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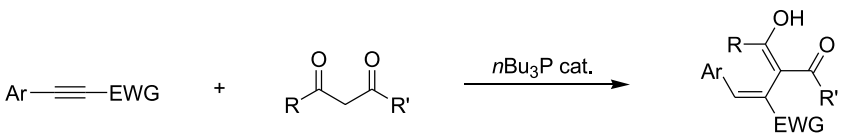
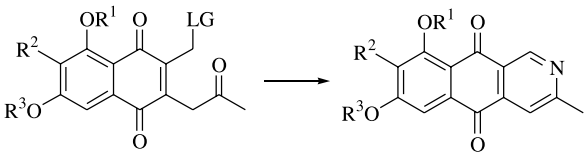
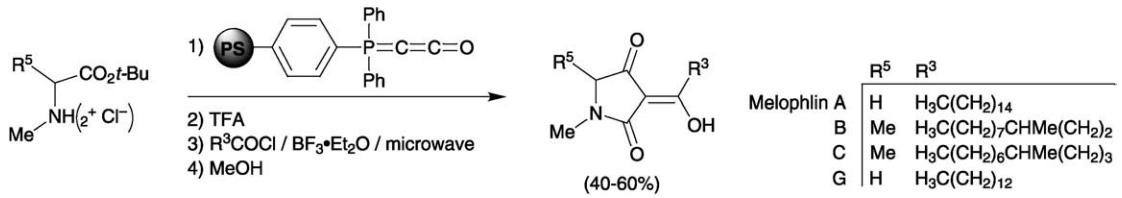
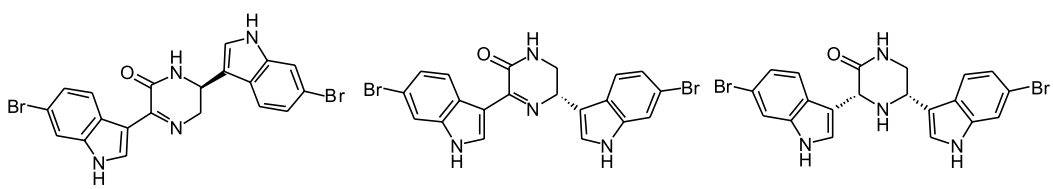
Contents



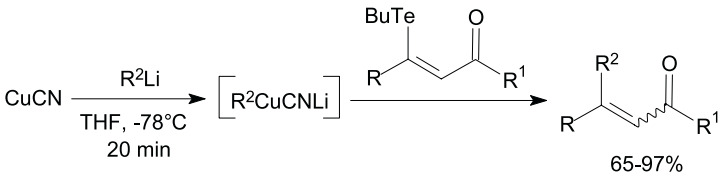


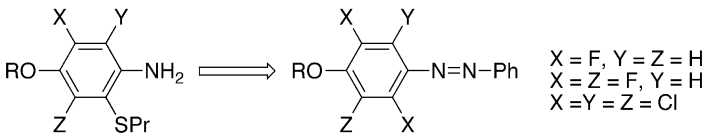


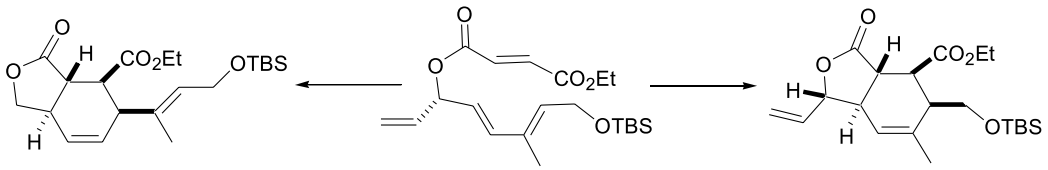
	R^5	R^3
Melophlin A	H	$H_3C(CH_2)_{14}$
B	Me	$H_3C(CH_2)_7CHMe(CH_2)_2$
C	Me	$H_3C(CH_2)_6CHMe(CH_2)_3$
G	H	$H_3C(CH_2)_{12}$

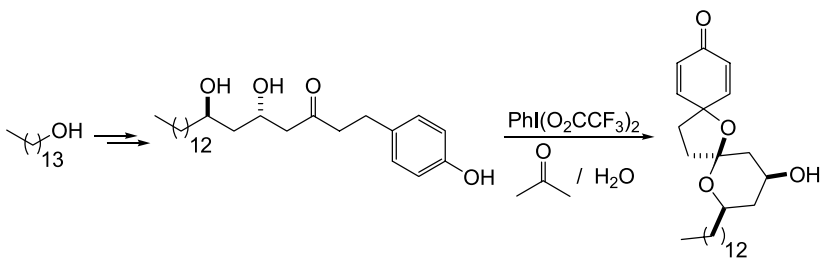


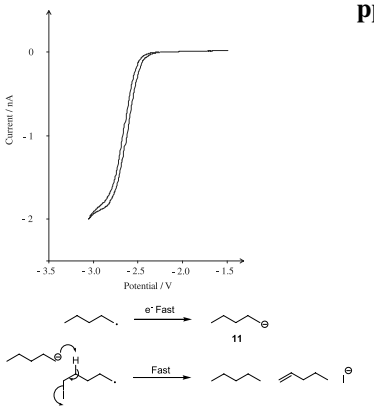
Hamacanthin A Hamacanthin B antipode of *cis*-Dihidrohamacanthin B

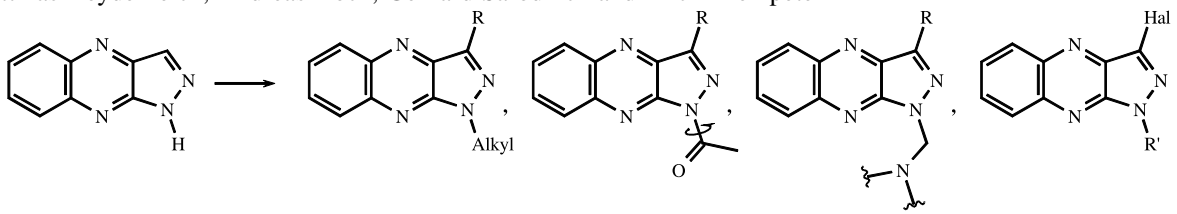


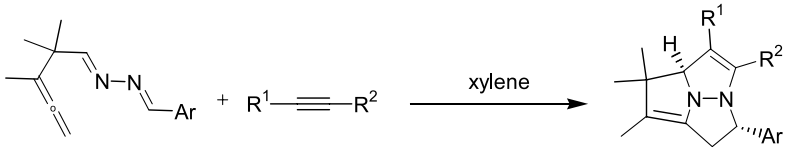


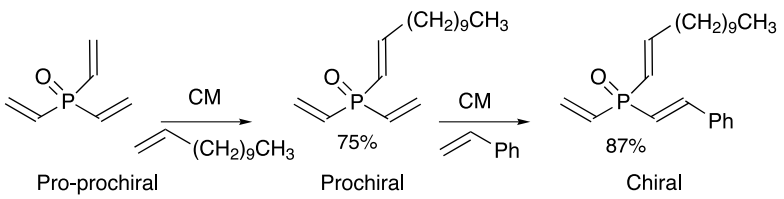


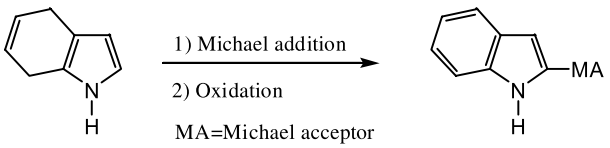




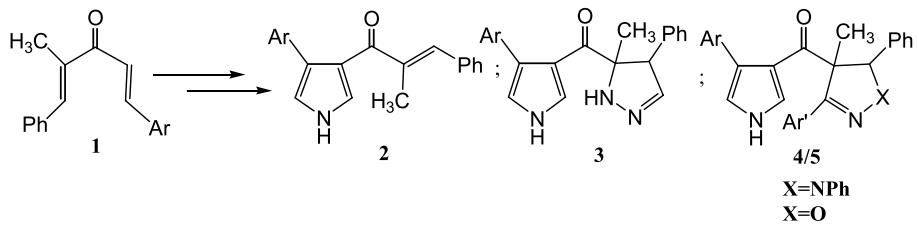




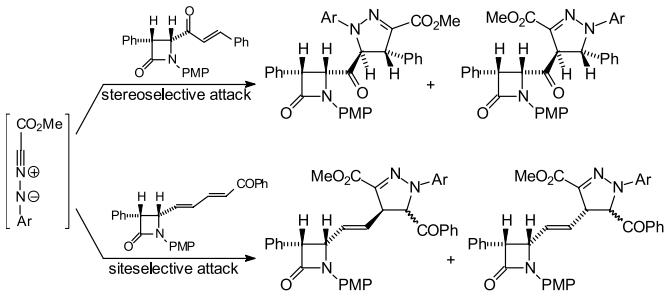


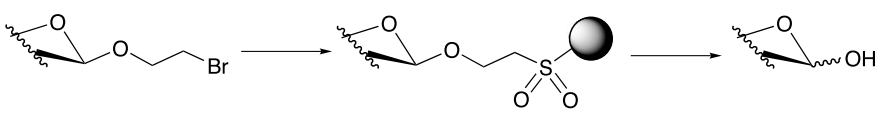


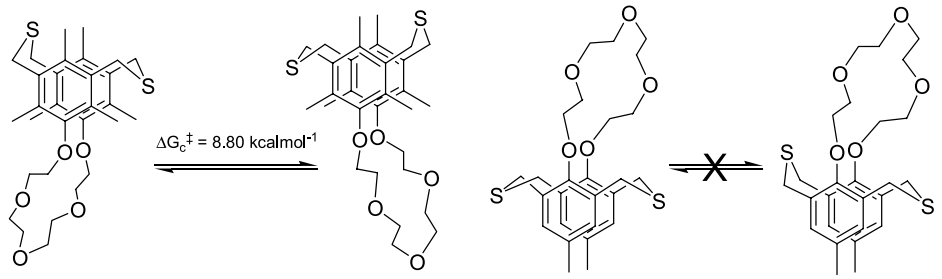
Synthesis of 2-substituted indole derivatives were realized by Michael reactions of 4,7-dihydroindole and oxidation of corresponding Michael adducts.

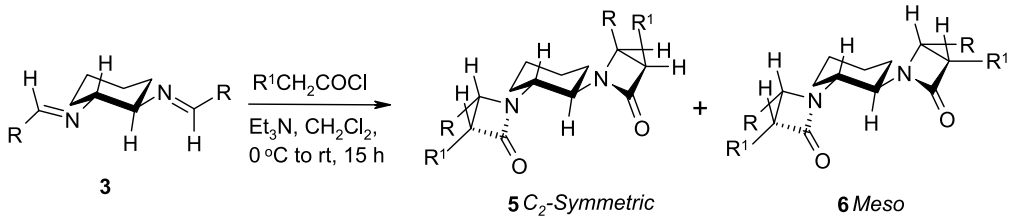


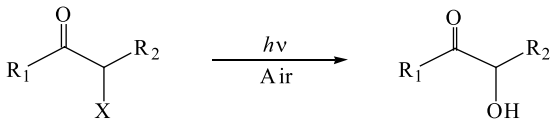
The 1,3-dipolar cycloaddition of tosyl methyl isocyanide, nitrile imines and nitrile oxides to 2-methyl-1-phenyl-5-aryl-1,4-pentadien-3-one (**1**) provides a simple, facile and elegant methodology to develop keto-linked bis heterocycles.

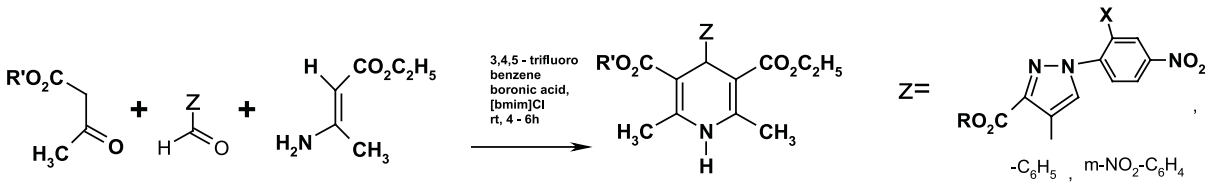


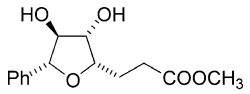






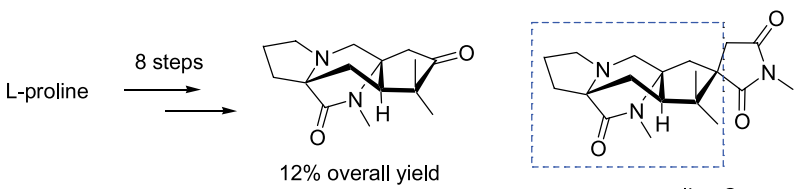


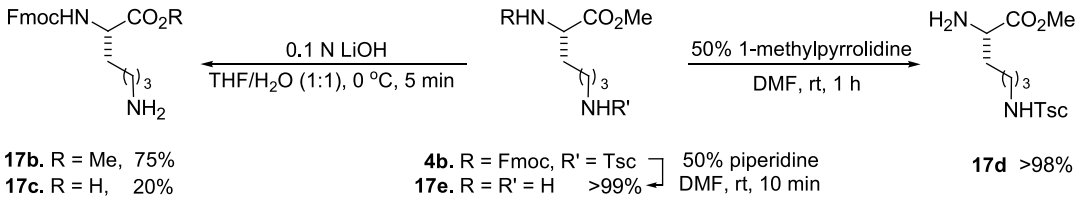


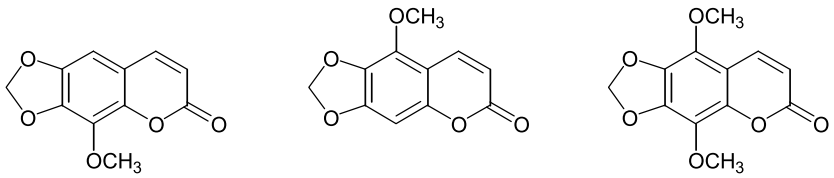


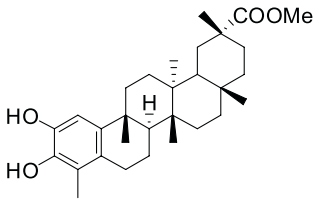
Goniothalesdiol

A synthesis of (+)-goniothalesdiol and its 7-epimer using Pd(II)-catalysed oxycarbonylation is described.

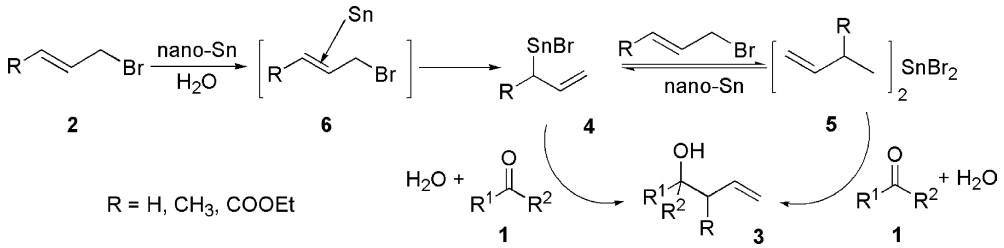


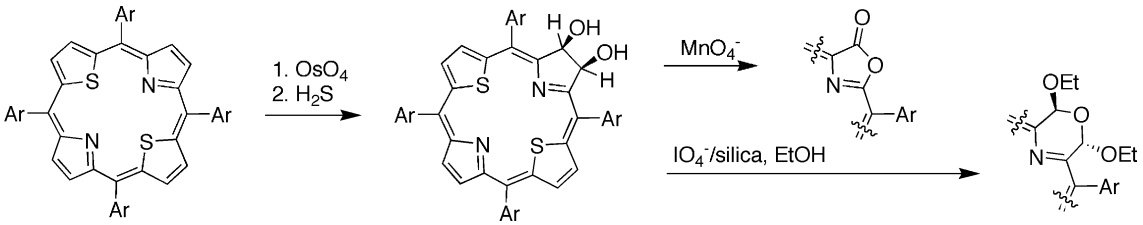


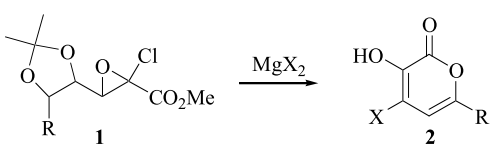




6-Deoxoblepharodol







Treatment of acetonide protected 4,5-dihydroxy-2-chloroglycidic ester **1** with magnesium halides gave 4-halo-3-hydroxy-2-pyrone **2** in excellent to reasonable yields in one pot. The mechanism of this novel rearrangement-cyclization reaction is also proposed.

OTHER CONTENTS

*Corresponding author
ⓘ+ Supplementary data available via ScienceDirect

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Publisher's announcement

Tetrahedron Prize for Creativity in Organic Chemistry for 2004

Professor Koji Nakanishi
Tetrahedron Prize 2004

The Executive Board of Editors and the Publisher of Tetrahedron Publications are pleased to announce that the Tetrahedron Prize for Creativity in Organic Chemistry for 2004 has been awarded to Professor Koji Nakanishi, Columbia University, New York.

Professor Nakanishi was awarded the Tetrahedron Prize for his pioneering research in the use of spectroscopic and chemical methods in determining the chemical structure of natural products, research which has led to the characterisation of over 200 bioactive compounds, many of which are endogenous and/or the first member of a new class. His studies with retinal analogs and retinal proteins have made seminal contributions in understanding the structural and mechanistic basis of animal vision and phototaxis.

The Tetrahedron Prize will be presented to Professor Nakanishi at the Fall ACS National Meeting in Washington. The provisional date for the Prize Symposium and presentation of the Award is Monday, 29 August 2005.

Professor Koji Nakanishi was born in Hong Kong in 1925. He received his bachelor's degree in chemistry from Nagoya University, Japan, in 1947 from Fujio Egami. Following two years of post-graduate work with Louis Fieser at Harvard University, he returned to Nagoya University where he completed his Ph.D. in 1954 with Yoshimasa Hirata. He was Assistant Professor at Nagoya until 1958 when he became Professor of Chemistry at Tokyo Kyoiku University. In 1963 he moved to Tohoku University in Sendai and remained there until 1969 when he joined the faculty of Columbia University, New York. Since 1980 he has held the title of Centennial Professor of Chemistry. He was a founding member and one of the six Directors of Research at the International Centre of Insect Physiology and Ecology (ICIPE) in Kenya, 1969–1977. In 1978 he became the first Director of the Suntory Institute for Bioorganic Research (Sunbor), Osaka, and served until 1991. He served as director of the chemistry unit at Biosphere 2, Arizona, operated by Columbia University from April 2001 until its termination in December 2003.

Professor Nakanishi's research covers isolation, structural and bioorganic studies of bioactive compounds, retinal proteins, interaction between ligands and neuroreceptors, development of various spectroscopic methods, especially circular dichroic spectroscopy.

Professor Nakanishi has published ca. 750 papers, and has authored, co-authored, or edited 9 books on spectroscopy and natural products. He has received awards from the USA, Japan, Bulgaria, China, the Czech Republic, Holland, Italy, Saudi Arabia, Sweden, Switzerland, Taiwan and the UK. A Nakanishi Prize of the American Chemical Society (ACS) and the Chemical Society of Japan (CSJ) started in 1996 and is awarded in alternate years in Japan and the USA.

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Regioselective cross-coupling reactions of multiple halogenated nitrogen-, oxygen-, and sulfur-containing heterocycles

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Contents

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1. Introduction and scope

Multiple carbon-substituted heterocycles belong to the most important organic compounds both in view of their mere production quantity and of their economic importance.[1] They are widespread in nature and many of them show interesting biological activities. The synthetic approaches towards multiple substituted heterocycles can be crudely divided into two categories. The first approach aims at a construction of the heterocyclic core after the substituents have been installed and properly functionalised. As an illustration of this approach, the key step in Marshall's synthesis of (−)-deoxypukalide[2] is shown in Figure 1 (TBDPS = *tert*-butyldiphenylsilyl). The 2,3,5-trisubstituted furan **2** was obtained by cyclisation of precursor **1** which contains the substituents essential to the further progress of the synthesis.

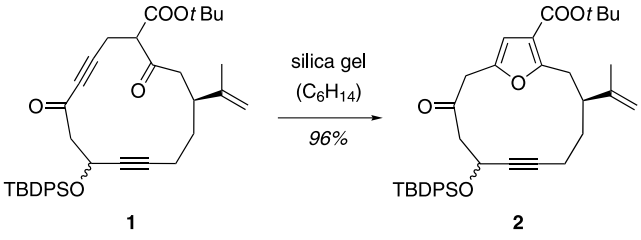


Figure 1. Key step in Marshall's synthesis of (−)-deoxypukalide.

The second approach is based on a preformed heterocycle to which carbon substituents are attached in successive order. This approach includes for example traditional aromatic substitution chemistry, directed metalation methods as well as halogen–metal exchange reactions. In this review we will focus on cross-coupling reactions[3,4] that allow for the formation of carbon-heterocycle bonds by selective displacement of halogen atoms. To be more precise only reactions are covered in which a selectivity was achieved for one of two or more identical halogen atoms. The definition excludes a coverage of the above-mentioned methods, of all transition-metal catalysed processes which form other but carbon–carbon bonds, and of reactions in which one of two different halogen atoms (e.g. I vs. Br) is substituted. Concerning the heterocycles included, we have made an attempt to comprehensively cover all multiple halogenated heterocycles containing nitrogen, oxygen and sulfur with $(4n+2)\pi$ electrons, for which regioselective cross-coupling reactions have been described. Typical substrates **3–6** are shown in Figure 2.

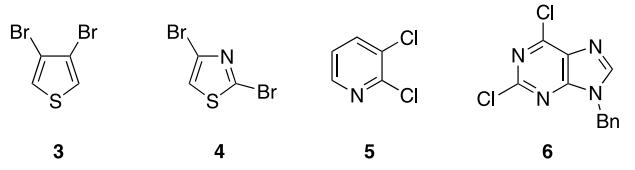


Figure 2. Typical heterocycles **3–6**, cross-coupling reactions of which are treated in this review.

In order to keep the length of this review within a reasonable limit, we have decided not to include cross-coupling reactions on lactams and lactones, although a lot of interesting work has been and is currently being done in this area.[5] We apologize for this limitation and we also apologize to all colleagues for any other omission. The literature was covered up to mid-2004. As a final remark, we are aware that the term 'regioselectivity' might not be considered fully correct based on previous definitions[6] and that the term 'site selectivity' might be more appropriate. Still, it has become common usage to describe the reactions as regioselective rather than calling them site selective.

2. Mechanistic considerations

A short look at the mechanistic picture for a typical cross-coupling reaction[3,7] (Fig. 3, X = I, Br, Cl) reveals three key steps in which a differentiation in favour of a certain position can be achieved. Although the mechanism is by far more complex than shown in Figure 3, a few simple considerations are useful to understand the regioselectivity of many cross-coupling reactions.

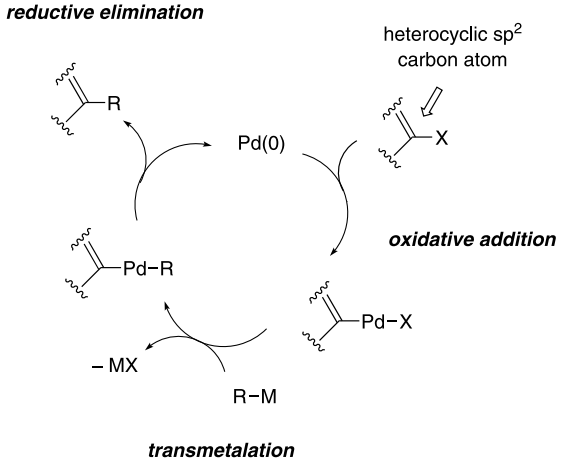


Figure 3. Mechanistic scheme for a Pd(0)-catalysed cross-coupling reaction (stereochemistry and ligands omitted).

A trivial argument is based on statistics. If the reaction can occur at two positions and if both positions show exactly identical reactivity, 1 equiv of reagent should give a 1:2:1 ratio of unreacted, monosubstituted, and disubstituted product. The yield for the 'regioselectively' obtained, monosubstituted product is 50% at best if both positions are chemically identical. If the positions are chemically different (but identical in reactivity) two products are obtained in a maximum yield of 25%. Any yield higher than the expected statistical yield clearly indicates a difference of reactivity. In many instances, this difference is due to the different electrophilicity of the carbon atoms at the heterocycle. In the oxidative addition step (Fig. 3), Pd(0) acts as a nucleophile and will preferentially attack the most electron-deficient position. Cross-coupling reactions for which the oxidative addition is rate determining, i.e. Sonogashira cross-coupling (vide infra), often show a high preference in favour of the most electrophilic position. The selectivity pattern follows the pattern for a nucleophilic aromatic substitution. The comparison given in Figure 4 illustrates the similarity in selectivity for both reactions. The nucleophilic substitution occurred at the acceptor-substituted 2,3-dibromofuran **7** at position C-2 to yield product **8**

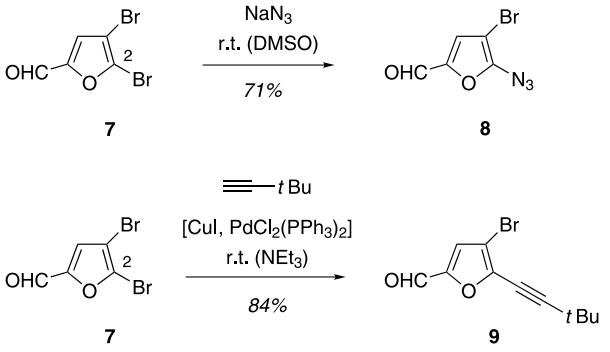


Figure 4. Comparison between a nucleophilic substitution reaction at 2,3-dibromofuran **7** and its regioselective Sonogashira cross-coupling reaction.

(Fig. 4).[8] Likewise, the same 2,3-dibromofuran **7** underwent a highly regioselective Sonogashira cross-coupling reaction to furnish 3-bromofuran **9**.[9] Even cross-coupling reactions which proceed by a fast oxidative addition can exhibit similar selectivities if the subsequent steps (transmetalation, reductive elimination) do not counteract the selectivity in the first step.

The oxidative addition step can be facilitated by a coordination of Pd(0) (or any other transition metal used as the catalyst) to a heteroatom. If this is the case, the reaction occurs in *ortho*-position to this heteroatom substituent or to the corresponding heteroatom within the heterocycle. With respect to the latter case, the basic nitrogen atom in nitrogen-containing heterocycles has often been invoked as a potential coordination site.

Although ligands have been omitted in Figure 3, it should be understood that steric parameters have a strong influence on the outcome of a heterocyclic cross-coupling reaction. The oxidative addition and the transmetalation step require space around the reacting metal centre. In an electronically comparable situation, a preference in favour of the more easily accessible position is expected and often found. Carbon substituents exceed halogen atoms in size (A values:[10] Cl: 0.53–0.64, Br: 0.48–0.67, I: 0.47–0.61; compare, for example, CH_3: 1.74). If there are two chemically identical adjacent positions in a heterocycle which can undergo cross-coupling reactions (i.e. in thiophene **3**, Fig. 2), the monosubstitution product will react significantly more slowly for steric reasons.

3. Cross-coupling reactions

This review addresses not only the expert in the field but also readers who are not so familiar with cross-coupling chemistry. We consider it therefore appropriate to say a few words about the individual cross-coupling reactions, which will be frequently mentioned in this review. Typical experimental procedures can be found in the references given in the individual sections or in the monographs mentioned above.[3]

3.1. Kumada cross-coupling

The cross-coupling of organomagnesium compounds with aryl halides was independently discovered by Kumada et al. and Corriu et al. in 1972.[11] This date marks the beginning of cross-coupling chemistry, as this cross-coupling reaction was the first to be reported. The reaction is normally conducted with the Grignard compound and the corresponding aryl halide in the presence of either a Ni catalyst, e.g. $NiCl_2$(dppp) (dppp = 1,3-bis(diphenyl-phosphino)-propane), or, less frequently, a Pd catalyst employing diethyl ether as the solvent.[12] An advantage of the reaction is that it proceeds readily, even at low temperature. A disadvantage is the limited functional group compatibility of Grignard reagents.

3.2. Negishi cross-coupling

In this review, Pd-catalysed reactions of organozinc reagents RZnX with hetaryl halides will be treated under this name.[13] The organozinc reagent can be either prepared from the corresponding halide RX by reductive metalation[14] or from other organometal compounds, often RLi, by transmetalation. The solvent for the transmetalation is diethyl ether or THF and the cross-coupling reaction is also often conducted in these solvents. $PdCl_2(PPh_3)_2$ or $PdCl_2$(dppf) (dppf = 1,1′-bis(diphenyl-phosphino)ferrocene) are commonly used catalysts.[15] The relatively high functional group tolerance of zinc compounds is an advantage. The cross-coupling normally occurs at room temperature or slightly above. Higher reaction temperatures can lead to degradation of the zinc compound.

3.3. Sonogashira cross-coupling

The Sonogashira protocol is the most frequently used method to affect the alkynylation of an aryl halide. The procedure has not changed much since the original report was published in 1975.[16] Alkynes undergo the cross-coupling reaction with aryl- and hetaryl halides in the presence of CuI and $PdCl_2(PPh_3)_2$ as catalysts and in an amine (e.g. NEt_2H, pyrrolidine, NEt_3) as the solvent.[17] The reaction is normally conducted at room temperature. THF has been recommended as a solvent if an excess amine is to be avoided.[18]

3.4. Stille cross-coupling

The cross-coupling reaction of stannanes and aryl halides (and other electrophiles) was extensively studied by the late J.K. Stille and was named after him.[19] The first Pd-catalysed reaction of a stannane and a carbon electrophile was an acylation.[20] The Stille cross-coupling requires a higher temperature to facilitate the transmetalation step from the weakly nucleophilic stannane to the intermediate arylpalladium halide (Fig. 3). A typically used inexpensive catalyst is $Pd(PPh_3)_4$.[21] Typical solvents include THF, toluene or DMF.

