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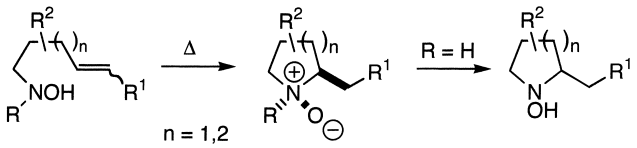

This report aims to summarize the salient features of the reverse Cope cyclisation, a useful method for the elaboration of pyrrolidines and, to a lesser extent piperidines, by pericyclic cyclisations of unsaturated hydroxylamines.

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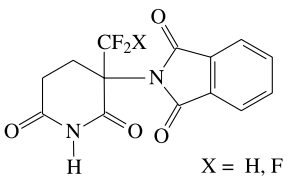

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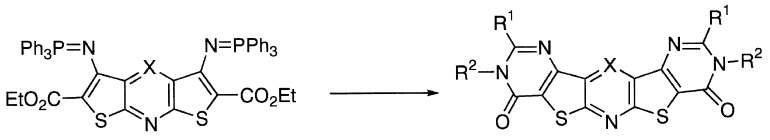

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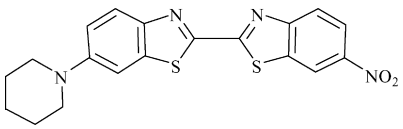

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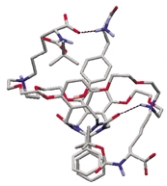

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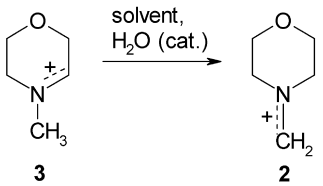

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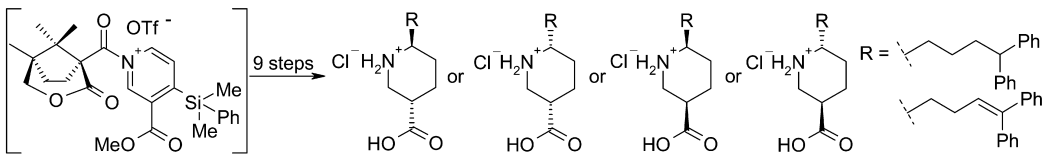

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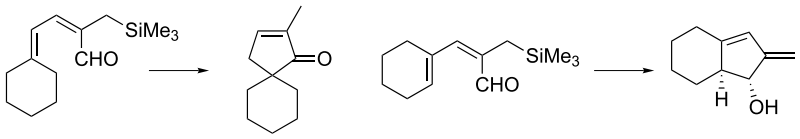

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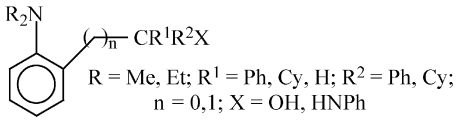

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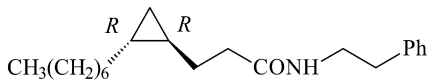

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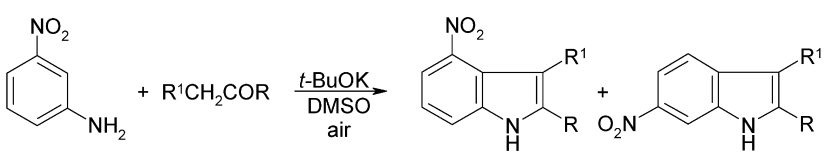

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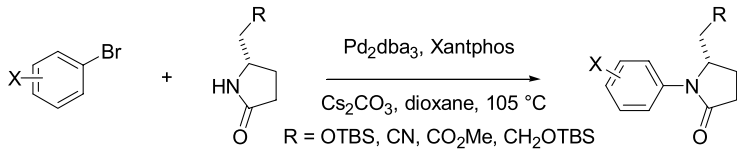

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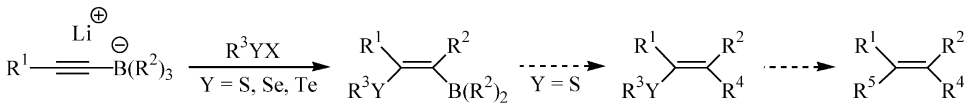

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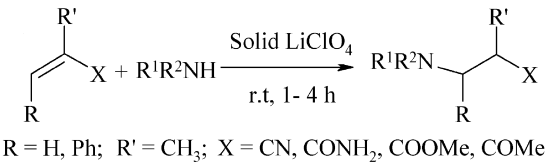

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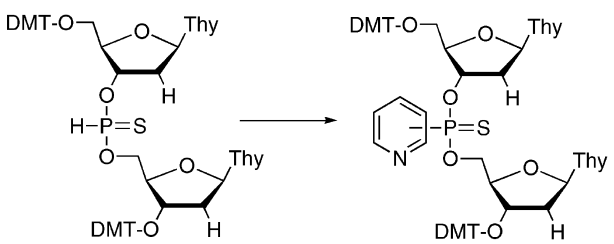

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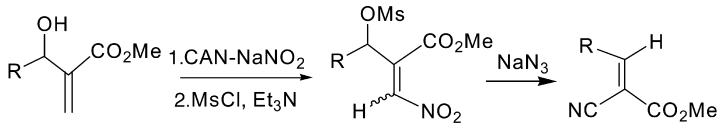

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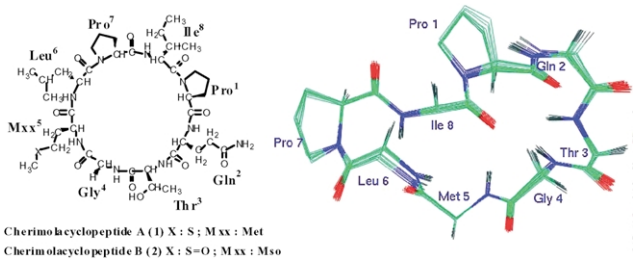

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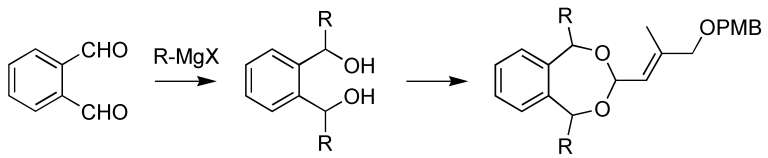

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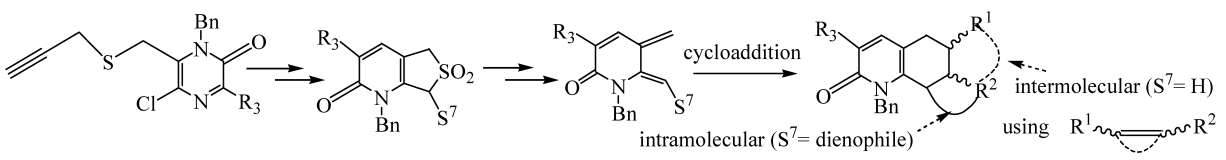

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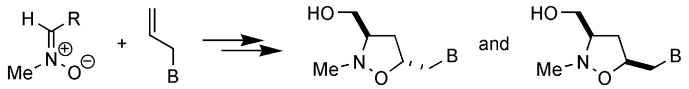

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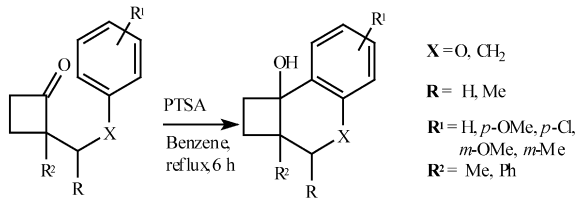

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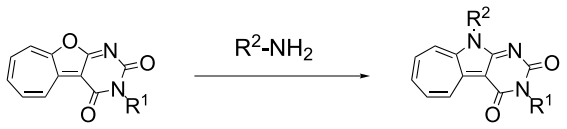

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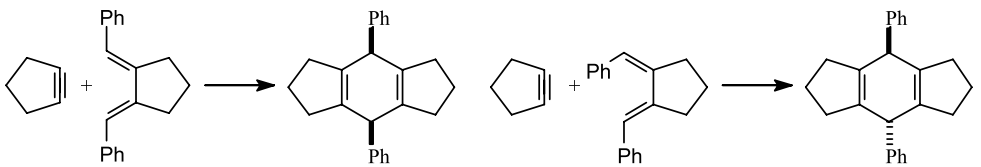

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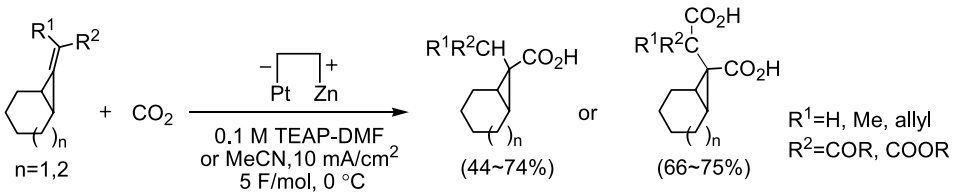

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The reverse Cope cyclisation: a classical reaction goes backwards

Nicholas J. Cooper and David W. Knight*

Cardiff School of Chemistry, Cardiff University, P.O. Box 912, Cardiff CF10 3TB, UK

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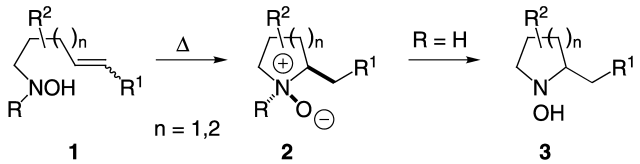
1. Introduction

Before beginning a discussion of this chemistry, it seems prudent to provide a definitive name for the process whereby an unsaturated hydroxylamine **1** undergoes a thermal cyclisation to give pyrrolidine- or piperidine-*N*-oxides **2** or the corresponding *N*-hydroxy derivatives **3** (Scheme 1)



1 **2** **3**

Scheme 1.

This has variously been referred to as the retro- or reverse Cope elimination, cyclisation or reaction and, more recently, the Cope–House cyclisation by Holmes (Section 6), the latter to highlight the key contribution to its discovery made by House (Sections 2 and 3). The term EPOC reaction, proposed in an ironic riposte to an unfavourable referee's comment by Ciganek (Section 2), is perhaps the least serious, but not without some merit. While not wishing to detract in any way from House's contribution and with some trepidation in disagreeing with our learned friend and colleague, Professor Holmes, we propose that the best descriptive term is 'the reverse Cope cyclisation,' in line with Ciganek's more serious suggestion. This is also consistent with a recent short review of the subject.[1]

The road to the current state of progress in the reverse Cope cyclisation is paved with serendipity and features a relatively lengthy period of dormancy. In these respects, it has some similarities with its relative, the Cope elimination. Although first reported in 1900,[2] it was not until the seminal work of the Cope group, initiated during the late 1940s, that this now classical reaction of tertiary amine-*N*-oxides was brought to prominence.[3] Furthermore, as pointed out by Ciganek,[4] it is likely that Cope was well aware of the possibility of the occurrence of reverse Cope reactions; despite this, while it is very likely that he and LeBel did indeed effect such a transformation, they did not isolate and identify the definitive product.[5] Thus, while noting a significant loss of material during distillation of the Cope elimination product **4**, they suggested that this was due to polymerisation rather than formation of the much less volatile reverse Cope elimination product, the piperidine-*N*-oxide **5** (Scheme 2). As ever, hindsight is a wonderful thing!

Keywords: Reverse Cope; Cyclisation; Hydroxylamines; Pyrrolidines; Piperidines; *N*-Oxides; Pyrrolidine-*N*-oxides; Pericyclic reaction; Alkynyl hydroxylamines; Nitrones.

* Corresponding author. Fax: +44-02920-874-210;
e-mail address: knightdw@cf.ac.uk

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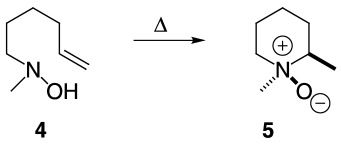
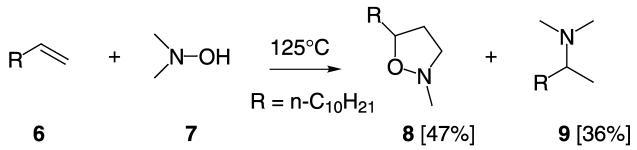


Scheme 2.

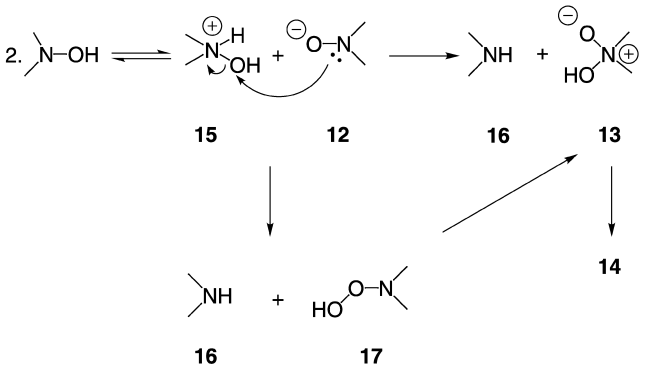
In addition, again as highlighted by Ciganek,[4] Cope and LeBel further reported[5] that partial pyrolysis of an isomeric mixture of the *trans*-*N*-oxide **5** and its *cis*-isomer allowed separation of the *trans*-isomer **5** into pentane. As it is highly unlikely that either very polar *N*-oxide isomer would be pentane-soluble, a more likely explanation is that the *trans*-isomer **5** selectively undergoes a Cope elimination by proton abstraction from the 2-methyl group, a pathway not available to the *cis*-isomer, to give the less polar hydroxylamine **4**. During subsequent manipulation in pentane, this must then have reverted selectively to the *trans*-*N*-oxide **5** by a reverse Cope cyclisation, prior to isolation and analysis. In retrospect, this has important implications for the mechanism of the reverse Cope process, as discussed below.

Interestingly, an isolated report, published in 1973,[6] may feature an example of an intermolecular reverse Cope elimination, given that one has sympathy with the complexities of hydroxylamine chemistry, wherein disproportionation can take a leading role. The exact example involved thermolysis at 125 °C of a mixture of 1-dodecene **6** and *N*,*N*-dimethylhydroxylamine **7** and gave two isolated products, the isoxazolidine **8** and the tertiary amine **9** (Scheme 3).



Scheme 3.

If one assumes a reverse Cope elimination takes place initially between the reactants, the first-formed product would be the amine-*N*-oxide **10**. This could then undergo reduction by the hydroxylamine **7** as suggested in Scheme 4. Thus, proton exchange, not unreasonable when one considers the relatively low pK_a (13.7) of the hydroxyl group in hydroxylamine,[7,8] could generate the ammonium salt **11** accompanied by the oxide **12**. This could then deoxygenate the salt **11**, either directly, as shown, or by *N*-hydroperoxide formation and rearrangement, to give the observed amine **9**, together with the intermediate **13**; loss of water would then generate the reactive nitrone **14**. This then adds with characteristic regioselectivity by a [1,3]-dipolar cycloaddition mechanism to the alkene **6** to give the isoxazolidine **8**. The latter nitrone could also be generated by a similar process, but one which involves proton exchange between two hydroxylamine molecules, resulting in overall disproportionation; presumably, the dimethylamine was too volatile to isolate (Scheme 5). It is also conceivable that all of these transformations could involve initial homolysis of the O–H bond of the hydroxylamine to give a nitroxide. Intermediate **13** could also be obtained by attack of the oxide **12** onto the protonated species **15** at oxygen to give the peroxide **17** that could rearrange to the nitrone hydrate **13**.

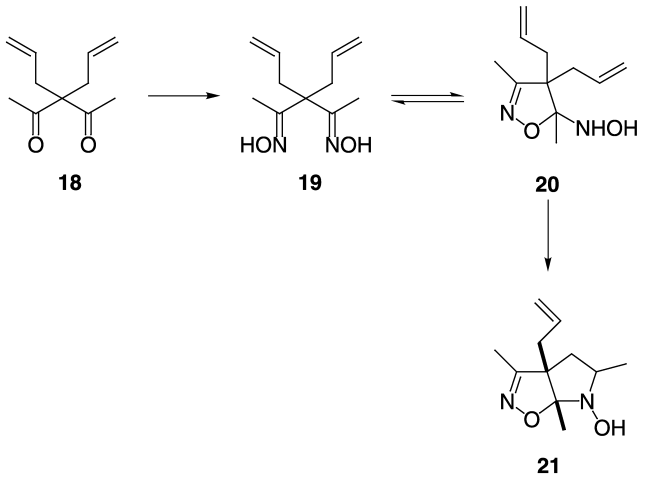


Scheme 4.

Scheme 5.

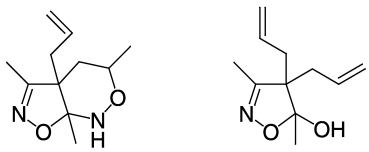
2. Discovery and mechanism

The first report of an authentic reverse Cope cyclisation was made by House in 1976.[8] This serendipitous discovery was made during attempts to prepare the dioxime **19** from the corresponding 1,3-dione **18** under standard conditions ($NH_2OH{\cdot}HCl$, NaOAc, aq. dioxane, reflux). Instead, the annulated pyrrolidine **21** was isolated as the main product and presumed to have arisen by a reverse Cope cyclisation of the 'anomeric' hydroxylamine **20**, which would be



Scheme 6.

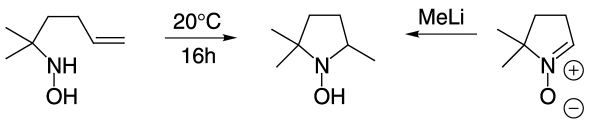
expected to be in equilibrium with the dioxime structure **19** (Scheme 6). The unexpected product **21** was isolated largely as a single diastereoisomer. The 5/5 ring fusion presumably dictates a *cis*-ring fusion, but the relative positioning of the new methyl group was not determined. A third minor product appeared to be a structural isomer rather than a stereoisomer and was not identified. In view of subsequent observations (see below), this might be the Meisenheimer rearrangement product **22** derived from the initial reverse Cope product **21**. That the equilibrium shown in Scheme 6 is reasonable is supported by the fact that the monoxime of dione **18** exists exclusively as the isoxazoline **23** (Scheme 7).[8]



22 **23**

Scheme 7.

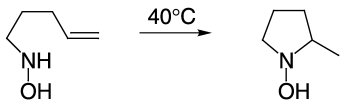
To further illustrate this unexpected observation, House then proceeded to synthesise the simpler and less structurally ambiguous hydroxylamine **24**. This was found to undergo smooth cyclisation to the *N*-hydroxypyrrolidine **25** upon standing at ambient temperature overnight or heating on a steam bath for 5 min. Its structure was proven by comparisons with authentic material and the derived *O*-benzoates obtained by the addition of methyl lithium to nitrone **26** (Scheme 8). House and Lee also defined some of the scope for the formation of piperidines by this pathway (see Section 3.3).[9]



24 **25** **26**

Scheme 8.

Further examples of the type of cyclisation shown in Scheme 8 were provided 2 years later by Black and Doyle (see Scheme 18).[10] The simplest version of the reverse Cope cyclisation (Scheme 9) was unexpectedly observed upon mild heating or prolonged storage of the hydroxylamine **27**, an intermediate required during Oppolzer's studies of intramolecular [1,3]-dipolar cycloadditions, leading to the *N*-hydroxypyrrolidine **28**.[11]



27 **28**

Scheme 9.

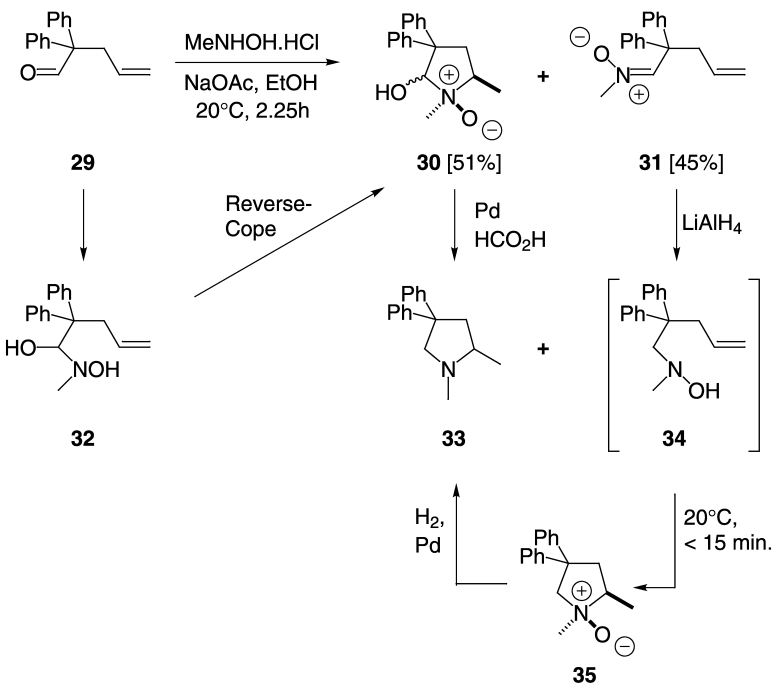
It seems likely that a further example of serendipitous science led Ciganek to deduce the existence of the reverse Cope cyclisation by a rather neat set of logical experiments. This all arose during a seemingly routine synthesis of the nitrone **31** from the aldehyde **29** and methylhydroxylamine (Scheme 10).[4,12] While the desired nitrone **31** was indeed isolated in 45% yield, a second major product (51%) was the α-hydroxypyrrolidine-*N*-oxide **30**, which was found, remarkably, to survive sublimation at 150 °C unchanged. Ciganek deduced that this could have been formed by reverse Cope cyclisation of the *N*-hydroxyhemiaminal **32**, in competition with simple dehydration to the nitrone **31**.

This idea was then correlated in a clever manner: careful partial reduction of the nitrone **31** lead to the (presumed) alkenylhydroxylamine **34**, which underwent rapid reverse Cope cyclisation during work-up to give the pyrrolidine-*N*-oxide **35** in ca. 90% yield. The two pathways were correlated by reduction of both *N*-oxides [**30** and **35**] to the same pyrrolidine **33**. One can only speculate if similar nitrone preparations carried out by others gave similar lower-than-expected yields but that the reason behind this remained obscure.

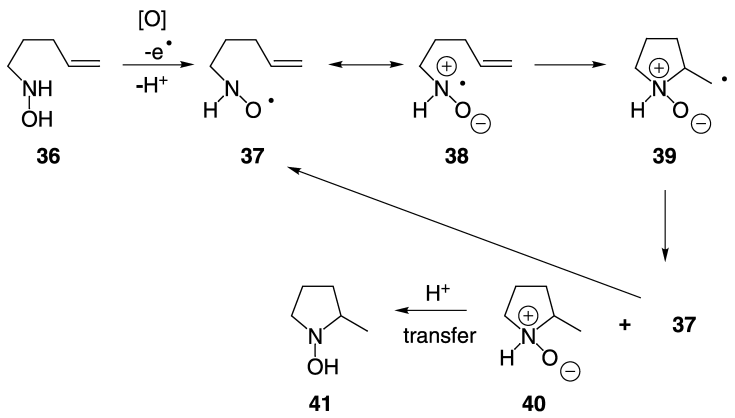
Other than just a few 'one-off' contributions, the topic lay apparently dormant for the whole of the 1980s. It was only during the early 1990s that this remarkable reaction was brought to prominence with the publication of seminal contributions from Ciganek of a seemingly long-term scope and limitations study[4,12,13] and from Oppolzer, who both defined the likely mechanism and also provided a most elegant illustration of the synthetic potential of the reaction.[14] This period then saw contributions from a number of other groups which have broadened the scope of the method, particularly as an efficient and usually highly stereoselective approach to pyrrolidines and related saturated five-membered heterocycles. A particularly notable feature of the reaction is that it is, effectively, a method for the addition of an amine nitrogen to an unactivated carbon–carbon double or triple bond. Initial mechanistic speculations by House suggested that the reverse Cope cyclisation operates by a radical-based mechanism. This conclusion was based on some electrochemical measurements and the experimental observation that the cyclisation appeared to be promoted by traces of oxidising agents. Thus, oxidation of an initial unsaturated hydroxylamine **36** could lead to an intermediate nitroxide **37** which, when represented as the radical cation **38**, shows how the central carbon–nitrogen bond formation could occur to give the pyrrolidine radical **39** (Scheme 11). This, in turn, could abstract a hydrogen radical from the starting material **36**, thereby initiating another cascade and leaving the resulting neutral species **40** to undergo a facile proton transfer to give the observed product **41**.

An inspiration for this suggestion came from earlier work by Motherwell and Roberts, who showed that nitroxide **43** could be efficiently generated by an oxidative cyclisation of the corresponding unsaturated hydroxylamine **42** using silver(I) oxide or carbonate (Scheme 12).[15] It is also conceivable that the pathway could be initiated by a hydroxylamine molecule being oxidised to a nitroso species; interaction of the latter with a second hydroxylamine could then give two molecules of the corresponding nitroxide [cf. **37**].

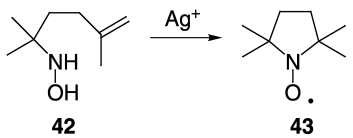
However, these ideas were soon undermined by the observations of Black and Doyle[10] who found that the



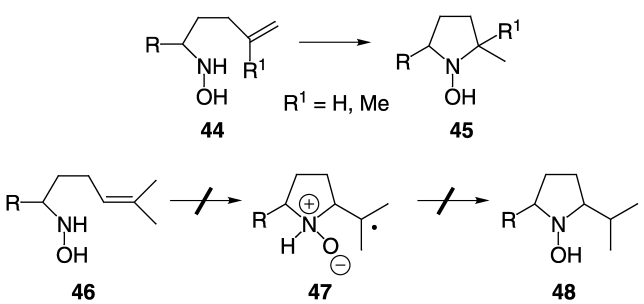
Scheme 10.



Scheme 11.



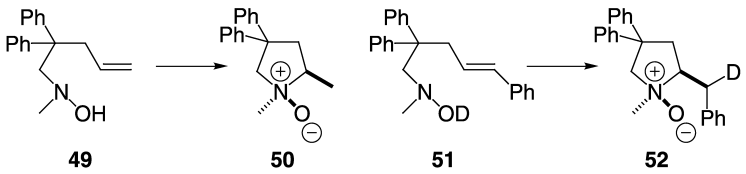
Scheme 12.



Scheme 13.

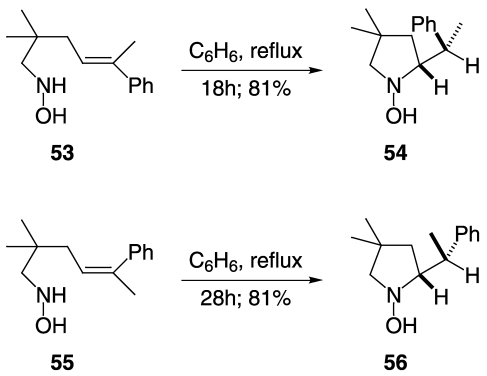
addition of radical inhibitors (hydroquinone, phenol or aniline) had no effect on the rate of reverse Cope cyclisations. Perhaps more seriously, they found that, while the hydroxylamines **44** underwent cyclisation with relative ease (20 °C for days or 80 °C, C_6H_6, 10–15 min) to give the *N*-hydroxypyrrolidines **45**, the homologous hydroxylamine **46**, having two distal substituents on the alkene function, failed to deliver the pyrrolidine **48** under similar or more forcing conditions, despite the fact that the radical intermediate **47** expected from the House mechanism should be more stable (Scheme 13). Steric arguments also do not provide support for the House mechanism in these cases.

Ciganek provided additional observations which were difficult to reconcile with a radical mechanism.[12] Firstly, reverse Cope cyclisation of a diphenyl-substituted precursor **49** gave a single diastereoisomer **50**, in which the new methyl group and the oxide oxygen were *cis* (Scheme 14). Subsequently, this has been shown to be a key



Scheme 14.

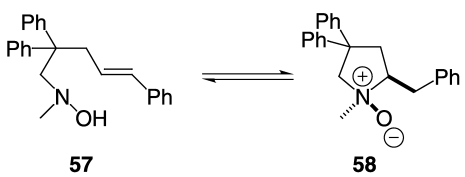
stereochemical theme running throughout the reverse Cope method. In a second experiment, cyclisation of the O-deuteriated hydroxylamine **51** gave only one isomer of the expected pyrrolidine-*N*-oxide **52**, again indicative of a concerted mechanism. Final definitive proof of a concerted mechanism was provided in a most elegant fashion by Oppolzer and his colleagues (Scheme 15).[14] They showed that the (*E*)-alkenylhydroxylamine **53** underwent reverse Cope cyclisation to provide only the pyrrolidine-*N*-oxide **54**, whereas the corresponding *Z*-isomer **55** was similarly converted into only the epimeric product **56**.



Scheme 15.

The conclusion must be that the cyclisation involves suprafacial formation of the new C–N and C–H bonds and thus proceeds by a planar five-membered transition state, in the same manner as the Cope elimination.[3,16,17] Both conclusions have subsequently been corroborated by ab initio and density function calculations,[17] which suggest an approximately synchronous process for both reactions.

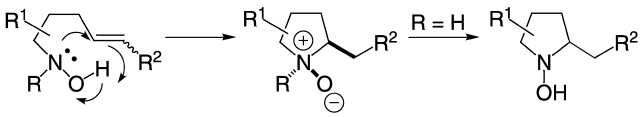
The observed solvent effects generally support these conclusions. Relatively polar solvents tend to favour the reverse Cope cyclisation, probably because these are more able to solvate the polar *N*-oxide (or hydroxylamine) products. A purely empirical judgement suggests that chloroform or perhaps methanol or DMSO are usually the solvents of choice. Revealing comparative data have been presented by Ciganek, some of which are not readily explained.[4,12] Although somewhat unusual, some reverse Cope cyclisations are themselves reversible at ambient temperature (Scheme 16): the highly substituted hydroxylamine **57** shows such behaviour in its interconversion



Scheme 16.

with the *N*-oxide **58**, which is very solvent dependent. In chloroform, methanol and DMSO containing TFA, the equilibrium lies entirely to the right in favour of the *N*-oxide **58**, whereas approximately equal amounts of **57** and **58** are observed in benzene, THF and neat DMSO, while acetone and acetonitrile strongly favour *N*-oxide **58** formation. The *N*-isopropyl homologue of hydroxylamine **57** shows complete conversion into the corresponding *N*-oxide in chloroform, but THF, DMF and DMSO all favour the hydroxylamine **57**. All this is not easily explained, but one message is clear: try a new reverse Cope cyclisation in chloroform first. However, despite the foregoing conclusions, spectacular success in this area has been achieved simply by thermolysis in benzene or xylene (see below).[14]

To conclude this section, the basic mechanism of the reverse Cope cyclisation is probably best represented as the $2\pi+2\sigma+2n$ process shown in Scheme 17. The requirement for a planar, five-centred transition state has considerable implications, both for the viability of the reaction and, naturally, for its stereochemical characteristics, as illustrated by much of the following chemistry.



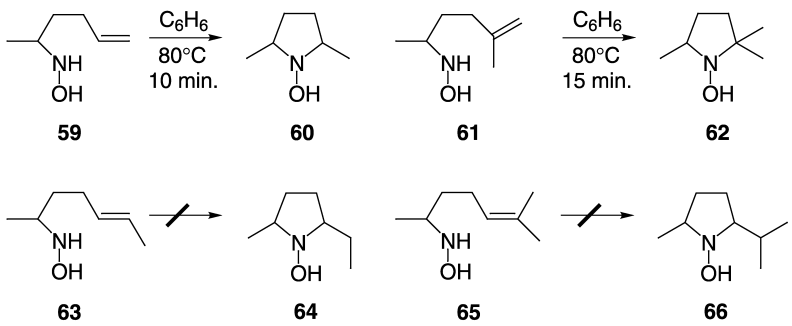
Scheme 17.

3. Scope and limitations

3.1. Basic pyrrolidine formation

In general, the reverse Cope cyclisation is most useful for the elaboration of pyrrolidine-*N*-oxides or *N*-hydroxypyrrolidines. Early results revealed the now-familiar facets of the substitution patterns, both at nitrogen and on the alkene function. Black and Doyle[10] observed that both the pent-4-enylhydroxylamine **59** and its 4-methyl homologue **61** underwent highly efficient cyclisation to the *N*-hydroxypyrrolidines **60** and **62**, respectively, during 10–15 min reflux in benzene or at ambient temperature for a few days (Scheme 18). In contrast, the hydroxylamines **63** and **65** having one or two substituent methyl groups at the distal end of the alkene function, failed to cyclise to the pyrrolidines **64** and **66**, respectively, upon heating until decomposition set in.

Although no stereochemistry was assigned to the 2,5-dimethylpyrrolidine **60**, it was clearly isolated as a single diastereoisomer, from the occurrence of two methyl

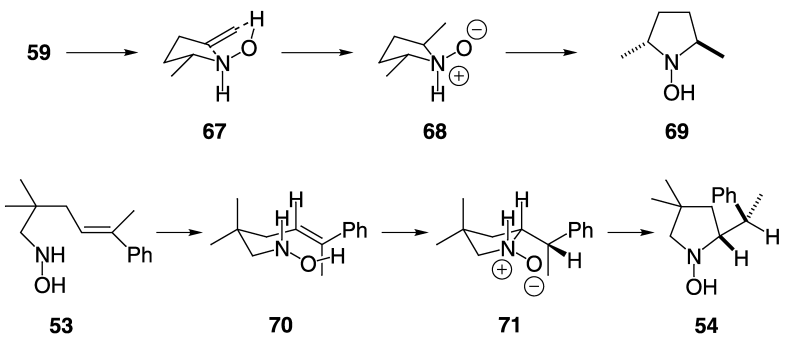


Scheme 18.

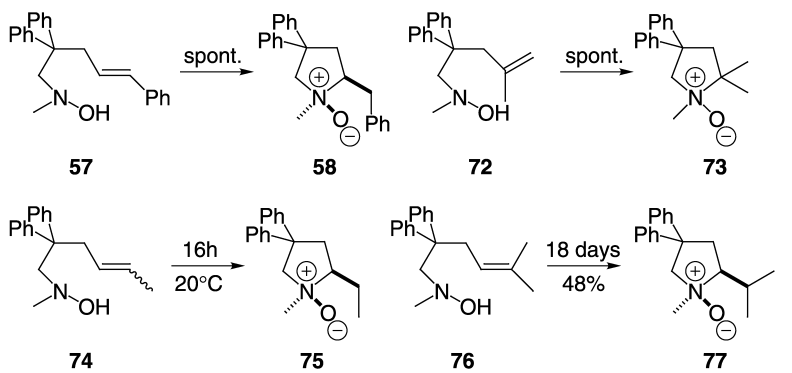
doublets at δ_H 1.15 and 1.22. These data, together with the requirement for a planar transition state and stereocontrol by the substituent methyl group, all suggest the formation of the *trans*-isomer **69** via a chair conformation **67** and an initial *N*-oxide **68** (Scheme 19).

Such an analysis is also consistent with the stereochemical outcomes of the cyclisations reported by Oppolzer (Scheme 15).[14] Thus, the (*E*)-isomer **53** should cyclise via the transition state conformation **70** to give, initially, the *N*-oxide **71** and, thence, the observed product **54**. Further revealing examples of this type have been provided by Ciganek (cf. Scheme 16).[4] Both the cinnamyl derivative **57** and the internally-substituted analogue **72** of a 2,2-diphenyl-substituted *N*-methylhydroxylamine underwent cyclisation during work-up, following their preparation by reduction of the corresponding nitrones, to give the pyrrolidine-*N*-oxides **58** and **73**, respectively, in essentially quantitative yields (Scheme 20). However, the related crotyl derivative **74** only partly cyclised to the *N*-oxide **75** under the same conditions and a further 16 h at ambient temperature was required for complete cyclisation. In contrast, the dimethyl analogue **76** gave only 48% of the *N*-oxide **77** after 18 days at ambient temperature in chloroform, together with 22% of the starting material **76**; the remainder was unidentified material.

A number of conclusions can be drawn from the foregoing discussion, which are backed up by subsequent results. First, *N*-methylhydroxylamines undergo cyclisation faster than the corresponding primary analogues. Secondly, distal substituents certainly retard the reverse Cope cyclisation, whereas internal substituents, at least methyl, seem to have little effect. Thirdly, the Thorpe–Ingold steric compression effect is enormously beneficial: the hydroxylamines **53**, **57**, **72** and **74** are clearly examples of this effect. It is most unusual to observe such facile cyclisations at ambient temperature with a distally substituted alkene in the absence of this or a related constraint. It does seem that the two reacting functionalities have to be held in close proximity for a facile cyclisation to occur. A further illustration of the

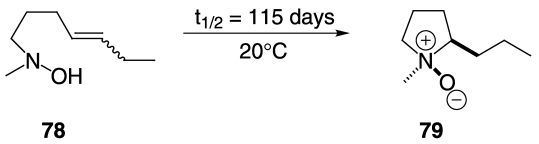


Scheme 19.



Scheme 20.

first effect is the finding[4] that the *N*-methylhydroxylamine **78** undergoes complete cyclisation to the *N*-oxide **79** (Scheme 21), although with $t_{1/2}$=115 days (!), whereas the related primary hydroxylamine **63** (Scheme 18) failed to cyclise.[10] The hydroxylamine **78** was a mixture of (*E*)- and (*Z*)-isomers and, while both underwent cyclisation, the latter isomer was less reactive in this respect, consistent with the transition state conformation **67** (Scheme 19); in the (*Z*)-isomer, the substituent ethyl group on the alkene would have to adopt a pseudoaxial position.



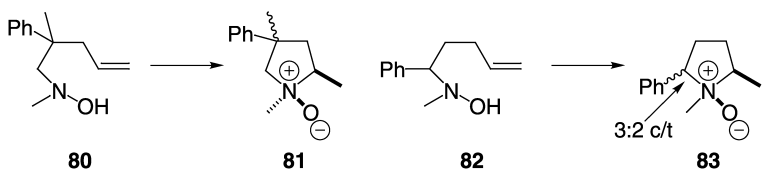
Scheme 21.

To return to some stereochemical features, while it is unsurprising that the substituted *N*-methylhydroxylamine **80** undergoes reverse Cope cyclisation to give a 3:2 mixture of the *N*-oxides **81**, perhaps less expected is the observation that a similar lack of stereoselectivity is shown in the cyclisation of the phenyl-substituted hydroxylamine **82**, which gives a 3:2 mixture **83** with a slight preference for the *cis*-isomer (Scheme 22). In a useful amplification of this phenomenon, Bagley and Tovey have shown that this is a general feature, and that increasing the size of the substituent adjacent to or attached to the nitrogen (cf. **82**) results in a distinct increase in the formation of the 2,5-*cis*-pyrrolidine-*N*-oxide. For example, the *N*-cyclohexyl-α-phenylhydroxylamine corresponding to precursor **82** cyclises to give essentially only the *cis*-isomer **84** (Scheme 23).[18] Presumably, this is a consequence of the substituent on nitrogen, which will inevitably destabilise the chair-like intermediate **85** [cf. **67** (Scheme 19)] related to that proposed to explain the formation of a single *trans*-2,5-substitution pattern from primary hydroxylamines. An alternative boat-like conformation **86**, in which the necessary planar, five-membered transition state essential for the reverse Cope cyclisation is retained, then explains the formation of largely or exclusively the 2,5-*cis*-diastereoisomers when either or both substituents R^1 and R^2 are increased in size.

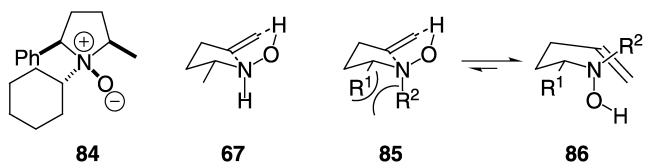
Preference for the formation of 2,5-*cis*-isomers can be further enhanced, as these are also the more thermodynamically-favoured isomers, by relying on the thermal reversibility of the reverse Cope cyclisation (see above). This is not as simple as it sounds; no doubt, thermolysis without solvent at 95 °C is currently the optimum method.[18] In contrast, heating in either chloroform or toluene gives mixed results, largely resulting from significant decomposition during the prolonged reaction times required to establish a synthetically-useful isomerisation.

3.2. Annulated pyrrolidines

The reverse Cope cyclisation can also be used to form annulated pyrrolidines. For example, addition of methylmagnesium chloride to the nitrone **87** gave the expected hydroxylamine **88**, which underwent partial cyclisation



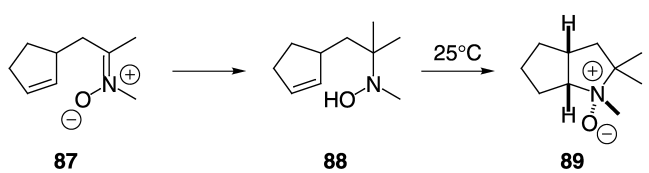
Scheme 22.



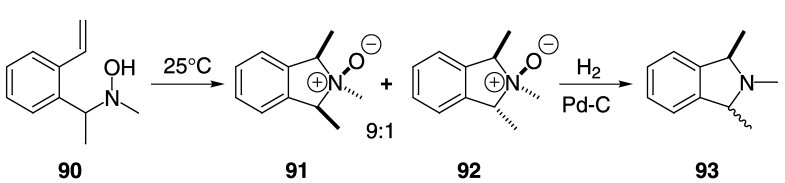
Scheme 23.

(2:1) during work-up, a process which was complete after 16 h at ambient temperature in dichloromethane (Scheme 24).[13] Although not assigned, the stereochemistry of the product **89** must surely feature a *cis*-ring fusion, although the relationship between this and the stereogenic nitrogen centre is unclear, but the isomer shown seems likely (cf. Scheme 19). No doubt, the Thorpe–Ingold effect engendered by the two methyl substituents is crucial in facilitating this cyclisation which, as yet, has not been developed further.

Isoindolines can similarly be prepared, again by Grignard addition to the corresponding nitrone, followed by cyclisation of the resulting hydroxylamine **90** during work-up, to give a 9:1 mixture of the *cis*- and *trans*-substituted products



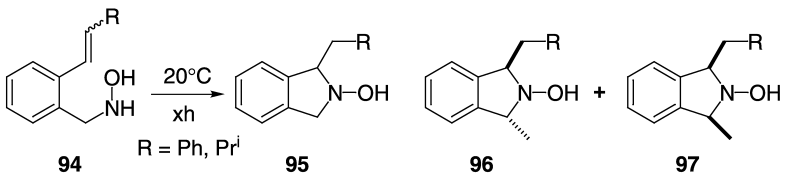
Scheme 24.



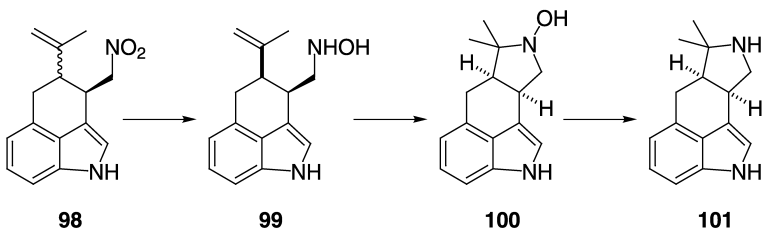
Scheme 25.

91 and **92** (Scheme 25).[13] Unfortunately, both these and the reduction product **93** are reported to be rather unstable upon exposure to air. However, the corresponding *N*-hydroxyisoindolines derived from reverse Cope cyclisation of the corresponding primary benzylic hydroxylamines turn out to be stable, although clearly sensitive to oxidation in solution.[19] Such cyclisations are also successful when the alkene carries a distal substituent and therefore probably benefit from the rotational restriction imposed by the benzene ring on the two reacting groups (Scheme 26). Cyclisations of the simple styrenes **94** at ambient temperature or in refluxing chloroform lead smoothly to the monosubstituted *N*-hydroxyisoindolines **95**, the (*Z*)-isomers of the precursors **94** cyclising considerably faster, possibly because, to achieve the necessary planar transition state, the alkene function must twist out of conjugation. The already slightly-twisted (*Z*)-styryl function would therefore require less energy to achieve this required conformation. Cyclisations of hydroxylamines having an additional benzylic substituent, prepared either by nitrone reduction or Mitsunobu displacement,[20] gave gross mixtures of products **96** and **97** when these were formed at 60 °C, but largely single *trans*-isomers **96** at ambient temperature. This therefore may be another example of a thermal equilibration to the more thermodynamically-stable isomer (cf. Scheme 23).[18] A similar reverse Cope mechanism may explain the formation of the pyrrolidine **101** from the nitroalkene **98** during reduction with zinc amalgam in acidic methanol (Scheme 27).[21] This would require partial reduction to the hydroxylamine **99** and cyclisation, a not unreasonable idea in view of both the activating *cis*-disposition of the reacting groups, which are also constrained in their rotational freedom by the cyclohexyl residue, together with the fact that alkenes having an 'internal' methyl substituent are known to undergo such reactions without rate retardation (see above). Given the veracity of this suggestion, it seems likely that the overall 10% yield of the final product **101** could be greatly improved by employing a more selective approach to the hydroxylamine **99** and possibly isolation of the *N*-hydroxypyrrolidine **100**.

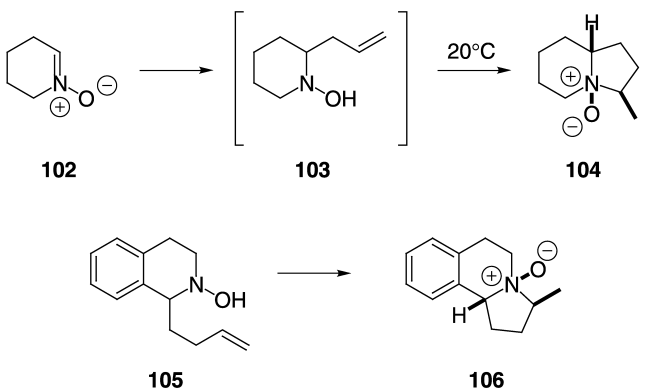
Annulated pyrrolidines having nitrogen at the ring junction are also accessible using the reverse Cope cyclisation. In a definitive example, Ciganek found that Grignard addition to the nitrone **102** gave the expected hydroxylamine **103**, which underwent cyclisation during work-up to give largely (85:15) the *cis*-perhydroindolizidine-*N*-oxide **104** (Scheme 28).[13] In just the same fashion, the hydroxylamine **105** gave only the pyrrolo[2,1-*a*]isoquinoline-*N*-oxide **106** as a single isomer. Further illustrations of this methodology have yet to be reported and the fact that the foregoing



Scheme 26.



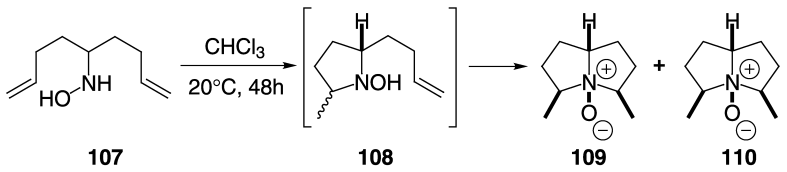
Scheme 27.



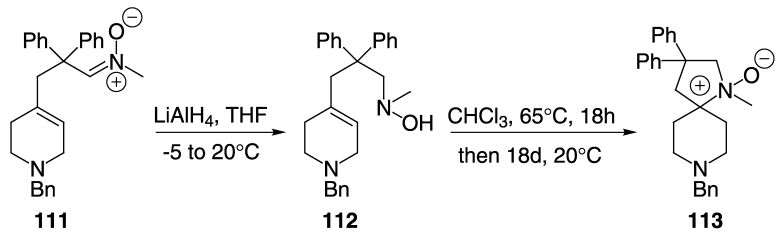
Scheme 28.

examples proceed so readily, presumably again assisted by the constraining ring, suggests that cyclisations of more highly-substituted examples, including those with a distal alkene substituent, should be viable.

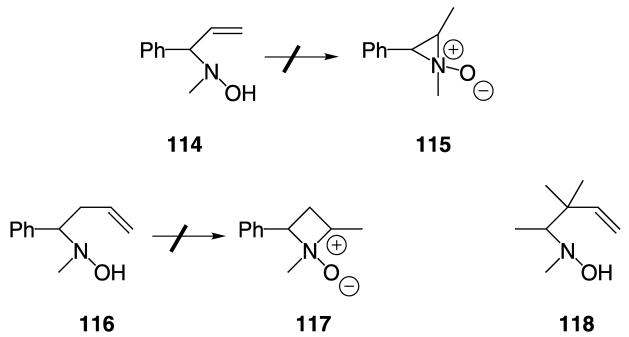
Two consecutive reverse Cope cyclisations are also possible (Scheme 29).[13] The precursor hydroxylamine **107** was obtained by cyanoborohydride reduction of the corresponding oxime and, after 2 days at ambient temperature, only 10% of the intermediate partially-cyclised hydroxylamine **108** remained. Rapid reduction of the *N*-oxides **109** and **110** using hexachlorodisilane was necessary to secure the corresponding pyrrolizidines, as, during the much slower reduction using H_2/Pd–C, a substantial quantity (some 40%) of the cycloreversion product **108** (isolated in a



Scheme 29.



Scheme 30.



Scheme 31.

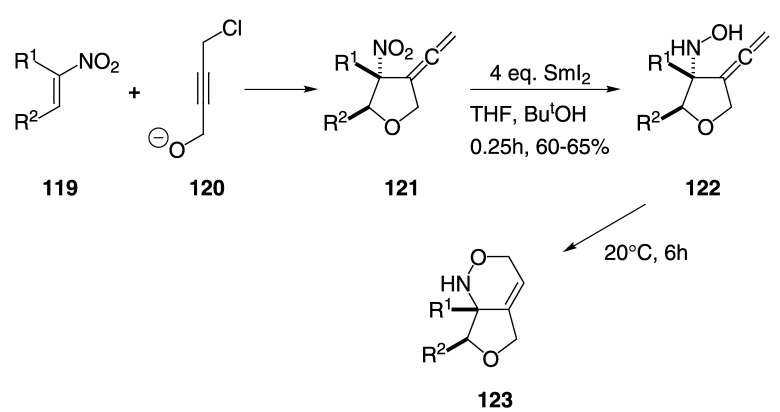
reduced form) was formed. Perhaps these somewhat slower cyclisations will also be viable using more highly-substituted substrates, but this has yet to be proven.

The *spiro*-pyrrolidine **113** can be prepared by reverse Cope cyclisation (Scheme 30).[13] The precursor hydroxylamine **112** was obtained by careful reduction of the corresponding nitrone **111**. Clearly, this is a much more difficult cyclisation, requiring overnight reflux, followed by 18 days at ambient temperature, to reach completion. No doubt, the very large Thorpe–Ingold effect of the *gem*-diphenyl group is crucial, the related unsubstituted analogue failing to cyclise. Despite this difficulty, there is clearly much synthetic potential in this method, given due regard to the substitution pattern.

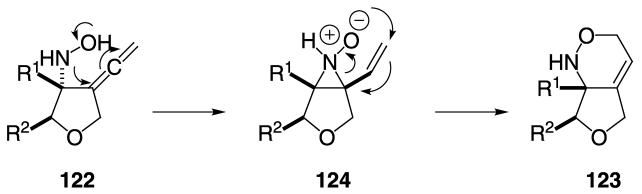
3.3. Other ring sizes

A few attempts have been made to extend the scope of the reverse Cope cyclisation to other ring sizes. On the grounds of ring strain alone, it is perhaps not surprising that the allylic hydroxylamine **114** failed to cyclise to the aziridine-*N*-oxide **115** (Scheme 31).[4] In any event, examples of the latter species, generated in other ways, are known to undergo exceptionally facile Cope eliminations to give hydroxylamines [cf. **114**].[22,23] An alternative decomposition pathway, which also occurs at low temperature (0 °C), is the cheletropic elimination of a nitrosoalkane.[22] Similarly, the homologous *N*-methylhydroxylamine **116** failed to cyclise to the corresponding azetidine-*N*-oxide **117**.[4,9] Despite the strain evident in any planar transition state leading to these ring sizes, it remains to be proven that more highly-substituted substrates also cannot be cyclised, as such reactions would benefit considerably from the Thorpe–Ingold buttressing effect. However, ominously, the hydroxylamine **118** also failed to cyclise before disproportionation to the related oxime set in.[9]

In an interesting caveat to these limitations, it is possible that a reverse Cope cyclisation constitutes a key step in novel routes to 3,6-dihydro-1,2-oxazines **123**. Elaboration of the nitrotetrahydrofurans **121** by sequential oxa-Michael addition-S_N2' substitution reactions between a nitro-alkene **119** and the chloroynolate **120**, followed by careful reduction using samarium iodide, leads to the allenic

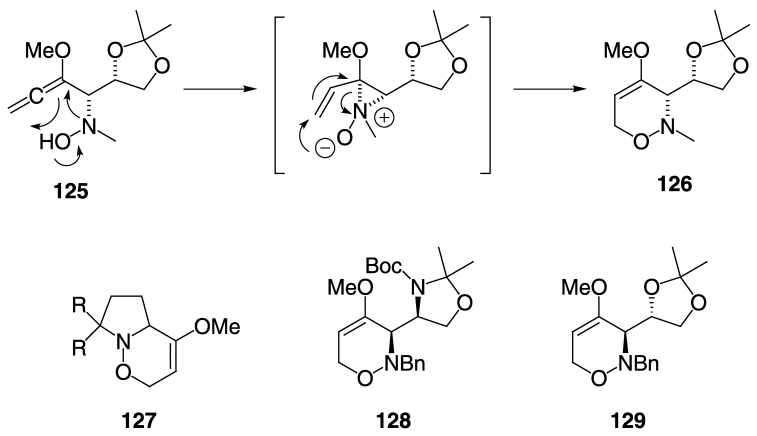


Scheme 32.

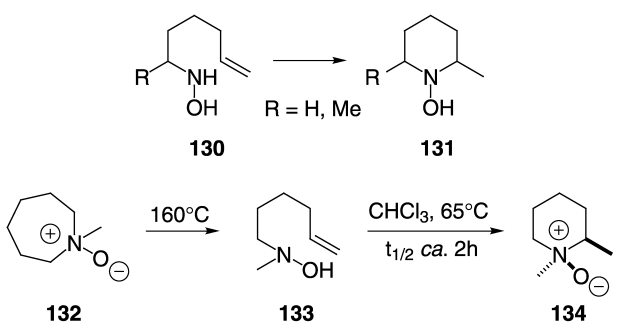


Scheme 33.

facile reverse Cope processes and by the knowledge that internal substituents can easily be accommodated (Scheme 33). This idea does require that the proposed intermediate *N*-oxides **124** undergo the second [2,3]-sigmatropic rearrangement step much faster than (what might be expected to be) a rapid proton transfer to the corresponding neutral *N*-hydroxy species. In much the same way, at least in the sense of precursors and products,



Scheme 34.

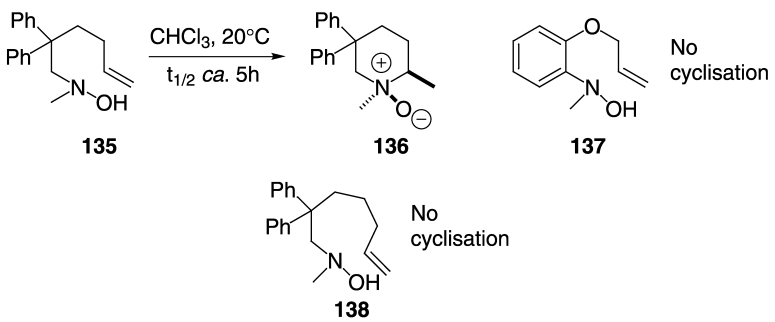


Scheme 35.

hydroxylamines **122** (Scheme 32).[24] On standing for 6 h at ambient temperature, these hydroxylamines are then converted into the oxazines **123** [R^1, R^2=*n*-alkyl, Ph or $(CH_2)_4$] in 62–92% yields. The corresponding cyclopentatetrahydrofuran [**122**; R^1, R^2=$(CH_2)_3$] by contrast took 15 days to undergo complete cyclisation. Initially, this was an unexplained phenomenon but, in a flight of fancy, one of the present authors (D.W.K.) suggested the involvement of a reverse Cope cyclisation when reviewing the preliminary communication of this work.[24a] This was inspired by the resemblance of the reaction conditions to many hydroxylamines [e.g. **125**] derived in a usually highly-stereoselective fashion from the corresponding nitrone and an excess of lithiated methoxyallene also undergo smooth, uncatalysed conversion into 1,2-oxazines [e.g. **126**] (Scheme 34).[25]

Similar chemistry can be used to obtain the annulated derivatives **127** from the corresponding pyrrolidine-based nitrones, together with the nitrogen analogues **128** and the *anti*-isomer **129** of the first example **126**, by precomplexation of the nitrone with diethylaluminium chloride. Whatever the mechanism, overall this is certainly useful chemistry!

In contrast to the failure to form isolable three- or four-membered cyclic *N*-oxides by reverse Cope cyclisations (Scheme 31), the method is most certainly applicable to piperidine formation, as first demonstrated by House and Lee.[9] However, more forcing conditions are usually required. For example, the unsaturated primary hydroxylamines **130** required heating in refluxing xylene for ca. 1 h (or neat at 160 °C) to secure the *N*-hydroxypiperidines [**131**; R=H, Me] (Scheme 35).[9] The 2,6-disubstituted piperidine [**131**; R=Me] was obtained as a mixture containing a

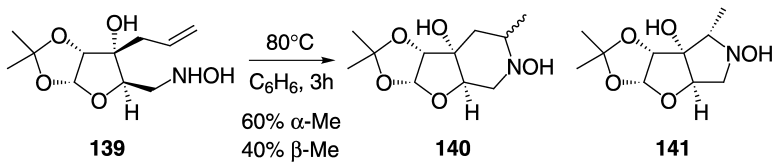


Scheme 36.

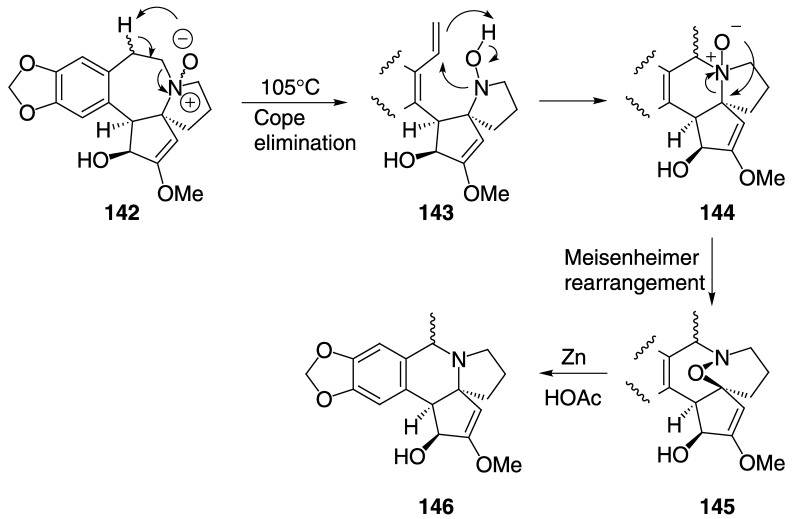
preponderance of the *trans*-isomer. However, as in the case of pyrrolidine synthesis, the corresponding *N*-methylhydroxylamines undergo cyclisation more easily. Thus, the hydroxylamine **133**, somewhat perversely prepared by a Cope elimination of the *N*-oxide **132**, while cyclizing very slowly at ambient temperature, underwent conversion into the piperidine-*N*-oxide **134** in refluxing chloroform with $t_{1/2}\simeq 2$ h.[4,12] Once again, Thorpe–Ingold restrictions accelerate the cyclisation, the *gem*-diphenyl analogue **135** converting into the *N*-oxide **136** at ambient temperature in chloroform with $t_{1/2}\simeq 5$ h (Scheme 36).[4] The aniline derivative **137**, however, failed to cyclise, despite the conformational restriction imposed by the benzene ring.[4] This can be explained by the much reduced basicity of the nitrogen. However, both of these activating effects in combination were insufficient to induce cyclisation of the one-carbon homologue **138** to the corresponding seven-membered *N*-oxide.[4] It may be that, in most cases, the reverse Cope cyclisations are restricted to the formation of five- and, to a lesser extent, six-membered rings. In the latter respect, there is still no published example of piperidine-*N*-oxide formation by reverse Cope cyclisation of an unsaturated hydroxylamine having a substituent at the alkene terminus, i.e. thus far, only α-methylpiperidines have been formed. Hence, it appears that this additional deactivating feature usually precludes the more difficult piperidine formation, when present. No doubt, given enough conformational constraint, such an example will some day come to light. An isolated example of the synthesis of an annulated piperidine illustrates a further synthetic potential of the reverse Cope method. The carbohydrate-derived hydroxylamine **139** was found to be isolable, but cyclised smoothly to a 3:2 mixture of the annulated piperidines **140** in 87% isolated yield, following a 3 h reflux in benzene (Scheme 37).[26] Unsurprisingly, in view of the foregoing examples (Schemes 24–26), the corresponding vinyl derivative was similarly converted into the 5/5 ring-fused system, but as a single isomer **141**.

A most interesting example of a reverse Cope cyclisation leading to a 'piperidine' accounts for the thermally-induced rearrangement chemistry of the homoharringtonine-*N*-oxides **142** (Scheme 38).[27] One pathway is a straightforward Meisenheimer rearrangement, while a second pathway, leading to the isolated products **145**, probably proceeds by an initial Cope elimination to give the *N*-hydroxypyrrolidine **143**, which then undergoes reverse Cope cyclisation to give the 'piperidine'-*N*-oxide **144**. This *N*-oxide then also undergoes a final Meisenheimer-type rearrangement to give the isolated products **145**. Subsequent reduction using zinc and acetic acid gives the ring-contracted homoharringtonine analogues **146**. Overall, these rearrangements are highly solvent dependent and probably quite restricted in their occurrence.

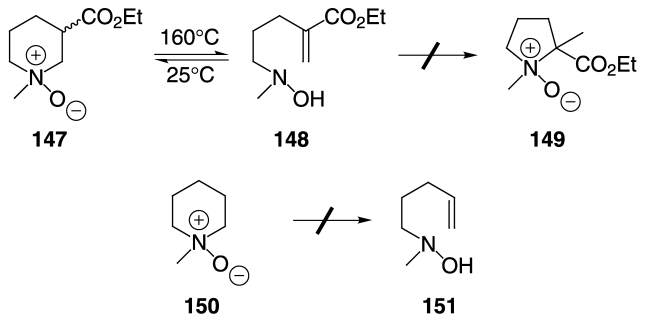
A final caveat regarding piperidine formation features a competition reaction between intramolecular Michael addition and reverse Cope cyclisation. On standing at ambient temperature, the hydroxylamine **148** cyclises to give the piperidine-*N*-oxide **147**, presumably by a Michael addition, rather than the pyrrolidine-*N*-oxide **149**, which would be formed by a reverse Cope process (Scheme 39).[4] This reactivity reflects the reverse processes: the hydroxylamine **148** can be formed from the *N*-oxide **147** by thermolysis, probably by a retro-Michael elimination rather than a Cope elimination which requires an unattainable



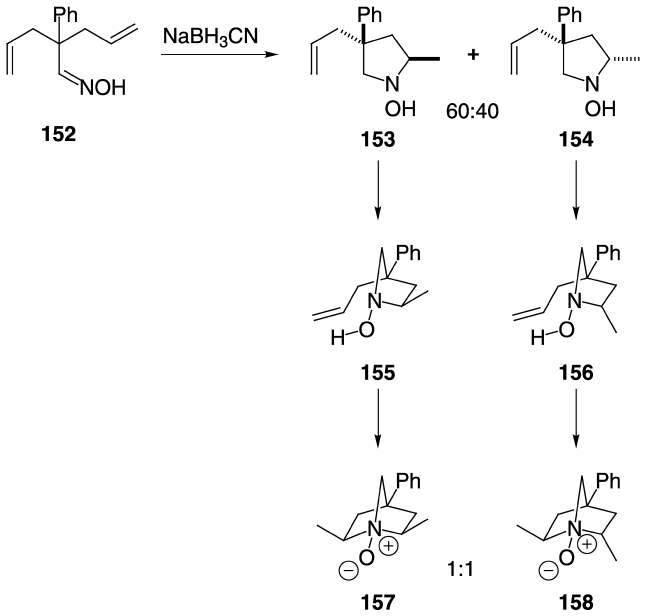
Scheme 37.



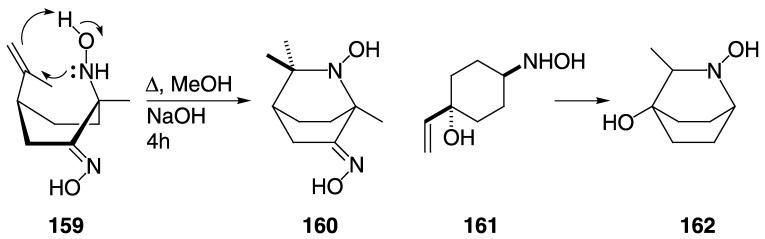
Scheme 38.



Scheme 39.



Scheme 40.



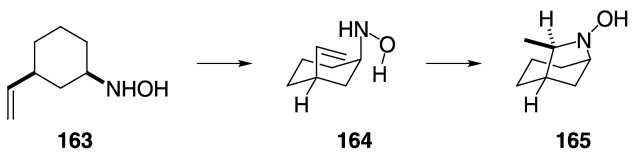
Scheme 41.

planar, five-membered transition state in this case. This is substantiated by the fact that the piperidine-*N*-oxide **150** does not break down to the hydroxylamine **151** when heated, as it also cannot undergo a Cope elimination for the same reason. Of course, this pattern of reactivity may not apply to other systems, which can undergo both retro-Michael and Cope eliminations.

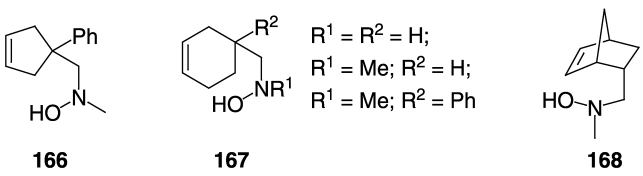
3.4. Transannular cyclisations

Given that the required planar transition state can be achieved with some ease, transannular variations of the reverse Cope cyclisation should then be viable and even favoured by the very conformational constraints that distinguish such precursors. This is, however, at present, a rather poorly developed area. A first example was reported by Ciganek (Scheme 40).[13] Cyanoborohydride reduction of the oxime **152** gives a quantitative yield of the *N*-hydroxypyrrolidines **153** and **154** in a 60:40 ratio, the cyclisation being clearly assisted by the presence of the phenyl substituent [cf. Scheme 20]. Subsequent transannular cyclisation is then effected during a 27 h reflux in chloroform (or at ambient temperature for 34 days) to give an equilibrium mixture of the two *N*-oxides [**157** and **158**] in equal amounts, together with 17% of the uncyclised *N*-hydroxypyrrolidine **154**. Separate experiments established the reversible nature of the final cyclisation, the stereochemical outcome suggesting the intermediacy of the transition state conformations **155** and **156**, which does explain why the minor *N*-hydroxypyrrolidine **154** undergoes a slower cyclisation due to an *endo*-methyl group. This also explains why the *endo*,*endo*-isomer of the final bicyclic products is not observed.

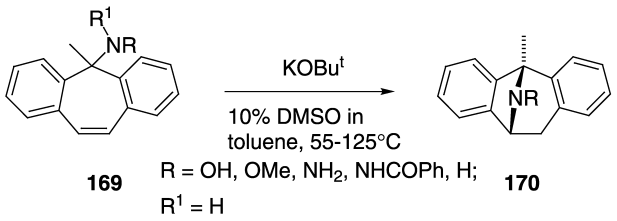
Our interest in such transannular cyclisations was provoked by a report that the hydroxylamine **159** underwent acid-catalysed cyclisation to the isoquinuclidine skeleton **160** (Scheme 41), whereas a series of derived amines failed to cyclise under similar conditions.[28] That this was indeed a reverse Cope process was proven by the fact that the hydroxylamine **159** underwent the same cyclisation in the presence of base, while the corresponding *O*-methyl or *O*-benzyl derivatives did not cyclise in the presence of acid or base.[29] Once again, an internal methyl group is found not to inhibit cyclisation, while the necessary boat-like conformation suggested some useful generality for this type of reaction. We were, however, concerned that this was a rather special case and therefore elected to test the cyclisation using simpler substrates. We were pleased to observe that the hydroxylamine **161** cyclised in refluxing chloroform to give only the bicyclic product **162** (Scheme 41). In both cases, it was encouraging to find that a less reactive primary hydroxylamine function participated easily in these cyclisations, suggesting that it might be possible to carry out such reactions using a terminally-substituted alkene, especially using a more reactive *N*-methylhydroxylamine. However, this has yet to be tested. We were also able to show that cyclisation of a cyclohexane having a 1,3-substitution pattern was also viable (Scheme 42). The hydroxylamine **163** was found to



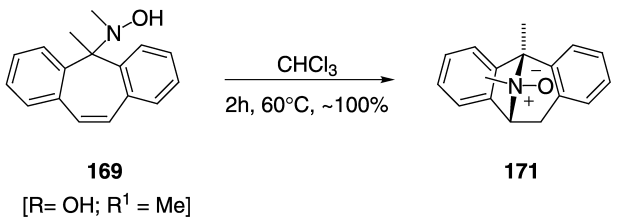
Scheme 42.



Scheme 43.



Scheme 44.



Scheme 45.

cyclise to the bicycle **165** under similar conditions; the high stereoselectivity in favour of essentially only the isomer shown probably reflects a preference for conformation **164**, in which interactions between the vinyl group and axial C–H bonds are avoided.

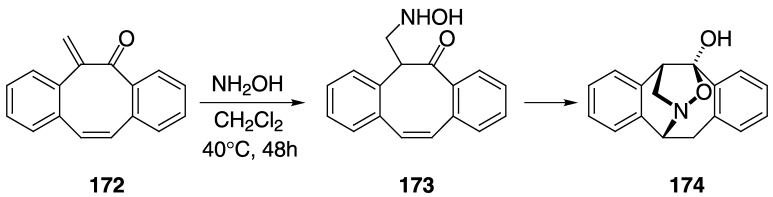
Naturally, not all model systems work; examples which do not undergo reverse Cope cyclisation include the structures **166**–**168** shown in Scheme 43.[4,9] Presumably, in each case, the required planar transition state cannot be accessed with sufficient ease.

Somewhat related transannular cyclisations leading to the azabicyclo[3.2.1]octanes **170** in general require activation by a strong base and forcing conditions for a variety of amine derivatives **169** (Scheme 44).[30] Clearly, in the case of the hydroxylamine derivative at least, such basic conditions should not be necessary as was indeed observed.[30] This has been further demonstrated by Ciganek,[4] who showed that the *N*-methylhydroxylamine [**169**; R=OH; R^1=Me] cyclised smoothly to the *N*-oxide **171** simply by heating in chloroform (Scheme 45). Interestingly, the corresponding primary hydroxylamine, while undergoing cyclisation by prolonged (16 h) reflux in toluene,[30] did not cyclise under the milder conditions shown in Scheme 45, again attesting to the activating effect of an *N*-methyl substituent.

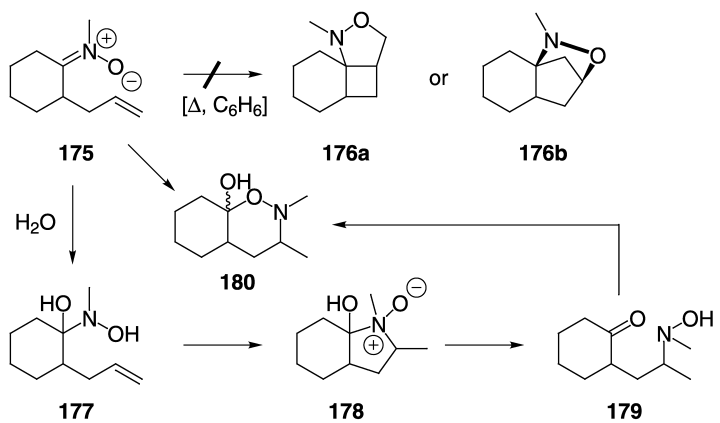
In an extension of this method to the homologous system **174**, a novel strategy was employed which could be applicable to many other transannular reverse Cope cyclisations (Scheme 46).[31] This consists of Michael addition to the enone function **172** to give the presumed hydroxylamine **173**, followed by a relatively facile and regiospecific cyclisation to the observed product **174**. Perhaps not surprisingly, none of the regioisomer where the nitrogen had become attached to the more distant end of the alkene was observed.

4. Alternative strategies for hydroxylamine formation

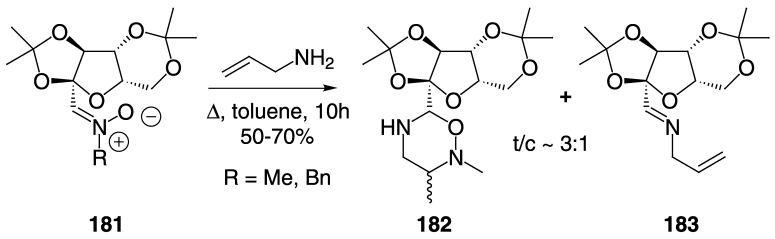
In general, hydroxylamines are not the easiest class of compounds to prepare.[32] Not surprisingly, therefore, a significant number of the more recent developments of the reverse Cope cyclisation also feature some new ways to access the necessary hydroxylamines. Firstly, it is worth mentioning one of the very few examples of a reverse Cope cyclisation reported during the 1980s. The nitrone **175** was found to be not amenable to intramolecular [1,3]-dipolar cycloaddition, presumably because this would involve



Scheme 46.



Scheme 47.



Scheme 48.

cyclobutane formation [**176a**] or a rather strained conformation leading to a perhydroindane **176b**. However, on being left at ambient temperature for 7 days, around 50% of the sample had converted into the oxazine **180** (Scheme 47).[33]

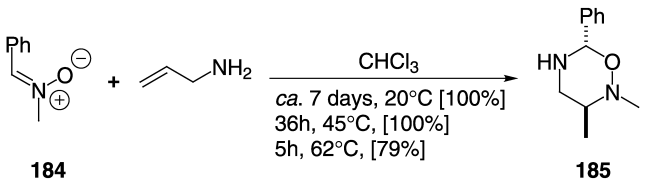
The sequence of events presumably involves hydration of the nitrone and reverse Cope cyclisation of the resulting hydroxy-hydroxylamine **177** to give the *N*-oxide **178**. This can then rearrange, effectively by a Meisenheimer rearrangement,[34] by ring opening to the keto-hydroxylamine **179** and reclosure to the observed product **180**. This isolated example may be a pointer to some future developments and also echoes the original observation of the reverse Cope cyclisation discovered by House (Scheme 6) and also the related cyclisations observed by Ciganek during nitrone formation (Scheme 10).

Our own involvement in the reverse Cope cyclisation began in a somewhat related manner. In an effort to improve the fairly abysmal levels of stereoselection observed in [1,3]-dipolar cycloadditions between the nitrones **181**, derived from the readily available hexulofuranosonic acid,[35] and *N*-acyl or *N*-carbamoyl derivatives of allylamine, we heated the nitrones with the unprotected allylamine. While we appreciated that the free amine group would probably add to the nitrone, it was reasoned that this would be an equilibrium process and would thus not interfere with the desired dipolar cycloaddition. In the event, three products were isolated after refluxing the reactants together in toluene for 10 h (Scheme 48).[36] These turned out to be the isomeric oxadiazinanes [**182**; R=Me, in a *trans*/*cis* ratio of ca. 3:1], together with a trace of the imine **183**. A similar result was obtained, but with slightly better yields, using the *N*-benzylnitrone [**182**; R=Bn].

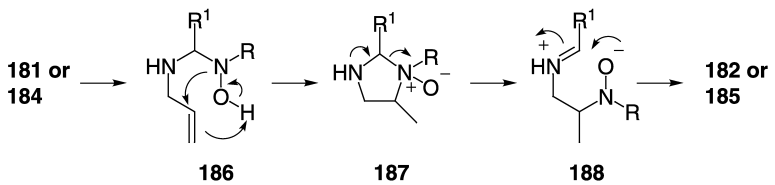
This unexpected result was further exemplified by treating the easily-handled benzaldehyde-derived nitrone **184** with allylamine in chloroform, when essentially quantitative yields of a single *trans*-oxadiazinane **185** could be obtained (Scheme 49).

We speculated that a reverse Cope cyclisation was a pivotal step in a four-step sequence leading to the observed product (Scheme 50). Addition of allylamine to a nitrone would give a hydroxylamine **186** (cf. Schemes 6, 10 and 47), which could undergo reverse Cope cyclisation to give an imidazolidine-*N*-oxide **187**. This could then undergo rapid ring opening triggered by the nucleophilic secondary amine to give the iminium species **188**, which could then undergo a facile 6-*endo* ring closure to give the observed products [**182** or **185**].

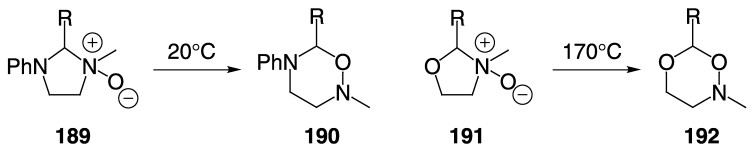
The latter steps amount to an *N*- to *O*-alkyl transfer, i.e. a Meisenheimer rearrangement.[34] All attempts to observe the intermediate *N*-oxide **187** were unsuccessful. This was not too surprising in view of the known analogous rearrangement of the *N*-oxides **189**, derived from the corresponding imidazolidines and *m*CPBA, to the oxadiazinanes **190**, which occurs at ambient temperature (Scheme 51).[37] A further precedent comes from an earlier report[38] of a similar rearrangement of a physostigmine-*N*-oxide. By contrast, the related oxazolidine-*N*-oxides **191** require thermolysis at



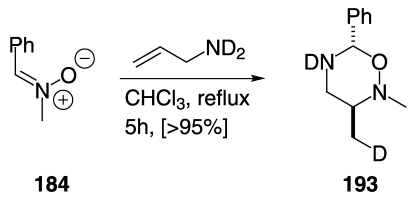
Scheme 49.



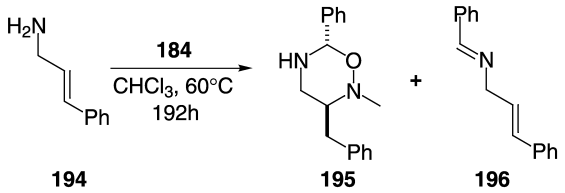
Scheme 50.

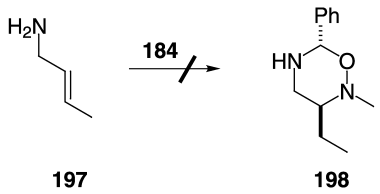


Scheme 51.

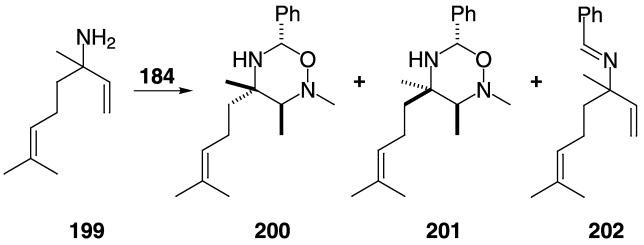


Scheme 52.





Scheme 53.

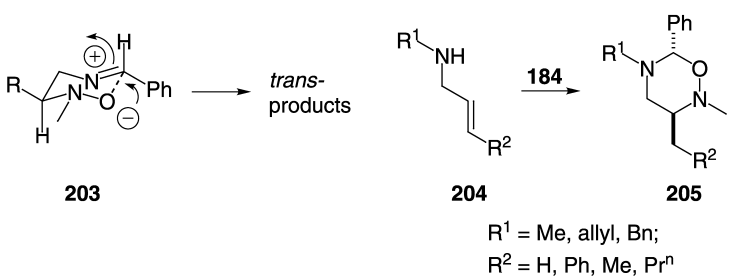


Scheme 54.

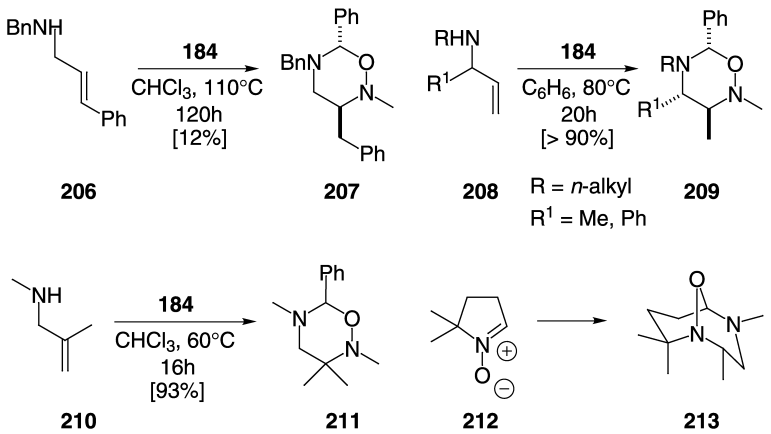
170 °C to achieve the same conversion into the dioxazinanes **192**, understandably in view of the less basic nature of the triggering oxygen.[39] Additionally consistent with the proposed mechanism was the finding that the reaction between the nitrone **184** and N-deuteriated allylamine gave only the 3-deuteriomethyl derivative **193** (Schemes 52, 53).[36] A typical feature of the reverse Cope cyclisation is that substitution at the terminus of the alkene function retards the reaction. This was reflected in the present chemistry: the reaction between the nitrone **184** and cinnamylamine **194** gave only a ca. 40% of the oxadiazinane **195**, along with a similar amount of the imine **196**, after a prolonged reaction time, while the corresponding crotyl derivative **197** gave only traces of the 3-ethyl analogue **198** (Scheme 51), along with much imine formation. Further substitution at the sp^3 centre in the allylamine did not, however, prevent the reaction: linalylamine **199** reacted to give largely the diastereoisomers **200** and **201**, together with a small amount of imine **202** (Scheme 54). Formation of diastereoisomer **200** is consistent with the previously-discussed transition state conformation of the reverse Cope cyclisation (Scheme 19). In general, imine formation presumably occurs by a simple exchange reaction between the allylamine and the nitrone, with expulsion of *N*-methylhydroxylamine. The 3,6-*trans*-stereocontrol is generated in the last ring closure step (Scheme 50), when the iminium species **188** adopts a chair-like conformation **203** in which the substituent(s) attached to the sp^3 carbon centres will assume equatorial positions (Scheme 55).

In order to prevent imine formation and possibly also to promote the whole sequence, we used, instead, the *N*-alkylallylamines **204** (Scheme 55).[36] Using unoptimised conditions (benzene or toluene, reflux, 20–120 h), we were able to secure good yields of the now-expected oxadiazinanes **205**, even when the reacting alkene was substituted at its terminus. While an *N*-allyl substituent did not appear to inhibit the sequence, an *N*-benzyl group certainly did: prolonged thermolysis of *N*-benzylcinnamylamine **206** with the nitrone **184** in chloroform gave only a 12% isolated yield of the oxadiazinane **207** (Scheme 56). The more positively allylically-substituted amines **208** gave essentially single diastereoisomers of the oxadiazinanes **209**; the vicinal *trans*-stereochemistry is presumably set during the reverse Cope cyclisation (Scheme 19), although the lack of information regarding the stereochemistry of the intermediate and non-isolable imidazolidine-*N*-oxide (Scheme 50) precludes detailed speculation as to the transition state conformation(s) involved. As illustrated previously (Schemes 14, 18, 20, 27 and 42), an internal methyl substituent on the alkene does not significantly inhibit the progress of the cyclisation; a further example is the efficient and relatively easy formation of the *gem*-dimethyl derivative **211** from allylamine **210** (Scheme 56). The somewhat unusual heterocycle **213** was similarly obtained from the pyrrolidine nitrone **212**, thus providing further evidence for the overall mechanism.

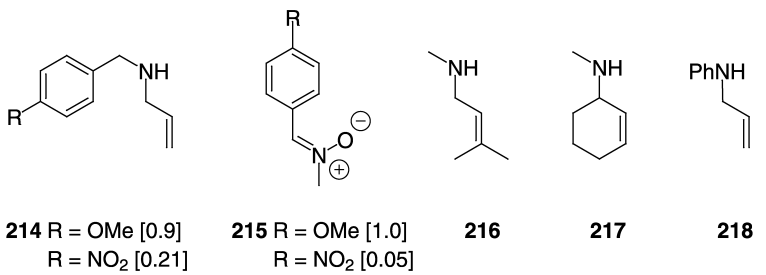
The multistep nature of the reaction and the probability of there being more than one rate-determining step were indicated by attempts to accelerate the sequence by using the amines **214** and the nitrones **215** having influential *para*-substituents. Two extremes are quoted (Scheme 57), along



Scheme 55.

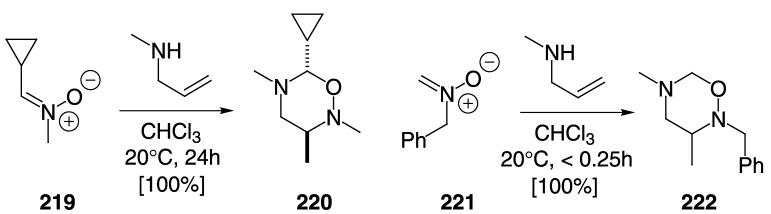


Scheme 56.

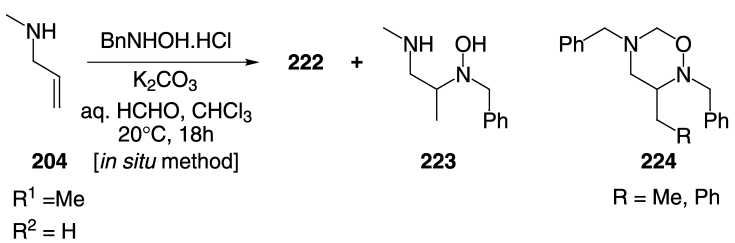


Scheme 57.

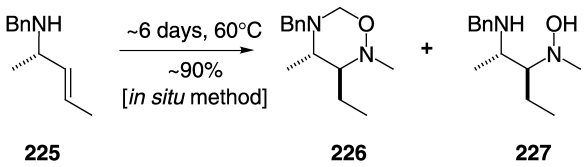
with rates relative to R=H. These and a number of related examples showed that the overall sequence was retarded by both electron-donating and, especially, electron-withdrawing substituents.[40] In line with many of the foregoing results, the allylamines **216**–**218** failed to form oxadiazinanes, probably due, respectively, to too much terminal substitution, an inability to adopt a planar transition state and a lack of amine nucleophilicity. The lengthy reaction times, together with some poor yields, then led us to use other nitrones, when we discovered that the phenyl group of the nitrone **184** engendered a significant overall rate retardation. For example, the *C*-cyclopropylnitrone **219** reacted smoothly with *N*-methylallylamine **204** (R^1=Me; R^2=H) at ambient temperature, to give a quantitative yield of the oxadiazinane **220** (Scheme 58).[36,40] The reaction even occurred during 3 days at −20 °C. Unfortunately, this enhanced reactivity was insufficient to overcome the rate retardation present in *N*-benzylcinnamylamine **206** (Scheme 56) at ambient temperature, while heating resulted in extensive decomposition. The next logical step was to dispense completely with the *C*-substituent of the nitrone. This proved to be a useful idea: the formaldehyde nitrone **221** reacted very rapidly (<0.25 h) at ambient temperature with *N*-methylallylamine **204** to give only the oxadiazinane **222**, despite the slight inhibiting effect of the *N*-benzyl group (Scheme 58).[40] The instability of the nitrone **221** led us to generate it in situ; after 18 h at ambient temperature, reaction with amine **204** gave the oxadiazinane **222** along with the amino-hydroxylamine **223** in 95% combined yield and in a ratio of 1.3:1 (Scheme 59). The latter compound



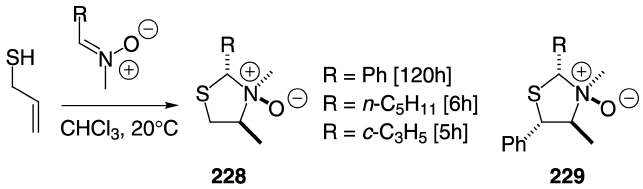
Scheme 58.



Scheme 59.



Scheme 60.



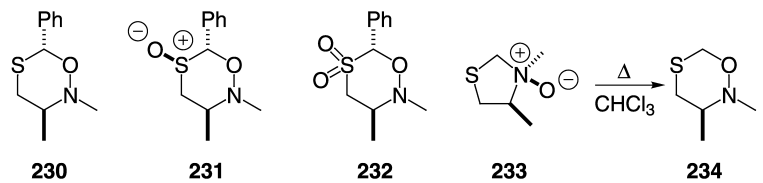
Scheme 61.

was presumably formed by interception of the Meisenheimer iminium salt intermediate (cf. Schemes 50 and 55) by water. Thus, although more convenient, the in situ method proceeded at a significantly slower rate than when using the isolated nitrone **221**. Despite this, very efficient if lengthy reactions (5–13 days) using the in situ method did deliver the products **224** derived from both *N*-benzylcinnamylamine **206** and *N*-benzylcrotylamine. While the reactions could be accelerated by heating, this advantage was offset by significant by-product formation, although an acceptable 90% yield of the expected products **226** and **227** (1.7:1) was obtained from amine **225** using the in situ method after 6 days at 60 °C (Scheme 60).[40]

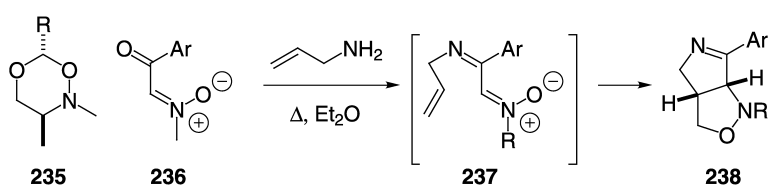
All of the foregoing trends were seen again in reactions between allylthiol and aldehyde-derived nitrones (Scheme 61).[41] These results also provided excellent evidence in support of the overall mechanism (Scheme 50), as the initial reverse Cope products, in this case the 1,3-thiazoline-*N*-oxides **228**, were isolated as the sole products. Again, the reaction was much faster when *C*-alkyl rather than *C*-aryl nitrones were used. Although more reactive, combinations of *C*-alkyl nitrones and terminally-substituted allylic thiols unfortunately did not undergo reverse Cope cyclisation at ambient temperature and gave a multitude of products when heated in chloroform. Reactions with 1-phenyl-2-propen-1-thiol gave the homologue **229**, although this chemistry may well be somewhat limited due to the relative instability of such thiols. This sequence therefore offers a unique opportunity to prepare thiazolidine-*N*-oxides (e.g. **228**), as oxidation of the parent system will always occur preferentially at sulfur. Indeed, if left in solution for a number of days, NMR evidence suggested that *N*- to *S*-oxygen transfer was occurring. The greater electronegativity of sulfur rendered the subsequent Meisenheimer rearrangement more difficult than when nitrogen acted as the trigger (Scheme 50). However, the *C*-phenyl nitrone product [**228**; R=Ph] did rearrange smoothly in refluxing chloroform to give a novel ring system, the 1,5,2-oxathiazinane **230** (Scheme 62). This compound was also obtained directly in ca. 90% yield from the precursor allylthiol and *C*-phenyl nitrone **184** by thermolysis in toluene at 70 °C in a sealed tube. Oxidation using *m*CPBA or $NaIO_4$ led to a single sulfoxide, assumed to have the stereochemistry shown [**231**], while use of $RuCl_3$–$NaIO_4$ led to the sulfone **232**. The in situ method (Scheme 59) with allylthiol delivered the thiazolidine-*N*-oxide **233**, which also underwent smooth rearrangement to the oxathiazinane **234**. Unfortunately, the related alkyl derivatives [**228**; R=alkyl] gave mixtures of products which, while containing the expected oxathiazinanes, also showed the presence of similar quantities of both thiazolidine- and oxathiazinane-*S*-oxides and unidentified elimination products.

Attempts to apply the same idea to allyl alcohol gave only trace amounts of dioxazinanes **235** (Scheme 63).[36,42] It is interesting to note that the foregoing sequences could have been discovered much earlier by Black's group. While investigating a neat idea for setting up intramolecular [1,3]-dipolar cycloaddition precursors by imine formation, it was found that attack of allylamine onto *C*-aroyl nitrones **236** occurred selectively at the carbonyl function to give the imines **237**, which then underwent smooth dipolar cycloaddition to give the hexahydro-pyrrolo[3,4-*c*]isoxazoles **238** (Scheme 63).[43] Had the addition occurred instead to the nitrone group, then presumably the chemistry reported above would have been uncovered!

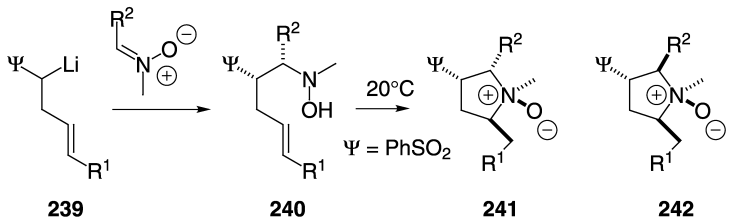
We then began to investigate if other carbon-based nucleophiles could be used to generate unsaturated hydroxylamines suitable for reverse Cope cyclisations. It was found that the lithiated sulfones **239** added very efficiently and stereoselectively to nitrones to give



Scheme 62.

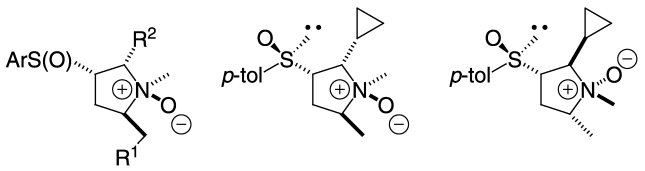


Scheme 63.



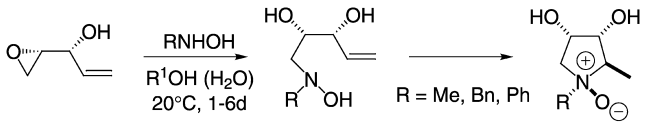
239 240 241 242

Scheme 64.



243 244 245

Scheme 65.



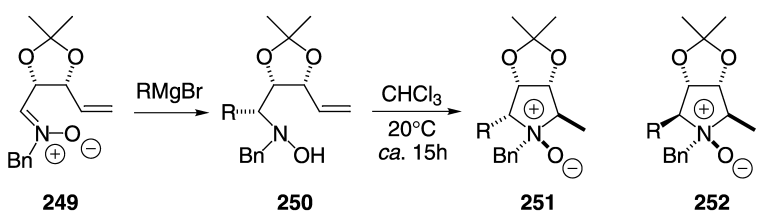
246 247 248

Scheme 66.

essentially single diastereoisomers of the hydroxylamines **240**, many of which cyclised at ambient temperature, a fortunate occurrence, as heating led to extensive decomposition (Scheme 64).[44] The resulting pyrrolidine-*N*-oxides were obtained with reasonably high levels of stereoselection (ca. 4–5:1) in favour of the 2,5-*trans* isomers **241**, but these underwent slow isomerization in chloroform solution to give mainly the corresponding and more thermodynamically stable 2,5-*cis* isomers **242** (cf. Scheme 23). Otherwise, the influence of the two substituents fell into a familiar pattern. When the alkene was unsubstituted [i.e. **240**; R^1=H], the cyclisations were completed during work-up of the initial condensation when R^2=alkyl or cyclopropyl. The rate retardation effect of a phenyl group was again in evidence as the unsubstituted hydroxylamine [**240**; R^1=H; R^2=Ph] in contrast took some 96 h to undergo complete cyclisation, while more substituted hydroxylamines [**240**; R^1=Ph, Me etc., R^2=Ph] failed to cyclise. However, such substituted hydroxylamines [i.e. **240**; R^1=Ph, Me; R^2=alkyl, cyclopropyl] did undergo smooth if slow (70–96 h) cyclisation at ambient temperature. The origins of the retardation effect of a phenyl group adjacent to the hydroxylamine are unclear. The fact that the isopropyl analogue [**240**; R^1=H; R^2=Pr^i) reacted very rapidly (ca. 0.5 h) suggests the effect is not steric; however, the styryl derivative [**240**; R^1=H; R^2=PhCH:CH] also cyclised very rapidly, indicating that any electronic effect is not transmitted by an olefinic linkage. One drawback to this method is the reduced yields obtained during the initial condensation step when using *C*-alkyl nitrones (i.e. R^2=*n*-alkyl), presumably due to competing deprotonation α- to the nitrone by the basic lithiated sulfone **239**.

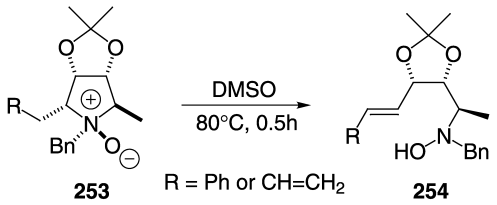
The slow isomerisation problem could be obviated by using the corresponding sulfoxides as nucleophiles, presumably due to their weaker electron-withdrawing effect. Otherwise, the characteristics of the reverse Cope cyclisations, which also occurred at ambient temperature, were much the same as with the foregoing sulfones **240** and delivered very largely the isomerically stable pyrrolidine-*N*-oxides **243** with ≥9:1 stereoselectivity, although the relative stereochemistry at sulfur was not determined (Scheme 65).[45] The use of a lithiated sulfoxide naturally gave the opportunity to prepare chiral, non-racemic products. Due to the lack of knowledge of the relative stereochemistry between the sulfoxide and the new adjacent stereogenic centre, a product from this sequence was either **244** or **245**, but which was obtained with >95% stereoselectivity. Although probably not all will be retained in subsequent synthetic transformations, it is interesting to note that this combination of two sequential reactions creates four additional stereogenic centres from a retained sulfoxide centre.

New methods for hydroxylamine synthesis are very welcome in this area. Both O'Neil[46] and Jäger[47] have used epoxide ring opening to secure suitable precursors for reverse Cope cyclisations leading to polyhydroxylated pyrrolidines (Scheme 66). Attack by *N*-methyl (or *N*-benzyl) hydroxylamine on the epoxide **246** is highly regioselective and cyclisations of the resulting hydroxylamines **247** are highly stereoselective at ambient temperature, giving excellent yields of the pyrrolidine-*N*-oxides **248**. Unusually in this area, methanol[46] or aqueous ethanol[47] proved to be the optimum solvents. Stereoselectivities were usually ≥9:1 in favour of the *N*-oxides **248** in these media. Similar cyclisations of the corresponding primary hydroxylamine were slower, as were those of the *N*-benzyl derivative, relative to the *N*-methyl analogues;[47] these are normal reverse Cope characteristics, despite the different solvent systems.



249 250 251 252

Scheme 67.

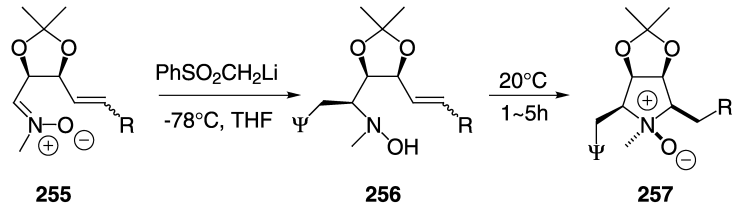


Scheme 68.

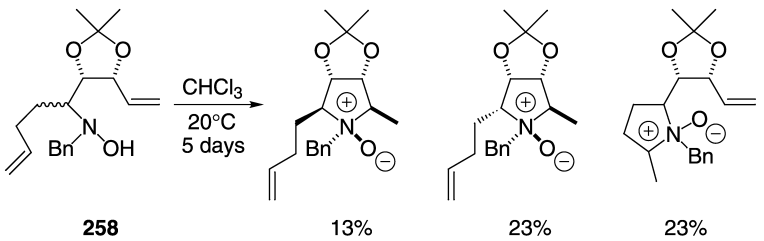
An alternative strategy for the preparation of similar, but protected, derivatives of the hydroxylamines **247** employs the addition of various organometallics to the nitrone **249** derived from D-ribose (Scheme 67).[48] The stereoselectivities of Grignard additions were quite variable, but had a tendency to favour the isomers **250**, as deduced from the predominant formation of the pyrrolidine-*N*-oxides **251** on leaving the intermediate hydroxylamines in chloroform overnight at ambient temperature. By contrast, additions of Grignard reagents modified by a Lewis acid (Et_2AlCl, $ZnCl_2{\cdot}OEt_2$) favoured the formation of the alternative epimer in which the new 'R' group is introduced on the opposite face to give a preponderance of the epimeric *N*-oxides **252**. These deductions seem reliable, as prolonged storage of the *N*-oxides **251** in chloroform did not lead to any isomerisation, indicating that these were indeed the initial reverse Cope products. Oddly, both the allyl and benzyl derivatives **253** underwent apparent Cope elimination, even at −25 °C, and in <0.5 h in DMSO at 80 °C, to give the alternative hydroxylamines **254** (Scheme 68). The stereochemistry of the *N*-oxides **253** suggests that this must be an inter- rather than an intramolecular process.

We investigated a similar strategy, using the alternative nitrones **255** also derived from D-ribose, based around the previously successful addition of lithiated sulfones (Scheme 64).[44] Thus, condensations between nitrones **255** and lithiated methyl phenyl sulfone gave very largely single isomers of the expected hydroxylamines **256**, the structures of which were deduced from those of the resulting pyrrolidine-*N*-oxides **257** which were all formed in good to excellent yields during 1–5 h in chloroform at ambient temperature (Scheme 69).[49] The relatively facile nature of these reverse Cope cyclisations, even with distally-substituted alkenes, strongly suggests that a significant activating effect is in operation which we had assumed, by design, to be the ring constraint provided by the *cis*-dioxolane ring. Further, the observed 'all-*cis*' geometry of the *N*-oxides **257** can be rationalised on the basis of a boat-like transition state in which the alkene and hydroxylamine groups are placed in close, planar proximity. However, the truth may be somewhat more subtle. In a competition experiment between the two unsubstituted alkene groups in the hydroxylamine **258**, three *N*-oxides were formed in fairly similar quantities (Scheme 70).[48] While the fact that hydroxylamine **258** was an epimeric mixture, which will influence transition state stabilities, clearly the *cis*-fused dioxolane ring did not provide complete control!

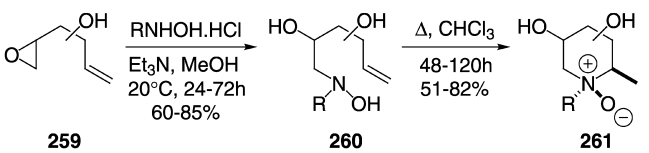
The preparation of hydroxylamines from epoxides (cf. Scheme 64)[46,47] was first highlighted by O'Neil in the context of reverse Cope chemistry in a neat approach to piperidine-*N*-oxides (Scheme 71).[50] Although reported in a limited way some 20 years previously, this very useful epoxide ring opening method seems to have escaped subsequent attention until this report. The optimum solvent for the initial ring openings of the epoxides **259** turned out to be methanol (use of THF or dichloromethane gave lower yields); subsequent prolonged reflux of the resulting hydroxylamines **260** in chloroform then delivered the piperidine-*N*-oxides **261** in respectable yields, as mixtures of diastereoisomers. Further studies of these reactions revealed that methanol might be an optimum solvent. Further, stereoselection was increased when sodium methoxide rather than triethylamine was used to liberate the initial hydroxylamine from its hydrochloride salt, suggesting that sodium ions may play a positive role in



Scheme 69.

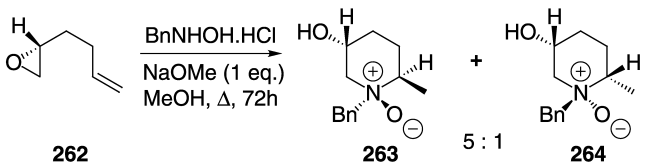


Scheme 70.



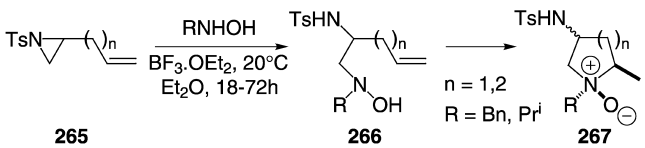
Scheme 71.

stereocontrol of the reverse Cope cyclisation.[51] Under these conditions, the reactions appear to be irreversible, perhaps due to hydrogen bonding between the solvent and the products. A combination of these observations resulted in a one-pot method for obtaining the piperidine-*N*-oxides **263** and **264** in a 5:1 ratio from the epoxide **262** (Scheme 72).[51] This idea has been successfully extended to similar and unprecedented ring openings of *N*-tosylaziridines **265** by hydroxylamines (Scheme 73).[52] The reaction requires boron trifluoride etherate as a trigger, when it occurs slowly at ambient temperature. In the context of reverse Cope cyclisations, both pyrrolidine- and piperidine-*N*-oxides **267** having *N*-tosylamino substituents have been prepared using this method. Pyrrolidine formation occurred at ambient temperature and hence the intermediate hydroxylamines [**266**; n=1] could not be isolated. In contrast, those leading to the piperidines [**267**; n=2] required heating in methanol for 48 h to complete the cyclisation and hence could be isolated. For future reference, it should be noted that substituted hydroxylamines can also readily be prepared by highly selective *cis*-Michael additions to α,β-unsaturated sulfones, nitriles and nitro compounds.[53] Interestingly, this stereochemical outcome, while it could be consistent with a Michael addition mechanism, suggests that an intermolecular reverse Cope cyclisation may be operating (Scheme 74), an idea supported by very recent theoretical studies.[54]



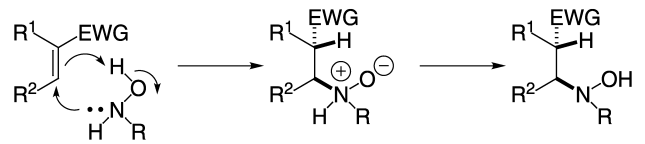
262 **263** **264**

Scheme 72.



265 **266** **267**

Scheme 73.

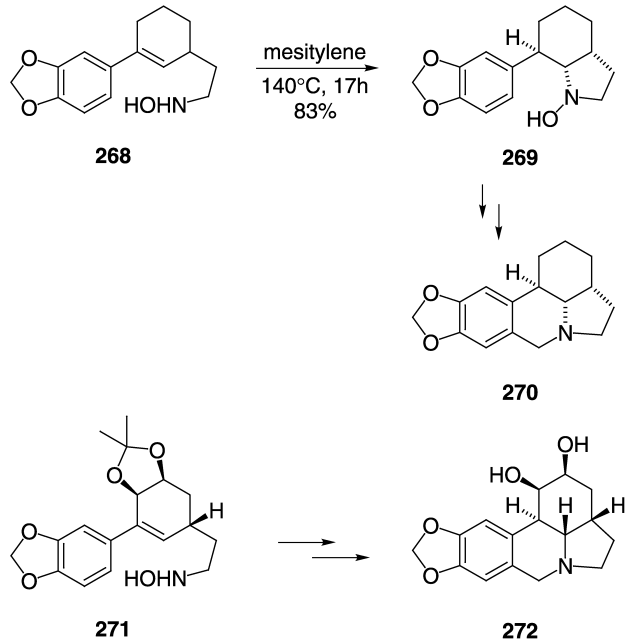


Scheme 74.

Finally, another useful way to convert secondary amines into the corresponding hydroxylamines involves sequential Michael addition to acrylonitrile, oxidation to the *N*-oxide level using *m*CPBA and lastly a Cope elimination of acrylonitrile.[55]

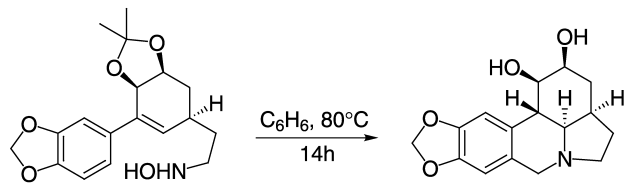
5. Applications in target synthesis

These have been slow to emerge, at least in the case of reverse Cope cyclisations onto alkenes. However, a very elegant use of the reaction is in Oppolzer's total syntheses of (±)-α-lycorane **270** and (+)-trianthine **272** (Scheme 75).[14] Although hardly activated in a reverse Cope sense, the primary hydroxylamine **268** underwent efficient conversion into the *N*-hydroxypyrrolidine **269** after harsh thermolysis in mesitylene. The synthesis of (±)-lycorane **270** was then completed by sequential N–O bond cleavage using Raney-nickel and a modified Pictet–Spengler ring closure (CH_2=N^+Me_2, THF, 40 °C, 15 h). Similarly, the more functionalized precursor **271**, obtained as a single enantiomer from (1*S*,2*S*)-3-chloro-cyclohexa-3,5-diene-1,2-diol, was converted into (+)-trianthine **272**. These elegant syntheses are remarkable examples of the reverse Cope methodology as a less reactive primary hydroxylamine is successfully cyclised onto a trisubstituted cycloalkene. It is also interesting to note that the epimer **273** of the trianthine precursor undergoes cyclisation in only 14 h in refluxing benzene to give the isomer **274** in 91% isolated yield (Scheme 76).[14] It is difficult to see a clear conformational reason for this; perhaps hydrogen bonding between the hydroxylamine hydroxyl and one of the now *syn*-dioxolane oxygens is responsible.



268 **269** **270** **271** **272**

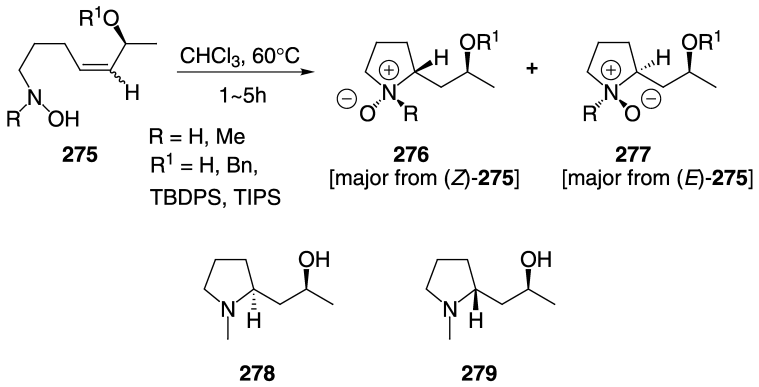
Scheme 75.



273 **274**

Scheme 76.

An unexpected activating effect by oxygen was certainly observed in the recent syntheses of the alkaloids (−)-hygroline **278** and (+)-pseudohygroline **279** (Scheme 77).[56] Our original speculation was that the pendant oxygen group (as OH or OBn) should hydrogen bond with the



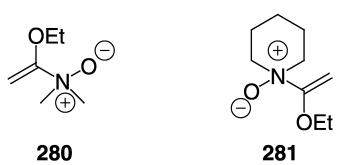
Scheme 77.

hydroxylamine function and hence provide a useful degree of stereocontrol. This proved not to be the case: the ratios of the two *N*-oxides [**276** and **277**; R=Me] were around 2–3:1 and were related to the alkene geometry, but relatively independent of the nature of the alcohol protecting group. However, the cyclisations proceeded with unexpected ease and even occurred at ambient temperature during 48–60 h. Even more surprising, in view of the failure of simple primary hydroxylamines having distal alkene substituents to cyclise (Scheme 18),[10] was the successful formation of the *N*-hydroxypyrrolidines derived from the initial products [**276** and **277**; R=H]. The sensitivity of the precursors [**275**; R=H] to heat proved no drawback, as these products were formed at ambient temperature during 3–8 h. It was concluded that this remarkable result was due to activation by the allylic oxygen atom. It may well be that this effect also benefited the foregoing trianthine synthesis (Scheme 73): while the simpler precursor **268** required heating to over 140 °C to effect cyclisation, the dioxolane derivatives [**271** and **273**] leading to trianthine underwent the same reaction at 80 °C, consistent with activation by the allylic oxygen present in the dioxolane ring. Further experiments will be necessary to confirm this conclusion; a few examples suggested that an internal allylic oxygen did not engender such an activation and, indeed, disfavoured cyclisation.[57]

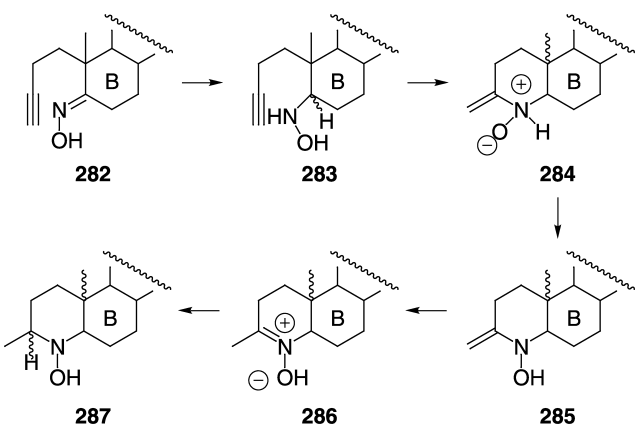
6. Cyclisation onto alkynes

The fact that hydroxylamines undergo intermolecular additions to alkynes has been established for some time.[58] While Michael additions to conjugated ynoates and ynones can be somewhat complicated, such chemistry can represent a very useful method for nitrone generation, especially if the latter are trapped intramolecularly.[59] Such nitrones are formed usually rapidly by isomerisation of the initial Michael adduct obtained by addition of an *N*-alkyl- or *N*-arylhydroxylamine. Clearly, such an isomerisation cannot occur in the case of an N,N-disubstituted hydroxylamine, exemplified by the isolation of excellent yields of the adducts **280** and **281** from ethoxyacetylene and *N*,*N*-dimethylhydroxylamine and *N*-hydroxypiperidine, respectively (Scheme 78).[4] In these cases, and possibly in the Michael additions, these are likely examples of intermolecular reverse Cope additions [cf. Schemes 3 and 74], although such reactions do not work with alkyl-substituted 1-alkynes.[59]

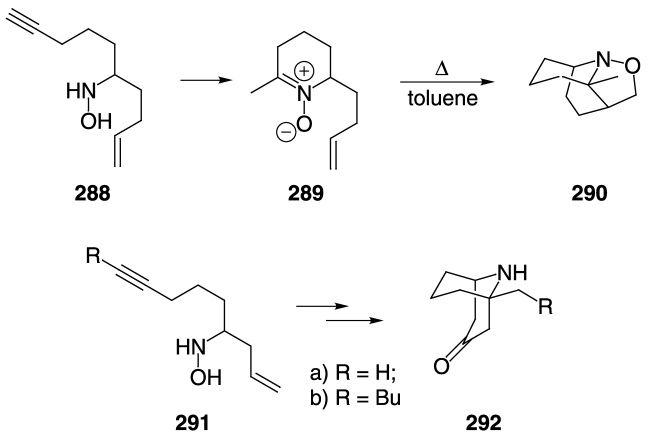
A possible example of an intramolecular reverse Cope cyclisation was reported in 1989 when the *N*-hydroxysteroid derivatives **287** were isolated from the reaction of the alkynyl oxime **282** with sodium borohydride in refluxing ethanol.[60] A plausible mechanism is outlined in Scheme 79: if an initial reduction gave the hydroxylamines **283**, subsequent reverse Cope cyclisation would then generate the *N*-oxides **284**. Rapid proton transfer and isomerisation (tautomerisation) of the resulting *N*-hydroxyenamines **285** to the nitrones **286** would allow final generation of the observed products **287** by hydride addition. True or not, such a sequence, at least at the reverse Cope stage, was certainly if unexpectedly observed during a preparation of the hydroxylamine **288** (Scheme 80).[61] Subsequent reaction with an aldehyde led not to the expected nitrone, but to the cyclic nitrone **289** without the anticipated incorporation of the aldehyde. The sequence of events presumably follows those detailed in Scheme 79; remarkably, no reverse Cope cyclisation onto the alkene group was observed, despite the fact that this would give an *N*-hydroxypyrrolidine.



Scheme 78.



Scheme 79.

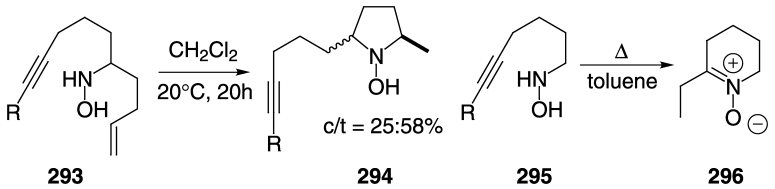


Scheme 80.

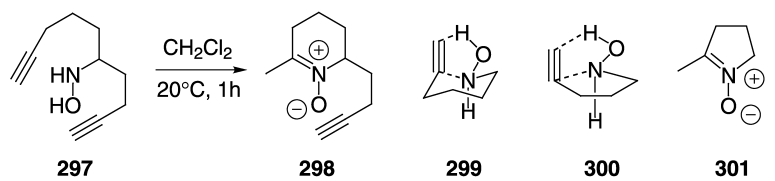
Preservation of the alkene function meant that a [1,3]-dipolar cycloaddition different to that originally planned could now be used to obtain the tricyclic product **290** in excellent overall yield. By using a faster work-up procedure, uncyclised nitrones derived from the hydroxylamine **288** could be obtained successfully without any intervention from the reverse Cope cyclisation.

Importantly, this version of the reverse Cope cyclisation is also successful for non-terminal alkynes (but see below) and also works well with the lower homologues **291**, leading to neat syntheses of the natural insect feeding deterrents (±)-euphococcinine **292a** and (±)-adaline **292b**.[62] In these examples, both the reverse Cope cyclisations and the subsequent [1,3]-dipolar cycloadditions were carried out in refluxing toluene for 9–12 h without nitrone isolation and in excellent overall yields of 71–76%. Despite this successful synthesis of adaline **292b**, no doubt substituted alkynes undergo cyclisation more reluctantly than do 1-alkynes; clearly, in the hydroxylamines **291**, reverse Cope cyclisation onto the alkene was precluded as this would give rise to a strained azetidine-*N*-oxide (cf. Scheme 31) This does not apply to 1-trialkylsilyl-1-alkynes: such a derivative of the hydroxylamine **288** undergoes rapid reverse Cope cyclisation to give cyclic nitrone **289** with loss of the silyl group after the reverse Cope step.[63,64] Remarkably, however, the hydroxylamine-alkene version of the reverse Cope cyclisation wins out in the case of the 2-alkyne analogue **293** of the terminal alkyne **288** (Scheme 81), with the isomeric pyrrolidines **294** being formed instead in a combined yield of 83%.[63,64] In the absence of a competing mode of cyclisation, internal alkynes will then undergo alkyne-hydroxylamine cyclisations successfully [cf. **291b**], a further example being the conversion of the simpler hydroxylamine **295** into nitrone **296**.[64] Clearly, more vigorous conditions are required with respect to the obviously favoured '5-*exo*' cyclisation of the hydroxylamine **293**, although the yield of nitrone remained excellent (94%). A final competitive experiment revealed an exclusive preference for six- rather than five-membered nitrone formation (Scheme 82). That the diynyl hydroxylamine **297** gave only the nitrone **298** can be understood by the lower strain energy inherent in the transition state **299** with respect to that [**300**] which would lead to the corresponding five-membered nitrone. Such nitrones [e.g. **301**] can be obtained using this chemistry, but their formation is clearly not especially favoured and hence the yields are rather lower from the more vigorous reaction conditions required. What is remarkable about these cyclisations is the often extreme ease with which they proceed, in the absence of activating substituent effects such as Thorpe–Ingold compression.

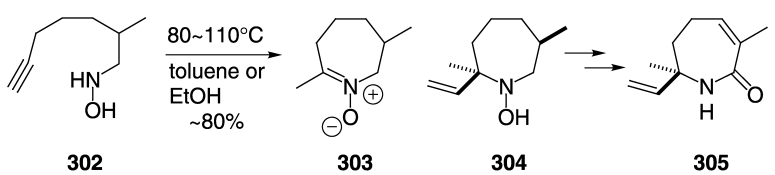
This type of cyclisation is also highly effective for the elaboration of azepines (Scheme 83).[64,65] Thus, thermolysis of the hydroxylamine **302** at 80–110 °C gave varying yields of the seven-membered nitrone **303**, with toluene or ethanol



Scheme 81.



Scheme 82.



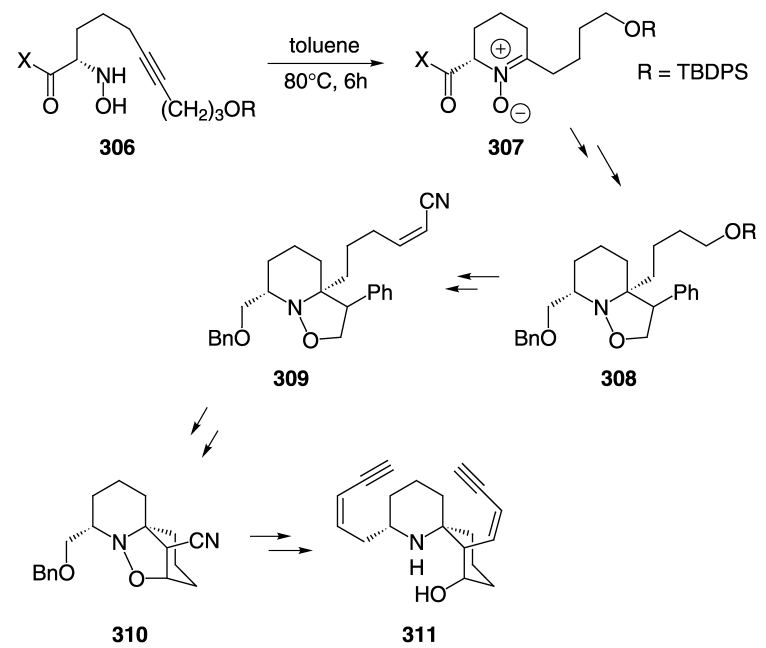
Scheme 83.

emerging as the optimum solvents; carbon tetrachloride or acetonitrile, while seemingly effective for the cyclisation step, proved to be too reactive and extensive decomposition resulted. Subsequent addition of vinylmagnesium bromide led exclusively to the *N*-hydroxyazepine **304** and thence to the proposed structure **305** for the natural product, acacialactam, which this work showed to be incorrect.

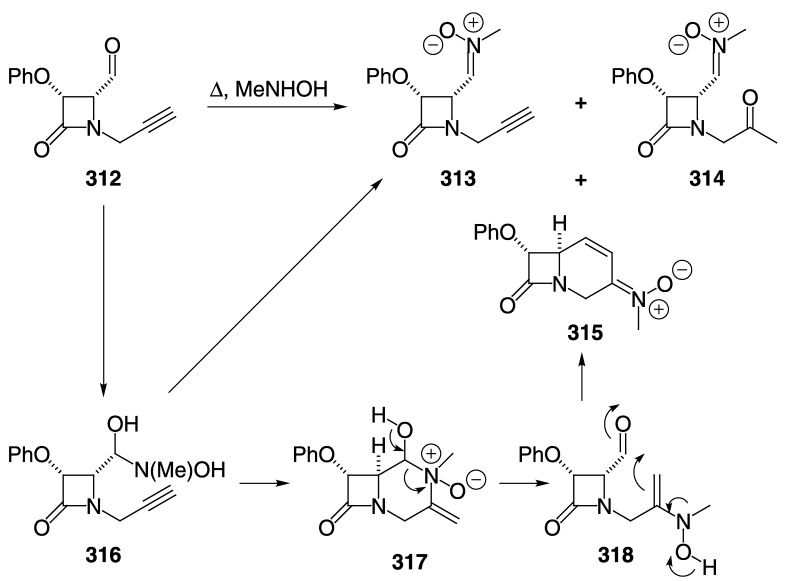
The Holmes group has subsequently applied this chemistry to a most notable total synthesis of (−)-histrionicotoxin **311** (Scheme 84).[66]

Reverse Cope alkyne–hydroxylamine cyclisation of the precursor **306**, obtained asymmetrically using Oppolzer sultam chemistry, proceeded smoothly in hot toluene to give the nitrone **307**, which was protected as its styrene adduct **308** while side-chain manipulations were carried out to give the (*Z*)-alkenylnitrile **309**. Thermolysis then resulted in a cycloreversion/cyclisation sequence of [1,3]-dipolar reactions to give the key tricyclic intermediate **310** and thence the target **311**, following relatively routine, but non-trivial, functional group manipulations and introduction of the side chains. Subsequently, similar tactics have been successfully applied to the elaboration of histrionicotoxins **259A**, **285C** and **285E**.[67]

This type of chemistry clearly has much potential but, in some cases, product control will need to be addressed. For example, treatment of the β-lactam aldehyde **312** with *N*-methylhydroxylamine gives rise to three products, the ratios of which depend very much on the exact reaction conditions (Scheme 85).[68] While the expected nitrone **313** is



Scheme 84.



Scheme 85.

formed, this can be accompanied by the ketone **314** and the annulated derivative **315**. An explanation of this chemistry echoes that described by Ciganek in one of his earliest studies of the reverse Cope cyclisation (Scheme 10)[4,12] and probably involves an alkyne-hydroxylamine cyclisation of the initial *N*-hydroxyaminal **316**, the competing dehydration of which leads to the expected nitrone **313**. The resulting heterocycle **317** can then fragment to give the *N*-hydroxy-enamine **318**, the precursor of both the ketone **314** following enamine hydrolysis and of the annulated derivative **315** formed by sequential ring closure and dehydration. Further heating of the nitrone **313** does not provide [1,3]-dipolar products (which would be highly strained 4/5 systems), although the corresponding *N*-4-pentynyl derivative was cyclised successfully in this manner.

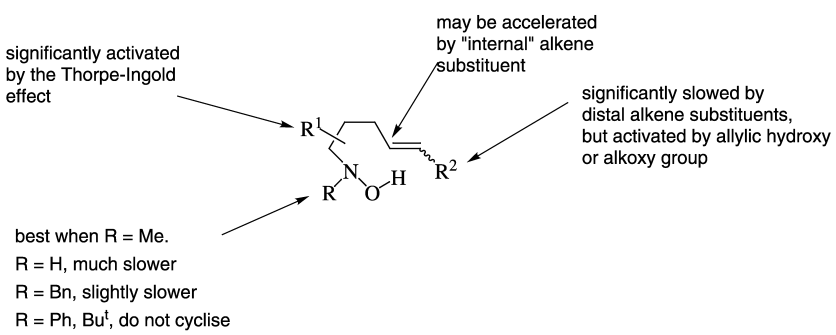
7. Conclusions—the salient features of the reverse Cope cyclisation

The conclusions and trends identified below are, in some cases, based on too few examples to be promulgated with any great certainty and, for sure, exceptions to these statements are likely to be discovered in future research. These should therefore be regarded as no more than guidelines that should be used with some caution, especially if applied in a negative sense to a new application of the reverse Cope cyclisation.

1. The optimum solvents are often chloroform or methanol, but hydrocarbons can be used to simply provide an inert diluent for thermolysis.
2. The cyclisation is retarded by distal alkene substituents, more so by alkyl than phenyl groups; recalcitrant substrates tend to undergo decomposition before cyclisation on increased heating, the hydroxylamine group usually being the weak point. Piperidine formation, which is more difficult than the comparable pyrrolidine syntheses, is currently restricted to α-methyl examples; as yet, no example of piperidine formation by cyclisation onto a distally-substituted alkene has been reported.
3. In contrast, an internal substituent (methyl groups only, thus far) does not retard and may even favour cyclisation.
4. The cyclisation is significantly accelerated by steric compression (the Thorpe–Ingold effect), especially when caused by geminal substituents or a fused ring in the chain connecting the two reacting functions. This may also facilitate transannular versions of the cyclisation.
5. Substituents at nitrogen are very influential: in general, *N*-methylhydroxylamines react significantly faster than primary hydroxylamines. *N*-benzyl groups, which are of course more easily removed, may slightly retard the cyclisation, but *N*-allyl groups (or other linear alkyls) may not; as yet, meaningful comparisons have not been reported. *N*-phenyl and *t*-butyl groups usually prevent cyclisation.
6. Allylic oxygen groups (OH, $OSiR_3$, OBn) strongly accelerate the cyclisation when positioned externally, but not when internal to the reacting alkene.
7. Alkyne-hydroxylamine cyclisations strongly favour the formation of six-membered cyclic nitrones at the expense of comparable five-membered rings. When in direct competition, cyclisation of a primary hydroxylamine completely favours reaction with a 1-alkene rather than a 1-alkyne when both modes would lead to a five-membered ring. Substituents at the alkyne terminus (alkyl groups) retard the cyclisation (e.g. a 1-alkyne cyclises at 20 °C, while an 'internal' alkyne requires heating in refluxing toluene). Seven-membered nitrones, however, can be efficiently obtained using this chemistry in contrast to hydroxylamine-alkene cyclisations
8. All cyclisations require a planar transition state geometry, which explains some of the failures but which can be used to deduce the expected kinetic stereochemical outcome of a particular cyclisation. Isomerisation to a more thermodynamically stable isomer can subsequently occur, however.

Many of the features, at least for pyrrolidine formation, are summarised in Scheme 86.

Overall, the reverse Cope cyclisation represents a useful method for C–N bond formation involving an unactivated alkene or alkyne. This places it firmly in the class of 1,3-azaprotio cyclotransfer reactions, as defined and exploited so well by the Grigg group.[69] It also resembles an ene reaction, but with the key difference that the latter is a $2\pi+2\sigma+2\pi$ process featuring a six-membered transition state, while the reverse Cope cyclisation constitutes a $2\pi+2\sigma+2n$ reaction which involves a five-membered transition state. In this respect, it resembles similar thermally-induced intramolecular additions of oximes to unactivated alkenes and alkynes and therefore represents a most useful 'disconnection' for the elaboration of azaheterocycles. No doubt, the reverse Cope cyclisation



Scheme 86.

has much potential in synthesis and many exciting and useful developments can be expected in the future.

Acknowledgements

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Biographical sketch

Nicholas J. Cooper was born in Pontypool in 1978 and educated at West Monmouth Comprehensive School and Gwent Tertiary College before being awarded a First Class Joint Honours degree in Chemistry and Biochemistry from Cardiff University in 1999. He then undertook a research project in the area of the Reverse Cope cyclisation under the supervision of Professor David W. Knight at Cardiff University. He now works for the Defence Science and Technology Laboratory [DSTL] at Porton Down as an organic chemist in the Detection Department and is about to submit his thesis for the award of a PhD degree.

Professor David W. Knight was born in Northampton in 1951 and gained his BSc degree from Nottingham University in 1972 and his PhD from the same Institution in 1975, for studies of the synthesis of natural butenolides, under the supervision of Professor Gerry Pattenden. He then secured a lectureship at University College, Cardiff in 1976 before returning to Nottingham University in 1980 as a lecturer and later (1989) a Reader in Organic Chemistry. 1995 was a good year, during which he was granted a Leverhulme Senior Research Fellowship and also a Chair of Synthetic Organic Chemistry at Cardiff University. His research interests are currently focussed in three main areas: novel aspects of benzyne chemistry, the development and applications of 5-*endo* cyclisations for the synthesis of saturated, semi-saturated and aromatic heterocycles and new versions and applications of the reverse Cope cyclisation.

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3-Trifluoromethyl- and 3-difluoromethyl-thalidomides

Sergej N. Osipov,[a] Pavel Tsouker,[b] Lothar Hennig[b] and Klaus Burger[b,*]

[a]*A.N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences, Vavilov street 28, GSP-1, RUS 117813 Moscow, Russian Federation*
[b]*Department of Organic Chemistry, University of Leipzig, Johannisallee 29, D-04103 Leipzig, Germany*

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Dedicated to Professor Dr. H.-D. Jakubke on the occasion of his 70th birthday

Abstract—Syntheses of racemic 3-trifluoromethyl- and 3-difluoromethyl-thalidomide starting from 2-(*tert*-butyloxycarbonylimino)-3,3,3-trifluoropropionate or -3,3-difluoropropionate as fluorine-containing building blocks are described.

1. Introduction

Thalidomide (**1**) [2-(2,6-dioxo-3-piperidyl)isoindoline-1,3-dione], a sedativum without the side effects of barbiturates, was introduced into the market by Chemie Grünenthal in 1956 with the trade name Contergan®.[1–3] Thalidomide was withdrawn from the market in 1962,[4] when its use was linked to severe birth defects.[3,5] Unexpected teratogenic side effects produced one of the most notorious medicinal disasters of modern medicinal history.

However, the unique and broad physiological properties discovered during recent years, prompted a reevaluation of its therapeutic potential.[6] Thus, thalidomide is currently applied for treatment of painful inflammations associated with leprosy (recently approved in the USA),[7] rheumatoid arthritis[8] and graft-versus host disease.[9] Furthermore, promising results in the case of treatment of AIDS,[10] Crohn's disease,[11] Behcet's syndrom[12] and cancer related pathologic angiogenesis[13] have been disclosed. Recently, thalidomide was effective in the treatment of high-risk, refractory multiple myeloma.[14]

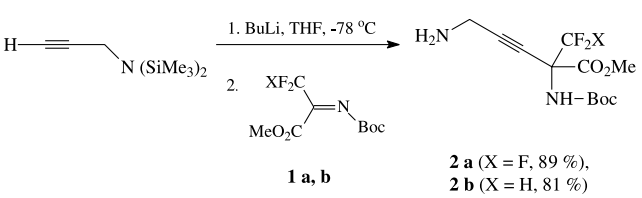
Overproduction of TNF-α is associated with these pathological disorders.[15] The effectivity of thalidomide in these diseases has mostly been attributed to its specific inhibitory activity on TNF-α production. Therefore, based on thalidomide as a lead structure several analogues have been developed.[16] We now report on concise syntheses of racemic 3-trifluoromethyl- and 3-difluoromethyl-thalidomides.

2. Results and discussion

Introduction of fluorine and/or fluoroalkyl groups into strategical positions of target molecules may considerably modify chemical properties, biological activity and selectivity.[17] Numerous fluoro- and fluoroalkyl-substituted pharmaceuticals, agrochemicals, dyes and polymers have been successfully commercialized.[18] The number of patents concerning fluorinated compounds shows growing tendency. Thus, one can anticipate that fluoro-modified compounds will continue to play a significant role in medicinal and agricultural chemistry as well as in material science.[19]

In an effort to improve the biological profile of thalidomide we synthesized new fluoroanalogues of thalidomide by replacing C(3)–H by a trifluoromethyl and a difluoromethyl group, respectively. Key step of the synthesis is the construction of the methyl 2-fluoroalkyl-2-(*tert*-butoxycarbonylamino)-5-aminopent-3-inoates **2**, which we already used as intermediates for the synthesis of α-trifluoromethyl and α-difluoromethyl ornithine[20] and arginine.[21] Compounds **2a** and **2b** are readily obtained in very good yields via addition of bis(trimethylsilyl)propargylamine to the highly electrophilic Boc-protected imines **1**[22] (Scheme 1).

The unsaturated ornithine derivatives **2a**,**b** obtained were subjected to catalytic hydrogenation to give the



Scheme 1.

Keywords: 2-Fluoroalkyl-2,5-diaminopent-3-inoates; 3-Fluoroalkyl-3-aminopiperidin-2-ones; 3-Fluoroalkyl-3-aminopiperidin-2,6-diones.
* Corresponding author. Fax: +49-341-9736599;
e-mail address: burger@organik.chemie.uni-leipzig.de

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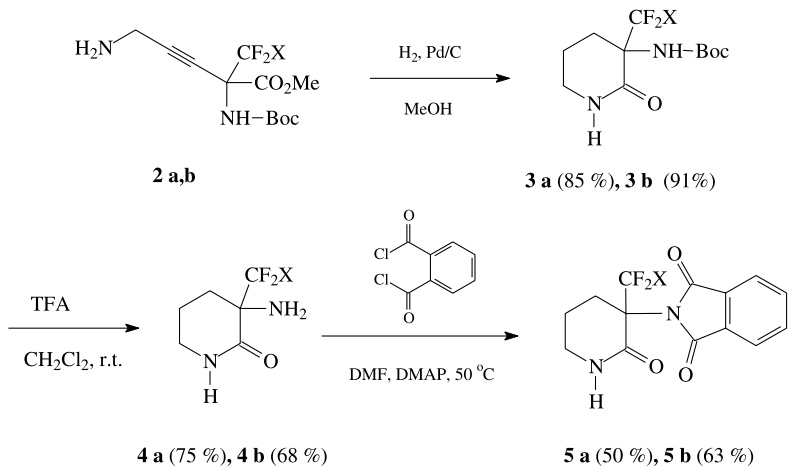
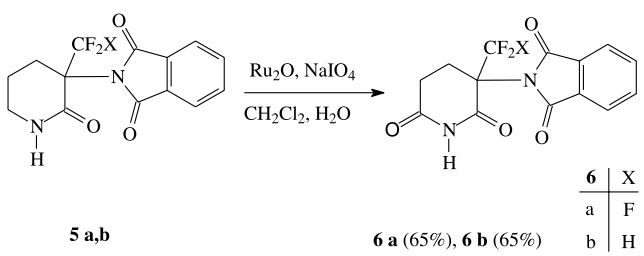


Scheme 2.

Boc-protected 2-fluoroalkyl-ornithine methylesters which spontaneously cyclize to give the Boc-protected 3-amino-3-fluoroalkylpiperidin-2-ones (**3**).[23] Compounds **3** are formed as racemic mixtures. Then the Boc group of **3** was removed on treatment with TFA at room temperature to furnish **4**. The amino group was diacylated with *o*-phthaloyl dichloride in the presence of DMAP (**4→5**)[24] (Scheme 2).

Finally, oxidation of **5** was performed using a catalytic amount of RuO_2 in the presence of excess sodium metaperiodate in a two phase system[25] to give the fluoroalkyl-substituted thalidomides **6a** and **6b** in 65 and 53% yield, respectively (Scheme 3).



Scheme 3.

Biological tests of compounds **5a**,**b** and **6a**,**b** are under current investigation.

3. Experimental

3.1. General

Melting points were determined on a Boetius heating table. IR spectra were obtained with a FTIR spectrometer (Genesis ATI Mattson/Unicam). ^{1}H NMR spectra were recorded with VARIAN Gemini 2000 spectrometers at 200 and 300 MHz. Chemical shifts were reported in ppm relative to tetramethylsilane (TMS, δ=0 ppm); *J* values are given in Hertz (Hz). ^{13}C NMR spectroscopy was performed at 50 and 75 MHz. ^{19}F spectra were recorded at 188 and 282 MHz with trifluoroacetic acid (TFA, δ=0 ppm) as external standard. HRMS spectra were performed at ESI-Mass Spectrometer: 7 T, Bruker Daltronics APEX II ESI-FT-ICR-MS in acetone/methanol solution; ESI ionisation and positive ion detection. For flash chromatography, silica gel (32–63 μm) was used with solvent systems given in text. Organic solvents were dried and distilled prior to use.

3.1.1. 3-Trifluoromethyl-3-(*tert*-butoxycarbonylamino)-piperidin-2-one (3a). A mixture of **2a**[21,22] (4.00 g, 12.9 mmol) and 10% Pd/C (0.80 g) in methanol (70 mL) was stirred under an atmosphere of hydrogen for 48 h. The catalyst was filtered off, and the filtrate was concentrated under reduced pressure. The remaining solid was washed with a hot mixture of ethyl acetate/hexanes (1:10), to give **3a** (3.09 g, 85%). The product was purified by column chromatography (eluent: ethyl acetate/hexanes, 1:1); mp 136 °C; IR (KBr): ν=3295, 3264, 1684, 1172 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ=1.48 (s, 9H, $OCMe_3$), 1.98 (m, 2H, CH_2), 2.56 (m, 1H, CH_2), 2.73 (m, 1H, CH_2), 3.45 (m, 2H, NCH_2), 5.63 (s, 1H, NH), 6.28 (s br, 1H, NH); ^{13}C NMR ($CDCl_3$): δ=19.18 (CH_2), 27.39 (CH_2), 28.47 (3×CH_3), 43.36 (NCH_2), 60.93 (q, $^2J_{CF}$=27.5 Hz, *C*CF_3), 81.03 (O*C*Me_3), 125.35 (d, $^1J_{CF}$=287.9 Hz, CF_3), 154.31 (C=O), 166.20 (C=O); ^{19}F NMR ($CDCl_3$): δ=5.03 (s, 3F, CF_3); HRMS $[M+Na]^+$. Found: *m*/*z*=305.10816; $C_{11}H_{17}F_3N_2NaO_3$ requires *m*/*z*=305.10835.

3.1.2. 3-Difluoromethyl-3-(*tert*-butoxycarbonylamino)-piperidin-2-one (3b). Applying the above protocol **2b**[21,22] (3.30 g, 11.3 mmol) was converted into **3b** (2.71 g, 91%); mp 158 °C; IR (KBr): ν=3389, 3203, 1662, 1063 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ=1.41 (s, 9H, $OCMe_3$), 1.95 (m, 2H, CH_2), 2.28 (m, 1H, CH_2), 2.42 (m, 1H, CH_2), 3.32 (m, 1H, NCH_2). 3.47 (m, 1H, NCH_2), 5.26 (s, 1H, NH), 6.04 (t, 1H, $^2J_{HF}$=57.1 Hz, CF_2H), 6.35 (s br, 1H, NH). ^{13}C NMR ($CDCl_3$): δ=26.98 (CH_2), 28.39 (CH_2), 42.17 (NCH_2), 59.50 (t, $^2J_{CF}$=24.0 Hz, *C*CF_2H), 80.79 (O*C*Me_3), 116.42 (t, $^1J_{CF}$=249.5 Hz, CF_2H), 154.39 (C=O), 167.88 (d, $^3J_{CF}$=5.3 Hz, C=O); ^{19}F NMR ($CDCl_3$): δ=−56.50 (dd_{ABX}, 1F, $^2J_{FF}$=282.3 Hz, $^2J_{FH}$=57.1 Hz, CF_2H); −48.31 (dd_{ABX}, 1F, $^2J_{FF}$=282.3 Hz, $^2J_{FH}$=57.1 Hz, CF_2H); HRMS $[M+Na]^+$. Found *m*/*z*=287.11777; $C_{11}H_{18}F_2NaN_2O_3$ requires *m*/*z*=287.11777.

3.1.3. 3-Trifluoromethyl-3-aminopiperidin-2-one (4a). TFA (10 mL) was added to a solution of **3a** (3.00 g, 10.6 mmol) in CH_2Cl_2 (50 mL) at 0 °C. The mixture was stirred for 6 h at rt. The volatiles were removed under

reduced pressure. The remaining solid was dissolved in ethyl acetate (100 mL), then the solution was treated with a saturated solution of $NaHCO_3$ (50 mL). The organic phase was separated, the aqueous layer was extracted with ethyl acetate (2×30 mL). The combined organic phase was dried over $MgSO_4$ and evaporated in vacuo to give **4a** (1.45 g, 75%); mp 115 °C; IR (KBr): ν=3394, 3319, 1671, 1141 cm^{-1}; ^1H NMR ($CDCl_3$): δ=1.95 (m, 5H, CH_2, NH_2), 2.25 (m, 1H, CH_2), 3.41 (m, 2H, NCH_2), 6.37 (s br, 1H, NH); ^{13}C NMR ($CDCl_3$): δ=18.75 (CH_2), 29.66 (d, $^3J_{CF}$=1.7 Hz, CH_2), 42.40 (NCH_2), 58.92 (q, $^2J_{CF}$=26.3 Hz, CCF_3), 125.45 (q, $^1J_{CF}$=286.3 Hz, CF_3), 169.00 (C=O); ^{19}F NMR ($CDCl_3$): δ=−0.15 (s, 3F, CF_3); MS: HRMS $[2M+Na]^+$. Found m/z=387.12210; $C_{12}H_{18}F_6NaN_4O_2$ requires m/z=387.12262.

3.1.4. 3-Difluoromethyl-3-aminopiperidin-2-one (4b). Applying the above protocol **3b** (1.20 g, 4.45 mmol) was transformed into **4b** (0.51 g, 68%); mp 147 °C; IR (KBr): ν=3389, 3204, 1665, 1063 cm^{-1}; ^1H NMR ($CDCl_3$): δ=1.98 (m, 6H, 2×CH_2, NH_2), 3.39 (m, 2H, NCH_2), 6.00 (t, 1H, $^2J_{HF}$=57.8 Hz, CF_2H), 6.57 (s br, 1H, NH); ^{13}C NMR ($CDCl_3$): δ=18.90 (CH_2), 26.52 (d, $^3J_{CF}$=4.5 Hz, CH_2), 42.55 (NCH_2), 58.14 (t, $^2J_{CF}$=22.6 Hz, CCF_2H), 117.85 (t, $^1J_{CF}$=271.5 Hz, CF_2H), 171.28 (d, $^3J_{CF}$=7.4 Hz, C=O); ^{19}F NMR ($CDCl_3$): δ=−62.85 (dd $_{ABX}$, 1F, $^2J_{FF}$=277.8 Hz, $^2J_{FH}$=57.8 Hz, CF_2H); −45.81 ppm (dd_{ABX}, 1F, $^2J_{FF}$=277.8 Hz, $^2J_{FH}$=57.8 Hz, CF_2H). HRMS $[2M+Na]^+$. Found m/z=351.14097; $C_{12}H_{20}F_4N_4NaO_2$ requires m/z=351.14146.

3.1.5. 3-Trifluoromethyl-3-(phthalimido)piperidin-2-one (5a). To a solution of **4a** (0.20 g, 1.1 mmol) and DMAP (0.27 g, 2.2 mmol) in $CHCl_3$ (50 mL) was added at 0 °C under argon a solution of *o*-phthaloyl dichloride (0.24 g, 1.18 mmol) in $CHCl_3$ (10 mL). The temperature was allowed to rise to rt, then after refluxing for 72 h, the mixture was washed with 1 N HCl (50 mL), then the organic phase was dried with $MgSO_4$ and concentrated in vacuo. The crude phthalimido derivative was purified by column chromatography on silica gel (eluent: ethyl acetate/hexanes, 1:1) to afford analytically pure **5a** (0.17 g, 50%); mp 203 °C; IR (KBr): ν=3402, 1733, 1339, 1334 cm^{-1}; ^1H NMR ($CDCl_3$): δ=1.88 (m, 1H, CH_2), 2.08 (m, 1H, CH_2), 2.41 (m, 1H, CH_2), 2.82 (m, 1H, CH_2), 3.44 (m, 2H, NCH_2), 6.37 (s, 1H, NH), 7.81 (m, 4H arom); ^{13}C NMR (d_6-acetone): δ=19.47 (CH_2), 28.64 (d, $^3J_{CF}$=1.8 Hz, CH_2), 41.61 (NCH_2), 65.54 (q, $^2J_{CF}$=28.0 Hz, CCF_3), 125.35 (q, $^1J_{CF}$=285.6 Hz, CF_3), 124.78, 132.80, 136.38 (C-arom), 164.14 (C=O), 168.25 (2×C=O); ^{19}F NMR ($CDCl_3$): δ=10.38 (s, 3F, CF_3); HRMS $[M+Na]^+$. Found m/z=335.06112; $C_{14}H_{11}F_3NaN_2O_3$ requires m/z=335.06140.

3.1.6. 3-Difluoromethyl-3-(phthalimido)piperidin-2-one (5b). Applying the above described protocol **4b** (0.24 g, 1.46 mmol) was transformed into **5b** (0.27 g, 63%); mp 214 °C; IR (KBr): ν=3377, 1719, 1376, 1066 cm^{-1}; ^1H NMR ($CDCl_3$): δ=1.98 (m, 1H, CH_2), 2.03 (m, 1H, CH_2), 2.30 (m, 1H, CH_2), 2.53 (m, 1H, CH_2), 3.40 (m, 2H, NCH_2), 6.46 (s, 1H, NH), 7.03 (t, 1H, $^1J_{HF}$=54.2 Hz, CF_2H), 7.76 (m, 4H arom); ^{13}C NMR ($CDCl_3$): δ=20.45 (CH_2), 27.95 (d, $^3J_{CF}$=3.6 Hz, CH_2), 42.13 (NCH_2), 63.77 (t, $^2J_{CF}$=25.3 Hz, CCF_2H), 114.36 (t, $^1J_{CF}$=247.3 Hz, CF_2H), 123.58, 131.62, 134.55 (C-arom), 165.93 (C=O), 167.87 (2×C=O); ^{19}F NMR ($CDCl_3$): δ=−44.9 (dd, 1F, $^2J_{FF}$=279.0 Hz, $^2J_{FF}$=54.9 Hz, CF_2H), −46.7 (dd, 1F, $^2J_{FF}$=279.0 Hz, $^2J_{FF}$=53.4 Hz, CF_2H); HRMS $[M+Na]^+$. Found m/z=317.07047; $C_{14}H_{12}F_2NaN_2O_3$ requires m/z=317.07082.

3.1.7. 3-Trifluoromethyl-3-(phthalimido)piperidin-2,6-dione (6a). A mixture of **5a** (0.10 g, 0.32 mmol) and 15 mg of ruthenium dioxide hydrate in CH_2Cl_2 (10 mL) was stirred at rt with 10 equiv. of 10% aqueous solution of $NaIO_4$ for 3 days. The layers were separated; the aqueous layer was extracted with CH_2Cl_2 (3×15 mL). To the combined organic layer methanol (0.1 mL) was added to destroy the excess of the oxidant. The mixture was filtered and the filtrate was washed with 5 mL of 10% aqueous $Na_2S_2O_3$. The solvent was removed under reduced pressure and the remaining solid was purified by column chromatography to give analytically pure **6a** (68 mg, 65%); mp 198 °C; IR (KBr): ν=3436, 3426, 3223, 1743, 1352, 1218 cm^{-1}; ^1H NMR ($CDCl_3$): δ=2.28 (m, 1H, CH_2), 2.65 (m, 1H, CH_2), 2.85 (m, 1H, CH_2), 3.71 (m, 1H, CH_2), 7.85 (m, 4H arom), 7.97 (s, 1H, NH); ^{13}C NMR (d_6-acetone): δ=22.74 (CH_2), 28.37 (CH_2), 64.01 (q, $^2J_{CF}$=28.5 Hz, CCF_3), 124.46, 125.05 (q, $^1J_{CF}$=285.7 Hz, CF_3), 132.00, 136.03 (C arom), 163.92 (C=O), 168.02 (2×C=O), 171.25 (C=O); ^{19}F NMR ($CDCl_3$): δ=3.43 (s, 3F, CF_3). HRMS $[2M+Na]^+$. Found m/z=675.09233; $C_{28}H_{18}F_6NaN_4O_8$ requires m/z=675.09265.

3.1.8. 3-Difluoromethyl-3-(phthalimido)piperidin-2,6-dione (6b). Applying the above protocol **5b** (25 mg, 0.294 mmol) was transformed into **6b** (14 mg, 65%); mp 209 °C; IR (KBr): ν=3434, 2363, 1722, 1375, 1067 cm^{-1}; ^1H NMR (d_6-acetone): δ=2.55 (m, 1H, CH_2), 2.81 (m, 2H, CH_2), 2.92 (m, 1H, CH_2), 7.04 (dd, $^2J_{HF}$=55.0 Hz, CF_2H), 7.95 (m, 4H, arom), 10.25 (s. br, 1H, NH); ^{13}C NMR (d_6-DMSO): δ=19.64 (CH_2), 27.78 (CH_2), 62.61 (t, $^2J_{CF}$=24.8 Hz, CCF_2H), 114.70 (t, $^1J_{CF}$=271.0 Hz, CF_2H), 123.84, 130.87, 135.00 (C arom), 164.01 (C=O), 167.34 (2×C=O), 171.98 (C=O); ^{19}F NMR (d_6-acetone): δ=−45.5 (dd, 1F, $^2J_{FH}$=55.0 Hz, $^2J_{FF}$=284.0 Hz, CF_2H), −49.3 (dd, 1F, $^2J_{FH}$=55.0 Hz, $^2J_{FF}$=284.0 Hz, CF_2H). HRMS $[M+Na]^+$. Found m/z=331.05046; $C_{14}H_{10}F_2NaN_2O_4$ requires 331.05008.

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Synthesis of pyrido and pyrazinodithienodipyrimidine-4,8(3*H*,9*H*)-dione derivatives by the aza-Wittig methodology

David Vázquez Vilarelle, Carlos Peinador Veira and José M. Quintela López*

Departamento de Química Fundamental, Facultad de Ciencias, Universidad de La Coruña, Campus de A Zapateira, E-15071 La Coruña, Spain

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Abstract—A one-pot synthesis of the hitherto unreported pyrido[5″,6″:4,5;3″2″:4′,5′]dithieno[3,2-*d*:3′,2′-*d*′]dipyrimidine-4,8(3*H*,9*H*)-dione **6a**–**o** and pyrazino[5″,6″:4,5;3″2″:4′,5′]dithieno[3,2-*d*:3′,2′-*d*′]dipyrimidine-4,8(3*H*,9*H*)-dione **6p**–**y** pentaheterocyclic systems, based on the tandem aza-Wittig heterocumulene-mediated annulation strategy is described.

1. Introduction

Synthetic heterocycles have widespread interest as herbicides, insecticides, dyes, organic-conductors, and drugs. Nitrogen-containing heterocycles are of broad pharmaceutical interest and this justifies continuing efforts in the development of structure-activity relationship in this series and of new synthetic strategies.[1] There is a enormous interest in the synthesis of new heterocyclic rings stimulated by recent reports that showed antitumor activity in a wide range of polyheterocyclic compounds isolated from marine organisms.[2] Compounds containing a fused pyrimidine ring have significant biological activity, particularly in cancer and virus research.[3] Among these heterocycles, thienopyrimidine derivatives are an important class of heterocyclic compounds in pharmaceutical discovery research. Anti-allergic,[4] antianaphilactic,[5] anti-inflammatory,[6] analgesic and antipyretic,[7] and antineoplasic[8] activities have been described for these compounds.

The aza-Wittig reaction has become one of the most important synthetic methods for constructing novel C═N, N═N, and S═N double bonds containing compounds, especially in modern nitrogen heterocyclic synthesis. In recent years, there has been a significant interest in the chemistry of iminophosphoranes (λ5-phosphazenes, phosphine imines) because of their utility for the construction of nitrogen-containing heterocycles compounds, and many interesting heterocyclization reactions involved functionalized iminophosphoranes have been reviewed.[9] These compounds can react with carbonyl compounds to form imines, and with isocyanates, isothiocyanates, carbon dioxide and carbon disulfide, giving rise to the corresponding heterocumulenes.[10] Aza-Wittig reactions can be divided into an intramolecular and an intermolecular variant. The intramolecular aza-Wittig reaction is a powerful tool reaction for the synthesis of 5–7 membered ring heterocycles[11] and the intermolecular aza-Wittig reaction followed by electrocyclization, intramolecular cycloaddition or heterocyclization, has been utilized for the synthesis of many important nitrogen heterocycles,[12] and, on the other hand, the utilization of the aza-Wittig reaction in the synthesis of biologically important heterocyclic natural products has been recently reviewed.[13]

Iminophosphoranes derived from *N*-aminoheterocycles are valuable precursors for the preparation of fused heterocycles which may be neutral, cationic or mesoionic.[14] Recently, we have reported the synthesis of fused pyrimidines based on the tandem aza-Wittig heterocumulene-mediated annulation strategy.[15]

2. Results and discussion

Work in our laboratories has been recently concerned with the discovery and development of synthesis of new heterocycles systems containing thienopyrimidine moiety in order to search for new pharmacological or biologically active compounds. We have previously reported on the synthesis of novel tri- and tetracyclic ring systems, containing the thienopyrimidine skeleton, with antiinflammatory and antihistaminic activity.[16] We now describe here, as a further extension of the aza-Wittig-type methodology the synthesis of the hitherto unreported pyrido

Keywords: Aza-Wittig; Pyrazinodithienodipyrimidine; Pyridodithienodipyrimidine.
* Corresponding author. Tel.: +34-981-167000; fax: +34-981-167065; e-mail address: jqqoqf@udc.es

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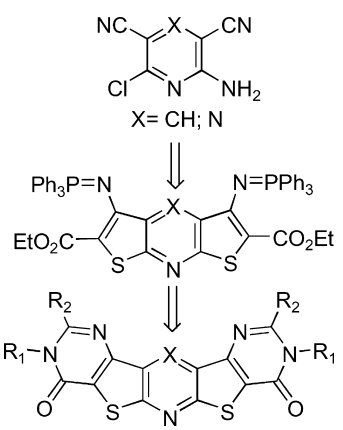
[5″,6″:4,5;3″2″:4′,5′]dithieno[3,2-*d*:3′,2′-*d*′]dipyrimidine-4,8(3*H*,9*H*)-dione **6a**–**o** and pyrido[5″,6″:4,5;3″2″:4′,5′]dithieno[3,2-*d*:3′,2′-*d*′]dipyrimidine-4,8(3*H*,9*H*)-dione **6p**–**y**, utilizing for the first time 2,6-dichloropyridine-3,5-dicarbonitrile **1a** and 3,5-dichloropyrazine-2,6-dicarbonitrile **1b** as the starting materials. The strategy used for the development of these compounds was focused as shown in Scheme 1. The bis *N*-heteroaryliminophosphoranes **3a**,**b** appear to serve as a good building block for these heterocycles. They can be synthesized from 2,6-dichloropyridine-3,5-dicarbonitrile and 2,6-dichloropyrazine-3,5-dicarbonitrile, respectively.

Pentaheterocyclic compounds **6a**–**o** and **6p**–**y** were obtained in a one-pot reaction of the corresponding iminophosphoranes of heteroaromatic β-enamino esters **3a** and **3b** with isocyanates, followed by heterocyclization on addition of amines.

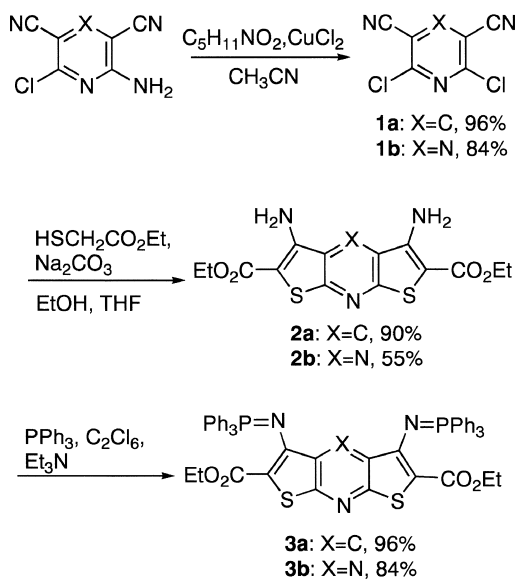
The starting compounds for the aza-Wittig reaction heterocyclization sequence were prepared from the readily available heterocyclic β-enaminoesters **2a**–**b**. First, 2,6-dichloropyridine-3,5-dicarbonitrile **1a** and 2,6-dichloropyrazine-3,5-dicarbonitrile **1b** were formed by nitrosation reaction of the corresponding 2-aminoderivatives[17] following a previously described procedure.[18] The thiophene rings were added on the pyridine and pyrazine rings by condensing **1a**–**b** with ethyl 2-mercaptoacetate in the presence of an equimolecular amount of potassium carbonate in refluxing ethanol to give ethyl 3,5-diamino-dithieno[3′,2′-*e*:2,3-*b*]pyridine-2,6-dicarboxylate **2a** and ethyl 3,5-diamino-dithieno[3′,2′-*e*:2,3-*b*]pyrazine-2,6-dicarboxylate **2b** in good yields.

The key iminophosphoranes **3a**–**b** were obtained by a modified Kirsanov reaction of the β-enamino esters **2a**–**b** with in situ prepared dichlorotriphenylphosphorane using a hexachloroethane-triphenylphosphine-triethylamine reagent system (Scheme 2).[19] The molecular structure of the iminophposphoranes were supported by the general data (IR, ^{1}H NMR, ^{13}C NMR, ^{31}P NMR, and mass spectra) and elemental analysis.

Aza-Wittig reaction of bisimonophosphoranes **3a**–**b** with arylisocyanates, followed by heterocyclization on addition of secondary amines directly affords substituted pyrido[5″,6″:4,5;3″2″:4′,5′]dithieno[3,2-*d*:3′,2′-*d*′]di-pyrimidine-4,8(3*H*,9*H*)-dione **6a**–**o** and pyrazino [5″,6″:4,5;3″2″:4′,5′]dithieno[3,2-*d*:3′,2′-*d*′]dipyrimidine-4,8(3*H*,9*H*)-dione **6p**–**y**. Reaction of bis-imino-phosphoranes with arylisocyanates and secondary amines at room temperature resulted in the formation of the corresponding guanidine-type intermediate derivatives **5a**–**f**, the key intermediates for the processes, that could be isolated in the above mentioned conditions. Pyrimido-annulation occurs via a heterocumulene moiety, available from the reaction of the *N*-heteroaryliminophosphorane and the isocyanate as highly reactive intermediates.



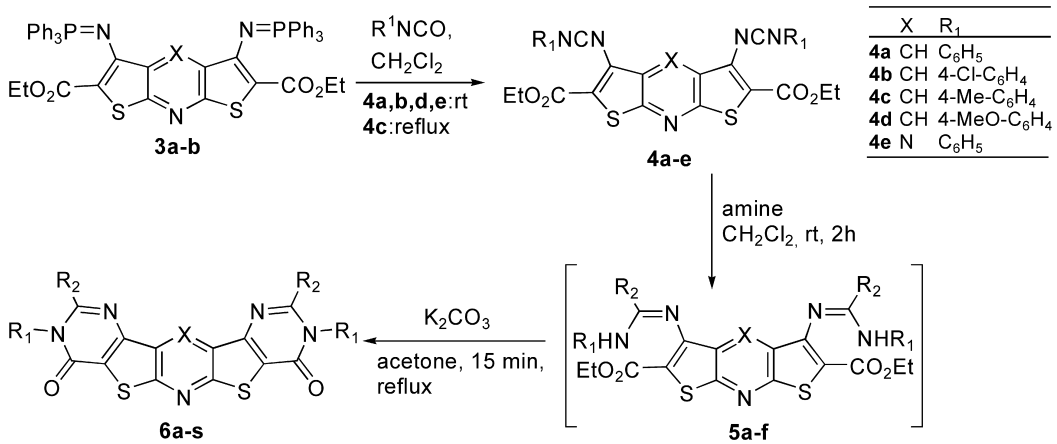
Scheme 1.



Scheme 2.

Those carbodiimide derivatives **4a**–**e** have been isolated by treatment of bis-triphenyliminophosphoranes **3a**–**b** with aryl isocyanates in dry CH_2Cl_2 at room temperature. Addition of a secondary amine to the highly reactive cumulenic system followed by intramolecular heteroconjugate addition annulation gives the final penta- and hexaaza-indenefluorenediones **6a**–**o** and **6p**–**y**. Direct cyclization of the initially formed carbodiimide via 1,3-OEt migration followed by electrocyclization (Wamhoff's pyrimidoannelation)[20] was not observed in this case. In the presence of anhydrous sodium carbonate, the separated guanidine-type intermediate derivatives **5a**–**f** underwent intramolecular heterocyclization across the electrophilic ester functionality to give the fused heterocyclic compounds **6a**–**o** and **6p**–**y** (Scheme 3).

The structures of carbodiimide compounds **4a**–**e**, guanidine compounds **5a**–**f**, and fused pyrimidines **6a**–**o** and **6p**–**y** were confirmed by their elemental analyses and spectroscopic data. The mass spectra showed the expected molecular ion peak and the IR spectra of guanidine-type intermediates **5a**–**f** showed a strong absorption at ν=3320–3373 cm^{-1} attributed to the NH group, while in the ^{1}H NMR spectra, the NH proton appear at δ=5.77–6.92 ppm as a singlet, in addition to the set of signals due to the ethoxy group. Also, the ^{13}C NMR spectra showed signals between δ=14.28–14.49 and 60.5–66.4 ppm due to ethoxy groups.



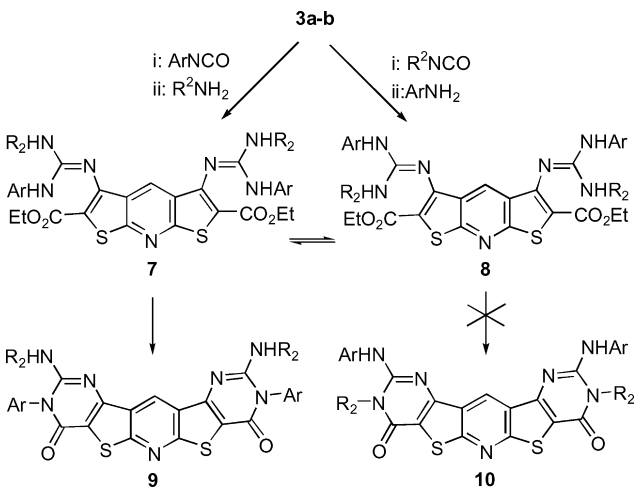
	X	R^1
4a	CH	C_6H_5
4b	CH	4-Cl-C_6H_4
4c	CH	4-Me-C_6H_4
4d	CH	4-MeO-C_6H_4
4e	N	C_6H_5

	X	R^1	R^2		X	R^1	R^2		X	R^1	R^2
5a	CH	C_6H_5	Thiomorpholino	**6f**	CH	4-Cl-C_6H_4	Piperidino	**6q**	N	C_6H_5	Morpholino
5b	CH	C_6H_5	Diethylamino	**6g**	CH	4-Me-C_6H_4	Morpholino	**6r**	N	C_6H_5	Piperidino
5c	CH	C_6H_5	Morpholino	**6h**	CH	4-Me-C_6H_4	Piperidino	**6s**	N	C_6H_5	Isopropylamino
5d	CH	4-MeO-C_6H_4	Morpholino	**6i**	CH	4-MeO-C_6H_4	Morpholino	**6t**	N	4-Cl-C_6H_4	Morpholino
5e	CH	4-Cl-C_6H_4	Piperidino	**6j**	CH	4-MeO-C_6H_4	Pyperidino	**6u**	N	4-Cl-C_6H_4	Piperidino
5f	CH	C_6H_5	Isopropylamino	**6k**	CH	C_6H_5	*n*-Butylamino	**6v**	N	4-Me-C_6H_4	Morpholino
6a	CH	C_6H_5	Diethylamino	**6l**	CH	C_6H_5	Isopropylamino	**6w**	N	4-Me-C_6H_4	Piperidino
6b	CH	C_6H_5	Thiomorpholino	**6m**	CH	4-Cl-C_6H_4	Isopropylamino	**6x**	N	4-MeO-C_6H_4	Morpholino
6c	CH	C_6H_5	Morpholino	**6n**	CH	4-Me-C_6H_4	Isopropylamino	**6y**	N	4-MeO-C_6H_4	Piperidino
6d	CH	C_6H_5	Piperidino	**6o**	CH	4-MeO-C_6H_4	Isopropylamino				
6e	CH	4-Cl-C_6H_4	Morpholino	**6p**	N	C_6H_5	Thiomorpholino				

Scheme 3.

After heterocyclization, the spectra of compounds **6a**–**o** and **6p**–**y** did not include those type of signals.

Two isomeric pyrimidothieno derivatives, **9** and **10**, may be produced in the treatment of bis-*N*-heteroarylimino-phosphoranes **3a**–**b** with ArNCO/R^2NH_2 or R^2NCO/$ArNH_2$ via guanidine-type intermediates **7** and **8** (Scheme 4), but these reactions afforded only **9**, compound **10** not being formed. In addition, only pentacyclic compound **9** was obtained by the reaction of carbodiimide **4a**–**e** with primary amines (the guanidine intermediate **5f** was isolated). These selectivity results can probably be explained by the large difference in cyclization rates due the steric hindrance around the Ph and



Scheme 4.

isopropyl or butyl groups.[21] Mass and spectroscopic data are in good agreement with the proposed structures. The FAB-mass spectra show the expected molecular ion peaks and the fragmentation pattern is in accord with the proposed structures. In particular, in the ^{1}H NMR spectra, the NH-isopropyl groups of compounds **6l**–**o** and **6 s** appear characteristically as broad doublets at δ=4.05–6.29 ppm. In addition, the NH-butyl proton in compound **6k** resonates as a triplet confirming the proposed structures.

In conclusion, the present study demonstrates that the tandem aza-Wittig-heterocumulene-mediated annulation strategy affords a facile, efficient and general one-pot route to previously unreported pentacyclic dipyrimidodithienopyridine **6a**–**o** and dipyrimidodithienopyrazine **6p**–**y** systems bearing various substituents on the pyrimidine ring. Pentaheterocyclic compounds **6a**–**o** and **6p**–**y** can be useful compounds in medicinal chemistry since the pyrimido and thiophene moieties display a broad range of biological activities and have been widely used as pharmaceuticals.

3. Experimental

All reagents used were comercial grade chemicals from freshly opened containers. Melting points were determinated on a Bibby SMP3 apparatus and are uncorrected. IR spectra were recorded as potassium bromide disks on a Bruker vector 22 FT-IR. ^{1}H and ^{13}C NMR spectra were obtained on a Bruker AC 200F instrument at room temperature. Mass spectra were obtained on a VG-QUATTRO spectrometer. The Silica gel 60F-254 used for analytical thin layer chromatography were

purchased from Merck. Microanalyses for C, H, N, and S were performed by the elemental analyses general services of the University of La Coruña.

3.1. Synthesis of 2,6-dichloropyridine-3,5-dicarbonitrile (1a) and 3,5-dichloro-pyrazine-2,6-dicarbonitrile (1b)

To a solution of 2-amino-6-chloropyridine-3,5-dicarbonitrile or 3-amino-5-chloropyrazine-2,6-dicarbonitrile (22.4 mmol) and $CuCl_2$ (33.6 mmol) in dry CH_3CN (200 mL), isoamilnitrite was added (33.6 mmol). The mixture was heated at 65 °C for 5 h (10 h for **1b**). The solution was acidified (HCl, 2 N) to pH=3 and extracted with CH_2Cl_2 (3×50 mL) and dried with Na_2SO_4. The solvent was removed under reduced pressure and the crude product was purified by flash chromatography using CH_2Cl_2 as eluent to yield **1a**,**b**.

3.1.1. 2,6-Dichloropyridine-3,5-dicarbonitrile (1a). (96%). Mp 198–200 °C. Lit[22] 210–214 °C. IR (KBr, cm^{-1}): 2740 (CN). ^1H NMR ($CDCl_3$): 8.27 (s, CH). ^{13}CNMR ($CDCl_3$): 110.3 (C3, C5); 112.2 (CN); 146.9 (C4); 155.7 (C2, C6). MS (EI, *m/z* %): 197 (M^+, 100); 162 (M^+-Cl, 59). Anal. calcd for $C_7HCl_2N_3$ C, 42.46; H, 0.51; N, 21.22. Found C, 42.63; H, 0.60; N, 21.33.

3.1.2. 3,5-Dichloro-pyrazine-2,6-dicarbonitrile (1b). (84%). Mp 177–179 °C. IR (KBr, cm^{-1}): 2361–2342 (CN). ^{13}C NMR (CD_3COCD_3): 113.33 (CN); 129.69 (CCN); 153.23 (CCl). MS (EI, *m/z* %): 198 (M^+, 100); 200 (M^++2, 62). Anal. calcd for $C_6Cl_2N_4$ C, 36.21; N, 28.15. Found C, 36.32; N, 28.01.

