **502e**, R=*t*-Bu, 41%; (iii) RLi; (iv) $D_2O$; (v) isomerization.




**Scheme 79.** Generation and trapping of 1(7)-quadricyclene **494**. (i) LTMP, 20–60 °C; (ii) anthracene, 35–45%; (iii) 2,5-dimethylfuran, 45%; (iv) 1,2,3-trimethylisoindole, 63%.



**Scheme 80.** Generation and trapping of a dichloro derivative of 1(7)-quadricyclene **511**. (i) *t*-butyllithium, ether/pentane, −78 °C; (ii) 1,3-DPIBF, −78 °C to room temperature.



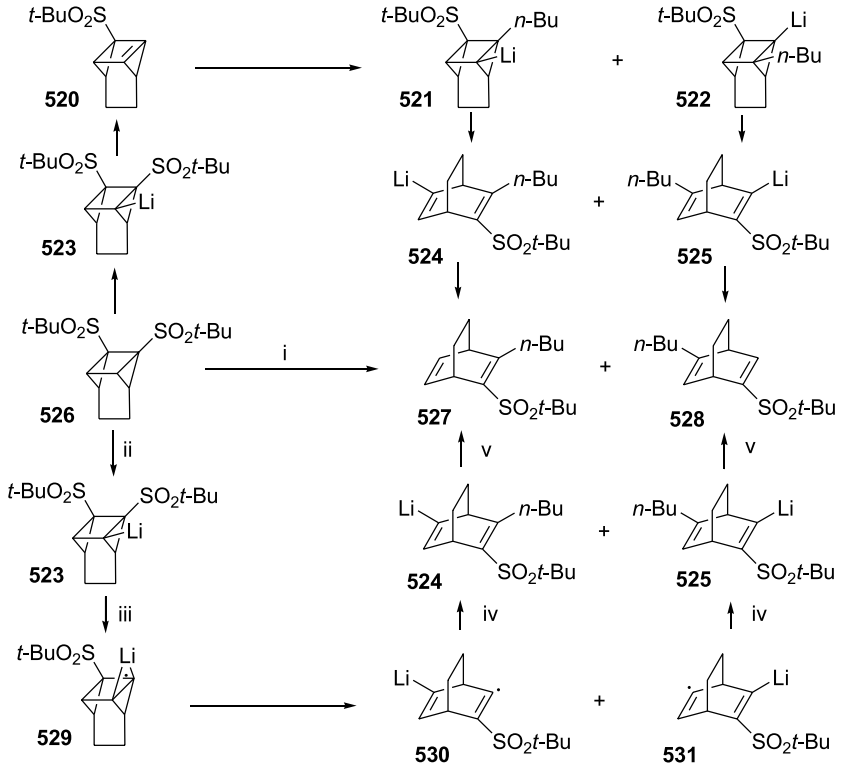
**Scheme 81.** Reaction of quadricyclane **515** with *n*-butyllithium. (i) *n*-butyllithium/diethyl ether, −50 °C; then, ethanol, −78 °C.

advocate **494** as the major, and **495** as the minor, intermediates of the aforementioned processes (Scheme 78).

Further evidence for the formation of 1(7)-quadricyclene **494** was obtained by trapping it as the Diels–Alder adducts with anthracene, 2,5-dimethylfuran or 1,2,3-trimethylisoindole (Scheme 79). Two facts are remarkable in these experiments. First, the formation of **509** is highly stereoselective, the other stereoisomer not being detected, probably as a consequence of steric differences. Secondly, and more important, in these trapping experiments no evidence for the formation of 1(5)-quadricyclene **495** was found. The absence of products arising from **495** could be a consequence of the base used in the trapping experiments, lithium 2,2,6,6-tetramethylpiperidide (LTMP), being weaker than the previously employed organolithium bases, is more selective towards metalation of C7 over C5.[151a–c] The reactivity of these cycloadducts was studied in some detail.[151c]

Moreover, ab initio calculations [TCSCF/6-31G(d)] suggest that **494** is more stable than **495**. Accordingly, the reaction of trichlorobromoquadricyclane **510** with *t*-butyllithium at −78 °C, followed by the addition of 1,3-DPIBF and warming to room temperature, led to a 55:45 mixture of the adducts **513** and **514**, derived from the alkene **511**. No trapping products from **512** were detected (Scheme 80).[150,157]

Worthy of note is that, more recently, Gleiter and Ohlbach tried to generate the 1(7)-quadricyclene derivative **516** (Scheme 81), and the related compound **520** (Scheme 82).



**Scheme 82.** Alternative pathways for the formation of **527** and **528** from **526**. (i) *n*-Butyllithium, diethyl ether, −20 °C; then, methanol; (ii) *n*-butyllithium; (iii) *n*-butyllithium, [−]*t*-BuSO$_2$Li; (iv) *n*-butyl radical; (v) methanol.

Reaction of quadricyclane **515** with *n*-butyllithium at −50 °C led to a mixture of three products **517**, **518** and **519**, the last two being the result of Michael addition of *n*-butyllithium and ethanol to **517**, respectively. In this experiment, neither quadricyclane derivatives, nor an addition product with the *n*-butyl residue adjacent to the sulfonyl group, were detected (Scheme 81).

On the other hand, the reaction of **526** with *n*-butyllithium in ether at −20 °C and subsequent quenching with methanol led to **527** and **528** (Scheme 82).

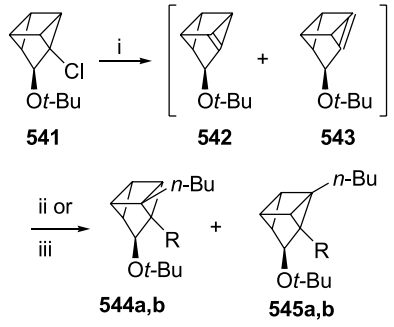
A possible explanation to account for the formation of **527** and **528** would involve the highly pyramidalized alkene **520**, followed by *n*-butyllithium addition, [2+2] cycloreversion and protonation. However, all the efforts directed to the trapping of **520** with 1,3-DPIBF were fruitless.[151d]

The above results contrast with those previously found by Szeimies, so Gleiter assumed that the desulfonylation of **515** and **526** does not involve highly pyramidalized alkenes. Alternatively, he proposed that a radical process initiated by single electron transfer (SET) from the organolithium compound is involved. Thus, the lithiated species **523** does not eliminate a sulfinate anion to generate **520**. Instead, a second molecule of the base provides an electron via an SET process to yield **529** that could lead to the isolated products through ring opening, recombination with the *n*-butyl radical and hydrolysis (Scheme 82).[151d]

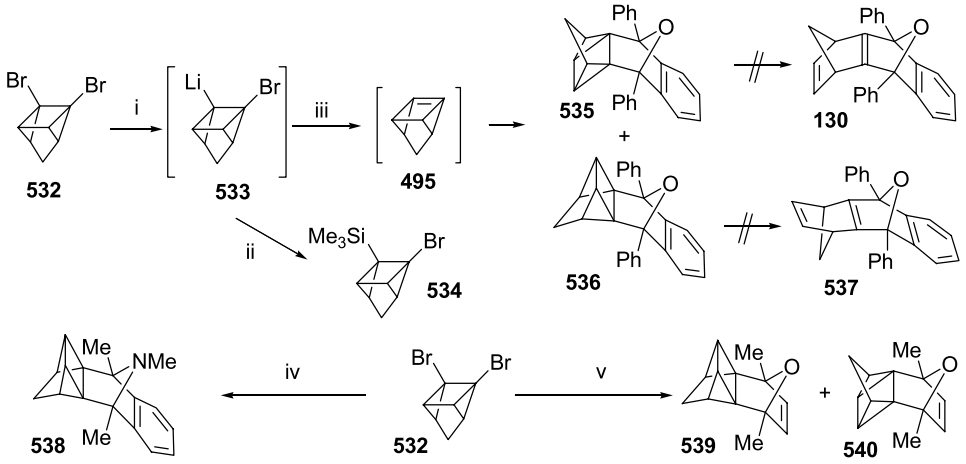
**7.1.2. 1(5)-Quadricyclene.** Ten years after the synthesis and trapping of **494**, Szeimies provided, in 1990, evidence for the existence of 1(5)-quadricyclene **495** as a reactive intermediate. Reaction of **532** with 2 equiv of *t*-butyllithium at −78 °C, followed by quenching with chlorotrimethylsilane, yielded the bromosilane **534** in 60% yield. This result indicated that lithium–bromine exchange indeed occurred, but that, at −78 °C, LiBr elimination to give **495** did not take place.[152] However, when the cooled solution of **533** was added to a solution of 1,3-DPIBF in THF and the solution was allowed to warm to 20 °C, a 16:84 mixture of the Diels–Alder adducts **535** and **536** was isolated in 40% yield. So far, several attempts at isomerizing quadricyclane **535** to the known *syn*-oxasesquinorbornatriene **130** (see Section 4.2) or **536** to the yet unknown *anti*-oxasesquinorbornatriene **537** were unsuccessful. The pyramidalized olefin was also trapped with 1,2,3-trimethylisoindole and 2,5-dimethylfuran in 65 and 23% yields, respectively. Interestingly, while trapping with 1,2,3-trimethylisoindole led only to the cycloadduct **538**, 2,5-dimethylfuran gave a 3:1 mixture of **539** and **540** (Scheme 83).[152]

It is interesting to note that the highly pyramidalized 1(5)-quadricyclene **495** is an isomer of bicyclo[2.2.1]hept-2-en-5-yne **129**, a reactive intermediate that has been recently generated by Kitamura and co-workers (see Scheme 24 in Section 4.2.).[66] MP2/6-31G(d) calculations predicted that **129** is 3.9 kcal/mol more stable than **495**.[61b]

**7.1.3. 1(2)-Quadricyclene.** The first experimental evidence for 1(2)-quadricyclene derivatives was reported by Szeimies and co-workers in 1983. They found that the reaction of **541** with an excess of *n*-butyllithium, followed by quenching with $H_2O$, led to a mixture of **544a** and **545a** in 61% total yield. When the quenching was carried out with $D_2O$, **544b** and **545b** were isolated. The formation of **544** and **545** can be easily explained by lithiation at the C-1 position of **541**, followed by LiCl elimination to give 1(2)-quadricyclene derivatives **542** and **543**, *n*-butyllithium addition to the less



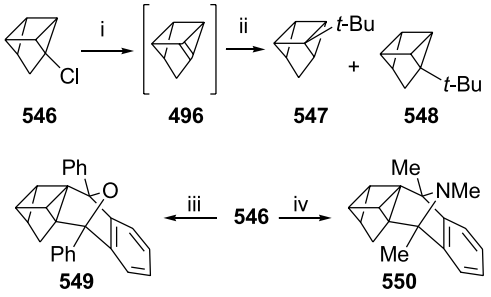

**Scheme 84.** Generation of quadricyclenes **542** and **543**. (i) 2.5 equiv *n*-butyllithium, ether, 20 h, rt; (ii) $H_2O$, **544a** and **545a**, R=H; (iii) $D_2O$, **544b** and **545b**, R=D.




**Scheme 83.** Generation and trapping of 1(5)-quadricyclene **495**. (i) 2.0 equiv *t*-butyllithium, THF/pentane, −78 °C; (ii) chlorotrimethylsilane; (iii) 1,3-DPIBF, 20 °C; (iv) 2.0 equiv *t*-butyllithium, THF/pentane, −78 °C to rt, 1,2,3-trimethylisoindole; (v) 2.0 equiv *t*-butyllithium, THF/pentane, −78 °C to rt, 2,5-dimethylfuran.

crowded carbon atom of the double bond and quenching (Scheme 84).[153a]

Ten years later, the same group reported the intermediacy of the parent alkene **496**. Deprotonation of 2-chloroquadricyclane **546** with an excess of *t*-butyllithium and aqueous workup led to a mixture of **547** and **548**, probably through **496**. Further evidence for the formation of **496** is found in the trapping experiments carried out with the less nucleophilic LDA in the presence of 1,3-DPIBF or 1,2,3-trimethylisoindole. Both experiments led stereoselectively to the Diels–Alder adducts **549** and **550**, respectively (Scheme 85).[153b]




**Scheme 85.** Generation and trapping of 1(2)-quadricyclene **496**. (i) Excess of *t*-butyllithium, ether, 0 °C; (ii) $H_2O$; (iii) LDA, THF, 0 °C, 1,3-DPIBF, 67%; (iv) LDA, THF, 0 °C, 1,2,3-trimethylisoindole.

## 7.2. Bicyclo[*n*.1.0]alk-1(*n*+2)-enes

Wiberg and co-workers have calculated the OSEs for compounds **551**–**554** (Fig. 19) and found values of 63, 68, 54 and 46 kcal/mol, respectively. The OSE of cyclopropene is 24 kcal/mol.[158]

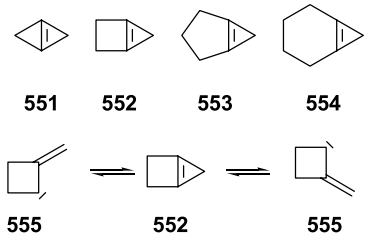



**Figure 19.** Bicyclo[*n*.1.0]alk-1(*n*+2)-enes, for *n*=1–4, and scrambling of **555** through **552**.

HF and MP2/6-31G(d) calculations suggested that **553** and **554** are fairly normal compounds, except for their high strain energy, whereas **552** may be a transition state for the carbon scrambling of 2-methylenecyclobutylidene **555**.[158] Compound **551**, with a carbon–carbon double bond length of 1.375 Å, and a pyramidalization angle of 35.6° [B3LYP/6-31G(d)],[13c] has a singlet ground state with an unusual charge-density distribution.[158]

More recently, Wiberg and Márquez, using MP2/6-31G(d) and B3LYP/6-311+G(d,p) calculations, found that, whereas **551** is indeed bent, the perfluoro derivative is almost planar, probably as a consequence of the known stabilization of cyclopropene by fluorine substitution.[159]

### 7.2.1. Bicyclo[1.1.0]but-1(3)-ene and its 2,4-bridged derivatives.

Recently, Yates calculated the pyramidalization angles for bicyclo[1.1.0]but-1(3)-ene **551** and its 2,4-bridged derivatives **556**–**559** (see Fig. 20).[13e] In comparing **551** with some of the previously studied pyramidalized alkenes, two features are remarkable. Firstly, whereas in the highly pyramidalized alkenes such as tricyclo[3.3.0.0$^{3,7}$]-oct-1(5)-ene **205a** or cubene **433**, pyramidalization is a consequence of structural constraints from an unpyramidalized bicyclic compound, bicyclo[3.3.0]oct-1(5)-ene **201** and bicyclo[2.2.0]hex-(4)-ene **38**, respectively, in the bicyclo[1.1.0]but-1(3)-ene **551**, pyramidalization occurs without these constraints. Secondly, while in the series of tricyclo[3.3.*n*.0]alk-3(7)-enes progressive shortening of the bridge led to an enormous increment in the pyramidalization (from **201** to **205a**, $\Phi$ increases by 56°), as bicyclo[1.1.0]-but-1(3)-ene **551** already has a strongly pyramidalized structure, bridging it to give **556** only leads to an increment of 21.7° in the pyramidalization angle.[12c]

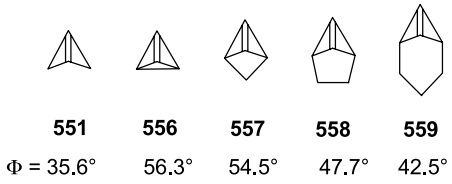
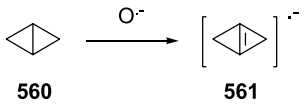


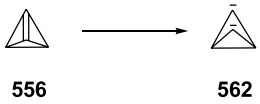

**Figure 20.** Pyramidalization angles [B3LYP/6-31G(d)] for bicyclo[1.1.0]-but-1(3)-ene **551** and its bridged derivatives **556**, **557**, **558** and **559**.

To date, bicyclo[1.1.0]but-1(3)-ene **551** and its bridged derivatives **556** and **557** have not been synthesized. However, Chou and Kass have reported the preparation of the bicyclo[1.1.0]but-1(3)-ene radical anion **561** by the reaction of bicyclo[1.1.0]butane **560** with atomic oxygen ion in the gas phase (Scheme 86).[160] Although most hydrocarbons do not form stable radical anions in the gas phase, because the loss of an electron is exothermic (the electron affinity is negative), the formation of **561** is quite reasonable, taking into account that, as previously noted, pyramidalization lowers the energy of the LUMO and increases the electron affinity.




**Scheme 86.** Formation of the bicyclo[1.1.0]but-1(3)-ene radical anion **561**.

Very interestingly, Sauers et al. have carried out a computational study at the RCCD/cc-pVDZ level of tetrahedrene **556**. Their calculations indicate that tetrahedrene is a metastable compound at best and rearrangement to the more stable bis-carbene **562** should be taken into

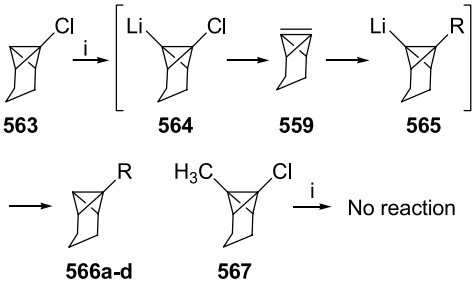



**Scheme 87.** Opening of tetrahedrene **556** to bis-carbene **562**.

account in any experimental effort to synthesize the yet unknown tetrahedrene (Scheme 87).[161]

Szeimies and co-workers have synthesized and extensively studied **558** and **559** and some related compounds. He comprehensively reviewed the topic in 1992 and no further work in this area has been carried out and, therefore, only a brief perspective of these highly pyramidalized olefins will be given here. The interested reader is referred to the review for further details.[150a]

The reaction of **563** with an excess of *n*-butyllithium at room temperature, followed by water addition, led to **566a** in 87% yield. Likewise, *s*-butyllithium, *t*-butyllithium and phenyllithium gave the corresponding 1-substituted tricycloheptanes in yields of 30, 30 and 62%, respectively. Taking into account that the starting material was recovered unchanged after exposure of **567** to *n*-butyllithium, the above results can be understood through the intermediacy of tricyclo[4.1.0.0$^{2,7}$]hept-1(7)-ene **559**, as depicted in Scheme 88.[162]




**Scheme 88.** Generation of tricyclo[4.1.0.0$^{2,7}$]hept-1(7)-ene **559**. (i) *n*-Butyllithium (for **566a**), *s*-butyllithium (for **566b**), *t*-butyllithium (for **566c**) and phenyllithium (for **566d**); then water.

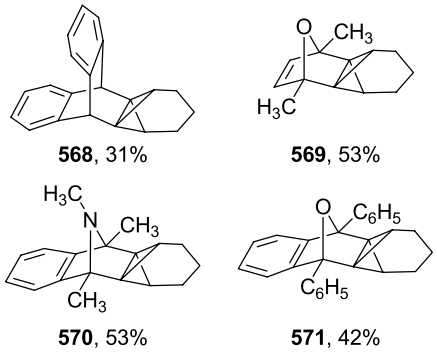


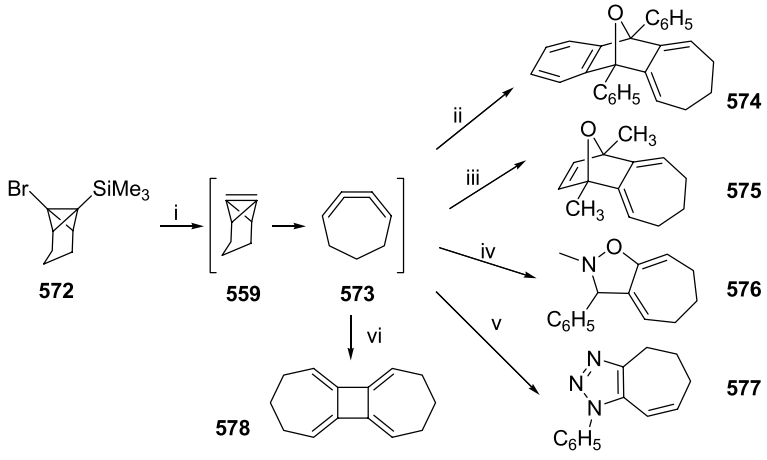

**Figure 21.** Diels–Alder adducts of highly pyramidalized alkene **559**.

When the generation of **559** was carried out in the presence of 1,3-dienes using the less nucleophilic LDA or LTMP, Diels–Alder adducts such as **568**–**571** were isolated in medium yields (Fig. 21).[163]

A very interesting feature of **559** is its thermal isomerization to cyclohepta-1,2,3-triene **573**. Szeimies found that **559** could also be generated by an elimination reaction involving fluoride-induced desilylation of **572** at higher temperatures (80–100 °C) than those previously used. Using these conditions, trapping of **559** with dienes (anthracene, 2,5-dimethylfuran, 1,3-DPIBF, etc) did not lead to Diels–Alder adducts of **554**, but to polycyclic cyclohepta-1,3-dienes such as **574** or **575**. Moreover, some 1,3-dipoles reacted with **573** to yield the expected heterocycles, some of which underwent a hydrogen shift to the corresponding more stable aromatic compounds.[164] It is well known that Ni(0) complexes catalyze the dimerization of 1,2,3-butatrienes.[165] Not unexpectedly, the reaction of **572** with cesium fluoride at 20 °C in the presence of [$(Ph_3P)_4Ni$] led to the dimer **578** in 32% yield (Scheme 89).[166]

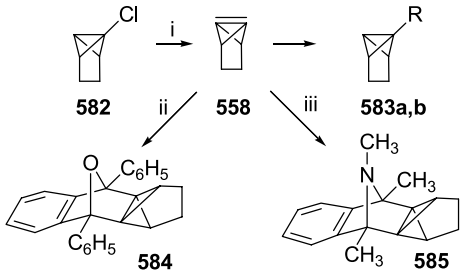
In addition to tricyclo[4.1.0.0$^{2,7}$]hept-1(7)-ene **559**, Szeimies' group has also reported the generation of some related compounds, such as **579**, **580** and **581** (Fig. 22). Their reactivity (Diels–Alder trapping, rearrangement to cyclohepta-1,2,3-trienes) is very similar to that of the parent compound.[150a,167]


**Figure 22.** Highly pyramidalized alkenes related to **559**.



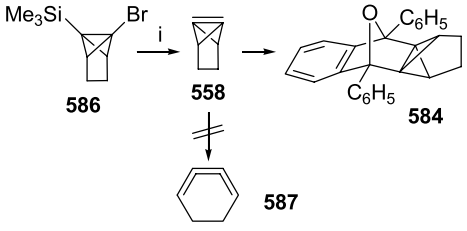

**Scheme 89.** Generation, trapping and dimerization of cyclohepta-1,2,3-triene, **573**. (i) KF, DMSO; (ii) 1,3-DPIBF, 59%; (iii) 2,5-dimethylfuran, 75%; (iv) *N*-methyl-α-phenylnitrone, 53%; (v) phenylazide, 50%; (vi) 10% [$(Ph_3P)_4Ni$], 32%.

Tricyclo[3.1.0.0$^{2,6}$]hex-1(6)-ene **558**, a lower homologue of **559**, was also first generated by a base-catalyzed elimination reaction.[167] Its behaviour is similar to that previously observed in **559**. For example, treatment of the chloride **582** with an excess of organolithium bases gave the corresponding addition products **583a**,**b**. In addition, the olefin was trapped as its Diels–Alder adduct with 1,3-DPIBF and 1,2,3-trimethylisoindole (Scheme 90).[168,169]

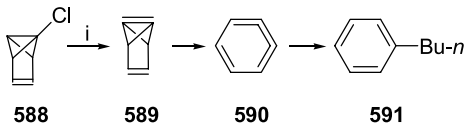



**Scheme 90.** Generation and trapping of tricyclo[3.1.0.0$^{2,6}$]hex-1(6)-ene, **558**. (i) For **583a**, R=*n*-Bu; *n*-butyllithium; then $H_2O$, quantitative; for **583b**, R=$C_6H_5$; *n*-phenyllithium; then $H_2O$, 65%; (ii) 1,3-DPIBF, 20%; (iii) 1,2,3-trimethylisoindole, 52%.

Interestingly, so far, all attempts to convert **558** into cyclohexa-1,2,3-triene **587** have failed.[170] Thus, when **558** was generated by fluorodesilylation of **586**, no evidence was obtained for the rearrangement (Scheme 91). The different behaviour of **558** and **559** can be understood taking into account that, according to ab initio calculations, **558** is only slightly more strained than **559** (OSE of **558** is only 8 kcal/mol higher than that of **559**), but **587** is considerably more strained than **573**. In fact, when an additional double bond was introduced into the skeleton of **558**, the rearrangement did occur, because the aromaticity of the rearranged product provides a driving force that favours it. Thus, the reaction of 1-chlorobenzvalene **588** with an excess of *n*-butyllithium at −105 °C yielded only *n*-butylbenzene **591**, probably formed by the addition of *n*-butyllithium to benzyne, a rearrangement product of dehydrobenzvalene **589** (Scheme 92).[171]

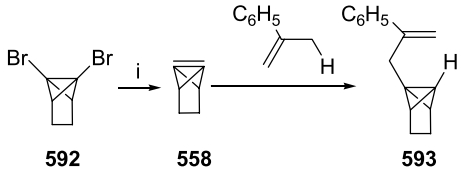



**Scheme 91.** Unsuccessful attempts to generate cyclohexa-1,2,3-triene, **587**. (i) CsF, 20–150 °C, 1,3-DPIBF.




**Scheme 92.** Generation of **589** and its rearrangement to **590**. (i) *n*-Butyllithium, −105 °C, 45%.

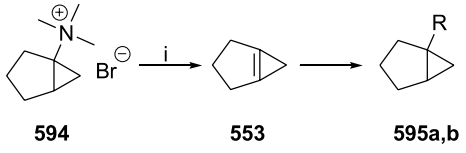
An interesting aspect of the reactivity of **558**, not explored with other pyramidalized alkenes, is the feasibility of undergoing ene reactions. For example, generation of **558** in the presence of α-methylstyrene led to **593**, the product of an ene reaction, in 48% yield (Scheme 93). Other olefinic traps, such as 2,3-dimethylbuta-1,3-diene, 2-methylpent-1-ene, isobutene and 2,3-dimethylbut-1-ene, were also successfully used.[172]




**Scheme 93.** Ene reaction of **558** with α-methylstyrene. (i) 2.5 equiv *t*-butyllithium, THF, −78 °C, 48%.

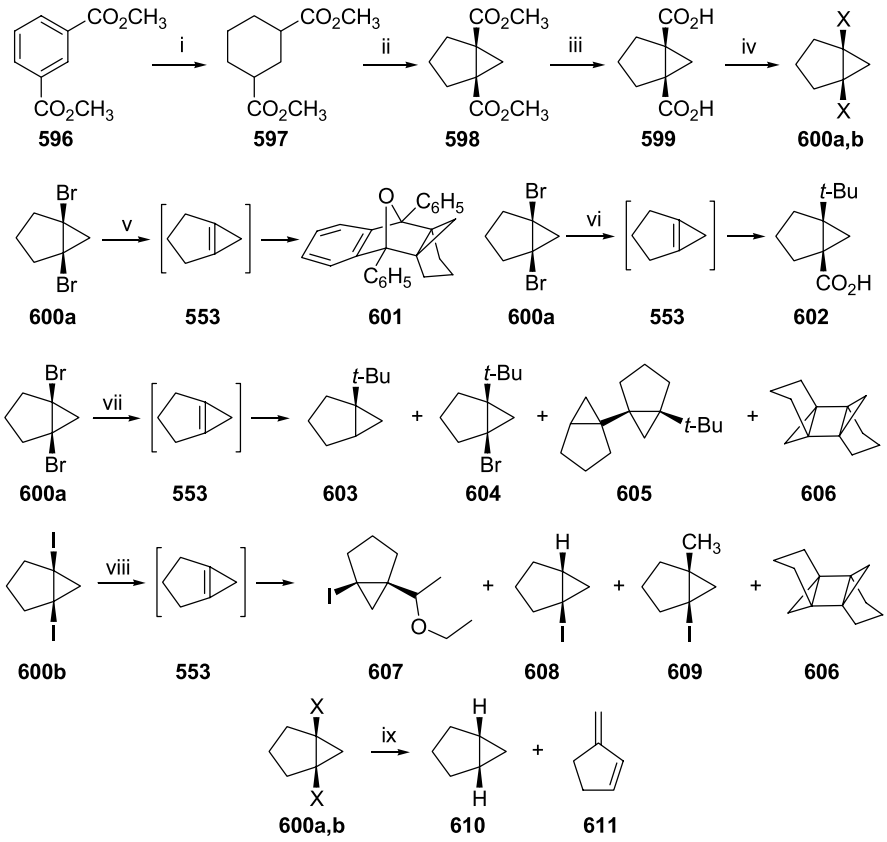
**7.2.2. Bicyclo[2.1.0]pent-1(4)-ene.** Bicyclo[2.1.0]pent-1(4)-ene **552** has not yet been synthesized, although the known 1(7)-quadricyclene **494**, can be envisaged as a derivative of **552** (see Section 7.1.1). As already noted, HF and MP2/6-31G(d) calculations suggest that **552** might be a transition state for the carbon scrambling of 2-methylenecyclobutyl carbene **555** (Fig. 19). In fact, the vibrational frequency analysis of **552** at the HF/6-31G(d) level found a single imaginary frequency. However, although HF/6-31G(d) calculations predicted that the carbene **555** is 22.2 kcal/mol more stable than **552**, at the MP3/6-31G(d,p)//MP2/6-31G(d) level, the carbene is only 1.5 kcal/mol more stable than **552**.[158] Thus, further work with this system is highly desirable.

**7.2.3. Bicyclo[3.1.0]hex-1(5)-ene.** The first evidence for the formation of bicyclo[3.1.0]-1(5)-ene **553** was reported by Blanchard et al. in 1965. They found that the reaction of 1-bicyclo[3.1.0]hexyltrimethylammonium bromide **594** with methyl- or phenyllithium led to the isolation of 1-methyl- or 1-phenylbicyclo[3.1.0]hexane **595a**,**b**, respectively. In order to account for the formation of these compounds, the authors proposed the intermediacy of **553** (Scheme 94).[173]




**Scheme 94.** Generation of bicyclo[3.1.0]hex-1(5)-ene **553**. (i) Methyllithium, 25 °C, ether, 5 days; then water, 30% **595a**, R=$CH_3$.

Later, Wiberg and co-workers further investigated the chemistry of **553**. The dihalides **600a**,**b** were readily prepared from the dicarboxylic acid **599** via halodecarboxylation reactions. Evidence for the formation of the cyclopropene intermediate was obtained by trapping with reactive dienes. For example, the reaction of **600a** with *t*-butyllithium in the presence of 1,3-diphenylisobenzofuran led to the Diels–Alder adduct **601** in 63% yield. When the diene was omitted from the reaction, a mixture of hydrocarbons that should have reasonably been produced via **553** was isolated. The intermediacy of **553** was further corroborated when the reaction of **600a** with *t*-butyllithium was repeated and the solution was treated with carbon



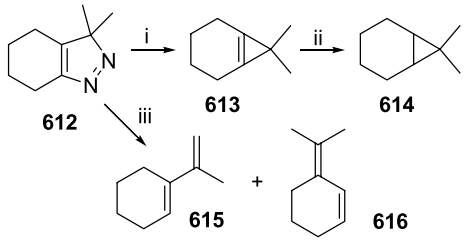

**Scheme 95.** Generation of bicyclo[3.1.0]hex-1(5)-ene **553**. (i) $H_2$, $Rh/Al_2O_3$, 99%; (ii) LDA, −78 °C, THF; then $I_2$, 93%; (iii) KOH, methanol–water; then HCl, 74%; (iv) HgO, $Br_2$, h$\nu$, $CH_2Cl_2$, 39% for **600a**; or IBDA, $I_2$, h$\nu$, cyclohexane, 37% for **600b**; (v) 1,3-diphenylisobenzofuran, *t*-butyllithium, −78 °C, THF; then water, 63%; (vi) *t*-butyllithium, −78 °C, THF; then dry ice; 33%; (vii) *t*-butyllithium, −78 °C, THF; then water, **603** (5%), **604** (8%), **605** (8%), and **606** (5%); (viii) methyllithium, −78 °C, THF; then water, **607** (28%), **608** (28%), **609** (7%), and **606** (12%); (ix) potassium atoms in an argon stream.

dioxide before workup. In this case, the carboxylic acid **602** was isolated in 33% yield (Scheme 95).[158a,174]

On the other hand, the reaction of **600b** with methyllithium gave 1-iodo-5-(1-ethoxyethyl)bicyclo[3.1.0]hexane **607** (28% yield), 1-iodobicyclo[3.1.0]hexane **608** (28%), dimer **606** (12%), 1-iodo-5-methylbicyclo[3.1.0]hexane **609** (7%), and very small amounts of two tetrameric compounds that could not be isolated.[158a]

Finally, Wiberg and co-workers studied the dehalogenation of **600b** in the gas phase. Either dehalogenation with potassium atoms or with solid methyllithium led to a mixture of bicyclo[3.1.0]hexane **610** and methylenecyclopentene **611**, in a 2:1 ratio. It is likely that **611** is formed from **553** via a vinylcarbene intermediate.

**7.2.4. Bicyclo[4.1.0]hept-1(6)-ene and related compounds.** Although the parent compound was not synthesized until much later, the first bicyclo[4.1.0]hept-1(6)-ene to be synthesized was its 7,7-dimethyl derivative **613**. As early as 1963, Closs and Boll reported that photolysis of 4,5,6,7-tetrahydro-3,3-dimethyl-3*H*-indazole **612**, at −65 °C, followed by hydrogenation at −40 °C, led to 7,7-dimethylbicyclo[4.1.0]heptane **614**, probably through the intermediacy of the 1(6)-unsaturated derivative **613** (Scheme 96). In addition, the irradiation of **612** in pentane at −20 °C, followed by workup at room temperature, led to a mixture of 3-isopropylidenecyclohexene **616** and 1-isopropenylcylohexene **615** and a mixture of dimers, which was not further investigated. Taking into account that this work was carried out 40 years ago, it is highly admirable that these researchers were even able to record the $^1$H NMR spectrum of **613** at −35 °C.[175]



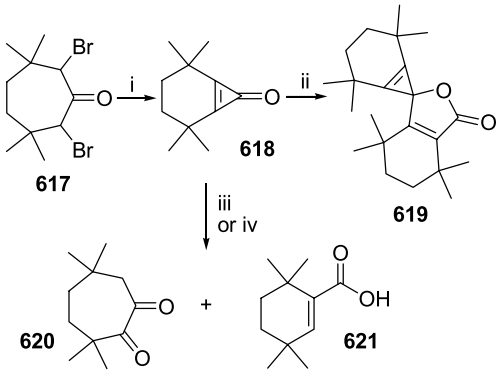

**Scheme 96.** Synthesis of 7,7-dimethylbicyclo[4.1.0]hept-1(6)-ene, **613**. (i) h$\nu$, ether/pentane, −65 °C; (ii) $H_2$/Pd–C, −40 °C; (iii) h$\nu$, pentane, −20 °C, then aqueous work-up at room temperature.

In 1974, Suda and Masamune reported the preparation of 2,2,5,5-tetramethylbicyclo[4.1.0]hept-1(6)-en-7-one **618**, by base-induced dehydrobromination of **617** at −20 °C. Compound **618** is very sensitive to basic and acidic media. Reaction of **618** with 0.05 N NaOH in aqueous THF at room temperature led to a 3:2 mixture of **620** and **621**. Upon brief treatment of **618** with 0.1 N $H_2SO_4$ at room temperature, quantitative conversion into **621** was observed. While **554** and **613** are very unstable compounds, **618** is thermally much more stable, probably as a consequence of the aromaticity of the cyclopropenone unit.[176] Notwithstanding,

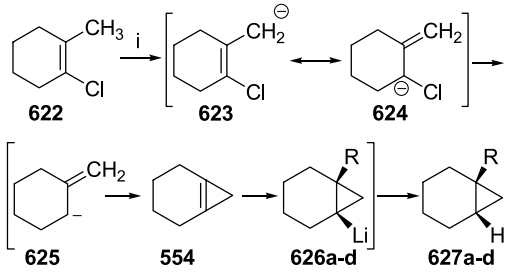
cyclopropenone **618** dimerizes in a thermal reaction to give the spirolactone **619** that also contains a bicyclo[4.1.0]hept-1(6)-ene unit (Scheme 97).[176b]

Very recently, Irngartinger and co-workers have reported the X-ray crystal structure of **619** and found a pyramidalization angle of 30.9° for this dimer. In this compound, pyramidalization is a mechanism for reducing the repulsion between the lactone oxygen lone pairs and the occupied π-orbital.[177]

In 1979, Gassman and co-workers reported the first evidence for the parent compound. They investigated in




**Scheme 97.** Synthesis and reactivity of **618**. (i) *t*-BuOK, THF, −20 °C, 41%; (ii) △; (iii) 0.05 N NaOH aqueous THF, rt, 3:2 mixture of **620** and **621** (iv) 0.1 N $H_2SO_4$, rt, **621** only.



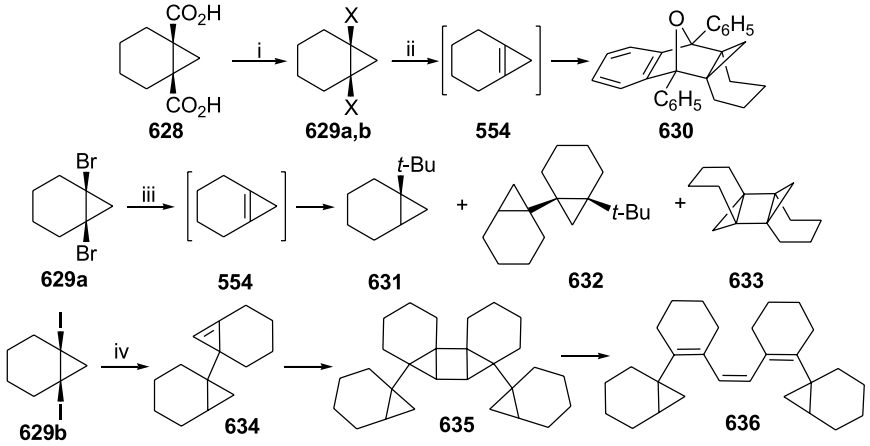

**Scheme 98.** Generation of **554** from **622**. (i) 5 equiv of organolithium, 0 °C, THF; then water. **627a**, R=vinyl, 30%; **627b**, R=*n*-Bu, 52%; **627c**, R=$C_6H_5$, 90%; **627d**, R=$CH_3$, 47%.

detail the reactions of 1-chloro-2-methylcyclohexene **622** with organolithium reagents to give 1-substituted bicyclo[4.1.0]heptanes, **627a–d**. They proved that the mechanism of these processes involved the deprotonation of **622** by an organolithium, α-elimination of lithium chloride to yield an allylic carbene, intramolecular addition of the carbene to the double bond to yield **554**, addition of the organolithium to **554**, and neutralization (Scheme 98).[178]

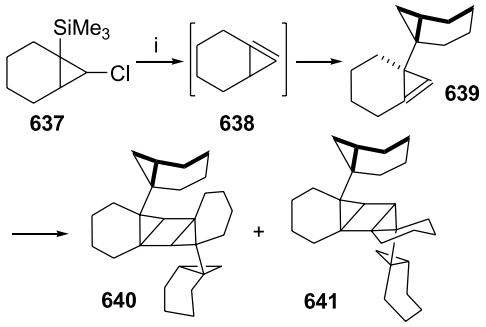
Later, Wiberg and co-workers further studied the chemistry of **554**. In work that parallels that carried out by the same group with **553**, the dihalides **629a**,**b** were prepared from the dicarboxylic acid **628**. Reaction of **629a** with *t*-butyllithium in the presence of 1,3-diphenylisobenzofuran led to the Diels–Alder adduct **630** in 71% yield. When the diene was omitted from the reaction, a mixture of hydrocarbons containing 1-*t*-butylbicyclo[4.1.0]heptane **631** as the major product was isolated.[158a,174] Interestingly, the reaction of **629b** with methyllithium led to a very complex mixture of products, which the tetramer **636**, either with a *Z* or *E* arrangement at the central C=C double bond, being the main component. The origin of **636** was explained taking into account that **554** can dimerize through an ene reaction to the dimer **634**, from which tetramers such as **635** and **636** could arise (Scheme 99).[158a]

Although in this work the stereochemistry of **634**, **635** and **636** was not determined, subsequently, Billups and co-workers reported that *n*-$Bu_4NF$-mediated gas phase elimination from 1-(trimethylsilyl)-7-chlorobicyclo[4.1.0]heptane **637** generated bicyclo[4.1.0]hept-1(7)-ene **638**, which dimerized below −90 °C to **639**. This dimer was isolated and fully characterized and, slowly, dimerized further, mainly to a cyclobutane derivative in 84% yield. The structure of this compound was shown by single-crystal X-ray analysis to be the tricyclohexane **640**. A minor tetramer, identified as **641** by X-ray crystallography, was also isolated. The carbon skeleton connectivity found in these X-ray analyses firmly established the stereochemistry of the precursor **639** (Scheme 100).[179]

More recently, in 1996, Billups, Wiberg and co-workers revisited, in a collaborative project, the chemistry of bicyclo[4.1.0]hept-1(6)-ene. They generated **554** from **642**

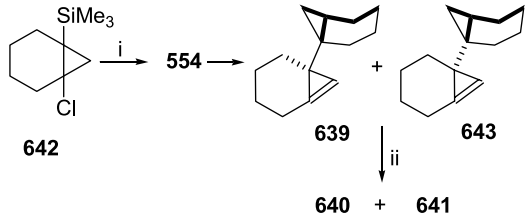



**Scheme 99.** Generation of **554**. (i) **629a**; X=Br: HgO, $Br_2$, $CH_2Cl_2$, 89%; **629b**; X=I: IBDA, $I_2$, cyclohexane, 47%; (ii) *t*-butyllithium, THF, −78 °C, 1,3-diphenylisobenzofuran, 71%; (iii) *t*-butyllithium, THF, −78 °C, **631** (25%), **632** (4%), **633** (traces); (iv) methyllithium, THF, −78 °C, **636** (51%).



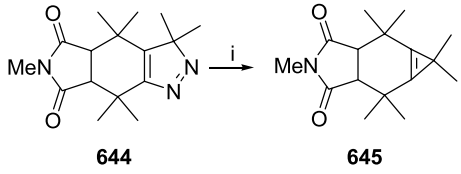

**Scheme 100.** Synthesis and dimerization of anti-Bredt alkene **638**. (i) Solid *n*-$Bu_4NF$, solid matrix, −196 °C; then warm to room temperature, 84% yield of **640**.

by $Me_3SiCl$ elimination over a solid fluoride at 25 °C and 10 mTorr. Under these conditions, alkene **554** underwent ene reactions to give the dimers **639** and **643**. The formation of two diastereomers from **554** stands in contrast to **637**, which gives only **639** (Scheme 101).[180]




**Scheme 101.** Gas phase generation of **554**. (i) Solid *n*-$Bu_4NF$, solid matrix, −196 °C; then warm to 0 °C; (ii) warm to room temperature, several days.

Although bicyclo[4.1.0]hex-1(6)-ene, is not a stable compound, Ando and co-workers have succeeded in synthesizing and fully characterizing its derivative **645**. Following Closs and Böll's methodology, photolysis of **644** in benzene at room temperature gave **645** (63% yield) (Scheme 102).[181]




**Scheme 102.** Synthesis of compound **645**. (i) h$\nu$, rt, benzene, 63%.

Surprisingly, **645** is a stable crystalline compound that was fully characterized. The X-ray crystal analysis of **645** revealed an essentially planar six-membered ring with an angle between this ring and the cyclopropene ring of 162.4°, which is only 3.1° larger than that previously computed [B3LYP/6-31G(d)] for the parent **554**. As expected, taking into account the pyramidalization of **638**, the $^{13}C$ NMR spectrum of **645** shows a large downfield shift for the olefinic carbon ($\delta=155.5$ ppm), ca. 30 ppm lower than those found for tetramethyl- and 3,3-dimethylcyclopropene.[181]

Some bicyclo[5.1.0]oct-1(7)-enes have been synthesized (Fig. 23) following sequences that parallel those of the corresponding bicyclo[4.1.0]oct-1(6)-enes.[175b,178b,182] The pyramidalization angle of bicyclo[5.1.0]oct-1(7)-en-8-one

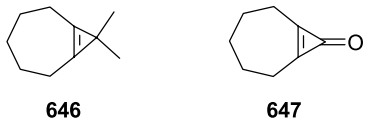



**Figure 23.** Bicyclo[5.1.0]oct-1(7)-ene derivatives.

**647** has been crystallographically determined ($\Phi=7.9°$).[177] Not surprisingly, **646** and **647** are fairly stable compounds.

It is worthy of note that Gleiter and co-workers have synthesized bicyclo[8.1.0]undec-1(10)-en-5-yn-11-one **648** and some related compounds **649** and **650** (Fig. 24). X-ray structural analysis of **648** showed an average pyramidalization angle of 3.6°.[183]

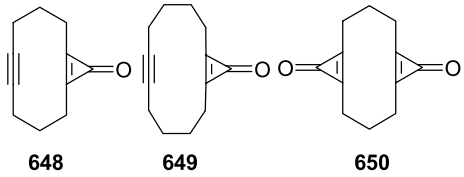



**Figure 24.** Bicyclo[8.1.0]undec-1(10)-en-5-yn-11-one **648** and related compounds **649** and **650**.

### 7.3. Tricyclo[3.2.1.$0^{2,4}$]oct-2(4)-ene, tricyclo[3.2.2.$0^{2,4}$]non-2(4)-ene and related compounds

Tricyclo[3.2.1.$0^{2,4}$]oct-2(4)-ene may be viewed either as a bicyclo[4.1.0]hept-1(6)-ene with one carbon atom bridge between C2 and C5 or, alternatively, as a bicyclo[3.1.0]hex-1(5)-ene derivative with an additional two carbon atom bridge between C2 and C4. Of course, one can also consider tricyclo[3.2.1.$0^{2,4}$]oct-2(4)-ene as a norbornene with a fused cyclopropene unit. On the other hand, tricyclo[3.2.2.$0^{2,4}$]non-2(4)-ene may be viewed as a derivative of bicyclo[4.1.0]hept-1(6)-ene with an additional two carbon atom bridge between C2 and C5.

In 2000, Williams, Colvin, Warrener and co-workers published a theoretical study of the cyclopropenyl-fused tricycles shown in Fig. 25.[72] Norbornene is only very slightly pyramidalized, but joining the cyclopropene ring substantially increases the pyramidalization. Ab initio (RHF, MP2, TCSCF) and DFT (B3LYP, B3PW91, SVWN) methods showed that **651**, **652**, **653** and **654** are very pyramidalized, with dihedral angles between the cyclopropene and the norbornene ring, $\zeta\approx41$–$50°$, and with both *endo* and *exo* bent isomers. In the norbornyl derivatives **651** and **652** the *endo* bent isomers were more stable than the *exo* bent isomers, whereas in **654** the *exo* bent isomer is the lower-energy form. Worthy of note is that, despite the symmetry-based expectation that the double bond of **653** should be planar, it is significantly pyramidalized [MP2/6-31G(d), $\zeta=45.8°$] in the degenerated *endo* and *exo* ground states. Williams et al. also calculated the activation barriers for the *endo*/*exo* interconversions and

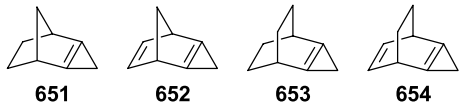
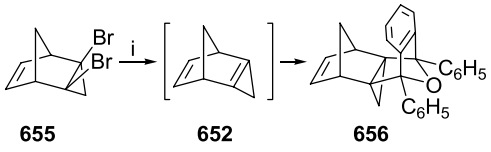


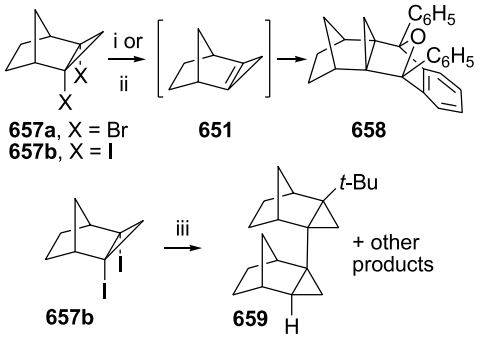

**Figure 25.** Pyramidalized alkenes **651–654**.

found relatively low values [HF/6-31G(d) level, $\Delta H^{\#} \approx 6$–13 kcal/mol].

**7.3.1. Tricyclo[3.2.1.0$^{2,4}$]oct-2(4)-ene and related compounds.** In 1991, Mühlebach and Neuenschwander generated and trapped tricyclo[3.2.1.0$^{2,4}$]octa-2(4),6-diene **652**, an unsaturated derivative of the title compound **651**. Diels–Alder reaction of cyclopentadiene with 1,2-dibromocyclopropene led to the precursor **655**. Reaction of **655** with an excess of *t*-butyllithium in THF at −78 °C in the presence of 1,3-DPIBF led to the cycloadduct **656** in 40% yield, the structure of which was determined by a careful NMR study (Scheme 103).[184]




**Scheme 103.** Synthesis and trapping of tricyclo[3.2.1.0$^{2,4}$]octa-2(4),6-diene **652**. (i) *t*-Butyllithium, THF, −78 °C, 1,3-DPIBF; 40% **656**.



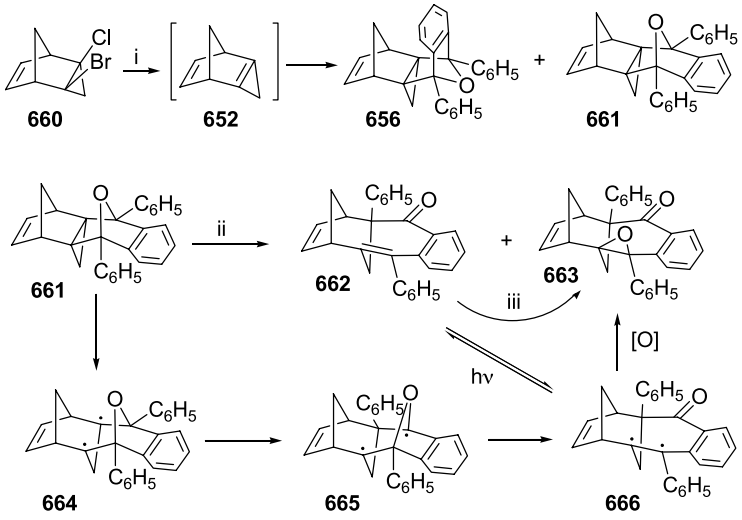

**Scheme 104.** Trapping of tricyclo[3.2.1.0$^{2,4}$]oct-2(4)-ene **651**. (i) **657a**, *t*-Butyllithium, THF, −78 °C, 1,3-DPIBF; **658** and other stereoisomer; (ii) **657b**, *t*-butyllithium, THF, −78 °C, 1,3-DPIBF; **658** and the three other stereoisomers; (iii) *t*-butyllithium, THF, −78 °C; then, methanol; complex mixture containing **659**.

The first evidence for the existence of tricyclo[3.2.1.0$^{2,4}$]-oct-2(4)-ene **651** was reported by Chenier and co-workers in 1992.[185] Reaction of dibromide **657a** or diiodide **657b** with *t*-butyllithium in THF at −78 °C in the presence of 1,3-DPIBF led mainly to Diels–Alder adducts derived from **651**. Interestingly, while the reaction with the dibromide gave mainly (what the authors believed to be) **658** and another stereoisomer that was not fully characterized, reaction with the diiodide gave evidence for the formation of the four possible stereoisomeric cycloadducts (Scheme 104).

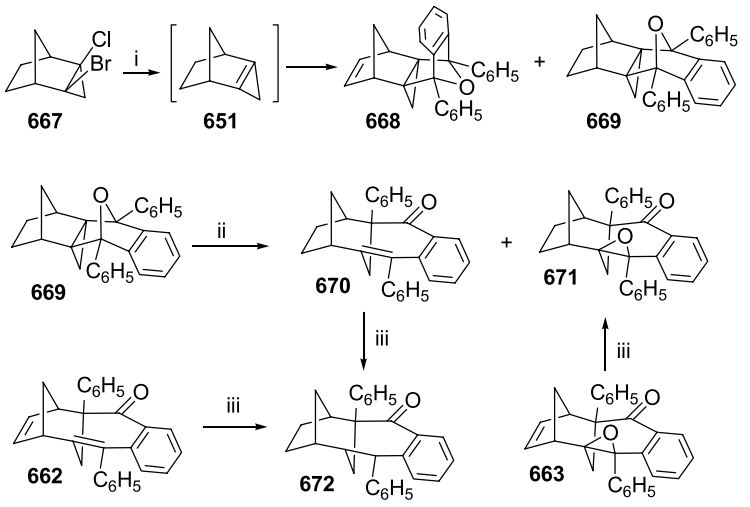
When the 1,3-DPIBF was omitted from the reaction, a very complex mixture of products was formed. Some dimeric products such as **659** were partially identified and probably arose via the well-known ene reaction of cyclopropenes that have already been encountered in bicyclo[4.1.0]hept-1(6)-ene.

Five years later, in 1997, Lee and co-workers further studied the chemistry of **651** and **652**. The precursor **660** was synthesized by a Diels–Alder reaction of cyclopentadiene with 1-bromo-2-chlorocyclopropene. Reaction of **660** with methyllithium in the presence of 1,3-DPIBF led to a mixture of two of the four possible stereoisomers, the known **656** and **661** in a 1:2 ratio (Scheme 105). Interestingly, when this mixture was allowed to stand at room temperature for several days, while **656** was stable and its structure could be secured by single-crystal X-ray analysis, **661** decomposed to a mixture of **662** and **663**, which were also fully characterized including X-ray analysis.[186] Taking into account that the intermediates of the well-known isomerization of tricyclo[3.2.1.0$^{2,4}$]oct-6-enes to tetracyclo-[3.3.0.0$^{2,7}$.0$^{4,6}$]octanes are biradicals,[187] Lee proposed that the isomerization of the cycloadduct **661** to the styrene derivative **662** occurs via biradical **666** (Scheme 105). The reaction of compound **661** with oxygen to form epoxide **663** also involved biradical **666**. In fact, irradiation of **662** in the presence of oxygen resulted in the formation of epoxide **663** in 94% yield (Scheme 105).[186]

Hydrogenation of **660** with rhodium on carbon furnished **667**. Reaction of **667** with methyllithium in ether in the



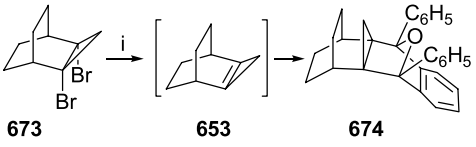

**Scheme 105.** Generation and trapping of **652** and chemistry of the Diels–Alder adduct **661**. (i) Methyllithium, 1,3-DPIBF, THF, **656** (31%); (ii) 5 d at rt, **662** (15%) and **663** (45%); (iii) oxygen, h$\nu$, 24 h, $CDCl_3$, 94%.




**Scheme 106.** Generation and trapping of **651** and chemistry of the Diels–Alder adduct **669**. (i) Methyllithium, 1,3-DPIBF, THF, **658** (63%); (ii) 5 d at rt, **670** (16%) and **671** (15%); (iii) 50 psi $H_2$/Pd–C, methanol, quant.

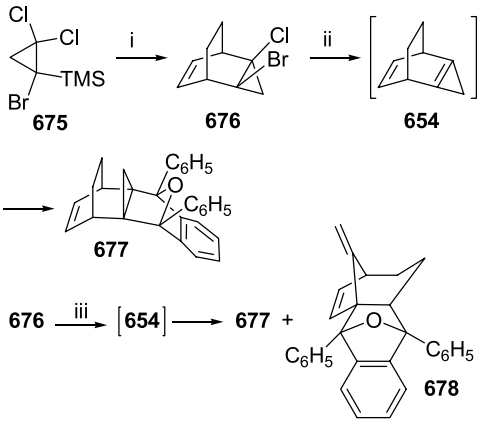
presence of 1,3-DPIBF gave a 2:1 mixture of **668** and **669**. Similar to the behavior of **661**, adduct **669** rearranged to a mixture of **670** and **671**. The structure of **668** was secured by single-crystal X-ray analysis. In order to determine the structure of **670**, compounds **662** and **670** were hydrogenated and both reactions led to the same compound **672**. Additionally, hydrogenation of **663** led to **671** (Scheme 106).[186]

**7.3.2. Tricyclo[3.2.2.0$^{2,4}$]non-2(4)-ene and related compounds.** The generation of tricyclo[3.2.2.0$^{2,4}$]non-2(4)-ene **653** was first described by Chenier and co-workers in 1989. Treatment of dibromide **673** with an excess of *t*-butyllithium in the presence of 1,3-DPIBF in THF at −78 °C, followed by quenching and column chromatography, allowed the isolation of one of the two possible stereoisomers. NMR studies suggested that the structure of this cycloadduct is **674**, with the methylene and oxygen in a *syn* configuration (Scheme 107).[188]




**Scheme 107.** Generation and trapping of **653**. (i) *t*-Butyllithium, −78 °C, THF, 1,3-DPIBF, 57%.

Ten years later, Lee and co-workers synthesized an unsaturated derivative of **653**, tricyclo[3.2.2.0$^{2,4}$]non-2(4),6-diene **654**. Its precursor **676** was prepared by the reaction of cyclohexa-1,3-diene with 1-bromo-2-chlorocyclopropene, which was generated in situ by the fluoride-induced elimination of 1-bromo-2,2-dichloro-1-trimethylsilylcyclopropane **675**. Elimination from **676** with methyllithium in ether at 0 °C yielded the desired **654**, which was trapped with 1,3-DPIBF. Only one of the four possible stereoisomers was detected. X-ray crystal analysis unambiguously assigned **677** as the structure of the Diels–Alder cycloadduct (Scheme 108).[189]

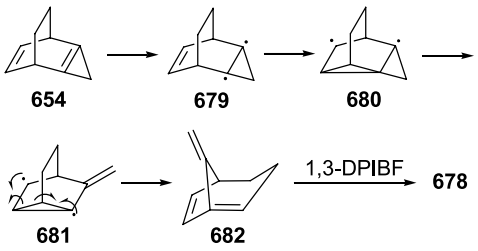



**Scheme 108.** Generation and trapping of **654**. (i) *n*-$Bu_4NF$, cyclohexa-1,3-diene, $CH_2Cl_2$, 12 h, 62%; (ii) methyllithium, THF, 1,3-DPIBF, 0 °C, 4 h, 82%; (iii) methyllithium, ether, 0 °C, 10 min.; then, 1,3-DPIBF in THF, 4 h at rt, **677** (36%) and **678** (43%).

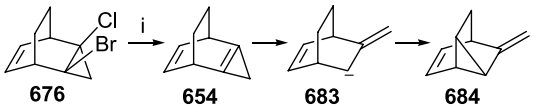
Very interestingly, when **676** was reacted with methyllithium at 0 °C for 30 min and then a solution of 1,3-DPIBF in THF was added to the mixture, in addition to **677**, another isomer was isolated. The structure of this isomer was shown by single-crystal X-ray analysis to be **678** (Scheme 108). This new compound was formed by trapping of the anti-Bredt compound **682**, which, in turn, was produced by the isomerization of **654**. The authors suggested a diradical mechanism for the isomerization that involved rearrangement of **654** to **680**, electrocyclic opening of the cyclopropyl radical **680** to give a new 1,4-diradical **681**, which was transformed to **682** by breaking the C2–C3 bond (Scheme 109).[189]

Very recently, Lee and co-workers have utilized the vacuum gas-solid reaction (VGSR) technique to generate **654** in order to study its chemistry in neat conditions. Interestingly, under these conditions, **654** did not rearrange to the anti-Bredt compound **682**, but to the tricyclic compound **684** via a vinyl carbene mechanism (Scheme 110).[189]

Finally, we should mention that Chenier has carried out an




**Scheme 109.** Possible mechanism for the rearrangement of **654** to **682**.




**Scheme 110.** VGSR generation of **654** and rearrangement to **684**. (i) Methyllithium, VGSR conditions, 94% **684**.

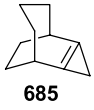
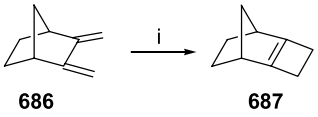



**Figure 26.** Tricyclo[3.3.2.0$^{2,4}$]dec-2(4)-ene **685**.

unsuccessful attempt to generate tricyclo[3.3.2.0$^{2,4}$]dec-2(4)-ene **685**, a higher analog of **651** and **653** (Fig. 26).[190]

Related to the aforementioned compounds, Aue and Reynolds reported that the photolysis of 2,3-dimethylenebicyclo[2.2.1]heptane **686** gives air-sensitive **687** in 80% yield.[191] Compound **687** features a norbornyl unit fused with a cyclobutene ring and thermally reversed to diene **686**, a process that has been experimentally and theoretically studied by Houk and co-workers.[192] B3LYP/6-31G(d) calculations showed a flap angle between the two rings of **687** of 18.5° (Scheme 111).[193]




**Scheme 111.** Synthesis of tricyclo[4.2.1.0$^{2,5}$]non-2(5)-ene **687**. (i) h$\nu$, pentane, 0 °C, 80%.

## 8. Anti-pyramidalized alkenes

Anti-pyramidalization is calculated to be energetically less costly than *syn*-pyramidalization. However, few studies have been carried out in the area of *anti*-pyramidalized alkenes and, most importantly, there is still a lack of highly *anti*-pyramidalized alkenes.

According to its X-ray crystal structure and DFT theoretical calculations, heptafulvalene **688** has an *anti*-pyramidalized $C_{2h}$ structure. This conformation is lower in energy than the *syn*-pyramidalized $C_{2v}$ conformation.[194]

Probably, the best known examples of *anti*-pyramidalized alkenes are bridged tetraarylethylenes, such as bianthranylidenes **689**, dixanthylenes **690**, biacrylidenes **691**,

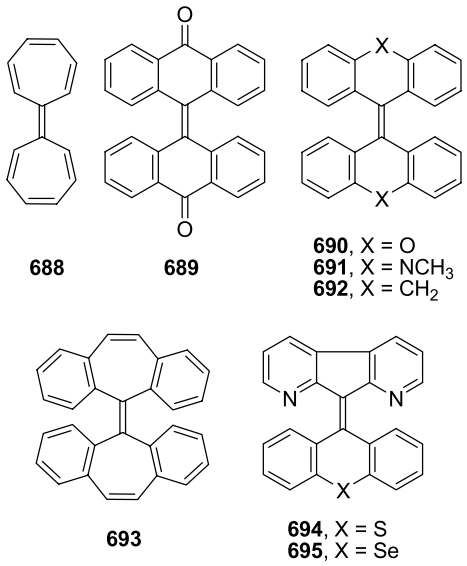



**Figure 27.** Anti-pyramidalized alkenes **688–695**.

bianthrylidenes **692**, and bi-5*H*-dibenzo[*a*,*d*]cyclohepten-5-ylidene **693** (Fig. 27).

According to Sandström, who reviewed this topic in 1997, coplanarity in these compounds is made impossible by the close approach of the neighbouring *peri* hydrogen atoms, and the compounds have two principal routes to minimize the steric strain. One way, twisting, is to rotate the two halves of the molecule about the formal double bond while retaining the planarity of the tricyclic parts, and another, folding, is to introduce pyramidalization at the double-bond carbon atoms, leading to *anti*- or *syn*-folding of the tricyclic parts.[3b]

Recently, Agranat and co-workers have reviewed the conformational- and stereochemical-related issues of several bistricyclic ethylenes, including compounds **689**, **690** and **693**, which showed very small pyramidalization angles (e.g., 4.8° for **690**).[195] More recently, the same group has reported the synthesis and crystal structures of 1,8-diazafluorenylidene-chalcoxanthenes **694** and **695** that have a higher degree of pyramidalization (ca. 17°) in the six-membered ring olefinic carbon atom.[196]

It is evident that, although very interesting advances have been carried out in the last few years, more work in this area is highly desirable.

## 9. Perspectives

Fifteen years have passed since the publication of the seminal review on pyramidalized alkenes by Borden in *Chemical Reviews* in 1989.[8b] In this period, many landmark achievements have been attained. The synthesis of several derivatives of the highly pyramidalized tricyclo[3.3.0.0$^{3,7}$]-oct-1(5)-ene, the synthesis of polyunsaturated dodecahedranes, the generation of acepentalene and related compounds, the dimerization of cubene and the synthesis of cyclopropene-fused norbornene derivatives are representative examples. On the other hand, pyramidalized alkenes

have started to show their potential as intermediates for the synthesis of more complex polycyclic compounds. The impressive work by Herges' group with the 9,9′,10,10′-tetradehydrodianthracene **8** is the best example.

Is there still work to do? For two enthusiasts of the topic, the answer is an emphatic 'yes'. To cite just a few very interesting targets that have been mentioned in the literature and that undoubtedly will stimulate the reader, we will mention two dehydroprismanes **701** and **702**, [6]-prismane derivative **704** (Fig. 28), and beltenes **705** and **706** (Fig. 29).

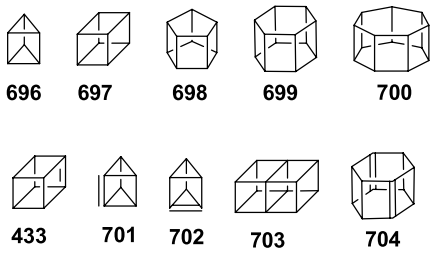



**Figure 28.** Prismanes **696–700** and some related compounds.

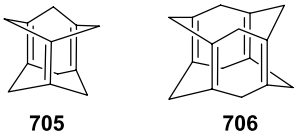



**Figure 29.** Beltenes **705** and **706**.

Prismanes are an infinite, aesthetically pleasing family of $(CH)_n$ polyhedranes that have long fascinated organic chemists.[197] While Katz and Acton reported the synthesis of [3]-prismane **696**[198] and Eaton and co-workers successfully accomplished the synthesis of [4]-prismane (cubane) **697**,[138,199] [5]-prismane (pentaprismane) **698**,[200] and an unsaturated derivative of cubane ('cubene') **433** (see Section 6.1), all higher-order prismanes, including [6]-prismane ('hexaprismane') **699**, and [7]-prismane ('hepta-heptaprismane') **700**, remain unknown.[197,201] Frenking and Jonas have carried out ab initio calculations on two [3]-prismenes, tetracyclo[2.2.0.0$^{2,6}$.0$^{3,5}$]hex-1(4)-ene **701**, in which the double bond is common to two four-membered rings, and tetracyclo[2.2.0.0$^{2,6}$.0$^{3,5}$]hex-1(2)-ene **702**, in which the double bond is common to a four- and a three-membered ring. These calculations showed that both compounds are minima on the $C_6H_4$ potential energy surface, and the most stable **702** should be detectable in appropriate experiments.[202]

On the other hand, some time ago, Schaefer and Seidl theoretically studied two beautifully symmetrical compounds, a face-fused dicubane **703** and its isomer **704**, a doubly unsaturated [6]-prismane.[203] We have theoretically revisited the structure of diene **704** using B3LYP/6-31G(d) calculations and found a flap angle between the two rings of $\zeta=41.8°$, a pyramidalization angle of $\Phi=78.1°$ and a distance between the two double bonds of 2.659 Å.[61b] Taking into account that cubene **433** posseses a pyramidalization angle of $\Phi=84.1°$,[12c] **704** could be an achievable target.

Beltenes **705** and **706** are also very interesting targets. Some years ago, Johnson carried out theoretical calculations on both compounds.[204] While **705** seems to be too pyramidalized to be isolable, pyramidalization in the tetraene **706** (29.3°) is comparable to that in the stable Wiberg's diene **44** (27.3°), so one might expect **706** to be isolable. Higher homologues in this series should pose no problems.[205]

Considering these and other targets that we have already mentioned in the review, such as tetrahedrene, we believe that new pyramidalized alkenes will be generated in the following years. Who dare to try?

## Acknowledgements

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**Biographical sketch**

**Santiago Vázquez** was born in Barcelona in 1968. He studied Pharmacy (1986–1991) at the Universitat de Barcelona. He obtained his PhD in Organic and Medicinal Chemistry at the same university in 1996 under the direction of Professor P. Camps. After spending 2 years (1998–1999) in the Christopher Ingold Laboratories (University College London) with Professor William B. Motherwell as a Marie Curie Research Fellow, he returned to Barcelona. In 2001 he took up his present position as 'Investigador Ramón y Cajal' at Universitat de Barcelona. His scientific interests include polycyclic cage compounds, drug synthesis and free radical and computational chemistry.

**Pelayo Camps** graduated in chemistry in the Universitat de Barcelona (UB). His PhD studies were carried out at the Organic Chemistry Institute (CSIC, Barcelona) under the direction of Prof. Dr. José Pascual, completing his doctoral thesis and obtaining the PhD degree from the same University in 1972. This year started his docent carrier at the Universitat Autònoma de Barcelona (UAB) as Assistant Professor. In 1978, after a postdoctoral stage at the University of Aix-Marseille-III with Prof. Dr. José Elguero, he was promoted to Associate Professor of the Faculty of Pharmacy of the Universidad de Valencia (UV), where he stayed for a year, returning to the UAB in 1979. Two years later obtained a Full Professor position in the Faculty of Chemistry (San Sebastian) of the Universidad del País Vasco where he spent 2 years. After five more years in the Faculty of Pharmacy of the UV, in 1988, he moved to his actual position as a Full Professor in the Faculty of Pharmacy of the UB where he is currently the Head of the Pharmaceutical Chemistry Unit. His research interest has been always related with the organic synthesis of different kind of compounds: polycyclic and cage compounds via highly pyramidalized alkenes, acetylcholinesterase inhibitors for the treatment of Alzheimer's disease, and the use of chiral auxiliaries for the asymmetric synthesis of drugs and related compounds. He has previously held a visiting professorship at the University of Bordeaux.

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# Acid-catalysed synthesis and deprotection of dimethyl acetals in a miniaturised electroosmotic flow reactor

Charlotte Wiles, Paul Watts* and Stephen J. Haswell

*Department of Chemistry, The University of Hull, Cottingham Road, Hull, HU6 7RX, UK*

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**Abstract**—Through incorporating a series of polymer-supported acid catalysts into a miniaturised EOF-based flow reactor, we demonstrate a clean and efficient technique for the protection of aldehydes as their respective dimethyl acetal. In addition, we also report the acid catalysed deacetalisation of 11 dimethyl acetals to their respective aldehyde. In all cases, the compounds described are obtained in high yield (>95%) and excellent purity (>99%) without the need for further product purification.


## 1. Introduction

As a result of increasing environmental pressure, the chemical industry as a whole are exploring many routes to improve both the cleanliness and efficiency of many synthetic processes. One such approach is the application of micro reaction technology, which enables reactions to be performed more rapidly, efficiently and selectively than traditional batch-scale reactions. Although many groups have demonstrated the advantages of synthesising small organic compounds in micro fabricated devices, few have addressed the problems associated with purification of reaction products prepared using continuous flow systems.[1] In order to address this, we recently investigated the use of silica-supported catalysts in a micro fabricated device whereby analytically pure products were synthesised.[2]

Compared to solid-phase techniques,[3] where reaction intermediates and products cannot be fully characterised until they are cleaved from the support, the use of solid-supported reagents is advantageous as reaction products remain in solution thus enabling the reaction to be monitored with time.[4] Additionally, as the supported reagent can be easily removed from the reaction mixture, excess amounts can be employed in order to drive the reaction to completion. Although solid-supported reagents have many advantages over their solution phase counterparts, one main limitation is the support degradation that occurs as a result of stirring or shaking. Therefore by performing reactions in continuous flow reactors, such as the one described herein, the support material undergoes minimal physical degradation, resulting in extended reagent lifetime and system reproducibility.[5–7]

Automation of this technique would therefore, enable the high-throughput synthesis of analytically pure compounds, suitable for the fine chemical industry or combinatorial applications. With these factors in mind, we propose that by incorporating a series of solid-supported acid catalysts into miniaturised flow reactors, problems such as corrosion of reactor vessels, generation of acidic waste and the inability to recover/recycle the catalyst can be addressed. In order to demonstrate the advantages associated with the proposed technique, the acid catalysed synthesis of dimethyl acetals and their deprotection was investigated.

### 1.1. Acid catalysed acetalisation

Acetals are one of the most common carbonyl protecting groups, prepared by the treatment of aldehydes (or ketones) with alcohols (or orthoformates) in the presence of an acid catalyst (Scheme 1). Although triflic acid and *p*-toluenesulfonic acid are generally used, other catalysts include ferric chloride,[8] ammonium nitrate[9] rhodium(III) complexes[10] and ethanolic hydrogen chloride.[11] In addition, numerous examples of solid-supported acid catalysts have been applied to the synthesis of acetals, these include, Amberlite resin,[12] Amberlyst-15 (dry),[13] polymer-supported lanthanides,[14] and Nafion-H.[15,16] As Scheme 1 illustrates, hydrolysis of an acetal with an aqueous acid, affords the respective carbonyl compound. Consequently, as

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* Corresponding author. Tel.: +44 1482 465471; fax: +44 1482 466416; e-mail: p.watts@hull.ac.uk

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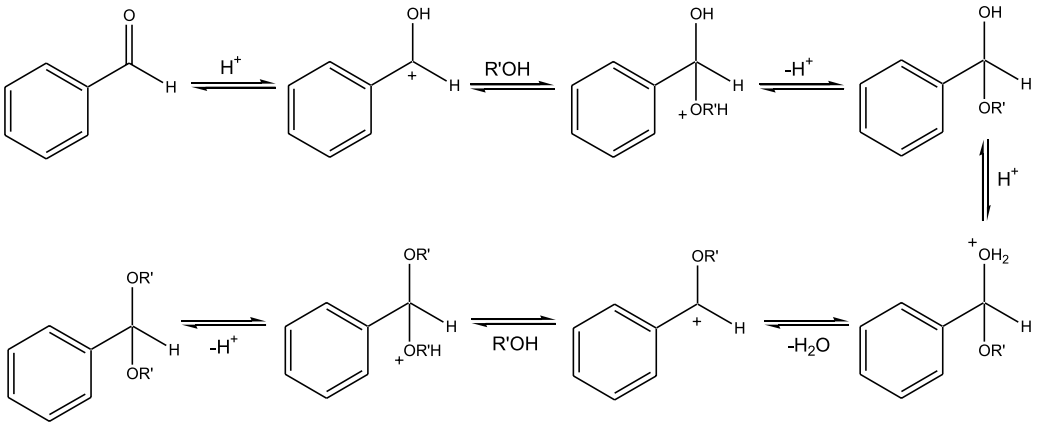



**Scheme 1.** Schematic illustrating the acid catalysed acetalisation of an aldehyde.

neither the forward or reverse reaction is base catalysed, acetals are frequently employed as protecting groups.

### 1.2. How are reactions performed?

To conduct a reaction, the starting materials are passed over a solid-supported reagent or catalyst and the reaction products are collected at the outlet (Fig. 1). The reaction mixture is then analysed by GC–MS whereby conversion of starting material to product is determined. If any residual starting material is observed the reaction is repeated, this time passing the reagents over the support at a slower flow rate, thus having the effect of increasing the reagents residence time within the reactor. When successfully optimised, the devices are operated continuously in order to prepare sufficient quantity of product for analysis by NMR spectroscopy and if required, elemental analysis. Using this approach, work-up is extremely simple, consisting of concentrating the reaction product in vacuo followed by analysis. By optimising the flow rate, and hence residence time within the reactor, it is possible to obtain complete conversion of starting materials to product in a single pass through the device (Scheme 3).

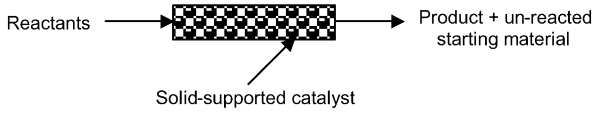



**Figure 1.** Schematic illustrating the use of solid-supported catalysts in a continuous flow reactor.

### 1.3. Pumping mechanism

Although examples of pressure-driven micro fluidic systems have featured widely in the literature,[17] owing to its simplicity, the evaluation of polymer-supported acid catalysts was carried out using electroosmotic flow (EOF). The advantages of using this approach are, it is simple to use, requires no mechanical parts, enables reproducible pulse-free flow, generates minimal back-pressure, can alter both the direction and magnitude of flow and can be easily automated. Of the many positive features associated with the use of EOF, in this case, the generation of minimal backpressure and reproducible flow are the most important.

### 1.4. Principle of electroosmotic flow

When an ionisable surface such as glass,[18] quartz[19] or teflon,[20] comes in contact with a suitable solvent system, the surface is neutralised with a diffuse layer of positive ions from the bulk liquid. A proportion of the counterions are adsorbed onto the surface resulting in an immobile layer and the remaining ions form a transient double layer (Fig. 2). Application of an electric field causes the double layer to move towards the oppositely charged electrode, inducing bulk flow within the channel/capillary.

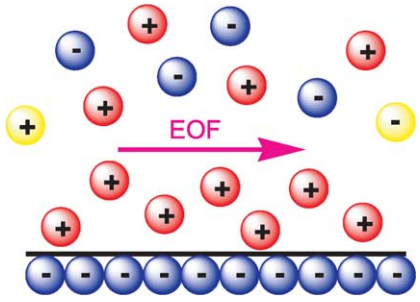



**Figure 2.** Schematic illustrating the principle of electroosmotic flow for a negatively charged glass surface.

As electrokinetic flow is a surface phenomenon, the physical properties of the fluid have a direct bearing on the flow rates observed (Eq. 1), consequently the technique is typically employed for polar, low viscosity solvent systems. In addition, in order to preserve the diffuse double layer, the solutions must be >pH 2. Below this, no EOF is observed as an immobile layer replaces the diffuse positive ions. Consequently, performing reactions that require acidic reagents can be problematic, in order circumvent this problem we recently demonstrated an alternative approach to the synthesis of esters[21] and McCreedy et al.[22] reported

$$v_{\mathrm{eof}} = -\frac{E\varepsilon\varepsilon_0\zeta}{\eta}$$

$v_{eof}$ = electroosmotic flow velocity, $E$ = applied field, $\varepsilon$ = relative dielectric constant of the fluid, $\varepsilon_0$ = the permittivity of free space, $\zeta$ = zeta potential and $\eta$ = viscosity.

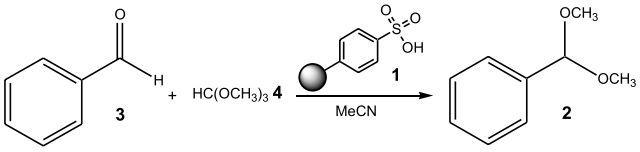
**Equation 1.** Determination of electroosmotic flow (EOF) velocity.[24]

the use of a sulphated zirconia catalyst for the dehydration of alcohols. More recently, Crocker et al.[23] reported the use of amine functionalised electrokinetic micro pumps for the mobilisation of acidic solutions (0.1% TFA in $H_2O$/MeCN) whereby nl $min^{-1}$ flow rates were obtained. Therefore, by incorporating polymer-supported acids into micro fabricated devices, we are able to conduct reactions that otherwise could not be performed efficiently within EOF-based devices.

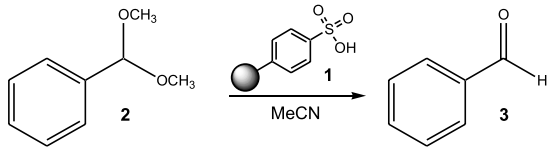
## 2. Results and discussion

### 2.1. Synthesis of dimethyl acetals using Amberlyst-15

Amberlyst-15 (dry) **1** is a sulfonic acid based cation exchange resin that has been widely employed for the preparation of acetals, ketals, tetrahydropyranyl ethers and enol ethers.[25] Using the synthesis of dimethoxymethyl benzene **2** as a model reaction, we investigated the use of Amberlyst-15 **1** in a micro fabricated device (Scheme 2).




**Scheme 2.** General scheme illustrating the acid catalysed synthesis of dimethoxymethyl benzene **2** using Amberlyst-15 **1**.




**Scheme 3.** Deacetalisation of dimethoxymethyl benzene **2** using Amberlyst-15 **1**.

Using EOF, the starting materials are passed over Amberlyst-15 **1**, the reaction mixture is then collected at the outlet and analysed by GC–MS. As Figure 3 illustrates, Amberlyst-15 **1** (dry) (2.5 mg, $1.05\times10^{-2}$ mmol) was packed into a borosilicate glass capillary (500 μm× 3.0 cm) and held in place using micro porous silica frits.[26] The capillary was then primed with MeCN to remove any

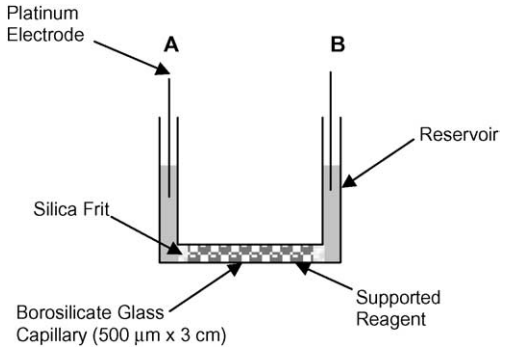



**Figure 3.** Schematic of the reaction set-up used for the evaluation of the polymer-supported acid catalysts.

air, ensuring the formation of a complete circuit, and the capillary attached to two glass reservoirs. The reagents were manipulated through the device via the application of a voltage to the platinum electrodes placed in the reagent reservoirs. As Figure 4 illustrates, benzaldehyde **3** and trimethylorthoformate **4** (40 μl, 1.0 and 2.0 M, respectively) in MeCN was placed in reservoir A and MeCN in reservoir B (40 μl). Application of 333 and 0 V $cm^{-1}$ respectively, resulted in the mobilisation of the reaction mixture at a flow rate of 1.75 μl $min^{-1}$. After 10 min, the reaction products were collected from reservoir B, diluted with MeCN, and analysed by GC–MS, whereby 100% conversion to dimethoxymethyl benzene **2** was obtained with respect to residual benzaldehyde **3**. In order to demonstrate both system reproducibility and the continuous synthesis of dimethoxymethyl benzene **2**, the reaction was repeated a further 14 times (2.5 h), whereby conversions of >99.6% were obtained (Table 1). After analysis by GC–MS, all reaction products were collected and concentrated in vacuo, to afford dimethoxymethyl benzene **2** as a pale yellow oil (0.025 g, 96.6%). In order to confirm product purity, the crude reaction mixture was analysed by NMR spectroscopy, whereby no residual aldehyde was observed.

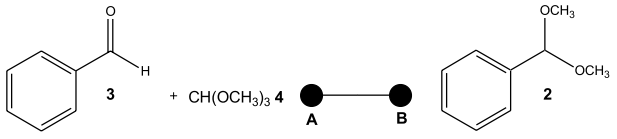



**Figure 4.** Schematic illustrating the manifold set-up used for the synthesis of dimethyl acetal **2** in an EOF-based micro reactor.

**Table 1**. Illustration of system stability over 15 runs for the synthesis of dimethoxymethyl benzene **2**

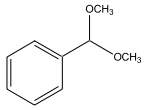
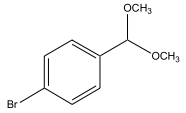
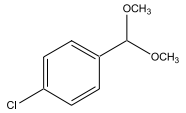
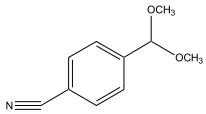
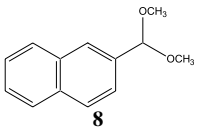
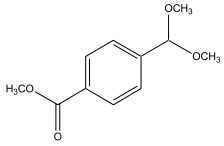
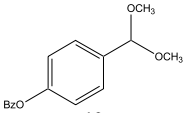
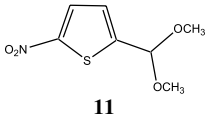
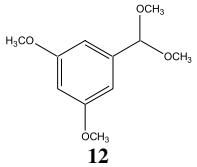
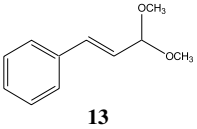
| Run No. | Conversion (%) |
|---|---|
| 1 | 100.0 |
| 2 | 99.58 |
| 3 | 99.68 |
| 4 | 99.83 |
| 5 | 99.87 |
| 6 | 99.69 |
| 7 | 99.65 |
| 8 | 99.75 |
| 9 | 99.70 |
| 10 | 99.74 |
| 11 | 99.71 |
| 12 | 99.63 |
| 13 | 99.90 |
| 14 | 100.0 |
| 15 | 99.80 |
| Mean=99.8%, % RSD=0.13 | |

In summary, we have synthesized 0.165 mmol of dimethoxymethyl benzene **2** using $1.05\times10^{-2}$ mmol of Amberlyst-15 **1**. This result not only demonstrates the successful incorporation of supported acids into an EOF-based device, but also the ability to recycle the supported reagent (>16 times) without any loss of activity. Although the activity of Amberlyst-15 **1** is also retained in batch, this approach is advantageous as macroreticular resins are difficult to recycle due to support degradation observed as a result of mechanical agitation; therefore limiting the number of times they can be recycled. In order to confirm that the observed reaction was due to the presence of a solid-

supported acid catalyst and not as a result of conducting the reaction in an electric field, the reaction was repeated in the absence of a catalyst.

Again, using the experimental set-up illustrated in Figure 3, unfunctionalised polystyrene beads (2% cross-linked with divinylbenzene) were packed into the device. A mixture of benzaldehyde **3** and trimethylorthoformate **4** (40 μl, 1.0 and 2.5 M, respectively) in MeCN was placed in reservoir A and MeCN in reservoir B (40 μl). Application of 100 and 0 V $cm^{-1}$, respectively, resulted in the mobilisation of the reaction mixture at a flow rate of 1.75 μl $min^{-1}$.[27] After 10 min, the reaction products from reservoir B were diluted with MeCN and analysed by GC–MS, whereby no acetal formation was detected. Having confirmed that the reaction was due to the catalytic activity of the Amberlyst-15 **1**, we went on to investigate generality of the technique, preparing dimethyl acetals **5**–**13** (Table 2). In all cases, no measurable by-products were observed by GC–MS or NMR spectroscopy.

**Table 2**. Summary of the conversions obtained for the synthesis of dimethyl acetals **2**,**5**–**13**

| Product | Flow rate (μl $min^{-1}$) | Conversion[a] (%) | RSD (%) | Yield (%) |
|---|---|---|---|---|
|  **2** | 1.75 | 99.77 | 0.13 | 96.6 |
|  **5** | 1.00 | 99.92 | 0.22 | 96.8 |
|  **6** | 1.60 | 99.78 | 0.15 | 98.0 |
|  **7** | 2.00 | 99.64 | 0.90 | 97.5 |
|  **8** | 1.40 | 99.83 | 0.26 | 95.2 |
|  **9** | 0.60 | 99.86 | 0.08 | 95.3 |
|  **10** | 0.35 | 99.70 | 0.15 | 98.13 |
|  **11** | 2.00 | 99.88 | 0.93 | 97.5 |
|  **12** | 0.50 | 99.84 | 0.24 | 98.4 |
|  **13** | 1.30 | 99.65 | 0.29 | 95.4 |

[a] ≥15 replicates were performed for each compound.

### 2.2. Other supported acid catalysts

Having demonstrated the successful incorporation of Amberlyst 15 **1** into an EOF-based miniaturised flow reactor, the investigation was extended to the use of ytterbium (III) polystyrylsulfonate **14** and polymer supported *p*-toluenesulfonic acid **15**.

Using the aforementioned methodology, 2.5 mg of ytterbium (III) polystyrylsulfonate **14** ($2.0\times10^{-3}$ mmol) was packed into a micro fabricated device. Again, a solution of benzaldehyde **3** and trimethylorthoformate **4** (40 μl, 1.0 and 2.5 M, respectively) in MeCN was placed in reservoir A and MeCN in reservoir B (40 μl). Application of 333 and 0 V $cm^{-1}$ respectively, resulted in mobilisation of the reaction mixture at 0.40 μl $min^{-1}$ (Table 3). After 10 min, the reaction products were collected, diluted with MeCN and analysed by GC–MS; whereby 99.7% conversion to dimethoxymethyl benzene **2** was observed. The reaction was repeated a further 14 times, whereby 0.010 g (94.7%) of dimethoxymethyl benzene **2** was obtained. Due to the slower flow rate observed with catalyst **14** cf. Amberlyst-15 **1**, less product is prepared over the same period of time (0.010 g cf. 0.025 g) however the catalyst is recycled >32 times. The catalyst was subsequently evaluated for the synthesis of dimethyl acetals **2**, **5–13** whereby conversions of greater than 99.7% and yields greater than 94.9% were obtained (Table 3).

**Table 3**. Summary of the conversions obtained for the synthesis of dimethyl acetals using ytterbium (III) polystyrylsulfonate resin **14**

| Product | Flow rate (μl $min^{-1}$) | Conversion[a] (%) | RSD (%) | Yield (%) |
|---|---|---|---|---|
| **2** | 0.40 | 99.72 | 0.13 | 94.7 |
| **5** | 0.40 | 99.96 | 0.06 | 98.8 |
| **6** | 0.28 | 99.97 | 0.08 | 96.3 |
| **7** | 0.52 | 99.92 | 0.05 | 96.8 |
| **8** | 0.40 | 99.87 | 0.15 | 97.7 |
| **9** | 0.40 | 99.72 | 0.06 | 97.2 |
| **10** | 0.70 | 99.88 | 0.03 | 98.7 |
| **11** | 0.55 | 99.83 | 0.08 | 95.5 |
| **12** | 0.95 | 99.83 | 0.12 | 98.6 |
| **13** | 0.90 | 99.64 | 0.14 | 96.1 |

[a] ≥15 replicates were performed for each compound.

Finally, polymer-supported *p*-toluenesulfonic acid **15** (2.5 mg, $5.3\times10^{-3}$ mmol) was evaluated, whereby again conversions of greater than 99.7% with respect to residual aldehyde were obtained for dimethyl acetals **2**, **5** and **13** (Table 4).

**Table 4**. Summary of the conversions obtained for the synthesis of dimethyl acetals using polymer supported *p*-toluenesulfonic acid **15**

| Product | Flow rate (μl $min^{-1}$) | Conversion[a] (%) | RSD (%) | Yield (%) |
|---|---|---|---|---|
| **2** | 1.10 | 99.80 | 0.20 | 96.8 |
| **5** | 0.30 | 99.86 | 0.27 | 96.0 |
| **6** | 1.40 | 99.85 | 0.19 | 97.6 |
| **7** | 0.79 | 99.93 | 0.21 | 95.9 |
| **8** | 1.00 | 99.77 | 0.21 | 98.3 |
| **9** | 0.70 | 99.74 | 0.12 | 95.8 |
| **10** | 0.60 | 99.64 | 0.25 | 95.7 |
| **11** | 5.00 | 99.87 | 0.17 | 97.8 |
| **12** | 1.00 | 99.85 | 0.15 | 94.9 |
| **13** | 1.70 | 99.70 | 0.11 | 98.5 |

[a] ≥15 replicates were performed for each compound.

### 2.3. Deacetalisation

One of the most important aspects of protecting a functional group is the ability to cleanly and efficiently remove it without affecting other moieties within the molecule. As previously mentioned, the hydrolysis of acetals, to afford their respective carbonyl derivative, is promoted in the presence of aqueous acids such as hydrochloric,[28] sulfuric,[29] acetic[30] and *p*-toluenesulfonic acid.[31] However, more recently, supported acids such as Amberlyst-15 **1** have been reported as efficient catalysts for the transformation whereby excellent yields were obtained.[32] In addition, Amberlyst-15 **1** has been shown to hydrolyse isomerisable acetals with no detectable epimerisation compared to 20% when aqueous HCl was employed. With this in mind, the investigation was extended to the deacetalisation of a series of dimethyl acetals to afford their respective aldehyde in the presence of Amberlyst-15 **1**.

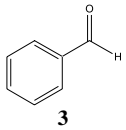
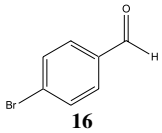
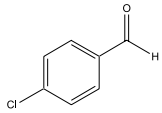
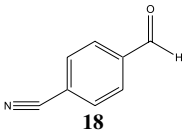
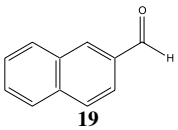
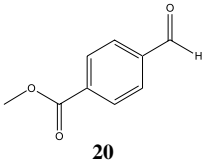
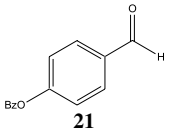
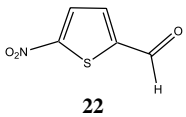
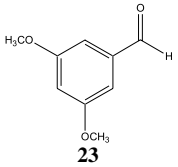
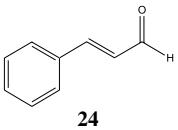
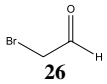
In order to investigate the deacetalisation, a solution of dimethoxymethyl benzene **2** (40 μl, 1.0 M) in MeCN was placed in reservoir A and MeCN in reservoir B (40 μl). Application of 167 and 0 V $cm^{-1}$ respectively, resulted in mobilisation of the reaction mixture through the packed-bed at 0.40 μl $min^{-1}$ (Table 5). After 10 min the reaction products were collected, diluted with MeCN and analysed by GC–MS; whereby 100% conversion to benzaldehyde **3** was observed with respect to residual dimethoxymethyl benzene **2**. The reaction was repeated a further 14 times, whereby 0.011 g (94.8%) of benzaldehyde **3** was obtained. The procedure was subsequently repeated for the remaining nine dimethyl acetals, affording the respective aldehydes in greater than 99.7% conversion and 94.8% yield (Table 5).

In addition to demonstrating the deacetalisation of acetals **2**, **5–13**, we extended the investigation to look at the in situ regeneration of volatile reagents (Scheme 4). Using commercially available bromoacetaldehyde dimethyl acetal **25**, the synthesis of bromoacetaldehyde **26** was investigated using Amberlyst-15 **1** in an EOF-based flow reactor. Bromoacetaldehyde dimethyl acetal **25** (40 μl, 1.0 M) in MeCN was placed in reservoir A and MeCN (40 μl) in reservoir B. Application of 167 V $cm^{-1}$ resulted in mobilisation of bromoacetaldehyde dimethyl acetal **25** at a flow rate of 0.25 μl $min^{-1}$. After 10 min, the reaction mixture was analysed by GC–MS, whereby 100% conversion of dimethyl acetal **25** to bromoacetaldehyde **26** was obtained. Compared to the standard batch approach, this technique is advantageous as it enables us to regenerate what is a volatile compound at the point of use, therefore enabling more efficient reactions to be performed.

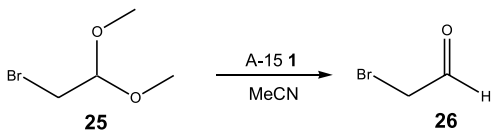
## 3. Conclusions

Compared to standard batch techniques, the approach described herein, is advantageous as supported reagents can be recycled without the need for filtration, resulting in more consistent results between reactions. Also, the absence of stirring or shaking greatly reduces mechanical degradation of the reagent, enabling the catalyst to be employed

**Table 5**. Summary of the conversions obtained for the deacetalisation of dimethyl acetals **2**, **5–13** and **25** using Amberlyst-15 **1**

| Product | Flow rate (μl $min^{-1}$) | Conversion[a] (%) | RSD (%) | Yield (%) |
|---|---|---|---|---|
|  **3** | 0.50 | 100.0 | 0.00 | 94.8 |
|  **16** | 1.00 | 99.85 | 0.10 | 99.5 |
|  **17** | 0.65 | 100.0 | 0.00 | 99.3 |
|  **18** | 0.80 | 99.93 | 0.03 | 99.0 |
|  **19** | 0.80 | 99.71 | 0.08 | 97.2 |
|  **20** | 0.50 | 99.81 | 0.01 | 98.6 |
|  **21** | 0.30 | 99.93 | 0.03 | 99.6 |
|  **22** | 0.53 | 100.0 | 0.00 | 99.7 |
|  **23** | 0.50 | 99.85 | 0.19 | 97.7 |
|  **24** | 0.55 | 99.99 | 0.02 | 98.5 |
|  **26** | 0.25 | 100.0 | 0.00 | — |

[a] ≥15 replicates were performed for each compound.




**25** **26**

**Scheme 4.** Synthesis of bromoacetaldehyde **26** using A-15 **1**.

for longer. In addition, the formation of localised concentration gradients enable reactions to be driven to completion without the need to employ large quantities of supported catalyst (typically <2.5 mg is used). Consequently, reaction conditions can be optimised rapidly enabling small quantities of analytically pure compounds to be prepared in min; alternatively, larger quantities of materials can be

synthesised by simply operating numerous reactors in parallel.[33] Applying the methodology described herein, further studies are currently underway within our laboratories to extend both the type of reagent and support employed, enabling more complex syntheses to be evaluated.

## 4. Experimental

All solvents were purchased as puriss grade (≥99.5%) over molecular sieves ($H_2O$<0.005%) from Fluka and unless otherwise stated reagents purchased from Sigma-Aldrich and Lancaster were used as received. Ytterbium (III) polystyrylsulfonate resin **14** (0.8 mmol $g^{-1}$) was purchased from Novabiochem. Ytterbium (III) polystyryl sulfonate resin **14**, polymer bound *p*-toluenesulfonic acid **15** (2.0 mmol $g^{-1}$) and Amberlyst-15 **1** (4.2 mmol $g^{-1}$) were ground and sieved (Endcotts) to afford 38 and 75 μm particles. All NMR spectra were recorded as solutions in deuteriochloroform ($CDCl_3$) using tetramethylsilane (TMS) as an internal standard. The spectra were recorded on a Joel GX400 spectrometer and the chemicals shifts given in parts per million (ppm) with coupling constants given in Hertz (Hz). The following abbreviations are used to report NMR data; s=singlet, d= doublet, t=triplet, br s=broad singlet, m=multiplet and $C_0$=quaternary carbon. Elemental analyses were performed using a Fisons Carlo Erba EA1108 CHN analyser. Gas Chromatography–mass spectrometry (GC–MS) was performed using a Varian GC (CP-3800) coupled to a Varian MS (Saturn 2000) with a CP-Sil 8 (30 m) column (Zebron ZB-5, Phenomenex) and ultra high purity helium (99.999%, Energas) carrier gas. Samples were analysed using the following method; injector temperature 250 °C, helium flow rate 1.0 ml $min^{-1}$, oven temperature 50 °C for 4 min and then ramped to 270 °C at 30 °C $min^{-1}$, with a 3.0 min filament delay.

### 4.1. Micro-scale methodology

The reactions described herein were carried out using a single capillary device, as illustrated in Figure 3, with dimensions of 500 μm (i.d.)×3.0 cm (length). To hold the polymer-supported reagent in place, micro porous silica frits were placed at either end of the capillary.[26] To mobilise reagents by EOF, platinum electrodes (0.5 mm o.d.× 2.5 cm) were placed within the reagent reservoirs and voltages applied using a Paragon 3B high-voltage power supply (HVPS), capable of applying 0–1000 V to four pairs of outputs (Kingfield Electronics). Automation of the HVPS was achieved using an in-house LabVIEW™ program. To enable the results obtained to be achieved using devices of different capillary dimensions, voltages are reported as applied fields (V $cm^{-1}$) that is voltage/capillary length. To monitor the progress of the reaction, experiments were conducted over a period of 10 min, after, which the contents of the product reservoir was analysed by GC–MS. Comparison of the amount of product with respect to residual aldehyde enabled the percentage conversion to be determined. In order to obtain NMR data of the compounds synthesised in the flow system, the reactor was operated continuously for 2.5–3.5 h (depending on the observed flow rate). After, which the reaction products were collected, concentrated in vacuo, dissolved in $CDCl_3$/TMS and analysed by NMR spectroscopy. In some cases, the products were subjected to elemental analysis.

**4.1.1. Dimethoxymethyl benzene 2.**[34] (0.025 g, 96.6%) as a pale yellow oil; $\delta_H$ (400 MHz, $CDCl_3$) 3.33 (6H, s, 2×$OCH_3$), 5.40 (1H, s, CH), 7.37 (3H, m, 3×Ar) and 7.45 (2H, m, 2×Ar); $\delta_C$ (100 MHz, $CDCl_3$) 52.7 ($OCH_3$), 103.2 (CH), 126.7 (2×CH), 128.2 (2×CH), 128.5 (CH) and 134.5 ($C_0$); 153 ($M^+$+1, 2%), 152 (3), 151 (5), 122 (10), 121 (100), 77 (30) and 51 (10); GC–MS retention time $R_T$=8.03 min.

**4.1.2. 1-Bromo-4-dimethoxymethyl benzene 5.**[35] (0.034 g, 96.8%) as a colourless oil; $\delta_H$ (400 MHz, $CDCl_3$) 3.49 (6H, s, 2×$OCH_3$), 5.30 (1H, s, CH), 7.69 (2H, d, *J*=8.7 Hz, 2×Ar) and 7.76 (2H, d, *J*=8.7 Hz, 2×Ar); $\delta_C$ (100 MHz, $CDCl_3$) 50.9 (2×$OCH_3$), 102.3 (CH), 129.8 ($C_0$Br), 131.0 (2×CH), 132.5 (2×CH) and 135.1 ($C_0$); 232 ($M^+$+1, 5%), 201 (100), 200 (90) and 77 (15); GC–MS retention time $R_T$=8.78 min.

**4.1.3. 1-Chloro-4-dimethoxymethyl benzene 6.**[35] (0.044 g, 98.0%) as a pale yellow oil; $\delta_H$ (400 MHz, $CDCl_3$) 3.31 (6H, s, 2×$OCH_3$), 5.37 (1H, s, CH), 7.34 (2H, d, *J*=8.7 Hz, 2×Ar) and 7.40 (2H, d, *J*=8.7 Hz, 2×Ar); $\delta_C$ (100 MHz, $CDCl_3$) 52.6 (2×$OCH_3$), 102.3 (CH), 128.2 (2×CH), 129.5 (2×CH), 134.3 ($C_0$Cl) and 136.7 ($C_0$); 187 ($M^+$+1, 2%), 185 (3), 157 (30), 165 (20), 155 (100) and 75 (20); GC–MS retention time $R_T$=9.05 min.

**4.1.4. 1-Cyano-4-dimethoxymethyl benzene 7.** (0.042 g, 97.5%) as a pale yellow oil (Found C, 68.00; H, 6.11; N, 7.88. $C_{10}H_{11}O_2N$ requires C, 67.78; H, 6.26; N, 7.90%); $\delta_H$ (400 MHz, $CDCl_3$) 3.33 (6H, s, 2×$OCH_3$), 5.45 (1H, s, CH), 7.58 (2H, d, *J*=8.3 Hz, 2×Ar) and 7.67 (2H, d, *J*=8.3 Hz, 2×Ar); $\delta_C$ (100 MHz, $CDCl_3$) 52.7 (2×$OCH_3$), 101.8 (CH), 117.7 (CN), 118.7 ($C_0$CN), 127.6 (2×CH), 132.1 (2×CH) and 143.2 ($C_0$); 178 ($M^+$+1, 2%), 177 (2), 176 (5), 146 (100) and 75 (10); GC–MS retention time $R_T$= 9.66 min.

**4.1.5. 2-Dimethoxymethyl naphthalene 8.** (0.080 g, 95.2%) as a pale yellow oil (Found C, 77.21; H, 7.16; $C_{13}H_{14}O_2$ requires C, 77.20; H, 6.98%); $\delta_H$ (400 MHz, $CDCl_3$) 3.37 (6H, s, 2×$OCH_3$), 5.56 (1H, s, CH), 7.50 (2H, m, 2×Ar), 7.61 (2H, m, 2×Ar), 7.94 (2H, m, 2×Ar) and 8.34 (1H, m, Ar); $\delta_C$ (100 MHz, $CDCl_3$) 52.8 (2×$OCH_3$), 103.2 (CH), 124.4 (CH), 126.1 (2×CH), 126.2 (CH), 127.7 (CH), 128.1 (CH), 128.3 (CH), 133.4 ($C_0$), 133.5 ($C_0$) and 135.5 ($C_0$); 203 ($M^+$+1, 3%), 201 (5), 172 (20), 171 (100), 126 (5) and 75 (10); GC–MS retention time $R_T$=10.70 min.

**4.1.6. 4-Dimethoxymethylbenzoic acid methyl ester 9.**[36] (0.018 g, 95.3%) as a pale yellow oil; $\delta_H$ (400 MHz, $CDCl_3$) 3.33 (6H, s, 2×$OCH_3$), 3.90 (3H, s, $OCH_3$), 5.44 (1H, s, CH), 7.53 (2H, d, *J*=8.3 Hz, 2×ArH) and 8.05 (2H, d, *J*= 8.3 Hz, 2×ArH); $\delta_C$ (100 MHz, $CDCl_3$) 52.2 (COO*C*$H_3$), 52.7 (2×$OCH_3$), 102.4 (CH), 126.8 (2×Ar), 129.5 (2× Ar), 130.2 ($C_0$), 143.0 (*C*$_0$COO$CH_3$) and 166.9 (CO); 211 ($M^+$+1, 2%) 210 (1), 179 (100) and 77 (5); GC–MS retention time $R_T$=10.21 min.

**4.1.7. 1-Benzyloxy-4-dimethoxymethyl benzene 10.** (0.200 g, 98.1%) as a pale yellow oil (Found C, 74.32; H,

7.23; $C_{16}H_{18}O_3$ requires C, 74.40; H, 7.02%); $\delta_H$ (400 MHz, $CDCl_3$) 3.31 (6H, 2×$OCH_3$), 5.06 (2H, s, $OCH_2$), 5.14 (1H, s, CH), 7.07 (2H, d, $J$=8.7 Hz, 2×Ar), 7.39 (5H, m, 5×Ar) and 7.83 (2H, d, $J$=8.7 Hz, 2×Ar); $\delta_C$ (100 MHz, $CDCl_3$) 52.6 (2×$OCH_3$), 70.3 ($OCH_2$), 103.1 (CH), 114.5 (2×CH), 127.9 (2×CH), 128.6 (2×CH), 128.7 (2×CH), 136.9 ($C_0$), 158.9 ($C_0O$); 259 ($M^+$+1, 1%), 258 (2), 257 (3), 228 (25), 227 (100), 91 (5) and 75 (15); GC–MS retention time $R_T$= 12.48 min.

**4.1.8. 2-Dimethoxymethyl-5-nitrothiophene 11.**[35] (0.039 g, 97.5%) as a pale yellow oil; $\delta_H$ (400 MHz, $CDCl_3$) 3.50 (6H, s, 2×$OCH_3$), 5.61 (1H, s, CH), 7.71 (1H, d, $J$=4.2 Hz, Ar) and 7.97 (1H, d, $J$=4.2 Hz, Ar); $\delta_C$ (100 MHz, $CDCl_3$) 52.7 (2×$OCH_3$), 98.8 (CH), 124.5 (CH), 128.4 (CH), 149.8 ($C_0$) and 151.2 ($C_0NO_2$); 203 ($M^+$, 1%), 202 (5), 187 (10), 172 (100), 157 (10), 142 (10), 97 (5) and 75 (%); GC–MS retention time $R_T$=10.23 min.

**4.1.9. 1-Dimethoxymethyl-3,5-dimethoxybenzene 12.** (0.030 g, 98.4%) as a colourless oil (Found C, 62.52; H, 7.41. $C_{11}H_{16}O_4$ requires C, 62.25; H, 7.60%); $\delta_H$ (400 MHz, $CDCl_3$) 3.34 (6H, s, 2×$OCH_3$), 3.80 (6H, s, 2×$OCH_3$), 5.30 (1H, s, CH), 6.43 (1H, t, $J$=2.2 Hz, 2×Ar) and 6.62 (2H, d, $J$=2.2 Hz, 2×Ar); $\delta_C$ (100 MHz, $CDCl_3$) 52.9 (2×$OCH_3$), 55.4 (2×$OCH_3$), 100.8 (CH), 103.1 (CH), 104.5 (2×CH), 140.5 ($C_0$) and 160.7 (2×$C_0OCH_3$); 213 ($M^+$+1, 5%), 212 (20), 182 (100), 134 (5) and 75 (5); GC–MS retention time $R_T$=10.32 min.

**4.1.10. 3,3-Dimethoxypropenyl benzene 13.**[36] (0.022 g, 95.4%) as a yellow oil; $\delta_H$ (400 MHz, $CDCl_3$) 3.38 (6H, s, 2×$OCH_3$), 4.96 (1H, d, $J$=4.9 Hz, CH), 6.16 (1H, dd, $J$= 4.9, 16.0 Hz, C*H*CH($OCH_3$)$_2$), 6.72 (1H, d, $J$=16.0 Hz, Ar) 7.30 (2H, m, 2×Ar), 7.43 (2H, m, 2×Ar) and 7.57 (1H, m, Ar); $\delta_C$ (100 MHz, $CDCl_3$) 52.8 (2×$OCH_3$), 102.9 (CH), 126.8 (2×CH), 128.5 (2×CH), 129.1 (CH) and 133.6 ($C_0$); 179 ($M^+$+1, 3%), 178 (20), 177 (15), 147 (100), 115 (10) and 77 (5); GC–MS retention time $R_T$=9.56 min.

The purity of aldehydes **3**, **16–24** synthesized in the miniaturized flow reactor was determined based on the comparison of GC–MS data with that obtained for commercially available standards.

**4.1.11. Benzaldehyde 3.** (0.011 g, 94.8%) as a colourless solid; 107 ($M^+$+1, 20%), 106 (15), 105 (100), 77 (25) and 51 (20); GC–MS retention time $R_T$=6.87 min.

**4.1.12. 4-Bromobenzaldehyde 16.** (0.027 g, 99.5%) as a white solid; 186 ($M^+$+1, 20%), 185 (100), 184 (75), 157 (15), 155 (15), 77 (20) and 50 (25); GC–MS retention time $R_T$=9.51 min.

**4.1.13. 4-Chlorobenzaldehyde 17.** (0.014 g, 99.3%) as a white solid; 142 ($M^+$+1, 20%), 141 (98), 140 (50), 139 (100), 110 (10) and 77 (10); GC–MS retention time $R_T$= 8.18 min.

**4.1.14. 4-Cyanobenzaldehyde 18.** (0.015 g, 99.0%) as a colourless solid; 132 ($M^+$+1, 15%), 131 (20), 130 (100), 103 (7), 102 (45), 76 (20) and 50 (20); GC–MS retention time $R_T$=8.85 min.

**4.1.15. 2-Naphthaldehyde 19.** (0.018 g, 97.2%) as a white solid; 157 ($M^+$+1, 25%), 156 (75), 155 (100), 128 (10), 127 (15), 126 (20) and 102 (5); GC–MS retention time $R_T$= 10.16 min.

**4.1.16. Methyl-4-formylbenzoate 20.** (0.012 g, 98.6%) as a pale orange solid; 165 ($M^+$+1, 50%), 164 (55), 163 (50), 133 (100), 105 (25) and 77 (10); GC–MS retention time $R_T$=9.46 min.

**4.1.17. 4-Benzyloxybenzaldehyde 21.** (0.013 g, 99.6%) as a white solid; 213 ($M^+$+1, 100%), 212 (74), 107 (10) and 91 (25); GC–MS retention time $R_T$=11.98 min.

**4.1.18. 5-Nitro-2-thiophenecarboxaldehyde 22.** (0.017 g, 99.7%) as a pale yellow solid; 158 ($M^+$+1, 75%), 157 (70), 156 (80), 141 (100), 127 (25), 112 (20), 99 (45), 98 (50), 71 (40) and 55 (25); GC–MS retention time $R_T$=9.38 min.

**4.1.19. 3,5-Dimethoxybenzaldehyde 23.** (0.015 g, 97.7%) as a white solid; 167 ($M^+$+1, 25%), 166 (100), 135 (25), 79 (10) and 64 (15); GC–MS retention time $R_T$=9.75 min.

**4.1.20. *trans*-Cinnamaldehyde 24.** (0.010 g, 98.5%) as a yellow oil; 133 ($M^+$+1, 10%), 132 (40), 131 (100), 103 (55), 77 (45) and 50 (25); GC–MS retention time $R_T$= 8.98 min.

**4.1.21. Bromoacetaldehyde 26.** 125 ($M^+$+1, 5%), 124 (4), 123 (7), 96 (100), 95 (25), 94 (100), 81 (25), 80 (2), 79 (25), 42 (30); GC–MS retention time $R_T$=2.69 min.

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# One-pot synthesis of phenol and cyclohexanone from cyclohexylbenzene catalyzed by *N*-hydroxyphthalimide (NHPI)

Yasuhiro Aoki, Satoshi Sakaguchi and Yasutaka Ishii*

*Department of Applied Chemistry and High Technology Research Center, Faculty of Engineering, Kansai University, 3-3-35 Yamate-cho, Suita, Osaka 564-8680, Japan*

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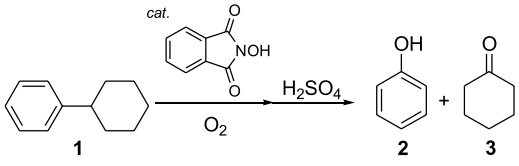
**Abstract**—Synthesis of phenol and cyclohexanone in one pot was examined by means of the NHPI-catalyzed aerobic oxidation of cyclohexylbenzene. The aerobic oxidation of cyclohexylbenzene catalyzed by NHPI followed by treatment with sulfuric acid afforded phenol and cyclohexanone in good selectivities. Thus, the reaction of cyclohexylbenzene under atmospheric dioxygen (1 atm) by NHPI at 100 °C for 3 h followed by treatment with 0.3 M sulfuric acid at room temperature for 2 h resulted in phenol and cyclohexanone in 96 and 91% selectivity, respectively, at 25% conversion. This method was successfully extended to the one-pot synthesis of 4-hydroxyacetophenone and cyclohexanone.


## 1. Introduction

Phenol is one of the most important classes of raw materials in chemical industry, and a variety of compounds are derived from phenols like resins, dyes, pharmaceuticals, etc.[1] In 2000, worldwide production of phenol was 6.6 megatons. Most of this phenol is produced by the Cumene process found by Hock and Lang in 1944.[2] The Cumene process involves the aerobic oxidation of propylbenzene to cumene hydroperoxide followed by treatment with sulfuric acid to produce a 1:1 mixture of phenol and acetone. So far, a large quantity of acetone is used as a raw material of methacrylic acid (MA), but most of MA has currently been produced by aerobic oxidation of isobutene. Therefore, co-production of phenol and acetone by the Hock method incurs a serious drawback, since recent demand of acetone has been deceasing more and more in contrast to increasing need of phenol. Therefore, development of an alternative route to phenol without formation of acetone is an important subject in the chemical industry worldwide. From this point of view, Sheldon et al. have recently reported the aerobic oxidation of cyclohexylbenzene (**1**) to cyclohexylbenzene-1-hydroperoxide (CHBPO) which is a precursor of phenol and cyclohexanone, using *N*-hydroxyphthalimide (NHPI) combined with several radical initiators.[3,4] In a previous paper, we reported the preparation of hydroperoxides by the NHPI-catalyzed aerobic oxidation of alkylbenzenes and alkylnaphtalenes.[5] To extend our study on the synthesis of phenol derivatives by using NHPI as a key catalyst, we examined the one-pot synthesis of phenol (**2**) and cyclohexanone (**3**) by aerobic oxidation of **1** using the NHPI catalyst (Eq. 1).




(1)

## 2. Results and discussion

In order to confirm optimal conditions for the conversion of cyclohexylbenzene (**1**) to phenol (**2**) and cyclohexanone (**3**), **1** was allowed to react in the presence of NHPI and AIBN under dioxygen in acetonitrile at 75 °C for 3 h followed by treatment with 0.3 M sulfuric acid (Table 1).

The conversion of **1** was found to be considerably increased with increasing of the oxygen concentration (Runs 1–3). Under dilute oxygen concentration ($O_2$–$N_2$ = 0.33:0.67 atm), **1** was only converted in 4% to give **2** (85%) and **3** (92%) along with small amounts of 1-phenylcyclohexanol (**4**) and 1-phenylcyclohexene (**5**) (Run 1). When a 1:1 mixture of $O_2$ (0.5 atm) and $N_2$ (0.5 atm) was employed, the conversion of **1** was increased

*Keywords*: Phenol; Cyclohexanone; Aerobic oxidation; Hydroperoxide; *N*-Hydroxyphthalimide.
* Corresponding author. Tel.: +81 6 6368 0793; fax: +81 6 6339 4026; e-mail: ishii@ipcku.kansai-u.ac.jp

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**Table 1**. Conversion of **1** to **2** and **3** under various conditions[a]

| Run | $O_2$:$N_2$/atm | Conv. % | Selectivity/% | | | |
|---|---|---|---|---|---|---|
| | | | **2** | **3** | **4** | **5** |
| 1 | 0.33:0.67 | 4 | 85 | 92 | 2 | 5 |
| 2 | 0.5:0.5 | 33 | 86 | 78 | 2 | 3 |
| 3 | 1:0 | 59 | 73 | 70 | 1 | 3 |
| 4[b] | 1:0 | 5 | 30 | 28 | nd | nd |
| 5[c] | 1:0 | | No reaction | | | |
| 6[d] | 1:0 | 27 | 72 | 73 | 2 | 2 |
| 7[e] | 1:0 | 59 | 72 | 72 | <2 | <2 |
| 8[f] | 1:0 | 60 | 70 | 67 | <2 | <2 |

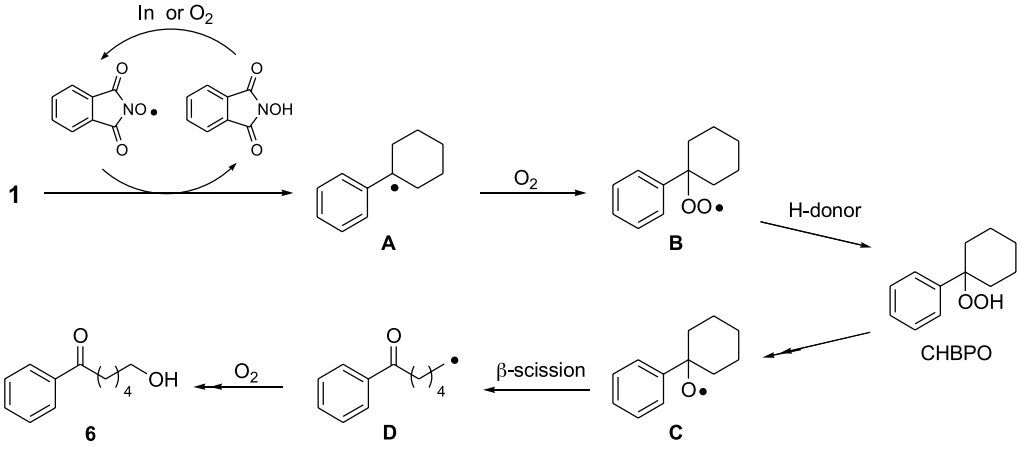
[a] **1** (2 mmol) was reacted in the presence of NHPI (0.4 mmol) and AIBN (0.06 mmol) in $CH_3CN$ (5 mL) at 75 °C for 3 h followed by treatment with 0.3 M $H_2SO_4$ (1 mL) at 25 °C for 2 h.
[b] In the absence of AIBN.
[c] In the absence of NHPI.
[d] BPO was used in the place of AIBN.
[e] Ambelyst® 36 (ca. 50 mg) was used in the place of 0.3 M $H_2SO_4$.
[f] Nafion® 350 (ca. 50 mg) was used in the place of 0.3 M $H_2SO_4$.

to 33% to lead to **2** (86%) and **3** (78%) (Run 2). Under atmospheric $O_2$ (1 atm), **1** was converted into 59% to afford **2** (73%) and **3** (70%) (Run 3). The selectivity to **2** and **3** from **1** was slightly decreased with increasing of the oxygen concentration because of the formation of further oxidation products, which is discussed latter. The reaction of **1** in the absence of either NHPI or AIBN under these conditions resulted in no formation of **2** and **3** (Runs 4 and 5). These results show that NHPI and AIBN were essential components for the aerobic oxidation of **1** under these conditions. When benzoyl peroxide (BPO) was used in place of AIBN as a radical initiator, the conversion of **1** was lowered to 27%, although the selectivity to **2** and **3** was almost the same as that by AIBN (Run 6). This may be due to the decomposition temperature of BPO (80 °C, $t_{1/2} \leq 10$ h) which is higher than that of AIBN (64 °C, $t_{1/2} \leq 10$ h). It was found that Ambelyst® 36 and Nafion® 350 could be used in place of 0.3 M $H_2SO_4$, leading to **2** and **3** (Runs 7 and 8). Additionally, an independent LC-MS analysis of the reactant showed that most of the NHPI catalyst (ca. 80%) exists in the reaction mixture without decomposition after the reaction. This may be due to that the present NHPI-catalyzed aerobic oxidation of **1** could be carried out under transition metal-free conditions.[6]

To identify the structure of further oxidation products, **1** was allowed to react for 15 h under the same conditions as Run 3 in Table 1. We found that 6-hydroxy-1-phenylhexanone (**6**) is formed in 7% yield as a main product of further oxidation. The formation of **6** can be explained by the following reaction pathway (Scheme 1).

The hydrogen atom of the tertiary C–H bond of **1** is first abstracted by the phthalimide-*N*-oxyl radical (PINO) generated from NHPI to form a phenylcyclohexyl radical which is readily trapped by $O_2$ to give cyclohexylbenzene-1-hydroperoxide (CHBPO). Under such reaction conditions, the hydroperoxide, CHBPO, formed is thought to be gradually decomposed to give rise to an oxy-radical **C**. It is well known that an oxy-radical undergoes β-scission to give an alkyl radical **D** which readily reacts with $O_2$ and eventually is converted into **6**. From NMR and GC–MS measurements of the reactants, it was found that a large part of **6** is formed prior to treatment with sulfuric acid.

Figure 1 shows the time-dependence curves for the one-pot synthesis of **2** and **3** from **1** under the same conditions as Run 3 in Table 1.




**Scheme 1.** A plausible path for the formation of **6**.

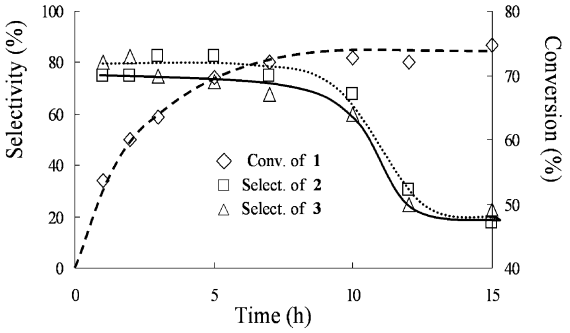
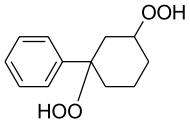



**Figure 1.** Time-dependence curves for oxidation of **1** under $O_2$ (1 atm).

**1** was almost linearly converted into **2** and **3** up to 3 h, and then the reaction became very slow. Although the selectivity of **2** and **3** was kept at about 70% for 5 h, the selectivity suddenly dropped at over 10 h. This observation suggests that drastic self-decomposition of the resulting CHBPO is induced by some radical species generated in the course of the reaction. Sheldon et al. reported that dihydroperoxide like **7** generated by the transannular hydrogen abstract from peroxy radical **B** is formed as a further oxidation product.[3] We failed to isolate **7** probably because of its easy decomposition during the isolation by column chromatography.




**7**

On the basis of these results, we next tried a one-pot synthesis of **2** and **3** by the oxidation of **1** without any solvent followed by the decomposition with 0.3 M sulfuric acid (Table 2).

By the reaction of **1** in the presence of NHPI and AIBN without a solvent at 75 °C, **1** was oxidized in low conversion (14%) to give **2** (57%) and **3** (55%) in low selectivities in addition to **4** (1%), **5** (13%), and **6** (4%) (Run 1). Therefore, the reaction was carried out at 100 °C for 3 h. The conversion of **1** was slightly increased, but the selectivity of **2** and **3** was decreased to about 50% (Run 2). It is interesting to note that **2** and **3** were obtained in very high selectivities of 96 and 91%, respectively, when the reaction was carried out under the influence of NHPI alone without AIBN (Run 3). This fact indicates that AIBN causes a serious side-reaction without a solvent under these conditions. The reaction was prolonged to 7 h under the same conditions to convert **1** into 53%, but the selectivity was found to be considerably lowered (Run 5).

From a practical synthetic point of view, the performance of the reaction of **1** under air (1 atm) is important. Thus, the one-pot synthesis of **2** and **3** was examined by the oxidation of **1** in the presence of NHPI under air (1 atm) at 100 °C. The time-dependence curves for the conversion of **1** to **2** and **3** are shown in Figure 2.

The reaction of **1** for 2 h led to **2** (97%) and **3** (99%) in very high selectivities, although the conversion of **1** was low (5%). Selectivities of both **2** and **3** were maintained at over 85% for 4 h, but it was gradually lowered with time. The reaction for 12 h afforded **2** in 62% and **3** in 55% at 52% conversion of **1**. To keep the selectivity of the present reaction over 80%, the reaction must be carried out at lower than 40% conversion.

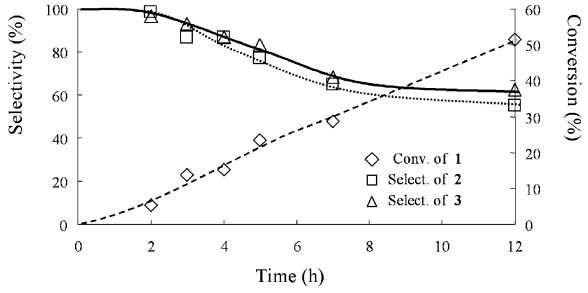


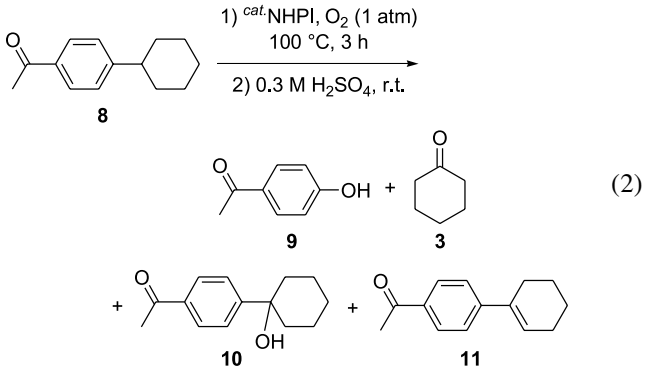

**Figure 2.** Time-dependence curves for oxidation of **1** under air (1 atm).

The present strategy was extended to several cyclohexylbenzene derivatives. 4-Cyclohexyl acetophenone (**8**) (5 mmol) was reacted in the presence of NHPI (0.05 mmol) without a solvent under $O_2$ (1 atm) at 100 °C for 3 h followed by treatment with 0.3 M sulfuric acid. 4-Hydroxyacetophenone (**9**) and **3** were obtained in 77 and 68% selectivities, respectively, at 34% conversion of **8** together with small amounts of **10** and **11** in about 5% yield (Eq. 2). Compound **9** is used as a raw material of pharmaceuticals.

**Table 2**. One-pot synthesis of **2** and **3** from **1** without solvent under several conditions[a]

| Run | Temp./°C | Time/h | Conv./% | Selectivity/% | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | **2** | **3** | **4** | **5** | **6** |
| 1[b] | 75 | 3 | 14 | 57 | 55 | 1 | 13 | 4 |
| 2[b] | 100 | 3 | 20 | 50 | 48 | 3 | 7 | 3 |
| 3 | 100 | 3 | 25 | 93 | 91 | 4 | 3 | 1 |
| 4 | 100 | 5 | 30 | 81 | 77 | 3 | 8 | 2 |
| 5 | 100 | 7 | 53 | 58 | 55 | 5 | 9 | 6 |
| 6[c] | 100 | 3 | 21 | 88 | 80 | 6 | 3 | 1 |

[a] **1** (5 mmol) was reacted in the presence of NHPI (0.1 mmol) under $O_2$ (1 atm) at 75 or 100 °C without solvent followed by treatment with 0.3 M $H_2SO_4$ (1 mL) at room temperature for 2 h.
[b] AIBN (0.06 mmol) was added.
[c] Under air (1 atm).




(2)

In conclusion, we have examined the one-pot synthesis of **2** and **3** from **1** by aerobic oxidation of **1** under the influence of NHPI followed by treatment with aqueous sulfuric acid. It was found that **1** could be converted into **2** and **3** in high selectivity by the oxidation with $O_2$ (1 atm) by NHPI alone at 100 °C without any solvent at the conversion less than 25%. This method may provide an alternative route to phenol (**2**), since the co-product, cyclohexanone (**3**), is easily transformed to **2** and cyclohexanone derivatives like cyclohexanone oxime which are widely used in the chemical industry. This method was successfully extended to the one-pot synthesis of 4-hydroxyacetophenone (**9**) and **3** from 4-cyclohexylacetoxyphenone (**8**).

## 3. Experimental

### 3.1. General procedure for the oxidation of 1 to 2 and 3

An acetonitrile (5 mL) solution of **1** (3 mmol), NHPI (0.3 mmol), and AIBN (0.09 mmol) was placed in a two-necked flask equipped with a balloon filled with $O_2$. The mixture was stirred at 75 °C for 3 h followed by treatment with 0.3 M $H_2SO_4$ in $CH_3CN$ (1 mL) at 25 °C for 2 h. Removal of the solvent under reduced pressure afforded a cloudy solution, which was purified by column chromatography on silica gel (*n*-hexane–ethyl acetate) to give **2** and **3**. Products were characterized by $^1H$ and $^{13}C$ NMR, IR, and GC–MS, respectively.

**3.1.1. Compound 6.** $^1H$ NMR $\delta$ 3.03 (t, $J=7.2$ Hz, 1H), 1.44–1.73 (m, 3H), 3.55 (t, $J=6.4$ Hz, 1H) 7.46–7.99 (m, 5H); $^{13}C$ NMR $\delta$ 146.4, 128.1, 127.0, 125.6, 46.0, 34.7, 25; IR (NaCl) 3367, 2935, 2863, 2361, 1601, 1597, 1512,1449, 1369, 1222, 1051 $cm^{-1}$; ESI-MS (M+H) 193.08.

## Acknowledgements

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# Simple and efficient preparation of sterically protected 1,4-diphosphafulvenes

Akitake Nakamura, Kozo Toyota and Masaaki Yoshifuji*

*Department of Chemistry, Graduate School of Science, Tohoku University, Aoba, Sendai 980-8578, Japan*

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**Abstract**—A new synthetic method for sterically protected 1,4-diphosphafulvenes (2-methylene-2,3-dihydro-1*H*-[1,3]diphospholes) has been developed starting from (arylethynyl)phosphines and ca. 0.25 molar amount of butyllithium. The catalytic mechanism of the reaction is discussed based on the results of deuterium-labelling experiments.


## 1. Introduction

Heterocycles containing heavier main group elements have long been compounds of importance in many research fields such as medicinal chemistry and materials chemistry. For example, fulvenes and fulvalenes containing hetero atoms have been of interest. Since the discovery of the first organic metal, tetrathiafulvalene-tetracyanoquinodimethane (TTF-TCNQ), the quest for new synthetic metals and superconductors has been very active.[1] Thus, 2-methylene-2,3-dihydro-1*H*-[1,3]dichalcogenole derivatives have attracted much attention, because of their high π electron-donating properties.[2] In contrast, research on 2-methylene-2,3-dihydro-1*H*-[1,3]diphosphole has been limited until now.

Very recently, we have reported the formation of 2,6-diphenyl-1,4-bis(2,4,6-tri-*t*-butylphenyl)-1,4-diphospha-1,4-dihydrofulvene (or 2-benzylidene-4-phenyl-2,3-bis(2,4,6-tri-*t*-butylphenyl)-2,3-dihydro-1*H*-[1,3]diphosphole) (Chart 1, **1a**)[3] in 37% yield together with 3-phenyl-1-(2,4,6-tri-*t*-butylphenyl)-1-phosphaallene (**2a**,[4] 5%) and a trace amount of 3,4-diphosphinidenecyclobutene derivative **3a** (hereafter, 3,4-*dip*hosphinidene*cyclo*-*but*ene, abbreviated as DPCB),[5] when (*Z*)-2-bromo-2-benzyl-1-(2,4,6-tri-*t*-butylphenyl)phosphaethene (**4**) was allowed to react with 2 molar amount of potassium *t*-butoxide. X-ray analysis of (*E*)-**1a** as well as a CV study was also reported.[3] Alternatively, Le Floch et al. reported the synthesis of a series of 1,4-diphosphafulvene derivative,[6] such as **5**, from a phosphorus version of the Arduengo carbene[7] and ketones or aldehydes. In the course of our continuing investigation of preparations and properties of DPCB derivatives,[8] we found that ethynylphosphines **6** (starting compounds in the syntheses of DPCB derivatives, Scheme 1) also afford **1** under certain conditions. Here, we report a simple and convenient method for the preparation of 1,4-diphosphafulvenes starting from ethynylphosphines bearing a bulky 2,4,6-tri-*t*-butylphenyl substituent[9] (abbreviated as Mes*).[10]

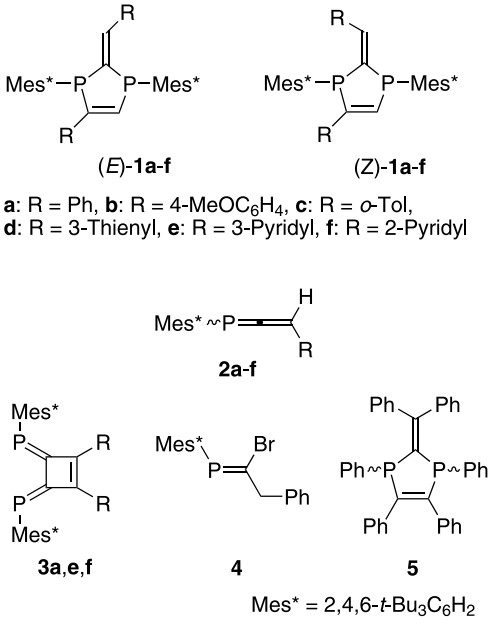


**Chart 1.**

*Keywords*: Phosphorus heterocycles; Phosphines; Phosphaallenes; Steric and strain effects.
* Corresponding author. Tel.: +81 22 795 6558; fax: +81 22 795 6562; e-mail: yoshifj@mail.tains.tohoku.ac.jp

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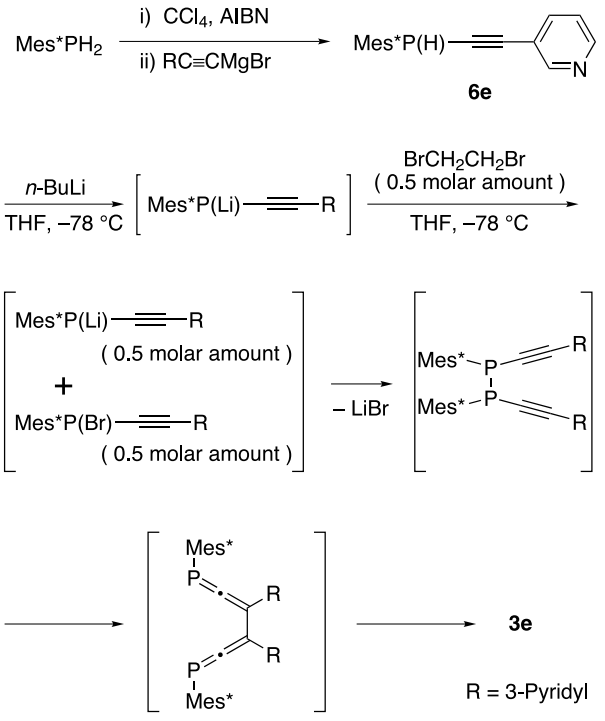
## 2. Results and discussion

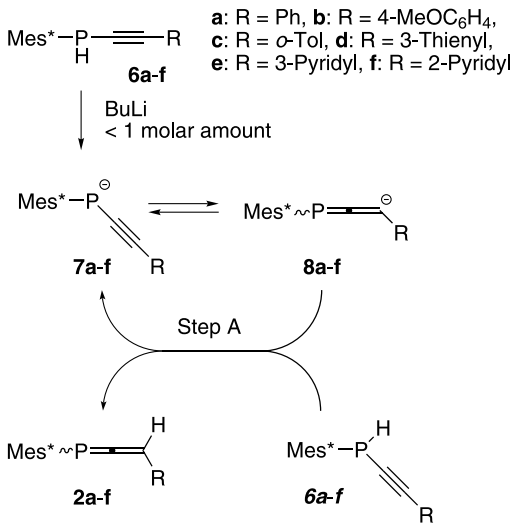
### 2.1. Preparation of 1,4-diphosphafulvenes

It has been established that a successive reaction of sterically protected ethynylphosphine **6** with *n*- or *t*-BuLi (1 molar amount) and 1,2-dibromoethane (0.5 molar amount) affords DPCB derivative **3**,[8a–f] as exemplified by the preparation of **3e**: Reaction of [(3-pyridyl)ethynyl]-phosphine **6e** with *n*-BuLi (1 molar amount) followed by reaction with 1,2-dibromoethane (0.5 molar amount) in THF at −78 °C affords the corresponding DPCB derivative **3e** in 21% yield based on the starting (2,4,6-tri-*t*-butylphenyl)-phosphine[11] (Scheme 1). In this reaction, it is likely that lithium [(3-pyridyl)ethynyl]phosphide reacts with 1,2-dibromoethane (0.5 molar amount) to form 0.5 molar amount of (bromo)[(3-pyridyl)ethynyl]phosphine. Coupling between the lithium phosphide and the (bromo)(pyridylethynyl)phosphine, followed by Cope rearrangement and electrocyclization, affords **3e**.



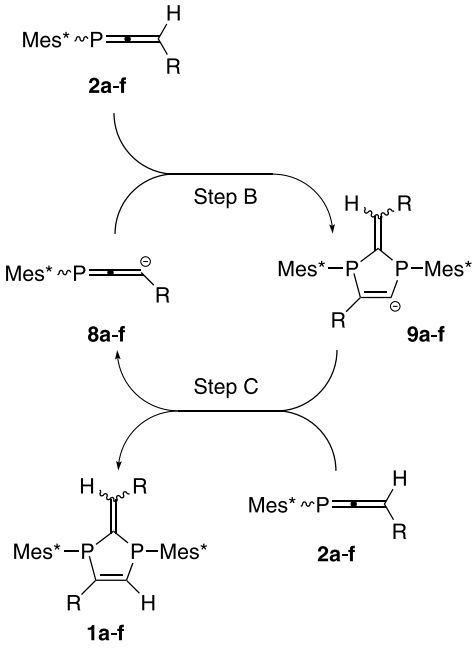

Scheme 1.

However, when a 2-pyridyl isomer **6f** (Scheme 2) was allowed to react with *n*-BuLi and 1,2-dibromoethane under similar conditions (crude **6f** was used because separation of **6f** from other products proved difficult), we found that **1f** instead of **3f** was formed by $^{31}P$ NMR spectroscopic monitoring, although only in trace yield due to difficulties in separation and purification [1.2% yield from starting $Mes^*PH_2$, **1f**: Orange solid, mp 237–239 °C (decomp.); $^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$) $\delta=28.0$ (d, $^2J_{PP}=26.2$ Hz) and 47.1 (d, $^2J_{PP}=26.2$ Hz). HRMS (SIMS). Found *m/z* 759.4934. Calcd for $C_{50}H_{68}N_2P_2$: $M^+ + H$, 759.4930]. This striking contrast prompted us to investigate reaction conditions of **6a–e**[12] with *n*-BuLi which led to an

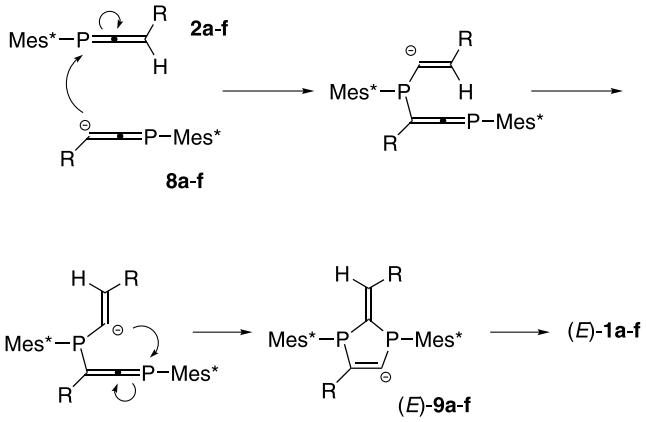



Scheme 2.

interesting discovery: Reactions of **6a–e** with *n*-BuLi (ca. 0.25 molar amount) in the absence of 1,2-dibromoethane at room temperature afforded **1a–e** (for purification of **1a–e**, see below), probably via a reaction between in situ prepared 1-phosphaallene **2a–e** and phosphaallenyl anion **8a–e** as shown in Schemes 2 and 3. This route includes three important steps A, B, and C. Step A (Scheme 2) is a very fast catalytic cycle, which involves, (i) partial lithiation of ethynylphosphine **6** with *n*-BuLi to form phosphide **7**, (ii) rearrangement of the anion **7** to the anion **8**,[13] and (iii) protonation of **8** by the starting ethynylphosphine **6** to form **2** and regenerate **8** (via **7**). Step B (Scheme 3) is a reaction between **2** (formed at Step A) and **8** to form **9**. Step B seems to proceed in a stepwise manner rather than a concerted manner, as shown in Scheme 4: compounds **2** and **8** first, react in a sterically less hindered manner, then bond rotation around the phosphorus-vinyl bond occurs, followed by cyclization in a sterically more congested manner to give




Scheme 3.




**Scheme 4.**

THF at room temperature yielded **1a** as a mixture of *E*- and *Z*-isomers [(*E*)-**1a**:(*Z*)-**1a**=2.7:1, determined by $^{31}$P NMR spectroscopy]. We obtained (*E*)-**1a** in 55% isolated yield (Table 1, entry 2).

We then carried out a reaction of ethynylphosphine **6a** using 0.25 molar amount of *n*-BuLi. A clean reaction proceeded to afford **1a** in 70% isolated yield (Table 1, entry 1), which supports the above catalytic mechanism. Furthermore, we examined the protonation step of **9** with **2**, using deuterated 1-phosphaallene **2a**$_d$ (Chart 2). Reaction of **2a**$_d$ (97% D) with 0.26 molar amount of *t*-BuLi in THF at room temperature (generation of phosphaallenyllithium **8a**) yielded a dideuterated diphosphafulvene **1a**$_{d2}$ in 38% isolated yield with good D-incorporation, (91% D on the *exo*-methylene carbon and 73% D at the 3-position of the 1,4-dihydrofulvene ring) which also supports the mechanism via **8a** and **9a**$_d$ (Steps B and C). It should be mentioned that the expected maximum D-content at the 3-position is 74% D, based on the above mechanism, because 0.26 molar amount of *t*-BuLi were used to initiate the reaction by abstraction of $D^+$ from **2a**$_d$. It should also be noted that **2a** did not form **1a** in the absence of butyllithium.

**Table 1**. Preparation and oxidation potential of (*E*)-**1a–e**

| Entry | Phosphine | R | *n*-BuLi[a] | Product | Yield[b]/% | $E_{1/2}$/V[c] |
|---|---|---|---|---|---|---|
| 1 | **6a** | Ph | 0.25[d] | **1a** | 70 | 0.02 |
| 2 | **6a** | Ph | 0.50 | **1a** | 55 | |
| 3 | **6b** | 4-MeOC$_6$H$_4$ | 0.25[d] | **1b** | 46 | −0.05 |
| 4 | **6c** | *o*-Tol | 0.30[d] | **1c** | 38[e] | 0.01[e] |
| 5 | **6d** | 3-Thienyl | 0.30[d] | **1d** | 52 | 0.03 |
| 6 | **6e** | 3-Pyridyl | 0.20[d] | **1e** | 61 | 0.20 |

[a] Molar amount based on **6**.
[b] Yields were calculated taking the reaction mechanism into account (two molecules of **6** give one molecule of **1**).
[c] Conditions: 1 mM in $CH_2Cl_2$ with 0.1 M *n*-$Bu_4NClO_4$ as support electrolyte. Working electrode: glassy carbon; Counter electrode: Pt wire; Reference electrode: Ag/0.01 M $AgNO_3$ in acetonitrile with 0.1 M *n*-$Bu_4NClO_4$ [$E_{1/2}$ ($Fc/Fc^+$)=0.23 V]; Scan rate: 100 mV/s.
[d] Optimized data. The experiments were carried out using either 0.15, 0.20, 0.25, 0.30, 0.40, or 0.50 molar amounts of *n*-BuLi.
[e] Mixture of (*E*)- and (*Z*)-isomers.

(*E*)-**1** as a major product. The cyclization is likely a kinetically controlled reaction, due to the difficulty of inversion of the sp$^2$-carbanion.

First, we thought **1** is simply a quenched product of **9**, but the mechanism turned out to be not so straightforward according to the following experimental results. Step C (Scheme 3) is considered to operate as the final step of this mechanism. Intermediate **9** appears to be protonated by the remaining 1-phosphaallene **2**, before work-up (see below), and regenerates the phosphaallenyl anion **8**.

Attempted deuteration of intermediate **9a** by addition of methanol-$d_4$ failed, suggesting that the protonation of **9** occurs before addition of methanol-$d_4$. Thus, a catalytic amount of **8** formed in situ is expected to convert two molecules of phosphaallene **2** to **1**. Indeed, the reaction of ethynylphosphine **6a** with 0.5 molar amount of *n*-BuLi in

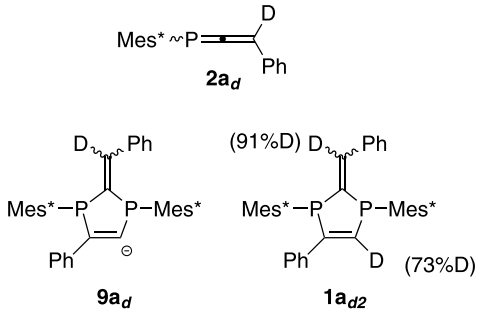



**Chart 2.**

## 2.2. Cyclic voltammogram of 1,4-diphosphafulvenes

Results of cyclic voltammetric measurements of compounds **1b–e** in dichloromethane are shown in Table 1, together with that of **1a**.[3] All compounds showed reversible

We then carried out a reaction of ethynylphosphine **6a** using 0.25 molar amount of *n*-BuLi. A clean reaction proceeded to afford **1a** in 70% isolated yield (Table 1, entry 1), which supports the above catalytic mechanism. Furthermore, we examined the protonation step of **9** with **2**, using deuterated 1-phosphaallene **2a**$_d$ (Chart 2). Reaction of **2a**$_d$ (97% D) with 0.26 molar amount of *t*-BuLi in THF at room temperature (generation of phosphaallenyllithium **8a**) yielded a dideuterated diphosphafulvene **1a**$_{d2}$ in 38% isolated yield with good D-incorporation, (91% D on the *exo*-methylene carbon and 73% D at the 3-position of the 1,4-dihydrofulvene ring) which also supports the mechanism via **8a** and **9a**$_d$ (Steps B and C). It should be mentioned that the expected maximum D-content at the 3-position is 74% D, based on the above mechanism, because 0.26 molar amount of *t*-BuLi were used to initiate the reaction by abstraction of $D^+$ from **2a**$_d$. It should also be noted that **2a** did not form **1a** in the absence of butyllithium.