3.5. Suzuki cross-coupling

The name Suzuki cross-coupling or Suzuki–Miyaura cross-coupling refers to the cross-coupling of organoboron compounds and carbon electrophiles R^1X.[22] In this review, aryl halides or, more specifically, hetaryl halides are the carbon electrophiles to be discussed. The broad availability

of organoboron compounds and a high functional group tolerance make the Suzuki cross-coupling particularly attractive. The key to the success of the reaction is the addition of a base, e.g. NaOH, NaOEt, KOH, or CsOH, which presumably activates the weakly nucleophilic boranes, borinates, or boronates for the transmetalation step. Nonetheless, high temperatures (80–110 °C) are often required, with $Pd(PPh_3)_4$ as a typical catalyst and benzene/H_2O or toluene/H_2O as typical solvent systems.[23]

In the following sections, we will discuss the individual reactions which occur at a given heterocycle. They are arranged according to the heterocyclic core, at which the reaction takes place. In the figures, particular emphasis has been given to sequences of reactions in which two or more cross-coupling reactions were combined to achieve a selective multiple substitution.

4. Five-membered ring heterocycles and their benzoderivatives

Multiple halogenated thiophenes, furans, thiazoles, and imidazoles have been most frequently employed in regioselective cross-coupling reactions. Since the benzoderivatives often show selectivity patterns similar to those of the monocyclic compounds, they are discussed directly after the parent heterocycle.

4.1. Thiophenes

Interest in the synthesis of thiophenes stems to a large extent from their use in materials science and in medicinal chemistry, while naturally occurring thiophenes are rare. Many examples of regioselective cross-coupling have been described. Indeed, due to the easy availability of multiple halogenated thiophenes, but also due to the high stability of the thiophene core, multiple substituted thiophenes represent good targets for cross-coupling chemistry. Only pyridines have been prepared as extensively as thiophenes by regioselective cross-coupling reactions. As stated above, naturally occurring thiophenes are rare and applications in natural product synthesis are therefore not known.

In thiophenes, there are two electronically different positions, i.e. the 2(5)- and the 3(4)-position. Based on our initial considerations (Section 2), a selectivity for the cross-coupling of 2,3-dihalo- and 2,4-dihalothiophenes can be expected and was indeed frequently observed (vide infra). For symmetrical 3,4-dihalothiophenes, the increased size of the introduced substituent can cause a differentiation, whereas, for symmetrical 2,5-dihalothiophenes, a general selectivity mode is not apparent.

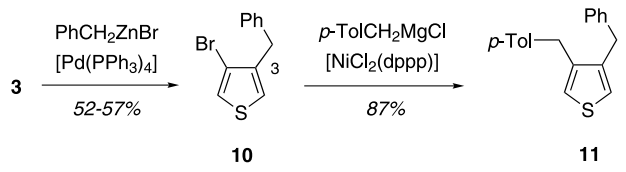


Figure 5. Synthesis of the 3,4-disubstituted thiophene **11** by successive cross-coupling reactions starting from 3,4-dibromothiophene (**3**).

One of the earliest regioselective cross-coupling reactions was described by Kumada et al. in 1980 (Fig. 5). 3,4-Dibromothiophene (**3**) underwent a regioselective reaction at the 3(4)-position with benzylzinc bromide to yield the monobromothiophene **10** which was further converted into the unsymmetrically substituted thiophene **11** by a Kumada cross-coupling (*p*-Tol = *para*-tolyl).[24]

Similar selectivities for the first cross-coupling step were observed in the reaction of 3,4-dibromothiophene (**3**) with an alkynylzinc reagent,[25] with arylboronic acids,[26] and with trimethylsilylacetylene (Sonogashira cross-coupling).[27] Treatment of **3** with 4 equiv of 3-thienylmagnesium bromide in the presence of $PdCl_2$(dppf) led mainly to disubstitution (50% yield).[28] On the contrary to this observation, the Stille reaction of 2-trimethyl-stannylthiazole with 3,4-diiodo-2,5-dimethyl-thiophene completely stopped after the monosubstitution was complete. A disubstitution could not be achieved under the reaction conditions.[29] The results obtained with 3,4-dibromothiophene (**3**) are in line with what has been said in Section 2 about a regioselectivity based on steric reasons. The carbon substituent in the 3-position retards the oxidative addition and transmetalation step at the adjacent 4-position. The strategy is successful unless highly reactive reagent combinations are used.

In 2,5-dihalo-substituted thiophenes, there is rarely a good differentiation between the two positions, i.e. a second cross-coupling can occur readily. The product distribution is often governed by statistics and symmetrical disubstituted products have been observed as major by-products. A high selectivity in favour of a monosubstitution is only to be expected if the newly introduced substituent deactivates the thiophene by increasing its electron density. Sonogashira cross-coupling reactions have frequently been used to install an alkynyl group at the 2(5)-position of thiophenes. Figure 6 (THP = 2-tetrahydropyranyl) shows a typical example in which 2,5-diiodothiophene (**12**) was employed as the substrate. The monosubstitution product **13** was isolated in 50% yield and was further transformed into the bithiophene **14** by a Stille reaction.[30]

Further examples of similar Sonogashira cross-coupling reactions at diiodothiophene **12** have been described.[31] They all proceeded in yields of 40–60%. Starting from

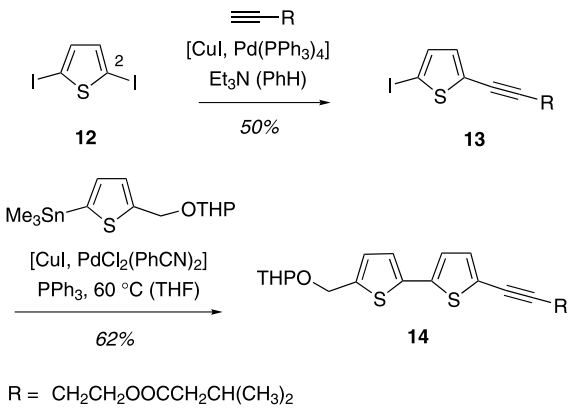


Figure 6. Synthesis of the 2,5-disubstituted thiophene **14** by successive cross-coupling reactions starting from 2,5-diiodothiophene (**12**).

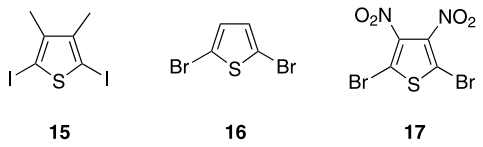


Figure 7. Structures of the 2,5-dihalothiophenes **15**–**17**.

2,5-diiodo-3,4-dimethyl-thiophene (**15**), a monoalkynyl-thiophene was prepared in an analogous fashion (Fig. 7).[32] Sonogashira cross-coupling with 2,5-dibromothiophene (**16**) did not prove to be more selective than the reactions with diiodide **12**. Rose et al. reported a 35–45% yield for the monosubstitution product along with a 10–15% yield for the disubstitution product.[33] A moderate yield was reported for the Stille cross-coupling of the same compound with an alkenylstannane.[34] Negishi cross-coupling of 2-furylzinc chloride with **16** in the presence of $PdCl_2$(dppb) (dppb = 1,4-bis(diphenyl-phosphino)butane) proceeded in moderate yield (45%),[35] as did the reaction of **16** with a bithienyl-magnesium bromide in the presence of $PdCl_2$(dppf) (38%).[36] Slightly better yields were achieved in the reaction of dibromide **16** with 2-thienylmagnesium bromide (58% + 34% of the corresponding terthiophene)[37] and with a pyrimidineboronic acid (62%).[38] The latter cross-coupling was directed towards the synthesis of 5-(bromoaryl)-substituted uracils and uridines. An arylboronic acid on a solid support was successfully cross-coupled with dibromide **16** to yield a monobromothiophene, which was then converted into the corresponding lithio compound by bromine–lithium exchange.[39] A monosubstitution in a Suzuki cross-coupling was reported for a related 2,5-dibromothiophene[40] and for 2,2′-dibromo-5,5′-bithiophene.[41]

5-(5-Iodothien-2-yl)-2′-deoxyuridine was obtained by a cross-coupling of diiodide **12** with an appropriate stannane in 50% yield.[42] The Stille cross-coupling of a 2-thienyl-stannane and dibromide **17** was reported to provide the corresponding monothienyl-substituted product in low chemical yield (17%).[43]

Due to the higher electrophilicity of the 2(5)-position, any cross-coupling reactions in which 2(5),3(4)-di-, tri-, or tetrahalosubstituted thiophenes are employed as starting materials are expected to proceed with high regioselectivity. A typical example is shown in Figure 8. Tetraiodothiophene

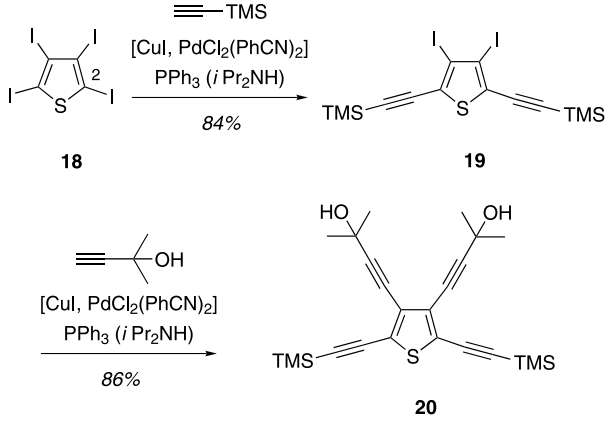


Figure 8. Synthesis of the tetrasubstituted thiophene **20** by successive cross-coupling reactions starting from tetraiodothiophene (**18**).

(**18**) reacted selectively in a Sonogashira cross-coupling with 2.2 equiv of trimethylsilyl-acetylene at the more electrophilic positions C-2 and C-5.[44] The dialkynyl substituted product **19** was obtained after 1 h at reflux. The first cross-coupling was succeeded by a second Sonogashira reaction which required under similar conditions (3 equiv alkyne) somewhat longer reaction times (reflux, 4 h). The tetrasubstituted thiophene **20** was obtained in very good overall yield.

A similar strategy based on the Sonogashira cross-coupling was applied to regioselective reactions of tetrabromothiophene[45] and of hexabromo-2,2′-bithiophene.[46] Not surprisingly, simpler dihalothiophenes such as 2,3-dibromothiophene (**21**) also reacted regioselectively in the Sonogashira reaction.[47] The latter compound has been extensively used in cross-coupling reactions. Figure 9 shows the typical behaviour of this compound and of its 2,4-dibromo analogue **23** in cross-coupling reactions. A high preference for a regioselective cross-coupling at the 2-position was recorded and the products **22** and **24** were obtained.[28]

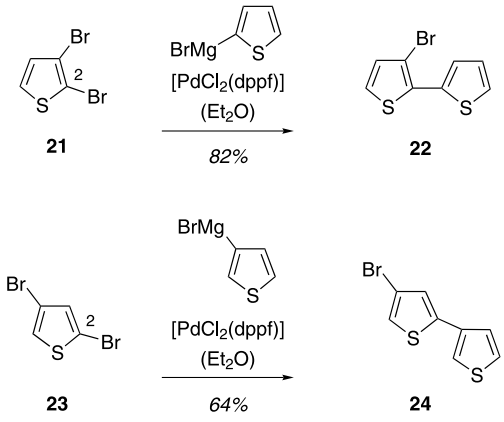


Figure 9. Regioselective Kumada cross-coupling of 2,3-dibromo- (**21**) and 2,4-dibromothiophene (**23**).

The same selectivity pattern was observed in Suzuki cross-coupling reactions of dibromide **21** which occurred with high regioselectivity at the 2-position.[48] The cross-coupling product **25** (Fig. 10) obtained from a Suzuki cross-coupling with phenylboronic acid was further converted into a 2,3-disubstituted thiophene **26** by a subsequent Stille reaction in the presence of $[Pd_2(dba)_3]P(tBu)_3$ (dba = dibenzylideneacetone).[47] In the same study, a regioselectivity optimisation of the Suzuki cross-coupling was conducted. Stille and Sonogashira reactions were reported to be more difficult to optimise. Regioselective Stille cross-coupling reactions of 2-furylstannanes and dibromide **21** were conducted with the stannane as the limiting agent (41–63% yield).[49]

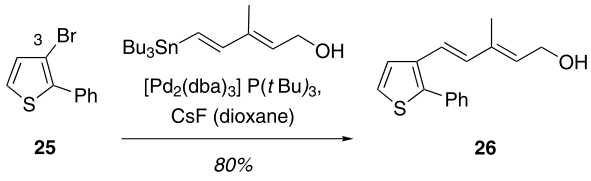
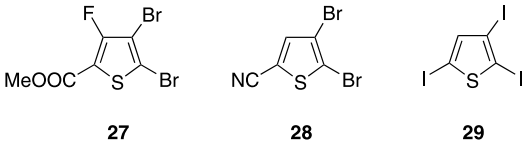


Figure 10. Construction of the 2,3-disubstituted thiophene **26** from Suzuki cross-coupling product **25**.

If the electrophilicity of the 2(5)-position is further enhanced by an electron-withdrawing substituent, the regioselectivity is even more pronounced. Suzuki cross-coupling of dibromide **27** (Fig. 11) with an arylboronic acid gave 83% of the desired substitution product in the 2-position and only 2% of its regioisomer.[50] A related 2,3-dibromothiophenealdehyde gave an 80% cross-coupling yield in the Suzuki cross-coupling with 4-fluoro-phenylboronic acid (1.1 equiv). The selectivity was 10:1 in favour of the monosubstitution product.[51] Dibromide **28** reacted in a similar fashion.[52] 2,3,5-Triiodothiophene (**29**) underwent a disubstitution in the 2- and 5-positions when treated with 2-thienylboronic acid in the presence of $Pd(PPh_3)_4$.[53]

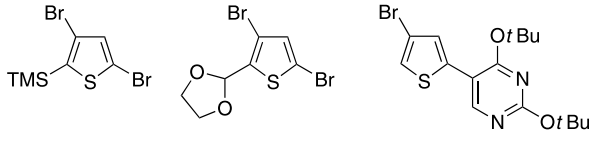


27 28 29

Figure 11. Structures of the thiophenes **27–29**.

Because of its slow selectivity-determining oxidative addition step the Negishi cross-coupling should be well suited for regioselective reactions on thiophenes. It is somewhat surprising to note that it has been rarely used in the thiophene series. Only 2,3-dibromothiophene (**21**) was converted regioselectively into 3-bromo-2-(2′-propenyl)-thiophene using the corresponding alkenylzinc chloride.[54]

What has been said about the selectivity with regard to the 2- versus 3-position in 2,3-dibromothiophenes is equally true for the preference 2- versus 4-position in 2,4-dibromothiophenes. One example has already been provided in Figure 9 (**23**→**24**). A similar selectivity was observed for the Kumada cross-coupling of a 2-thienylmagnesium bromide with **23**[55] and with 3,3′,5,5′-tetrabromo-2,2′-bithiophene.[56] Further examples include the regioselective Sonogashira cross-coupling reaction of dibromide **23**,[57] the Suzuki cross-coupling of **23**,[58] and the Stille reaction of dibromide **30** (Fig. 12) with a 2-thienylstannane.[59] The work by Irie et al. on dithienylethenes as photoswitches has established many regioselective reactions on bromothiophenes,[60] including among others the regioselective Suzuki cross-coupling of dibromide **31** with phenylboronic acid (55% yield).[60b] Another beautiful application of a regioselective Suzuki cross-coupling was provided by Gronowitz et al. who reported the formation of thiophene **32** from 2,4-dibromothiophene (**23**) in 76% yield.[38]

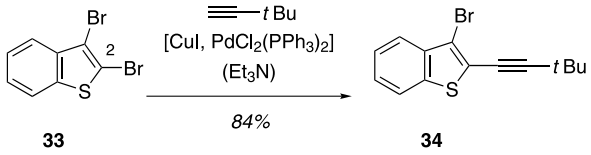


30 31 32

Figure 12. Structures of the thiophenes **30–32**.

4.2. Benzothiophenes

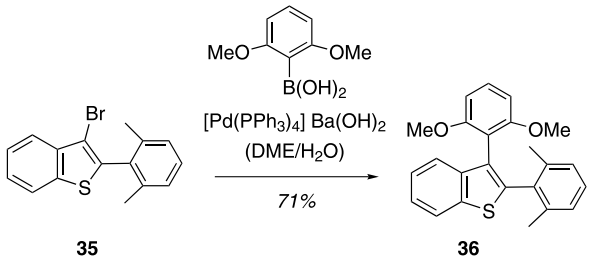
Benzothiophenes have been less extensively used in regioselective cross-coupling reactions than thiophenes. In all instances, 2,3-dibromobenzothiophene (**33**) served as an easily available starting material. Eberbach et al. performed a regioselective Sonogashira cross-coupling reaction, which proceeded exclusively at the more electron-deficient 2-position.[61] Figure 13 shows the reaction of *t*-butylacetylene with dibromide **33**, yielding the 3-bromothiophene **34**.



33 34

Figure 13. Regioselective Sonogashira cross-coupling at dibromobenzothiophene **33**.

Suzuki[62] and Stille[63] cross-coupling reactions have also been reported to occur selectively at the 2-position. Compound **35** (Fig. 14) obtained from dibromide **33** in 95% yield was further converted into the diarylbenzothiophene **36** by a second Suzuki cross-coupling using $Ba(OH)_2$ as the base (instead of Na_2CO_3 in the first Suzuki cross-coupling) and DME/H_2O (instead of DME/EtOH) at reflux.[62]



35 36

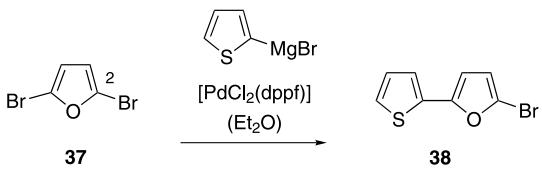
Figure 14. Synthesis of diarylbenzothiophene **36** from the Suzuki cross-coupling product **35**.

4.3. Furans

The low stability of furans in particular under aerobic and acidic conditions makes cross-coupling reactions more delicate and the product isolation more difficult than in the thiophene series. The selectivity pattern is similar to thiophenes as expected based on the similar electronic structure of the two heterocycles. Applications of regioselective cross-coupling reactions in the synthesis of naturally occurring furans are, as yet, rare.

Rossi et al. have used a regioselective approach to 2-thienyl-5-bromofuran (**38**) from 2,5-dibromofuran (**37**) in their research on the synthesis of heterocyclic bi- and triaryls (Fig. 15).[37a] The compound proved unstable, however, and a yield was not reported.

An attempted Suzuki cross-coupling of the dibromide **37** with 4-carboxybenzeneboronic acid in acetonitrile/H_2O was



37 38

Figure 15. Synthesis of 2-thienylfuran **38** from 2,5-dibromofuran (**37**).

sluggish and gave the substitution product in only 22% yield.[64] $Pd(PPh_3)_4$ was used as the catalyst and Na_2CO_3 as the base. The conversion of **37** into a pyrimidyl derivative by Suzuki cross-coupling was more successful. Reaction with the boronic acid **40** (Fig. 16) yielded the monosubstitution product (58%).[38] Indeed, as previously mentioned, several (bromohetaryl)-substituted uracils and uridines have been obtained from cross-coupling reactions of this boronic acid with hetaryl dibromides. 2,4-Dibromofuran (**39**) was converted selectively into the 4-bromofuran **41** in 86% yield (Fig. 16). The higher yield and better selectivity in the reaction of 2,4-dibromofuran (**39**) as compared to 2,5-dibromofuran (**37**) can be accounted for by the clear electronic difference of the two positions in the former compound.

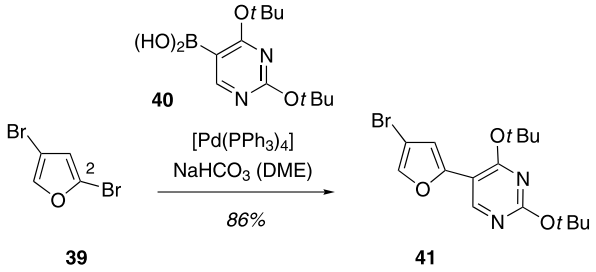


Figure 16. Regioselective Suzuki cross-coupling of boronic acid **40** with 2,4-dibromofuran (**39**).

Positions C-2 and C-3 in 2,3-dibromofuran are as easily differentiated as positions C-2 and C-4 in 2,4-dibromofuran (**39**). Indeed, regioselective Stille[9b] and Sonogashira[3b] cross-coupling reactions have been reported for this compound. 2,3-Dibromofuran is prepared by the decarboxylation of 2,3-dibromo-5-furancarboxylic acid. An access to 2,3-disubstituted furans is therefore also possible by selective cross-coupling reactions of the latter compound or its derivatives prior to decarboxylation. A simple example of this strategy is provided by the synthesis of rosefuran (**45**) from dibromide **42** (Fig. 17).[9b,65] Initial cross-coupling occurred at position C-2 to yield 3-bromofuran **43** which was further converted into the trisubstituted furan **44** by a second Stille cross-coupling. Saponification and decarboxylation completed the sequence.

The acceptor substituent renders the oxidation-sensitive furan skeleton more stable. In this respect, the cross-coupling of 2(5)-furancarboxylates and 2(5)-furfurals is

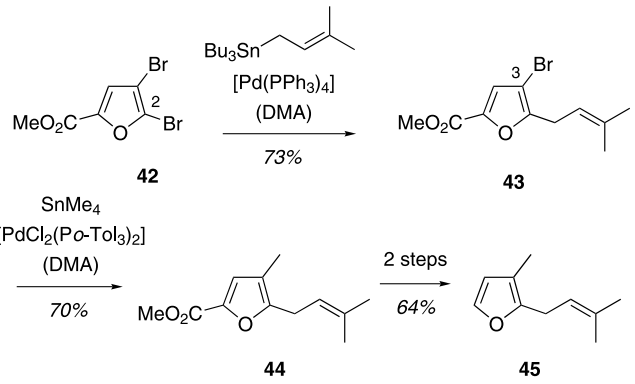


Figure 17. Synthesis of rosefuran (**45**) from dibromide **42**.

often straightforward. Needless to say, the formyl or alkoxycarbonyl substituent can be used for further functionalisation, as demonstrated by the synthesis of F_5 furan fatty acid (**48**) (Fig. 18).[9] Product **46**, which was selectively obtained by a Sonogashira cross-coupling from 2,3-dibromofurfural (**7**) (cf. Fig. 4), was elongated by a Wittig reaction. A second cross-coupling introduced the methyl group at carbon atom C-3, before hydrogenation and saponification of intermediate **47** gave the target compound. It is interesting to note that the cross-coupling at carbon atom C-3 leading to compound **47** was possible by a Negishi cross-coupling at room temperature, whereas the introduction of the methyl group into compound **43** required the use of $SnMe_4$ at 90 °C. The difference was attributed to the more confined steric situation in compound **43**, which contains a much bulkier substituent at carbon atom C-2.

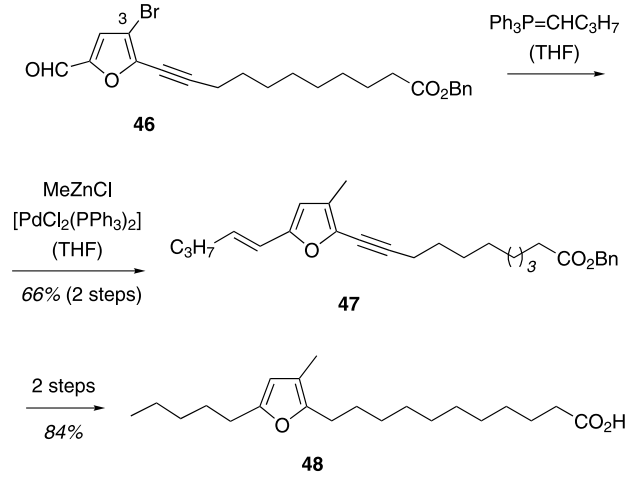


Figure 18. Synthesis of F_5 furan fatty acid (**48**).

4.4. Benzofurans

In benzofurans, as in benzothiophenes, the most reactive position towards attack by Pd(0) is the 2-position. Consequently, Sonogashira,[66] Negishi,[66] and Stille[67] cross-coupling reactions at 2,3-dibromo- and 2,6-dibromo-benzofurans occur selectively at C-2. Typical substrates (**49** and **50**) for these reactions are shown in Figure 19.

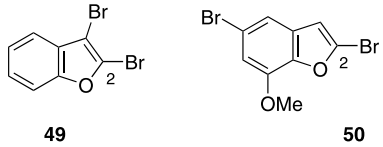


Figure 19. Typical substrates for a regioselective cross-coupling at carbon atom C-2 in benzofurans.

In connection with the synthesis of neolignan eupomatenoids, it was discovered that a three-fold sequential cross-coupling was possible in benzofurans (Fig. 20).[68] The sequence commenced with 2,3,5-tribromobenzofuran **51**, which underwent regioselective Negishi cross-coupling to yield dibromide **52**. The Kumada cross-coupling was the method of choice to differentiate between the sterically different, but electronically similar, positions C-3 and C-5. A 1-prop-1-enyl group was established by this means to yield the monobromide **53**. Finally, the least reactive

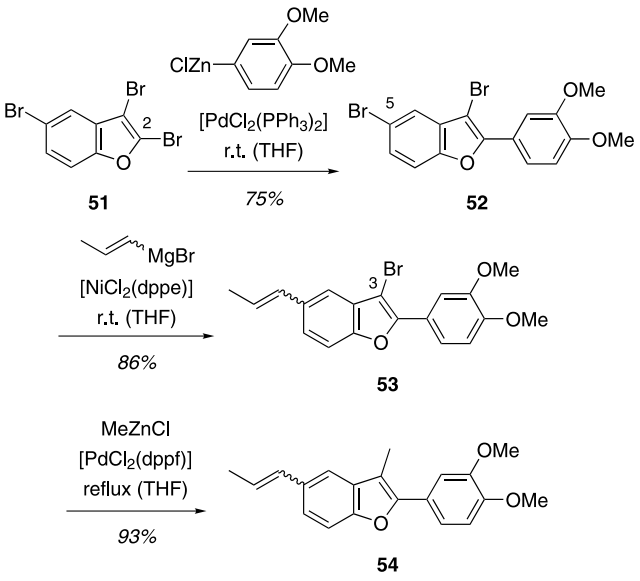


Figure 20. Synthesis of eupomatenoid 4 ((*E*)-**54**) from 2,3,5-tribromobenzofuran (**51**).

position at carbon atom C-3 was addressed in a Negishi cross-coupling with an excess of methylzinc chloride. Quantitative isomerisation of the double bond (I_2, *hν*, THF) in compounds **54** led exclusively to the more stable naturally occurring (*E*)-configurated eupomatenoid 4 ((*E*)-**54**) and completed the reaction sequence. Several eupomatenoids (eupomatenoids 3, 5, 6 and 15) were synthesised using this approach in good overall yields of 29–54%.

4.5. Pyrroles

A differentiation of two chemically identical positions has been achieved in the Suzuki cross-coupling of a pyrrole-3,4-ditriflate **55** (Fig. 21).[69] The heterocycle is activated towards cross-coupling by the two methoxycarbonyl groups at carbon atoms C-2 and C-5 which additionally render the pyrrole a higher stability. The high selectivity for monosubstitution can be explained by steric reasons. A further cross-coupling at C-4 in pyrrole **56** is disfavoured, due to the large aryl substituent introduced at carbon atom C-3.

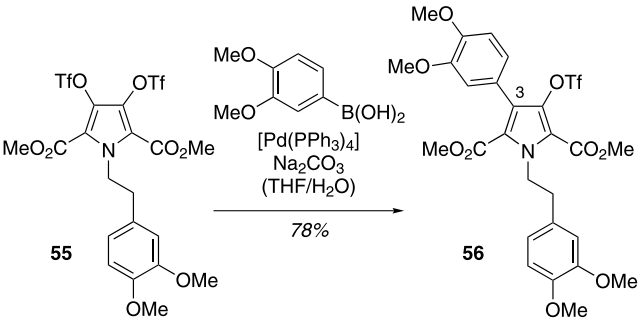


Figure 21. Regioselective Suzuki cross-coupling of an arylboronic acid with ditriflate **55**.

4.6. Indoles

Regioselective cross-coupling reactions of indoles and imidazoles (see Section 4.11) were closely studied by Ohta et al. in their work on the total synthesis of nortopsentins. The regioselectivity for Suzuki cross-coupling reactions on the *N*-protected (TBDMS = *tert*-butyldimethylsilyl) 2,6-dibromoindole (**57**) was found to be in favour of the 6-position (Fig. 22). Several arylboronic acids were used as nucleophiles, providing the 6-substituted products, such as compound **58**, in 52–78% yield.[70]

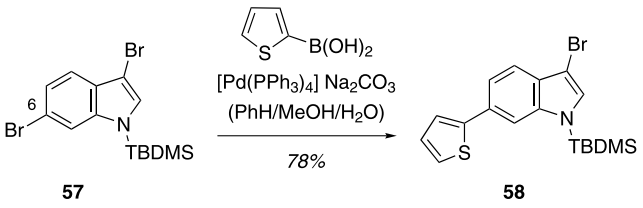


Figure 22. Regioselective cross-coupling on indole **57**.

Interestingly, the bromine–lithium exchange (*t*BuLi, −78 °C, THF) on compound **57** exhibited opposite regioselectivity and occurred selectively at the 3-position. Similar observations were made in 3,5-dibromo-benzofurans, such as **52**.[66]

4.7. 1,2-Thiazoles (isothiazoles)

The preferred position for cross-coupling on di- or trihalogenated isothiazoles is the 5-position. In the Sonogashira cross-coupling reaction with phenylacetylene, the 4,5-diiodoisothiazole **59** gave 4-iodoisothiazole **60** as the only cross-coupling product (Fig. 23).[71] The corresponding 5-deiodinated isothiazole was observed as a major by-product. Compound **60** underwent a second cross-coupling at carbon atom C-4 to yield the dialkynylisothiazole **61**.