3.2. Synthesis of diethyl 3,5-diaminodithieno[3′,2′-*e*:2,3-*b*]pyridine-2,6-dicarboxylate (2a) and diethyl 3,5-diaminodithieno[3′,2′-*e*:2,3-*b*]]pyrazine-2,6-dicarboxylate (2b)

To a solution of **1a** or **1b** (18.27 mmol) and ethyl tioglycolate (43.7 mmol) in a mixture of EtOH/THF (5:1) (240 mL), K_2CO_3 (43.7 mmol) was added, and the mixture was refluxed for 1 h. After cooling, the solid was filtered and washed with water. The product is pure enough to be used in the next step, but it can be purified by recristallization from EtOH/DMF (**2a**) or purified by flash chromatography using CH_2Cl_2 as eluent to yield **2b**.

3.2.1. Diethyl 3,5-diaminodithieno[3′,2′-*e*:2,3-*b*]pyridine-2,6-dicarboxylate (2a). (6.0 g, 90%). Mp >300. IR (KBr, cm^{-1}): 3378, 3280 (NH_2), 1678 (C=O). ^1H NMR (DMSO): 9.09 (s, 1H, CH); 7.09 (s, 4H, NH_2); 4.26 (q, 4H, OCH_2, *J*=7.1 Hz); 1.29 (t, 6H, OCH_2CH_3, *J*=7.1 Hz). ^{13}C NMR (DMSO): 17.73 (OCH_2CH_3); 60.52 (OCH_2); 93.89; 123.13; 127.05 (CH); 148.18; 161.18; 164.55. MS (IE, *m/z* %): 365 (M^+, 100). Anal. calcd for $C_{15}H_{15}N_3O_4S_2$, C, 49.30; H, 4.14; N, 11.50; S, 17.55. Found C, 49.59; H, 4.21; N,11.26; S, 17.31.

3.2.2. Diethyl 3,5-diaminodithieno[3′,2′-*e*:2,3-*b*]pyrazine-2,6-dicarboxylate (2b). (55%). Mp 240–242 °C. IR (KBr, cm^{-1}): 3474–3330 (NH_2), 1680 (C=O). ^1H NMR (CD_3Cl): 6.24 (s, 4H, NH_2); 4.41 (q, 4H, OCH_2, *J*=7.1 Hz); 1.44 (t, 6H, CH_3, *J*=7.1 Hz). ^{13}C NMR (CD_3Cl): 14.45 (CH_3); 61.06 (OCH_2); 99.63; 138.30; 144.71; 155.85; 164.85. MS (EI, *m/z* %) 366 (M^+, 100). Anal. calcd for $C_{14}H_{14}N_4O_4S_2$: C, 45.89; H, 3.85; N, 15.29; S, 17.50. Found C, 46.13; H, 3.72; N, 14.96; S, 17.54.

3.2.3. Synthesis of diethyl 3,5-di[(trifenilfosforanilidene) amino]ditieno[3′,2′-*e*:2,3-*b*]pyridine-2,6-dicarboxylate (3a). *Method A*. A solution of the **2a** (0.2 g, 0.55 mmol) triphenylphosphine (0.43 g, 1.64 mmol), hexachloroethane (0.39 g, 1.64 mmol) and triethylamine (0.28 g, 2.74 mmol) in toluene (3 mL), was heated in a sealed tube at 100 °C for 48 h. After cooling, the solid formed was filtered off, washed with water and recrystallized from EtOH/CH_2Cl_2, to yield **3a** (0.39 g, 80%).

Method B. A mixture of **2a** (1.5 g, 4.11 mmol), triphenylphosphine (3.23 g, 12.3 mmol), hexachloroethane (2.92 g, 12.3 mmol) and triethylamine (2.07 g, 20.5 mmol) in dry THF (60 mL), was heated in a sealed tube at 60 °C for 48 h. After cooling, the solid formed was filtered off and washed with THF, and the filtrate and the washings were combined and evaporated. The solid obtained was purified by flash chromatography using CH_2Cl_2/AcOEt as eluent to yield **3a** (3.5 g, 96%). Mp 265–266 °C; IR (KBr. cm^{-1}): 1686 (C=O), 1542, 1376, 1194, 527. ^1H NMR ($CDCl_3$): 8.80 (s, 1H, CH); 7.42 (m, 30H, Ph); 3.80 (q, 4H, OCH_2, *J*=7.1 Hz); 1.00 (t, 6H, CH_3, *J*=7.1 Hz). ^{13}C NMR ($CDCl_3$): 14.35 (OCH_2CH_3); 59.47 (OCH_2); 128.11; 128.36; 128.68; 130.85; 131.22; 131.20; 131.29; 131.45; 132.35; 132.55; 133.54; 134.58; 149.67; 161.12; 163.38. ^{31}P NMR ($CDCl_3$): 8.26. MS (FAB, *m/z* %): 886 (MH^+, 9);. Anal. calcd for $C_{51}H_{41}N_3O_4P_2S_2$ C, 69.14; H, 4.66; N, 4.74; S, 7.24. Found C, 68.85; H, 4.65; N, 4.70; S, 7.35.

3.2.4. Synthesis of diethyl 3,5-di[(triphenylphosphoranylidene)amino]ditieno[3′,2′-*e*:2,3-*b*]pyrazine-2,6-dicarboxylate (3b). A mixture of the heterocyclic amine **2b** (0.2 g, 0.55 mmol) triphenylphosphine (0.43 g, 1.64 mmol), hexachloroethane (0.39 g, 1.64 mmol) and triethylamine (0.28 g, 2.74 mmol) in toluene (3 mL), was heated in a sealed tube at 100 °C for 48 h. After cooling, the solid formed was filtered off, washed with water and recrystallized from EtOH/CH_2Cl_2, to yield **3b** (0.40 g, 84%). Mp 269–271 °C. IR (KBr, cm^{-1}): 1699 (C=O), 1524, 1437, 1222, 1183, 721. ^1H NMR ($CDCl_3$): 7.24–7.97 (m, 30H, Ph); 3.83 (q, 4H, OCH_2, *J*=7.1 Hz); 1.08 (t, 6H, CH_3, *J*=7.1 Hz). ^{13}C NMR ($CDCl_3$): 14.36 (CH_3); 59.80 (OCH_2); 88.45; 110.79; 128.05; 128.29; 130.97; 131.24; 131.29; 132.82; 133.02; 145.66; 148.79; 154.43; 163.51; 163.54. ^{31}P NMR ($CDCl_3$): 5.53. MS (FAB, *m/z* %) 887 (MH^+, 30); 279 (100). Anal. calcd for $C_{50}H_{40}N_4O_4P_2S_2$ C, 67.71; H, 4.55; N, 6.32; S, 7.23. Found C, 67.53; H, 4.50; N, 6.31; S, 7.35.

3.3. Synthesis of diethyl 3,5-bis(arylimino-methylenamino)dithieno[3′,2′-*e*:2,3-*b*]pyridine(or pyrazine)-2,6-dicarboxylate (4a–e)

To a solution of **3** (0.23 mmol) in CH_2Cl_2 (10 mL) (THF for **3b**) was added the appropriate isocyanate (0.54 mmol). After the mixture was stirred at room temperature for 3–5 h (*p*-tolylisocyanate: reflux). The solvent was evaporated, ether (5 mL) was added, and the mixture was stirred at room temperature for 0.5 h. The solid formed was filtered off and purified by flash chromatography using hexanes/CH_2Cl_2 (1:1 v/v) as eluent.

3.3.1. Diethyl 3,5-bis(phenyliminomethyleneamino)dithieno[3′,2′-*e*:2,3-*b*]pyridine-2,6-dicarboxylate (4a). (54%). Mp 200–203 °C. IR (KBr, cm^{-1}): 2150 (NCN); 1706 (CO); 1460; 1259; 760. ^1H NMR ($CDCl_3$): 8.79 (s, 1H, CH); 7.27 (m, 10H, Ph); 4.40 (q, 4H, OCH_2, J=7.1 Hz); 1.39 (t, 6H, CH_3, J=7.1 Hz). ^{13}C NMR ($CDCl_3$): 14.31 (CH_3); 61.89 (OCH_2); 118.40; 124.76; 15.48; 125.96; 126.71; 127.64; 129.42; 134.34; 136.49; 160.09; 162.19. Anal. calcd for $C_{29}H_{21}N_5O_4S_2$ C, 61.36; H, 3.73; N, 12.34; S, 11.30. Found C, 61.50; H, 3.98; N, 12.51; S, 11.63.

3.3.2. Diethyl 3,5-bis(4-chlorophenyliminomethyleneamino)dithieno[3′,2′-*e*:2,3-*b*]pyridine-2,6-dicarboxylate (4b). (53%). Mp 174–175 °C. IR (KBr, cm^{-1}): 2158 (NCN); 1698 (C═O); 1258; 827. ^1H NMR ($CDCl_3$): 8.75 (s, 1H, CH); 7.32 (m, 8H, Ph); 4.40 (q, 4H, OCH_2, J=7.1 Hz); 1.39 (t, 6H, CH_3, J=7.1 Hz). RMN ^{13}C ($CDCl_3$): 14.29 (CH_3); 61.84 (OCH_2); 118.49; 126.00; 126.61; 127.46; 129.52; 129.79; 131.42; 134.04; 135.19; 160.06; 162.18. MS (FAB, *m/z* %): 636 (MH^+, 2). Anal. calcd for $C_{29}H_{19}Cl_2N_5O_4S_2$ C, 54.72; H, 3.01; N, 11.00; S, 10.08. Found C, 54.84; H, 3.05; N, 10.84; S, 10.09

3.3.3. Diethyl 3,5-bis(4-methylphenyliminomethyleneamino)dithieno[3′,2′-*e*:2,3-*b*]pyridine-2,6-dicarboxylate (4c). (63%). Mp 160–162 °C. IR (KBr, cm^{-1}): 2151 (NCN); 1697 (C═O); 1467; 1261; 558. ^1H NMR ($CDCl_3$): 8.81 (s, 1H, CH); 7.23 (m, 8H, Ph); 4.40 (q, 4H, OCH_2, J=7.1 Hz); 2.35 (s, 6H, CH_3); 1.39 (t, 6H, OCH_2CH_3, J=7.1 Hz). ^{13}C NMR ($CDCl_3$): 14.32 (CH_3); 21.04 (CH_3); 61.75 (OCH_3); 124.57; 126.78; 127.53; 127.73; 129.50; 130.01; 133.56; 134.75; 135.86; 162.22. Anal. calcd for $C_{31}H_{25}N_5O_4S_2$ C, 62.50; H, 4.23; N, 11.76; S, 10.77. Found C, 62.70; H, 4.36; N, 11.53; S, 10.31

3.3.4. Diethyl 3,5-bis(4-methoxyphenylimino-methyleneamino)dithieno[3′,2′-*e*:2,3-*b*]pyridine-2,6-dicarboxylate (4d). (56%). Mp 155 °C. IR (KBr, cm^{-1}): 2150 (NCN); 1698 (C═O); 1500; 1247; 830. ^1H NMR ($CDCl_3$): 8.78 (s, 1H, CH); 6.93 (m, 8H, Ph); 4.4 (q, 4H, OCH_2, J=7.1 Hz); 3.82 (s, 6H, CH_3); 1.39 (t, 6H, OCH_2CH_3, J=7.1 Hz). ^{13}C NMR ($CDCl_3$): 14.33 (CH_3); 55.48 (CH_3); 61.69 (OCH_2); 114.67; 117.84; 125.88; 126.75; 127.00; 127.68; 128.78; 129.47; 135.13; 157.75; 160.13; 162.25. Anal. calcd for $C_{31}H_{25}N_5O_6S_2$ C, 59.32; H, 4.01; N, 11.16; S, 10.22. Found C, 58.98; H, 3.93; N, 10.99; S, 10.14.

3.3.5. Diethyl 3,5-bis(phenyliminomethyleneamino)dithieno[3′,2′-*e*:2,3-*b*]pyrazine-2,6-dicarboxylate (4e). (75%). Mp 165–167 °C. IR (KBr, cm^{-1}): 2152 (NCN); 1686 (CO); 1228, 1061, 752. ^1H NMR ($CDCl_3$): 7.11–7.45 (m, 10H, Ph); 4.50 (q, 4H, OCH_2, J=7.1 Hz); 1.45 (t, 6H, CH_3, J=7.1 Hz). ^{13}C NMR ($CDCl_3$): 14.26 (CH_3); 62.18 (OCH_2); 124.92, 125.92, 129.34 (Ph); 122.23; 134.79; 136.11; 142.50; 153.84; 161.53. Anal. calcd for $C_{28}H_{20}N_6O_4S_2$ C, 59.14; H, 3.55; N, 14.78; S, 11.28. Found C, 58.87; H, 3.34; N,14.46; S, 11.52.

3.4. Synthesis of diethyl dithieno[3′,2′-*e*:2,3-*b*]pyridine-2,6-dicarboxylates (5a–f)

A solution of the appropriate isocyanate (0.55 mmol) and **3a** (0.2 g, 0.23 mmol) in CH_2Cl_2 (10 mL). The mixture was stirred at room temperature (*p*-tolylisocyanate: reflux) until the iminophosphorane had disappeared (TLC monitored) and it was therefore treated with an appropriate amine (0.55 mmol). The resultant solution was stirred at room temperature for 2 h. The solvent was evaporated, ether (5 mL) was added, and the mixture was stirred at room temperature for 0.5 h. The solid formed was filtered off and purified by recristallization from $EtOH/CH_2Cl_2$.

3.4.1. Diethyl 3,5-bis[anilino(thiomorpholino)methyleneamino]dithieno[3′,2′-*e*:2,3-*b*]pyridine-2,6-dicarboxylate (5a). (60%). Mp >300 °C. IR (KBr, cm^{-1}): 3329 (NH), 1687 (C═O), 1624, 1230, 1052, 933. ^1H NMR ($CDCl_3$): 8.28 (s, 1H, CH); 7.11 (m, 10H, Ph); 6.92 (br s, 2H, NH); 4.25 (m, 4H, OCH_2); 3.84 (m, 8H, H_2CNCH_2); 2.76 (m, 8H, H_2CSCH_2); 1.27 (m, 6H, CH_3). ^{13}C NMR ($CDCl_3$): 30.21 (SCH_2); 49.50 (NCH_2); 66.00 (OCH_2); 115.77; 125.38; 126.38; 128.65; 128.79; 129.05; 136.73; 149.75; 157.47; 158.89; 163.93. MS (FAB, *m/z* %): 774 (MH^+, 22). Anal. calcd for $C_{37}H_{39}N_7O_4S_4$ C, 57.41; H, 5.08; N, 12.67; S, 16.57. Found C, 57.64; H, 5.22; N, 12.35; S, 16.29.

3.4.2. Diethyl 3,5-bis[anilino(diethylamino)methyleneamino]dithieno[3′,2′-*e*:2,3-*b*]pyridine-2,6-dicarboxylate (5b). (55%). Mp 205–206 °C. IR (KBr, cm^{-1}): 3373–3291 (NH), 1706 (C═O), 1594, 1583, 1239, 1049. ^1H NMR ($CDCl_3$): 8.39 (s, 1H, CH); 6.73 (m, 10H, Ph); 5.77 (s, 2H, NH); 4.30 (q, 4H, OCH_2, J=7.1 Hz); 3.55 (q, 4H, NCH_2, J=7.1 Hz); 1.35 (m, 18H, CH_3). ^{13}C NMR ($CDCl_3$): 13.25 (NCH_2CH_3); 14.49 (OCH_2CH_3); 42.94 (NCH_2); 60.54 (OCH_2); 118.57; 122.18; 126.92; 128.08; 140.74; 151.89; 161.11; 163.32. MS (FAB, *m/z* %): 714 (MH^+, 53); 641 (MH^+-CO_2Et, 11). Anal. calcd for $C_{37}H_{43}N_7O_4S_2$ C, 62.25; H, 6.07; N, 13.73; S, 8.98. Found C, 62.41; H, 5.94, N, 13.50; S, 8.92.

3.4.3. Diethyl 3,5-bis[anilino(morpholino)methyleneamino]dithieno[3′,2′-*e*:2,3-*b*]pyridine-2,6-dicarboxylate (5c). (50%). Mp 210–211 °C. IR (KBr, cm^{-1}): 3320 (NH), 1702 (C═O), 1614, 1600, 1237, 1108, 1049, 966. ^1H NMR ($CDCl_3$): 8.30 (s, 1H, CH); 7.13 (m, 10H, Ph); 6.92 (s, 2H, NH); 4.23 (m, 4H, OCH_2); 3.60 (m, 8H, H_2COCH_2); 3.44 (m, 8H, H_2CNCH_2); 1.23 (m, 6H, CH_3). ^{13}C NMR ($CDCl_3$): 14.28 (CH_3); 47.62 (NCH_2); 60.84 (H_2COCH_2); 66.35 (OCH_2); 119.99; 122.90; 126.90; 127.89; 129.02; 134.91; 140.54; 153.18; 160.98; 162.86. MS (FAB, *m/z* %): 742 (MH^+, 54). Anal. calcd for $C_{37}H_{39}N_7O_6S_2$ C, 59.90; H, 5.30; N, 13.22; S, 8.64. Found C, 59.52; H, 5.38; N, 12.95; S, 8.75.

3.4.4. Diethyl 3,5-bis[4-methoxyanilino(morpholino) methyleneamino]dithieno[3′,2′-*e*:2,3-*b*]]pyridine-2,6-dicarboxylate (5d). (55%). Mp 238–239 °C. IR (KBr, cm^{-1}): 3333 (NH), 1712 (C═O), 1625, 1511, 1111, 823. ^1H NMR ($CDCl_3$): 8.25 (s, 1H, CH); 7.11 (m, 8H, Ph); 6.59 (s, 2H, NH); 4.17 (m, 4H, OCH_2,); 3.72 (m, 14H, CH_2OCH_2+ OCH_3); 3.48 (m, 8H, CH_2NCH_2); 1.24 (m, 6H, CH_3). ^{13}C NMR ($CDCl_3$): 14.31 (CH_3); 47.62 (NCH_2); 55.38 (OCH_3) 60.75 (OCH_2); 66.39 (CH_2OCH_2); 111.31; 114.24; 122.39; 127.00; 127.92; 131.97; 132.17, 133.66; 148.50; 153.95; 155.76; 151.04; 162.84. MS (FAB, *m/z* %): 802 (MH^+, 16). Anal. calcd for $C_{39}H_{43}N_7O_8S_2$ C, 58.41; H, 5.40; N, 12.23; S, 8.00. Found C, 58.15; H, 5.32; N, 11.93; S, 7.70.

3.4.5. Diethyl 3,5-bis[4-chloroanilino(piperidino)methyleneamino]dithieno[3′,2′-*e*:2,3-*b*]pyridine-2,6-dicarboxylate (5e). (54%). Mp 237–238 °C. IR (KBr, cm^{-1}): 3337 (NH), 1714 (C=O), 1620, 1233, 1053, 824. ^1H NMR ($CDCl_3$): 8.21 (s, 1H, CH); 7.13 (m, 8H, Ph); 6.60 (s, 2H, NH); 4.20 (m, 4H, OCH_2,); 3.45 (m, 8H, H_2CNCH_2); 1.39 (m, 18H, $NCH_2CH_2CH_2$+CH_3). ^{13}C NMR ($CDCl_3$): 14.30 (CH_3); 24.7 ($NCH_2CH_2CH_2$); 25.4 (NCH_2CH_2) 48.3 (NCH_2); 60.80 (OCH_2); 120.93; 127.26, 128.06; 139.70; 152.70; 161.00. MS (FAB, *m/z* %): 806 (MH^+, 16). Anal. calcd for $C_{39}H_{41}Cl_2N_7O_4S_2$ C, 58.06; H, 5.12; N, 12.15; S, 7.95. Found C, 57.94; H, 5.15; N, 11.76; S, 7.79.

3.4.6. Diethyl 3,5-bis[anilino(isopropylamino)methyleneamino]dithieno[3′,2′-*e*:2,3-*b*]pyridine-2,6-dicarboxylate (5f). (40%). Mp >300 °C. IR (KBr, cm^{-1}): 3345 (NH), 1677 (C=O), 1633, 1530, 1491, 1051. ^1H NMR ($CDCl_3$): 8.45 (s, 1H, CH); 7.35 (m, 10H, Ph); 7.08 (m, 4H, NH+NHPh); 4.29 (m, 6H, HNCH+OCH_2); 1.23 (m, 18H, $HNCH_2CH3$+OCH_2CH_3). ^{13}C NMR ($CDCl_3$): 14.34 (CH_3); 23.04 ($HNCHCH_3$); 43.33 (HNCH); 60.74 (OCH_2); 124.02, 124.57; 128.35; 128.67; 129.43; 138.68; 148.37; 149.23; 160.85; 163.17. MS (FAB, *m/z* %): 686 (MH^+, 100); 687 (MH^++1, 39); 688 (MH^++2.18). Anal. calcd for $C_{35}H_{39}N_7O_4S_2$ C, 61.29; H, 5.73; N, 14.30; S, 9.35. Found C, 61.42; H, 5.85; N, 14.41; S, 9.49.

3.5. Synthesis of pyrido(or pyrazino)[5″,6″:4,5;3″2″:4′,5′]dithieno[3,2-*d*:3′,2′-*d*′]dipyrimidine-4,8(3*H*,9*H*)-diones (6a–y)

A solution of the appropriate isocyanate (0.55 mmol) and **3a** or **3b** (0.23 mmol) in CH_2Cl_2 (10 mL). The mixture was stirred at room temperature (*p*-tolylisocyanate: reflux) until the iminophosphorane had disappeared (3 h, TLC monitored) and it was therefore treated with an appropriate amine (0.55 mmol). The resultant solution was stirred at room temperature for 2 h. The solvent was evaporated and the residue was solved in acetone (8 mL), a catalytic amount of K_2CO_3 was added, the mixture was refluxed for 0.5 h and the solid obtained was filtered off, washed with water, acetone and recrystallized from EtOH/CH_2Cl_2. Compounds **6a** and **6f** could not be purified because their insolubility in ordinary solvents.

3.5.1. 2,10-Bis(diethylamino)-3,9-diphenylpyrido[5″,6″:4,5;3″2″:4′,5′]dithieno[3,2-*d*:3′,2′-*d*′]dipyrimidine-4,8(3*H*,9*H*)-dione (6a). (69%). Mp >300 °C. IR (KBr, cm^{-1}): 1675 (C=O), 1530, 1378, 1282, 699. MS (FAB, *m/z* %): 622 (MH^+, 10); 623 (MH^++1, 4); 550 (MH^+−diethylamine, 3).

3.5.2. 3,9-Diphenyl-2,10-dithiomorpholinpyrido[5″,6″:4,5;3″2″:4′,5′]dithieno[3,2-*d*:3′,2′-*d*′]dipyrimidine-4,8(3*H*,9*H*)-dione (6b). (89%). Mp >300 °C. IR (KBr, cm^{-1}): 1677 (C=O), 1534, 1409. ^1H NMR ($CDCl_3$): 8.91 (s, 1H, CH); 7.47 (m, 10H, Ph); 3.62 (m, 8H, NCH_2); 2.39 (m, 8H, SCH_2). ^{13}C NMR ($CDCl_3$): 26.49 (SCH_2); 51.93 (NCH_2); 125.42; 128.64; 129.01; 135.12; 137.05; 149.68; 158.17; 159.05. MS (FAB, *m/z* %): 682 (MH^+, 4); 580 (MH^+−thiomorpholine, 4). Anal. calcd for $C_{33}H_{27}N_7O_2S_4$ C, 58.13; H, 3.99; N, 14.38; S, 18.81. Found C, 58.40; H, 4.03; N, 14.58; S, 19.02.

3.5.3. 2,10-Dimorpholino-3,9-diphenylpyrido[5″,6″:4,5;3″2″:4′,5′]dithieno[3,2-*d*:3′,2′-*d*′]dipyrimidine-4,8(3*H*,9*H*)-dione (6c). (75%). Mp >300 °C. IR (KBr, cm^{-1}): 2856, 1677 (C=O), 1529, 1118, 918. ^1H NMR ($CDCl_3$): 8.86 (s, 1H, CH); 7.47 (m, 10H, Ph); 3.54 (m, 8H, OCH_2); 3.32 (m, 8H, NCH_2). MS (FAB, *m/z* %): 650 (MH^+, 10). Anal. calcd for $C_{33}H_{27}N_7O_4S_2$ C, 61.00; H, 4.19; N, 15.09; S, 9.87. Found C, 61.45; H, 4.18; N, 15.08; S, 9.73.

3.5.4. 3,9-Diphenyl-2,10-dipiperidinopyrido[5″,6″:4,5;3″2″:4′,5′]dithieno[3,2-*d*:3′,2′-*d*′]dipyrimidine-4,8(3*H*,9*H*)-dione (6d). (60%). Mp >300 °C. IR (KBr, cm^{-1}): 2929, 1675 (C=O), 1589, 1532, 1251, 707. ^1H NMR ($CDCl_3$): 8.90 (s, 1H, CH); 7.42 (m, 10H, Ph); 3.30 (m, 8H, NCH_2); 1.49–1.35 (m, 12H, $NCH_2CH_2CH_2$). ^{13}C NMR ($CDCl_3$): 24.13 ($NCH_2CH_2CH_2$); 24.94 (NCH_2CH_2); 50.48 (NCH_2); 115.06; 125.49; 126.48; 128.16; 128.79; 128.98; 137.48; 150.12; 158.48; 159.22; 163.96. MS (FAB, *m/z* %): 646 (MH^+, 8). Anal. calcd $C_{35}H_{31}N_7O_2S_2$ C, 65.09; H, 4.84; N, 15.18; S, 9.93. Found C, 64.71; H, 4.83; N, 14.94; S, 10.01.

3.5.5. 3,9-Bis(4-chlorophenyl)-2,10-dimorpholinopyrido-[5″,6″:4,5;3″2″:4′,5′]dithieno[3,2-*d*:3′,2′-*d*′]dipyrimi-dine-4,8(3*H*,9*H*)-dione (6e). (54%). Mp >300 °C. IR (KBr, cm^{-1}): 2847, 1678 (C=O), 1635, 1530, 1250, 833. ^1H NMR ($CDCl_3$): 7.46 (m, 8H, Ph); 6.40 (s, 1H, CH); 3.70 (m, 8H, OCH_2,); 3.40 (m, 8H, NCH_2); ^{13}C NMR ($CDCl_3$): 44.2 (NCH_2); 66.4 (OCH_2); 121.25; 128.30; 128.44; 128.85; 131.90; 132.09; 137.33; 154.85. Anal. calcd for $C_{33}H_{25}Cl_2N_7O_4S_2$ C, 55.15; H, 3.51; N, 13.64; S, 8.92. Found C, 55.48; H, 3.85; N, 13.54; S, 8.66.

3.5.6. 3,9-Bis(4-chlorophenyl)-2,10-dipiperidinopyrido-[5″,6″:4,5;3″2″:4′,5′]dithieno[3,2-*d*:3′,2′-*d*′]dipyrimidine-4,8(3*H*,9*H*)-dione (6f). (67%). Mp >300 °C. IR (KBr, cm^{-1}): 2935, 1677 (C=O), 1530, 1403, 1253, 769. MS (FAB, *m/z* %) 714 (MH^+, 3); 716 (MH^++2, 3).

3.5.7. 2,10-Dimorpholino-3,9-di-*p*-tolylpyrido[5″,6″:4,5;3″2″:4′,5′]dithieno[3,2-*d*:3′,2′-*d*′]dipyrimidine-4,8(3*H*,9*H*)-dione (6g). (77%). Mp >300 °C. IR (KBr, cm^{-1}): 2852, 2360, 1674 (C=O), 1534, 1117. ^1H NMR ($CDCl_3$): 8.84 (s, 1H, CH); 7.31 (m, 8H, Ph); 3.56 (m, 8H, OCH_2); 3.33 (m, 8H, NCH_2); 2.45 (s, 6H, Me). ^{13}C NMR ($CDCl_3$): 21.24 (Me); 49.47 (NCH_2); 66.05 (OCH_2); 115.65; 125.39; 126.24; 128.43; 129.66; 134.06; 138.58; 149.68; 157.55 Ms (FAB, *m/z* %): 678 (MH^+, 12). Anal. calcd for $C_{35}H_{31}N_7O_4S_2$ C, 62.02; H, 4.61; N, 14.47; S, 9.46. Found C, 62.13; H, 4.39; N, 14.41; S, 9.33.

3.5.8. 2,10-Dipiperidino-3,9-di-*p*-tolylpyrido[5″,6″:4,5;3″2″:4′,5′]dithieno[3,2-*d*:3′,2′-*d*′]dipyrimidine-4,8(3*H*,9*H*)-dione (6h). (64%). Mp >300 °C. IR (KBr, cm^{-1}): 2932, 1675 (C=O), 1586, 1530, 1407, 1254, 751. ^1H NMR ($CDCl_3$): 8.96 (s, 1H, CH); 7.30 (m, 8H, Ph); 3.29 (m, 8H, NCH_2); 2.44 (s, 6H, Me); 1.35 (m, 12H, $NCH_2CH_2CH_2$). ^{13}C NMR ($CDCl_3$): 21.23 (CH_3); 24.15 ($NCH_2CH_2CH_2$); 24.98 (NCH_2CH_2); 50.41 (NCH_2); 115.10; 125.69; 126.45; 128.52; 129.47; 134.80; 138.04; 150.12; 158.55; 159.37; 164.08. MS (FAB, *m/z* %): 674 (MH^+, 8). Anal. calcd for $C_{37}H_{35}N_7O_2S_2$ C, 65.95; H, 5.24; N, 14.55; S, 9.52. Found C, 65.87; H, 5.30; N, 14.73; S, 9.59.

3.5.9. 3,9-Bis(4-methoxyphenyl)-2,10-dimorpholinopyrido[5″,6″:4,5;3″2″:4′,5′]dithieno[3,2-*d*:3′,2′-*d*′]dipyrimidine-4,8(3*H*,9*H*)-dione (6i). (61%). Mp >300 °C. IR (KBr, cm^{-1}): 2963, 1676 (C═O), 1536, 1507, 1246, 917. ^1H NMR ($CDCl_3$): 8.66 (s, 1H, CH); 7.15 (m, 8H, Ph); 3.87 (s, 6H, OCH_3); 3.36 (m, 8H, OCH_2); 3.34 (s, 8H, NCH_2). ^{13}C NMR ($CDCl_3$): 49.49 (NCH_2); 55.47 (OCH_3); 66.12 (OCH_2); 114.14; 115.47; 125.19; 126.1; 129.85; 149.58; 157.68; 159.09; 159.36; 163.72. MS (FAB, *m/z* %): 710 (MH^+, 13). Anal. calcd for $C_{35}H_{31}N_7O_6S_2$ C, 59.22; H, 4.40; N, 13.81; S, 9.04. Found C, 59.25; H, 4.41; 13.55; S, 9.13.

3.5.10. 3,9-Bis(4-methoxyphenyl)-2,10-dipiperidinopyrido[5″,6″:4,5;3″2″:4′,5′]dithieno[3,2-*d*:3′,2′-*d*′]dipyrimidine-4,8(3*H*,9*H*)-dione (6j). (62%). Mp >300 °C. IR (KBr, cm^{-1}): 2933, 1675 (C═O), 1532, 1511, 1251, 915. ^1H NMR ($CDCl_3$): 8.89 (s, 1H, CH); 7.13 (m, 8H, Ph); 3.88 (s, 6H, OCH_3); 3.31 (m, 8H, NCH_2); 1.45 (m, 12H, $NCH_2CH_2CH_2$). ^{13}C NMR ($CDCl_3$): 24.15 ($NCH_2CH_2CH_2$); 25.08 (NCH_2CH_2); 50.44 (NCH_2); 55.47 (OCH_3); 114.06; 115.06; 125.61; 126.41; 129.87; 130.01; 150.06; 158.68; 159.06; 159.50; 164.01. MS (FAB, *m/z* %): 706 (MH^+, 52). Anal. calcd for $C_{37}H_{35}N_7O_4S_2$ C, 62.96; H, 5.00; N, 13.89; S, 9.09. Found C, 62.46; H, 4.97; N, 13.68; S, 8.89.

3.5.11. 2,10-Bis(butylamino)-3,9-diphenylpyrido[5″,6″:4,5;3″2″:4′,5′]dithieno[3,2-*d*:3′,2′-*d*′]dipyrimidine-4,8(3*H*,9*H*)-dione (6k). (40%). Mp >300 °C. IR (KBr, cm^{-1}): 3429–3368 (NH), 2931; 1678 (C═O), 1549, 1324, 772. ^1H NMR ($CDCl_3$): 8.93 (s, 1H, CH); 7.41 (m, 10H, Ph); 4.28 (t, 3H, NH); 3.60 (m, 4H, NCH_2); 1.61 (m, 4H, NCH_2CH_2); 1.38 (m, 4H, $NCH_2CH_2CH_2$); 1.00 (t, 6H, CH_3). ^{13}C NMR ($CDCl_3$): 13.76 (CH_3); 20.00 ($NCH_2CH_2CH_2$); 31.24 (NCH_2CH_2); 41.98 (NCH_2); 110.84; 125.61; 126.49; 129.00; 130.01; 130.62; 134.38; 151.78; 153.23; 158.44; 164.37. MS (FAB, *m/z* %): 622 (MH^+, 100). Anal. calcd for $C_{33}H_{31}N_7O_2S_2$ C; 63.75; H, 5.03; N, 15.77; S, 10.31. Found C, 63.36; H, 4.97; N, 15.54; S, 10.26.

3.5.12. 2,10-Bis(isopropylamino)-3,9-diphenylpyrido-[5″,6″:4,5:3″2″:4′,5′]dithieno[3,2-*d*:3′,2′-*d*′]dipyrimidine-4,8(3*H*,9*H*)-dione (6l). (45%). Mp >300 °C. IR (KBr, cm^{-1}): 3436 (NH), 3061, 2974; 1676 (C═O), 1547, 1289, 1176, 770. ^1H NMR ($CDCl_3$): 8.89 (s, 1H, CH); 7.52 (m, 10H, Ph); 4.50 (m, 2H, NCH); 4.05 (d, 2H, HN, *J*=7.3 Hz); 1.26 (d, 12H, CH_3, *J*=6.4 Hz). ^{13}C NMR ($CDCl_3$): 22.84 (CH_3); 44.09 (NCH); 110.76; 125.55, 126.44, 129.02; 129.94; 130.57, 134.34; 151.81; 152.54; 158.45; 164.35. MS (FAB, *m/z* %): 594 (MH^+, 32). Anal. calcd for $C_{31}H_{27}N_7O_2S_2$ C, 62.71; H, 4.58; N, 16.51; S, 10.80. Found 62.61; H, 4.47; N, 16.84; S, 10.92.

3.5.13. 3,9-Bis(4-chlorophenyl)-2,10-bis(isopropylamino)pyrido[5″,6″:4,5;3″2″:4′,5″]dithieno[3,2-*d*:3′,2′-*d*′]dipyrimidine-4,8(3*H*,9*H*)-dione (6m). (33%). Mp >300 °C. IR (KBr, cm^{-1}): 3323 (NH), 2973; 1627 (C═O), 1560, 1238. ^1H NMR (CD_3COCD_3): 7.80 (s, 1H, CH); 7.30 (m, 8H, Ph); 5.58 (d, 2H, NH, *J*=7.3 Hz); 3.87 (m, 2H, NCH,); 1.12 (d, 12H, CH_3, *J*=6.8 Hz). ^{13}C NMR (CD_3COCD_3): 23.30 (CH_3); 42.30 (NCH); 120.11; 126.17; 129.23; 140.66; 155.18; 194.49. Anal. calcd for $C_{31}H_{25}Cl_2N_7O_2S_2$ C, 56.19; H, 3.80; N, 14.80; S, 9.68. Found C, 56.58; H, 4.12; N, 14.79; S, 10.01.

3.5.14. 2,10-Bis(isopropylamino)-3,9-di-*p*-tolylpyrido-[5″,6″:4,5;3″2″:4′,5′]dithieno[3,2-*d*:3′,2′-*d*′]dipyrimidine-4,8(3*H*,9*H*)-dione (6n). (70%). Mp >300 °C. IR (KBr, cm^{-1}): 3412 (NH), 2970; 1675 (C═O), 1546, 1320, 1176, 773. ^1H NMR ($CD_2Cl_2/CDCl_3$): 9.07 (s, 1H, CH); 7.30 (m, 8H, Ph); 4.50 (m, 2H, NCH); 4.12 (d, 2H, HN, *J*=7.8 Hz); 2.48 (s, 6H, CH_3) 1.24 (d, 12H, $NCHCH_3$, *J*=6.6 Hz). ^{13}C NMR ($CDCl_3$): 21.53 (CH_3); 22.92 (CH_3); 44.46 (NCH); 126.51; 126.92; 128.89; 131.72; 132.02; 133.61; 140.83; 152.30; 153.30; 158.97; 164.65. MS (FAB, *m/z* %): 622 (MH^+, 88). Anal. calcd for $C_{33}H_{31}N_7O_2S_2$ C, 63.75; H, 5.03; N, 15.77; S, 10.31. Found C, 63.90; H, 4.99; N, 15.64; S, 10.21.

3.5.15. 2,10-Bis(isopropylamino)-3,9-bis(4-methoxyphenyl)pyrido[5″,6″:4,5;3″2″:4′,5′]dithieno[3,2-*d*:3′,2′-*d*′]dipyrimidine-4,8(3*H*,9*H*)-dione (6o). (86%). Mp >300 °C. IR (KBr, cm^{-1}): 3383–3428 (NH), 2967; 1674 (C═O), 1511, 1246, 1039, 771. ^1H NMR (CD_5N): 9.71 (s, 1H, CH); 7.44 (m, 4H, Ph); 6.90 (m, 4H, Ph); 6.29 (d, 2H, HN, *J*=8.3 Hz); 4.70 (m, 2H, NCH,); 3.52 (s, 6H, OCH_3); 1.20 (d, 12H, $NCHCH_3$, *J*=6.8 Hz). MS (FAB, *m/z* %): 654 (MH^+, 10). Anal. calcd for $C_{33}H_{31}N_7O_4S_2$ C, 60.63; H, 4.78; N, 15.00; S, 9.81. Found C, 60.55; H, 4.70; N, 14.59; S, 9.62.

3.5.16. 3,9-Diphenyl-2,10-dithiomorpholinopyrazino-[5″,6″:4,5:3″2″:4′,5′]dithieno[3,2-*d*:3′,2′-*d*′]dipyrimidine-4,8(3*H*,9*H*)-dione (6p). (30%). Mp >300 °C. IR (KBr, cm^{-1}): 2911, 1678 (C═O), 1531, 1197, 761. ^1H NMR ($CDCl_3$): 7.41–7.63 (m, 10H, Ph); 3.67 (m, 8H, NCH_2); 2.35 (m, 8H, SCH_2). ^{13}C NMR ($CDCl_3$): 26.39 (SCH_2); 51.86 (NCH_2); 128.67, 128.93, 129.41 (Ph); 137.04; 158.48; 159.36. MS (FAB, *m/z* %): 683 (MH^+, 10). Anal. calcd for $C_{32}H_{26}N_8O_2S_4$: C, 56.28; H, 3.84; N, 16.41; S, 18.78. Found C, 56.34; H, 4.03; N, 16.58; S, 19.02.

3.5.17. 2,10-Dimorpholino-3,9-diphenylpyrazino[5″,6″:4,5:3″2″:4′,5′]dithieno[3,2-*d*:3′,2′-*d*′]dipyrimidine-4,8(3*H*,9*H*)-dione (6q). (40%). Mp >300 °C. IR (KBr, cm^{-1}): 2855, 2368, 1679 (C═O), 1532, 1200, 922. ^1H NMR ($CDCl_3$): 7.45–7.61 (m, 10H, Ph); 3.51 (m, 8H, OCH_2); 3.36 (m, 8H, NCH_2). ^{13}C NMR ($CDCl_3$): 49.36 (NCH_2); 65.93 (OCH_2); 128.34, 128.96, 129.37 (Ph); 136.75; 142.21; 148.47; 157.72; 159.23. MS (FAB, *m/z* %): 651 (MH^+, 85); (MH^+−morpholine, 40). Anal. calcd for $C_{32}H_{26}N_8O_4S_2$: C, 59.06; H, 4.03; N, 17.22; S, 9.86. Found C, 58.72; H, 3.94; N, 17.62; S, 9.80.

3.5.18. 3,9-Diphenyl-2,10-dipiperidinopyrazino[5″,6″:4,5;3″2″:4′,5′]dithieno[3,2-*d*:3′,2′-*d*′]dipyrimidine-4,8(3*H*,9*H*)-dione (6r). (30%). Mp >300 °C. IR (KBr, cm^{-1}): 2934, 1678 (C═O), 1531, 1193, 922. ^1H NMR ($CDCl_3$): 7.41–7.59 (m, 10H, Ph); 3.34–1.31 (m, 12H, $NCH_2CH_2CH_2$). ^{13}C NMR ($CDCl_3$): 23.96 ($NCH_2CH_2CH_2$); 24.84 (NCH_2CH_2); 50.35 (NCH_2); 128.52, 128.47, 129.12 (Ph); 118.74; 137.45; 142.24; 148.82; 157.78; 158.78; 159.57. MS (FAB, *m/z* %): 647 (MH^+, 100); 648 (MH^++1, 50). Anal. calcd for $C_{34}H_{30}N_8O_2S_2$: C, 63.14; H, 4.68; N, 17.32; S, 9.92. Found C, 63.12; H, 4.59; N, 17.28; S, 9.77.

3.5.19. 2,10-Bis(isopropylamino)-3,9-diphenylpyrazino-[5″,6″:4,5;3″2″:4′,5′]dithieno[3,2-*d*:3′,2′-*d*′]dipyrimidine-4,8(3*H*,9*H*)-dione (6s). (46%). Mp >300 °C. IR (KBr,

cm^{-1}): 3431 (NH), 1678 (C=O), 1548, 1200, 759. ^{1}H NMR ($CDCl_3$): 7.26–7.72 (m, 10H, Ph); 4.64 (m, 2H, NCH); 4.13 (d, 2H, HN, J=8.3 Hz); 1.21 (d, 12H, CH_3, J=6.8 Hz). ^{13}C NMR ($CDCl_3$): 22.89 ($NCHCH_3$); 44.10 (NCH); 128.63, 130.36, 130.88 (Ph); 120.68; 129.15; 134.05; 142.11; 150.32; 152.19; 158.67 MS (FAB, *m/z* %): 595 (MH^+, 100); 596 (MH^++1, 50). Anal. calcd for $C_{30}H_{26}N_8O_2S_2$ C, 60.59; H, 4.41; N, 18.84; S, 10.78. Found C, 60.69; H, 4.14; N, 18.62; S, 10.53.

3.5.20. 3,9-Bis(4-chlorophenyl)-2,10-dimorpholinopyrazino[5″,6″:4,5;3″2″:4′,5′]dithieno[3,2-*d*:3′,2′-*d*′]di-pyrimidine-4,8(3*H*,9*H*)-dione (6t). (27%). Mp >300 °C. IR (KBr, cm^{-1}): 2962, 2855, 1680 (C=O), 1533, 1201, 922. ^{1}H NMR ($CDCl_3$): 7.39–7.57 (m, 8H, Ph); 3.56 (m, 8H, OCH_2,); 3.36 (m, 8H, NCH_2); ^{13}C NMR ($CDCl_3$): 49.43 (NCH_2); 65.96 (OCH_2); 129.59, 129.70 (Ph); 134.96; 135.02; 142.04; 148.38; 157.52; 157.56; 158.98. MS (FAB, *m/z* %): 719 (MH^+, 5); 217 (100). Anal. calcd for $C_{32}H_{24}Cl_2N_8O_4S_2$: C, 53.41; H, 3.36; N, 15.57; S, 8.91. Found C, 53.48; H, 3.35; N, 15.74; S, 8.61.

3.5.21. 3,9-Bis(4-chlorophenyl)-2,10-dipiperidinopyrazino[5″,6″:4,5;3″2″:4′,5′]dithieno[3,2-*d*:3′,2′-*d*′]di-pyrimidine-4,8(3*H*,9*H*)-dione (6u). (42%). Mp >300 °C. IR (KBr, cm^{-1}): 2937, 1675 (C=O), 1530, 1193, 1092. ^{1}H NMR ($CDCl_3$): 7.26–7.55 (m, 8H, Ph); 3.32 (m, 8H, NCH_2); 1.26–1.50 (m, 12H, $NCH_2CH_2CH_2$). ^{13}C NMR ($CDCl_3$): 23.89 ($NCH_2CH_2CH_2$); 24.88 (NCH_2CH_2); 50.39 (NCH_2); 129.33, 129.85 (Ph); 118.79; 134.42; 135.75; 142.12; 148.74; 157.78; 158.56; 159.30. MS (FAB, *m/z* %) 715 (MH^+, 5). Anal. calcd for $C_{34}H_{28}Cl_2N_8O_2S_2$ C, 57.06; H, 3.94; N, 15.66; S, 8.96. Found C, 57.30; H, 3.96; N, 15.29; S, 9.10.

3.5.22. 2,10-Dimorpholino-3,9-di-*p*-tolylpyrazino [5″,6″:4,5;3″2″:4′,5′]dithieno[3,2-*d*:3′,2′-*d*′]dipyrimidine-4,8(3*H*,9*H*)-dione (6v). (27%). Mp >300 °C. IR (KBr, cm^{-1}): 2963, 2853, 1679 (C=O), 1530. ^{1}H NMR ($CDCl_3$): 7.27–7.35 (m, 8H, Ph); 3.52 (m, 8H, OCH_2); 3.37 (m, 8H, NCH_2); 2.46 (s, 6H, Me). ^{13}C NMR ($CDCl_3$): 21.28 (Me); 49.32 (NCH_2); 65.97 (OCH_2); 127.97, 129.96 (Ph); 119.60; 120.19; 134.07; 139.05; 142.32; 148.48; 157.76; 159.38. MS (FAB, *m/z* %): 679 (MH^+, 60); 592 (MH^+−morpholine, 30). Anal. calcd for $C_{34}H_{30}N_8O_4S_2$ C, 60.16; H, 4.45; N, 16.51; S, 9.45. Found C, 60.13; H, 4.39; N, 16.41; S, 9.33.

3.5.23. 2,10-Dipiperidino-3,9-di-*p*-tolylpyrazino [5″,6″:4,5;3″2″:4′,5′]dithieno[3,2-*d*:3′,2′-*d*′]dipyrimidine-4,8(3*H*,9*H*)-dione (6w). (28%). Mp >300 °C. IR (KBr, cm^{-1}): 2935, 1678 (C=O), 1529, 1119. ^{1}H NMR ($CDCl_3$): 7.27–7.32 (m, 8H, Ph); 3.31–3.36 (m, 8H, NCH_2); 2.45 (s, 6H, Me); 1.49–1.34 (m, 12H, $NCH_2CH_2CH_2$). ^{13}C NMR ($CDCl_3$): 21.24 (Me); 24.00 ($NCH_2CH_2CH_2$); 24.88 (NCH_2CH_2); 50.31 (NCH_2); 128.16, 129.74 (Ph); 118.70; 134.77; 138.45; 142.28; 148.78; 158.89; 159.72. MS (FAB, *m/z* %): 675 (MH^+, 95); 590 (M^+−piperidine, 40). Anal. calcd for $C_{36}H_{34}N_8O_2S_2$: C, 64.07; H, 5.08; N, 16.60; S, 9.50. Found C, 64.17; H, 5.20; N, 16.73; S, 9.59.

3.5.24. 3,9-Bis(4-methoxyphenyl)-2,10-dimorpholino-pyrazino[5″,6″:4,5;3″2″:4′,5′]dithieno[3,2-*d*:3′,2′-*d*′]dipyrimidine-4,8(3*H*,9*H*)-dione (6x). (28%). Mp >300 °C. IR (KBr, cm^{-1}): 2960, 1680 (C=O), 1508, 1521, 1249. ^{1}H NMR ($CDCl_3$): 7.04–7.39 (m, 8H, Ph); 3.89 (s, 6H, OMe); 3.54 (m, 8H, OCH_2); 3.37 (s, 8H, NCH_2). ^{13}C NMR ($CDCl_3$): 49.36 (NCH_2); 55.57 (OCH_3); 66.05 (OCH_2); 114.56, 129.34 (Ph); 119.55; 129.34; 142.21; 148.37; 157.75; 157.93; 159.50; 159.59. MS (FAB, *m/z* %): 711 (MH^+, 85); (MH^+−morpholine, 15). Anal. calcd for $C_{34}H_{30}N_8O_6S_2$ C, 57.45; H, 4.25; N, 15.76; S, 9.02. Found C, 57.82; H, 3.96; N, 15.59; S, 8.96.

3.5.25. 3,9-Bis(4-methoxyphenyl)-2,10-dipiperidino-pyrazino[5″,6″:4,5;3″2″:4′,5′]dithieno[3,2-*d*:3′,2′-*d*′]dipyrimidine-4,8(3*H*,9*H*)-dione (6y). (26%). Mp >300 °C. IR (KBr, cm^{-1}): 2934, 1679 (C=O), 1508, 1530, 1252, 1190, 920. ^{1}H NMR ($CDCl_3$): 7.02–7.39 (m, 8H, Ph); 3.89 (s, 6H, OCH_3); 3.34–3.37 (m, 8H, NCH_2); 1.35–1.48 (m, 12H, $NCH_2CH_2CH_2$). ^{13}C NMR ($CDCl_3$): 24.02 ($NCH_2CH_2CH_2$); 24.99 (NCH_2CH_2); 50.32 (NCH_2); 55.54 (OCH_3); 114.64, 129.48 (Ph); 118.68; 129.97; 142.35; 148.78; 157.75; 158.93; 159.26; 159.86. MS (FAB, *m/z* %): 707 (MH^+, 90). Anal. calcd for $C_{36}H_{34}N_8O_4S_2$ C, 61.17; H, 4.85; N, 15.85; S, 9.07. Found C, 61.46; H, 4.97; N, 15.68; S, 8.89.

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Synthesis and non-linear optical and redox properties of 6-nitro-6′-piperidyl-2,2′-bisbenzothiazole: a new type of push–pull molecules

Francisco López-Calahorra,[a,*] Mariano Martínez-Rubio,[a] Dolores Velasco,[a] Enric Brillas[b] and Lluís Julià[c]

[a]*Departament de Química Orgànica, Universitat de Barcelona, c/ Martí i Franquès, 1-11, 08028 Barcelona, Spain*
[b]*Departament de Química Física, Universitat de Barcelona, c/ Martí i Franquès, 1-11, 08028 Barcelona, Spain*
[c]*Departament de Química Orgànica Biològica, Institut d'Investigacions Químiques i Ambientals de Barcelona (CSIC), c/ Jordi Girona, 18-26, 08034 Barcelona, Spain*

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Abstract—The present paper describes the synthesis, the non-linear optical and redox properties of 6-nitro-6′-piperidyl-2,2′-bisbenzothiazole, the first described member of a new family of push–pull structures based in the 2,2′-bisbenzothiazole.

1. Introduction

Our research on new organic materials includes an interest in new molecules with non-linear optical (NLO) properties[1] and other dipolar moment-dependent properties. Organic molecules with large delocalized π-electron systems are good candidates for the display of large non-linear responses.[2] The main factor involved in presenting such properties is the presence and nature of electron-donating and -accepting groups. Furthermore, the extension and kind of conjugation path is crucial for the transfer of charge between the substituents in the presence of electric fields. A number of factors prompted us to synthesize and study the properties of 6-nitro-6′-piperidyl-2,2′-bisbenzothiazole (**1**): (a) our experience in the chemistry of benzothiazoles and 2,2′-bisbenzothiazoles,[3] (b) the scarce mention in the literature of related systems,[4] (c) the high thermal stabilities of systems derived from benzothiazole, characteristic very adequate for possible technological applications of this molecules, and (d) the good theoretical value for β(0) (34×10^{-30} esu) predicted for **1**,[5] similar to the described[6] for 4-(*N*,*N*-dimethylamino)-nitrostilbene (DANS) ($\beta(0)=55\times10^{-30}$ esu.

2. Results and discussion

Scheme 1 shows the synthetic path followed to prepare **1**. The strategy was to prepare the two benzothiazoles conveniently functionalized and link both by a coupling reaction. The first half of the molecule was prepared from 4-(*N*-piperidyl)aniline. The problem of the construction of substituted benzothiazoles consists in the formation of the corresponding 2-aminothiophenol from the adequate aniline. Several procedures[7] for performing this process are known but in general the yields are low, the manipulation difficult, or the methods incompatible with various functional groups. The only method that proved adequate in our case is the one described by Levkoev et al.[8] This method consists in reacting aniline and sodium thiosulfate in an oxidative medium. The second half-molecule was prepared by means of a standard Sandmeyer reaction[9] from commercial 2-amino-6-nitrobenzothiazole. Finally, the coupling reaction was done via reaction of the organozinc derivative of 6-(*N*-piperidyl)benzothiazole with the above bromoderivative.[10] The yields from this reaction are never high and the formation of some amount of the symmetric compound 6,6′-di(*N*-piperidyl)2,2′ bisbenzothiazole in unavoidable.

After preparing the desired compound, we studied its non-linear optic behavior by means the EFISH method, which permitted the calculation $\mu\beta(0)$ from the experimental value of $\mu\beta$ by using a simple two-level model.[11] The low solubility of **1** in the common organic solvents prevented us from determining the dipolar moment, μ; hence in this

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* Corresponding author. Tel.: +34-93-4021252; fax: +34-93-3397878; e-mail address: flopezcalahorra@ub.edu

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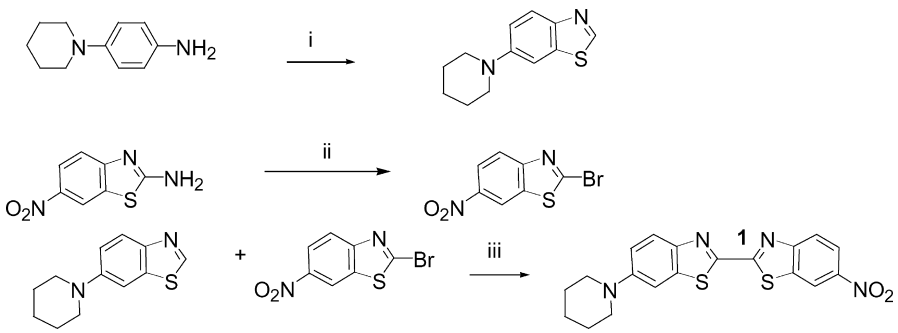


Scheme 1. *Reagents and conditons*. (i) $Na_2S_2O_3{\cdot}5H_2O$, $K_2Cr_2O_7$, AcOH, 0 °C, 8 h, r.t. ovemigth, 34%. (ii) $NaNO_2$, CuBr, HBr 48%. (iii) Bu–Li, anh. $ZnCl_2$, CuI.

paper the experimental results are expressed as $\mu\beta$ (375×10^{-48} esu) and $\mu\beta(0)$ (276×10^{-48} esu) in CH_2Cl_2 (λ=1.9 μm, static electric field=5 kV). Our calculated theoretical value for $\beta(0)$ is 34×10^{-30} esu, and for μ is 8.3×10^{-18} esu; consequently, the theoretically estimated value for $\mu\beta(0)$ is 283×10^{-48} esu. The concordance between this value and the experimental one is excellent, showing that the semiempirical method (AM1-RHF) used is very adequate in this kind of molecules.

To study the redox properties of **1**, we applied two complementary techniques: cyclic voltamperommetry and EPR.

As can be seen in Figure 1a, the cyclic voltammogram for the reduction of **1** in CH_2Cl_2 solution with tetrabutylammonium perchlorate (0.1 M) as electrolyte on Pt at 25 °C displayed two consecutive quasi-reversible one-electron redox couples, with standard potentials $E_1^o=-1.07$ V and $E_2^o=-1.46$ V vs SSCE (NaCl-saturated calomel electrode). Both peaks had the same cathodic and anodic heights and showed an increasing difference between their corresponding anodic and catodic peak potentials ($E_p^a-E_p^c$) from 0.10 V at a scan rate (ν) of 20 mV s^{-1} to 0.17 V at ν=200 mV s^{-1}. They can be ascribed to the equilibrium processes $\mathbf{1}+e^-\leftrightarrow\mathbf{1}^{\cdot-}$ and $\mathbf{1}^{\cdot-}+e^-\leftrightarrow\mathbf{1}^{2-}$. Similar results were obtained using DMF as solvent, indicating a large stability of the radical anion $\mathbf{1}^{\cdot-}$ and the dianion $\mathbf{1}^{2-}$ in both media. For the oxidation of the same solutions, their cyclic voltammograms exhibited an anodic irreversible peak either in DMF or in CH_2Cl_2 for $\nu<50$ mV s^{-1}. At higher scan rates in CH_2Cl_2 solution, its associated cathodic peak was already observed, the process behaving $\mathbf{1}\leftrightarrow\mathbf{1}^{\cdot+}+e^-$ as a quasi-reversible one-electron redox pair ($(E_p^a-E_p^c)$=0.12 V at ν=200 mV s^{-1}) with a standard potential E^o=0.95 V vs SSCE (Fig. 1b). These results indicate the electron accepting and donating ability of **1**, the radical cation species being of much lower stability than the radical anion.

The above cyclic-voltammetric behavior was confirmed by electron paramagnetic resonance (EPR) spectroscopy. So, while $\mathbf{1}^{\cdot-}$ was easily detected by chemical reduction (see Section 4), we were not able to detect $\mathbf{1}^{\cdot+}$.

To characterize the EPR spectrum of $\mathbf{1}^{\cdot-}$, we had previously registered the spectra of the radical anions chemically derived from 6-nitrobenzothiazole (**2**) and 2,2′-bisbenzothiazole (**3**). A multiplet of lines (g=2.0052; peak to peak linewidth, ΔH_{pp}=0.2 G) of a very stable radical was obtained when a degassed DMSO solution of **2** was treated with potassium *t*-butoxide at room temperature (Fig. 2a).

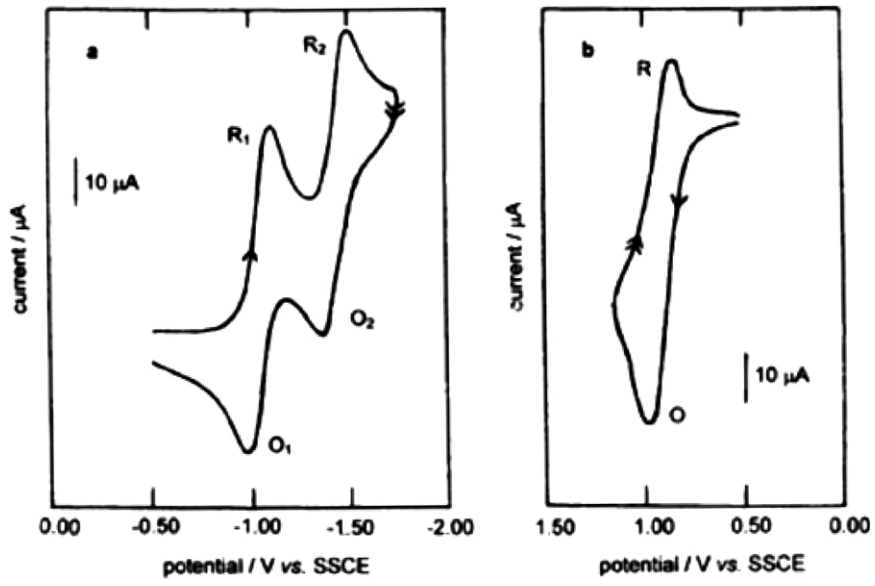


Figure 1. Cyclic voltammograms for the (a) reduction and (b) oxidation of a 1 mM **1** solution in CH_2Cl_2 with 0.1 M tetrabutylammonium perchlorate at 200 mV s^{-1} and at 25 °C on a 0.093 cm^2 Pt electrode. Initial potential: (a) −0.50 V, (b) 0.50 V. Reversal potential: (a) −1.800 V, (b) 1.200 V.

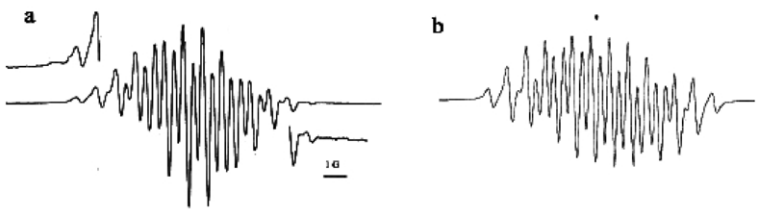


Figure 2. (a) EPR spectrum of $\mathbf{2}^{\cdot-}$ in DMSO solution at room temperature. (b) Computer simulation with the values given in Table 1.

The intensity of the lines slightly increased with short periods of ultraviolet irradiation.

This spectrum (Fig. 2b) was simulated[12] using the hyperfine splitting (hfs) values showed in Table 1, and was attributed to $\mathbf{2}^{\cdot-}$. The assignment of hfs values to the different nuclei in the molecule was verified by molecular orbital calculations, using the semiempirical MINDO/3 method as shown also in Table 1.

Anion radicals from thiazolyl derivatives have already been detected and well characterized by EPR;[13] however, as far as we know, no spectra of the reduced species from benzothiazolyls have been reported to date. Our attempts to generate the anion radical from the parent compound benzothiazole or from 6-morpholinebenzothiazole, a benzothiazole with a secondary amine as substituent, were unsuccessful. Therefore, the presence of an electron withdrawing group such as the nitro group is necessary to facilitate the electron transfer reaction and to stabilize the corresponding charged species.

Similarly, when degassed DMSO solution of 2,2′-bisbenzothiazole (**3**), treated with potassium *t*-butoxide, were prolonged irradiated (1 h) with UV light a persistent multiplet of very narrow lines (g=2.0043; ΔH_{pp}=0.09 G) was detected by EPR (Fig. 3a). This spectrum (Fig. 3b) was simulated by using the hfs values displayed in Table 1 and was attributed to $\mathbf{3}^{\cdot-}$. As before, the assignment was performed by MINDO/3. Two different conformations could be expected for 2,2′-bisbenzothiazole, however the spectrum at room temperature revealed the presence of only one radical species. As in the case of 2,2′-bisthiazole, the free rotation around C–C bond is hindered in the neutral molecule, and the energy barrier to rotation expected for the anion radical should be larger considering the partial double bond character, similar as it is suggested in 2,2′-bisthiazole by Pedully et al.[13] The consequence is the presence of only one isomer in solution.

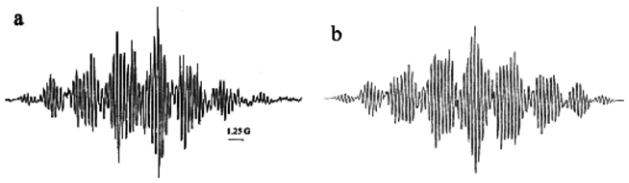
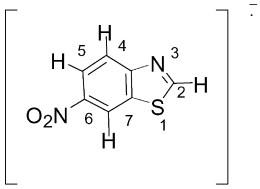


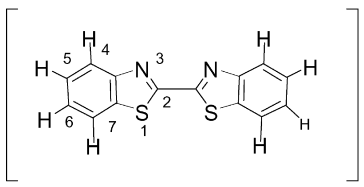
Figure 3. (a) EPR spectrum of $\mathbf{3}^{\cdot-}$ in DMSO solution at room temperature. (b) Computer simulation with the values given in Table 1.

When a degassed solution of 6-nitro-6′-(*N*-piperidy)-2,2′-bisbenzothiazole (**1**) ($\sim 10^{-2}$ M) in THF–DMSO (1:1) with an excess of potassium *t*-butoxide was irradiated with UV light, a symmetric multiplet of lines centered at g=2.0048 was detected by EPR (Fig. 4a). This radical species was stable and was attributed to $\mathbf{1}^{\cdot-}$. One of the simulations which roughly fits to the experimental spectrum (Fig. 4b) was performed by using the following hfs values in gauss: a(N)=6.87, a(N)=2.87, a(1H)=2.20, a(1H)=1.94, a(3H)=0.9, ΔH_{pp}=0.7 G. Values from other nuclei in the molecule should be less than the linewidth. As before, the presence of only one radical species suggests only one isomer in solution at room temperature.

Table 1. Experimental and calculated hyperfine coupling constants (a) for radical anions derived from 6-nitrobenzothiazole (**2**) and 2,2′-bisbenzothiazole (**3**)



2 $^{\cdot-}$



3 $^{\cdot-}$

	a (exp)[a]	a (theor)[b]		a (exp)[a]	a (theor)[b]
$\mathbf{2}^{\cdot-}$	1.7(N3)	614	$\mathbf{3}^{\cdot-}$		684
	0.85(N6)	511		3.34(N3,N3′)	806
	2.02(H2)	1175		2.16(H4,H4′)	718
	0.85(H4)	670		0.56(H5,H5′)	791
	0.85(H5)	898		1.88(H6,H6′)	672
	1.28(H7)	1110		0.28(H7,H7′)	

[a] In Gauss.
[b] Arbitrary units.

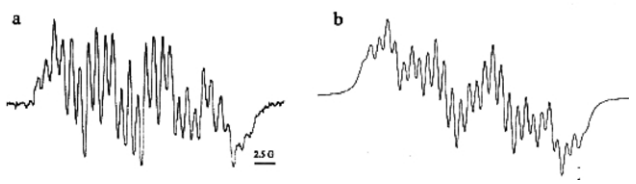


Figure 4. (a) EPR spectrum of $\mathbf{1}^{\cdot-}$ THF–DMSO (1:1) solution at room temperature. (b) Computer simulation with the values given in the text.

3. Conclusion

We report the first synthesis of 6-nitro-6′-(*N*-piperidy)-2,2′-bisbenzothiazole, a new push–pull molecule. This molecule shows good NLO properties and a dual, oxidative and reductive, three-stage single-electron redox character. It shows a quite stable radical anion detected by EPR. Related to this radical anion, the first EPR spectra of radical anions derived from bisbenzothiazoles is also described

4. Experimental

4.1. General

Melting points were determined using a Köfler apparatus provided with a Reichert Thermovar microscope and are uncorrected. TLC was carried out on SiO_2 (Alugram SIL G/UV$_{254}$ Macherey–Nagel 0.25 mm) and spots were located with UV light. Flash chromatography was carried out on SiO_2 (Silica Gel 60 A CC, Merck). Organic extracts were dried over anhydrous $MgSO_4$, and solutions were evaporated under reduced pressure with a rotatory evaporator. IR spectra were recorded on a Nicolet 510 FT-IR spectrometer. NMR spectra were measured with Varian Gemini-200 (200 MHz) and Varian Unity-300 (300 MHz) spectrometers; data are given in δ/ppm, referenced to TMS for ^{1}H NMR, to $CDCl_3$ (77.0 ppm) for ^{13}C NMR and J values are given in Hz. Mass spectra were measured in chemical impact (CI, NH_3) mode with a Hewlett–Packard 5988A spectrometer, or with a Fisons VG-Quattro spectrometer. The samples were then introduced into a matrix of 2-nitrobenzyl alcohol for FAB analysis and subjected to bombardment with cesium atoms.

4.1.1. Electron spin resonance of radical anions from 6-nitro-6′-piperidyl-2,2′-bisbenzothiazole (1), 6-nitrobenzothiazole (2) and 2,2′-bisbenzothiazole (3). (a) *Preparation of the samples*: solutions of **1**, **2** and **3** (10^{-2} M) in dimethylsulfoxide in a quartz tube were degassed by bubbling argon while an excess of dimethylsulfoxide solution of potassium *t*-butoxide was added. These colored solutions were introduced into the cavity of the spectrometer at room temperature and their spectra were registered while irradiated with light from a high-pressure mercury lamp (500 W).

(b) EPR spectra were recorded with a Varian E-109 spectrometer working in the X band. Determinations of the g values of the radicals were made with DPPH (g=2.0037) as standard.

4.1.2. Synthesis of 6-(*N*-piperidyl)benzothiazole. Dihydrogensulfate of *N*-(4-aminophenyl)piperidine (1.59 g, 4.25 mmol) and sodium thiosulfate pentahydrate (2.04 g, 8.23 mmol) were dissolved in 18% aqueous solution of acetic acid (3.2 mL) at 0 °C. A solution of potassium dichromate (411 mg, 1.40 mmol) in diluted acetic acid (6.5%, 8.3 mL) was added for 1 h. The reaction mixture was stirred in an ice bath for 8 h and overnight at room temperature. The formed precipitate was filtered, washed with water, suspended in formic acid (15 mL) and heated under reflux for 3 h. The formic acid was removed, the residue diluted with water (15 mL), neutralized with sodium bicarbonate and extracted with methylene chloride. The solvent was removed and 6-(*N*-piperidyl)benzothiazole (305 mg, 34%) was isolated as a white solid by column chromatography over silicagel, eluting with CH_2Cl_2–$EtOOCCH_3$ 9:1; mp 87–88 °C; TLC (SiO_2, CH_2Cl_2–$EtOOCCH_3$ 9:1); R_f=0.34; IR (KBr): ν=2935, 2854 (C–H st.); 1600, 1542 (arom.); 1480, 1383 (thiazole); 1237 (C–N st.); 940, 876, 824 (C_{ar}–H) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$, TMS_{int}): δ=8.72 (s, H^6, 1H), 7.93 (d, H^4, J_{3-4}=9.2 Hz, 1H), 7.34 (d, H^1, J_{1-3}=2.2 Hz, 1H), 7.17 (dd, H^3, J_{1-3}=2.2 Hz, J_{3-4}=9.2 Hz, 1H), 3.19 (t, H^8, J_{8-9}=5.4 Hz, 4H), 1.71 (sc, H^9, J_{8-9}=5.4 Hz, 4H), 1.59 (sc, H^{10}, 2 H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ=150.49 (C^6), 146.50 (C^5), 135.21 (C^7), 123.30 (C^4), 117.83 (C^3), 107.11 (C^1), 51.32 (C^8), 25.81 (C^9), 24.20 (C^{10}) ppm; MS (70 eV, CI, NH_3): m/z: 219 [M+1]$^+$.

4.1.3. Synthesis of 2-bromo-6-nitrobenzothiazole. 2-Amino-6-nitrobenzothiazole (5 g, 25.6 mmol) was mixed under vigorous stirring with 85% phosphoric acid (23 mL) at 50 °C. The solution was cooled to −20 °C and a solution of sodium nitrite (1.91 g) and water (2.2 mL) was slowly added. After 1 h, the resulting suspension was poured over a solution of cuprous bromide (4.51 g, 31.4 mmol) in 48% hydrobromic acid (25 mL) at room temperature and mechanically stirred. After 1 h, the mixture was heated at 40 °C for 2 h, diluted to a final volume of 500 mL and extracted repeatedly with methylene chloride. The organic layer was dried over anhydrous magnesium sulfate, the solvent removed and 2-bromo-6-nitrobenzothiazole (4.66 g, 70%) isolated as an orange solid; mp 202–204 °C dec. (lit. 206–7 °C); TLC (SiO_2, CH_2Cl_2); R_f=0.46; IR (KBr): ν=3100 (C_{ar}–H st.); 1601, 1568 (sis. arom.); 1510 (C_{ar}–NO_2 st. as.); 1344 (C_{ar}–NO_2 st. si.); 884, 843, 751 (C_{ar}–H) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$, TMS_{int}):-$\delta_{=8.76\ (d,\ H}{}^1$, J_{1-3}=1.2 Hz, 1H), 8.35 (dd, H^3, J_{1-3}=1.2 Hz, J_{3-4}=9.2 Hz, 1H), 8.08 (d, H^4, J_{3-4}=9.2 Hz, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ=155.89 (C^5), 145.33 (C^2), 144.67 (C^7), 137.69 (C^6), 123.19 (C^4), 122.14 (C^3), 117.37 (C^1) ppm.; MS (70 eV, CI, CH_4): m/z=259, 261 [M+H$^+$].

4.1.4. Synthesis of 6-nitro-6′-piperidyl-2.2′-bisbenzothiazole. 6-(*N*-piperidyl)benzothiazole (2.40 g, 11.0 mmol) was dissolved in anhydrous tetrahydrofurane (35 mL) under inert atmosphere and at −100 °C. Over this solution butyllithium (7,5 mL 1.6 M in hexane, 12.0 mmol) was slowly added. After addition, the mixture was stirred in the same condition for further 20 min and anhydrous zinc chloride (1.67 g, 12.2 mmol) in anhydrous tetrahydrofurane (15 mL) was added. The reaction mixture was maintained for 40 min and 2-bromo-6-nitrobenzothiazole (2.90 g, 11.2 mmol),

dichlorobis(triphenylphosphine)palladium(II) (488 mg, 0.70 mmol) and cuprous iodide (353 mg, 1.85 mmol) were added in this order and in solid state. The mixture was heated for 15 h at 50 °C. The solvent was removed, and the residue was treated with hydrochloric acid (250 mL 0.1 M). The aqueous layer was extracted repeatedly with methylene chloride, the organic layer dried with anhydrous magnesium sulfate, filtered and the solvent was removed. 6-nitro-6′-piperidyl-2.2′-bisbenzothiazole was isolated as a red solid (1.41 g, 32%) by column chromatography over silicagel, eluting with CH_2Cl_2–$EtOOCCH_3$ in a gradient from 10:0 to 9:1. The product was purified for elemental analysis by sublimation at 280 °C and 0.5 mm Hg; mp 298–300 °C; TLC (SiO_2, CH_2Cl_2–$EtOOCCH_3$ 30:1); R_f=0.48; IR (KBr): ν=3115 (C_{ar}–H st.); 2937, 2860 (C–H st.); 1603, 1546 (sis. arom.); 1517 (C_{ar}–NO_2 st. as.); 1453, 1383 (thiazol); 1337 (C_{ar}–NO_2 st. si.); 1229 (C–N st.); 895, 858, 814 (C_{ar}–H) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, TMS_{int}): δ=8.83 (d, H^8, J_{8-10}=2.4 Hz, 1H), 8.34 (dd, H^{10}, J_{8-10}=2.4 Hz, J_{10-11}=8.7 Hz, 1H), 8.13 (d, H^{11}, J_{10-11}=8.7 Hz, 1H), 7.94 (d, H^4, J_{3-4}=9.0 Hz, 1H), 7.28 (d, H^1, J_{1-3}=2.4 Hz, 1H), 7.19 (dd, H^3, J_{1-3}=2.4 Hz, J_{3-4}=9.0 Hz, 1H), 3.32 (t, H^{15}, J_{15-16}=5.4 Hz, 4H), 1.73 (sc, H^{16}, J_{15-16}=5.4 Hz, 4H), 1.65 (sc, H^{17}, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=167.46 (C^{12}), 157.28 (C^{13}), 155.37 (C^6), 151.50 (C^9), 146.67 (C^5), 145.37 (C^2), 138.73 (C^{14}), 135.81 (C^7), 124.52 (C^{11}), 123.68 (C^4), 122.03 (C^{10}), 118.42 (C^8), 117.95 (C^3), 105.49 (C^1), 50.19 (C^{15}), 25.62 (C^{16}), 24.23 (C^{17}) ppm; UV (CH_2Cl_2): $\lambda_{máx}$ (nm)/ε ($M^{-1}\,cm^{-1}$)=450/2,6×10^4, 347/1,0×10^4, 302/1,5×10^4; MS-FAB(+): m/z=396 ($M^{\cdot+}$); elemental analysis: found C: 57.55%, H: 3.94%, N: 14.20%, S: 16.12%, $C_{19}H_{16}N_4O_2S_2$ requires C: 57.57%, H: 4.07%, N: 14.13%, S: 16.17%).

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Enantioselective binding of amino acids and amino alcohols by self-assembled chiral basket-shaped receptors

Beatriu Escuder,*,† Alan E. Rowan, Martinus C. Feiters* and Roeland J. M. Nolte

Department of Organic Chemistry, Katholieke Universiteit Nijmegen, Toernooiveld 1, NL-6525 ED Nijmegen, The Netherlands

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Abstract—Amino acid appended diphenylglycoluril-based chiral molecular receptors **2** and **3** have been prepared and their aggregation has been studied in water at various pH's and in chloroform. The binding of several biologically relevant guests with aromatic moieties to these aggregates has been studied with UV–Vis spectroscopy in competition experiments with 4-(4-nitrophenylazo)resorcinol (Magneson) and 2-(4-hydroxyphenylazo)benzoic acid (HABA) as probes. Aggregates of chiral host **2b** showed binding of catecholamines and aromatic amino acids in an aqueous environment, as well as discrimination between amino acid enantiomers, and can be considered a mimic for adrenergic receptors.

1. Introduction

The design of synthetic molecular receptors that mimic the natural binding sites for hormones, neurotransmitters, and other essential messengers is a topic of intense research with a special emphasis on their enantioselective recognition. Although there is significant progress toward the understanding of the natural systems, synthesis of model compounds can contribute to this understanding and in addition find applications in drug delivery, catalysis, etc.[1,2] L-Adrenaline has some important biological functions. It belongs to the family of adrenal medulla hormones that have a large influence on the storage and mobilisation of glycogen and fatty acids and the corresponding metabolic pathways. In addition, it is a neurotransmitter of the adrenergic nervous system and has an effect on α and β receptors. The biosynthetic precursors of adrenaline, the catecholamines, have also very interesting biological properties and are of great therapeutical value. In the recent years a great effort has been made in the X-ray crystallographic characterization and modeling of membrane-bound proteins as well as the design of synthetic model receptors for their binding sites.[3–5] Schrader described phosphonate containing cyclophanes that bind catecholamines and amino acids in organic solvents such as DMSO or methanol and in water.[6–12] Other authors have reported several crown ether containing receptors that bind, and in some cases transport, adrenaline, ephedrine, L-dopa and dopamine in water although with moderately low binding constants.[13–20] More recently, a copper complex of a pyrazole-containing cryptand that binds dopamine in water with a high binding constant has been reported.[21,22]

Diphenylglycoluril based clip molecules have been prepared and extensively studied in the Nolte group over the past 10 years. These hosts possess a well defined cavity that allows the binding of different phenolic guests via a combination of several non covalent interactions (H-bonding, π–π stacking, and the cavity effect).[23] The introduction of crown ether chains and alkyl tails to these receptors leads to a new generation of the so-called amphiphilic basket receptors, which are able to bind also alkaline metal ions and ammonium salts, and aggregate in water into well defined nanostructures.[24,25] Here we describe a new series of amino acid appended diphenylglycoluril based receptors bearing L-lysine and L-2,3-diamino propionic acid residues that bind aromatic amino acids and catecholamines in water at different pH values and, in some cases, recognize them enantioselectively.[26] As these receptor molecules have pronounced polar and apolar sides, they are amphiphilic and can be expected to aggregate in both aqueous and organic media.[27]

2. Results and discussion

2.1. Synthesis

The synthesis of molecular receptors **2a**,**b** and **3a**,**b** was carried out as described in Scheme 1. Compounds **2a**,**b** were

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* Corresponding authors. Tel.: +34-964-728235; fax: +34-964-728214; e-mail address: escuder@qio.uji.es
† Present address: Dep. Química Inorgànica i Orgànica, Universitat Jaume I, E-12080 Castelló, Spain.

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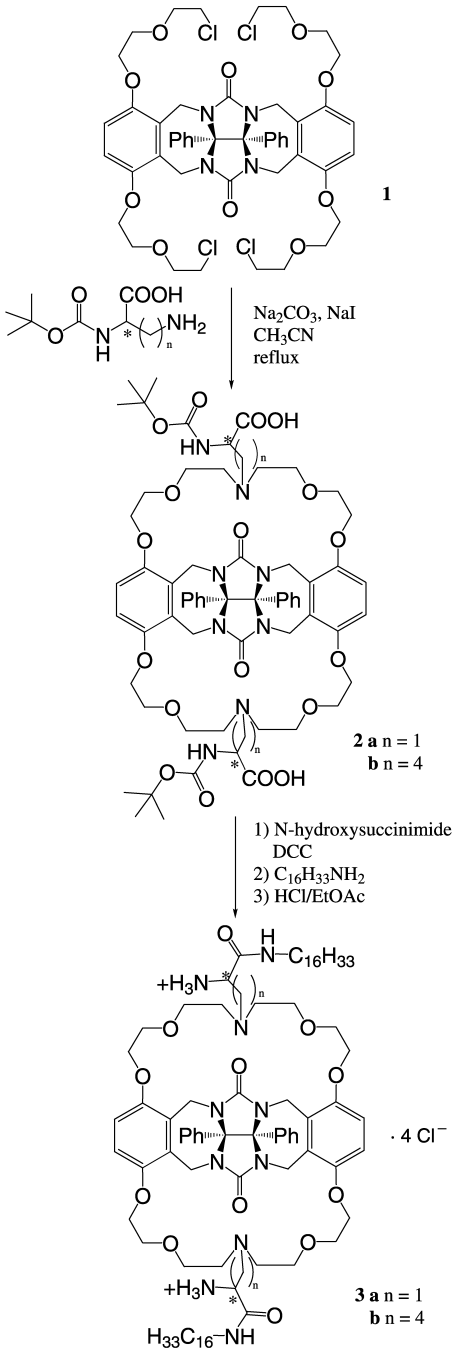

Scheme 1.

prepared in a good yield from the tetrachloride **1** and the corresponding N^{α}-Boc protected amino acid using Finkelstein conditions. The carboxylic acid functions were coupled with two equivalents of hexadecyl amine to give the *N*-protected precursors of amphiphiles **3a**,**b**. The *t*-butoxy-carbonyl protecting group was removed with 4 M HCl in ethyl acetate to give the corresponding hydrochloride as a white precipitate. After slightly basic work-up the free amines were fully characterised by NMR, MS and elemental analysis.

2.2. Aggregation studies

The aggregation behaviour of compounds **2a**,**b** and **3a**,**b** was studied in water.[28] The critical aggregation concentration (CAC) of these compounds at 20 °C was determined by measuring the conductivity at different concentrations. As can be seen in Figure 1, a change in the slope of the plot of the conductivity against the concentration is clearly produced at 3.5×10^{-5} and 1.5×10^{-6} M for **2a** and **2b** respectively, and at 3×10^{-6} and 4×10^{-6} M for **3a** and **3b**. The observed differences are the result of an increase in the mobility of the ions as well as in the number of independent charge carriers upon going from an aggregated towards a non-aggregated state. The difference of one order of magnitude observed between the CAC of compounds **2a** and **2b** is significant enough to be noteworthy. Both compounds exist as zwitterionic species in water but in the case of compound **2a** a six-membered cyclic intramolecular ionic pair could be formed between the carboxylate group and the protonated tertiary nitrogen atom of the aza-crown moiety.

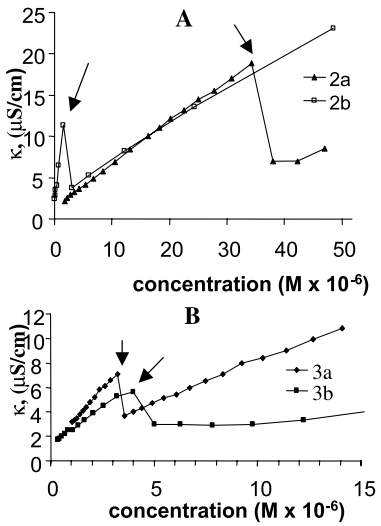

Figure 1. Plot of the conductivity vs concentration of solutions of compounds **2a**,**b** (A) and (B) **3a**,**b** in water at 20 °C. (The critical aggregation concentration for each compound is pointed by an arrow. All the experiments were carried out in duplo).

Transmission electron microscopy reveals that receptor **2b** forms vesicles in water with diameters ranging between 50 and 100 nm (Fig. 2B). The vesicular structure of the aggregates was confirmed by encapsulation of ethydium bromide. A dispersion of compound **2b** was prepared in the presence of 10^{-4} M ethidium bromide and subsequently filtered through a Sephadex G25 column monitoring the absorbance of **2b** and the fluorescence of the entrapped dye. Fractions containing both compounds were found at elution volumes of ca. 25–100 mL, whereas the free dye was

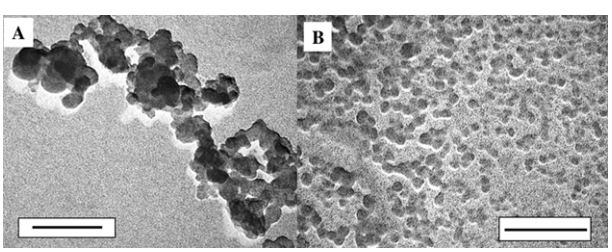

Figure 2. (A) Transmission electron micrograph of a 1% wt dispersion of compound **2a** in water. (B) idem of a dispersion of compound **2b** in water (Pt-shadowing, bars represent 200 nm).

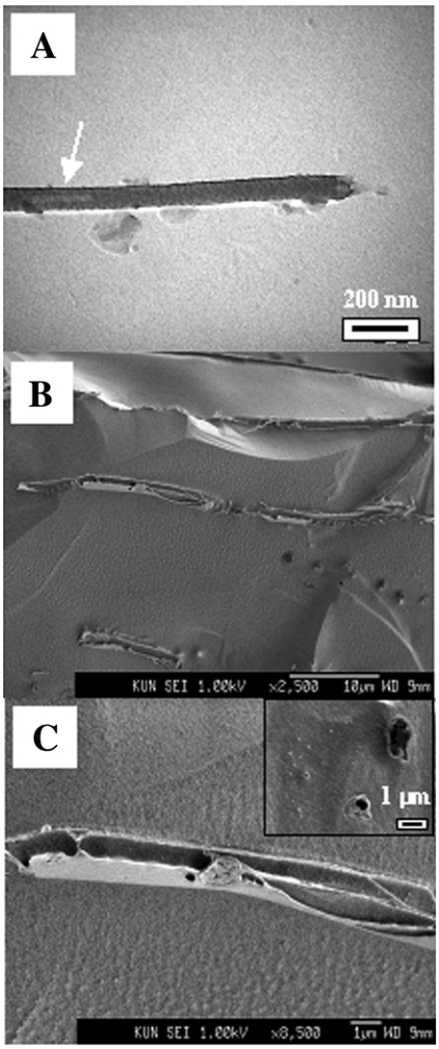

Figure 3. (A) Transmission electron micrographs of a 1% wt dispersion of compound **3a** in water showing tubular architectures (Pt-shadowing,). (B) and (C) Cryo-scanning electron micrographs of a 1% wt dispersion of compound **3a** in water showing hollow tubes. The inset shows the side view of the tubes.

retained at the top of the column. In contrast, compound **2a** at the same concentration formed similar but slightly less-defined assemblies in water, only a mixture of round and flat lamellae could be observed (Fig. 2A).

The effect of pH was studied for compound **2b** by transmission electron microscopy (not shown). The dispersion was prepared in 1 mL of 20 mM sodium monophosphate (pH=4.5) and the electron micrographs revealed the presence of the vesicles and their preference for further assembly. The vesicles clustered forming elongated aggregates of various micrometers of length and less than 100 nm width. In contrast to **2b**, compound **3a** aggregates to form thin lamellae in water that roll up to form large tubular objects of several micrometers of length (Fig. 3A). Cryo-SEM micrographs clearly revealed that these tubular objects are in fact hollow tubes of ca. 1 μm diameter and more than 10 μm in length (Fig. 3B).

Transmission electron microscopy of host **3b** in water revealed a mixture of different aggregates (vesicle-like,

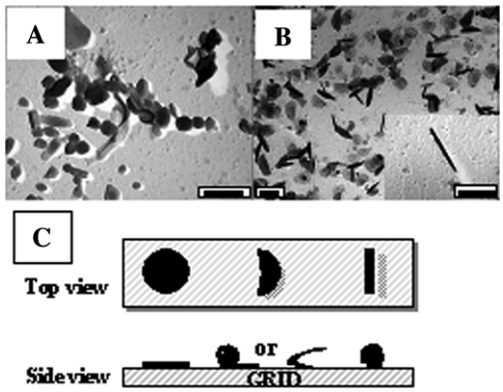

Figure 4. (A) Transmission electron micrographs of a 1% wt dispersion of compound **3b** in water 1 h after sonication. (B) idem after one day. (Pt-shadowing, bars represent 400 nm). (C) Schematic drawing of the aggregates onto the grid.

tubes, flat tapes, see Figure 4A). Upon standing for 1 day, they reorganized to give more uniform lamellar structures. As can be seen in Figure 4B, compound **3b** self-assembles to form flat disks that can fold or roll up to various degrees to give semicircular flat objects and extended structures (Fig. 4C). The same grid was investigated by scanning electron microscopy and it was revealed that flat disk-like objects of ca. 550 nm diameter and 50 nm thickness occur at various angles, along with folded semicircular structures and extended structures which we propose to arise from completely rolled up disks.[29] The same aggregates were also observed when the experiment was carried out in 0.1 M HCl (Fig. 5A and B). It is logical to assume that all the amino groups would be protonated in water as well as in the acidic solution. When the assemblies were made in a 0.1 M NaOH aqueous solution, different aggregates were found (Fig. 5C). Flat tapes with lengths between 400 nm and 2.5 μm and widths between 200 and 400 nm were observed together with tubes of 50 nm diameter and similar lengths.

As amphiphiles constructed from lysine and its analogues contain many moieties that can be involved in intermolecular hydrogen bonding, we considered it of interest to also study the aggregation of compounds **2a**,**b** and **3a**,**b** in a solvent that would allow the formation of such hydrogen bonds, like chloroform. The strong aggregation of these compounds was already evidenced by the broadening of the ^{1}H NMR signals in $CDCl_3$, in contrast to the sharp resonances observed for solutions of the previously reported *N*-functionalised hosts of this type, and was further confirmed by electron microscopy. Compound **2b** self-assembled into well-defined thin tube-like structures (diameter ca. 5 nm) in chloroform as can be seen in Figure 6A inset. After few hours, these tubular structures further aggregate to give a flat array of aligned and superimposed layers of tubes (Fig. 6A).

In contrast to the previously reported receptors these compounds possess amino acid arms which are the potential sites for additional H-bonding or electrostatic interactions. This feature is thought to be responsible for the observed aggregation behaviour since intermolecular hydrogen bonds can now also be formed between the amide functions leading to extended structures. The aggregation behaviour of molecular receptors **3a** and **3b**, possessing two alkyl tails

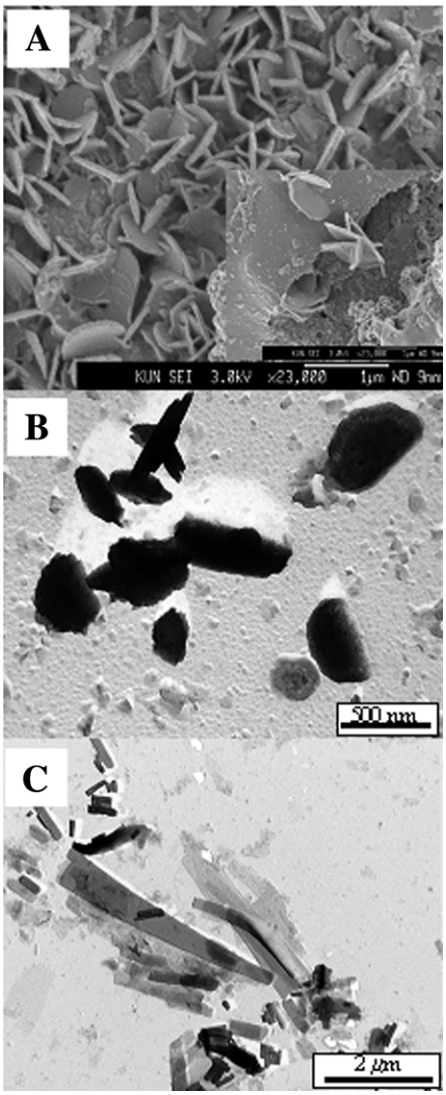

Figure 5. (A) SEM picture of a dispersion of compound **3b** in 0.1 N HCl. (B) Transmission electron micrographs of a dispersion of compound **3b** in 0.1 N HCl (Pt-shadowing). (C) idem in 0.1 N NaOH.

in its structure, was also studied in chloroform by transmission electron microscopy revealing curved bilayer aggregates (Fig. 6B and C).

2.3. Binding studies

The binding of adrenaline and other catecholamines and amino acids by their natural receptors is thought to occur via a combination of non-covalent interactions (viz. electrostatic interactions between aspartate or glutamate protein residues and the ammonium groups of the substrates, H-bonding between the substrate and serine or lysine residues, $\pi-\pi$ interactions between the substrate aromatic moiety and the aromatic residues of the protein, and the $\pi-$cation interaction between the ammonium group and the electron-rich aromatic system of tyrosine and tryptophan residues).[5] On the other hand, an important goal for the design of synthetic receptors is the enantioselective recognition of guests. Considerable work has been devoted to the design and syntheses of chiral hosts for amino acids and other biologically relevant guests.[30–39] Compounds

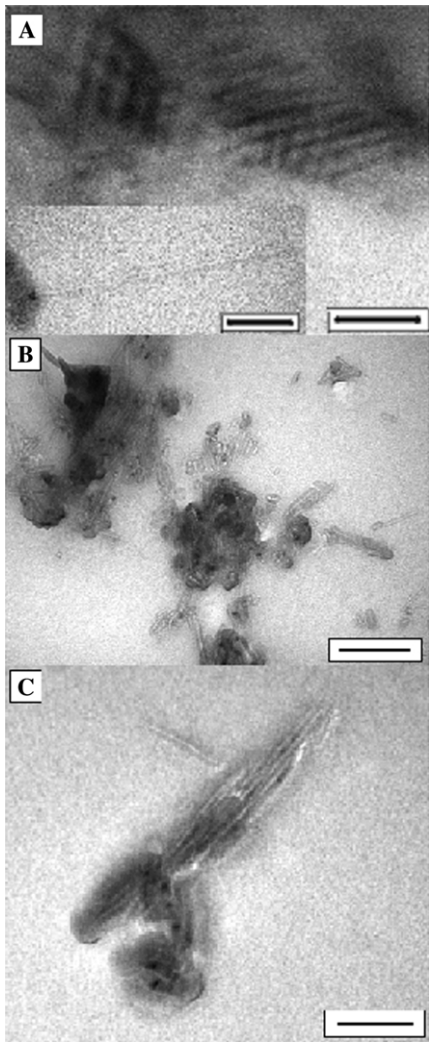

Figure 6. Transmission electron micrographs of 1% wt. $CHCl_3$ solutions of (A) compound **2b**, (B) compound **3b** and (C) compound **3a**. (Pt-shadowing, bars represent 100 nm).

2a,**b** possess the chiral functionalities required to perform such enantioselectivity. The hosts present a pocket-like geometry and also their aggregation behaviour suggests that they could be incorporated easily into a membrane as a carrier or membrane-bound receptor mimic.

UV–Vis spectroscopy was used for the determination of the binding constants. The absorption signals of both the host and the guest unfortunately overlapped and here a competition experiment was carried out using Magneson (**4**, 4-(4-nitrophenylazo)resorcinol) or HABA (**5**, 2-(4-hydroxyphenylazo)benzoic acid) as a competing dye (Chart 1). The binding of Magneson by compound **2b** was studied in water at 20 °C by UV–Vis spectroscopy above its CAC.[40] When a sample containing the dye (**4**) was titrated with **2b** an increase in the absorbance at 450 nm was observed reaching almost complete saturation when ca. 2 equiv. of the host molecule were added. It was recently shown that for similar host molecules, this behaviour is in accordance with the formation of vesicles in which only half of the sites are available for binding the guest.[25] The addition of excess host induced small changes in the UV spectra probably because the vesicle bilayer is not a

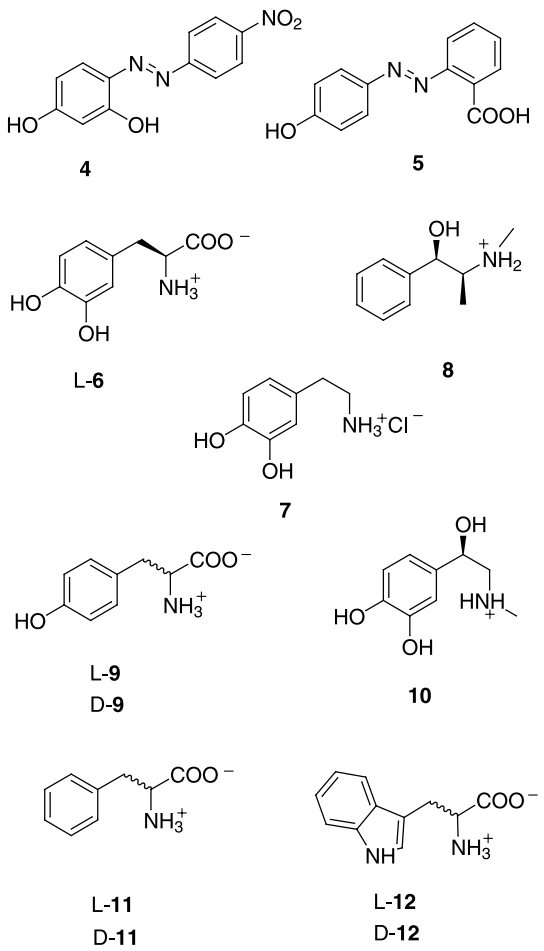

Chart 1.

sufficiently impermeable barrier and some molecules of Magneson (**4**) can cross it and be bound by the inner binding sites. The binding constant for Magneson (**4**) was calculated by fitting the data assuming only half of the hosts bound in a 1:1 host–guest ratio, $K_{ass}=(4.4\pm1.2)\times10^4\ M^{-1}$ (Table 1).

The binding of the different guests (Chart 1) with compound **2b** was first studied above its CAC at pH=8 by UV–Vis competition by adding different amounts of the guest to a solution containing the host **2b** and Magneson (**4**).[41] The Magneson absorption band at 450 nm decreases with the addition of the guest and the presence of an isosbestic point at ca. 290 nm agrees with the presence of a single complexation equilibrium which can be fitted to a 1:1 complex stoichiometry.

Table 1. Binding parameters of compound **2b** with the probes **4** and **5** at 20 °C

Probe	Solvent	K_{ass} (M^{-1})[a,b]	$\Delta\varepsilon$[b,c]	ΔG (kJ mol^{-1})[b]
4	pH 8 buffer[d]	$(4.4\pm1.2)\times10^4$	17,150	−26.0(0.7)
5	pH 4.5 buffer[d]	$(2.5\pm0.2)\times10^4$	3724	−24.7(0.2)

[a] All the experiments were carried out in duplo.
[b] Errors are given between parentheses.
[c] Difference between the extinction coefficients of guest and complex in absolute value.
[d] 0.02 M phosphate buffer solutions.

Table 2. Estimated binding parameters for **2b** and guests **6**–**12** determined by UV–Vis competition with Magneson **4** and HABA **5** at 20 °C

Probe	Guest	K_{ass} ($\times10^3\ M^{-1}$)[a]	ΔG (kJ mol^{-1})[a]	$\Delta\Delta G$ (kJ mol^{-1})[b]
4[c]	**6**	4(1)	−20.2(0.6)	—
4[c]	**7**	0.9(0.5)	−16.5(1.3)	—
4[c]	**8**	4.7(0.4)	−20.6(0.2)	—
4[c]	L-**9**	10(3)	−22.4(0.7)	—
5[d]	**6**	1.9(0.3)	−18.4(0.4)	—
5[d]	**7**	1.7(0.4)	−18.1(0.6)	—
5[d]	**8**	4.7(0.5)	−20.6(0.3)	—
5[d]	L-**9**	2.2(0.5)	−18.7(0.6)	4.9
5[d]	D-**9**	16(2)	−23.6(0.3)	
5[d]	**10**	12.8(0.5)	−23.0(0.1)	—
5[d]	L-**11**	26(5)	−24.7(0.5)	−1.8
5[d]	D-**11**	12(1)	−22.9(0.2)	
5[d]	L-**12**	17(2)	−23.7(0.3)	2.9
5[d]	D-**12**	56(7)	−26.6(0.3)	

[a] Errors given between parentheses.
[b] Value for the difference $\Delta G_L-\Delta G_D$.
[c] Magneson (**4**), pH 8, 450 nm.
[d] HABA (**5**), pH 4.5, 350 nm.

For guests **6**–**9** moderate values for the binding constant were found (Table 2). Upon comparison of the relative guest structures the differences in K_{ass} can be attributed to either the presence or absence of the hydroxyl functions in the aromatic ring and the carboxylate group in the side chain. The highest binding constant was observed for L-tyrosine (L-**9**), $K_{ass}=(10\pm3)\times10^3\ M^{-1}$. This value slightly decreases when either the phenolic group is not present as in the case of ephedrine (**8**), $K_{ass}=(4.7\pm0.4)\times10^3\ M^{-1}$, or when an extra hydroxyl is introduced, as in L-dopa (L-**6**), $K_{ass}=(4\pm1)\times10^3\ M^{-1}$. The effect of repulsion of a negative charge in the guest by the negatively charged carboxylates in the host is noticeable in the in K_{ass} going from dopamine (**7**), which lacks the carboxylate, to L-dopa (**6**), where it is present. As is well known, one of the main forces responsible for the binding of guests in hosts in water is the hydrophobic interaction. The release of water molecules from the cavity when the guest is bound and the decrease of the apolar surface in contact with water in the complex both favour binding. This will be a common factor for all the guests that we studied. All of them possess a hydrophobic aromatic moiety by which the molecule is pulled into the

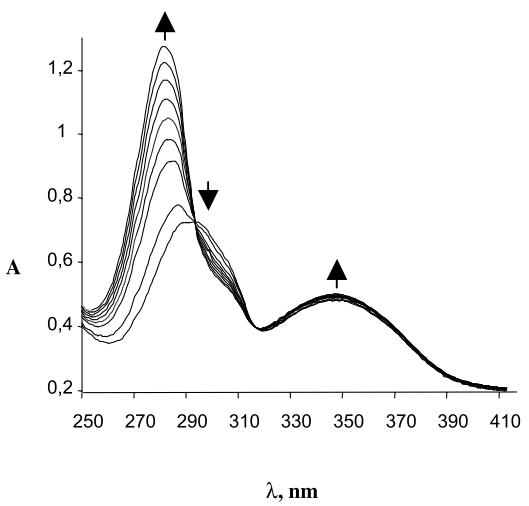

Figure 7. UV/VIS binding competition curves for the **2b**:2-(4-hydroxyphenylazo)benzoic acid (**5**) complex with L-dopa (**6**) at pH=4.5.

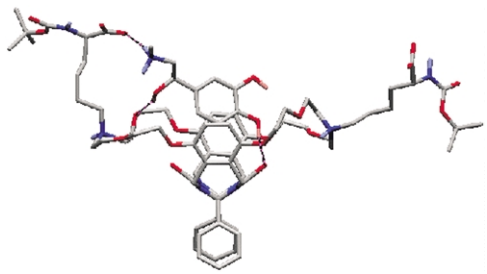

Figure 8. Calculated minimum energy geometry for the 1:1 complex of **2b** and adrenaline (**10**), hydrogen atoms have been omitted for clarity.

cavity while the differences in binding between them are caused by differences in solvation and the differing complementarity between the guests and the host. Thus, an increase in the number of hydroxyl functions will, in principle, increase the solvation of the guest in water and then decrease slightly the binding constant as is obvious from a comparison of the binding constants of dopamine (**7**) with ephedrine (**8**). The later which lacks OH groups would be more poorly solvated by water and then bound deeper in the cavity. Although it is a more polar group, the presence of a carboxylate also exerts a favourable effect, either by orientating the guest inside the cavity or by electrostatic charge–charge or dipole–charge interactions.

The important role that π–cation interactions play in biological binding sites is well documented.[42,43] The protonated nitrogen atoms on the aza-crown moiety could play a role in the binding process. In order to ensure the full protonation of the tertiary amino functions of the azacrown moieties the binding studies were also carried out at slightly acidic conditions in a 0.02 M NaH_2PO_4 buffer solution of pH 4.5.[44] For these studies, HABA (2-(4-hydroxyphenyl-azo)benzoic acid, **5**), with a binding constant of $(2.5\pm0.2)\times10^4\ M^{-1}$ for the 1:1 complex with **2b**, was used as a UV–Vis probe instead of Magneson (**4**), because the later had inconvenient additional absorption bands at low pH. Following a similar procedure as for the former case the binding of guests **6**–**12** with host **2b** was studied (Table 2). The absorption spectra for the competition experiments with HABA (**5**) and L-dopa (**6**) in host **2b** are shown in Figure 7. In this case, the absorption band of HABA at ca. 350 nm increases upon the addition of the guest.

The binding constants for host **2b** with L-dopa (L-**6**), dopamine (**7**) and ephedrine (**8**) measured at pH 4.5 were similar to those observed at higher pH. In contrast to binding at pH 8, the binding of L-tyrosine (L-**9**) is reduced at pH 4.5 (Table 2). The binding of adrenaline (**10**) as a guest was also studied giving a binding constant of $(12.8\pm0.5)\times10^3\ M^{-1}$, one order of magnitude larger than those obtained for the former guests, and considerably higher than the values found in literature in aqueous solution.[10,16] In this case, the presence of the methyl group increases the hydrophobicity of the guest resulting in a strong binding spite of the presence of OH groups in the molecule. In order to prove the role played by the carboxylate groups in the binding of this kind of guests both enantiomers of the amino acids phenylalanine (L-**11**, D-**11**) and tryptophan (L-**12**, D-**12**) as well as the D-tyrosine (D-**9**) were also studied. In all cases, the binding constants were one order of magnitude higher than those obtained for dopamine (**7**) and ephedrine (**8**). It is clear that electrostatic or charge–dipole interactions play an important role in the binding process.

2.4. Enantioselective binding

Enantioselective binding was observed when the pair of enantiomers of tyrosine (L-**9**, D-**9**), phenylalanine (L-**11**, D-**11**) and tryptophan (L-**12**, D-**12**) were studied (see Table 2). In the first case, a $\Delta\Delta G$ ($\Delta G_L - \Delta G_D$) of 4.9 kJ/mol was found in favour of the D-enantiomer (D-**9**). In a racemic guest solution almost 90% of the binding sites would be occupied by the D-enantiomer. For the pair of enantiomers of phenylalanine (L-**11**, D-**11**) there is 1.8 kJ/mol more loss of free energy for the binding of the L-enantiomer (L-**11**) and in the case of tryptophan (L-**12**, D-**12**) the difference was of

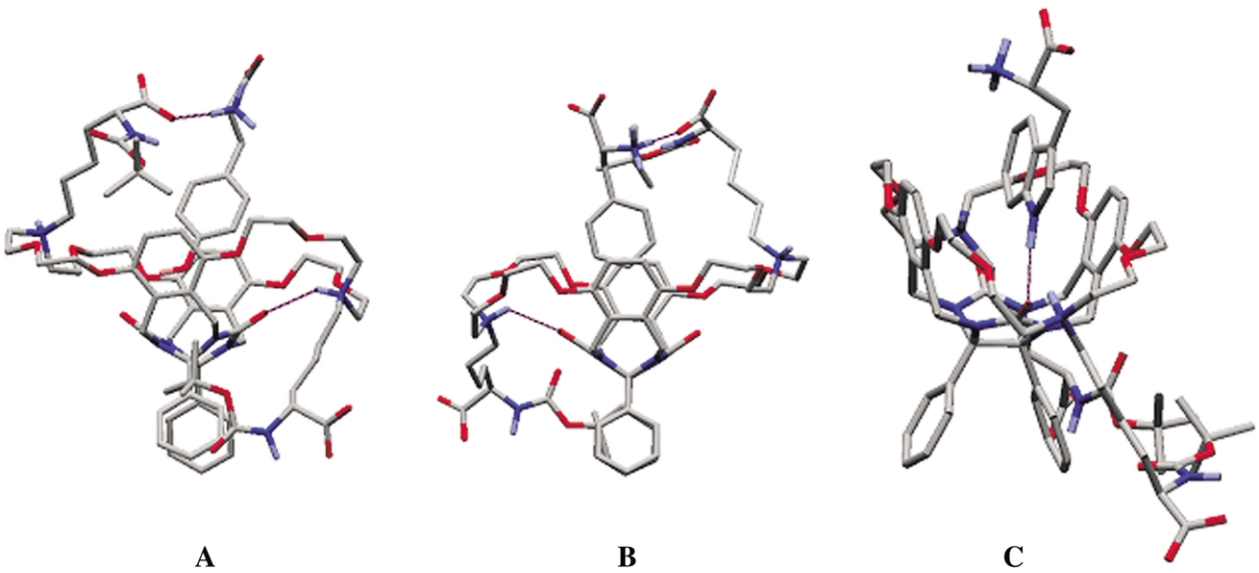

Figure 9. Calculated minimum energy complexation geometries for the 1:1 complexes of **2b** and (A) D-tyrosine (D-**9**), (B) L-phenylalanine (L-**11**) and (C) D-tryptophan (D-**12**), hydrogen atoms have been omitted for clarity.

2.9 kJ/mol in favour of the D-enantiomer (D-**12**). Although the enantioselectivities observed are moderate they are significant. The binding geometries for the three pairs of enantiomers at first glance seem to be quite similar and independent of the different aromatic moieties they present. The reverse enantioselectivity of the complex with **11** as compared to **9** and **12**, which contain a phenolic hydroxy group and an indole nitrogen, respectively, must be due to H-bonding interactions inside the cavity, as confirmed by our modelling studies (see Section 2.5).

2.5. Modelling studies[45]

Computational studies have been widely used in the last years for the modelling of chiral recognition systems such as cyclodextrins, proteins and synthetic receptors.[46–50] Here we used a Monte Carlo/Molecular dynamics mixed approach for an approximation of the structure of the host–guest complexes coherent with the experimental results (see Section 4 for details). In most cases, the minimum energy conformers found showed the guest placed inside the cavity. For the same host–guest complex, the main difference between the calculated energy of the collected structures was in the Van der Waals and solvation terms, in agreement with the hydrophobic effect being the driving force of the inclusion process. In fact, the minimum energy conformations always showed the smallest molecular surface area exposed to the solvent. On the other hand, the largest favourable energetic term seems to correspond to the electrostatic interactions. This could explain the higher binding observed when the guest contained a carboxylate group in its structure as in tyrosine (**9**), phenylalanine (**11**), and tryptophan (**12**) compared with dopamine (**7**) and ephedrine (**8**).

In general, the lowest energy conformations of the complexes between **2b** and the different guests always showed the guest bound inside the cavity. As an example, Figure 8 shows the calculated structure for the complex between adrenaline (**10**) and **2b**. It can be seen that the binding again involves electrostatic interactions, this time between the ammonium group of the guest and one of the carboxylates of the host, in addition to the extra hydrophobicity provided by the methyl group, as mentioned earlier (cf. previous section) as well as H-bonding and aromatic hydrophobic interactions. The complex structures found for the guests **9**, **11** and **12** are also in agreement with the enantioselectivity observed in the experimental binding studies (Fig. 9). For the complex between **2b** and D-tyrosine (D-**9**) all the minimum energy conformers have the guest placed inside the cavity. The main difference between the different minima is the possibility of H-bonding between the phenolic OH of the guest and the C=O of the uril moieties. In the case of the binding of the enantiomer L-tyrosine (L-**9**) the conformations found for its complex with **2b** showed a more flexible geometry. Thus, the guest L-**9** appeared in different dispositions inside the cavity and bound by the lysine arms in a smaller energy range of less than 20 kJ/mol. Nevertheless, a clear energetic preference was calculated for those complexes with the guest located inside the cavity, and no structures were found with the guest outside the cavity. Even more clear results were calculated in the case of tryptophan (**12**) guests. The D-enantiomer (D-**12**) fits into the cavity and seems to be clipped-on by a H-bond between the indole NH group and the carbonylic oxygen from the uril moiety whereas L-tryptophan (L-**12**) is more flexible. The distance between the uril carbonylic oxygen and the indole NH of tryptophan as well as the phenolic OH of the tyrosine was monitored during the Molecular Dynamics simulation. As can be seen in Figure 10C, the 80% of the population of conformers showed an average distance in the range of 1.5–3.5 Å in the case of D-**12** and no conformation in a distance above 7 Å was found, whereas for the diastereomeric complex L-**12** the 70% of the population was found within this average distance, 25% between 3.6 and 7 Å and 5% above 7 Å. The majority of the conformers show for both enantiomers distances below 4 Å and agrees with the guest being confined into the cavity, the presence of conformations with larger distances in the L-enantiomer being related to the larger looseness of the complex. In the case of

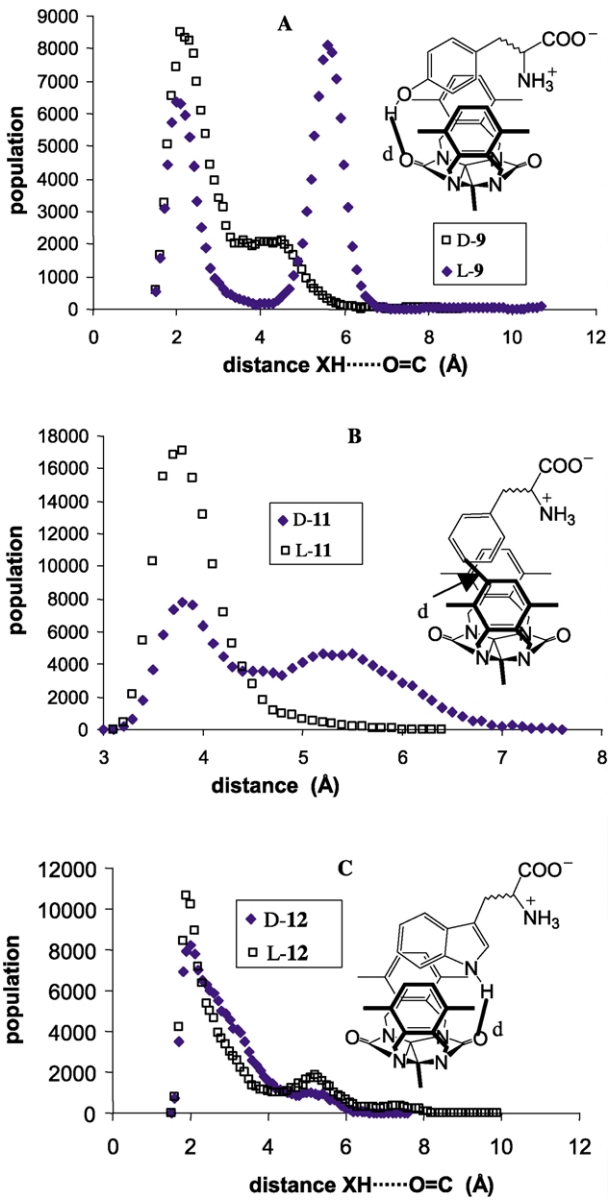

Figure 10. Distribution of complexation geometries (133,333 structures) during 2000 ps of molecular dynamics simulation vs the selected host–guest distances for **2b** and (A) tyrosine (**9**), (B) phenylalanine (**11**) and (C) tryptophan (**12**).

tyrosine, there is a clear difference between the observed behaviour of the two complexes (Fig. 10A). Whereas the complex with D-**9** shows a major population of conformers between 1.6 and 3.5 Å the diastereomeric complex with L-**9** presents two clearly different populations, the first at 2–3 Å and the second at 5–7 Å. In this case the guest D-**9** is much better accommodated into the cavity than the guest L-**9**. In the case of phenylalanine (**11**), the conformational population also points to a more defined complex with the experimentally preferred enantiomer, L-**11** (Fig. 10B).

3. Conclusions

We have presented a new series of diphenylglycoluril-based amino acid-tethered cavity containing receptors with remarkably versatile aggregation behaviour in both water and chloroform solutions. In particular, compound **2b** forms thin tubules in chloroform, whereas it forms vesicles in water. The long tail derivatives **3a**,**b** form large aggregates that can also be tuned with the pH of the medium. Compounds **2a**,**b** present a variety of interaction sites that allow the strong binding of biologically relevant molecules such as amino acids and catecholamines via a combination of several non-covalent interactions. In general, the binding constants calculated for **2b** with these guests are moderate to high and a remarkable enantioselectivity for D-tyrosine (D-**9**), L-phenylalanine (L-**11**) and D-tryptophan (D-**12**) with respect to their antipodes is shown at pH 4.5. The aggregation and binding features described here will be exploited in the future with the incorporation of these receptors into membranes for their study as cell-surface adrenergic receptor mimics, as well as their potential use in drug delivery or catalysis.

4. Experimental

4.1. General remarks

NMR spectra were recorded on a Bruker AC-300 (^{1}H NMR 300 MHz) and Bruker FAMX500 (^{1}H NMR 500 MHz) spectrometers in $CDCl_3$ with TMS as internal standard. UV–Vis spectra were recorded with a Varian Cary 50Conc spectrophotometer. Compound **1** was prepared as reported before[51] and the N^{α}-Boc protected amino acids were obtained from FLUKA. Magneson (**4**) and HABA (**5**) were purchased from Aldrich.

4.1.1. Molecular receptor 2(a,b). A mixture of compound **1** (4.05 mmol), NaI (40 g, 0.27 mol) and Na_2CO_3 (13.3 g, 0.13 mol) in 500 mL of acetonitrile was refluxed under nitrogen for 4 h. The N^{α}-Boc-protected amino acid (12.2 mmol) was then added in small portions over a period of 2 days and the mixture was refluxed for one week. After filtration and evaporation of the solvent the crude white solid was suspended in $CHCl_3$ and washed with 10% citric acid and water. The organic layer was dried (Na_2SO_4) and concentrated under vacuum. After column chromatography (neutral alumina, eluent 0.1–0.5% MeOH/$CHCl_3$, v/v) pure **2**(**a**,**b**) was obtained as a solid. **2a** (87%). Mp 180 °C dec. $[\alpha]_D^{20}$=+8.72° (c=1, $CHCl_3$). ^{1}H NMR ($CDCl_3$/CD_3OD, 8/2): 1.3 (m, 18H); 2.5–2.8 (m, 6H); 3.5–4.1 (m, 36H); 5.4 (m, 4H); 6.7 (m, 4H); 7.0 (s, 10H). ESI-MS m/z=626.5 $[M+2H]^{2+}$. Anal. Calcd for $C_{64}H_{82}N_8O_{18}$: C. 61.43; H. 6.60; N. 8.95. Found: C. 61.01; H. 6.82; N. 8.64. **2b** (62%). Mp 128 °C. $[\alpha]_D^{20}$=+5.85° (c=0.65, $CHCl_3$). ^{1}H NMR ($CDCl_3$): 1.2–2.0 (m+s, broad, 32H); 2.3–3.0 (m, 12H); 3.5–4.6 (m, 30H); 5.5 (m, 4H); 6.71 (m, 4H); 7.10 (s, broad, 10H). FAB-MS m/z=1335.8 $[M+H]^+$. Anal. Calcd for $C_{70}H_{94}N_8O_{18}$: C. 62.95; H. 7.09; N. 8.39. Found: C. 62.71; H. 6.78; N. 8.17.

4.1.2. Amphiphilic receptor 3 (a,b). Compound **2**(**a**,**b**) (0.34 mmol) and *N*-hydroxysuccinimide (0.69 mmol) were dissolved in dry dimethoxy ethane and cooled at 0 °C. Then DCC was added and the mixture was kept in the refrigerator for 24 h. Afterwards, the white precipitate was filtered off and to the resulting solution hexadecylamine (0.69 mmol) was added at 0 °C. The reaction was stirred overnight at room temperature and the white solid formed was filtered-off and washed with a small amount of diethyl ether. Finally, the solid was suspended in a 4 M HCl solution in ethyl acetate and after stirring at room temperature during 2 h compound **3**(**a**,**b**) precipitated as the hydrochloride. Further slightly basic work-up lead to the free amines. **3a**: (63%). Mp 235 °C dec. $[\alpha]_D^{20}$=−6.11° (c=0.4, CH_3OH). ^{1}H NMR ($CDCl_3$): 0.87 (t, 6H); 1.2–1.4 (s+m, 56H); 2.5–3.3 (m, 6H); 3.5–4.3 (m, 40H); 5.6 (m, 4H); 6.7 (m, 4H); 7.1 (s, 10H). ESI-MS m/z=896.5 $[M-2(C_{16}H_{33}NHCOCH^{2-})+Na]^+$. Anal. Calcd for $C_{86}H_{132}N_{10}O_{12}$: C. 69.84; H. 8.88; N. 9.35. Found: C. 69.71; H. 9.08; N. 9.11. **3b**:(58%). Mp 250 °C dec. $[\alpha]_D^{20}$=+3.04° (c=0.23, CH_3OH). ^{1}H NMR ($CDCl_3$): 0.87 (t, 6H); 1.24 (s broad, 52H); 1.5–2.2 (m broad, 16H); 3.2–4.2 (m broad, 42H); 5.6 (m, 4H); 6.7 (m, 4H); 7.1 (s, 10H). FAB-MS m/z=1583.2 $[M+H]^+$. Anal. Calcd for $C_{92}H_{144}N_{10}O_{12}$: C. 69.84; H. 9.17; N. 8.85. Found: C. 69.51; H. 9.42; N. 8.44.

4.2. Electron microscopy

Aggregates preparation. The compounds were dissolved in ca. 50 mL of methanol, injected into the aqueous solution at room temperature to a final concentration of 0.1–1 mg/mL and sonicated at 40 °C for 30 min. Different samples were studied between two hours and few days after sonication. Chloroform samples were made by dissolving 1 mg or less of the compound in 1mL of the solvent.

Transmission electron microscopy. TEM was carried out with a JEOL JEM.1010 electron microscope. The aqueous samples were prepared by adding a drop of the solution over a copper grid covered with a thin layer of formvar. After a few seconds (depending on the concentration of the sample and its affinity for the polymer surface) the sample was drained and left to dry at room temperature overnight. When chloroform was used as a solvent, the samples were prepared in a similar way but over a hydrophobic carbon coated copper grid. Before observation, the samples were shadowed with Pt at 45°.

Scanning electron microscopy. The samples where studied with a Field Emission Scanning Electron Microscope Jeol JSM-6330F. They were prepared in a similar way as before on a copper grid covered with a thin layer of formvar and then they were sputtered with 1.5 nm of Au/Pd.

Cryo-scanning electron microscopy. The samples where studied with a Field Emission Scanning Electron Microscope Jeol JSM-6330F. A drop of the sample solution was placed in a stub and it was quickly cooled down at −220 °C with under-cooled nitrogen as slush. The sample was then introduced into the microscope cooling pre-chamber and it was allowed to warm up until −95 °C. At this temperature the upper part of the drop was fractured with a cool knife and etched for 2 min. Then, the pre-chamber was cooled down until −120 °C and the sample was sputtered in situ with 1.5 nm of Au/Pd. Finally, it was transferred into the microscope chamber were the temperature was kept below −130 °C to avoid the formation of ice crystals.

4.3. Conductivity measurements

Conductivity measurements were performed in duplo with a Schott Geräte CG 852 Conductimeter with a platinum electrode at room temperature. Stock solutions of the receptors were diluted several times until very low concentrations were achieved while continuously monitoring the conductivity.

4.4. Encapsulation of ethydium bromide

The encapsulation of ethydium bromide was measured by gel permeation chromatography (GPC) in combination with fluorescence and UV–Vis spectroscopy. The desired vesicular dispersion was prepared in water containing 10^{-4} M ethydium bromide and passed over a Sephadex G25 column with water as eluent. The fluorescence intensity of ethydium bromide (λ_{ex}=480 nm, λ_{em}=630 nm) as well as the absorbance of the host molecule at 288 nm was monitored.

4.5. UV binding studies

All the experiments were carried out using double distilled water or freshly distilled chloroform to prepare the solutions. In a typical experiment a conveniently buffered solution of the dye (ca. 2×10^{-5} M) was titrated by adding small amounts of a solution containing the host and the dye (ca. 2×10^{-5} M). The change in the absorbance (450 nm for Magneson (**4**) and 350 nm for HABA (**5**)) was plotted against the total host concentration. The data were fitted using Eq. 1 with an Excel spreadsheet.

$$[HG]_i = 0.5((H_t + G_t + 1/K_{ass}) - \sqrt{(H_t + G_t + 1/K_{ass}) - (4H_tG_t)}) \quad (1)$$

The fitting was compared with the double-reciprocal plot graphical method,[52,53] giving a linear plot for the data, corresponding to the first 0.5 equiv. of guest in the case of Magneson, in agreement with the values estimated before with non-linear fitting of expression 1.

In a typical competition experiment, an appropriate buffer solution containing the host and the probe in ca. 3×10^{-5} and 1.6×10^{-5} M concentration, respectively, was titrated with a guest solution which was also 1.6×10^{-5} M in the probe. The binding constant for each guest was calculated at several total guest concentrations, always in the range of 20 to 80% of complexation, using the following equations in an Excel spreadsheet

$$A_i = \varepsilon_D[D]_i + \varepsilon_{DH}[HD]_i = \varepsilon_D D_t + (\varepsilon_{DH} - \varepsilon_D)[HD]_i \quad (2)$$

$$[HD]_i = \frac{A_i - \varepsilon_D D_t}{\varepsilon_{DH} - \varepsilon_D} \quad (3)$$

$$[D]_i = D_t - [HD]_i \quad (4)$$

$$[H]_i = \frac{[HD]_i}{K_D[D]_i} \quad (5)$$

$$K_G = \frac{[HG]_i}{[H]_i[G]_i} = \frac{H_t - [H]_i - [HD]_i}{[H]_i(G_t - (H_t - [H]_i - [HD]_i))} \quad (6)$$

where A_i is the absorbance at the studied wavelength for the experiment i, $[X]_i$ the concentration of the host (H), guest (G), dye (D), host–probe complex (HD) and host–guest complex (HG) for the experiment i, X_t the total concentration of host (H), guest (G) and dye (D) in the experiment i, $K_D$the known binding constant of the probe (D), and $K_G$is the calculated binding constant for the guest G.

The binding constant values estimated were finally averaged and the standard deviations calculated. The extinction coefficients were calculated in separate experiments and blank experiments were carried out to check possible interferences of the guest on the absorption band of the dye in the absence of host.

4.6. Modelling studies

Molecular mechanics docking calculations were performed for the complex structures using the Monte Carlo conformational search method implemented in the Macromodel V7.0 program.[54] The AMBER* force field was used in a water continuous solvent simulation (GB/SA).[55] Energy minima were found and the conformational space close to them was explored by performing molecular dynamics simulations. Starting structures were drawn with different disposition of the guest inside and outside the cavity of the host. In each case, the conformational search was performed with 3000 iterations for each step and structures were collected in a 50 kJ/mol energy window. Then, molecular dynamics simulations were performed on the energy minima obtained with a total simulation time of 2000 ps.

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Studies on the carbenium-iminium ions derived from *N*-methylmorpholine-*N*-oxide (NMMO)

Thomas Rosenau,* Antje Potthast and Paul Kosma

Institute of Chemistry, University of Natural Resources and Applied Life Sciences, Christian-Doppler-Labor, A-1190 Vienna, Austria

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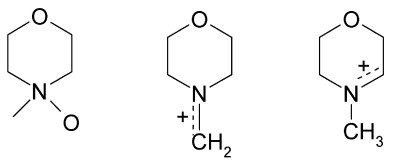
Abstract—Two carbenium-iminium ions, an *exo*-centered species **2** and a ring-centered form **3**, are derived from the widely used oxidant and cellulose solvent *N*-methylmorpholine-*N*-oxide (**1**) by heterolytic degradation. **3** rearranges into **2** in the presence of water, in an endothermic, bimolecular reaction involving a highly organized transition state, which is the first example of a carbenium-iminium ion interconversion. The reaction mechanism was investigated by a combined approach consisting of trapping reactions, isotopic labeling, kinetic studies, and computations on the DFT level.

1. Introduction

N-Methylmorpholine-*N*-oxide (NMMO, **1**) is a frequently applied oxidant in organic synthesis,[1] which is mainly applied in combination with catalytic amounts of transition metal catalysts.[2] It is also used in bulk quantities as a solvent for cellulose in the industrial Lyocell process, which is a new and environmentally benign approach to production of man-made cellulosic fibers.[3] NMMO dissolves cellulose directly without chemical derivatization to give a dope which is spun simply into water. This is in complete contrast to viscose rayon production, which requires intensive use of both derivatization and spinning bath chemicals.

NMMO is a relatively strong oxidant that tends toward uncontrollable decomposition reactions. Both upon usage as oxidant in organic synthesis,[4] as well as upon industrial utilization of NMMO as cellulose solvent[5] there have been reports on the instability of NMMO solutions and on the occurrence of unpredictable thermal runaway reactions. Due to these irregularities great caution must be exercised in all processes involving NMMO. It is evident that the interest in side reactions of NMMO and the NMMO-derived chemical species involved therein originate from very different areas of NMMO utilization.

In previous studies on side reactions of NMMO we have reported on radicals derived from this amine *N*-oxide, i.e., species which are formed by cleavage of the N–O bond with simultaneous transfer of one electron. In these processes NMMO acted as a one-electron oxidant.[6] In the present work, we wish to communicate the peculiar behavior of carbenium-iminium ions (C-I ions, Mannich intermediates) derived from NMMO, the second major class of NMMO-derived intermediates. These rather labile species are generated by breaking the N–O bond of the amine *N*-oxide with concomitant two-electron transfer. In the case of NMMO, two of such species can be expected, the *exo*-centered C-I ion **2** and the ring-centered C-I ion **3**.



1 **2** **3**

C-I ions have been shown to be able to cause *O*-alkylation of tertiary amine *N*-oxides. The alkylation step is immediately followed by fragmentation in a concerted mechanism regenerating the C-I ion. The reaction, being an auto-catalytic and highly exothermic process,[7] thus easily becomes uncontrollable causing complete degradation of the parent amine *N*-oxide. Also in the case of NMMO reaction mixtures, C-I ion intermediates catalyze its autocatalytic degradation, and are thus mainly responsible for the observed instabilities and exothermicities in NMMO reaction mixtures,[4] which gave the impetus to the present study.

Keywords: Carbenium-iminium ions; *N*-Methylmorpholine-*N*-oxide (NMMO); Mannich intermediates; Trapping; Isotopic labeling; Cellulose solvents.
* Corresponding author. Tel.: +43-1-36006-6071; fax: +43-1-36006-6059; e-mail address: thomas.rosenau@boku.ac.at

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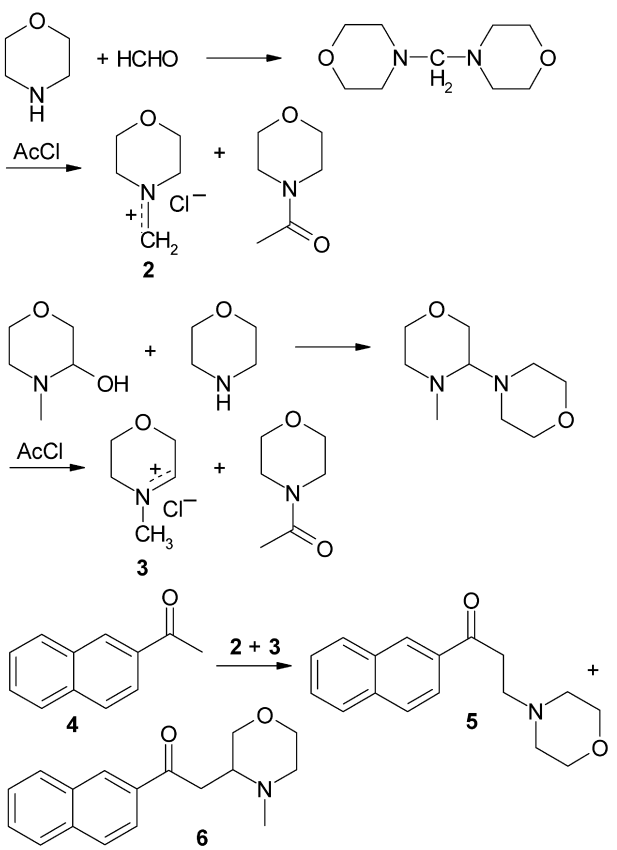
2. Results and discussion

Even though **3** might appear more stable at a first glance, since its ring-centered positive charge seems 'better accommodated' than the one in **2**, it is the latter which occurs predominantly in all different types of side reactions starting from NMMO. In fact, intermediate **2** was produced exclusively in NMMO reaction mixtures containing water,[8] whereas in non-aqueous solutions of NMMO also smaller amounts of **3** were found besides **2**.[9] Thus, both the presence of water and higher temperatures generally seemed to promote the consumption of **3** in favor of **2**.

To study the reactions of these two NMMO-derived *Mannich* intermediates in more detail, the crystalline chloride forms of **2** and **3** were used, which were prepared according to Scheme 1. As reporter method, the trapping with 2-acetonaphthone (**4**) in a Mannich reaction was used. The trapping agent reacts with C-I ions in a fast and neat reaction to give the corresponding Mannich bases **5** and **6**, respectively, which are readily extractable even from very complex mixtures due to their lipophilic naphthalene moiety. Another advantage is the usability of the trap also at elevated temperatures (e.g., in NMMO melts), since the resulting Mannich bases are relatively thermostable and do not undergo elimination to the α,β-unsaturated ketone below 130 °C.

As shown in Table 1, trapping of both **2** and **3** in non-aqueous organic solution at room temperature provided the



Scheme 1. Synthesis of stable carbenium-iminium chlorides **2** and **3** and their trapping with 2-acetonaphthone in a Mannich reaction.

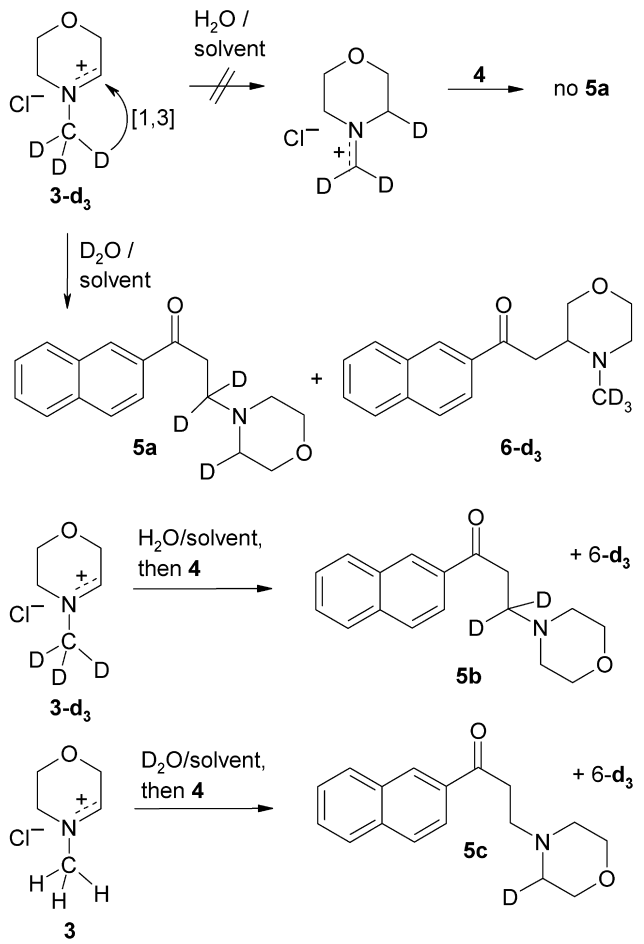
Table 1. Different reaction conditions for the conversion of C-I ion **3** into C-I ion **2** followed by trapping

Starting material	Solvent (50 mL), treatment (24 h) before addition of trap	Product ratio
2	Dry toluene, stirring at rt	**5** only
3	Dry toluene, stirring at rt	**6** only
2	Wet toluene (2% H_2O), stirring at rt	**5** only
3	Wet toluene (2% H_2O), stirring at rt	12/88
2	Dry dioxane, stirring at rt	**5** only
3	Dry dioxane, stirring at rt	**6** only
2	Dioxane/water (3/1), stirring at rt	**5** only
3	Dioxane/water (3/1), stirring at rt	8/92
2	Dry toluene, reflux	**5** only
3	Dry toluene, reflux	**6** only
2	Wet toluene (2% H_2O), reflux	**5** only
3	Wet toluene (2% H_2O), reflux	83/17
2	Dry dioxane, reflux	**5** only
3	Dry dioxane, reflux	**6** only
2	Dioxane/water (3/1), reflux	**5** only
3	Dioxane/water (3/1), reflux	79/21
3	Dry DMF, stirring at 120 °C	**5** only
3	DMF/water (9/1), stirring at 120 °C	90/10
3	Dry DMF, stirring at 120 °C	**5** only

corresponding Mannich bases **5** and **6**, respectively, quantitatively. The same was true for the reaction of **2** in aqueous dioxane, **3** afforded small amounts of **5** besides the expected trapping product **6**. Refluxing **2** in aqueous dioxane for 24 h before carrying out the trapping reaction had no effect as compared to the room temperature process: only **5** was detected. In the case of **3**, however, **5** and **6** were formed in a 83/17 ratio. Thus, the major part of **3** must have rearranged during the refluxing into **2**.[10] A similar refluxing test carried out in dry dioxane or dry toluene gave no indications of such a reaction: in the case of **2** as the starting material only **5** was produced, and in the case of **3** only **6**. In refluxing wet toluene, in contrast, the rearrangement of **3** into **2** occurred. In general, replacing the refluxing procedure by room-temperature stirring provided essentially the same results in all solvents, but the **3** into **2** conversion proceeded much slower. The results of the experiments are summarized in Table 1. It was evident that higher temperatures and the presence of water favored **2** at the expense of **3**.

First, we assumed that **3** might undergo a [1,3]-sigmatropic shift to give **2**, meaning that **2** basically would be a more stable tautomeric form of *N*-(alkylene)-morpholinium ions. If this assumption was true, **3-d$_3$** should have rearranged into **2-d$_3$**, which in turn should have produced **5a** upon trapping (see Scheme 2). However, this product was not observed, but only **5b**, the bisdeuterated compound, was found. No incorporation of deuterium into the *N*-methylene group of the morpholine ring—and thus no [1,3]-shift—had occurred. Consequently, the proton entering the morpholine ring must have come from the solvent. Indeed, reaction of **3** in dioxane/D_2O (or toluene/D_2O) provided **5c**, which proved the participation of water as a solvent component in the reaction. Thus, a solvent proton is incorporated into the morpholine ring, while a proton from the *exo*-methyl group is lost into the solvent (Scheme 2).

Kinetic studies have shown the reaction to be of second



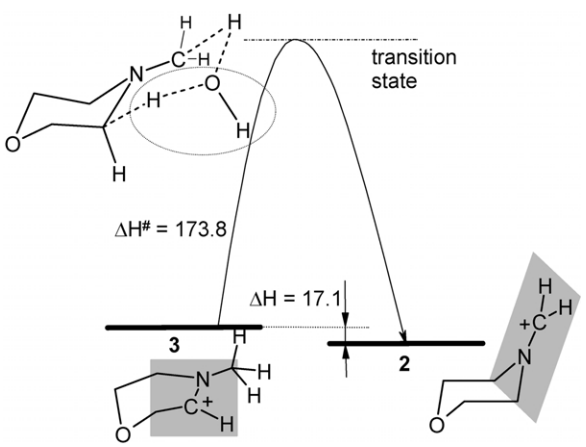
Scheme 2. Use of isotopically labeled material to clarify the reaction mechanism of the C-I ion conversion.

order, i.e., first order with respect to both water and C-I ion **3**. Thus, the reaction was assumed to be a bimolecular process according to rate law $d[\mathbf{2}]/dt=k[\mathbf{3}][H_2O]$. The kinetic rate constant was determined to be $k=1.40\times10^{-4}$ L mol^{-1} s^{-1}.[11] Evaluation of the temperature dependence of k according to the Eyring equation[12] produced the activation parameters of the reaction: a rather large activation enthalpy $\Delta H^{\#}=167.4\pm7.2$ kJ mol^{-1}, the Arrhenius activation energy thus being $E_A=\Delta H^{\#}+RT=169.9\pm7.2$ kJ mol^{-1} at 298 K, and a strongly negative activation entropy $\Delta S^{\#}=-142\pm13.8$ J(mol K)$^{-1}$ indicating a high degree of order in the transition state with limited mobility of the two coreactants as compared to the starting material.

The transmutation of **3** into **2** was prevented by addition of either acids or alkali. In the case of OH^- the C-I ion was evidently quenched to the corresponding *N*-hydroxyalkyl compound, so that neither rearrangement nor reaction with the trapping agent occurred.[13] The presence of strong acids (1 equiv. rel. to **3**) suppressed the transformation of **3** into **2** almost completely, whereas simple trapping proceeded faster than in the neutral case due to acid catalysis effect. This led us to the assumption that the basic oxygen functions in water were required for the C-I ion conversion, which was no longer present due to protonation in acidic media. In summary, the kinetic data indicated that a molecule of **3** and a molecule of water were involved in the rate-determining step of the reaction, having a highly organized transition state.

The stability of the two C-I ions was assessed by means of DFT computations, which showed that **2** is by 2.9 kJ mol^{-1} more stable than **3**.[14] In the minimum geometries of both **2** and **3** the positive carbons are sp^2-hybrids with trigonal planar geometry (Scheme 3). The four atoms of the *N*-(methylene) group in **2** lie in one plane; the morpholine ring is nevertheless able to adopt its typical chair conformation. In contrast, the morpholine ring of C-I-ion **3** is forced into a distorted chair geometry by the trigonal planar geometry of the carbenoid carbon. Thus, the spatial arrangement of the three substituents at the carbenium center can only in **2** be accommodated without additional strain, the resulting twist of the morpholine chair rendering **3** energetically more unfavorable than **2** (Scheme 3). However, this rather small energy difference could neither account for the experimentally observed preference of **2**, nor explain the conversion of **3** into **2**. Thus, in the next step a DFT analysis of the system ($\mathbf{3}+H_2O$)[15] was performed, which now produced a plausible picture that agreed with the experimental data (Scheme 3).

According to Scheme 3 the conversion **3**→**2** follows a reaction path that requires a rather high activation energy of $\Delta H^{\#}=173.8$ kJ mol^{-1}, which compares very favorably with the experimental value of $E_A=169.9$ kJ mol^{-1}. Going from **3** to the transition state, the positive charge must be localized at the nitrogen, so that the double bond becomes located and the resonance stabilization of the carbenium-iminium ion is lost. In the transition state, water and the CI-ion **3** arrange in a way that places the reaction centers into a favorable six-membered chair-geometry. One water hydrogen is placed into a distance of 1.26 Å to the ring-carbon, which comes close to the length of a C–H single bond in the $N-CH_2$ groups of *N*-alkylamines with 1.1 Å. The ring carbon reaction center, which is nearly trigonal planar in **3**, already adopts a tetragonal environment in the transition state, which removes the strain from the six-membered ring system. The C–C–N angle (109.83°) almost



Scheme 3. Schematic representation of the computed reactant and transition state geometries as well as reaction energetics for the C-I ion conversion of **3** into **2**. Values are given in kJ mol^{-1}. The trigonal planar environments of the carbenoid carbons are shaded in gray. The participating water molecule is circled by a gray line.

equals the normal value of a tetrahedral angle in carbon sp^3 hybrids. Compared to the $N-CH_3$ group in *N*-methylmorpholine having a C–H length of 1.097 Å, the activated C–H bond in the *exo*-CH_3 group is stretched to 1.61 Å, which indicates advanced bond cleavage. The *exo*-carbon almost obtained the trigonal planar geometry of an sp^2-hybrid, with the H–C–H plane standing roughly perpendicular on the C–N–C plane of the morpholine ring. The distances of the three protons bound to the water oxygen are nearly equal (0.99–1.08 Å), close to that in a hydronium ion H_3O^+ (0.98 Å). Thus, the overall geometry of the transition state is rather close to that of the products, **2** and H_2O, indicating a 'late' transition state on the reaction coordinate. The water involved has consequently the effect of a catalyst, which per definitionem is regenerated after the reaction, although the conversion of **3** into **2** is accompanied by a proton exchange in that water molecule: one proton of the *exo*-CH_3 group is taken up, while a proton is donated to the ring carbon. Finally, going from the transition state to the product **2** requires rotation of the *exo*-methylene group, so that the H–C–H plane and the C–N–C plane fall together, re-establishing carbenium-iminium resonance stabilization.

The absence of the reverse reaction **2→3** can be explained by the stability of intermediate *N*-hydroxymethyl-morpholine (HMM), which is formed by addition of a hydroxyl ion to **2** (or addition of water with subsequent loss of a proton). HMM subsequently gives morpholine and formaldehyde, from which regeneration of **2** under neutral conditions is very slow. In contrast, 3-hydroxy-*N*-methylmorpholine, formed by formal addition of a hydroxyl ion into 3-position of **3**, is less stable, so that **3** can readily be regenerated by the reversed process. Moreover, formation of 2-(aminomethyl)ethoxy-acetaldehyde—the open-chain form of the cyclic semiaminal 2-hydroxy-*N*-methylmorpholine—is negligible and does not consume **3**, as does the formation of morpholine and HCHO from HMM in the case of C-I ion **2**.

In summary, the NMMO-derived ring-centered carbenium-iminium ion **3** is rearranged into its counterpart, the NMMO-derived *exo*-centered carbenium-iminium ion **2** in the presence of water. The conversion is an endothermic, bimolecular reaction involving **3** and water. The two coreactants pass through a highly organized transition state in which water, acting as a catalyst, is simultaneously accepting and donating a proton. The generated **2** is consumed by formation of the quite stable *N*-hydroxymethylmorpholine, morpholine and formaldehyde, so that the reversed reaction **2→3** is largely prevented. These findings agree completely with empirical data from NMMO oxidation chemistry and from the Lyocell fiber-making process. Especially under the rather drastic reaction conditions of the latter—working in a melt of NMMO monohydrate at temperatures around 100 °C—the C-I ion conversion is likely to account for the observed nearly complete absence of **3**.

The described process is the first example of a direct conversion between two Mannich intermediates. Studies on the general synthetic applicability of the reaction with regard to a *N*-demethylation involving a carbenium-iminium ion conversion step are underway.

3. Experimental

3.1. General

All chemicals were commercially available. Thin layer chromatography (TLC) was performed on silica gel 60 plates (5×10 cm, 0.25 mm) with fluorescence detection under UV light at 254 nm. Column chromatography was performed on silica gel G60 (40–63 μm). Melting points, determined on a Kofler-type micro hot stage with Reichert-Biovar microscope, are uncorrected. ^1H NMR spectra were recorded at 300.13 MHz, ^{13}C NMR spectra at 75.47 MHz in $CDCl_3$ as the solvent and TMS as the internal standard. Data are given in ppm. ^{13}C peaks were assigned by means of APT, HMQC and HMBC spectra; 'd.i.' denotes peaks with double intensity.

Computations, as implemented through Spartan Pro 02 by Wavefunction, Inc., Irvine, CA, USA, were carried out on geometries pre-optimized by the semi-empirical PM3 method. For full geometry optimization the widely employed B3LYP hybrid method, which includes a mixture of HF and DFT exchange terms and the gradient-corrected correlation functional of Lee, Yang and Parr[16] parametrized by Becke,[17] was used, along with the double-zeta split valence basis sets 6-31+G*,[18] which includes diffuse functions. Transition states and minima were confirmed by analysis of the calculated vibrational spectrum, and by intrinsic reaction coordinate analysis. For all transition states the number of imaginary frequencies was 1, for all minimum geometries it was 0.

3.1.1. *N*-(Methylene)morpholinium chloride (2). Formaline (35%, 8.6 mL, 0.1 mol) was cooled to −10 °C (ice/NaCl bath) and morpholine (17.4 g, 0.2 mol) was added under stirring. Within about 30 min the mixture was allowed to reach r.t. Anhydrous solid K_2CO_3 was added until the aqueous phase disappeared. The solids were crushed by a sufficiently powerful magnetic stirrer, removed by filtration, washed with Et_2O, and the combined phases were dried again over K_2CO_3. Et_2O was stripped off and the residue was distilled under reduced pressure to give bis(4-morpholino)methane, bp_{35}=78 °C. This product was dissolved in dry Et_2O in an inert atmosphere. Acetyl chloride (7.9 g, 7.1 mL, 0.1 mol) was added at 0 °C under stirring. The resulting precipitate was collected under exclusion of moisture, washed with Et_2O, and dried in vacuo to give *N*-(methylene)morpholinium chloride (**2**) as white crystals (8.05 g, 80.4%). ^1H NMR ($CDCl_3$): δ 3.58 (t, 4H), 4.08 (t, 4H), 8.53 (s, b, 2H). ^{13}C NMR: δ 56.2 (d.i.), 65.5 (d.i.), 167.7. Anal. calcd for $C_5H_{10}NOCl$ (135.59): C 44.29, H 7.43, N 10.33, Cl 26.15. Found: C 44.11, H 7.62, N 10.05, Cl 25.89. Computated thermodynamic data for the cation (without anion): ΔH=100.5 kcal mol^{-1}, ΔS=78.05 cal (mol K)$^{-1}$, ΔG_{298}=77.2 kcal mol^{-1}, zero-point vibrational energy 96.6 kcal mol^{-1}.

3.1.2. 4-Methyl-3,6-dihydro-2*H*-[1,4]oxazinium chloride (3). 3-Hydroxy-4-methylmorpholine (11.72 g, 0.1 mol) was cooled to −10 °C (ice/NaCl bath) and morpholine (17.4 g, 0.2 mol) was added under stirring. Within about 30 min the mixture was allowed to reach rt. Anhydrous solid K_2CO_3 was added until the aqueous phase disappeared. The solids

were removed by filtration, washed with Et_2O, and the combined phases were dried again over K_2CO_3. Et_2O was stripped off and the residue was distilled under reduced pressure to give bis(4-morpholino)methane, bp_{20}=112 °C. The product was dissolved in dry Et_2O in an inert atmosphere. Acetyl chloride (7.9 g, 7.1 mL, 0.1 mol) was added at 0 °C under stirring. The resulting precipitate was collected under exclusion of moisture, washed with Et_2O, and dried in vacuo to give 4-methyl-3,6-dihydro-2*H*-[1,4]oxazinium chloride (**3**) as white crystals (6.25 g, 62.4%). ^{1}H NMR ($CDCl_3$): δ 3.42 (s, 3H), 3.68 (d, b, 2H, ^3J=6.1 Hz), 4.19 (m, 2H), 4.62 (m, 2H), 9.15 (t, b, ^3J=6.1 Hz). ^{13}C NMR: δ 46.9, 55.1, 62.0, 72.4, 147.7. Anal. calcd for $C_5H_{10}NOCl$ (135.59): C 44.29, H 7.43, N 10.33, Cl 26.15. Found: C 44.41, H 7.25, N 10.17, Cl 26.03. Computed thermodynamic data from the cation (without anion): ΔH=100.4 kcal mol^{-1}, ΔS=80.1 cal (mol K)$^{-1}$, ΔG_{298}=76.5 kcal mol^{-1}, zero-point vibrational energy 96.0 kcal mol^{-1}.

3.2. General experimental procedure for trapping of carbenium-iminium ions

A solution of the carbenium-iminium chloride **2** or **3** (1 mmol) was dissolved in the respective solvent (20 mL), for the solvents used see Table 1. The mixture was stirred for 24 h either under reflux or at room temperature (see Table 1). At room temperature, a solution of 2-acetonaphthone (0.51 g, 7 mmol) in the same solvent (20 mL) and H_2SO_4 (conc., 0.1 mL) was added at once. The consumption of C-I ions was complete after less than 10 min (DC control). After additional stirring for 30 min, water (100 mL) and chloroform (100 mL) were added and the phases were separated. The organic phase was washed twice with water and dried over Na_2SO_4. The solvents were carefully removed in vacuo. For determination of the product composition, the remaining waxy solid was re-dissolved in n-hexane (15 mL). Ethereal HCl (3 mL, 2 M) was added, the mixture was left standing for 30 min, and the resulting white, crystalline precipitate was removed by filtration and dried in vacuo. An aliquot of the solid was dissolved in $CDCl_3$ and directly analyzed by NMR using the integrals of the β-methylene group in naphthone **5** (~2.95 ppm) and the β-methine proton in naphthone **6** (~3.10 ppm) for determination of the product ratio. For purification of the products, the above crude solid obtained after drying and solvent evaporation was re-dissolved in 5 mL of toluene and chromatographed on silica gel (toluene/ethyl acetate, v/v=9/1). For better storage, the obtained waxy morpholinonaphthones were converted into their crystalline hydrochlorides by treatment with ethereal HCl.

3.2.1. 3-(Morpholin-4-yl)propionaphthone (5). ^{1}H NMR ($CDCl_3$): δ 2.18 (s, b, 1H), 2.60 (t, 4H, ^3J=5.0 Hz, N–C*H*$_2$–CH$_2$–O), 2.93 (t, 2H, ^3J=7.0 Hz, CH$_2$–C*H*$_2$–CO), 3.46 (t, 2H, ^3J=7.0 Hz, C*H*$_2$–CH$_2$–CO), 3.78 (t, 4H, ^3J=5.0 Hz N–CH$_2$–C*H*$_2$–O), 7.58–7.66 (m, 2H, ^{Ar}C*H*), 7.86–8.08 (m, 4H, ^{Ar}C*H*), 8.45 (s, 1H, ^{Ar}C*H*). ^{13}C NMR: δ 33.7, 53.1, 53.2 (d.i.), 64.7 (d.i.), 124.4, 128.2, 128.8, 129.6, 130.1, 130.8, 131.6, 133.5, 134.2, 136.8, 198.0. Anal. calcd for $C_{17}H_{19}NO_2$ (269.35): C 75.81, H 7.11, N 5.20. Found: C 75.92, H 7.29, N 5.22.

3.2.2. 3,3-Dideutero-3-(3-deutero-morpholin-4-yl)-propio-naphthone (5a). ^{1}H NMR ($CDCl_3$): δ 2.54 (m, 1H, C*H*D), 2.68 (t, 2H, ^3J=5.2 Hz, N–C*H*$_2$–CH$_2$–O), 2.98 (s, b, 1H), 3.12 (s, 2H, C*H*$_2$–CD$_2$–CO), 3.76 (t, 2H, ^3J=5.2 Hz N–CH$_2$–C*H*$_2$–O), 3.78 (dd, 2H, N–CHD–C*H*$_2$–O), 7.58–7.65 (m, 2H, ^{Ar}C*H*), 7.86–8.05 (m, 4H, ^{Ar}C*H*), 8.45 (s, 1H, ^{Ar}C*H*). ^{13}C NMR: δ 30.1, 51.0 (quint), 51.2 (t), 57.7, 63.9, 64.7, 124.4, 128.0, 128.8, 129.5, 130.1, 130.8, 131.5, 133.6, 134.2, 136.6, 197.4. Anal. calcd for $C_{17}H_{16}NO_2D_3$ (272.36): C 74.96, H 7.03, N 5.14. Found: C 75.08, H 6.98, N 5.20.

3.2.3. 3,3-Dideutero-3-(morpholin-4-yl)propio-naphthone (5b). ^{1}H NMR ($CDCl_3$): δ 2.24 (s, b, 1H), 2.65 (t, 4H, ^3J=5.0 Hz, N–C*H*$_2$–CH$_2$–O), 3.36 (s, 2H, C*H*$_2$–CD$_2$–CO), 3.74 (t, 4H, ^3J=5.0 Hz N–CH$_2$–C*H*$_2$–O), 7.58–7.65 (m, 2H, ^{Ar}C*H*), 7.82–8.06 (m, 4H, ^{Ar}C*H*), 8.44 (s, 1H, ^{Ar}C*H*). ^{13}C NMR: δ 30.2, 51.2 (quint), 52.9 (d.i.), 64.6 (d.i.), 124.4, 128.1, 128.8, 129.6, 130.0, 130.7, 131.6, 133.4, 134.3, 136.6, 198.0. Anal. calcd for $C_{17}H_{17}NO_2D_2$ (271.36): C 75.24, H 7.06, N 5.16. Found: C 75.44, H 7.12, N 5.34.

3.2.4. 3-(3-Deutero-morpholin-4-yl)propionaphthone (5c). ^{1}H NMR ($CDCl_3$): δ 2.54 (m, 1H, C*H*D), 2.67 (t, 2H, ^3J=5.1 Hz, N–C*H*$_2$–CH$_2$–O), 2.84 (s, b, 1H), 2.91 (t, 2H, ^3J=7.0 Hz, CH$_2$–C*H*$_2$–CO), 3.44 (t, 2H, ^3J=7.0 Hz, C*H*$_2$–CH$_2$–CO), 3.76 (t, 2H, ^3J=5.1 Hz, N–CH$_2$–C*H*$_2$–O), 3.78 (dd, 2H, N–CHD–C*H*$_2$–O), 7.58–7.65 (m, 2H, ^{Ar}C*H*), 7.86–8.08 (m, 4H, ^{Ar}C*H*), 8.45 (s, 1H, ^{Ar}C*H*). ^{13}C NMR: δ 30.1, 51.4, 51.5 (t), 57.7, 64.0, 64.7, 124.3, 128.0, 128.7, 129.5, 130.1, 130.7, 131.7, 133.6, 134.2, 136.8, 198.0. Anal. calcd for $C_{17}H_{18}NO_2D$ (270.35): C 75.52, H 7.08, N 5.18. Found: C 75.35, H 7.18, N 5.29.

3.2.5. 2-(4-Methyl-morpholin-3-yl)-1-naphthalen-2-yl-ethanone (6). ^{1}H NMR ($CDCl_3$): δ 2.42 (s, 3H, CH$_3$), 2.67 (m, 2H, N–C*H*$_2$), 3.10 (m, 1H, N–CH), 3.18–3.38 (m, 2H, C*H*$_2$–CO), 3.68 (m, 2H, N–CH$_2$–C*H*$_2$–O), 3.89 (m, 2H, N–CH–C*H*$_2$–O), 4.12 (s, b, 1H), 7.54–7.62 (m, 2H, ^{Ar}C*H*), 7.84–8.02 (m, 4H, ^{Ar}C*H*), 8.46 (s, 1H, ^{Ar}C*H*). ^{13}C NMR: δ 39.7, 49.1, 53.8, 61.2, 65.3, 71.4, 124.6, 128.0, 128.8, 129.3, 130.3, 131.0, 131.4, 133.0, 134.4, 136.6, 198.7. Anal. calcd for $C_{17}H_{19}NO_2$ (269.35): C 75.81, H 7.11, N 5.20. Found: C 76.01, H 7.20, N 5.13.

Acknowledgements

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10. It was checked that **6** was stable under the prevailing conditions, and did not transform into **5**. Thus, formation of **5** must be due to the conversion of **3** into **2** rather than a transformation of the trapping products.
11. The overall reaction order was determined using equivalent starting concentrations. Applying a large excess (80 equiv.) of water, the water concentration could be regarded constant over the reaction time, and the reaction became pseudo-first order with regard to the starting material **3**, i.e., $d[2]/dt = k'[3]$, with $k' = k[H2O]$.
12. Graphical representation of $\ln(k/T)$ versus $1/T$ produced a straight line $y = ax + b$ with the slope $a = -\Delta H^{\#}/R$ in J mol^{-1} und $b = \Delta S^{\#}/R + 23.76$ in J(mol K)$^{-1}$.
13. Trapping after reacidification proved that indeed not only the trapping reaction, but also the rearrangement itself was prevented.
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15. This comprised localization of transition states and geometry minima, supported by vibrational frequency analysis and intrinsic reaction coordinate analysis.
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First asymmetric syntheses of 6-substituted nipecotic acid derivatives

Cornelia E. Hoesl, G. Höfner and Klaus T. Wanner*

Department Pharmazie-Zentrum für Pharmaforschung, LMU München, Butenandtstr. 5-13, D-81377 München, Germany

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Dedicated with the very best wishes to Professor Wolfgang Steglich on the occasion of his 70th birthday

Abstract—Various nipecotic acid derivatives are known to be potent GABA uptake inhibitors thus being useful in the treatment of a number of neurological and psychological disorders. In this paper, the first asymmetric syntheses of 6-substituted nipecotic acid derivatives are presented. The synthetic strategy was designed to provide access to a large variety of enantiomerically pure 6-substituted nipecotic acid derivatives. The synthesis starts from the chiral *N*-acyldihydropyridines **15** and **16** obtained via asymmetric electrophilic α-amidoalkylation reaction of a chiral *N*-acylpyridinium ion. These were utilized for the preparation of enantiomerically pure 6-(4,4-diphenylbutyl)nipecotic acids and 6-(4,4-diphenylbutenyl)nipecotic acids in a multistep synthesis, including the removal of the dimethylphenylsilyl blocking group from the dihydropyridine ring, the reduction of the dihydropyridine heterocycle, a Horner–Wittig reaction and the removal of the chiral auxiliary. The obtained target molecules, however, showed only negligible affinity to the GAT-1- and GAT-3 transport proteins.

1. Introduction

γ-Aminobutyric acid (GABA) is recognized as the predominant inhibitory neurotransmitter in the mammalian brain. Malfunctions in GABAergic neurotransmission are likely to contribute to the development of certain psychiatric and neurological disorders such as epilepsy, Huntington's Chorea and Parkinson's disease.[1] One of the various pharmacological approaches to palliate GABA deficiency in vivo is to inhibit the uptake of the neurotransmitter, thereby increasing the synaptic level of GABA and enhancing inhibitory neurotransmission. In contrast to the direct enhancement of GABA neurotransmission by $GABA_A$ agonists or benzodiazepines, GABA uptake inhibition results in a selective potentiation of endogenously released GABA and therefore is thought not to give rise to the development of tolerance.[2] Four different GABA transporters have been identified so far (GAT-1, GAT-2, GAT-3 and BGT-1), which differ in their cellular distribution in the brain and in their sensitivity to pharmacological agents.[3] A number of cyclic amino acids such as (*RS*)-piperidine-3-carboxylic acid (nipecotic acid, **1**) and 1,2,5,6-tetrahydropyridine-3-carboxylic acid (guvacine, **2**), which may be considered as conformationally restricted GABA analogues, display in vitro activity as inhibitors of [^{3}H]-GABA uptake.[4] These cyclic amino acids do not readily cross the blood brain barrier, but have been used as the basis for the design of some lipophilic and highly potent GABA uptake inhibitors, e.g. SK&F-89976-A[5] (**3**) and Tiagabine[6] (**5**) with GAT-1-selectivity and (*S*)-SNAP-5114[7] (**4**) with GAT-3-selectivity. Using structure-activity data and molecular modeling, Wermuth et al.[8] developed a pharmacophore model of GABA uptake inhibitors which suggests that for binding the lipophilic side chain is located in the vicinity of position 6 of the piperidine ring. He successfully confirmed his model by synthesizing 6-[(3,3-diphenyl)propyl]guvacine (**6**) which he found to be a potent GABA uptake inhibitor. The biological evaluation of compound **6** was performed, however, with a test system not clearly distinguishing between GAT-1 and GAT-3 uptake. Dhar and coworkers[9] synthesized quinolizidine derivatives (e.g., **7**) with a diphenylmethyl substituent in position 8 as conformationally restricted analogues of the nipecotic acid derivative **6**. Although, these analogues were in accordance with the pharmacophore model proposed by Wermuth, their affinity for GAT-1 or GAT-3 was very low. In the context with a study aimed at the development of new GABA uptake inhibitors we were interested in 6-substituted nipecotic acid derivatives. Since it is well known that (*R*)-nipecotic acid derivatives are more potent for GAT-1 than (*S*)-nipecotic acid derivatives and that the opposite is true for (*S*)-nipecotic acid derivatives exhibiting higher affinity to GAT-3 than compounds derived from (*R*)-nipecotic acid, it seemed reasonable to evaluate the enantiopure compounds. Thus, we performed the first asymmetric synthesis of 6-substituted nipecotic acid derivatives, which we,

Keywords: GABA uptake; Nipecotic acid; Asymmetric synthesis.
* Corresponding author. Tel.: +49-89-2180-77249; fax: +49-89-2180-77247; e-mail address: klaus.wanner@cup.uni-muenchen.de

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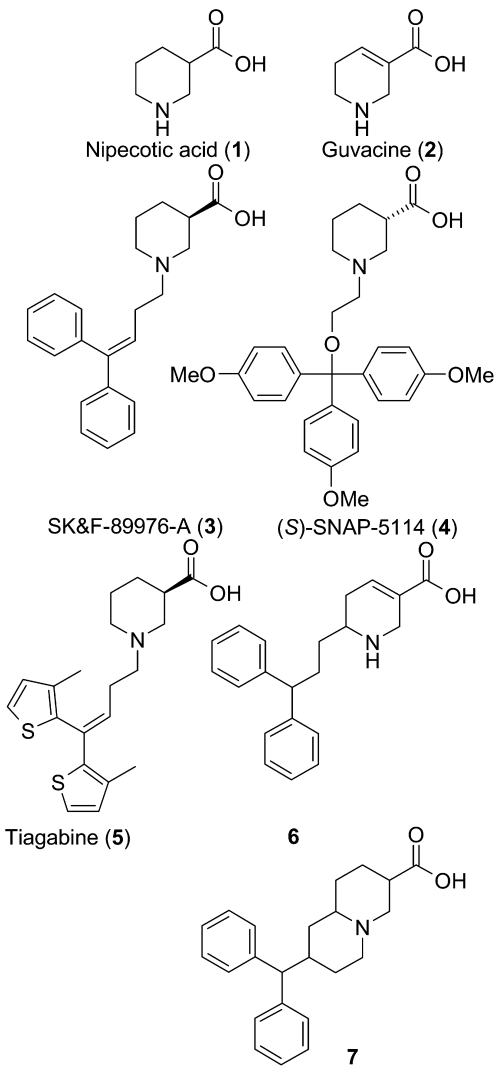
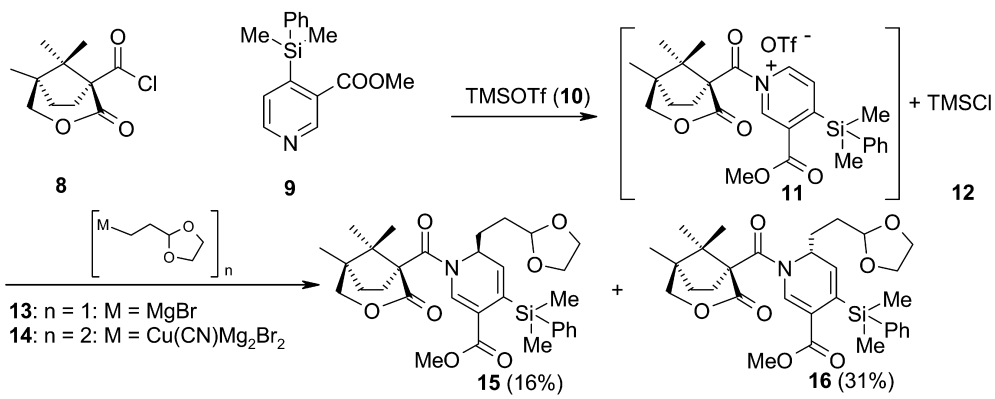


Scheme 1.

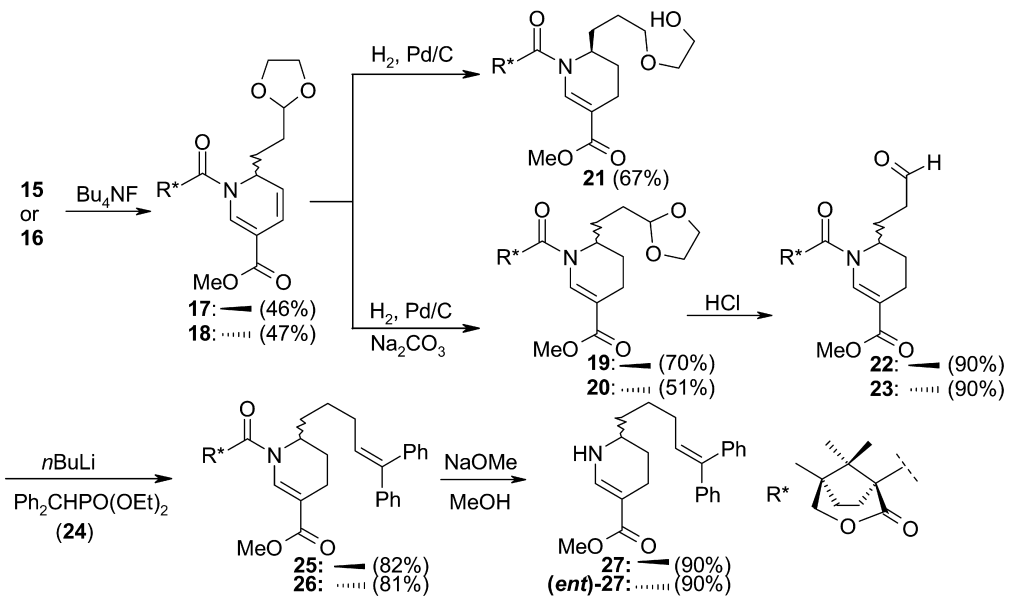
furthermore, investigated for their biological potential (Scheme 1).