The scope and limitations of this methodology were then investigated. Reactions of ethynylphosphines **6b–e** afforded (*E*)-**1b–e** and (*Z*)-**1b–e** (Table 1). Although (*E*)-**1c** and (*Z*)-**1c** were not separated from the mixture, compounds (*E*)-**1b**,**d**,**e** were isolated. However, when ethynylphosphines **6** bearing primary alkyl (R=*n*-Bu), secondary alkyl (R=cyclohexyl), tertiary alkyl (R=*t*-Bu), trimethylsilyl, (*t*-butyldimethylsilyloxy)methyl, or *p*-(trifluoromethyl)-phenyl were employed, the results were unsatisfactory due to partial formation of the corresponding phosphaallenes.

It should be noted that Table 1 (entries 1, 3–6) shows optimized result with respect to the molar amount of butyllithium. When less butyllithium than the optimized amount was used, recovery of the starting ethynylphosphine **6** increased. When more butyllithium than the optimized amount was used, yield of the by-product **2** increased.

oxidation peaks. Among the five 1,4-diphosphafulvenes, **1b** showed the lowest oxidation potential and the order was **1b** < **1c** < **1a** < **1d** < **1e**. This tendency indicates that electron-donating substituents lower the oxidation potentials. The compounds **1a–e** showed relatively good electron-donating activities with $E_{ox}$ values ranging from −0.05 to 0.20 V. This relatively large range for the $E_{ox}$ values of **1** indicates significant effects of the substituent at the 2- or 6-positions on the redox properties of **1** and the tendency found here may become a good guide for developing new material containing the diphosphafulvene structure.

## 3. Conclusion

In summary, we have developed a new synthetic methodology for diphosphafulvene via sterically protected 1-phosphaallene intermediates. The reaction mechanism turned out interestingly to involve phosphaallenyllithium as catalyst. As the experimental procedure is simple and the starting ethynylphosphines are easily prepared from (2,4,6-tri-*t*-butylphenyl)phosphine, these facts merit this preparation method.

## 4. Experimental

### 4.1. General

Melting points were measured on a Yanagimoto MP-J3 micro melting point apparatus and were uncorrected. NMR spectra were recorded on a Bruker Avance-400 or a Bruker AM-600 spectrometer. IR spectra were obtained on a Horiba FT-300 spectrometer. FT-ICR-MS spectra were measured on a Bruker APEX III spectrometer. Cyclic voltammograms were recorded on a BAS-CV-50W voltammetric analyzer under nitrogen. Reactions were performed under an argon atmosphere while work-up was carried out in air, unless otherwise specified.

**4.1.1. 2,6-Diphenyl-1,4-bis(2,4,6-tri-*t*-butylphenyl)-1,4-diphospha-1,4-dihydrofulvene (1a).** To a solution of **6a** (182.7 mg, 0.483 mmol) in THF (1.0 mL) was added 0.075 mL of *n*-BuLi (1.60 M solution in hexane) at room temperature and the resulting mixture was stirred overnight. The solvent was removed under reduced pressure. Column chromatography ($SiO_2$) of the residue provided a mixture of (*E*)-**1a** and (*Z*)-**1a**. To this mixture was added acetone and insoluble (*E*)-**1a**[3] was obtained (127.2 mg, 70% yield) by filtration.

*Compound* (*Z*)-**1a**. $^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$) $\delta$= 48.9 (d, $^2J_{PP}$=19.5 Hz) and 25.2 (d, $^2J_{PP}$=19.5 Hz).

**4.1.2. 2,6-Bis(4-methoxyphenyl)-1,4-bis(2,4,6-tri-*t*-butylphenyl)-1,4-diphospha-1,4-dihydrofulvene (1b).** To a solution of **6b** (122.4 mg, 0.300 mmol) in THF (0.6 mL) was added 0.050 mL of *n*-BuLi (1.54 M solution in hexane) at room temperature and the resulting mixture was stirred overnight. The solvent was removed under reduced pressure and a residual mixture of (*E*)-**1b** and (*Z*)-**1b** was obtained. To the residue was added acetone and insoluble (*E*)-**1b** was obtained (56.7 mg, 46% yield) by filtration.

*Compound* (*E*)-**1b**. Yellow solid, mp 185–188 °C (decomp.); $^1H$ NMR (600 MHz, $CDCl_3$) $\delta$=1.35 (18H, s, *p*-*t*-Bu), 1.64 (36H, br, *o*-*t*-Bu), 3.70 (3H, s, $OCH_3$), 3.75 (3H, s, $OCH_3$), 6.28 (2H, d, $^3J_{HH}$=8.4 Hz, *o*-arom.), 6.43 (2H, d, $^3J_{HH}$=8.4 Hz, *m*-arom.), 6.45 (1H, dd, $^3J_{PH}$=19.8, 6.6 Hz, C*H*Anis), 6.66 (2H, d, $^3J_{HH}$=8.4 Hz, *m*-arom.′), 6.69 (1H, dd, $^2J_{PH}$=37.2 Hz and $^3J_{PH}$=13.2 Hz, PC*H*), 7.07 (2H, d, $^3J_{HH}$=8.4 Hz, *o*-arom.′), and 7.51 (4H, br, *m*-Mes*); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) $\delta$=31.2 (s, *p*-C*Me*$_3$), 31.3 (s, *p*-C*Me*$_3$), 33.5 (br, *o*-C*Me*$_3$), 34.0 (br, *o*-C*Me*$_3$), 34.7 (s, *p*-*C*Me$_3$), 34.9 (s, *p*-*C*Me$_3$), 39.6 (d, $^3J_{PC}$=4.5 Hz, *o*-*C*Me$_3$), 39.8 (br, *o*-*C*Me$_3$), 55.0 (s, $OCH_3$), 55.1 (s, $OCH_3$), 113.1 (s, Anis), 113.2 (s, Anis), 123.5 (br, *m*-Mes*), 124.8 (dd, $^1J_{PC}$=22.6 Hz, $^2J_{PC}$=10.6 Hz, P*C*H), 127.9 (dd, $^3J_{PC}$=4.5 Hz, $^4J_{PC}$=1.5 Hz, Anis), 128.9 (dd, $^4J_{PC}$=5.3 Hz, 2.3 Hz, Anis), 129.2 (d, $^1J_{PC}$=61.9 Hz, *ipso*-Mes*), 129.3 (dd, $^1J_{PC}$=61.9 Hz, $^3J_{PC}$=3.0 Hz, *ipso*-Mes*), 130.9 (dd, $^2J_{PC}$=21.9 Hz, $^3J_{PC}$=2.3 Hz, *ipso*-Anis), 131.3 (d, $^3J_{PC}$=4.5 Hz, *ipso*-Anis), 131.4 (dd, $^1J_{PC}$= 42.3 Hz, 34.7 Hz, P*C*P), 134.6 (dd, $^2J_{PC}$=27.2 Hz, 24.1 Hz, *C*HAnis), 142.1 (t, $J_{PC}$=14.3 Hz, P*C*Anis), 150.6 (s, *p*-Mes*), 150.6 (s, *p*-Mes*), 151.6 (s, *o*-Mes*), 151.6 (s, *o*-Mes*), 157.5 (s, Anis), and 158.5 (s, Anis); $^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$) $\delta$=53.8 (d, $^2J_{PP}$=22.5 Hz) and 23.1 (d, $^2J_{PP}$=22.5 Hz); UV–Vis (hexane) 256 (log $\varepsilon$ 4.54), 295 (sh, 4.45), and 406 nm (3.92); IR (KBr) $\nu$/cm$^{-1}$ 2958, 2906, 2833, 1601, 1504, 1466, 1392, 1360, 1294, 1248, 1211, 1176, 1117, 1038, 874, 804, and 754. HRMS (ESI). Found *m*/*z* 816.5162. Calcd for $C_{54}H_{74}O_2P_2^+$: $M^+$, 816.5159. Found: C, 74.97; H, 8.91%. Calcd for $C_{54}H_{74}O_2P_2\cdot 3H_2O$: C, 74.45; H, 9.26%.

*Compound* (*Z*)-**1b**. $^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$) $\delta$= 49.3 (d, $^2J_{PP}$=17.9 Hz) and 25.6 (d, $^2J_{PP}$=17.9 Hz).

**4.1.3. 2,6-Bis(2-methylphenyl)-1,4-bis(2,4,6-tri-*t*-butylphenyl)-1,4-diphospha-1,4-dihydrofulvene (1c).** Compound **6c** (138.4 mg, 0.353 mmol) in THF (0.7 mL) was converted to **1c**, by a method similar to that of **1b**, by using 0.070 mL of *n*-BuLi (1.54 M solution in hexane). The residue was recrystallized from hexane to give 52.4 mg (38% yield) of a mixture of (*E*)-**1c** and (*Z*)-**1c**.

*Compound* (*E*)-**1c**. $^1H$ NMR (600 MHz, $CDCl_3$) $\delta$=1.28 (18H, s, *p*-*t*-Bu), 1.59 (36H, br, *o*-*t*-Bu), 1.87 (3H, s, $CH_3$), 2.56 (3H, s, $CH_3$), 6.14 (1H, dd, $^3J_{PH}$=16.8 Hz, 7.2 Hz, C*H*Tol), 6.20 (1H, br d, arom.), 6.42 (1H, t, $^3J_{HH}$=7.5 Hz, arom.), 6.48 (1H, dd, $^2J_{PH}$=36.9 Hz, $^3J_{PH}$=13.5 Hz, PC*H*), 6.76 (1H, t, $^3J_{HH}$=7.2 Hz, arom.), 6.84 (1H, d, $^3J_{HH}$= 7.2 Hz, arom.), 6.96 (1H, t, $^3J_{HH}$=7.2 Hz, arom.′), 7.05 (1H, t, $^3J_{HH}$=7.5 Hz, arom.′), 7.18 (1H, d, $^3J_{HH}$=7.8 Hz, arom.′), 7.36 (1H, d, $^3J_{HH}$=7.2 Hz, arom.′), 7.36 (2H, br, *m*-Mes*), and 7.47 (2H, s, *m*-Mes*); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) $\delta$=19.9 (s, $CH_3$), 21.4 (s, $CH_3$), 31.1 (s, *p*-C*Me*$_3$), 31.3 (s, *p*-C*Me*$_3$), 33.4 (br, *o*-C*Me*$_3$), 33.9 (br, *o*-C*Me*$_3$), 34.7 (s, *p*-*C*Me$_3$), 34.9 (s, *p*-*C*Me$_3$), 39.4 (d, $^3J_{PC}$=3.0 Hz, *o*-*C*Me$_3$), 39.5 (d, $^3J_{PC}$=3.0 Hz, *o*-*C*Me$_3$), 123.4 (br, *m*-Mes*), 125.0 (s, Tol), 125.2 (s, Tol), 125.4 (s, Tol), 125.7 (d, $^4J_{PC}$=9.1 Hz, Tol), 126.2 (s, Tol), 126.8 (d, $^1J_{PC}$=57.3 Hz, *ipso*-Mes*), 128.4 (dd, $^3J_{PC}$=7.5 Hz, $^4J_{PC}$=4.5 Hz, Tol), 129.0 (s, Tol), 131.0 (t, $^2J_{PC}$=7.5 Hz, *C*HTol), 131.1 (s, Tol), 131.6 (d, $^1J_{PC}$=67.9 Hz, *ipso*-Mes*), 131.6 (dd, $^1J_{PC}$=21.9 Hz, $^2J_{PC}$=11.3 Hz, P*C*H),

134.7 (s, Tol), 134.9 (dd, $^{1}J_{PC}=42.3$ Hz, 30.2 Hz, P*C*P), 135.5 (s, Tol), 136.3 (m, *ipso*-Tol), 138.7 (d, $^{2}J_{PC}=21.1$ Hz, *ipso*-Tol), 141.3 (dd, $^{1}J_{PC}=22.6$ Hz, $^{2}J_{PC}=15.1$ Hz, P*C*Tol), 150.8 (s, *p*-Mes*), and 151.5 (s, *o*-Mes*); $^{31}P\{^{1}H\}$ NMR (162 MHz, $CDCl_3$) $\delta=64.1$ (d, $^{2}J_{PP}=26.6$ Hz) and 24.2 (d, $^{2}J_{PP}=26.6$ Hz). HRMS [ESI, mixture of (*E*)-**1c** and (*Z*)-**1c**]. Found *m*/*z* 784.5265. Calcd for $C_{54}H_{74}P_2^+$: $M^+$, 784.5260.

*Compound* (*Z*)-**1c**. $^{31}P\{^{1}H\}$ NMR (162 MHz, $CDCl_3$) $\delta=$ 53.4 (d, $^{2}J_{PP}=20.7$ Hz) and 26.1 (d, $^{2}J_{PP}=20.7$ Hz).

**4.1.4. 2,6-Bis(3-thienyl)-1,4-bis(2,4,6-tri-*t*-butylphenyl)-1,4-diphospha-1,4-dihydrofulvene (1d).** Compound **6d** (151.3 mg, 0.395 mmol) in THF (0.8 mL) was converted to (*E*)-**1d** (78.0 mg, 52% yield), by a method similar to that of **1b**, by using 0.075 mL of *n*-BuLi (1.54 M solution in hexane).

*Compound* (*E*)-**1d**. Yellow solid, mp 203–205 °C (decomp.); $^{1}H$ NMR (600 MHz, $CDCl_3$) $\delta=1.38$ (9H, s, *p*-*t*-Bu), 1.39 (9H, s, *p*-*t*-Bu), 1.63 (36H, br, *o*-*t*-Bu), 5.33 (1H, s, Thienyl), 6.04 (1H, s, Thienyl′), 6.45 (1H, d, $^{3}J_{HH}=$ 4.8 Hz, Thienyl), 6.73 (1H, dd, $^{3}J_{PH}=17.7$ Hz, 4.5 Hz, C*H*,Thienyl), 6.76 (1H, dd, $^{2}J_{PH}=37.8$ Hz, $^{3}J_{PH}=13.2$ Hz, PC*H*), 6.93 (1H, dd, $^{3}J_{HH}=4.8$ Hz, $^{4}J_{HH}=2.4$ Hz, Thienyl), 7.09–7.14 (2H, m, Thienyl′), 7.53 (2H, br, *m*-Mes*), and 7.56 (2H, br, *m*-Mes*); $^{13}C\{^{1}H\}$ NMR (151 MHz, $CDCl_3$) $\delta=31.2$ (s, *p*-C*Me*$_3$), 31.4 (s, *p*-C*Me*$_3$), 33.4 (br, *o*-C*Me*$_3$), 33.9 (d, $^{4}J_{PC}=4.5$ Hz, *o*-C*Me*$_3$), 34.8 (s, *p*-*C*Me$_3$), 35.0 (s, *p*-*C*Me$_3$), 39.5 (d, $^{3}J_{PC}=4.5$ Hz, *o*-*C*Me$_3$), 39.9 (br, *o*-*C*Me$_3$), 121.4 (t, $J_{PC}=3.8$ Hz, Thienyl), 121.5 (dd, $^{4}J_{PC}=6.0$ Hz, 4.5 Hz, Thienyl), 123.4 (s, Thienyl), 123.4 (br, *m*-Mes*), 124.2 (s, Thienyl), 125.5 (dd, $^{1}J_{PC}=22.6$ Hz, $^{2}J_{PC}=10.6$ Hz, P*C*H), 125.8 (d, $J_{PC}=4.5$ Hz, Thienyl), 127.5 (dd, $^{1}J_{PC}=59.6$ Hz, $^{3}J_{PC}=2.3$ Hz, *ipso*-Mes*), 128.3 (s, Thienyl), 129.2 (d, $^{1}J_{PC}=63.4$ Hz, *ipso*-Mes*), 129.3 (t, $^{2}J_{PC}=26.4$ Hz, *C*H,Thienyl), 133.1 (dd, $^{1}J_{PC}=41.5$ Hz, 37.0 Hz, P*C*P), 137.2 (t, $J_{PC}=11.3$ Hz, P*C*Thienyl), 138.9 (dd, $^{2}J_{PC}=23.4$ Hz, $^{3}J_{PC}=2.3$ Hz, *ipso*-Thienyl), 139.6 (d, $^{3}J_{PC}=6.0$ Hz, *ipso*-Thienyl), 151.3 (s, *p*-Mes*), 151.3 (s, *p*-Mes*), 152.2 (s, *o*-Mes*), and 152.2 (s, *o*-Mes*); $^{31}P\{^{1}H\}$ NMR (162 MHz, $CDCl_3$) $\delta=48.0$ (d, $^{2}J_{PP}=24.9$ Hz) and 19.7 (d, $^{2}J_{PP}=24.9$ Hz); UV–Vis (hexane) 255 (log $\varepsilon$ 4.55), 285 (sh, 4.40), and 400 nm (3.92); IR (KBr) $\nu$/cm$^{-1}$ 2960, 2906, 2868, 1595, 1558, 1392, 1360, 1236, 1211, 1120, 874, 854, and 768. HRMS (ESI). Found *m*/*z* 768.4079. Calcd for $C_{48}H_{66}P_2S_2^+$: $M^+$, 768.4076.

*Compound* (*Z*)-**1d**. $^{31}P\{^{1}H\}$ NMR (162 MHz, $CDCl_3$) $\delta=$ 46.6 (d, $^{2}J_{PP}=15.2$ Hz) and 23.8 (d, $^{2}J_{PP}=15.2$ Hz).

**4.1.5. 2,6-Bis(3-pyridyl)-1,4-bis(2,4,6-tri-*t*-butylphenyl)-1,4-diphospha-1,4-dihydrofulvene (1e).** Compound **6e** (160.2 mg, 0.422 mmol) in THF (0.8 mL) was converted to **1e** (78.0 mg, 52% yield), by a method similar to that of **1b**, by using 0.055 mL of *n*-BuLi (1.54 M solution in hexane).

*Compound* (*E*)-**1e**. Yellow solid, mp 207–210 °C (decomp.); $^{1}H$ NMR (600 MHz, $CDCl_3$) $\delta=1.28$ (9H, s, *p*-*t*-Bu), 1.29 (9H, s, *p*-*t*-Bu), 1.56 (18H, br, *o*-*t*-Bu), 1.59 (18H, br, *o*-*t*-Bu), 6.27 (1H, d, $^{3}J_{HH}=7.8$ Hz, Pyr), 6.36 (1H, dd, $^{3}J_{PH}=$ 16.8 Hz, 6.0 Hz, C*H*Pyr), 6.60 (1H, dd, $^{3}J_{HH}=7.5$ Hz, 5.1 Hz, Pyr), 6.80 (1H, dd, $^{2}J_{PH}=37.5$ Hz, $^{3}J_{PH}=12.3$ Hz, PC*H*), 6.99 (1H, dd, $^{3}J_{HH}=7.5$ Hz, 5.1 Hz, Pyr′), 7.25 (1H, d, $^{3}J_{HH}=7.2$ Hz, Pyr′), 7.41 (2H, s, *m*-Mes*), 7.49 (2H, s, *m*-Mes*), 7.96 (1H, s, Pyr), 8.08 (1H, d, $^{3}J_{HH}=4.2$ Hz, Pyr), 8.34 (1H, d, $^{3}J_{HH}=4.2$ Hz, Pyr′), and 8.51 (1H, s, Pyr′); $^{13}C\{^{1}H\}$ NMR (151 MHz, $CDCl_3$) $\delta=31.1$ (s, *p*-C*Me*$_3$), 31.2 (s, *p*-C*Me*$_3$), 33.3 (br, *o*-C*Me*$_3$), 33.9 (d, $^{4}J_{PC}=4.5$ Hz, *o*-C*Me*$_3$), 34.7 (s, *p*-*C*Me$_3$), 34.9 (s, *p*-*C*Me$_3$), 39.5 (d, $^{3}J_{PC}=4.5$ Hz, *o*-*C*Me$_3$), 39.6 (d, $^{3}J_{PC}=4.5$ Hz, *o*-*C*Me$_3$), 122.7 (s, Py), 123.6 (br, *m*-Mes*), 124.1 (br, *m*-Mes*), 126.0 (d, $^{1}J_{PC}=54.3$ Hz, *ipso*-Mes*), 127.4 (d, $^{1}J_{PC}=58.9$ Hz, *ipso*-Mes*), 128.0 (dd, $^{1}J_{PC}=22.6$ Hz, $^{2}J_{PC}=10.6$ Hz, P*C*H), 129.7 (dd, $^{2}J_{PC}=30.2$ Hz, 22.6 Hz, *C*HPyr), 132.4 (dd, $^{4}J_{PC}=7.5$ Hz, 3.0 Hz, Pyr), 133.4–133.7 (m, *ipso*-Py), 133.5 (m, Py), 137.5 (dd, $^{1}J_{PC}=41.5$ Hz, 37.0 Hz, P*C*P), 139.3 (t, $J_{PC}=15.8$ Hz, P*C*Pyr), 145.8 (s, Py), 147.7 (t, $J_{PC}=3.0$ Hz, Pyr), 147.8 (s, Py), 149.7 (t, $^{4}J_{PC}=3.8$ Hz, Pyr), 151.4 (s, *p*-Mes*), 151.5 (s, *p*-Mes*), 152.4 (s, *o*-Mes*), and 152.4 (s, *o*-Mes*); $^{31}P\{^{1}H\}$ NMR (162 MHz, $CDCl_3$) $\delta=54.2$ (d, $^{2}J_{PP}=31.0$ Hz) and 25.1 (d, $^{2}J_{PP}=31.0$ Hz); UV–Vis (hexane) 256 (log $\varepsilon$ 4.59), 290 (sh, 4.38), and 419 nm (3.95); IR (KBr) $\nu$/cm$^{-1}$ 2960, 2906, 2868, 1591, 1527, 1473, 1398, 1360, 1238, 1209, 1182, 1124, 1024, 876, 791, and 708. HRMS (ESI). Found *m*/*z* 759.4926. Calcd for $C_{50}H_{68}N_2P_2^+$: $MH^+$, 759.4930. Found: C, 77.26; H, 8.99; N, 3.62%. Calcd for $C_{50}H_{68}N_2P_2\cdot H_2O$: C, 77.28; H, 9.08; N, 3.61%.

*Compound* (*Z*)-**1e**. $^{31}P\{^{1}H\}$ NMR (162 MHz, $CDCl_3$) $\delta=$ 50.3 (d, $^{2}J_{PP}=21.7$ Hz) and 24.6 (d, $^{2}J_{PP}=21.7$ Hz).

**4.1.6. 1,2-Bis(3-pyridyl)-3,4-bis[(2,4,6-tri-*t*-butylphenyl)-phosphinidene]cyclobutene (3e).** A mixture of (2,4,6-tri-*t*-butylphenyl)phosphine (275.4 mg, 0.989 mmol) and AIBN (10.3 mg, 0.0627 mmol) in $CCl_4$ (3 mL) was refluxed for 4 h. The solvent was removed under reduced pressure and 2 mL of THF was added. In a separate flask, 1.01 mmol of ethylmagnesium bromide (0.96 M solution in THF) was added to a THF (2 mL) solution of 3-ethynylpyridine (103.2 mg, 1.00 mmol) at 0 °C. The resulting solution was stirred at 0 °C for 10 min., allowed to warm to room temperature, and added to the THF solution of chloro(2,4,6-tri-*t*-butylphenyl)phosphine prepared above. The resulting mixture was stirred for 10 min and passed through short silica-gel column using EtOAc as eluent. Removal of the solvent afforded [(3-pyridyl)ethynyl]phosphine **6e**, which was used for the following reactions as obtained. To a solution of **6e** in THF (2 mL) was added 1.00 mmol of *n*-BuLi (1.59 M solution in hexane) at −78 °C and the resulting solution was stirred for 10 min, 1,2-dibromoethane (0.0499 mmol) was added, and stirred for 10 min. The resulting mixture was then allowed to warm to room temperature and stirred for 1 h. The solvent was removed under reduced pressure, 2 mL of toluene was added to the residue, and the toluene solution was refluxed for 30 min. Removal of the solvent under vacuum followed by column chromatographic separation ($SiO_2$/hexane–EtOAc) provided 79.6 mg of **3e** [21% based on the starting (2,4,6-tri-*t*-butylphenyl)phosphine].

Yellow solid, mp 266–269 °C (decomp.); $^{1}H$ NMR (400 MHz, $CDCl_3$) $\delta=1.37$ (18H, s, *p*-*t*-Bu), 1.55 (36H,

br, *o*-*t*-Bu), 6.50 (2H, d, $^{3}J_{HH}=8.0$ Hz, Pyr), 6.71 (2H, dd, $^{3}J_{HH}=8.0$ Hz, 4.8 Hz, Pyr), 7.33 (4H, s, *m*-Mes*), 7.86 (2H, s, Pyr), and 8.22 (2H, d, $^{3}J_{HH}=4.8$ Hz, Pyr); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) $\delta=32.0$ (s, *p*-C*Me*$_3$), 33.7 (br, *o*-C*Me*$_3$), 35.5 (s, *p*-*C*Me$_3$), 38.7 (s, *o*-*C*Me$_3$), 122.3 (s, arom.), 123.3 (s, arom.), 128.1 (s, arom.), 134.5 (pseudo t, $J_{PC}=28.3$ Hz, *ipso*-Mes*), 135.2 (s, Pyr), 148.8 (s, arom.), 148.9 (s, arom.), 151.1 (s, *o*-Mes*), 152.7 (pseudo t, $J_{PC}=7.0$ Hz, P=C–*C*), 155.2 (s, *o*-Mes*), and 175.6 (dd, $^{1}J_{PC}=18.4$ Hz, $^{2}J_{PC}=8.1$ Hz, P=C); $^{31}P\{^{1}H\}$ NMR (162 MHz, $CDCl_3$) $\delta=179.6$; UV–Vis (hexane) 246 (log $\varepsilon$ 4.45), 325 (4.53), and 377 nm (sh, 4.03); IR (KBr) $\nu$/cm$^{-1}$ 2954, 1591, 1471, 1400, 1363, and 1242. HRMS (ESI). Found *m*/*z* 757.4773. Calcd for $C_{50}H_{67}N_2P_2^+$: $MH^+$, 757.4774.

### 4.2. Reaction of 2a$_d$ with *t*-butyllithium

To a solution of **2a**$_d$ (127.7 mg, 0.337 mmol, 97% D) in THF (1.0 mL) was added 0.088 mmol (0.26 molar amount) of *t*-BuLi (1.46 M solution in pentane) and the resulting solution was stirred overnight. The solvent was evaporated under reduced pressure. $^{31}P$ NMR spectrum of the residue showed signals due to (*E*)- and (*Z*)-diphosphadihydrofulvenes as well as the starting **2a**$_d$. To the residue was added acetone and the insoluble (*E*)-**1a**$_{d2}$ was obtained (48.2 mg, 38% yield) by filtration. D content of the product was determined by $^{1}H$ NMR spectroscopy.

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# Regio- and stereoselective synthesis of bis-spiropyrazoline-5,3′-chroman(thiochroman)-4-one derivatives via bis-nitrilimines

Kamal M. Dawood*

*Department of Chemistry, Faculty of Science, Cairo University, Giza 12613, Egypt*

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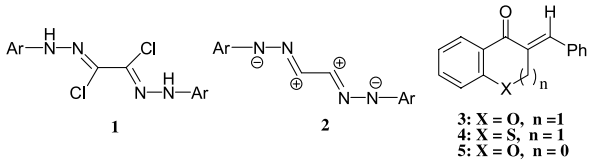
**Abstract**—Regioselective 1,3-dipolar cycloaddition of the bis-nitrilimines with the benzylidene derivatives of chroman-4-one and thiochroman-4-one afforded the corresponding bis-spiropyrazoline derivatives. X-ray analysis was used in the elucidation of the regio- and stereochemistry of the products. Similar reactions of the bis-nitrilimines with 2-benzylidene-3-coumaranone furnished 3,3′-bipyrazole derivatives.


## 1. Introduction

Chromanone derivatives have drawn much attention due to their anti-human immunodeficiency virus (HIV-1) that causes the Acquired Immune Deficiency Syndrome (AIDS).[1–3] The chromanone moiety is also found in several natural products.[4,5] Thiochromanone derivatives were also reported as biologically active compounds.[6] In addition, bipyrazole derivatives are involved in wide variety of medicinals and pharmacueticals.[7,8] 1,3-Dipolar cycloaddition is one of the most versatile methods for the construction of five-membered heterocycles.[9] Although bis-nitrilimines **2** have been known for more than three decades,[10] their 1,3-dipolar cycloaddition with any exocyclic olefin for synthesis of bis-spiroheterocycles has not yet been reported. In continuation of our research work on the chemistry of bis-hydrazonoyl chlorides **1**,[11–13] 3-benzylidene derivatives of chromanone **3**[14] and thiochromanone **4**,[15] we report herein not only the utility of these versatile substrates in the synthesis of bis-spiropyrazoles but also the regio- and stereochemistry of the reaction products.

## 2. Results and discussion




1 2

The 1,3-dipolar cycloaddition reactions of the bis-nitrilimines **2a**,**b** [obtained in situ from the reaction of the bis-hydrazonoyl chlorides **1a**,**b** with triethylamine] with the benzylidene derivatives **3** and **4** were thoroughly investigated. At first, the reaction between (*E*)-3-benzylidene-chroman-4-one (**3**) with the bis-nitrilimine **2a** (in 2:1 molar ratio) was attempted in refluxing dry benzene until the starting substrates were completely consumed (36 h). This reaction resulted in the formation of a single product as examined by TLC. The elemental analysis and mass spectrum of the reaction product proved that the reaction proceeded in 2:1 molar ratio, compatible with the molecular formula $C_{46}H_{34}N_4O_4$. The bis-nitrilimine **2a** has two 1,3-dipole sites, thus there are three possible cycloaddition structures **6a**, **7a** or **8a** for the reaction product, as postulated in Scheme 1. The $^1$H and $^{13}$C NMR spectra excluded the unsymmetrical 1,3-dipolar cycoaddition structure **8a**, where only one pyrazoline-CH signal was observed in both spectra. The $^1$H NMR spectrum revealed characteristic singlet signal at $\delta$ 4.91 in addition to two doublets at $\delta$ 4.31 and 4.71 having the same *J* value 12.3 Hz. The appearance of the singlet at $\delta$ 4.91 is consistent with the pyrazoline-4H proton (typically $\delta$ 4.7–5.1)[16,17]and not with the pyrazoline-

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* Corresponding author at present address: Institute of Organic Chemistry, Hannover University, Schneiderberg 1B, D-30167 Hannover, Germany; e-mail addresses: dr_dawood@yahoo.com; kamal.dawood@oci.uni-hannover.de

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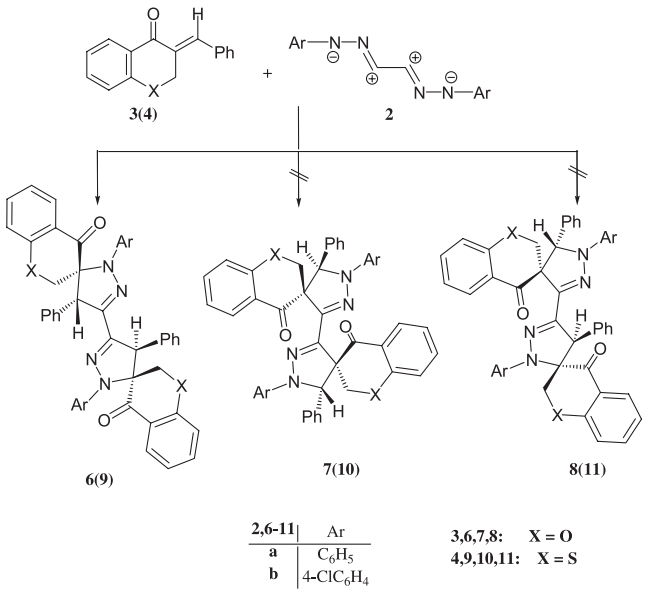



**Scheme 1.**

5H proton (typically more downfield than $\delta$ 5.6).[18] In addition, the $^{13}$C NMR spectrum exhibited three signals at $\delta$ 60.1, 68.7 and 74.3 corresponding to three sp$^3$ carbon atoms. The signal at $\delta$ 74.3 is characteristic for the spiropyrazoline-5-carbon atom, which is in accord with similar reported structures.[16] Moreover, the conjugated carbonyl absorption at 1664 cm$^{-1}$ of compound **3**[19] was converted into an unconjugated one and shifted to a higher value 1681 cm$^{-1}$ of the reaction product. All the above mentioned spectroscopic data provide firm support for the formation of the bis-spiropyrazoline-5,3′-chroman-4-one derivative **6a** and rule out the other regioisomer **7a** (Scheme 1). Furthermore, the regio- and stereoselectivity in the 1,3-dipolar cycloaddition reaction was unequivocally determined by carrying out a single crystal X-ray analysis of compound **6a** (Fig. 1).

In addition, regioselective 1,3-dipolar cycloaddition reaction of the bis-nitrilimine **2b** with the benzylidene derivative **3** was also conducted under similar reaction conditions and afforded the bis-spiropyrazoline-5,3′-chroman-4-one derivative **6b**, Scheme 1.

Furthermore, when (*E*)-3-benzylidenethiochroman-4-one (**4**) was allowed to react with the bis-nitrilimine **2a** in 2:1 molar ratio under prolonged reflux in dry benzene, it afforded only one isolable product by TLC. Spectroscopic analyses established the regioselective 1,3-dipolar cycloaddition of the bis-nitrilimines **2a** to the exocyclic double bond of **4** to furnish the corresponding bis-spiropyrazoline-5,3′-thiochroman-4-one derivative **9a** and excluded the other regioisomeric structures **10a** and **11a**, as shown in Scheme 1. The $^1$H NMR spectrum of compound **9a** revealed a singlet signal at $\delta$ 4.80 due to the pyrazoline-4-CH proton in addition to two doublets at $\delta$ 3.45 and 4.34 with the same *J* value 13.2 Hz due to the methylene protons at position 2 of the thiochromanone moiety. In addition, the $^{13}$C NMR spectrum revealed three sp$^3$ carbon signals at $\delta$ 31.6, 61.8 and 75.8. The signals at $\delta$ 61.8 and 75.8 are corresponding to the pyrazoline C-4 and C-5, respectively. Moreover, the carbonyl absorption at 1659 cm$^{-1}$ of compound **4**[19] was shifted to a higher value 1678 cm$^{-1}$ of the reaction product.

In a similar fashion, the reaction of the bis-nitrilimine **2b** with the benzylidene derivative **4** was also carried out under the same reaction conditions and afforded the corresponding bis-spiropyrazoline-5,3′-thiochroman-4-one derivative **9b** as shown in Scheme 1. All spectroscopic data are in complete accordance with the assigned structure.

The reaction of the bis-nitrilimine **2a** with 2-benzylidene-3-coumaranone **5** was performed under similar conditions and afforded only one isolable product. On the basis of its spectroscopic data, the structure of the reaction product was identified as 5,5′-di-(2-hydroxybenzoyl)-1,1′,4,4′-tetraphenyl-3,3′-bipyrazole (**13a**) and not the expected bis-spiropyrazolocoumaranone derivative **12a** (Scheme 2). The $^1$H NMR spectrum of the reaction product exhibited the

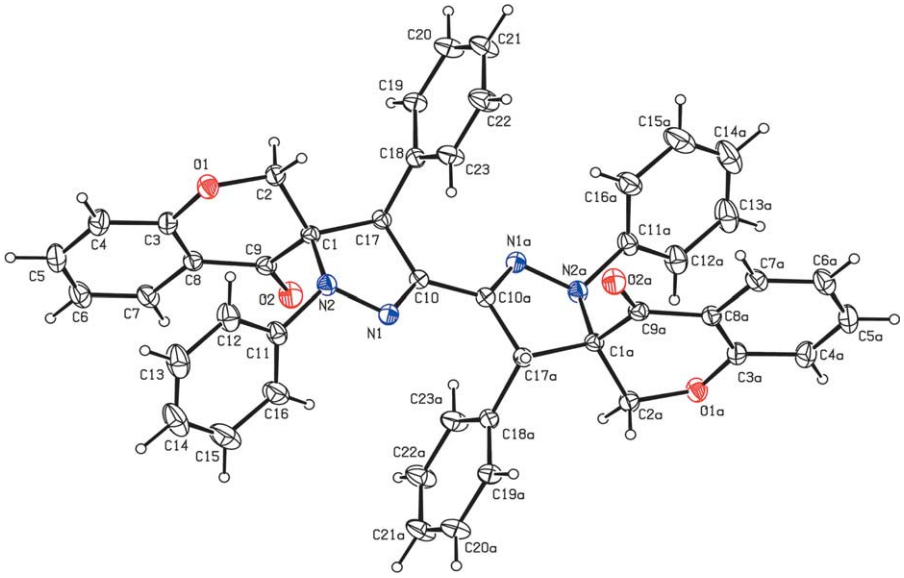
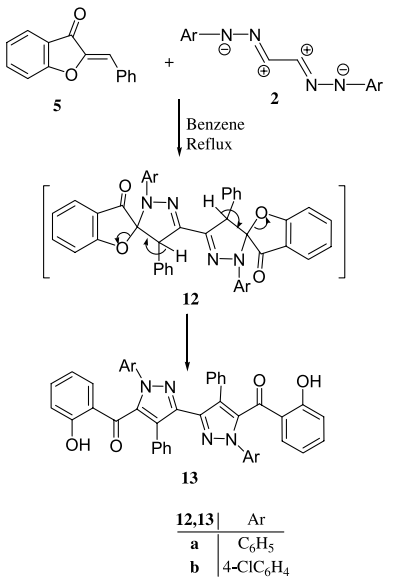



**Figure 1.** X-ray structure of compound **6a**.




**Scheme 2.**

presence of characteristic phenolic protons at $\delta$ 11.49 ($D_2O$-exchangeable) and the absence of the pyrazoline-CH proton signal near $\delta$ 5 ppm. The $^{13}C$ NMR was also free of the pyrazoline C-4 and C-5 $sp^3$-carbons that appeared in compounds **6** and **9**. The formation of the phenolic compound **13a** is assumed to occur via the regioselective 1,3-dipolar cycloaddition of the bis-nitrilimine **2a** to the exocyclic double bond of **5** to give the non-isolable bis-spiropyrazoline derivative **12a** followed by aromatization of the pyrazoline rings accompanied with ring-closure of the coumaranone moieties via 1,3-hydrogen shift to give the phenolic compound **13a** as outlined in Scheme 2. In a similar manner, the bis-nitrilimine **2b** reacted with compound **5** to give the corresponding bipyrazole derivative **13b** as established from its spectroscopic and elemental analyses.

In conclusion, we described some interesting regio- and stereoselective 1,3-dipolar double cycloadditions of bis-nitrilimines to some exocyclic olefins and in all cases they furnished the symmetrical products rather than the other possible regioisomers.

## 3. Experimental

### 3.1. General

Melting points were measured with a Gallenkamp apparatus. IR spectra were recorded on Shimadzu FT-IR 8101 PC infrared spectrophotometer. The $^1H$ NMR spectra were measured in $CDCl_3$ or DMSO-$d_6$ at 300 MHz on a Varian Mercury VX 300 NMR spectrometer using TMS as an internal standard. Mass spectra were measured on a GCMS-QP1000 EX spectrometer at 70 eV. Elemental analyses were carried out at the Microanalytical Center of Cairo University.

Bis-hydrazonoyl chlorides **1**,[10,13] and the benzylidene derivatives of chroman-4-one **3**,[19] thiochroman-4-one **4**,[19] and coumaran-3-one **5**[20] were prepared according to the literature procedures.

### 3.2. Bis-[1,4-diaryl-spiropyrazoline-5,3′-chroman-4-ones] 6a,b and bis-[1,4-diaryl-spiropyrazoline-5,3′-thiochroman-4-ones] 9a,b

To a mixture of the appropriate bis-hydrazonoyl chloride **1a** or **1b** (1 mmol) and the appropriate (*E*)-3-benzylidene-chroman-4-one (**3**) or (*E*)-3-benzylidenethiochroman-4-one (**4**) (2 mmol each) in dry benzene (20 mL), triethylamine (0.2 mL, 2 mmol) were added and the reaction mixture was heated under refluxing condition. The reaction was controlled by TLC and continued until the starting substrates were completely consumed (36–40 h), then left to cool to room temperature. The solvent was removed, in each case, under reduced pressure and the residue was triturated with methanol to give yellow or pale-brown colored products. The solid products that formed were filtered off, washed with ethanol and dried. Recrystallization from dimethylformamide (DMF) afforded the corresponding bis-[1,4-diaryl-spiropyrazoline-5,3′-chroman-4-ones] **6a**,**b** and their thio-analoges **9a**,**b** in 62–75% yields.

*Compound* **6a**. Yellow crystals (0.53 g, 75%); mp >300 °C; IR (KBr) $\nu$ 1681 (C=O), 1603 (C=N) $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$) $\delta$ 4.31 (d, 2H, $J$=12.3 Hz), 4.71 (d, 2H, $J$=12.3 Hz), 4.91 (s, 2H), 6.78–6.96 (m, 8H), 7.01–7.10 (m, 6H), 7.19–7.22 (m, 4H), 7.34–7.40 (m, 6H), 7.53–7.59 (m, 2H), 7.84 (d, 2H, $J$=8.1 Hz); $^{13}C$ NMR $\delta$ 60.1, 68.7, 74.3, 118.5, 119.1, 120, 122.7, 123.1, 128.2, 128.4, 128.6, 129, 135.4, 137.7, 143.4, 145.1, 161, 189.1; MS *m*/*z* (%), 707 ($M^+$+1, 40.8), 706 ($M^+$, 82.6), 586 (44.4), 558 (33.3), 466 (96.8), 388 (14.4), 348 (20.0), 258 (29.5), 207 (36.1), 118 (31), 77 (100). For $C_{46}H_{34}N_4O_4$ Calcd: C, 78.17; H, 4.85; N, 7.93. Found: C, 78.06; H, 5.03; N, 8.05%.

*Compound* **6b**. Pale brown solid (0.53 g, 68%); mp >300 °C; IR (KBr) $\nu$ 1680 (C=O), 1613 (C=N) $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$) $\delta$ 4.28 (d, 2H, $J$=12.6 Hz), 4.71 (d, 2H, $J$=12.6 Hz), 4.86 (s, 2H), 6.81–6.99 (m, 8H), 7.11–7.32 (m, 8H), 7.47–7.58 (m, 6H), 7.64–7.71 (m, 2H), 8.01 (d, 2H, $J$=8.1 Hz); MS *m*/*z* (%), 777 ($M^+$+2, 15.8), 776 ($M^+$+1, 37.5), 775 ($M^+$, 44.8), 604 (6.8), 467 (34.5), 390 (15.2), 361 (10.7), 272 (33.1), 221 (24.5), 117 (41.5), 77 (100). For $C_{46}H_{32}Cl_2N_4O_4$ Calcd: C, 71.23; H, 4.16; N, 7.22. Found: C, 71.16; H, 4.12; N, 7.31%.

*Compound* **9a**. Yellow needles (0.52 g, 71%); mp 203–205 °C; IR (KBr) $\nu$ 1678 (C=O), 1593 (C=N) $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$) $\delta$ 3.45 (d, 2H, $J$=13.2 Hz), 4.34 (d, 2H, $J$=13.2 Hz), 4.80 (s, 2H), 6.82–6.95 (m, 6H), 7.10–7.19 (m, 6H), 7.26–7.38 (m, 12H), 7.53–7.59 (m, 2H), 8.03 (d, 2H, $J$=8.1 Hz); $^{13}C$ NMR $\delta$ 31.6, 61.8, 75.8, 118.9, 121.8, 125.3, 126.1, 128.1, 128.3, 128.4, 128.7, 131.1, 131.4, 133.9, 134.6, 140.8, 143.1, 160.1, 189.5; MS *m*/*z* (%), 739 ($M^+$+1, 17.0), 738 ($M^+$, 45.8), 466 (72), 386 (31.3), 350 (21.6), 258 (43.3), 136 (13.7), 119 (28), 77 (100). For $C_{46}H_{34}N_4O_2S_2$ Calcd: C, 74.77; H, 4.64; N, 7.58; S, 8.68. Found: C, 74.68; H, 4.51; N, 7.26; S, 8.64%.

*Compound* **9b**. Yellow needles (0.50 g, 62%); mp 209–211 °C; IR (KBr) $\nu$ 1682 (C=O), 1588 (C=N) $cm^{-1}$; $^1H$

NMR (DMSO-$d_6$) $\delta$ 3.43 (d, 2H, $J=12.8$ Hz), 4.36 (d, 2H, $J=12.8$ Hz), 4.81 (s, 2H), 6.93–7.07 (m, 8H), 7.13–7.21 (m, 4H), 7.27–7.46 (m, 8H), 7.66–7.80 (m, 4H), 8.02 (d, 2H, $J=7.9$ Hz); $^{13}$C NMR $\delta$ 31.5, 61.7, 75.8, 119, 122, 125.4, 128.2, 128.5, 128.7, 131.2, 131.4, 133.2, 134, 134.3, 140.8, 143.3, 159.8, 189.1; MS *m/z* (%), 809 ($M^+ +2$, 10.8), 808 ($M^+ +1$, 28.9), 807 ($M^+$, 64.3), 482 (11.5), 465 (41.2), 319 (36.6), 251 (28.1), 214 (12.5), 150 (23.7), 108 (62.4), 90 (49), 77 (100). For $C_{46}H_{32}Cl_2N_4O_2S_2$ Calcd: C, 68.39; H, 3.99; N, 6.94; S, 7.94. Found: C, 68.25; H, 4.11; N, 6.86; S, 7.91%.

### 3.3. X-ray structure determination of compound 6a

The X-ray diffraction measurement was made on Stoe IPDS area detector diffractometer at temperature 300(2) K and wavelength 0.71073 Å. Crystal data for compound **6a**: $C_{46}H_{34}N_4O_4$, $fw=706.77$, crystal system, space group: monoclinic, $P2_1/n$; unit cell dimensions: $a=7.722(1)$ Å, $b=21.368(2)$ Å, $c=11.338(2)$ Å, $\alpha=90°$, $\beta=100.34(1)°$, $\gamma=90°$; volume: 1840.4(4) $A^3$; $Z$, 2; calculated density: 1.275 mg/m$^3$; absorption coeffecient: 0.082 mm$^{-1}$; $F(000)$: 740; crystal size: $1.1\times0.28\times0.22$ mm$^3$; $\theta$ range for data collection: 1.91–24.18°; completeness to $2\theta$: 97.3%; refinement method: full-matrix least-square on $F^2$; data/restraints/parameters: 2851/0/245; goodness-of-fit on $F^2$: 1.034; final $R$ indices [$I>2\sigma(I)$]: $R1=0.0388$, $wR2=0.0684$; $R$ indices (all data): $R1=0.0621$, $wR2=0.0746$; extinction coefficient: 0.0053(7); largest diff. peak and hole: 0.155 and $-0.171$ e $A^{-3}$.

Crystallographic data for the structural analysis of compound **6a** has been deposited with the Cambridge Crystallographic Data Center (CCDC) under the number 265649. Copies of the information may be obtained free of charge from The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk or www: http://www.ccdc.cam.ac.uk).

### 3.4. Synthesis of 3,3′-bipyrazole derivatives 13a,b

A mixture of the bis-hydrazonoyl chloride **1a** or **1b** (1 mmol) and the 2-benzylidenecoumaran-3-one (**5**) (2 mmol) in dry benzene (20 mL), in the presence of triethylamine (0.2 mL, 2 mmol) was heated at refluxing temperature. The reflux was continued until the starting substrates were completely consumed (30–36 h), as examined by TLC. After the reaction mixture was cooled to room temperature, the solvent was removed under vacuum and the residue was triturated with methanol to give, in each case, a gray-colored precipitate, which was filtered off, washed with ethanol and dried. Recrystallization from dimethylformamide/ethanol afforded the corresponding 3,3′-bipyrazole derivatives **13a**,**b**, respectively.

*Compound* **13a**. Gray solid (0.37 g, 55%); mp 182–183 °C; IR (KBr) $\nu$ 3124 (br OH), 1635 (C=O), 1599 (C=N) cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 6.98–7.06 (m, 4H), 7.20–7.33 (m, 16H), 7.49–7.61 (m, 8H), 11.49 (s, 2H, $D_2O$-exchangeable); $^{13}$C NMR $\delta$ 114.8, 115.1, 115.3, 124.8, 124.9, 129.2, 130.2, 130.4, 131.1, 131.4, 132.5, 133.7, 138.9, 139.6, 147.3, 163.2, 193.9; MS *m/z* (%), 679 ($M^+ +1$, 9.6), 678 ($M^+$, 26.8), 636 (22.1), 621 (8.8), 465 (14.5), 411 (78.4), 295 (37.2), 223 (59.7), 167 (94.5), 121 (86.2). For $C_{44}H_{30}N_4O_4$ Calcd: C, 77.86; H, 4.46; N, 8.25. Found: C, 77.94; H, 4.39; N, 8.47%.

*Compound* **13b**. Gray solid (0.44 g, 59%); mp 196–198 °C; IR (KBr) $\nu$ 3094 (br OH), 1638 (C=O), 1600 (C=N) cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 6.91–7.02 (m, 6H), 7.21–7.34 (m, 10H), 7.58–7.72 (m, 10H), 11.51 (s, 2H, $D_2O$-exchangeable); MS *m/z* (%), 749 ($M^+ +2$, 18.3), 748 ($M^+ +1$, 53), 747 ($M^+$, 80.6), 676 (42.4), 559 (31.9), 397 (12.3), 265 (19.5), 186 (62.7), 148 (68.8), 126 (33.4). For $C_{44}H_{28}Cl_2N_4O_4$ Calcd: C, 70.69; H, 3.77; N, 7.49. Found: C, 70.50; H, 3.52; N, 7.22%.

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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.2005.03.083

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# Ring-closure reactions through intramolecular substitution of thiophenoxide by oxygen and nitrogen nucleophiles: simple stereospecific synthesis of 4,5-dihydroisoxazoles and 4,5-dihydropyrazoles

Mariola Zielinska-Błajet, Rafał Kowalczyk and Jacek Skarżewski*

*Institute of Organic Chemistry, Biochemistry and Biotechnology, Wrocław University of Technology, 50-370 Wrocław, Poland*

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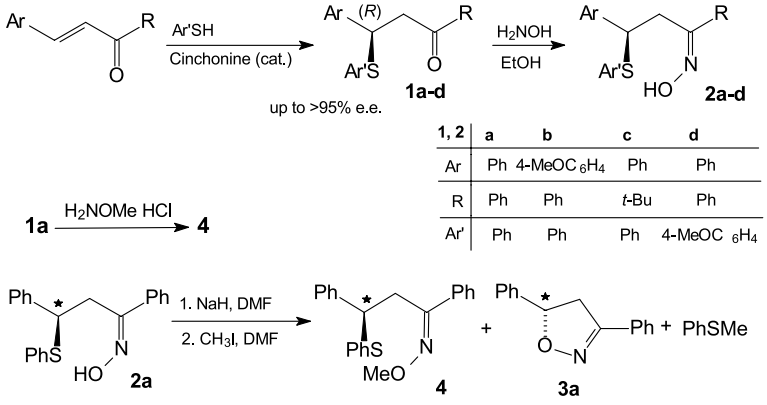
**Abstract**—A new and simple method for the stereospecific synthesis of 3,5-disubstituted-4,5-dihydro-isoxazoles (chiral isoxazolines) from readily available oximes of chiral Michael adducts of thiophenol to chalcones is reported. An analogous reaction with the *N*-arylhydrazones of the Michael adduct gave nonracemic 1-(aryl)-3,5-diphenyl-4,5-dihydro-1*H*-pyrazoles (chiral pyrazolines), but these products are configurationally unstable. The key step of the synthesis is the ring-closure reaction, which occurs by a stereospecific intramoleculer nucleophilic substitution of thiophenoxide.


## 1. Introduction

The stereocontrolling ability of the ligand in a metal-catalyzed asymmetric reaction is determined mainly by the type of donor atoms present and by the overall ligand structure. Accordingly, heterodonating *N*, *S*-ligands have been applied successfully in the Pd-catalyzed allylic substitutions and their stereoelectronic *trans*-effects were considered as the main cause of enantioselectivity.[1] These results turned our attention to the catalytic application of the *N*, *S*-ligands prepared from the enantiomerically enriched adduct of thiophenol to chalcone. The respective Michael addition was catalyzed by (+)-cinchonine and after crystallization gave almost optically pure adducts **1** (91→95% ee) in multi-gram quantities.[2] The obtained ketone (+)-**1a** was then converted into the oxime (+)-**2a** and its *R*-configuration was proved by X-ray analysis of the corresponding Beckmann rearrangement product.[2] For further derivatization of the nitrogen-containing functionality, we attempted to *O*-methylate (+)-**2a** (NaH in DMF




**Scheme 1.**

*Keywords*: Cyclization; Nucleophilic substitution of thiophenoxide; Chiral isoxazolines; Pyrazolines.
* Corresponding author. Tel.: +4871 3203224; fax: +4871 3284064; e-mail: jacek.skarzewski@pwr.wroc.pl

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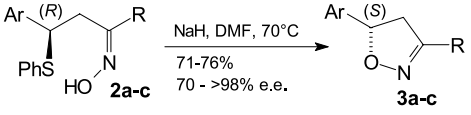
followed by MeI). However, besides the expected methyl oxime ether **4**, we isolated isoxazoline (4,5-dihydroisoxazol) **3a** together with thioaniosole (Scheme 1).

The desired *E*-(+)-**4** was simply prepared by treatment of ketone (+)-**1a** with *O*-methylhydroxylamine hydrochloride in buffered solution. At this stage, we decided to examine the unexpectedly observed ring-closure and the results obtained are reported herein.

## 2. Results and discussion

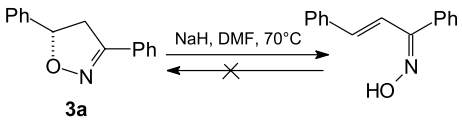
The enantiomerically enriched (+)-*R*-*E*-oximes **2a–d** were treated with sodium hydride in DMF and kept at 70 °C for 1–1.5 h. After an aqueous work-up, the corresponding isoxazolines **3a–c** were isolated in 71–76% yield. The products were dextrorotatory (57–86% ee) and, after recrystallization, of high enantiomeric excess of >98, 70, and 86%, respectively, as demonstrated by $^1$H NMR spectra measured in the presence of Eu(hfc)$_3$ (Scheme 2).




**Scheme 2.**

One of them, (+)-**3a** has already been reported in the literature as an enantioenriched (+)-*S*-isomer.[3,4] This assignment[4] was based on chemical correlation to the known optically active β-hydroxyketone.[5] Thus, the intramolecular nucleophilic substitution occurred and *R*-**2a–d** cyclized to the products **3a–c** of *S*-configuration. Moreover, we prepared enantioenriched *S*-**2a** using the corresponding adduct *S*-**1a** (57% ee). This material was obtained after twofold crystallization of the primary 14% ee product of the Michael addition of thiophenol to chalcone in the presence of cinchonidine.[2] Thus, the obtained (−)-*S*-*E*-**2a** (ca. 57% ee) underwent cyclization giving (−)-*R*-**3a** (55% ee).

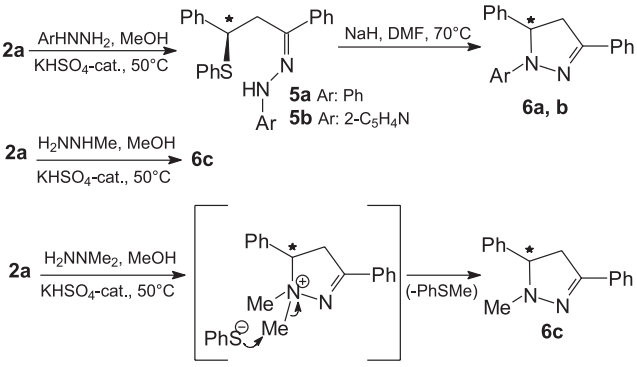
The observed inversion of configuration strongly suggests an S$_N$2-type mechanism, where an oximate ion with the nucleophilicity enhanced by the α-effect expels a thiophenoxide ion directly. To the best of our knowledge, there is only one precedent of the reaction of this kind that has been reported.[6] Namely, cyclopropanone dithioacetals were formed by an intermolecular substitution of thiophenoxide and this ring-closure was considered as an apparently unique example of the S$_N$2 reaction. An analogous reaction leading to four- and five-membered rings did not work.[6] On the other hand, some nucleophilic displacements of thiophenoxide were accounted for by an elimination–addition mechanism.[7] However, the observed reaction enantiospecifity seems to exclude this mechanism in our case. Interestingly, when the reaction of **2a** was run for over 2 h, along with the main **3a**, the oxime of chalcone[8] was isolated as a side elimination product formed in 5–12% yield. When the cyclization of this product was attempted under the same reaction conditions in a separate experiment, no isoxazoline **3a** could be detected (Scheme 3). Thus, the elimination–addition mechanism does not operate here.




**Scheme 3.**

Furthermore, an analogous intermolecular substitution, specifically the reaction between acetophenone oximate and benzyl phenyl sulfide did not lead to the respective nucleophilic substitution product. Thus, it seems that the observed unusual substitution is caused by the close proximity of the nucleophile to the reaction center (*E*-configuration of oxime). The five-membered ring closure *5-exo-tet* process is highly favored for the stereoelectronic reasons.[9] The reaction is clearly enantioselective and offers a simple synthetic route to 4,5-dihydroisoxazoles in enantioenriched forms.

In order to test the scope of ring closure we tried to prepare various hydrazones of (+)-**2a**. The *N*-phenyl and *N*-2-pyridyl derivatives **5a** and **b** were obtained easily, and the hydrazones were cyclized to the corresponding pyrazolines **6a** and **b**, respectively. An attempted preparation of *N*-methyl and *N*,*N*-dimethylhydrazones failed. Instead, in both cases the same cyclized product **6c** was formed. In the last reaction, in addition to **6c** thioanisole was produced, accordingly documenting demethylation of the primary cyclization product (Scheme 4).




**Scheme 4.**

Thus, obtained pyrazolines (4,5-dihydropyrazoles) showed only small to medium optical activity (no ee could be established) and quickly underwent complete racemization. Anyhow, even this activity supports the S$_N$2-type mechanism operating here. Moreover, along with the pyrazoline **6c**, its aromatization product (pyrazole) was obtained. It seems that in spite of their easy formation via the nucleophilic displacement of thiophenoxide, the pyrazolines **6** unlike isoxazolines **3** are configurationally unstable and their easy aromatization, if reversible, can be responsible for this instability.

In conclusion, an exceptional example of the intramolecular S$_N$2-type reaction, with thiophenoxide as a leaving group was observed. The reaction leading to the ring-closure offers a simple route for the stereospecific synthesis of chiral isoxazolines and pyrazolines, but, the second products can

be prepared in racemic form only because of their configurational instability.

## 3. Experimental

### 3.1. General

Melting points were determined using a Boetius hot-stage apparatus and are uncorrected. IR spectra were recorded on a Perkin Elmer 1600 FTIR spectrophotometer. $^1$H NMR and $^{13}$C NMR spectra were measured on a Bruker CPX ($^1$H, 300 MHz) or a Bruker Avance ($^1$H, 500 MHz) spectrometer using TMS as an internal standard. GC/MS spectra were determined on a Hewlett–Packard 5890 II gas chromatograph (25 m capillary column) with a Hewlett–Packard mass spectrometer 5971A operating on the electron impact mode (70 eV). Optical rotations at 578 nm were measured using an Optical Activity Ltd Model AA-5 automatic polarimeter. Separations of products by chromatography were performed on silica gel 60 (230–400 mesh) purchased from Merck. TLC was performed using silica gel 60 precoated plates (Merck).

### 3.2. Preparation of the chiral Michael adducts 1

The addition was carried out in 2 mmol scale as reported before.[2] The products obtained as white crystals were further enantioenriched by recrystallization from hexane/methylene chloride. For **1a**, *ent*-**1a**, and **1d** the enantiomeric forms were isolated from the mother liquors and had lower mps than the corresponding racemic crystals. For **1b** and **1c**, the enantioenriched crystals were separated and had higher mps than the respective racemates. All spectral data for the Michael adducts were described earlier.[2]

**3.2.1. (3*R*)-(+)-1,3-Diphenyl-3-phenylsulfanylpropan-1-one (1a).** Yield: 446 mg, 70%, mp 96–97 °C; $[\alpha]_D=+136$ (*c* 1.02, $CH_2Cl_2$), >95% ee by $^1$H NMR in the presence of Eu(hfc)$_3$.

**3.2.2. (3*S*)-(−)-1,3-Diphenyl-3-phenylsulfanylpropan-1-one (*ent*-1a).** The title compound was obtained in the addition catalyzed by cinchonidine.[2] Yield: 121 mg, 19%, mp 96–97 °C; $[\alpha]_D=-72$ (*c* 0.94, $CH_2Cl_2$), 57% ee by $^1$H NMR in the presence of Eu(hfc)$_3$.

**3.2.3. (3*R*)-(+)-3-(4-Methoxyphenyl)-1-phenyl-3-phenylsulfanylpropan-1-one (1b).** Yield: 502 mg, 72%, mp 87.5–88.0 °C; $[\alpha]_D=+148$ (*c* 0.98, $CH_2Cl_2$), 93% ee by $^1$H NMR in the presence of Eu(hfc)$_3$.

**3.2.4. (*R*)-(+)-4,4-Dimethyl-1-phenyl-1-phenylsulfanylpentan-3-one (1c).** Yield: 113 mg, 19%, mp 103–104 °C; $[\alpha]_D=+170$ (*c* 0.94, $CH_2Cl_2$), 91% ee by $^1$H NMR in the presence of Eu(hfc)$_3$.

**3.2.5. (3*R*)-(+)-3-(4-Methoxyphenylsulfanyl)-1,3-diphenylpropan-1-one (1d).** Yield: 425 mg, 61%, mp 91.5–92.0 °C; $[\alpha]_D=+110$ (*c* 0.98, $CH_2Cl_2$), 94% ee by $^1$H NMR in the presence of Eu(hfc)$_3$.

### 3.3. Preparation of oximes 2

The preparation of oximes was carried out in 2 mmol scale as described before.[2] The crude products (containing up to 9% of *Z*-stereoisomers by $^1$H NMR) were purified by column chromatography on silica gel using as eluent *tert*-BuOMe/$CHCl_3$/hexane (2.5:2.0:14.0 for **2a**,**b**,**d** and 2.5:2.0:12.0 for **2c**). All the oximes were obtained as colorless oils.

**3.3.1. *E*-(3*R*)-(+)-1,3-Diphenyl-3-phenylsulfanylpropan-1-one oxime (2a).** Yield: 600 mg, 90%; $[\alpha]_D=+105$ (*c* 1.48, $CH_2Cl_2$). All spectral data were reported earlier in the literature.[2]

**3.3.2. *E*-(3*S*)-(−)-1,3-Diphenyl-3-phenylsulfanylpropan-1-one oxime (*ent*-2a).** Yield: 480 mg, 72%; $[\alpha]_D=-71$ (*c* 0.58, $CH_2Cl_2$). All spectral data were reported earlier in the literature.[2]

**3.3.3. *E*-(3*R*)-(+)-3-(4-Methoxyphenyl)-1-phenyl-3-phenylsulfanylpropan-1-one oxime (2b).** Yield: 632 mg, 87%; $R_f$ 0.22 (*tert*-BuOMe/$CHCl_3$/hexane, 2.5:2.0:14.0); $[\alpha]_D=+95$ (*c* 1.11, $CH_2Cl_2$); $\nu_{max}$ (liquid film) 3267, 3058, 1610, 1512, 1439, 1304, 1250, 1177, 1035, 959, 762, 693 cm$^{-1}$; $\delta_H$ (300 MHz, $CDCl_3$) 3.42 (d, 2H, *J*=8.0 Hz, C*H*$_2$), 3.74 (s, 3H, O*Me*), 4.57 (t, 1H, *J*=8.0 Hz, C*H*), 6.72 (d, 2H, *J*=8.7 Hz, ArH), 7.13–7.35 (m, 12H, ArH), 8.43 (br s, 1H, O*H*); $\delta_C$ (75 MHz, $CDCl_3$): 33.6 (C-2), 49.3 (C-3), 55.2 (OMe), 113.6, 126.7, 127.2, 128.4, 128.7, 128.9, 129.1, 132.5, 132.7, 134.8, 135.6 (Ph and Ar moiety), 157.4 (C-1), 158.8 (ArOMe). Anal. Calcd for $C_{22}H_{21}NO_2S$ (363.49): C, 72.70; H, 5.82; N, 3.86; S, 8.82. Found: C, 72.59; H, 5.93; N, 3.80; S, 8.89%.

**3.3.4. *E*-(*R*)-(+)-4,4-Dimethyl-1-phenyl-1-phenylsulfanylpentan-3-one oxime (2c).** Yield: 508 mg, 81%; $R_f$ 0.46 (*tert*-BuOMe/$CHCl_3$/hexane, 2.5:2.0:12.0); $[\alpha]_D=+99$ (*c* 0.88, $CH_2Cl_2$); $\nu_{max}$ (liquid film) 3253, 2967, 1602, 1583, 1481, 1453, 1365, 1026, 956, 926, 746, 698 cm$^{-1}$; $\delta_H$ (300 MHz, $CDCl_3$) 0.87 (s, 9H, *t-Bu*), 2.72 (dd, 1H, *J*=13.6, 9.7 Hz, C*H*$_2$), 3.10 (dd, 1H, *J*=13.6, 5.6 Hz, C*H*$_2$), 5.27 (dd, 1H, *J*=9.7, 5.6 Hz, C*H*), 7.15–7.40 (m, 10H, ArH), 8.63 (s, 1H, O*H*); $\delta_C$ (75 MHz, $CDCl_3$) 28.0 (*t*-Bu), 28.8 (C-4), 35.1 (C-2), 48.1 (C-1), 126.6, 128.2, 128.4, 128.7, 131.1, 135.7, 139.2, 141.9 (each Ph), 164.0 (C-3). Anal. Calcd for $C_{19}H_{23}NOS$ (313.47): C, 72.80; H, 7.40; N, 4.47; S, 10.23. Found: C, 72.62; H, 7.30; N, 4.53; S, 10.35%.

**3.3.5. *E*-(3*R*)-(+)-3-(4-Methoxyphenylsulfanyl)-1,3-diphenylpropan-1-one oxime (2d).** Yield: 691 mg, 95%; $R_f$ 0.26 (*tert*-BuOMe/$CHCl_3$/hexane, 2.5:2.0:14.0); $[\alpha]_D=+82$ (*c* 1.20, $CH_2Cl_2$); $\nu_{max}$ (liquid film) 3243, 3060, 1591, 1492, 1453, 1286, 1245, 1172, 1030, 960, 827, 755, 695 cm$^{-1}$; $\delta_H$ (300 MHz, $CDCl_3$) 3.42 (d, 2H, *J*=7.9 Hz, C*H*$_2$), 3.75 (s, 3H, O*Me*), 4.39 (t, 1H, *J*=7.9 Hz, C*H*), 6.72 (d, 2H, *J*=8.8 Hz, ArH), 7.15–7.33 (m, 12H, ArH), 8.41 (br s, 1H, O*H*); $\delta_C$ (75 MHz, $CDCl_3$) 33.1 (C-2), 51.1 (C-3), 55.3 (OMe), 114.3, 126.6, 127.3, 127.9, 128.2, 128.5, 129.1, 132.7, 135.6, 135.9, 140.9 (Ph and Ar moiety), 157.4 (C-1), 159.7 (ArOMe). Anal. Calcd for $C_{22}H_{21}NO_2S$

(363.49): C, 72.70; H, 5.82; N, 3.86; S, 8.82. Found: C, 72.58; H, 5.61; N, 3.95; S, 8.90%.

### 3.4. Heterocyclization of oximes to isoxazolines 3

A suspension of NaH (0.072 g in mineral oil (50%), washed twice with hexane, 1.5 mmol) in hexane (1 mL) was added in one portion to a magnetically stirred solution of the oxime (1.0 mmol) in dry DMF (10 mL) at rt under argon atmosphere. The stirring was continued for 10 min. Then, the mixture was heated at 70 °C under slightly reduced pressure for 1–1.5 h, until most of the solvent was distilled off. Finally, the reaction residue was dissolved in water (10 mL) and extracted with $Et_2O$ (3×10 mL). The combined extracts were washed with water, brine, dried over $Na_2SO_4$, and the solvent was evaporated under the reduced pressure. The crude product was purified by column chromatography on silica gel using the *tert*-BuOMe/$CHCl_3$/hexane mixture as an eluent. The ee of the title compound was determined by $^1$H NMR in $CCl_4$ using Eu(hfc)$_3$ (ca. 0.5 equiv) as a chiral shift reagent. The products **3a**, **3b** obtained as white solids were then enantioenriched by crystallization from hexane/methylene chloride and their ees were measured again.

**3.4.1. (5*S*)-(+)-3,5-Diphenyl-4,5-dihydro-isoxazole (3a).** Yield: 170 mg, 76% (83% ee). This product was recrystallized twice forming 121 mg (54% yield) of white crystals; mp 83.7–84.2 °C; $[\alpha]_D=+262$ (*c* 0.88, $CH_2Cl_2$); >98% ee; $\nu_{max}$ (KBr) 3027, 2876, 1563, 1493, 1447, 1364, 1052, 895, 751, 687 cm$^{-1}$; $\delta_H$ (300 MHz, $CDCl_3$) 3.33 (dd, 1H, *J*=16.6, 8.3 Hz, C*H*$_2$), 3.77 (dd, 1H, *J*=16.6, 11.0 Hz, C*H*$_2$), 5.73 (dd, 1H, *J*=11.0, 8.3 Hz, *C*H*), 7.34–7.41 (m, 8H, ArH), 7.68–7.71 (m, 2H, ArH); $^1$H NMR (300 MHz, $CCl_4$, Eu(hfc)$_3$) $\Delta\delta$ 0.094 ppm for the *C*H* signal, the major dextrorotatory (*S*)-enantiomer shifted upfield; GC retention time: 20.1 min (from 120 to 280 °C, 5 °C/min); *m/z* (EI, 70 eV) 223 (38, M$^+$), 193 (4), 117 (18), 115 (25), 104 (100), 103 (19), 91 (21), 78 (25), 77 (43), 51 (33%). This spectral characteristic is in agreement with the literature data for the racemic form.[10]

**3.4.2. (5*R*)-(−)-3,5-Diphenyl-4,5-dihydro-isoxazole (*ent*-3a).** Yield: 112 mg, 50%, $[\alpha]_D=-141$ (*c* 0.50, $CH_2Cl_2$); 55% ee, $^1$H NMR (300 MHz, $CCl_4$, Eu(hfc)$_3$) $\Delta\delta$ 0.094 ppm for the *C*H* signal, the major laevorotatory (*R*)-enantiomer shifted downfield.

**3.4.3. (5*S*)-(+)-5-(4-Methoxyphenyl)-3-phenyl-4,5-dihydro-isoxazole (3b).** Yield: 180 mg, 71% (57% ee). This product was recrystallized twice forming 117 mg (46% yield) of the title compound as a white solid, mp 104–104.5 °C; $[\alpha]_D=+244$ (*c* 0.92, $CH_2Cl_2$); 70% ee; $\nu_{max}$ (KBr) 2957, 1615, 1586, 1518, 1445, 1367, 1303, 1255, 1177, 1031, 899, 815, 754, 688 cm$^{-1}$; $\delta_H$ (300 MHz, $CDCl_3$) 3.33 (dd, 1H, *J*=16.7, 8.6 Hz, C*H*$_2$), 3.73 (dd, 1H, *J*=16.7, 10.8 Hz, C*H*$_2$), 3.80 (s, 3H, O*Me*), 5.69 (dd, 1H, *J*=10.8, 8.6 Hz, *C*H*), 6.90 (d, 2H, *J*=8.7 Hz, ArH), 7.32 (d, 2H, *J*=8.7 Hz, ArH), 7.40–7.42 (m, 3H, ArH); 7.67–7.72 (m, 2H, ArH); $^1$H NMR (300 MHz, $CCl_4$, Eu(hfc)$_3$) $\Delta\delta$ 0.143 ppm for the *C*H* signal, the major dextrorotatory (*S*)-enantiomer shifted upfield; GC retention time: 19.7 min (from 130 to 290 °C, 6 °C/min); *m/z* (EI, 70 eV) 253 (18, M$^+$), 134 (100), 119 (17), 117 (9), 91 (17), 77 (16), 65 (10), 51 (12%). IR and NMR spectra are in agreement with the literature for the racemic form.[11]

**3.4.4. (5*S*)-(+)-3-(*t*-Butyl)-5-phenyl-4,5-dihydro-isoxazole (3c).** Yield: 150 mg, 74%, a colorless oil; $R_f$ 0.42 (*tert*-BuOMe/$CHCl_3$/hexane, 2.5:2.0:16.0); $[\alpha]_D=+157$ (*c* 1.04, $CH_2Cl_2$); 86% ee; $\nu_{max}$ (liquid film) 2967, 1603, 1458, 1366, 1248, 878, 758, 699 cm$^{-1}$; $\delta_H$ (300 MHz, $CDCl_3$) 1.24 (s, 9H, *t-Bu*), 2.94 (dd, 1H, *J*=16.8, 8.1 Hz, C*H*$_2$), 3.41 (dd, 1H, *J*=16.8, 10.7 Hz, C*H*$_2$), 5.55 (dd, 1H, *J*=10.7, 8.1 Hz, *C*H*), 7.27–7.41 (m, 5H, ArH); $^1$H NMR (300 MHz, $CCl_4$, Eu(hfc)$_3$) $\Delta\delta$ 0.351 ppm for the *C*H* signal, the major dextrorotatory (*S*)-enantiomer shifted upfield; GC retention time: 12.6 min (from 120 to 280 °C, 5 °C/min); *m/z* (EI, 70 eV) 203 (7, M$^+$), 188 (2), 131 (6), 104 (100), 97 (20), 91 (8), 82 (12), 77 (15), 57 (32), 51 (12%). All data are in agreement with those reported earlier for the racemic form.[12]

### 3.5. Preparation of *O*-methyl-oxime 4

The Michael adduct **1a** (0.637 g, 2 mmol), *O*-methylhydroxylamine hydrochloride (0.184 g, 2.2 mmol) and $Na_2CO_3$ (0.117 g, 1.1 mmol) were dissolved in MeOH (8 mL). Then, AcOH (0.5 mL) was added to the stirred solution to adjust the pH to 4.5 and the mixture was refluxed for 3 h. The cooled mixture was diluted with water (2 mL), extracted with $CHCl_3$ (2×4 mL) and the combined organic phase was washed with water (2×3 mL) and dried over $Na_2SO_4$. The solvent was evaporated and the crude product was purified by column chromatography on florisil (hexane/$CHCl_3$, 9:1). The crude product contained *E*/*Z* isomers in 4.7:1 ratio. The main *E*-stereoisomer ($R_f$ 0.27) was isolated in pure form, while the minor one ($R_f$ 0.18) was identified by its $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 3.03–3.13 (m, 2H, C*H*$_2$), 3.70 (s, 3H, O*Me*), 4.13 (t, 1H, *J*=7.9 Hz, C*H*), 7.07–7.31 (m, 15H, ArH).

**3.5.1. *E*-(3*R*)-(+)-1,3-Diphenyl-3-phenylsulfanylpropan-1-one *O*-methyl-oxime (4).** Yield: 535 mg, 77%; a light yellow oil; $R_f$ 0.27 (hexane/$CHCl_3$, 9.0:1.0); $[\alpha]_D=+121$ (*c* 1.0, $CH_2Cl_2$); $\nu_{max}$ (liquid film) 3059, 2935, 1583, 1481, 1439, 1329, 1048, 895, 749, 693 cm$^{-1}$; $\delta_H$ (500 MHz, $CDCl_3$) 3.29 (d, 2H, *J*=8.0 Hz, C*H*$_2$), 3.81 (s, 3H, O*Me*), 4.44 (t, 1H, *J*=8.0 Hz, C*H*), 7.06–7.17 (m, 15H, ArH); $\delta_C$ (125 MHz, $CDCl_3$) 34.5 (C-2), 50.6 (C-3), 62.2 (OMe), 127.0, 127.6, 127.8, 128.2, 128.6, 128.7, 129.1, 129.3, 132.8, 135.2, 136.0, 141.2 (Ph moiety), 156.4 (C-1); GC retention time: 19.8 min (from 140 to 280 °C, 8 °C/min); *m/z* (EI, 70 eV) 347 (10, M$^+$), 316 (3), 238 (55), 206 (17), 199 (44), 165 (8), 121 (100), 109 (11), 103 (14), 91 (8), 77 (15%). Anal. calcd for $C_{22}H_{21}NOS$ (347.49): C, 76.04; H, 6.09; N, 4.03; S, 9.23. Found: C, 76.20; H, 6.28; N, 3.84; S, 9.23%.

### 3.6. Preparation of hydrazones 5

A solution of the Michael adduct **1a** (0.479 g, 1.5 mmol) and $PhNHNH_2$ (0.195 g, 1.8 mmol) or 2-$(H_2NNH)C_5H_4N$ (0.180 g, 1.65 mmol) in MeOH (20 mL) was placed in a flask with a catalytic amount of $KHSO_4$ (30 mg, 20 mol%). The mixture was stirred for 4 h at 50 °C and then kept

overnight at 25 °C. In the case **5a** of the resulting yellow crystals were filtered off and washed with MeOH (2.5 mL). For **5b** the reaction mixture was evaporated and the products were isolated by column chromatography on silica gel. Finally, both title products were recrystallized from hexane/$CH_2Cl_2$.

**3.6.1. (3*R*)-(+)-1,3-Diphenyl-3-phenylsulfanylpropan-1-one phenylhydrazone (5a).** Yield: 509 mg, 83%; mp 144.5–145.5 °C, yellow crystals; $[\alpha]_D=+358$ (*c* 0.98, $CH_2Cl_2$); $\nu_{max}$ (KBr) 3335, 1601, 1513, 1488, 1453, 1253, 1146, 1074, 747, 692 $cm^{-1}$; $\delta_H$ (500 MHz, $CDCl_3$) 3.21–3.38 (m, 2H, C*H*$_2$), 4.35 (dd, 1H, *J*=9.3, 4.4 Hz, C*H*), 6.82 (d, 3H, *J*=7.7 Hz, ArH), 7.01 (s, 1H, N*H*), 7.15–7.52 (m, 17H, ArH); $\delta_C$ (125 MHz, $CDCl_3$) 35.1 (C-2), 51.5 (C-3), 113.6, 120.6, 126.0, 127.9, 128.7, 129.4, 129.5, 133.7, 134.7, 138.2, 141.9, 142.2 (Ph moiety), 145.5 (C-1). Anal. Calcd for $C_{27}H_{24}N_2S$ (408.57): C, 79.37; H, 5.92; N, 6.86; S, 7.85. Found: C, 79.17; H, 5.69; N, 6.60; S, 7.60%.

**3.6.2. (3*R*)-(+)-1,3-Diphenyl-3-phenylsulfanylpropan-1-one 2-pirydylhydrazone (5b).** Yield: 233 mg, 38% (50% of **1a** recovered); yellow crystals; mp 107–109 °C; $[\alpha]_D=+118$ (*c* 1.22, $CH_2Cl_2$); $\nu_{max}$ (KBr) 3316, 1591, 1574, 1491, 1456, 1437, 1260, 1142, 1076, 751, 694 $cm^{-1}$; $\delta_H$ (300 MHz, $CDCl_3$) 3.33 (m[†], 2H, *J*=18.2, 14.7, 7.4 Hz, C*H*$_2$), 4.43 (dd, 1H, *J*=8.5, 6.2 Hz, C*H*), 6.74–6.78 (m, 1H, ArH), 7.16–7.35 (m, 14H, ArH), 7.52–7.56 (m, 3H, ArH), 8.05 (s, 1H, N*H*), 8.12–8.14 (m, 1H, ArH); $\delta_C$ (75 MHz, $CDCl_3$) 34.1 (C-2), 50.8 (C-3), 107.7, 115.9, 126.0, 127.4, 127.9, 128.1, 128.3, 128.4, 128.9, 132.8, 134.2, 137.6, 137.9, 140.9, 143.4, 147.6, 157.0 (C-1). Anal. Calcd for $C_{26}H_{23}N_3S$ (409.55): C, 76.25; H, 5.66; N, 10.26; S, 7.83. Found: C, 75.99; H, 6.00; N, 10.15; S, 7.71%.

### 3.7. Preparation of the pyrazolines 6

The cyclization of hydrazones was run in dry DMF/NaH in 1 mmol scale according to the procedure described above for the cyclization of oximes.

**3.7.1. 1,3,5-Triphenyl-4,5-dihydro-1*H*-pyrazole (6a).** Yield: 277 mg, 93% directly after chromatography, $[\alpha]_D=-26$ (*c* 0.86, $CH_2Cl_2$). This material was recrystallized twice to yield yellow crystals, 176 mg, 59%, mp 138–139.5 °C; $[\alpha]_D=-49$ (*c* 0.84, $CH_2Cl_2$). After 6 days the specific rotation value diminished to zero. $\nu_{max}$ (KBr) 3022, 1596, 1504, 1394, 1325, 1125, 873, 759, 692 $cm^{-1}$; $\delta_H$ (300 MHz, $CDCl_3$) 3.14 (dd, 1H, *J*=17.1, 7.2 Hz, C*H*$_2$), 3.84 (dd, 1H, $J_1$=17.1, 12.4 Hz, C*H*$_2$), 5.27 (dd, 1H, *J*=12.4, 7.2 Hz, C*H*), 6.78 (t, 1H, *J*=7.2 Hz, ArH), 7.06–7.41 (m, 12H, ArH), 7.72 (d, 2H, *J*=7.4 Hz, ArH); GC retention time: 21.0 min (from 130 to 290 °C, 8 °C/min); *m/z* (EI, 70 eV) 298 (100, $M^+$), 221 (38), 194 (12), 115 (9), 104 (10), 91 (41), 77 (24), 64 (9), 51 (12%). All spectra data are in agreement with the literature data for the racemic form.[13]

**3.7.2. 1-(2-Pirydyl)-3,5-diphenyl-4,5-dihydro-1*H*-pyrazole (6b).** The title product was isolated by chromatography (silica gel, hexane/$CHCl_3$/*tert*-BuOMe/, 12.0:3.0:2.0). The proper fraction was recrystallized twice forming yellow crystals; yield: 111 mg, 37%; mp 134–136 °C; $[\alpha]_D=-2.0$ (*c* 1.6, $CH_2Cl_2$). All the optical activity was lost after 2 days. $\nu_{max}$ (KBr) 3027, 1588, 1473, 1442, 1086, 865, 765, 694 $cm^{-1}$; $\delta_H$ (300 MHz, $CDCl_3$) 3.20 (dd, 1H, *J*=17.2, 5.3 Hz, C*H*$_2$), 3.83 (dd, 1H, *J*=17.2, 12.3 Hz, C*H*$_2$), 5.82 (dd, 1H, *J*=12.3, 5.3 Hz, C*H*), 6.62–6.66 (m, 1H, ArH), 7.22–7.54 (m, 10H, ArH), 7.76–7.79 (m, 2H, ArH), 8.05–8.07 (m, 1H, ArH); $\delta_C$ (75 MHz, $CDCl_3$) 42.6 (C-4), 61.8 (C-5), 109.1, 114.4, 125.8, 126.0, 127.1, 128.6, 128.7, 129.1, 132.6, 137.1, 143.3, 147.8, 149.3 (Ph and Ar moiety), 155.5 (C-3); GC retention time 26.5 min (120–290 °C, 6 °C/min); *m/z* (EI, 70 eV) 299 (30, $M^+$), 195 (100), 155 (12), 78 (14%). Anal. Calcd for $C_{20}H_{17}N_3$ (299.36): C, 80.24; H, 5.72; N, 14.04. Found: C, 80.04; H, 6.01; N, 14.15%.

**3.7.3. 1-Methyl-3,5-diphenyl-4,5-dihydro-1*H*-pyrazole (6c).** This product was obtained directly in the attempted syntheses (1.5 mmol scale) of **1a** *N*,*N*-dimethyl- and *N*-methylhydrazone according to the procedure given above for the hydrazones **5a** and **b**. Yields: 184 mg, 52% and 195 mg, 55%, respectively, oil; $R_f$ 0.55 (*tert*-BuOMe/$CHCl_3$/hexane, 2.5:2.0:16.0); $[\alpha]_D=-1.3$ and $-1.1$, respectively (*c* 0.8, $CH_2Cl_2$); $\nu_{max}$ (liquid film) 3061, 2861, 2834, 1586, 1496, 1446, 1362, 1194, 1132, 1037, 940, 756, 694 $cm^{-1}$; $\delta_H$ (300 MHz, $CDCl_3$) 2.85 (s, 3H, *Me*), 3.01 (dd, 1H, *J*=16.1, 14.5 Hz, C*H*$_2$), 3.49 (dd, 1H, *J*=16.1, 10.0 Hz, C*H*$_2$), 4.13 (dd, 1H, *J*=14.5, 10.0 Hz, C*H*), 7.32–7.51 (m, 8H, ArH), 7.66 (dd, 2H, *J*=8.1, 1.5 Hz, ArH); GC retention time 19.8 min (120–290 °C, 5 °C/min); *m/z* (EI, 70 eV) 236 (58, $M^+$), 159 (100), 132 (9), 131 (11), 118 (11), 115 (21), 104 (24), 103 (18), 91 (21), 77 (47), 51 (33%). In both reactions leading to **6c** also the corresponding aromatization product (1-methyl-3,5-diphenylpyrazole)[14] was isolated in 35% (123 mg) and 40% (141 mg) yield, respectively; $R_f$ 0.31 (*tert*-BuOMe/$CHCl_3$/hexane, 2.5:2.0:16.0). $^1H$ NMR and IR spectra are in agreement with the literature data for the racemic form of **6c** and for the aromatization product.[14]

[†] The reported *J* values are those observed from the splitting patterns in the spectrum and may not reflect the true coupling constant values.

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# Chiral NADH model systems functionalized with Zn(II)-cyclen as flavin binding site

Stefan C. Ritter, Martin Eiblmaier, Veronika Michlova and Burkhard König*

*Institut für Organische Chemie, Universität Regensburg, Universitätsstr. 31, D-93040 Regensburg, Germany*

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**Abstract**—A series of chiral peptides has been prepared, bearing a 1,4-dihydronicotine amide and a zinc cyclen moiety. The metal complex reversibly binds flavins in aqueous solution, while the dihydronicotine amide serves as a NADH model transferring a hydride to the flavin within the assembly. The reaction rate of the redox reaction was monitored and determined by UV spectroscopy. The reaction rates of the substituted compounds were slower if compared to the non-substituted parent compound **1-H**, but still show a 30–100 fold rate enhancement compared to the compound missing a flavin binding site. It was anticipated to probe the cryptic stereoselectivity of the hydride transfer from dihydropyridine to flavin. Spectroscopic data indicate that the introduction of deuterium labels upon reduction of the pyridinium salts to 1,4-dihydropyridine in $D_2O$ proceeds diastereoselectively, but identical isotope effects on the rate of flavin reduction as with a non-chiral NADH model revealed that the hydride transfer within the assembly proceeds not stereoselective. A more rigid chiral NADH model compound must be prepared to achieve this goal.


## 1. Introduction

Flavins and nicotine amides are the two most important biological redox cofactors.[1] Nicotine amide nucleotides[2] are the strongest reducing agents found in biology and can transfer electrons to flavins in a thermodynamically allowed process. The transfer of reduction equivalents is catalyzed by enzymes, which bind both cofactors to allow very efficient intramolecular electron transfer. We have recently reported a chemical model system,[3] which mimics this process under physiological conditions.

Enzymatic reactions that involve nicotine amide cosubstrates show stereospecificity in two aspects: the transfer of a hydride to a prochiral substrate is usually highly stereospecific and from the two hydrogen atoms available in the dihydronicotine amide only the pro-*R* or pro-*S* hydrogen atom is transferred. L-Lactate dehydrogenase, as a prominent example, catalyzes the transfer of the pro-*R* hydrogen atom of NADH to pyruvate, whereby only L-lactate, and no D-lactate, is obtained. The arising $NAD^+$ contains the remaining pro-*S* hydrogen atom. The stereospecific transfer of the pro-*S* hydrogen atom from NADH leads to the same $NAD^+$ and the cryptic stereospecificity of the process can only be observed by isotope labeling (Scheme 1). All investigated dehydrogenases transfer stereospecifically either the pro-*R* or the pro-*S* hydrogen atom of NADH, with nearly equal distribution.[4] Several explanations for the observations have been proposed. While historical models[5] conclude the evolution of the enzyme families from a common ancestor and random selection of either stereospecificity, because it is a non-adaptive property without selection pressure, this has been criticized by Benner et al.[4] If the specificity is without biological or chemical function, it is a surprisingly conserved property. All lactate dehydrogenases transfer the pro-*R* hydrogen atom of NADH[6] and, therefore, the cryptic stereospecificity is older than the evolutionary separation of life into bacteria, archaee and eucaryonts. The substrate specificity, one of the most important properties of an enzyme, shows a much faster drift. Functional models try to explain the chemical phenomenon with a biological function.[7] The cryptic stereoselectivity is now seen as an adaptive property under selection pressure.[8] The strength as a reducing agent of NADH may be different in its *syn*- and *anti*-conformation. Enzymes, that react with easily reducible substrates may prefer one conformation, while enzymes reacting with substrates that are difficult to reduce use NADH in the other conformation.[9] The high complexity of enzymes makes it difficult to derive conclusive experimental evidence for the phenomenon. Therefore, we were interested to adapt our previously reported chemical model to target stereochemical issues of the hydride transfer from NADH to flavin under

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* Corresponding author. Tel.: +49 941 9434576; fax: +49 941 9431717; e-mail: burkhard.koenig@chemie.uni-regensburg.de

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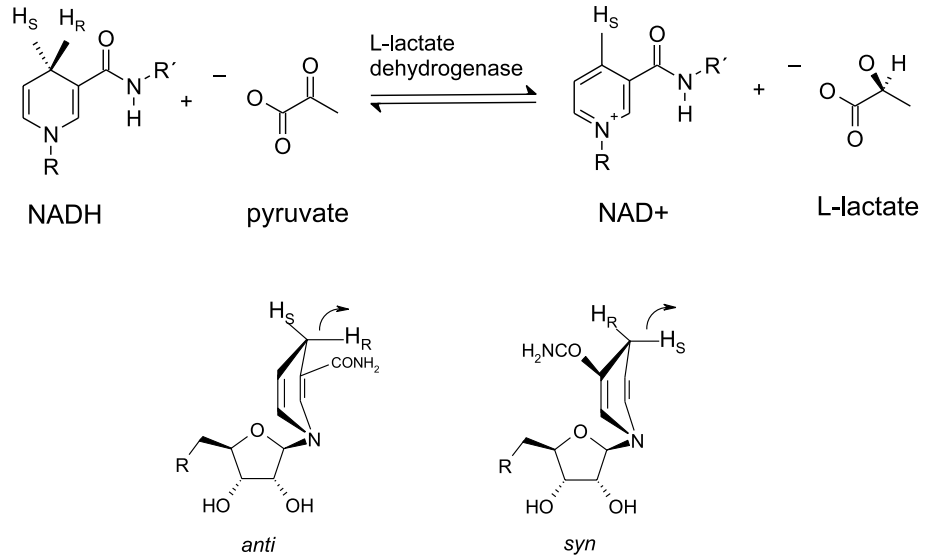



**Scheme 1.** Stereochemistry of L-lactate dehydrogenase and conformations of NADH in dehydrogenases.

physiological conditions. We report here the synthesis of chiral NADH model compounds, the kinetics of the redox reaction within NADH–flavin aggregates, the diastereoselective reduction of the NAD+ model compounds introducing deuterium atoms and observed deuterium isotope effects in intra-assembly flavin reduction (Scheme 1).

## 2. Results and discussion

### 2.1. Synthesis

Figure 1 shows the proposed conformation of the reversible assembly of flavin and the NADH model for the redox reaction. Model compounds with the depicted linker between the zinc cyclen complex and dehydronicotine amide gave the fastest hydride transfer reaction rates in previous studies. Therefore, we chose compound **1** as a starting point and introduced chirality into the linker. Scheme 2 shows the structures of the chiral NADH model compounds prepared and investigated in this study.

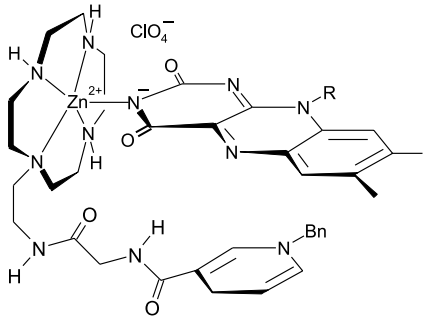
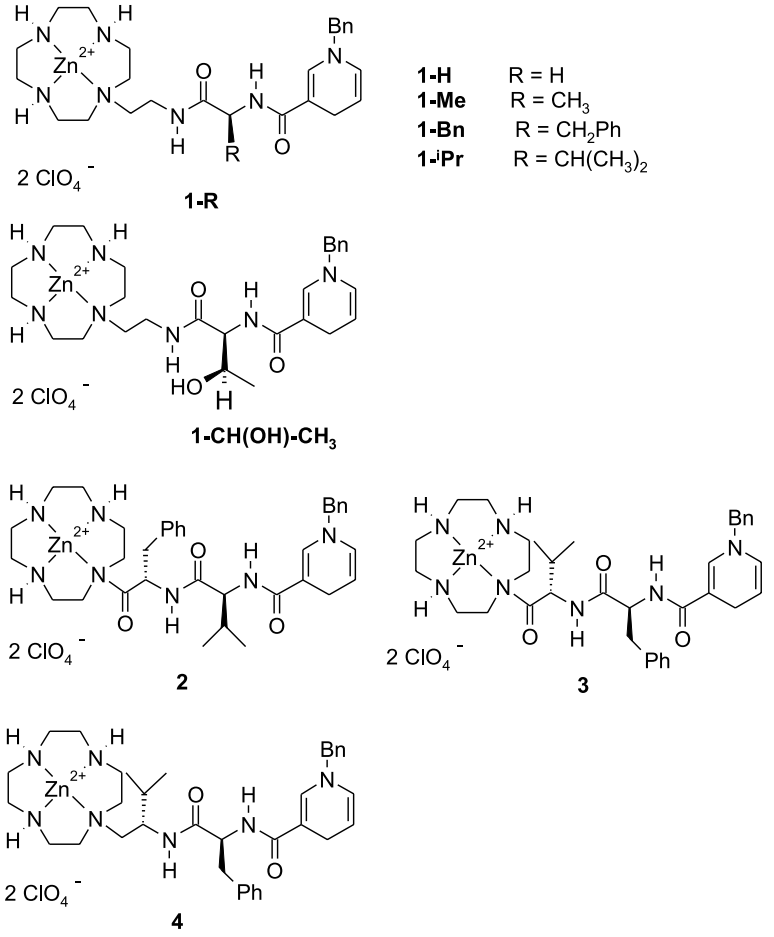


**Figure 1.** Proposed conformation of the aggregate **1-flavin** for the internal redox reaction (R=ribityl).

By introduction of chirality into the spacer between the zinc–cyclen flavin binding site and the nicotine amide, the methylene protons of the dehydronicotine amide become diastereotopic and are, therefore, distinguishable by NMR. In addition, a diastereoselective introduction of deuterium in the reduction of the nicotinium amide may be possible.

The synthesis of compounds **1-Me**, **1-Bn**, **1-$^i$Pr** and **1-CH(OH)–CH$_3$** uses **5** as a common precursor (Scheme 3). The synthesis of **5** has been described previously.[3] The coupling of the Fmoc-protected amino acids **6** to **5** proceeded under standard conditions using HATU and HOAt in high yield. The Fmoc protection group in **7** was removed with TBAF in acetonitrile. These conditions proved to be superior to standard piperidine, but acetonitrile as solvent is essential. Benzylated nicotinic acid was coupled to amines **8** using EDC and HOAt in DMF at room temperature. Isolated product yields range from 75 to 95% depending on the substituent R. The Boc-protecting groups were removed with TFA and the free amine was generated by eluation from a basic ion exchange resin. The stereocenters do not racemize under these conditions as confirmed by control experiments.[10] Finally, the zinc ion is introduced by refluxing compounds **12** with zinc bisperchlorate in ethanol. The choice of the solvent is important to obtain quantitative complexation of the macrocyclic ligand. The zinc complexes are stable salts. For kinetic measurements of the flavin reduction, **13** is reduced to 1,4-dihydronicotinamide **1-R** by treatment with sodium dithionite in aqueous solution. Compounds **1-R** must be handled under strict exclusion of oxygen to avoid rapid reoxidation and decomposition.

The syntheses of compounds **2** and **3** use threefold Boc-protected cyclen **14**[11] as the starting material (Scheme 4). Peptide coupling with Fmoc-protected Phe (**6-Bn**) or Val (**6-$^i$Pr**) proceeds in nearly quantitative yields. Compound **15** was deprotected, again using TBAF in acetonitrile, and the second amino acid was introduced yielding the isomeric compounds **17-Bn-$^i$Pr** and **17-$^i$Pr-Bn** in good yield. The nicotine amide was introduced after deprotection to yield **19**. Removal of all Boc protecting groups and eluation from a basic ion exchange resin[12] set the stage for complexing the macrocyclic ligand. Experiments using methanol as solvent for the complexation reaction were unsuccessful. However,




**Scheme 2.** Structure of compound **1**-**H** and of chiral model compounds **1**–**4** prepared and investigated in this study.

in acetonitrile solution complexes **22** are obtained in good yields as stable salts. For the reduction to **2** and **3** only a small excess of sodium carbonate is added to avoid hydrolysis of the cyclen acyl bond, which has been observed in other cases in basic aqueous solution. Acetonitrile must be added to the reaction mixture to ensure sufficient solubility of starting materials and products.

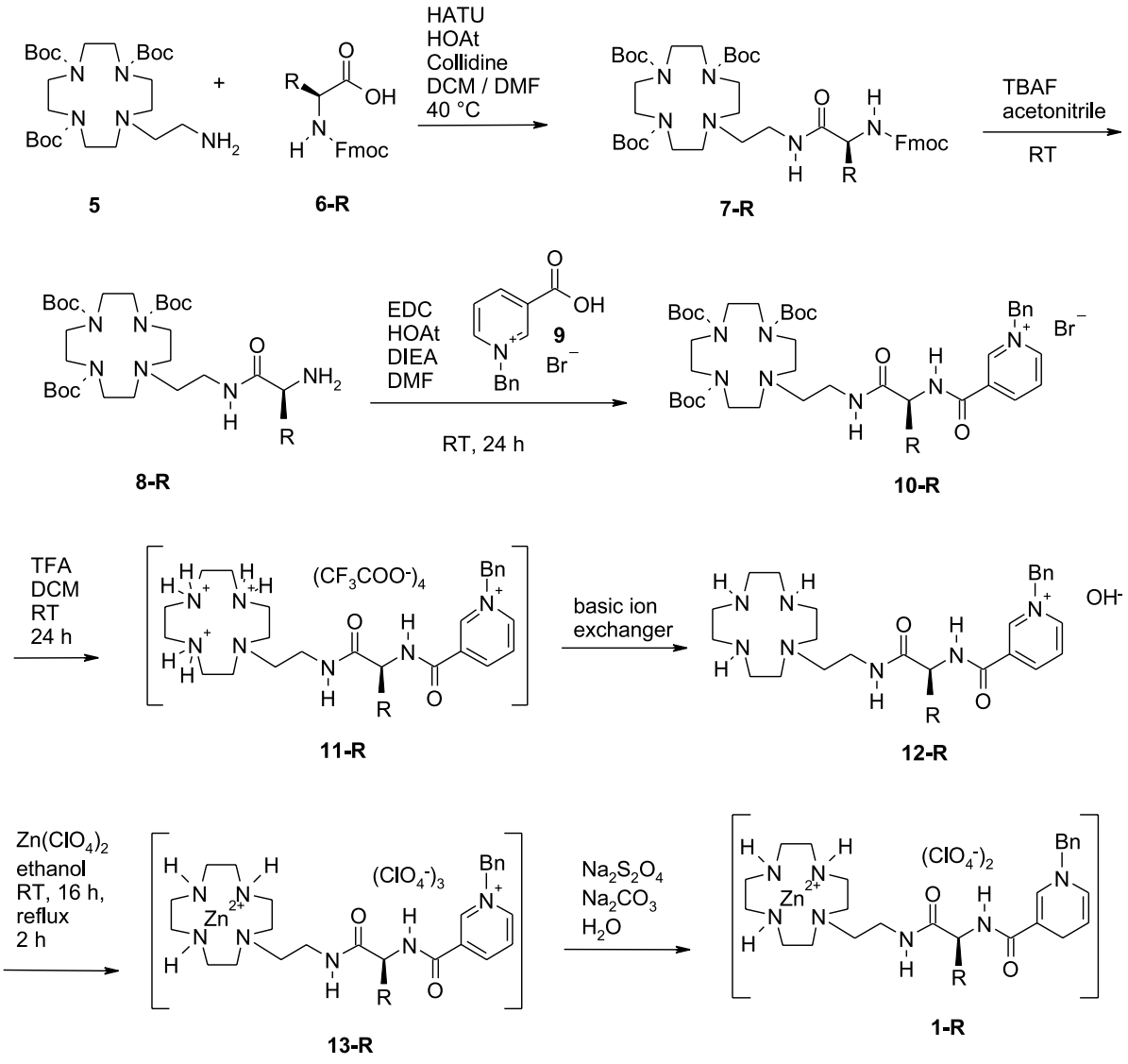
Dipeptide **4** is prepared from **16**-$^{i}$**Pr** (Scheme 5). Reduction of the amide bond with $BH_3$–THF proceeds cleanly, but the isolated yield of **23** was only 51%. Peptide coupling with **6**-**Bn**, deprotection and introduction of the nicotine amide follows the previously described procedures. Compound **26** was Boc deprotected and converted into the zinc complex **28**. Reduction using dithionite gave compound **4** in good yield. A round bottom flask under argon atmosphere was charged with the zinc-complex, sodium carbonate, sodium dithionite, degassed water, and degassed acetonitrile. Stirring of this mixture at room temperature for 3 h under strictly exclusion of oxygen afforded a yellow solution. The solvent was evaporated, degassed acetonitrile was added, and the resulting suspension was filtered. The filtrate was evaporated in vacuum to afford the dihydropyridine as a yellow solid, which is highly sensitive to oxygen. (See Supporting information for experimental details). The absorption maxima of the substituted pyridinium salts and 1,4-dihydroniconine amides are similar to the values of the parent compound **1**-**H** (see Table S-1; Supporting information).

## 2.2. Kinetics of NADH–flavin redox reaction

The redox reaction of the NADH model compounds with riboflavin in buffered aqueous solution was monitored spectroscopically using the UV absorption at 450 nm. The experimental set up and the methods to derive the reaction rate constant were the same as described earlier.[3] Table 1 summarizes the determined second order rate constants of the redox reaction. The values of previously tested compounds are given for comparison. With the exception of compound **4** introduction of a substituent into the dipeptide linker of **1**-**H**, significantly reduces the reaction rate. Most likely, substitution makes the conformation of the peptide linker necessary for the arrangement of 1,4-dihydronicotine amide and flavin for hydride transfer less favourable. Due to the limited number of compounds investigated, no predictive relation of molecular structure and chirality, and the reaction rate could be derived.[13]

## 2.3. Diastereoselective reduction of NADH model and deuterium isotope effects in flavin reduction

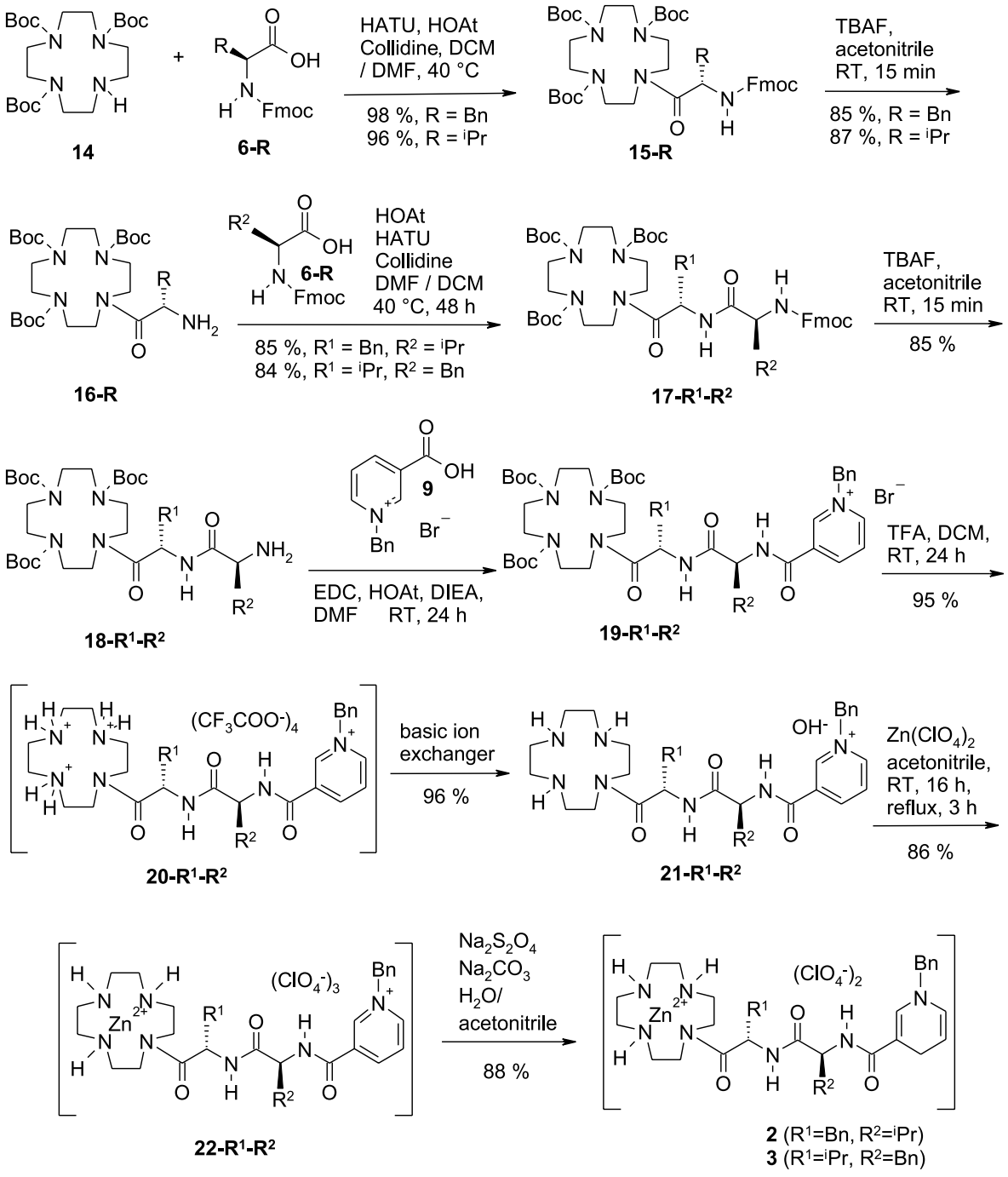
The reduction step of the pyridinium salt to 1,4-dihydronicotine amide in water was exemplarily investigated more




**Scheme 3.** Synthesis of compounds **1-Me**, **1-Bn**, **1-*i*Pr** and **1-CH(OH)–CH$_3$** from **5**. R = Bn, $^i$Pr, Me and 1-*R*-1-hydroxyethyl.

closely for **1-CH(OH)–CH$_3$**. Upon reduction, the aromatic resonances of the pyridinium ring between $\delta = 7.8$–$9.4$ almost disappear.[14] Three new signals appear at $\delta = 4.7$, 5.9 and 7.1, which are assigned to the CH-proton resonances of the dihydropyridine ring (see Supporting information for spectra and assignment). The resonance of the methylene group is in the 1 D proton spectrum in the same region as the resonances of the other 20 methylene protons, but can be identified from HSQC at $\delta = 3.1$–$3.3$ (see Supporting information for spectrum). In the reduced form, some of the compounds resonance signals broaden or show a double set of signals. This process, which is reversed by oxidation back to the pyridinium salt, indicates the formation of conformers that slowly interconvert on the NMR time scale. Intramolecular coordination of appended hydroxyl- or carbonyl groups onto the Lewis-acidic zinc cyclen complex has been observed in other cases. The reduction reaction in $D_2O$ leads to a compound with nearly identical spectra. The incorporation of deuterium is confirmed by an approximately half integral for the methylene resonance in the proton spectrum and the multiplicity edited HSQC spectrum, which clearly indicates that only one proton is attached to the methylene carbon (see Supporting information for spectrum). To probe the stereochemistry of the reduction reaction variable temperature spectra were recorded to diminish signal broadening or doubling. At 393 K most resonances show coalescence giving a single set of resonances for the compound, which may indicate stereospecific deuteration yielding one diastereomere. A similar diastereoselective non-enzymatic reduction has been described for NAD$^+$.[15] Traces of the pyridinium salt, the air sensitivity, and thermal instability of the compound above 400 K unfortunately prevent a more rigorous structure elucidation.

The reaction rate of deuterated **1-H**, **1-CH(OH)–CH$_3$** and **3** with flavin in aqueous buffer was measured and compared to the rates of the corresponding non-deuterated compounds. All determined isotope effects were identical within their error limits: 1.29 for **1-H**, 1.31 for **1-CH(OH)–CH$_3$** and 1.27 for compound **3**. This shows that either the deuterium incorporation into the pyridinium ring was not diastereoselective, which we cannot finally exclude, or the hydride/deuteride transfer within the assembly is not stereoselective.

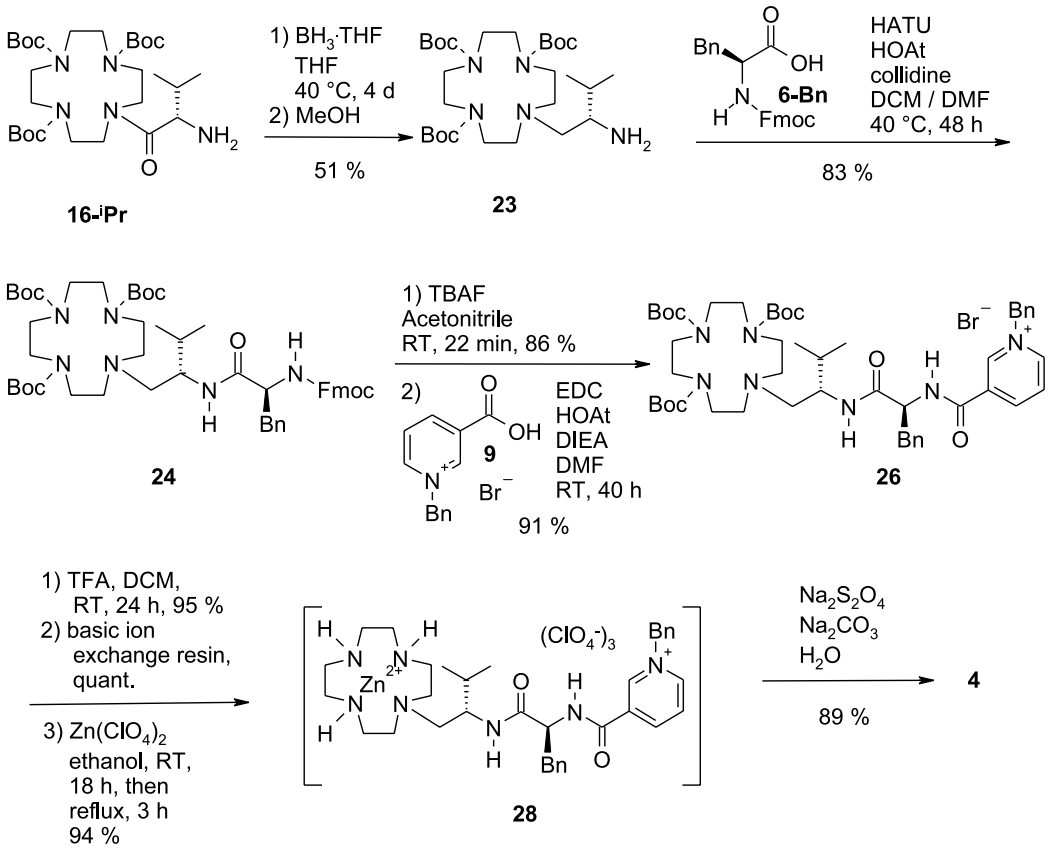



**Scheme 4.** Synthesis of compounds **2** and **3**. R = Bn or $^{i}$Pr.

In any case is the investigated model system not suitable to probe cryptic stereoselectivity of NADH reduction reactions.

## 3. Conclusion

We have prepared a series of chiral NADH model compounds to probe stereochemical effects on the rate of the redox reaction between 1,4-dehydronicotine amide and flavin within a reversible aggregate in buffered water. Chiral α-amino acids were introduced into the linker tethering a zinc cyclen complex, which serves as the flavin-binding site, and nicotine amide. The redox reaction was followed by UV spectroscopy and measurements revealed a decrease in reaction rate in substituted compounds in comparison to the non-substituted parent compound **1-H**. We explain this by substituent effects on the conformation of the linker, which force the flavin binding site and 1,4-dehydropyridine in less favorable relative orientation for the redox reaction with flavin. Reduction of the pyridinium salts to 1,4-dihydronicotine amides in $D_2O$ leads to deuterium incorporation. For compound **1-CH(OH)–CH$_3$** NMR measurements indicate the formation of only one diastereomere, similar to the non-enzymatic reduction of $NAD^+$. However, identical deuterium isotope effects on the redox reaction




**Scheme 5.** Synthesis of compound **4**.

with flavin show that the hydride transfer within the assembly is not stereospecific. The pro-*R* and pro-*S* hydrogen atoms of the 1,4-dehydropyridine are randomly transferred to coordinated flavin, which reveals that the conformational flexibility of the peptide linker between zinc cyclen and 1,4-dehydropyridine does not sufficiently confine the reactive conformation. A more rigid linker structure within the NADH model restricting the rotation of the 1,4-dehydropyridine is necessary to obtain a NADH model compound, which will selectively transfer either its pro-*R* or pro-*S* hydrogen atom to a bound substrate.

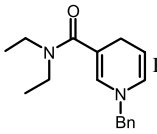
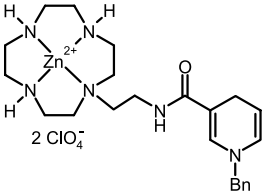
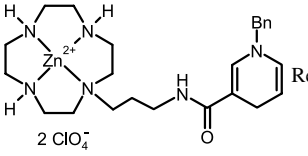
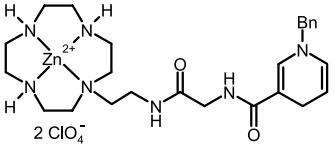
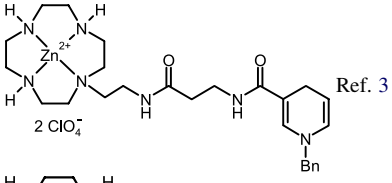
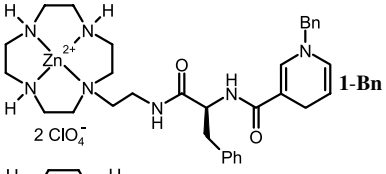
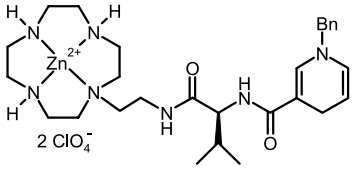
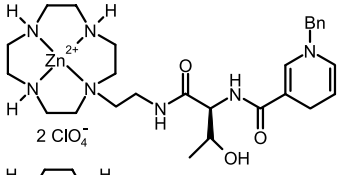
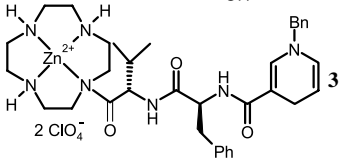
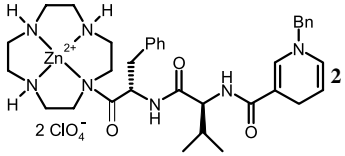
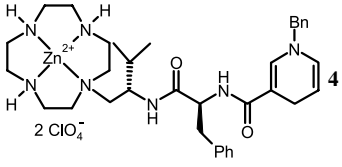
## 4. Experimental

### 4.1. General procedure 1 (GP 1) for the synthesis of compounds 7-Bn, 7-$^{i}$Pr, 7-Me, 7-CH(OH)–CH$_3$, 15-Bn, 15-$^{i}$Pr, 17-Bn-$^{i}$Pr, 17-$^{i}$Pr-Bn, 24

A round bottom flask was charged with the amine (1.0 equiv), Fmoc-protected amino acid (1.1 equiv), coupling reagents HOAt and HATU (each 1.2 equiv) and collidine (9.0 equiv). The compounds were dissolved in a 1:1-mixture of dry DMF and dry DCM. A minimum amount of solvent was used. The yellow solution was stirred at 40 °C for 2 days and then diluted with 100 ml of DCM. The reaction conversion was monitored by TLC. The mixture was extracted with 50 ml of aqueous HCl ($c$=1 mol/l), the organic layer was dried over $NaSO_4$ and concentrated under reduced pressure. CC with ethyl acetate–petroleum ether (EE/PE) afforded the fully protected compounds as colourless solids.

**4.1.1. 10-{2-[2-(9*H*-Fluoren-9-yl-methoxycarbonylamino)-2-benzyl-acetylamino]-ethyl}-1,4,7,10-tetraazacyclododecan-1,4,7-tricarbonicacid-tri-*tert*-butylester (7-Bn).** The synthesis follows GP 1 using **5** (1.00 g, 1.94 mmol), **6-Bn** (0.83 g, 2.13 mmol), HOAt (0.32 g, 2.35 mmol), HATU (0.89 g, 2.35 mmol) and collidine (2.12 g, 2.3 ml, 17.5 mmol). CC with PE/EE (40:60) to PE/EE (20:80) afforded **7-Bn** in a yield of 1.66 g (1.88 mmol, 97%); $R_f$=0.10 (EE/PE=1:1); mp: 103–105 °C. $^1$H NMR (600 MHz, $CD_2Cl_2$): $\delta$=1.48 (s, 18H, Boc-CH$_3$), 1.49 (s, 9H, Boc-CH$_3$), 2.56–2.65 (m, 6H, CH$_2$), 3.09–3.11 (m, 2H, Phe-CH$_2$), 3.24–3.51 (m, 14H, CH$_2$), 4.23 (dd, $^3J$=6.9 Hz, 1H, Fmoc-CH), 4.30–4.33 (m, 1H, Fmoc-CH$_2$), 4.44 (dd, $^3J$=6.9 Hz, $^2J$=10.5 Hz, 1H, Fmoc-CH$_2$), 4.47 (m, 1H, C*H), 5.66 (d, $^3J$=7.0 Hz, 1H, NH), 6.67 (m, 1H, NH), 7.22–7.23 (m, 2H, arom. CH), 7.25–7.28 (m, 1H, arom. CH), 7.30–7.36 (m, 4H, arom. CH), 7.44 (dd, $^3J$=7.5 Hz, 2H, arom. Fmoc-CH), 7.59–7.62 (m, 2H, arom. Fmoc-CH), 7.82 (d, $^3J$=7.5 Hz, 2H, arom. Fmoc-CH); $^{13}$C NMR (150.1 MHz, $CD_2Cl_2$): $\delta$=28.7 (+, Boc-CH$_3$), 28.8 (+, Boc-CH$_3$), 36.5 (−), 39.2 (−, Phe), 47.6 (+, Fmoc-CH), 48.2 (−), 48.7 (−), 50.1 (−), 52.4 (−), 54.9 (−), 56.3 (+, C*H), 67.2 (−, Fmoc-CH$_2$), 79.5 (C$_{quat}$, Boc), 79.8 (C$_{quat}$, Boc), 120.3 (+, 2 arom. Fmoc-C), 125.4 (+, 1 arom. Fmoc-C), 125.5 (+, 1 arom. Fmoc-C), 127.2 (+, 1 arom. C), 127.4, (+, 2 arom. C), 128.1 (+, 2 arom. Fmoc-C), 128.8 (+, 2 arom. C), 129.9 (+, 2 arom. C), 137.2

**Table 1**. Reaction rate constants of the redox reaction of the respective NADH-model compound with 1 equiv of riboflavin tetraacetate in aqueous solution (HEPES/KOH pH 7.4); $c = 4.51 \cdot 10^{-5}$ mol/l. UV detection at 447 nm. Rate constants are derived from a minimum of two independent measurements

| Compound | $k_2$ [l mol$^{-1}$ s$^{-1}$] | Relative rates |
|---|---|---|
|  Ref. 3 | 22 | 1 |
|  Ref. 3 | 408 ± 26 | 18 |
|  Ref. 3 | 671 ± 37 | 29 |
|  **1-H** | 3998 ± 321 | 175 |
|  Ref. 3 | 646 ± 67 | 28 |
|  **1-Bn** | 643 ± 132 | 28 |
|  **1-$^i$Pr** | 706 ± 141 | 31 |
|  **1-CH(OH)CH$_3$** | 725 ± 65 | 32 |
|  **3** | 783 ± 151 | 34 |
|  **2** | 806 ± 155 | 37 |
|  **4** | 2352 ± 228 | 103 |

(arom. $C_{quat}$), 141.7 (arom. $C_{quat}$), 144.4 (arom. $C_{quat}$), 144.4 (arom. $C_{quat}$), 155.8 ($C_{quat}$, urethane-C), 156.1 ($C_{quat}$, urethane-C), 156.3 ($C_{quat}$, urethane-C), 171.1 ($C_{quat}$, amide-C); UV–vis ($CH_3CN$): $\lambda$ (log $\varepsilon$)=205 nm (4.781), 265 nm (4.246), 289 nm (3.674), 300 nm (3.747); MS (ESI, $CH_2Cl_2$/MeOH): $m/z$=885.6 [$MH^+$] (100%), 907.7 [$M+Na^+$] (10%); MS-HR (FAB, $CH_2Cl_2$): [$MH^+$] (Calcd)=885.5116, [$MH^+$] (found)=885.5116±0.58 ppm; IR (KBr): $\tilde{\nu}$ [$cm^{-1}$]=3064, 2970, 2932, 1683, 1534, 1462, 1250, 1161, 742; MF: $C_{49}H_{68}N_6O_9$; MW=885.12.

See electronic Supporting information for the synthesis and characterisation of compounds **7-$^i$Pr**, **7-Me**, **7-CH(OH)–CH$_3$**, **15-Bn**, **15-$^i$Pr**, **17-Bn-$^i$Pr**, **17-$^i$Pr-Bn**, **24**.

### 4.2. General procedure 2 (GP 2) for the synthesis of compounds 8-$^i$Pr, 8-Bn, 8-Me, 8-CH–(OH)CH$_3$, 16-$^i$Pr, 18-Bn-$^i$Pr, 18-$^i$Pr-Bn, 25

In a round bottom flask the Fmoc-protected product from GP 1 is dissolved in a solution of tetrabutylammonium fluoride–trihydrate (TBAF) in acetonitrile ($c$=0.05 mol/l, 2.0 equiv of TBAF) and stirred at room temperature for 17 min. The reaction conversion was monitored by TLC. Then 150 ml of DCM were added to stop the reaction. The mixture was extracted twice with 75 ml of water. The combined aqueous layers were extracted with 75 ml of DCM, the combined organic layers were dried over $NaSO_4$ and concentrated under reduced pressure. CC with EE/PE or methylene chloride–methanol (DCM/MeOH) afforded the Fmoc-deprotected compounds as colourless solids.

**4.2.1. 10-[2-(2-Amino-3-methyl-butyrylamino)-ethyl]-1,4,7,10-tetraazacyclododecan-1,4,7-tri-carbonicacid-tri-*tert*-butylester (8-$^i$Pr).** The synthesis follows GP 2 using 1.36 g (1.62 mmol) of **7-$^i$Pr** and 1.03 g (3.24 mmol) of TBAF. CC with EE/PE (70:30) to $CH_2Cl_2$/MeOH (95:5) gave **8-$^i$Pr** (0.87 g, 1.41 mmol, 87%); $R_f$=0.42 (DCM/MeOH=9:1); mp: 81–84 °C. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$=0.75 (d, $^3J$=6.9 Hz, 3H, Val-$CH_3$), 0.91 (d, $^3J$=6.9 Hz, 3H, Val-$CH_3$), 1.38 (s, 18H, Boc-$CH_3$), 1.40 (s, 9H, Boc-$CH_3$), 1.63 (bs, 2H, $NH_2$), 2.19 (dhept, $^3J$=4.2, 6.9 Hz, 1H, Val-CH), 2.60–2.65 (m, 6H, 3$CH_2$), 3.12 (d, $^3J$=4.2 Hz, 1H, C*H), 3.24–3.46 (m, 14H, 7$CH_2$), 7.39 (m, 1H, NH); $^{13}$C NMR (75.5 MHz, $CDCl_3$): $\delta$=16.2 (+, Val-$CH_3$), 19.67 (+, Val-$CH_3$), 28.5 (+, Boc-$CH_3$), 28.6 (+, Boc-$CH_3$), 30.8 (+, Val-CH), 35.2 (−, 1C), 48.0 (−, 4C), 49.8 (−, 2C), 51.9 (−, 1C), 54.2 (−, 1C), 55.3 (−, 1C), 60.2 (+, C*H), 79.3 ($C_{quat}$, Boc), 79.6 ($C_{quat}$, Boc), 155.4 ($C_{quat}$, urethane-C), 155.8 ($C_{quat}$, urethane-C), 156.1 ($C_{quat}$, urethane-C), 174.7 ($C_{quat}$, amide-C); MS (ESI, MeOH): $m/z$=615.6 [$MH^+$] (100%), 1251.9 [$2M+Na^+$] (0.7%), 1345.8 [$2M+H^+$+$CH_3COOH$] (1.0%); IR (KBr): $\tilde{\nu}$ [$cm^{-1}$]=3391, 2974, 2931, 1695; MF: $C_{30}H_{58}N_6O_7$; MW=614.83.

See electronic Supporting information for the synthesis and characterisation of compounds **8-Bn**, **8-Me**, **8-CH(OH)–CH$_3$**, **16-Bn**, **16-$^i$Pr**, **18-Bn-$^i$Pr**, **18-$^i$Pr-Bn**, **25**.

### 4.3. General procedure 3 (GP 3) for the synthesis of compounds 10-Bn, 10-$^i$Pr, 10-Me, 10-CH(OH)–CH$_3$, 19-Bn-$^i$Pr, 19-$^i$Pr-Bn, 26

A round bottom flask was charged with the amine (1.0 equiv), the nicotinic acid derivative (1.1 equiv), coupling reagents HOAt and EDC (each 1.2 equiv) and *N*-ethyldiiso-propylamine (1.2 equiv). The mixture was dissolved in the minimum amount of dry DMF. The yellow solution was stirred at room temperature for 24 h and the reaction conversion was monitored by TLC. The mixture was evaporated and dried in vacuum. The resulting oil was dissolved in 50 ml of DCM and extracted three times with 10 ml of aqueous HBr ($c$=1 mol/l) to remove excess coupling reagents and amine. The combined organic layers were dried over $NaSO_4$ and concentrated under reduced pressure. CC (DCM/MeOH) afforded the fully Boc-protected compounds as reddish solids.

**4.3.1. 1-Benzyl-3-{2-phenyl-1-[2-(4,7,10-tris-*tert*-butoxy-carbonyl-1,4,7,10-tertaaza-cyclododec-1-yl)-ethylcarbamoyl]-ethylcarbamoyl}-pyridinium-bromide (10-Bn).** The synthesis follows GP 3 using **8-Bn** (1.10 g, 1.66 mmol), **9** (0.54 g, 1.83 mmol), HOAt (0.27 g, 2.01 mmol), EDC (0.31 g, 0.36 ml, 2.01 mmol) and *N*-ethyldiisopropylamine (0.26 g, 0.34 ml, 2.01 mmol). CC with $CH_2Cl_2$/MeOH (98:2) to $CH_2Cl_2$/MeOH (87:13). After concentrating the solution under reduced pressure and drying in vacuum the obtained solid was diluted in as little dry DCM as possible and stored at −18 °C over night. Any separated silica gel was removed by filtration and the obtained solution was dried in vacuum. This afforded **10-Bn** in a yield of 1.34 g (1.43 mmol, 86%); $R_f$=0.16 ($CH_2Cl_2$/MeOH=9:1); mp: 146–149 °C. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$=1.42 (s, 18H, Boc-$CH_3$), 1.45 (s, 9H, Boc-$CH_3$), 2.67–2.74 (m, 6H, $CH_2$), 3.26–3.48 (m, 16H, $CH_2$), 4.87–4.92 (m, 1H, C*H), 6.05 (bs, 2H, Bn–$CH_2$), 7.09–7.12 (m, 1H, arom. CH), 7.15–7.18 (m, 2H, arom. CH), 7.34–7.36 (m, 2H, arom. CH), 7.41–7.45 (m, 3H, arom. CH), 7.60–7.62 (m, 2H, arom. CH), 7.67 (bs, 1H, NH), 7.98–8.02 (m, 1H, py-CH), 8.95 (d, $^3J$=8.2 Hz, 1H, py-CH), 9.09 (d, $^3J$=5.2 Hz, 1H, py-CH), 9.51 (m, 1H, NH), 10.22 (s, 1H, py-CH); $^{13}$C NMR (100.6 MHz, $CDCl_3$): $\delta$=28.5 (+, Boc-$CH_3$, 6C), 28.7 (+, Boc-$CH_3$, 3C), 35.4, (−, 1C), 38.2 (−, Phe), 47.9 (−, 4C), 49.8 (−, 2C), 50.5 (−, 1C), 53.9 (−, 1C), 55.0 (−, 1C), 57.4 (+, C*H), 65.0 (−, Bn), 79.4 ($C_{quat}$, Boc, 1C), 79.6 ($C_{quat}$, Boc, 2C), 126.7 (+, 1 arom. C), 127.9 (+, 1 py-C), 128.4 (+, 2 arom. C), 129.4 (+, 2 arom. C), 129.7 (+, 2 arom. C), 129.9 (+, 2 arom. C), 130.5 (+, 1 arom. C), 131.9 (arom. $C_{quat}$), 134.4 (arom. $C_{quat}$), 137.3 (arom. $C_{quat}$), 144.7 (+, 1 py-C), 145.1 (+, 1 py-C), 145.3 (+,1 py-C), 155.5 ($C_{quat}$, urethane-C), 155.8 ($C_{quat}$, urethane-C), 156.1 ($C_{quat}$, urethane-C), 160.7 ($C_{quat}$, amide-C), 171.0 ($C_{quat}$, amide-C); UV–vis (MeOH): $\lambda$ (log $\varepsilon$)=264 nm (3.755), 204 nm (4.577); MS (ESI, $H_2O$/MeOH/AcN): $m/z$=429.9 [$(M^+ + H^+)^{2+}$] (20%), 858.6 [$M^+$] (100%); IR (KBr): $\tilde{\nu}$ [$cm^{-1}$]=3063, 2977, 2930, 2856, 1679, 1545, 1460, 1416, 1366, 1250, 1162, 749, 702; $[\alpha]_D^{20}$ (MeOH)=−2±1°; MF: $C_{47}H_{68}N_7O_8Br$; MW=939.00.

See electronic Supporting information for the synthesis and

characterisation of compounds **10-$^{i}$Pr**, **10-Me**, **10-CH(OH)–CH$_3$**, **19-Bn-$^{i}$Pr**, **19-$^{i}$Pr-Bn**, **26**.

### 4.4. General procedure 4 (GP 4) for the synthesis of compounds 11-Bn, 11-$^{i}$Pr, 20-Bn-$^{i}$Pr, 20-$^{i}$Pr-Bn, 27

In a round-bottomed flask the Boc-protected product from GP 3 (1 equiv) was dissolved in DCM and treated with trifluoroacetic acid (TFA) (42 equiv). The yellow solution was stirred at room temperature for 24 h and was then evaporated and dried in vacuum. This afforded the fully deprotected compounds as yellow solids in sufficient purity for use in subsequent steps.

#### 4.4.1. 1-Benzyl-3-{2-phenyl-1-[2-(1,4,7,10-tertaaza-cyclododec-1-yl)-ethylcarbamoyl]-ethyl-carbamoyl}-pyridinium-trifluoroacetate-trihydro-trifluoroacetate (11-Bn).

The synthesis follows GP 4 using 1.28 g (1.36 mmol) of **10-Bn** dissolved in 60 ml $CH_2Cl_2$ and 6.53 g (4.4 ml, 57.30 mmol) of TFA. This gave 1.24 g of **11-Bn** (1.22 mmol, 90%); mp: 92–94 °C. $^1$H NMR (400 MHz, $CD_3CN$): $\delta$=2.61–3.18 (m, 19H), 3.10 (dd, $^2J$=13.8 Hz, $^3J$=11.9 Hz, 1H, Phe-$CH_2$), 3.44–3.51 (m, 1H, $CH_2$), 3.56 (dd, $^2J$=13.8 Hz, $^3J$=3.4 Hz, 1H, Phe-$CH_2$), 4.88 (ddd, $^3J$=3.4, 8.6, 11.9 Hz, 1H, C*H), 5.86 (s, 2H, Bn–$CH_2$), 7.11–7.21 (m, 3H, arom. CH), 7.38–7.40 (m, 2H, arom. CH), 7.45–7.49 (m, 3H, arom. CH), 7.54–7.57 (m, 2H, arom. CH), 8.01 (dd, $^3J$=6.2, 8.1 Hz, 1H, py-CH), 8.23 (t, $^3J$=6.0 Hz, 1H, NH), 8.82–8.83 (m, $^3J$=6.2 Hz, 1H, py-CH), 8.96 (dt, $^3J$=8.1 Hz, $^4J$=1.3 Hz, 1H, py-CH), 9.47 (d, $^3J$=8.6 Hz, 1H, NH), 9.82 (m, 1H, py-CH); $^{13}$C NMR (100.6 MHz, $CD_3CN$): $\delta$=37.6 (−, Phe), 39.1 (−, 1C, $CH_2$–NH), 43.1 (−, 4C, cyclen), 45.3 (−, 2C, cyclen), 50.2 (−, 1C, cyclen), 50.7 (−, 1C, cyclen), 55.7 (−, 1C, $CH_2$–N), 57.3 (+, C*H), 65.5 (−, Bn), 127.6 (+, 1 arom. C), 129.2 (+, 1 py-C), 129.3 (+, 2 arom. C), 130.4 (+, 2 arom. C), 130.5 (+, 4 arom. C), 131.0 (+, 1 arom. C), 133.9 (arom. $C_{quat}$, 1C), 135.2 (arom. $C_{quat}$, 1C), 139.3 (arom. $C_{quat}$, 1C), 145.8 (+, 1 py-C), 146.1 (+, 1 py-C), 146.9 (+, 1 py-C), 163.2 ($C_{quat}$, amide-C), 173.4 ($C_{quat}$, amide-C); UV–vis (MeOH): $\lambda$ (log $\varepsilon$)=264 nm (3.889), 205 nm (4.626); MS (ESI, $CH_3CN$): $m/z$=391.9 [($M^+$+$H^+$+KCl+$CF_3COOH$+HCl)$^{2+}$] (68%), 392.9 [($M^+$+$H^+$+KCl+HBr+2HCl)$^{2+}$] (75%), 419.4 (100%), 558.4 [$M^+$] (20%), 694.3 [$M^+$+$CF_3COONa$] (4%), 746.3 [$M^+$+KCl+$CF_3COOH$] (6%), 748.3 [$M^+$+KCl+HBr+HCl] (8%); IR (KBr): $\tilde{\nu}$ [cm$^{-1}$]=3432, 3070, 2970, 2856, 2362, 1676, 1545, 1497, 1458, 1200, 1135, 706; MF: [$C_{32}H_{47}N_7O_2$]$^{4+}$($CF_3COO^-$)$_4$/$C_{40}H_{47}N_7O_{10}F_{12}$; MW=1013.83; $[\alpha]_D^{20}$ (MeOH)=−13±1°.

See electronic Supporting information for the synthesis and characterisation of compounds **11-$^{i}$Pr**, **20-Bn-$^{i}$Pr**, **20-$^{i}$Pr-Bn**, **27**.

### 4.5. General procedure 5 (GP 5) for the synthesis of compounds 12-Me, 12-CH(OH)CH$_3$, 21-Bn-$^{i}$Pr, 21-$^{i}$Pr-Bn

The TFA-salt (1 equiv) from *GP 4* was dissolved in water and passed over a strongly basic ion-exchanger column (loading: 0.9 mmol/ml, 6 equiv). The obtained solution was lyophilized to afford the corresponding amine as a pale yellow solid.

#### 4.5.1. 1-Benzyl-3-{1*S*-1-[2-(1,4,7,10-tetraazacyclododec-1-yl)-ethylcarbamoyl]-ethylcarbamoyl}-pyridinium-hydroxide (12-Me).

The synthesis follows GP 5 using 245 mg (0.30 mmol) of **11-Me** and 2.0 ml of the basic ion-exchanger (1.80 mmol). This afforded **12-Me** in a yield of 145 mg (0.29 mmol, 97%); mp: 85–87 °C. UV–vis ($CH_3CN$): $\lambda_{max}$ [nm] (log $\varepsilon$)=322 (3.829); MS (ESI, MeOH/$CH_3CN$+0.1% TFA): $m/z$ (%)=196.4 (30) [($K^+$+$H^+$–Bn)$^{2+}$], 216.9 (45), 241.5 (100) [($K^+$+$H^+$)$^{2+}$], 392.1 (64) [($K^+$−Bn)$^+$], 482.3 (93) [$K^+$], 596.4 (24) [$K^+$+$CF_3CO_2H$)]; IR (KBr): $\tilde{\nu}$ [cm$^{-1}$]=704, 735, 1179, 1212, 1279, 1348, 1413, 1456, 1540, 1665, 2830, 2934, 3424; $[\alpha]_D^{20}$ ($CH_3CN$)=−68±7°; MF: $C_{26}H_{41}N_7O_3$; MW=499.66.

See electronic Supporting information for the synthesis and characterisation of compounds **12-CH**(OH)-**CH$_3$**, **21-Bn-$^{i}$Pr**, **21-*i*Pr-Bn**.

### 4.6. General procedure 6 (GP 6) for the synthesis of compounds 22-Bn-$^{i}$Pr, 22-$^{i}$Pr-Bn

In a round bottom flask $Zn(ClO_4)_2\cdot 6H_2O$ was dissolved in acetonitrile and a suspension of the amine in acetonitrile was slowly added. The resulting reddish solution was stirred at room temperature for 16 h and then heated to reflux for 4 h. After cooling to room temperature the solvent was evaporated to afford the crude product as orange oil. Ethanol (2 ml) was added and the resulting pale red precipitate was treated with ultrasound for 15 min. After filtration, the solid was washed with 2 ml of ethanol and dissolved in 1.5 ml of acetonitrile. Any resulting precipitate was removed by centrifugation. Drying of the solution in vacuum afforded the zinc-complex as a hygroscopic orange solid.

#### 4.6.1. 1-Benzyl-3-{1-[1-benzyl-2-oxo-2-(1,4,7,10-tetraaza-cyclododec-1-yl)-ethyl-carbamoyl]-2-methyl-propylcarbamoyl}-pyridinium-zinc-(II)-tri-perchlorate (22-Bn-$^{i}$Pr).

The synthesis follows GP 6 using 0.22 g (0.60 mmol, 3 equiv) $Zn(ClO_4)_2\cdot 6H_2O$ dissolved in 5 ml acetonitrile and a suspension of **21-Bn-$^{i}$Pr** (0.13 g, 0.20 mmol) in 7 ml acetonitrile. This gave **22-Bn-*i*Pr** in a yield of 0.17 g (0.18 mmol, 88%); mp: 230 °C (dis.).

$^1$H NMR (400 MHz, $CD_3CN$): $\delta$=0.95 (d, $^3J$=6.7 Hz, 3H, Val-$CH_3$), 0.98 (d, $^3J$=6.7 Hz, 3H, Val-$CH_3$), 2.05–2.13 (m, $^3J$=6.7 Hz, 1H, CH), 2.31–2.36 (m, 1H, $CH_2$), 2.48–2.61 (m, 1H, $CH_2$), 2.68–2.93 (m, 9H, $CH_2$), 3.00–3.13 (m, 5H, $CH_2$), 3.28–3.35 (m, 1H, $CH_2$), 3.48–3.54 (m, 1H, $CH_2$), 3.67–3.71 (m, 1H, NH), 3.83–3.86 (m, 1H, NH), 3.95–3.97 (m, 1H, NH), 4.53–4.56 (m, 1H, Val-C*H), 4.71–4.75 (m, 1H, Phe-C*H), 5.80 (d, $^2J$=14.8 Hz, 1H, Bn–$CH_2$), 5.84 (d, $^2J$=14.8 Hz, 1H, Bn–$CH_2$), 7.22–7.31 (m, 6H, arom. CH), 7.44–7.52 (m, 4H, arom. CH), 7.82 (d, $^3J$=8.3 Hz, 1H, Val-NH), 8.06 (dd, $^3J$=6.1, 8.0 Hz, 1H, py-CH), 8.05–8.08 (m, 1H, Phe-NH), 8.76 (d, $^3J$=6.1 Hz, 1H, py-CH), 8.93 (d, $^3J$=8.0 Hz, 1H, py-CH), 9.66 (bs, 1H, py-CH); $^{13}$C NMR (100.6 MHz, $CD_3CN$): $\delta$=18.5 (+, Val-$CH_3$), 19.3 (+, Val-$CH_3$), 32.8 (+, Val-CH), 37.3 (−, Phe), 42.8 (−, 1C), 45.2 (−, 1C), 45.5 (−, 1C), 46.1–46.4 (−, 3C), 46.7 (−, 1C), 48.9 (−, 1C), 55.1 (+, Phe-C*H), 59.4 (+, Val-C*H), 65.8 (−, 1C, Bn), 128.3 (+, 1 arom. C), 129.2 (+, 1 py-C), 129.7 (+, 2 arom. C), 130.3 (+, 2

arom. C), 130.4 (+, 1 arom. C), 130.5 (+, 1 arom. C), 130.8 (+, 1 arom. C), 133.8 (arom. $C_{quat}$), 135.6 (arom. $C_{quat}$), 136.4 (arom. $C_{quat}$), 145.9 (+, py-C), 146.1 (+, py-C), 146.7 (+, py-C), 162.3 ($C_{quat}$, amide-C), 173.0 ($C_{quat}$, amide-C), 175.3 ($C_{quat}$, amide-C); UV–vis ($CH_3CN$): $\lambda$ (log $\varepsilon$)=264 (3.813), 385 nm (2.609); MS (ESI,$CH_3CN$): $m/z$=338.7 [$(M^{3+}-H^+)^{2+}$] (90%), 356.6 [$(M^{3+}+Cl^-)^{2+}$] (100%), 368.6 [$(M^{3+}+CH_3COO^-)^{2+}$] (35%), 388.6 [$(M^{3+}+ClO_4^-)^{2+}$] (50%), 586.3 [$(M^{3+}-H^+-Bn^+)^+$] (20%), 712.4 [$(M^{3+}-H^++Cl^-)^+$] (10%), 776.4 [$(M^{3+}-H^++ClO_4^-)^+$] (6%), 876.4 [$(M^{3+}+2ClO_4^-)^+$] (4%); IR (KBr): $\tilde{\nu}$ [$cm^{-1}$]=3386, 3078, 2966, 2928, 1642, 1539, 1497, 1455, 1367, 1096, 746, 703; $[\alpha]_D^{20}$ ($CH_3CN$)=+5±1°; MF: $[C_{35}H_{48}N_7O_3Zn]^{3+}(ClO_4^-)_3$/$C_{35}H_{48}N_7O_{15}Cl_3Zn$; MW=978.54.

See electronic Supporting information for the synthesis and characterisation of compound **22-$^i$Pr-Bn**.

### 4.7. General procedure 7 (GP 7) for the synthesis of compounds 1-Bn, 1-Me, 1-$^i$Pr, 1-CH(OH)–$CH_3$, 2, 3, 4

A round bottom flask under argon atmosphere was charged with the zinc-complex (obtained from GP 6, GP 8 or GP 9), sodium carbonate, sodium dithionite, 4 ml of degassed water and 2 ml of degassed acetonitrile. Stirring of this mixture at room temperature for 3 h under strictly exclusion of oxygen afforded a yellow solution. The solvent was evaporated, 2 ml of degassed acetonitrile were added and the resulting suspension was filtered and the filtrate evaporate in vacuum to afford the dihydropyridine as a yellow solid, which is highly sensitive to oxygen.