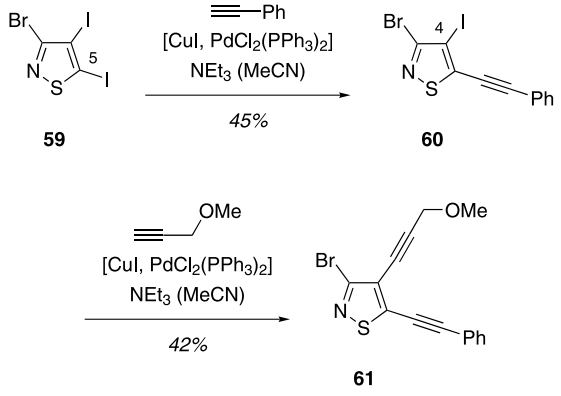


Figure 23. Sequential cross-coupling on diiodoisothiazole **59**.

3,4,5-Tribromoisothiazole (**62**) (Fig. 24) reacted similarly, yielding selectively 5-alkynylisothiazoles as products (20–56% yield). In the latter case, no further Sonogashira cross-coupling could be achieved in the 3- or 4-position.

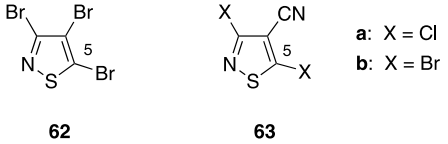


Figure 24. Isothiazole substrates for a regioselective cross-coupling.

A differentiation between the 3- and 5-position in isothiazoles was observed upon Suzuki cross-coupling of various arylboronic acids and dihalides **63**.[72]

The preference of compound **59**, **62**, and **63** to react in the 5-position selectively is in agreement with the facile nucleophilic substitution occurring in the 5-position of isothiazoles. As an example, nucleophilic substitution reactions of compound **63a** with O-, N-, and S-nucleophiles have been reported to proceed exclusively at C-5.[73]

4.8. 1,3-Thiazoles (thiazoles)

The occurrence of multiple substituted thiazoles in natural products has spurred interest in cross-coupling reactions on preformed thiazoles. The reactions can serve as an attractive alternative to the classical Hantzsch reaction commonly used for thiazole formation. The preferred position for a regioselective cross-coupling is the 2-position. Both 2,5-dibromothiazole (**64**) and 2,4-dibromothiazole (**4**) reacted selectively, as shown in Figure 25. Bromothiazoles **65** and **66** were obtained as the products in excellent yields.

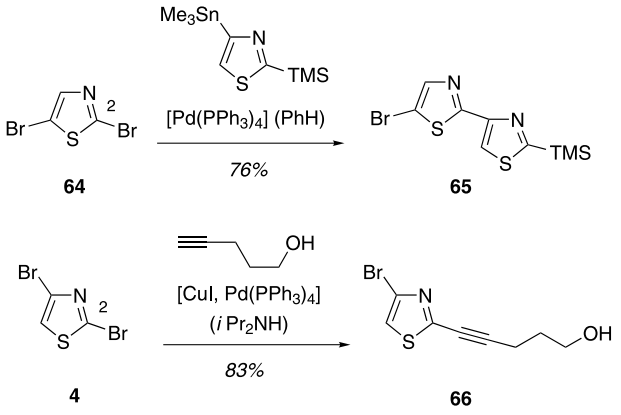


Figure 25. Regioselective cross-coupling reaction on the dibromothiazoles **64** and **4**.

The first example in Figure 25 was described by Dondoni et al. who aimed at the synthesis of bi- and terthiazoles.[74] The second example, showing a Sonogashira cross-coupling, was found by Nicolaou et al. in connection with the synthesis of epothilone and its analogues.[75,76] 2,4-Dibromothiazole (**4**) has also been successfully used in regioselective Suzuki[38] and Negishi cross-coupling reactions.[77] The Negishi reaction was a key step in the synthesis of the endothelin-converting enzyme inhibitor WS 75624 A[78] and in the synthesis of a thiazolylpeptide fragment.[79] The remaining 4-position in 4-bromothiazoles can be further used for cross-coupling chemistry as shown in Figure 26.[80] Regioselective Negishi cross-coupling delivered 4-bromothiazole **67**, which was converted into a nucleophile by bromine–lithium exchange and transmetalation to zinc. The 4-thiazolylzinc chloride underwent another cross-coupling with another equivalent of 2,4-dibromothiazole (**4**) to yield the bithiazole **68**, which bears a residual bromine atom at the 4-position. Subsequent cross-coupling was possible either with stannanes or with boronic acids. The coupling depicted is a Suzuki cross-coupling, which afforded an immediate precursor **69** to the natural product, cystothiazole E.[80]

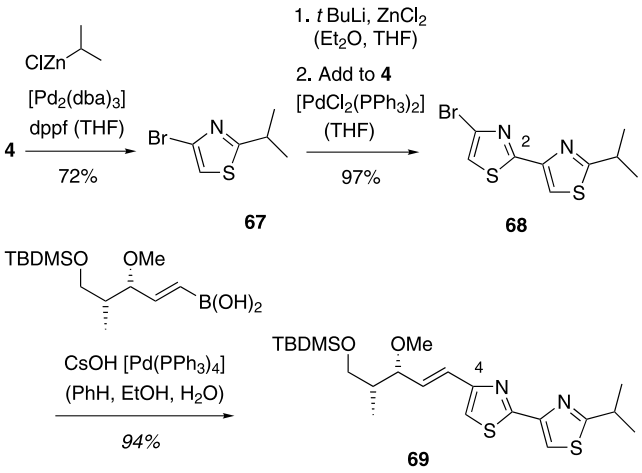


Figure 26. Sequential cross-coupling reactions used in the synthesis of the naturally occurring bithiazole, cystothiazole E.

A similar strategy was used for the synthesis of 2,4-diarylthiazoles[77a] and for other 2,4-bithiazoles.[77b] Generally speaking, the functionalisation of 2,4-dibromothiazole (**4**) is best achieved by conducting first a regioselective Sonogashira or Negishi cross-coupling at the 2-position and, subsequently, a Stille or Suzuki cross-coupling at carbon atom C-4. A related strategy was reported by Panek et al. for the corresponding 2,4-ditriflate.[81]

4.9. Benzothiazoles

The facile displacement of halogen atoms at the 2-position in thiazoles indicates the same reactivity pattern in the benzoderivative. Any cross-coupling of a 2,*n*-dihalobenzothiazole should occur preferentially at carbon atom C-2. This expectation was corroborated by the reaction shown in Figure 27 in which an excess of hexamethyldistannane was used to mediate the coupling between dichloride **70** and triflate **71**.[82] It is likely that the more reactive triflate was first converted into the stannane which then underwent a 'normal' Stille cross-coupling to yield regioselectively benzothiazole **72**.

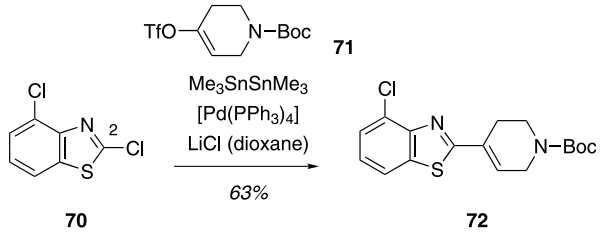


Figure 27. Regioselective tin-mediated coupling of triflate **71** with 2,4-dichlorobenzothiazole (**70**).

4.10. 1,3-Oxazoles (oxazoles)

Multiple halogenated oxazoles are not as easily accessible as the corresponding thiazoles. Studies regarding their cross-coupling reactions are rare. A 2,5-dibromooxazole was reported to yield a complex product mixture under standard Suzuki conditions ($PhB(OH)_2$, $Pd(PPh_3)_4$, K_2CO_3 in PhMe at 90 °C), with mono- and disubstituted coupled products as well as debrominated oxazoles being detected.[83]

4.11. Imidazoles

As mentioned previously (Section 4.6), synthetic studies by Ohta et al. have been devoted to regioselective cross-coupling reactions of imidazoles. They revealed a selectivity in cross-coupling reactions for the 2-position both in 2,4,5-tribromo-[70,84] and 2,4,5-triiodoimidazoles.[70] A second cross-coupling was observed preferentially at the 5-position, as shown in Figure 28. Suzuki cross-coupling of 1 equiv of phenylboronic acid with the *N*-MOM-protected (MOM=methoxymethyl) imidazole **73** gave the dibromide **74** in almost quantitative yield. A second Suzuki cross-coupling occurred at carbon atom C-5 to produce the imidazole **75**. For the initial substitution, a Negishi cross-coupling proved also suitable, giving product **74** in 45% yield together with 9% of reductively dimerised starting material. Similar successive Suzuki cross-coupling reactions were used by Ravesz et al. for the synthesis of potential kinase inhibitors and anti-inflammatory drugs.[85]

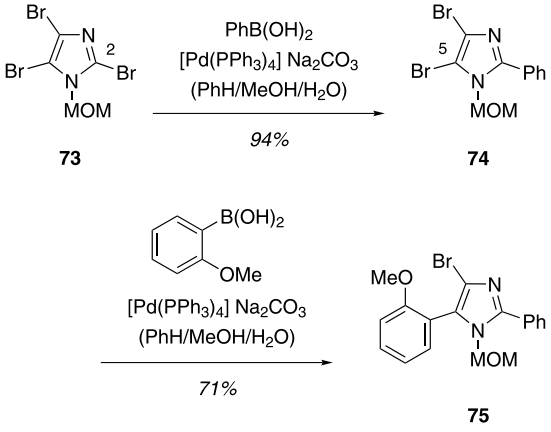


Figure 28. Regioselective Suzuki cross-couplings on tribromide **73**.

Another study by Ravesz et al.[86] confirmed the preference for cross-couplings at C-5 versus C-4 earlier established by Ohta et al. for an *N*-SEM-protected 4,5-dibromoimidazole (SEM=trimethylsilyl-ethyloxymethyl).[87] In the example shown in Figure 29, the dibromide **76** was first converted into imidazole **77** by a Stille cross-coupling and this was further transformed into the triarylimidazole **78** by a Suzuki reaction.[86]

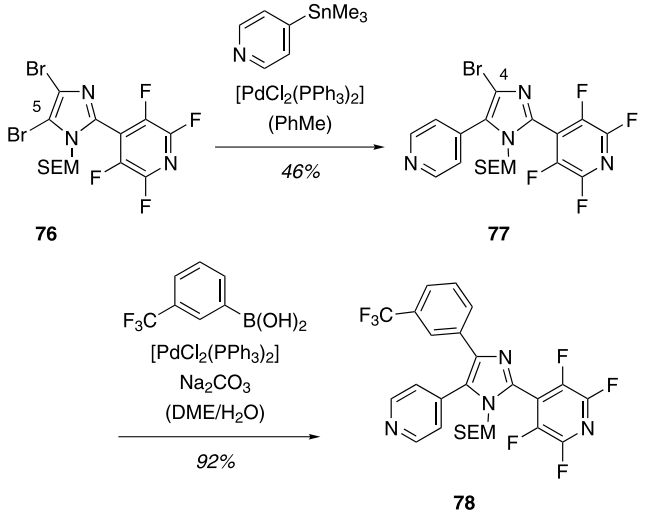


Figure 29. Regioselective sequential cross-coupling reactions as an approach to potential p38 MAP kinase inhibitors, such as **78**.

Hazeltine and Wang studied the cross-coupling reactions of *N*-benzyl-2,4-dibromo-5-methylimidazole.[88] They found a Stille cross-coupling to be better suited than the Suzuki cross-coupling to establish a high regioselectivitiy in favour of C-2. Whereas 1 equiv of phenylboronic acid ($Pd(PPh_3)_4$, Na_2CO_3 in toluene/H_2O/EtOH) gave 43% of the disubstitution product, 1 equiv of phenyltrimethylstannane ($PdCl_2(PPh_3)_2$ in toluene) resulted in monosubstitution (58% yield).

5. Six-membered ring heterocycles and their benzoderivatives

5.1. Pyridines

The area of regioselective pyridine substitution has been a playground for many synthetic chemists interested in cross-coupling chemistry. As in the thiophene section, the discussion of the individual examples will start with symmetrical substrates, in which a substitution took place at one out of two identical positions.

Typical 2,6-dihalopyridines **79**–**82**, for which a monosubstitution was achieved in cross-coupling reactions, are shown in Figure 30. Dibromide **79** has been a particularly popular starting material.

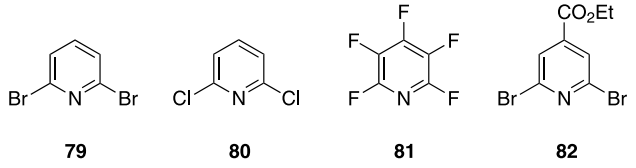


Figure 30. 2,6-Dihalopyridines as substrates for regioselective cross-coupling.

Sonogashira cross-coupling with pyridine **79** proceeded well in several examples.[31b,89] As expected, an excess of acetylene facilitated double substitution and product mixtures were obtained. Figure 31 shows a well-behaved Sonogashira reaction of a highly functionalised alkyne with dibromide **79** to the bromopyridine **83**.[31b] Similar observations have been made with **79** in Kumada,[90] Negishi,[91] Stille,[92] and Suzuki[38,93] cross-coupling reactions. The yields often exceeded 50%, which is due to a reduced reactivity of the substitution product. The reactivity difference may be of electronic origin, i.e. if an electron-donating substituent was introduced, or it may be associated with a pre-coordination of the transition metal to the pyridine. The latter process is retarded by a large substituent in the 2-position. A regioselective Kumada cross-coupling reaction was reported for compound **80**.[35] A regioselective Ni(0)-catalysed Stille cross-coupling was observed in the 2-position of pentafluoropyridine (**81**).[94] Dibromide **82** was shown to undergo two successive cross-coupling reactions.[95] In the first step, position C-2 was addressed using 1 equiv of stannane to yield the bipyridine **84**, which was

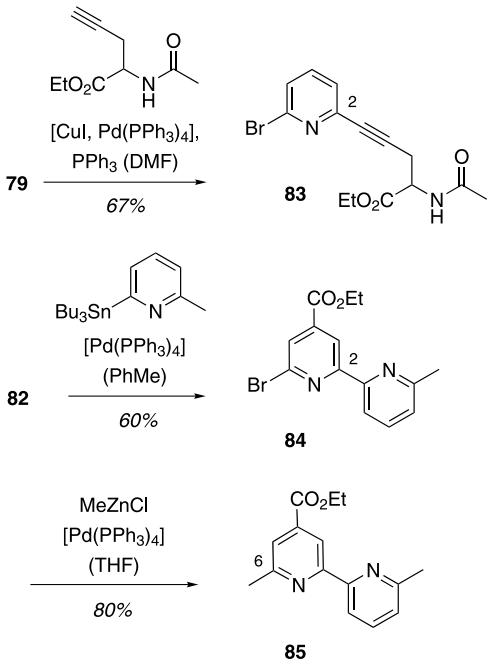


Figure 31. Examples of regioselective cross-coupling reactions on 2,6-dihalopyridines.

further methylated in a Negishi cross-coupling with methylzinc chloride to yield the final product **85**.

In a recent study, unsymmetrical 2,6-dihalopyridines were examined with regard to regioselective Suzuki cross-coupling reactions.[96] It was found that the preference for monosubstitution changes upon changing the catalyst. Substrate **86** reacted with a distinct preference for the sterically more accessible 6-position (to yield compound **87**), as compared to the 2-position (regioisomeric ratio r.r.= 5:1) if $Pd(PPh_3)_4$ was used as the catalyst (Fig. 32). The same compound **86** gave with the pre-catalyst PXPd2 ($Pd_2Cl_4(PtBu_2Cl)_2$) or with $PdCl_2$(dppf) preferentially the 2-substitution product (r.r.=2:1 or 2.9:1, respectively). It was argued that a chelation is responsible for the observed effect and that the chelation is enhanced if coordinatively unsaturated Pd(0) intermediates are generated. The best results in favour of the 2-substitution were recorded with dichloride **88** which afforded monosubstitution products

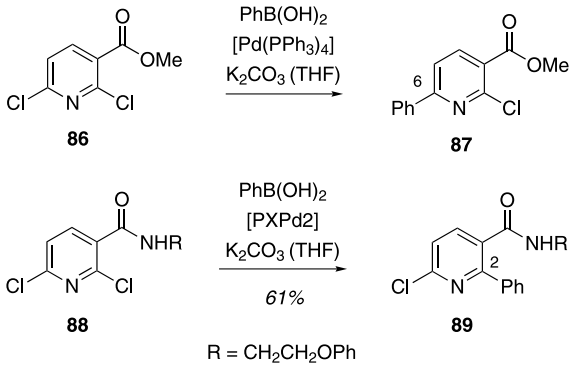


Figure 32. Choice of catalyst as regioselectivity-determining factor in Suzuki cross-coupling reactions of 2,6-dichloropyridine-3-carboxylic acid derivatives.

such as **89** in yields of 51–61% and with regioselectivities of 4:1 to 15:1.

3,5-Dihalopyridines have been less frequently used than the 2,6-dihalo compounds. A modification of the Sonogashira reaction, in which the copper acetylide was generated from the corresponding trimethylsilane, was used to establish the first C–C bond at carbon atom C-3 of 3,5-dibromopyridine (**90**).[97] Bromopyridine **91** was then converted into the 3,5-disubstituted product **92** (Fig. 33) By analogy with the monosubstitution **90**→**91**, Negishi[98] and Kumada[99] cross-coupling reactions have been conducted with the dibromide **90**.

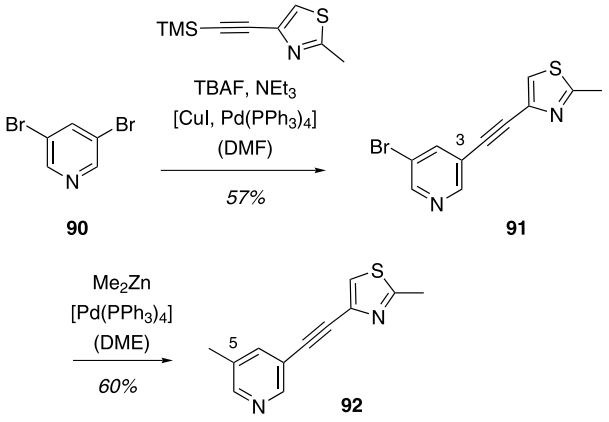


Figure 33. Sequential cross-coupling on 3,5-dibromopyridine (**90**).

The regioselectivity of cross-coupling reactions on 2,4-dihalopyridines was studied for dichloropyridine 93[100] and for 3,5-difluoro-2,4,6-tribromopyridine (**95**).[101] In the former case,[100] a Sonogashira cross-coupling delivered exclusively the 2-substitution product **94** (Fig. 34).

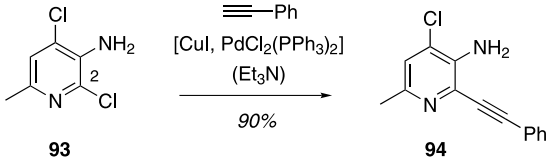


Figure 34. Regioselective Sonogashira cross-coupling on 2,4-dichloropyridine **93**.

In the latter case,[101] both Suzuki and Sonogashira cross-coupling resulted in a disubstitution at the 2- and the 6-position with 2 equiv of the reagent. With an excess reagent, the 4-position was also attacked. The regioselectivity was ascribed to a directing role by the ring nitrogen atom. Nucleophilic substitution reactions at 3,5-difluoro-2,4,6-tribromopyridine (**95**) were shown to occur at C-4 with soft and at C-3/C-5 with hard nucleophiles (Fig. 35).

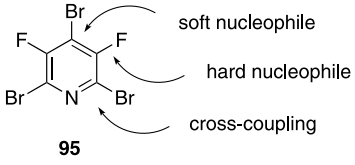


Figure 35. Positions of nucleophilic attack at 3,5-difluoro-2,4,6-tribromopyridine (**95**).

2,3-Dihalo- and 2,5-dihalopyridines are well behaved substrates which allow a perfect regioselectivity in many cross-coupling reactions. The more electrophilic 2-position is preferentially substituted and Figure 36 provides an example.[102] 2,3-Dichloropyridine (**5**) underwent an initial cross-coupling at carbon atom C-2 to yield compound **96**. This intermediate was first converted into dichlorobipyridine **97**, which was subsequently reacted with an excess of a 3-pyridylborane. The cross-coupling allowed for simultaneous substitution at the 3- and at the 2′-position to yield the quaterpyridine **98**.

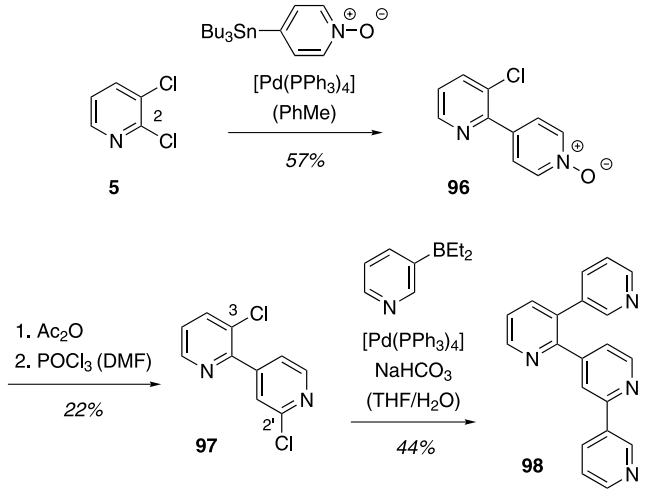


Figure 36. Synthesis of quaterpyridine **98** from 2,3-dichloropyridine (**5**).

Selective Negishi[103] and Sonogashira[104] cross-coupling reactions on 2,3-dichloropyridine (**5**) have been reported. Another example of a regioselecitve cross-coupling on 2,3-dihalopyridines is shown in Figure 37.[105] Dibromide **99** gave the monosubstitution product **100** with complete regiocontrol.

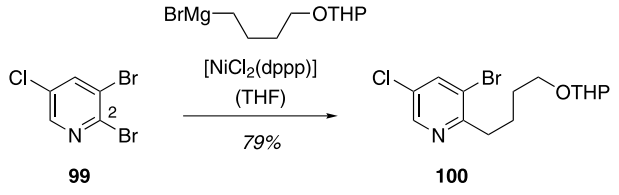


Figure 37. Regioselective Kumada cross-coupling on 2,3-dibromopyridine **99**.

2,5-Dibromopyridine (**101**) is the prototypical pyridine employed to achieve a regioselective cross-coupling in the 2- versus 5-position. In several cases, the selectivity has been used to establish a 2,5-disubstitution by combining two cross-coupling reactions. Two examples shown in Figure 38 illustrate this point. The first reaction sequence **101**→**102** includes the unusual cross-coupling of indium reagents, which occurs in an S_E2' fashion.[106] After cross-coupling at carbon atom C-2 with 1 equiv of the allenylindium reagent obtained from propargyl bromide, disubstitution was achieved in one pot with the reagent derived from 1-bromobut-2-yne and the same catalyst combination. In the second example, a Sonogashira cross-coupling gave the monosubstitution product, which underwent a second

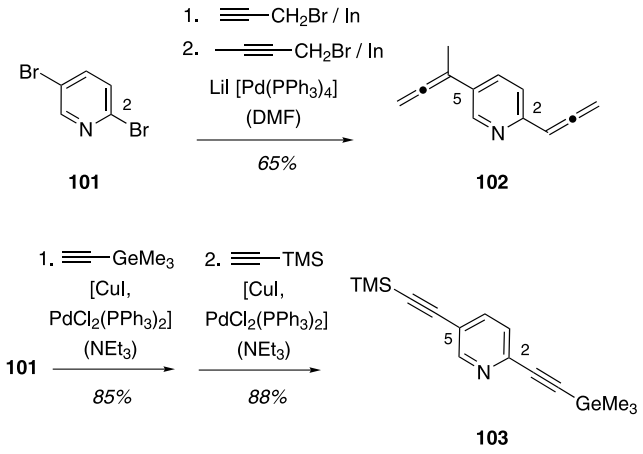


Figure 38. Sequential cross-coupling reactions on 2,5-dibromopyridine (**101**) as an access to 2,5-disubstituted pyridines.

Sonogashira cross-coupling reaction to yield product **103**.[107]

Further selective cross-coupling reactions of substrate **101** include Kumada,[90,108] Negishi,[91,109] Stille,[110] Sonogashira,[109,111] and Suzuki[112] reactions. An example of the cross-coupling of a functionalised borane (9-BBN= 9-borabicyclo[3.3.1]nonyl) with compound **101** to give the bromopyridine **104** is shown in Figure 39.[112]

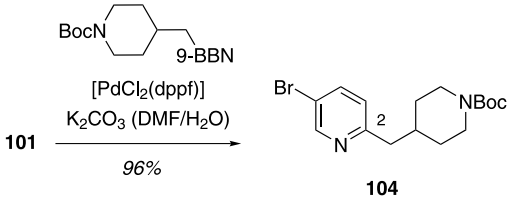


Figure 39. Regioselective Suzuki cross-coupling on 2,5-dibromopyridine (**101**).

In addition to 2,5-dibromopyridine, 2,5-dichloropyridine was successfully employed in regioselective Negishi cross-coupling reactions.[103a]

5.2. Quinolines

Due to the annelated benzol ring, quinolines possess only one highly electrophilic position at carbon atom C-2. A halogen atom at this position is preferably replaced in cross-coupling reactions irrespective of what position another halogen substituent may occupy. Shiota and Yamamori observed that this selectivity is opposite to the selectivity achieved in nucleophilic displacement reactions using no Pd catalyst.[113] 2,4-Dichloroquinoline (**105**) reacted with the benzylic zinc reagent **106** at room temperature in the presence of LiCl preferentially in the 4-position, yielding quinoline **107** as the major product (Fig. 40). On the contrary to this observation, the corresponding Negishi cross-coupling proceeded with high selectivity at the 2-position and gave quinoline **108**. If an initial cross-coupling was conducted at C-2 (e.g. **105**→**109**), a successive Negishi cross-coupling could be achieved at position C-4, yielding quinoline **110**. The regioselective installation of a phenyl group in position C-2 was not only

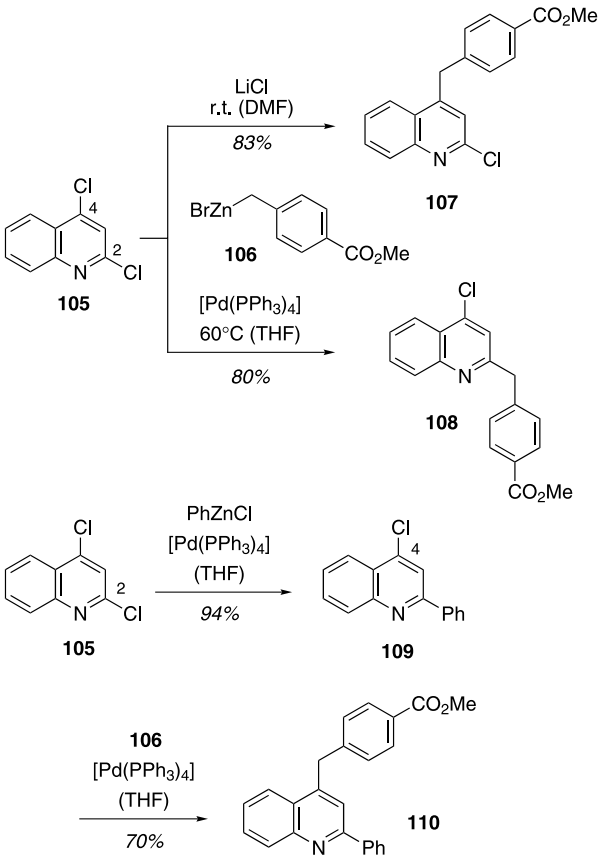


Figure 40. Examples of regioselective cross-coupling reactions achieved with 2,4-dichloroquinoline (**105**).

possible by a Negishi, but also by a Suzuki and a Stille, reaction. The regioselectivity in the first cross-coupling step was ascribed to the coordinating effect of the pyridine nitrogen atom to the Pd catalyst.

Selective Stille cross-coupling reactions of the dichloride **105** with 1-ethoxyvinyltributylstannane at the 2-position and of 4,7-dichloroquinoline (**112**) at the 4-position have been reported (Fig. 41).[114] Upon hydrolytic work-up (1 M aq. HCl) the acetyl-substituted quinolines **111** and **113** were isolated. Compound **112** was also employed in regioselective Negishi[103a] and Suzuki[115] cross-coupling reactions.

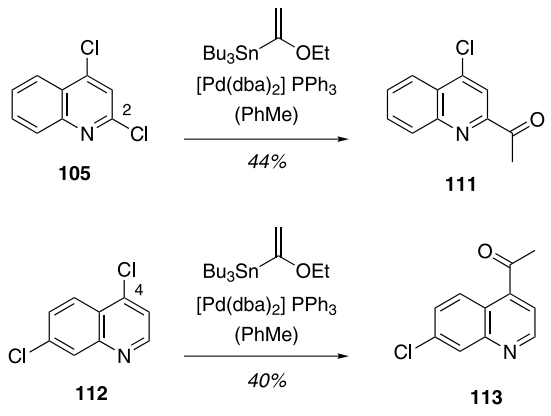


Figure 41. Selective access to acetylquinolines based on regioselective Stille cross-coupling reactions of dichloroquinolines **105** and **112**.

Dibromoquinolines which have been used as starting materials in regioselective cross-coupling reactions are shown in Figure 42. Sonogashira cross-coupling reactions were extensively studied. They occurred on 2,4-dibromoquinolines **114**[116] and **115** preferentially at position C-2[117] and on 5,7-dibromoquinoline **116** at position C-5.[118] The latter compound was also subjected to Suzuki cross-coupling reactions with arylboronic acids, which occurred also at position C-5. A Suzuki cross-coupling reaction conducted with 2,3-dibromoquinoline (**117**) showed a preference for position C-2, yielding a 2-aryl-3-bromoquinoline which was further converted into the alkaloid, quindoline.[119]

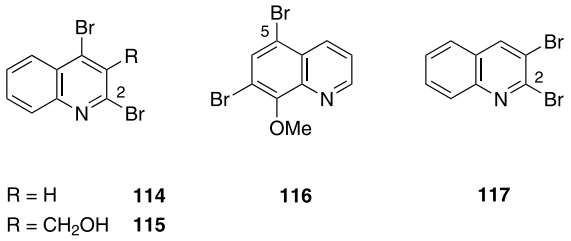


Figure 42. Dibromoquinolines which have served as substrates for regioselective cross-coupling reactions.