2. Synthetic strategy

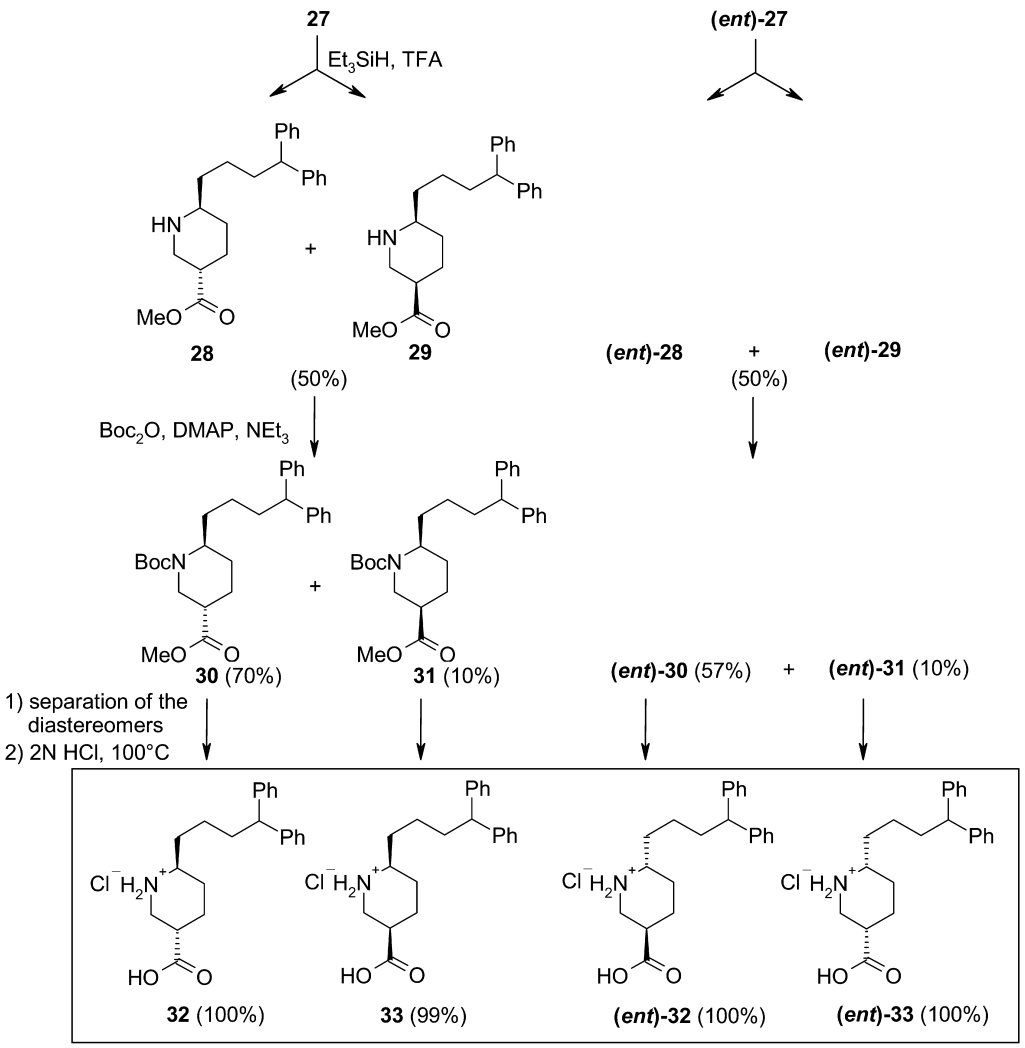
The overall strategy used for the stereoselective preparation of the 6-substituted nipecotic acid derivates is based on a method termed as asymmetric electrophilic α-amidoalkylation (AEαA).[10] In this type of reaction the new stereocenter is formed by stereoselectively adding a suitable nucleophile to a chiral *N*-acyliminium ion. In former studies of our group the carboxylic acid depicted as acid chloride **8** has proven to be a useful chiral auxiliary for the synthesis of pyrrolidines, piperidines, 1,2,3,4-tetrahydroisoquinolines and β-carbolines via AEαA.[11] Previously, we reported the successful generation of the chiral *N*-acylpyridinium ion **11** from acid chloride **8** and methyl (4-dimethylphenylsilyl)-nicotinate (**9**)[12] by means of trimethylsilyl triflate.[13] The dimethylphenylsilyl group, served as a blocking substituent in subsequent trapping reactions preventing addition reactions to position 4 of the pyridinium ring. Reaction of the *N*-acyl-4-dimethylphenylsilylpyridinium salt **11** with {[1,3]-dioxolan-2-ylethyl}magnesium bromide (**13**) led to the *N*-acyl-1,6-dihydropyridines **15** as the main product (**15**/**16**=87.2/12.8).[13] Meanwhile further experiments revealed that the sense of asymmetric induction is switched and compound **16** becomes the major diastereomer when the higher order cyanocuprate **14** (Scheme 2) is employed (see below). Having both diastereomers **15** and **16** available in reasonable amounts we set out to utilize these compounds as the basis for the synthesis of a series of 6-substituted nipecotic acid derivates. With regard to the above mentioned [6-(3,3-diphenylpropyl)]guvacine (**6**) and considering the structure of the GABA uptake inhibitor SK&F-89976-A (**3**) with a diphenylbutenyl substituent bound to the nitrogen atom we planned to transform the side chain present in **15** and **16**—via the respective aldehyde—to a diphenylbutenyl residue by employing a Horner–Emmons-reaction or to a diphenylbutyl substituent. Besides, the [1,3]-dioxolan-2-ylethyl substituent may open the way to various functional groups, e. g. alcohols or ethers, or to bicyclic ring systems either by intramolecular Schiff-Base-reaction or by α-aminonitrile formation according to the method of Husson et al.[14] The dimethylphenylsilyl substituent, which serves as a blocking group in the trapping reaction as described above, may either be removed thereby providing access to nipecotic acid derivatives unsubstituted in the 4-position or it may serve as a masked hydroxyl group[15] leading to 4-hydroxynipecotic acid derivatives. Furthermore, elimination of the generated hydroxyl group might afford guvacine derivatives. Both, 4-hydroxynipecotic acid as well as guvacine, are promising substructures for potential GABA uptake inhibitors.



Scheme 2.



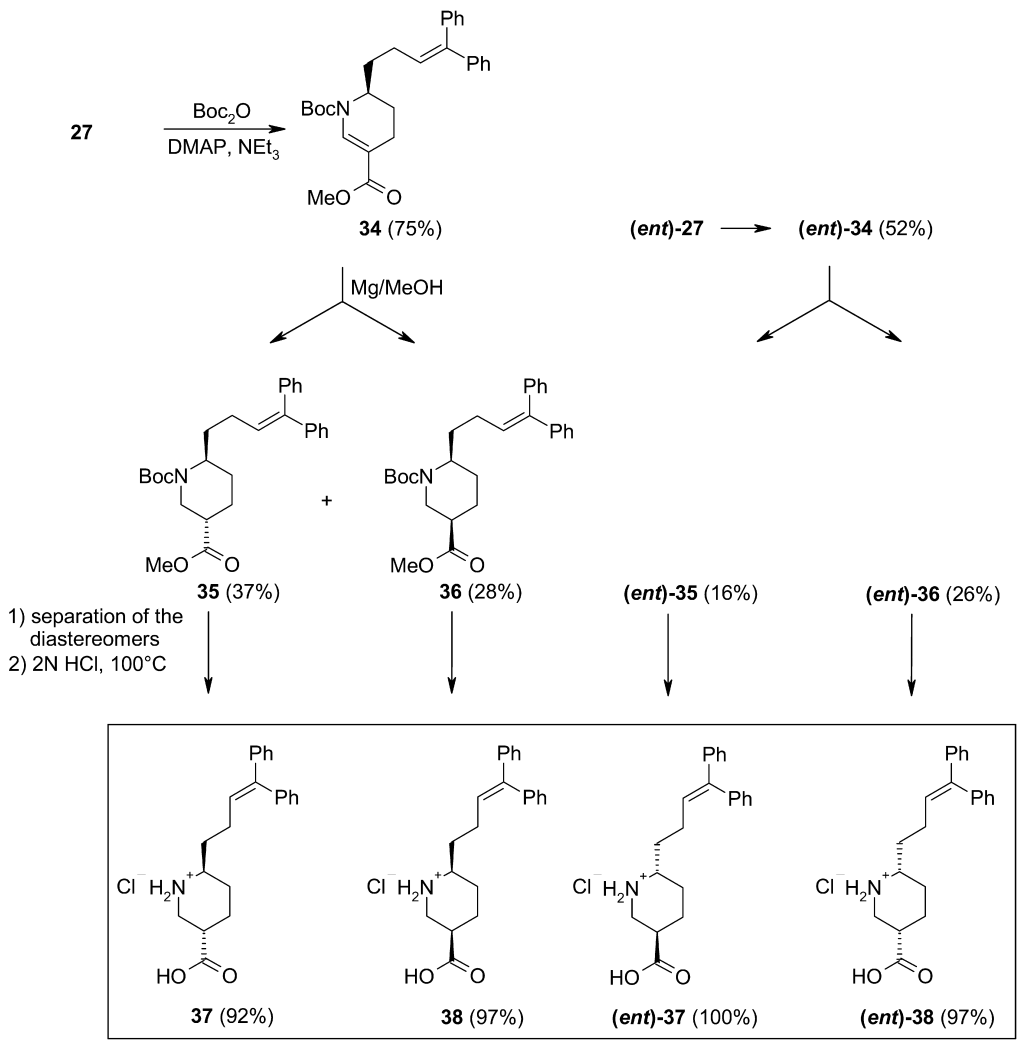
Scheme 3.



Scheme 4.

3. Results and discussion

Diastereomer **15** was available from a trapping reaction of **11** employing the Grignard reagent **13**,[16] which yielded a mixture of **15** and **16** in a ratio of 87.2 to 12.8. Interestingly, the sense of asymmetric induction observed for the Grignard reagent was inverted when the cyanocuprate **14** was used (**15**/**16**=34.0/66.0, total yield: 47%). Consequently, the reaction mixture resulting from this addition reaction was utilized to get access to diastereomer **16** in pure form which became available upon chromatography in a yield of 31%. Both diastereomers, **15** and **16**, were separately converted to the target molecules **32**, **33**, (*ent*)-**32** and (*ent*)-**33** in a multi-step synthesis. Though in the following only one of the two sequences, the one starting from **15** and leading to **32** and **33** is described, the synthesis of the enantiomers (*ent*)-**32** and (*ent*)-**33** was performed accordingly starting with the *N*-acyl-1,6-dihydropyridine **16**. The dimethylphenylsilyl group was removed by treating **15** with tetrabutyl-ammonium fluoride leading to product **17** (46%). In the next step compound **17** was subjected to catalytic hydrogenation, which yielded the 1,4,5,6-tetrahydropyridine derivative **19** in 70% yield, but only when Na_2CO_3 was present. Otherwise, in the absence of Na_2CO_3, only alcohol **21** was obtained by hydrogenolysis of the acetal moiety (68% yield, see Scheme 3). Following cleavage of the acetal group in compound **19** (90%), the resulting aldehyde **22** was successfully converted to the diphenylbutenyl derivative **25** carrying out a Wittig–Horner reaction. Deprotonation of phosphonate **24** with *n*BuLi[17] and reaction of the resulting carbanion with the aldehyde **22** gave the desired product **25** in 82% yield. The removal of the chiral auxiliary was achieved straightforwardly in a yield of 90% by heating compound **25** with NaOMe in methanol at 120 °C in a sealed tube (Scheme 3).[13,18] As the resulting enamino ester **27** was unstable, it became necessary to immediately reduce the double bond of the enamino ester unit. Thus compound **27** was treated with triethylsilane in trifluoroacetic acid at 50 °C using a method developed by Rosentreter[19] for the synthesis of piperidine derivatives from 1,4-dihydropyridines. Employing these reaction conditions, the enamine-double bond and the double bond in the side chain were reduced yielding diastereomers **28** and **29** (total yield for amide cleavage and reduction: 50%, d.s.=83/17 determined by ^{1}H NMR). The reduction of both double bonds was not very surprising but quite useful, as it provided an even easier access to the desired nipecotic acid derivates with a saturated side chain. Since we were not able to separate the diastereomers at this stage, we decided to convert them to the Boc-protected derivatives **30** and **31**.[20] Compounds **30** and **31** were then

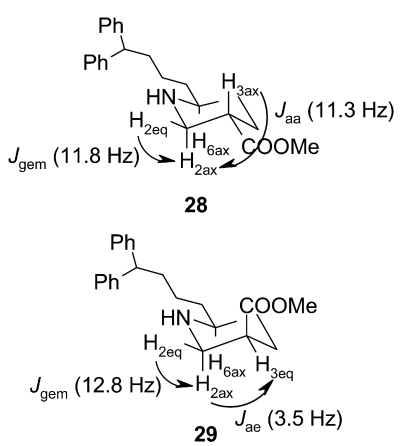


Scheme 5.

easily separable by chromatography. By refluxing in 2 M HCl the methyl ester and the carbamate function were simultanously cleaved yielding the target molecules **32** and **33**, each in 99% yield (Scheme 4).

To access target molecules with a diphenylbutenyl side chain, the enamino ester **27** was first protected with a Boc group providing **34** (yield: 75%). Upon subsequent reduction of the enamido ester double bond in **34** with magnesium in methanol the piperidine derivatives **35** and **36** were obtained (yield: 65%, d.s.=57/43, determined by ^{1}H NMR). Chromatographic separation of the diastereomers followed by the concurrent cleavage of the amide and the ester bond by HCl yielded 92% of the target molecule **37** and 97% of the target molecule **38**. The enantiomers (*ent*)-**37** and (*ent*)-**38** were synthesized accordingly starting from compound (*ent*)-**27** (Scheme 5).

The relative stereochemistry of the piperidine derivatives **28** and **29** became apparent from their ^{1}H NMR spectra. The absolute stereochemistry of the precursor **15** had been established in a former study by X-ray analysis.[13] Thus, piperidine derivative **28** obtained from **15** must be of (*S*)-configuration in position 6 of the heterocycle, as it is the case for **15**. In the ^{1}H NMR spectrum of **28** the signal of 6-H (δ=2.28–2.45 ppm) is a multiplet due to coupling with 5-H and the hydrogen atoms of the alkyl chain. A large coupling constant of J=12.1 Hz was identified to the hydrogen atoms in position 5. Thus, 6-H must adopt an axial orientation. The signal of one hydrogen in position 2 (δ=2.60 ppm) of the heterocycle is split to a doublet of doublets by a geminal (J=11.8 Hz) and by a vicinal coupling (J=11.3 Hz). Consequently, this proton (2-H) and the proton in position 3 of the piperidine ring must be in an axial position. Therefore, the residues in position 3 and 6 must both occupy equatorial positions and diastereomer **28**, as the major diastereomer of the reduction, must, consequently, be of (3*S*,6*S*)-configuration. As the minor isomer **29** differs from **28** only with respect to the stereochemistry at 3-C of the ring system, it must have the stereochemistry indicated [(3*R*,6*S*)], which in further support of this assignment could also be delineated from the ^{1}H NMR spectrum of this compound. (6-H: δ=2.30–2.45 ppm, J=12.1 Hz in addition to small coupling constants; 2-H_{ax}: δ=2.71 ppm, J=12.8/3.5 Hz; 2-H_{eq}: δ=3.31 ppm, J=12.8/2.5 Hz) (Scheme 6).



Scheme 6.

The configuration of the nipecotic acid derivatives **37** and **38** was determined from the ^{1}H NMR spectra of the Boc-protected compounds **35** and **36**. Analysis of the coupling pattern of the 2-H and 6-H signal in the ^{1}H NMR spectrum leads to the configuration of **35**. For 6-H (δ=4.15–4.24 ppm) only small coupling constants (J=2.0/8.1 Hz) are observed for the hydrogen atoms in position 6 indicating, that the diphenylbutenyl substituent is positioned axially. This orientation of the side chain is to be seen as a result of the allylic strain arising from the carbamate function.[21] As the ester function at 3-C adopts an axial position which becomes apparent from the coupling constants between 2-H and 3-H (2-H_{ax}: 2.93 ppm, J=14.0/4.1 Hz; 2-H_{eq}: 4.41 ppm, J=14.0/1.2 Hz) compound **35** must, consequently, be (3*S*,6*S*)-configurated. Finally compound **36** by differing from the aforementioned diastereomer **35** only in the configuration at 3-C exhibiting the ester function must be the (3*R*,6*S*)-stereoisomer.

4. Biological test results

The enantiomerically pure nipecotic acid derivates were evaluated for their in vitro activity as GABA uptake inhibitors by a radioligand-receptor binding assay.[22] The results are depicted in Table 1 and are given as percentage of GABA uptake compared to the control experiment without test substance. To determine IC_{50} values did not seem appropriate as none of the 6-substituted nipecotic acid derivatives **32**, **33**, (*ent*)-**32**, (*ent*)-**33**, **37**, **38**, (*ent*)-**37** and (*ent*)-**38** displayed a reasonable potency neither at GAT-1 nor at GAT-3 (see Table 1). For comparison purposes in Table 1 also the data for SK&F-89976A (**3**), 6-[(3,3,-diphenylpropyl)]guvacine (**6**) and (*S*)-SNAP-5114 (**4**) from the literature are included. The low potency of the herein synthesized target molecules is surprising considering the high affinity of 6-[(3,3-diphenylpropyl)]guvacine (**6**). However, our results are in accordance with biological test results reported by Dhar[9] for conformationally restricted 6-substituted nipecotic acid derivatives (e.g., **7**) also having low affinity for GAT-1 and GAT-3.

Table 1.

Compound	IC_{50}±SEM	
	GAT-1	GAT-3
6	0.1 μM[a,8,23]	
3	0.13±0.03 μM[b]	944±110 μM[b]
4	388±92 μM[b,7]	5±1 μM[b,7]
32	100 μM: 96.5%[c]	100 μM: 97.6%[c]
33	100 μM: 75.3%[c]	100 μM: 95.3%[c]
(*ent*)-**32**	100 μM: 98.3%[c]	100 μM: 85.5%[c]
(*ent*)-**33**	100 μM: 86.0%[c]	100 μM: 94.8%[c]
37	100 μM: 91.6%[c]	100 μM: 71.8%[c]
38	100 μM: 77.7%[c]	100 μM: 74.5%[c]
(*ent*)-**37**	100 μM: 89.7%[c]	100 μM: 65.0%[c]
(*ent*)-**38**	100 μM: 93.4%[c]	100 μM: 69.9%[c]

[a] [^{3}H]GABA-synaptosomal uptake in rat brain given as IC_{50}.
[b] determined for hGAT-1 and hGAT-3 given as IC_{50} according to Borden.[24]
[c] % uptake compared to a control experiment without test substance, each experiment performed as triplicate.[22]

5. Conclusion

In summary, the first asymmetric synthesis for 6-substituted nipecotic acid derivatives was developed. The synthetic strategy was designed to provide a flexible access to a wide range of nipecotic acid derivatives. The educts **15** and **16** were prepared by asymmetric electrophilic α-amidoalkylation via the chiral *N*-acylpyridinium ion **11**. In multistep syntheses the four enantiomerically pure isomers of 6-(4,4-diphenylbutyl)nipecotic acid and of 6-(4,4-diphenylbutyl)-nipecotic acid were obtained. The synthesized nipecotic acid derivatives were evaluated for their in vitro activity at the GAT-1 and GAT-3 transport proteins, but did not show any reasonable potency.

6. Experimental

6.1. General

All reactions were carried out in vacuum dried glassware sealed with rubber septa under argon atmosphere whenever necessary. All reagents were used as commercially available. The solvents were dried and distilled. Mp (uncorrected values): Büchi melting point apparatus no. 510 (Dr. Tottoli). Optical rotations: Polarimeter 241 MC (Perkin–Elmer). IR: Perkin–Elmer FT-IR spectrophotometer Paragon 1000. ^{1}H NMR: JEOL JNMR-GX 400 spectrometer (400 MHz) with TMS as internal standard. MS spectra: Hewlett Packard 5989 with 59980 B particle beam LC/MS interface. Elemental analysis: CHN Rapid (Heraeus). TLC: TLC plates Merck 60 F-254. Column chromatography (CC): Flash chromatography on silica gel (Merck 60 F-254, 0.040–0.063 mm). Analytical HPLC: L-6000 pump, L-4000 UV/VIS detector, D-7500 Chromato Integrator (Merck–Hitachi), column: LiChroCart® with Lichrospher® Si 60 cartridge (5 μm, 250×4 mm with precolumn 4×4 mm), (Merck). Preparative HPLC: L-6000 pump, L-4000 UV/Vis, D-2000 Chromato Integrator (Merck–Hitachi), column: Hibar RT LiChrosorb® Si 60 (7 μm, 250×25 mm) (Merck).

6.1.1. Methyl (*S*)-(4-(dimethylphenylsilyl)-6-(2-[1,3]dioxolan-2-ylethyl)-1-[(1*S*,5*R*)-5,8,8-trimethyl-2-oxo-3-oxabicyclo[3.2.1]octylcarbonyl]-1,6-dihydropyridine-3-carboxylate (15) and methyl (*R*)-(4-(dimethylphenylsilyl)-6-(2-[1,3]dioxolan-2-ylethyl)-1-[(1*S*,5*R*)-5,8,8-trimethyl-2-oxo-3-oxabicyclo[3.2.1]octylcarbonyl]-1,6-dihydropyridine-3-carboxylate (16). The generation of the *N*-acylpyridinium triflate **11** was performed according to literature[13] starting from 3.0 mmol of acylchloride **8**, 816 mg (3.0 mmol) of pyridine **9** and 543 μl (3.0 mmol) of trimethylsilyl triflate in 15 ml CH_2Cl_2. To this solution another solution was added at −78 °C over 3 min, that had been prepared by addition of 18 ml (18.0 mmol, 2.0 equiv.) of 2-([1,3]dioxolan-2-yl)ethylmagnesium bromide (1.0 M in THF) to a suspension of 806 mg (9.0 mmol, 1.0 equiv.) of CuCN in 35 ml THF at −78 °C and had been allowed to react at 0 °C for 10 min. After 3 h at −30 °C the reaction mixture was quenched at −30 °C with phosphate buffer (pH=7, c=1.0 M). Work up, purification and separation of the diastereomers according to literature[13] afforded 272 mg (16%) of **15** and 528 mg (31%) of **16**, which were identical in all respect with authentic samples.[13]

6.1.2. Methyl (*S*)-6-(2-[1,3]dioxolan-2-ylethyl)-1-[(1*S*,5*R*)-5,8,8-trimethyl-2-oxo-3-oxabicyclo[3.2.1]octylcarbonyl]-1,6-dihydropyridine-3-carboxylate (17). 880 μl (0.880 mmol, 5 equiv.) of Bu_4NF (1 M in THF) were slowly added to a solution of 100 mg (0.176 mmol) of **15** in 1760 μl THF over a period of 3 h. Phosphate buffer (pH=7, c=1.0 M) was added. The reaction mixture was extracted with CH_2Cl_2. The combined organic layer were dried (Na_2SO_4) and concentrated in vacuo. Purification by CC (*n*-heptane/EtOAc)=50:50) afforded 35 mg (46%) of compound **17**.

Compound **17**. Colorless oil. TLC: R_f=0.20 (*n*-heptane/EtOAc=50:50). $[\alpha]_D^{20}$=+436.3 (c=0.16, CH_2Cl_2). IR (KBr): $\tilde{\nu}$=2955 cm^{-1}, 1718, 1677, 1219. ^{1}H NMR (nitrobenzene-d$_5$, 140 °C): δ=0.90 ppm (s, 3H, CH_3), 1.07 (s, 3H, CH_3), 1.42 (s, 3H, CH_3), 1.77–2.00 (m, 6H, CH_2CH_2, CH_2CH$_2$), 2.28–2.40 (m, 1H, CH$_2$CH_2), 2.50–2.60 (m, 1H, CH$_2$CH_2), 3.77 (s, 3H, COOCH_3), 3.74–3.80 (m, 2H, OCH$_2$CH$_2$O), 3.86–3.93 (m, 2H, OCH$_2$CH$_2$O), 3.99 (d, J=10.9 Hz, 1H, OCH$_2$), 4.19 (dd, J=10.9/1.9 Hz, 1H, OCH$_2$), 4.87 (t, 1H, J=4.8 Hz, OCHO), 5.13–5.16 (m, 1H, NCHCH$_2$), 5.84 (dd, J=9.9/5.6 Hz, 1H, NCHCH=CH), 6.53 (d, J=9.9 Hz, 1H, NCH=CCH), 7.94 (s, 1H, NCH=C). MS (70 eV); *m/z* (%): 433 [M$^+$] (1), 332 (23), 195 (100), 167 (28), 139 (31). $C_{23}H_{31}NO_7$ (433.50): calcd C 63.73, H 7.21, N 3.23; found C 63.90, H 7.26, N 2.96.

6.1.3. Methyl (*R*)-6-(2-[1,3]dioxolan-2-ylethyl)-1-[(1*S*,5*R*)-5,8,8-trimethyl-2-oxo-3-oxabicyclo[3.2.1]octylcarbonyl]-1,6-dihydropyridine-3-carboxylate (18). Synthesis as described for the preparation of **17** from 985 mg (1.734 mmol) of **16** and 8.67 ml (8.670 mmol, 5 equiv.) of Bu_4NF (1 M in THF). Purification by CC (*iso*-hexane/Et_2O=25:75) afforded 355 mg (47%) of **18**.

Compound **18**. Colorless oil. TLC: R_f=0.20 (*iso*-hexane/Et_2O=25:75). $[\alpha]_D^{20}$=−357.6 (c=0.88, CH_2Cl_2). IR (KBr): $\tilde{\nu}$=2958 cm^{-1}, 1718, 1676, 1578, 1210. ^{1}H NMR (CD_2Cl_2, 120 °C): δ=0.93 ppm (s, 3H, CH_3), 0.97 (s, 3H, CH_3), 1.22 (s, 3H, CH_3), 1.62–1.81 (m, 4H, CH_2CH_2), 1.87–2.00 (m, 2H, CH_2CH$_2$), 2.31–2.44 (m, 1H, CH$_2$CH_2), 2.73–2.87 (m, 1H, CH$_2$CH_2), 3.78 (s, 3H, COOCH_3), 3.80–3.85 (m, 2H, OCH$_2$CH$_2$O), 3.92–3.96 (m, 2H, OCH$_2$CH$_2$O), 3.98 (d, J=11.0 Hz, 1H, OCH$_2$), 4.20 (dd, J=11.0/2.1 Hz, 1H, OCH$_2$), 4.88 (t, 1H, J=4.7 Hz, OCHO), 5.25–5.33 (m, 1H, NCHCH$_2$), 5.70 (dd, J=9.9/5.6 Hz, 1H, NCHCH=CH), 6.44 (d, J=9.9 Hz, 1H, NCH=CCH), 7.66 (s, 1H, NCH=C). MS (70 eV); *m/z* (%): 433 [M$^+$] (2), 402 (2), 332 (29), 195 (100), 167 (27), 139 (30). $C_{23}H_{31}NO_7$ (433.50): calcd C 63.73, H 7.21, N 3.23; found C 64.01, H 7.42, N 2.74.

6.1.4. Methyl (*R*)-6-(2-[1,3]dioxolan-2-ylethyl)-1-[(1*S*,5*R*)-5,8,8-trimethyl-2-oxo-3-oxabicyclo[3.2.1]octylcarbonyl]-1,4,5,6-tetrahydropyridine-3-carboxylate (19). 681 mg Pd/C (10% Pd) were added to a suspension of 681 mg (1.571 mmol) of compound **17** and 666 mg (6.284 mmol, 4 equiv.) of Na_2CO_3 in 31 ml of CH_3OH. The resulting mixture was hydrogenated for 48 h under normal pressure. Then the mixture was filtered and concentrated in vacuo. Purification by CC (*iso*-hexane/Et_2O=20:80) afforded 478 mg (70%) of **19**.

Compound **19**. Colorless crystals, mp 68 °C. TLC: R_f=0.22 (*iso*-hexane/Et_2O=20:80). $[\alpha]_D^{20}$=+195.1 (*c*=0.61, CH_2Cl_2). IR (KBr): $\tilde{\nu}$=2954 cm^{-1}, 1728, 1623, 1244, 1187. ^1H NMR ($C_2D_2Cl_4$, 120 °C): δ=0.94 ppm (s, 3H, CH_3), 1.03 (s, 3H, CH_3), 1.36 (s, 3H, CH_3), 1.60 (m, 1H, NCHCH_2CH$_2$C=), 1.69–1.81 (m, 5H, CH_2CH_2, NCHCH_2-CH$_2$C=), 1.86–1.97 (m, 2H, CH_2CH$_2$), 2.01 (dd, *J*=12.9/5.6 Hz, 1H, NCH=CCH_2), 2.32 (dd, *J*=12.9/6.4 Hz, 1H, NCH=CCH_2), 2.38–2.47 (m, 2H, CH$_2$CH_2), 3.76 (s, 3H, COOCH_3), 3.81–3.86 (m, 2H, OCH$_2$CH$_2$O), 3.93–3.98 (m, 2H, OCH$_2$CH$_2$O), 3.97 (d, *J*=11.0 Hz, 1H, OCH$_2$), 4.18 (d, *J*=11.0 Hz, 1H, OCH$_2$), 4.51–4.59 (m, 1H, NC*H*CH$_2$), 4.92 (t, 1H, *J*=4.0 Hz, OCHO), 7.76 (s, 1H, NC*H*=C). MS (70 eV); *m*/*z* (%): 435 [M^+] (1), 404 (4), 336 (100), 240 (13), 195 (81), 167 (25). $C_{23}H_{33}NO_7$ (435.52): calcd C 63.43, H 7.63, N 3.22; found C 63.23, H 7.74, N 3.05.

6.1.5. Methyl (*S*)-6-(2-[1,3]dioxolan-2-ylethyl)-1-[(1*S*,5*R*)-5,8,8-trimethyl-2-oxo-3-oxabicyclo[3.2.1]octylcarbonyl]-1,4,5,6-tetrahydropyridine-3-carboxylate (20). Synthesis as described for the preparation of **19** from 129 mg (0.298 mmol) of **18**, 129 mg of Pd/C (10% Pd) and 126 mg (1.192 mmol, 4 equiv.) of Na_2CO_3 in 6 ml CH_3OH, hydrogenation time: 24 h. Purification by CC (*iso*-hexane/Et_2O=25:75) afforded 67 mg (51%) of **20**.

Compound **20**. Colorless crystals, mp 160–161 °C. TLC: R_f=0.24 (*iso*-hexane/Et_2O=25:75). $[\alpha]_D^{20}$=−36.1 (*c*=0.51, CH_2Cl_2). IR (KBr): $\tilde{\nu}$=2950 cm^{-1}, 1717, 1676, 1610, 1238, 1173. ^1H NMR ($C_2D_2Cl_4$, 120 °C): δ=0.94 ppm (s, 3H, CH_3), 1.00 (s, 3H, CH_3), 1.30 (s, 3H, CH_3), 1.61 (m, 1H, NCHCH_2CH$_2$C=), 1.63–1.76 (m, 4H, CH_2CH_2), 1.92 (m, 1H, NCHCH_2CH$_2$C=), 1.90–2.06 (m, 2H, CH_2CH$_2$), 2.26 (ddd, *J*=18.3/7.4/5.9 Hz, 1H, NCH=CCH_2), 2.31–2.43 (m, 1H, CH$_2$CH_2), 2.46 (dd, *J*=18.3/5.9 Hz, 1H, NCH=CCH_2), 2.57–2.80 (m, 1H, CH$_2$CH_2), 3.76 (s, 3H, COOCH_3), 3.81–3.86 (m, 2H, OCH$_2$CH$_2$O), 3.92–3.97 (m, 2H, OCH$_2$CH$_2$O), 3.97 (d, *J*=11.0 Hz, 1H, OCH$_2$), 4.20 (d, *J*=11.0 Hz, 1H, OCH$_2$), 4.76–4.83 (m, 1H, NC*H*CH$_2$), 4.90 (t, 1H, *J*=4.2 Hz, OCHO), 7.79 (s, 1H, NC*H*=C). MS (CI, CH_5^+); *m*/*z* (%): 436 [M^++1] (6), 404 (4), 336 (100), 195 (89). $C_{23}H_{33}NO_7$ (435.52): calcd C 63.43, H 7.63, N 3.22; found C 63.36, H 7.74, N 3.14.

6.1.6. Methyl (*R*)-6-[3-(1-hydroxyethoxy)propyl]-1-[(1*S*,5*R*)-5,8,8-trimethyl-2-oxo-3-oxabicyclo[3.2.1]octylcarbonyl]-1,4,5,6-tetrahydropyridine-3-carboxylate (21). Synthesis as described for the preparation of **19** from 84 mg (0.194 mmol) of **17** in 3.8 ml CH_3OH, 168 mg of Pd/C (10% Pd) and without Na_2CO_3, hydrogenation time: 48 h. Purification by CC (*iso*-hexane/Et_2O=20:80) afforded 57 mg (67%) of **21**.

Compound **21**. Colorless oil. TLC: R_f=0.25 (*iso*-hexane/Et_2O=20:80). $[\alpha]_D^{20}$=+170.1 (*c*=0.64, CH_2Cl_2). IR (film): $\tilde{\nu}$=3532 cm^{-1}, 2953, 1730, 1676, 1624, 1244, 748, 706. ^1H NMR (nitrobenzene-d_5, 140 °C): δ=0.91 ppm (s, 3H, CH_3), 1.09 (s, 3H, CH_3), 1.41 (s, 3H, CH_3), 1.59–1.84 (m, 4H, CH_2CH_2), 1.87–1.94 (m, 1H, NCH=CCH$_2$CH_2), 1.89–2.00 (m, 2H, CH_2CH$_2$), 2.01–2.11 (m, 1H, NCH=CCH$_2$-CH_2), 2.29–2.47 (m, 2H, NCH=CCH_2), 2.47–2.62 (m, 2H, CH$_2$CH_2), 3.26–3.36 (m, 5H, NCHCH$_2$CH$_2$CH_2O, OCH$_2$-CH$_2$O), 3.36–3.45 (m, 1H, NCHCH$_2$CH$_2$CH_2O), 3.74 (s, 3H, COOCH_3), 3.99 (d, *J*=11.1 Hz, 1H, OCH$_2$), 4.19 (d, *J*=11.1 Hz, 1H, OCH$_2$), 4.39–4.47 (br, 1H, OH), 4.58–4.68 (m, 1H, NC*H*CH$_2$), 8.07 (s, 1H, NC*H*=C). MS (70 eV); *m*/*z* (%): 437 [M^+] (3), 406 (100), 334 (6), 195 (16), 167 (9), 139 (8). $C_{23}H_{35}NO_7$ (437.53): calcd C 63.14, H 8.06, N 3.20; found C 63.48, H 8.00, N 3.16.

6.1.7. Methyl (*R*)-6-(3-oxopropyl)-1-[(1*S*,5*R*)-5,8,8-trimethyl-2-oxo-3-oxabicyclo[3.2.1]octylcarbonyl]-1,4,5,6-tetrahydropyridine-3-carboxylate (22). 3.6 ml of HCl (5% in H_2O) were added to a solution of 478 mg (1.102 mmol) of **19** in 7.3 ml THF. The reaction mixture was stirred for 18 h and was then quenched with phosphate buffer (pH 7, *c*=1.0 M). The reaction mixture was extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Purification by CC (*iso*-hexane/Et_2O=25:75) afforded 389 mg (90%) of **22**.

Compound **22**. Colorless crystals, mp 83 °C. TLC: R_f=0.22 (*iso*-hexane/Et_2O=25:75). $[\alpha]_D^{20}$=+191.8 (*c*=0.34, CH_2Cl_2). IR (KBr): $\tilde{\nu}$=2954 cm^{-1}, 2724, 1723, 1673, 1621, 1246, 1180. ^1H NMR ($C_2D_2Cl_4$, 120 °C): δ=0.94 ppm (s, 3H, CH_3), 1.04 (s, 3H, CH_3), 1.37 (s, 3H, CH_3), 1.71–1.84 (m, 2H, NCHCH_2CH$_2$C=, CH_2CH$_2$-CHO), 1.85–1.98 (m, 4H, CH_2CH$_2$, CH_2CH$_2$CHO, NCHCH_2CH$_2$C=), 2.27–2.40 (m, 2H, CH$_2$CH_2, CH$_2$CH_2-CHO), 2.40–2.55 (m, 3H, NCH=CCH_2, CH$_2$CH_2, CH$_2$-CH_2CHO), 2.56–2.67 (m, 1H, NCH=CCH_2), 3.78 (s, 3H, COOCH_3), 3.98 (d, *J*=11.0 Hz, 1H, OCH$_2$), 4.19 (dd, *J*=1.7, 11.0 Hz, 1H, OCH$_2$), 4.57–4.63 (m, 1H, NC*H*(CH$_2$)), 7.75 (s, 1H, NC*H*=C), 9.80 (s, 1H, CHO). MS (CI, CH_5^+); *m*/*z* (%): 392 [M^++1] (35), 360 (100), 305 (9), 195 (57), 167 (44), 139 (51). $C_{21}H_{29}NO_6$ (391.46): calcd C 64.43, H 7.47, N 3.58; found C 64.16, H 7.46, N 3.44.

6.1.8. Methyl (*S*)-6-(3-oxopropyl)-1-[(1*S*,5*R*)-5,8,8-trimethyl-2-oxo-3-oxabicyclo[3.2.1]octylcarbonyl]-1,4,5,6-tetrahydropyridine-3-carboxylate (23). Synthesis as described for the preparation of **22** from 132 mg (0.302 mmol) of **20** in 2 ml THF with 1.0 ml of HCl (5% in H_2O). Purification by CC (*iso*-hexane/ethyl acetate=55:45) afforded 106 mg (90%) of **23**.

Compound **23**. Colorless crystals, mp 52–55 °C. TLC: R_f=0.27 (*iso*-hexane/ethyl acetate=55:45). $[\alpha]_D^{20}$=−40.2 (*c*=0.53, CH_2Cl_2). IR (KBr): $\tilde{\nu}$=2958 cm^{-1}, 1725, 1670, 1618, 1243, 1184. ^1H NMR ($C_2D_2Cl_4$, 120 °C): δ=0.95 ppm (s, 3H, CH_3), 0.98 (s, 3H, CH_3), 1.29 (s, 3H, CH_3), 1.76–2.03 (m, 6H, NCHCH_2CH$_2$C=, CH_2CH$_2$CHO, CH_2CH$_2$), 2.20–2.39 (m, 2H, CH$_2$CH_2, CH$_2$CH_2CHO), 2.42–2.60 (m, 3H, CH$_2$CH_2, CH$_2$CH_2CHO, NCH=CCH_2), 2.64–2.85 (m, 1H, NCH=CCH_2), 3.77 (s, 3H, COOCH_3), 3.98 (d, *J*=11.1 Hz, 1H, OCH$_2$), 4.22 (dd, *J*=11.1/1.8 Hz, 1H, OCH$_2$), 4.80–4.85 (m, 1H, NC*H*CH$_2$), 7.78 (s, 1H, NC*H*=C), 9.79 (s, 1H, CHO). MS (CI, CH_5^+); *m*/*z* (%): 392 [M^++1] (22), 360 (31), 195 (536), 180 (100), 167 (26), 139 (14). $C_{21}H_{29}NO_6$ (391.46): calcd C 64.43, H 7.47, N 3.58; found C 64.11, H 7.75, N 3.22.

6.1.9. Methyl (*S*)-6-(4,4-diphenylbut-3-enyl)-1-[(1*S*,5*R*)-5,8,8-trimethyl-2-oxo-3-oxabicyclo[3.2.1]octylcarbonyl]-1,4,5,6-tetrahydropyridine-3-carboxylate (25).

722 μl (1.156 mmol, 1.2 equiv.) of *n*BuLi (1.6 M in hexane) were added to 700 μl of THF. After cooling to 0 °C 327 mg (1.156 mmol, 1.2 equiv.) of ethyl benzhydrylphosphonate (**24**) in 1.6 ml THF were added. The reaction mixture was warmed to room temperature. After 2.5 h a solution of 377 mg (0.963 mmol) of **22** in 4.6 ml THF were added dropwise and the reaction mixture was stirred for 18 h. The reaction was quenched with phosphate buffer (pH 7, c=1.0 M). Then it was extracted with CH_2Cl_2 and the combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Purification by CC (*iso*-hexane/Et_2O=40:60) afforded 429 mg (82%) of **25**.

Compound **25**. Colorless crystals, mp 185 °C. TLC: R_f=0.22 (*iso*-hexane/Et_2O=40:60). $[\alpha]_D^{20}$=+136.9 (c=0.49, CH_2Cl_2). IR (KBr): $\tilde{\nu}$=2951 cm^{-1}, 1731, 1707, 1674, 1622, 1243, 1186, 810, 764, 702. ^1H NMR (nitrobenzene-d_5, 140 °C): δ=0.92 ppm (s, 3H, CH_3), 1.09 (s, 3H, CH_3), 1.43 (s, 3H, CH_3), 1.81–1.87 (m, 2H, NCHCH_2CH$_2$C=), 1.87–2.04 (m, 4H, CH_2CH_2), 2.22–2.36 (m, 3H, NCH=CCH_2, CH_2CH$_2$), 2.41 (dd, J=17.3/5.8 Hz, 1H, NCH=CCH_2), 2.48–2.59 (m, 2H, CH$_2$CH_2), 3.76 (s, 3H, $COOCH_3$), 3.99 (d, J=11.1 Hz, 1H, OCH_2), 4.21 (d, J=11.1 Hz, 1H, OCH_2), 4.56–4.64 (m, 1H, NCHCH$_2$), 6.19 (t, J=6.8 Hz, 1H, HC=CPh$_2$), 7.18–7.37 (m, 8H, $H_{arom.}$), 7.37–7.45 (m, 2H, $H_{arom.}$), 8.07 (s, 1H, NCH=C). MS (CI, CH_5^+); m/z (%): 542 [M^++1] (27), 510 (37), 346 (37), 271 (12), 195 (100), 167 (40), 139 (38). $C_{34}H_{39}NO_5$ (541.69): calcd C 75.39, H 7.26, N 2.59; found C 75.14, H 7.26, N 2.47.

6.1.10. Methyl (*R*)-6-(4,4-diphenylbut-3-enyl)-1-[(1*S*,5*R*)-5,8,8-trimethyl-2-oxo-3-oxabicyclo[3.2.1]octylcarbonyl]-1,4,5,6-tetrahydropyridine-3-carboxylate (26). Synthesis as described for the preparation of **25** using 137 μl (0.218 mmol, 1.2 equiv.) of *n*BuLi (1.6 M in hexane), 137 μl of THF, 66 mg (0.218 mmol, 1.2 equiv.) of ethyl benzhydrylphosphonate (**24**) in 296 μl THF, 71 mg (0.182 mmol) of **23** in 865 μl THF. Purification by CC (*iso*-hexane/Et_2O=40:60) afforded 80 mg (81%) of **26**.

Compound **26**. Colorless crystals, mp 75 °C. TLC: R_f=0.30 (*iso*-hexane/Et_2O=40:60). $[\alpha]_D^{20}$=−23.9 (c=0.93, CH_2Cl_2). IR (KBr): $\tilde{\nu}$=2952 cm^{-1}, 1729, 1682, 1235, 1178, 763, 701. ^1H NMR ($C_2D_2Cl_4$, 120 °C): δ=0.93 ppm (s, 3H, CH_3), 0.95 (s, 3H, CH_3), 1.29 (s, 3H, CH_3), 1.50–1.70 (m, 3H, CH_2CH$_2$, NCHCH_2CH$_2$C=), 1.80–1.97 (m, 3H, CH$_2$CH_2, NCHCH_2CH$_2$C=), 2.04–2.22 (m, 3H, NCH=CCH_2, CH_2CH$_2$), 2.28–2.56 (m, 3H, CH$_2$CH_2, NCH=CCH_2), 3.76 (s, 3H, $COOCH_3$), 3.96 (d, J=11.0 Hz, 1H, OCH_2), 4.18 (dd, J=11.1/1.2 Hz, 1H, OCH_2), 4.71–4.79 (m, 1H, NCHCH$_2$), 6.12 (t, J=7.5 Hz, 1H, HC=CPh$_2$), 7.14–7.44 (m, 10H, $H_{arom.}$), 7.77 (s, 1H, NCH=C). MS (CI, CH_5^+); m/z (%): 542 [M^++1] (100), 510 (23), 195 (20), 167 (14), 139 (14). $C_{34}H_{39}NO_5$ (541.69): calcd C 75.39, H 7.26, N 2.59; found C 75.37, H 7.56, N 2.44.

6.1.11. Methyl (*S*)-6-(4,4-diphenylbut-3-enyl)-1,4,5,6-tetrahydropyridine-3-carboxylate (27). A mixture of 600 μl of freshly prepared NaOMe (0.5 M in CH_3OH_{abs}) and 25 mg (0.046 mmol) of **25** in 230 μl THF was reacted at 120 °C for 18 h in a sealed tube. The reaction was quenched with phosphate buffer (pH 7, c=1.0 M). The reaction mixture was extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Purification by CC (CH_2Cl_2/CH_3OH=95:5) afforded 15 mg (90%) of **27**. As product **27** appeared to be labile, it could not be fully characterized. It was immediately transformed to either the compounds **28** and **29** or **34**.

Compound **27**. Colorless oil. TLC: R_f=0.68 (CH_2Cl_2/CH_3OH=95:5). ^1H NMR (CD_2Cl_2): δ=1.53–1.62 ppm (m, 3H, NCHCH_2CH$_2$C=, NCHCH$_2$CH_2CH–CPh$_2$), 1.70–1.78 (m, 1H, NCHCH_2CH$_2$C=), 2.14–2.21 (m, 3H, NCH=CCH_2, NCHCH_2CH$_2$CHCPh$_2$), 2.22–2.31 (m, 1H, NCH=CCH_2), 3.12–3.21 (m, 1H, NCHCH$_2$), 3.58 (s, 3H, $COOCH_3$), 4.16 (br, 1H, NH), 6.07 (t, J=6.8 Hz, 1H, HC=CPh$_2$), 7.12–7.29 (m, 7H, $H_{arom.}$, NCH=C), 7.29–7.45 (m, 4H, $H_{arom.}$). MS (CI, CH_5^+); m/z (%): 348 [M^++1] (100), 316 (13), 237 (1), 138 (12).

6.1.12. Methyl (*R*)-6-(4,4-diphenylbut-3-enyl)-1,4,5,6-tetrahydropyridine-3-carboxylate [(*ent*)-27]. Synthesis as described for the preparation of **27** from 37 mg (0.067 mmol) of **26** in 340 μl THF with 1.2 ml of freshly prepared NaOMe (0.5 M in $CH_3OH_{abs.}$). Purification by CC (CH_2Cl_2/ CH_3OH=95:5) afforded 22 mg (90%) of (*ent*)-**27**. As product (*ent*)-**27** appeared to be labile, it could not be fully characterized. It was immediately transformed to either the compounds (*ent*)-**28** and (*ent*)-**29** or (*ent*)-**34**.

Compound (*ent*)-**27**. Colorless oil. ^1H NMR as described for **27**. MS (CI, CH_5^+); m/z (%): 348 [M^++1] (100), 316 (12), 237 (21), 138 (23).

6.1.13. Methyl (3*S*,6*S*)-6-(4,4-diphenylbutyl)piperidine-3-carboxylate (28) and methyl (3*R*,6*S*)-6-(4,4-diphenylbutyl)piperidine-3-carboxylate (29). The starting material **27** was prepared as described above from 430 mg (0.794 mmol) of **25** in 4 ml THF and 18 ml of freshly prepared NaOMe (0.5 M in $CH_3OH_{abs.}$). Following purification by CC (CH_2Cl_2/CH_3OH=95:5) the solvent was removed in vacuo and the residue was dissolved in 1.8 ml of CF_3CO_2H. 380 μl (278 mg, 2.392 mmol, 3 equiv.) of Et_3SiH were added dropwise and the reaction mixture was stirred for 3 h at 50 °C. The reaction was quenched with saturated $NaHCO_3$ solution. The reaction mixture was extracted with CH_2Cl_2 and the combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Purification by CC (Et_2O/$EtMe_2N$=98:2) afforded 140 mg (50%) of a mixture of **28** and **29**.

Compounds **28** and **29**. Colorless oil. TLC: R_f=0.28 (Et_2O/$EtMe_2N$=98:2). ^1H NMR (CD_2Cl_2): δ=0.93–1.05 ppm (m, 1H, NCHCH_2 (**28**), NCHCH_2 (**29**)), 1.22–1.40 (m, 4H, CH_2CH_2), 1.40–1.52 (m, 0.8×1H, NCHCH_2 (**28**)), 1.53–1.61 (m, 0.2×1H, NCHCH_2 (**29**)), 1.65–1.75 (m, 1H, NCH$_2$CHCH_2 (**28**), NCH$_2$CHCH_2 (**29**)), 1.96–2.15 (m, 3H, NCH$_2$CHCH_2 (**28**), NCH$_2$CHCH_2 (**29**), CH_2CHPh$_2$ (**28**), CH_2CHPh$_2$ (**29**)), 2.28–2.37 (m, 1.8H, NHCH_{ax} (**28**) one large coupling J=12.1 Hz was identifiable, CHCOO (**28**), CHCOO (**29**)), 2.38–2.43 (m, one large coupling J=12.1 Hz was identifiable, 0.2H, NHCH_{ax} (**29**)), 2.60 (dd, J=11.8/11.3 Hz, 0.8×1H, NCH$_{2ax}$ (**28**)), 2.71 (dd, J=12.8/3.5 Hz, 0.2×1H, NCH$_{2ax}$ (**29**)), 3.20 (dd, J=11.8/4.1 Hz, 0.8×1H, NCH$_{2eq}$ (**28**)), 3.31 (dd, J=12.8/2.5 Hz,

0.2×1H, NCH_{2eq} (**29**)), 3.61 (s, 0.8×3H, $COOCH_3$ (**28**)), 3.66 (s, 0.2×3H, $COOCH_3$ (**29**)), 3.89 (t, J=7.7 Hz, 0.2×1H, Ph_2CH (**29**)), 3.90 (t, J=7.7 Hz, 0.8×1H, Ph_2CH (**28**)), 7.11–7.20 (m, 2H, $H_{arom.\ para}$), 7.21–7.35 (m, 8H, $H_{arom.\ ortho,\ meta}$); **28/29**=83/17. MS (CI, CH_5^+); *m/z* (%): 352 [M^++1] (100), 320 (3), 274 (3), 142 (20). HRM (70 eV) for $C_{23}H_{29}NO_2$: calcd 351.2198; found 351.2195 (M^+). $C_{23}H_{29}NO_2$ (355.22): calcd C 78.65, H 8.31, N 3.99; found C 77.36, H 8.66, N 3.68.

6.1.14. Methyl (3*R*,6*R*)-6-(4,4-diphenylbutyl)piperidine-3-carboxylate [(*ent*)-28] and methyl (3*S*,6*R*)-6-(4,4-diphenylbutyl)piperidine-3-carboxylate [(*ent*)-29]. Synthesis as described for the preparation of **28** and **29** from 203 mg (0.345 mmol) of **26** in 1.9 ml of THF with 6.7 ml of freshly prepared NaOMe (0.5 M in $CH_3OH_{abs.}$), 950 μl of CF_3CO_2H and 193 μl (141 mg, 1.214 mmol, 3.5 equiv.) of Et_3SiH. Purification by CC (Et_2O/$EtMe_2N$=98:2) afforded 66 mg (50%) of a mixture of (*ent*)-**28** and (*ent*)-**29**.

Compounds (*ent*)-**28** and (*ent*)-**29**. ^{1}H NMR and IR as described for **28** and **29**, respectively. Colorless oil. HRM (70 eV) for $C_{23}H_{29}NO_2$: calcd 351.2198; found 351.2193 (M^+).

6.1.15. Methyl (3*S*,6*S*)-1-*tert*-butyloxycarbonyl-6-(4,4-diphenylbutyl)piperidine-3-carboxylate (30) and methyl (3*R*,6*S*)-1-*tert*-butyloxycarbonyl-6-(4,4-diphenylbutyl)-piperidine-3-carboxylate (31). 44 μl (32 mg, 0.313 mmol, 1.0 equiv.) of NEt_3, 307 mg (1.407 mmol, 4.4 equiv.) of di-*tert*-butyldicarbonate and 39 mg (0.319 mmol, 1.0 equiv.) of DMAP were added to a solution of 110 mg (0.313 mmol) of a mixture of **28** and **29** (**28/29**=83/17) in 1.7 ml of THF. The reaction mixture was stirred for 3 days at room temperature. Phosphate buffer (pH 7, c=1.0 M) was added. The reaction mixture was extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Purification by CC (*iso*-hexane/Et_2O/$EtMe_2N$=80:20:2) afforded 81 mg (70%) of **30** and 17 mg (10%) of **31**.

Compound **30**. Colorless oil. TLC: R_f=0.14 (*iso*-hexane/Et_2O/dimethylethyl amine=80:20:2). $[\alpha]_D^{20}$=+38.7 (c=1.16, CH_2Cl_2). IR: $\tilde{\nu}$=2932 cm^{-1}, 1736, 1688, 1418, 1365, 1162, 741, 702. ^{1}H NMR (CD_2Cl_2): δ=1.10–1.25 ppm (m, 2H, $CH_2CH_2CHPh_2$), 1.29–1.36 (m, 1H, $NCHCH_2$), 1.34 (s, 9H, *t*Bu), 1.36–1.44 (m, 1H, $NCHCH_2$), 1.64–1.84 (m, 3H, NCH_2CHCH_2, $CH_2CH_2CH_2CHPh_2$), 1.89–1.92 (m, 1H, NCH_2CHCH_2), 1.98–2.14 (m, 2H, CH_2CHPh_2), 2.47–2.53 (m, 1H, $CHCOO$), 2.89 (dd, J=14.0/4.0 Hz, 1H, NCH_2CHCOO), 3.66 (s, 3H, $COOCH_3$), 3.87 (t, J=7.7 Hz, 1H, Ph_2CH), 4.06–4.16 (m, 1H, $NCHCH_2$), 4.32 (d, J=14.0 Hz, 1H, NCH_2CHCOO), 7.09–7.20 (m, 2H, $H_{arom.\ ortho}$), 7.21–7.30 (m, 8H, $H_{arom.\ meta,\ para}$). MS (CI, CH_5^+); *m/z* (%): 452 [M^++1] (2), 396 (91), 352 (100), 142 (89). $C_{28}H_{37}NO_4$ (451.61): calcd C 74.47, H 8.26, N 3.10; found C 74.66, H 8.52, N 3.09.

Compound **31**. Colorless oil. TLC: R_f=0.26 (*iso*-hexane/Et_2O/$EtMe_2N$=80:20:2). $[\alpha]_D^{20}$=−22.6 (c=0.73, CH_2Cl_2). IR: $\tilde{\nu}$=2933 cm^{-1}, 1731, 1682, 1420, 1265, 1161, 740, 706. ^{1}H NMR (CD_2Cl_2): δ=1.09–1.24 ppm (m, 2H, $CH_2CH_2CHPh_2$), 1.33 (s, 9H, *t*Bu), 1.30–1.45 (m, 1H, $NCHCH_2$), 1.51–1.79 (m, 4H, $NCHCH_2$, NCH_2CHCH_2, $CH_2CH_2CH_2CHPh_2$), 1.79–1.88 (m, 1H, NCH_2CHCH_2), 1.97–2.16 (m, 2H, CH_2CHPh_2), 2.35 (dddd, J=11.9/11.6/4.3/4.0 Hz, 1H, $CHCOO$), 2.63–2.86 (br_{koal}, 1H, NCH_2CHCOO), 3.66 (s, 3H, $COOCH_3$), 3.88 (t, J=7.7 Hz, 1H, Ph_2CH), 3.96–4.34 (br_{koal}, 2H, $NCHCH_2$, NCH_2CHCOO), 7.11–7.40 (m, 10H, $H_{arom.}$). ^{1}H NMR (CD_2Cl_2, −78 °C): 0.93–1.09 ppm (m, 2H, $CH_2CH_2CHPh_2$), 1.15 (s, 0.65×9H, *t*Bu), 1.30 (s, 0.35×9H, *t*Bu), 1.41–1.67 (m, 4H, $CH_2CH_2CH_2CHPh_2$, $NCHCH_2$), 1.71–1.82 (m, 2H, CH_2CHPh_2), 1.82–1.94 (m, 1H, NCH_2CHCH_2), 1.95–2.06 (m, 1H, NCH_2CHCH_2), 2.23–2.35 (m, 1H, $CHCOO$), 2.65 (dd, J=13.7/12.5 Hz, 0.65×1H, NCH_2CHCOO_{ax}), 2.73 (dd, J=13.7/12.5 Hz, 0.35×1H, NCH_2CHCOO_{ax}), 3.57 (s, 0.65×3H, $COOCH_3$), 3.58 (s, 0.35×3H, $COOCH_3$), 3.79 (t, J=6.4 Hz, 1H, Ph_2CH), 3.95 (dd, J=13.7/2.9 Hz, 0.35×1H, NCH_2CHCOO_{eq}), 3.98–4.06 (m, 0.65×1H, $NCHCH_2$), 4.05–4.17 (m, 1H, $NCHCH_2$, NCH_2CHCOO_{eq}), 7.04–7.16 (m, 2H, $H_{arom.\ ortho}$), 7.15–7.30 (m, 8H, $H_{arom.\ meta,\ para}$); ratio of rotamers: 65/35. MS (CI, CH_5^+); *m/z* (%): 452 [M^++1] (1), 396 (86), 352 (100), 142 (75). HRM (70 eV) for $C_{28}H_{37}NO_4$: calcd 451.2723; found 451.2721 (M^+).

6.1.16. Methyl (3*R*,6*R*)-1-*tert*-butyloxycarbonyl-6-(4,4-diphenylbutyl)piperidine-3-carboxylate [(*ent*)-30] and methyl (3*S*,6*R*)-1-*tert*-butyloxycarbonyl-6-(4,4-diphenyl-butyl)piperidine-3-carboxylate (32). Synthesis as described for **30** and **31** from 59 mg (0.167 mmol) of a mixture of (*ent*)-**28** and (*ent*)-**29** [(*ent*)-**29**/(*ent*)-**28**=79/21] in 290 μl of THF with 23 μl (17 mg, 0.167 mmol, 1.0 equiv.) of NEt_3, 164 mg (0.751 mmol, 4.4 equiv.) of di-*tert*-butyldicarbonate and 21 mg (0.319 mmol, 1.9 equiv.) of DMAP, reaction time: 2 days. Purification by CC (*iso*-hexane/Et_2O/$EtMe_2N$=80:20:2) afforded 43 mg (57%) of (*ent*)-**30** and 17 mg (10%) of (*ent*)-**31**.

Compound (*ent*)-**30**. Colorless Oil. ^{1}H NMR and IR as described for **30**. $[\alpha]_D^{20}$=−37.8° (c=0.68, CH_2Cl_2). $C_{28}H_{37}NO_4$ (451.61): calcd C 74.47, H 8.26, N 3.10; found C 74.07, H 8.23, N 3.08.

Compound (*ent*)-**31**. Colorless Oil. ^{1}H NMR and IR as described for **31**. $[\alpha]_D^{20}$=+22.8 (c=0.365, CH_2Cl_2). HRM (70 eV) for $C_{28}H_{37}NO_4$: calcd 451.2723; found 451.2721 (M^+).

6.1.17. (3*S*,6*S*)-6-(4,4-Diphenylbutyl)piperidine-3-carboxylic acid hydrochloride (32). 34 mg (0.075 mmol) of **30** in 9 ml of 2 M HCl were refluxed for 3 h. After cooling to room temperature the solvent was removed in vacuo and the residue was dried over P_2O_5. Yield: 28 mg (100%).

Compound **32**. Colorless crystals, mp 249 °C. $[\alpha]_D^{20}$=+7.6 (c=0.38, DMSO). IR: $\tilde{\nu}$=3423 cm^{-1}, 2940, 2804, 2501, 1724, 1200, 1180, 765, 699. ^{1}H NMR (DMSO-d_6): δ=1.15–1.29 ppm (m, 2H, $Ph_2CHCH_2CH_2$), 1.28–1.40 (m, 1H, $NCHCH_2$), 1.42–1.55 (m, 2H, $NCHCH_2$, $Ph_2CH(CH_2)_2CH_2$), 1.60–1.71 (m, 1H, $Ph_2CH(CH_2)_2CH_2$), 1.74–1.84 (m, 1H, NCH_2CHCH_2), 1.93–2.09 (m, 3H, Ph_2CHCH_2, NCH_2CHCH_2), 2.59–2.69 (m, 1H, $CHCOOH$), 2.86 (dd, J=13.7/12.0 Hz, 1H, $NCH_{2ax}CHCOO$), 2.90–3.00 (m, 1H, $NCHCH_2$), 3.30 (d, J=13.7 Hz, 1H, $NCH_{2eq}CHCOO$), 3.92 (t, J=7.0 Hz, 1H, Ph_2CH), 7.02–7.19 (m, 2H, $H_{arom.}$), 7.20–7.35 (m, 8H, $H_{arom.}$), 8.62–9.03 (br, 2H,

NH_2^+), 12.54–12.89 (br, 1H, COOH). MS (70 eV); *m/z* (%): 337 [M^+−HCl] (5), 319 (4), 260 (1) 167 (12), 128 (100). $C_{22}H_{28}NO_2Cl{\cdot}0.5H_2O$ (382.93): calcd C 69.00, H 7.63, N 3.66; found C 68.87, H 7.57, N 3.54.

6.1.18. (3*R*,6*S*)-6-(4,4-Diphenylbutyl)piperidine-3-carboxylic acid hydrochloride (33). Synthesis as described for the preparation of **32** from 14 mg (0.031 mmol) of **31** in 3.8 ml of 2 M HCl. Yield: 12 mg (99%).

Compound **33**. Colorless crystals, mp 215 °C. $[\alpha]_D^{20}=-0.5$ (c=0.38, DMSO). $[\alpha]_D^{20}=-0.5$ (c=0.19, DMSO). IR: $\tilde{\nu}$=3423 cm^{-1}, 2928, 2862, 1710, 1223, 1107, 762, 701. ^1H NMR (DMSO-d_6): δ=1.18–1.26 ppm (m, 2H, $Ph_2CHCH_2CH_2$), 1.28–1.37 (m, 1H, NCHCH_2), 1.51–1.65 (m, 2H, $Ph_2CH(CH_2)_2CH_2$), 1.67–1.77 (m, 2H, NCHCH_2, NCH_2CHCH_2), 1.87–1.98 (m, 1H, NCH_2CHCH_2), 1.98–2.11 (m, 2H, Ph_2CHCH_2), 2.77–2.84 (m, 1H, C*H*COOH), 3.00–3.12 (m, 2H, NCH_2CH, NCH_{2ax}CHCOO), 3.30 (d, J=13.7 Hz, 1H, NCH_{2eq}CHCOO), 3.93 (t, J=7.6 Hz, 1H, Ph_2CH), 7.11–7.22 (m, 2H, $H_{arom.}$), 7.21–7.37 (m, 8H, $H_{arom.}$), 7.88–8.06 (br, 1H, NH_2^+), 8.84–9.05 (br, 1H, NH_2^+), 12.78–12.98 (br, 1H, COOH). MS (70 eV); *m/z* (%): 337 [M^+−HCl] (10), 167 (11), 128 (100). HRM (70 eV) for $C_{22}H_{27}NO_2$: calcd 337.2035; found 337.2030 (M^+).

6.1.19. (3*R*,6*R*)-6-(4,4-Diphenylbutyl)piperidine-3-carboxylic acid hydrochloride [(*ent*)-32]. Synthesis as described for the preparation of **32** from 27 mg (0.060 mmol) of (*ent*)-**30** in 7 ml of 2 M HCl. Yield: 22 mg (100%).

Compound (*ent*)-**32**. Colorless crystals. ^1H NMR and IR as described for **32**. $[\alpha]_D^{20}=-7.4$ (c=0.19, DMSO). $C_{22}H_{28}NO_2Cl{\cdot}0.5H_2O$ (382.93): calcd C 69.00, H 7.63, N 3.66; found C 69.21, H 7.63, N 3.66.

6.1.20. (3*S*,6*R*)-6-(4,4-Diphenylbutyl)piperidine-3-carboxylic acid hydrochloride [(*ent*)-33]. Synthesis as described for the preparation of **33** from 6.6 mg (0.015 mmol) of (*ent*)-**31** in 1.8 ml of 2 M HCl. Yield: 5.5 mg (100%).

Compound (*ent*)-**33**. Colorless crystals. ^1H NMR and IR as described for **33**. $[\alpha]_D^{20}=+0.7$ (c=0.08, DMSO). HRM (70 eV) for $C_{22}H_{27}NO_2$: calcd 337.2035; found 337.2031 (M^+).

6.1.21. (*S*)-Methyl [1-*tert*-butyloxycarbonyl-6-(4,4-diphenylbut-3-enyl)-1,4,5,6-tetrahydropyridine-3-carboxylate] (34). The starting material **27** was prepared as described above from 352 mg (0.650 mmol) of **25** in 3.2 ml of THF with 11.5 ml of freshly prepared NaOMe (0.5 M in $CH_3OH_{abs.}$). After purification by CC (CH_2Cl_2/CH_3OH=95:5) the solvent was removed in vacuo and the residue was dissolved in 1.24 ml of THF. 101 μl (74 mg, 0.728 mmol, 1.12 equiv.) of NEt_3, 716 mg (3.282 mmol, 5.05 equiv.) of di-*tert*-butyldicarbonate and 92 mg (0.755 mmol, 1.16 equiv.) of DMAP were added. The reaction mixture was stirred for 3 days. Phosphate buffer (pH 7, c=1.0 M) was added. The reaction mixture was extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Purification by CC (*iso*-hexane/Et_2O=80:20) afforded 217 mg (75%) of **34**.

Compound **34**. Colorless oil. TLC: R_f=0.24 (*iso*-hexane/Et_2O=80:20)-$[\alpha]_D^{20}=+48.5$ (c=0.46 in CH_2Cl_2). IR (Film): $\tilde{\nu}$=2946 cm^{-1}, 1634, 1455, 1416, 1028, 739, 700. ^1H NMR ($C_2D_2Cl_4$, 120 °C): δ=1.51 ppm (s, 9H, *t*Bu), 1.57–1.75 (m, 3H, NCHCH_2, $Ph_2CCHCH_2CH_2$), 1.83 (ddt, J=13.5/5.8/2.3 Hz, 1H, NCHCH_2), 2.06–2.27 (m, 3H, NCHCCH_2, Ph_2CCHCH_2), 2.40 (dd, J=18.4/4.9 Hz, 1H, NCHCCH_2), 3.76 (s, 3H, $COOCH_3$), 4.21–4.28 (m, 1H, NC*H*CH_2), 6.11 (t, J=7.6 Hz, 1H, *H*C=CPh_2), 7.17–7 44 (m, 10H, $H_{arom.}$), 8.01 (s, 1H, NC*H*=C). MS (CI, CH_5^+); *m/z* (%): 448 [M^++1] (54), 416 (9), 392 (100), 348 (98), 182 (29), 142 (34), 138 (24). $C_{28}H_{33}NO_4$ (447.57): calcd C 75.14, H 7.45, N 3.13; found C 74.64, H 7.95, N 2.66.

6.1.22. (*R*)-Methyl [1-*tert*-butyloxycarbonyl-6-(4,4-diphenylbut-3-enyl)-1,4,5,6-tetrahydropyridine-3-carboxylate] [(*ent*)-34]. The starting material (*ent*)-**27** was prepared as described above from 118 mg (0.218 mmol) of **26** in 1.2 ml of THF, 4.2 ml of freshly prepared NaOMe (0.5 M in $CH_3OH_{abs.}$). The synthesis of (*ent*)-**34** was performed in analogy to the preparation of **34** from 71 mg of (*ent*)-**27** in 0.4 ml of THF with 101 μl (25 mg, 0.245 mmol, 1.12 equiv.) of NEt_3, 241 mg (1.105 mmol, 5.05 equiv.) of di-*tert*-butyldicarbonate and 31 mg (0.254 mmol, 1.16 equiv.) of DMAP. Purification by CC (*iso*-hexane/Et_2O=80:20) afforded 51 mg (52%) of (*ent*)-**34**.

Compound (*ent*)-**34**. Colorless oil. ^1H NMR and IR as described for **34**. $[\alpha]_D^{20}=-47.4$ (c=1.35, CH_2Cl_2). $C_{28}H_{33}NO_4$ (447.57): calcd C 75.14, H 7.45, N 3.13; found C 74.84, H 7.56, N 3.04.

6.1.23. (3*S*,6*S*)-Methyl [1-*tert*-butyloxycarbonyl-6-(4,4-diphenylbut-3-enyl)piperidine-3-carboxylate] (35) and (3*R*,6*S*)-methyl [1-*tert*-butyloxycarbonyl-6-(4,4-diphenylbut-3-enyl)piperidine-3-carboxylate] (36). 428 mg of magnesium powder were added to 185 mg (0.141 mmol) of **34** in 1.64 ml of CH_3OH. After 20 min in a sonicator 5 ml of CH_3OH were added, followed by the addition of 4 ml of CH_3OH after 1 h. Following stirring for 18 h phosphate buffer (pH 7, c=1.0 M) was added and the reaction mixture was extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Purification by CC (*iso*-hexane/Et_2O=70:30) and separation by prep. HPLC (*iso*-hexane/Et_2O=70:30; 9 ml/min) yielded 69 mg (37%) of **35** (t_R=42.14 min) and 51 mg (28%) of **36** (t_R=26.20 min). Analytical HPLC (*iso*-hexane/Et_2O=70:30; 1.0 ml/min); **36**: t_R=10.41 min, 42.4%; **35**: t_R=18.36 min, 57.6%.

Compound **35**. Colorless oil. TLC: R_f=0.21 (*iso*-hexane/Et_2O=70:380)-$[\alpha]_D^{20}=+45.2$ (c=0.5, CH_2Cl_2). IR: $\tilde{\nu}$=2928 cm^{-1}, 1738, 1693, 1418, 1364, 1364, 1168, 764, 701. ^1H NMR (CD_2Cl_2): δ=1.41 ppm (s, 9H, *t*Bu), 1.36–1.45 (m, 2H, NCHCH_2), 1.49–1.60 (m, 1H, CH_2CH_2-$CHCPh_2$), 1.67–1.90 (m, 2H, $CH_2CH_2CHCPh_2$, NCH_2-$CHCH_2$), 1.95–2.16 (m, 3H, NCH_2CHCH_2, CH_2CHCPh_2), 2.52–2.57 (m, 1H, C*H*COO), 2.93 (dd, J=14.0/4.1 Hz, 1H, NCH_2CHCOO), 3.66 (s, 3H, $COOCH_3$), 4.15–4.24 (m, 1H, NC*H*CH_2), 4.41 (d, J=14.0 Hz, 1H, NCH_2CHCOO), 6.10 (t, J=7.6 Hz, 1H, Ph_2C=C*H*), 7.14–7.44 (m, 10H, $H_{arom.}$).

MS (CI, CH_5^+); *m/z* (%): 450 [M^++1] (2), 350 (100), 142 (49). $C_{28}H_{35}NO_4$ (449.59): calcd C 74.80, H 7.85, N 3.12; found C 74.80, H 8.00, N 2.90.

Compound **36**. Colorless oil. TLC: R_f=0.31 (*iso*-hexane/Et_2O=70:30). $[\alpha]_D^{20}$=−12.8 (*c*=0.5, CH_2Cl_2). IR: $\tilde{\nu}$=2924 cm^{-1}, 1734, 1691, 1416, 1164, 765, 701. ^1H NMR (CD_2Cl_2): δ=1.32–1.45 ppm (br_{koal}, 9H, *t*Bu), 1.45–1.75 (m, 4H, NCHCH_2, C$H_2$$CH_2CHCPh_2$), 1.75–1.93 (m, 2H, NCH_2CHCH_2), 1.96–2.15 (m, 2H, CH_2CHCPh_2), 2.30–2.48 (m, 1H, C*H*COO), 2.66–2.86 (br_{koal}, 1H, NCH_2CHCOO), 3.68 (s, 3H, $COOCH_3$), 3.97–4.35 (br_{koal}, 2H, NC*H*CH_2, NCH_2CHCOO), 6.09 ppm (t, *J*=8.1 Hz, 1H, Ph_2C=CH), 7.11–7.40 (m, 10H, $H_{arom.}$). MS (CI, CH_5^+); *m/z* (%): 450 [M^++1] (2), 394 (15), 350 (100), 142 (43). $C_{28}H_{35}NO_4$ (449.59): calcd C 74.80, H 7.85, N 3.12; found C 74.67, H 7.91, N 3.01.

6.1.24. (3*R*,6*R*)-Methyl [1-*tert*-butyloxycarbonyl-6-(4,4-diphenylbut-3-enyl)piperidine-3-carboxylate] [(*ent*)-35] and (3*S*,6*R*)-methyl [1-*tert*-butyloxycarbonyl-6-(4,4-diphenylbut-3-enyl)piperidine-3-carboxylate] [(*ent*)-36]. Synthesis as described for **35** and **36** from 65 mg (0.145 mmol) of (*ent*)-**34** with 150 mg magnesium powder and 0.6 ml of CH_3OH. Purification by CC (*iso*-hexane/Et_2O=70:30) and separation by prep. HPLC (*iso*-hexane/Et_2O=70:30; 9 ml/min) yielded 10 mg (16%) of (*ent*)-**35** (t_R=42.14 min) and 17 mg (26%) of (*ent*)-**36** (t_R=26.20 min). Analytical HPLC (*iso*-hexane/Et_2O=70:30; 1.0 ml/min); (*ent*)-**36**: t_R=10.41 min, 42.6%; (*ent*)-**35**: t_R=18.36 min, 57.4%.

Compound (*ent*)-**35**. Colorless oil. ^1H NMR and IR as described for **35**. $[\alpha]_D^{20}$=−45.6° (*c*=0.82, CH_2Cl_2). HRM (70 eV) for $C_{28}H_{35}NO_4$: calcd 449.2566; found 449.2614 (M^+).

Compound (*ent*)-**36**. Colorless oil. ^1H NMR and IR as described for **36**. $[\alpha]_D^{20}$=+10.2 (*c*=0.50, CH_2Cl_2). HRM (70 eV) for $C_{28}H_{35}NO_4$: calcd 429.2566; found 449.2560 (M^+).

6.1.25. (3*S*,6*S*)-6-(4,4-Diphenylbutyl)piperidine-3-carboxylic acid hydrochloride (37). Synthesis as described for the preparation of **32** from 48 mg (0.107 mmol) of **35** in 13 ml of 2 M HCl. Yield: 38 mg (92%).

Compound **37**. Colorless crystals, mp 234–236 °C (decomp.). $[\alpha]_D^{20}$=+13.6 (*c*=0.53, DMSO). $\tilde{\nu}$=3445 cm^{-1}, 2930, 2730, 2361, 1734, 1162, 766, 703, 696. ^1H NMR (DMSO-d_6): δ=1.26–1.40 ppm (m, one large coupling *J*=12.9 Hz was identifiable, 1H, NCHCH_2), 1.40–1.55 (m, 1H, NCH_2CHCH_2), 1.55–1.67 (m, 1H, Ph_2CCHCH_2CH_2), 1.67–1.77 (m, 1H, NCHCH_2), 1.77–1.87 (m, 1H, Ph_2CCHCH_2CH_2), 1.93–2.03 (m, 1H, NCH_2CHCH_2), 2.09–2.15 (m, 2H, Ph_2CCHCH_2), 2.62–2.72 (m, 1H, C*H*COOH), 2.90 (dd, *J*=13.0/11.6 Hz, 1H, NC$H_2$$CHCOO_{ax}$), 2.95–3.04 (m, 1H, NC*H*CH_2), 3.39–3.44 (m, 1H, NC$H_2$$CHCOO_{eq}$), 6.10 (t, *J*=7.0 Hz, 1H, Ph_2CCH), 7.07–7.50 (m, 10H, $H_{arom.}$), 8.76–9.08 (br, 2H, NH_2^+), 12.61–12.91 (br, 1H, COOH). MS (CI, CH_5^+); *m/z* (%): 336 [M^++1-HCl] (37). $C_{22}H_{28}NO_3Cl$ (389.92): calcd C 67.77, H 7.24, N 3.59; found C 67.97, H 7.02, N 3.59.

6.1.26. (3*R*,6*R*)-6-(4,4-Diphenylbutyl)piperidine-3-carboxylic acid hydrochloride [(*ent*)-37]. Synthesis as described for the preparation of **37** from 10 mg (0.022 mmol) of (*ent*)-**35** in 2.8 ml of 2 M HCl. Yield: 8 mg (100%).

Compound (*ent*)-**37**. Colorless crystals. ^1H NMR and IR as described for **37**. $[\alpha]_D^{20}$=−14.3° (*c*=0.37, DMSO). HRM (70 eV) for $C_{28}H_{35}NO_4$: calcd 335.1885; found 335.1884 (M^+).

6.1.27. (3*R*,6*S*)-6-(4,4-Diphenylbuty-3-enyl)piperidine-3-carboxylic acid hydrochloride (38). Synthesis as described for the preparation of **32** from 32 mg (0.071 mmol) of **36** in 8.7 ml of 2 M HCl. Yield: 28 mg (97%).

Compound **38**. Colorless crystals, mp 150 °C (decomp.). $[\alpha]_D^{20}$=+12.7° (*c*=0.48, DMSO). IR: $\tilde{\nu}$=3425 cm^{-1}, 2926, 2360, 1733, 1445, 767, 698. ^1H NMR (DMSO-d_6): δ=1.21–1.35 ppm (m, 1H, NC*H*CH_2), 1.60–1.73 (m, 3H, NCHCH_2, NCH_2CHCH_2, Ph_2CCHCH_2CH_2), 1.73–1.83 (m, 1H, Ph_2CCHCH_2CH_2), 1.87–1.97 (m, 1H, NCH_2CHCH_2), 2.04–2.17 (m, 2H, Ph_2CCHCH_2), 2.78–2.85 (m, 1H, C*H*COOH), 3.03–3.14 (m, 2H, NC*H*CH_2, NCH_2-$CHCOO_{ax}$), 3.29 (dd, *J*=13.2, 4.8 Hz, 1H, NCH_2-$CHCOO_{eq}$), 6.11 (t, *J*=7.7 Hz, 1H, Ph_2CCH), 7.06–7.57 (m, 10H, $H_{arom.}$), 7.88–8.31 (br, 1H, NH_2^+), 8.88–9.34 (br, 1H, NH_2^+), 12.60–13.15 (br, 1H, COOH). MS (CI, CH_5^+); *m/z* (%): 336 [M^++1-HCl] (72), 167 (11), 128 (100). $C_{22}H_{28}NO_3Cl$ (389.92): calcd. C 67.76, H 6.97, N 3.59; found C 67.70, H 6.93, N 3.77.

6.1.28. (3*S*,6*R*)-6-(4,4-Diphenylbutyl)piperidine-3-carboxylic acid hydrochloride [(*ent*)-38]. Synthesis as described for the preparation of **32** from 13 mg (0.028 mmol) of (*ent*)-**36** in 4.2 ml of 2 M HCl. Yield: 10 mg (99%).

Compound (*ent*)-**38**. Colorless crystals. ^1H NMR and IR as described for **38**. $[\alpha]_D^{20}$=−11.2° (*c*=0.37, DMSO). HRM (70 eV) for $C_{28}H_{35}NO_4$: calcd 335.1885; found 335.1871 (M^+).

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Synthesis of spiro[4.5]decane and bicyclo[4.3.0]nonane ring systems by self-cyclization of (*Z*)- and (*E*)-2-(trimethylsilylmethyl)pentadienal derivative

Chiaki Kuroda,* Shigenobu Honda, Yuki Nagura, Hiroyuki Koshio, Taku Shibue and Tokio Takeshita

Department of Chemistry, Rikkyo University, Nishi-Ikebukuro, Toshima-ku, Tokyo 171-8501, Japan

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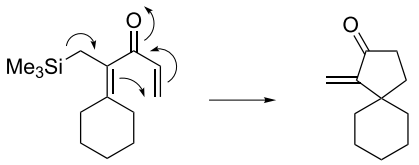
Abstract—The two title carbon frameworks were synthesized utilizing a new type of iron-induced cyclization reaction of 2-(trimethylsilylmethyl)pentadienal. 2-Methylspiro[4.5]dec-2-en-1-one was obtained from (*Z*)- and (*E*)-4-cyclohexylidene-2-(trimethylsilylmethyl)but-2-enal. It was found that the (*Z*)-substrate isomerized to (*E*)-intermediate followed by cyclization to afford the initial product, 2-methylenespiro[4.5]dec-3-en-1-ol, which was isomerized to the above product. The cyclization of 4-(4-alkyl)cyclohexylidene-2-(trimethylsilylmethyl)but-2-enal proceeded stereoselectively. While, (*E*)-3-(cyclohex-1-en-1-yl)-2-(trimethylsilylmethyl)prop-2-en-1-al cyclized immediately affording 8-methylenebicyclo[4.3.0]non-9-en-7-ol. The corresponding (*Z*)-isomer gave several cyclization products as a complex mixture.

1. Introduction

α-(Trialkylsilylmethyl)-α,β-unsaturated carbonyl is a unique building block in organic synthesis since the β-carbon reacts as an allylsilane[1] but not as an unsaturated carbonyl, and therefore, this moiety acts as a carbon 1,3-dipole based on the nucleophilicity of the β-carbon and the electrophilicity of the carbonyl carbon.[2] By using this unit, various five-membered compounds were synthesized.[3,4] For example, we obtained γ-lactones by the reaction with aldehyde[5] or ketone.[6] Cyclopentane ring was also synthesized by the reaction with an enone.[7] Nishitani et al. prepared γ- and δ-lactones by the reaction with either an aldehyde[8] or an epoxide,[9] respectively.

Further conjugation of C=C double bond to this moiety enables self-cyclization to form a five-membered ring compound, and therefore, the reaction is not expected to be a simple extension. There are two ways for further conjugation, namely on the C=C side or on the carbonyl side, leading to β-(trialkylmethyl)-α,β,γ,δ-unsaturated carbonyl or α-(trialkylmethyl)divinyl ketone, respectively. We previously reported the synthesis of spiro[4.5]decane **2** by Lewis acid promoted Nazarov cyclization of α-(trimethylsilylmethyl)divinyl ketone **1**,[10] in which the reaction was activated by an allylic trimethylsilyl group. The formal reaction mechanism from **1** to **2** is illustrated in Scheme 1. Related silicon directed Nazarov cyclization is well documented by Denmark et al.[11]



1 **2**

Scheme 1.

In contrast to the classic Nazarov cyclization of cross-conjugated divinyl ketone, linearly conjugated α,β,γ,δ-unsaturated carbonyl compounds, such as penta-2,4-dienal, are not suitable substrates for the Nazarov or related type of self-cyclization, since the δ-carbon is too electron deficient to react with the carbonyl group. We envisioned that the α,β,γ,δ-unsaturated carbonyl can also cyclize with itself if this moiety is substituted by a trimethylsilylmethyl group at β-position. Namely, by the presence of this substituent, the δ-carbon of **3** becomes nucleophilic, as a part of allylsilane, which is expected to react with the carbonyl to form the five-membered ring compound **4** (Scheme 2, Eq. A). However, in our previous study, ethyl 2-(trimethylsilylmethyl)penta-2,4-dienoate **5** or -dienoic acid **6** (R^1=R^2=CH_3, R^1,R^2=$(CH_2)_4$) did not cyclize in this way but produced

Keywords: Spiro[4.5]decane; Bicyclo[4.3.0]nonane; Allylsilane; Pentadienal; Cyclization.
* Corresponding author. Tel.: +81-3-3985-2396; fax: +81-3-5992-3434; e-mail address: kuroda@rikkyo.ac.jp

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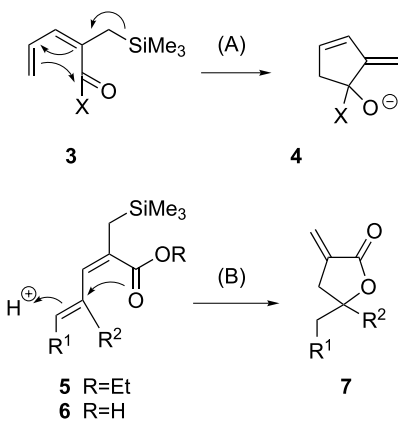


Scheme 2.

γ-lactone **7** via a protonic acid treatment (Eq. B).[12] This is probably due to the low reactivity of the ester group. Thus, we planned to use an aldehyde instead of an ester in order to obtain a five-membered carbocycle via the reaction mode shown in Eq. A.

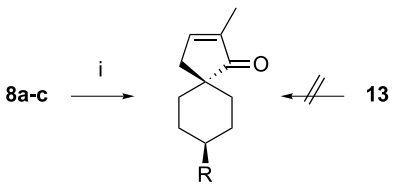
To compare this new type of cyclization with the Nazarov cyclization of our previous report, we first chose the spiro[4.5]decane ring as the synthetic target. Spiro[4.5]-decane is one of the basic ring systems in natural sesquiterpenes such as acoranes or vetispiranes.[13,14] Here we report the synthesis of the spiro[4.5]decane ring system by a new spiro-cyclopentannulation using the cyclization of linearly conjugated pentadienal.[15] Synthesis of bicyclo[4.3.0]nonane ring system by the same method is also described.

2. Results and discussion

2.1. Synthesis of spiro[4.5]decane ring system

As the initial study, compound **8a** was designed as the cyclization precursor. The substrate was synthesized as shown in Scheme 3. Namely, to 2-cyclohexylideneacetaldehyde (**9a**), prepared from cyclohexanone by Horner–Emmons reaction followed by DIBAL-H reduction and MnO_2 oxidation, a β-(ethoxycarbonyl)allylsilane unit was introduced by using Hoffman's reagent[4] $(EtO)_2P(O)CH(CO_2Et)CH_2SiMe_3$ giving **10a** in a 51% yield. The geometry of the double bond in **10a** was determined to be *Z* based on the chemical shift of the olefinic proton (see Section 4). The DIBAL-H reduction of **10a** afforded **11a** in a 92% yield, which was subsequently oxidized by MnO_2 giving substrate **8a** (89%).

The cyclization of **8a** was carried out by the same procedure reported for the Nazarov cyclization.[10] Namely, **8a** was treated with ca. 2 equiv. of $FeCl_3$ in CH_2Cl_2 at −60 °C followed by slow warming to room temperature over 7 h. As a result, a spiro[4.5]decane compound was obtained but this was not the expected dienol but enone **12a** (78% yield, Scheme 4). Some other Lewis acids, such as $AlCl_3$, Et_2AlCl and BF_3OEt_2 were also used but without success.



Scheme 4. *Reagents and conditions*: (i) $FeCl_3$, CH_2Cl_2, −60 °C to rt.

The stereochemistry of the cyclization reaction was then studied using the substrates **8b** and **8c**, which were prepared analogously from 4-*t*-butyl- and 4-methylclohexanone, respectively, in accordance to Scheme 3. When **8b** was treated under the same reaction conditions, spiro[4.5]decanone **12b** was obtained as a single diastereomer in 80% yield (Scheme 4). The stereostructure of **12b** was determined from the NOE signal observed between allylic methylene and the axial protons on the cyclohexane ring as shown in Figure 1. Similarly, **8c** afforded **12c** in a 70% yield, which was again obtained as a single diastereomer, and its structure was determined independently in the same way (Fig. 1).

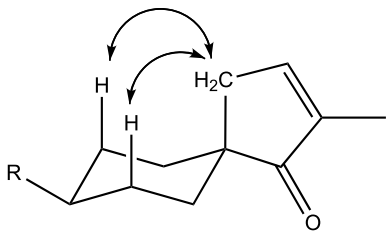
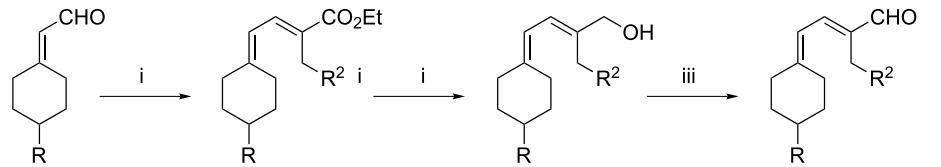
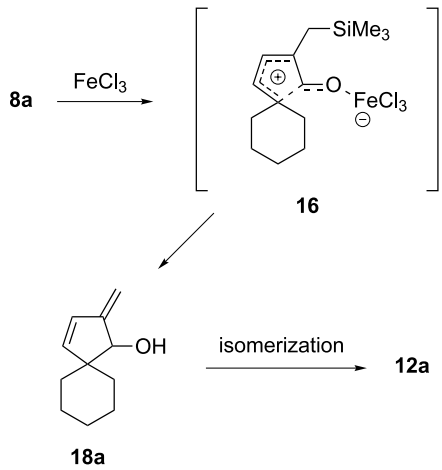


Figure 1.



Scheme 3. *Reagents and conditions*: (i) for **10a–c**: $(EtO)_2P(O)CH(CO_2Et)CH_2SiMe_3$, NaH, DME, rt; for **14**: $(EtO)_2P(O)CH(CO_2Et)CH_3$, NaH, DME, rt; (ii) DIBAL-H, CH_2Cl_2, −60 °C; (iii) MnO_2, CH_2Cl_2, rt.

To demonstrate whether the reaction proceeds via a silicon-stabilized carbocation as the intermediate, the desilylated substrate **13** was prepared (Scheme 3). Under the same reaction conditions described above, **13** did not afford any cyclization product, as expected, but was recovered without reaction (Scheme 4). From this result, it is obvious that the cyclization from **8a** to **12a** proceeds via the silicon-stabilized carbocation **16** as the intermediate (Scheme 5). Since the two reaction sites in **8a** are too far apart to react (cf. two sites are close for its (*E*)-isomer **17a**), it is easily expected that **8a** could cyclize after isomerization to (*E*)-intermediate (vide infra) by the aid of Lewis acid. The related isomerization from (*Z*)-β-carbonylallylsilane to its (*E*)-isomer was also observed previously in the reaction of α-(trimethylsilylmethyl)-α,β,γ,δ-unsaturated carboxylic acid.[12] From **16**, the initial cyclization product via the expected mode should be dienol **18a** (see also Scheme 1). Although, the reaction mechanism cannot be specified at this stage, isomerization from **18a** to the enone **12a** is considered to be a plausible pathway.



Scheme 5.

Recently, we established a new method to prepare (*E*)-β-(ethoxycarbonyl)allylsilanes from aldehydes via the Ando-HWE (Horner–Wadsworth–Emmons) reaction.[16] In order to clarify the above reaction mechanism, we prepared the (*E*)-substrate **17a** by this method (Scheme 6). Namely, **19a** was synthesized from **9a** by using $(PhO)_2P(O)CH(CO_2Et)CH_2SiMe_3$ giving a mixture of both the (*E*)-isomer **19a** and the (*Z*)-isomer **10a** in an 89% yield (**19a/10a**=9:1). DIBAL-H reduction (**20a**, 86%) followed by MnO_2 oxidation afforded **17a** in a 71% yield after separation from its (*Z*)-isomer.

The result of the cyclization reaction of **17a** is listed in Table 1 and Scheme 7. As expected, the reaction was much faster than in the case of **8a**. When **17a** was treated with $FeCl_3$ in CH_2Cl_2 at 0 °C, the reaction proceeded within 20 min and β,γ-unsaturated enone **21a** was afforded instead of the conjugated compound **12a** (Entries 1,2) Interestingly, when the reaction was carried out at −60 °C, the originally expected dienol **18a** was obtained in good yield (Entry 4).

Table 1. Cyclization of **17a**[a]

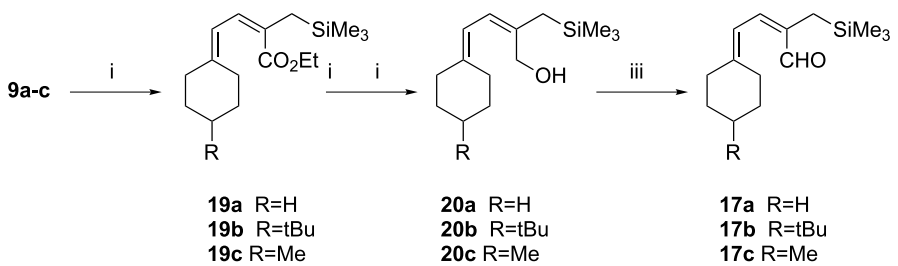
Entry	$FeCl_3$ (equiv.)	Temp (°C)	Product	Yield (%)
1	1	0	**21a**	41
2	Excess[b]	0	**21a**	83
3	1	−60	**18a**	34
4	Excess[b]	−60	**18a**	78

[a] All reactions were carried out in CH_2Cl_2 for 20 min under Ar atmosphere.
[b] About 10 equiv.

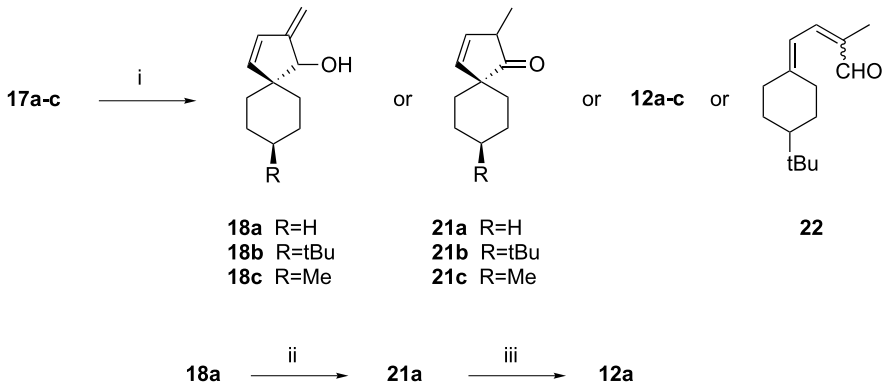
From these results, it could be considered that the initial cyclization product from **17a** or **8a** is **18a**, the originally expected product. Also, it is very likely that **21a** is the isomerization product at higher temperature, and in addition, that **12a** is the final isomerization product with a longer reaction time. To demonstrate this, **18a** was treated with the same reagent except that the reaction was carried out at 0 °C for 20 min to afford **21a** in 97% yield. Similarly, when **21a** was treated under the same reaction condition as for **8a** (−60 °C to room temperature, 2 days), **12a** was obtained in an 87% yield. These results clearly indicate that the cyclization of **8a** or **17a** proceeded via the intermediates **18a** and **21a**.

Cyclization of the substituted compounds **17b** and **17c** were also studied and the results are shown in Table 2. From **17b**, the initial cyclization product **18b** could not be isolated when the reaction was carried out at −60 °C. Under this condition, the desilylated product **22** (a mixture of *E*- and *Z*-isomers) was detected together with **21b** (Entry 3). The isomerization reaction of **21b** was also carried out under the same reaction conditions as Entry 4 affording **12b** in a 71% yield. The results of the cyclization of **17c** (Entries 5–7) were almost consistent with those of **17b**, except that **18c** was obtained in a low yield at −60 °C and a lack of experimental reproducibility (Entry 6). These results indicate that dienols **18b**,**c** are not stable enough for handling.

The stereoselectivity of the cyclization reaction from **17b** or **17c** (so as **8b** and **8c**) can be rationalized by a preferential equatorial attack to the exocyclic double bond (Scheme 8).[17]



Scheme 6. *Reagents and conditions*: (i) $(PhO)_2P(O)CH(CO_2Et)CH_2SiMe_3$, NaH, THF, rt; (ii) DIBAL-H, CH_2Cl_2, −60 °C; (iii) MnO_2, CH_2Cl_2, rt.



Scheme 7. *Reagents and conditions*: (i) see Table 1; (ii) $FeCl_3$, CH_2Cl_2, 0 °C; (iii) $FeCl_3$, CH_2Cl_2, −60 °C to rt.

Table 2. Cyclization of **17b** and **17c**[a]

Entry	Substrate	Temp (°C)	Time	Product	Yield (%)
1	**17b**	0	20 min	**21b**	93
2	**17b**	−15	20 min	**21b**	89
3	**17b**	−60	20 min	**21b**, **22**	Not determined
4	**17b**	−60 to rt	2 days	**12b**	81
5	**17c**	0	20 min	**21c**	74
6	**17c**	−60	20 min	**18c**	18[b]
7	**17c**	−60 to rt	2 days	**12c**	64

[a] All reactions were carried out in CH_2Cl_2 under Ar atmosphere with about 4 equiv. of $FeCl_3$.
[b] The result was not reproducible.

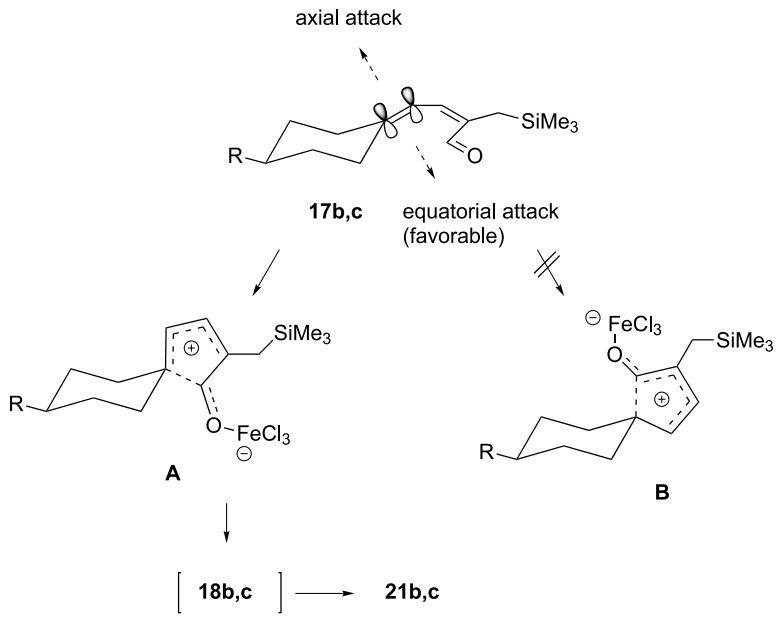
Namely, transition state **B** is less favorable than **A** since the carbonyl oxygen, together with bulky Lewis acid, comes over the cyclohexane ring. From the transition state **A**, **21b**,**c** is considered to be obtained via **18b**,**c**. It is interesting that this stereoselectivity was much higher than the related Nazarov cyclization.[10]

2.2. Synthesis of bicyclo[4.3.0]nonane ring system

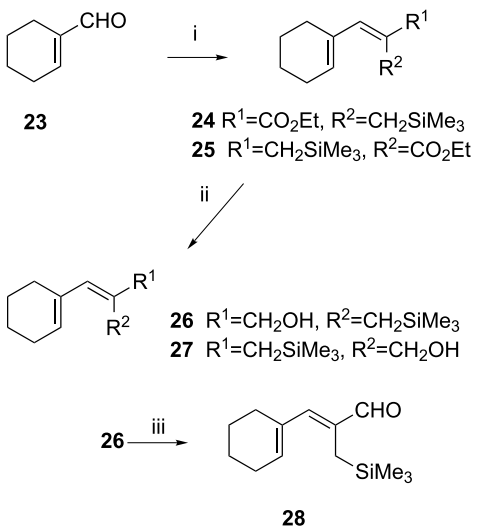
Following the success of the synthesis of the spiro[4.5]-decane carbon skeleton, we next focused on the use of this method to synthesize the hydrindane, or bicyclo[4.3.0]-nonane, carbon framework from cyclohexane derivatives. Hydrindane is one of the key structures in various terpenoid,[13,14] which also appears as the CD rings of steroids.

The cyclization of both (*Z*)- and (*E*)-allylsilanes were studied. The substrates were synthesized in accordance to Scheme 9. Namely, to the α,β-unsaturated aldehyde **23** was introduced the β-(ethoxycarbonyl)allylsilane moiety by treatment with $(EtO)_2P(O)CH(CO_2Et)CH_2SiMe_3$/NaH in DME to afford **24** and **25** in a 61% yield (**24**/**25**=6:1). Reduction of the ester group with DIBAL-H yielded alcohols **26** and **27** after separation by column chromatography. The (*Z*)-isomer **26** was oxidized by MnO_2 to afford **28** in a 92% yield. When $(PhO)_2P(O)CH(CO_2Et)CH_2SiMe_3$ was used as the Horner–Wadsworth–Emmons reagent, **25** was obtained preferentially (*E*/*Z*=97:3, 95% yield). The alcohol **27** was then obtained by DIBAL-H reduction followed by purification.

In contrast to the oxidation of **26**, when **27** was subjected to



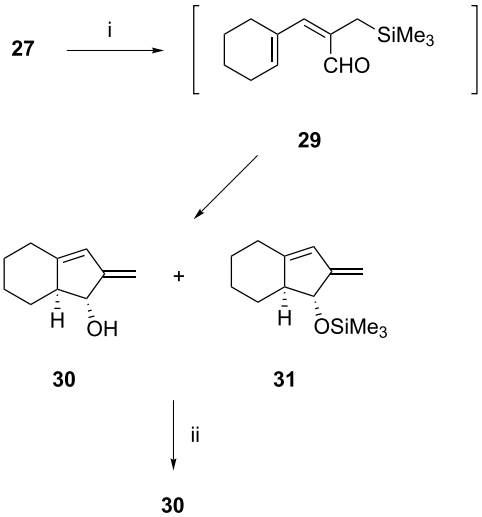
Scheme 8.



Scheme 9. *Reagents and conditions*: (i) for **24**: $(EtO)_2P(O)CH(CO_2Et)CH_2SiMe_3$, NaH, DME, rt; for **25**: $(PhO)_2P(O)CH(CO_2Et)CH_2SiMe_3$, NaH, THF, rt; (ii) DIBAL-H, CH_2Cl_2, −60 °C; (iii) MnO_2, CH_2Cl_2, rt.

MnO_2 oxidation, the corresponding aldehyde **29** was not obtained but the cyclization product **30** (20%) was afforded together with its trimethylsilyl ether **31** (63%) (Scheme 10). However, the yields of the two products varied, and in some case, only **30** was afforded in good yield (93%). Since **31** was too volatile to isolate, the reaction mixture was treated with Bu_4NF giving **30** effectively without being accompanied by **31**. The formation of the aldehyde **29** could not be detected on a TLC, which indicates that the oxidation product was immediately cyclized. The stereochemistry of **30** was determined from the ^1H NMR spectrum including NOE which was observed between the proton attached to the hydroxy-bearing carbon (7-H) and one of the axial protons on the cyclohexane ring (5-H) as shown in Figure 2.

The stereoselective formation of **30** can easily be explained by the *s-trans* conformation of the enone moiety in the precursor enal **29** (Scheme 11). Although both the *s-trans* conformer **C** and the *s-cis* conformer **D** are possible with



Scheme 10. *Reagents and conditions*: (i) MnO_2, CH_2Cl_2, rt, (ii) Bu_4NF, Et_2O, rt.

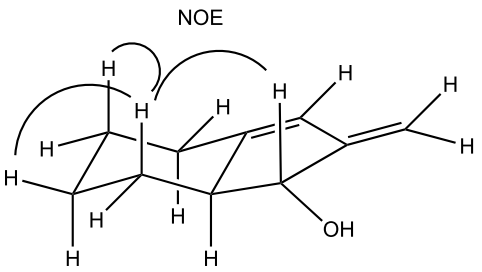
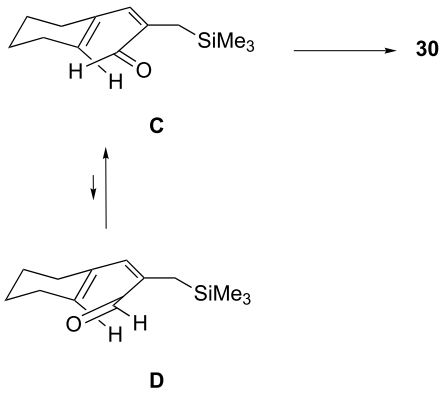


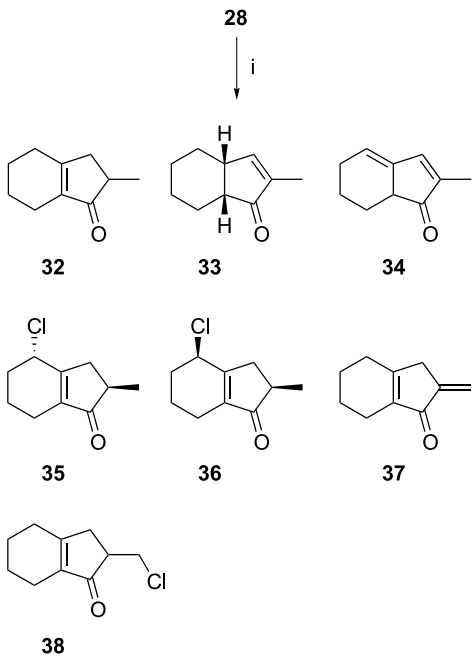
Figure 2.



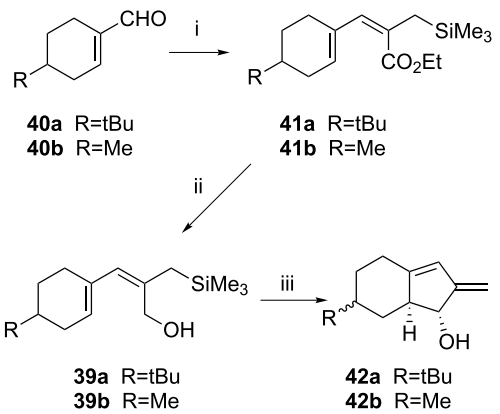
Scheme 11.

respect to the enone moiety, conformer **C** is favorable over **D**, since the carbonyl oxygen takes on a congested position in **D**.

The cyclization of **28** was also studied by the treatment with ca. 1.5 equiv. of $FeCl_3$ in CH_2Cl_2 at room temperature. The reaction proceeded slowly, and after for 4 days, many products were detected on a TLC. This complex mixture of the products was roughly separated by silica-gel column chromatography, and five compounds **32**–**36** could be



Scheme 12. *Reagents and conditions*: (i) $FeCl_3$, CH_2Cl_2, rt.



Scheme 13. *Reagents and conditions*: (i) $(PhO)_2P(O)CH(CO_2Et)CH_2$-$SiMe_3$, NaH, THF, rt; (ii) DIBAL-H, CH_2Cl_2, −60 °C; (iii) (a) MnO_2, CH_2Cl_2, rt; (b) SiO_2, Et_2O, rt; (c) Bu_4NF, Et_2O, rt.

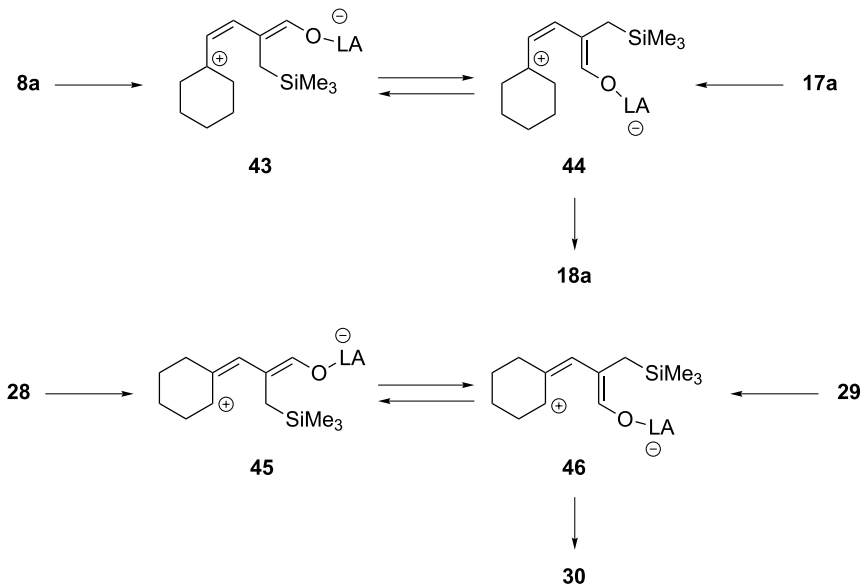
identified from the ^1H NMR and mass spectra (Scheme 12), among which **32** was found to be the major product (ca. 36% yield). The other compounds include isomeric enone **33**, dienone **34**, and two chlorides **35** and **36**. The structure of these products was determined by ^1H and ^{13}C NMR and mass spectra. The stereochemistry of two chlorides **35** and **36** were established by NOE experiment. Namely, NOE was observed between C*H*Cl (2-H) and 9β-H for **35**; between C*H*Cl and 9α-H for **36**. The *cis*-fused structure for **33** was deduced from *J*-value of methine proton (6-H). Compound **34** is considered to be formed from **33** by further oxidation caused by $FeCl_3$.[11b] Two chlorides must be chlorination products from **32**. When the reaction was carried out with ca. 4 equiv. of $FeCl_3$, the two oxidized products **37** and **38** were also found in the mixture. Some other Lewis acids such as Et_2AlCl, $AlCl_3$, and $TiCl_4$ were tested instead of $FeCl_3$ but none of them gave us satisfactory results.

The substituent effect for the cyclization of (*E*)-isomer was examined. The cyclization precursor, alcohols **39a** and **39b**, were prepared in same way (Scheme 13). The MnO_2 promoted cyclization of **39a** and **39b** proceeded slower than the case of **27**, and the reaction completed after stirring with silica gel to afford **42a** (94%) and **42b** (94%), respectively, after treatment with Bu_4NF. In contrast to the synthesis of spiro[4.5]decane ring, no stereoselectivity was observed. Namely, both dienols **42a** and **42b** were obtained in 1:1 mixture of diastereomers.

As mentioned above, a remarkable difference in reactivity based on the geometry of 2-(trimethylsilylmethyl)pentadienal was observed for the case of (*Z*)-isomer **28** and (*E*)-isomer **29**. While in contrast, the same spiro[4.5]decane ring compounds **12a**–**c** were obtained from both (*Z*)-isomers **8a**–**c** and (*E*)-isomers **17a**–**c**. This difference can be rationalized by an easier isomerization from **8** to (*E*)-intermediate (i.e., **43**–**44**) than from **28** (i.e., **45**–**46**) in the presence of Lewis acid (Scheme 14). Namely, the intermediate carbocation is tertiary for **43** (and **44**) and secondary for **45** (and **46**). Since **18** and **21**, the products from **17** at lower temperature, were not obtained from **8**, it can be predicted that *Z*/*E* isomerization requires more energy than the cyclization.

3. Conclusion

A new cyclization reaction of linearly conjugated pentadienal assisted by allylic trimethylsilyl group was established. Both spiro[4.5]decane and bicyclo[4.3.0]nonane carbon frameworks were synthesized by this method. In the synthesis of spiro[4.5]decane, it was found that (1) both (*Z*)- and (*E*)-precursors afford the same product enone in good yields under appropriate conditions, (2) the reaction proceeds via a silicon-stabilized carbocation as the intermediate to afford the initial product dienol, (3) isomerization reaction occurs from dienol to conjugated enone, and (4) the cyclization reaction is stereoselective. While, a remarkable difference in reactivity based on (*Z*)- or (*E*)-precursor was observed for the synthesis of bicyclo[4.3.0]-nonane. Therefore, (*E*)-precursor is required for the



Scheme 14. LA=Lewis acid.

cyclization of 4,5-disubstituted-2-(trimethylsilylmethyl)-pentadienal, while geometry of the functionalized allylsilane is not an important factor for the cyclization reaction of 5,5-disubstituted derivative.

4. Experimental

4.1. General procedure

Melting points were measured on a Laboratory Devices Mel-Temp apparatus. IR spectra were recorded on a Jasco FT/IR-230 spectrometer. Both ^{1}H and ^{13}C NMR spectra were measured on a Jeol GSX-400 (400 MHz for ^{1}H; 100 MHz for ^{13}C) spectrometer. Chemical shifts were reported on the δ scale (ppm) with solvent ($CHCl_3$=7.26) as an internal standard, unless otherwise noted. The signal of the solvent ($CDCl_3$=77.0) was used as a standard for all ^{13}C NMR spectra. Both low-resolution mass spectra (MS) and high-resolution mass spectra (HRMS) were obtained on a Jeol SX-102A, JMS-DX303, CMATE II, or Shimadzu GCMS-QP5050 mass spectrometer with the EI method unless otherwise noted. Analytical TLC was done on precoated TLC plates (Kieselgel 60 F254, layer thickness 0.2 mm). Wakogel C-200 or C-300 was used for column chromatography. Anhydrous Na_2SO_4 or $MgSO_4$ was used for drying the extracted organic layers.

4.2. (*Z*)-Selective HWE reaction

To a stirred suspension of NaH (1018 mg, 23.3 mmol; 55% in mineral oil which was removed by washing with dry hexane) in dry DME (80 cm^3; distilled from CaH_2) was added $(EtO)_2P(O)CH_2CO_2Et$ (4.2 cm^3, 21.2 mmol) dropwise at 0 °C under Ar. After being stirred for 40 min, iodomethyltrimethylsilane (3.6 cm^3, 24.3 mmol) was added, and the mixture was heated to 70 °C for 4 h. The flask was cooled to 0 °C again, and a second portion of NaH (960 mg, 22.0 mmol; mineral oil was not removed) was added. After being stirred at 0 °C for 2 h, a solution of 2-cyclohexylideneacetaldehyde (1.648 g, 13.3 mmol) in DME (28 cm^3) was added, and the mixture was stirred at room temperature for 14 h. An aqueous solution of NH_4Cl was added, and the resulting aqueous mixture was extracted with Et_2O, and dried. Evaporation of the solvent followed by silica gel (80 g) column chromatography using hexane/AcOEt (99.5:0.5) as eluent afforded **10a** (1.891 g, 51%). Similarly, **10b** and **10c** were obtained in 35 and 58% yields, respectively. For the preparation of **14**, methyl iodide was used instead of iodomethyltrimethylsilane (32% yield). See Ref. [12] for the synthesis and the spectral data of **24**.

4.2.1. (*Z*)-Ethyl 4-cyclohexylidene-2-(trimethylsilylmethyl)but-2-enoate (10a). An oil; IR (neat) 1702 (C=O), 1630, 1258, 851, and 754 cm^{-1}; ^{1}H NMR δ=−0.01 (9H, s, $SiMe_3$), 1.30 (3H, t, *J*=7.1 Hz, OCH_2CH_3), 1.54–1.62 (6H, m, $(CH_2)_3$), 1.93 (2H, br s, CH_2SiMe_3), 2.19–2.24 (2H, m, C=CCH_2), 2.36–2.41 (2H, m, C=CCH_2), 4.19 (2H, q, *J*=7.1 Hz, OCH_2CH_3), 5.94 (1H, br d, *J*=11.9 Hz, C_{ring}=CH), and 7.40 (1H, d, *J*=11.9 Hz, C*H*=CCO_2Et); ^{13}C NMR δ=−1.06 (3C), 14.36, 17.32, 26.70, 27.99, 28.80, 29.72, 38.19, 60.39, 118.68, 127.54, 130.33, 150.66, and 169.06; MS *m*/*z* 280 (M^+, 34%), 265 (18), 235 (11), 162 (32), 133 (40), 91 (54), and 73 (100); HRMS [Found: *m*/*z* 280.1907 (M^+). Calcd for $C_{16}H_{28}O_2Si$: M, 280.1859].

4.2.2. (*Z*)-Ethyl 4-(4-*t*-butylcyclohexylidene)-2-(trimethylsilylmethyl)but-2-enoate (10b). An oil; IR (neat) 1704 (C=O), 1633, 1365, 1250, 852, and 755 cm^{-1}; ^{1}H NMR δ=0.00 (9H, s, $SiMe_3$), 0.85 (9H, s, *t*Bu), 0.99–1.28 (3H, m), 1.30 (3H, t, *J*=7.1 Hz, OCH_2CH_3), 1.80–1.98 (3H, m), 1.93 (2H, br s, CH_2SiMe_3), 2.12–2.21 (1H, m), 2.31–2.38 (1H, m), 2.96–3.01 (1H, m), 4.19 (2H, q, *J*=7.1 Hz, OCH_2CH_3), 5.93 (1H, br d, *J*=10.8 Hz, C_{ring}=CH), and 7.40 (1H, d, *J*=10.8 Hz, C*H*=CCO_2Et); ^{13}C NMR δ=−1.05 (3C), 14.36, 17.32, 27.59 (3C), 28.63, 29.43, 29.48, 32.46, 38.01, 48.27, 60.38, 118.33, 127.52, 130.42, 150.67, and 169.05; MS *m*/*z* 336 (M^+, 100%), 205 (7), 189 (89), and 107 (15); HRMS [Found: *m*/*z* 336.2438 (M^+). Calcd for $C_{20}H_{36}O_2Si$: M, 336.2486].

4.2.3. (*Z*)-Ethyl 4-(4-methylcyclohexylidene)-2-(trimethylsilylmethyl)but-2-enoate (10c). An oil; IR (neat) 1704 (C=O), 1632, 1260, and 852 cm^{-1}; ^{1}H NMR δ=−0.01 (9H, s, $SiMe_3$), 0.91 (3H, d, *J*=6.5 Hz, Me), 0.95–1.11 (2H, m), 1.30 (3H, t, *J*=7.1 Hz, OCH_2CH_3), 1.54–1.66 (1H, m), 1.77–1.97 (3H, m), 1.93 (2H, br s, CH_2SiMe_3), 2.14–2.33 (2H, m), 2.85–2.92 (1H, m), 4.19 (2H, q, *J*=7.1 Hz, OCH_2CH_3), 5.95 (1H, br d, *J*=10.8 Hz, C_{ring}=CH), and 7.40 (1H, d, *J*=10.8 Hz, C*H*=CCO_2Et); ^{13}C NMR δ=−1.06 (3C), 14.36, 17.32, 21.81, 28.92, 32.70, 35.99, 36.81, 37.48, 60.38, 118.77, 127.58, 130.41, 150.24, and 169.05; MS *m*/*z* 294 (M^+, 100%), 279 (7), 237 (7), 147 (97), 143 (91), and 75 (98); HRMS [Found: *m*/*z* 294.1990 (M^+). Calcd for $C_{17}H_{30}O_2Si$: M, 294.2016].

4.2.4. (*E*)-Ethyl 4-cyclohexylidene-2-methylbut-2-enoate (14). An oil; IR (neat) 1704 (C=O), 1635, 1447, 1256, 1112, and 752 cm^{-1}; ^{1}H NMR (Me_4Si=0.00) δ=1.31 (3H, t, *J*=7.1 Hz, OCH_2CH_3), 1.55–1.68 (6H, m, $(CH_2)_3$), 1.93 (3H, d, *J*=2.1 Hz, C=CCH_3), 2.20–2.27 (2H, m, C=CCH_2), 2.37–2.43 (2H, m, C=CCH_2), 4.21 (2H, q, *J*=7.1 Hz, OCH_2CH_3), 6.07 (1H, br d, *J*=11.8 Hz, C_{ring}=CH), and 7.51 (1H, dq, *J*=11.8, 1.3 Hz, C*H*=CCO_2Et); ^{13}C NMR δ=12.31, 14.37, 26.64, 27.93, 28.67, 29.72, 38.16, 60.38, 117.97, 124.67, 133.59, 152.39, and 169.07; MS *m*/*z* 208 (M^+, 88%), 196 (100), 182 (93), 150 (90), 137 (100), 96 (99), and 68 (99); HRMS [Found: *m*/*z* 208.1427 (M^+). Calcd for $C_{13}H_{20}O_2$: M, 208.1464].

4.3. (*E*)-Selective HWE reaction

To a stirred suspension of NaH (242 mg, 5.57 mmol; 55% in mineral oil) in dry THF (20 cm^3; distilled from $LiAlH_4$) was added a solution of $(PhO)_2P(O)CH(CO_2Et)CH_2SiMe_3$ (1.98 g, 4.87 mmol) in THF (15 cm^3) dropwise at 0 °C under Ar. After being stirred for 30 min, the mixture was cooled to −60 °C, and a solution of 2-cyclohexylideneacetaldehyde (446.1 mg, 3.59 mmol) in THF (20 cm^3) was added. The stirring was continued at −60 °C for 4 h, then the mixture was allowed to warm to room temperature followed by stirring at room temperature for 12 h. An aqueous solution of NH_4Cl was added, and the resulting aqueous mixture was extracted with AcOEt, and dried. Evaporation of the solvent followed by silica gel (40 g)

column chromatography using hexane/AcOEt (97:3) as eluent afforded a mixture of **19a** and **10a** (1007.6 mg, 51%, **19a/10a**=9:1). Similarly, **19b**, **19c**, **41a**, and **41b** were obtained in 62, 88, 97, and 96% yields, respectively. These compounds were obtained together with a small amount of corresponding (*Z*)-isomer (ca. 1–10%) which were removed at later stage. See Ref. 16 for the synthesis of **25**.

4.3.1. (*E*)-Ethyl 4-cyclohexylidene-2-(trimethylsilylmethyl)but-2-enoate (19a). An oil; IR (neat) 1703 (C=O), 1630, 1198, 1159, and 852 cm^{-1}; ^1H NMR δ=0.00 (9H, s, $SiMe_3$), 1.32 (3H, t, *J*=7.2 Hz, OCH_2CH_3), 1.54–1.62 (6H, m, $(CH_2)_3$), 1.82 (2H, s, CH_2SiMe_3), 2.18–2.23 (2H, m, $C{=}CCH_2$), 2.29–2.34 (2H, m, $C{=}CCH_2$), 4.20 (2H, q, *J*=7.2 Hz, OCH_2CH_3), 6.51 (1H, d, *J*=12.0 Hz, $CH{=}CCO_2Et$), and 6.77 (1H, br d, *J*=12.0 Hz, $C_{ring}{=}CH$); ^{13}C NMR δ=−1.61 (3C), 14.30, 24.66, 26.77, 27.82, 28.51, 28.91, 37.97, 60.09, 119.28, 126.30, 132.29, 148.42, and 168.30; MS *m*/*z* 280 (M^+, 36%), 265 (16), 235 (16), 162 (51), 133 (55), 91 (68), and 73 (100); HRMS [Found: *m*/*z* 280.1948 (M^+). Calcd for $C_{16}H_{28}O_2Si$: M, 280.1859].

4.3.2. (*E*)-Ethyl 4-(4-*t*-butylcyclohexylidene)-2-(trimethylsilylmethyl)but-2-enoate (19b). An oil; IR (neat) 1703 (C=O), 1631, 1365, 1178, 852, and 756 cm^{-1}; ^1H NMR δ=0.01 (9H, s, $SiMe_3$), 0.85 (9H, s, *t*Bu), 0.98–1.34 (3H, m), 1.32 (3H, t, *J*=7.2 Hz, OCH_2CH_3), 1.75–1.94 (5H, m), 2.09–2.18 (1H, m), 2.32–2.39 (1H, m), 2.85–2.92 (1H, m), 4.20 (2H, q, *J*=7.2 Hz, OCH_2CH_3), 6.51 (1H, d, *J*=11.6 Hz, $CH{=}CCO_2Et$), and 6.77 (1H, br d, *J*=11.6 Hz, $C_{ring}{=}CH$); ^{13}C NMR δ=−1.60 (3C), 14.31, 24.65, 27.59 (3C), 28.45, 28.69, 29.10, 32.47, 37.79, 48.32, 60.10, 118.96, 126.32, 132.38, 148.40, and 168.29; MS *m*/*z* 336 (M^+, 33%), 321 (15), 237 (21), 169 (29), 119 (45), and 73 (100); HRMS [Found: *m*/*z* 336.2441 (M^+). Calcd for $C_{20}H_{36}O_2Si$: M, 336.2486].

4.3.3. (*E*)-Ethyl 4-(4-methylcyclohexylidene)-2-(trimethylsilylmethyl)but-2-enoate (19c). An oil; IR (neat) 1693 (C=O), 1628, 1190, and 852 cm^{-1}; ^1H NMR δ=0.00 (9H, s, $SiMe_3$), 0.90 (3H, d, *J*=6.5 Hz, Me), 0.95–1.14 (2H, m), 1.32 (3H, t, *J*=7.1 Hz, OCH_2CH_3), 1.50–1.94 (6H, m), 2.11–2.21 (1H, m), 2.26–2.33 (1H, m), 2.75–2.83 (1H, m), 4.20 (2H, q, *J*=7.1 Hz, OCH_2CH_3), 6.51 (1H, d, *J*=10.8 Hz, $CH{=}CCO_2Et$), and 6.78 (1H, br d, *J*=10.8 Hz, $C_{ring}{=}CH$); ^{13}C NMR δ=−1.61 (3C), 14.11, 24.68, 28.14, 31.58, 32.77, 35.90, 36.59, 37.27, 60.08, 119.42, 126.41, 132.36, 147.93, and 168.29; MS *m*/*z* 294 (M^+, 3%), 279 (1), 237 (3), 176 (9), 147 (12), 119 (18), and 73 (100); HRMS [Found: *m*/*z* 294.2011 (M^+). Calcd for $C_{17}H_{30}O_2Si$: M, 294.2016].

4.3.4. (*E*)-Ethyl 3-(cyclohex-1-en-1-yl)-2-(trimethylsilylmethyl)prop-2-enoate (25). An oil; IR (neat) 1722 (C=O), 1626, 1373, 1219, and 850 cm^{-1}; ^1H NMR δ=0.02 (9H, s, $SiMe_3$), 1.28 (3H, t, *J*=7.1 Hz, OCH_2CH_3), 1.51–1.62 (4H, m), 1.72 (2H, br s, CH_2SiMe_3), 2.01–2.11 (4H, m), 4.15 (2H, q, *J*=7.1 Hz, OCH_2CH_3), 5.60–5.64 (1H, m, $C{=}CHCH_2$), and 5.82 (1H, br s, $CH{=}CCO_2Et$); ^{13}C NMR δ=−1.60 (3C), 14.08, 21.98, 22.68, 25.65, 25.76, 26.89, 60.33, 128.50, 128.62, 133.61, 135.23, and 171.00; MS *m*/*z* 266 (M^+, 2%), 251 (1), 237 (2), 221 (3), 148 (18), 119 (17), 91 (19), and 73 (100); HRMS (CI) [Found: *m*/*z* 267.1758 (M^++H). Calcd for $C_{15}H_{27}O_2Si$: M, 267.1780].

4.3.5. (*E*)-Ethyl 3-(4-*t*-butylcyclohex-1-en-1-yl)-2-(trimethylsilylmethyl)prop-2-enoate (41a). An oil; IR (neat) 1722 (C=O), 1632, 1365, 1248, 1088, and 854 cm^{-1}; ^1H NMR δ=0.03 (9H, s, $SiMe_3$), 0.85 (9H, s, *t*-Bu), 1.05–1.17 (1H, m), 1.22–1.32 (1H, m), 1.29 (3H, t, *J*=7.1 Hz, OCH_2CH_3), 1.69 (1H, d, *J*=13.8 Hz, $CHHSiMe_3$), 1.76 (1H, d, *J*=13.8 Hz, $CHHSiMe_3$), 1.77–1.92 (2H, m), 2.02–2.17 (3H, m), 4.14 (1H, dq, *J*=11.0, 7.1 Hz, $OCHHCH_3$), 4.19 (1H, dq, *J*=11.0, 7.1 Hz, $OCHHCH_3$), 5.63–5.68 (1H, m, $C{=}CHCH_2$), and 5.85 (1H, br s, $CH{=}CCO_2Et$); ^{13}C NMR δ=−1.56 (3C), 14.12, 24.10, 25.73, 27.11 (3C), 27.49, 28.19, 32.15, 43.67, 60.37, 128.48, 129.42, 133.23, 135.05, and 171.00; MS *m*/*z* 322 (M^+, 3%), 307 (1), 277 (2), 204 (16), 175 (9), 147 (12), 119 (15), and 73 (100); HRMS (CI) [Found: *m*/*z* 323.2341 (M^++H). Calcd for $C_{19}H_{35}O_2Si$: M, 323.2406].

4.3.6. (*E*)-Ethyl 3-(4-methylcyclohex-1-en-1-yl)-2-(trimethylsilylmethyl)prop-2-enoate (41b). An oil; IR (neat) 1720 (C=O), 1624, 1248, 1219, and 852 cm^{-1}; ^1H NMR δ=0.03 (9H, s, $SiMe_3$), 0.94 (3H, d, *J*=6.3 Hz, Me), 1.18 (1H, ddt, *J*=5.2, 12.4, 10.8 Hz), 1.28 (3H, t, *J*=7.2 Hz, OCH_2CH_3), 1.58–1.74 (3H, m), 1.70 (1H, d, *J*=13.6 Hz, $CHHSiMe_3$), 1.74 (1H, d, *J*=13.6 Hz, $CHHSiMe_3$), 1.99–2.20 (3H, m), 4.13 (1H, dq, *J*=10.7, 7.2 Hz, $OCHHCH_3$), 4.16 (1H, dq, *J*=10.7, 7.2 Hz, $OCHHCH_3$), 5.57–5.61 (1H, m, $C{=}CHCH_2$), and 5.83 (1H, br s, $CH{=}CCO_2Et$); ^{13}C NMR δ=−1.57 (3C), 14.11, 21.75, 25.68, 26.88, 28.01, 30.99, 34.39, 60.34, 128.17, 128.75, 133.31, 134.86, and 171.01; MS *m*/*z* 280 (M^+, 2%), 235 (2), 162 (14), 133 (18), 91 (18), and 73 (100); HRMS (CI) [Found: *m*/*z* 281.1985 (M^++H). Calcd for $C_{16}H_{29}O_2Si$: M, 281.1937].

4.4. DIBAL-H reduction

In a 50 cm^3 two-necked flask was placed a solution of **10a** (152.6 mg, 554.1 mmol) in dry CH_2Cl_2 (12 cm^3; distilled from CaH_2) with stirring under Ar. To this was added DIBAL-H (1.63 cm^3, 1.63 mmol; 1 M solution in hexane) at −60 °C, and the stirring was continued for 30 min at the same temperature. MeOH (2 cm^3) was added, and the flask was quickly warmed to room temperature. After being stirred for 30 min, a saturated aqueous solution of Rochelle salt (30 cm^3) was added, and the mixture was extracted with CH_2Cl_2 and dried. Evaporation of the solvent followed by silica gel (1 g) column chromatography using hexane/AcOEt (96:4) as eluent afforded **11a** (120.1 mg, 93%). Similarly, **10b**, **10c**, **14**, **19a**, **24**, **25**, **41a**, and **41b** afforded **11b**, **11c**, **15**, **20a**, **26**, **27**, **39a**, and **39b** in 96, 91, 74, 86, 91, 98, 82, and 81% yields, respectively.

Compounds **19b** and **19c** were reduced by $LiAlH_4$ in Et_2O giving **20b** and **20c** in 99 and 92% yields, respectively.

4.4.1. (*Z*)-4-Cyclohexylidene-2-(trimethylsilylmethyl)-but-2-en-1-ol (11a). An oil; IR (neat) 3320 (OH), 1608, 1447, 1248, 852, and 691 cm^{-1}; ^1H NMR δ=0.04 (9H, s, $SiMe_3$), 1.49–1.58 (7H, m, $(CH_2)_3$ and OH), 1.71 (2H, br s, CH_2SiMe_3), 2.13–2.18 (2H, m, $C{=}CCH_2$), 2.24–2.30 (2H, m, $C{=}CCH_2$), 4.03 (2H, br s, CH_2OH), 5.83 (1H, br d,

J=11.2 Hz, C_{ring}=CH), and 6.20 (1H, br d, J=11.2 Hz, C*H*=CCH_2OH); ^{13}C NMR δ=−0.71 (3C), 19.40, 26.87, 27.80, 28.79, 29.15, 37.77, 68.95, 118.01, 118.17, 137.25, and 142.24; MS m/z 238 (M^+, 9%), 193 (4), 148 (34), 133 (22), 105 (83), and 73 (199); HRMS [Found: m/z 238.1791 (M^+). Calcd for $C_{14}H_{26}OSi$: M, 238.1754].

4.4.2. (*Z*)-4-(4-*t*-Butylcyclohexylidene)-2-(trimethylsilylmethyl)but-2-en-1-ol (11b). An oil; IR (neat) 3310 (OH), 1609, 1364, 1248, and 839 cm^{-1}; ^1H NMR δ=0.04 (9H, s, $SiMe_3$), 0.85 (9H, s, *t*Bu), 0.95–1.91 (7H, m), 1.71 (2H, br s, CH_2SiMe_3), 2.05–2.15 (1H, m), 2.24–2.31 (1H, m), 2.82–2.88 (1H, m), 4.03 (2H, br s, CH_2OH), 5.83 (1H, br d, J=11.2 Hz, C_{ring}=CH), and 6.20 (1H, br d, J=11.2 Hz, C*H*=CCH_2OH); ^{13}C NMR δ=−0.70 (3C), 19.40, 27.62 (3C), 28.43, 28.93, 29.39, 32.46, 37.60, 48.42, 68.95, 117.82, 118.09, 137.28, and 142.25; MS m/z 294 (M^+, 42%), 275 (66), 247 (100), 213 (98), 198 (75), 116 (61), and 86 (80); HRMS [Found: m/z 294.2338 (M^+). Calcd for $C_{18}H_{34}OSi$: M, 294.2380].

4.4.3. (*Z*)-4-(4-Methylcyclohexylidene)-2-(trimethylsilylmethyl)but-2-en-1-ol (11c). An oil; IR (neat) 3310 (OH), 1608, 1456, 1248, and 839 cm^{-1}; ^1H NMR δ=0.03 (9H, s, $SiMe_3$), 0.99 (3H, d, J=6.5 Hz, Me), 0.82–1.88 (7H, m), 1.70 (2H, br s, CH_2SiMe_3), 2.07–2.26 (2H, m), 2.70–2.79 (1H, m), 4.02 (2H, br s, CH_2OH), 5.84 (1H, br d, J=11.2 Hz, C_{ring}=CH), and 6.20 (1H, br d, J=11.2 Hz, C*H*=CCH_2-OH); ^{13}C NMR δ=−0.71 (3C), 19.40, 22.00, 28.37, 32.84, 35.91, 36.90, 37.06, 68.93, 118.09, 118.29, 137.33, and 141.78; MS m/z 252 (M^+, 86%), 193 (84), 147 (96), 135 (87), 121 (100), and 77 (97); HRMS [Found: m/z 252.1893 (M^+). Calcd for $C_{15}H_{28}OSi$: M, 252.1910].

4.4.4. (*E*)-4-Cyclohexylidene-2-methylbut-2-en-1-ol (15). Mp 38.5–40.5 °C; IR (Nujol) 3340 (OH), 1008, and 861 cm^{-1}; ^1H NMR (Me_4Si=0.00) δ=1.00–1.75 (7H, m, $(CH_2)_3$ and OH), 1.79 (3H, s, C=CCH_3), 2.15–2.21 (2H, m, C=CCH_2), 2.26–2.32 (2H, m, C=CCH_2), 4.08 (2H, s, CH_2OH), 5.97 (1H, br d, J=11.4 Hz, C_{ring}=CH), and 6.30 (1H, d sext, J=11.4, 1.2 Hz, C*H*=CCH_2OH); ^{13}C NMR δ=13.96, 26.81, 27.77, 28.68, 29.13, 37.71, 69.22, 117.29, 120.78, 134.51, and 143.93; MS m/z 166 (M^+, 6%), 165 (M^+−H, 44), 148 (73), 121 (13), 105 (35), and 43 (100); HRMS [Found: m/z 166.1322 (M^+). Calcd for $C_{11}H_{18}O$: M, 166.1358].

4.4.5. (*E*)-4-Cyclohexylidene-2-(trimethylsilylmethyl)-but-2-en-1-ol (20a). An oil; IR (neat) 3390 (OH), 1624, 1448, 1248, and 852 cm^{-1}; ^1H NMR δ=0.03 (9H, s, $SiMe_3$), 1.50–1.58 (7H, m, $(CH_2)_3$ and OH), 1.68 (2H, s, CH_2SiMe_3), 2.11–2.17 (2H, m, C=CCH_2), 2.23–2.28 (2H, m, C=CCH_2), 4.19 (2H, br s, CH_2OH), and 6.01 (2H, br s, C=CH–CH=C); ^{13}C NMR δ=−1.32 (3C), 26.00, 26.83, 27.68, 28.56, 28.88, 37.60, 61.85, 116.95, 121.67, 136.46, and 141.68; MS m/z 238 (M^+, 4%), 148 (27), 133 (23), 105 (92), and 73 (199); HRMS [Found: m/z 238.1715 (M^+). Calcd for $C_{14}H_{26}OSi$: M, 238.1754].

4.4.6. (*E*)-4-(4-*t*-Butylcyclohexylidene)-2-(trimethylsilylmethyl)but-2-en-1-ol (20b). An oil; IR (neat) 3360 (OH), 1604, 1365, 1248, and 850 cm^{-1}; ^1H NMR δ=0.03 (9H, s, $SiMe_3$), 0.85 (9H, s, *t*Bu), 0.97–1.92 (7H, m), 1.69 (2H, br s, CH_2SiMe_3), 2.05–2.15 (1H, m), 2.24–2.31 (1H, m), 2.78–2.85 (1H, m), 4.18 (1H, d, J=12.0 Hz, C*H*OH), 4.21 (1H, d, J=12.0 Hz, CH*H*OH), and 6.01 (2H, s, CH=CH); ^{13}C NMR δ=−1.31 (3C), 26.04, 27.61 (3C), 28.32, 28.69, 29.14, 32.48, 37.45, 48.40, 61.91, 116.62, 121.78, 136.48, and 141.69; MS m/z 294 (M^+, 4%), 276 (20), 204 (21), 105 (42), 73 (100), and 57 (100); HRMS [Found: m/z 294.2336 (M^+). Calcd for $C_{18}H_{34}OSi$: M, 294.2380].

4.4.7. (*E*)-4-(4-Methylcyclohexylidene)-2-(trimethylsilylmethyl)but-2-en-1-ol (20c). An oil; IR (neat) 3320 (OH), 1604, 1454, 1246, 1011, and 849 cm^{-1}; ^1H NMR δ=0.03 (9H, s, $SiMe_3$), 0.85–1.88 (7H, m), 0.90 (3H, d, J=6.6 Hz, Me), 1.68 (2H, br s, CH_2SiMe_3), 2.06–2.26 (2H, m), 2.68–2.77 (1H, m), 4.18 (1H, d, J=11.9 Hz, C*H*OH), 4.20 (1H, d, J=11.9 Hz, CH*H*OH), and 6.01 (2H, s, CH=CH); ^{13}C NMR δ=−1.32 (3C), 21.99, 26.04, 28.13, 32.81, 35.81, 36.68, 36.92, 61.90, 117.06, 121.79, 136.53, and 141.26; MS m/z 252 (M^+, 2%), 162 (23), 147 (14), 105 (94), 91 (53), and 57 (100); HRMS [Found: m/z 252.1918 (M^+). Calcd for $C_{15}H_{28}OSi$: M, 252.1910].

4.4.8. (*Z*)-3-(Cyclohex-1-en-1-yl)-2-(trimethylsilylmethyl)prop-2-en-1-ol (26). An oil; IR (neat) 3320 (OH), 1689, 1643, 1437, 1248, 1028, and 852 cm^{-1}; ^1H NMR δ=0.04 (9H, s, $SiMe_3$), 1.53–1.68 (5H, m), 1.84 (2H, br s, CH_2SiMe_3), 2.05–2.13 (4H, m), 3.98 (2H, br s, CH_2OH), 5.60–5.64 (1H, m, C=C*H*CH_2), and 5.71 (1H, br s, C*H*=CCH_2OH); ^{13}C NMR δ=−0.57 (3C), 19.76, 22.20, 22.96, 25.58, 29.37, 69.49, 125.44, 126.09, 128.97, and 135.13; MS m/z 224 (M^+, 1%), 134 (12), 119 (44), 105 (57), 91 (100), and 73 (100); HRMS [Found: m/z 224.1590 (M^+). Calcd for $C_{13}H_{24}OSi$: M, 224.1597].

4.4.9. (*E*)-3-(Cyclohex-1-en-1-yl)-2-(trimethylsilylmethyl)prop-2-en-1-ol (27). An oil; IR (neat) 3325 (OH), 1637, 1437, 1246, 1016, and 850 cm^{-1}; ^1H NMR δ=0.01 (9H, s, $SiMe_3$), 1.51–1.64 (4H, m), 1.63 (2H, br s, CH_2SiMe_3), 1.77 (1H, br, OH), 1.95–2.01 (2H, m), 2.03–2.10 (2H, m), 4.16 (2H, s, CH_2OH), 5.40–5.44 (1H, m, C=C*H*CH_2), and 5.50 (1H, br s, C*H*=CCH_2OH); ^{13}C NMR δ=1.27 (3C), 22.12, 22.81, 25.04, 25.48, 29.42, 62.89, 125.41, 128.96, 135.08, and 136.97; MS m/z 224 (M^+, 1%), 134 (10), 119 (40), 105 (52), 91 (94), and 73 (100); HRMS (CI) [Found: m/z 225.1576 (M^++H). Calcd for $C_{13}H_{25}OSi$: M, 225.1675].

4.4.10. (*E*)-3-(*t*-Butylcyclohex-1-en-1-yl)-2-(trimethylsilylmethyl)prop-2-en-1-ol (39a). An oil; IR (neat) 3390 (OH), 1637, 1467, 1365, 1245, and 854 cm^{-1}; ^1H NMR δ=0.03 (9H, s, $SiMe_3$), 0.87 (9H, s, *t*-Bu), 1.10–1.30 (2H, m), 1.45 (1H, br, OH), 1.63 (1H, d, J=13.5 Hz, C*H*H$SiMe_3$), 1.67 (1H, d, J=13.5 Hz, CH*H*$SiMe_3$), 1.78–1.92 (2H, m), 2.05–2.16 (3H, m), 4.12 (1H, d, J=12.0 Hz, OC*H*HOH), 4.24 (1H, d, J=12.0 Hz, OCH*H*OH), 5.44–5.48 (1H, m, C=C*H*CH_2), and 5.55 (1H, br s, C*H*=CCH_2-OH); ^{13}C NMR δ=−1.26 (3C), 24.19, 25.14, 27.14, 27.18 (3C), 30.94, 32.19, 43.81, 62.70, 125.85, 128.54, 134.93, and 137.01; MS m/z 280 (M^+, 1%), 251 (1), 190 (4), 175 (5), 133 (26), 106 (34), 91 (52), 73 (89), and 57 (100); HRMS (CI) [Found: m/z 281.2343 (M^++H). Calcd for $C_{17}H_{33}OSi$: M, 281.2301].

4.4.11. (*E*)-3-(Methylcyclohex-1-en-1-yl)-2-(trimethylsilylmethyl)prop-2-en-1-ol (39b). An oil; IR (neat) 3330 (OH), 1637, 1458, 1248, 1012, and 856 cm^{-1}; ^1H NMR δ=0.03 (9H, s, $SiMe_3$), 0.95 (3H, d, J=6.6 Hz, Me), 1.16–1.27 (1H, m), 1.56–1.74 (6H, m), 1.97–2.19 (3H, m), 4.13 (1H, d, J=12.2 Hz, OC*H*HOH), 4.21 (1H, d, J=12.2 Hz, OCH*H*OH), 5.38–5.42 (1H, m, C=C*H*CH_2), and 5.53 (1H, br s, C*H*=CCH_2OH); ^{13}C NMR δ=−1.29 (3C), 21.76, 24.98, 28.08, 29.47, 31.05, 34.07, 62.61, 125.00, 128.62, 134.67, and 136.99; MS *m*/*z* 238 (M^+, 1%), 223 (1), 148 (12), 133 (23), 106 (64), 91 (86), and 73 (100); HRMS [Found: *m*/*z* 238.1738 (M^+). Calcd for $C_{14}H_{26}OSi$: M, 238.1753].

4.5. MnO_2 oxidation

In a 50 cm^3 round-bottomed flask fitted with $CaCl_2$ drying tube was placed a solution of **11a** (104.3 mg, 473.4 mmol) in dry CH_2Cl_2 (15 cm^3; distilled from CaH_2) at room temperature, and to this was added a suspension of MnO_2 (2.1 g) in CH_2Cl_2 (3 cm^3) with vigorous stirring. After this had been stirred for 15 h, the mixture was filtered through Celite, and the filtrate was concentrated. The resultant crude oil was chromatographed on silica gel (1 g) using hexane/AcOEt (99:1) as eluent to afford **8a** (91.7 mg, 89%). Similarly, **11b**, **11c**, **15**, **20a**, **20b**, **20c**, and **26** afforded **8b**, **8c**, **13**, **17a**, **17b**, **17c**, and **28** in 88, 81, 51, 71, 64, 75, and 85% yields, respectively. These compounds were purified free from their geometrical isomers at this stage.

4.5.1. (*Z*)-4-Cyclohexylidene-2-(trimethylsilylmethyl)but-2-enal (8a). An oil; IR (neat) 2705 (CHO), 1675 (C=O), 1627, 1447, 1249, and 854 cm^{-1}; ^1H NMR δ=−0.02 (9H, s, $SiMe_3$), 1.60–1.67 (6H, m, $(CH_2)_3$), 1.85 (2H, br s, C*H*$_2SiMe_3$), 2.25–2.30 (2H, m, C=CCH_2), 2.40–2.46 (2H, m, C=CCH_2), 6.16 (1H, d quint, J=11.6, 0.9 Hz, C_{ring}=CH), 7.02 (1H, d, J=11.6 Hz, C*H*=CCHO), and 9.39 (1H, s, CHO); ^{13}C NMR δ=−1.05 (3C), 14.74, 26.58, 28.05, 28.80, 29.87, 38.39, 118.81, 138.90, 141.62, 153.97, and 194.96; MS *m*/*z* 236 (M^+, 30%), 221 (26), 193 (38), 180 (15), 91 (17), and 73 (100); HRMS [Found: *m*/*z* 236.1565 (M^+). Calcd for $C_{14}H_{24}OSi$: M, 236.1597].

4.5.2. (*Z*)-4-(4-*t*-Butylcyclohexylidene)-2-(trimethylsilylmethyl)but-2-enal (8b). An oil; IR (neat) 2707 (CHO), 1677 (C=O), 1628, 1365, 1248, 1226, and 855 cm^{-1}; ^1H NMR δ=−0.02 (9H, s, $SiMe_3$), 0.87 (9H, s, *t*Bu), 1.02–1.32 (3H, m), 1.85 (2H, br s, C*H*$_2SiMe_3$), 1.88–2.02 (3H, m), 2.17–2.27 (1H, m), 2.38–2.44 (1H, m), 2.96–3.03 (1H, m), 6.15 (1H, br d, J=11.5 Hz, C_{ring}=CH), 7.01 (1H, d, J=11.5 Hz, C*H*=CCHO), and 9.39 (1H, s, CHO); ^{13}C NMR δ=−1.04 (3C), 14.74, 27.58 (3C), 28.70, 29.44, 29.63, 32.48, 38.20, 48.18, 118.48, 138.88, 141.72, 153.97, and 194.94; MS *m*/*z* 292 (M^+, 91%), 277 (87), 194 (98), 180 (86), and 73 (100); HRMS [Found: *m*/*z* 292.2202 (M^+). Calcd for $C_{18}H_{32}OSi$: M, 292.2224].

4.5.3. (*Z*)-4-(4-Methylcyclohexylidene)-2-(trimethylsilylmethyl)but-2-enal (8c). An oil; IR (neat) 2707 (CHO), 1676 (C=O), 1626, 1248, 1223, and 855 cm^{-1}; ^1H NMR δ=−0.02 (9H, s, $SiMe_3$), 0.93 (3H, d, J=6.5 Hz, Me), 0.99–1.15 (2H, m), 1.55–1.73 (1H, m), 1.82–2.04 (3H, m), 1.85 (2H, br s, C*H*$_2SiMe_3$), 2.19–2.39 (2H, m), 2.86–2.93 (1H, m), 6.17 (1H, br d, J=11.6 Hz, C_{ring}=CH), 7.01 (1H, d, J=11.6 Hz, C*H*=CCHO), and 9.38 (1H, s, CHO); ^{13}C NMR δ=1.05 (3C), 14.74, 21.70, 29.08, 32.62, 36.00, 36.76, 37.67, 118.90, 138.94, 141.69, 153.56, and 194.95; MS *m*/*z* 250 (M^+, 100%), 235 (99), 193 (94), 180 (6), 147 (5), and 75 (94); HRMS [Found: *m*/*z* 250.1725 (M^+). Calcd for $C_{15}H_{26}OSi$: M, 250.1754].

4.5.4. (*E*)-4-Cyclohexylidene-2-methylbut-2-enal (13). An oil; IR (neat) 2708 (CHO), 1681 (C=O), 1629, 1447, 1234, 1223, 1187, and 1011 cm^{-1}; ^1H NMR (Me_4Si=0.00) δ=1.13–1.91 (6H, m, $(CH_2)_3$), 1.84 (3H, d, J=1.0 Hz, C=CCH_3), 2.28–2.33 (2H, m, C=CCH_2), 2.42–2.48 (2H, m, C=CCH_2), 6.28 (1H, br d, J=11.8 Hz, C_{ring}=CH), 7.17 (1H, dq, J=11.8, 1.1 Hz, C*H*=CCHO), and 9.45 (1H, s, CHO); ^{13}C NMR δ=9.19, 26.50, 27.99, 28.66, 29.89, 38.37, 118.09, 135.71, 144.46, 155.85, and 195.35; MS *m*/*z* 164 (M^+, 97%), 149 (3), 135 (3), and 121 (100); HRMS [Found: *m*/*z* 164.1161 (M^+). Calcd for $C_{11}H_{16}O$: M, 164.1202].

4.5.5. (*E*)-4-Cyclohexylidene-2-(trimethylsilylmethyl)but-2-enal (17a). An oil; IR (neat) 1660 (C=O), 1626, 1248, 856, and 739 cm^{-1}; ^1H NMR δ=−0.02 (9H, s, $SiMe_3$), 1.57–1.66 (6H, m, $(CH_2)_3$), 1.72 (2H, s, C*H*$_2$-$SiMe_3$), 2.22–2.27 (2H, m, C=CCH_2), 2.33–2.38 (2H, m, C=CCH_2), 6.77 (1H, br d, J=12.4 Hz, C_{ring}=CH), 7.07 (1H, d, J=12.4 Hz, C*H*=CCHO), and 10.03 (1H, s, CHO); ^{13}C NMR δ=−1.60 (3C), 19.93, 26.62, 27.87, 28.56, 28.94, 38.18, 114.99, 134.89, 138.48, 151.04, and 190.11; MS *m*/*z* 236 (M^+, 7%), 221 (8), 193 (19), 180 (7), 91 (12), 73 (100), and 45 (37); HRMS [Found: *m*/*z* 236.1585 (M^+). Calcd for $C_{14}H_{24}OSi$: M, 236.1597].

4.5.6. (*E*)-4-(4-*t*-Butylcyclohexylidene)-2-(trimethylsilylmethyl)but-2-enal (17b). An oil; IR (neat) 1662 (C=O), 1630, 1365, 1248, and 856 cm^{-1}; ^1H NMR δ=−0.02 (9H, s, $SiMe_3$), 0.87 (9H, s, *t*Bu), 1.00–1.30 (3H, m), 1.69 (1H, d, J=13.0 Hz, C*H*$HSiMe_3$), 1.74 (1H, d, J=13.0 Hz, CH*H*$SiMe_3$), 1.79–2.00 (3H, m), 2.14–2.24 (1H, m), 2.36–2.41 (1H, m), 2.89–2.95 (1H, m), 6.77 (1H, br d, J=12.6 Hz, C_{ring}=CH), 7.07 (1H, d, J=12.6 Hz, C*H*=CCHO), and 10.30 (1H, s, CHO); ^{13}C NMR δ=−1.60 (3C), 19.90, 27.57 (3C), 28.52, 28.71, 29.16, 32.48, 38.00, 48.21, 114.67, 134.86, 138.61, 151.03, and 190.12; MS *m*/*z* 292 (M^+, 3%), 277 (4), 193 (32), and 73 (100); HRMS [Found: *m*/*z* 292.2223 (M^+). Calcd for $C_{18}H_{32}OSi$: M, 292.2224].

4.5.7. (*E*)-4-(4-Methylcyclohexylidene)-2-(trimethylsilylmethyl)but-2-enal (17c). An oil; IR (neat) 1660 (C=O), 1626, 1248, 1146, and 856 cm^{-1}; ^1H NMR δ=−0.02 (9H, s, $SiMe_3$), 0.93 (3H, d, J=6.5 Hz, Me), 0.98–1.16 (2H, m), 1.70 (1H, d, J=12.8 Hz, C*H*$HSiMe_3$), 1.73 (1H, d, J=12.8 Hz, CH*H*$SiMe_3$), 1.58–1.96 (4H, m), 2.17–2.36 (2H, m), 2.79–2.86 (1H, m), 6.78 (1H, br d, J=12.4 Hz, C_{ring}=CH), 7.06 (1H, d, J=12.4 Hz, C*H*=CCHO), and 10.29 (1H, s, CHO); ^{13}C NMR δ=−1.59 (3C), 19.97, 21.74, 28.18, 32.68, 35.88, 36.58, 37.48, 115.10, 134.98, 138.54, 150.61, and 190.11; MS *m*/*z* 250 (M^+, 4%), 235 (5), 193 (25), 103 (16), and 73 (100); HRMS [Found: *m*/*z* 250.1758 (M^+). Calcd for $C_{15}H_{26}OSi$: M, 250.1754].

4.5.8. (*Z*)-3-(Cyclohex-1-en-1-yl)-2-(trimethylsilylmethyl)prop-2-enal (28). An oil; IR (neat) 1680 (C=O), 1615, 1249, and 856 cm^{-1}; ^1H NMR δ=−0.01 (9H, s, $SiMe_3$), 1.58–1.74 (4H, m), 2.02 (2H, br s, CH_2SiMe_3), 2.20–2.26 (2H, m), 2.31–2.37 (2H, m), 6.12–6.17 (1H, m, C=C*H*CH_2), 6.53 (1H, br s, C*H*=CCHO), and 9.31 (1H, s, CHO); ^{13}C NMR δ=−0.94 (3C), 15.53, 21.63, 22.59, 26.41, 28.33, 135.80, 136.61, 138.15, 150.66, and 196.19; MS *m/z* 221 (M^+− H, 3%), 207 (3), 180 (6), 131 (7), 117 (9), 104 (10), 91 (18), and 73 (100); HRMS [Found: *m/z* 222.1428 (M^+). Calcd for $C_{13}H_{22}OSi$: M, 222.1441].

4.6. Cyclization of 27

By the same procedure described above, compound **27** (25.6 mg, 0.114 mmol) was treated with MnO_2 (260 mg) in dry CH_2Cl_2 (10 cm^3) at room temperature for 75 min. After filtration through Celite, the filtrate was concentrated and chromatographed on silica gel (1 g) using pentane/Et_2O (99:1) as eluent to afford **30** (5.1 mg, 20%) and **31** (10.7 mg, 63%).

4.6.1. 8-Methylenebicyclo[4.3.0]non-9-en-7-ol (30). An oil; IR (neat) 3350 (OH), 1639, 1446, 1036, 868, and 739 cm^{-1}; ^1H NMR δ=1.04 (1H, dq, *J*=3.3, 12.5 Hz, 5β-H), 1.17–1.44 (2H, m, 3β-H and 4α-H), 1.68 (1H, br d, *J*=6 Hz, OH), 1.77–1.89 (2H, m, 3α-H and 4β-H), 2.06 (1H, br dt, *J*=5, 13 Hz, 2α-H), 2.14–2.22 (1H, m, 5α-H), 2.34–2.41 (1H, m, 6-H), 2.49 (1H, ddt, *J*=4.0, 13.9, 2.2 Hz, 2β-H), 4.26 (1H, br s, 7-H), 4.88 (1H, br s, C=C*H*H), 4.91 (1H, d, *J*=1.5 Hz, C=CH*H*), and 5.79 (1H, br s, 9-H); ^{13}C NMR δ=25.57, 26.91, 29.47, 29.69, 32.75, 79.65, 102.55, 123.05, 153.61, and 156.61; MS *m/z* 150 (M^+, 74%), 135 (17), 121 (81), 108 (81), 91 (79), and 79 (100); HRMS [Found: *m/z* 150.1040 (M^+). Calcd for $C_{10}H_{14}O$: M, 150.1045].

4.6.2. 8-Methylene-7-(trimethylsilyloxy)bicyclo[4.3.0]non-9-ene (31). An oil; IR (CH_2Cl_2) 1458, 1097, 1030, and 802 cm^{-1}; ^1H NMR δ=0.18 (9H, s, $SiMe_3$), 1.03 (1H, dq, *J*=3.3, 12.5 Hz), 1.16–1.44 (2H, m), 1.76–1.88 (2H, m), 1.98–2.19 (2H, m), 2.35–2.50 (2H, m), 4.31 (1H, dt, *J*=3.4, 2.2 Hz, C*H*OSiMe$_3$), 4.75 (1H, br s, C=C*H*H), 4.86 (1H, d, *J*=1.6 Hz, C=CH*H*), and 5.78 (1H, br s, CH=C); ^{13}C NMR δ=0.43 (3C), 25.61, 26.72, 29.47, 32.65, 53.56, 80.15, 102.17, 123.43, 152.43, and 155.70; MS *m/z* 222 (M^+, 31%), 207 (10), 180 (18), 117 (23), 104 (27), 91 (32), and 73 (100); HRMS [Found: *m/z* 222.1438 (M^+). Calcd for $C_{13}H_{22}OSi$: M, 222.1441].

4.7. Cyclization of 39a,b

By the same procedure, compound **39a** (34.2 mg, 0.122 mmol) was treated with MnO_2 (450 mg) at room temperature for 5 min. After the mixture had been filtered through Celite, the solvent was evaporated off. The resultant oily residue was dissolved in Et_2O (5 cm^3), silica gel (ca. 100 mg) was added, and the mixture was stirred for 3 days. The silica gel was filtered off, washed with Et_2O, and the solvent was partly evaporated. Et_2O was added to a volume of ca. 5 cm^3 again, and Bu_4NF (31 mg) was added. After the mixture had been stirred at room temperature for 4 h, an aqueous solution of NH_4Cl was added, and the mixture was extracted with Et_2O and dried. Evaporation of the solvent followed by florisil (2 g) column chromatography using hexane/Et_2O (99:1) as eluent afforded **42a** (23.2 mg, 94%). Similarly, **39b** (20.5 mg, 0.086 mmol) afforded **42b** (13.3 mg, 94%).

4.7.1. 4-*t*-Butyl-8-methylenebicyclo[4.3.0]non-9-en-7-ol (42a). An oil; IR (neat) 3390 (OH), 1639, 1365, 1265, 1072, 866, and 737 cm^{-1}; ^1H NMR δ=0.87 (9H of one isomer, s, *t*-Bu), 0.87 (9H of one isomer, s, *t*-Bu), 0.79–2.69 (9H, m), 4.24–4.32 (1H, m, C*H*OH), 4.84–4.90 (2H, m, C=CH_2), 5.77 (1H of one isomer, s, C=C*H*C=CH_2), and 5.82 (1H of one isomer, s, C=C*H*C=CH_2); ^{13}C NMR δ=23.51, 25.92, 27.56 (3C), 27.64 (3C), 27.77, 29.21, 29.66, 32.49, 32.98, 33.72, 43.10, 43.31, 50.59, 54.60, 79.88, 81.24, 101.58, 102.36, 122.67, 123.68, 153.09, 153.60, 156.81, and 157.02; MS *m/z* 206 (M^+, 1%), 188 (31), 173 (9), 131 (48), 104 (32), 57 (39), and 43 (100); HRMS (CI) [Found: *m/z* 207.1652 (M^++H). Calcd for $C_{14}H_{23}O$: M, 207.1749].

4.7.2. 4-Methyl-8-methylenebicyclo[4.3.0]non-9-en-7-ol (42b). An oil; IR (neat) 3370 (OH), 1639, 1265, 1049, 868, and 739 cm^{-1}; ^1H NMR δ=0.71–2.63 (9H, m), 0.93 (3H of one isomer, d, *J*=6.5 Hz, Me), 1.08 (3H of one isomer, d, *J*=7.1 Hz, Me), 4.25 (1H, br s, C*H*OH), 4.87–4.92 (2H, m, C=CH_2), and 5.79 (1H, s, C=C*H*C=CH_2); ^{13}C NMR δ=16.88, 22.14, 24.24, 27.75, 28.93, 31.99, 32.06, 35.25, 38.07, 41.04, 48.98, 54.22, 79.63, 80.01, 102.54 (for both isomers), 122.84, 123.12, 153.24, 153.86, 156.58, and 156.83; MS *m/z* 164 (M^+, 48%), 149 (33), 131 (44), 122 (61), 91 (61), and 79 (100); HRMS (CI) [Found: *m/z* 165.1274 (M^++H). Calcd for $C_{11}H_{17}O$: M, 165.1279].

4.8. Cyclization of 8a–c and 17a–c

To a stirred solution of $FeCl_3$ (63.4 mg, 391 mmol) in dry CH_2Cl_2 (6 cm^3; distilled from CaH_2) was added a solution of **8a** (42.8 mg, 181 mmol) in CH_2Cl_2 (10 cm^3) dropwise at −60 °C under Ar. Monitoring on TLC, the mixture was slowly warmed to room temperature over 7 h. A saturated aqueous solution of $NaHCO_3$ was added, and the mixture was extracted with CH_2Cl_2 and dried. Evaporation of the solvent followed by silica gel (15 g) column chromatography using hexane/AcOEt (98:2) afforded **12a** (23.3 mg, 78%). Similarly, **8b** and **8c** gave **12b** and **12c** in 80 and 70% yields, respectively. See Tables 1 and 2 for the modified reaction conditions of the cyclization of **17a–c**.

4.8.1. 2-Methylspiro[4.5]dec-2-en-1-one (12a). An oil; UV (EtOH) λ_{max} 227.4 nm (ε 1.0×10^{-4}); IR (neat) 1702 (C=O), 1640, 1261, 1098, 1021, and 804 cm^{-1}; ^1H NMR δ=1.20–1.40 (6H, m), 1.52–1.77 (4H, m), 1.77 (3H, dt, *J*=1.3, 2.3 Hz, Me), 2.42 (2H, quint, *J*=2.3 Hz, C=CCH_2), and 7.23 (1H, tq, *J*=2.3, 1.3 Hz, C=CH); ^{13}C NMR δ=10.39, 23.05 (2C), 25.25, 33.40 (2C), 39.97, 48.08, 139.65, 155.74, and 214.42; MS *m/z* 164 (M^+, 16%), 149 (7), 121 (16), 109 (100), 96 (28), 79 (16), and 41 (31); HRMS [Found: *m/z* 164.1216 (M^+). Calcd for $C_{11}H_{16}O$: M, 164.1202].

4.8.2. 8-*t*-Butyl-2-methylspiro[4.5]dec-2-en-1-one (12b). An oil; IR (neat) 1706 (C=O), 1637, and 1009 cm^{-1}; ^1H

NMR δ=0.85 (9H, s, *t*Bu), 1.00–1.11 (3H, m), 1.24–1.35 (2H, m), 1.53–1.66 (2H, m), 1.73–1.80 (2H, m), 1.77 (3H, dt, J=1.4, 2.2 Hz, Me), 2.39 (2H, quint, J=2.2 Hz, C=CCH_2), and 7.23 (1H, tq, J=2.2, 1.4 Hz, C=C*H*); ^{1}H NMR (C_6D_6=7.15) δ=0.79 (9H, s, *t*Bu), 0.76–0.96 (3H, m, 7_{ax}-H, 8-H, and 9_{ax}-H), 1.15–1.21 (2H, m, 6_{eq}-H and 10_{eq}-H), 1.52–1.59 (2H, m, 7_{eq}-H and 9_{eq}-H), 1.70 (3H, dt, J=1.4, 2.2 Hz, Me), 1.74 (2H, br dt, J=3.5, 13 Hz, 6_{ax}-H and 10_{ax}-H), 1.91 (2H, quint, J=2.2 Hz, C=CCH_2), and 6.57 (1H, tq, J=2.2, 1.4 Hz, C=C*H*); ^{13}C NMR δ=10.39 (CH_3), 24.04 ($2CH_2$), 27.43 ($3CH_3$), 32.40 (C), 34.07 ($2CH_2$), 39.90 (CH_2), 46.93 (CH), 48.08 (C), 139.84 (C), 155.82 (CH), and 214.66 (CO); MS *m*/*z* 220 (M^+, 7%), 205 (3), 163 (100), 109 (97), and 57 (98); HRMS [Found: *m*/*z* 220.1783 (M^+). Calcd for $C_{15}H_{24}O$: M, 220.1828].

4.8.3. 2,8-Dimethylspiro[4.5]dec-2-en-1-one (12c). An oil; UV (EtOH) λ_{max} 227.8 nm (ε 1.0×10^{-4}); IR (neat) 1703 (C=O), 1641, 1452, 1072, and 1021 cm^{-1}; ^{1}H NMR δ=0.90 (3H, d, J=6.5 Hz, Me), 0.93–1.05 (2H, m, 7_{ax}-H and 9_{ax}-H), 1.21–1.28 (2H, m, 6_{eq}-H and 10_{eq}-H), 1.36–1.49 (1H, m, 8-H), 1.61 (2H, br dt, J=3.5, 13 Hz, 6_{ax}-H and 10_{ax}-H), 1.66–1.72 (2H, m, 7_{eq}-H and 9_{eq}-H), 1.77 (3H, dt, J=1.4, 2.3 Hz, Me), 2.39 (2H, quint, J=2.3 Hz, C=CCH_2), and 7.23 (1H, tq, J=2.3, 1.4 Hz, C=C*H*); ^{13}C NMR δ=10.40, 22.64, 31.55, 31.87 (2C), 33.53 (2C), 39.84, 47.81, 139.80, 155.85, and 214.69; MS *m*/*z* 178 (M^+, 18%), 121 (16), 109 (98), and 96 (100); HRMS [Found: *m*/*z* 179.1402 (M^+-H). Calcd for $C_{12}H_{19}O$: M, 179.1437].

4.8.4. 2-Methylenespiro[4.5]dec-3-en-1-ol (18a). An oil; IR (neat) 3390 (OH), 1643, 1450, 1101, 1947, 870, 800, and 735 cm^{-1}; ^{1}H NMR δ=1.24–1.68 (11H, m), 4.18 (1H, br s, C*H*OH), 5.02–5.05 (2H, m, C=CH_2), 6.12 (1H, d, J=6.4 Hz, C*H*=CH–C=C), and 6.21 (1H, br d, J=6.4 Hz, CH=C*H*–C=C); ^{13}C NMR δ=22.93, 23.37, 26.00, 31.05, 36.04, 51.18, 80.80, 105.61, 129.40, 144.67, and 155.81; MS *m*/*z* 164 (M^+, 5%), 149 (14), 135 (23), 121 (100), 108 (54), 91 (60), 79 (59), 67 (51), and 41 (82); HRMS [Found: *m*/*z* 164.1297 (M^+). Calcd for $C_{11}H_{16}O$: M, 164.1202].

4.8.5. 2-Methylspiro[4.5]dec-3-en-1-one (21a). An oil; IR (neat) 1738 (C=O), 1676, 1624, 1452, and 1161 cm^{-1}; ^{1}H NMR δ=1.15 (3H, d, J=7.5 Hz, Me), 1.20–1.78 (10H, m), 2.96 (1H, tq, J=2.2, 7.5 Hz, C*H*Me), 6.03 (1H, dd, J=2.2, 7.2 Hz, C*H*=CH), and 6.30 (1H, dd, J=2.2, 7.2 Hz, CH=C*H*); ^{13}C NMR δ=15.96, 22.18, 22.34, 25.68, 33.48, 33.59, 46.51, 54.01, 132.15, 135.87, and 195.70; MS *m*/*z* 164 (M^+, 5%), 136 (100), 121 (21), 107 (68), 94 (34), 79 (92), and 41 (68); HRMS [Found: *m*/*z* 164.1169 (M^+). Calcd for $C_{11}H_{16}O$: M, 164.1202].

4.8.6. 8-*t*-Butyl-2-methylspiro[4.5]dec-3-en-1-one (21b). Mp 43–45 °C; IR (neat) 1739 (C=O), 1676, 1630, 1450, 1365, and 856 cm^{-1}; ^{1}H NMR δ=0.87 (9H, s, *t*Bu), 1.11–1.77 (9H, m), 1.15 (3H, d, J=7.6 Hz, Me), 2.96 (1H, tq, J=2.1, 7.6 Hz, C*H*Me), 6.05 (1H, dd, J=2.0, 7.2 Hz, C*H*=CH), and 6.37 (1H, dd, J=2.2, 7.2 Hz, CH=C*H*); ^{13}C NMR (C_6D_6=128.00) δ=15.96, 23.54, 23.71, 27.46 (3C), 32.36, 34.40, 34.54, 46.44, 47.51, 54.31, 132.65, 135.32, and 221.13; MS *m*/*z* 220 (M^+, 4%), 192 (43), 149 (11), 135 (28), 121 (28), 93 (38), 79 (57), and 57 (100); HRMS [Found: *m*/*z* 220.1818 (M^+). Calcd for $C_{15}H_{24}O$: M, 220.1828].

4.8.7. 2,8-Dimethylspiro[4.5]dec-3-en-1-one (21c). An oil; IR (CH_2Cl_2) 1738 (C=O), 1450, 1377, 955, and 883 cm^{-1}; ^{1}H NMR δ=0.91 (3H, d, J=6.5 Hz, Me), 1.00–1.69 (9H, m), 1.13 (3H, d, J=7.5 Hz, Me), 2.94 (1H, tq, J=2.1, 7.5 Hz, COC*H*Me), 6.03 (1H, dd, J=2.1, 7.1 Hz, C*H*=CH), and 6.36 (1H, dd, J=2.1, 7.1 Hz, CH=C*H*); ^{13}C NMR (C_6D_6=128.00) δ=15.95, 22.65, 31.28, 31.42, 32.30, 33.97, 34.03, 46.90, 54.03, 132.63, 135.28, and 221.24; MS *m*/*z* 178 (M^+, 4%), 150 (95), 135 (20), 121 (45), 93 (67), 79 (87), and 41 (100); HRMS [Found: *m*/*z* 178.1366 (M^+-H). Calcd for $C_{12}H_{18}O$: M, 178.1358].

4.9. The cyclization products obtained from 28

The following compounds were detected from ^{1}H and ^{13}C NMR spectra and GC–MS after partial separation into several groups, however, it was difficult to isolate each compounds.

4.9.1. 8-Methylbicyclo[4.3.0]non-1(6)-en-7-one (32). ^{1}H NMR δ=1.17 (3H, d, J=7.3 Hz, Me), 1.61–1.76 (4H, m, 3-H_2 and 4-H_2), 2.03–2.15 (3H, m, 2-H_2 and 9-H), 2.26–2.32 (2H, m, 5-H_2), 2.38 (1H, d quint, J=2.0, 7.3 Hz, 8-H), and 2.72 (1H, dm, J=ca. 18 Hz, 9-H); ^{13}C NMR δ=16.58, 20.09, 21.71, 22.18, 28.43, 39.16, 39.81, 137.43, 171.82, and 211.59; GC–MS *m*/*z* 150 (M^+, 43%), 135 (91), 122 (23), 107 (45), 91 (30), and 79 (100).

4.9.2. *cis*-8-Methylbicyclo[4.3.0]non-8-en-7-one (33). ^{1}H NMR δ=1.06–2.02 (8H, m), 1.78 (3H, t, J=1.5 Hz, Me), 2.41 (1H, q, J=6.4 Hz, 6-H), 2.80–2.88 (1H, m, 1-H), and 7.23 (1H, sextet, J=1.5 Hz, 9-H); ^{13}C NMR δ=10.26, 21.09, 21.27, 22.84, 28.09, 38.64, 45.50, 139.83, 161.31, and 211.96; GC–MS *m*/*z* 150 (M^+, 54%), 135 (12), 121 (39), 107 (29), 93 (28), 79 (80), 69 (94), and 41 (100).

4.9.3. 8-Methylbicyclo[4.3.0]nona-1,8-dien-7-one (34). ^{1}H NMR δ=1.06–2.02 (3H, m), 1.85 (3H, br s, Me), 2.08–2.19 (1H, m, 3-H), 2.25 (1H, ddt, J=4.5, 12.7, 3.5 Hz, 5-H), 2.37 (1H, dm, J=ca. 18 Hz, 3-H), 2.69 (1H, dd-like, J=4.9, 12.0 Hz, 6-H), 5.77 (1H, br t, J=3 Hz, 2-H), and 7.37 (1H, br s, 9-H); ^{13}C NMR δ=10.29, 22.13, 22.58, 25.73, 46.95, 121.83, 139.00, 140.90, 150.85, and 207.61; GC–MS *m*/*z* 148 (M^+, 63%), 133 (26), 120 (25), 105 (95), 91 (100), 77 (47), and 51 (47).

4.9.4. *trans*-2-Chloro-8-methylbicyclo[4.3.0]non-1(6)-en-7-one (35). ^{1}H NMR δ=1.19 (3H, d, J=7.3 Hz, Me), 1.69–1.94 (2H, m, 4-H_2), 2.03 (1H, dm, J=ca. 18 Hz, 9β-H), 2.04–2.18 (3H, m, 3-H_2 and 5-H), 2.27 (1H, dm, J=ca. 18 Hz, 5-H), 2.46 (1H, d quint, J=2.2, 7.3 Hz, 8α-H), 3.13 (1H, ddt, J=6.7, 18.2, 2.2 Hz, 9α-H), and 4.69 (1H, br t, J=4.5 Hz, 2β-H); ^{13}C NMR δ=16.38, 18.27, 19.99, 32.80, 36.38, 40.03, 54.94, 139.74, 165.89, and 211.54; GC–MS *m*/*z* 186 (M^+ for ^{37}Cl, 14%), 184 (M^+ for ^{35}Cl, 39), 169 (44), 149 (30), 121 (65), 91 (90), and 79 (100).