**4.7.1. 1-Benzyl-1,4-dihydropyridin-3-carbonicacid-{[2-phenyl-1-[2-(1,4,7,10-tetraaza-cyclododec-1-yl)-ethylcarbamoyl]-ethyl}-amide-zinc(II)-di-perchlorate (1-Bn).** The synthesis follows GP 7 using **13-Bn** (32 mg, 35 μmol), sodium carbonate (15 mg, 139 μmol, 4 equiv) and sodium dithionite (15 mg, 87 μmol, 2.5 equiv). This afforded **1-Bn** in a yield of 26 mg (31 μmol, 90%). $^1$H NMR (300 MHz, $CD_3CN$): $\delta$= 2.50–3.67 (m, 27H, $CH_2$), 4.30 (s, 2H, Bn–$CH_2$), 4.60–4.67 (m, 1H, C*H), 4.74 (dt, $^3J$=8.1, 3.3 Hz, 1H, CH), 5.86 (dd, $^3J$=8.1 Hz, $^4J$=1.3 Hz, 1H, CH), 6.08 (d, $^3J$=7.0 Hz, 1H, NH), 7.06 (d, $^4J$=1.3 Hz, 1H, CH), 7.18–7.49 (m, 11H, arom. CH+NH); $^{13}$C NMR (75.5 MHz, $CD_3CN$): $\delta$=22.9 (−), 36.6 (−, 1C), 38.5 (−, 1C), 43.3 (−, 2C), 44.9 (−, 2C), 45.4 (−, 2C), 52.8 (−, 2C), 55.2 (−, 1C), 56.8 (+, C*H), 57.6 (−, 1C), 103.6 (+), 127.8 (+, 1arom. C), 128.5 (+, 2 arom. C), 128.8 (+), 129.4 (+, 2 arom. C), 129.9 (+, 2 arom. C), 130.3 (+), 130.3 (+, 2 arom. C), 130.4 (+, 1 arom. C), 137.6 ($C_{quat}$), 139.5 ($C_{quat}$), 139.8 ($C_{quat}$), 169.2 ($C_{quat}$, amide-C), 175.2 ($C_{quat}$, amide-C); UV–vis ($H_2O$): $\lambda_{max}$ (log $\varepsilon$)=361 nm (3.794); MF: $[C_{32}H_{45}N_7O_2Zn]^{2+}(ClO_4^-)_2$/$C_{32}H_{45}N_7O_{10}Cl_2Zn$; MW=824.04.

See electronic Supporting information for the synthesis and characterisation of compounds **1-Me**, **1-$^i$Pr**, **1-CH(OH)–$CH_3$**, **2**, **3**, **4**.

### 4.8. General procedure 8 (GP 8) for the synthesis of compounds 13-Bn, 13-$^i$Pr, 28

The TFA-salt (1 equiv) was dissolved in water and passed over a strongly basic ion-exchanger column (loading: 0.9 mmol/ml, 6 equiv). The obtained solution was lyophilized to afford the corresponding amine as a pale yellow solid. In a round bottom flask $Zn(ClO_4)_2\cdot 6H_2O$ was dissolved in ethanol and a solution of the amine in 5 ml of ethanol was slowly added. A white precipitate formed immediately. The suspension was stirred at room temperature for 16 h and then heated to reflux for 2 h. The white precipitate became an orange oil which separated from the solution. The solution was removed and the oil was dried in vacuum. Ethanol (1 ml) was added and the resulting pale red precipitate was treated with ultrasound for 15 min. After filtration, the solid was washed with 2 ml of ethanol and was dissolved in 1.5 ml of acetonitrile. Any resulting precipitate was removed by centrifugation. Evaporation of the solution in vacuum afforded the zinc-complex as a hygroscopic orange solid.

**4.8.1. 1-Benzyl-3-{2-phenyl-1-[2-(1,4,7,10-tetraaza-cyclododec-1-yl)-ethylcarbamoyl]-ethyl-carbamoyl}-pyridinium-zinc-(II)-tri-perchlorate (13-Bn).** The synthesis follows GP 8 using 101 mg (0.1 mmol) of **11-Bn** and 74 mg (0.2 mmol, 2 equiv) $Zn(ClO_4)_2\cdot 6H_2O$ dissolved in 3 ml ethanol. This afforded **13-Bn** in a yield of 92 mg (0.1 mmol, 100%); mp: 142–145 °C. $^1$H NMR (300 MHz, $CD_3CN$): $\delta$=2.70–3.17 (m, 19H, $CH_2$), 3.32–3.55 (m, 6H, $CH_2$+3 NH), 4.80–4.87 (m, 1H, C*H), 5.80 (s, 2H, Bn–$CH_2$), 7.21–7.30 (m, 5H, arom. CH), 7.45–7.49 (m, 5H, arom. CH), 7.99 (d, $^3J$=6.6 Hz, 1H, Phe-NH), 8.10 (dd, $^3J$=6.1, 8.0 Hz, 1H, py-CH), 8.21 (m, 1H, NH), 8.73–8.76 (m, $^3J$=8.1 Hz, 1H, py-CH), 8.82–8.84 (m, $^3J$=6.1 Hz, 1H, py-CH), 9.09 (m, 1H, py-CH); $^{13}$C NMR (75.5 MHz, $CD_3CN$): $\delta$=37.6 (−, 1C, Phe), 39.5 (−, 1C), 43.3 (−, 2C), 44.8 (−, 1C), 45.1 (−, 1C), 45.3 (−, 1C), 45.4 (−, 1C), 52.7 (−, 1C), 52.9 (−, 1C), 55.2 (−, 1C), 57.2 (+, C*H), 66.0 (−, 1C), 128.0 (+, 1 arom. C), 129.7 (+, 2 arom. C), 129.7 (+, 1 py-C), 130.3 (+, 2 arom. C), 130.6 (+, 2 arom. C), 130.6 (+, 2 arom. C), 131.1 (+, 1 arom. C), 133.5 (arom. $C_{quat}$), 135.0 (arom. $C_{quat}$), 137.8 (arom. $C_{quat}$), 145.3 (+, py-C), 145.4 (+, py-C), 147.4 (+, py-C), 163.0 ($C_{quat}$, amide-C), 177.1 ($C_{quat}$, amide-C); UV–vis ($CH_3CN$): $\lambda$ (log $\varepsilon$)=265 nm (3.863); MS (pos. ESI, $CH_3CN$): $m/z$= 310.7 [$(M^{3+}-H^+)^{2+}$] (100%), 530.2 [$(M^{3+}-H^+-Bn^+)^+$] (18%), 720.3 [$(M^{3+}-H^++ClO_4^-)^+$] (12%), 820.2 [$(M^{3+}+2ClO_4^-)^+$] (1%); MS (neg. ESI, $CH_3CN$): $m/z$=918.1 [$(M^{3+}-H^++3ClO_4^-)^-$] (100%), 1018.1 [$(M^{3+}+4ClO_4^-)^-$] (30%); IR (KBr): $\tilde{\nu}$ [$cm^{-1}$]=3426, 3297, 3082, 2963, 2933, 1658, 1627, 1539, 1495, 1458, 1092, 748, 703; $[\alpha]_D^{20}$ ($CH_3CN$)=−24±2°; MF: $[C_{32}H_{44}N_7O_2Zn]^{3+}(ClO_4^-)_3$/$C_{32}H_{44}N_7O_{14}Cl_3Zn$; MW=922.48.

See electronic Supporting information for the synthesis and characterisation of compounds **13-$^i$Pr**, **28**.

### 4.9. General procedure 9 (GP 9) for the synthesis of compounds 13-Me, 13-CH(OH)–$CH_3$

In a round bottom flask $Zn(ClO_4)_2\cdot 6H_2O$ was dissolved in ethanol and a solution of the amine in 5 ml of ethanol was added slowly. A white precipitate formed immediately. The suspension was stirred at room temperature for 16 h and then heated to reflux for 2 h. The white precipitate became an orange oil which separated from the solution. The

solution was removed and the oil was dried in vacuum. Ethanol (1 ml) was added and the resulting pale red precipitate was treated with ultrasound for 15 min. After filtration, the solid was washed with 2 ml of ethanol and was dissolved in 1.5 ml of acetonitrile. Any resulting precipitate was removed by centrifugation. Evaporation of the solution in vacuum afforded the zinc-complex as a hygroscopic orange solid.

**4.9.1. 1-Benzyl-3-{1*S*-1-[2-(1,4,7,10-tetraazacyclododec1-yl)-ethylcarbamoyl]-ethylcarbamoyl}-pyridinium-zink-(II)-tri-perchlorate (13-Me).** The synthesis follows GP 9 using 134 mg (0.36 mmol, 2 equiv) $Zn(ClO_4)_2 \cdot 6H_2O$ dissolved in 3 ml ethanol and 90 mg (0.18 mmol) **12-Me**. This afforded **13-Me** in a yield of 135 mg (0.16 mmol, 91%), mp: 105–108 °C. $^1$H NMR (400 MHz, $CD_3CN$): $\delta = 1.56$ (d, $^3J = 7.2$ Hz, 3H, $CH_3$), 2.66–3.11 (m, 18H, $CH_2$), 3.35 (m, 1H, NH), 3.41–3.57 (m, 4H, $2CH_2$, 2 NH), 4.57 (dq, $^3J = 1.5$, 7.2 Hz, 1H, CH), 5.84 (s, 2H, $CH_2$), 7.48–7.54 (m, 5H, CH), 8.10–8.11 (m, 1H, NH), 8.16 (dd, $^3J = 6.3$, 6.6 Hz, 1H, CH), 8.38 (bs, 1H, NH), 8.85–8.87 (m, 1H, CH), 8.91–8.93 (m, 1H, CH), 9.27 (s, 1H, CH); $^{13}$C NMR (100.6 MHz, $CD_3CN$): $\delta = 17.2$ (+), 40.1 (−), 43.4 (−), 43.4 (−), 45.0 (2C, −), 45.3 (2C, −), 52.4 (+), 53.3 (2C, −), 56.0 (−), 66.0 (−), 129.7 (+), 130.5 (2C, +), 130.6 (2C, +), 131.1 (+), 133.6 ($C_{quat}$), 134.9 ($C_{quat}$), 145.6 (+), 145.8 (+), 147.5 (+), 163.4 ($C_{quat}$), 180.0 ($C_{quat}$); UV–vis ($CH_3CN$): $\lambda_{max}$ [nm] ($\log \varepsilon$) = 264 (3.713); MS (ESI, $CH_3CN$): $m/z$ (%) = 272.5 (100) $[(L^+ - H^+ + Zn^{2+})^{2+}]$, 454.1 (21), 644.3 (5) $[(L^+ - H^+ + Zn^{2+} + ClO_4^-)^+]$, 746.3 (1) $[(L^+ + Zn^{2+} + 2ClO_4^-)^+]$; IR (KBr): $\bar{\nu}$ [$cm^{-1}$] = 626, 706, 749, 1091, 1454, 1497, 1542, 1669, 2938, 3079, 3294, 3407; $[\alpha]_D^{20}$ ($CH_3CN$) = +13 ± 1°; MF: $(C_{26}H_{40}N_7O_2Zn)^{3+}$ $(ClO_4^-)_3$, respectively $C_{26}H_{40}N_7O_{14}Cl_3Zn$; MW = 846.39.

See electronic Supporting information for the synthesis and characterisation of compound **13-CH(OH)-CH$_3$**.

### 4.10. Electronic supporting information

The electronic Supporting information contains experimental procedures and characterization of new compounds, copies of proton and/or carbon NMR spectra of new compounds, a table of the UV absorption maxima of compounds **1–4**, copies of multiplicity edited HSQC and variable temperature spectra of deuterated **1CH(OH)–CH$_3$**.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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.2005.03.081

## References and notes


1. (a) How important they are, is illustrated best by the consequences of non-sufficient supply in human nutrition. Until the end of the 19th century the disease Pellagra (from Italian 'pelle agra' for rough skin) was widespread. Since 1918 it was recognized that the disease resulted from insufficient supply of riboflavine and nicotinic acid. From 1938 on nicotinic acid and amide was added to cereal products in the USA, which drastically reduced the number of deaths from Pellagra. (b) Offermanns, H.; Kleemann, A.; Tanner, H.; Beschke, H.; Friedrich, H. In *Kirk-Othmer Encyclopedia of Chemical Technology*, *Vol. 24*; Wiley: New York, 1984. (c) Gopalan, C.; Rao, K. S. J. *Vitam. Horm.* **1975**, *33*, 505.
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13. Force field and semi-empirical calculations of minimum energy conformations have been performed, but results from gas phase cannot reliably predict conformations in aqueous solution, which would be needed to predict and correlate reaction rates.
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# $Pd_2(dba)_3$/Xantphos-catalyzed cross-coupling of thiols and aryl bromides/triflates

Clotilde Mispelaere-Canivet,[a] Jean-Francis Spindler,[b] Stéphane Perrio[a,*] and Pierre Beslin[a]

[a]*Laboratoire de Chimie Moléculaire et Thio-organique (UMR CNRS 6507), ENSICaen-Université de Caen Basse-Normandie, 6 Boulevard du Maréchal Juin, F-14050 Caen, France*
[b]*RHODIA, Centre de Recherches de Lyon, POP/ISV, 85 Avenue des Frères Perret, BP 62, F-69192 Saint-Fons, France*

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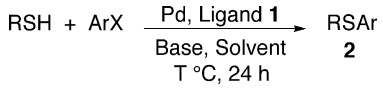
**Abstract**—The cross-coupling of aliphatic and aromatic thiols and aryl bromides/triflates mediated by a $Pd_2(dba)_3$/Xantphos catalytic system in refluxing xylene (140 °C) affords the corresponding aryl thioethers in good to excellent yields.


## 1. Introduction

Aryl sulfides are useful intermediates in organic synthesis. In addition, this sulfur fragment is incorporated in a number of natural products or compounds exhibiting important biological activities.[1] The more conventional route to these compounds involves the displacement reaction of an arenethiolate with the appropriate alkyl halide.[2] Other reported procedures are based on the creation of the aryl–sulfur bond, thus including nucleophilic aromatic substitution[3] or treatment[4] of aryllithium or Grignard reagents with sulfurated electrophiles. In 1980, Migita introduced the Pd-catalyzed cross-coupling reaction of aryl bromides with thiols.[5] Since then, various efficient catalytic systems using bidentate phosphines or dialkylphosphine oxides **1** have been described (Scheme 1).[6–9] Furthermore, reactions mediated with other transition metals (Ni, Cu) have been investigated very recently.[10–11]




**Scheme 1.** Pd-catalyzed Ar–S bond formation.

The Pd-catalyzed strategy previously mentioned is particularly attractive for industry, as revealed by the recent contributions in this area.[12] One major reason of this interest is the use of readily available phenol derivatives (i.e., triflates) or aryl bromides as starting materials. As part of our program concerning the creation of a carbon–sulfur bond on an aromatic ring, our motivation turned towards this chemistry.[13] Among the few examples already described when we initiated the project, we paid particularly attention to a work from Merck dedicated to the palladium cross-coupling of thiols with aryl triflates.[6] The protocol involves an initial deprotonation of the mercaptan with sodium *t*-butoxide followed by heating the resulting sodium thiolate with the aromatic triflate in the presence of $Pd(OAc)_2$ and (*R*)-(+)-Tol-BINAP **1a** (see Table 1 for the ligand structure). However the methodology suffers from a few limitations, such as the incompatibility with aromatic thiols. As a consequence, the search of novel conditions leading to various thioethers, especially both alkyl aryl and diaryl compounds remained of interest. Additional attractive features would be to proceed under mild and friendly conditions (base, solvent) compatible with industrial constraints and allow bromo arenes[14] as substrates. We wish to present herein the results from our investigation that led to the development of a new catalytic system.

## 2. Results and discussion

In our initial screening experiments, *n*-butanethiol and phenyltriflate were selected as substrates for discovery of optimal conditions. Reaction times were arbitrary set at 24 h. Selected conditions we tested are listed in Table 1. We began with the conditions developed by the Merck group for, which *n*-butyl phenyl sulfide was isolated in 71.5% yield (entry 1). Various bidentate phosphine ligands,

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* Corresponding author. Tel.: +33 231 452 884; fax: +33 231 452 877; e-mail: stephane.perrio@ensicaen.fr

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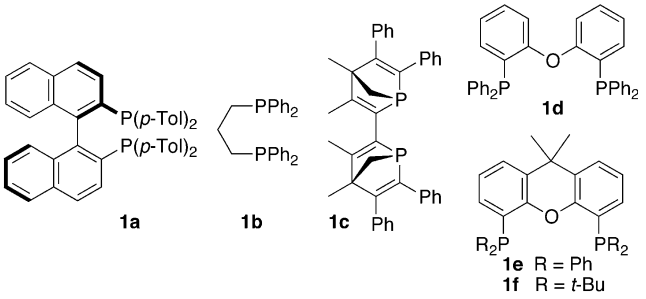
**Table 1**. Evaluation of various catalytic systems for cross-coupling of *n*-BuSH and PhOTf to give sulfide **2a** (R=*n*-Bu, Ar=Ph) according to Scheme 1[a]




| Entry | Base | Pd source | Ligand | Solvent, *T* (°C) | Yield (%) |
|---|---|---|---|---|---|
| 1 | *t*-BuONa | $Pd(OAc)_2$ | **1a** | Toluene, 80 | 71.5 |
| 2 | *t*-BuONa | $Pd(OAc)_2$ | **1b** | Toluene, 80 | 7.5 |
| 3 | *t*-BuONa | $Pd(OAc)_2$ | **1c** | Toluene, 80 | 33 |
| 4 | *t*-BuONa | $Pd(OAc)_2$ | **1d** | Toluene, 80 | 0 |
| 5 | *t*-BuONa | $Pd(OAc)_2$ | **1e** | Toluene, 80 | 20 |
| 6 | *t*-BuONa | $Pd_2(dba)_3$ | **1a** | Toluene, 80 | 88 |
| 7 | *t*-BuONa | $Pd_2(dba)_3$ | **1e** | Toluene, 80 | 0 |
| 8 | *t*-BuONa | $Pd_2(dba)_3$ | **1e** | Toluene, 110 | 74 |
| 9 | *t*-BuONa | $Pd_2(dba)_3$ | **1e** | Xylene, 140 | 82 |
| 10 | $K_2CO_3$ | $Pd_2(dba)_3$ | **1e** | Xylene, 140 | 80 |
| 11 | $K_2CO_3$ | $Pd_2(dba)_3$ | **1f** | Xylene, 140 | Traces |
| 12 | $K_2CO_3$ | $Pd_2(dba)_3$ | **1f** | Toluene, 110 | 0 |

[a] Reaction conditions: *n*-BuSH (1 mmol), base (0.5 mmol), PhOTf (0.8 mmol), Pd source (0.08 mmol), ligand **1** (0.09 mmol), solvent (12 mL) for 24 h.

including dppp **1b**, *meso*-BIPNOR **1c**, DPEphos **1d** and Xantphos **1e** were tested but all afforded disappointing results, with chemical yields below 33% (entries 2–5). Use of $Pd_2(dba)_3$ as a direct palladium(0) source in the presence of (*R*)-(+)-Tol-BINAP **1a** led to an excellent 88% yield (entry 6). In contrast, no cross-coupling was observed when combined with Xantphos **1e** (entry 7). However, an elevation of the temperature to 110 °C (refluxing toluene) and even to 140 °C (reflux of xylene) in the presence of this ligand **1e** led to a dramatic improvement. In the last case, the product was obtained in 82% yield (entry 9). Using potassium carbonate as base instead of sodium *t*-butoxide gave an analogous excellent yield (entry 10). As the use of a bulkier and more electron-rich ligand could in principle allow a reduced reaction temperature, we designed the unprecedented Xantphos analogue **1f** with bis-(*t*-butylphosphino) substituents (see Fig. 1 for the X-ray structure). Unfortunately, all attempts with this ligand failed and a total inhibition of the coupling was observed (entries 11 and 12).

In summary, these preliminary studies revealed that the best reaction conditions involve potassium thiolates obtained by mixing the thiol precursor with a stoichiometric amount of potassium carbonate and a Xantphos **1e**/$Pd_2(dba)_3$ as the catalytic system in refluxing xylene (entry 10).[15] The main features of these cross-coupling conditions are the combined use of a cheap, stable, mild and easy handling mineral base and the readily available ligand **1e**. Even if the boiling point of xylene is relatively high (140 °C), this is not a crucial drawback for further industrial applications, the products being in general non-volatile solids. The catalyst loading was deliberately not optimized at our laboratory scale (1 mmol) and more significant results involving until 500 ppm of Pd can in principle be obtained during a scale-up investigation on a specific substrate. In addition the effect of the Pd/ligand ratio was not examined at this point. Important to note is that during the preparation of this manuscript, a Japanese group reported the same catalytic system for this reaction.[16] The difference consists in the use of *i*-$Pr_2NEt$ or $Cs_2CO_3$ (2 equiv) and 1,4-dioxane, respectively, as base and solvent.

To investigate the scope of the reaction, a broad range of aliphatic thiols including primary, secondary and tertiary structures were then used. The thiolate was generated by deprotonation of the thiol at 0 °C and was then added to a mixture of all other reagents. When all reaction components were simply mixed together, lower conversions to the desired product were observed. For example, sulfide **2a** was

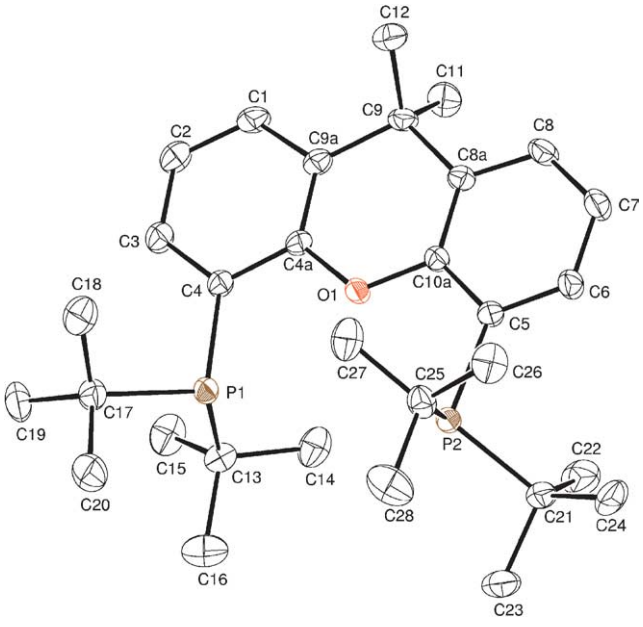



**Figure 1.** ORTEP diagram of ligand **1f**.

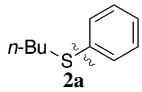
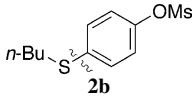
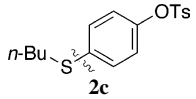
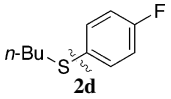
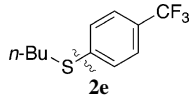
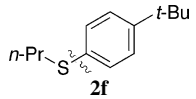
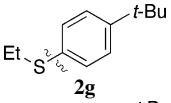
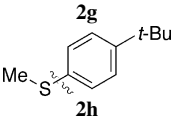
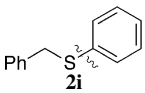
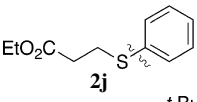
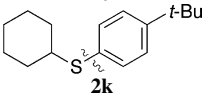
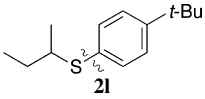
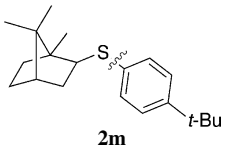
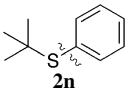
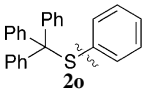
obtained only in 43% yield (compare with the 80% yield obtained above).

All alkyl aryl sulfides were produced in good to excellent yields as outlined in Table 2, except for the trityl derivative (entry 17). Bromobenzene was shown to be an efficient electrophile (entry 2) and the use of the chloride analogue led to a lower 19% yield (entry 3). However, chlorinated arenes can be suitable substrates when activated with an electron withdrawing group. For example, the cross-coupling of compound possessing a trifluoromethyl substituent gave rise to a 75% yield (entry 7). Total chemoselectivities were observed with substrates possessing two potential leaving groups. Substitution took place only at the more reactive C–Br or C–OTf bonds and the mesyl, tosyl and fluoro groups remained unchanged (entries 4–6). Interestingly, sterically hindered thiols were also suitable substrates, thioethers derived from bornane-2-thiol and *t*-butanethiol being isolated in 59 and quantitative yields, respectively. With ethanethiol, a disappointing 35% yield was obtained and this was interpreted by the volatility of the precursor (entry 9). A significant improvement leading to a 94% yield was observed employing an isolated and accurately weighted thiolate (deprotonation with NaOH followed by concentration and drying under vacuum until constant weight). As a consequence, we were also able to couple efficiently commercially available sodium methanethiolate (entry 10). A base sensitive functional groups, namely a methyl ester, in the starting thiol was also tolerated (entry 12). Interestingly, β-sulfanylesters that can thus be produced have very recently been identified as convenient and efficient thiol surrogates.[17]

Arenethiols were also found to be effective nucleophiles under the reactions conditions as can be seen from Table 3. Important to remember is that such substrates were problematic with the Merck procedure. Reaction of simple thiophenol with bromobenzene and phenyltriflate afforded diphenyl sulfide **2p** in quantitative yields (entries 1 and 2). Extension to the access of a naphthyl derivative was also achieved in an excellent 93% yield (entry 3). Introduction of an *ortho*-methoxy group on the aromatic thiol led to the sulfide product in a moderate 41% yield. As can be seen from the results in entries 4 and 6, the protocol can be even applied to electron-deficient thiols. A lower conversion was however observed with the thiol possessing an *N*,*N*-dimethylaminoethyl group (entry 7), probably due to a competing complexation of the nitrogen atom on palladium. Furthermore, pyridine-2-thiol did not react under these reaction conditions (entry 8).

While the precise mechanistic details of the C–S coupling reaction remain to be established, it is assumed that the overall catalytic cycle of the synthesis is similar to that postulated for palladium catalyzed aminations and etherations.[18] The reasons for the beneficial influence of the Xantphos **1e** ligand are not straightforward to elucidate. It is likely that the close proximity of the oxygen atom to the palladium center (with the possibility of assisting the displacement of the leaving group from palladium)[19] and the known ability of chelating diphosphines with large bite angles[20] to accelerate reductive elimination rates[21] play a crucial role.

**Table 2**. Coupling of aliphatic thiols with $Pd_2(dba)_3$/Xantphos **1e** according to Scheme 1[a]

| Entry | X of ArX | Sulfide | Yield (%)[b] |
|---|---|---|---|
| 1 | OTf | | 80 |
| 2 | Br |  **2a** | 80 |
| 3 | Cl | | 19[c] |
| 4 | Br |  **2b** | 80 |
| 5 | Br |  **2c** | 87 |
| 6 | Br |  **2d** | 93[c] |
| 7 | Cl |  **2e** | 75[d] |
| 8 | Br |  **2f** | 75 |
| 9 | Br |  **2g** | 35 (94) |
| 10 | Br |  **2h** | −(86) |
| 11 | Br |  **2i** | 97 |
| 12 | Br |  **2j** | 84 |
| 13 | Br |  **2k** | 94 |
| 14 | Br |  **2l** | 89 |
| 15 | Br |  **2m** | 59 |
| 16 | Br |  **2n** | 100 |
| 17 | Br |  **2o** | 0 |

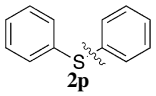
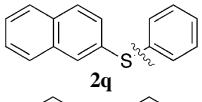
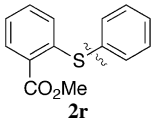
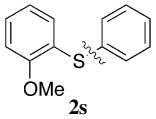
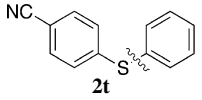
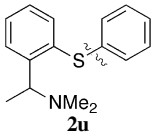
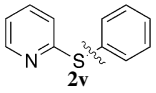
[a] Reaction conditions: RSH (1 mmol), $K_2CO_3$ (0.5 mmol), ArX (0.8 mmol), $Pd_2(dba)_3$ (0.08 mmol), Xantphos **1e** (0.09 mmol) in xylene (12 mL) at 140 °C for 24 h.

[b] The yields obtained using isolated sodium thiolates are shown in parentheses.

[c] Deprotonation with *t*-BuONa.

[d] Yield of the corresponding sulfone **3** obtained after oxidation of sulfide **2e** with *m*-CPBA.

**Table 3**. Coupling of aromatic thiols with $Pd_2(dba)_3$/Xantphos **1e** according to Scheme 1[a]

| Entry | X of ArX | Sulfide | Yield (%) |
|---|---|---|---|
| 1 | Br |  **2p** | 100 |
| 2 | OTf | | 100 |
| 3 | Br |  **2q** | 93 |
| 4 | Br |  **2r** | 83 |
| 5 | Br |  **2s** | 41 |
| 6 | Br |  **2t** | 57 |
| 7 | Br |  **2u** | 25[19] |
| 8 | Br |  **2v** | 0 |

[a] Reaction conditions: RSH (1 mmol), $K_2CO_3$ (0.5 mmol), ArX (0.8 mmol), $Pd_2(dba)_3$ (0.08 mmol), Xantphos **1e** (0.09 mmol) in xylene (12 mL) at 140 °C for 24 h.

In conclusion, we have developed an efficient and fairly general Pd(0)-catalyzed aryl–sulfur bond formation from aromatic and aliphatic thiols. The successful reaction partners are aryl bromides, triflates and even activated chlorobenzenes. An important value of the protocol we described lies in the use of a classical mild mineral base ($K_2CO_3$) and a readily available and cheap catalytic system based on $Pd_2(dba)_3$ and Xantphos.

## 3. Experimental

### 3.1. General

All reactions were performed in oven-dried Schlenk tubes, under an atmosphere of dry nitrogen. Due to the stench of thiols, all glassware and syringes were washed with bleach after use. Reactions were purified by chromatography column with Merck silica gel Geduran Si 60 (0.040–0.063 nm). Thin layer chromatography was carried out on silica gel 60 $F_{254}$ (1.1 mm, Merck) with spot detection under UV light or through $I_2$ or $KMnO_4$ oxidation. Melting points were obtained on a Reichert 7905 hot-stage microscope or an Electrothermal IA9000 capillary apparatus and are uncorrected. NMR spectra were recorded at room temperature on Bruker DPX 250 or DRX 400 spectrometers. All chemical shifts ($\delta$) and coupling constants are quoted in parts per million (ppm) and Hertz (Hz), respectively. The following abbreviations are used to designate the multiplicity of the signals: s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet, and combinations thereof. The chemical shifts are calibrated to TMS ($\delta$ H 0.00) or residual proton and carbon resonance of the solvent $CDCl_3$ ($\delta$ H 7.26 and $\delta$ C 77.16). $^{31}P$ and $^{19}F$ chemical shifts are referred to external 85% phosphoric acid and $CFCl_3$, respectively. IR spectra were recorded on a Perkin–Elmer 16 PC FT-IR instrument. Mass spectra were recorded on a Varian GC/MS/MS instrument. Only peaks of an intensity $>10\%$ (except decisive ones) are listed. Elemental analyses were performed with a C, H, N, S, O Thermoquest apparatus.

### 3.2. Ligand 1f

**3.2.1. Synthesis of 1f.** *n*-BuLi (1.7 mL of a 1.6 M solution in hexanes, 2.9 mmol) was added dropwise at room temperature to a stirred solution of 9,9-dimethylxantene (200 mg, 0.9 mmol) and TMEDA (360 µL, 2.3 mmol) in heptane (6 mL). After stirring for 15 h, neat chlorodi-*t*-butylphosphine (3 mmol) was added dropwise and the reaction mixture was stirred at 60 °C for 24 h. The solvent was removed in vacuo and the resulting beige residue was dissolved in $CH_2Cl_2$ (10 mL). The resulting solution was washed with water, dried over $MgSO_4$ and concentrated to dryness. The resulting oil was then washed with petroleum ether and crystallized from *n*-propyl alcohol to afford the desired diphosphine **1f** as air-stable crystals (170 mg, 0.34 mmol, 38%). White crystals, mp 155–156 °C (*n*-propyl alcohol). $^1H$ NMR (250 MHz): $\delta$ 1.21–1.26 (m, 36H), 1.57 (s, 6H), 7.02 (t, $J=7.6$ Hz, 2H), 7.38 (dd, $J=7.6$, 1.5 Hz, 2H), 7.60 (d, $J=7.6$ Hz, 2H). $^{13}C$ NMR (100.63 MHz): $\delta$ 30.8 (m), 31.1, 32.7 (m), 35.0, 121.5, 125.5 (m), 126.6 (m), 130.7 (m), 133.7, 155.8 (m). $^{31}P$ NMR (101.3 MHz): $\delta$ 12.4. Anal Calcd for $C_{31}H_{48}OP_2$, C: 74.65, H: 9.71. Found: C: 74.71, H: 9.63.

**3.2.2. Crystal structure determination of 1f.** Single crystals of ligand **1f** suitable for X-ray crystallographic analysis were obtained by slow evaporation of *n*-propyl alcohol solution. X-ray diffraction experiments for monocrystal of **1f** were performed at 293.2 K with graphite-monochromatized Mo $K_\alpha$ radiation on an Enraf-Nonius CAD-4 diffractometer. Formula $C_{31}H_{48}OP_2$, formula weight 498, crystal system triclinic, space group $P^{-1}$ (no 2), $a=12.477(4)$ Å, $b=12.550(4)$ Å, $c=12.934(3)$ Å, $\alpha=117.00(2)°$, $\beta=92.82(4)°$, $\gamma=116.98(3)°$, $V=1523.(1)$ Å$^3$, $Z=2$, $\rho_{calcd}=1.087$ g/cm$^3$, $\mu=1.430$ mm$^{-1}$, $R=0.046$, $wR=0.056$. Selected bond lengths (Å) and angles (deg): P1–C4 1.847(2), P1–C13 1.882(3), P1–C17 1.901(2), P2–C5 1.850(2), P2–C21 1.892(2), P2–C25 1.881(2), O1–C4a 1.378(2), O1–C10a 1.378(2), C4–P1–C13 100.6(1), C4–P1–C17 105.7(1), C13–P1–C17 111.4(1), C5–P2–C21 105.3(1), C5–P2–C25 100.2(1), C21–P2–C25 111.1(1), C4a–O1–C10a 120.6(2). Data reduction: TEXSAN (Molecular Structure Corporation). Program(s) used to solve structure: SIR92. Program(s) used to refine structure: TEXSAN. Software used to prepare material for publication: TEXSAN. Crystallographic data for compound **1f** have been deposited at the Cambridge Crystallographic Data Centre, CCDC No 255820. Copies of this information may be obtained free of charge from The Director, CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (+44 1223

336408; e-mail: deposit@ccdc.cam.ac.uk or http://www.ccdc.cam.ac.uk).

### 3.3. Typical experimental procedure for cross-coupling

In a Schlenk tube were charged successively $K_2CO_3$ (74 mg, 0.5 mmol) and degassed xylene (2 mL). After purging with $N_2$ using 3 evacuate-fill cycles, the slurry was cooled to 0 °C and the thiol (1 mmol) was added dropwise. The resulting mixture was then allowed to warm to room temperature and stirred for 1 h. To a Schlenk tube were placed successively the aryl substrate (0.8 mmol), $Pd_2(dba)_3$ (0.08 mmol), Xantphos **1e** (0.09 mmol) and degassed xylene (10 mL). After purging with $N_2$ using 3 evacuate-fill cycles, the mixture was stirred at room temperature for 20 min and transferred via a cannula to the previously formed potassium thiolate. The dark solution was then purged with $N_2$ and heated to reflux for 24 h. After cooling to room temperature, the mixture was diluted with EtOAc (20 mL), washed with water (3×20 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was then purified by silica gel chromatography to afford the anticipated thioether **2**.

### 3.4. Spectral data of sulfides 2

**3.4.1. Butylsulfanylbenzene 2a (entries 1–3, Table 1).**[11e] Colorless oil. $^1$H NMR (250 MHz): $\delta$0.90 (t, $J$=7.4 Hz, 3H), 1.43 (sextet, $J$=7.4 Hz, 2H), 1.62 (quint, $J$=7.4 Hz, 2H), 2.90 (t, $J$=7.4, 2H), 7.12–7.33 (m, 5H, m). $^{13}$C NMR (62.9 MHz): $\delta$ 13.7, 22.0, 31.3, 33.3, 125.6, 128.7, 128.8, 137.1. MS (EI) *m/z* (relative intensity) 166 (M+, 46), 123 (28), 110 (100), 45 (38), 41 (53), 39 (478).

**3.4.2. 4-Butylsulfanylphenyl methanesulfonate 2b (entry 4, Table 1).** White solid, mp 54 °C. $^1$H NMR (250 MHz): $\delta$ 0.93 (t, $J$=7.2 Hz, 3H), 1.44 (sextet, $J$=7.2 Hz, 2H), 1.61 (quint, $J$=7.2 Hz, 2H), 2.92 (t, $J$=7.2 Hz, 2H), 3.13 (s, 3H), 7.17–7.35 (m, 4H). $^{13}$C NMR (62.9 MHz): $\delta$ 13.7, 22.1, 31.2, 33.6, 37.5, 122.6, 130.1, 137.0, 147.2. MS (EI) *m/z* (relative intensity) 260 (M+, 44), 181 (100), 125 (97), 57 (72). HRMS (EI) *m/z* 260.0499 (Calcd for $C_{11}H_{16}O_3S_2$ 260.0541).

**3.4.3. 4-Butylsulfanylphenyl 4-methylbenzenesulfonate 2c (entry 5, Table 1).** Yellowish oil. $^1$H NMR (250 MHz): $\delta$ 0.90 (t, $J$=7.2 Hz, 3H), 1.49 (sextet, $J$=7.2 Hz, 2H), 1.59 (quint, $J$=7.2 Hz, 2H), 2.42 (s, 3H), 2.87 (t, $J$=7.2 Hz, 2H), 6.84–6.91 (m, 2H), 7.15–7.20 (m, 2H), 7.27–7.31 (m, 2H), 7.66–7.70 (m, 2H). $^{13}$C NMR (62.9 MHz): $\delta$ 13.6, 21.7, 21.9, 31.0, 33.3, 122.8, 128.5, 129.4, 129.5, 132.3, 136.4, 145.5, 147.5. MS (EI) *m/z* (relative intensity) 336 (M+, 55), 181 (100), 125 (33), 91 (15). HRMS (EI) *m/z* 336.0820 (Calcd for $C_{17}H_{20}O_3S_2$ 336.0854).

**3.4.4. 1-(Butylsulfanyl)-4-fluorobenzene 2d (entry 6, Table 1).**[22a] Colorless oil. $^1$H NMR (250 MHz): $\delta$0.90 (t, $J$=7.2 Hz, 3H), 1.37–1.62 (m, 4H), 2.85 (t, $J$=7.2 Hz, 2H), 6.93–7.00 (m, 2H), 7.24–7.35 (m, 2H). $^{13}$C NMR (62.9 MHz): $\delta$13.5, 21.7, 31.2, 34.6, 115.8 (d, $J_{CF}$= 21.4 Hz), 131.9 (d, $J_{CF}$=3.1 Hz), 132.0 (d, $J_{CF}$=7.5 Hz), 161.6 (d, $J_{CF}$=245.3 Hz). $^{19}$F NMR (235.3 MHz): $\delta$−116.6. MS (EI) *m/z* (relative intensity) 184 (M+, 41), 128 (100), 83 (29), 45 (44).

**3.4.5. 1-(Butylsulfanyl)-4-trifluoromethylbenzene 2e (entry 7, Table 1).**[22b] Due to contamination with di-*n*-butyl disulfide and difficult separation of both products, the mixture was subjected to oxidation with *m*-CPBA. Spectral data of the sulfone **3** derived from sulfide **2e** thus obtained.

*1-(Butylsulfonyl)-4-trifluoromethylbenzene* **3**. White solid, mp 40 °C. $^1$H NMR (250 MHz): $\delta$0.91 (t, $J$=7.3 Hz, 3H), 1.42 (sextet, $J$=7.3 Hz, 2H), 1.64–1.77 (m, 2H), 3.09–3.16 (m, 2H), 7.75–7.79 (m, 2H), 7.97–8.00 (m, 2H). $^{13}$C NMR (62.9 MHz): $\delta$13.5, 21.6, 24.6, 56.1, 123.2 (q, $J_{CF}$= 270.4 Hz), 126.5 (q, $J_{CF}$=3.8 Hz), 128.9, 135.4 (q, $J_{CF}$= 33.3 Hz), 142.9. $^{19}$F NMR (235.3 MHz): $\delta$−63.6. MS (EI) *m/z* (relative intensity) 267 (MH+, 1), 145 (26), 57 (100), 56 (37). HRMS (EI) *m/z* 266.0629 (Calcd for $C_{11}H_{13}F_3O_2S$ 266.0588).

**3.4.6. 1-(1,1-Dimethylethyl)-4-propylsulfanylbenzene 2f (entry 8, Table 1).**[22c] Yellowish oil. $^1$H NMR (250 MHz): $\delta$1.01 (t, $J$=7.3 Hz, 3H), 1.29 (s, 9H), 1.65 (sextet, $J$= 7.3 Hz, 2H), 2.86 (t, $J$=7.3 Hz, 2H), 7.25–7.31 (m, 4H). $^{13}$C NMR (62.9 MHz): $\delta$ 13.5, 22.8, 31.4, 34.5, 36.2, 126.0, 129.4, 133.4, 149.0. MS (EI) *m/z* (relative intensity) 209 (MH+, 49), 208 (89), 195 (40), 194 (80), 193 (100), 149 (34), 45 (54), 43 (95).

**3.4.7. 1-Ethylsulfanyl-4-(1,1-dimethylethyl)benzene 2g (entry 9, Table 1).**[22d] Colorless oil. $^1$H NMR (250 MHz): $\delta$1.30 two signals overlapping (t, $J$=7.3 Hz, 3H) and (s, 9H), 2.92 (q, $J$=7.3 Hz, 2H), 7.25–7.35 (m, 4H). $^{13}$C NMR (62.9 MHz): $\delta$14.7, 28.2, 31.4, 34.6, 126.0, 129.5, 133.1, 149.3. MS (EI) *m/z* (relative intensity) 194 (M+, 27), 179 (100), 151 (38), 116 (31), 77 (35).

**3.4.8. 1-(1,1-Dimethylethyl)-4-methylsulfanylbenzene 2h (entry 10, Table 1).**[22e] White solid, mp 30–31 °C. $^1$H NMR (250 MHz): $\delta$1.29 (s, 9H), 2.45 (s, 3H), 7.18–7.33 (m, 4H). $^{13}$C NMR (62.9 MHz): $\delta$16.2, 31.2, 34.3, 125.8, 126.8, 134.8, 148.3. MS (EI) *m/z* (relative intensity) 180 (M+, ·99), 165 (100), 150 (22), 137 (46), 117 (24), 45 (22).

**3.4.9. (Phenylmethylsulfanyl)benzene 2i (entry 11, Table 1).**[16] White solid, mp 41–41.5 °C. $^1$H NMR (250 MHz): $\delta$3.98 (s, 2H), 7.00–7.22 (m, 10H). $^{13}$C NMR (100 MHz): $\delta$39.48, 126.76, 127.59, 128.90, 129.25, 130.26, 136.80, 137.89. MS (EI) *m/z* (relative intensity) 200 (M+, 100), 51 (50).

**3.4.10. 3-Phenylsulfanylpropanoic acid ethyl ester 2j (entry 12, Table 2).**[22f] Colorless oil. $^1$H NMR (250 MHz): $\delta$1.24 (t, $J$=7.1 Hz, 3H), 2.61 (t, $J$=7.4 Hz, 2H), 3.16 (t, $J$=7.4 Hz, 2H), 4.13 (q, $J$=7.1 Hz, 2H), 7.16–7.38 (m, 5H). $^{13}$C NMR (62.9 MHz): $\delta$14.2, 29.1, 34.5, 60.7, 126.5, 129.0, 130.1, 135.4, 171.7. IR (NaCl, cm$^{-1}$) 1732 (C=O). MS (EI) *m/z* (relative intensity) 210 (M+, 77), 196 (35), 137 (100), 135 (30), 123 (32), 109 (25).

**3.4.11. 1-Cyclohexylsulfanyl-4-(1,1-dimethylethyl)-benzene 2k (entry 13, Table 1).**[11b] Colorless oil. $^1$H NMR (250 MHz): $\delta$1.22–1.34 (m, 5H), 1.29 signal

overlapping with the previous multiplet (s, 9H), 1.54–1.62 (m, 1H), 1.74–1.78 (m, 2H), 1.90–1.99 (m, 2H), 2.99–3.09 (m, 1H), 7.26–7.35 (m, 4H). $^{13}$C NMR (62.9 MHz): δ25.9, 26.1, 31.4, 33.5, 34.5, 46.9, 125.8, 131.9, 132.2, 149.9. MS (EI) *m/z* (relative intensity) 248 (M+, 25), 166 (42), 151 (100), 122 (40), 90 (33), 55 (96).

**3.4.12. 1-(1,1-Dimethylethyl)-4-(1-methylpropylsulfanyl)benzene 2l (entry 14, Table 1).** Colorless oil. $^1$H NMR (250 MHz): δ 1.01 (t, *J*=7.4 Hz, 3H), 1.25 (d, *J*=6.7 Hz, 3H), 1.31 (s, 9H), 1.42–1.72 (m, 2H), 3.10 (sextet, *J*=6.7 Hz, 1H), 7.27–7.32 (m, 4H). $^{13}$C NMR (62.9 MHz): δ 11.6, 20.7, 29.6, 31.4, 34.6, 45.2, 125.8, 131.9, 132.2, 150.0. MS (EI) *m/z* (relative intensity) 222 (M+, 100), 207 (49), 166 (70), 151 (28). HRMS (EI) *m/z* 222.1368 (Calcd for $C_{14}H_{22}S$ 222.1442). Anal Calcd for $C_{14}H_{22}S$, C: 75.61, H: 9.97, S: 14.42. Found: C: 75.57, H: 9.86, S: 14.77.

**3.4.13. (*exo*)-2-Phenylsulfanylbornane 2m (entry 15, Table 1).** Orange oil. $^1$H NMR (250 MHz): δ 0.77 (s, 3H), 0.94 and 0.95 (2 s, 3H each), 1.12–1.16 (m, 2H), 1.30 (s, 9H), 1.60–1.80 (m, 3H), 1.95–2.05 (m, 2H), 3.15–3.30 (m, 1H), 7.26–7.30 (m, 4H). $^{13}$C NMR (62.9 MHz): δ 14.0, 20.2, 20.5, 27.8, 31.4, 34.4, 38.5, 41.2, 45.9, 47.5, 49.8, 56.7, 125.8, 129.4, 135.8, 148.8. MS (EI) *m/z* (relative intensity) 302 (M+, 14), 137 (66), 95 (26), 81 (100). HRMS (EI) *m/z* 302.2082 (Calcd for $C_{20}H_{30}S$ 302.2068).

**3.4.14. 1,1-Dimethylethylsulfanylbenzene 2n (entry 16, Table 1).**[6a] Colorless oil. $^1$H NMR (250 MHz): δ1.29 (s, 9H), 7.31–7.55 (m, 5H). $^{13}$C NMR (62.9 MHz): δ31.1, 45.9, 128.6, 128.8, 132.9, 137.6. MS (EI) *m/z* (relative intensity) 166 (M+, 34), 110 (100), 109 (36), 65 (28), 57 (75).

**3.4.15. Phenylsulfanylbenzene 2p (entries 1 and 2, Table 2).**[11e] Colorless oil. $^1$H NMR (250 MHz): δ7.31–7.48 (m, 10H). $^{13}$C NMR (62.9 MHz): δ126.9, 129.1, 130.9, 135.7. MS (EI) *m/z* (relative intensity) 186 (M+, 100), 77 (24), 65 (25), 51 (57).

**3.4.16. 2-Phenylsulfanylnaphthalene 2q (entry 3, Table 2).**[22g] White solid, mp 50 °C. $^1$H NMR (250 MHz): δ7.22–7.46 (m, 8H), 7.71–7.82 (m, 4H). $^{13}$C NMR (62.9 MHz): δ 126.7, 127.0, 127.5, 127.9, 128.2, 129.2, 129.3, 129.7, 130.4, 131.4, 132.8, 133.5, 134.3, 136.3. MS (EI) *m/z* (relative intensity) 236 (M+, 100), 235 (67), 234 (48), 118 (27).

**3.4.17. 2-Phenylsulfanylbenzoic acid methyl ester 2r (entry 4, Table 2).**[11e] White solid, mp 46–47.5 °C. $^1$H NMR (250 MHz): δ3.93 (s, 3H), 6.81 (d, *J*=8.0 Hz, 1H), 7.13 (t, *J*=7.2 Hz, 1H), 7.21 (dt, *J*=8.0, 1.6 Hz, 1H), 7.39–7.42 (m, 3H), 7.53–7.57 (m, 2H), 7.97 (dd, *J*=8.0, 1.6 Hz, 1H). $^{13}$C NMR (62.9 MHz): δ52.1, 124.3, 126.8, 127.4, 129.0, 129.7, 131.0, 132.3, 132.6, 135.5, 143.1, 166.8. IR (KBr, $cm^{-1}$) 1716 (C=O). MS (EI) *m/z* (relative intensity) 244 (M+, 73), 200 (100), 50 (93).

**3.4.18. 1-Methoxy-2-phenylsulfanylbenzene 2s (entry 5, Table 2).**[11e] Colorless oil. $^1$H NMR (250 MHz): δ3.85 (s, 3H), 6.82–6.90 (m, 2H), 7.06–7.10 (m, 1H), 7.19–7.37 (m, 6H, m). $^{13}$C NMR (62.9 MHz): δ56.0, 111.0, 121.3, 124.2, 127.1, 128.4, 129.2, 131.5, 131.7, 134.6, 157.4. MS (EI) *m/z* (relative intensity) 216 (M+, 100), 201 (11).

**3.4.19. 2-Phenylsulfanylbenzonitrile 2t (entry 6, Table 2).**[11c] White solid, mp 39–40 °C. $^1$H NMR (250 MHz): δ7.14–7.21 (m, 2H), 7.33–7.52 (m, 7H). $^{13}$C NMR (62.9 MHz): δ108.8, 118.8, 127.4, 129.8, 130.0, 130.9, 132.4, 134.6, 145.8. IR (KBr, $cm^{-1}$) 2224 (C≡N). MS (EI) *m/z* (relative intensity) 211 (M+, 100), 210 (70), 51 (25).

**3.4.20. 1-[1-(*N*,*N*-Dimethylaminoethyl)]-2-phenylsulfanylbenzene 2u (entry 7, Table 2).** Brown oil. $^1$H NMR (250 MHz): δ 1.28 (d, *J*=6.6 Hz, 3H), 2.20 (s, 6H), 3.93 (q, *J*=6.6 Hz, 1H), 7.14–7.29 (m, 9H), 7.54–7.58 (m, 1H). $^{13}$C NMR (62.9 MHz): δ 19.7, 43.4, 62.0, 126.6, 127.4, 127.6, 128.1, 129.2, 130.4, 133.4, 134.0, 137.4, 146.9. MS (EI) *m/z* (relative intensity) 257 (M+, 28), 242 (100), 72 (68). HRMS (EI) *m/z* 257.1288 (Calcd for $C_{16}H_{19}NS$ 257.1238).

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# Total synthesis of cimiracemate B and analogs

Fabienne Fache,* Nicolas Suzan and Olivier Piva*

*Université Claude Bernard Lyon I, UMR CNRS 5181, Laboratoire de Chimie Organique, Photochimie et Synthèse, Bât. Raulin, 43 bd du 11 novembre 1918, 69622 Villeurbanne cedex, France*

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**Abstract**—The synthesis of the biologically active cimiracemate B and some analogs is described. The key step of the synthesis is a coupling between a bromoketone and a cinnamic acid derivative.

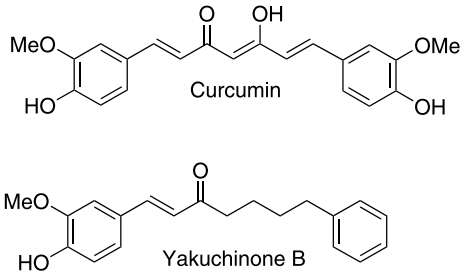

## 1. Introduction

Naturally occurring compounds possessing a 1,7-diaryl skeleton have been widely described and present significant biological activities[1] (Fig. 1).

For example, curcumin, a natural pigment isolated from *Curcuma longa* has been reported to inhibit growth of several types of malignant cells[2] and more particularly in the case of HIV infection.[3] Yakuchinone B extracted[4] from the seeds of *Alpina oxyphylla* is active against hypercholesterolemia and atherosclerosis.[5] Cimiracemates, phenylpropanoic acid esters isolated[6] from the rhizome of *Cimifuga racemosa* are used in traditional medicine to treat menopausal symptoms[7] and inflammation.[8] Recent studies[9] have shown that they could have additional health benefits as reactive oxygen species scavengers. Nevertheless, they are produced in very few amounts as they represented, respectively, 0.001% for cimiracemate A and 0.0006% for cimiracemate B of the dry weight of the methanolic extract.[9] Therefore, to go further in the search for other potential biological activities, reasonable amount of these products need to be synthesized. To our knowledge, the total synthesis of cimiracemates has not been reported to date. Only one synthesis[10] of petasiphenol, an anti mutagen compound isolated from *Petasites japonicum* (Fig. 1) with a structure close to cimiracemate B was described in 1992. We report herein a straightforward access to cimiracemate B and analogs starting from inexpensive commercial eugenol and different cinnamic acids bearing hydroxy- or methoxy groups on various positions on the aromatic ring.

## 2. Results and discussion

Two retrosyntheses have been considered (Fig. 2). The first was based on the obvious esterification of a cinnamic acid **1** with an appropriate primary alcohol **2**, the second required a coupling between the carboxylate salt of the same acid **1** with a compound bearing a good leaving group typically a tosylate or a bromide (**3**) which could be activated by the presence of a suitable keto group in α-position.



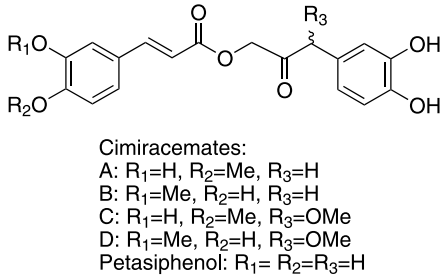




**Figure 1.** Some natural diaryl biologically active molecules.

*Keywords*: Phenylpropanoic acid; *Cimifuga racemosa*; Cimiracemate B; Synthesis.
* Corresponding authors. Tel.: +33 472 44 85 21; fax: 33 472 44 81 36; e-mail addresses: fache@univ-lyon1.fr; piva@univ-lyon1.fr

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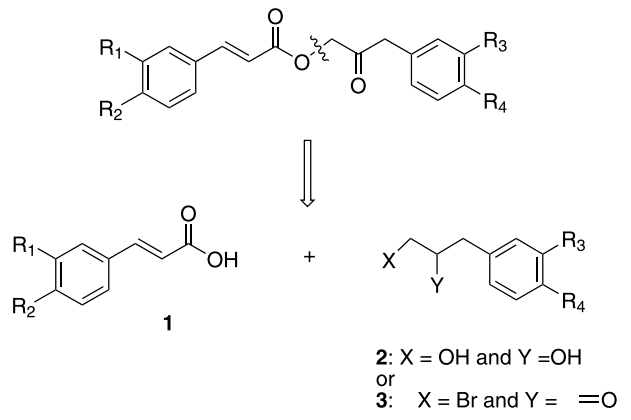


**Figure 2.** Retrosynthetic analysis.

To have a rapid access to the target molecule, a direct esterification of the α,β-unsaturated acid **1** with the primary hydroxyl group of diol **2** was first investigated. Dihydroxylation of silylated eugenol **5a** afforded the corresponding diol **2a** in an acceptable yield. However, coupling of this compound with cinnamic acid **1d** under DCC activation gave very disappointing results. The reaction led to a complex mixture of mono- and diester without control of the regioselectivity. Therefore, we explored an alternative strategy based on the coupling between a bromoketone and a carboxylate. By this way, the moderate nucleophilicity of the carboxylic group could be balanced by the activation of the leaving group of the bromoketone.

Commercially available eugenol **4a** was converted into catechol **4b** by treatment with *n*-$Bu_4NI$ and $BCl_3$ as described by Brooks et al.[11] This reaction was stopped before complete conversion (50%) but afforded the expected catechol as the only new and easily isolated compound (40%). Unfortunately, the direct hydroxybromation of both phenols **4a** and **4b** led to a complex mixture of products and low yields of the expected bromohydrins. Therefore, these compounds were protected as TBDMS ethers, which were expected to resist to moderate acidic conditions. While Fukami et al.[10] used during the synthesis of petasiphenol the ring opening of an epoxide by HBr to obtain the corresponding bromohydrin, we chose alternatively the direct hydroxybromation promoted by NBS in aqueous DMSO[12] which seems more suitable to avoid the cleavage of the protecting groups of **5a** and **5b** (Fig. 3). Dess Martin oxidation[13] delivered ketones **3a** and **3b** in acceptable yields while oxidation with PCC, PDC or Swern conditions were less efficient. The coupling between acids **1a–d** and ketones **3a** or **3b** was achieved under phase transfer catalysis and led to the protected cimiracemate analogs **9a–g** in good yields. Finally, deprotection of the silylethers was not a trivial step. The classically used *n*$Bu_4NF$ method led in our case to complex mixtures and low isolated yields. This surprising reactivity could be due to the presence of the ketone which could easily be deprotonated by this reagent.[14] Aqueous HF in acetonitrile was more efficient. The low to moderate isolated yields (10–45%) obtained could be attributed to the great affinity of polyphenols **10a–g** for water.

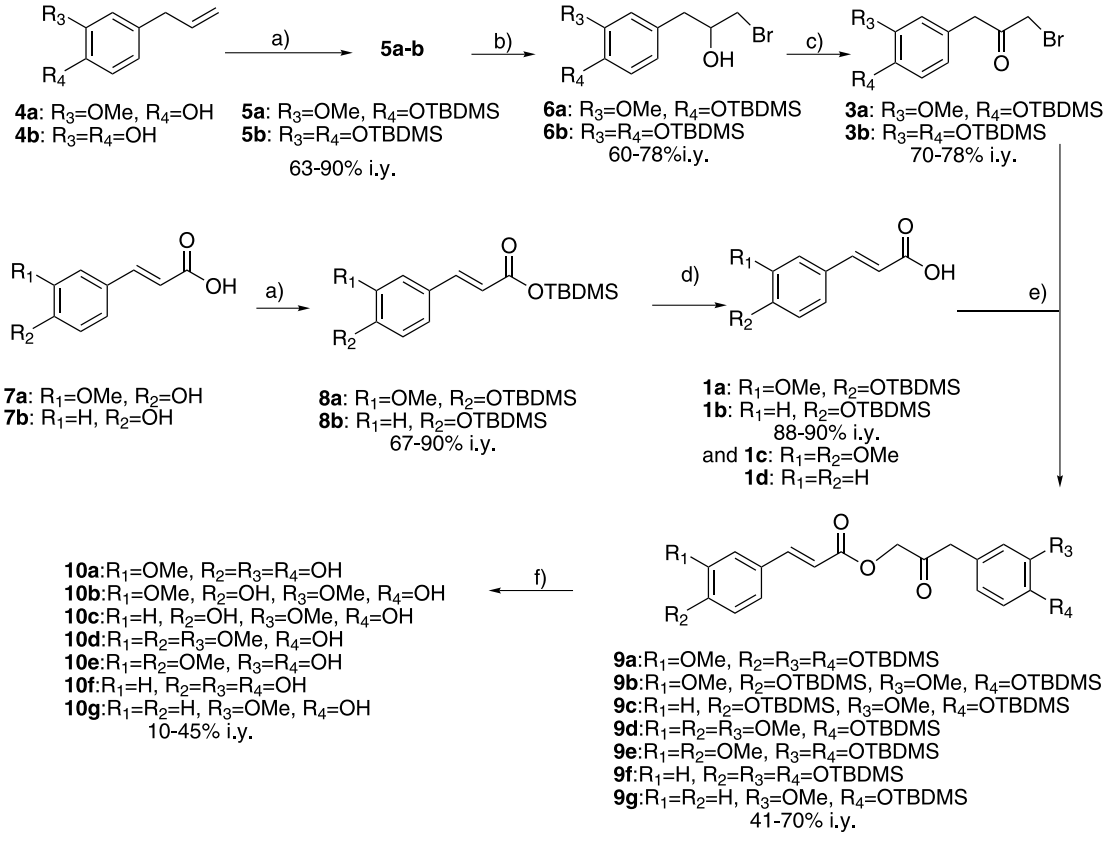


**Figure 3.** (a) TBDMSCl, imidazole, DMAP, $CH_2Cl_2$ (b) NBS, $H_2O$, DMSO, 0 °C (c) Dess–Martin oxidation (d) THF, MeOH, $K_2CO_3$ (e) *n*-$Bu_4NBr$, toluene, $NaOH_{aq}$ (f) at 0 °C $HF_{aq}$, $CH_3CN$, then NaOH.

## 3. Conclusion

In conclusion, we have described in this paper a simple and straightforward synthesis of cimiracemate B and some analogs. The possibility of varying the substituents on both reagents makes this approach general. These new products will be tested widely and some works are already in progress in that perspective with the Chimiothèque Nationale of the CNRS.

## 4. Experimental

### 4.1. General

Melting points were measured with a Büchi melting point apparatus. IR spectra were recorded on a Perkin Elmer 'spectrum one' spectrometer. NMR spectra were recorded on a Bruker AC 300 spectrometer. Mass spectra were recorded on a Finigan-MAT 95 XL instrument. Column chromatography was carried out with silica gel 60 A 40–63 μm (SDS). Analytical thin layer chromatography was performed on Merck Kieselgel 60F254 0.25 mm thickness plates.

### 4.2. General procedure for the silylation[15] of phenol derivatives with *t*-butyldimethylsilyl chloride (TBDMSCl)

Under nitrogen, to a stirred solution of phenol derivative (1 equiv/OH), imidazole (1.1 equiv/OH) and DMAP (0.15 equiv/OH) in $CH_2Cl_2$ (6.5 M) were added at 0 °C 1.1 equiv/OH of TBDMSCl. The solution was allowed to return to room temperature and was stirred until the reaction was finished. After addition of $NH_4Cl$, the reaction mixture was extracted three times with $CH_2Cl_2$ and dried over $MgSO_4$. The organic phase was concentrated and the residue purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate 9:1) to give the desired protected phenol.

**4.2.1. Protected eugenol 5a.** According to the general procedure from **4a**: isolated yield 90%; colourless oil[16]; IR (neat) 2930, 1514, 1260, 1155, 1126, 1041, 889, 840 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 0.21 (s, 6H), 1.06 (s, 9H), 3.37 (d, $J=6.4$ Hz, 2H), 3.83 (s, 3H), 5.09 (m, 1H), 5.13 (m, 1H), 6.01 (m, 1H), 6.70 (m, 2H), 6.82 (d, $J=7.9$ Hz, 1H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ −4.17 ($CH_3$–Si), 19.8 (C), 26.2 ($CH_3$), 40.4 ($CH_2$), 55.9 ($OCH_3$), 113.1 (*CH*=$CH_2$), 115.9 (CH=*$CH_2$*), 121.1 (CH), 121.2 (CH), 133.9 (C), 138.3 (CH), 143.7 (C), 151.2 (C).

**4.2.2. 4-Propenyl-catechol 4b.** Under nitrogen,[11] to a stirred solution of eugenol **4a** (0.5 g, 3.05 mmol) in 9 mL of dry $CH_2Cl_2$ was added anhydrous $nBu_4NI$ (1.24 g, 3.35 mmol). Then at 5 °C, 3.35 mL of $BCl_3$ in $CH_2Cl_2$ (1 M) were added. The reaction mixture stood for 2 h stirring at 5 °C and then was hydrolyzed by 10 mL of iced water. After 15 min, a saturated aqueous solution of $NaHCO_3$ was added and the extraction was performed with $CH_2Cl_2$. After drying of the organic phase with $MgSO_4$, filtration and evaporation of $CH_2Cl_2$, the crude product was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate 3:1) to give the bisphenol **4b** (183 mg, 1.22 mmol, 40% isolated yield) as an oil.[17] 40% of the starting material were recovered.

$^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 3.27 (d, $J=6.9$ Hz, 2H), 5.06 (m, 2H), 5.56 (m, OH), 5.94 (m, 1H), 6.71 (m, 3H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 39.9 ($CH_2$), 115.7 (*CH*=$CH_2$), 115.9 (CH=*$CH_2$*), 116.1 (CH), 121.3 (CH), 133.6 (C), 138.1 (CH), 142.1 (C), 143.9 (C).

**4.2.3. 3-(3,4-Di-*t*-butyldimethylsilyloxy)phenyl propene 5b.** According to the general procedure from **4b**: isolated yield 63%; colourless oil; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 0.18 (s, 12H), 0.98 (s, 18H), 3.25 (d, $J=6.4$ Hz, 2H), 5.01 (m, 1H), 5.05 (m, 1H), 5.92 (m, 1H), 6.64 (m, 2H), 6.74 (d, $J=7.9$ Hz, 1H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ −3.7 ($CH_3$–Si), 18.8 (C), 26.3 ($CH_3$), 39.8 ($CH_2$), 115.7 (CH=*$CH_2$*), 121.2 (CH), 121.7 (CH), 121.8 (CH), 133.4 (C), 138.2 (CH), 145.4 (C), 150.0 (C).

In the case of acid phenol derivatives, the presence of the acid function has to be taken into account to evaluate the quantities of imidazole, DMAP and TBDMSCl.

**4.2.4. Protected 3-methoxy-4-hydroxycinnamic acid 8a.** According to the general procedure from **7a**: isolated yield 90%; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 0.17 (s, 6H), 0.32 (s, 6H), 0.99 (s, 18H), 3.84 (s, 3H), 6.27 (d, $J=15.5$ Hz, 1H), 6.92 (m, 3H), 7.55 (d, $J=15.5$ Hz, 1H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ −4.2 ($CH_3$–Si), 18.2 (C), 18.9 (C), 26.0 ($CH_3$), 55.8 ($OCH_3$), 111.2 (CH), 118.12 (CH), 121.4 (CH), 122.7 (CH), 128.7 (C), 145.6 (CH), 147.9 (C), 151.6 (C), 167.5 (C=O).

**4.2.5. Protected coumaric acid 8b.** According to the general procedure from **7b**: isolated yield 67%;[18] $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 0.22 (s, 6H), 0.32 (s, 6H), 0.98 (s, 18H), 6.27 (d, $J=15.5$ Hz, 1H), 6.84 (d, $J=8.5$ Hz, 2H), 7.40 (d, $J=8.5$ Hz, 2H), 7.57 (d, $J=15.5$ Hz, 1H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$: −4.3 and −4.0 ($CH_3$–Si), 18.1 and 18.6 (C), 25.96 and 26.04 ($CH_3$), 118.1 (CH), 120.8 (CH), 128.1 (C), 130.0 (CH), 145.2 (CH), 158.1 (C), 167.6 (C=O).

### 4.3. General procedure for the bromohydrin synthesis[12]

To a stirred solution of alkene in $H_2O$ (2 equiv)/DMSO: 5/95 was added at 0 °C 1.1 equiv of freshly recrystallized NBS. The reaction was monitored by TLC. At the end of the reaction, the mixture was hydrolyzed with $NaHCO_3$ (10%), extracted with $Et_2O$ and dried over $MgSO_4$. After filtration and concentration, the crude product was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate 85:15) to give the desired bromohydrin as an oil.

Some deprotection of the silylether was noticed and the corresponding bromohydrin was also isolated. It could be also silylated to improve the isolated yields of **5** and **6**.

**4.3.1. 1-Bromo-2-hydroxy-3-(3-methoxy-4-*t*-butyldimethylsilyloxy)phenyl propane 6a.** According to the general procedure from **5a**: 78% isolated yield; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 0.14 (s, 6H), 0.99 (s, 9H), 2.83

(d, $J=6.6$ Hz, 2H), 3.38 (dd, $J=10.5$ Hz, $J=6$ Hz, 1H), 3.49 (dd, $J=10.5$ Hz, $J=4.1$ Hz, 1H), 3.79 (s, 3H), 3.99 (m, 1H), 6.70 (m, 2H), 6.78 (d, $J=7.9$ Hz, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$: −4.2 ($CH_3$–Si), 18.8 (C), 26.1 ($CH_3$), 39.5 ($CH_2$), 41.5 ($CH_2$), 55.9 ($CH_3$), 72.2 (CH), 113.6 (CH), 121.4 (CH), 121.9 (CH), 130.6 (C), 144.3 (C), 151.4 (C).

**4.3.2. 1-Bromo-2-hydroxy-3-(3,4-di-*t*-butyldimethylsilyloxy)phenyl propane 6b.** According to the general procedure from **5b**: 60% isolated yield; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 0.21 (s, 12H), 1.00 (s, 18H), 2.80 (t, $J=6$ Hz, 2H), 3.38 (dd, $J=10.5$ Hz, $J=6$ Hz, 1H), 3.49 (dd, $J=10.5$ Hz, $J=4.1$ Hz, 1H), 3.96 (m, 1H), 6.70 (m, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$: −3.7 ($CH_3$–Si), 18.8 (C), 26.3 ($CH_3$), 39.4 ($CH_2$), 41.1 ($CH_2$), 72.2 (CH), 121.5 (CH), 122.5 (CH), 130.1 (C), 146.2 (C), 147.2 (C).

### 4.4. Dess–Martin oxidation[13]

To a solution of alcohol (1 equiv) in $CH_2Cl_2$ (0.2 M) was added 1.1 equiv of the commercial Dess–Martin reagent in $CH_2Cl_2$ (15%). The reaction mixture was stirred at room temperature under argon for 15 h. Then, $Et_2O$ and NaOH (1.3 M) were added and the organic phase was washed with water, dried other $MgSO_4$, filtered and concentrated. After flash column chromatography on silica gel (petroleum ether/ethyl acetate 85:15) the pure ketone was obtained.

**4.4.1. 1-Bromo-2-keto-3-(3-methoxy-4-*t*-butyldimethylsilyloxy)phenyl propane 3a.** According to the general procedure from **6a**: 78% isolated yield; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$: 0.16 (s, 6H), 1.00 (s, 9H), 3.80 (s, 3H), 3.83 (s, 2H), 3.91 (s, 2H) 6.75 (m, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$: −4.2 ($CH_3$–Si), 18.8 (C), 26.0 ($CH_3$), 47.1 ($CH_2$), 47.9 ($CH_2$), 55.9 ($CH_3$), 113.5 (CH), 121.5 (CH), 122.2 (CH), 126.4 (C), 144.9 (C), 151.6 (C), 200.5 (C=O).

**4.4.2. 1-Bromo-2-keto-3-(3,4-di-*t*-butyldimethylsilyloxy)phenyl propane 3b.** According to the general procedure from **6b**: 70% isolated yield; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$: 0.21 (s, 12H), 1.00 (s, 18H), 3.81 (s, 2H), 3.90 (s, 2H), 6.71 (m, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$: −3.7 ($CH_3$–Si), 18.8 (C), 26.3 ($CH_3$), 33.6 ($CH_2$), 46.6 ($CH_2$), 121.7 (CH), 122.6 (CH), 122.7 (CH), 126.4 (C), 146.8 (C), 147.5 (C); 200.0 (C=O).

### 4.5. Saponification of the silylester[19]

To a solution of silyl ester in THF (4.5 mL/mmol)/MeOH (12.7 mL/mmol) was added drop wise at room temperature, 0.003 equiv of an aqueous solution of $K_2CO_3$ (0.7 mmol/L). After 30 min, the organic solvents were evaporated. $Et_2O$ and saturated solution of NaCl were added. At 0 °C, the aqueous phase was acidified with HCl 10% to pH 6 and extracted with $Et_2O$. After drying of the organic phase with $MgSO_4$, filtration and evaporation of ether, the product was recovered quantitatively and used in the following step without further purification.

**4.5.1. 3-Methoxy-4-*t*-butyldimethylsilyloxy-cinnamic acid 1a.** According to the general procedure from **8a**: isolated yield 90%; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$: 0.18 (s, 6H), 1.0 (s, 9H), 3.84 (s, 3H), 6.31 (d, $J=15.8$ Hz, 1H), 6.86 (d, $J=8.4$ Hz, 1H), 7.05 (m, 2H), 7.72 (d, $J=15.8$ Hz, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$: −4.2 ($CH_3$–Si), 18.9 (C), 26.0 ($CH_3$), 55.8 ($OCH_3$), 111.4 (CH), 115.3 (CH), 121.5 (CH), 123.1 (CH), 128.3 (C), 147.6 (C), 148.4 (CH), 151.6 (C), 173.0 (C=O).

**4.5.2. 4-*O*-*t*-Butyldimethylsilylcoumaric acid 1b.** According to the general procedure from **8b**: isolated yield 88%[20]; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$: 0.22 (s, 6H), 0.99 (s, 9H), 6.29 (d, $J=15.8$ Hz, 1H), 6.86 (d, $J=8.4$ Hz, 2H), 7.45 (d, $J=8.4$ Hz, 2H), 7.74 (d, $J=15.8$ Hz, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$: −4.0 ($CH_3$–Si), 18.6 (C), 26.0 ($CH_3$), 115.1 (CH), 120.9 (CH), 127.7 (C), 130.4 (CH), 147.1 (CH), 158.6 (C), 172.8 (C=O).

### 4.6. Coupling reaction

The acid was dissolved in an aqueous solution of NaOH (0.19 M, 1.2 equiv) and added to a solution of bromoketone in toluene (1 equiv, 0.16 M) and $NBu_4Br$ (0.5 equiv). The reaction mixture was stirred at room temperature for 12–24 h. After extraction with toluene–water, the organic phase was dried with $MgSO_4$, concentrated and purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate 8:2).

**4.6.1. Synthesis of 9a.** According to the general procedure from **1a** and **3b**: isolated yield 57%; oil; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$: 0.18 (s, 12H), 0.2 (s, 6H), 1.00 (s, 27H), 3.64 (s, 2H), 3.84 (s, 3H), 4.68 (s, 2H), 6.38 (d, $J=15.8$ Hz, 1H), 6.67–7.03 (m, 6H), 7.66 (d, $J=15.8$ Hz, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$: −4.2 and −3.7 ($CH_3$–Si), 18.8 (C), 26.01 and 26.03 ($CH_3$), 46.7 ($CH_2$), 55.8 ($OCH_3$), 67.7 ($CH_2$), 111.3 (CH), 115.5 (CH), 121.5 (CH), 121.6 (CH), 122.4 (CH), 122.7 (CH), 123.1 (CH), 126.3 (C), 128.4 (C), 146.8 (CH), 147.7 (C), 148.2 (C), 151.6 (C), 169.7(C=O), 202.5(C=O).

**4.6.2. Synthesis of 9b.** According to the general procedure from **1a** and **3a**: isolated yield 51%; oil; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 0.16 (s, 6H), 0.19 (s, 6H), 1.00 (s, 9H), 1.01 (s, 9H), 3.71 (s, 2H), 3.81 (s, 3H), 3.85 (s, 3H), 4.82 (s, 2H), 6.39 (d, $J=15.8$ Hz, 1H), 6.69–7.26 (m, 6H), 7.70 (d, $J=15.8$ Hz, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$: −4.23 and −4.19 ($CH_3$–Si), 18.8 (C), 26.04 and 26.10 ($CH_3$), 46.7 ($CH_2$), 55.8 ($OCH_3$), 67.7 ($CH_2$), 111.3 (CH), 113.5 (CH), 114.8 (CH), 121.5 (CH), 122.2 (CH), 122.9 (CH), 126.5 (C), 128.4 (C), 144.8 (C), 146.7 (CH), 148.2 (C), 151.6 (C), 166.7 (C=O), 202.5 (C=O).

**4.6.3. Synthesis of 9c.** According to the general procedure from **1b** and **3a**: isolated yield 62%; oil; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$: 0.15 (s, 6H), 0.22 (s, 6H), 0.99 (s, 18H), 3.70 (s, 2H), 3.78 (s, 3H), 4.80 (s, 2H), 6.37 (d, $J=15.9$ Hz, 1H), 6.7–6.85 (m, 5H), 7.43 (d, $J=8.5$ Hz, 1H), 7.69 (d, $J=15.9$ Hz, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$: −4.2 and −4.0 ($CH_3$–Si), 18.6 and 18.8 (C), 26.0 and 26.1 ($CH_3$), 46.6 ($CH_2$), 55.8 ($OCH_3$), 67.8 ($CH_2$), 113.5 (CH), 114.8 (CH), 120.9 (CH), 121.5 (CH), 122.2 (CH), 126.5 (C), 130.3 (CH), 144.8 (C), 146.3 (C), 151.5 (C), 158.5 (C), 166.7 (C=O), 202.5 (C=O).

**4.6.4. Synthesis of 9d.** According to the general procedure

from **1c** and **3a**: isolated yield 41%; oil; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$: 0.16 (s, 6H), 1.01 (s, 9H), 3.72 (s, 2H), 3.81 (s, 3H), 3.93 (s, 6H), 4.83 (s, 2H), 6.40 (d, $J$=15.5 Hz, 1H), 6.69–7.18 (m, 6H), 7.70 (d, $J$=15.5 Hz, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$: −4.2 ($CH_3$–Si), 18.8 (C), 26.1 ($CH_3$), 46.7 ($CH_2$), 55.9, 56.3 and 56.4 ($OCH_3$), 67.7 ($CH_2$), 110.0, 111.4, 114.8, 121.5, 122.2 and 123.3 (CH), 126.5 (C), 127.5 (C), 146.5 (CH), 151.6 (C), 151.8 (C=O), 202.4 (C=O).

**4.6.5. Synthesis of 9e.** According to the general procedure from **1c** and **3b**: this product turned out to be very unstable and therefore was immediately engaged in the following step without purification to give **10e** after deprotection.

**4.6.6. Synthesis of 9f.** According to the general procedure from **1b** and **3b**: isolated yield 66%; oil; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$: 0.17 (s, 6H), 0.18 (s, 6H), 0.2 (s, 6H), 0.97 (s, 27H), 3.63 (s, 2H), 4.76 (s, 2H), 6.36 (d, $J$=15.8 Hz, 1H), 6.63–6.89 (m, 5H), 7.41 (d, $J$=8.4 Hz, 2H), 7.68 (d, $J$=15.8 Hz, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$: −3.9 and −3.7 ($CH_3$–Si), 18.6 and 18.8 (C), 26.0 and 26.3 ($CH_3$), 46.4 ($CH_2$), 67.7 ($CH_2$), 114.8 (CH), 120.9 (CH), 121.7 (CH), 122.7 (CH), 126.2 (C), 127.9 (C), 130.2 (CH), 146.3 (CH), 146.7 (C), 147.4 (C), 166.7 (C), 175.7 (C), 202.4 (C=O).

**4.6.7. Synthesis of 9g.** According to the general procedure from **1d** and **3a**: isolated yield 70%; oil; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$: 0.15 (s, 6H), 1.00 (s, 9H), 3.71 (s, 2H), 3.79 (s, 3H), 4.82 (s, 2H), 6.52 (d, $J$=15.8 Hz, 1H), 6.68 (m, 2H), 6.85 (d, $J$=8.4 Hz, 1H), 7.39 (m, 3H), 7.53 (m, 2H), 7.76 (d, $J$=15.8 Hz, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$: −4.2 ($CH_3$–Si), 18.8 (C), 26.1 ($CH_3$), 46.7 ($CH_2$), 55.9 ($OCH_3$), 67.8 ($CH_2$), 113.5, 117.2, 121.5, 122.2 and 128.6 (CH), 129.3 (C), 131.0 (CH), 146.6 (CH), 150.0 (C), 151.6 (C), 166.4 (C=O), 202.3 (C=O).

### 4.7. Deprotection of the silyl ethers[20]

To a diluted solution of silyl ether in acetonitrile (0.2 M) was added carefully aqueous HF (48–51%) (two volumes of $CH_3CN$ for one volume $HF_{aq}$). The solution was stirred at room temperature for 30 min and then aqueous NaOH (8%) was added. The organic phase was extracted with $CH_2Cl_2$, dried over $MgSO_4$, concentrated and the crude product was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate 1:1).

**4.7.1. Synthesis of cimiracemate B 10a.**[6] According to the general procedure from **9a**: isolated yield 10%; $^1$H NMR (300 MHz, $CD_3OD$) $\delta$: 3.69 (s, 2H), 3.90 (s, 3H), 4.87 (s, 2H), 6.43 (d, $J$=15.8 Hz, 1H), 6.60–6.84 (m, 4H), 7.08–7.21 (m, 2H), 7.66 (d, $J$=15.8 Hz, 1H); $^{13}$C NMR (75 MHz, $CD_3OD$) $\delta$: 46.6 ($CH_2$), 56.7 ($CH_3$), 68.8 ($CH_2$), 112.1, 114.8, 116.2, 116.8, 117.9, 122.3 and 124.3 (CH), 124.6, 126.3, 127.9, 128.1 and 145.9 (C), 146.8 (CH), 147.2, 148.0, 149.7and 151.1 (C), 168.6 (C=O), 204.9 (C=O); CI-LRMS $m/z$ 359 ($M+H^{+\cdot}$), 313, 235, 217, 195 (100), 177, 167; CI-HRMS calcd for $C_{19}H_{19}O_7$ ($M+H^{+\cdot}$) 359.1131, found 359.1133.

**4.7.2. Synthesis of 10b.** According to the general procedure from **9b**: isolated yield 32%; mp=113–115 °C; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$: 3.66 (s, 2H), 3.81 (s, 3H), 3.85 (s, 3H), 4.80 (s, 2H), 6.32 (d, $J$=15.8 Hz, 1H), 6.67–7.03 (m, 6H), 7.63 (d, $J$=15.8 Hz, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$: 46.3 ($CH_2$), 56.1 ($OCH_3$), 67.7 ($CH_2$), 109.8, 112.1, 114.1, 115.0, 115.1, 122.5, 123.6, 124.7 (CH), 126.8 and 145.2 (C), 146.6 (CH), 147.1 and 148.6 (C), 166.7 (C=O), 202.5 (C=O); CI-LRMS $m/z$ 373 ($M+H^{+\cdot}$), 372 ($M^{+\cdot}$), 195, 177; CI-HRMS calcd for $C_{20}H_{21}O_7$ ($M+H^{+\cdot}$) 373.1287, found 373.1288.

**4.7.3. Synthesis of 10c.** According to the general procedure from **9c**: isolated yield 26%; mp=99–100 °C; $^1$H NMR (300 MHz, $CDCl_3+CD_3OD$) $\delta$: 3.64 (s, 2H), 3.78 (s, 3H), 4.75 (s, 2H), 6.27 (d, $J$=15.8 Hz, 1H), 6.63–6.78 (m, 5H), 7.34 (d, $J$=8.5 Hz, 1H), 7.64 (d, $J$=15.8 Hz, 1H); $^{13}$C NMR (75 MHz, $CDCl_3+CD_3OD$) $\delta$: 46.2 ($CH_2$), 56.0 ($OCH_3$), 67.6 ($CH_2$), 112.3, 113.2, 115.2, 116.1, 122.4 and 124.5 (CH), 126.0, 130.4 and 145.3 (C), 146.8 (CH), 147.4 and 159.7 (C), 167.1 (C=O), 203.1 (C=O); EI-LRMS $m/z$ 342 ($M^{+\cdot}$), 205, 147, 137; EI-HRMS calcd for $C_{19}H_{18}O_6$ ($M^{+\cdot}$) 342.1103, found 342.1105.

**4.7.4. Synthesis of 10d.** According to the general procedure from **9d**: isolated yield 45% (oil); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$: 3.71 (s, 2H), 3.86 (s, 3H),3.91 (s, 6H), 4.84 (s, 2H), 6.40 (d, $J$=15.8 Hz, 1H), 6.72–6.88 (m, 4H), 7.10 (m, 2H), 7.7 (d, $J$=15.8 Hz, 1H); $^{13}$C NMR (75 MHz, $CDCl_3+CD_3OD$) $\delta$: 46.24 ($CH_2$), 56.3 ($CH_3$), 67.8 ($CH_2$), 110.1, 111.4, 112.2, 114.7, 115.1, 122.7 and 123.4 (CH), 124.9, 127.5 and 145.4 (C), 146.6 (CH), 147.2, 149.6 and 151.8 (C), 166.7 (C=O), 202.6 (C=O); EI-LRMS $m/z$ 386 ($M^{+\cdot}$), 249, 208, 191(100), 163, 137; EI-HRMS calcd for $C_{21}H_{22}O_7$ ($M^{+\cdot}$) 386.1365, found 386.1369.

**4.7.5. Synthesis of 10e.** According to the general procedure from **9e** (see above): isolated yield 12% in two steps; $^1$H NMR (300 MHz, $CDCl_3+CD_3OD$) $\delta$: 3.40 (s, 2H), 3.66 (s, 6H), 4.59 (s, 2H), 6.14 (d, $J$=15.8 Hz, 1H), 6.33–6.91 (m, 6H), 7.46 (d, $J$=15.8 Hz, 1H); $^{13}$C NMR (75 MHz, $CDCl_3+CD_3OD$) $\delta$: 46.2 ($CH_2$), 57.6 ($OCH_3$), 62.3 ($CH_2$), 111.6, 112.8, 115.8, 117.2, 118.0, 122.6 (CH), 124.7, 125.9, 128.8, 145.8 and 146.7 (C),148.0 (CH), 150.8 (C=O), 204.9 (C=O); CI-LRMS $m/z$ 373 ($M+H^{+\cdot}$), 355, 209 (100), 191, 165; CI-HRMS calcd for $C_{20}H_{21}O_7$ ($M+H^{+\cdot}$) 373.1287, found 373.1285.

**4.7.6. Synthesis of 10f.** According to the general procedure from **9f**: isolated yield 30%; mp=172–177 °C; $^1$H NMR (300 MHz, $CDCl_3+CD_3OD$) $\delta$: 3.59 (s, 2H), 3.78 (s, 3H), 4.76 (s, 2H), 6.28 (d, $J$=15.8 Hz, 1H), 6.53–6.80 (m, 5H), 7.36 (m, 2H), 7.62 (d, $J$=15.8 Hz, 1H); $^{13}$C NMR (75 MHz, $CDCl_3+CD_3OD$) $\delta$: 46.0 ($CH_2$), 67.5 ($CH_2$), 113.1, 115.6, 115.9, 116.3 and 121.2 (CH), 124.5 and 125.8 (C), 130.3 (CH), 144.2 and 145.0(C), 146.7 (CH), 159.8 (C), 167.2 (C=O), 203.4 (C=O); CI-LRMS $m/z$ 329 ($M+H^{+\cdot}$), 183, 165, 147; CI-HRMS calcd for $C_{18}H_{17}O_6$ ($M+H^{+\cdot}$) 329.1025, found 329.1025.

**4.7.7. Synthesis of 10g.** According to the general procedure from **9g**: isolated yield 44%; $P_F$ $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 3.64 (s, 2H), 3.88 (s, 3H), 4.83 (s, 2H), 6.52 (d, $J$=15.9 Hz, 1H), 6.74 (m, 2H), 6.87 (m, 1H), 7.41 (m, 3H), 7.53

(m, 2H), 7.76 (d, $J=15.8$ Hz, 1H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 46.5 ($CH_2$), 56.3 ($OCH_3$), 67.9 ($CH_2$), 112.1, 113.7, 115.1, 117.1, 122.7 (CH), 124.9 (C), 128.6, 129.3 and 131.0 (CH), 134.5 and 145.4 (C), 146.7 (CH), 147.2, 166.5 (C=O), 202.4 (C=O); EI-LRMS *m/z* 326 ($M^{+\cdot}$), EI-HRMS calcd for $C_{19}H_{18}O_5$ ($M^{+\cdot}$) 326.1154, found 326.1161.

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# Organozinc alkoxide-promoted aldol-Tishchenko reaction of aliphatic aldehydes: an expedient entry to prepare the α-methylene ketones

Yung-Son Hon[a,b,*] and Chun-Ping Chang[a]

[a]*Department of Chemistry and Biochemistry, National Chung Cheng University, Chia-Yi 621, Taiwan, ROC*
[b]*Institute of Chemistry, Academia Sinica, Nankang, Taipei 115, Taiwan, ROC*

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**Abstract**—*i*-PrOZnEt is an excellent reagent to promote the aldol-Tishchenko reaction of the aliphatic aldehydes tethered with other labile functional groups. The 1,3-diol monoesters **4** were formed as the major products, which could be converted to α-methylene ketones **7** in two steps in good yields.


## 1. Introduction

For enolizable aldehydes, both aldol addition and Tishchenko reaction are two major possible pathways. For the aldol addition, the presence of only basic sites in the catalysts is sufficient, whereas for the Tishchenko reaction, the presence of both acidic sites and basic sites in the catalysts is required. Interestingly, sequential aldol-Tishchenko reaction can become competing if the catalyst first, accomplishes the aldol reaction, which is followed by Tishchenko esterification by the Lewis acidic nature of the same catalyst. In many cases, traditional Tishchenko[1] and aldol-Tishchenko reactions[2] are competing with each other.[3] However, sequential aldol-Tishchenko reaction can become competing if the catalyst is sufficiently basic, such as a basic metal hydroxide catalyst.[4,5] Some other catalysts, such as metal alkoxides of monofunctional alcohols,[3a,6] simple metal hydroxides.[6] Lithium monoalcoholate of 1,3-diol,[7] $LiWO_2$,[8] $Cp^*2Sm(thf)_2$,[9] polynuclear carbonyl ferrate,[10] and arylmagnesium halide in HMPT[11] have also been used. The aldol-Tishchenko reaction of the aldehyde gives 1,3-diol monoesters from the trimerization of the aldehyde. Trimerization of isobutyraldehyde to 2,2,4-trimethylpentane-1,3-diol mono-isobutyrates, which are the most common coalescing agents, for example, in latex paints,[12] has been industrialized since, 1988 by use of binary metal oxide BaO–CaO.[13]

We found that the aliphatic aldehyde **1a** reacted with a catalytic amount of diisobutylaluminium hydride (Dibal-H) in pentane to give ester **2a** in good to excellent yields via a Tishchenko reaction intermediate **A** in which an intramolecular hydride shift took place. The aluminium alkoxide **B** formed in the reaction reacted with aldehyde **1a** to establish the catalytic reaction cycle (Fig. 1).[14] This observation provokes us to investigate the influence of the metal ions on the metal alkoxides-promoted Tishchenko reactions. Interestingly, we found that the change of the metal ion of the alkoxide **B** will switch the reaction pathway from Tishchenko reaction to aldol-Tishchenko reaction. Herein, we wish to report the results of our studies on the homogeneous aldol-Tishchenko reaction promoted by magnesium and zinc alkoxides. The further synthetic

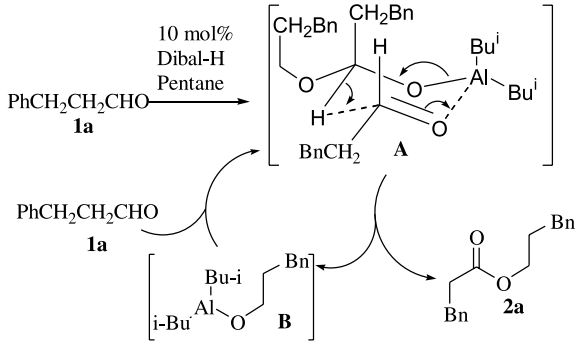


**Figure 1.** The plausible mechanism for the reaction of aldehyde **1a** with catalytic amount of Dibal-H to give the corresponding ester **2a**.

*Keywords*: Organozinc alkoxide; Aldol-Tishchenko reaction; Tishchenko reaction; 1,3-Diol monoester; α-Methylene ketones.
* Corresponding author. Tel.: +886 5 2720411x6412; fax: +886 5 2721040; e-mail: cheysh@ccu.edu.tw

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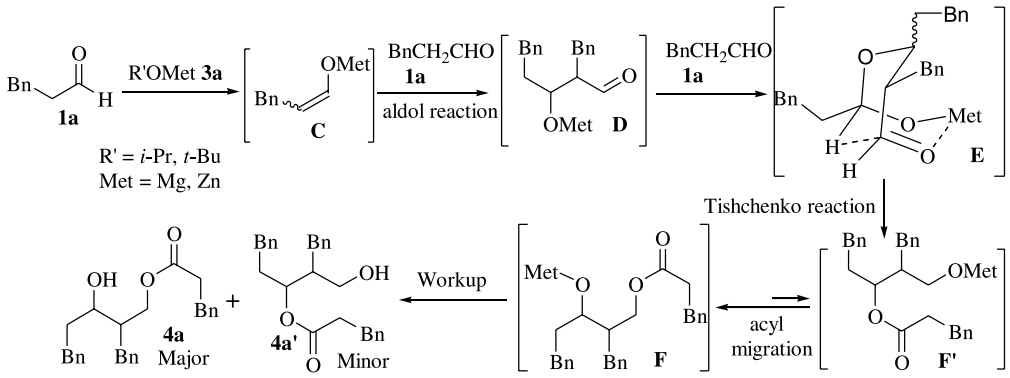



**Figure 2.** The proposed aldol-Tishchenko reaction mechanism for the formation of compounds **4a** and **4a′** from 3-phenylpropanal (**1a**) promoted by metal alkoxides.

applications of their products in the synthesis of the α-methylene ketones will also be discussed.

## 2. Results and discussions

### 2.1. The reaction pathway is metal ion-dependent in the reactions of aliphatic aldehydes with metal alkoxides

A solution of 0.1 mol equiv of $Ph(CH_2)_3OMgCl$ (**3a**), prepared from equal mol of the 3-phenylpropyl alcohol with MeMgCl in THF at 0 °C, was added dropwise in 5 min to 3-phenylpropanal (**1a**) in THF at 0 °C. After the addition, the reaction was stirred at ambient temperature for 12 h. We found that no Tishchenko reaction product **2a** was formed and a mixture of 1,3-diol monoesters **4a′** and **4a** were isolated as major products (Fig. 2). The formation of these two compounds was rationalized as follows. An aldol reaction of the aldehyde first takes place and the aldol reaction product **D** forms a hemiacetal-like intermediate **E** with the free aldehyde. The hemiacetal-like intermediate **E** reacts to give the 1,3-diol monoester **4a′** via a Tishchenko reaction in which an intramolecular hydride shift takes place. The monoester intermediate **F′** is equilibrated with **F** via an acyl group migration (Fig. 2). Each of compounds **4a′** and **4a** contain two chiral centers. All these possible isomers are too close in polarity to be separated by silica gel column chromatography. In addition, it is very difficult to determine their ratio and identify, which is the major isomer from the 400 MHz $^1$H NMR spectrum of the mixtures.

In order to find an optimal condition for the aldol-Tishchenko reaction, we tried to employ different kinds of metal alkoxides. We chose *i*-propanol or *tert*-butanol as reagents to generate the corresponding alkoxide based on their basicity, steric factor and readily availability. The metal alkoxides were generated from the reaction of alcohols with phenylmagnesium chloride (2.0 M solution in THF) or diethylzinc (1.0 M solution in hexanes) at 0 °C in THF. A solution of the metal alkoxide in THF was added dropwise in 5 min to 3-phenylpropanal (**1a**) in THF at 0 °C. After the addition, the reaction was stirred at ambient temperature. A mixture of the 1,3-diol monoesters **4a′** and **4a** were obtained and their yield was shown in Table 1.

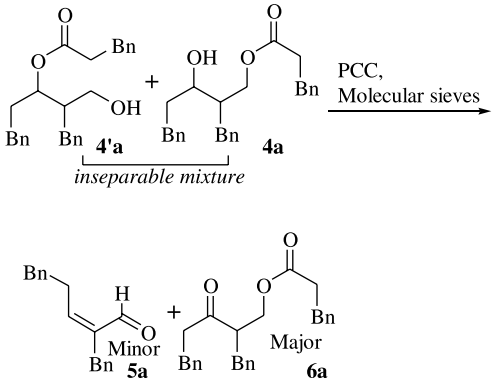
**Table 1**. The effect of the metal alkoxide on the aldol-Tishchenko reaction of the 3-phenylpropanal (**1a**) at 0 °C

| Entry | Base | Mol equiv | Time (h) | **4a** +**4a′** (%) |
|---|---|---|---|---|
| 1 | *i*-PrOMgCl | 0.33 | 12 | 81 |
| 2 | *i*-PrOMgCl | 0.17 | 12 | 75 |
| 3 | *t*-BuOMgCl | 0.33 | 4 | 73 |
| 4 | *t*-BuOMgCl | 0.17 | 5 | 61 |
| 5 | *i*-PrOZnEt | 0.33 | 12 | 91 |
| 6 | *i*-PrOZnEt | 0.17 | 12 | 73 |

When *i*-PrOMgCl (0.33 mol equiv) was used as the promoter to react with aldehyde **1a** at 0 °C, a mixture of the aldol-Tishchenko products **4a** and **4a′** were isolated in 81% yield (entry 1, Table 1). When the mol equiv of *i*-PrOMgCl was dropped to 0.17, the chemical yield of the aldol-Tishchenko products was slightly dropped to 75% (entry 2). When *t*-BuOMgCl (0.33 mol equiv) was used as the promoter, we isolated the aldol-Tishchenko products **4a** and **4a′** in 73% yield (entry 3). When the mol equiv of *t*-BuOMgCl was dropped to 0.17, the chemical yield of the aldol-Tishchenko products was decreased slightly to 61% (entry 4). Although the chemical yields are not improved by using *t*-BuOMgCl, their reaction times are shorter. When *i*-PrOZnEt (0.33 mol equiv) was used as the promoter, we isolated the aldol-Tishchenko products in 91% yield (entry 5). When the mol equiv of *i*-PrOZnEt was dropped to 0.17, the chemical yield of the aldol-Tishchenko products was decreased slightly to 73% (entry 6). The results of Table 1 indicate that *i*-PrOZnEt is an excellent reagent to promote the aldol-Tishchenko reaction from aliphatic aldehydes. The yield is high and the potential side reactions are minimized when 0.33 mol equiv of this reagent was used (entry 5). This conclusion is rationalized as follows. The Lewis acidity of the metal ion is responsible to the formation of the intermediate **E** in Figure 2. As for the Lewis acidity, zinc ion is stronger than that of magnesium ion. The zinc ion may be the better promoter to generate the hemiacetal intermediate **E** (Met=Zn) from the β-alkoxyaldehyde **D** and aldehyde **1a**. According to the literature report, the trimerization of aliphatic aldehydes to 1,3-diol monoesters is also effected by some sorts of metal alkoxides and phenoxides such as $Ca(OEt)_2$,[3b] $Mg[Al(OEt)_4]_2$,[3b] PhOMgX,[11b] and $Me_3C_6H_2OMgX$.[11b] However, in these reactions, significant amounts of esters of the type $RCO_2CH_2R$ derived by a dismutation of aldehydes are usually produced as by-products, together with significant amounts of aldol-condensation products. In the present study, we do

not observe the above-mentioned side reactions when *i*-PrOZnEt was used. Therefore, we consider adapting the *i*-PrOZnEt as promoter to the aldol-Tishchenko reaction.

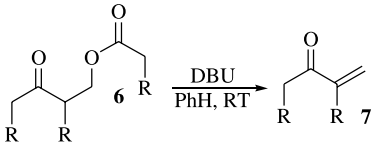
In order to evaluate the possibility of the further synthetic applications, the ratio of the aldol-Tishchenko products **4a** and **4a′** is an important factor. Unfortunately, due to the difficulty in separation and in analyzing the $^1$H NMR spectrum, we did not know the ratio of products **4a** and **4a′** in each cases of the Table 1. Therefore, we tried to use an indirect method to estimate their ratio based on the yields of their oxidized products. A mixture of the aldol-Tishchenko products obtained from entry 5 (Table 1) were treated with PCC in the presence of 4 Å molecular sieves to give α,β-unsaturated aldehyde **5a** in 8% yield and β-acyloxyketone **6a** in 84% yield. Compounds **5a** and **6a** were easily separated by simple silica gel column chromatography. The $^1$H NMR spectrum of the minor compound **5a** is identical to the one reported in the literature.[15] Presumably, the primary alcohol **4a′** was oxidized by PCC to give the corresponding β-acyloxyaldehyde, which then simultaneously underwent β-elimination to give the conjugated aldehyde **5a** (Eq. 1). Therefore, we can estimate the mole ratio of **4a′** and **4a** approximately about 1:10.5. In other words, we have demonstrated that the *i*-PrOZnEt is an excellent reagent to promote the aldol-Tishchenko reaction from aliphatic aldehyde **1a** and the predominant product is 1,3-diol monoester **4a**, which could be converted to β-acyloxyketone **6a** in excellent yield.




(1)

## 2.2. Organozinc isopropoxide-promoted aldol-Tishchenko reaction and its application to the formation of the corresponding α-methylene ketone

In our laboratory, we are interested in developing the methodology to prepare the α-methylene-aldehydes,[16] -ketones,[17] -esters,[18] -lactones[19] and its application in the total synthesis of the methylenolactocin.[20] There are several different methods to prepare the α-methylene ketone. The most general and useful one was the acid-catalyzed Mannich reaction of the appropriate saturated ketone **9**, formaldehyde, and secondary amine hydrochloride,[21] followed by thermal β-elimination from the Mannich base **8**[22] or the corresponding quaternary ammonium derivatives (Pathway A, Fig. 3).[23] Previously, we reported an one pot process to carry out the α-methylenation of the aryl alkyl ketones with a mixture of dibromomethane and diethylamine under microwave irradiation. The mannich base was formed as a transient intermediate before elimination.[17] Since, β-acyloxyketone **6** can be easily prepared from simple aldehdye **1** in two steps in high yield. We envisioned that the β-acyloxyketone **6** is a potential candidate to prepare α-methylene ketone **7** by the elimination reaction (Pathway B, Fig. 3). Furthermore, the eliminated by product, i.e., carboxylic acid **1′**, should be easily interconverted to the corresponding aldehyde **1**. We found that the β-acyloxyketone **6a** was treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in benzene at rt for 5 h to give the α-methylene ketone **7a** in 75% yield (R= –$CH_2$Ph, Eq. 2; entry 1, Table 2). Therefore, this proposed methodology to prepare the α-methylene ketone is completely different from the common approaches appeared in the literature.




(2)

*i*-PrOZnEt can also be applied to promote the aldol-Tishchenko reaction of the simple aliphatic aldehyde **1b** and aldehyde tethered with olefinic moieties (**1c** and **1d**) to give the corresponding 1,3-diol monoesters in good to excellent yields (entries 2–4). These 1,3-diol monoesters were oxidized by PCC followed by elimination with DBU to give the corresponding α-methylene ketones **7b–7d** in good yields (entries 2–4) In order to understand how general and versatile of our methodology in the aldol-Tshchenko reaction and in their further transformation to the α-methylene ketones, the starting aldehydes tethered with several different labile functionalities were employed. By similar reaction sequences, we were able to prepare the α-methylene ketones **7e** and **7f** tethered with methoxycarbonyl group (entries 5 and 6), **7g** and **7h** tethered with dimethylacetal group (entries 7 and 8), and **7i** tethered with

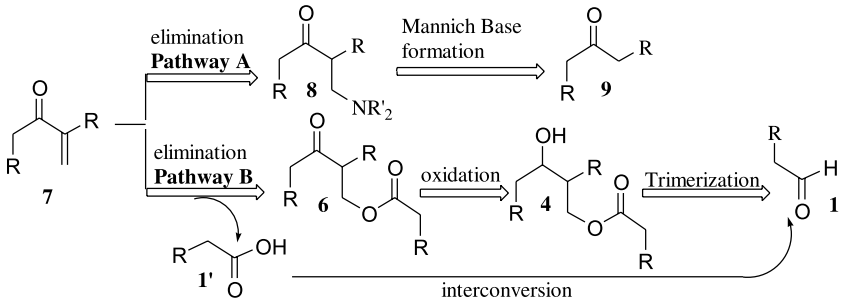
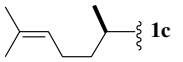
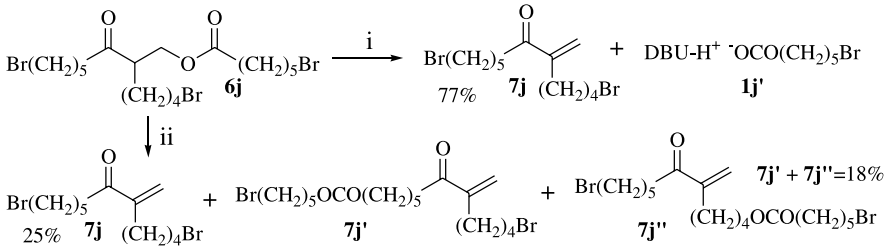



**Figure 3.** Retrosynthetic analysis of the preparation of the α-methylene ketone.

**Table 2**. *i*-PrOZnEt-promoted aldol-Tishchenko reaction of aldehydes, followed by oxidation with PCC and elimination with DBU

| Entry | $RCH_2CHO$ **1** R= | aldol-Tishchenko | | Oxidation | | Elimination | |
|---|---|---|---|---|---|---|---|
| | | Time (h) | Yields (%) | Time (h) | Yield (%) | Time (h) | Yield (%) |
| 1 | $PhCH_2$– **1a** | 18 | **4a′**+**4a** 91 | 6 | **6a** 84 | 5 | **7a** 75 |
| 2 | *n*-Pentyl- **1b** | 12 | **4b′**+**4b** 90 | 3 | **6b** 75 | 6 | **7b** 76 |
| 3 |  **1c** | 14 | **4c′**+**4c** 56 | 6 | **6c** 80 | 7 | **7c** 70 |
| 4 | $H_2C{=}CH(CH_2)_7$– **1d** | 18 | **4d′**+**4d** 84 | 5 | **6d** 80 | 10 | **7d** 71 |
| 5 | $MeO_2C(CH_2)_5$– **1e** | 24 | **4e′**+**4e** 68 | 8 | **6e** 91 | 10 | **7e** 75 |
| 6 | $MeO_2C(CH_2)_3$– **1f** | 24 | **4f′**+**4f** 50 | 12 | **6f** 56 | 8 | **7f** 80 |
| 7 | $(MeO)_2CH(CH_2)_5$– **1g** | 20 | **4g′**+**4g** 73 | 4 | **6g** 64 | 7 | **7g** 90 |
| 8 | $(MeO)_2CH(CH_2)_3$– **1h** | 22 | **4h′**+**4h** 72 | 4 | **6h** 62 | 10 | **7h** 92 |
| 9 | $MeCO(CH_2)_7$– **1i** | 15 | **4i′**+**4i** 50 | 8 | **6i** 85 | 10 | **7i** 80 |
| 10 | $Br(CH_2)_4$– **1j** | 20 | **4j′**+**4j** 87 | 12 | **6j** 70 | 12 | **7j** 77 |




**Scheme 1.** Reagents and conditions: (i) DBU, PhH, 0 °C to rt, 12 h; (ii) DBU, PhH, rt, 6 h.

acetyl group (entry 9) and **7j** tethered with bromo group (entry 10).

It is worthy to mention that the reaction temperature is crucial to the formation of the desired elimination product **7j** from compound **6j**. When the keto-ester **6j**, which was derived from the aldol-Tishchenko product of the 6-bromohexanal (**1j**), was treated with DBU at rt, the desired product **7j** was isolated in only 25% yield. We could also isolate an inseparable mixtures of ester–enone **7j′** and **7j″** in 18% yield (Scheme 1). The ratio of these two side products is 0.3:1 as estimated from their $^1$H NMR chemical shifts at $\delta$ 4.14 and 4.06 ppm. These two characteristic peaks are the absorption of the methylene groups adjacent to the carboxyl group (–$CH_2$OCOR) of compounds **7j′** and **7j″**. However, we do not know the exact structure of the major product. The formations of **7j′** and **7j″** may be rationalized as follows. Each one of the bromides in compound **7j** is replaced by 6-bromocarboxylate **1j′**, a product formed from the elimination of compound **6j** by DBU, at rt. Fortunately, these side products can be avoided by carrying out the elimination reaction at 0 °C and the α-methylene ketone **7j** was formed in 77% yield (entry 10).

## 3. Conclusions

We have demonstrated that *i*-PrOZnEt is an excellent reagent to promote the aldol-Tishchenko reaction of aliphatic aldehydes tethered with several functional groups. Both 1,3-diol monoesters **4** and **4′** were formed and the primary alkyl carboxylate **4** was formed as the major product. The ratio of **4** and **4′** in each case are approximately 10:1. The major isomer **4** can be used for the preparation of the α-methylene ketones **7** by treatment with DBU. Therefore, we have developed a new methodology to prepare the α-methylene ketones **7** from the simple aldehyde **1** via aldol-Tishchenko, oxidation and elimination sequences in good yields in three steps.

## 4. Experimental

All reactions were carried out under nitrogen. Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification. The $^1$H and $^{13}$C NMR spectra were recorded on a Bruker Avance DPX400 spectrometer, and chemical shifts were given in ppm downfield from tetramethylsilane (TMS). The $^1$H and $^{13}$C NMR spectra were recorded on a Bruker Avance DPX-400 and chemical shifts were given in ppm downfield from tetramethylsilane (TMS). IR spectra were taken with a Perkin–Elmer 682 spectrophotometer and only noteworthy absorption was listed. Mass spectra were measured on a VG-Trio-2000GC/MS spectrometer (National Chiao-Tung University) by electronic impact at 70 eV (unless otherwise indicated). High Resolution Mass Spectroscopy (HRMS) was measured on a Finnigan/Thermo Quest MAT 95XL (National Chung Hsing University) and FAB Mass spectra were recorded with 3-nitrobenzyl alcohol matrix using argon or xenon as the target gas. Aldehydes used in this study were either commercially available or prepared by the literature method. The undec-10-enal (**1d**),[24] 10-oxoundecanal (**1i**),[25] and 6-bromohexanal (**1j**)[16b] were prepared from their corresponding alcohols by PCC oxidation. 8-Oxooctanoic acid methyl ester (**1e**), 6-oxohexanoic acid methyl ester (**1f**), 8,8-dimethoxyoctanal (**1g**) and 6,6-dimethoxyhexanal (**1h**) were prepared according to the literature procedure from their corresponding cycloalkenes.[26]

### 4.1. General procedure to carry out the aldol-Tishchenko reaction of the aldehyde and the mixture of the reaction products were subsequently oxidized by PCC

*i*-PrOZnEt was obtained from the reaction of $Et_2Zn$ (1.0 M in hexane, 0.90 mL, 0.90 mmol) and isopropanol (0.07 mL, 0.90 mmol) in THF (3 mL) at rt for 5 min. To a solution of hydrocinnamaldehyde (**1a**) (603.8 mg, 4.5 mmol) in 10 mL of THF, *i*-PrOZnEt was added the dropwise at 0 °C in a period of 5 min. The reaction was warmed slowly to rt and stirred at this temperature for 12 h. The reaction is quenched with 1 N HCl and extracted with ethyl ether. The organic layer was dried over $MgSO_4$, concentrated, and chromatographed on silica gel column to give a mixture of the 1,3-diol monoesters **4a′** and **4a** (549.5 mg, 4.09 mmol) in 91% yield. To a mixture of the 1,3-diol monoesters **4a′** and **4a** (549.5 mg, 4.09 mmol) in 10 mL of $CH_2Cl_2$, PCC (pyridinium chlorochromate, 1102 mg, 5.11 mmol) and anhydrous 4 Å molecular sieves (500 mg) was added at 0 °C. The reaction was warmed slowly to rt and stirred at this temperature for 3 h. To the crude reaction mixture, ether was added and most of the chromium salts were precipitated out. After filtration, the filtrate was concentrated, and chromatographed on silica gel column to give the β-acyloxyketone **6a** (1372 mg, 3.43 mmol) in 84% yield as a colorless oil and α,β-unsaturated aldehyde **5a**[15] (82.5 mg, 0.33 mmol) in 8% yield.

**4.1.1. 3-Phenylpropionic acid 2-benzyl-3-oxo-5-phenylpentyl ester (6a).** TLC $R_f$=0.60 (hexane/EtOAc=10:1); $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 2.41–2.49 (m, 1H), 2.54–2.59 (m, 2H), 2.61–2.85 (m, 5H), 2.85–2.93 (m, 2H), 3.04–3.12 (m, 1H), 4.20 (d, $J$=6.5 Hz, 2H, –C$H_2$O$_2$C–), 7.06–7.29 (m, 15H, Ph-H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 29.1 (2°), 30.8 (2°), 34.8 (2°), 35.6 (2°), 45.4 (2°), 52.6 (3°), 64.3 (2°, –$C$H$_2$O$_2$C–), 126.0 (3°), 126.3 (3°), 126.7 (3°), 128.2 (3°), 128.3 (3°), 128.4 (3°), 128.5 (3°), 128.7 (3°), 128.8 (3°), 138.1 (4°), 140.2 (4°), 140.9 (4°), 172.4 (4°, –$C$O$_2$–), 210.2 (4°, –C=O); IR (KBr, neat): 3061, 3027, 2928, 1737, 1720, 1604, 1496, 1454, 1371, 1245, 1160, 1078, 1030, 749 cm$^{-1}$; MS *m*/*z* (relative intensity): 400 (M$^+$, 1), 250 (100), 91 (31); HRMS Calcd for $C_{27}H_{28}O_3$: 400.2038. Found: 400.2047.

**4.1.2. Heptanoic acid 3-oxo-2-pentylnonyl ester (6b).** Followed the general procedure to prepare the aldol-Tishchenko products (**4b′** and **4b**) from the aldehyde **1b** in 90% yield. According to the general procedure, the aldol-Tishchenko products (**4b′** and **4b**) were then oxidized by PCC to give compound **6b** in 75% yield as a colorless oil; TLC $R_f$=0.72 (hexane/EtOAc=10:1); $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 0.83–0.87 (m, 9H), 1.21–1.40 (m, 18H), 1.53–1.59 (m, 6H), 2.23 (t, $J$=7.6 Hz, 2H, –CO$_2$C$H_2$–), 2.42 (t, $J$=7.2 Hz, 2H, –C$H_2$), 2.80 (qu, $J$=6.8 Hz, 1H, –CHCO), 4.14 (d, $J$=6.8 Hz, 2H, AB system, –C$H_2$O$_2$C–); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 13.88 (1°), 13.93 (1°), 22.3 (2°), 22.4 (2°), 22.5 (2°), 23.3 (2°), 24.8 (2°), 26.7 (2°), 28.6 (2°), 28.7 (2°), 28.8 (2°), 31.4 (2°), 31.6 (2°), 31.8 (2°), 34.2 (2°), 43.0 (2°), 50.8 (3°), 64.5 (2°, –$C$H$_2$O$_2$C–), 173.4 (4°, C=O), 211.9 (4°, C=O); IR (KBr, neat): 2961, 2930, 2862, 1741 (C=O), 1720 (C=O), 1469, 1378, 1231, 1167, 1103 cm$^{-1}$; MS *m*/*z* (relative intensity): 340 (M$^+$, 1), 113 (100), 85 (31); HRMS Calcd for $C_{21}H_{40}O_3$: 340.2977. Found: 340.2969.

**4.1.3. 3,7-Dimethyloct-6-enoic acid 2-(1,5-dimethylhex-4-enyl)-5,9-dimethyl-3-oxodec-8-enyl ester (6c).** Followed the general procedure to prepare the aldol-Tishchenko products (**4c′** and **4c**) from the aldehyde **1c** in 56% yield. According to the general procedure, the aldol-Tishchenko products (**4c′** and **4c**) were then oxidized by PCC to give compound **6c** in 80% yield as a colorless oil; TLC $R_f$=0.78 (hexane/EtOAc=10:1); $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 0.85–0.91 (m, 9H, –CH$_3$), 1.15–1.34 (m, 6H, –CH$_2$), 1.58 (s, 6H, –CH$_3$), 1.60 (s, 3H, –CH$_3$), 1.67 (s, 6H, CH$_3$), 1.68 (s, 3H, CH$_3$), 1.88–2.07 (m, 10H), 2.21–2.27 (m, 2H, –CH$_2$), 2.39 (dd, $J$=16.7, 5.1 Hz, 1H), 2.72–2.76 (m, 1H, –CH), 4.21–4.26 (m, 2H, –C$H_2$O$_2$C–), 5.04–5.09 (m, 3H, –C$H$=C(CH$_3$)$_2$); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 15.9 (1°), 17.6 (1°), 17.6 (1°), 17.7 (1°), 19.5 (1°), 19.7 (1°), 25.4 (2°), 25.5 (2°), 25.6 (2°), 25.7 (1°), 28.3 (1°), 29.93 (1°), 29.98 (3°), 32.2 (3°), 35.1 (2°), 36.8 (2°), 37.0 (2°), 41.7 (2°), 50.6 (2°), 55.0 (3°), 62.0 (2°, –C$H_2$O$_2$C–), 123.8 (3°), 124.2 (3°), 124.3 (3°), 131.4 (4°, –C=$C$(CH$_3$)$_2$), 131.5 (4°, –C=$C$(CH$_3$)$_2$), 131.9 (4°, –C=$C$(CH$_3$)$_2$), 173.0 (4°, –$C$O$_2$), 210.8 (4°, –C=O); IR (KBr, neat): 2967, 2925, 2851, 1739, 1720, 1457, 1378, 1286, 1244, 1152, 986 cm$^{-1}$; MS *m*/*z* (relative intensity): 461 (M$^+$+1, 3), 272 (21), 290 (21), 109 (65); HRMS Calcd for $C_{30}H_{52}O_3$: 460.3916. Found: 460.3923.

**4.1.4. Undec-10-enoic acid 2-dec-9-enyl-3-oxotridec-12-enyl ester (6d).** Followed the general procedure to prepare the aldol-Tishchenko products (**4d′** and **4d**) from the aldehyde **1d** in 84% yield. According to the general procedure, the aldol-Tishchenko products (**4d′** and **4d**) were then oxidized by PCC to give compound **6d** in 80% yield as a colorless oil; TLC $R_f$=0.63 (hexane/EtOAc=10:1); $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 1.24–1.36 (m, 30H), 1.56–1.58 (m, 6H), 2.00 (pseudo q, $J$=6.6 Hz, 6H, CH$_2$=CHC$H_2$–), 2.22 (t, $J$=6.8 Hz, 2H, –CH), 2.41 (t, $J$=7.4 Hz, 2H), 2.79 (qu, $J$=6.9 Hz, 1H), 4.13 (d, $J$=6.8 Hz, 2H, –C$H_2$O$_2$C–), 4.88–4.97 (m, 6H, –CH=C$H_2$), 5.71–5.81 (m, 3H, –C$H$=CH$_2$); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 23.2 (2°), 24.8 (2°), 27.0 (2°), 28.5 (2°), 28.75 (2°), 28.80 (2°), 28.88 (2°), 28.96 (2°), 28.98 (2°), 29.00 (2°), 29.09 (2°), 29.10 (2°), 29.19 (2°), 29.23 (2°), 29.3 (2°), 29.5 (2°), 33.6 (2°), 33.7 (2°), 34.1 (2°), 42.9 (2°), 50.7 (3°), 64.5 (2°, –$C$H$_2$O$_2$C–), 114.0 (2°, –CH=$C$H$_2$), 114.1 (2°, –CH=$C$H$_2$), 138.9 (3°, –$C$H=CH$_2$), 139.0 (3°, –$C$H=CH$_2$), 173.3 (4°, –$C$O$_2$–), 211.7 (4°, –C=O); IR (KBr, neat): 3076, 2926, 2855, 1740, 1717, 1640, 1464, 1167, 994, 909 cm$^{-1}$; MS (FAB) *m*/*z* (relative intensity): 503 (M$^+$+1, 5), 319 (55), 149 (25); HRMS (FAB) Calcd for [M+H]$^+$ $C_{33}H_{59}O_3$: 503.4464. Found: 503.4453.

**4.1.5. 7-(7-Methoxycarbonylheptanoyloxymethyl)-8-oxopentadecanedioic acid dimethyl ester (6e).** Followed the general procedure to prepare the aldol-Tishchenko products (**4e′** and **4e**) from the aldehyde **1e** in 68% yield. According to the general procedure, the aldol-Tishchenko products (**4e′** and **4e**) were then oxidized by PCC to give compound **6e** in 91% yield as a colorless oil; TLC $R_f$=0.79 (hexane/EtOAc=1:1); $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 1.22–1.54 (m, 24H), 2.15–2.23 (m, 8H, –CH$_2$), 2.37 (t, $J$=7.2 Hz, 2H), 2.73 (qu, $J$=6.8 Hz, 1H, –CH), 3.57 (s, 9H, –OCH$_3$), 4.07 (d, $J$=6.8 Hz, 2H, –C$H_2$O$_2$C–); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 22.8 (2°), 24.3 (2°), 24.4 (2°), 24.45 (2°), 24.47

(2°), 26.5 (2°), 28.1 (2°), 28.43 (2°), 28.45 (2°), 28.53 (2°), 28.7 (2°), 28.8 (2°), 33.57 (2°), 33.65 (2°), 33.67 (2°), 33.8 (2°), 42.7 (2°), 50.5 (3°), 51.1 (1°), 51.2 (1°), 64.2 (2°, –$CH_2O_2C$–), 173.0 (4°, –C=O), 173.65 (4°, –$CO_2$), 173.74 (4°, –$CO_2$), 173.75 (4°, –$CO_2$), 211.2 (4°, –C=O); IR (KBr, neat): 2938, 2860, 1739, 1437, 1362, 1172, 1011, 879, 731 $cm^{-1}$; MS (FAB) *m/z* (relative intensity): 515 ($M^+ + 1$, 4), 307 (27), 154 (100), 137 (57); HRMS (FAB) Calcd for $[M+H]^+$ $C_{27}H_{47}O_9$: 515.3220. Found: 515.3228.

**4.1.6. 5-(5-Methoxycarbonylpentanoyloxymethyl)-6-oxoundecanedioic acid dimethyl ester (6f).** Followed the general procedure to prepare the aldol-Tishchenko products (**4f′** and **4f**) from the aldehyde **1f** in 50% yield. According to the general procedure, the aldol-Tishchenko products (**4f′** and **4f**) were then oxidized by PCC to give compound **6f** in 56% yield as a colorless oil; TLC $R_f$=0.50 (ether/hexane=2:1); $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 1.56–1.64 (m, 12H), 2.27–2.34 (m, 8H, –$CH_2$), 2.48–2.51 (m, 2H, –$CH_2$), 2.82 (qu, $J$=6.4 Hz, 1H, –CH), 3.67 (s, 9H, –$OCH_3$), 4.18 (d, $J$=6.3 Hz, 2H, –$CH_2O_2C$–); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 22.3 (2°), 22.6 (2°), 24.16 (2°), 24.20 (2°), 24.3 (2°), 27.8 (2°), 33.50 (2°), 33.58 (2°), 33.67 (2°), 33.70 (2°), 42.3 (2°), 50.5 (3°), 51.4 (1°, –$OCH_3$), 51.5 (1°, –$OCH_3$), 64.2 (2°, –$CH_2O_2C$–), 172.8 (4°, –$CO_2CH_3$), 173.3 (4°, –$CO_2CH_3$), 173.55 (4°, –$CO_2CH_3$), 173.64 (4°, –$CO_2CH_3$), 210.6 (4°, –C=O); IR (KBr, neat): 2952, 1738, 1436, 1368, 1171 $cm^{-1}$; MS (FAB) *m/z* (relative intensity): 431 ($M^+ + 1$, 29), 271 (55), 239 (38), 154 (100), 137 (81), 111 (46); HRMS (FAB) Calcd for $C_{21}H_{35}O_9$ $[M+H]^+$: 431.2281. Found: 431.2272.

**4.1.7. 8,8-Dimethoxyoctanoic acid 2-(6,6-dimethoxyheptyl)-10,10-dimethoxy-3-oxodecyl ester (6g).** Followed the general procedure to prepare the aldol-Tishchenko products (**4g′** and **4g**) from the aldehyde **1g** in 73% yield. According to the general procedure, the aldol-Tishchenko products (**4g′** and **4g**) were then oxidized by PCC to give compound **6g** in 64% yield as a pale yellow oil; TLC $R_f$=0.83 (ether/hexane=3:1); $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 1.20–1.35 (m, 20H), 1.45–1.55 (m, 10H), 2.20 (t, $J$=7.5 Hz, 2H, –OC=OC$H_2$–), 2.39 (t, $J$=7.3 Hz, 2H, –C$H_2$CO–), 2.76 (qu, $J$=6.8 Hz, 1H, –CHC=O), 3.25 (s, 18H, –$OCH_3$), 4.10 (d, $J$=6.8 Hz, 2H, –C$H_2O_2C$–), 4.27–4.31 (m, 3H, –C$H$($OCH_3$)$_2$); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 23.1 (2°), 24.2 (2°), 24.28 (2°), 24.31 (2°), 24.6 (2°), 27.0 (2°), 28.4 (2°), 28.89 (2°), 28.96 (2°), 29.01 (2°), 29.2 (2°), 29.4 (2°), 32.27 (2°), 32.31 (2°), 32.33 (2°), 34.0 (2°), 42.9 (2°), 50.7 (3°), 52.49 (1°, –$OCH_3$), 52.52 (1°, –$OCH_3$), 64.4 (2°, –$CH_2O_2C$–), 104.3 (3°), 104.4 (3°), 173.3 (4°, –$CO_2$), 211.6 (4°, –C=O); IR (KBr, neat): 2939, 1739, 1718 (C=O), 1463, 1385, 1127, 728 $cm^{-1}$; MS *m/z* (relative intensity): 561 ($M^+ - 1$, 3), 435 (36), 403 ($M^+ - 159$), 391 (16), 307 (18), 154 (100); HRMS Calcd for ($M^+ - 159$) $C_{21}H_{39}O_7$: 403.2696. Found: 403.2704.

**4.1.8. 6,6-Dimethoxyhexanoic acid 2-(4,4-dimethoxybutyl)-8,8-dimethoxy-3-oxooctyl ester (6h).** Followed the general procedure to prepare the aldol-Tishchenko products (**4h′** and **4h**) from the aldehyde **1h** in 72% yield. According to the general procedure, the aldol-Tishchenko products (**4h′** and **4h**) were then oxidized by PCC to give compound **6h** in 62% yield as a pale yellow oil; TLC $R_f$=0.32 (ether/hexane=2:1); $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 1.26–1.33 (m, 6H), 1.49–1.57 (m, 12H), 2.21 (t, $J$=7.5 Hz, 2H, –$CH_2$), 2.41 (t, $J$=7.2 Hz, 2H, –$CH_2$), 2.76 (qu, $J$=6.7 Hz, 1H, –CH), 3.24 (s, 18H, –$OCH_3$), 4.10 (d, $J$=7.6 Hz, 2H, –C$H_2O_2C$–), 4.25–4.30 (m, 3H, –CH($OCH_3$)$_2$); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 22.1 (2°), 23.0 (2°), 23.97 (2°), 24.02 (2°), 24.5 (2°), 28.2 (2°), 32.0 (2°), 32.2 (2°), 32.4 (2°), 33.9 (2°), 42.8 (2°), 50.6 (3°), 52.58 (1°, –$OCH_3$), 52.64 (1°, –$OCH_3$), 52.8 (1°, –$OCH_3$), 64.3 (2°, –$CH_2O_2C$–), 104.0 (3°), 104.15 (3°), 104.19 (3°), 173.0 (4°, –$CO_2$), 211.2 (4°, –C=O); IR (KBr, neat): 2947, 2830, 1739, 1462, 1386, 1197, 1127, 1054, 957, 736 $cm^{-1}$; MS (FAB) *m/z* (relative intensity): 478 ($M^+$, 2), 351 (28), 127 (73), 75 (100); HRMS (FAB) Calcd for $C_{24}H_{46}O_9$: 478.3142. Found: 478.3132.

**4.1.9. 10-Oxoundecanoic acid 3,12-dioxo-2-(8-oxononyl)-tridecyl ester (6i).** Followed the general procedure to prepare the aldol-Tishchenko products (**4i′** and **4i**) from the aldehyde **1i** in 50% yield. According to the general procedure, the aldol-Tishchenko products (**4i′** and **4i**) were then oxidized by PCC to give compound **6i** in 85% yield as a white solid; mp 55 °C; TLC $R_f$=0.47 (hexane/EtOAc=3:1); $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 1.15–1.25 (m, 24H), 1.45–1.48 (m, 12H), 2.03 (s, 9H, –$CH_3$), 2.16 (t, $J$=7.5 Hz, 2H, –O=CC$H_2$–), 2.30–2.37 (m, 8H, –$CH_2$), 2.72 (qu, $J$=6.8 Hz, 1H, –CH), 4.06 (d, $J$=6.8 Hz, 2H, –C$H_2O_2C$–); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 23.1 (2°), 23.5 (2°), 23.6 (1°), 24.6 (2°), 26.8 (2°), 28.3 (2°), 28.80 (2°), 28.83 (2°), 28.86 (2°), 28.88 (2°), 28.90 (2°), 28.96 (2°), 29.00 (2°), 29.03 (2°), 29.2 (2°), 29.6 (2°), 33.9 (2°), 42.7 (2°), 43.4 (2°), 43.5 (2°), 50.6 (3°), 64.3 (2°, –$CH_2O_2C$–), 173.2 (4°, –$CH_2CO_2$–), 208.79 (4°, –C=O), 208.84 (4°, –C=O), 211.6 (4°, –C=O); IR (KBr, neat): 2931, 2856, 1730, 1717, 1460, 1413, 1361, 1233, 1168, 735 $cm^{-1}$; MS (FAB) *m/z* (relative intensity): 551 ($M^+ + 1$, 13), 351 (100), 183 (51), 137 (25); HRMS (FAB) Calcd for $[M+H]^+$ $C_{33}H_{59}O_6$: 551.4312. Found: 551.4321.

**4.1.10. 6-Bromohexanoic acid 8-bromo-2-(4-bromobutyl)-3-oxooctyl ester (6j).** Followed the general procedure to prepare the aldol-Tishchenko products (**4j′** and **4j**) from the aldehyde **1j** in 87% yield. According to the general procedure, the aldol-Tishchenko products (**4j′** and **4j**) were then oxidized by PCC to give compound **6j** in 70% yield as a pale yellow oil; TLC $R_f$=0.51 (hexane/EtOAc=5:1); $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 1.39–1.45 (m, 7H), 1.57–1.62 (m, 5H), 1.81–1.86 (m, 6H), 2.27 (t, $J$=7.4 Hz, 2H, –O=CC$H_2$–), 2.47 (td, $J$=7.2, 1.8 Hz, 2H), 2.80 (quin, $J$=5.6 Hz, 1H), 3.37–3.40 (m, 6H, –$CH_2$Br), 4.15 (t, $J$=5.2 Hz, 2H, –C$H_2O_2C$–); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 22.3 (2°), 23.9 (2°), 25.6 (2°), 27.51 (2°), 27.53 (2°), 27.6 (2°), 32.3 (2°), 32.5 (2°), 33.1 (2°), 33.4 (2°), 33.5 (2°), 33.8 (2°), 42.6 (2°), 50.7 (3°), 64.3 (2°, $CH_2O_2C$–), 172.9 (4°, –C=O), 210.9 (4°, –C=O); IR (KBr, neat): 2938, 2863, 1736, 1720, 1637, 1457, 1366, 1266, 1173, 737 $cm^{-1}$; MS (FAB) *m/z* (relative intensity): 539 (5), 537 (10), 535 (11), 533 (5), 453 (8), 341 (37), 177 (49), 137 (18); HRMS (FAB) Calcd $[M+H]^+$ for $C_{18}H_{32}O_3{}^{79}Br_3$: 532.9902. Found: 532.9910.

### 4.2. General procedure to prepare the α-methylene ketone via elimination of the β-acyloxyketone

To a solution of the β-acyloxyketone **6a** (152 mg,

0.38 mmol) in 5 mL of benzene was added DBU (0.06 mL, 0.42 mmol) and the reaction mixture was stirred at rt for 5 h. The reaction mixture was concentrated to give the crude residues, which were chromatographed on silica gel column to give the α-methylene ketone **7a** (71.3 mg, 0.29 mmol) in 75% yield as a pale yellow oil.

**4.2.1. 2-Benzyl-5-phenylpent-1-en-3-one (7a).**[22d] TLC $R_f$=0.66 (hexane/EtOAc=10:1); $^1$H NMR ($CDCl_3$, 400 MHz) δ 2.99–3.07 (m, 4H, –$CH_2$), 3.69 (s, 2H), 5.67 (t, $J$=1.32 Hz, 1H, –C=C$H_2$), 6.10 (s, 1H, –C=C$H_2$), 7.22–7.35 (m, 10H, Ph-H); $^{13}$C NMR ($CDCl_3$, 100 MHz) δ 30.2 (2°), 37.0 (2°), 39.5 (2°), 125.2 (3°), 125.95 (3°), 126.13 (2°, –C=$CH_2$), 128.25 (3°), 128.33 (3°), 128.4 (3°), 129.0 (3°), 139.0 (4°), 141.1 (4°), 148.2 (4°, –$C$=$CH_2$), 200.1 (4°, –C=O); IR (KBr, neat): 3085, 3061, 3027, 2925, 1678, 1627, 1603, 1495, 1453, 1432, 1409, 1368, 1078, 941, 745, 700 cm$^{-1}$; MS $m/z$ (relative intensity): 250 ($M^+$, 100), 91 (22); HRMS Calcd for $C_{18}H_{18}O$: 250.1358. Found: 250.1349.

**4.2.2. 2-Pentyl-non-1-en-3-one (7b).** Followed the general procedure to carry out the elimination of β-acyloxy ketone **6b** to give α-methylene ketone **7b** in 76% yield as a pale yellow oil; TLC $R_f$=0.70 (hexane/EtOAc=10:1); $^1$H NMR ($CDCl_3$, 400 MHz) δ 0.85–0.88 (m, 6H), 1.24–1.40 (m, 12H), 1.53–1.59 (m, 2H), 2.24 (t, $J$=7.8 Hz, 2H, –$CH_2$C=$CH_2$), 2.64 (t, $J$=7.5 Hz, 2H), 5.67 (s, 1H, –C=C$H_2$), 5.94 (s, 1H, –C=C$H_2$); $^{13}$C NMR ($CDCl_3$, 100 MHz) δ 13.9 (1°), 14.0 (1°), 22.4 (2°), 22.5 (2°), 24.6 (2°), 28.1 (2°), 29.0 (2°), 30.9 (2°), 31.5 (2°), 31.6 (2°), 37.8 (2°), 123.1 (2°, –$C$=$CH_2$), 149.2 (2°, –$C$=$CH_2$), 202.4 (4°, –C=O); IR (KBr, neat): 3095, 2928, 2857, 1739, 1679 (C=O), 1623, 1464, 1378, 1121, 931 cm$^{-1}$; MS $m/z$ (relative intensity): 210 ($M^+$, 100), 125 (11); HRMS Calcd for $C_{14}H_{26}O$: 210.1984. Found: 210.1976.

**4.2.3. (6*R*,10*R*)-2,6,10,14-Tetramethyl-7-methylene-pentadeca-2,13-dien-8-one (7c).** Followed the general procedure to carry out the elimination of β-acyloxy ketone **6c** to give α-methylene ketone **7c** in 70% yield as a pale yellow oil; TLC $R_f$=0.83 (hexane/EtOAc=20:1); $^1$H NMR ($CDCl_3$, 400 MHz) δ 0.89 (d, $J$=6.6 Hz, 3H, –$CH_3$), 1.01 (d, $J$=6.8 Hz, 3H, –$CH_3$), 1.19–1.48 (m, 5H),1.56 (s, 3H, C=C(C$H_3$)$_2$), 1.59 (s, 3H, C=C(C$H_3$)$_2$), 1.67 (s, 6H, C=C(C$H_3$)$_2$), 1.87–2.07 (m, 5H), 2.46 (dd, $J$=8.1 Hz, 1H), 2.63–2.68 (m, 1H), 2.78–2.84 (m, 1H), 5.08 (br t, 2H, =C$H$(C$H_3$)$_2$), 5.66 (s, 1H, =C$H_2$), 5.98 (s, 1H, –C=C$H_2$); $^{13}$C NMR ($CDCl_3$, 100 MHz) δ 17.6 (1°), 19.8 (1°), 20.1 (1°), 20.2 (1°), 25.5 (2°), 25.7 (1°), 25.9 (2°), 29.7 (3°), 32.6 (3°), 36.3 (2°), 37.2 (2°), 45.5 (2°), 121.8 (2°), 124.40 (3°, –$CH$=C(C$H_3$)$_2$), 124.43 (3°, –$CH$=C(C$H_3$)$_2$), 131.40 (4°, –CH=$C$(C$H_3$)$_2$), 131.43 (4°, –CH=$C$(C$H_3$)$_2$), 154.8 (4°, –$C$=$CH_2$), 202.2 (4°, –C=O); $[\alpha]_D^{28}=-32.7$ ($c$=3.0×10$^{-4}$, $CH_2Cl_2$); IR (KBr, neat): 3095, 2967, 2925, 2851, 1677, 1457, 1378, 931 cm$^{-1}$; MS $m/z$ (relative intensity): 290 ($M^+$, 13), 233 (20), 207 (31), 165 (38), 109 (70); HRMS Calcd for $C_{20}H_{34}O$: 290.2610. Found: 290.2613.

**4.2.4. 12-Methylenedocosa-1,21-dien-11-one (7d).** Followed the general procedure to carry out the elimination of β-acyloxy ketone **6d** to give α-methylene ketone **7d** in 71% yield as a pale yellow oil; TLC $R_f$=0.92 (hexane/EtOAc=30:1); $^1$H NMR ($CDCl_3$, 400 MHz) δ 1.27–1.38 (m, 20H), 1.54–1.59 (m, 2H), 2.01 (pseudo q, $J$=6.8 Hz, 4H, $CH_2$=CHC$H_2$–), 2.23 (t, $J$=7.5 Hz, 2H, –C$H_2$C=O–), 2.63 (t, $J$=7.4 Hz, 2H, –$CH_2$), 4.88–4.98 (m, 4H, –CH=C$H_2$), 5.65 (s, 1H, –C=C$H_2$), 5.72–5.82 (m, 2H, –C$H$=$CH_2$), 5.92 (s, 1H, –CH=C$H_2$); $^{13}$C NMR ($CDCl_3$, 100 MHz) δ 24.6 (2°), 28.4 (2°), 28.8 (2°), 28.98 (2°), 29.00 (2°), 29.20 (2°), 29.25 (2°), 29.33 (2°), 30.9 (2°), 33.7 (2°), 37.8 (2°), 114.0 (2°, –CH=$CH_2$), 123.1 (4°, –$C$=$CH_2$), 139.0 (3°, –$C$H=$CH_2$), 149.1 (4°, –$C$=$CH_2$), 202.2 (4°, –C=O); IR (KBr, neat): 3078, 2927, 2855, 1679, 1643, 1469, 1433, 1366, 909 cm$^{-1}$; MS (FAB) $m/z$ (relative intensity): 319 (M+1, 46), 179 (9), 149 (13), 109 (22); HRMS (FAB) Calcd for $[M+H]^+$ $C_{22}H_{39}O$: 319.3001. Found: 319.3004.

**4.2.5. 7-Methylene-8-oxo-pentadecanedioic acid dimethyl ester (7e).** Followed the general procedure to carry out the elimination of β-acyloxy ketone **6e** to give α-methylene ketone **7e** in 75% yield as a pale yellow oil; TLC $R_f$=0.83 (hexane/EtOAc=10:1); $^1$H NMR ($CDCl_3$, 400 MHz) δ 1.27–1.60 (m, 14H), 2.20–2.27 (m, 6H, –$CH_2$), 2.61 (t, $J$=7.4 Hz, 2H, –$CH_2$), 3.61 (s, 6H, –$OCH_3$), 5.65 (s, 1H, –C=C$H_2$), 5.92 (s, 1H, –C=C$H_2$); $^{13}$C NMR ($CDCl_3$, 100 MHz) δ 24.3 (2°), 24.59 (2°), 24.64 (2°), 28.0 (2°), 28.7 (2°), 28.80 (2°), 28.81 (2°), 30.6 (2°), 33.8 (2°), 37.5 (2°), 51.3 (1°, –$OCH_3$), 123.5 (2°, –C=$C$H$_2$), 148.7 (4°, –$C$=$CH_2$), 174.00 (4°, –$CO_2$), 174.01 (4°, –$CO_2$), 201.9 (4°, –C=O); IR (KBr, neat): 2940, 2860, 1739, 1678, 1619, 1437, 1361, 1257, 1173, 1005, 938 cm$^{-1}$; MS (FAB) $m/z$ (relative intensity): 327 ($M^+$+1, 60), 149 (100), 137 (71), 107 (27); HRMS (FAB) Calcd for $[M+H]^+$ $C_{18}H_{31}O_5$: 327.2171. Found: 327.2180.

**4.2.6. 5-Methylene-6-oxoundecanedioic acid dimethyl ester (7f).** Followed the general procedure to carry out the elimination of β-acyloxy ketone **6f** to give α-methylene ketone **7f** in 80% yield as a pale yellow oil; TLC $R_f$=0.70 (ether/hexane=2:1); $^1$H NMR ($CDCl_3$, 400 MHz) δ 1.28–1.69 (m, 6H), 2.21–2.27 (m, 6H, –$CH_2$), 2.64 (br t, 2H, –$CH_2$), 3.59–3.60 (m, 6H, –$OCH_3$), 5.70 (s, 1H, –C=C$H_2$), 5.96 (s, 1H, –C=C$H_2$); $^{13}$C NMR ($CDCl_3$, 100 MHz) δ 23.5 (2°), 23.7 (2°), 24.4 (2°), 30.1 (2°), 33.4 (2°), 33.7 (2°), 37.1 (2°), 51.3 (1°, –$OCH_3$), 124.2 (2°, –C=$C$H$_2$), 147.8 (4°, –$C$=$CH_2$), 173.6 (4°, –$CO_2$–), 173.7 (4°, –$CO_2$–), 201.0 (4°, –C=O); IR (KBr, neat): 2952, 1737, 1677, 1437, 1368, 1199, 1173, 1005, 938 cm$^{-1}$; MS $m/z$ (relative intensity): 270 ($M^+$, 7), 206 (21), 123 (89), 95 (100); HRMS Calcd for $C_{14}H_{22}O_5$: 270.1467. Found: 270.1476.

**4.2.7. 2-(6,6-Dimethoxyhexyl)-10,10-dimethoxydec-1-en-3-one (7g).** Followed the general procedure to carry out the elimination of β-acyloxy ketone **6g** to give α-methylene ketone **7g** in 90% yield as a pale yellow oil; TLC $R_f$=0.50 (hexane/EtOAc=3:1); $^1$H NMR ($CDCl_3$, 400 MHz) δ 1.30–1.39 (m, 12H), 1.53–1.57 (m, 6H), 2.23 (t, $J$=7.0 Hz, 2H, –$CH_2$), 2.63 (t, $J$=7.4 Hz, 2H, –$CH_2$), 3.28 (s, 12H, –$OCH_3$), 4.32 (t, $J$=5.7 Hz, 2H, –C$H$($OCH_3$)$_2$), 5.66 (s, 1H, –CH=C$H_2$), 5.93 (s, 1H, –C=C$H_2$); $^{13}$C NMR ($CDCl_3$, 100 MHz) δ 24.3 (2°), 24.4 (2°), 24.5 (2°), 28.4 (2°), 29.13 (2°), 29.19 (2°), 29.23 (2°), 30.8 (2°), 32.39 (2°), 32.41 (2°), 37.7 (2°, –$CH_2$C=O), 52.6 (1°, –$OCH_3$), 104.5 (3°, –$CH$($OCH_3$)$_2$), 123.3 (2°, –C=$C$H$_2$), 149.0 (4°,

–*C*=$CH_2$), 202.2 (4°, –C=O); IR (KBr, neat): 3060, 2938, 2861, 1739, 1676, 1467, 1394, 1370, 1273, 1127, 1048, 939, 739 $cm^{-1}$; MS *m/z* (relative intensity): 357 ($M^+-1$, 3), 296 ($M^+-62$, 6), 263 (60), 154 (20), 149 (36), 75 (100); HRMS Calcd for ($M^+-62$) $C_{18}H_{32}O_3$: 296.2351. Found: 296.2347.

**4.2.8. 2-(4,4-Dimethoxybutyl)-8,8-dimethoxyoct-1-en-3-one (7h).** Followed the general procedure to carry out the elimination of β-acyloxy ketone **6h** to give α-methylene ketone **7h** in 92% yield a pale yellow oil; TLC $R_f$=0.72 (ether/hexane=4:1); $^1H$ NMR ($CDCl_3$, 400 MHz) δ 1.31–1.41 (m, 4H), 1.52–1.60 (m, 6H), 2.23 (t, *J*=7.6 Hz, 2H, C*H*$_2$C=C), 2.63 (t, *J*=7.3 Hz, 2H, –$CH_2$C=O), 3.26 (s, 12H, –$OCH_3$), 4.31 (t, *J*=5.6 Hz, 2H, –C*H*($OCH_3$)$_2$), 5.68 (s, 1H, –C=C*H*$_2$), 5.94 (s, 1H, –C=C*H*$_2$); $^{13}C$ NMR ($CDCl_3$, 100 MHz) δ 23.3 (2°), 24.20 (2°), 24.22 (2°), 30.5 (2°), 32.1 (2°), 32.3 (2°), 37.5 (2°, –*C*$H_2$C=O), 52.61 (1°, –$OCH_3$), 52.64 (1°, –$OCH_3$), 104.3 (3°, –*C*H($OCH_3$)$_2$), 123.7 (2°, –C=*C*$H_2$), 148.5 (4°, –*C*=$CH_2$), 201.7 (4°, –C=O); IR (KBr, neat): 2947, 2830, 1738, 1680, 1458, 1386, 1192, 1128, 1072, 953 $cm^{-1}$; MS (FAB) *m/z* (relative intensity): 302 ($M^+$, 4), 271 (10), 147 (43), 75 (100); HRMS (FAB) Calcd for $C_{16}H_{30}O_5$: 302.2093. Found: 302.2095.

**4.2.9. 10-Methyleneheneicosane-2,11,20-trione (7i).** Followed the general procedure to carry out the elimination of β-acyloxy ketone **6i** to give α-methylene ketone **7i** in 80% yield as a white solid; mp 57–58 °C; TLC $R_f$=0.53 (hexane/EtOAc=3:1); $^1H$ NMR ($CDCl_3$, 400 MHz) δ 1.22–1.35 (m, 16H), 1.40–1.60 (m, 6H), 2.09 (s, 6H, –$COCH_3$), 2.20 (t, *J*=7.5 Hz, 2H, –$CH_2$), 2.37 (t, *J*=7.4 Hz, 4H, –$CH_2$), 2.61 (t, *J*=7.4 Hz, 2H, –$CH_2$), 5.65 (s, 1H, –C=C*H*$_2$), 5.92 (s, 1H, –C=C*H*$_2$); $^{13}C$ NMR ($CDCl_3$, 100 MHz) δ 23.7 (2°), 24.5 (2°), 28.3 (2°), 28.99 (2°), 29.01 (2°), 29.07 (2°), 29.13 (2°), 29.2 (2°), 29.7 (2°), 30.8 (2°), 37.7 (2°), 43.7 (2°), 123.3 (2°, –C=*C*$H_2$), 149.0 (4°, –*C*=$CH_2$), 202.3 (4°, –C=O), 209.1 (4°, –C=O); IR (KBr, neat): 3057, 2929, 2855, 1714, 1676, 1627, 1410, 1361, 1269, 1166, 937, 737 $cm^{-1}$; MS (FAB) *m/z* (relative intensity): 351 ($M^+$+1, 12), 111 (14), 83 (45); HRMS (FAB) Calcd for $[M+H]^+$ $C_{22}H_{39}O_3$: 351.2899. Found: 351.2894.