A combination of two successive cross-coupling reactions was used to prepare the radiolabelled compound **120** (Fig. 43).[120] Starting from 2,6-dibromoquinoline **118**, an initial Negishi cross-coupling with a serine-derived zinc reagent yielded quinoline **119**. Conversion into the target was achieved using ^{14}C-labelled methylzinc iodide employing an Ni catalyst. Attempts to achieve the Negishi cross-coupling at carbon atom C-6 by Pd catalysis were not successful.

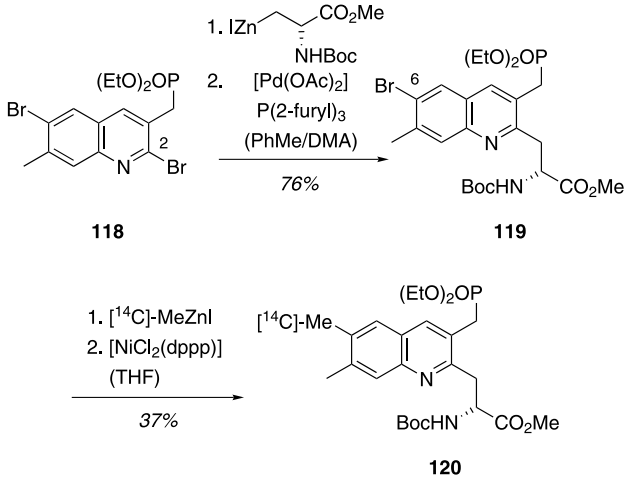


Figure 43. Preparation of radiolabelled compound **120** by sequential cross-coupling reactions on dibromoquinoline **118**.

5.3. Isoquinolines

Regioselective cross-coupling reactions on isoquinolines have been frequently studied on 1,3-dihalogenated substrates, i.e. on 1,3-dichloro- (**121**) and on 1,3-dibromoisoquinoline. A clear preference for a reaction at position C-1 was observed and this can be explained by the ease of

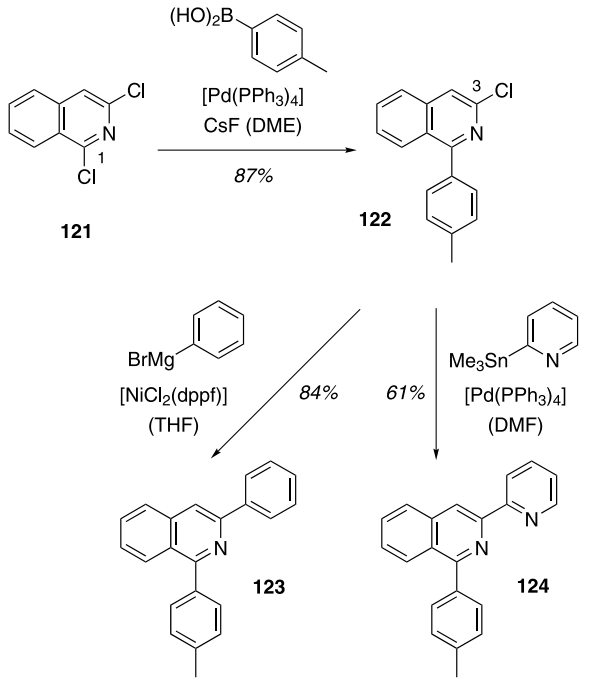


Figure 44. Sequential cross-coupling reactions on 1,3-dichloroisoquinoline (**121**) as an access to 1,3-disubstituted isoquinolines.

oxidative addition at this electrophilic position. Some fine examples of sequential reactions have been reported by Woodward et al. a selection of which are shown in Figure 44.[121] Initial Suzuki cross-coupling of dichloride **121** was followed by either a Kumada cross-coupling or a Stille cross-coupling which both allowed for the introduction of a substituent into the 3-position of intermediate **122**. The 1,3-disubstituted isoquinoline **123** and the new *N*,*N*-chelate ligand **124** were obtained following this route.

The previously mentioned acylation reaction (Fig. 41) was also applied to 1,3-dichloroisoquinoline (**121**) yielding 1-acetyl-3-chloroisoquinoline.[114] 1,3-Dibromoisoquinoline underwent a regioselective Sonogashira cross-coupling with propargyl alcohol.[122]

5.4. Pyridazines

Symmetrically substituted 3,6-dihalopyridazines should yield essentially statistical cross-coupling results. Indeed, the Stille cross-coupling of 3,6-dichloropyridazine (**125**) with the acyl anion equivalent, 1-ethoxyvinyl-tributyl-stannane, gave 54% yield in the first reaction step (Fig. 45). After hydrolysis, the second cross-coupling was facilitated by the electron-withdrawing acetyl group in the chloropyridazine **126** and the desired product **127** was obtained in 83% yield.[123] The Sonogashira cross-coupling of dichloride **125** with phenylacetylene proceeded only in 37% yield and the dialkynylated product was also obtained.[124]

5.5. Pyrimidines

Many substituted pyrimidines have been synthesised by regioselective, sequential cross-coupling reactions. The pioneering studies of Undheim and his co-workers on Stille

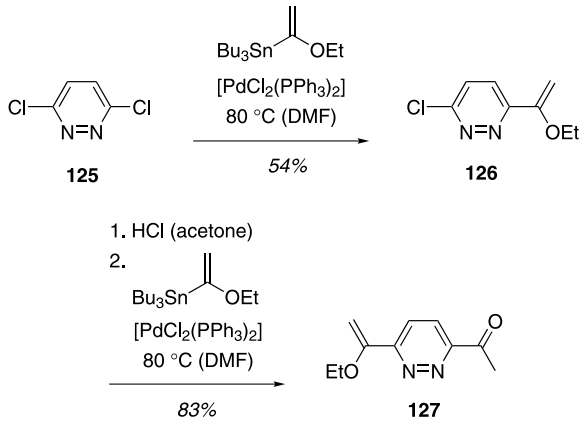


Figure 45. Sequential cross-coupling reactions on 3,6-dichloropyridazine (**125**) as an access to the 3,6-disubstituted pyridazine **127**.

reactions have been summarised in an instructive early account.[125] Some results of this work are shown in Figure 46. They provide a good overview of the selectivity pattern to be expected in pyrimidines. In increasing order, the reactivity for the different positions is $5<2<4$.

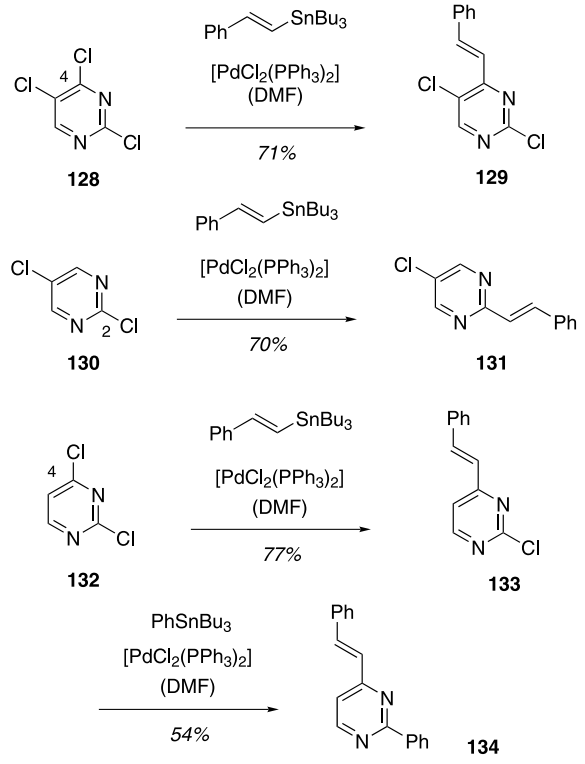


Figure 46. Regioselective Stille cross-coupling reactions on trichloropyrimidine **128** and on dichloropyrimidines **130** and **132**.

The preference for the most electrophilic pyrimidine position is illustrated by 2,4,5-trichloropyrimidine (**128**), which reacted selectively at position C-4 to yield the dichloride **129**. If the 2-position and the 5-position compete for the organometallic nucleophile, the 2-position wins. Product **131** consequently prevailed in the Stille cross-coupling of 2,5-dichloropyrimidine (**130**). Finally, a sequence of two cross-coupling reactions is depicted, which allowed the preparation of 2,4-disubstituted pyrimidine **134** starting from 2,4-dichloropyrimidine (**132**). As in

all of the other examples, the cross-coupling was performed with a slight excess of stannane (1.1 equiv), yielding the alkenyl-substituted pyrimidine **133** (70 °C in DMF), which was further converted at higher temperature (130 °C) into the product **134**. The preferred regioselectivity in favour of the 4-position had been previously observed in a Suzuki cross-coupling reaction of dichloride **132**.[126] It is in line with the preferred oxidative addition of Pd(0) into the C-4-chlorine bond. 4-Pyrimidylpalladium (II) complexes have been isolated from dichloride **132** and related compounds.[127] Further reactions in which the regioselectivity in the 2,4-dihalogenated pyrimidine **132** has been synthetically employed include the Pd-catalysed cross-coupling of alanes,[128] the Suzuki cross-coupling of pyridylboronic acids,[129] the Pd-catalysed cross-coupling of alkenylzirconocenes,[130] and the Sonogashira cross-coupling.[130] A more recent example in which an Fe-catalysed Kumada cross-coupling has been used for a monoalkylation is shown in Figure 47.[131] Remarkably, the conversion **132**→**135** occurred at −78 °C.

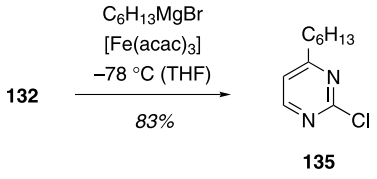


Figure 47. Regioselective Fe-catalysed Kumada cross-coupling on 2,4-dichloropyrimidine (**132**).

Alkyl- and aryl-substituted 2,4-dichloropyrimidines show the same regioselectivity preference for a reaction in the 4-position as the parent compound.[132] In a fully analogous fashion, the 2,4-dibromides[38,133] and 2,4-ditriflates[132b] give preferential cross-coupling reactions at the 4-position although by far less examples exist. Not surprisingly, 2,4,6-trichloropyrimidine (**136**) reacts with high preference at the 4(6)-position. Selective disubstitution to 4,6-dialkynyl-[134] and 4,6-diaryl-2-chloropyrimidines[135] has been reported. It was also possible to achieve a monosubstitution both in Suzuki[135] and in Negishi[136] cross-coupling reactions. In Figure 48, such a reaction is depicted. Reaction of trichloride **136** with 1 equiv of phenylboronic acid gave the dichloride **137**, whereas a 4,6-disubstitution was observed using 2 equiv of the same reagent.[135] The example shown in Figure 48 also illustrates the typical cross-coupling behaviour of 4,6-dihalopyrimidines. A more or less pronounced selectivity for a monosubstitution is possible with 1 equiv of the organometallic reagent. With an excess of reagent, a di- or (for trichlorides such as **136**) even a trisubstitution can be achieved.[64,103a,137]

2,5-Dibromopyrimidine underwent a Suzuki reaction with phenylboronic acid (3.0 equiv) to yield 43% of the monosubstituted 5-bromo-2-phenylpyrimidine and 32% of the disubstitution product.[138]

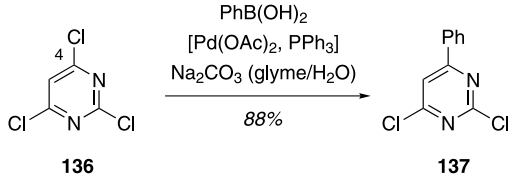


Figure 48. Regioselective Suzuki cross-coupling on 2,4,6-trichloropyrimidine (**136**).

5.6. Quinazolines

The reaction behaviour of 2,4-dichloroquinazolines in cross-coupling parallels that of 2,4-dichloropyrimidines. The preference for a cross-coupling at position C-4 is clear-cut.[128,139] It exceeds even the intrinsically higher reactivity of bromides at another less activated position. In a Sonogashira cross-coupling, the dichloride **138** (Fig. 49) reacted only at position C-4 to yield the alkynylated product **139**.[130]

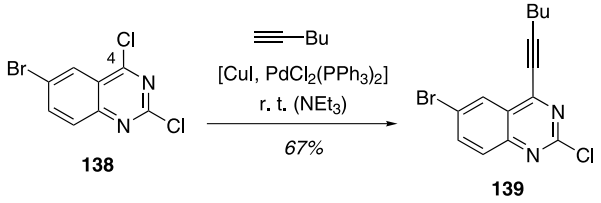


Figure 49. Regioselective Sonogashira cross-coupling on 2,4-dichloro-6-bromoquinazoline (**138**).

5.7. Pyrazines

The symmetry of the pyrazine core makes any position in 2,3-, 2,5- and 2,6-dihalopyrazines, which do not carry additional substituents, identical. Monosubstitution in symmetrical pyrazines has been achieved for a 2,5-dibromopyrazine in a Suzuki cross-coupling,[140] for a 2,5-dichloropyrazine in a Negishi cross-coupling,[141] and for 2,6-dichloropyrazine in an Fe-catalysed Kumada cross-coupling.[131]

Heteroatom substituents adjacent to a C-halogen bond facilitate regioselective reactions in unsymmetrical pyrazines. Both amino and alkoxy groups have been employed for this purpose. The directing effect may be attributed to chelation of the heteroatom to the Pd species, which undergoes the oxidative addition step. With the 2-aminopyrazine **140**, an initial Stille cross coupling could be achieved at position C-3.[142] Figure 50 shows the reaction with a 2-thiophenylstannane which furnished bromopyrazine **141**. This product was further converted into pyrazine **142**, which served as precursor for the synthesis of

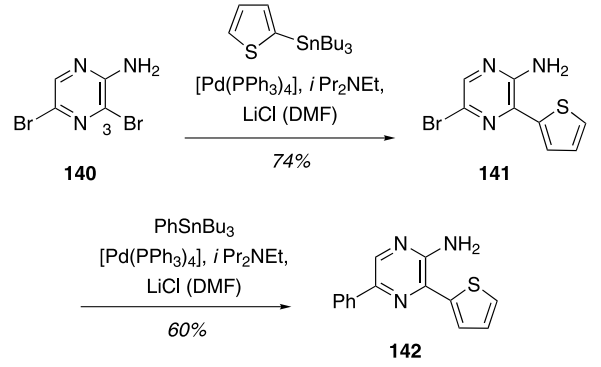


Figure 50. Sequential cross-coupling reactions on 2-amino-3,5-di-bromopyrazine (**140**) as an access to 2-amino-3,5-disubstituted pyrazines.

a coelenterazine analogue. In a similar fashion, a regioselective Sonogashira cross-coupling followed by a Stille cross-coupling were the key steps in the synthesis of DL-cypridina luciferin and its analogues.[143]

An approach to dragmacidin D, a highly active bis(indole) secondary metabolite, was designed based on regioselective cross-coupling methodology (Fig. 51).[144] Starting from 2,5-dibromo-3-methoxypyrazine (**143**), an initial cross-coupling reaction occurred at position C-2 and yielded the dibromide **144**. The bromine atom in the pyrazine ring was more readily replaced in a second cross-coupling than the bromine atom in the phenyl ring of the indole. After changing the protecting groups (**144a**→**144c**), the Stille cross-coupling proceeded readily at position C-5. It led, however, to partial deprotection. After the time for cross-coupling was prolonged from 12 to 24 h, complete deprotection had taken place (**145**, $R^1=R^2=H$) and a single product was isolated in 92% yield.

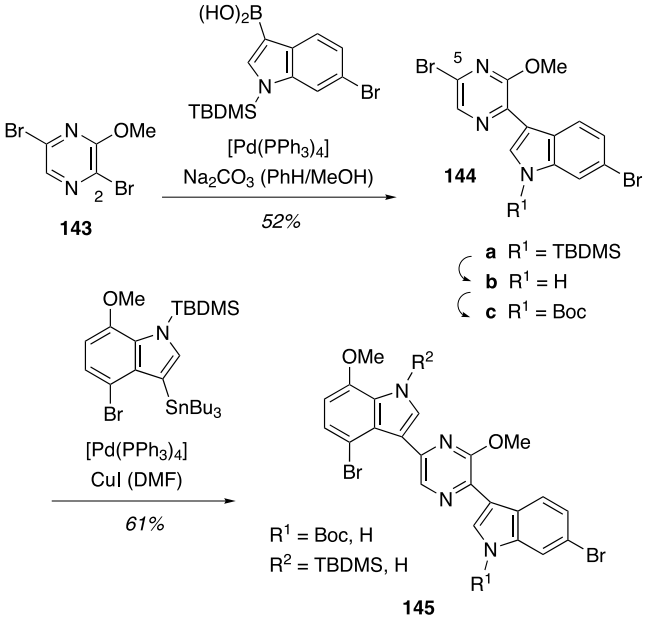


Figure 51. Sequential cross-coupling reactions on 2,5-dibromo-3-methoxypyrazine (**143**) as an access to 2,5-disubstituted 3-methoxypyrazines.

5.8. Quinoxalines

Benzannelation to the 5,6-position of pyrazines leaves only the 2- and the 3-position for a maximum of two halogen substituents within the heterocyclic core. The *ortho*-relationship of these halogen atoms should allow a regioselective displacement based on steric reasons. Indeed, 2,3-dichloroquinoxaline (**146**) underwent selective Sonogashira cross-coupling reactions, as exemplified in Figure 52.[145] Treatment of dichloride **146** with slightly superstoichiometric amounts of an alkyne (1.4 equiv) resulted in a monosubstitution, yielding chloro-quinoxaline **147**. With an excess of the same alkyne (3 equiv), the disubstituted product was obtained (66%).

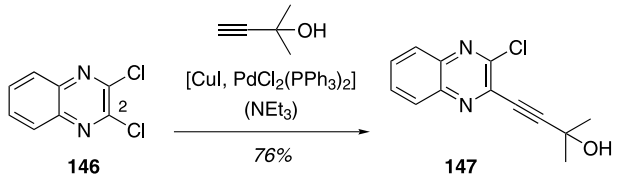


Figure 52. Regioselective Sonogashira cross-coupling on 2,3-dichloroquinoxaline (**146**).

The higher reactivity of chlorine atoms within a pyrazine ring as compared to a phenyl ring was corroborated in the Sonogashira cross-coupling of 2,6-dichloroquinoxaline (**148**). The reactions occurred preferentially at position C-2 (Fig. 53), yielding 2-substituted products such as compound **149**.[146]

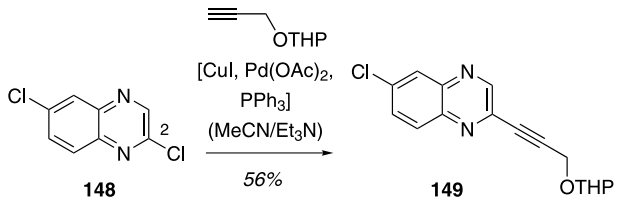


Figure 53. Regioselective Sonogashira cross-coupling on 2,6-dichloroquinoxaline (**148**).

6. Other condensed heterocycles

6.1. Pyrazolopyrimidines

In the previously mentioned study by Shiota and Yamamori,[113] the directing ability of a nitrogen lone pair, which was observed in quinolines (Section 5.2 and Fig. 40), was also employed for the regioselective substitution at 5,7-dichloropyrazolo[1,5-*a*]pyrimidine (**150**, Fig. 54). As expected, the Negishi cross-coupling yielded predominantly the C-5 substitution product **151**, accompanied by 7% of its regioisomer. A subsequent Suzuki cross-coupling furnished the desired product **152**.

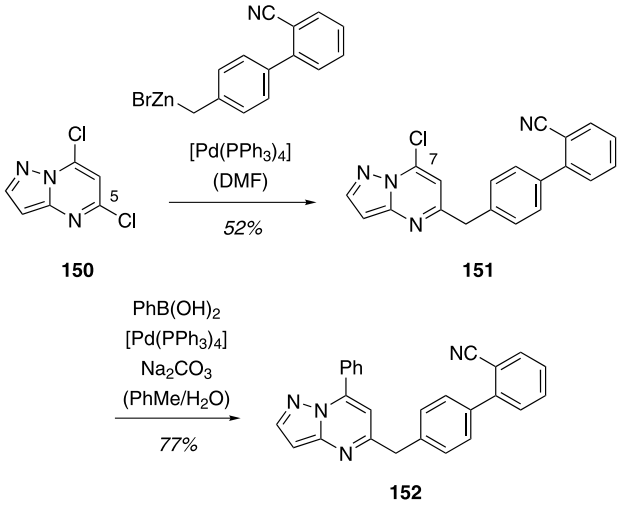


Figure 54. Sequential cross-coupling reactions on 5,7-dichloropyrazolo[1,5-*a*]pyrimidine (**150**) as an access to 5,7-disubstituted pyrazolo[1,5-*a*]pyrimidines.

6.2. Purines

The occurrence of the purine heterocycle in nucleosides and its biological relevance make it an attractive target for chemical modification.[147] The synthesis of purines by

metal- or organometal-mediated C–C bond-forming reactions has been recently reviewed.[148] There are three positions in purines which are amenable to C–C bond-forming cross-coupling reactions, i.e. positions C-2, C-6, and C-8. By looking at the reactions of 2,6-dichloropurines and 6,8-dichloropurines, it becomes evident that cross-coupling at position C-6 is preferred (Fig. 55). This observation is in line with the observed preference for a cross-coupling at positions C-4 in pyrimidines (Section 5.5) and in quinazolines (Section 5.6). The first example in Figure 55 describes the reaction of the 9-benzylpurine **6** with benzylzinc bromide which occurred exclusively at position C-6 to yield 2-chloropurine **153**.[149] In the second example, a Stille cross-coupling was employed to install a thiophenyl substituent selectively at position C-6 of purine **154**.[150]

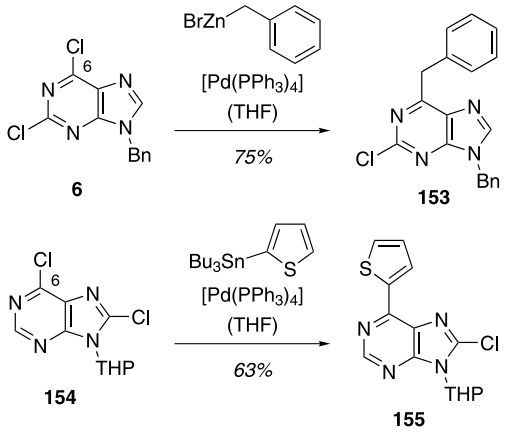


Figure 55. Regioselective cross-coupling reactions on dichloropurines **6** and **154**.

The general preference for substitution at position C-6 is also observed in 7-protected purines. In most synthetic examples, however, 9-protected purines were employed. Along these lines, Stille,[149,151,152] Suzuki,[153] Kumada,[154] Negishi,[152,154] and Sonogashira[152] cross-coupling reactions have been reported to occur at position C-6 of 9-protected 2,6-dichloropurines. More recent studies confirmed the regioselectivity of the Suzuki cross-coupling reaction of 9-protected 6,8-dichloropurines as mentioned above, but also showed an intriguing reversal of the selectivity in an Fe-catalysed Kumada cross-coupling (vide infra).[155] Attempts to achieve regioselective cross-coupling reactions with a 9-THP-protected 2,6,8-trichloropurine have been not fully successful.[156] It is confirmed, however, the higher reactivity of positions C-6 and C-8, as compared to position C-2. The Suzuki cross-coupling with phenylboronic acid proceeded in 46% yield to the corresponding 2,8-dichloro-6-phenylpurine.

Sequential cross-coupling reactions have been conducted, as the 2-position in products like **153** and the 8-position in products like **155** are amenable to cross-coupling reactions. Figure 56 shows this strategy for the synthesis of 2,6-disubstituted purines. In the first example,[154] an initial cross-coupling was performed with MeZnBr (1.2 equiv) and dichloropurine **6** at 50 °C in THF. Monosubstitution to intermediate **156** was mainly observed, but 15% of the disubstituted product was also isolated. The subsequent

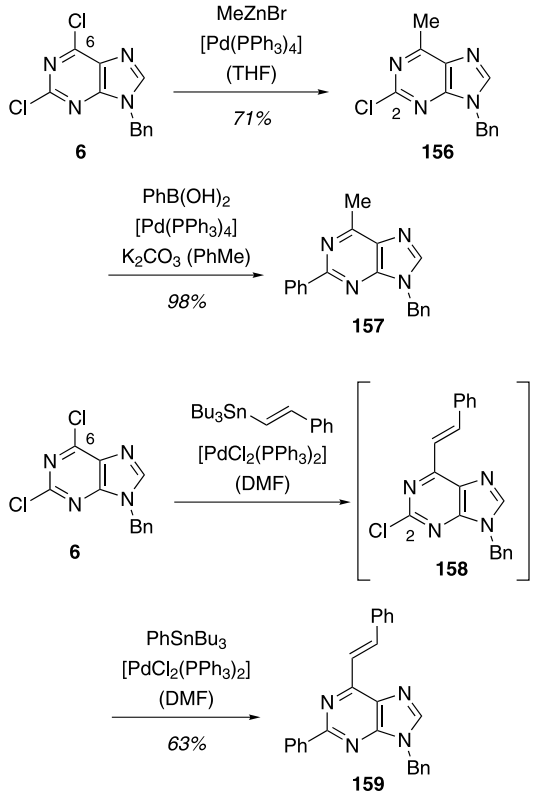


Figure 56. Sequential cross-coupling reactions on 9-benzyl-2,6-dichloropurine (**6**) as an access to 2,6-disubstituted purines.

Suzuki cross-coupling proceeded smoothly with an excess (2 equiv) of phenylboronic acid at 90 °C to furnish the target compound **157**. In the second example,[151a] two Stille cross-coupling reactions were conducted successively in one pot. The first reaction to 2-chloropurine **158** was performed at 70–85 °C with 1.2 equiv of stannane. After completion of the first cross-coupling step, a second stannane, e.g. phenyltributylstannane (1.2 equiv), was added and the reaction mixture was heated to 120 °C. As a result of this one-pot Stille coupling, the 2,6-disubstituted product **159** was obtained.

As mentioned previously, the Fe-catalysed Kumada cross-coupling of dichloride **154** gave the unexpected 8-substituted product **160** (Fig. 57).[155] The regioselectivity was only observed with MeMgCl (1.1 equiv), but not with PhMgBr nor with BnMgCl. Besides the monosubstitution

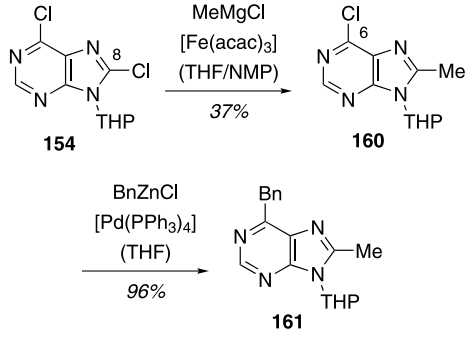


Figure 57. Sequential cross-coupling reactions on 6,8-dichloropurine **154** as an access to the 6,8-disubstituted purine **161**.

product **160**, 14% of the disubstituted product was isolated. An access to 6,8-disubstituted purines was easily feasible by combining the Kumada with a Stille or—as shown in Figure 57—with a Negishi cross-coupling. The 6,8-disubstituted purine **161** was obtained.

7. Conclusions and perspective

It is apparent from the many results mentioned in the text and from the figures that regioselective cross-coupling reactions facilitate the introduction of various highly functionalised substituents in specific positions of a heterocyclic core. By using multiple halogenated heterocycles as a scaffold, the design and synthesis of heterocyclic libraries becomes feasible which can in turn be useful tools to investigate the chemical space. Research in this direction progresses rapidly[157] and we hope that this review will stimulate further work in this area. In terms of methodology, the long-term goal in consecutive cross-coupling reactions is certainly to conduct the reaction in one pot by variation of the reaction conditions and the ligand. The same parameters may help to modulate the regioselectivity of a given cross-coupling reactions at will, i.e. to address one position selectively with one set of reaction conditions and to address another position with another set of conditions. Another challenge, which awaits to be explored, concerns the regioselective introduction of carbon fragments with stereogenic centres directly attached to the heterocycle. As further progress is being made in these areas, many applications in synthesis can be foreseen. We look forward to future work in this exciting field at the intersection of heterocyclic, organometallic and medicinal chemistry.

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Many colleagues have made in many discussions useful suggestions and comments on regioselective cross-coupling chemistry. For reasons of space, we cannot acknowledge them here, but their input is very much appreciated. Finally, T.B. owes thanks to Dr. Kurt Ritter (Aventis Pharma, Frankfurt/Main) who—a long time ago—encouraged him to try cross-coupling chemistry in natural product synthesis.

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Biographical sketch

Sven Schröter (left) was born in November 1977 in Wetzlar. He studied chemistry at the Technical University of Munich where he finished his diploma thesis in November 2003 in the research group of Professor T. Bach. Since February 2004, he performs his Ph.D. in the same group, working in the area of regioselective cross-coupling reactions.

Christoph Stock (middle) was born in July 1976 in Königswinter. He studied chemistry at the University of Bonn, were he carried out his diploma thesis under the guidance of Professor A. Gansäuer. His diploma work in Bonn was concerned with new alkylation chemistry of enolates. In October 2001, he joined the group of Professor T. Bach at the Technical University of Munich, where he is about to finish his Ph.D. work on the synthesis of marine natural products. He will continue his career as a post-doctoral fellow with Professor B. Feringa at the University of Groningen.

Thorsten Bach (right) was born in April 1965 in Ludwigshafen/Rhein. He studied chemistry at the University of Heidelberg and at the University of Southern California, where he carried out his diploma thesis under the guidance of Professor G.A. Olah. He received his Ph.D. in 1991 from the University of Marburg working with Professor M.T. Reetz. After a postdoctoral stay at Harvard with Professor D.A. Evans, he started his independent research at the University of Münster in 1992. In 1997, he became Professor of Organic Chemistry at the University of Marburg and in April 2000 he was appointed Full Professor of Organic Chemistry at the Technical University of Munich. He currently serves as the vice dean of the Chemistry Department and is one of the regional editors of Synthesis. He has been a visiting professor at the universities of Helsinki (1996) and Kyoto (1999). Scientific awards he has received include the Dozentenstipendium des Fonds der Chemischen Industrie in 1997, the 2001 Astra Zeneca research award in Organic Chemistry, and the 2003 Novartis European Young Investigator Award in Chemistry. His prime research interests are preparative organic photochemistry, organometallic chemistry and stereoselective synthesis.