4.9.5. *cis*-2-Chloro-8-methylbicyclo[4.3.0]non-1(6)-en-7-one (36). ^{1}H NMR δ=1.21 (3H, d, J=7.4 Hz, Me), 1.70–1.94 (2H, m, 4-H_2), 2.03–2.17 (3H, m, 3-H_2 and 5-H), 2.26

(1H, dm, J=ca. 18 Hz, 5-H), 2.42–2.50 (2H, m, 8α-H, 9α-H), 2.69 (1H, m, 9β-H), and 4.70 (1H, br t, J=4.5 Hz, 2α-H); ^{13}C NMR δ=16.22, 18.30, 19.96, 32.79, 36.45, 40.16, 54.91, 139.80, 166.09, and 211.33; GC–MS m/z 186 (M^+ for ^{37}Cl, 17%), 184 (M^+ for ^{35}Cl, 44), 169 (45), 149 (29), 121 (69), 91 (96), and 79 (100).

4.9.6. 8-Methenebicyclo[4.3.0]non-1(6)-en-7-one (37). ^{1}H NMR δ=1.62–1.79 (4H, m, 3-H_2 and 4-H_2), 2.19–2.25 (2H, m, 2-H_2 or 5-H_2), 2.34–2.40 (2H, m, 5-H_2 or 2-H_2), 3.07 (2H, sept, J=1.3 Hz, 9-H_2), 5.34 (1H, q, J=1.3 Hz, C=C*H*H), and 6.05 (1H, q, J=1.3 Hz, C=CH*H*); ^{13}C NMR δ=20.29, 21.64, 22.12, 28.05, 35.49, 115.20, 140.73, 142.05, 167.84, and 195.40; GC–MS m/z 148 (M^+, 73%), 133 (11), 120 (26), 105 (51), and 91 (100).

4.9.7. 8-(Chloromethyl)bicyclo[4.3.0]non-1(6)-en-7-one (38). ^{1}H NMR δ=1.62–1.79 (4H, m, 3-H_2 and 4-H_2), 2.10–2.17 (2H, m, 2-H_2 or 5-H_2), 2.32–2.38 (2H, m, 5-H_2 or 2-H_2), 2.51 (1H, dm, J=18 Hz, 9-H), 2.65–2.79 (2H, m, 8-H and 9-H), 3.73 (1H, dd, J=6.6, 10.8 Hz, C*H*HCl), and 3.82 (1H, dd, J=3.7, 10.8 Hz, CH*H*Cl); ^{13}C NMR δ=19.99, 21.54, 22.03, 28.48, 34.88, 44.75, 46.82, 138.54, 173.36, and 206.15; GC–MS m/z 186 (M^+ for ^{37}Cl, 7%), 184 (M^+ for ^{35}Cl, 21), 149 (35), 107 (100), and 79 (71).

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Synthesis and molecular structures of (2-dialkylaminophenyl)alcohols and of 2-phenylaminoalkyl-dimethylaminobenzene derivatives

Harbi Tomah Al-Masri,[a] Joachim Sieler,[a,†] Peter Lönnecke,[a,†] Steffen Blaurock,[a,†] Konstantin Domasevitch[b,†] and Evamarie Hey-Hawkins[a,*]

[a]*Institut für Anorganische Chemie der Universität Leipzig, Johannisallee 29, D-04103 Leipzig, Germany*
[b]*Inorganic Chemistry Department, Kiev University, Volodimirska Str. 64, Kiev, Ukraine*

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Abstract—*N*,*N*-Dimethyl-*o*-toluidine, *N*,*N*-dimethylaniline, and *N*,*N*-diethylaniline were treated with *n*-butyllithium-tmeda in diethyl ether–hexane solution to give *o*-lithioarylamines, which react with various electrophiles (benzophenone, dicyclohexyl ketone, benzaldehyde, and Ph(H)C=NPh) to form the corresponding (2-dialkylaminophenyl)alcohols 1-HOCPh$_2$-2-NMe$_2$C$_6$H$_4$ (**1**), 1-HOCCy$_2$-2-NMe$_2$C$_6$H$_4$ (**2**), 1-HOCPh$_2$CH$_2$-2-NMe$_2$C$_6$H$_4$ (**4**), 1-HOC(H)PhCH$_2$-2-NMe$_2$C$_6$H$_4$ (**6**), and 1-HOCPh$_2$-2-NEt$_2$C$_6$H$_4$ (**7**), and the 2-phenylaminoalkyl-dimethylaminobenzene derivatives 1-NMe$_2$-2-NH(Ph)C(H)PhC$_6$H$_4$ (**3**) and 1-NMe$_2$-2-NH(Ph)C(H)PhCH$_2$C$_6$H$_4$ (**5**). Compounds **1**–**7** were characterized spectroscopically (NMR, IR, MS) and by crystal structure determination.

1. Introduction

Organolithium compounds are very versatile reagents in organic and organometallic chemistry.[1] The use of nitrogen as a neighboring heteroatom to effect selective metalation with *n*-butyllithium has been investigated,[2–4] and the reaction of the *ortho*-metalation product with ketones[4–11] has already been described. *ortho*-Lithiation is, however, not restricted to compounds containing nitrogen donor atoms; other directing groups are also frequently encountered.[12] Here we report the reaction of *N*,*N*-dimethyl-*o*-toluidine, *N*,*N*-dimethylaniline, and *N*,*N*-diethylaniline with *n*-butyllithium-tmeda in diethyl ether–hexane solution to give *o*-lithioarylamines, which react in situ with benzophenone, dicyclohexyl ketone, bezaldehyde, and Ph(H)C=NPh to form the corresponding (2-dialkylaminophenyl)alcohols 1-HOCPh$_2$-2-NMe$_2$C$_6$H$_4$ (**1**), 1-HOCCy$_2$-2-NMe$_2$C$_6$H$_4$ (**2**), 1-HOCPh$_2$CH$_2$-2-NMe$_2$C$_6$H$_4$ (**4**), 1-HOC(H)PhCH$_2$-2-NMe$_2$C$_6$H$_4$ (**6**), and 1-HOCPh$_2$-2-NEt$_2$C$_6$H$_4$ (**7**), and the 2-phenylaminoalkyl-dimethylaminobenzene derivatives 1-NMe$_2$-2-NH(Ph)C(H)PhC$_6$H$_4$ (**3**) and 1-NMe$_2$-2-NH(Ph)C(H)PhCH$_2$C$_6$H$_4$ (**5**). Compounds **1**–**7** were characterized spectroscopically (NMR, IR, MS), and crystal structures were determined for **1**–**7**. Compounds **1**[11] and **4**[10] were previously reported but not structurally characterized. A modified procedure for the synthesis of **1** is reported.

The Li derivatives of compounds **1**–**7**[13] are useful starting materials for main group and transition metal compounds,[14] in which they act as hemilabile *O*,*N*- or *N*,*N*-chelating ligands forming six- and seven-membered chelate rings.

2. Results and discussion

2.1. Synthesis

N,*N*-Dimethylaniline and *N*,*N*-diethylaniline were treated with *n*-butyllithium in diethyl ether–hexane solution for one week, but the yields of the *ortho*-lithiated products were low. It was anticipated that *N*,*N*-dimethyl-*o*-toluidine should undergo metalation with *n*-butyllithium at the 2-methyl position, since the 2-methyl protons are more acidic than the ring protons, and a five-membered cyclic intermediate could be formed.[10] We found that when *N*,*N*-dimethyl-*o*-toluidine, *N*,*N*-dimethylaniline, and *N*,*N*-diethylaniline were treated with *n*-butyllithium-tmeda in diethyl ether–hexane, not only did metalation occur much more rapidly (2–3 h) and selectively than with *n*-butyllithium alone, but the overall yields were also increased. The lithium reagents 1-Li-2-NR$_2$C$_6$H$_4$ (R=Me, Et) and 1-LiCH$_2$-2-NMe$_2$C$_6$H$_4$ were treated with various electrophilic compounds, followed by hydrolytic acidic workup to form the corresponding

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* Corresponding author. Tel.: +49-341-9736151; fax: +49-341-9739319; e-mail address: hey@rz.uni-leipzig.de
† Crystal structure determination.

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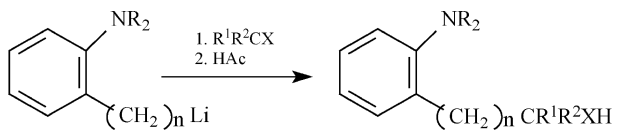


n	R	R^1	R^2	X	
0	Me	Ph	Ph	O	**1**
0	Me	Cy	Cy	O	**2**
0	Me	H	Ph	N(Ph)	**3**
1	Me	Ph	Ph	O	**4**
1	Me	H	Ph	N(Ph)	**5**
1	Me	H	Ph	O	**6**
0	Et	Ph	Ph	O	7

Scheme 1. Preparation of **1**–**7**.

(2-dialkylaminophenyl)alcohols and 2-phenylaminoalkyl-dimethylaminobenzene derivatives, as illustrated in Scheme 1.

The NMe_2-substituted compounds **1**–**6** were obtained in 60–70% yield, while the NEt_2 derivative **7** was obtained in only 20% yield.

2.2. Spectroscopic properties

2.2.1. IR spectra. The infrared spectra of **1**, **2**, **4**, **6**, and **7** showed broad hydroxyl bands in the 3450–3290 cm^{-1} region. The spectrum of the 2-phenylaminoalkyl-dimethyl-aminobenzene derivatives **3** and **5** exhibited sharp peaks around 3290 cm^{-1} and 1600–1540 cm^{-1} for secondary amino groups.[15] These bands have their origin in strong O–H···N and N–H···N intramolecular hydrogen bonds. The presence of both acidic and basic groups in these molecules makes this type of hydrogen bonding the most favorable interaction. In many amino acids such intra-molecular interaction between the acidic and the basic groups in the form $^{+}N–H\cdots O^{-}$ was found in the solid state.[16]

The IR spectrum of each compound showed one sharp peak in the range of 770–690 cm^{-1}, indicative of an *ortho*-disubstituted aromatic ring and ascribable to the four adjacent aromatic hydrogen atoms.[17] In addition to the peaks mentioned above, the IR spectrum of each compound, except for **7**, showed a strong peak in the range of 855–837 cm^{-1}, which can be attributed to the unaltered dimethylaminomethyl group.[16] Absorptions in the range of 1042–1010, 690–670 and 760–750 cm^{-1} are observed for the phenyl groups.

2.2.2. Mass spectrometry. The mass spectra of **1**–**7** showed parent-ion peaks at *m/z* 302.9 (**1**), 314.9 (**2**), 302.4 (**3**), 316.8 (**4**), 316.0 (**5**), 241.3 (**6**) and 331.3 (**7**), which agree with the calculated distribution pattern.

2.2.3. ^{1}H and ^{13}C NMR spectra. In the ^{1}H NMR spectra, the most noticeable signal is that due to the $N(CH_3)_2$ protons, which give rise to a singlet for each compound in the range 2.38–2.78 ppm. The resonances corresponding to the benzylic protons are observed at 3.74 (**4**) as a singlet, and at 2.93, 4.32 (**5**) and 3.10, 4.94 ppm (**6**) as doublets. The singlet at 4.39 (**3**) and the triplets at 3.20 (**5**) and 3.21 ppm

Table 1. Selected bond lengths (Å) and angles (deg) for **1**, **2**, **3** and **7**

	C(3)–N(1)	C(3)–C(8)	C(8)–C(9)	C(9)–O(1) or C(9)–N(2)	N(1)–C(3)–C(8)	C(3)–C(8)–C(9)	C(8)–C(9)–O(1) or C(8)–C(9)–N(2)	C(3)–N(1)–C	C(1)–N(1)–C(2)	C(9)–O(1)–H or C(9)–N(2)–H
1	1.457(2)	1.401(2)	1.544(2)	1.440(2)	119.7(2)	121.7(2)	109.9(2)	111.9(2), 111.9(2)	111.2(2)	104(1)
2	1.453(2)	1.399(2)	1.550(2)	1.426(2)	121.0(1)	124.9(1)	112.2(1)	113.4(2), 111.4(1)	111.6(2)	107(1)
3	1.432(2)	1.408(2)	1.522(2)	1.452(2)	119.0(1)	121.6(1)	108.4(1)	115.7(2), 112.0(1)	111.4(2)	116.7(8)
7	1.453(2)	1.405(2)	1.548(2)	1.429(2)	119.6(2)	121.7(2)	110.2(1)	113.4(2), 111.2(2)	112.0(2)[a]	104(1)

[a] Corresponds to C(23)–N(1)–C(2).

Table 2. Selected bond lengths (Å) and angles (deg) for **4**–**6**

	4a	4b	5	6
C(3)–N(1)	1.449(2)	1.447(3)	1.427(2)	1.435(2)
C(3)–C(8)	1.403(2)	1.406(2)	1.408(2)	1.398(2)
C(8)–C(9)	1.517(2)	1.512(2)	1.508(3)	1.518(2)
C(9)–C(10)	1.547(2)	1.546(2)	1.540(3)	1.533(2)
C(10)–O or C(10)–N(2)	1.435(2)	1.435(2)	1.447(2)	1.472(2)
N(1)–C(3)–C(8)	118.4(2)	118.4(2)	118.6(2)	118.8(2)
C(3)–C(8)–C(9)	123.1(2)	122.5(2)	122.7(2)	122.7(2)
C(8)–C(9)–C(10)	113.9(2)	113.7(2)	112.9(2)	114.2(2)
C(9)–C(10)–O or C(9)–C(10)–N(2)	109.7(2)	109.9(2)	108.3(2)	110.8(2)
C(3)–N(1)–C	114.8(2), 112.0(2)	115.0(2), 112.6(2)	114.6(2), 112.1(2)	113.5(2), 111.9(2)
C(1)–N(1)–C(2)	109.5(2)	110.0(2)	111.3(3)	110.0(2)
C(10)–O(1)–H or C(10)–N(2)–H	108.7	106.6	114.4(2)	110.4(2)

(**6**) are characteristic for an X–CH proton (X=O, N), while a signal at 6.17 ppm (**3**) or 6.10 ppm (**5**) is indicative of an NH proton. Also, a signal for the OH proton is observed at 9.80 (**1**), 10.69 (**2**), 8.55 (**4**), 7.02 (**6**), and 10.50 ppm (**7**). A quartet at 2.61, 2.77 and a triplet at 0.92 ppm (**7**) are characteristic for NCH_2CH_3 protons. The resonances corresponding to the cyclohexyl protons are observed at 1.10–1.80 ppm (**2**) as broad peaks. The aromatic rings of each compound give rise to the characteristic proton signals in the expected range of 6.70–7.42 ppm.

The ^{13}C NMR spectra of **1**–**6** reveal signals of the $N(CH_3)_2$ carbon atoms at 45.4–47.3 ppm. Singlets at 76.5–84.6 ppm are assigned to the C–O carbon atom in **1**, **2**, **4**, **6**, and **7**. Signals for the methylene carbon atoms are observed at 45.0 (**4**), 42.0 (**5**), and 44.6 ppm (**6**), while the resonances at 56.2 (**3**), 62.1 (**5**), and 65.9 ppm (**6**) are characteristic of X–CH carbon atoms (X=O, N). The resonances at 12.5 and 49.1 ppm (**7**) are characteristic for NCH_2CH_3 carbon atoms. The resonances of the aromatic carbon atoms (111.8–154.0 ppm) and the cyclohexyl groups (27.4–47.1 ppm) are in the expected ranges.

2.3. Molecular structures of 1–7

Colorless crystals of **1**–**7** were obtained as described in the experimental section. Selected interatomic distances and angles are collected in Tables 1 and 2. The molecular structures are depicted in Figures 1–7.

The common feature of the molecular structures of **1**, **2**, **4**, **5**, **6**, and **7** is the intramolecular O(1)–H···N(1) or N(2)–H···N(1) hydrogen bond (Table 3), which results in six-membered $C_3OH\cdots N$ rings in **1**, **2**, and **7** (the atoms N(1)–C(3)–C(8)–C(9) are coplanar), and seven-membered $C_4XH\cdots N$ (X=O(1), N(2)) rings in **4**–**6** (the atoms N(1)–C(3)–C(8)–C(9)–C(10) are coplanar). No intramolecular N(2)–H···N(1) or intermolecular hydrogen bond is observed in **3**.

The intramolecular O(1)–H···N(1) hydrogen bonds of **1**, **2**, **4**, **6**, and **7** are stronger than the intramolecular N–H···O hydrogen bonds reported for $(p\text{-}CH_3C_6H_4)_2BOCH_2CH_2NH_2$ and $(C_6H_5)_2BOCH_2CH_2NH_2$ (N···O=2.982(2) or 2.896(2) Å),[18] as well as those reported for related

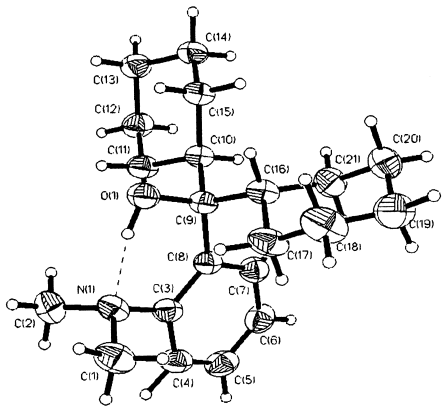


Figure 2. Molecular structure of **2**.

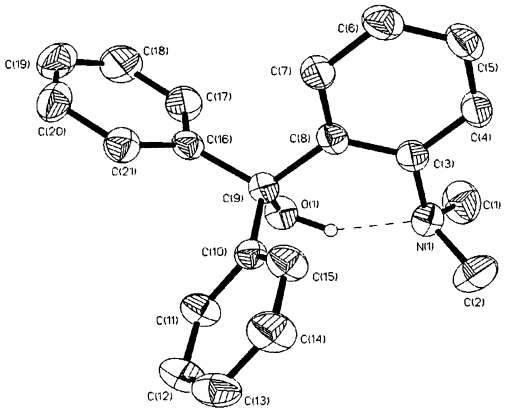


Figure 1. Molecular structure of **1**.

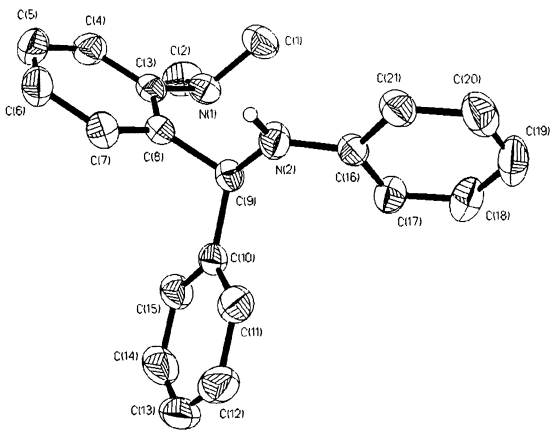
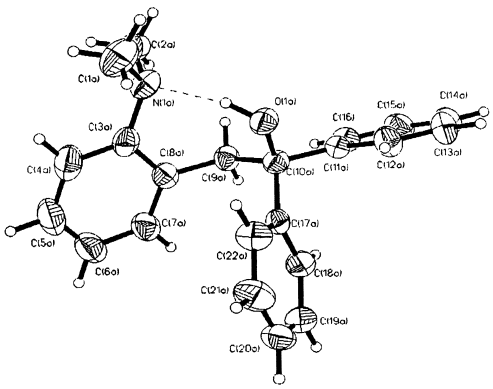


Figure 3. Molecular structure of **3**.



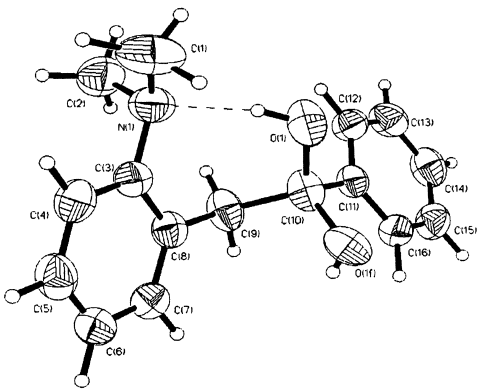


Figure 6. Molecular sturcture of **6** (disordered COH group is shown).

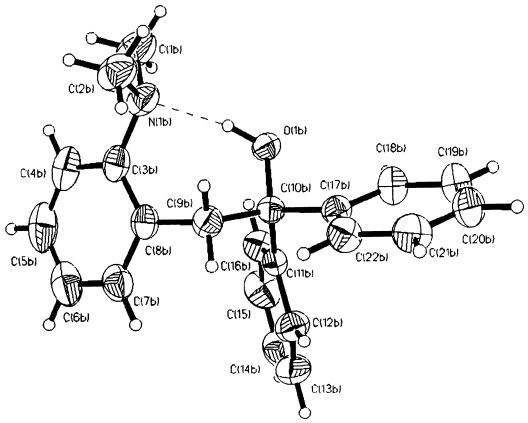


Figure 4. Molecular structure of **4a** and **4b**.

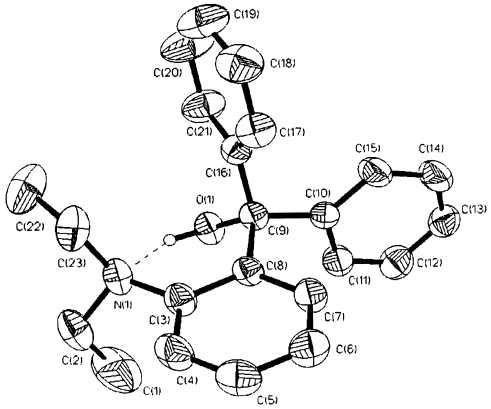


Figure 7. Molecular structure of **7**.

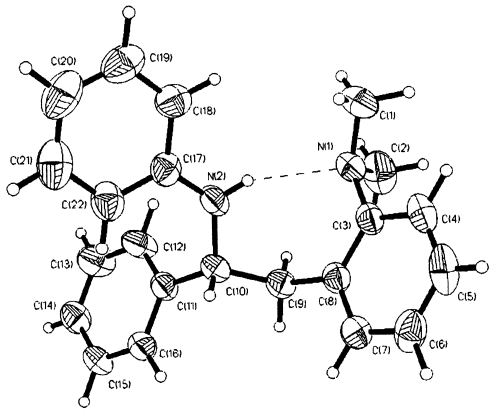


Figure 5. Molecular structure of **5**.

five- and six-membered rings (N–H···O: N···O=2.702(2)–2.752(3) Å, O–H···O: O···O=2.674(2)–2.703(3) Å, and N–H···N: N···N=3.024(4)–3.054(2) Å).[19]

The intramolecular N(2)–H···N(1) hydrogen bond of **5** is weaker than intramolecular N–H···N, N–H···O, and O–H···O hydrogen bonds reported previously.[19] Unlike compounds **1**, **2**, and **7**, in which the O–H moiety forms an intramolecular hydrogen bond with a nitrogen atom, the N(2)–H proton in **3** is not involved in any hydrogen bonding (N···N=4.134 Å). This is presumably the result of steric blocking of the N(2)–H proton by the bulky phenyl groups. The N···N distance for the N(2)–H···N(1) interaction in **5** is longer than those observed for N–H···N hydrogen bonds in monocationic compounds, which range up to 2.626 Å for linear systems[20] and comparable to the mean value of the 2.949 Å for noncationic N–H···N hydrogen bonds in crystalline organic compounds.[21] The O(1)–H···N(1)

Table 3. Hydrogen bond data for **1**, **2**, **4a**, **4b**, **5**, **6**, and **7**

	O(1)–H or N(2)–H	N(1)···H	O(1)···N(1) or N(2)···N(1)	O(1)–H···N(1) or N(2)–H···N(1)
1	0.95(2)	1.82(2)	2.659(2)	146(2)
2	0.92(2)	1.73(2)	2.591(1)	155(2)
4a	0.94[a]	1.83[a]	2.757(2)	167[a]
4b	0.94[a]	1.82[a]	2.747(2)	166[a]
5	0.84(2)	2.23(2)	3.019(2)	155(2)
6	0.89(3)	1.80(3)	2.686(6)	168(3)
7	0.91(2)	1.83(2)	2.663(2)	151(2)

[a] No standard deviation given as OH proton is in a calculated position.

hydrogen bonds in **1**, **2**, and **7** are stronger than the X–H···N(1) (X=O(1), N(2)) hydrogen bonds in **4**, **5**, and **6**, consistent with the fact that increasing the ring size from six- to seven-membered weakens the O(1)–H···N(1) hydrogen bond. Also, the O(1)–H···N(1) hydrogen bond is stronger than the N(2)–H···N(1) hydrogen bond.

The structural data of the six-membered $C_3OH\cdots N$ rings in **1**, **2**, **3** and **7** (Table 1) show the expected bond lengths and angles.[19–21] Only in **1**, **2**, and **7** the C(8)–C(9)–O(1) bond angles (109.9–112.3°) are slightly larger, and the C(9)–O(1)–H bond angles (104–107°) slightly smaller, than expected, owing to the formation of intramolecular O(1)–H···N(1) hydrogen bonds.

The structural data of compounds **4**–**6** with seven-membered $C_4XH\cdots N$ (X=O(1), N(2)) rings (Table 2) are as expected.[19,20,21] Only the C(8)–C(9)–C(10) bond angle is slightly larger (112.9–114.2°) than expected. The C(3)–C(8) distances in **1**–**7** agree with the mean literature value of 1.394 Å.[22]

The nitrogen atom N(1), which is bound to the aromatic ring, has a distorted environment with large C(1)–N(1)–C(2) (109.5–11.3°) and C(3)–N(1)–C (113.5–115.0°; 111.9–112.6°) bond angles.

Compounds **3**, **5** and **6** are obtained as racemic mixtures. The molecular structure of **6** shows disorder of the (C)–O–H and (C(10))–H groups (71.3% C–O(1)–H and 28.7% C–O(1f)–H).

3. Experimental

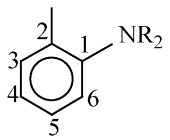
3.1. General

All experiments were carried out under purified dry nitrogen. Solvents were dried and freshly distilled under nitrogen. The NMR spectra were recorded with an AVANCE DRX 400 spectrometer (Bruker). Infrared spectra were recorded with a Perkin–Elmer System 2000 FT-IR spectrometer between 4000 and 400 cm^{-1} using KBr disks. Elemental analyses were determined with a VARIO EL (Heraeus). Melting points (Gallenkamp) are uncorrected. Mass spectra were recorded with a MAT-8230 (EI-MS, 70 eV). Crystallographic data were collected with a Siemens CCD (SMART) diffractometer. All observed reflections were used for determination of the unit cell parameters. Empirical absorption correction with SADABS.[23] The structures were solved by direct methods (SHELXTL PLUS).[24] H atoms were located by difference maps and refined isotropically. Details concerning the crystal structure determination are given in Table 4.

3.1.1. (2-Dimethylaminophenyl)diphenylmethanol (1). A dry 250 ml two-necked flask was filled with 10 g (0.082 mol) of *N*,*N*-dimethylaniline, 120 ml of anhydrous diethyl ether and 12.37 ml of tmeda and the solution was stirred under nitrogen atmosphere. 60 ml of a 1.5 M solution of *n*-butyllithium in hexane was added at −78 °C. The solution was allowed to warm to room temperature, stirred for 2 h and refluxed for 2 h. Then a solution of 14.9 g (0.082 mol) of benzophenone in 40 ml of anhydrous diethyl ether was added dropwise to the reaction mixture and with stirring over 30 min. The resulting deep green solution was stirred for an additional 0.5 h and then poured into a vigorously stirred solution of 13 g (0.22 mol) glacial acetic acid in 40 ml of diethyl ether. The solution was stirred overnight at room temperature. Then the solution was successively extracted with 50 ml of distilled water and with five 50 ml portions of aqueous 5% hydrochloric acid. The aqueous extracts were combined and made alkaline with aqueous 10% sodium hydroxide.

The alkaline aqueous mixture was heated to boiling and maintained at this temperature until the escaping vapor was no longer basic to moistened pH paper. The mixture was then cooled, and the white solid product which separated was collected on a Buchner funnel and washed with three 20 ml portions of water. The crude product was recrystallized from hexane/ethyl acetate solution at 20 °C to give the product as colorless crystals in 70% yield. Mp 177–178 °C. ^1H NMR ($CDCl_3$, δ/ppm): 2.38 (s, 6H, $N(CH_3)_2$), 6.70–7.38 (m, 14H, C_6H_4 and C_6H_5), 9.80 (s, 1H, OH). ^{13}C NMR ($CDCl_3$, δ/ppm): 46.3 (s, $N(CH_3)_2$), 83.6 (s, C–O), 124.2 (s, C6 in C_6H_4), 125.8 (s, C4 in C_6H_4), 126.4 (s, C3 in C_6H_4), 127.5 (s, C5 in C_6H_4), 128.3 (s, *p*-C in C_6H_5), 128.9 (s, *o*-C in C_6H_5), 131.1 (s, *m*-C in C_6H_5), 143.7 (s, C2 in C_6H_4), 148.3 (s, C1 in C_6H_4), 152.8 (s, *ipso*-C in C_6H_5). IR (KBr): 3423–2800 br., 1989 w, 1600 w, 1597 w, 1546 vs, 1392 vs, 1313 s, 1267 vs, 1205 s, 1166 s, 1154 vs, 1078 vs, 1051 vs, 1010 vs, 986 s, 969 s, 962 vs, 907 vs, 876 vs, 848 s, 771 s, 703 s, 587 s, 524 m, 516 m, 496 s, 442 m, 414 m cm^{-1}. MS: *m*/*z* 302.9 (68%, M^+), 225.9 (65%, M^+-Ph), 209.8 (94%, $M^+-Ph-OH$), 193.8 (20%, $M^+-Ph-OH-CH_3$), 164.9 (30%, $M^+-Ph-OH-N(CH_3)_2$), 90.9 (100%, $C_7H_7^+$), 76.9 (86%, $C_6H_5^+$), 50.9 (20%, $C_4H_3^+$). Found: C 84.0; H 7.65; N 4.37%. Calcd for $C_{21}H_{21}NO$: C 83.13; H 6.98; N 4.62%.

Phenyl ring numbering scheme:



3.1.2. (2-Dimethylaminophenyl)dicyclohexylmethanol (2). The reaction was carried out by the same procedure as described for **1**, except that 16.0 g (0.082 mol) of dicyclohexyl ketone was used instead of benzophenone, and that the colorless crystals were obtained from a saturated hexane/benzene solution (5:1) at 0 °C in 70% yield. Mp 160–165 °C. ^1H NMR ($CDCl_3$, δ/ppm): 1.10–1.80 (br., 22H, C_6H_{11}), 2.65 (s, 6H, $N(CH_3)_2$), 7.10–7.32 (m, 4H, C_6H_4), 10.69 (s, 1H, OH). ^{13}C NMR ($CDCl_3$, δ/ppm): 27.4 (s, C4 in C_6H_{11}), 27.5 (s, C3/C5 in C_6H_{11}), 28.6 (s, C2/C6 in C_6H_{11}), 47.1 (s, C1 in C_6H_{11}), 47.3 (s, $N(CH_3)_2$), 84.6 (s, C–O), 123.7 (s, C6 in C_6H_4), 126.0 (s, C4 in C_6H_4), 127.6 (s, C3 in C_6H_4), 128.6 (s, C5 in C_6H_4), 139.3 (s, C2 in C_6H_4), 154.0 (s, C1 in C_6H_4). IR (KBr): 2930 vs, 2850 vs, 2788 s, 1919 w, 1703 w, 1601 s, 1574 w, 1451 s, 1335 w, 1263 w, 1187 s, 1145 s, 1101 s, 1043 s, 993 s, 932 s, 851 w, 892 s, 827 s, 759 s, 716 s, 565 s, 517 m, 483 w cm^{-1}. MS: *m*/*z* 314.9 (6%, M^+), 298.0 (10%, M^+-OH), 232.8

Table 4. Crystal data and structure refinement for **1**–**7**

	1	2	3	4	5	6	7
Formula	$C_{21}H_{21}NO$	$C_{21}H_{33}NO$	$C_{21}H_{22}N_2$	$C_{22}H_{23}NO$	$C_{22}H_{24}N_2$	$C_{16}H_{19}NO$	$C_{23}H_{25}NO$
M_r	303.39	315.48	302.41	317.41	316.43	240.31	331.44
Temp (K)	213(2)	218(2)	223(2)	223(2)	213(2)	223(2)	213(2)
Crystal system	Monoclinic	Triclinic	Monoclinic	Orthorhombic	Monoclinic	Orthorhombic	Orthorhombic
Space group	$P2_1/n$	$P\bar{1}$	$C2/c$	$Pca2_1$	Cc	$Pbca$	$Pbca$
a (Å)	8.856(2)	9.929(1)	26.774(3)	17.765(1)	14.220(2)	14.916(1)	8.532(1)
b (Å)	12.538(3)	10.330(1)	9.3063(9)	5.9999(3)	13.679(2)	8.1647(8)	16.361(2)
c (Å)	15.556(3)	10.926(1)	18.661(2)	33.712(2)	11.553(2)	22.681(2)	27.735(4)
α (°)	90	101.609(2)	90	90	90	90	90
β (°)	100.77(3)	101.094(2)	132.950(1)	90	125.227(2)	90	90
γ (°)	90	114.919(2)	90	90	90	90	90
V (Å^3)	1696.8(6)	945.9(2)	3403.3(6)	3593.3(3)	1835.7(5)	2762.2(5)	3871.5(9)
Z	4	2	8	8	4	8	8
ρ_{calcd} (mg m^{-3})	1.188	1.108	1.180	1.173	1.145	1.156	1.137
$F(000)$	648	348	1296	1360	680	1032	1424
Abs coeff (mm^{-1})	0.072	0.066	0.069	0.071	0.067	0.072	0.069
No. of rflns coll.	10063	6226	11103	19386	5639	16472	23266
No. of indep rflns	2647	4293	4202	7338	3004	3439	4614
R_{int}	0.0489	0.0158	0.0291	0.0232	0.0217	0.0385	0.0292
No. of params	209	341	296	433	313	249	326
$R1$ ($I>2\sigma(I)$)	0.0431	0.0434	0.0384	0.0375	0.0349	0.0512	0.0467
$wR2$ (all data)	0.0925	0.1420	0.0893	0.0994	0.0821	0.1480	0.1279
$(\Delta/\rho)_{min}$ (e Å^{-3})	0.225	0.210	0.160	0.162	0.108	0.242	0.210
$(\Delta/\rho)_{max}$ (e Å^{-3})	−0.185	−0.184	−0.164	−0.152	−0.136	−0.140	−0.181
CCDC depos. no.	190705	190712	190708	190707	190711	190709	190710

(100%, M^+-Cy), 214.7 (15%, $M^+-Cy-OH$), 148.0 (8%, M^+-2Cy), 132.4 (30%, $M^+-2Cy-OH$), 83.4 (10%, Cy^+), 54.9 (15%, $C_4H_7^+$). Found: C 80.10; H 12.40; N 4.17%. Calcd for $C_{21}H_{33}NO$: C 79.95; H 10.54; N 4.44%.

3.1.3. 2-(Phenylamino-phenyl)methyl-dimethylamino-benzene (3). The reaction was carried out by the same procedure as described for **1**, except that 14.9 g (0.082 mol) of *N*-benzylidenaniline was used instead of benzophenone, and that the colorless crystals were obtained from toluene/hexane solution (1:3) at 20 °C in 65% yield. Mp 133–135 °C. ^{1}H NMR ($CDCl_3$, δ/ppm): 2.61 (s, 6H, $N(CH_3)_2$), 4.39 (s, 1H, CH), 6.17 (s, 1H, NH), 6.54–7.36 (m, 14, C_6H_4 and C_6H_5). ^{13}C NMR ($CDCl_3$, δ/ppm): 45.5 (s, $N(CH_3)_2$), 56.2 (s, CH), 113.1 (s, C6 in C_6H_4), 117.2 (s, C4 in C_6H_4), 121.4 (s, C3 in C_6H_4), 124.3 (s, C5 in C_6H_4), 126.7 (s, *p*-C in C_6H_5), 129.1 (s, *o*-C in C_6H_5), 138.9 (s, *m*-C in C_6H_5), 144.1 (s, C2 in C_6H_4), 147.6 (s, C1 in C_6H_4), 152.4 (s, *ipso*-C in C_6H_5). IR (KBr): 3315 vs, 3100 m, 3080 m, 3000 s, 2920 m, 2900 m, 2840 s, 2820 m, 2785 vs, 1950 w, 1601 vs, 1583 vs, 1506 vs, 1448 vs, 1429 vs, 1351 s, 1314 vs, 1300 vs, 1266 s, 1183 vs, 1154 vs, 1047 s, 1027 m, 945 vs, 888 s, 840 vs, 744 vs, 730 vs, 695 vs, 585 m, 509 m cm^{-1}. MS: *m*/*z* 302.4 (50%, M^+), 286.9 (10%, M^+-NH), 209.9 (100%, $M^+-Ph-NH$), 193.9 (25%, $M^+-Ph-NH-CH_3$), 179.9 (8%, $M^+-Ph-NH-2CH_3$), 90.9 (64%, $C_7H_7^+$), 76.9 (25%, $C_6H_5^+$), 50.9 (8%, $C_4H_3^+$). Found: C 83.60; H 7.29; N 9.48%. Calcd for $C_{21}H_{22}N_2$: C 83.40; H 7.33; N 9.26%.

3.1.4. 2-(2-Dimethylaminophenyl)-1,1′-diphenylethanol (4). Compound **4** was prepared as described in the literature.[10] The crude product was recrystallized from hexane/ethyl acetate (4:1) solution at 20 °C to give the product as colorless crystals in 70% yield. Mp 151–153 °C (lit. 153–155 °C, from benzene/hexane).[10] ^{1}H NMR ($CDCl_3$, δ/ppm): 2.74 (s, 6H, $N(CH_3)_2$), 3.74 (s, 2H, CH_2), 6.49–7.40 (m, 14H, C_6H_4 and C_6H_5), 8.55 (s, 1H, OH). ^{13}C NMR ($CDCl_3$, δ/ppm): 45.0 (s, CH_2), 45.4 (s, $N(CH_3)_2$), 78.6 (s, C–O), 120.0 (s, C6 in C_6H_4), 125.0 (s, C4 in C_6H_4), 126.2 (s, C3 in C_6H_4), 126.3 (s, C5 in C_6H_4), 128.4 (s, *p*-C in C_6H_5), 128.5 (s, *o*-C in C_6H_5), 133.2 (s, *m*-C in C_6H_5), 133.5 (s, C2 in C_6H_4), 147.9 (s, C1 in C_6H_4), 151.8 (s, *ipso*-C in C_6H_5). IR (KBr): 3428 br., 3083 s, 3054 s, 3021 s, 2994 m, 2946 m, 2931 m, 2861 s, 2831 vs, 2801 s, 2784 s, 1948 w, 1597 w, 1580 vs, 1492 vs, 1474 s, 1460 s, 1446 vs, 1230 m, 1180 s, 1105 s, 1058 s, 1038 m, 955 s, 937 s, 862 s, 845 w, 786 s, 767 vs, 757 vs, 701 vs, 647 m, 608 s, 534 m cm^{-1}. MS: *m*/*z* 316.8 (8%, M^+), 299.8 (5%, M^+-OH), 239.8 (9%, M^+-Ph), 134.9 (100%, $M^+-2Ph-2CH_3$), 90.9 (15%, $C_7H_7^+$), 76.9 (25%, $C_6H_5^+$), 50.9 (6%, $C_4H_3^+$). Found: C 83.10; H 7.10; N 4.71%. Calcd for $C_{22}H_{23}NO$: C 83.24; H 7.30; N 4.41%.

3.1.5. 2-(2-Phenylamino-2-phenyl)ethyl-dimethylamino-benzene (5). The reaction was carried out by the same procedure as described for **3**, except that 11.1 g (0.082 mol) of *N*,*N*-dimethyl-*o*-toluidine was used instead of *N*,*N*-dimethylaniline, and that the colorless crystals were obtained from toluene at 20 °C in 60% yield. Mp 145–150 °C. ^{1}H NMR ($CDCl_3$, δ/ppm): 2.78 (s, 6H, $N(CH_3)_2$), 3.20 (t, $^3J_{H-H}$=12 Hz, 1H, CH), 2.93 (d, $^3J_{H-H}$=12 Hz, 1H, CH_2), 4.32 (d, $^3J_{H-H}$=12 Hz, 1H, CH_2), 6.10 (s, 1H, NH), 6.20–7.42 (m, 14H, C_6H_4 and C_6H_5). ^{13}C NMR ($CDCl_3$, δ/ppm): 42.0 (s, CH_2), 46.1 (s, $N(CH_3)_2$), 62.1 (s, CH), 113.5 (s, C6 in C_6H_4), 116.8 (s, C4 in C_6H_4), 120.6 (s, C3 in C_6H_4), 125.2 (s, C5 in C_6H_4), 127.5 (s, *p*-C in C_6H_5), 129.6 (s, *o*-C in C_6H_5), 135.2 (s, *m*-C in C_6H_5), 145.2 (s, C2 in C_6H_4), 148.6 (s, C1 in C_6H_4), 153.5 (s, *ipso*-C in C_6H_5). IR (KBr): 3290 vs, 3105 m, 3082 m, 2996 s, 2980 m, 2944 m, 2880 s, 2825 m, 2785 vs, 1960 w, 1600 vs, 1523 vs, 1490 vs, 1450 vs, 1435 vs, 1351 s, 1324 vs, 1293 vs, 1277 s, 1179 vs, 1154 vs, 1041 s, 1028 m, 940 vs, 845 vs, 774 s, 758 vs, 748 vs, 693 vs, 546 m, 527 m cm^{-1}. MS: *m*/*z* 316.0 (11%, M^+), 223.9 (5%, $M^+-Ph-NH$), 207.9 (5%, $M^+-Ph-NH-CH_3$),

192.9 (8%, $M^+-Ph-NH-2CH_3$), 180.9 (100%, $M^+-Ph-NH-NMe_2$), 90.9 (20%, $C_7H_7^+$), 76.9 (38%, $C_6H_5^+$), 50.9 (18%, $C_4H_3^+$). Found: C, 82.60; H, 8.13; N, 8.62%. Calcd for $C_{22}H_{24}N_2$: C, 83.50; H, 7.64; N, 8.85%.

3.1.6. 2-(2-Dimethylaminophenyl)-1-phenylethanol (6). The reaction was carried out by the same procedure as described for **4**, except that 8.7 g (0.082 mol) of benzaldehyde instead of benzophenone was used and that the colorless crystals were obtained from toluene at 25 °C in 70% yield. Mp 152–157 °C. ^{1}H NMR ($CDCl_3$, δ/ppm): 2.78 (s, 6H, $N(CH_3)_2$), 3.21 (t, $^3J_{H-H}$=12 Hz, 1H, CH), 3.10 (d, $^3J_{H-H}$=12 Hz, 1H, CH_2), 4.94 (d, $^3J_{H-H}$=12 Hz, 1H, CH_2), 7.02 (s, 1H, OH), 7.24–7.39 (m, 9H, C_6H_4 and C_6H_5). ^{13}C NMR ($CDCl_3$, δ/ppm): 44.6 (s, CH_2), 45.6 (s, $N(CH_3)_2$), 65.9 (s, CH), 76.5 (s, C–O), 120.8 (s, C6 in C_6H_4), 126.0 (s, C4 in C_6H_4), 126.3 (s, C3 in C_6H_4), 127.6 (s, C5 in C_6H_4), 128.6 (s, *p*-C in C_6H_5), 129.2 (s, *o*-C in C_6H_5), 132.7 (s, *m*-C in C_6H_5), 135.6 (s, C2 in C_6H_4), 146.1 (s, C1 in C_6H_4), 152.6 (s, *ipso*-C in C_6H_5). IR (KBr): 3366 br., 3060 w, 2940 m, 2859 m, 2829 m, 2786 s, 1951 w, 1597 s, 1580 vs, 1492 vs, 1451 vs, 1293 vs, 1267 vs, 1156 vs, 1100 vs, 1057 vs, 1005 vs, 939 s, 863 vs, 845 w, 759 vs, 699 vs, 635 s cm^{-1}. MS: *m*/*z* 241.3 (18%, M^+), 164.9 (5%, M^+-Ph), 134.0 (100%, $M^+-Ph-2CH_3$), 118.0 (22%, $M^+-Ph-NMe_2$), 90.9 (20%, $C_7H_7^+$), 76.9 (15%, $C_6H_5^+$), 50.9 (8%, $C_4H_3^+$). Found: C 79.30; H 8.09; N 6.48%. Calcd for $C_{16}H_{19}NO$: C 79.62; H 7.87; N 5.81%.

3.1.7. (2-Diethylaminophenyl)diphenylmethanol (7). The reaction was carried out by the same procedure as described for **1**, except that 12.5 g (0.082 mol) of *N*,*N*-diethylaniline was used instead of *N*,*N*-dimethylaniline and that the colorless crystals were obtained from diethyl ether at −10 °C in 20% yield. Mp 165–170 °C. ^{1}H NMR ($CDCl_3$, δ/ppm): 0.92 (t, $^3J_{H-H}$=8 Hz, 6H, $N(CH_2CH_3)_2$), 2.61 (q, $^3J_{H-H}$=8 Hz, 2H, $N(CH_2CH_3)_2$), 2.77 (q, $^3J_{H-H}$=8 Hz, 2H, $N(CH_2CH_3)_2$), 6.75–7.29 (m, 14H, C_6H_4 and C_6H_5), 10.50 (s, 1H, OH). ^{13}C NMR ($CDCl_3$, δ/ppm): 12.5 (s, $N(CH_2CH_3)_2$), 49.1 (s, $N(CH_2CH_3)_2$), 83.3 (s, C–O), 111.8 (s, C6 in C_6H_4), 115.4 (s, C4 in C_6H_4), 124.4 (s, C3 in C_6H_4), 124.9 (s, C5 in C_6H_4), 126.8 (s, *p*-C in C_6H_5), 128.3 (s, *o*-C in C_6H_5), 132.1 (s, *m*-C in C_6H_5), 144.7 (s, C2 in C_6H_4), 146.0 (s, C1 in C_6H_4), 148.1 (s, *ipso*-C in C_6H_5). IR (KBr): 3060–2845 br., 1951 w, 1596 s, 1567 w, 1427 vs, 1385 vs, 1361 s, 1295 s, 1218 s, 1161 vs, 1115 vs, 1102 s, 1027 vs, 938 s, 833 vs, 759 vs, 699 vs, 636 vs, 596 s, 564 m, 523 m, 490 m, 452 m cm^{-1}. MS: *m*/*z* 331.3 (34%, M^+), 316.2 (15%, M^+-CH_3), 298.2 (5%, M^+-CH_3-OH), 254.2 (45%, M^+-Ph), 238.1 (47%, $M^+-Ph-CH_3$), 210.2 (15%, $M^+-Ph-CH_3-Et$), 165.0 (13%, $M^+-Ph-OH-N(CH_2CH_3)_2$), 76.9 (64%, $C_6H_5^+$), 50.9 (20%, $C_4H_3^+$). Found: C, 82.40; H, 7.54; N, 3.99%. Calcd for $C_{23}H_{25}NO$: C, 83.34; H, 7.60; N, 4.23%.

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The absolute stereochemistry of grenadamide

Juma'a R. Al Dulayymi, Mark S. Baird* and Keith Jones

Department of Chemistry, University of Wales, Bangor, Gwynedd Wales LL57 2UW, UK

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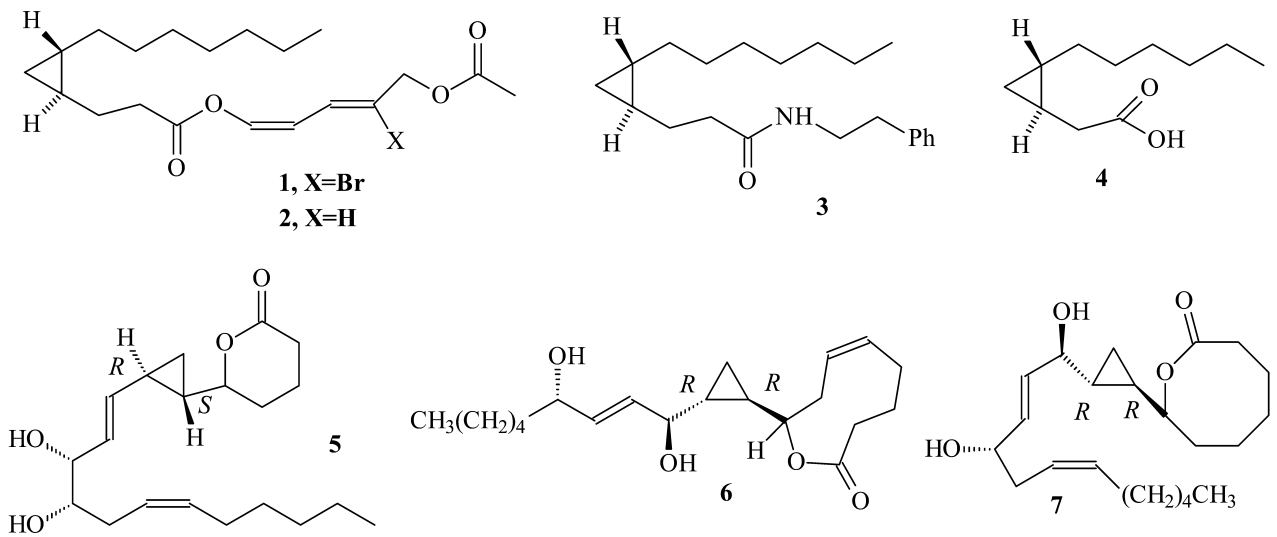
Abstract—3-(2*S*-Heptylcycloprop-1*S*-yl)propanoic acid 2-phenylethanamide was synthesised from *cis*-cyclopropan-1,2-dimethanol via enzymatic desymmetrisation of the dibutyrate; it gave identical NMR spectroscopic data to those reported for grenadamide but had an equal and opposite absolute rotation, indicating that the latter is the 2*R*,1*R*-enantiomer.

Sitachitta and Gerwick have reported the isolation of three cyclopropane containing metabolites, grenadadiene (**1**), debromogrenadadiene (**2**) and grenadamide (**3**) from the organic extracts of the marine cyanobacterium *Lyngyba majuscule*, and established their *trans*-cyclopropane relative stereochemistry (Scheme 1).[1] Although the racemic esters (**1**) and (**2**) have been synthesised,[2] there appears to be no information concerning the absolute stereochemistry of these three molecules. Related simple *trans*-cyclopropane fatty acids have been isolated from other species, such as cascarillic acid (**4**) from cascarilla bark, again of unreported absolute stereochemistry.[3] More complex derivatives such as the costanolactones are of known stereochemistry, as shown for costanolactone E (**5**).[4] The reverse absolute stereochemistry of the cyclopropane is reported for the acid and alkyl derived side chains of related halicholactones such as (**6**),[5] and in solandelactones such as (**7**).[6]

The related *cis*-cyclopropane fatty acids, lactobacillic acid (**8**)[7] is reported to have the 9*R*,10*S*-configuration. On the other hand, cepaciamide, a derivative of the acid (**9**),[8] the corresponding hydroxy acid chain of plakoside A,[9] and a derivative of the acid (**10**) isolated from the slime mould *Pyhysarum polycephalum*,[10] all have *S,R*-configuration of fatty acid and alkyl chains respectively (Scheme 2). A number of other natural *cis*-cyclopropane fatty acids are of unknown absolute stereochemistry.[11]



Scheme 1.

Keywords: Grenadamide; Stereochemistry; Synthesis.
* Corresponding author. Tel.: +44-124-838-2374; fax: +44-124-837-0528; e-mail address: chs028@bangor.ac.uk

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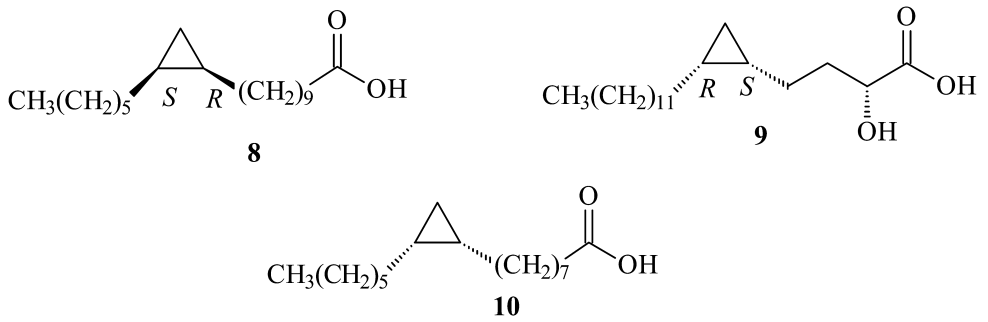


Scheme 2.

As part of a study designed to complete the assignment of absolute stereochemistry to the full range of natural cyclopropane fatty acids, we now establish the absolute stereochemistry of granadamide through the synthesis of its enantiomer.

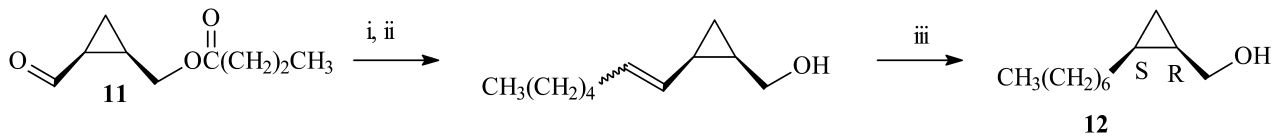
The alcohol (**12**) was prepared from aldehyde (**11**)[7c,12] (Scheme 3), following a procedure applied to a lower homologue,[7c] and closely related to that developed by Grandjean et al.[12] The aldehyde was obtained as before by selective enzymatic hydrolysis of *cis*-cyclopropane-1,2-dimethanol di-*n*-butyrate to (2*R*-*n*-butyryloxymethyl-cycloprop-1*S*-yl)methanol, followed by oxidation and gave an optical rotation consistent with an ee of >95% as established through the use of chiral lanthanide shift reagents,[12] and the formation of diastereomeric esters in earlier work.[7c]

Oxidation to (**13**) and epimerisation using sodium methoxide in methanol,[13] gave a 19:1 mixture of (**14**) and (**13**); reaction of the mixture with ethoxycarbonyl triphenylphosphorane in toluene gave after chromatography the *trans*-ester (**15**). The double bond was removed by reaction with di-potassium azodicarboxylate and ethanoic acid in methanol at room temperature to give the ester (**16**).[14] This was hydrolysed, converted into the corresponding acid chloride and treated with 2-phenylethylamine to give the amide (**18**) (Scheme 4).

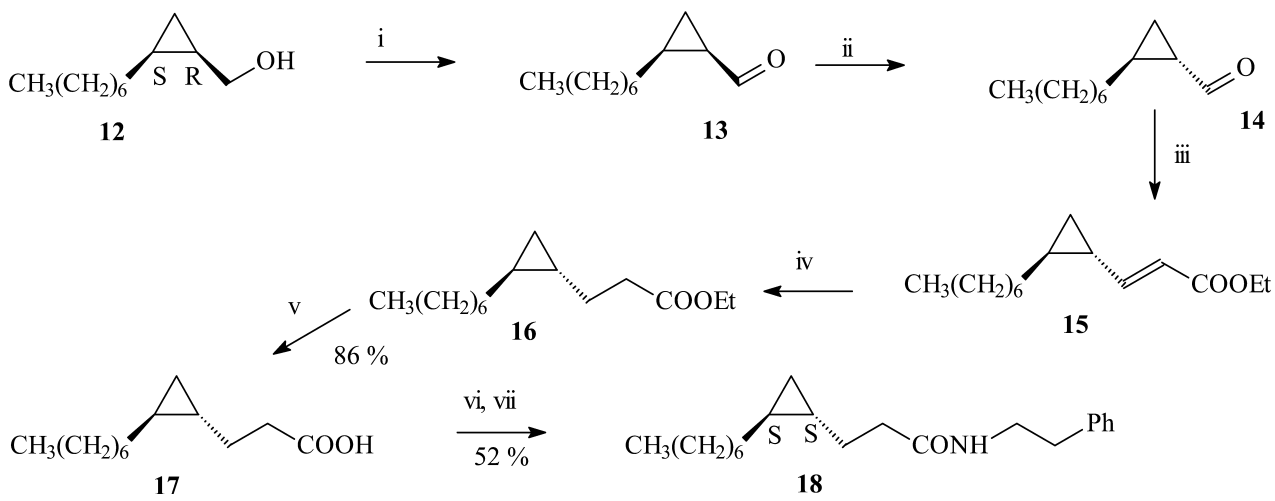
The amide gave a ^{1}H NMR spectrum that was identical to that reported for granadamide;[1] however, its $[\alpha_D]^{22}$ was+12.6 (*c* 0.84, $CHCl_3$) whereas, that for the natural product is reported to be −11.0 (*c* 0.1, $CHCl_3$).[1] The natural material is therefore characterised as the *R*,*R*-enantiomer (**19**) (Scheme 5).[15]

1. Experimental

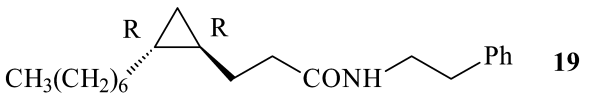
Ether and tetrahydrofuran were dried over sodium wire. Petroleum ether was of boiling point 40–60 °C. Reactions which had to be carried under inert conditions, were carried out under a slow stream of dry nitrogen. Silica (Merck 7736 silica gel) and silica plates used for thin layer and column



Scheme 3. (i) $BrPh_3P(CH_2)_5CH_3$, *n*BuLi, THF, −78 °C (55%; *Z*:*E* 4.6:1); (ii) k_2CO_3, MeOH (86%); (iii) aq. $CuSO_4$, hydrazine hydrate, $NaIO_4$, iPrOH, AcOH (86%).



Scheme 4. (i) PCC, CH_2Cl_2 (91%); (ii) NaOMe, MeOH, reflux, 48 h (84%; 19:1 *trans*:*cis*); (iii) $Ph_3PCHCOOEt$, toluene (71%); (iv) $KO_2CN{=}NCO_2K$, AcOH, MeOH, rt, 48 h (83%); (v) KOH, EtOH, water, rt (86%); (vi) $SOCl_2$; (vii) $PhCH_2CH_2NH_2$ (52%).



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Scheme 5.

chromatography were obtained from Aldrich. GLC was carried out on the Perkin–Elmer Model 8410 on a capillary column (15 m×0.53 mm). Unless otherwise stated products were one spot on TLC or one peak on GLC. IR spectra were carried out on the Perkin–Elmer 1600 FTIR spectrometer as liquid films. NMR spectra were recorded in $CDCl_3$ on the Bruker AC250 at a frequency of 250 MHz for protons. $[\alpha]_D$ values were recorded in $CHCl_3$ on the POLAAR 2001 Optical Activity polarimeter. (1*S*,2*R*)-2-*n*-butyryloxymethyl-1-formylcyclopropane $[\alpha]_D^{22}$+61.1 (*c* 1.42, $CHCl_3$) [lit. $[\alpha]_D^{22}$+59.8 (*c* 2.68, CH_2Cl_2), corresponding to >95% ee],[12]was prepared as described earlier and gave identical ^1H and ^{13}C NMR and IR spectra to those reported.[7c,12]

1.1. (1*R*,2*S*)-2-(Heptylcycloprop-1-yl)methanol (12)

n-Butyl lithium (27.5 mL, 44 mmol, 1.6 M, in hexane) was added dropwise to a suspension of 1-hexyl-triphenylphosphonium bromide (16.4 g, 38 mmol, 1.3 mol.eq.) in dry THF (120 mL) at −78 °C under nitrogen. The reaction was allowed to reach room temperature for 1 h when a deep orange colour appeared, then cooled again to −78 °C when (1*S*,2*R*)-2-butyryloxymethyl-1-formylcyclopropane (5 g, 0.03 mol) in dry THF (10 mL) was added slowly by syringe. The reaction was stirred overnight at room temperature, then quenched with sat.aq. ammonium chloride (50 mL) and extracted with ether (3×100 mL). The combined organic layers were washed with water (50 mL), dried and evaporated to give a residue which was stirred with petroleum/ether (50 mL) for 10 min. The resulting precipitate was filtered off and the filtrate was evaporated to give an oil. Chromatography on silica eluting with petrol/ether (5:1) gave a colourless oil, *(1R,2R)-1-butyryloxymethyl-2-[Z/E-hept-1-en-1-yl]cyclopropane* (3.65 g, 55%) as a mixture of two isomers in ratio 4.6:1; (major *Z*-isomer) [Found M^+: 238.1923, $C_{15}H_{26}O_2$ requires: 238.1933]; δ_H: 5.45 (1H, dtd, *J*=0.9, 7.0, 11.5 Hz), 5.03 (1H, br.dd, *J*=9.1, 11.5 Hz), 4.15 (1H, dd, *J*=7.0, 11.6 Hz), 3.9 (1H, dd, *J*=8.0, 11.6 Hz), 2.27 (2H, t, *J*=7.3 Hz), 2.21 (2H, br.m), 1.8–1.5 (3H, m, including a pentet, *J* ca. 7 Hz), 1.4–1.2 (7H, m), 1.05 (1H, dt, *J*=4.8, 8.5 Hz), 0.95–0.8 (6H, m, including a triplet, *J* ca. 7 Hz), 0.38 (1H, br.q, *J*=5.8); δ_H (minor E-isomer): 5.58 (1H, m), 5.2 (1H, br.d, *J* ca. 15 Hz), the remaining signals were obscured by the major isomer, IR (film) 2960, 2930, 1736 cm^{-1}. Anhydrous potassium carbonate (2.4 g, 0.017 mol) was added to a stirred solution of the cyclopropane (4.13 g, 0.16 mol) in methanol (30 mL). After 4 h, TLC showed no starting material remained. The K_2CO_3 was then filtered and washed with ether (2×20 mL). The filtrate was evaporated to give a yellow oil, (1*R*, 2*R*)-2-((Z/E-hept-1-en-1-yl)-1-cycloprop-1-yl)methanol (2.5 g, 86%). This was used for the next stage without purification.

To the crude product (2.5 g, 0.015 mol) in isopropyl alcohol (100 mL) was added sat.aq. $CuSO_4$ (2 mL), acetic acid (2 mL) and hydrazine hydrate (20 mL), and the mixture was heated to 56 °C. Sodium periodate (31.8 g, 0.15 mol) in hot water (100 mL) was added dropwise over 1.5 h. The mixture was stirred for 2 h, allowed to reach room temperature, then diluted with ether (150 mL). The organic layer was separated and the aqueous layer extracted with ether (2×50 mL). The combined organic layers were dried ($MgSO_4$) and evaporated. Chromatography on silica eluting with petrol/ether (5:2) gave *(1R, 2S)-(2-heptylcycloprop-1-yl)methanol* (2.2 g, 86%) (**12**) as a colourless oil [Found M^+-H_2O:152.1581, $C_{11}H_{20}$ requires: 152.1565], $[\alpha]_D^{25}$+23.6 (*c* 1.14, $CHCl_3$); δ_H: 3.65 (1H, dd, *J*=7.9, 11.3 Hz), 3.55 (1H, dd, *J*=11.3, 7.9 Hz), 1.8 (1H, br.s), 1.5–1.2 (13H, m), 1.1 (1H, m), 0.87 (3H, t, *J*=7.3 Hz), 0.7 (1H, dt, *J*=4.2, 8.2 Hz), −0.03 (1H, br.q, *J*=5.2 Hz); δ_C: 64.8, 33.4, 31.7, 31.1, 30.8, 30.0, 24.1, 19.6, 17.6, 15.6, 10.9; IR (film) 3430 cm^{-1}.

1.2. *cis*-(1*R*,2*S*)-2-Heptyl-1-formylcyclopropane (13)

(1*R*,2*S*)-2-Heptylcycloprop-1-ylmethanol (2 g, 0.012 mol) in dichloromethane (10 mL) was added to a stirred suspension of PCC (5.1 g, 0.023 mol) in dichloromethane (100 mL) at room temperature. The reaction was stirred for 2 h, when a black precipitate had formed. The mixture was poured into ether (100 mL) and filtered on a bed of celite with silica gel and washed with ether. This was then evaporated to yield the crude product as a yellow oil. Chromatography on silica eluting with petrol/ether (5:2), gave *cis-(1R,2S)-2-heptyl-1-formylcyclo-propane* (**13**) (1.8 g, 91%) as a colourless oil [Found M^+:168.1539, $C_{11}H_{20}O$ requires: 168.1514], $[\alpha]_D^{24}$+14.7 (*c* 0.95, $CHCl_3$); δ_H: 9.34 (1H, d, *J*=5.5 Hz), 1.87 (1H, m), 1.7–1.1 (15H, m), 0.88 (3H, t, *J*=7 Hz); δ_C: 203.3, 33.3, 31.5, 30.6, 29.7, 29.3, 26.3, 24.1, 16.2, 15.6; IR (film) 2925, 2855, 1705 cm^{-1}.

1.3. *trans*-(1*R*,2*S*)-2-Heptyl-1-formylcyclopropane (14)

cis-(1*R*,2*S*)-2-Heptyl-1-formylcyclopropane (1.7 g, 0.01 mol) was to added to a stirred solution of sodium methoxide (0.6 g, 0.011 mol) in methanol (130 mL) and refluxed for 48 h. The mixture was quenched with sat.aq. ammonium chloride (20 mL), and extracted with ether (2×50 mL). The combined organic layers were dried and evaporated to yield a yellow oil. Chromatography on silica gel eluting with petrol/ether (5:1) gave *(1R,2S)-2-heptyl-1-formylcyclopropane* (**14**) as a colourless oil containing ca. 5% of the *cis*-isomer (1.43 g, 84%) [Found M^+: 168.1510, $C_{11}H_{20}O$ requires: 168.1514], $[\alpha]_D^{22}$+41.4 (*c* 1.45, $CHCl_3$); δ_H: 9.00 (1H, d, *J*=5.5 Hz), 1.61 (1H, m), 1.51–1.22 (14H, m), 0.97–0.86 (4H, m, including 3H, t, *J*=7 Hz at 0.88); δ_C: 202.5, 34.1, 33.3, 32.0, 30.7, 30.6, 24.2, 24.1, 16.3, 15.5; IR (film) 2925, 2855, 1709 cm^{-1}.

1.4. (*E*)-3-((1*S*,2*S*)-2-Heptylcycloprop-1-yl)acrylic acid ethyl ester (15)

The above *trans*-(1*R*,2*S*)-2-heptyl-1-formylcyclopropane (0.43 g, 0.0025 mol) in toluene (2 mL) was added to a stirred solution of (ethoxycarbonylmethylene)triphenyl phosphorane (1.13 g, 0.0032 mol) in toluene (10 mL) and stirred at room temperature for 24 h. The toluene was rotary evaporated, and the residue was treated with petrol/ether (5:2) (30 mL) and refluxed for 10 min. The solid residual phosphonium oxide was filtered off and washed with

petrol/ether (2×15 mL) and the filtrate was rotary evaporated. The crude product was then columned on silica gel eluting with petrol/ether (5:1) to give *(E)-3-((1S, 2S)-(2-heptylcycloprop-1-yl)acrylic acid ethyl ester* (**15**) (0.43 g, 71%) as a colourless oil [Found M^+: 238.1945, $C_{15}H_{26}O_2$ requires: 238.1933], $[\alpha]_D^{24}$+66.8 (*c* 1.28, $CHCl_3$); δ_H: 6.49 (1H, dd, *J*=10.4, 15.4 Hz), 5.89 (1H, d, *J*=15.4), 4.17 (2H, q, *J*=7.3 Hz), 1.4–1.2 (16H, br.m), 1.0 (1H, m). 0.86 (3H, t, *J*=6.7 Hz), 0.85–0.74 (2H, m); IR (film) 2923, 2854, 1718, 1644, 1465 cm^{-1}. Less than 5% of the *cis*-isomer could be detected by NMR.

1.5. 3-((1*S*,2*S*)-2-Heptylcycloprop-1-yl)propionic acid ethyl ester (16)

Freshly distilled acetic acid (1.13 g, 0.019 mol) in methanol (3 mL) was add slowly to a stirred solution of (*E*)-3-((1*S*, 2*S*)-2-heptylcycloprop-1-yl)acrylic acid ethyl ester (0.3 g, 0.0012 mol) and dipotassium azodicarboxylate (2.4 g, 0.012 mol) at room temperature. The mixture was stirred for 24 h then additional dipotassium azo-dicarboxylate (2.4 g) and acetic acid (1.2 g) were added. After a further 24 h, the mixture was diluted with water (15 mL) and extracted with dichloromethane (3×10 mL). The combined organic layers were washed with sat.aq. sodium bicarbonate (15 mL), dried and evaporated, to give a residue which was columned on silica gel eluting with petrol/ether (10: 0.5) to give *3-((1S,2S)-(2-heptylcycloprop-1-yl)propionic acid ethyl ester* (**16**) (0.25 g, 83%) as a colourless oil [Found M^+: 240.2096, $C_{15}H_{28}O_2$ requires: 240.2089], $[\alpha]_D^{24}$+12.5 (*c* 0.69, $CHCl_3$); δ_H: 4.14 (2H, q, *J*=7 Hz), 2.37 (2H, t, *J*=7.6 Hz), 1.6–1.1 (17H, m), 0.89 (3H, t, *J*=7 Hz), 0.43 (2H, m), 0.2 (2H, m); δ_C: 173.8, 61.5, 34.5, 34.1, 31.9, 29.7, 29.6, 29.5, 29.3, 22.7, 18.8, 18.1, 14.2, 14.1, 11.8; IR (film) 2923, 2854, 1736, 1178 cm^{-1}.

1.6. 3-((1*S*,2*S*)-2-Heptylcycloprop-1-yl)propionic acid (17)

3-((1*S*,2*S*)-2-Heptylcycloprop-1-yl)propionic acid ethyl ester (0.2 g, 0.83 mmol) was added to a stirred solution of potassium hydroxide (0.46 g, 8.3 mmol) in ethanol (3 mL) and water (0.5 mL). The mixture was stirred for 1 h when TLC showed no starting remained, then diluted with water (6 mL), ether (15 mL) and acidified to pH 2 with sulphuric acid (5%). The organic layer was separated and the aqueous layer was re-extracted with ether (2×10 mL). The combined organic layers were dried and evaporated to give *3-((1S, 2S)-(2-heptylcyclo-prop-1-yl)propionic acid* (**17**) as a thick yellow oil (0.152 g, 86%) [Found M^+: 212.1777, $C_{13}H_{24}O_2$ requires: 212.1776], $[\alpha]_D^{24}$+14.8 (*c* 1.05, $CHCl_3$); δ_H: 2.45 (2H, t, *J*=7.25 Hz), 1.63–1.5 (2H, m), 1.4–1.21 (12H, m), 1.15 (1H, m), 0.91 (3H, t, *J*=6.6 Hz), 0.47 (2H, m), 0.24 (2H, m); δ_C: 179.6, 34.2, 34.1, 31.9, 29.6, 29.5, 29.4, 29.3, 22.7, 18.9, 18.1, 14.1, 11.8; IR (film) 3397, 2923, 2854, 1709, 1178 cm^{-1}.

1.7. 3-((1*S*,2*S*)-2-Heptylcycloprop-1-yl)-*N*-phenethylpropionamide (18)

3-((1*S*, 2*S*)-2-Heptylcycloprop-1-yl)propionic acid (0.15 g, 0.71 mmol) was treated with thionyl chloride (3 mL) and refluxed for 2 h. The excess of thionyl chloride was distilled off to give a residue of 3-((1*S*,2*S*)-(2-heptylcyclopropyl)-propionyl chloride which showed δ_H: 2.9 (2H, t, *J*=7.3 Hz), 1.7 (2H, m), 1.5–1.16 (11H, m), 1.02–0.8 (4H, m, including a triplet with coupling constant 6.7 Hz), 0.47 (2H, m), 0.26 (2H, m); δ_C: 173.7, 47.3, 34.0, 31.9, 29.8, 29.6, 29.5, 29.3, 22.7, 19.0, 17.5, 14.2, 11.9; the residue was cooled to 5 °C and treated with phenylethyl amine (0.85 g, 7.1 mmol) under nitrogen. A white precipitates was formed and the reaction was stirred for 2 h. The mixture was diluted with water and the product was extracted with ether (2×10 mL). The combined organic layers were washed with brine, dried and evaporated to give a crude product which was purified by chromatography on silica eluting with petrol/ethyl acetate (1:1) to give *3-((1S,2S)-(2-heptyl-cycloprop-1-yl)-N-phenethylpropionamide* (**18**) (0.115 g, 52.3%) as a pale yellow solid [Found M^+: 315.2561, $C_{21}H_{33}NO$, requires: 315.2562] $[\alpha]_D^{22}$+12.6 (*c* 0.82, $CHCl_3$) (lit. $[\alpha]_D$-11.0 (*c* 0.1, $CHCl_3$))[1]; δ_H: 7.35–7.2 (5H, m), 5.6 (1H, br.s), 3.54 (2H, q, *J*=6.4 Hz), 2.83 (2H, t, *J*=6.7 Hz), 2.21 (2H, t, *J*=7.6 Hz), 1.52 (2H, m), 1.4–1.25 (10H, m), 1.15 (2H, m), 0.89 (3H, t, *J*=6.7 Hz), 0.4 (2H, m), 0.182 (2H, m); δ_C 173.0, 138.9, 128.75, 128.6, 126.5, 40.5, 36.9, 35.7, 34.1, 31.9, 30.4, 29.6, 29.5, 29.4, 22.7, 18.9, 18.2, 14.1, 11.8; IR (film) 3310, 2918, 2850, 1637 cm^{-1}.

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15. This could readily be prepared from the enantiomer of (**11**), prepared by enzyme catalysed monobutyration of cis-cyclopropan-1,2-dimethanol,[7b] using the same sequence as described above.

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Synthesis of 4- and 6-substituted nitroindoles

Nikolai Moskalev, Michał Barbasiewicz and Mieczysław Mąkosza*

Institute of Organic Chemistry, Polish Academy of Sciences, ul. Kasprzaka 44, PO Box 58, 01-224 Warszawa 42, Poland

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Abstract—Enolizable ketones react with *m*-nitroaniline in the presence of strong base such as *t*-BuOK to give 4- and 6-substituted nitroindoles. The reaction proceeds via oxidative nucleophilic substitution of hydrogen in *m*-nitroaniline with enolate anions in positions *ortho* to the amino group giving anionic σ^H adducts that are additionally stabilized by intramolecular interaction between the amino and the carbonyl group. Spontaneous oxidation of the σ^H adducts followed by the Bayer type condensation of the produced *ortho*-aminonitrobenzyl ketones gives 4- and 6-substituted nitroindoles. The scope of this reaction and its basic mechanistic features are discussed.

Numerous important natural products, drugs, plant protection agents, dyes, etc.[1,2] contain the indole ring system and, therefore, great attention is continuously directed towards novel, efficient methods of indole synthesis.[3] Although many methods of construction of the indole ring system are known, new and simple processes serving this purpose are in great demand.[4] Of particular interest are simple and efficient methods of the synthesis of indoles containing various substituents in defined positions of the five and six membered rings of the indole. Since the nitro group is one of the most versatile substituents, which can be converted into many other functionalities and also can promote numerous reactions,[5] synthesis of nitroindoles deserves special attention.[6] There are many ways of synthesising nitroindoles: via nitration of indoles under various conditions,[7] Fischer cyclization of starting materials containing the nitro group,[8] Bergman approach, utilizing 2-methyl-3-nitroanilines, etc.[9] One of the most general and versatile approach to the nitroindole ring construction appears to be nucleophilic substitution of hydrogen (NSH) in nitroarenes with carbon nucleophiles and subsequent cyclizations.[10] Thus, vicarious nucleophilic substitution of hydrogen (VNS) in *m*-nitrobenzoisonitriles with chloromethyl aryl sulfones followed by cyclization directly gives substituted 4- and/or 6-nitroindoles.[11a] To this category belongs the cyclization of 3-nitroanilides of chloroacetic acid via intramolecular VNS,[11b] and intramolecular oxidative nucleophilic substitution of hydrogen (ONSH) in *m*-nitroacetanilides and their analogues, leading to nitrooxindoles.[11c]

In our preliminary communication, we reported a much simpler method of synthesis of 4- and/or 6-nitroindoles—the direct condensation of 3-nitroanilines with ketones.[12]

A similar reaction of 3-nitroaniline **1a** with aliphatic nitriles results in formation of 2-amino-4-nitro- and 2-amino-6-nitroindoles.[13] The reaction apparently proceeds via ONSH in the nitroaromatic ring with the respective carbanions, followed by intramolecular reaction of the amino group with the carbonyl or the cyano groups. The process seems to be directed and assisted by an interaction between these groups within the σ^H adduct and/or in the course of the addition process.

In this paper, a full account of our studies on the synthesis of nitroindoles via this interesting and useful reaction between ketones and nitroanilines is presented.

Nucleophilic substitution of hydrogen in nitroarenes with carbon, nitrogen or oxygen nucleophiles is a well known and established process. Formation of anionic σ^H adducts and further oxidative or eliminative transformations of these short lived intermediates are accepted mechanistic features.[14,15]

Reactions of enolate anions with nitroarenes have been studied for more than 100 years. Reaction of acetone enolate with *m*-dinitrobenzene to form a σ^H adduct and its subsequent oxidation with an excess of the nitroarene to dinitrobenzyl methyl ketone are known as the Janovsky and the Zimmerman reactions, respectively.[16] ONSH in simple mononitroarenes: nitrobenzene, *p*-chloronitrobenzene etc. with the enolate of acetophenone was reported by Hamana.[17] Fluoride anion promoted reaction of trimethylsilyl enol ethers with nitroarenes produces σ^H adducts of the respective enolates that appear to be additionally stabilized by *O*-silylation of the nitro group. These σ^H adducts can be

Keywords: Enolates; Indoles; Nitroarenes; Nucleophilic addition.
* Corresponding author. Tel.: +48-22-6318788; fax: +48-22-6326681; e-mail address: icho-s@icho.edu.pl

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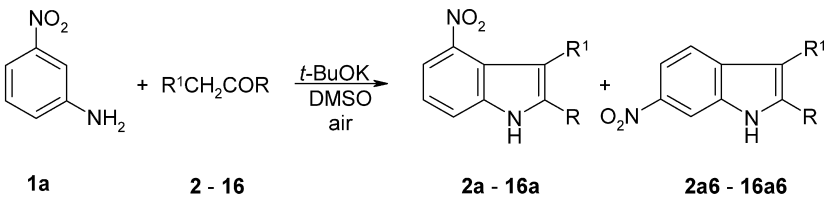
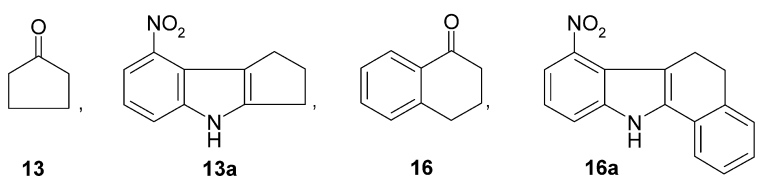


1a **2 - 16** **2a - 16a** **2a6 - 16a6**

Ketones **2-16**

Compound	R^1	R	Compound	R^1	R
2	H	Me	**10**	Me	Me
3	H	*cyclo*-C_3H_5	**11**	Me	Et
4	H	*t*-Bu	**12**	Me	Ph
5	H	Ph	**13**		-$(CH_2)_3$-
6	H	2-Py	**14**		-$(CH_2)_4$-
7	H	2-furyl	**15**		-$(CH_2)_5$-
8	H	2-thienyl	**16**		-$(CH_2)_2C_6H_4$-
9	H	2-(*N*-Me)pyrryl			

Exemplification of structures of some starting ketones and the corresponding products:



13 **13a** **16** **16a**

Scheme 1.

further oxidized to give products of ONSH in nitroarenes with enolate anions.[18] Reductive cyclization of the *o*-nitrobenzyl ketones obtained in this way provides the corresponding indoles.[18] Addition of enolates of some α-haloketones to nitroarenes leads to σ^H adducts that undergo base induced β-elimination of hydrogen halide giving products of VNS–nitrobenzyl ketones.[19] There are many examples of reactions of polynitroarenes with ketones producing bi- and tricyclic adducts, some of them found application in synthesis.[20] However, to the best of our knowledge, there are no preceeding reports on reactions of enolates with *m*-nitroanilines.

1. Results and discussion

Treatment of a solution of 3-nitroaniline **1a** and acetone **2** in DMSO with *t*-BuOK results in a moderately exothermic reaction and dark-red coloration of the mixture. Acidification of the mixture and standard work up gave 2-methyl-4-nitroindole **2a** with a minor amount of the isomeric 6-nitroindole. Thus, the overall result is that hydrogen in position 2- and 6- of **1a** (*ortho*- and *para*- to the NO_2 and *ortho*- to the NH_2 group) has been replaced with the acetone moiety. This unusual orientation in the reaction-preference of the nucleophilic addition of the enolate to the most hindered position 2- of 3-nitroaniline is well precedented in the nucleophilic substitution of hydrogen in nitroarenes. During our previous studies of the VNS reaction in nitroarenes containing a variety of substituents Z in position 3- we have observed a strong preference for replacement of hydrogen in position 2- for Z=halogens, OMe, Me, NMe_2, etc. and discussed reasons for such orientation.[21]

Under similar conditions a variety of other ketones react with **1a** giving 4- and 6-nitroindoles. The DMSO/*t*-BuOK system appears to be a reagent of choice for this transformation. Indeed, acetophenone reacts satisfactorily with **1a** in the presence of *t*-BuOK in DMSO, whereas in THF, Et_2O, PhCl and CH_2Cl_2 only traces of the expected indoles were produced, and most of the reactants were recovered. DMF and HMPT are acceptable, but less practical solvents, because of decomposition of the former and toxicity of the latter. The reactions of **1a** with a variety of ketones **2**–**16** in DMSO are presented in Scheme 1 and Table 1.

All methyl ketones CH_3COR in which R does not contain acidic hydrogen atoms, in the reaction with **1a** form predominantly 4-nitro-2-*R*-indoles **2a**–**9a** resulted from addition of the enolates to position 2- of 3-nitroaniline. The observation that these ketones react exclusively in position 2-, reported in our preliminary communication,[12] was only partially confirmed in the present studies. Thus, in the reaction of **1a** with acetone **2** and acetophenone **5** we were also able to isolate minor quantities (7 and 8%), of 6-nitro-2-methyl and 6-nitro-2-phenyl-indoles **2a6** and **5a6**. One cannot exclude that in the reactions of **1a** with some other methyl ketones small quantities of substituted 6-nitroindoles are also formed, but they were not isolated in

Table 1. Substituted 4- and 6-nitroindoles obtained from **1a** and ketones **2**–**16** as in Scheme 1

Ketone	Products and yields (%)		Ketone	Products and yields (%)	
2	**2a**, 58	**2a6**, 7	**10**	**10a**, 32	**10a6**, 26
3	**3a**, 60	[a]	**11**	**11a**, 33	**11a6**, 30
4	**4a**, 42	[a]	**12**	**12a**, 16	**12a6**, 38
5	**5a**, 67	**5a6**, 8	**13**	**13a**, 16	**13a6**, 12
6	**6a**, 53	[a]	**14**	**14a**, 34	**14a6**, 13
7[b]	**7a**, 50	[a]	**15**	**15a**, 23	**15a6**, 13
8[b]	**8a**, 50	[a]	**16**	**16a**, 24	**16a6**, 12
9[c]	**9a**, 12	[a]			

[a] Small amounts (<5%) of 6-nitroindoles are perhaps formed but not isolated and identified.
[b] Reactions were performed with 3-fold excess of **1a** to ketone.
[c] Reaction with 2-acetylpyrrole failed, ketone was *N*-methylated with CH_3I and then reaction with **1a** and *t*-BuOK was performed.

routine column chromatography separation technique. Interestingly, the reaction of **1a** with methyl ethyl ketone **10**, gave two isomeric products, 4- and 6-nitro-2,3-dimethylindoles **10a**, and **10a6**, derived from the secondary enolate, produced via deprotonation of the methylenic group. We failed to find any evidence of the presence of 4- or 6-nitro-2-ethyl-indoles, which would be derived from the reaction of the isomeric primary enolate. Preference for the reactions of thermodynamically controlled secondary enolates over those kinetically controlled is a well established phenomenon.[22] The addition of the more sterically demanding secondary enolate occurs in both positions 2- and 6- of **1a** giving a mixture of 2,3-dimethyl-4-nitro- and 2,3-dimethyl-6-nitro indoles **10a** and **10a6**. Similarly, diethyl ketone **11** and propiophenone **12** in the reaction with **1a** gave two isomeric products: 2-ethyl-3-methyl-4-nitro- and -6-nitroindoles **11a** and **11a6** and 3-methyl-4-nitro-2-phenyl- and -6-nitroindoles **12a** and **12a6**, respectively. Interestingly, the ratio of the two isomeric 4- and 6-nitroindoles produced from the aliphatic ketones **10** and **11** was close to 1 (1.2 and 1.1), whereas in the reaction of propiophenone **12** the 6-nitroisomer was the major product, ratio **12a/12a6**≈0.4. The reaction of secondary enolates of cyclic ketones **13**, **14**, **15** and **16** also proceeds via the addition to positions 2-and 6- of 3-nitroaniline giving substituted 4- and 6-nitroindoles, always the 4-nitroisomer being isolated in larger yield (ratio 4-/6-nitro between 1.5 and 2.6). Thus, even sterically bulky secondary enolates attack preferentially the more sterically hindered position 2- of 3-nitroaniline.

3-Nitroanilines containing halogens also enter the reaction with a variety of enolates giving the corresponding halonitroindoles. Thus, in the reaction of 6-chloro-3-nitroaniline **1b** with ketones substituted 4-nitro-7-chloroindoles were produced. In no cases did we observe formation of the indoles resulting from nucleophilic displacement of the halogen in **1b**, namely 6-nitroindoles. However, in the majority of experiments some amounts of side products of dechlorination, 4-nitroindoles, were obtained. These compounds were identical to the indoles produced in the analogous reaction of **1a** itself. In separate experiments, chloronitroindole **5b** was subjected to the standard reaction conditions and was recovered unreacted, without loss of Cl. Therefore, we concluded that dechlorination took place at an intermediate stage, whereas the final products—the chloronitroindoles are stable under the reaction conditions. As one could expect the dehalogenation process proceeded to a much higher degree in the case of the analogous bromoaniline. The reaction of 6-bromo-3-nitroaniline **1c** with acetophenone **5** gave the expected 2-phenyl-4-nitro-7-bromoindole **5c** and the debrominated product **5a** in almost equal amounts. Similarly to chloroindole **5b**, bromoindole **5c** was stable under the reaction conditions, and the debromination product **5a** was not detected by TLC when **5a** was treated with *t*-BuOK in DMSO.

The reactions of enolates with fluoronitro anilines were somewhat more complicated, because of the competing process of nucleophilic substitution of halogen. The observed formation of the expected fluoronitroindoles via ONSH reaction was the major process, however, nitroindoles derived from S_NAr of fluorine were also isolated. Thus, in the reaction of 6-fluoro-3-nitro aniline **1d** with acetophenone **5** besides the expected 7-fluoro-2-phenyl-4-nitro-indole **5d** some amount of 6-nitro-2-phenylindole **5a**, identical to that obtained from **1a** and **5**, was produced (Scheme 2, Table 2).

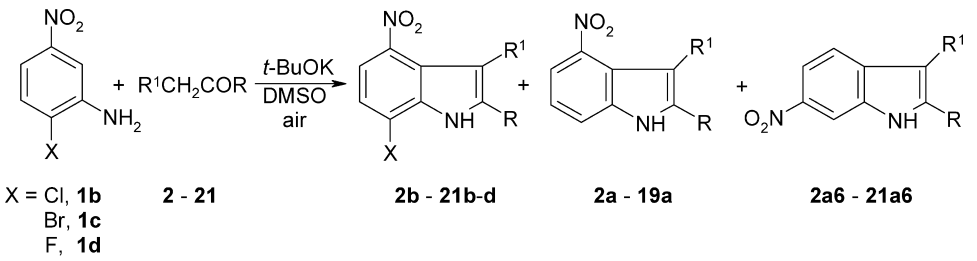
On the other hand, the reaction of 4-fluoro-3-nitroaniline **1e** with enolate anions via ONSH process can occur at positions 2- or 6- giving 5-fluoro-4- and 6-nitroindoles. Acetone was found to react with **1e** in the same manner as with **1a**, via addition to the most sterically hindered position giving 5-fluoro-2-methyl-4-nitroindole **2e**, whereas secondary enolates of diethyl ketone **11** and butyrophenone **22** gave predominantly or exclusively 6-nitroindoles **11e6** and **22e6** (Scheme 3, Table 2).

Usually the reaction of enolates with fluoro nitro anilines gave lower yields of nitroindoles, perhaps because of some competing reactions of substitution of fluorine by other nucleophiles present in the system. It is worth noting, that in the reaction of fluoronitroanilines **1d** and **1e** dehalogenation

Table 2. Substituted halonitroindoles obtained from halo-*m*-nitroanilines **1b**–**e** and ketones **2**–**21** as in Schemes 2 and 3

Aniline	Ketone	Products and yields (%)	
1b	**2**	**2b**, 51	
1b	**5**	**5b**, 61	**5a**, 5
1b	**7**	**7b**, 43	**7a**, 13
1b	**8**	**8b**, 60	**8a**, 7
1b	**11**	**11b**, 61	**11a**, 7
1b	**14**	**14b**, 30	**14a**, 1
1b	**16**	**16b**, 50	**16a**, 13
1b	**17**	**17b**, 55	
1b	**18**	**18b**, 46	**18a**, 16
1b	**19**	**19b**, 42	**19a**, 9
1b	**20**	**20b**, 27	
1b	**21**	**21b**, 23	
1c	**5**	**5c**, 37	**5a**, 33
1d	**2**	**2d**, 33	**2a6**, 3[a]
1d	**5**	**5d**, 50	**5a6**, 7[a]
1d	**11**	**11d**, 40	**11a6**, 15[a]
1d	**22**	**22d**, 34	**22a6**, 12[a]
1d	**19**	**19d**, 34	**19a6**, 12[a]
1e	**2**	**1e**, 21	
1e	**18**	**18e**, 5	**18e6**, 20
1e	**22**		**22e6**, 22

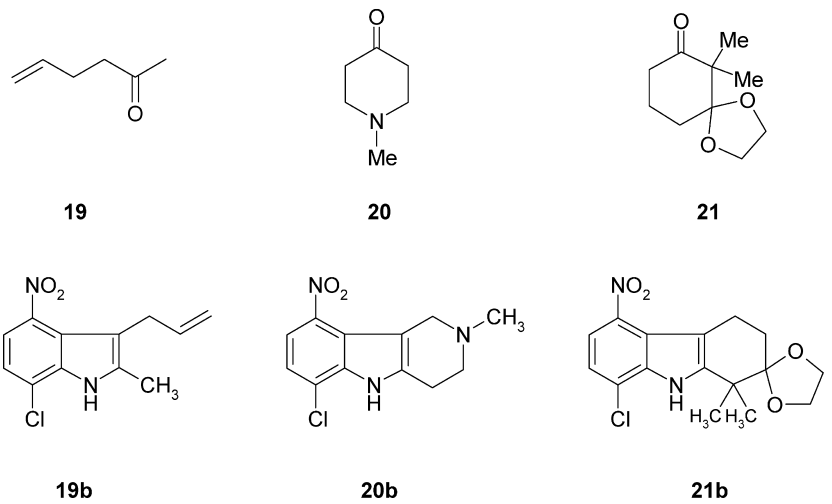
[a] Formed via substitution of F.



Ketones **17**-**22** not listed in scheme 1

R^1	R	No
H	1-Naphthyl	**17**
Et	*n*-Pr	**18**
Allyl	Me	**19**
—$CH_2N(Me)CH_2CH_2$—		**20**
—$(CH_2)_2$ $C(CH_3)_2$—		**21**

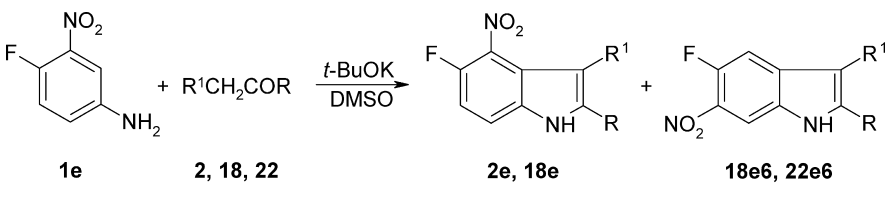
Exemplification of structures of some ketones and products:



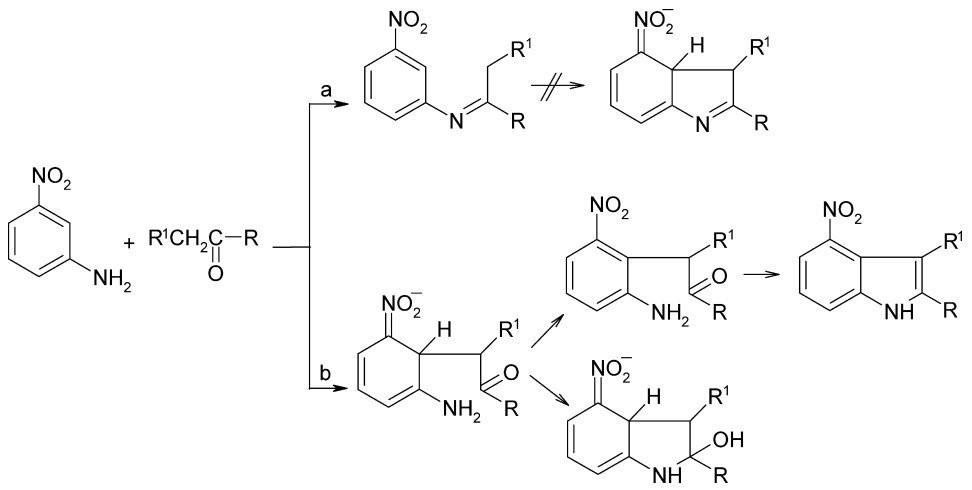
Scheme 2.

was not observed. Indoles **2a6**–**22a6** that do not contain fluorine were formed as the result of nucleophilic substitution of fluorine and further cyclization.

Formation of the indole ring in the base-induced reaction of ketones with **1a** can, in principle, occur in two ways: (a) initial condensation of the amino functionality with the carbonyl group of the ketones giving 3-nitroaryl imines, which upon treatment with base form carbanions that enter intramolecular ONSH resulting in the indole ring closure; (b) initial addition of the enolate anions to the nitroaromatic ring (*ortho*- or *para*- to the nitro group and *ortho*- to the



Scheme 3.

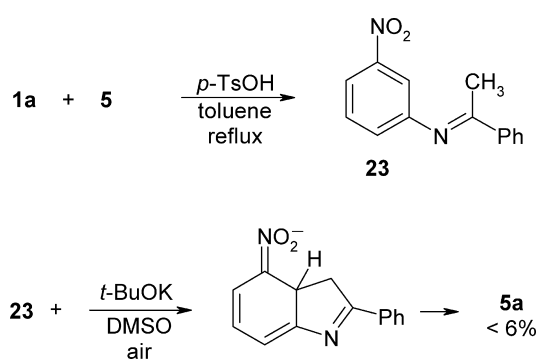


Scheme 4.

amino group) followed by oxidation of the produced σ^H adducts resulting in ONSH to form *ortho*-aminonitrobenzyl ketones, further intramolecular condensation of which gives nitroindoles.[23] These alternative pathways are shown in Scheme 4.

In order to clarify which of these alternative series of transformations is the actual reaction pathway, the corresponding imine **23** was prepared from acetophenone and 3-nitroaniline and subjected to the reaction conditions (Scheme 5).

However, the expected 4-nitro-2-phenylindole **5a** was found in the reaction mixture in less than 6% overall yield, moreover, it appears that in this case the indole was formed due to decomposition of the imine to the aniline and ketone followed by the reaction as in Scheme 1. This result indicates that the path a (Scheme 4), including initial condensation between the amino and the carbonyl group is not the reaction pathway and should be excluded from further consideration. The alternative path b, should, therefore, be considered as an actual reaction pathway. The absence of acylic products of this reaction *ortho*- to the nitro group and *para*- to the amino group indicates that there is a strong preference for the ONSH reaction in the vicinity of the amino group. This can be rationalized by the supposition that formation of a σ^H adduct is assisted by either non-covalent interaction between the amino and the carbonyl group or stabilization of the σ^H adduct by formation of cyclic aminal takes place. Further oxidation

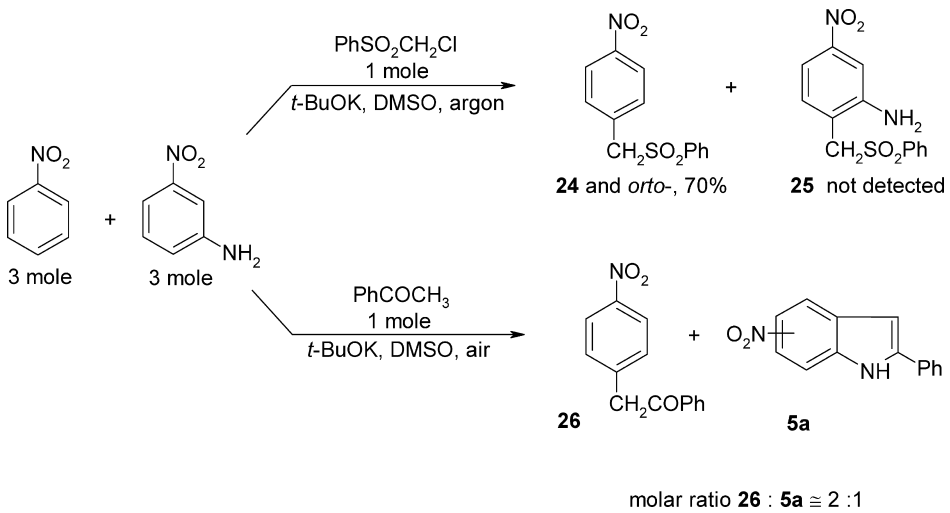


Scheme 5.

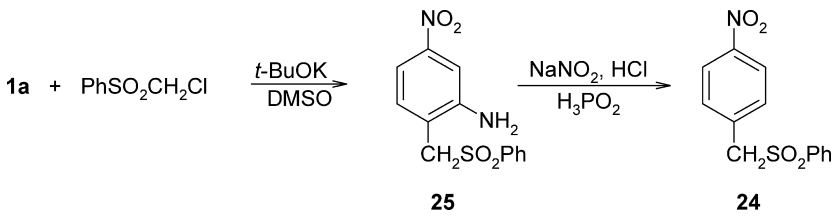
of the σ^H adducts gives the corresponding ONSH products–nitrobenzyl ketones which subsequently undergo the Baeyer type cyclisation[23] to give nitroindoles. Oxidation of the σ^H adducts in the form of aminal should give the same final results. Differentation between these two possible ways of stabilization of σ^H adducts was not attempted in our studies.

Additional stabilization of the σ^H adducts explains the relatively high activity of 3-nitroanilines as electrophilic partners in the reaction with enolate anions. It was observed earlier that **1a** is of rather low activity in its reactions with carbanions, due to the presence of the strong electrondonating amino group that deactivates the aromatic ring towards nucleophilic addition. Moreover, partial deprotonation of the amino group should enhance this effect substantially. The hypothesis that there is a specific tendency to form and stabilize σ^H adducts of enolates to **1a** in vicinity of the amino groups was verified experimentally in competitive experiments. In these experiments, we have directly compared rates of the VNS reaction in nitrobenzene and **1a** with the carbanion of chloromethyl phenyl sulfone, which is unable to form intramolecular bonding with the amino group, and rates of the ONSH reaction in nitrobenzene and **1a** with acetophenone (Scheme 6).

Results of these competitive experiments, presented in Scheme 6, indicate that the rate of VNS in nitrobenzene with the carbanion of chloromethyl phenyl sulfone is more than 100 times higher than the rate of this reaction with **1a**. In fact, the product of the latter process was not detected in the reaction mixture. On the other hand, the ONSH reaction with the enolate of acetophenone in nitrobenzene is only about two times faster than formation of the nitroindole via ONSH in **1a**, which suggests that the deactivating effect of the amino group on the electrophilic activity of **1a** is compensated by the additional stabilization of the σ^H adduct. Thus, as we have supposed, addition of the enolate to **1a** is favored, apparently because the corresponding σ^H adduct is additionally stabilized, and upon its oxidation forms 4-nitro-2-phenylindole. Although these data are only qualitative they indicate unambiguously that there is a strong effect promoting addition of enolates to **1a**. Such an effect does not operate in the reaction of carbanions unable to experience additional interactions with amino groups, for



Scheme 6.



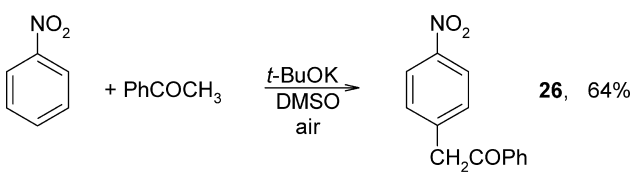
Scheme 7.

instance, those generated from chloromethyl phenyl sulfone.

The carbanion of chloromethyl phenyl sulfone is our standard nucleophile for the VNS reaction with nitroarenes. In the presence of *t*-BuOK in DMSO and also in other base–solvent systems it reacts with nitrobenzene to give a mixture of *ortho*- and *para*-nitrobenzyl phenyl sulfones **24**.[24] Since the VNS reaction of this sulfone with **1a** was not reported (we reported earlier that this reaction does occur with 3-nitro-*N*,*N*-dimethylaniline)[21] we have shown in a separate experiment that the VNS reaction of chloromethyl phenyl sulfone with **1a** proceeds satisfactorily giving a single product **25** (Scheme 7).

For unambiguous identification, compound **25** was diazotized and the diazonium salt reduced in situ with hypophosphorous acid, giving *para*-nitrobenzyl phenyl sulfone **24**, identical to that reported in our early paper.[24] Thus, VNS in **1a** proceeded in a position *para*- to the nitro group giving 2-amino-4-nitrobenzyl phenyl sulfone **25**. Under similar conditions, nitrobenzene reacts with acetophenone to give *para*-nitrobenzyl phenyl ketone **26** (Scheme 8).

This reaction under somewhat different conditions, was reported by Hamana[17] to give a mixture of *ortho*- and *para*-

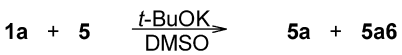


Scheme 8.

nitrobenzyl phenyl ketones. Some discrepancy in the orientation of ONSH in nitrobenzene with acetophenone enolate is apparently due to the differences in the conditions. The results presented in Scheme 6 indicate that there is an effect promoting the reaction of enolates with **1a** which does not operate in the case of nitrobenzene and which we assign to an interaction between the carbonyl and the amino groups as shown in Scheme 4.

Another important question is identity of the oxidant oxidizing the σ^H adducts of enolates to **1a**. We believe that these σ^H adducts are oxidized by the air oxygen always present in the reaction mixtures. Indeed when the reaction of acetophenone **5** with **1a** was carried out in the strictly deoxygenated solvent under argon yields of the indoles were substantially lower. On the other hand saturation of the system with oxygen does not change the outcome substantially as shown in Scheme 9

The identity of the oxidizing agents and effect of conditions on the oxidation process need further studies.



	Isolated yields, %	
air (open flask)	67	8
oxygen bubbled	66	4
degassed solvent, argon	28	4

Scheme 9.

In conclusion, the reported method of synthesis of nitroindoles from inexpensive and readily available starting materials offers the simplest and the most efficient approach to these valuable intermediates, particularly taking into account that as well as of standard transformations of the nitro group, further reactions of nucleophilic substitution of hydrogen such as VNS in nitroindoles[25] are possible so polycyclic heterocyclic systems can be readily produced.[26]

2. Experimental

Unless otherwise noted all reagents and solvents were used commercial without further purification. Chromatographic columns were filled with silica gel 60 (0.040–0.063 mm, 230–400 mesh). ^{1}H NMR spectra were recorded at 200 MHz.

The nitroindoles are stable yellow to dark-red crystalline compounds, however some of them show instability in solution on prolonged storage. 4-Nitroisomers are usually less soluble and produce orange to brown spots on TLC, while 6-nitroisomers are better soluble and produce lighter spots on TLC. Halogenated indoles are less polar (TLC) and better soluble.

The reactions were monitored by TLC (aluminium sheets, silica gel 60 F_{254}, Merck) using toluene as eluent. For the reaction with *N*-methyl-4-piperidone, methylene chloride–methanol, (4:1) was used as eluent. Samples of the reaction mixtures for TLC were treated with aqueous NH_4Cl and extracted with EtOAc. Usually, all the reactions were complete within 2 h, however, we recommend stopping the reaction when starting *m*-nitroaniline is not detected by TLC in the reaction mixture.

Typical TLC retention factors (R_f, toluene) components of the reaction mixture: *m*-nitroaniline=0.25 (yellow spot, UV lamp helps to find trace amounts), 6-NO_2 indoles=0.30–0.40 (yellow to orange spots), 4-NO_2 indoles=0.40–0.45 (orange to brown spots).

For methyl aryl ketones (for example see reaction of **1a** with **5**), retention factors of the both isomers are very close. Due to low abundance of 6-NO_2 isomer in the reaction mixture and low solubility of 4-nitroisomer ('diffusion' of sample) detection of 6-NO_2 isomer often becomes difficult. For these cases hexane–ethyl acetate (2:1) should be used as an eluent, where order of elution of isomers is reversed (R_f, hexane–ethyl acetate, 2:1): 4-NO_2 indoles=0.35–0.40 (orange to brown spots), 6-NO_2 indoles=0.45–0.50 (yellow to orange spots).

2-Bromo-5-nitroaniline **1c** was obtained by simple bromination of **1a** in glacial acetic acid at 10 °C and subsequent recrystallization from ethanol (yield 25%) mp 136–139 °C (lit.[27] 140 °C) similarly to the procedure described.[27]

Chloromethylphenylsulfone was obtained from bromochloromethane and benzenesulfinic acid sodium salt.[28]

Ethylene glycol monoacetal of dimedone (2,2-dimethylcyclohexane-1,3-dione) **21** was prepared as reported.[29]

2.1. General procedure

To a stirred solution of *m*-nitroaniline (5 mmol) and ketone (7 mmol) in DMSO (15 mL) at 15–20 °C (water bath), *t*-BuOK (12 mmol) was added in one portion. All operations were made in open flask under air. Deep red or red-violet colour indicated the reaction progress. After 2 h of stirring aqueous NH_4Cl (60 mL) was added, the mixture was extracted with ethyl acetate (3×50 mL) and the extract dried with $MgSO_4$. Chromatographic separation on silica gel with hexane–toluene (1:1) eluent, then pure toluene on 20 cm×5 cm column is efficient for 5 mmol scale preparations. We do not recommend hexane–ethyl acetate eluent for separation of crude reaction mixtures after workup. For reaction of **1a** with methylaryl ketones **5**–**9** procedure for isolation of minor amounts of 6-NO_2 isomers is recommended. Analytical samples were finally purified by recrystallization from heptane–toluene mixture.

2.2. General procedure for isolation of minor amounts of 6-NO_2 isomers

Reaction was performed as in general procedure. Combined extracts were dried with $MgSO_4$, filtered, silica gel was added to the solution and solvent was evaporated. Gel was put on chromatographic column with toluene (5×5 cm, silica gel). Large amount (up to 1 L) of toluene was passed through and solvent was evaporated. Residue was crystallized from heptane–toluene mixture (left in well isolated can in refrigerator for slow cooling). Precipitated crystals were filtered, washed with heptane–toluene mixture and dried to obtain 4-nitroindole derivatives (for **5a** 57%). Solution was evaporated with silica gel and put on chromatographic column with hexane–ethyl acetate (4:1 then 1:1) (5×15 cm, silica gel). After collection and evaporation of fractions 6-nitroindole derivatives (for **5a6** 8%) (first eluted product) and 4-nitroindole derivatives (for **5a** 10%) (second eluted product) were obtained.

2.2.1. Reaction with *N*-methyl-2-acetylpyrrole. To a stirred mixture of 2-acetylpyrrole (597 mg, 5.5 mmol) and *t*-BuOK (614 mg, 5.5 mmol) in DMSO (10 mL) at 20 °C, CH_3I (2.5 g, 17.6 mmol) was added in one portion. Reaction was moderately exothermic. After 1.5 h, TLC showed that reaction was completed and excess of CH_3I was removed in vacuo. To this solution *m*-nitroaniline **1a** (765 mg, 5.5 mmol) and *t*-BuOK (1368 mg, 12.2 mmol) were added consecutively. After 2 h of stirring in open flask under air aqueous NH_4Cl (60 mL) was added and product isolated as in general procedure to give 4-nitro-2-(*N*-methyl-pyrrol-2-yl)-indole **9a** (150 mg, 12%).

2.2.2. Reactions with 2-acetylthiophene and 2-acetylfuran. Reactions were performed as in general procedure, but 3-fold excess of *m*-nitroaniline was used (15 mmol) on ketone (5 mmol).

2.2.3. Reaction with α-tetralone. To a stirred solution of *m*-nitroaniline **1a** (693 mg, 5 mmol) and α-tetralone **16** (1040 mg, 7.1 mmol) in DMSO (15 mL) at 17 °C, *t*-BuOK (1127 mg, 10.1 mmol) was added in one portion. Deep blue colour appeared and after 45 min of stirring in open flask

under air aqueous NH_4Cl (60 mL) was added. Insoluble solid product was filtered and dried. Filtrate was extracted with ethyl acetate (2×25 mL) and dried with $MgSO_4$. Dried solid was added to extracts, silica gel was added to the mixture and then solvent was evaporated. Residue adsorbed on gel was put on 3 cm layer of silica gel. Then toluene and ethyl acetate was passed through. Solvent was evaporated and 40 mL of toluene was added. Mixture was heated to boiling for 10 min, then cooled, and the precipitate was filtered, washed with toluene and dried to obtain 5,6-dihydro-7-nitrobenzo[*a*]carbazole **16a** (416 mg, 31%). Organic solutions were put on chromatographic column with toluene and separated to obtain: 5,6-dihydro-7-nitrobenzo[*a*]carbazole **16a** (78 mg, 6%) and 5,6-dihydro-9-nitrobenzo[*a*]carbazole **16a6** (249 mg, 19%).

2.2.4. Synthesis of imine 23 and attempts of cyclization (Scheme 5). *m*-Nitroaniline **1a** (416 mg; 3 mmol), acetophenone **5** (127 mg; 1.06 mmol) and *p*-toluenesulphonic acid (TsOH; 7 mg; 3%) in toluene (50 mL) were refluxed overnight with Soxlet apparatus filled with well-dried molecular sieves. The solvent was evaporated and the residue separated by flash chromatography (toluene, silica gel (25 g) treated with NEt_3 (5 g) in 50 mL toluene overnight, then washed with 200 mL toluene on column). Evaporation of solvent and recrystallization from hexane gave *N*-(3-nitrophenyl)-*N*-[(*E*)-1-phenylethylidene]amine **23** as yellow-brown crystals (0.108 g; 43%), mp 90–91 °C, ^{1}H NMR δ (500 MHz, $CDCl_3$) 2.27 (s, 3H, CH_3), 7.13 (ddd, *J*=7.9, 2.0, 2.0 Hz, 1H), 7.45–7.54 (m, 3H), 7.67 (dd, *J*=2.0, 2.0 Hz, 1H), 7.95 (ddd, *J*=8.0, 2.0, 2.0 Hz, 1H), 7.97–8.00 (m, 2H). EIMS *m/e* (relative intensity): 240 (M^+, 54), 225 (100), 179 (55). Anal. Calcd for $C_{14}H_{12}N_2O_2$: C, 69.99; H, 5.03; N, 11.66. Found: C, 70.15; H, 4.96; N, 11.58.

To a solution of *N*-(3-nitrophenyl)-*N*-[(*E*)-1-phenylethylidene]amine **23** (119 mg; 0.5 mmol) in DMSO (5 mL), *t*-BuOK (133 mg; 1.2 mmol) was added in one portion and the mixture was stirred for 2 h in open flask under air, aqueous NH_4Cl (25 mL) was added, extracted with ethyl acetate (2×25 mL) and combined organic layers were dried with $MgSO_4$. Separation by column chromatography on toluene gave 4-nitro-2-phenylindole **5a** (7 mg; 6%, structure confirmed by ^{1}H NMR) as the only isolable product.

2.2.5. Competitive reaction of 1a and nitrobenzene with chloromethyl phenyl sulfone (Scheme 6). Nitrobenzene (375 mg, 3 mmol), *m*-nitroaniline **1a** (416 mg, 3 mmol) and chloromethylphenylsulfone (208 mg, 1 mmol) were dissolved in degassed DMSO (9 mL) under argon. Then *t*-BuOK, 0.224 g (2 mmol) was added in one portion and the mixture was stirred at 20 °C for 20 min. After this aqueous NH_4Cl (60 mL) was added and the mixture was extracted with ethyl acetate (2×30 mL), and extracts were treated with 2×100 mL HCl_{aq} (1:1), washed with water dried with $MgSO_4$. After evaporation of solvent residue was separated on short column (toluene then toluene–ethyl acetate 10:1) to give the mixture of *ortho*- and *para*-nitrobenzyl phenyl sulfones (194 mg, 70%, detected by TLC and confirmed by ^{1}H NMR). The acidic solution was made alkaline with KOH and extracted with ethyl acetate (3×25 mL) to give *m*-nitroaniline **1a** (394 mg, 95%). Product of the reaction with *m*-nitroaniline (**25**) was not detected by TLC and ^{1}H NMR in organic phase nor in aqueous extracts.

2.2.6. Competitive reaction of 1a and nitrobenzene with 5 (Scheme 6). To a solution of nitrobenzene (370 mg, 3 mmol), *m*-nitroaniline **1a** (414 mg, 3 mmol) and acetophenone **5** (119 mg, 1 mmol) in DMSO (9 mL), *t*-BuOK (224 mg, 2 mmol) was added in one portion and the mixture was stirred at open flask under air for 20 min at 20 °C. The mixture was diluted with aqueous NH_4Cl (60 mL), extracted with ethyl acetate (3×25 mL), the combined extracts were treated with HCl_{aq} (1:1, 2×100 mL), washed with water and dried with $MgSO_4$. After evaporation of the solvent residue was separated on short column (toluene then toluene–ethyl acetate 10:1) to give mixture of nitroindoles (**5a**, **5a6**) and *p*-nitrobenzyl phenyl ketone **26** (166 mg, about 60% of all compounds). Basification of the acidic solution with KOH and extraction with ethyl acetate (3×25 mL) gave *m*-nitroaniline **1a** (330 mg, 80%).

^{1}H NMR analysis of the crude reaction mixture showed *p*-nitrobenzyl phenyl ketone **26** to nitroindoles (**5a**, **5a6**) ratio close to 2:1.

2.2.7. Reaction of 1a with chloromethylphenylsulfone (synthesis of 25, Scheme 7). *m*-Nitroaniline **1a** (416 mg, 3 mmol) and chloromethylphenylsulfone (193 mg, 1 mmol) were dissolved in degassed DMSO (9 mL) under argon and *t*-BuOK (225 mg, 2 mmol) was added in one portion. The mixture was stirred for 20 min at 20 °C, aqueous NH_4Cl (60 mL) was added and extracted with ethyl acetate (3×30 mL). Separation on short column with toluene then toluene–ethyl acetate (10:1) gave 5-nitro-2-[(phenyl sulfonyl)methyl]aniline **25** (164 mg, 56%) as yellow solid. Mp 216–218 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 4.74 (s, 2H), 5.80 (s, 2H), 7.06 (d, *J*=8.4 Hz, 1H), 7.24 (dd, *J*=8.4, 2.4 Hz, 1H), 7.44 (d, *J*=2.4 Hz, 1H), 7.58–7.62 (m, 2H), 7.70–7.75 (m, 1H), 7.78–7.82 (m, 2H). EIMS *m/e* (relative intensity): 292 (M^+, 8), 151 (100). IR (cm^{-1}, KBr): 3473, 3390, 1636, 1510, 1353, 1300, 1145, 1081, 750, 725, 694, 594, 517. Anal. Calcd for $C_{13}H_{12}N_2O_4S$: C, 53.42; H, 4.14; N, 9.58; S 10.97. Found: C, 53.42; H, 4.06; N; 9.58; S 10.91.

2.2.8. Conversion of 25 into 24 (Scheme 7). To a suspension of 5-nitro-2-[(phenylsulfonyl)methyl]aniline **25** (97 mg, 0.33 mmol) in a mixture of 36% aqueous HCl (3.3 g) and 50% aqueous H_3PO_2 (3.2 g) at −5 °C aqueous solution of $NaNO_2$ (120 mg, 1.7 mmol in 600 mg of water) was added slowly. The mixture was warmed to room temperature during 1 h. Water (50 mL) was added and the mixture was extracted with ethyl acetate (2×30 mL) combined organic layers were washed with brine (2×100 mL) and dried with $MgSO_4$. Column chromatography (toluene then toluene–ethyl acetate 10:1) gave 4-nitrobenzyl phenyl sulfone **24** (42 mg, 46%) mp 210–210.5 °C (lit.[24] 207 °C) (confirmed by ^{1}H NMR spectrum).

2.2.9. Reaction of 5 with nitrobenzene (synthesis of 26, Scheme 8). To a solution of nitrobenzene (373 mg, 3 mmol) and acetophenone **5** (117 mg, 1 mmol) in DMSO (9 mL) *t*-BuOK (233 mg, 2.1 mmol) was added in one portion. The mixture was stirred in open flask under air for 20 min at

20 °C and then aqueous solution of NH_4Cl (50 mL) was added, the whole was extracted with ethyl acetate (2×30 mL) and dried. Separation on short column with hexane–ethyl acetate (20:1 to 4:1) gave *p*-nitrobenzyl phenyl ketone **26** as white solid (151 mg, 64%), mp 141.5–143 °C (lit.[30] 138–140 °C). ^{1}H NMR δ ($CDCl_3$) 4.42 (s, 2H), 7.40–7.67 (m, 5H), 7.98–8.06 (m, 2H), 8.16–8.24 (m, 2H). LSIMS *m/z*: 242 [M^++1]. Anal. Calcd for $C_{14}H_{11}NO_3$: C, 69.70; H, 4.60; N, 5.81. Found: C, 70.07; H, 4.59; N, 5.92 and unidentified yellow product (EIMS: M^+343) (19 mg).

2.2.10. Influence of oxygen on the reaction (Scheme 9). The reactions **1a** with **5** were performed according to the general procedure for isolation of minor amounts of 6-NO_2 isomers. For experiment without oxygen, DMSO was dried with CaH_2 overnight, distilled in a stream of argon under reduced pressure, degassed by 3-fold repeated freeze–pump–thaw technique (see Ref. 31) and argonated before experiment. Experiment with oxygen was performed with continuous bubbling of oxygen through the reaction mixture 10 min before and during the reaction.

2.3. Physicochemical and spectral data

Representative IR spectra are given for compounds **2a**, **2a6**, **5a**, **5a6**, **12a** and **12a6**.

2.3.1. 2-Methyl-4-nitroindole (2a). Mp 202 °C (lit.[9b] 197–198 °C). IR (cm^{-1}, KBr): 3301, 1580, 1505, 1478, 1321, 1231, 980, 779, 735.

2.3.2. 2-Methyl-6-nitroindole (2a6). Mp 118–119 °C (lit.[32] 113.5–114.5 °C). IR (cm^{-1}, KBr): 3314, 1589, 1543, 1501, 1463, 1316, 1069, 821, 733. ^{1}H NMR ($CDCl_3$) δ 2.55 (d, *J*=0.8 Hz, 3H), 6.35–6.37 (m, 1H), 7.53 (d, *J*=8.8 Hz, 1H), 8.01 (dd, *J*=8.8, 2.2 Hz, 1H), 8.29–8.31 (m, 1H), 8.55 (s br, 1H). EIMS *m/e* (relative intensity): 176 (M^+, 100), 146 (28), 130 (55). Anal. Calcd for $C_9H_8N_2O_2$: C, 61.36; H, 4.58; N, 15.90. Found: C, 61.51; H, 4.41; N, 15.80.

2.3.3. 7-Chloro-2-methyl-4-nitroindole (2b). Mp 208–209 °C. ^{1}H NMR δ ($CDCl_3$) 2.57 (d, *J*=0.9 Hz, 3H), 7.03–7.06 (m, 1H), 7.17 (d, *J*=8.7 Hz, 1H), 8.05 (d, *J*=8.7 Hz, 1H), 8.50 (br s, 1H). EIMS *m/e* (relative intensity): 210, 212 (M^+, 100, 34), 180, 182 (40, 14), 164, 166 (47, 15). Anal. Calcd for $C_9H_7ClN_2O_2$: C, 51.32; H, 3.35; N, 13.30. Found: C, 51.45; H, 3.23; N, 13.06.

2.3.4. 7-Fluoro-2-methyl-4-nitroindole (2d). Mp 228–229 °C. ^{1}H NMR ($CDCl_3$) δ 2.56 (d, *J*=0.8 Hz, 3H), 6.89 (dd, *J*=9.7, 8.9 Hz, 1H), 7.02–7.07 (m, 1H), 8.09 (dd, *J*=8.9, 4.3 Hz, 1H), 8.45 (br s, 1H). EIMS *m/e* (relative intensity): 194 (M^+, 100), 164 (28), 148 (52). Anal. Calcd for $C_9H_7N_2O_2F$: C, 55.67; H, 3.63; N, 14.43. Found: C, 55.87; H, 3.50; N, 14.30.

2.3.5. 5-Fluoro-2-methyl-4-nitroindole (2e). Mp 194–195 °C. ^{1}H NMR δ (DMSO-d_6) 2.48 (s, 3H), 6.65–6.69 (m, 1H), 7.20 (dd, *J*=12.5, 8.7 Hz, 1H), 7.68 (ddd, *J*=8.7, 3.8, 0.8 Hz, 1H), 11.94 (br s, 1H). EIMS *m/e* (relative intensity): 194 (M^+, 100), 164 (42), 148 (69). Anal. Calcd for $C_9H_7FN_2O_2$: C, 55.67; H, 3.63; N, 14.43. Found: C, 55.66; H, 3.39; N, 14.26.

2.3.6. 2-Cyclopropyl-4-nitroindole (3a). Mp 192–193 °C. ^{1}H NMR δ ($CDCl_3$) 0.87–1.01 (m, 2H), 1.03–1.17 (m, 2H), 1.96–2.11 (m, 1H), 6.88–6.92 (m, 1H), 7.16 (dd, *J*=8.0, 8.0 Hz, 1H), 7.57 (ddd, *J*=8.0, 0.9, 0.9 Hz, 1H), 8.09 (dd, *J*=8.1, 0.9 Hz, 1H), 8.42 (br s, 1H). EIMS *m/e* (relative intensity): 202 (M^+, 100), 185 (89), 155 (95), 128 (64). Anal. Calcd for $C_{11}H_{10}N_2O_2$: C, 65.34; H, 4.98; N, 13.85. Found: C, 65.23; H, 4.87; N, 14.04.

2.3.7. 2-*tert*-Butyl-4-nitroindole (4a). Mp 173 °C (lit.[12] 173 °C).

2.3.8. 2-Phenyl-4-nitroindole (5a). Mp 205 °C (lit.[9b] 203–206 °C). IR (cm^{-1}, KBr): 3339, 1500, 1481, 1454, 1374, 1325, 1272, 983, 766.

2.3.9. 2-Phenyl-6-nitroindole (5a6). Mp 214.5–216 °C. ^{1}H NMR (DMSO-d_6) δ 7.16 (s, 1H), 7.38–7.60 (m, 3H), 7.72 (d, *J*=8.8 Hz, 1H), 7.82–7.99 (m, 3H), 8.29 (d, *J*=2.0 Hz, 1H), 12.36 (s br, 1H). EIMS *m/e* (relative intensity): 238 (M^+, 100), 208 (35), 192 (44), 165 (28). IR (cm^{-1}, KBr): 3323, 1502, 1487, 1461, 1298, 1065, 757, 731. Anal. Calcd for $C_{14}H_{10}N_2O_2$: C, 70.58; H, 4.23; N, 11.76. Found: C, 71.47; H, 4.29; N, 11.62.

2.3.10. 7-Chloro-4-nitro-2-phenylindole (5b). Mp 200–202 °C. ^{1}H NMR δ (DMSO-d_6) 7.40 (d, *J*=8.6 Hz, 1H), 7.43–7.60 (m, 4H), 8.07 (d, *J*=8.6 Hz, 1H), 8.06–8.14 (m, 2H), 12.42 (br s, 1H). EIMS *m/e* (relative intensity): 272, 274 (M^+, 100, 37), 242, 244 (25, 9), 226, 228 (21, 7), 191 (27). Anal. Calcd for $C_{14}H_9ClN_2O_2$: C, 61.66; H, 3.33; N, 10.27. Found: C, 61.81; H, 3.01; N, 10.08.

2.3.11. 7-Bromo-4-nitro-2-phenylindole (5c). Mp 197.5–198 °C. ^{1}H NMR ($CDCl_3$) δ 7.43 (d, *J*=8.6 Hz, 1H), 7.42–7.60 (m, 3H), 7.67 (d, *J*=2.5 Hz, 1H), 7.78–7.85 (m, 2H), 8.05 (d, *J*=8.6 Hz, 1H), 8.81 (s br, 1H). EIMS *m/e* (relative intensity): 316, 318 (M^+, 100, 97), 286, 288 (28, 27), 270, 272 (25, 24), 191 (99). Anal. Calcd for $C_{14}H_9N_2O_2Br$: C, 53.02; H, 2.86; N, 8.83; Br, 25.20. Found: C, 53.30; H, 2.67; N, 8.84; Br, 24.76.

2.3.12. 7-Fluoro-4-nitro-2-phenylindole (5d). Mp 204–206 °C. ^{1}H NMR δ (DMSO-d_6) 7.19 (dd, *J*=10.2, 8.9 Hz, 1H) 7.41–7.60 (m, 4H), 8.03–8.10 (m, 2H), 8.11 (dd, *J*=8.9, 4.1 Hz, 1H), 12.77 (br s, 1H). EIMS *m/e* (relative intensity): 256 (M^+, 100), 226 (27), 210 (42). Anal. Calcd for $C_{14}H_9FN_2O_2$: C, 65.62; H, 3.54; N, 10.93. Found: C, 65.53; H, 3.29; N, 10.78.

2.3.13. 4-Nitro-2-(2-pyridyl)indole (6a). Mp 167 °C (lit.[12] 167 °C).

2.3.14. 2-(Furan-2-yl)-4-nitroindole (7a). Mp 211–212 °C. ^{1}H NMR (DMSO-d_6) δ 6.73 (dd, *J*=3.4, 1.8 Hz, 1H), 7.17 (dd, *J*=3.4, 0.6 Hz, 1H), 7.32 (dd, *J*=8.0, 8.0 Hz, 1H), 7.33 (dd, *J*=2.2, 0.8 Hz, 1H), 7.85 (dt, *J*=8.0, 0.9 Hz, 1H), 7.92 (dd, *J*=1.8, 0.7 Hz, 1H), 8.07 (dd, *J*=8.0, 0.8 Hz, 1H), 12.49 (s, 1H). EIMS *m/e* (relative intensity): 228 (M^+, 100), 198 (8), 182 (34). Anal. Calcd for $C_{12}H_8N_2O_3$: C, 63.16; H, 3.53; N, 12.28. Found: C, 63.30; H, 3.32; N, 12.30.

2.3.15. 7-Chloro-2-(2′-furyl)-4-nitroindole (7b). Mp 209–210 °C. ^{1}H NMR δ ($CDCl_3$) 6.60 (dd, *J*=3.4, 1.7 Hz, 1H),

6.92 (dd, *J*=3.4, 0.6 Hz, 1H), 7.24 (d, *J*=8.6 Hz, 1H), 7.49–7.62 (m, 2H), 8.10 (d, *J*=8.6 Hz, 1H), 8.97 (br s, 1H). EIMS *m/e* (relative intensity): 262, 264 (M^+, 100, 34), 232, 234 (22, 7), 216, 218 (47, 16). Anal. Calcd for $C_{12}H_7ClN_2O_3$: C, 54.88; H, 2.69; N, 10.67. Found: C, 54.60; H, 2.53; N, 10.52.

2.3.16. 4-Nitro-2-(2′-thienyl)-indole (8a). Mp 220–221 °C. ^{1}H NMR (DMSO-d_6) δ 7.24 (dd, *J*=5.0, 3.7 Hz, 1H), 7.29 (dd, *J*=2.2, 0.8 Hz, 1H), 7.31 (dd, *J*=8.0, 8.0 Hz, 1H), 7.72 (dd, *J*=5.0, 1.2 Hz, 1H), 7.75 (dd, *J*=3.7, 1.2 Hz, 1H), 7.85 (ddd, *J*=8.0, 0.8, 0.8 Hz, 1H), 8.07 (dd, *J*=8.0, 0.8 Hz, 1H), 12.50 (s br, 1H). EIMS *m/e* (relative intensity): 244 (M^+, 100), 214 (27), 198 (44). Anal. Calcd for $C_{12}H_8N_2O_2S$: C, 59.01; H, 3.30; N, 11.47. Found: C, 59.20; H, 3.14; N, 11.42.

2.3.17. 7-Chloro-4-nitro-2-(2′-thienyl)indole (8b). Mp 211–213 °C. ^{1}H NMR δ (acetone-d_6) 7.21 (dd, *J*=5.1, 3.7 Hz, 1H), 7.36 (d, *J*=8.6 Hz, 1H), 7.43 (d, *J*=2.0 Hz, 1H), 7.66 (dd, *J*=5.1, 1.1 Hz, 1H), 7.82 (dd, *J*=3.7, 1.1 Hz, 1H), 8.08 (d, *J*=8.7 Hz, 1H), 11.50 (br s, 1H). EIMS *m/e* (relative intensity): 278, 280 (M^+, 100, 37), 248, 250 (40, 15). Anal. Calcd for $C_{12}H_7ClN_2O_2S$: C, 51.71; H, 2.53; N, 10.05. Found: C, 51.63; H, 2.26; N, 10.02.

2.3.18. 4-Nitro-2-(1-methyl-1*H*-pyrrol-2-yl)-1*H*-indole (9a). Mp 216–218 °C. ^{1}H NMR (DMSO-d_6) δ 3.91 (s, 3H), 6.18 (dd, *J*=3.8, 2.6 Hz, 1H), 6.71 (dd, *J*=3.8, 1.8 Hz, 1H), 7.02 (dd, *J*=2.1, 2.0 Hz, 1H), 7.17 (d, *J*=1.5 Hz, 1H), 7.26 (dd, *J*=8.0, 8.0 Hz, 1H), 7.79 (d, *J*=7.9 Hz, 1H), 8.03 (dd, *J*=8.1, 0.7 Hz, 1H), 12.03 (s, 1H). EIMS *m/e* (relative intensity): 241 (M^+, 100), 195 (36). Anal. Calcd for $C_{13}H_{11}N_3O_2$: C, 64.72; H, 4.60; N, 17.42. Found: C, 64.48; H, 4.42; N, 17.57.

2.3.19. 2,3-Dimethyl-4-nitroindole (10a). Mp 173 °C (lit.[33] 175 °C).

2.3.20. 2,3-Dimethyl-6-nitroindole (10a6). Mp 142 °C (lit.[34] 142 °C).

2.3.21. 2-Ethyl-3-methyl-4-nitroindole (11a). Mp 175 °C (lit.[8d] 175 °C).

2.3.22. 2-Ethyl-3-methyl-6-nitroindole (11a6). Mp 165 °C (lit.[8d] 164 °C).

2.3.23. 7-Chloro-2-ethyl-3-methyl-4-nitroindole (11b). Mp 150–151 °C. ^{1}H NMR δ ($CDCl_3$) 1.34 (t, *J*=7.6 Hz, 3H), 2.29 (s, 3H), 2.85 (q, *J*=7.6 Hz, 2H), 7.11 (d, *J*=8.5 Hz, 1H), 7.72 (d, *J*=8.5 Hz, 1H), 8.35 (br s, 1H). EIMS *m/e* (relative intensity): 238, 240 (M^+, 41, 14), 221, 223 (69, 25), 191, 193 (100, 39). Anal. Calcd for $C_{11}H_{11}ClN_2O_2$: C, 55.36; H, 4.65; N, 11.74. Found: C, 55.64; H, 4.78; N, 11.59.

2.3.24. 2-Ethyl-7-fluoro-3-methyl-4-nitroindole (11d). Mp 155–156 °C. ^{1}H NMR δ ($CDCl_3$) 1.33 (t, *J*=7.7 Hz, 3H), 2.30 (s, 3H), 2.84 (q, *J*=7.6 Hz, 2H), 6.82 (dd, *J*=9.5, 8.8 Hz, 1H), 7.78 (dd, *J*=8.8, 4.5 Hz, 1H), 8.40 (br s, 1H). EIMS *m/e* (relative intensity): 222 (M^+, 44), 205 (62), 175 (100). Anal. Calcd for $C_{11}H_{11}FN_2O_2$: C, 59.46; H, 4.99; N, 12.61. Found: C, 59.41; H; 4.84; N, 12.61.

2.3.25. 2-Ethyl-5-fluoro-3-methyl-4-nitroindole (11e). Mp 162–163 °C. ^{1}H NMR δ ($CDCl_3$) 1.30 (t, *J*=7.6 Hz, 3H), 2.11 (s, 3H), 2.78 (q, *J*=7.6 Hz, 2H), 6.92 (dd, *J*=10.4, 8.8 Hz, 1H), 7.33 (dd, *J*=8.8, 3.9 Hz, 1H), 8.10 (br s, 1H). EIMS *m/e* (relative intensity): 222 (M^+, 50), 205 (48), 175 (100). Anal. Calcd for $C_{11}H_{11}FN_2O_2$: C, 59.46; H, 4.99; N, 12.61. Found: C, 60.48; H, 5.15; N, 12.45.

2.3.26. 2-Ethyl-5-fluoro-3-methyl-6-nitroindole (11e6). Mp 197–198 °C. ^{1}H NMR δ ($CDCl_3$) 1.32 (t, *J*=7.7 Hz, 3H), 2.21 (s, 3H), 2.82 (q, *J*=7.7 Hz, 2H), 7.21 (d, *J*=12.1 Hz, 1H), 8.09 (d, *J*=6.1 Hz, 1H), 8.23 (br s, 1H). EIMS *m/e* (relative intensity): 222 (M^+, 100), 207 (48), 192 (31), 161 (51). Anal. Calcd for $C_{11}H_{11}FN_2O_2$: C, 59.46; H, 4.99; N, 12.61. Found: C, 60.49; H, 5.24; N, 12.18.

2.3.27. 3-Methyl-4-nitro-2-phenylindole (12a). Mp 207–208 °C (lit.[35] 205–206 °C), ^{1}H NMR δ ($CDCl_3$) 2.43 (s, 3H), 7.20 (d, *J*=8.0 Hz, 1H), 7.40–7.62 (m, 5H), 7.62 (dd, *J*=8.1, 0.9 Hz, 1H), 7.78 (dd, *J*=7.9, 0.9 Hz, 1H), 8.40 (br s, 1H). EIMS *m/e* (relative intensity): 252 (M^+, 63), 235 (37), 205 (100). IR (cm^{-1}, KBr): 3357, 1504, 1328, 1286, 1055, 993, 810, 764, 772, 700. Anal. Calcd for $C_{15}H_{12}N_2O_2$: C, 71.42; H, 4.79; N, 11.10. Found: C, 71.25; H, 4.64; N, 10.97.

2.3.28. 3-Methyl-6-nitro-2-phenylindole (12a6). Mp 208–210 °C (lit.[35] 205–206 °C), ^{1}H NMR δ ($CDCl_3$) 2.48 (s, 3H), 7.39–7.66 (m, 6H), 8.06 (dd, *J*=8.8, 2.0 Hz, 1H), 8.34 (dd, *J*=2.0, 0.5 Hz, 1H), 8.45 (br s, 1H). EIMS *m/e* (relative intensity): 252 (M^+, 100), 222 (23), 206 (24). IR (cm^{-1}, KBr): 3339, 1495, 1464, 1297, 1238, 1062, 775, 755, 709. Anal. Calcd for $C_{15}H_{12}N_2O_2$: C, 71.42; H, 4.79; N, 11.10. Found: C, 71.69; H, 4.46; N, 10.82.

2.3.29. 8-Nitro-1,2,3,4-tetrahydro-cyclopent[*b*]indole (13a). Mp 198–199 °C (lit.[36a] 199 °C).

2.3.30. 6-Nitro-1,2,3,4-tetrahydro-cyclopent[*b*]indole (13a6). Mp 139–141 °C (lit.[36a] 153 °C), ^{1}H NMR (DMSO-d_6) δ 2.41–2.58 (m, 2H), 2.72–2.85 (m, 2H), 2.85–2.97 (m, 2H), 7.45 (d, *J*=8.8 Hz, 1H), 7.85 (dd, *J*=8.8, 2.2 Hz, 1H), 8.22 (d, *J*=2.2 Hz, 1H), 11.69 (s, 1H). EIMS *m/e* (relative intensity): 202 (M^+, 100), 172 (13), 156 (35). Anal. Calcd for $C_{11}H_{10}N_2O_2$: C, 65.34; H, 4.98; N, 13.85. Found: C, 65.36; H, 5.21; N, 13.76.

2.3.31. 5-Nitro-1,2,3,4-tetrahydrocarbazole (14a). Mp 152 °C (lit.[36b] 153–156 °C).

2.3.32. 7-Nitro-1,2,3,4-tetrahydrocarbazole (14a6). Mp 169 °C (lit.[36b] 170–171 °C).

2.3.33. 8-Chloro-5-nitro-1,2,3,4-tetrahydrocarbazole (14b). Mp 208–209 °C (lit.[37] 214 °C), ^{1}H NMR δ ($CDCl_3$) 1.77–2.00 (m, 4H), 2.79–2.96 (m, 4H), 7.10 (d, *J*=8.5 Hz, 1H), 7.79 (d, *J*=8.5 Hz, 1H), 8.35 (br s, 1H). MS: 250, 252 (M^+, 32, 10), 233, 235 (100, 32), 203, 205 (77, 26). Anal. Calcd for $C_{12}H_{11}ClN_2O_2$: C, 57.50; H, 4.42; N, 11.17. Found: C, 57.46; H, 4.19; N, 11.10.

2.3.34. 1-Nitro-5,6,7,8,9,10-hexahydro-cyclohepta[*b*]indole (15a). Mp 147–148 °C (lit.[35] 148–149 °C).

2.3.35. 3-Nitro-5,6,7,8,9,10-hexahydro-cyclohepta[*b*] indole (15a6). Mp 134–136 °C (lit.[35] 135–136 °C).

2.3.36. 5,6-Dihydro-7-nitrobenzo[*a*]carbazole (16a). Mp 258–259 °C (dec.). ^{1}H NMR (DMSO-d_6) δ 2.93–3.15 (m, 4H), 7.25 (dd, *J*=8.0, 8.0 Hz, 1H), 7.30–7.41 (m, 3H), 7.70–7.78 (m, 2H), 7.82 (dd, *J*=8.0, 1.0 Hz, 1H), 12.36 (br s, 1H). EIMS *m/e* (relative intensity): 264 (M^+, 32), 247 (68), 217 (100). Anal. Calcd for $C_{16}H_{12}N_2O_2$: C, 72.72; H, 4.58; N, 10.60. Found: C, 72.57; H, 4.28; N, 10.41.

2.3.37. 5,6-Dihydro-9-nitrobenzo[*a*]carbazole (16a6). Mp 253–254 °C (lit.[38] 226–228 °C), ^{1}H NMR (DMSO-d_6) δ 2.96–3.16 (m, 4H), 7.30–7.48 (m, 3H), 7.72 (d, *J*=8.8 Hz, 1H), 7.76–7.83 (m, 1H), 7.97 (dd, *J*=8.8, 2.1 Hz, 1H), 8.32 (d, *J*=2.1 Hz, 1H), 12.35 (br s, 1H). EIMS *m/e* (relative intensity): 264 (M^+, 100), 234 (22), 217 (90). Anal. Calcd for $C_{16}H_{12}N_2O_2$: C, 72.72; H, 4.58; N, 10.60. Found: C, 72.71; H, 4.37; N, 10.69.

2.3.38. 10-Chloro-5,6-dihydro-7-nitrobenzo[*a*]carbazole (16b). Mp 206–207 °C. ^{1}H NMR δ (DMSO-d_6) 2.91–3.11 (m, 4H), 7.33 (d, *J*=8.5 Hz, 1H), 7.31–7.38 (m, 3H), 7.84 (d, *J*=8.5 Hz, 1H), 8.06–8.14 (m, 1H), 12.35 (br s, 1H). MS: 298, 300 (M^+, 38, 13), 281, 283 (100, 33), 251, 253 (65, 23). Anal. Calcd for $C_{16}H_{11}ClN_2O_2$: C, 64.33; H, 3.71; N, 9.38. Found: C, 64.61; H, 3.62; N, 9.01.

2.3.39. 7-Chloro-2-(1′-naphtyl)-4-nitroindole (17b). Mp 213–214 °C. ^{1}H NMR δ (DMSO-d_6) 7.36 (d, *J*=2.1 Hz, 1H), 7.47 (d, *J*=8.6 Hz, 1H), 7.58–7.86 (m, 4H), 8.05–8.20 (m, 3H), 8.13 (d, *J*=8.6 Hz, 1H), 12.80 (br s, 1H). EIMS *m/e* (relative intensity): 322, 324 (M^+, 100, 34), 276, 278 (20, 6). Anal. Calcd for $C_{18}H_{11}ClN_2O_2$: C, 66.99; H, 3.44; N, 8.68. Found: C, 67.14; H, 3.20; N, 8.42.

2.3.40. 3-Ethyl-4-nitro-2-*n*-propylindole (18a). Mp 144–145 °C. ^{1}H NMR δ ($CDCl_3$) 0.98–1.11 (m, 6H) 1.61–1.81 (m, 2H), 2.72–2.86 (m, 4H), 7.12 (dd, *J*=7.9 Hz, 1H), 7.52 (dd, *J*=7.9, 1.0 Hz, 1H), 7.74 (dd, *J*=7.9, 1.0 Hz, 1H), 8.27 (br s, 1H). EIMS *m/e* (relative intensity): 232 (M^+, 100), 215 (65). Anal. Calcd for $C_{13}H_{16}N_2O_2$: C, 67.22; H, 6.94; N, 12.06. Found: C, 67.42; H, 6.98; N, 12.05.

2.3.41. 7-Chloro-3-ethyl-4-nitro-2-*n*-propylindole (18b). Mp 151–152 °C. ^{1}H NMR δ ($CDCl_3$) 0.98–1.11 (m, 6H), 1.65–1.86 (m, 2H), 2.73–2.87 (m, 4H), 7.12 (d, *J*=8.5 Hz, 1H), 7.72 (d, *J*=8.5 Hz, 1H), 8.38 (br s, 1H). EIMS *m/e* (relative intensity): 266, 268 (M^+, 100, 33), 249, 251 (70, 23), 221, 223 (39, 14). Anal. Calcd for $C_{13}H_{15}ClN_2O_2$: C, 58.54; H, 5.67; N, 10.50. Found: C, 58.38; H, 5.70; N, 10.51.

2.3.42. 3-Allyl-2-methyl-4-nitroindole (19a). Mp 129–130 °C. ^{1}H NMR δ ($CDCl_3$) 2.44 (s, 3H), 3.54–3.59 (m, 2H), 4.71–4.84 (m, 1H), 4.86–4.95 (m, 1H), 5.82–6.03 (m, 1H), 7.12 (dd, *J*=8.0 Hz, 1H), 7.52 (dd, *J*=8.0, 1.0 Hz, 1H), 7.74 (dd, *J*=8.0, 1.0 Hz, 1H), 8.35 (br s, 1H). EIMS *m/e* (relative intensity): 216 (M^+, 27), 199 (64), 168 (100). Anal. Calcd for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.59; N, 12.95. Found: C, 66.47; H, 5.65; N, 12.75.

2.3.43. 3-Allyl-2-methyl-6-nitroindole (19a6). Mp 119–121 °C. ^{1}H NMR δ ($CDCl_3$) 2.45 (s, 3H), 3.41–3.50 (m, 2H), 4.96–5.03 (m, 1H), 5.05–5.08 (m, 1H), 5.84–6.06 (m, 1H), 7.50 (d, *J*=8.8 Hz, 1H), 7.98 (dd, *J*=8.8, 2.0 Hz, 1H), 8.25 (d, *J*=2.0 Hz, 1H), 8.37 (br s, 1H). EIMS *m/e* (relative intensity): 216 (M^+, 100), 201 (20), 189 (51). Anal. Calcd for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.59; N, 12.95. Found: C, 66.51; H, 5.56; N, 12.82.

2.3.44. 3-Allyl-7-chloro-2-methyl-4-nitroindole (19b). Mp 136–137 °C. ^{1}H NMR δ ($CDCl_3$) 2.48 (s, 3H), 3.53–3.58 (m, 2H), 4.71–4.84 (m, 1H), 4.87–4.96 (m, 1H), 5.81–6.02 (m, 1H), 7.13 (d, *J*=8.5 Hz, 1H), 7.71 (d, *J*=8.5 Hz, 1H), 8.49 (br s, 1H). EIMS *m/e* (relative intensity): 250, 252 (M^+, 54, 18), 233, 235 (83, 38), 209, 211 (100, 32). Anal. Calcd for $C_{12}H_{11}ClN_2O_2$: C, 57.50; H, 4.42; N, 11.17. Found: C, 57.31; H, 4.24; N, 11.00.

2.3.45. 3-Allyl-7-fluoro-2-methy-4-nitroindole (19d). Mp 119–120 °C. ^{1}H NMR δ ($CDCl_3$) 2.47 (s, 3H), 3.55–3.62 (m, 2H), 4.70–4.84 (m, 1H), 4.87–4.97 (m, 1H), 5.82–6.04 (m, 1H), 6.84 (dd, *J*=9.3, 8.9 Hz, 1H), 7.78 (dd, *J*=8.8, 4.5 Hz, 1H), 8.52 (br s, 1H). EIMS *m/e* (relative intensity): 234 (M^+, 37), 217 (70), 186 (100). Anal. Calcd for $C_{12}H_{11}FN_2O_2$: C, 61.53; H, 4.73; N, 11.96. Found: C, 61.31; H, 4.62; N, 11.82.

2.3.46. 8-Chloro-5-nitro-1,2,3,4-tetrahydro-γ-carboline (20b). Mp 189–190 °C. ^{1}H NMR δ ($CDCl_3$) 2.57 (s, 3H), 2.78–2.87 (m, 2H), 2.93–3.03 (m, 2H), 3.91 (t, *J*=1.6 Hz, 2H), 7.14 (d, *J*=8.6 Hz, 1H), 7.91 (d, *J*=8.6 Hz, 1H), 8.65 (br s, 1H). EIMS *m/e* (relative intensity): 265, 267 (M^+, 9, 3), 248, 250 (100, 32), 218, 220 (88, 30). Anal. Calcd for $C_{12}H_{12}ClN_3O_2$: C, 54.25; H, 4.55; N, 15.81. Found: C, 54.48; H, 4.48; N, 15.59.

2.3.47. Ethylene glycol monoacetal of 8-chloro-1,1-dimethyl-5-nitro-1,2,3,4-tetrahydro-carbazol-2-one (product of reaction of ethylene glycol monoacetal of dimedone with 2-chloro-5-nitroaniline) (21b). Mp 234–236 °C. ^{1}H NMR ($CDCl_3$) δ 1.44 (s, 6H), 2.04 (t, *J*=6.6 Hz, 2H), 3.07 (t, *J*=6.6 Hz, 2H), 3.99–4.15 (m, 4H), 7.14 (d, *J*=8.5 Hz, 1H), 7.82 (d, *J*=8.5 Hz, 1H), 8.28 (br s, 1H). EIMS *m/e* (relative intensity): 336, 338 (M^+, 41, 14), 319, 321 (25, 9), 250, 252 (100, 33). Anal. Calcd for $C_{16}H_{17}N_2O_4Cl$: C, 57.06; H, 5.09; N, 8.32. Found: C, 57.05; H, 5.17; N, 8.11.

2.3.48. 3-Ethyl-5-fluoro-6-nitro-2-phenylindole (22e6). Mp 164–165 °C. ^{1}H NMR δ ($CDCl_3$) 1.31 (t, *J*=7.6 Hz, 3H), 2.87 (q, *J*=7.6 Hz, 2H), 7.40 (d, *J*=12 Hz, 1H), 7.44–7.61 (m, 5H), 8.19 (d, *J*=6.1 Hz, 1H), 8.37 (br s, 1H). EIMS *m/e* (relative intensity): 284 (M^+, 71), 269 (100), 223 (48). Anal. Calcd for $C_{16}H_{13}FN_2O_2$: C, 67.60; H, 4.61; N, 9.85. Found: C, 67.77; H, 4.39; N, 9.89.

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Palladium-catalyzed aryl-amidation. Synthesis of non-racemic *N*-aryl lactams

R. Greg Browning, Vivek Badarinarayana, Hossen Mahmud and Carl J. Lovely*

Department of Chemistry and Biochemistry, The University of Texas at Arlington, Box 19065, Arlington, TX 76019, USA

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Abstract—The Buchwald/Hartwig aryl amination method was used to construct a series of chiral, non-racemic *N*-aryl pyrrolidinones from a common pyrrolidinone precursor and the corresponding aryl bromide. The stereochemical integrity of the *N*-aryl lactam after cross-coupling was proven by synthesis of the racemic compounds and comparison by ^{1}H NMR spectroscopy using Pirkle's chiral solvating agent.

1. Introduction

The *Martinella* alkaloids, martinelline (**1**) and martinellic acid (**2**), have garnered significant interest from the synthetic community since their isolation by Witherup and co-workers in 1995.[1] These partially reduced heterocycles possess noteworthy biological activity in that they are among the few naturally occurring non-peptidic bradykinin antagonists. These compounds are also of interest from a structural perspective, containing up to three guanidino groups, coupled with the fact that they are the only known examples of natural products containing the pyrrolo[3,2-*c*]quinoline ring structure. The combination of these structural and biological factors have contributed to these alkaloids being the subject of synthetic efforts in a number of groups.[2–13]

To date, the *Martinella* alkaloids have been prepared by total synthesis in three groups,[7c,8c,11] with two of the syntheses giving the racemate.[7c,8c] Our own efforts toward the assembly of these compounds have focused primarily on the utility of an intramolecular azomethine ylide–alkene [3+2] cycloaddition.[6] Initial studies employing C2-truncated models established the viability of this route,[6b] and subsequently, we have explored approaches to the preparation of cyclization precursors containing the C2-side chain. The results of these studies have led to the evolution of the approach depicted in Figure 1 in which the three-carbon C2-side chain is introduced as a pyroglutamate derivative through a palladium-catalyzed aryl-amidation reaction.[14] Although approaches to related *N*-aryl lactams have been previously reported in the literature, they typically involve multistep sequences or require fairly harsh reaction conditions.[15,16] Other approaches to *N*-arylamides are known utilizing copper-catalyzed cross-couplings of amides with triarylbismuth,[17] boronic acids,[18] as well as aryl halides.[19] Palladium-catalyzed cross-couplings similar to the methodology reported herein have been used for the *N*-arylation of carbamates.[20–22] Further motivation for the development of this chemistry is due to the fact that a number of other natural products are known that contain a chiral pyrrolidine or pyrrolidinone-derived subunit, such as mitomycin C (**8**)[23] and gephyrotoxin (**9**).[24] The Pd-catalyzed cross-coupling methodology we describe herein could potentially be utilized to introduce a key C–N bond, thereby permitting asymmetric total syntheses of these compounds.

Our earliest attempts with aryl amination reactions utilized a differentially protected amine derived from (*S*)-glutamic acid and bromobenzene derivatives; however, we were unable to effect this transformation.[25] During the course of these experiments, a study by Shakespeare reported a cross-coupling reaction of lactams, including pyrrolidinone, with bromobenzenes, which prompted us to investigate a related cross-coupling reaction with a protected pyroglutamate derivative.[26] Attempts to construct *N*-aryl pyrrolidinones **12** utilizing conditions analogous to those in the Shakespeare report (aryl bromide **10**, silylated lactam **11**, *t*-BuONa, 5 mol% $Pd(OAc)_2$, 6 mol% dppf) proved to be rather low-yielding, and only highly electron-deficient aryl bromides (*p*-NO_2 and *p*-CN) reacted appreciably (Scheme 1).

Optimization of the reaction was attempted and we were able to obtain up to 70% yield of the *N*-arylpyrrolidinones, although rather high catalyst (15 mol% $Pd(OAc)_2$, 30 mol% dppf) loadings were required to achieve these results. Furthermore, the reaction was essentially limited to these

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* Corresponding author. Tel.: +1-817-272-5446; fax: +1-817-272-3808; e-mail address: lovely@uta.edu

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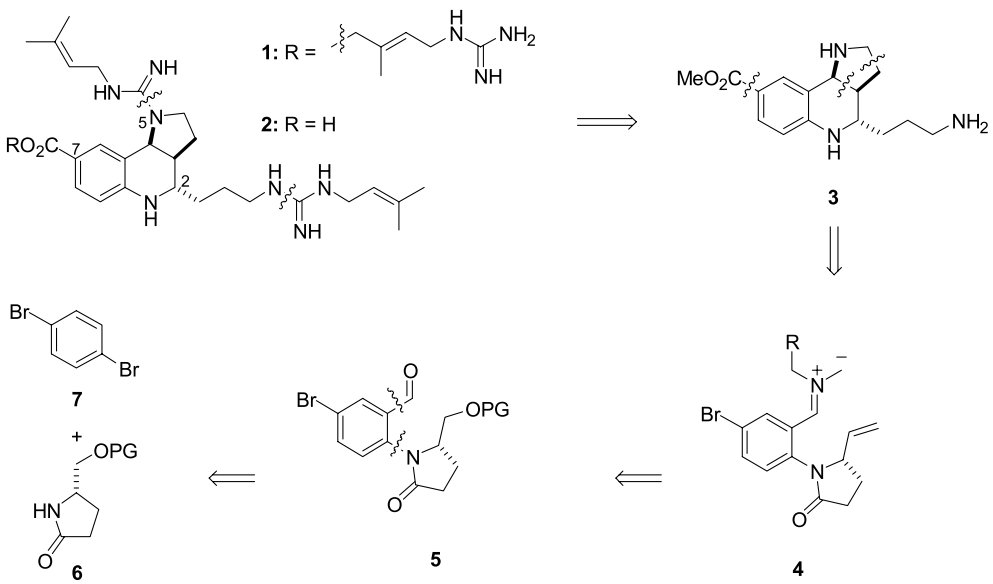
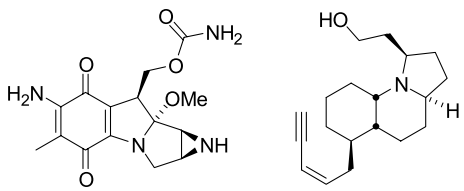


Figure 1. Retrosynthetic analysis of the *Martinella* alkaloids.



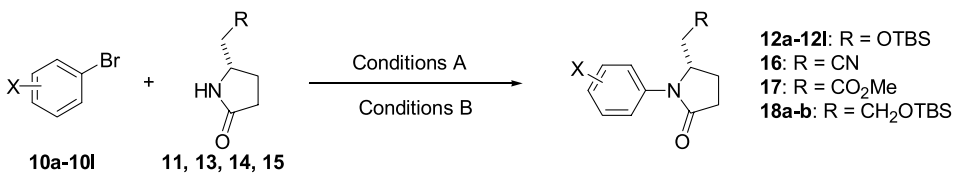
8 **9**

two electron-deficient systems. As these experiments were being conducted, it was reported by Buchwald that both inter- and intramolecular cross-coupling of amides (both cyclic and acyclic) would proceed efficiently with the appropriate choice of ligand system.[27]

When Buchwald's conditions for the intermolecular cross-coupling were applied to pyroglutamate **11** with 4-bromobenzonitrile (**10a**), we were delighted to find that a reaction had taken place in 3.5 h to give **12a** in 95% yield. Once we had determined that these conditions worked efficiently, the reaction was conducted with a series of substituted aryl bromides (**10b**–**l**) to establish the scope of the transformation (Table 1). As can be seen in Table 1, the reaction proceeds efficiently with most of the electron deficient systems investigated, providing the *N*-aryl pyrrolidinones **12** in 54–95% yields. Interestingly, and in contrast with the Shakespeare report, some *o*-substituted bromobenzenes underwent the cross-coupling reaction in moderate to good yield (Table 1, entries 10 and 11, X=*o*-CN and *o*-NO_2). As expected, the reaction proceeded poorly or failed completely with larger or less electron deficient *ortho* substituents (X=*o*-CO_2Me and *o*-CHO). In contrast to both Shakespeare's and Buchwald's results, simple bromobenzene did not participate efficiently in the cross-coupling reaction. Presumably, subtle electronic differences in the intermediate Pd-complexes retard addition of the hindered amide, or subsequent reductive elimination of the cross-coupled product. The cross-coupling reaction occurs chemoselectively, as demonstrated by the cross-coupling of **11** with 4-iodobromobenzene (**10g**), in which substitution takes place at iodide rather than bromide.

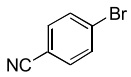
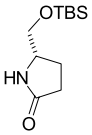
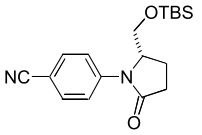
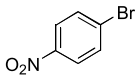
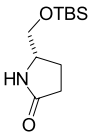
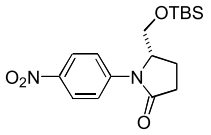
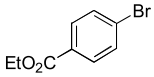
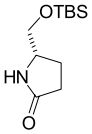
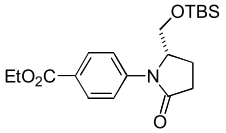
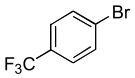
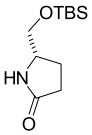
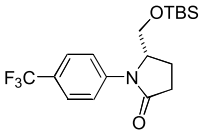
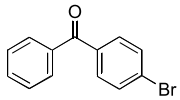
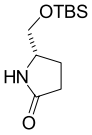
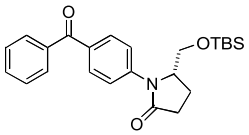
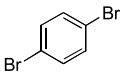
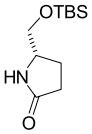
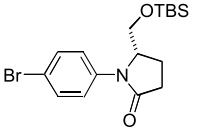
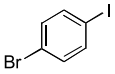
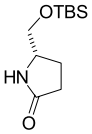
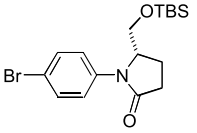
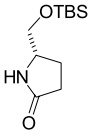
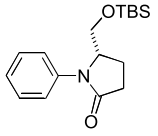
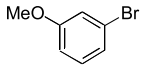
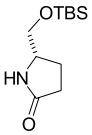
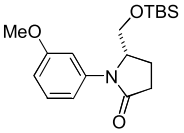
The successful use of these cross-coupling conditions was not limited to lactam **11**; indeed a series of functionalized lactams (**13**–**15**) were prepared and evaluated.[28–30] These functionalized lactams participated in the cross-coupling quite effectively, providing yields of 55–91% of the *N*-aryl lactams (Table 1, entries 13–16). The utility of several of these products as intermediates in total synthesis efforts toward **1**, **2**, **8** and **9** is being investigated.

We also investigated the necessity of the reaction conditions described in Scheme 1 by interchanging the catalyst, ligand and solvent, using **10a** as the test substrate. Variation of the catalyst and ligand system did not change the overall yield of the reaction by a significant amount. When $Pd(OAc)_2$ was substituted for Pd_2dba_3, the yield of the reaction remained essentially the same at 91%, although the time required for completion of the reaction was longer by 1 h. Using $Pd(OAc)_2$ as the catalyst and dppf as the ligand, the yield dropped slightly to 83%. The largest difference was seen when the solvent was changed to toluene. With the Buchwald catalyst/ligand system (Pd_2dba_3, Xantphos), performing the cross-coupling reaction in toluene resulted in a lower yield of 65%.



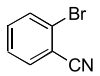
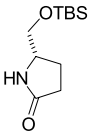
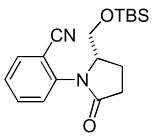
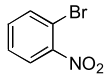
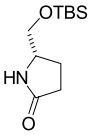
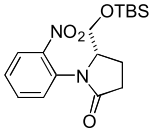
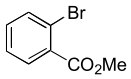
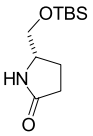
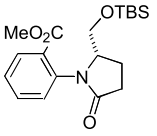
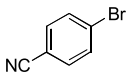
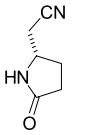
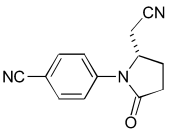
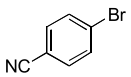
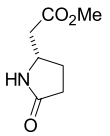
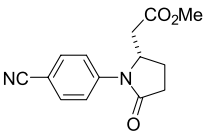
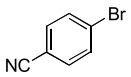
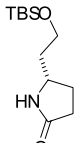
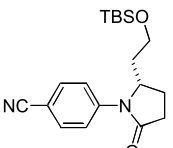
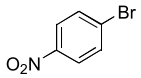
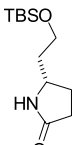
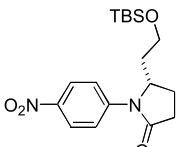
Scheme 1. *Conditions* A=15 mol% $Pd(OAc)_2$, 30 mol% dppf, NaOBu-*t*, $PhCH_3$. *Conditions* B=2.5 mol% $Pd_2(dba)_3$, 7.5 mol% Xantphos, Cs_2CO_3, dioxane.

Table 1. Products and yields from the cross-coupling reactions

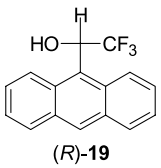
Entry	Aryl bromide	Lactam	Product	Yield (%)[a]	Time (h)	$[\alpha]_D$ (*c*)[b]
1	 **10a**	 **11**	 **12a**	95	3.5	−11.4 (0.5)
2	 **10b**	 **11**	 **12b**	91	3.5	+22.2 (0.5)
3	 **10c**	 **11**	 **12c**	91	8	+15.0 (2.0)
4	 **10d**	 **11**	 **12d**	95	6	−33.6 (0.3)
5	 **10e**	 **11**	 **12e**	91	12	+41.8 (0.5)
6	 **10f**	 **11**	 **12f**	86	4	−31.2 (0.5)
7	 **10g**	 **11**	 **12f**[c]	84	4	−30.8 (0.5)
8	 **10h**	 **11**	 **12h**	15	24	−12.4 (2.0)
9	 **10i**	 **11**	 **12i**	87	6	−41.8 (0.5)

(*continued on next page*)

Table 1 (*continued*)

Entry	Aryl bromide	Lactam	Product	Yield (%)[a]	Time (h)	$[\alpha]_D$ (*c*)[b]
10	 **10j**	 **11**	 **12j**	74	48	−50.8 (0.5)
11	 **10k**	 **11**	 **12k**	52	48	−171.2 (0.5)
12	 **10l**	 **11**	 **12l**	5	48	Nd
13	 **10a**	 **13**	 **16**	90	4	+22.0 (0.5)
14	 **10a**	 **14**	 **17**	55	16	+31.0 (0.5)
15	 **10a**	 **15**	 **18a**	91	6	+29.4 (0.5)
16	 **10b**	 **15**	 **18b**	82	6	+70.2 (0.5)

[a]The yields are the average of two runs and were obtained using conditions B. [b]The optical rotations were recorded as solutions in $CHCl_3$ at 25 °C (*c*=g/100 mL). [c]In this case the reaction occurred with displacement of the iodide substituent.


(*R*)-**19**

One question that remained to be answered was that of the stereochemical integrity of the products following the cross-coupling reaction. Although unlikely, there was a possibility that racemization of the chiral center might occur, e.g. via elimination and readdition of a palladium hydride species. To determine whether or not the chiral center had been compromised under the reaction conditions, we carried out the cross-coupling reactions using (±)-**11** and aryl bromides **10a**–**l** to give the racemic *N*-aryl pyrrolidinones (±)-**12a**–**l**.[31] The products from both the racemic and non-racemic lactams were studied by ^{1}H NMR spectroscopy using Pirkle's chiral solvating agent (*R*)-**19**.[32] These experiments

demonstrated unequivocally that the cross-couplings has occurred with retention of stereochemistry.[33]

When 4 equiv. of (*R*)-**19** were added to $CDCl_3$ solutions of the racemic *N*-aryl lactams (±)-**12**, the *t*-butyl signals were well resolved. Under identical conditions, only one *t*-butyl signal was found in the spectra of the cross-coupling products **12** derived from lactam (*S*)-**11**. Doping experiments showed that >2% of the other stereoisomer could be detected under the conditions used to determine the optical purity and therefore the products were obtained in >95% ee.

In summary, an effective protocol for the construction of non-racemic *N*-aryl lactams has been developed which relies on application of reaction conditions reported by the Buchwald group.[27] Application of similar conditions reported by Shakespeare were less effective in our hands.[25] The utility of these products in total synthesis efforts is being explored and will be published in the near future.

2. Experimental[34]

2.1. General procedure for the cross-couplings

A 10 mL Schlenk tube was charged with the lactam (1.2 mmol), $Pd_2(dba)_3$ (23 mg, 0.025 mmol), xantphos (44 mg, 0.075 mmol), and Cs_2CO_3 (456 mg, 1.4 mmol) and alternately purged and backfilled with N_2. The aryl bromide (1.00 mmol) and 1,4-dioxane (1 mL) were added and the stirred mixture was heated at 105 °C until the reaction was complete by TLC as evidenced by disappearance of the aryl bromide. The resulting mixture was cooled to room temperature, diluted with CH_2Cl_2 (~20 mL), filtered through Celite, and concentrated. The residue was purified by flash chromatography on SiO_2 with the specified ratio of hexanes and EtOAc as eluant.

2.1.1. 4-[(2*S*)-2-*tert*-Butyldimethylsilyloxymethyl-5-oxo-1-pyrrolidinyl]benzonitrile (12a). The product was purified by flash chromatography (SiO_2, 3:2 hexanes/EtOAc), yielding **12a** as a colorless powder. (315 mg, 95%). Mp 79–80 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68–7.62 (m, 4H), 4.39–4.37 (m, 1H), 3.68 (dd, *J*=10.5, 3.7 Hz, 1H), 3.60 (dd, *J*=10.5, 2.6 Hz, 1H), 2.78–2.71 (m, 1H), 2.50 (ddd, *J*=14.1, 10.3, 3.9 Hz, 1H), 2.32–2.24 (m, 1H), 2.14–2.08 (m, 1H), 0.80 (s, 9H), −0.09 (s, 3H), −0.16 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.2, 142.1, 133.0, 122.5, 118.8, 108.1, 62.9, 60.4, 32.0, 25.8, 21.3, 18.1, −5.6, −5.7. FT-IR (KBr, cm^{-1}) 3357, 3185, 3075, 2945, 2855, 2215, 1687, 1595. Anal. Calcd for $C_{18}H_{26}N_2O_2Si$: C, 65.45; H, 7.93; N, 8.48. Found C, 65.27; H, 7.95; N, 8.36.

2.1.2. (5*S*)-5-*tert*-Butyldimethylsilyloxymethyl-1-(4-nitrophenyl)-2-pyrrolidinone (12b). The product was purified by flash chromatography (SiO_2, 7:3 hexanes/EtOAc), yielding **12b** as a yellow powder. (317 mg, 91%). Mp 79–80 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.22 (d, *J*=8.9 Hz, 2H), 7.74 (d, *J*=8.9 Hz, 2H), 4.44 (m, 1H), 3.72 (dd, *J*=10.7, 3.2 Hz, 1H), 3.63 (dd, *J*=10.7, 1.6 Hz, 1H), 2.77 (m, 1H), 2.52 (m, 1H), 2.30 (m, 1H), 2.13 (m, 1H), 0.80 (s, 9H), −0.09 (s, 3H), −0.16 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.4, 144.0, 143.9, 124.7, 121.9, 63.0, 60.5, 32.1, 25.8, 21.4, 18.1, −5.6, −5.7. FT-IR (KBr, cm^{-1}) 3357, 3185, 3075, 2945, 2855, 2215, 1687, 1595. Anal. Calcd for $C_{17}H_{26}N_2O_4Si$: C, 58.28; H, 7.48; N, 7.99. Found C, 58.46; H, 7.53; N, 7.96.

2.1.3. Ethyl 4-[(2*S*)-2-*tert*-butyldimethylsilyloxymethyl-5-oxo-1-pyrrolidinyl]benzoate (12c). The product was purified by flash chromatography (SiO_2, 3:1 hexanes/EtOAc), yielding **12c** as a colorless solid (343 mg, 91%). Mp 76–77 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 (d, *J*=8.9 Hz, 2H), 7.58 (d, *J*=8.9 Hz, 2H), 4.38–4.34 (m, 3H), 3.67 (dd, *J*=10.6, 3.9 Hz, 1H), 3.59 (dd, *J*=10.6, 1.2 Hz, 1H), 2.74 (ddd, *J*=18.0, 10.0, 4.0 Hz, 1H), 2.50 (ddd, *J*=14.2, 10.0, 4.0 Hz, 1H), 2.32–2.24 (m, 1H), 2.16–2.10 (m, 1H), 1.38 (t, *J*=7.2 Hz, 3H), 0.82 (s, 9H), −0.08 (s, 3H), −0.13 (s, 3H) ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.1, 166.1, 141.9, 130.4, 126.8, 122.1, 62.8, 60.9, 60.6, 31.9, 25.7, 21.2, 18.1, 14.3, −5.6, −5.7. FT-IR (KBr, cm^{-1}) 3058, 2929, 2856, 1712, 1606, 1382. Anal. Calcd for $C_{20}H_{31}NO_4Si$: C, 63.62; H, 8.28; N, 3.71. Found C, 63.75; H, 8.22; N, 3.44.

2.1.4. (5*S*)-5-*tert*-Butyldimethylsilyloxymethyl-1-[(4-trifluoromethyl)phenyl]-2-pyrrolidinone (12d). The product was purified by flash chromatography (SiO_2, 3:2 hexanes/EtOAc), yielding **12d** as a colorless oil (354 mg, 95%) that partially solidified upon standing. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 (s, 4H), 4.35 (m, 1H), 3.65 (ddd, *J*=10.7, 3.7, 0.8 Hz, 1H), 3.58 (ddd, *J*=10.7, 2.7, 1.0 Hz, 1H), 2.77–2.70 (m, 1H), 2.53–2.47 (m, 1H), 2.32–2.24 (m, 1H), 2.13–2.09 (m, 1H), 0.81 (s, 9H), −0.08 (s, 3H), −0.13 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.2, 141.1, 126.14, 126.11, 125.2, 123.1, 62.9, 60.8, 31.8, 25.7, 21.3, 18.1, −5.67, −5.70. FT-IR (neat, cm^{-1}) 3067, 2955, 2932, 2859, 1704, 1614, 1520, 1386. Anal. Calcd for $C_{18}H_{26}F_3NO_2Si$: C, 57.89; H, 7.02; N, 3.75. Found C, 57.69; H, 6.74; N, 3.98.