**4.2.10. 10-Bromo-2-(4-bromobutyl)-oct-1-en-3-one (7j).** Followed the general procedure to carry out the elimination of β-acyloxy ketone **6j** to give α-methylene ketone **7j** in 77% yield as a pale yellow oil; TLC $R_f$=0.82 (hexane/EtOAc=5:1); $^1H$ NMR ($CDCl_3$, 400 MHz) δ 1.43–1.66 (m, 6H, –$CH_2$), 1.84–1.90 (m, 4H, –$CH_2$C=O), 2.29 (t, *J*=7.7 Hz, 2H, –C*H*$_2$–C=$CH_2$), 2.70 (t, *J*=7.3 Hz, 2H, –$CH_2$), 3.40 (t, *J*=6.8 Hz, 4H, –C*H*$_2$Br), 5.75 (s, 1H, –C=C*H*$_2$), 6.00 (s, 1H, –C=C*H*$_2$); $^{13}C$ NMR ($CDCl_3$, 100 MHz) δ 23.6 (2°), 27.1 (2°), 27.8 (2°), 30.0 (2°), 32.4 (2°), 32.6 (2°), 33.4 (2°), 33.5 (2°), 37.4 (2°), 124.0 (2°, –C=*C*$H_2$), 148.3 (4°, –*C*=$CH_2$), 201.5 (4°, –C=O); IR (KBr, neat): 3102, 2937, 2861, 1677, 1626, 1437, 1366, 1265, 937, 738 $cm^{-1}$; MS (FAB) *m/z* (relative intensity): 343 (36), 341 (100), 339 (68), 261 (50), 259 (51); HRMS Calcd $[M+H]^+$ for $C_{12}H_{20}{}^{79}Br_2O$: 338.9959. Found: 338.9952.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# Two-dimensional oligoarylenes: synthesis and structure–properties relationships

Zhong Hui Li,[a] Man Shing Wong[a,*] and Ye Tao[b,*]

[a]*Department of Chemistry and Centre for Advanced Luminescence Materials, Hong Kong Baptist University, Kowloon Tong, Hong Kong SAR, China*

[b]*Institute for Microstructural Sciences, National Research Council of Canada, M-50 Montreal Road, Ottawa, Ont., Canada K1A 0R6*

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**Abstract**—A novel series of two-dimensional π-conjugated oligoarylenes has been synthesized by a divergent approach using Pd-catalysed Suzuki cross-coupling of tetraiodophenylbenzene and arylboronic acid as a key step. It has been shown that the 'X-branched' structure can provide a useful platform to construct amorphous molecular materials as it can enhance the morphological and thermal stability as well as to facilitate solubility and processibility of a material when compared to those of the corresponding linear oligomers. The diphenylamino end-capped two-dimensional oligoarylenes were found useful as a hole transporting/emitting layer for light emitting applications.


## 1. Introduction

Conjugated molecular materials[1] such as low molar mass molecules and oligomers have continuously drawn considerable attentions for their potential applications in next-generation electronic and opto-electronic devices such as organic light-emitting diodes (OLEDs)[2] and field effect transistors[3] as well as in the emerging photonic technologies such as plastic laser[4] and three-dimensional optical storage[5] in the past few years. Tremendous progress has already been made in understanding and optimising the electronic and optical properties of linear π-conjugated molecules or oligomers.[6] Recently, there is a great interest to increase the structural or spatial dimensions of π-conjugated molecules in order to tune and acquire more favourable physical i.e. morphological and functional properties of a material.[7] For instance, various novel structures of π-conjugated molecules such as star-burst molecules,[8] tetrahedral-arranged chromophores,[9] spiro-linked oligomers[10] and dendritic macromolecules[11] have been designed and synthesized in order to prevent molecular aggregation and facilitate amorphous glass formation of electroluminescent materials, which would enhance the fluorescence efficiency and stability of OLEDs as well as induce the formation of morphologically stable glassy states of photonic molecular materials, which could prevent light scattering caused by grain boundaries in optical waveguides. On the other hand, we have shown that acentrically oriented donor-acceptor oligophenylenes built onto the calix[4]arene framework exhibits fluorescence enhancement.[12] Over the last few years, we have been investigating the structural factors that would enhance the technologically useful functional and material properties of oligomers[13] and macromolecules[14] as they are essential towards a rational design and an optimization of functional organic and polymeric materials. Moving along the same direction, we report herein a facile synthesis and structure–properties of a novel series of two-dimensional π-conjugated oligoarylenes as morphologically stable amorphous molecular materials based on the 'X-branched' structure in which π-conjugated arylene moieties extend around 1,2,4,5-positions of an aromatic core, **4**–**9**. Their optical, electronic and thermal properties were characterized and compared with the corresponding linear oligomer, **4′**–**9′**. Furthermore, the electroluminescent properties of **5**- and **9**-based OLEDs were investigated. The use of tetra-substituted benzene as a platform for the construction of two-dimensional π-conjugated systems has been reported; however, most of the systems employed ethynyl linkages between the benzene core and the conjugated arms.[15]

## 2. Results and discussion

We found that palladium catalysed Suzuki cross coupling

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* Corresponding authors. Tel.: +852 3411 7069; fax: +852 3411 7348 (M.S.W.); Tel.: +1 613 998 2485; fax: +1 613 990 0202 (Y.T.); e-mail addresses: mswong@hkbu.edu.hk; ye.tao@nrc.ca

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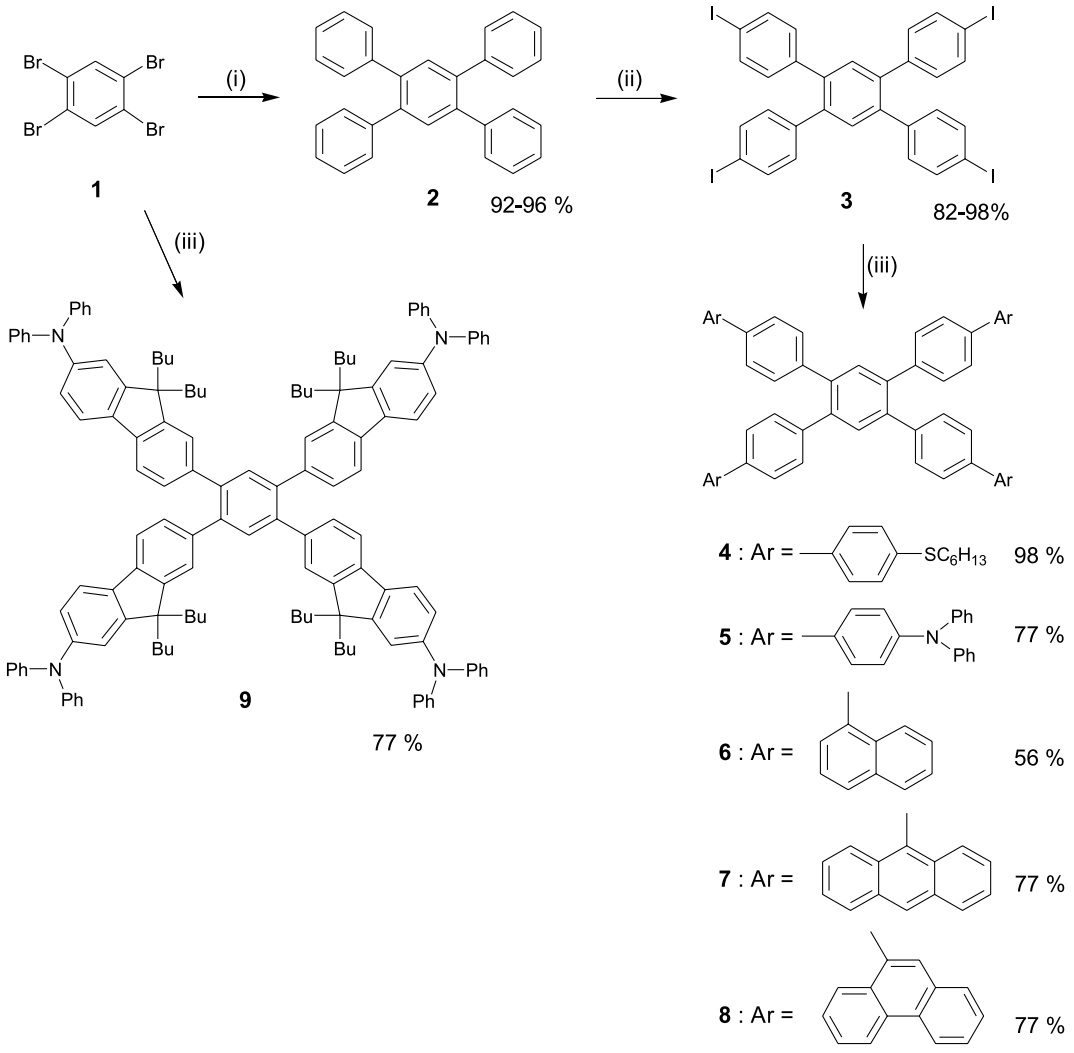
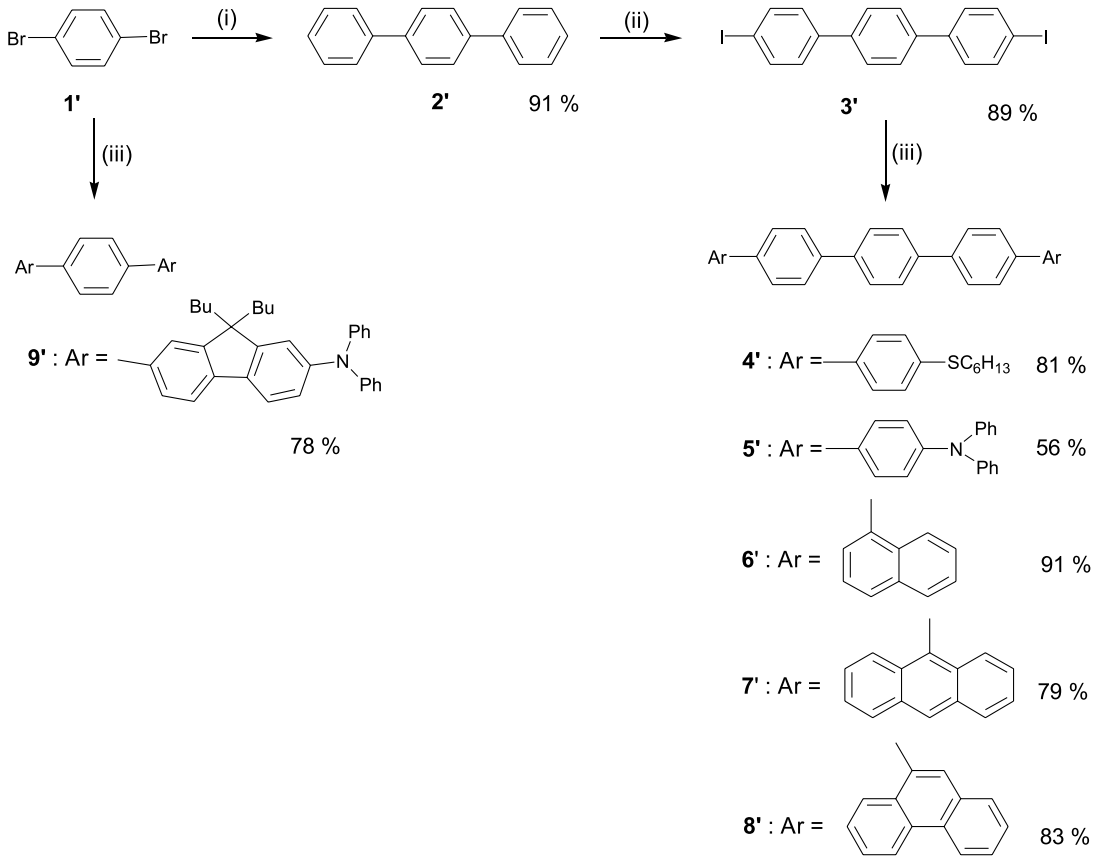



**Scheme 1.** Synthesis of two-dimensional oligoarylenes, **4–9**. Reagents and conditions: (i) Ph–B–$(OH)_2$, 5 mol% $Pd(OAc)_2$–2P(*o*-tol)$_3$, $K_2CO_3$, toluene–methanol, 75 °C, overnight; (ii) $I_2$, $HIO_4$, $H_2SO_4$, HOAc, $CCl_4$, 80 °C, 6 h; (iii) Ar–B–$(OH)_2$, 5 mol% $Pd(OAc)_2$–2P(*o*-tol)$_3$, $K_2CO_3$, toluene–methanol, 75 °C, 6–12 h.

was particularly versatile for the facile divergent synthesis of two-dimensional π-conjugated oligoarylenes and their linear counterparts. The general scheme for the syntheses of two-dimensional oligoarylenes, **4–9** is outlined in Scheme 1. Cross coupling of 1,2,4,5-tetrabromobenzene, **1** and phenylboronic acid in the presence of catalytic $Pd(OAc)_2$: 2 P(*o*-tol)$_3$ complex afforded tetraphenylbenzene, **2** in excellent yields. Iodination of **2** using $HIO_4/I_2$ also gave tetraiodophenylbenzene, **3** in excellent yields. Cross coupling of **3** and the corresponding arylboronic acid, which was generally prepared by lithium–bromide exchange of the aryl bromide at −78 °C followed by the reaction with trimethyl borate at room temperature and subsequently acid hydrolysis, afforded the desired two-dimensional oligophenylenes, **4–8** in good to excellent yields. It is worth mentioning that direct cross coupling of **1** with the corresponding biphenylboronic acids afforded either two-dimensional oligophenylene in a low yield (i.e., **4** in 42% yield) or no desired product (i.e., **5**). This is likely due to the steric crowdedness imposed by the proximate assembled biphenyl units. Nevertheless, cross coupling of **1** and 9,9-bis(*n*-butyl)-2-diphenylamino-7-fluorenylboronic acid afforded **9** under typical conditions in a good yield (77%). Using the same divergent approach, the corresponding linear oligomers, **4′–9′** were also synthesized as shown in Scheme 2. All the new two-dimensional oligoarylenes were fully characterized by $^1H$ NMR, $^{13}C$ NMR, MS, and elemental analyses or HRMS and found to be in good agreement with the expected structures.

In view of electronic absorption spectra, the absorption bands/maxima of the two-dimensional oligoarylenes are generally structureless and blue shifted (<12 nm) relative to the corresponding linear oligomer. (Fig. 1) This indicates that the two-dimensional oligoarylenes are less planar than the linear oligomers in their electronic ground state.[16] In contrast to the linear analogues, the fluorescence spectra of the two-dimensional oligoarylenes are also less structured but slightly red shifted (0–16 nm) indicating that the non-planarity does not improve in a great extent even in the excited state.[13] As found from the PM3-optimized geometry of two-dimensional oligoarylenes[17] that the severe distortion from planarity arises from the proximate extended π-conjugated aryl arms around the central aromatic core




**Scheme 2.** Synthesis of linear oligoarylenes, **4′**–**9′**. Reagents and conditions: (i) Ph–B–$(OH)_2$, 5 mol% $Pd(OAc)_2$–2P(*o*-tol)$_3$, $K_2CO_3$, toluene–methanol, 75 °C, overnight; (ii) $I_2$, $HIO_4$, $H_2SO_4$, HOAc, $CCl_4$, 80 °C, 6 h; (iii) Ar–B–$(OH)_2$, 5 mol% $Pd(OAc)_2$–2P(*o*-tol)$_3$, $K_2CO_3$, toluene–methanol, 75 °C, 6–12 h.

and the torsion angles between the aryl arm and the aromatic core is ~80° (Fig. 2). Such a twisting from planarity in both ground- and excited-states leads to a decrease in the fluorescence quantum yields of these two-dimensional π-conjugated molecules (41–90%) as compared to those of the corresponding linear counterparts (63–99%). On the other hand, the fluorescence lifetimes of the two-dimensional oligoarylenes and their corresponding linear oligomers are very similar which are in the nanosecond timescale (Table 1) indicating that emission comes from the singlet excited states.

The redox properties of these oligoarylenes were studied by cyclic voltametry, which was carried out in a three-electrode cell set-up with 0.1 M of $Bu_4NPF_4$ as a supporting electrolyte in $CH_2Cl_2$. All the potentials reported are referenced to $Fc/Fc^+$ standard and the results are tabulated in Table 1. The diphenylamino endcapped two-dimensional oligoarylenes **5** and **9**, exhibit a reversible four-electron anodic redox couples with $E_{1/2}=0.45$ and 0.32 V, respectively corresponding to the arylamino oxidation (Fig. 3); on the other hand; other oligoarylenes exhibit an irreversible oxidation at comparatively high potentials (0.84–1.46 V), corresponding to the generation of radical cation on the oligoarylenes. No reduction peak was observed for all the two-dimensional oligoarylenes in the CV under the same experimental conditions. In spite of the severe twisting around the core, the two-dimensional oligoarylenes exhibit relatively smaller oxidation potential than their linear analogous (Table 1), consistent with the fluorescence results, suggesting a slight improvement in π-electron delocalization in this two-dimensional π-conjugated structure. The superior solubility in common organic solvents of the two-dimensional oligoarylenes is prominent when compared with those of the linear analogues. For instance, the solubility of the linear oligomer **4′** is so low that the CV measurement is not possible.

The thermal property and the morphological stability of these oligoarylenes were investigated by TGA and DSC analyses, respectively. In general, the two-dimensional oligoarylenes exhibit a higher thermal stability and most of the two-dimensional oligoarylenes also exhibit a high glass transition, $T_g$ when compared with those of the linear counterparts. This suggests that the non-planar conformation of this branched structure can be used to induce or further stabilize morphologically stable glass formation (Table 1).

To investigate their electroluminescent properties, multilayer OLEDs using the newly synthesized two-dimensional oligoarylenes bearing diphenylamino end-caps as a hole transporting/emitting layer were fabricated with a structure of ITO/two-dimensional oligoarylenes (40 nm)/PBD (40 nm)/LiF (1 nm)/Al (150 nm). The electroluminescence (EL) spectra of **5**-based devices exhibit a peak maximum at 429 nm with a narrow bandwidth and slightly blue-shifted relative to those of the linear counterparts (Fig. 4); however,

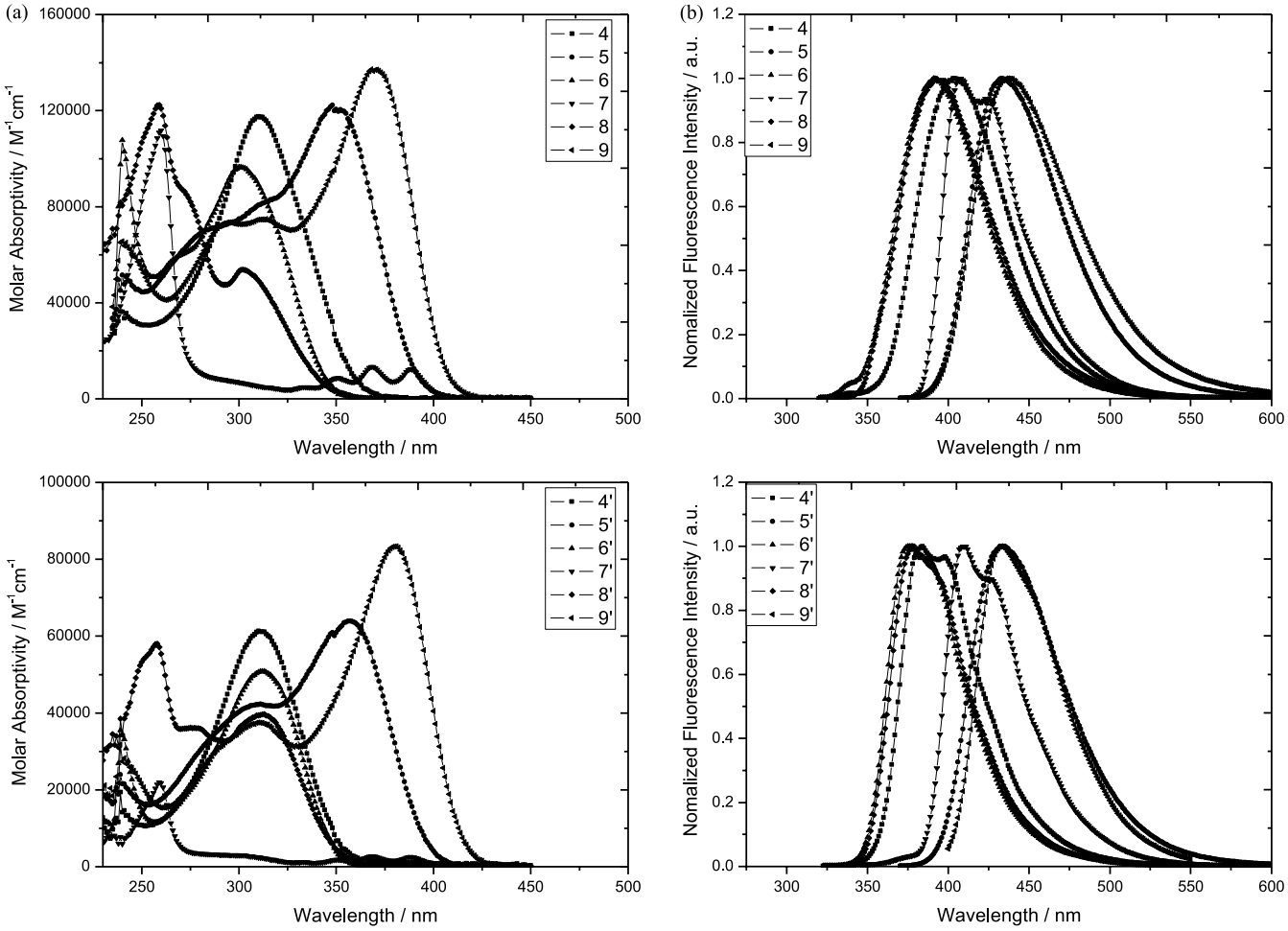



**Figure 1.** (a) Absorption and (b) emission spectra of two-dimensional oligoarylenes, **4**–**9** and linear oligoarylenes **4′**–**9′** measured in $CHCl_3$.

maximum luminance and device efficiency were found to be lower than those of the linear analogous based OLEDs.[18] On the other hand, although the EL spectrum of **9**-based device, emitting at 550 nm, does not vary with the bias voltage, its emission maximum is ~40 nm red-shifted relative to the broad solid-state PL spectrum. Such a red shift may be due to the aggregation formation leading to the low energy trapping sites.[19] To overcome the drawback, bulky or spiro-linked substituents could be introduced at the 9-position of fluorene units to suppress the aggregation formation[8] or **9** could be used as a dopant emitter dispersing in a host matrix.[2c] Despite such a simple two-layer structure, the luminance efficiency can reach up to 2.8 cd/A with a maximum brightness of 1700 cd/m$^2$ (Fig. 5).

## 3. Conclusions

In summary, a new class of two-dimensional π-conjugated oligoarylenes was first prepared and investigated. Their

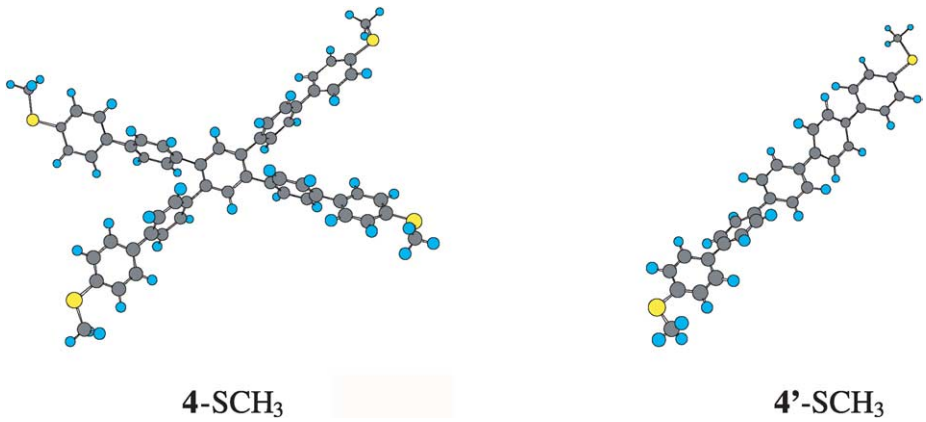



**Figure 2.** PM3-optimized geometries of **4**–$SCH_3$ and **4′**–$SCH_3$.

**Table 1**. Summaries of physical measurements of two-dimensional oligoarylenes **4–9** and their linear analogous **4′–9′**

| | $\lambda_{max}^{abs}$ [a]/nm ($\varepsilon_{max}$ $10^4/M^{-1}$ $cm^{-1}$) | $\lambda_{max}^{em}$ [a,b]/nm | $\Phi_{FL}$ [a,c] | $\tau$ [a,d]/ns | Oxid $E_{1/2}$ [e]/V | $T_g$ [f]/°C | $T_m$ [f]/°C | $T_{dec}$ [g]/°C |
|---|---|---|---|---|---|---|---|---|
| **4** | 309 (11.8) | 404 | 0.70 | 1.38 | 0.93(i) | 178 | 280 | 394 |
| **5** | 349 (12.2) | 433 | 0.48 | 1.34 | 0.45 | 177 | 301 | 589 |
| **6** | 301 (6.90) | 392 | 0.65 | 1.47 | 1.46(i) | 131 | 286 | 581 |
| **7** | 388 (0.38) | 425 | 0.90 | 3.05 | 0.84(i) | No | 352 | 571 |
| **8** | 302 (0.47) | 394 | 0.47 | 1.36 | 1.20(i) | No | 414 | 607 |
| **9** | 371 (13.7) | 435 | 0.41 | 1.44 | 0.32 | 135 | No | 474 |
| **4′** | 319 (6.10) | 384, 398 | 0.77 | 1.07 | (nd) | No | 187 | 330 |
| **5′** | 358 (6.38) | 433 | 0.84 | 1.06 | 0.47 | 115 | 191 | 560 |
| **6′** | 313 (5.07) | 377, 386 | 0.82 | 0.75 | 1.60(i) | No | 234 | 560 |
| **7′** | 388 (0.22) | 424 | 0.95 | 3.04 | 0.87(i) | No | 393 | 542 |
| **8′** | 313 (0.58) | 378 | 0.63 | 2.44 | 1.25(i) | No | 341 | 487 |
| **9′** | 381 (8.25) | 433 | 0.99 | 1.06 | 0.36 | 101 | 254 | 449 |

[a] Measured in $CHCl_3$.
[b] Excited at the absorption maxima.
[c] Using 9,10-diphenylanthrancene ($\Phi_{360}=0.9$) as a standard.
[d] Using nitrogen laser as excitation source.
[e] $E_{1/2}$ versus $Fc^+/Fc$ estimated by CV method using platinum disc electrode as a working electrode, platinum wire as a counter electrode, and SCE as a reference electrode with an agar salt bridge connecting to the oligomer solution and all the potentials were calibrated with ferrocene, $E_{1/2}$ ($Fc/Fc^+$)=0.45 V versus SCE. (i) denotes irreversible reaction and (nd) denotes not determined due to highly insoluble.
[f] Determined by differential scanning calorimeter from re-melt after cooling with a heating rate of 10 °C/min under $N_2$.
[g] Determined by thermal gravimetric analyser with a heating rate of 10 °C/min under $N_2$.

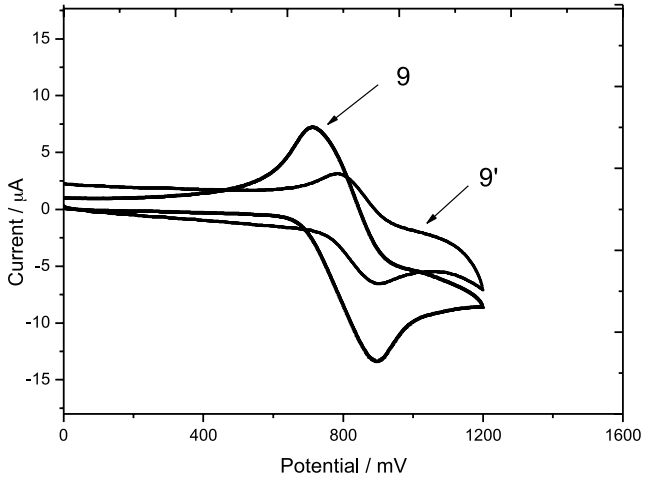



**Figure 3.** Cyclic voltammograms of **9** and **9′**.

optical, electrochemical and thermal properties have been characterized and compared with those of the corresponding linear oligomers. According to the PM3 semi-empirical calculations, the twisting of the extended arylenes around the central aromatic core in the optimised geometry is substantial. However, the 'X-branched' structure can still provide improvement in π-electron delocalisation leading to slightly red-shift of emission spectra and lowering of the first oxidation potential. In addition, these two-dimensional oligoarylenes show enhancing morphological ($T_g$=131–178 °C) and thermal ($T_{dec}$=394–607 °C) stabilities as well as superior solubility and processibility as compared to those of the linear counterparts. The potential use of the diphenylamino end-capped two-dimensional oligoarylenes as a hole transporting/emitting layer for OLEDs was explored and showed that OLEDs fabricated by these two-dimensional luminophores exhibit a luminance efficiency up to 2.8 cd/A and a maximum brightness of 1700 cd/$m^2$.

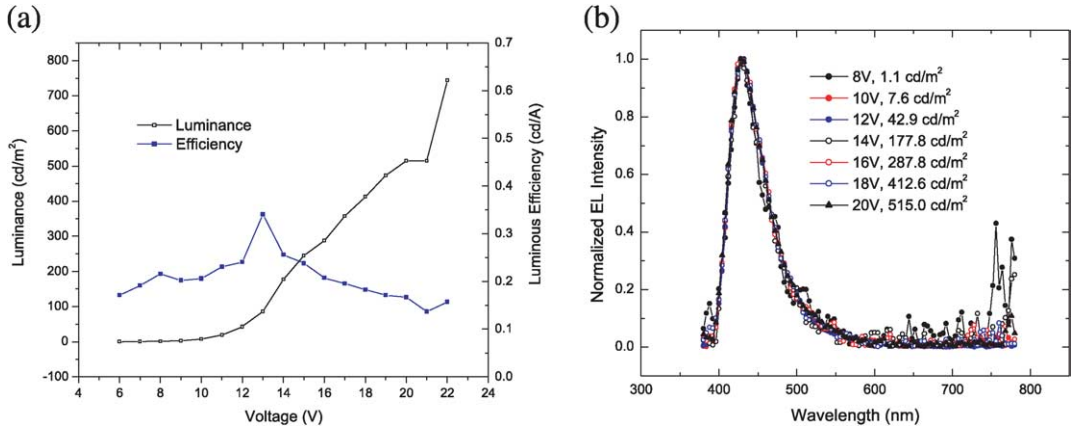



**Figure 4.** (a) Luminance–voltage–efficiency plot of **5**-based OLED device. (b) EL spectra of **5**-based OLEDs.

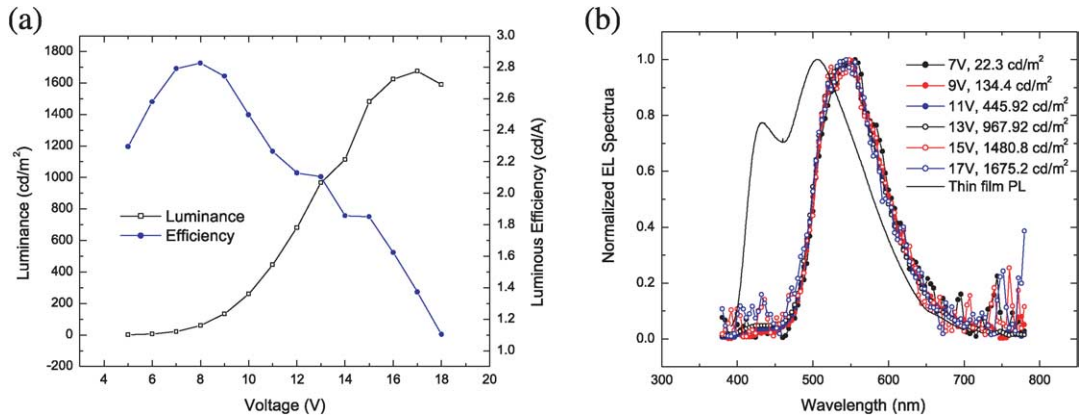



**Figure 5.** (a) Luminance–voltage–efficiency plot of **9**-based OLED device. (b) EL and PL spectra of **9**-based OLEDs.

## 4. Experimental

### 4.1. General

All the solvents were dried by the standard methods wherever needed. Thermal stabilities were determined by thermal gravimetric analyser with a heating rate of 10 °C/min under $N_2$. The glass transitions and melting transitions were extracted from the second run DSC traces which were determined by differential scanning calorimeter with a heating rate of 10 °C/min under $N_2$. All the physical measurements were performed in $CHCl_3$ including electronic absorption (UV–vis) and fluorescence spectra. The fluorescence quantum yields in chloroform were determined by dilution method using 9,10-diphenylanthrancene ($\lambda_{exc}$= 360 nm, $\Phi$=0.9) as a standard. The fluorescence decay curves were recorded at room temperature using nitrogen laser as excitation. The lifetimes were estimated from the measured fluorescence decay using iterative fitting procedure. $E_{1/2}$ versus $Fc^+$/Fc was estimated by cyclic voltammetric method using platinum disc electrode as a working electrode, platinum wire as a counter electrode, and SCE as a reference electrode with an agar salt bridge connecting to the oligomer solution dissolved in $CH_2Cl_2$ using 0.1 M of $Bu_4NPF_6$ as a supporting electrolyte with a scan rate of 100 mV/s and all the potentials were calibrated with ferrocene, ($E_{1/2}$(Fc/$Fc^+$)=0.45 V vs SCE) as an external standard. The procedures for multi-layer OLED device fabrication reported previously were followed.[11a] The device structures for **5**- and **9**-based OLED are ITO/**5** or **7** (40 nm)/PBD (40 nm)/LiF (1 nm)/Al (150 nm).

**4.1.1. 1,2,4,5-Tetraphenylbenzene 2.** A mixture of 1,2,4,5-tetrabromobenzene, **1** (787 mg, 2 mmol), palladium (II) acetate (22 mg, 0.1 mmol), tri(*o*-tolyl)phosphine (61 mg, 0.2 mmol), phenylboronic acid (1.46 g, 12 mmol), toluene (30 mL), methanol (10 mL), and 2 M $K_2CO_3$ (8 mL) was heated at 75 °C for overnight under a nitrogen atmosphere while maintaining with good stirring. After the reaction mixture was cooled to room temperature, it was poured into water and extracted with dichloromethane (3×50 mL). The combined organic layer was dried with anhydrous $Na_2SO_4$ and evaporated to dryness. The crude product was further purified by silica gel column chromatography using petroleum ether–dichloromethane as eluent affording the title compound as a white solid of 94% yield. $^1$H NMR (400 MHz, $CDCl_3$, $\delta$) 7.55 (s, 2H), 7.24 (s, 20H). $^{13}$C NMR (100 MHz, $CDCl_3$, $\delta$) 140.9, 139.6, 133.0, 129.9, 128.0, 126.6. MS (FAB) *m/z* 382.4 ($M^+$). HRMS (ESI-TOF) calcd for $C_{30}H_{22}Na$ 405.1619, found 405.1637 ($M^+$+Na).

**4.1.2. 1,2,4,5-Tetrakis(*p*-iodophenyl)benzene 3.** A mixture of 1,2,4,5-tetraphenylbenzene, **2** (601 mg, 1.57 mmol), acetic acid (20 mL), water (1 mL), concentrated sulfuric acid (1 mL), iodine (957 mg, 3.77 mmol), iodic acid (859 mg, 3.77 mmol), and carbon tetrachloride (5 mL) was heated at 80 °C for 4 h with good magnetic stirring. After the product slurry was cooled to room temperature, it was poured into water and extracted with dichloromethane (3×50 mL). The combined dark purple organic layer was decolourised with sodium sulfite, washed with water, dried with anhydrous $Na_2SO_4$, filtered and evaporated to dryness. Purification of the crude product by recrystallization in a mixture solvent of chloroform/ethanol (v/v=4:1) afforded the title compound as a colorless crystal in 98% yield. $^1$H NMR (400 MHz, $CDCl_3$, $\delta$) 7.58 (d, $J$=8.40 Hz, 8H), 7.38 (s, 2H), 6.90 (d, $J$=8.40 Hz, 8H). $^{13}$C NMR (100 MHz, $CDCl_3$, $\delta$) 139.7, 138.8, 137.4, 132.7, 131.6, 93.0. MS (FAB) *m/z* 886.1 ($M^+$). HRMS (MALDI-TOF) calcd for $C_{30}H_{18}I_4$ 885.7587, found 885.7558 ($M^+$).

**4.1.3. 1,2,4,5-Tetrakis[4′-(1-hexylsulfanyl)biphenyl-4-yl]benzene 4.** A mixture of 1,2,4,5-tetrakis(*p*-iodophenyl)-benzene, **3** (443 mg, 0.5 mmol), palladium (II) acetate (22 mg, 0.1 mmol), tri(*o*-tolyl)phosphine (61 mg, 0.2 mmol), toluene (40 mL), methanol (20 mL), 2 M $K_2CO_3$ (6 mL), 4-(*n*-hexylsulfanyl)phenylboronic acid (740 mg, 3 mmol) was heated at 75 °C for overnight under a nitrogen atmosphere with good stirring. After the reaction mixture was cooled to room temperature, it was poured into water and extracted with dichloromethane (3×50 mL). The combined organic layer was dried with anhydrous $Na_2SO_4$ and evaporated to dryness. The crude product was purified by silica gel chromatography using petroleum ether–dichloromethane as eluent affording a white solid with an isolated yield of 98%. $^1$H NMR (400 MHz, $CDCl_3$, $\delta$) 7.64 (s, 2H), 7.51 (t, $J$=9.60 Hz, 16H), 7.35 (t, $J$=7.20 Hz, 16H), 2.94 (t, $J$=7.20 Hz, 8H), 1.67 (m, 8H), 1.44 (m, 8H), 1.29 (m, 16H), 0.89 (t, $J$=7.00 Hz, 12H). $^{13}$C NMR (100 MHz, $CDCl_3$, $\delta$) 139.8, 139.2, 138.7, 137.9, 136.2,

130.6, 130.1, 129.3, 128.8, 127.5, 127.0, 126.7, 126.1, 33.5, 29.1, 28.5, 22.5, 14.3, 13.7. MS (FAB) *m/z* 1152.0 ($M^+ + 1$). Anal. Calcd for $C_{78}H_{86}S_4$: C, 81.34; H, 7.53; S, 11.13. Found: C, 81.20; H, 7.62. Mp 280 °C.

**4.1.4. 1,2,4,5-Tetrakis[(4′-diphenylamino)biphenyl-4-yl]benzene 5.** The synthetic procedure of **4** was followed using 4-diphenylaminophenylboronic acid (361 mg, 1.25 mmol) and 1,2,4,5-tetrakis(*p*-iodophenyl)benzene **3** (221 mg, 0.25 mmol). The pure product was separated by silica gel column chromatography using 6:1 petroleum ether–dichloromethane as eluent affording 261 mg (77%) of a milky white solid. $^1$H NMR (400 MHz, $CDCl_3$, $\delta$) 7.62 (s, 2H), 7.47 (d, $J=7.20$ Hz, 14H), 7.31 (d, $J=7.20$ Hz, 8H), 7.24 (t, $J=7.20$ Hz, 18H), 7.10 (d, $J=7.60$ Hz, 24H), 7.01 (t, $J=7.00$ Hz, 8H). $^{13}$C NMR (100 MHz, $CDCl_3$, $\delta$) 147.6, 147.2, 139.5, 139.3, 138.7, 134.5, 133.0, 130.3, 129.2, 127.6, 126.1, 124.3, 124.0, 122.9. MS (FAB) *m/z* 1355.9 ($M^+$). Anal. Calcd for $C_{102}H_{74}N_4$: C, 90.37; H, 5.50; N, 4.13. Found: C, 90.27; H, 5.58; N, 4.29. Mp 301 °C.

**4.1.5. 1,2,4,5-Tetrakis[4-(1-naphthyl)phenyl-1-yl] benzene 6.** The synthetic procedure of **4** was followed using 1-naphthylboronic acid (516 mg, 3 mmol) and 1,2,4,5-tetrakis(*p*-iodophenyl)benzene **3** (443 mg, 0.50 mmol). The pure product was separated by silica gel column chromatography using 4:1 petroleum ether–dichloromethane as eluent affording 250 mg (56%) of a white solid. $^1$H NMR (400 MHz, $CDCl_3$, $\delta$) 7.94 (d, $J=8.40$ Hz, 4H), 7.90 (d, $J=8.40$ Hz, 4H), 7.86 (d, $J=6.80$ Hz, 4H), 7.85 (s, 2H), 7.52 (m, 8H), 7.46 (m, 20H), 7.38 (t, $J=7.60$ Hz, 4H). $^{13}$C NMR (100 MHz, $CDCl_3$, $\delta$) 140.0, 139.9, 139.7, 139.2, 133.8, 133.0, 131.6, 129.9, 129.8, 128.3, 127.7, 126.9, 126.1, 125.9, 125.7, 125.4. MS (FAB) *m/z* 886.7 ($M^+ - 1$). Anal. Calcd for $C_{70}H_{46}$: C, 94.77; H, 5.23. Found: C, 94.60; H, 5.36. Mp 286 °C.

**4.1.6. 1,2,4,5-Tetrakis[4′-(9″-anthryl)phenyl-1′-yl] benzene 7.** The synthetic procedure of **4** was followed using 9-anthracylboronic acid (400 mg, 1.8 mmol) and 1,2,4,5-tetrakis(*p*-iodophenyl)benzene, **3** (266 mg, 0.30 mmol). The pure product was separated by silica gel column chromatography using 4:1 petroleum ether–dichloromethane as eluent affording 250 mg (77%) of a yellow solid. $^1$H NMR (400 MHz, $CDCl_3$, $\delta$) 8.51 (s, 4H), 8.05 (t, $J=8.80$ Hz, 10H), 7.74 (d, $J=8.80$ Hz, 4H), 7.70 (d, $J=8.00$ Hz, 8H), 7.47 (d, $J=8.40$ Hz, 8H), 7.39 (t, $J=7.60$ Hz, 10H), 7.17 (t, $J=8.00$ Hz, 10H). MS (FAB) *m/z* 1086.5 ($M^+ - 1$). Anal. Calcd for $C_{86}H_{54}$: C, 94.99; H, 5.01. Found: C, 94.92; H, 5.19. Mp 352 °C.

**4.1.7. 1,2,4,5-Tetrakis[4′-(9″-phenanthryl)phenyl-1′-yl] benzene 8.** The synthetic procedure of **4** was followed using 9-phenanthrylboronic acid (400 mg, 1.8 mmol) and 1,2,4,5-tetrakis(*p*-iodophenyl)benzene, **3** (266 mg, 0.30 mmol). The pure product was separated by silica gel column chromatography using 4:1 petroleum ether–dichloromethane as eluent affording 250 mg (77%) of a light-yellow solid. $^1$H NMR (400 MHz, $CDCl_3$, $\delta$) 8.78 (d, $J=8.00$ Hz, 4H), 8.72 (d, $J=7.60$ Hz, 4H), 7.97 (d, $J=8.00$ Hz, 4H), 7.90 (d, $J=4.80$ Hz, 6H), 7.75 (s, 4H), 7.63 (m, 12H), 7.55 (d, $J=2.40$ Hz, 12H), 7.49 (m, 8H). $^{13}$C NMR (100 MHz, $CDCl_3$, $\delta$) 140.1, 139.8, 139.3, 138.5, 133.1, 131.6, 131.1, 130.6, 130.0, 129.8, 128.7, 127.5, 126.9, 126.6, 126.5, 122.9, 122.5. MS (FAB) *m/z* 1087.5 ($M^+$). Anal. Calcd for $C_{86}H_{54}$: C, 94.99; H, 5.01. Found: C, 95.05; H, 4.98. Mp 414 °C.

**4.1.8. 1,2,4,5-Tetrakis[2′-diphenylamino-9′,9′-bis(*n*-butyl)-7′-fluorenyl]benzene 9.** To a mixture of 1,2,4,5-tetrabromobenzene, **5** (76 mg, 0.19 mmol), 9,9-bis(*n*-butyl)-2-diphenylamino-7-fluorenylboronic acid (570 mg, 1.14 mmol), $Pd(OAc)_2$ (8.5 mg, 5 mol%) and tri(*o*-tolyl)-phosphine (23 mg, 10 mol %) in a 100 mL round-flask were added toluene (10 mL), methanol (5 mL) and 2 M aqueous solution of $K_2CO_3$ (2.5 mL). The reaction mixture was stirred under a nitrogen atmosphere at 75 °C for overnight. After cooling to room temperature, the reaction mixture was poured into cool water and extracted with dichloromethane (3×50 mL). The combined organic layer was dried with anhydrous $Na_2SO_4$ and evaporated to dryness. The crude product was then purified by column chromatography with petroleum ether–dichloromethane (v/v=4:1) as eluent affording the desired product as a white solid (270 mg, 77% yield). $^1$H NMR (400 MHz, $CDCl_3$, $\delta$) 7.69 (s, 2H), 7.46 (t, $J=7.0$ Hz, 8H), 7.28 (d, $J=7.6$ Hz, 4H), 7.22 (t, $J=7.6$ Hz, 20H), 7.10 (d, $J=7.6$ Hz, 16H), 7.05 (s, 4H), 6.98 (dd, $J=7.2$ Hz, 12H), 1.69–1.70 (m, 16H), 0.93–0.99 (m, 16H), 0.67 (t, $J=7.0$ Hz, 40H). $^{13}$C NMR (100 MHz, $CDCl_3$, $\delta$) 152.2, 150.5, 148.0, 146.9, 140.1, 139.5, 139.2, 136.0, 133.4, 129.1, 128.8, 124.4, 123.7, 123.3, 122.4, 120.4, 119.3, 118.7, 54.8, 39.9, 26.1, 22.9, 14.0. MS (FAB) *m/z* 1852.8 ($M^+$). HRMS (ESI-MS) calcd for $C_{138}H_{138}N_4$: 1853.1032 ($M^+ + 1$). Found: 1853.0970.

**4.1.9. Bis(4-*n*-hexylsulfanyl-1-yl)pentaphenyl 4′.** A mixture of bis(*p*-iodophenyl)benzene, **3′** (443 mg, 0.5 mmol), palladium (II) acetate (22 mg, 0.1 mmol), tri(*o*-tolyl)phosphine (61 mg, 0.2 mmol), toluene (30 mL), methanol (15 mL), 2 M $K_2CO_3$ (3 mL), and 4-(*n*-hexylsulfanyl)-phenylboronic acid (370 mg, 1.5 ) was heated at 75 °C for 3–4 h under a nitrogen atmosphere with good stirring. After the reaction mixture was cooled to room temperature, it was poured into water and extracted with dichloromethane (3×50 mL). The combined organic layer was dried with anhydrous $Na_2SO_4$ and evaporated to dryness. The crude product was purified by silica gel column chromatography using dichloromethane as eluent affording a white solid (256 mg) with an isolated yield of 88%. $^1$H NMR (400 MHz, $CDCl_3$, $\delta$) 7.67–7.21 (m, 20H), 2.97 (t, $J=7.20$ Hz, 4H), 1.67–1.71 (m, 4H), 1.46–1.43 (m, 4H), 1.29–1.32 (m, 8H), 0.89 (t, $J=6.00$ Hz, 6H). MS (FAB) *m/z* 583.9 ($M^+ + 1$). Anal. Calcd for $C_{78}H_{86}S_2$: C, 86.55; H, 7.95; S, 11.00. Found: C, 86.38; H, 8.05; S, 10.95. Mp 187 °C.

**4.1.10. Bis(4-diphenylamino-1-yl)pentaphenyl 5′.** The synthetic procedure of **4′** was followed using 4-diphenyl-aminophenylboronic acid (1.68 g, 5.84 mmol) and bis(*p*-iodophenyl)benzene, **3′** (936 mg, 1.94 mmol). The pure product was separated by silica gel column chromatography using petroleum ether–dichloromethane as gradient eluent affording 1261 mg (91%) of a milky white solid. $^1$H NMR (400 MHz, $CDCl_3$, $\delta$) 7.73 (d, $J=3.60$ Hz, 4H), 7.70 (d, $J=8.40$ Hz, 4H), 7.65 (d, $J=8.40$ Hz, 4H), 7.52 (d, $J=8.40$ Hz, 4H), 7.27 (t, $J=8.40$ Hz, 8H), 7.15 (m, 12H), 7.03 (t, $J=7.40$ Hz, 4H). $^{13}$C NMR (100 MHz, $CDCl_3$, $\delta$) 147.6,

147.3, 139.6, 139.6, 139.0, 134.4, 129.3, 127.6, 127.4, 127.3, 127.0, 124.5, 123.8, 123.0. MS (FAB) *m/z* 716.3 ($M^+$). Anal. Calcd for $C_{54}H_{40}N_2$: C, 90.47; H, 5.62; N, 3.91. Found: C, 90.39; H, 5.68; N, 3.91. Mp 191 °C.

**4.1.11. Bis[4′-(1″-naphthyl)phenyl-1′-yl] benzene 6′.** The synthetic procedure of **4′** was followed using 1-naphthylboronic acid (413 mg, 2.4 mmol) and bis(*p*-iodophenyl)-benzene, **3′** (386 mg, 0.80 mmol). The pure product was separated by silica gel column chromatography using 4:1 petroleum ether–dichloromethane as eluent affording 350 mg (91%) of a white solid. $^1$H NMR (400 MHz, $CDCl_3$, $\delta$) 8.00 (d, $J$=8.00 Hz, 2H), 7.92 (d, $J$=8.80 Hz, 2H), 7.88 (d, $J$=8.00 Hz, 2H), 7.82 (s, 4H), 7.80 (d, $J$=8.40 Hz, 4H), 7.61 (d, $J$=8.40 Hz, 4H), 7.53 (t, $J$=8.00 Hz, 2H), 7.46 (m, 6H). $^{13}$C NMR (100 MHz, $CDCl_3$, $\delta$) 139.9, 139.8, 139.8, 139.5, 133.8, 131.6, 130.6, 128.3, 127.7, 127.5, 127.0, 126.9, 126.1, 126.0, 125.8, 125.4. MS (FAB) *m/z* 482.5 ($M^+$). Anal. Calcd for $C_{38}H_{26}$: C, 94.57; H, 5.43. Found: C, 94.34; H, 5.48. Mp 234 °C.

**4.1.12. Bis[4′-(9″-anthracyl)phenyl-1′-yl]benzene 7′.** The synthetic procedure of **4′** was followed using 9-anthracylboronic acid (368 mg, 1.66 mmol) and bis(*p*-iodophenyl)-benzene, **3′** (266 mg, 0.55 mmol). The pure product was separated by silica gel column chromatography using 4:1 petroleum ether–dichloromethane as eluent affording 253 mg (79%) of a light-yellow solid. $^1$H NMR (400 MHz, $CDCl_3$, $\delta$) 8.52 (s, 2H), 8.06 (d, $J$=8.40 Hz, 4H), 7.90 (d, $J$=6.40 Hz, 8H), 7.77 (d, $J$=8.80 Hz, 4H), 7.54 (d, $J$=8.00 Hz, 4H), 7.48 (t, $J$=8.00 Hz, 4H), 7.38 (t, $J$=8.00 Hz, 4H). $^{13}$C NMR (100 MHz, $CDCl_3$, $\delta$) 139.7, 137.8, 133.2, 131.7, 131.3, 130.1, 128.3, 127.5, 126.9, 126.7, 126.6, 125.6, 125.3, 125.1. MS (FAB) *m/z* 582.5 ($M^+$). Anal. Calcd for $C_{46}H_{30}$: C, 94.81; H, 5.19. Found: C, 95.01; H, 5.15. Mp 393 °C.

**4.1.13. Bis[4′-(9″-phenanthryl)phenyl-1′-yl]benzene 8′.** The synthetic procedure of **4′** was followed using 9-phenanthrylboronic acid (200 mg, 0.90 mmol) and bis-(*p*-iodophenyl)benzene, **3′** (145 mg, 0.30 mmol). The pure product was separated by silica gel column chromatography using 6:1 petroleum ether–dichloromethane as eluent affording 145 mg (83%) of a light-yellow solid. $^1$H NMR (400 MHz, $CDCl_3$, $\delta$) 8.80 (d, $J$=8.40 Hz, 2H), 8.74 (d, $J$=8.40 Hz, 2H), 8.02 (d, $J$=8.40 Hz, 2H), 7.92 (d, $J$=7.60 Hz, 2H), 7.83 (d, $J$=9.20 Hz, 8H), 7.75 (s, 2H), 7.65 (m, 10H), 7.57 (t, $J$=8.00 Hz, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$, $\delta$) 139.9, 139.8, 139.7, 138.4, 135.2, 131.1, 130.9, 130.6, 128.7, 127.6, 126.9, 126.8, 126.7, 126.6, 126.5, 125.0, 123.0, 122.6. MS (FAB) *m/z* 583.9 ($M^+$+1). Anal. Calcd for $C_{46}H_{30}$: C, 94.81; H, 5.19. Found: C, 94.67; H, 5.24. Mp 341 °C.

**4.1.14. 1,4-Bis[2′-diphenylamino-9′,9′-bis(*n*-butyl)-7′-fluorenyl]benzene 9′.** To a mixture of 1,4-dibromobenzene **1′** (94 mg, 0.40 mmol), 9,9-bis(*n*-butyl)-2-diphenylamino-7-fluorenylboronic acid (470 mg, 0.96 mmol), palladium(II) acetate (11 mg, 5 mol%) and tri(*o*-tolyl)phosphine (30 mg, 10 mol%) in a 100 mL round-flask were added toluene (20 mL), methanol (10 mL) and 2 M aqueous solution of $K_2CO_3$ (2 mL). The reaction mixture was stirred under the atmosphere of nitrogen at 75 °C for 12 h. After cooling to room temperature, the reaction mixture was poured into cool water and extracted with dichloromethane (3×50 mL). The combined organic layer was dried with anhydrous $Na_2SO_4$ and evaporated to dryness. The crude product was then purified by silica column chromatography using petroleum ether–dichloromethane (v/v=6:1) as eluent affording the desired product as a light-yellow solid (301 mg, 78% yield). $^1$H NMR (400 MHz, $CDCl_3$, $\delta$) 7.75 (s, 4H), 7.67 (d, $J$=7.6 Hz, 2H), 7.61–7.55 (m, 6H), 7.24 (t, $J$=7.8 Hz, 8H), 7.13 (d, $J$=7.6 Hz, 10H), 7.01 (dd, $J$=7.6 Hz, 6H), 1.86–1.94 (m, 8H), 1.06–1.11 (m, 8H), 0.70 (t, $J$=7.6 Hz, 20H). $^{13}$C NMR (100 MHz, $CDCl_3$, $\delta$) 152.4, 151.3, 148.0, 147.1, 140.3, 140.3, 138.7, 135.9, 129.1, 127.4, 125.8, 123.8, 123.4, 122.5, 121.2, 120.4, 119.4, 119.3, 55.0, 40.0, 26.1, 23.0, 13.9. MS (FAB) *m/z* 965.2 ($M^+$). Anal. Calcd for $C_{72}H_{72}N_2$ (%): C, 89.58; H, 7.52; N, 2.90. Found: C, 89.38; H, 7.45; N, 3.08. Mp 254 °C.

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# Substituent effects in the ring-chain tautomerism of 4-aryl-1,3,4,6,7,11b-hexahydro-2*H*-pyrimido[6,1-*a*]isoquinolines

Zita Zalán, Anasztázia Hetényi, László Lázár and Ferenc Fülöp*

*Institute of Pharmaceutical Chemistry, University of Szeged, H-6701 Szeged, POB 121, Hungary*

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Dedicated to Professor Alajos Kálmán on the occasion of his 70th birthday

**Abstract**—By condensation of 1-(2′-aminoethyl)-1,2,3,4-tetrahydroisoquinoline derivatives with substituted benzaldehydes, 1,6-unsubstituted and diastereomers of 1-methyl- or 6-methyl-substituted 4-aryl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2*H*-pyrimido[6,1-*a*]isoquinolines were prepared. The ring-chain tautomeric equilibria of most of these compounds in $CDCl_3$ at 300 K were found to be shifted nearly totally towards either the cyclic or the open tautomeric forms, while the (6*R**,11b*R**)-6-methyl substituted compounds proved to be three-component tautomeric mixtures, the equilibria of which could be characterized by a Hammett-type equation. The conformational equilibria of the cyclic forms turned out to be strongly influenced by the 1- and 6-methyl substituents and the configurations of the substituted carbons (C-1 or C-6 and C-4) relative to C-11b.


## 1. Introduction

Ring-chain tautomerism, the reversible intramolecular addition of a hydroxy, mercapto or amino group to a C=N double bond, is a characteristic phenomenon for saturated, *N*-unsubstituted, five- and six-membered 1,3-*X*,*N* heterocycles (X=O, S, NR). It is often exploited advantageously in different areas of organic synthesis, and also in physical, medicinal and peptide chemistry.[1,2]

Substituent effects influencing the ring-chain tautomeric process have been studied thoroughly in recent decades. For the tautomeric equilibria of oxazolidines and tetrahydro-1,3-oxazines bearing a substituted phenyl group at position 2, in both the liquid and the gas phase, a linear Hammett-type correlation was found between the log *K* (*K*=[ring]/[chain]) values of the equilibria and the electronic character ($\sigma^+$) of the substituents X on the 2-phenyl group (Eq. 1). The value of $\rho$ in Eq. 1 was found to be characteristic of the ring system and dependent on the temperature and the nature of the solvent.[1,2]

$$\log K_X = \rho\sigma^+ + \log K_{X=H} \quad (1)$$

Recent studies on 2-aryl-substituted imidazolidines,[3,4] hexahydropyrimidines,[5–7] 1,2,3,4-tetrahydro quina zolines,[6,8] perhydroquinazolines[9] and 3-arylhexahydroimidazo[5,1-*a*]- and -[1,5-*b*]isoquinolines[10] led to the conclusion that, similarly to their 1,3-*O*,*N* analogues, the ring-chain tautomeric equilibria of these compounds could likewise be characterized by Eq. 1. Complex 1,3-*N*,*N* heterocyclic tautomeric mixtures containing regioisomeric open and/or diastereomeric cyclic forms could also be characterized by Eq. 1.[7,9,10] For *N*-substituted 2-aryl-1,3-*N*,*N* heterocycles, the tautomeric process and the values of $\rho$ and $\log K_{X=H}$ in Eq. 1 were found to be dependent on the steric and electronic characters of the substituent on the nitrogen. In contrast with the 1,3-*O*,*N* analogues, the value of $\rho$ did not prove to be characteristic of the 1,3-*N*,*N* ring system.[2]

As a continuation of our previous studies on the ring-chain tautomerism of five- and six-membered 1,3-*N*,*N* heterocycles[2] and stereochemical investigations on 1,2,3,4-tetrahydro isoquinoline-condensed 1,3- and 1,2,3-heterocycles,[11] our primary present aim was to determine the influence of the substituents and the relative configuration of the substituted carbon atoms on the ring-chain tautomeric character and the conformation of 4-aryl-1,3,4,6,7,11b-hexahydro-2*H*-pyrimido[6,1-*a*]isoquinolines. In the knowledge of the significant substituent effects on both the ring-chain tautomeric and conformational equilibria of saturated 1,3-heterocycles,[2,12] a further aim was to study the consequences of methyl substitution at positions 1 and 6 of the hexahydropyrimido[6,1-*a*]isoquinoline ring system.

*Keywords*: Diamines; Isoquinolines; Hexahydropyrimidines; Ring-chain tautomerism; Conformation.
* Corresponding author. Tel.: +36 62 545564; fax: +36 62 545705; e-mail: fulop@pharm.u-szeged.hu

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## 2. Results and discussion

### 2.1. Synthesis

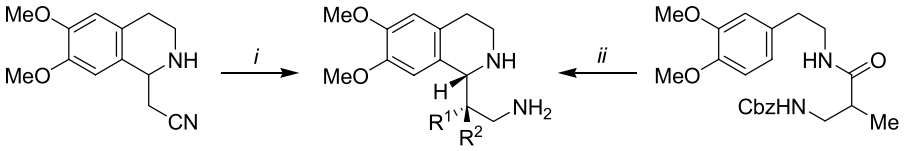
For the synthesis of the target hexahydropyrimido[6,1-*a*] isoquinolines, the appropriate 1-(2′-aminoethyl)-1,2,3,4-tetrahydroisoquinolines bearing a methyl substituent at either position 3 or position 1′ of the side-chain were required. The usual methods applied earlier for the synthesis of 1-aminoalkyl-1,2,3,4-tetrahydroisoquinolines involve reduction of the corresponding isoquinolines bearing nitrogen-containing functional groups (nitrile, carboxamide or nitro) in the side-chain and procedures based on the Bischler–Napieralski or Pictet–Spengler ring-closures, using the appropriate *N*-protected amino acids or amino aldehydes,[13] both of which were utilized in the preparation of the 1′- or 3-methyl-substituted tetrahydroisoquinoline diamines.

The unsubstituted diamine **2a** was obtained by the catalytic hydrogenation of 6,7-dimethoxy-1,2,3,4-tetrahydro-1-isoquinolylacetonitrile (**1**)[14] (Scheme 1). The 1′-methyl-substituted tetrahydroisoquinoline diamine diastereomers (**2b**,**c**) were prepared via a highly diastereoselective, four-step process, starting from 3-benzyloxycarbonylamino-2-methyl-*N*-[2-(3,4-dimethoxyphenyl)ethyl]propanamide (**3**). The formation of either the (1*R**,1′*S**) (**2b**) or the (1*R**,1′*R**) isomer (**2c**) as major product was found to be dependent on the sequence of reduction and deprotection steps applied.[15]

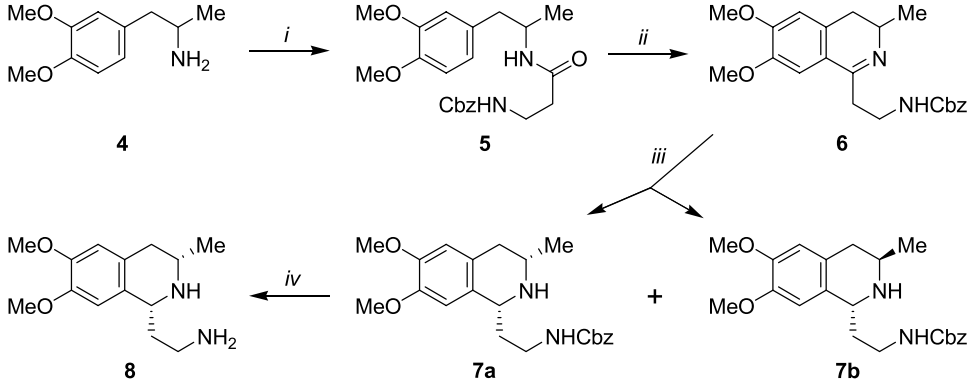
The 3-methyl-substituted tetrahydroisoquinoline diamine diastereomers (**8** and **11**) were prepared using different synthetic pathways. (1*R**,3*S**)-1-(2′-aminoethyl)-6,7-dimethoxy-3-methyl-1,2,3,4-tetrahydroisoquinoline (**8**) was obtained by applying a procedure analogous to that used for the synthesis of **2b**. In the $NaBH_4$ reduction of dihydroisoquinoline **6**, obtained in two steps from *N*-protected β-alanine and α-methylhomoveratrylamine (**4**), a 12:1 mixture of tetrahydroisoquinoline isomers (1*R**,3*S**)-**7a** and (1*R**,3*R**)-**7b** was formed, from which **7a** was obtained by crystallization and was converted into the pure (1*R**,3*S**) diamine diastereomer **8** by removal of the Cbz group (Scheme 2). The *cis* selectivity of the reduction can be rationalized by the steric effect of the 3-methyl group, which directs the hydride attack to the sterically less hindered side, resulting in **7a** as the main product.[16–18] The relative configuration (1*R**,3*S**) of **8** was deduced from the NOE data on H-1 and H-3.

The (1*R**,3*R**) diamine diastereomer **11** was prepared by $LiAlH_4$ reduction of (1*R**,3*R**)-6,7-dimethoxy-3-methyl-1,2,3,4-tetrahydroisoquinoline-1-acetamide (**10**), which was obtained in a highly diastereoselective two-step procedure[16,17] (monoethyl malonate addition and subsequent amidation) from 3-methyl-6,7-dimethoxy-3,4-dihydroisoquinoline (**9**) (Scheme 3).

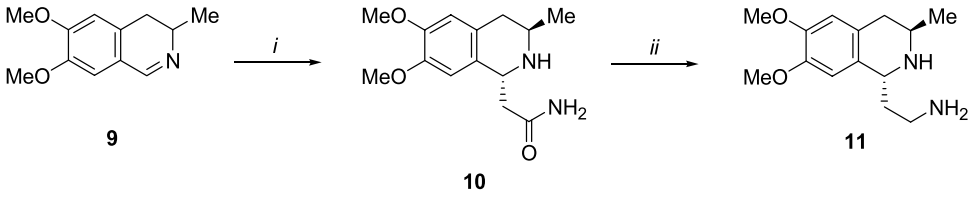
Condensations of diamines **2a–c**, **8** and **11** with equivalent amounts of *p*-nitro- and *p*-(dimethylamino)benzaldehyde resulted in model hexahydropyrimido[6,1-*a*]isoquinoline compounds **12–16** mainly as crystalline products (Scheme 4). In the knowledge of the strong influence of the electronic effects of the aromatic substituents on the ring-chain tautomeric behaviour of 1,3-*X*,*N* heterocyclic compounds,[1,2] aromatic aldehydes were chosen according to their opposite electronic character, which favour the predominance of either the cyclic (in the case of *p*-$NO_2$) or the open (in the case of *p*-$NMe_2$) form.



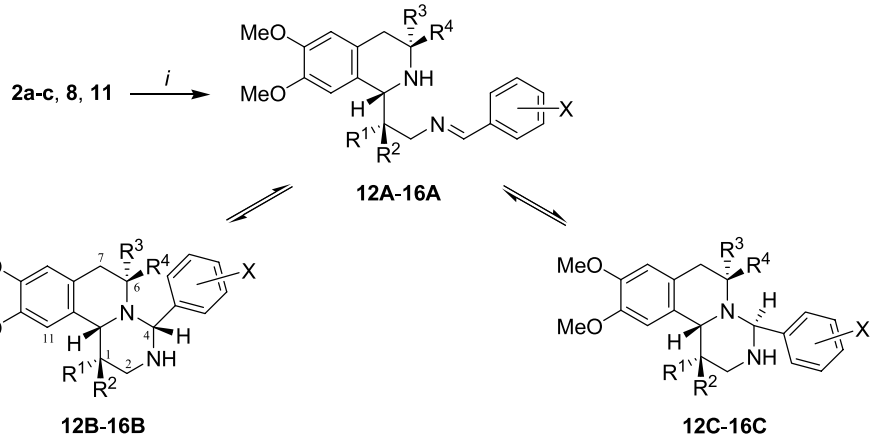

**Scheme 1.** Reagents and conditions: (i) see Ref. 14 (**1**→**2a**); (ii) see Ref. 15 (**3**→**2b**,**c**).




**Scheme 2.** Reagents and conditions: (i) ClCOOEt, *N*-Cbz-β-alanine, toluene, −10 °C, △, 5 min, 84%; (ii) $POCl_3$, $CHCl_3$, △, 3 h, 78%; (iii) $NaBH_4$, MeOH, 0 °C, 3 h, then rt, 3 h, **7a**:**7b**=12:1, 82% (**7a**); (iv) 1. 33% HBr in AcOH, rt, 30 min, 2. NaOH, 74%.




**Scheme 3.** Reagents and conditions: (i) see Ref. 17; (ii) $LiAlH_4$, THF, reflux, 7 h, 82%.




**Scheme 4.** Reagents and conditions: (i) $XC_6H_4CHO$, MeOH, rt, 1 h, 43–100%. (For the meanings of $R^1$–$R^4$ and X, see Table 1).

## 2.2. Ring-chain tautomerism

Quantitative studies on the ring-chain tautomeric equilibria of 2-aryl-substituted 1,3-*X*,*N* heterocycles (X=O, S, NR) are based on the integration of the well-separated X-C*H*Ar-N (ring) and N=C*H*Ar (chain) proton singlets in the $^1$H NMR spectra.[1,2] The proportions of the chain (**A**) and diastereomeric ring forms (**B** and **C**) of the tautomeric equilibria of **12**–**16** were determined by this method (Table 1). The $^1$H NMR ($CDCl_3$, 300 K) spectroscopic data on the 1-unsubstituted and 1-methyl-substituted model compounds (**12**–**14**) revealed that, independently of the electronic character of the aromatic substituents and the presence of the methyl group at position 1, their tautomeric equilibria were shifted totally towards the cyclic forms (**B** and **C**). The NOESY spectra unequivocally showed that the major ring forms in the tautomeric equilibria of **12**–**14** contain H-4 and H-11b in the *cis* position (**B**). The proportion of the minor cyclic tautomer, possessing H-4 and H-11b in the *trans* position (**C**), was found to be increased in (1*R**,11b*R**)-1-methylhexahydropyrimido[6,1-*a*]isoquinoline **14**.

The 6-methyl substitution caused a dramatic change in the tautomeric ratios. For (6*S**,11b*R**)-6-methyl-substituted hexahydropyrimido[6,1-*a*]isoquinolines **15**, the tautomeric equilibrium was found to be shifted entirely towards the open tautomer (**A**), even in **15a**, which bears an electron-withdrawing *p*-nitro substituent on the aromatic ring.

The tautomeric ratios determined for (6*R**,11b*R**) 6-methyl-substituted 4-(*p*-nitrophenyl)- (**16a**) and 4-[*p*-(dimethylamino)phenyl]hexahydropyrimido[6,1-*a*]isoquinoline (**16g**) suggested that the ring-chain equilibrium of this model compound was sensitive to the electronic effects of the 4-aryl substituents (Table 1). Accordingly, a full set of 4-(X-phenyl)-substituted derivatives was prepared, with substituent X exhibiting different electronic characters (**16a**–**g**). In consequence of the very similar NMR spectroscopic characteristics of **16a**–**g**, the relative configurations of the major (**B**) and minor (**C**) ring-closed tautomers were determined only for **16a**. The proportion of the minor cyclic form (**C**) was found to be decreased to below the limit of detection in the event of strongly electron-donating 4-aryl substituents (*p*-OMe and *p*-$NMe_2$).

Data on **16a** and **16g** were chosen to illustrate the $^1$H NMR spectra of this type of prepared tautomeric compound (see Section 4). 4-Aryl substituents did not change the sequence of the chemical shifts of the characteristic N–C*H*Ar–N and N=C*H*Ar protons. The configuration of the azomethine double bond was found to be *E*, according to the NOE interaction observed between H-2 and N=C*H*.

When Eq. 1 was applied to the log $K_X$ values ($K_X$=[ring]/[chain]) of **16a**–**g**, good linear correlations were obtained versus the Hammett–Brown parameter $\sigma^+$ of the substituent X on the 4-phenyl group, for both the *cis*-chain (**B**⇌**A**) and the *trans*-chain (**C**⇌**A**) equilibria (Fig. 1 and Table 2).

The data in Table 2 show that both the slope ($\rho$) and the intercept (log $K_{X=H}$) of the regression line were strongly influenced by the relative configuration of C-4 and C-11b. A comparison of the intercepts in Table 2, which indicate the stability of the given cyclic form,[1,2] indicates, that the attached tetrahydroisoquinoline ring makes both cyclic forms of **16** more stable than the corresponding monocyclic analogue 2-aryl-1-isopropylhexahydropyrimidine (**17B**). The difference in the values of $\rho$ for the *cis*-chain (**16B**⇌**16A**) and *trans*-chain (**16C**⇌**16A**) equilibria, which reflects the difference in the sensitivities of the

**Table 1**. Proportions (%) of tautomeric forms (**A**, **B** and **C**) in tautomeric equilibria for compounds **12–16** ($CDCl_3$, 300 K)

| Comp. | $R^1$ | $R^2$ | $R^3$ | $R^4$ | X | $\sigma^+$ | **A** | **B** | **C** |
|---|---|---|---|---|---|---|---|---|---|
| **12a** | H | H | H | H | *p*$NO_2$ | 0.79 | 0 | 92.6 | 7.4 |
| **12b** | H | H | H | H | *p*$NMe_2$ | −1.7 | 0 | 100 | 0 |
| **13a** | Me | H | H | H | *p*$NO_2$ | 0.79 | 0 | 100 | 0 |
| **13b** | Me | H | H | H | *p*$NMe_2$ | −1.7 | 0 | 100 | 0 |
| **14a** | H | Me | H | H | *p*$NO_2$ | 0.79 | 0 | 65.4 | 34.6 |
| **14b** | H | Me | H | H | *p*$NMe_2$ | −1.7 | 0 | 81.3 | 18.7 |
| **15a** | H | H | Me | H | *p*$NO_2$ | 0.79 | 100 | 0 | 0 |
| **15b** | H | H | Me | H | *p*$NMe_2$ | −1.7 | 100 | 0 | 0 |
| **16a** | H | H | H | Me | *p*$NO_2$ | 0.79 | 10.7 | 74.7 | 14.6 |
| **16b** | H | H | H | Me | *m*Br | 0.405 | 17.6 | 75.4 | 7.0 |
| **16c** | H | H | H | Me | *p*Br | 0.15 | 24.1 | 69.2 | 6.7 |
| **16d** | H | H | H | Me | H | 0 | 31.4 | 64.9 | 3.7 |
| **16e** | H | H | H | Me | *p*Me | −0.311 | 40.8 | 57.2 | 2.0 |
| **16f** | H | H | H | Me | *p*OMe | −0.778 | 54.9 | 45.1 | 0 |
| **16g** | H | H | H | Me | *p*$NMe_2$ | −1.7 | 79.4 | 20.6 | 0 |

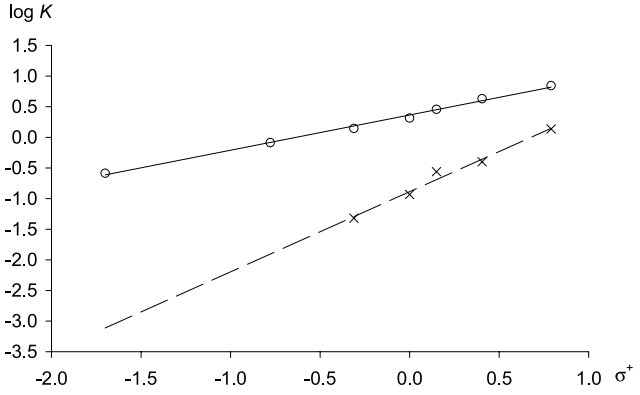



**Figure 1.** Plots of log $K_X$ for **16B** (○) and **16C** (×) versus Hammett–Brown parameter $\sigma^+$.

reactions to electron supply or withdrawal, was found to be considerable higher ($\Delta\rho=0.94$) than that observed for the ring-chain tautomeric equilibria of the analogous 3-aryl-hexahydroimidazo[5,1-*a*]isoquinolines ($\Delta\rho=0.04$).[2,10] The different values of $\rho$ for the *cis*-chain (**16B**⇌**16A**) and *trans*-chain (**16C**⇌**16A**) equilibria can probably be rationalized by the different hyperconjugative (anomeric) effects[10] in **16B** and **16C**, possessing different predominant B/C ring connections (see Section 2.3). The polarization along all the single bonds associated with C-4 changes the extent of the orbital overlaps between the nitrogen lone pairs and the antibonding orbitals. Because of the dihedral angles between the interacting orbitals ($n_N-\sigma^*_{C\text{-}Ar}=-66.9$ and 67.9), the hyperconjugative effect is higher in **16B**, containing *trans*-connected rings B/C, than that in **16C**, with a predominant *cis*[1] conformation ($n_N-\sigma^*_{C\text{-}Ar}=-167.9$ and 37.3).

The substantial increase in the proportions of the open tautomers for the equilibria of **15** and **16**, as compared with the tautomeric ratios for **12–14**, can be rationalized by the increased steric hindrance of the *N*-substituent caused by the 6-methyl group. Earlier data on the ring-chain tautomeric equilibria of 1,3-*N*,*N*-heterocycles indicated that the proportion of the ring-closed form decreases with increasing bulkiness of the *N*-substituent.[2]

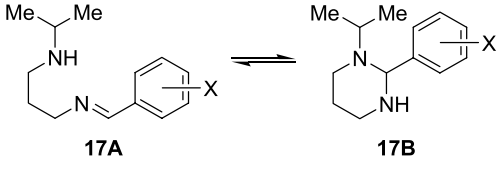
## 2.3. Conformations

The stereostructure of tetrahydroisoquinoline-fused six-membered saturated heterocycles can be described by a conformational equilibrium of *cis*[1]–*trans*–*cis*[2] type. In the *trans* structure, the B/C hetero rings are *trans*-connected, with H-11b and the N-5 lone pair *trans-diaxial*. In the two other configurations, the hetero rings are *cis*-connected, where in the *cis*[1] conformation C-1 is in the inside, while in the *cis*[2] conformation C-1 is in the outside position (Fig. 2).[19] The conformational equilibria of 1-, 2- and 4-substituted saturated 1,3-oxazino[4,3-*a*]-,[11] 1,2,3-oxathiazino[4,3-*a*]-[20] and 1,3,2-oxazaphosphorino [4,3-*a*]isoquinolines[21] and 1,3,2-diazaphosphorino[6,1-*a*]isoquinolines[15] have been thoroughly studied, but fewer data are available on the analogous hexahydropyrimido[6,1-*a*]isoquinolines. A slight predominance of the conformer with *trans*-connected B/C

**Table 2**. Linear regression data on compounds **16** and 2-aryl-1-isopropylhexahydropyrimidines (**17**)

| Equilibrium | No. of points | Slope[a] ($\rho$) | Intercept[a] | Correlation coefficient |
|---|---|---|---|---|
| **16A**⇌**16B** | 7 | 0.36(5) | 0.57(6) | 0.995 |
| **16A**⇌**16C** | 5 | 1.30(9) | −0.88(6) | 0.982 |
| **17A**⇌**17B**[b] | 6 | 0.77(3) | −1.04(4) | 0.985 |

[a] Standard deviations are given in parentheses.
[b] Data from Ref. 6.




**17A** **17B**

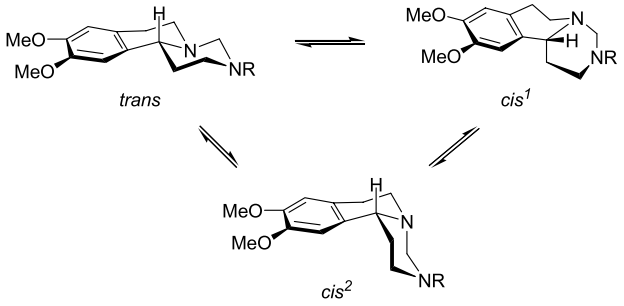



**Figure 2.** Possible steric structures of 1,3,4,6,7,11b-hexahydro-2*H*-pyrimido[6,1-*a*]isoquinolines.

rings was found for the conformational equilibrium of the 3-methyl-substituted parent compound in $CDCl_3$.[22]

Conformational analysis of the prepared hexahydropyrimido[6,1-*a*]isoquinolines was performed only for the 4-(*p*-nitrophenyl)-substituted derivatives, which contain the cyclic tautomers in the highest proportions. To determine the mode of connection of the B/C rings $^1$H NMR spectroscopic methods were used, since the geometries of the B/C ring connections of *cis*[1] or *cis*[2] or *trans* type produce different patterns of cross-peaks derived from the 1,3-diaxial protons in the NOESY spectra. While the stereostructure of the major cyclic forms (**B**) of the prepared model compounds could be determined in each case (**12a**–**14a** and **16a**), the relatively low abundance of the minor cyclic form (**C**) meant that its conformational analysis could be performed only for **14a**.

For **12aB** and **13aB**, the NOESY spectra showed H-11b–H-$6_{ax}$, H-11b–H-4, and H-4–H-$6_{ax}$ NOE cross-peaks, which are typical for a B/C *trans*-arranged ring junction with an equatorial aromatic substituent. For **14aB**, however, the NOESY spectrum revealed H-1–H-$6_{ax}$, H-11b–H-$2_{ax}$ and H-11b–H-4 NOE cross-peaks, which unequivocally proved the *cis*[1] connection of the B/C rings. For **14aC**, the NOESY cross-peaks for H-11b with H-$2_{ax}$, H-$6_{ax}$ and the *ortho* protons of the 4-(*p*-nitrophenyl) substituents pointed to a *trans* B/C ring junction with an axial aromatic substituent. The NOESY cross-peaks for the (6*R**,11b*R**)-6-methyl-substituted C-4 epimeric model compounds (**16aB** and **16aC**) could be characterized by different B/C ring junctions: *trans* for **16aB** (NOESY cross-peaks: H-11b-H-$2_{ax}$, H-11b-H-4 and H-4-Me-$6_{ax}$), and *equatorial* and *cis*[1] for **16aC** (NOESY cross-peaks: H-11b–H-$2_{ax}$, H-4–Me-$6_{ax}$) with an *axial* 4-(*p*-nitrophenyl) substituent.

The structures of the C-4 epimers of **14a** and **16a** were confirmed by molecular modelling. The conformational protocol comprised a stochastic search, using the Merck Molecular Force Field (MMFF94). Figure 3 depicts the typical minimum-energy molecular structures for **14aB** and **14aC** and for **16aB** and **16aC**. The steric hindrance between H-11 and the 1-methyl group (for **14aB**), or between the 6-methyl and 4-(*p*-nitrophenyl) groups (for **16aC**), makes the predominant conformation with *trans*-arranged B/C rings unfavourable and shifts the conformational equilibrium towards the *cis*[1] structure.

## 3. Conclusions

Both the ring-chain tautomeric and conformational equilibria of 4-aryl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2*H*-pyrimido[6,1-*a*]isoquinolines proved to be sensitive to the effects of the methyl substituents at position 1 or 6 and the configurations of the substituted carbons (C-1 or C-6 and C-4) relative to C-11b. For the 1,6-unsubstituted parent compound **12**, NMR spectroscopic investigations revealed the predominance of the ring form **B** (*cis* H-4 and H-11b) with a *trans* B/C anellated conformation in $CDCl_3$ at 300 K. (1*R**,11b*R**)-1-Methyl substitution (**14**) caused changes in the ratios of the C-4 epimeric ring-closed tautomers (**B** and **C**). 6-Methyl substitution resulted in dramatic decreases in the ratios of the ring-closed forms, leading either to a total shift of the equilibrium towards the open forms (**A**) for the 6*S**,11b*R** isomers (**15**) or to the existence of three-component tautomeric equilibria for the 6*R**,11b*R** compounds (**16**), which could be characterized by a

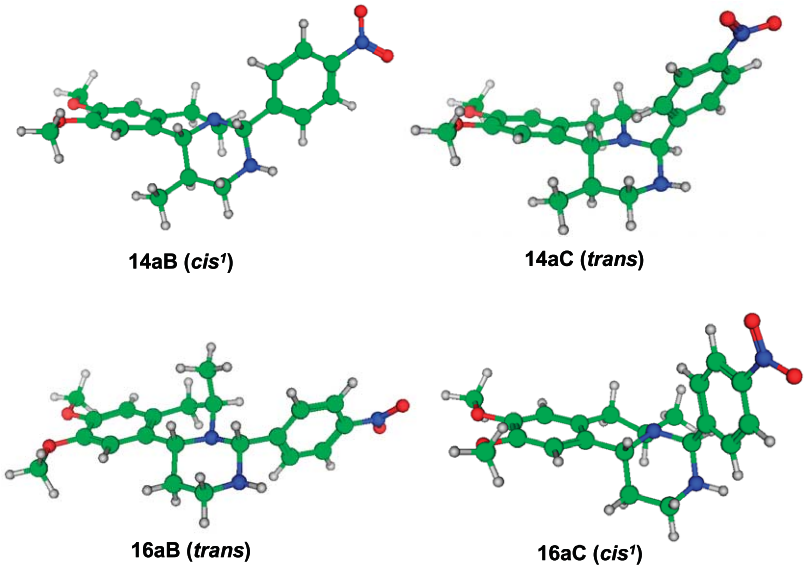



**Figure 3.** Typical minimum-energy structures for **14aB** and **14aC** and for **16aB** and **16aC**.

Hammett-type equation. For **14a** and **16a**, steric hindrance between the substituents resulted in different predominant conformations (*cis*[1] for **14aB** and **16aC**; *trans* for **14aC** and **16aB**) for the C-4 epimeric ring forms (**B** and **C**).

## 4. Experimental

### 4.1. General

The $^1$H NMR spectra were recorded in $CDCl_3$ or in $D_2O$ solutions at 300 K on a Bruker AVANCE DRX 400 spectrometer at 400.13 MHz ($^1$H NMR) and at 100.03 MHz ($^{13}$C NMR). Chemical shifts are given in $\delta$ (ppm) relative to TMS ($CDCl_3$) or to DSS ($D_2O$) as internal standards; multiplicites were recorded as s (singlet), bs (broad singlet), d (doublet), dd (double doublet), ddd (double double doublet), dt (double triplet), t (triplet), q (quartet) and m (multiplet). In the cases of **12–16**, the solutions were left to stand at ambient temperature for 1 day for the equilibria to be established before the $^1$H NMR spectra were run. IR spectra were run in KBr discs on a Perkin–Elmer Paragon 1000 PC FT-IR spectrometer controlled by GRAMS Analyst for PE 1000 3.01A software. Mass spectra were recorded on a Finnigan MAT 95S instrument, using electron impact ionization. Melting points were recorded on a Kofler hot-plate microscope apparatus and are uncorrected.

Compounds **2a–c**,[14,15] **4**[23] and **10**[17] were prepared according to known procedures.

**4.1.1. 3-Benzyloxycarbonylamino-*N*-[1-methyl-2-(3,4-dimethoxyphenyl)ethyl]propanamide (5).** To a stirred and ice-salt bath-cooled solution of *N*-benzyloxycarbonyl-β-alanine (11.16 g, 0.05 mol) and triethylamine (5.06 g, 0.05 mol) in anhydrous toluene (150 mL), ethyl chloroformate (5.43 g, 0.05 mol) was added dropwise at a rate low enough to keep the internal temperature below −10 °C. After 5 min, a solution of 1-methyl-2-(3,4-dimethoxyphenyl)ethylamine (**4**) (9.76 g, 0.05 mol) in $CH_2Cl_2$ (60 mL) was added dropwise, the internal temperature being kept below 0 °C. When the addition was complete, the reaction mixture was heated under reflux for 5 min. The mixture was allowed to cool down to room temperature and $CHCl_3$ (300 mL) was added. The mixture was next washed with saturated $NaHCO_3$ solution (3×75 mL) and water (2×75 mL), and then dried ($Na_2SO_4$), and the solvent was removed in vacuo to give a crude oily (**2**) product, which crystallized on treatment with $Et_2O$. The crystals were filtered off, washed with $Et_2O$ and recrystallized from EtOAc.

Compound **5**. A white solid; yield: 16.75 g (84%); mp 107–108 °C; [found: C, 65.76; H, 6.98; N, 7.05. $C_{22}H_{28}N_2O_5$ requires C, 65.98; H, 7.05; N, 6.99%]; $\nu_{max}$ 3335, 1690, 1636, 1542, 1262 cm$^{-1}$; $^1$H NMR $\delta$ ($CDCl_3$) 1.10 (3H, d, $J$=6.6 Hz, C$H_3$), 2.28–2.41 (2H, m, COC$H_2$), 2.60 (1H, dd, $J$=13.6, 7.4 Hz, ArC$H_2$), 2.76 (1H, dd, $J$=13.6, 5.9 Hz, ArC$H_2$), 3.44 (2H, q, $J$=6.0 Hz, NC$H_2$), 3.83 (3H, s, OC$H_3$), 3.85 (3H, s, OC$H_3$), 4.15–4.27 (m, 1H, NC$H$), 5.09 (2H, s, OC$H_2$), 5.38 (1H, bs, N$H$), 5.45 (1H, d, $J$=6.8 Hz, N$H$), 6.66–6.71 (2H, m, C$_6H_3$), 6.77 (1H, d, $J$=8.2 Hz, C$_6H_3$), 7.28–7.38 (5H, m, C$_6H_5$); MS $m/z$ 400 [M+1]$^+$.

**4.1.2. 1-[2′-(Benzyloxycarbonylamino)ethyl]-3-methyl-6,7-dimethoxy-3,4-dihydroisoquinoline (6).** To a stirred solution of the propanamide (**2**, 16.02 g, 0.04 mol) in dry $CHCl_3$ (300 mL), $POCl_3$ (18.40 g, 0.12 mol) was added. The mixture was heated under reflux for 3 h, and then evaporated in vacuo. The oily residue was dissolved in water (250 mL) under gentle warming, and the solution was cooled and extracted with EtOAc (2×75 mL). The aqueous phase was made alkaline with 25% NaOH solution with cooling, and extracted with $CHCl_3$ (4×150 mL). The combined organic extracts were dried ($Na_2SO_4$) and evaporated to give a crystalline product, which was filtered off and washed with $Et_2O$. This crude product was used in the next step without further purification.

Compound **6**. Yield: 11.98 g (78%). An analytical sample of **6** was recrystallized from MeOH to give beige needles, mp 128–130 °C; [found: C, 68.91; H, 6.87; N, 7.48. $C_{22}H_{26}N_2O_4$ requires C, 69.09; H, 6.85; N, 7.32%]; $\nu_{max}$ 3192, 2956, 1701, 1517, 1280 cm$^{-1}$; $^1$H NMR $\delta$ ($CDCl_3$) 1.33 (3H, d, $J$=6.8 Hz, C$H_3$), 2.38 (1H, dd, $J$=15.6, 12.3 Hz, 4-C$H_2$), 2.65 (1H, dd, $J$=15.6, 5.4 Hz, 4-C$H_2$), 2.77–2.96 (2H, m, 1′-C$H_2$), 3.49–3.67 (3H, m, 3-C$H$, 2′-C$H_2$), 3.91 (6H, s, 2×OC$H_3$), 5.09 (2H, s, OC$H_2$), 5.70 (1H, bs, N$H$), 6.66 (1H, s, C$_6H_2$), 7.01 (1H, s, C$_6H_2$), 7.27–7.38 (5H, m, C$_6H_5$); MS $m/z$ 382 [M+1]$^+$.

**4.1.3. (1*R**,3*S**)-1-[2′-(Benzyloxycarbonylamino)ethyl]-3-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (7a).** To a stirred and ice-cooled solution of dihydroisoquinoline **6** (11.47 g, 30 mmol) in MeOH (250 mL), $NaBH_4$ (3.40 g, 90 mmol) was added in small portions. The resulting mixture was stirred for 3 h with ice-water bath cooling and for 3 h without, and then evaporated in vacuo. The residue was dissolved in 5% HCl (250 mL), and the solution was made alkaline with 20% NaOH while cooled, and then extracted with $CHCl_3$ (4×150 mL). The combined organic extracts were dried ($Na_2SO_4$) and evaporated in vacuo to give an oily product, containing diastereomers **7a** and **7b** in a 12:1 ratio. The oil crystallized on treatment with *n*-hexane. The crystalline product, which was filtered off and washed with *n*-hexane, proved to be diastereomerically pure **7a**. The crude crystalline product was used in the next step without further purification.

Compound **7a**. Yield: 9.46 g (82%). An analytical sample of **7a** was recrystallized from $Et_2O$ to give a white solid, mp 69–72 °C; [found: C, 67.80; H, 6.97; N, 7.59. $C_{22}H_{28}N_2O_4$ requires C, 68.73; H, 7.34; N, 7.29%]; $\nu_{max}$ 3346, 1687, 1532, 1247, 1094 cm$^{-1}$; $^1$H NMR $\delta$ ($CDCl_3$) 1.19 (3H, d, $J$=6.0 Hz, C$H_3$), 1.82–1.92 (1H, m, 1′-C$H_2$), 2.04–2.14 (1H, m, 1′-C$H_2$), 2.45 (1H, dd, $J$=15.5, 10.7 Hz, 4-C$H_2$), 2.56 (1H, dd, $J$=15.5, 2.9 Hz, 4-C$H_2$), 2.85–2.95 (1H, m, 2′-C$H_2$), 3.26–3.35 (2H, m, 3-C$H$, 2′-C$H_2$), 3.80 (6H, s, 2×OC$H_3$), 4.13–4.19 (1H, m, 1-C$H$), 5.05 (2H, s, OC$H_2$), 6.13 (1H, bs, N$H$), 6.52 (1H, s, C$_6H_2$), 6.61 (1H, s, C$_6H_2$), 7.23–7.35 (5H, m, C$_6H_5$); MS $m/z$ 384 [M+1]$^+$.

**4.1.4. (1*R**,3*S**)-1-(2′-Aminoethyl)-3-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline dihydrobromide**

**(8·2HBr).** A mixture of compound **7a** (7.69 g, 20 mmol) and 33% HBr in AcOH (25 mL) was heated gently in a flask equipped with a $CaCl_2$ tube, with occasional shaking, until all of the substance had dissolved. The bubbling solution was left to stand at ambient temperature for 30 min, and $Et_2O$ (25 mL) was then added. The yellow crystals of the dihydrobromide of **8** which formed were filtered off, washed with a mixture of MeOH and $Et_2O$, dried and recrystallized from 90% MeOH–$Et_2O$.

Compound **8**·2HBr. White crystals; yield: 6.10 g (74%); mp 250–252 °C; [found: C, 40.97; H, 5.76, N, 6.89. $C_{14}H_{24}Br_2N_2O_2$ requires C, 40.80, H, 5.87; N, 6.80%]; $\nu_{max}$ 3410, 1613, 1522, 1256, 1009 $cm^{-1}$; $^1H$ NMR $\delta$ ($D_2O$) 1.57 (3H, d, $J=6.6$ Hz, C$H_3$), 2.48–2.72 (2H, m, 1′-C$H_2$), 2.96–3.10 (2H, m, 4-C$H_2$), 3.20–3.37 (2H, m, 2′-C$H_2$), 3.57–3.68 (1H, m, 3-C*H*), 3.90 (3H, s, OC$H_3$), 3.93 (3H, s, OC$H_3$), 4.81–4.85 (1H, m, 1-C*H*), 6.94 (1H, s, $C_6H_2$), 6.96 (1H, s, $C_6H_2$); MS *m/z* 250 $[M+1]^+$.

**4.1.5. (1*R**,3*R**)-1-(2′-Aminoethyl)-3-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline dihydrochloride (11·2HCl).** To a stirred and cooled suspension of $LiAlH_4$ (3.42 g, 90 mmol) in dry THF (120 mL), (1*R**,3*R**)-6,7-dimethoxy-3-methyl-1,2,3,4-tetrahydroisoquinoline-1-acetamide (**10**)[17] (7.93 g, 30 mmol) was added in small portions. The mixture was stirred and refluxed for 4 h and then cooled, and the excess of $LiAlH_4$ was decomposed by the addition of a mixture of water (6.8 mL) and THF (30 mL). The inorganic salts were filtered off and washed with EtOAc (3×50 mL). The combined organic filtrate and washings were dried ($Na_2SO_4$) and evaporated under reduced pressure to give an oily product, which was converted to the crystalline dihydrochloride of **11** by treatment of its solution in MeOH with an excess of 22% ethanolic HCl and $Et_2O$. The crystalline dihydrochloride of **11** was filtered off, dried and recrystallized from MeOH–$H_2O$–$Et_2O$.

Compound **11**·2HCl. A white solid, yield: 4.37 g (45%); mp 240–245 °C; [found: C, 51.97; H, 7.56, N, 8.74. $C_{14}H_{24}Cl_2N_2O_2$ requires C, 52.02, H, 7.48; N, 8.67%]; $\nu_{max}$ 3157, 1618, 1521, 1259, 1117 $cm^{-1}$; $^1H$ NMR $\delta$ ($D_2O$) 1.54 (3H, d, $J=6.3$ Hz, C$H_3$), 2.43–2.49 (2H, m, 1′-C$H_2$), 2.88 (1H, dd, $J=10.0$, 17.5 Hz, 4-C$H_2$), 3.24–3.35 (3H, m, 2′-C$H_2$, 4-C$H_2$), 3.90 (3H, s, OC$H_3$), 3.91 (3H, s, OC$H_3$), 3.94–3.98 (1H, m, 3-C*H*), 4.75 (1H, t, $J=6.5$ Hz, 1-C*H*), 6.90 (1H, s, $C_6H_2$), 6.97 (1H, s, $C_6H_2$); MS *m/z* 250 $[M+1]^+$.

Pure diamine bases **8** and **11** were obtained from the above dihydrohalides by alkaline treatment (20% NaOH), extraction ($CH_2Cl_2$) and evaporation under reduced pressure. The free bases were dried in a vacuum desiccator for 24 h before further transformations.

### 4.2. General procedure for the preparation of 4-Aryl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2*H*-pyrimido[6,1-*a*]isoquinolines (12–16)

To a solution of the corresponding tetrahydroisoquinoline diamine (**2a–c**, **8** and **11**) (3 mmol) in absolute MeOH (25 mL), an equivalent amount of aromatic aldehyde was added (for liquid aldehydes, a freshly distilled sample was used), and the mixture was allowed to stand at ambient temperature for 1 h. The solvent was then evaporated off and the oily product crystallized on treatment with $Et_2O$ or *n*-hexane. The crystalline products (**12a**,**b**, **13a**,**b**, **14a**,**b**, **15a**,**b** and **16a**,**c**,**d**,**e**,**g**) were filtered off and recrystallized. In the cases of **16b** and **16f**, the evaporation was repeated after the addition of toluene (10 mL), and the oily products (obtained in nearly quantitative yields) were dried in a vacuum desiccator for 24 h. The NMR spectrum proved that the purity of these compounds was >95%.

In consequence of the small relative concentrations, only the characteristic N–C*H*Ar–N and N=C*H*Ar protons are listed for the detectable minor tautomeric forms of **12a**,**b**, **13a**,**b**, **14b** and **15a**,**b**; a full NMR characterization is given for **12aB**, **13aB**, **14aB**, **14aC** and **15aA**. With regard to the similarities in the $^1H$ NMR data for **16a–g**, the full spectra of the major tautomers are described only for two representatives of this set of compounds (**16aB** and **16gA**). The protons of the open form (**A**) are numbered according to the corresponding protons of the 1,3,4,6,7,11b-hexahydro-2*H*-[6,1-*a*]isoquinoline ring forms (**B** and **C**).

**4.2.1. Compound 12a.** Beige crystals; yield: 0.83 g (75%); mp: 150–151 °C (*i*$Pr_2O$–EtOAc); [found: C, 65.25; H, 6.13; N, 11.48. $C_{20}H_{23}N_3O_4$ requires C, 65.03; H, 6.28; N, 11.37%]; $\nu_{max}$ 2910, 1520, 1224, 1099, 745 $cm^{-1}$; $^1H$ NMR $\delta$ ($CDCl_3$) 1.77 (1H, dd, $J=4.3$, 12.6 Hz, H-1), 2.18–2.30 (2H, m, H-1, H-6), 2.54 (1H, dt, $J=3.8$, 16.1 Hz, H-7), 2.66–2.74 (1H, m, H-6), 2.88 (1H, dd, $J=2.8$, 16.1 Hz, H-7), 3.37 (1H, ddd, $J=1.3$, 4.0, 13.4 Hz, H-2), 3.70 (1H, d, $J=$ 10.6 Hz, H-11b), 3.86 (3H, s, OC$H_3$), 3.87 (3H, s, OC$H_3$), 4.40 (1H, s, H-4), 6.58 (1H, s, H-8), 6.71 (1H, s, H-11), 7.68–7.74 (2H, m, Ar), 8.22–8.26 (2H, m, Ar), $^{13}C$ NMR $\delta$ ($CDCl_3$) 29.5, 32.4, 46.4, 46.6, 56.6, 56.8, 62.8, 81.1, 108.8, 112.2, 124.7, 127.4, 128.9, 130.6, 148.4 (3×), 149.9 (tautomeric form **B**); 4.92 (1H, s, 4-H) (tautomeric form **C**); MS *m/z* 369 $[M+1]^+$.

**4.2.2. Compound 12b.** Beige crystals; yield: 0.62 g (56%); mp: 100–103 °C (*i*$Pr_2O$); [found: C, 72.21; H, 8.02; N, 11.31. $C_{22}H_{29}N_3O_2$ requires C, 71.90; H, 7.95; N, 11.43%]; $\nu_{max}$ 2938, 1610, 1517, 1253, 820 $cm^{-1}$; $^1H$ NMR $\delta$ ($CDCl_3$) 4.15 (N–C*H*Ar–N) (tautomeric form **B**); MS *m/z* 367 $[M+1]^+$.

**4.2.3. Compound 13a.** Orange-yellow crystals; yield: 0.49 g (43%); mp: 86–90 °C (*n*-hexane); [found: C, 66.02; H, 6.45; N, 10.88. $C_{21}H_{25}N_3O_4$ requires C, 65.78; H, 6.57; N, 10.96%]; $\nu_{max}$ 2964, 1519, 1343, 1133, 861 $cm^{-1}$; $^1H$ NMR $\delta$ ($CDCl_3$) 1.02 (3H, d, $J=6.8$ Hz, C$H_3$), 2.12 (1H, ddd, $J=3.3$, 11.8 Hz, H-6), 2.31–2.43 (2H, m, H-1, H-7), 2.54–2.61 (1H, m, H-6), 2.83–2.93 (1H, m, H-7), 3.10 (1H, dd, $J=1.3$, 13.6 Hz, H-2), 3.28 (1H, dd, $J=3.3$, 13.6 Hz, H-2), 3.72 (1H, s, H-11b), 3.86 (3H, s, OC$H_3$), 3.87 (3H, s, OC$H_3$), 4.22 (1H, s, H-4), 6.56 (1H, s, H-8), 6.69 (1H, s, H-11), 7.68–7.74 (2H, m, Ar), 8.22–8.28 (2H, m, Ar), $^{13}C$ NMR $\delta$ ($CDCl_3$) 12.6, 29.5, 32.7, 48.3, 52.5, 56.5, 56.8, 66.4, 82.1, 108.4, 112.0, 124.8, 128.7, 129.3, 148.0 (2×), 148.5, 150.6 (tautomeric form **B**); 4.87 (H-4) (tautomeric form **C**); MS *m/z* 383 $[M+1]^+$.

**4.2.4. Compound 13b.** Pale-yellow crystals; yield: 0.80 g (70%); mp: 129–131 °C (*n*-hexane); [found: C, 72.26; H,

8.30; N, 10.89. $C_{23}H_{31}N_3O_2$ requires C, 72.41; H, 8.19; N, 11.01%]; $\nu_{max}$ 2904, 1611, 1249, 1131, 820 $cm^{-1}$; $^1H$ NMR $\delta$ ($CDCl_3$) 4.00 (N–C*H*Ar–N) (tautomeric form **B**); MS *m/z* 381 $[M+1]^+$.

**4.2.5. Compound 14a.** Yellow crystals; yield: 0.75 g (65%); mp: 147–149 °C (EtOH); [found: C, 65.50; H, 6.38; N, 10.73. $C_{21}H_{25}N_3O_4$ requires C, 65.78; H, 6.57; N, 10.96%]; $\nu_{max}$ 2910, 1513, 1350, 1123, 834 $cm^{-1}$; $^1H$ NMR $\delta$ ($CDCl_3$) 0.99 (3H, d, $J=6.3$ Hz, C$H_3$), 1.99–2.13 (2H, m, H-1), 2.37 (1H, dd, $J=7.3$, 11.3 Hz, H-2), 2.64 (1H, dd, $J=4.0$, 16.1 Hz, H-7), 2.75–2.98 (2H, m, H-2, H-7), 3.06 (1H, ddd, $J=4.3$, 11.3 Hz, H-6), 3.36 (1H, dd, $J=4.3$, 13.1 Hz, H-2), 3.77–3.81 (1H, m, H-11b), 3.85 (3H, s, OC$H_3$), 3.86 (3H, s, OC$H_3$), 5.12 (1H, s, H-4), 6.62 (2H, s, H-8, H-11), 7.72–7.78 (2H, m, Ar), 8.17–8.24 (2H, m, Ar), $^{13}C$ NMR $\delta$ ($CDCl_3$) 17.4, 29.2, 29.8, 36.7, 54.9, 56.2 (2×), 67.2, 78.0, 112.1, 112.5, 123.8, 127.1, 128.4, 129.2, 146.5, 148.2 (3×) (tautomeric form **B**); $^1H$ NMR $\delta$ ($CDCl_3$) 0.85 (3H, d, $J=6.6$ Hz, C$H_3$), 1.99–2.13 (1H, m, H-1), 2.50 (1H, dd, $J=10.3$, 13.9 Hz, H-6), 2.75–2.98 (3H, m, H-2, H-6, H-7), 3.08–3.16 (1H, m, H-7), 3.49 (1H, d, $J=9.6$ Hz, H-11b), 3.60 (1H, ddd, $J=4.8$, 10.8 Hz, H-2), 3.79 (3H, s, OC$H_3$), 3.88 (3H, s, OC$H_3$), 4.89 (1H, s, H-4), 6.46 (2H, s, H-8), 6.67 (2H, s, H-11), 7.92–7.98 (2H, m, Ar), 8.17–8.24 (2H, m, Ar), $^{13}C$ NMR $\delta$ ($CDCl_3$) 17.5, 28.9, 30.3, 45.7, 48.6, 56.4, 56.5, 59.7, 76.0, 112.1, 112.2, 124.0, 127.0, 128.7, 129.3, 147.8, 148.2, 148.4, 148.9 (tautomeric form **C**); MS *m/z* 383 $[M+1]^+$.

**4.2.6. Compound 14b.** White crystals; yield: 0.49 g (43%); mp: 123–125 °C (*i*$Pr_2O$); [found: C, 72.08; H, 8.03; N, 10.81. $C_{23}H_{31}N_3O_2$ requires C, 72.41; H, 8.19; N, 11.01%]; $\nu_{max}$ 2929, 1519, 1225, 1125, 812 $cm^{-1}$; $^1H$ NMR $\delta$ ($CDCl_3$) 4.99 (N–C*H*Ar–N) (tautomeric form **B**); 4.70 (N–C*H*Ar–N) (tautomeric form **C**); MS *m/z* 381 $[M+1]^+$.

**4.2.7. Compound 15a.** A pale-beige solid; yield: 0.72 g (63%); mp: 108–109 °C (*n*-hexane–$Et_2O$); [found: C, 65.59; H, 6.41; N, 11.10. $C_{21}H_{25}N_3O_4$ requires C, 65.78; H, 6.57; N, 10.96%]; $\nu_{max}$ 2860, 1517, 1350, 1219, 855 $cm^{-1}$; $^1H$ NMR $\delta$ ($CDCl_3$) 1.24 (3H, d, $J=6.3$ Hz, C$H_3$), 2.03–2.14 (1H, m, H-1), 2.36–2.51 (2H, m, H-1, H-7), 2.62 (1H, dd, $J=3.3$, 15.9 Hz, H-7), 2.94–3.05 (1H, m, H-6), 3.75–3.92 (8H, m, 2×H-2, 2×OC$H_3$), 4.27 (1H, d, $J=7.3$ Hz, H-11b), 6.55 (1H, s, H-8), 6.71 (1H, s, H-11), 7.84–7.90 (2H, m, Ar), 8.24–8.30 (2H, m, Ar), 8.35 (1H, s, N=C*H*Ar), $^{13}C$ NMR $\delta$ ($CDCl_3$) 23.1, 37.7, 38.4, 49.3, 55.7, 56.2, 56.5, 58.9, 108.9, 112.0, 124.3, 128.5, 129.1, 130.3, 142.0, 147.7, 159.4 (tautomeric form **A**); MS *m/z* 383 $[M+1]^+$.

**4.2.8. Compound 15b.** A pale-beige solid; yield: 0.66 g (58%); mp: 69–72 °C (*n*-hexane-$Et_2O$); [found: C, 72.60; H, 8.27; N, 11.16. $C_{23}H_{31}N_3O_2$ requires C, 72.41; H, 8.19; N, 11.01%]; $\nu_{max}$ 3581, 2904, 1610, 1219, 817 $cm^{-1}$; $^1H$ NMR $\delta$ ($CDCl_3$) 8.12 (N=C*H*Ar) (tautomeric form **A**); MS *m/z* 381 $[M+1]^+$.

**4.2.9. Compound 16a.** Pale-yellow crystals; yield: 0.91 g (79%); mp: 135–139 °C (*n*-hexane–EtOAc); [found: C, 65.96; H, 6.40; N, 11.09. $C_{21}H_{25}N_3O_4$ requires C, 65.78; H, 6.57; N, 10.96%]; $\nu_{max}$ 2927, 1512, 1343, 1108, 999 $cm^{-1}$; $^1H$ NMR $\delta$ ($CDCl_3$) 8.46, $^{13}C$ NMR $\delta$ ($CDCl_3$) 159.3 (tautomeric form **A**); $^1H$ NMR $\delta$ ($CDCl_3$) 0.86 (3H, d, $J=6.6$ Hz, C$H_3$), 1.70 (1H, ddd, $J=4.5$, 12.8 Hz, H-1), 2.22 (1H, d, $J=15.6$ Hz, H-7), 2.30–2.37 (1H, m, H-1), 2.89–2.93 (1H, m, H-6), 3.02 (1H, ddd, $J=2.8$, 13.4 Hz, H-2), 3.10 (1H, dd, $J=5.5$, 15.6 Hz, H-7), 3.32 (1H, ddd, $J=1.5$, 4.0, 13.4 Hz, H-2), 3.84–3.87 (7H, m, H-11b, 2×OC$H_3$), 4.50 (1H, s, H-4), 6.55 (1H, s, H-8), 6.71 (1H, s, H-11), 7.65–7.71 (2H, m, Ar), 8.22–8.28 (2H, m, Ar) $^{13}C$ NMR $\delta$ ($CDCl_3$) 10.0, 34.2, 36.1, 45.3, 48.0, 55.5, 56.2, 56.4, 78.6, 108.2, 112.5, 124.6 (2×), 125.7, 129.0, 147.6, 149.6 (3×) (tautomeric form **B**); $^1H$ NMR $\delta$ ($CDCl_3$) 5.24, $^{13}C$ NMR $\delta$ ($CDCl_3$) 69.6 (tautomeric form **C**); MS *m/z* 383 $[M+1]^+$.

**4.2.10. Compound 16b.** An orange foam; [found: C, 60.72; H, 5.89; N, 6.78. $C_{21}H_{25}BrN_2O_2$ requires C, 60.44; H, 6.04; N, 6.71%]; $\nu_{max}$ 2829, 1508, 1250, 1018, 779 $cm^{-1}$; $^1H$ NMR $\delta$ ($CDCl_3$) 8.21 (N=C*H*Ar) (tautomeric form **A**); 4.27 (N–C*H*Ar–N) (tautomeric form **B**); 4.99 (N–C*H*Ar–N) (tautomeric form **C**); MS *m/z* 416 $[M+1]^+$.

**4.2.11. Compound 16c.** A pale-yellow solid; yield: 0.90 g (72%); mp: 113–116 °C (*n*-hexane–EtOAc); [found: C, 60.17; H, 5.89; N, 6.92. $C_{21}H_{25}BrN_2O_2$ requires C, 60.44; H, 6.04; N, 6.71%]; $\nu_{max}$ 2945, 1513, 1248, 1002, 737 $cm^{-1}$; $^1H$ NMR $\delta$ ($CDCl_3$) 8.33 (N=C*H*Ar) (tautomeric form **A**); 4.37 (N-C*H*Ar-N) (tautomeric form **B**); 5.07 (N–C*H*Ar–N) (tautomeric form **C**); MS *m/z* 416 $[M+1]^+$.

**4.2.12. Compound 16d.** Yellow crystals; yield: 0.77 g (76%); mp: 88–91 °C (*n*-hexane–EtOAc); [found: C, 74.77; H, 7.52; N, 8.40. $C_{21}H_{26}N_2O_2$ requires C, 74.52; H, 7.74; N, 8.28%]; $\nu_{max}$ 2921, 1513, 1251, 1108, 794 $cm^{-1}$; $^1H$ NMR $\delta$ ($CDCl_3$) 8.30 (N=C*H*Ar) (tautomeric form **A**); 4.31 (N–C*H*Ar–N) (tautomeric form **B**); 4.97 (N–C*H*Ar–N) (tautomeric form **C**); MS *m/z* 338 $[M+1]^+$.

**4.2.13. Compound 16e.** Yellow crystals; yield: 0.66 g (62%); mp: 73–75 °C (*n*-hexane); [found: C, 75.12; H, 8.20; N, 7.81. $C_{22}H_{28}N_2O_2$ requires C, 74.97; H, 8.01; N, 7.95%]; $\nu_{max}$ 2959, 1514, 1251, 1109, 780 $cm^{-1}$; $^1H$ NMR $\delta$ ($CDCl_3$) 8.35 (N=C*H*Ar) (tautomeric form **A**); 4.37 (N–C*H*Ar–N) (tautomeric form **B**); 5.02 (N–C*H*Ar–N) (tautomeric form **C**); MS *m/z* 352 $[M+1]^+$.

**4.2.14. Compound 16f.** A yellow oil; [found: C, 72.02; H, 7.51; N, 7.69. $C_{22}H_{28}N_2O_3$ requires C, 71.71; H, 7.66; N, 7.60%]; $\nu_{max}$ 2936, 1606, 1248, 1032, 833 $cm^{-1}$; $^1H$ NMR $\delta$ ($CDCl_3$) 8.21 (N=C*H*Ar) (tautomeric form **A**); 4.25 (N–C*H*Ar–N) (tautomeric form **B**); MS *m/z* 368 $[M+1]^+$.

**4.2.15. Compound 16g.** Yellow crystals; yield: 0.97 g (85%); mp: 111–114 °C (*n*-hexane–EtOAc); [found: C, 72.68; H, 8.07; N, 10.86. $C_{23}H_{31}N_3O_2$ requires C, 72.41; H, 8.19; N, 11.01%]; $\nu_{max}$ 2835, 1607, 1517, 1224, 1092 $cm^{-1}$; $^1H$ NMR $\delta$ ($CDCl_3$) 1.18 (3H, d, $J=6.3$ Hz, C$H_3$), 1.94–2.05 (1H, m, H-1), 2.08–2.08 (1H, m, H-1), 2.39 (1H, dd, $J=10.3$, 16.2 Hz, H-7), 2.66 (1H, dd, $J=3.8$, 16.2 Hz, H-7), 3.01 (6H, s, N($CH_3$)$_2$), 3.15–3.27 (1H, m, H-6), 3.69–3.79 (1H, m, H-2), 3.81–3.83 (7H, m, H-2, 2×OC$H_3$), 4.11 (1H, dd, $J=2.8$, 10.3 Hz, H-11b), 6.53 (1H, s, H-8), 6.60 (1H, s, H-11), 6.67–6.72 (2H, m, Ar), 7.69–7.64 (2H, m, Ar), 8.23 (N=C*H*Ar), $^{13}C$ NMR $\delta$ ($CDCl_3$) 23.0, 37.6, 38.4, 40.6, 42.9, 55.0, 56.2, 56.4, 60.1, 110.2, 111.9, 112.0, 112.5,

124.9, 127.2, 129.8, 131.9, 147.5, 147.6, 152.4, 161.6 (tautomeric form **A**); 4.29 (N–C*H*Ar–N) (tautomeric form **B**); MS *m*/*z* 381 $[M+1]^+$.

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# Synthesis of naturally occurring bioactive butyrolactones: maculalactones A–C and nostoclide I☆

Anirban Kar, Sanjib Gogoi and Narshinha P. Argade*

*Division of Organic Chemistry (Synthesis), National Chemical Laboratory, Pune 411 008, India*

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**Abstract**—Starting from citraconic anhydride (**13**), a simple multistep (9–10 steps) synthesis of naturally occurring butyrolactones maculalactone A (**3**), maculalactone B (**1**), maculalactone C (**2**) and nostoclide I (**4**) have been described with good overall yields via dibenzylmaleic anhydride (**20**) and benzylisopropylmaleic anhydride (**27**). The two anhydrides **20** and **27** were prepared by $S_N2'$ coupling reactions of appropriate Grignard reagents with dimethyl bromomethylfumarate (**14**), LiOH-induced hydrolysis of esters to acids, bromination of carbon–carbon double bond, in situ dehydration followed by dehydrobromination and chemoselective allylic substitution of bromoatom in disubstituted anhydrides **19** and **26** with appropriate Grignard reagents. The $NaBH_4$ reduction of these anhydrides **20** and **27** furnished the desired lactones **21** and **29**, respectively. The lactone **21** on Knoevenagel condensation with benzaldehyde, furnished maculalactone B (**1**), which on isomerization gave maculalactone C (**2**). Selective catalytic hydrogenation of **1** gave maculalactone A (**3**). The conversion of lactone **29** to nostoclide I (**4**) is known.


## 1. Introduction

A very large number of natural and unnatural butyrolactones are known in the literature.[1] Recently several diverse skeletons with butyrolactone as a core unit have been isolated as bioactive natural products[2–11] and some of them have been depicted in Figure 1. These butyrolactones possess cytotoxic, antibiotic and antimicrobial activities.[3,6,8] Maculalactones A–C have been isolated from the epilithic-encrusting cyanobacterium *Kyrtuthrix maculans* from Hong Kong island and they possess marine anti-fouling activity.[2,12] The natural (+)-maculalactone A has been assigned *S*-configuration. To date only one synthesis of these butyrolactones **1**-**3** has been reported in the literature.[12] Nostoclide I (**4**) has been isolated from the culture of a symbiotic blue-green alga, *Nostoc* sp., from the lichen *Peltigera canina* and it has cytotoxic activity.[3] To date two syntheses of **4** are known in the literature.[13] These butyrolactones are generally synthesized via Stobbe condensation,[12] Stille coupling reaction[13b] and conversion of furan to the required lactone.[13a] Since 1997, using cyclic anhydrides as potential precursors, we have designed several bioactive natural products in our group.[14] We felt that the synthesis of suitably disubstituted maleic anhydrides, followed by their reductive conversion to the respective lactones, and then the Knoevenagel condensation with different aldehydes will provide an easy access to these novel butenolide skeletons. In continuation of our ongoing studies on cyclic anhydrides to bioactive natural products,[14] now we herein report the synthesis of naturally occurring maculalactones A–C (**3**,**1**,**2**) and nostoclide I (**4**), starting from citraconic anhydride (**13**) via the unsymmetrical bromomethylmaleic anhydrides **19** and **26** (Schemes 1 and 2).

## 2. Results and discussion

Recently, we studied the NBS-allylic bromination of dimethyl methylmaleate,[15] chemoselective $S_N2'$ coupling reactions of Grignard reagents prepared from primary alkyl halides with dimethyl bromomethylfumarate (**14**) in absence of CuI,[16–18] and chemoselective allylic substitution of bromide in (bromomethyl)methylmaleic anhydride with Grignard reagents prepared from primary alkyl halides in presence of CuI,[19] to design the bioactive natural products. Using these reactions we designed natural products 1,7 (*Z*)-nonadecadiene-2,3-dicarboxylic acid,[16] chaetomellic acid A,[16] 2-(β-carboxyethyl)-3-hexylmaleic, 2-(β-carboxyethyl)-3-octylmaleic and 2-carboxymethyl-3-hexylmaleic anhydrides[17,18] and unnatural products isochaetomellic acid B, 2,3-dihexylmaleic anhydride and 2,3-dioctylmaleic

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* Corresponding author. Tel.: +91 20 25893153; fax: +91 20 25893153; e-mail: argade@dalton.ncl.res.in

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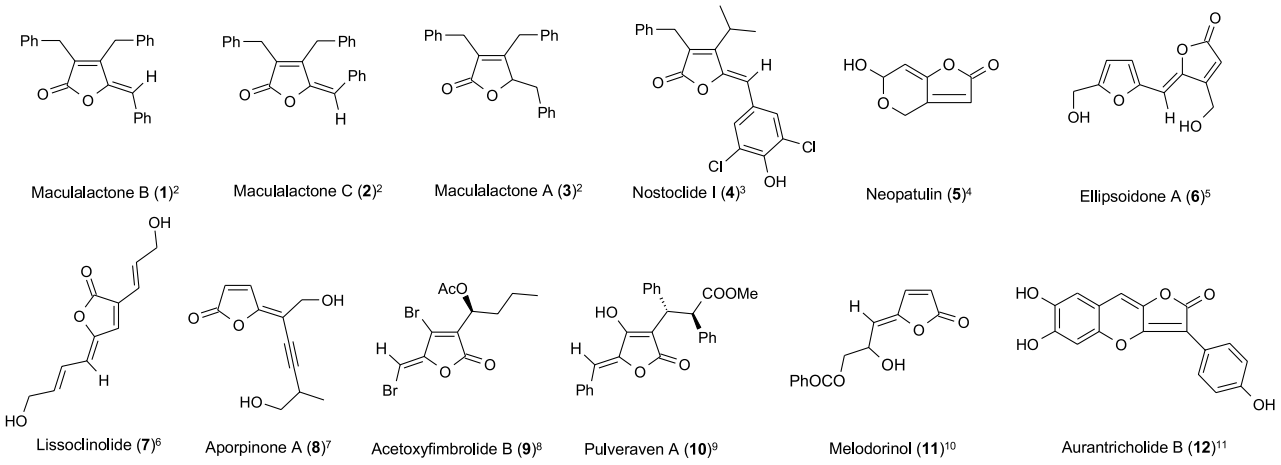
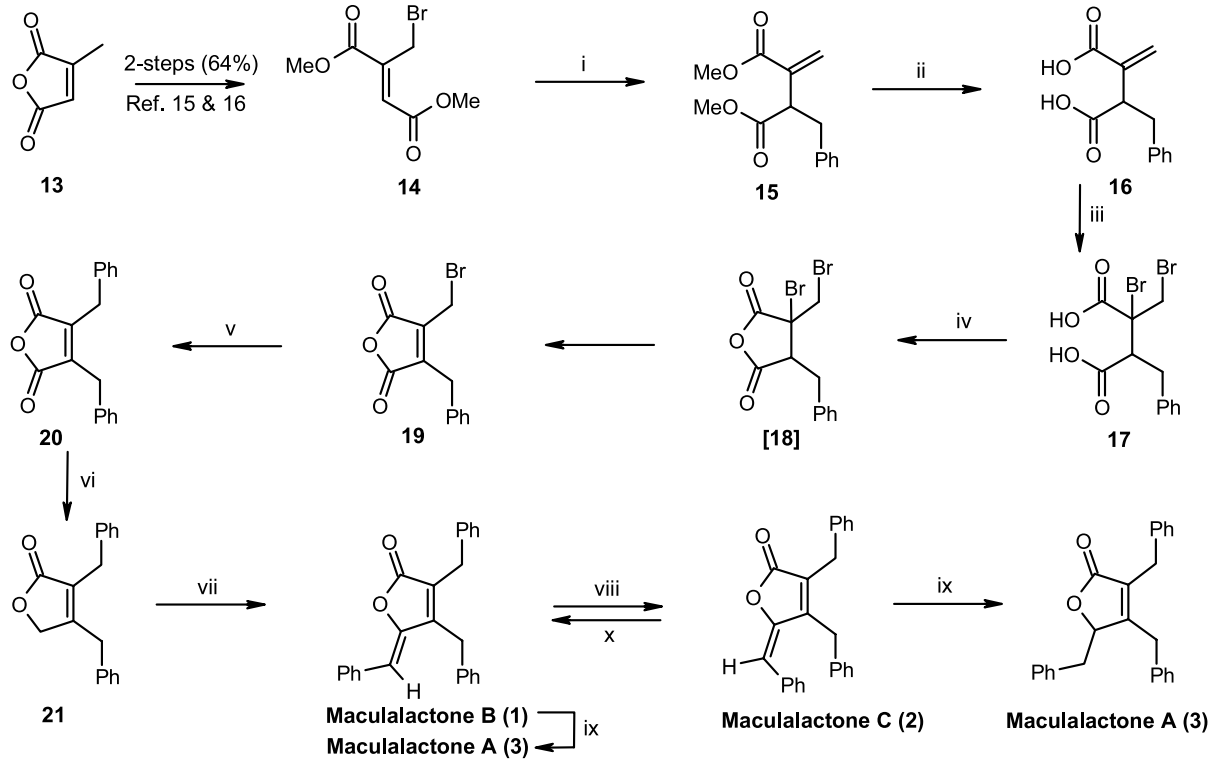
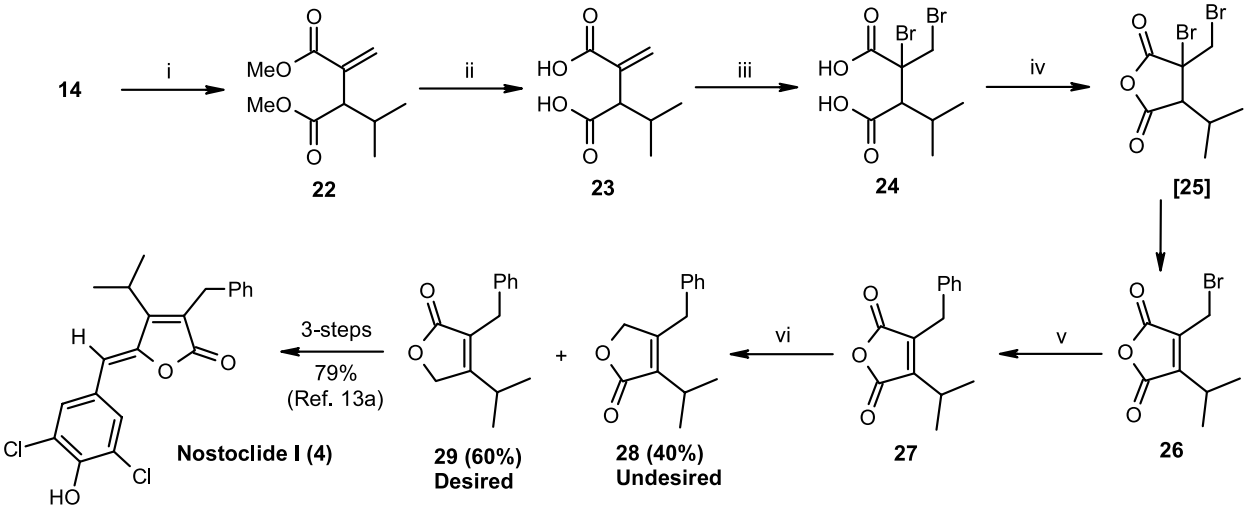



**Figure 1.** Naturally occurring bioactive butyrolactones and analogs.

anhydride.[16–18] Herein, we planned to study the above two coupling reactions with Grignard reagents from secondary alkyl halides, benzyl halides and aryl halides to design the desired substituted maleic anhydrides **20** and **27**. Citraconic anhydride (**13**) was converted to bromodiester **14** in 2-steps with 64% overall yield using known procedure[16] (Scheme 1). The $S_N2'$ coupling reaction of benzylmagnesium bromide with **14** furnished the diester **15** in 70% yield, with an *exo* carbon–carbon double bond. Lithium hydroxide hydrolysis of diester **15** at room temperature, followed by acidification with hydrochloric acid gave the desired dicarboxylic acid **16** in 92% yield, without isomerization of carbon–carbon double bond. The addition of molecular bromine to the carbon–carbon double bond in **16** gave a mixture of all possible isomers of dibromodicarboxylic acid **17** in ~100% yield. The dibromodicarboxylic acid **17** underwent a very smooth in situ dehydration followed by dehydrobromination reaction in presence of acetic anhydride at reflux to give unsymmetrical (bromomethyl)benzylmaleic anhydride (**19**) in ~100% yield via the unisolable intermediate dibromosuccinic anhydride **18**. The chemoselective allylic substitution of the bromide in anhydride **19** with phenylmagnesium bromide furnished dibenzylmaleic anhydride (**20**) in 45% yield. Sodium borohydride reduction




**Scheme 1.** Reagents, conditions and yields: (i) $PhCH_2MgBr$ (1.5 equiv), THF, HMPA, −20 °C, 0.5 h (70%); (ii) (a) LiOH (10 equiv), THF+$H_2O$ (3:1), rt, 18 h, (b) $H^+$/HCl (92%); (iii) $Br_2$ (1.5 equiv), $CCl_4$, rt, 6 h (~100%); (iv) $Ac_2O$, reflux, 1.5 h (~100%); (v) $C_6H_5MgBr$ (5 equiv) CuI (0.1 equiv), $Et_2O$, HMPA, −5 to 0 °C (45%); (vi) $NaBH_4$ (2.5 equiv), THF, 0 °C, 2 h (91%); (vii) Piperidine (0.7 equiv), PhCHO (1 equiv), MeOH, rt, 16 h (77%); (viii) $CHCl_3$, rt, 8 days (50%); (ix) $H_2$, Pd/C, EtOAc, 12 h (75%); (x) △, 200 °C, 3 h (100%).




**Scheme 2.** Reagents, conditions and yields: (i) $C_3H_7MgBr$ (1.5 equiv), THF, HMPA, −20 °C, 0.5 h (79%); (ii) (a) LiOH (10 equiv), THF+$H_2O$ (3:1), rt, 18 h, (b) $H^+$/HCl (91%); (iii) $Br_2$ (1.5 equiv), $CCl_4$, rt, 6 h (~100%); (iv) $Ac_2O$, reflux, 1.5 h (~100%); (v) $C_6H_5MgBr$ (5 equiv), CuI (0.1 equiv), $Et_2O$, HMPA, −5 to 0 °C (43%); (vi) $NaBH_4$ (2.5 equiv), THF, 0 °C, 4 h (70%).

of dibenzylmaleic anhydride (**20**) in THF at room temperature gave the desired lactone **21** in 91% yield. The Knoevenagel condensation of lactone **21** with benzaldehyde furnished the naturally occurring maculalactone B (**1**) in 77% yield. The maculalactone B (**1**) on palladium–charcoal catalyzed chemoselective hydrogenation gave the (±)-maculalactone A (**3**) in 75% yield. The photochemical conversion of maculalactone B (**1**) to the maculalactone C (**2**) is known in 80% yield.[12] The maculalactone B (**1**) is thermodynamically more stable than the maculalactone C (**2**), but due to the presence of associated π-stacking interaction between the two phenyl groups,[2] it slowly transforms to maculalactone C (**2**). The maculalactone B (**1**) in chloroform at room temperature underwent nearly 50% conversion to maculalactone C (**2**) in 8 days (by $^1$H NMR). We isolated and heated the neat 50:50 mixture of maculalactones B and C at 200 °C for 3 h and obtained exclusively the maculalactone B (**1**) proving that it is thermodynamically more stable than maculalactone C (**2**). The maculalactones B plus C mixture on catalytic hydrogenation also gave the maculalactone A (**3**) in same 75% yield. The analytical and spectral data obtained for maculalactones A–C were in complete agreement with reported data.[2,12]

Our next plan was to design the bioactive natural product nostoclide I (**4**). Starting from diester **14**, we similarly prepared the benzylisopropylmaleic anhydride (**27**) in 5-steps with 20% overall yield via $S_N2'$ Grignard coupling, hydrolysis, bromination, in situ dehydration followed by dehydrobromination and allylic substitution pathway (Scheme 2). The sodium borohydride induced regioselective reduction of unsymmetrical maleic anhydride **27** in THF at 0 °C gave the separable mixture of desired and undesired lactones **29** and **28** with 70% yield in 3:2 ratio, respectively. The analytical and spectral data obtained for lactone **29** was in complete agreement with reported data. The conversion of lactone **29** to nostoclide I (**4**) is well known in the literature.[13]

## 3. Conclusion

In summary, starting from readily available citraconic anhydride we have demonstrated the multi-step synthesis of novel bioactive natural products maculalactone A (10-steps, 10%), maculalactone B (9-steps, 13%), maculalactone C (10-steps, 7%) via the three different types of carbon–carbon coupling reactions. In the synthesis of these unusual natural products with three phenyl rings, the first phenyl ring unit was loaded by $S_N2'$ Grignard reaction, the second phenyl ring was coupled via allylic substitution reaction, while the third phenyl ring unit was attached using Knoevenagel condensation reaction. Similarly, we have also completed the formal synthesis of bioactive natural product nostoclide I (**4**), the desired precursor **29** was obtained in 8-steps with 14% overall yield. We feel that our present approach is general in nature and can be used to design diverse butyrolactone skeletons for the structure–activity relationship studies.

## 4. Experimental

### 4.1. General

Melting points are uncorrected. The $^1$H NMR spectra were recorded on Bruker AC 200 NMR spectrometer and Bruker MSL 300 NMR spectrometer with TMS as an internal standard. The $^{13}$C NMR spectra were recorded on Bruker AC 200 NMR spectrometer (50 MHz) and Bruker MSL 300 NMR spectrometer (75 MHz). IR spectra were recorded on Shimadzu FTIR instrument. Microanalytical data were obtained using a Carlo-Erba CHNS-O EA 1108 elemental analyzer. Column chromatographic separations were carried out on silica gel (60–120 mesh) and flash chromatographic separation was carried out using 230–400 mesh size silica gel. Commercially available citraconic anhydride, benzyl bromide, 2-bromopropane, bromobenzene, magnesium turnings, HMPA, CuI, lithium hydroxide, piperidine, acetic anhydride, $NaBH_4$ and benzaldehyde were used.

**4.1.1. Dimethyl 1-buten-4-phenyl-2,3-dicarboxylate (15).** A fresh solution of benzylmagnesium bromide in ether was prepared as follows. A solution of benzyl bromide (4.10 g, 24 mmol) in LAH–dried ether (20 mL) was added at room temperature to magnesium turnings (1.73 g, 72 mmol) in ether (20 mL) under argon with constant stirring in three equal portions at an interval of 10 min. The reaction mixture was stirred at room temperature for a further 4 h. This freshly generated Grignard reagent was added drop wise to a solution of HMPA (14.34 g, 80 mmol) and **14** (3.79 g, 16 mmol) in anhydrous ether (40 mL) under argon at −20 °C and the reaction mixture was stirred at the same temperature for a further 30 min. The reaction was quenched by the addition of a saturated ammonium chloride solution (50 mL). An additional quantity of ether (50 mL) was added to the reaction mixture and the organic layer was separated. The aqueous layer was extracted with ether (30 mL×3), the combined ether extract was washed with water and brine, dried with $Na_2SO_4$ and concentrated in vacuo. The residue was chromatographed over silica gel using petroleum ether/ethyl acetate (9.5:0.5) to give **15**: 2.78 g (70% yield); thick oil; $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ 2.96 (dd, $J$=14, 6 Hz, 1H), 3.25 (dd, $J$=14, 8 Hz, 1H), 3.63 (s, 3H), 3.76 (s, 3H), 3.75–3.90 (m, 1H), 5.67 (s, 1H), 6.31 (s, 1H), 7.10–7.40 (m, 5H); $^{13}$C NMR ($CDCl_3$, 50 MHz) $\delta$ 37.3, 48.6, 51.9, 52.0, 126.3, 127.3, 128.2, 128.8, 137.5, 138.6, 166.2, 172.8; IR ($CHCl_3$) $\nu_{max}$ 1730, 1725, 1630 cm$^{-1}$. Anal. Calcd for $C_{14}H_{16}O_4$: C, 67.73; H, 6.50. Found: C, 67.81; H, 6.44.

**4.1.2. Dimethyl 1-penten-4-methyl-2,3-dicarboxylate (22).** Repetition of above procedure using 2-propylmagnesium bromide (prepared from 2-bromopropane (2.95 g, 24 mmol) and magnesium (1.73 g, 72 mmol)) and **14** (3.79 g, 16 mmol) gave the corresponding diester **22**: 2.53 g (79% yield); thick oil; $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ 0.87 (d, $J$=7 Hz, 3H), 0.97 (d, $J$=7 Hz, 3H), 2.10–2.50 (m, 1H), 3.41 (d, $J$=10 Hz, 1H), 3.66 (s, 3H), 3.76 (s, 3H), 5.92 (s, 1H), 6.41 (s, 1H); $^{13}$C NMR ($CDCl_3$, 50 MHz) $\delta$ 19.8, 20.7, 31.2, 51.4, 51.9, 52.3, 127.0, 137.6, 166.8, 173.3; IR (neat) $\nu_{max}$ 2961, 1736, 1726, 1626 cm$^{-1}$. Anal. Calcd for $C_{10}H_{16}O_4$: C, 59.98; H, 8.06. Found: C, 59.93; H, 8.11.

**4.1.3. 1-Buten-4-phenyl-2,3-dicarboxylic acid (16).** A solution of lithium hydroxide (2.40 g in 18 mL water) was added to a solution of **15** (2.48 g, 10 mmol) in tetrahydrofuran (54 mL) at room temperature and the reaction mixture was stirred for 18 h. The reaction mixture was then concentrated in vacuo. To the residue was added ethyl acetate (100 mL) and then acidified to pH 2 with 2 M hydrochloric acid. The organic layer was separated and the aqueous layer was further extracted with ethyl acetate (30 mL×3). The combined organic layer was washed with water and brine, dried over $Na_2SO_4$ and concentrated in vacuo. The residue was chromatographed over silica gel using petroleum ether/ethyl acetate (6:4) to give **16**: 2.02 g (92% yield); thick oil; $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ 3.03 (dd, $J$=14, 10 Hz, 1H), 3.38 (dd, $J$=14, 6 Hz, 1H), 3.60–3.75 (m, 1H), 5.61 (s, 1H), 6.42 (s, 1H), 7.00–7.40 (m, 5H), 10.6 (bs, 2H); $^{13}$C NMR ($CDCl_3$, 50 MHz) $\delta$ 36.6, 48.8, 126.6, 128.5, 128.9, 131.0, 136.4, 138.3, 171.7, 179.0; IR (Nujol) $\nu_{max}$ 2700–2500, 1709, 1705, 1628 cm$^{-1}$. Anal. Calcd for $C_{12}H_{12}O_4$: C, 65.45; H, 5.49. Found: C, 65.52; H, 5.43.

**4.1.4. 1-Penten-4-methyl-2,3-dicarboxylic acid (23).** It was prepared similarly from **22** (2.00 g, 10 mmol) and aqueous lithium hydroxide solution (2.40 g in 18 mL water) as described above to obtain the corresponding dicarboxylic acid **23**: 1.57 g (91% yield); thick oil; $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ 0.92 (d, $J$=6 Hz, 3H), 1.06 (d, $J$=6 Hz, 3H), 2.05–2.35 (m, 1H), 3.40 (d, $J$=10 Hz, 1H), 6.07 (s, 1H), 6.62 (s, 1H), 10.16 (bs, 2H); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 19.9, 20.8, 31.1, 52.3, 130.3, 136.7, 172.0, 179.3; IR ($CHCl_3$) $\nu_{max}$ 3020, 2968, 2700–2500, 1703, 1701, 1624 cm$^{-1}$. Anal. Calcd for $C_8H_{12}O_4$: C, 55.81; H, 7.02. Found: C, 55.73; H, 7.00.

**4.1.5. 1,2-Dibromobutan-4-phenyl-2,3-dicarboxylic acid (17).** A solution of bromine (1.92 g, 12 mmol) in $CCl_4$ (20 mL) was added dropwise to a solution of **16** (1.76 g, 8 mmol) in $CCl_4$ (30 mL) at room temperature and the reaction mixture was stirred for 6 h. The reaction mixture was then concentrated in vacuo, and the residue was dissolved in ethyl acetate (50 mL). The organic layer was washed with saturated sodium metabisulphite, water and brine, dried over $Na_2SO_4$ and concentrated in vacuo, to obtain **17**: 3.03 g (∼100% yield); thick oil; $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ 3.00–3.40 (m, 2H), 3.64 (t, $J$=6 Hz, 1H), 3.85–4.25 (m, 2H), 7.00–7.60 (m, 5H), 11.01 (bs, 2H); IR (Nujol) $\nu_{max}$ 2700–2500, 1757, 1713, 1605 cm$^{-1}$. Anal. Calcd for $C_{12}H_{12}Br_2O_4$: C, 37.93; H, 3.18. Found: C, 37.97; H, 3.11.

**4.1.6. 1,2-Dibromopentan-4-methyl-2,3-dicarboxylic acid (24).** It was prepared similarly from **23** (1.38 g, 8 mmol) and bromine (1.92 g, 12 mmol) as described above to obtain the corresponding diacid **24**: 2.65 g (∼100% yield); thick oil; $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ 0.80–1.40 (m, 6H), 2.00–2.45 (m, 1H), 3.30–3.55 (m, 1H), 3.80–4.50 (m, 2H), 8.76 (bs, 2H); IR ($CHCl_3$) $\nu_{max}$ 1714, 1711 cm$^{-1}$. Anal. Calcd for $C_8H_{12}Br_2O_4$: C, 28.94; H, 3.64. Found: C, 29.01; H, 3.66.

**4.1.7. 2-Bromomethyl-3-benzylmaleic anhydride (19).** A solution of **17** (3.03 g, 8 mmol) in acetic anhydride (20 mL) was gently heated at reflux for 1.5 h and the reaction mixture was concentrated under vacuo at 50 °C. The residue was diluted with ethyl acetate (40 mL) and the organic layer was washed with water and brine, dried with $Na_2SO_4$ and concentrated in vacuo to obatin **19**: 2.24 g (∼100% yield); thick oil; $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ 3.91 (s, 2H), 4.05 (s, 2H), 7.15–7.50 (m, 5H); $^{13}$C NMR ($CDCl_3$, 50 MHz) $\delta$ 15.9, 30.7, 127.6, 128.9, 129.1, 133.6, 139.0, 144.7, 163.6, 164.6; IR ($CHCl_3$) $\nu_{max}$ 1828, 1773, 1705, 1638 cm$^{-1}$. Anal. Calcd for $C_{12}H_9BrO_3$: C, 51.27; H, 3.23. Found: C, 51.33; H, 3.18.

**4.1.8. 2-Bromomethyl-3-isopropylmaleic anhydride (26).** It was prepared similarly from **24** (2.65 g, 8 mmol) and acetic anhydride (20 mL) as described above to obtain the corresponding anhydride **26**: 1.86 g (∼100% yield); thick oil; $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 1.36 (d, $J$=9 Hz, 6H), 3.09 (sept, $J$=9 Hz, 1H), 4.21 (s, 2H); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 15.8, 19.5, 26.7, 137.7, 151.2, 163.6, 163.7; IR ($CHCl_3$) $\nu_{max}$ 1850, 1832, 1773, 1707, 1655 cm$^{-1}$. Anal. Calcd for $C_8H_9BrO_3$: C, 41.23; H, 3.89. Found: C, 41.17; H, 3.85.

**4.1.9. 2,3-Dibenzylmaleic anhydride (20).** A fresh solution of phenylmagnesium bromide in ether was prepared as follows. A solution of bromobenzene (3.93 g, 25 mmol) in LAH–dried ether (20 mL) was added at room temperature to magnesium turnings (1.80 g, 75 mmol) in ether (20 mL) under argon with constant stirring in three equal portions at an interval of 10 min. The reaction mixture was stirred at room temperature for a further 4 h. This freshly generated Grignard reagent was added dropwise to a solution of **19** (1.41 g, 5 mmol) and copper (I) iodide (95 mg, 0.5 mmol) in ether (30 mL) and HMPA (10 mL) under argon at −5 to 0 °C over 15–20 min with stirring. The reaction mixture was allowed to reach room temperature and stirred for a further 8 h. It was diluted with ether (30 mL) and acidified with 4 M $H_2SO_4$ (30 mL), and the aqueous layer was further extracted with ether (30 mL×3). The combined organic layer was washed with water, brine and dried over $Na_2SO_4$ and concentrated in vacuo. The residue was chromatographed over silica gel using petroleum ether/ethyl acetate (9.5:0.5) to give **20**: 626 mg (45% yield); thick oil; $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ 3.78 (s, 4H), 7.05–7.20 (m, 4H), 7.20–7.35 (m, 6H); $^{13}$C NMR ($CDCl_3$, 50 MHz) $\delta$ 29.9, 127.1, 128.6, 128.8, 134.9, 142.7, 165.6; IR ($CHCl_3$) $\nu_{max}$ 1769 cm$^{-1}$. Anal. Calcd for $C_{18}H_{14}O_3$: C, 77.68; H, 5.07. Found: C, 77.75; H, 5.14.

**4.1.10. 2-Benzyl-3-isopropylmaleic anhydride (27).** Repetition of above procedure using phenylmagnesium bromide (prepared from bromobenzene (3.93 g, 25 mmol) and magnesium (1.80 g, 75 mmol)), **26** (1.17 g, 5 mmol), copper (I) iodide (95 mg, 0.5 mmol) and HMPA (10 mL) gave the corresponding anhydride **27**: 495 mg (43% yield); thick oil; $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 1.28 (d, $J$=9 Hz, 6H), 3.06 (sept, $J$=9 Hz, 1H), 3.81 (s, 2H), 7.15–7.45 (m, 5H); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 20.0, 26.4, 29.8, 126.2, 127.3, 127.9, 128.6, 129.0, 135.7, 141.2, 149.1, 164.4, 165.8; IR (neat) $\nu_{max}$ 1773, 1703, 1605 cm$^{-1}$. Anal. Calcd for $C_{14}H_{14}O_3$: C, 73.03; H, 6.13. Found: C, 72.96; H, 6.07.

**4.1.11. 3,4-Dibenzyl-5*H*-furan-2-one (21).** To a stirred solution of **20** (300 mg, 1.08 mmol) in THF, $NaBH_4$ (102 mg, 2.70 mmol) was added at 0 °C and the reaction mixture was further stirred at 0 °C for 2 h and then quenched with water and acidified with dilute HCl and extracted with ethyl acetate (50 mL×3). The organic layer was washed with brine, dried with $Na_2SO_4$, concentrated in vacuo. The residue was purified by silica gel column chromatography using a mixture of ethyl acetate and petroleum ether (1:4) to furnish **21**: 259 mg (91% yield); thick oil; $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ 3.72 (s, 2H), 3.74 (s, 2H), 4.53 (s, 2H), 6.95–7.10 (m, 2H), 7.15–7.50 (m, 8H); $^{13}$C NMR ($CDCl_3$, 50 MHz) $\delta$ 29.6, 33.5, 71.2, 126.6, 126.8, 127.2, 128.6, 128.7, 129.0, 130.1, 135.8, 138.0, 159.7, 174.6; IR ($CHCl_3$) $\nu_{max}$ 1755, 1672, 1601 cm$^{-1}$. Anal. Calcd for $C_{18}H_{16}O_2$: C, 81.79; H, 6.10. Found: C, 81.83; H, 6.05.