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Neurosteroid analogues: synthesis of 6-aza-allopregnanolone

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Abstract—An efficient synthesis of 6-azapregnane derivatives and their biological activity is described. The nitrogen was introduced into the B ring using Beckmann rearrangement of the (*E*)-oxime of 6-oxo-B-nor-5α-pregnane derivatives. The required 3α-hydroxyl was produced either by solvolysis of the corresponding 3β-mesyloxy group or by the Meerwein–Ponndorf–Verley reduction of the 3-oxo group; this reduction could be carried out selectively with an unprotected 3,20-dioxo derivative. The binding of the 6-aza-steroids to the γ-aminobutyric acid receptor ($GABA_A$) was measured using [^{35}S]-*tert*-butyl-bicyclo[2.2.2]phosphorothionate (TBPS) and [^{3}H]flunitrazepam. The only analogue to be slightly active was that lacking any oxygen function in position 3.

1. Introduction

In the search for biologically active analogues of natural hormones, substitution of a heteroatom for a carbon atom has often been successful. Total[1] or partial syntheses[2–4] have led to a number of steroids with a nitrogen atom in the skeleton. The substitution can modify the chemical nature of functionalities present in the molecule: for example, oxo derivatives are thus converted into lactams[5,6] (e.g., **1**, see Fig. 1) or their vinylogues[7] (e.g., **2**). The analogues could mimic an original hormone but not fulfil its functions[8,9] or behave as the original.[10–12] Recently, 6-aza-5α-cholestan-3β-ol (**3**) and its pregnane derivative **4** were found to be specific phosphatidylinositol phospholipase C inhibitors with antitumour activity.[13] Further, analogues with a heteroatom in the skeleton can also be useful for the study of interactions[14] between a ligand and its receptor.

Functional groups essential for neuronal activity of allopregnanolone (3α-hydroxy-5α-pregnan-20-one, **5**) comprise the 3α-hydroxy and 20-oxo groups. Since the B ring seems to be distant enough from these critical points, we envisaged that the introduction of a nitrogen atom into position 6 of allopregnanolone (**5**) would have no detrimental effect on its biological activity. In contrast, we hoped to obtain products with increased solubility, since low solubility of our earlier analogues in body liquids[15,16] often marred their biological activity and the usual ways of making compounds more soluble did not help: even though some quaternary ammonium salts (e.g., compounds **6** and **7**)[15] functioned well on isolated receptors, they were inactive in a living organism.

Several methods are known for the preparation of 6-azasteroids, all based on oxidation of 5-unsaturated steroids into 5-oxo-7-oic acids or their derivatives. This process[13] is less efficient in 3-substituted seco-steroids which easily lose the 3-substituents. The loss could be prevented by the use of 3-silylated intermediates[17] or exploited in a different route described by Sharp.[18] Here we present an alternative synthesis of 6-azapregnane derivatives (3α-hydroxy-6-aza-5α-pregnan-20-one, **8**, 3α-hydroxy-6-aza-5α-pregnane-7,20-dione, **9**): the loss of one carbon atom, required for the synthesis of the piperidine B ring, takes place during the preparation of the starting material—a 7-norsteroid derivative.

2. Results and discussion

2.1. Synthesis

The starting material, (20*R*)-7-norpregn-5-ene-3β,20-diyl acetate benzoate[19] (**10**, see Scheme 1) was converted into 6α-bromo-5β-alcohol **11** and then epoxide **12**. The 5β,6β-configuration of the epoxide was apparent from its ^{1}H NMR spectrum (a narrow multiplet of H-3α, typical[20] of 3β-hydroxy-5β-steroids). Lewis acid treatment of the epoxide **12** yielded the desired 6-ketone **13**. Although 6-oxosteroids of the normal series give a single oxime only, ketone **13** reacted with hydroxylamine to give two oximes (**14**, **15**). Their ^{1}H NMR spectra[21] were conspicuously different with

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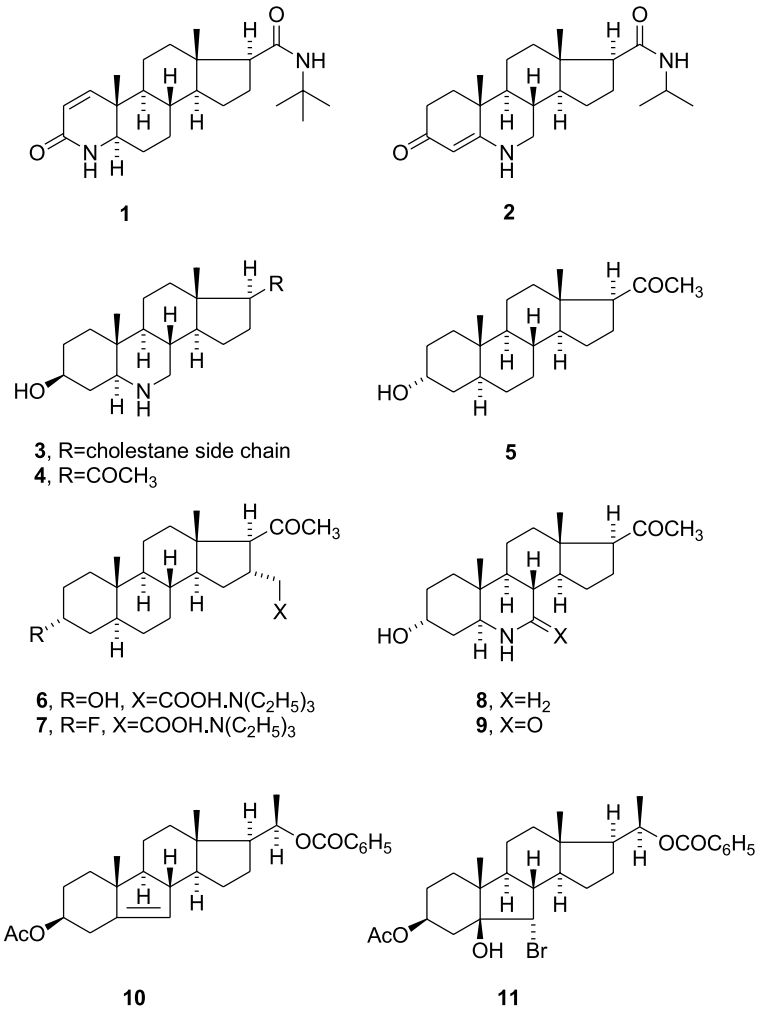
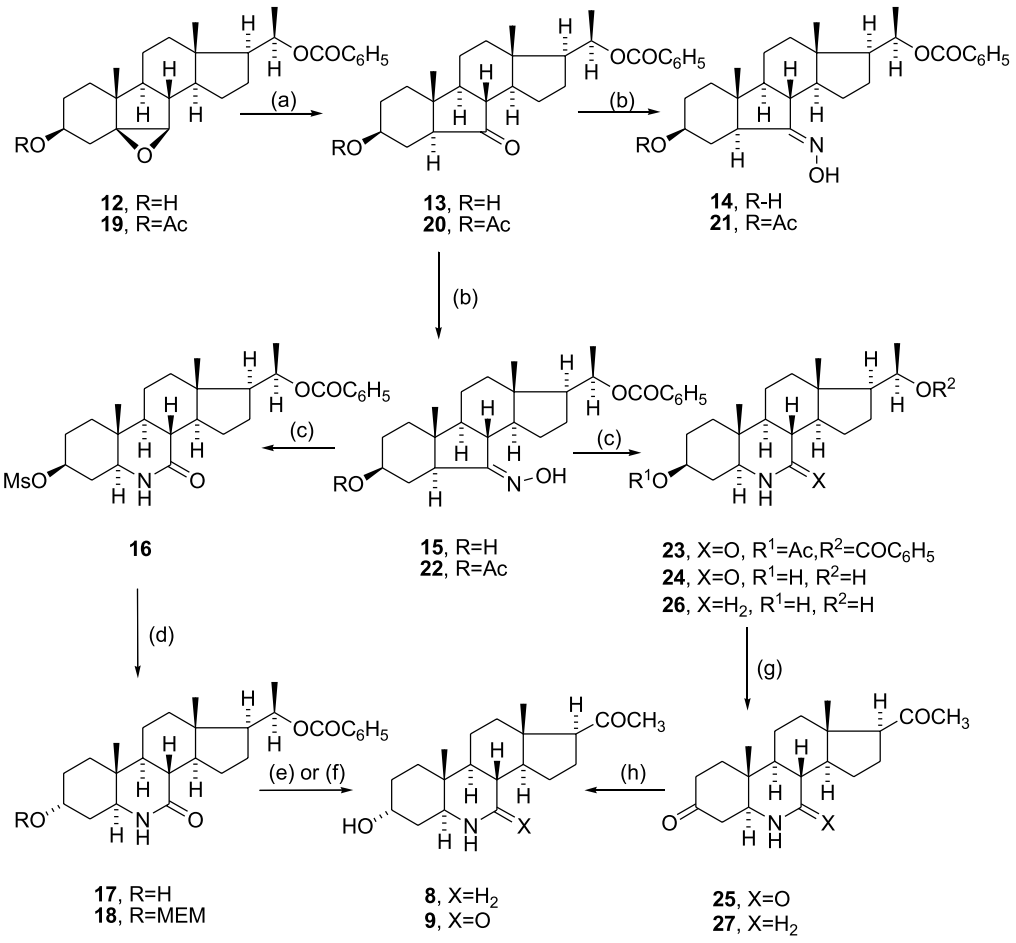


Figure 1.

the presence or absence of a signal at δ 3.04. To distinguish between the *E*- and *Z*-configuration of the oximes, the complete structural assignment of all proton and carbon signals in their ^{1}H and ^{13}C NMR spectra was carried out using homonuclear and heteronuclear 2D-COSY experiments (for data—see Table 1). The stereochemical assignment of methylene protons (in α- and β-position) was derived from 2D-ROESY spectra using mainly the NOE contacts of β-protons with the 18- and/or 19-Me group. The comparison of proton chemical shifts in both isomers shows a significant downfield shift (0.95 ppm) for H-4α in the minor and more lipophilic oxime **14**, while the major and less lipophilic oxime **15** shows a smaller downfield shift (0.37 ppm) for H-15α. The inspection of models indicates that H-4α is sterically closer to the oxime oxygen atom in the isomer with the *Z*-configuration and the H-15α appears very close to the oxime oxygen atom in the isomer with the *E*-configuration (H···O distances are ca. 2.4 and 2.6 Å, respectively); the van der Waals deshielding effect is presumably responsible for the observed downfield shifts. Analogous downfield shifts were observed also for the corresponding carbon atoms (1.99 ppm for C-4 and 1.59 ppm for C-15). Therefore, the *Z*-configuration could be assigned to oxime **14** and *E*-configuration to oxime **15**.

The major oxime **15** was submitted to the Beckman rearrangement, induced with mesyl chloride in pyridine. The ^{1}H NMR spectrum of the resulting 3β-mesyloxy lactam **16** confirmed the above assignment of configuration: the proton next to the nitrogen atom (i.e., the H-5) interacted strongly with H-4 hydrogens ($J=12.6$, 3.2 Hz). The solvolysis of the mesylate **16** in the presence of potassium nitrite in DMSO produced alcohol **17** with the required 3α-configuration. Before the subsequent transformations, its hydroxy group was protected by etherification: the 20-benzoyloxy group in the methoxyethoxymethoxy (MEM) ether **18** was hydrolysed, and oxidised; deprotection afforded the 6-aza analogue of 7-oxo-allopregnanolone **9**. Equally, the MEM-ether **18** was reduced with lithium aluminium hydride, oxidised and deprotected to yield the desired 6-aza analogue of allopregnanolone **8** (Table 2).

The low yield of the above solvolysis, however, failed to justify the orthogonal protection of both hydroxy groups in the starting material. Therefore, the hydroxy epoxide **12** was first acetylated to 3-acetate **19** and only then treated with boron trifluoride etherate. 3β-Acetoxy ketone **20** also yielded a mixture of two oximes (**21**, **22**), whose respective structures were assigned analogously to the earlier mentioned oximes **14** and **15**. The major and more polar oxime **22** was rearranged upon action of mesyl chloride in pyridine yielding cleanly the 3β-acetoxy lactam sought (**23**).



Scheme 1. Reagents and conditions: (a) $BF_3 \cdot Et_2O$, 64% or 94%; (b) $NH_2OH \cdot HCl$, $KHCO_3$, MeOH; 52%; (c) MsCl, py, 0 °C, 4 h; 97%; (d) KNO_2, DMSO, 115 °C; 26%; (e) KOH, then PCC, then HCl; 72%; (f) LAH, then CrO_3, then HCl, 20%; (g) CrO_3, 57%; (h) H_2IrCl_6, H_3PO_3, $(Me)_2CHOH$; 57 or 83%.

Table 1. Proton and carbon-13 chemical shifts of oximes **14**, **15**, **21** and **22** in $CDCl_3$

Proton	**14**	**15**	**21**	**22**	Carbon	**14**	**15**	**21**	**22**
1α	1.13	1.17	1.17	1.21	1	34.28	34.52	34.13	34.38
1β	1.65	1.68	1.67	1.70	2	30.49	30.88	26.63	26.88
2α	1.87	1.88	1.89	1.90	3	71.97	71.60	73.46	73.33
2β	1.57	1.54	1.60	1.60	4	33.07	31.08	29.36	27.35
3	3.71	3.69	4.80	4.77	5	53.86	53.46	53.53	53.12
4α	3.05	2.10	3.03	2.11	6	163.84	163.76	163.54	163.40
4β	1.65	1.35	1.74	1.43	8	44.88	44.01	44.77	43.88
5	2.13	2.05	2.15	2.09	9	57.00	58.92	56.94	58.90
8	2.35	2.46	2.34	2.46	10	40.67	40.48	40.57	40.37
9	1.00	1.11	1.02	1.13	11	21.01	21.16	20.99	21.13
11α	1.45	1.45	1.45	1.46	12	38.89	39.70	38.89	39.67
11β	1.28	1.28	1.29	1.27	13	44.76	45.28	44.73	45.28
12α	1.25	1.26	1.27	1.31	14	53.36	54.24	53.38	54.19
12β	1.90	1.94	1.92	1.94	15	25.81	27.39	25.11	27.37
14	1.53	1.59	1.54	1.61	16	25.07	25.50	25.77	25.50
15α	1.35	1.74	1.38	1.75	17	54.38	54.57	54.42	54.59
15β	1.81	1.82	1.97	1.84	18	13.07	13.40	13.09	13.40
16α	1.37	1.31	1.36	1.32	19	14.01	12.62	13.89	12.49
16β	1.95	1.78	1.81	1.77	20	73.17	73.36	73.18	73.33
17	1.79	1.82	1.81	1.82	21	20.04	19.98	20.04	19.97
18-Me	0.69	0.76	0.69	0.76	C═O	165.68	165.71	165.69	165.71
19-Me	0.82	0.68	0.84	0.69	Ac: C═O	—	—	170.47	170.52
20	5.15	5.17	5.15	5.17	CH_3	—	—	21.34	21.32
21-Me	1.28	1.27	1.28	1.28	C_6H_5: *i*-	130.75	130.79	130.80	130.82
N-OH	7.89	7.59	7.00	7.32	C_6H_5: *o*-	129.63	129.63	129.64	129.64
OAc	—	—	2.03	2.04	C_6H_5: *m*-	128.34	128.34	128.35	128.34
C_6H_5: *o*-	8.05	8.05	8.05	8.06	C_6H_5: *p*-	132.74	132.73	132.74	132.72
C_6H_5: *m*-	7.44	7.45	7.44	7.44					
C_6H_5: *p*-	7.56	7.56	7.55	7.56					

Table 2. Proton and carbon-13 chemical shifts of aza-derivatives **8**, **9**, **30**, **32** and **34** in $CDCl_3$

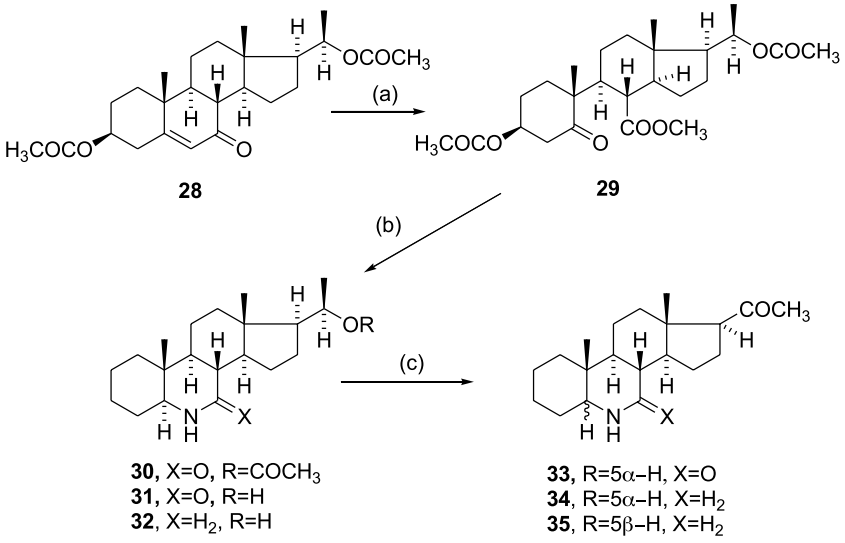
Proton	**8**	**9**	**30**	**32**	**34**	Carbon	**8**	**9**	**30**	**32**	**34**
1α	1.34	~1.46	0.99	0.89	0.90	1	30.32	28.89	34.45	36.53	36.50
1β	1.50	~1.46	1.65	1.66	1.66	2	28.56	28.46	21.01	21.53	21.47
2α	~1.65	~1.76	1.56	1.46	1.48	3	66.73	65.76	24.48	25.64	25.56
2β	~1.65	~1.70	1.52	1.39	1.42	4	35.67	34.16	27.34	28.70	28.53
3α	—	—	1.31	1.29	1.31	5	58.66	55.04	61.72	65.67	65.59
3β	4.15	4.19	1.76	1.71	1.73	7	52.44	173.52	173.43	52.64	52.36
4α	~1.58	~1.60	1.37	~1.36	~1.39	8	35.96	42.35	42.32	35.83	35.83
4β	~1.58	~1.60	1.42	~1.36	~1.39	9	53.67	51.55	51.60	54.16	53.98
5	2.69	3.59	3.01	2.18	2.20	10	36.36	35.33	35.36	36.42	36.40
7α	2.36	—	—	2.30	2.32	11	20.41	20.69	20.73	20.29	20.41
7β	3.02	—	—	2.99	3.01	12	38.91	38.44	38.92	40.02	38.94
8	1.57	2.20	2.18	1.57	1.57	13	44.34	45.66	44.27	42.68	44.34
9	0.90	1.40	1.49	0.78	0.81	14	53.95	52.24	52.02	53.24	53.98
11α	1.62	1.67	1.57	1.50	1.60	15	23.87	26.25	25.74	25.76	23.86
11β	1.31	1.32	1.25	1.28	1.31	16	22.97	23.51	26.05	23.93	22.95
12α	1.43	1.39	1.20	1.24	1.42	17	63.50	62.59	54.13	58.34	63.54
12β	2.03	2.06	1.84	2.05	2.02	18	13.50	13.48	12.68	12.62	13.49
14	1.17	1.58	1.28	1.03	1.16	19	10.94	9.42	10.35	12.08	12.03
15α	~1.63	2.21	1.73	1.65	1.62	20	209.48	209.77	72.95	70.55	209.50
15β	1.20	1.75	1.26	1.16	1.20	21	31.52	31.55	19.92	23.65	31.50
16α	1.66	1.73	1.67	1.09	1.63	OAc: C=O	—	—	170.38	—	—
16β	2.17	2.14	2.15	1.54	2.15	CH_3	—	—	21.54	—	—
17	2.52	2.49	1.59	1.32	2.51						
18-Me	0.62	0.69	0.68	0.76	0.62						
19-Me	0.86	0.87	0.86	0.88	0.88						
20	—	—	4.86	3.72	—						
21-Me	2.12	2.12	1.16	1.13	2.12						
OAc	—	—	2.02	—	—						
NH	[a]	5.38	5.22	[a]	[a]						

[a] Position of NH signal was not determined.

Hydrolysis and oxidation converted the lactam **23** into 3β,20-dihydroxy- and 3,20-dioxo lactams **24** and **25**. The Henbest[22] reaction of the latter (i.e., partial reduction of the 3-oxo group with 2-propanol catalysed with hexachloroiridic acid in the presence of phosphorous acids) produced a monohydroxy ketone identical with the above 3α-hydroxy lactam **9**.

Analogously, the lactam **23** was reduced with lithium aluminium hydride in dioxane yielding dihydroxy amine **26**. Oxidation with chromic acid afforded dioxo amine **27**, the Henbest reduction of which produced a monohydroxy ketone identical with the above 3α-hydroxy-6-aza-5α-pregnan-20-one (**8**).

For comparison, a few 3-deoxy analogues were prepared from (20*R*)-7-oxopregn-5-ene-3β,20-diyl diacetate[23] (**28**, see Scheme 2): oxidation according to a literature protocol[24] yielded crude 5,7-seco-6-nor acid **29** which was treated with ammonia, and hydrogenated: ^{13}C and ^{1}H NMR spectra of lactam **30** proved the loss of the substituent in position 3. The lactams **30** and **31** were converted to lactam **33** and amines **32** and **34** by routine reactions (see Scheme 2). Since the last compound was not found identical with recently



Scheme 2. (a) HIO_4, $KMnO_4$, K_2CO_3, $(CH_3)_3COH$, 45 °C, 6 h; then MeOH, CH_2N_2; (b) NH_3, MeOH, 55 °C, 20 h, then H_2/Pt; 14% of **30** from compound **28**.

published[13] '6-aza-pregnan-20-one' (**35**), additional ^{1}H NMR experiments were carried out to establish the C-5 configuration. The NOE contacts observed in 2D-H,H-ROESY spectrum allowed us to distinguish protons on the α- and β-side of the steroid skeleton: the absence of NOE contact between H-5 proton at δ 2.20 and 19-methyl protons on one side and the observed NOE contact of H-5 with axial protons H-1α, H-3α, H-7α and H-9α on the other side indicate unequivocally the 5α-configuration for our 6-aza-pregnan-20-one **34**. Thus the earlier produced '6-aza-pregnan-20-one' should be given the 5β-configuration (**35**).

2.2. Activity evaluation

Neuronal activity of 6-aza-allopregnanolone (**8**) and its 7-oxo derivative **9** was routinely checked by in vitro tests using [^{3}H]muscimol and [^{35}S]*tert*-butylbicyclo[2.2.2]-phosporothionate (TBPS) and [^{3}H]flunitrazepam as radiolabelled ligands to γ-aminobutyric acid receptors ($GABA_A$). The former two tests utilised receptors isolated from male rat brain and binding of the ligands was measured in the absence and presence of the tested compounds. For the last test, primary neuronal culture, obtained from young rat brains, was used and the binding of [^{3}H]flunitrazepam in neurones was measured in the presence of the varying concentration of the tested compounds. Allopregnanolone was used as a standard to check the viability of the methods. Preliminary results revealed that neither amine **8** nor lactam **9** exerted any binding in the three tests. Surprisingly, low activity only was found in a 3-deoxy analogue **34**. Complete biological results will be published in a separate paper dealing primarily with the testing methods.

3. Conclusions

While the synthesis proceeded according to expectation, no neuronal activity mediated through the γ-aminobutyric acid receptor was found in allopregnanolone analogues **8** and **9**. Nevertheless, even these results can have their value: they may demonstrate that the steroid binding site of the $GABA_A$ receptor requires a steroid compound having no electronegative substitution in the B ring. The earlier report on inactivity of 6-oxa-allopregnanolone[25] points to the same conclusion. Thus the structure–activity consideration should concentrate not only on the presence of polar groups in position 3 and 20, but should also reflect the lipophilic region at the B ring. Hydrophobic interactions between the steroid and the $GABA_A$ receptor apparently have a much greater role than hitherto taken for granted and any replacement of the hydrophobic B ring may lead to the loss of activity. The low activity of the 3-deoxy amine **34** may be explained by the presence of a different binding site within the receptor.

4. Experimental

4.1. General methods and equipment

Melting points were determined on a Koefler melting point micro apparatus Boetius (Germany) and are uncorrected. Analytical samples were dried over phosphorus pentoxide at 50 °C /100 Pa. Optical rotations were measured in chloroform using an Autopol IV (Rudolf Research Analytical, Flanders, USA, $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1}). IR spectra were recorded on a Bruker IFS 88 spectrometer in chloroform solutions, wave-numbers are given in cm^{-1}. Detailed NMR study of selected compounds was performed on Bruker AVANCE-500 instruments (^{1}H at 500.13 MHz; ^{13}C at 125.77 MHz). Proton NMR spectra of other compounds were measured on Varian UNITY-200 (at 200 MHz) and/or Bruker AVANCE-400 spectrometer (at 400 MHz) in $CDCl_3$ with tetramethylsilane as internal reference. Chemical shifts are given in ppm (δ-scale) and coupling constants in Hz. Unless otherwise stated, the data were interpreted as the first-order spectra. Thin-layer chromatography (TLC) was performed on silica gel (ICN Biochemicals). Preparative TLC (PLC) was carried out on 200×200 mm plates coated with a 0.7-mm thick layer of the same material. For column chromatography, 60–120 μ silica gel was used. Whenever aqueous solutions of hydrochloric acid, potassium hydrogencarbonate or carbonate were used, their concentration was 5%. Solvents were evaporated on a rotary evaporator in vacuo (0.2 kPa, bath temperature 40 °C).

The [^{3}H]flunitrazepam test of binding of the products was carried out by using neurones in culture.[26] The TBPS and muscimol test was done with $GABA_A$ receptors.[15]

4.1.1. (20*R*)-6α-Bromo-5-hydroxy-7-nor-5β-pregnane-3β,20-diyl acetate benzoate (11). A solution of olefin **10** (3.9 g, 8.66 mmol) in dioxane (40 mL) was treated with perchloric acid (10%, 2 mL) and N-bromo acetamide (1.8 g, 13.8 mmol) at 15 °C. After 1 h, the mixture was poured into a cold solution of potassium hydrogen sulfite (7%, 100 mL). The precipitate formed was filtered off, the product was dissolved in chloroform (100 mL) and washed with water (30 mL). The solution was dried over sodium sulfate and filtered through a layer of silica gel (10 g) and the solvent was evaporated in vacuo to give the title compound **11** (4.7 g, 99%) as a colourless oil. A small sample was purified by thin layer chromatography; [found: C, 63.1; H, 7.4; Br, 14.1. $C_{29}H_{39}BrO_5$ requires C, 63.32; H, 7.18; Br, 14.61%]. δ_H (200 MHz, $CDCl_3$) 8.04 (2H, m, *ortho*-Ar*H*), 7.60 (1H, m, *meta*-Ar*H*), 7.45 (2H, t, *para*-Ar*H*), 5.35–5.10 (1H, m, *H*-3), 5.21–5.10 (1H, m, *H*-20), 4.34 (1H, d, J=6.2 Hz, *H*-6), 2.06 (3H, s, *Me*CO), 1.28 (3H, d, J=6.0 Hz, *H*-21), 0.90 (3H, s, *H*-19), 0.72 (3H, s, *H*-18).

4.1.2. (20*R*)-5,6β-Epoxy-3β-hydroxy-7-nor-5β-pregnan-20-yl benzoate (12). A solution of bromohydrin **11** (2.5 g, 4.57 mmol) in methanol (40 mL) was treated with the solution of potassium carbonate (1.5 g, 10.9 mmol) in water (10 mL) under stirring at laboratory temperature. After 20 h, the solution was concentrated in vacuo to a quarter of its volume and the product was precipitated on addition of brine (50 mL). The product was filtered off, dissolved in methylene chloride (10 mL), washed with water (2× 40 mL) and dried. The solvent was evaporated in vacuo to give the title compound as a white amorphous solid **12** (1.88 g, 97%), mp 88–90 °C; [found: C, 76.2; H, 8.6. $C_{27}H_{36}O_4$ requires C, 76.38; H, 8.55%]; $[\alpha]_D$=−37.1 (*c* 0.3, $CHCl_3$); ν_{max} ($CHCl_3$) 3609, 1728, 1707, 1451, 1284, 1050, 714; δ_H (200 MHz, $CDCl_3$) 8.04 (2H, m, *ortho*-Ar*H*),

7.60 (1H, m, *meta*-Ar*H*), 7.45 (2H, t, *para*-Ar*H*), 5.22–5.04 (1H, m, *H*-20), 4.0–3.84 (1H, m, *H*-3), 3.19 (1H, s, *H*-6), 2.37–2.25 (1H, m, *H*-16), 1.27 (3H, d, $J=6.0$ Hz, *H*-21), 0.84 (3H, s, *H*-19), 0.64 (3H, s, *H*-18).

4.1.3. (20*R*)-3β-Hydroxy-6-oxo-7-nor-5α-pregnan-20-yl benzoate (13). To a solution of epoxide **12** (1.880 g, 4.23 mmol) in tetrahydrofuran (50 mL) was added a solution of boron trifluoride etherate (0.3 mL, 2.37 mmol) in ether (50 mL) under stirring at laboratory temperature. After 20 h, the solution was diluted with ether (150 mL), washed with the solution of potassium hydrogen carbonate (50 mL) and brine (50 mL). The solvents were removed in vacuo and the product was purified by chromatography on silica (80 g, toluene–ether 5:1). The major component (1.21 g, 64%) consisted of the title compound **13**. Mp 174–176 °C (acetone–heptane); [found: C, 76.1; H, 8.6. $C_{27}H_{36}O_4$ requires C, 76.38; H, 8.55%]; $[\alpha]_D=+47.9$ (*c* 0.3, $CHCl_3$); ν_{max} ($CHCl_3$) 3609, 1729; 1707, 1284, 1274, 1050, 960, 714; δ_H (200 MHz, $CDCl_3$) 8.06 (2H, m, *ortho*-Ar*H*), 7.57 (1H, m, *meta*-Ar*H*), 7.45 (2H, t, *para*-Ar*H*), 5.24–5.08 (1H, m, *H*-20), 3.71–3.54 (1H, m, *H*-3), 1.28 (3H, d, $J=6.0$ Hz, *H*-21), 0.84 (3H, s, *H*-19), 0.64 (3H, s, *H*-18).