2.1.5. (5*S*)-1-(4-Benzoylphenyl)-5-*tert*-butyldimethylsilyloxymethyl-2-pyrrolidinone (12e). The product was purified by flash chromatography (SiO_2, 3:1 hexanes/EtOAc), yielding **12e** as a colorless powder (374 mg, 91%). Mp 89–90 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86–7.83 (m, 2H), 7.79–7.78 (m, 2H), 7.64–7.61 (m, 2H), 7.60–7.56 (m, 1H), 7.49–7.46 (m, 2H), 4.43–4.39 (m, 1H), 3.71–3.69 (m, 1H), 3.63–3.60 (m, 1H), 2.80–2.73 (m, 1H), 2.56–2.51 (m, 1H), 2.34–2.26 (m, 1H), 2.17–2.11 (m, 1H), 0.83 (s, 9H), −0.06 (s, 3H), −0.12 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.8, 175.3, 141.8, 137.8, 134.0, 132.4, 131.3, 130.3, 128.4, 122.3, 62.9, 60.7, 32.0, 25.8, 21.4, 18.2, −5.60, −5.62. FT-IR. (KBr, cm^{-1}) 3064, 2955, 2927, 2856, 1705, 1651, 1598. Anal. Calcd for $C_{24}H_{31}NO_3Si$: C, 70.38; H, 7.63; N, 3.42. Found C, 70.26; H, 7.61; N, 3.47.

2.1.6. (5*S*)-1-(4-Bromophenyl)-5-*tert*-butyldimethylsilyloxy-methyl-2-pyrrolidinone (12f). The product was purified by flash chromatography (SiO_2, 3:2 hexanes/EtOAc), yielding **12f** as a colorless powder (333 mg, 86% from 1,4-dibromobenzene; 323 mg, 84% from 1-bromo-4-iodobenzene). Mp 52–54 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49–7.30 (m, 4H), 4.25–4.21 (m, 1H), 3.61 (dd, *J*=10.7, 3.9 Hz, 1H), 3.54 (dd, *J*=10.7, 2.7 Hz, 1H) 2.72–2.65 (m, 1H), 2.52–2.44 (m, 1H), 2.30–2.22 (m, 1H), 2.12–2.06 (m, 1H), 0.83 (s, 9H), −0.06 (s, 3H), −0.10 (s, 3H). ^{13}C NMR

(125 MHz, $CDCl_3$) δ 175.1, 136.9, 132.1, 129.1, 125.5, 124.3, 118.9, 62.9, 61.1, 31.7, 25.8, 21.4, 18.2, −5.60, −5.61. FT-IR (KBr, cm^{-1}) 3070, 3041, 2956, 2929, 2856, 1687, 1492, 1395. Anal. Calcd for $C_{17}H_{26}BrNO_2Si$: C, 53.12; H, 6.82; N, 3.64. Found C, 52.91; H, 6.76; N, 3.95.

2.1.7. (5*S*)-5-*tert*-Butyldimethylsilyloxymethyl-1-phenyl-2-pyrrolidinone (12h). The product was purified by flash chromatography (SiO_2, 3:2 hexanes/EtOAc), yielding **12h** as a light brown semi-solid (45 mg, 15%). ^1H NMR (500 MHz, $CDCl_3$) δ 7.38 (m, 4H), 7.19 (t, J=6.9 Hz, 1H), 4.24 (m, 1H), 3.61 (dd, J=10.5, 3.7 Hz, 1H), 3.54 (dd, J=10.5, 2.1 Hz, 1H), 2.70 (ddd, J=17.1, 9.1, 9.1 Hz, 1H), 2.49 (ddd, J=14.7, 10.2, 4.5 Hz, 1H), 2.27 (m, 1H), 2.11 (m, 1H), 0.84 (s, 9H), −0.06 (s, 3H), −0.10 (s, 3H). ^{13}C NMR (125 MHz) δ 174.9, 137.5, 128.9, 125.8, 124.2, 62.7, 61.3, 31.7, 25.7, 21.3, 18.1, −5.5, −5.6. FT-IR (KBr, cm^{-1}): 3114, 2934, 2863, 1696, 1594, 1376, 1251, 840.

2.1.8. (5*S*)-5-*tert*-Butyldimethylsilyloxymethyl-1-(3-methoxyphenyl)-2-pyrrolidinone (12i). The product was purified by flash chromatography (SiO_2, 3:2 hexanes/EtOAc), yielding **12i** as a colorless powder (293 mg, 87%). Mp 51–53 °C. ^1H NMR (500 MHz, $CDCl_3$) δ 7.40–7.35 (m, 1H), 7.05 (dd, J=2.5, 2.0 Hz, 1H), 6.94 (ddd, J=8.1, 2.0, 0.7 Hz, 1H), 6.74 (ddd, J=8.1, 2.5, 0.7 Hz, 1H), 4.26–4.20 (m, 1H), 3.79 (s, 3H), 3.63 (dd, J=10.6, 4.0 Hz, 1H), 3.54 (dd, J=10.6, 2.5 Hz, 1H), 2.70 (ddd, J=17.1, 10.0, 8.6 Hz, 1H), 2.51–2.45 (m, 1H), 2.28–2.21 (m, 1H), 2.12–2.08 (m, 1H), 0.84 (s, 9H), −0.05 (s, 3H), −0.09 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.1, 160.1, 138.9, 129.7, 116.2, 111.7, 110.1, 62.9, 61.4, 55.4, 31.9, 25.8, 21.4, 18.2, −5.57, −5.59. FT-IR (KBr, cm^{-1}) 3108, 2931, 2857, 1684, 1602, 1581, 1396. Anal. Calcd for $C_{18}H_{29}NO_3Si$: C, 64.44; H, 8.71; N, 4.17. Found C, 64.43; H, 8.89; N, 4.32.

2.1.9. 2-[(2*S*)-2-*tert*-Butyldimethylsilyloxymethyl-5-oxo-1-pyrrolidinyl]benzonitrile (12j). The product was purified by flash chromatography (SiO_2, 3:2 hexanes/EtOAc), yielding **12j** as a yellow solid (244 mg, 74%). Mp 54–56 °C. ^1H NMR (500 MHz, $CDCl_3$) δ=7.69 (dd, J=7.8, 1.4 Hz, 1H), 7.63 (td, J=7.8, 1.4 Hz, 1H), 7.43 (d, J=7.8 Hz, 1H), 7.39 (td, J=7.8, 1.4 Hz, 1H), 4.39 (m, 1H), 3.54 (d, J=2.8 Hz, 2H), 2.64–2.68 (m, 1H), 2.55–2.58 (m, 1H), 2.36–2.40 (m, 1H), 2.06–2.08 (m, 1H), 0.82 (s, 9H), −0.05 (s, 3H), −0.07 (s, 3H). ^{13}C NMR (125 MHz) δ 175.7, 141.0, 133.6, 133.5, 129.7, 127.7, 116.7, 111.5, 63.7, 61.9, 30.9, 25.8, 21.9, 18.1, −5.6. FT-IR (KBr, cm^{-1}): 3078, 2929, 2231, 1707, 840, 770. Anal. Calcd for $C_{18}H_{26}N_2O_2Si$: C, 65.41; H, 7.93; N, 8.48. Found: C, 65.20; H, 7.56; N, 8.41.

2.1.10. (5*S*)-5-*tert*-Butyldimethylsilyloxymethyl-1-(2-nitrophenyl)-2-pyrrolidinone (12k). The product was purified by flash chromatography (SiO_2, 7:3 hexanes/EtOAc), yielding **12k** as a yellow solid (182 mg, 52%). Mp 87–89 °C. ^1H NMR (500 MHz, $CDCl_3$) δ 8.02 (dd, J=7.8, 1.4 Hz, 1H), 7.63 (td, J=7.8, 1.4 Hz, 1H), 7.45 (d, J=7.8 Hz, 1H), 7.42 (d, J=7.8 Hz, 1H), 4.16 (m, 1H), 3.63 (d, J=2.4 Hz, 2H), 2.57–2.61 (m, 1H), 2.48–2.53 (m, 1H), 2.36–2.40 (m, 1H), 2.06–2.08 (m, 1H), 0.82 (s, 9H), −0.02 (s, 3H), −0.04 (s, 3H) ^{13}C NMR (125 MHz) δ 175.6, 146.5, 133.7, 131.9, 128.1, 125.6, 64.0, 62.3, 30.6, 25.8, 22.1, 18.1, −5.5. FT-IR (KBr, cm^{-1}): 2930, 2858, 1692, 850, 772. Anal. Calcd for $C_{17}H_{26}N_2O_4Si$: C, 58.26; H, 7.48; N, 7.99. Found: C, 58.04; H, 7.67; N, 8.29.

2.1.11. 4-[(2*S*)-2-Cyanomethyl-5-oxo-1-pyrrolidinyl]benzonitrile (16). The product was purified by flash chromatography (SiO_2, 1:9 hexanes/EtOAc), yielding **16** as a pale yellow solid (202 mg, 90%). Mp 113–115 °C. ^1H NMR (500 MHz, $CDCl_3$) δ 7.70 (d, J=8.7 Hz, 2H), 7.60 (d, J=8.7 Hz, 2H), 4.60–4.56 (m, 1H), 2.86–2.80 (m, 1H), 2.72–2.52 (m, 4H), 2.16–2.11 (m, 1H). ^{13}C NMR (125 MHz) δ 173.9, 140.5, 133.5, 123.4, 118.5, 116.1, 109.3, 54.9, 53.8, 30.7, 23.4. FT-IR ($CHCl_3$, cm^{-1}) 3110, 3066, 2963, 2250, 2227, 1699, 1602, 1507, 1460, 841, 736. Anal. Calcd for $C_{13}H_{11}N_3O$: C, 69.32; H, 4.92; N, 18.66. Found: C, 69.45; H, 5.05; N, 18.64.

2.1.12. 4-[(2*S*)-2-Carbomethoxymethyl-5-oxo-1-pyrrolidinyl]benzonitrile (17). The product was purified by flash chromatography (SiO_2, 1:4 hexanes/EtOAc), yielding **21** as a waxy solid (142 mg, 55%). ^1H NMR (500 MHz, $CDCl_3$) δ 7.67–7.65 (m, 4H) 4.71–4.68 (m, 1H), 3.67 (s, 3H), 2.72–2.65 (m, 2H), 2.60–2.53 (m, 1H), 2.48–2.40 (m, 2H), 1.98–1.91 (m, 1H). ^{13}C NMR (125 MHz) δ 174.4, 170.7, 141.3, 133.2, 122.3, 118.7, 108.4, 55.6, 52.1, 37.6, 30.9, 24.1. FT-IR ($CHCl_3$, cm^{-1}) 2953, 2225, 1709, 1707, 1602, 1508, 1435, 841, 731.

2.1.13. 4-[(2*S*)-2-[2-(*tert*-Butyldimethylsilyloxy)ethyl]-5-oxo-1-pyrrolidinyl]benzonitrile (18a). The product was purified by flash chromatography (SiO_2, 2:3 hexanes/EtOAc), yielding **18a** as a colorless oil (313 mg, 91%). ^1H NMR (500 MHz, $CDCl_3$) δ 7.70 (d, J=8.7 Hz, 2H), 7.60 (d, J=8.7 Hz, 2H), 4.53–4.49 (m, 1H), 3.73–3.64 (m, 2H), 2.70–2.64 (m, 1H), 2.55–2.49 (m, 1H), 2.39–2.31 (m, 1H), 2.01–1.90 (m, 2H), 1.60–1.54 (m, 1H), 0.92 (s, 9H), 0.06 (s, 6H). ^{13}C NMR (125 MHz) δ 174.9, 141.9, 133.1, 122.1, 121.5, 118.9, 58.7, 56.4, 35.3, 31.4, 25.9, 23.8, 18.3, −5.3, −5.4. FT-IR ($CHCl_3$, cm^{-1}) 2951, 2226, 1697, 1602, 1508, 1387, 841, 734.

2.1.14. (5*S*)-5-[2-(*tert*-Butyldimethylsilyloxy)ethyl]-1-(4-nitrophenyl)-2-pyrrolidinone (18b). The product was purified by flash chromatography (SiO_2, 1:1 hexanes/EtOAc), yielding **18b** as a light yellow solid (299 mg, 82%). Mp 88–90 °C. ^1H NMR (500 MHz, $CDCl_3$) δ 8.21 (d, J=9.2 Hz, 2H), 7.87 (d, J=9.2 Hz, 2H), 4.57–4.54 (m, 1H), 3.77–3.73 (m, 1H), 3.70–3.65 (m, 1H), 2.60–2.54 (m, 1H), 2.39–2.31 (m, 1H), 2.10–1.95 (m, 2H), 1.62–1.56 (m, 2H), 0.93 (s, 9H), 0.07 (s, 6H). ^{13}C NMR (125 MHz) δ 174.9, 143.9, 143.5, 124.7, 120.6, 59.3, 56.4, 35.2, 31.5, 25.9, 23.6, 18.3, −5.3, −5.4. FT-IR ($CHCl_3$, cm^{-1}) 2953, 2856, 1704, 1596, 1509, 1464, 835, 751. Anal. Calcd for $C_{18}H_{28}N_2O_4Si$: C, 59.31; H, 7.74; N, 7.69. Found: C, 59.01; H, 7.57; N, 7.68.

Note added in proof

After submission of this manuscript the following article describing an alternate approach to the Martinella alkaloids appeared—Makino, K.; Hara, O.; Takiguchi, Y.; Katano, T.;

Asakawa, Y.; Hatano, K.; Hamada, Y. *Tetrahedron Lett.* **2003**, *44*, 8925.

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33. The enantiomeric purities of the higher homologs (**16**, **17**, **18a**,**b**) were not established experimentally since there was no evidence of racemization in any of the lower homologs.
34. For general details see Ref. 6b.

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Transformation of β-chalcogeno alkenylboranes into tetrasubstituted olefins

Julien Gerard and László Hevesi*

Département de Chimie, Facultés Universitaires Notre-Dame de la Paix; 61, rue de Bruxelles, B-5000 Namur, Belgium

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Abstract—In view of generating trisubstituted vinylic chalcogen derivatives, β-chalcogeno alkenylboranes generated through the chalcogen electrophile induced rearrangements of 1-alkynyltrialkyl borates have been subjected to Suzuki–Miyaura coupling and to boron to copper transmetalation followed by alkylation. Some of the trisubstituted vinyl sulfides obtained by this latter strategy have been converted efficiently into the title olefins through the $NiCl_2$(dmpe) catalyzed coupling with various Grignard reagents.

1. Introduction

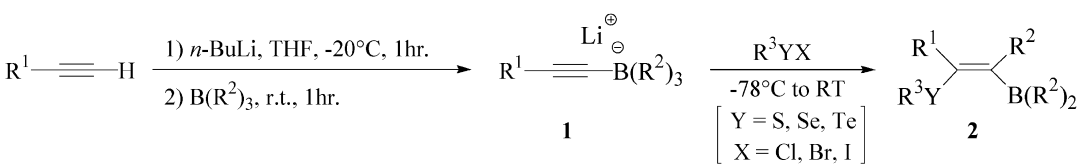
Recently we have reported on the efficient and highly stereoselective rearrangement of 1-alkynyltrialkyl borates triggered by chalcogen (S, Se, Te) electrophiles.[1] We have also shown that the β-chalcogeno alkenylboranes produced via this rearrangement can be protodeborylated with essentially complete retention of stereochemistry to produce the corresponding vinyl sulfides, -selenides or -tellurides in excellent yields. Finally, the latter have been converted into trisubstituted olefins either by nickel catalyzed coupling with Grignard reagents, or through Te/Li exchange (in the case of alkylvinyl tellurides) followed by reaction of the so obtained vinyllithiums with carbonyl compounds.

We now wish to report a detailed account of our efforts aimed at the conversion of the β-chalcogeno alkenylboranes into the title olefins. As previously,[1] these key intermediates **2** are formed in high yield on reaction of various chalcogenyl halides with the in situ prepared lithium 1-alkynyltrialkyl borates **1** (Scheme 1).

Some of these compounds are stable crystalline solids on which X-ray structure determination have been carried out. In all the cases examined, the boron and chalcogen moieties have shown a *cis* relationship, attesting thereby the high stereoselectivity of the rearrangement. Our goal will be to preserve this stereochemistry throughout the two successive steps leading to the target olefins: (i) electrophilic substitution of the boron moiety by a carbon fragment and (ii) replacement of the chalcogenyl group.

2. Results and discussion

Considering the much greater sensitivity of the C–B bond as compared to the C–S(Se,Te) bonds, we decided to transform first the β-chalcogeno alkenylboranes into fully substituted vinyl chalcogenides **3** (Scheme 2). For this purpose, we have investigated two different strategies: (i) the Suzuki–Miyaura coupling and (ii) the boron to copper exchange followed by alkylation.



Scheme 1.

Keywords: Rearrangement of 1-alkynyltrialkyl borates; Trisubstituted vinyl chalcogenides; Tetrasubstituted olefins; Alkenylboranes; Suzuki–Miyaura coupling; Transmetalation; Nickel catalyzed coupling with Grignard reagents.
* Corresponding author. Fax: +32-81725451; e-mail address: laszlo.hevesi@fundp.ac.be

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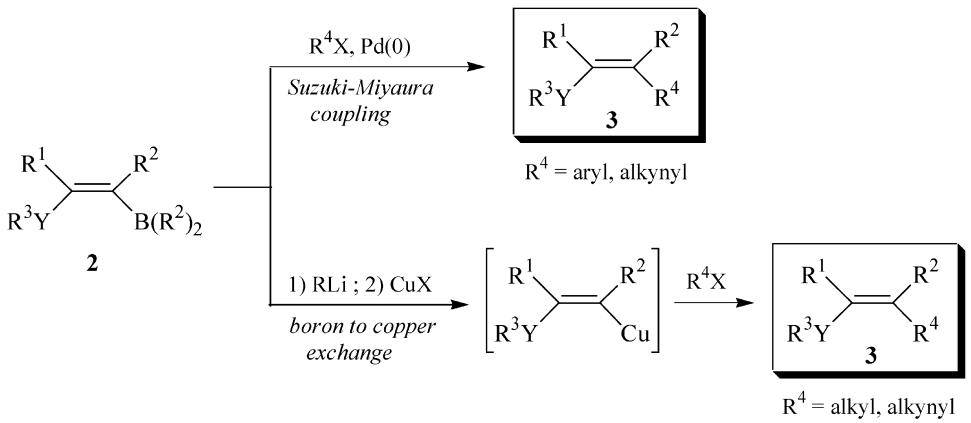


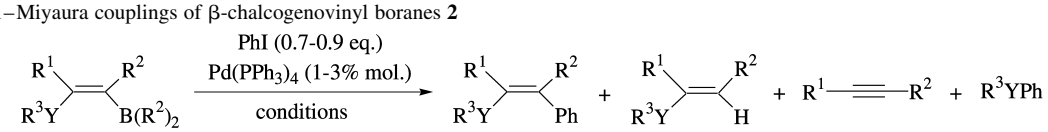
Scheme 2.

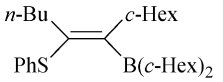
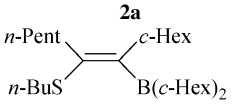
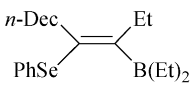
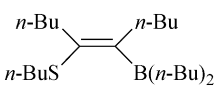
2.1. Suzuki–Miyaura coupling of β-chalcogeno alkenylboranes

The palladium catalyzed reaction between organoboron compounds and alkynyl, alkenyl and aryl halides has appeared to be a powerful and useful methodology for the formation of carbon–carbon bonds.[2] Since the reagents and conditions of the so-called Suzuki–Miyaura coupling should not alter the vinylchalcogen moiety, we have tested it on four different β-chalcogeno alkenylboranes under various conditions. The quite limited success of the method is illustrated by the results shown in Table 1.

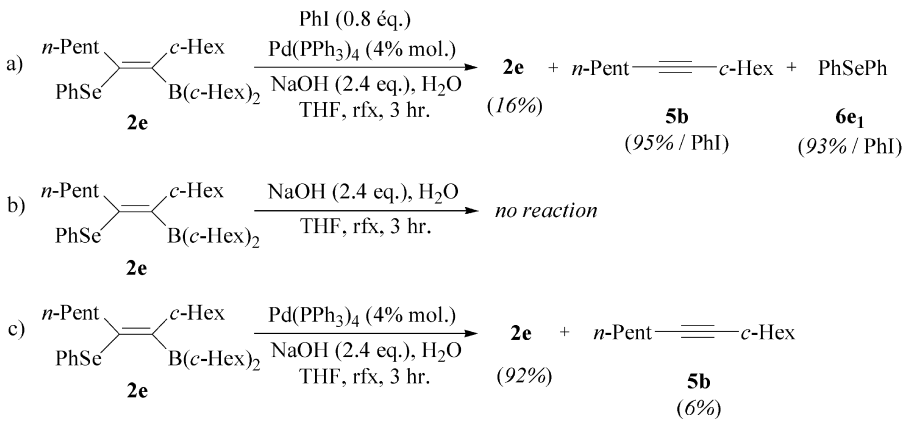
It turns out that the two major side reactions competing with the desired coupling are the elimination of both heteroatomic moieties leading to an internal alkyne and the protodeborylation producing vinyl chalcogenides. These reactions can occur separately or concomitantly. In order to gain some insight into the details of these side reactions, we have carried out a few additional experiments. Thus, (*E*)-1-cyclohexyl-1-(dicyclohexylboryl)-2-(phenylseleno)-1-heptene **2e** has been subjected to a typical Suzuki–Miyaura coupling reaction using iodobenzene as electrophile (Scheme 3a). As can be seen, none of the desired vinyl selenide was observed. Instead, *n*-pentylcyclohexylacetylene **5b** and diphenylselenide **6e$_1$** were formed in almost quantitative yields (with respect to the amount of iodobenzene used). In this case, elimination of the boron and selenium moieties, accompanied by the consumption of iodobenzene by the insipient selenolate anion producing

Table 1. Suzuki–Miyaura couplings of β-chalcogenovinyl boranes **2**



Entry	Reagent	Base (equiv./PhI)	Conditions	Yield (%)			
				3	**4**	**5**	**6**
1	 **2a**	NaOH aq. (3.0)	THF, rfx 3 h	33 (**3a$_1$**)	—	62 (**5a**)	59 (**6a$_1$**)
2	**2a**	K_3PO_4 (3.0)	DMF/THF rfx, 18 h	33 (**3a$_1$**)	—	58 (**5a**)	58 (**6a$_1$**)
3	**2a**	Na_2HPO_4 (3.0)	DMF/THF rfx, 16 h	0[a] (**3a$_1$**)	—	—	—
4	**2a**	Na_2CO_3 (2.4)	DMF/THF rfx, 16 h	0[a] (**3a$_1$**)	—	—	—
5	**2a**	Bu_4NF (2.0)	THF, rfx 13 h	37 (**3a$_1$**)	27 (**4a**)	35 (**5a**)	37 (**6a$_1$**)
6	 **2b**	Bu_4NF (2.0)	THF, rfx 13 h	70 (**3b$_1$**)	Traces (**4b**)	9 (**5b**)	—
7[b]	 **2c**	NaOH aq. (3.0)	THF, rfx 16 h	0 (**3c$_1$**)	61 (**4c**)	—	—
8[b]	 **2d**	Bu_4NF (2.0)	THF, rfx 20 h	37 (**3d$_1$**)	[c]	—	—
9[b]	**2d**	K_3PO_4 (2.0)	DMF/THF rfx, 28 h	34 (**3d$_1$**)	[c]	—	—

[a] **2a** was recovered quantitatively.
[b] These experiments were carried out in situ, without isolation of the alkenylborane.
[c] The formation of these compounds has not been quantified.



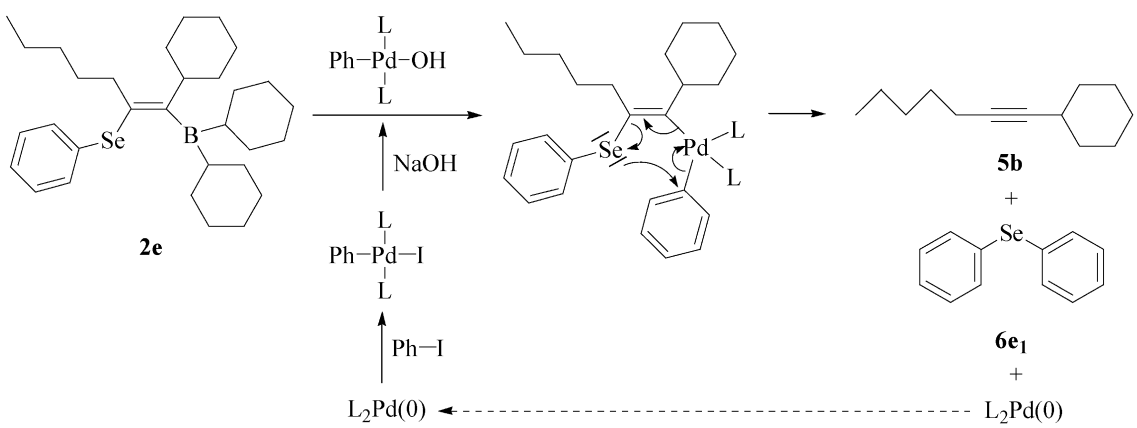
Scheme 3.

diphenylselenide,[3] completely predominated. However, when **2e** was refluxed in THF with aqueous sodium hydroxide, no elimination occurred and the starting material was recovered entirely (Scheme 3b). Similarly, refluxing **2e** under the same conditions but in the presence of the palladium catalyst produced only trace amounts of the internal alkyne **5b**, leaving 92% of **2e** unchanged (Scheme 3c). These results indicate that coordination of hydroxide ion onto the boron atom of the starting β-chalcogeno alkenylboranes is not responsible for the elimination. Therefore, this side reaction must occur at the level of a β-chalcogeno alkenylpalladium intermediate. Moreover, the latter species should contain the phenyl group already attached to palladium, since withdrawing iodobenzene from the reaction mixture brings about a remarkable decrease of the alkyne's yield. Scheme 4 shows the series of events which seems the most probable.

In the light of the above, it is much easier to understand the results of Table 1. Indeed, entry 1 shows that the behaviour of β-phenylthio alkenylborane **2a** towards the Suzuki–Miyaura coupling is fairly comparable to that of **2e**; the difference lies in the ratio of coupling to elimination, that is roughly 1:2 for **2a** instead of 0:100 for **2e**. Clearly, the phenylthio group (a weaker leaving group than the phenylseleno group) allows the coupling reaction to compete to some extent with *syn*-elimination. In agreement with this view, β-butylthio alkenylborane **2b** led to a good yield of vinyl sulfide $\mathbf{3b_1}$ and only to a small amount of *n*-pentylcyclohexylacetylene **5b** (Table 1, entry 6).

The nature of the 'base' required for the Suzuki–Miyaura couplings does not seem to be decisive here since the amounts of coupling product formed from **2a** were almost identical, regardless of whether NaOH, K_3PO_4 or Bu_4NF were used (Table 1, entries 1, 2, and 5). Surprisingly, in the presence of sodium hydrogenphosphate or sodium carbonate, no reaction took place at all (Table 1, entries 3 and 4).

As mentioned above, the second major side reaction observed was protodeborylation of β-chalcogeno alkenylboranes **2** producing the corresponding vinyl chalcogenides **4**. According to earlier findings,[4] secondary alkyl and cycloalkyl substituted alkenylboranes are usually very reluctant to this reaction, whereas primary alkyl derivatives undergo protodeborylation efficiently. While this trend is reasonably well confirmed by entries 6 and 7 of Table 1, we cannot rationalize the presence of (*E*)-1-cyclohexyl-2-(phenythio)-1-hexene **4a** (27%) among the products in entry 5. In view of the nearly quantitative yield in *n*-pentylcyclohexylacetylene **5b** in the experiment with **2e** (Scheme 3a), formation of only traces of 3-tetradecyne **5c** from **2c** is also rather puzzling (Table 1, entry 7). In this case, the main product appeared to be (*E*)-4-(phenylseleno)-3-tetradecene **4c** (61%) arising from protodeborylation. It is interesting to note that this latter process does not appear to take place exclusively by coordination of hydroxide ion



Scheme 4.

onto **2e** to form a vinylic borate complex followed by reaction with water. Indeed, refluxing **2e** for 16 h with aqueous sodium hydroxide in THF gave only a 35% yield of vinyl selenide **4c**. This suggests that protodeborylation may also be subject to palladium catalysis,[5] in an analogous way to the *syn*-elimination outlined in Scheme 4. Finally, the experiments carried out on **2d** (Table 1, entries 8 and 9) confirm the difficulty to get good yields of coupling product when the boron atom is substituted with primary alkyl groups.

Over the years, several alternative protocols appeared in the literature aiming to improve the performance of the less efficient Suzuki–Miyaura couplings. We tried two of these: the first one, introduced by Soderquist and co-workers,[6] consists in transforming the starting alkenylborane into vinylborinate by anhydrous Me_3NO mediated oxidation before applying the coupling conditions; the second alternative involves boron to copper transmetalation prior to coupling.[7] In our case, neither procedure allowed us to improve the yield of vinyl sulphide **3d$_1$**, starting from **2d**.

Additionally, we also carried out Suzuki–Miyaura coupling experiments on β-butylthio alkenylborane **2b** (the best performing one in Table 1) using benzyl bromide and 1-bromo-1-heptyne as electrophiles. The first one (Scheme 5a) gave deceptively bad results; the *syn*-elimination side reaction largely predominated, in spite of the *n*-butylthio substituant on the starting compound, and only trace amounts of the desired vinyl sulphide **3b$_2$** were formed. In contrast, coupling of **2b** with 1-bromo-1-heptyne produced the butylthioenyne **3b$_3$** in excellent yield (Scheme 5b). The high propensity of 1-halogeno-1-alkynes for Suzuki–Miyaura coupling had been noted earlier.[8]

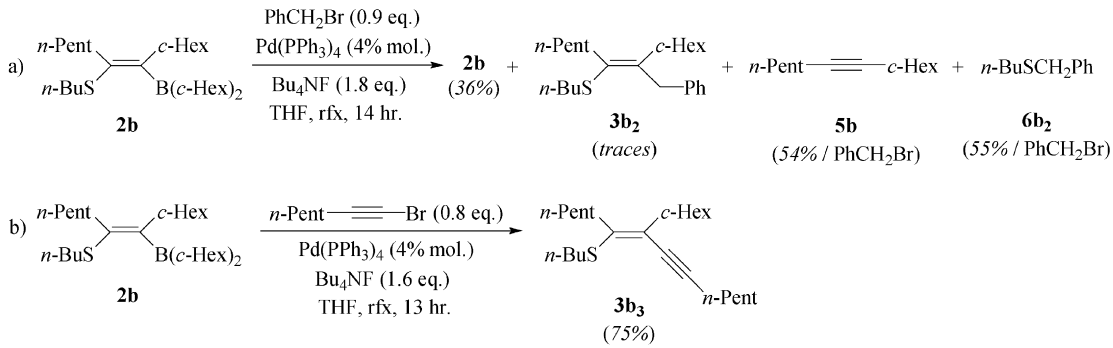
In all cases, the *Z*/*E* ratio of isolated vinyl sulphides (determined by GC) was greater than 98:2. While the absolute stereochemistry of all compounds was not rigorously established, a reasonable assumption is made that the coupling reaction proceeds as usual, with retention of configuration.[2] Finally, in spite of this satisfactory stereochemical outcome and due to the two side reactions occuring competitively with the desired cross-coupling, the whole methodology turns out to be mainly unsuitable for the electrophilic substitution of our intermediates. Nevertheless, in some specific cases, this procedure allows an efficient and straightforward synthesis of trisubstituted vinylsulfides with almost complete control of the stereochemistry.

2.2. Boron to copper transmetalation followed by alkylation

This is a well documented method for carrying out carbodeborylation of various boron derivatives, particularly alkenylboranes leading to olefinic products.[9] Starting from our β-chalcogeno alkenylboranes **2**, we should synthesize fully substituted vinyl chalcogenides which in turn should lead to a variety of olefins with high degrees of regio- and stereoselectivities.

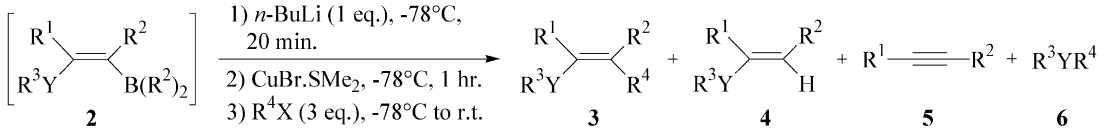
Two types of experimental procedures have been explored. In the first one, both the activation of β-chalcogeno alkenylboranes **2** and the transmetalation have been carried out at low temperature (−78 °C) and in the absence of additives. The results of this procedure using various substrates and electrophiles are displayed in Table 2. Clearly, several situations can be distinguished. Whatever the electrophile used, methyl iodide or allyl bromide, carbodeborylations of β-phenylseleno- and β-phenyltelluro alkenylboranes failed almost completely (Table 2, entries 16–19). As in the coupling experiments, *syn* elimination leading to the appropriate internal alkyne and to phenylmethyl (or allyl) chalcogenides was largely predominating.[10] Somewhat unexpectedly, B–Cu transmetalation followed by allylation of **2k** gave the product **3k$_4$** in excellent yield (Table 2, entry 15). Conjunction of factors such as a sterically less congested vinylcopper intermediate, the weakest leaving group, and the more reactive electrophile may be responsible for this observation.

In all the remaining experiments of Table 2, β-phenylthio- or β-butylthio alkenylboranes have been used as substrates in the presence of various electrophiles. Although *syn* elimination did occur on β-phenylthio derivatives in a few poorly performing reactions, this side reaction was no longer a serious competitor in most of the cases. Thus, high yields of vinyl sulphide could be obtained with methyl iodide (Table 2, entries 7 and 12), allyl bromide (Table 2, entries 1, 2, and 13) and 1-iodo-1-heptyne (Table 2, entries 3 and 14) as electrophiles. Surprisingly, ethylation and benzylation gave poor results (Table 2, entries 4, 8, and 9); once again, significant *syn* elimination and protodeborylation were observed, as illustrated by the formation

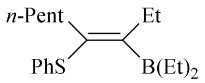
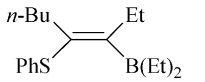
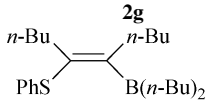
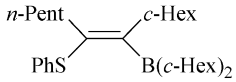
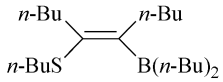
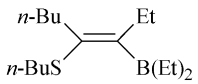
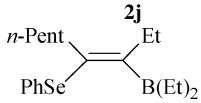
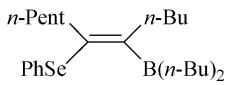
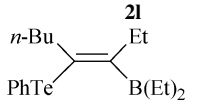


Scheme 5.

Table 2. Carbodeborylation of β-chalcogenovinyl boranes **2**



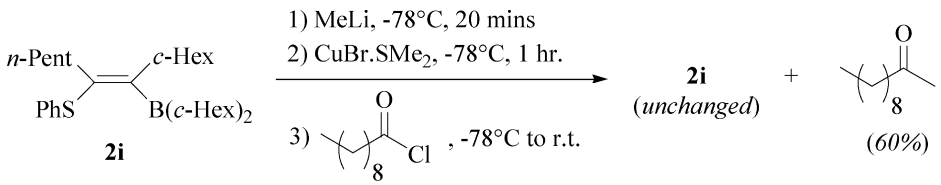
2 **3** **4** **5** **6**

Entry	Reagent	R^4X (equiv.)	Yield (%)			
			3	**4**	**5**	**6**
1	 **2f**	CH_2=CH–CH_2Br	81 (**3f$_4$**)	—	—	—
2[a]	 **2g**	CH_2=CH–CH_2Br	74 (**3g$_4$**)	—	—	—
3	**2g**	*n*-Pent-C≡C–I[b]	63 (**3g$_3$**)	—	—	—
4	**2g**	$PhCH_2Br$	13 (**3g$_2$**)	[c]	[c]	[c]
5	**2g**	MeCOCl	29 (**3g$_5$**)	[c]	[c]	[c]
6	**2g**	PhCOCl	32 (**3g$_6$**)	[c]	[c]	[c]
7	 **2h**	MeI	72 (**3h$_7$**)	[c]	—	—
8	**2h**	EtI	3 (**3h$_8$**)	11 (**4h**)	41 (**5h**)	5 (**6h$_8$**)
9	**2h**	$PhCH_2Br$	11 (**3h$_2$**)	[c]	[c]	[c]
10[d]	 **2i**	MeI	0[e] (**3i$_7$**)	—	—	—
11[d,f]	**2i**	MeI	6[g] (**3i$_7$**)	—	—	—
12	 **2d**	MeI	68 (**3d$_7$**)	[c]	—	—
13	 **2j**	CH_2=CH–CH_2Br	74 (**3j$_4$**)	—	—	—
14	**2j**	*n*-Pent-C≡C–I[b]	59 (**3j$_3$**)	—	—	—
15	 **2k**	CH_2=CH–CH_2Br	71 (**3k$_4$**)	—	—	—
16	 **2l**	MeI	0 (**3l$_7$**)	—	67 (**5l**)	56 (**6l$_7$**)
17[a]	**2l**	MeI	0 (**3l$_7$**)	—	70 (**5l**)	54 (**6l$_7$**)
18	 **2m**	CH_2=CH–CH_2Br	0 (**3m$_4$**)	[c]	—	—
19[a]	**2m**	CH_2=CH–CH_2Br	0 (**3m$_4$**)	[c]	[c]	61 (**3m$_4$**)

[a] MeOLi was used instead of *n*-BuLi.
[b] 1.25 equiv. were introduced.
[c] The formation of these compounds has not been quantified.
[d] These experiments were carried out with isolated starting material.
[e] **2i** was recovered quantitatively.
[f] MeLi was used instead of *n*-BuLi.
[g] 88% of **2i** were recovered.

of the side products **4h** and **5h** during the carbodemetalation of **2h** with ethyl iodide (Table 2, entry 8). This latter process seemed to occur in the acylation reactions as well, although it does not explain alone the modest yields in β-phenylthio enones (Table 2, entries 5 and 6). Nevertheless, it has been reported that simple vinylcopper species display only limited reactivity towards acid chlorides.[11] Finally, it should be noted that the activation step can be carried out with lithium methoxide instead of *n*-butyllithium without a significant decrease in the vinyl sulfide's yield (Table 1, compare entries 1 and 2).

On the other hand, transmetalation of sterically hindered alkenylboranes was unsuccessful using *n*-butyllithium and only slightly better using methyllithium (Table 2, entries 10 and 11). That steric inhibition prevents the complexation of



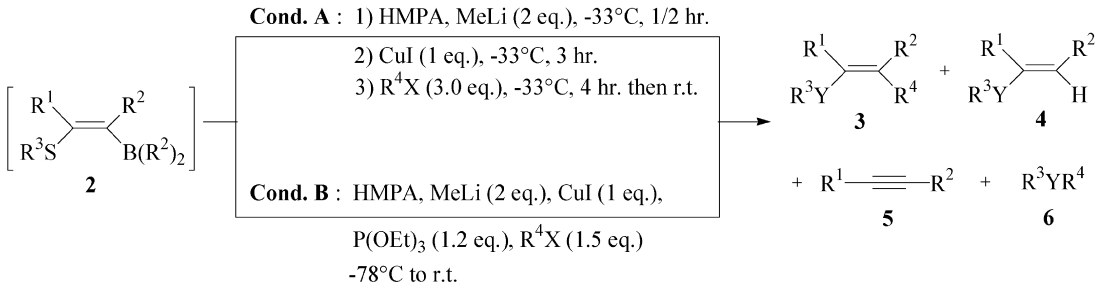
Scheme 6.

the base on the borane in these cases is attested by two observations: (i) the starting β-phenylthio alkenylborane **2i** was recovered unchanged and (ii) when methyl iodide was replaced by decanoyl chloride in the experiment of Table 2, entry 11, 2-undecanone was formed in good yield (Scheme 6), supporting the intermediary formation of methylcopper instead of the desired vinylcopper.

On the basis of the above observations regarding the synthesis of fully substituted vinyl selenides and -tellurides, we decided to limit our further investigations to the improvement of the carbodemetalation efficiency of the sulfur derivatives. This was achieved for most of the unsatisfactory results shown in Table 2 by means of the second type of experimental procedure for boron to copper transmetalation, consisting in carrying out the process in the presence of additives (such as HMPA or $P(OEt)_3$) and/or at somewhat higher temperature.[12,13] Quite spectacular improvements have been observed (Table 3).

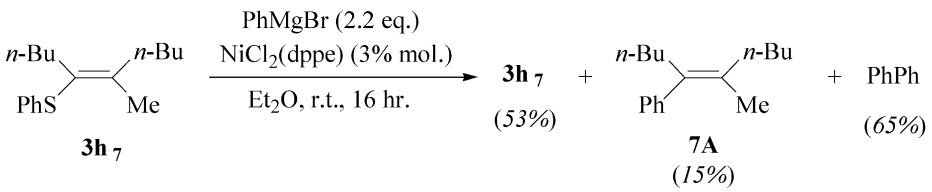
Remarkably, even the sterically hindered alkenylboranes appeared to undergo efficient transmetalation (Table 3,

Table 3. Carbodeborylation of β-chalcogenovinyl boranes **2**



Entry	Reagent		R^4X	Condition	Yield (%)			
					3	**4**	**5**	**6**
1[a]	*n*-Pent, *c*-Hex, PhS, B(*c*-Hex)$_2$	**2i**	MeI	A	69 (**3i$_7$**)	—	[b]	—
2[a]	*n*-Bu, *sec*-Bu, *n*-BuS, B(*sec*-Bu)$_2$	**2n**	CH_2=CH–CH_2Br	A	71 (**3n$_4$**)	—	—	—
3[a]	*n*-Pent, *c*-Hex, PhS, B(*c*-Hex)$_2$	**2i**	EtI	A	28 (**3i$_8$**)	—	24 (**5b**)	—
4	*n*-Bu, *n*-Bu, PhS, B(*n*-Bu)$_2$	**2h**	EtI	A	29 (**3h$_8$**)	—	33 (**5h**)	24 (**6h$_8$**)
5	*n*-Bu, *n*-Bu, PhS, B(*n*-Bu)$_2$	**2h**	EtI	B	45 (**3h$_8$**)	—	21 (**5h**)	19 (**6h$_8$**)
6	*n*-Bu, *n*-Bu, *n*-BuS, B(*n*-Bu)$_2$	**2d**	EtI	B	66 (**3d$_8$**)	—	[b]	[b]
7	*n*-Bu, *n*-Bu, PhS, B(*n*-Bu)$_2$	**2h**	$PhCH_2Br$	B	62 (**3h$_2$**)	—	[b]	[b]
8	*n*-Bu, *n*-Bu, *n*-BuS, B(*n*-Bu)$_2$	**2d**	$PhCH_2Br$	B	64 (**3d$_2$**)	—	[b]	[b]

[a] These experiments were carried out with isolated starting material.
[b] The formation of these compounds has not been quantified.



Scheme 7.

entries 1–3) under conditions A (MeLi, HMPA, −33 °C). Consequently, methylation and allylation of the vinyl copper intermediates gave the desired products in high yield. However, ethyl iodide gave only a modest yield in vinyl sulfide **3i$_8$** because, in this case, the less reactive electrophile allowed *syn* elimination to compete to a larger extent. This interpretation is supported by the next three runs (Table 3, entries 4–6). Indeed, the considerably less hindered alkenylborane **2h** gave essentially the same results (Table 3, compare entries 3 and 4), whereas at lower temperature (conditions B: MeLi, HMPA, $P(OEt)_3$, −78 °C), the ethylation yield increased to 45% (Table 3, entry 5). Applying conditions B to vinylborane **2d** carrying the poorer butylthio leaving group in β position led to ethylation product **3d$_8$** in good yield (Table 3, compare entries 5 and 6). These latter conditions also allowed to carry out benzylation reactions in a satisfactory manner (Table 3, entries 7 and 8).

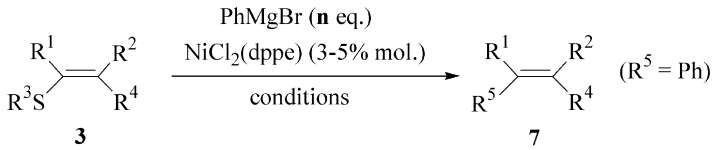
The boron to copper transmetalation of alkenylboranes is known to occur with almost complete retention of the configuration.[9] For all the experiments described here, the ratio of stereoisomers in the crude product was greater than 98:2, in favour of the structures drawn in Tables 2 and 3 (vide infra for ascertainment of stereochemistry). Furthermore, in most of the cases, no trace of the other stereoisomer could be detected after purification, neither by ^{1}H NMR nor GC. At this point, we can therefore conclude that the present strategy gives access to a fairly large variety of fully substituted vinyl sulfides with excellent stereochemical control. In itself, this is an appreciable achievement taking into account the usefulness of this class of compounds, and especially that of the corresponding vinyl sulfoxides and -sulfones.[14]

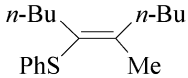
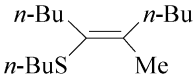
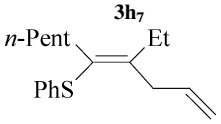
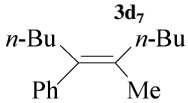
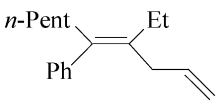
2.3. Synthesis of tetrasubstituted olefins from vinylsulfides

We have reported on the efficient conversion of various vinyl chalcogenides into trisubstituted olefins using the well known nickel catalyzed coupling with Grignard reagents.[1] Starting from vinyl sulfides, this transformation appeared to occur with excellent yield and stereoselectivity by the use of 1,2-bis-(diphenylphosphinoethane) nickel chloride ($NiCl_2$-(dppe)). However, applying the conditions used earlier to the coupling of fully substituted vinyl sulfide **3h$_7$** with phenylmagnesium bromide gave disappointing results: the desired olefin was formed in low yield and about half of the starting material was recovered unchanged (Scheme 7). Prolonging the reaction time did not bring about higher conversion.

In addition, GC and GC–MS monitoring of the coupling reaction revealed the presence in the reaction mixture of a substantial amount of 5-methyldecen-6-thiol. Formation of this thioenol (or of its magnesium salt) could be due to the

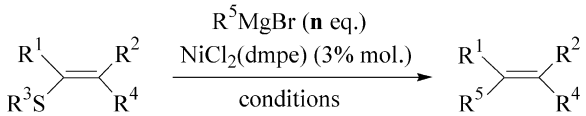
Table 4. Synthesis of tetrasubstituted olefins



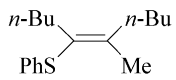
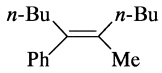
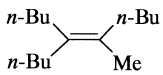
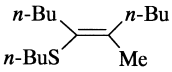
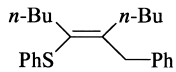
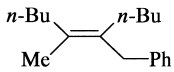
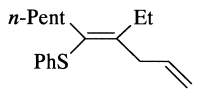
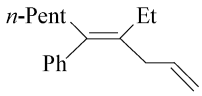
Entry	Reagent		*n*	Conditions	Product		Yield (%)
1		**3h$_7$**	2.4	Et_2O, rfx, 48 h		**7A**	28
2	**3h$_7$**		10	Et_2O, rt, 16 h	**7A**		13
3		**3d$_7$**	1.5	Et_2O, rt, 15 h	**7A**		0[a]
4	**3d$_7$**		2	Benzene, rfx, 15 h	**7A**		0[a]
5		**3f$_4$**	2.4	Et_2O, rt, 18 h		**7B**	26[b]
6	**3f$_4$**		2.4	Et_2O, rfx, 38 h	**7B**		27

[a] **3d$_7$** was recovered quantitatively.
[b] 43% of **3f$_4$** were recovered, and 59% of biphenyl were also formed.

Table 5. Synthesis of tetrasubstituted olefins



3 **7**

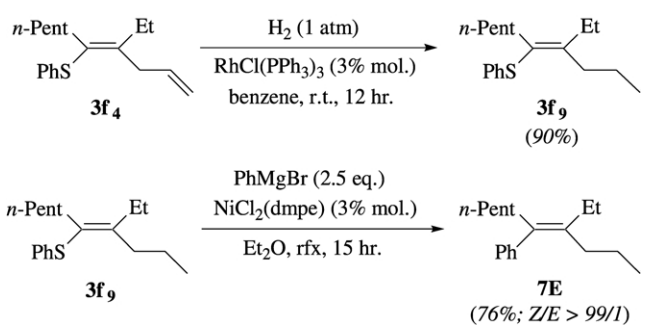
Entry	Reagent	R^5	*n*	Conditions	Product	*E*/*Z*	Yield (%)
1	 **3h₇**	Ph	5	Et_2O, rfx, 16 h	 **7A**	>98:2	66
2	**3h₇**	Ph	5	Et_2O, rfx, 24 h	**7A**	>96:4	75
3	**3h₇**	Ph	5	Et_2O, rt, 24 h	**7A**	>96:4	36[a]
4	**3h₇**	Ph	2.5	Et_2O, rfx, 14.5 h	**7A**	>99:1	82
5	**3h₇**	*n*-Bu	2.5	Et_2O, rfx, 22.5 h	 **7C**	—	70
6	 **3d₇**	Ph	5	Et_2O, rfx, 16 h	**7A**	—	0[b]
7	**3d₇**	Ph	3	Bu_2O, 90 °C, 15 h	**7A**	—	0[b]
8	 **3h₂**	Me	2.5	Et_2O, rfx, 10 days	 **7D**	>99:1	24[c]
9	 **3f₄**	Ph	2.5	Et_2O, rfx, 23 h	 **7B**	<1:99	38
10	**3f₄**	Ph	5	Et_2O, rfx, 22.5 h	**7B**	<1:99	38

[a] 43% of **3h₇** were recovered.
[b] **3d₇** was recovered quantitatively.
[c] 60% of **3h₂** were recovered.

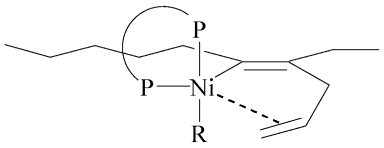
preferential insertion of Ni(0) during the catalytic cycle into the S–phenyl bond instead of the S–vinyl bond, itself arising from the notably higher steric congestion of the vinylic moiety in **3h₇**. The resulting thioenolate may have led to blocking of the reaction, leaving a large part of starting **3h₇** unchanged. Furthermore, the limited performance of $NiCl_2$(dppe) is not restricted to the case displayed in Scheme 7; it is a poor catalyst for the coupling under different conditions of other fully substituted vinyl sulfides too (Table 4).

In connection with the coupling of unsaturated halogen compounds with vinylic and allylic Grignard reagents, Kumada and co-workers found that 1,2-bis-(dimethylphosphinoethane) nickel chloride ($NiCl_2$(dmpe)[15]) exhibited superior activity as compared to the corresponding dppe and dppp catalysts.[16] We anticipated that the more electron donating and less bulky dmpe ligand would confer higher activity to this catalyst in the coupling reactions of our sterically congested vinyl sulfides too. As witnessed in Table 5, this expectation was confirmed, at least in part. Indeed, the reaction of **3h₇** with phenylmagnesium bromide has now produced the desired olefin **7A** in excellent yield (Table 5, entry 4; compare to Scheme 7), and it also works well with butylmagnesium bromide (Table 5, entry 5). Nevertheless, it can be seen (Table 5, entries 1–4) that the reaction conditions, especially the ratio of reactants and reaction time, play an important role in the efficiency as well as the stereoselectivity of these couplings. Unfortunately, even this catalyst was found unable to couple butylvinyl sulfide **3d₇** which was recovered quantitatively from two different runs (Table 5, entries 6 and 7). Phenylvinyl sulfides bearing benzyl (**3h₂**) or allyl (**3f₄**) moieties next to the phenylthio group represent intermediary cases in which the conversion was not higher than 20–40% (Table 5, entries 8–10). The reason for this limited conversion is unclear, but it is interesting to note that vinylsulfide **3f₉**, produced by catalytic hydrogenation of compound **3f₄**, gave the olefin **7E** in high yield on coupling with PhMgBr (Scheme 8).

Therefore, the ability of nickel to coordinate C,C double bonds appears responsible for the above limitations, possibly through intramolecular coordination of the terminal double bond in the vinylnickel intermediate (Scheme 9).



Scheme 8.



R = SPh, SMgBr, Ph

Scheme 9.

Finally, DiffNOE experiment carried out on olefin **7D** gave the anticipated result: irradiation of the benzylic hydrogens (s, 3.40 ppm) brought about disappearance of almost all the signals in the difference spectrum with the exception of a large singlet persisting at 1.72 ppm due to the methyl group *cis* to benzyl group. This shows thereby that both steps of the transformation of β-phenylthio alkenylboranes into tetrasubstituted olefins have taken place with retention of configuration of the C,C double bond.

3. Conclusion

In conclusion, we had shown that chalcogen electrophile induced rearrangements of 1-alkynyltrialkyborates give access with good to excellent efficiencies and in well defined regio- and stereochemical ways to a large variety of disubstituted vinyl sulfides, -selenides and -tellurides (see Ref. 1). Due to the weaker vinylic C–Se and C–Te bonds leading to higher leaving propensity of the selenium and tellurium moieties, only trisubstituted vinyl sulfides can be obtained in satisfactory yields through the carbodeborylation protocol (boron to copper transmetalation followed by alkylation). With the exception of a few cases, all the accessible vinyl sulfides can be transformed into the corresponding tri- or tetrasubstituted olefins by means of the nickel catalyzed coupling with aliphatic or aromatic Grignard reagents.

4. Experimental

4.1. General

All glassware, syringes and needles were oven dried at 120 °C for several hours prior to use. The glassware were assembled while hot and cooled under a stream of argon. ^{1}H (400 and 90 MHz) and ^{13}C (100.4 and 22.5 MHz) NMR spectra were recorded on either a JEOL JNM EX-400 or a JEOL JNM EX-90 with $CDCl_3$ as solvent and Me_4Si as internal standard. IR spectra were recorded on a BIORAD FTS-165 spectrometer. Elemental analysis were carried out using a Carlo-Erba NA 1500 C,H,N analyser. Low resolution mass measurements were carried out using a Hewlett–Packard HP6890 GC–MS instrument (ionization potential: 70 eV); relative intensities of the ions are given in parentheses. High resolution mass spectra were recorded on a Micromass AutoSpec 6F mass spectrometer. Merck silica gel 9385 (0.040–0.063 mm) and 5111 (0.015–0.040 mm) were used for column chromatography. THF and Et_2O were distilled from sodium/benzophenone. HMPA was distilled from CaH_2. Methyl iodide, ethyl iodide, iodobenzene, allyl bromide, benzyl bromide, acetyl chloride, benzoyl chloride, decanoyl chloride, and triethyl phosphite were purchased from Aldrich and distilled prior to use. The other reagents were purchased from Aldrich and used without further purification, except tetrakis(triphenylphosphine)palladium,[17] 1-halo-1-heptynes,[18] and 1,2-bis-(dimethylphosphinoethane) nickel chloride,[15] which were synthesized according to the reported procedures. The synthesis and characterization of the starting β-chalcogeno alkenylboranes has been described previously.[1]

4.2. Suzuki–Miyaura couplings

4.2.1. Representative procedure (RP-1) for the Suzuki–Miyaura coupling of isolated alkenylboranes. Synthesis of (*Z*)-1-cyclohexyl-1-phenyl-2-(phenylthio)-1-hexene ($\mathbf{3a_1}$). In a 25 mL two-necked flask, equipped with an argon inlet and a magnetic stirring bar, were successively introduced a THF solution (3 mL) of **2a** (0.450 g; 1 mmol), tetrakis(triphenylphosphine)palladium (0.045 g; 4 mol%), and a THF solution (2 mL) of iodobenzene (0.163 g; 0.8 mmol; 0.8 equiv.). Tetrabutylammonium fluoride (1.6 mL of a 1 M solution in THF; 1.6 mmol; 1.6 equiv.) was added, and the reaction mixture was heated to reflux for 13 h. After cooling to room temperature, the solution was diluted with 15 mL of Et_2O, washed with water, dried over $MgSO_4$, and concentrated. The crude product was purified by column chromatography (silica gel; pentane) to afford 0.046 g of *n*-butylcyclohexylacetylene **5a** (35% yield), 0.055 g of diphenylsulphide $\mathbf{6a_1}$ (37% yield), 0.073 g of (*E*)-1-cyclohexyl-2-(phenylthio)-1-hexene **4a** (27% yield),[1] and 0.103 g of $\mathbf{3a_1}$ (37% yield) as a colorless liquid. IR (neat): 3074, 3058, 3020, 2930, 2855, 1584, 1476, 1441, 1072, 1025, 909, 739, 706 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.89 (3H, t, J=7.3 Hz), 0.94–1.04 (1H, m), 1.07–1.18 (2H, m), 1.28–1.37 (4H, m), 1.51–1.61 (3H, m), 1.74 (4H, m), 2.33 (2H, t, J=7.3 Hz), 2.77 (1H, tt, J=12.0, 2.9 Hz), 7.00–7.30 (10H, m); ^{13}C NMR (100.4 MHz, $CDCl_3$): δ 14.0, 22.4, 25.7, 26.6, 31.5, 31.7, 32.0, 42.4, 125.5, 126.4, 127.5, 128.6, 129.0, 129.4, 130.6, 136.9, 141.0; MS (EI): 350 (M^+, 100), 273 (54), 226 (8), 217 (9), 183 (14), 171 (8), 155 (13), 141 (19), 129 (20), 117 (23), 91 (33), 55 (11); HRMS: *m/z* for $C_{24}H_{30}S$, calcd: 350.2068. Found: 350.2060.

4.2.2. (*Z*)-2-(*n*-Butythio)-1-cyclohexyl-1-phenyl-1-heptene ($\mathbf{3b_1}$). Synthesized according to RP-1 and starting from **2b**. Column chromatography (silica gel; pentane) afforded *n*-pentylcyclohexylacetylene **5b** (9% yield) and $\mathbf{3b_1}$ (70% yield), as a colorless liquid. IR (neat): 3078, 3055, 3025, 2956, 2929, 2854, 1595, 1489, 1450, 1378, 1271, 1140, 1072, 891, 769, 701 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.86 (3H, t, J=7.2 Hz), 0.96 (3H, t, J=6.8 Hz), 0.97–1.10 (3H, m), 1.22–1.44 (10H, m), 1.60–1.73 (7H, m), 2.38–2.45 (4H, m), 2.69 (1H, tt, J=11.7, 3.2 Hz), 6.95–6.98 (2H, m), 7.24–7.34 (3H, m); ^{13}C NMR (22.5 MHz, $CDCl_3$): δ 13.6, 14.1, 21.9, 22.6, 25.8, 26.6, 29.1, 30.5, 31.4, 31.7, 31.8, 32.1, 42.2, 126.1, 127.3, 130.0, 130.8, 141.3, 147.7; MS (EI): 344 (M^+, 65), 287 (100), 253 (7), 231 (5), 217 (6), 205 (6), 183 (13), 171 (8), 155 (6), 141 (12), 129 (14), 115 (16), 91 (18), 55 (12). Anal. Calcd for $C_{23}H_{36}S$: C, 80.17; H, 10.53. Found: C, 79.93; H, 10.55.

4.2.3. (*E*)-3-(*n*-Butylthio)-2-cyclohexyl-1-phenyl-2-octene ($\mathbf{3b_2}$). The attempted synthesis of $\mathbf{3b_2}$ was performed according to RP-1 and starting from **2b**. Traces of $\mathbf{3b_2}$ were

detected by GC–MS in the crude product. Column chromatography (silica gel; pentane) afforded **2b** (36% yield), *n*-pentylcyclohexylacetylene **5b** (54% yield) and benzyl-*n*-butylthioether **6b$_2$** (55% yield; ^{1}H NMR (90 MHz, $CDCl_3$): δ 0.88 (3H, t, J=7.0 Hz), 1.26–1.63 (4H, m), 2.41 (2H, t, J=6.9 Hz), 3.70 (2H, s), 7.25–7.32 (5H, m); MS (EI): 180 (M^+, 29), 91 (100), 65 (8)).

4.2.4. (*Z*)-6-(*n*-Butylthio)-7-cyclohexyl-6-tetradecene-8-yne (3b$_3$). Synthesized according to RP-1 and starting from **2b**. Column chromatography (silica gel; pentane/Et_2O, 99:1) afforded **3b$_3$** (75% yield), as a yellow liquid. IR (neat): 2958, 2930, 2856, 2212, 1570, 1463, 1452, 1380, 1262, 1101, 890 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.91 (9H, m), 1.10–1.67 (24H, m), 1.74–1.78 (2H, m), 2.30 (2H, t, J=7.8 Hz), 2.35 (1H, m), 2.41 (2H, t, J=6.8 Hz), 2.73 (2H, t, J=7.4 Hz); ^{13}C NMR (22.5 MHz, $CDCl_3$): δ 13.7, 14.0, 14.0, 19.8, 22.1, 22.2, 22.5, 25.9, 26.4, 28.7, 29.1, 31.2, 31.6, 31.8, 31.9, 41.0, 79.0, 97.6, 127.5, 139.1; MS (EI): 362 (M^+, 23), 305 (100), 249 (55), 223 (33), 181 (36), 167 (14), 115 (7), 91 (13), 81 (26), 55 (21); HRMS: *m*/*z* for $C_{24}H_{42}S$, calcd: 362.3007. Found: 362.3013.

4.2.5. Representative procedure (RP-2) for the in situ Suzuki–Miyaura coupling of air-sensitive alkenylboranes. Synthesis of (*Z*)-6-(*n*-butylthio)-5-phenyl-5-decene (3d$_1$). A 50 mL two-necked flask, equipped with a reflux condenser, an argon inlet and a magnetic stirring bar, was charged with a THF solution (4 mL) of 1-hexyne (0.164 g; 2 mmol). At −20 °C were added 1.25 mL of *n*-butyllithium (1.6 M in hexane; 2 mmol). After 1 h of stirring at −20 °C, 2 mL of tributylborane (1 M solution in THF; 2 mmol) were introduced and the reaction mixture was allowed to warm to room temperature for 1 h. After cooling to −78 °C, a THF solution (4 mL) of *n*-butylsulfenyl chloride (0.249 g; 2 mmol) was added dropwise. The cooling bath was then removed and the mixture was stirred for 30 min at room temperature. To this solution was successively added tetrakis(triphenylphosphine)palladium (0.092 g; 4 mol%), a THF solution (1 mL) of iodobenzene (0.367 g; 1.8 mmol; 0.9 equiv.) and 3.6 mL of tetrabutylammonium fluoride (1 M in THF; 3.6 mmol; 1.8 equiv.). The reaction mixture was heated to reflux for 20 h. After cooling to room temperature, the solution was diluted with 15 mL of Et_2O, washed with water, dried over $MgSO_4$, and concentrated. The crude product was purified by column chromatography (silica gel; pentane) to afford 0.204 g of **3d$_1$** (37% yield) as a colorless liquid. IR (neat): 3055, 3020, 2958, 2930, 2871, 1597, 1490, 1463, 1441, 1379, 1135, 1101, 1070, 769, 700 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$): δ 0.77–1.05 (9H, m), 1.14–1.71 (12H, m), 2.38 (6H, m), 7.04–7.33 (5H, m); ^{13}C NMR (22.5 MHz, $CDCl_3$): δ 13.6, 13.9, 14.1, 21.9, 22.6, 22.7, 30.5, 31.3, 31.4, 31.6, 31.8, 35.2, 126.2, 127.7, 128.8, 130.8, 142.9, 143.5; MS (EI): 304 (M^+, 100), 261 (35), 247 (94), 205 (10), 191 (20), 171 (9), 157 (10), 143 (15), 129 (42), 115 (21), 91 (27), 57 (13). Anal. Calcd for $C_{20}H_{32}S$: C, 78.88; H, 10.59. Found: C, 79.05; H, 10.20.

4.2.6. (*Z*)-3-Phenyl-4-(phenylseleno)-3-tetradecene (3c$_1$). The attempted synthesis of **3c$_1$** was performed according to RP-2, through the preparation of **2c**. Sodium hydroxide (3.0 equiv.) was used instead of tetrabutylammonium fluoride, and the mixture was heated to reflux for 16 h. Column chromatography (silica gel; pentane) afforded (*E*)-4-(phenylseleno)-3-tetradecene **4c** (61% yield), as a yellowish liquid. IR (neat): 3071, 2961, 2927, 2854, 1580, 1475, 1462, 1439, 1377, 1144, 1068, 1023, 725 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.88 (3H, t, J=6.8 Hz), 1.01 (3H, t, J=7.3 Hz), 1.21–1.37 (14H, m), 1.47 (2H, m), 2.14 (2H, quint., J=7.6 Hz), 2.24 (2H, t, J=7.6 Hz), 5.93 (1H, t, J=7.3 Hz), 7.21–7.27 (3H, m), 7.45 (2H, m); ^{13}C NMR (22.5 MHz, $CDCl_3$): δ 14.1, 22.7, 22.8, 29.0, 29.1, 29.3, 29.5, 29.6, 31.9, 32.8, 126.7, 129.0, 131.1, 131.6, 132.5, 139.7; MS (EI): 352 (M^+, 76), 226 (99), 198 (32), 183 (15), 158 (67), 145 (13), 111 (17), 97 (38), 83 (51), 69 (100), 55 (99); HRMS: *m*/*z* for $C_{20}H_{32}Se$, calcd: 352.1669. Found: 352.1674.

4.3. Boron to copper transmetalation

4.3.1. Representative procedure (RP-3) for the boron to copper transmetalation (Scheme 6). Synthesis of (*Z*)-4-ethyl-5-(phenylthio)-1,4-decadiene (3f$_4$). A 100 mL two-necked flask, equipped with a reflux condenser, an argon inlet and a magnetic stirring bar, was charged with a THF solution (26 mL) of 1-heptyne (1.538 g; 16 mmol). At −20 °C were added 10 mL of *n*-butyllithium (1.6 M in hexane; 16 mmol). After 1 h of stirring at −20 °C, 16 mL of triethylborane (1 M solution in THF; 16 mmol) were introduced and the reaction mixture was allowed to warm to room temperature for 1 h. After cooling to −78 °C, a THF solution (18 mL) of benzenesulfenyl chloride (2.312 g; 16 mmol) was added dropwise. The cooling bath was then removed and the mixture was stirred for 30 min at room temperature. The reaction flask was cooled to −78 °C and 10 mL of *n*-butyllithium (1.6 M in hexane; 16 mmol) were introduced. After 20 min, the mixture was transferred via cannula to a separate reaction flask containing 3.290 g of $CuBr{\cdot}SMe_2$ (16 mmol) in 16 mL of THF maintained at −78 °C. After an additional hour of stirring at −78 °C, 4.15 mL of allyl bromide (48 mmol; 3 equiv.) were added, and the reaction flask was gradually warmed to room temperature. The mixture was then diluted with 80 mL of Et_2O, and washed three times with 30 mL of a mixture of saturated aqueous NH_4Cl and NH_4OH (4:1, v/v), and two times with 20 mL of water. The organic phase was dried over $MgSO_4$, and concentrated. The crude product was purified by column chromatography (silica gel; pentane) to afford 3.568 g of **3f$_4$** (81% yield) as a colorless liquid. IR (neat): 3075, 2960, 2873, 1639, 1584, 1477, 1439, 1376, 1086, 1025, 994, 912, 739, 692 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.85 (3H, t, J=7.1 Hz), 1.09 (3H, t, J=7.6 Hz), 1.18–1.29 (4H, m), 1.50 (2H, m), 2.21 (2H, t, J=7.8 Hz), 2.24 (2H, q, J=7.6 Hz), 3.20 (2H, d, J=6.4 Hz), 4.99–5.05 (2H, m), 5.77 (1H, ddt, J=16.9, 10.0, 6.3 Hz), 7.10–7.15 (1H, m), 7.17–7.26 (4H, m); ^{13}C NMR (22.5 MHz, $CDCl_3$): δ13.3, 14.0, 22.5, 25.4, 29.0, 31.6, 32.9, 38.6, 115.5, 125.2, 128.2, 128.4, 128.7, 136.3, 137.1, 147.1; MS (EI): 274 (M^+, 39), 197 (100), 183 (6), 127 (16), 109 (11), 91 (17), 79 (21), 67 (12), 55 (10). Anal. Calcd for $C_{18}H_{26}S$: C, 78.77; H, 9.55. Found: C, 78.22; H, 9.66.

4.3.2. (*Z*)-4-Ethyl-5-(phenylthio)-1,4-nonadiene (3g$_4$). Synthesized according to RP-3, through the preparation of **2g**. The activation step was performed by transfer (through

cannula) of the alkenylborane mixture on a suspension of lithium methoxide in THF, previously cooled to −78 °C (prepared by addition of 1 equiv. of *n*-butyllithium over a THF solution of methanol at −78 °C, followed by stirring at room temperature for 1 h). Column chromatography (silica gel; pentane) afforded **3g$_4$** (74% yield), as a colorless liquid. IR (neat): 3075, 2961, 2932, 2873, 1638, 1614, 1584, 1477, 1459, 1439, 1376, 1215, 1086, 1025, 942, 912, 739, 692 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$): δ 0.85 (3H, t, J=6.8 Hz), 1.09 (3H, t, J=7.5 Hz), 1.13–1.59 (4H, m), 2.15–2.29 (4H, m), 3.21 (2H, d, J=6.4 Hz), 4.91–5.12 (2H, m), 5.78 (1H, ddt, J=17.4, 9.4, 6.2 Hz), 7.15–7.28 (5H, m); ^{13}C NMR (22.5 MHz, $CDCl_3$): δ13.3, 14.0, 22.5, 25.4, 31.5, 32.7, 38.6, 115.5, 125.2, 128.2, 128.3, 128.7, 136.3, 137.1, 147.1; MS (EI): 260 (M$^+$, 42), 183 (100), 127 (17), 109 (13), 91 (18), 79 (23), 67 (13), 55 (9). Anal. Calcd for $C_{17}H_{24}S$: C, 78.40; H, 9.29. Found: C, 77.91; H, 9.32.

4.3.3. (*Z*)-5-(*n*-Butylthio)-4-ethyl-1,4-nonadiene (3j$_4$). Synthesized according to RP-3, through the preparation of **2j**. Column chromatography (silica gel; pentane) afforded **3j$_4$** (74% yield), as a colorless liquid. IR (neat): 3078, 2961, 2932, 2873, 1638, 1609, 1461, 1434, 1377, 1216, 994, 909 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$): δ 0.88–1.06 (9H, m), 1.14–1.67 (8H, m), 2.13 (2H, q, J=7.4 Hz), 2.26 (2H, t, J=7.7 Hz), 2.55 (2H, t, J=7.2 Hz), 3.16 (2H, d, J=6.2 Hz), 4.88–5.09 (2H, m), 5.77 (1H, ddt, J=17.6, 9.3, 6.2 Hz); ^{13}C NMR (22.5 MHz, $CDCl_3$): δ13.3, 13.7, 14.1, 22.0, 22.6, 25.3, 31.1, 31.5, 31.8, 31.9, 38.3, 114.9, 129.5, 136.7, 142.1; MS (EI): 240 (M$^+$, 9), 183 (100), 169 (8), 149 (8), 127 (31), 107 (19), 93 (20), 79 (19), 67 (13), 55 (12); HRMS: *m*/*z* for $C_{15}H_{28}S$, calcd: 240.1912. Found: 240.1919.

4.3.4. (*Z*)-4-Ethyl-5-(phenylseleno)-1,4-decadiene (3k$_4$). Synthesized according to RP-3, through the preparation of **2k**. Column chromatography (silica gel; pentane) afforded **3k$_4$** (71% yield), as a yellowish liquid. IR (neat): 3072, 2960, 2931, 2868, 1638, 1580, 1438, 1376, 1069, 1023, 994, 912, 735, 692 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.84 (3H, t, J=7.1 Hz), 1.07 (3H, t, J=7.6 Hz), 1.19–1.31 (4H, m), 1.49 (2H, m), 2.23 (2H, q, J=7.3 Hz), 2.26 (2H, t, J=7.8 Hz), 3.20 (2H, d, J=6.4 Hz), 4.99–5.05 (2H, m), 5.77 (1H, ddt, J=16.8, 10.0, 6.8 Hz), 7.18–7.26 (3H, m), 7.36 (2H, m); ^{13}C NMR (100.4 MHz, $CDCl_3$): δ 13.4, 14.0, 22.5, 25.2, 29.4, 31.5, 34.7, 41.0, 115.5, 126.1, 128.7, 128.9, 131.4, 131.9, 136.4, 145.3; MS (EI): 322 (M$^+$, 50), 245 (100), 175 (7), 157 (11), 123 (8), 109 (25), 95 (54), 91 (32), 79 (40), 67 (51), 55 (41); HRMS: *m*/*z* for $C_{18}H_{26}Se$, calcd: 322.1200. Found: 322.1202.

4.3.5. (*E*)-6-(*n*-Butylthio)-5-methyl-5-decene (3d$_7$). Synthesized according to RP-3, through the preparation of **2d** and the use of methyl iodide as electrophile. Column chromatography (silica gel; pentane) afforded **3d$_7$** (68% yield), as a colorless liquid. IR (neat): 2959, 2931, 2861, 1619, 1464, 1377, 1273, 1222, 1103, 993, 744 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$): δ 0.83–0.98 (9H, m), 1.13–1.65 (12H, m), 1.92 (3H, s), 2.04–2.33 (4H, m), 2.55 (2H, t, J=7.0 Hz); ^{13}C NMR (22.5 MHz, $CDCl_3$): δ 13.7, 14.0, 20.8, 22.0, 22.6, 22.8, 30.7, 31.4, 31.9, 31.9, 32.1, 34.6, 127.9, 139.3; MS (EI): 242 (M$^+$, 75), 199 (50), 185 (100), 143 (26), 129 (10), 109 (19), 101 (23), 95 (16), 87 (17), 81 (12), 69 (21), 67 (21), 55 (24); HRMS: *m*/*z* for $C_{15}H_{30}S$, calcd: 242.2068. Found: 242.2063.

4.3.6. (*E*)-5-Methyl-6-(phenylthio)-5-decene (3h$_7$). Synthesized according to RP-3, through the preparation of **2h** and the use of methyl iodide as electrophile. Column chromatography (silica gel; pentane) afforded **3h$_7$** (72% yield), as a colorless liquid. IR (neat): 3072, 2958, 2930, 2861, 1620, 1584, 1477, 1466, 1440, 1377, 1086, 1025, 738, 692 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.86 (3H, t, J=7.4 Hz), 0.96 (3H, t, J=7.0 Hz), 1.26 (2H, m), 1.39 (2H, m), 1.43–1.50 (4H, m), 1.98 (3H, s), 2.24 (2H, t, J=7.6 Hz), 2.25 (2H, t, J=7.6 Hz), 7.09–7.13 (1H, m), 7.17 (2H, m), 7.22–7.26 (2H, m); ^{13}C NMR (22.5 MHz, $CDCl_3$): δ14.0, 14.0, 21.2, 22.5, 22.9, 30.7, 31.4, 33.4, 34.6, 124.9, 126.5, 127.5, 128.7, 137.6, 144.8; MS (EI): 262 (M$^+$, 100), 219 (32), 164 (39), 149 (32), 135 (19), 123 (16), 109 (19), 95 (13), 81 (12), 67 (21), 55 (28). Anal. Calcd for $C_{17}H_{26}S$: C, 77.80; H, 9.98. Found: C, 77.41; H, 10.44.

4.3.7. (*Z*)-6-Ethyl-5-(phenylthio)-5-tridecene-7-yne (3g$_3$). Synthesized according to RP-3, through the preparation of **2g** and the use of 1-iodo-1-heptyne (1.25 equiv.) as electrophile. Column chromatography (silica gel; pentane) afforded **3g$_3$** (63% yield), as a yellowish liquid. IR (neat): 3072, 3060, 2959, 2932, 2861, 2218, 1731, 1583, 1475, 1465, 1440, 1377, 1329, 1068, 1086, 1025, 743, 692 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$): δ 0.78–0.94 (6H, m), 1.15 (3H, t, J=7.5 Hz), 1.20–1.57 (10H, m), 2.11–2.41 (6H, m), 7.16–7.38 (5H, m); ^{13}C NMR (22.5 MHz, $CDCl_3$): δ13.5, 13.7, 13.9, 19.6, 22.2, 22.3, 26.8, 28.5, 31.0, 31.1, 31.5, 80.4, 96.3, 126.5, 127.3, 128.6, 131.2, 135.3, 138.5; MS (EI): 314 (M$^+$, 25), 258 (7), 237 (37), 205 (12), 181 (100), 149 (7), 119 (7), 105 (10), 91 (21), 77 (12), 55 (9); HRMS: *m*/*z* for $C_{21}H_{30}S$, calcd: 314.2068. Found: 314.2072.

4.3.8. (*Z*)-5-(*n*-Butylthio)-6-ethyl-5-tridecene-7-yne (3j$_3$). Synthesized according to RP-3, through the preparation of **2j** and the use of 1-iodo-1-heptyne (1.25 equiv.) as electrophile. Column chromatography (silica gel; pentane/Et_2O, 99.5:0.5) afforded **3j$_3$** (59% yield), as a colorless liquid. IR (neat): 2959, 2931, 2861, 2218, 1580, 1462, 1378, 1329, 1271, 1133, 1101, 1061, 746 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$): δ 0.84–0.99 (9H, m), 1.08 (3H, t, J=7.6 Hz), 1.19–1.62 (14H, m), 2.08–2.48 (6H, m), 2.74 (3H, t, J=7.6 Hz); ^{13}C NMR (22.5 MHz, $CDCl_3$): δ 13.5, 13.7, 13.9, 14.0, 19.7, 22.0, 22.2, 22.6, 26.7, 28.6, 31.1, 31.3, 31.6, 31.8, 80.4, 96.5, 123.3, 139.7; MS (EI): 294 (M$^+$, 23), 237 (35), 205 (8), 181 (100), 125 (11), 107 (7), 91 (9), 55 (5); HRMS: *m*/*z* for $C_{19}H_{34}S$, calcd: 294.2381. Found: 294.2387.

4.3.9. (*Z*)-3-Benzyl-4-(phenylthio)-3-octene (3g$_2$). Synthesized according to RP-3, through the preparation of **2g** and the use of benzyl bromide as electrophile. Kugelrohr distillation followed by column chromatography (silica gel; pentane) afforded **3g$_2$** (13% yield), as a yellowish liquid. IR (neat): 3062, 3027, 2960, 2931, 2872, 1601, 1584, 1494, 1477, 1454, 1441, 1117, 1089, 1027, 739, 699 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.86 (3H, t, J=7.2 Hz), 1.06 (3H, t, J=7.6 Hz), 1.26 (2H, m), 1.53 (2H, m), 2.17 (2H, q, J=7.5 Hz), 2.27 (2H, t, J=7.8 Hz), 3.86 (2H, s), 7.10–7.28 (10H, m); ^{13}C NMR (100.4 MHz, $CDCl_3$): δ 13.4, 14.0,

22.5, 25.0, 31.6, 32.6, 39.6, 125.3, 125.9, 128.3, 128.3, 128.7, 128.8, 137.1, 140.2, 148.0; MS (EI): 310 (M^+, 100), 281 (9), 219 (10), 177 (8), 167 (8), 157 (11), 145 (23), 129 (44), 117 (21), 105 (8), 91 (65), 65 (8). Anal. Calcd for $C_{21}H_{26}S$: C, 81.23; H, 8.44. Found: C, 81.10; H, 8.73.

4.3.10. (*Z*)-3-Ethyl-4-(phenylthio)-3-octen-2-one ($3g_5$). Synthesized according to RP-3, through the preparation of **2g** and the use of acetyl chloride as electrophile. Column chromatography (silica gel; pentane/Et_2O, 95:5) afforded $\mathbf{3g_5}$ (29% yield), as a yellow liquid. IR (neat): 3060, 2960, 2933, 2873, 1692, 1583, 1478, 1440, 1377, 1350, 1241, 1140, 1096, 1025, 744, 692 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.80 (3H, t, J=7.3 Hz), 1.10 (3H, t, J=7.6 Hz), 1.21 (2H, m), 1.45 (2H, m), 2.18 (2H, t, J=7.8 Hz), 2.40 (3H, s), 2.41 (2H, q, J=7.5 Hz), 7.22–7.32 (5H, m); ^{13}C NMR (100.4 MHz, $CDCl_3$): δ 13.4, 13.8, 22.3, 24.2, 30.5, 31.1, 31.2, 126.9, 129.0, 130.4, 134.6, 134.8, 147.7, 204.7; MS (EI): 262 (M^+, 60), 247 (7), 185 (6), 153 (100), 135 (6), 110 (19); HRMS: m/z for $C_{16}H_{22}OS$, calcd: 262.1391. Found: 262.1395.

4.3.11. (*Z*)-2-Ethyl-1-phenyl-3-(phenylthio)-hept-2-ene-1-one ($3g_6$). Synthesized according to RP-3, through the preparation of **2g** and the use of benzoyl chloride as electrophile. Column chromatography (silica gel; pentane/Et_2O, 95:5) afforded $\mathbf{3g_5}$ (32% yield), as a yellowish liquid. IR (neat): 3060, 2959, 2932, 2873, 1665, 1597, 1581, 1478, 1449, 1315, 1279, 1245, 1026, 1168, 1024, 897, 743, 711, 691 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.89 (3H, t, J=7.3 Hz), 1.10 (3H, t, J=7.6 Hz), 1.33 (2H, m), 1.59 (2H, m), 2.29 (2H, t, J=7.8 Hz), 2.51 (2H, q, J=7.6 Hz), 7.15–7.25 (5H, m), 7.46 (2H, m), 7.54 (1H, m), 7.95 (2H, m); ^{13}C NMR (100.4 MHz, $CDCl_3$): δ 13.1, 13.9, 22.5, 25.1, 30.7, 30.8, 31.1, 126.7, 128.6, 128.8, 129.1, 130.5, 132.9, 133.0, 134.5, 137.0, 146.6, 198.1; MS (EI): 324 (M^+, 35), 281 (11), 247 (8), 215 (79), 173 (31), 159 (12), 145 (14), 105 (100), 77 (57); HRMS: m/z for $C_{21}H_{24}OS$, calcd: 324.1548. Found: 324.1552.

4.3.12. Representative procedure (RP-4) for the boron to copper transmetalation (Scheme 7, conditions A). Synthesis of (*E*)-2-cyclohexyl-3-(phenylthio)-2-octene ($3i_7$). A three-necked 25 mL flask equipped with a septum and a flexible side-arm containing 0.191 g (1 mmol) of copper(I) iodide was placed under argon, and charged with a THF solution (3 mL) of **2i** and 0.5 mL of HMPA. At −33 °C, 1.42 mL of methyllithium were introduced (1.4 M in ether; 2 mmol; 2 equiv.) and the flask was keeped at this temperature for 30 min before the addition of the copper iodide. The mixture was maintained at −33 °C for 3 h under vigorous stirring before the introduction of methyl iodide (0.19 mL; 3 mmol; 3 equiv.). The stirring was continued for 4 h at −33 °C and then the cooling bath was removed. The reaction mixture was diluted with 20 mL of Et_2O and washed with a mixture (4:1, v/v) of saturated aqueous ammonium chloride and aqueous ammonium hydroxide (28%), and with water; the organic phase was dried over $MgSO_4$ and made free of solvent under reduced pressure. The purification by column chromatography (silica gel; pentane) gave a mixture of $\mathbf{3i_7}$ and *n*-pentylcyclohexylacetylene **5b**. The latter was removed by Kugelrohr distillation under reduced pressure to give essentially pure $\mathbf{3i_7}$ (69% yield). IR (neat): 3071, 3061, 2930, 2854, 1611, 1584, 1476, 1448, 1376, 1143, 1086, 1025, 738, 691 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$): δ 0.86 (3H, t, J=6.2 Hz), 1.15–1.85 (16H, m), 1.89 (3H, s), 2.27 (2H, t, J=7.4 Hz), 2.60 (1H, m), 7.09–7.24 (5H, m); ^{13}C NMR (22.5 MHz, $CDCl_3$): δ 14.0, 16.6, 22.5, 26.1, 26.6, 29.1, 31.2, 31.5, 33.6, 42.5, 124.8, 125.7, 127.3, 128.7, 137.7, 149.3; MS (EI): 302 (M^+, 100), 287 (7), 225 (65), 164 (46), 149 (12), 135 (18), 123 (13), 109 (22), 91 (18), 81 (28), 67 (18), 55 (29). Anal. Calcd for $C_{20}H_{30}S$: C, 79.41; H, 9.99. Found: C, 79.36; H, 10.01.

4.3.13. (*E*)-4-*sec*-Butyl-5-(*n*-butylthio)-1,4-nonadiene ($3n_4$). Synthesized according to RP-4, starting from **2n** and using allyl bromide as electrophile. Column chromatography (silica gel; pentane) afforded $\mathbf{3n_4}$ (71% yield), as a colorless liquid. IR (neat): 3079, 2961, 2931, 2874, 1637, 1601, 1461, 1425, 1378, 1215, 993, 907 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.82 (3H, t, J=7.4 Hz), 0.89–0.99 (9H, m), 1.34–1.52 (10H, m), 2.21 (1H, m), 2.39 (1H, m), 2.49–2.73 (3H, m), 2.97 (1H, dd, J=15.2, 6.4 Hz), 3.15 (1H, dd, J=15.2, 6.4 Hz), 4.94–5.02 (2H, m), 5.11 (1H, ddt, J=16.9, 10.5, 6.2 Hz); ^{13}C NMR (22.5 MHz, $CDCl_3$): δ 12.4, 13.7, 14.1, 19.6, 22.0, 22.6, 28.2, 30.6, 31.4, 31.9, 32.0, 33.9, 38.6, 114.5, 130.6, 138.2, 143.4; MS (EI): 268 (M^+, 10), 239 (23), 211 (75), 183 (66), 169 (9), 155 (100), 141 (7), 121 (13), 107 (18), 93 (23), 79 (23), 67 (16), 57 (22). Anal. Calcd for $C_{17}H_{32}S$: C, 76.05; H, 12.01. Found: C, 76.07; H, 11.98.

4.3.14. (*E*)-3-Cyclohexyl-4-(phenylthio)-3-nonene ($3i_8$). Synthesized according to RP-4, starting from **2i** and using ethyl iodide as electrophile. The purification by column chromatography (silica gel; pentane) gave a mixture of $\mathbf{3i_8}$ and *n*-pentylcyclohexylacetylene **5b**. The latter was removed by Kugelrohr distillation under reduced pressure (24% yield of **5b**) to give essentially pure $\mathbf{3i_8}$ (28% yield), as a colorless liquid. IR (neat): 3071, 2930, 2854, 1584, 1476, 1450, 1376, 1085, 1025, 892, 738, 691 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.86 (3H, t, J=7.1 Hz), 1.02 (3H, t, J=7.3 Hz), 1.15–1.48 (11H, m), 1.59–1.83 (5H, m), 2.19 (2H, t, J=7.8 Hz), 2.32 (2H, q, J=7.5 Hz), 2.60 (1H, tt, J=11.6, 3.4 Hz), 7.08–7.25 (5H, m); ^{13}C NMR (22.5 MHz, $CDCl_3$): δ 14.0, 15.5, 22.5, 24.0, 26.1, 26.7, 29.4, 31.4, 31.7, 32.8, 42.9, 124.9, 126.6, 127.8, 128.7, 137.7, 154.7; MS (EI): 316 (M^+, 100), 287 (86), 239 (46), 178 (27), 163 (9), 149 (8), 135 (13), 123 (16), 109 (17), 95 (24), 81 (25), 67 (21), 55 (29); HRMS: m/z for $C_{21}H_{32}S$, calcd: 316.2225. Found: 316.2218.

4.3.15. Representative procedure (RP-5) for the boron to copper transmetalation (Scheme 7, conditions B). Synthesis of (*E*)-5-ethyl-6-(phenylthio)-5-decene ($3h_8$). A three-necked 50 mL flask equipped with a septum and a flexible side-arm containing 0.382 g (2 mmol) of copper(I) iodide was placed under argon. A THF solution (3 mL) of 1-hexyne (0.164 g; 2 mmol) was introduced and cooled to −20 °C; *n*-butyllithium (1.6 M in hexane; 1.25 mL; 2 mmol) was added and the mixture was stirred for 1 h. 2 mL of tri-*n*-butylborane (1 M in THF; 2 mmol) were then introduced, the cooling bath was removed and the mixture was stirred for 1 h at room temperature. After cooling to −78 °C, a solution of benzenesulfenyl chloride (0.289 g; 2 mmol) in 3 mL THF was added dropwise; the flask was

warmed to room temperature for 15 min, and cooled again to −78 °C. Methyllithium (1.4 M in ether; 2.9 mL; 4 mmol; 2 equiv.) was introduced and the mixture was stirred for 15 min before successive addition of copper iodide, HMPA (2 mL), triethylphosphite (0.41 mL; 2.4 mmol; 1.2 equiv.) and ethyl iodide (0.24 mL; 3 mmol; 1.5 equiv.). The cooling bath was allowed to warm-up to room temperature and stirring was continued overnight. The reaction mixture was diluted with 20 mL of Et_2O and washed with a mixture (4:1, v/v) of saturated aqueous ammonium chloride and aqueous ammonium hydroxide (28%), and with water; the organic phase was dried over $MgSO_4$ and made free of solvent under reduced pressure. GC analysis via calibration using tridecane as internal standard revealed the presence of 5-decyne **5h** (21% yield) and ethylthiobenzene **6h$_8$** (19% yield). Kugelrohr distillation followed by column chromatography (silica gel; pentane) afforded **3h$_8$** (45% yield), as a colorless liquid. IR (neat): 3069, 2959, 2931, 2872, 1583, 1477, 1459, 1439, 1377, 1085, 1025, 738, 691 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$): δ 0.85–1.08 (9H, m), 1.19–1.50 (8H, m), 2.08–2.36 (4H, m), 2.41 (2H, q, J=7.6 Hz), 7.07–7.25 (5H, m); ^{13}C NMR (22.5 MHz, $CDCl_3$): δ 13.7, 14.0, 22.4, 23.1, 27.7, 31.2, 31.5, 32.0, 32.8, 124.9, 126.2, 127.7, 128.7, 137.6, 150.7; MS (EI): 276 (M^+, 100), 233 (34), 178 (37), 163 (22), 149 (8), 135 (19), 123 (23), 109 (14), 95 (15), 81 (24), 69 (23), 55 (24); HRMS: m/z for $C_{18}H_{28}S$, calcd: 276.1912. Found: 276.1910.

4.3.16. (*E*)-6-(*n*-Butylthio)-5-ethyl-5-decene (3d$_8$). Synthesized according to RP-5, through the preparation of **2d**. Column chromatography (silica gel; pentane) afforded **3d$_8$** (66% yield), as a colorless liquid. IR (neat): 2960, 2931, 2862, 1611, 1461, 1378, 1272, 1222, 1102, 745 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$): δ 0.87–1.03 (12H, m), 1.13–1.64 (12H, m), 2.01–2.33 (4H, m), 2.37 (2H, q, J=7.6 Hz), 2.54 (2H, t, J=7.0 Hz); ^{13}C NMR (22.5 MHz, $CDCl_3$): δ 13.4, 13.7, 14.0, 14.1, 22.0, 22.6, 22.9, 27.2, 31.1, 31.4, 31.7, 31.9, 31.9, 127.5, 145.4; MS (EI): 256 (M^+, 61), 213 (37), 199 (100), 157 (16), 143 (7), 123 (7), 109 (7), 101 (15), 95 (12), 81 (21), 69 (17), 67 (15), 55 (20). Anal. Calcd for $C_{16}H_{32}S$: C, 74.92; H, 12.57. Found: C, 74.71; H, 12.48.

4.3.17. (*Z*)-5-Benzyl-6-(phenylthio)-5-decene (3h$_2$). Synthesized according to RP-5, through the preparation of **2h** and the use of benzyl bromide as electrophile. Kugelrohr distillation followed by column chromatography (silica gel; pentane) afforded **3h$_2$** (62% yield). IR (neat): 3062, 3027, 2958, 2931, 2862, 1601, 1584, 1494, 1477, 1451, 1440, 1379, 1088, 1026, 739, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.86 (3H, t, J=7.3 Hz), 0.91 (3H, t, J=7.3 Hz), 1.27 (2H, m), 1.33 (2H, m), 1.45 (2H, m), 1.54 (2H, m), 2.13 (2H, t, J=7.8 Hz), 2.27 (2H, t, J=7.8 Hz), 3.86 (2H, s), 7.11–7.28 (10H, m); ^{13}C NMR (100.4 MHz, $CDCl_3$): δ 14.0, 22.5, 22.9, 31.0, 31.5, 31.7, 32.6, 40.0, 125.3, 125.9, 128.2, 128.3, 128.6, 128.8, 129.1, 137.1, 140.2, 146.7; MS (EI): 338 (M^+, 100), 281 (9), 247 (13), 185 (14), 143 (17), 129 (38), 117 (22), 91 (73). Anal. Calcd for $C_{23}H_{30}S$: C, 81.60; H, 8.93. Found: C, 81.64; H, 9.05.

4.3.18. (*Z*)-5-Benzyl-6-(*n*-butylthio)-5-decene (3d$_2$). Synthesized according to RP-5, through the preparation of **2d** and the use of benzyl bromide as electrophile. Kugelrohr distillation followed by column chromatography (silica gel; pentane) afforded **3d$_2$** (64% yield), as a yellowish liquid. IR (neat): 3083, 3062, 3027, 2958, 2930, 2862, 1602, 1494, 1456, 1379, 1273, 1221, 1100, 1030, 957, 729, 700 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$): δ 0.93–1.00 (9H, m), 1.14–1.66 (12H, m), 2.02 (2H, t, J=7.3 Hz), 2.33 (2H, t, J=7.4 Hz), 2.54 (2H, t, J=6.9 Hz), 3.82 (2H, s), 7.03–7.24 (5H, m); ^{13}C NMR (22.5 MHz, $CDCl_3$): δ 13.7, 13.9, 14.1, 21.9, 22.7, 22.8, 30.9, 31.2, 31.4, 31.7, 31.9, 39.7, 125.7, 128.2, 128.6, 130.4, 140.7, 141.9; MS (EI): 318 (M^+, 100), 275 (16), 261 (32), 227 (39), 185 (31), 171 (22), 143 (24), 129 (63), 91 (68); HRMS: m/z for $C_{21}H_{34}S$, calcd: 318.2381. Found: 318.2377.

4.4.. Nickel catalyzed coupling of vinylsulfides

4.4.1. Representative procedure (RP-6) for the cross-coupling of vinylsulfides with Grignard reagents. Synthesis of (*E*)-5-methyl-6-phenyl-5-decene (7A). In a 25 mL two-necked flask, equipped with an argon inlet and a magnetic stirring bar, were introduced a solution of **3h$_7$** (0.210 g; 0.8 mmol) in Et_2O (7 mL) and $NiCl_2$(dmpe) (0.007 g; 0.025 mmol; 3% mol.). Phenylmagnesium bromide (0.67 mL of a 3 M solution in Et_2O; 2 mmol; 2.5 equiv.) was added and the reaction mixture was stirred at room temperature for 14.5 h before the addition of 1 mL of saturated aqueous NH_4Cl. After dilution with Et_2O, the organic layer was separated, washed with 10 mL of aqueous NaOH (1 M) and with water, dried over $MgSO_4$, and concentrated. The crude product was purified by column chromatography (silica gel; pentane) providing 0.152 g of biphenyl and 0.151 g of **7A** (82% yield) as a colorless liquid. IR (neat): 3078, 3058, 3022, 2958, 2929, 2860, 1600, 1574, 1492, 1465, 1442, 1378, 1133, 1105, 1071, 771, 744, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.85 (3H, t, J=7.2 Hz), 0.97 (3H, t, J=7.1 Hz), 1.19–1.28 (4H, m), 1.36–1.49 (4H, m), 1.50 (3H, s), 2.18 (2H, t, J=7.7 Hz), 2.34 (2H, t, J=7.3 Hz), 7.07–7.10 (2H, m), 7.19–7.23 (1H, m), 7.27–7.33 (2H, m); ^{13}C NMR (22.5 MHz, $CDCl_3$): δ 14.0, 14.2, 19.9, 22.7, 22.9, 30.8, 33.7, 33.7, 125.6, 127.8, 129.0, 131.3, 135.8, 144.4; MS (EI): 230 (M^+, 65), 187 (16), 173 (27), 145 (35), 131 (100), 117 (40), 105 (13), 91 (43). Anal. Calcd for $C_{17}H_{26}$: C, 88.63; H, 11.37. Found: C, 88.59; H, 11.13.

4.4.2. (*Z*)-4-Ethyl-5-phenyl-1,4-decadiene (7B). Synthesized according to RP-6, starting from **3f$_4$**. The reaction mixture was heated to reflux for 23 h. Column chromatography (silica gel; pentane) afforded **7B** (38% yield), as a colorless liquid. IR (neat): 3078, 3058, 3021, 2962, 2931, 2873, 2861, 1636, 1600, 1491, 1460, 1440, 1376, 1071, 994, 910, 766, 702 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$): δ 0.83 (3H, t, J=6.4 Hz), 1.04 (3H, t, J=7.4 Hz), 1.15–1.30 (6H, m), 2.18 (2H, q, J=7.4 Hz), 2.31 (2H, t, J=7.6 Hz), 2.58 (2H, d, J=6.4 Hz), 4.78–5.02 (2H, m), 5.77 (1H, ddt, J=18.2, 8.6, 6.1 Hz), 7.02–7.31 (5H, m); ^{13}C NMR (22.5 MHz, $CDCl_3$): δ 13.4, 14.0, 22.6, 23.7, 28.1, 31.8, 34.0, 37.2, 114.9, 125.9, 127.8, 128.7, 134.7, 137.3, 137.7, 143.7; MS (EI): 242 (M^+, 100), 213 (27), 185 (10), 171 (99), 157 (20), 143 (64), 129 (67), 115 (20), 105 (12), 91 (55); HRMS: m/z for $C_{18}H_{26}$, calcd: 242.2035. Found: 242.2033.

4.4.3. 5-*n*-Butyl-6-methyl-5-decene (7C). Synthesized according to RP-6, using *n*-butylmagnesium bromide

(0.5 M in Et_2O) as the Grignard reagent. The reaction mixture was heated to reflux for 22.5 h. Column chromatography (silica gel; pentane) afforded **7C** (70% yield), as a colorless liquid. IR (neat): 2958, 2929, 2861, 1656, 1465, 1341, 1289, 1222, 1151, 1106, 896, 727 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$): δ 0.90 (9H, m), 1.11–1.41 (12H, m), 1.61 (3H, s), 1.98 (6H, m); ^{13}C NMR (22.5 MHz, $CDCl_3$): δ 14.1, 17.9, 22.8, 23.0, 23.1, 31.0, 31.1, 31.5, 31.8, 32.1, 33.9, 128.4, 133.3; MS (EI): 210 (M^+, 38), 153 (13), 125 (12), 112 (45), 97 (58), 83 (50), 69 (100), 55 (69); HRMS: *m/z* for $C_{15}H_{30}$, calcd: 210.2348. Found: 210.2354.

4.4.4. (*E*)-5-Benzyl-6-methyl-5-decene (7D). Synthesized according to RP-6, starting from **3h$_2$**, and using methylmagnesium bromide (3 M in Et_2O) as the Grignard reagent. The reaction mixture was heated to reflux for 10 days. Column chromatography (silica gel; pentane) afforded **3h$_2$** (60% yield), and a mixture of (*E*)-5-benzyl-5-decene (2% yield) and **7D** (24% yield) in a 8:92 ratio (determined by ^1H NMR), as a colorless liquid. IR (neat): 3084, 3063, 3028, 2958, 2929, 2861, 1603, 1494, 1455, 1378, 1103, 1074, 1030, 727, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.86 (3H, t, *J*=7.1 Hz), 0.93 (3H, t, *J*=7.3 Hz), 1.23–1.44 (8H, m), 1.72 (3H, s), 1.95 (2H, t, *J*=7.8 Hz), 2.09 (2H, t, *J*=7.8 Hz), 3.40 (2H, s), 7.13–7.18 (3H, m), 7.24–7.28 (2H, m); ^{13}C NMR (22.5 MHz, $CDCl_3$): δ 14.0, 14.1, 18.6, 23.0, 31.0, 31.2, 31.6, 34.0, 37.6, 125.5, 128.2, 128.4, 131.0, 131.3, 141.2; MS (EI): 244 (M^+, 80), 187 (97), 145 (38), 131 (72), 117 (50), 105 (21), 97 (32), 91 (10%), 83 (20), 69 (23), 55 (72); HRMS: *m/z* for $C_{18}H_{28}$, calcd: 244.2191. Found: 244.2198.

4.4.5. (*Z*)-4-Ethyl-5-phenyl-4-decene (7E). Synthesized according to RP-6, starting from **3f$_9$**. The reaction mixture was heated to reflux for 15 h. Column chromatography (silica gel; pentane) afforded **7E** (76% yield), as a colorless liquid. IR (neat): 3078, 3057, 3021, 2961, 2930, 2871, 1600, 1575, 1491, 1465, 1442, 1377, 1133, 1071, 770, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.72 (3H, t, *J*=7.3 Hz), 0.83 (3H, t, *J*=6.8 Hz), 1.05 (3H, t, *J*=7.3 Hz), 1.21–1.26 (6H, m), 1.28 (2H, m), 1.78 (2H, t, *J*=7.8 Hz), 2.17 (2H, q, *J*=7.5 Hz), 2.28 (2H, t, *J*=6.8 Hz), 7.05 (2H, m), 7.17–7.21 (1H, m), 7.26–7.30 (2H, m); ^{13}C NMR (22.5 MHz, $CDCl_3$): δ 13.7, 14.1, 14.2, 22.0, 22.6, 23.7, 28.1, 31.9, 34.1, 34.5, 125.6, 127.7, 129.0, 136.0, 137.2, 144.3; MS (EI): 244 (M^+, 100), 215 (23), 201 (10), 187 (6), 173 (45), 159 (18), 145 (84), 131 (98), 117 (84), 105 (21), 91 (69), 77 (10), 69 (9), 55 (13). Anal. Calcd for $C_{18}H_{28}$: C, 88.45; H, 11.55. Found: C, 88.87; H, 11.72.

4.4.6. Catalytic hydrogenation of 3f$_4$. Synthesis of (*Z*)-4-ethyl-5-(phenylthio)-4-decene (3f$_9$). A two-necked 25 mL flask equipped with a septum was placed under hydrogen atmosphere. A solution of **3f$_4$** (1.067 g; 3.89 mmol) in hydrogen flushed benzene and chlorotris(triphenylphosphine)rhodium(I) (0.111 g; 0.12 mmol; 3 mol%) were successively introduced, and the resulting brown solution was stirred at room temperature for 12 h. The solvent was removed under reduced pressure, and the residue was extracted with Et_2O (3×15 mL). The combined organic layers were filtered over celite, and then concentrated under reduced pressure. Column chromatography (silica gel; pentane) afforded 0.962 g of **3f$_9$** (90% yield), as a colorless liquid. IR (neat): 3072, 2961, 2932, 2872, 1584, 1477, 1463, 1440, 1377, 1133, 1087, 1067, 1025, 739, 691 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.84 (3H, t, *J*=7.1 Hz), 0.90 (3H, t, *J*=7.6 Hz), 1.09 (3H, t, *J*=7.3 Hz), 1.17–1.29 (4H, m), 1.39–1.52 (4H, m), 2.19 (2H, t, *J*=7.8 Hz), 2.23 (2H, q, *J*=7.3 Hz), 2.38 (2H, t, *J*=7.8 Hz), 7.09–7.13 (1H, m), 7.17 (2H, m), 7.21–7.25 (2H, m); ^{13}C NMR (22.5 MHz, $CDCl_3$): δ 13.5, 14.0, 14.2, 22.3, 22.6, 22.6, 29.1, 31.6, 32.9, 36.1, 125.0, 126.8, 127.8, 128.7, 137.6, 150.3; MS (EI): 276 (M^+, 100), 247 (34), 178 (50), 163 (19), 149 (7), 135 (17), 123 (21), 109 (12), 95 (22), 81 (22), 69 (23), 55 (30). Anal. Calcd for $C_{18}H_{28}S$: C, 78.20; H, 10.21. Found: C, 77.83; H, 10.21.

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$LiClO_4$ Accelerated Michael addition of amines to α,β-unsaturated olefins under solvent-free conditions

Najmedin Azizi and Mohammad R. Saidi*

Department of Chemistry, Sharif University of Technology, P.O. Box 11365-9516, Tehran 11365, Iran

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Abstract—Several primary and secondary amines were added to α,β-unsaturated esters, nitriles, amides, and ketones to give the corresponding saturated amines mediated by solid lithium perchlorate under solvent-free and environmentally friendly conditions at room temperature.

1. Introduction

The synthesis of β-amino esters has gained considerable attention[1] due to their biologically important properties, their occurrence in natural products and their use as precursors for the preparation of β-lactams.[1] The β-amino acids, in free form, show interesting pharmacological properties. For instance, hypoglycemic and antiketogenic activities were observed in rats after oral intake of emeriamine. Functionalized β-amino acids are the key component of a variety of bioactive molecules such as taxol, which is one of the most active antitumor agents. During the past few years the synthesis of β-amino acid derivatives with different substitution patterns at the carbon chain has become a field of increasing interest in organic synthetic.[2] Among the different synthetic methodologies the literature for the preparation of β-amino esters, one of the simplest and most widely used methods is the conjugate addition of amines to α,β-unsaturated ester derivatives. Although Michael addition of amines to α,β-unsaturated acids failed, their addition to α,β-unsaturated nitriles, esters and ketones were known. These methods usually require basic conditions, or acid catalysis.[3] Also, a number of alternative procedures have been developed in the past few years and in particular, various Lewis acid-induced reactions have been reported.[4] Unfortunately, many of these procedures often require a large excess of reagents, long reaction time and drastic reaction conditions in acetonitrile or 1,2-dichloroethane which are toxic. In some cases, a stoichiometric amount of Lewis acid such as $AlCl_3$, $TiCl_4$ or $SnCl_4$ are required.[4]

Recently, $LiClO_4$ has emerged as a powerful promoter in many chemical processes and in different organic media.[5] In this context, it is worthy to note that, due to the remarkable tolerance of $LiClO_4$ toward coordinating functional groups, even strongly coordinating amines can be used in the presence of $LiClO_4$.[6] We have taken advantage of this compatibility in developing a practical, simple and environmentally benign methodology for the conjugate addition of amines to α,β-unsaturated esters, nitriles, amides and ketones under neutral and solvent-free conditions. So far there are not any reports in the literature on the Michael addition to α,β-unsaturated olefins mediated by $LiClO_4$ under solvent-free conditions. Herein we report the $LiClO_4$ accelerated Michael addition of amines to α,β-unsaturated compounds under solvent-free conditions and at room temperature.

The Michael reaction of pyrrolidine with methylacrylate in the presence of solid $LiClO_4$ gave the Michael adduct in high yield and in a short time. The results and conditions are summarized in Table 1. The data in Table 1 clearly show that the reaction of different aliphatic amines and methylacrylate give the corresponding β-amino ester in high yield at room temperature without using any solvent. Primary amines, such as butylamine and benzylamine reacted with α,β-unsaturated esters to give only the mono alkylated adduct. No side product was observed by using excess of the reactants. When aromatic amines, such as aniline, were added to α,β-unsaturated ester (entry 6, Table 1), the Michael adduct was formed in low yield. The difference in the reactivity of aromatic amines shows the chemoselectivity of Michael addition of aliphatic amines in this method. Thus, when a mixture of aniline and pyrrolidine were exposed to excess methylacrylate in the presence of solid $LiClO_4$, the pyrrolidine adduct was obtained as the sole product (Scheme 1).

Keywords: Michael addition; Amine; α,β-Unsaturated olefins; Lithium perchlorate.
* Corresponding author. Tel.: +98-21-600-5718; fax: +98-21-601-2983; e-mail address: saidi@sharif.edu

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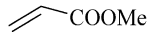
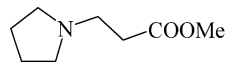
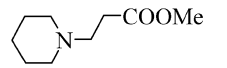
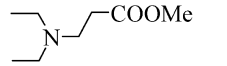
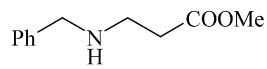
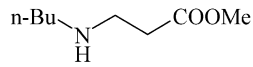
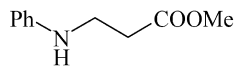
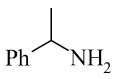
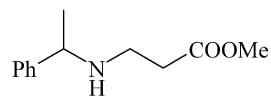
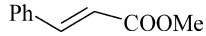
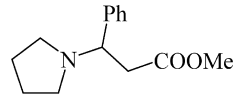
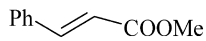
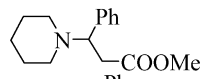
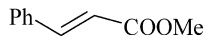
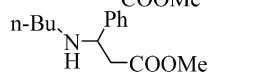
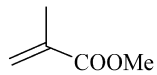
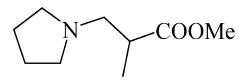
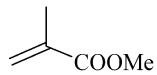
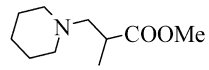
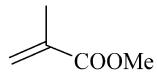
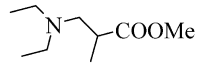
Table 1. Micheal addition of amines to α,β-unsaturated esters under solvent-free condition

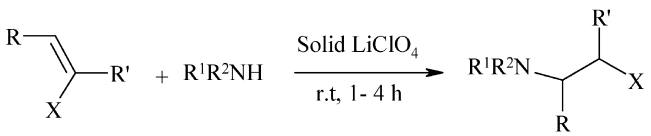
Entry	Amines	Ester	Product	Yield (%)[a] (time, h)[b]
1				86 (1)[4f]
2				84 (1)[4f]
3				88 (1)[4f]
4				89 (2)[1b]
5				90 (2)[1b]
6				30 (4)[1b]
7				88 (2)[1a]
8				80 (2)[4f]
9				76 (2)[4f]
10				60 (2)[1a]
11				90 (2)[1b]
12				86 (1.5)[1b]
13				80 (2)[1b]
14				78 (2)[1b]
15				82 (2)[1b]

[a] Isolated yields.
[b] References.

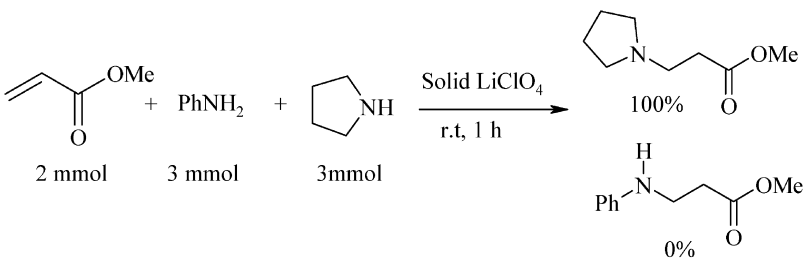
The Michael addition reaction of amines to α,β-unsaturated esters in the presence of solid $LiClO_4$ is temperature dependent. When the reaction was carried out at room temperature, only Michael adducts were formed. By elevating the temperature to 60 °C, the corresponding amides were obtained (Scheme 2).

This method also works well for α,β-unsaturated nitriles, amides, and ketones. Thus, the Michael reaction of pyrrolidine to these α,β-unsaturated compounds in the presence of solid $LiClO_4$ gave the corresponding Michael adducts in high yield and in a short time. The results and conditions are summarized in Table 2. On the other hand, in the case of α,β-unsaturated aldehydes, such as cinnamaldehydes, 1,2-addition is preferred and aminals were obtained exclusively.

In conclusion, we have developed a new method for accelerating the Michael reaction of amines with α,β-unsaturated olefins by using the inexpensive reagent $LiClO_4$. Although $LiClO_4$ is relatively cheap in comparison with many other Lewis acids used for these transformations, due to stability of $LiClO_4$ in water, it is possible to recover it by simple filtration and use it again after reactivating it by heating in vacuum at 160 °C. We believe that, these are improved conditions the Michael additions. The present procedure provides an efficient and general methodology for the preparation of β-amino esters, ketones and nitriles.

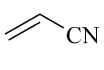
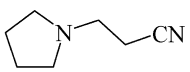
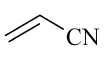
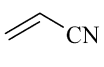
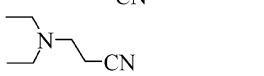
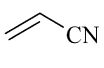
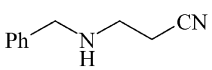
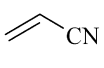
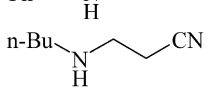
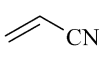
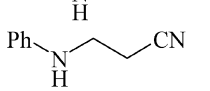
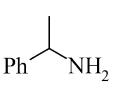
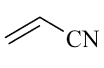
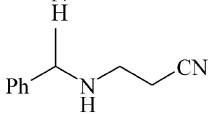
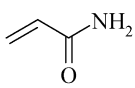
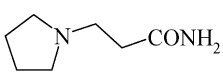
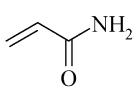
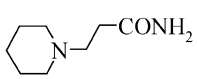
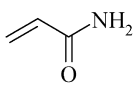
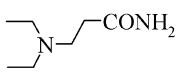
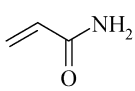
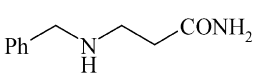
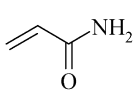
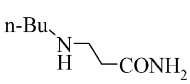
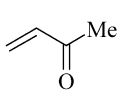
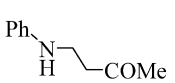


R = H, Ph; R' = CH_3; X = CN, $CONH_2$, COOMe, COMe

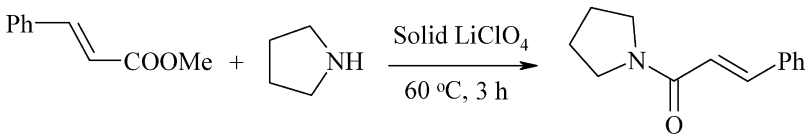


Scheme 1.

Table 2. Micheal addition of amines to α,β-unsaturated esters under solvent-free condition

Entry	Amines	Ethylenic compound	Product	Yield (%)[a] (time, h)[b])
1				82 (1)[4b]
2				80 (1)[4b]
3				83 (2)[1b]
4	$PhCH_2NH_2$			90 (2)[1b]
5	*n*-$BuNH_2$			93 (2)[1b]
6	$PhNH_2$			28 (4)[1a]
7				84 (2)[1a]
8				84 (1)[1c]
9				80 (1)[1c]
10				82 (2)[1c]
11	$PhCH_2NH_2$			76 (2)[1a]
12	*n*-$BuNH_2$			78 (2)[1a]
13[c]	$PhNH_2$			95 (1)[1b]

[a] Isolated yields.
[b] References.
[c] Only 20 mol% of solid $LiClO_4$ was used.



Scheme 2.

2. Experimental

2.1. General

NMR spectra were recorded on a Bruker ACF 500. IR spectra were measured using a Perkin–Elmer 1600 FTIR spectrometer. Column chromatography was performed on silica gel, Merck grade 60. CH_2Cl_2 was distilled before use. All reactions were performed under argon. Anhydrous $LiClO_4$ and other chemicals were purchased from Fluka or Merck.

Caution. Although we did not have any accident while using or drying $LiClO_4$, it is advisable to dry lithium perchlorate in hood using suitable lab-shield.

2.2. General procedure for the preparation of the Michael reaction of amines with α,β-unsaturated olefins

To a mixture of $LiClO_4$ (2 mmol) and methyl acrylate (2 mmol) was added pyrrolidine (3 mmol) and was stirred at room temperature under an argon atmosphere for 1 h. After completion of the reaction, CH_2Cl_2 (10 mL) was added, and $LiClO_4$ was removed by filtration. The solvent was evaporated and the product was isolated in almost pure from. Further purification was carried out by short column chromatography on silica gel eluting with ethyl acetate/petroleum ether. All compounds were characterized by retention times in GC and on the basis of their spectroscopic data (IR, NMR, MS) and by comparison with those reported in the literature.

2.2.1. Methyl 3-pyrrolidinyl-propionate. See Table 1, entry 1.[4f]

2.2.2. Methyl 3-piperidinyl-propionate. See Table 1, entry 2.[4f]

2.2.3. Methyl 3-(*N*,*N*-diethylamino)-propionate. See Table 1, entry 3.[4f]

2.2.4. Methyl 3-(*N*-benzylamino)-propionate. See Table 1, entry 4.[4f]

2.2.5. Methyl 3-(*N*-buthylamino)-propionate. See Table 1, entry 5.[1b]

2.2.6. Methyl 3-(*N*-phenylamino)-propionate. See Table 1, entry 6.[1b]

2.2.7. Methyl 3-(1-phenylethylamino)-propionate. See Table 1, entry 7.[1a]

2.2.8. Methyl 3-phenyl-3-pyrrolidinylpropionate. See Table 1, entry 8.[4f]

2.2.9. Methyl 3-phenyl-3-(*N*-buthylamino)-propionate. See Table 1, entry 10.[4f]

2.2.10. Methyl 2-methyl-3-pyrrolidinylpropionate. See Table 1, entry 11.[1b]

2.2.11. Methyl 2-methyl-3-(*N*,*N*-diethylamino)propionate. See Table 1, entry 13.[1b]

2.2.12. 3-Pyrrolidinyl-propionitrile. See Table 2, entry 1.[4b]

2.2.13. 3-(*N*,*N*-Diethylamino)-propionitrile. See Table 1, entry 3.[1b]

2.2.14. 3-(*N*-Buthylamino)-propionitril. See Table 1, entry 5.[1a]

2.2.15. 3-Pyrrolidinylpropionamide. See Table 2, entry 8.[1c]

2.2.16. 3-(*N*,*N*-Diethylamino)-propionamide. See Table 2, entry 10.[1c]

2.2.17. 4-(*N*-Phenylamino)-2-butanone. See Table 2, entry 13.[1b]

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Nucleoside H-phosphonates. Part 19: Efficient entry to novel nucleotide analogues with 2-pyridyl- and 4-pyridylphosphonothioate internucleotide linkages

Tommy Johansson and Jacek Stawinski*

Arrhenius Laboratory, Department of Organic Chemistry, Stockholm University, S-106 91 Stockholm, Sweden

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Abstract—Synthetic and ^{31}P NMR spectroscopy studies resulted in the development of efficient protocols for the stereospecific synthesis of a novel type of nucleotide analogues, 2-pyridyl- and 4-pyridylphosphonothioates. The underlying chemistry involves formation of the P–C bond via a base-promoted reaction of suitably protected dithymidine H-phosphonothioates with *N*-methoxypyridinium tosylate in acetonitrile, or with trityl chloride in pyridine, to produce high yields of nucleotide analogues with a 2-pyridyl- or 4-pyridyl moiety directly bound to the phosphorus centre.

1. Introduction

Pyridylphosphonate derivatives represent an important class of organophosphorus compounds with a wide range of technical applications, for example, corrosion inhibitors,[1] sensitisers for photovoltaic cells,[2] dispersing and emulsifying agents,[3] lubricant additives,[4] etc. Apart from these, they also show diverse biological activity and are known as potent insecticides,[5] fungicides,[6] and herbicides.[7] Recently, 2-pyridylphosphonates emerged as broad spectrum drugs with anti-proliferating and anti-PAF activity,[8] as inhibitors of fructose-1,6-bisphosphates[9] (and thus of potential use in diabetics therapy), and as lucitropic agents for the treatment of cardiovascular diseases.[10] These can probably be traced back to a structural similarity of 2-pyridylphosphonates to α-aminophosphonates[11] (P-analogues of α-amino acids), that are potent inhibitors of proteases[12] and exhibit pronounced antineoplastic activity.[13]

This diverse array of biological activity of simple dialkyl pyridylphosphonates recently prompted us to explore the possibility of incorporating this functionality into nucleic acid fragments, kindled with the hope that it may confer novel properties that could be useful when designing new antisense and antigene therapeutics. For this purpose, we have developed efficient methods for the conversion of dinucleoside H-phosphonates into 4-pyridyl-,[14] 3-pyridyl-,[15] and 2-pyridylphosphonate[16] analogues. As an extension of these studies, we attempted to develop a synthetic method for a new nucleotide analogue in which the phosphoryl oxygen atom of the pyridylphosphonate moiety was replaced by sulfur. Since a 2-pyridylphosphonate moiety may act as a bidentate chelating ligand[17] for transition metals, the replacement of oxygen by sulfur may significantly change its affinity for particular types of metal cations and thus be of importance in designing new artificial nucleases,[18] and reporter groups for investigation of electron transfer (ET) phenomena in nucleic acids.[19]

In contrast to pyridylphosphonates, their thiophosphonate counterparts are rare compounds. Also their biological properties are largely unexplored, apart from a few reports in the patent literature where these compounds have been advocated as activators and enhancers in certain compositions of herbicides and insecticides.[20] These most limited applications are probably due to the lack of convenient methods for the preparation of pyridylphosphonothioates. The only method of synthetic value affords the target thiophosphonates in mediocre yields,[21] and requires lengthy thiation of their oxygen congeners with P_2S_5 in toluene under reflux. Recently, an approach based on the metalation-induced rearrangement of 3-pyridyl phosphorothioates was reported,[22] but this produced mixtures of 2- and 4-pyridylphosphonothioates (3:1) in rather low yields (ca. 30%).

In this paper, ^{31}P NMR spectroscopy investigations and synthetic studies on the formation of 2-pyridyl- and 4-pyridylphosphonothioates from the corresponding H-phosphonothioate diesters, are described.

Keywords: H-Phosphonates; H-Phosphonothioates; Pyridylphosphonothioates.
* Corresponding author. Tel.: +46-8-16-24-85; fax: +46-8-15-49-08; e-mail address: js@organ.su.se

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2. Results and discussion

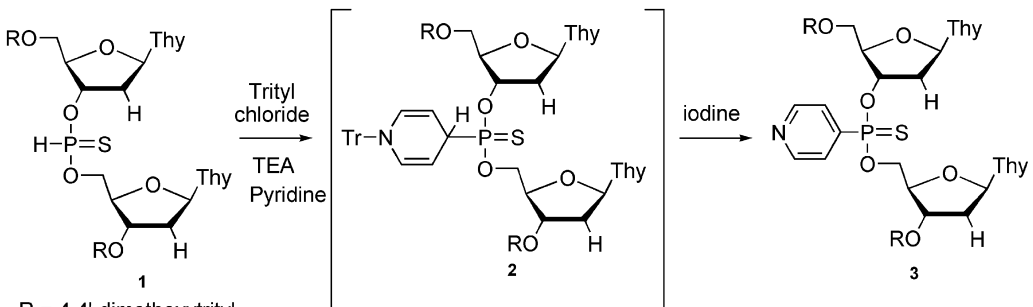
As viable means to synthesize 4-pyridyl- and 2-pyridylphosphonothioates, we considered 1,8-diazabicylo[5.4.0]undec-7-ene (DBU)-promoted reactions of dinucleoside H-phosphonothioates with the pyridine-trityl chloride reagent system and with *N*-methoxypyridinium salts, respectively, analogously to the recently developed methods for the preparation of pyridylphosphonate derivatives.[14] Despite apparent similarities between H-phosphonate and H-phosphonothioate diesters, the latter ones are more prone to side reactions and, under basic conditions, undergo a ligand exchange process[23] that may scramble substituents around the phosphorus center.

We assumed that synthesis of 4-pyridylphosphonothioates **3** could be effected via in situ generation of *N*-tritylpyridinium cation (from e.g., pyridine and trityl chloride), followed by an attack of a phosphorus nucleophile (e.g., H-phosphonothioate) at the less sterically hindered C-4 carbon of the pyridine ring (Scheme 1). Indeed, the reaction of dinucleoside H-phosphonothioate **1** in pyridine with trityl chloride (Tr-Cl, 1.2 equiv.) in the presence of DBU (2.4 equiv.) was rapid (ca. 10 min, ^{31}P NMR spectroscopy) but, apart from the expected 1,4-dihydropyridine intermediate **2** (70%, 2 signals at ca. 94 ppm) and the desired product **3** (10%, 2 signals at ca. 84 ppm), also afforded 5′-*O*-dimethoxytritylthymidin-3′-yl 3′-*O*-dimethoxytritylthymidin-5′-yl phosphorothioate diesters (20%, signals at 56.5 and 56.5 ppm), apparently due to oxidation of the starting material **1**. Use of more DBU (8 equiv.) speeded up the reaction and reduced the amount of the oxidation product to ca. 7%, but simultaneously another side products appeared (ca. 6%; signals at ca. 87 and 88 ppm). We hypothesized that formation of the phosphorothioate diesters under the reaction conditions was probably due to air oxidation of a highly reactive tervalent phosphite form generated from H-phosphonothioate **1** in the presence of a strong base (DBU). To remedy this problem, we replaced DBU by triethylamine (TEA), assuming that in the presence of a weaker base a concentration of a phosphite form generated from H-phosphonothioate **1** should be lower, and thus formation of the oxidation product should be suppressed.

Indeed, when dinucleoside H-phosphonothioate **1** (a diastereomeric mixture, 1:1; δ_P=69.9 and 71.6 ppm, $^1J_{PH}$=675, 674 Hz, $^3J_{PH}$=9.8 Hz, dq) was treated in pyridine with Tr-Cl (1.2 equiv.) in the presence of TEA (2.4 equiv.), the reaction was still rapid (<10 min) and produced 1,4-dihydropyridine derivatives **2** (δ_P=93.9, 94.5 ppm) practically quantitatively (Scheme 1). No dinucleoside phosphorothioate diesters or any other side products could be detected by ^{31}P NMR spectroscopy. Here, however, an unexpected problem arose: 1,4-dihydropyridylphosphonothioate intermediate **2** turned out to be rather stable and, in contrast to the 1,4-dihydropyridylphosphonate, that collapsed spontaneously to the corresponding pyridylphosphonate derivative,[14] it underwent only slow conversion into the product, 4-pyridylphosphonothioate diester **3** (δ_P=83.0, 84.3 ppm; ca. 20% conversion after a few hours).

To facilitate rearomatization of the 1,4-dihydropyridine intermediate and to convert it into 4-pyridylphosphonothioate **3**, we elaborated in situ oxidation of **2** with iodine. Although phosphorothioate diesters undergo rapid desulfurization in the presence of iodine,[24] uncharged phosphorus compounds bearing the thiophosphoryl function are resistant towards desulfurization (e.g., phosphorothioate triesters,[24] H-phosphonothioate diesters **1**[25]) and thus these reaction conditions should not affect the integrity of the produced pyridylphosphonothioates **3**. To check the efficacy of this approach, the reaction mixture containing 1,4-dihydropyridine intermediate **2** (obtained as described above) was treated with iodine (2 equiv.) in pyridine. ^{31}P NMR spectroscopy revealed rapid formation of the desired product **3** (ca. 50% after 10 min), however, with time, signals from dinucleoside phosphorothioate diesters (18%; 2 signals at ca. 56 ppm)[26] also appeared in the ^{31}P NMR spectrum. In this instance, the phosphorothioate diesters could be formed due to a possible reversibility of the dihydropyridine intermediate **2** formation[14] that can generate small equilibrium amounts of the starting material **1**. This, in the presence of iodine and adventitious water could produce, via the intermediacy of phosphorothioiodidates, the corresponding dinucleoside phosphorothioates.

We thought that this problem could be overcome by using more iodine for the reaction. The higher iodine concentration should increase the rate of rearomatization of **2** and thus lessen the problem of reversibility of the 1,4-dihydropyridine intermediate formation. It was rewarding



Scheme 1.

to see that addition of 4 equiv. of iodine to the reaction mixture containing 1,4-dihydrointermediate **2**, afforded, after 15 min the desired 4-pyridylphosphonothioate diester **3** exclusively. In a preparative run, using the developed reaction conditions, 4-pyridylphsophonothioates **3** were obtained in ca. 80% yield, after silica gel column chromatography (see the Section 4).

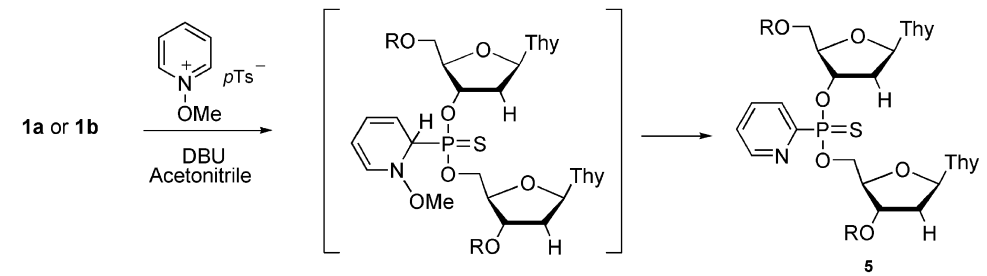
The stereochemical course of the reaction sequence as in Scheme 1 was investigated by performing this transformation on the separate diastereomers of dithymidine H-phosphonothioate **1**.[27] It was found that H-phosphonothioate diester **1a** (R_P diastereomer[27,28] resonating at higher field in the ^{31}P NMR spectrum) afforded pyridylphosphonothioate **3a** (the diastereomer resonating at higher field) with the intermediacy of 1,4-dihydropyridylphosphonothioate **2a**, while the diastereomer **1b** (S_P diastereomer,[27,28] resonating at lower field in the ^{31}P NMR spectrum) gave pyridylphosphonothioate **3b** (resonating at lower field), with the intermediacy of **2b**. Thus, the transformation was found to be stereospecific and, assuming the reaction pathway shown in Scheme 1, it most likely proceeded with an overall retention of configuration. On this basis we tentatively assigned the configuration at the phosphorus center in pyridylphosphonothioate **3a** as R_P, and that in **3b** diastereomer, as S_P.

As to the synthesis of dinucleoside 2-pyridylphosphonothioates **5**, a protocol consisting of a reaction of H-phosphonothioate diesters **1** in acetonitrile with *N*-methoxypyridinium *p*-toluenesulfonate (2 equiv.) in the presence of DBU (4 equiv.), was designed (Scheme 2). The reaction was rapid (<5 min), but along with the desired 2-pyridylphosphonothioates **5** (δ_P=78.2 and 79.3 ppm; ca. 50%), ^{31}P NMR spectroscopy revealed the presence in the reaction mixture of the isomeric 4-pyridylphosphonates **3** (δ_P=83.0 and 84.3 ppm; ca. 15%) and also other side products resonating close to 2-pyridylphosphonatates **5** (two signals at ca. 78 ppm and two signals a ca. 80 ppm; total, 25%). When the order of addition of *N*-methoxypyridinium *p*-toluenesulfonate and DBU was changed that is DBU was added before the pyridinium salt, the reaction showed higher chemoselectivity (65% of 2-pyridylphosphonothioates **5** and 5% of 4-pyridyl isomers **3**), however, the amount of the unidentified side products increased (ca. 30%). Premixing of *N*-methoxypyridinium *p*-toluenesulfonate with DBU, followed by the addition of H-phosphonothioate **1**, severely decreases the formation of the desired 2-pyridylphosphonothioate derivatives, apparently due to the known instability of *N*-alkoxypyridinium salts under basic conditions.[29]

To remedy these problems, we first wanted to identify structures of the side products formed. On the basis of their chemical shift values (that were close to those of dinucleoside pyridylphosphonothioates **5**), multiplicity of the signals in the ^{31}P NMR spectra, and by considering viable reaction pathways, we assumed that the observed side products were, most likely, isomeric nucleoside methyl 2-pyridylphosphonothioates.[30] This was consistent with a putative decomposition pathway of *N*-methoxy-1,2-dihydropyridine intermediate **4** (Scheme 2) that along with 2-pyridylphophonothioates **5** should also generate a methoxide anion. Since, H-phosphonothioate diesters are susceptible to nucleophilic substitution at the phosphorus center,[23] this could cause a partial replacement of the 5′- or 3′-nucleosidic unit in H-phosphonothioate **1** by the methoxide anion, and ultimately lead to the formation of the observed side products.

Various approaches were tried to suppress the transesterification phenomena of **1** by the generated methoxide anion. The most successful one consisted of adding DBU before *N*-methoxypyridinium *p*-toluenesulfonate and decreasing the amount of the latter one to 1.2 equiv.[31] Under these conditions, the formation of methyl nucleoside pyridylphosphonothioates was completely eliminated, and 2-pyridylphosphonothioates **5** were formed as major products (95%, ^{31}P NMR spectroscopy). No further attempts were made to eliminate the formation of 4-pyridylphosphonothioates **3** (ca. 5%) as these were easily removed during silica gel chromatography.

A mechanism for the investigated reaction (Scheme 2) is probably similar to that of 4-pyridylphosphonothioates **3** formation, and involves intermediacy of the corresponding 1,2-dihydropyridine derivatives **4**. However, in contrast to 1,4-dihydropyridylphosphonate **2**, 1,2-dihydropyridine intermediate **4** could not be detected by ^{31}P NMR spectroscopy, probably due to its high lability under basic conditions. Since intermediate **4** spontaneously collapsed to 2-pyridylphosphonothioate **5** with expulsion of a methoxide group, this reaction did not require a separate rearomatization step. When carried out on a preparative scale under the



Scheme 2.

optimised conditions, the reaction of H-phosphonothioate **1** with *N*-methoxypyridinium salt in the presence of DBU afforded dinucleoside 2-pyridylphosphonothioates **5** in ca. 80% yield, after silica gel column chromatography.

In the context of regioselectivity of the above reaction, that is formation of 2-pyridyl- versus 4-pyridylphosphonothioate derivatives (vide supra), an interesting observation was made. In all instances, when the reactions of H-phosphonothioates **1** with *N*-methoxypyridinium *p*-toluenesulfonate were promoted by DBU, the major products formed were 2-pyridyl derivatives **5**. The other positional isomer, 4-pyridylphosphonothioates **3**, was detected only in small amounts (5–15%, vide supra) in these reaction mixtures. By contrast, use of triethylamine instead of DBU, afforded 4-pyridylphosphonothioates **3** as the major products (80%; ^{31}P NMR spectroscopy).[32] Although the precise factors that produce the strikingly different results in the two reactions are not known, it seems that kinetic versus thermodynamic control may be responsible for this phenomenon. Since, the base participates, most likely, in the collapse of *N*-methoxy-1,2-dihydropyridine derivative **4**, this process should be fast in the presence DBU, and thus formation of the kinetic products,[33] 2-pyridylphosphonothioate **5**, should be favored. In the presence of triethylamine, however, the collapse of 1,2-dihydropyridine derivative **4**, is expected to be slower, and thus, this initially formed intermediate may isomerise to the thermodynamically more stable one, the 1,4-dihydropyridyl derivative,[33] from which elimination of methoxide anion can occur. This ultimately will lead to the formation of isomeric 4-pyridylphosphonothioates **3**.

The stereochemical course of the formation of 2-pyridylphosphonothioates **5** (Scheme 2) was elucidated analogously to that of 4-pyridylphosphonothioates using ^{31}P NMR spectroscopy. The exclusive formation of 2-pyridylphosphonothioate **5a** ('fast' diastereomer, resonating at higher field in the ^{31}P NMR spectrum) from H-phosphonothioate **1a** (R_P diastereomer), and **5b** ('slow' diastereomer, resonating at lower field in the ^{31}P NMR spectrum) from H-phosphonothioate **1b** (S_P diastereomer), established this reaction as stereospecific. Assuming a mechanism as proposed in Scheme 2, the reaction in this instance also most likely occurs with overall retention of configuration at the phosphorus center and the produced pyridylphosphonothioates **5a** and **5b**, should have R_P and S_P configurations, respectively.

To facilitate spectral characterization of the produced 4- and 2-pyridylphosphonothioate diesters, compounds **3a**, **3b**, **5a** and **5b**, were subjected to detritylation with 80% aqueous acetic acid. The unprotected compounds, **3c**, **3d**, **5c** and **5d**, respectively, showed the expected pattern of signals in the ^{1}H NMR spectra, characteristic for the respective isomeric 4- and 2-pyridylphosphonothioate derivatives.

3. Conclusions

We have developed simple and efficient methods for the preparation of new types of nucleotide analogues bearing 2- and 4-pyridylphosphonothioate internucleotide linkages. The methods make use of easily available starting materials, H-phosphonothioate diesters, and afford the target pyridylphosphonothioates in high yields under mild reaction conditions. The underlying chemical reactions are stereospecific and can be extended to the preparation of other types of biologically important phosphorus compounds bearing these types of modifications.

4. Experimental

4.1. Material and methods

^{1}H and ^{31}P NMR spectra were recorded on a Varian Unity 400 BB VT spectrometer. The ^{31}P NMR spectroscopy experiments were carried out at 25 °C in 5 mm tubes using 0.1 M concentrations of phosphorus-containing compounds in appropriate solvents (0.6 mL), and the spectra were referenced to 2% H_3PO_4 in D_2O (external standard). TLC analyses were carried out on Merck silica gel 60 F_{254} precoated plates using the following solvent systems: (A) CH_3Cl/CH_3OH 8:2 (v/v); (B) toluene/ethyl acetate 8:2 (v/v). Pyridine (LabScan Ltd.) and anhydrous acetonitrile (LabScan Ltd.) were stored over molecular sieves 4 Å. 1,8-Diazabicylo[5.4.0]undec-7-ene (DBU) and triethylamine (from Aldrich) were freshly distilled. The starting materials for the synthesis, dinucleoside H-phosphonothioates **1** were obtained according to published procedure.[34]

The assignments of signals in the ^{31}P NMR spectra to particular products or intermediates were carried out on the basis of their chemical shifts, multiplicity of the signals in ^{1}H-coupled and ^{1}H-decoupled spectra, by spiking the reaction mixtures with appropriate species and, if possible, by isolation of a compound in question from reaction mixtures. The assignment of proton and carbon resonances of **3** and **5** was carried out on the basis of known or expected chemical shifts in conjunction with ^{1}H–^{1}H, ^{1}H–^{13}C, and DEPT correlated NMR spectroscopy. Subscripts 'a' and 'b' in the ^{1}H NMR spectroscopy data refer to the protons in nucleosid-3′-yl and nuclosid-5′-yl units, respectively.

4.2. General procedure for the preparation of 4-pyridylphosphonothioates 3a and 3b

The separate diastereomers of 5′-*O*-dimethoxytritylthymidin-3′-yl 3′-*O*-dimethoxytritylthymidin-5′-yl H-phosphonothioate **1** (0.26 mmol) were rendered anhydrous by repeated evaporation of added acetonitrile (3×10 mL), and the residue was treated in pyridine (5 mL) with trityl chloride (1.2 equiv.) and triethylamine (2.4 equiv.). When the starting material **1** disappeared (<10 min, TLC analysis), iodine was added (4 equiv.), and after 15 min the reaction mixture was concentrated, partitioned between a solution of aq. $Na_2S_2O_3/NaHCO_3$ (3:1, v/v; 20 mL) and CH_2Cl_2 (20 mL), and the aqueous phase was washed with CH_2Cl_2 (2×20 mL). The organic layer was dried over anhydrous Na_2SO_4, concentrated and the residue was purified by silica gel column chromatography using a stepwise gradient of methanol (1–2%) in toluene/ethyl acetate (1:1, v/v) containing 0.01% TEA. Purity of the isolated compounds >98% (^{1}H NMR spectroscopy).

4.2.1. 5′-*O*-Dimethoxytritylthymidin-3′-yl 3′-*O*-dimethoxytritylthymidin-5′-yl pyridyl-4-phosphonothioate 3a (from faster moving H-phosphonate diastereomer 1a). White solid (0.263 mg), yield 82%. HRMS $[M+H]^+$ found: 1227.4069; $C_{67}H_{66}N_5O_{14}PS$ requires: 1227.4065.

^{1}H NMR. δ_H (in ppm, $CDCl_3$) 8.97 and 8.96 (2×s, 2H, 2×NH), 8.71 (m, 2H, pyr-H2, pyr-H6), 7.52–7.57 (m, 3H, H_a6, pyr-H3, pyr-H5), 7.44–7.14 (m, 18H, ArH), 7.09 (s, 1H, H_b6), 6.85–6.82 (m, 8H, ArH *ortho* to OMe), 6.36 (m, 1H, H_a1′), 6.23 (m, 1H, H_b1′), 5.46 (m, 1H, H_a3′), 4.24 (d, J=6.2 Hz, 1H, H_b3′), 3.95 (m, 2H, 2×H4′), 3.93–3.70 (m, 2H, H_b5′), 3.80, 3.79, 3.77 (3×s, 12H, 4×CH_3O), 3.35–3.23 (m, 2H, H_a5′), 2.49–2.30 (m, 2H, H_a2′), 2.03–1.98, 1.77–1.72 (2×m, 2H, H_b2′), 1.77 (s, 3H, C_b5–CH_3), 1.47 (s, 3H, C_a5–CH_3).

^{31}P NMR. δ_P ($CDCl_3$) 83.04 ppm.

^{13}C NMR. δ_C (in ppm, $CDCl_3$) 163.87 and 163.84 (2×C4), 158.95, 158.93 and 158.91 (4C of DMT), 150.57, 150.44, 150.39, 150.33 (pyr-C2, pyr-C6, 2×C2), 144.91 and 144.19 (2C of DMT), 141.15 (d, J=151 Hz, pyr-C4), 136.02 (2C of DMT), 135.78 (C_b6), 135.21 (C_a6), 135.09 and 135.05 (2C of DMT), 130.33, 130.27, 130.13, 128.22, 128.19, 128.12 (16C of DMT), 127.35 (2C of DMT), 123.88 (d, J=9.9 Hz, pyr-C3, pyr-C5), 113.58 and 113.48 (8C of DMT), 111.88 and 111.27 (2× C5), 87.59 and 87.34 (2×C DMT), 86.51 (C_b1′), 84.57 and 84.51 (C_a4′, C_a1′), 84.19 (d, J=8.4 Hz, C_b4′), 78.40 (d, J=4.6 Hz, C_a3′), 74.30 (C_b3′), 66.78 (d, J=6.1 Hz, C_b5′), 63.20 (C_a5′), 55.38 (4×CH_3O), 39.31 (C_a2′), 39.08 (C_b2′), 12.48 (C_b5–CH_3), 11.91 (C_a5–CH_3).

4.2.2. 5′-*O*-Dimethoxytritylthymidin-3′-yl 3′-*O*-dimethoxytritylthymidin-5′-yl pyridyl-4-phosphonothioate 3b (from slower moving H-phosphonate diastereomer 1b). White solid (0.245 g), yield 77%. HRMS $[M+H]^+$ found: 1227.4071; $C_{67}H_{66}N_5O_{14}PS$ requires: 1227.4065.

^{1}H NMR. δ_H (in ppm, $CDCl_3$) 8.77–8.74 (m, 3H, pyr-H2, pyr-H6, NH), 8.58 (s, 1H, NH), 7.58–7.52 (m, 3H, H_a6, pyr-H3, pyr-H5), 7.42–7.14 (m, 18H, ArH), 6.93 (s, 1H, H_b6), 6.86–6.79 (m, 8H, ArH *ortho* to OMe), 6.40 (m, 1H, H_a1′), 6.19 (m, 1H, H_b1′), 5.40 (m, 1H, H_a3′), 4.22 (s, 1H, H_a4′), 4.11 (d, J=6.6 Hz, 1H, H_b3′), 3.95 (s, 1H, H_b4′), 79, 3.76, 3.75 (3×s, 12H, 4×CH_3O), 3.78–3.70 (m, 2H, H_b5′), 3.48–3.39 (m, 2H, H_a5′), 2.36–2.32 (m, 2H, H_a2′), 1.84–1.76, 1.46–1.38 (2×m, 2H, H_b2′), 1.76 (s, 3H, C_b5–CH_3), 1.45 (s, 3H, C_a5–CH_3).

^{31}P NMR. δ_P ($CDCl_3$) 84.32 ppm.

^{13}C NMR. δ_C (in ppm, $CDCl_3$) 163.81 and 163.64 (2×C4), 158.93 (4C of DMT), 150.64, 150.49, 150.37, 150.29 (pyr-C2, pyr-C6, 2×C2), 144.83 and 144.20 (2C of DMT), 141.06 (d, J=150 Hz, pyr-C4), 135.95 and 135.94 (2C of DMT), 135.26, 135.12, 135.05 (2C of DMT, 2×C6), 130.28, 130.24, 130.15, 128.27, 128.23, 128.20, 128.15 (16C of DMT), 127.39 and 127.34 (2C of DMT), 123.99 (d, J=9.2 Hz, pyr-C3, pyr-C5), 113.53 (8C of DMT), 111.93 and 111.32 (2×C5), 87.55 and 87.48 (2×C DMT), 85.39 (C_b1′), 85.32 (d, J=3.1 Hz, C_a4′), 84.50 (C_a1′), 83.96 (d, J=8.4 Hz, C_b4′), 78.90 (d, J=4.6 Hz, C_a3′), 74.03 (C_b3′), 66.85 (C_b5′), 63.21 (C_a5′), 55.39 and 55.36 (4× CH_3O), 39.15 (2×C2′), 12.60 (C_b5–CH_3), 11.87 (C_a5–CH_3).

4.2.3. Thymidin-3′-yl thymidin-5′-yl pyridyl-4-phosphonothioates 3c and 3d. The diastereomers of fully protected 4-pyridylphosphonothioates **3a** and **3b** (0.130 mmol) were dissolved separately in 80% acetic acid (aq) (15 mL) and were left while stirring for 4 h. Water (15 mL) was then added and the mixture was washed with diethyl ether (3×30 mL). The aqueous layer was separated, evaporated to dryness and the product was freeze-dried from benzene-methanol (4:1, v/v).

Compound **3c** (from faster moving diastereomer **3a**). White solid (0.069 g), 85%. Anal. calcd for $C_{25}H_{30}N_5O_{10}PS$: C, 48.15; H, 4.85; N, 11.23. Found: C, 47.95; H 4.95; N 11.00.

^{1}H NMR. δ_H (in ppm, CD_3OD), 8.78 (m, 2H, pyr-H2, pyr-H6), 7.89 (m, 2H, pyr-H3, pyr-H5), 7.81 (d, J=1.3 Hz, 1H, H6), 7.52 (d, J=1.1 Hz, 1H, H6), 6.34 (m, 1H, H_a1′), 6.27 (t, J=6.7 Hz, 1H, H_b1′), 5.42 (m, 1H, H_a3′), 4.46–4.42 (m, 1H, H_b3′), 4.46–4.33 (m, 1H, H_b5′), 4.15–4.10 (m, 2H, 2×H4′), 3.78–3.69 (m, 2H, H_a5′), 2.63–2.58, 2.43–2.36 (2×m, 2H, H_a2′), 2.33–2.28 (m, 2H, H_b2′), 1.90 (d, J=1.1 Hz, 3H, C5–CH_3), 1.83 (d, J=1.1 Hz, 3H, C5–CH_3).

^{31}P NMR. δ_P (CD_3OD) 82.40 ppm.

Compound **3d** (from slower moving diastereomer **3b**). White solid (0.065 g), 80%. Anal. calcd for $C_{25}H_{30}N_5O_{10}PS$: C, 48.15; H, 4.85; N, 11.23. Found: C, 47.99; H 4.98; N 11.06.

^{1}H NMR. δ_H (in ppm, CD_3OD), 8.76 (m, 2H, pyr-H2, pyr-H6), 7.89 (m, 2H, pyr-H3, pyr-H5), 7.80 (d, J=0.9 Hz, 1H, H6), 7.42 (d, J=1.3 Hz, 1H, H6), 6.30 (m, 1H, H_a1′), 6.22 (t, J=6.9 Hz, 1H, H_b1′), 5.40 (m, 1H, H_a3′), 4.42–4.36 (m, 3H, H_b3′, H_b5′), 4.32 (m, 1H, H_a4′), 4.10 (m, 1H, H_b4′), 3.84 (m, 2H, H_a5′), 2.42–2.29 (2×m, 2H, H_a2′), 2.31–2.20 (m, 2H, H_b2′), 1.89 (d, J=1.1 Hz, 3H, C5–CH_3), 1.83 (d, J=1.1 Hz, 3H, C5–CH_3).

^{31}P NMR. δ_P (CD_3OD) 83.22 ppm.

4.3. General procedure for the preparation of 2-pyridylphosphonothioates 5a and 5b

To a solution of separate diastereomers of 5′-*O*-dimethoxytritylthymidin-3′-yl 3′-*O*-dimethoxytritylthymidin-5′-yl H-phosphonothioate **1** (0.26 mmol) in acetonitrile (10 mL) DBU (4 equiv.) and *N*-methoxypyridinium tosylate (1.2 equiv.) were added. *Caution*: the reagents have to be added swiftly and in the above mentioned order to ensure the efficient formation of 2-pyridylphosphonothioate **5**. After 5 min (^{31}P NMR) the reaction mixture was concentrated, partitioned between 10% aq. $NaHCO_3$ (20 mL) and CH_2Cl_2 (20 mL), and the aqueous layer was extracted with CH_2Cl_2 (2×20 mL). The organic layer was dried over anhyd Na_2SO_4, concentrated and the residue was purified by silica gel column chromatography using toluene/ethyl acetate/methanol (49:49:2, v/v/v). Purity of the isolated compounds >98% (^{1}H NMR spectroscopy).

4.3.1. 5′-*O*-Dimethoxytritylthymidin-3′-yl 3′-*O*-dimethoxytritylthymidin-5′-yl pyridyl-2-phosphonothioate 5a (from faster moving H-phosphonate diesters 1a). White solid (0.253 g), yield 79%. HRMS $[M+H]^+$ found: 1227.4070; $C_{67}H_{66}N_5O_{14}PS$ requires: 1227.4065.

^{1}H NMR. δ_H (in ppm $CDCl_3$) 8.55 and 8.48 (2×s, 2H, 2×NH), 8.43 (d, 1H, J=4.8 Hz, pyr-H6), 7.81 (m, 1H, pyr-H3), 7.71 (m, 1H, pyr-H4), 7.54 (s, 1H, H_a6), 7.45–7.15 (m, 20H, ArH, pyr-H5, H_b6), 6.83 (m, 8H, ArH *ortho* to OCH_3), 6.41–6.34 (m, 2H, 2× H1′), 5.47 (m, 1H, H_a3′), 4.34 (d, J=6.2 Hz, 1H, H_b3′), 4.14 (s, 1H, H_a4′), 4.05–3.67 (m, 2H, H_b5′), 3.85 (s, 1H, H_b4′), 3.79, 3.77 (2×s, 12H, 4× CH_3O), 3.33 (m, 2H, H_a5′), 2.45–2.31 (m, 2H, H_a2′), 2.07–1.87 (m, 2H, H_b2′), 1.73 (s, 3H, C_b5–CH_3), 1.43 (s, 3H, C_a5–CH3).

^{31}P NMR. δ_P ($CDCl_3$) 78.15 ppm.

^{13}C NMR. δ_C (in ppm, $CDCl_3$) 163.86 and 163.78 (2×C4), 158.91 (4C of DMT), 154.55 (d, J=192 Hz, pyr-C2), 150.49, 150.43, 150.20 (2×C2, pyr-C6), 145.04 and 144.30 (2C of DMT), 136.51 (d, J=13.0 Hz, pyr-C4), 136.25 and 136.44 (2C of DMT), 136.00 (Cb6), 135.34 (2C of DMT), 135.21 (C_a6), 130.31, 130.18, 128.40, 128.22, 128.18 (16C of DMT), 127.32 (2C of DMT), 127.04 (d, J=29.8 Hz, pyr-C3), 126.28 (pyr-5H), 113.58 and 113.46 (8C of DMT), 111.75 and 111.15 (2×C5), 87.57 and 87.29 (2×C DMT), 85.80 (C_b1′), 84.80 (C_a4′), 84.52 (C_a1′, C_b4′) 78.50 (C_a3′), 74.91 (C_b3′), 67.02 (C_b5′), 63.44 (C_a5′), 55.40 (4×CH_3O), 39.42 (C_a2′, C_b2′), 12.34 (C_b5–CH_3), 11.82 (C_a5–CH_3).

4.3.2. 5′-*O*-Dimethoxytritylthymidin-3′-yl 3′-*O*-dimethoxytritylthymidin-5′-yl pyridyl-2-phosphonothioate 5b (from slower moving H-phosphonate diesters 1b). White solid (0.255 mg), yield 80%. HRMS $[M+H]^+$ found: 1227.4067; $C_{67}H_{66}N_5O_{14}PS$ requires: 1227.4065.

^{1}H NMR. δ_H (in ppm, $CDCl_3$) 8.58 (d, 1H, J=4.4 Hz, pyr-H6), 8.35, 8.24 (2×s, 2H, 2×NH), 7.94 (m, 1H, pyr-H3), 7.79 (m, 1H, pyr-H4), 7.56 (s, 1H, H_a6), 7.41–7.17 (m, 20H, ArH, pyr-H5, H_b6), 6.82 (m, 8H, ArH *ortho* to OCH_3), 6.43–6.33 (m, 2H, 2×H1′), 5.46 (m, 1H, H_a3′), 4.23 (d, J=5.6 Hz, 1H, H_b3′), 4.15 (s, 1H, H_a4′), 3.79–3.69 (m, 3H, H_b4′, H_b5′), 3.79, 3.76 (2×s, 12H, 4×CH_3O), 3.41 (m, 2H, H_a5′), 2.44–2.25 (m, 2H, H_a2′), 1.93–1.63 (m, 2H, H_b2′), 1.76 (s, 3H, C_b5–CH_3), 1.56 (s, 3H, C_a5–CH_3).

^{31}P NMR. δ_P ($CDCl_3$) 79.29 ppm.

^{13}C NMR. δ_C (in ppm, $CDCl_3$) 163.71 (2×C4), 158.93 and 158.87 (4C of DMT), 154.62 (d, J=192 Hz, pyr-C2), 150.51, 150.38, 150.27 (2×C2, pyr-C6), 145.02 and 144.25 (2C of DMT), 136.58 (d, J=13.0 Hz, pyr-C4), 136.22 and 136.13 (2C of DMT), 135.88 (C_b6), 135.34 (2C of DMT), 135.17 (C_a6), 130.34, 130.28, 130.21, 128.35, 128.22 (16C of DMT), 127.37, 127.27 (2C of DMT), 127.33 (d, J=31.3 Hz, pyr-C3), 126.45 (pyr-5H), 113.52 (8C of DMT), 111.65 and 111.37 (2×C5), 87.52 and 87.41 (2×C DMT), 85.17 (d, J=4.6 Hz, C_a4′), 84.98 (C_b1′), 84.60 (C_a1′), 84.42 (d, J=8.4 Hz, C_b4′), 78.67 (C_a3′), 74.62 (C_b3′), 66.65 (C_b5′), 63.20 (C_a5′), 55.41 and 55.38 (4×CH_3O), 39.25 (C_a2′, C_b2′), 12.35 (C_b5–CH_3), 11.81 (C_a5–CH_3).

4.3.3. Thymidin-3′-yl thymidin-5′-yl pyridyl-2-phosphonothioate 5c and 5d. Separate diastereomers of 2-pyridylphosphonothioates **5a** and **5b** were deprotected analogously as it was described above to the 4-pyridyl derivatives **3a** and **3b**.

Compound **5c** (from faster moving diastereomer **5a**). White solid (0.068 g), yield 84%. Anal. calcd for $C_{25}H_{30}N_5O_{10}PS$: C, 48.15; H, 4.85; N, 11.23. Found: C, 48.03; H 4.99; N 11.11.

^{1}H NMR. δ_H (in ppm CD_3OD) 8.76 (d, 1H, J=4.4 Hz, pyr-H6), 8.12 (m, 1H, pyr-H3), 7.99 (m, 1H, pyr-H4), 7.82, 7.67 (2×s, 2H, 2×6), 7.60 (m, 1H, pyr-H5), 6.36–6.27 (m, 2H, 2×H1′), 5.43 (m, 1H, H_a3′), 4.52–4.39 (m, 3H, H_b3′, H_b5′), 4.22 (s, 1H, H_a4′), 4.15 (s, 1H, H_b4′,), 3.80 (m, 2H, H_a5′), 2.61–2.35 (m, 2H, H_a2′), 2.33–2.22 (m, 2H, H_b2′), 1.89, 1.80 (2× s, 6H, 2× C5–CH_3).

^{31}P NMR. δ_P ($CDCl_3$) 78.81 ppm.

Compound **5d** (from slower moving diastereomer **5b**). White solid (0.065 g), yield 80%. Anal. calcd for $C_{25}H_{30}N_5O_{10}PS$: C, 48.15; H, 4.85; N, 11.23. Found: C, 47.99; H 4.93; N 11.05.

^{1}H NMR. δ_H (in ppm, CD_3OD) 8.77 (d, 1H, J=4.4 Hz, pyr-H6), 8.15 (m, 1H, pyr-H3), 7.99 (m, 1H, pyr-H4), 7.82, 7.65 (2×s, 2H, 2×6), 7.60 (m, 1H, pyr-H5), 6.36–6.28 (m, 2H, 2×H1′), 5.42 (m, 1H, H_a3′), 4.55–4.34 (m, 2H, H_b5′), 4.47 (m, 2H, H_b3′), 4.31 (m, 1H, H_a4′), 4.15 (s, 1H, H_b4′), 3.85 (m, 2H, H_a5′), 2.50–2.27 (m, 2H, H_a2′), 2.24–2.19 (m, 2H, H_b2′), 1.89, 1.83 (2×s, 6H, 2×C5–CH_3).

^{31}P NMR. δ_P ($CDCl_3$) 79.26 ppm.

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26. After 1 h, the reaction mixture consisted of intermediate **2** (21%), 4-pyridylphosphonothioate **3** (61%) and a dinucleoside phosphorothioate diester (18%).
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30. This assignment was supported by an independent synthesis of methyl 5′-*O*-dimethoxytritylthymidin-3′-yl and methyl 3′-*O*-dimethoxytritylthymidin-5′-yl 2-pyridylphosphonothioates, and their comparison with the side products formed in the investigated reaction.
31. The amount of DBU used in this reaction (4 equiv.) was also critical for efficient formation of pyridylphosphonothioates **5**. When the reaction of H-phosphonothioate **1** was carried out with 1.2 equiv. of *N*-methoxypyridinium *p*-toluenesulfonate in the presence of only 2 equiv. of DBU, complex reaction mixture was formed (pyridylphosphonate **5**, ca. 70% methyl nucleoside 2-pyridylphosphonothioates, ca. 4% dinucleoside hydroxymethylphosphonates, ca. 18% and 4-pyridylphosphonothioates **3**, ca. 8%).
32. The reaction was carried out in acetonitrile using H-phosphonothioate **1**, 2 equiv. of *N*-methoxypyridinium *p*-toluenesulfonate and 4 equiv. of triethylamine (rt, 5 min). Further studies on regioselectivity in this type of reactions are in progress.
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$NaNO_2$–Ceric ammonium nitrate mediated conversion of acrylic esters and Baylis–Hillman derived acrylic esters into corresponding β-nitro acrylic esters☆

K. Jayakanthan,[a] K. P. Madhusudanan[b] and Yashwant D. Vankar[a,*]

[a]*Department of Chemistry, Indian Institute of Technology, Kanpur 208 016, India*
[b]*Medicinal Chemistry Division and RSIC, Central Drug Research Institute, Lucknow 226 001, India*

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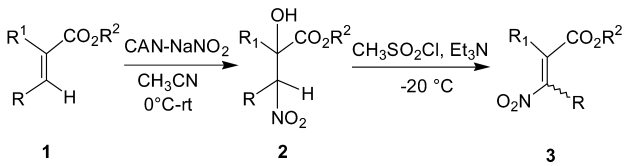
Abstract—A variety of acrylic esters, including those derived from Baylis–Hillman reactions, react with $NaNO_2$–ceric ammonium nitrate to form the corresponding β-nitro alcohols **2** and **5** whose dehydration, via their mesylates, leads to β-nitro acrylic esters, in good to excellent yields. Further, β-nitro acrylic esters containing a mesylate group **6**, obtained from the Baylis–Hillman products, react with NaN_3 to form 2-cyano-3-substituted acrylic esters **10** in excellent yields.

β-Nitro acrylic esters have been found to be excellent dienophiles[2] in organic synthesis. The nitro group in the β-nitro acrylic esters, owing to its more powerful electron withdrawing nature than the ester moiety, directs[2e] the regiochemical outcome in Diels–Alder reactions. This aspect has been elegantly used in the synthesis of isogabaculine,[3] gelesmine,[4] and calicheamycinone.[5] In addition, the nitro group can be eliminated[2b,h] using a base such as DBU thereby making β-nitro acrylic esters as propiolic ester equivalents. Further, the nitro group can be reduced[5] to an amino functionality with $NaBH_4$–$NiCl_2$, and to an amino[4] and amino hydroxyl[2c,d] functionalities with Al–Hg. Recently, such reductions of β-nitro acrylate derived Diels–Alder adducts have been used in the synthesis of polyhydroxylated cyclohexyl-β-amino acids[6a] and in the asymmetric synthesis of (−)-oryzoxymycin.[6b] Besides this, possibilities of employing the Nef reaction,[1] and reductive elimination[7] of the nitro group in Diels–Alder adducts also exist to obtain nitro free products. Apart from the studies in Diels–Alder reactions, β-nitro acrylic esters have also been used as Michael acceptors. Recently,[8a] nucleophiles derived from some amino acids and organo-zinc cuprates[8b–d] have been added to β-nitro acrylic esters especially in procuring optically active β-amino acids.[8c,d] Michael addition on a β-nitro acrylic ester has also been used in the synthesis of a 'template for stabilization of a peptide α-helix'.[9] Overall, these studies clearly indicate the importance of β-nitro acrylic esters in organic synthesis.

Preparation of β-nitro acrylic esters has been reported by Shechter et al.[10a] by nitrating the corresponding acrylic esters with dinitrogen tetroxide.[10b] Besides this, nitryl chloride,[11] nitrosyl chloride,[12] fuming nitric acid[12] and $NaNO_2$–aq.CH_3CO_2H[13] have also been employed to prepare β-nitro acrylic esters from the corresponding acrylic esters. Although these methods have found application, the low boiling nature of some of these reagents makes them inconvenient, especially if the reactions need to be done on small scales. Further, a general and simple approach is needed to prepare these class of compounds. Recently we have reported[14] $NaNO_2$–ceric ammonium nitrate (CAN) in CH_3CN as a novel reagent system for one pot conversion of olefins into vicinal nitro amides. In an attempt to explore the scope of this reagent system, we have now found that acrylic esters undergo smooth reaction with this reagent system forming β-nitro alcohols **2** in good yields along with a small amount (~5%) of β-nitro acrylates **3** (Scheme 1). Compounds **2** were readily converted into **3** via their mesylates by following modified McMurry's method[15] in good yields (entries 1–3, Table 1). Thus, in our initial



Scheme 1.

☆ Part 11 in the series, 'Chemistry of Nitro Compounds'. For part 10, see Ref. 1.

Keywords: Ceric ammonium nitrate; Sodium nitrite; β-Nitro acrylic esters; Baylis–Hillman derived acrylic esters.
* Corresponding author. Tel.: +91-512-2597169; fax: +91-512-2590007; e-mail address: vankar@iitk.ac.in

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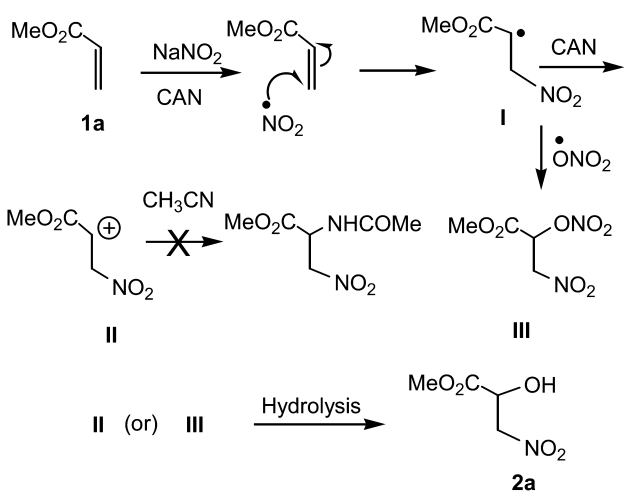
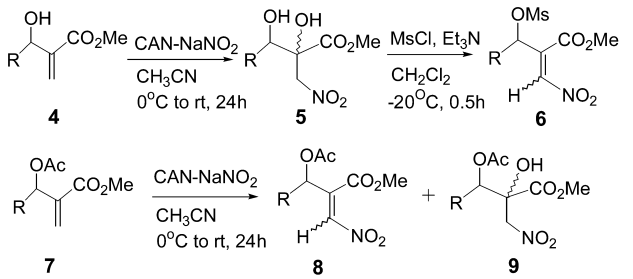
Table 1.

Entry	Acrylic esters (**1**)			Yield (%)	
	R	R^1	R^2	**2**	**3** (*E*:*Z*)
a	H	H	C_2H_5	62	75 (1:0)
b	CH_3	H	CH_3	62	90 (1:0)
c	H	CH_3	CH_3	78	73 (1:0)
d	Ph	H	C_2H_5	—	64[12] (1:1.7)
e	*p*-Tolyl	H	CH_3	—	81 (1:2)
f	*p*-Anisyl	H	CH_3	—	57 (1:1)

experiments, the reaction of ethyl acrylate with $NaNO_2$–CAN in acetonitrile resulted in the formation of ethyl 2-hydroxy-3-nitro propionate **2a**[10a] in 62% yield. Conversion of this alcohol to *trans*-ethyl 3-nitro acrylate **3a** (entry 1, Table 1) was performed via its mesylate in 75% yield. Likewise, methyl methacrylate **1c** and methyl crotonate **1b** also gave 2-hydroxy-3-nitro propionates **2b** and **2c** in 62 and 78% yields (entries b and c, Table 1) which were converted to the corresponding β-nitro acrylates in 90 and 73% yields, respectively. Interestingly, these β-nitro acrylates were found to be exclusively *E*-isomers, possibly because of the ensuing E_1cB reaction on the corresponding mesylates. On the other hand, cinnamic esters directly gave the corresponding β-nitro acrylates, (entries d–f, Table 1) without forming the intermediate hydroxy compounds, possibly because of the extended conjugation in these molecules. However, each of these compounds (**3d**–**f**) was obtained as a mixture of the corresponding *E* and *Z* isomers as revealed by their ^1H NMR spectra (Section 1). Although the mechanism of this reaction has not been investigated by us, we presume that nitrite radicals formed upon oxidation[16] of nitrite ions by CAN, add on to an acrylic ester as shown in Scheme 2 forming an intermediate **I**. This intermediate radical **I** can either be further oxidised to a carbocation **II** or react with a nitrate radical to form **III**. Hydrolysis of **III**, during work up, will lead to the observed product **2a**. Alternatively, the carbocation **II** will react with water to form **2a**. It is also likely that the intermediate **III** is derived from carbocation **II** upon reaction with nitrate ions from CAN.[17] However, hydration of the carbocation **II** is unlikely since the reaction conditions are anhydrous. Further, had the



Scheme 2.



Scheme 3.

Table 2.

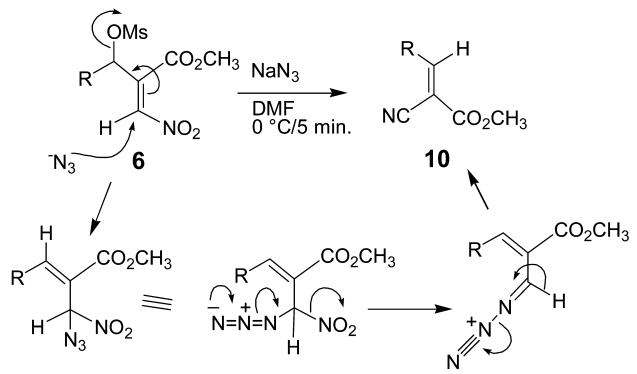
Entry		Yield (%)	
	4 *R*	**5**	**6** (*E*:*Z*)
a	Ph	62	37 (0:1)
b	*m*-Cl-Ph	56	70 (0:1)
c	*p*-Cl-Ph	63	79 (0:1)
d	C_2H_5	47	51 (1:13)
e	C_3H_7	45	51 (0:1)

carbocation formed it would have also reacted with acetonitrile to form the corresponding amide via a typical Ritter reaction[18] which we have not observed. We, therefore, feel that the pathway via the radical formation is most likely in the present case. This is also because the carbocation **II** is of high energy and thus less likely to form.

To further extend the scope of this reaction we considered using acrylic esters **4** (Scheme 3) derived from the Baylis–Hillman reaction.[19] Thus, a series of such esters were reacted with the present reagent system to form the corresponding diols **5** which could be readily dehydrated via their mesylates into the corresponding β-nitro acrylates **6** in fair to good yields (Table 2). β-Nitro acrylates **6** were found be exclusively the *Z*-isomers (entries 6a–c and e) or with the *Z*-isomer as the major product (entry 6d). The geometry of the olefinic bond was established on the basis of nOe experiments in which irradiation of either of the allylic proton or the olefinic proton led to the enhancement of the other peak. The corresponding acetates **7** were also reacted with $NaNO_2$–CAN, however, they gave almost 1:1 mixture of nitro olefin **8** and nitro alcohol **9** in modest yields (Table 3). Compound **8** was obtained as a mixture of *E*- and *Z*-isomers in which either the *Z*-isomer was the major product (entries a, c, f and g, Table 3) or the only product (entries b, d and e, Table 3). Once again the geometry of the

Table 3.

Entry		Yield (%)	
	7 *R*	**8** (*E*:*Z*)	**9**
a	Ph	49 (1:6)	31
b	*o*-Cl	45 (0:1)	53
c	*m*-Cl	46 (1:4)	51
d	*p*-Cl	50 (0:1)	47
e	*o*-NO_2	43 (0:1)	50
f	C_2H_5	48 (1:6)	50
g	C_3H_7	40 (1:6)	58



Scheme 4.

Table 4.

Entry	**6** *R*	**10** Yield (%)
a	Ph	90
b	*m*-Cl–Ph	81
c	*p*-Cl–Ph	76

double bond in **8** was established using nOe experiments (vide supra) after chromatographically separating the mixture of **8** and **9**.

Compounds **6a–e** appear to be very interesting since they possess a good leaving group as a mesylate along with the β-nitro acrylate system. In our preliminary experiments, we have reacted some of these compounds **6a–c** (with R=aryl) with NaN_3, and it was interesting to find that these compounds led to the formation of the corresponding cyano derivatives **10a–c**[20] (Scheme 4, Table 4) in a highly stereoselective manner. The geometry of the double bond was established by comparison with the reported ^{1}H NMR spectral data[20] for these compounds and also by the X-ray analysis of **10a** (R=Ph). A tentative mechanism for the formation of **10** could be written as shown in Scheme 4. When *R* is an aliphatic moiety, the reaction was found to be unclean and hence was not further pursued. Although, these compounds **10a–c** can be readily obtained by the classical Knovenagel type condensation of cyanoacetic esters with aldehydes, the mechanism through which these are obtained in the present cases is interesting.

In summary, we have demonstrated that $NaNO_2$–CAN is an excellent reagent to obtain β-nitro acrylic esters from a variety of acrylic esters in good to excellent yields. We have performed this preparation on scales ranging from 1 to 50 mmol without any change in the yields. In view of the fact that such nitro acrylates have already found use in organic synthesis[2–6] and since our method of preparation is very simple and high yielding, this methodology should find widespread application in organic synthesis. Some of these products, derived from the Baylis–Hillman based acrylic esters **6**, which contain a mesylate group also, lead to 2-cyano-3-substituted acrylic esters in excellent yields. Further work to explore the potential of compounds **6** and **8** and also to explore the potential of $NaNO_2$–CAN reagent system with other α,β-unsaturated compounds is in progress.