**4.1.12. 3-Isopropyl-4-benzyl-5*H*-furan-2-one (28) and 3-benzyl-4-isopropyl-5*H*-furan-2-one (29).** Repetition of above procedure using **27** (248 mg, 1.08 mmol) and $NaBH_4$ (102 mg, 2.70 mmol) gave the mixture of both the corresponding lactones (**28**:**29**=40:60) 163 mg (70% yield). The mixture was separated by flash column chromatography using a mixture of ethyl acetate and petroleum ether (1:17) to furnish **28** (65 mg) and **29** (98 mg). **28**: thick oil; $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 1.30 (d, $J$=9 Hz, 6H), 2.97 (sept, $J$=9 Hz, 1H), 3.77 (s, 2H), 4.49 (s, 2H), 7.15 (dd, $J$=9, 3 Hz, 2H), 7.25–7.45 (m, 3H); IR ($CHCl_3$) $\nu_{max}$ 1746, 1665, 1603 cm$^{-1}$. Anal. Calcd for $C_{14}H_{16}O_2$: C, 77.75; H, 7.46. Found: C, 77.67; H, 7.52.

**29**: thick oil; $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 1.11 (d, $J$=9 Hz, 6H), 3.08 (sept, $J$=9 Hz, 1H), 3.63 (s, 2H), 4.73 (s, 2H), 7.10–7.40 (m, 5H); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 20.9, 27.3, 29.4, 68.7, 124.5, 126.5, 128.4, 128.6, 138.2, 166.9, 175.1; IR ($CHCl_3$) $\nu_{max}$ 1753, 1666, 1603 cm$^{-1}$. Anal. Calcd for $C_{14}H_{16}O_2$: C, 77.75; H, 7.46. Found: C, 77.81; H, 7.53.

**4.1.13. 3,4-Dibenzyl-5*Z*-benzylidine-5*H*-furan-2-one (maculalactone B, 1).** To a stirred solution of lactone **21** (200 mg, 0.76 mmol) in methanol, piperidine (0.05 mL, 0.53 mmol) and benzaldehyde (0.08 mL, 0.76 mmol) were added at room temperature and the reaction mixture was stirred for another 15 h. Removal of solvent in vacuo followed by column chromatographic purification of the residue using a mixture of ethyl acetate and petroleum ether (1:9) furnished **1**: 206 mg (77% yield); mp=102–103 °C; $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ 3.74 (s, 2H), 3.93 (s, 2H), 5.97 (s, 1H), 7.05–7.40 (m, 13H), 7.71 (dd, $J$=6, 2 Hz, 2H); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 29.8, 30.6, 110.4, 126.7, 127.0, 127.7, 127.9, 128.2, 128.4, 128.6, 128.7, 128.8, 128.9, 129.3, 130.5, 133.1, 136.6, 137.5, 148.3, 150.7, 170.2; IR ($CHCl_3$) $\nu_{max}$ 1755, 1649, 1603 cm$^{-1}$. Anal. Calcd for $C_{25}H_{20}O_2$: C, 85.20; H, 5.72. Found: C, 85.27; H, 5.66.

**4.1.14. 3,4-Dibenzyl-5*E*-benzylidine-5*H*-furan-2-one (maculalactone C, 2).** A solution of **1** (100 mg) in $CHCl_3$ (10 mL) was kept at room temperature for 8 days. Concentration of above $CHCl_3$ solution in vacuo furnished 100 mg of 50:50 mixture of **1** and **2**. In $^1$H NMR ($CDCl_3$), the vinylic proton in **2** appeared at $\delta$ 6.84. The preparative HPLC separation of mixture of **1** and **2** is known.[12]

**4.1.15. 3,4,5-Tribenzyl-5*H*-furan-2-one (maculalactone A, 3).** A mixture of **1** (100 mg, 0.28 mmol) and a catalytic amount of Pd/C in ethyl acetate (8 mL) was subjected to hydrogenation at 65-psi hydrogen pressure for 16 h at room temperature. The reaction mixture was filtered through celite and the filtrate was concentrated in vacuo. The residue was purified by silica gel column chromatography using a mixture of ethyl acetate and petroleum ether (1:4) to furnish **3**: 75 mg (75% yield); thick oil; $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 2.82 (dd, $J$=12, 6 Hz, 1H), 3.23 (dd, $J$=12, 3 Hz, 1H), 3.48 (d, $J$=15 Hz, 1H), 3.57 (d, $J$=15 Hz, 1H), 3.64 (d, $J$=15 Hz, 1H), 3.92 (d, $J$=15 Hz, 1H), 4.94 (dd, $J$=6, 3 Hz, 1H), 6.88 (m, 2H), 7.02 (m, 2H), 7.05–7.40 (m, 11H); $^{13}$C NMR ($CDCl_3$, 50 MHz) $\delta$ 29.3, 33.1, 37.9, 81.5, 126.3, 127.1, 127.3, 128.1, 128.5 (3-carbons), 128.6, 129.0, 129.4, 134.8, 135.9, 137.6, 161.7, 173.5; IR (neat) $\nu_{max}$ 1755, 1668, 1603 cm$^{-1}$. Anal. Calcd for $C_{25}H_{22}O_2$: C, 81.06; H, 5.98. Found: C, 80.93; H, 5.86.

## Acknowledgements

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# Synthesis of 2,3-dihydroimidazo[1,2-*a*]pyrimidin-5(1*H*)-ones by the domino Michael addition retro-ene reaction of 2-alkoxyiminoimidazolidines and acetylene carboxylates

Jarosław Sączewski,[a,*] Zdzisław Brzozowski[a] and Maria Gdaniec[b]

[a]*Department of Chemical Technology of Drugs, Medical University of Gdańsk, Poland*
[b]*Department of Crystallography, A. Mickiewicz University, 60-780 Poznań, Poland*

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**Abstract**—2-Alkoxyiminoimidazolidines **2**–**3** react with acetylene dicarboxylates and ethyl phenylpropiolate to give 8-alkoxy-imidazo[1,2-*a*]pyrimidin-5(3*H*)-ones **C**, which subsequently undergo a sterically induced multihetero-retro-ene fragmentation to give imidazo[1,2-*a*]pyrimidin-5(1*H*)-ones **4**–**7** together with formaldehyde or benzaldehyde. On the other hand, a similar reaction of **2**–**3** with ethyl propiolate gives corresponding 8-alkoxy-imidazo[1,2-*a*]pyrimidin-5(3*H*)-ones **8**–**10**. The unsubstituted imidazo[1,2-*a*]pyrimidin-5(1*H*)-one **11** can be prepared by retro-ene reaction of **9** upon prolonged heating in refluxing ethanol. A direct synthetic approach to 1-formyl-7-phenyl-imidazo[1,2-*a*]pyrimidine-5(1*H*)-one **14** is reported using DMF/sulfonyl chloride as a new Vilsmeier-type *N*-formylating reagent.


## 1. Introduction

Imidazo[1,2-*a*]pyrimidine-5-ones possess diverse biological activities and this structural motif is present in analgesics and inflammation inhibitors[1,2] benzodiazepine receptor ligands[3] as well as insecticidal, acaricidal and nematocidal agents.[4] The structural feature of imidazo[1,2-*a*]pyrimidine nucleus is related to the purine ring system, and therefore, we were interested in the synthesis of various substituted compounds of type **A** and **B** (Fig. 1) in anticipation of their anticancer activity.

The existing methods for building up the imidazo[1,2-*a*] pyrimidine core, which include the elaboration of 2-aminopyrimidines[5] or reaction of 2-aminoimidazoline with acetylene carboxylates,[1] are either multistep procedures or require ion exchange chromatography to obtain the free base of 2-aminoimidazoline. Moreover, the above methods are not general and the parent compound **B** (R, $R^1$=H) was not obtained.

Herein we report a new strategy for preparation of the compounds of type **A** and **B** based on two consecutive reactions: the well-established reaction of 2-aminoimidazolines with acetylene carboxylates[1], which leads to 2,8-dihydroimidazo[1,2-*a*]pyrimidin-5(3*H*)-ones (**A**, R= alkoxyl), and the retro-ene fragmentation associated with $N^1$-alkoxyamidine[6,7] giving rise to the formation of 2,3-dihydroimidazo[1,2-*a*]pyrimidin-5(1*H*)-ones (**B**).

## 2. Results and discussion

The domino reactions have been defined as a process involving two or more bond-forming transformations which take place under the same reaction conditions without adding additional reagents and catalysts, and where the subsequent reaction results as a consequence of the functional group formed in the previous step.[8,9]

In developing a new strategy for the synthesis of


2,8- dihydroimidazo[1,2-*a*] pyrimidin-5(3*H*)-ones

2,3- dihydroimidazo[1,2-*a*] pyrimidin-5(1*H*)-ones

**Figure 1.** Structures of imidazo[1,2-*a*]pyrimidin-5-ones.

*Keywords*: 2,3-Dihydroimidazo[1,2-*a*]pyrimidin-5(1*H*)-ones; 8-Alkoxy-imidazo[1,2-*a*]pyrimidin-5(3*H*)-ones; Domono Michael addition retro-ene reacion; N-alkylation; N-acylation; N-formylation; X-ray crystal structure analysis.
* Corresponding author. Tel.: +48 58 3493250; fax: +48 58 3493257; e-mail: js@amg.gda.pl

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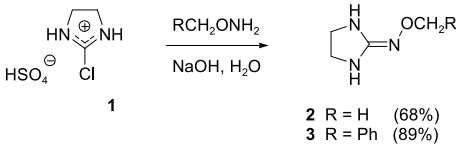
imidazo[1,2-*a*]pyrimidin-5-ones, we first focused on the ability to synthesize a bis-nucleophilic 2-alkoxyiminoimidazolidine that could undergo cyclocondensation upon treatment with acetylene carboxylates. As illustrated in Scheme 1, the desired 2-alkoxyiminoimidazolidines **2** and **3** were obtained in 68–89% yield from 2-chloro-4,5-dihydroimidazole (**1**) and commercially available *O*-methyl- and *O*-benzyl-hydroxylamines. The molecular structure of these compounds was confirmed by X-ray crystal structure analysis of **3** [CCDC 259437].




**Scheme 1.** Preparation of 2-alkoxyiminoimidazolidines **2** and **3**.

Novel reagents **2** and **3** thus developed were first utilized for the preparation of known[1] imidazo[1,2-*a*]pyrimidin-5-ones **4** and **7** as well as novel derivatives **5** and **6** as shown in Scheme 2. The two reagents were each reacted with acetylene dicarboxylates, ethyl phenylpropiolate or ethyl butynoate in suitable alcohol at reflux. The reaction sequence involves as the key intermediate, 8-alkoxyimidazopyrimidine **C**, which eludes isolation under the reaction conditions, and undergoes subsequent retro-ene fragmentation with simultaneous extrusion of aldehyde. Formaldehyde was trapped by dimedone, while the presence of benzaldehyde was confirmed by isolation of its 2,4-dinitrophenyl-hydrazone derivative.

It should be noted that the reaction of **2** and **3** with less reactive ethyl butynoate required 10 h to reach completion. The end products **4** and **7** were found to be identical in all respects (mp, IR, NMR and MS) with authentic samples synthesized independently.[1]

The fact that compounds **4**–**7** could be obtained without contamination by alternative products of type **D** (Scheme 2) underlines regiospecificity of the reaction. In order to identify nucleophilic sites in 2-iminoimidazolidine and 2-methoxyiminoimidazolidine (**2**) atomic charges were calculated.[15] As shown in Figure 2, introduction of an alkoxy group into 2-iminoimidazolidine evidently lowers the

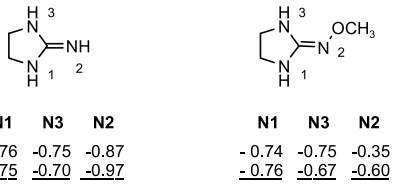



**Figure 2.** Calculated[15] atomic charges and charges derived from the electrostatic potential (underlined) of the nitrogen atoms of 2-iminoimidazolidine and 2-methoxyiminoimidazolidine (**2**).

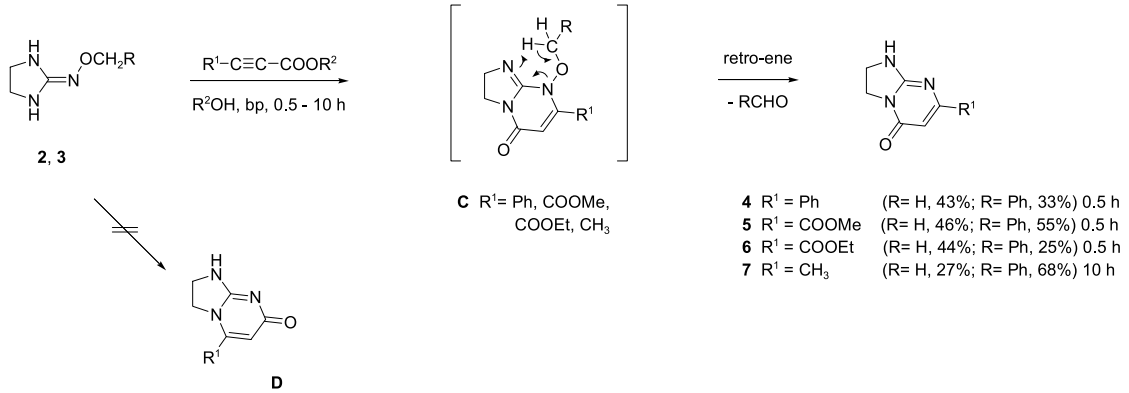
nucleophilicity of the exocyclic nitrogen atom sufficiently to prevent reaction with carboxylate.

Having established that the domino reaction takes place with both **2** and **3**, our attention was turned to its primary purpose: its ability to provide parent 2,3-dihydroimidazo[1,2-*a*]pyrimidine-5(1*H*)-one (**11**).

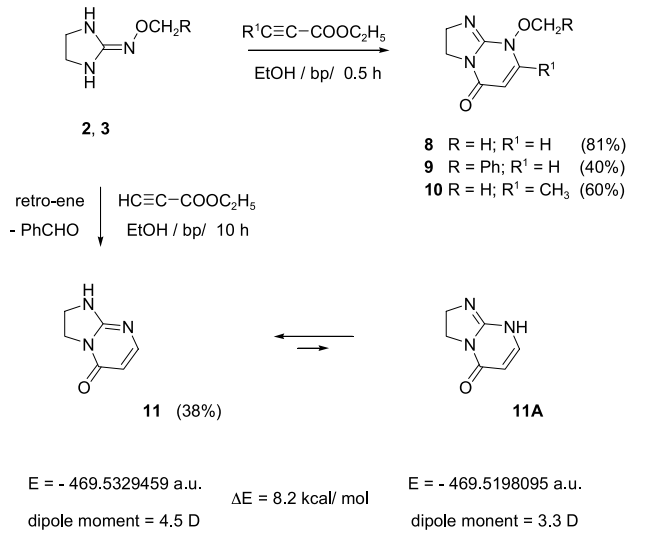
The reaction of **2** and **3** with ethyl propiolate in boiling ethanol for 0.5 h led to the formation of 8-alkoxyimidazo[1,2-*a*]pyrimidin-5-ones **8** and **9** (Scheme 3), the molecular structure of which was confirmed by X-ray crystal structure analysis [CCDC 259433 (**8**); CCDC 259436 (**9**)]. A similar reaction of 2-methoxyiminoimidazolidine (**2**) with ethyl butynoate gave 8-methoxyimidazo[1,2-*a*]pyrimidin-5-one (**10**) in 60% yield.

Apparently, the 8-alkoxy derivatives **8**, **9** and **10** are less reactive than **C** under identical conditions and can be separated from the reaction mixture in 81, 40 and 60% yield, respectively. It is well known that rates of retro-ene reactions may be enhanced[10–12] or diminished[13,14] by steric effects. The difference in reactivity between the **C** and **8**–**9** is presumably the result of the steric augmentation, i.e. the retro-ene process is induced by steric hindrance caused by bulky substituents at position 7 of **C**. The steric hindrance between the 7-phenyl or 7-alkoxycarbonyl and 8-alkoxy groups in **C** inhibits free rotation of the latter, which results in a fixed conformation that is conductive to a retro-ene mechanism.

We examined several reaction parameters including solvent, temperature, reaction time and type of bis-nucleophilic reagent **2** and **3**. At room temperature or shorter reaction time, the imidazopyrimidine **9** formation was incomplete. However, at higher temperature and reaction time greater




**Scheme 2.** Preparation of imidazo[1,2-*a*]pyrimidin-5-ones **4**–**7**.




**Scheme 3.** Reaction of 2-alkoxyiminoimidazolidines **2**–**3** with ethyl propiolate and ethyl butynoate.

than 10 h, the reaction of **3** with ethyl propiolate gave the desired parent compound **11** in 38% yield (Scheme 3). In contrast, an analogous reaction of **2** failed to give compound **11** and the 8-alkoxy derivative **8** was obtained as a sole product.

The ab initio geometry optimization at HF/6-31G** level[15] was performed on the imidazopyrimidin-5-one **11** to examine its two possible tautomers **11** and **11A** as shown in Scheme 3. These computations revealed that the N1–H tautomer **11** was favored over N8–H tautomer **11A** by 8.2 kcal/mol. On the basis of their calculated dipole moments, **11** (4.5 Debye) would be predicted to predominate over **11A** (3.3 Debye) in polar solvents. It was shown by NMR spectroscopy that the low-energy tautomer **11** is present in DMSO-$d_6$ solution. The methylene groups of the imidazoline moiety are nonequivalent, and the NOE was observed between an upfield-shifted C2–H protons and the N–H proton (Supplementary data).

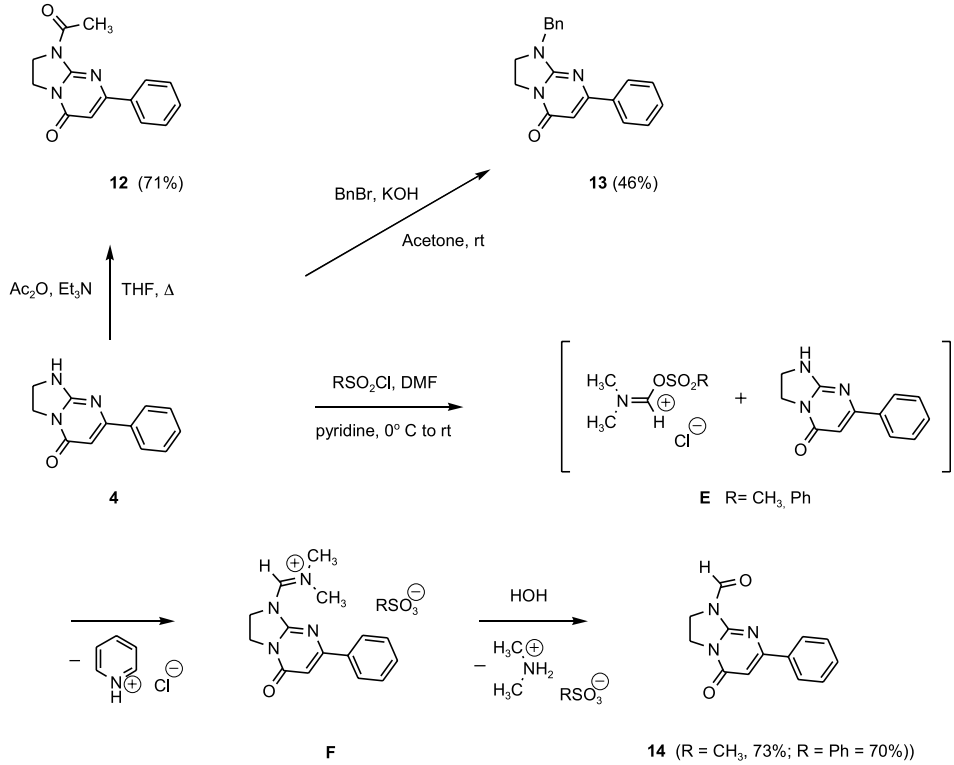
Acetylation of **4** with acetic anhydride and alkylation with benzyl bromide occurred exclusively at the site of the imidazolino nitrogen to furnish **12** and **13**, respectively, in good yields (Scheme 4).

We have also attempted to prepare 1-phenylsulfonyl- and 1-methanesulfonyl-2,3-dihydroimidazo[1,2-*a*]pyrimidin-5(1*H*)-one by treatment of **4** with corresponding sulfonyl chloride in pyridine/DMF. However, we were surprised to observe that the 1-formyl derivative **14** was obtained instead.

A possible mechanism for this reaction is outlined in Scheme 4. Initial reaction of sulfonyl chloride with dimethyl formamide gives a new type of Vilsmeier reagent **E** (*N*,*N*-dimethylphenylsulfonyloxymethylene-ammonium chloride) which then reacts under mild reaction conditions with **4** to give the amidinium salt **F**. Hydrolyis of **F** upon work-up completes the sequence.

It should noted that the use of DMF to formylate secondary amines was previously reported using chlorotrimethylsilane and imidazole[16], *tetra*-butylchloro-dimethylsilane and *N*,*N*-dimethyl-4-aminopyridine[17] as well as DMF acetals.[18]

The structures of **13** and **14** were unequivocally established




**Scheme 4.** Preparation of 1-acetyl-, 1-benzyl- and 1-formyl derivatives of **4**.

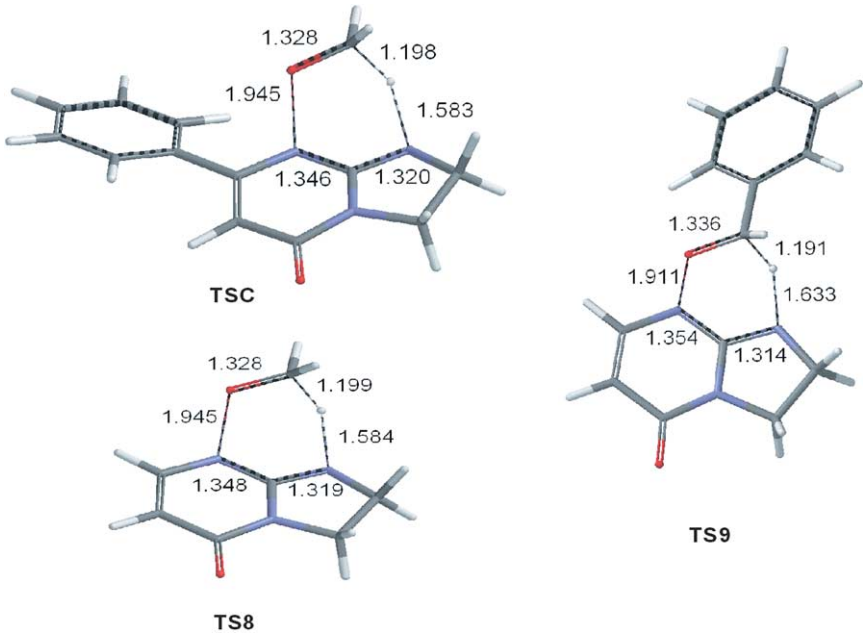



**Figure 3.** Calculated transition states **TSC**, **TS8** and **TS9**.

by X-ray crystal structure analysis [CCDC 259434 (**13**); CCDC 259435 (**14**)].

The one-pot procedure developed for the conversion of 2-alkoxyiminoimidazolidines (**2**–**3**) into imidazo[1,2-*a*]pyrimidin-5-ones **4**–**7** via retro-ene fragmentation of 2-O, 3-N, 5-N ene adduct merits further discussion. Previously there has been a single report of a retro ene reaction taking place in 5-(methoxyamino)-3-aryl-1,3,4-oxadiazol-2(3*H*)-ones on heating at reflux in the presence of Hünig's base.[6] To gain a closer insight into the retro-ene process, however, we still have to understand the transition state (**TS**) pertaining to the aldehyde extrusion reaction.

B3LYP/6-31G** calculations[19] were performed for 8-alkoxy-imidazopyrimidines **C** (R=H, $R^1$=Ph), **8** and **9**, reacting to imidazopyrimidines **4** or **11** and formaldehyde or benzaldehyde via transition states **TSC**, **TS8** and **TS9** (Fig. 3). Table 1 lists the bond lengths of interest in the reactants and transition states. In all cases the chair **TS** features the transfer of a hydrogen atom from methyl or methylene group to the nitrogen atom of the amidine moiety with lengthening of the N–O bond compared to the starting material [1.945 Å in **TSC** (1.385 Å in **C**); 1.945 Å in **TS8** (1.390 Å in **8**); 1.911 Å in **TS9** (1.388 Å in **9**)] and the long bond lengths (1.583–1.633 Å) of the N–H forming bonds, i.e. the N–O bond cleavage is more advanced than N–H bond formation. The IRC calculations confirmed that the breakage of two bonds (O–N and C–H) with loss of RCHO from **C**, **8** and **9** is asynchronous.

The calculated activation energies, presented in Table 2, give a barrier for **TSC** of 29.1 kcal/mol, **TS8** of 32.6 kcal/mol and **TS9** of 30.0 kcal/mol.

As shown in Table 2, the reaction of 8-benzyloxy **9** is calculated to be exothermic by −43 kcal/mol, 11 kcal/mol more than the 8-methoxy derivative **8**. The highly favorable thermodynamics associated with the reaction is due largely to the formation of the very strong carbon-hetero (C=O) double bond at the expense of the energy required to break the weak hetero-hetero (N–O) single bond. Apparently, the exothermicity of the fragmentation reaction of **9** is higher than in the case of **8** because of the conjugation in the benzaldehyde product.

**Table 1**. Bond lengths of reactants and transition states for the retro-ene reactions calculated at the B3LYP/6-31G** level

| Structure | HC1 | C1O2 | O2N3 | N3C4 | C4N5 | N5H |
|---|---|---|---|---|---|---|
| **C** | 1.092 | 1.443 | 1.384 | 1.386 | 1.280 | |
| **TSC** | 1.198 | 1.328 | 1.945 | 1.346 | 1.320 | 1.583 |
| **8** | 1.092 | 1.442 | 1.390 | 1.388 | 1.279 | |
| **TS8** | 1.199 | 1.328 | 1.945 | 1.348 | 1.319 | 1.584 |
| **9** | 1.093 | 1.463 | 1.388 | 1.386 | 1.281 | |
| **TS9** | 1.191 | 1.336 | 1.911 | 1.354 | 1.314 | 1.633 |

**Table 2**. Relative energies (kcal/mol) for the retro-ene reactions of **C**, **8** and **9** (Schemes 2 and 3) calculated at the B3LYP/ 6-31G** level

| C | TSC | 11+formaldehyde | 8 | TS8 | 11+formaldehyde | 9 | TS9 | 11+benzaldehyde |
|---|---|---|---|---|---|---|---|---|
| 0 | 29.1 | −35.4 | 0 | 32.6 | −31.7 | 0 | 30.0 | −43.3 |

The above results indicate that the steric hindrance serves as a partial driving force for the retro-ene reaction of **C**, while the higher reactivity of **9** in comparison with **8** is due to thermodynamic factors.

Samples of the compounds **4**, **5**, **8** and **12**–**14** were submitted to the National Cancer Institute for screening against human tumor cell lines. In the primary anticancer assay, compound **13** at concentration $10^{-4}$ M was found to reduce the growth of cell lines to 8% (NCI–H460, non-small cell lung cancer) and 25% (MCF-7, breast cancer), respectively.

## 3. Conclusions

The results presented in this paper illustrate the generality of the retro-ene reaction which takes place upon heating $N^1$-alkoxyamidine-containing compounds in alcohol.

*N*,*N*-dimethylphenyl(methane)sulfonyloxymethylene-ammonium chloride generated in situ from corresponding sulfonyl chloride and DMF in pyridine solution serves as a new Vilsmeier-type *N*-formylating reagent.

## 4. Experimental

### 4.1. General

Melting points determined on a Boetius melting point apparatus and are not corrected. IR spectra were recorded on a FTIR Perkin Elmer 1600 apparatus using a mixture of the compound and KBr. $^1$H and $^{13}$C NMR spectra were taken on a Varian Unity Plus-500 spectrometer at 500 and 125 MHz, respectively. Chemical shifts were measured relative to the residual solvent signal at 2.50 or 7.26 ppm and 39.5 or 77 ppm, respectively. MS spectra were recorded on a Finnigan MAT-95 spectrometer at 70 eV. All reagents were used directly as obtained commercially. 2-Chloro-4,5-dihydroimidazolium hemisulfate[20] (**1**) was prepared according to a previous literature procedure.

**4.1.1. 2-Methoxyiminoimidazolidine (2).** 2-Chloro-4,5-dihydroimidazolium hemisulfate (**1**) (5 g, 24.9 mmol) and *O*-methylhydroxylamine hydrochloride (2 g, 24 mmol) were dissolved in 10% NaOH aqueous solution (25 mL). Within 15 min another 15 mL of 10% NaOH was added portionwise. After 2 h, the solution was extracted with $CH_2Cl_2$. Combined organic layers were dried, evaporated to dryness and the crude product **2** was purified by flash chromatography (EtOAc/MeOH 10:1); yield 1.68 g (68%); mp 111–122 °C; $^1$H NMR ($CDCl_3$) $\delta$ 3.46 (m, 4H, $CH_2$), 3.66 (s, 3H, $OCH_3$), 3.83 (br s, 1H, NH), 4.74 (br s, 1H, NH); $^{13}$C NMR ($CDCl_3$) $\delta$ 43.0, 61.6, 160.2; IR cm$^{-1}$ 3390, 3204, 2935, 2883, 1655; EIMS *m*/*z* (relative intensity) 115 ($M^+$, 100), 100 ($M^+-CH_3$, 52), 70 ($M^+-NOCH_3$, 66). Anal. Calcd for $C_4H_9N_3O$: C, 41.73; H, 7.88; N, 36.50. Found: C, 42.25; H, 7.68; N, 37.01.

**4.1.2. 2-Benzyloxyiminoimidazolidine (3).** 2-Chloro-4,5-dihydroimidazolium hemisulfate (**1**) (1.65 g, 8.12 mmol) was dissolved in 10% NaOH aqueous solution (25 mL). Then, *O*-benzylhydroxylamine (1 g, 8.12 mmol) was added and the reaction mixture was stirred at room temperature for 12 h. The product was extracted with $CH_2Cl_2$, dried, filtered and evaporated to dryness. Crude product **3** thus obtained was purified by crystallization from methanol; yield 1.38 g (89%); mp 127–130 °C (methanol); $^1$H NMR ($CDCl_3$) $\delta$ 3.31 (s, 4H, $CH_2$), 4.38 (br s, 1H, NH), 4.76 (s, 2H, $CH_2$), 4.84 (br s, 1H, NH), 7,25 (m, 5H, CH); $^{13}$C NMR ($CDCl_3$) $\delta$ 43.2, 76.0, 128.0, 128.6, 128.7, 139.1, 161.1; IR cm$^{-1}$ 3228, 2282, 1643, 1496, 1452. Anal. Calcd for $C_{10}H_{13}N_3O$: C, 62.81; H, 6.85; N, 21.97. Found: C, 62.26; H, 7.14; N, 22.13.

**4.1.3. 7-Phenyl-2,3-dihydro-1*H*-imidazo[1,2-*a*]pyrimidin-5-one (4).** Compound **2** or **3** (4.35 mmol) and ethyl phenylpropiolate (0.76 g, 4,35 mmol) were refluxed in ethanol (6 mL) for 0.5 h. Solid that precipitated was filtered off, washed with ethanol and crystallized from ethanol; yield for **2** 0.40 g (43%); yield for **3** 0.31 g (33%); mp 274–275 °C (Ref. 1 mp 269–271 °C); $^1$H NMR (DMSO-$d_6$) $\delta$ 3.62 (m, 2H, $CH_2$), 4.04 (m, 2H, $CH_2$), 6.15 (s, 1H, CH), 7.42 (m, 3H, CH), 7.92 (m, 2H, CH), 8.06 (s, 1H, NH); $^{13}$C NMR (DMSO-$d_6$) $\delta$ 42.9, 98.5, 127.3, 129.1, 130.6, 137.9, 159.2, 162.0, 162.9; IR cm$^{-1}$ 3125, 2898, 1678, 1610, 1555, 1438. Anal. Calcd for $C_{12}H_{11}N_3O$: C, 67.59; H, 5.20; N, 19.71. Found: C, 68.11; H, 5.35; N, 19.43.

**4.1.4. 5-Oxo-1,2,3,5-tetrahydro-imidazo[1,2-*a*]pyrimidine-7-carboxylic acid methyl ester (5).** Compound **2** or **3** (4.35 mmol) and dimethyl acetylenedicarboxylate (0.62 g, 4,35 mmol) were heated at reflux in methanol (6 mL) for 0.5 h. Solid that precipitated was filtered off, washed with methanol, and recrystallized from DMF; yield for **2** 0.39 g (46%); yield for **3** 0.46 g (55%); mp 296–298 °C (DMF); $^1$H NMR (DMSO-$d_6$) $\delta$ 3.76 (s, 3H, $CH_3$) 3.62 (t, 2H, $CH_2$, $J$= 10 Hz), 4.03 (t, 2H, $CH_2$, $J$=10 Hz), 6.15 (s, 1H, CH), 8.31 (s, 1H, NH); IR cm$^{-1}$ 3445, 3115, 1737, 1690, 1633, 1562, 1455; EIMS *m*/*z* (relative intensity) 195 ($M^+$, 84), 164 ($M^+-OCH_3$, 9), 137 ($M^+-COOCH_3$, 100). Anal. Calcd for $C_8H_9N_3O_3$: C, 49.23; H, 4.65; N, 21.53. Found: C, 49.52; H, 4.35; N, 21.12.

**4.1.5. 5-Oxo-1,2,3,5-tetrahydro-imidazo[1,2-*a*]pyrimidine-7-carboxylic acid ethyl ester (6).** Compound **2** or **3** (4.35 mmol) and diethyl acetylenedicarboxylate (0.74 g, 4,35 mmol) were heated at reflux in ethanol (6 mL) for 0.5 h. Precipitate was filtered off, washed and recrystallized from DMF; yield for **2** 0.40 g (44%); yield for **3** 0.23 g (25%); mp 289–290 °C (DMF); $^1$H NMR (DMSO-$d_6$) $\delta$ 1.24 (t, 3H, $CH_3$, $J$=7 Hz), 3.62 (m, 2H, $CH_2$), 4.02 (m, 2H, $CH_2$), 4.22 (q, 2H, $CH_2$, $J$=7 Hz), 6.15 (s, 1H, CH), 8.34 (s, 1H, NH); $^{13}$C NMR (DMSO-$d_6$) $\delta$ 14.0, 42.4, 61.3, 104.3, 154.6, 159.7, 161.4, 165.2; IR cm$^{-1}$ 3445, 3115, 1737, 1690, 1633, 1562. Anal. Calcd for $C_9H_{11}N_3O_3$: C, 51.67; H, 5.30; N, 20.09. Found: C, 51.42; H, 5.35; N, 20.01.

**4.1.6. 7-Methyl-2,3-dihydro-1*H*-imidazo[1,2-*a*]pyrimidin-5-one (7).** Compound **2** or **3** (1.57 mmol) and ethyl 2-butyonate (0.17 g, 1.73 mmol) were heated at reflux in ethanol (6 mL) for 10 h. Solid that precipitated was filtered off, washed with ethanol and recrystallized from 1-butanol; yield for **2** 0.065 g (27%); yield for **3** 0.16 g (68%); mp 232–234 °C (lit.[1] 228–230 °C); $^1$H NMR ($CDCl_3$) $\delta$ 2.02 (s, 3H, $CH_3$), 3.65 (t, 2H, $CH_2$, $J$=8.6 Hz), 4.06 (t, 2H, $CH_2$, $J$=8.6 Hz), 5.52 (s, 1H, CH), 6.45 (br s, 1H, NH); IR cm$^{-1}$ 3130, 3068, 2893,

1670, 1625, 1440. Anal. Calcd for $C_7H_9N_3O$: C, 55.62; H, 6.00; N, 27.80. Found: C, 55.32; H, 5.84; N, 28.00.

**4.1.7. 8-Metoxy-2,8-dihydro-3*H*-imidazo[1,2-*a*]pyrimidin-5-one (8).** Compound **2** (0.5 g, 4.35 mmol) and ethyl propiolate (0.42 g, 4,35 mmol) were heated at reflux in ethanol (6 mL) for 0.5 h. The reaction mixture was concentrated to a volume of 2 mL under reduced pressure and diethyl ether (10 mL) was added. Pure compound **8** that precipitated was filtered off and washed with diethyl ether; yield 0.59 g (81%); mp 135–137 °C (diethyl ether); $^1$H NMR (DMSO-$d_6$) $\delta$ 3.74 (m, 4H, $CH_2$), 3.86 (s, 3H, $CH_3$), 5.13 (d, 1H, CH, $J$=8.2 Hz), 7.71 (d, 1H, CH, $J$=8.2 Hz); $^{13}$C NMR (DMSO-$d_6$) $\delta$ 44.5, 50.3, 64.0, 97.0, 142.7, 148.0, 159.8; IR cm$^{-1}$ 1683, 1643, 1624, 1439. Anal. Calcd for $C_7H_9N_3O_2$: C, 50.29; H, 5.43; N, 25.14. Found: C, 50.63; H, 5.75; N, 24.83.

**4.1.8. 8-Benzyloxy-2,8-dihydro-3*H*-imidazo[1,2-*a*]pyrimidin-5-one (9).** Compound **3** (0.3 g, 1.57 mmol) and ethyl propiolate (0.17 g, 1.73 mmol) were heated at reflux in ethanol (4 mL) for 0.5 h. Then, the reaction mixture was evaporated to dryness and the oily residue was extracted with diethyl ether. Combined organic layers were dried and evaporated to dryness. Product **9** was recrystallized from diethyl ether; yield 0.15 g (40%); mp 102–105 °C; $^1$H NMR ($CDCl_3$) $\delta$ 4.03 (m, 4H, $CH_2$), 5.07 (d, 1H, CH, $J$=8.3 Hz), 5.21 (s, 2H, $CH_2$), 6.70 (d, 1H, CH, $J$=8.3 Hz), 7.44 (m, 5H, CH); $^{13}$C NMR ($CDCl_3$) $\delta$ 31.9, 37.3, 65.8, 85.1, 116.2, 116.9, 117.4, 120.5, 129.5, 136.3, 147.0; IR cm$^{-1}$ 3073, 2877, 1679, 1645, 1444. Anal. Calcd for $C_{13}H_{13}N_3O_2$: C, 64.19; H, 5.39; N, 17.27. Found: C, 64.08; H, 5.03; N, 17.67.

**4.1.9. 8-Metoxy-7-methyl-2,8-dihydro-3*H*-imidazo[1,2-*a*]pyrimidin-5-one (10).** Compound **2** (0.5 g, 4.35 mmol) and ethyl 2-butyonate (0.48 g, 4.35 mmol) were refluxed in ethanol (6 mL) for 0.5 h. The reaction mixture was evaporated under reduced pressure and the residue was subjected to flash chromatography (AcOEt/ methanol 5:2); yield 0.47 g (60%); mp 115–119 °C; $^1$H NMR ($CDCl_3$) $\delta$ 2.17 (s, 3H, $CH_3$) 3.95 (m, 4H, $CH_2$), 3.97 (s, 3H, $OCH_3$), 5.07 (s, 1H, CH); IR cm$^{-1}$ 1683, 1644, 1607, 1451; EIMS *m/z* (relative intensity) 181 ($M^+$, 53), 151 ($M^+-OCH_3$, 100). Anal. Calcd for $C_8H_{11}N_3O_2$: C, 53.03; H, 6.12; N, 23.19. Found: C, 52.71; H, 6.43; N, 23.63.

**4.1.10. 2,3-Dihydro-1*H*-imidazo[1,2-*a*]pyrimidin-5-one (11).** Compound **3** (0.3 g, 1.57 mmol) and ethyl propiolate (0.17 g, 1.73 mmol) were refluxed in ethanol (4 mL) for 10 h. Then, the reaction mixture was evaporated to dryness, washed with diethyl ether and subjected to flash chromatography (AcOEt/MeOH 9:1); yield of product **11**: 0.08 g (38%); mp 157–161 °C (acetone); $^1$H NMR (DMSO-$d_6$) $\delta$ 3.58 (t, 2H, $CH_2$, $J$=8.8 Hz), 4.00 (t, 2H, $CH_2$, $J$=8.8 Hz), 5.54 (d, 1H, CH, $J$=6.3 Hz), 7.50 (d, 1H, CH, $J$=6.3 Hz), 7.94 (br s, 1H, NH); $^{13}$C NMR (DMSO-$d_6$) $\delta$ 39.5, 42.6, 102.8, 156.1, 159.3, 161.0; IR cm$^{-1}$ 3262, 3115, 2979, 2867, 1674, 1614, 1433, 1285. Anal. Calcd for $C_6H_7N_3O$: C, 52.55; H, 5.14; N, 30.64. Found: C, 52.61; H, 5.43; N, 30.22.

**4.1.11. 1-Acetyl-7-phenyl-2,3-dihydro-1*H*-imidazo[1,2-*a*]pyrimidin-5-one (12).** Compound **4** (0.2 g 0.93 mmol), acetic anhydride (2 mL) and $Et_3N$ (2.5 mL) were refluxed in THF (15 mL) for 0.5 h. After cooling to room temperature, pure product **12** that precipitated was collected by filtration and washed; yield 0.17 g (71%); mp 256–257 °C (THF); $^1$H NMR (DMSO-$d_6$) $\delta$ 2.72 (s, 3H, $CH_3$), 4.02 (s, 4H, $CH_2$), 6.69 (s, 1H, CH), 7.52 (m, 3H, CH), 8.08 (m, 2H, CH); $^{13}$C NMR (DMSO-$d_6$) $\delta$ 25.3, 42.3, 102.5, 127.1, 129.1, 130.9, 136.3, 152.0, 160.8, 161.0, 169.3; IR cm$^{-1}$ 3064, 1677, 1607, 1579, 1548, 1495. Anal. Calcd for $C_{14}H_{13}N_3O_2$: C, 65.87; H, 5.13; N, 16.46. Found: C, 65.42; H, 5.25; N, 15.98.

**4.1.12. 1-Benzyl-7-phenyl-2,3-dihydro-1*H*-imidazo[1,2-*a*]pyrimidin-5-one (13).** Powdered potassium hydroxide (0.7 g, 12.5 mmol) was added to a stirred suspension of compound **4** (0.5 g 2.35 mmol) in acetone (12 mL). After 5 min benzyl bromide (0.31 mL, 2.61 mmol) was added in one portion. Potassium bromide that precipitated was filtered off. The filtrate was evaporated under reduced pressure and the oily residue was subjected to flash chromatography (AcOEt); yield 0.13 g (46%); mp 167 °C; $^1$H NMR (DMSO-$d_6$) $\delta$ 3.59 (t, 2H, $CH_2$, $J$=9.5 Hz), 4.01 (t, 2H, $CH_2$, $J$=9.5 Hz), 4.66 (s, 2H, $CH_2$), 6.25 (s, 1H, CH), 7.30 (m, 1H, CH), 7.38 (m, 4H, CH), 7.44 (m, 3H, CH), 8.01 (m, 2H, CH); $^{13}$C NMR (DMSO-$d_6$) $\delta$ 39.8, 40.2, 98.4, 126.9, 127.8, 128.2, 128.8, 128.9, 130.4, 136.6, 137.2, 156.0, 161.6, 162.0; IR cm$^{-1}$ 1668, 1575, 1553, 1409, 1485. Anal. Calcd for $C_{19}H_{17}N_3O$: C, 75.23; H, 5.65; N, 13.85. Found: C, 75.42; H, 5.16; N, 14.00.

**4.1.13. 5-Oxo-7-phenyl-2,3-dihydro-5*H*-imidazo[1,2-*a*]pyrimidine-1-carboxaldehyde (14).** To a cooled solution (0 °C) of compound **4** (0.23 g, 1.08 mmol) in pyridine (4 mL) and DMF (1 mL), benzenesulfonyl chloride (0.14 mL, 1.09 mmol) was added dropwise. After stirring for 24 h at room temperature, the reaction mixture was concentrated to a volume of 2 mL under reduced pressure. Then, water (5 mL) was added and the resulting precipitate was separated by suction and subjected to flash chromatography (AcOEt/$CHCl_3$ 1:3); yield 0.165 g (73%); mp 181–184 °C; $^1$H NMR (DMSO-$d_6$) $\delta$ 4.04 (m, 4H, $CH_2$), 6.71 (s, 1H, CH), 7.52 (m, 3H, CH), 8.13 (m, 2H, CH), 9.34 (s, 1H, CH); $^{13}$C NMR (DMSO-$d_6$) $\delta$ 41.4, 103.4, 127.1, 128.9, 130.9, 135.9, 152.4, 159.6, 160.7, 160.9; IR cm$^{-1}$ 1668, 1669, 1613, 1579, 1543, 1593; EIMS *m/z* (relative intensity) 241 ($M^+$, 60), 212 ($M^+-CHO$, 100), 186 (10). Anal. Calcd for $C_{13}H_{11}N_3O_2$: C, 64.72; H, 4.60; N, 17.42. Found: C, 65.22; H, 4.55; N, 16.97.

An analogous reaction of **4** with methanesulfonyl chloride gave the product **14** in 70% yield.

### 4.2. X-ray structure determination

The intensity data for the crystals have been collected using a diffractometer equipped with a CCD camera. The crystal structures have been solved with SHELXS-97[21] and refined with SHELXL-97.[22]

*Crystal data* for $C_{10}H_{13}N_3O$ (**3**, CCDC 259437): orthorhombic, space group *Pbca*, $a$=10.5139(4) Å, $b$=8.0906(3) Å, $c$=23.4330(7) Å, $V$=1993.30(12) Å$^3$, $Z$=8, $\lambda$=0.71073 Å, $T$=130 K, $R_1$=0.0331, $wR_2$=0.0830 for 1860 independent reflections with $I>2\sigma(I)$.

*Crystal data* for $C_7H_9N_3O_2$ (**8**, CCDC 259433): monoclinic, space group $P2_1/c$, $a=8.0951(11)$ Å, $b=11.7902(12)$ Å, $c=7.8891(11)$ Å, $(=93.212(8)°$, $V=751.78(17)$ Å$^3$, $Z=4$, $\lambda=0.71073$ Å, $T=110$ K, $R_1=0.0328$, $wR_2=0.0749$ for 1128 independent reflections with $I>2\sigma(I)$.

*Crystal data* for $C_{13}H_{13}N_3O_2$ (**9**, CCDC 259436): monoclinic, space group $P2_1/c$, $a=11.7377(7)$ Å, $b=12.1676(8)$ Å, $c=8.3598(6)$ Å, $\beta=93.871(5)°$, $V=1191.22(14)$ Å$^3$, $Z=4$, $\lambda=0.71073$ Å, $T=160$ K, $R_1=0.0391$, $wR_2=0.1068$ for 1839 independent reflections with $I>2\sigma(I)$.

*Crystal data* for $C_{19}H_{17}N_3O$ (**13**, CCDC 259434): monoclinic, space group $P2_1/c$, $a=13.7543(6)$ Å, $b=8.9734(4)$ Å, $c=14.0010(6)$ Å, $\beta=117.186(4)°$, $V=1537.14(12)$ Å$^3$, $Z=4$, $\lambda=0.71073$ Å, $T=130$ K, $R_1=0.0356$, $wR_2=0.0930$ for 2280 independent reflections with $I>2\sigma(I)$.

*Crystal data* for $C_{13}H_{11}N_3O_2$ (**14**, CCDC 259435): triclinic, space group, $a=7.4335(19)$ Å, $b=7.606(2)$ Å, $c=10.846(3)$ Å, $\alpha=78.19(2)°$, $\beta=75.79(2)°$, $\gamma=80.55(2)°$, $V=577.7(3)$ Å$^3$, $Z=2$, $\lambda=0.71073$ Å, $T=293$ K, $R_1=0.0371$, $wR_2=0.0846$ for 1290 independent reflections with $I>2\sigma(I)$.

Crystallographic data for the structure (excluding structure factors) in this paper have been deposited with the Cambridge Crystallographic data Centre (CCDC) as supplementary publication number CCDC. Copies of the data can be obtained free of charge, on application to CCDC, 12 Union Road Cambridge, CB2 1EZ, UK (fax: +44-1223-336033) or e-mail: data_request@ccdc.cam.ac.uk).

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## Supplementary data

Crystallographic data for the structures **3**, **8**, **9**, **13** and **14**; $^1$H, $^{13}$C and 1D NOESY NMR spectra of **11**; Cartesian coordinates, computed total energies and imaginary frequencies of transition states **TSC**, **TS8** and **TS9** are available free of charge.

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2005.03.063

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# Syntheses of (±)-thuriferic acid ethyl ester, its analogues and (±)-picropodophyllone

Manat Pohmakotr,* Taweechote Komutkul, Patoomratana Tuchinda, Samrarn Prabpai, Palangpon Kongsaeree and Vichai Reutrakul*

*Department of Chemistry, Faculty of Science, Mahidol University, Rama 6 Road, Bangkok 10400, Thailand*

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**Abstract**—(±)-Thuriferic acid ethyl ester, its analogues as well as (±)-picropodophyllone have been prepared. The synthetic strategy is based on the utility of vicinal dianions derived from α-aroylsuccinic esters.


## 1. Introduction

Considerable research work on the isolation and synthesis of lignan natural products and analogues such as podophyllotoxin and derivatives[1] has been extensively investigated due to their wide range of biological activities including antineoplastic activity. Among these compounds, thuriferic acid (**1**) isolated from the hexane extracts of *Juniperus thurifera* leaves exhibits interesting cytotoxic activity.[2] The syntheses of thuriferic acid and derivatives, together with the precusor (±)-picropodophyllone (**2**) have been accomplished by several methods.[3] In connection with our efforts to utilize vicinal dianions derived from α-aroylsuccinates as reagents for synthesis of γ-butyrolactones and some lignan natural products, we have recently reported a general synthetic entry to α-aroylparaconic esters **3** by reacting the vicinal dianion with aromatic aldehydes in the presence of $ZnCl_2$. Compounds of type **3**[4] have been used as useful starting materials for the preparation of α-arylidene-γ-butyrolactones, which embodied all the necessary carbon framework for the aryltetralone precursor of thuriferic acid type lignans.[5] Based on this highly versatile technique, we herein report the preparation of thuriferic acid ethyl ester (**4a**) and analogues as well as pricropodophyllone (**2**),[3a,6] an important precursor for many synthetic entries to podophyllotoxin (Fig. 1).

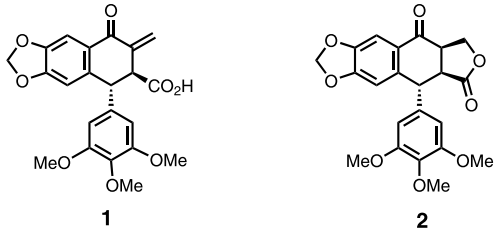


**Figure 1.**

## 2. Results and discussion

Starting from α-aroylsuccinic ester **5**, vicinal dianion **6** was generated by treatment with 2 equiv of lithium diisopropylamide (LDA) in tetrahydrofuran (THF) at −78 °C for 1 h. It was allowed to react with aromatic aldehydes (1.1 equiv) in the presence of $ZnCl_2$ (1 equiv) at −78 °C for 1 h, followed by slowly warming up to reach room temperature overnight to provide α-aroylparaconic esters **3** (50–60%) as diastereomeric mixtures of (3,4-*trans*),(4,5-*cis*)-isomer (*TC*-isomer), (3,4-*trans*),(4,5-*trans*)-isomer (*TT*-isomer), (3,4-*cis*),(4,5-*trans*)-isomer (*CT*-isomer) and (3,4-*cis*),(4,5-*cis*)-isomer (*CC*-isomer). In each case, the *TC*-isomer was obtained as the major isomer and could be separated from the other diastereomers by recrystallisation (Scheme 1). Considering α-aroylparaconic esters of type **3** as important starting materials, our study towards the construction of aryltetralone basic skeleton of thuriferic acid by acid-catalyzed rearrangement of **3a** employing $SnCl_4/CHCl_3$, concd $H_2SO_4/CHCl_3$ or $P_2O_5/MeSO_3H$ to provide **7**[1d,6a,c] was undertaken. However, it was found that only 5–8% yields of **7** were obtained together with the unidentified products. The low yield of aryltetralone **8** may be due to the fact that

*Keywords*: α-Aroylparaconic ester; Picropodophyllone; α-Aroylsuccinic ester; Vicinal dianion.
* Corresponding authors. Tel.: +66 2 2015158; fax: +66 2 6445126; e-mail addresses: scmpk@mahidol.ac.th; scvrt@mahidol.ac.th

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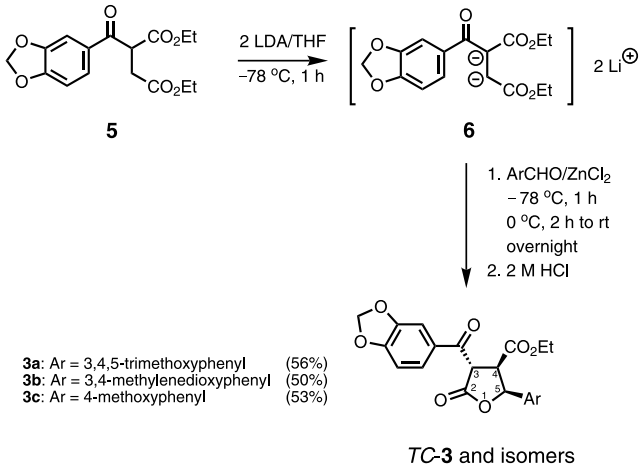
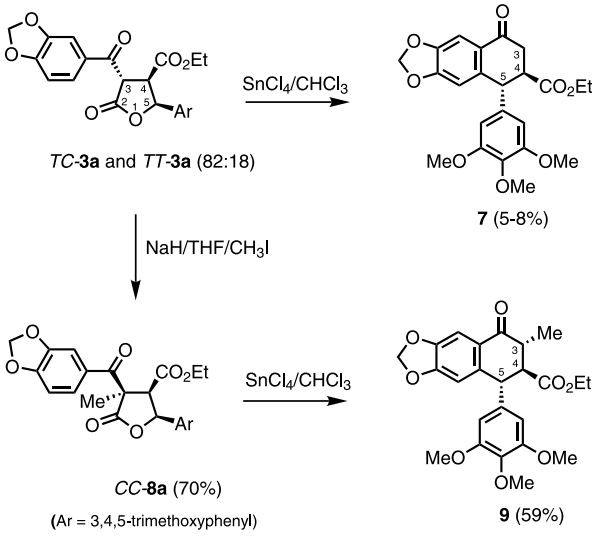


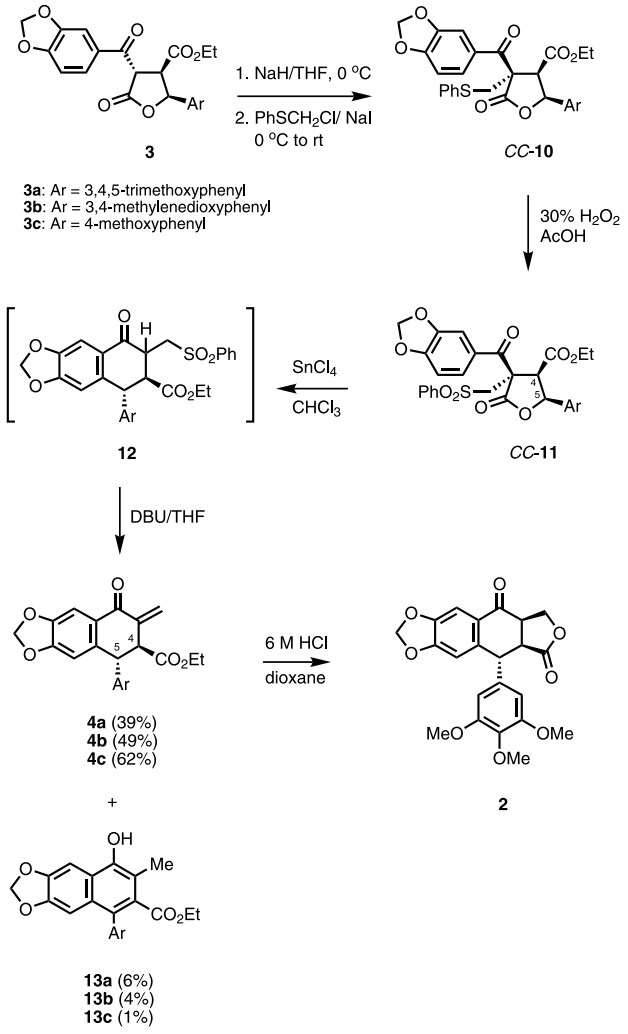

**Scheme 1.**

enolization at 3-position of **3a** occurs rapidly under the attempted conditions. This avoids the intramolecular electrophilic aromatic substitution of the initially formed carbonium ion at the 5-carbon of **3a**. To circumvent this problem, the cyclisation of α-methylated α-aroylparaconic ester **8a** was studied. Thus, α-methylated γ-lactone **8a** was prepared by treatment of the enolate anion derived from an 82:18 mixture of *TC*- and *TT*-isomers of **3a** with methyl iodide (NaH/THF/0 °C) to provide *CC*-**8a**[7] (70% yield) and *CT*-**8a** (10% yield) after chromatography. As expected, the reaction of *CC*-**8a** with $SnCl_4$ (10 equiv) in $CHCl_3$ at 60 °C for 6 h afforded aryltetralone **9** in 59% yield as a single diastereomer after chromatography (Scheme 2). The (3,4-*trans*),(4,5-*trans*) stereochemistry of **9** was established by a series of NOE experiments. Thus, irradiation of H-5 signal resulted in 9.8% enhancement of H-3 signal, but no enhancement of H-4 signal was observed.




**Scheme 2.**

This successful synthesis of aryltetralone **9** from compound **8** led us to propose a synthethic route to thuriferic acid ethyl ester and its analogues. As shown in Scheme 3, it occurred to us that Lewis acid-catalyzed rearrangement of compound **11** would provide compound **12** and then thuriferic acid




**Scheme 3.**

derivatives **4** after elimination. Therefore, the requisite α-phenylsulfanylmethylparaconic ester **10a** was prepared in good yield from α-aroylparaconic ester *TC*-**3a** by employing NaH/THF/$PhSCH_2Cl$/NaI at 0 °C to room temperature overnight, followed by oxidation of the resulting **10a** with acetic acid/30% $H_2O_2$ (0 °C to rt, overnight).[6] Compound **11a** was obtained as a single diastereomer (*CC*-isomer). The relative stereochemistry at the 4,5-position was assigned by analysis of the coupling constant between H-4 and H-5 which appeared in the $^1H$ NMR spectrum as doublets at $\delta$ 4.88 and 6.16 ($J=6.9$ Hz) ppm, respectively. The structure of compound **11a** was finally confirmed by X-ray crystallography as shown in Figure 2.[8] Similarly, the major isomers *CC*-**11b** and *CC*-**11c** were prepared in good overall yields starting from **3b** (*TC*/*TT*=82:18) and *TC*-**3c**, respectively.

Having compound **11a** in hand, it was subjected to Lewis acid-catalyzed rearrangement by reacting with $SnCl_4$ (10 equiv) in $CHCl_3$ at room temperature overnight. The reaction afforded, presumably the intermediate **12a** which was treated immediately with diazabicycloundecane (DBU) in THF at room temperature for 1 h to provide the required thuriferic ethyl ester (**4a**) in 39% overall yield together with the arylnapthalene **13a** as the minor product in 6% yield. By employing the same reaction sequence, **4b**, **4c**, **13b** and **13c**

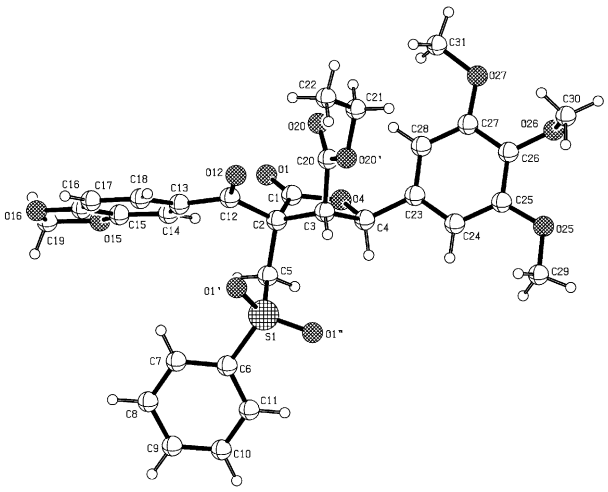



**Figure 2.** X-ray crystal structure of compound **11a**.

were obtained in 49, 62, 4 and 1% yields, respectively. The relative stereochemistries at C-4 and C-5 of these compounds were assigned by comparing their coupling constants at $\delta$ 4.62–4.65 ppm ($J_{trans}$=4.0–4.1 Hz) with those of compound **9**.

Hydrolysis of the ester group of **4a** with 6 M HCl in dioxane under reflux for 15 h furnished (±)-picropodophyllone (**2**)[3a,6b–e] in 43% yield after chromatography instead of the expected (±)-thuriferic acid. The formation of **2** was believed to occur via the acid-catalyzed lactonisation of the initially formed thuriferic acid (**1**). (±)-Picropodophyllone has been demonstrated to be a useful precursor for the preparation of thuriferic acid (**1**).[3a,b,d,e]

## 3. Conclusion

In conclusion, we have described an efficient and general route to (±)-thuriferic acid ethyl ester (**4a**) and analogues as well as (±)-picropodophyllone (**2**) by exploiting α-aroylparaconic esters **3** obtained from the reaction of vicinal dianions derived from α-aroylsuccinic esters with aromatic aldehydes. This method should find wide application in synthesis of series of related aryltetralin derivatives.

## 4. Experimental

### 4.1. General

Melting points (uncorrected) were determined on a Büchi 501 Melting Point Apparatus. IR spectra were recorded on a Spectrum GX FT-IR system (Perkin Elmer) spectrometer. $^1$H NMR (300 MHz) and $^{13}$C NMR (75 MHz) spectra were recorded on a Bruker DPX-300 spectrometer in $CDCl_3$ with TMS as an internal standard. Mass spectra were obtained on a Thermo Finnigan Polaris Q mass spectrometer. High resolution mass spectra were obtained on a Micromass model VQ-TOF2 mass spectrometer. Elemental analyses were determined on a Perkin Elmer Elemental Analyzer 2400 CHN. The X-ray crystallography was performed by Kappa CCD. Silica gel 60H and silica gel plates (Merck, Kieselgel 60 $F_{254}$, 0.5 mm) were used for column chromatography and preparative TLC, respectively.

**4.1.1. Preparation of diethyl α-(3,4-methylenedioxybenzoyl)succinate (5).** By modification of the known procedure,[9] a solution of piperonal (30.07 g, 200 mmol) in methanol (100 mL) was added dropwise to a solution of dimethylammonium chloride (32.74 g, 401 mmol) and potassium cyanide (26.24 g, 402 mmol) in water (100 mL). The resulting mixture was heated under reflux for 4 h. The solvent was removed under reduced pressure, and water (150 mL) was then added to the residue and extracted with EtOAc (4×100 mL). The combined organic layers were washed with saturated aqueous $NaHSO_3$ (100 mL), water (2×100 mL), brine and dried over anhydrous $MgSO_4$. Evaporation of solvent under reduced pressure gave a crude product of 2-(*N*,*N*-dimethylamino)-2-(3,4-methylenedixoyphenyl)ethanenitrile, which was further used without purification.

A solution of the crude α-aminonitrile in THF (50 mL) was slowly added to a THF (50 mL) solution of sodium ethoxide [prepared by reacting Na metal (7.04 g, 305 mmol) with absolute ethanol (145 mL)] at room temperature under an argon atmosphere. After stirring at room temperature for 1 h, a solution of diethyl fumarate (52.70 g, 306 mmol) in THF (50 mL) was added dropwise. The reaction mixture was stirred at the same temperature overnight (15 h), then diluted with water (200 mL) and extracted with EtOAc (3× 150 mL). The combined organic extracts were washed with water (3×100 mL), brine and dried over anhydrous $MgSO_4$. Evaporation of solvent under reduced pressure gave diethyl α-[1-*N*,*N*-dimethylamino-1-cyano-1-(3,4-methylenedioxyphenyl)methyl]succinate of which was subjected to hydrolysis in the next step.

A solution of $CuSO_4 \cdot 5H_2O$ (75.18 g, 301 mmol) in water (80 mL) was added to a solution of the crude product in ethanol (200 mL). The resulting mixture was heated under reflux for 1 h. The reaction mixture was cooled to room temperature, diluted with water (200 mL) and extracted with EtOAc (3×150 mL). The combined extracts were washed with water (3×100 mL), brine and dried over anhydrous $MgSO_4$. After removal of solvent under reduced pressure, the crude product obtained was purified by column chromatography ($SiO_2$, 10–20% EtOAc in hexanes) to give a yellow viscous liquid of diethyl α-(3,4-methylenedioxybenzoyl)succinate (**5**) (42.21 g, 66% yield). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.68 (dd, $J$=8.1, 1.9 Hz, 1H, Ar*H*), 7.49 (d, $J$=1.9 Hz, 1H, Ar*H*), 6.88 (d, $J$=8.1 Hz, 1H, Ar*H*), 6.05 (s, 2H, $OCH_2O$), 4.76 (app t, $J$=7.2 Hz, 1H, $COCHCO_2Et$), 4.18–4.09 (m, 4H, $2\times CO_2CH_2CH_3$), 3.07 (dd, ABX-system, $J$=17.3, 7.7 Hz, 1H, $CHHCO_2Et$), 2.99 (dd, ABX-system, $J$=17.3, 6.6 Hz, 1H, $CHHCO_2Et$), 1.23 (t, $J$=7.0 Hz, 3H, $CO_2CH_2CH_3$), 1.18 (t, $J$=7.0 Hz, 3H, $CO_2CH_2CH_3$). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 192.0 (C=O), 171.2 (C=O), 168.7 (C=O), 152.3 (C–O), 148.2 (C–O), 130.6 (C), 125.5 (CH), 108.5 (CH), 107.9 (CH), 101.9 ($OCH_2O$), 61.7 ($OCH_2$), 60.9 ($OCH_2$), 49.3 (CH), 33.3 ($CH_2$), 14.0 ($CH_3$), 13.8 ($CH_3$). IR (neat): $\nu_{max}$ 2984m, 2939w, 2908w, 1732s, 1681m, 1605m, 1505m, 1489m, 1444s, 1369m, 1353m, 1259s, 1177m, 1036s, 932m, 861m, 809m cm$^{-1}$. MS: *m*/*z* (%) relative intensity 323 ($M^+$+1,

35), 322 ($M^+$, 14), 277 (10), 149 (100), 121 (2), 65 (6). Anal. Calcd for $C_{16}H_{18}O_7$: C, 59.63; H, 5.63. Found: C, 59.23; H, 5.63.

### 4.2. Generation and reaction of the vicinal dianion 6 with aromatic aldehydes

**4.2.1. Preparation of ethyl 4-(1,3-benzodioxol-5-carbonyl)-2-(3,4,5-trimethoxyphenyl)-5-oxotetrahydrofuran-3-carboxylate (3a).** A solution of **5** (636.1 mg, 1.98 mmol) in THF (1 mL) was added dropwise at −78 °C to a THF solution of lithium diisopropylamide (LDA) under an argon atmosphere [prepared by reacting diisopropylamine (0.6 mL, 4.25 mmol) in THF (4 mL) with *n*-BuLi (1.49 M in hexane, 2.8 mL, 4.17 mmol) at −78 °C for 30 min]. After stirring at −78 °C for 1 h, a cooled (0 °C) mixture of 3,4,5-trimethoxybenzaldehyde (433.9 mg, 2.21 mmol) in THF (1 mL) and $ZnCl_2$ (1 M in THF, 2.3 mL, 2.3 mmol) was added dropwise to a solution of the vicinal dianion **6**. The resulting mixture was stirred at −78 °C for a further 1 h, and then at 0 °C for 2 h, followed by slowly warming up to room temperature overnight (15 h). It was quenched with 2 M HCl (4 mL), diluted with water (50 mL) and extracted with EtOAc (3×50 mL). The combined organic layers were washed with water, brine and dried over anhydrous $Na_2SO_4$. After removal of solvent under reduced pressure, the crude product obtained was purified by column chromatography ($SiO_2$, 30% EtOAc in hexanes) to give a pale yellow solid of ethyl 4-(1,3-benzodioxol-5-carbonyl)-2-(3,4,5-trimethoxyphenyl)-5-oxotetrahydrofuran-3-carboxylate (**3a**) (523.6 mg, 56% yield) as a 67:3:25:5 mixture of *TC*/*CC*/*TT*/*CT* diastereomers. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.48 (dd, $J$=8.2, 1.5 Hz, 1H, Ar*H* of *TC*-isomer), 7.78 (br d, $J$=8.3 Hz, 1H, Ar*H* of *CT*-isomer), 7.73 (dd, $J$=8.2, 1.6 Hz, 1H, Ar*H* of *TT*-isomer), 7.66 (br d, $J$=9.4 Hz, 1H, Ar*H* of *CC*-isomer), 7.58 (*TC*) and 7.54 (*TT* and *CT*) (each d, $J$=1.5 Hz, 1H, Ar*H*), 7.45 (br s, 1H, Ar*H* of *CC*-isomer), 6.95 (*TC*), 6.93 (*TT* and *CT*) and 6.86 (*CC*) (each d, $J$=8.2, 8.3, 8.6 Hz, respectively, 1H, Ar*H*), 6.77 (*CT*), 6.68 (*TT*) and 6.56 (*TC* and *CC*) (each s, 2H, Ar*H*), 6.09 (br s, 2H, OC$H_2$O of *TC*-, *CC*-, *TT*- and *CT*-isomers and 1H, OC*H*Ar of *CT*-isomer), 5.92 (*TC*), 5.74 (*CC*) and 5.57 (*TT*) (each d, $J$=7.7, 8.4, 8.9 Hz, respectively, 1H, OC*H*Ar), 5.05 (*TT* and *CT*), 5.01 (*TC*) and 4.48 (*CC*) (each d, $J$=8.9, 3.7, 8.4 Hz, respectively, 1H, COC*H*CO), 4.24 (dd, $J$=7.7, 3.7 Hz, 1H, C*H*$CO_2$Et of *TC*-isomer), 4.20–4.02 (m, 1H, C*H*$CO_2$Et of *TT*-isomer, 2H, $CO_2CH_2CH_3$ of *TT*-isomer, 2H, $CO_2CH_2$-$CH_3$ of *CT*-isomer and 1H, C*H*$CO_2$Et of *CC*-isomer), 3.89–3.79 (m, 9H, 3×OC$H_3$ of *TC*-, *CC*-, *TT*- and *CT*-isomers, and 1H, $CO_2CH$*H*$CH_3$ of *TC*-isomer) 3.78–3.56 (m, 1H, $CO_2CH$*H*$CH_3$ of *TC*-isomer, 2H, $CO_2CH_2CH_3$ of *CC*-isomer and 1H, C*H*$CO_2$Et of *CT*-isomer), 1.20 (*TT*), 1.09 (*CT*), 0.89 (*TC*) and 0.81 (*CC*) (each t, $J$=7.1, 7.1, 7.2, 7.1 Hz, respectively, 3H, $CO_2CH_2CH_3$). IR ($CHCl_3$): $\nu_{max}$ 3025m, 2941m, 2907m, 2843w, 1779s, 1733s, 1675s, 1596s, 1507s, 1490m, 1464s, 1446s, 1425m, 1379m, 1356m, 1334m, 1256s, 1185s, 1162s, 1130s, 1041s, 1003m, 936m, 852m, 833m, 810m cm$^{-1}$.

The pale yellow solid of **3a** (diastereomeric mixture) was recrystallized with EtOAc–hexanes to give a pure white solid of *TC*-**3a** (mp 139–141 °C). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.83 (dd, $J$=8.3, 1.8 Hz, 1H, Ar*H*), 7.58 (d, $J$=1.8 Hz, 1H, Ar*H*), 6.94 (d, $J$=8.3 Hz, 1H, Ar*H*), 6.56 (s, 2H, Ar*H*), 6.09 (s, 2H, OC$H_2$O), 5.92 (d, $J$=7.8 Hz, 1H, OC*H*Ar), 5.01 (d, $J$=3.7 Hz, 1H, COC*H*CO), 4.24 (dd, $J$=7.8, 3.7 Hz, 1H, C*H*$CO_2$Et), 3.89–3.81 (m, 1H, $CO_2$-C*H*$HCH_3$), 3.88 (s, 6H, 2×OC$H_3$), 3.84 (s, 3H, OC$H_3$), 3.79–3.63 (m, 1H, $CO_2CH$*H*$CH_3$), 0.90 (t, $J$=7.2 Hz, 3H, $CO_2CH_2CH_3$). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 188.9 (C=O), 170.4 (C=O), 169.5 (C=O), 153.2 (2×C–O), 153.1 (C–O), 148.4 (C–O), 138.2 (C–O), 130.4 (C), 129.4 (C), 127.2 (CH), 108.9 (CH), 108.1 (CH), 102.8 (2×CH), 102.1 ($OCH_2O$), 81.2 (OCHAr), 61.4 ($OCH_2$), 60.7 (OC$H_3$), 56.2 (2×OC$H_3$), 52.2 (CH), 50.2 (CH), 13.5 ($CH_3$). IR (nujol): $\nu_{max}$ 1755s, 1734s, 1668s, 1602s, 1509m, 1456s, 1333s, 1287s, 1255s, 1232s, 1196m, 1154s, 1127s, 1040m, 1005m, 995m, 939m, 837m, 730m, 718m cm$^{-1}$. MS: *m*/*z* (%) relative intensity 472 ($M^+$, 25), 399 (4), 295 (10), 283 (10), 282 (38), 250 (7), 249 (6), 237 (17), 236 (16), 203 (14), 196 (91), 195 (100), 191 (10), 149 (14), 121 (3), 67 (5). Anal. Calcd for $C_{24}H_{24}O_{10}$: C, 61.02; H, 5.12. Found: C, 60.88; H, 5.06.

Attempted separation of the other diastereomers from the filtrate obtained after recrystallization of **3a** was made by preparative thin-layer chromatography ($SiO_2$, 20% EtOAc in hexanes; triple runs) to give a white solid of *TC*-**3a** (less polar) and a yellow viscous liquid of *TT*-**3a**. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.78 (*CT*) and 7.72 (*TT*) (each dd, $J$=8.3, 1.7 Hz, 1H, Ar*H*), 7.54 (d, $J$=1.7 Hz, 1H, Ar*H* of *TT*- and *CT*-isomers), 6.93 (d, $J$=8.3 Hz, 1H, Ar*H* of *TT*- and *CT*-isomers), 6.76 (*CT*) and 6.67 (*TT*) (each s, 2H, Ar*H*), 6.09 (s, 2H, OC$H_2$O of *TT*- and *CT*-isomers), 6.06 (*CT*) and 5.56 (*TT*) (each d, $J$=9.5, 8.5 Hz, respectively, 1H, OC*H*Ar), 5.04 (d, $J$=9.5 Hz, 1H, COC*H*CO of *TT*- and *CT*-isomers), 4.26–4.09 (m, 1H, C*H*$CO_2$Et of *TT*-isomer, 2H, $CO_2CH_2CH_3$ of *TT*-isomers and 2H, $CO_2CH_2CH_3$ of *CT*-isomer), 3.89–3.86 (m, 9H, 3×OC$H_3$ of *TT*- and *CT*-isomers), 3.60 (app t, $J$=9.2 Hz, C*H*$CO_2$Et of *CT*-isomer), 1.20 (*TT*) and 1.01 (*CT*) (each t, $J$=7.1 Hz, 3H, $CO_2CH_2CH_3$).

**4.2.2. Preparation of ethyl 4-(1,3-benzodioxol-5-carbonyl)-2-(1,3-benzodioxol-5-yl)-5-oxotetrahydrofuran-3-carboxylate (3b).** According to the general procedure as described for compound **3a**, the solution of the vicinal dianion **6** (8.89 mmol) in THF (23 mL) was treated with a THF (6 mL) solution of piperonal (2.0028 g, 13.34 mmol). The crude product was purified by column chromatography ($SiO_2$, 20% EtOAc in hexanes) to give a pale yellow solid of **3b** (1.8926 g, 50% yield) as a 85:0:13:2 mixture of *TC*/*CC*/*TT*/*CT* diastereomers. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.82 (dd, $J$=8.2, 1.5 Hz, 1H, Ar*H* of *TC*-isomer), 7.72 (br d, $J$=8.4 Hz, 1H, Ar*H* of *TT*- and *CT*-isomers), 7.57 (d, $J$=1.5 Hz, 1H, Ar*H* of *TC*-isomer), 7.54 (br s, 1H, Ar*H* of *TT*- and *CT*-isomers), 6.94 (*TC*) and 6.89 (*TT* and *CT*) (each d, $J$=8.2, 8.4 Hz, respectively, 1H, Ar*H*), 6.84–6.76 (m, 3H, Ar*H* of *TC*-, *TT*- and *CT*-isomers), 6.09–5.96 (m, 2H, OC$H_2$O of *TC*-, *TT*- and *CT*-isomers and 1H, OC*H*Ar of *CT*-isomer), 5.89 (*TC*) and 5.51 (*TT*) (each d, $J$=8.2, 8.8 Hz, respectively, 1H, OC*H*Ar), 5.04 (*TC*), 5.03 (*TT*) and 5.02 (*CT*) (each d, $J$=5.9, 6.3, 9.1 Hz, respectively, 1H, COC*H*CO), 4.34 (dd, $J$=8.2, 5.9 Hz, 1H, C*H*$CO_2$Et of *TC*-isomer), 4.23–4.13 (m, 1H, C*H*$CO_2$Et of *TT*-isomer, 2H, $CO_2CH_2CH_3$ of *TT*-isomer and 2H, $CO_2CH_2CH_3$ of

*CT*-isomer), 3.95–3.75 (m, 2H, $CO_2CH_2CH_3$ of *TC*-isomer), 3.67 (app t, $J=7.0$ Hz, 1H, $CHCO_2Et$ of *CT*-isomer), 1.18 (*TT*), 0.99 (*TC*) and 0.89 (*CT*) (each t, $J=7.3$, 7.2, 6.6 Hz, respectively, 3H, $CO_2CH_2CH_3$). IR ($CHCl_3$): $\nu_{max}$ 3029m, 2986m, 2904m, 1778s, 1735s, 1676s, 1605m, 1505s, 1490s, 1446s, 1376m, 1353m, 1255s, 1185m, 1162m, 1101m, 1041s, 937m, 810m $cm^{-1}$.

The pale yellow solid of the diastereomeric mixture of **3b** was recrystallized from EtOAc–hexanes to give a white solid of *TC*-**3b** (mp 160–161 °C). $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 7.81 (dd, $J=8.2$, 1.8 Hz, 1H, Ar*H*), 7.56 (d, $J=1.8$ Hz, 1H, Ar*H*), 6.93 (d, $J=8.2$ Hz, 1H, Ar*H*), 6.79 (m, 3H, Ar*H*), 6.07 (s, 2H, $OCH_2O$), 5.98 and 5.97 (each d, $J=1.4$ Hz, 2H, $OCH_2O$), 5.88 (d, $J=8.3$ Hz, 1H, OC*H*Ar), 5.04 (d, $J=5.7$ Hz, 1H, COC*H*CO), 4.33 (dd, $J=8.3$, 5.7 Hz, 1H, $CHCO_2Et$), 3.94–3.74 (m, 2H, $CO_2CH_2CH_3$), 0.99 (t, $J=7.2$ Hz, 3H, $CO_2CH_2CH_3$). $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ 189.0 (C=O), 170.5 (C=O), 169.1 (C=O), 153.0 (C–O), 148.4 (C–O), 148.0 (C–O), 147.8 (C–O), 129.6 (C), 128.8 (C), 127.2 (CH), 119.7 (CH), 108.9 (CH), 108.2 (CH), 108.1 (CH), 106.3 (CH), 102.1 ($OCH_2O$), 101.3 ($OCH_2O$), 80.5 (OCHAr), 61.5 ($OCH_2$), 51.1 (CH), 49.9 (CH), 13.6 ($CH_3$). IR (nujol): $\nu_{max}$ 1779s, 1714s, 1664s, 1602m, 1505m, 1488m, 1448s, 1302 m, 1252s, 1190s, 1161s, 1113m, 1041m, 1030m, 1012m, 996m, 874m, 814m $cm^{-1}$. MS: *m*/*z* (%) relative intensity 426 ($M^+$, 3), 382 (1), 352 (1), 326 (8), 308 (28), 291 (6), 276 (7), 249 (8), 231 (5), 227 (10), 225 (18), 209 (10), 204 (17), 203 (100), 202 (48), 149 (18), 121 (4), 105 (25), 77 (15). Anal. Calcd for $C_{22}H_{18}O_9$: C, 61.97; H, 4.26. Found: C, 61.55; H, 4.19.

**4.2.3. Preparation of ethyl 4-(1,3-benzodioxol-5-carbonyl)-2-(4-methoxyphenyl)-5-oxotetrahydrofuran-3-carboxylate (3c).** According to the general procedure as described for compound **3a**, the solution of the vicinal dianion **6** (5.20 mmol) in THF (13 mL) was treated with a THF (4 mL) solution of *p*-methoxybenzaldehyde (1.0655 g, 7.83 mmol). The crude product was purified by column chromatography ($SiO_2$, 20% EtOAc in hexanes) to give a pale yellow solid of **3c** (1.1261 g, 53% yield) as a 85:0:12:3 mixture of *TC*/*CC*/*TT*/*CT* diastereomers. $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 7.83 (*TC*) and 7.73 (*TT* and *CT*) (each dd, $J=8.2$, 1.5, 8.1, 1.6 Hz, respectively, 1H, Ar*H*), 7.58 (*TC*) and 7.55 (*TT* and *CT*) (each d, $J=1.5$, 1.6 Hz, respectively, 1H, Ar*H*), 7.39 (br d, $J=8.5$ Hz, 2H, Ar*H* of *TT*- and *CT*-isomers), 7.24 (m, 2H, Ar*H* of *TC*-isomer), 6.96–6.89 (m, 3H, Ar*H* of *TC*-, *TT*- and *CT*-isomers), 6.09 (s, 2H, $OCH_2O$ of *TC*-, *TT*- and *CT*-isomers), 6.08 (*CT*), 5.93 (*TC*) and 5.55 (*TT*) (each d, $J=8.6$, 8.3, 8.9 Hz, respectively, 1H, OC*H*Ar), 5.07 (*TC*), 5.04 (*TT*) and 5.03 (*CT*) (each d, $J=5.7$, 10.1, 9.0 Hz, respectively, 1H, COC*H*CO), 4.36 (dd, $J=8.3$, 6.2 Hz, 1H, $CHCO_2Et$ of *TC*-isomer), 4.27–4.05 (m, 1H, $CHCO_2Et$ of *TT*-isomer, 2H, $CO_2CH_2CH_3$ of *TT*-isomer and 2H, $CO_2CH_2CH_3$ of *CT*-isomer), 3.89–3.79 (m, 1H, $CO_2CHHCH_3$ of *TC*-isomer and 3H, $OCH_3$ of *TC*-, *TT*- and *CT*-isomers), 3.76–3.65 (m, 1H, $CO_2CHHCH_3$ of *TC*-isomer and 1H, $CHCO_2Et$ of *CT*-isomer), 1.17 (*TT*), 1.11 (*CT*) and 0.93 (*TC*) (each t, $J=7.2$, 7.0, 7.2 Hz, respectively, 3H, $CO_2CH_2CH_3$). IR ($CHCl_3$): $\nu_{max}$ 3014m, 2978m, 2904m, 1778s, 1734s, 1676s, 1613m, 1516s, 1506m, 1489m, 1445s, 1381m, 1303m, 1287m, 1254s, 1178s, 1112m, 1040s, 937m, 851m, 810m $cm^{-1}$.

The pale yellow solid of **3c** (diastereomeric mixture) was recrystallized from EtOAc–hexanes to give a white solid of *TC*-**3c** (mp 123–124 °C). $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 7.82 (dd, $J=8.2$, 1.8 Hz, 1H, Ar*H*), 7.57 (d, $J=1.8$ Hz, 1H, Ar*H*), 7.26–7.22 (m, 2H, Ar*H*), 6.95–6.87 (m, 3H, Ar*H*), 6.08 (s, 2H, $OCH_2O$), 5.93 (d, $J=8.3$ Hz, 1H, OC*H*Ar), 5.07 (d, $J=5.8$ Hz, 1H, COC*H*CO), 4.36 (dd, $J=8.3$, 5.8 Hz, 1H, $CHCO_2Et$), 3.89–3.78 (m, 1H, $CO_2CHHCH_3$), 3.81 (s, 3H, $OCH_3$), 3.76–3.65 (m, 1H, $CO_2CHHCH_3$), 0.93 (t, $J=7.2$ Hz, 3H, $CO_2CH_2CH_3$). $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ 189.2 (C=O), 170.7 (C=O), 169.2 (C=O), 160.0 (C–O), 153.0 (C–O), 148.4 (C–O), 129.8 (C), 127.3 (2×CH), 127.20 (CH), 127.1 (C), 113.8 (2×CH), 108.9 (CH), 108.1 (CH), 102.1 ($OCH_2O$), 80.6 (OCHAr), 61.4 ($OCH_2$), 55.3 ($OCH_3$), 51.1 (CH), 49.9 (CH), 13.6 ($CH_3$). IR (nujol): $\nu_{max}$ 1769s, 1736s, 1726s, 1673s, 1613m, 1520m, 1505m, 1356s, 1245s, 1185m, 1160s, 1103s, 1032s, 981m, 937m, 875m, 856m, 820m, 812m, 724m $cm^{-1}$. MS: *m*/*z* (%) relative intensity 412 ($M^+$, 3), 384 (10), 366 (4), 339 (5), 338 (8), 321 (6), 288 (14), 287 (8), 249 (25), 235 (13), 222 (22), 203 (34), 189 (7), 175 (9), 149 (68), 135 (100), 121 (18), 119 (6), 107 (6), 92 (3), 91 (6), 77 (12), 65 (11). Anal. Calcd for $C_{22}H_{20}O_8$: C, 64.07; H, 4.89. Found: C, 63.88; H, 4.84.

### 4.3. Attempted preparation of ethyl 6,7-methylenedioxy-1-oxo-4-(3,4,5-trimethoxyphenyl)-1,2,3,4-tetrahydronaphthalene-3-carboxylate (7)

**4.3.1. Using concentrated $H_2SO_4$.** A solution of **3a** (402.2 mg, 0.85 mmol) as an 82:14:4 mixture of *TC*/*TT*/*CT* diastereomers in $CHCl_3$ (22 mL) was stirred in the presence of concd $H_2SO_4$ (98%, 0.1 mL) at room temperature overnight (15 h). The crude product contained a small amount of the expected product **7** as revealed by $^1H$ NMR spectrum. Attempted separation by preparative thin-layer chromatography ($SiO_2$, 50% EtOAc in hexanes) gave a white solid of **7** [16.6 mg, 5% yield; mp 150–151 °C ($CH_2Cl_2$), lit.[6a,c,7] mp 152–153 °C ($CH_2Cl_2$)]. The $^1H$ NMR data were consistent with the literature. $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 7.45 (s, 1H, Ar*H*), 6.35 (s, 1H, Ar*H*), 6.25 (s, 2H, Ar*H*), 5.95 and 5.93 (each br s, 2H, $OCH_2O$), 4.41 (d, $J=7.5$ Hz, 1H, C*H*Ar), 4.01–3.91 (m, 2H, $CO_2CH_2CH_3$), 3.77 (s, 3H, $OCH_3$), 3.72 (s, 6H, 2×$OCH_3$), 3.27–3.20 (m, 1H, $CHCO_2Et$), 2.84 (dd, $J=17.0$, 8.7 Hz, 1H, COC*H*H), 2.73 (dd, $J=17.0$, 4.6 Hz, 1H, COCH*H*), 1.00 (t, $J=7.1$ Hz, 3H, $CO_2CH_2CH_3$). IR (nujol): $\nu_{max}$ 1728s, 1677s, 1615w, 1587m, 1501m, 1424m, 1328m, 1268s, 1233m, 1186s, 1124s, 1038m, 1012m, 995m, 930m, 846m $cm^{-1}$. MS: *m*/*z* (%) relative intensity 428 ($M^+$, 59), 382 (4), 355 (100), 340 (9), 324 (25), 323 (25), 291 (9), 188 (29), 186 (21).

**4.3.2. Using $P_2O_5$ in $CH_3SO_3H$.**[10] A solution of $P_2O_5$ (0.39 g) in $CH_3SO_3H$ (3 mL) was added to a $CH_3SO_3H$ (0.9 mL) solution of **3a** (183.2 mg, 0.39 mmol) as an 82:14:4 mixture of *TC*/*TT*/*CT* diastereomers at room temperature under an argon atmosphere. After stirring at room temperature overnight (15 h), the mixture was poured onto crushed ice and extracted with EtOAc (3×20 mL). The combined extracts were washed with saturated aqueous $NaHCO_3$ (3×20 mL), water (3×20 mL), brine and dried over anhydrous $Na_2SO_4$. After removal of solvent under reduced pressure, the crude product containing a small amount of the expected product **7** was obtained as a revealed

by $^1$H NMR spectrum. Purification was made by column chromatography ($SiO_2$, 30% EtOAc in hexanes) to give a white solid of **7** (13.8 mg, 8% yield).

### 4.4. Preparation of α-methylated aryltetralone 9

**4.4.1. Preparation of ethyl 4-(1,3-benzodioxol-5-carbonyl)-2-(3,4,5-trimethoxyphenyl)-4-methyl-5-oxotetrahydrofuran-3-carboxylate (8a).** Sodium hydride (80% dispersion in oil, 37.5 g, 1.25 mmol) was washed with dry hexanes (3 times) and suspended in THF (2 mL) at 0 °C under an argon atmosphere. A THF (2 mL) solution of **3a** (492.4 mg, 1.04 mmol) as an 82:18 mixture of *TC*/*TT* diastereomers was added. The resulting suspension was stirred at 0 °C for 1 h, after which methyl iodide (0.14 mL, 2.24 mmol) was added and the resulting mixture was slowly warmed up from 0 °C to room temperature overnight (15 h). The reaction mixture was quenched with 0.5 M HCl (1 mL), diluted with water (30 mL) and extracted with EtOAc (3×30 mL). The combined organic layers were washed with 5% $Na_2S_2O_5$, water, brine and dried over anhydrous $Na_2SO_4$. After removal of solvent under reduced pressure, the crude product which consisted of an 80:20 mixture of *CC*/*CT* diastereomers of **8a** was purified by column chromatography ($SiO_2$, 30% EtOAc in hexanes) to give two fractions of product **8a**.

The less polar fraction ($F_1$) was obtained as a white solid of the pure diastereomer *CT*-**8a** [49 mg, 10% yield; mp 172–174 °C (EtOAc–hexanes)]. $^1$H NMR (300 MHz, $CDCl_3$): δ 7.84 (dd, *J*=8.2, 1.8 Hz, 1H, Ar*H*), 7.59 (d, *J*=1.8 Hz, 1H, Ar*H*), 6.88 (d, *J*=8.2 Hz, 1H, Ar*H*), 6.74 (s, 2H, Ar*H*), 6.06 (s, 2H, OC$H_2$O), 5.83 (d, *J*=9.7 Hz, 1H, OC*H*Ar), 4.27–4.06 (m, 2H, $CO_2CH_2CH_3$), 3.90 (s, 6H, 2×OC$H_3$), 3.85 (s, 3H, OC$H_3$), 3.15 (d, *J*=9.7 Hz, 1H, C*H*$CO_2$Et), 2.02 (s, 3H, C$H_3$), 1.23 (t, *J*=7.2 Hz, 3H, $CO_2CH_2CH_3$). $^{13}$C NMR (75 MHz, $CDCl_3$): δ 193.4 (C=O), 173.5 (C=O), 168.7 (C=O), 153.2 (2×C–O), 151.9 (C–O), 147.8 (C–O), 138.3 (C–O), 133.1 (C), 129.5 (C), 126.2 (CH), 109.4 (CH), 107.9 (CH), 103.8 (2×CH), 101.9 (OC$H_2$O), 80.6 (OCHAr), 62.1 (C), 61.0 (OC$H_2$), 60.7 (OC$H_3$), 60.4 (CH), 56.2 (2×OC$H_3$), 23.9 (C$H_3$), 13.9 (C$H_3$). IR (nujol): $\nu_{max}$ 1770s, 1734s, 1681s, 1616m, 1598s, 1512s, 1493s, 1437m, 1424m, 1374s, 1349s, 1330s, 1281m, 1259s, 1241s, 1204s, 1172s, 1127s, 1101s, 1077m, 1040s, 1019s, 1004s, 973s, 936m, 886m, 868m, 837m, 700m, 686m cm$^{-1}$. MS: *m*/*z* (%) relative intensity 486 ($M^+$, 7), 385 (25), 384 (79), 347 (11), 346 (46), 342 (25), 328 (6), 318 (9), 301 (24), 300 (100), 282 (59), 281 (23), 271 (14), 253 (11), 236 (52), 226 (10), 215 (12), 213 (14), 195 (25), 149 (35), 121 (9), 91 (2), 65 (6).

The more polar fraction ($F_2$) was obtained as a white solid of the pure diastereomer *CC*-**8a** [352.1 mg, 70% yield; mp 160–162 °C (EtOAc–hexanes)]. $^1$H NMR (300 MHz, $CDCl_3$): δ 7.84 (dd, *J*=8.2, 1.7 Hz, 1H, Ar*H*), 7.60 (d, *J*=1.7 Hz, 1H, Ar*H*), 6.88 (d, *J*=8.2 Hz, 1H, Ar*H*), 6.57 (s, 2H, Ar*H*), 6.05 (s, 2H, OC$H_2$O), 5.76 (d, *J*=5.8 Hz, 1H, OC*H*Ar), 3.85 (s, 6H, 2×OC$H_3$), 3.83 (s, 3H, OC$H_3$), 3.79–3.67 (m, 2H, $CO_2CH_2CH_3$), 3.62 (d, *J*=5.8 Hz, 1H, C*H*$CO_2$Et), 1.93 (s, 3H, C$H_3$), 0.85 (t, *J*=7.2 Hz, 3H, $CO_2CH_2CH_3$). $^{13}$C NMR (75 MHz, $CDCl_3$): δ 194.9 (C=O), 173.0 (C=O), 169.5 (C=O), 153.2 (2×C–O), 151.7 (C–O), 147.5 (C–O), 137.9 (C–O), 129.6 (C), 128.8 (C), 127.2 (CH), 110.3 (CH), 107.5 (CH), 102.6 (2×CH), 101.8 (OC$H_2$O), 77.2 (OCHAr), 61.0 (C), 60.9 (OC$H_2$), 60.7 (OC$H_3$), 58.8 (CH), 56.1 (2×OC$H_3$), 22.5 (C$H_3$), 13.5 (C$H_3$). IR (nujol): $\nu_{max}$ 1784s, 1730s, 1660s, 1608s, 1597s, 1508s, 1428m, 1393m, 1376s, 1352s, 1333s, 1298s, 1283s, 1243s, 1194s, 1124s, 1096s, 1059m, 1042s, 1020s, 999s, 973m, 939m, 924m, 889m, 864m, 834m, 819m, 759m, 701m, 667m cm$^{-1}$. MS: *m*/*z* (%) relative intensity 486 ($M^+$, 16), 442 (14), 396 (2), 359 (7), 358 (7), 341 (6), 301 (7), 293 (21), 220 (4), 219 (10), 201 (17), 195 (8), 149 (100), 121 (10), 91 (2), 65 (6). HRMS (ESI-TOF) Calcd for $C_{25}H_{27}O_{10}$ ($M^+ + 1$): 487.1604. Found 487.1605.

**4.4.2. Preparation of ethyl 2-methyl-6,7-methylenedioxy-1-oxo-4-(3,4,5-trimethoxyphenyl)-1,2,3,4-tetrahydronaphthalene-3-carboxylate (9).** A solution of $SnCl_4$ (1 M in $CHCl_3$, 13 mL, 13 mmol) was added to a $CHCl_3$ (18 mL) solution of *CC*-**8a** (594.6 mg, 1.22 mmol) at room temperature under an argon atmosphere. The reaction mixture was heated at 60 °C for 6 h. After the mixture was allowed to cool, the content was poured onto crushed ice and partitioned with EtOAc (3×30 mL). The combined extracts were washed with saturated aqueous $NaHCO_3$ (3×20 mL), water (3×20 mL), brine and dried over anhydrous $Na_2SO_4$. After removal of solvent under reduced pressure, the crude product obtained was purified by column chromatography ($SiO_2$, 30% EtOAc in hexanes) to give a white solid of the pure isomer *TT*-**9** [318.9 mg, 59% yield; mp 209–211 °C ($CH_2Cl_2$-hexanes)]. $^1$H NMR (300 MHz, $CDCl_3$): δ 7.51 (d, *J*=1.2 Hz, 1H, Ar*H*), 6.38 (s, 2H, Ar*H*), 6.27 (s, 1H, Ar*H*), 6.01–5.99 (m, 2H, OC$H_2$O), 4.34 (d, *J*=11.0 Hz, 1H, C*H*Ar), 4.06–3.91 (m, 2H, $CO_2CH_2CH_3$), 3.86 (s, 3H, OC$H_3$), 3.83 (s, 6H, 2×OC$H_3$), 3.07 (dd, *J*=12.6, 11.0 Hz, 1H, C*H*$CO_2$Et), 2.99–2.88 (m, 1H, COC*H*$CH_3$), 1.26 (d, *J*=6.5 Hz, 3H, COCHC$H_3$), 0.99 (t, *J*=7.0 Hz, 3H, $CO_2CH_2CH_3$). $^{13}$C NMR (75 MHz, $CDCl_3$): δ 195.9 (C=O), 172.3 (C=O), 153.3 (2×C–O), 152.2 (C–O), 147.2 (C–O), 141.6 (C), 137.2 (C–O), 136.6 (C), 126.5 (C), 108.3 (CH), 106.2 (CH), 105.9 (2×CH), 101.7 (OC$H_2$O), 60.8 (OC$H_3$), 60.5 (OC$H_2$), 56.6 (CH), 56.1 (2×OC$H_3$), 49.4 (CH), 44.3 (CH), 13.9 (C$H_3$), 13.1 (C$H_3$). IR (nujol): $\nu_{max}$ 1727s, 1664s, 1610m, 1592s, 1499s, 1467s, 1430s, 1342m, 1305m, 1256s, 1181s, 1131s, 1035s, 1031s, 931m, 892m, 845m, 787m, 690m cm$^{-1}$. MS: *m*/*z* (%) relative intensity 442 ($M^+$, 52), 397 (2), 370 (23), 369 (100), 354 (12), 338 (19), 337 (14), 274 (7), 202 (7), 201 (45), 178 (8), 149 (4), 115 (3), 55 (2). Anal. Calcd for $C_{24}H_{26}O_8$: C, 65.15; H, 5.92. Found: C, 65.47; H, 6.04.

**4.4.3. Preparation of ethyl 4-(1,3-benzodioxol-5-carbonyl)-2-(3,4,5-trimethoxyphenyl)-5-oxo-4-(phenylsulfanylmethyl)tetrahydrofuran-3-carboxylate (10a).** Sodium hydride (80% dispersion in oil, 45.7 mg, 1.52 mmol) was washed with dry hexanes (3 times) and suspended in THF (3 mL) at 0 °C under an argon atmosphere. A THF (4 mL) solution of pure diastereomer *TC*-**3a** (589.8 mg, 1.25 mmol) was added. The resulting reaction mixture was stirred at 0 °C for 1 h and a THF (1 mL) solution of chloromethyl phenyl sulfide (396.8 mg, 2.5 mmol) was added, followed by the addition of a solution of NaI (413.4 mg, 2.76 mmol) in THF (3 mL). The reaction mixture was stirred at 0 °C and slowly warmed up to room temperature overnight (15 h). It was then quenched with 0.5 M HCl (1.5 mL), diluted with

water (30 mL) and extracted with EtOAc (3×30 mL). The combined organic layers were washed with 5% $Na_2S_2O_5$, water, brine and dried over anhydrous $Na_2SO_4$. Filtration followed by evaporation gave a crude product, which was purified by column chromatography ($SiO_2$, 30% EtOAc in hexanes) to give a pale yellow viscous liquid of *CC*-**10a** (448.3 mg, 60% yield). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.85 (dd, $J$=8.3, 1.8 Hz, 1H, Ar*H*), 7.53 (d, $J$=1.8 Hz, 1H, Ar*H*), 7.43–7.39 (m, 2H, SAr*H*), 7.32–7.25 (m, 3H, SAr*H*), 6.82 (d, $J$=8.3 Hz, 1H, Ar*H*), 6.39 (s, 2H, ArH), 6.03 (s, 2H, OC$H_2$O), 5.62 (d, $J$=5.9 Hz, 1H, OC*H*Ar), 3.98 (d, $J$=14.2 Hz, 1H, C*H*HSPh), 3.92 (d, $J$=5.9 Hz, 1H, C*H*$CO_2$Et), 3.83 (s, 6H, 2×OC$H_3$), 3.81 (s, 3H, OC$H_3$), 3.77–3.66 (m, 2H, $CO_2CH_2CH_3$ and 1H, CH*H*SPh), 0.83 (t, $J$=7.2 Hz, 3H, $CO_2CH_2CH_3$). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 192.0 (C=O), 171.3 (C=O), 169.4 (C=O), 153.1 (2×C–O), 151.7 (C–O), 147.5 (C–O), 137.9 (C–O), 134.1 (S–C), 131.8 (2×CH), 129.36 (C), 129.30 (2×CH), 129.1 (C), 127.9 (CH), 127.1 (CH), 110.2 (CH), 107.5 (CH), 102.5 (2×CH), 101.8 ($OCH_2O$), 77.8 (OCHAr), 67.0 (C), 61.0 ($OCH_2$), 60.8 ($OCH_3$), 56.2 (2×$OCH_2$), 55.1 (CH), 39.9 ($SCH_2$), 13.5 ($CH_3$). IR (nujol): $\nu_{max}$ 1781s, 1725s, 1661m, 1594s, 1505s, 1487s, 1338s, 1242s, 1194s, 1162s, 1126s, 1036s, 931m, 863w, 820w, 746m, 722m, 695m cm$^{-1}$. MS: *m*/*z* (%) relative intensity 594 ($M^+$, 6), 486 (3), 485 (8), 471 (3), 440 (6), 439 (24), 421 (9), 411 (5), 393 (4), 367 (5), 336 (5), 317 (15), 289 (13), 282 (3), 266 (9), 261 (8), 236 (7), 215 (4), 196 (13), 195 (24), 181 (3), 150 (51), 149 (100), 122 (6), 109 (2), 65 (6).

**4.4.4. Preparation of ethyl 4-(1,3-benzodioxol-5-carbonyl)-2-(1,3-benzodioxol-5-yl)-5-oxo-4-(phenylsulfanylmethyl)-tetrahydrofuran-3-carboxylate (10b).** According to the general procedure as described for compound **10a**, a THF (10 mL) solution of **3b** (1.3856 g, 3.25 mmol) as a 82:18 mixture of *TC*/*TT* diastereomers was added dropwise at 0 °C to a suspension of NaH (80% dispersion in oil, 107 mg, 3.57 mmol) in THF (7 mL). After stirring at 0 °C for 1 h, a THF (3 mL) solution of chloromethyl phenyl sulfide (1.0315 g, 6.50 mmol) was added, followed by the addition of a solution of NaI (1.0758 g, 7.18 mmol) in THF (7 mL). The reaction mixture was stirred at 0 °C and slowly warmed up to room temperature overnight (15 h). The crude product was purified by column chromatography ($SiO_2$, 20% EtOAc in hexanes) to give two fractions of **10b**.

The less polar fraction ($F_1$) was obtained as a yellow viscous liquid of **10b** (103.3 mg, 6% yield) as a 70:30 mixture of *CT*/*TT* diastereomers. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.69 (dd, $J$=9.1, 1.7 Hz, 1H, Ar*H* of *CT*-isomer), 7.48–7.12 (m, 7H, Ar*H*), 6.96–6.74 (m, 4H, Ar*H*), 5.99 and 5.92 (s, 4H, 2×OC$H_2$O of *CT*-isomer), 5.98 and 5.91 (s, 4H, 2×OC$H_2$O of *TT*-isomer), 5.74 (*CT*) and 5.28 (*TT*) (each d, $J$=9.4, 9.0 Hz, respectively, 1H, OC*H*Ar), 4.29 and 3.55 (d, AB system, $J$=14.0 Hz, 2H, C$H_2$SPh of *CT*-isomer), 4.19–3.92 (m, 2H, $CO_2CH_2CH_3$), 3.99 (d, $J$=9.4 Hz, 1H, C*H*$CO_2$Et of *CT*-isomer), 3.78 and 3.63 (d, AB system, $J$=14.0 Hz, 2H, C$H_2$SPh of *TT*-isomer), 3.28 (d, $J$=9.0 Hz, 1H, C*H*$CO_2$Et of *TT*-isomer), 1.22–1.12 (m, 3H, $CO_2CH_2CH_3$ of *TT*-isomer) 1.09 (t, $J$=7.0 Hz, 3H, $CO_2CH_2CH_3$ of *CT*-isomer).

The more polar fraction ($F_2$) was obtained as a pale yellow viscous liquid of the pure diastereomer *CC*-**10b** (1.2318 g, 69% yield). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.84 (dd, $J$=8.3, 1.8 Hz, 1H, Ar*H*), 7.51 (d, $J$=1.8 Hz, 1H, Ar*H*), 7.39–7.34 (m, 2H, SAr*H*), 7.29–7.24 (m, 3H, SAr*H*), 6.81 (d, $J$=8.3 Hz, 1H, Ar*H*), 6.76 (d, $J$=8.6 Hz, 1H, Ar*H*), 6.69–6.67 (m, 2H, Ar*H*), 6.02 (s, 2H, OC$H_2$O), 5.94 (br s, 2H, OC$H_2$O), 5.62 (d, $J$=5.9 Hz, 1H, OC*H*Ar), 3.96 (d, $J$=14.1 Hz, 1H, C*H*HSPh), 3.90 (d, $J$=5.9 Hz, 1H, C*H*$CO_2$Et), 3.79–3.70 (m, 2H, $CO_2CH_2CH_3$), 3.69 (d, $J$=14.1 Hz, 1H, CH*H*SPh), 0.89 (t, $J$=7.2 Hz, 3H, $CO_2CH_2CH_3$). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 192.0 (C=O), 171.3 (C=O), 169.2 (C=O), 151.7 (C–O), 147.7 (C–O), 147.6 (C–O), 147.5 (C–O), 133.9 (S–C), 131.7 (2×CH), 129.2 (2×CH), 129.1 (C), 127.9 (CH), 127.4 (C), 127.1 (CH), 119.2 (CH), 110.2 (CH), 108.0 (CH), 107.5 (CH), 106.3 (CH), 101.8 ($OCH_2O$), 101.2 ($OCH_2O$), 77.7 (OCHAr), 66.9 (C), 60.9 ($OCH_2$), 55.3 (CH), 40.0 ($SCH_2$), 13.5 ($CH_3$). IR ($CHCl_3$): $\nu_{max}$ 3030w, 2963w, 2902w, 1782s, 1737m, 1665m, 1606m, 1505s, 1489s, 1442s, 1376m, 1348m, 1256s, 1245s, 1159m, 1108m, 1041s, 937m, 866m, 813m cm$^{-1}$. MS: *m*/*z* (%) relative intensity 439 ($M^+$−109, 13), 425 (4), 394 (3), 393 (14), 379 (3), 365 (4), 349 (3), 321 (4), 290 (3), 289 (8), 271 (9), 259 (4), 243 (11), 216 (3), 215 (5), 151 (37), 149 (100), 121 (10), 110 (2), 109 (2), 65 (8).

**4.4.5. Preparation of ethyl 4-(1,3-benzodioxol-5-carbonyl)-2-(4-methoxyphenyl)-5-oxo-4-(phenylsulfanylmethyl) tetrahydrofuran-3-carboxylate (10c).** According to the general procedure as described for compound **10a**, a THF (9 mL) solution of **3c** (734.3 mg, 1.78 mmol; *TC*-isomer as the major isomer and a trace amount of *TT*-isomer) was added dropwise at 0 °C to the suspension of NaH (80% dispersion in oil, 61.2 mg, 2.04 mmol) in THF (4 mL). After stirring at 0 °C for 1 h, a THF (2 mL) solution of chloromethyl phenyl sulfide (602.1 mg, 3.80 mmol mmol) was added, followed by the addition of a solution of NaI (602 mg, 4.02 mmol) in THF (6 mL). The reaction mixture was stirred at 0 °C and slowly warmed up to room temperature overnight (15 h). The crude product was purified by column chromatography ($SiO_2$, 20% EtOAc in hexanes) to give a white solid of the pure diastereomer *CC*-**10c** [724.1 mg, 76% yield; mp 140–141 °C (EtOAc–hexanes)]. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.84 (dd, $J$=8.3, 1.8 Hz, 1H, Ar*H*), 7.52 (d, $J$=1.8 Hz, 1H, Ar*H*), 7.39–7.34 (m, 2H, SAr*H*), 7.29–7.24 (m, 3H, SAr*H*), 7.14 (br d, $J$=8.8 Hz, 2H, Ar*H*), 6.85 (br d, $J$=8.8 Hz, 2H, Ar*H*), 6.81 (d, $J$=8.3 Hz, 1H, Ar*H*), 6.02 (s, 2H, OC$H_2$O), 5.69 (d, $J$=5.9 Hz, 1H, OC*H*Ar), 3.97 (d, $J$=14.0 Hz, 1H, C*H*HSPh), 3.93 (d, $J$=5.9 Hz, 1H, C*H*$CO_2$Et), 3.78 (s, 3H, OC$H_3$), 3.74–3.61 (m, 2H, $CO_2CH_2CH_3$), 3.71 (d, $J$=14.0 Hz, 1H, CH*H*SPh), 0.83 (t, $J$=7.1 Hz, 3H, $CO_2CH_2CH_3$). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 192.2 (C=O), 171.5 (C=O), 169.3 (C=O), 159.7 (C–O), 151.6 (C–O), 147.5 (C–O), 133.9 (S–C), 131.7 (2×CH), 129.3 (2×CH), 129.2 (C), 127.9 (CH), 127.1 (CH), 126.9 (2×CH), 125.7 (C), 113.6 (2×CH), 110.2 (CH), 107.5 (CH), 101.7 ($OCH_2O$), 77.8 (OCHAr), 66.9 (C), 60.9 ($OCH_2$), 55.3 (CH), 55.2 ($OCH_3$), 40.0 ($SCH_2$), 13.4 ($CH_3$). IR (nujol): $\nu_{max}$ 1782s, 1724s, 1652m, 1602m, 1506m, 1487m, 1441s, 1340m, 1305m, 1259m, 1244s, 1199m, 1158m, 1112m, 1020m, 958m, 933m, 862m, 821m, 748m, 693m cm$^{-1}$. MS: *m*/*z* (%) relative intensity 535 ($M^+$+1, 3), 489 (1), 426 (17), 425 (69), 411 (13), 397 (5), 381 (31), 380 (19), 379 (71), 365 (9), 351 (9), 335 (11), 307 (9), 289 (12), 271 (7), 257 (9), 243

(14), 242 (17), 241 (14), 229 (8), 150 (46), 149 (100), 136 (13), 135 (36), 122 (15), 110 (4), 109 (3), 65 (12).

**4.4.6. Preparation of ethyl 4-(1,3-benzodioxol-5-carbonyl)-2-(3,4,5-trimethoxyphenyl)-5-oxo-4-(phenylsulfonylmethyl)tetrahydrofuran-3-carboxylate (11a).** The pure diastereomer *CC*-**10a** (164.8 mg, 0.28 mmol) was dissolved in glacial acetic acid (1.5 mL) and cooled to 0 °C. 30% Hydrogen peroxide (0.14 mL, 1.4 mmol) was then added dropwise. The reaction mixture was stirred at 0 °C and slowly warmed up to room temperature overnight (15 h). The mixture was diluted with a mixture of water (2 mL) and EtOAc (4 mL), neutralized with 10% NaOH at 0 °C and then extracted with EtOAc (3×10 mL). The combined organic layers were washed with 10% NaOH, water, 0.5 M $NH_4Cl$, brine and dried over anhydrous $Na_2SO_4$. After removal of solvent under reduced pressure, the crude product was purified by column chromatography ($SiO_2$, 30% EtOAc in hexanes) to give a white solid of *CC*-**11a** [113.4 mg, 65% yield; mp 162–164 °C (EtOAc–hexanes)]. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.85–7.82 (m, 2H, $SO_2ArH$), 7.71–7.65 (m, 1H, $SO_2ArH$), 7.58–7.52 (m, 2H, $SO_2ArH$ and 1H, Ar*H*), 7.34 (d, $J$=1.9 Hz, 1H, Ar*H*), 6.81 (d, $J$=8.2 Hz, 1H, Ar*H*), 6.63 (s, 2H, Ar*H*), 6.16 (d, $J$=6.9 Hz, 1H, OC*H*Ar), 6.03 and 6.02 (each d, $J$=1.1 Hz, 2H, $OCH_2O$), 4.88 (d, $J$=6.9 Hz, 1H, $CHCO_2Et$), 4.16 (d, $J$=14.6 Hz, 1H, $CHHSO_2Ph$), 3.88 (s, 6H, 2×$OCH_3$), 3.83 (s, 3H, $OCH_3$), 3.82 (d, $J$=14.6 Hz, 1H, $CHHSO_2Ph$), 3.68–3.48 (m, 2H, $CO_2CH_2CH_3$), 0.79 (t, $J$=7.2 Hz, 3H, $CO_2CH_2CH_3$). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 190.9 (C=O), 171.1 (C=O), 168.9 (C=O), 153.1 (2×C–O), 151.7 (C–O), 147.7 (C–O), 138.8 (C–O), 137.9 ($SO_2C$), 134.6 (CH), 129.5 (2×CH), 129.4 (C), 128.8 (C), 128.0 (2×CH), 126.0 (CH), 109.7 (CH), 107.6 (CH), 103.0 (2×CH), 101.9 ($OCH_2O$), 78.7 (OCHAr), 61.3 ($OCH_2$), 61.1 (C), 60.7 ($OCH_3$), 58.8 ($SO_2CH_2$), 56.2 (2×$OCH_3$), 53.3 (CH), 13.3 ($CH_3$). IR (nujol): $\nu_{max}$ 1779s, 1719s, 1680s, 1610m, 1593m, 1511m, 1493s, 1449s, 1350s, 1336s, 1201s, 1160s, 1132s, 1106s, 1034m, 1000m, 951m, 930m, 866m, 828m, 797m, 762m, 720m, 691m cm$^{-1}$. MS: *m*/*z* (%) relative intensity 626 ($M^+$, 16), 484 (4), 440 (4), 439 (4), 411 (5), 395 (5), 394 (11), 367 (4), 363 (7), 348 (7), 336 (7), 335 (9), 289 (14), 282 (20), 261 (7), 245 (9), 236 (21), 216 (4), 196 (11), 195 (20), 181 (4), 149 (100), 121 (12), 78 (7), 77 (7), 65 (9). HRMS (ESI-TOF) Calcd for $C_{31}H_{31}O_{12}S$ ($M^+$+1): 627.1536. Found 627.1516.

**4.4.7. Preparation of ethyl 4-(1,3-benzodioxol-5-carbonyl)-2-(1,3-benzodioxol-5-yl)-5-oxo-4-(phenylsulfonylmethyl)-tetrahydrofuran-3-carboxylate (11b).** According to the general procedure as described for compound **10a**, the pure diastereomer *CC*-**10b** (814.1 mg, 1.48 mmol) was dissolved in glacial acetic acid (10 mL) and cooled to 0 °C. 30% Hydrogen peroxide (0.74 mL, 7.4 mmol) was then added dropwise. The reaction mixture was stirred at 0 °C and slowly warmed up to room temperature overnight (15 h). After usual work-up, the crude product was purified by column chromatography ($SiO_2$, 30% EtOAc in hexanes) to give a pale yellow viscous liquid of *CC*-**11b** (670.3 mg, 78% yield). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.81 (d, $J$=7.4 Hz, 2H, $SO_2ArH$), 7.66 (app t, $J$=7.4 Hz, 1H, $SO_2ArH$), 7.58–7.50 (m, 2H, $SO_2ArH$ and 1H, Ar*H*), 7.34 (d, $J$=1.7 Hz, 1H, Ar*H*), 6.88 (dd, $J$=8.3, 1.7 Hz, 2H, Ar*H*), 6.82 (d, $J$=8.3 Hz, 1H, Ar*H*), 6.79 (d, $J$=8.3 Hz, 1H, Ar*H*), 6.12 (d, $J$=6.7 Hz, 1H, OC*H*Ar), 6.03 and 6.02 (each d, $J$=1.0 Hz, 2H, $OCH_2O$), 5.96 and 5.95 (each d, $J$=1.5 Hz, 2H, $OCH_2O$), 4.79 (d, $J$=6.7 Hz, 1H, $CHCO_2Et$), 4.15 (d, $J$=14.5 Hz, 1H, $CHHSO_2Ph$), 3.82 (d, $J$=14.5 Hz, 1H, $CHHSO_2Ph$), 3.74–3.55 (m, 2H, $CO_2CH_2CH_3$), 0.86 (t, $J$=7.2 Hz, 3H, $CO_2CH_2CH_3$). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 191.1 (C=O), 171.0 (C=O), 168.8 (C=O), 151.7 (C–O), 147.8 (C–O), 147.7 (C–O), 147.6 (C–O), 138.8 ($SO_2C$), 134.6 (CH), 129.5 (2×CH), 128.8 (C), 128.0 (2×CH), 127.5 (C), 126.2 (CH), 119.7 (CH), 109.8 (CH), 108.0 (CH), 107.6 (CH), 106.7 (CH), 101.9 ($OCH_2O$), 101.2 ($OCH_2O$), 78.7 (OCHAr), 61.4 (C), 61.3 ($OCH_2$), 58.7 ($SO_2CH_2$), 53.3 (CH), 13.4 ($CH_3$). IR ($CHCl_3$): $\nu_{max}$ 3030m, 2987w, 2904m, 1787s, 1732s, 1673m, 1606m, 1505s, 1490s, 1448s, 1376m, 1326s, 1155s, 1108m, 1085m, 1041s, 937m, 867m, 809m, 687m cm$^{-1}$. MS: *m*/*z* (%) relative intensity 580 ($M^+$, 1), 440 (2), 439 (6), 411 (4), 393 (9), 365 (7), 349 (3), 321 (3), 289 (6), 243 (6), 237 (6), 236 (31), 216 (4), 190 (10), 150 (26), 149 (100), 121 (8), 78 (3), 77 (2), 65 (5). HRMS (ESI-TOF) Calcd for $C_{29}H_{24}O_{11}SNa$ ($M^+$+Na): 603.0937. Found 603.0928.

**4.4.8. Preparation of ethyl 4-(1,3-benzodioxol-5-carbonyl)-2-(4-methoxyphenyl)-5-oxo-4-(phenylsulfonylmethyl) tetrahydrofuran-3-carboxylate (11c).** According to the general procedure as described for compound **10a**, the pure diastereomer *CC*-**10c** (188.6 mg, 0.35 mmol) was dissolved in glacial acetic acid (3 mL) and cooled to 0 °C. 30% Hydrogen peroxide (0.18 mL, 1.8 mmol) was then added dropwise. The reaction mixture was stirred at 0 °C and slowly warmed up to room temperature overnight (15 h). After usual work-up, the crude product was purified by column chromatography ($SiO_2$, 30% EtOAc in hexanes) to give a white solid of *CC*-**11c** [163.7 mg, 83% yield; mp 167–168 °C (EtOAc–hexanes)]. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.82 (m, 2H, $SO_2ArH$), 7.66 (m, 1H, $SO_2ArH$), 7.58–7.50 (m, 2H, $SO_2ArH$ and 1H, Ar*H*), 7.34 (d, $J$=1.3 Hz, 1H, Ar*H*), 7.33 (br d, $J$=9.0 Hz, 2H, Ar*H*), 6.89 (br d, $J$=9.0 Hz, 2H, Ar*H*), 6.81 (d, $J$=8.3 Hz, 1H, Ar*H*), 6.17 (d, $J$=6.8 Hz, 1H, OC*H*Ar), 6.03 and 6.02 (each d, $J$=1.0 Hz, 2H, $OCH_2O$), 4.81 (d, $J$=6.8 Hz, 1H, $CHCO_2Et$), 4.16 (d, $J$=14.8 Hz, 1H, $CHHSO_2Ph$), 3.83 (d, $J$=14.8 Hz, 1H, $CHHSO_2Ph$), 3.80 (s, 3H, $OCH_3$), 3.66–3.47 (m, 2H, $CO_2CH_2CH_3$), 0.80 (t, $J$=7.1 Hz, 3H, $CO_2CH_2CH_3$). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 191.3 (C=O), 171.2 (C=O), 168.9 (C=O), 159.9 (C–O), 151.7 (C–O), 147.6 (C–O), 139.0 ($SO_2C$), 134.5 (CH), 129.5 (2×CH), 129.0 (C), 128.0 (2×CH), 127.4 (2×CH), 126.2 (CH), 125.9 (C), 113.6 (2×CH), 109.8 (CH), 107.6 (CH), 101.9 ($OCH_2O$), 78.8 (OCHAr), 61.5 (C), 61.2 ($OCH_2$), 58.9 ($SO_2CH_2$), 55.3 ($OCH_3$), 53.4 (C), 13.3 ($CH_3$). IR (nujol): $\nu_{max}$ 1789s, 1721s, 1652m, 1602m, 1584w, 1503m, 1487m, 1338s, 1306m, 1263s, 1245s, 1199m, 1152s, 1111m, 1086m, 1038m, 1019m, 959m, 927m, 862m, 821m, 757m, 710m, 689m cm$^{-1}$. MS: *m*/*z* (%) relative intensity 567 ($M^+$+1, 2), 566 ($M^+$, 1), 425 (18), 397 (14), 381 (22), 380 (22), 379 (28), 351 (16), 335 (12), 307 (12), 303 (3), 275 (12), 230 (5), 229 (7), 223 (14), 222 (41), 203 (6), 151 (55), 149 (100), 137 (24), 135 (75), 121 (15), 77 (6), 65 (12). Anal. Calcd for $C_{29}H_{26}O_{10}S$: C, 61.48; H, 4.63. Found: C, 61.84; H, 4.69.

### 4.5. Preparation of thuriferic acid ethyl ester (4a) and analogues 4b and 4c

**4.5.1. Preparation of ethyl 2-methylene-6,7-methylenedioxy-1-oxo-4-(3,4,5-trimethoxyphenyl)-1,2,3,4-tetrahydronaphthalene-3-carboxylate (4a).** A solution of $SnCl_4$ (1 M in $CHCl_3$, 6.7 mL, 6.7 mmol) was added to a $CHCl_3$ (10 mL) solution of *CC*-**11a** (424 mg, 0.67 mmol) at room temperature under an argon atmosphere. The reaction mixture was allowed to stir at room temperature overnight (15 h). The mixture was poured onto crushed ice and extracted with EtOAc (3×30 mL). The combined extracts were washed with saturated aqueous $NaHCO_3$ (3×20 mL), water (3×20 mL), brine and dried over anhydrous $Na_2SO_4$. After removal of solvent under reduced pressure, the crude product was dissolved in THF (6 mL) under an argon atmosphere and a THF (0.5 mL) solution of DBU (88.3 mg, 0.58 mmol) was then added. After stirring at room temperature for 1 h, the reaction mixture was quenched with 0.5 M HCl (1 mL), diluted with water (20 mL) and extracted with EtOAc (3×20 mL). The combined organic extracts were washed with water, brine and dried over anhydrous $Na_2SO_4$. Filtration followed by evaporation gave a crude product, which was purified by preparative thin-layer chromatography ($SiO_2$, 15% EtOAc in hexanes; multiple runs) to give two bands; $PLC_1$ and $PLC_2$ of **4a** and **13a**, respectively.

$PLC_1$ (less polar) was obtained as a pale yellow solid of **4a** [114.5 mg, 39% yield; mp 154–155 °C ($CH_2Cl_2$–hexanes)]. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.60 (s, 1H, Ar*H*), 6.55 (s, 1H, Ar*H*), 6.36 (br s, 1H, C=C*H*H), 6.25 (s, 2H, Ar*H*), 6.03 (s, 2H, OC$H_2$O), 5.36 (br s, 1H, C=CH*H*), 4.62 (d, $J$=4.1 Hz, 1H, C*H*Ar), 4.07 (q, $J$=7.2 Hz, 2H, $CO_2CH_2CH_3$), 3.89 (d, $J$=4.1 Hz, 1H, C*H*$CO_2$Et), 3.81 (s, 3H, OC$H_3$), 3.75 (s, 6H, 2×OC$H_3$), 1.10 (t, $J$=7.2 Hz, 3H, $CO_2CH_2CH_3$). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 184.1 (C=O), 171.4 (C=O), 153.2 (2×C–O), 152.8 (C–O), 147.9 (C–O), 139.7 (C), 138.4 (C–O), 137.0 (2×C), 127.4 (C), 125.6 ($CH_2$), 108.8 (CH), 106.6 (CH), 105.3 (2×CH), 101.9 ($OCH_2O$), 61.3 ($OCH_2$), 60.7 ($OCH_3$), 56.0 (2×$OCH_3$), 55.5 (CH), 48.3 (CH), 13.9 ($CH_3$). IR (nujol): $\nu_{max}$ 1731s, 1660s, 1593s, 1500s, 1432s, 1337s, 1270s, 1159s, 1128s, 1095s, 1038s, 1012s, 936s, 897m, 844m, 809m, 694m cm$^{-1}$. MS: *m*/*z* (%) relative intensity 440 ($M^+$, 32), 395 (2), 394 (6), 368 (25), 367 (100), 352 (3), 351 (5), 337 (6), 336 (16), 308 (7), 306 (4), 305 (5), 291 (4), 277 (3). Anal. Calcd for $C_{24}H_{24}O_8$: C, 65.45; H, 5.49. Found: C, 65.19; H, 5.89.

$PLC_2$ (more polar) was obtained as a yellow solid of **13a** (18 mg, 6% yield; mp 163–164 °C). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.48 (s, 1H, Ar*H*), 6.89 (s, 1H, Ar*H*), 6.56 (s, 2H, Ar*H*), 6.01 (s, 2H, OC$H_2$O), 5.35 (br s, 1H, ArO*H*), 4.05 (q, $J$=7.2 Hz, 2H, $CO_2CH_2CH_3$), 3.91 (s, 3H, OC$H_3$), 3.83 (s, 6H, 2×OC$H_3$), 2.33 (s, 3H, C$H_3$), 0.99 (t, $J$=7.2 Hz, 3H, $CO_2CH_2CH_3$). $^{13}$C NMR (75 MHz, $CDCl_3$):$\delta$ 169.7 (C=O), 152.7 (2×C–O), 148.1 (C–O), 148.0 (C–O), 147.9 (C–O), 137.2 (C–O), 133.9 (C), 131.5 (C), 129.3 (C), 128.7 (C), 121.4 (C), 111.6 (C), 107.7 (2×CH), 102.9 (CH), 101.2 ($OCH_2O$), 98.2 (CH), 61.0 ($OCH_2$), 60.9 ($OCH_3$), 56.1 (2×$OCH_3$), 13.8 ($CH_3$), 12.6 ($CH_3$). IR ($CHCl_3$): $\nu_{max}$ 3604w, 3014w, 2964w, 2939w, 2906w, 1717s, 1583s, 1503m, 1463s, 1414m, 1369s, 1353s, 1129s, 1043s, 1012w, 950m, 865w cm$^{-1}$. MS: *m*/*z* (%) relative intensity 440 ($M^+$, 100), 426 (53), 412 (2), 398 (7), 397 (27), 395 (7), 394 (9), 380 (3), 379 (8), 365 (10), 364 (27), 363 (64), 353 (11), 352 (6), 351 (9), 337 (14), 336 (13), 335 (15), 321 (16), 320 (12), 319 (25), 309 (8), 307 (8), 293 (9), 279 (8), 263 (7), 235 (5), 207 (4), 181 (5), 153 (8), 152 (7).

**4.5.2. Preparation of ethyl 2-methylene-6,7-methylenedioxy-1-oxo-4-(1,3-benzodioxol-5-yl)-1,2,3,4-tetrahydronaphthalene-3-carboxylate (4b).** According to the general procedure as described for compound **4a**, a solution of $SnCl_4$ (1 M in $CHCl_3$, 5.7 mL, 5.7 mmol) was added to a $CHCl_3$ (8.8 mL) solution of *CC*-**11b** (329.5 mg, 0.57 mmol) and stirred at room temperature overnight (15 h). The crude product obtained was dissolved in THF (2 mL) and then a THF (0.5 mL) solution of DBU (80.2 mg, 0.53 mmol) was added. The reaction mixture was stirred at room temperature for 1 h. The crude product was purified by preparative thin-layer chromatography ($SiO_2$, 10% EtOAc in hexanes; multiple runs) to give two bands; $PLC_1$ and $PLC_2$ of **4b** and **13b**, respectively.

$PLC_1$ (less polar) was obtained as a pale yellow viscous liquid of **4b** (109.2 mg, 49% yield). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.60 (s, 1H, Ar*H*), 6.70 (d, $J$=7.7 Hz, 1H, Ar*H*), 6.53–6.48 (m, 3H, Ar*H*), 6.33 (br s, 1H, C=C*H*H), 6.02 and 6.01 (each br s, 2H, OC$H_2$O), 5.92 and 5.91 (each br s, 2H, OC$H_2$O), 5.32 (br s, 1H, C=CH*H*), 4.63 (d, $J$=4.0 Hz, 1H, C*H*Ar), 4.07 (q, $J$=7.3 Hz, 2H, $CO_2CH_2CH_3$), 3.85 (d, $J$=4.0 Hz, 1H, C*H*$CO_2$Et), 1.11 (t, $J$=7.3 Hz, 3H, $CO_2CH_2CH_3$). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 184.1 (C=O), 171.4 (C=O), 152.8 (C–O), 147.89 (C–O), 147.86 (C–O), 146.6 (C–O), 139.8 (C), 138.2 (C), 135.3 (C), 127.5 (C), 125.6 ($CH_2$), 121.6 (CH), 108.8 (CH), 108.5 (CH), 108.2 (CH), 106.7 (CH), 101.9 ($OCH_2O$), 101.1 ($OCH_2O$), 61.3 ($OCH_2$), 55.8 (CH), 47.7 (CH), 13.9 ($CH_3$). IR ($CHCl_3$): $\nu_{max}$ 3029m, 2928m, 2856m, 1727s, 1672m, 1614m, 1505s, 1481s, 1444m, 1387m, 1250s, 1183m, 1100w, 1041s, 939m, 864w cm$^{-1}$. MS: *m*/*z* (%) relative intensity 394 ($M^+$, 16), 348 (5), 322 (19), 321 (100), 293 (16), 291 (12), 263 (16), 235 (13), 233 (10), 205 (10), 177 (8), 176 (7), 149 (5). HRMS (ESI-TOF) Calcd for $C_{22}H_{18}O_7Na$ ($M^+$+Na): 417.0950. Found 417.0937.

$PLC_2$ (more polar) was obtained as a yellow solid of **13b** (8.8 mg, 4% yield; mp 196–200 °C). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.48 (s, 1H, Ar*H*), 6.87–6.75 (m, 4H, Ar*H*), 6.02 and 6.01 (each br s, 2H, OC$H_2$O), 6.00 and 5.99 (each br s, 2H, OC$H_2$O), 5.25 (br s, 1H, ArO*H*), 4.08 (q, $J$=7.1 Hz, 2H, $CO_2CH_2CH_3$), 2.32 (s, 3H, C$H_3$), 1.05 (t, $J$=7.1 Hz, 3H, $CO_2CH_2CH_3$). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 169.5 (C=O), 148.0 (C–O), 147.9 (C–O), 147.8 (C–O), 147.2 (C–O), 146.9 (C–O), 132.0 (C), 129.1 (C), 128.9 (C), 123.9 (CH), 121.4 (C), 111.5 (C), 111.2 (CH), 107.9 (2×CH), 103.0 (CH), 101.2 ($OCH_2O$), 101.0 ($OCH_2O$), 98.1 (CH), 60.9 ($OCH_2$), 13.8 ($CH_3$), 12.7 ($CH_3$). IR ($CHCl_3$): $\nu_{max}$ 3604w, 3027w, 2903w, 1721s, 1503s, 1490m, 1463s, 1351m, 1137w, 1114w, 1042s, 949m, 865w, 818w cm$^{-1}$. MS: *m*/*z* (%) relative intensity 394 ($M^+$, 100), 366 (26), 349 (23), 348 (40), 320 (17), 319 (33), 318 (48), 293 (16), 291 (40), 290 (36), 263 (13), 262 (14), 261 (11), 233 (12), 205 (13), 177 (12), 175 (11), 165 (7), 151 (8), 150 (4), 88 (6).

**4.5.3. Preparation of ethyl 2-methylene-6,7-methylenedioxy-1-oxo-4-(4-methoxyphenyl)-1,2,3,4-tetrahydronaphthalene-3-carboxylate (4c).** According to the general procedure as described for compound **4a**, a solution of $SnCl_4$ (1 M in $CHCl_3$, 2.9 mL, 2.9 mmol) was added to a $CHCl_3$ (4.5 mL) solution of *CC*-**11c** (163.7 mg, 0.29 mmol) and stirred at room temperature overnight (15 h). The crude product obtained was dissolved in THF (3 mL) and then a THF (0.5 mL) solution of DBU (41.7 mg, 0.27 mmol) was added. The reaction mixture was stirred at room temperature for 1 h. The crude product was purified by preparative thin-layer chromatography ($SiO_2$, 10% EtOAc in hexanes; multiple runs) to give two bands; $PLC_1$ and $PLC_2$ of **4c** and **13c**, respectively.

$PLC_1$ (less polar) was obtained as a white solid of **4c** [67.9 mg, 62% yield; mp 215–217 °C ($Et_2O$–hexanes)]. $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 7.59 (s, 1H, Ar*H*), 6.95 (br d, $J=8.7$ Hz, 2H, Ar*H*), 6.79 (br d, $J=8.7$ Hz, 2H, Ar*H*), 6.51 (s, 1H, Ar*H*), 6.32 (br s, 1H, C=C*H*H), 6.00 and 5.99 (each d, $J=1.2$ Hz, 2H, OC$H_2$O), 5.29 (br s, 1H, C=CH*H*), 4.65 (d, $J=4.1$ Hz, 1H, C*H*Ar), 4.10–4.00 (m, 2H, $CO_2CH_2$-$CH_3$), 3.86 (d, $J=4.1$ Hz, 1H, C*H*$CO_2$Et), 3.76 (s, 3H, $OCH_3$), 1.09 (t, $J=7.2$ Hz, 3H, $CO_2CH_2CH_3$). $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ 184.3 (C=O), 171.5 (C=O), 158.5 (C–O), 152.7 (C–O), 147.7 (C–O), 140.2 (C), 138.3 (C), 133.4 (C), 129.2 (2×CH), 127.5 (C), 125.5 ($CH_2$), 113.9 (2×CH), 108.8 (CH), 106.6 (CH), 101.8 ($OCH_2O$), 61.2 ($OCH_2$), 55.8 (CH), 55.1 ($OCH_3$), 47.3 (CH), 13.9 ($CH_3$). IR ($CHCl_3$): $\nu_{max}$ 3027w, 3009w, 2929w, 2855w, 1727s, 1676w, 1612m, 1512s, 1480s, 1464w, 1380w, 1251s, 1179m, 1039s, 939w, 841w $cm^{-1}$. MS: *m*/*z* (%) relative intensity 380 ($M^+$, 25), 349 (6), 334 (6), 308 (21), 307 (100), 306 (26), 279 (19), 277 (5), 276 (5), 249 (11), 221 (6), 189 (3), 178 (3). HRMS (ESI-TOF) Calcd for $C_{22}H_{20}O_6Na$ ($M^+$+Na): 403.1158. Found 403.1125.

$PLC_2$ (more polar) was obtained as a yellow viscous liquid of **13c** (0.9 mg, 1% yield). $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 7.49 (s, 1H, Ar*H*), 7.23 (d, $J=8.5$ Hz, 2H, Ar*H*), 6.95 (d, $J=8.5$ Hz, 2H, Ar*H*), 6.81 (s, 1H, Ar*H*), 5.99 (s, 2H, OC$H_2$O), 5.05 (br s, 1H, ArO*H*), 4.01 (q, $J=7.1$ Hz, 2H, $CO_2CH_2CH_3$), 3.86 (s, 3H, OC$H_3$), 2.34 (s, 3H, $CH_3$), 0.97 (t, $J=7.1$ Hz, 3H, $CO_2CH_2CH_3$).

**4.5.4. Preparation of (±)-picropodophyllone (2).** A solution of thuriferic acid ethyl ester (**4a**) (25.5 mg, 0.06 mmol) in dioxane (0.8 mL) containing HCl (6 M, 0.3 mL) was heated under reflux for 15 h. After removal of dioxane under reduced pressure, water (10 mL) was added to the residue and extracted with EtOAc (3×10 mL). The combined organic layers were washed with water, brine and dried over anhydrous $Na_2SO_4$. After removal of solvent under reduced pressure, the crude product was purified by column chromatography ($SiO_2$, 30% EtOAc in hexanes) to give a white solid of (±)-picropodophyllone (**2**) [10.6 mg, 43% yield; mp 182–183 °C (MeOH): the spectral data were identical to those reported in the literature[6b,d–f]. $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 7.50 (s, 1H, Ar*H*), 6.69 (s, 1H, Ar*H*), 6.24 (s, 2H, Ar*H*), 6.05 and 6.04 (each d, $J=1.1$ Hz, 2H, OC$H_2$O), 4.76 (d, $J=9.2$ Hz, 1H, OC*H*H), 4.69 (s, 1H, C*H*Ar), 4.38–4.33 (m, 1H, OCH*H*), 3.80 (s, 3H, OC$H_3$), 3.76 (s, 6H, 2×OC$H_3$), 3.31 and 3.29 (each br s, 2H, C*H*CO and C*H*COO). $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ 193.4 (C=O), 175.5 (C=O), 153.8 (C–O), 153.7 (2×C–O), 148.4 (C–O), 139.5 (C), 137.9 (C–O), 137.2 (C), 127.2 (C), 109.4 (CH), 106.0 (CH), 104.6 (2×CH), 102.2 ($OCH_2O$), 70.4 ($OCH_2$), 60.7 ($OCH_3$), 56.1 (2×$OCH_3$), 46.6 (CH), 43.4 (CH), 43.3 (CH). IR ($CHCl_3$): $\nu_{max}$ 3025m, 2937m, 1778s, 1670s, 1615s, 1591s, 1505s, 1481s, 1257s, 1131s, 1040s, 1023s, 1002m, 939m, 892w $cm^{-1}$. MS: *m*/*z* (%) relative intensity 412 ($M^+$, 8), 369 (25), 368 (100), 367 (24), 354 (30), 353 (76), 339 (8), 337 (8), 325 (10), 293 (15), 278 (15), 263 (10), 237 (10), 235 (11), 207 (15), 202 (19), 201 (30), 194 (10), 189 (5), 181 (7), 168 (8), 154 (10), 153 (13), 152 (14), 105 (14), 104 (21), 91 (20), 78 (21), 77 (10), 76 (9), 51 (6). Anal. Calcd for $C_{22}H_{20}O_8$: C, 64.08; H, 4.89. Found: C, 64.50; H, 5.12. HRMS (ESI-TOF) Calcd for $C_{22}H_{20}O_8Na$ ($M^+$+Na): 435.1056. Found 435.1042.

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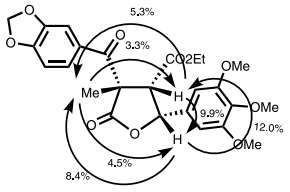
7. The relative stereochemistry of *CC*-**8a** was established by the NOE experiments as shown below.




*CC*-**8a**

8. X-ray crystal structure analysis of compound **11a**. Crystal data for **11a**: $C_{31}H_{30}O_{12}S$, $M_W=626.63$, triclinic, space group $P\bar{1}$, $a=10.0515$ (4) Å, $b=10.7450$ (2) Å, $c=15.2055$ (5) Å, $\alpha=109.525$ (2)°, $\beta=100.379$ (2)°, $\gamma=94.111$ (2)°, $V=1506.99$ (8) Å$^3$, $Z=2$, $D_{calc}=1.381$ mg/m$^3$. A total of 6064 unique reflections (4888 observed, $|F_o|>4\sigma/|F_o|$) was measured at room temperature from a $0.20\times0.15\times0.10$ mm$^3$ colorless crystal using graphite monochromated Mo K$\alpha$ radiation ($\lambda=0.71073$ Å) on a Bruker–Nonius kappaCCD diffractometer. The crystal structure was solved by direct methods using SIR-97, and then all atoms except hydrogen atoms were refined anisotropically on $F^2$ using SHELXL-97 to give a final $R$-factor of 0.0773 and $wR=0.2378$ (all data). Atomic coordinates, bond lengths, bond angles, and thermal parameters have been deposited with the Cambridge Crystallographic Data Center, 12 Union Road, Cambridge CB2 1EZ, England (CCDC 254984).
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# The rapid preparation of 2-aminosulfonamide-1,3,4-oxadiazoles using polymer-supported reagents and microwave heating

Ian R. Baxendale,[a] Steven V. Ley[a,*] and Marisa Martinelli[b]

[a]*Department of Chemistry, University of Cambridge, Lensfield Road, Cambridge CB2 1EW, UK*
[b]*NiKem Research srl, Via Zambeletti 25, Baranzate di Bollate, Milano, Italy*

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**Abstract**—Herein, we report on the preparation of a library of 5-substituted-2-amino-1,3,4-oxadiazoles and the corresponding thiadiazole analogues. Presented is a one-pot preparation of the 2-aminosulfonylated analogues through a three component coupling of an acylhydrazine, an isocyanate and sulfonyl chloride promoted by a polymer-supported phosphazine base under microwave dielectric heating. Also described is the optimization process and details pertaining to the elucidation of the reaction products.


## 1. Introduction

As part of an ongoing investigation into small molecule binders as potential modulators of therapeutic targets we required an expedient synthetic route to the versatile compound class **1** (5-substituted-2-amino-1,3,4-oxadiazoles; Figure 1) which had been identified as an excellent structural template for rapid chemical elaboration. Indeed, 1,3,4-oxadiazoles and the related 1,3,4-thiadiazolium derivatives have attracted considerable interest in medicinal chemistry as surrogates of carboxylic acids, esters and carboxamides;[1] moreover, these compounds have also demonstrated a broad spectrum of biological activity in both agrochemical and pharmaceutical fields showing antibacterial,[2] antimicrobial,[3] insecticidal,[4] herbicidal/fungicidal,[5] anti-inflammatory,[6] hypoglycaemic,[7] and hypotension[8] characteristics. In particular the 2-amino-1,3,4-oxadiazoles **1** have recently been reported to exhibit promising anti-tumour activity.[9]

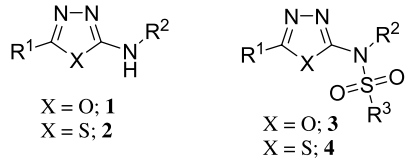


**Figure 1.** 5-Substituted-2-amino-1,3,4-oxadiazoles **1**, 5-substituted-2-amino-1,3,4-thiodiazoles **2**, 2*N*,5-disubstituted 2-amino-1,3,4-oxadiazoles **3** and 2*N*,5-disubstituted-2-amino-1,3,4-thiodiazoles **4**.