4.1.4. (*Z*,20*R*)-3β-Hydroxy-6-oximino-7-nor-5α-pregnan-20-yl benzoate (14). A solution of ketone **13** (200 mg, 0.47 mmol) in methanol (10 mL) was stirred with potassium hydrogen carbonate (280 mg, 2.8 mmol) and hydroxylamine hydrochloride (200 mg, 1.76 mmol) at reflux temperature. After 5 h, the mixture was diluted with brine (60 mL) and cooled in a refrigerator. The precipitate was dissolved in methylene chloride (50 mL) and washed with the potassium hydrogen carbonate solution (2× 20 mL). The solvent was removed in vacuo and the product applied on a column of silica (50 mL). A mixture of ethyl acetate and toluene (3:1) eluted the title compound **14** (62 mg, 29%) as a colourless solid. Mp 164–167 °C (toluene); [found: C, 73.8; H, 8.4; N, 2.8. $C_{27}H_{37}NO_4$ requires C, 73.77; H, 8.48; 3.19% N]; $[\alpha]_D=+38.2$ (*c* 0.2, $CHCl_3$); ν_{max} ($CHCl_3$) 3604, 3297, 3169, 1707, 1666, 1452, 1282, 1052, 965, 941, 714; δ_H (200 MHz, $CDCl_3$) 8.06 (2H, m, *ortho*-Ar*H*), 7.56 (1H, m, *meta*-Ar*H*), 7.44 (2H, t, *para*-Ar*H*), 5.25–5.07 (1H, m, *H*-20), 3.82–3.61 (1H, m, *H*-3), 3.05 (1H, bd, $J=12.0$ Hz, *H*-4α), 1.28 (3H, d, $J=6.0$ Hz, *H*-21), 0.82 (3H, s, *H*-19), 0.69 (3H, s, *H*-18).

4.1.5. (*E*,20*R*)-3β-Hydroxy-6-oximino-7-nor-5α-pregnan-20-yl benzoate (15). The more polar eluate of the above chromatography yielded the title compound **15** (107 mg, 52%) as white crystals, mp 155–157 °C (methanol–ether); [found: C, 73.8; H, 8.4; N, 2.9. $C_{27}H_{37}NO_4$ requires C, 73.77; H, 8.48; N, 3.19%]; $[\alpha]_D=+27.8$ (*c* 0.1, $CHCl_3$); ν_{max} ($CHCl_3$) 3610, 3589, 3295, 1706, 1667, 1603, 1586, 1277, 1049, 969; δ_H (200 MHz, $CDCl_3$) 8.06 (2H, m, *ortho*-Ar*H*), 7.56 (1H, m, *meta*-Ar*H*), 7.44 (2H, t, *para*-Ar*H*), 5.26–5.08 (1H, m, *H*-20), 3.79–3.60 (1H, m, *H*-3), 2.47 (1H, t, $J=10.2$ Hz, H-8), 1.27 (3H, d, $J=6.0$ Hz, *H*-21), 0.77 (3H, s, *H*-19), 0.68 (3H, s, *H*-18).

4.1.6. (20*R*)-6-Aza-7-oxo-5α-pregnane-3β,20-diyl mesylate benzoate (16). Mesyl chloride (0.2 mL, 2.6 mmol) was dripped into a solution of oxime **15** (140 mg, 0.32 mmol) in pyridine (1 mL) at 0 °C under stirring. After 4 h, the reagent was destroyed with crushed ice (10 g) and the precipitate was filtered off. The product was dissolved in methylene chloride (40 mL) and washed with the solution of hydrochloric acid (10 mL), water (5 mL) and potassium hydrogen carbonate (10 mL). The extract was dried over sodium sulfate and the solvent was evaporated to give the title compound **16** (160 mg, 97%) mp 201–202 °C (CH_2Cl_2 and ether);[found: C, 65.3; H, 7.3; N, 3.0. $C_{28}H_{39}NO_6S$ requires C, 64.96; H, 7.59; N, 2.71%]; $[\alpha]_D=-17.2$ (*c* 0.3, $CHCl_3$); ν_{max} ($CHCl_3$) 3390, 1706, 1657, 1603, 1585, 1344, 1358, 1175, 714, 533; δ_H (200 MHz, $CDCl_3$) 8.05 (2H, m, *ortho*-Ar*H*), 7.56 (1H, m, *meta*-Ar*H*), 7.44 (2H, t, *para*-Ar*H*), 5.34 (1H, s, *H*–N), 5.24–5.09 (1H, m, *H*-20), 4.77–4.56 (1H, m, *H*-3), 3.03 (3H, s, *Me*OSO_2), 1.28 (3H, d, $J=6.0$ Hz, *H*-21), 0.90 (3H, s, *H*-19), 0.72 (3H, s, *H*-18).

4.1.7. (20*R*)-3α-Hydroxy-6-aza-7-oxo-5α-pregnan-20-yl benzoate (17). A solution of mesylate **16** (80 mg, 0.15 mmol) in DMSO (2 mL) was stirred at 115 °C with potassium nitrite (250 mg, 2.94 mmol) under nitrogen. Brine (5 mL) was added and the mixture cooled in a refrigerator. The precipitate was filtered off, washed with water (25 mL) and dried. The product purified by PLC (ethyl acetate). The most polar component was identified the title compound **17** (18 mg, 26%), mp 153–154 and then 233–235 °C (acetone–heptane); [found: C, 73.6; H, 8.4; N, 3.0. $C_{27}H_{37}NO_4$ requires: C, 73.77; H, 8.48; N, 3.19% N]; $[\alpha]_D=-10.0$ (*c* 0.3, $CHCl_3$); ν_{max} ($CHCl_3$) 3614, 3392, 1706, 1651, 1603, 1281, 1586, 1006, 714; δ_H (200 MHz, $CDCl_3$) 8.05 (2H, m, *ortho*-Ar*H*), 7.56 (1H, m, *meta*-Ar*H*), 7.44 (2H, t, *para*-Ar*H*), 5.25–5.08 (1H, m, *H*-20), 4.78–4.68 (2H, m, OCH_2O), 4.26–4.16 (1H, m, *H*-3), 3.58 (1H, dd, $J=4.6$, 11.6 Hz, *H*-5), 2.19 (1H, t, $J=10.6$ Hz, *H*-16), 1.28 (3H, d, $J=6.0$ Hz, *H*-21), 0.82 (3H, s, *H*-19), 0.72 (3H, s, *H*-18).

4.1.8. (20*R*)-3α-(2′-Methoxyethoxy)methoxy-6-aza-7-oxo-5α-pregnan-20-yl benzoate (18). A solution of 3-alcohol **17** (260 mg, 0.59 mmol) in dichloromethane (3 mL) and *N,N*-diisopropylethylamine (0.5 mL, 3.1 mmol) was treated with (2-methoxyethoxy)methyl chloride (0.3 mL, 2.6 mmol) at laboratory temperature. After 18 h, the mixture was diluted with chloroform (30 mL), washed with an aqueous solution of citric acid (5%, 10 mL) and water (10 mL), and dried. The solvent was evaporated in vacuo to yield the title compound **18** (312 mg, 100%) as colourless oil. $[\alpha]_D=-10.3$ (*c* 0.3, $CHCl_3$). ν_{max} ($CHCl_3$) 3392, 2824, 1707, 1651, 1282, 1177, 989, 714; δ_H (400 MHz, $CDCl_3$) 8.05 (2H, m, *ortho*-Ar*H*), 7.56 (1H, m, *meta*-Ar*H*), 7.44 (2H, t, *para*-Ar*H*), 5.20–5.11 (1H, m, *H*-20), 3.97–3.92 (1H, m, *H*-3), 3.50 (1H, dd, $J=11.8$, 4.8 Hz, *H*-5), 3.40 (3H, s, O*Me*), 2.22 (1H, t, $J=10.6$ Hz, *H*-16), 1.27 (3H, d, $J=6.0$ Hz, *H*-21), 0.83 (3H, s, *H*-19), 0.72 (3H, s, *H*-18).

4.1.9. 3α-Hydroxy-6-aza-5α-pregnane-7,20-dione (9). (a) *By modification of the side chain*. Benzoate **18** (200 mg, 0.38 mmol) was dissolved in methanol (50 mL) and heated to boiling point with a solution of potassium hydroxide (500 mg, 8.9 mmol) in water (15 drops). After 8 h, the solution was concentrated in vacuo to a quarter of its volume, diluted with brine (50 mL) and placed in a refrigerator. The precipitate formed was filtered off, washed

with water (15 mL), dried with sodium sulfate, and concentrated in vacuo to yield (20*R*)-20-hydroxy-3α-(2′-methoxyethoxy)methoxy-6-aza-5α-pregnan-7-one (152 mg, 95%)—as a colourless solid. This crude material was dissolved in methylene chloride (2 mL) and stirred with pyridinium chlorochromate (500 mg, 2.3 mmol) and the suspension of potassium acetate (350 mg, 3.6 mmol) in methylene chloride (3 mL). After 18 h, the mixture was filtered through a column of Celite (5 mL), which was then washed with additional methylene chloride. The combined filtrate and eluate was evaporated in vacuo. The product was deprotected using hydrochloric acid (0.2 mL) in tetrahydrofuran (4 mL). After 18 h, the mixture was diluted with toluene (10 mL), partly evaporated and purified by TLC (ethyl acetate). Elution of the major zone with a mixture of acetone in chloroform (1:6) and evaporation afforded the title compound **9** (91 mg, 72%) as white crystals; mp 231–233 °C (acetone); [found: C, 70.2; H, 8.9; N, 3.8. $C_{20}H_{31}NO_3 \cdot 0.5H_2O$ requires: C, 70.14; H, 9.42; N, 4.09%]; $[\alpha]_D = +39.7$ (*c* 0.2, $CHCl_3$). ν_{max} ($CHCl_3$) 3614, 3392, 1652, 1359, 1007, 1701; δ_H (400 MHz, $CDCl_3$) 5.45–5.39 (1H, m, *H*–N), 4.22–4.15 (1H, m, *H*-3), 3.59 (1H, dd, $J=12.4$, 4.0 Hz, *H*-5α), 2.50 (1H, t, $J=9.3$ Hz, *H*-17), 2.13 (3H, s, *Me*CO), 0.86 (3H, s, *H*-19), 0.69 (3H, s, *H*-18). (b) *From the diketone* **25**. The reagent was prepared from hydrogen hexachloroiridate (50 mg, 0.12 mmol), phosphorous acid (400 mg, 4.9 mmol), 2-propanol (10 mL, 130.5 mmol) and water (2 mL). Part of this solution (1 mL) was added to a test tube containing 3,20-diketone **25** (40 mg, 0.12 mmol). The test tube was sealed and kept in a bath at 85 °C for 18 h. After cooling, the mixture was diluted with ethyl acetate (15 mL), the solution was washed with the solution of potassium hydrogen carbonate and water, dried over sodium sulfate and concentrated in vacuo. The product was purified by TLC (chloroform, acetone 6:1) to yield the title compound **9** (23 mg, 57%), mp 231–233 °C (acetone), identical with the sample prepared above.

4.1.10. 3α-Hydroxy-6-aza-5α-pregnan-20-one (8). (a) *From the 3α-alkoxy derivative* **18**. A solution of compound **18** (300 mg, 0.57 mmol) and lithium aluminium hydride (ca. 200 mg, 5.2 mmol) in dioxane (10 mL) was heated to boiling point under argon. After 5 h, the excess of the reagent was destroyed with wet ether (about 20 mL) and then an aqueous solution of Na_2SO_4 (about 5 mL). The mixture was saturated with anhydrous Na_2SO_4, inorganic material was filtered off and washed with ethyl acetate (60 mL). The filtrate was concentrated in vacuo. The remainder (230 mg, 99%, 0.56 mmol) was dissolved in methylene chloride (3 mL) and added to a suspension of pyridinium chlorochromate (700 mg, 3.25 mmol) and potassium acetate (350 mg, 3.56 mmol) in methylene chloride (4 mL). The mixture was stirred for 18 h at room temperature and then filtered through a layer of Celite (5 mL). The combined filtrate and eluate was evaporated and the remainder was dissolved in tetrahydrofuran (6 mL) containing hydrochloric acid (0.3 mL). After 4 h, the solution was made alkaline with ammonia, partly concentrated in vacuo, and extracted with chloroform (40 mL). The solution was dried over Na_2SO_4, and evaporated. The remainder (110 mg) was purified by chromatography on a column of silica gel (10 mL) in ammoniacal chloroform. Elution of the major zone afforded the title compound **8** (36 mg, 20%), mp 253–255 °C (aqueous methanol); [found: C, 74.9; H, 10.4; N, 4.3. $C_{20}H_{33}NO_2$ requires: C, 75.19; H, 10.41; N, 4.38%]; $[\alpha]_D = +56.7$ (*c* 0.18, $CHCl_3$). ν_{max} ($CHCl_3$) 3615, 3320, 1699, 1386, 1358, 1005; δ_H (400 MHz, $CDCl_3$) 4.17–4.11 (1H, m, *H*-3), 3.02 (1H, dd, $J=11.7$, 4.4 Hz, *H*-7β), 2.69 (1H, dd, $J=12.3$, 4.3 Hz, *H*-5α), 2.52 (1H, t, $J=8.8$ Hz, *H*-17), 2.36 (1H, t, $J=11.7$ Hz, *H*-7α), 2.12 (3H, s, *Me*CO), 0.86 (3H, s, H-19), 0.63 (3H, s, H-18); *m/z* (EI) 319 (M^+, 82), 304 (37), 276 (10), 246 (100%). (b) *From diketone* **27**. Compound **27** (160 mg, 0.50 mmol), hydrogen hexachloroiridate (31 mg, 0.08 mmol), and phosphorous acid (220 mg, 2.68 mmol) were put into a test tube and 2-propanol (3.5 mL, 45.7 mmol) and water (0.7 mL) were added. The tube was sealed and heated at 95 °C. The black mixture turned into a pale solution within the first half an hour. After 18 h, the mixture was diluted with ethyl acetate (50 mL) and transferred into a flask. Potassium carbonate (370 mg, 2.68 mmol) was added and organic solvents were evaporated. The content of the flask was made alkaline with ammonia (5 mL) and steroid products were extracted with chloroform (3×20 mL). The extract was washed with water (10 mL), dried and concentrated in vacuo. The remainder was purified by chromatography on a column of silica gel (25 g). Ammoniacal chloroform with 2% of methanol eluted the title compound **8** (133 mg, 83%) identical with the above sample.

4.1.11. (20*R*)-5,6β-Epoxy-7-nor-5β-pregnane-3β,20-diyl acetate benzoate (19). Epoxide **12** (450 mg, 1.1 mmol) was acetylated with acetic anhydride (0.4 mL) in pyridine (1 mL) at laboratory temperature. After 20 h, the mixture was poured into brine (10 mL), the precipitate formed was extracted with dichloromethane (3×20 mL), washed with the solution of potassium hydrogencarbonate (2×10 mL) and water, and dried. Evaporation of solvents in vacuo was repeated after dilution with toluene (10 mL) in order to remove pyridine from the title compound **19** (450 mg, 91%); the colourless oil failed to crystallise from usual solvents;[found: C, 74.4; H, 8.3. $C_{29}H_{38}O_5$ requires: C, 74.65; 8.21% H]; $[\alpha]_D$ −4.3° (*c* 0.3, $CHCl_3$). ν_{max} ($CHCl_3$) 1728, 1709, 1255, 1071, 1037, 1027, 961, 714; δ_H (200 MHz, $CDCl_3$) 8.04 (2H, m, *ortho*-Ar*H*), 7.55 (1H, m, *meta*-Ar*H*), 7.43 (2H, t, *para*-Ar*H*), 5.23–5.07 (1H, m, *H*-20), 5.04–4.88 (1H, m, *H*-3), 3.19 (1H, s, *H*-6), 2.04 (3H, s, *Me*CO), 1.28 (3H, d, $J=6.0$ Hz, *H*-21), 0.84 (3H, s, *H*-19), 0.63 (3H, s, *H*-18); *m/z* (EI) 406 (16), 344 (6), 284 (13), 209 (14), 149 (14), 105 (46), 91 (100%).

4.1.12. (20*R*)-7-Nor-6-oxo-5α-pregnane-3β,20-diyl acetate benzoate (20). In analogy with the preparation of ketone **13**, epoxide **19** (17.8 g, 38.1 mmol) was treated with a solution of boron trifluoride etherate (3.0 mL, 23.67 mmol) in a mixture of ether (900 mL) and tetrahydrofuran (400 mL). After 20 h, the reaction mixture was worked up as above and the product was purified by chromatography a column of silica (400 g). Ether in toluene (1:30) eluted the title compound **20** (16.8 g, 94%), mp 145–146 °C (ether–heptane); [found: C, 74.7; H, 8.5. $C_{29}H_{38}O_5$ requires C, 74.65; H, 8.21% H]; $[\alpha]_D = +48.1$ (*c* 0.28, $CHCl_3$); ν_{max} ($CHCl_3$) 1730, 1709, 1451, 1283, 1271, 1259, 1044, 994; δ_H (200 MHz, $CDCl_3$) 8.06 (2H, m, *ortho*-Ar*H*), 7.60 (1H, m, *meta*-Ar*H*), 7.45 (2H, t, *para*-Ar*H*), 5.25–5.09 (1H, m, *H*-20), 4.70–4.60 (1H, m, *H*-3), 2.23 (1H, bd, $J=10.8$ Hz,

H-5), 2.04 (3H, s, *Me*CO), 1.28 (3H, d, $J=6.0$ Hz, *H*-21), 0.85 (3H, s, *H*-19), 0.66 (3H, s, *H*-18).

4.1.13. (*Z*,20*R*)-6-Oximino-7-nor-5α-pregnane-3β,20-diyl acetate benzoate (21). A solution of ketone **20** (750 mg, 1.6 mmol) in methanol (10 mL) was stirred with potassium hydrogen carbonate (1 g, 9.99 mmol) and hydroxylamine hydrochloride (750 mg, 10.8 mmol) at reflux temperature. After 5 h, the mixture was worked up as in the preparation of oxime **14** and the product was applied on a column of silica (80 g). Ether in toluene (1:10) eluted the title compound **21** (176 mg, 23%), mp 193–195 °C (ether–heptane); [found: C, 72.3; H, 8.4; 2.8. $C_{29}H_{39}NO_5$ requires: C, 72.32; H, 8.16; N, 2.91%]; $[\alpha]_D=+40.2$ (*c* 0.2, $CHCl_3$); ν_{max} ($CHCl_3$) 3587, 3 298, 1729, 1708, 1452, 1281, 1271, 1262, 1246, 1047, 1033, 965, 941, 714. δ_H (200 MHz, $CDCl_3$) 8.05 (2H, m, *ortho*-Ar*H*), 7.56 (1H, m, *meta*-Ar*H*), 7.44 (2H, t, *para*-Ar*H*), 5.23–5.07 (1H, m, *H*-20), 4.90–4.70 (1H, m, *H*-3), 3.03 (1H, bd, $J=10.8$ Hz, *H*-4α), 2.03 (3H, s, *Me*CO), 1.28 (3H, d, $J=6.0$ Hz, *H*-21), 0.84 (3H, s, *H*-19), 0.69 (3H, s, *H*-18).

4.1.14. (*E*,20*R*)-6-Oximino-7-nor-5α-pregnane-3β,20-diyl acetate benzoate (22). A more polar fractions from the above chromatography yielded the title compound **22** (384 mg, 51%) as white crystals, mp 203–205 °C (ether–heptane); [found: C, 72.2; H, 8.3; N, 2.7. $C_{29}H_{39}NO_5$ requires C, 72.32; H, 8.16; N, 2.91%]; $[\alpha]_D=+30.2$ (*c* 0.2, $CHCl_3$); ν_{max} ($CHCl_3$) 3586, 3 296, 1728, 1708, 1667, 1451, 1282, 1274, 1259, 1049, 1033, 957, 924, 965, 714; δ_H (200 MHz, $CDCl_3$) 8.06 (2H, m, *ortho*-Ar*H*), 7.56 (1H, m, *meta*-Ar*H*), 7.44 (2H, t, *para*-Ar*H*), 5.26–5.09 (1H, m, *H*-20), 4.86–4.68 (1H, m, *H*-3), 2.46 (1H, bt, $J=9.9$ Hz, *H*-8β), 2.03 (3H, s, *Me*CO), 1.28 (3H, d, $J=6.0$ Hz, *H*-21), 0.76 (3H, s, *H*-19), 0.69 (3H, s, *H*-18).

4.1.15. (20*R*)-6-Aza-7-oxo-5α-pregnane-3β,20-diyl acetate benzoate (23). Oxime **22** (360 mg, 0.75 mmol) was dissolved in pyridine (1.0 mL) and cooled to 0 °C under stirring. Mesyl chloride (0.3 mL, 3.9 mmol) was dripped into the solution. After 2 h, the reagent was destroyed with crushed ice (10 g) and the precipitate was filtered off. The product was dissolved in methylene chloride (20 mL) and washed with the solution of hydrochloric acid, water and the potassium hydrogen carbonate solution. The extract was dried over sodium sulfate and the solvent was evaporated to yield the title compound **23** (360 mg, 100%) as white crystals. Mp 211–214 °C (278 mg, 77%, acetone–heptane); [found: C, 71.9; H, 8.3; N 2.80. $C_{29}H_{39}NO_5$ requires C, 72.32; H, 8.16; N, 2.91%]; $[\alpha]_D=-19.7$ (*c* 0.2, $CHCl_3$); ν_{max} ($CHCl_3$) 3392, 1731, 1709, 1654, 1273, 1252, 1036, 1027, 964, 714; δ_H (200 MHz, $CDCl_3$) 8.04 (2H, m, *ortho*-Ar*H*), 7.57 (1H, m, *meta*-Ar*H*), 7.44 (2H, t, *para*-Ar*H*), 5.24–5.09 (1H, m, *H*-20), 4.85–4.65 (1H, m, *H*-3), 4.16–3.62 (1H, m, *H*–N), 3.21 (1H, bd, $J=12.0$ Hz, *H*-5), 2.03 (3H, s, *Me*CO), 1.28 (3H, d, $J=6.0$ Hz, *H*-21), 0.88 (3H, s, *H*-19), 0.74 (3H, s, *H*-18); *m*/*z* (EI) 481 (M^+, 27), 359 (25), 344 (14), 224 (8), 105 (40), 65 (44), 43 (100%).

4.1.16. (20*R*)-3β,20-Dihydroxy-6-aza-5α-pregnan-7-one (24). Diester **23** (43 mg, 0.09 mmol) was treated with a boiling solution of potassium hydroxide (104 mg, 1.85 mmol) in aqueous methanol (2 drops of water, 10 mL of methanol). After 8 h, the solution was concentrated in vacuo, diluted with brine (5 mL) and placed in a refrigerator. The title compound **23** (29 mg, 100%) formed precipitate, which was filtered off and washed with water (15 mL); mp 274–275 °C (acetone); [found: C, 69.7; H, 9.9; N, 3.9. $C_{20}H_{33}NO_3\cdot 0.5H_2O$ requires C, 69.73; H, 9.95; N, 4.07%]; $[\alpha]_D=-10.1$ (*c* 0.35, $CHCl_3$). ν_{max} ($CHCl_3$) 3609, 3393, 1653, 1042; δ_H (200 MHz, $CDCl_3$) 5.27–5.19 (1H, m, *H*–N), 3.82–3.62 (2H, m, *H*-3, *H*-20), 3.05 (1H, dd, $J=12.2$, 3.6 Hz, *H*-5), 1.15 (3H, d, $J=6.1$ Hz, *H*-21), 0.92 (3H, s, *H*-19), 0.80 (3H, s, *H*-18).

4.1.17. (20*R*)-6-Aza-5α-pregnane-3β,20-diol (26). Dry lactam **23** (147 mg, 0.31 mmol) was put in a dripping funnel placed between a reflux condenser and a flask with a boiling solution of lithium aluminium hydride (ca. 200 mg, 5.27 mmol) in dioxane (10 mL). The substrate was gradually dissolved in the solvent condensed and washed into the solution. After 6 h, the solution was cooled, the excess of reagent was destroyed with ethyl acetate and a saturated, aqueous solution of sodium sulfate. Anhydrous sodium sulfate was added and the solution was filtered over sodium sulfate. The filter cake was washed with hot chloroform (3×30 mL). The solvent was evaporated in vacuo to yield the title compound **26** (69 mg, 70%), mp 189–192 °C (chloroform); [found: C, 67.2; H, 10.7; N, 3.5. $C_{20}H_{35}NO_2.2H_2O$ requires C, 67.19; H, 10.99; N, 3.92%]; $[\alpha]_D=-7.8$ (*c* 0.13, $CHCl_3$) ν_{max} ($CHCl_3$) 3614, 3394, 1045; δ_H (200 MHz, $CDCl_3$) 3.81–3.52 (2H, m, *H*-3, *H*-20), 3.13 (1H, dd, $J=12.4$, 4.8 Hz, *H*-5), 1.14 (3H, d, $J=6.2$ Hz, *H*-21), 0.90 (3H, s, *H*-19), 0.76 (3H, s, *H*-18).

4.1.18. 6-Aza-5α-pregnane-3,7,20-trione (25). Diol **24** (135 mg, 0.38 mmol) was dissolved in acetone (20 mL) and treated with Jones reagent at laboratory temperature. After 15 min, the reagent was decomposed with methanol (1 mL), the solution diluted with chloroform (100 mL) and its volume was reduced in vacuo to quarter of its volume. The mixture was washed with a solution of potassium hydrogen carbonate and brine. The mixture was dried over sodium sulfate and the solvent was evaporated. Purification of the crude product by PLC (ammoniacal chloroform with 10% of acetone) yielded the title compound **25** (77 mg, 58%), mp 249–250 °C (acetone–heptane); [found: C, 70.4; H, 8.6; N, 4.0. $C_{20}H_{29}NO_3\cdot 0.5H_2O$ requires C, 70.56; H, 8.88; N, 4.11%]; $[\alpha]_D=+37.4$ (*c* 0.36, $CHCl_3$); ν_{max} ($CHCl_3$) 3390, 1714, 1704, 1660, 1418, 1356, 1322; δ_H (200 MHz, $CDCl_3$) 5.34–5.27 (1H, s, *H*–N), 3.42 (1H, dd, $J=12.8$, 5.5 Hz, *H*-5), 2.14 (3H, s, *H*-21), 1.10 (3H, s, *H*-19), 0.72 (3H, s, H-18); *m*/*z* (EI) 317 (M^+, 6), 302 (5), 279 (3), 246 (100%).

4.1.19. 6-Aza-5α-pregnane-3,20-dione (27). A solution of chromium trioxide (230 mg, 2.3 mmol) in water (8 drops) was added to a solution of diol **26** (286 mg, 0.89 mmol) in acetic acid (13 mL) under stirring at room temperature. After 24 h, the mixture was cooled with ice and made alkaline with ammonia (30 mL). The resulting precipitate was extracted with ether, the extract washed with water and dried. Chromatography on a silica column (16 g) in ammoniacal chloroform yielded the title compound **27** (162 mg, 56%), mp 202–204 °C (toluene–heptane); $[\alpha]_D=+79.5$ (*c* 0.3, $CHCl_3$); δ_H (200 MHz, $CDCl_3$) 3.05 (1H, dd, $J=11.7$, 4.3 Hz, *H*-5), 2.52 (1H, t, $J=8.7$ Hz,

H-17), 2.12 (3H, s, *H*-21), 1.07 (3H, s, *H*-19), 0.66 (3H, s, *H*-18); HRMS (EI) M^+ found 317.23539. $C_{20}H_{31}NO_2$ requires 317.23548.%H, 10.46%, 4.16% N.

4.1.20. (20*R*)-6-Aza-7-oxo-5α-pregnan-20-yl acetate (30). To a solution of (20*R*)-7-oxopregn-5-ene-3β,20-diyl diacetate (**28**, 8.0 g, 19.2 mmol) in 2-methyl-2-propanol (480 mL) were added[24] aqueous solutions of potassium carbonate (5.0 g, 36.2 mmol in 140 mL of water), potassium permanganate (70 mg, 0.44 mmol in 9 mL of water), and sodium periodate (7 g, 32.7 mmol in 80 mL of water). The mixture was stirred for 30 min at laboratory temperature and then an additional solution of sodium periodate (28.0 g, 130.9 mmol, in 350 mL of water) and several crystals of potassium permanganate were added. The solution was stirred for a further 6 h at 45 °C, then potassium hydrogen pyrosulfite was added until the solution became colourless. The solution was partially evaporated, sulfuric acid (5 mL, 93.1 mmol) was added and the organic substance was taken up into diethyl ether. The extract was washed with brine and concentrated in vacuo. Crude seco acid was dissolved in methanol (70 mL) and esterified with diazomethane (140 mL of ether solution). On evaporation, ester **29** was dissolved in methanol (16 mL), transferred into an autoclave and cooled to −60 °C. Liquid ammonia (ca. 20 mL) was added and the autoclave was sealed and heated to 55 °C for 20 h. The mixture was concentrated in vacuo and hydrogenated in acetic acid (50 mL) on Adam's catalyst (240 mg). Flash chromatography on a column of silica gel (toluene–ethyl acetate, 10:1) yielded the title compound **30** (940 mg, 14%); mp 280–282 °C (acetone); [found: C, 72.7; H, 10.2; N, 3.9. requires C, 73.09; H, 9.76; N, 3.87%]; $[\alpha]_D=+25.2$ (*c* 0.4, $CHCl_3$). ν_{max} ($CHCl_3$) 3392, 1723, 1651, 1258, 1050; δ_H (200 MHz, $CDCl_3$) 5.43–5.33 (1H, bs, *H*–N), 4.94–4.76 (1H, s, *H*-20), 3.01 (1H, dd, $J=10.0$, 5.0 Hz, *H*-5), 2.02 (3H, s, *Me*CO), 1.16 (1H, d, $J=6.2$ Hz, *H*-20), 0.87 (3H, s, *H*-19), 0.68 (3H, s, *H*-18); *m/z* (EI): 361 (M^+, 100), 333 (12), 318 (7), 302 (36), 286 (24), 206 (22), 192 (35%).