1. Experimental

1.1. General

Infrared spectra were recorded on Bruker FT/IR Vector 22 spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on JEOL LA-400 (400 and 100 MHz, respectively) spectrometer in solutions of $CDCl_3$ using tetramethylsilane as the internal standard. The mass spectra were recorded on a Micromass Quattro II Triple Quadrupole Mass Spectrometer. Elemental analyses were carried out on a Thermoquest CE-instruments EA-1110 C, H, N, S analyser. Column chromatography was performed on silicagel (100–200 mesh) and thin layer chromatography (TLC) was performed on Silica gel plates made by using grade G silica gel obtained from s.d.fine-chem Ltd, Mumbai. Melting points were determined using a Fischer–John melting point apparatus. All solvents and common reagents were purified by established procedures.[21] Ceric ammonium nitrate and sodium nitrite were dried at 80 °C/0.2 mm for 3 h.

1.2. General procedure for the nitration of acrylic esters

To a stirred solution of an acrylic ester (1 mmol) in anhydrous CH_3CN (5 mL) were added CAN (1.64 g, 3 mmol) and $NaNO_2$ (207 mg, 3 mmol) at 0 °C under nitrogen. The reaction mixture was vigorously stirred for 24 h at rt, diluted with water and extracted with ethyl acetate. The organic layer was washed sequentially with saturated solution of $NaHCO_3$, brine and dried over anhydrous Na_2SO_4. The residue obtained after evaporation of the solvent was purified by column chromatography to get the nitro alcohols.

1.3. General procedure for the dehydration of nitro alcohols

To a stirred solution of a nitro alcohol (1 mmol) in dry CH_2Cl_2 (mL) were added $MeSO_2Cl$ (0.2 mL, 3 mmol), Et_3N (0.4 mL, 3 mmol) at −20 °C in succession. After the reaction was over (TLC monitoring), it was poured into ice-cold water and extracted with CH_2Cl_2, washed with water, brine and then dried over anhydrous Na_2SO_4. Evaporation of the solvent gave a crude product, which was purified by column chromatography.

1.4. General procedure for the conversion of mesylates into cyano derivatives

To a stirred solution of a mesylate (0.15 mmol) in dry DMF (1 mL) at 0 °C was added NaN_3 (12 mg, 0.17 mmol) under nitrogen. After disappearance of the mesylate (TLC monitoring after 5 min), the reaction mixture was poured into ice water, extracted with diethyl ether followed by washing with brine, drying over anhydrous Na_2SO_4, and then concentrated in vacuum. The crude solid residue was purified by column chromatography.

1.4.1. Methyl 2-hydroxy-3-nitro-butyrate (2b). Pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.47–5.16 (m, 2H), 3.85 (br s, 3H), 3.84 (br s, 1H), 1.21 and 1.20 (2d, J=6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.2, 163.1, 87.8, 87.7, 87.1, 87.0, 53.9, 53.8, 11.9, 11.8; ν_{max}

(neat film) 3487 (br), 1736, 1555, 1367 cm^{-1}. ESMS: *m/z* 186 $[M+Na]^+$. Anal. calcd for $C_5H_9NO_5$: C, 36.81; H, 5.56; N, 8.59%. Found: C, 36.77; H, 5.58; N, 8.57%.

1.4.2. Methyl 2-hydroxy-2-methyl-3-nitro-propionate (2c). Pale yellow oil; ^1H NMR (400 MHz, $CDCl_3$) δ 4.80 (d, J=13.7 Hz, 1H), 4.52 (d, J=13.7 Hz, 1H), 3.81 (s, 3H), 1.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.9, 80.9, 72.5, 53.5, 23.6; ν_{max} (neat film) 3550 (br), 1759, 1565, 1384 cm^{-1}. ESMS: *m/z* 186 $[M+Na]^+$. Anal. calcd for $C_5H_9NO_5$: C, 36.81; H, 5.56; N, 8.59%. Found: C, 36.83; H, 5.61; N, 8.56%.

1.4.3. (*E*)-Ethyl 3-nitro-acrylate (3a). Yellow solid, mp 39–40 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, J=13.6 Hz, 1H), 7.09 (d, J=13.6 Hz, 1H), 4.33 (q, J=7.1 Hz, 2H), 1.35 (t, J=7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.5, 148.8, 127.6, 62.3, 13.9; ν_{max} (neat film) 1730, 1541, 1356 cm^{-1}. ESMS: *m/z*: 145 $[M^+]$, 116 $[M^+-29]$. Anal. calcd for $C_5H_7NO_4$: C, 41.38; H, 4.86; N, 9.65%. Found: C, 41.44; H, 4.79; N, 9.54%.

1.4.4. (*E*)-Methyl 3-nitro-but-2-enoate (3b). Yellow oil; ^1H NMR (400 MHz, $CDCl_3$) δ 6.90 (q, J=1.7 Hz, 1H), 3.89 (s, 3H), 2.11 (d, J=1.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 140.6, 135.9, 53.1, 17.5; ν_{max} (neat film) 1734, 1526, 1349 cm^{-1}. ESMS: *m/z* 145 $[M^+]$. Anal. calcd for $C_5H_7NO_4$: C, 41.38; H, 4.86; N, 9.65%. Found: C, 41.53; H, 4.85; N, 9.63%.

1.4.5. (*E*)-Methyl 2-methyl-3-nitro-acrylate (3c). Yellow oil; ^1H NMR (400 MHz, $CDCl_3$) δ 7.08 (q, J=1.2 Hz, 1H), 3.84 (s, 3H), 2.60 (d, J=1.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.6, 160.1, 120.9, 52.6, 14.0; ν_{max} (neat film) 1731, 1540, 1368 cm^{-1}. ESMS: *m/z* 168 $[M+Na]^+$. Anal. calcd for $C_5H_7NO_4$: C, 41.38; H, 4.86; N, 9.65%. Found: C, 41.36; H, 4.90; N, 9.54%.

1.4.6. (*E*)-Ethyl 3-nitro-3-phenyl-acrylate (3d). Mixture with (*Z*)-**3d**. Yellow solid; ^1H NMR (400 MHz, $CDCl_3$) δ 7.53–7.42 (m, 6H), 4.38 (q, J=7.1 Hz, 2H), 1.35 (t, J=7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2, 136.5, 132.1, 130.4, 129.7, 129.3, 63.0, 14.0.

1.4.7. (*Z*)-3d. ^1H NMR (400 MHz, $CDCl_3$) δ 8.08 (s, 1H), 7.53–7.42 (m, 5H), 4.44 (q, J=7.1 Hz, 2H), 1.37 (t, J=7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.1, 140.1, 132.9, 132.3, 129.3, 128.2, 63.1, 13.7; ν_{max} (neat film) 1732, 1644, 1535, 1321 cm^{-1}. ESMS: *m/z* 244 $[M+Na]^+$. Anal. calcd for $C_{11}H_{11}NO_4$: C, 59.73; H, 5.01; N, 6.33%. Found: C, 59.71; H, 5.04; N, 6.24%.

1.4.8. (*E*)-Methyl 3-nitro-3-*p*-tolyl-acrylate (3e). Mixture with (*Z*)-**3e**. Yellow solid; ^1H NMR (400 MHz, $CDCl_3$) δ 8.03 (s, 1H), 7.36–7.22 (m, 4H), 3.94 (s, 3H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.7, 143.6, 140.5, 136.9, 130.4, 129.9, 125.8, 53.4, 21.4.

1.4.9. (*Z*)-3e. ^1H NMR (400 MHz, $CDCl_3$) δ 7.49 (s, 1H), 7.29–7.17 (m, 4H), 3.87 (s, 3H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.6, 143.2, 138.7, 132.9, 129.9, 129.7, 125.7, 53.2, 21.3; ν_{max} (neat film) 1740, 1546, 1362 cm^{-1}. ESMS: *m/z* 244 $[M+Na]^+$. Anal. calcd for $C_{11}H_{11}NO_4$: C, 59.73; H, 5.01; N, 6.33%. Found: C, 59.81; H, 5.03; N, 6.24%.

1.4.10. Methyl 3-anisyl-3-nitro-acrylate (3f). (1:1, *E:Z* isomers). Yellow oil; ^1H NMR (400 MHz, $CDCl_3$) δ 7.49–6.90 (m, 5H), 3.89 (2s, 3H), 3.84 (2s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.8, 160.0, 137.6, 136.9, 132.9, 132.1, 121.1 (m), 114.9, 114.8, 114.2, 114.1, 55.5, 55.4, 53.5, 53.3; ν_{max} (neat film) 1732, 1602, 1528 cm^{-1}. ESMS: *m/z* 260 $[M+Na]^+$, 238 $[M+1]^+$. Anal. calcd for $C_{11}H_{11}NO_5$: C, 55.70; H, 4.67; N, 5.90%. Found: C, 55.62; H, 4.70; N, 5.98%.

1.4.11. Methyl 2,3-dihydroxy-2-nitromethyl-3-phenyl-propionate (5a). Viscous oil; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35–7.24 (m, 5H), 5.46 (s, 1H), 5.33–4.77 (m, 2H), 3.87 (s, 3H), 3.70 (br s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 141.3, 136.7, 128.3, 126.7, 78.8, 75.4, 71.1, 53.2; ν_{max} (neat film) 3493 (br), 1743, 1561, 1379 cm^{-1}. ESMS: *m/z* 278 $[M+Na]^+$. Anal. calcd for $C_{11}H_{13}NO_6$: C, 51.77; H, 5.13; N, 5.49%. Found: C, 51.69; H, 5.09; N, 5.47%.

1.4.12. Methyl 3-(3-chloro-phenyl)-2,3-dihydroxy-2-nitromethyl-propionate (5b). Colourless solid, mp 122–123 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35–7.13 (m, 4H), 5.47 and 5.31 (2s, 1H), 5.08–4.37 (m, 2H), 3.87 and 3.75 (2s, 3H), 3.14 (br s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.6, 170.9, 139.20, 139.1, 134.5, 134.3, 129.7, 129.6, 129.2, 129.0, 127.4, 127.1, 125.4, 125.0, 78.7, 78.6, 78.3, 78.1, 75.8, 74.9, 53.8, 53.2; ν_{max} (neat film) 3503 (br), 1750, 1566, 1382 cm^{-1}. ESMS: *m/z* 312 $[M+Na]^+$. Anal. calcd for $C_{11}H_{12}ClNO_6$: C, 45.61; H, 4.18; N, 4.84%. Found: C, 45.57; H, 4.19; N, 4.81%.

1.4.13. Methyl 3-(4-chloro-phenyl)-2,3-dihydroxy-2-nitromethyl-propionate (5c). Colourless solid, mp 132–133 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34–7.29 (m, 4H), 5.50 and 5.29 (2s, 1H), 4.99–4.30 (m, 2H), 3.88 and 3.86 (2s, 3H), 3.73 (br s, 1H), 3.57 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.6, 171.0, 136.7, 136.4, 134.1, 134.0, 128.7, 128.5, 128.1, 128.0, 79.1, 78.9, 76.6, 75.5, 74.6, 72.8, 53.1, 52.7; ν_{max} (neat film) 3522 (br), 1753, 1566, 1388 cm^{-1}. ESMS: *m/z* 312 $[M+Na]^+$. Anal. calcd for $C_{11}H_{12}ClNO_6$: C, 45.61; H, 4.18; N, 4.84%. Found: C, 45.59; H, 4.17; N, 4.81%.

1.4.14. Methyl 2,3-dihydroxy-2-nitromethyl-pentanoate (5d). Colourless solid, mp 96–97 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 4.95–4.59 (2dd, J=13.9 Hz, 2H), 4.11 (br d, J=13.1 Hz, 1H), 3.81 and 3.80 (2s, 3H), 3.50 (m, 1H), 2.70 (br s, 1H), 1.59–1.36 (m, 1H), 1.22 (m,1H), 0.95–0.90 (2t, J=7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.2, 172.0, 79.2, 78.6, 78.3, 78.2, 75.8, 74.7, 53.6, 53.5, 24.0, 23.6, 10.1, 9.9; ν_{max} (neat film) 3498 (br), 1743, 1561, 1381 cm^{-1}. ESMS: *m/z* 230 $[M+Na]^+$. Anal. calcd for $C_7H_{13}NO_6$: C, 40.58; H, 6.32; N, 6.76%. Found: C, 40.56; H, 6.28; N, 6.72%.

1.4.15. Methyl 2,3-dihydroxy-2-nitromethyl-hexanoate (5e). Colourless solid, mp 84–86 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 5.02–4.66 (2d, J=13.9 Hz, 2H), 3.94 (br s, 1H), 3.92 (s, 3H), 3.68 (t, J=8.4 Hz, 1H), 2.24 (br d, J=8.5 Hz,

1H), 1.63–1.51 (m, 2H), 1.39–1.26 (m, 2H), 0.94 (t, J=7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.2, 78.7, 78.1, 74.3, 53.8, 33.2, 18.9, 13.6; ν_{max} (neat film) 3484 (br), 1740, 1559, 1372 cm^{-1}. ESMS: m/z 244 $[M+Na]^+$. Anal. calcd for $C_8H_{15}NO_6$: C, 43.44; H, 6.83; N, 6.33%. Found: C, 43.42; H, 6.79; N, 6.32%.

1.4.16. (*Z*)-Methyl 2-(methanesulfonyloxy-phenyl-methyl)-3-nitro-acrylate (6a). Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44–7.34 (m, 5H), 7.16 (d, J=1.7 Hz, 1H), 6.40 (d, J=1.7 Hz, 1H), 3.70 (s, 3H), 2.82 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.5, 139.2, 138.1, 132.3, 130.5, 129.2, 127.6, 78.6, 53.2, 39.0; ν_{max} (neat film) 1743, 1543, 1363 cm^{-1}. ESMS: m/z 338 $[M+Na]^+$. Anal. calcd for $C_{12}H_{13}NO_7S$: C, 45.71; H, 4.16; N, 4.44; S, 10.17%. Found: C, 45.85; H, 4.02; N, 4.32; S, 10.12%.

1.4.17. (*Z*)-Methyl 2-[(3-chloro-phenyl)-methanesulfonyloxy-methyl]-3-nitro-acrylate (6b). Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46–7.31 (m, 4H), 7.15 (d, J=1.7 Hz, 1H), 6.37 (d, J=1.7 Hz, 1H), 3.75 (s, 3H), 2.93 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.4, 138.6, 138.5, 135.3, 134.5, 130.8, 130.7, 127.7, 125.8, 77.5, 53.6, 39.4; ν_{max} (neat film) 1743, 1545, 1363 cm^{-1}. ESMS: m/z 372 $[M+Na]^+$. Anal. calcd for $C_{12}H_{12}ClNO_7S$: C, 41.21; H, 3.46; N, 4.00; S, 9.17%. Found: C, 41.10; H, 3.41; N, 4.07; S, 9.19%.

1.4.18. (*Z*)-Methyl 2-[(4-chloro-phenyl)-methanesulfonyloxy-methyl]-3-nitro-acrylate (6c). Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46–7.23 (m, 4H), 7.15 (d, J=1.5 Hz, 1H), 6.39 (br s, 1H), 3.74 (s, 3H), 2.89 (s, 3H); ^{13}C NMRδ 162.4, 138.8, 138.3, 136.8, 131.0, 129.7, 129.2, 77.7, 53.6, 39.4; ν_{max} (neat film) 1750, 1551, 1373 cm^{-1}. ESMS: m/z 372 $[M+Na]^+$. Anal. calcd for $C_{12}H_{12}ClNO_7S$: C, 41.21; H, 3.46; N, 4.00; S, 9.17%. Found: C, 41.29; H, 3.42; N, 3.97; S, 9.12%.

1.4.19. (*E*)-Methyl 3-methanesulfonyloxy-2-nitromethylene-pentanoate (6d). Mixture with (*Z*)-**6d**. Colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (s, 1H), 5.82 (m, 1H), 3.87 (s, 3H), 3.02 (s, 3H), 1.99–1.88 (m, 2H), 1.06 (t, J=7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.9, 143.2, 136.4, 71.4, 53.2, 37.9, 28.1, 10.1.

1.4.20. (*Z*)-6d. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 (s, 1H), 5.26 (t, J=6.2 Hz, 1H), 3.92 (s, 3H), 3.10 (s, 3H), 1.99–1.88 (m, 2H), 1.04 (t, J=7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.9, 139.9, 137.9, 78.4, 53.6, 38.9, 27.1, 8.9; ν_{max} (neat film) 1742, 1541, 1357 cm^{-1}. ESMS: m/z 290 $[M+Na]^+$. Anal. calcd for $C_8H_{13}NO_7S$: C; 35.95; H, 4.90; N, 5.24; S, 12.00%. Found: C, 36.04; H, 4.94; N, 5.19; S, 12.17%.

1.4.21. (*Z*)-Methyl 3-methanesulfonyloxy-2-nitromethylene-hexanoate (6e). Colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 (d, J=1.0 Hz, 1H), 5.31 (br t, J=6.5 Hz, 1H), 3.92 (s, 3H), 3.10 (s, 3H), 1.86 (m, 2H), 1.48 (m, 2H), 0.98 (t, J=7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.9, 140.2, 137.9, 77.1, 53.6, 38.9, 35.8, 18.0, 13.2; ν_{max} (neat film) 1744, 1543, 1359 cm^{-1}. ESMS: m/z 304 $[M+Na]^+$. Anal. calcd for $C_9H_{15}NO_7S$: C, 38.43; H, 5.38; N, 4.98; S, 11.40%. Found: C, 38.37; H, 5.32; N, 5.01; S, 11.38%.

1.4.22. (*E*)-Methyl 2-(acetoxy-phenyl-methyl)-3-nitro-acrylate (8a). Mixture with (*Z*)-**8a**. Pale yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (s, 1H), 7.02 (s, 1H), 7.42–7.34 (m, 5H), 3.76 (s, 3H), 2.07 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.4, 163.2, 142.8, 135.1, 132.8, 128.8, 128.5, 127.3, 70.5, 53.1, 20.4.

1.4.23. (*Z*)-8a. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42–7.34 (m, 5H), 7.05 (d, J=1.7 Hz, 1H), 6.62 (d, J=1.7 Hz, 1H), 3.72 (s, 3H), 2.13 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.6, 163.3, 141.5, 137.2, 134.0, 129.6, 128.9, 127.5, 72.3, 53.1, 20.6; ν_{max} (neat film) 1747, 1359, 1359 cm^{-1}. ESMS: m/z 302 $[M+Na]^+$. Anal. calcd for $C_{13}H_{13}NO_6$: C, 55.92; H, 4.69; N, 5.02%. Found: C, 55.86; H, 4.70; N, 5.06%.

1.4.24. (*Z*)-Methyl-2-[acetoxy-(2-chloro-phenyl)-methyl]-3-nitro-acrylate (8b). Yellow solid, mp 96–97 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44–7.21 (m, 4H), 6.98 (d, J=1.4 Hz, 1H), 6.96 (d, J=1.4 Hz, 1H), 3.74 (s, 3H), 2.13 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.4, 162.9, 140.1, 137.9, 133.0, 132.0, 130.7, 129.9, 128.6, 127.4, 69.0, 53.3, 20.4; ν_{max} (neat film) 1750, 1538, 1355 cm^{-1}. ESMS: m/z 336 $[M+Na]^+$. Anal. calcd for $C_{13}H_{12}NO_6Cl$: C, 49.78; H, 3.86; N, 4.47%. Found: C, 49.81; H, 3.88; N, 4.43%.

1.4.25. (*E*)-Methyl-2-[acetoxy-(3-chloro-phenyl)-methyl]-3-nitro-acrylate (8c). Mixture with (*Z*)-**8c**. Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (s, 1H), 7.53–7.26 (m, 4H), 7.00 (s, 1H), 3.79 (s, 3H), 2.09 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3, 163.0, 143.7, 137.2, 134.4, 132.4, 129.8, 128.9, 127.3, 125.4, 69.4, 53.2, 20.3.

1.4.26. (*Z*)-8c. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53–7.26 (m, 4H), 7.09 (s, 1H), 6.58 (s, 1H), 3.74 (s, 3H), 2.16 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.5, 162.9, 143.4, 140.5, 137.5, 136.0, 134.8, 130.2, 127.5, 125.7, 71.6, 53.2, 20.6; ν_{max} (neat film) 1748, 1540, 1360 cm^{-1}. ESMS: m/z 336 $[M+Na]^+$. Anal. calcd for $C_{13}H_{12}NO_6Cl$: C, 49.78; H, 3.86; N, 4.47%. Found: C, 49.74; H, 3.82; N, 4.49%.

1.4.27. (*Z*)-Methyl-2-[acetoxy-(4-chloro-phenyl)-methyl]-3-nitro-acrylate (8d). Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92–7.27 (m, 4H), 7.08 (d, J=1.4 Hz, 1H), 6.58 (d, J=1.5 Hz, 1H), 3.74 (s, 3H), 2.14 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.4, 163.0, 140.8, 137.3, 135.7, 132.6, 129.2, 129.0, 71.7, 53.3, 20.6; ν_{max} (neat film) 1747, 1539, 1360 cm^{-1}. ESMS: m/z 336 $[M+Na]^+$. Anal. calcd for $C_{13}H_{12}NO_6Cl$: C, 49.78; H, 3.86; N, 4.47%. Found: C, 49.82; H, 3.85; N, 4.46%.

1.4.28. (*Z*)-Methyl-2-[acetoxy-(2-nitro-phenyl)-methyl]-3-nitro-acrylate (8e). Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09–7.58 (m, 4H), 7.25 (d, J=1.4 Hz, 1H), 7.12 (d, J=1.4 Hz, 1H), 3.81 (s, 3H), 2.15 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.4, 162.8, 147.8, 139.9, 138.3, 134.1, 130.4, 130.2, 128.9, 125.1, 67.6, 53.4, 20.5; ν_{max} (neat film) 1745, 1533, 1353 cm^{-1}. ESMS: m/z 347 $[M+Na]^+$. Anal. calcd for $C_{13}H_{12}N_2O_8$: C, 48.16; H, 3.73; N, 8.64%. Found: C, 48.12; H, 3.76; N, 8.63%.

1.4.29. (*E*)-Methyl-3-acetoxy-2-nitromethylene-pentanoate (8f). Mixture with (*Z*)-**8f**. Yellow oil; ^{1}H NMR

(400 MHz, $CDCl_3$) δ 7.49 (s, 1H), 5.81 (dd, J=9.1, 4.8 Hz, 1H), 3.86, (s, 3H), 2.03 (s, 3H), 1.92–1.77 (m, 2H), 1.00 (t, J=7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 163.6, 142.7, 135.9, 70.9, 53.3, 26.5, 20.5, 10.3.

1.4.30. (*Z*)-8f. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.01 (d, J=1.2 Hz, 1H), 5.47 (td, J=6.3, 1.0 Hz, 1H), 3.90 (s, 3H), 2.13 (s, 3H), 1.92–1.77 (m, 2H), 0.97 (t, J=7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 163.7, 142.0, 137.0, 71.9, 53.4, 26.0, 20.7, 9.1; ν_{max} (neat film) 1743, 1535, 1358 cm^{-1}. ESMS: m/z 254 $[M+Na]^+$. Anal. calcd for $C_9H_{13}NO_6$: C, 46.76; H, 5.67; N, 6.06%. Found: C, 46.82; H, 5.71; N, 5.98%.

1.4.31. (*E*)-Methyl-3-acetoxy-2-nitromethylene-hexanoate (8g). Mixture with (*Z*)-**8g**. Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (s, 1H), 5.90–5.87 (dd, J=9.5, 3.9 Hz,1H), 3.86 (s, 3H), 2.02 (s, 3H), 1.79 (q, J=6.6 Hz, 2H), 1.48–1.34 (m, 2H), 0.97 (t, J=6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1, 163.5, 142.4, 136.2, 69.3, 53.1, 34.9, 20.3, 18.9, 13.3.

1.4.32. (*Z*)-8g. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.03 (s, 1H), 5.51 (t, J=6.3 Hz, 1H), 3.90 (s, 3H), 2.12 (s, 3H), 1.77 (q, J=6.6 Hz, 2H), 1.48–1.34 (m, 2H), 0.95 (t, J=6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.4, 163.6, 142.2, 136.7, 70.6, 53.2, 34.7, 20.5, 18.0, 13.4; ν_{max} (neat film) 1744, 1538, 1363 cm^{-1}. ESMS: m/z 268 $[M+Na]^+$. Anal. calcd for $C_{10}H_{15}NO_6$: C, 48.98; H, 6.17; N, 5.71%. Found: C, 48.92; H, 6.21; N, 5.68%.

1.4.33. Methyl 3-acetoxyl-2-hydroxy-2-nitromethyl-3-phenyl-propionate (9a). Yellow solid, mp 98–99 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30–7.20 (m, 5H), 5.85 and 5.81 (2s, 1H), 4.91–4.15 (2dd, J=13.9 Hz, 2H), 3.77 and 3.71 (2s, 3H), 2.05 and 1.98 (2s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 170.5, 169.5, 168.9, 133.6, 133.5, 129.3, 129.2, 128.5, 128.3, 128.0, 127.5, 78.2, 77.9, 77.3, 77.0, 75.8, 75.6, 53.8, 53.7, 20.7, 20.5; ν_{max} (neat film) 3493 (br), 1755, 1563, 1377 cm^{-1}. ESMS: m/z 320 $[M+Na]^+$. Anal. calcd for $C_{13}H_{15}NO_7$: C, 52.53; H, 5.09; N, 4.71%. Found: C, 52.35; H, 5.13; N, 4.68%.

1.4.34. Methyl-3-acetoxy-3-(2-chlorophenyl)-2-hydroxy-2-nitromethyl-propionate (9b). Colourless solid, mp 70–71 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17–7.25 (m, 4H), 6.48 and 6.46 (2s, 1H), 5.28–4.12 (m, 2H), 3.93 and 3.83 (2s, 3H), 2.12 and 2.05 (2s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 170.5, 169.2, 168.7, 143.1, 139.1, 133.1, 133.0, 131.7, 131.5, 130.6, 130.4, 129.9, 129.3, 127.3, 126.9, 77.9, 77.4, 71.6, 71.4, 53.9, 52.2, 38.2, 31.5, 20.7, 20.5; ν_{max} (neat film) 3496, 1748, 1563, 1375 cm^{-1}. ESMS: m/z 354 $[M+Na]^+$. Anal. calcd for $C_{13}H_{14}ClNO_7$: C, 47.07; H, 4.25; N, 4.22%. Found: C, 47.13; H, 4.14; N, 4.17%.

1.4.35. Methyl-3-acetoxy-3-(3-chlorophenyl)-2-hydroxy-2-nitromethyl-propionate (9c). Colourless solid, mp 78–79 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42–7.18 (m, 4H), 5.88 and 5.84 (2s, 1H), 4.98–4.25 (2dd, J=13.7, 13.8 Hz, 2H), 3.87 and 3.82 (2s, 3H), 2.16 and 2.08 (2s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 170.3, 169.4, 168.9, 135.6, 135.5, 134.4, 134.2, 129.7, 129.6 (2s), 129.4, 128.1, 127.7, 126.2, 125.7, 78.1, 77.8, 76.9, 77.4, 75.1, 74.9, 53.9, 53.8, 20.7, 20.5; ν_{max} (neat film) 3498 (br), 1760, 1568, 1378 cm^{-1}. ESMS: m/z 354 $[M+Na]^+$. Anal. calcd for $C_{13}H_{14}ClNO_7$: C, 47.07; H, 4.25; N, 4.22%. Found: C, 47.13; H, 4.30; N, 4.27%.

1.4.36. Methyl-3-acetoxy-3-(4-chlorophenyl)-2-hydroxy-2-nitromethyl-propionate (9d). Colourless solid, mp 82–84 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35–7.26 (m, 4H), 5.89 and 5.84 (2s, 1H), 4.98–4.22 (2dd, J=13.9, 13.7 Hz, 2H), 3.87 and 3.81 (2s, 3H), 2.14 and 2.07 (2s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 170.4, 169.4, 168.9, 135.4, 135.2, 132.2, 132.1, 129.5, 129.0, 128.7, 128.6, 78.2, 77.8, 77.4, 76.9, 75.1, 75.0, 53.9 (2s), 20.7, 20.5; ν_{max} (neat film) 3506, 1761, 1566, 1378 cm^{-1}. ESMS: m/z 354 $[M+Na]^+$. Anal. calcd for $C_{13}H_{14}ClNO_7$: C, 47.07; H, 4.25; N, 4.22%. Found: C, 47.13; H, 4.17; N, 4.18%.

1.4.37. Methyl-3-acetoxy-2-hydroxy-2-nitromethyl-3-(2-nitrophenyl)-propionate (9e). Yellow solid, mp 102–103 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98–7.51 (m, 4H), 6.88 and 6.57 (2s, 1H), 5.32–4.19 (2dd, J=13.9, 13.8 Hz, 2H), 3.96 and 3.85 (2s, 3H), 2.16 and 2.02 (2s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 170.6, 168.8 (2s), 149.3, 148.7, 133.5, 132.9, 131.3, 130.2, 130.1, 130.0, 129.1, 128.5, 124.7, 124.3, 78.2, 77.3, 77.2, 76.3, 69.5, 69.4, 54.4, 54.3, 20.7, 20.4; ν_{max} (neat film) 3500, 1760, 1566, 1535 cm^{-1}. ESMS: m/z 365 $[M+Na]^+$. Anal. calcd for $C_{13}H_{14}N_2O_9$: C, 45.62; H, 4.12; N, 8.18%. Found: C, 45.94; H, 4.08; N, 8.13%.

1.4.38. Methyl-3-acetoxy-2-hydroxy-2-nitromethyl-pentanoate (9f). Pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.05 (m, 1H), 4.67 (m, 2H), 3.90 and 3.86 (2s, 3H), 2.15 and 2.10 (2s, 3H), 1.65 (m, 2H), 1.17 and 1.53 (2t, J=7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.5, 171.4, 170.5, 170.0, 78.1, 77.6, 76.8, 76.7, 75.2, 75.1, 54.0, 53.6, 21.9, 21.8, 20.5, 20.4, 9.7 (2s); ν_{max} (neat film) 3490, 1746, 1562, 1376 cm^{-1}. ESMS: m/z 272 $[M+Na]^+$. Anal. calcd for $C_9H_{15}NO_7$: C, 43.38; H, 6.07; N, 5.62%. Found: C, 43.16; H, 6.13; N, 5.58%.

1.4.39. Methyl-3-acetoxy-2-hydroxy-2-nitromethyl-hexanoate (9g). Pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.13 (m, 1H), 4.90–4.62 (2dd, J=13.9 Hz, 2H), 3.89 and 3.86 (2s, 3H), 2.13 and 2.08 (2s, 3H), 1.71–1.21 (m, 4H), 0.93 and 0.88 (2t, J=13.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.5, 171.4, 170.4, 169.9, 78.0, 77.7, 76.8, 76.7, 73.6, 73.5, 53.9, 53.5, 30.7, 30.5, 20.5, 20.4, 18.5, 18.4, 13.5, 13.4; ν_{max} (neat film) 3502, 1747, 1563, 1377 cm^{-1}. ESMS: m/z 286 $[M+Na]^+$. Anal. calcd for $C_{10}H_{17}NO_7$: C, 45.63; H, 6.51; N, 5.32%. Found: C, 45.53; H, 6.49; N, 5.28%.

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Sequence and solution structure of cherimolacyclopeptides A and B, novel cyclooctapeptides from the seeds of *Annona cherimola*

Alassane Wélé,[a] Céline Landon,[b] Henri Labbé,[b,†] Françoise Vovelle,[b] Yanjun Zhang[a] and Bernard Bodo[a,*]

[a]*Laboratoire de Chimie des Substances Naturelles, UMR 5154 CNRS, Muséum National d'Histoire Naturelle, 63 rue Buffon, 75005 Paris, France*
[b]*Centre de Biophysique Moléculaire, UPR 4301 CNRS, affiliated to Orléans university, rue Charles Sadron, 45071 Orléans Cedex 02, France*

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Abstract—Two new cyclooctapeptides, cherimolacyclopeptide A, *cyclo*(Pro[1]-Gln[2]-Thr[3]-Gly[4]-Met[5]-Leu[6]-Pro[7]-Ile[8]-) (**1**) and the related cherimolacyclopeptide B, *cyclo*(Pro[1]-Gln[2]-Thr[3]-Gly[4]-Mso[5]-Leu[6]-Pro[7]-Ile[8]-) (**2**), have been isolated from the methanol extract of the seeds of *Annona cherimola* Miller. The sequences were elucidated on the basis of the MS/MS fragmentation, using a Q-TOF mass spectrometer equipped with an ESI source, chemical degradation and extensive 2D-heteronuclear NMR. The three-dimensional solution structure of cherimolacyclopeptide A (**1**) determined by ^{1}H NMR data and molecular modelling is characterised by the presence of two β turns and a new type of β-bulge.

1. Introduction

Annona cherimola Miller (Annonaceae) is a small tree native to Ecuador and Peru, now widespread in subtropical areas, America, Africa and Asia and even in the south of Europa where it is cultivated for its edible fruits. The plant is also used in folk medicine as a parasiticide and an insecticide. *A. cherimola* has been described to produce many natural compounds of biological interest, such as alkaloids,[1,2] mainly of the isoquinoline group for which no less than 70 compounds have been isolated, acetogenins,[3–6] and dimeric amides.[7,8]

In continuation of our programme on cyclopeptides from plants,[9–11] we have investigated *A. cherimola*, and isolated from the seeds two new cyclooctapeptides, cherimolacyclopeptides A (**1**) and B (**2**). Although several cyclic octapeptides have been isolated from various natural sources, such as agardhipeptin B[12] from cyanobacteria, hymenistatin I[13] and axinellin C[14] from marine sponges, pseudostellarin H,[15] cyclolinopeptides D and E,[16] cyclogossin B,[9] pohlianin C[10] and cyclosquamosins B–D[17] from plants, only few tri-dimensional studies are devoited to such peptides. The conformations of cyclic peptides are of interest by themselves, as they can be used as models for the study of recurring structural features of proteins. The very limited number of 3D studies on cyclooctapeptides concern mainly synthetic peptides involving L-amino acids,[18] and mostly structurally symmetrical compounds.[19,20]

In this paper we report on the isolation, the sequence determination based on tandem mass spectroscopy and 2D NMR of cherimolacyclopeptides A (**1**) and B (**2**), and on the solution structure of **1**. This conformation including two β-turns and a new type of β-bulge is compared to that of other cyclopeptides. Cherimolacyclopeptide A (**1**) was found to be cytotoxic against tumoral KB cells, with an IC_{50} 0.6 μM, whereas cherimolacyclopeptide B (**2**) was less active with IC_{50} 45 μM.

2. Results and discussion

2.1. Isolation of cherimolacyclopeptides A and B

The dried and ground seeds of *A. cherimola* were extracted with methanol and cherimolacyclopeptides A (**1**) and B (**2**) were isolated from the ethyl acetate soluble fraction of this extract. They were purified successively by exclusion chromatography, silica gel column chromatography and C_{18} reversed-phase-HPLC. Positive reaction with chlorine/*o*-tolidine reagent suggested that they were peptides and the absence of coloration with ninhydrin of the spots on thin

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* Corresponding author. Tel.: +33-1-40-79-3129; fax: +33-1-40-79-3135; e-mail: bodo@mnhn.fr
† Deceased on August 5, 2003.

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layer chromatography (TLC), that these peptides were cyclic. The total acidic hydrolysis and amino acid analysis of the hydrolysate after derivatization indicated the presence of Glx (1), Gly (1), Ile (1), Leu (1), Met (1), Pro (2) and Thr (1), for cherimolacyclopeptide A (**1**) and Glx (1), Gly (1), Ile (1), Leu (1), Mso (1), Pro (2) and Thr (1), for cherimolacyclopeptide B (**2**). The amino acids in the acidic hydrolysate were converted into the *n*-propyl esters of their *N*-trifluoroacetyl derivatives. These esters were analysed by gas chromatography on a chiral capillary column and their retention times were compared with those of standards. All the chiral amino acids were L. The Glx in the hydrolysate was further identified as Gln from the absence of carboxylic acid group and from ^{1}H NMR data for both peptides, **1** and **2**.

2.2. Sequence determination by mass spectrometry

The molecular weight 837 for cherimolacyclopeptide A (**1**) was deduced from the positive ESI-qTOF mass spectrum, which displayed the protonated molecular $[M+H]^+$ ion at *m/z* 838, and the $[M+Na]^+$ and $[M+K]^+$ adduct ions at *m/z* 860 and 876, respectively. According to the amino acid analysis, the molecular formula $C_{38}H_{62}N_9O_{10}S$ was assigned to **1**, in agreement with the presence of eight residues in the cyclopeptide. Similarly, the molecular formula $C_{38}H_{63}N_9O_{11}S$ was assigned to **2**, taking into account the protonated molecular $[M+H]^+$ ion observed at *m/z* 854 in the ESI-qTOF spectrum, together with the $[M+K]^+$ adduct ion at *m/z* 992 and the $[M+Na]^+$ adduct ion at *m/z* 876 and its amino acid composition: **2** differs from **1** by the replacement of the Met residue by a methionine sulfoxyde (Mso).

Cyclopeptides are not easily sequenced, even by mass spectrometry. The reason is that multiple and indiscriminate ring-opening reactions occur during the CID of cyclic peptides. This results in the superimposition of random fragment ions, making the interpretation difficult.[21–23] However, due to the presence of a proline in the sequence, a specific fragmentation occurs at the peptidyl-prolyl (Xaa-Pro) level, leading to one linear peptide C-ended by an acylium ion (b_n), which undergoes further fragmentation and generates a series of acylium ions from which the sequence could be deduced.[10]

The collisional induced decomposition (CID) experiment on the protonated molecular $[M+H]^+$ ion of **1** at *m/z* 838 allowed the sequence determination (Fig. 1). The ring opening occurred at the Ile-Pro amide bond level and a series of adjacent acylium ions (b_n) at *m/z* 725, 628, 515, 384, 327 and 226 was generated: amino acids residues were lost sequentially from the *C*- to the *N*-terminus of the linearised peptide derived from **1**. The successive loss of Ile/Leu, Pro, Leu/Ile, Met, Gly and Thr was observed, yielding to the *N*-terminal dipeptide Pro-Gln (Fig. 2A). A second series of main peaks was observed at *m/z* 820, 707, 610, 497, 366 and 198, having 18 mass units less than the preceding b_n ions, and corresponding to the loss of a water molecule at the Thr level. A third significant series of ions was observed at *m/z* 810, 697, 600, 487, 356, 299 and 198 which were assigned to adjacent a_n ions related to the above b_n ion series. The mass spectral results suggested the sequence $[H\text{-}Pro^1\text{-}Gln^2\text{-}Thr^3\text{-}Gly^4\text{-}Met^5\text{-}Leu/Ile^6\text{-}Pro^7\text{-}Ile/Leu^8]^+$ for the linear peptide ion derived from cherimolacyclopeptide A, and thus the structure *cyclo*(Pro^1-Gln^2-Thr^3-Gly^4-Met^5-Leu^6-Pro^7-Ile^8) for the natural cyclooctapeptide **1**, with an ambiguity on the respective position of Leu and Ile.

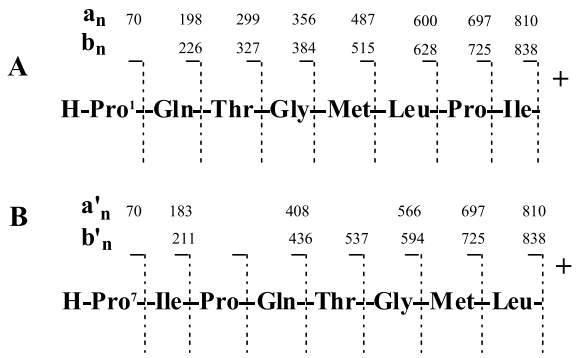

Figure 1. MS/MS fragmentation of the cherimolacyclopeptide A (**1**) $[M+H]^+$ ion (*m/z*=838): **A**) cleavage of the cyclopeptide at the Ile^8-Pro^1 amide bond level; **B**) cleavage of the cyclopeptide at the Leu^6-Pro^7 amide bond level.

A second linearised peptide was formed from the $[M+H]^+$ ion at *m/z* 838, due to the cleavage at the Leu^6-Pro^7 amide bond level and the resulting b'n and a'n ions were detected (Fig. 1B). The b'n ions series was characterized by ions at *m/z* 725, 594, 537, 436 and 211 corresponding to the successive loss of Leu/Ile, Met, Gly, Thr, (Pro-Gln) and yielding to the *N*-terminal dipeptide Pro-Ile/Leu, in agreement with the above proposed sequence.

Similarly, the CID spectrum of the $[M+H]^+$ ion at *m/z* 854 of cherimolacyclopeptide B (**2**) showed a main series of adjacent b_n peaks at *m/z* 741, 644, 531, 384, 327 and 226, corresponding to the successive loss of Ile/Leu, Pro, Leu/Ile, Mso, Gly and Thr, yielding the terminal dipeptide ion [H-Pro-Gln]$^+$ and suggesting the sequence $H\text{-}Pro^1\text{-}Gln^2\text{-}Thr^3\text{-}Gly^4\text{-}Mso^5\text{-}Leu/Ile^6\text{-}Pro^7\text{-}Ile/Leu^8$ for the linearised peptide. A second series of b_n type ions, at *m/z* 741, 594, 537, 436, 308 and 211, due to a cleavage at the Leu^6-Pro^7 amide bond level, indicated the successive loss of Leu, Mso, Gly, Thr, Gln, Pro and yielding the terminal dipeptide ion [H-Pro-Ile]$^+$, which confirmed the sequence *cyclo*(Pro^1-Gln^2-Thr^3-Gly^4-Mso^5-Leu^6-Pro^7-Ile^8) for **2**, with however, an ambiguity related to the respective location of Leu and Ile. Cherimolacyclopeptide **2** appeared to be an analogue of **1**, by Mso/Met substitution. An NMR study was undertaken to solve the above indecision, and in addition to assign the chemical shifts for the conformational study.

2.3. ^{1}H and ^{13}C NMR studies: sequence-specific assignment

The ^{1}H and ^{13}C NMR spectra of cherimolacyclopeptide A (**1**) were recorded in pyridine-d_5 (Table 1) and DMSO-d_6 solution (Table 2), and a major stable conformation (>90%) was observed in both solvents. However, the optimal conditions for **1** were in pyridine-d_5 at 263 K, where the minor component was negligeable. The six amide protons were clearly identified in the ^{1}H NMR spectrum, as well as the presence of eight carbonyl groups in the ^{13}C NMR spectrum, in agreement with an octapeptide structure including two prolines. The ^{1}H NMR spectrum of

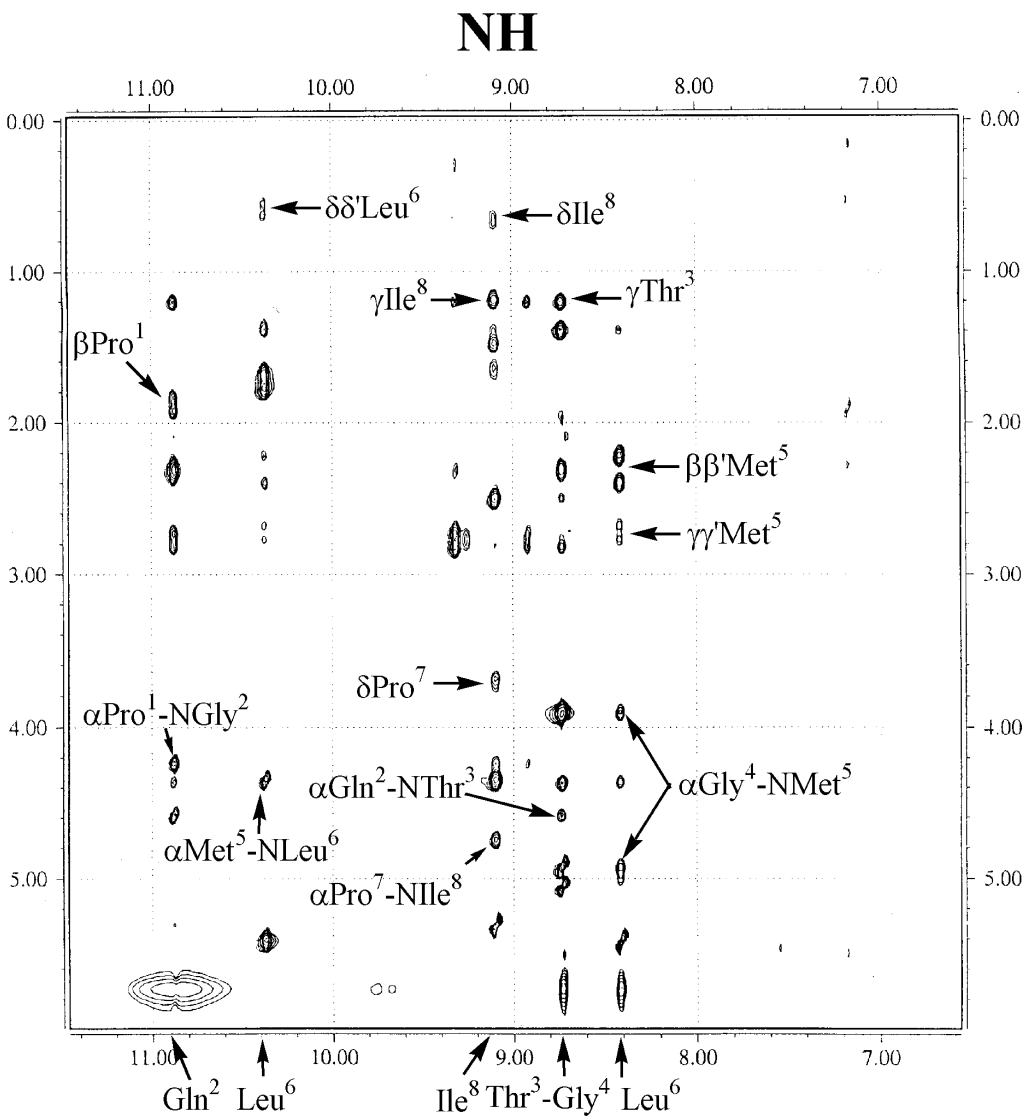

Figure 2. Part of the NOESY spectrum (120 ms) showing the NH to α and to side-chain proton correlations.

cherimolacyclopeptide A (**1**) was assigned via standard sequential assignment methods developed by Wüthrich.[24–26] The entire spin systems of individual amino acid residues were identified through COSY and TOCSY experiments and the ^{13}C NMR spectrum was assigned through HSQC and HMBC experiments (Table 1).

The final peptide sequence determination was based on the data of the HMBC experiment. All the amino acid spin systems were identified using scalar spin–spin couplings determined from the ^{1}H–^{1}H COSY and TOCSY experiments.[27] The ^{13}C NMR assignments of the protonated carbons were obtained from the proton detected heteronuclear HSQC spectrum. This experiment, with the HMBC experiment optimised for a long-range *J*-value of 7 Hz, for the non-protonated carbons allowed the carbonyl groups assignment. Carbonyl carbons of Pro^{1}, Gln^{2}, Thr^{3}, Met^{5} and Pro^{7} were easily identified from their intra-residue ^{3}J correlations with β protons, those of Gly^{4} and Leu^{6} from the strong intra-residue connectivities with the α protons (Table 1). Accordingly, the sequence determination was performed from the observation of the connectivities between the carbonyl of residue *i* with the amide and/or α protons of residue *i*+1.

$^{3}J_{CH}$ CO(*i*)/αH(*i*+1) correlations between the leucine and Pro^{7} and between the isoleucine and Pro^{1} on the HMBC spectrum, indicates univocally that the Leu residue is at position 6 and Ile at position 8. Other connectivities are in full agreement with the structure deduced from the mass spectrometry study.

The NOESY spectrum recorded at 263 K in pyridine-d_5 clearly depicted strong or medium NOE $d_{NN(i,i+1)}$ interactions from Gln^{2} to Met^{5}, a weak one between Met^{5} and Leu^{6} and a stretch of $d_{\alpha N(i,i+1)}$ sequential connectivities from Pro^{1} to Leu^{6} and between Pro^{7} and Ile^{8} (Figs. 2 and 3). The strong NOE between Gln^{2} and Thr^{3} suggested the presence of a β-turn with Gln^{2} at the *i*+2 position. In addition, strong NOE correlations were observed between the α proton of Ile^{8} and both δ and δ′ protons of Pro^{1}, indicating that the Ile^{8}-Pro^{1} amide bond is in *trans* configuration, while a strong correlation between the α protons of Leu^{6} and Pro^{7} indicates that the Leu^{6}-Pro^{7} amide

Table 1. ^{13}C and ^{1}H NMR data and HMBC correlations of cherimolacyclopeptide A (**1**), in pyridine-d_5 (400 MHz, 308 K; s: singulet; d: doublet; dd: doublet of doublet; t: triplet; m: multiplet)

Residue	δ_C	δ_H	m (*J* Hz)	HMBC correlations with H
Pro^1_b CO	174.7	—		αH, βH Pro^1; NH Gln^2
αCH	64.1	4.37	dd 8.7, 6.2	
βCH_2	30.1	2.16	m	
	—	2.03	m	
γCH_2	25.3	1.95	m	
	—	1.75	m	
δCH_2	48.7	4.22	m	
Gln^2 CO	172.9	—		αH, βH Gln^2; NH Thr^3
NH	—	10.50	d 3.9	
αCH	57.8	4.53	ddd 8.7, 4.2, 3.9	
βCH_2	26.2	2.35	m	
γCH_2	32.7	2.79	M	
	—	2.68	m	
δCO	177.7	—		βH, γH Gln^2
εNH_2	—	8.83	s	
	—	8.37	s	
Thr^3 CO	172.3	—		αH, βH Thr^3; NH Gly^4
NH	—	8.59	d 9.2	
αCH	60.4	4.99	dd 9.2, 2.8	
βCH	69.1	4.95	dd 6.5, 2.8	
γCH_3	20.0	1.41	d 6.5	
Gly^4 CO	169.1	—		αH Gly^4; NH, *α*H Met^5
NH	—	8.55	dd 7.8, 4.8	
αCH_2	43.5	4.83	dd 17.0, 7.8	
	—	3.86	dd 17.0, 4.8	
Met^5 CO	173.3	—		αH, βH, Met^5; NH Leu^6
NH	—	8.21	d 9.2	
αCH	51.9	5.30	dt 9.2, 7.4	
βCH_2	33.9	2.39	m	
	—	2.28	m	
γCH_2	30.1	2.71	m	
	—	2.71	m	
εCH_3	14.9	1.85	s	
Leu^6 CO	172.0	—		αH Leu^6; αH Pro^7
NH	—	9.83	d 5.4	
αCH	52.2	4.40	m	
βCH_2	38.9	1.87	m	
	—	1.45	ddd 13.6, 10.0, 2.9	
γCH	25.3	1.76	m	
δCH_3	20.9	0.77	d 6.5	
$\delta' CH_3$	23.2	0.70	d 6.5	
Pro^7_a CO	171.1	—		αH, βH Pro^7; NH, *α*H Ile^8
αCH	61.5	4.72	d 7.6	
βCH_2	31.6	2.82	m	
	—	2.09	m	
γCH_2	22.5	1.80	m	
δCH_2	47.3	3.79	dd 11.0, 7.5	
	—	3.63	dd 11.0, 9.0	
Ile^8 CO	171.8	—		αH Ile^8; αH Pro^1
NH	—	8.99	d 9.8	
αCH	56.0	5.26	dd 9.8, 9.8	
βCH	35.1	2.50	ddd 9.8, 6.6, 3.3	
γCH_2	24.9	1.61	dqd 13.5, 7.4, 3.3	
	—	1.27	m	
$\gamma' CH_3$	16.8	1.24	d 6.6	
δCH_3	10.3	0.83	t 7.4	

bond is in *cis* configuration. These stereochemistries are further confirmed by the γ carbons ^{13}C chemical shifts of Pro^1 and Pro^7 at 25.3 and 22.5 ppm, respectively, in agreement with the presence of *trans*-Pro^1 and *cis*-Pro^7 amide bonds.[28] All the data indicate the cyclic structure **1** for cherimolacyclopeptide A, including only one *cis*-amide bond.

The ^{1}H and ^{13}C NMR spectra of cherimolacyclopeptide B (**2**) were recorded in DMSO-d_6, assigned via 2-D homo- and heteronuclear experiments and compared to those of **1** (Table 2). The CO of Pro^7 gave a strong correlation with the NH of Ile^8 and the CO of Mso^5 with the NH of Leu^6 leading to a non-ambiguous location of the position of the Leu and Ile residues in the sequence of **2**. A strong Hα(8)-Hδ(1)

Table 2. ^{13}C and ^{1}H NMR data for cherimolacyclopeptides A (**1**) and B (**2**) in DMSO-d_6 (298 K; s: singulet; d: doublet; dd: doublet of doublet; t: triplet; m: multiplet; Mxx: Met for **1** and Mso for **2**)

Residue	**1**			**2**		
	δ_C	δ_H	m (*J* Hz)	δ_C	δ_H	m (*J* Hz)
Pro_b^1 CO	173.3	—		173.5		
αCH	50.9	3.85	m	62.6	3.82	m
βCH_2	29.0	2.10	m	29.0	2.12	ddd 12.2, 8.4, 6.1
	—	1.83	m	—	1.85	m
γCH_2	24.4	1.93	m	24.5	1.95	m
	—	1.74	m	—	1.75	m
δCH_2	47.7	3.78	m	47.7	3.78	m
	—	3.49	m	—	3.69	m
Gln^2 CO	171.7	—		171.8	—	
NH	—	9.41	d 4.0	—	9.42	d 3.8
αCH	55.9	3.91	m	56.0	3.90	m
βCH_2	25.4	1.89	m	25.4	1.90	m
γCH_2	31.3	2.26	t 6.5	31.4	2.28	t 6.5
δCO	175.2	—		175.2	—	
εNH_2	—	7.57	s	—	7.58	s
	—	7.13	s	—	7.13	s
Thr^3 CO	170.9	—		171.0	—	
NH	—	7.99	d 8.9	—	7.97	d 9.0
αCH	59.1	4.17	dd 8.9, 3.1	59.1	4.18	dd 9.0, 3.0
βCH	67.7	4.23	dd 6.7, 3.1	67.5	4.26	dq 6.6, 3.0
γCH_3	19.2	1.12	d 6.7	19.3	1.12	d 6.6
OH	—	4.41	d 10.7	—		
Gly^4 CO	167.8	—		168.0	—	
NH	—	7.84	dd 7.9, 4.8	—	7.84	dd 7.5, 5.0
αCH_2	42.1	4.10	dd 17.3, 7.9	42.1	4.12	dd 17.2, 7.5
	—	3.33	dd 17.3, 4.8	—	3.33	dd 17.2, 5.0
Mxx^5 CO	171.2	—		171.0	—	
NH	—	7.34	d 9.2	—	7.35	d 9.1
αCH	50.4	4.53	ddd 9.2, 7.0, 7.0	49.8	4.63	ddd 9.1, 7.5, 7.5
βCH2	33.3	1.72	m	26.3	1.81	m
	—	1.64	m	—	1.81	m
γCH_2	28.8	2.42	m	48.3	2.81	dt 13.7, 7.6
	—	2.30	m	—	2.66	dt 13.7, 7.6
δCH_3	14.5	2.00	s	37.7	2.49	s
Leu^6 CO	170.6	—		170.7	—	
NH	—	8.61	d 4.7	—	8.73	d 5.0
αCH	62.6	3.84	m	51.0	3.84	m
βCH_2	37.5	1.40	m	37.6	1.50	m
	—	1.31	m	—	1.36	m
γCH	24.1	1.69	m	24.2	1.70	m
δCH_3	20.3	0.78	d 6.6	20.3	0.79	d 6.5
δCH_3	23.1	0.89	d 6.6	23.1	0.89	d 6.6
Pro_a^7 CO	170.1	—		170.1	—	
αCH	60.2	4.38	m	60.2	4.39	d 7.8
βCH_2	30.7	2.39	m	30.7	2.39	ddd 11.6, 7.8, 6.3
	—	2.01	m	—	2.02	m
γCH_2	21.7	1.85	m	21.7	1.87	m
	—	1.48	m	—	1.50	m
δCH_2	46.4	3.40	m	46.4	3.40	m
	—	3.27	m	—	3.30	m
Ile^8 CO	170.2	—		170.1	—	
NH	—	8.22	d 9.6	—	8.20	d 9.7
αCH	54.8	4.62	dd 10.0, 9.6	54.7	4.62	dd 10.2, 9.7
βCH	34.1	2.00	m	34.0	2.02	m
γCH_2	23.7	1.41	m	23.7	1.42	m
	—	0.98	m	—	1.00	m
$\gamma' CH_3$	16.2	0.89	d 6.6	16.2	0.89	d 6.6
δCH_3	10.2	0.81	t 7.5	10.2	0.81	t 7.4

NOE connectivity together with a Cγ chemical shifts at 24.5 ppm for Pro^1 allowed to identify a *trans* configuration for the Leu^8-Pro^1 amide bond. The Leu^6-Pro^7 peptide bond was easily identified as a *cis*-isomer by its Cγ chemical shifts at 21.7 ppm and the presence of a strong correlation between α protons of Leu^6 and Pro^7 in the NOESY spectrum. Peptide **2** appears thus to differ from **1** only by the Met/Mso substitution.

Figure 3. NMR data for peptide **1**: sequential connectivities (strong, medium and weak), temperature coefficients of amide protons (ppb k^{-1}) and H/D exchange rate for cherimolacyclopeptide A in pyridine-d_5 [s (slow): exchanged in more than 5 h; m (medium): exchanged in 1 to 5 h; f (fast): exchanged in less than 1 h, at 293 K].

2.4. Solution structure of 1

The 3-D structure of cherimolacyclopeptide A (**1**) was determined using a restraint file including 30 intra-residual, 40 sequential restraints, six (i,i+2) restraints between Gln^2 and Ile^8, Thr^3 and Met^5 and between Pro^7 and Pro^1 and finally, ten non-sequential restraints (Table 3) among which three connect Thr^3 to Ile^8 and three involve Pro^1. Five dihedral angle restraints were deduced from the $^3J_{NH,H\alpha}$ coupling constants.

Among the 100 structures generated with DYANA, 87 display a target function smaller than 1 Å^2. The RMS deviation between the Cα atoms of 40 best structures (Target function ≤0.21 Å^2) was only 0.06±0.04 Å. In order to enhance the conformational space sampling, these 40 structures were subjected to simulated annealing and energy minimizations in the cartesian coordinates space as described in the Section 3. Twenty structures showing the smallest number of residual violations were selected for further analysis. The pairwise RMSD between the Cα backbone atoms of the 20 selected structures (0.18±0.08 Å) remains very small, showing that the structures are well defined by the NMR data. Most side-chains adopt a well-defined conformation due to the presence of numerous NOEs, the only side-chain showing a large conformational variability is Gln^2.

The 20 selected structures are in very good agreement with all experimental data and the standard covalent geometry. There are no distance violation larger than 0.2 Å, no angle violations larger than 5° and the root-mean-square deviations (RMSD) with respect to the standard covalent geometry are low. Both negative van der Waals and electrostatic energy terms are indicative of favorable non-bonded interactions (Table 4). Moreover, 100% of the (ϕ,ψ) angles of all structures are in the most favored regions of the Ramachandran plot and additional allowed regions according to the PROCHECK software nomenclature.[38]

Table 3. Non-sequential NOEs

NH Gln^2	αH Ile^8
NH Gln^2	γCH$_3$ Ile^8
NH Thr^3	βCH Ile^8
NH Thr^3	γCH$_3$ Ile^8
γCH$_3$ Thr^3	NH Met^5
γCH$_3$ Thr^3	NH Ile^8
αH Pro^7	δCH$_2$ Pro^1
εH or ε′H Gln^2	γCH$_3$ Ile^8
δCH$_3$ or δ′CH$_3$ Leu^6	βH or β′H Pro^1
δCH$_3$ or δ′CH$_3$ Leu^6	δH or δ′H Pro^1

Table 4. Structural statistics of the 20 models of cherimolacyclopeptide A (**1**)[a]

Restraint violations	
Distance restraints >0.2 Å	0
Deviation from standard geometry	
Bond lengths>0.05 Å	0
Bond angles >10°	0
Final energies (kcal mol^{-1})[a]	
$E_{electrostatic}$	−61±3
E_{vdw}	−21±4
RMSD	
	Pairwise (Å)
Backbone	0.18±0.08
All atoms	1.04±0.18

[a] The energy terms were calculated using the CHARMM force field.

The overall fold of cherimolacyclopeptide A (**1**) (Figs. 4–6) includes two β turns. The first one, formed with Met^5 at position i+1 and Ile^8 at position i+3, can be classified as a VIa turn. It is characterized by the presence of a *cis*-proline at position i+2 and (ϕ,ψ) angles for residues i+1 and i+2 (Table 5) closed from the standard values: (−60, +120) and (−90, 0), respectively.[29] This turn is stabilized by the

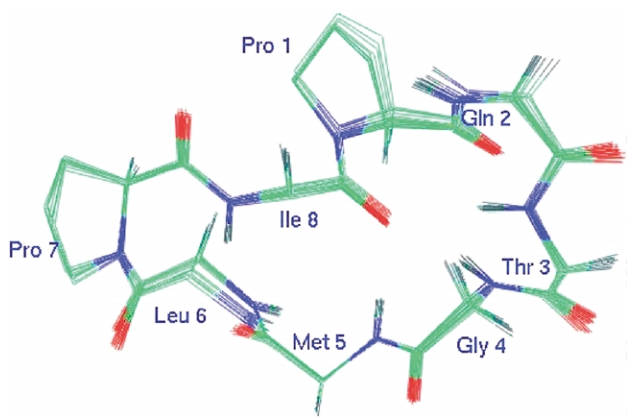

Figure 4. Superposition of the 20 NMR derived structures of cherimolacyclopeptide A (**1**) in pyridine-d_5 (263 K).

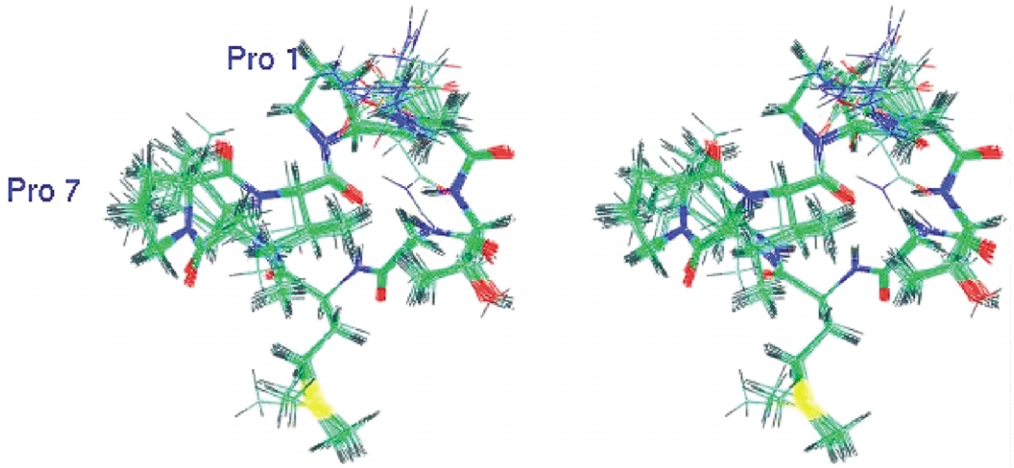

Figure 5. Stereoview of a superposition of the 20 NMR structures of cherimolacyclopeptide A (**1**) in pyridine-d_5 (263 K) showing the side-chain and the polypeptide backbone.

Table 5. Main chain torsional angles

Residue	ϕ (°)	ψ (°)
Pro[1]	−42.6±3.4	−44.8±4.5
Gln[2]	−31.4±3.5	−40.1±6.4
Thr[3]	−112.5±2.1	−34.9±11.6
Gly[4]	−117.1±4.9	36.6±4.5
Met[5]	−132.8±2.5	65.1±3.8
Leu[6]	−36±1.8	117.0±5.1
Pro[7]	−99.3±2.1	31.0±2.4
Ile[8]	−115.1±0.7	62.0±4.5

canonical hydrogen bond between the C═O group of Met[5] and the NH of Ile[8] with an average O–H_N hydrogen bond distance of 1.86 Å. This is in agreement with the low value of the chemical shift dependence of the NH of Ile[8], as well as its low exchange rate with D_2O. Another β-turn is formed between Ile[8] and Thr[3]. This turn is a type I β-turn with *trans*-Pro[1] at position $i+1$, it is very distorted because of the proline. A rather similar conformation was previously found for the sequence Phe-Pro-Ala-Arg of the cyclic peptide *cyclo*(RGDFPA)[30] where the proline was also in *trans*-configuration. However, as in cherimolacyclopeptide A (**1**) structure the turn is stabilized by a trifurcated hydrogen bond between the C═O group of Ile[8] and the NH groups of Thr[3], Gly[4] and Met[5], with average O–H_N distances of 2.14, 1.97 and 1.97 Å, respectively, the distortion could be due to this particular hydrogen bonding. The temperature coefficients ($\Delta\delta/\Delta T$) for the amide resonances of these three residues, in pyridine as well as in DMSO solution, are in accordance with the hydrogen bond network found on the 20 structures (Table 3, Fig. 2). It should be noted that the values measured in pyridine are about two times larger than those measured in DMSO. The low values, in the range −3 to −5 ppb K^{-1} for Thr[3], Gly[4], Met[5] and Ile[8] in pyridine (Fig. 3) and which are in the range −1 to −2 ppb K^{-1} in DMSO (Table 6) indicated that they are involved in intramolecular hydrogen bonds, whereas the large temperature coefficient values found in pyridine for Leu[6] (−12 ppb K^{-1}), for Gln[2] (−8 ppb K^{-1}) and also for the εNH_2 protons of Gln[2] side-chain (−10.7 and −12 ppb K^{-1}) indicated they are solvent exposed (Fig. 3). Large values are also observed in DMSO-d_6 (Table 6).

The cyclooctapeptide **1** appeared to be structured with two β-turns of type VIa and I, the latter being stabilized by a

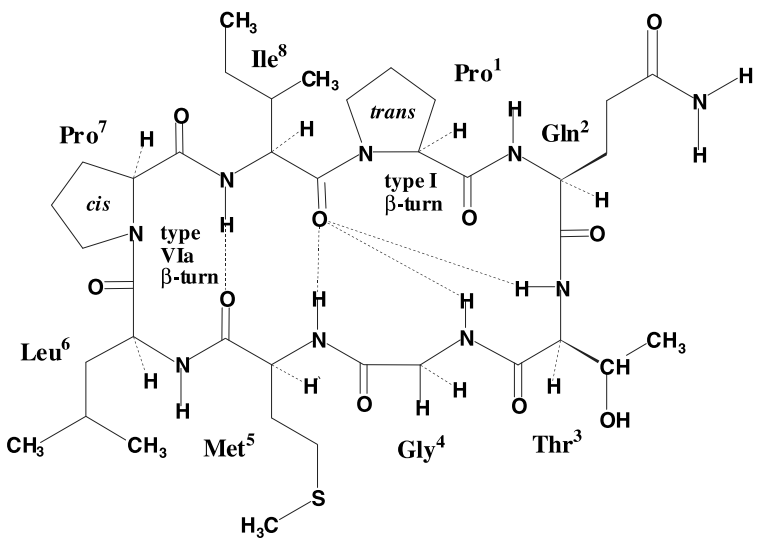

Figure 6. Schematic diagram of the turn types and the hydrogen bonds (broken lines) for cherimolacyclopeptide A (**1**).

Table 6. Temperature coefficients ($-\Delta\delta/\Delta T$, ppb K^{-1}) for amide protons of cherimolacyclopeptides A (**1**) and B (**2**) in DMSO-d_6

	Pro^1_b	Gln^2	Thr^3	Gly^4	Mxx^5	Leu^6	Pro^7_a	Ile^8	ε Gln^2
(**1**)	—	4.2	1.6	2.0	1.9 (Met)	5.0	—	1.2	4.8; 4.0
(**2**)	—	4.0	1.6	1.7	1.8 (Mso)	4.9	—	1.0	3.6; 3.6

trifurcated hydrogen bond. It is interesting to note that cyclohexapeptides are usually organized with two β-turns stabilized by two hydrogen bonds, and that cycloheptapeptides are usually organized with two β-turns, one stabilized by a normal hydrogen bond and the second by a bifurcated hydrogen bond forming a β-bulge.[10] A new type of β-bulge is observed in the structure of **1**, involving a trifurcated hydrogen bonding instead of a bifurcated one. All the NMR data (Tables 2 and 6) indicates that cyclopeptides **1** and **2** adopt a similar conformation in solution.

Due to the presence of side-chain side-chain and side-chain backbone connectivities (Table 3), most side-chains adopt a well-defined orientation. This is particularly striking for Thr^3 and Ile^8, the only residues showing variability are Gln^2 and to a less extend Leu^6 (Fig. 5). However, these residues adopt always the same orientation with respect to the backbone and the variability is limited to the δCH_3 groups of Leu^6 and to the amide group of Gln^2.

3. Experimental

Optical rotations were measured with a Perkin–Elmer model 341 Polarimeter and the $[\alpha]_D^{22}$ values are given in deg cm^2 g^{-1}. Melting points were determined on a Büchi melting point B-545 apparatus. Mass spectra were recorded on an API Q-STAR PULSAR *i* of Applied Biosystem. For the CID spectra, the collision energy was 40 eV and the collision gas was nitrogen.

^1H NMR spectra were recorded either on an INOVA 600 Varian spectrometer operating at 600 MHz or a Bruker Avance 400 spectrometer operating at 400.13 MHz equipped with X-WIN NMR (version 2.6). The coupling constant used to establish the necessary delay for the selection of the proton coupled to the carbon in the HSQC spectrum was 135 Hz, corresponding to a delay of 3.7 ms; the delay for the HMBC spectra was 70 ms corresponding to a long-range coupling constant of 7 Hz.

3.1. Plant material

Fruits of *Annona cherimola* Miller (Annonaceae) were collected in the south of Spain in December 2000. The seeds were collected and were immediately washed with distilled water and were dried at room temperature. Samples were deposited in the Herbarium of the National Museum of Natural History (Paris).

3.2. Extraction and isolation

The dried and powdered seeds of *A. cherimola* (3.0 kg) were macerated three times with cyclohexane (3 L), the combined extracts yielded an oil (531 g) which was discarded. The seeds were then extracted three times with MeOH (3 L) at room temperature to give after evaporation of the solvent under reduced pressure the MeOH extract (126 g) which was partitioned between EtOAc and water. The organic phase was concentrated to dryness and the residue (61.5 g) was dissolved in MeOH and chromatographed on Sephadex LH-20 column with MeOH. The head fraction (33.6 g) containing peptides and acetogenins was subjected to repeated silica gel column chromatography (Kieselgel 60 H Merck) eluted with CH_2Cl_2 containing increasing amount of MeOH from 5 to 20% yielding to three peptide fractions (I-III), characterised by TLC on silica gel 60 F_{254} Merck, with CH_2Cl_2/MeOH 9:1 as eluent system. The peptides were detected with Cl_2/*o*-tolidine reagent as blue spots with *Rf* 0.24 (I, 260 mg), 0.43 (II, 690 mg) and 0.45 (III, 410 mg). The two last peptide fractions II and III were purified by isochratic reversed phase HPLC (Kromasil C_{18}, 250×7.8 mm, 5 μm, AIT France; flow rate 2 mL/min, detection 220 nm). Fraction II using MeOH/H_2O: 55:45 with 0.1% TFA, yielded cherimolacyclopeptide A (**1**, retention time (t_R) 23.9 min, 185 mg); Fraction III using MeOH/H_2O: 55:45 with 0.1% TFA, yielded cherimolacyclopeptide B (**2**, t_R 10.6 min, 199 mg).

3.3. Absolute configuration of amino acids

Solutions of **1** and **2** (each containing 1 mg of peptide) in 6 N HCl (1 mL) were heated at 110 °C for 24 h in sealed tubes. After cooling, the solutions were concentrated to dryness. The hydrolysates were dissolved in anhydrous solution of 3 N HCl in 2-propanol and heated at 110 °C for 30 min. The reagent were evaporated under reduce pressure. The residues were dissolved in CH_2Cl_2 (0.5 mL) and 0.5 mL trifluoracetic anhydride was added. The mixtures were kept in a screw-capped tubes at 110 °C for 20 min. The reagents were evaporated and the mixtures analysed on a Chirasil-*L*-Val (*N*-propionyl-L-valine-*tert*-butylamide polysiloxane) quartz capillary column with helium (1.1 bar) as carrier gas and temperature program of 50–130 °C at 3 °C/min and 130–190 °C at 10 °C/min, with a HEWLETT PACKARD series 5890 apparatus. Comparison of Rt values with those of standard amino acids was used: L-Glu (29.3), Gly (14.6), L-Ile (16.9), L-Leu (19.2), L-Met (27.9), L-Mso (27.8), L-Pro (18.2) and L-Thr (15.2).

3.3.1. Cherimolacyclopeptide A. $C_{38}H_{63}N_9O_{10}S$: colourless solid, mp 192–193 °C (MeOH); $[\alpha]_D^{22}$ −8.5 (*c* 0.9, MeOH). ESI-qTOF, *m/z*: 876 $[M+K]^+$, 860 $[M+Na]^+$, 838 $[M+H]^+$. ESI-qTOF MS/MS on $[M+H]^+$(ce 40 eV) *m/z* (%): 838 (11), 820 (3), 810 (9), 725 (23), 707 (13), 697 (17), 649 (7), 628 (37), 611 (20), 610 (24), 600 (41), 594 (7), 583 (14), 566 (5), 552 (14), 537 (5), 515 (57), 497 (24), 487 (13), 439 (50), 436 (11), 408 (3), 404 (10), 403 (21), 401 (14), 384 (44), 366 (11), 356 (2), 327 (70), 309 (32), 299 (5), 290 (37), 283 (8), 243 (9), 226 (100), 211 (11), 198 (57), 183 (10), 115 (10), 170 (10).

3.3.2. Cherimolacyclopeptide B. $C_{38}H_{63}N_9O_{11}S$: colourless solid, mp 228–229 °C (MeOH); $[\alpha]_D^{22}$ −8.3 (*c* 2, MeOH). ESI-qTOF, *m/z*: 892 $[M+K]^+$, 876 $[M+Na]^+$, 854 $[M+H]^+$.

ESI-qTOF MS/MS on $[M+H]^+$(ce 40 eV) *m/z* (%): 854 (23), 836 (5), 826 (22), 741 (27), 723 (7), 713 (22), 677 (26), 649 (22), 644 (70), 626 (27), 616 (85), 599 (17), 594 (5), 580 (53), 566 (6), 562 (19), 552 (53), 537 (12), 531 (100), 516 (25), 513 (26), 509 (2), 503 (3), 496 (16), 467 (85), 449 (18), 439 (39), 436 (21), 419 (48), 418 (7), 408 (7), 391 (23), 384 (43), 366 (15), 356 (6), 327 (82), 318 (14), 309 (35), 306 (65), 299 (7), 226 (59), 211 (8), 198 (4), 183 (7), 170 (5).

3.4. Nuclear magnetic resonance spectroscopy

The NMR spectra were recorded either in DMSO-d_6 or in pyridine-d_5 (0.7 mL of 25 mM solution). At 298 K the ^{1}H NMR spectrum showed two sets of signals, indicating the occurrence of two slowly interconverting conformations (I and II), presumably due to a *cis*/*trans* isomerism of one proline. NMR spectra were recorded at 258, 263, 273, 278, 383, 298 and 318 K, showing a temperature dependence of the I:II ratio. At 263 K, the second set of signals become negligible, therefore, NMR spectra subsequently used for NOE quantification were recorded at 263 K.

The temperature coefficients of amide protons were obtained by 5 K temperature increments, in the 278–318 K range: the variation was linear indicating no variation of the conformation with the temperature and the NH coupling constants were unchanged.

A conventional set of one (1-D) and two dimensional (2-D) ^{1}H NMR TOCSY and NOESY spectra, was acquired at a temperature of 263 K on a VARIAN INOVA NMR spectrometer equipped with a *z*-axis field-gradient unit and operating at a proton frequency of 600 MHz. The TOCSY spectrum was collected with a spin lock time of 80 ms using the MLEV-17 mixing scheme[31] and NOESY spectra were recorded with mixing times of 120 and 300 ms. 2D NMR spectra were processed on a SGI O_2 workstation using the NMR Pipe/Draw software.[32] The NMR data sets were analysed with XEASY.[33]

NOESY cross peaks recorded with a mixing time of 120 ms were converted into upper distance limit restraints using the CALIBA program included in the DYANA package. In order to assess possible contributions from spin diffusion effects, some NOEs only observable on the 300 ms mixing time NOESY map were taken into account with a 6 Å upper bound. The minimum distance constraint between two protons was limited by their van der Waals radii (2.0 Å). All these restraints were brought together in a distance restraint file used as input to initial steps of molecular modelling. In addition, in DYANA, the cyclization was ensured by a set of distance constraints on the backbone atoms of the first and last residue, the corresponding van der Waals constraints were removed. Backbone ϕ dihedral angle restraints were deduced from the 1D COSY spectrum. These ϕ angles were restrained to $-60\pm30°$ for $^3J_{NH-H\alpha}<6.5$ Hz and $-120\pm40°$ for $^3J_{NH-H\alpha}\geq8$ Hz.

3.5. Structure calculations

Structure calculations were performed using an hybrid method including simulated annealing in the torsion angle space with DYANA[34,35] followed by simulated annealing in cartesian coordinates with XPLOR 3.1.[36]

A set of 100 structures was generated from random-built initial models using the annealing procedure of the variable target function program DYANA. In order to increase the sampling of the conformational space, a subset of 40 structures, with a target function ≤0.21 Å^2 were submitted to simulated annealing using the standard protocol of XPLOR 3.1. Finally these structures were energy minimised using Powell's algorithm and CHARMM force field parameters[37] implemented in X-PLOR 3.1 software. Twenty structures showing the smallest number of residual violations were selected as representative of the cherimolacyclopeptide A (**1**) structure and analysed using PROCHECK[38] and PROMOTIF.[39]

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Synthesis of α,β-unsaturated dioxanes, dioxolanes and dioxepanes by *trans*-acetalisation of dimethylacetals with *meso* or C_2-symmetrical 1,2-, 1,3- and 1,4-diols

Loïc Lemiègre,[a] Fleur Lesetre,[a] Jean-Claude Combret[b] and Jacques Maddaluno[a,*]

[a]*Laboratoire des Fonctions Azotées & Oxygénées Complexes de l'IRCOF, UMR 6014 CNRS, Université de Rouen, 76821 Mont St Aignan Cedex, France*
[b]*Laboratoire des Sciences et Méthodes Séparatives de l'IRCOF, UPRES 2659, Université de Rouen, 76821 Mont St Aignan Cedex, France*

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Abstract—Several *o*-dibenzylic diols were prepared reacting organometallics with *o*-phthalaldehyde at room temperature in ether. The identity of the *meso* and C_2-symmetrical (D,L) isomers as well as their ratio were determined by chiral gas chromatography. The *meso* and C_2 (racemic) stereoisomeric diols were easily separated by flash chromatography on silica gel. A set of 18 α,β-unsaturated acetals were then prepared reacting those, as well as commercially available 1,2, 1,3 and 1,4 diols, with the corresponding methylacetals in acidic medium. A *trans*-acetalisation procedure adapted to the cases of fragile allylic alcohols or unfavorable 1,6 diols-derived dioxonanes based on a Dean–Stark trapping of methanol was also employed.

1. Introduction

The intramolecular Diels–Alder (IMDA) cycloaddition is a remarkably efficient tool for the convergent and stereocontrolled synthesis of functionalized polycyclic systems.[1–3] Classically, the direct-demand version of this reaction relies on trienes featuring an electron-rich dienic moiety and an electron-deficient dienophile. Therefore, research aimed at simple and versatile accesses to such substrates remains of synthetic importance.[4–6] We have previously described a new route to a set of such trienes taking advantage of the sensitivity of α,β-unsaturated cyclic acetals such as dioxolanes or dioxanes to the base-induced conjugate-elimination (Fig. 1).[7,8] The final IMDA step showed this approach could open a relatively efficient route to medium-ring lactones. However, the yield and the stereoselectivity of this reaction is largely depending on the exact structure of the tether connecting the diene to the dienophile, and therefore to the nature of the 'embedded' diol.

To pursue our work on this class of trienes, we thought a detailed investigation on a general access to this sensitive class of reagents would deserve a separate investigation. In particular, our previous study did not address the central problem of the control of the stereogenic centers newly created by the IMDA. Introducing the asymmetry through the diols was a relatively simple way of tackling this problem, provided the chiral elements borne by the tether after ring fission were able to secure the diastereocontrol of the cycloaddition step. In this perspective, one could rely either on the ring fission of chiral cyclic acetals (derived from either non-symmetrical or C_2-symmetrical diols), or on the opening of achiral acetals (derived this time from *meso* diols). The alcohol resulting from the action of an achiral base on acetals derived from C_2-symmetrical chiral diols will necessarily be chiral while the opening of the *meso* derivatives will require the use of chiral bases to eventually escape their achiral origin (Fig. 2).

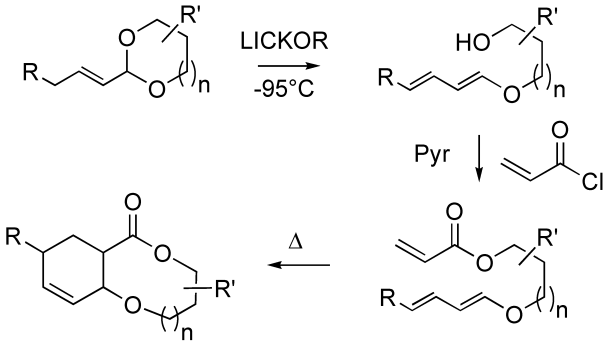

Figure 1. From diox(ol)anes to medium-ring lactones (LICKOR=*n*-BuLi+*t*-BuOK).

The aim of this paper is twofold. It first gathers results

Keywords: Diols; C_2-Symmetry; *meso* Compounds; Acetals.
* Corresponding author. Tel.: +33-235-522-446; fax: +33-235-522-971; e-mail address: jmaddalu@crihan.fr

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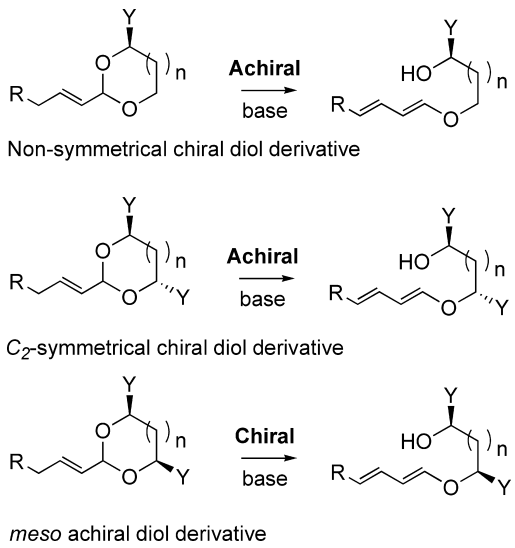
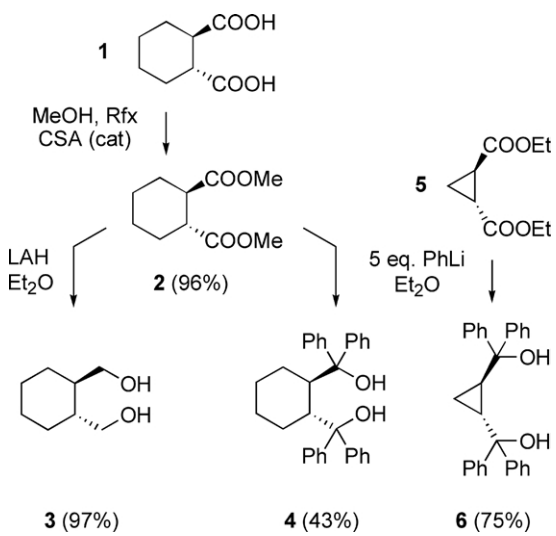


Figure 2. Opening acetal derived from C_2-symmetrical or *meso* diols.

regarding new 1,4-diols (including a family of dibenzylic diols prepared from *o*-phthalaldehyde) that are good precursors for acetals fitting one or the other of the above categories. It is then centered on the access to α,β-unsaturated cyclic acetals of various sizes through adapted *trans*-acetalisation processes.

2. Results and discussion

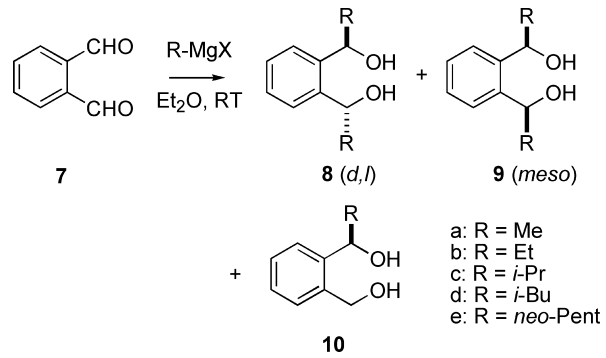
Synthesis of diols. A relatively large variety of chiral and achiral 1,2-, 1,3- and 1,4-diols is commercially available and was used directly in the *trans*-acetalisation experiments presented in the next paragraph. In addition, a set of racemic 1,4 diols was prepared in-house by various methods. The *anti*-cyclohexanedimethanol **3** was synthesized from commercially available racemic *anti*-1,2-cyclohexane-dicarboxylic acid **1** (Scheme 1) following a described procedure.[9,10] The addition of an excess of phenyllithium on the intermediate diester **2** led to known[11] dibenzhydrilic diol **4**, following Seebach et al. procedure.[12] Similarly, the cyclopropylic diol **6** was readily prepared from the



Scheme 1.

corresponding commercially available diethyl ester **5** (Scheme 1).

For the sake of an easy final deprotection, dibenzylic 1,4-diols **8**, **9** were also considered (Scheme 2). Those were initially prepared as racemic mixtures by direct addition of an excess of alkyl Grignard reagents to *o*-phthalaldehyde **7** by Weyerstahl et al.[13] A stereoselective synthesis of **8b** (R=Et) was later studied by Shibata and colleagues who obtained disappointing results reacting diethyl zinc with **7** in the presence of Ti(*i*-PrO)$_4$ and 1*S*,2*R*-PHONE, a chiral thiophosphoramidate.[14] Simultaneously, Brown et al. described an efficient access to chiral **8f** (R=allyl: d.e.=98%, e.e.≥98%) adding allyldiisopinocampheyl borane also to *o*-phthalaldehyde **7**.[15] This procedure was, however, restricted to allyl derivatives. Very recently, van Koten et al. have obtained high **8/9** ratios and good enantioselectivities reacting **7** in a two-step, one-pot procedure involving first complexation between a chiral aminothiolate and organozincs then Grignard reagents.[16]



Scheme 2.

We chose to resort to the convenient Weyerstahl's procedure[12] since racemic C_2-symmetrical diols were fully sufficient to later evaluate the IMDA step. However, the diastereoselectivities of the alkylmagnesium reagents addition to *o*-phthalaldehyde, not given in the original paper, remained to be determined. Reacting commercial or home-made solutions of methyllithium or organo-magnesium compounds with **7** in diethyl ether, either following a direct (organometallic added to the dialdehyde) or inverse (vice versa) procedure at room temperature led to the results displayed in Table 1. The D,L and *meso* diastereomers were conveniently identified by a single gas chromatography run on a chiral Supelco β-Dex column, leading to the separation of the diastereomers as well as to the 50:50 splitting of the D,L signal (Fig. 3).

The results in Table 1 call for several comments. First, the amount of diols **10**, a side-product resulting from a single nucleophilic addition and a reduction, seemed related to the bulkiness of the organometallic reagent employed (entries 1–10). Obviously, this remark did not apply to nucleophiles devoid of β-protons such as neo-pentylmagnesium bromide or bulky such as *t*-butylmagnesium chloride (entries 11 and 12). Interestingly in this latter case, a lactol resulting from a single addition and analogous to that isolated by van Koten from organozinc reagents, was obtained in good yield in ether (but not in THF, following a direct or an inverse procedure). Note also that neither the solvent (diethylether

Table 1. Addition of organometallics to *o*-phthalaldehyde at room temperature (Scheme 1)

Entry	Reagent	Solvent	Addition[a]	Yield (%)[b]	**8/9/10**
1	MeLi	Et_2O	Inverse	92	39:61:0
2	EtMgBr	Et_2O	Direct	63	62:21:17
3	*i*-PrMgCl	Et_2O	Direct	72	59:10:31
4	*i*-PrMgCl	THF	Direct	68	70:8:22
5	*i*-PrMgCl	Et_2O	Inverse	67	48:15:37
6	*i*-PrMgBr	Et_2O	Inverse	66	41:10:49
7	*i*-PrMgBr	THF	Inverse	51	65:14:21
8	*i*-BuMgCl	Et_2O	Inverse	84	24:10:66
9	*i*-BuMgCl	Et_2O	Inverse	68	23:14:63
10	*i*-BuMgBr	THF	Inverse	61	26:8:66
11	*neo*-Pent-MgBr	Et_2O	Direct	16[c]	100:0:0
12	*t*-BuMgCl	Et_2O	Direct	83[d]	0:0:0

[a] The organometallic was added to the aldehyde solution (direct) or vice versa (inverse).
[b] Overall yield calculated for **8**+**9**+**10**.
[c] Only diol **8e** was isolated from the crude reaction mixture.
[d] Only lactol B (Fig. 4, R=*t*-Bu) was obtained in this case.

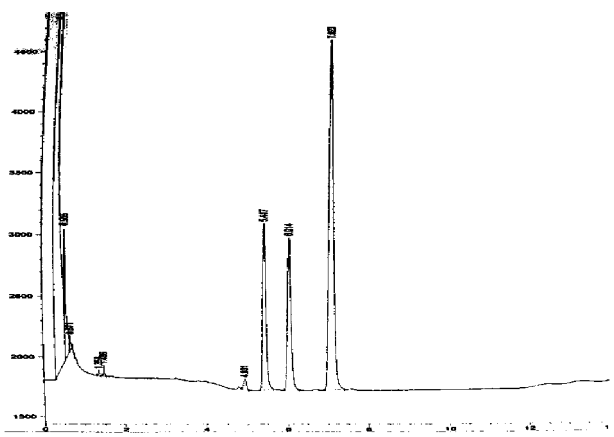


Figure 3. GC chromatograms of a mixture of diols D,L **8a** and *meso* **9a** on a Supelco β-Dex chiral column.

versus THF, entries 3 and 4), the Grignard counterion (chloride or bromine, entries 5 and 6 or 9 and 10) nor the order of the introduction of the reagents (direct versus inverse, entries 3 and 5) seem to have a significant influence neither on the yields nor on the selectivities.

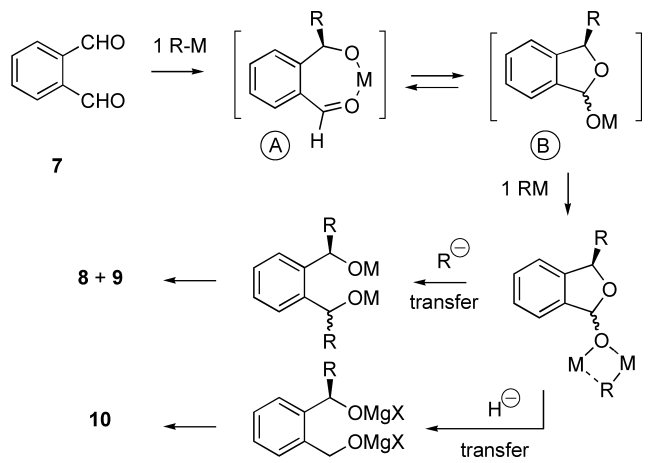


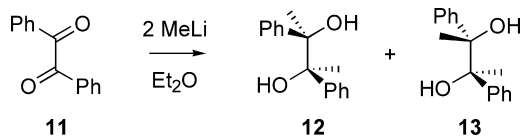
Figure 4. Proposed mechanism for the addition of Grignard reagents to *o*-phthalaldehyde **7**.

These data provide hints on the mechanism of this reaction (Fig. 4). The alcoholate resulting from the first addition can be regarded either as an aldehyde undergoing an intramolecular Lewis acid activation (form A) or, more likely, as a lactolate (form B). This later can probably further aggregate with a second equivalent of the organometallic leading

- to the expected SN_2 type substitution with smaller nucleophiles, opening the temporary 5-membered heterocycle and yielding diols **8** and **9** (on structure B) or to the nucleophilic addition on the aldehyde (on form A), in ratios obviously depending on the size of R.
- to a β-hydride transfer with cumbersome reagents (such as *i*-propyl or *i*-butyl magnesium chloride), triggering the second aldehyde reduction and thus leading to diols **10** plus the corresponding olefin.

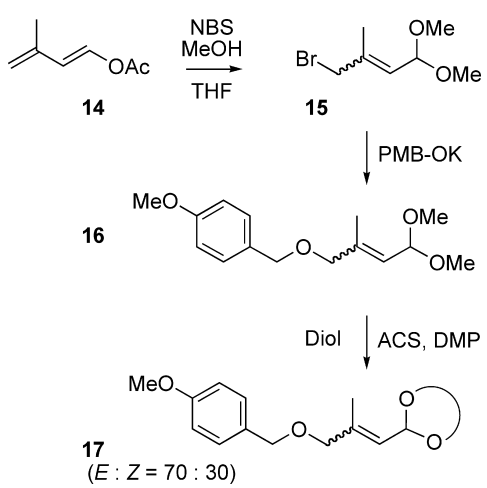
This mechanism fits the various observations in Table 1. Similar side-product and steric effects, such as a diastereoselectivity increase in favor of the D,L isomer induced by the bulky nucleophiles, have also been underlined by van Koten.[15]

Finally, benzil **11** was treated with 2 equiv. methyllithium in ether (Scheme 3). The expected diols **12** and **13** were obtained in 64% yield and 84% d.e. (in favor of *meso* **13**), in perfect agreement with the literature results, obtained in THF.[17]



Scheme 3.

Synthesis of cyclic acetals. We have recently reported[18] that dimethylacetal **16** can be prepared (as a *E*/*Z* mixture ≈70:30) in very high yields from isoprenyl acetate **14** following the efficient method of Venturello and colleagues[19] (Scheme 4). The poor control of the double bond configuration in **15** and **16** is meaningless here since we have shown in similar situations that this parameter has



Scheme 4.

little, if any, effect on the stereocontrol of the diene resulting from the elimination reaction.[20] Also, we retained a *p*-methoxybenzyl (PMB) ether substituent as an easily removable protecting group from the perspective of possible applications of these synthons to sugars and carbasugars synthesis.

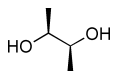
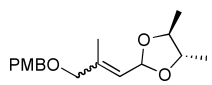
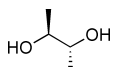
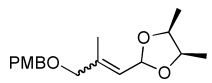
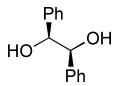
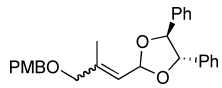
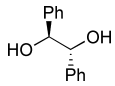
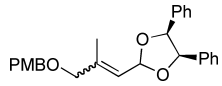
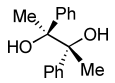
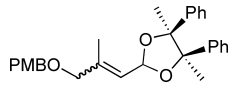
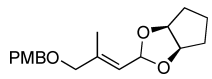
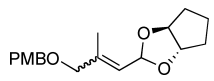
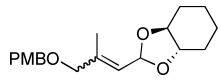
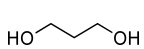
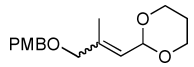
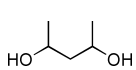
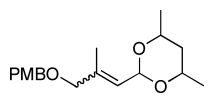
In Venturello's procedure, the reacting alcohol (methanol) is introduced as a co-solvent to THF. This can be a drawback when it comes to heavy (or expensive) diols that, if used in large excess, render the purification stage tedious or the experiment exceedingly costly. We, therefore, resorted to a *trans*-acetalisation procedure expected to favor the transformation of acyclic **16** to cyclic ketals **17**. Practically, this was achieved in most cases by simply adding 1.2–2.2 equiv. of diol to acetals **16** in the presence of trace amounts of dry camphorsulfonic acid (CSA) and 2,2-dimethoxypropane.[21] A few alterations to this general procedure turned out to be necessary for some diols, and they are presented below.

Three different families of chiral (racemic) or achiral 5, 6 and 7-membered cyclic acetals (dioxolanes, dioxanes and dioxepanes) were thus prepared, as well as one example of nine-membered acetal (dioxonane), from either commercially available diols or those described above (Tables 2 and 4).

The results in Table 2 deserve some comments. First, the yields were in general relatively good, and in all cases the configuration of the double bond remained unchanged. All the acetals derived from *meso* diols were obtained as a mixture of stereoisomers, the acetalic proton being oriented *cis* or *trans* to the two *syn* X substituents of the heterocycle (Fig. 5). The acetalic carbon is in this case pseudo-asymmetric (it bears two identical substituents but one is *R* and the other *S*) and can be defined as *r* or *s*,[22] keeping in mind that the *R* center has priority over the *S* one. The proportions between these pseudo-diasteromers as well as the configuration of the major one could be determined in a few cases through NOESY experiments (Table 3). Obviously, acetals derived from *anti* diols do not exhibit this pseudo-asymmetry feature.

Entries 7 and 8 of Table 2 show that the *trans*-relationship in 1,2-diols borne by five or six-membered rings is not compatible with the dioxolane ring closure. The strain generated by such *trans* ring-junctions is probably at the

Table 2. Chiral (racemic) and *meso* diox(ol)anes prepared from acetal **16** (Scheme 4)

Entry	Diol	Equiv.	Acetal	Compound no.	Yield (%)
1		1.5		**17a**	100
2		1.2		**17b**	59
3		1.2		**17c**	70
4		1.2		**17d**	53
5		1.2		**17e**	43
6[a]		1.5		**17f**	64
7		1.5		**17g**	0
8		1.7		**17h**	0
9		2.2		**17i**	80
10		1.3		**17j**	73

[a] The *trans*-acetalisation was run on pure (*E*)-**16** in this case.

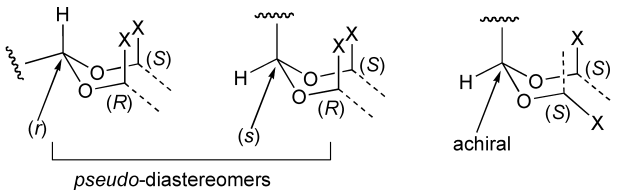


Figure 5. Symmetry elements in acetals derived from *meso* (left) or C_2-symmetrical (right) diols.

Table 3. *cis*/*trans* Ratios in acetals **17** derived from *meso* diols

Entry	Acetal	*cis*/*trans*
1	**17b**	77:23
2	**17k**	50:50
3	**17p**	80:20
4	**17u**	66:33 (*E*) 50:50 (*Z*)

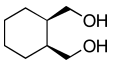
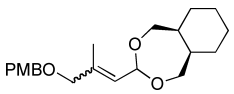
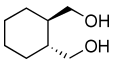
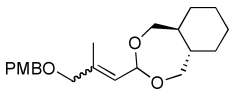
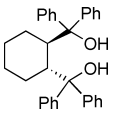
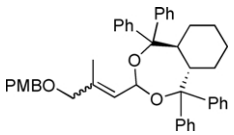
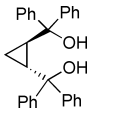
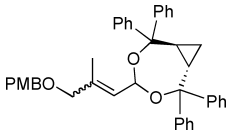
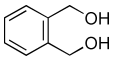
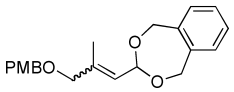
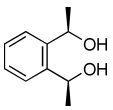
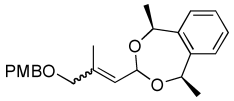
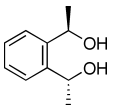
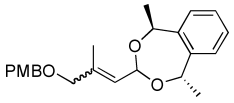
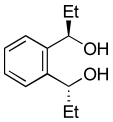
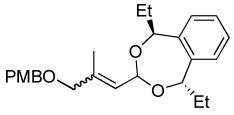
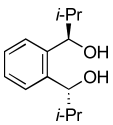
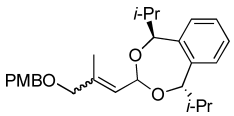
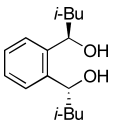
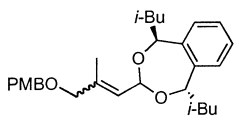
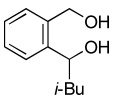
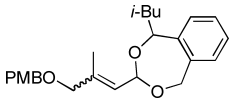
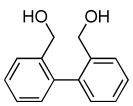
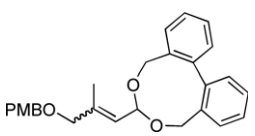
origin of this failure, as inferred from a semiempirical (AM1) study.[23]

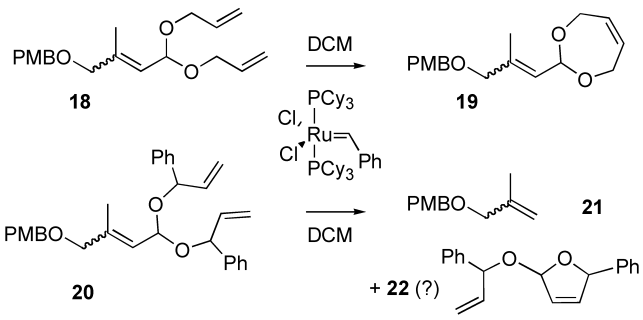
When it comes to dioxepanes and dioxonanes (Table 4), the same protocol can be followed, albeit the use of dimethoxypropane is not recommended in entries 6, 7, 10, and 11 since it reacts with the corresponding diols, yielding an entangled mixture of acetals. The *trans*-acetalisation with the two TADDOL-like diols (entries 3 and 4) failed, probably because of the high stabilization of the triply-benzylic intermediate cations. Entries 6–10 rely on dibenzylic diols **8** and **9** described above. The *trans*-acetalisation yields tended to decrease with the increasing size of the benzylic substituents. One unsymmetrical acetal (**17u**, entry 11) and one dioxonane (**17v**, entry 12) were also prepared, respectively, from mono-alkylated diol **10d** or from commercially available 2,2′-biphenyldimethanol, a model for biarylic diols featuring a chiral axis. With **10d**, the standard *trans*-acetalisation procedure proved efficient, while it did not yield any identified product in the case of biphenyldimethanol. The classical sulfuric acid catalysis and Dean–Stark trapping at reflux of benzene[24] also proved too harsh for **16**. Actually, only a few syntheses of such acetals have been reported. Finally, a methanol/dichloromethane azeotropic distillation in presence of trace amounts of acetic acid,[25] afforded **17v** in 51% yield. The very fragile allylic acetals **18** and **20** were obtained following this same procedure in 53 and 60% conversion, respectively. Actually, **18** was prepared in an attempt to access dioxepine **19** by a ring closing metathesis (RCM). We resorted for this step to the use of a ruthenium carbene complex (Grubb's catalyst)[26] that has previous been reported to perform RCM of other acid sensitive substrates.[25] Unfortunately, it led here to a partial or total failure (Scheme 5). Dioxepine **19** was indeed obtained, but in only 27% after 12 h at room temperature.

Its dibenzylic analogue **20** led to a complex mixture out of which only olefin **21** could be characterized. This by-product suggests that the RCM takes place rather between the trisubstituted inner double bond and one of the terminal allyl groups than between the two acetalic appendages. The complementary cyclic mixed-acetal **22** should therefore be obtained as well, although we did not isolate this fragile looking compound.

The origin of this unexpected difficulty probably stems from the strong preference for a five-membered ring closing over a seven-membered one. A comparable competition, leading

Table 4. Chiral (racemic) and *meso* dioxepanes and dioxonane prepared from acetal **16** (Scheme 4)

Entry	Diol	Equiv.	Acetal	No.	Yield (%)
1		1.5		**17k**	61
2		1.3		**17l**	54
3		1.3		**17m**	0
4		1.2		**17n**	0
5		1.2		**17o**	70
6		1.5		**17p**	81
7		1.5		**17q**	60
8		1.5		**17r**	67
9		1.5		**17s**	50
10		1.5		**17t**	52
11		1.5		**17u**	68
12		2.0		**17v**	51



Scheme 5.

to a similar conclusion, has been published by Harrity and colleagues lately.[25]

3. Conclusion

The results presented in this paper describe a family of dibenzylic diols prepared by double addition of alkylmagnesium reagents onto *o*-phthalaldehyde. This procedure provided, in most cases, the D,L diastereomers as the major products. These compounds, together with a set of homemade or commercially available 1,2, 1,3 or 1,4 diols were reacted with α,β-unsaturated dimethyl acetal **16**. A standard acidic *trans*-acetalisation procedure provided the expected dioxolanes, dioxanes and dioxepanes in medium to good yields. For dioxonane or allylic acetals, an azeotropic trapping of methanol was found necessary. An attempt to cyclize the latter allylic acetals using Grubb's catalyst turned out unsuccessful. Despite this final failure, 18 different cyclic acetals were prepared that are potential substrates for the base-induced conjugated ring-fission, the transformation of the corresponding alcoholates into trienic substrates as well as the thermal and hyperbaric IMDA final step. These results will be reported in a near future.

4. Experimental

4.1. General remarks

^{1}H NMR spectra were recorded at 300 MHz and ^{13}C NMR spectra at 75 MHz; chemical shift (δ) are given in parts per million (ppm) and the coupling constants (J) in Hertz. The solvent was deuterochloroform or deuterobenzene. IR spectra were recorded by transmission. Gas chromatography analysis were performed on high resolution DB-1 or HP-5MS columns (30 m×0.25 mm×0.25 μm). GC/MS analysis were performed on instruments equipped with the same columns. The chiral gas chromatography runs were performed on a Supelco β-Dex column (15 m× 0.25 mm×0.25 μm). The mass spectra under electron impact conditions (EI) were recorded at 70 eV ionizing potential; methane (CH_4), isobutane (*t*-BuH), or ammonia (NH_3) were used for chemical ionization (CI). The silica gel used for flash chromatography was 230–400 Mesh. All reagents were of reagent grade and were used as such or distilled prior to use.

4.1.1. *anti*-Cyclohexane dimethanol (3). A solution of diester **2** (2.00 g, 1 equiv., 9.99 mmol, prepared refluxing commercial *anti*-cyclohexane-1,2-dicarboxylic acid in methanol containing camphorsulfonic acid) in ether (50 mL) was added to a dispersion of LAH (1.52 g, 3.6 equiv., 36.3 mmol) in ether (20 mL). After 2 h, H_2O (2 mL), NaOH 4 M (2 mL) and H_2O (6 mL) were added successively into the reaction mixture. The aqueous phase was extracted by ether (3×15 mL), the combined organic phases were dried (Na_2SO_4) and evaporated under reduce pressure to afford 1.38 g (96%) of diol **3** as a white solid (mp=60 °C) pure enough to be used as such. ν_{max} (film)/cm^{-1} 3301, 2914, 2848, 1428, 1020. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm)=1.00 (m, 2H), 1.23 (m, 4H), 1.58 (d, J=13.6 Hz, 2H), 1.71 (m, 2H), 3.47 (dd, J=6.4, 10.7 Hz, 2H), 3.57 (d, J=10.7 Hz, 2H), 4.09 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm)=26.5, 30.2, 45.2, 68.1. EIMS (70 eV) *m/z* 144 ($M^{+\cdot}$, 0.3), 126 ($M^{+\cdot}-18$, 11), 108 (8), 96 (100), 81 (67). Anal. Calcd for $C_8H_{16}O_2$: C, 66.63%; H, 11.18%. Found: C, 66.58%; H, 11.26%.

4.1.2. 1,2-Bis(1-hydroxyethyl)benzene (8a, 9a). A solution of *o*-phthalaldehyde (4.0 g, 1 equiv., 29.8 mmol) in ether (30 mL), was added, at room temperature, to a solution of MeLi (65 mL, 3.5 equiv., 1.6 mol L^{-1}, 104.3 mmol) in ether (30 mL). The reaction mixture was stirred for 3 h, before H_2O (10 mL) then HCl 1 N (20 mL) were added carefully. The pH of the aqueous phase was brought to 5 then extracted with ether (3×20 mL) and the combined organic phases were dried (Na_2SO_4) and evaporated under reduce pressure. The ratio **8a/9a/10a** was found to be, in the crude mixture, 40:60:0 according to GC. Most of the *syn* isomer was selectively precipitated out of a 60:40, heptane/AcOEt mixture. The two isomers in the residual liquor were separated by flash chromatography (eluting with heptane/AcOEt, 40:60). The total amount in diols (**8a**+**9a**) was 4.5 g (92%), the *syn* isomer being isolated as a white solid (mp=90 °C) and the *anti* one as a colorless oil.

ν_{max} (film)/cm^{-1} 3354, 2974, 2928, 1448, 1372, 1068, 734. *syn* Isomer **8a**. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm)=1.54 (d, J=6.6 Hz, 6H), 2.53 (bs, 2H), 5.25 (q, J=6.6 Hz, 2H), 7.32 (m, 2H), 7.50 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm)=23.7, 65.9, 125.7, 128.4, 142.4. *anti* Isomer **9a**. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm)=1.55 (d, J=6.4 Hz, 6H), 2.16 (bs, 2H), 5.25 (q, J=6.4 Hz, 2H), 7.29 (m, 2H), 7.47 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm)=24.8, 67.5, 126.5, 128.1, 142.6. EIMS (70 eV) *m/z* 148 ($M^{+\cdot}-18$, 32), 133 (100), 105 (58), 77 (54). Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26%; H, 8.49%. Found: C, 72.14%; H, 8.85%.

4.1.3. 1,2-Bis(1-hydroxypropyl)benzene (8b, 9b). *Direct procedure*. A solution of ethylmagnesium bromide (1.8 mL, 3 M, 3.5 equiv., 5.2 mmol) in ether was added dropwise, at room temperature, to a solution of *o*-phthalaldehyde (0.20 g, 1 equiv., 1.5 mmol) also in ether (3 mL). The reaction mixture was stirred for 1 h and 30 min. Then H_2O (2 mL) and HCl 1 N (4 mL) were added carefully. The pH of the aqueous phase was brought to 5 and extracted with ether (3×5 mL). The resulting organic phase was dried (Na_2SO_4) and evaporated under reduce pressure. The ratio **8b/9b/10b** was found to be, in the crude mixture, 62:21:17 according to GC. A flash chromatography afforded the pure *anti* isomer **8b** as a white solid (mp=77 °C) The others diols were not

separated and a total of 0.18 g **8b**+**9b**+**10b** was recovered (63%).

Compound **8b**. ν_{max} (film)/cm^{-1} 3286, 2964, 1456, 1326, 972, 754. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm)=0.95 (t, J=7.5 Hz, 6H), 1.81 (m, 4H), 2.40 (s, 2H), 4.88 (t, J=5.8 Hz, 2H), 7.26 (m, 2H), 7.39 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm)=11.1, 31.8, 72.9, 126.8, 128.1, 141.8. EIMS (70 eV) m/z 176 ($M^{+\cdot}-18$, 4), 165 (24), 147 (100), 129 (69), 91 (39). Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19%; H, 9.34%. Found: C, 74.21%; H, 9.39%.

Compound **9b**. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm)=0.89 (t, J=7.4 Hz, 6H), 1.72 (m, 4H), 2.69 (s, 2H), 4.74 (t, J=6.0 Hz, 2H), 7.23 (m, 4H).

Compound **10b**. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm)=0.91 (t, J=9.0 Hz, 6H), 1.69 (s, 1H), 1.82 (m, 2H), 2.62 (s, 1H), 4.60 (d, J=12.1 Hz, 1H), 4.71 (d, J=12.1 Hz, 1H), 4.78 (t, J=7.1 Hz, 1H), 7.20 (m, 4H).

4.1.4. 1,2-Bis(1-hydroxy-2-methylpropyl)benzene (8c, 9c) and 1-(2-hydroxymethyl-phenyl)-2-methyl-propan-1-ol (10c). These compounds were prepared as above following either a direct or inverse procedure, in ether or THF and with *i*-propylmagnesium chloride or bromide (See Table 1).

Direct procedure in ether with isopropylmagnesium chloride. To a solution of *o*-phthalaldehyde (0.20 g, 1 equiv., 1.5 mmol) in ether (4 mL) was added, dropwise and at room temperature, a solution of isopropylmagnesium chloride (2.8 mL, 3.5 equiv., 2.0 M, 5.2 mmol). After 1.5 h of reaction and the same treatment, a GC analysis of the crude mixture led to a **8c/9c/10c** ratio=59:10:31. A flash chromatography (eluting with heptane/AcOEt, 60:40) afforded 23 mg of alcohol **10c**, as a yellowish oil, 94 mg of diol *anti* **8c**, as a colorless oil and 10 mg of its *syn* isomer **9c**, as a white solid (mp=70 °C). Total amount of products: 1.1 mmol (72%).

Inverse procedure in THF with isopropylmagnesium bromide. The isopropylmagnesium bromide was prepared from 2-bromopropane (0.55 g, 3 equiv., 4.5 mmol) in THF (3 mL) and 0.11 g of magnesium shaves (3 equiv., 4.5 mmol) in THF (1 mL). After 1 h of stirring at room temperature, a solution of *o*-phthalaldehyde (0.20 g, 1 equiv., 1.5 mmol) in THF (3 mL) was added dropwise. The same work-up and analysis led to a **8c/9c/10c** ratio=65:14:21 in an overall yield of 51%.

Compound **8c/9c**. ν_{max} (film)/cm^{-1} 3420, 3064, 2958, 2872, 1468, 1002, 760. *anti* Isomer **8c**. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm)=0.79 (d, J=6.8 Hz, 6H), 1.07 (d, J=6.4 Hz, 6H), 1.98 (s, 2H), 2.02 (m, 2H), 4.64 (d, J=7.9 Hz, 2H), 7.27 (m, 2H), 7.40 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm)=19.0, 20.0, 35.4, 76.6, 127.0, 127.9, 141.5. *syn* Isomer **9c**. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm)=0.75 (d, J=6.8 Hz, 6H), 1.10 (d, J=6.4 Hz, 6H), 2.10 (m, 2H), 2.15 (s, 2H), 4.61 (d, J=8.3 Hz, 2H), 7.28 (m, 2H), 7.41 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm)=19.3, 20.3, 34.5, 75.7, 127.1, 128.2, 141.6. CIMS (CH_4) m/z 205 (MH^+-18, 39), 187 (15), 161 (46), 143 (55), 91 (100). Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.63%; H, 9.97%. Found: C, 75.76%; H, 10.09%.

Compound **10c**. ν_{max} (film)/cm^{-1} 3453, 3064, 2958, 1468, 1013, 759. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm)=0.76 (d, J=6.8 Hz, 3H), 1.11 (d, J=6.4 Hz, 3H), 2.11 (m, 1H), 2.49 (s, 2H), 4.53 (d, J=8.3 Hz, 1H), 4.73 (s, 2H), 7.33 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm)=19.6, 20.0, 34.4, 63.4, 77.7, 127.9, 128.0, 128.5, 129.9, 138.3, 142.3. CIMS (CH_4) m/z 162 ($M^{+\cdot}-18$, 29), 161 (76), 143 (33), 119 (87), 91 (100). Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30%; H, 8.95%. Found: C, 73.25%; H, 9.49%.

4.1.5. 1,2-Bis(1-hydroxy-3-methylbutyl)benzene (8d, 9d) and 1-(2-hydroxymethyl-phenyl)-3-methyl-butan-1-ol (10d). *Inverse procedure*. A solution of *o*-phthalaldehyde (2.00 g, 1 equiv., 14.9 mmol) in ether (30 mL) was added to a solution of isobutylmagnesium chloride (30 mL, 4 equiv., 2.0 mol L^{-1}, 60.0 mmol) in the same solvent (20 mL). After 1.5 h of reaction, a work-up and analysis as above led to a **8c/9c/10c** ratio=24:10:66. A flash chromatography (eluting with heptane/AcOEt, 60:40) afforded 1.60 g of **10d**, as a white solid (mp=85 °C), 750 mg of diol *anti* **8d**, as a white solid (mp=79 °C) and 340 mg of diol *syn* **9d**, also as a white solid (mp=51 °C) in an overall yield of 84%.

Compound **8d/9d**. ν_{max} (film)/cm^{-1} 3317, 3061, 2952, 2867, 1462, 1054, 760. *anti* Isomer **8d**. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm)=0.97 (d, J=6.4 Hz, 6H), 0.99 (d, J=7.1 Hz, 6H), 1.51 (m, 2H), 1.78 (m, 2H), 1.84 (m, 2H), 1.96 (d, J=3.4 Hz, 2H), 5.08 (dt, J=3.4, 9.0 Hz, 2H), 7.27 (m, 2H), 7.44 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm)=22.3, 23.9, 25.5, 48.5, 69.3, 126.4, 128.1, 142.1. *syn* Isomer **9d**. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm)=0.97 (d, J=6.4 Hz, 6H), 0.99 (d, J=7.1 Hz, 6H), 1.46 (m, 2H), 1.83 (m, 4H), 1.95 (d, J=3.4 Hz, 2H), 5.16 (dt, J=3.4, 9.2 Hz, 2H), 7.30 (m, 2H), 7.48 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm)=22.3, 24.0, 25.5, 48.5, 67.9, 126.2, 128.3, 142.2. CIMS (CH_4) m/z 233 (MH^+-18, 9), 231 (21), 215 (83), 175 (82), 159 (100), 147 (59). Anal. Calcd for $C_{16}H_{26}O_2$: C, 76.75%; H, 10.47%. Found: C, 77.21%; H, 10.57%.

Compound **10d**. ν_{max} (film)/cm^{-1} 3295, 2954, 2866, 1463, 1041, 763. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm)=0.97 (d, J=6.4 Hz, 3H), 0.98 (d, J=6.4 Hz, 3H), 1.61 (m, 1H), 1.83 (m, 2H), 2.47 (bs, 1H), 2.53 (bs, 1H), 4.70 (dd, J=4.5, 12.1 Hz, 1H), 4.80 (dd, J=3.8, 12.1 Hz, 1H), 5.03 (bs, 1H), 7.3–7.5 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm)=22.5, 23.8, 25.5, 46.6, 64.3, 70.0, 126.9, 128.2, 128.9, 130.2, 138.4, 143.3. CIMS (CH_4) m/z 191 (10), 175 (21), 159 (MH^+-36, 100), 119 (37). Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19%; H, 9.34%. Found: C, 74.24%; H, 9.52%.

4.1.6. 1,2-Bis(1-hydroxy-3,3-dimethylbutyl)benzene (8e). *Inverse procedure*. The neopentylmagnesium bromide was prepared from 1-bromo-3,3-dimethyl-butane (10.1 g, 3 equiv., 66.9 mmol) in ether (20 mL) and 1.63 g of magnesium shaves (3 equiv., 67.1 mmol) in THF (20 mL). After 1 h of stirring at room temperature, a solution of *o*-phthalaldehyde (3.00 g, 1 equiv., 22.4 mmol) in ether (20 mL) was added dropwise. After 2 h, the reaction was

quenched by 50 mL of saturated ammonium chloride; the rest of the work-up was as above and led to a complex mixture out of which a flash chromatography on silica gel (eluting with cyclohexane/AcOEt, 60:40 mixture) afforded 1.00 g *anti* diol **8e** as a colorless oil (16%). ν_{max} (film)/cm^{-1} 3418, 2952, 2868, 1476, 1364, 1058, 734. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm)=1.04 (m, 18H), 1.61 (dd, J=2.6, 14.7 Hz, 2H), 1.81 (dd, J=9.0, 14.7 Hz, 2H), 1.98 (s, 2H), 5.18 (d, J=9.0 Hz, 2H), 7.26 (m, 2H), 7.44 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm)=30.7, 31.3, 52.8, 69.2, 126.7, 128.0, 142.9. CIMS (CH_4) m/z 261 (MH^+-18, 5), 243 (MH^+-36, 11), 189 (100), 173 (21), 161 (18), 133 (28).

4.1.7. 3-*t*-Butyl-1,3-dihydro-isobenzofuran-1-ol (B with R=*t*-Bu and M=H). *Inverse procedure*. A solution of *o*-phthalaldehyde (0.20 g, 1 equiv., 1.5 mmol) in ether (3 mL) was added dropwise and at room temperature, to a solution of *t*-butylmagnesium chloride (2.6 mL, 2 M, 3.5 equiv., 5.2 mmol) in ether. After 1.5 h of reaction, a work-up and analysis as above led to a yellow oil that was purified by flash chromatography on silica gel (eluting with cyclohexane/AcOEt, 70:30 mixture). A pale yellow oil (235 mg), identified as an unseparable mixture (75:25) of the *syn* and *anti* diastereomers of lactol **B**, was recovered in an overall yield of 83%.

syn Isomer. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm)=0.89 (s, 9H), 3.00 (d, J=8.7 Hz, 1H), 4.98 (d, J=2.3 Hz, 1H), 6.40 (dd, J=8.7, 2.3 Hz, 1H), 7.20 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm)=26.0, 36.5, 91.5, 101.0, 123.0 -141.0 unidentified aromatic peaks together with isomer *anti*.

anti Isomer. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm)=0.98 (s, 9H), 2.99 (d, J=8.3 Hz, 1H), 4.80 (s, 1H), 6.31 (d, J=8.3 Hz, 1H), 7.22 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm)=26.4, 35.0, 92.2, 100.0, 123.0–141.0 unidentified aromatic peaks together with isomer *syn*.

4.1.8. 2,3-Diphenyl-butane-2,3-diol (12 and 13). To a solution of 1,2-diphenyl-ethane-1,2-dione (benzil, 2.5 g, 1 equiv., 11.9 mmol) in ether (20 mL), were added 20 mL of a solution of MeLi/LiBr (1:1) in ether at 0 °C. The reaction mixture was then stirred at room temperature for 2 h and 30 min. Next, 20 mL of HCl (3 M) were added and the resulting aqueous phase was extracted by ether (3×15 mL). The combined organic solutions were dried (Na_2SO_4) and evaporated under reduce pressure. The residue was precipitated in heptane/ether (80:20) to afford 1.85 g (64%) of a mixture of diols **12** and **13** as a white solid (mp=111 °C) and with a *syn*/*anti*: 92:8 ratio as determined by NMR. ν_{max} (film)/cm^{-1} 3508, 3058, 2982, 1598, 1445, 900. *syn* Isomer **12**. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm)=1.58 (s, 6H), 2.27 (bs, 2H), 7.23 (m, 10H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm)=25.5, 79.0, 127.3, 127.7, 127.8, 144.2. *anti* Isomer **13**. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm)=1.50 (s, 6H), 2.27 (bs, 2H), 7.23 (m, 10H). EIMS (70 eV) m/z 224 ($M^{+\cdot}-18$, 4), 206 (M^+-36, 11), 181 (73), 165 (15), 121 (100), 105 (32). Anal. Calcd for $C_{16}H_{18}O_2$: C, 79.31%; H, 7.49%. Found: C, 79.13%; H, 7.61%.

4.2. General procedure for cyclic acetals 17

To a solution of dimethylacetal **16** in dichloromethane, were added 1.2–1.5 equiv. of appropriate diol in the presence of a catalytic amount of camphorsulfonic acid (CSA) and of 2,2-dimethoxypropane (when precised). The reaction mixture was stirred at room temperature for 2 h and a saturated solution of sodium bicarbonate was added. The aqueous phase was extracted with dichloromethane and the resulting organic solution was dried ($MgSO_4$) and evaporated under reduce pressure to afford the crude product. A flash chromatography on silica gel (eluting with an AcOEt/heptane, 30:70 mixture) afforded the pure cyclic acetals. The *E*/*Z* ratio of the double bond remained unchanged under these conditions.

4.2.1. 2-[2-Methyl-3-(*p*-methoxy-benzyloxy)-prop-2-enyl]-4,5-*anti*-dimethyl-[1,3]dioxolane (17a). The above procedure was applied to 500 mg (1 equiv., 1.88 mmol) of dimethylacetal **16** (*E*/*Z*, 70:30) and 250 mg (1.5 equiv., 2.77 mmol) of *anti*-butane-2,3-diol in dichloromethane (10 mL) in presence of 0.1 mL of 2,2-dimethoxypropane. The reaction was monitored by TLC and upon completion, a solution of saturated $NaHCO_3$ (3 mL) was added. After flash chromatography, 550 mg (100%) of dioxolane **17a** were obtained as a colorless oil (*E*/*Z*, 70:30). ν_{max} (film)/cm^{-1} 2972, 2864, 1680, 1612, 1512, 1248, 1080, 820. *E* isomer. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm)=1.12–1.32 (m, 6H), 1.77 (s, 3H), 3.62 (m, 2H), 3.77 (s, 3H), 3.88 (s, 2H), 4.37 (s, 2H), 5.52 (d, J=7.3 Hz, 1H), 5.69 (d, J=7.3 Hz, 1H), 6.84 (d, J=8.8 Hz, 2H), 7.23 (d, J=8.8 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm)=14.5, 17.3, 17.6, 55.6, 71.7, 74.7, 78.6, 80.2, 99.5, 114.1, 124.5, 129.7, 130.5, 140.8, 159.6. *Z* isomer. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm)=1.12–1.32 (m, 6H), 1.81 (s, 3H), 3.62 (m, 2H), 3.77 (s, 3H), 4.05 (s, 2H), 4.37 (s, 2H), 5.43 (d, J=7.3 Hz, 1H), 5.63 (d, J=7.3 Hz, 1H), 6.84 (d, J=8.8 Hz, 2H), 7.23 (d, J=8.8 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm)=17.5, 21.8, 55.6, 68.0, 71.7, 78.6, 80.2, 98.1, 114.1, 126.7, 129.7, 130.5, 141.2, 159.6. EIMS (70 eV) m/z 292 ($M^{+\cdot}$, 1.8), 121 (100). Anal. Calcd for $C_{17}H_{24}O_4$: C, 69.84%; H, 8.27%. Found: C, 69.98%; H, 8.83%.

4.2.2. 2-[2-Methyl-3-(*p*-methoxy-benzyloxy)-prop-2-enyl]-4,5-*syn*-dimethyl-[1,3]dioxolane (17b). The above procedure was applied to 2.0 g (1 equiv., 7.51 mmol) of dimethylacetal **16** (*E*/*Z*, 70:30) and 813 mg (1.2 equiv., 9.03 mmol) of *syn*-butane-2,3-diol in dichloromethane (20 mL) in presence of 0.2 mL of 2,2-dimethoxypropane. The reaction was monitored by TLC and upon completion, a solution of saturated $NaHCO_3$ (4 mL) was added. After flash chromatography, 1.30 g (59%) of dioxolane **17b** were obtained as a colorless oil (*E*/*Z*, 70:30) as two epimers. For the *E* isomer, a *syn*/*anti* ratio=73:27 was measured. ν_{max} (film)/cm^{-1} 2976, 2908, 1684, 1612, 1514, 1248, 1084, 820. *E anti* isomer. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm)=1.17 (d, J=6.0 Hz, 6H), 1.77 (d, J=1.0 Hz, 3H), 3.79 (s, 3H), 3.88 (s, 2H), 4.14 (m, 2H), 4.39 (s, 2H), 5.51 (dd, J=7.5, 1.0 Hz, 1H), 5.57 (d, J=7.5 Hz, 1H), 6.86 (d, J=8.6 Hz, 2H), 7.25 (d, J=8.6 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm)=14.6, 15.9, 55.7, 71.9, 74.9, 75.0, 98.9, 114.1, 124.4, 129.7, 130.8, 141.0, 159.5. Other isomers: ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm)=1.1–1.3 (6H), 1.7–1.9 (3H), 3.79 (s, 3H), 3.8–4.0 (2H), 4.1–4.3 (2H), 4.39 (s, 2H), 5.4–5.6 (1H), 6.86 (d, J=8.6 Hz, 2H), 7.25 (d, J=8.6 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm)=14.5–21.8,

15.9, 52.7–55.7, 71.9, 68.1–74.9, 75.0, 98.1–98.9, 114.1, 124–128, 129.7, 130.8, 139–141, 159.5. EIMS (70 eV) *m/z* 292 ($M^{+\cdot}$, 1), 219 (2), 155 (23), 121 (100). Anal. Calcd for $C_{17}H_{24}O_4$: C, 69.84%; H, 8.27%. Found: C, 69.73%; H, 8.54%.

4.2.3. 2-[2-Methyl-3-(*p*-methoxy-benzyloxy)-prop-2-enyl]-4,5-*anti*-diphenyl-[1,3]dioxolane (17c). The above procedure was applied to 1.0 g (1 equiv., 3.75 mmol) of dimethylacetal **16** (*E*/*Z*, 70:30) and 965 mg (1.2 equiv., 4.50 mmol) of *anti*-1,2-diphenylethane-1,2-diol in dichloromethane (10 mL) in presence of 0.1 mL of 2,2-dimethoxypropane. The reaction was monitored by TLC and upon completion, a solution of saturated $NaHCO_3$ (4 mL) was added. After flash chromatography, 1.11 g (70%) of dioxolane **17c** were obtained as a colorless oil (*E*/*Z*, 70:30). ν_{max} (film)/cm^{-1} 3032, 2918, 1684, 1612, 1512, 1248, 1068, 820. *E* isomer. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm)=1.95 (s, 3H), 3.82 (s, 3H), 4.04 (s, 2H), 4.52 (s, 2H), 4.87 (s, 2H), 5.92 (d, *J*=7.2 Hz, 1H), 6.27 (d, *J*=7.2 Hz, 1H), 6.95 (d, *J*=8.7 Hz, 2H), 7.34 (m, 12H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm)=14.9, 55.7, 72.1, 74.8, 85.3, 87.2, 101.5, 114.3, 123.7, 126.8, 127.4, 128.6, 128.96, 129.04, 129.8, 130.8, 137.3, 138.9, 141.4, 159.7. *Z* isomer. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm)=1.99 (s, 3H), 3.82 (s, 3H), 4.24 (s, 2H), 4.52 (s, 2H), 4.81 (d, *J*=7.5 Hz, 1H), 4.86 (d, *J*=7.5 Hz, 1H), 5.81 (d, *J*=7.2 Hz, 1H), 6.20 (d, *J*=7.2 Hz, 1H), 6.95 (d, *J*=8.7 Hz, 2H), 7.34 (m, 12H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm)=22.1, 55.7, 68.5, 71.9, 85.3, 87.2, 100.7, 114.3, 126.2, 126.8, 127.4, 128.6, 128.96, 129.04, 129.9, 130.8, 137.3, 138.9, 141.6, 159.7. CIMS (*i*-BuH) *m/z* 417 (MH^+, 9), 197 (12), 121 (100). Anal. Calcd for $C_{27}H_{28}O_4$: C, 77.86%; H, 6.78%. Found: C, 77.92%; H, 6.94%.

4.2.4. 2-[2-Methyl-3-(*p*-methoxy-benzyloxy)-prop-2-enyl]-4,5-*syn*-diphenyl-[1,3]dioxolane (17d). The above procedure was applied to 2.0 g (1 equiv., 7.51 mmol) of dimethylacetal **16** (*E*/*Z*, 70:30) and 1.93 g (1.2 equiv., 9.01 mmol) of *syn*-1,2-diphenylethane-1,2-diol in dichloromethane (20 mL) in presence of 0.2 mL of 2,2-dimethoxypropane. The reaction was monitored by TLC and upon completion, a solution of saturated $NaHCO_3$ (4 mL) was added. After flash chromatography, 1.65 g (53%) of dioxolane **17d** were obtained as a colorless oil (*E*/*Z*, 70:30) as two epimers (90:10). Only the major isomer could be isolated. ν_{max} (film)/cm^{-1} 3030, 2914, 1686, 1612, 1512, 1248, 1066, 820. *E* isomer. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm)=1.92 (s, 3H), 3.82 (s, 3H), 4.04 (s, 2H), 4.52 (s, 2H), 5.37 (s, 2H), 6.01 (s, 2H), 6.93 (d, *J*=8.6 Hz, 2H), 7.05 (m, 10H), 7.35 (d, *J*=8.6 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm)=15.0, 55.7, 72.1, 74.8, 82.8, 100.4, 114.3, 122.6, 127.4, 127.8, 128.0, 130.1, 130.7, 137.6, 142.4, 159.7. *Z* isomer. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm)=2.00 (s, 3H), 3.81 (s, 3H), 4.21 (s, 2H), 4.48 (s, 2H), 5.47 (s, 2H), 5.92 (s, 2H), 6.93 (d, *J*=8.6 Hz, 2H), 7.05 (m, 10H), 7.35 (d, *J*=8.6 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm)=22.0, 55.7, 67.5, 71.9, 81.7, 99.6, 114.3, 124.6, 127.2, 127.8, 128.1, 129.8, 130.7, 137.6, 142.4, 159.7. CIMS (NH_3) *m/z* 434 ($M+NH_4^+$, 16), 238 (47), 121 (100). Anal. Calcd for $C_{27}H_{28}O_4$: C, 77.86%; H, 6.78%. Found: C, 77.78%; H, 7.04%.

4.2.5. 2-[3-(4-Methoxy-benzyloxy)-2-methyl-propenyl]-4,5-*syn*-dimethyl-4,5-diphenyl-[1,3]dioxolane (17e). The above procedure was applied to 1.0 g (1 equiv., 3.76 mmol) of dimethylacetal **16** (*E*/*Z*, 70:30) and 1.2 g (1.3 equiv., 4.96 mmol)of *syn*-1,2-diphenyl-1,2-dimethylethane-1,2-diol in dichloromethane (20 mL). The reaction was monitored by TLC and upon completion, a solution of saturated $NaHCO_3$ (4 mL) was added. After flash chromatography, 720 mg (43%) of dioxolane **17e** were obtained as a colorless oil (*E*/*Z*, 70:30) and as a single (undetermined) epimer. ν_{max} (film)/cm^{-1} 3058, 2994, 2922, 2854, 1612, 1514, 1248, 1072, 820, 698. *E* isomer. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm)=1.81 (s, 6H), 1.94 (d, *J*=1.1 Hz, 3H), 3.82 (s, 3H), 4.04 (s, 2H), 4.51 (s, 2H), 6.04 (d, *J*=7.2 Hz, 1H), 6.24 (d, *J*=7.2 Hz, 1H), 6.91 (d, *J*=8.7 Hz, 2H), 7.00 (m, 10H), 7.32 (d, *J*=8.7 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm)=15.0, 22.9, 55.7, 71.9, 74.9, 87.8, 97.1, 114.2, 123.9, 126.4, 126.8, 127.5, 129.8, 130.8, 141.6, 143.8, 159.6. *Z* isomer. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm)=1.74 (s, 6H), 1.99 (d, *J*=1.1 Hz, 3H), 3.80 (s, 3H), 4.22 (s, 2H), 4.47 (s, 2H), 5.94 (d, *J*=6.8 Hz, 1H), 6.13 (d, *J*=6.8 Hz, 1H), 6.91 (d, *J*=8.7 Hz, 2H), 7.00 (m, 10H), 7.32 (d, *J*=8.7 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm)=22.0, 22.9, 55.7, 68.4, 71.7, 87.8, 96.4, 114.2, 125.9, 126.4, 126.8, 127.5, 129.8, 130.8, 141.6, 143.8, 159.6.

4.2.6. 2-[3-(4-Methoxy-benzyloxy)-2-methyl-propenyl]-tetrahydro-cyclopenta[1,3]dioxolane (17f). The above procedure was applied to 1.0 g (1 equiv., 3.76 mmol) of pure *E* dimethylacetal **16** and 575 mg (1.5 equiv., 5.63 mmol) of *syn*-1,2-cyclopentanediol in dichloromethane (15 mL) in the presence of 0.1 mL of 2,2-dimethoxypropane. The reaction was monitored by TLC and upon completion, a solution of saturated $NaHCO_3$ (4 mL) was added. After flash chromatography, 730 mg (64%) of dioxolane **17f** were obtained as a colorless oil. Two epimers were detected (88:12) but only the major isomer could be isolated. ν_{max} (film)/cm^{-1} 2926, 1686, 1612, 1514, 1248, 1040, 820. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm)=1.39 (m, 2H), 1.56 (m, 1H), 1.76 (m, 1H), 1.77 (s, 3H), 1.93 (dd, *J*=6.0, 13.6 Hz, 2H), 3.79 (s, 3H), 3.90 (s, 2H), 4.39 (s, 2H), 4.53 (d, *J*=4.5 Hz, 2H), 5.41 (d, *J*=7.1 Hz, 1H), 5.54 (d, *J*=7.1 Hz, 1H), 6.86 (d, *J*=8.7 Hz, 2H), 7.24 (d, *J*=8.7 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm)=14.8, 22.7, 33.5, 55.7, 72.0, 74.9, 82.0, 99.6, 114.2, 122.8, 129.7, 130.8, 141.6, 159.7. CIMS (*i*-BuH) *m/z* 305 (MH^+, 15), 203 (3), 121 (100).

4.2.7. 2-[2-Methyl-3-(*p*-methoxy-benzyloxy)-prop-2-enyl]-[1,3]dioxane (17i). The above procedure was applied to 500 mg (1 equiv., 1.88 mmol) of dimethylacetal **16** (*E*/*Z*, 70:30) and 0.30 mL (2.2 equiv., 4.15 mmol) of propanediol in dichloromethane (10 mL) in presence of 0.1 mL of 2,2-dimethoxypropane. The reaction was monitored by TLC and upon completion, a solution of saturated $NaHCO_3$ (3 mL) was added. After flash chromatography, 420 mg (80%) of dioxolane **17i** were obtained as a colorless oil (*E*/*Z*, 70:30). ν_{max} (film)/cm^{-1} 2958, 2850, 1666, 1612, 1514, 1248, 1092, 820. *E* isomer. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm)=1.35 (d, *J*=13.6 Hz, 1H), 1.76 (s, 3H), 2.14 (m, 1H), 3.79 (s, 3H), 3.85 (m, 4H), 4.13 (dd, *J*=4.9, 11.3 Hz, 2H), 4.37 (s, 2H), 5.24 (d, *J*=6.4 Hz, 1H), 5.55 (d, *J*=6.4 Hz, 1H), 6.85 (d, *J*=8.7 Hz, 2H), 7.24 (d, *J*=8.7 Hz, 2H). ^{13}C

NMR (75 MHz, $CDCl_3$) δ (ppm)=15.0, 26.1, 55.7, 67.4, 71.8, 74.8, 98.9, 114.1, 124.7, 129.7, 130.8, 139.4, 159.5. *Z* isomer. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm)=1.35 (d, *J*=13.6 Hz, 1H), 1.81 (s, 3H), 2.14 (m, 1H), 3.79 (s, 3H), 3.85 (m, 4H), 4.04 (dd, *J*=4.9, 11.7 Hz, 2H), 4.39 (s, 2H), 5.14 (d, *J*=6.4 Hz, 1H), 5.45 (d, *J*=6.4 Hz, 1H), 6.85 (d, *J*=8.7 Hz, 2H), 7.24 (d, *J*=8.7 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm)=20.3, 26.1, 55.7, 67.4, 72.9, 74.8, 98.2, 114.8, 126.7, 129.7, 130.8, 139.4, 159.5. CIMS (*i*-BuH) *m/z* 279 ($MH^{+\cdot}$, 25), 121 (100). HRMS Calcd for $C_{16}H_{22}O_4$: 279.1596. Found: 279.1596.

4.2.8. 2-[2-Methyl-3-(*p*-methoxy-benzyloxy)-prop-2-enyl]-3,5-*syn*-dimethyl-[1,3]dioxane (17j). The above procedure was applied to 2.0 g (1 equiv., 7.52 mmol) of dimethylacetal **16** (*E*/*Z*, 70:30) and 1.08 mL (1.3 equiv., 9.85 mmol) of pentane-1,3-diol (mixture of isomers) in dichloromethane (30 mL) in presence of 0.1 mL of 2,2-dimethoxypropane. The reaction was monitored by TLC and upon completion, a solution of saturated $NaHCO_3$ (5 mL) was added. After flash chromatography, 441 mg of *syn-E*-**17j**, 144 mg of *syn-Z*-**17j** and 1.09 g as a mixture of isomers. A total of 1.67 g (73%) dioxanes was recovered. ν_{max} (film)/cm^{-1} 2932, 2854, 1612, 1514, 1248, 1036, 820. *E* isomer. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm)=1.26 (m, 7H), 1.53 (dt, *J*=12.3, 2.3 Hz, 1H), 1.76 (s, 3H), 3.79 (m, 5H), 3.89 (s, 2H), 4.38 (s, 2H), 5.26 (d, *J*=6.4 Hz, 1H), 5.60 (d, *J*=6.4 Hz, 1H), 6.85 (d, *J*=8.3 Hz, 2H), 7.24 (d, *J*=8.3 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm)= 14.9, 22.1, 40.7, 55.7, 71.9, 72.8, 75.1, 98.1, 114.1, 124.8, 129.7, 130.9, 139.2, 159.5. *Z* isomer. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm)=1.22 (m, 7H), 1.49 (dt, *J*=2.3, 13.2 Hz, 1H), 1.81 (s, 3H), 3.71 (m, 2H), 3.80 (s, 3H), 4.05 (s, 2H), 4.39 (s, 2H), 5.18 (d, *J*=6.8 Hz, 1H), 5.51 (d, *J*=6.8 Hz, 1H), 6.87 (d, *J*=8.7 Hz, 2H), 7.26 (d, *J*=8.7 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm)=21.6, 22.0, 40.5, 55.7, 68.7, 71.5, 72.8, 97.3, 114.1, 126.7, 129.8, 130.9, 139.3, 159.5. CIMS (NH_3) *m/z* 324 ($M+NH_4^+$, 100), 307 (MH^+, 90), 238 (10), 121 (72). Anal. Calcd for $C_{18}H_{26}O_4$: C, 70.56%; H, 8.55%. Found: C, 70.59%; H, 8.66%.

4.2.9. 3-[3-(4-Methoxy-benzyloxy)-2-methyl-propenyl]-hexahydro-benzo[*e*]-[1,3]dioxepane (17k). The above procedure was applied to 2.0 g (1 equiv., 7.52 mmol) of dimethylacetal **16** (*E*/*Z*, 70:30) and 1.63 g (1.5 equiv., 11.3 mmol) of *syn*-1,2-cyclohexane dimethanol in dichloromethane (15 mL) in presence of 0.1 mL of 2,2-dimethoxypropane. The reaction was monitored by TLC and upon completion, a solution of saturated $NaHCO_3$ (3 mL) was added. After flash chromatography, 1.60 g (61%) of dioxepane **17k** (*E*/*Z*, 70:30) were recovered as a colorless oil and as a mixture of two epimers (50:50). ν_{max} (film)/cm^{-1} 2926, 2856, 1612, 1512, 1248, 1144, 820. *E* isomer (*syn*, *anti*). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm)=1.36 (m, 4H), 1.65 (m, 6H), 1.66 (s, 3H), 3.4–3.8 (m, 4H), 3.68 (s, 3H), 3.79 (s, 2H), 4.30 (s, 1H), 4.32 (s, 1H), 5.31 (d, *J*=6.4 Hz, 0.5H), 5.33 (d, *J*=6.4 Hz, 0.5H), 5.54 (d, *J*=6.4 Hz, 1H), 6.77 (d, *J*=8.5 Hz, 2H), 7.17 (d, *J*=8.5 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm)=14.7, 24.7, 27.2, 27.4, 40.0, 40.2, 55.6, 67.9, 71.8, 71.9, 75.0, 97.9, 98.3, 114.1, 125.0, 129.7, 130.8, 137.8, 159.6. *Z* isomer (*syn*, *anti*). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm)=1.36 (m, 4H), 1.65 (m, 6H), 1.73 (s, 3H), 3.4–3.8 (m, 4H), 3.68 (s, 3H), 3.98 (s, 2H), 4.29 (s, 1H), 4.30 (s, 1H), 5.25 (d, *J*=7.2 Hz, 0.5H), 5.27 (d, *J*=7.2 Hz, 0.5H), 5.46 (d, *J*=7.2 Hz, 1H), 6.77 (d, *J*=8.5 Hz, 2H), 7.17 (d, *J*=8.5 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm)=21.3, 24.7, 27.2, 27.4, 40.0, 40.2, 55.6, 67.9, 68.5, 71.8, 71.9, 97.7, 97.3, 114.1, 127.2, 129.7, 130.8, 138.1, 159.6. EIMS (70 eV) *m/z* 347.2 (MH^+, 15), 220 (45), 156 (56), 137 (100), 121 (85). Anal. Calcd for $C_{21}H_{30}O_4$: C, 72.80; H, 8.73%. Found: C, 72.58%; H, 8.64%.

4.2.10. 3-[3-(4-Methoxy-benzyloxy)-2-methyl-propenyl]-hexahydro-benzo[*e*]-[1,3]dioxepane (17l). The above procedure was applied to 709 mg (1 equiv., 2.67 mmol) of dimethylacetal **16** *E*/*Z*, 70:30 were used with 500 mg (1.3 equiv., 3.47 mmol) of *anti*-1,2-cyclohexane dimethanol in dichloromethane (10 mL) in presence of 0.1 mL of 2,2-dimethoxypropane. The reaction was monitored by TLC and upon completion, a solution of saturated $NaHCO_3$ (3 mL) was added. After flash chromatography, 500 mg (54%) of dioxepane **17l** (*E*/*Z*, 70:30) were recovered as a colorless oil. ν_{max} (film)/cm^{-1} 2924, 2854, 1612, 1514, 1248, 1032, 820. *E* isomer. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm)=0.86 (m, 2H), 1.25 (m, 4H), 1.62 (m, 2H), 1.74 (s, 3H), 1.78 (m, 2H), 3.2–3.7 (m, 4H), 3.78 (s, 3H), 3.86 (s, 2H), 4.39 (s, 2H), 5.42 (d, *J*=6.4 Hz, 1H), 5.61 (d, *J*=6.4 Hz, 1H), 6.86 (d, *J*=8.3 Hz, 2H), 7.24 (d, *J*=8.3 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm)=15.7, 26.6, 28.9, 29.2, 46.6, 55.6, 67.6, 71.8, 75.0, 97.7, 114.1, 125.1, 129.7, 130.8, 137.8, 159.5. *Z* isomer. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm)=0.86 (m, 2H), 1.25 (m, 4H), 1.62 (m, 2H), 1.80 (s, 3H), 1.78 (m, 2H), 3.2–3.7 (m, 4H), 3.78 (s, 3H), 4.05 (s, 2H), 4.39 (s, 2H), 5.42 (d, *J*=6.4 Hz, 1H), 5.52 (d, *J*=6.4 Hz, 1H), 6.86 (d, *J*=8.3 Hz, 2H), 7.24 (d, *J*=8.3 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm)=21.6, 26.6, 28.9, 29.2, 46.6, 55.6, 68.5, 71.8, 72.9, 97.0, 114.1, 127.3, 129.4, 130.8, 138.1, 159.5. EIMS (70 eV) *m/z* 347.2 (MH^+, 7), 210 (50), 155 (47), 122 (100). HRMS Calcd for $C_{21}H_{31}O_4$ (MH^+) 347.2222. Found: 347.2216.

4.2.11. 3-[3-(4-Methoxy-benzyloxy)-2-methyl-propenyl]-benzo[*e*]-[1,3]dioxepane (17o). The above procedure was applied to 3.0 g (1 equiv., 11.3 mmol) of dimethylacetal **16** (*E*/*Z*, 70:30) and 2.34 g (1.5 equiv., 16.9 mmol) of (2-hydroxymethyl-phenyl)-methanol in dichloromethane (30 mL) in presence of 0.2 mL of 2,2-dimethoxypropane. The reaction was monitored by TLC and upon completion, a solution of saturated $NaHCO_3$ (5 mL) was added. After flash chromatography, 2.66 g (70%) of dioxepane **17o** (*E*/*Z*, 70:30) as a colorless oil. ν_{max} (film)/cm^{-1} 2954, 2852, 1612, 1512, 1248, 1088, 1032, 820. *E* isomer. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm)=1.76 (d, *J*=0.8 Hz, 3H), 3.73 (s, 3H), 3.85 (s, 2H), 4.34 (s, 2H), 4.86 (s, 4H), 5.55 (d, *J*=6.0 Hz, 1H), 5.65 (dd, *J*=6.0, 1.1 Hz, 1H), 6.80 (d, *J*=8.7 Hz, 2H), 7.1–7.3 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm)=15.0, 55.7, 71.1, 71.9, 74.9, 103.5, 114.2, 124.5, 127.6,127.7, 129.8, 130.8, 139.3, 159.6. *Z* isomer. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm)=1.77 (s, 3H), 3.73 (s, 3H), 4.05 (s, 2H), 4.37 (s, 2H), 4.75 (d, *J*=13.9 Hz, 2H), 4.82 (d, *J*=13.9 Hz, 2H), 5.49 (d, *J*=6.4 Hz, 1H), 5.55 (d, *J*=6.4 Hz, 1H), 6.80 (d, *J*=8.7 Hz, 2H), 7.1–7.3 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm)=21.7, 55.7, 68.8, 71.2, 71.9, 103.1, 114.2, 126.6, 127.6, 127.7, 129.8, 130.8, 139.1, 159.6. CIMS (*i*-BuH) *m/z* 341 (MH^+, 100), 259 (15), 121 (98). Anal.

Calcd for $C_{21}H_{24}O_4$: C, 74.09%; H, 7.11%. Found: C, 74.15%; H, 7.25%.

4.2.12. 3-[3-(4-Methoxy-benzyloxy)-2-methyl-propenyl]-1,5-*syn*-dimethyl-benzo[*e*]-[1,3]dioxepane (17p). The above procedure was applied to 1.41 g (1 equiv., 5.30 mmol) of dimethylacetal **16** (*E*/*Z*, 70:30) and 1.32 g (1.5 equiv., 7.95 mmol) of *syn*-diol **9a** in dichloromethane (20 mL). The reaction was monitored by TLC and upon completion, a solution of saturated $NaHCO_3$ (4 mL) was added. After flash chromatography, 1.54 g (81%) of dioxepane **17p** (*E*/*Z*, 70:30) were obtained as a colorless oil and as a mixture of two epimers (*syn*/*anti*: 80:20). ν_{max} (film)/cm^{-1} 2978, 2854, 1612, 1512, 1246, 1094, 818. *E* (*anti*) isomer. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm)=1.69 (d, *J*=6.4 Hz, 6H), 1.80 (s, 3H), 3.79 (s, 3H), 3.88 (s, 2H), 4.37 (s, 2H), 5.20 (q, *J*=6.4 Hz, 1H), 5.60 (d, *J*=6.0 Hz, 1H), 5.84 (d, *J*=6.0 Hz, 1H), 6.85 (d, *J*=8.7 Hz, 2H), 7.1–7.3 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm)=15.0, 19.8, 55.7, 71.9, 75.2, 75.4, 105.2, 114.1, 125.4, 126.5, 128.0, 129.8, 130.9, 137.5, 142.5, 159.5. *Z* (*anti*) isomer. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm)=1.65 (d, *J*=6.4 Hz, 6H), 1.80 (s, 3H), 3.80 (s, 3H), 4.10 (s, 2H), 4.37 (s, 2H), 5.08 (q, *J*=6.4 Hz, 1H), 5.51 (d, *J*=6.0 Hz, 1H), 5.78 (d, *J*=6.0 Hz, 1H), 6.85 (d, *J*=8.7 Hz, 2H), 7.1–7.3 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm)=19.8, 21.6, 55.7, 68.8, 71.9, 75.2, 104.4, 114.2, 125.4, 126.5, 128.0, 129.8, 130.9, 137.5, 142.5, 159.5. EIMS (70 eV) *m*/*z* 368.2 ($M^{+\cdot}$, 1), 232 (8), 220 (12), 177 (70), 132 (100), 121 (55). Anal. Calcd for $C_{23}H_{28}O_4$: C, 74.97%; H, 7.66%. Found: C, 74.63%; H, 7.84%.

4.2.13. 3-[3-(4-Methoxy-benzyloxy)-2-methyl-propenyl]-1,5-*anti*-dimethyl-benzo[*e*]-[1,3]dioxepane (17q). The above procedure was applied to 1.20 g (1 equiv., 4.51 mmol) of dimethylacetal **16** (*E*/*Z*, 70:30) and 1.10 g (1.5 equiv., 6.63 mmol) of *anti*-diol **8a** in dichloromethane (20 mL). The reaction was monitored by TLC and upon completion, a solution of saturated $NaHCO_3$ (4 mL) was added. After flash chromatography, 1.00 g (60%) of dioxepane **17q** (*E*/*Z*, 70:30) was obtained as a colorless oil. ν_{max} (film)/cm^{-1} 2978, 2934, 1612, 1512, 1248, 1104, 1034, 820, 754. *E* isomer. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm)=1.55 (m, 6H), 1.73 (s, 3H), 3.73 (s, 3H), 3.85 (s, 2H), 4.34 (s, 2H), 5.07, 5.26 (2q, *J*=6.8 Hz, 2H), 5.57 (d, *J*=6.0 Hz, 1H), 5.67 (d, *J*=6.0 Hz, 1H), 6.81 (d, *J*=8.7 Hz, 2H), 7.1–7.2 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm)=15.0, 20.3, 22.1, 55.7, 68.2, 71.9, 75.1, 76.3, 97.4, 114.2, 124.9, 126.1, 126.3, 127.5, 127.6, 129.7, 130.8, 139.3, 141.2, 143.1, 159.6. *Z* isomer. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm)=1.78 (s, 3H), 3.73 (s, 3H), 4.05 (s, 2H), 4.34 (s, 2H), 4.95, 5.10 (2q, *J*=6.8 Hz, 2H), 5.56 (d, *J*=6.0 Hz, 1H), 5.67 (d, *J*=6.0 Hz, 1H), 6.80 (d, *J*=8.7 Hz, 2H), 7.1–7.3 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm)=25.0, 55.7, 67.3, 72.9, 73.6, 76.2, 96.4, 114.2, 125.4, 126.1, 126.3, 127.5, 127.6, 129.7, 130.8, 139.3, 140.6, 142.6, 159.6. EIMS (70 eV) *m*/*z* 368.2 ($M^{+\cdot}$, 1), 220 (10), 177 (57), 131 (100), 121 (57). Anal. Calcd for $C_{23}H_{28}O_4$: C, 74.97%; H, 7.66%. Found: C, 74.48%; H, 7.93%.

4.2.14. 3-[3-(4-Methoxy-benzyloxy)-2-methyl-propenyl]-1,5-*anti*-diethyl-benzo[*e*]-[1,3]dioxepane (17r). The above procedure was applied to 1.50 g (1 equiv., 5.63 mmol) of dimethylacetal **16** (*E*/*Z*, 70:30) and 1.64 g (1.5 equiv., 8.45 mmol) of *anti*-diol **8b** in dichloromethane (15 mL) in presence of 0.1 mL of 2,2dimethoxypropane. The reaction was monitored by TLC and upon completion, a solution of saturated $NaHCO_3$ (4 mL) was added. After flash chromatography, 1.50 g (67%) of dioxepane **17r** (*E*/*Z*, 70:30) were recovered as a colorless oil. ν_{max} (film)/cm^{-1} 2930, 2874, 1612, 1514, 1248, 1070, 1036, 820. *E* isomer. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm)=1.04 (t, *J*=6.0 Hz, 3H), 1.07 (t, *J*=5.7 Hz, 3H), 1.79 (s, 3H), 1.93 (m, 2H), 2.13 (m, 2H), 3.80 (s, 3H), 3.91 (s, 2H), 4.41 (s, 2H), 4.90 (dd, *J*=3.8, 8.3 Hz, 1H), 5.07 (dd, *J*=4.5, 8.6 Hz, 1H), 5.64 (d, *J*=6.0 Hz, 1H), 5.74 (d, *J*=6.0 Hz, 1H), 6.87 (d, *J*=8.6 Hz, 2H), 7.1–7.3 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm)=10.6, 11.0, 15.1, 26.3, 28.4, 55.1, 71.8, 73.7, 75.1, 81.5, 97.6, 114.3, 125.3, 126.5, 127.4, 129.7, 130.8, 138.7, 140.3, 142.0, 159.5. *Z* isomer. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm)=1.04 (t, *J*=6.0 Hz, 3H), 1.07 (t, *J*=5.7 Hz, 3H), 1.85 (s, 3H), 1.93 (m, 2H), 2.13 (m, 2H), 3.80 (s, 3H), 3.96 (d, *J*=12.2 Hz, 1H), 4.10 (d, *J*=12.2 Hz, 1H), 4.38 (s, 2H), 4.79 (dd, *J*=3.7, 8.3 Hz, 1H), 5.06 (m, 1H), 5.59 (d, *J*=6.0 Hz, 1H), 5.74 (d, *J*=6.0 Hz, 1H), 6.87 (d, *J*=8.6 Hz, 2H), 7.1–7.3 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm)=10.6, 11.0, 21.1, 26.3, 28.4, 55.1, 68.8, 71.8, 73.7, 81.5, 95.5, 114.3, 125.3, 126.5, 127.4, 129.7, 130.8, 138.7, 140.3, 142.0, 159.5. EIMS (70 eV) *m*/*z* 396.2 ($M^{+\cdot}$, 1), 205 (7), 177 (55), 159 (100), 121 (62). Anal. Calcd for $C_{25}H_{32}O_4$: C, 75.73; H, 8.13%. Found: C, 75.86%; H, 8.11%.

4.2.15. 3-[3-(4-Methoxy-benzyloxy)-2-methyl-propenyl]-1,5-*anti*-diisopropyl-benzo[*e*]-[1,3]dioxepane (17s). The above procedure was applied to 1.50 g (1 equiv., 5.63 mmol) of dimethylacetal **16** (*E*/*Z*, 70:30) and 1.90 g (1.5 equiv., 8.56 mmol) of *anti*-diol **8c** in dichloromethane (15 mL) in presence of 0.1 mL of 2,2dimethoxypropane. The reaction was monitored by TLC and upon completion, a solution of saturated $NaHCO_3$ (5 mL) was added. After flash chromatography, 1.20 g (50%) of dioxepane **17s** (*E*/*Z*, 70:30) were recovered as a colorless oil. ν_{max} (film)/cm^{-1} 2960, 2872, 1612, 1514, 1248, 1076, 1034, 822. *E* isomer. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm)=0.88 (m, 6H), 1.03 (d, *J*=6.8 Hz, 3H), 1.11 (d, *J*=6.8 Hz, 3H), 1.80 (s, 3H), 2.4–2.6 (m, 2H), 3.80 (s, 3H), 3.92 (s, 2H), 4.42 (s, 2H), 4.81 (d, *J*=3.0 Hz, 1H), 4.91 (d, *J*=4.5 Hz, 1H), 5.56 (d, *J*=6.0 Hz, 1H), 5.74 (d, *J*=6.0 Hz, 1H), 6.87 (d, *J*=8.7 Hz, 2H), 7.2–7.3 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm)=15.2, 16.4, 16.9, 20.6, 21.2, 29.7, 31.5, 55.7, 71.9, 75.2, 76.6, 83.9, 98.1, 114.2, 125.3, 126.9, 127.0, 129.7, 130.8, 138.6, 140.9, 141.9, 159.5. *Z* isomer. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm)=0.88 (m, 6H), 1.03 (d, *J*=6.8 Hz, 3H), 1.11 (d, *J*=6.8 Hz, 3H), 1.85 (s, 3H), 2.4–2.6 (m, 2H), 3.80 (s, 3H), 4.06 (d, *J*=12.8 Hz, 1H), 4.13 (d, *J*=12.8 Hz, 1H), 4.39 (s, 2H), 4.71 (d, *J*=3.4 Hz, 1H), 4.89 (m, 1H), 5.51 (d, *J*=6.4 Hz, 1H), 5.60 (d, *J*=6.4 Hz, 1H), 6.87 (d, *J*=8.7 Hz, 2H), 7.2–7.3 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm)=16.6, 17.2, 19.4, 20.0, 21.6, 29.5, 31.8, 55.7, 68.8, 71.9, 76.6, 84.4, 97.1, 114.2, 125.3, 126.9, 127.0, 129.7, 130.8, 138.6, 140.9, 141.9, 159.5. Anal. Calcd for $C_{27}H_{36}O_4$: C, 76.38; H, 8.55%. Found: C, 76.44%; H, 8.85%.

4.2.16. 3-[3-(4-Methoxy-benzyloxy)-2-methyl-propenyl]-1,5-*anti*-diisobutyl-benzo[*e*]-[1,3]dioxepane (17t). The

above procedure was applied to 500 mg (1 equiv., 1.88 mmol) of dimethylacetal **16** (*E*/*Z*, 70:30) and 700 mg (1.5 equiv., 2.80 mmol)of *anti*-diol **8d** in dichloromethane (5 mL). The reaction was monitored by TLC and upon completion, a solution of saturated $NaHCO_3$ (2 mL) was added. After flash chromatography (heptane/AcOEt, 80/20 as eluent), 446 mg (52%) of dioxepane **17t** (*E*/*Z*, 70:30) were recovered as a colorless oil. ν_{max} (film)/cm^{-1} 2954, 2867, 1612, 1513, 1247, 1084, 820, 750. *E* isomer. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm)=1.00 (m, 12H), 1.7–2.0 (m, 6H), 1.77 (s, 3H), 3.80 (s, 3H), 3.91 (s, 2H), 4.41 (s, 2H), 5.09 (dd, *J*=3.6, 10.2 Hz, 1H), 5.23 (m, 1H), 5.64 (d, *J*=6.3 Hz, 1H), 5.73 (d, *J*=6.3 Hz, 1H), 6.87 (d, *J*=6.8 Hz, 2H), 7.24 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm)=15.0, 22.2, 22.4, 24.2, 24.7, 42.8, 45.1, 55.7, 71.0, 71.9, 75.1, 78.4, 97.2, 114.2, 125.5, 126.3, 126.4, 127.5, 129.6, 130.8, 138.5, 140.4, 142.9, 159.5. *Z* isomer. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm)=1.00 (m, 12H), 1.7–2.0 (m, 6H), 3.80 (s, 3H), 4.00, 4.11 (2d, *J*=16.7 Hz, 2H), 4.38 (s, 2H), 5.01 (dd, *J*=3.6, 10.2 Hz, 1H), 5.23 (m, 1H), 5.60 (d, *J*=6.3 Hz, 1H), 5.73 (d, *J*=6.3 Hz, 1H), 6.87 (d, *J*=6.8 Hz, 2H), 7.24 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm)=21.6, 22.2, 22.4, 24.2, 24.7, 42.8, 45.1, 55.7, 68.8, 71.0, 71.9, 78.4, 96.2, 114.2, 125.5, 126.3, 126.4, 127.5, 129.6, 130.8, 138.8, 140.4, 142.9, 159.5. EIMS (70 eV) *m*/*z* 452.3 ($M^{+\cdot}$, 1), 231 (100), 215 (80), 121 (55). Anal. Calcd for $C_{29}H_{40}O_4$: C, 76.95; H, 8.91%. Found: C, 76.55%; H, 8.96%.

4.2.17. 5-Isobutyl-3-[3-(4-methoxy-benzyloxy)-2-methyl-propenyl]-benzo[*e*]-[1,3]dioxepane (17u). The above procedure was applied to 1.00 g (1 equiv., 3.76 mmol) of dimethylacetal **16** (*E*/*Z*, 70:30) and 1.1 g (1.5 equiv., 5.67 mmol) of *anti*-diol **10d** in dichloromethane (15 mL). The reaction was monitored by TLC and upon completion, a solution of saturated $NaHCO_3$ (4 mL) was added. After flash chromatography (heptane/AcOEt, 75:25 as eluent), 1.01 g (68%) of dioxepane **17u** (*E*/*Z*, 70:30) were obtained as a yellowish oil, each stereoisomer being a mixture of two epimers (*E*: 33:66, *Z*, 50:50). ν_{max} (film)/cm^{-1} 2953, 2865, 1611, 1512, 1247, 1086, 820, 747. Major isomer *syn* or *anti* *E*. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm)=1.00 (m, 6H), 1.81 (s, 3H), 1.7–2.1 (m, 3H), 3.79 (s, 3H), 3.90 (s, 2H), 4.39 (s, 2H), 4.8–5.1 (m, 3H), 5.74 (s, 2H), 6.86 (d, *J*=8.7 Hz, 2H), 7.1–7.4 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm)=15.0, 22.0, 24.6, 42.5, 55.7, 71.1, 71.9, 73.7, 75.0, 104.0, 114.2, 125.5, 127.7, 128.1, 128.7, 129.71, 129.74, 130.7, 138.0, 139.3, 143.7, 159.5. Other isomers. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm)=0.98 (m, 6H), 1.7–2.1 (m, 6H), 3.79 (s, 3H), 4.09 (s, 2H), 4.42 (s, 2H), 4.8–5.1 (m, 3H), 5.56–5.78 (m, 2H), 6.86 (d, *J*=8.7 Hz, 2H), 7.1–7.4 (m, 6H). EIMS (70 eV) *m*/*z* 397.2 (MH^+, 1), 260 (8), 220 (25), 175 (77), 119 (100). Anal. Calcd for $C_{25}H_{32}O_4$: C, 75.73; H, 8.13%. Found: C, 75.52%; H, 8.51%.

4.2.18. 2-[3-(4-Methoxy-benzyloxy)-2-methyl-propenyl]-dibenzo[*e*,*g*]-[1,3]dioxonane (17v). A solution of dimethylacetal **16** (500 mg, 1 equiv., 1.88 mmol) in dichloromethane (25 mL) and (2′-hydroxymethyl-biphenyl-2-yl)-methanol (806 mg, 2 equiv., 3.76 mmol) were put in a flask equipped with a heavy-solvent designed Dean–Stark device. The mixture was refluxed in presence of 0.05 mL acetic acid. After 24 h, 4 mL saturated $NaHCO_3$ were added and the aqueous phase was extracted with dichloromethane (2×10 mL). The resulting organic phase was dried ($MgSO_4$) and evaporated under reduce pressure. A flash chromatography on silica gel (eluting with heptane/AcOEt, 70:30) afforded 399 mg (51%) of dioxonane **17v**. ν_{max} (film)/cm^{-1} 3060, 2932, 1674, 1612, 1514, 1248, 1076, 822, 760. *E* isomer. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm)=1.63 (s, 3H), 3.79 (s, 3H), 3.86 (s, 2H), 4.05 (d, *J*=12.3 Hz, 1H), 4.29 (d, *J*=10.9 Hz, 1H), 4.39 (s, 2H), 4.53 (d, *J*=10.9 Hz, 1H), 4.74 (d, *J*=12.3 Hz, 1H), 5.01 (d, *J*=6.4 Hz, 1H), 5.63 (d, *J*=6.4 Hz, 1H), 6.86 (d, *J*=8.7 Hz, 2H), 7.15–7.45 (m, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm)=14.9, 55.7, 65.7, 72.0, 74.1, 75.1, 101.4, 114.2, 126.6, 128.4, 128.8, 128.9, 129.0, 129.7, 130.1, 130.2, 130.6, 131.0, 130.8, 135.6, 136.9, 137.0, 141.8, 142.0, 159.7. *Z* isomer. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm)=1.80 (s, 3H), 3.79 (s, 3H), 3.94 (d, *J*=12.4 Hz, 1H), 4.04 (s, 2H), 4.27 (d, *J*=10.9 Hz, 1H), 4.39 (s, 2H), 4.51 (d, *J*=10.9 Hz, 1H), 4.66 (d, *J*=12.4 Hz, 1H), 5.01 (d, *J*=6.4 Hz, 1H), 5.53 (d, *J*=6.4 Hz, 1H), 6.86 (d, *J*=8.7 Hz, 2H), 7.15–7.45 (m, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm)=21.7, 55.7, 65.6, 69.0, 72.0, 73.9, 100.7, 114.2, 126.6, 128.4, 128.8, 128.9, 129.0, 129.7, 130.1, 130.2, 130.6, 131.0, 130.8, 135.6, 136.9, 137.0, 141.8, 142.0, 159.7. CIMS (*i*-BuH) *m*/*z* 417 (MH^+, 6), 335 (4), 197 (24), 121 (100).

4.2.19. 1,1-Diallyloxy-3-methyl-4-(*p*-methoxy-benzyloxy)-but-2-ene (18). A solution of dimethylacetal **16** (500 mg, 1 equiv., 1.88 mmol) in dichloromethane (25 mL) and allylic alcohol (1.09 g,10 equiv., 18.8 mmol) were put in a flask equipped with a heavy-solvent designed Dean–Stark device. The reaction mixture was refluxed in presence of acetic acid (0.05 mL). After 12 h, $NaHCO_3$ (4 mL) was added and the aqueous phase extracted with dichloromethane (2×10 mL). The resulting organic phase was dried ($MgSO_4$) and evaporated under reduce pressure. A flash chromatography on silica gel (eluting with heptane/AcOEt, 70:30) afforded 320 mg (53%) of diallylacetal **18** as a colorless oil. *E* isomer. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 1.75 (s, 3H), 3.79 (s, 3H), 3.89 (s, 2H), 4.06 (m, 4H), 4.39 (s, 2H), 5.24 (m, 5H), 5.60 (d, *J*=6.8 Hz, 1H), 6.87 (d, *J*=8.7 Hz, 2H), 7.25 (d, *J*=8.7 Hz, 2H). *Z* isomer. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 1.82 (s, 3H), 3.79 (s, 3H), 4.06 (m, 4H), 4.39 (s, 2H), 5.24 (m, 5H), 5.49 (d, *J*=6.8 Hz, 1H), 6.87 (d, *J*=8.7 Hz, 2H), 7.25 (d, *J*=8.7 Hz, 2H).

4.2.20. 2-[3-(4-Methoxy-benzyloxy)-2-methyl-propenyl]-4,7-dihydro-[1,3]dioxepine (19). Diallyl acetal **18** (207 mg, 1 equiv., 0.651 mmol) was dissolved in 10 mL dichloromethane containing 60 mg Grubbs catalyst (0.1 equiv., 0.073 mmol) under argon and at room temperature. After 2 h, a second load of 50 mg (0.09 equiv., 0.061 mmol) catalyst was added. The reaction mixture was stirred overnight then evaporated under reduce pressure. A flash chromatography on silica gel (eluting with heptane/AcOEt, 70:30) afforded 52 mg (27%) of dioxepine **19** as a colorless oil. *E* isomer. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 1.77 (s, 3H), 3.79 (s, 3H), 3.89 (s, 2H), 4.20 (d, *J*=15.1 Hz, 2H), 4.44 (m, 4H), 5.50 (d, *J*=6.0 Hz, 1H), 5.70 (d, *J*=6.0 Hz, 1H), 5.73 (s, 2H), 6.86 (d, *J*=8.7 Hz, 2H), 7.25 (d, *J*=8.7 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 14.9, 55.7, 65.2, 72.0, 74.9, 100.1, 114.2, 124.2, 129.7, 130.4, 130.7, 139.1, 159.6. *Z*

isomer. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 1.83 (s, 3H), 3.79 (s, 3H), 4.07 (s, 2H), 4.20 (d, J=15.1 Hz, 2H), 4.44 (m, 4H), 5.44 (d, J=6.0 Hz, 1H), 5.6 (d, J=6.0 Hz, 1H), 5.73 (s, 2H), 6.86 (d, J=8.7 Hz, 2H), 7.25 (d, J=8.7 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 21.6, 55.7, 65.2, 68.7, 72.0, 99.5, 114.2, 126.4, 129.8, 130.3, 130.7, 139.3, 159.6.