The classical synthesis of oxadiazoles usually involves rather harsh reaction conditions employing for example, $SOCl_2$, $POCl_3$, strong mineral acids or various mercury salts,[10] although a few more recent publications have reported milder cyclisation methods albeit for specifically substituted molecules.[11] In an attempt to avoid the use of these potentially problematic reagents and nongeneral conditions a number of groups have developed alternative procedures more amenable to automated high throughput synthesis. In 2001 Brain et al. reported on the synthesis of simple 1,3,4-oxadiazoles via cyclodehydration of 1,2-diacylhydrazines using a polymer-supported Burgess reagent or the polymer-bound phosphazine base PS-BEMP[12] in the presence of toluenesulfonyl chloride as a dehydrating agent.[13] Brown[14] and Kilburn[15] have also shown that 2-amino-1,3,4-oxadiazoles of type **1** can be prepared in excellent yields on solid phase from the corresponding immobilised 1,4-disubstituted semicarbazides using either 1,3-diisopropylcarbodiimide (DIPC), 1,3-dicyclohexylcarbodiimide (DCC) or 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC·HCl) as the cyclisation mediator. However, these latter on-bead preparations are somewhat restrictive because of the necessity for extended reaction times (as well as attachment and cleavage steps) and the inherent difficulties of monitoring the reactions progress especially for the preparation of diverse compound libraries. In addition they are often difficult to directly scale up in order to prepare significant quantities of material for further processing

*Keywords*: Polymer-supported reagents; Oxaziazole; Thiadiazole; Combinatorial chemistry; Microwave.
* Corresponding author. Tel.: +44 (0)1223 336398; fax: +44 (0)1223 336442; e-mail: svl1000@cam.ac.uk

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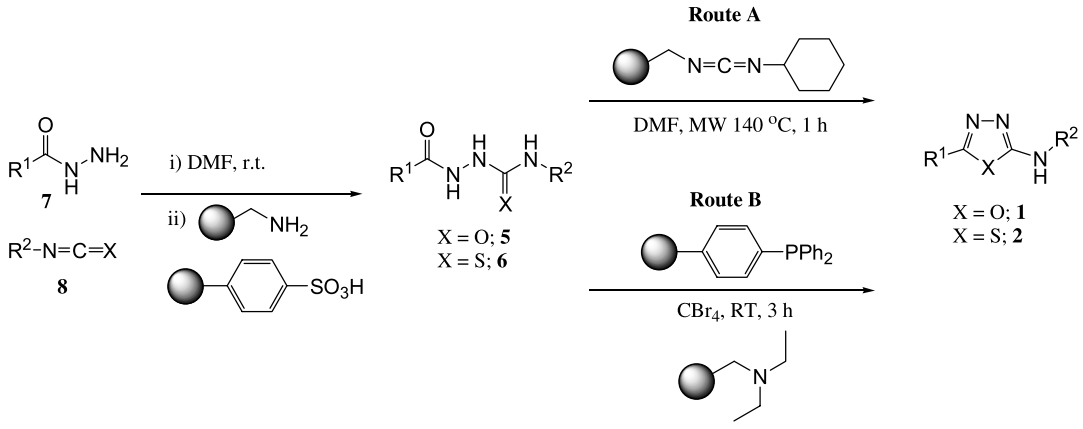
doi:10.1016/j.tet.2005.03.062




**Scheme 1.** Preparation of 1,4-disubstituted-(thio)semicarbazides **5/6** and their transformation to 5-substituted-2-amino-1,3,4-oxadiazoles **1** using (a) polymer-supported DCC reagent and (b) carbon tetrabromide and supported triphenylphosphine.

without intensive optimization. Due to our extensive experience and successes in the fields of solid-supported reagents[16] and microwave-assisted[17] organic chemistry we decided to investigate the symbiotic combination of these two enabling technologies to the rapid generation of combinatorial libraries based on the general structures **1**–**4** (Fig. 1).[18]

## 2. Results and discussion

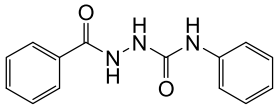
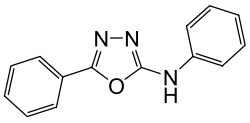
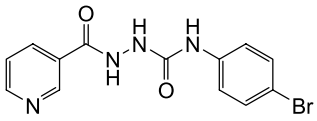
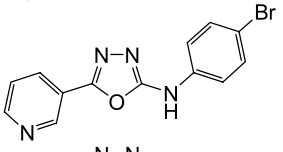
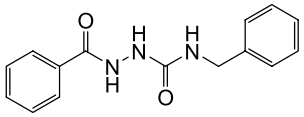
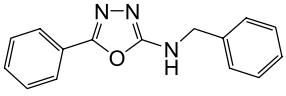
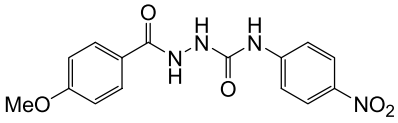
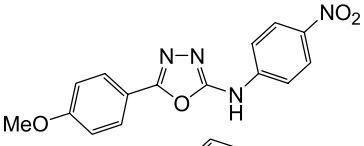
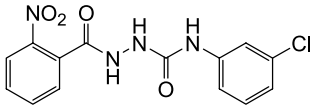
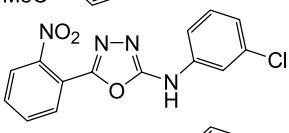
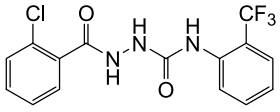
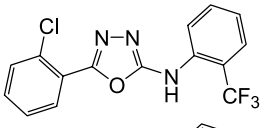
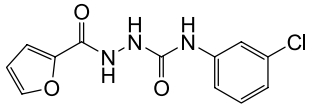
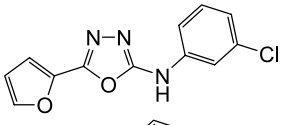
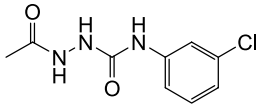
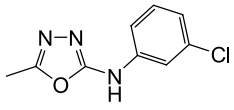
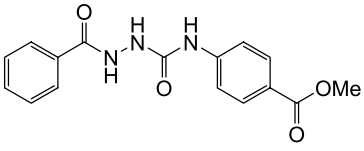
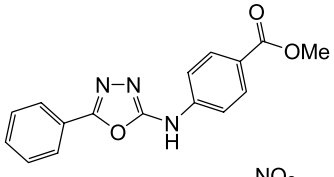
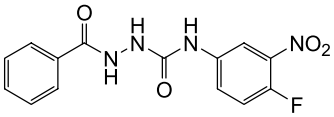
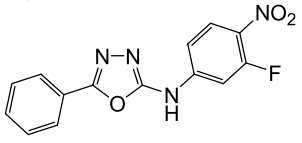
As a result of the literature precedent for successful on bead synthesis we initially investigated the analogous solution phase cyclisation of a range of semicarbazides **5** promoted by an immobilised DCC reagent[19] (Scheme 1; Route A). The prerequisite 1,4-disubstituted (thio)semicarbazides **5/6** were prepared directly via a condensation reaction of the appropriately substituted acylhydrazine **7** and the iso(thio)-cyanate **8**. The reaction conditions were not optimized to maximize the attainable yield but biased to facilitate rapid access to the clean products. Therefore, following a scavenging sequence utilizing a mixture of macroporous sulfonic acid and aminomethyl polystyrene to sequester any unreacted hydrazine **7** and/or iso(thio)cyanate **8** the semicarbazides **5** or **6** were isolated in moderate to high yields but in all cases in excellent purity (Fig. 2).[20] The semicarbazides **5/6** thus prepared were analyzed by LC-MS with a small subset being further characterised by $^1$H NMR (all compounds exceeded a required 95% minimum purity). The cyclodehydration of a selection of the semicarbazide compounds **5** with a resin bound DCC equivalent (6 equiv) in DMF at 140 °C (1 h) under microwave irradiation[21] was encouraging, leading cleanly to the desired heterocyclic product (Scheme 1; Route A; Table 1). Repeating the reaction in the absence of the supported DCC resulted in no cyclisation and permitted quantitative recovery of the starting material.

Although the described protocol was extremely effective for the cyclisation we were unable to devise a generic procedure that permitted a significant reduction in the number of equivalents of the supported DCC reagent. This proved somewhat problematic (especially for scaling) because the use of six equivalents required large volumes of solvent due to the resins swelling characteristics in DMF and also the need for effective post reaction washing in order to facilitate the isolation of the product. Experiments involving different solvents systems or substitution of the core resin matrix[22] as well as altering other reaction parameters (time, temperature, concentration) failed to give any significant benefits in terms of higher yields or potential scalability. It should be noted that during the preparation of these compound libraries Evans and co-workers reported[23] on the same preparative route to compounds of type **1** using a polymer-supported (PS) DCC cyclisation procedure at 80 °C (reaction times of 60 h). Their protocol also required the use of five equivalents of the immobilised reagent.

We therefore pursued an alternative approach to inducing cyclisation using a mixture of a PS-triphenylphosphine equivalent and carbon tetrabromide.[24] In order to regulate the pH of the system an immobilised triethylamine variant was also added (Scheme 1; Route B). This proved to be a particularly effective combination giving excellent conversions to the corresponding oxadiazoles although the initial purity (~78–92%) of the product was somewhat lower than for the material obtained in the previous PS-DCC mediated method. However, we discovered that simple filtration of the reaction mixture through a functionalised silica packed cartridge (aminopropyl-$NH_2$) significantly improved the purity (>95% as determined by LC-MS; Table 2).[25]

Having determined two routes to the 2-amino heterocycles **1**, we turned our attention to methods for the direct preparation of the correspondingly sulfonylated material as our intended targets for biological evaluation. Our premise was, that in accordance with the work by Brain et al.[14] we could facilitate the desired cyclisation of **5** using a combination of PS-BEMP and an excess of an appropriately functionalised sulfonyl chloride, which would then lead directly to the protected sulfonamide **3** in a one-pot combinatorial fashion. Indeed, this proved a successful strategy enabling the preparation of a small exploratory compound set based on the 1,4-disubstituted semicarbazides **5** and a selection of 25 commercially available sulfonyl chlorides (Table 3). The optimised conditions were eventually found to be treatment of semicarbazide **5** with PS-BEMP (3.5 equiv) and sulfonyl chloride (2.3 equiv) in acetonitrile at 150 °C. The choice of solvent proved critical (see later discussion) as did the number of equivalents of

**Table 1**. 2-Amino-1,3,4-oxadiazoles **1** prepared using an PS- DCC reagent (Scheme 1; Route A)

| Entry | Substrate | Product | Isolated yield |
|---|---|---|---|
| 1 |  |  | 73 |
| 2 |  |  | 81 |
| 3 |  |  | 70 |
| 4 |  |  | 88 |
| 5 |  |  | 69 |
| 6 |  |  | 64 |
| 7 |  |  | 77 |
| 8 |  |  | 76 |
| 9 |  |  | 80 |
| 10 |  |  | 83 |

All compounds showed a purity >95% as determined by LC-MS.

the two reagents which were configured to suppress the formation of the unprotected amine **1**, which at lower concentrations was always present as a major by-product. However, this observation was of obvious interest with respect to the preparation of compound **1** and hence it was decided to further investigate the feasibility of devising two parallel synthetic routes, which would lead respectively to the sulfonamide **3** and the unprotected heterocycle **1** by simple modification of the reaction parameters.

### 2.1. 2-Amino-1,3,4-oxadiazoles the effect of the base

Initial observations concerning the reactions of the semicarbazides **5** with PS-BEMP and toluene-4-sulfonyl chloride **11** (TsCl) indicated that it was critical to use an excess of the immobilised phosphazine base. Lower quantities (<2 equiv) always resulted in efficient cyclodehydration but the product mixture comprised of varying amounts of the sulfonamide protected material **3** and free heterocyclic amine **1**. Altering the ratio of sulfonyl chloride beyond two equivalents had little effect on the product composition if sub-quantities of PS-BEMP were used. In order to fully evaluate the effect of the base concentration and its identity a more comprehensive screening programme was conducted (for selected results see Table 4).

From the tabulated information it is evident that there is a specific correlation between the relative basicity of the

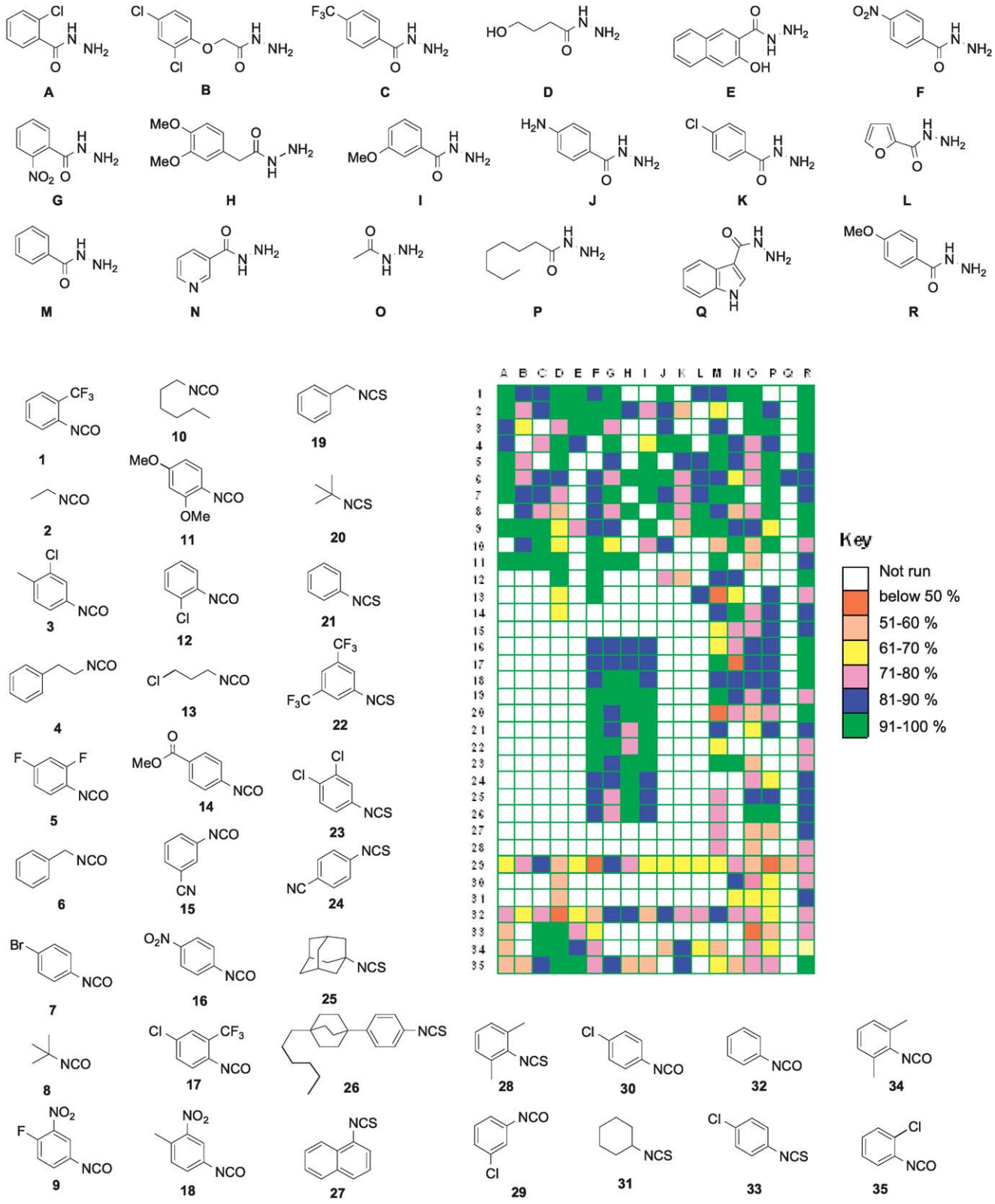



**Figure 2.**

polymer and the proportions of starting material **34**, cyclised adduct **35** and protected product **36** present in the final reaction mixture. The more basic polymers PS-BEMP and the polymer-bound guanidine base 1,3,4,6,7,8-hexahydro-1-methyl-2*H*-pyrimido[1,2-*a*]pyrimidine (PS-TBD) gave good conversions to the cyclised products **35** and **36**. Whereas, the more weakly basic species such as PS-diisopropylethylamine (PS-DIEA), the tetraalkylammonium carbonate (PS-$NaCO_3$), PS-morpholine (PS-NMM) and Amberlyst A21, although all showing some ability to promote the initial condensation reaction, failed to catalyse the following sulfonation step (only 13% for PS-NMM;

**Table 2**. Preparation of 2-amino-1,3,4-oxadiazoles using PS-triphenylphosphine and carbon tetrabromide (Scheme 1; Route B)

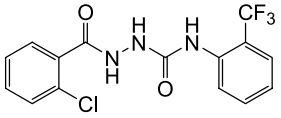
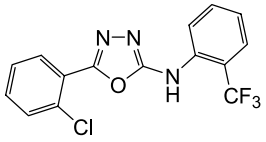
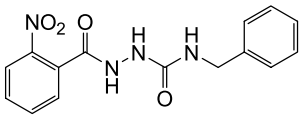
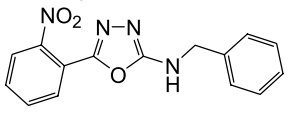
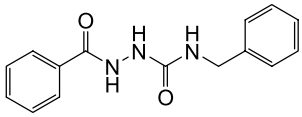
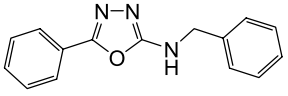
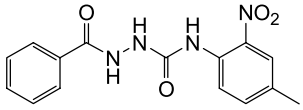
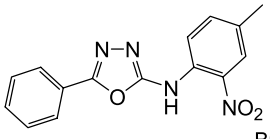
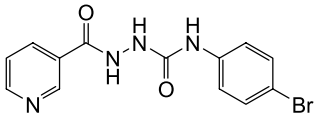
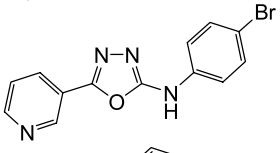
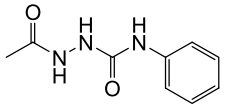
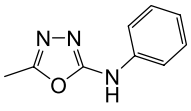
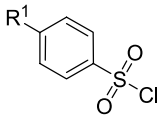
| Entry | Substrate | Product | Yield |
|---|---|---|---|
| 1 |  |  | 68 |
| 2 |  |  | 71 |
| 3 |  |  | 77 |
| 4 |  |  | 59 |
| 5 |  |  | 83 |
| 6 |  |  | 81 |

Table 4, entry 21). Interestingly, both polymer-bound dimethylaminopyridine (PS-DMAP) and to some extent polyvinyl pyridine (PVP) were effective additives for catalysing the initial cyclisation step presumably by formation of a more activated sulfonylating agent,[26] although being weak bases they do not assist the subsequent protection step. This seemed to present an ideal solution to our requirements providing with a simple substitution of the polymeric resins the selective formation of either of the two desired products **35** or **36**. Unfortunately, on a more extensive evaluation the cyclisation reaction catalysed by PS-DMAP proved to be very substrate dependent and variable amounts of starting material **5** were always detected at the end of reaction (3–12%). However, due to the difference in solubility and basicity between the starting material **5** and product **1**, a relatively simple catch and release purification was possible using a sulfonic acid silica bonded sorbent (SCX-II) giving products of >98% purity on release. Therefore, in a typical procedure, the urea, prepared in situ from an acylhydrazide **7** and isocyanate **8** in THF, was cyclodehydrated in a microwave oven (120 °C, 30 min) in the presence of PS-DMAP (3 equiv) and TsCl (2 equiv). Using this procedure a small collection of 120 compounds was formed in moderate to good yields (Table 5 for a representative sample).

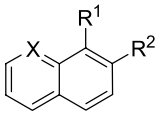
## 2.2. Sulfonamide protected 2-amino-1,3,4-oxadiazoles the effect of the solvent

A number of potential solvents systems were screened for the one-pot cyclisation/protection sequence leading to compounds of type **3**. The solvents dichloromethane,

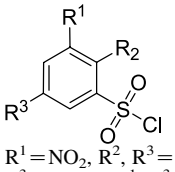
**Table 3**. The various sulfonic acid chlorides used in the construction of heterocyclic sulfonamides **3**



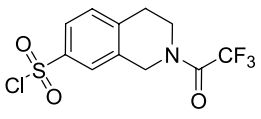
$R^1$=H, **9**; Ph, **10**; Me, **11**; MeO, **12**; F, **13**; Cl, **14**; Br, **15**; I, **16**; $NO_2$, **17**; $MeSO_2$, **18**; butoxy, **19**; $CF_3$, **20**; PhO, **21**.



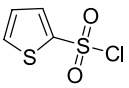
$R^1$=H, $R^2$=$SO_2Cl$, X=CH, **22**; $R^1$=$SO_2Cl$, $R^2$=H, X=CH, **23**; $R^1$=$SO_2Cl$, $R^2$=H, X=N, **24**.



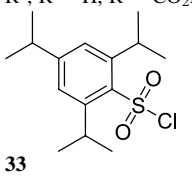
$R^1$=$NO_2$, $R^2$, $R^3$=H, **25**; $R^1$=$CF_3$, $R^2$=H, $R^3$=Br, **26**; $R^1$, $R^3$=H, $R^2$=$CF_3$, **27**; $R^1$, $R^3$=H, $R^2$=CN, **28**; $R^1$, $R^3$=H, $R^2$=$NO_2$, **29**; $R^1$, $R^3$=H, $R^2$=$CO_2Me$, **30**.



**31**

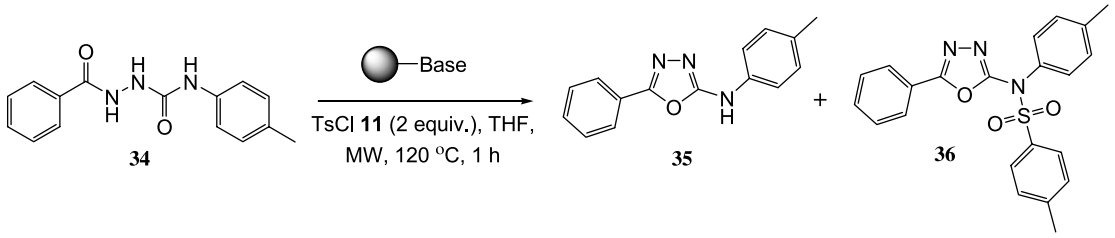


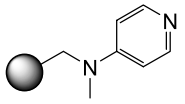
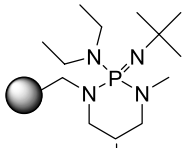
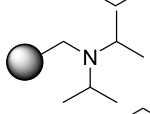
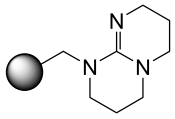
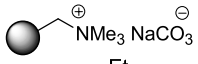
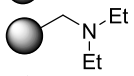
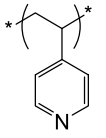
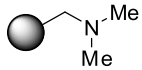
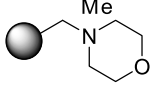
**32**



**33**

**Table 4**. Optimisation of the immobilised base used for the cyclodehydration of urea compound **34**




| Entry | Base | Polymer structure | Equiv | **34**[a] | **35**[a] | **36**[a] |
|---|---|---|---|---|---|---|
| 1 | No base[b] | | — | 88 | 12 | — |
| 2 | PS-DMAP |  | 5 | | 95 | — |
| 3 | | | 3 | 12 | 88 | — |
| 4 | | | 1 | 52 | 48 | — |
| 5[c] | | | 2 | 38 | 62 | — |
| 6 | | | 2 | 28 | 72 | — |
| 7 | | | 2.5 | 24 | 76 | — |
| 8 | PS-BEMP |  | 5 | — | — | 99 |
| 9 | | | 3.5 | — | — | 99 |
| 10 | | | 2 | — | 16 | 84 |
| 11 | | | 1 | — | 48 | 52 |
| 12 | PS-DIEA |  | 5 | 55 | 45 | — |
| 13 | PS-TBD |  | 5 | — | 60 | 40 |
| 14 | | | 3 | 2 | 86 | 20 |
| 15 | | | 1 | 22 | 56 | 22 |
| 16 | PS-$NaCO_3$ |  | 5 | 80 | 20 | — |
| 17 | PS-TEA |  | 5 | 64 | 36 | — |
| 18 | PVP[c] |  | 5 | 61 | 39 | — |
| 19 | | | 5 | 45 | 55 | — |
| 20 | Amberlyst A21 |  | 5 | 82 | 18 | — |
| 21 | PS-NMM |  | 5 | 42 | 45 | 13 |

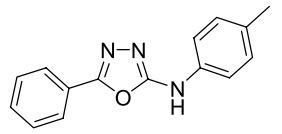
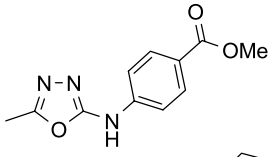
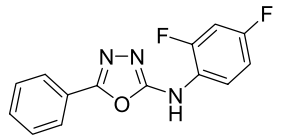
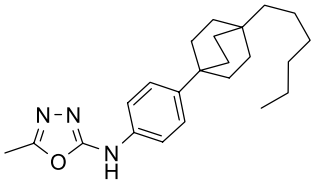
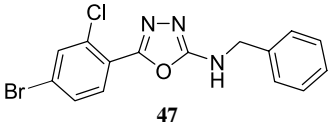
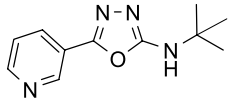
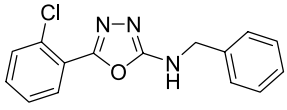
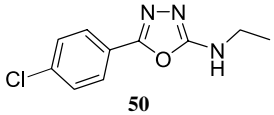
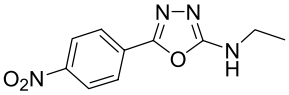
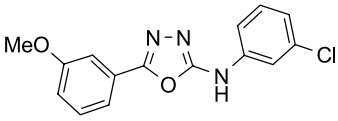
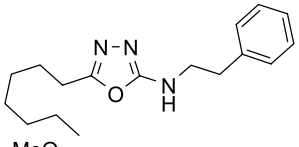
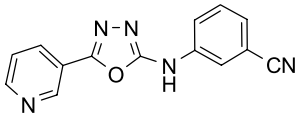
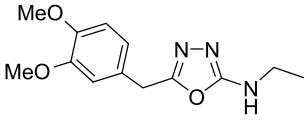
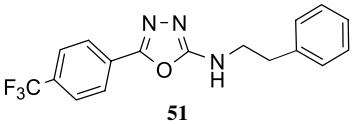
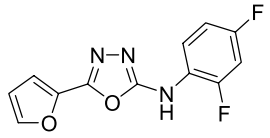
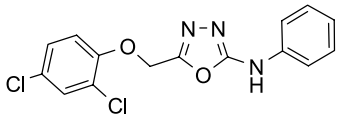
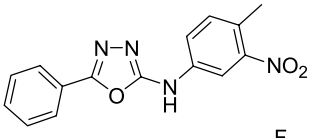
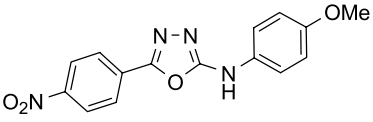
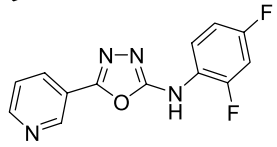
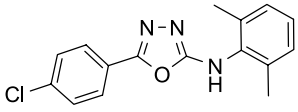
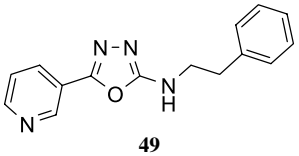
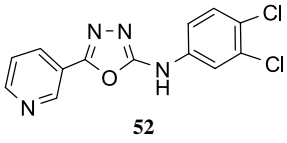
[a] Determined by LC-MS, 254 nm detection.
[b] Heated for 1 h at 120 °C in tetrahydrofuran.
[c] Heated for 30 min at 120 °C.

chloroform, 1,2-dichlorobenzene and toluene all gave complex mixtures under the standard conditions (PS-BEMP (3.5 equiv), TsCl (2.2 equiv) at 120 °C for 20 min) (Scheme 2). The use of dimethylformaldehyde (DMF) also proved problematic giving a single alternative product which was later identified as the sulfonyl protected enol derivative. When the reaction was carried out in THF or similarly 1,4-dioxane all the starting material was consumed but the solution upon isolation contained two compounds with identical molecular weights in a 4:1 ratio.

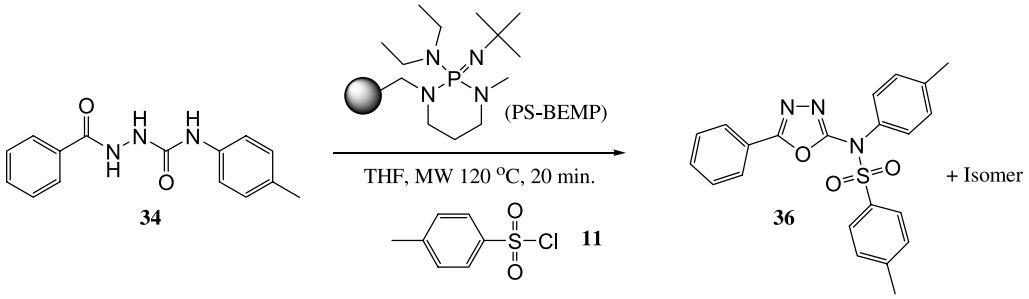
There are a number of potential structural isomers which could be formed through the cyclodehydration and resulting protection sequence of the semicarbazide compounds **5**. The most likely rationalization for the formation of two species under our reaction conditions would be as a consequence of the bidentate nucleophilic behavior of the intermediate heterocycle **1** through tautomerism with the imino-oxadiazoline form **37** (Scheme 3). These two species could then react independently with the electrophile at either the ring or exocyclic nitrogens leading to two distinct regioisomers **3** and **38**.[27] Presumably, the driving force for the formation of compound **38** would be the avoidance of steric congestion around the *N*-5 site that would be apparent in the bis-substituted amine isomer **3**.

In addition we must also consider the possible heterocyclic structures that could result from nucleophilic attack of the (5-*N*) nitrogen to form the alternative cyclisation product namely the 1,3,4-triazole **39** and its subsequently sulfonylated derivatives **41** and **42** (Scheme 3). In order to gain some insight into the reaction and determine the potential for any

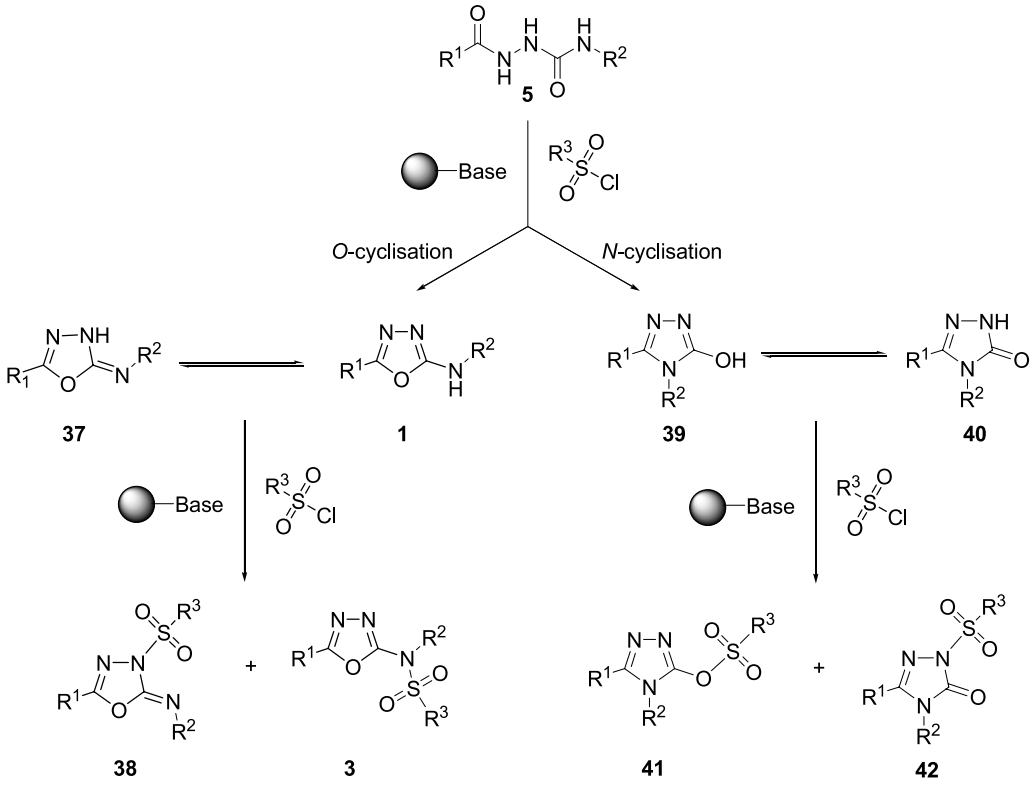
**Table 5**. 2-Amino-1,3,4-oxadiazoles synthesis

| Entry | Product | Yield | Entry | Product | Yield |
|---|---|---|---|---|---|
| 1 |  | 60 | 12 |  | 53 |
| 2 |  | 55 | 13 |  | 59 |
| 3 |  **47** | 82 | 14 |  | 68 |
| 4 |  | 56 | 15 |  **50** | 75 |
| 5 |  **48** | 78 | 16 |  | 77 |
| 6 |  | 72 | 17 |  | 82 |
| 7 |  | 77 | 18 |  **51** | 77 |
| 8 |  | 64 | 19 |  | 64 |
| 9 |  | 52 | 20 |  | 80 |
| 10 |  | 88 | 21 |  | 68 |
| 11 |  **49** | 90 | 22 |  **52** | 76 |

experimental control of the regioselectivity we embarked on a more detailed study of the reaction components of the model system depicted in Scheme 2. Preliminary investigations of the IR spectra and attempted correlation to the literature reported compounds proved inconclusive. Therefore, a selection of acyl semicarbazide derivatives **5** were analyzed and a characteristic C=O stretching band in the range of 1710–1665 $cm^{-1}$ was identified which in the corresponding major cyclisation products was replaced with equally strong absorptions between 1655 and 1600 $cm^{-1}$ corresponding to the finger print region for a C=N stretch consistent with a cyclic strained structure. The




**Scheme 2.** Model system for reaction optimization.




**Scheme 3.** Tautomerism in the 2-amino-1,3,4-oxadiazoles **1**;[28] formation of compounds **3** and **38**. The alternative cyclisation product 1,3,4-triazole **39** and the possible sulfonyl protected forms **41** and **42**.

imino-oxadiazoline species **37** would be expected to show a higher absorbance at 1695–1640 $cm^{-1}$ in accordance with the exocyclic C═NR stretch as seen in IR spectra of mixtures containing the minor product.[29] Alternatively, compound **42** would be expected to display a characteristic absorption frequency corresponding to the carbonyl (C═O; 1725–1695 $cm^{-1}$) signal which was not observed.[30] From these pieces of data we could provisionally propose the structures **3** (major product) and **38** (minor product) to the isomer mixtures. In addition more indirect evidence to support the presence of structure **38** was found when upon attempted separation the minor regioisomer decomposed to yield the derivative of form **1**. However, in order to fully validate the identity of the two product components we decided to prepare by know literature methods[31] compounds **35** and **43** which were subsequently sulfonylated (TsCl **11**),[32] resulting in the clean formation of two additional compounds **36** and **44**, respectively for which single crystal X-ray data was obtained (Fig. 3). We were therefore able to immediately match the major products from the reactions of **34** and **11** with PS-BEMP, namely **36** (Scheme 2) and in the case of PS-DMAP product **35** (Table 4) which also matches the decomposition product of the minor isomer from the model system. In addition the possible structure regioisomer **44** could be conclusively eliminated from consideration as a possible candidate for the minor isomeric partner of **35**. Interestingly, all attempts to prepare the alternative regioisomer of **44** based on the structure **40** failed allowing only isolation of compound **44**. Presumably, the sulfonamide **44** is favored because of the lability of the *O*-sulfonyl and the potential for steric hindrance with the adjacent *N*-tolyl group which prevents the *O*-protected assembly.

A number of other substrates showed the same behavior giving two regioisomers (Table 6). In all cases attempted isolation of the minor product resulted in its decomposition and only the nonsulfonylated material **1** could be recovered. Indeed, even on standing at ambient temperature the minor

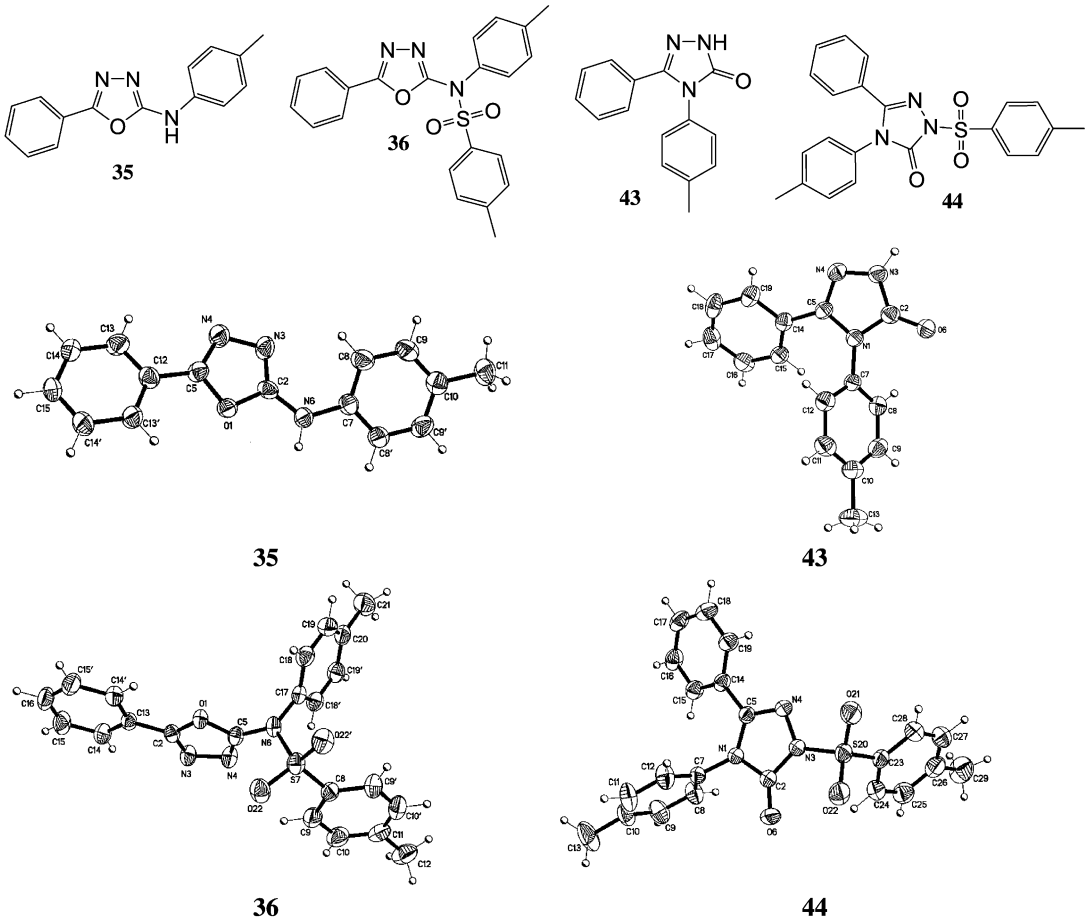



**Figure 3.** X-ray crystal structures for compounds **35**, **36**, **43** and **44**.

product spontaneously eliminated the corresponding sulfonic acid to give the 2-amino-ozadiazole **1**. This process could be accelerated with the addition of an alcoholic solvent such as methanol/water or by the addition of a nucleophilic amine leading to the formation of the sulfonamide adduct.

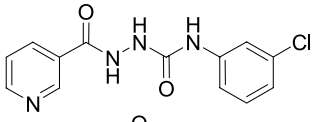
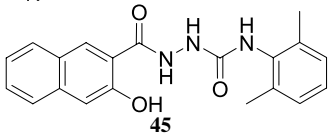
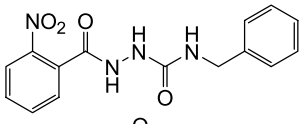
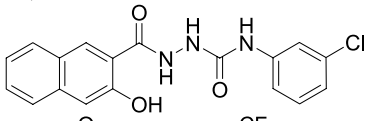
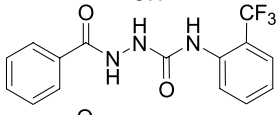
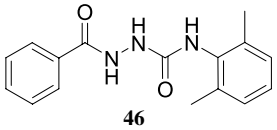
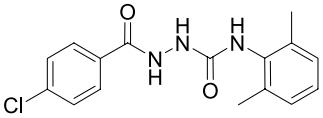
The synthetic inconvenience of producing a mixed regioisomer product was avoided in the majority of cases by simply changing the solvent to acetonitrile. This proved highly beneficial yielding the protected oxazolidine **3** as the exclusive product after only 15 min although this required the temperature to be elevated to 150 °C. At lower temperatures extended reaction times were required and the final products purity was lower. Again, work-up and purification was facile requiring only filtration through a short plug of silica and solvent evaporation. Although the use of acetonitrile as the solvent did result in the formation of a single product, in the majority of cases certain compounds were still obtained as mixtures, the exact ratio was found to be highly dependant on the steric nature of the coupling partners. However, in all cases the use of acetonitrile always gave a preferentially biased mixture in favour of the oxadiazole **3** (Table 6).

Accordingly a library of *N*-substituted-2-amino-1,3,4-oxazolidines **3** were prepared from the previously described urea library **5** (Table 7; see Fig. 2 for details of the semicarbazides **5** and Table 3 for a list of the sulfonyl chlorides employed). In total, a compound collection comprising of over 850 distinct and isolated compounds was generated. All compound purities were determined by LC-MS and a small random selection of the compounds were chosen for full characterisation.

### 2.3. Cyclodehydration of thiosemicarbazides 6

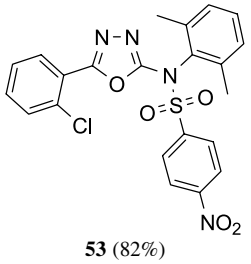
In addition to the formation of the oxadiazole species **3** we were also interested in preparing the corresponding 2-amino-1,3,4-thiadiazole analogues **4**. When the same standardized reaction conditions were applied to the cyclisation of the thiosemicarbazides **6**, a substrate dependant transformation to either the thiadiazoles **4** or oxadiazoles **3** occurred (Table 8). The selectivity of the reaction was found to be highly dependant on the electronic characteristics of the $R^1$ and $R^2$ substituents. Rationalization of the differing reactivity of the thiourea compounds **6** could be ascribed to the relative nucleophilicity of the thiocarbonyl and carbonyl functionality as influenced by the interaction of electron-withdrawing or electron-donating groups. In entries 4–10 (Table 8), the pyridine ring (likewise the 4-nitro group in entries 27–29; Table 8) reduces the electron density of the acylhydrazine moiety. This would result in an increase in acidity of the *N*-2 proton permitting rapid enol tautomerism. Facile *O*-sulfonylation of the enolate would yield a reactive intermediate possessing an electrophilic centre and associated leaving group. Spontaneous intramolecular cyclisation through attack of

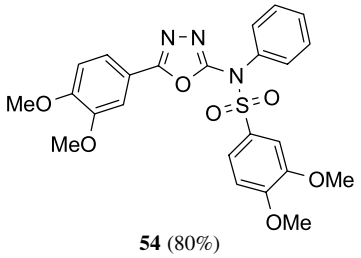
**Table 6**. Effect of solvent on product composition

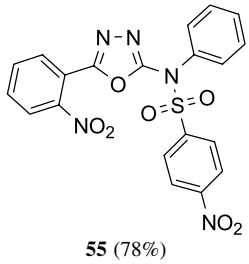
| Substrate | $RSO_2Cl$ | Solvent | Ratio 3:38 |
|---|---|---|---|
|  | **14** | THF<br>MeCN | 6:5<br>3:1 |
|  **45** | **14** | THF<br>MeCN | 1:1<br>5:2 |
|  | **15** | THF<br>MeCN | 3:2<br>5:1 |
|  | **27** | THF<br>MeCN | 1:1<br>4:1 |
|  | **32** | THF<br>MeCN | 6:1<br>20:1 |
|  **46** | **12** | THF<br>MeCN | 3:1<br>9:1 |
|  | **12** | THF<br>MeCN | 3:2<br>5:1 |

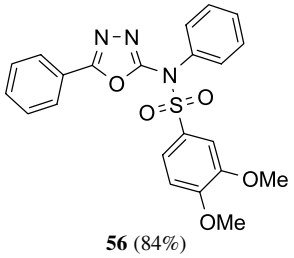
the thiocarbonyl would then lead to exclusive formation of the thiadiazole product **4**. To a lesser extent the same effect can also be seen in entries 1–3 where the phenyl group would likewise assist the deprotonation step (PS-BEMP is well known to be able to remove N–H amidic protons). Conversely, electron donating or simple alkyl groups at $R^1$ would increase the nucleophilicity of the sulfur in the thiourea making this the more likely centre for sulfonylation and therefore creation of the required leaving group (in addition to arguments of activation following the above argument for the *N*-2 proton acidity). Again, the analogous intramolecular cyclisation by the carbonyl oxygen would result in formation of the alternative product the oxadiazole **3**. As can be see from entries 17–19 (Table 8) the two processes are quite finely balanced although there is probably some inherent bias towards the formation of the

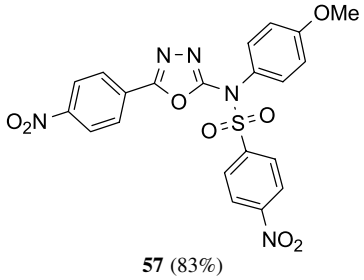
**Table 7**. Examples of N-substituted-2-sulfonamide-1,3,4-oxadiazoles prepared from semicarbazide library **5**


**53** (82%)


**54** (80%)


**55** (78%)


**56** (84%)


**57** (83%)

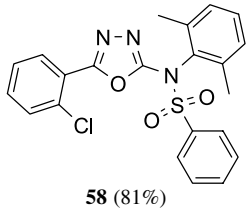
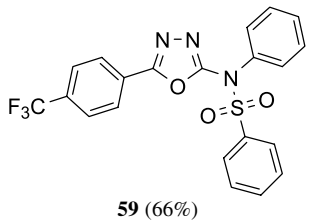
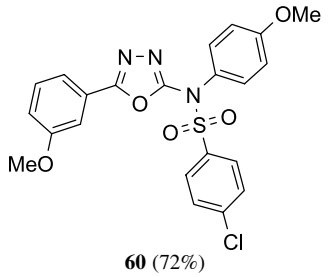

**58** (81%)

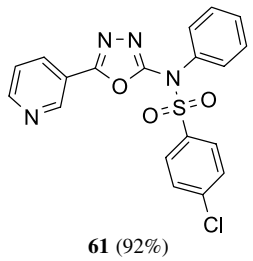
Table 7 (*continued*)



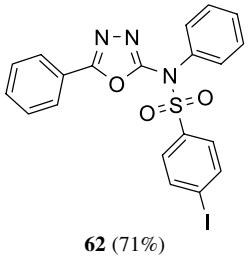
**59** (66%)



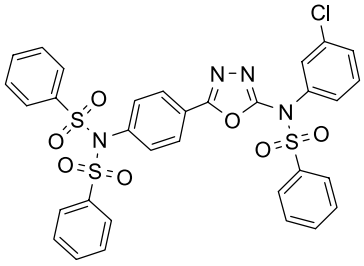
**60** (72%)



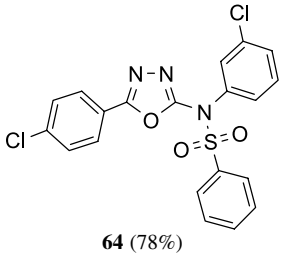
**61** (92%)



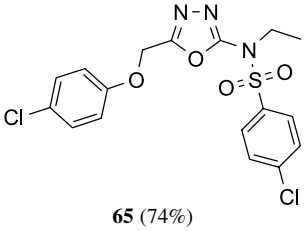
**62** (71%)



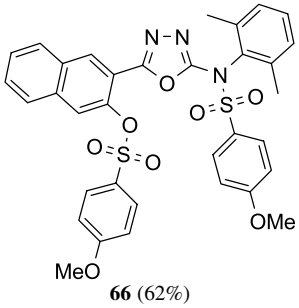
**63** (49%)



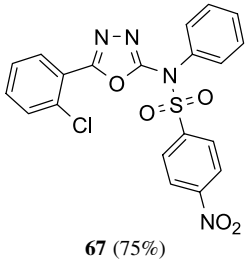
**64** (78%)



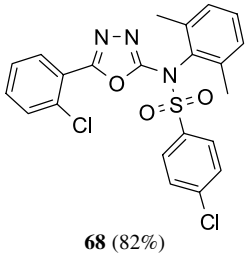
**65** (74%)



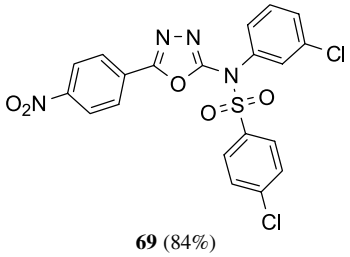
**66** (62%)



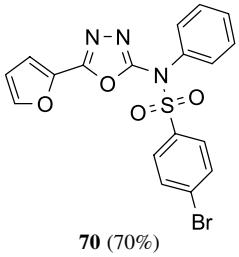
**67** (75%)



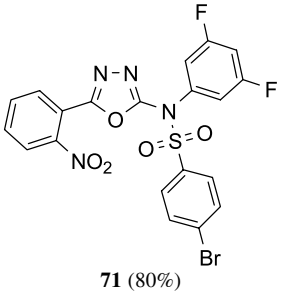
**68** (82%)



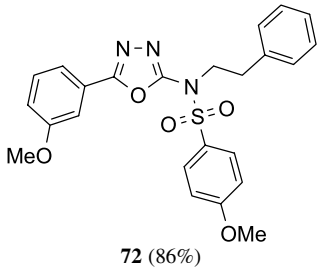
**69** (84%)



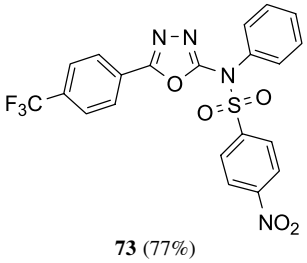
**70** (70%)



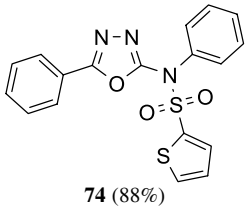
**71** (80%)



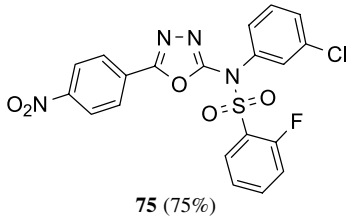
**72** (86%)



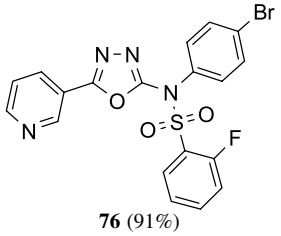
**73** (77%)



**74** (88%)

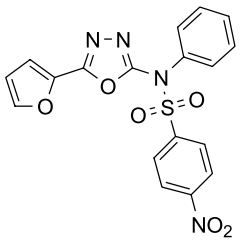


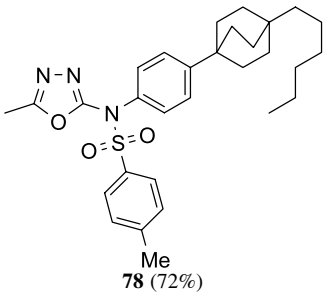
**75** (75%)



**76** (91%)

Table 7 (*continued*)


**77** (85%)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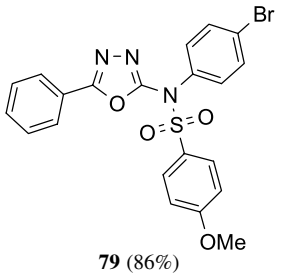
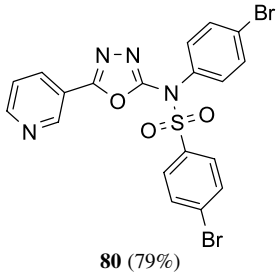

**79** (86%)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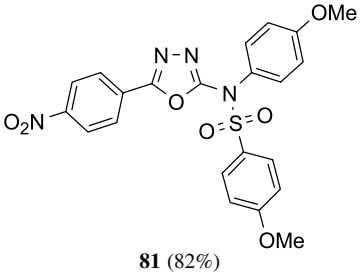
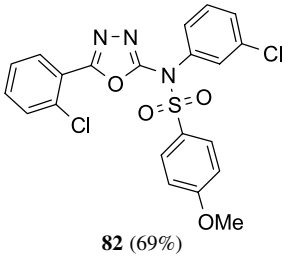
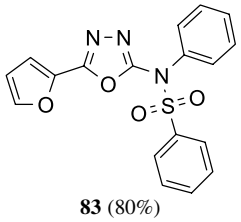
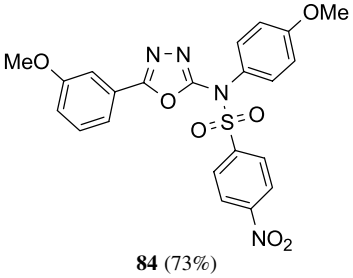
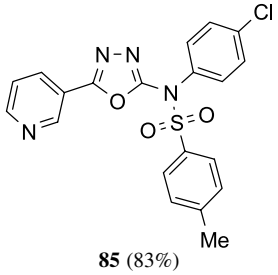
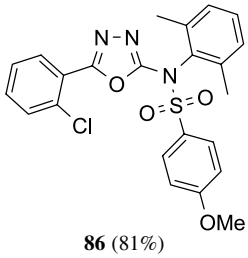

**81** (82%)

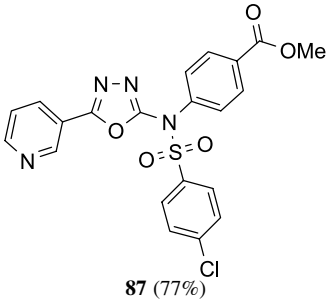

**82** (69%)

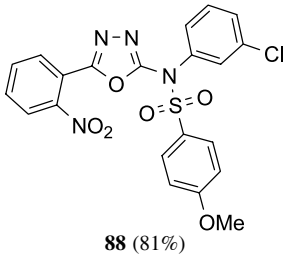

**83** (80%)

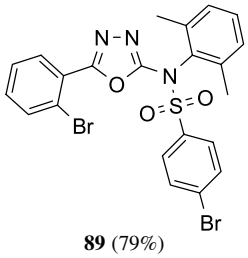

**84** (73%)

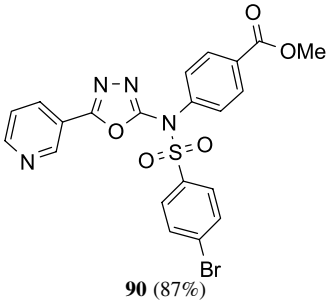

**85** (83%)

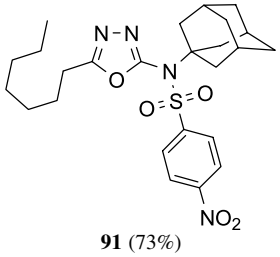

**86** (81%)


**87** (77%)


**88** (81%)


**89** (79%)


**90** (87%)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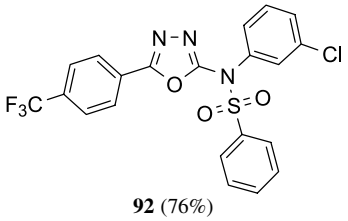
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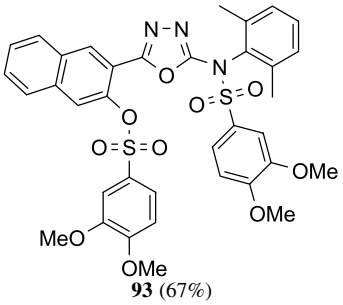
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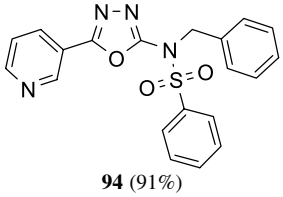
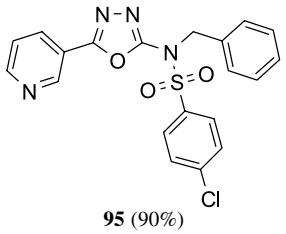
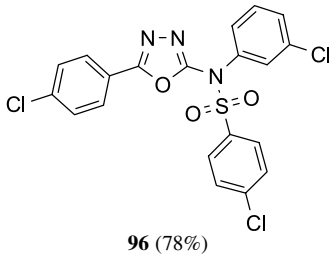
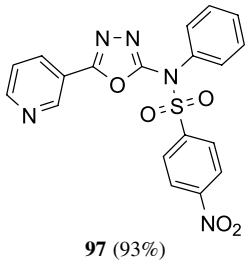
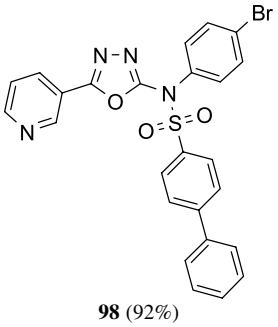
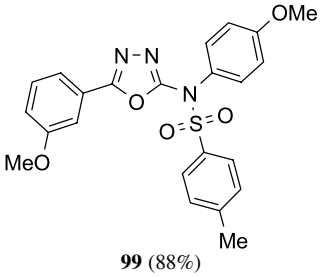

**94** (91%)

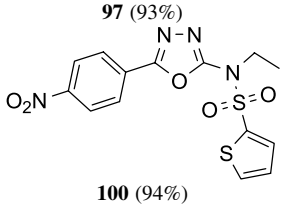

**95** (90%)

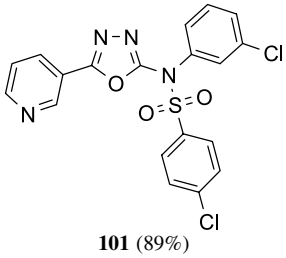

**96** (78%)

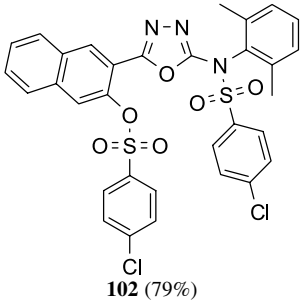

**97** (93%)

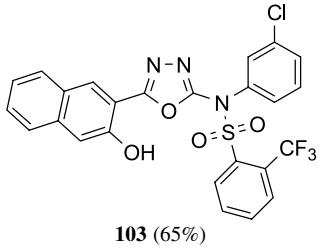

**98** (92%)


**99** (88%)


**100** (94%)


**101** (89%)


**102** (79%)


**103** (65%)

thiadiazole product **4** because of the higher oxophilicity of the sulfonyl chloride reagents.

### 2.4. Single pot strategy

We next turned our attention to enhancing this synthetic methodology by validating a new three step one-pot synthetic procedure. According to this protocol the 1,2-diacylhydrazine **3** was generated in situ starting from acylhydrazide and isocyanate in acetonitrile at ambient temperature; after stirring the reaction mixture for 5 min PS-BEMP and the corresponding sulfonyl chloride was added and the mixture heated under microwave irradiation at 150 °C for 15 min (Table 9). In general the final compounds were obtained in high purity and yield, with the exception of compounds derived from sulfonyl chlorides substituted in the ortho position (Table 9; entries 15–18). This was consistent with the observations from the previous preparation (see Table 8).

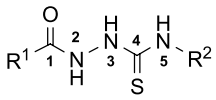
## 3. Conclusion

In conclusion we have successfully developed and validated two convenient routes to 5-substituted-2-amino-1,3,4-oxadiazoles **2** and their 2-aminosulfonylated derivatives **4** using polymer-supported reagents to expedite their preparation and purification. In total over 15 hundred discrete compounds have been prepared which are being screening and evaluated against a range of medicinal and agrochemical targets.

## 4. Experimental

Poly-DMAP was pre-washed with DCM, MeOH, $Et_2O$ then dried at 60 °C for 20 h. Tetrahydrofuran (THF) was distilled over sodium benzophenone and dichloromethane over calcium hydride. All others solvents and reagents were used as supplied unless otherwise specified. Analytical TLC was peformed using precoated glass-backed plates (Merck Kieselgel 60 F254) and visualized by ultra-violet radiation, acidic ammonium molybdate (IV) or potassium permanganate. $^1$H spectra were recorded on a Bruker Advance DPX-400 or DPX-500 spectrometer with residual chloroform as the internal reference ($\delta_H$=7.26 ppm). $^{13}$C NMR spectra were recorded in $CDCl_3$ on the same spectrometers with the central peak of chloroform as the internal reference ($\delta_C$=77.0 ppm). DEPT 135 and two-dimensional (COSY, HMQC and HMBC) NMR spectroscopy were used, where appropriate, to aid in the assignment of signal in the $^1$H and $^{13}$C NMR spectra. Infra-red spectra were recorded on a Perkin–Elmer Spectrum One FT-IR spectrometer neat, letters in the parentheses refer to relative absorbancy of the peak w-weak less than 40% of the main peak, m-medium ca. 41–74% of the main peak, s-strong greater than 74% of the most intense peak. LC-MS analysis was performed on a Hewlett–Packard HPLC 1100 chromatograph (Mercury hexyl-phenyl column) attached to a HP LC/MSD Platform LC APCI mass spectrometer. Elution was carried out using the gradient given in Table A.

**Table 8**. Cyclodehydration reaction on thiourea derivatives **6**



**6**

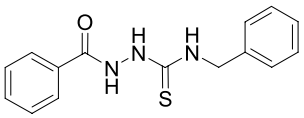
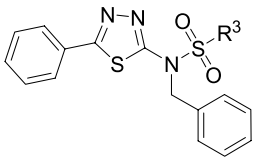
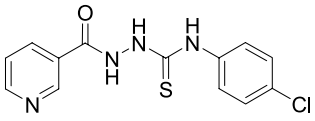
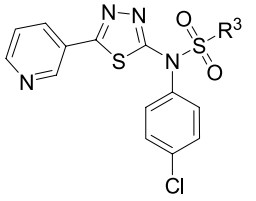
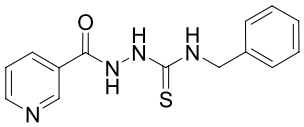
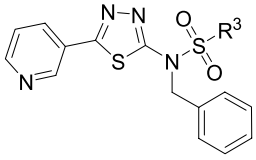
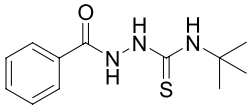
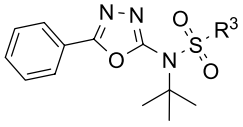
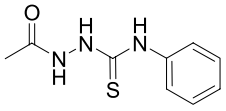
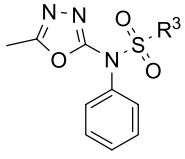
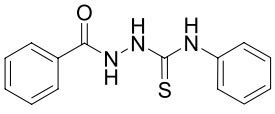
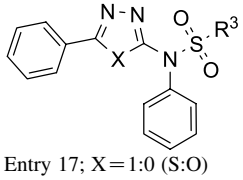
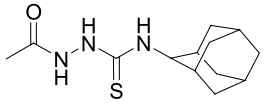
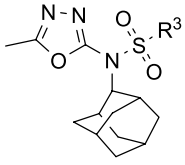
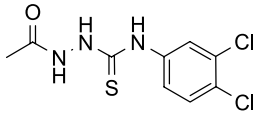
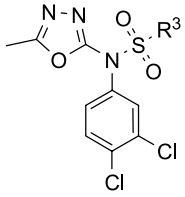
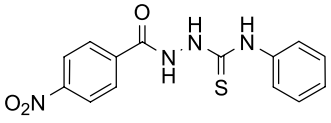
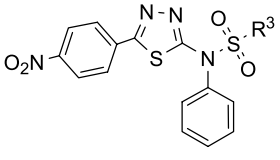
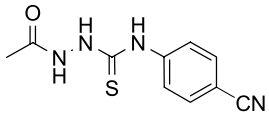
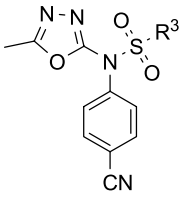
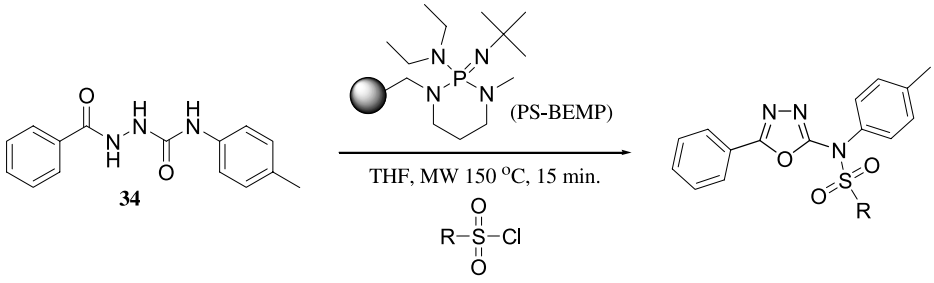
| Entry | Substrate | $R^3SO_2Cl$ | Product[a] | Yield[b] | Purity[c] |
|---|---|---|---|---|---|
| 1 |  | **12** |  | 83 | 90 |
| 2 | | **13** | | 80 | 90 |
| 3 | | **22** | | 84 | 90 |
| 4 |  | **14** |  | 70 | 90 |
| 5 | | **11** | | 79 | 95 |
| 6 | | **13** | | 77 | 95 |
| 7 |  | **14** |  | 76 | 92 |
| 8 | | **11** | | 98 | 98 |
| 9 | | **10** | | 89 | 98 |
| 10 | | **16** | | 70 | 95 |
| 11 |  | **32** |  | 89 | 90 |
| 12 | | **13** | | 80 | 90 |
| 13 |  | **13** |  | 81 | 90 |
| 14 | | **17** | | 80 | 90 |
| 15 | | **14** | | 80 | 90 |
| 16 | | **11** | | 89 | 90 |
| 17 |  | **32** |  | 98 | 98 |
| 18 | | **12** | | 83 | 95 |
| 19 | | **13** | | 88 | 98 |
| | | | Entry 17; X = 1:0 (S:O)<br>Entry 18; X = 2:1 (S:O)<br>Entry 19; X = 9:5 (S:O) | | |
| 20 |  | **13** |  | 70 | 90 |
| 21 | | **14** | | 81 | 90 |
| 22 | | **11** | | 78 | 95 |
| 23 |  | **13** |  | 85 | 90 |
| 24 | | **17** | | 88 | 90 |
| 25 | | **14** | | 88 | 90 |
| 26 | | **10** | | 90 | 90 |
| 27 |  | **12** |  | 79 | 95 |
| 28 | | **13** | | 81 | 95 |
| 29 | | **14** | | 90 | 95 |

Table 8 (*continued*)

| Entry | Substrate | $R^3SO_2Cl$ | Product[a] | Yield[b] | Purity[c] |
|---|---|---|---|---|---|
| 30 |  | **11** |  | 65 | 90 |
| 31 | | **13** | | 75 | 95 |
| 32 | | **17** | | 81 | 95 |

[a] General reaction conditions used were: substrate (0.5 mmol), BEMP (4.3 equiv, 2.2 mmol/g from Fluka) and sulfonylchloride (2.3 equiv) were irradiated in a microwave apparatus at 150 °C for 20 min.
[b] Yields of isolated products.
[c] Determined by LC-MS, 254 nm detection.

**Table 9**. Data for the synthesis of 2-sulfonamide-1,3,4-oxadiazoles **3** in a single pot reaction sequence, $RSO_2Cl$ compounds are listed in Table 3




| Entry | $RSO_2Cl$ | Yield (%)[a] | Purity (%)[b] |
|---|---|---|---|
| 1 | **10** | 78 | >99 |
| 2 | **13** | 61 | >99 |
| 3 | **14** | 75 | >99 |
| 4 | **28** | 80 | >99 |
| 5 | **15** | 80 | 98 |
| 6 | **16** | 65 | 98 |
| 7 | **11** | 77 | >99 |
| 8 | **12** | 73 | 98 |
| 9 | **17** | 43 | 95 |
| 10 | **20** | 71 | 95 |
| 11 | **19** | 58 | 95 |
| 12 | **21** | 72 | >99 |
| 13 | **18** | 68 | 95 |
| 14 | **10** | 70 | >99 |
| 15 | **28** | 49 | 89 |
| 16 | **30** | 44 | > 70 |
| 17 | **27** | 60 | >75 |
| 18 | **26** | 42 | > 70 |
| 19 | **31** | 70 | >99 |
| 20 | **32** | 60 | >99 |
| 21 | **22** | 66 | 85 |
| 22 | **23** | 75 | 90 |

[a] Yields of isolated products.
[b] Determined by LC-MS, 254 nm detection.

**Table A**. Elution gradient for LC-MS

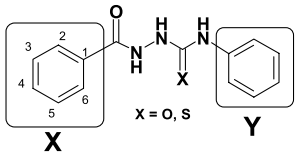
| Time/min | A %[a] | B %[b] | Flow rate (mL/min) |
|---|---|---|---|
| 0.00 | 95 | 5 | 0 |
| 3.00 | 5 | 95 | 0.6 |
| 5.00 | 5 | 95 | 0.6 |
| 5.50 | 95 | 5 | 0.6 |
| 8.00 | 95 | 5 | 0.6 |

[a] Water + 0.1% trifluoroacetic acid.
[b] Acetonitrile + 0.1% trifluoroacetic acid.

### 4.1. Preparation of 1,4-disubstituted (thio)semicarbazide 2

Isothiocyanate or isocyanate (5.5 mmol) was added to a solution of substituted hydrazines (5 mmol) in DMF (10 mL) and stirred for 4 h at ambient temperature. The reaction mixture was added to a suspension of polymer-supported sulfonic acid (MP-TsOH) (1.4 mmol, 1.5 mmol $g^{-1}$) and polymer supported-amine ($PS\text{-}NH_2$)

(1.4 mmol, 1.3 mmol N/g) in DMF (10 mL) and stirred for a further 12 h at ambient temperature. The resulting suspension was filtered to remove polymer-supported reagents and the solvent was removed in vacuo.




**4.1.1. 1-(4-Chlorobenzoyl)-4-(2,6-dimethylphenyl)semicarbazide.** LC-MS $R_f$ 3.222 M+H 318.1; $^1$H NMR ($d_6$-DMSO; 600 MHz) $\delta$ ppm 10.38 (1H, br s, NH), 8.10 (1H, br s, NH), 8.04 (1H, br s, NH), 7.94 (2H, d, $J$=8.8 Hz, $H_X$-2/6), 7.53 (2H, d, $J$=8.8 Hz, $H_X$-3/5), 7.04 (3H, m, $H_Y$-3/4/5), 2.19 (6H, s, 2×Me).

**4.1.2. 1-Benzoyl-4-(*p*-tolyl)semicarbazide 34.** LC-MS $R_f$ 3.543 M+H 270.1; $^1$H NMR ($d_6$-DMSO; 400 MHz) $\delta$ ppm 10.27 (1H, br s, NH), 8.77 (1H, br s, NH), 8.18 (1H, br s, NH), 7.94 (2H, d, $J$=7.6 Hz, $H_X$-2/6), 7.60 (1H, t, $J$=7.4 Hz, $H_X$-4), 7.52 (2H, br t, $H_X$-3/5), 7.38 (2H, d, $J$=8.1 Hz, $H_Y$-3/5), 7.04 (2H, d, $J$=8.1 Hz, $H_Y$-2/6), 2.23 (3H, s, Me); $^{13}$C NMR ($d_6$-DMSO; 100 MHz) $\delta$ ppm 166.79 (C), 156.06 (C), 137.48 (C), 132.09 (CH), 133.00 (C), 131.06 (C), 129.39 (CH), 128.72 (CH), 127.92 (CH), 119.02 (CH), 20.69 ($CH_3$). IR $\nu$ (neat)=3263.6 (w), 3059.1 (w), 1651 (m), 1644.4 (s), 1594.0 (m), 1537.7 (s), 1515.3 (m), 1493.0 (m), 1343.9 (m), 1329.9 (m), 1307.9 (m), 1290.3 (m), 1231.7 (s), 1193.3 (m), 916.8 (m), 826.3 (m), 807.8 (m), 784.8 (m), 774.7 (w), 755.6 (w), 687.6 (s) cm$^{-1}$. HRMS Calcd for $C_{15}H_{16}N_3O_2$ 270.1243; found 270.1239.

**4.1.3. 1-Benzoyl-4-(2,6-dimethylphenyl)semicarbazide 46.** LC-MS $R_f$ 2.853 M+H 286.1; $^1$H NMR ($d_6$-DMSO; 400 MHz) $\delta$ ppm 10.28 (1H, br s, NH), 8.07 (1H, br s, NH), 8.02 (1H, br s, NH), 7.94 (2H, d, $J$=7.3 Hz, $H_X$-2/6), 7.94 (1H, t, $J$=7.3 Hz, $H_X$-4), 7.47 (2H, t, $J$=7.3 Hz, $H_X$-3/5), 7.03 (3H, m, $H_Y$-3/4/5), 2.20 (6H, s, 2×Me); $^{13}$C NMR ($d_6$-DMSO; 100 MHz) $\delta$ ppm 166.89 (C), 157.03 (C), 136.42 (C), 135.77 (C), 133.15 (C), 131.99 (CH), 128.62 (CH), 128.01 (CH), 127.91 (CH), 126.35 (CH), 18.53 ($CH_3$).

**4.1.4. 1-(1*H*-indol-3-carbonyl)-4-benzyl semicarbazide.** LC-MS $R_f$ 3.008 M+H 309.1; $^1$H NMR ($d_6$-DMSO; 600 MHz) $\delta$ ppm 10.86 (1H, br s, NH), 9.88 (1H, br s, NH), 8.63 (1H, br s, NH), 8.05 (1H, br s, NH), 7.62 (1H, d, $J$=8.2 Hz), 7.41 (2H, d, $J$=8.2 Hz), 7.35 (1H, d, $J$=8.2 Hz), 7.25 (4H, m), 7.09 (1H, t, $J$=7.7 Hz), 6.98 (1H, t, $J$=7.4 Hz), 6.94 (1H, t, $J$=7.4 Hz), 3.62 (2H, s, $CH_2$).

**4.1.5. 1-Hexyl-4-(4-methoxyphenyl) semicarbazide.** LC-MS $R_f$ 3.699 M+H 308.2; $^1$H NMR ($d_6$-DMSO; 600 MHz) $\delta$ ppm 9.53 (1H, br s, NH), 8.46 (1H, br s, NH), 7.87 (1H, br s, NH), 7.32 (2H, d, $J$=8.3 Hz, X), 6.82 (2H, d, $J$=8.3 Hz, X), 3.68 (3H, s, OMe), 2.11 (2H, t, $J$=7.4 Hz, $H_X$-1), 1.52 (2H, m, $H_X$-2), 1.13 (8H, m), 0.84 (3H, t, $J$=7.2 Hz, $H_X$-7); $^1$H NMR ($d_6$-DMSO; 600 MHz) $\delta$ ppm 172.58 (C), 156.00 (C), 154.83 (C), 133.06 (C), 120.55 (CH), 114.19 (CH), 55.50 ($CH_3$), 33.57 ($CH_2$), 31.54 ($CH_2$), 28.95 ($CH_2$), 28.83 ($CH_2$), 25.27 ($CH_2$), 22.42 ($CH_2$), 14.29 ($CH_3$).

**4.1.6. 1-Pentyl-4-(4-methoxyphenyl)semicarbazide.** LC-MS $R_f$ 2.622 M+H 299.1; $^1$H NMR ($d_6$-DMSO; 600 MHz) $\delta$ ppm 9.84 (1H, br s, NH), 7.95 (1H, br s, NH), 7.90 (1H, br s, NH), 7.64 (2H, d, $J$=8.8 Hz, $H_X$-2/6), 7.06 (3H, m, $H_Y$-3/4/5), 6.57 (2H, d, $J$=8.8 Hz, $H_X$-3/5), 5.64 (2H, s, $NH_2$), 2.20 (6H, s, 2×Me).

**4.1.7. 1-Nicotinoyl-4-(3-chloropropane)semicarbazide.** LC-MS $R_f$ 1.025 M+H 257.0; $^1$H NMR ($d_6$-DMSO; 600 MHz) $\delta$ ppm 10.32 (1H, br s, NH), 9.05 (1H, br s, NH), 8.72 (1H, br s, NH), 8.22 (1H, dt, $J$=7.7, 1.6 Hz, X), 7.95 (1H, s, X), 7.53 (1H, dd, $J$=X Hz, X), 6.72 (1H, br s, X), 3.62 (2H, t, $J$=6.6 Hz, $H_Y$-3), 3.15 (2H, dt, $J$=6.6, 6.0 Hz, $H_Y$-1), 1.85 (3H, tt, $J$=6.6, 6.0 Hz, $H_Y$-2).

**4.1.8. 1-(4-Nitrobenzoyl)-4-(4-methoxyphenyl)semicarbazide.** LC-MS $R_f$ 2.990 M+H 331.1; $^1$H NMR ($d_6$-DMSO; 600 MHz) $\delta$ ppm 10.58 (1H, br s, NH), 8.72 (1H, br s, NH), 8.31 (2H, d, $J$=8.8 Hz, $H_X$-3/5), 8.21 (1H, br s, NH), 8.12 (2H, d, $J$=8.8 Hz, $H_X$-2/6), 7.35 (2H, d, $J$=8.8 Hz, $H_Y$-2/6), 6.83 (2H, d, $J$=8.8 Hz, $H_Y$-3/5), 3.70 (3H, s, OMe).

**4.1.9. 1-(Propan-3-ol)-4-(4-methoxyphenyl)semicarbazide.** LC-MS $R_f$ 1.630 M+H 250.1; $^1$H NMR ($d_6$-DMSO; 600 MHz) $\delta$ ppm 9.53 (1H, br s, NH), 8.48 (1H, br s, NH), 7.84 (1H, br s, NH), 7.32 (2H, d, $J$=8.7 Hz, X), 6.82 (2H, d, $J$=8.7 Hz, $H_Y$-3/5), 3.69 (3H, s, OMe), 3.41 (2H, m, $H_X$-3), 2.17 (2H, t, $J$=7.5 Hz, $H_X$-1), 1.69 (2H, m, $H_X$-2).

**4.1.10. 1-(3-Hydroxynaphthoyl-2-)-4-(2,6-dimethylphenyl)semicarbazide 45.** LC-MS (Method B) $R_f$ 4.00 M+H 348.3; $^1$H NMR ($d_6$-DMSO; 600 MHz) $\delta$ ppm 11.52 (1H, br s, OH), 10.58 (1H, br s, NH), 8.53 (1H, br s, NH), 8.38 (1H, br s, NH), 8.11 (1H, s), 7.87 (1H, d, $J$=8.4 Hz), 7.73 (1H, d, $J$=8.4 Hz), 7.50 (1H, m), 7.35 (1H, m), 7.26 (1H, s), 7.04 (3H, m), 2.20 (6H, s, 2×Me).

**4.1.11. 1-Nicotinoyl-4-*tert*-butyl semicarbazide.** LC-MS (Method B) $R_f$ 2.60 M−H 236.4; $^1$H NMR ($d_6$-DMSO; 400 MHz) $\delta$ ppm 10.26 (1H, br s, NH), 9.03 (1H, d, $J$=2.2 Hz, $H_X$-2), 8.73 (1H, dd, $J$=4.7, 1.8 Hz, $H_X$-4), 8.21 (1H, dt, $J$=8.05, 1.8 Hz, $H_X$-6), 7.72 (1H, br s, NH), 7.52 (1H, dd, $J$=8.05, 4.7 Hz, $H_X$-5), 6.18 (1H, br s, NH), 1.24 (9H, s, 3×Me).

**4.1.12. 1-Nicotinoyl-4-hexyl semicarbazide.** LC-MS $R_f$ 2.443 M+H 265.2; $^1$H NMR ($d_6$-DMSO; 400 MHz) $\delta$ ppm 10.30 (1H, br s, NH), 9.05 (1H, d, $J$=1.8 Hz, $H_X$-2), 8.72 (1H, dd, $J$=4.8, 1.8 Hz, $H_X$-4), 8.22 (1H, dt, $J$=8.05, 1.8 Hz, $H_X$-6), 7.88 (1H, br s, NH), 7.53 (1H, ddd, $J$=8.05, 4.8, 0.7 Hz, $H_X$-5), 6.56 (1H, t, $J$=5.12 Hz, NH), 3.02 (2H, m, $H_Y$-1), 1.39 (2H, m, $H_Y$-2), 1.25 (6H, m), 1.24 (3H, t, $J$=7.3 Hz, Me); $^{13}$C NMR ($d_6$-DMSO; 100 MHz) $\delta$ ppm 165.30 (C), 158.54 (C), 152.49 (CH), 148.94 (CH), 135.68 (CH), 128.84 (C), 123.82 (CH), 39.60 ($CH_2$), 31.42 ($CH_2$), 30.18 ($CH_2$), 26.34 ($CH_2$), 22.44 ($CH_2$), 14.29 ($CH_3$).

**4.1.13. 1-Methyl-4-(adamantane)thiosemicarbazide.** LC-MS $R_f$ 3.004 M+H 268.1; $^1$H NMR ($d_6$-DMSO;

600 MHz) $\delta$ ppm 9.64 (1H, br s, NH), 8.92 (1H, br s, NH), 7.06 (1H, br s, NH), 2.18 (6H, m), 1.98 (3H, m), 1.85 (3H, s, $H_Z$-Me), 1.60 (6H, m); $^{13}$C NMR ($d_6$-DMSO; 125 MHz) $\delta$ ppm 186.76 (C), 170.50 (C), 41.32 ($CH_2$), 36.35 ($CH_2$), 29.43 (CH), 29.41 (CH), 21.07 ($CH_3$).

**4.1.14. 1-(3-Methoxyphenyl)-4-(3-nitro-4-fluorophenyl)-semicarbazide.** LC-MS $R_f$ 2.727 M+H 315.1; $^1$H NMR ($d_6$-DMSO; 400 MHz) $\delta$ ppm 10.29 (1H, br s, NH), 9.34 (1H, br s, NH), 8.50 (1H, br s, NH), 8.40 (1H, dd, $J$=6.8, 2.7 Hz), 7.84 (1H, m), 7.51–7.47 (3H, m), 7.45 (1H, t, $J$=7.9 Hz), 7.14 (1H, m), 3.81 (3H, s, OMe); $^{13}$C NMR ($d_6$-DMSO; 100 MHz) $\delta$ ppm 166.59 (C), 159.55 (C), 148.69 (C), 137.13 (C), 137.10 (C), 136.65 (C), 134.25 (C), 129.91 (CH), 120.22 (CH), 118.98 (CH), 118.77 (CH), 118.09 (CH), 115.17 (CH), 113.09 (CH), 55.70 ($CH_3$).

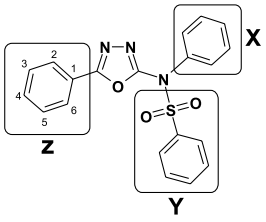
**4.1.15. 1-(3,4-Dimethoxyphenylmethylene)-4-ethyl semicarbazide.** LC-MS $R_f$ 1.966 M+H 282.1; $^1$H NMR ($d_6$-DMSO; 400 MHz) $\delta$ ppm 9.64 (1H, br s, NH), 7.70 (1H, br s, NH), 6.90 (1H, br s, NH), 6.85 (1H, d, $J$=8.2 Hz), 6.78 (1H, d, $J$=8.2 Hz), 6.26 (1H, m), 3.72 (3H, s, OMe), 3.69 (3H, s, OMe), 3.34 (2H, s, $CH_2$Ph), 3.05 (2H, m, $H_Y$-1), 0.93 (3H, t, $J$=7.05 Hz, $H_Y$-2); $^{13}$C NMR ($d_6$-DMSO; 100 MHz) $\delta$ ppm 170.55 (C), 158.30 (C), 148.78 (C), 147.83 (C), 128.54 (C) 121.69 (CH), 113.25 (CH), 112.02 (CH), 55.87 ($CH_3$), 55.73 ($CH_3$), 40.12 ($CH_2$), 34.35 ($CH_2$), 15.86 ($CH_3$).

### 4.2. General procedure for 1

A mixture of acylhydrazide **3** (0.5 mmol) and isocyanate **4** (1 equiv) in $CH_3CN$ (5 mL) in a microwave tube was stirred for 5 min. PS-BEMP (4.3 equiv, 2.2 mmol/g from Fluka) and sulfonylchloride (2.3 equiv) were added and the reaction was irradiated in a microwave apparatus at 150 °C for 20 min. After cooling to room temperature in the microwave cavity the reaction mixture was purified on silica cartridge using DCM (15 mL) as eluent. The organic solvent were evaporated and the residue precipitated with $Et_2O$ or $i$Pr$_2$O.

### 4.3. General procedure for 2

A mixture of acylhydrazide **3** (0.5 mmol) and isocyanate **4** (1 equiv) in THF (5 mL) in a microwave tube was stirred for 5 min. PS-DMAP (3 equiv, 2.2 mmol/g from Fluka) and TsCl (1.8 equiv) were added and the reaction was irradiated in a microwave apparatus at 120 °C for 30 min. After cooling to room temperature in the microwave cavity the reaction mixture was purified on SCXII cartridge.




**4.3.1. (5-Phenyl-[1,3,4]oxadiazol-2-yl)-4-methylbenzeneamine 35.** LC-MS $R_f$ 3.028 M+H 252.1; $^1$H NMR ($CDCl_3$; 600 MHz) $\delta$ ppm 9.64 (1H, br s, NH), 8.81 (2H, m, $H_Z$-2/6), 7.37 (5H, m, $H_Z$-3/4/5 and $H_X$-3/4), 6.92 (2H, d, $J$=8.3 Hz, $H_X$-2/6), 2.11 (3H, s, $H_X$-Me); $^{13}$C NMR ($d_6$-DMSO; 125 MHz) $\delta$ ppm 135.94 (C), 133.56 (C), 131.59 (C), 130.51 (CH), 129.44 (CH), 128.79 (CH), 125.68 (CH), 124.28 (C), 117.59 (CH), 95.23 (C), 20.57 ($CH_3$). IR $\nu$ (neat)=3292 (w), 3045.1 (w), 1610.8 (s), 1580.3 (s), 1556.9 (m), 1543.3 (m), 1516.5 (m), 1488.4 (m), 1446.8 (w), 1417.4 (w), 1321.4 (w), 1298.8 (w), 1287.0 (w), 1244.0 (w), 1231.1 (w), 1127.6 (w), 1067.4 (w), 1049.7 (m), 1024.4 (m), 958.9 (w), 866.8 (w), 817.3 (s), 797.6 (m), 767.2 (s), 718.8 (s), 680.6 (s) cm$^{-1}$. HRMS Calcd for $C_{15}H_{14}N_3O$ 252.1137; found 252.1139. Anal. ($C_{15}H_{13}N_3O$) Calcd C 71.70, H 5.21, N 16.72, O 6.37; found C 71.79, H 5.20, N 16.77, O 6.24. The crystal structure has been deposited at the Cambridge Crystallographic Data Centre under the deposition number 252367.

**4.3.2. 4-Methyl-*N*-(5-phenyl-[1,3,4]oxadiazol-2-yl)-*N*-4-methylbenzenesulfonamide 36.** LC-MS $R_f$ 3.559 M+H 406.1; $^1$H NMR ($d_6$-DMSO; 400 MHz) $\delta$ ppm 7.88 (2H, m, $H_Z$-2/6), 7.77 (2H, d, $J$=8.4 Hz, $H_Y$-2/6), 7.64–7.55 (3H, m), 7.51 (2H, m), 7.26 (2H, d, $J$=8.6 Hz), 7.21 (2H, d, $J$=8.6 Hz), 2.43 (3H, s, Me), 2.31 (3H, s, Me); $^{13}$C NMR ($d_6$-DMSO; 100 MHz) $\delta$ ppm 163.38 (C), 158.66 (C), 146.02 (C), 140.06 (C), 134.08 (CH), 133.10 (C), 131.88 (C), 130.98 (CH), 130.48 (CH), 129.87 (CH), 128.82 (CH), 128.77 (CH), 126.68 (CH), 123.21 (C), 21.55 ($CH_3$), 21.05 ($CH_3$). IR $\nu$ (neat)=1596.1 (w), 1564.1 (s), 1542.4 (m), 1506.9 (m), 1490.1 (m), 1449.4 (m), 1361.2 (s), 1294.7 (w), 1266.9 (m), 1208.0 (m), 1190.0 (m), 1167.2 (s), 1021.8 (m), 965.9 (m), 957.7 (m), 936.3 (s), 815.1 (s), 777.0 (m), 711.0 (s), 685.9 (s), 666.5 (s) cm$^{-1}$. HRMS Calcd for $C_{22}H_{20}N_3O_3S$ 406.1225; found 406.1220. Anal. ($C_{22}H_{19}N_3O_3S$) Calcd C 65.17, H 4.72, N 10.36, O 11.84, S 7.91; found C 65.29, H 4.88, N 10.21. The crystal structure has been deposited at the Cambridge Crystallographic Data Centre under the deposition number 252366.

**4.3.3. 5-Phenyl-4-*p*-tolyl-2,4-dihydro-[1,2,4]triazol-3-one 43.** MS $R_f$ 3.721 M+H 252.10; $^1$H NMR ($d_6$-DMSO; 400 MHz) $\delta$ ppm 7.41–7.24 (5H, m, Ph), 7.19 (2H, d, $J$=8.05 Hz, $H_Y$-3/5), 7.08 (2H, d, $J$=8.05 Hz, $H_Y$-2/6), 2.33 (3H, s, Me); $^{13}$C NMR ($d_6$-DMSO; 100 MHz) $\delta$ ppm 155.01 (C), 145.77 (C), 138.38 (C), 131.53 (C), 130.13 (CH), 130.09 (CH), 128.86 (C), 127.92 (CH), 127.85 (CH), 127.53 (C), 21.04 ($CH_3$). IR $\nu$ (neat)=3151.7 (w), 3040.0 (w), 1692.5 (s), 1579.2 (w), 1550.9 (w), 1514.8 (m), 1494.3 (w), 1448.4 (m), 1417.3 (m), 1328.4 (m), 1180.1 (w), 1141.8 (w), 1108.5 (w), 1039.9 (w), 967.4 (w), 939.0 (w), 803.7 (m), 776.2 (s), 745.6 (s), 696.6 (s), 676.8 (w) cm$^{-1}$. HRMS Calcd for $C_{15}H_{14}N_3O$ 252.1137; found 252.1144. Anal. ($C_{15}H_{13}N_3O$) Calcd C 71.70, H 5.21, N 16.72, O 6.37; found C 71.67, H 5.23, N 16.78, O 6.31. The crystal structure has been deposited at the Cambridge Crystallographic Data Centre under the deposition number 252368.

**4.3.4. 5-Phenyl-2-(toluene-4-sulfonyl)-4-*p*-tolyl-2,4-dihydro-[1,2,4]triazol-3-one 44.** MS $R_f$ 2.987 M+H 406.1; $^1$H NMR ($d_6$-DMSO; 400 MHz) $\delta$ ppm 7.94 (2H, d, $J$=8.05 Hz), 7.52 (2H, d, $J$=8.05 Hz), 7.44 (1H, m), 7.39–7.30 (4H, m), 7.30–7.15 (4H, m), 2.41 (3H, s, Me), 2.28 (3H, s, Me); $^{13}$C NMR ($d_6$-DMSO; 100 MHz) $\delta$ ppm 150.68 (C),

148.36 (C), 146.56 (C), 139.45 (C), 134.20 (C), 131.40 (CH), 130.73 (CH), 130.27 (CH), 130.19 (C), 128.95 (CH), 128.69 (CH), 128.19 (CH), 128.08 (CH), 125.69 (C), 21.58 ($CH_3$), 21.05 ($CH_3$). IR $\nu$ (neat)=1739.1 (s), 1593.1 (w), 1548.0 (w), 1515.4 (m), 1496.7 (m), 1450.5 (m), 1386.1 (s), 1318.4 (m), 1207.6 (s), 1191.9 (s), 1175.5 (s), 1149.8 (m), 1091.4 (m), 1073.7 (w), 963.1 (m), 846.7 (w), 823.0 (m), 785.2 (m), 739.0 (s), 692.7 (s), 661.6 (s) $cm^{-1}$. HRMS Calcd for $C_{22}H_{20}N_3O_3S$ 406.1225; found 406.1229. ($C_{22}H_{19}N_3O_3S$) Calcd C 65.17, H 4.72, N 10.36, O 11.84, S 7.91; found C 65.20, H 4.78, N 10.42. The crystal structure has been deposited at the Cambridge Crystallographic Data Centre under the deposition number 252365.

**4.3.5. Benzyl-[5-(4-bromo-2-chlorophenyl)-[1,3,4]oxadiazol-2-yl]amine 47.** $^1$H NMR ($CDCl_3$; 400 MHz) $\delta$ ppm 8.04 (1H, d, $J$=2.6 Hz, $H_Z$-6), 7.50 (1H, dd, $J$=8.4, 2.6 Hz, $H_Z$-Ar), 7.45–7.30 (6H, m, $H_Z$-Ar/$H_X$-Ph), 5.12 (1H, t, $J$=5.6 Hz, NH), 4.63 (2H, d, $J$=5.6 Hz, $H_X$-1).

**4.3.6. Ethyl-[5-(4-nitrophenyl)-[1,3,4]oxadiazol-2-yl]-amine 48.** LC-MS $R_f$ 2.926 M+H 235.1; $^1$H NMR ($CDCl_3$; 400 MHz) $\delta$ ppm 8.32 (2H, d, $J$=9.15 Hz, $H_Z$-3/5), 8.08 (2H, d, $J$=9.15 Hz, $H_Z$-2/6), 4.80 (1H, br t, NH), 3.53 (2H, dq, $J$=7.1, 5.8 Hz, $H_X$-1), 1.34 (3H, t, $J$=7.1 Hz, $H_X$-2).

**4.3.7. Phenethyl-(5-pyridin-3-yl-[1,3,4]oxadiazol-2-yl)-amine 49.** $^1$H NMR ($d_6$-DMSO; 500 MHz) $\delta$ ppm 9.05 (1H, d, $J$=1.6 Hz, $H_Z$-2), 8.82 (1H, d, $J$=4.7, 1.6 Hz, $H_Z$-4), 8.26 (1H, ddd, $J$=7.9, 2.2, 1.9 Hz, $H_Z$-6), 7.66 (1H, ddd, $J$=7.9, 4.7, 1.6 Hz, $H_Z$-5), 7.24 (5H, m, $H_X$-Ph), 4.12 (2H, t, $J$=7.25 Hz, $H_X$-1), 3.05 (2H, t, $J$=7.25 Hz, $H_X$-2); $^{13}$C NMR ($d_6$-DMSO; 125 MHz) $\delta$ ppm 161.05 (C), 158.77 (C), 153.04 (CH), 147.34 (CH), 142.66 (CH), 137.82 (C), 135.77 (C), 134.34 (CH), 130.75 (CH), 129.37 (CH), 128.88 (CH), 35.10 ($CH_2$), 31.15 ($CH_2$). IR $\nu$ (neat)=1675.8 (m), 1632.3 (w), 1585.2 (m), 1568.1 (m), 1545.3 (m), 1370.2 (m), 1199.9 (s), 1165.0 (s), 1128.9 (s), 1023.9 (m), 1006.7 (m), 822.9 (m), 799.2 (m), 757.6 (s), 720.0 (s), 701.1 (s), 683.3 (s) $cm^{-1}$. HRMS Calcd for $C_{15}H_{15}N_4O$ 267.1246; found 267.1249.

**4.3.8. [5-(4-Chlorophenyl)-[1,3,4]oxadiazol-2-yl]-ethyl-amine 50.** LC-MS $R_f$ 3.188 M+H 224.0 and 226.0; $^1$H NMR ($CDCl_3$; 400 MHz) $\delta$ ppm 7.85 (2H, d, $J$=8.8 Hz, $H_Z$-3/5), 7.43 (2H, d, $J$=8.8 Hz, $H_Z$-2/6), 4.96 (1H, br s, NH), 3.49 (2H, dq, $J$=7.3, 5.8 Hz, $H_X$-1), 1.34 (3H, t, $J$=7.3 Hz, $H_X$-2).

**4.3.9. Phenethyl-[5-(4-trifluoromethylphenyl)-[1,3,4]-oxadiazol-2-yl]amine 51.** LC-MS $R_f$ 3.697 M+H 334.1; $^1$H NMR ($CDCl_3$; 400 MHz) $\delta$ ppm 8.02 (2H, d, $J$=8.05 Hz, $H_Z$-3/5), 7.73 (2H, d, $J$=8.05 Hz, $H_Z$-2/6), 7.34 (2H, m, $H_X$-Ph), 7.25 (3H, m, $H_X$-Ph), 4.96 (1H, t, $J$=6.4 Hz, NH), 3.76 (2H, dt, $J$=7.3, 6.4 Hz, $H_X$-1), 3.02 (2H, t, $J$=7.3 Hz, $H_X$-2).

**4.3.10. (3,4-Dichlorophenyl)-(5-pyridin-3-yl-[1,3,4]oxadiazol-2-yl)amine 52.** $^1$H NMR ($d_6$-DMSO; 500 MHz) $\delta$ ppm 11.20 (1H, br s, NH), 9.08 (1H, dd, $J$=2.2, 0.6 Hz, $H_Z$-2), 8.76 (1H, dd, $J$=4.7, 1.6 Hz, $H_Z$-4), 8.27 (1H, dt, $J$=8.2, 1.9 Hz, $H_Z$-6), 7.95 (1H, d, $J$=2.5 Hz, $H_X$-2), 7.63 (1H, d, $J$=8.8 Hz, $H_X$-5), 7.62 (1H, ddd, $J$=8.2, 4.7, 0.95 Hz, $H_Z$-5), 7.55 (1H, dd, $J$=8.8, 2.5 Hz, $H_X$-6); $^{13}$C NMR ($d_6$-DMSO; 125 MHz) $\delta$ ppm 160.15 (C), 156.78 (C), 152.19 (C), 146.85 (CH), 139.09 (C), 133.70 (CH), 131.88 (C), 131.49 (CH), 124.18 (CH), 123.98 (C), 120.69 (C), 118.82 (CH), 117.93 (CH). IR $\nu$ (neat)=1634.4 (s), 1610.8 (m), 1588.5 (s), 1571.4 (m), 1556.9 (m), 1549.5 (m), 1477.1 (s), 1401.9 (m), 1302.2 (w), 1250.2 (w), 1135.1 (w), 1058.2 (m), 1027.9 (m), 957.4 (m), 867.8 (m), 813.7 (m), 797.5 (s), 700.5 (s), 681.9 (m), 674.3 (m) $cm^{-1}$. HRMS Calcd for $C_{13}H_9N_4OCl_2$ 307.0153; found 307.0145.

**4.3.11. *N*-[5-(2-Chlorophenyl)-[1,3,4]oxadiazol-2-yl]-*N*-(2,6-dimethylphenyl)-4-nitro-benzenesulfonamide 53.** $^1$H NMR ($d_6$-DMSO; 500 MHz) $\delta$ ppm 8.56 (2H, d, $J$=9.1 Hz, $H_Y$-3/5), 8.42 (2H, d, $J$=9.1 Hz, $H_Y$-2/6), 7.84 (1H, d, $J$=7.6, 1.6 Hz, $H_Z$-Ar), 7.63 (2H, m, 2×$H_Z$-Ar), 7.55 (1H, m, $H_Z$-Ar), 7.36 (1H, t, $J$=7.6 Hz, $H_X$-4), 7.26 (2H, d, $J$=7.6 Hz, $H_X$-3/5), 2.10 (6H, s, 2×Me); $^{13}$C NMR ($d_6$-DMSO; 125 MHz) $\delta$ ppm 160.74 (C), 158.20 (C), 151.55 (C), 143.07 (C), 134.10 (C), 134.20 (C), 133.92 (CH), 132.14 (C), 131.77 (CH), 131.49 (CH), 131.19 (CH), 130.79 (CH), 129.85 (CH), 128.40 (CH), 125.42 (CH), 122.40 (C), 18.53 ($CH_3$). IR $\nu$ (neat)=1630.2 (m), 1606.9 (w), 1556.8 (m), 1530.1 (s), 1515.6 (s), 1488.1 (w), 1449.1 (w), 1404.8 (w), 1384.0 (s), 1347.4 (s), 1318.2 (w), 1304.9 (w), 1278.9 (m), 1196.1 (w), 1176.8 (s), 1165.2 (s), 1110.9 (m), 1084.1 (m), 1010.2 (m), 928.8 (m), 905.8 (m), 888.3 (s), 861.6 (s), 853.9 (s), 769.2 (m), 758.9 (m), 738.6 (s), 695.1 (s), 679.9 (s) $cm^{-1}$. HRMS Calcd for $C_{22}H_{17}N_4O_5SCl$ 485.0686; found 485.0702.

**4.3.12. 3,4-Dimethoxy-*N*-[5-(3,4-dimethoxyphenyl)-[1,3,4]oxadiazol-2-yl]-*N*-phenyl-benzenesulfonamide 54.** $^1$H NMR ($d_6$-DMSO; 500 MHz) $\delta$ ppm 7.52–7.45 (3H, m), 7.38 (1H, dd, $J$=2.5, 1.6 Hz), 7.31 (1H, d, $J$=2.5 Hz), 7.23 (1H, d, $J$=8.8 Hz), 7.20 (1H, ddd, $J$=8.2, 2.5, 0.95 Hz), 7.02 (2H, d, $J$=9.1 Hz), 3.90 (3H, s, OMe), 3.85 (3H, s, OMe), 3.80 (3H, s, OMe), 3.79 (3H, s, OMe); $^{13}$C NMR ($d_6$-DMSO; 125 MHz) $\delta$ ppm 163.21 (C), 160.53 (C), 160.13 (C), 159.08 (C), 154.30 (C), 149.18 (C), 131.29 (CH), 130.81 (CH), 129.11 (C), 128.02 (C), 124.53 (C), 123.34 (CH), 119.04 (CH), 118.59 (CH), 115.30 (CH), 111.88 (CH), 111.61 (CH), 111.02 (CH), 56.53 ($CH_3$), 56.26 ($CH_3$), 55.99 ($CH_3$), 55.92 ($CH_3$). IR $\nu$ (neat)=1604.9 (w), 1586.8 (w), 1560.3 (m), 1542.6 (m), 1508.4 (s), 1491.9 (s), 1462.4 (m), 1445.5 (w), 1436.9 (w), 1411.7 (w), 1364,2 (s), 1346.5 (w), 1320.8 (w), 1267.4 (s), 1250.8 (m), 1232.6 (s), 1202.4 (m), 1183.8 (m), 1163.6 (s), 1137.8 (m), 1096.3 (m), 1071.3 (w), 1030.2 (s), 1017.8 (s), 990.6 (w), 951.4 (m), 925.9 (m), 873.5 (w), 852.3 (s), 833.0 (w), 797.4 (m), 767.4 (w), 723.0 (m), 700.2 (m), 674.7 (s) $cm^{-1}$. HRMS Calcd for $C_{24}H_{24}N_3O_7S$ 498.1335; found 498.1345.

**4.3.13. 4-Nitro-*N*-[5-(2-nitrophenyl)-[1,3,4]oxadiazol-2-yl]-*N*-phenyl-benzenesulfonamide 55.** $^1$H NMR ($d_6$-DMSO; 500 MHz) $\delta$ ppm 8.51 (2H, d, $J$=9.1 Hz, $H_Y$-3/5), 8.19 (1H, m, $H_Z$-5), 8.16 (2H, d, $J$=9.1 Hz, $H_Y$-2/6), 7.99–7.90 (3H, m, $H_Z$-3/4/6), 7.54 (3H, m, 3×$H_X$-Ar), 7.38 (2H, m, 2×$H_X$-Ar); $^{13}$C NMR ($d_6$-DMSO; 125 MHz) $\delta$ ppm 160.13 (C), 158.92 (C), 151.47 (C), 148.07 (C), 141.95 (C), 135.86 (C), 134.40 (CH), 134.21 (CH), 132.00 (CH), 130.90 (CH), 130.66 (CH), 130.58 (CH), 129.31 (CH),

125.44 (CH), 125.40 (CH), 116.98 (C). IR $\nu$ (neat)=1608.2 (w), 1573.0 (w), 1557.4 (m), 1529.3 (s), 1486.8 (w), 1405.2 (w), 1382.7 (m), 1365.4 (w), 1342.1 (s), 1315.7 (w), 1273.8 (m), 1200.9 (m), 1177.1 (s), 1085.8 (w), 1021.8 (w), 963.3 (w), 942.6 (m), 913.0 (w), 854.7 (s), 789.4 (m), 738.5 (s), 711.1 (m), 697.4 (s), 680.4 (s), 654.8 (s) $cm^{-1}$. HRMS Calcd for $C_{20}H_{14}N_5O_7S$ 468.0614; found 468.0700.

**4.3.14. 3,4-Dimethoxy-*N*-phenyl-*N*-(5-phenyl-[1,3,4]oxadiazol-2-yl)benzenesulfonamide 56.** $^1H$ NMR ($d_6$-DMSO; 500 MHz) $\delta$ ppm 7.90 (2H, m), 7.62 (3H, m), 7.50 (4H, m), 7.38 (2H, m), 7.29 (1H, d, $J$=2.5 Hz), 7.23 (1H, d, $J$=8.8 Hz), 3.90 (3H, s, OMe), 3.88 (3H, s, OMe); $^{13}C$ NMR ($d_6$-DMSO; 125 MHz) $\delta$ ppm 163.51 (C), 158.81 (C), 154.36 (C), 149.17 (C), 136.83 (C), 132.73 (CH), 130.24 (CH), 129.94 (CH), 129.92 (C), 129.12 (CH), 127.92 (C), 126.78 (CH), 123.37 (CH), 123.35 (CH), 111.94 (CH), 111.01 (CH), 56.55 ($CH_3$), 56.25 ($CH_3$). IR $\nu$ (neat)=1592.4 (w), 1568.1 (w), 1536.9 (s), 1508.4 (s), 1490.8 (m), 1470.3 (w), 1452.5 (w), 1439.3 (w), 1414.3 (s), 1366.5 (m), 1281.9 (m), 1264.0 (s), 1242.6 (m), 1182.8 (w), 1167.1 (s), 1143.5 (m), 1092.1 (s), 1019.3 (s), 964.3 (w), 946.0 (w), 916.6 (w), 887.6 (w), 846.5 (w), 819.5 (w), 767.9 (w), 717.7 (m), 699.2 (m), 691.9 (s), 685.5 (s), 675.6 (s), 654.5 (w) $cm^{-1}$. HRMS Calcd for $C_{22}H_{20}N_3O_5S$ 438.1124; found 438.1113.

**4.3.15. *N*-(4-Methoxy-phenyl)-4-nitro-*N*-[5-(4-nitrophenyl)-[1,3,4]oxadiazol-2-yl]-benzenesulfonamide 57.** $^1H$ NMR ($d_6$-DMSO; 500 MHz) $\delta$ ppm 8.52 (2H, d, $J$=8.5 Hz, $H_Y$-3/5), 8.39 (2H, d, $J$=8.8 Hz, $H_Z$-3/5), 8.21 (2H, d, $J$=8.5 Hz, $H_Y$-2/6), 8.10 (2H, d, $J$=8.8 Hz, $H_Z$-2/6), 7.33 (2H, d, $J$=8.7 Hz, $H_X$-2/6), 7.04 (2H, d, $J$=8.7 Hz, $H_X$-3/5), 3.79 (3H, s, OMe); $^{13}C$ NMR ($d_6$-DMSO; 125 MHz) $\delta$ ppm 161.79 (C), 160.80 (C), 159.03 (C), 151.34 (C), 149.64 (C), 143.52 (C), 141.95 (C), 130.95 (CH), 130.66 (CH), 128.10 (CH), 128.04 (C), 125.30 (CH), 125.02 (CH), 115.49 (CH), 55.97 ($CH_3$). IR $\nu$ (neat)=1606.4 (w), 1555.9 (w), 1542.2 (w), 1531.6 (s), 1519.1 (s), 1506.1 (s), 1448.5 (w), 1379.8 (m), 1341.5 (s), 1314.8 (m), 1305.0 (m), 1255.9 (s), 1195.3 (w), 1170.5 (s), 1110.8 (m), 1101.1 (w), 1057.5 (m), 1034.8 (m), 1009.5 (m), 914.8 (w), 897.9 (w), 854.0 (s), 831.8 (w), 739.3 (s), 716.4 (w), 703.8 (m), 680.5 (m) $cm^{-1}$. HRMS Calcd for $C_{21}H_{17}N_5O_8S$ 498.0720; found 498.0773.

**4.3.16. *N*-[5-(2-Chlorophenyl)-[1,3,4]oxadiazol-2-yl]-*N*-(2,6-dimethylphenyl)benzenesulfonamide 58.** $^1H$ NMR ($d_6$-DMSO; 500 MHz) $\delta$ ppm 8.16 (2H, dd, $J$=8.5, 1.3 Hz, $H_Y$-2/6), 7.88 (2H, m), 7.77 (2H, m), 7.64 (2H, m), 7.54 (1H, m), 7.32 (1H, m), 7.23 (2H, X, m), 2.09 (6H, s, 2×Me); $^{13}C$ NMR ($d_6$-DMSO; 125 MHz) $\delta$ ppm 160.49 (C), 158.60 (C), 139.00 (C), 138.13 (C), 135.63 (CH), 134.58 (C), 133.86 (CH), 132.10 (C), 131.73 (CH), 131.48 (CH), 130.51 (CH), 130.22 (CH), 129.72 (CH), 129.25 (CH), 128.40 (CH), 122.55 (C), 18.41 ($CH_3$). IR $\nu$ (neat)=1581.0 (m), 1566.9 (s), 1532.4 (w), 1448.8 (m), 1363.6 (s), 1289.9 (m), 1278.7 (w), 1195.4 (w), 1179.7 (s), 1088.5 (m), 1027.0 (w), 966.9 (w), 943.5 (m), 900,4 (w), 777.7 (m), 728.2 (s), 718.8 (m), 684.0 (s) $cm^{-1}$. HRMS Calcd for $C_{22}H_{19}N_3O_3SCl$ 440.0836; found 440.0840.

**4.3.17. *N*-Phenyl-*N*-[5-(4-trifluoromethylphenyl)-[1,3,4]-oxadiazol-2-yl]benzenesulfonamide 59.** $^1H$ NMR ($d_6$-DMSO; 500 MHz) $\delta$ ppm 8.13–7.71 (9H, m), 7.58–7.34 (6H, m); $^{13}C$ NMR ($d_6$-DMSO; 125 MHz) $\delta$ ppm 162.35 (C), 159.04 (C), 136.97 (C), 136.41 (C), 135.45 (CH), 130.46 (CH), 130.31 (CH), 130.19 (CH), 129.96 (CH), 128.88 (CH), 127.65 (CH), 127.12 (C), 126.90 and 126.87 ($CF_3$). IR $\nu$ (neat)=1538.6 (s), 1492.7 (w), 1447.7 (w), 1397.7 (w), 1325.9 (s), 1284.1 (w), 1182.3 (m), 1163.7 (m), 1123.1 (m), 1092.8 (m), 1066.7 (m), 1011.7 (w), 964.1 (w), 944.7 (w), 915.3 (w), 853.6 (m), 757.5 (w), 724.6 (s), 715.8 (m), 695.0 (s), 683.0 (s) $cm^{-1}$. HRMS Calcd for $C_{21}H_{15}N_3O_3SF_3S$ 446.0786; found 446.0923.

**4.3.18. 4-Chloro-*N*-[5-(4-methoxyphenyl)-[1,3,4]oxadiazol-2-yl]-*N*-3-methoxyphenyl-benzenesulfonamide 60.** $^1H$ NMR ($d_6$-DMSO; 500 MHz) $\delta$ ppm 7.91 (2H, d, $J$=8.6 Hz, $H_Y$-2/6), 7.80 (2H, d, $J$=8.6 Hz, $H_Y$-3/5), 7.51 (1H, t, $J$=8.0 Hz, $H_Z$-Ar), 4.47 (1H, dt, $J$=8.0, 1.3 Hz, $H_Z$-Ar), 7.38 (1H, dd, $J$=2.5, 1.6 Hz, $H_Z$-2), 7.30 (2H, d, $J$=9.1 Hz, $H_X$-3/5), 7.21 (1H, ddd, $J$=8.0, 2.5, 1.3 Hz, $H_Z$-Ar), 7.05 (2H, d, $J$=9.1 Hz, $H_X$-2/6), 3.83 (3H, s, OMe), 3.80 (3H, s, OMe); $^{13}C$ NMR ($d_6$-DMSO; 125 MHz) $\delta$ ppm 163.39 (C), 160.68 (C), 160.10 (C), 158.68 (C), 140.39 (C), 135.75 (C), 131.29 (CH), 130.80 (CH), 130.32 (CH), 128.59 (C), 124.43 (C), 119.12 (CH), 118.68 (CH), 115.47 (CH), 111.62 (CH), 56.00 ($CH_3$), 55.90 ($CH_3$). IR $\nu$ (neat)=1563.9 (m), 1542.9 (m), 1506.6 (m), 1493.8 (m), 1381.8 (s), 1368.9 (m), 1277.7 (w), 1250.5 (m), 1234.1 (m), 1182.9 (w), 1171.1 (s), 1089.4 (m), 1028.4 (m), 956.9 (w), 935.0 (w), 847.7 (w), 792.8 (w), 756.3 (s), 721.5 (m), 705.3 (m), 686.4 (w) $cm^{-1}$. HRMS Calcd for $C_{22}H_{19}N_3O_5SCl$ 472.0734; found 472.0558.

**4.3.19. 4-Chloro-*N*-phenyl-*N*-(5-pyridin-3-yl-[1,3,4]oxadiazol-2-yl)benzenesulfonamide 61.** $^1H$ NMR ($d_6$-DMSO; 500 MHz) $\delta$ ppm 9.08 (1H, d, $J$=1.6 Hz, $H_Z$-2), 8.81 (1H, dd, $J$=5.0, 1.6 Hz, $H_Z$-4), 8.24 (1H, dt, $J$=7.9, 1.6 Hz, $H_Z$-6), 7.92 (2H, d, $J$=8.8 Hz, $H_Y$-2/6), 7.80 (2H, d, $J$=8.8 Hz, $H_Y$-3/5), 7.63 (1H, ddd, $J$=7.9, 5.0, 0.95 Hz, $H_Z$-5), 7.52 (3H, m, $H_X$-Ar), 7.40 (2H, m, $H_X$-Ar); $^{13}C$ NMR ($d_6$-DMSO; 125 MHz) $\delta$ ppm 161.88 (C), 158.78 (C), 153.17 (CH), 147.50 (CH), 140.53 (C), 136.27 (C), 135.66 (C), 134.55 (CH), 130.87 (CH), 130.58 (CH), 130.41 (CH), 130.39 (CH), 129.24 (CH), 124.82 (CH), 120.03 (C). IR $\nu$ (neat)=1608.1 (w), 1579.3 (w), 1561.2 (w), 1532.6 (s), 1487.7 (w), 1476.5 (w), 1401.0 (s), 1382.2 (m), 1370.3 (m), 1294.7 (m), 1198.8 (m), 1177.5 (s), 1098.6 (s), 1082.6 (m), 1056.6 (m), 1019.7 (w), 1012.5 (w), 960.8 (m), 916.7 (w), 889.8 (w), 822.0 (w), 753.6 (s), 721.0 (m), 705.4 (m), 693.0 (s), 668.1 (m) $cm^{-1}$. HRMS Calcd for $C_{19}H_{13}N_4O_3SCl$ 413.0475; found 413.0507.

**4.3.20. 4-Iodo-*N*-phenyl-*N*-(5-phenyl-[1,3,4]oxadiazol-2-yl)benzenesulfonamide 62.** $^1H$ NMR ($d_6$-DMSO; 500 MHz) $\delta$ ppm 8.12 (2H, d, $J$=8.85 Hz, $H_Y$-2/6), 7.90 (2H, d, $J$=6.9 Hz, $H_Z$-2/6), 7.64 (2H, d, $J$=8.85 Hz, $H_Y$-3/5), 7.58 (3H, m, $H_Z$-3/4/5), 7.51 (3H, m, 3×$H_X$-Ar), 7.39 (2H, m, 2×$H_X$-Ar); $^{13}C$ NMR ($d_6$-DMSO; 125 MHz) $\delta$ ppm 163.61 (C), 158.42 (C), 139.13 (CH), 136.54 (C), 136.37 (C), 132.76 (CH), 130.49 (CH), 130.41 (CH), 130.30 (CH), 129.95 (CH), 129.15 (CH), 126.83 (CH), 123.25 (C). IR $\nu$ (neat)=1593.6 (w), 1566.9 (s), 1536.9 (s), 1488.6 (s), 1455.2 (w), 1411.4 (m), 1385.2 (m), 1371.1 (m), 1279.1 (m), 1188.0 (m), 1170.1 (s), 1093.1 (m), 1052.1 (m), 1025.6 (m), 1004.1 (s), 961.9 (m), 942.9 (m), 915.5 (m), 888.3 (m),

816.1 (s), 734.4 (s), 715.3 (s), 684.9 (m) $cm^{-1}$. HRMS Calcd for $C_{20}H_{15}N_3O_3SI$ 503.9879; found 503.9961.

**4.3.21. *N*-[5-(*N*,*N*-Dibenzenesulfonamide-4-aminophenyl)-[1,3,4]oxadiazol-2-yl]-*N*-(3-chlorophenyl)benzenesulfonamide 63.** $^1H$ NMR ($d_6$-DMSO; 500 MHz) $\delta$ ppm 7.98–7.93 (4H, m), 7.89–7.82 (7H, m), 7.77–7.69 (6H, m), 7.62 (1H, ddd, $J=8.2$, 2.3, 1.0 Hz), 7.54 (1H, t, $J=8.2$ Hz), 7.50 (1H, t, $J=1.9$ Hz), 7.37 (1H, t, $J=8.2$, 1.9, 0.95 Hz), 7.27 (2H, d, $J=7.5$); $^{13}C$ NMR ($d_6$-DMSO; 125 MHz) $\delta$ ppm 162.60 (C), 158.57 (C), 138.66 (C), 137.54 (C), 136.83 (C), 136.63 (C), 135.68 (CH), 135.43 (CH), 134.13 (C), 132.99 (CH), 131.82 (CH), 130.57 (CH), 130.33 (CH), 130.20 (CH), 129.18 (CH), 128.94 (CH), 128.53 (CH), 128.07 (CH), 128.00 (CH), 125.20 (C). IR $\nu$ (neat)= 1608.9 (w), 1581.9 (w), 1566.1 (m), 1544.6 (m), 1477.6 (m), 1447.9 (m), 1380.1 (s), 1361.7 (s), 1301.7 (w), 1281.0 (w), 1261.1 (m), 1208.1 (w), 1161.0 (s), 1089.7 (s), 956.2 (m), 958.0 (m), 912.5 (s), 820.5 (m), 795.9 (m), 762.9 (m), 753.1 (m), 718.9 (s), 693.8 (m), 681.2 (s) $cm^{-1}$. HRMS Calcd for $C_{32}H_{23}N_4O_7S_3Cl$ 707.0496; found 707.0684.

**4.3.22. *N*-(3-Chlorophenyl)-*N*-[5-(4-chlorophenyl)-[1,3,4]oxadiazol-2-yl]benzenesulfonamide 64.** $^1H$ NMR ($d_6$-DMSO; 500 MHz) $\delta$ ppm 7.93 (2H, d, $J=8.2$ Hz, $H_Y$-2/6), 7.90 (2H, d, $J=8.5$ Hz, $H_Z$-2/6), 7.86 (1×H, m, $H_Y$-4), 7.73 (2H, m, $H_Y$-3/5), 7.66 (2H, d, $J=8.5$ Hz, $H_Z$-3/5), 7.61 (1H, ddd, $J=8.2$, 1.9, 1.0 Hz, $H_X$-Ar), 7.53 (1H, t, $J=8.2$ Hz, $H_X$-5), 7.49 (1H, t, $J=1.9$ Hz, $H_X$-2), 7.36 (1H, ddd, $J=8.2$, 1.9, 1.0 Hz, $H_X$-Ar); $^{13}C$ NMR ($d_6$-DMSO; 125 MHz) $\delta$ ppm 162.85 (C), 158.31 (C), 137.52 (C), 137.47 (C), 136.65 (C), 135.64 (CH), 134.13 (C), 131.81 (CH), 130.57 (CH), 130.29 (CH), 130.13 (CH), 129.19 (CH), 128.92 (CH), 128.64 (CH), 127.99 (CH), 122.23 (C). IR $\nu$ (neat)=1623.5 (w), 1589.4 (s), 1565.6 (s), 1542.1 (s), 1482.2 (s), 1448.0 (m), 1373.4 (m), 1171.0 (s), 1090.2 (s), 1047.8 (w), 1012.8 (s), 964.0 (w), 834.7 (m), 780.8 (m), 753.5 (m), 722.7 (s), 682.3 (s) $cm^{-1}$. HRMS Calcd for $C_{20}H_{14}N_3O_3SCl_2$ 446.0133; found 446.0210.

**4.3.23. 4-Chloro-*N*-[5-(2,4-dichlorophenoxymethyl)-[1,3,4]oxadiazol-2-yl]-*N*-ethyl-benzenesulfonamide 65.** $^1H$ NMR ($d_6$-DMSO; 500 MHz) $\delta$ ppm 7.99 (2H, d, $J=8.8$ Hz, $H_Y$-2/6), 7.73 (2H, d, $J=8.8$ Hz, $H_Y$-3/5), 7.64 (1H, d, $J=2.5$ Hz, $H_Z$-5), 7.42 (1H, dd, $J=8.8$, 2.5 Hz, $H_Y$-7), 7.35 (1H, d, $J=8.8$ Hz, $H_Y$-8), 5.51 (2H, s, CH-$_2$O), 3.89 (2H, q, $J=6.9$ Hz, $H_X$-1), 1.22 (3H, t, $J=6.9$ Hz, $H_X$-2); $^{13}C$ NMR ($d_6$-DMSO; 125 MHz) $\delta$ ppm 160.87 (C), 158.97 (C), 152.21 (C), 140.11 (C), 136.72 (C), 130.32 (CH), 130.08 (CH), 130.05 (CH), 128.65 (C), 126.61 (CH), 123.49 (C), 116.80 (CH), 61.35 ($CH_2$), 46.48 ($CH_2$), 14.56 ($CH_3$). IR $\nu$ (neat)=1606.7 (w), 1554.1 (s), 1537.3 (m), 1478.9 (s), 1421.1 (m), 1381.7 (w), 1367.1 (m), 1286.9 (m), 1267.0 (m), 1244.0 (m), 1228.7 (m), 1176.4 (s), 1166.9 (s), 1093.8 (m), 1085.0 (m), 1058.1 (m), 1024.8 (m), 882.7 (m), 824.9 (m), 805.0 (s), 766.9 (s), 757.2 (s), 724.2 (m) $cm^{-1}$. HRMS Calcd for $C_{17}H_{16}N_3O_4SCl_2$ 428.0239; found 428.0241.

**4.3.24. 4-Methoxybenzenesulfonic acid 3-{5-[(2,6-dimethylphenyl)-(4-methoxybenzenesulfonyl)-amino]-[1,3,4]oxadiazol-2-yl}naphthalen-2-yl ester 66.** $^1H$ NMR ($d_6$-DMSO; 500 MHz) $\delta$ ppm 8.38 (1H, s), 8.12 (1H, d, $J=7.6$ Hz), 8.10 (2H, d, $J=8.9$ Hz), 8.04 (1H, d, $J=7.9$ Hz), 7.91 (1H, s), 7.72–7.64 (2H, m), 7.44 (2H, d, $J=8.9$ Hz), 7.34 (1H, dd, $J=8.2$, 6.9 Hz), 7.27 (2H, d, $J=9.14$ Hz), 7.25 (2H, m), 6.92 (2H, d, $J=9.1$ Hz), 3.90 (3H, s, OMe), 3.80 (3H, s, OMe), 2.17 (6H, s, 2×Me); $^{13}C$ NMR ($d_6$-DMSO; 125 MHz) $\delta$ ppm 164.68 (C), 164.66 (C), 159.66 (C), 158.68 (C), 142.81 (C), 139.16 (C), 134.64 (C), 134.47 (C), 132.09 (CH), 131.83 (CH), 131.13 (C), 130.89 (CH), 130.44 (CH), 129.78 (CH), 129.75 (CH), 129.53 (C), 129.20 (CH), 128.37 (CH), 124.96 (C), 122.61 (CH), 116.44 (C), 115.33 (CH), 115.23 (CH), 56.48 ($CH_3$), 56.36 ($CH_3$), 18.52 ($CH_3$). IR $\nu$ (neat)=15.93.3 (m), 1578.4 (m), 1556.8 (m), 1496.6 (m), 1442.7 (w), 1366.1 (s), 1314.4 (w), 1264.1 (s), 1194.5 (m), 1166.6 (s), 1132.9 (m), 1091.3 (s), 1027.3 (m), 959.0 (w), 938.5 (m), 912.6 (m), 824.3 (s), 803.9 (s), 775.9 (s), 763.7 (s), 715.8 (m), 685.6 (s) $cm^{-1}$. HRMS Calcd for $C_{34}H_{30}N_3O_8S_2$ 672.1474; found 672.1455.

**4.3.25. *N*-[5-(2-Chlorophenyl)-[1,3,4]oxadiazol-2-yl]-4-nitro-*N*-phenyl-benzenesulfonamide 67.** $^1H$ NMR ($d_6$-DMSO; 500 MHz) $\delta$ ppm 8.53 (2H, d, $J=9.1$ Hz, $H_Y$-3/5), 8.20 (2H, d, $J=9.1$ Hz, $H_Y$-2/6), 7.88 (1H, dd, $J=7.9$, 1.6 Hz, $H_X$-Ar), 7.68 (2H, m), 7.55 (4H, m), 7.42 (2H, m); $^{13}C$ NMR ($d_6$-DMSO; 125 MHz) $\delta$ ppm 161.55 (C), 158.55 (C), 151.46 (C), 142.08 (C), 135.96 (C), 134.00 (CH), 132.19 (C), 131.71 (CH), 131.60 (CH), 130.70 (CH), 130.55 (CH), 129.42 (CH), 128.41 (CH), 125.43 (CH), 122.34 (C). IR $\nu$ (neat)=1607.6 (w), 1566.4 (m), 1536.8 (s), 1486.8 (w), 1460.2 (w), 1404.9 (w), 1381.7 (s), 1365.1 (w), 1348.7 (s), 1317.7 (w), 1273.7 (m), 1243.6 (w), 1201.8 (m), 1175.1 (s), 1101.8 (m), 1085.6 (m), 1020.6 (m), 962.7 (m), 943.1 (m), 912.6 (m), 861.9 (m), 854.9 (m), 765.9 (m), 748.4 (w), 739.2 (s), 696.9 (m), 680.6 (s), 657.9 (s) $cm^{-1}$. HR-MS Calcd for $C_{20}H_{14}N_4O_5ClS$: 457.0373; found 457.0372.

**4.3.26. 4-Chloro-*N*-[5-(2-chlorophenyl)-[1,3,4]oxadiazol-2-yl]-*N*-(2,6-dimethylphenyl)benzenesulfonamide 68.** $^1H$ NMR ($d_6$-DMSO; 500 MHz) $\delta$ ppm 8.19 (2H, d, $J=8.85$ Hz, $H_Y$-2/6), 7.85 (3H, m, $H_Y$-3/5/$H_Z$-Ar), 7.65 (2H, m, 2×$H_Z$-Ar), 7.53 (1H, m, $H_Z$-Ar), 7.35 (1H, t, $J=7.6$ Hz, $H_X$-4), 7.26 (2H, d, $J=7.6$ Hz, $H_X$-3/5), 2.12 (6H, s, 2×Me); $^{13}C$ NMR ($d_6$-DMSO; 125 MHz) $\delta$ ppm 160.53 (C), 158.42 (C), 140.74 (C), 138.96 (C), 136.87 (C), 134.37 (C), 133.87 (CH), 132.11 (C), 131.74 (CH), 131.47 (CH), 131.29 (CH), 130.62 (CH), 130.40 (CH), 129.77 (CH), 128.39 (CH), 122.49 (C), 18.46 ($CH_3$). IR $\nu$ (neat)=1578.9 (w), 1563.6 (s), 1539.0 (w), 1462.9, 1368.1 (s), 1290.7 (w), 1279.3 (m), 1167.1 (s), 1090.3 (m), 1079.5 (m), 1024.1 (w), 932.4 (m), 839.8 (m), 828.9 (m), 783.1 (w), 753.2 (s), 728.0 (m), 705.3 (m), 692.9 (m) $cm^{-1}$. HR-MS Calcd for $C_{22}H_{18}N_3O_3SCl_2$: 474.0446; found 474.0467.

**4.3.27. 4-Chloro-*N*-(3-chlorophenyl)-*N*-[5-(4-nitrophenyl)-[1,3,4]oxadiazol-2-yl]-benzenesulfonamide 69.** $^1H$ NMR ($d_6$-DMSO; 500 MHz) $\delta$ ppm 8.40 (2H, d, $J=9.1$ Hz, $H_Z$-3/5), 8.12 (2H, d, $J=9.1$ Hz, $H_Z$-2/6), 7.97 (2H, d, $J=8.9$ Hz, $H_Y$-2/6), 7.83 (2H, d, $J=8.9$ Hz, $H_Y$-3/5), 7.64 (1H, ddd, $J=8.1$, 2.1, 1.0 Hz, $H_X$-Ar), 7.58 (1H, br t, $J=2.1$ Hz, $H_X$-2), 7.56 (1H, d, $J=8.0$ Hz, $H_X$-Ar), 7.41 (1H, ddd, $J=8.0$, 2.1, 1.0 Hz, $H_X$-Ar); $^{13}C$ NMR ($d_6$-DMSO; 125 MHz) $\delta$ ppm 161.88 (C), 158.80 (C), 149.70 (C), 140.81 (C), 137.23 (C), 135.38 (C), 134.23 (C), 131.89 (CH), 131.00 (CH), 130.84 (CH), 130.47 (CH), 129.51 (C), 128.90 (CH), 128.28 (CH), 125.12 (CH). IR $\nu$

(neat)=1610.3 (w), 1573.8 (s), 1538.6 (s), 1515.4 (s), 1484.7 (m), 1473.7 (m), 1429.2 (m), 1398.1 (m), 1356.7 (m), 1340.2 (s), 1300.8 (m), 1282.2 (s), 1210.4 (w), 1180.3 (m), 1168.6 (s), 1087.3 (s), 1054.2 (m), 1024.6 (w), 1001.7 (w), 967.9 (s), 943.2 (m), 922.2 (w), 853.0 (s), 831.6 (m), 817.7 (w), 782.5 (w), 762.6 (s), 740.8 (s), 715.9 (s), 683.0 (s), 656.9 (s) $cm^{-1}$. HRMS Calcd for $C_{20}H_{13}N_4O_5SCl$ 490.9984; found 490.9965.

**4.3.28. 4-Bromo-*N*-(5-furan-2-yl-[1,3,4]oxadiazol-2-yl)-*N*-phenyl-benzenesulfonamide 70.** $^1H$ NMR ($d_6$-DMSO; 500 MHz) $\delta$ ppm 8.05 (1H, dd, $J=1.8$, 0.8 Hz, $H_Z$-3), 7.94 (2H, d, $J=8.8$ Hz, $H_Y$-2/6), 7.80 (2H, d, $J=8.8$ Hz, $H_Y$-3/5), 7.50 (3H, m, $H_X$-2/4/6), 7.39 (2H, m, $H_X$-3/5), 7.32 (1H, dd, $J=3.6$, 0.8 Hz, $H_Z$-5), 6.78 (1H, dd, $J=3.6$, 1.8 Hz, $H_Z$-4); $^{13}C$ NMR ($d_6$-DMSO; 125 MHz) $\delta$ ppm 157.70 (C), 156.55 (C), 147.76 (CH), 138.28 (C), 136.22 (C), 136.00 (C), 133.32 (CH), 130.82 (CH), 130.57 (CH), 130.44 (CH), 129.71 (C), 129.14 (CH), 115.54 (CH), 113.15 (CH). IR $\nu$ (neat)=1592.6 (w), 1573.7 (s), 1545.9 (m), 1491.5 (w), 1455.7 (w), 1360.0 (w), 1350.0 (w), 1285.6 (m), 1264.5 (m), 1218.9 (m), 1163.6 (s), 1042.1 (m), 1021.4 (m), 1011.7 (m), 837.5 (m), 744.2 (s), 697.4 (m), 688.6 (m) $cm^{-1}$. HR-MS Calcd for $C_{18}H_{12}N_3O_4SBr$: 445.98106; found 445.9787.

**4.3.29. 4-Bromo-*N*-[5-(2,4-difluorophenyl)-[1,3,4]oxadiazol-2-yl]-*N*-(2-nitrophenyl)benzenesulfonamide 71.** $^1H$ NMR ($d_6$-DMSO; 500 MHz) $\delta$ ppm 8.18 (1H, m), 7.98–7.87 (7H, m), 7.62 (2H, m), 7.30 (1H, m); $^{13}C$ NMR ($d_6$-DMSO; 125 MHz) $\delta$ ppm 158.77 (C), 157.99 (C), 147.53 (C), 135.58 (C), 133.85 (CH), 133.62 (CH), 133.22 (CH), 133.14 (CH), 132.96 (CH), 131.37 (CH), 130.34 (CH), 130.00 (CH), 129.66 (C), 124.85 (CH), 116.33 (C), 113.08, 112.87 (CF), 105.76, 105.75, 105.57 (CF). IR $\nu$ (neat)=1589.7 (m), 1572.3 (m), 1557.5 (s), 1530.2 (s), 1502.0 (s), 1471.5 (w), 1384.7 (m), 1343.9 (m), 1277.5 (w), 1246.4 (w), 1187.6 (s), 1178.3 (s), 1142.5 (m), 1090.1 (m), 1010.1 (w), 984.3 (w), 961.1 (w), 928.0 (m), 852.5 (m), 787.9 (w), 744.2 (s), 709.7 (m) $cm^{-1}$. HRMS Calcd for $C_{20}H_{12}N_4O_5SBRf._2$ 536.9680; found 536.9692.

**4.3.30. 4-Methoxy-*N*-[5-(3-methoxyphenyl)-[1,3,4]oxadiazol-2-yl]-*N*-phenethyl-benzenesulfonamide 72.** $^1H$ NMR ($d_6$-DMSO; 500 MHz) $\delta$ ppm 7.91 (2H, d, $J=8.8$ Hz, $H_Y$-2/6), 7.53 (1H, t, $J=7.8$ Hz, $H_Z$-Ar), 7.48 (1H, d, $J=7.8$ Hz, $H_Z$-Ar), 7.33 (1H, m, $H_Z$-2), 7.28 (7H, m, Ph/$H_Y$-3/5), 7.25 (1H, m, $H_Z$-Ar), 7.20 (1H, m, $H_Z$-Ar), 4.11 (2H, t, $J=7.25$ Hz, $H_X$-1), 3.88 (3H, s, OMe), 3.89 (3H, s, OMe), 3.00 (2H, t, $J=7.25$ Hz, $H_X$-2); $^{13}C$ NMR ($d_6$-DMSO; 125 MHz) $\delta$ ppm 163.75 (C), 162.10 (C), 159.59 (C), 158.12 (C), 137.40 (C), 130.77 (CH), 130.28 (CH), 128.78 (CH), 128.57 (C), 128.35 (CH), 126.50 (CH), 124.09 (C), 118.43 (CH), 117.95 (CH), 114.81 (CH), 110.87 (CH), 55.87 ($CH_3$), 55.40 ($CH_3$), 51.16 ($CH_2$), 34.41 ($CH_2$). IR $\nu$ (neat)=1592.7 (m), 1575.2 (s), 1544.8 (s), 1491.9 (m), 1367.2 (m), 1349.1 (m), 1316.9 (w), 1285.2 (m), 1263.5 (s), 1218.4 (m), 1174.1 (w), 1155.9 (s), 1040.9 (s), 1020.9 (s), 1010.1 (m), 867.3 (m), 836.7 (s), 805.5 (m), 785.0 (s), 756.0 (m), 745.3 (m), 708.5 (m), 687.3 (s), 680.3 (s) $cm^{-1}$. HRMS Calcd for $C_{24}H_{24}N_3O_5S$ 466.1437; found 466.1439.

**4.3.31. 4-Nitro-*N*-phenyl-*N*-[5-(4-trifluoromethyl-phenyl)-[1,3,4]oxadiazol-2-yl]benzenesulfonamide 73.** $^1H$ NMR ($d_6$-DMSO; 500 MHz) $\delta$ ppm 8.53 (2H, d, $J=9.1$ Hz, $H_Y$-3/5), 8.21 (2H, d, $J=9.1$ Hz, $H_Y$-2/6), 8.09 (2H, d, $J=8.2$ Hz, $H_Z$-3/5), 7.97 (2H, d, $J=8.2$ Hz, $H_Z$-2/6), 7.53 (3H, m, $H_X$-2/4/6), 7.43 (2H, m, $H_X$-3/5); $^{13}C$ NMR ($d_6$-DMSO; 125 MHz) $\delta$ ppm 162.46 (C), 158.64 (C), 151.48 (C), 142.03 (C), 125.94 (C), 130.86 (CH), 130.73 (CH), 130.54 (CH), 129.44 (CH), 127.76 (CH), 127.04 (C), 126.93 (C), 126.90 (CH), 125.44 (CH). IR $\nu$ (neat)=1597.8 (w), 1568.5 (w), 1541.3 (s), 1530.1 (s), 1504.8 (w), 1489.3 (w), 1423.9 (w), 1406.4 (m), 1347.2 (m), 1322.5 (s), 1284.3 (m), 1167.6 (s), 1124.6 (s), 1094.6 (m), 1067.1 (s), 1051.3 (m), 1026.7 (m), 1013.2 (m), 962.4 (w), 943.4 (w), 916.5 (w), 888.3 (w), 852.0 (s), 821.1 (w), 746.5 (m), 738.6 (s), 717.1 (m), 693.7 (s), 681.5 (s), 666.2 (m) $cm^{-1}$. HRMS Calcd for $C_{21}H_{14}N_4O_5SF_3$ 491.0637; found 491.0654.

**4.3.32. Thiophene-2-sulfonic acid phenyl-(5-phenyl-[1,3,4]oxadiazol-2-yl)amide 74.** $^1H$ NMR ($d_6$-DMSO; 500 MHz) $\delta$ ppm 8.24 (1H, dd, $J=5.0$, 1.3 Hz, $H_Y$-3), 7.90 (2H, d, $J=6.9$ Hz, $H_Z$-2/6), 7.86 (1H, dd, $J=3.8$, 1.3 Hz, $H_Y$-5), 7.61 (3H, m, $H_Z$-3/4/5), 7.50 (3H, m, $H_X$-2/4/6), 7.40 (2H, m, $H_X$-3/5), 7.35 (1H, dd, $J=5.0$, 3.8 Hz, $H_Y$-4); $^{13}C$ NMR ($d_6$-DMSO; 125 MHz) $\delta$ ppm 161.83 (C), 158.55 (C), 153.15 (CH), 147.49 (CH), 135.57 (C), 134.52 (CH), 133.39 (CH), 132.45 (CH), 131.41 (CH), 124.80 (CH), 123.93 (C), 120.01 (C), 117.71 (CH), 117.52 (CH). IR $\nu$ (neat)=1593.6 (w), 1568.0 (w), 1536.5 (s), 1485.6 (m), 1452.5 (w), 1412.4 (m), 1396.4 (m), 1374.7 (m), 1341.4 (w), 1296.4 (w), 1280.4 (m), 1227.8 (w), 1170.9 (s), 1094.8 (s), 1070.6 (m), 1053.0 (m), 1027.7 (m), 1015.4 (s), 961.2 (m), 942.7 (m), 913.8 (m), 887.6 (m), 856.8 (m), 775.7 (m), 751.6 (w), 728.0 (s), 717.4 (s), 693.0 (s), 676.0 (s) $cm^{-1}$. HRMS Calcd for $C_{18}H_{14}N_3O_3S_2$ 384.0477; found 384.0489.

**4.3.33. *N*-(3-Chlorophenyl)-2-fluoro-*N*-[5-(4-nitrophenyl)-[1,3,4]oxadiazol-2-yl]benzenesulfonamide 75.** $^1H$ NMR ($d_6$-DMSO; 500 MHz) $\delta$ ppm 8.41 (2H, d, $J=9.1$ Hz, $H_Z$-2/6), 8.12 (2H, d, $J=9.1$ Hz, $H_Z$-3/5), 8.03 (2H, m, 2×$H_Y$-Ar), 7.64 (1H, ddd, J=8.2, 2.2, 0.95 Hz, $H_X$-Ar), 7.61 (4H, m, 2×$H_Y$-Ar, 2×$H_X$-Ar), 7.39 (1H, ddd, $J=7.9$, 2.2, 0.95 Hz, $H_X$-Ar); $^{13}C$ NMR ($d_6$-DMSO; 125 MHz) $\delta$ ppm 167.25 (C), 165.22 (C), 161.90 (C), 158.86 (C), 149.70 (C), 137.30 (C), 134.21 (C), 132.53 (CH), 132.45 (CH), 131.86 (CH), 130.78 (CH), 129.48 (CH), 128.90 (C), 128.26 (CH), 128.17 (CH), 125.11 (CH), 117.73 (CH), 117.55 (CH). IR $\nu$ (neat)=1574.3 (s), 1541.0 (s), 1523.8 (s), 1487.0 (w), 1473.7 (w), 1429.7 (w), 1399.0 (w), 1361.7 (m), 1340.4 (s), 1300.2 (w), 1286.7 (w), 1236.9 (m), 1177.0 (s), 1157.8 (s), 1094.5 (s), 1052.9 (m), 968.3 (m), 943.9 (w), 918.3 (w), 893.9 (w), 853.8 (s), 842.0 (s), 833.2 (m), 781.8 (w), 754.4 (w), 716.0 (s), 707.0 (m), 693.7 (m), 683.4 (s), 672.2 (s) $cm^{-1}$. HRMS Calcd for $C_{20}H_{13}N_4O_5SFCl$ 475.0279; found 475.0259.

**4.3.34. *N*-(4-Bromophenyl)-2-fluoro-*N*-(5-pyridin-3-yl-[1,3,4]oxadiazol-2-yl)benzenesulfonamide 76.** $^1H$ NMR ($d_6$-DMSO; 500 MHz) $\delta$ ppm 9.06 (1H, dd, $J=2.2$, 0.6 Hz, $H_Z$-2), 8.80 (1H, dd, $J=4.7$, 1.6 Hz, $H_Z$-4), 8.25 (1H, ddd, $J=8.0$, 2.2, 1.6 Hz, $H_Z$-6), 8.00 (2H, m), 7.69 (2H, d, $J=8.8$ Hz, $H_X$-3 and $H_X$-5), 7.61 (1H, ddd, $J=8.0$, 4.7, 0.95 Hz, Hz-5), 7.57 (2H, app. t, $J=8.8$ Hz, $H_Y$-4 and $H_Y$-5), 7.29 (2H, d, $J=8.8$ Hz, $H_X$-2 and $H_X$-6); $^{13}C$ NMR ($d_6$-DMSO; 125 MHz) $\delta$ ppm 167.18 (C), 165.15 (C),

161.82 (C), 158.55 (C), 153.15 (CH), 147.49 (CH), 135.57 (C), 134.52 (CH), 133.39 (CH), 132.45 (CH), 132.36 (CH), 131.41 (CH), 124.80 (CH), 123.93 (C), 120.01 (C), 117.71 (CH), 117.52 (CH). IR $\nu$ (neat)=1585.6 (m), 1568.9 (w), 1537.7 (s), 1489.8 (s), 1404.1 (m), 1381.0 (w), 1365.5 (m), 1340.0 (w), 1292.9 (m), 1240.5 (m), 1211.4 (w), 1175.1 (s), 1149.1 (s), 1096.4 (s), 1066.4 (m), 1012.8 (m), 961.9 (m), 924.4 (w), 838.8 (m), 817.9 (m), 703.1 (s), 664.9 (s) $cm^{-1}$. HRMS Calcd for $C_{19}H_{13}N_4O_3SBRf$ 474.9876; found 474.9901.

**4.3.35. *N*-(5-Furan-2-yl-[1,3,4]oxadiazol-2-yl)-4-nitro-*N*-phenyl-benzenesulfonamide 77.** $^1H$ NMR ($d_6$-DMSO; 500 MHz) $\delta$ ppm 8.51 (2H, d, $J$=8.9 Hz, $H_Y$-2/6), 8.14 (2H, d, $J$=8.9 Hz, $H_Y$-3/5), 8.03 (1H, dd, $J$=1.89, 0.6 Hz, $H_Z$-3), 7.52 (3H, m, $H_X$-3/4/5), 7.40 (2H, m, $H_X$-2/6), 7.33 (1H, dd, $J$=3.5, 0.6 Hz, $H_Z$-5), 6.78 (1H, dd, $J$=3.5, 1.9 Hz, $H_Z$-4); $^{13}C$ NMR ($d_6$-DMSO; 125 MHz) $\delta$ ppm 157.46 (C), 156.63 (C), 151.46 (C), 147.83 (CH), 141.92 (C), 138.21 (C), 135.94 (C), 130.81 (CH), 130.70 (CH), 130.55 (CH), 129.25 (CH), 125.41 (CH), 115.68 (C), 113.18 (C). IR $\nu$ (neat)=1630.4 (w), 1607.0 (w), 1556.9 (m), 1531.3 (s), 1516.0 (m), 1488.3 (w), 1449.3 (w), 1404.5 (w), 1383.8 (s), 1366.7 (w), 1347.8 (s), 1317.7 (w), 1304.8 (w), 1279.1 (m), 1196.1 (w), 1178.0 (s), 1165.8 (s), 1111.2 (m), 1084.8 (m), 1010.6 (m), 985.5 (w), 970.6 (m), 929.5 (m), 906.0 (m), 889.0 (m), 862.2 (m), 854.1 (m), 768.6 (m), 759.0 (m), 739.9 (s), 695.8 (s), 680.8 (s) $cm^{-1}$. HRMS Calcd for $C_{18}H_{13}N_4O_6S$ 413.0556; found 413.0566.

**4.3.36. *N*-(4-hexyl-bicyclo[2.2.2]oct-1-yl)-4-methyl-*N*-(5-methyl-[1,3,4]oxadiazol-2-yl)-benzenesulfonamide 78.** $^1H$ NMR ($d_6$-DMSO; 500 MHz) $\delta$ ppm 7.73 (2H, d, $J$=8.5 Hz, $H_Y$-2/6), 7.49 (2H, d, $J$=8.5 Hz, $H_Y$-3/5), 7.40 (2H, d, $J$=8.8 Hz, $H_X$-3/5), 7.15 (2H, d, $J$=8.8 Hz, $H_Y$-2/6), 2.39 (3H, s, $H_Z$-Me), 2.38 (3H, s, Me), 1.74 (6H, m), 1.44 (6H, m), 1.24 (10H, m), 0.86 (3H, t, $J$=7.3 Hz, $H_Y$-Me); $^{13}C$ NMR ($d_6$-DMSO; 125 MHz) $\delta$ ppm 164.11 (C), 158.55 (C), 152.10 (C), 145.89 (C), 134.40 (C), 133.96 (C), 130.50 (C), 130.49 (CH), 128.76 (CH), 128.63 (C), 128.41 (CH), 127.37 (CH), 41.68 ($CH_2$), 32.45 ($CH_2$), 31.79 ($CH_2$), 31.41 ($CH_2$), 30.19 ($CH_2$), 23.62 ($CH_2$), 22.55 ($CH_2$), 21.63 ($CH_3$), 14.42 ($CH_3$), 11.34 ($CH_3$). IR $\nu$ (neat)=2918.8 (s), 2853.2 (s), 1614.5 (w), 1596.8 (w), 1540.9 (s), 1510.9 (m), 1437.2 (w), 1411.1 (s), 1385.6 (m), 1303.7 (w), 1243.9 (m), 1185.4 (m), 1175.1 (s), 1094.7 (s), 1050.6 (w), 1019.2 (m), 962.2 (m), 916.4 (m), 810.0 (s) $cm^{-1}$. HRMS Calcd for $C_{30}H_{40}N_3O_3S$ 522.2790; found 522.2793.