4.1.21. (20*R*)-20-Hydroxy-6-aza-5α-pregnan-7-one (31). Acetate **30** (860 mg, 2.38 mmol) was hydrolysed in a solution of hydrochloric acid (8.0 mL, 97.4 mmol) in chloroform (15 mL) and methanol (100 mL) at 50 °C for 44 h. A mixture was concentrated in vacuo to a quarter of its volume. After addition of brine (50 mL), the title compound **31** (585 mg, 77%) precipitated; mp 264–265 °C (toluene); [found: C, 75.3; H, 10.6; N,4.3. $C_{20}H_{33}NO_2$ requires C, 75.19; H, 10.41; 4.38%N]; $[\alpha]_D=-16.1$ (*c* 0.3, $CHCl_3$). ν_{max} ($CHCl_3$) 3609, 3392, 1648, 1102, 1093; Circular dichroism: $\Delta\varepsilon_{221}$ −1.2, $\Delta\varepsilon_{244}$ +0.3; δ_H (200 MHz, $CDCl_3$) 5.37–5.27 (1H, m, *H*–N), 3.84–3.66 (1H, m, *H*-20), 3.01 (1H, dd, $J=10.5$, 4.9 Hz, *H*-5), 1.15 (3H, d, $J=6.1$ Hz, *H*-21), 0.87 (3H, s, *H*-19), 0.80 (3H, s, *H*-18).

4.1.22. 6-Aza-5α-pregnan-7,20-dione (33). Alcohol **31** (100 mg, 0.33 mmol) was oxidised with Jones reagent in acetone (130 mL) at laboratory temperature. Excessive reagent was reduced with methanol, the solvent was partially removed on a rotary evaporator, and the product was precipitated with the solution of potassium hydrogen carbonate. Organics were extracted with chloroform, washed and dried. The solvent was evaporated in vacuo to yield the title compound **33** (88 mg, 89%); mp 247–251 °C (toluene); [found: C, 75.2; H, 9.8; N, 4.2. $C_{20}H_{31}NO_2$ requires C, 75.67; H, 9.84; N, 4.41%]; $[\alpha]_D=+48.5$ (*c* 0.1, $CHCl_3$). ν_{max} ($CHCl_3$) 3391, 1701, 1652, 1357; δ_H (200 MHz, $CDCl_3$) 5.37–5.27 (1H, m, *H*–N), 3.02 (1H, dd, $J=10.5$, 4.9 Hz, *H*-5), 2.13 (3H, s, *H*-21), 0.88 (3H, s, *H*-19), 0.69 (3H, s, *H*-18).

4.1.23. (20*R*)-6-Aza-5α-pregnan-20-ol (32). Lactam **31** (430 mg, 1.35 mmol) was reduced with lithium aluminium hydride as in Section 4.1.17. The chloroform extract was evaporated in vacuo to yield the title compound **32** (365 mg, 88%); mp 160–162 °C (acetone–heptane); [found: C, 78.4; H, 11.7; N, 4.4. $C_{20}H_{35}NO$ requires C, 78.63; H, 11.55; N, 4.58%]; $[\alpha]_D=-10.2$ (*c* 0.2, $CHCl_3$). δ_H (200 MHz, $CDCl_3$) 3.81–3.63 (1H, m, *H*-20), 1.14 (3H, d, $J=6.1$ Hz, *H*-21), 0.88 (3H, s, *H*-19), 0.76 (3H, s, *H*-18).

4.1.24. 6-Aza-5α-pregnan-20-one (34). Alcohol **32** (100 mg, 0.33 mmol) was oxidised as in Section 4.1.19. The solvent evaporated and the product was purified by PLC (ammoniacal $CHCl_3$ and 5% MeOH) to yield the title compound **34** (58 mg, 58%); mp 129–131 °C (ether); [found: C, 78.8; H, 11.1; N, 4.54. $C_{20}H_{33}NO$ requires C, 79.15; H, 10.96; N, 4.62%]; $[\alpha]_D=+81.0$ (*c* 0.1, $CHCl_3$). δ_H (200 MHz, $CDCl_3$) 3.02 (1H, dd, $J=11.6$, 4.4 Hz, *H*-7), 2.51 (1H, t, $J=8.4$ Hz, *H*-17), 2.11 (3H, s, *H*-21), 0.87 (3H, s, *H*-19), 0.62 (3H, s, *H*-18).

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Silver (I)-promoted asymmetric halohydrin reaction of chiral *N*-enoyl-2-oxazolidinones: scope and limitations

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Abstract—The halohydrin reaction of chiral *N*-enoyl-2-oxazolidinones **1** by halogen (Br_2/I_2) and water were efficiently carried out in aqueous organic solvent promoted by silver(I) with high anti- and regioselectivity and moderate to good diastereoselectivities. The alkenoyl, cinnamoyl and electron-deficient cinnamoyl substrates smoothly underwent bromohydrin reaction in aqueous acetone but no iodohydrin reaction, where as electron-rich cinnamoyl substrates preferred to undergo iodohydrin reaction in aqueous acetone with moderate diastereoselectivity and enhanced diastereoselectivity was observed in aqueous THF.

1. Introduction

Carboxyhalohydrins especially α-halo-β-hydroxycarboxylic acid derivatives are versatile and useful synthetic intermediates because of their facile transformation to a variety of important compounds. These moieties are present in precursors to many biologically active compounds.[1] Carboxyhalohydrins are also good precursors for stereoselective radical reactions.[2] A potentially straightforward method for the synthesis of carboxyhalohydrins is the stereoselective halohydrin reaction of α,β-unsaturated carboxylic acid derivatives.[3] Only few reports on the asymmetric halohydrin reaction are known in literature.[4–6] Henry et al. first reported palladium(II)-catalyzed enantioselective hydroxychlorination of terminal alkenes with a metal chloride—mechanistically it is a hydroxychlorination to alkenes and there is no involvement of halonium (X^+) intermediate.[4] Sudalai et al. described $NaIO_4$ mediated oxidative enantioselective halohydrination of alkenes (encapsulated in β-cyclodextrin) using alkali metal halides with moderate enantioselectivity.[5] Barluenga et al. reported a highly diastereoselective iodohydrination of terpene derivatives using Py_2IBF_4.[6]

There are only a few methods, other than halohydrin reaction, for the stereoselective synthesis of the α-halo-β-hydroxycarboxylic acid derivatives.[7–9] Reagent controlled aldol reaction of chiral α-halogenated imide enolates with suitable aldehydes provide selectively both *anti*- and *syn*-α-halo-β-hydroxycarboxylic acid derivatives.[7] Genet et al. reported the catalytic asymmetric hydrogenation of α-chloro-β-ketocarboxylic acid esters for the enantioselective synthesis of α-chloro-β-hydroxycarboxylic acid esters.[8] Under controlled reaction conditions, epoxide ring opening of β-alkyl-α,β-epoxycarboxylic acids/derivatives provide stereoselectively α-halo-β-hydroxy-, as well as α-hydroxy-β-halocarboxylic acids/derivatives.[9] However, epoxide ring opening of the β-aryl-α,β-epoxycarboxylic acid derivatives with halides give either poor regioselectivity or selectively α-hydroxy-β-halocarboxylic acid derivatives.[9b,d]

In this paper we report in full the silver(I)-promoted asymmetric halohydrin reaction of chiral *N*-enoyl-2-oxazolidinones **1**,[10] in which high regio- and diastereoselectivities up to 82:18 of *anti*-α-halo-β-hydroxy carbonyls **3** and **4** with good yields are demonstrated.

2. Results and discussion

Initially (4*S*)-*N*-cinnamoyl-4-(1-methylethyl)-2-oxazolidinones were selected as substrates for the development of the diastereoselective halohydrin reaction. It was assumed that the β-aryl group of the three-member halonium intermediate **2** would enhance the electrophilicity towards the water nucleophile to achieve high regioselectivity (Scheme 1; R = Ar and R′ = *i*-Pr) and also these carboxyhalohydrins are very important precursors to many biologically active compounds.[1] Moreover our research group is involved in the chelation controlled stereoselective radical

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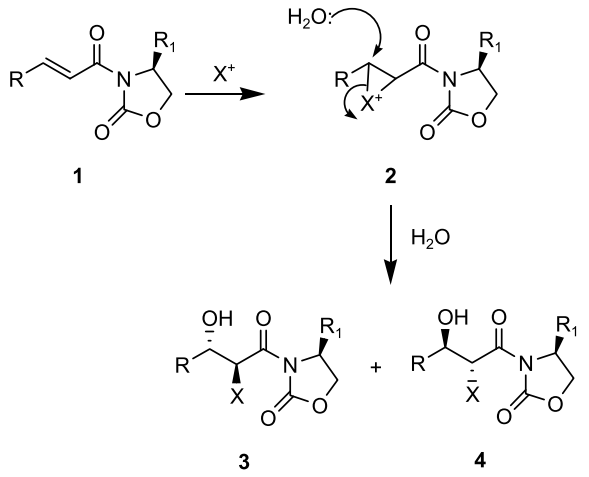


Scheme 1.

reaction of chiral β-aryl-α-halo-β-oxycarboxylic acid esters for the enantioselective synthesis of lignans.[11] However, there is no suitable method, other than the aldol reaction,[7] for the synthesis of the chiral β-aryl-α-halo-β-oxycarboxylic acid derivatives.

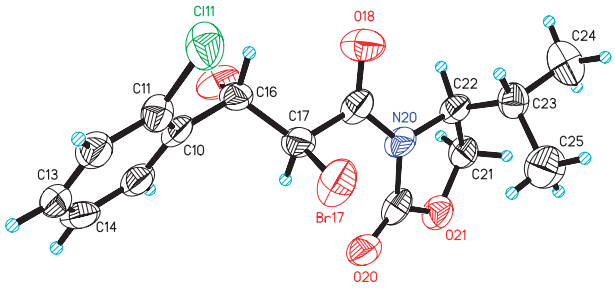
There are only a few reports for the halohydrin reactions of α,β-unsaturated carbonyls.[2d,3,12] By screening these methods, we found that halogen (Br_2/I_2) and silver nitrate ($AgNO_3$) is an effective combination for the halohydrin reaction of *N*-cinnamoyl-2-oxazolidinoes **1** over aromatic electrophilic substitutions. Halohydrin reaction of **1a** (R= Ph and R′=*i*-Pr) with Br_2 and $AgNO_3$ in aqueous acetone gave the desired carboxybromohydrine, along with a minor amount of a non-separable mixture of diastereoisomers (dr 60:40) of a dibromo compounds -*anti*-(4*S*)-3-(2′,3′-dibromo-3′-phenyl-propionyl)-4-(1-methylethyl)-2-oxazolidinone (**5a**). The formation of **5a** varied with the amount of water in the reaction media. A systematic study showed that when the acetone/water ratio was maintained between 4:1 and 6:1, it gave >95:05 of carboxybromohydrins; lower as well as higher amount of water enhanced the formation of **5a**. The compound **5a** was characterized by the ^1H and ^{13}C NMR spectra analysis and compared with the authentic dibromo compound, prepared on reaction of **1a** with Br_2 in CCl_4. It was also found that there was no reaction in 50% aqueous acetone and no appreciable change in the product distribution when the concentrations of the reaction medium were varied between 0.1 M and 0.5 M in a 4:1 (v/v) acetone/water ratio. All halohydrin reactions were performed in aqueous organic solvent (solvent: H_2O, 4:1 v/v) at 0.2 M concentration.

To establish suitable reaction conditions, initially $AgNO_3$-promoted halohydrin reactions of three electronically different cinnamoyl substrates **1a**–**1c**, containing (4*S*)-4-(1-methylethyl)-2-oxazolidinone as chiral auxiliary were studied (Table 1). When a solution of **1a** in aqueous acetone (acetone/water 4:1) was treated with $AgNO_3$ (1.2 equiv) and Br_2 (1.2 equiv) at rt (25 °C), it gave the desired carboxybromohydrin with poor diastereoselectivity (dr 52:48; entry 1) and the diastereomeric ratio was increased to 65:35 (entry 2) when the reaction was performed at 0–5 °C. The bromohydrin reaction of **1a** in aqueous acetonitrile was comparable (entry 3) with aqueous acetone. However, there was no bromohydrin reaction in aqueous DMF, DMSO and THF (entry 4). Iodohydrin reaction of **1a** under the same reaction conditions gave <5% of the desired compounds (entry 5), also there was no improvement even with the use of excess reagents and under different reaction conditions. While the bromohydrin reaction of **1b** was performed under the same reaction conditions, it gave mixture of products (entry 6). However, **1b** smoothly underwent iodohydrin reaction with 70:30 diastereoselectivity (entry 8) in aqueous acetone. There is no appreciable change in diastereomeric ratio and yield when the reaction was performed at rt (25 °C) (entry 7). Unlike **1a**, **1b** underwent iodohydrin reaction in aqueous THF with improved diastereoselectivity of 80:20 (entry 9). Bromohydrin reaction was also studied for the

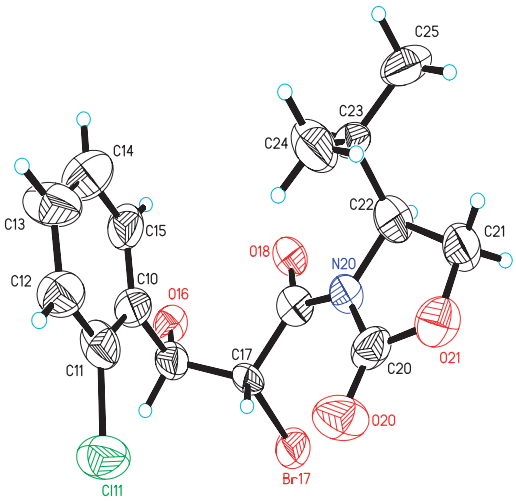
Table 1. $AgNO_3$-promoted halohydrin reactions of **1** under different reaction conditions

	Substrate	R	R_1	Solvent	X	Ratio[a] (**3**:**4**)	Yield[b] (%)
1[c]	**1a**	Ph	*i*-Pr	Acetone	Br	52:48 (55:45)	88
2	**1a**	Ph	*i*-Pr	Acetone	Br	65:35 (66:34)	92
3	**1a**	Ph	*i*-Pr	CH_3CN	Br	64: 36 (62:38)	82
4	**1a**	Ph	*i*-Pr	DMF or DMSO or THF	Br		NR
5	**1a**	Ph	*i*-Pr	Acetone or THF or CH_3CN	I	ND	<5%[d]
6	**1b**	4-$MeOC_6H_4$	*i*-Pr	Acetone	Br	ND	[e]
7[c]	**1b**	4-$MeOC_6H_4$	*i*-Pr	Acetone	I	65:35 (68:32)	86
8	**1b**	4-$MeOC_6H_4$	*i*-Pr	Acetone	I	70:30 (70:30)	89
9	**1b**	4-$MeOC_6H_4$	*i*-Pr	THF	I	80:20 (82:18)	92
10	**1c**	2-ClC_6H_4	*i*-Pr	Acetone	Br	62:38 (65:35)	91
11[c]	**1c**	2-ClC_6H_4	*i*-Pr	Acetone	Br	52:48	87
12	**1c**	2- ClC_6H_4	*i*-Pr	Acetone	I		NR
13	**1d**	Ph	Ph	Acetone	Br/I	ND	[e]
14	**1e**	Ph	Ph_2CH	Acetone	Br/I	ND	[e]
15	**1f**	4-$MeOC_6H_4$	Ph	Acetone	Br/I	ND	[e]
16	**1 g**	4-$MeOC_6H_4$	Ph_2CH	Acetone	Br/I	ND	[e]

[a] Determined from the ^1H NMR spectrum of the crude reaction mixture. Ratio in the parentheses refer to the ratio of isolated **3** and **4** after column chromatography.
[b] Combined isolated yields of **3** and **4** after chromatography.
[c] Reaction at room temperature (25 °C).
[d] >90% of **1a** was recovered.
[e] Mixture of products. ND: Not determined; NR: No reaction.



compound **3c**



compound **4c**

Figure 1. ORTEP diagram of **3c** and **4c**.

electron-deficient substrate **1c**, obtaining moderate diastereoselectivity with good yield (entry 10). Like **1a**, when the bromohydrination of **1c** was performed at rt, it also showed poor diastereoselectivity (entry 11) as well as not responding to the iodohydrin reaction (entry 12). The configurational assignments for the diastereomeric carboxyhalohydrins **3** and **4** were made by confirming the stereochemistry of **3a** and **4a** on comparison with the literature data.[7d,13] This was confirmed by the single crystal X-ray analysis[14] of **3c** and **4c** (Fig. 1), crystallized from $CHCl_3$.

Since, the (4*S*)-4-(1-methylethyl)-2-oxazolidinone chiral auxiliary gave moderate to good diastereoselectivities, we also examined other oxazolidinone chiral auxiliaries viz (4*S*)-4-phenyl- and (4*S*)-4-(diphenylmethyl)-2-oxazolidinones.[10,15] Unfortunately, halohydrin reaction of substrates **1d**–**1e**, having different oxazolidinone chiral auxiliaries (R′=Ph, Ph_2CH) using Br_2 and/or I_2, gave mixture of products. Only 12% of an undesired compound was obtained in pure form from the bromohydrin reaction of **1d**. The same compound was obtained in 56% yield, along with minor amount (26%) of another undesired product, when **1d** was treated with $AgNO_3$ and Br_2 in dry acetone i.e. in the absence of any external nucleophile at 0–5 °C. Recently, Barluenga et al. found that phenyl group present in the terpene moiety undergoes halocarbocyclization during the iodohydrination of alkenes tethered in terpene derivatives with Py_2IBF_4.[6] Spectral analysis of the undesired compounds were found to be bromo-carbocyclized product, but the regio- and stereochemistry of the bromo-carbocylized products could not be confirmed. Our several attempts were also failed to get single crystal X-ray difraction quality crystals.[16]

To assess whether the counter anion of the Ag(I) salt affects the diastereoselctivity of the halohydrin reactions, product studies were carried out employing the electronically different cinnamoyl substrates **1a**–**1c**, using AgOAc and Ag_2O instead of $AgNO_3$ as a promoter, under a variety of reaction conditions (Table 2). $AgNO_3$ (Eq. 1) and AgOAc (Eq. 2) produce acids on reaction with a halogen in water, whereas Ag_2O does not produce any acid (Eq. 3) under the same reaction conditions. When the halohydrin reactions of **1a**-**1c** were performed in the presence of AgOAc instead of $AgNO_3$, similar results were obtained, that is, **3** was produced as the major diastereoisomer (Table 2; entries 1–3). But in the case of Ag_2O-mediated reactions, **1a** and the electron-deficient **1c** showed very poor diastereoselectivities (entries 4 and 6), whereas **1b** still showed **3b** as the

Table 2. AgOAc- and Ag_2O-promoted halohydrin reaction of **1**[a]

Entry	Substrate	Ag(I) salt	Additive	X	Ratio[b] (**3**:**4**)	Yield[c] (%)
1	**1a**	AgOAc	None	Br	65:35	94
2	**1b**	AgOAc	None	I	80:20	91
3	**1c**	AgOAc	None	Br	60:40	90
4	**1a**	Ag_2O	None	Br	50:50	97
5	**1b**	Ag_2O	None	I	65:35	88
6	**1c**	Ag_2O	None	Br	50:50	94
7	**1a**	Ag_2O	HNO_3	Br	67:33 (66:34)	96 (95)
8	**1b**	Ag_2O	HNO_3	I	79:21 (77:23)	90 (87)
9	**1c**	Ag_2O	HNO_3	Br	61:39 (62:38)	94 (91)

[a] Halohydrin reactions were performed using 0.7 equiv of Ag_2O and 1.2 equiv of halogen (X_2) in aqueous organic solvent (**1a** and **1c** in aqueous acetone and **1b** in aqueous THF) at 0–5 °C for 30 min.
[b] Determined from the ^1H NMR spectrum of the crude reaction mixture.
[c] Isolated yields: ratios in parentheses refer to the reactions in the presence of AcOH.

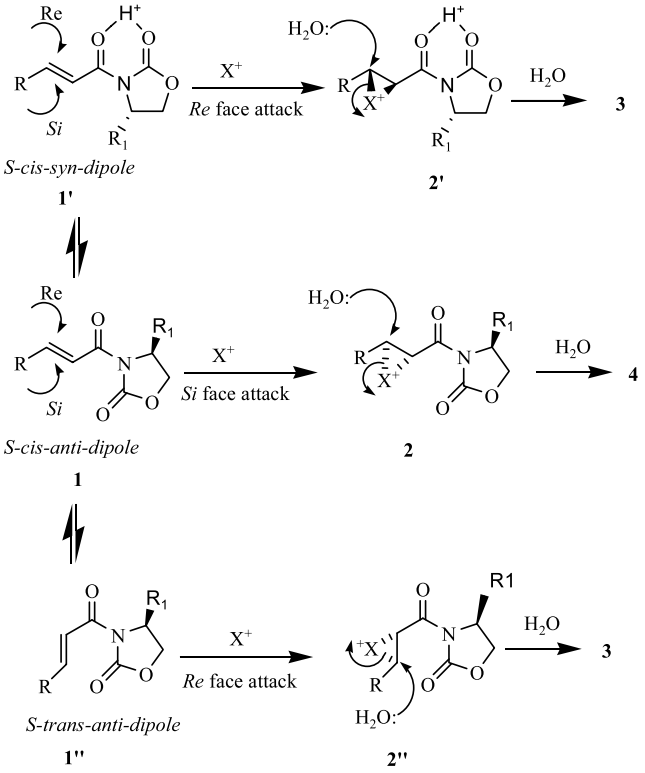
major diastereomer with dr of 65:35 (Table 2; entry 5). When the Ag_2O-promoted halohydrin reactions of **1a–1c** were performed in the presence of either HNO_3 or AcOH as an additive, these showed diastereoselectivities (Table 2; entries 7–9) similar to either $AgNO_3$- or AgOAc-promoted reactions (Table 1, entries 2, 9 and 10 and Table 2, entries 1–3).

$$AgNO_3 + X_2 + H_2O \rightarrow AgX\downarrow + HOX + HNO_3 \quad (1)$$

$$AgOAc + X_2 + H_2O \rightarrow AgX\downarrow + HOX + AcOH \quad (2)$$

$$Ag_2O + 2X_2 + 2H_2O \rightarrow 2AgX\downarrow + 2HOX \quad (3)$$

Unchelated *N*-cinnamoyl-2-oxazolidinone usually exists in the *S-cis-anti-dipole* conformation **1**,[17] so it was also expected to give carboxyhalohydrin **4** as a major diastereoisomer for the above halohydrin reactions, but that was not observed. So it might be concluded here that in either $AgNO_3$ or AgOAc promoted reactions, the H^+-chelated *S-cis-syn-dipole* conformation **1′** might be involved in the halohydrin reaction. The preferred attack of X^+ from the *Re*-face of conformation **1′** and subsequent opening of the halonium intermediate **2′** by *anti*-nucleophilic attack of H_2O at the β-position yielded **3** as the major diastereoisomer (Scheme 2). The poor diastereoselectivities of the cinnamoyl- and electron-deficient cinnamoyl substrates **1a** and **1c** in Ag_2O-promoted reactions i.e. under unchelated conditions (Table 2; entries 4 and 6) might be accounted for by the involvement of both the equilibrated *S-cis-* and *S-trans-anti-dipole* conformations **1** and **1″**. The iodohydrination of electron-rich cinnamoyl substrate **1b** promoted by Ag_2O, that is, under unchelated conditions still showed carboxyhalohydrin **3b** a major diastereoisomer. This could be due to the extensive conjugation of the electron-donating substituent at the *p*-position with the α,β-unsaturated carbonyls, equilibrium might be shifted more towards the unchelated *S-trans-anti-dipole* conformation **1″** and involve the *Re*-face of *S-trans-anti-dipole* conformation **1″**, providing **3b** as the major diastereoisomer. This was supported by the Ag_2O-mediated reactions performed in the presence of either HNO_3 or AcOH as an additive (Table 2; entries 7–9).



Scheme 2.

It was found that either $AgNO_3$ or AgOAc as a promoter and (4*S*)-4-(1-methylethyl)-2-oxazolidinone as a chiral auxiliary are a better combination for the Ag(I)-promoted halohydrin reaction. So, to generalize this asymmetric halohydrin reaction, the reaction was further studied for a variety of enoyl substrates containing (4*S*)-4-(1-methylethyl)-2-oxazolidinone as a chiral auxiliary (Table 3). Substrate **1h** possessing strong electron-withdrawing substituents, for example, $-NO_2$ group on the aromatic ring, smoothly underwent bromohydrin reaction in aqueous acetone under the same reaction conditions with moderate diastereoselectivity (entry 1). Similar to **1c**, no iodohydrin reaction was observed for **1h**. Substrate **1i** with an electron-donating substituent on the aromatic ring efficiently underwent iodohydrin reaction under the same reaction conditions in aqueous acetone with moderate diastereoselectivity (entry 2). Like **1b**, the iodohydrin reaction of **1i** in aqueous THF provided improved diastereoselectivity (entry 3). Another two electron-rich cinnamoyl substrates **1j** and **1k** also responded to the iodohydrin reaction in aqueous THF with dr of 82:18 and 78:22, respectively (entries 4 and 5). However, due to instability of the minor isomers **4j** and **4k** in silica-gel during column chromatography, they could not

Table 3. $AgNO_3$-promoted halohydrin reaction of different substrates **1**

	Substrate	R	Solvent	X	Ratio[a] (**3**:**4**)	Yield[b] (%)
1	**1 h**	2-$NO_2C_6H_4$	Acetone	Br	60:40	86
2	**1i**	4-$BnOC_6H_4$	Acetone	I	64:36	91
3	**1i**	4-$BnOC_6H_4$	THF	I	80:20	92
4	**1j**	3, 4-$MeOC_6H_3$	THF	I	82:18	77[c]
5	**1k**	4-BnO-3-$MeOC_6H_3$	THF	I	78:22	74[c]
6	**1 l**	3, 5-Br-4-$BnOC_6H_2$	Acetone	Br	65:35	87
7	**1m**	2-naphthyl	Acetone	I	68:32	88
8	**1n**	CH_3	Acetone	Br	62:38[d]	86[e]

[a] Determined from the ^1H NMR spectrum of the crude reaction mixture.
[b] Combined isolated yields of **3** and **4** after chromatography otherwise it is noted.
[c] Isolated yield of the isomer **3**.
[d] Along with 15% of other regio-isomers
[e] Combined isolated yield of **3n**, **4n** and the other regio-isomers.

be obtained in pure form. While the bromohydrin reaction of **1i–1k** were performed under the same reaction conditions; these gave a mixture of products. We have also studied the halohydrin reaction of electronically different cinnamoyl substrates, where **1l** behaved like an electron-deficient cinnamoyl substrate, that is, responded to the bromohydrin reaction in aqueous acetone (entry 6) but no iodohydrin reaction. On the other hand, **1m** acted as an electron-rich cinnamoyl substrate and smoothly underwent iodohydrin reaction in aqueous acetone (entry 7), whereas bromohydrin reaction gave mixture of products. We have also studied the halohydrin reaction of alkenoyl substrate **1n**. This responded to the bromohydrin reaction with moderate diastereoselectivity (entry 8), along with 15% of other regio-isomers, minor isomer **4n** was always obtained as a non-separable mixture with regio-isomers.

3. Conclusion

In conclusion, we have described Ag(I)-promoted asymmetric halohydrin reaction of chiral *N*-enoyl-2-oxazolidinones **1** with high regio- and *anti*-selectivity and moderate to good diastereoselectivity in good yields. Alkenoyl, cinnamoyl and electron-deficient cinnamoyl substrates smoothly undergo bromohydrin reactions but no iodohydrin reactions, whereas electron-rich cinnamoyl substrates prefer to undergo iodohydrin reactions. $AgNO_3$ and AgOAc are found to be better promoters than Ag_2O for promoting diastreoselectivity. It was found that the acids produced on reactions of $AgNO_3$ and AgOAc with halogen in aqueous media were responsible for the involvement of the H^+-chelated *S-cis-syn-dipole* conformation and provided better diastereoselectivity for the halohydrin reactions of *N*-enol-2-oxazolidinoes. It was also found that the oxazolidinone chiral auxiliary should contain alkyl substituents, more specifically non-nucleophilic substituents; otherwise that would act as a competitive nucleophile. This methodology, that is, the direct use of halogen and water promoted by Ag(I), offers an alternative method for the asymmetric synthesis of carboxyhalohydrins, that is, *anti*-α-halo-β-hydroxycarboxylic acid derivatives. We are currently applying the concept of halohydrin reaction to other halonucleophilic (X^+ Nu^-) addition reactions for the asymmetric 1,2-hetero-bifunctionalization of alkenes.

4. Experimental

The ^1H NMR spectra were measured on a Bruker-200 (200 MHz) and Bruker-500 (500 MHz) using $CDCl_3$ as solvent. The ^{13}C NMR spectra were measured with Bruker-200 (50 MHz) and Bruker-500 (125 MHz) using $CDCl_3$ as solvent. ^1H NMR chemical shifts are expressed in parts per million (δ) downfield to $CHCl_3$ ($\delta=7.26$); ^{13}C NMR chemical shifts are expressed in parts per million (δ) relative to the central $CDCl_3$ resonance ($\delta=77.0$). Coupling constants in ^1H NMR are in Hz. IR spectra were recorded using Thermo Nicolet FT-IR spectroscopy. Elemental analyses were carried out using Perkin–Elmer 2400-II and mass spectra were analyzed by Waters LCT mass spectrometer.

Commercial grade reagents were used without further purification. Solvents are used after distillation following usual protocols. For the halohydrin reaction distilled water is used. Flash chromatography was carried out using Acme silica gel (230–400 mesh). Substrates **1** were synthesized following the literature procedures.[10,18]

4.1. General experimental procedure for the halohydrin reaction

To a solution of the substrate **1** (1 mmol) in aqueous organic solvent (20 ml; acetone or THF; organic solvent/H_2O 4:1) Ag(I) (for $AgNO_3$ and AgOAc 1.2 mmol and Ag_2O (0.7 mmol) and halogen (Br_2 or I_2, 1.2 mmol) were added, respectively, at 0–5 °C and allowed to stir for 20–30 min. The reaction mixture was extracted with Et_2O at least three times, washed with water, dried over Na_2SO_4. The organic solution was filtered through a small cellite pad (otherwise locking problem or poor base line was found in the ^1H NMR of the crude mixture) and the filtrate was concentrated under vacuum. Flash column chromatography of the crude mixture using petroleum ether-EtOAc as eluent gave desired carboxyhalohydrins in pure form.