4.2.21. 1,1-Bis-[1′-phenyl-prop-2′-en-1′-yloxy]-3-methyl-4-(*p*-methoxy-benzyloxy)-but-2-ene (20). A solution of dimethylacetal **16** (500 mg, 1 equiv., 1.88 mmol) in dichloromethane (25 mL) and 1-phenyl-prop-2-en-1-ol (1.01 g, 4 equiv., 7.52 mmol) were put in a flask equipped with a heavy-solvent designed Dean–Stark device. The reaction mixture was refluxed in presence of acetic acid (0.05 mL). After 30 h, $NaHCO_3$ (4 mL) was added and the aqueous phase extracted with dichloromethane (2×10 mL). The resulting organic phase was dried ($MgSO_4$) and evaporated under reduce pressure. A flash chromatography on silica gel (eluting with heptane/AcOEt, 70:30) afforded 509 mg (60%) of acetal **20** as an inseparable mixture of diastereoisomers. Mixture of isomers: ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 1.5 (s, 3H), 3.79 (s, 5H), 4.9–5.7 (m, 10H), 5.95 (m, 2H), 6.86 (d, J=8.3 Hz, 2H), 7.1–7.4 (m, 12H).

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Generation of 5,6-dimethylene-2(1*H*)-pyridinones from [3,4-*b*] sulfolene pyridinones and application in Diels–Alder reactions

Tom C. Govaerts, Ilse A. Vogels, Frans Compernolle and Georges J. Hoornaert*

Laboratorium voor Organische Synthese, Department of Chemistry, K.U. Leuven, Celestijnenlaan 200F, B-3001 Leuven, Belgium

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Abstract—2(1*H*)-Pyrazinones were converted into various [3,4-*b*] sulfolene pyridinones **19**–**21**, serving as precursors for thermolytic conversion into the corresponding 5,6-dimethylene 2(1*H*)-pyridinone *ortho*-quinodimethanes. These were trapped in situ by reaction with various dienophiles. Tethering of precursor **19** with a dienophilic side chain attached to the 7-position of the [3,4-*b*] sulfolene pyridinone also enabled intramolecular cycloaddition when no rearrangement by 1,5-H-shift was viable.

1. Introduction

During the last decade a vast number of publications have appeared on heteroaromatic *ortho*-quinodimethanes (*o*-QDM).[1] These highly reactive species are commonly generated in situ from various precursors,[2] e.g. by thermal extrusion of SO_2 from sulfolene-fused heterocyclic precursors.[3] In a preceding paper we described the use of [3,4-*c*] sulfolene pyridinones as precursors for generation of 3,4-dimethylene-2(1*H*)-pyridinone *o*-QDM and subsequent cycloaddition.[4,5] Here we present a study on the isomeric [3,4-*b*] sulfolene pyridinone precursor type. Upon extrusion of SO_2 the latter is transformed into the novel 5,6-dimethylene-2(1*H*)-pyridinone *o*-QDM system, which can be trapped in inter- and intramolecular Diels–Alder reactions to afford various unknown polycyclic pyridinones. In recent years, substituted pyridinones have regained interest, based on their biological and pharmacological properties.[6]

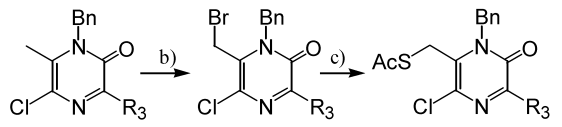
2. Results and discussion

2.1. Synthesis of the precursors

Our synthetic approach is depicted in Schemes 1 and 2. To generate the required 5,7-dihydrothieno[3,4-*b*]pyridin-2(1*H*)-one ring system, we envisaged bromination of the 6-methyl group of pyrazinones **2**–**4**, followed by functional group interconversion to introduce the 2-propynylsulfanyl group as a dienophilic side chain. The latter can undergo addition–elimination reaction with the pyrazinone azadiene to form the dihydrothiophene-fused bicyclic pyridinone. Oxidation of the ring sulfur atom finally can produce the desired [3,4-*b*] sulfolene pyridinone precursor.

The synthesis of the precursors started with nucleophilic substitution of the reactive imidoyl chloride function by treatment with sodium methoxide, sodium ethanethiolate, or tetraphenyltin to produce the 3-substituted pyrazinones **2**–**4**. Following bromination of the 6-methyl group the resulting bromides **5**–**7** were made to react with thiolacetic acid and triethylamine to give thioesters **8**–**10** (Scheme 1, Table 1).

Compounds **8**–**10** were converted into thioethers **11**–**13** by treatment with sodium methoxide to generate the thiolate anion followed by in situ reaction with propargyl bromide. Thioethers **11** and **13** were stable at room temperature but bis-thioether **12** had to be stored at low temperature. Internal cycloaddition of **11**–**13** was effected by heating in boiling toluene to afford dihydrothienopyridinones **16**–**18** exclusively. The preferred expulsion of cyanogen chloride from the intermediate cycloadducts **15** is in accord with our



1 R_3 = Cl

a) → **2** R_3 = OMe (95%), **3** R_3 = SEt (97%), **4** R_3 = Ph (69%); **5** R_3 = OMe (70%), **6** R_3 = SEt (89%), **7** R_3 = Ph (86%); **8** R_3 = OMe (80%), **9** R_3 = SEt (94%), **10** R_3 = Ph (90%)

Scheme 1. Synthesis of the thioesters **8**–**10**. *Reagents and conditions*: (a) **2**: 1.1 equiv. NaOMe, MeOH, room temperature; **3**: 1.2 equiv. NaSEt, THF, room temperature; **4**: 1.2 equiv. $SnPh_4$, 0.01 equiv. $Pd(P(Ph)_3)_4$, toluene, reflux, 1 week; (b) 1.2 equiv. NBS, CCl_4, reflux, cat. $(PhCOO)_2$; (c) 1.2 equiv. $HSCOCH_3$, Et_3N, THF, room temperature, 1 h.

Keywords: *ortho*-Quinodimethane; Pyridinone; Diels–Alder reaction.
* Corresponding author. Tel.: +32-16-32-74-09; fax:+32-16-32-79-90; e-mail address: georges.hoornaert@chem.kuleuven.ac.be

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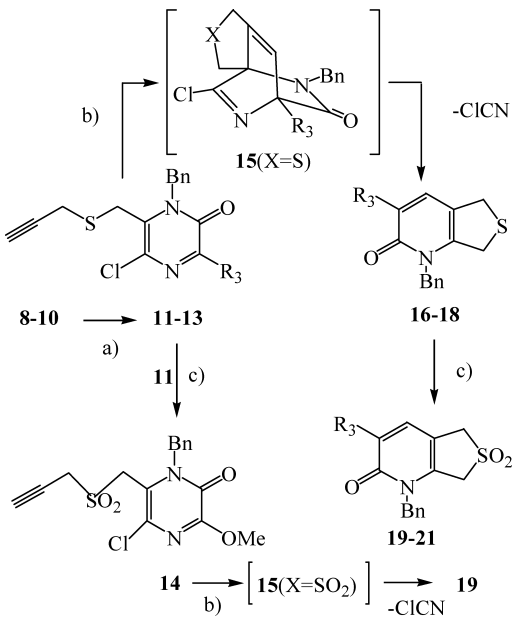


Scheme 2. Synthesis of sulfolene pyridinones. *Reagents and conditions*: (a) (i) 1.3 equiv. NaOMe, MeOH, room temperature, (ii) 3 equiv. propargyl bromide, room temperature; (b) toluene, reflux; (c) 3 equiv. *m*-CPBA, CH_2Cl_2, room temperature.

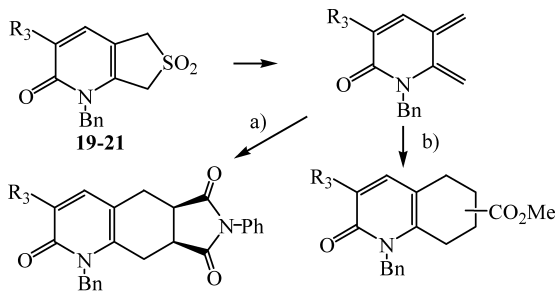
previous findings, which indicated that concurrent loss of benzyl isocyanate is a less favourable process.[7,8] The reaction times required for conversion of **11**–**13** into cyclic sulfides **16**–**18** were largely different. For instance, compound **12** (R_3=SEt) underwent Diels–Alder reaction already at room temperature, but subsequent elimination of cyanogen chloride from cycloadduct **15** to form **17** required further heating in boiling toluene for 15 h. By contrast, compounds **11** and **13** were converted directly into the final products **16** and **18** after heating for 6 and 3 h, respectively. Clearly, the activation energy for cycloaddition of the azadiene system and subsequent cycloreversion is affected in a different way by substituents in position 3 of the pyrazinone. Final oxidation of the cyclic sulfides **16**–**18** using *meta*-chloroperoxybenzoic acid (*m*-CPBA) furnished the required sulfolene pyridinones **19**–**21** (note: R_3=SO_2Et in the case of **20**). In an alternative route, the cycloaddition/oxidation sequence was reversed: following oxidation of thioether **11** using *m*-CPBA, the resulting sulfone **14** was heated in toluene for 2 h to produce *o*-QDM precursor **19** (Scheme 2). The latter route is less preferred, mainly because the yield of the cycloaddition–elimination reaction is significantly lower.

Table 1. Synthesis of the sulfolene pyridinones

Starting compound	Product	R_3	Yield (%)
8	**11**	OMe	90
9	**12**	SEt	88
10	**13**	Ph	70
11	**14**	OMe	70
11	**16**	OMe	74
12	**17**	SEt	93
13	**18**	Ph	65
14	**19**	OMe	64
16	**19**	OMe	80
17	**20**	SO_2Et	50
18	**21**	Ph	57

2.2. Intermolecular Diels–Alder reactions

To study the reactivity of the pyridinone *o*-QDM generated from precursors **19**–**21** and the regioselectivity in subsequent cycloaddition reactions, different types of dienophiles were applied in the thermolysis experiments. These were carried out by heating a mixture of precursor **19**–**21** and *N*-phenylmaleimide (NPMA) or methyl acrylate in *o*-dichlorobenzene (*o*-DCB) in a sealed glass tube at 150 to 160 °C (Scheme 3).



Scheme 3. Intermolecular Diels–Alder reactions. *Reagents and conditions*: (a) 3 equiv. NPMA, 150–160 °C, *o*-DCB; (b) 10 equiv. methyl acrylate, 150–160 °C, *o*-DCB.

The cycloadducts **22**–**24** formed with NPMA were isolated in good yields. The structure and conformational behaviour of these adducts were determined on the basis of coupling constants and NOESY as illustrated for adduct **24** (Fig. 1). Proton H-4 exhibits a strong NOE-correlation (dashed lines) with an *ortho*-proton of the phenyl group and with the coplanar equatorial proton H-5eq (δ 3.12, dd, 1H, $^2J_{5eq-5ax}$=15.0 Hz, $^3J_{5eq-5a}$=1.7 Hz). Obviously H-5eq can be connected to H-5ax (δ 2.75, dd, 1H, $^2J_{5ax-5eq}$=15.0 Hz, $^3J_{5ax-5a}$=5.0 Hz), which in turn shows a strong NOE with the angular proton H-5a. Since such a correlation is not observed for H-5eq, the latter must have a *trans*-relationship with H-5a. This, in turn, implies an equatorial orientation of H-5a, according with the conformational structure proposed in Figure 1 and the small coupling constant values observed for $^3J_{5eq-5a}$ (1.7 Hz) and $^3J_{5ax-5a}$ (5.0 Hz). For the analogous cycloadducts **22** and **23** a comparable conformational structure was inferred, based on similar coupling patterns and NOE-correlations.

In spite of the different electronic nature of the substituents introduced in 3-position of the pyridinone precursors **19**–**21**, reaction of the corresponding *o*-QDM with methyl acrylate failed to show a clear-cut effect on the regioselectivity of the

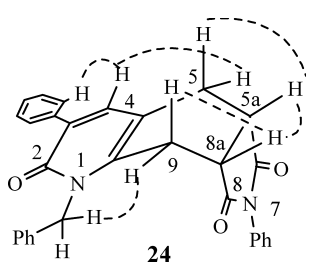


Figure 1. NOE-couplings in adduct **24**.

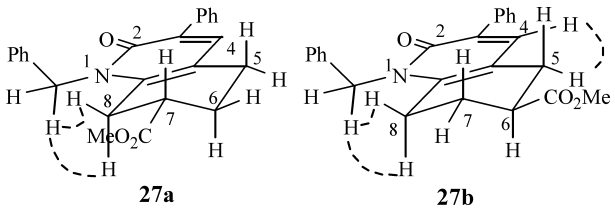


Figure 2. Mixture of regiomeric adducts **27**.

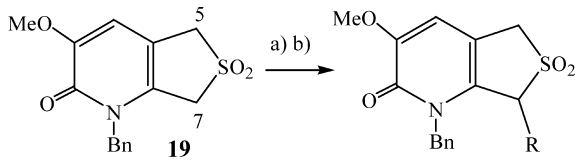
cycloaddition as the product ratio invariably approached a value 1:1. For the determination of the isomeric ratio we again relied on ^{1}H NMR analysis as exemplified for the adduct mixture **27a**,**b** (R_3=Ph, Fig. 2).

The ^{1}H spectrum of **27a**,**b** run in $CDCl_3$ was unresolved; hence C_6D_6 was used as a solvent to unravel the signals corresponding to the aliphatic protons H-5 and H-8 (Aromatic Solvent Induced Shift). For regioisomer **27b** the geminal protons H-5 appeared as two dd signals: the signal at 2.52 ppm (^2J=15.9 Hz, ^3J=9.8 Hz) was assigned to H-5ax and that at 3.90 ppm (^2J=15.9 Hz, ^3J=5.1 Hz) to H-5eq. The assignment of H-5eq was confirmed by a NOE with H-4. For regioisomer **27a** protons H-8ax and H-8eq were identified as two dd absorptions at 2.63 and 2.30 ppm (^2J=17.5 Hz, ^3J=8.8, 5.6 Hz, respectively), both of which showed a NOE with the benzylic protons as in **27b**. The ratio **27a/27b** (43/57) was based on integration values. The isomeric products in other adduct mixtures were attributed in a similar way: **25a/25b** (47/53) and **26a/26b** (55/45).

Precursor **19** (R_3=OMe) also was thermolysed in the presence of other dienophiles; the results of these experiments are shown in Table 2. The cycloaddition with dimethyl maleate yielded the *cis*-substituted diester **28** (77%) as shown by NMR-analysis. When precursor **19** was thermolysed with 1,4-naphthoquinone the fully aromatised compound **29** was isolated as the only product. In the reaction with dimethyl acetylenedicarboxylate, the intermediate adduct also readily underwent aromatisation to produce quinolone **30**. The reaction with *p*-toluenesulfonyl cyanide furnished a separable mixture of naphthyridines **31** and **32**. The structural assignment of the regioisomers again was based on their ^{1}H NMR and NOE-diff spectra. In the spectrum of compound **31**, H-4 was identified as a singlet at 6.97 ppm; presaturation of this proton resulted in a NOE-enhancement of the signal due to H-5 (δ 8.30). The $^1J_{CH}$ values (184 and 170 Hz) corresponding to coupling of C-8 with H-8 (δ 8.63) and C-5 with H-5 respectively, clearly show that the nitrogen atom is in position 7. In the spectrum of adduct **32**, a similar NOE was observed between H-4 (δ 6.92) and H-5 (δ 8.70). The $^1J_{CH}$ values (185 and 169 Hz) corresponding to coupling with H-5 and H-8 (δ 8.10) respectively, now reveal the 6-position of the nitrogen atom. Thermolysis in presence of dihydrofuran led to a complex mixture of regioisomers and decomposition products, the adducts were not isolated and thus not characterized. The existence of **33** was demonstrated via mass spectral analysis.

2.3. Substitution of precursor 19

One advantage of a sulfolene precursor is the ability to abstract a proton at an acidic α-position of the sulfone to generate an anion that can be submitted to reaction with various electrophiles. Starting from sulfolene pyridinone **19** (R_3=OMe), we applied this strategy to attach some dienophilic side chains (Scheme 4, Table 3).



Scheme 4. Substitution of sulfolene pyridinone **19**. *Reagents and conditions*: (a) 1.1 equiv. NaH, DMF, 0 °C; (b) 1.5 equiv. RX.

To effect substitution at the more acidic α-position 7, a solution of **19** in dry DMF was treated at 0 °C with 1.1 equiv. of NaH. After 15 min 2 equiv. of electrophile were added to the reaction mixture. When tetrabutylammonium fluoride was used as a base, the reaction had to proceed at room temperature and the yields were appreciably lower. Attempts to substitute the less acidic α-position 5 by treatment of **19** with 2.1 equiv. of KH or BuLi followed by addition of an electrophile, met with failure. Hence no dianion could be generated from the [3,4-*b*] type precursor **19** even under strongly basic conditions. This finding stays in contrast to the double proton abstraction observed for the isomeric [3,4-*c*] sulfolene pyridinone, which has the less acidic α-methylene group in *peri*-position of the carbonyl function.

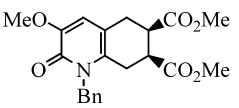
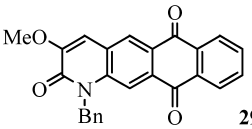
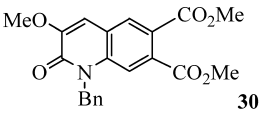
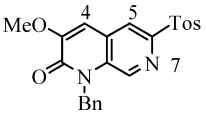
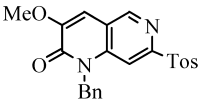
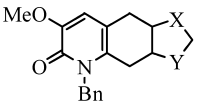
Ester precursor **37** could easily be deprotonated at the 7-position to produce a stable anion. However, further functionalisation of this unreactive species was unsuccessful even when using reactive electrophiles such as methyl chloroformate and benzyl bromide. Attempts to transform the ester into the corresponding amide compounds equally failed.

The sulfolene pyridinone also could be regioselectively brominated by irradiating a solution of **19** and NBS (1.1 equiv.) in CCl_4 for 1 h (500 W tungsten-lamp). This furnished 7-bromo derivative **39** in 45% yield. Apparently this low yield was due to decomposition of compounds **19** and/or **39** upon irradiation. When bromination was carried out under thermal conditions (CCl_4, NBS, benzoylperoxide, reflux) compound **39** was isolated in 67% yield.

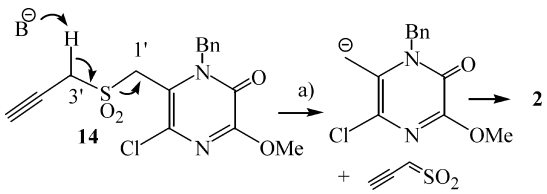
The substituted compounds were characterised by NMR-analysis, which confirmed that substitution indeed had occurred at position 7. Indeed, whereas the spectrum of **19** displayed a singlet signal for the benzylic protons, an AB quartet was observed for the substituted analogues, due to the *peri*-interaction of the 7-substituent and the benzyl group (Table 4). In the spectrum of the 1,7-dibenzyl compound **34**, proton H-7 was identified as a triplet (4.17 ppm, t, ^3J=5.5 Hz). A NOESY experiment further revealed a strong NOE correlation between H-7 and one of the benzylic protons on the pyridinone nitrogen atom. A weak NOE correlation also was observed between protons of the benzylic methylene groups at the 1- and 7-position.

Attempts to substitute one of the α-positions 1′ or 3′ in the side chain of monocyclic sulfone **14** were unsuccessful.

Table 2. Intermolecular Diels–Alder reactions with various dienophiles

Dienophile	Adduct
Dimethyl maleate	 **28** (77%)
1,4-Naphthoquinone	 **29** (70%)
Dimethyl acetylenedicarboxylate	 **30** (60%)
p-Toluenesulfonylcyanide	 **31** (40%)  **32** (27%)
Dihydrofuran	 50 % (crude) **33a** X = O, Y = CH_2 **33b** X = CH_2, Y = O

Various conditions using different bases and solvents invariably led to isolation of pyrazinone **2** in 30–45% yield. Presumably, the anion generated at position 3′ triggers an elimination reaction producing a sulfene and a stabilised 6-methyl carbanion, which eventually yields pyrazinone **2** upon aqueous workup of the reaction mixture (Scheme 5).



Scheme 5. Attempted substitution of sulfone **14**. *Reagents and conditions*: (a) (i) 1.1 equiv. BuLi, −78 °C, THF, (ii) 2 equiv. BnBr; (b) (i) 2.1 equiv. BuLi, −78 °C, THF, (ii) 2 equiv. BnBr; (c) (i) 1.1 equiv. NaH, −0 °C, DMF, (ii) 2 equiv. BnBr; (d) (i) 1.2 equiv. KO*t*Bu, 0 °C to room temperature, THF, (ii) 2 equiv. BnBr.

2.4. Intramolecular Diels–Alder reactions

Substitution of precursor **19** allowed to introduce various dienophilic side chains at the 7-position. The 7-substituted compounds **35**, **36**, and **38** now were submitted to thermolysis in order to generate the corresponding *o*-QDM intermediates. Upon intramolecular cycloaddition, these can produce polycyclic pyridinones. To this end a solution of the substituted precursor in *o*-DCB was heated at 150 °C for several hours. Table 5 shows the outcome of these experiments.

Table 3. Substitution of sulfolene pyridinone **19**

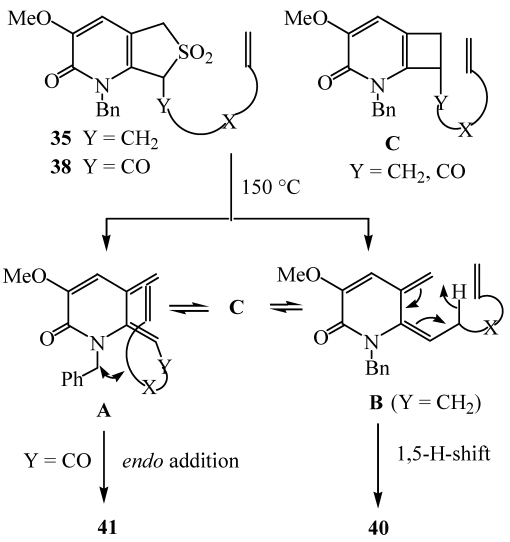
Electrophile RX	R	Product number (yield)
Benzylbromide	$CH_2C_6H_5$	**34** (60)
5-Bromopentene	$(CH_2)_3CH{=}CH_2$	**35** (57)
Allyl chloroformate	$CO_2CH_2CH{=}CH_2$	**36** (61)
Methyl chloroformate	CO_2CH_3	**37** (59)
N,*N*-Diallylcarbamoyl chloride	$CON(allyl)_2$	**38** (58)

Table 4. Selected NMR data

Compound number	H-benzyl (ppm)	^2J
19	5.23	/
34	4.33/5.70	16.0
35	4.95/5.45	15.7
36	4.96/5.88	15.9
37	4.99/5.41	15.7
38	4.37/5.68	15.8
39 (7-Br)	4.83/6.10	15.9

Thermolysis of compound **35** exclusively produced rearranged product **40**. Extrusion of SO_2 may result in generation of the *Z*- or *E*-*o*-QDM intermediate **A** or **B**, both of which experience a large steric repulsion with either the exocyclic methylene group or the *N*-benzyl substituent in *peri*-position (Scheme 6). *o*-QDM **B** now can undergo a 1,5-sigmatropic hydrogen shift to afford the rearranged product **40**. Furthermore, equilibration of **A** and **B** conceivably may proceed via cyclobutene intermediate **C**.

Thermolysis of **36** furnished a complex mixture of products, which were not further characterised. Finally, from the thermolysis of precursor **38** the *cis*-fused adduct **41** was isolated as a single product. Again both **A** and **B** type

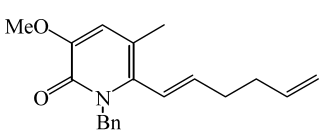
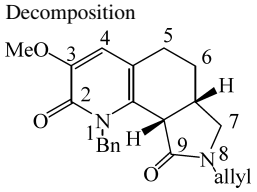


Scheme 6. Intramolecular cycloaddition/rearrangement.

intermediates (Y=CO) may be generated. However, in this case **B** cannot undergo a 1,5-H-shift since no H-atoms are available. Furthermore, cycloaddition involving type **B** intermediates (Y=CH_2, CO) is disfavoured as this requires a highly strained *exo* transition state. Hence, cycloaddition can proceed only starting from intermediate **A** (Y=CO): the more favourable *endo* transition state then leads to the formation of *cis*-fused adduct **41**.

The *cis*-fused structure of *endo*-adduct **41** was established by NMR-spectroscopy. Proton H-9a was identified as a doublet at 3.57 ppm showing coupling (^3J=6.3 Hz) with H-6a (δ 2.43). The presumed *cis*-disposition of the angular protons H-9a and H-6a was confirmed by their strong NOE correlation. A NOE also was observed between H-9a and one of the benzylic protons (δ 5.49). The signals at 2.94 ppm (d, 1H, ^2J=10 Hz) and 3.48 ppm (dd, ^2J=10 Hz, ^3J=6 Hz) were assigned to the geminal protons H-7, both of which display a NOE with H-6a. This implies the occurrence of half-chair **A**. By conformational modelling **A** was shown to be more stable (ca. 3.5 kcal/mol) than half-chair **B**, which displays a highly unfavourable axial 6-methylene group (Fig. 3).

Table 5. Intramolecular Diels–Alder reactions

Substituted precursor	Product number (yield, %)
35	 **40** (55)
36	Decomposition
38	 **41** (65)

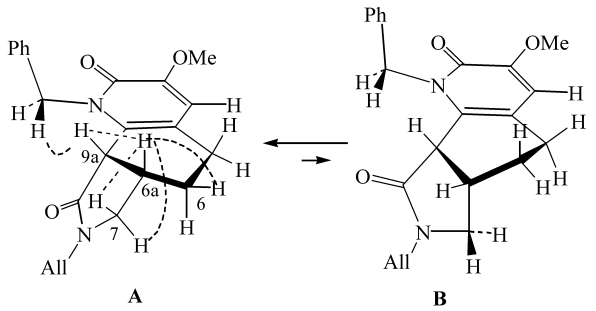


Figure 3. NOE correlations observed for adduct **41**.

3. Conclusion

In this work we established a route leading to various substituted [3,4-*b*] sulfolene pyridinones. Upon thermolysis these were converted into the corresponding pyridinone *o*-QDM intermediates, which in the presence of dienophiles allowed for intermolecular Diels–Alder reactions. However, no regioselectivity was observed for cycloadditions with non-symmetric dienophiles. When dienophilic side chains were introduced, intramolecular cycloaddition only succeeded if no competing rearrangement involving a 1,5-H-shift of the *o*-QDM intermediate was viable.

4. Experimental

Melting points were determined using a Reichert–Jung Thermovar apparatus and an Electrothermal IA 9000 digital melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin–Elmer 297 grating IR spectrophotometer and a Perkin–Elmer 1720 Fourier transform spectrometer. Mass spectra were run using a Hewlett–Packard MS-Engine 5989A apparatus for EI and CI spectra, and a Kratos MS50TC instrument for exact mass measurements performed in the EI mode at a resolution of 10,000. For the NMR spectra (δ, ppm) a Bruker Avance 300 and a Bruker AMX 400 spectrometer were used. All NMR spectra were taken up in $CDCl_3$ with TMS as an internal standard unless otherwise stated. Analytical and preparative thin layer chromatography was carried out using Merck silica gel 60 PF-224, for column chromatography 70–230 mesh silica gel 60 (E. M. Merck) was used as the stationary phase.

4.1. Synthesis of the precursors 19–21

The preparation and the analytical data of the pyrazinones **1**, **2** and **4** were reported previously.[8] The substituted pyrazinone **3** was prepared analogously using sodium ethanethiolate in THF.

4.1.1. 1-Benzyl-5-chloro-3-(ethylsulfanyl)-6-methyl-2(1*H*)-pyrazinone 3. Yield: 90%; yellow crystals; mp 82.5–83.3 °C (ethanol); IR (KBr/cm^{-1}): 3061, 2971, 1706, 1650, 1567; ^{1}H NMR: δ 1.38 (t, 3H, ^3J=7.4 Hz, CH_3), 2.34 (s, 3H, 6-CH_3), 3.08 (q, 2H, ^3J=7.4 Hz, CH_2), 5.30 (s, 2H, CH_2–N), 7.17 (d, 2H, J_o=6.7 Hz, H–Ph), 7.26–7.32 (m, 3H, H–Ph); ^{13}C NMR: δ 13.5 (CH_3), 16.2 (CH_3), 24.1 (CH_2), 48.6 (CH_2–N), 126.8 (C-6), 126.9 (CH), 128.4 (C-5), 128.9 (CH), 134.5 (C-*ipso*), 154.4 (C-3), 156.3 (C-2); MS [*m*/*z* (%)]: EI: 294 (26, $M^{+\cdot}$), 203 (7, $M^{+\cdot}-C_7H_7$), 91 (100,

$C_7H_7^+$); HRMS: calcd for $C_{14}H_{15}N_2OSCl$: 294.0594; found: 294.0591.

The experimental data of the bromomethyl substituted pyrazinones **5** and **7** were reported previously.[8] Compound **6** was prepared using the same procedure.

4.1.2. 1-Benzyl-6-bromomethyl-5-chloro-3-(ethylsulfanyl)-2(1*H*)-pyrazinone 6. Yield: 90%; yellow crystals; mp 73.2–75.1 °C (ethanol); IR (KBr/cm^{-1}): 3050, 2973, 1680, 1592; ^{1}H NMR: δ 1.39 (t, 3H, ^3J=7.4 Hz, CH_3), 3.10 (q, 2H, ^3J=7.4 Hz, CH_2), 4.41 (s, 3H, CH_2–Br), 5.47 (s broad, 2H, CH_2–N), 7.18 (d, 2H, J_o=6.8 Hz, H–Ph), 7.29–7.35 (m, 3H, H–Ph); ^{13}C NMR: δ 13.3 (CH_3), 24.4 (CH_2), 25.4 (CH_2) 47.7 (CH_2–N), 126.5 (C-6), 126.4 (CH), 128.0 (CH), 128.5 (C-5), 129.2 (CH), 134.9 (C-*ipso*), 153.8 (C-3), 161.1 (C-2); MS [*m*/*z* (%)]: EI: 371 (6, $M^{+\cdot}$), 293 (7, $M^{+\cdot}-Br$), 265 ($M^{+\cdot}-Br$, –CO), 91 (100, $C_7H_7^+$); HRMS: calcd for $C_{14}H_{14}N_2BrClOS$: 371.9699; found: 371.9720.

4.2. General procedure for the synthesis of thioesters 8–10

To a stirred solution of bromide **5**–**7** (0.1 mol) and thiolacetic acid (0.12 mol) in dry THF (500 mL) was added dropwise NEt_3 (0.3 mol) under an inert atmosphere. After completion of the reaction, water (500 mL) was added and the mixture was extracted with CH_2Cl_2 (3×200 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was evaporated. The residue was purified by column chromatography (Silica gel, 5 EtOAc/95 CH_2Cl_2) to afford the following compounds.

4.2.1. *S* ^{1}-[(1-Benzyl-3-chloro-1,6-dihydro-5-methoxy-6-oxo-2-pyrazinyl)methyl]ethanethioate 8. Yield: 80%; pale yellow crystals; mp 134.5–136 °C (ethanol); IR (KBr/cm^{-1}): 2991, 1671, 1587; ^{1}H NMR: δ 2.36 (s, 3H, CH_3), 4.02 (s, 3H, OCH_3), 4.17 (s, 2H, CH_2S), 5.32 (s, 2H, CH_2–N), 7.21 (d, 2H, ^3J=7.0 Hz, H–Ph), 7.30–7.33 (m, 3H, H–Ph); ^{13}C NMR: δ 27.9 (CH_2), 30.2 (CH_3), 48.1 (CH_2–N), 55.3 (CH_3), 124.5 (C), 125.5 (C), 126.7 (CH), 128.1 (CH), 129.0 (CH), 135.0 (C-*ipso*), 151.3 (C), 154.6 (C), 193.9 (C); MS [*m*/*z* (%)]: EI: 338 (15, $M^{+\cdot}$), 295 (9, $M^{+\cdot}-C_2H_3O$), 263 (11, $M^{+\cdot}-C_2H_3OS$), 247 (15, $M^{+\cdot}-C_7H_7$), 205 (27, $M^{+\cdot}-C_7H_7$, $-C_2H_3O$), 91 (100, $C_7H_7^+$); HRMS: calcd for $C_{15}H_{15}N_2O_3SCl$: 338.0492; found 338.0489. CHN analysis: calcd for $C_{15}H_{15}ClN_2O_3S$: C 53.18, H 4.46, N 8.27; found: C 53.41, H 4.18, N 8.10.

4.2.2. *S* ^{1}-{[1-Benzyl-3-chloro-1,6-dihydro-5-(ethylsulfanyl)-6-oxo-2-pyrazinyl}methyl]ethanethioate 9. Yield: 94%; yellow crystals; mp 102–102.5 °C (ethanol); IR (KBr/cm^{-1}): 2963, 1701, 1646, 1563; ^{1}H NMR: δ 1.39 (t, 3H, ^3J=7.2 Hz, CH_3), 2.37 (s, 3H, CH_3), 3.08 (q, 2H, ^3J=7.2 Hz, CH_2), 4.18 (s, 2H, 6-CH_2), 5.30 (s, 2H, CH_2–N), 7.20–7.34 (m, 5H, H–Ph); ^{13}C NMR: δ 13.3 (CH_3), 24.3 (CH_2), 27.9 (CH_2), 30.2 (CH_3), 48.2 (CH_2–N), 126.7 (C-6), 126.8 (CH), 128.1 (CH), 128.5 (C-5), 129.0 (CH), 134.9 (C-*ipso*), 154.1 (C-3), 159.3 (C-2), 193.8 (CO); MS [*m*/*z* (%)]: EI: 368 (15, $M^{+\cdot}$), 325 (4, $M^{+\cdot}-C_2H_3O$), 293 (14, $M^{+\cdot}-C_2H_3OS$), 277 (16, $M^{+\cdot}-C_7H_7^+$), 235 (32, $M^{+\cdot}-C_7H_7NCO$), 91 (100, $C_7H_7^+$); HRMS: calcd for $C_{16}H_{17}N_2O_2S_2Cl$: 368.0420; found: 368.0416. CHN analysis: calcd for $C_{16}H_{17}ClN_2O_2S_2$: C 52.09, H 4.64, N 7.59; found: C 51.86, H 4.68, N 7.44.

4.2.3. *S* ^{1}-[(1-Benzyl-3-chloro-1,6-dihydro-5-phenyl-6-oxo-2-pyrazinyl)methyl]ethanethioate 10. Yield: 90%; yellow crystals; mp 146–147 °C (ethanol); IR (KBr/cm^{-1}): 3052, 2965, 1648, 1546; ^{1}H NMR: δ 2.38 (s, 3H, CH_3), 4.27 (s, 2H, CH_2), 5.42 (s, 2H, CH_2–N), 7.23–7.34 (m, 5H, H–Ph), 7.43–7.45 (m, 3H, H–Ph), 8.39–8.42 (m, 2H, H–Ph);^{13}C NMR: δ 28.2 (CH_2), 30.1 (CH_3), 48.5 (CH_2–N), 126.7 (C-5), 127.9 (CH), 128.0 (CH), 128.1 (C-6), 129.1 (CH), 129.3 (CH), 130.7 (CH), 132.8 (CH), 134.1 (C-*ipso*), 135.5 (C-*ipso*), 150.7 (C-3), 155.1 (C-2), 194.4 (CO); MS [*m*/*z* (%)]: EI: 384 (30, $M^{+\cdot}$), 341 (19, $M^{+\cdot}-C_2H_3O$), 309 (12, $M^{+\cdot}-C_2H_3OS$), 251 (39, $M^{+\cdot}-C_7H_7NCO$), 91 (100, $C_7H_7^+$); HRMS: calcd for $C_{20}H_{17}N_2O_2SCl$: 384.0699, found: 384.0698; CHN analysis: calcd for $C_{20}H_{17}ClN_2O_2S$: C 62.41, H 4.45, N 7.28; found: C 62.10, H 4.45, N 7.28.

4.3. General procedure for the synthesis of thioethers 11–13

To a solution of thioesters **8**–**10** (0.05 mol) in methanol (250 mL) was added under an inert atmosphere 1.3 equiv. of sodium methoxide. After reaction at room temperature for 1 h, 3 equiv. of propargylic bromide were added. Subsequently, the reaction mixture was stirred at room temperature for another 2.5 h and neutralised with a dilute solution of HCl in MeOH. The solution was concentrated, the residue redissolved in CH_2Cl_2 (150 mL), and the CH_2Cl_2 solution washed with water (2×150 mL). The organic layer was dried over $MgSO_4$ and the solvent was evaporated. The residue was purified by column chromatography (Silica gel, 70 Hexane/30 EtOAc) to afford thioether compounds **11**–**13**.

4.3.1. 1-Benzyl-5-chloro-3-methoxy-6-[(2-propynylsulfanyl)methyl]-2-(1*H*)-pyrazinone 11. Yield: 90%; yellow crystals; mp 147.5–149.0 °C (CH_2Cl_2/hexane); IR (KBr/cm^{-1}): 2993, 1668, 1583; ^{1}H NMR: δ 2.21 (t, 1H, ^4J=2.5 Hz, ≡CH), 3.36 (d, 2H, ^4J=2.5 Hz, CH_2), 3.87 (s, 2H, 6-CH_2), 4.03 (s, 3H, OCH_3), 5.55 (s, 2H, CH_2–N), 7.16 (d, 2H, ^3J=7.0 Hz, H–Ph), 7.26–7.32 (m, 3H, H–Ph); ^{13}C NMR: δ 20.8 (CH_2), 29.7 (CH_2), 47.5 (CH_2–N), 55.2 (CH_3), 71.6 (CH), 79.5 (C), 123.9 (C) 125.8 (CH), 126.4 (CH), 127.9 (CH), 135.2 (C-*ipso*), 151.4 (C), 154.4 (C); MS [*m*/*z* (%)]: EI: 334 (19, $M^{+\cdot}$), 299 (5, $M^{+\cdot}-Cl$), 264 (21, $M^{+\cdot}-C_3H_3S$), 243 (4, $M^{+\cdot}-C_7H_7$), 91 (100, $C_7H_7^+$); HRMS: calcd for $C_{16}H_{15}N_2O_2SCl$: 334.0543, found: 334.0543; CHN analysis: calcd for $C_{16}H_{15}ClN_2O_2S$: C 57.40, H 5.52, N 8.37; found: C 57.33, H 5.38, N 8.27.

4.3.2. 1-Benzyl-5-chloro-3-(ethylsulfanyl)-6-[(2-propynylsulfanyl)methyl]-2(1*H*)-pyrazinone 12. Yield: 88%; unstable yellow oil; ^{1}H NMR: δ 1.38 (t, 3H, ^3J=7.2 Hz, CH_3), 2.21 (t, 1H, ^4J=2.6 Hz, ≡CH), 3.08 (q, 2H, ^3J=7.2 Hz, CH_2), 3.37 (d, 2H, ^4J=2.6 Hz, CH_2), 3.89 (s, 2H, 6-CH_2S), 5.52 (s, 2H, CH_2–N), 7.14 (d, 2H, J_o=6.9 Hz, H–Ph), 7.20–7.35 (m, 3H, H–Ph); ^{13}C NMR: δ 13.4 (CH_3), 19.9 (CH_2S), 24.4 (CH_2), 29.9 (CH_2-6), 47.6 (CH_2–N), 71.8 (CH), 79.5 (C), 126.6 (C-6), 126.7 (CH), 128.1 (CH), 128.5 (C-5), 129.1 (CH), 134.9 (C-*ipso*), 154.1 (C-3), 159.1 (C-2);

MS [*m*/*z* (%)]: CI: 365 (90, MH^+), 304 (65, MH^+-ClCN), 293 (100, $MH^+-C_3H_4S$), 91 (10, $C_7H_7^+$).

4.3.3. 1-Benzyl-5-chloro-3-phenyl-6-[(2-propynylsulfanyl)methyl]-2(1*H*)-pyrazinon 13. Yield: 70%; yellow crystals; mp 94–94.5 °C; IR (KBr/cm^{-1}): 3027, 2940, 1654, 1543; ^{1}H NMR: δ 2.19 (t, 1H, ^4J=2.5 Hz, ≡CH), 3.34 (d, 2H, ^4J=2.5 Hz, CH_2), 3.90 (s, 2H, CH_2S), 5.56 (s, 2H, CH_2–N), 7.15 (d, 2H, J_o=7.0 Hz, H–Ph), 7.25–7.29 (m, 3H, H–Ph), 7.39–7.41 (m, 3H, H–Ph), 8.40–7.42 (m, 2H, H–Ph); ^{13}C NMR: δ 19.9 (CH_2), 29.9 (CH_2), 47.8 (CH_2–N), 71.8 (CH), 79.2 (C), 126.3 (C-5), 127.1 (CH), 127.8 (CH), 127.9 (C-6), 128.8 (CH), 129.6 (CH), 130.5 (CH), 133.1 (CH), 134.6 (C-*ipso*), 134.8 (C-*ipso*), 150.2 (C-3), 154.9 (C-2); MS [*m*/*z* (%)]: EI: 380 (4, $M^{+\cdot}$), 341 (2, $M^{+\cdot}-C_3H_3$), 319 (29, $M^{+\cdot}-ClCN$), 247 (28, $M^{+\cdot}-C_7H_7NCO$), 91 (100, $C_7H_7^+$); HRMS: calcd for $C_{21}H_{17}N_2OSCl$: 380.0750; found: 380.0749.

4.3.4. 1-Benzyl-5-chloro-3-methoxy-6-[(2-propynylsulfonyl)methyl]-2-(1*H*)-pyrazinon 14. To a solution of thienopyridinone **11** (2 g, 0.006 mol) in dry CH_2Cl_2 (100 mL) are added 3 mol equiv. of *m*-CPBA. The mixture is stirred for 3 h at room temperature. Then a saturated solution of $NaHCO_3$ (50 mL) is added, and stirring is continued for 1 h. The organic phase is separated and the aqueous phase is further extracted with CH_2Cl_2. The combined organic layers are washed with water and dried over $MgSO_4$ and the solvent evaporated. The residue is purified by column chromatography (alumina, 15 EtOAc/85 CH_2Cl_2).

Yield: 70%; white powder; mp 48.5 °C (decomposition); IR (KBr/cm^{-1}): 2947, 1964, 1684, 1339, 1128, 1576; ^{1}H NMR: δ 2.54 (t, 1H, ^4J=2.7 Hz, CH), 4.00 (d, 2H, ^4J=2.7 Hz, CH_2), 4.07 (s, 3H, OCH_3), 4.57 (s broad, 2H, CH_2), 5.62 (s broad, 2H, CH_2–N), 7.15 (d, 2H, H–Ph), 7.26–7.34 (m, 3H, H–Ph); ^{13}C NMR: δ 47.06 (CH_2), 48.5 (CH_2), 52.3 (CH_2), 55.6 (CH_3), 70.7 (C), 77.3 (CH), 118.4 (C-5), 126.6 (CH), 128.3 (CH), 129.3 (CH), 133.6 (C-6), 134.6 (C-*ipso*), 151.0 (C), 155.7 (C); MS [*m*/*z* (%)]: EI: 366 (7, $M^{+\cdot}$), 305 (2, $M^{+\cdot}-ClCN$), 263 (75 ($M^{+\cdot}-C_3H_3O_2S$), 233 (21, $M^{+\cdot}-C_7H_7NCO$), 91 (100, $C_7H_7^+$); HRMS: calcd for $C_{16}H_{15}N_2O_4SCl$: 366.0441; found: 366.0436. CHN analysis: calcd for $C_{16}H_{15}ClN_2O_4S$: C 52.39, H 4.12, N 7.64; found: C 52.70, H 3.85, N 7.45.

4.4. General procedure for the synthesis of thienopyridinones 16–18

A solution of thioether **11**–**13** (0.04 mol) in dry toluene (300 mL) was refluxed under an inert atmosphere (6–48 h depending on the thioether). The solvent was evaporated and the residue was purified by column chromatography (silica gel, 15 EtOAc/85 CH_2Cl_2) to give cyclic sulfides **16**–**18**.

4.4.1. Benzyl-3-methoxy-5,7-dihydrothieno[3,4-*b*]pyridin-2(1*H*)-one 16. Yield: 74%; yellow crystals; mp 51–52 °C; IR (KBr/cm^{-1}): 3031, 2935, 1662, 1605; ^{1}H NMR: δ 3.83 (s, 3H, OCH_3), 4.05 (s broad, 4H, 2×CH_2), 5.27 (s, 2H, CH_2–N), 6.55 (s, 1H, CH), 7.18–7.29 (m, 5H, H–Ph); ^{13}C NMR: δ 35.6 (CH_2), 35.9 (CH_2), 48.9 (CH_2–N), 55.9 (CH_3), 109.6 (CH-4), 114.7 (C-7a), 126.9 (CH), 127.6 (CH), 128.7 (CH), 134.8 (C-4a), 135.9 (C-*ipso*), 148.4 (C-3), 158.0 (C-2); MS [*m*/*z* (%)]: EI: 273 (39, $M^{+\cdot}$), 182 (22, $M^{+\cdot}-C_7H_7$), 91 (100, $C_7H_7^+$); HRMS: calcd for $C_{15}H_{15}NO_2S$: 273.0824; found: 273.0823.

4.4.2. 1-Benzyl-3-(ethylsulfanyl)-5,7-dihydrothieno[3,4-*b*]pyridin-2(1*H*)-one 17. Yield: 93%; yellow oil; IR (NaCl/cm^{-1}): 2966, 1650; ^{1}H NMR: δ 1.35 (t, 3H, ^3J=7.4 Hz, CH_3), 2.87 (q, 2H, ^3J=7.4 Hz, CH_2), 4.03 (d, 2H, ^2J=18.5 Hz, CH_2), 4.09 (d, 2H, ^2J=18.5 Hz, CH_2), 5.26 (s, 2H, CH_2–N), 7.04 (s, 1H, H-4), 7.19 (d, 2H, J_o=7.0 Hz), 7.24–7.29 (m, 3H, H–Ph); ^{13}C NMR: δ 13.3 (CH_3), 25.1 (CH_2), 35.6 (CH_2), 35.9 (CH_2), 49.1 (CH_2–N), 116.6 (CH-4), 127.0 (C-7a), 127.7 (CH), 128.8 (CH), 129.3 (CH), 129.5 (C-4a), 135.9 (C-*ipso*), 141.0 (C-3), 160.6 (C-2); MS [*m*/*z* (%)]: EI: 303 (52, $M^{+\cdot}$), 270 (39, $M^{+\cdot}-HS$), 242 (2, $M^{+\cdot}-C_2H_5S$), 212 (11, $M^{+\cdot}-C_7H_7$), 91 (100, $C_7H_7^+$); HRMS: calcd for $C_{17}H_{17}NOS_2$: 303.0752; found: 303.0748.

4.4.3. 1-Benzyl-3-phenyl-5,7-dihydrothieno[3,4-*b*]pyridin-2(1*H*)-one 18. Yield: 65%; yellow crystals; mp 183–184 °C (ethanol); IR (KBr/cm^{-1}): 3029, 2919, 1650, 1597; ^{1}H NMR: δ 4.08 (d, 1H, ^2J=17.5 Hz, CH_2), 4.12 (d, 1H, ^2J=17.7 Hz, CH_2), 4.15 (2×d, 2H, ^2J=17.7 Hz, CH_2), 5.29 (s, 2H, CH_2–N), 7.20–7.40 (m, 9H, H–Ph+H-4), 7.65–7.70 (m, 2H, H–Ph); ^{13}C NMR: δ 35.6 (CH_2), 36.3 (CH_2), 49.1 (CH_2–N), 116.9 (C-7a), 126.9 (CH), 127.9 (CH), 127.8 (CH), 128.1 (CH), 128.6 (CH), 128.9 (CH), 129.8 (C-4a), 134.4 (C-4), 136.5 (C-*ipso*), 137.3 (C-*ipso*), 145.2 (C-3), 162.2 (C-2); MS [*m*/*z* (%)]: CI: 320 (100, MH^+). HRMS: calcd for $C_{20}H_{17}NOS$: 319.1031; found: 319.1029.

4.5. General procedure for the oxidation of cyclic sulfides 16–18

To a solution of thienopyridinone **16**–**18** (0.02 mol) in dry CH_2Cl_2 (150 mL) was added *m*-CPBA (0.06 mol). The mixture was stirred for 18 h at room temperature. Then a saturated solution of $NaHCO_3$ (50 mL) was added, and stirring was continued for 4 h. The organic phase was separated and the aqueous phase further extracted with CH_2Cl_2. The combined organic layers were washed with water and dried over $MgSO_4$ and the solvent evaporated. The residue was purified by column chromatography (Silica gel, 15 EtOAc/85 CH_2Cl_2) to afford sulfones **19**–**21**.

4.5.1. 1-Benzyl-3-methoxy-5,7-dihydro-6,6-dioxothieno[3,4-*b*]pyridin-2(1*H*)-one 19. Yield: 80%; white crystals; mp 148 °C (decomposition); IR (KBr/cm^{-1}): 2986, 1652, 1601, 1321, 1134; ^{1}H NMR: δ 3.57 (s, 3H, OCH_3), 4.13 (s, 2H, CH_2), 4.22 (s, 2H, CH_2), 5.23 (s, 2H, CH_2–N), 6.58 (s, 1H, H-4), 7.17 (d, 2H, ^3J=7.0 Hz, H–Ph), 7.26–7.35 (m, 3H, H–Ph); ^{13}C NMR: δ 49.4 (CH_2–N), 55.5 (CH_3), 56.2 (CH_2), 56.8 (CH_2), 107.4 (C-7a), 108.7 (CH-4), 129.2 (C-4a), 126.9 (CH), 127.1 (CH), 128.2 (CH), 134.9 (C-*ipso*), 150.8 (C-3), 157.9 (C-2); MS [*m*/*z* (%)]: EI: 305 (19, $M^{+\cdot}$), 241 (26,$M^{+\cdot}-SO_2$), 91 (100, $C_7H_7^+$); HRMS: calcd for $C_{15}H_{15}NO_4S$: 305.0722; found: 305.0718.

When compound **14** was heated in toluene at reflux temperature for 2 h the yield of **19** was 64%.

4.5.2. 1-Benzyl-3-(ethylsulfonyl)-5,7-dihydro-6,6-dioxothieno [3,4-*b*]pyridin-2(1*H*)-one 20. Yield: 50%; white

crystals; mp 152.5–153 °C (decomposition); IR (KBr/cm^{-1}): 2974, 1652, 1536, 1304, 1120; ^{1}H NMR: δ 1.29 (t, 3H, ^3J=7.4 Hz, CH_3), 3.54 (q, 2H, ^3J=7.4 Hz, CH_2), 4.26 (s, 2H, CH_2), 4.29 (s, 2H, CH_2), 5.25 (s, 2H, CH_2–N), 7.17 (dd, 2H, J_o=7.9 Hz, J_m=2.1 Hz, H–Ph), 7.33–7.40 (m, 3H, H–Ph), 8.12 (s, 1H, H-4); ^{13}C NMR: δ 6.9 (CH_3), 47.3 (CH_2–N), 49.4 (CH_2), 55.7 (CH_2), 55.8 (CH_2), 108.3 (CH-4), 127.0 (CH), 128.8 (CH), 129.5 (CH), 129.8 (C-4a), 133.6 (C-*ipso*), 140.3 (C-7a), 145.2 (C-3), 157.6 (C-2); MS [*m*/*z* (%)]: EI: 367 (25, $M^{+\cdot}$), 303 (11, $M^{+\cdot}-SO_2$), 211 (18, $M^{+\cdot}-SO_2$, $-C_7H_7$), 91 (100, $C_7H_7^+$); HRMS: calcd for $C_{16}H_{17}NO_5S_2$: 367.0548; found: 367.0549.

4.5.3. 1-Benzyl-3-phenyl-5,7-dihydro-6,6-dioxothieno[3,4-*b*]pyridin-2(1*H*)-one 21. Yield: 57%; white crystals; mp 160 °C (decomposition); IR (KBr/cm^{-1}): 3029, 2958, 1647, 1596; ^{1}H NMR: δ 4.23 (s, 2H, CH_2), 4.27 (s, 2H, CH_2), 5.27 (s broad, 2H, CH_2–N), 7.21–7.42 (m, 9H, H–Ph+H-4), 7.65–7.09 (m, 2H, H–Ph); ^{13}C NMR: δ 49.8 (CH_2–N), 56.3 (CH_2), 56.9 (CH_2), 109.0 (C-7a), 126.9 (CH), 128.3 (CH), 128.5 (CH), 128.6 (CH), 129.2 (CH), 133.8 (C-4), 134.3 (C-4a), 135.4 (C-4a), 136.2 (C-*ipso*), 136.8 (C-*ipso*); MS [*m*/*z* (%)]: EI: 351 (24, $M^{+\cdot}$), 287 (78, $M^{+\cdot}-SO_2$), 91 (100, $C_7H_7^+$).

4.6. Intermolecular Diels–Alder reactions of sulfolene pyridinones 19–21

General procedure. A solution of 0.2 g sulfolene pyridinones **19**–**21** and 5 equiv. of a dienophile in 10 mL *o*-dichlorobenzene is brought into a glass tube and the solution is subjected to three consecutive freeze–pump–thaw cycles. The tube is sealed off and is then heated in an oven at 160 °C for 12 h. After cooling, the tube is opened, and the solvent is removed by Kugelrohr distillation. The products are purified by column chromatography (silica gel, CH_2Cl_2/EtOAc: 95/5 to 85/15) to give the following adducts.

4.6.1. ((5a*R* *,8a*S* *)-1-Benzyl-3-methoxy-7-phenyl-5,5a,8a,9-tetrahydro-1*H*-pyrrolo[3,4-*g*]quinoline-2,6,8(7*H*)-trione 22. Yield: 70%; yellow crystals; mp 197 °C (ethanol); IR (KBr/cm^{-1}): 3061, 2933, 1710, 1651, 1599; ^{1}H NMR: 2.51 (dd, 1H, ^2J=15.6 Hz, $^3J_{ax-eq}$=5.0 Hz, H-5_{ax}), 2.71 (dd, 1H, ^2J=14.0 Hz, $^3J_{ax-eq}$=4.5 Hz, H-9_{ax}), 3.06 (dd, 1H, ^2J=14.0 Hz, $^3J_{eq-eq}$=2.0 Hz, H-9_{eq}), 3.34–3.36 (m, 2H, H-5a+H-8a), 3.42 (dd, 1H, ^2J=15.6 Hz, $^3J_{eq-eq}$=2.2 Hz, H-5_{eq}), 5.06 (d, 1H, ^2J=16.0 Hz, CH_2–N), 5.86 (d, 1H, ^2J=16.0 Hz, CH_2–N), 6.51 (s, 1H, H-4), 6.98 (dd, 2H, J_o=8.0 Hz, J_m=1.0 Hz, H–Ph), 7.17 (d, 2H, J_o=7.3 Hz, H–Ph), 7.25–7.42 (m, 6H, H–Ph); ^{13}C NMR: δ 25.9 (CH_2-5), 28.6 (CH_2-9), 39.5 (CH), 39.8 (CH), 47.2 (CH_2–N), 55.9 (CH_3), 111.5 (C-9a), 113.6 (CH-4), 126.2 (CH), 126.7 (CH), 127.5 (CH), 128.8 (CH), 129.2 (CH), 131.4 (C-4a), 132.2 (C-*ipso*), 136.5 (C-*ipso*), 148.8 (C-3), 158.5 (C-2), 177.4 (C), 177.9 (C); MS [*m*/*z* (%)]: EI: 414 (72, $M^{+\cdot}$), 323 (15, $M^{+\cdot}-C_7H_7$), 176 (75, $M^{+\cdot}-C_7H_7$,$-C_8H_5NO_2$; HRMS: calcd for $C_{25}H_{22}N_2O_4$: 414.1580; found: 414.1584.

4.6.2. (5a*R* *,8a*S* *)-1-Benzyl-3-(ethylsulfonyl)-7-phenyl-5,5a,8a,9-tetrahydro-1*H*-pyrrolo[3,4-*g*]quinoline-2,6,8(1*H*,7*H*)-trione 23. Yield: 60%; yellow crystals, mp 124–125 °C (CH_2Cl_2/hexane); IR (KBr/cm^{-1}): 2974, 1652, 1536, 1304, 1120; ^{1}H NMR: δ 1.22 (t, 3H, ^3J=7.4 Hz, CH_3), 2.66 (dd, 1H, ^2J=15.9 Hz, ^3J=5.5 Hz, H-9ax), 2.75 (dd, 1H, ^2J=15.5 Hz, ^3J=6.2 Hz, H-5ax), 3.11 (dd, 1H, ^2J=15.5 Hz, ^3J=2.4 Hz, H-5eq), 3.39 (m, 3H, H-9eq+H-5a+H-8a), 3.50 (q, 2H, ^3J=7.4 Hz, CH_2), 5.10 (d, 1H, ^2J=15.7 Hz, CH_2–N), 5.86 (d, 1H, ^2J=15.7 Hz, CH_2–N), 6.98 (d, 2H, J_o=8 Hz, H–Ph), 7.10 (d, 2H, J_o=8 Hz, H–Ph), 7.20–7.40 (m, 6H, H–Ph), 8.06 (s, 1H, H-4); ^{13}C NMR: δ 7.0 (CH_3), 27.7 (C-9), 28.4 (C-5), 39.4 (CH), 39.5 (CH), 47.0 CH_2–N), 47.4 (CH_2–SO_2), 112.6 (C), 125.7, 126.4, 127.0 (C), 128.4, 129.3, 129.6, 131.6 (C), 135.7 (C-*ipso*), 143.7 (CH), 151.6 (C-3), 158.7 (C-2), 177.2 (CO), 177.4 (CO); MS [*m*/*z* (%)]: EI: 476 (24, $M^{+\cdot}$), 385 (3, $M^{+\cdot}-C_7H_7$), 91 (100, $C_7H_7^+$); HRMS: calcd for $C_{26}H_{24}N_2O_5$: 476.1406; found: 476.1412.

4.6.3. (5a*R* *,8a*S* *)-1-Benzyl-3,7-diphenyl-5,5a,8a,9-tetrahydro-1*H*-pyrrolo[3,4-*g*]quinoline-2,6,8(1*H*,7*H*)-trione 24. Yield: 87%; pale yellow crystals, mp 98–98.5 °C; IR (KBr/cm^{-1}): 3032, 2953, 1711, 1643, 1595; ^{1}H NMR: δ 2.65 (dd, 1H, ^2J=14.0 Hz, ^3J=3.8 Hz, H-9ax), 2.75 (dd, 1H, ^2J=15.0 Hz, ^3J=3.9 Hz, H-5ax), 3.12 (dd, 1H, ^2J=15.0 Hz, ^3J=1.7 Hz, H-5eq), 3.37 (m, 2H, H-5a+H-8a), 3.49 (dd, 1H, ^2J=14.0 Hz, ^3J=1.6 Hz, H-9eq), 5.11 (d, 1H, ^2J=15.6 Hz, CH_2–N), 5.89 (d, 1H, ^2J=15.6 Hz, CH_2–N), 7.03 (d, 2H, J_o=7.0 Hz, H–Ph), 7.21–7.42 (m, 12H, H–Ph+H-4), 7.71 (d, 2H, J_o=7.1 Hz, H–Ph); ^{13}C NMR: δ 27.1 (CH_2), 28.6 (CH_2), 39.8 (CH), 39.9 (CH), 47.8 (CH_2–N), 113.1 (C-9a), 126.1 (CH), 126.7 (CH), 127.5 (CH), 127.8 (CH), 128.1 (CH), 128.6 (CH), 128.8 (CH), 128.9 (CH), 129.1 (CH), 130.2 (C-*ipso*), 131.9 (C-4a), 137.0 (C-*ipso*), 137.1 (C-*ipso*), 138.6 (C-4), 142.3 (C-3), 162.3 (C-2), 177.7 (C-8), 178.2 (C-6); MS [*m*/*z* (%)]: EI: 460 (57, $M^{+\cdot}$), 369 (7, $M^{+\cdot}-C_7H_7$), 383 (2, $M^{+\cdot}-C_6H_5$), 222 (57, $M^{+\cdot}-C_7H_7$,$-C_6H_5NC_2O_2$), 91 (100, $C_7H_7^+$); HRMS: calcd for $C_{30}H_{24}N_2O_3$: 460.1787; found: 460.1788.

4.6.4. Methyl 1-benzyl-3-methoxy-5,6,7,8-tetrahydro-2-oxo-1*H*-quinoline-7-carboxylate 25a and methyl 1-benzyl-3-methoxy-5,6,7,8-tetrahydro-2-oxo-1*H*-quinoline-6-carboxylate 25b. Yield: 70%; yellow oil; ^{1}H NMR (C_6D_6): δ 1.34–1.44 (m, 0.5H, H–CH_2), 1.47–1.53 (m, 0.5H, H–CH_2), 1.59–1.64 (m, 0.5H, H–CH_2), 1.66–1.72 (m, 0.5H, H–CH_2), 1.85–1.93 (m, 0.5H, H–CH_2), 2.05–2.20 (m, 2.5H, H-7 **a**+H-6 **b**+3×H–CH_2), 2.32 (dd, 0.5H, ^2J=16 Hz, ^3J=5.2 Hz, H-5eq **b**), 2.42 (dd, 0.5H, ^2J=17 Hz, ^3J=5.6 Hz, H-8eq **a**), 2.54 (dd, 0.5H, ^2J=16 Hz, ^3J=8 Hz, H-5ax **b**), 2.58 (dd, 0.5H, ^2J=17 Hz, ^3J=9 Hz, H-8ax **a**), 3.24 (s, 1.5H, OCH_3 **a**), 3.34 (s, 1.5H, OCH_3 **b**), 3.42 (s, 3H, OCH_3 **a**+**b**), 4.99–5.30 (m breed, 2H, CH_2N **a**+**b**), 5.96 (s, 0.53H, H-4 **b**), 5.99 (s, 0.47H, H-4 **a**), 6.96–7.16 (m, 5H, H–Ph **a**+**b**).

($CDCl_3$): δ 1.74–1.82 (m, 1H, H–CH_2), 2.06–2.11 (m, 1H, H–CH_2), 2.53–2.82 (m, 5H, 2×H–CH_2+H–CH), 5.10–5.50 (m, 2H, CH_2N), 6.40 (s, 0.53H, H-4), 6.42 (s, 0.47H, H-4), 7.11–7.28 (m, 5H, H–Ph); ^{13}C NMR: δ 24.4 (CH_2), 24.6 (CH_2), 25.1 (CH_2), 26.7 (CH_2), 27.7 (CH_2), 29.8 (CH_2), 38.2 (CH), 38.9 (CH), 46.5 (CH_2N), 51.6 (OCH_3), 51.7 (OCH_3), 55.5 (OCH_3), 110.9 (C), 111.9 (C), 114.3 (CH), 114.4 (CH), 126.2 (CH-arom), 126.3 (CH-arom), 126.9 (CH-arom), 128.4 (CH-arom), 131.3, 132.4, 136.4 (C-*ipso*), 147.5 (C-3), 158.3 (C-2), 174.3 (CO), 174.5 (CO); MS [*m*/*z*

(%)]: EI: 327 (40, $M^{+\cdot}$), 295 (20, $M^{+\cdot}-MeOH$), 236 (45, $M^{+\cdot}-C_7H_7$), 91 (100, $C_7H_7^+$); HRMS: calcd for $C_{19}H_{21}NO_4$: 327.1471; found: 327.1480.

4.6.5. Methyl 1-benzyl-3-(ethylsulfonyl)-5,6,7,8-tetrahydro-2-oxo-1*H*-quinoline-7-carboxylate 26a and methyl 1-benzyl-3-(ethylsulfonyl)-5,6,7,8-tetrahydro-2-oxo-1*H*-quinoline-6-carboxylate 26b. Yield: 94%; yellow oil; IR (NaCl/cm^{-1}): 3032, 2951, 1737, 1659, 1593; ^1H NMR: δ 1.28 (t, 3H, ^3J=8.7 Hz, CH_3–Et), 1.77–1.86 (m, 1H, H–CH_2), 2.03–2.16 (m, 1H, H–CH_2), 2.66–3.00 (m, 5H, 2×CH_2+H–CH), 3.54 (q, 2H, ^3J=8.7 Hz, CH_2–Et), 3.67 (s, 1.3H, OCH_3), 3.69 (s, 1.7H, OCH_3), 5.12–5.23 (m, 2H, CH_2N), 7.10–7.91 (m, 5H, H–Ph), 8.00 (s, 0.45H, H-4 b), 8.10 (s, 0.55H, H-4 a); MS [*m*/*z* (%)]: EI: 389 (28, $M^{+\cdot}$), 330 (22, $M^{+\cdot}-CO_2Me$), 298 (7, $M^{+\cdot}-C_7H_7$), 91 (100, $C_7H_7^+$); HRMS: calcd for $C_{20}H_{23}NO_5S$: 389.1297; found: 389.1296.

4.6.6. Methyl 1-benzyl-3-phenyl-5,6,7,8-tetrahydro-2-oxo-1*H*-quinoline-7-carboxylate 27a and methyl 1-benzyl-3-phenyl-5,6,7,8-tetrahydro-2-oxo-1*H*-quinoline-6-carboxylate 27b. Yield: 85%; light yellow oil; IR (NaCl/cm^{-1}): 3029, 2950, 1735, 1650, 1599; ^1H NMR ($CDCl_3$): δ 7.76–1.85 (m, 1H, H–CH_2), 2.07–2.13 (m, 1H, H–CH_2), 2.61–2.91 (m, 5H, 2×CH_2+H–CH), 5.30–5.52 (m broad, 2H, CH_2N), 7.15–7.22 (m, 3H, H–Ph), 7.26–7.30 (4H, H–Ph+H-4), 7.35–7.37 (m, 2H, H–Ph), 7.71–7.73 (m, 2H, H–Ph); (C_6D_6): δ 1.33–1.40 (m, 0.5H, H–CH_2), 1.43–1.50 (m, 0.5H, H–CH_2), 1.57–1.61 (m, 0.5H, H–CH_2), 1.64–1.69 (m, 0.5H, H–CH_2), 1.88–1.97 (m, 0.5H, H–CH_2), 2.02–2.25 (m, 2.5 H, 2×CH_2+H–CH), 2.36 (dd, 0.5H, ^2J=17.5 Hz, ^3J=5.6 Hz, H-8 **a**), 2.36 (dd, 0.5H, ^2J=15.9 Hz, ^3J=5.1 Hz, H-5 **b**), 2.52 (dd, 0.5H, ^2J=15.9 Hz, ^3J=9.8 Hz, H-5 **b**), 2.63 (dd, 0.5H, ^2J=17.5 Hz, ^3J=8.8 Hz, H-8 **a**), 3.24 (s, 1.4H, OCH_3 **a**), 3.34 (s, 1.6H, OCH_3 **b**), 5.00–5.50 (m broad, 2H, CH_2N **a**+**b**), 6.97 (s, 0.43H, H-4 **a**), 6.99 (s, 0.57H, H-4 **b**), 7.04–7.10 (m, 4H, H–Ph), 7.16–7.20 (m, 2H, H–Ph), 7.29–7.33 (m, 2H, H–Ph), 8.00–8.02 (m, 2H, H–Ph); ^{13}C NMR: δ 24.6 (CH_2), 24.7 (CH_2), 26.1 (CH_2), 26.3 (CH_2), 28.7 (CH_2), 29.6 (CH_2), 38.3 (CH), 38.9 (CH), 46.9 (CH_2N), 51.8 (OCH_3), 51.9 (OCH_3), 112.5 (C), 113.4 (C), 126.3 (CH-arom), 126.4 (CH-arom), 127.1 (CH-arom), 127.4 (CH-arom), 127.9 (CH-arom), 128.5 (CH-arom), 128.7 (CH-arom), 136.5 (C-*ipso*), 136.6 (C-*ipso*), 136.9, 139.2, 139.3, 140.7, 141.6, 161.8 (C-2), 174.3 (CO), 174.6 (CO); MS [*m*/*z* (%)]: EI: 373 (100, $M^{+\cdot}$), 314 (56, $M^{+\cdot}-CO_2Me$), 282 ($M^{+\cdot}-C_7H_7$), 222 ($M^{+\cdot}-C_7H_7$, $-CO_2Me$), 91 (60, $C_7H_7^+$); HRMS: calcd for $C_{24}H_{23}NO_3$: 373.1678; found: 373.1681.

4.6.7. Dimethyl (6*R,7*S**) 1-benzyl-3-methoxy-5,6,7,8-tetrahydro-2-oxo-1*H*-quinoline-6,7-dicarboxylate 28.** Yield: 77%; white crystals; mp 152–153 °C; IR (KBr/cm^{-1}): 3029, 2949, 1743, 1655, 1598; ^1H NMR: δ 1.75–2.91 (m, 2H), 2.90–3.10 (m, 4H), 3.55 (s, 3H, OCH_3), 3.59 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 5.24 (d, 1H, ^2J=20.1 Hz, CH_2–N), 5.41 (d, 1H, ^2J=20.1 Hz, CH_2–N), 6.37 (s, 1H, H-4), 7.09 (d, 2H, J_o=8.0 Hz, H–Ph), 7.15–7.22 (m, 3H, H–Ph); ^{13}C NMR: δ 26.5 (CH_2), 28.1 (CH_2), 39.2 (CH), 39.7 (CH), 46.7 (CH_2–N), 52.0 (CH_3), 52.1 (CH_3), 55.7 (CH_3), 110.9 (C-8a), 114.1 (CH-4), 126.5 (CH), 127.2 (CH), 128.6 (CH), 131.4 (C-4a), 136.9 (C-*ipso*), 148.4 (C-3), 158.9 (C-2), 172.6 (C), 172.9 (C); MS [*m*/*z* (%)]: EI: 385 (71, $M^{+\cdot}$), 354 (8, $M^{+\cdot}-OCH_3$), 326 (41, $M^{+\cdot}-C_2H_3O_2$), 294 (19, $M^{+\cdot}-C_7H_7$), 266 ($M^{+\cdot}-C_2H_3O_2$, $-C_2H_3O_2$), 234 (20, $M^{+\cdot}-C_2H_3O_2$, $-C_7H_7$), 91 (100, $C_7H_7^+$); HRMS: calcd for $C_{21}H_{23}NO_6$: 385.1525; found: 385.1525.

4.6.8. 1-Benzylnaphto[2,3-*g*]quinoline-2,6,11(1*H*)-trione 29. Yield: 80%; yellow oil; ^1H NMR: δ 4.07 (s, 3H, CH_3), 5.70 (s, 2H, CH_2–N), 7.06 (s, 1H, H-4), 7.24–7.38 (m, 6H, H-arom), 7.76–7.79 (m, 2H, H-arom), 8.22 (s, 1H, CH), 8.25–8.30 (m, 2H, H-arom), 8.40 (s, 1H, CH); ^{13}C NMR: δ 46.9 (CH_2–N), 56.4 (CH_3), 109.9, 113.5, 125.4, 127.1, 127.3, 127.8, 127.9, 128.9, 131.7, 133.7, 133.8, 134.1, 134.2, 135.5 (C-*ipso*), 138.3, 150.7 (C-3), 158.2 (C-2), 182.0 (CO), 182.3 (CO); MS [*m*/*z* (%)]: EI: 395 (28, $M^{+\cdot}$), 304 (7, $M^{+\cdot}-C_7H_7$), 91 (100, $C_7H_7^+$); HRMS: calcd for $C_{25}H_{17}NO_4$: 395.1158, found: 395.1153.

4.6.9. Dimethyl 1-benzyl-3-methoxy-2-oxo-1*H*-quinoline-6,7-dicarboxylate 30. Yield: 77%; yellow oil; IR (KBr/cm^{-1}): 2952, 1793, 1657, 1622; ^1H NMR: δ 3.56 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 5.17 (d, 1H, ^2J=20 Hz, CH_2–N), 5.63 (d, 1H, ^2J=20 Hz, CH_2–N), 6.51 (s, 1H, H-4), 7.24–7.30 (m, 6H, H-8+H–Ph), 7.47 (s, 1H, H-5); ^{13}C NMR: δ 47.6 (CH_2–N), 52.7 (CH_3), 52.9 (CH_3), 56.5 (CH_3), 113.2 (CH), 116.4 (CH-4), 127.3, 127.4, 127.9, 128.9, 129.2, 130.1, 136.8 (C-*ipso*), 151.2 (C-3), 158.0 (C-2), 163.0, 166.5 (CO), 171.4 (CO); MS [*m*/*z* (%)]: EI: 383 (29, $M^{+\cdot}$), 324 (21, $M^{+\cdot}-C_2H_3O_2$), 292 (19, $M^{+\cdot}-C_7H_7$), 91 (100, $C_7H_7^+$); HRMS: Calcd for $C_{21}H_{21}NO_6$: 383.1369, Found: 383.1368.

4.6.10. 1-Benzyl-3-methoxy-6-[(4-methylfenyl)sulfonyl][1,7]naphthyridin-2(1*H*)-one 31. Yield: 40%; yellow crystals; mp 237–238 °C; IR (KBr/cm^{-1}): 3067, 2930, 1660, 1319, 1158; ^1H NMR: δ 2.39 (s, 3H, CH_3), 4.03 (s, 3H, OCH_3), 5.58 (s, 2H, CH_2–N), 6.97 (s, 1H, H-4), 7.18–7.30 (m, 7H, H–Ph), 7.90 (d, 2H, J_o=8.3 Hz, H–Ph), 8.30 (s, 1H, H-5), 8.63 (s, 1H, H-8); ^{13}C NMR: δ 21.6 (CH_3), 46.6 (CH_2), 56.6 (CH_3), 107.9 (CH), 119.4 (CH), 126.8 (CH), 127.3 (C), 128.0 (C), 128.8 (CH), 129.1 (CH), 129.8 (CH), 132.0 (C), 134.8 (C), 136.1 (C), 137.4 (CH), 144.7 (C), 151.9 (C), 152.9 (C); MS [*m*/*z* (%)]: EI: 420 (2, $M^{+\cdot}$), 355 (83, $M^{+\cdot}-SO_2$, –H), 91 (100, $C_7H_7^+$); HRMS: calcd for $C_{23}H_{20}N_2O_4S$: 420.1144, found: 420.1139; CHN analysis: calcd for $C_{23}H_{20}N_2O_4S$: C 65.70, H 4.79, N 6.66; found: C 65.36, H 4.94, N 6.33.

4.6.11. 1-Benzyl-3-methoxy-7-[(4-methylphenyl)sulfonyl][1,6]naphthyridin-2(1*H*)-one 32. Yield: 27%; pale yellow crystals; mp 218–220 °C; IR (KBr/cm^{-1}): 3058, 2927, 1668, 1316, 1158; ^1H NMR: δ 2.38 (s, 3H, CH_3), 3.99 (s, 3H, OCH_3), 5.62 (s, 2H, CH_2–N), 6.92 (s, 1H, H-4), 7.23–7.33 (m, 7H, H–Ph), 7.76 (d, 2H, J_o=8.3 Hz, H–Ph), 8.10 (s, 1H, H-8), 8.70 (s, 1H, H-5); ^{13}C NMR: δ 21.6 (CH_3), 46.6 (CH_2–N), 56.5 (OCH_3), 106.7 (CH), 108.2 (CH), 118.9 (C), 127.3 (CH), 128.0 (CH), 128.8 (CH), 129.1 (CH), 129.8 (CH), 134.7 (C), 135.9 (C), 140.3 (C), 144.8 (C), 149.2 (C), 151.2 (C), 156.1 (C), 158.0 (C); MS [*m*/*z* (%)]: EI: 420 (6, $M^{+\cdot}$), 356 (43, $M^{+\cdot}-SO_2$), 265 (9, $M^{+\cdot}-SO_2$, $-C_7H_7$), 91 (100, $C_7H_7^+$); HRMS: calcd for $C_{23}H_{20}N_2O_4S$: 420.1144, found: 420.1147.

4.7. Substitution of sulfolene pyridinone 19 in position 7

General procedure A. To a solution of 0.2 g (0.65 mmol) of the precursor **19** in dry THF (25 mL) under argon atmosphere was added slowly 1.3 equiv. of tetrabutylammonium fluoride. After stirring at room temperature for 1 h, 2 equiv. of electrophile were added. The reaction mixture was stirred for 12 h at room temperature; then a solution of NH_4Cl (25 mL) was added, the mixture was stirred further at room temperature for 1 h and extracted with CH_2Cl_2 (3×10 mL). The combined organic phases were dried ($MgSO_4$) and evaporated to give a residue that was purified by column chromatography (alumina, 15 EtOAc/85 CH_2Cl_2).

General procedure B. To a cooled (0 °C) suspension of 1.1 equiv. of NaH in DMF (10 mL) was added under a nitrogen atmosphere a solution of 0.2 g (0.65 mmol) sulfolene pyridinone **19**. Stirring was continued at 0 °C for 1 h, after which time 2 equiv. of an electrophile was added. The reaction mixture was allowed to slowly warm to room temperature. After work up by adding 20 mL of saturated NH_4Cl solution and extraction with CH_2Cl_2 (3×15 mL), the combined organic layers were dried over $MgSO_4$. The solvent was evaporated and the residue was purified by column chromatography (alumina, 15 EtOAc/85 CH_2Cl_2).

4.7.1. 1,7-Dibenzyl-5,7-dihydro-3-methoxy-6,6-dioxothieno [3,4-*b*]pyridin-2(1*H*)-one 34. Yield: 60% (procedure B); 40% (procedure A); oil; IR (NaCl/cm^{-1}): 3055, 2976, 1607, 1325, 1124; ^{1}H NMR: δ 3.21 (dd, 1H, ^2J=14.7 Hz, ^3J=5.5 Hz, CH_2–Ph), 3.39 (dd, 1H, ^2J=14.7 Hz, ^3J=5.5 Hz, CH_2–Ph), 3.58 (d, 1H, ^2J=15.0 Hz, H-5), 3.82 (s, 3H, OCH_3); 3.87 (d, 1H, ^2J=15.0 Hz, H-5), 4.17 (t, 1H, ^3J=5.5 Hz, H-7), 4.33 (d, 1H, ^2J=16.0 Hz, CH_2–N), 5.70 (d, 1H, ^2J=16.0 Hz, CH_2–N), 6.38 (s, 1H, H-4), 7.03–7.07 (m, 4H, H–Ph), 7.24–7.29 (m, 6H, H–Ph); ^{13}C NMR: δ 36.9 (CH_2-5), 48.3 (CH_2–N), 54.8 (CH_2–Bn), 56.2 (CH_3), 64.9 (CH-7), 108.8 (C-7a), 108.9 (CH-4), 126.4 (CH), 127.8 (CH), 128.6 (CH), 128.8 (CH), 129.1 (CH), 129.7 (CH), 132.1 (C-4a), 134.1 (C-*ipso*), 135.1 (C-*ipso*), 150.6 (C-3), 157.9 (C-2); MS [*m*/*z* (%)]: EI: 395 (42, $M^{+\cdot}$), 331 (60, $M^{+\cdot}-SO_2$), 304 (12, $M^{+\cdot}-C_7H_7$), 240 (35, $M^{+\cdot}-SO_2$, $-C_7H_7$), 91 (100, $C_7H_7^+$); HRMS: calcd for $C_{22}H_{21}NO_4S$: 395.1112, found: 395.1120.

4.7.2. 1-Benzyl-5,7-dihydro-3-methoxy-7-(4-pentenyl)-6,6-dioxothieno[3,4-*b*]pyridin-2(1*H*)-one 35. Yield: 57% (method B), 25% (method A); yellow crystals; mp 54.6–55.8 °C (CH_2Cl_2/hexane); IR (KBr/cm^{-1}): 3064, 2925, 1658, 1607, 1315, 1125; ^{1}H NMR: δ 1.33–1.51 (m, 2H, CH_2-3′), 1.69–1.92 (m, 4H, CH_2-1′+CH_2-2′), 3.79 (s, 3H, OCH_3), 3.91 (dd, 1H, ^3J=7.7, 3.2 Hz, H-7), 4.03 (d, 1H, ^2J=15.4 Hz, H-5), 4.10 (d, 1H, ^2J=15.4 Hz, H-5), 4.89 (dt, 1H, $^3J_{trans}$=16.9 Hz, ^4J=1.3 Hz, H-5′), 4.92 (d broad, 1H, $^3J_{cis}$=9.0 Hz, H-5′), 4.96 (d, 1H, ^2J=15.8 Hz, CH_2–N), 5.45 (d, 1H, ^2J=15.8 Hz, CH_2–N), 5.60 (ddt, 1H, $^3J_{trans}$=16.9 Hz, $^3J_{cis}$=9.0 Hz, ^3J=7.0 Hz, H-4′), 6.48 (s, 1H, H-4), 7.58 (dd, 2H, J_o=6.4 Hz, J_m=1.8 Hz, H–Ph), 7.22–7.27 (m, 3H, H–Ph); ^{13}C NMR: δ 25.3 (CH_2), 30.5 (CH_2), 33.4 (CH_2), 48.6 (CH_2–N), 55.7 (CH_2-5), 56.6 (CH_3), 64.7 (CH-7), 108.1 (C-7a), 109.4 (CH-4), 116.0 (CH_2-5′), 126.0 (CH), 127.9 (CH), 129.0 (CH), 132.5 (C-4a), 135.5 (C-*ipso*), 137.5 (CH-4′), 150.9 (C-3), 158.5 (C-2); MS [*m*/*z* (%)]: EI: 373 (24, $M^{+\cdot}$), 309 (25, $M^{+\cdot}-SO_2$), 254 (38, $M^{+\cdot}-SO_2$, $-C_4H_7$), 218 (37, $M^{+\cdot}-SO_2$, $-C_4H_7$), 91 (100, $C_7H_7^+$); HRMS: calcd for $C_{20}H_{23}NO_4S$: 373.1348, found: 373.1350.

4.7.3. Allyl 1-benzyl-5,7-dihydro-3-methoxy-2,6,6-trioxo-1*H*-thieno[3,4-*b*]pyridine-7-carboxylate 36. Yield: 61% (method B); yellow oil; ^{1}H NMR: δ 3.88 (s, 3H, OCH_3), 4.17 (d, 1H, ^2J=14.8 Hz, H-5), 4.39 (d, 1H, ^2J=14.8 Hz, H-5), 4.46 (dt, 2H, ^3J=6.0 Hz, ^4J=1.3 Hz, H-3′), 4.87 (s, 1H, H-7), 4.96 (d, 1H, ^2J=15.9 Hz, CH_2–N), 5.27 (dd, 1H, $^3J_{cis}$=10.4 Hz, ^4J=1.3 Hz, H-5′), 5.32 (dd, 1H, $^3J_{trans}$=17.2 Hz, ^4J=1.3 Hz, H-5′), 5.44 (d, 1H, ^2J=15.9 Hz, CH_2–N), 5.80 (ddt, 1H, $^3J_{trans}$=17.2 Hz, $^3J_{cis}$=10.4 Hz, ^3J=6.0 Hz, H-4′), 6.56 (s, 1H, H-4), 7.12 (d, 2H, J_o=6.0 Hz, H–Ph), 7.28–7.30 (m, 3H, H–Ph); ^{13}C NMR: δ 48.8 (CH_2–N), 56.1 (OCH_3), 56.2 (CH_2-5), 67.6 (CH_2-3′), 69.1 (CH-7), 108.5 (CH-4), 110.3 (C-7a), 120.0 (CH_2-5′), 126.6 (CH), 127.4 (C-4a), 128.1 (CH), 128.9 (CH), 130.3 (CH-4′), 134.4 (C-*ipso*), 151.4 (C-3), 157.6 (C-2), 162.5 (C-1′); MS [*m*/*z* (%)]: EI: 389 (20, $M^{+\cdot}$), 325 (6, $M^{+\cdot}-SO_2$), 284 (14, $M^{+\cdot}-SO_2$, $-C_3H_5$), 240 (19, $M^{+\cdot}-SO_2$, $-C_4H_5O_2$), 234 (2, $M^{+\cdot}-SO_2$, $-C_7H_7$), 91 (100, $C_7H_7^+$); HRMS: calcd for $C_{19}H_{19}NO_6S$: 389.0933, found: 389.0939.

4.7.4. Methyl 1-benzyl–5,7-dihydro-3-methoxy-2,6,6-trioxo-1*H*-thieno[3,4-*b*]pyridine-7-carboxylate 37. Yield: 59% (method B); yellow oil; IR (NaCl/cm^{-1}): 3055, 2926, 1750, 1655, 1319, 1110; ^{1}H NMR: δ 3.62 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 4.15 (d, 1H, ^2J=14.8 Hz, H-5), 4.40 (d, 1H, ^2J=14.8 Hz, H-5), 4.86 (s, 1H, H-7), 4.99 (d, 1H, ^2J=15.7 Hz, CH_2–N), 5.41 (d, 1H, ^2J=15.7 Hz, CH_2–N), 6.55 (s, 1H, H-4), 7.12 (dd, 2H, J_o=6.8 Hz, J_m=1.5 Hz, H–Ph), 7.26–7.30 (m, 3H, H–Ph); ^{13}C NMR: δ 48.9 (CH_2–N), 54.0 (OCH_3), 56.2 (CH_2-5), 56.3 (OCH_3), 69.2 (CH-7), 108.5 (CH-4), 110.3 (C-7a), 126.7 (CH), 127.5 (C-4a), 128.2 (CH), 129.0 (CH), 134.4 (C-*ipso*), 151.6 (C), 157.9 (C-2), 163.4 (C); MS [*m*/*z* (%)]: EI: 363 (22, $M^{+\cdot}$), 299 (14, $M^{+\cdot}-SO_2$), 240 (17, $M^{+\cdot}-SO_2$, $-C_7H_7$), 91 (100, $C_7H_7^+$); HRMS: calcd for $C_{17}H_{17}NO_6S$: 363.0777, found: 363.0778.

4.7.5. *N*,*N*-Diallyl-1-benzyl-5,7-dihydro-3-methoxy-2,6,6-trioxo-1*H*-thieno[3,4-*b*]pyridine-7-carboxamide 38. Yield: 58% (method B); yellow oil; IR (NaCl/cm^{-1}): 3070, 2936, 1660, 1609, 1329, 1129; ^{1}H NMR: δ 3.71 (m, 2H, 2×CH_2–allyl), 3.78 (s, 3H, OCH_3), 3.89 (dd, 1H, ^3J=6 Hz, ^2J=17 Hz, CH_2–allyl), 4.09 (d, 1H, ^2J=14.6 Hz, CH_2-5), 4.13 (dd, 1H, ^3J=6 Hz, ^2J=15.1 Hz, CH_2–allyl), 4.35 (d, 1H, ^2J=14.6 Hz, CH_2-5), 4.38 (d, 1H, ^2J=16.5 Hz, CH_2–N), 4.98 (d+m, 2H, ^2J=16.5 Hz, CH_2–N+H–C=), 5.03 (s, 1H, H-7), 5.14 (dd, 1H, ^3J=6 Hz, ^4J=1.3 Hz, =CH_2), 5.19 (dd, 1H, ^3J=13 Hz, ^4J=1.3 Hz, =CH_2), 5.54 (m, 2H, =CH_2), 5.68 (m, H, H–C=), 6.50 (s, 1H, H-4), 6.94 (d, 2H, J_o=8.5 Hz, H–Ph), 7.20–7.25 (m, 3H, H–Ph); ^{13}C NMR: 48.7 (CH_2), 49.2 (CH_2), 50.3 (CH_2), 56.2 (CH_2), 56.5 (OCH_3), 66.8 (CH), 108.7 (CH), 110.0 (C), 118.7 (CH_2), 119.2 (CH_2), 125.6 (C-arom), 127.8 (C-arom), 128.9 (C-arom), 131.4 (CH), 131.6 (CH), 134.4 (C-*ipso*), 151.1 (C-3), 157.6 (C-2), 161.6 (C-1′); MS [*m*/*z* (%)]: EI: 428 (10, $M^{+\cdot}$), 364 (100, $M^{+\cdot}-SO_2$), 273 (36, $M^{+\cdot}-SO_2$, $-C_7H_7$), 190 (74, $M^{+\cdot}-SO_2$, $-C_7H_7$, $-C_6H_{11}$), 91 (76, $C_7H_7^+$); HRMS: calcd for $C_{22}H_{24}N_2O_5S$: 428.1406, found: 428.1412.

4.7.6. 1-Benzyl-7-bromo-5,7-dihydro-3-methoxy-6,6-dioxothieno[3,4-*b*]pyridin-2(1*H*)-one 39. (A) A solution

of 0.1 g (0.32 mmol) 2(1*H*)-pyrazinone **19** and 1.1 equiv. NBS in CCl_4 was irradiated with a 500 W tungsten-lamp for 1 h, then the solvent was evaporated. The residue was chromatographed (silica gel, 85 CH_2Cl_2/15 EtOAc) to yield 45% of compound **39**.

(B) A solution of **19** and NBS (1.1 equiv.) and a catalytic amount of benzoylperoxide in CCl_4 was refluxed for 3 h to afford compound **39**, in 67% yield, after chromatographic purification.

Yellow oil; ^{1}H NMR: δ 3.87 (s, 3H, CH_3), 4.08 (d, 1H, J=16 Hz, H-5), 4.29 (d, 1H, J=16 Hz, H-5), 4.83 (d, 1H, ^2J=15.7 Hz, CH_2–N), 5.09 (s, 1H, H-7), 6.10 (d, 1H, ^2J=15.7 Hz, CH_2–N), 6.67 (s, 1H, H-4), 7.05–7.12 (m, 2H, H–Ph), 7.13–7.35 (m, 3H, H–Ph); ^{13}C NMR: δ 50.0 (CH_2–N), 55.0 (OCH_3), 57.5 (CH_2-5), 70.1 (CH-7), 110.1 (CH-4), 113.3 (C-7a), 126.7 (CH), 128.0 (C), 128.2 (CH), 129.0 (CH), 134.4 (C-*ipso*), 152.8 (C), 160.1 (C), 164.1 (C); MS [*m*/*z* (%)]: EI: 305 (61, $M^{+\cdot}-Br$), 241 (20, $M^{+\cdot}-Br,-SO_2$), 91 (100, $C_7H_7^+$).

4.8. Intramolecular Diels–Alder reactions

4.8.1. 1-Benzyl-6-[(1*E*)-1,5-hexadienyl]-3-methoxy-5-methyl-2(1*H*)-pyridinone 40. Yield: 55%; yellow oil; IR (NaCl/cm^{-1}): 3004, 2933, 1650, 1605; ^{1}H NMR: δ 2.09 (s, 3H, CH_3), 2.16 (t broad, 2H, ^3J=6.7 Hz, CH_2), 2.24 (t, 2H, ^3J=6.6 Hz, CH_2), 3.83 (s, 3H, OCH_3), 4.90 (d, 1H, ^3J=9.0 Hz, H-6′), 5.01 (d, 1H, ^3J=16.5 Hz, H-6′), 5.34 (s broad, 2H, CH_2–N), 5.65–5.72 (m, 2H, H-2′+H-5′), 5.92 (d, 1H, $^3J_{trans}$=16.1 Hz, H-1′), 6.54 (s, 1H, H-4), 7.12–7.26 (m, 5H, H–Ph); ^{13}C NMR: δ 19.0 (CH_3), 32.0 (CH_2), 32.7 (CH_2), 48.4 (CH_2–N), 55.6 (OCH_3), 111.9 (C-5), 115.3 (CH_2-6′), 116.1 (CH-4), 122.0 (CH), 126.9 (CH), 128.2 (CH), 128.5 (CH), 134.6 (C-4), 136.9 (C-*ipso*), 137.3 (CH), 139.7 (CH), 147.8 (C-3), 157.7 (C-2); MS [*m*/*z* (%)]: EI: 309 (100, $M^{+\cdot}$), 294 (15, $M^{+\cdot}-CH_3$), 254 (82, $M^{+\cdot}-C_4H_7$), 218 (42, $M^{+\cdot}-C_7H_7$), 190 (12, $M^{+\cdot}-C_7H_7$, –CO), 91 (84, $C_7H_7^+$); HRMS: calcd for $C_{20}H_{23}NO_2$: 309.1729, found: 309.1733.

4.8.2. (6a*S,9a*S**)-8-Allyl-1-benzyl-3-methoxy-5,6,6a,7,8,9a-hexahydro-1*H*-pyrrolol[3,4-*b*]quinoline-2,9-dione 41.** Yield: 65%; dark yellow oil; IR (NaCl/cm^{-1}): 2934, 1683, 1609; ^{1}H NMR: δ 1.66 (ddd, ^3J=13, 9.1, 6 Hz, H-6ax), 1.79 (ddd, 1H, ^3J=13, 8, 4 Hz, H-6eq), 2.43 (m, 1H, H-6a), 2.50–2.64 (m, 2H, H-5), 2.94 (d, 1H, ^2J=10 Hz, H-7), 3.48 (dd, 1H, ^2J=10 Hz, ^3J=6 Hz, H-7), 3.57 (d, 1H, ^3J=6.2 Hz, H-9a), 3.81 (m, 1H, H-8′), 3.83 (s, 3H, OCH_3), 3.97 (dd, 1H, ^2J=15 Hz, ^3J=6 Hz, H-8′), 5.18 (dd 1H, $^{trans}J$=19 Hz, ^4J=1.3 Hz, H-8‴), 5.21 (d, 1H, ^{cis}J=9 Hz, H-8‴), 5.47 (d, 1H, ^2J=16.8 Hz, CH_2–N), 5.71 (ddt, 1H, $^{trans}J$=19 Hz, ^{cis}J=9 Hz, ^3J=6 Hz, H-8″), 6.21 (d, 1H, ^2J=16.8 Hz, CH_2–N), 6.40 (s, 1H, H-4), 7.05 (d, 2H, J_o=8.8 Hz, H–Ph), 7.17–7.28 (m, 3H, H–Ph); ^{13}C NMR: δ 24.9 (C-6), 26.5 (C-5), 32.1 (C-6a), 43.2 (C-9a), 45.6 (C-8′), 46.8 (CH_2–N), 50.4 (C-7), 55.6 (OCH_3), 113.9 (C), 114.0 (C-4), 118.7 (C-8‴), 126.0 (C–Ph_{ortho}), 126.8 (C–Ph_{para}), 128.6 (C–Ph_{meta}), 128.8 (C), 131.8 (C-8″), 137.4 (C-*ipso*), 148.6 (C-3), 158.5 (C-2), 171.0 (C-9); MS [*m*/*z* (%)]: EI: 364 (91, $M^{+\cdot}$), 323 (4, $M^{+\cdot}-C_3H_5$), 273 (39, $M^{+\cdot}-C_7H_7$), 190 (100, $M^{+\cdot}-C_7H_7$, $-CONC_3H_5$), 91 (92, $C_7H_7^+$); HRMS: calcd for $C_{22}H_{24}N_2O_3$: 364.1787, found: 364.1788.

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Diastereoselective synthesis of homo-*N*,*O*-nucleosides

Ugo Chiacchio,[a,*] Filippo Genovese,[b] Daniela Iannazzo,[b] Vito Librando,[a] Pedro Merino,[c,*] Antonio Rescifina,[a] Roberto Romeo,[b] Antonio Procopio[b] and Giovanni Romeo[b,*]

[a]*Dipartimento di Scienze Chimiche, Università di Catania, Viale Andrea Doria 6, 95125 Catania, Italy*
[b]*Dipartimento Farmaco-Chimico, Università di Messina, Viale SS. Annunziata, 98168 Messina, Italy*
[c]*Departamento de Quimica Organica, Facultad de Ciencias-ICMA, Universidad de Zaragoza-CSIC, E-50009 Zaragoza, Aragon, Spain*

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Abstract—A new class of homo-*N*,*O*-nucleosides has been designed, based on the 1,3-dipolar cycloaddition of *C*-substituted nitrones with allyl nucleobases. The *N*-methyl-*C*-ethoxycarbonyl nitrone **1**, and the *C*-α-silyloxymethyl-*N*-methyl nitrone **7** have been exploited: the stereochemical features of the obtained nucleosides are dependent on the nature of the dipole. The results obtained with DFT calculations fully agree with the experimental results and successfully reproduce the experimentally observed reversal of *endo*/*exo* selectivity for nitrones **1** and **7**.

1. Introduction

Structural modifications at the level of the sugar moiety and/or the heterocyclic base in nucleosides have long been recognized to improve their antiviral or anticancer activities: in this context, the synthesis of nucleoside analogues has recently received a great deal of attention.[1]

In natural nucleosides, which possess a *N*-glycosidic linkage, the presence of an anomeric centre is one of the most important factors which contribute to the conformational behaviour of the nucleoside and, hence, to its biological features.[2] The physiological properties, in fact, may change dramatically if the anomeric aminal function is removed from the nucleoside: when replacing, for example, the furanose ring by a carbocyclic five membered ring, the biological activity changes drastically.[3] Another way of removing the anomeric centre is the introduction of a carbon bridge between the base and the carbohydrate part, leading to homo-*N*-nucleosides. In this case, besides an increased resistance to hydrolytic or enzymatic cleavage, compared to the relatively reactive aminal linkage of common nucleosides, more conformational flexibility and rotational freedom is introduced in the molecule.[4] In oligonucleotides composed of these modified nucleosides, the distance between the backbone and base moiety is increased; this feature allows a lowering of the electrostatic repulsion by maintaining the ability to build Watson–Crick base pairs with unnatural DNA or RNA strain, due to a better alignment of complementary nucleobases.[5]

Accordingly, different synthetic approaches towards 1′-homo-*C*- and *N*-nucleosides and the relative biological evaluation as antiviral or antiproliferative agents have been reported in literature. In particular, homo-*N*-nucleosides with a guanine or adenine base moiety exhibit a good antiviral activity against herpes simplex virus[6] (HSV-1 and HSV-2): the analogous uracil homo-*N*-nucleosides have been described as selective inhibitors of viral uracil-DNA glycosylases (UDGs), while having little effect on the human enzyme.[7] Moreover, also the 1′-*C*-azanucleosides have proved very valuable as sequence-specific glycosidase inhibitors and thus as potentially effective anti-HIV drugs.[8]

Recently, we have focused our attention on the synthesis of new classes of modified nucleosides where the sugar moiety has been replaced by an isoxazolidine ring: some of the new *N*,*O*-nucleosides have been shown to possess interesting biological activities.[9]

In this context, as many glycosidases may recognize different glycon moieties and differ only with the type of glycosidic linkage,[10] we have envisaged to synthesize a series of 1′-homo-*N*-nucleosides, in which the sugar unit has been changed into an isoxazolidine ring and the formal insertion of a carbon bridge into the glycosidic bond lengthens the separation between the nucleobase and the heterocyclic system. Thus, we report in this paper the design

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* Corresponding authors. Tel.: +39-95-7385014; fax: +39-6-233208980 (U.C.); tel.: +34-976-762075; fax: +34-976-762075 (P.M.); tel.: +39-90-6766562; fax: +39-90-355613 (G.R.);
e-mail addresses: uchiacchio@unict.it; pmerino@posta.unizar.es; gromeo@unime.it

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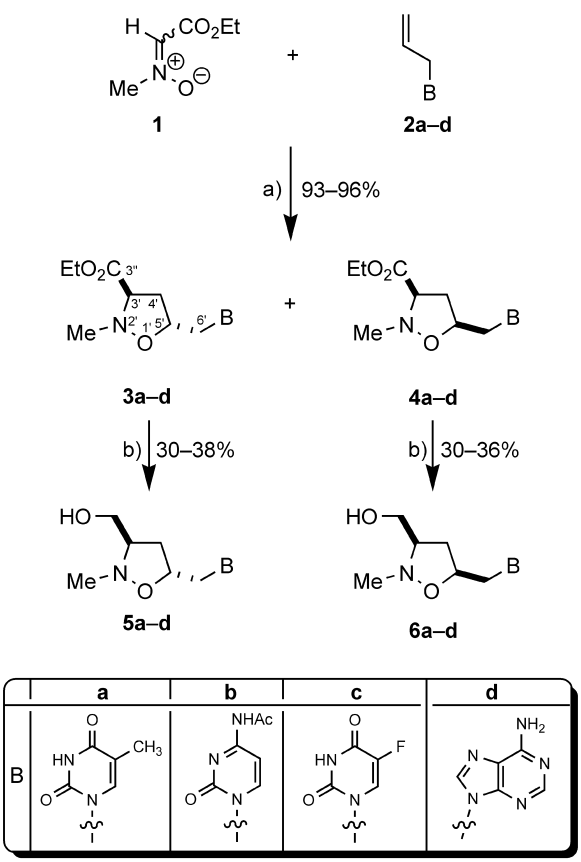
and the synthesis of a new class of {[3-(hydroxymethyl)-2-methylisoxazolidin-5-yl]methyl}-pyrimidine and purine derivatives in an effort to develop specific glycosidase inhibitors.

2. Results and discussion

The cycloaddition reaction between *N*-methyl-*C*-ethoxycarbonyl nitrone **1** (*E*/*Z* ratio 4:1)[9c] and allyl nucleobases **2** proceeded smoothly in anhydrous toluene, at 80 °C for 14 h, to give a mixture of epimeric isoxazolidines **3** and **4** in ca. 2:1 ratio and 93–96% yield (Table 1), which were separated by flash chromatography (Scheme 1, Table 1).

Table 1. Cycloaddition of nitrone **1** and allylbases **2**

Entry	Allylbase	Isoxazolidines	**3**:**4** ratio	Yield (%)
1	**2a**	**3a** and **4a**	2.1:1	96
2	**2b**	**3b** and **4b**	2.2:1	95
3	**2c**	**3c** and **4c**	2.0:1	95
4	**2d**	**3d** and **4d**	1.8:1	93



Scheme 1. (a) Toluene, sealed tube, 80 °C, 1 h; (b) $LiAlH_4$, THF, 0 °C, 1 h.

Structural determinations were performed with the aid of NOE experiments. Thus, for the major 3′,5′-*anti* isomers **3a**–**d**, irradiation of $H_{5'}$ induced a positive NOE effect on $H_{4'b}$, the downfield resonance of methylene protons at $C_{4'}$, while irradiation of $H_{3'}$ gave rise to NOE enhancement for $H_{4'a}$. These results are clearly indicative of a *trans* relationship between $H_{3'}$ and $H_{5'}$ (Fig. 1).

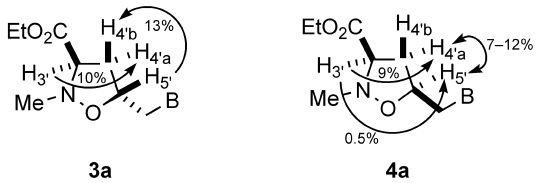


Figure 1. Selected NOEs observed for compounds **3a** and **4a**.

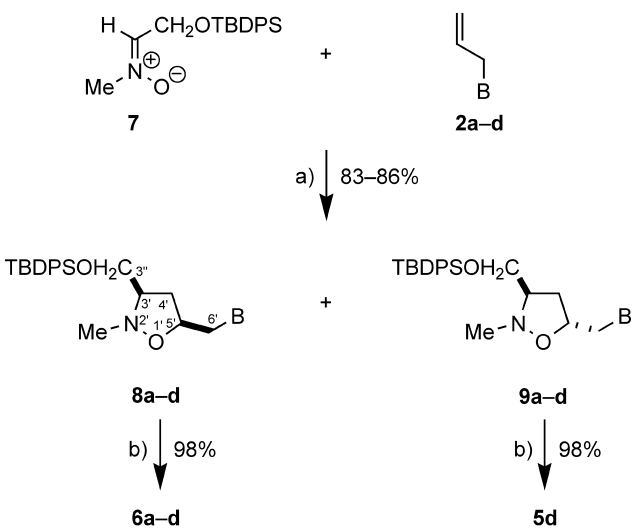
Conversely, in derivatives **4**, the positive NOE correlation between $H_{3'}$ and $H_{5'}$ confirms the *cis* topological arrangement between these protons.

The synthetic scheme was completed by reduction of the ester moiety. A series of different reducing agents have been exploited; the best results have been performed by treatment with $LiAlH_4$ in anhydrous THF to afford the target nucleosides **5** (α) and **6** (β) in moderate yields (~35%) (Scheme 1).

The designed reaction route appears to be versatile and of general application; however, serious limitations are represented by the low yields, due to the difficult reduction of ester groups, and by the obtainment of α isomers as major adducts. We have, however, achieved a successful implementation of the synthetic strategy by the use of nitrone **7**, containing a silyl ether in place of the ester as a masked alcohol functionality.

C-α-silyloxymethyl-*N*-methyl nitrone **7** was prepared in good yields starting from D-mannitol, as previously reported.[10]

The cycloaddition reaction of **7** with allyl nucleobases **2** (Scheme 2), in anhydrous THF at room temperature for 24 h, has been found to proceed with a good stereoselectivity, affording a mixture of epimeric isoxazolidines **8a**–**c** and **9a**–**c** in a relative ratio ca. 7:1 (Table 2, entries 1–3). In the case of allyladenine **2d**, only a moderate stereoselectivity is obtained with the formation of **8d** and **9d** in a 2:1 ratio (Table 2, entry 4).



Scheme 2. (a) Toluene (THF for **2d**), sealed tube, 80 °C, 24 h; (b) TBAF, THF, rt, 1 h

Table 2. Cycloaddition of nitrone **7** and allylbases **2**

Entry	Allylbase	Isoxazolidines	**8**:**9** ratio	Yield (%)
1	**2a**	**8a** and **9a**	7.1:1	85
2	**2b**	**8b** and **9b**	7.0:1	83
3	**2c**	**8c** and **9c**	7.2:1	86
4	**2d**	**8d** and **9d**	2:1	83

The crude mixtures were purified by flash chromatography (chloroform/methanol 95:5 as eluent) and cycloadducts **8a**–**d**, the major products, and **9d** were obtained in pure form.

The structure of the obtained adducts has been assigned on the basis of ^{1}H NMR data and confirmed by NOE experiments. Thus, products **8** show the resonance of $H_{3'}$ as a multiplet in the range 2.77–2.90 ppm; $H_{4'}$ protons give rise to two doublets of doublets centered at 1.75–1.87 and 2.56–2.68 ppm, while $H_{5'}$ resonate as a multiplet at 4.23–4.40 ppm. The methylene group at $C_{5'}$ resonate as two doublets of doublets in the range 3.20–4.10 ppm. In compound **9d**, the resonance of $H_{4'}$ protons appears at 1.98 and 2.76 ppm, respectively, as a doublet of doublets of doublets, whereas $H_{3'}$ appears at 2.88 ppm as a doublet of doublets of doublets of doublets and $H_{5'}$ resonates as a multiplet at 4.20 ppm.

The stereochemistry of the adducts was readily deduced by means of NOE measurements (Fig. 2). In compounds **8a**, chosen as model compound, irradiation of $H_{5'}$ produced strong enhancements for the methylene protons at $C_{5'}$ (2.2%) and $H_{4'b}$ (20%); conversely, when $H_{4'b}$ was irradiated, a positive NOE effect was observed for $H_{5'}$ (8%), $H_{4'a}$ (15%) and $H_{3'}$ (8%). These data support a *cis* relationship between $H_{4'b}$, $H_{3'}$ and $H_{5'}$. In compound **9d**, irradiation of $H_{3'}$ produced a positive NOE effect, together with $H_{4'b}$ (9.3%) and the methylene protons at $C_{3'}$ (6.4%), also with the methylene protons at $C_{6'}$ (1.8%) so indicating a *cis* relationship between $H_{3'}$ and the methylene group at $C_{5'}$.

In the previously reported cycloaddition reaction of *C*-ethoxycarbonyl-*N*-methyl nitrone **1** with the same dipolarophiles **2**, a worse diastereoselectivity had been obtained: isoxazolidines **3** and **4** were obtained in a relative ratio 2:1 (Scheme 1). The stereochemical outcome obtained in the cycloaddition process of nitrone **7** can be explained by considering that **7** has been shown by ^{1}H NMR and NOE data to be the *Z*-isomer;[11] thus, the major products **8a**–**d**

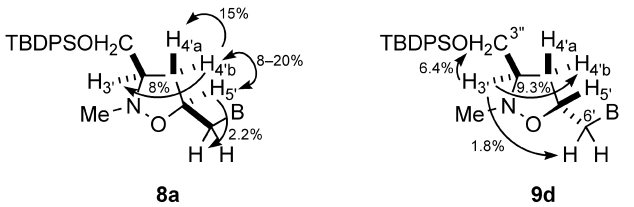


Figure 2. Selected NOEs observed for compounds **8a** and **9d**.

could be formed by the *Z* nitrone reacting in an *exo* mode, according to the results reported for similar α-alkoxy-alkylnitrones.[12]

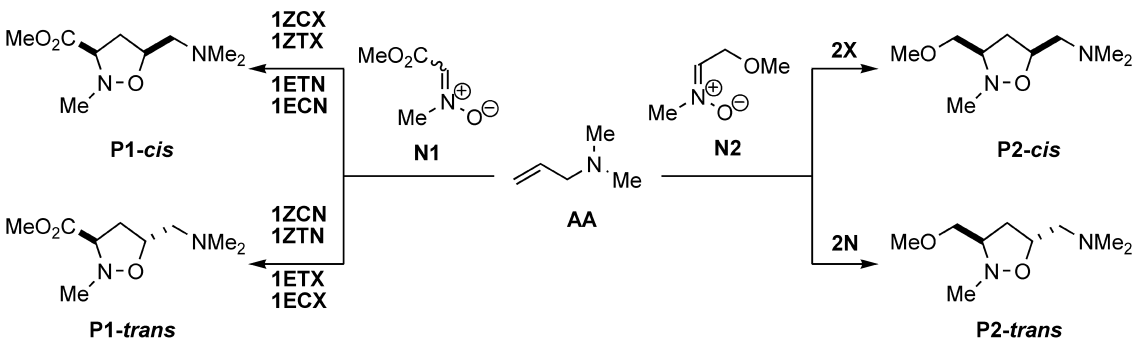
The subsequent removal of the silyl group by treatment of derivatives **8a**–**d** with TBAF afforded β-nucleosides **6a**–**c** in good global yields (71–74%), while the yield for **6d** was 54% (Scheme 2).

3. Theoretical study

In order to assess the importance of electronic and steric effects in the outcome of the cycloaddition reactions of nitrones **1** and **7** with allylbases **2**, we carried out a DFT investigation. We aimed to clarify which is the reactive isomer of nitrone **1** in this reaction[13] and to rationalize the experimentally observed differences in *endo*/*exo* (*cis*/*trans*) selectivities[14] for nitrones **1** and **7**.

Geometry optimizations of the stationery points (reactants, transition structures and products) were carried out by using the B3LYP[15] functional with the 6-31G(d) basis set.[16] All transition structures were found to have only one negative eigenvalue with the corresponding eigenvector involving the formation of the newly created C–C and C–O bonds. Vibrational frequencies were calculated (1 atm, 298.15 K) for all B3LYP/6-31G(d) optimized structures and used unscaled, to compute ZPVE and activation energies. All calculations were performed using the Gaussian 03 revision B.01 suite of programs.[17]

Simplified models were defined to avoid excessively lengthy calculations. Nitrones **N1** and **N2** were considered suitable models for nitrones **1** and **7**, respectively, and *N*,*N*-dimethyl allylamine (**AA**) was chosen to represent the allylbase. Due to its configurational instability the nitrone **N1** could, in principle, react as the corresponding *E*- or *Z*-isomers. In addition, *cisoid* and *transoid* conformations



Scheme 3.

should be considered because of their close values in energy.[13] So, we have evaluated, for the cycloaddition between **N1** and **AA**, a total of eight transition states (*E*/*Z* isomers, *cisoid*/*transoid* conformers and *endo*/*exo* approaches) leading to the 3,5-disubstituted isoxazolidines **P1**-*cis* and **P1**-*trans* (Scheme 3).

For the cycloaddition between **N2** and **AA** the *endo* and *exo* approaches leading to the 3,5-disubstituted isoxazolidines **P2**-*trans* and **P2**-*cis* were studied. The transition states are named as follows: the number indicates the nitrone, i.e. **1** for **N1** and **2** for **N2**, the first letter indicates the nitrone isomer (*Z* or *E*). Then it is added C for a *cisoid* conformation and T for a *transoid* conformation; finally we used N and X for *endo* and *exo* approaches, respectively. For instance, **1ETN** corresponds to the transition state of the reaction between the *E*-isomer in a *transoid* conformation of **N1** and **AA** through an *endo* approach leading to **P1**-*cis*. For the transition states corresponding to the reactions of **N2**, **2N** correspond to the *endo* transition state and **2X** to the *exo* one.

The optimized geometries and the lengths of forming bonds of the more stable transition states for each cycloaddition are displayed in Figure 3. The values of total and relative energies for the different stationary points are given in Table 3. All reactions showed to be exothermic (in terms of enthalpy) in the range of −19.2 to −23.5 kcal/mol, the most stable products being the *trans* isomers.

For the reaction between **N1** and **AA**, clearly the most favoured approach is the *E*-*exo* one.[18] The lowest energy value correspond to transition structure **1ECX**, predicting the preferential formation of **P1**-*trans*. These results are in agreement with the experimental observations described in Table 1.

For the reaction between **N2** and **AA**, the calculated activation energies predict the formation of the *cis* adduct **P2**-*cis* as the major product. The differences in energy

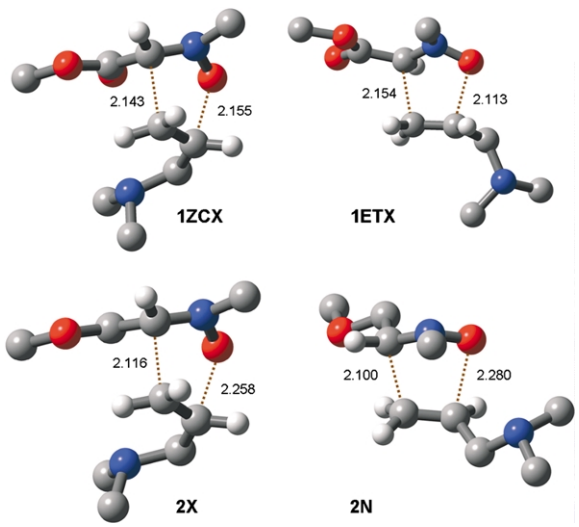


Figure 3. Optimized geometries at B3LYP/6-31G(d) level for the most favoured transition structures leading to **P1**-*cis*, **P1**-*trans*, **P2**-*cis* and **P2**-*trans*. Some hydrogen atoms have been omitted for clarity. Distances of forming bonds are given in angstroms.

Table 3. B3LYP/6-31G(d) electronic energies (*G*), free energies (*E*) and relative values (ΔE and ΔG) for the stationary points of the reactions between **AA** and nitrones **N1** and **N2**

	E[a]	ΔE[b]	G[a]	ΔG[b]
s-cis (E)-**N1**	−436.875858		−436.909646	
s-trans (E)-**N1**	−436.870147		−436.904864	
s-cis (Z)-**N1**	−436.869533		−436.903599	
s-trans (Z)-**N1**	−436.869637		−436.903709	
N2	−362.811582		−362.844905	
AA	−251.711773		−251.742859	
1ZCN	−688.550731	23.16[c]	−688.594505	36.40[c]
1ZCX	−688.556165	19.75[c]	−688.599393	33.33[c]
1ECN	−688.556064	19.81[c]	−688.600376	32.71[c]
1ECX	−688.562154	15.99[c]	−688.606713	28.73[c]
1ZTN	−688.550634	23.22[c]	−688.594788	36.22[c]
1ZTX	−688.554816	20.59[c]	−688.599180	33.46[c]
1ETN	−688.552037	22.34[c]	−688.596081	35.41[c]
1ETX	−688.557936	18.63[c]	−688.602782	31.20[c]
2N	−614.490789	20.44[d]	−614.533699	33.93[d]
2X	−614.494573	18.06[d]	−614.537473	31.56[d]
P1-*cis*	−688.616775	−18.29[c]	−688.661713	−5.78[c]
P1-*trans*	−688.617209	−18.56[c]	−688.661822	−5.85[c]
P2-*cis*	−614.558353	−21.96[d]	−614.601821	−8.32[d]
P2-*trans*	−614.558528	−22.07[d]	−614.601015	−8.82[d]

[a] Hartrees.
[b] kcal/mol.
[c] Referred to *s-cis (E)*-**N1**+**AA**.
[d] Referred to **N2**+**AA**.

barriers between *endo* and *exo* approaches for these reaction agree very well with the experimentally observed ratio reported in Table 2. Also, for this reaction the *trans* product is the most stable. So, it can be assumed that the reaction is kinetically controlled, although the differences between energies of **P2**-*cis* and **P2**-*trans*, not differing enough from the calculation errors, are not decisive. The higher inverse barriers when compared with the direct one makes that the reaction cannot be considered as a reversible process.

According to the calculations, the *cis*/*trans* selectivity observed for the reaction of **AA** with nitrone **N1** is due to the equilibrium between *E*- and *Z*-isomers, since in all cases the *exo* approach is favoured with respect to the *endo* one. The preferential formation of the *trans* isomer is caused by the higher reactivity of the *E*-isomer as inferred from the energy differences between optimized transition structures. With nitrone **N2**, which exists only as the *Z*-isomer, also the *exo* approach is clearly favoured and, in consequence, the reaction is more selective giving rise preferentially to the *cis* isomer.

4. Conclusions

In conclusion, a versatile approach towards a new class of homo-*N*,*O*-nucleosides has been designed, based on the 1,3-dipolar cycloaddition of *C*-substituted nitrones with allyl nucleobases. Two different nitrones have been exploited: the stereochemical features of the obtained nucleosides are dependent on the nature of the dipole. While the configurationally unstable nitrone **1** affords 2:1 mixtures in which the α isomer is predominant, the *Z* nitrone **7** leads preferentially to β-isomers with a good level of selectivity, 7:1. Only in the case of the allylbase **2d** a lower 2:1 selectivity was observed. The results obtained with DFT

calculations fully agree with the experimental results and successfully reproduce the experimentally observed reversal of *endo*/*exo* selectivity for nitrones **1** and **7**. In the case of nitrone **1** the *E*-isomer is showed to be more reactive than the *Z*-isomer.

5. Experimental

5.1. General information

Melting points were measured on a Kofler apparatus and are uncorrected. ^{1}H NMR spectra were measured on a 500 MHz Varian Unity Inova instrument in $CDCl_3$ as solvent. Chemical shifts are in ppm (δ) from TMS as internal standard. NOE difference spectra were obtained by subtracting alternatively right-off-resonance free induction decays (FIDS) from right-on-resonance-induced FIDS. IR spectra were recorded using an FTIR-8300 (Shimadzu) spectrophotometer. MS spectra were measured with a JEOL JMS-D 300 spectrometer. Elemental analyses were performed on a Perkin–Elmer 240B microanalyzer. Merck silica gel 60H was used for preparative short-column chromatography. Allyl nucleobases **2**–**5** have been prepared as reported in literature.[19]

5.2. Preparation of *N*,*O*-nucleosides 3 and 4

General procedure. A solution of nitrone **1** (1.31 g, 10 mmol) and allylnucleobase (10 mmol) in anhydrous toluene (20 mL) in sealed tube was heated at 80 °C for 14 h. The reaction mixture was evaporated and the residue purified by flash chromatography (chloroform/methanol 98:2) to give isoxazolidines **3** and **4**.

5.2.1. Reaction of nitrone 1 with allylthymine 2a. First eluted product was ethyl (3*RS*,5*RS*)-2-methyl-5-[(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)methyl]isoxazolidine-3-carboxylate **3a**. (65.0%, 1.93 g), colourless sticky oil; δ_H (500 MHz, $CDCl_3$) 1.26 (t, 3H, *J*=6.6 Hz), 1.89 (d, 3H, *J*=0.9 Hz), 2.30 (m, 1H, $H_{4'a}$), 2.65 (m, 1H, $H_{4'b}$), 2.77 (s, 3H, *N*–CH_3), 3.40 (m, 1H, $H_{3'}$), 3.80 (dd, 1H, $H_{6'a}$, *J*=5.7, 14.5 Hz), 4.06 (dd, 1H, $H_{6'b}$, *J*=5.9, 14.5 Hz), 4.20 (q, 2H, *J*=6.6 Hz), 4.40 (m, 1H, $H_{5'}$), 7.16 (q, 1H, H_6, *J*=0.9 Hz), 10.10 (bs, 1H, NH); δ_C (125 MHz, $CDCl_3$) 12.1, 18.8, 35.6, 42.5, 49.4, 61.4, 69.5, 76.1, 94.4, 110.3, 141.2, 151.2, 179.5. Anal. calcd for $C_{13}H_{19}N_3O_5$: C, 52.52; H, 6.44; N, 14.13. Found: C, 52.44; H, 6.42; N, 14.15. Exact mass calculated for $C_{13}H_{19}N_3O_5$: 297.1325. Found: 297.1323.

Second eluted compound was ethyl (3*RS*,5*SR*)-2-methyl-5-[(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)methyl]isoxazolidine-3-carboxylate **4a**. (31.0%, 920 mg), colourless sticky oil; δ_H (500 MHz, $CDCl_3$) 1.28 (t, 3H, *J*=6.6 Hz), 1.87 (d, 3H, *J*=1.0 Hz), 2.30 (m, 1H, $H_{4'a}$), 2.75 (m, 1H, $H_{4'b}$), 2.74 (s, 3H, *N*–CH_3), 3.45 (m, 1H, $H_{3'}$), 4.12 (dd, 1H, $H_{6'a}$, *J*=3.5, 15.0 Hz), 4.19 (dd, 1H, $H_{6'b}$, *J*=2.5, 15.0 Hz), 4.22 (q, 2H, *J*=6.6 Hz), 4.45 (m, 1H, $H_{5'}$), 7.24 (q, 1H, H_6, *J*=1.0 Hz), 9.95 (bs, 1H, NH); δ_C (125 MHz, $CDCl_3$) 13.9, 19.1, 35.4, 44.4, 50.3, 61.5, 68.8, 76.9, 101.3, 109.8, 142.1, 151.3, 170.2. Anal. calcd for $C_{13}H_{19}N_3O_5$: C, 52.52; H, 6.44; N, 14.13. Found: C, 52.39; H, 6.46; N, 14.17. Exact mass calculated for $C_{13}H_{19}N_3O_5$: 297.1325. Found: 297.1322.

5.2.2. Reaction of nitrone 1 with allyl-*N*-acetylcytosine 2b. First eluted product was ethyl (3*RS*,5*RS*)-5-{[4-(acetylamino)-2-oxopyrimidin-1(2*H*)-yl]methyl}-2-methylisoxazolidine-3-carboxylate **3b**. (65.3%, 2.11 g), light yellow sticky oil; δ_H (500 MHz, $CDCl_3$) 1.20 (t, 3H, *J*=7.1 Hz), 2.20 (ddd, 1H, $H_{4'a}$, *J*=7.7, 8.7, 13.1 Hz), 2.22 (s, 3H, CH_3), 2.59 (ddd, 1H, $H_{4'b}$, *J*=6.1, 7.6, 13.1 Hz), 2.70 (s, 3H, *N*–CH_3), 3.25 (dd, 1H, $H_{3'}$, *J*=6.1, 8.7 Hz), 3.88 (dd, 1H, $H_{6'a}$, *J*=5.5, 14.0 Hz), 4.13 (q, 2H, *J*=7.1 Hz), 4.20 (dd, 1H, $H_{6'b}$, *J*=2.8, 14.0 Hz), 4.38 (dddd, 1H, $H_{5'}$, *J*=2.8, 5.5, 7.6 and 7.7 Hz), 7.36 (d, 1H, H_5, *J*=7.2 Hz), 7.64 (d, 1H, H_6, *J*=7.2 Hz), 10.42 (bs, 1H, NH); δ_C (125 MHz, $CDCl_3$) 13.9, 24.6, 35.4, 44.5, 51.4, 61.3, 68.5, 74.8, 96.6, 149.8, 156.0, 163.0, 169.5, 171.3. Anal. calcd for $C_{14}H_{20}N_4O_5$: C, 51.85; H, 6.22; N, 17.27. Found: C, 52.05; H, 6.23; N, 17.21. Exact mass calculated for $C_{14}H_{20}N_4O_5$: 324.1433. Found: 324.1430.

Second eluted compound was ethyl (3*RS*,5*SR*)-5-{[4-(acetylamino)-2-oxopyrimidin-1(2*H*)-yl]methyl}-2-methylisoxazolidine-3-carboxylate **4b**. (29.7%, 962 mg), colourless sticky oil; δ_H (500 MHz, $CDCl_3$) 1.22 (t, 3H, *J*=7.1 Hz), 2.21 (ddd, 1H, $H_{4'a}$, *J*=6.3, 8.5, 13.2 Hz), 2.28 (s, 3H, CH_3), 2.78 (s, 3H, *N*–CH_3), 2.79 (ddd, 1H, $H_{4'b}$, *J*=5.0, 7.5, 13.2 Hz), 3.33 (dd, 1H, $H_{3'}$, *J*=5.0, 6.3 Hz), 3.95 (dd, 1H, $H_{6'a}$, *J*=5.0, 11.3 Hz), 4.20 (q, 2H, *J*=7.1 Hz), 4.30 (dd, 1H, $H_{6'b}$, *J*=1.5, 11.3 Hz), 4.45 (dddd, 1H, $H_{5'}$, *J*=1.5, 5.0, 7.5, 8.5 Hz), 7.38 (d, 1H, H_5, *J*=7.2 Hz), 7.45 (d, 1H, H_6, *J*=7.1 Hz), 10.10 (bs, 1H, NH); δ_C (125 MHz, $CDCl_3$) 12.9, 25.0, 36.4, 44.5, 52.1, 61.5, 67.8, 74.8, 96.7, 150.0, 156.1, 162.9, 170.5, 171.8. Anal. calcd for $C_{14}H_{20}N_4O_5$: C, 51.85; H, 6.22; N, 17.27. Found: C, 51.71; H, 6.19; N, 17.31. Exact mass calculated for $C_{14}H_{20}N_4O_5$: 324.1433. Found: 324.1435.

5.2.3. Reaction of nitrone 1 with allyl-5-fluorouracil 2c. First eluted product was ethyl (3*RS*,5*RS*)-5-[(5-fluoro-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)methyl]-2-methylisoxazolidine-3-carboxylate **3c**. (63.4%, 1.91 g), light yellow sticky oil; δ_H (500 MHz, $CDCl_3$) 1.32 (t, 3H, *J*=7.1 Hz), 2.29 (m, 1H, $H_{4'a}$), 2.75 (m, 1H, $H_{4'b}$), 2.77 (s, 3H, *N*–CH_3), 3.49 (dd, 1H, $H_{3'}$, *J*=8.7, 9.3 Hz), 3.68 (dd, 1H, $H_{6'a}$, *J*=9.3, 14.2 Hz), 4.13 (dd, 1H, $H_{6'b}$, *J*=2.5, 14.2 Hz), 4.23 (q, 2H, *J*=7.1 Hz), 4.43 (m, 1H, $H_{5'}$), 7.43 (d, 1H, H_6, *J*=5.8 Hz), 10.45 (bs, 1H, NH); δ_C (125 MHz, $CDCl_3$) 14.4, 35.7, 44.5, 50.7, 62.1, 69.2, 74.7, 101.7, 130.9, 141.9, 150.1, 170.5. Anal. calcd for $C_{12}H_{16}N_3O_5F$: C, 47.84; H, 5.35; N, 13.95. Found: C, 48.01; H, 5.36; N, 13.93. Exact mass calculated for $C_{12}H_{16}N_3O_5F$: 301.1074. Found: 301.1072.

Second eluted compound was ethyl (3*RS*,5*SR*)-5-[(5-fluoro-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)methyl]-2-methylisoxazolidine-3-carboxylate **4c**. (31.6%, 952 mg), light yellow sticky oil; δ_H (500 MHz, $CDCl_3$) 1.36 (t, 3H, *J*=7.1 Hz), 2.33 (m, 1H, $H_{4'a}$), 2.78 (m, 1H, $H_{4'b}$), 2.84 (s, 3H, *N*–CH_3), 3.40 (m, 1H, $H_{3'}$), 3.70 (dd, 1H, $H_{6'a}$, *J*=7.1, 15.1 Hz), 4.18 (dd, 1H, $H_{6'b}$, *J*=2.5, 15.1 Hz), 4.26 (q, 2H, *J*=7.1 Hz), 4.45 (m, 1H, $H_{5'}$), 7.45 (d, 1H, H_6, *J*=5.8 Hz), 10.50 (bs, 1H, NH); δ_C (125 MHz, $CDCl_3$) 18.2, 35.9, 46.5,

47.2, 62.1, 69.5, 74.7, 101.3, 129.0, 141.9, 150.1, 170.5. Anal. calcd for $C_{12}H_{16}N_3O_5F$: C, 47.84; H, 5.35; N, 13.95. Found: C, 47.90; H, 5.36; N, 13.91. Exact mass calculated for $C_{12}H_{16}N_3O_5F$: 301.1074. Found: 301.1073.

5.2.4. Reaction of nitrone 1 with allyladenine 2d. First eluted product was ethyl (3*RS*,5*RS*)-5-[(6-amino-9*H*-purin-9-yl)methyl]-2-methylisoxazolidine-3-carboxylate **3d**. (59.8%, 1.83 g), light yellow sticky oil; δ_H (500 MHz, $CDCl_3$) 1.30 (t, 3H, *J*=7.1 Hz), 2.18 (ddd, 1H, $H_{4'a}$, *J*=7.2, 9.1, 15.0 Hz), 2.73 (ddd, 1H, $H_{4'b}$, *J*=7.1, 8.1, 15.0 Hz), 2.76 (s, 3H, *N*–CH_3), 3.15 (dd, 1H, $H_{3'}$, *J*=8.1, 9.1 Hz), 4.18 (q, 2H, *J*=7.1 Hz), 4.40 (m, 2H, $H_{6'}$), 4.48 (m, 1H, $H_{5'}$), 6.42 (bs, 2H, NH_2), 7.96 (s, 1H, H_3), 8.35 (s, 1H, H_8); δ_C (125 MHz, $CDCl_3$) 13.9, 35.5, 44.5, 46.0, 61.5, 74.6, 76.6, 118.9, 135.3, 153.0, 155.7, 156.0, 169.5. Anal. calcd for $C_{13}H_{18}N_6O_3$: C, 50.97; H, 5.92; N, 27.43. Found: C, 50.80; H, 5.91; N, 27.47. Exact mass calculated for $C_{13}H_{18}N_6O_3$: 306.1440. Found: 306.1443.

Second eluted compound was ethyl (3*RS*,5*SR*)-5-[(6-amino-9*H*-purin-9-yl)methyl]-2-methylisoxazolidine-3-carboxylate **4d**. (33.2%, 1.01 g), light yellow sticky oil; δ_H (500 MHz, $CDCl_3$) 1.25 (t, 3H, *J*=7.1 Hz), 2.35 (ddd, 1H, $H_{4'a}$, *J*=5.8, 9.10, 15.2 Hz), 2.77 (s, 3H, *N*–CH_3), 2.78 (m, 1H, $H_{4'b}$), 3.42 (dd, 1H, $H_{3'}$, *J*=6.5, 9.1 Hz), 4.21 (q, 2H, *J*=7.1 Hz), 4.19 (m, 2H, $H_{6'}$), 4.55 (m, 1H, $H_{5'}$), 6.42 (bs, 2H, NH_2), 7.94 (s, 1H, H_3), 8.33 (s, 1H, H_8); δ_C (125 MHz, $CDCl_3$) 13.9, 35.4, 45.0, 44.9, 61.5, 69.0, 75.3, 118.9, 135.5, 152.9, 155.7, 156.0, 169.5. Anal. calcd for $C_{13}H_{18}N_6O_3$: C, 50.97; H, 5.92; N, 27.43. Found: C, 50.79; H, 5.94; N, 27.46. Exact mass calculated for $C_{13}H_{18}N_6O_3$: 306.1440. Found: 306.1444.

5.3. Preparation of *N*,*O*-nucleosides 5 and 6 from 3 and 4

General procedure. To a solution of nucleosides **3** and **4** (1 mmol) in anhydrous THF (20 mL), at 0 °C, $LiAlH_4$ (60.0 mg, 1.5 mmol) was added and the mixture was stirred for 1 h. At the end of this time, the solvent was removed and the residue was subjected to column chromatography on neutral alumina (chloroform/methanol 95:5).

5.3.1. Reaction of 3a with $LiAlH_4$. 1-{[(3*RS*,5*RS*)-3-(Hydroxymethyl)-2-methylisoxazolidin-5-yl]methyl}-5-methylpyrimidine-2,4(1*H*,3*H*)-dione **5a**. (38.0%, 57 mg), colourless sticky oil; δ_H (500 MHz, $CDCl_3$) 1.92 (d, 3H, *J*=1.3 Hz), 2.09 (ddd, 1H, $H_{4'a}$, *J*=8.4, 8.6, 12.6 Hz), 2.35 (ddd, 1H, $H_{4'b}$, *J*=5.5, 7.5, 12.6 Hz), 2.76 (s, 3H, *N*–CH_3), 2.83 (dddd, 1H, $H_{3'}$, *J*=3.7, 5.2, 5.5, 8.4 Hz), 3.57 (dd, 1H, $H_{3'a}$, *J*=5.5, 11.5 Hz), 3.65 (dd, 1H, $H_{3'b}$, *J*=3.7, 11.5 Hz), 3.68 (dd, 1H, $H_{6'a}$, *J*=6.9, 14.5 Hz), 4.11 (dd, 1H, $H_{6'b}$, *J*=3.0, 14.5 Hz), 4.25 (dddd, 1H, $H_{5'}$, *J*=3.0, 3.7, 7.5, 8.6 Hz), 7.13 (q, 1H, H_6, *J*=1.3 Hz), 8.80 (bs, 1H, NH); δ_C (125 MHz, $CDCl_3$) 12.3, 34.2, 45.8, 50.2, 61.8, 68.7, 76.1, 110.3, 141.3, 151.0, 164.1. IR (neat) 3550, 3440, 3090, 2950, 2870, 1680, 1645, 1475, 1290, 1020, 865, 740 cm^{-1}. Anal. calcd for $C_{11}H_{17}N_3O_4$: C, 51.76; H, 6.71; N, 16.46. Found: C, 51.60; H, 6.72; N, 16.49. Exact mass calculated for $C_{11}H_{17}N_3O_4$: 255.1219. Found: 255.1216.

5.3.2. Reaction of 4a with $LiAlH_4$. 1-{[(3*RS*,5*SR*)-3-(Hydroxymethyl)-2-methylisoxazolidin-5-yl]methyl}-5-methylpyrimidine-2,4(1*H*,3*H*)-dione **6a**. (35.0%, 89 mg), white foam; δ_H (500 MHz, $CDCl_3$) 1.79 (ddd, 1H, $H_{4'a}$, *J*=6.0, 6.1, 12.7 Hz), 1.91 (d, 3H, *J*=1.2 Hz), 2.59 (ddd, 1H, $H_{4'b}$, *J*=8.3, 8.5, 12.7 Hz), 2.72 (s, 3H, *N*–CH_3), 2.99 (dddd, 1H, $H_{3'}$, *J*=3.8, 6.0, 6.4, 8.3 Hz), 3.50 (dd, 1H, $H_{3'a}$, *J*=6.4, 11.6 Hz), 3.57 (dd, 1H, $H_{6'a}$, *J*=8.5, 14.3 Hz), 3.60 (dd, 1H, $H_{3'b}$, *J*=3.8, 11.6 Hz), 4.12 (dd, 1H, $H_{6'b}$, *J*=2.7, 14.3 Hz), 4.46 (dddd, 1H, $H_{5'}$, *J*=2.7, 6.1, 8.5, 8.5 Hz), 7.55 (q, 1H, H_6, *J*=1.2 Hz), 8.95 (bs, 1H, NH); δ_C (125 MHz, $CDCl_3$) 12.3, 33.8, 44.3, 50.6, 62.3, 69.0, 74.7, 110.2, 141.8, 150.8, 163.9. IR (KBr) 3580, 3420, 3095, 2930, 2910, 1655, 1625, 1485, 1302, 1035, 855, 749 cm^{-1}. Anal. calcd for $C_{11}H_{17}N_3O_4$: C, 51.76; H, 6.71; N, 16.46. Found: C, 51.70; H, 6.69; N, 16.48. Exact mass calculated for $C_{11}H_{17}N_3O_4$: 255.1219. Found: 255.1215.

5.3.3. Reaction of 3b with $LiAlH_4$. *N*-(1-{[(3*RS*,5*RS*)-3-(Hydroxymethyl)-2-methylisoxazolidin-5-yl]methyl}-2-oxo-1,2-dihydropyrimidin-4-yl)acetamide **5b**. (32.0%, 90 mg), colourless sticky oil; δ_H (500 MHz, $CDCl_3$) 2.02 (s, 3H, CH_3), 2.10 (ddd, 1H, $H_{4'a}$, *J*=6.0, 9.5, 12.5 Hz), 2.42 (ddd, 1H, $H_{4'b}$, *J*=6.5, 7.2, 12.5 Hz), 2.82 (s, 3H, *N*–CH_3), 2.90 (m, 1H, $H_{3'}$), 3.58 (dd, 1H, $H_{3'a}$, *J*=4.8, 11.3 Hz), 3.64 (dd, 1H, $H_{3'b}$, *J*=4.5, 11.3 Hz), 3.75 (dd, 1H, H $H_{6'a}$, *J*=6.2, 13.8 Hz), 4.15 (dd, 1H, $H_{6'b}$, *J*=3.2, 13.8 Hz), 4.22 (m, 1H, $H_{5'}$), 7.28 (d, 1H, H_5, *J*=7.5 Hz), 7.68 (d, 1H, H_6, *J*=7.5 Hz), 10.50 (bs, 1H, NH); δ_C (125 MHz, $CDCl_3$) 18.8, 37.6, 38.5, 53.6, 64.0, 68.7, 81.2, 98.0, 130.0, 156.2, 168.2, 179.4. IR (neat) 3520, 3480, 3070, 2925, 2870, 1675, 1660, 1655, 1430, 1285, 1080, 830, 780 cm^{-1}. Anal. calcd for $C_{12}H_{18}N_4O_4$: C, 51.05; H, 6.43; N, 19.85. Found: C, 50.95; H, 6.41; N, 19.92. Exact mass calculated for $C_{12}H_{18}N_4O_4$: 282.1328. Found: 282.1330.

5.3.4. Reaction of 4b with $LiAlH_4$. *N*-(1-{[(3*RS*,5*SR*)-3-(Hydroxymethyl)-2-methylisoxazolidin-5-yl]methyl}-2-oxo-1,2-dihydropyrimidin-4-yl)acetamide **6b**. (30.0%, 85 mg), white foam; δ_H (500 MHz, $CDCl_3$) 1.98 (s, 3H, CH_3), 2.20 (ddd, 1H, $H_{4'a}$, *J*=5.8, 8.5 and 12.8 Hz), 2.43 (ddd, 1H, $H_{4'b}$, *J*=6.7, 8.2, 12.8 Hz), 2.78 (s, 3H, *N*–CH_3), 2.98 (m, 1H, $H_{3'}$), 3.60 (dd, 1H, $H_{3'a}$, *J*=4.5, 10.8 Hz), 3.64 (dd, 1H, $H_{3'b}$, *J*=3.9, 10.8 Hz), 3.68 (dd, 1H, H $H_{6'a}$, *J*=6.5, 13.5 Hz), 4.18 (dd, 1H, $H_{6'b}$, *J*=3.2, 13.5 Hz), 4.35 (m, 1H, $H_{5'}$), 7.32 (d, 1H, H_5, *J*=7.5 Hz), 7.58 (d, 1H, H_6, *J*=7.5 Hz), 10.25 (bs, 1H, NH); δ_C (125 MHz, $CDCl_3$) 18.5, 37.8, 39.5, 54.6, 62.0, 67.7, 83.1, 99.5, 131.0, 155.2, 162.8, 180.7. IR (KBr) 3570, 3490, 3080, 2930, 2875, 1690, 1670, 1660, 1430, 1290, 1080, 840, 775 cm^{-1}. Anal. calcd for $C_{12}H_{18}N_4O_4$: C, 51.05; H, 6.43; N, 19.85. Found: C, 51.20; H, 6.41; N, 19.89. Exact mass calculated for $C_{12}H_{18}N_4O_4$: 282.1328. Found: 282.1325.

5.3.5. Reaction of 3c with $LiAlH_4$. 5-Fluoro-1-{[(3*RS*,5*RS*)-3-(hydroxymethyl)-2-methylisoxazolidin-5-yl]methyl}pyrimidine-2,4(1*H*,3*H*)-dione **5c**. (38.0%, 98 mg), white foam; δ_H (500 MHz, $CDCl_3$) 2.01 (ddd, 1H, $H_{4'a}$, *J*=5.3, 10.6, 12.6 Hz), 2.39 (ddd, 1H, $H_{4'b}$, *J*=6.0, 7.2, 12.6 Hz), 2.79 (s, 3H, *N*–CH_3), 2.91 (m, 1H, $H_{3'}$), 3.37 (dd, 1H, $H_{3'a}$, *J*=7.7, 14.8 Hz), 3.68 (m, 2H, $H_{6'}$), 4.27 (dd, 1H, $H_{3'b}$, *J*=2.9, 14.8 Hz), 4.28 (m, 1H, $H_{5'}$), 7.47 (d, 1H, H_6, *J*=5.7 Hz); δ_C (125 MHz, $CDCl_3$) 34.6, 37.6, 46.9, 50.6, 61.8, 75.7, 102.1, 130.5, 149.7, 157.4. IR (KBr) 3490, 3430, 3120, 2940, 2890, 1670, 1654, 1510, 1350, 1280, 1120, 970,

850 cm^{-1}. Anal. calcd for $C_{10}H_{14}N_3O_4F$: C, 46.33; H, 5.44; N, 16.21. Found: C, 46.48; H, 5.43; N, 16.26. Exact mass calculated for $C_{10}H_{14}N_3O_4F$: 259.0968. Found: 259.0971.

5.3.6. Reaction of 4c with $LiAlH_4$. 5-Fluoro-1-{[(3*RS*,5*SR*)-3-(hydroxymethyl)-2-methylisoxazolidin-5-yl]methyl}pyrimidine-2,4(1*H*,3*H*)-dione **6c**. (36.0%, 93 mg), white foam; δ_H (500 MHz, $CDCl_3$) 1.84 (ddd, 1H, $H_{4'a}$, *J*=6.3, 6.4, 12.7 Hz), 2.58 (ddd, 1H, $H_{4'b}$, *J*=8.3, 8.4, 12.7 Hz), 2.74 (s, 3H, *N*–CH_3), 2.96 (dddd, 1H, $H_{3'}$, *J*=3.5, 5.7, 6.4, 8.3 Hz), 3.56 (dd, 1H, $H_{3'a}$, *J*=5.7, 11.7 Hz), 3.59 (dd, 1H, $H_{6'a}$, *J*=8.8, 14.2 Hz), 3.66 (dd, 1H, $H_{3'b}$, *J*=3.5, 11.7 Hz), 4.13 (dd, 1H, $H_{6'b}$, *J*=2.6, 14.2 Hz), 4.44 (dddd, 1H, $H_{5'}$, *J*=2.6, 6.3, 8.4, 8.8 Hz), 7.51 (d, 1H, H_6, *J*=5.7 Hz); δ_C (125 MHz, $CDCl_3$) 34.1, 44.3, 50.8, 62.2, 69.0, 74.2, 130.4, 139.1, 141.0, 149.7. IR (KBr) 3520, 3440, 3100, 2920, 2895, 1690, 1640, 1500, 1360, 1270, 1180, 920, 860 cm^{-1}. Anal. calcd for $C_{10}H_{14}N_3O_4F$: C, 46.33; H, 5.44; N, 16.21. Found: C, 46.49; H, 5.46; N, 16.17. Exact mass calculated for $C_{10}H_{14}N_3O_4F$: 259.0968. Found: 259.0971.

5.3.7. Reaction of 3d with $LiAlH_4$. {(3*RS*,5*RS*)-5-[(6-Amino-9*H*-purin-9-yl)methyl]-2-methylisoxazolidin-3-yl}-methanol **5d**. (30.2%, 78 mg), white foam; δ_H (500 MHz, $CDCl_3$) 1.85 (ddd, 1H, $H_{4'a}$, *J*=5.5, 7.6, 13.2 Hz), 2.25 (ddd, 1H, $H_{4'b}$, *J*=4.8, 6.5, 13.2 Hz), 2.82 (s, 3H, *N*–CH_3), 2.92 (m, 1H, $H_{3'}$), 3.52 (dd, 1H, $H_{3'a}$, *J*=5.5, 11.8 Hz), 3.68 (dd, 1H, $H_{6'a}$, *J*=4.2, 14.0 Hz), 3.70 (dd, 1H, $H_{3'b}$, *J*=3.5, 11.8 Hz), 4.10 (dd, 1H, $H_{6'b}$, *J*=3.2, 14.0 Hz), 4.54 (m, 1H, $H_{5'}$), 8.15 (s, 1H, H_3), 8.35 (s, 1H, H_8); δ_C (125 MHz, $CDCl_3$) 36.8, 38.5, 56.2, 62.3, 68.7, 82.3, 127.0, 143.0, 146.9, 151.8, 155.0. IR (KBr) 3538, 3495, 3110, 2890, 2885, 1690, 1640, 1580, 1420, 1290, 1035, 985, 820, 750 cm^{-1}. Anal. calcd for $C_{11}H_{16}N_6O_2$: C, 50.00; H, 6.10; N, 31.80. Found: C, 49.84; H, 6.12; N, 31.87. Exact mass calculated for $C_{11}H_{16}N_6O_2$: 264.1335. Found: 264.1333.

5.3.8. Reaction of 4d with $LiAlH_4$. {(3*RS*,5*SR*)-5-[(6-Amino-9*H*-purin-9-yl)methyl]-2-methylisoxazolidin-3-yl}-methanol **6d**. (30.4%, 80 mg), colourless sticky oil; δ_H (500 MHz, $CDCl_3$) 2.07 (ddd, 1H, $H_{4'a}$, *J*=4.8, 6.7, 13.8 Hz), 2.35 (ddd, 1H, $H_{4'b}$, *J*=5.2, 6.5, 13.8 Hz), 2.78 (s, 3H, *N*–CH_3), 2.95 (m, 1H, $H_{3'}$), 3.60 (dd, 1H, $H_{3'a}$, *J*=6.5, 12.7 Hz), 3.78 (dd, 1H, $H_{6'a}$, *J*=4.9, 13.8 Hz), 3.80 (dd, 1H, $H_{3'b}$, *J*=3.5, 12.7 Hz), 4.07 (dd, 1H, $H_{6'b}$, *J*=4.2, 13.8 Hz), 4.62 (m, 1H, $H_{5'}$), 8.10 (s, 1H, H_3), 8.32 (s, 1H, H_8); δ_C (125 MHz, $CDCl_3$) 34.8, 37.5, 57.6, 60.9, 69.7, 84.0, 126.0, 145.6, 147.9, 151.6, 156.0. IR (neat) 3600, 3510, 3120, 2860, 2855, 1700, 1670, 1560, 1420, 1295, 1020, 990, 830, 760 cm^{-1}. Anal. calcd for $C_{11}H_{16}N_6O_2$: C, 50.00; H, 6.10; N, 31.80. Found: C, 50.08; H, 6.08; N, 31.90. Exact mass calculated for $C_{11}H_{16}N_6O_2$: 264.1335. Found: 264.1337.

5.4. Preparation of *N,O*-nucleosides 8a–d and 9d

General procedure. A solution of nitrone **7** (5.73 g, 17.5 mmol) and allyl nucleobases (18 mmol) in anhydrous toluene (THF, in the case of allyladenine **2d**), was stirred at 80 °C, in a sealed tube, for 24 h. At the end of this time, the solvent was removed and the residue was subjected to silica gel column chromatography (chloroform/methanol 95:5) to give compounds **8a–d** and **9d**.

5.4.1. 1-{[(3*RS*,5*SR*)-3-({[*tert*-Butyl(diphenyl)silyl]oxy}-methyl)-2-methylisoxazolidin-5-yl]methyl}-5-methylpyrimidine-2,4(1*H*,3*H*)-dione 8a. (74.5%, 6.43 g), light yellow sticky oil; δ_H (500 MHz, $CDCl_3$) 1.06 (s, 9H), 1.75 (ddd, $H_{4'a}$, *J*=5.8, 6.5, 13.1 Hz), 1.94 (d, 3H, *J*=1.2 Hz), 2.58 (ddd, 1H, $H_{4'b}$, *J*=8.3, 8.4, 13.1 Hz), 2.77 (s, 3H, *N*–CH_3), 2.90 (dddd, 1H, $H_{3'}$, *J*=3.5, 5.8, 6.5, 8.3 Hz), 3.20 (dd, 1H, $H_{6'a}$, *J*=8.0, 15.5 Hz), 3.65 (dd, 2H, $H_{3'}$, *J*=5.8, 14.1 Hz), 4.02 (dd, 1H, $H_{6'b}$, *J*=1.5, 15.5 Hz), 4.35 (dddd, 1H, $H_{5'}$, *J*=1.5, 5.8, 8.0, 8.4 Hz), 7.05 (q, 1H, H_6, *J*=1.2 Hz), 7.40–7.60 (m, 10H), 8.70 (bs, 1H, NH). δ_C (125 MHz, $CDCl_3$) 13.8, 19.1, 27.2, 35.6, 45.1, 51.0, 65.0, 79.1, 74.3, 110.3, 128.0, 130.2, 133.4, 135.9, 141.3, 151.0, 164.0. Anal. calcd for $C_{27}H_{35}SiN_3O_4$: C, 65.69; H, 7.15; N, 8.51. Found: C, 65.87; H, 7.13; N, 8.53. Exact mass calculated for $C_{27}H_{35}SiN_3O_4$: 493.2397. Found: 493.2394.

5.4.2. *N*-(1-{[(3*RS*,5*SR*)-3-({[*tert*-Butyl(diphenyl)silyl]-oxy}methyl)-2-methylisoxazolidin-5-yl]methyl}-2-oxo-1,2-dihydropyrimidin-4-yl)acetamide 8b. (72.6%, 6.61 g), colorless sticky oil; δ_H (500 MHz, $CDCl_3$) 1.08 (s, 9H), 1.89 (ddd, 1H, $H_{4'a}$, *J*=5.9, 6.8, 12.0 Hz), 2.58 (ddd, 1H, $H_{4'b}$, *J*=7.8, 8.0, 12.0 Hz), 2.63 (s, 3H, *N*–CH_3), 2.89 (m, 1H, $H_{3'}$), 3.58 (dd, 2H, $H_{3'}$, *J*=4.2, 12.3 Hz), 4.08 (dd, 2H, $H_{6'}$, *J*=2.2, 14.8 Hz), 4.38 (m, 1H, $H_{5'}$), 7.30 (d, 1H, H_5, *J*=7.0 Hz), 7.40–7.60 (m, 10H), 7.64 (d, 1H, H_6, *J*=7.0 Hz); δ_C (125 MHz, $CDCl_3$) 18.5, 24.6, 25.1, 34.6, 45.1, 52.6, 63.3, 69.8, 75.4, 92.3, 127.1, 129.8, 133.0, 134.9, 136.5, 158.1, 160.2, 169.8. Anal. calcd for $C_{28}H_{36}SiN_4O_4$: C, 64.59; H, 6.97; N, 10.76. Found: C, 64.84; H, 6.95; N, 10.74. Exact mass calculated for $C_{28}H_{36}SiN_4O_4$: 520.2506. Found: 520.2508.

5.4.3. 1-{[(3*RS*,5*SR*)-3-({[*tert*-Butyl(diphenyl)silyl]oxy}-methyl)-2-methylisoxazolidin-5-yl]methyl}-5-fluoropyrimidine-2,4(1*H*,3*H*)-dione 8c. (75.5%, 6.32 g), white foam; δ_H (500 MHz, $CDCl_3$) 1.10 (s, 9H), 1.87 (ddd, 1H, $H_{4'a}$, *J*=6.3, 6.4, 12.8 Hz), 2.68 (ddd, 1H, $H_{4'b}$, *J*=8.3, 8.4, 12.8 Hz), 2.74 (s, 3H, *N*–CH_3), 2.77 (dddd, 1H, $H_{3'}$, *J*=3.5, 5.7, 6.4, 8.3 Hz), 3.50 (dd, 1H, $H_{6'a}$, *J*=8.8, 14.1 Hz), 3.70 (dd, 2H, $H_{3'}$, *J*=3.5, 11.8 Hz), 4.05 (dd, 1H, $H_{6'b}$, *J*=1.5, 14.1 Hz), 4.40 (dddd, 1H, $H_{5'}$, *J*=1.5, 6.3, 8.3, 8.8 Hz), 7.20–7.60 (m, 11H, H_6 and ArH), 9.40 (bs, 1H, NH). δ_C (125 MHz, $CDCl_3$) 19.5, 27.1, 35.5, 44.1, 51.5, 64.3, 68.9, 74.0, 128.1, 130.2, 131.0, 135.3, 135.5, 159.7. Anal. calcd for $C_{26}H_{32}SiN_3O_4$: C, 65.24; H, 6.74; N, 8.78. Found: C, 65.02; H, 6.73; N, 8.79. Exact mass calculated for $C_{26}H_{32}SiN_3O_4$: 478.2162. Found: 478.2159.

5.4.4. 9-{[(3*RS*,5*SR*)-3-({[*tert*-Butyl(diphenyl)silyl]oxy}-methyl)-2-methylisoxazolidin-5-yl]methyl}-9*H*-purin-6-amine 8d. (55.3%, 4.86 g), white foam; δ_H (500 MHz, $CDCl_3$) 1.05 (s, 9H), 1.85 (ddd, 1H, $H_{4'a}$, *J*=6.0, 6.8, 12.0 Hz), 2.56 (ddd, 1H, $H_{4'b}$, *J*=8.3, 8.4, 12.0 Hz), 2.72 (s, 3H, *N*–CH_3), 2.83 (dddd, 1H, $H_{3'}$, *J*=3.5, 5.7, 6.8, 8.3 Hz), 3.60 (m, 2H, $H_{3'}$), 4.10 (m, 2H, $H_{6'}$), 4.23 (m, 1H, $H_{5'}$), 5.88 (bs, 2H, NH_2), 7.37–7.46 (m, 10H, ArH), 7.92 (s, 1H, H_8), 8.29 (s, 1H, H_2). δ_C (125 MHz, $CDCl_3$) 16.8, 22.1, 37.8, 41.2, 56.7, 67.5, 70.0, 82.3, 128.0, 130.2, 135.0, 137.3, 139.4, 142.0, 158.7, 160.0. Anal. calcd for $C_{27}H_{34}SiN_6O_2$: C, 64.51; H, 6.82; N, 16.72. Found: C, 64.61; H, 6.80; N, 16.68. Exact mass calculated for $C_{27}H_{34}SiN_6O_2$: 502.2512. Found: 502.2515.

5.4.5. 9-{[(3*RS*,5*RS*)-3-({[*tert*-Butyl(diphenyl)silyl]oxy}-methyl)-2-methylisoxazolidin-5-yl]methyl}-9*H*-purin-6-amine 9d. (27.7%, 2.43 g), white foam; δ_H (500 MHz, $CDCl_3$) 1.10 (s, 9H), 1.98 (ddd, 1H, $H_{4'a}$, J=5.5, 6.7, 11.5 Hz), 2.76 (ddd, 1H, $H_{4'b}$, J=7.3, 8.2, 11.5 Hz), 2.86 (s, 3H, $N-CH_3$), 2.88 (dddd, 1H, $H_{3'}$, J=3.9, 6.2, 7.8, 9.2 Hz), 3.72 (m, 2H, $H_{3'}$), 3.95 (m, 2H, $H_{6'}$), 4.20 (m, 1H, $H_{5'}$), 6.18 (bs, 2H, NH_2), 7.30–7.58 (m, 10H, ArH), 7.90 (s, 1H, H_8), 8.32 (s, 1H, H_2). δ_C (125 MHz, $CDCl_3$) 18.8, 24.2, 38.2, 45.2, 58.6, 69.7, 72.0, 84.8, 109.4, 130.0, 131.2, 136.0, 138.2, 141.8, 144.0, 158.5, 162.0. Anal. calcd for $C_{27}H_{34}SiN_6O_2$: C, 64.51; H, 6.82; N, 16.72. Found: C, 64.33; H, 6.79; N, 16.77. Exact mass calculated for $C_{27}H_{34}SiN_6O_2$: 502.2512. Found: 502.2515.

5.5. Preparation of *N*,*O*-nucleosides 5d and 6a–d from 8a–d and 9d

General procedure. To a solution of isoxazolidine **8a–d** and **9d** (1 mmol) in dry THF, 1 M TBAF in THF (1.1 mmol, 1.1 mL) wad added and the solution was stirred at rt for 1 h. After evaporation of the solvent in vacuo, the residue was purified by flash chromatography, using chloroform/methanol (95:5) as eluent, to gave nucleosides **5d** and **6a–d** in 98% yields.

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Use of cyclobutyl derivatives as intermediates in the synthesis of 1,2a,3,8b-tetrahydro-2*H*-cyclobuta[*c*]chromenes

Angela M. Bernard, Costantino Floris, Angelo Frongia, Pier P. Piras* and Francesco Secci

Dipartimento di Scienze Chimiche, Università di Cagliari, Complesso Universitario di Monserrato, S.S. 554, Bivio per Sestu, I-09042 Monserrato (Cagliari), Italypppiras@unica.it

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Abstract—Starting from cyclobutanones and tertiary cyclobutanols several new chromenes containing a cyclobutane ring have been prepared by acid catalyzed intramolecular alkylation of an oxygen-carrying aromatic ring. Interestingly one of the cyclobutanols leads to 3-[(4-methoxyphenoxy)methyl]-2,2,3-trimethylcyclopentanone that is a precursor in the synthesis of the carotenoid pigment capsorubin.

1. Introduction

Cyclobutanones are the basic structure of several natural products and are useful intermediates in the synthesis of many natural products and different molecules.[1,2] While they are mostly synthesized by [2+2] cycloaddition reactions between ketenes and olefins, much effort is now being devoted to methods that use suitably substituted cyclopropanes as starting material.[2,3] The most common reactions using cyclobutanones as useful intermediates include their transformation into γ-lactones, pyrrolidones, cyclopentanones and cyclohexanones.[1] They easily undergo the Favorskii rearrangement to give cyclopropanecarboxylic acids[4] and react very easily with vinyl metals to give the corresponding 1-vinylcyclobutanols that can undergo many useful transformations.[1]

We now report a new use of the cyclobutanones **3a**–**f**, **i** and the tertiary cyclobutanols **9a**-**d** as intramolecular alkylating reagents of oxygen substituted aromatic rings upon treatment with acid. Both give access to a new versatile class of benzopyrans **4a**-**f** (derivatives **3g**, **3h** are unreactive) and **10a**-**d** and to the unstable 6-methoxy-2a-methyl-2,2a,3,4-tetrahydrocyclobuta[*a*]naphthalen-8b(1*H*)-ol **4i** that is converted into the corresponding tosylate **5i**. Interestingly, the cyclobutanol **9c**, by acid treatment gave, as major product, 3-[(4-methoxyphenoxy)methyl]-2,2,3-trimethylcyclopentanone **11** that after deprotection of the alcoholic function led to the cyclopentanone **12** that has been previously used as an intermediate in the synthesis of the carotenoid pigment capsorubin.[5]

2. Results and discussion

The cyclobutanones **3a**-**i** were prepared by lithium iodide induced ring enlargement[6] of the oxaspiropentanes **2a**-**i**,[7] obtained by epoxidation of the easily accessible[8] alkylidenecyclopropanes **1a**-**i** (Scheme 1). After treating **3a**-**f** with catalytic amounts of PTSA in refluxing dry benzene for 6 h, the new derivatives **4a**-**f** were obtained in 30–70% yields (Table 1). The stereochemistry of the R^2 and the OH group in the derivatives **4a**-**f** was demonstrated to be *cis* by NOE experiments (Scheme 1).

In the case of derivative **3e** using a catalytic amount of PTSA, the corresponding compound **4e** was formed together with the isoflavene **5e** carrying a two carbon

Table 1. Reaction of cyclobutanones **3a**-**i** with catalytic PTSA

	X	R	R^1	R^2	**4** Yield (%)[a]
3a	O	H	H	Me	50
3b	O	H	*p*-OCH_3	Me	70
3c	O	H	*p*-Cl	Me	65
3d	O	H	*m*-CH_3	Me	70[b]
3e	O	H	H	Ph	60
3f	O	CH_3	H	Me	30[c]
3g	CH_2	H	H	Me	0
3h	CH_2	H	*p*-OCH_3	Me	0
3i	CH_2	H	*m*-OCH_3	Me	0[d]

[a] Isolated yield.
[b] Yields referred to the two regioisomers **4d** and **4d′** formed in a 3:4 ratio.
[c] Only the diastereoisomer (S^*,R^*)-**3f** underwent cyclization (vide infra).
[d] Instead of the chromene **4i** the corresponding tosylate **5i** was isolated.

Keywords: Cyclopropanes; Cyclobutanones; Electrophilic aromatic substitutions; Ring opening; Kinetic resolution; Capsorubin.
* Corresponding author. Fax: +39-0706754388;
e-mail address: pppiras@vaxca1.unica.it;

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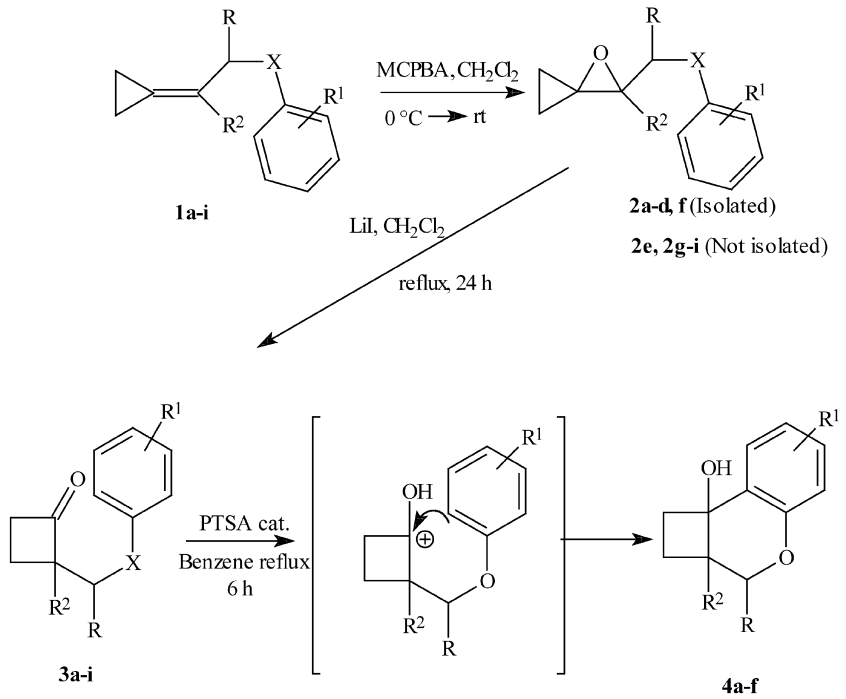
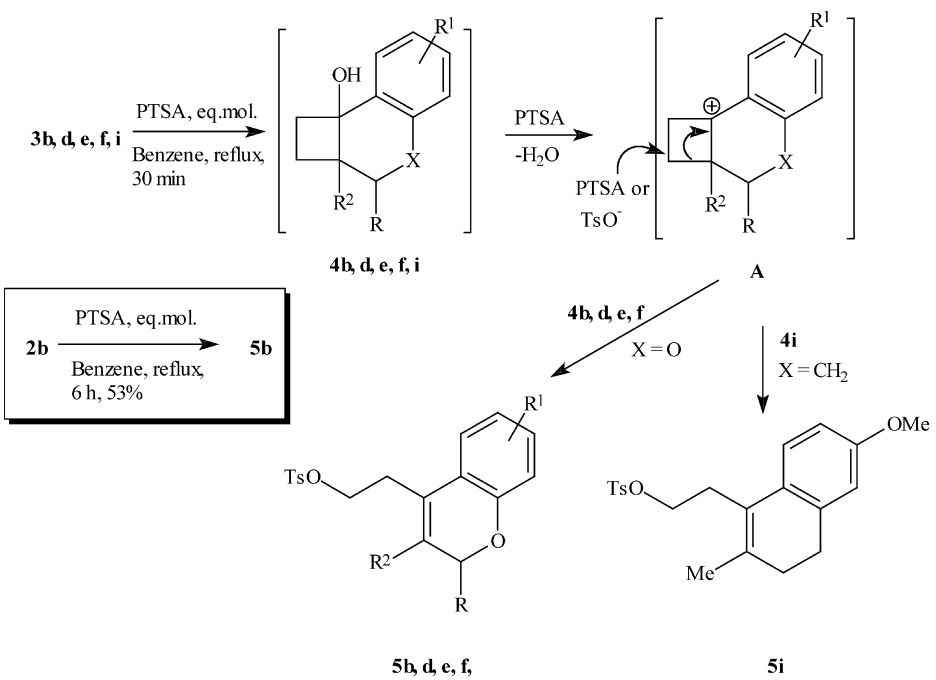


Scheme 1.

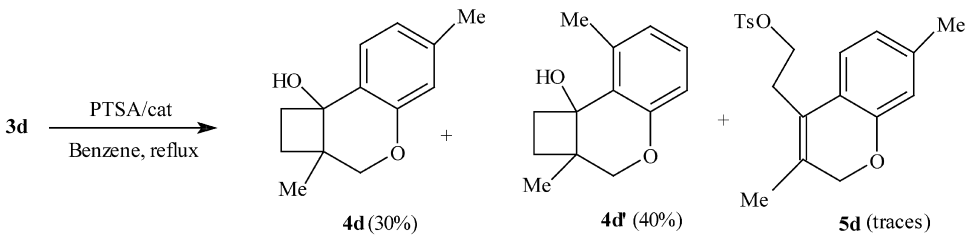
chain with a terminal tosyloxy group, probably coming from the ring fission of the intermediate cyclobutyl cation **A** by PTSA or its anion (Scheme 2). We checked the possibility of transforming derivatives of type **3** into chromenes **5**, through the intermediacy of chromenes **4**, by treating **3b**,**d**,**e**,**f**,**i**. with an equimolar amount of PTSA. We found that they were completely transformed, after 30 min, into the fragile tosylates **5b**,**d**,**e**,**f**,**i** in satisfactory yields (35–90%) probably through the same mechanism as described above (Scheme 2).

As it is well known that the oxaspiropentanes can undergo ring enlargement to the corresponding cyclobutanones by acid treatment, we envisaged the possibility that by reaction with equimolar amounts of PTSA, derivatives **2** could give the corresponding tosylates **5**, through a cascade reaction. We were pleased to find that **2b** gave 53% of the tosylate **5b** in a one pot reaction with an equimolar amount of PTSA in refluxing benzene for 6 h (Scheme 2).

Cyclization occurs for **3a-f** due to the presence of the



Scheme 2.



Scheme 3.

activating *ipso*-oxygen atom, while **3g** and **3h**, lacking this activation, are unreactive. On the contrary, derivative **3i**, which also lacks the activating *ipso*-oxygen atom, but carries a *meta*-methoxy group reacts cleanly (but gives **5i**, Scheme 2), as the methoxy group is suitably placed to activate the electrophilic attack to close a six-membered ring.

Derivative **3d** gave roughly the same quantities of the two possible regioisomers **4d** and **4d′**, easily identifiable from the aromatic region of their ^{1}H NMR spectra, accompanied by small quantities of the chromene **5d** coming from the cyclobutyl ring fission of the derivative **4d** (Scheme 3).

Derivative **3f** prepared as a mixture (60:40) of the two possible diastereoisomers, is particularly interesting in terms of the stereochemistry of the corresponding ring closure product. Using catalytic amounts of PTSA in refluxing benzene for 6 h it was only possible to isolate from the reaction mixture the cyclobutanol (*R***S***R**)-**4f** accompanied by small amounts of the chromene **5f** and the most abundant unreacted diastereoisomer (*S***S**)-**3f** of the starting cyclobutanone, through a kinetic resolution (Scheme 4).

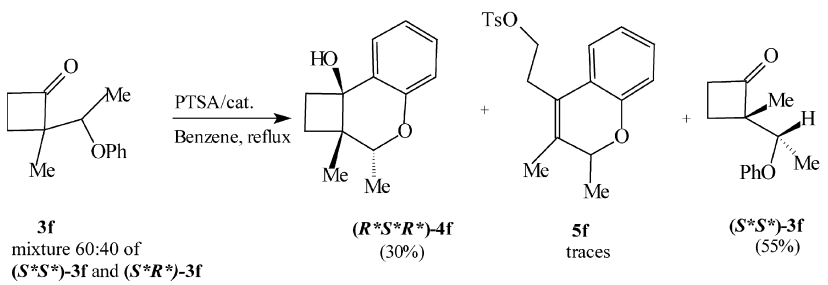
The stereochemistry of the cyclobutanol (*R***S***R**)-**4f**, assigned on the basis of NOE experiments, shows that the relative position of the two methyl groups is *trans*, while the apical methyl group, at 1.24 ppm, and the alcoholic OH are in relative *cis* position. On the basis of the steric constraints present during the cyclization step only the diastereoisomer (*S***R**)-**3f** can give rise to the isolated chromene (*R***S***R**)-**4f**. The unreacted diastereoisomer of **3f** therefore has the *S***S** stereochemistry and its unreactivity could be explained by the unfavourable steric hindrance present in the generation of the other possible chromene, which would have all three groups *cis* to each other.

As a consequence of this fact we planned the same reaction sequence using non-racemic substrates as reported in Scheme 5.

According to a literature procedure[9] we first prepared the optically pure 2-phenoxypropionic acid starting from (*S*)-ethyl lactate. The 2-phenoxypropionic acid was reacted with methyl lithium to give the corresponding ketone **6**.[10]

The ketone **6** was then reacted with the cyclopropylidene triphenylphosphonium bromide to give the alkylidene cyclopropane **1f**. Attempts to check the optical purity at this stage both with chiral HPLC or using ^{1}H NMR spectroscopy with chiral shift reagents were unfruitful. We then transformed **1f** into the corresponding oxaspiropentane **2f** obtained, with practically no stereoselectivity, as an inseparable mixture of diastereoisomers (60:40) that, by reaction with lithium iodide, gave the cyclobutanone **3f** as a mixture (60:40) of the two diastereoisomers **3f′** and **3f″**. To check the % ee of the two diastereoisomers of **3f** we treated it with (2*R*,3*R*)(−)-2,3-butanediol to give the corresponding ketals **7** and **8**. GC–MS analysis of the latter showed the presence of four diastereoisomers and this fact is a clear indication that epimerization had occurred on the original lactate stereogenic centre. Considering the experimental conditions of every step to arrive at the cyclobutanone **3f**, it is possible that epimerization could have occurred during the alkylidenation step as a consequence of the basic nature of the ylide. We exclude that epimerization could occur during the LiI catalyzed ring expansion of the oxaspiropentanes **2f** as it is generally accepted that this transformation occurs with inversion of configuration at the migrating terminus and without significant loss of stereochemistry.[2e] As a consequence of this epimerization, the next cyclization step led to the expected chromene **4f″** together with the unreacted cyclobutanone **3f′** (both not enantiomerically pure). Using GC–MS of the ketals **8** formed from **3f′** and comparing with the GC–MS of the ketals **7** and **8** from **3f**, the % ee of **4f″** and **3f′** was determined to be 50%.