**4.3.37. *N*-(4-Bromophenyl)-4-methoxy-*N*-(5-phenyl-[1,3,4]oxadiazol-2-yl)benzenesulfonamide 79.** $^1H$ NMR ($d_6$-DMSO; 500 MHz) $\delta$ ppm 7.91 (2H, d, $J$=6.9 Hz, $H_Z$-2/6), 7.85 (2H, d, $J$=9.1 Hz, $H_Y$-2/6), 7.70 (2H, d, $J$=8.8 Hz, $H_X$-2/6), 7.60 (3H, dm, $J$=6.9 Hz, $H_Z$-3/4/5), 7.33 (2H, d, $J$=8.8 Hz, $H_X$-3/5), 7.22 (2H, d, $J$=9.1 Hz, $H_Y$-3/5), 3.91 (3H, s, OMe); $^{13}C$ NMR ($d_6$-DMSO; 125 MHz) $\delta$ ppm 164.64 (C), 163.50 (C), 158.45 (C), 136.00 (C), 133.29 (CH), 132.72 (CH), 131.40 (CH), 131.21 (CH), 129.95 (CH), 127.86 (C), 126.81 (CH), 123.57 (C), 123.31 (C), 115.42 (CH), 56.46 ($CH_3$). IR $\nu$ (neat)=1593.2 (m), 1569.5 (m), 1542.1 (m), 1496.5 (m), 1485.6 (m), 1449.9 (w), 1399.8 (w), 1367.3 (m), 1296.4 (s), 1185.1 (m), 1159.4 (s), 1088.8 (s), 1068.6 (m), 1022.7 (m), 1011.8 (s), 960.5 (w), 920.8 (m), 833.1 (m), 802.8 (m), 775.8 (w), 706.0 (s), 680.0 (s), 689.7 (s), 665.7 (s) $cm^{-1}$. HRMS Calcd for $C_{21}H_{17}N_3O_4SBr$ 486.0123; found 486.0148.

**4.3.38. 4-Bromo-*N*-(4-bromophenyl)-*N*-(5-pyridin-3-yl-[1,3,4]oxadiazol-2-yl)-benzenesulfonamide 80.** $^1H$ NMR ($d_6$-DMSO; 500 MHz) $\delta$ ppm 9.06 (1H, dd, $J$=2.2, 0.7 Hz, $H_Z$-2), 8.82 (1H, dd, $J$=5.0, 1.6 Hz, $H_Z$-4), 8.25 (1H, dt, $J$=7.9, 2.1 Hz, $H_Z$-6), 7.97 (2H, d, $J$=8.5 Hz, $H_Y$-2/6), 7.86 (2H, d, $J$=8.5 Hz, $H_Y$-3/5), 7.73 (2H, d, $J$=8.8 Hz, $H_X$-3/5), 7.62 (1H, ddd, $J$=7.9, 5.0, 0.7 Hz, $H_Z$-5), 7.38 (2H, d, $J$=8.8 Hz, $H_X$-2/6); $^{13}C$ NMR ($d_6$-DMSO; 125 MHz) $\delta$ ppm 161.82 (C), 158.48 (C), 153.17 (CH), 147.50 (CH), 35.82 (C), 135.50 (C), 134.56 (CH), 133.43 (CH), 133.42 (CH), 131.43 (CH), 130.91 (CH), 129.91 (C), 124.83 (C), 123.99 (C), 120.01 (CH). IR $\nu$ (neat)=1609.1 (w), 1586.2 (m), 1571.2 (m), 1539.3 (s), 1493.3 (m), 1481.2 (m), 1403.5 (s), 1389.6 (m), 1382.2 (m), 1369.4 (m), 1294.7 (m), 1208.9 (w), 1170.3 (s), 1097.9 (m), 1085.7 (m), 1011.5 (s), 963.2 (m), 926.4 (m), 898.0 (m), 822.9 (s), 811.6 (m), 743.5 (s), 721.3 (m), 701.1 (s) $cm^{-1}$. HRMS Calcd for $C_{19}H_{13}N_4O_3SBr_2$ 534.9075; found 534.9110.

**4.3.39. 4-Methoxy-*N*-(4-methoxyphenyl)-*N*-[5-(4-nitrophenyl)-[1,3,4]oxadiazol-2-yl]benzenesulfonamide 81.** $^1H$ NMR ($d_6$-DMSO; 500 MHz) $\delta$ ppm 8.39 (2H, d, $J$=9.1 Hz, $H_Z$-2/6), 8.10 (2H, d, $J$=9.1 Hz, $H_Z$-3/5), 7.86 (2H, d, $J$=8.8 Hz, $H_Y$-2/6), 7.26 (2H, d, $J$=8.3 Hz, $H_X$-3/5), 7.23 (2H, d, $J$=8.8 Hz, $H_Y$-3/5), 7.01 (2H, d, $J$=8.3 Hz, $H_X$-2/6), 3.85 (3H, s, OMe), 3.79 (3H, s, OMe); $^{13}C$ NMR ($d_6$-DMSO; 125 MHz) $\delta$ ppm 164.54 (C), 161.61 (C), 160.58 (C), 159.72 (C), 149.65 (C), 142.66 (CH), 131.41 (CH), 130.92 (CH), 128.96 (C), 128.86 (C), 128.15 (C), 128.06 (CH), 125.13 (CH), 115.34 (CH), 56.44 ($CH_3$), 56.00 ($CH_3$). IR $\nu$ (neat)=1594.6 (w), 1571.7 (m), 1535.2 (s), 1514.8 (s), 1496.0 (m), 1399.4 (w), 1366.4 (w), 1340.7 (s), 1301.9 (w), 1286.4 (w), 1256.4 (s), 1185.6 (w), 1164.7 (s), 1092.7 (m), 1058.8 (m), 1028.6 (m), 962.2 (m), 913.7 (w), 889.9 (w), 856.1 (m), 830.4 (m), 802.3 (m), 757.7 (w), 718.6 (m), 696.0 (w) $cm^{-1}$. HRMS Calcd for $C_{22}H_{19}N_4O_7S$ 483.0974; found 483.0991.

**4.3.40. *N*-(3-Chlorophenyl)-*N*-[5-(4-chlorophenyl)-[1,3,4]oxadiazol-2-yl]-4-methoxybenzenesulfonamide 82.** LC-MS $R_f$ 4.261 M+H 476.0; $^1H$ NMR ($d_6$-DMSO; 500 MHz) $\delta$ ppm 7.92 (2H, dX, $J$=8.5 Hz, $H_Z$-2/6), 7.86 (2H, d, $J$=8.8 Hz, $H_Y$-2/6), 7.68 (2H, d, $J$=8.5 Hz, $H_Z$-3/5), 7.63 (1H, ddd, $J$=8.2, 1.9, 0.95 Hz, $H_X$-Ar), 7.54 (1H, t, $J$=8.2 Hz, $H_X$-Ar), 7.50 (1H, t, $J$=2.2 Hz, $H_X$-2), 7.32 (1H, ddd, J=8.2, 1.9, 0.95 Hz, $H_X$-Ar), 7.24 (2H, d, $J$=8.8 Hz, $H_Y$-3/5), 3.91 (3H, s, OMe); $^{13}C$ NMR ($d_6$-DMSO; 125 MHz) $\delta$ ppm 164.72 (C), 162.72 (C), 158.50 (C), 137.76 (C), 137.42 (C), 134.09 (C), 131.77 (CH), 131.46 (CH), 130.42 (CH), 130.14 (CH), 129.15 (CH), 128.63 (CH), 127.90 (CH), 127.79 (C), 122.26 (C), 115.43 (CH), 56.49 ($CH_3$). IR $\nu$ (neat)=1587.3 (m), 1579.0 (m), 1561.0 (m), 1540.5 (s), 1496.4 (m), 1483.1 (s), 1472.7 (m), 1439.7 (m), 1424.2 (w), 1396.1 (m), 1370.4 (m), 1303.8 (w), 1287.3 (w), 1262.5 (s), 1211.6 (m), 1184.7 (m), 1175.5 (m), 1162.3 (s), 1091.4 (s), 1055.2 (m), 1023.1 (m), 1011.5 (m), 969.2 (m), 943.5 (w), 921.9 (w), 899.0 (w), 871.6 (w), 834.6 (m), 827.5 (s), 805.9 (s), 782.3 (m), 746.7 (m), 733.7 (m), 726.0

(s), 713.7 (m), 682.9 (s), 670.7 (s) $cm^{-1}$. HRMS Calcd for $C_{21}H_{16}N_3O_4SCl_2$ 476.0239; found 476.0250.

**4.3.41. *N*-(5-Furan-2-yl-[1,3,4]oxadiazol-2-yl)-*N*-phenyl-benzenesulfonamide 83.** $^1H$ NMR ($d_6$-DMSO; 500 MHz) $\delta$ ppm 8.04 (1H, dd, $J=1.9$, 0.6 Hz, $H_Z$-3), 7.90 (2H, dd, $J=8.2$, 0.95 Hz, $H_Y$-2/6), 7.82 (1H, m, $H_Y$-4), 7.71 (2H, m, $2\times H_Y$-Ar), 7.49 (3H, m, $2\times H_Z$-Ar, $H_X$-5), 6.80 (1H, dd, $J=3.7$, 1.9 Hz, $H_Z$-4); $^{13}C$ NMR ($d_6$-DMSO; 125 MHz) $\delta$ ppm 157.86 (C), 156.59 (C), 147.76 (CH), 138.32 (C), 136.84 (C), 136.42 (C), 135.42 (CH), 130.41 (CH), 130.34 (CH), 130.18 (CH), 129.04 (CH), 128.85 (CH), 115.51 (CH), 113.15 (CH). IR $\nu$ (neat)=1551.8 (s), 1519.7 (s), 1491.0 (m), 1450.7 (m), 1425.1 (w), 1416.9 (w), 1402.9 (w), 1385.4 (m), 1289.7 (w), 1162.1 (s), 1094.8 (m), 1087.8 (m), 1027.2 (w), 1006.2 (m), 964.5 (w), 934.4 (m), 914.9 (w), 756.4 (s), 722.5 (s), 694.3 (s), 684.4 (s), 664.9 (m) $cm^{-1}$. HRMS Calcd for $C_{18}H_{14}N_3O_4S$ 368.0705; found 368.0760.

**4.3.42. *N*-[5-(3,4-Dimethoxyphenyl)-[1,3,4]oxadiazol-2-yl]-4-nitro-*N*-phenyl-benzenesulfonamide 84.** $^1H$ NMR ($d_6$-DMSO; 500 MHz) $\delta$ ppm 8.50 (2H, d, $J=8.75$ Hz, $H_Y$-3/5), 8.15 (2H, d, $J=8.75$ Hz, $H_Y$-2/6), 7.51 (1H, t, $J=7.9$ Hz, $H_Z$-5), 7.46 (1H, dt, $J=7.9$, 1.3 Hz, $H_Z$-6), 7.36 (1H, dt, $J=1.6$, 1.3 Hz, $H_Z$-2), 7.32 (2H, d, $J=8.8$ Hz, $H_X$-3/5), 7.20 (1H, ddd, $J=7.9$, 1.6, 1.3 Hz, $H_Z$-4), 7.03 (2H, d, $J=8.8$ Hz, $H_X$-2/6), 3.93 (3H, s, OMe), 3.90 (3H, s, OMe); $^{13}C$ NMR ($d_6$-DMSO; 125 MHz) $\delta$ ppm 163.51 (C), 160.82 (C), 160.10 (C), 158.42 (C), 151.38 (C), 142.10 (C), 131.32 (CH), 130.88 (CH), 130.66 (CH), 128.28 (C), 125.37 (CH), 124.35 (C), 119.19 (CH), 118.74 (CH), 115.58 (CH), 111.68 (CH), 56.04 ($CH_3$), 55.92 ($CH_3$). IR $\nu$ (neat)=1603.3 (w), 1559.6 (w), 1543.4 (m), 1524.8 (s), 1493.4 (s), 1464.6 (m), 1440.0 (m), 1417.5 (w), 1404.4 (w), 1384.6 (s), 1371.0 (m), 1347.7 (m), 1293.0 (m), 1278.0 (m), 1250.1 (s), 1229.5 (s), 1201.5 (w), 1172.2 (s), 1109.3 (m), 1088.3 (m), 1053.2 (w), 1026.1 (s), 999.5 (w), 971.8 (w), 930.4 (m), 874.3 (w), 852.1 (s), 833.8 (s), 803.9 (m), 792.1 (m), 736.8 (s), 719.8 (m), 702.3 (m), 684.0 (s) $cm^{-1}$. HRMS Calcd for $C_{22}H_{19}N_4O_7S$ 483.0974; found 483.1003.

**4.3.43. *N*-(4-Chlorophenyl)-4-methyl-*N*-(5-pyridin-3-yl-[1,3,4]oxadiazol-2-yl)benzenesulfonamide 85.** $^1H$ NMR ($d_6$-DMSO; 500 MHz) $\delta$ ppm 9.09 (1H, dd, $J=2.1$, 0.6 Hz, $H_Z$-2), 8.73 (1H, dd, $J=5.0$, 1.6 Hz, $H_Z$-4), 8.31 (1H, ddd, $J=8.3$, 2.1, 1.6 Hz, $H_Z$-6), 7.96 (2H, d, $J=8.2$ Hz, $H_Y$-2/6), 7.59 (2H, d, $J=8.9$ Hz, $2\times H_X$-Ar), 7.57 (1H, ddd, $J=8.3$, 5.0, 1.6 Hz, $H_Z$-5), 7.52 (2H, d, $J=8.2$ Hz, $H_Y$-3/5), 7.32 (2H, d, $J=8.9$ Hz, $2\times H_X$-Ar), 2.41 (3H, s, Me); $^{13}C$ NMR ($d_6$-DMSO; 125 MHz) $\delta$ ppm 163.17 (C), 163.07 (C), 152.35 (CH), 148.22 (CH), 146.49 (C), 136.83 (C), 135.17 (CH), 133.91 (C), 131.95 (CH), 130.82 (CH), 130.37 (CH), 130.34 (C), 128.99 (C), 128.61 (CH), 124.78 (CH), 21.67 ($CH_3$). IR $\nu$ (neat)=1639.4 (w), 1593.8 (m), 1566.8 (m), 1542.5 (w), 1528.3 (w), 1488.5 (s), 1424.7 (s), 1412.8 (s), 1368.1 (s), 1293.9 (m), 1274.7 (m), 1187.2 (m), 1174.1 (s), 1162.9 (m), 1088.4 (s), 1026.3 (m), 1015.9 (s), 964.0 (m), 931.6 (m), 813.5 (s), 772.1 (m), 703.1 (s), 663.4 (s) $cm^{-1}$. HRMS Calcd for $C_{20}H_{15}N_4O_3SCl$ 427.0632; found 427.0620.

**4.3.44. 4-Methoxy-*N*-[5-(2-chlorophenyl)-[1,3,4]oxadiazol-2-yl]-*N*-(2,6-dimethylphenyl)benzenesulfonamide 86.** $^1H$ NMR ($d_6$-DMSO; 500 MHz) $\delta$ ppm 8.10 (2H, d, $J=9.1$ Hz, $H_Y$-2/6), 7.83 (1H, dd, $J=7.9$, 1.6 Hz, $H_Z$-Ar), 7.63 (2H, m, $2\times H_Z$-Ar), 7.52 (1H, m, $H_Z$-Ar), 7.42 (1H, m), 7.30 (1H, t, $J=7.6$ Hz, $H_X$-4), 7.26 (2H, d, $J=9.1$ Hz, $H_Y$-3/5), 7.24 (2H, d, $J=7.6$ Hz, $H_X$-3/5), 3.90 (3H, s, OMe), 2.11 (6H, s, $2\times$Me); $^{13}C$ NMR ($d_6$-DMSO; 125 MHz) $\delta$ ppm 164.71 (C), 160.21 (C), 158.73 (C), 138.93 (C), 134.78 (CH), 133.79 (C), 132.08 (C), 131.80 (CH), 131.68 (CH), 131.47 (CH), 130.38 (CH), 129.65 (CH), 129.35 (C), 128.40 (CH), 122.59 (C), 115.31 (CH), 56.48 ($CH_3$), 18.47 ($CH_3$). IR $\nu$ (neat)=1291.8 (m), 1582.5 (m), 1564.7 (m), 1545.5 (m), 1496.9 (m), 1460.2 (w), 1442.6 (w), 1380.7 (w), 1368.1 (s), 1291.8 (m), 1264.0 (s), 1188.8 (m), 1161.6 (s), 1085.5 (m), 1023.4 (m), 974.3 (w), 927.3 (m), 888.7 (m), 834.8 (s), 804.7 (m), 776.0 (w), 729.4 (s), 669.5 (s) $cm^{-1}$. HRMS Calcd for $C_{23}H_{21}N_3O_4SCl$ 470.0941; found 470.0926.

**4.3.45. 3-[(4-Chlorobenzenesulfonyl)-(5-pyridin-3-yl-[1,3,4]oxadiazol-2-yl)-amino]benzoic acid methyl ester 87.** $^1H$ NMR ($d_6$-DMSO; 500 MHz) $\delta$ ppm 9.08 (1H, dd, $J=2.2$, 0.6 Hz, $H_Z$-2), 8.80 (1H, dd, $J=4.7$, 1.6 Hz, $H_Z$-4), 8.26 (1H, ddd, $J=8.2$, 2.2, 1.6 Hz, $H_Z$-6), 8.10 (1H, m, $H_X$-Ar), 7.92 (3H, m, $H_Y$-2/6, $H_X$-Ar), 7.80 (2H, d, $J=8.8$ Hz, $H_Y$-3/5), 7.69 (2H, m, $H_X$-Ar), 7.60 (1H, ddd, $J=8.2$, 4.7, 0.95 Hz, $H_Z$-5), 3.89 (3H, s, OMe); $^{13}C$ NMR ($d_6$-DMSO; 125 MHz) $\delta$ ppm 165.47 (C), 161.92 (C), 158.55 (C), 153.16 (CH), 147.51 (CH), 140.76 (C), 136.57 (C), 135.35 (C), 134.56 (CH), 134.07 (CH), 131.76 (C), 131.12 (CH), 131.10 (CH), 130.94 (CH), 130.47 (CH), 129.91 (CH), 124.81 (CH), 120.04 (C), 53.03 ($CH_3$). IR $\nu$ (neat)=1715.8 (s), 1606.8 (w), 1582.2 (m), 1536.7 (m), 1540.4 (s), 1485.1 (m), 1473.2 (w), 1432.1 (m), 1406.2 (s), 1367.9 (m), 1294.3 (s), 1274.6 (s), 1207.5 (w), 1175.8 (s), 1159.5 (m), 1112.0 (w), 1099.0 (s), 1082.5 (s), 1063.9 (m), 1018.1 (m), 1009.5 (m), 1003.9 (m), 993.1 (s), 984.0 (s), 960.4 (m), 893.4 (m), 831.7 (m), 809.3 (m), 759.7 (s), 753.0 (s), 719.9 (m), 709.0 (m), 700.7 (s), 686.1 (s), 655.0 (s) $cm^{-1}$. HRMS Calcd for $C_{21}H_{16}N_4O_5SCl$ 471.0530; found 471.0518.

**4.3.46. *N*-(3-Chloro-4-methylphenyl)-4-methoxy-*N*-[5-(2-nitrophenyl)-[1,3,4]oxadiazol-2-yl]benzenesulfonamide 88.** $^1H$ NMR ($d_6$-DMSO; 500 MHz) $\delta$ ppm 8.19 (1H, m, $H_Z$-5), 7.97 (3H, m, $H_Z$-3/4/6), 7.82 (2H, d, $J=9.1$ Hz, $H_Y$-2/6), 7.48 (1H, d, $J=8.5$ Hz, $H_X$-5), 7.40 (1H, d, $J=2.5$ Hz, $H_X$-2), 7.21 (2H, d, $J=9.1$ Hz, $H_Y$-3/5), 7.17 (1H, dd, $J=8.5$, 2.5 Hz, $H_X$-6), 3.90 (3H, s, OMe), 2.37 (3H, s, Me); $^{13}C$ NMR ($d_6$-DMSO; 125 MHz) $\delta$ ppm 164.71 (C), 159.79 (C), 159.25 (C), 148.10 (C), 138.33 (C), 135.16 (C), 134.33 (CH), 134.15 (C), 134.08 (CH), 132.54 (CH), 131.89 (CH), 131.41 (CH), 129.50 (CH), 127.88 (CH), 127.74 (C), 125.34 (CH), 117.10 (C), 115.41 (CH), 56.47 ($CH_3$), 19.80 ($CH_3$). IR $\nu$ (neat)=1592.5 (m), 1570.5 (m), 1531.4 (s), 1489.0 (m), 1442.0 (w), 1367.2 (m), 1348.1 (m), 1309.6 (w), 1262.8 (s), 1186.6 (m), 1162.6 (s), 1090.3 (m), 1052.5 (m), 1024.6 (m), 965.9 (w), 945.0 (w), 914.6 (w), 852.4 (w), 834.9 (w), 802.8 (w), 786.7 (w), 755.1 (w), 715.0 (w), 700.6 (m), 669.9 (s) $cm^{-1}$. HRMS Calcd for $C_{21}H_{16}N_4O_6SCl$ 487.0479; found 487.0498.

**4.3.47. 4-Bromo-*N*-[5-(2-chlorophenyl)-[1,3,4]oxadiazol-2-yl]-*N*-(2,6-dimethylphenyl)benzenesulfonamide 89.** $^1H$ NMR ($d_6$-DMSO; 500 MHz) $\delta$ ppm 8.09 (2H, d, $J=8.8$ Hz,

$H_Y$-2/6), 8.00 (2H, d, $J$=8.8 Hz, $H_Y$-3/5), 7.84 (1H, dd, $J$=7.9, 1.6 Hz, $H_Z$-Ar), 7.63 (2H, m, $H_Z$-Ar), 7.54 (1H, m, $H_Z$-Ar), 7.31 (1H, t, $J$=7.9 Hz, $H_X$-4), 7.22 (2H, d, $J$=7.6 Hz, $H_X$-3/5), 2.10 (6H, s, 2×Me); $^{13}$C NMR ($d_6$-DMSO; 125 MHz) $\delta$ ppm 160.52 (C), 158.41 (C), 138.96 (C), 137.29 (C), 134.36 (C), 133.88 (CH), 133.36 (CH), 132.11 (C), 131.75 (CH), 131.48 (CH), 131.27 (CH), 130.62 (CH), 129.92 (C), 129.77 (CH), 128.40 (CH), 122.49 (C), 18.48 ($CH_3$). IR $\nu$ (neat)=1563.2 (s), 1539.8 (m), 1462.9 (w), 1444.5 (w), 1368.5 (s), 1290.6 (m), 1279.6 (m), 1188.8 (w), 1166.0 (s), 1083.6 (w), 1066.9 (w), 932.7 (m), 826.9 (m), 782.4 (m), 763.1 (s), 740.8 (s), 727.5 (s) cm$^{-1}$. HRMS Calcd for $C_{22}H_{18}N_3O_3SBr_2$ 561.9436; found 561.9388.

**4.3.48. 3-[(4-Bromobenzenesulfonyl)-(5-pyridin-3-yl-[1,3,4]oxadiazol-2-yl)-amino]benzoic acid methyl ester 90.** $^1$H NMR ($d_6$-DMSO; 500 MHz) $\delta$ ppm 9.04 (1H, dd, $J$=2.2, 0.95 Hz, $H_Z$-2), 8.81 (1H, dd, $J$=4.7, 1.6 Hz, $H_Z$-4), 8.26 (1H, ddd, $J$=7.9, 2.2, 1.6 Hz, $H_Z$-6), 8.10 (1H, m, $H_Z$-Ar), 7.98 (2H, d, $J$=8.8 Hz, $H_X$-3/5), 7.96 (1H, m), 7.84 (2H, d, $J$=8.8 Hz, $H_X$-2/6), 7.68 (2H, m, 2×$H_Y$-Ar), 7.63 (1H, ddd, $J$=7.9, 4.7, 0.95 Hz, $H_Z$-5), 3.88 (3H, s, OMe); $^{13}$C NMR ($d_6$-DMSO; 125 MHz) $\delta$ ppm 165.47 (C), 161.91 (C), 158.54 (C), 153.17 (CH), 147.51 (CH), 136.57 (C), 135.79 (C), 134.57 (CH), 134.07 (CH), 133.43 (CH), 131.75 (C), 131.13 (CH), 131.11 (CH), 130.90 (CH), 129.96 (CH), 129.92 (C), 124.82 (CH), 120.04 (C), 53.04 ($CH_3$). IR $\nu$ (neat)=1716.4 (s), 1606.7 (w), 1583.4 (w), 1572.6 (m), 1563.1 (m), 1540.4 (s), 1484.0 (m), 1467.6 (m), 1432.8 (m), 1406.0 (m), 1388.6 (m), 1368.0 (m), 1294.9 (s), 1274.1 (s), 1207.7 (m), 1169.3 (s), 1159.6 (s), 1099.5 (m), 1083.1 (m), 1064.8 (m), 1016.9 (w), 1004.2 (m), 993.4 (m), 960.5 (m), 891.9 (m), 829.2 (m), 755.1 (m), 745.8 (s), 720.0 (s), 699.9 (s), 686.5 (s), 654.0 (m) cm$^{-1}$. HRMS Calcd for $C_{21}H_{16}N_4O_5SBr$ 515.00225; found 515.0037.

**4.3.49. *N*-Adamantan-1-yl-*N*-(5-hexyl-[1,3,4]oxadiazol-2-yl)benzenesulfonamide 91.** $^1$H NMR ($d_6$-DMSO; 500 MHz) $\delta$ ppm 8.26 (2H, d, $J$=9.1 Hz, $H_X$-3/5), 7.81 (2H, d, $J$=9.1 Hz, $H_X$-2/6), 2.60 (2H, t, $J$=7.25 Hz, $H_Z$-1-$CH_2$), 2.04 (3H, m), 1.91 (5H, m), 1.60 (8H, m), 1.26 (8H, m), 0.83 (3H, t, $J$=6.9 Hz, $H_Z$-Me); $^{13}$C NMR ($d_6$-DMSO; 125 MHz) $\delta$ ppm 161.97 (C), 147.24 (C), 144.06 (C), 142.61 (C), 127.28 (CH), 125.03 (CH), 41.40 ($CH_2$), 36.35 ($CH_2$), 31.56 ($CH_2$), 29.33 (CH), 28.74 ($CH_2$), 28.67 ($CH_2$), 26.42 ($CH_2$), 24.86 ($CH_2$), 22.49 ($CH_2$), 14.38 ($CH_3$). IR $\nu$ (neat)=2903.7 (s), 2850.1 (s), 1625.9 (s), 1573.3 (s), 1515.5 (w), 1468.9 (w), 1454.3 (w), 1389.7 (w), 1361.6 (m), 1334.3 (m), 1307.2 (m), 1249.0 (w), 1225.3 (w), 1180.2 (m), 1136.3 (w), 976.0 (w), 932.1 (m), 852.7 (m), 817.0 (w), 727.8 (m) cm$^{-1}$. HRMS Calcd for $C_{25}H_{35}N_4O_5S$ 503.2328; found 503.2298.

**4.3.50. *N*-(3-Chlorophenyl)-*N*-[5-(4-trifluoromethylphenyl)-[1,3,4]oxadiazol-2-yl]benzenesulfonamide 92.** $^1$H NMR ($d_6$-DMSO; 500 MHz) $\delta$ ppm 8.11 (2H, d, $J$=8.2 Hz), 7.96 (3H, m), 7.88 (1H, m), 7.74 (2H, m), 7.61 (1H, ddd, $J$=8.0, 2.1, 1.1 Hz, $H_X$-Ar), 7.54 (1H, t, $J$=8.0 Hz, $H_X$-Ar), 7.51 (1H, t, $J$=2.1 Hz, $H_X$-Ar), 7.39 (1H, ddd, $J$=8.0, 2.1, 1.1 Hz, $H_X$-Ar); $^{13}$C NMR ($d_6$-DMSO; 125 MHz) $\delta$ ppm 162.39 (C), 158.69 (C), 137.47 (C), 136.66 (C), 135.66 (CH), 134.15 (C), 131.79 (CH), 130.61 (CH), 130.28 (CH), 129.29 (CH), 128.96 (CH), 128.09 (CH), 127.67 (CH), 126.92 and 126.89 and 126.86 and 126.83 ($CF_3$). IR $\nu$ (neat)=1571.3 (w), 1537.7 (s), 1505.9 (w), 1472.4 (w), 1449.9 (w), 1424.9 (w), 1367.2 (w), 1327.9 (s), 1285.5 (w), 1181.6 (m), 1161.1 (s), 1123.8 (m), 1095.6 (s), 1068.9 (s), 1015.3 (m), 968.5 (m), 946.4 (m), 925.6 (w), 847.4 (s), 788.9 (m), 745.0 (m), 719.3 (s), 679.8 (s) cm$^{-1}$. HR-MS Calcd for $C_{20}H_{14}N_3O_3ClF_3S$: 480.0347; found 480.0401.

**4.3.51. 3,4-Dimethoxybenzenesulfonic acid 3-{5-[(3,4-dimethoxy-benzenesulfonyl)-(2,6-dimethylphenyl)-amino]-[1,3,4]oxadiazol-2-yl}naphthalen-2-yl ester 93.** $^1$H NMR ($d_6$-DMSO; 500 MHz) $\delta$ ppm 8.44 (1H, s), 8.12 (1H, dd, $J$=7.9 Hz), 8.03 (1H, d, $J$=7.9 Hz), 7.90 (1H, s), 6.68 (3H, m), 7.33 (1H, m), 7.29 (1H, d, $J$=8.8 Hz), 7.23 (2H, m), 7.17 (1H, dd, $J$=8.5, 2.5 Hz), 7.08 (1H, d, $J$=2.2 Hz), 6.98 (1H, d, $J$=8.8 Hz), 3.91 (3H, s, OMe), 3.81 (6H, s, 2×OMe), 3.60 (3H, s, OMe), 2.13 (6H, s, 2×Me); $^{13}$C NMR ($d_6$-DMSO; 125 MHz) $\delta$ ppm 159.68 (C), 158.83 (C), 154.60 (C), 154.58 (C), 149.25 (C), 149.23 (C), 142.86 (C), 139.12 (C), 134.81 (C), 134.42 (C), 131.93 (CH), 131.13 (C), 130.40 (CH), 129.79 (CH), 129.67 (CH), 129.27 (C), 129.12 (CH), 128.39 (CH), 128.35 (CH), 124.87 (C), 123.79 (CH), 123.17 (CH), 122.42 (CH), 116.65 (C), 112.03 (CH), 111.69 (CH), 111.57 (CH), 110.81 (CH), 56.60 ($CH_3$), 56.46 ($CH_3$), 56.32 ($CH_3$), 56.09 ($CH_3$), 18.47 ($CH_3$). IR $\nu$ (neat)=1630.3 (w), 1582.9 (m), 1544.4 (m), 1508.2 (s), 1464.3 (m), 1441.8 (m), 1407.5 (m), 1369.6 (s), 1264.3 (s), 1238.2 (s), 1188.5 (m), 1174.0 (m), 1163.4 (m), 1140.5 (s), 1092.2 (s), 1054.3 (w), 1013.5 (s), 928.3 (w), 911.8 (m), 893.8 (m), 854.8 (w), 817.4 (m), 765.9 (s), 741.2 (m) cm$^{-1}$. HRMS Calcd for $C_{36}H_{34}N_3O_{10}S_2$ 732.1686; found 732.1684.

**4.3.52. *N*-Benzyl-*N*-(5-pyridin-3-yl-[1,3,4]oxadiazol-2-yl)benzenesulfonamide 94.** $^1$H NMR ($d_6$-DMSO; 500 MHz) $\delta$ ppm 9.10 (1H, dd, $J$=2.5, 0.95 Hz, $H_Z$-2), 8.72 (1H, dd, $J$=5.0, 1.6 Hz, $H_Z$-4), 8.30 (1H, ddd, $J$=8.2, 2.2, 1.6 Hz, $H_Z$-6), 8.00 (2H, dd, $J$=7.25, 0.95 Hz, $H_Y$-2/6), 8.81 (1H, m, $H_Y$-4), 7.69 (2H, m, $H_Y$-3/5), 7.56 (1H, ddd, $J$=8.2, 5.0, 0.95 Hz, $H_Z$-5), 7.40 (2H, m, 2×$H_X$-Ar), 7.33 (2H, m, 2×$H_X$-Ar), 7.29 (1H, m, $H_X$-Ar), 5.23 (2H, s, $NCH_2$); $^{13}$C NMR ($d_6$-DMSO; 125 MHz) $\delta$ ppm 162.95 (C), 161.85 (C), 152.29 (CH), 148.19 (CH), 137.10 (C), 135.82 (C), 135.41 (CH), 135.16 (CH), 130.57 (CH), 128.97 (CH), 128.31 (CH), 128.28 (CH), 127.72 (CH), 126.13 (C), 124.74 (CH), 53.10 ($CH_2$). IR $\nu$ (neat)=1584.6 (w), 1570.1 (w), 1494.8 (w), 1444.0 (s), 1413.5 (s), 1366.8 (s), 1336.2 (m), 1275.3 (m), 1252.8 (m), 1185.5 (m), 1166.3 (s), 1105.1 (m), 1088.8 (m), 1077.7 (m), 1025.6 (m), 1012.4 (s), 983.0 (m), 971.9 (m), 832.6 (s), 820.7 (m), 806.0 (m), 760.1 (s), 722.0 (s) cm$^{-1}$. HR-MS Calcd for $C_{20}H_{17}N_4O_3S$: 393.1021; found 393.1014.

**4.3.53. *N*-Benzyl-4-chloro-*N*-(5-pyridin-3-yl-[1,3,4]-oxadiazol-2-yl)benzenesulfonamide 95.** $^1$H NMR ($d_6$-DMSO; 500 MHz) $\delta$ ppm 9.06 (1H, dd, $J$=2.2, 0.95 Hz, $H_Z$-2), 8.69 (1H, dd, $J$=4.7, 1.6 Hz, $H_Z$-4), 8.22 (1H, ddd, $J$=7.9, 2.2, 1.6 Hz, $H_Z$-6), 7.90 (2H, d, $J$=8.8 Hz, $H_Y$-2/6), 7.61 (2H, d, $J$=8.8 Hz, $H_Y$-3/5), 7.50 (1H, ddd, $J$=7.9, 4.7, 0.95 Hz, $H_Z$-5), 7.40 (2H, m, 2×$H_X$-Ar), 7.29 (3H, m, 3×$H_X$-Ar), 5.20 (2H, s, $H_X$-1); $^{13}$C NMR ($d_6$-DMSO; 125 MHz) $\delta$ ppm 162.86 (C), 161.58 (C),

152.00 (CH), 148.10 (CH), 140.61 (C), 135.90 (C), 135.37 (C), 134.80 (CH), 130.35 (CH), 129.40 (CH), 128.74 (CH), 128.38 (CH), 128.18 (CH), 126.16 (C), 124.39 (CH), 53.27 ($CH_2$). IR $\nu$ (neat)=1584.6 (m), 1565.9 (m), 1496.4 (m), 1479.4 (m), 1446.9 (s), 1419.3 (s), 1401.2 (m), 1357.9 (s), 1274.5 (m), 1250.3 (m), 1165.6 (s), 1108.6 (m), 1083.7 (m), 1019.9 (m), 1013.2 (m), 980.9 (m), 848.4 (m), 837.3 (m), 823.1 (m), 756.6 (s), 748.2 (s), 696.3 (s), 656.7 (s) $cm^{-1}$. HR-MS Calcd for $C_{20}H_{15}N_4O_3SCl$: 427.0553; found 427.0632.

**4.3.54. 4-Chloro-*N*-(3-chloro-phenyl)-*N*-[5-(4-chloro-phenyl)-[1,3,4]oxadiazol-2-yl]benzenesulfonamide 96.** $^1H$ NMR ($d_6$-DMSO; 500 MHz) $\delta$ ppm 7.83 (2H, d, $J$=8.5 Hz, $H_Y$-2/6), 7.90 (2H, d, $J$=8.8 Hz, $H_Z$-2/6), 7.83 (2H, d, $J$=8.5 Hz, $H_Y$-3/5), 7.68 (2H, d, $J$=8.8 Hz, $H_Z$-3/5), 7.63 (1H, ddd, $J$=8.2, 2.4, 1.0 Hz, $H_X$-Ar), 7.56 (2H, m, 2×$H_X$-Ar), 7.39 (1H, ddd, $J$=7.9, 2.4, 1.0 Hz, $H_X$-Ar); $^{13}C$ NMR ($d_6$-DMSO; 125 MHz) $\delta$ ppm 162.76 (C), 158.17 (C), 140.73 (C), 137.46 (C), 137.33 (C), 135.41 (C), 134.21 (C), 131.90 (CH), 130.74 (CH), 130.46 (CH), 130.15 (CH), 130.09 (CH), 129.35 (CH), 128.67 (CH), 128.09 (CH), 122.21 (C). IR $\nu$ (neat)=1605.4 (w), 1584.2 (s), 1562.8 (s), 1541.8 (s), 1474.3 (s), 1376.3 (m), 1302.3 (w), 1281.7 (w), 1172.2 (s), 1091.9 (s), 1055.1 (m), 1028.7 (w), 1012.3 (s), 964.1 (m), 946.8 (m), 833.6 (m), 784.2 (m), 757.2 (s), 729.3 (m), 704.5 (m), 682.4 (s) $cm^{-1}$. HR-MS Calcd for $C_{20}H_{13}N_3O_3SCl_3$: 479.9743; found 479.9767.

**4.3.55. 4-Nitro-*N*-phenyl-*N*-(5-pyridin-3-yl-[1,3,4]oxadiazol-2-yl)benzenesulfonamide 97.** $^1H$ NMR ($d_6$-DMSO; 500 MHz) $\delta$ ppm 9.08 (1H, dd, $J$=2.1, 0.95 Hz, $H_Z$-2), 8.81 (1H, dd, $J$=4.7, 1.6 Hz, $H_Z$-4), 8.54 (2H, d, $J$=8.8 Hz, $H_Y$-3/5), 8.26 (1H, dd, $J$=7.9, 2.1 Hz, $H_Z$-6), 8.20 (2H, d, $J$=8.8 Hz, $H_Y$-2/6), 7.64 (1H, ddd, $J$=7.9, 4.7, 0.95 Hz, $H_Z$-5), 7.52 (3H, m, 2×$H_X$-Ar), 7.41 (2H, m, 2×$H_X$-Ar); $^{13}C$ NMR ($d_6$-DMSO; 125 MHz) $\delta$ ppm 162.01 (C), 158.54 (C), 153.22 (CH), 151.47 (C), 147.54 (CH), 142.01 (C), 135.98 (C), 134.62 (CH), 130.81 (C), 130.72 (CH), 130.53 (CH), 129.34 (CH), 125.44 (CH), 124.84 (CH), 119.97 (C). IR $\nu$ (neat)=1606.9 (w), 1579.3 (w), 1567.4 (w), 1538.9 (m), 1524.7 (s), 1488.5 (m), 1406.4 (s), 1370.1 (w), 1345.9 (s), 1312.3 (m), 1290.2 (m), 1173.3 (s), 1121.6 (w), 1096.2 (m), 1052.4 (s), 1027.7 (s), 1008.4 (s), 959.9 (m), 914.8 (w), 888.8 (w), 854.3 (s), 815.0 (m), 754.5 (m), 738.9 (s), 723.1 (m), 698.9 (s), 683.9 (s), 666.6 (m) $cm^{-1}$. HR-MS Calcd for $C_{19}H_{14}N_5O_5S$: 424.0716; found 424.0734.

**4.3.56. Biphenyl-4-sulfonic acid (4-bromophenyl)-(5-pyridin-3-yl-[1,3,4]oxadiazol-2-yl)amide 98.** $^1H$ NMR ($CDCl_3$; 400 MHz) $\delta$ ppm 9.19 (1H, dd, $J$=2.2, 0.7 Hz, $H_Z$-2), 8.77 (1H, dd, $J$=4.7, 1.5 Hz, $H_Z$-4), 8.29 (1H, ddd, $J$=8.05, 2.2, 1.5 Hz, $H_Z$-6), 7.96 (2H, d, $J$=8.4 Hz, $H_Y$-2/6), 7.76 (2H, d, $J$=8.4 Hz, $H_Y$-3/5), 7.64 (2H, m), 7.57 (2H, d, $J$=8.7 Hz, $H_X$-2/6), 7.53–7.40 (4H, m), 7.29 (2H, d, $J$=8.7 Hz, $H_X$-3/5).

**4.3.57. 4-Methoxy-N-[5-(3-methoxyphenyl)-[1,3,4]oxadiazol-2-yl]-*N*-4-methylbenzenesulfonamide 99.** $^1H$ NMR ($CDCl_3$; 400 MHz) $\delta$ ppm 7.88 (2H, d, $J$=8.8 Hz, $H_Y$-2/6), 7.55 (1H, dt, $J$=8.05, 1.4 Hz, $H_Z$-Ar), 7.52 (1H, m, $H_Z$-Ar), 7.41 (1H, t, $J$=8.05 Hz, $H_Z$-Ar), 7.24 (2H, d, $J$=8.4 Hz, $H_X$-2/6), 7.21 (2H, d, $J$=8.4 Hz, $H_X$-3/5), 7.08 (1H, ddd, $J$=8.4, 2.6, 1.1 Hz, $H_Z$-Ar), 7.02 (2H, d, $J$=8.8 Hz, $H_Y$-3/5), 3.91 (3H, s, OMe), 3.86 (3H, s, OMe), 2.40 (3H, s, Me).

**4.3.58. Thiophene-2-sulfonic acid ethyl-[5-(4-nitro-phenyl)-[1,3,4]oxadiazol-2-yl]amide 100.** LC-MS $R_f$ 3.755 M+H 381.0; $^1H$ NMR ($CDCl_3$; 400 MHz) $\delta$ ppm 8.40 (2H, d, $J$=8.8 Hz, $H_Z$-3/5), 8.21 (2H, d, $J$=8.8 Hz, $H_Z$-2/6), 7.85 (1H, dd, $J$=4.0, 1.5 Hz, $H_Y$-4), 7.73 (1H, d, $J$=5.1, 1.5 Hz, $H_Y$-5), 7.18 (1H, dd, $J$=5.1, 4.0 Hz, $H_Y$-4), 4.08 (2H, q, $J$=7.1 Hz, $H_X$-1), 1.42 (3H, t, $J$=7.1 Hz, $H_X$-2).

**4.3.59. 4-Chloro-*N*-(3-chlorophenyl)-*N*-(5-pyridin-3-yl-[1,3,4]oxadiazol-2-yl)benzenesulfonamide 101.** LC-MS $R_f$ 4.509 M+H 446.9; $^1H$ NMR ($CDCl_3$; 400 MHz) $\delta$ ppm 9.18 (1H, br s, $H_Z$-2), 8.77 (1H, d, $J$=4.0 Hz, $H_Z$-4), 8.26 (1H, dt, $J$=8.05, 1.8 Hz, $H_Z$-6), 7.85 (2H, d, $J$=8.78 Hz, $H_Y$-2/6), 7.54 (2H, d, $J$=7.78 Hz, $H_Y$-3/5), 7.48–7.31 (4H, m), 7.23 (1H, m); $^{13}C$ NMR ($d_6$-DMSO; 100 MHz) $\delta$ ppm 162.67 (C), 159.02 (C), 153.22 (CH), 148.17 (CH), 141.85 (C), 138.34 (C), 136.10 (C), 135.73 (C), 134.38 (CH), 131.04 (CH), 130.78 (CH), 130.71 (CH), 130.00 (CH), 129.45 (CH), 127.26 (C), 124.19 (CH), 120.26 (C). IR $\nu$ (neat)=1571.8 (m), 1541.9 (s0, 1529.8 (s), 1488.8 (m), 1473.9 (m), 1416.7 (m), 1395.9 (w), 1372.9 (m), 1286.9 (m), 1173.9 (s), 1161.9 (m), 1081.0 (s), 1047.7 (w), 971.7 (m), 945.5 (w), 928.8 (w), 853.2 (w), 831.0 (m), 760.2 (s), 739.6 (m), 712.5 (m), 684.9 (s), 656.2 (m) $cm^{-1}$.

**4.3.60. 4-Chloro-benzenesulfonic acid 3-{5-[(4-chloro-benzenesulfonyl)-(2,6-dimethylphenyl)amino]-[1,3,4]-oxadiazol-2-yl}-naphthalen-2-yl ester 102.** LC-MS $R_f$ 5.261 M+H 680.0; $^1H$ NMR ($CDCl_3$; 400 MHz) $\delta$ ppm 8.20 (1H, s), 8.09 (2H, d, $J$=8.8 Hz), 7.77 (3H, m), 7.57–7.39 (6H, m), 7.22 (2H, d, $J$=8.4 Hz), 7.19 (1H, m), 7.10 (2H, d, $J$=7.7 Hz), 2.11 (6H, s, 2×Me); $^{13}C$ NMR ($d_6$-DMSO; 100 MHz) $\delta$ ppm 160.45 (C), 159.12 (C), 143.24 (C), 141.51 (C), 141.81 (C), 139.69 (C), 137.68 (C), 134.86 (C), 134.48 (C), 133.31 (C), 132.12 (CH), 131.48 (C), 131.24 (CH), 130.58 (CH), 130.34 (CH), 129.94 (CH), 129.90 (CH), 129.61 (CH), 129.01 (CH), 128.30 (CH), 128.21 (CH), 122.51 (CH), 116.58 (C), 19.02 ($CH_3$). IR $\nu$ (neat)=1543.8 (s), 1473.8 (m), 1358.9 (s), 1281.9 (m), 1191.0 (s), 1176.2 (s), 1085.9 (s), 1015.2 (m), 933.9 (m), 897.6 (m), 817.0 (s), 779.6 (s), 758.3 (s), 703.7 (m), 669.6 (m) $cm^{-1}$.

**4.3.61. *N*-(3-Chloro-4-methylphenyl)-*N*-[5-(3-hydroxy-naphthalen-2-yl)-[1,3,4]oxadiazol-2-yl]-2-trifluoro-methylbenzenesulfonamide 103.** LC-MS $R_f$ 4.965 M+H 560.0; $^1H$ NMR ($CDCl_3$; 400 MHz) $\delta$ ppm 8.54 (1H, m), 8.37 (1H, m), 8.14 (1H, m), 8.02–7.86 (3H, m), 7.84–7.67 (3H, m), 7.62–7.55 (3H, m), 7.49 (1H, m), 7.20 (1H, m), 2.32 (3H, s, Me); $^{13}C$ NMR ($d_6$-DMSO; 100 MHz) $\delta$ ppm 162.18 (C), 158.85 (C), 142.86 (C), 138.82 (C), 135.32 (C), 140.05 (C), 134.95 (CH), 134.78 (C), 134.66 (CH), 134.06 (CH), 133.30 (CH), 133.05 (C), 132.96 (CH), 132.48 (CH), 131.97 (CH), 131.55 (C), 130.02 (CH), 129.69 (CH), 129.13 (CH), 128.20 (CH), 128.17 (C), 127.75 (CH), 122.13 (CH), 116.76 (C), 20.27 ($CH_3$). IR $\nu$ (neat)=1628.6 (m), 1607.4 (m), 1544.8 (m), 1513.5 (w), 1496.3 (m), 1466.4 (w), 1439.5 (w), 11406.5 (w), 1353.9 (s), 1311.1 (s), 1274.0 (m), 1188.8

(m), 1177.8 (s), 1146.5 (s), 1115.9 (s), 1095.1 (w), 1047.6 (m), 1034.1 (m), 1025.4 (m), 907.8 (m), 892.4 (m), 827.5 (s), 805.6 (s), 796.6 (s), 743.5 (s), 720.9 (s), 690.0 $cm^{-1}$.

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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.2005.03.062

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19. PS-carbodiimide (1.1–1.13 mmol $g^{-1}$) available from Argonaut Technologies was used without further purification.
20. For the pyridyl derivative (*N*; Fig. 2) a benzaldehyde functionalised resin (PS-benzaldehyde; polystyrene backbone 1–2% cross-linked with divinylbenzene available from Argonaut Technologies) was substituted for the sulfonic acid. Additionally, for the chloroalkyl containing isocyanate reactions the aminomethylpolystyrene was excluded from the scavenging process.
21. A mono-mode single cavity microwave instrument with pressure and temperature sensing, and an integrated liquid handling robot (Emrys Synthesizer) was used for the library preparation and an Emrys optimizer EXP for investigative and early stage development work. Both machines are available from Personal Chemistry a subdivision of Biotage.
22. *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide on polystyrene (EDC polymer bound) available from Aldrich cat. no. 09657 and *N*-ethyl-*N*′-(3-dimethylaminopropyl)carbodiimide on JandaJel both proved to be less effective for this cyclisation.
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# Synthesis, characterization and ion transportation studies of some novel cyclophane amides

Perumal Rajakumar[a,*] and A. Mohammed Abdul Rasheed[b]

[a]Department of Organic Chemistry, University of Madras, Guindy Campus, Chennai 600 025, India
[b]Amrutanjan Limited, Research and Development Centre, Egattur, Tamil nadu 603103, India

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**Abstract**—Various novel cyclophane amides with a large cavity have been synthesized. The structures of cyclophane amides **14** and **15** were resolved using XRD studies. Cyclophane amide **28** shows a shift in $\lambda_{max}$ in the UV/Vis. spectra when treated with Cu (II) ion as well as with Pb (II) ion. Ion transportation studies were carried out with cyclophane amide **14** which proved that the $Na^+$ ion passes through the cavity while $K^+$ ions are retained.


## 1. Introduction

The synthesis of new supramolecules for studying biomolecular interactions stimulates the imaginative skill of synthetic chemists. Synthesis of amide based supramolecular system has been reported in the literature.[1–17] Cyclic peptides[18] with open pores are useful as transport vehicles for biologically important ions or neutral molecules[19] or as catalysts[20] and for studying host-guest chemistry. Synthesis and complexation studies with tyrosinophanes has been reported earlier.[21] Cystine based cyclic peptide has the ability to form a double—helical structure.[22] The self-assembly of acyclic peptides and hence their ability to form beta-sheet structures has also been demonstrated.[23,24] The conformational aspects and molecular recognition ability of cystinophanes are well known.[25] Adamantane based systems also form double-helical cyclic structures.[24,26] The ability of cyclic peptides to form nanotubes has been well documented.[27,28] Serinophanes form a tubular structure due to aromatic π–π interactions.[29]

The ion transport properties of macrocycles are biologically relevent[30] and ion transport through membranes has been characterized with adamantane based cyclophanes[31] and with norbornene based cyclic peptides.[32] Thus cyclic amides play an important role in various biological systems and hence, by varying the size of the cavity, cyclic amides can be used for the transport of a particular ion in preference to the other ions. Once the synthesis of the targeted cyclic amide is carried out, the cyclic amide can be impregnated into a membrane and can be used for ion transport.[33] Intramolecular hydrogen bonding can collapse the cyclic peptide to a minimum accompanied by folding of the backbone.[34] However, due to intermolecular hydrogen bonding the cyclic amide can show self assembling properties that would eventually lead to tubular structure and hence have potential to be used as nano material devices. Furthermore such cyclic amides can form complexes with metal ions like Cd (II),[35] Fe (III)[20] and Cu (II) and hence they can be used for selective metal ion complexation studies[36] and also as a neutral host for anion complexation.[37] Amides are also used as molecular receptors[38] and in the molecular recognition[39] of biologically interacting substrates including anti-HIV active macrocyclic amides.[40] With such views in mind we focused our attention on the synthesis of various cyclic amides. Herein we report the synthesis and characterization of various cyclic amides with varied cavity size. Furthermore we describe herein the ion transport studies of some of the cyclic amides.

## 2. Results and discussion

Diacid chlorides **1–5** were prepared and used for the synthesis of cyclophane amides.

*Keywords*: Cyclophane amides; Adamantane; Macrocyclic amides.
* Corresponding author. Tel.: +44 2235 1269; fax: +91 44 2235 2494; e-mail: perumalrajakumar@hotmail.com

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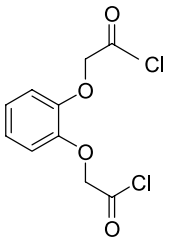


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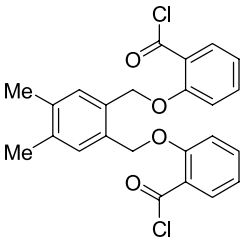


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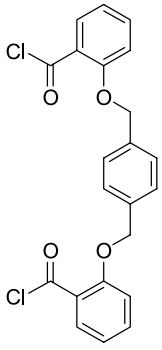


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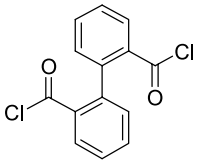


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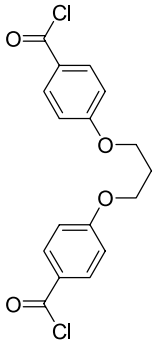


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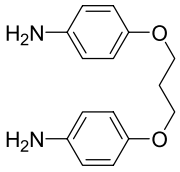


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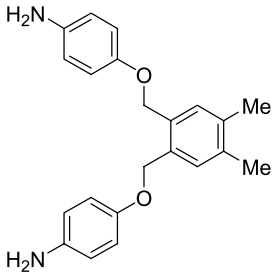


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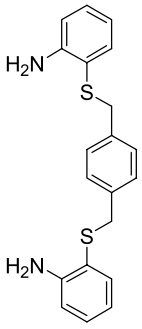


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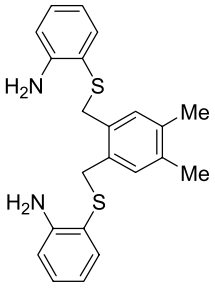


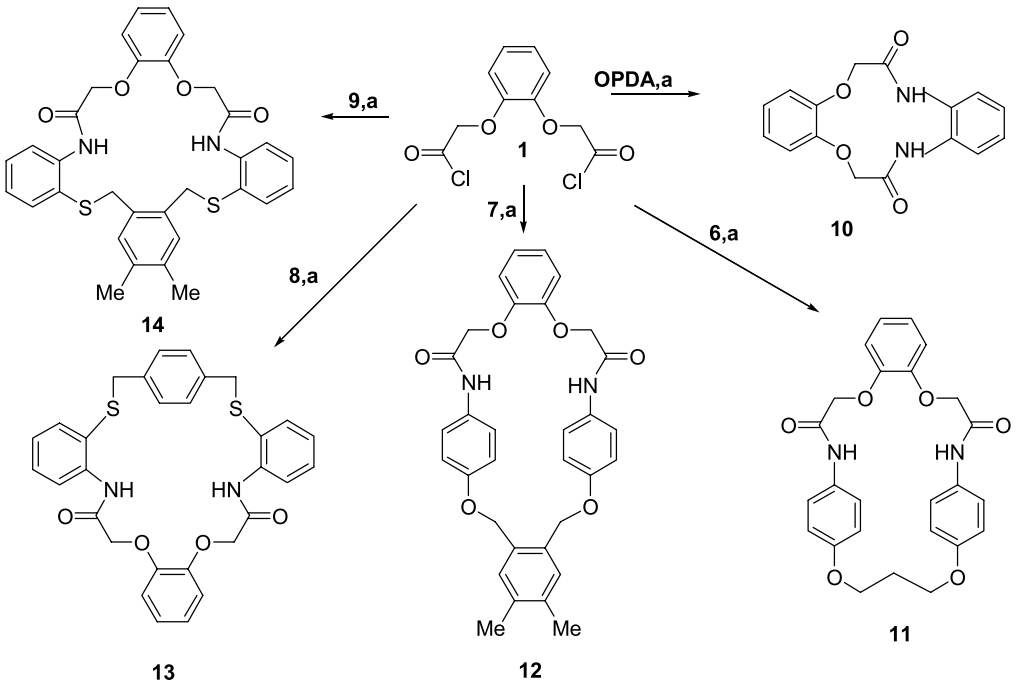

9

Reaction of catechol with 2.1 equiv of ethyl chloroacetate in the presence of potassium carbonate followed by the hydrolysis of the resulting diethyl ester gave the corresponding diacid, which was then reacted with thionyl chloride to give diacid chloride **1**.[41] The diacid derived for diacid chloride **1** was also prepared from the respective diol.[42] Reaction of 4,5-bis (chloromethyl)-*o*-xylene[43] with 2.1 equiv of methyl salicylate followed by hydrolysis of the resulting dimethyl ester and subsequent reaction with thionyl chloride gave diacid chloride **2**. Diacid chloride **3** was obtained from the corresponding dicarboxylic acid. The respective dicarboxylic acid was reported earlier[44] in 55% overall yield by the reaction of *p*-xylylene dibromide with methyl salicylate in the presence of NaH in THF followed by hydrolysis. However in the present investigation the diacid was obtained in 95% overall yield by the alkylation of *p*-xylylene dibromide with methyl salicylate in the presence of anhydrous potassium carbonate and KI in acetonitrile followed by hydrolysis of the resulting diester. Reaction of the corresponding dicarboxylic acid with thionyl chloride in methylene chloride gave diacid chloride **3** in quantitative yield. Diphenic acid chloride **4** was prepared by the reaction of diphenic acid and thionyl chloride. The diacid chloride **5** was obtained from the corresponding diacid which was reported earlier.[45] The diacid was also prepared from 1,3-dibromopropane and *p*-hydroxybenzoic acid in presence of NaOH in DMSO.[46] By another method, 1,3-dibromopropane was reacted with methyl *p*-hydroxybenzoate and the resulting diester was hydrolyzed to give the dicarboxylic acid.[47] In the current investigation the later method was employed and the resulting dicarboxylic acid was reacted with thionyl chloride to give diacid chloride **5**.

Diamines **6–9** were prepared and used for the synthesis of cyclophane amides.

Diamine **6** has been used previously for polymerization.[48] In the earlier method[49] 1,3-dibromopropane was treated with *p*-nitrophenol and the resulting dinitro compound was then reduced to give diamine **6**. In a later method[50] 1,3-dibromopropane was treated with 4-hydroxy acetanilide and resulting product was hydrolyzed to give **6**. However, in both the references cited above detailed experimental procedure was not available as the reported methods were patented. Hence, in the present investigation 1,3-dibromopropane was treated with 2.1 equiv of *p*-nitrophenol in acetonitrile in the presence of anhydrous potassium carbonate and KI and the resulting dinitro compound was reduced with hydrogen in the presence of Pd/C to give the diamine **6** in 65% overall yield. Similarly diamine **7** was also prepared by the reaction of 4,5-bis (chloromethyl)-*o*-xylene with *p*-nitrophenol by the usual procedure to give dinitro compound, which was reduced with hydrogen in the presence of Pd/C to give diamine **7**. Though diamine **8** was reported recently,[51] in the present investigation 2.1 equiv of *o*-aminothiophenol were treated with *p*-xylylene dibromide to give diamine **8** in 90% yield. Diamine **9** was also prepared by a similar method from the reaction of 4,5-bis (chloromethyl)-*o*-xylene with *o*-aminothiophenol.

The diester derived from diacid chloride **1** has been extensively used for the formation of macrocyclic amides.[52] Diacid chloride **1** has been also used for the preparation of macrocyclic amides.[53] Similarly the reaction of diacid chloride **1** with arylamines has also been studied.[54] In the current investigation, diacid chloride **1** was used for the synthesis of cyclophane amides. Reaction of diacid choride **1** with *o*-phenylenediamine (OPDA) in chloroform and in the presence of triethylamine afforded cyclophane amide **10** in 50% yield. Cyclophane amide **10** in the $^1$H NMR showed the $OCH_2$ and NH protons at $\delta$ 4.76, at $\delta$ 9.71 in addition to




**Scheme 1.** (a) Triethyl amine, $CHCl_3$, rt, 6 h.

aromatic protons at $\delta$ 7.04 to 7.63 and in the mass spectrum the molecular ion appeared at *m/z* 298. Similarly acid chloride **1** with various diamines **6**, **7**, **8** and **9** gave cyclophane amides **11**, **12**, **13** and **14** in 45%, 50%, 40% and 45% yield respectively. The reaction sequence is given in Scheme 1.

Compound **11** in the $^1$H NMR displayed the $OCH_2CH_2$-$CH_2O$ protons at $\delta$ 1.83 and $\delta$ 4.15 and $OCH_2CO$ protons appeared as a singlet at $\delta$ 4.59 and the NH proton appeared at $\delta$ 9.55 in addition to the aromatic protons. Compound **12** in the $^1$H NMR displayed the aromatic methyl protons at $\delta$ 2.23 and the two sets of $OCH_2$ protons appeared at $\delta$ 4.56 and $\delta$ 5.00 in addition to the aromatic protons. Compound **13** in the $^1$H NMR displayed the $SCH_2$ and $OCH_2$ protons at $\delta$ 3.79 and $\delta$ 4.55 respectively and the NH protons at $\delta$ 9.39 in addition to the aromatic protons. In the $^1$H NMR, cyclophane **14** displayed signals at $\delta$ 1.99, $\delta$ 3.91, $\delta$ 4.51 and

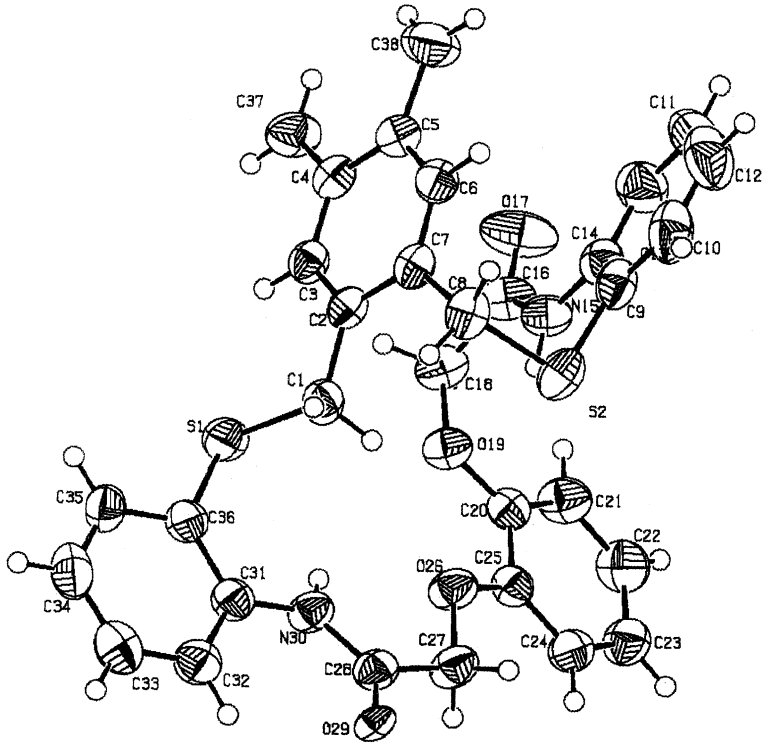



**Figure 1.** ORTEP diagram for **14**.

$\delta$ 9.48 for aromatic methyl, $SCH_2$, $OCH_2$ and NH protons, respectively, in addition to the aromatic protons at $\delta$ 6.45 to $\delta$ 8.39.

X-ray diffraction (XRD) studies on cyclophane **14**[55] showed the presence of intramolecular hydrogen bonding and hence cyclophane **14** is not planar and one of the benzene rings is puckered (Figs. 1 and 2). Though cyclophane **14** can show self-assembling properties and hence can generate channel, XRD showed only intramolecular hydrogen bonding rather than intermoleculer hydrogen bonding.

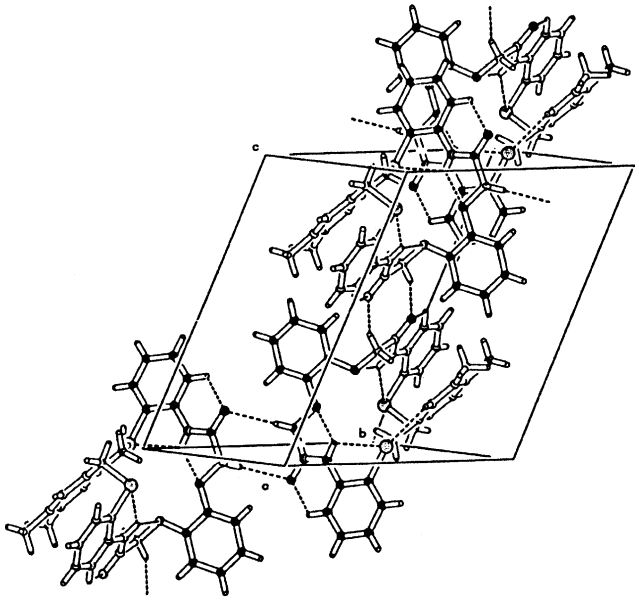
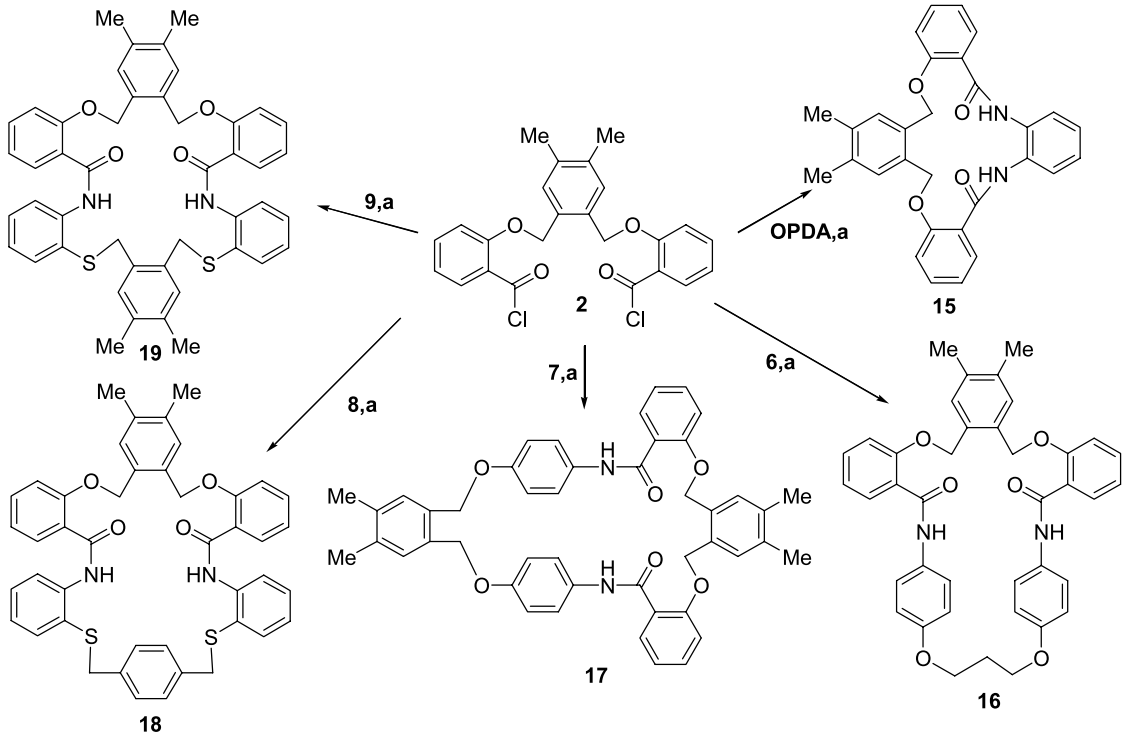


**Figure 2.** Crystal lattice diagram for **14**.

In order to synthesize large cavity cyclophanes with amide linkages diacid chloride **2** was used. In order to test the suitability of diacid chloride **2** for the formation of cyclophane, diacid chloride **2** was reacted with *o*-phenylenediamine and cyclic diamide **15** was obtained in 50% yield. In the $^1$H NMR the aromatic methyl, $OCH_2$ and NH protons appeared at $\delta$ 2.23, $\delta$ 5.24 and $\delta$ 9.64, respectively, in addition to the aromatic protons. In the mass spectrum the molecular ion appeared at *m*/*z* 478. Similarly reaction of diacid chloride **2** with diamines **6**, **7**, **8** and **9** gave cyclophanes **16**, **17**, **18** and **19** in 47, 43, 50 and 50% yield, respectively (Scheme 2).

XRD studies were carried out for cyclophane **15**.[56] One of the benzene rings derived from the *o*-phenylenediamine unit is orthogonal to the xylenyl unit and the molecule is not planar due to intramolecular hydrogen bonding and XRD shows the dimeric structure in crystal packing (Figs. 3 and 4). Cyclophane **16** in the $^1$H NMR displayed aromatic methyl and $OCH_2$ protons at $\delta$ 2.30 and $\delta$ 5.23. The $OCH_2$ $CH_2$ $CH_2O$ protons group appeared at $\delta$ 1.95 and $\delta$ 4.08 and NH protons at $\delta$ 9.57. Cyclophane **17** in the $^1$H NMR displayed two types of aromatic methyl at $\delta$ 2.22 and $\delta$ 2.29 and two sets of $OCH_2$ protons appeared at $\delta$ 5.04 and $\delta$ 5.38 and the NH protons appeared at $\delta$ 9.60 in addition to the aromatic protons. Cyclophane **18** in the $^1$H NMR displayed singlet at $\delta$ 2.21, $\delta$ 3.94, $\delta$ 5.01 and $\delta$ 11.07 for aromatic methyl, $SCH_2$, $OCH_2$ and NH protons in addition to the aromatic protons and the molecular ion appeared at *m*/*z* 722 in the FAB mass spectrum. Cyclophane amide **19** showed two types of aromatic methyl protons at $\delta$ 1.87 and $\delta$ 2.02 and $SCH_2$, $OCH_2$ and NH protons at $\delta$ 3.70, $\delta$ 5.26 and $\delta$ 10.42, respectively, in the $^1$H NMR.

Further, we focused attention on the synthesis of cyclophane




**Scheme 2.** (a) Triethyl amine, $CHCl_3$,rt, 6 h.

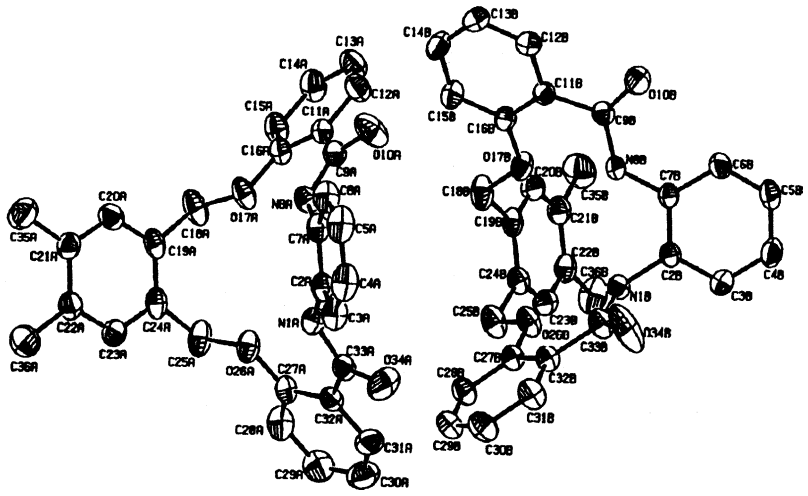


**Figure 3.** ORTEP diagram for **15**.

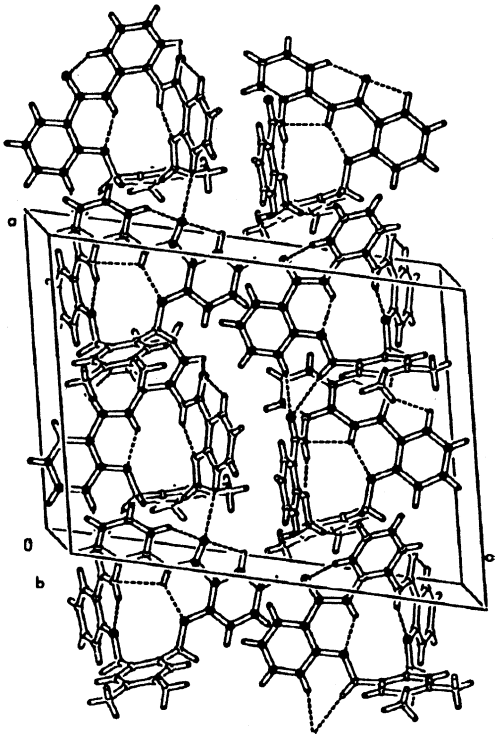


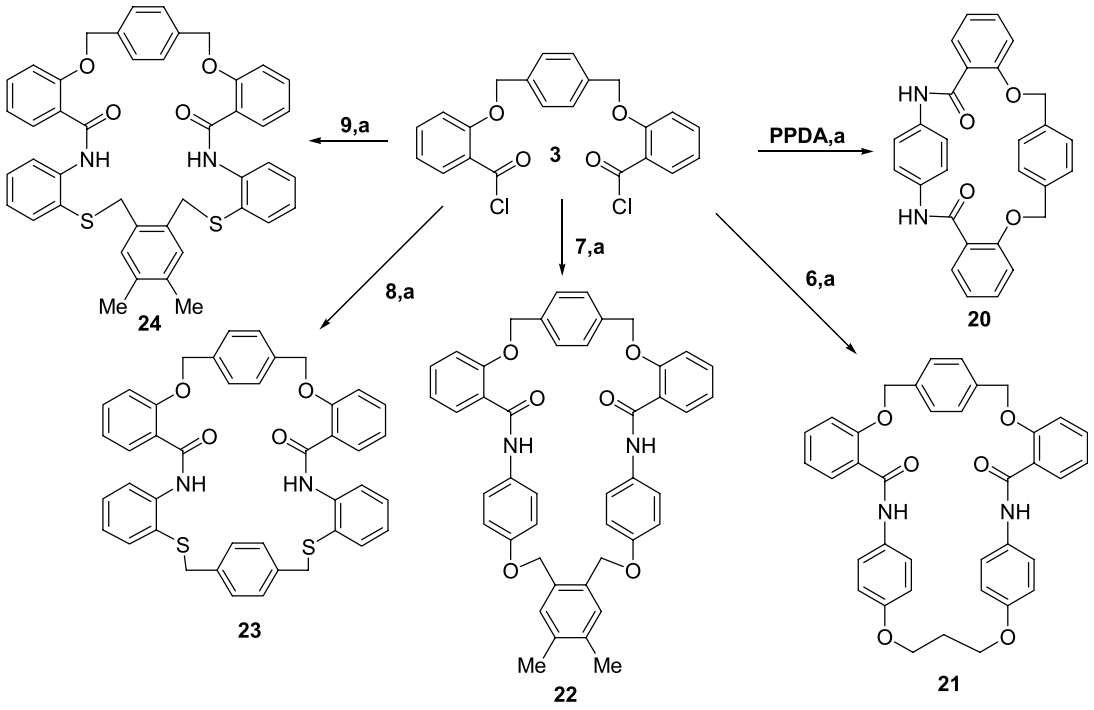
**Figure 4.** Crystal lattice diagram for **15**.

amides based on diacid chloride **3** because of the fact that the cavity size could still be large due to the *p*-xylenyl spacer. Reaction of diacid chloride **3** with *p*-phenylenediamine and diamines **6**, **7**, **8** and **9** gave cyclophanes **20**, **21**, **22**, **23**, and **24** in 45, 42, 48, 50 and 48% yield, respectively (Scheme 3).

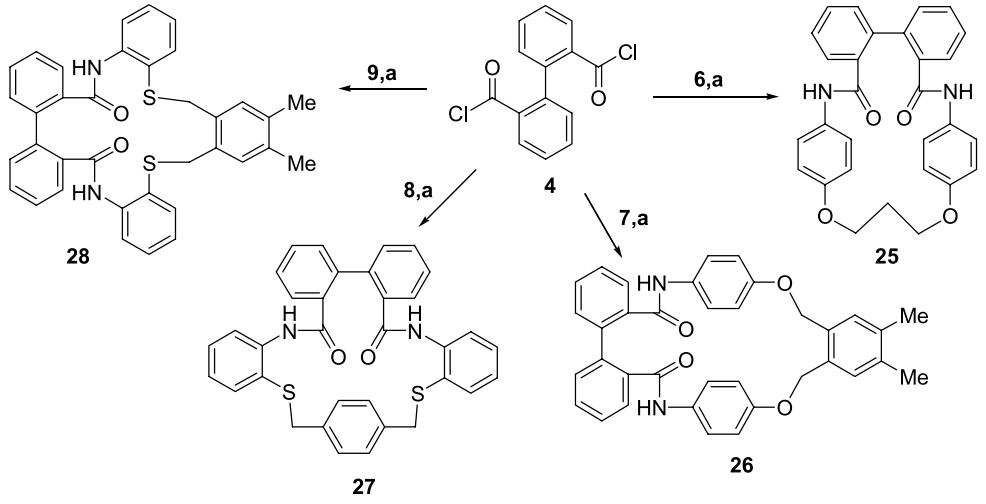
Cyclophane amides **20**, **21**, **22**, **23**, and **24** displayed molecular ions at *m*/*z* 450 (EI), 600 (EI), 690 (EI), 694 (FAB mass spectrum) and 722 (FAB Mass spectrum), respectively. Cyclophane **20** in the $^1$H NMR displayed singlet at $\delta$ 5.01 and $\delta$ 9.61 for $OCH_2$ and NH protons in addition to aromatic protons. Cyclophane **21** in the $^1$H NMR displayed a two-proton quintet at $\delta$ 2.09 and a four-proton triplet at $\delta$ 4.17. $OCH_2$ protons at *p*-xylenyl unit and NH protons appeared as singlets at $\delta$ 5.27 and $\delta$ 9.79 in addition to the aromatic protons. Cyclophane **22** in the $^1$H NMR displayed aromatic methyl, two sets of $OCH_2$ protons and NH protons at $\delta$ 2.26, $\delta$ 5.05, $\delta$ 5.27 and $\delta$ 9.80 in addition to the aromatic protons. Diamide **23** in the $^1$H NMR displayed $SCH_2$, $OCH_2$ and NH protons at $\delta$ 3.84, $\delta$ 5.18 and $\delta$ 10.58 in addition to the aromatic protons. Similarly cyclophane amide **24** also showed aromatic methyl, $SCH_2$, $OCH_2$ and NH protons at $\delta$ 1.93, $\delta$ 3.48, $\delta$ 5.26 and $\delta$ 10.50 in addition to the aromatic protons.

It is of interest to use the acid chloride derived from diphenic acid because biphenyl compounds can show atropisomerism. With this view, various cyclophane amides were synthesized from diphenic acid chloride. Diacid chloride **4** was obtained by the reaction of diphenic acid with thionyl chloride. Diacid chloride **4** on reaction with various amines **6**, **7**, **8** and **9** under the usual condition gave cyclophane amides **25**, **26**, **27** and **28** in 40, 44, 40 and 45% yield, respectively (Scheme 4).

In the mass spectrum cyclophanes **25**, **26**, **27** and **28** displayed molecular ion at *m*/*z* 464 (EI), 554 (EI), 558 (EI) and 586 (EI), respectively. In the $^1$H NMR cyclophane **25** showed the $OCH_2$ $CH_2$ $CH_2O$ protons at $\delta$ 1.88 and $\delta$ 4.10 for two and four protons in addition to the NH protons at $\delta$ 9.90 and aromatic protons at $\delta$ 7.30 to $\delta$ 7.56. A singlet was observed at $\delta$ 6.38 for four protons which apparently indicates that one of the phenyl rings derived from the amine is orthogonal to the other and due to free rotation all the four protons of the benzene ring is continuously shielded in the aromatic $\pi$ clouds of the other benzene ring and hence four aromatic protons appear at a different region than the other aromatic protons. $^1$H NMR of cyclophane **26** displayed aromatic methyl, $OCH_2$ and NH protons at $\delta$ 2.27, $\delta$ 4.88 and $\delta$ 5.01 (ABq, $J$=10.8 Hz) and $\delta$ 9.32 respectively in addition to the aromatic protons. As evidenced earlier one of the benzene rings lies perpendicular to the other and due to shielding effect four aromatic protons are observed as a doublet at $\delta$ 6.36 with $J$=9.3 Hz. Cyclophane **27** in the $^1$H NMR displayed $SCH_2$ protons as an AB quartet at $\delta$ 3.72 and $\delta$ 3.92 with $J$= 11.7 Hz in addition to the aromatic protons and NH protons

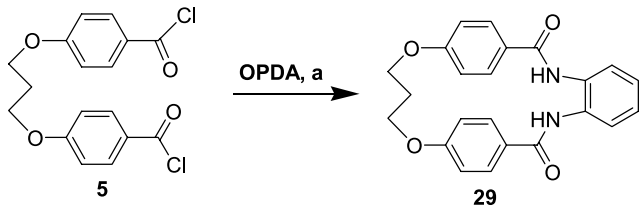



**Scheme 3.** (a)Triethyl amine, $CHCl_3$, rt, 6 h.




**Scheme 4.** (a) Triethyl amine, $CHCl_3$,rt, 6 h.

at $\delta$ 8.46. Similarly, cyclophane **28** in the $^1$H NMR displayed aromatic methyl at $\delta$ 1.99 and $SCH_2$ protons appeared as an AB quartet at $\delta$ 3.40 and $\delta$ 3.56 with $J=$ 12.7 Hz and the NH protons appeared at $\delta$ 8.48 in addition to the aromatic protons.




**Scheme 5.** (a) Triethyl amine, $CHCl_3$, rt, 6 h.

Finally the utilization of acid chloride **5** for the synthesis of cyclophane diamide was explored by employing with *o*-phenylenediamine. Cyclophane diamide **29** was obtained in 35% yield by the reaction of acid chloride **5** with *o*-phenylenediamine (Scheme 5).

In the $^1$H NMR compound **29** displayed the $OCH_2$ $CH_2$ $CH_2O$ protons at $\delta$ 1.91 and $\delta$ 4.20 and the aromatic protons appeared as an AB quartet at $\delta$ 6.67 and $\delta$ 7.47 with $J=$ 8.8 Hz for eight protons and the aromatic protons derived from the *o*-phenylenediamine moiety appeared at $\delta$ 7.34 as a broad singlet and the NH protons were observed at $\delta$ 9.10. Some of the cyclophanes synthesized were tested for their complexation behavior with metal ions like copper (II) and lead (II) as well as for ion transportation studies.

## 3. X-ray diffraction study

Recrystallisation of the cyclophane **14** in chloroform/hexane afforded a single crystal suitable for the XRD studies. The bond lengths and the bond angles have been reported earlier.[55] The crystal parameters are given in Table 1 and ORTEP diagram as well as crystal lattice diagram are shown in Figures 1 and 2.

**Table 1**. Crystal data for cyclophane **14**

| | |
|---|---|
| $C_{32}H_{30}N_2O_4S_2$ | $Z=2$ |
| $M_r=570.70$ | $D_x=1.314$ Mg m$^{-3}$ |
| Triclinic, $P\bar{1}$ | Mo $K\alpha$ radiation |
| $a=8.5860$ (7) Å | Cell parameters from 2732 reflections |
| $b=12.9090$ (10) Å | $\theta=2.7$–$26.3°$ |
| $c=14.7552$ (11) Å | $\mu=0.23$ mm$^{-1}$ |
| $\alpha=65.065$ (1)° | $T=293$ (2) K |
| $\beta=84.701$ (1)° | Needle, colourless |
| $\gamma=76.522$ (1)° | $0.25\times0.19\times0.14$ mm |
| $V=1442.1$ (2) Å$^3$ | |

XRD studies proved that intramolecular hydrogen bonding exists in cyclophane **14** and hence it is not planar though aromatic rings were introduced to make the molecule planar.

Similarly XRD studies were carried out with cyclophane **15** after obtaining a crystal from chloroform/methanol and the crystal parameters are given in Table 2. The ORTEP diagram and lattice crystal diagram are shown in Figures 3 and 4. Again in cyclophane **15** one of the benzene rings is orthogonal to the rest of the molecule. XRD studies of cyclophanes **19** and **23** are currently under investigation.

**Table 2**. Crystal data for cyclophane **15**

| | |
|---|---|
| $C_{30}H_{26}N_2O_4$ | $D_x=1.288$ Mg m$^{-3}$ |
| $M_r=478.53$ | Mo $K\alpha$ radiation |
| Monoclinic, $P2_1/n$ | Cell parameters from 5463 reflections |
| $a=15.5767$ (9) Å | $\theta=2.3$–$21.7°$ |
| $b=15.7746$ (9) Å | $\mu=0.09$ mm$^{-1}$ |
| $c=20.5721$ (12) Å | $T=293$ (2) K |
| $\beta=102.541$ (1)° | Block, colourless |
| $V=4934.3$ (5) Å$^3$ | $0.24\times0.20\times0.16$ mm |
| $Z=8$ | |

Though intermolecular hydrogen bonding could lead to self-assembling properties, cyclophane **14** and **15** did not exhibit such properties. Thus from the X- ray diffraction studies, it is clear that intramolecular hydrogen bonding predominates over intermolecular hydrogen bonding under solid state conditions.

## 4. UV/Vis spectral studies

Cyclophane amide **14**, **19** and **24** in $CH_3CN$ showed $\lambda_{max}$ in the UV/Vis. spectrum at 209, 206 and 290, 208 and 287 nm, respectively. However, no shift in $\lambda_{max}$ was observed even after the addition of required amount of either Cu (II) acetate or Pb (II) acetate to cyclophane amide **14**, **19** and **24** in $CH_3CN$. Cyclophane amide **28** shows $\lambda_{max}$ at 221 nm in $CH_3OH$ in the UV spectrum and after the addition of Cu (II) acetate, $\lambda_{max}$ was observed at 273 nm. Similarly when Pb (II) acetate was added to the solution of cyclophane amide **28** in $CH_3OH$, $\lambda_{max}$ was observed at 235 nm. The shift in $\lambda_{max}$ observed by the addition of Cu (II) acetate as well as Pb (II) acetate in the case of cyclophane amide **28**, could be due to the formation of metal receptor complex. However the complexes could not be thoroughly characterized, due to their instability, insolubility in usual NMR solvents and further because of paramagnetic behavior.

## 5. Ion transportation studies

In the current investigation, a glass vessel as depicted in Figure 5 was fabricated in order to test the ability of cyclophane amides towards ion transporting phenomenon. Though cyclophane amides **14** and **15** do not exhibit self-assembling characteristics in solid phase as evidenced by XRD studies, it is of interest to test the ion transport property in solution phase.

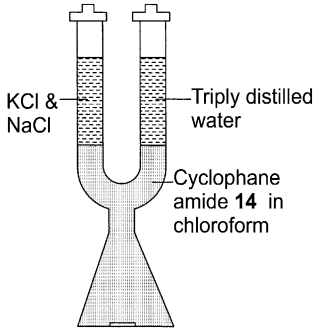



**Figure 5.** Apparatus used for ion transport study by cyclophane amide **14**.

Cyclophane amide **14** was dissolved in chloroform and kept in a conical flask fitted with a U tube as shown in Figure 5. One arm of the U tube is filled with water in which NaCl and KCl were dissolved and the other arm is filled with triply distilled water. The chloroform layer was stirred for 5 days. The arm that was filled with triply distilled water showed the presence of $Na^+$ ion and $K^+$ ion level was below the detecting limit (less than 0.4 mg/l). Thus the experiment proved that $Na^+$ ions were transported by cyclophane amide **14** from one arm to the other. The size of $Na^+$ ion (ionic radius: 0.95 Å) and the cavity dimension of cyclophane **14** ($4.4\times6.1$ Å$^2$) are complementary to each other, whereas the size of $K^+$ ion (ionic radius: 1.33 Å) does not match with cavity size. Hence cyclophane amide **14** could be used as a potential ion filtering system for retaining the biologically important $K^+$ ion and eliminating $Na^+$ ion. It is noteworthy to mention that $K^+$ ion play a vital role in blood brain barrier. A blank experiment was also performed in chloroform without cyclophane amide and no such ion mobility was observed. Currently, we are investigating such preferential ion mobility of other cyclophane amides. Further, impregnation of the cyclophane amide **14** on membrane and ion transport studies over such membranes are under further investigation.

## 6. Conclusion

We have synthesized 20 cyclophane diamides, and fully characterized by spectral, physical and analytical data. XRD

studies were carried out for cyclophane amides **14** and **15**, which proved the existence of intramolecular hydrogen bonding. Cyclophane amide **14** shows preference for transportation of $Na^+$ ion over $K^+$ ion and hence can be used as ion filter in biological system.

## 7. Experimental

### 7.1. General

All $^1H$ NMR and $^{13}C$ NMR were recorded in $CDCl_3$ and DMSO-$d_6$ with JEOL Model: GSX 400. EI-MS spectra were recorded using JEOL DX-303 mass spectrometer and FAB MS spectra were recorded using JEOL SX 102/DA-6000 mass spectrometer using a *m*-nitro benzyl alcohol (NBA) matrix. Melting points were recorded with Gallenkamp melting point apparatus. UV/Vis spectra were recorded with Jasco-V550. FT-IR spectra were recorded with Perkin–Elmer. Atomic absorption spectra were recorded using DEP-Vision (model: 381E). Pre-coated silica gel plates from Merck were used for TLC. Column chromatography was carried out using silica gel (60–120 mesh) purchased from Acme.

**7.1.1. Diacid chloride 1.** A mixture of catechol (11.0 g, 0.10 mol), ethyl chloroacetate (27.0 g, 0.22 mol), anhydrous potassium carbonate (16.5 g, 0.25 mol) and KI (0.5 g) in acetonitrile (100 mL) was refluxed for 12 h. After completion of the reaction, the reaction mixture was poured into ice water (300 mL) and then added NaOH solution (10% w/v, 100 mL). The gelatinous precipitate formed was filtered and the clear filtrate was acidified with dil HCl (6 M, 150 mL). The precipitated diacid was filtered, washed with cold water and air dried as an off-white solid (14.7 g, 65%). Mp 179–181 °C.[42] A mixture of the diacid (0.113 g, 0.5 mmol), thionyl chloride (0.5 mL) triethylamine (0.1 mL) in methylene chloride (25 mL) was refluxed for 3 h. The solvent and excess thionyl chloride were removed under vacuum to give diacid chloride **1** as a light brown solid.[41]

**7.1.2. Diacid chloride 2.** A mixture of 4,5-bis (chloromethyl)-*o*-xylene (2.0 g, 9.8 mmol), methyl salicylate (3.5 g, 23 mmol), anhydrous potassium carbonate (1.3 g, 23 mmol) and KI (0.1 g) in acetonitrile (25 mL) was refluxed for 8 h. The reaction mixture was cooled to rt and then quenched into ice water (100 mL) and the solid diester obtained was filtered with suction. The diester was washed with cold water and dried with suction as a white solid (4.2 g, 97%). Mp 121–123 °C; IR (KBr, $cm^{-1}$) 1732, 1600; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 2.29 (s, 6H), 3.84 (s, 6H), 5.26 (s, 4H), 6.97–7.81 (m, 10H). Mass spectrum: *m*/*z* 434 ($M^+$). Elemental analysis calcd for $C_{26}H_{26}O_6$: C, 71.88; H, 5.99. Found: C, 71.79; H, 5.98. The diester (2.0 g, 4.5 mmol) was treated with ethanolic KOH (5% w/v, 50 mL). The reaction mixture was then filtered and the clear filtrate was acidified with dil HCl (6 M, 30 mL) to give the diacid, which was filtered with suction and washed with water. The diacid was dried in vacuum as a white solid (1.7 g, 90%). Mp 178–180 °C; IR (KBr, $cm^{-1}$) 2917, 1695, 1600; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 2.31 (s, 6H), 5.32 (s, 4H), 7.10–8.21 (m, 10H). Mass spectrum: *m*/*z* 406 ($M^+$). Elemental analysis calcd for $C_{24}H_{22}O_6$: C, 70.93; H, 5.41. Found: C, 70.85; H, 5.42. The diacid (0.204 g, 0.5 mmol) in methylene chloride (25 mL) was refluxed with thionyl chloride (0.5 mL) and triethylamine (0.1 mL). After refluxing for 2 h, the solvent and excess thionyl chloride were removed under vacuum to give diacid chloride **2** as a pale yellow solid.

**7.1.3. Diacid chloride 3.** A mixture of *p*-xylylene dibromide (2.0 g, 7.5 mmol) methyl salicylate (2.6 g, 17 mmol), anhydrous potassium carbonate (2.5 g, 18 mmol) and KI (0.1 g) in acetonitrile (30 mL) was refluxed for 8 h. After completion of the reaction, the reaction mixture was poured into ice water (100 mL). The precipitated diester was filtered, washed with cold water and dried as an off-white solid (2.8 g, 90%). Mp 125–127 °C.[44] The diester (2.0 g, 4.9 mmol) was treated with ethanolic KOH (5% w/v, 50 mL). The reaction mixture was filtered and the clear filtrate was acidified with dil HCl (6 M, 30 mL) to give the diacid, which was filtered with suction and washed with water. The diacid was dried in vacuum as a white solid (1.76 g, 95%). Mp 238–240 °C.[44] The diacid (0.189 g, 0.5 mmol), thionyl chloride (0.5 mL) and triethylamine (0.1 mL) in methylene chloride (25 mL) was refluxed for 2 h. The solvent and excess thionyl chloride were removed under vacuum to give diacid chloride **3** as a light brown solid.

**7.1.4. Diacid chloride 4.** A mixture of diphenic acid (0.121 g, 0.5 mmol), thionyl chloride (0.5 mL), triethylamine (0.1 mL) and methylene chloride (25 mL) was refluxed for 2 h. The solvent and excess thionyl chloride were removed under vacuum to get the diacid chloride **4** as a light brown solid.

**7.1.5. Diacid chloride 5.** A mixture of 1,3-dibromopropane (2.56 g, 12.7 mmol), methyl *p*-hydroxybenzoate (4.0 g, 26.3 mmol), anhydrous potassium carbonate (4.0 g, 29 mmol) and KI (0.1 g) in acetonitrile (25 mL) was refluxed for 20 h. The reaction mixture was then poured into ice water and extracted with methylene chloride (2× 75 mL). The combined organic layer was washed with NaOH solution (5% w/v, 25 mL) till no methyl *p*-hydroxybenzoate was present and after washing with water (25 mL), dried over magnesium sulphate. Methylene chloride was concentrated to 25 mL and cooled with freezing mixture for 3 h. The diester was filtered at suction and dried as an off-white solid (3.27 g, 75%). Mp 134–136 °C. The diester (2.0 g, 5.8 mmol) was refluxed with ethanolic KOH (5% w/v, 50 mL) for 1 h. The reaction mixture was then filtered and to the clear filtrate dil HCl (6 M, 30 mL) was added to give the diacid, which was filtered with suction and washed with water. The diacid was dried in vacuum as a white solid (1.65 g, 90%). Mp >295 °C.[45–47] The diacid (0.158 g, 0.5 mmol) was refluxed in methylene chloride (25 mL) with thionyl chloride (0.5 mL) and triethylamine (0.1 mL) for 3 h. The solvent and excess thionyl chloride were removed under vacuum to give the diacid chloride **5** as a light brown solid.

**7.1.6. Diamine 6.** A mixture of 1,3-dibromopropane (2.0 g, 10 mmol), *p*-nitrophenol (4.0 g, 32 mmol), anhydrous potassium carbonate (4.0 g, 29 mmol) and KI (0.1 g) in

acetonitrile (40 mL) was refluxed for 48 h. The reaction mixture was poured into ice water (100 mL) and made alkaline with NaOH solution (5% w/v, 25 mL). The solid dinitro compound was filtered and washed with water (2× 20 mL) and recrystallised from chloroform and hexane (1:1) to give pure dinitro compound as a pale yellow solid (2.2 g, 80%). Mp 128–130 °C.[49] A mixture of dinitro compound (0.57 g, 2 mmol) and 10% Pd/C (25 mg) in methanol (100 mL) was warmed to 40 °C and hydrogen gas was bubbled through the reaction mixture. Immediately after the completion of the reaction, the reaction mixture was filtered and the filtrate was concentrated to approximately 10 mL and cooled to 0–10 °C to give diamine **6** as a beige solid after washing with cold methanol, (0.41 g, 80%). Mp 109–111 °C.[49,50]

**7.1.7. Diamine 7.** A mixture of 4,5-bis (chloromethyl)-*o*-xylene (2.0 g, 10 mmol), *p*-nitrophenol (3.5 g, 28 mmol), anhydrous potassium carbonate (4.0 g, 29 mmol) and KI (0.1 g) in acetonitrile (25 mL) was refluxed for 4 h. Then the reaction mixture was poured into ice water (100 mL). The solid was filtered, washed with cold water and dried to give the dinitro compound as a pale yellow solid in almost pure and quantitative yield. Mp 211–213 °C; IR (KBr, $cm^{-1}$) 1500, 1330; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 2.25 (s, 6H), 5.30 (s, 4H), 7.16–8.15 (m, 10H). Mass spectrum: *m*/*z* 408 ($M^+$). Elemental analysis calcd for $C_{22}H_{20}N_2O_6$: C, 64.70; H, 4.90; N, 6.86. Found: C, 64.59; H, 4.91; N, 6.87. A mixture of dinitro compound (0.6 g, 1.6 mmol) and 10% Pd/C (20 mg) in methanol (100 mL) was warmed to 40 °C. Hydrogen gas was bubbled through the reaction mixture for 1 h. The reaction mixture was filtered and the filtrate was concentrated to 15 mL. On cooling, diamine **7** crystallized, which was filtered and washed with cold methanol as a light brown solid (0.5 g, 90%). Mp 190–192 °C; IR (KBr, $cm^{-1}$) 3425, 1620; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 2.25 (s, 6H), 3.25 (br s, 4H) 5.00 (s, 4H), 6.60–7.24 (m, 10H). Mass spectrum: *m*/*z* 348 ($M^+$). Elemental analysis calcd for $C_{22}H_{24}N_2O_2$: C, 75.86; H, 6.89; N, 8.04.Found: C, 75.79; H, 6.88; N, 8.03.

**7.1.8. Diamine 8.** To a solution of KOH (1.3 g, 19.7 mmol) in methanol (40 mL) was added *o*-aminothiophenol (2.4 g, 19.2 mmol) followed by *p*-xylylene dibromide (2.0 g, 7.5 mmol) at 30 °C with stirring. After stirring for 2 h, the solid obtained was filtered with suction and washed with methanol (25 mL). Then the solid was washed with water (50 mL) and dried with suction to give pure diamine **8**, brown solid (2.4 g, 90%). Mp 141–143 °C.[51]

**7.1.9. Diamine 9.** To a solution of KOH (1.3 g, 19.7 mmol) in methanol (40 mL) was added *o*-aminothiophenol (2.4 g, 19.2 mmol) followed by 4,5-bis (chloromethyl)-*o*-xylene (1.52 g, 7.5 mmol) at 30 °C with stirring. After stirring for 8 h, the solid obtained was filtered with suction, washed with methanol (10 mL), then with water (50 mL) and dried to give diamine **9** as a light violet solid (2.3 g, 80%). Mp 129–131 °C; IR (KBr, $cm^{-1}$) 3444, 1604; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 2.14 (s, 6H), 3.92 (s, 4H), 4.30 (br s, 4H), 6.61–7.26 (m, 10H). Mass spectrum: *m*/*z* 380 ($M^+$). Elemental analysis calcd for $C_{22}H_{24}N_2S_2$: C, 69.47; H, 6.31; N, 7.36. Found: C, 69.39; H, 6.32; N, 7.35.

### 7.2. General procedure for the synthesis of cyclophane amides

A solution of the diacid chloride (0.5 mmol) in dry chloroform (100 mL) and a solution of the diamine (0.5 mmol) and triethylamine (1.1 mmol) in dry chloroform (100 mL) were simultaneously added dropwise to a well-stirred solution of chloroform (500 mL) during 6 h. After the addition was complete, the reaction mixture was stirred for another 6 h. The solvent was removed at reduced pressure and the residue obtained was then dissolved in chloroform (300 mL), washed with water (2×100 mL) to remove the triethylammonium chloride and dried over magnesium sulphate. Removal of the chloroform gave the cyclophane as a crude material, which was purified by column chromatography with suitable eluting solvent as mentioned under each cyclophane.

**7.2.1. Cyclophane 10.** White hairy crystalline solid. Eluent for column chromatography: chloroform to chloroform/methanol (49:1); yield: 50%; $R_f$ 0.65 (chloroform/methanol, 9:1). Mp 220–222 °C; IR (KBr, $cm^{-1}$) 3312, 1723, 1676; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 4.76 (s, 4H), 7.04–7.63 (m, 8H), 9.71 (s, 2H). Mass spectrum: *m*/*z* 298 ($M^+$). Elemental analysis calcd for $C_{16}H_{14}N_2O_4$: C, 64.42; H, 4.69; N, 9.39. Found: C, 64.48; H, 4.68; N, 9.38.

**7.2.2. Cyclophane 11.** Off-white solid. Eluent for column chromatography: chloroform to chloroform/methanol (49:1); yield: 45%; $R_f$ 0.55 (chloroform/methanol, 9:1). Mp 238–240 °C; IR (KBr, $cm^{-1}$) 3375, 1684, 1596; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 1.83 (quint, 2H, $J$=5.9 Hz), 4.15 (t, 4H, $J$=5.9 Hz), 4.59 (s, 4H), 6.57–7.16 (m, 12H), 9.55 (s, 2H). Mass spectrum: *m*/*z* 448 ($M^+$). Elemental analysis calcd for $C_{25}H_{24}N_2O_6$: C, 66.96; H, 5.35; N, 6.25.Found: C, 66.89; H, 5.29; N, 6.18.

**7.2.3. Cyclophane 12.** Off-white solid. Eluent for column chromatography: chloroform to chloroform/methanol (99:1); yield: 50%; $R_f$ 0.80 (chloroform/methanol, 9:1). Mp 304–306 °C; IR (KBr, $cm^{-1}$) 3382, 1684, 1597; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 2.23 (s, 6H), 4.56 (s, 4H), 5.00 (s, 4H), 6.51–8.04 (m, 14H), 9.22 (s, 2H). Mass spectrum: *m*/*z* 538 ($M^+$). Elemental analysis calcd for $C_{32}H_{30}N_2O_6$: C, 71.37; H, 5.57; N, 5.20.Found: C, 71.42; H, 5.56; N, 5.19.

**7.2.4. Cyclophane 13.** Lemon yellow solid. Eluent for column chromatography: hexane to hexane/chloroform (1:1); yield: 40%; $R_f$ 0.55 (toluene/ethyl acetate, 9:1). Mp 204–208 °C; IR (KBr, $cm^{-1}$) 3350, 1684, 1577; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 3.79 (s, 4H), 4.55 (s, 4H), 6.86–8.46 (m, 16H), 9.39 (s, 2H); $^{13}$C NMR (100.4 MHz, $CDCl_3$) $\delta$ 29.9, 43.0,70.2, 117.5, 120.5, 123.4, 124.1, 125.1, 129.3, 130.7, 136.6, 136.8, 140.0, 148.6, 166.5. Mass spectrum: *m*/*z* 542 ($M^+$). Elemental analysis calcd for $C_{30}H_{26}N_2O_4S_2$: C, 66.42; H, 4.79; N, 5.16. Found: C, 66.37; H, 4.78; N, 5.17.

**7.2.5. Cyclophane 14.** Off-white crystalline solid. Eluent for column chromatography: hexane to hexane/chloroform (1:1); yield: 45%; $R_f$ 0.60 (toluene/ethyl acetate, 9:1). Mp 226–228 °C; IR (KBr, $cm^{-1}$) 3378, 1685, 1595. $^1$H NMR

(400 MHz, $CDCl_3$) $\delta$ 1.99 (s, 6H), 3.91 (s, 4H), 4.51 (s, 4H), 6.45–8.39 (m, 14H), 9.48 (s, 2H); $^{13}C$ NMR (100.4 MHz, $CDCl_3$) $\delta$ 19.0, 38.5, 68.8, 113.9, 120.2, 122.8, 123.5, 124.6, 129.9, 131.0, 131.8, 135.3, 136.2, 139.2, 147.2, 166.2. Mass spectrum: *m/z* 570 ($M^+$). Elemental analysis calcd for $C_{32}H_{30}N_2O_4S_2$; C, 67.36; H, 5.26; N, 4.91.Found; C, 67.31; H, 5.27; N, 4.92.

**7.2.6. Cyclophane 15.** Beige crystalline solid. Eluent for column chromatography: chloroform to chloroform/methanol (99:1); Yield: 50%; $R_f$ 0.75 (chloroform/methanol, 9:1). Mp 278–281 °C; IR (KBr, $cm^{-1}$) 3353, 1663, 1597; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 2.23 (s, 6H), 5.24 (s, 4H), 6.91–8.21 (m, 14H), 9.64 (s, 2H); $^{13}C$ NMR (100.4 MHz, $CDCl_3$) $\delta$ 19.4, 29.6, 70.4, 112.8,121.6, 121.8, 124.3, 125.1, 129.7, 131.4, 132.2, 132.9, 133.1, 138.2, 156.3, 163.8. Mass spectrum: *m/z* 478 ($M^+$). Elemental analysis calcd for $C_{30}H_{26}N_2O_4$: C, 75.31; H, 5.44; N, 5.85. Found: C, 75.39; H, 5.45; N, 5.86.

**7.2.7. Cyclophane 16.** White solid. Eluent for column chromatography: chloroform to chloroform/methanol (99:1); yield: 47%; $R_f$ 0.80 (chloroform/methanol, 9:1). Mp 234–236 °C; IR (KBr, $cm^{-1}$) 3340, 1658, 1598; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 1.95 (quint, 2H, $J=5.8$ Hz), 2.30 (s, 6H), 4.08 (t, 4H, $J=5.8$ Hz), 5.23 (s, 4H), 6.44–8.06 (m, 18H), 9.57 (s, 2H); FAB Mass spectrum: *m/z* 628 ($M^+$). Elemental analysis calcd for $C_{39}H_{36}N_2O_6$: C, 74.52; H, 5.73; N, 4.45. Found: C, 74.57; H, 5.78; N, 4.44.

**7.2.8. Cyclophane 17.** Off-white solid. Eluent for column chromatography: chloroform to chloroform/methanol (99:1); yield: 43%; $R_f$ 0.75 (chloroform/methanol, 9:1). Mp >300 °C; IR (KBr, $cm^{-1}$) 3348, 1662, 1598; $^1H$ NMR (400 MHz, DMSO-$d_6$) $\delta$ 2.22 (s, 6H), 2.29 (s, 6H), 5.04 (s, 4H), 5.38 (s, 4H), 6.57–8.10 (m, 20H), 9.60 (s, 2H); FAB Mass spectrum: *m/z* 718 ($M^+$). Elemental analysis calcd for $C_{46}H_{42}N_2O_6$: C, 76.88; H, 5.84; N, 3.89. Found: C, 76.94; H, 5.77; N, 3.81.

**7.2.9. Cyclophane 18.** Off-white solid. Eluent for column chromatography: hexane to hexane/chloroform (1:1); yield: 50%; $R_f$ 0.50 (toluene/ethyl acetate, 9:1). Mp 254–256 °C (decomp.); IR (KBr, $cm^{-1}$) 3291, 1658, 1581; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 2.21 (s, 6H), 3.94 (s, 4H), 5.01 (s, 4H), 6.68–8.69 (m, 22H), 11.07 (s, 2H); $^{13}C$ NMR (100.4 MHz, $CDCl_3$) $\delta$ 19.9, 41.6, 69.4, 114.9, 122.3, 122.7, 123.6, 124.8, 125.4, 129.0, 129.6, 131.1, 133.4, 133.8, 137.1, 137.2, 140.4, 157.1, 164.2; FAB Mass spectrum: *m/z* 722 ($M^+$). Elemental analysis calcd for $C_{44}H_{38}N_2O_4S_2$: C, 73.13; H, 5.26; N, 3.87. Found: C, 72.95; H, 5.20; N, 3.91.

**7.2.10. Cyclophane 19.** Off-white solid. Eluent for column chromatography: hexane to hexane/chloroform (1:1); yield: 50%; $R_f$ 0.70 (toluene/ethyl acetate, 9:1). Mp 224–227 °C; IR (KBr, $cm^{-1}$) 3337, 1661, 1600; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 1.87 (s, 6H), 2.02 (s, 6H), 3.70 (s, 4H), 5.26 (s, 4H), 6.48–8.53 (m, 20H), 10.42 (s, 2H); $^{13}C$ NMR (100.4 MHz, $CDCl_3$) $\delta$ 18.8, 19.2, 38.3, 69.8, 113.7, 121.5, 121.9, 123.6, 123.8, 124.3, 129.4, 130.4, 131.3, 131.7, 132.4, 132.8, 132.9, 135.1, 135.9, 137.3, 140.2, 156.7, 163.8; FAB Mass spectrum: *m/z* 750 ($M^+$). Elemental analysis calcd for $C_{46}H_{42}N_2O_4S_2$: C, 73.6; H, 5.60; N, 3.73. Found: C, 73.65; H, 5.55; N, 3.78.

**7.2.11. Cyclophane 20.** Off-white solid. Eluent for column chromatography: chloroform to chloroform/methanol (99:1); yield: 45%; $R_f$ 0.62 (chloroform/methanol, 9:1). Mp 268–270 °C (decomp.); IR (KBr, $cm^{-1}$) 3333, 1702, 1654, 1601; $^1H$ NMR (400 MHz, DMSO-$d_6$) $\delta$ 5.01 (s, 4H), 7.09–8.26 (m, 16H), 9.61 (s, 2H). Mass spectrum: *m/z* 450 ($M^+$). Elemental analysis calcd for $C_{28}H_{22}N_2O_4$: C, 74.66; H, 4.88; N, 6.22. Found: C, 74.71; H, 4.73; N, 6.30.

**7.2.12. Cyclophane 21.** White crystalline solid. Eluent for column chromatography: chloroform to chloroform/methanol (49:1); yield: 42%; $R_f$ 0.84 (chloroform/methanol, 9:1). Mp 251-253 °C; IR (KBr, $cm^{-1}$) 3354, 1663, 1597; $^1H$ NMR (400 MHz, DMSO-$d_6$) $\delta$ 2.09 (quint, 2H, $J=5.8$ Hz), 4.17 (t, 4H, $J=5.8$ Hz) 5.27 (s, 4H), 6.80–8.18 (m, 20H), 9.79 (s, 2H). Mass spectrum: *m/z* 600 ($M^+$). Elemental analysis calcd for $C_{37}H_{32}N_2O_6$: C, 74.0; H, 5.33; N, 4.66. Found: C, 73.8; H, 5.29; N, 4.72.

**7.2.13. Cyclophane 22.** White solid. Eluent for column chromatography: chloroform to chloroform/methanol (49:1); yield: 48%; $R_f$ 0.86 (chloroform/methanol, 9:1). Mp 292-294 °C; IR (KBr, $cm^{-1}$) 3348, 1663, 1597, 1542; $^1H$ NMR (400 MHz, DMSO-$d_6$) $\delta$ 2.26 (s, 6H), 5.05 (s, 4H), 5.27 (s, 4H), 6.86–8.14 (m, 22H), 9.80 (s, 2H); FAB Mass spectrum: *m/z* 690 ($M^+$). Elemental analysis calcd for $C_{44}H_{38}N_2O_6$: C, 76.52; H, 5.50; N, 4.05. Found: C, 76.65; H, 5.48; N, 4.07.

**7.2.14. Cyclophane 23.** Off-white crystalline solid. Eluent for column chromatography: hexane to hexane/chloroform (1:1); yield: 50%; $R_f$ 0.66 (toluene/ethyl acetate, 9:1). Mp 200–202 °C; IR (KBr, $cm^{-1}$) 3335, 1665, 1595, 1576; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 3.84 (s, 4H), 5.18 (s, 4H), 6.85–8.53 (m, 24H), 10.58 (s, 2H); $^{13}C$ NMR (100.4 MHz, $CDCl_3$) $\delta$ 40.3, 71.2, 113.6, 121.7, 121.8, 122.6, 124.3, 124.8, 127.2, 128.7, 128.8, 132.5, 132.9, 133.1, 135.6, 136.0, 139.1, 156.6, 163.6; FAB Mass spectrum: *m/z* 694 ($M^+$). Elemental analysis calcd for $C_{42}H_{34}N_2O_4S_2$: C, 72.62; H, 4.89; N, 4.03. Found: C, 72.55; H, 4.79; N, 4.10.

**7.2.15. Cyclophane 24.** Light brown crystalline solid. Eluent for column chromatography: hexane to hexane/chloroform (1:1); yield: 48%; $R_f$ 0.52 (toluene/ethyl acetate, 9:1). Mp 202-204 °C; IR (KBr, $cm^{-1}$) 3279, 1668, 1576; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 1.93 (s, 6H), 3.48 (s, 4H), 5.26 (s, 4H), 6.35–8.54 (m, 22H), 10.50 (s, 2H); $^{13}C$ NMR (100.4 MHz, $CDCl_3$) $\delta$ 19.0, 37.0, 70.9, 112.7, 121.6, 121.7, 122.6, 123.7, 124.2, 128.0, 129.0, 131.8, 132.5, 132.8, 133.2, 134.3, 135.5, 136.2, 139.6, 156.5, 163.5; FAB Mass spectrum: *m/z* 722 ($M^+$). Elemental analysis calcd for $C_{44}H_{38}N_2O_4S_2$: C, 73.13; H, 5.26; N, 3.87. Found: C, 73.19; H, 5.18; N, 3.89.

**7.2.16. Cyclophane 25.** White crystalline solid. Eluent for column chromatography: chloroform to chloroform/methanol (99:1); yield: 40%; $R_f$ 0.72 (chloroform/methanol, 9:1). Mp 300–304 °C; IR (KBr, $cm^{-1}$) 3343, 2940, 1668, 1532; $^1H$ NMR (400 MHz, DMSO-$d_6$) $\delta$ 1.88 (quint, 2H, $J=$ 5.8 Hz), 4.10 (t, 4H, $J=5.8$ Hz), 6.38 (s, 4H), 7.30–7.56 (m,

12H), 9.90 (s, 2H). Mass spectrum: *m/z* 464 ($M^+$). Elemental analysis calcd for $C_{29}H_{24}N_2O_4$: C, 75.0; H, 5.17; N, 6.03. Found: C, 75.07; H, 5.11; N, 6.10.

**7.2.17. Cyclophane 26.** White solid. Eluent for column chromatography: chloroform to chloroform/methanol (99:1); yield: 44%; $R_f$ 0.54 (chloroform/methanol, 9:1). Mp 316–318 °C; IR (KBr, $cm^{-1}$) 3433, 1681, 1530; $^1H$ NMR (400 MHz, DMSO-$d_6$) $\delta$ 2.27 (s, 6H), 4.88, 5.01 (ABq, 4H, $J=10.8$ Hz), 6.36 (d, 4H, $J=9.3$ Hz), 7.18–7.62 (m, 14H), 9.32 (s, 2H); $^{13}C$ NMR (100.4 MHz, DMSO-$d_6$) $\delta$ 18.2, 77.9, 78.2, 114.5, 119.7, 126.2, 127.0, 129.0, 132.1, 132.4, 133.2, 135.6, 139.7, 155.0, 168.8. Mass spectrum: *m/z* 554 ($M^+$). Elemental analysis calcd for $C_{36}H_{30}N_2O_4$: C, 77.97; H, 5.41; N, 5.05. Found: C, 77.89; H, 5.38; N, 5.12.

**7.2.18. Cyclophane 27.** Pale yellow solid. Eluent for column chromatography: hexane to hexane:chloroform (1:1); yield: 40%; $R_f$ 0.48 (toluene/ethyl acetate, 9:1). Mp 220–224 °C; IR (KBr, $cm^{-1}$) 3352, 1666, 1577; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 3.72, 3.92 (ABq, 4H, $J=11.7$ Hz), 6.77 (s, 4H), 7.02–8.02 (m, 16H), 8.46 (s, 2H); $^{13}C$ NMR (100.4 MHz, $CDCl_3$) $\delta$ 41.4, 121.9, 125.0, 125.8, 127.4, 128.3, 128.4, 128.6, 130.1, 130.3, 135.6, 136.5, 138.6, 139.9, 166.9. Mass spectrum: *m/z* 558 ($M^+$). Elemental analysis calcd for $C_{34}H_{26}N_2O_2S_2$: C, 73.11; H, 4.65; N, 5.01. Found: C, 73.20; H, 4.61; N, 5.10.

**7.2.19. Cyclophane 28.** Off-white solid. Eluent for column chromatography: hexane to hexane:chloroform (1:1); yield: 45%; $R_f$ 0.46 (toluene/ethyl acetate, 9:1). Mp 226–228 °C; IR (KBr, $cm^{-1}$) 3321, 1670, 1577; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 1.99 (s, 6H), 3.40, 3.56 (ABq, 4H, $J=12.7$ Hz), 6.39 (s, 4H), 6.83–8.38 (m, 14H), 8.48 (s, 2H); $^{13}C$ NMR (100.4 MHz, $CDCl_3$) $\delta$ 19.0, 37.9, 119.5, 121.9, 123.9, 128.2, 129.3, 129.8, 130.3, 130.8, 130.9, 131.3, 135.2, 135.9, 136.3, 136.9, 140.0, 167.6. Mass spectrum: *m/z* 586 ($M^+$). Elemental analysis calcd for $C_{36}H_{30}N_2O_2S_2$: C, 73.72; H, 5.11; N, 4.77. Found: C, 73.68; H, 5.08; N, 4.81.

**7.2.20. Cyclophane 29.** White solid. Eluent for column chromatography: chloroform to chloroform/methanol (99:1); yield: 35%; $R_f$ 0.66 (chloroform/methanol, 9:1). Mp 296–298 °C; IR (KBr, $cm^{-1}$) 3242, 1646, 1603, 1522; $^1H$ NMR (400 MHz, DMSO-$d_6$) $\delta$ 1.91 (quint, 2H, $J=$ 5.3 Hz), 4.20 (t, 4H, $J=5.3$ Hz), 6.67, 7.47 (ABq, 8H, $J=$ 8.8 Hz), 7.34 (br s, 4H), 9.10 (s, 2H). Mass spectrum: *m/z* 388 ($M^+$). Elemental analysis calcd for $C_{23}H_{20}N_2O_4$: C, 71.13; H, 5.15; N, 7.25. Found: C, 71.09; H, 5.10; N, 7.29.

### 7.3. UV/Vis spectral studies

Cyclophane amides **14/19/24** (0.023 g/ 0.026 g/0.025 g) were dissolved in $CH_3CN$ (50 mL) and UV/Vis spectra were recorded. Cyclophane amide **14** showed $\lambda_{max}$ at 209 nm, cyclophane amide **19** showed $\lambda_{max}$ at 206 nm, 290 nm and cyclophane amide **24** had absorption at 208, 287 nm. To a solution of cyclophane amides **14/19/24** (0.023 g/0.030 g/ 0.029 g, $4\times10^{-2}$ mmol) added a solution of Cu (II) acetate (0.008 g, $4\times10^{-2}$ mmol) and left at rt for 5 days under $N_2$ atm. In the UV/Vis. spectra no appreciable change in $\lambda_{max}$ could be observed. Similarly by adding Pb (II) acetate no shift in $\lambda_{max}$ was observed. However, cyclophane amide **28** (0.0234 g) dissolved in methanol (50 mL) displayed absorption at 222 nm. By adding Cu (II) acetate (0.008 g, $4\times10^{-2}$ mmol) to the cyclophane amide **28** (0.0234 g, $4\times10^{-2}$ mmol) new absorption maximum were observed at 209 and 273 nm and similarly by adding Pb (II) acetate (0.0117 g, $4\times10^{-2}$ mmol) $\lambda_{max}$ was observed at 235 nm.

### 7.4. Ion transportation studies

A solution of cyclophane amide **14** (65 mg, $11.4\times10^{-2}$ mmol) in chloroform (40 mL) was kept in a conical flask fitted with a U tube (Fig. 5). A solution of NaCl (585 mg, 10 mmol) and KCl (745 mg, 10 mmol) in triply distilled water (10 mL) was kept in one arm of the U tube and the other arm was filled with triply distilled water (10 mL). After properly stoppering the arms of the U tube, the chloroform layer was stirred vigorously for 5 days. The arm, which was filled with triply distilled water showed the presence of NaCl (21.1 mg/l) and $K^+$ ion level was below the detecting limit (less than 0.40 mg/l).

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# Modular synthesis of triaroylbenzene-derived crownophanes

F. Christopher Pigge,* Fatemeh Ghasedi, Angela V. Schmitt, Mayuri K. Dighe and Nigam P. Rath

*Department of Chemistry and Biochemistry, University of Missouri, St. Louis, One University Boulevard, St. Louis, MO 63121-4499, USA*

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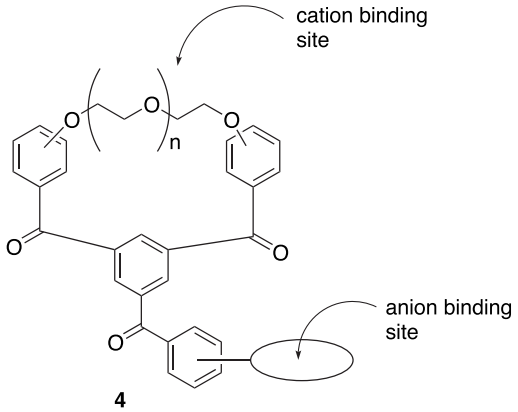
**Abstract**—An isomeric series of homologous crownophanes (i.e., macrocycles possessing structural features of crown ethers and cyclophanes) has been prepared via a concise and modular synthetic route. Macrocyclization is achieved in reasonable yield during the course of an enaminone-triggered benzannulation with bis(aryl ethynyl ketone) reaction partners. The crownophanes examined were active alkali cation binding agents in the gas phase, but failed to exhibit ionophoric properties in solution. On the basis of X-ray crystallographic analysis, it is concluded that the cyclophane framework of these macrocycles is too large and rigid to allow efficient interaction with the cations examined.


## 1. Introduction

Crownophane is a generic term used to describe structurally hybrid materials that possess elements of traditional cyclophanes and crown ethers.[1] In many instances, crownophanes retain the ionophoric properties inherent in crown ethers, while the presence of cyclophane scaffolds provides greater structural and synthetic versatility. Additionally, cyclophane frameworks acting in concert with appended crown ether moieties may produce cation binding agents with enhanced selectivities, transport abilities, and/or cation sensing abilities.

Many architecturally distinct crownophanes have been prepared and characterized. For example, crown ethers prepared from calixarene precursors are well-established and exhibit a range of interesting properties.[2] Other crownophane ring systems have also been constructed through conventional condensation chemistry[3] or via alternative macrocyclization strategies. Nishimura has developed a photocycloaddition approach suitable for accessing cyclobutane-derived alkali- and transition metal-binding crownophanes.[4] McMurry-type couplings have been used as a macrocyclization tactic in the preparation of various crownophanes possessing alkene and allene linkages.[5] Cycloaddition-based methods have been utilized as well.[6] Aside from general functions as ionophores, certain crownophanes have been examined in the context of membrane transport,[7] photoresponsive metal binding,[5b] and rotaxane assembly.[8]

We recently reported an enaminone-directed benzannulation–macrocyclization approach to new cyclophane ring systems.[9] This method was also successfully applied in the synthesis of crownophane **3** as shown in Eq. 1. The reaction proceeds via initial Michael-type condensation of enaminone **2** with an alkynyl group of bis(alkyne) **1**. A second intramolecular condensation followed by elimination of $Me_2NH$ then affords **3**.[10] The resulting crownophane was obtained in reasonable yield and has an intriguing structural feature in that the methoxy-substituted arene ring is not part of the cyclophane macrocycle. Consequently, we envisioned that this 'dangling' arene




**4**

**Figure 1.** Potential crownophane-based ditopic receptor.

*Keywords*: Cyclophane; Macrocyclization; Crownophane; Benzannulation.
* Corresponding author. Tel.: +1 3145165340; fax: +1 3145165342; e-mail: piggec@jinx.umsl.edu

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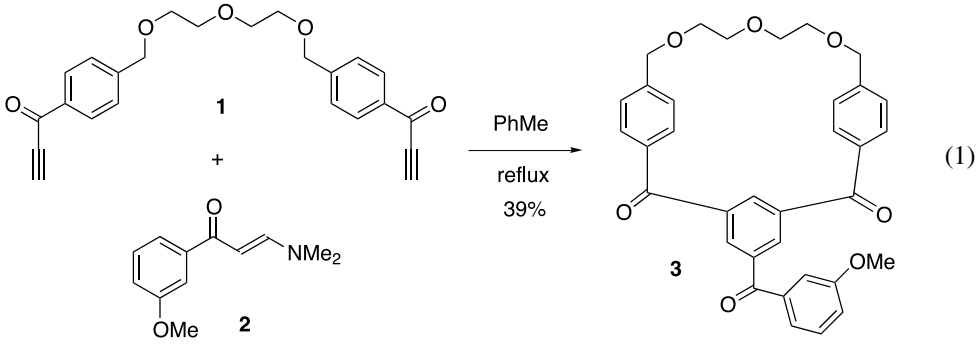
could potentially serve as a site of attachment for additional elements of molecular recognition. For example, new ditopic receptors for ion pairs possessing the general structure **4** (Fig. 1) may result after functionalization of the dangling arene with a suitable anion-binding unit (e.g., a urea functional group or an azamacrocycle).[11] In turn, such ditopic receptors may ultimately yield new complexing agents for inorganic salts and organic zwitterions (such as short polypeptides).[12]




(1)

With this initial goal in mind, a modular and general preparative route was designed for the rapid construction of three homologous series of isomeric crownophanes **5**–**7** (Fig. 2). At the outset, it was expected that **5**–**7** would serve as precursors to viable multitopic receptors of the type depicted in Figure 1. We report herein the results of synthetic studies leading to crownophanes structurally related to the archetypal constructs shown in Figure 2 along with an initial assessment of their cation binding ability.

## 2. Results and discussion

### 2.1. Synthesis

Crownophanes of the type shown in Figure 2 were prepared in straightforward fashion via similar synthetic routes. In contrast to **3** (Eq. 1), the crown ether and cyclophane moieties are connected through phenolic linkages rather than benzyl ethers due to the ready availability of hydroxy benzaldehyde starting materials. All the crownophanes in this report were prepared using essentially identical procedures; thus, only a representative example will be discussed in detail (Scheme 1).

Treatment of 4-hydroxybenzaldehyde with triethylene glycol ditosylate and $K_2CO_3$ in refluxing acetonitrile gave known dialdehyde **8** in 81% isolated yield.[13] Conversion of **8** to the corresponding bis(ethynyl) ketone was accomplished through a two-step process that entailed addition of ethynyl magnesium bromide followed by oxidation of the resulting secondary alcohols. This process afforded **9** in 84% overall yield. Macrocyclization was then achieved by heating an equimolar solution of **9** and enaminone **10**[14] in toluene under moderately high dilution conditions. After 5 days, TLC indicated complete consumption of the starting materials. The desired crownophane **11** was subsequently isolated in 34% yield after flash column chromatography. Product isolation was greatly simplified by the absence of tractable by-products with the remaining mass balance presumably being consumed in the formation of oligomeric materials that separated from the reaction mixture as a dark tar. Evidence of successful enaminone/alkyne trimerization is easily obtained from $^1$H NMR spectroscopy as the hydrogens present on the 1,3,5-trisubstitued arene ring resonate at distinctive downfield chemical shifts in an integrated ratio of 2:1 (these signals appear at 8.77 and 7.84 ppm in **11**). The methoxy substituent on the dangling arene ring provides a convenient spectroscopic handle as well.

The isolated yield of 34% is comparable to yields obtained using other macrocyclization protocols.[15] Moreover, the events leading to **11** require formation of three new C–C bonds along with concomitant generation of a

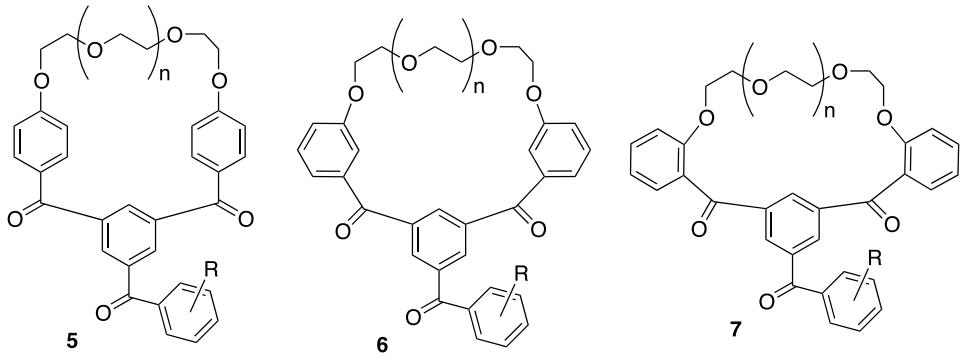
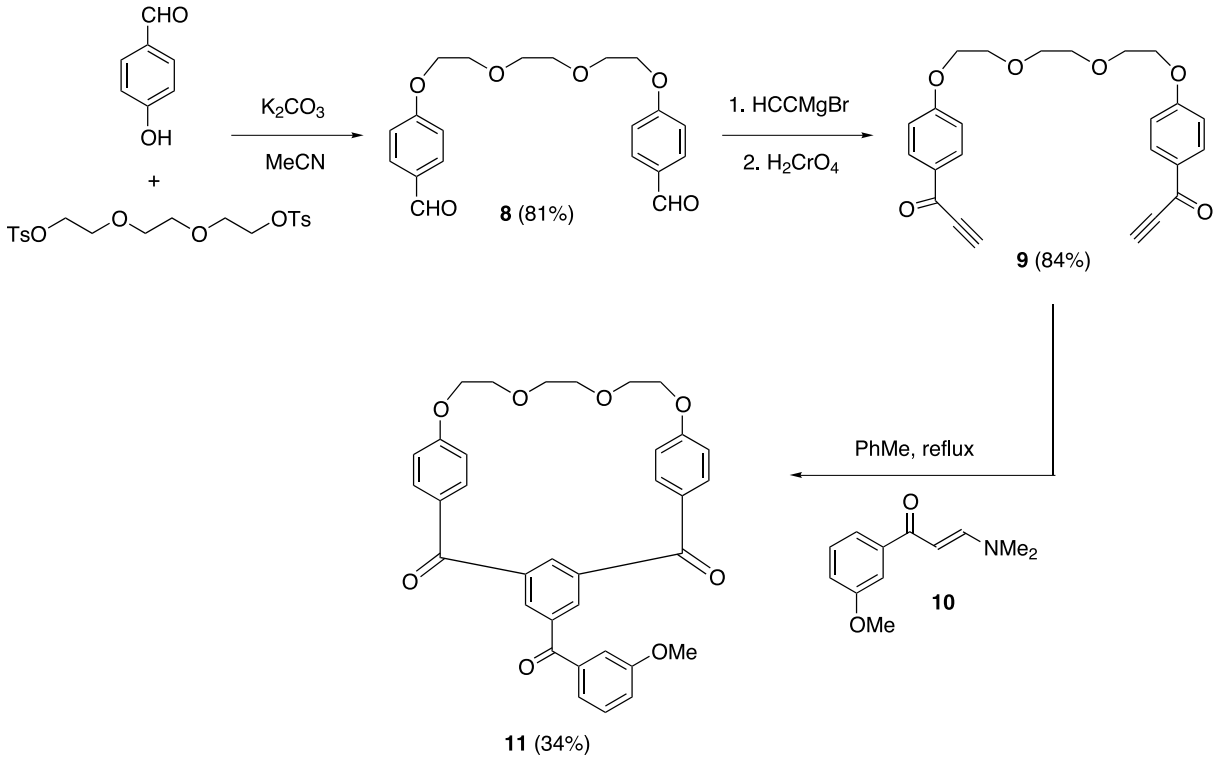


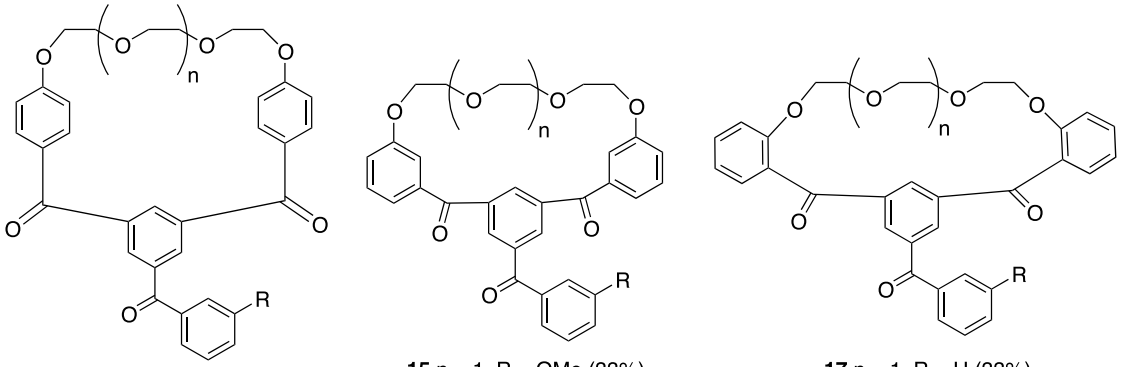

**Figure 2.** Targeted *para*-, *meta*-, and *ortho*-linked crownophane frameworks.




**Scheme 1.** Representative synthesis of triaroylbenzene-derived crownophanes.

six-membered and a 23-membered ring. Some effort was directed toward improving the macrocyclization process by performing the benzannulation reaction in the presence of alkali metal cations. It was hoped that an appropriately sized cation might template the assembly of the crownophane ring. Performing the enaminone-directed macrocyclization described above in the presence of $NaPF_6$, $KPF_6$, or $Cs_2CO_3$ additives, however, had no effect on the reaction efficiency.[16]

The preparative route illustrated in Scheme 1 was employed for the synthesis of isomeric and homologous crownophanes **12–19** (Scheme 2). These crownophanes are derived from either *o*-, *m*-, or *p*-hydroxy benzaldehyde precursors connected via alkylation with ethylene glycol ditosylates of varying lengths. Conversion to bis(ethynyl) ketones and enaminone-triggered macrocyclization then gave the indicated products. Numbers in parentheses reflect the isolated yield of the key benzannulation step. In general, these yields are comparable across the crownophane series for macrocyclic ring sizes between 19 (**17**) and 29 (**14**). Exceptions were noted for the *ortho*-linked cyclophanes **17–19**, in which the yield decreased as a function of ring size. The *para*- and *meta*-linked crownphanes were obtained as pale yellow solids, while the *ortho*-linked congeners were all isolated as viscous oils. In general, reaction mixtures leading to **12–16** were relatively uncomplicated and product isolation was straightforward. In reactions leading to **17–19**, however, the bis(alkyne) partners were consumed before the enaminone reactants, thus necessitating careful chromatographic separation of the crownophanes from unreacted starting material.




**Scheme 2.** Crownophanes prepared using the route shown in Scheme 1. Percentages refer yields of benzannulation reactions.

The development of a four-step modular synthetic route suitable for accessing the novel crownophane frameworks described above provides a foundation for further study of triaroylbenzene-derived cyclophanes. Indeed, one can imagine numerous permutations of this preparative method that would afford a variety of structurally intriguing heterocyclic and carbocyclic cyclophanes. As alluded to previously, we envisioned utilizing crownophanes related to **11–19** as ion pair receptors with the oligo(ethylene glycol) bridges serving as cationic receptor sites and functionality introduced onto the dangling arene ring serving as anion binding sites. As a prelude to continuing studies along these lines, the cation binding abilities of **11–19** were assessed as described below.

### 2.2. Gas phase binding studies

An initial indication of crownophane cation-binding ability was determined in a qualitative fashion by examining their behavior in the gas phase using ESI mass spectrometry. Mass spectrometry is increasingly being used to detect supramolecular interactions,[17] particularly in the context of ionophore–substrate associations.[18] For our studies, the relative affinity of crownophanes **11–12** and **15–16** toward alkali metal ($Li^+$, $Na^+$, $K^+$, $Cs^+$) and $NH_4^+$ cations was examined. A relative cation-binding selectivity scale for each crownophane was determined by preparing a sample consisting of all five cationic species and an excess of a given crownophane. Analysis of the mixture by ESI-MS revealed cationic adducts with *m*/*z* ratios corresponding to the various possible [crownophane cation]$^+$ complexes. A simple comparison of the relative peak intensities was then used to create a gas-phase selectivity scale (Table 1).

**Table 1**. Relative gas phase cation affinities of selected crownophanes

| Cation | **11** | **12** | **15** | **16** |
|---|---|---|---|---|
| $Li^+$ | n.d. | 1.0 | 1.0 | 1.7 |
| $Na^+$ | 1.1 | 18 | 14 | 6.6 |
| $K^+$ | 1.0 | 12 | 4.0 | 2.5 |
| $Cs^+$ | 1.7 | 15 | 4.3 | 2.1 |
| $NH_4^+$ | n.d. | 4.0 | 1.8 | 1.0 |

n.d.—not detected.

The data presented in Table 1 indicate that both *para*-linked crownophanes **11** and **12** interact essentially equally well with $Na^+$, $K^+$, and $Cs^+$, while neither shows any particular affinity for $Li^+$ or $NH_4^+$. In contrast, the *meta*-linked isomer **16** displays similar affinity for all the cations tested. The only crownophane out of four used in this study that seemed to exhibit any selectivity was **15**, which showed a preference for $Na^+$ over all other cations. It is important to note that these experiments provide no information regarding the site of cation–crownophane interaction. However, based on apparent differences in cation affinity across the series, it would seem that structural differences in the crownophanes examined (i.e., number of ether oxygens, cyclophane substitution pattern) are important factors that affect binding ability, at least in the gas phase.

### 2.3. Solution phase binding studies

With qualitative evidence for cation binding in hand, attention was next directed toward solution phase studies, in particular picrate extraction experiments.[19] These studies were easily performed by measuring the absorbance of an aqueous solution of alkali or *t*-$BuNH_3^+$ picrate before and after agitation with a $CHCl_3$ solution of crownophane.[20] The percent picrate extraction was then calculated according to the equation $(A_o-A_f)/A_o\times 100$ where $A_o$ and $A_f$ represent the initial and final picrate absorbance, respectively. Crownophanes **13–19** were used in these experiments along with 18-crown-6 as a positive control. Unfortunately, none of the crownophanes tested exhibited any significant picrate salt extraction ability (i.e., % extraction $<5\%$ in all cases). In contrast, under identical experimental conditions, the percentage picrate extraction of $K^+$, $Na^+$, and $Li^+$ picrate by 18-crown-6 was found to be 60%, 40%, and $<5\%$, respectively. Thus, it appears that the triaroylbenzene-derived crownophanes are ineffective solution phase ionophores for alkali and ammonium cations. This assertion is further substantiated through $^1$H NMR binding studies performed on selected substrates. Crownophanes **14** and **18–19** were each treated with various alkali and ammonium salts (KI, CsI, $NH_4Cl$) in DMSO-$d_6$. Upon varying the relative [crownophane]/[salt] concentration from 1:1 to ~1:20, however, the $^1$H- and $^{13}$C NMR spectra for all the crownophanes remained essentially unchanged.

The results of X-ray diffraction studies (described in the next section) seem to indicate that the molecular cavities in these crownophanes are simply too large to accommodate relatively small alkali cation guests. Consequently, the potential interactions of selected crownophanes (**15** and **16**) with larger alkyl and aryl ammonium salts were briefly examined. Specifically, the $^1$H NMR spectrum of **15** was determined in the presence of either benzyl ammonium iodide or *n*-butyl ammonium iodide ($CD_3CN$ as solvent). In each case, neither the crownophane nor the ammonium ion displayed any complexation-induced chemical shift changes at guest/host ratios ranging from 1:1–10:1. Likewise, no interaction was detected by NMR between **16** and anilinium iodide. Secondary ammonium salts (dibenzyl ammonium $PF_6$ and di-*n*-butyl ammonium $PF_6$) were also screened as potential crownophane guests and/or components of new pseudorotaxanes.[21] The 26- and 29-membered crownophanes **12** and **14** were used in this study. Disappointingly, however, admixture of the secondary ammonium salts and the selected crownophanes in $CD_3CN$ provided no evidence of solution-phase interactions.

Interestingly, the only substrate examined that showed any sign of solution-phase complexation with crownophane hosts was *N*-methyl pyridinium iodide (NMI), an ammonium salt devoid of hydrogen bond donors. When a $CDCl_3$ solution of NMI (2.0 mM) was treated with either **11** or **12** the signals corresponding to the pyridine and N-methyl hydrogens experienced small upfield shifts. While the magnitude of the chemical shift differences varied as a function of crownophane concentration, the overall effect was quite small even at crownophane/NMI ratios of 22.5:1.[22] Such small complexation induced shifts may be a consequence of very weak host–guest associations. Indeed, attempts to determine equilibrium binding constants from NMR titration experiments were thwarted by the

inability to approach saturation binding, even in the presence of a large excess of crownophane.

### 2.4. X-ray crystallographic studies

Given the disappointing results obtained from solution phase binding experiments, X-ray crystallographic studies were initiated in the hope that solid-state structural information might provide insight into the apparent failure of these materials to function as ionophores in solution. While *ortho*-linked crownophanes **17**–**19** exist as oils (thus precluding structure determination), **11**–**16** are all solids amenable to purification by recrystallization. Single crystals of **13** were obtained from $CHCl_3$/hexane solution and the molecular structure of this crownophane is shown in Figure 3. The ethylene oxy groups are distorted from the ideal 'crown' conformation, in line with solid-state conformations exhibited by other metal-free crown ethers.[23] The cyclophane portion of the macrocycle appears to be relatively rigid, and this structural feature may be important in mitigating the anticipated ionophoric properties of these materials. Indeed, the O1–O5 distance in **13** is 6.371 Å in the crystal and it is difficult to imagine a significant decrease of this span in solution. This distance far exceeds the ionic diameter of all cations examined, thus precluding both phenolic oxygens from simultaneously participating in a metal binding event. Likewise, the O2–O4 distance of 4.027 Å is also too long to accommodate an alkali metal cation.

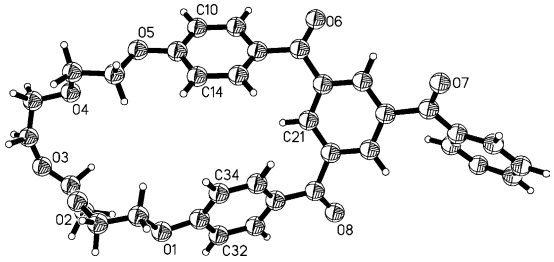



**Figure 3.** Molecular structure (ORTEP, 50% probability) of crownophane **13**. Selected intra-annular atomic distances (Å): O1–O5—6.371; O2–O4—4.027; C21–O3—9.695; C10–C32—7.421; C14–C34—4.061.

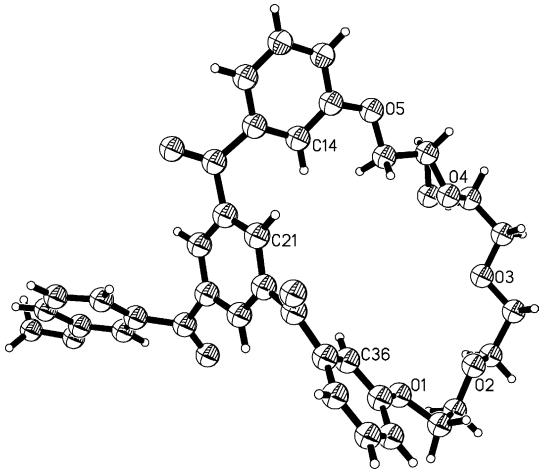



**Figure 4.** Molecular structure (ORTEP, 50% probability) of crownophane **16**. One oxygen (O4) is slightly disordered. Selected intra-annular distances (Å): O1–O5—8.125; O2–O4—5.033; C21–O3—8.241; C14–C36—6.379.

The rigidifying effect exerted by the cyclophane framework appears to be even more pronounced in **16**. As shown in Figure 4, the crownophane adopts a cleft-like conformation with the central 1,3,5-trisubstituted arene ring oriented roughly perpendicular to the macrocyclic ring. The phenolic oxygens on opposite sides of the macrocycle are substantially farther apart (O1–O5 distance = 8.125 Å) than the analogous atoms in **13**. The O2–O4 distance is also greater in **16** (5.033 Å) than in the *para*-linked isomer. Once again, it seems that the crownophane macrocycle is simply too large and rigid to efficiently interact with alkali metal cations (or larger ammonium salts) in solution. Presumably, similar structural constraints are also operative in the *ortho*-linked crownophanes **17**–**19**.

## 3. Conclusions

A concise, efficient, and modular synthetic route to triaroylbenzene-based crownophanes has been developed. The key macrocyclization is accomplished during the course of an enaminone-triggered benzannulation reaction of bis(aryl ethynyl ketones). Although it was originally envisioned that the crownophanes prepared in this study would be capable of binding alkali metal cations, it appears that structural features inherent in this particular family of macrocycles impede such interactions. While several crownophanes did display cation binding ability in the gas phase, ionophoric properties were not evident in solution. This fact highlights the importance of coupling mass spectrometric binding studies with solution phase measurements. Electrostatic attractions are naturally accentuated in the gas phase and results obtained in this medium are not always transferable to solution (as is the case in this study). While crownophanes **11**–**19** do not function as originally envisaged, the modular synthetic approach implemented for their construction should facilitate the preparation of second generation crownophanes that are expected to display greater cation binding ability. Additionally, the partially enforced macrocyclic cavities evident in the crystal structures of **13** and **16** offers the intriguing possibility of utilizing these materials (or homologues thereof) as components of novel rotaxane-based supramolecular assemblies.[8,24] Studies along these lines are in progress.

## 4. Experimental

All commercially available reagents and solvents were used as received unless otherwise noted. Tetrahydrofuran was distilled from Na-benzophenone, $CH_2Cl_2$ and toluene were distilled from $CaH_2$. All reactions were performed in oven-dried glassware under a blanket of dry argon. Thin-layer chromatography was performed on Whatman silica gel 60 glass-backed TLC plates (250 μm). Flash column chromatography was performed using Natland International silica gel 60 (200–400 mesh). $^1$H- and $^{13}$C NMR spectra were obtained on a Varian XL-300, Varian Unity 300, or Bruker Avance 300 spectrometer. Chemical shifts ($\delta$) are reported relative to residual solvent ($CHCl_3$) peaks (7.27 and 77.23 ppm for $^1$H- and $^{13}$C NMR, respectively). IR spectra were recorded on a Perkin–Elmer Model 1600 FTIR spectrophotometer. UV/visible spectrophotometry was

performed using a Cary 50 spectrophotometer. Melting points were determined using a Thomas–Hoover melting point apparatus and are uncorrected. High-resolution mass spectra were obtained using a JEOL M-Station 700 spectrometer. Combustion analyses were obtained from Atlantic Microlabs, Norcross, GA. Dialdehyde **8**[13] and related dialdehyde precursors to **12–14** and **17–19** were prepared using literature procedures.[5b,13,25]

### 4.1. Preparation of *meta*-$CHOC_6H_4O(CH_2CH_2O)_n$-$CH_2CH_2OC_6H_4CHO$ ($n=2$, 3), precursors to crownophanes 15–16

To a solution of 3-hydroxybenzaldehyde (1.70 g, 14.0 mmol) in 40 mL of $CH_3CN$ was added anhydrous $K_2CO_3$ (19.8 g, 143 mmol) and triethylene glycol ditosylate (2.00 g, 4.36 mmol). The reaction was heated to reflux for 24 h. The $CH_3CN$ was removed and the residue was partitioned between $CH_2Cl_2$ and $H_2O$. The layers were separated and the organic phase was washed sequentially with $H_2O$, 1 N aq NaOH solution, $H_2O$, and brine. After drying over $MgSO_4$, the solvent was evaporated to afford a solid that was further purified by flash column chromatography ($CH_2Cl_2$). The title compound ($n=2$) was isolated as a colorless solid (1.28 g, 82%), mp 65–66 °C. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 3.73 (s, 4H), 3.85 (m, 4H), 4.15 (m, 4H), 7.16 (m, 2H), 7.35–7.40 (m, 6H), 9.92 (s, 2H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 67.8, 69.7, 70.9, 113.1, 122.0, 123.6, 130.1, 137.8, 159.4, 192.1. IR (thin film) $\nu$ ($cm^{-1}$) 1684. Anal Calcd for $C_{20}H_{22}O_6\cdot(H_2O)_{0.25}$: C 66.19, H 6.25. Found: C 66.14, H 6.04. Using an identical procedure, 3-hydroxybenzaldehyde (2.19 g, 17.9 mmol) and tetraethylene glycol ditosylate (3.00 g, 5.97 mmol) gave the title compound ($n=3$) as a colorless oil (2.13 g, 89%). $^1$H NMR 300 MHz, $CDCl_3$) $\delta$ 3.67–3.74 (m, 8H), 3.86 (d, 4H, $J=4.0$ Hz), 4.17 (d, 4H, $J=4.0$ Hz), 7.19 (dt, 2H, $J=2.4$, 6.9 Hz), 7.38 (m, 6H), 9.95 (s, 2H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 67.9, 69.8, 70.9, 71.0, 113.1, 122.2, 123.8, 130.2, 137.9, 159.6, 192.2. IR (thin film) $\nu$ ($cm^{-1}$) 1685. Anal Calcd for $C_{22}H_{26}O_7$: C 65.66, H 6.51. Found: C 65.73, H 6.45.

### 4.2. General procedure for the preparation of bis(ethynyl ketones)

The procedure used for the preparation of **9** is representative. Dialdehyde **8** (1.75 g, 4.96 mmol) was dissolved in ~15 mL of THF and cooled to 0 °C in an ice bath. Ethynyl magnesium bromide (0.5 M in THF, 25.0 mL, 12.5 mmol) was added via syringe and the reaction was maintained for 2 h. The reaction was quenched by addition of saturated aqueous $NH_4Cl$ solution (~30 mL). The resulting mixture was extracted several times with $Et_2O$ and the combined organic layers were washed with brine and dried over $MgSO_4$. Filtration of the crude product through a plug of silica gel followed by evaporation of the solvent gave the desired diol as a thick oil. Without further characterization, the diol was dissolved in ~15 mL of acetone. A solution of $H_2CrO_4$ (Jones reagent) was added dropwise until the red color indicative of excess Cr(VI) persisted. The reaction was quenched by addition of propan-2-ol and the insoluble Cr(III) salts were removed by filtration through a pad of Celite. The filtrate was diluted with $Et_2O$ and washed sequentially with $H_2O$, saturated aq $NaHCO_3$ solution, and brine. After drying over $MgSO_4$, the solvent was evaporated and the residue purified by flash column chromatography (2:1 hexanes/EtOAc) to afford **9** (84% over two steps) as a yellow solid, mp 79–81 °C. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 3.38 (s, 2H), 3.77 (s, 4H), 3.90 (dd, 4H, $J=4.2$, 5.4 Hz), 4.22 (dd, 4H, $J=4.2$, 5.4 Hz), 6.97 (dt, 4H, $J=2.5$, 9.0 Hz), 8.12 (dt, 4H, $J=2.5$, 9.0 Hz). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 68.0, 69.8, 71.2, 80.3, 80.6, 114.7, 130.0, 132.3, 164.2, 176.1. IR (thin film) $\nu$ ($cm^{-1}$) 3229, 2092, 1639. HRMS ($FAB^+$, NBA) calcd for $C_{24}H_{23}O_6$ $[M+H]^+$ 407.1494; found 407.1494. Other ethynyl ketones were prepared in an analogous fashion from the appropriate oligo(ethylene glycol)-linked dialdehydes.

**4.2.1. *para*-Tetra(ethylene glycol)-linked bis(ethynyl ketone) [precursor to 12 and 13].** 86%, mp 85–86 °C. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 3.48 (s, 2H), 3.68–3.76 (m, 8H), 3.89 (dd, 4H, $J=4.2$, 5.4 Hz), 4.21 (dd, 4H, $J=4.2$, 5.4 Hz), 6.98 (dt, 4H, $J=2.4$, 9.0 Hz), 8.12 (dt, 4H, $J=2.4$, 9.0 Hz). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 68.0, 69.7, 70.9, 71.1, 80.3, 80.6, 114.7, 129.9, 132.3, 164.2, 176.1. IR (thin film) $\nu$ ($cm^{-1}$) 3233, 2091, 1638. HRMS ($FAB^+$, NBA) calcd for $C_{26}H_{27}O_7$ $[M+H]^+$ 451.1757; found 451.1757.

**4.2.2. *para*-Penta(ethylene glycol)-linked bis(ethynyl ketone) [precursor to 14].** 78%, mp 50–54 °C. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 3.40 (s, 2H), 3.65–3.68 (m, 8H), 3.70–3.72 (m, 4H), 3.87 (t, 4H, $J=4.8$ Hz), 4.20 (t, 4H, $J=4.8$ Hz), 6.96 (ddd, 4H, $J=1.4$, 3.4, 8.4 Hz), 8.10 (ddd, 4H, $J=1.4$, 3.4, 8.4 Hz). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 69.7, 70.8, 71.1, 80.3, 80.6, 114.7, 129.9, 132.3, 164.2, 176.1. IR (thin film) $\nu$ ($cm^{-1}$) 2092, 1642. HRMS ($FAB^+$, NBA) calcd for $C_{28}H_{31}O_8$ $[M+H]^+$ 495.2019; found 495.2029. Anal Calcd for $C_{28}H_{30}O_8$ $(H_2O)_{0.5}$: C 66.79, H 6.12. Found: C 66.82, H 6.05.

**4.2.3. *meta*-Tri(ethylene glycol)-linked bis(ethynyl ketone) [precursor to 15].** 86%, mp 69–70 °C. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 3.44 (s, 2H), 3.77 (s, 4H), 3.90 (dd, 4H, $J=4.0$, 5.3 Hz), 4.20 (dd, 4H, $J=4.0$, 5.3 Hz), 7.20 (ddd, 2H, $J=0.9$, 2.7, 8.4 Hz), 7.39 (t, 2H, $J=8.0$ Hz), 7.66 (dd, 2H, $J=1.5$, 2.7 Hz) 7.78 (dt, 2H, $J=1.5$, 8.0 Hz). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 67.9, 69.9, 71.1, 80.5, 80.9, 114.0, 122.1, 123.3, 129.9, 137.6, 159.2, 177.3. IR (thin film) $\nu$ ($cm^{-1}$) 3239, 2092, 1648. HRMS ($FAB^+$, NBA) calcd for $C_{24}H_{23}O_6$ $[M+H]^+$ 407.1494; found 407.1491.

**4.2.4. *meta*-Tetra(ethylene glycol)-linked bis(ethynyl ketone) [precursor to 16].** 80%, colorless oil. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 3.44 (s, 2H), 3.68–3.76 (m, 8H), 3.88 (dd, 4H, $J=4.1$, 5.5 Hz), 4.19 (dd, 4H, $J=4.1$, 5.5 Hz), 7.20 (ddd, 2H, $J=1.3$, 2.6, 8.1 Hz), 7.40 (t, 2H, $J=8.1$ Hz), 7.65 (dd, 2H, $J=1.3$, 2.6 Hz), 7.79 (ddd, 2H, $J=0.9$, 1.3, 8.0 Hz). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 67.9, 69.8, 70.9, 71.1, 80.5, 80.9, 114.0, 122.2, 123.3, 130.0, 137.7, 159.3, 177.3. IR (thin film) $\nu$ ($cm^{-1}$) 3235, 2092, 1648. HRMS ($FAB^+$, NBA) calcd for $C_{26}H_{27}O_7$ $[M+H]^+$ 451.1757; found 451.1756.

**4.2.5. *ortho*-Tri(ethylene glycol)-linked bis(ethynyl ketone) [precursor to 17].** 78%, oil. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 3.46 (s, 2H), 3.80 (s, 4H), 3.93 (t, 4H, $J=4.8$ Hz),

4.24 (t, 4H, $J$=4.8 Hz), 6.98–7.06 (m, 4H), 7.51 (ddd, 2H, $J$=1.6, 7.0, 8.7 Hz), 7.98 (dd, 2H, $J$=1.6, 7.8 Hz). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 68.9, 69.6, 71.3, 77.4, 80.1, 82.8, 113.5, 120.8, 126.5, 132.7, 135.5, 159.4, 176.1. IR (thin film) $\nu$ ($cm^{-1}$) 2092, 1650. HRMS ($FAB^+$, NBA) calcd for $C_{24}H_{23}O_6$ $[M+H]^+$ 407.1494; found 407.1502.

**4.2.6. *ortho*-Tetra(ethylene glycol)-linked bis(ethynyl ketone) [precursor to 18].** 83%, oil. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 3.56–3.59 (m, 4H), 3.61 (s, 2H), 3.64–3.67 (m, 4H), 3.82 (t, 4H, $J$=4.8 Hz), 4.14 (t, 4H, $J$=4.8 Hz), 6.89–6.94 (m, 4H), 7.42 (ddd, 2H, $J$=1.6, 7.3, 8.4 Hz), 7.86 (dd, 2H, $J$=1.6, 8.1 Hz). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 68.8, 69.4, 70.8, 71.2, 80.5, 82.8, 113.5, 120.7, 126.5, 132.4, 135.5, 159.4, 176.2. IR (thin film) $\nu$ ($cm^{-1}$) 2091, 1650. HRMS ($FAB^+$, NBA) calcd for $C_{26}H_{27}O_7$ $[M+H]^+$ 451.1757; found 451.1757. Anal Calcd for $C_{26}H_{26}O_7\cdot(H_2O)_{0.2}$: C 68.77, H 5.82. Found: C 68.85, H 5.79.

**4.2.7. *ortho*-Penta(ethylene glycol)-linked bis(ethynyl ketone) [precursor to 19].** 86%, oil. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 3.59 (s, 2H), 3.65–3.69 (m, 8H), 3.74–3.77 (m, 4H), 3.93 (t, 4H, $J$=4.8 Hz), 4.25 (t, 4H, $J$=4.8 Hz), 6.98–7.04 (m, 4H), 7.51 (ddd, 4H, $J$=1.6, 7.1, 8.7 Hz), 7.96 (dd, 2H, $J$=1.6, 7.8 Hz). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 68.9, 69.6, 70.8, 70.9, 71.2, 77.4, 80.6, 113.5, 120.8, 132.4, 135.5, 159.5. IR (thin film) $\nu$ ($cm^{-1}$) 2091, 1650. HRMS ($FAB^+$, NBA) calcd for $C_{28}H_{31}O_8$ $[M+H]^+$ 495.2019; found 495.2015. Anal Calcd for $C_{28}H_{30}O_8\cdot(H_2O)_{0.2}$: C 67.51, H 6.12. Found: C 67.47, H 6.16.

### 4.3. General procedure for macrocyclization-preparation of crownophane 11

The reaction leading to **11** is representative. From separate addition funnels, bis(alkyne) **9** (1.00 g, 2.45 mmol) in 50 mL of toluene and enaminone **10**[13] (0.51 g, 2.45 mmol) in 50 mL of toluene were simultaneously added dropwise to 150 mL of refluxing toluene. Once the addition was complete, the reaction was maintained for 5 days, at which time TLC indicated complete consumption of starting materials. The toluene was evaporated and the tarry residue was purified by flash column chromatography (1:1 hexanes/EtOAc) to afford **11** as a yellow solid (0.45 g, 34%). An analytical sample was obtained by recrystallization from hexanes/EtOAc, mp 190–191 °C. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 3.75 (s, 3H), 3.86–3.90 (m, 8H), 4.29 (t, 4H, $J$=4.2 Hz), 7.02 (t, 4H, $J$=8.7 Hz), 7.19–7.22 (m, 1H), 7.37–7.49 (m, 3H), 7.57–7.75 (m, 4H), 7.84 (s, 1H), 8.77 (s, 2H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 55.8, 68.1, 69.5, 71.3, 114.4, 114.6, 120.1, 123.3, 129.9, 130.1, 132.3, 134.0, 136.9, 137.7, 138.2, 140.7, 160.1, 162.8, 194.0, 195.2. IR (thin film) $\nu$ ($cm^{-1}$) 1739. Anal Calcd for $C_{34}H_{30}O_8\cdot(H_2O)_{0.5}$: C 70.94, H 5.25. Found: C 70.92, H 5.38. Crownophanes **12–19** were prepared using the procedure described above from the appropriate bis(alkyne) precursor and either enaminone **10** or its unsubstituted analogue.[13]

**4.3.1. Crownophane 12.** 33%, mp 168–169 °C ($CHCl_3$/hexanes). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 3.69–3.76 (m, 8H), 3.89–3.92 (m, 7H), 4.22–4.25 (m, 4H), 7.01 (dd, 4H, $J$=2.4, 4.8 Hz), 7.17–7.21 (m, 1H), 7.39–7.47 (m, 3H), 7.82 (dd, 4H, $J$=2.4, 4.8 Hz), 7.92 (t, 1H, $J$=1.5 Hz), 8.58 (d, 2H, $J$=1.5 Hz). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 55.8, 68.2, 69.5, 70.8, 71.1, 117.4, 120.1, 123.3, 129.7, 129.9, 132.5, 134.2, 135.8, 137.7, 138.1, 140.1, 160.1, 163.0, 193.8, 195.2. IR (thin film) $\nu$ ($cm^{-1}$) 1664. HRMS ($FAB^+$, NBA) calcd for $C_{36}H_{34}O_9Na$ $[M+Na]^+$ 633.2100; found 633.2104. Anal Calcd for $C_{36}H_{34}O_9$ $(CHCl_3)_{0.5}$: C 65.40, H 5.19. Found: C 65.00, H 5.19.

**4.3.2. Crownophane 13.** 49%, mp 183–184 °C (hexanes/EtOAc). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 3.67–3.75 (m, 8H), 3.90 (t, 4H, $J$=4.2 Hz), 4.23 (t, 4H, $J$=4.2 Hz), 7.01 (d, 4H, $J$=8.8 Hz), 7.54–7.57 (m, 2H), 7.63–7.67 (m, 1H), 7.81 (d, 4H, $J$=8.8 Hz), 7.87–7.92 (m, 3H), 8.57 (d, 2H, $J$=1.5 Hz). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 68.2, 69.4, 70.8, 71.0, 114.4, 128.9, 129.7, 130.4, 132.5, 133.4, 134.2, 135.8, 136.8, 137.7, 140.0, 162.0, 193.8, 195.4. IR (thin film) $\nu$ ($cm^{-1}$) 1652. HRMS ($FAB^+$, NBA) calcd for $C_{35}H_{33}O_8$ $[M+H]^+$ 581.2175; found 581.2174. Anal Calcd for $C_{35}H_{32}O_8$: C 72.40, H 5.56. Found: C 72.28, H 5.43.

**4.3.3. Crownophane 14.** 29%, mp 174–175 °C ($CHCl_3$/hexanes). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 3.66–3.73 (m, 12H), 3.87 (t, 4H, $J$=4.4 Hz), 4.20 (t, 4H, $J$=4.4 Hz), 6.97 (d, 4H, $J$=8.8 Hz), 7.49–7.54 (m, 2H), 7.60–7.63 (m, 1H), 7.80 (d, 4H, $J$=8.8 Hz), 7.84–7.87 (m, 2H), 7.94 (t, 1H, $J$=1.5 Hz) 8.52 (d, 2H, $J$=1.5 Hz). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 68.1, 69.7, 71.0, 71.1, 71.3, 114.6, 128.9, 129.5, 130.4, 132.6, 133.4, 134.1, 134.6, 136.8, 137.9, 140.1, 163.1, 193.7, 195.3. IR (thin film) $\nu$ ($cm^{-1}$) 1650. HRMS ($FAB^+$, NBA) calcd for $C_{37}H_{37}O_9$ $[M+H]^+$ 625.2438; found 625.2432. Anal Calcd for $C_{37}H_{36}O_9$ $(CHCl_3)_{0.84}$: C 62.69, H 5.12. Found: C 62.74, H 5.16.

**4.3.4. Crownophane 15.** 33%, mp 50–55 °C (hexanes/EtOAc). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 3.69 (s, 4H), 3.84 (dd, 4H, $J$=3.6, 5.4 Hz), 3.90 (s, 3H), 4.12 (dd, 4H, $J$=3.6, 5.4 Hz), 7.12–7.22 (m, 4H), 7.38–7.51 (m, 8H), 8.07 (t, 1H, $J$=1.5 Hz), 8.51 (d, 2H, $J$=1.5 Hz). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 55.8, 68.1, 69.7, 71.0, 114.4, 116.8, 119.6, 120.1, 121.9, 123.2, 129.9, 130.4, 133.7, 133.9, 138.0, 138.1, 138.2, 139.6, 158.7, 160.1, 194.9, 195.2. Anal Calcd for $C_{34}H_{30}O_8\cdot(H_2O)_{0.5}$: C 70.94, H 5.25. Found: C 70.54, H 5.64.

**4.3.5. Crownophane 16.** 32%, 165–166 °C (hexanes/EtOAc). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 3.62–3.69 (m, 8H), 3.84 (dd, 4H, $J$=4.0, 5.5 Hz), 3.88 (s, 3H), 4.14 (dd, 4H, $J$=4.0, 5.5 Hz), 7.16–7.23 (m, 4H), 7.35–7.50 (m, 8H), 8.17 (t, 1H, $J$=1.5 Hz), 8.47 (d, 2H, $J$=1.5 Hz). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 55.8, 68.1, 69.8, 70.9, 71.0, 114.3, 116.8, 119.9, 120.0, 122.3, 123.1, 129.7, 130.2, 133.3, 134.1, 137.8, 138.0, 139.0, 158.6, 159.9, 194.7, 194.8. IR (thin film) $\nu$ ($cm^{-1}$) 1658. HRMS ($FAB^+$, NBA) calcd for $C_{36}H_{35}O_9$ $[M+H]^+$ 611.2281; found 611.2280. Anal Calcd for $C_{36}H_{34}O_9$: C 70.81, H 5.61. Found: C 70.73, H 5.73.

**4.3.6. Crownophane 17.** 33%, $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 3.38 (s, 4H), 3.56 (t, 4H, $J$=4.1 Hz), 4.12 (t, 4H, $J$=4.1 Hz), 6.99 (d, 2H, $J$=8.7 Hz), 7.11 (t, 2H, $J$=7.5 Hz), 7.48–7.53 (m, 6H), 7.58–7.63 (m, 1H), 7.82–7.85 (m, 2H), 8.39 (d, 2H, $J$=1.5 Hz), 8.59 (t, 1H, $J$=1.5 Hz). $^{13}$C NMR

(75 MHz, $CDCl_3$) $\delta$ 68.8, 69.3, 71.2, 112.3, 121.6, 128.0, 128.7, 130.5, 133.2, 133.3, 133.9, 135.2, 136.6, 137.8, 138.1, 156.7, 194.8, 195.3. IR (thin film) $\nu$ ($cm^{-1}$) 1660. Anal Calcd for $C_{33}H_{28}O_7$ ($H_2O$): C 71.47, H 5.26. Found: C 71.52, H 5.18.

**4.3.7. Crownophane 18.** 19%, $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 3.38–3.47 (m, 8H), 3.66 (t, 4H, $J=4.3$ Hz), 4.11 (t, 4H, $J=4.3$ Hz), 6.98 (d, 2H, $J=8.4$ Hz), 7.06 (t, 2H $J=7.5$ Hz), 7.41–7.51 (m, 6H), 7.58–7.64 (m, 1H), 7.80–7.83 (m, 2H), 8.33 (d, 2H, $J=1.5$ Hz), 8.53 (t, 1H, $J=1.5$ Hz). $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 68.9, 69.4, 70.7, 71.4, 112.7, 121.2, 127.9, 128.8, 130.3, 130.4, 133.2, 133.4, 133.7, 135.0, 136.7, 138.1, 138.8, 157.1, 194.7, 195.2. IR (thin film) $\nu$ ($cm^{-1}$) 1661. HRMS ($FAB^+$, NBA) calcd for $C_{35}H_{33}O_8$ $[M+H]^+$ 581.2175; found 581.2173. Anal Calcd for $C_{35}H_{32}O_8$ $(EtOAc)_{2.3}$: C 67.78, H 5.15. Found: C 67.78, H 5.18.

**4.3.8. Crownophane 19.** 9%, $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 3.46–3.54 (m, 12H), 3.65 (t, 4H, $J=4.9$ Hz), 4.11 (t, 4H, $J=4.9$ Hz), 6.99–7.08 (m, 4H), 7.40–7.50 (m, 6H), 7.57–7.62 (m, 1H), 7.79–7.83 (m, 2H), 8.34 (d, 2H, $J=1.7$ Hz) 8.48 (t, 1H, $J=1.7$ Hz). $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 68.7, 69.3, 70.8, 70.8, 71.0, 113.1, 121.2, 127.9, 128.7, 130.2, 130.4, 133.1, 133.3, 133.6, 134.7, 136.6, 138.0, 138.8, 157.1, 194.6, 195.1. IR (thin film) $\nu$ ($cm^{-1}$) 1662. HRMS ($FAB^+$, NBA) calcd for $C_{37}H_{37}O_9$ $[M+H]^+$ 625.2438; found 625.2437. Anal Calcd for $C_{37}H_{36}O_9\cdot(H_2O)_{1.9}$: C 67.45, H 5.81. Found: C 67.44, H 5.57.

### 4.4. General procedure for mass spectrometric binding studies

Separately, 60 μL aliquots of crownophane solution (1 mg/mL in $CHCl_3$) were combined with 50 μL aliquots of alkali metal and ammonium hydroxide solutions ($1\times10^{-4}$ M, except for $Cs^+$, in which CsI was used). Each mixture was diluted to 1.0 mL with MeOH. Aliquots from each sample (100 μL) were combined and the resulting mixture was diluted to 1.0 mL with MeOH. This results in a mixture in which the crownophane concentration is ~20 times the concentration of each individual cation. Analysis of this solution (20 μL) using ESI-MS was then performed at a flow rate of 0.2 mL $min^{-1}$.

### 4.5. General procedure for picrate extraction experiments.[20]

Equal volumes (1 mL) of a crownophane solution ($1.2\times10^{-3}$ M in $CHCl_3$) and an aqueous solution consisting of alkali metal or ammonium hydroxide (0.1 M) and picric acid ($7.5\times10^{-4}$ M) were combined in a test tube and vigorously agitated for 1.0 h. The test tube was stoppered and centrifuged to facilitate separation of the layers. The absorbance of the aqueous phase before and after agitation with crownophane solution was then compared to determine the % extraction.

### 4.6. X-ray crystallography

Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publication numbers CCDC 240816 and CCDC 240817. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

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# Synthesis and crystalline state photochromism of 3,3′-diaryl biindenylidenedione derivatives

Xu Li,[a] Lili Xu,[a] Jie Han,[a] Meili Pang,[a] Hong Ma[b] and Jiben Meng[a,*]

[a]*Department of Chemistry, Nankai University, Weijin Road, 300071 Tianjin, People's Republic of China*
[b]*Department of Materials Science and Engineering, University of Washington, Seattle, WA 98195, USA*

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**Abstract**—A new series of 3,3′-diaryl biindenylidenedione derivatives were synthesized through Grignard reaction. Some of their stereoisomers were obtained by photochemical transformation upon heating and a plausible reaction mechanism was proposed. Most of these compounds exhibited photochromism in crystalline states as well as generation of stable organic radicals. The absolute configurations of the stereoisomers were determined by single crystal X-ray crystallography. The results showed that the position of substituent could dramatically affect molecular structure and photochemical properties of the biindenylidenedione derivatives.


## 1. Introduction

Quite few kinds of molecules were found to be photochromic in a crystalline state among a large number of photochromic ones investigated in solution. In recent years, photochromic organic crystals have received considerable attention due to their potential applications such as information storage, electronic display, optical switching devices and so on.[1] Typical examples include N-salicylideneanilines,[2,3] dinitrobenzylpyridines,[4,5] diphenylmaleonitriles,[6] triarylimidazole dimmers,[7,8] aziridines,[9] diarylperfluorocyclopentenes,[10] diarylethenes[11] and biindenylidenedione derivatives.[12] Among them the biindenylidene derivatives are unusual materials exhibiting single-crystalline photochromism as well as generation of stable organic radicals.[13–16] In our previous studies,[15,16] we developed a novel approach to prepare a series of photochromic 3,3′-dialkyl biindenylidenedione derivatives, proposed the mechanisms of reaction and photomagnetism, and presented the photochemical properties of the compounds in the crystalline state. In this paper, we report the preparation of a new series of 3,3′-diaryl biindenylidenedione derivatives, the transformation of stereoisomers and its plausible mechanism, and the study of the correlation between the crystal structure and photochemical properties, which provide further insight to the mechanism of crystalline state photochromism in this kind of compounds.

*Keywords*: 3,3′-Diaryl biindenylidenedione derivatives; Photochromism; Electron spin resonance; Free radical; Crystal structure; Synthesis.
* Corresponding author. Tel.: +86 2223 509 933; fax: +86 2223 502 230; e-mail: mengjiben@nankai.edu.cn

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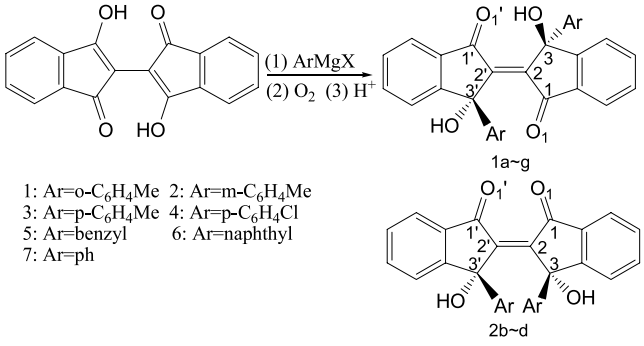
## 2. Results and discussion

### 2.1. Syntheses of 3,3′-diaryl biindenylidenedione derivatives

The syntheses of 3,3′-diaryl biindenylidenedione derivatives were based on our earlier successful method.[15] The key step was to perform an unusual oxidation procedure before adding saturated $NH_4Cl$ aqueous solution during the general Grignard reaction (Scheme 1).



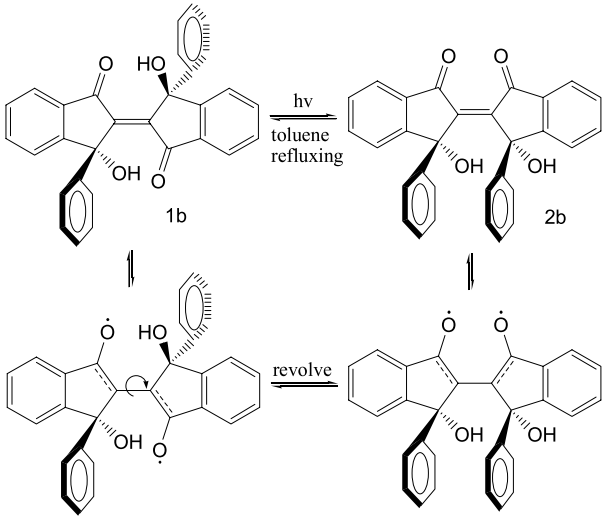

**Scheme 1.**

### 2.2. The transformation of *trans-anti*-1b to its isomer *cis-syn*-2b

The saturated solution of yellow crystal **1b** in toluene was refluxed for 10 h upon the irradiation with a 400 W high-pressure mercury lamp. The yellow plate crystal **1b** and red prism crystal of **2b** were precipitated out slowly from the

solution and separated by a mechanical method under microscope. It was apparent that only part of **1b** transformed into **2b** in solution. The transformation could not be made in crystalline or solid state. If the reaction was performed in dark, **2b** was not produced. If the reaction was run without heating, **2b** could not be obtained even after 10 days.

The molecular structure of **1b** was transferred to that of **2b** by rotating 180° along the bond linking the two indanone loops. However, the double bond of **1b** could not be rotated without undergoing a single bond transition state. A plausible mechanism of the transformation was shown in Scheme 2. Irradiation of **1b** resulted in the reorganization of electron distribution and generated a diradical stabilized by extended π-conjugated system. The original double bond of **1b** became somewhat single bond, and a molecule in solution could get more free space compared to that in the solid state. Thus, two indanone loops of **1b** rotated around the pseudo-single bond when enough energy was supplied upon heating, which could overturn the energy fort in the photoreaction. In addition, there was a π–π interaction between the two-phenyl groups, which could stabilize **2b** (the diplanar angle of two phenyl substituents is 10.7°; center–center distance of two phenyl substituents is 3.661 Å). **2c** and **2d** were obtained by the similar method to that of **2b**. Alkyl substituted *cis-syn* isomers were not obtained through the photochemical transformation of *trans-anti* compounds upon heating, probably ascribed to the absence of strong interaction between two alkyl substituents to stabilize the structure.




**Scheme 2.** The transformation of **1b** to its isomer **2b**.

## 2.3. Photochemical properties in single crystals

The red prism *cis-syn*-3,3′-diphenyl biindenylidenedione **2b** had no color change upon exposure to either sunlight or ultraviolet light, while the yellow plate *trans-anti*-biindenylidenedione **1b** turned to green on irradiation for a few minutes with the visible or ultraviolet light. The color change in the solid state was monitored every 5 min by UV–vis spectra (Fig. 1). After photoirradiation in the solid state, an absorption band around 500–700 nm appeared. The green photogenerated isomer was very stable at room

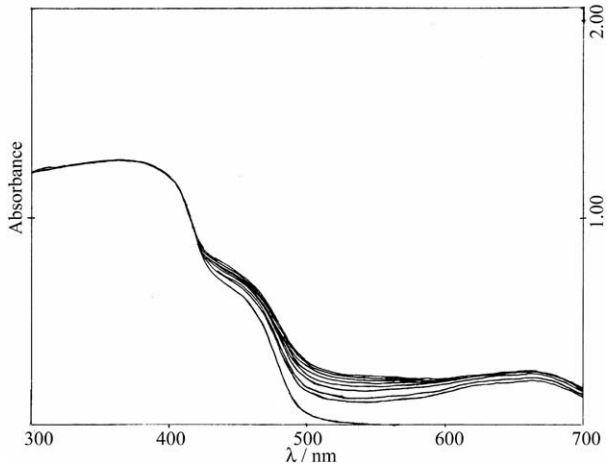



**Figure 1.** UV–vis spectral changes of **1b** in the solid state on irradiation.

temperature, and it could return to the initial yellow isomer **1b** upon heating at 117 °C or irradiation with an appropriate wavelength of light.

The electron spin resonance (ESR) measurement was carried out at room temperature. After irradiation for a period of time, the red crystal **2b** had no ESR signal, while **1b** produced distinct ESR peaks (Fig. 2).

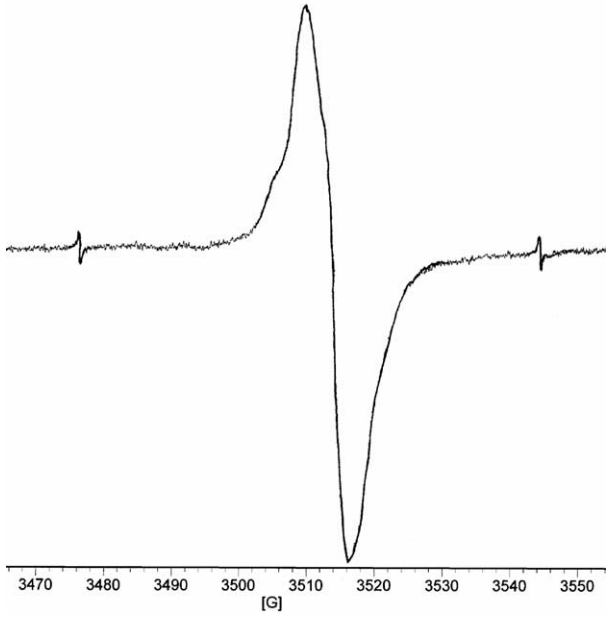



**Figure 2.** ESR spectrum of **1b** (after irradiation) in the solid state. Measurement conditions: center field, 3505.000 G; sweep width, 50.000 G; modulation frequency, 100.00 KHz; modulation amplitude, 0.20 G.

The ESR signals of the irradiated **1b** decayed with the decrease of temperature and disappeared completely on cooling to the liquid nitrogen temperature. The ESR peaks were gradually regenerated along warming to room temperature. These phenomena showed the existence of a ground-state singlet biradical. On account of the stable radical, its ESR signals could be observed at room temperature even after 3 months. Photochemical properties of compounds **1a–g**, **2b–d** were listed in Table 1.

**Table 1**. The crystal data and photochemical properties of compounds **1**, **2**

| Compound | $C_2$–$C_2$' | $\alpha$–$\beta$ (°) | $\alpha$–$\beta$ (Å) | $\gamma$–$\delta$ | Photochromism | ESR |
|---|---|---|---|---|---|---|
| **1a** | 1.353(16) | 0.0 | 0.2767 | 0.0 | Yes | Yes |
| **1b** | 1.345(6) | 0.0 | 0.3536 | 0.0 | Yes | Yes |
| **1c–g** | — | — | — | — | Yes | Yes |
| **2b** | 1.343(2) | 22.0 | — | 146.4 | No | No |
| **2c** | 1.316(11) | 26.7 | — | 32.3 | No | No |
| **$2d_1$** | 1.345(5) | 25.4 | — | 28.4 | No | No |
| **$2d_2$** | 1.336(5) | 21.0 | — | 34.4 | No | No |

## 2.4. The relationship between the crystal structure and the photochemical properties

Table 1 showed the X-ray crystallographic data of biindenylidenedione derivatives. For the compounds **1a–b**, the two indanone loops (left plane $\alpha$ and right plane $\beta$), linked by a double bond $C_2$–$C_2'$, were perfectly parallel with very short perpendicular distance (Figs. 3 and 5). The aromatic substituents were located on different sides of double bond and along *trans* direction of the indanone planes. The two carbonyl groups and the double bond were coplanar with the corresponding indanone loops, and the angle between plane $C_2C_2'O_1C_1$ (plane $\gamma$) and plane $C_2C_2'O_1'C_1'$ (plane $\delta$) was equal to 0.0°. This arrangement was beneficial to form the extended π-conjugation to the whole molecular system. The structures of **1a–b** were consistent with ones derived from the reaction mechanism proposed for the synthesis of 3,3′-dialkyl substituted biindenylidenedione derivatives.[15] **1c–g** should have the similar structures to those of **1a–b** according to that mechanism. Light irradiation of **1** at room temperature resulted in the reorganization of electron distribution to generate two unpaired radicals; the singlet biradical exhibiting ESR signals was stabilized by extended π-conjugation connected with the double bond to the whole molecular system. The crystallographic analyses of **1a–b** supported the proposed mechanism of photomagnetism.[16]

The *cis-syn*-isomers **2b–d**, which did not show photochemical properties, had two linked indanone loops too (Scheme 1, Figs. 4–8). However, the aryl (Ar) substituents

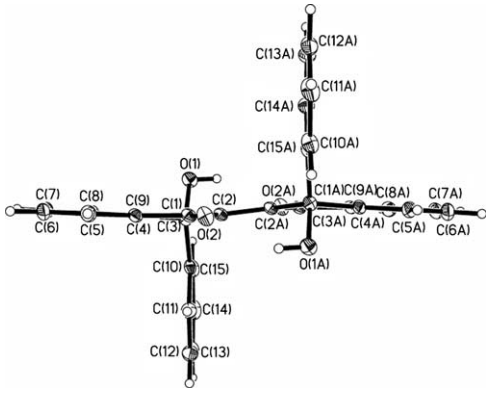



**Figure 3.** Side-elevation photo of compound **1b** molecular structure viewed along the biindenylidenedione framework.

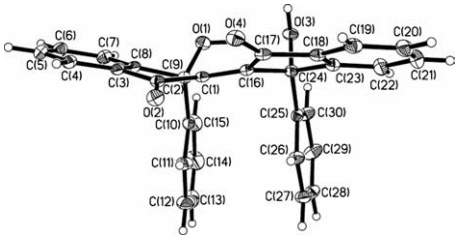



**Figure 4.** The intramolecular π–π interaction between two phenyl substituents of **2b**.

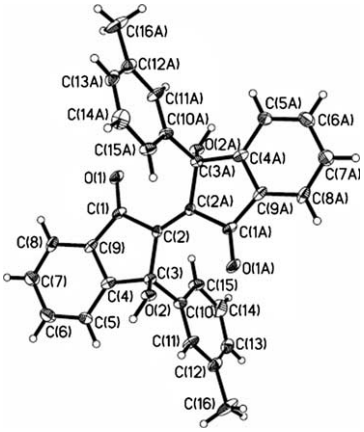



**Figure 5.** Molecular structure of **1a**.

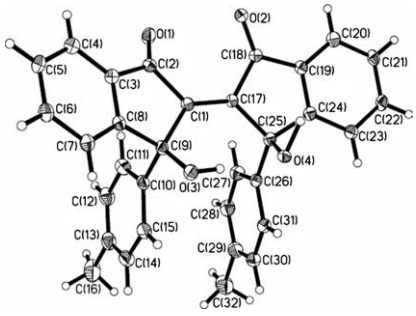



**Figure 6.** Molecular structure of isomer **2c**.

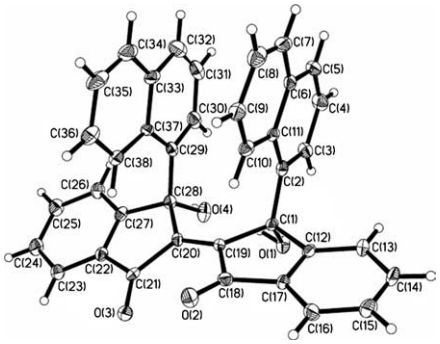



**Figure 7.** Molecular structure of **$2d_1$**.

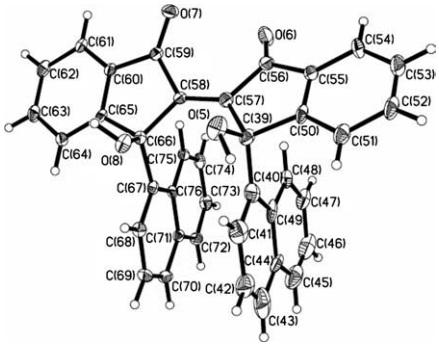



**Figure 8.** Molecular structure of isomer $\mathbf{2d_2}$.

were located on the same sides of the double bond and along *cis* direction of the indanone planes. The two aryl groups were close to form somewhat π–π interaction, so the two indanone loops were not coplanar. The angles between the indanone loops were 21.0–26.7°. The carbonyl groups were not coplanar with the indanone loops, and the angles between the two intramolecular carbonyl groups were 28.4–146.4°. The space effects of the substitutes distorted the double bonds and the main biindenylidene skeleton was not coplanar. The extended π-conjugation could not be formed and the photogenerated radical could not be stabilized, so the photochromism could not be observed. The structural data and negative photochromism of **2b**–**d** further supported the plausible mechanism of photomagnetism for *trans-anti*-3,3′-disubstituted biindenylidenedione derivatives.[16]

## 3. Conclusion

Seven *trans-anti*-3,3′-diaryl biindenylidenedione derivatives were prepared and three *cis-syn*-stereoisomers were obtained through photochemical transformation upon heating. The plausible reaction mechanism was that light irradiation resulted in the reorganization of electron distribution in the *trans-anti*-isomers to generate two unpaired radicals, and then two indanone loops could rotate upon heating to form *cis-syn*-isomers. The *trans-anti* compounds, which showed photochemical properties, had the similar structures. The Ar groups were located on different sides of the double bond and along *trans* direction of the indanone planes. The two indanone loops, linked by a double bond $C_2$–$C_2'$, were perfectly parallel. This family of *trans-anti* compounds could undergo photochromism as well as the generation of stable radicals in the single crystalline state. On the contrary, the *cis-syn* isomers did not show photochemical properties. The Ar groups were located on the same sides of the double bond and along *cis* direction of the indanone planes, and the two indanone loops were not parallel.

## 4. Experimental

### 4.1. Materials and apparatus

All chemicals were purchased from commercial sources, and solvents were dried by refluxing under $N_2$ over an appropriate drying agent and distilled prior to use. $^1$H NMR spectra were recorded at 200 MHz on a Bruker-P200 instrument using tetramethylsilane as an internal reference. Elemental analysis was performed on a YANACO CHN CORDER MT-3 apparatus. Ultraviolet–visible spectra were recorded on TU-1901 UV–vis spectrophotometer. ESR measurement was carried out on a Bruker EMX-6/1 EPR spectrometer. X-ray crystallographic analysis was performed on a Bruker SMART 1000 diffractometer.

### 4.2. General procedure for the synthesis of 1a–g, 2b–d

To a three-necked 250-mL round-bottomed flask containing a stirrer bar, fitted with a pressure-equalizing dropping funnel and a reflux condenser, was added Mg (1.2 g, 0.050 mol), anhydrous ether (10 mL), and trace amount of $I_2$ crystal under $N_2$ atmosphere. To this suspension was added the solution of aryl bromide (0.055 mol) in anhydrous ether (40 mL) from the pressure-equalizing funnel at such a rate as to create a gentle reflux. The resulting mixture was stirred under reflux for additional 1 h. The pressure-equalizing funnel was recharged with 2,2′-biindanylidene-1,1′,3,3′-tetraone (2.88 g, 0.010 mol) suspended in dry benzene (30 mL). The suspension was added portion-wise over a period of 20 min. The dark green reaction mixture was stirred at room temperature under a nitrogen atmosphere for 12–15 h, and then exposed to the air for another 4–5 h. Finally, quenching the reaction with an excess amount of saturated $NH_4Cl$ aqueous solution gave two immiscible liquid phases. The crude desired compounds **1a**–**g**, [2,2′-bi-1*H*-indene]-3,3′-diaryl-3,3′-dihydroxyl-1,1′-diones, precipitated as insoluble yellow powder between the organic and aqueous phases. Filtration afforded crude products, which were purified by column chromatography on silica gel. Compounds **1a**,**b** were crystallized from dichloromethane at room temperature to produce the crystals suitable for X-ray crystallographic analysis.

The saturated solution of **1b**–**d** (0.2 mmol) in toluene (10 mL) was refluxed for 10 h on irradiation with a 400 W high-pressure mercury lamp. The crystals of **2b**–**d** were precipitated out slowly from the solutions.

**4.2.1. *trans-anti*-3,3′-Di-*m*-tolyl-3,3′-dihydroxyl-[2,2′-bi-1*H*-indene]-1,1′-dione (1a).** Yellow prism (40.2%), mp 317–319 °C. $^1$H NMR (200 MHz, $CDCl_3$): δ: 7.55–6.84 (m, 16H, Ar), 6.78 (s, 2H, OH), 2.12 (s, 6H, $CH_3$). IR (KBr): ν 3428, 1677 cm$^{-1}$. Ms (ESI): *m*/*z* 472.15 ($M^+$). Anal. Calcd for $C_{32}H_{24}O_4$: C 81.34, H 5.12. Found: C 81.01, H 5.57.

**4.2.2. *trans-anti*-3,3′-Diphenyl-3,3′dihydroxyl-[2,2′-bi-1*H*-indene]-1,1′-dione (1b).** Yellow plate (31.5%), mp 290–292 °C. $^1$H NMR (200 MHz, $CDCl_3$): δ: 7.71–7.51 (m, 8H, Ar), 7.27–7.17 (m, 10H, Ar), 6.95 (s, 2H, OH). IR (KBr): ν 3331, 1680 cm$^{-1}$. Ms (ESI): *m*/*z* 444.46 ($M^+$). Anal. Calcd for $C_{30}H_{20}O_4$: C 81.07, H 4.54. Found: C 80.79, H 4.79.

**4.2.3. 3,3′-Di-*p*-tolyl-3,3′-dihydroxyl-[2,2′-bi-1*H*-indene]-1,1′-dione (1c).** Yellow powder (31.7%), mp 318–320 °C. $^1$H NMR (200 MHz, $CDCl_3$): δ: 7.70–7.03 (m, 16H, Ar), 6.91 (s, 2H, OH), 2.24 (s, 6H, $CH_3$). IR (KBr): ν 3430, 1678 cm$^{-1}$. Ms (ESI): *m*/*z* 472.59 ($M^+$). Anal.

Calcd for $C_{32}H_{24}O_4$: C 81.34, H 5.12. Found: C 80.94, H 5.32.

**4.2.4. 3,3′-Dinaphthy-3,3′-dihydroxyl-[2,2′-bi-1*H*-indene]-1,1′-dione (1d).** Yellow powder (51.4%), mp 300–302 °C. $^1$H NMR (200 MHz, DMSO) $\delta$: 7.97–7.01 (m, 22H, Ar), 6.48 (s, 2H, OH). IR (KBr) $\nu$: 3415, 1675 cm$^{-1}$. Ms (ESI): *m*/*z* 544 ($M^+$). Anal. Calcd for $C_{38}H_{24}O_4$: C 83.81, H 4.44. Found: C 83.36, H 4.77.

**4.2.5. 3,3′-Di-benzyl-3,3′-dihydroxyl-[2,2′-bi-1*H*-indene]-1,1′-dione (1e).** Yellow powder (19.1%), mp 223–225 °C. $^1$H NMR (200 MHz, $CDCl_3$) $\delta$: 7.63–7.08 (m, 8H, Ar), 6.88–6.44 (m, 10H, Ar), 6.40 (s, 2H, OH), 3.26 (s, 4H, $CH_2$). IR (KBr) $\nu$: 3423, 1660 cm$^{-1}$. Ms (ESI): *m*/*z* 472.34 ($M^+$). Anal. Calcd for $C_{32}H_{24}O_4$: C 81.34, H 5.12. Found: C 81.04, H 5.33.

**4.2.6. 3,3′-Di-*p*-chlorphthy-3,3′-dihydroxyl-l [2,2′-bi-1*H*-indene]-1,1′-dione (1f).** Yellow powder (38.8%), mp 315–317 °C, $^1$H NMR (200 MHz, $CDCl_3$) $\delta$: 7.57–7.04 (m, 16H, Ar), 6.70 (s, 2H, OH). IR (KBr) $\nu$: 3330, 1680 cm$^{-1}$. Ms (ESI): *m*/*z* 513.06 ($M^+$). Anal. Calcd for $C_{30}H_{18}Cl_2O_4$: C 70.19, H 3.53. Found: C 70.57, H 3.12.

**4.2.7. 3,3′-Di-*o*-tolyl-3,3′-dihydroxyl-[2,2′-bi-1*H*-indene]-1,1′-dione (1g).** Yellow powder (36.0%), mp 310–312 °C. $^1$HNMR (200 MHz, $CDCl_3$) $\delta$: 7.51–6.77 (m, 16H, Ar), 6.37 (s, 2H, OH), 1.72 (s, 6H, $CH_3$). IR (KBr) $\nu$: 3439, 1677 cm$^{-1}$. Ms (ESI) (*m*/*z*): 472.12 ($M^+$). Anal. Calcd for $C_{32}H_{24}O_4$: C 81.34, H 5.12. Found: C 80.85, H 5.43.

**4.2.8. *cis-syn*-3,3′-Diphenyl-3,3′-dihydroxyl-[2,2′-bi-1*H*-indene]-1,1′-dione (2b).** Yellow prism, mp 300–302 °C. $^1$H NMR (200 MHz, $CDCl_3$) $\delta$: 7.66–7.10 (m, 18H, Ar), 6.55 (s, 2H, OH). IR (KBr) $\nu$: 3334, 1700, 1680 cm$^{-1}$. Ms (ESI): *m*/*z* 444.46 ($M^+$). Anal. Calcd for $C_{30}H_{20}O_4$: C 81.07, H 4.54. Found: C 81.21, H 4.68.

**4.2.9. *cis-syn*-3,3′-Di-*p*-tolyl-3,3′-dihydroxyl-[2,2′-bi-1*H*-indene]-1,1′-dione (2c).** Yellow prism, mp 319–320 °C. $^1$H NMR (200 MHz, $CDCl_3$) $\delta$: 7.81–7.14 (m, 16H, Ar), 6.63 (s, 2H, OH), 2.24 (s, 6H, $CH_3$). IR (KBr) $\nu$: 3431, 1710, 1680 cm$^{-1}$. Ms (ESI): *m*/*z* 471.35 ($M^+-1$). Anal. Calcd for $C_{32}H_{24}O_4$: C 81.34, H 5.12. Found: C 80.94, H 5.32.

**4.2.10. *cis-syn*-3,3′-Dinaphthy-3,3′-dihydroxyl-[2,2′-bi-1*H*-indene]-1,1′-dione (2d).** Yellow prism, mp 311–312 °C, $^1$H NMR (200 MHz, DMSO) $\delta$: 8.01–7.15 (m, 22H, Ar), 6.22 (s, 2H, OH). IR (KBr) $\nu$: 3416, 1705, 1685 cm$^{-1}$. Ms (ESI): *m*/*z* 544 ($M^+$). Anal. Calcd for $C_{38}H_{24}O_4$: C 83.81, H 4.44. Found: C 83.36, H 4.71.

Crystal structure data are filed with the Cambridge Crystallographic Data Centre, CCDC Nos. (CCDC 260383–260387).

## Acknowledgements

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# Utilization of 2-ethoxymethylene-3-oxobutanenitrile in the synthesis of heterocycles possessing biological activity

Petra Černuchová,[a,b] Giang Vo-Thanh,[b] Viktor Milata,[a,*] André Loupy,[b,*] Soňa Jantová[c] and Marica Theiszová[c]

[a]*Department of Organic Chemistry, Faculty of Chemical and Food Technology, Slovak Technical University, Radlinského 9, SK-812 37 Bratislava, Slovak Republic*
[b]*Laboratory of Selective Reactions on Supports, ICMMO, CNRS UMR 8615, Building 410, Paris-South University, 914 05 Orsay-Cedex, France*
[c]*Department of Biochemistry and Microbiology, Faculty of Chemical and Food Technology, Slovak Technical University, Radlinského 9, SK-812 37 Bratislava, Slovak Republic*

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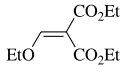
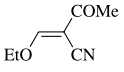
**Abstract**—2-Ethoxymethylene-3-oxobutanenitrile is a versatile trifunctional reagent that allows the introduction of a three-carbon moiety to amine-substrates. The reaction of the title compound with hydrazines has been studied leading to appropriate substituted pyrazoles **4**–**11**. Reactions with other dinitrogen nucleophiles were studied giving access to a set of fused pyrimidines **13**. All types of compounds displayed biological activity against bacteria, filamentous fungi and tumour HeLa cells, but not for yeasts. Pyrazole **10** and pyrimidine **13d** have been found to possess the broadest activity.


## 1. Introduction

Pyrazoles,[1–3] pyrimidines[4–7] and [1,2,4]triazolo[1,5-*a*]pyrimidines[8] have been the subject of chemical and biological studies due to their interesting pharmacology including antipyretic,[9,10] analgesic,[11] antiinflammatory,[12] potential herbicidal,[13] fungicidal[14,15] and leishmanicidal[16,17] properties. Diethyl ethoxymethylenemalonate (EMME) is an attractive building block for the synthesis of biologically relevant heterocyclic or carbocyclic compounds.[18–20] Pyrazolones can be efficiently prepared by reaction of EMME with aryl and benzylhydrazines.[21] Pyrimidines and triazines could be easily accessed by reaction of EMME with aliphatic or aromatic amidines.[22] Stimulated by these findings, we report here on the application of (*E*)-2-ethoxymethylene-3-oxobutanenitrile **1**, a synthetic equivalent of EMME, where the two ester groups were replaced by ketone and nitrile moieties. The *E* geometry of **1** was confirmed by NMR studies. Full characterization of $^{1}H$–$^{13}C$ shifts as well as $^{1}H$–$^{13}C$ coupling constant was recently reported by our laboratory.[23]



**EMME**

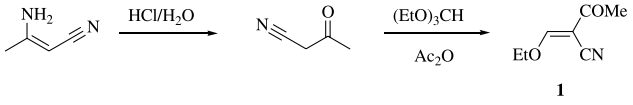


**1**

## 2. Results and discussion

### 2.1. Chemistry

The preparation of 2-ethoxymethylene-3-oxobutanenitrile **1** was described earlier by our laboratory.[18a,19a] In situ prepared 3-oxobutanenitrile reacted with 3 equiv of triethyl orthoformate and a catalytic amount of acetic anhydride to give **1** in good yields (Scheme 1).



**1**

**Scheme 1.**

### 2.2. Reaction of 1 with hydrazines

Reaction of **1** with various hydrazines can give at least four different types of pyrazoles, depending on:

*Keywords*: Pyrazoles; Pyrimidines; Biological activity; Aminobenzothiazole; Aminobenzimidazole.
* Corresponding authors. Tel.: +33 1 69 15 7650; fax: +33 1 69 15 4679; e-mail addresses: viktor.milata@stuba.sk; aloupy@icmo.u-psud.fr

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(i) which one of the nitrogens of hydrazine is implied in the addition–elimination reaction (way a or b).
(ii) which one of the withdrawing groups (CN or COMe) reacts during the subsequent intramolecular cyclization when R′=H (way c or d) (Scheme 2).[24]

The main results obtained by reacting **1** with various substituted hydrazines are given in Table 1 (Scheme 3).

Reactions of **1** with hydrazines under solvent-free conditions were conducted at room temperature for 10 min. On the other hand, when the starting hydrazines were used as their hydrochlorides, the reactions were carried out in refluxing ethanol in the presence of triethylamine. We thus obtained pyrazoles in all cases (**4**–**11**) except for the reaction of disubstituted hydrazines which led to non-cyclized products **2** and **3** resulting from attack via pathway a.

In the case of the reaction with methylhydrazine, all the four possible pyrazoles **5**–**8** were obtained. They were separated by column chromatography, except the compound **6** which could not be isolated as a pure substance. The ratio **5**:**6**= 73:27 was evaluated by GC-MS and confirmed by $^1$H NMR analysis of the crude reaction mixture. Traces of **7** and **8** were successfully isolated and their structures were attributed by NMR spectra.

In all other cases, only products, resulting from addition–elimination of the primary amino group of hydrazine on **1** (pathway a, Scheme 2), have been detected. Distinction of the reacting group (pathway c or d, Scheme 2) was based on the $^{13}$C NMR spectra and IR analysis, where the presence or the absence of the signal for cyano or acetyl groups could be detected. The structural distinction between 4,5- and 3,4-disubstituted pyrazoles **5**–**8** is based on the variation in chemical shifts $\Delta\delta$ ($^1$H NMR) between solvents of different polarity ($CDCl_3$ and DMSO-$d_6$). As already reported in the literature,[25–27] this variation for the ring proton H5 of pyrazole ($\Delta\delta$=1.03 ppm) is clearly more important than for H3 ($\Delta\delta$=0.32 ppm). On the other hand, careful recrystallisation of pyrazole **5** allowed its analysis by X-ray diffraction, confirming our previous structural assignments (Fig. 1).

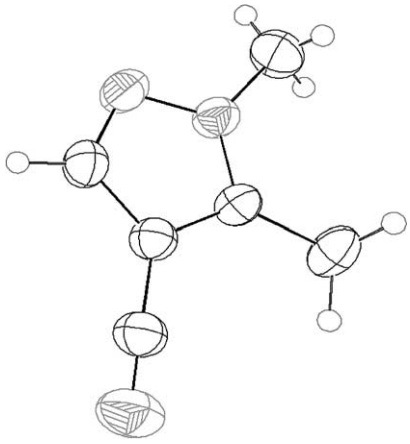
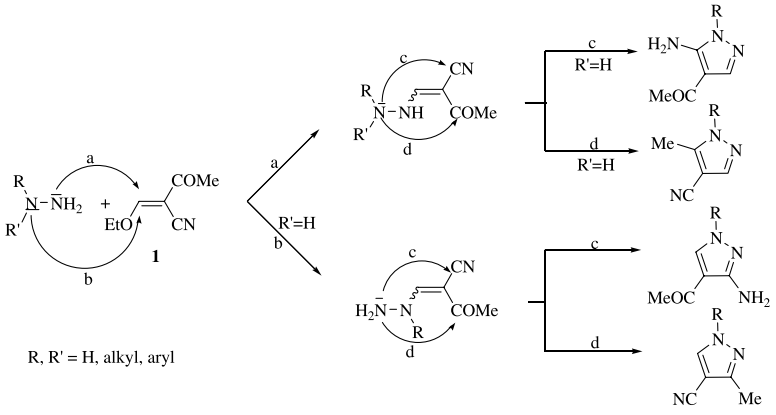


**Figure 1.** X-ray diagram of compound **5**.

The intermediates resulting from the addition–elimination reaction (pathway a) were isolated only in the case of pentafluorophenylhydrazine. After 15 min in refluxing ethanol, the two isomeric enhydrazines **11a** (*Z* and *E*) were observed in a 64:36 ratio as precipitates in the reaction

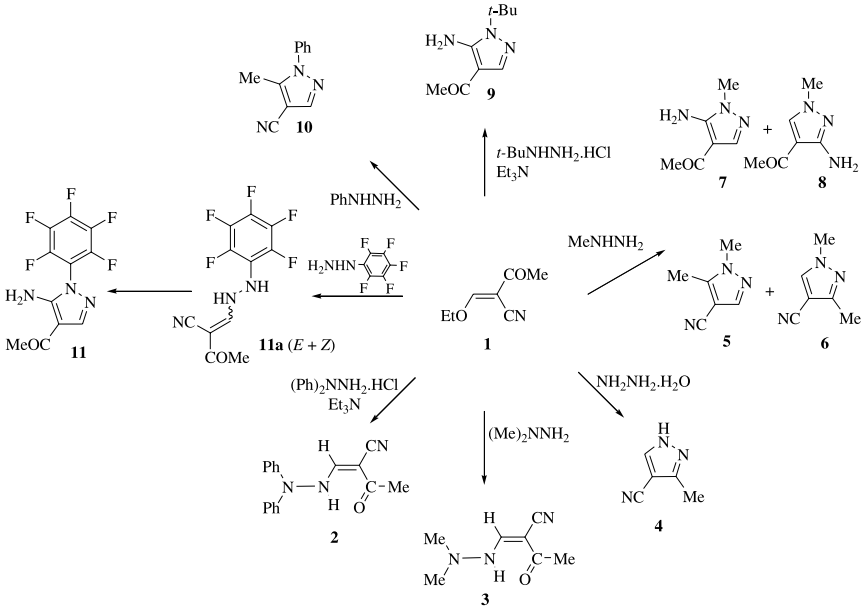



**Scheme 2.**

**Table 1**. Reaction of **1** with hydrazines

| R | R′ | Conditions | Temperature (°C) | Time (min) | Products (yields%)[a] |
|---|---|---|---|---|---|
| Ph | Ph | HCl, $Et_3N$/EtOH | 78 | 25 | **2** (80) |
| Me | Me | Solvent-free | 25 | 10 | **3** (84) |
| H | H | Solvent-free | 25 | 10 | **4** (84) |
| Me | H | Solvent-free | 25 | 10 | **5** (52), **6** (32)[b], **7** (2), **8** (4) |
| *t*-Bu | H | HCl, $Et_3N$/EtOH | 78 | 25 | **9** (61) |
| Ph | H | Solvent-free | 25 | 10 | **10** (83) |
| $C_6F_5$ | H | EtOH | 78 | 240 | **11** (79) |

[a] Yields in isolated products.
[b] Yields determined by GC and $^1$H NMR of the crude reaction mixture.



**Scheme 3.**

mixture. Two pairs of NH-proton signals confirmed the fact that the primary amino group is the most reactive (Scheme 2, pathway a) (major isomer: 9.03, 8.14, 8.01, 2.21 ppm; minor isomer: 10.81, 10.38, 8.88, 2.31 ppm). By extending the reaction time up to 4 h, the cyclic product **11** was obtained in satisfactory yield (79%).

On the other hand, when reactions were carried out between *N*,*N*-disubstituted hydrazines and **1**, only enhydrazines **2** and **3** with the *Z* geometry were obtained. The stereochemistry of the double bond is presumably due to the formation of a hydrogen bond between the NH group and the carbonyl function which stabilizes for *Z* conformation. This was in fact confirmed by NMR analysis. The presence of a doublet with a coupling constant about 11 Hz indicates the antiperiplanar position between H of the amino group and ethylenic H. The $^{3}J$ coupling constant about 5.2 Hz, measured by $^{13}C$ NOE NMR clearly shows, on the other hand, the *Z* geometry of the ethylenic H and the cyano group. Moreover, the stereochemistry in the mechanism of nucleophilic vinylic substitution was confirmed by quantum chemical calculations.[28]

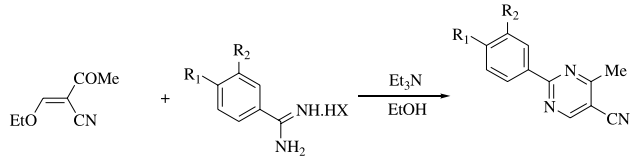
### 2.3. Reaction of 1 with amidines

We also wish to report a simple method for preparing a set of 2-aryl-5-cyano-4-methylpyrimidines, by reacting a series of arylamidines **12a–d** with **1** (Scheme 4).

It is worth noting that this reaction was quite sensitive to the stochiometry of the substrates. An excess of arylamidine hydrochloride (2 equiv) and triethylamine (4 equiv) was necessary to ensure that the pyrimidines **13a–d** were obtained in good yields (Table 2).

### 2.4. Reaction of 1 with aminotriazoles

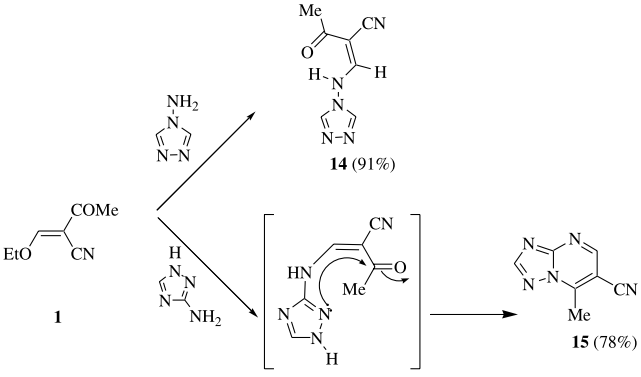
The reaction of **1** with 3-amino-1,2,4-triazole in boiling



a) $R_1 = R_2 = H$, X = Cl
b) $R_1$ = Cl, $R_2$ = H, X = I
c) $R_1$ = Me, $R_2$ = H, X = Cl
d) $R_1$ = H, $R_2 = NO_2$, X = Cl

**Scheme 4.**

toluene gave the bicyclic triazolo-pyrimidine **15** in 78% yield. On the other side, the cyclization in the case of 4-amino-1,2,4-triazole did not occur and only the product of addition–elimination reaction **14** was isolated in 91% yield. This behaviour is due to the absence of a nitrogen atom in position 3 on the triazole ring which is necessary for cyclization (Scheme 5).



**Scheme 5.**

**Table 2**. Influence of the relative amount of the substrates during the reaction of **1** with **12a–d**

| Compound **13** | Yield **13** (%)[a] Ratio **1**: **12**: $Et_3N$ | |
|---|---|---|
| | 1:1:2 | 1:2:4 |
| **a** | 56 | 72 (67) |
| **b** | 52 | 66 (60) |
| **c** | 50 | 76 (70) |
| **d** | 65 | 98 (92) |

[a] Yields in crude product, isolated yields are given in brackets.

### 2.5. Reaction of 1 with heteroarylamines

Finally, the reactivity of **1** was studied in the addition–elimination reaction with aminopyridine derivatives, aniline, aminobenzothiazole and aminobenzimidazole (Scheme 6). In the case of 2-aminobenzimidazole (two hydrogen atoms are present on the amino group and one on the cycle), condensed pyrimidines **20** were obtained. If only two hydrogen atoms are present on amino group, the cyclization producing fused product did not occur and only addition–elimination products **16a–d** and **19** were isolated. Satisfactory yields (81–88%) were obtained within a very short reaction time (2–10 min) at 70–80 °C.

Aniline produced the corresponding anilinomethylene derivative **17** which could be cyclized using aluminum chloride to 1-(4-aminoquinolin-3-yl)-ethanone **18**.

## 3. Biological activity

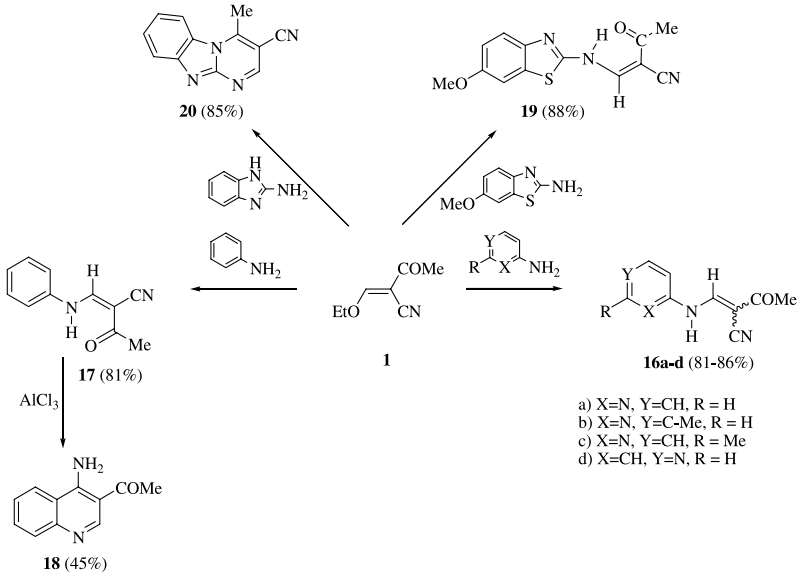
### 3.1. Materials and methods

*Materials*. Bacterial strains *Escherichia coli* CCM 3988, *Pseudomonas aeruginosa* CCM 3955, *Bacillus subtilis* CCM 1718, *Staphylococcus aureus* CCM 3953, the yeasts *Candida albicans* 1696, *Candida parapsilosis* and the filamentous fungi *Rhizopus oryzae*, *Mucor* sp., *Aspergillus niger* CCM F-237 (obtained from the collection of microorganisms available in the department of Biochemistry and Microbiology, Slovak University of Technology) were used. The cytotoxic activity of the prepared derivatives was studied on the transformed tumor cell line HeLa. The compounds were used at concentrations of 150, 100, 50, 10, 1 and 0.1 mg/L. Chromatographically pure derivatives were dissolved in DMSO whose final concentration never exceeded 1% (v/v) in either control or treated samples.

*Antibacterial assay*. The antibacterial effect has been assayed by a microdilution method in 96-well microtitration plates.[29] The bacteria were cultivated on Müller–Hinton medium at 30 °C. An overnight inoculum was prepared 12–16 h before the test. The growing inoculum was filtered and a 1.5% suspension of bacteria was prepared for the experiments. This suspension (180 μL) was added to 20 μL of the tested complex solution and cultured for 6 h on a reciprocal shaker in a thermostat at 30 °C. The time course of absorbance ($A_{630}$) has been then determined in three parallel runs. To compare the antimicrobial activity, ampicillin at concentrations of 100, 50, 10, 1, and 0.1 mg/L and amphothericine at concentrations of 250, 150, 100, 50, 10, 1 and 0.1 mg/L have been used as standard.

*Effects on yeasts*. The yeasts have been cultivated on Sabourand-glucose medium at 28 °C.[30] 7 mL of culture medium have been inoculated with 0.5 mL of culture growing overnight and 75 μL solution of the tested compounds. The cultures of yeasts were then cultured for 6 h on a reciprocal shaker in a thermostat at 28 °C. The $A_{650}$ of triplicate sets of tubes were measured at 2 h intervals.

*Antifungal assay*. The effect on filamentous fungi was tested during static culturing. 0.05 mL DMSO solution of the tested compounds has been added into petri dishes (diameter 50 mm) immediately before pouring 5 mL of Sabourand-glucose agar to obtain desired concentrations of inhibitors. The solidified plates were then inoculated in the center with 5 μL of the spore suspension. Triplicate sets of agar plates




**Scheme 6.**

were incubated at 25 °C and the diameter of growing colonies was measured at intervals.

The antimicrobial effect was determined by $IC_{50}$ values, i.e. the minimal concentration of a substance which inhibits bacterial, yeast and fungal growth by 50% relative to the control, and MIC values, i.e. the minimal concentration of a substance which totally inhibits the bacterial, yeast and fungal growth. The $IC_{50}$ and MIC values have been determined from toxicity curves.

*Cytotoxic assay*. A three-day culture of HeLa cells has been trypsinized and than used to prepare a suspension with concentration $5.0\times10^4$ cells/200 μL. The experiments have been carried out in 96-well plates into which 200 μL/well of the above-mentioned suspension were pipetted. After 24 h of static culturing at 37 °C, the culture medium has been emptied and then was added 200 μL of medium containing the appropriate concentration of test derivatives. After 48 h, the intensity of growth of the HeLa cells has been evaluated using the Kenacid blue assay[31] determination of the total cell protein content. The cytotoxic activity of the tested derivatives was determined from the inhibitory concentrations $IC_{50}$ and $IC_{100}$ (i.e., such concentration of a derivative which, in comparison to the control, inhibited the contents of total cell proteins by 50 or 100%, respectively) which were read from the toxicity curves.

## 4. Results and discussion

The biological activities of the tested derivatives against selected organisms ($IC_{50}$ and MIC) are summarized in Table 3.

The widest antimicrobial activity has been manifested by the derivative **13d**, which was effective against bacteria *Bacillus subtilis*, *Staphylococcus aureus* and with filamentous fungi *Aspergillus niger* ($IC_{50}=150$ mg/L for *B. subtilis* and *S. aureus* and $IC_{50}=50$ mg/L for *A. niger*). The broadest antibacterial effect was found with derivatives **13b** and **16c**, which was effective against $G^+$ and $G^-$ bacteria ($IC_{50}=150$ mg/L for *B. subtilis* and *S. aureus* and $IC_{50}=100$ mg/L or 150 mg/L for *E. coli*). The derivative **13d** influenced $G^+$ *Bacillus subtilis* and *Staphylococcus aureus* ($IC_{50}=150$ mg/L). A certain antibacterial effect on $G^+$ was demonstrated for derivatives **10**, **3** and **9**, which were effective against bacteria *Bacillus subtilis* ($IC_{50}=$ 150 mg/L). The sensitivity of $G^+$ bacteria to the derivatives was higher than that of $G^-$ bacteria. None of the derivatives influenced the $G^-$ *Pseudomonas aeruginosa* and the tested yeasts. Most effective against filamentous fungi were derivatives **19**, **13d**, **10** and **2**, as $IC_{50}$ values have been lower than for amphotericin.

The cytotoxic activities of the tested derivatives were studied on human tumour cell line HeLa. The compound **13d** ($IC_{50}=11.9$ mg/L) has manifested the highest activity. A certain effect was demonstrated by derivatives **13a**, **19**, **13b**, **10** and **9**, their values were $IC_{100}\leq100$ mg/L. The other tested molecules were inactive.

There is no clear relation between structure and biological activity of the studied compounds. Represented were almost all of pyrimidines (**3** from **4** synthesized), two pyrazoles and four enaminonitriles, one of them possessing 2-aminobenzothiazole moiety. The most potent compounds against bacteria, filamentous fungi and HeLa cells are **13d**—containing two potentially biologically active sub-units: a nitro group in position 3 on the phenyl ring and pyrimidine one, and the second, **10** bears a pyrazole ring, which could explain the results we obtained.

## 5. Conclusion

2-Ethoxymethylene-3-oxobutanenitrile **1** represents a very versatile and reactive group of enol ethers which can be widely used in the synthesis of heterocycles. Its reaction with hydrazines or amidines led to new pyrazolic or pyrimidinic compounds. Reactions with other dinitrogen nucleophiles gave access to fused pyrimidines. All these products as well as some intermediates have been tested for biological activities against bacteria, filamentous fungi, yeasts and tumor HeLa cells. Compounds **10** and **13d** displayed the broadest biological activity, **2** and **10** are the more active against fungi in some cases like standard Amphotericin used.

## 6. Experimental

Melting points were measured with a Kofler bank. NMR spectra were recorded in $CDCl_3$ or DMSO-$d_6$. $^1H$ NMR spectra were recorded at 200, 250 or 300 MHz. Chemical shifts ($\delta$) are reported in ppm relative to TMS as internal standard. $J$ values are given in Hz. $^{13}C$ NMR spectra were

**Table 3**. Biological activity of the tested derivatives ($IC_{50}$, mg/l)[a]

| Compound | *B. subtilis* | *S. aureus* | *E. coli* | *P. aeruginosa* | *Rhizopus oryzae* | *Mucor* sp. | *Aspergillus niger* | *HeLa* |
|---|---|---|---|---|---|---|---|---|
| **2** | 150 | 150 | 150 | >150 | >100 | 24.8 | >100 | >100 |
| **3** | >150 | >150 | >150 | >150 | 100 | 100 | >100 | 100 |
| **9** | >150 | >150 | >150 | >150 | >100 | >100 | >100 | 100 |
| **10** | 150 | 150 | >150 | >150 | >100 | >100 | 50 | 100 |
| **13a** | 150 | 150 | 100 | >150 | >100 | >100 | >100 | 65.1 |
| **13b** | 150 | >150 | >150 | >150 | 84 | 150 | >100 | 100 |
| **13d** | >150 | >150 | >150 | >150 | >100 | 24.8 | >100 | 11.9 |
| **16c** | 150 | >150 | >150 | >150 | >100 | >100 | >100 | >100 |
| **19** | 150 | >150 | >150 | >150 | >100 | >100 | >100 | 100 |
| Ampicillin | 0.7 | 0.015 | 0.28 | >100 | — | — | — | — |
| Amphotericin | — | — | — | — | 182.9 | 250 | 152.5 | — |

[a] The values $IC_{50}$ of other derivatives tested were higher than 150 mg/L. All derivatives were inactive on the yeasts *Candida albicans* and *Candida parapsilosis*.

recorded at 75, 62.5 or 50 MHz, respectively. IR spectra were registered on a FT-IR Perkin–Elmer instrument. X-ray data recordings at room temperature were obtained with a Bruker-AXS X8-Apex2 area detector diffractometer using graphite-monochromated Mo Kα radiation (0.71073 Å). Crystallographic data for the structure reported have been deposited in the Cambridge Crystallographic Data Center (CCDC 252735).[33] TLC was carried out with 0.2 mm thick silica gel plates ($GF_{254}$). Visualisation was accomplished by UV light or phosphomolybdic acid solution or $KMnO_4$ stain. The columns were hand packed with silica gel 60 (200–300 mesh).

All reagents and solvents were purchased from commercial sources (Acros or Aldrich) and were used without any further purification.

### 6.1. General procedure for the reaction of 1 with hydrazines

*Method A* (*compounds* **3**–**8**, **10**). Hydrazine derivative (10 mmol) was added to compound **1** (1.39 g, 10 mmol) and the mixture was stirred at room temperature for 10 min. After evaporation of EtOH formed during the reaction, the residue was purified by flash chromatography or recrystallized.

*Method B* (*compounds* **2**, **9**). A solution of **1** (1 g, 7.19 mmol), hydrazine hydrochloride (7.19 mmol) and triethylamine (1.1 mL, 0.8 g, 7.91 mmol, 1.1 equiv) in ethanol (15 mL) was refluxed for 25 min. The solvent was evaporated, water (15 mL) was added and the resulting precipitate was filtered. The crude product was purified by recrystallization.

*Method C* (*compound* **11**). A solution of **1** (1 g, 7.19 mmol) and pentafluorophenylhydrazine (1.4 g, 7.19 mmol) in ethanol (15 mL) was refluxed for 4 h. The reaction mixture was cooled to room temperature. Solvent was evaporated and the residue was recrystallized from toluene to give **11**.

**6.1.1. (*Z*)-2-*N*,*N*-diphenylhydrazinomethylene -3-oxobutanenitrile 2.** Purification by recrystallization (EtOH/$H_2O$=9/1) gave **2** (1.59 g, 80%) as pale green crystals. Mp 138–139 °C. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 2.32 (s, 3H), 7.02–7.36 (m, 10H), 7.58 (d, $J$=11 Hz, 1H), 11.77 (d, $J$=11 Hz, 1H), $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 27.9, 83.4, 118.9, 120.2, 124.8, 129.6, 145.8, 159.2, 196.3; IR (cm$^{-1}$): $\tilde{\nu}$ = 3181, 3040, 2206, 1646, 1600; Anal. Calcd. for $C_{17}H_{15}N_3O$: C, 73.63; H, 5.45; N, 15.15; Found C, 73.51; H, 5.43; N, 15.02.

**6.1.2. (*Z*)-2-*N*,*N*-dimethylhydrazinomethylene-3-oxobutanenitrile 3.** Purification by recrystallization (hexane/AcOEt=9/1) gave **3** (1.29 g, 84%) as dull crystals. Mp 115 °C. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 2.26 (s, 3H), 2.59 (s, 6H), 7.53 (d, $J$=11 Hz, 1H), 10.73 (d, $J$=11 Hz, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 28.0, 48.7, 80.5, 120.0, 157.5, 196.6; IR (cm$^{-1}$): $\tilde{\nu}$ = 3196, 2963, 2878, 2203, 1651, 1599; Anal. Calcd. for $C_7H_{11}N_3O$: C, 54.89; H, 7.24; N, 27.43. Found C, 54.65; H, 7.21; N, 27.66.

**6.1.3. 3-Methyl-1*H*-pyrazole-4-carbonitrile 4.** Purification by recrystallization (toluene) gave **4** (0.9 g, 84%) as yellowish crystals. Mp 141–142 °C (lit.[32]: 142 °C). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 2.50 (s, 3H), 7.86 (s, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 11.0, 91.9, 113.7, 139.4, 148.4; IR (cm$^{-1}$): $\tilde{\nu}$ = 3197, 3163, 3119, 3059, 2878, 2235, 1597, 1570, 1519, 1445; Anal. Calcd. for $C_5H_5N_3$: C, 56.07; H, 4.71; N, 39.23; Found C, 55.57; H, 4.76; N, 39.42.

**6.1.4. 1,5-Dimethyl-1*H*-pyrazole-4-carbonitrile 5.** Purification by flash chromatography (hexane/AcOEt=9/1) gave **5** (0.63 g, 52%) as colorless crystals. Mp 80 °C. $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 2.36 (s, 3H), 3.76 (s, 3H), 7.58 (s, 1H); $^1$H NMR (200 MHz, DMSO-$d_6$) $\delta$ 2.38 (s, 3H), 3.78 (s, 3H), 7.89 (s, 1H); $\Delta\delta$ (DMSO-$d_6$ $CDCl_3$)=0.31 ppm; $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$ 10.3, 36.8, 91.8, 114.0, 140.6, 144.9; IR (cm$^{-1}$): $\tilde{\nu}$ = 3117, 2952, 2228, 1549, 1505, 1451; Anal. Calcd. for $C_6H_7N_3$: C, 59.49; H, 5.82; N, 34.69; Found C, 59.29; H, 5.86; N, 34.53.

**6.1.5. 1-(5-Amino-1-methyl-1*H*-pyrazol-4-yl)-ethanone 7.** Purification by flash chromatography (AcOEt) gave **7** (30 mg, 2%) as colorless crystals. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 2.34 (s, 3H), 3.61 (s, 3H), 5. 57 (s, 1H), 7.59 (s, 1H); $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 2.20 (s, 3H), 3.50 (s, 3H), 6.63 (s, 1H), 7.65 (s, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 27.0, 33.7, 106.3, 139.4, 149.0, 192.7.

**6.1.6. 1-(3-Amino-1-methyl-1*H*-pyrazol-4-yl)-ethanone 8.** Purification by flash chromatography (AcOEt) gave **8** (60 mg, 4%) as colorless crystals, $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 2.33 (s, 3H), 3.73 (s, 3H), 5.10 (s, 1H), 7.54 (s, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 27.4, 39.0, 108.7, 133.0, 156.5, 192.4.

**6.1.7. 1-(5-Amino-1-*tert*-butyl-1*H*-pyrazol-4-yl)-ethanone 9.** Purification by recrystallization (water) gave **9** (0.8 g, 61%) as colorless crystals. Mp 130–131 °C. $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 1.63 (s, 9H), 2.33 (s, 3H), 5.88 (s, 2H), 7.57 (s, 1H); $^1$H NMR (200 MHz, DMSO-$d_6$) $\delta$ 1.46 (s, 9H), 2.15 (s, 3H), 6.61 (s, 2H), 7.56 (s, 1H); $\Delta\delta$ (DMSO-$d_6$-$CDCl_3$)=−0.002 ppm; $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 26.9, 28.7, 58.7, 106.9, 138.1, 148.8, 192.9; IR (cm$^{-1}$): $\tilde{\nu}$ = 3418, 3314, 1627, 1540, 1504; Anal. Calcd. for $C_9H_{15}N_3O$: C, 59.64; H, 8.34; N, 23.19; Found C, 59.19; H, 8.25; N, 23.11.

**6.1.8. 5-Methyl-1-phenyl-1*H*-pyrazole-4-carbonitrile 10.** Purification by flash chromatography (hexane/AcOEt=9/1) gave **10** (1.5 g, 83%) as brown solid. Mp 43–46 °C (lit.[27]: 46–48 °C). $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 2.50 (s, 3H), 7.41–7.55 (m, 5H), 7.88 (s, 1H); $^1$H NMR (200 MHz, DMSO-$d_6$) $\delta$ 2.38 (s, 3H), 7.50 (m, 5H), 8.13 (s, 1H); $\Delta\delta$ (DMSO-$d_6$-$CDCl_3$)=0.25 ppm; $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 11.5, 93.4, 113.6, 124.8, 128.9, 129.3, 138.1, 141.6, 145.3; IR (cm$^{-1}$): $\tilde{\nu}$ = 3069, 2973, 2230, 1598, 1553, 1507; Anal. Calcd. for $C_{11}H_9N_3$: C, 72.11; H, 4.95; N, 22.94; Found C, 71.83; H, 4.97; N, 22.66.

**6.1.9. 1-(5-Amino-1-pentafluorophenyl-1*H*-pyrazol-4-yl)-ethanone 11.** Purification by recrystallization (toluene) gave **11** (1.65 g, 79%) as white powder. Mp 160–161 °C. $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 2.41 (s, 3H), 5.84 (s, 2H), 7.88 (s, 1H); $^1$H NMR (200 MHz, DMSO-$d_6$) $\delta$ 2.31 (s, 3H), 7.17 (s, 2H), 8.07 (s, 1H); $\Delta\delta$ (DMSO-$d_6$-$CDCl_3$)=0.19 ppm; $^{13}$C NMR (50 MHz, DMSO-$d_6$) $\delta$ 26.9, 103.8, 112.4, 135.6,

139.5, 142.2, 143.4, 146.2, 151.8, 191.1; IR ($cm^{-1}$): $\tilde{\nu}$ = 3499, 3411, 3357, 1629, 1549, 1518; Anal. Calcd. for $C_{11}H_9N_3$: C, 45.37; H, 2.08; F, 32.62 N, 14.43; Found C, 45.23; H, 2.08; F, 32.42; N, 14.43.

### 6.2. General procedure for the reaction of 1 with amidines (compounds 13a–d)

To a solution of **1** (0.7 g, 5 mmol) in ethanol (10 mL) were added benzamidine hydrochloride derivatives (10 mmol) and triethylamine (2.8 mL, 20 mmol). The mixture was refluxed for 5 min. The reaction mixture was cooled to room temperature and the precipitate products **13a–d** were filtered and recrystallized from DMF.

**6.2.1. 4-Methyl-2-phenylpyrimidine-5-carbonitrile 13a. 13a** (0.65 g, 67%) as white crystals. Mp 173–174 °C. $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 2.78 (s, 3H), 7.49–7.57 (m, 3H), 8.48 (d, $J$=7 Hz, 2H), 9.03 (s, 1H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) $\delta$ 22.2, 104.8, 113.9, 127.3, 127.6, 130.8, 134.5, 158.9, 163.6, 168.6; IR ($cm^{-1}$): $\tilde{\nu}$ = 3063, 2225, 1574, 1531; Anal. Calcd. for $C_{12}H_9N_3$: C, 73.83; H, 4.65; N, 21.52; Found C, 73.43; H, 4.58; N, 21.49.

**6.2.2. 2-(4-Chlorophenyl)-4-methylpyrimidine-5-carbonitrile 13b. 13b** (0.48 g, 42%) as white crystals. Mp 170 °C. $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 2.72 (s, 3H), 7.63 (d, $J$=7 Hz, 2H), 8.41 (d, $J$=7 Hz, 2H), 9.24 (s, 1H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) $\delta$ 23.3, 106.3, 115.4, 129.0, 130.2, 134.4, 137.2, 160.8, 163.0, 170.3; IR ($cm^{-1}$): $\tilde{\nu}$ = 3048, 2227, 1579, 1568; Anal. Calcd. for $C_{12}H_8ClN_3$: C, 62.76; H, 3.51; N, 18.30; Cl, 15.44; Found C, 62.53; H, 3.49; N, 18.33; Cl, 15.63.

**6.2.3. 4-Methyl-2-*p*-tolylpyrimidine-5-carbonitrile 13c. 13c** (0.73 g, 70%) as white crystals. Mp 194–195 °C. $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 2.39 (s, 3H), 2.69 (s, 3H), 7.36 (d, $J$=8 Hz, 2H), 8.30 (d, $J$=8 Hz, 2H), 9.17 (s, 1H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) $\delta$ 20.8, 23.0, 106.0, 115.4, 128.3, 129.3, 132.6, 142.2, 160.4, 168.2, 169.8; IR ($cm^{-1}$): $\tilde{\nu}$ = 2925, 2957, 2220, 1570, 1525; Anal. Calcd. for $C_{13}H_{11}N_3$: C, 74.62; H, 5.30; N, 20.08; Found C, 74.61; H, 5.33; N, 20.01.

**6.2.4. 3-Methyl-2-(3-nitrophenyl)-pyrimidine-5-carbonitrile 13d. 13d** (1.1 g, 92%) as dull crystals. Mp 223–226 °C. $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 2.75 (s, 3H), 7.83 (t, $J$= 8.1 Hz, $J$=7.8 Hz, 1H), 8.40 (d, $J$=8.1 Hz, 1H), 8.74 (d, $J$=7.5 Hz, 1H), 9.03 (s, 1H), 9.29 (s, 1H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) $\delta$ 23.4, 107.3, 115.3, 122.7, 126.6, 130.8, 134.4, 137.2, 148.3, 161.1, 170.8; IR ($cm^{-1}$): $\tilde{\nu}$ = 3081, 2862, 2230, 1574, 1526, 1346; Anal. Calcd. for $C_{12}H_8N_4O_2$: C, 60.00; H, 3.36; N, 23.32; Found C, 59.87; H, 3.28; N, 23.36.

### 6.3. General procedure for the reaction of 1 with aminotriazoles (compounds 14, 15)

A solution of **1** (1 g, 7.19 mmol) and the appropriate aminotriazole (0.60 g, 7.19 mmol) in toluene (15 mL) has been refluxed for 30 min. After cooling the reaction mixture, the precipitate formed was filtered and recrystallized to afford **14** or **15** as a solid.

**6.3.1. 2-Acetyl-3-([1,2,4]triazol-4-ylamino)-acrylonitrile 14.** Purification by recrystallization (DMSO/water=9/1) gave **14** (1.16 g, 91%) as dark pink powder. Mp 258–260 °C. $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 2.19 (s, 3H), 8.58 (s, 1H), 9.38 (s, 2H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) $\delta$ 24.6, 80.6, 118.6, 139.6, 159.5, 187.6; IR ($cm^{-1}$): $\tilde{\nu}$ = 3097, 3038, 2239, 1614, 1544, 1523, 1431, 1374; Anal. Calcd. for $C_7H_7N_5O$: C, 47.46; H, 3.98; N, 39.53; Found C, 46.88, H 3.98; N, 39.49.

**6.3.2. 7-Methyl-[1,2,4]triazolo[1,5-*a*]pyrimidine-6-carbonitrile 15.** Purification by recrystallization (toluene) gave **15** (0.9 g, 78%) as orange powder. Mp 145–146 °C. $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 3.00 (s, 3H), 8.85 (s, 1H), 9.13 (s, 1H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) $\delta$ 16.61, 97.4, 114.4, 154.4, 155.1, 155.3, 157.2; IR ($cm^{-1}$): $\tilde{\nu}$ = 3134, 3102, 3026, 2214, 1571, 1416, 1396; Anal. Calcd. for $C_7H_7N_5$: C, 52.83; H, 3.17; N, 44.01; Found C, 52.42; H, 3.19; N, 43.97.

### 6.4. General procedure for the reaction of 1 with arylamines (compounds 16a-d, 17–20)

A solution of **1** (1 g, 7.19 mmol) and arylamine (7.19 mmol) in ethanol (15 mL) was refluxed for 10 min. The reaction mixture was then cooled to room temperature and the resulting precipitate was filtered and recrystallized.

### 6.5. Preparation of compound 16c

6-Methylpyridin-2-ylamine (0.78 g, 7.19 mmol) was added to **1** (1 g, 7.19 mmol) and the mixture was stirred at 80 °C for 10 min. After cooling, ethanol (15 mL) was added, the precipitated was filtered and purified by recrystallization from toluene to give **16c**.

### 6.6. Preparation of compounds 17, 18

Aniline (2 g, 21.6 mmol) and **1** (3 g, 21.6 mmol) were heated at 70 °C for 2 min. The reaction mixture was cooled to room temperature, EtOH formed during the reaction was evaporated and the product was then recrystallized from toluene to give **17**.

Aluminum chloride (2.1 g, 16.14 mmol) was added to **17** (1 g, 5.38 mmol) and the mixture was stirred at 180 °C for 1 h. The reaction mixture was poured into ice, saturated with $K_2CO_3$ powder and extracted with dichloromethane (3× 20 mL). After evaporation, the residue was purified by flash chromatography (Hexane/AcOEt=8/2 then AcOEt) to give **18**.

**6.6.1. 2-Acetyl-3-(pyridin-2-ylamino)-acrylonitrile 16a.** Purification by recrystallization (ethanol) gave **16a** (1.16 g, 86%) as white crystals. Mp 165 °C. $^1$H NMR (300 MHz, DMSO-$d_6$) two isomers *E* and *Z* were observed *E*/*Z*=80/20; $\delta$ 2.30 (s, 3H, (*E*)), 2.32 (s, 3H, (*Z*)), 7.15–7.24 (m, 1H), 7.35 (d, $J$=8 Hz, 1H, (*E*)), 7.53 (d, $J$=8 Hz, 1H, (*Z*)), 7.79–7.85 (m, 1H), 8.36 (d, $J$=5 Hz, 1H), 8.61 (d, $J$=12 Hz, 1H, (*Z*)), 9.06 (s, 1H, (*E*)), 11.22 (s, 1H, (*E*)), 12.00 (d, $J$=11 Hz, 1H, (*Z*)); $^{13}$C NMR (75 MHz, DMSO-$d_6$) $\delta$ 26.7 (*E*), 28.4 (*Z*), 85.2 (*Z*), 87.1 (*E*), 112.6 (*Z*), 113.0 (*E*), 116.6, 120.2 (*E*), 121.0 (*Z*), 139.1 (*E*), 139.2 (*Z*), 148.2 (*E*), 148.3 (*Z*), 149.0

(*E*), 149.8 (*E*), 149.9 (*Z*), 150.4 (*E*), 191.5 (*E*), 195.7 (*Z*); IR ($cm^{-1}$): $\tilde{\nu}$ = 3183, 3052, 2201, 1646, 1599, 1554; Anal. Calcd. for $C_{10}H_9N_3O$: C, 64.16; H, 4.85; N, 22.45; Found C, 64.01; H, 4.81; N, 22.55.

**6.6.2. 2-Acetyl-3-(5-methyl-pyridin-2-ylamino)-acrylonitrile 16b.** Purification by recrystallization (DMF/water = 9/1) gave **16b** (1.27 g, 88%) as white crystals. Mp 173 °C. $^1$H NMR (300 MHz, DMSO-$d_6$) two isomers *E* and *Z* were observed *E*/*Z* = 78/22, $\delta$ 2.23 (s, 3H), 2.28 (s, 3H, (*E*)), 2.30 (s, 3H, (*Z*)), 7.23 (d, *J* = 9 Hz, 1H, (*E*)), 7.40 (d, *J* = 8 Hz, 1H, (*Z*)), 7.61 (d, *J* = 9 Hz, 1H), 8.16 (s, 1H), 8.53 (d, *J* = 13 Hz, 1H, (*Z*)), 8.99 (s, 1H, (*E*)), 11.13 (s, 1H, (*E*)), 11.97 (d, *J* = 13 Hz, 1H, (*Z*)); $^{13}$C NMR (75 MHz, DMSO-$d_6$) $\delta$ 17.1, 26.7 (*E*), 28.3 (*Z*), 84.7, 86.5 (*Z*) + (*E*), 112.1 (*Z*), 112.5 (*E*), 116.8, 129.4 (*E*), 130.3 (*Z*), 139.4, 147.9, 148.1 (*E*) + (*Z*), 148.3, 148.9 (*E*), 149.8 (*Z*), 191.4 (*E*), 195.6 (*Z*); IR ($cm^{-1}$): $\tilde{\nu}$ = 3188, 3052, 2204, 1657, 1602, 1558; Anal. Calcd. for $C_{11}H_{11}N_3O$: C, 65.66; H, 5.51; N, 20.88; Found C, 65.56; H, 5.44; N, 20.87.

**6.6.3. 2-Acetyl-3-(6-methyl-pyridin-2-ylamino)-acrylonitrile 16c.** Purification by recrystallization (toluene) gave **16c** (1.24 g, 86%) as white crystals. Mp 169–171 °C. $^1$H NMR (200 MHz, DMSO-$d_6$) two isomers *E* and *Z* were observed *E*/*Z* = 86/14, $\delta$ 2.29 (s, 3H, (*E*)), 2.31 (s, 3H, (*Z*)), 2.43 (s, 3H), 7.02 (d, *J* = 7 Hz, 1H), 7.14 (d, *J* = 8 Hz, 1H, (*E*)), 7.32 (d, *J* = 8 Hz, 1H, (*Z*)), 7.69 (t, *J* = 8 Hz, *J* = 7 Hz, 1H), 8.60 (d, *J* = 13 Hz, 1H, (*Z*)), 9.04 (d, *J* = 13 Hz, 1H (*E*)), 11.18 (d, *J* = 14 Hz, 1H, (*E*)), 11.94 (d, *J* = 13 Hz, 1H, (*Z*)); $^{13}$C NMR (62.5 MHz, DMSO-$d_6$) $\delta$ 23.7 (*Z*), 23.9 (*E*), 26.9 (*E*), 28.4 (*Z*), 84.9, 86.5 (*Z*) + (*E*), 109.4 (*Z*), 110.0 (*E*), 116.0 (*Z*), 116.9 (*E*), 119.6 (*E*), 120.4 (*Z*), 139.2 (*E*), 139.4 (*Z*), 148.9 (*E*), 149.0, 149.7 (*Z*), 157.1 (*E*), 157.3 (*Z*), 191.4 (*E*), 195.7 (*Z*); IR ($cm^{-1}$): $\tilde{\nu}$ = 3194, 3091, 3058, 2204, 1655, 1608, 1559; Anal. Calcd. for $C_{11}H_{11}N_3O$: C, 65.66; H, 5.51; N, 20.88; Found C, 65.75; H, 5.44; N, 21.04.

**6.6.4. 2-Acetyl-3-(pyridin-4-ylamino)-acrylonitrile 16d.** Purification by recrystallization (DMF/water = 9/1) gave **16d** (1.24 g, 81%) as dull powder. Mp 206–209 °C. $^1$H NMR (200 MHz, DMSO-$d_6$) two isomers *E* and *Z* were observed *E*/*Z* = 75 / 25, $\delta$ 2.32 (s, 3H, (*Z*)), 2.34 (s, 3H, (*E*)), 7.47 (d, *J* = 6 Hz, 2H, (*E*)), 7.53 (d, *J* = 6 Hz, 2H, (*Z*)), 8.46–8.51 (m, 3H, (*E* + *Z*)); $^{13}$C NMR (62.5 MHz, DMSO-$d_6$) $\delta$ 26.4 (*E*), 28.5 (*Z*), 85.9 (*Z*), 89.2 (*E*), 112.2 (*E*), 112.3(*Z*), 116.0 (*E*), 119.5 (*Z*), 145.2 (*Z*), 146.5 (*E*), 150.5 (*E*), 150.7 (*Z*), 151.3 (*E*), 152.0 (*Z*), 191.8 (*E*), 196.0 (*Z*); IR ($cm^{-1}$): $\tilde{\nu}$ = 3197, 3068, 2210, 1686, 1664, 1626, 1592, 1595, 1565; Anal. Calcd. for $C_{10}H_9N_3O$: C, 64.16; H, 4.85; N, 22.45; Found C, 63.58; H, 4.81; N, 22.31.

**6.6.5. 2-Acetyl-3-phenylamino-acrylonitrile 17.** Purification by recrystallization (toluene) gave **17** (3.25 g, 81%) as pale yellow crystals. Mp 148–151 °C. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 2.42 (s, 3H), 7.14 (d, *J* = 8 Hz, 2H), 7.24 (t, *J* = 8 Hz, 1H), 7.41 (t, *J* = 8 Hz, *J* = 8 Hz, 2H), 7.84 (d, *J* = 12,9 Hz, 1H), 12.29 (d, *J* = 11,4 Hz, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 28.5, 84.8, 117.6, 119.7, 126.3, 130.0, 138.0, 151.5, 197.2; IR ($cm^{-1}$): $\tilde{\nu}$ = 3143, 3056, 2205, 1647, 1581; MS (Da): 186; Anal. Calcd. for $C_{11}H_{10}N_2O$: C, 70.95; H, 5.41; N, 15.04; Found C, 70.95; H, 5.45; N, 14.98.

**6.6.6. 3-(4-Aminoquinolin-3-yl)-ethanone 18.** Purification by flash chromatography (hexane/AcOEt = 8/2, then AcOEt) gave **18** (0.45 g, 45%) as brown powder. Mp 217–219 °C. $^1$H NMR (200 MHz, DMSO-$d_6$) $\delta$ 2.65 (s, 1H), 7.51 (t, *J* = 8 Hz, 1H), 7.75–7.85 (m, 2H), 8.41 (d, *J* = 8 Hz, 1H), 8.99 (s, 1H); $^{13}$C NMR (62.5 MHz, DMSO-$d_6$) $\delta$ 27.8, 107.9, 118.4, 123.4, 124.9, 129.0, 131.5, 148.5, 153.1, 153.6, 199.5; IR ($cm^{-1}$): $\tilde{\nu}$ = 3302, 3053, 1623, 1612, 1584; MS (Da): 186; Anal. Calcd. for $C_{11}H_{10}N_2O$: C, 70.95; H, 5.41; N, 15.04; Found C, 70.80; H, 5.50; N, 14.36.

**6.6.7. 2-Acetyl-3-(6-methoxybenzothiazol-2-ylamino)-acrylonitrile 19.** Purification by recrystallization (DMSO/water = 8/2) gave **19** (1.7 g, 88%) as pale green powder. Mp 227–228 °C. $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 2.33 (s, 3H), 3.78 (s, 3H), 7.01 (d, *J* = 9 Hz, 1H), 7.51 (s, 1H), 7.64 (d, *J* = 9 Hz, 1H), 8.68 (s, 1H), 12.17 (s, 1H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) $\delta$ 26.7, 55.5, 89.9, 105.2, 114.9, 115.8, 121.2, 133.3, 143.6, 149.1, 156.3, 158.0, 191.4; IR ($cm^{-1}$): $\tilde{\nu}$ = 3096, 2969, 2213, 1652, 1597; Anal. Calcd. for $C_{13}H_{11}N_3O_2S$: C, 57.13; H, 4.06; N, 15.37; Found C, 57.03; H, 4.07; N, 15.27.

**6.6.8. 4-Methyl-benzo[4,5]imidazo[1,2-*a*]pyrimidine-3-carbonitrile 20.** Purification by recrystallization (DMF) gave **20** (1.27 g, 85%) as pale red powder. Mp: > 300 °C. $^1$H NMR (250 MHz, DMSO-$d_6$) $\delta$ 3.27 (s, 1H), 7.53 (t, *J* = 8 Hz, 1H), 7.69 (t, *J* = 8 Hz, 1H), 7.96 (d, *J* = 8 Hz, 1H), 8.35 (d, *J* = 8 Hz, 1H), 9.00 (s, 1H); $^{13}$C NMR (62.5 MHz, DMSO-$d_6$) $\delta$ 19.9, 116.8, 119.6, 122.9, 127.0, 149.2, 154.8, 176.3; IR ($cm^{-1}$): $\tilde{\nu}$ = 3091, 3070, 3052, 2926, 2231, 1621, 1595; Anal. Calcd. for $C_{12}H_8N_4$: C, 69.22; H, 3.87; N, 26.91; Found C, 69.23; H, 3.85; N, 27.01.

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# Tri-component reaction of 2-alkyl-4,5-dichloropyridazin-3(2*H*)-ones: synthesis of 5-cyano-5-(pyrimidin-2-yl)-2,7-dialkyl-5*H*-dipyridazino-[4,5-*b*:4,5-*e*]-4*H*-thiopyran-1,6-dione and 2-(4-cyanophenoxy) pyrimidine

Jung-Won Park,[a] Jeum-Jong Kim,[a] Ho-Kyun Kim,[a] Hyun-A Chung,[a] Su-Dong Cho,[b,*] Sang Gyeong Lee,[a] Motoo Shiro[c] and Yong-Jin Yoon[a,*]

[a]*Department of Chemistry and Environmental Biotechnology, National Core Research Center, Gyeongsang National University, Chinju 660-701, South Korea*
[b]*Department of Chemistry, Research Institute of Basic Sciences, Changwon National University, Changwon 641-773, South Korea*
[c]*Rikagu Corporation, 3-9-12 Matsubara-cho, Akishima-shi, Tokyo 196-8666, Japan*

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**Abstract**—Reaction of 2-alkyl-4,5-dichloropyridazin-3(2*H*)-ones with *p*-cyanophenol and 2-mercaptopyrimidine in the presence of base gave 2,4,5-trisubstituted-pyridazin-3(2*H*)-ones **4**–**9**, 2-(4-cyanophenoxy)pyrimidine (**10**) and 5-cyano-5-(pyrimidin-2-yl)-2,7-dialkyl-5*H*-dipyridazino[4,5-*b*:4,5-*e*]-4*H*-thiopyran-1,6-diones **11** as a novel heterocycle.


## 1. Introduction

In the previous report,[1,2] we reported the replacement of 4-cyanophenoxy group of 2-methyl-4-halo-5-(4-cyanophenoxy)pyridazin-3(2*H*)-ones by alkoxy groups such as methoxy and ethoxy. Therefore, we tried the regioselective substitution of 4-chloro-2-methyl-5-(4-cyanophenoxy)-pyridazin-3(2*H*)-one with 2-mercaptopyrimidine. In this preliminary experiment, we detected the several products on the tlc. As part of our research program for the regioselective displacement of 4,5-dichloropyridazin-3(2*H*)-one, we studied the tri-component reactions of 2-alkyl-4,5-dichloropyridazin-3(2*H*)-ones with 4-cyanophenol and 2-mercaptopyrimidine.

In this paper, we would like to report on the reaction results and new compounds in the title reaction.

## 2. Results and discussion

Reaction of **1a** with **2** and **3** in the presence of triethylamine in refluxing acetonitrile gave compounds **4a** (42%) and **8a** (25%) (entry 1 in Table 1), whereas this reaction was carried out in the presence of potassium carbonate instead of triethylamine to afford **6a** (22%) and **7a** (43%) (entry 2 in Table 1) (Scheme 1).

Treatment of **1b** with **2** and **3** in the presence of potassium carbonate in refluxing acetonitrile yielded **6b** (6%), **7b** (41%) and **8b** (26%) (entry 3 in Table 1). On the other hand, compound **1c** was reacted with **2** and **3** in the presence of potassium carbonate in refluxing acetonitrile afforded **6c** (7%), **7c** (32%), **8c** (28%) and phenyl pyrimidin-2-yl ether **10** (9%) as a new product (entry 4 in Table 1). Also this reaction was carried out in the presence of cesium carbonate instead of potassium carbonate to give **10** (42%) as the main and **11c** (6%) as another new product (entry 5 in Table 1). Tri-component reaction of **1d** with **2** and **3** in the presence of potassium carbonate in refluxing acetonitrile gave **5d** (15%), **7d** (44%) and **8d** (19%) (entry 6 in Table 1).

In order to elucidate the formation pathway of the new compounds **10** and **11c**, we attempted some further

*Keywords*: Tri-component reaction; 2-Alkyl-4,5-dichloropyridazin-3(2*H*)-ones; 5-Cyano-5-(pyrimidin-2-yl)-2,7-dialkyl-5*H*-dipyridazino[4,5-*b*:4,5-*e*]-4*H*-thiopyran-1,6-diones; 2-(4-Cyanophenoxy)pyrimidine.
* Corresponding authors. Tel.: +82 055 751 6019; fax: +82 055 761 0244 (Y.-J.Y.); e-mail: yjyoon@nongae.gsnu.ac.kr

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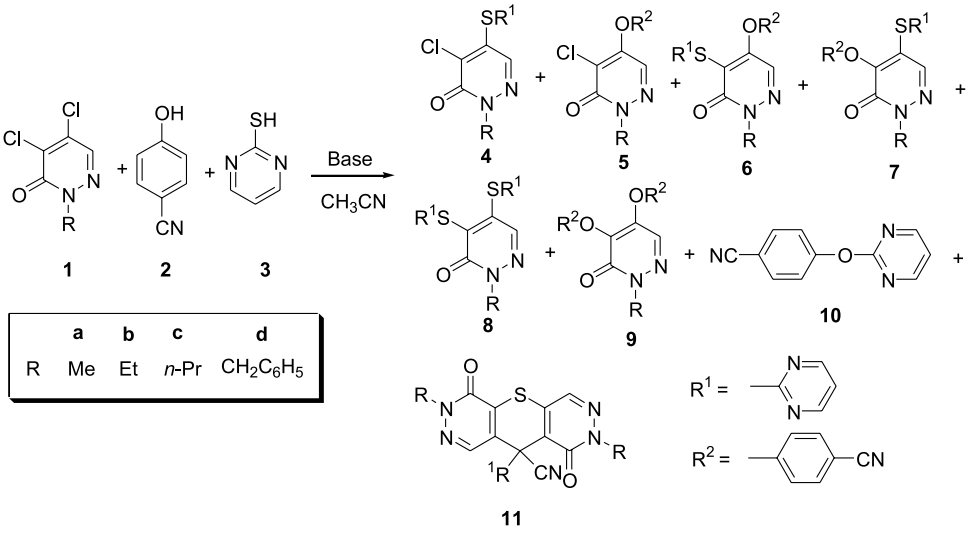
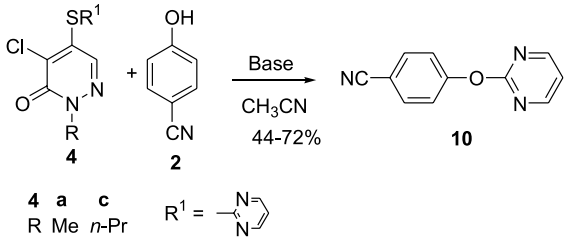
**Table 1**. Reaction of **1** with **2** and **3** in the presence of bases in refluxing acetonitrile

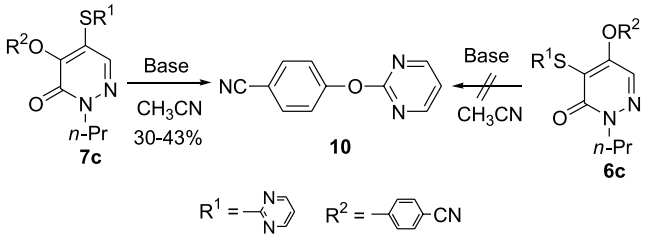
| Entry | **1**(R) | Base | Reaction time (h) | Product distribution (isolated yield, %) | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | **4** | **5** | **6** | **7** | **8** | **9** | **10** | **11** |
| 1 | **a** Me | $Et_3N$ | 21 | 42 | — | — | — | 25 | — | — | — |
| 2 | **a** Me | $K_2CO_3$ | 44 | — | — | 22 | 43 | — | — | — | — |
| 3 | **b** Et | $K_2CO_3$ | 16 | — | — | 6 | 41 | 26 | — | | — |
| 4 | **c** *n*-Pr | $K_2CO_3$ | 27 | — | Trace | 7 | 32 | 28 | — | 9 | — |
| 5 | **c** *n*-Pr | $Cs_2CO_3$ | 115 | — | — | — | — | — | — | 42 | 6 |
| 6 | **d** $CH_2Ph$ | $K_2CO_3$ | 5 | — | 15 | Trace | 44 | 19 | — | — | — |




**Scheme 1.**




**Scheme 2.**




**Scheme 3.**

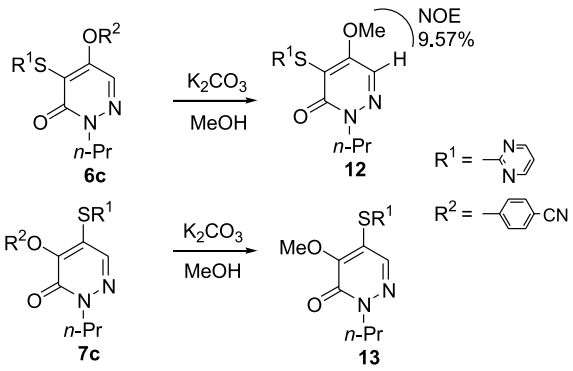
reactions. First, the reaction of **4c** with phenol **2** in the presence of potassium carbonate in refluxing acetonitrile for 8 days gave **10** in 40% yield, whereas the reaction which was carried out in the presence of cesium carbonate instead of potassium carbonate for 4 days, afforded **10** in 44% yield. The treatment of **4a** with **2** in the presence of potassium carbonate in refluxing acetonitrile also gave **10** in 72% yield. These are similar to the previously reported results.[3,4] However, **4b** and **4d** did not form compound **10** under the same conditions.

Compound **5** was also treated with **3** in the presence of potassium carbonate in refluxing acetonitrile to form compounds **6**, **7** and **10**. This reaction involved the *ipso* substitution of **5** by 2-mercaptopyrimidine anion to **4** at C5 (Scheme 2).

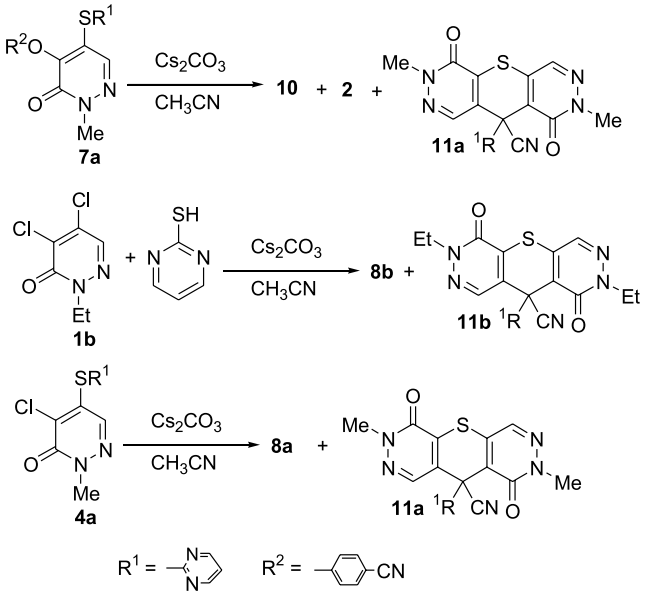
Reaction of **7c** with some other bases such as $K_2CO_3$, $Cs_2CO_3$ and $Rb_2CO_3$ in refluxing acetonitrile afforded **10** (30–43%) and 4-cyanophenol (**2**). However, treatment of compound **6c** with these bases did not form compound **10** (Scheme 3).

Thus, it is possible that compound **10** may have been formed via two pathways. *Pathway A*: **1**→**4**→**7**→**10**. *Pathway B*: **1**→**5**→**4**→**7**→**10**. Compound **7** is a key intermediate for the synthesis of **10**. The formation of **10** from **7** under our condition was an unusual reaction.

In order to establish the structures of compound **6** and **7**, we attempted methoxylation of **6c** and **7c**. Compound **6** and **7** were treated with potassium carbonate in methanol to **12** and **13**, respectively.[5] The substituted position of the methoxy group for **12** and **13** was established easily by




**Scheme 4.**




**Scheme 5.**

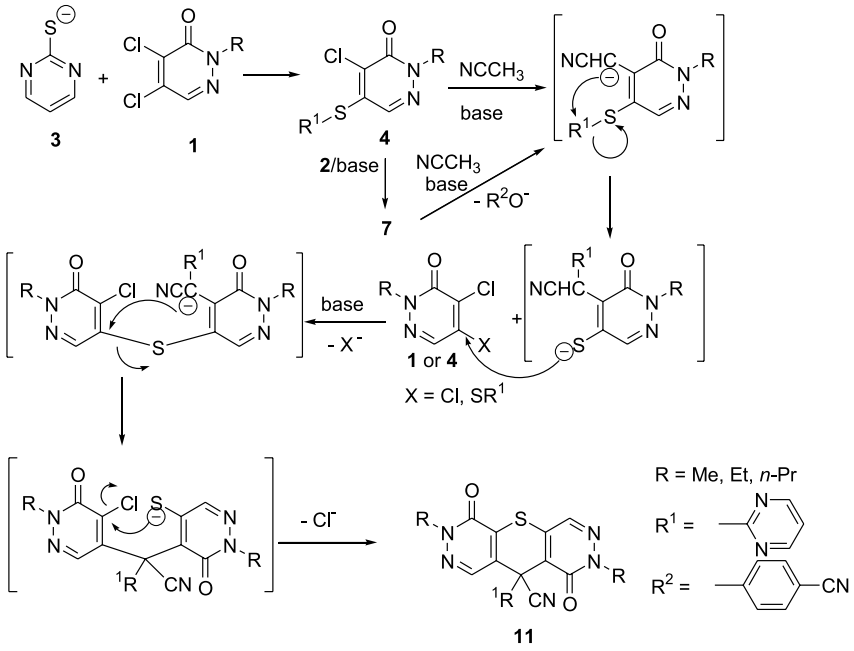
the NOE (between C5–OMe protons and C6–H proton for **12** in Scheme 4). The structures of **4**, **5**, **8**, **9** and **10** were established by IR, NMR, and elemental analysis.

On the other hand, we also attempted further reactions in order to elucidate the formation pathway(mechanism) of the new type heterocycles **11**. Reaction of **7a** with cesium carbonate in refluxing acetonitrile gave **10** (17%), **11a** (12%) and 4-cyanophenol (**2**, 69%). Compound **1b** was reacted with **3** in the presence of cesium carbonate in refluxing acetonitrile and it gave **8b** (36%) and **11b** (13%). Treatment of **4a** with cesium carbonate in refluxing acetonitrile afforded **11a** (55%) and **8a** (40%) (Scheme 5).

However, compound **5**, **6**, **8** and **9** did not form **11** under our condition. Thus, compound **11** may have been formed via two pathways. *Pathway A*: **1**→**4**→**7**→**11**. *Pathway B*: **1**→**4**→**11**. The synthetic mechanism of **11** under our condition is also showed in Scheme 6. The structures of **11** were established by IR, NMR, elemental analysis and X-ray diffraction for **11a** (Fig. 1).[6]

## 3. Conclusion

In summary, we report herein the results of the tri-component reaction of 2-alkyl-4,5-dichloropyridazin-3(2*H*)-ones with *p*-cyanophenol and 2-mercaptopyrimidine to give 2,4,5-trisubstituted-pyridazin-3(2*H*)-ones (**4**-**9**), 2-(4-cyanophenoxy)pyrimidine (**10**) and 5-cyano-5-(pyrimidin-2-yl)-2,7-dialkyl-5*H*-dipyridazino[4,5-*b*:4,5-*e*]-4*H*-thiopyran-1,6-diones **11**. The formation of ether **10** and tricyclic fused heterocycles **11** from 2-alkyl-4,5-dichloropyridazin-3(2*H*)-ones is a new type of reaction. Also compound **11** is a novel heterocycle. Further work including the chemical transformation and application of novel compounds are under way in our laboratory.




**Scheme 6.** Proposed mechanism for the synthesis of **11**.

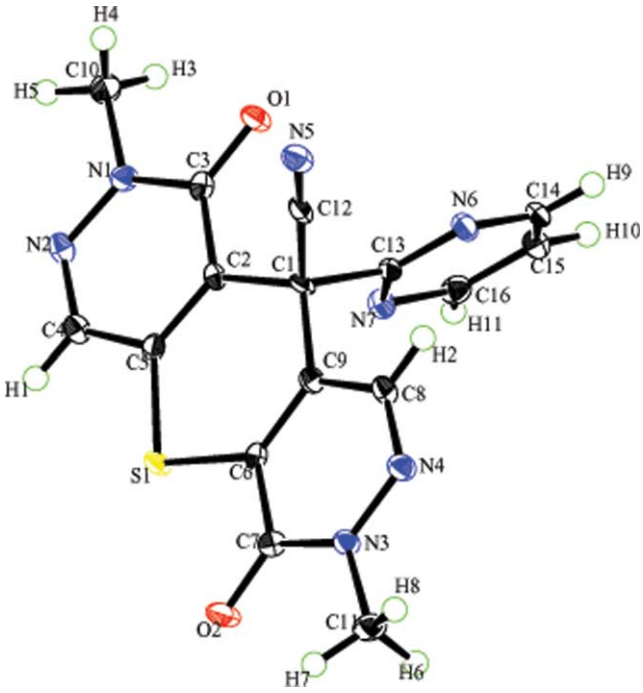



**Figure 1.** ORTEP plot for X-ray crystal structures of **11a**.

## 4. Experimental

### 4.1. General

Melting points were determined with a Thomas-Hoover capillary apparatus and were uncorrected. $^1$H and $^{13}$C NMR spectra were obtained on a Bruker FT NMR-DRX 500 or Varian Inova 500 spectrometer and with chemical shift values reported in $\delta$ units (part per million) relative to an internal standard (teteramethylsilane). IR spectra were obtained on a Hitachi 270-50 or Mattson Genesis Series FT-IR spectrophotometer. Elemental analyses were performed with a Perkin–Elmer 240C. X-ray diffraction data were obtained with a Rigaku AFC7R diffractometer with filtered Cu K$\alpha$ radiation and a rotating anode generator. TLC was performed on $SiO_2$ (silica gel 60 F254, Merck). The spots were located by UV light. Column chromatography was carried out on $SiO_2$ (silica gel 60, 70–230 mesh). Compounds **1** were prepared from 4,5-dichloropyridazin-3(2*H*)-one by the literature method.[7]

### 4.2. Reaction of 1 with 2 and 3

*Method A*. A mixture of **1** (5.586 mmol), **2** (5.586 mmol), **3** (5.586 mmol), base (5.586 mmol) and acetonitrile (50 mL) was refluxed until **1** was disappeared. After cooling to room temperature, the mixture was filtered and washed with acetonitrile (35 mL×2). The combined filtrate was evaporated under reduced pressure. The residue was applied to the top of an open-bed silica gel column (3×22 cm). The column was eluted with ethyl acetate/n-hexane (1:1, v/v). Fractions involving each product were combined and evaporated under reduced pressure to give the product.

**4.2.1. 2-Methyl-4-chloro-5-(pyirimidin-2-ylsulfanyl)-pyridazin-3(2*H*)-one (4a).** Mp 134–135 °C; IR (potassium bromide): $\nu$ 3030, 2970, 1650, 1549, 1497, 1376, 1313, 1229, 1172, 1018, 954, 873, 797, 769, 748, 707, 628 cm$^{-1}$; $^1$H NMR (deuteriochloroform): $\delta$ 3.87 (s, 3H), 7.17 (t, 1H, $J$=4.9 Hz), 7.98 (s, 1H), 8.60 (d, 2H, $J$ =4.9 Hz); $^{13}$C NMR (deuteriochloroform) $\delta$ 41.4, 119.0, 135.5, 138.6, 138.8, 157.2, 158.5, 168.7. Anal. Calcd for $C_9H_7ClN_4OS$: C, 42.44; H, 2.77; N, 22.00; S, 12.59. Found: C, 42.15; H, 2.24; N, 21.97; S, 12.51.

**4.2.2. 2-Benzyl-4-chloro-5-(4-cyanophenoxy)pyridazin-3(2*H*)-one (5d).** Mp 196–197 °C; IR (potassium bromide): $\nu$ 3090, 2970, 2950, 2232, 1659, 1608, 1587, 1489, 1395, 1330, 1311, 1260, 1224, 1151, 1100, 1076, 1007, 938, 858, 747, 699, 559 cm$^{-1}$; $^1$H NMR (deuteriochloroform): $\delta$ 5.36 (s, 2H), 7.09–7.15 (m, 2H), 7.30–7.38 (m, 3H), 7.44–7.48 (m, 2H), 7.58 (s, 1H), 7.69–7.73 (m, 2H); $^{13}$C NMR (deuteriochloroform) $\delta$ 56.4, 109.1, 117.9, 119.0, 123.4, 128.4, 128.7, 129.2, 130.5, 134.7, 135.2, 151.5, 157.3, 158.2. Anal. Calcd for $C_{18}H_{12}ClN_3O_2$: C, 64.01; H, 3.58; N, 12.44; Cl, 10.50. Found: C, 64.04; H, 3.61; N, 12.49; Cl, 10.56.

**4.2.3. 2-Methyl-4-(pyirimidin-2-ylsulfanyl)-5-(4-cyanophenoxy)pyridazin-3(2*H*)-one (6a).** Mp 207–208 °C; IR (potassium bromide): $\nu$ 3117, 3072, 2226, 1648, 1586, 1551, 1497, 1375, 1267, 1229, 1172, 1069, 840, 769, 543 cm$^{-1}$; $^1$H NMR (deuteriochloroform): $\delta$ 3.82 (s, 3H), 7.03 (t, 1H, $J$=4.8 Hz), 7.14–7.18 (m, 2H), 7.61 (s, 1H), 7.61–7.67 (m, 2H), 8.46 (d, 2H, $J$=4.8 Hz); $^{13}$C NMR (deuteriochloroform) $\delta$ 41.0, 108.7, 117.9, 118.0, 119.1, 120.2, 130.2, 134.4, 156.8, 157.6, 158.0, 160.1, 168.9. Anal. Calcd for $C_{16}H_{11}N_5O_2S$: C, 56.96; H, 3.29; N, 20.76; S, 9.50. Found: C, 57.00; H, 3.32; N, 20.82; S, 9.55.

**4.2.4. 2-Ethyl-5-(4-cyanophenoxy)-4-(pyrimidin-2-ylsulfanyl)pyridazin-3(2*H*)-one (6b).** Mp 183–184 °C; IR (potassium bromide): $\nu$ 3070, 2970, 2250, 1650, 1600, 1550, 1500, 1380, 1320, 1260, 1230, 1170, 1070, 840, 760, 540 cm$^{-1}$; $^1$H NMR (deuteriochloroform): $\delta$ 1.40 (t, 3H, $J$=7.2 Hz), 4.25 (q, 2H, $J$=7.2 Hz), 6.99 (t, 1H, $J$= 4.9 Hz), 7.13–7.15 (m, 2H), 7.60 (s, 1H), 7.60–7.64 (m, 2H), 8.44 (d, 2H, $J$=4.9 Hz); $^{13}$C NMR (deuteriochloroform) $\delta$ 13.4, 48.1, 108.8, 117.8, 118.0, 119.2, 120.7, 130.3, 134.4, 156.5, 157.6, 158.1, 159.7, 169.2. Anal. Calcd for $C_{17}H_{13}N_5SO_2$: C, 58.11; H, 3.73; N, 19.93; S, 9.13. Found: C, 58.14; H, 3.80; N, 20.00; S, 9.16.

**4.2.5. 2-Propyl-4-(pyrimidin-2-ylsulfanyl)-5-(4-cyanophenoxy)pyridazin-3(2*H*)-one (6c).** Mp 109–110 °C; IR (potassium bromide): $\nu$ 3008, 2969, 2229, 1649, 1590, 1550, 1499, 1375, 1310, 1255, 1225, 1174, 1079, 841, 770, 750 cm$^{-1}$; $^1$H NMR (deuteriochloroform): $\delta$ 0.97 (t, 3H, $J$=7.4 Hz), 1.83–1.88 (m, 2H), 4.17 (t, 2H, $J$=7.4 Hz), 7.00 (t, 1H, $J$=4.9 Hz), 7.13–7.17 (m, 2H), 7.60 (s, 1H), 7.63–7.66 (m, 2H), 8.45 (d, 2H, $J$=4.9 Hz); $^{13}$C NMR (deuteriochloroform) $\delta$ 11.3, 21.7, 53.8, 108.3, 117.9, 118.3, 119.1, 121.2, 130.7, 134.9, 154.3, 157.4, 158.3, 159.9, 168.9. Anal. Calcd for $C_{18}H_{15}N_5SO_2$: C, 59.16; H, 4.14; N, 19.17; S, 8.78. Found: C, 59.21; H, 4.20; N, 19.21; S, 8.82.

**4.2.6. 2-Methyl-4-(pyirimidin-2-ylsulfanyl)-5-(4-cyanophenoxy)pyridazin-3(2*H*)-one (7a).** Mp 160–161 °C; IR (potassium bromide): $\nu$ 3100, 3070, 2945, 2226, 1650, 1549,

1501, 1384, 1298, 1240, 951, 826, 765 $cm^{-1}$; $^1H$ NMR (deuteriochloroform): $\delta$ 3.82 (s, 3H), 7.01–7.06 (m, 2H), 7.11 (t, 1H, $J$=4.8 Hz), 7.55–7.60 (m, 2H), 8.00 (s, 1H), 8.52 (d, 2H, $J$=4.8 Hz); $^{13}C$ NMR (deuteriochloroform) $\delta$ 40.2, 107.3, 117.4, 118.4, 118.5, 125.8, 133.8, 139.8, 150.4, 155.8, 158.0, 158.9, 168.7. Anal. Calcd for $C_{16}H_{15}N_5O_2S$: C, 56.96; H, 3.29; N, 20.76; S, 9.50. Found: C, 57.01; H, 3.34; N, 20.80; S, 9.59.

**4.2.7. 2-Ethyl-4-(4-cyanophenoxy)-5-(pyrimidin-2-ylsulfanyl)pyridazin-3(2*H*)-one (7b).** Mp 110–111 °C; IR (potassium bromide): $\nu$ 3080, 3000, 2250, 1660, 1600, 1560, 1500, 1460, 1380, 1310, 1260, 1170, 1020, 960, 840, 780, 750, 630, 550 $cm^{-1}$; $^1H$ NMR (deuteriochloroform): $\delta$ 1.41 (t, 3H, $J$=7.2 Hz), 4.22 (q, 2H, $J$=7.2 Hz), 7.01–7.03 (m, 2H), 7.08 (t, 1H, $J$=4.9 Hz), 7.52–7.57 (m, 2H), 8.02 (s, 1H), 8.51 (d, 2H, $J$=4.9 Hz); $^{13}C$ NMR (deuteriochloroform) $\delta$ 13.4, 47.4, 107.4, 117.4, 118.4, 118.5, 125.6, 133.9, 139.7, 150.4, 155.4, 158.0, 159.0, 168.9. Anal. Calcd for $C_{17}H_{13}N_5SO_2$: C, 58.11; H, 3.73; N, 19.93; S, 9.13. Found: C, 58.15; H, 3.78; N, 20.01; S, 9.18.

**4.2.8. 2-Propyl-4-(4-cyanophenoxy)-5-(pyrimidin-2-ylsulfanyl)pyridazin-3(2*H*)-one (7c).** Mp 91–92 °C; IR (potassium bromide): $\nu$ 3062, 2962, 2875, 2228, 1650, 1590, 1553, 1496, 1381, 1306, 1248, 1169, 945, 843, 767 $cm^{-1}$; $^1H$ NMR (deuteriochloroform): $\delta$ 0.97 (t, 3H, $J$=7.4 Hz), 1.83–1.88 (m, 2H), 4.13 (t, 2H, $J$=7.4 Hz), 7.00–7.04 (m, 2H), 7.09 (t, 1H, $J$=4.9 Hz), 7.55–7.59 (m, 2H), 8.02 (s, 1H), 8.51 (d, 2H, $J$=4.9 Hz); $^{13}C$ NMR (deuteriochloroform) $\delta$ 11.1, 21.7, 53.7, 107.3, 117.4, 118.4, 118.5, 125.5, 133.8, 139.6, 150.4, 155.6, 158.0, 158.9, 168.8. Anal. Calcd for $C_{18}H_{15}N_5SO_2$: C, 59.16; H, 4.14; N, 19.17; S, 8.78. Found: C, 59.22; H, 4.21; N, 19.22; S, 8.84.

**4.2.9. 2-Benzyl-4-(4-cyanophenoxy)-5-(pyrimidin-2-ylsulfanyl)pyridazin-3(2*H*)-one (7d).** Mp 106–107 °C; IR (potassium bromide): $\nu$ 3061, 3000, 2225, 1657, 1590, 1553, 1494, 1379, 1303, 1244, 1165, 951, 835, 760, 736, 700, 627 $cm^{-1}$; $^1H$ NMR (deuteriochloroform): $\delta$ 5.32 (s, 2H), 6.99–7.01 (m, 2H), 7.08 (t, 1H, $J$=4.9 Hz), 7.30–7.34 (m, 3H), 7.44–7.45 (m, 2H), 7.55–7.57 (m, 2H), 8.03 (s, 1H), 8.50 (d, 2H, $J$ =4.9 Hz); $^{13}C$ NMR (deuteriochloroform) $\delta$ 55.6, 103.3, 117.3, 118.4, 118.5, 126.0, 128.3, 128.7, 129.1, 133.8, 135.5, 139.9, 150.5, 155.5, 158.0, 158.8, 168.7. Anal. Calcd for $C_{22}H_{15}N_5O_2S$: C, 63.91; H, 3.66; N, 16.94; S, 7.76. Found: C, 64.13; H, 3.72; N, 17.11.

**4.2.10. 2-Methyl-4,5-di(pyirimidin-2-ylsulfanyl)pyridazin-3(2*H*)-one (8a).** Mp 125–126 °C; IR (potassium bromide): $\nu$ 3064, 2980, 1660, 1554, 1383, 1250, 1167, 1024, 947, 865, 806, 769, 745, 625 $cm^{-1}$; $^1H$ NMR (deuteriochloroform): $\delta$ 3.82 (s, 3H), 7.02–7.16 (m, 2H), 8.05 (s, 1H), 8.47–8.58 (m, 4H); $^{13}C$ NMR (deuteriochloroform) $\delta$ 40.9, 117.9, 118.5, 136.6, 138.2, 141.9, 157.6, 158.0, 158.2, 168.9, 169.2. Anal. Calcd for $C_{13}H_{10}N_6OS_2$: C, 47.26; H, 3.05; N, 25.44; S, 19.41. Found: C, 47.30; H, 3.12; N, 25.51; S, 19.47.

**4.2.11. 2-Ethyl-4,5-di(pyrimidin-2-ylsulfanyl)pyridazin-3(2*H*)-one (8b).** Mp 121–123 °C; IR (potassium bromide): v 3100, 3050, 3000, 1740, 1650, 1560, 1450, 1430, 1380, 1240, 1170, 1050, 990, 940, 840, 810, 770, 750, 700, 630 $cm^{-1}$; $^1H$ NMR (deuteriochloroform): $\delta$ 1.43 (t, 3H, $J$=7.2 Hz), 4.24 (q, 2H, $J$=7.2 Hz), 7.02 (t, 1H, $J$=4.9 Hz), 7.12 (t, 1H, $J$=5.0 Hz), 8.07 (s, 1H), 8.49 (d, 2H, $J$=4.8 Hz), 8.57 (d, 2H, $J$=4.9 Hz); $^{13}C$ NMR (deuteriochloroform) $\delta$ 13.3, 48.0, 117.8, 118.4, 137.1, 138.2, 141.5, 157.5, 157.8, 158.0, 169.3, 169.6. Anal. Calcd for $C_{14}H_{12}N_6OS_2$: C, 48.82; H, 3.51; N, 24.40; S, 18.62. Found: C, 48.90; H, 3.61; N, 24.51; S, 18.70.

**4.2.12. 2-Propyl-4,5-di(pyrimidin-2-ylsulfanyl)pyridazin-3(2*H*)-one (8c).** Mp 98–100 °C; IR (potassium bromide): $\nu$ 3057, 2963, 2930, 1655, 1548, 1426, 1373, 1300, 1268, 1167, 1056, 945, 805, 768, 745, 625 $cm^{-1}$; $^1H$ NMR (deuteriochloroform): $\delta$ 0.97 (t, 3H, $J$=7.4 Hz), 1.84–1.90 (m, 2H), 4.14 (t, 2H, $J$=7.4 Hz), 7.02 (t, 1H, $J$ = 4.9 Hz), 7.11 (t, 1H, $J$=4.9 Hz), 8.05 (s, 1H), 8.48 (d, 2H, $J$=4.9 Hz), 8.56 (d, 2H, $J$=4.9 Hz); $^{13}C$ NMR (deuteriochloroform) $\delta$ 11.5, 22.0, 54.7, 118.2, 118.8, 137.5, 138.4, 141.6, 157.9, 158.3, 158.4, 169.5, 169.8. Anal. Calcd for $C_{15}H_{14}N_6OS_2$: C, 50.26; H, 3.94; N, 23.45; S, 17.89. Found: C, 50.31; H, 4.02; N, 23.51; S, 17.93.

**4.2.13. 2-Benzyl-4,5-di(pyrimidin-2-ylsulfanyl)pyridazin-3(2*H*)-one (8d).** Mp 167–168 °C; IR (potassium bromide): $\nu$ 3115, 3075, 3028, 1660, 1549, 1454, 1350, 1164, 967, 876, 824, 769, 723, 627 $cm^{-1}$; $^1H$ NMR (deuteriochloroform): $\delta$ 5.34 (s, 2H), 7.00 (t, 1H, $J$=4.9 Hz), 7.10 (t, 1H, $J$=4.9 Hz), 7.29–7.34 (m, 3H), 7.40–7.49 (m, 2H), 8.06 (s, 1H), 8.44 (d, 2H, $J$=4.6 Hz), 8.55 (d, 2H, $J$=4.9 Hz); $^{13}C$ NMR (deuteriochloroform) $\delta$ 56.1, 117.8, 118.5, 128.0, 128.6, 128.9, 135.9, 137.2, 138.3, 141.9, 157.5, 157.9, 158.0, 169.0, 169.4. Anal. Calcd for $C_{19}H_{14}N_6OS_2$: C, 56.14; H, 3.47; N, 20.67; S, 15.78. Found: C, 56.21; H, 3.52 N, 20.71; S, 15.83.

**4.2.14. 2-(4-Cyanophenoxy)pyrimidine (10).** Mp 108–109 °C; IR (potassium bromide): $\nu$ 3095, 3059, 2231, 1602, 1568, 1503, 1405, 1289, 1222, 1161, 1017, 901, 862, 820, 791, 626 $cm^{-1}$; $^1H$ NMR (deuteriochloroform): $\delta$ 7.12 (t, 1H, $J$=4.8 Hz), 7.32–7.36 (m, 2H), 7.72–7.75 (m, 2H), 8.60 (d, 2H, $J$=4.8 Hz); $^{13}C$ NMR (deuteriochloroform) $\delta$ 109.2, 117.2, 118.4, 122.6, 133.9, 156.3, 159.9, 164.5. Anal. Calcd for $C_{11}H_7N_3O$: C, 67.00; H, 3.58; N, 21.31. Found: C, 67.03; H, 3.62; N, 21.36.

**4.2.15. 5-Cyano-5-(pyrimidin-2-yl)-2,7-dipropyl-5*H*-dipyridazino[4,5-*b*:4,5-*e*]-4*H*-thiopyran-1,6-dione (11c).** Mp 185–186 °C; IR (potassium bromide): $\nu$ 3060, 2970, 2880, 1640, 1610, 1570, 1400 $cm^{-1}$; $^1H$ NMR (deuteriochloroform): $\delta$ 0.88 (t, 3H, $J$=4.5 Hz), 0.95 (t, 3H, $J$=4.5 Hz), 1.76 (q, 2H, $J$=4.5 Hz), 1.82 (q, 2H, $J$=4.5 Hz), 4.00–4.06 (m, 4H), 7.26–7.30 (m, 1H), 7.79 (s, 1H), 8.18 (s, 1H), 8.77 (d, 2H, $J$=4.9 Hz); $^{13}C$ NMR (deuteriochloroform) $\delta$ 10.9, 11.1, 21.5, 21.6, 49.2, 53.6, 53.9, 116.9, 120.4, 124.4, 128.4, 131.8, 133.1, 134.9, 135.5, 155.4, 156.3, 158.3, 166.4. Anal. Calcd for $C_{20}H_{19}N_7O_2S$: C, 56.99; H, 4.54; N, 23.26; S, 7.61. Found: C, 57.02; H, 4.61; N, 23.32; S, 7.70.

### 4.3. Synthesis of compound 10

*Method B*. Reaction of **4a** or **4c** with **2**. A mixture of **4** (0.393 mmol), **2** (47 mg, 0.393 mmol) and base (potassium

carbonate for **4a**; cesium carbonate for **4c**, 0.393 mmol) and acetonitrile (20 mL) was refluxed until **4** was disappeared. After cooling to room temperature, the mixture was filtered and washed with acetonitrile (35 mL×2). The combined filtrate was evaporated under reduced pressure. The residue was applied to the top of an open-bed silica gel column (3× 12 cm). The column was eluted with methylene chloride. Fractions involving **10** were combined and evaporated under reduced pressure to give **10** as yellowish crystal in 44% (for **4c**) and 72% (for **4a**) yield, respectively.

*Method C*. Reaction of **7** with base. A mixture of **7** (2.74 mmol) and base such as $K_2CO_3$, $Cs_2CO_3$ and $Rb_2CO_3$ (5.9 mmol) and acetonitrile (50 mL) was refluxed until **7** was disappeared. After cooling to room temperature, the mixture was filtered and washed with acetonitrile (25 mL× 2). The combined filtrate was evaporated under reduced pressure. The residue was applied to the top of an open-bed silica gel column (5×18 cm). The column was eluted with ethyl acetate/n-hexane (1:2, v/v). Fractions involving **10** were combined and evaporated under reduced pressure to give **10** in 43% yield. Fractions involving 4-cyanophenol were combined and evaporated under reduced pressure to afford 4-cyanophenol (39%).

### 4.4. Reaction of 6c or 7c with potassium carbonate/ methanol

A mixture of **6c** or **7c** (1.375 mmol), potassium carbonate (228 mg, 1.65 mmol) and MeOH (30 mL) was stirred until **6c** or **7c** was disappeared at room temperature. The mixture was coevaporated with silica gel (600 mg) under reduced pressure. The residue was applied to the top of an open-bed silica gel column (3×12 cm). The column was eluted with methylene chloride/diethyl ether (30:1, v/v). Fractions involving 4-cyanophenol were combined and evaporated under reduced pressure to give 4-cyanophenol. Fractions involving **12** or **13** were combined and evaporated to afford **12** (74%) or **13** (58%).

### 4.5. Synthesis of 11a and 11b from 7a, 1b and 4a

*Method D*. A mixture of **7a** (0.35 g, 1.04 mmol), cesium carbonate (0.74 g, 2.28 mmol) and acetonitrile (20 mL) was refluxed for 24 hours. After cooling to the room temperature, the mixture was filtered and evaporated under reduced pressure. The residue was applied to the top of an open-bed silica gel column (3×12 cm). The column was eluted with methylene chloride. Fractions involving **10** were combined and evaporated under reduced pressure to give **10** (17%). Fractions involving 4-cyanophenol were combined and evaporated under reduced pressure to give 4-cyanophenol (**2**, 69%). Fractions involving **11a** were combined and evaporated to afford **11a** (12%).

*Method E*. A mixture of **1b** (1 g, 5.19 mmol), **3** (582 mg, 5.19 mmol), cesium carbonate (3.38 g, 10.38 mmol) and acetonitrile (30 mL) was refluxed for 48 hours. After cooling to the room temperature, the mixture was filtered and evaporated under reduced pressure. The residue was applied to the top of an open-bed silica gel column (3× 12 cm). The column was eluted with methylene chloride. Fractions involving **11b** were combined and evaporated under reduced pressure to give **11b** (13%). Fractions involving **8b** were also combined and evaporated to afford **8b** (36%).

*Method F*. A mixture of **4a** (50 mg, 0.2 mmol), cesium carbonate (130 mg, 0.4 mmol) and acetonitrile (30 mL) was refluxed for 20 hours. After cooling to the room temperature, the mixture was filtered and evaporated under reduced pressure. The residue was applied to the top of an open-bed silica gel column (3×12 cm). The column was eluted with methylene chloride. Fractions involving **11a** were combined and evaporated under reduced pressure to give **11a** (55%). Fractions involving **8a** were also combined and evaporated to afford **8a** (40%).

**4.5.1. 5-Cyano-5-(pyrimidin-2-yl)-2,7-dimethyl-5*H*-dipyridazino[4,5-*b*:4,5-*e*]-4*H*-thiopyran-1,6-dione (11a).** Mp 186 °C; IR (potassium bromide): $\nu$ 3080, 3020, 2970, 1650, 1580, 1420, 1280, 1250, 1040, 875, 780 $cm^{-1}$; $^1H$ NMR (deuteriochloroform): $\delta$ 3.72 (s, 3H), 3.78 (s, 3H), 7.29 (t, 1H, $J$=4.90 Hz), 7.79 (s, 1H), 8.17 (s, 1H), 8.77 (d, 2H, $J$=4.89 Hz); $^{13}C$ NMR (deuteriochloroform) $\delta$ 40.20, 40.25, 53.45, 116.79, 120.47, 124.18, 128.63, 131.56, 133.08, 134.90, 135.81, 155.59, 156.56, 158.35, 166.24. Anal. Calcd for $C_{16}H_{11}N_7O_2S$: C, 52.60; H, 3.03; N, 26.84; S, 8.78. Found: C, 52.66; H, 3.09; N, 26.88; S, 8.90.

**4.5.2. 5-Cyano-5-(pyrimidin-2-yl)-2,7-diethyl-5*H*-dipyridazino[4,5-*b*:4,5-*e*]-4*H*-thiopyran-1,6-dione (11b).** Mp 227–228 °C; IR (potassium bromide): $\nu$ 3080, 3050, 2990, 2950, 2880, 1640, 1600, 1570, 1450, 1410, 1380, 1350, 1310, 1270, 1240, 1220, 1180, 1150, 1090, 1060, 1010, 1000, 960, 880, 850, 830, 760, 740, 700 $cm^{-1}$; $^1H$ NMR (deuteriochloroform): $\delta$ 1.29–1.41 (m, 6H), 4.08–4.24 (m, 4H), 7.30 (t, 1H, $J$=5.0 Hz), 7.83 (s, 1H), 8.18 (s, 1H), 8.78 (d, 2H, $J$=5.0 Hz); $^{13}C$ NMR (deuteriochloroform) $\delta$ 13.2, 13.3, 47.2, 47.6, 49.1, 116.9, 120.5, 124.3, 128.4, 131.8, 133.2, 135.0, 135.6, 155.1, 156.1, 158.3, 166.3. Anal. Calcd for $C_{18}H_{15}N_7O_2S$: C, 54.95; H, 3.84; N, 24.92; S, 8.15. Found: C, 55.02; H, 3.90; N, 24.99; S, 8.21.

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6. Crystal data for **11a**: $C_{36}H_{32}N_{14}O_5S_2$, formula weight = 804.86, Crystal system = triclinic, lattice type = primitive, lattice parameters $a = 9.410(2)$ Å, $b = 13.055(3)$ Å, $c = 16.915(3)$ Å, $\alpha = 103.96(5)^\circ$ $\beta = 101.55(3)^\circ$, $\gamma = 109.33(7)^\circ$, $V = 1811.7(14)$ Å$^3$, space group *P*-1 (#2), *Z* value = 2, $D_{calc} = 1.475$ g/cm$^3$, $F_{000} = 836.00$, $\mu$(Mo K$\alpha$) 2.14 cm$^{-1}$, Data were collected on a Rigaku RAXIS-RAPID imaging plate diffractometer with graphite monochromated Mo K$\alpha$ radiation ($\lambda = 0.71075$ Å). Detector aperture = 270 mm × 256 mm, Data images = 44 exposures, $\omega$ oscillation range ($\chi = 45.0$, ($\Phi = 0.0$) = 130.0–190.0°, exposure rate = 12.0 s/°, $\omega$ oscillation range ($\chi = 45.0$, $\Phi = 180.0$) = 0–160.0°, exposure rate = 12.0 s/°, detector position = 127.40 mm, pixel size = 0.100 mm, $2\theta_{max} = 60.1^\circ$, no. of reflections measured = total: 21,521, unique: 10,443 ($R_{int} = 0.096$), corrections Lorentz-polarizationabsorption (trans. factors: 0.902–0.989), no. observations (all reflections) = 10,443, reflection/parameter ratio = 20.28, residuals: *R*1 ($I > 2.00\sigma(I)$) = 0.053, residuals: *R* (all reflections) = 0.124, residuals: *wR*2 (all reflections) = 0.097, goodness of fit indicator = 0.924, max shift/error in final cycle = 0.001, maximum peak in final diff. map = 0.50 e/Å$^3$, minimum peak in final diff. map = −0.41 e/Å$^3$.
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