Aiming at the synthesis of compounds with the same chromenic skeleton **4** but with different substituents, we planned the transformation of the carbonyl function into the corresponding alcohol to attempt the ring closure by acid



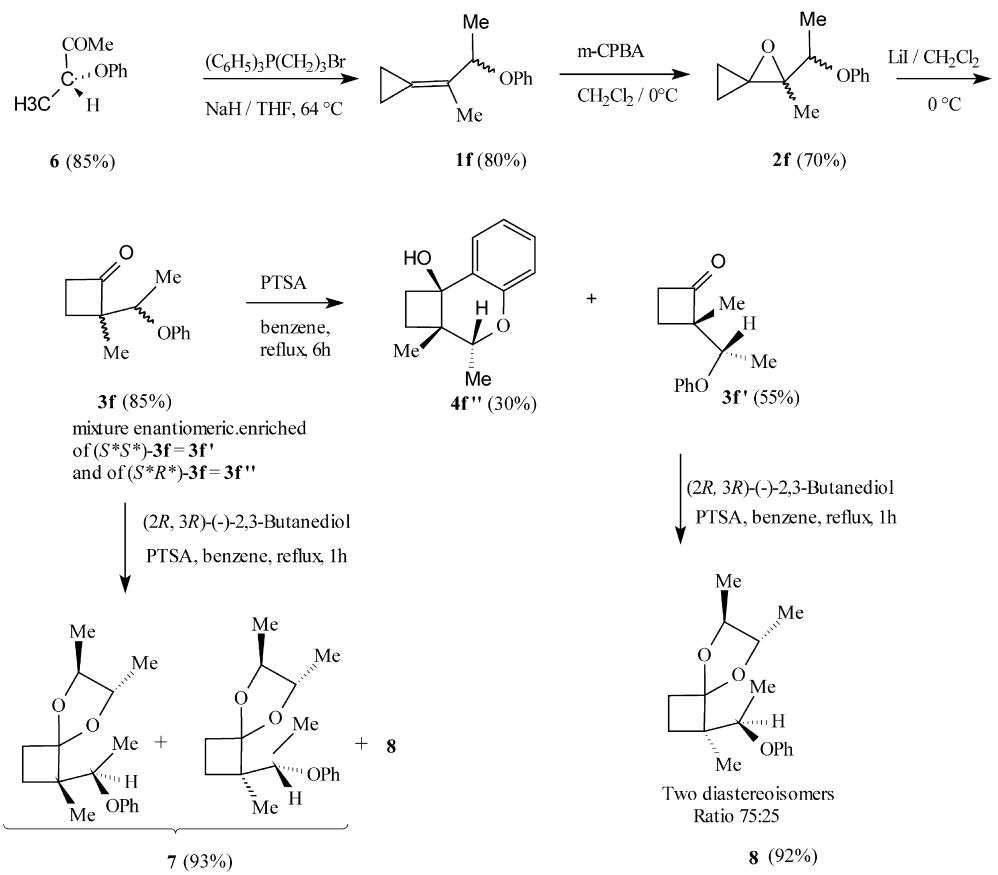
3f
mixture 60:40 of
(*S***S**)-**3f** and (*S***R**)-**3f**

(*R***S***R**)-**4f**
(30%)

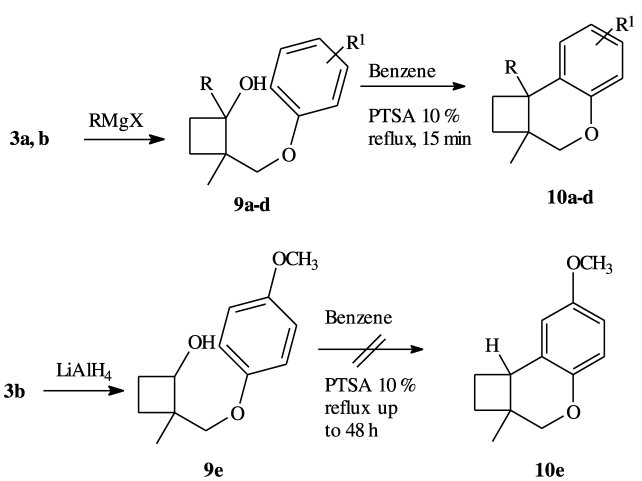
5f
traces

(*S***S**)-**3f**
(55%)

Scheme 4.



Scheme 5.

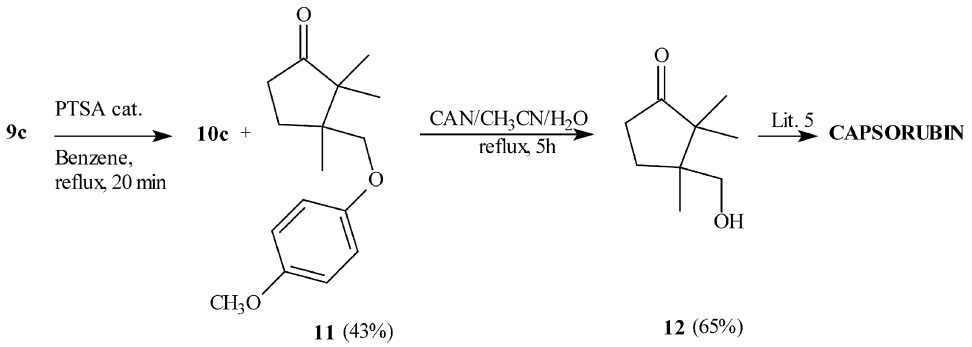


St.mat.	R	R^1	Products (yield%)	
3b	H	*p*-OCH_3	**9e** (76)	**10c** (0)
3b	C_6H_5	*p*-OCH_3	**9a**	**10a** (77)
3a	$CH{=}CH_2$	H	**9b**	**10b** (50)
3b	$C(CH_3){=}CH_2$	*p*-OCH_3	**9c** (70)	**10c** (30)
3a	$CH_2C_6H_5$	H	**9d**	**10d** (45)

Scheme 6.

treatment. We transformed the cyclobutanones **3a**,**b** into the corresponding *E*/*Z* mixtures of the tertiary cyclobutanols **9a**-**d** by reaction with a set of Grignard reagents and reduced the cyclobutanone **3b** into the corresponding cyclobutanol **9e** as a 60:40 mixture of *E*/*Z* isomers. Treatment of the cyclobutanols **9a**-**d** so obtained with a catalytic amount of PTSA in refluxing benzene for 15 min caused clean cyclization to occur to provide the corresponding chromenes **10a**-**d**, always isolated as a single diastereoisomer with *cis* stereochemistry as determined on the basis of NOE experiments. The unsubstituted cyclobutanol **9e** was recovered unchanged from the reaction mixture, even after longer reaction times (Scheme 6). Interestingly, the cyclobutanol **9c** gave the chromene **10c** as a minor product together with the cyclopentanone **11** (Scheme 7) probably through a protonation of the double bond of the isopropenyl moiety and subsequent ring enlargement of the cyclobutane ring.

The acid catalyzed ring expansion of 1-(prop-2-enyl) cyclobutanol has been previously[11] accomplished with sulfuric acid in the presence of 2,4-dinitrophenylhydrazine to convert the intermediate 2,2-dimethyl cyclopentanone into the corresponding hydrazone. Our result is, therefore, the first example of this kind of transformation carried out under mild conditions and, moreover, the ready transformation of the cyclopentanone **11** into the cyclopentanone **12**, by treatment with CAN in acetonitrile, represents a formal synthesis of the natural derivative capsorubin.[5] As 2,2-substituted cyclopentanones are present in the carbon skeleton of several natural products these results are



Scheme 7.

particularly important and deserve further studies that are in progress in our laboratory to establish their generality and results will be reported in due course.

3. Conclusion

We have reported a synthesis of a new class of chromenes fused to a cyclobutane ring that is susceptible to ring opening (as a consequence of its strain) to give new functionalized chromenes. This transformation is particularly important as it represents a versatile access to the family of the isoflav-3-enes bearing a 2*H*-1-benzopyran nucleus that are gaining increasing importance for their antiestrogen activity.[12] Moreover, we have achieved a formal synthesis of the natural product capsorubin.

4. Experimental

4.1. General

Reagent-grade commercially available reagents and solvents were used. ^{1}H and ^{13}C NMR spectra were recorded with a 300 MHz spectrometer with tetramethylsilane as internal reference; δ values are given in ppm and J values in Hz. GC–MS analyses were carried out with a gas chromatograph equipped with a mass selective detector. TLC were carried out on precoated TLC plates with silica gel 60 F-254. For column chromatography silica gel 60 (230–400 mesh) was used. Melting points were determined on a Tottoli apparatus and are uncorrected. IR spectra were recorded using NaCl plates. Optical activity was determined on a polarimeter with a path length of 1 dm. Concentrations are given in g/100 mL. Microanalyses were carried out on a Carlo Erba 1106 Elemental Analyzer. Derivatives **1a**,**c**,**e**;[8a] **1b**, **1d**;[8b] **1f**, **3e**, **4e**, **5e**;[8f] **1g**;[8c] **2a**-**b**, **3a**;[8d] **3b**, **9a**,**b**,**d**[8e] have been previously reported, while **1h** and **1i** were prepared according to the method reported in Ref. 8a using 4-(4-methoxyphenyl)-2-butanone and 4-(3-methoxyphenyl)-2-butanone.[13]

4.1.1. 1-(3-Cyclopropylidenebutyl)-4-methoxybenzene (1h). Colourless oil. 1.5 g. Yield: 67%. ^{1}H NMR ($CDCl_3$) δ: 0.92 (m, 4H), 1.83 (s, 3H), 2.39–2.45 (m, 2H), 2.72–2.77 (m, 2H), 3.75 (s, 3H), 6.80–7.31 (m, 4H). ^{13}C NMR ($CDCl_3$) δ: 1.4, 2.8, 20.6, 33.1, 38.7, 55.1, 113.5, 115.8, 123.4, 129.1, 134.6, 157.5. IR (neat, cm^{-1}):1580, 3050. Anal. Calcd for $C_{14}H_{18}O$: C, 83.12; H, 8.97. Found: C, 83.04; H, 8.79.

4.1.2. 1-(3-Cyclopropylidenebutyl)-3-methoxybenzene (1i). Colourless oil. 1.7 g. Yield 99%. ^{1}H NMR ($CDCl_3$) δ: 0.94 (m, 4H), 1.84 (s, 3H), 2.45 (t, 2H, J=8.4 Hz), 2.81 (t, 2H, J=8.4 Hz), 3.76 (s, 3H), 7.14–7.27 (m, 4H). ^{13}C NMR ($CDCl_3$) δ: 1.4, 2.8, 20.7, 34.1, 38.3, 55.0, 110.8, 114.1, 115.8, 120.7, 123.4, 129.0, 144.2, 159.4. IR (neat, cm^{-1}): 1580, 3030. Anal. Calcd for $C_{14}H_{18}O$: C, 83.12; H, 8.97. Found: C, 83.21; H, 8.76.

4.2. General method for the synthesis of 2a-i

To a stirred solution of **1** (17 mmol) in CH_2Cl_2 (80 mL) at 0 °C, *m*-CPBA (70% active, 4.1 g, 17 mmol) was added portionwise. After stirring for 20 h at room temperature, the solution was filtered and treated several times with a saturated solution of $NaHCO_3$. The organic phase was dried (Na_2SO_4) and after filtration evaporated under vacuum. The remaining oil was chromatographed on a silica gel column (light petroleum/diethyl ether, 5:1) to give the purified product in 75–90% yields.

4.2.1. 2-[(4-Chlorophenoxy)methyl]-2-methyl-1-oxaspiro[2,2]pentane (2c). Yellow oil. Yield: 70%. ^{1}H NMR ($CDCl_3$) δ: 0.92–1.28 (m, 4H), 1.59 (s, 3H), 4.07 (d, 1H, J=10.5 Hz), 4.11 (d, 1H, J=10.5 Hz), 6.85–7.25 (m, 4H). ^{13}C NMR ($CDCl_3$) δ: 1.7, 2.8, 17.7, 61.8, 62.8, 72.4, 116.0, 129.3, 129.5, 157.3. IR (neat, cm^{-1}): 1230, 1590, 3040. Anal. Calcd for $C_{12}H_{13}O_2Cl$: C, 64.15; H, 5.83. Found: C, 64.32; H, 5.79.

4.2.2. 2-Methyl-2-[(3-methylphenoxy)methyl]-1-oxaspiro[2,2]pentane (2d). Colourless oil. Yield 75%. ^{1}H NMR ($CDCl_3$) δ: 0.95–1.11 (m, 4H), 1.60 (s, 3H), 2.33 (s, 3H), 4.12 (d, 1H, J=10.5 Hz), 4.17 (d, 1H, J=10.5 Hz), 6.76–7.25 (m, 4H). ^{13}C NMR ($CDCl_3$) δ: 1.9, 2.8, 17.7, 21.5, 61.9, 62.9, 72.0, 111.5, 115.5, 121.8, 129.6, 139.5, 158.7. IR (neat, cm^{-1}): 1240, 1590, 3030. Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.35; H, 7.84.

4.2.3. 2-Methyl-2-(1-phenoxyethyl)-1-oxaspiro[2,2]pentane (2f). Colourless oil. Yield: 70%. Inseparable mixture of two diastereoisomers in the ratio 60:40. ^{1}H NMR ($CDCl_3$) δ: 0.81–1.22 (m, 8H), 1.30 (major isomer, d, 3H, J=6.3 Hz), 1.44 (minor isomer, d, 3H, J=6.6 Hz), 1.52 (s, 3H), 1.55 (s, 3H), 4.27 and 4.33 (two q, 1H each, J=6.3 Hz), 6.86–7.30 (m, 10H). ^{13}C NMR ($CDCl_3$) δ: 1.2, 2.3, 3.1, 3.4,

15.2, 15.3, 15.5, 17.0, 61.5, 63.9, 64.6, 65.4, 77.9, 78.1, 116.2, 116.9, 121.0, 121.6, 129.3, 129.4, 157.8, 158.1. IR (neat, cm^{-1}): 1240, 1590, 3050. Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.55; H, 7.87.

4.3. General method for the synthesis of 3a-i

A solution of **2** (4.5 mmol) in CH_2Cl_2 (10 mL) was treated with LiI (0.03 g, 0.22 mmol, 5 mol%) and refluxed for 24 h. The mixture was washed repeatedly with brine and then dried over Na_2SO_4. Evaporation of CH_2Cl_2 left an oil that was purified by chromatography on silica gel column (light petroleum/diethyl ether, 3:1) to give the expected cyclobutanone **3**.

4.3.1. 2-[(4-Chlorophenoxy)methyl-2-methylcyclobutanone (3c). Yellow oil. Yield 72%. ^{1}H NMR ($CDCl_3$) δ: 1.27 (s, 3H), 1.80–1.89 (m, 1H), 2.32–2.41 (m, 1H), 3.06–3.13 (m, 2H), 3.79 (d, 1H, J=9.0 Hz), 4.00 (d, 1H, J=9.0 Hz), 6.73–7.27 (m, 4H). ^{13}C NMR ($CDCl_3$) δ: 18.0, 21.8, 43.5, 63.8, 70.6, 115.7, 129.2, 129.4, 157.2, 213.2. IR (neat, cm^{-1}) 1770. MS *m/z*: 224 (M^+(0.3)), 130 (4), 128 (12), 97 (15), 69 (51), 55 (62), 55 (100). Anal. Calcd for $C_{12}H_{13}O_2Cl$: C, 64.15; H, 5.83. Found: C, 64.38; H, 5.74.

4.3.2. 2-Methyl-2-[(3-methylphenoxy)methyl]cyclobutanone (3d). Colourless oil. Yield 80%. ^{1}H NMR ($CDCl_3$) δ: 1.27 (s, 1H), 1.78–1.86 (m, 1H), 2.31 (s, 3H), 2.33–2.42 (m, 1H), 2.97–3.17 (m, 2H), 3.81 (d, 1H, J=9.0 Hz), 4.01 (d, 1H, J=9.0 Hz), 6.66–7.24 (m, 4H). ^{13}C NMR ($CDCl_3$) δ: 18.1, 21.4, 21.9, 43.6, 64.1, 70.3, 111.3, 115.4, 121.8, 129.1, 139.4, 158.6, 213.2. IR (neat, cm^{-1}) 1776. MS *m/z*: 204 (M^+(5)), 147 (25),108 (100), 97 (23), 69 (50), 55 (43), 41 (61). Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.32; H, 7.98.

4.3.3. 2-Methyl-2-(1-phenoxyethyl)cyclobutanone (3f). Colourless oil. Yield: 85%. Unseparable 60:40 mixture of two diastereoisomers (S^*S^*)-**3f** and (S^*R^*)-**3f**. The diastereoisomer (S^*S^*)-**3f** was obtained pure during the cyclization reaction in 55% yield. ^{1}H NMR ($CDCl_3$) δ: 1.27 (s, 3H), 1.33 (d, 3H, J=6.3 Hz), 1.68–1.78 (m, 1H), 2.27–2.37 (m, 1H), 2.96–3.08 (m, 2H), 4.33 (q, 1H, J=6.3 Hz), 6.86–7.30 (m, 5H). ^{13}C NMR ($CDCl_3$) δ: 15.0, 18.9, 22.2, 43.4, 67.9, 76.7, 115.8, 121.0, 129.4, 157.8, 213.5. IR (neat, cm^{-1}) 1776. MS *m/z*: 204 (M^+(2)), 111 (67), 94 (100), 83 (44), 69 (78), 55 (73), 41 (71). Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.52; H, 7.78.

(S^*R^*)-**3f** (Data worked out from the NMR spectra of the mixture of the two diastereoisomers). ^{1}H NMR ($CDCl_3$) δ: 1.22 (d, 3H, J=6.3 Hz) 1.24 (s, 3H), 1.68–1.80 (m, 1H), 2.43–2.53 (m, 1H), 2.97–3.09 (m, 2H), 4.44 (q, 1H, J=6.3 Hz), 6.87–7.31 (m, 5H). ^{13}C NMR ($CDCl_3$) δ: 15.0, 17.8, 20.5, 43.1, 68.3, 75.7, 116.6, 121.2, 129.4, 157.5, 214.0. MS *m/z*: same peaks as (S^*S^*)-**3f**.

4.3.4. 2-Methyl-2-phenethylcyclobutanone (3g). Colourless oil. Yield 80%. ^{1}H NMR ($CDCl_3$) δ: 1.28 (s, 3H), 1.73–2.03 (m, 4H), 2.53–2.75 (m, 2H), 2.98–3.05 (m, 2H), 7.15–7.29 (m, 5H). ^{13}C NMR ($CDCl_3$) δ: 20.5, 24.1, 30.9, 37.9, 42.3, 64.1, 125.9, 128.2, 128.4, 141.8, 215.3. IR (neat, cm^{-1}): 1782. MS *m/z*: 188 (M^+(4)), 146 (11), 131 (7), 104 (20), 91 (100), 77 (5). Anal. Calcd for $C_{13}H_{16}O$: C, 82.94; H, 8.57. Found: C, 82.84; H, 8.69.

4.3.5. 2-(4-Methoxyphenethyl)-2-methylcyclobutanone (3h). Colourless oil. Yield 80%. ^{1}H NMR ($CDCl_3$) δ: 1.24 (s, 3H), 1.73–1.99 (m, 4H), 2.44–2.63 (m, 2H), 2.96–3.03 (m, 2H), 3.76 (s, 3H), 6.78–7.08 (m, 4H). ^{13}C NMR ($CDCl_3$) δ: 20.6, 24.1, 30.0, 38.2, 42.3, 55.2, 64.1, 113.8, 129.1, 133.9, 157.8, 215.4. IR (neat, cm^{-1}): 1750. MS *m/z*: 218 (M^+(35)), 176 (25), 134 (10), 121 (100), 91 (18), 77 (25). Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 76.84; H, 8.49.

4.3.6. 2-(3-Methoxyphenethyl)-2-methylcyclobutanone (3i). Colourless oil. Yield 65%. ^{1}H NMR ($CDCl_3$) δ: 1.27 (s, 3H), 1.77–1.98 (m, 4H), 2.54–2.72 (m, 2H), 2.99–3.06 (m, 2H), 3.79 (s, 3H), 6.72–7.28 (m, 4H). ^{13}C NMR ($CDCl_3$) δ: 20.5, 24.1, 31.0, 37.8, 42.3, 55.1, 64.1, 111.2, 113.9, 120.6, 129.4, 143.5, 159.7, 215.3. IR (neat, cm^{-1}): 1770. MS *m/z*: 218 (M^+(23)), 176 (36), 161 (38), 134 (36), 121 (100), 91 (33), 77 (17). Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 76.94; H, 8.27.

4.4. General procedure for the preparation of chromenes 4a-f

A stirred solution of cyclobutanone **3** (2.7 mmol) and *p*-toluenesulfonic acid (0.046 g, 0.27 mmol,) in dry benzene (10 mL) was refluxed for 6 h in a Dean–Stark apparatus. The reaction mixture was diluted with CH_2Cl_2 and washed with 10% $NaHCO_3$ and brine, dried (Na_2SO_4) and evaporated to remove the solvent. The residue was chromatographed on silica gel with diethyl ether/light petroleum, 1:1.

4.4.1. 2a-Methyl-1,2,2a,3-tetrahydro-8b*H*-cyclobuta[*c*]-chromen-8b-ol (4a). Yellow oil. Yield 45%. ^{1}H NMR ($CDCl_3$) δ: 1.13 (s, 3H), 1.30–1.39 (m, 1H), 1.63–1.75 (m, 1H), 1.93–2.00 (m, 1H), 2.19 (br s, 1H), 2.31–2.42 (m, 1H), 3.31 (d, 1H, J=11.4 Hz), 3.68 (d, 1H, J=11.4 Hz), 6.67–6.97 (m, 4H). ^{13}C NMR ($CDCl_3$) δ: 16.6, 19.7, 35.3, 45.2, 68.1, 69.3, 117.2, 121.9, 127.9, 128.4, 130.8, 153.7. IR (neat, cm^{-1}): 3450. MS *m/z*: 190 (M^+(10)), 175 (4), 162 (100), 147 (60), 121 (90). Anal. Calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 75.65; H, 7.54.

4.4.2. 7-Methoxy-2a-methyl-1,2,2a,3-tetrahydro-8b*H*-cyclobuta[*c*]chromen-8b-ol (4b). Yellow oil. Yield 70%. ^{1}H NMR ($CDCl_3$) δ: 1.13 (s, 3H), 1.30–1.38 (m, 1H), 1.63–1.75 (m, 1H), 1.92–2.00 (m, 1H), 2.10 (br s, 1H), 2.31–2.42 (m, 1H), 3.31 (d, 1H, J=11.4 Hz), 3.68 (d, 1H, J=11.4 Hz), 3.69 (s, 3H), 6.67–6.97 (m, 3H). ^{13}C NMR ($CDCl_3$) δ: 16.7, 19.7, 35.3, 45.1, 55.7, 69.5, 69.8, 111.0, 115.6, 118.1, 128.5, 147.9, 154.5. IR (neat, cm^{-1}): 3320. MS *m/z*: 220 (M^+(40)), 192 (100), 177 (46), 151 (93). Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32. Found: C, 70.75; H, 7.44.

4.4.3. 7-Chloro-2a-methyl-1,2,2a,3-tetrahydro-8b*H*-cyclobuta[*c*]chromen-8b-ol (4c). Yellow oil. Yield: 65%. ^{1}H NMR ($CDCl_3$) δ: 1.22 (s, 3H), 1.40–1.48 m, 1H), 1.70–1.81 (m, 1H), 2.00–2.08 (m, 1H), 2.04 (br s, 1H), 2.39–2.50

(m, 1H), 3.41 (d, 1H, J=11.4 Hz), 3.82 (d, 1H, J=11.4 Hz), 6.73–7.52 (m, 3H). ^{13}C NMR ($CDCl_3$) δ:16.5, 19.7, 35.5, 45.1, 69.4, 69.6, 116.6, 118.8, 127.7, 128.6, 129.5, 152.4, 154.3. IR (neat, cm^{-1}): 3340. MS *m/z*: 226 (M^++2 (9)), 224 (M^+(26)), 196 (100), 181 (66), 155 (95), 128 (11). Anal. Calcd for $C_{12}H_{13}O_2Cl$: C, 64.15; H, 5.83. Found: C, 64.35; H, 5.74.

4.4.4. 2a,6-Dimethyl-1,2,2a,3-tetrahydro-8b*H*-cyclobuta[*c*]chromen-8b-ol (4d). Yellow oil. Yield 30%. ^{1}H NMR ($CDCl_3$) δ: 1.20 (s, 3H), 1.42 (m, 1H), 1.75 (m, 1H), 1.94 (br s, 1H), 2.00 (m, 1H), 2.30 (s, 3H), 2.44 (m, 1H), 3.43 (d, 1H, J=11.4 Hz), 3.79 (d, 1H, J=11.4 Hz), 6.71 (s, 1H), 6.84 (d, J=8.1 Hz), 7.41 (d, 1H, J=8.1 Hz). ^{13}C NMR ($CDCl_3$) δ: 16,6, 19.8, 21.1, 35.4, 45.2, 69.2, 69.4, 117.4, 123.1, 126.1, 127.7, 138.6, 153.6. IR (neat, cm^{-1}): 3400. MS *m/z*: 204 (M^+(13)), 189 (5), 176 (100), 161 (61), 135 (97). Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.34; H, 7.76.

4.4.5. 2a,8-Dimethyl-1,2,2a,3-tetrahydro-8b*H*-cyclobuta[*c*]chromen-8b-ol (4d′). Yellow oil. Yield 40%. ^{1}H NMR ($CDCl_3$) δ: 1.23 (s, 3H), 1.50, (m, 1H), 1.73 (m, 1H), 1.74 (br s, 1H), 2.25 (m, 1H), 2.43 (s, 3H), 2.51 (m, 1H), 3.56 (d, 1H, J=11.1 Hz), 3.82 (d, 1H, J=11.1 Hz), 6.73 (d, 1H, J=8.4 Hz), 6.80 (d, 1H, J=7.2 Hz), 7.07 (unresolved dd, 1H). ^{13}C NMR ($CDCl_3$) δ: 17.1, 20.8, 21.2, 34.1, 44.5, 69.1, 69.8, 115.1, 124.6, 125.1, 128.2, 139.5, 154.3. IR (neat, cm^{-1}): 3450. MS *m/z*: 204 (M^+(25)), 189 (2), 176 (79), 161 (73), 135 (100). Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.36; H, 7.78.

4.4.6. 2a,3-Dimethyl-1,2,2a,3-tetrahydro-8b*H*-cyclobuta[*c*]chromen-8b-ol (*RS*R*-4f).** White crystals, mp 98 °C. Yield 30%. ^{1}H NMR ($CDCl_3$) δ:1.24 (s, 3H), 1.25 (d, 3H, J=6.6 Hz)), 1.30–1.37 (m, 1H), 1.68 (m, 1H), 1.94–2.02 (m, 2H, one D_2O exchangeable), 2.37–2.48 (m, 1H) 3.54 (q, 1H, J=6.6 Hz), 6.89–7.50 (m, 4H). ^{13}C NMR ($CDCl_3$) δ: 15.6, 17.0, 17.5, 35.1, 49.0, 69.8, 73.8, 117.1, 121.8, 127.7, 128.4, 129.0, 153.5. IR (neat, cm^{-1}): 3400. MS *m/z*: 204 (M^+(10)), 186 (8), 176 (32), 161 (100), 121 (65). Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.52; H, 7.78.

4.5. General procedure for the preparation of chromenes 5b, d, f, i

A stirred solution of cyclobutanone **3** (2.7 mmol) and *p*-toluenesulfonic acid (0.46 g, 2.7 mmol,) in dry benzene (10 mL) was refluxed for 30 min in a Dean–Stark apparatus. The reaction mixture was diluted with CH_2Cl_2 and washed with 10% $NaHCO_3$ and brine, dried (Na_2SO_4) and evaporated to remove the solvent. The residue was chromatographed on silica gel with diethyl ether/light petroleum (1:1).

4.5.1. 2-(6-Methoxy-3-methyl-2*H*-chromen-4-yl)ethyl 4-methylbenzenesulfonate (5b). Yellow oil. Yield 86%. ^{1}H NMR ($CDCl_3$) δ: 1.73 (s, 3H), 2.39 (s, 3H), 2.82 (t, 2H, J=7.5 Hz), 3.72 (s, 3H), 4.05 (t, 2H, J=7.5 Hz), 4.44 (s, 2H), 6.81–7.64 (m, 7H). ^{13}C NMR ($CDCl_3$) δ: 15.8, 21.4, 26.5, 55.6, 68.0, 69.1, 108.4, 112.3, 116.0, 121.6, 123.6, 127.5, 129.7, 130.3, 132.7, 144.6, 147.1, 154.1. IR (neat, cm^{-1}): 1170, 1350. Anal. Calcd for $C_{20}H_{22}O_5S$: C, 64.15; H, 5.92; S, 8.56. Found: C, 64.22; H, 5.78; S, 8.48.

4.5.2. 2-(3,7-Dimethyl-2*H*-chromen-4-yl)ethyl 4-methylbenzenesulfonate (5d). Yellow oil. Yield 80%. ^{1}H NMR ($CDCl_3$) δ: 1.72 (s, 3H), 2.25 (s, 3H), 2.41 (s, 3H), 2.83 (t, 2H, J=7.2 Hz), 4.05 (t, 2H, J=7.2 Hz), 4.49 (s, 2H), 6.57–7.73 (m, 7H). ^{13}C NMR ($CDCl_3$) δ: 15.7, 21.1, 21.6, 26.5, 68.2, 69.3, 116.4, 120.1, 121.6, 121.9, 122.0, 127.8, 128.0, 129.7, 132.9, 138.3, 144.7, 153.3. IR (neat, cm^{-1}): 1180, 1370. Anal. Calcd for $C_{20}H_{22}O_4S$: C, 67.02; H, 6.19; S, 8.94. Found: C, 67.12; H, 6.28; S, 8.88.

4.5.3. 2-(2,3-Methyl-2*H*-chromen-4-yl)ethyl 4-methylbenzenesulfonate (5f). Yellow oil. Yield 35%. ^{1}H NMR ($CDCl_3$) δ: 1.24 (d, 3H, J=6.3 Hz), 1.76 (s, 3H), 2.41 (s, 3H), 2.85 (t, 2H, J=7.5 Hz), 3.96–4.11 (m, 2H), 4.62 (q, 1H, J=6.3 Hz), 6.75–7.08 (m, 4H), 7.28 (d, 2H, J=8.4 Hz), 7.73 (d, 2H, J=8.4 Hz). ^{13}C NMR ($CDCl_3$) δ: 16.0, 18.2, 21.6, 26.6, 29.6, 68.1, 74.8, 116.7, 120.6, 120.9, 122.0, 127.7, 128.1, 129.7, 132.9, 133.4, 144.7, 151.6. IR (neat, cm^{-1}) 1200, 1380. Anal. Calcd for $C_{20}H_{22}O_4S$: C, 67.02; H, 6.19; S, 8.94. Found: C, 67.22; H, 5.98; S, 8.78.

4.5.4. 2-(6-Methoxy-2-methyl-3,4-dihydro-1-naphthalenyl)ethyl 4-methylbenzenesulfonate (5i). Yellow oil. Yield 90%. ^{1}H NMR ($CDCl_3$) δ: 1.84 (s, 3H), 2.15 (t, 2H, J=7.8 Hz), 2.42 (s, 3H), 2.63 (t, 2H, J=7.8 Hz), 2.88 (t, 2H, J=7.8 Hz), 3.77 (s, 3H), 4.04 (t, 2H, J=7.8 Hz), 6.61–6.64 (m, 2H), 6.94 (d, 1H, J=8.4 Hz), 7.29 (d, 2H, J=8.4 Hz), 7.75 (d, 2H, J=8.4 Hz). ^{13}C NMR ($CDCl_3$) δ: 20.1, 21.5, 27.8, 28.6, 30.4, 55.2, 68.7, 110.8, 113.6, 122.8, 123.1, 127.8, 129.7, 133.2, 133.6, 137.4, 144.6, 157.7. IR (neat, cm^{-1}): 1180, 1360. Anal. Calcd for $C_{21}H_{24}O_4S$: C, 67.72; H, 6.49; S, 8.61. Found: C, 67.52; H, 6.78; S, 8.48.

Spectral data of **1f**, **2f**, **3f′**, **4f″**, enantiomerically enriched, were identical with those of the corresponding racemic samples.

4.5.5. 1-(2-Cyclopropylidene-1-methylpropoxy)benzene (1f). $[\alpha]_D^{19}$=−26.12 (c=2.68, $CHCl_3$).

4.5.6. 2-Methyl-2-(1-phenoxyethyl)cyclobutanone. (3f′). $[\alpha]_D^{20}$=−19.76 (c=0.753, $CHCl_3$).

4.5.7. 2a,3-Dimethyl-1,2,2a,3-tetrahydro-8b*H*-cyclobuta[*c*]chromen-8b-ol (4f″). $[\alpha]_D^{19}$=+20.19 (c=3.07, $CHCl_3$).

4.5.8. (*R*)-(+)-3-phenoxy-2-butanone (6). A stirred solution of (*R*)-2-phenoxypropionic acid (1.3 g, 7.8 mmol) in dry THF (60 mL) was cooled to 0 °C (ice bath) and treated rapidly (ca. 20 s) with 1.6 M methyllithium in ether (19.4 mL, 31 mmol,). After 2 h at 0 °C, freshly distilled Me_3SiCl (20 mL, 15.6 mmol) was rapidly added while stirring continued. The ice bath was removed and the reaction mixture allowed to reach room temperature. 1 N HCl (58 mL) was added, and the resulting two phase system was stirred at room temperature for 0.5 h. The mixture was then extracted with diethyl ether and the ethereal layers were washed with brine and dried with Na_2SO_4. Removal of the solvent in vacuo gave the crude

methyl ketone **6** which was purified by chromatography on silica gel using diethyl ether/light petroleum, 5:1. Yield 85%. $[\alpha]_D^{23}$=+55.13 (*c*=5.604, $CHCl_3$). (lit.[10] $[\alpha]_D^{20}$=+50 (*c* 2.1, $CHCl_3$).

4.6. Ketalization of the mixture of the cyclobutanones 3f′ and 3f″

A stirred solution of cyclobutanone **3f** (120 mg, 0.58 mmol), *p*-toluenesulfonic acid (10 mg, 0.058 mmol), (2*R*,3*R*)-(−)-butanediol (52 mg, 0.58 mmol) in dry benzene (20 mL) was refluxed for 1 h. Then the reaction mixture was washed with 10% $NaHCO_3$ and brine, dried (Na_2SO_4) and evaporated to remove the solvent. The residue was chromatographed on silica gel with diethyl ether/light petroleum (1:1) to give 150 mg (yield 93%) of an oil as a mixture of four diastereoisomers **7** (75:25) and **8** (75:25). (**7**/**8**=40:60).

4.6.1. 1,6,7-Trimethyl-1-(1-phenoxyethyl)-5,8-dioxaspiro [3.4]octane (7 and 8). Data for the mixture of the four diastereoisomers **7** and **8**. ^{1}H NMR ($CDCl_3$) δ: 0.69–1.29 (doublets and singlets, 48H), 1.34–1.74 (m, 8H), 1.99–2.43 (m, 8H), 3.32–3.63 (m, 8H), 4.65 and 4.66 (two q, 2H, *J*=6.0, 6.3 Hz), 4.75 and 4.77 (two q, 2H, *J*=6.3, 6.6 Hz), 6.86–7.28 (m, 20H). MS *m*/*z* for **7** (major diastereoisomer): 183 (M^+−93 (85)), 155 (40), 114 (38), 94 (24), 83 (67), 69 (44), 55 (100). MS *m*/*z* for **7** (minor diastereoisomer): 183 (M^+−93 (43)), 155 (32), 114 (20), 94 (16), 83 (90), 65 (45), 55 (100).

4.7. Ketalization of the cyclobutanone 3f′

Same method followed for the mixture of cyclobutanones **3f′** and **3f″**. Yield 92%.

4.7.1. 1,6,7-Trimethyl-1-(1-phenoxyethyl)-5,8-dioxaspiro[3.4]octane (8). Data for the mixture of two diastereoisomers **8**. ^{1}H NMR ($CDCl_3$) δ: 0.69–1.29 (dublets and singlets, 24H), 1.34–1.74 (m, 4H), 1.99–2.43 (m, 4H), 3.32–3.63 (m, 4H), 4.75 and 4.77 (two q, 2H, *J*=6.3, 6.6 Hz), 6.86–7.28 (m, 10H). MS *m*/*z* (major diastereoisomer): 183 (M^+−93 (62)), 155 (30), 114 (36), 94 (34), 83 (58), 69 (32), 55 (100)). MS *m*/*z* (minor diastereoisomer): 183 (M^+−93(65)), 155 (28), 114 (31), 94 (12), 83 (60), 69 (34), 55 (70), 32 (100).

4.7.2. 1-Isopropenyl-2-[(4-methoxyphenoxy)methyl]-2-methylcyclobutanol (9c). To a stirred THF solution of cyclobutanone **3b** (1 g, 4.5 mmol) a solution of isopropenyl magnesium bromide prepared from magnesium (432 mg, 18 mmol) and 2-bromopropene (1.6 mL, 18 mmol), was added at −20 °C. The solution was allowed to gradually reach room temperature and stirring was continued for 20 h. The mixture was then quenched with saturated aqueous NH_4Cl and extracted with diethyl ether. The organic layer washed with brine, dried and evaporated gave an oil (*E*/*Z* ratio 70:30, from the ^{1}H NMR of the crude mixture) from which, after chromatography on a silica gel column with light petroleum/AcOEt 10:1 it was only possible to isolate the *E* isomer (global yield 70%). *E* isomer. ^{1}H NMR ($CDCl_3$) δ: 1.34 (s, 3H), 1.62–1.82 (m, 3H), 1.79 (s, 3H), 2.45–2.54 (m, 1H), 2.81 (br s, 1H), 3.66 (d, 1H, *J*=8.7 Hz), 3.71 (d, 1H, *J*=8.7 Hz), 3.75 (s, 3H), 4.91 (s, 2H), 6.80 (m, 4H). ^{13}C NMR ($CDCl_3$) δ: 18.4, 19.1, 24.9, 29.4, 46.6, 55.7, 73.3, 80.5, 111.3, 114.5, 115.2, 146.5, 153.5, 153.6. IR (neat, cm^{-1}): 3380. MS *m*/*z*: 262 (M^+(3)), 178 (11), 163 (3), 124 (100), 109 (20). Anal. Calcd for $C_{16}H_{22}O_3$: C, 73.25; H, 8.45, Found: C, 73.32; H, 8.58. *Z isomer*. ^{1}H NMR ($CDCl_3$) data worked out from the NMR spectra of the mixture of the two diastereisomers) δ: 1.13 (s, 3H), 1.62–2.02 (m, 3H), 1.85 (s, 3H), 2.45–2.54 (m, 1H), 2.81 (br s, 1H), 3.77 (s, 3H), 3.87 (d, 1H, *J*=9 Hz), 4.15 (d, 1H, *J*=9 Hz), 4.99 and 5.02 (each 1H, each br s), 6.80 (m, 4H). IR (neat, cm^{-1}): 3480. MS *m*/*z*: same peaks as the *E* isomer:262 (M^+(3)),178 (11), 163 (3), 124 (100), 109 (20).

4.7.3. 2-[(4-Methoxyphenyl)methyl]-2-methyl cyclobutanol (9e). To a stirred solution of thecyclobutanone **3b** (220 mg, 1 mmol) in THF (10 mL) under argon, a 1 M solution of $LiAlH_4$ (1 mmol, 1 mL) in the same solvent was added at 0 °C. After 30 min, wet sodium sulfate was added and then the reaction mixture was filtered and the solvent evaporated. The residue was chromatographed on silica gel with diethyl ether/light petroleum, 1:1 to give 170 mg of **9e** as a 60:40 mixture of *E*/*Z* isomers. Viscous liquid. Yield 76%. ^{1}H NMR ($CDCl_3$) δ: 1.21 (s, 3H), 1.39–1.49 (m, 1H), 1.61–1.70 (m, 1H), 1.84–2.02 (m, 1H), 1.88 (d, 1H, D_2O exchangeable, *J*=6.3 Hz), 2.01–233 (m, 1H), 1.59 (d, 1H, D_2O exchangeable, *J*=8.1 Hz), 3.66 (d, 1H, *J*=9.0 Hz), 3.69 (d, 1H, *J*=9.0 Hz), 3.72 (s, 3H), 3.77 (s, 3H), 3.95 (d, 1H, *J*=9.0 Hz), 4.02 (d, 1H, *J*=9.0 Hz), 4.06 (dt, 1H, *J*=8.4, 7.2 Hz), 4.25 (dt, 1H, *J*=7.5, 7.2 Hz), 6.83–6.92 (m, 4H). ^{13}C NMR ($CDCl_3$) δ: 16.0, 22.5, 23.6, 23.8, 27.6, 28.4, 44.9, 45.2, 55.7, 69.3, 73.2, 74.7, 75.1, 114.6, 114.7, 115.5, 115.6, 153.0, 153.5, 153.8, 154.1. IR (neat, cm^{-1}): 3280. MS *m*/*z* (The same for the two isomers): 222 (M^+(10)),178 (2), 149 (3), 124 (100) 109 (35). Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 70.14; H, 8.13.

4.8. Synthesis of chromenes 10a-d

They were prepared by reacting the cyclobutanols **9a-d** according to the above reported general procedure for chromenes **4a-f**.

4.8.1. 7-Methoxy-2a-methyl-8b-phenyl-1,2a,3,8b-tetrahydro-2*H*-cyclobuta[*c*]chromene (10a). Colourless oil. Yield 77%. ^{1}H NMR ($CDCl_3$) δ: 0.78 (s, 3H), 1.47–1.58 (m, 1H), 1.90–1.96 (m, 1H), 2.27–2.35 (m, 1H), 3.04–3.11 (m, 1H), 3.57 (s, 3H), 3.68 (d, 1H, *J*=8,4 Hz), 3.82 (d, 1H, *J*=8,4 Hz), 6.66–7.29 (m, 8H). ^{13}C NMR ($CDCl_3$) δ: 19.8, 23.6, 29.5, 42.6, 48.1, 55.5, 70.2, 113.1, 115.3, 117.5, 125.9, 127.9, 132.0, 145.0, 148.0, 154.0. MS *m*/*z*: 280 (M^+(48)), 265 (9), 252 (71), 237 (100), 225 (17), 165 (25), 91 (7), 77 (7). Anal. Calcd for $C_{19}H_{20}O_2$: C, 81.40; H, 7.19. Found: C, 81.28; H, 6.98.

4.8.2. 2a-Methyl-8b-vinyl-1,2a,3,8b-tetrahydro-2*H*-cyclobuta[*c*]chromene (10b). Colourless oil. Yield 50%. ^{1}H NMR ($CDCl_3$) δ: 1.07 (s, 3H), 1.43–1.56 (m, 1H), 1.68–1.75 (m, 1H), 2.14–2.71 (m, 1H), 2.61–2.71 (m, 1H), 3.51 (d, 1H, *J*=11.7 Hz), 3.80 (d, 1H, *J*=11.7 Hz), 5.16 (dd, 1H, *J*=1.2, 17.1 Hz), 5.29 (dd, 1H, *J*=1.2, 10.5 Hz), 5.83–5.88 (dd, 1H, *J*=10.5, 17.1 Hz), 6.89–7.29 (m, 4H). ^{13}C NMR ($CDCl_3$) δ: 19.35, 24.1, 29.2, 41.4, 46.0, 70.4, 114.9, 117.1,

121.4, 127.0, 129.1, 130.2, 140.7, 154.2. MS *m/z*: 200 (M^+(36)), 185 (14), 172 (56), 157 (100), 145 (25), 128 (23), 115 (31), 91 (15), 77 (15). Anal. Calcd for $C_{14}H_{16}O$: C, 83.96; H, 8.05. Found: C, 83.78; H, 7.98.

4.8.3. 8b-Isopropenyl-7-methoxy-2a-methyl-1,2a,3,8b-tetrahydro-2*H*-cyclobuta[*c*]chromene (10c). Colourless oil. Yield 30%. ^{1}H NMR ($CDCl_3$) δ:1.03 (s, 3H), 1.25–1.37 (m, 1H), 1.47 (s, 3H), 1.61–1.68 (m, 1H), 2.13–2.23 (m, 1H), 2.64–2.74 (m, 1H), 3.72 (s, 3H), 3.55 (d,1H, J=11.4 Hz), 3.77 (d,1H, J=11.4 Hz), 4.99 and 5.08 (each 1H, each br s), 6.60–6.85 (m, 3H). ^{13}C NMR ($CDCl_3$) δ: 18.2, 21.2, 23.4, 29.7, 41.0, 49.4, 55.6, 70.5, 112.9, 113.0, 113.4, 117.7, 129.1, 147.0, 148.4, 154.3. MS *m/z*: 244 (M^+(84)), 216 (100), 201 (96), 189 (34), 175 (30), 161 (20), 115 (20), 91 (19), 77 (15). Anal. Calcd for $C_{16}H_{20}O_2$: C, 78.65; H, 8.25. Found: C, 78.78; H, 8.18.

4.8.4. 8b-Benzyl-2a-Methyl-8b-vinyl-1,2a,3,8b-tetrahydro-2*H*-cyclobuta[*c*]chromene (10d). Colourless oil. Yield 45%. ^{1}H NMR ($CDCl_3$) δ:1.26 (s, 3H), 1.43–1.49 (m, 1H), 1.81–2.14 (m, 2H), 2.37–2.47 (m, 1H), 3.08, 3.41 (AB q, 2H, J=14.7 Hz), 3.19 (d, 1H, J=10.8 Hz), 3.59 (d, 1H, J=10.8 Hz), 6.83–7.37 (m, 9H). ^{13}C NMR ($CDCl_3$) δ: 18.9, 25.1, 34.9, 41.4, 42.2, 43.0, 70.3, 117.1, 121.2, 125.8, 126.8, 127.8, 129.1, 129.8, 130.7, 138.9, 154.5. MS *m/z*: 264 (M^+(14)), 236 (100), 221 (61), 173 (30), 145 (77), 131 (41), 91 (50), 77 (17). Anal. Calcd for $C_{19}H_{20}O$: C, 86.32; H, 7.63. Found: C, 86.28; H, 7.78.

4.8.5. 3-[(4-Methoxyphenoxy)methyl]-2,2,3-trimethylcyclopentanone (11). From the reaction mixture of **9c** with PTSA to give **10c** the major isolated product was the cyclopentanone **11** as a colourless oil. Yield 43%. ^{1}H NMR ($CDCl_3$) δ: 0.96 (s, 3H), 1.01 (s, 3H), 1.05 (s, 3H), 1.79–1.89 (m, 1H), 2.02–2.09 (m, 1H), 2.29–2.54 (m, 2H), 3.70 (d,1H, J=8.7 Hz), 3.75 (d,1H, J=8.7 Hz), 3.75 (s, 3H), 6.73–6.82 (m, 4H). ^{13}C NMR ($CDCl_3$) δ: 17.8, 19.1, 21.0, 30.2, 34.3, 44.5, 50.4, 55.7, 75.2, 114.5, 115.1, 152.8, 153.9, 222.4. IR (neat, cm^{-1}): 1680. MS *m/z*: 262 (M^+(70)), 124 (100), 109 (52), 95 (18), 69 (31). Anal. Calcd for $C_{16}H_{22}O_3$: C, 73.25; H, 8.45. Found: C, 73.38; H, 8.58.

4.8.6. 3-(Hydroxymethyl)-2,2,3-trimethylcyclopentanone (12). To a stirred solution of **11** (250 mg, 0.95 mmol), in CH_3CN (20 mL) at room temperature, CAN (1.56 g, 2.85 mmol) in H_2O (10 mL) was added, and stirring was continued for 5 h. To the mixture was added CH_2Cl_2 (20 mL) and then it was washed with 10% NaOH and brine and finally dried (Na_2SO_4), filtered and concentrated in vacuo. Purification by column chromatography (silica gel; eluent diethyl ether) gave **12** (96 mg) as white crystals, mp 197 °C. Yield 65%. (lit.[5] mp 197–198 °C).

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Alternative synthesis and novel oxidizing ability of 6,9-disubstituted cyclohepta[*b*]pyrimido[5,4-*d*]pyrrole-8(6*H*),10(9*H*)-dione derivatives

Shin-ichi Naya, Yusuke Iida and Makoto Nitta*

Department of Chemistry, School of Science and Engineering, Waseda University, Shinjuku-ku, Tokyo 169-8555, Japan

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Abstract—Synthesis of 6,9-disubstituted cyclohepta[*b*]pyrimido[5,4-*d*]pyrrole-8(6*H*),10(9*H*)-diones **7a**–**g** was accomplished by ring opening and ring closure sequences of 9-substituted cyclohepta[*b*]pyrimido[5,4-*d*]furan-8,10(9*H*)-dione derivatives induced by several amines. Furthermore, alternative synthetic methodology for compounds **7a**–**e** was also accomplished by single-step reaction of 2-chlorotropone with 6-aminouracil derivatives under mild conditions. X-ray crystal analysis of **7a** was carried out to clarify the structural characteristics. The properties of **7a**–**e** were studied by the UV–vis spectra and reduction potentials (−1.24 to −1.39 V vs $Ag/AgNO_3$). Novel photo-induced oxidation reaction of **7a**–**d** toward some amines under aerobic conditions was carried out to give the corresponding imines in more than 100% yield [based on compounds **7a**–**d**], suggesting the oxidation reaction occurs in an autorecycling process.

1. Introduction

Dehydrogenation reactions represent a major category of processes mediated by a subclass of flavoenzymes known as oxidases.[1] Included in this group are the oxidative transformations of alcohols to carbonyl compounds, of amines to imines, and of fatty acid esters to their α,β-unsaturated analogs.[2] The photo-induced oxidizing reaction of amines by 3-methyllumiflavin (**1**) (Fig. 1) and its related cations has been investigated to clarify the mechanistic aspects.[3] Furthermore, the flavin-redox systems have been investigated extensively through synthetic model systems and theoretical calculations.[4] Among these, 5-deazaflavins **2a** have been studied extensively in both enzymatic[5] and model systems,[6,7] in the hope of gaining mechanistic insight into flavin-catalyzed reactions. In this relation, 5-deaza-10-oxaflavin **2b** (2*H*-chromeno[2,3-*d*]pyrimidine-2,4(3*H*)-dione),[8] in which the nitrogen atom is replaced by an oxygen, has also been synthesized and found to possess a strong function to oxidize alcohols to the corresponding carbonyl compounds. On the basis of the above observations, we have recently reported the synthesis, properties, and reactivity of 7,9-dimethylcyclohepta[*b*]pyrimido[5,4-*d*]furan-8(7*H*),10(9*H*)-dionylium tetrafluoroborate (**3a**·BF_4^-)[9,10] and its sulfur and nitrogen analogues **3b**–**d**·BF_4^-.[11,12]

Furthermore, novel photo-induced autorecycling oxidizing reactions of **3a**–**d**·BF_4^- toward some alcohols are studied as well.[10–12] Thus, the uracil-annulated heteroazulenes such as **3a**–**d**·BF_4^- are very interesting from the viewpoint of exploration of novel functions.

On the other hand, we have previously studied preparations of 6-substituted 9-methylcyclohepta[*b*]pyrimido[5,4-*d*]pyrrole-8(6*H*),10(9*H*)-diones (**7a**–**d**)[13] (Scheme 3) and 9-substituted cyclohepta[*b*]pyrimido[5,4-*d*]furan-8,10(9*H*)-diones (**4a**,**f**,**g**)[14] (Fig. 1), which are structural isomers of 5-deazaflavin **2a** and 5-deaza-10-oxaflavin **2b**. In the studies, we have clarified that **4a**,**f**,**g** have oxidizing ability toward

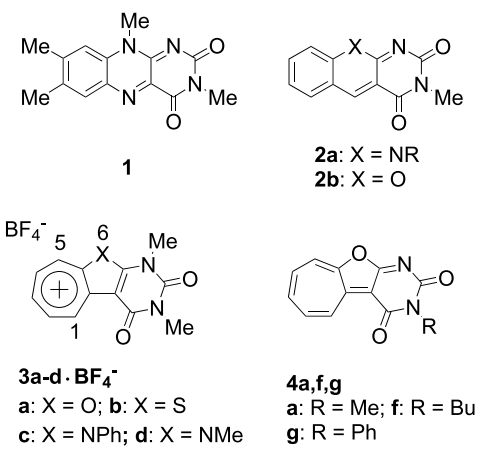

Figure 1.

Keywords: 6,9-Disubstituted cyclohepta[*b*]pyrimido[5,4-*d*]pyrrole-8(6*H*),10(9*H*)-diones; Ring-transformation; Reduction potential; Photo-induced oxidation reaction.

* Corresponding author. Tel.: +81-3-5286-3236; fax: +81-3-3208-2735; e-mail address: nitta@waseda.jp

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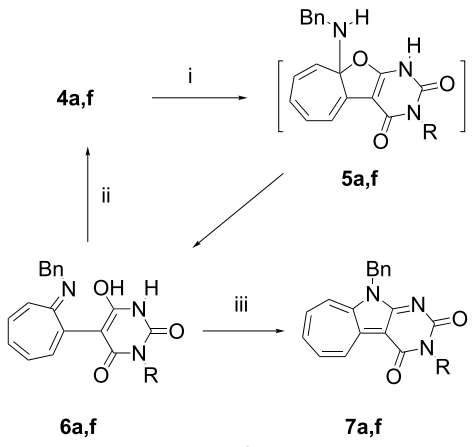
some alcohols. In a search for the reactivity and functions of uracil-anuulated heteroazulenes, we investigated the ring-transformation of **4a**,**f**,**g** to **7a**–**g**. Furthermore, alternative synthetic methodology for compounds **7a**–**e** was also accomplished, and their oxidizing ability toward some amines was studied as well. We report herein the results in detail.

2. Results and discussion

2.1. Ring-transformation of 4a,f,g to 7a,f,g

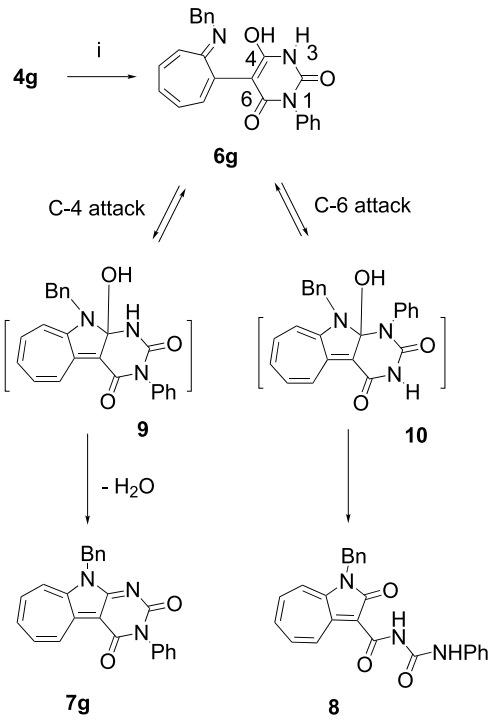
The reactions of **4a**,**f** with benzylamine afforded compounds **6a**,**f**, respectively, which were derived from 5a-adducts **5a**,**f** (Scheme 1, Table 1, Entries 1 and 2). When compounds **6a**,**f** were kept at room temperature for 10 h in the presence of benzylamine, no reaction proceeded. Upon treatment with TFA in $CHCl_3$, compounds **6a**,**f** regenerated **4a**,**f** in good yields. On the contrary, heating of the solutions of compounds **6a**,**f** in 1,4-dioxane at 90 °C afforded compounds **7a**,**f** in good yields (Scheme 1, Table 1, Entries 1 and 2). Thus, the thermal cyclization of **6a**,**f** would proceed via nucleophilic attack of the nitrogen of the troponeimine moiety. Unlike in the cases of **4a**,**f**, reaction of compound **6g** generated by the reaction of **4g** with benzylamine at room temperature proceeded under mild conditions to give **7g** and **8** (Scheme 2). The ring cleavage reaction giving **8** proceeded more quickly as compared with the dehydration reaction to give **7g** (Table 1, Entries 3 and 4): the reaction of **4g** with benzylamine for 0.5 h afforded **6g** and **8**, while the longer reaction time (24 h) resulted in the formation of **7g**



Scheme 1. *Reagents and conditions*: (i) $BnNH_2$, CH_2Cl_2, rt, 0.5 h; (ii) TFA–$CHCl_3$ (1/10), rt, 0.5 h; (iii) 1,4-dioxane, reflux, 5 h.

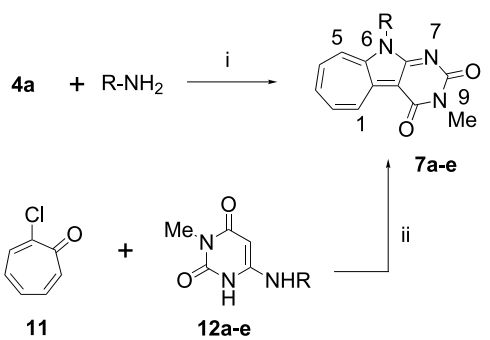
Table 1. Results for the reactions of **4a**,**f**,**g** with benzylamine and thermal cyclization of **6a**,**f**

Entry	4	R	Reaction with benzylamine		Thermal cyclization of 6a,f	
			Time (h)	Product (Yield (%))	6	Product (Yield (%))
1	**4a**	Me	0.5	**6a** (89)	**6a**	**7a** (70)
2	**4f**	Bu	0.5	**6f** (93)	**6f**	**7f** (72)
3	**4g**	Ph	0.5	**6g** (55), **8** (24)	–	–
4	**4g**	Ph	24	**7g** (17), **8** (70)	–	–



Scheme 2. *Reagents and conditions*: (i) $BnNH_2$, CH_2Cl_2, rt.

and **8**. The features are explained as follows: intermediate **9** generated by the C-4 attack underwent dehydration to give **7g**. On the contrary, intermediate **10** generated by the C-6 attack underwent a ring-opening reaction to give **8**. The facility of the latter reaction is probably due to the resonance effect of the Ph-group toward the nitrogen anion. Compounds **6a**,**f**,**g**, were fully characterized on the basis of the ^1H and ^{13}C NMR, IR, and mass spectral data as well as high-resolution mass spectra. Compounds **7f**,**g** and **8** were also characterized on the basis of the ^1H and ^{13}C NMR, IR, and mass spectral data as well as elemental analyses. Furthermore, we have accomplished convenient preparation of **7a**–**e** from **4a** and amines without isolation of troponeimine **6a** and its derivatives. The mixtures of **4a** with some amines in 1,4-dioxane were heated at 90 °C to afford compounds **7a**–**e** in good yields (Scheme 3, Table 2). Compounds **7a**–**d** were identified on the basis of a comparison of the physical data with those reported in the literature.[13] In addition, new



a: R = Bn; **b**: R = 4-Cl-C_6H_4
c: R = Ph; **d**: R = 4-$MeOC_6H_4$; **e**: R = 4-$Me_2NC_6H_4$

Scheme 3. *Reagents and conditions*: (i) 1,4-dioxane, 90 °C; (ii) Bu^tNH_2, EtOH, rt, 40 h.

Table 2. Results for the preparation of **7a–e** from **4a** and primary amine

Entry	4	Amine	Time (h)	Product	Yield (%)
1	**4a**	$BnNH_2$	24	**7a**	84
2	**4a**	$4\text{-}ClC_6H_4NH_2$	40	**7b**	75
3	**4a**	$PhNH_2$	40	**7c**	81
4	**4a**	$4\text{-}MeOC_6H_4NH_2$	20	**7d**	86
5	**4a**	$4\text{-}Me_2NC_6H_4NH_2$	10	**7e**	90

compound **7e** was fully characterized on the basis of the ^1H and ^{13}C NMR, IR, and mass spectral data as well as elemental analysis.

2.2. Alternative synthetic method for 7a–e

Previously, we have reported that the reaction of 2-chlorotropone **11** with 6-aminouracil derivatives **12a–d** in the presence of Et_3N and K_2CO_3 in 1,4-dioxane afforded compounds **7a–d**.[13] However, this reaction was carried out under reflux, and thus, column chromatography was necessary to purify the products. In the present study, we have accomplished the facile preparation of **7a–e** from similar starting materials. Thus, the reactions of **11** with **12a–e** in EtOH in the presence of Bu^tNH_2 at room temperature were carried out to give **7a–e** in good to moderate yields (Scheme 3, Table 3). In this reaction, few by-products were generated due to the mild conditions. Moreover, the products **7a–e** were slightly soluble in EtOH at room temperature. Thus, filtration of the reaction mixtures afforded pure samples of **7a–e**.

2.3. Properties and reactivity

The UV–vis spectra of **7a–e** in acetonitrile are shown in Figure 2. The spectra of **7a–e** are similar and the longest wavelengths absorption maxima show similar values (Table 4). Although benzylamine was added to the solution, the visible region of the spectra of **7a–e** was not changed. Thus, addition reaction of **7a–e** with benzylamine would not proceed under the measurement conditions of the UV–vis spectra. A single crystal of **7a** was obtained by recrystallization from EtOH. Thus, in order to clarify the structural details, X-ray structure analysis was carried out and the ORTEP drawing of **7a** is shown in Figure 3.[15] The π-system of compound **7a** has a nearly planar structure. The bond lengths of C1–C2, C3–C4, and C5–C6 are shorter than those of C2–C3, C4–C5, C6–C7, and C7–C1. This fact suggests the existence of large bond alternation in the seven-membered ring. In contrast to the cations **3a–d**·BF_4^-,[9–12] the bond length of N1–C9 of **7a** is slightly longer than that of N1–C6. The reduction potentials of **7a–e** were determined by cyclic voltammentry (CV) in CH_3CN. The reduction waves of **7a–e** were irreversible under the conditions of the CV measurements; the peak potentials are summarized in Table 4, together with those of the reference compounds **3c**·BF_4^-.[12] The $E1_{red}$ of **7a–e** are more negative by 0.40–0.55 V than that of **3c**·BF_4^-. The irreversible nature is probably due to the formation of tropyl

Table 3. Results for the preparation of **7a–e** from 2-chlorotropone **11** and 6-aminouracil **12a–e**

Entry	12	R	Product	Yield (%)
1	**12a**	Bn	**7a**	90
2	**12b**	$4\text{-}ClC_6H_4$	**7b**	73
3	**12c**	Ph	**7c**	83
4	**12d**	$4\text{-}MeOC_6H_4$	**7d**	71
5	**12e**	$4\text{-}Me_2NC_6H_4$	**7e**	36

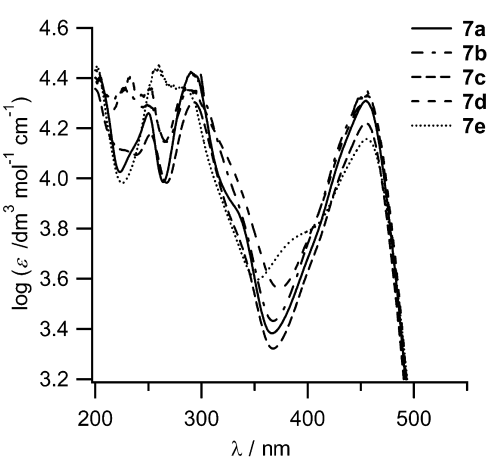


Figure 2. UV–vis spectra of **7a–e** in CH_3CN.

Table 4. The longest wavelength absrobtion maxima and reduction potentials[a] of **7a–e** and reference compound **3a**·BF_4^-

Compound (R)	λ_{max} (nm) (log ε (dm^3 mol^{-1} cm^{-1}))	Reduction potential $E1_{red}$ (V)
7a (Bn)	455 (4.31)[b]	−1.39
7b (4-ClC_6H_4)	456 (4.35)[b]	−1.24
7c (Ph)	456 (4.22)[b]	−1.31
7d (4-$MeOC_6H_4$)	456 (4.33)[b]	−1.32
7e (4-$Me_2NC_6H_4$)	456 (4.16)	−1.35
3c·BF_4^-[c]	414 (4.11)	−0.84

[a] V vs $Ag/AgNO_3$; cathodic peak potential.
[b] Ref. 13.
[c] Ref. 12.

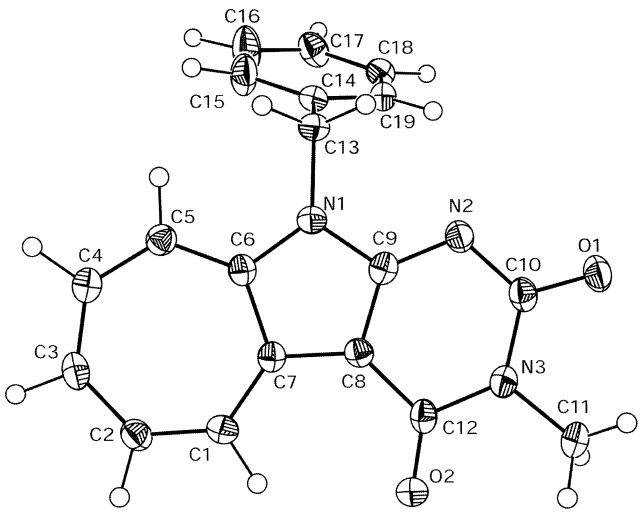
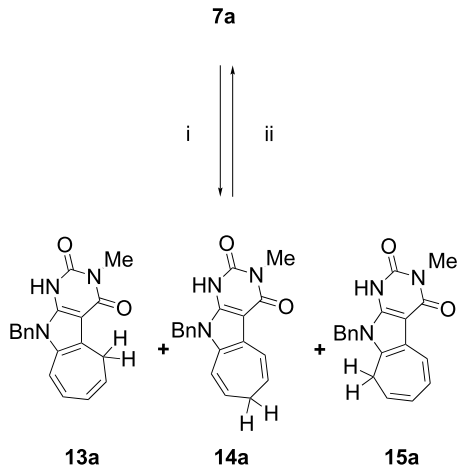


Figure 3. ORTEP drawing of **7a** with thermal ellipsoid plot (50% probability). Selected bond lengths (Å); N1–C6 1.376(4), N1–C9 1.381(4), C1–C2 1.380(4), C2–C3 1.404(4), C3–C4 1.380(4), C4–C5 1.394(4), C5–C6 1.381(4), C6–C7 1.463(4), C1–C7 1.403 (4), C7–C8 1.398(4), C8–C9 1.404 (4).



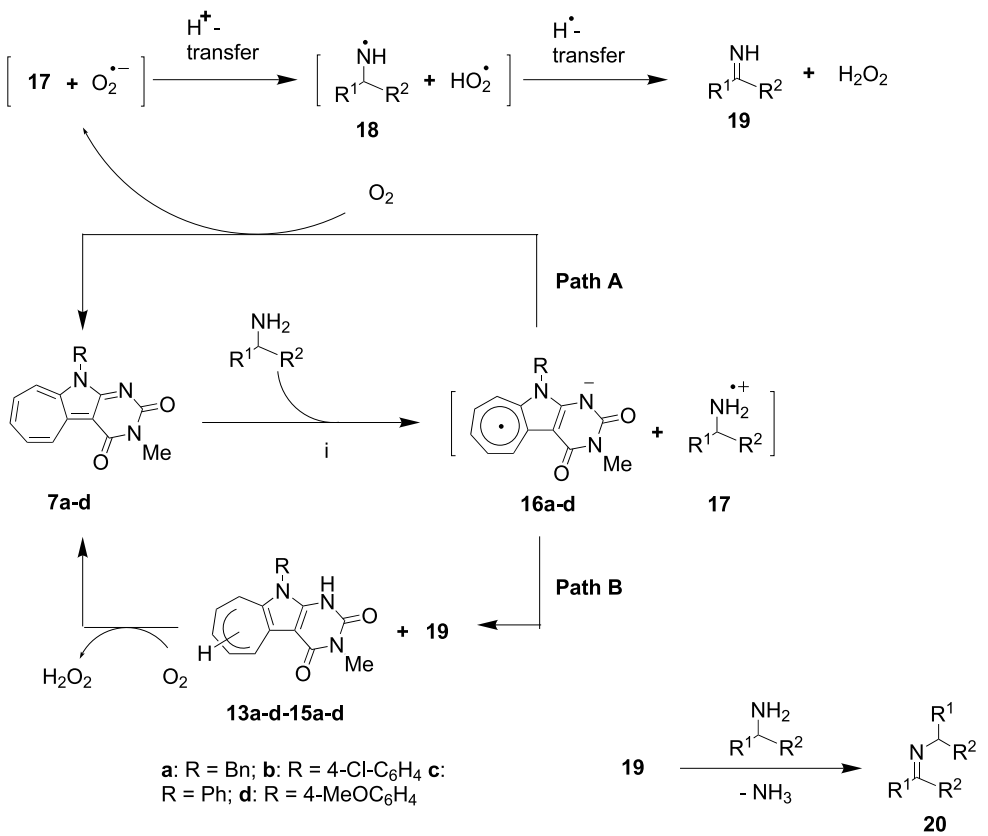
Scheme 4. *Reagents and conditions*: (i) $NaBH_4$, EtOH, rt, 1 h; (ii) DDQ, CH_2Cl_2, rt, 1 h.

radicals and their dimerization. This reduction behavior seems to be a typical property of uracil-annulated heteroazulenes, such as **3a**–**d**·BF_4^-.[9–12] Compound **7a** was reduced with $NaBH_4$ to give a mixture of three compounds **13a**–**15a**, and the mixture was oxidized by DDQ to regenerate **7a** in quantitatively yield. Since the regioisomers could not be separated, the structural assignments were based on the NMR, IR, mass spectral data as well as high-resolution mass spectrum of the mixture. The ^1H NMR spectra of the mixture of three regioisomers could be assigned by using the H–H COSY spectra (Scheme 4).

2.4. Autorecycling oxidation

We have previously reported that compounds **3a**–**d**·BF_4^- undergo autorecycling oxidation toward some alcohols under photo-irradiation.[10–12] In this context and in a search for the functions of **7a**–**e**, we examined the oxidation of some amines by using **7a**–**e** under aerobic and photo-irradiation conditions (RPR-100, 350 nm lamps). Although compound **7e** did not oxidize amines, we found that compounds **7a**–**d** have oxidizing ability toward some amines to give the corresponding imines. Imine **19** is produced at first; however, it reacts with another amine to result in the formation of $R^1R^2C{=}N{-}CHR^1R^2$ (**20**) (Scheme 5). The results are summarized in Table 5. Direct irradiation of the amines in the absence of **7a**–**e** (named 'blank') gives the imines in low to modest yields. Thus, the yields are calculated by subtraction of the blank yield from the yields in the presence of **7a**–**e**. More than 100% yields are obtained [based on compounds **7a**–**d**] (Table 5), and thus, autorecycling oxidation clearly proceeds; however, cyclohexylamine was not oxidized (Table 5, Entry 22).

In a previous study, the fluorescence spectra of **3a**,**b**·BF_4^- were quenched by addition of 1-phenylethanol, suggesting an interaction of the singlet excited state of the cations with the alcohol.[10,11] Thus, in a search for the mechanistic aspect of the photo-induced oxidation reaction, the fluorescence spectrum of **7a** was studied; however, very weak fluorescence of **7a** appeared at 514 nm. The quantum yield (Φ) of **7a** was determined to be 0.001 by using quinine bisulfate as standard.[18] In addition, by addition of benzylamine (500 equiv.) to the solution of **7a** (under similar conditions



Scheme 5. *Reagents and conditions*: (i) *hv*, aerobic, CH_3CN, rt.

Table 5. Autorecycling oxidation of some amines by **7a**–**e** under photo-irradiation[a]

Entry	Compound	(6-R)	Amine	Time (h)	Imines[b]	Yield[c] (%)
1	**7a**	(Bn)	$PhCH_2NH_2$	1	$PhCH{=}NCH_2Ph$	371
2	**7a**	(Bn)	$PhCH_2NH_2$	2	$PhCH{=}NCH_2Ph$	874
3	**7a**	(Bn)	$PhCH_2NH_2$	4	$PhCH{=}NCH_2Ph$	1413
4	**7a**	(Bn)	$PhCH_2NH_2$	8	$PhCH{=}NCH_2Ph$	2224
5	**7a**	(Bn)	$PhCH_2NH_2$	12	$PhCH{=}NCH_2Ph$	4762
6	**7a**	(Bn)	$PhCH_2NH_2$	16	$PhCH{=}NCH_2Ph$	8573
7	**7a**	(Bn)	$PhCH_2NH_2$	24	$PhCH{=}NCH_2Ph$	12825
8	**7a**	(Bn)	$PhCH_2NH_2$	32	$PhCH{=}NCH_2Ph$	14238
9	**7b**	(4-ClC_6H_4)	$PhCH_2NH_2$	16	$PhCH{=}NCH_2Ph$	9343
10	**7c**	(Ph)	$PhCH_2NH_2$	16	$PhCH{=}NCH_2Ph$	7993
11	**7d**	(4-$MeOC_6H_4$)	$PhCH_2NH_2$	16	$PhCH{=}NCH_2Ph$	6049
12	**7e**	(4-$Me_2NC_6H_4$)	$PhCH_2NH_2$	16	$PhCH{=}NCH_2Ph$	0[d]
13	**7a**	(Bn)	$PhCH(Me)NH_2$	16	$PhMeC{=}NCHMePh$	6447
14	**7b**	(4-ClC_6H_4)	$PhCH(Me)NH_2$	16	$PhMeC{=}NCHMePh$	4693
15	**7c**	(Ph)	$PhCH(Me)NH_2$	16	$PhMeC{=}NCHMePh$	4760
16	**7d**	(4-$MeOC_6H_4$)	$PhCH(Me)NH_2$	16	$PhMeC{=}NCHMePh$	3927
17	**7e**	(4-$Me_2NC_6H_4$)	$PhCH(Me)NH_2$	16	$PhMeC{=}NCHMePh$	0[d]
18	**7a**	(Bn)	4-$MeOC_6H_4CH_2NH_2$	16	4-$MeOC_6H_4CH{=}NCH_2$(4-$MeOC_6H_4$)	4753
19	**7a**	(Bn)	4-$MeC_6H_4CH_2NH_2$	16	4-$MeC_6H_4CH{=}NCH_2$(4-MeC_6H_4)	8293
20	**7a**	(Bn)	4-$ClC_6H_4CH_2NH_2$	16	4-$ClC_6H_4CH{=}NCH_2$(4-ClC_6H_4)	8573
21	**7a**	(Bn)	4-$PyCH_2NH_2$	16	4-$PyCH{=}NCH_2$(4-Py)	3101
22	**7a**	(Bn)	Cyclohexylamine	16	*N*-Cyclohexylcyclohexanone imine	0[d]

[a] CH_3CN solution was irradiated by RPR-100, 350 nm lamps under aerobic conditions.
[b] Isolated by converting to the corresponding 2,4-dinitrophenylhydrazone.
[c] Based on **7a**–**e** used; the yield is calculated by subtraction of the 'blank' yield from the total yield of carbonyl compound in the presence of **7a**–**e**.
[d] The 'blank' yield was higher than the yield in the presence of **7**.

for the oxidation reaction), no quenching of the fluorescence was observed. These features suggest very small interaction of the singlet excited state of **7a** with amines, but the triplet excited state may intervene in the oxidation reaction.

In order to clarify the details of the oxidizing reaction, time dependency was investigated. The results are summarized in Table 5 (Entries 1–8) and Figure 4. As the irradiation time was prolonged to 24 h, the yield of benzaldimine was increased simply. After irradiation for 32 h, the yield of benzaldimine is not so increased, suggesting plausible decomposition of **7a**. When the photo-irradiation of CD_3CN solution of **7a** in the absence of amines under aerobic conditions was carried out, no decomposition of **7a** was observed. Thus, **7a** would be decomposed in the oxidation cycle. Furthermore, in the oxidation of benzylamine by using **7b**–**e**, the yields of the imines became larger in the order **7e** (0%) ≪**7d**<**7c**<**7b**. This fact is probably due to the more positive $E1_{red}$ values in the order **7e**<**7d**<**7c**<**7b**

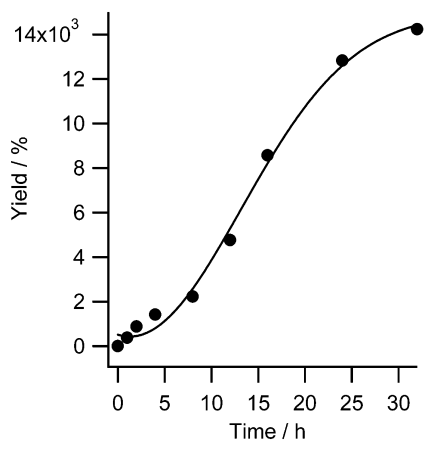


Figure 4. Time dependency of autorecycling oxidation of benzylamine by **7a**.

(Table 5, Entries 9–12). [The reduction potentials of **7b**–**e** in the ground state would be correlated with their LUMO's, and thus, the LUMO's of these compounds would be lower in the order **7e**>**7d**>**7c**>**7b**. In the excited state of these compounds, the electron-accepting orbital would be the singly occupied HOMO's. In as much as the UV–vis spectra of these compounds are similar, and the energy level of HOMO's of the compounds is expected to be lower in the order **7e**>**7d**>**7c**>**7b**, the autorecycling oxidation of amines thus seems to be more efficient in the order **7e**<**7d**<**7c**<**7b**.] A similar tendency was obtained in the case of the oxidation of 1-phenylethylamine (Table 5, Entries 14–17). However, in spite of the more negative $E1_{red}$ value, compound **7a** has high oxidizing ability toward benzylamine and 1-phenylethylamine (Table 5, Entries 6 and 13).

In a search for the substituent effect of benzylamine, the oxidation reactions of 4-substituted benzylamines and picolylamine were carried out by using **7a** under aerobic and photo-irradiation conditions (Table 5, Entries 18–21). The yields of imines are plotted against Hammet constants σ_p[16] of substituents on the phenyl group and 4-picolylamine in Figure 5. The plots seem to show a maximum value, and the yield of photo-induced oxidation of amines becomes low at either the high value (σ_p 0.23, 4-$ClC_6H_4CH_2NH_2$) or the low value (σ_p −0.27, 4-$MeOC_6H_4CH_2NH_2$). The yields of the imine derived from 4-picolylamine, which corresponds to the benzylamine having strong electron-withdrawing substituent, becomes low and may be close to the yield expected from 4-nitrobenzylamine. Thus, the oxidizing reaction by using **7a** becomes less effective for the amines, which have both lower and higher oxidation potential. This feature is similar to the case of photo-induced oxidation reaction of benzylalcohol by using a flavin analoge,[17] and it is rationalized by the electron-transfer pathways (vide infra).

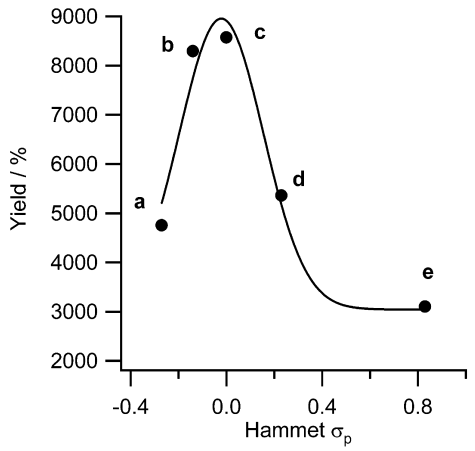


Figure 5. The Hammet plot of autorecycling oxidation of 4-substituted benzylamine by **7a**. (**a**, 4-$MeOC_6H_4CH_2NH_2$; **b**, 4-$MeC_6H_4CH_2NH_2$; **c**, $PhCH_2NH_2$; **d**, 4-$ClC_6H_4CH_2NH_2$; **e**, 4-$PyCH_2NH_2$).

The postulated mechanistic pathways for the present photo-induced oxidation of amines are depicted in Scheme 5.[17] The electron-transfer from amine to the excited triplet state of **7a**–**d** would occur to produce anions radical **16a**–**d** and a cation radical **17**. An electron transfer from radical species **16a**–**d** to molecular oxygen may give the superoxide anion radical and **7a**–**d**, since tropyl radical derivatives are known to be readily oxidized by molecular oxygen.[19] Then, a proton-transfer from cation radical **17** to a superoxide anion radical may occur, followed by formation of the products **19** and H_2O_2 (Path A). Compound **19** reacts with excess amine to give imine **20**. Substituted benzylamine having a more negative oxidation potential favors the electron transfer process from amine to the excited triplet **7a**, but disfavors the proton transfer process from cation radical **17** to the superoxide anion radical. On the contrary, substituted benzylamine having a more positive oxidation potential disfavors the electron transfer process from amine to the excited triplet state of **7a**, while the proton transfer process from cation radical **17** to the superoxide anion radical becomes more favorable. As such, a sensitive balance between the electron donor ability of amines and the proton donor ability of cation radical **17** is required to achieve the efficient photo-induced oxidation reaction of amines by using **7a**. On the other hand, there is an alternative mechanistic pathway (Path B), in which compounds **13a**–**d**–**15a**–**d** in addition to the imines are generated from **16a**–**d** and **17**; the former compounds are oxidized under aerobic and photo-irradiation conditions to regenerate **7a**–**d**. Under aerobic and photo-irradiation conditions, the CD_3CN solution of **13a**–**15a** was easily oxidized to regenerated **7a** quantitatively. Thus, autorecycling oxidation would also be possible in this Path B. However, attempted detection of compound **16a** or its dimers or compounds **13a**–**15a** is unsuccessful in the oxidation reaction of benzylamine under degassed and photo-irradiation conditions (degassed by freeze-pump-thaw cycles). Thus, further investigations are required to clarify the mechanistic aspect of the reaction.

3. Conclusion

The reaction of 9-substituted cyclohepta[*b*]pyrimido[5,4-*d*]furan-8,10(9*H*)-diones **4a**,**f**,**g** with benzylamine was investigated to explore the ring-transformation of **4a**,**f**,**g** to 6,9-disubstituted cyclohepta[*b*]pyrimido[5,4-*d*]pyrrole-8(6*H*),10(9*H*)-diones **7a**–**g**. Furthermore, alternative synthetic methodology for compounds **7a**–**e** was also accomplished. X-ray crystal analysis of **7a** was carried out to clarify the structural characteristics. The properties of **7a**–**e** were studied by the UV–vis spectra and reduction potentials (−1.24 to −1.39 V vs $Ag/AgNO_3$). The photo-induced oxidation reactions of **7a**–**d** toward some amines under aerobic conditions were carried out to give the corresponding imines in more than 100% yield [based on compounds **7a**–**d**], suggesting that the oxidation proceeds in an autorecycling process.

4. Experimental

4.1. General

IR spectra were recorded on a HORIBA FT-710 spectrometer. Mass spectra and high-resolution mass spectra were run on JMS-AUTOMASS 150 and JMS-SX102A spectrometers. Unless otherwise specified, ^1H NMR spectra and ^{13}C NMR spectra were recorded on JNM-AL 400, JNM-lambda 500, and AVANCE 600 spectrometers using $CDCl_3$ as the solvent, and the chemical shifts are given relative to internal $SiMe_4$ standard: *J*-values are given in Hz. Mps were recorded on a Yamato MP-21 apparatus and were uncorrected.

4.2. Reaction of 4a,f with benzylamine

A solution of **4a**,**f** (0.5 mmol) and benzylamine (107 mg, 1.0 mmol) in CH_2Cl_2 (5 mL) was stirred at rt for 0.5 h. To the mixture was added EtOH (50 mL) and the precipitates were collected by filtration to give **6a**,**f**. The results are summarized in Table 1.

4.2.1. 5-(1′-Benzyliminocycloheptatrien-2′-yl)-4-hydroxy-1-methylpyrimidine-2(3*H*),6(1*H*)-dione (6a). Reddish powder; mp 169–171 °C dec (from CH_2Cl_2). ^1H NMR (500 MHz, DMSO-d_6) δ 3.32 (3H, s, Me), 4.69 (2H, s, CH_2), 7.20 (1H, d, *J*=12.2 Hz, H-7), 7.27–7.34 (2H, m, *p*-Ph, H-5), 7.33–7.37 (2H, m, *m*-Ph), 7.50–7.54 (3H, m, *o*-Ph, H-4), 7.69 (1H, dd, *J*=12.2, 8.1 Hz, H-6), 8.17 (1H, d, *J*=9.6 Hz, H-3), 9.81 (1H, br s, NH), 9.97 (1H, s, OH); ^{13}C NMR (125.7 MHz, DMSO-d_6) δ 26.4, 47.2, 89.2, 123.2, 127.0, 127.3, 128.5, 133.6, 135.4, 137.9, 142.0, 143.2, 145.6, 151.9, 161.3, 162.2, 165.8; IR (KBr) ν 3402, 3226, 1685, 1620, 1589 cm^{-1}; MS (FAB) *m/z* 336 (M^++H); HRMS calcd for $C_{19}H_{17}N_3O_3$: 336.1348 (M+H). Found: 336.1346 (M^++H).

4.2.2. 5-(1′-Benzyliminocycloheptatrien-2′-yl)-1-butyl-4-hydroxypyrimidine-2(3*H*),6(1*H*)-dione (6f). Reddish powder; mp 163–165 °C dec (from CH_2Cl_2). ^1H NMR (500 MHz, DMSO-d_6) δ 0.88 (3H, t, *J*=7.6 Hz, Bu-4), 1.28 (2H, sex, *J*=7.6 Hz, Bu-3), 1.49 (2H, quint, *J*=7.6 Hz, Bu-2), 3.72 (2H, t, *J*=7.6 Hz, Bu-1), 4.68 (2H, s, CH_2), 7.19 (1H, d, *J*=12.0 Hz, H-7), 7.26–7.30 (1H, m, *p*-Ph), 7.30 (1H, dd, *J*=10.2, 8.1 Hz, H-5) 7.33–7.37 (2H, m, *m*-Ph), 7.52 (1H, dd, *J*=10.2, 9.8 Hz, H-4) 7.52–7.55 (2H, m, *o*-Ph), 7.69 (1H, dd, *J*=12.0, 8.1 Hz, H-6), 8.17 (1H, d, *J*=9.8 Hz,

H-3), 9.87 (1H, br s, NH), 9.91 (1H, s, OH); ^{13}C NMR (150.9 MHz, DMSO-d_6) δ 13.8, 19.7, 30.3, 39.6, 47.2, 89.3, 123.0, 126.9, 127.3, 128.4, 133.5, 135.4, 137.9, 142.0, 143.0, 145.5, 151.7, 161.4, 161.9, 166.0; IR (KBr) ν 3410, 3255, 1670, 1589, 1576 cm^{-1}; MS (FAB) *m/z* 378 (M^++H); HRMS calcd for $C_{22}H_{23}N_3O_3$: 378.1881 (M+H). Found: 378.1849 (M^++H).

4.3. Reaction of 6a,f with TFA

A solution of **6a**,**f** (0.5 mmol) in $CHCl_3$ (5 mL) and TFA (0.5 mL) was stirred at rt for 0.5 h. To the mixture was added EtOH (50 mL) and the precipitates were collected by filtration to give **4a**,**f** (**4a**: 95%, **4b**: 100%).

4.4. Thermal cyclization of 6a,f

A solution of **6a**,**f** (0.05 mmol) in 1,4-dioxane (5 mL) was stirred at 90 °C for 5 h. The mixture was cooled to rt, and the resulting precipitates were collected by filtration to give **7a**,**f**. The results are summarized in Table 1. Compound **7a** was identical with the authentic specimen.[13]

4.4.1. 6-Benzyl-9-buthylcyclohepta[*b*]pyrimido[5,4-*d*]pyrrole-8(6*H*),10(9*H*)-dione (7f). Orange plates; mp 203–205 °C (from EtOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.98 (3H, t, *J*=7.3 Hz, Bu-4), 1.45 (2H, sex, *J*=7.3 Hz, Bu-3), 1.73 (2H, quint, *J*=7.3 Hz, Bu-2), 4.13 (2H, t, *J*=7.3 Hz, Bu-1), 5.68 (2H, s, CH_2), 7.23–7.36 (5H, m, Bn), 7.65 (1H, dd, *J*=9.3, 9.3 Hz, H-3), 7.71 (1H, dd, *J*=9.3, 9.3 Hz, H-4), 7.76 (1H, d, *J*=9.3 Hz, H-5), 7.88 (1H, dd, *J*=10.5, 9.3 Hz, H-2), 9.29 (1H, d, *J*=10.5 Hz, H-1); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 13.9, 20.4, 30.3, 40.6, 45.2, 99.2, 122.7, 127.1, 128.2, 129.0, 132.3, 134.6, 135.7, 136.0, 138.4, 143.6, 148.2, 159.3, 161.4, 164.0; IR (KBr) ν 1683, 1635, 1588, 1508 cm^{-1}; MS (FAB) *m/z* 360 (M^++H); HRMS calcd for $C_{22}H_{21}N_3O_2$: 360.1712 (M+H). Found: 360.1669 (M^++H). Anal. calcd for $C_{22}H_{21}N_3O_2{\cdot}1/5H_2O$: C, 72.79; H, 5.94; N, 11.57. Found: C, 73.0; H, 5.9; N, 11.7%.

4.5. Reaction of 4g with benzylamine

A solution of **4g** (145 mg, 0.5 mmol) and benzylamine (107 mg, 1.0 mmol) in CH_2Cl_2 (5 mL) was stirred at rt for 0.5 h. To the mixture was added EtOH (50 mL) and the precipitates were collected by filtration to give **6g** (109 mg, 55%). The filtrate was concentrated in vacuo and the resulting residue was purified by column chromatography on SiO_2 using AcOEt as the eluent to give **8** (48 mg, 24%).

On the other hand, a solution of **4g** (145 mg, 0.5 mmol) and benzylamine (107 mg, 1.0 mmol) in CH_2Cl_2 (5 mL) was stirred at rt for 24 h. The mixture was concentrated in vacuo and the resulting residue was chromatographed on SiO_2 using AcOEt as the eluent to give **7g** (32 mg, 17%) and **8** (139 mg, 70%).

4.5.1. 5-(1′-Benzyliminocycloheptatrien-2′-yl)-4-hydroxy-1-phenylpyrimidine-2(3*H*),6(1*H*)-dione (6g). Orange powder; mp 167–169 °C dec (from CH_2Cl_2). ^{1}H NMR (500 MHz, DMSO-d_6) δ 4.71 (2H, s, CH_2), 7.20 (1H, d, *J*=8.2 Hz, H-7), 7.26–7.41 (9H, m, Ph, H-5, *o*-Bn, *p*-Bn), 7.33–7.37 (2H, m, *m*-Bn), 7.70 (1H, dd, *J*=10.0, 8.2 Hz, H-6), 8.19 (1H, d, *J*=9.8 Hz, H-3), 10.05 (1H, br s, NH), 10.14 (1H, s, OH); ^{13}C NMR (150.9 MHz, DMSO-d_6) δ 47.2, 89.2, 123.1, 126.7, 127.0, 127.3, 127.9, 128.5, 129.6, 133.6, 135.4, 137.3, 137.9, 142.1, 143.1, 145.2, 151.5, 161.8, 161.9, 166.1; IR (KBr) ν 3410, 3286, 1685, 1581 cm^{-1}; MS (FAB) *m/z* 398 (M^++H); HRMS calcd for $C_{24}H_{19}N_3O_3$: 398.1504 (M+H). Found: 398.1530 (M^++H).

4.5.2. 6-Benzyl-9-phenylcyclohepta[*b*]pyrimido[5,4-*d*]pyrrole-8(6*H*),10(9*H*)-dione (7g). Yellow powder; mp 299–301 °C (from EtOH). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.73 (2H, s, CH_2), 7.27–7.38 (7H, m, *o*-Ph, Bn), 7.41 (1H, t, *J*=7.4 Hz, *p*-Ph), 7.51 (2H, dd, *J*=8.3, 7.4 Hz, *m*-Ph), 7.67 (1H, dd, *J*=9.3, 9.3 Hz, H-3), 7.74 (1H, dd, *J*=9.7, 9.3 Hz, H-4), 7.83 (1H, d, *J*=9.7 Hz, H-5), 7.88 (1H, dd, *J*=10.6, 9.3 Hz, H-2), 9.24 (1H, d, *J*=10.6 Hz, H-1); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 45.4, 99.5, 123.0, 127.2, 128.1, 128.4, 128.8, 129.2, 129.3, 132.6, 134.6, 136.0, 136.4, 136.8, 138.8, 144.1, 148.5, 159.3, 161.6, 164.8; IR (KBr) ν 1684, 1654, 1586, 1508 cm^{-1}; MS (FAB) *m/z* 380 (M^++H); HRMS calcd for $C_{24}H_{17}N_3O_2$: 380.1399 (M+H). Found: 380.1379 (M^++H). Anal. calcd for $C_{24}H_{17}N_3O_2{\cdot}1/2\ H_2O$: C, 74.21; H, 4.67; N, 10.82. Found: C, 74.3; H, 4.4; N, 10.7%.

4.5.3. *N*-(1-Benzyl-1,2-dihydro-2-oxocyclohepta[*b*]pyrrol-3-yl)carbonyl-*N*′-phenylurea (8). Yellow needles; mp 232–233 °C (from AcOEt). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.30 (2H, s, CH_2), 7.09 (1H, t, *J*=7.5 Hz, *p*-Ph), 7.21–7.36 (7H, m, *m*-Ph, Bn), 7.43 (1H, dd, *J*=10.0, 9.0 Hz, H-6), 7.46 (1H, d, *J*=9.5 Hz, H-8), 7.54 (1H, dd, *J*=10.0, 9.5 Hz, H-7), 7.63 (2H, d, *J*=7.5 Hz, *o*-Ph), 7.72 (1H, dd, *J*=11.0, 9.0 Hz, H-5), 9.45 (1H, d, *J*=11.0 Hz, H-4), 10.89 (1H, s, NH), 10.91 (1H, s, NH); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 43.9, 99.1, 118.8, 120.1, 123.7, 127.0, 128.1, 128.9, 129.1, 131.7, 133.5, 135.2, 137.6, 138.1, 145.5, 148.1, 151.3, 165.0, 167.1; IR ($CHCl_3$) ν 1675, 1653, 1589, 1539, 1478, 1447 cm^{-1}; MS (FAB) *m/z* 398 (M^++H); HRMS calcd for $C_{24}H_{19}N_3O_3$: 398.1505 (M+H). Found: 398.1469 (M^++H). Anal. calcd for $C_{24}H_{19}N_3O_3$: C, 72.53; H, 4.82; N, 10.57. Found: C, 72.3; H, 4.9; N, 10.3%.

4.6. Ring transformation of 4a to 7a–e

To a solution of **4a** (46.5 mg, 0.2 mmol) in 1,4-dioxane (20 mL) was added amine (0.4 mmol). The mixture was stirred at 90 °C until the reaction was completed (Table 2). The mixture was cooled to rt and the resulting precipitates were collected by filtration to give **7a**–**e**. The results are summarized in Table 2. Compounds **7a**–**d** were identical with the authentic specimen.[13]

4.6.1. 6-Dimehtylaminophenyl-9-methylcyclohepta[*b*]-pyrimido[5,4-*d*]pyrrole-8(6*H*),10(9*H*)-dione (7e). Reddish powder; mp>310 °C (from MeOH/CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.05 (6H, s, NMe_2), 3.49 (3H, s, NMe), 6.85 (2H, d, *J*=9.0 Hz, H-3′, H-5′), 7.24 (2H, d, *J*=9.0 Hz, H-2′, H-6′), 7.65–7.80 (3H, m, H-2, H-4, H-5), 7.86–7.93 (1H, m, H-3), 9.33 (1H, d, *J*=10.5 Hz, H-1); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 27.5, 40.5, 99.0, 113.0, 120.8, 123.5, 128.8, 132.3, 135.7, 136.1, 138.2, 142.9, 150.5, 151.2, 159.7, 161.9, 165.2; IR (KBr) ν 1682, 1635, 1592,

1510 cm^{-1}; MS (FAB) *m/z* 347 (M^++H); HRMS calcd for $C_{20}H_{18}N_4O_2$: 347.1508 (M+H). Found: 347.1467 (M^++H). Anal. calcd for $C_{20}H_{18}N_4O_2 \cdot 1/5\ H_2O$: C, 68.65; H, 5.30; N, 16.01. Found: C, 69.0; H, 5.2; N, 16.2%.

4.7. Althernative synthetic method for 7a–e

To a solution of **11** (28 mg, 0.2 mmol) and **12a–e** (0.2 mmol) in EtOH (20 mL) was added Bu^tNH_2 (36.5 mg, 0.5 mmol). The mixture was stirred at rt for 40 h and the precipitates were collected by filtration to give **7a–e**. The results are summarized in Table 3. Compounds **7a–d** were identical with the authentic specimen.[13]

4.8. Cyclic voltammetry of 7a–e

The reduction potential of **7a–e** was determined by means of CV-27 voltammetry controller (BAS Co). A three-electrode cell was used, consisting of Pt working and counter electrodes and a reference $Ag/AgNO_3$ electrode. Nitrogen was bubbled through an acetonitrile solution (4 mL) of **7a–e** (0.5 mmol dm^{-3}) and Bu_4NClO_4 (0.1 mol dm^{-3}) to deaerate it. The measurements were made at a scan rate of 0.1 V s^{-1} and the voltammograms were recorded on a WX-1000-UM-019 (Graphtec Co) X–Y recorder. Immediately after the measurements, ferrocene (0.1 mmol) ($E_{1/2}$=+0.083) was added as the internal standard, and the observed peak potential was corrected with reference to this standard. Compounds **7a–e** exhibited one irreversible reduction wave, and they are summarized in Table 4.

4.9. Reaction of 7a with $NaBH_4$

A solution of **7a** (1.0 mmol) and $NaBH_4$ (76 mg, 2.0 mmol) in EtOH (30 mL) was stirred at rt for 1 h and concentrated in vacuo. The residue was dissolved in 3% HCl and the solution was extracted with CH_2Cl_2. The extract was dried over Na_2SO_4 and concentrated in vacuo to give a mixture of **13a–15a** (314 mg, 98%, **13a**:**14a**:**15a**=2:1:10).

4.9.1. A mixture of 6-benzyl-1,7-dihydro-9-methylcyclohepta[*b*]pyrimido[5,4-*d*]pyrrole-8(7*H*),10(9*H*)-dione (13a), 6-benzyl-3,7-dihydro-9-methylcyclohepta[*b*]pyrimido[5,4-*d*]pyrrole-8(7*H*),10(9*H*)-dione (14a), and 6-benzyl-5,7-dihydro-9-methylcyclohepta[*b*]pyrimido[5,4-*d*]pyrrole-8(7*H*),10(9*H*)-dione (15a). Pale yellow powder; mp 198–199 °C (from CH_2Cl_2); IR (KBr) ν 3276, 1703, 1645, 1614 cm^{-1}; MS (FAB) *m/z* 320 (M^++H); HRMS calcd for $C_{19}H_{17}N_3O_2$: 320.1417 (M+H). Found: 320.1390 (M^++H).

Compound **13a**. ^{1}H NMR (500 MHz, DMSO-d_6) δ 3.34 (2H, d, *J*=6.5 Hz, H-1), 3.35 (3H, s, Me), 5.40 (2H, s, CH_2Ph), 5.53 (1H, dd, *J*=10.1, 6.5 Hz, H-2), 6.03 (1H, dd, *J*=10.1, 6.1 Hz, H-3), 6.25 (1H, dd, *J*=11.4, 6.1 Hz, H-4), 6.75 (1H, d, *J*=11.4 Hz, H-5), 7.31–7.44 (5H, m, Ph).

Compound **14a**. ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.33 (2H, dd, *J*=6.9, 6.5 Hz, H-3), 3.28 (3H, s, Me), 5.30–5.40 (2H, m, H-2, 4), 5.46 (2H, s, CH_2Ph), 6.57 (1H, d, *J*=9.7 Hz, H-5), 7.09 (1H, d, *J*=9.7 Hz, H-1), 7.31–7.44 (5H, m, Ph).

Compound **15a**. ^{1}H NMR (500 MHz, DMSO-d_6) δ 3.02 (2H, d, *J*=6.4 Hz, H-5), 3.25 (3H, s, Me), 5.44 (2H, s, CH_2Ph), 5.22 (1H, dd, *J*=10.0, 6.4 Hz, H-4), 6.07 (1H, dd, *J*=10.0, 6.0 Hz, H-3), 6.32 (1H, dd, *J*=11.2, 6.0 Hz, H-2), 7.29 (1H, d, *J*=11.2 Hz, H-1), 7.31–7.44 (5H, m, Ph).

4.10. Oxidation of a mixture of 13a–15a by using DDQ

To a stirred solution of a mixture of **13a–15a** (64 mg, 0.2 mmol) in CH_2Cl_2 (10 mL) was added DDQ (70 mg, 0.3 mmol), and the mixture was stirred at rt for 1 h. After evaporation of the CH_2Cl_2, the residue was purified by column chromatography on Al_2O_3 using AcOEt as the eluent to give **7a** (63 mg, 100%).

4.11. X-ray structure determination of 7a[†]

Yellow prism, $C_{19}H_{15}N_3O_2$, *M*=317.35, monoclinic, space group *C*2/*c*, *a*=15.147(9) Å, *b*=16.52(1) Å, *c*=14.06(1) Å, β=123.99(5)°, *V*=2917.5(4) $Å^3$, *Z*=8, *Dc*=1.445 g mL^{-1}, crystal dimensions 0.40×0.40×0.30 mm^3. Data were measured on a Rigaku RAXIS-RAPID radiation diffractometer with graphite monochromated Mo Kα radiation. Total 13722 reflections were collected, using the ω–2θ scan technique to a maximum 2θ value of 55.0°. The structure was solved by direct methods and refined by a full-matrix least-squares method using SIR92 structure analysis software,[15] with 232 variables and 3274 observed reflections [$I>3.00\sigma(I)$]. The non-hydrogen atoms were refined anisotropically. The weighting scheme $w=[0.1000\times\sigma_c^2(F_0)+0.0010\times F_0^2+0.0200]^{-1}$ gave satisfactory agreement analysis. The final *R* and *Rw* values were 0.0360 and 0.0510. The maximum peak and minimum peak in the final difference map were 0.22 and −0.18 $e^-Å^{-3}$.

4.12. General procedure for the autorecycling oxidation of amines catalyzed by 7a–e

A CH_3CN (16 mL) solution of compounds **7a–e** (0.005 mmol) and amines (2.5 mmol, 500 equiv.) in a Pyrex tube was irradiated by RPR-100, 350 nm lamps under aerobic conditions for the period indicated in Table 5. The reaction mixture was concentrated in vacuo and diluted with Et_2O and filtered. The ^{1}H NMR spectra of the filtrates revealed the formation of the corresponding imines (Table 5). The filtrate was treated with a saturated solution of 2,4-dinitrophenylhydrazine in 6% HCl to give 2,4-dinitrophenylhydrazone. The results are summarized in Table 5.

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Stereochemistry of the [2+4] cycloaddition of cyclopentyne

John C. Gilbert[a,*] and Duen-Ren Hou[b]

[a]*Department of Chemistry and Biochemistry, The University of Texas at Austin, 1 University Station Stop A5300, Austin, TX 78712, USA*
[b]*Department of Chemistry, National Central University. No. 300, Jung-Da Road, Jung-Li City, Taoyuan 320, Taiwan, ROC*

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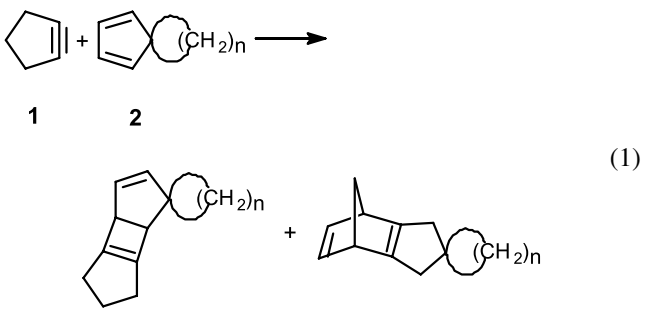
Abstract—The [2+4] cycloaddition of cyclopentyne with a pair of diastereomeric 1,3-dienes is found to occur with high stereoselectivity. The results support the applicability of the principles of orbital symmetry even in the case of this exceedingly reactive dienophile.

1. Introduction

Cyclopentyne (**1**) undergoes both [2+2] and [2+4] cycloaddition reactions with spiro-1,3-cyclopentadienes **2** (n=2, 4) as shown in Eq. 1.[1] Remarkably, the [2+2] process is completely diastereoselective when stereochemically

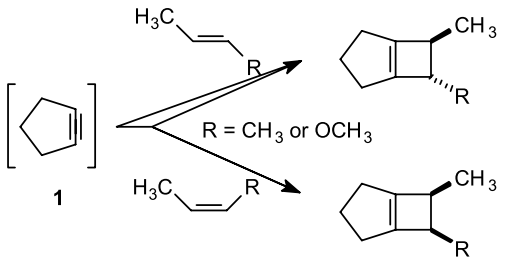


(1)

labeled alkenes are used to trap **1** (Scheme 1).[2] This result, which could be taken as a signal for concert,[3] is inconsistent with the principle of orbital symmetry,[4] and we have recently proposed an alternate mechanism to account for this outcome.[5] The essence of the alternative is that the [2+2] cycloadduct forms by stereospecific ring expansion of a cyclopropylcarbene, itself derived by [2+1] cycloaddition of cyclopentyne to the alkene (Eq. 2).

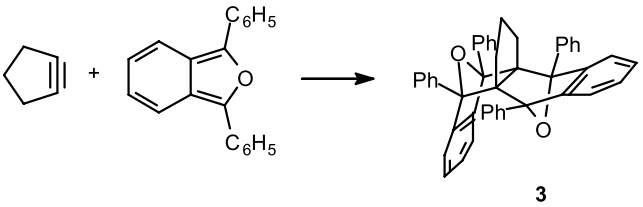
(2)

The [2+4] process has precedent in Wittig's isolation of the double Diels–Alder adduct **3** from reaction of **1** with



Scheme 1.

2,5-diphenylisobenzofuran (Eq. 3).[6] Although this is a thermally-allowed reaction and should be stereospecific,[4] two



(3)

factors stimulated our interest in exploring the Diels–Alder reaction of **1** with a pair of diastereomeric 1,3-dienes capable of stereorandomization in a non-concerted process: (1) the unusual nature of the [2+2] cycloaddition with cyclopentyne and (2) the predicted diradical character of the in-plane π-bond of the cycloalkyne;[7] the latter property could foster a stepwise process leading to stereorandomization (Scheme 2).

Fitjer, et al., had previously reported that reaction of cyclopentyne with 1,3-butadiene afforded the corresponding [2+2] cycloadduct exclusively.[8] We surmised that this was because the diene exists predominantly in its *s-trans* conformation and dictated our probing the stereochemistry of the Diels–Alder reaction of cyclopentyne using a system

Keywords: Cyclopentyne; Diels–Alder Reaction; Stereochemistry; Orbital symmetry.
* Corresponding author. Tel.: +1-5124713220; fax: +1-5124714998; e-mail address: jgilbert@mail.utexas.edu

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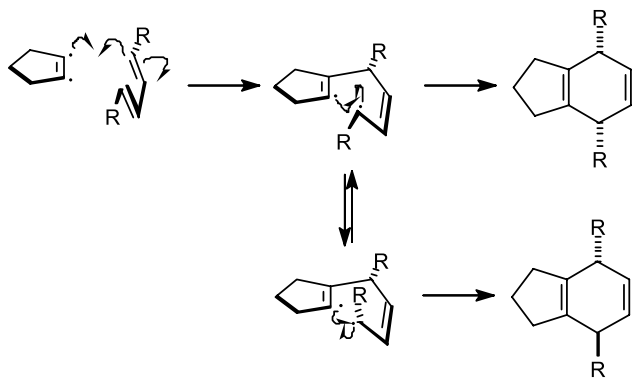
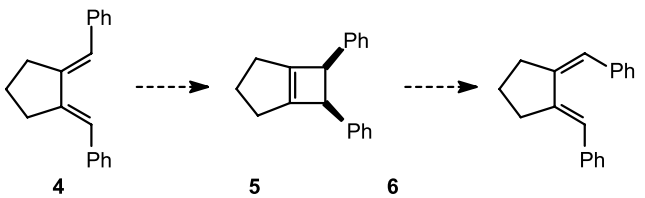


Scheme 2.

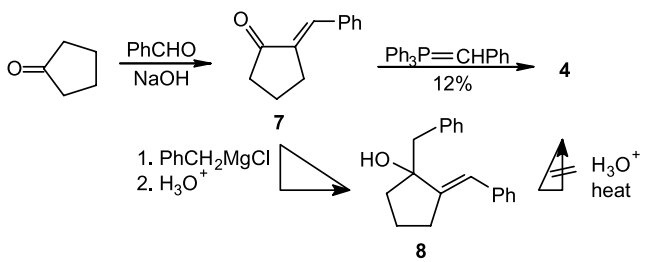
wherein the diene moiety is locked *s-cis*. Dienes **4** and **5** (Eq. 4) were selected for the following reasons: (1) the presence of identical substituents at the termini of the diene simplifies characterization of the cycloadducts; (2) 1,2-dialkylidenecyclopentanes generally react faster in Diels–Alder reactions than do their six-membered ring analogs[9] (3) synthesis of diastereomerically pure **4** had been reported[10]—because the yields of pericyclic reactions involving cyclopentyne and unactivated 1,3-dienes are usually low,[1] contamination of the substrate with a minor amount of a diastereomer could clearly compromise interpretation of the experimental results; (4) although synthesis of **5** had not been reported, we anticipated that it could be prepared by photocyclization of **4**[11] and thermally-induced conrotatory ring-opening of the resulting cyclobutene **6** (Eq. 4).[12]



(4)

2. Synthesis of dienes

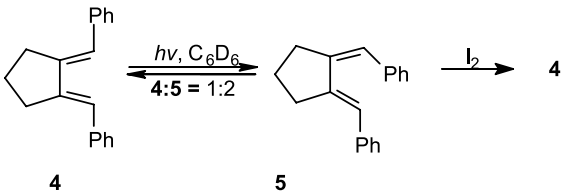
It was reported that (*E*,*E*)-1,2-dibenzylidenecyclopentane (**4**) could be formed from **7**, itself the product of benzylidenation of cyclopentanone, by reaction with either benzylidenetriphenylphosphorane,[10a] or with phenylmagnesium bromide followed by dehydration (Scheme 3).[10b] In our hands, only the Wittig reaction gave the diene, however. Attempted acid-catalyzed dehydration



Scheme 3.

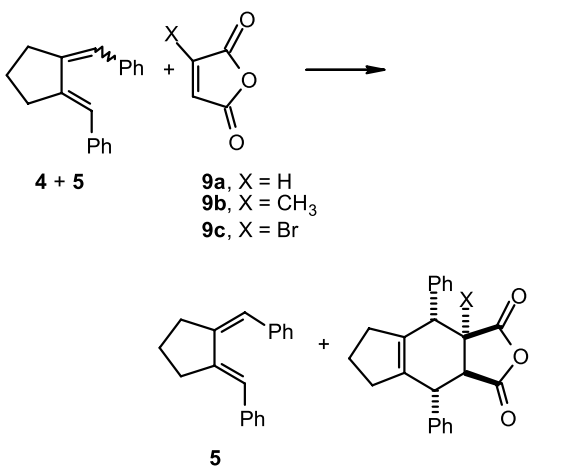
of the alcohol **8** returned only starting alcohol and polymer. As previously reported,[13] **4** was diastereomerically pure.

Turning to our proposed synthesis of the (*E*,*Z*)-diene **5**, irradiation (300–350 nm) transformed **4** into a mixture of **5** and the starting diene. The ^{1}H NMR spectrum of the reaction mixture contained two new vinylic absorptions of equal intensity and three new resonances ascribable to methylene groups. No resonances could be detected for cyclobutene **6**. That the isomer formed by irradiation of **4** was **5** was shown by adding a catalytic amount of molecular iodine to the NMR solution of the two isomers, whereupon quantitative conversion to **4** occurred, as judged from the ^{1}H NMR spectrum (Eq. 5)[†] A photoequilibrium of **4**/**5**=1:2 was established upon prolonged irradiation.



(5)

Because attempts to separate **4** and **5** by column chromatography proved unsuccessful, their kinetic resolution was explored (Eq. 6). Proposed transition states for the Diels–Alder reaction of **4** and **5** with anhydrides **9** are shown in Figure 1. Where the phenyl rings of **4** and **5** coplanar with the diene function, steric interactions with the incoming dienophile should be comparable for both diastereomers and no kinetic resolution would be expected. Such coplanarity, however, is unlikely, given the differing



(6)

steric repulsions expected in the dienes. Distortion from planarity should be particularly prominent for the phenyl group on the *Z* double bond of **5**, hindering approach to the dienophile and thereby increasing the energy of the transition state for the Diels–Alder reaction. Although steric interactions involving the dienophile and the phenyl groups of **4** are likely as well, they should be less important because of decreased distortion from planarity. This isomer should thus react faster than **5** with dienophiles **9**.

To test our assumptions computationally, the geometries of the (*E*,*E*)- and (*E*,*Z*)-dienes were calculated using AM1 and

[†] Iodine is known to promote *cis–trans* isomerization to thermodynamically more stable alkenes or dienes.[14]

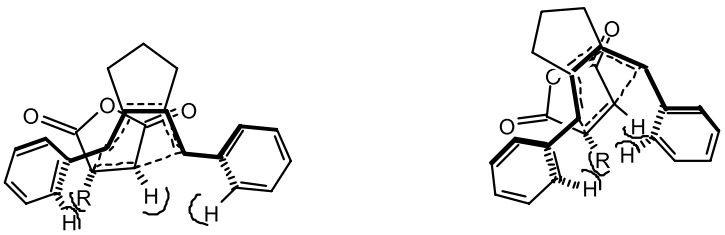


Figure 1. Possible steric effects in Diels–Alder reaction of **4** and **5** with maleic anhydrides **9**.

MM2 methodologies. Table 1 lists the dihedral angle of the phenyl rings relative to the plane of the diene moiety. Both computational approaches predict greater rotation out of the plane for the phenyl ring on the *Z* double bond of **5**. Other calculated properties of the two dienes that might define kinetic selectivity in [2+4] cycloadditions, for example, bond lengths and HOMO/LUMO energies, are very similar to each other. Consequently, the success of a kinetic resolution of **4** and **5** according to Eq. 6 appeared to depend on differing steric environments of the reacting π-systems.

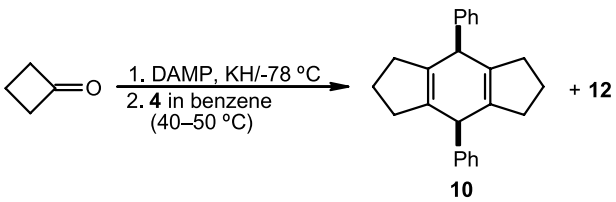
Table 1. Calculated dihedral angles (°) between the diene plane and a phenyl ring

	AM1	MM2
E,*E*-diene **4**	40.9	49.4
E,*Z*-diene **5** (*E*-phenyl)	38.8	50.0
E,*Z*-diene **5** (*Z*-phenyl)	64.2	59.7

In the event, bromomaleic anhydride (**9c**) afforded the best selectivity between **4** and **5** of the three anhydrides evaluated, presumably because the bromo substituent simultaneously increases the steric hindrance and the electrophilicity of dienophile **9c**; **9b**, which also has increased steric hindrance but decreased electrophilicity compared to maleic anhydride itself, is inert toward the two dienes.[15] In practice, treating a 2:1 mixture of **4** and **5** with 0.5 equiv. of **9c** afforded a 1:73 ratio of the two dienes, as determined by integration of the ^{1}H NMR spectrum; thus, (*E*,*Z*)-diene **5** was contaminated with slightly over 1% of the (*E*,*E*) diastereomer.

3. Reactions of cyclopentyne with (*E*,*E*)-diene 4 and (*E*,*Z*)-diene 5

Reaction of **4** with a solution derived by adding cyclobutanone to diethyl diazomethylphosphonate (DAMP)[4] and sodium hydride (Eq. 7), a combination of reagents known to produce cyclopentyne,[2b] afforded two 1:1 adducts of cyclopentyne and **4** in a ratio of 1:1.6.



(7)

Both the ^{1}H and ^{13}C NMR spectra of the earlier-eluting fraction were consistent with its being *cis*-4,8-diphenyl-1,2,3,4,5,6,7,8-octahydro-*s*-indacene (**10**). Definitive proof of the structure was obtained through X-ray crystallography, and an ORTEP plot is provided in Figure 2. The *cis* relationship of the phenyl rings was defined by the existence of a two-fold rotation axis of symmetry perpendicular to and through the center of the cyclohexadiene ring (Fig. 2a). This stereochemical relationship is seen in Figure 2b. The C2–C6 and C2′–C6′ bond distance is 1.33 Å, typical for a carbon–carbon double bond, and the C1–C2–C6–C1′ dihedral angle is 1.9°, showing that the cyclohexadiene ring is essentially planar.

The second isomer formed in the reaction (Eq. 7) had a more complicated ^{1}H NMR spectrum than **10**, possessing among

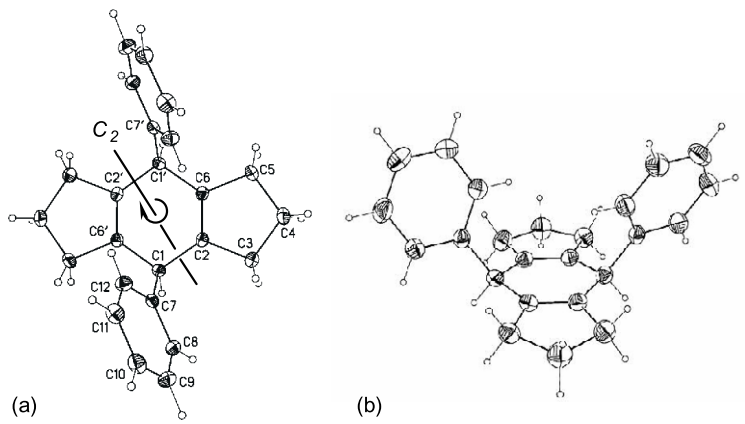
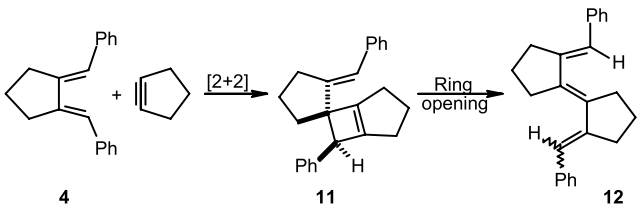


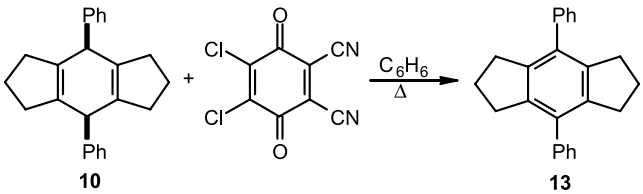
Figure 2. ORTEP plot of cycloadduct **10**: (a) top view and (b) edge view.

other absorptions four vinylic resonances in the range, δ 4.4–6.9 ppm. Although the lability of this product precluded its isolation, the NMR data are consistent with its being a diastereomer of the triene **12**, which could be derived from thermally promoted conrotatory ring-opening of the [2+2] cycloadduct **11** (Eq. 8). That the product was not the *trans* isomer of **10** is clear from the NMR analysis, however. Assuming our tentative structural assignment of **12** is correct and that it arises from **11**, the ratio of [2+2]:[2+4] cycloaddition in the reaction of **4** with cyclopentyne is 1:1.6.‡



(8)

Treating **10** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) fostered aromatization to **13** in 75% isolated yield (Eq. 9).[16] This product was characterized spectroscopically and provided NMR and MS data entirely consistent with the structural assignment. Formation of **13** was useful for the subsequent analysis of the products from reaction of (*E*,*Z*)-diene **5** with cyclopentyne (vide infra).

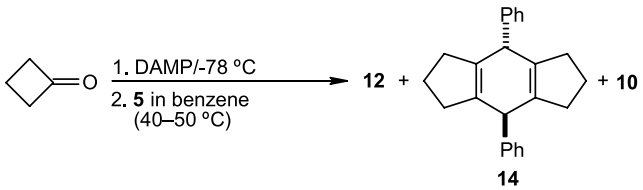


(9)

The result obtained from the reaction of cyclopentyne (**1**) with (*E*,*E*)-diene **4** (Eq. 7) demonstrates that the [2+4] cycloaddition is stereospecific. Such an outcome is entirely consistent with the transformation being concerted, despite the unusual nature of the π system of **1** that is involved in the cycloaddition.

Extending the study of the stereochemistry of the Diels–Alder reaction to (*E*,*Z*)-diene **5** was complicated by various factors. Two isomers having the proper value of *m*/*z* for a 1:1 adduct of **1** and **5** were formed. One had a GC retention time identical to that of the product **12** derived from [2+2] cycloaddition and was assigned as such (Eq. 10), whereas the second was tentatively assigned as the [2+4] cycloadduct **14**. Its retention time was less than that of **10**, as shown by GC analysis of the reaction mixture spiked with authentic **10**.§ Unfortunately, the low yield (3–5%) of this isomer and the presence of impurities generated by treating the reaction mixture with maleic anhydride to remove excess (*E*,*Z*)-diene **5** prevented purification. Diene **5** has a lower reactivity toward maleic anhydride as compared to **4**, and this meant that a longer reaction time was required to remove the excess of it; consequently undesired reactions of the diene, for example, oligomerization and isomerization, apparently occurred. The similarity in R_f value of the cycloadduct and its contaminants, their presence in relatively large amounts, and its low yield made isolation of the cycloadduct impossible.

These difficulties necessitated using an indirect method to characterize the presumed [2+4] cycloadduct. Treating the reaction mixture with DDQ effected aromatization to **13**. Interpretation of this experimental result, however, was complicated by the fact that the starting (*E*,*Z*)-diene **5** was contaminated slightly over 1% of the *E*,*E*-isomer **4**, so that reaction of this contaminant would produce **10**; this in turn would afford **13** upon treatment of the reaction mixture with DDQ. Indeed, careful examination by GC of the crude reaction mixture obtained from the Diels–Alder reaction of **5** with cyclopentyne (Eq. 10) revealed a peak having a retention time identical to that of **10**. Fortunately, the area of this peak was only 3–4% of that assigned as *trans*-cycloadduct **14**, whereas the amount of terphenyl **13** produced by oxidation of the reaction mixture was 17–22% of that of the original **14**.¶ This proves that the majority of the **13** formed arose from an isomer different from **10** and is consistent with this isomer being **14**. Thus, although the structure of **14** has not been proven unambiguously, we firmly believe it to be the *trans* isomer.



(10)

It might be argued that the formation of **10** in a yield greater than of percentage (~1%) of diene **4** that contaminants **5** represents diastereomerization during the course of the [2+4] cycloaddition of **5**. However, knowing that **4** reacts much faster with dienophiles (vide supra) than does **5**, we ascribe the increase in yield of **10** to this kinetic factor and believe that **5** reacts in a concerted fashion in the [2+4] cycloaddition as does **4**.

4. Conclusion

The stereochemistry of the Diels–Alder reaction of cyclopentyne with the (*E*,*E*)-diene **4** afforded cycloadduct **12** stereospecifically within experimental error; less than 2% of the diastereomer **14** relative to **10** could have been detected had it been formed. The result with the (*E*,*Z*)-diene **5** is less definitive because of contamination with **4**, but a 'worst-case scenario' would make the [2+4] cycloaddition in this case greater than 95% stereoselective with retention. Given the enhanced reactivity of **4** relative to **5**

‡ The fact that [2+4] cycloaddition is favored over the [2+2] analog is consistent with our previous observations for the reaction of cyclopentyne with 1,3-cyclopentadienes.[1]

§ The shorter retention time of **14** relative to **10** on GC columns is also consistent with the *trans* structure. The lower yield of oxidation product, relative to that obtained from **10**, may be associated with the known[16] slower rate of oxidation of *trans*-3,6-disubstituted-1,3-cyclohexadienes as compared to the *cis*-isomers.

¶ These percentages are based on the GC integrations in which two impurities that are unreactive toward DDQ served as internal standards.

in the Diels–Alder reaction, however, we believe this cycloaddition to be stereospecific as well. Consequently, it can be concluded that the stereocontrol associated with the principle of orbital symmetry[4] still applies, despite the abnormal characteristics associated with the in-plane π-bond of cyclopentyne.

5. Experimental

5.1. General

All reactions were performed under an atmosphere of dry N_2 in flamed-dried one-neck flasks equipped for magnetic stirring. Low-temperature baths of −40 °C were obtained with an immersion cooler using acetone as the bath liquid. Ice/water, dry ice/acetone and isooctane/$N_{2(l)}$ were used for 0, −78 and −107 °C baths, respectively. Commercially available chemicals were used without further purification unless noted otherwise. Solvents were dried and distilled under an inert atmosphere before use. Et_2O and THF were distilled from sodium benzophenone ketyl, CH_2Cl_2 from CaH_2, and diisopropylamine from KOH. Solutions were concentrated by rotary evaporation at water aspirator pressures.

Quantitative GC analyses were obtained with an analytical gas chromatograph interfaced with an recording integrator and equipped with a 25 m×0.25 mm AT-1 (100% dimethylpolysiloxane) capillary column and a flame-ionization detector; the carrier gas was helium (1.2 mL/min). GC/MS analyses were performed using a 12 m×0.22 mm GB-5 (95% dimethyl-, 5% diphenylpolysiloxane) capillary column with helium as the carrier gas (1.0 mL/min) and interfaced with an electron impact ion trap detector mass spectrometer. High-resolution MS analyses were obtained using the EI mode (70 eV).

^{1}H NMR spectra were obtained at 250 MHz, unless otherwise noted, and ^{13}C NMR spectra were measured at 125 MHz. All chemical shifts are referenced to the solvent, which was $CDCl_3$ unless otherwise noted.

5.1.1. (*E*,*Z*)-1,2-Dibenzylidenecyclopentane (5). A solution of *E*,*E*-1,2-dibenzylidenecyclopentane[11] (1.02 g, 4.14 mmol) in benzene (35 mL) in a 100-mL Pyrex flask equipped with a septum was exposed to UV light (Hanovia 450-W lamp) for 11 h, after which the solution was filtered to remove precipitates and concentrated. The residual oil (0.65 g) was combined with $CHCl_3$ (11 mL), and $NaHCO_3$ (100 mg, 1.2 mmol) in a 50-mL flask. This solution was cooled to 0 °C, bromomaleic anhydride (233 mg, 1.32 mmol) was added, and the mixture was stirred for 18 h. Filtration, concentration, and chromatography over silica gel using ethyl acetate–hexane (1:19) as eluant afforded **5** (R_f=0.58, 303 mg, 1.23 mmol, 30%) as a colorless oil.

Spectral data. ^{1}H NMR (500 MHz): δ 1.81 (2H, m), 2.53 (2H, m), 2.76 (2H, m) 6.48 (1H, s) 6.76 (1H, s); ^{13}C NMR (C_6D_6): δ 24.2, 33.3, 36.0, 119.0, 123.4, 125.8, 126,.0, 127.7, 128–129 (4C), 138.8, 139.2, 140.7, 144.0; HRMS *m*/*z* calcd for C_9H_{18} 246.1409, found 246.1401.

5.1.2. Isomerization of (*E*,*Z*)-1,2-dibenzylidenecyclopentane (5) to (*E*,*E*)-1,2-dibenzylidenecyclopentane (4). A solution of diene **4** (20 mg) in C_6D_6 (1 mL) in an NMR tube was exposed to UV light for 1 h. The ^{1}H NMR spectrum of the resulting solution indicated formation of a 1:1 mixture of the dienes **4** and **5**. Iodine (2 mg) was added and the resulting dark brown solution was immediately analyzed by ^{1}H NMR spectroscopy; only resonances of the diene **4** were observed.

5.1.3. *cis*-4,8-Diphenyl-1,2,3,4,5,6,7,8-octahydro-*s*-indacene (10). Potassium hydride (657 mg, 5.75 mmol, 35% in mineral oil) in a 50-mL flask was washed with pentane (3×10 mL). Dry CH_2Cl_2 (1.5 mL) was added, the slurry was cooled to −78 °C, and a solution of diethyl (diazomethyl)-phosphonate (DAMP)[17] (760 mg, 4.27 mmol) in CH_2Cl_2 (3 mL) was transferred into the flask by syringe. The slurry was stirred for 15 min at −78 °C, cyclobutanone (200 mg, 2.85 mmol) was added, and the reaction mixture was stirred at −78 °C for an additional 15 min. The cooling bath was removed, and a warm (50–60 °C) solution of (*E*,*E*)-1,2-dibenzylidenecyclopentane (773 mg, 3.14 mmol) in benzene (15 mL) was immediately added by syringe. The solution became dark red, and nitrogen evolution occurred. The reaction mixture was stirred at rt for 1 h, maleic anhydride (0.8 g, 8.2 mmol) was added, and the resulting mixture was stirred for 8 h. The dark-red slurry was poured into pentane (150 mL), and insoluble material was removed by vacuum filtration. Concentration of the filtrate followed by chromatography over silica gel using pentane as eluant afforded **10** (R_f=0.45, 12.8 mg, 0.04 mmol, 1.4%) as a colorless solid, and the presumed [2+2] cycloadduct (R_f, 7.8 mg, 0.025 mmol, 0.9%) as an amorphous solid. Analytical GC conditions: initial/temperatures: 120, 250 °C; initial/final time for temperature program: 1, 10 min; ramp rate: 15 °C/min; retention time of **10**: 12.9 min.

Spectral data. ^{1}H NMR: δ 1.72 (2H, m), 1.86 (2H, m), 2.09 (8H, m), 3.86 (2H, s), 7.10–7.33 (10H, s); ^{13}C NMR: δ 22.2, 33.8, 46.1, 126.2, 128.3 (2C), 136.5, 142.5; HRMS *m*/*z* calcd for $C_{24}H_{25}$ 313.1956, found 313.1948.

X-ray crystallographic analysis for **10**: Crystals were grown as colorless blocks by slow evaporation from a two-phase solution of pentane–$CHCl_3$. The data crystal was cut from a larger crystal and had approximate dimensions, 0.35×0.35×0.49 mm^3. The data were collected at −90 °C on a Siemens P3 diffractometer, equipped with a Nicolet LT-2 low-temperature device and using a graphite monochromator with Mo Kα radiation (λ=0.71073 Å).[‖]

5.1.4. Reaction of cyclopentyne with (*E*,*Z*)-1,2-dibenzylidenecyclopentane (5). The procedure used for preparing **10** was used with the following amounts of reagents: KH (542 mg, 4.74 mmol, 35% in mineral oil), DAMP (500 mg, 2.80 mmol), cyclobutanone (166 mg,

[‖] Crystallographic data for the structure in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 218855. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax:+44-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

2.37 mmol), *E*,*Z*-1,2-dibenzylidenecyclopentane (292 mg, 1.19 mmol), and maleic anhydride (0.3 g, 3 mmol). The filtered pentane solution was concentrated to 10 mL and passed through a short silica plug before analysis by GC to afford 47 mg of crude **14**. GC conditions were the same as used for **10**, and the retention time of **14** was found to be 12.6 min.

5.1.5. 4,8-Diphenyl-1,2,3,5,6,7-hexahydro-*s*-indacene (13). A solution of **10** (23 mg, 0.074 mmol) and DDQ (20 mg, 0.064 mmol) in benzene (5 mL) contained in a 10-mL flask was heated under reflux for 1.5 h, during which time the solution turned from light yellow to dark black. Filtration, concentration, and chromatography over silica gel using ethyl acetate–hexane (1:19) as eluant afforded **13** (R_f (0.49, 15 mg, 0.048 mmol, 75%) as a colorless solid (mp 178–180 °C). Using the same GC conditions as with **10**, the retention time of **13** was 15.9 min.

Spectra data. ^{1}H NMR: δ 1.95 (4H, quintet, J=7 Hz), 2.81 (8H, t, J=7 Hz), 7.26–7.44 (10H, m); ^{13}C NMR: δ 26.2, 32.7, 126.7, 128.8, 129.6, 133.9, 140.3, 141.1; HRMS *m*/*z* calcd for $C_{24}H_{23}$ 311.1799, found 311.1790.

5.1.6. Dehydrogenation of *trans*-4,8-diphenyl-1,2,3,4,5,6,7,8-octahydro-*s*-indacene (14). The procedure used for oxidizing **10** was used with the following amounts of reagents: Crude **14** (47 mg) and DDQ (50 mg, 0.22 mmol). The solution was heated under reflux for 4.5 h, and the color of the solution turned from light yellow to dark black. The resulting solution was vacuum-filtered and concentrated. The crude product was passed through a silica gel plug using ethyl acetate–hexane (1:19) as eluant. Analysis by GC showed that **13** had been formed, and no **14** remained.

Acknowledgements

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Electrochemical carboxylation of bicyclo[*n*.1.0]alkylidene derivatives

Morshed Alam Chowdhury, Hisanori Senboku and Masao Tokuda*

Laboratory of Organic Synthesis, Division of Molecular Chemistry, Graduate School of Engineering, Hokkaido University, Sapporo 060-8628, Japan

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Abstract—Electrochemical carboxylation of bicyclo[*n*.1.0]alkylidene derivatives (ring-fused alkylidenecyclopropanes) in a suitable aprotic solvent using a one-compartment electrochemical cell equipped with a platinum plate cathode and a zinc plate anode under an atmospheric pressure of carbon dioxide afforded either mono- or dicarboxylic acid in moderate to good yields.

1. Introduction

Electrochemical carboxylation is one of the most useful methods for the fixation of carbon dioxide to organic molecules because it is a clean and environmentally benign process. It takes place efficiently even in an atmospheric pressure of CO_2 under neutral and mild conditions to give carboxylic acids in high yields when a reactive-metal such as magnesium or aluminum is used as a sacrificial anode in the electrolysis.[1–4] Carbon dioxide is non-toxic and can work as an electrophile in the reaction of anion species to give carboxylic acids with one carbon elongation. We have already reported that electrochemical fixation of carbon dioxide to various organic molecules such as allylic halides,[5] propargylic bromide,[6] 2-bromomethyl-1,4-dibromobut-2-ene,[7] vinyl bromides,[8] and vinyl triflates[9] proceeded efficiently, regio- and chemoselectively to give the corresponding carboxylic acids in high yields. We have also reported an efficient synthesis of 2-phenylsuccinic acid derivatives by electrochemical dicarboxylation of phenyl substituted alkenes.[10] In addition, it has been reported by several researchers that electrochemical carboxylation of activated olefins having electron-withdrawing groups gave mono- or dicarboxylic acids.[11] However, only simple activated olefins such as methyl vinyl ketone, acrylonitrile, and methyl acrylate were used in these electrochemical carboxylation as substrates. To the best of our knowledge, there has been no report of the electrochemical carboxylation reactions of alkylidenecyclopropane derivatives. Methylene- and alkylidenecyclopropanes are very attractive substrates in organic reactions due to their unique reactivities originating from their highly strain structures. They have been widely used for many kind of organic reactions; i.e., cycloaddition reactions,[12,13] photochemical reactions,[14] and transition-metal catalyzed reactions.[15–20] Besides alkylidenecyclopropanes are widely used for the syntheses of various heterocycles which have been summarized in a review.[21] Recently we reported a facile method for the preparation of alkylidenecyclopropane derivatives carrying activated olefin unit[22] and its transformation to alkylidenecyclobutanes.[23] As an extension of our studies on electrochemical carboxylations, we recently carried out the electrochemical carboxylation of bicyclo[*n*.1.0]alkylidene derivatives (ring-fused alkylidenecyclopropanes), and wish to report here the results. By electrolysis of a system containing both carbon dioxide and ring-fused alkylidenecyclopropane derivatives **1** or **4** in one-compartment electrochemical cell using a platinum plate cathode and a zinc plate anode under atmospheric pressure in a suitable aprotic solvent such as DMF or MeCN, it is possible to achieve either a direct synthesis of monocarboxylic acid **2** or **5**/or dicarboxylic acid **3** or **6** (Scheme 1).

2. Results and discussion

Electrochemical carboxylation of bicyclo[4.1.0]hept-7-ylidene derivatives **1** was carried out in a dry DMF solution containing tetraethylammonium perchlorate (TEAP) as a supporting electrolyte under a slow stream of carbon dioxide gas in a one-compartment electrochemical cell equipped with a platinum plate cathode (2×3 cm^2) and a zinc plate anode (2×3 cm^2) (Scheme 2). The results are summarized in Table 1. In all cases, compounds **1** were

Keywords: Electrochemical carboxylation; Bicyclo[*n*.1.0]alkylidene derivative; Ring-fused alkylidenecyclopropane; Carbon dioxide; Carboxylic acid.
* Corresponding author. Tel.: +81-11-706-6599; fax: +81-11-706-6598; e-mail address: tokuda@org-mc.eng.hokudai.ac.jp

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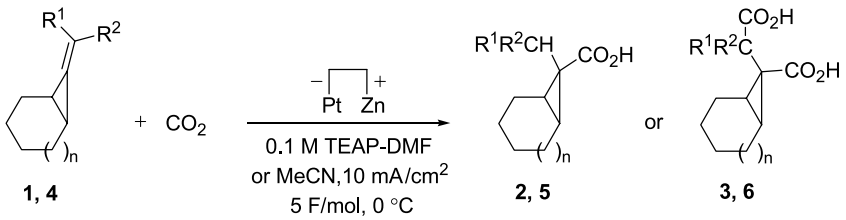
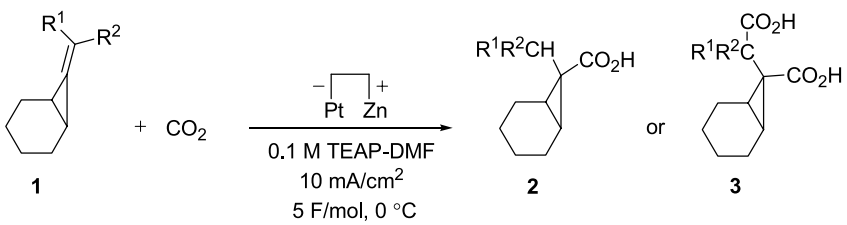


1-3 (n=1) 4-6 (n=2)	R^1	R^2
a	H	COOMe
b	H	COOEt
c	H	COMe
d	Me	COOMe
e	$CH_2CH=CH_2$	COOMe

Scheme 1.



Scheme 2.

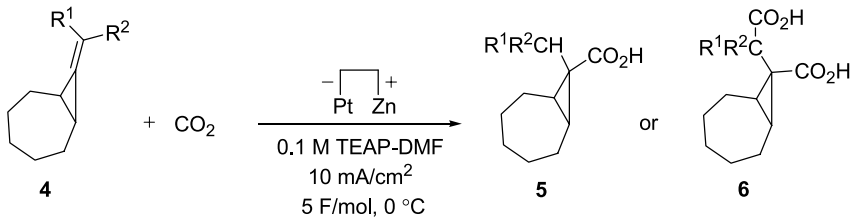
Table 1. Electrochemical carboxylation of bicyclo[4.1.0]hept-7-ylidene derivatives **1** in DMF[a]

R^1	R^2	Product	Yield (%)[b]
H	COOMe (**1a**)	**2a**	44
H	COOEt (**1b**)	**3b**	48
H	COMe (**1c**)	**2c**	61
Me	COOMe (**1d**)	**2d**	47
$CH_2CH=CH_2$	COOMe (**1e**)	**2e**	74

[a] **1** (2 mmol), Et_4NClO_4 (2 mmol), DMF (20 mL) in a one-compartment electrochemical cell.
[b] Isolated yields.

carboxylated under a constant current until 5 F/mol of charge with a current density of 10 mA/cm^2 had passed through the cell at 0 °C.

Electrochemical carboxylation of **1c** and **1e** took place efficiently to give the corresponding monocarboxylic acids **2c** and **2e** in isolated yields of 61 and 74%, respectively. On the other hand, electrochemical carboxylation of **1a** and **1d** occurred less effectively to give **2a** and **2d** in the yield of 44 and 47%, respectively. However, similar electrochemical carboxylation of **1b** under the same conditions gave no



Scheme 3.

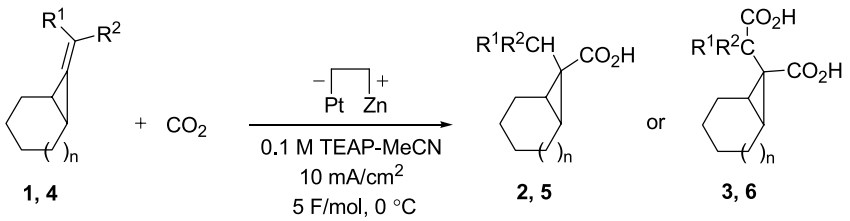
Table 2. Electrochemical carboxylation of bicyclo[5.1.0]oct-8-ylidene derivatives **4** in DMF[a]

R^1	R^2	Product	Yield (%)[b]
H	COOMe (**4a**)	**6a**	34
H	COOEt (**4b**)	**6b**	48
Me	COOMe (**4d**)	**5d**	65
$CH_2CH=CH_2$	COOMe (**4e**)	**5e**	68

[a] **4** (2 mmol), Et_4NClO_4 (2 mmol), DMF (20 mL) in a one-compartment electrochemical cell.
[b] Isolated yields.

monocarboxylic acid and, instead, dicarboxylic acid **3b** was obtained in 48% yield.

Electrochemical carboxylation of bicyclo[5.1.0]oct-8-ylidene derivatives **4** was carried out under the same conditions as those applied for bicyclo[4.1.0]hept-7-ylidene derivatives (Scheme 3). The results are summarized in Table 2. Carboxylation of **4a** and **4b** afforded dicarboxylic acids **6a** and **6b** in 34 and 48% isolated yields, respectively. On the other hand, **4d** and **4e** afforded no dicarboxylic acids and, instead, monocarboxylic acids **5d** and **5e** were



Scheme 4.

Table 3. Electrochemical carboxylation of bicyclo[*n*.1.0]alkylidene derivatives **1** and **4** in MeCN[a]

n	R^1	R^2	Product	Yield (%)[b]
1	H	COOEt (**1b**)	**3b**	71
1	Me	COOMe (**1d**)	**2d**	24
2	H	COOMe (**4a**)	**6a**	66
2	H	COOEt (**4b**)	**6b**	75

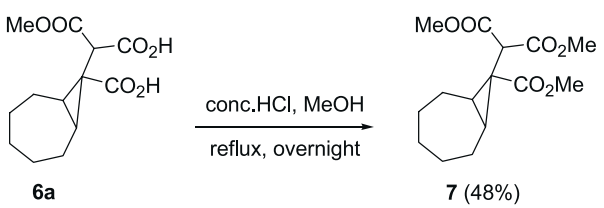
[a] **1** or **4** (2 mmol), Et_4NClO_4 (2 mmol), MeCN (20 mL) in a one-compartment electrochemical cell.
[b] Isolated yields.

obtained exclusively in the yield of 65 and 68%, respectively.

Some electrochemical carboxylation reactions of **1** and **4** were carried out in dry MeCN to investigate whether the yields increase or not. The carboxylation was carried out in a dry MeCN solution containing TEAP as a supporting electrolyte in a one-compartment electrochemical cell equipped with a platinum plate cathode (2×3 cm^2) and a zinc plate anode (2×3 cm^2) (Scheme 4). In all cases, compounds **1** and **4** were carboxylated under a slow stream of carbon dioxide gas at a constant current of 10 mA/cm^2 until 5 F/mol of charge had passed through the cell at 0 °C. The results are summarized in Table 3.

The electrochemical carboxylation of **1b**, **4a** and **4b** in MeCN took place more efficiently to give the dicarboxylic acids **3b**, **6a** and **6b** in 71, 66 and 75% isolated yields, respectively, whereas in DMF these were 48, 34 and 48%, respectively. On the other hand, electrochemical carboxylation of **1d** in MeCN under the same conditions took place less efficiently and afforded monocarboxylic acid **2d** in 24% isolated yield whereas in DMF it gave the same product **2d** in 47% yield. It is not clear the reasons in this moment why monocarboxylation is better in DMF and dicarboxylation is better in MeCN regardless the bicyclic systems of the ring-fused alkylidenecyclopropanes.

The structures of dicarboxylic acids **3** or **6** were determined by those spectral data and the following results. When the dicarboxylic acid **6a** containing a methyl ester group was refluxed with concentrated hydrochloric acid in methanol



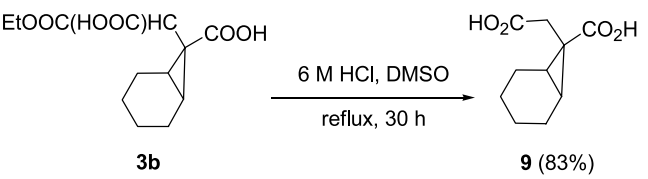
Scheme 5.

for overnight, trimethyl ester **7** was obtained in the yield of 48% (Scheme 5). ^1H NMR spectra of **7** showed two peaks of methoxy groups with different chemical shifts at δ 3.65 (s, 3H) and at δ 3.77 (s, 6H) indicating the presence of two carboxyl groups in **6a** which were esterified to methyl esters.

Stirring of **6a** with 6 M hydrochloric acid in DMSO under reflux for 30 h, decarboxylation of one carboxylic group took place along with the conversion of methyl ester to acid and afforded **8** in 94% yield (Scheme 6). It also indicates the presence of two carboxyl groups in **6a**.

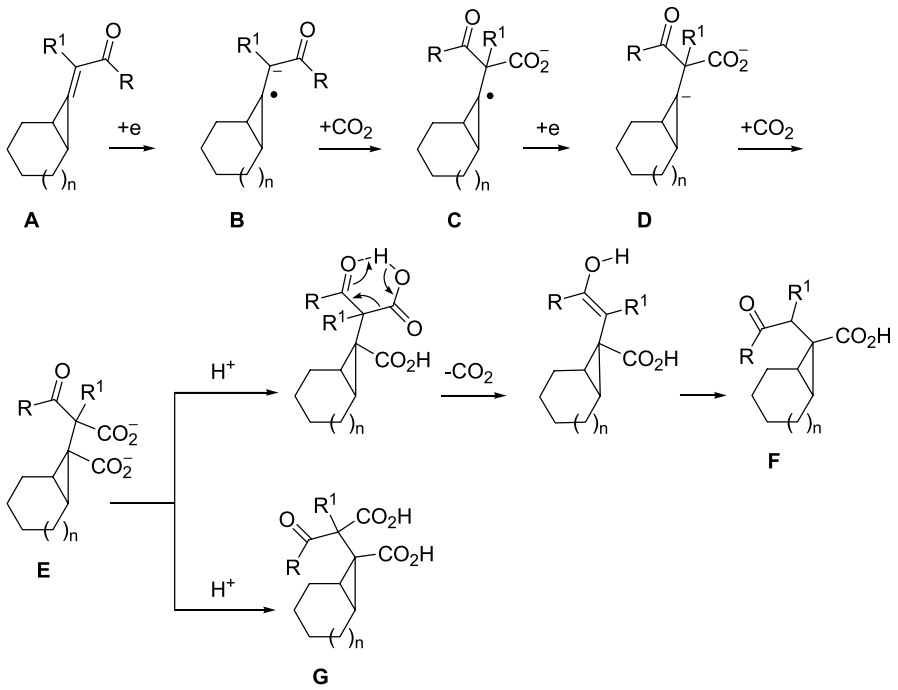
Scheme 6.

The *endo*- or *exo*-configuration of the mono- and dicarboxylic acids **2**, **3** and **5**, **6** was established by comparing the spectral data of its derivatives with those reported in the literature.[24] Stirring of **3b** with 6 M hydrochloric acid in DMSO under reflux for 30 h afforded **9** in 83% yield (Scheme 7). The melting point and spectral data of **9** supported the 7-*endo*-substituted-7-*exo*-carboxylic acid configuration of **3b**.[24] Usually, activated ring-fused alkylidenecyclopropanes favour nucleophilic attack from *exo*-direction.[25]



Scheme 7.

The electrochemical carboxylation of olefinic substrates with CO_2 in aprotic solvents has already been proposed as a useful procedure for the production of mono- and dicarboxylic acids.[11] Proposed reaction pathways of the present electrochemical carboxylations are shown in Scheme 8. Activated olefins **A** are easier to be reduced than CO_2, since reduction potential of bicyclo[*n*.1.0]alkylidene derivatives **1a**–**1e**, **4a**–**4e** and CO_2 are −2.35–−2.71 V, −2.56–−2.71 V and −2.90 V vs Ag/Ag^+, respectively.[26] Therefore, a one-electron reduction of activated olefins **A** would give the anion radical **B**, which



Scheme 8.

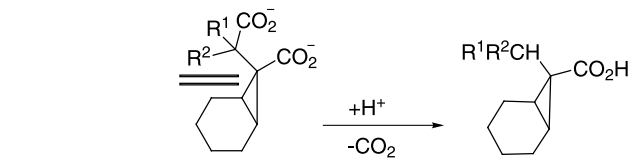


Figure 1.

undergoes a nucleophilic attack on CO_2 to give the anion radical **C**. Further one-electron reduction of **C** affords the carbanion **D**,[11a,27] which would react with another CO_2 at the *exo*-position of **D** to give dicarboxylate anion **E**. Similar pathways in the electrochemical reduction of α,β-unsaturated carbonyl compounds have been pointed out by Wawzonek and co-workers.[28] We assume that the present electrochemical carboxylation of both mono- and disubstituted bicyclo[*n*.1.0]alkylidene derivatives give dicarboxylate anions **E**. On acidification during work-up the dicarboxylate anions **E** of all mono (except **1b**) and disubstituted bicyclo[4.1.0]hept-7-ylidene derivatives **1a**, **1c–e** and disubstituted bicyclo[5.1.0]oct-8-ylidene derivatives **4d–e** gave monocarboxylic acids **F** via decarboxylation of one carboxyl group bearing carbonyl group at the α-position. On the other hand, in the case of monosubstituted bicyclo[5.1.0]oct-8-ylidene derivatives **4a–b**, acidification of **E** gave dicarboxylic acids **G** (Scheme 8).

Dicarboxylated bicyclo[4.1.0]heptane derivatives are spatially more rigid, greater ring-strain and sterically more hindered. Therefore, decarboxylation of one carboxyl group can release the strain and afforded monocarboxylic acids (Fig. 1). It is not clear at the present stage that no

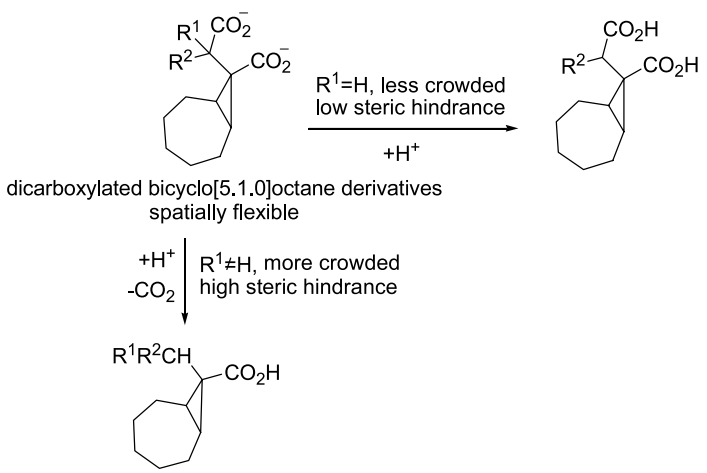


Figure 2.

decarboxylation occurred to give dicarboxylic acid **3b** only in the case of bicyclo[4.1.0]hept-7-ylideneacetic acid ethyl ester (**1b**).

On the other hand, dicarboxylated bicyclo[5.1.0]octane derivatives are spatially flexible and sterically less hindered when R^1=H but more hindered when R^1≠H. As a result, decarboxylation of one carboxylic group minimizes the steric hindrance and afforded monocarboxylic acids when R^1≠H. However, when R^1=H no such steric hindrance prevails and afforded dicarboxylic acids (Fig. 2).

3. Experimental

3.1. General

Melting points were uncorrected and measured with a Yanagimoto micro mp apparatus. IR spectra were determined for nujol mulls, unless otherwise noted, with a JASCO IR-810 infrared spectrometer. ^{1}H and ^{13}C NMR spectra were recorded at 270 MHz and 67.5 MHz, respectively, with a JEOL JNM EX-270 high-resolution spectrometer using $CDCl_3$ as a solvent. Chemical shifts are given in ppm down field (δ) from TMS as an internal standard. MS spectra were determined using a JEOL JMS FABmate or JMS HX-110. Cyclic voltammetries were measured with a BAS CV-50W voltammetry analyzer using a gold disk electrode (1.6 mmϕ) and Ag:$AgNO_3$ as a reference electrode. Bicyclo[*n*.1.0]alkylidene derivatives (ring-fused alkylidenecyclopropanes) were prepared according to our reported method.[22]

3.2. General procedure for electrochemical carboxylation of bicyclo[*n*.1.0]alkylidene derivatives 1 and 4

A mixture of **1** or **4** (2 mmol) and TEAP (2 mmol) in dry DMF or MeCN (20 mL) was taken into a one-compartment electrochemical cell equipped with a platinum plate cathode (2×3 cm^2) and a zinc plate anode (2×3 cm^2). The solution was electrolyzed at a constant current of 10 mA/cm^2 under a slow stream of carbon dioxide gas until electricity of 5 F/mol of substrate was passed at 0 °C. The electrolyzed solution was acidified with 2 N HCl and extracted with diethyl ether (3×25 mL). The combined ether extracts were washed successively with water (2×25 mL) and saturated aqueous sodium hydrogen carbonate (75 mL). The aqueous layer was washed with diethyl ether (2×20 mL) and again acidified with 2 N HCl and extracted with diethyl ether (3×25 mL). The combined ether extracts were washed with brine (25 mL) and dried over $MgSO_4$. Evaporation of the solvents in vacuo afforded either monocarboxylic acid **2** or **5**, or dicarboxylic acid **3** or **6**. Analytical samples were obtained by recrystallization.

3.2.1. 7-Methoxycarbonylmethylbicyclo[4.1.0]heptane-7-carboxylic acid (2a). Electrochemical carboxylation of bicyclo[4.1.0]hept-7-ylideneacetic acid methyl ester (**1a**) (332 mg, 2 mmol) in DMF gave 7-methoxycarbonylmethylbicyclo[4.1.0]heptane-7-carboxylic acid (**2a**) (188 mg, 44%): mp 136–138 °C (pet. ether); IR ν 3600–2000 (broad), 1742, 1674 cm^{-1}; ^{1}H NMR δ 1.05–1.55 (m, 6H), 1.75–2.15 (m, 4H), 2.65 (s, 2H), 3.70 (s, 3H); ^{13}C NMR δ 18.78, 21.51, 23.70, 27.42, 30.35, 51.83, 172.36, 181.56; FABMS *m*/*z* (relative intensity) 213 (MH$^+$, 22), 195 (35), 154 (100), 136 (83), 107 (27), 89 (28), 77 (27), 55 (15); HRMS calcd for $C_{11}H_{17}O_4$ *m*/*z* 213.1127. Found *m*/*z* 213.1136. Anal. calcd for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 62.10; H, 7.59.

3.2.2. 2-(7-Carboxybicyclo[4.1.0]hept-7-yl)malonic acid monoethyl ester (3b). Electrochemical carboxylation of bicyclo[4.1.0]hept-7-ylideneacetic acid ethyl ester (**1b**) (360 mg, 2 mmol) in MeCN gave 2-(7-carboxybicyclo-[4.1.0]hept-7-yl)malonic acid monoethyl ester (**3b**) (383 mg, 71%): mp 167–169 °C (ethyl acetate); IR ν 3600–2000 (broad), 1753, 1709, 1677 cm^{-1}; ^{1}H NMR δ 1.12–1.61 (m, 6H), 1.27 (t, *J*=7.26 Hz, 3H), 1.75–2.14 (m, 4H), 3.24 (s, 1H), 4.21 (q, *J*=7.26 Hz, 2H); ^{13}C NMR δ 13.23, 18.00, 18.07, 20.61, 22.12, 22.41, 30.33, 48.22, 60.19, 168.29, 169.33, 175.09; FABMS *m*/*z* (relative intensity) 271 (MH$^+$, 34), 253 (79), 154 (100), 136 (91), 107 (32), 89 (32), 77 (32), 55 (19); HRMS calcd for $C_{13}H_{19}O_6$ *m*/*z* 271.1182. Found *m*/*z* 271.1154. Anal. calcd for $C_{13}H_{18}O_6$: C, 57.77; H, 6.71. Found: C, 57.68; H, 6.69.

3.2.3. 7-(2-Oxopropyl)bicyclo[4.1.0]heptane-7-carboxylic acid (2c). Electrochemical carboxylation of bicyclo[4.1.0]hept-7-ylidenepropan-2-one (**1c**) (300 mg, 2 mmol) in DMF gave 7-(2-oxopropyl)bicyclo[4.1.0]heptane-7-carboxylic acid (**2c**) (239 mg, 61%): mp 96–97 °C (pet. ether); IR ν 3600–2000 (broad), 3322, 1727 cm^{-1}; ^{1}H NMR δ 1.05–1.50 (m, 6H), 1.65–2.10 (m, 4H), 1.73 (bs, 3H), 2.45 (bs, 2H); ^{13}C NMR δ 19.43, 21.60, 23.04, 28.30, 29.29, 180.70; EIMS *m*/*z* (relative intensity) 196 (M$^+$, 10), 178 (31), 153 (57), 135 (73), 107 (88), 93 (35), 79 (57); HRMS calcd for $C_{11}H_{16}O_3$ *m*/*z* 196.1099. Found *m*/*z* 196.1100. Anal. calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.03; H, 8.18.

3.2.4. 7-(1-Methoxycarbonylethyl)bicyclo[4.1.0]heptane-7-carboxylic acid (2d). Electrochemical carboxylation of 2-bicyclo[4.1.0]hept-7-ylidenepropanoic acid methyl ester (**1d**) (360 mg, 2 mmol) in DMF gave 7-(1-methoxycarbonylethyl)bicyclo[4.1.0]heptane-7-carboxylic acid (**2d**) (213 mg, 47%): mp 145–147 °C (ethyl acetate); IR ν 3600–2000 (broad), 1737, 1679 cm^{-1}; ^{1}H NMR δ 1.12–1.55 (m, 6H), 1.41 (d, *J*=6.93 Hz, 3H), 1.55–2.15 (m, 4H), 2.34 (q, *J*=6.93 Hz, 1H), 3.70 (s, 3H); ^{13}C NMR δ 14.04, 19.03, 19.23, 21.57, 21.82, 23.74, 25.84, 33.39, 35.94, 51.97, 175.09, 180.72; EIMS *m*/*z* (relative intensity) 226 (M$^+$, 2), 208 (24), 195 (12), 180 (100), 166 (37), 148 (61), 121 (80), 93 (72), 79 (56), 67 (42), 55 (27); HRMS calcd for $C_{12}H_{18}O_4$ *m*/*z* 226.1205. Found *m*/*z* 226.1183. Anal. calcd for $C_{12}H_{18}O_4$: C, 63.70; H, 8.02. Found: C, 63.91; H, 8.07.

3.2.5. 7-(1-Methoxycarbonylbut-3-enyl)bicyclo[4.1.0]-heptane-7-carboxylic acid (2e). Electrochemical carboxylation of 2-bicyclo[4.1.0]hept-7-ylidenepent-4-enoic acid methyl ester (**1e**) (412 mg, 2 mmol) in DMF gave 7-(1-methoxycarbonylbut-3-enyl)bicyclo[4.1.0]heptane-7-carboxylic acid (**2e**) (373 mg, 74%): mp 100–101 °C (pet. ether); IR ν 3600–2000 (broad), 1742, 1678 cm^{-1}; ^{1}H NMR δ 1.15–1.57 (m, 6H), 1.57–2.10 (m, 4H), 2.15–2.35 (m, 2H), 2.95–3.10 (m, 1H), 3.71 (s, 3H), 4.95–5.15 (m,

2H), 5.91–6.12 (m, 1H); ^{13}C NMR δ 19.09, 19.28, 21.51, 21.71, 23.90, 26.17, 33.86, 34.76, 41.69, 52.01, 115.69, 137.65, 174.66, 180.50; FABMS *m/z* (relative intensity) 253 (MH^+, 6), 154 (100), 136 (79), 107 (27), 89 (28), 77 (25), 55 (15); HRMS calcd for $C_{14}H_{21}O_4$ *m/z* 253.1440. Found *m/z* 253.1447. Anal. calcd for $C_{14}H_{20}O_4$: C, 66.65; H, 7.99. Found: C, 66.52; H, 7.89.

3.2.6. 2-(8-Carboxybicyclo[5.1.0]oct-8-yl)malonic acid monomethyl ester (6a). Electrochemical carboxylation of bicyclo[5.1.0]oct-8-ylideneacetic acid methyl ester (**4a**) (360 mg, 2 mmol) in MeCN gave 2-(8-carboxybicyclo-[5.1.0]oct-8-yl)malonic acid monomethyl ester (**6a**) (356 mg, 66%): mp 190–193 °C (ethyl acetate); IR ν 3600–2000 (broad), 1756, 1694 cm^{-1}; ^{1}H NMR δ 0.85–1.51 (m, 5H), 1.72–2.19 (m, 7H), 3.32 (s, 1H), 3.74 (s, 3H); ^{13}C NMR δ 25.33, 25.40, 27.85, 29.83, 29.95, 31.86, 33.68, 48.36, 51.71, 169.32, 169.64, 175.16; FABMS *m/z* (relative intensity) 271 (MH^+, 16), 253 (33), 154 (100), 136 (79), 107 (28), 89 (28), 77 (29), 55 (14); HRMS calcd for $C_{13}H_{19}O_6$ *m/z* 271.1182. Found *m/z* 271.1201. Anal. calcd for $C_{13}H_{18}O_6$: C, 57.77; H, 6.71. Found: C, 57.85; H, 6.77.

3.2.7. 2-(8-Carboxybicyclo[5.1.0]oct-8-yl)malonic acid monoethyl ester (6b). Electrochemical carboxylation of bicyclo[5.1.0]oct-8-ylideneacetic acid ethyl ester (**4b**) (388 mg, 2 mmol) in MeCN gave 2-(8-carboxybicyclo-[5.1.0]oct-8-yl)malonic acid monoethyl ester (**6b**) (426 mg, 75%): mp 173–175 °C (ethyl acetate); IR ν 3600–2000 (broad), 1750, 1697 cm^{-1}; ^{1}H NMR δ 0.85–1.51 (m, 5H), 1.26 (t, J=6.93 Hz, 3H), 1.69–2.19 (m, 7H), 3.28 (s, 1H), 4.17 (q, J=6.93 Hz, 2H); ^{13}C NMR δ 12.99, 24.94, 27.44, 29.26, 29.29, 31.38, 33.16, 47.98, 59.84, 168.21, 169.11, 174.25; FABMS *m/z* (relative intensity) 285 (MH^+, 22), 267 (59), 154 (100), 136 (89), 107 (33), 89 (37), 77 (39), 55 (24); HRMS calcd for $C_{14}H_{21}O_6$ *m/z* 285.1338. Found *m/z* 285.1353. Anal. calcd for $C_{14}H_{20}O_6$: C, 59.14; H, 7.09. Found: C, 59.06; H, 7.12.

3.2.8. 8-(1-Methoxycarbonylethyl)bicyclo[5.1.0]octane-8-carboxylic acid (5d). Electrochemical carboxylation of 2-bicyclo[5.1.0]oct-8-ylidenepropanoic acid methyl ester (**4d**) (388 mg, 2 mmol) in DMF gave 8-(1-methoxycarbonylethyl)bicyclo[5.1.0]octane-8-carboxylic acid (**5d**) (312 mg, 65%): mp 153–155 °C (ethyl acetate); IR ν 3600–2000 (broad), 1743, 1677 cm^{-1}; ^{1}H NMR δ 0.85–1.52 (m, 5H), 1.35 (d, J=6.93 Hz, 3H), 1.69–2.25 (m, 7H), 2.37 (q, J=6.93 Hz, 1H), 3.67 (s, 3H); ^{13}C NMR δ 14.49, 25.90, 26.26, 28.36, 28.66, 30.50, 32.65, 33.62, 35.89, 36.79, 51.88, 175.02, 180.72; FABMS *m/z* (relative intensity) 241 (MH^+, 3), 154 (100), 136 (66), 107 (25), 89 (25), 77 (27), 69 (19), 55 (25), 41 (26); HRMS calcd for $C_{13}H_{21}O_4$ *m/z* 241.1440. Found *m/z* 241.1416. Anal. calcd for $C_{13}H_{20}O_4$: C, 64.98; H, 8.39. Found: C, 64.95; H, 8.36.

3.2.9. 8-(1-Methoxycarbonylbut-3-enyl)bicyclo[5.1.0]-octane-8-carboxylic acid (5e). Electrochemical carboxylation of 2-bicyclo[5.1.0]oct-8-ylidenepent-4-enoic acid methyl ester (**4e**) (440 mg, 2 mmol) in DMF gave 8-(1-methoxycarbonylbut-3-enyl)bicyclo[5.1.0]octane-8-carboxylic acid (**5e**) (362 mg, 68%): mp 140–142 °C (pet. ether); IR ν 3600–2000 (broad), 1744, 1678 cm^{-1}; ^{1}H NMR δ 0.85–1.52 (m, 5H), 1.72–2.27 (m, 7H), 2.27–2.39 (m, 2H), 2.92–3.10 (m, 1H), 3.68 (s, 3H), 4.95–5.15 (m, 2H), 5.89–6.12 (m, 1H); ^{13}C NMR δ 26.29, 26.42, 28.36, 28.63, 30.84, 32.56, 33.75, 34.90, 36.91, 41.85, 51.92, 115.78, 137.59, 174.41, 180.47; FABMS *m/z* (relative intensity) 267 (MH^+, 69), 249 (100), 225 (54), 189 (26), 161 (25), 154 (27), 137 (35), 107 (27), 91 (40), 79 (35), 67 (27), 55 (25), 41 (37); HRMS calcd for $C_{15}H_{23}O_4$ *m/z* 267.1596. Found *m/z* 267.1601. Anal. calcd for $C_{15}H_{22}O_4$: C, 67.65; H, 8.33. Found: C, 67.47; H, 8.38.

3.3. Acid treatment of the carboxylated products

3.3.1. 2-(8-Methoxycarbonylbicyclo[5.1.0]oct-8-yl)-malonic acid dimethyl ester (7). 2-(8-Methoxycarbonyl-bicyclo[5.1.0]oct-8-yl)malonic acid dimethyl ester (**7**) was prepared in a 48% yield from 2-(8-carboxybicyclo-[5.1.0]oct-8-yl)malonic acid monomethyl ester (**6a**). To a solution of dicarboxylic acid **6a** (270 mg, 1 mmol) in methanol (5 mL) was added concentrated hydrochloric acid (3 mL). The mixture was heated under reflux for overnight, and then the solvent was evaporated and extracted with ethyl acetate (5 mL×3). The combined organic phases were washed successively with water, saturated brine and dried over $MgSO_4$. Filtration, concentration in vacuo and column chromatography on silica eluting with a mixture of ether/hexane (3:2) afforded 2-(8-methoxycarbonylbicyclo-[5.1.0]oct-8-yl)malonic acid dimethyl ester (**7**) (143 mg, 48%); IR (neat) ν 1751, 1741, 1727 cm^{-1}; ^{1}H NMR δ 0.85–1.52 (m, 5H), 1.79–2.18 (m, 7H), 3.38 (s, 1H), 3.65 (s, 3H), 3.77 (s, 6H); ^{13}C NMR δ 25.91, 28.41, 30.62, 32.54, 34.54, 48.84, 52.08, 52.58, 169.16, 173.55; EIMS *m/z* (relative intensity) 298 (M^+, 7), 266 (70), 239 (100), 234 (39), 207 (65), 202 (28), 179 (29), 175 (54), 147 (39), 119 (68), 91 (41), 79 (30), 59 (52); HRMS calcd for $C_{15}H_{22}O_6$ *m/z* 298.1416. Found *m/z* 298.1405.

3.3.2. 8-Carboxymethylbicyclo[5.1.0]octane-8-carboxylic acid (8). 8-Carboxymethylbicyclo[5.1.0]octane-8-carboxylic acid (**8**) was prepared in a 94% yield from 2-(8-carboxybicyclo[5.1.0]oct-8-yl)malonic acid monomethyl ester (**6a**). To a solution of dicarboxylic acid **6a** (270 mg, 1 mmol) in DMSO (5 ml) was added 6 M hydrochloric acid (3 mL). The mixture was heated under reflux for 30 h, and then the solvent was evaporated and extracted with ethyl acetate (5 mL×3). The combined organic phases were washed successively with water, saturated brine and dried over $MgSO_4$. Filtration and concentration in vacuo afforded 8-carboxymethylbicyclo[5.1.0]octane-8-carboxylic acid (**8**) (200 mg, 94%): mp 237–240 °C (ethyl acetate); IR ν 3600–2000 (broad), 1718, 1687 cm^{-1}; ^{1}H NMR δ 0.81–1.47 (m, 5H), 1.55–2.11 (m, 7H), 2.61 (s, 2H); ^{13}C NMR δ 24.21, 27.32, 28.36, 28.81, 29.22, 31.11, 172.43, 175.22; FABMS *m/z* (relative intensity) 213 (MH^+, 25), 195 (44), 154 (100), 136 (87), 107 (33), 89 (35), 77 (31); HRMS calcd for $C_{11}H_{17}O_4$ *m/z* 213.1127. Found *m/z* 213.1117. Anal. calcd for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 61.98; H, 7.78.

3.3.3. 7-*endo*-Carboxymethylbicyclo[4.1.0]heptane-7-*exo*-carboxylic acid (9). To a solution of 2-(7-carboxy-bicyclo[4.1.0]hept-7-yl)malonic acid monoethyl ester (**3b**) (270 mg, 1 mmol) in DMSO (5 mL) was added 6 M hydrochloric acid (3 mL). The mixture was heated under reflux for 30 h, and then the solvent was evaporated and the

residue was extracted with ethyl acetate (5 mL×3). The combined organic phases were washed successively with water and saturated brine, and dried over $MgSO_4$. Evaporation of the solvent in vacuo afforded 164 mg (83%) of 7-*endo*-carboxymethylbicyclo[4.1.0]heptane-7-*exo*-carboxylic acid (**9**) whose spectral data are identical with reported values.[24] Mp 191–194 °C (lit.[24] 193 °C); IR ν 3600–2000 (broad), 1717, 1686 cm^{-1}; ^1H NMR (DMSO) δ 1.10–1.50 (m, 6H), 1.60–1.75 (m, 2H), 1.85–2.05 (m, 2H), 2.60 (s, 2H); ^{13}C NMR δ 18.02, 20.84, 21.49, 26.46, 30.02, 173.37, 176.80; FABMS *m/z* (relative intensity) 199 (MH^+, 17), 181 (17), 154 (100), 136 (60), 107 (19), 89 (19), 77 (23). Anal. calcd for $C_{10}H_{14}O_4$: C, 60.59; H, 7.12. Found: C, 60.36; H, 7.16.

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