4.1.1. *anti*-(4*S*, 2′*S*, 3′*S*)-3-[3′-Hydroxy-2′-iodo-3′-(4-methoxyphenyl)-propionyl]-4-(1-methylethyl)-2-oxazolidinone (3b). Gummy liquid, $[\alpha]_D^{21}$ +88.4° (*c* 1.0, $CHCl_3$); FTIR (KBr) 3459 (br, OH), 2963, 2837, 1778, 1694, 1612, 1586, 1515, 1484, 1463, 1387, 1303, 1250, 1205, 1178, 1142, 1103, 1022, 971, 835, 789, 768, 728, 694, 565 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.33 (d, $J=8.6$ Hz, 2H), 6.89 (d, $J=8.6$ Hz, 2H), 6.13 (d, $J=7.9$ Hz, 1H), 5.15 (d, $J=7.9$ Hz, 1H), 4.47 (m, 1H), 4.30–4.20 (m, 2H), 3.80 (s, 3H), 3.40 (br s, 1H), 2.5–2.33 (m, 1H), 0.95 (t, $J=6.3$ Hz, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 170.9, 159.7, 152.9, 131.7, 128.3 (2C), 113.9 (2C), 75.4, 63.4, 58.2, 55.2, 27.9, 25.0, 17.7, 15.0. Anal. Calcd for $C_{16}H_{20}INO_5$: C, 44.36; H, 4.65; N, 3.23. Found: C, 44.18; H, 4.45; N, 2.92%.

4.1.2. *anti*-(4*S*, 2′*R*, 3′*R*)-3-[3′-Hydroxy-2′-iodo-3′-(4-methoxyphenyl)-propionyl]-4-(1-methylethyl)-2-oxazolidinone (4b). Gummy liquid; $[\alpha]_D^{22}$ +8.6° (*c* 1.0, $CHCl_3$); FTIR (KBr) 3473 (br OH), 2962, 2929, 1777, 1697, 1611, 1514, 1485, 1463, 1386, 1303, 1250, 1202, 1177, 1120, 1030, 972, 830, 789, 769, 694, 562 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.33 (d, $J=8.7$ Hz, 2H), 6.87 (d, $J=8.7$ Hz, 2H), 6.18 (d, $J=7.0$ Hz, 1H), 5.10 (d, $J=7.0$ Hz, 1H), 4.49–4.11 (m, 3H), 3.79 (s, 3H), 2.37–2.12 (m, 1H), 0.85 (d, $J=7.0$ Hz, 3H), 0.65 (d, $J=7.0$ Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 171.2, 159.7, 153.0, 131.6, 128.0 (2C), 113.9 (2C), 75.8, 63.4, 59.0, 55.3, 28.5, 23.8, 17.8, 14.3. Anal. Calcd for $C_{16}H_{20}INO_5$: C, 44.36; H, 4.65; N, 3.23. Found: C, 44.54; H, 4.86; N, 3.02%.

4.1.3. *anti*-(4*S*, 2′*S*, 3′*S*)-3-[2′-Bromo-3′-hydroxy-3′-(2-chlorophenyl)-propionyl]-4-(1-methylethyl)-2-oxazolidinone (3c). Mp 108–109 °C; $[\alpha]_D^{22}$ +69.9° (*c* 1.0, $CHCl_3$); FTIR (KBr) 3450 (br OH), 2964, 2920, 2849, 1782, 1702, 1464, 1439, 1386, 1302, 1203, 1120, 1049, 1024, 971, 763, 717, 686, 636, 599, 465 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.55–7.51 (m, 1H), 7.42–7.24 (m, 3H), 6.12 (d, $J=7.3$ Hz, 1H), 5.66 (br d, 1H), 4.44 (m, 1H), 4.23 (m, 2H), 3.72 (br s, 1H), 2.5–2.3 (m, 1H), 0.93 (d, $J=7.0$ Hz, 6H); ^{13}C NMR

(50 MHz, $CDCl_3$) δ 169.0, 152.7, 136.5, 133.4, 129.8, 129.7, 128.4, 127.2, 71.7, 63.5, 58.3, 43.1, 28.0, 17.8, 14.8. Anal. Calcd for $C_{15}H_{17}BrClNO_4$: C, 46.12; H, 4.39; N, 3.59. Found: C, 46.08; H, 4.18; N, 3.59%.

4.1.4. *anti*-(4*S*, 2′*R*, 3′*R*)-3-[2′-Bromo-3′-hydroxy-3′-(2-chlorophenyl)-propionyl]-4-(1-methylethyl)-2-oxazolidinone (4c). Mp 123–124 °C; $[\alpha]_D^{21}$ −6.4° (*c* 1.0, $CHCl_3$); FTIR (KBr) 3455 (br OH), 2964, 2926, 1779, 1703, 1676, 1593, 1483, 1465, 1438, 1385, 1301, 1201, 1120, 1049, 1023, 973, 755, 718, 684, 669, 632, 464 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.60–7.45 (m, 1H), 7.40–7.20 (m, 3H), 6.22 (d, J=6.5 Hz, 1H), 5.58 (d, J=6.5 Hz, 1H), 4.42 (m, 1H), 4.33–4.14 (m, 2H), 2.30–2.15 (m, 1H), 0.86 (d, J=7.0 Hz, 3H), 0.60 (d, J=7.0 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 169.1, 152.8, 136.5, 133.2, 129.7, 129.6, 128.2, 127.1, 72.3, 63.4, 58.9, 42.0, 28.3, 17.7, 14.3. Anal. Calcd for $C_{15}H_{17}BrClNO_4$: C, 46.12; H, 4.39; N, 3.59. Found: C, 46.34; H, 4.24; N, 3.54%.

4.1.5. *anti*-(4*S*, 2′*S*, 3′*S*)-3-[2′-Bromo-3′-hydroxy-3′-(2-nitrophenyl)-propionyl]-4-(1-methylethyl)-2-oxazolidinone (3h). Mp 155–156 °C; $[\alpha]_D^{23}$ +113.6° (*c* 1.0, $CHCl_3$); FTIR (KBr) 3381 (br OH), 2965, 1748, 1707, 1529, 1488, 1403, 1393, 1364, 1300, 1281, 1227, 1217, 1143, 1119, 1043, 1018, 972, 853, 780, 749, 719, 674, 608, 504 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.95 (dd, J=8.0, 0.9 Hz, 1H), 7.85–7.60 (m, 2H), 7.57–7.45 (m, 1H), 6.08 (d, J=8.0 Hz, 1H), 5.93 (d, J=8.0 Hz, 1H), 4.49 (m, 1H), 4.35–4.18 (m, 2H), 3.75 (br s, 1H), 2.50–2.33 (m, 1H), 0.94 (d, J=7.0 Hz, 3H), 0.92 (d, J=7.0 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 168.4, 152.8, 149.1, 133.7, 133.3, 129.4, 129.3, 124.6, 69.6, 63.6, 58.3, 43.8, 28.0, 17.7, 14.7. Anal. Calcd for $C_{15}H_{17}BrN_2O_6$: C, 44.90; H, 4.27; N, 6.98. Found: C, 44.60; H, 4.03; N, 6.73%.

4.1.6. *anti*-(4*S*, 2′*R*, 3′*R*)-3-[2′-Bromo-3′-hydroxy-3′-(2-nitrophenyl)-propionyl]-4-(1-methylethyl)-2-oxazolidinone (4h). Gummy liquid; $[\alpha]_D^{22}$ −39.1° (*c* 1.0, $CHCl_3$); FTIR (KBr) 3453 (br OH), 2964, 2927, 2876, 1779, 1704, 1608, 1580, 1529, 1485, 1464, 1386, 1351, 1300, 1203, 1142, 1120, 1052, 1020, 972, 853, 786, 750, 713, 672 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.97 (dd, J=8.0, 0.9 Hz, 1H), 7.87–7.60 (m, 2H), 7.57–7.42 (m, 1H), 6.16 (d, J=7.4 Hz, 1H), 5.90 (d, J=7.4 Hz, 1H), 4.43 (m, 2H), 4.40–4.15 (m, 2H), 2.48–2.15 (m, 1H), 0.89 (d, J=7.0 Hz, 3H), 0.71 (d, J=7.0 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 168.6, 152.9, 148.9, 134.1, 133.4, 129.3, 129.0, 124.8, 70.6, 63.6, 59.1, 42.6, 24.4, 17.7, 14.5. Anal. Calcd for $C_{15}H_{17}BrN_2O_6$: C, 44.90; H, 4.27; N, 6.98. Found: C, 44.67; H, 4.13; N, 6.73%.

4.1.7. *anti*-(4*S*, 2′*S*, 3′*S*)-3-[3′-Hydroxy-2′-iodo-3′-(4-benzyloxyphenyl)-propionyl]-4-(1-methylethyl)-2-oxazolidinone (3i). Mp 163–164 °C; $[\alpha]_D^{22}$ +63.0° (*c* 1.0, $CHCl_3$); FTIR (KBr) 3465 (br OH), 3033, 2959, 2921, 2874, 1768, 1678, 1608, 1515, 1487, 1455, 1429, 1388, 1366, 1329, 1307, 1247, 1221, 1206, 1178, 1119, 1101, 1078, 1049, 1021, 1003, 970, 922, 857, 841, 821, 800, 760, 749, 729, 702, 694, 626, 562, 509, 490 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.50–7.25 (m, 7H), 6.97 (d, J=8.7 Hz, 2H), 6.13 (d, J=7.9 Hz, 1H), 5.16 (d, J=7.9 Hz, 1H), 5.06 (s, 2H), 4.52–4.38 (m, 1H), 4.33–4.18 (m, 2H), 3.44 (br s, 1H), 2.51–2.30 (m, 1H), 0.96 (quasi t, J=5.90, 6.8 Hz, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 171.0, 159.0, 152.9, 136.8, 131.9, 128.5 (2C), 128.3 (2C), 128.0, 127.4 (2C), 114.9 (2C), 75.5, 70.1, 63.0, 58.2, 28.0, 24.9, 17.8, 15.1. Anal. Calcd for $C_{22}H_{24}INO_5$: C, 51.88; H, 4.75; N, 2.75. Found: C, 51.99; H, 4.79; N, 2.67%.

4.1.8. *anti*-(4*S*, 2′*R*, 3′*R*)-3-[3′-Hydroxy-2′-iodo-3′-(4-benzyloxyphenyl)-propionyl]-4-(1-methylethyl)-2-oxazolidinone (4i). Gummy liquid, $[\alpha]_D^{23}$ +8.6° (*c* 1.0, $CHCl_3$); FTIR (KBr) 3459 (br OH), 2962, 2925, 1777, 1695, 1609, 1512, 1485, 1463, 1454, 1384, 1302, 1202, 1175, 1120, 1020, 829, 738, 697, 624, 558 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.48–7.25 (m, 7H), 6.96 (d, J=8.7 Hz, 2H), 6.19 (d, J=7.0 Hz, 1H), 5.13–5.05 (m, 3H), 4.51–4.08 (m, 3H), 3.63 (br d, J=7.0 Hz, 1H), 2.32–2.15 (m, 1H), 0.84 (d, J=7.0 Hz, 3H), 0.64 (d, J=7.0 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 171.1, 158.9, 153.0, 136.8, 131.9, 128.5 (2C), 128.0 (2C), 127.9, 127.3 (2C), 114.9 (2C), 75.8, 70.0, 63.4, 58.9, 28.4, 23.7, 17.7, 14.3. Anal. Calcd for $C_{22}H_{24}INO_5$: C, 51.88; H, 4.75; N, 2.75. Found: C, 51.93; H, 4.57; N, 2.75%.

4.1.9. *anti*-(4*S*, 2′*S*, 3′*S*)-3-[3′-Hydroxy-2′-iodo-3′-(3,4-dimethoxyphenyl)-propionyl]-4-(1-methylethyl)-2-oxazolidinone (3j). Mp 164–165 °C; $[\alpha]_D^{23}$ +54.6° (*c* 1.0, $CHCl_3$); FTIR (KBr) 3473 (br OH), 3024, 2964, 1761, 1702, 1607, 1591, 1517, 1484, 1465, 1448, 1438, 1421, 1388, 1365, 1332, 1298, 1262, 1236, 1218, 1201, 1160, 1137, 1119, 1105, 1071, 1052, 1024, 1002, 969, 889, 835, 761, 700, 655, 618, 576 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.10–6.70 (m, 3H), 6.17 (d, J=7.6 Hz, 1H), 5.13 (d, J=7.6 Hz, 1H), 4.45 (m, 1H), 4.25 (m, 2H), 3.90 (s, 3H), 3.88 (s, 3H), 2.51–2.30 (m, 1H), 0.95 (t, J=6.5 Hz, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 171.0, 152.8, 149.0, 148.9, 131.9, 119.4, 110.9, 109.8, 75.6, 63.3, 58.1, 55.9, 55.8, 27.8, 24.6, 17.8, 15.0. Anal. Calcd for $C_{17}H_{22}INO_6$: C, 44.07; H, 4.79; N, 3.02. Found: C, 44.11; H, 4.77; N, 2.85%.

4.1.10. *anti*-(4*S*, 2′*S*, 3′*S*)-3-[3′-Hydroxy-2′-iodo-3′-(4-benzyloxy-3-methoxyphenyl)-propionyl]-4-(1-methylethyl)-2-oxazolidinone (3k). Gummy liquid: $[\alpha]_D^{23}$ +64.3° (*c* 1.0, $CHCl_3$); FTIR (KBr) 3455 (br OH), 2963, 2929, 2875, 1778, 1694, 1594, 1514, 1485, 1463, 1454, 1422, 1386, 1303, 1262, 1203, 1141, 1102, 1020, 971, 912, 857, 804, 767, 734, 697, 648, 617, 563, 456 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.50–725 (m, 7H), 6.94 (s, 1H), 6.87 (m, 2H), 6.15 (d, J=7.6 Hz, 1H), 5.14 (m, 3H), 4.48–4.35 (m, 1H), 4.29–4.16 (m, 2H), 3.90 (s, 3H), 3.57 (br s, 1H), 2.50–2.31 (m, 1H), 0.94 (t, J=6.6 Hz, 6H), ^{13}C NMR (50 MHz, $CDCl_3$) δ 170.9, 152.7, 149.5, 148.1, 136.8, 132.4, 128.4 (2C), 127.4, 127.1 (2C), 119.2, 113.5, 110.3, 75.6, 70.8, 63.2, 58.0, 55.9, 27.7, 24.5, 17.7, 14.9. Anal. Calcd for $C_{23}H_{26}INO_6$: C, 51.22; H, 4.86; N, 2.60. Found: C, 51.06; H, 4.91; N, 2.68%.

4.1.11. *anti*-(4*S*, 2′*S*, 3′*S*)-3-[2′-Bromo-3′-hydroxy-3′-(4-benzyloxy-3, 5-dibromophenyl)-propionyl]-4-(1-methylethyl)-2-oxazolidinone (3l). Mp 170–171 °C; $[\alpha]_D^{22}$ +45.6° (*c* 1.0, $CHCl_3$); FTIR (KBr) 3448 (br OH), 2960, 2922, 2853, 1781, 1700, 1645, 1456, 1380, 1256, 1200, 1116, 1047, 742, 701, 620, 532 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.65–7.55 (m, 4H), 7.51–7.32 (m, 3H), 5.74 (d, J=8.3 Hz, 1H), 5.12 (d, J=8.3 Hz, 1H), 5.03 (s, 2H), 4.50

(m, 1H), 4.42–4.18 (m, 2H), 2.67 (br s, 1H), 2.52–2.25 (m, 1H), 0.99 (d, $J=7.1$ Hz, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 168.7, 152.9, 152.8, 137.8, 136.0, 131.6 (2C), 128.4 (5C), 118.5 (2C), 74.6, 73.3, 63.6, 58.3, 44.6, 28.0, 17.7, 14.7. Anal. Calcd for $C_{22}H_{22}Br_3NO_5$: C, 42.61; H, 3.58; N, 2.26. Found: C, 42.86; H, 3.42; N, 2.19%.

4.1.12. *anti*-(4*S*, 2′*R*, 3′*R*)-3-[2′-Bromo-3′-hydroxy-3′-(4-benzyloxy-3, 5-dibromophenyl)-propionyl]-4-(1-methylethyl)-2-oxazolidinone (4l). Gummy liquid, $[\alpha]_D^{22}$ +6.88° (*c* 1.0, $CHCl_3$); FTIR (KBr) 3473 (br OH), 3064, 3032, 2963, 2926, 2874, 1781, 1705, 1548, 1497, 1485, 1455, 1386, 1303, 1256, 1202, 1141, 1105, 1053, 1019, 970, 914, 875, 740, 697, 632, 537 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.65–7.45 (m, 4H), 7.44–7.33 (m, 3H), 5.87 (d, $J=7.4$ Hz, 1H), 5.09 (d, $J=7.4$ Hz, 1H), 5.03 (s, 2H), 4.45 (m, 1H), 4.40–4.19 (m, 2H), 2.42–2.18 (m, 1H), 0.84 (d, $J=6.9$ Hz, 3H), 0.75 (d, $J=6.9$ Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 168.8, 153.0, 152.8, 137.9, 135.9, 131.4 (2C), 128.4 (5C), 118.6 (2C), 74.6, 73.8, 63.6, 59.0, 43.9, 28.4, 17.7, 14.4.. Anal. Calcd for $C_{22}H_{22}Br_3NO_5$: C, 42.61; H, 3.58; N, 2.26. Found: C, 42.45; H, 3.52; N, 2.08%.

4.1.13. *anti*-(4*S*, 2′*S*, 3′*S*)-3-[3′-Hydroxy-2′-iodo-3′-(2-naphthyl)-propionyl]-4-(1-methylethyl)-2-oxazolidinone (3m). Mp 90–91 °C; $[\alpha]_D^{22}$ +118.3° (*c* 0.8, $CHCl_3$); FTIR (KBr) 3444 (br OH), 2963, 2925, 1779, 1693, 1601, 1386, 1304, 1202, 1142, 1122, 1049, 1019, 819, 749, 694, 479 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.90–7.75 (m, 4H), 7.55–7.45 (m, 3H), 6.30 (d, $J=7.6$ Hz, 1H), 5.33 (d, $J=7.6$ Hz, 1H), 4.41 (m, 1H), 4.19 (m, 2H), 2.49–2.28 (m, 1H), 0.94 (t, $J=7.5$ Hz, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 171.0, 152.8, 136.8, 133.3, 133.0, 128.5, 128.2, 127.6, 126.6, 126.3 (2C), 124.2, 76.1, 63.4, 58.1, 27.9, 24.2, 17.7, 15.0. Anal. Calcd for $C_{19}H_{20}INO_4$: C, 50.35; H, 4.45; N, 3.09. Found: C, 50.40; H, 4.42; N, 3.02%.

4.1.14. *anti*-(4*S*, 2′*R*, 3′*R*)-3-[3′-Hydroxy-2′-iodo-3′-(2-naphthyl)-propionyl]-4-(1-methylethyl)-2-oxazolidinone (4m). Gummy liquid, $[\alpha]_D^{22}$ +14.4° (*c* 0.5, $CHCl_3$); FTIR (KBr) 3458 (br OH), 2963, 1777, 1694, 1601, 1463, 1385, 1303, 1272, 1199, 1120, 1056, 1019, 819, 750, 693, 479 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.90–7.78 (m, 4H), 7.55–7.45 (m, 3H), 6.35 (d, $J=6.7$ Hz, 1H), 5.29 (d, $J=6.7$ Hz, 1H), 4.42–4.08 (m, 3H), 3.90 (br s, 1H), 2.19–1.95 (m, 1H), 0.76 (d, $J=7.0$ Hz, 3H), 0.37 (d, $J=7.0$ Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 171.1, 152.9, 136.6, 133.2, 133.0, 128.4, 128.0, 127.5, 126.2 (2C), 126.1, 124.0, 76.2, 63.3, 58.8, 28.3, 22.8, 17.6, 13.9. Anal. Calcd for $C_{19}H_{20}INO_4$: C, 50.35; H, 4.45; N, 3.09. Found: C, 50.26; H, 4.26; N, 3.03%.

4.1.15. *anti*-(4*S*, 2′*S*, 3′*S*)-3-(2′-Bromo-3′-hydroxy-butionyl)-4-(1-methylethyl)-2-oxazolidinone (3n). Gummy liquid, $[\alpha]_D^{22}$ +60.7° (*c* 1.0, $CHCl_3$); FTIR (KBr) 3442 (br OH), 1783, 1708, 1389, 1333, 1215, 1117, 1028, 772, 714 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.43 (d, $J=8.3$ Hz, 1H); 4.40 (m, 1H); 4.31–4.18 (m, 5H); 3.58 (br s, 1H), 2.39–2.27 (m, 1H); 1.40 (d, $J=6.3$ Hz, 3H); 0.87 (d, $J=7.0$ Hz, 3H); 0.83 (d, $J=7.0$ Hz, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 169.5, 153.8, 69.6, 64.2, 59.7, 47.0, 29.0, 20.5, 18.3, 15.1. MS (*m*/*z*) for $C_{10}H_{16}BrNO_4$: calculated $(M+H)^+$ 294.024, found 294.015 $(M+H)^+$, 296.013 $(M+H+2)^+$. Anal. Calcd for $C_{10}H_{16}BrNO_4$: C, 40.83; H, 5.48; N, 4.76. Found: C, 40.48; H, 5.31; N, 4.75%.

4.1.16. *anti*-(4*S*, 2′*R*, 3′*R*)-3-(2′-Bromo-3′-hydroxy-butionyl)-4-(1-methylethyl)-2-oxazolidinone (4n). Oily liquid, $[\alpha]_D^{22}$ +18.4° (*c* 1.0, $CHCl_3$); FTIR (KBr) 3445 (br OH), 1773, 1702, 1377, 1318, 1200, 1104, 1012, 767, 708, 655 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.35 (d, $J=8.6$ Hz, 1H); 4.45 (m, 1H); 4.30–4.17 (m, 5H); 2.70 (br S, 1H), 2.37–2.27 (m, 1H); 1.39 (d, $J=6.3$ Hz, 3H); 0.87 (dd, $J=2.4$, 6.9 Hz, 6H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 169.6, 153.4, 68.8, 64.0, 58.7, 46.8, 28.5, 20.4, 18.2, 15.2. Anal. Calcd for $C_{10}H_{16}BrNO_4$: C, 40.83; H, 5.48; N, 4.76. Found: C, 40.46; H, 5.17; N, 4.86%.

4.1.17. *anti*-(4*S*)-3-(2′,3′-Dibromo-3′-phenyl-propionyl)-4-(1-methylethyl)-2-oxazolidinone (5a). Non-seperable mixture of diastereomers (60:40); light yellow solid, mp 76–80 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.60–7.26 (m, 5H), 6.58 (d, $J=11.6$ Hz, 1H), 5.51 (d, $J=11.6$ Hz, 1H), 4.65–4.50 (m, 1H), 4.47–4.20 (m, 2H), 2.60– 2.40 (m, 1H), 0.98 (d, $J=6.8$ Hz, 1.8H), 0.97 (d,, $J=6.9$ Hz, 2.4H), 0.95 (d, $J=6.8$ Hz, 1.8H). ^{13}C NMR (125 MHz, $CDCl_3$): major δ 167.6, 153.6, 138.0, 129.9, 129.4 (2C), 128.8 (2C), 64.1, 58.9, 50.6, 44.3, 28.5, 18.2, 15.3. minor δ 167.8, 153.5, 137.9, 129.8, 129.3 (2C), 128.7 (2C), 63.9, 59.5, 51.2, 43.9, 28.7, 18.3, 15.2.

4.2. Bromocarbocyclized product

4.2.1. Major compound. White amorphous solid, mp 156–158 °C. FTIR (KBr) 1760, 1706, 1450, 1382, 1304, 1187, 1109, 1008, 750, 693, 589, 532, 485 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.40–7.20 (m, 9H); 6.01 (d, $J=7.4$ Hz, 1H); 4.45 (dd, $J=8.8$, 3.4 Hz, 1H); 5.08 (d, $J=7.4$ Hz, 1H); 4.74 (t, $J=8.7$ Hz, 1H); 4.25 (dd, $J=8.8$, 3.4 Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 168.8, 152.5, 138.6, 137.7, 129.0 (3C), 128.3 (3C), 126.6 (2C), 125.2 (2C), 75.0, 69.9, 57.7, 44.1. MS (ESI; *m*/*z*) for $C_{18}H_{14}BrNO_3$ calculated $(M+H)^+$ 372.024, found 371.996 $(M+H)^+$, 373.995 $(M+H+2)^+$. Anal. Calcd for $(C_{18}H_{14}BrNO_3+1H_2O)$: C, 55.40; H, 4.13; N, 3.59. Found: C, 55.53; H, 4.04; N, 3.75%.

4.2.2. Minor compound. White amorphous solid, mp 151–153 °C, FTIR (KBr) 1777, 1696, 1460, 1399, 1338, 1224, 1130, 1076, 1040,766, 685, 604, 523 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.60–7.20 (m, 9H); 5.91 (d, $J=8.2$ Hz, 1H); 5.44 (dd, $J=8.6$, 4 Hz, 1H); 5.12 (d, $J=8.2$ Hz, 1H); 4.68 (t, $J=9$ Hz, 1H); 4.26 (dd, $J=8.6$, 4 Hz, 1H) ^{13}C NMR (50 MHz, $CDCl_3$) δ 168.9, 153.1, 139.4, 138.1, 129.7 (2C), 129.4, 129.2, 129.0 (2C), 127.6 (2C), 126.1 (2C), 75.2, 70.5, 58.1, 45.5. Anal. Calcd for $(C_{18}H_{14}BrNO_3 +1H_2O)$: C, 55.40; H, 4.13; N, 3.59. Found: C, 55.38; H, 3.98; N, 3.75%.

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Tributylphosphine as a superior catalyst for the α-*C*-addition of 1,3-dicarbonyl compounds to electron-deficient alkynes

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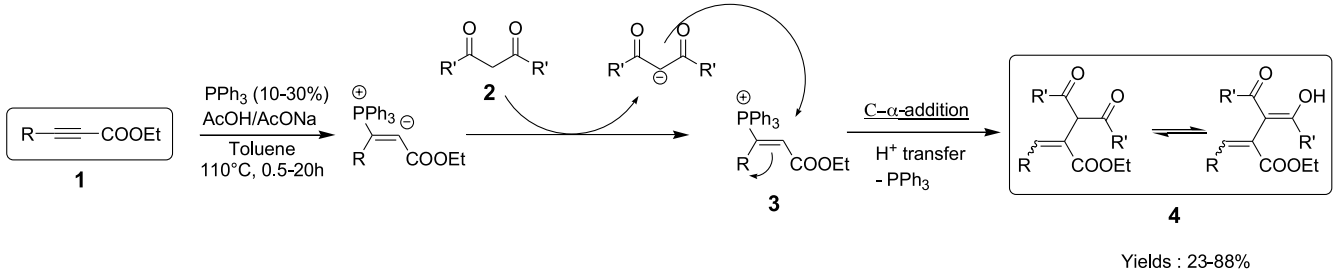
Abstract—The present work describes an improved one pot access to α-(*gem*-difunctional) cinnamate esters and to conjugated 1,3-diketones exploiting the addition of 1,3-diketones, β-keto esters and malonates to alkynoates catalyzed by phosphines. Among the catalysts, nBu$_3$P was found as one of the most effective allowing the reaction to proceed in milder conditions and in a more general manner than with other phosphines.

1. Introduction

1,3-Dicarbonyl compounds are an interesting class of compounds presenting several properties including metal complexation,[1] anticancer[2] and antioxidant activities.[3] Among the earliest and most extensively studied precursors of multiple metal ligands have been β-diketones.[4] Luminescent rare earth 1,3-dicarbonyls complexes, particularly europium and terbium β-diketonates, have been intensively studied with respect to applications for luminescence, laser materials and as organic electroluminescent devices.[5] Connection of the activated methylene group of 1,3-dicarbonyl moieties to unsaturated systems is of particular interest because such transformation provides the possibility to conjugate chromogenic or electron-transporting materials to the metal chelating moiety. Although arylation of 1,3-dicarbonyl substrates are well documented,[6] carbon–carbon bound formations allowing the synthesis of olefins bearing 1,3-dicarbonyl moieties has been much less developed.[7] We recently reported a new carbon–carbon coupling reaction allowing the linkage of 1,3-diketones, malonates, β-ketoesters and β-ketophosphonates to unsaturated systems through a PPh_3-catalyzed α-*C*-addition of these activated methylenes on alkynoates.[8] This reaction provided an easy access to new α-(*gem*-dicarbonyl) acrylic esters **4** in moderate to good yields (Scheme 1).

The proposed mechanism of this reaction was inspired by the work of B. M. Trost et al. who first described nucleophilic α-addition of nitrogen pro-nucleophiles to alkynoates.[9] The first step of the process involves a Michael addition of PPh_3 to alkynoate **1** generating an active phosphonium intermediate **3**, after proton exchange with the 1,3-dicarbonyl compound **2**, which undergoes nucleophilic α-*C*-addition of the enolate followed by a H^+-transfer and elimination of PPh_3 generating product **4**. No α-*O*



Scheme 1. Addition of 1,3-dicarbonyl pro-nucleophiles to alkynoates rerouted by triphenyl phosphine.

Keywords: 1,3-Dicarbonyl compounds; Electrophilic alkyne; Nucleophilic α-addition; Acrylic esters; Phosphine.
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adducts neither Michael type adducts were observed demonstrating the ability of the phosphine to redirect the regio- and chemo-selectivity from the classical β-addition mode. However, drastic conditions were necessary and moderate yields were obtained when substituted propiolates were used. For instance, the reaction of phenyl-ethyl-propiolate with acetylacetone required heating at 110 °C for 19 h in the presence of 20% of PPh_3 to yield 62% of product **4a** (R=Ph, R′=Me) as a mixture of *E*/*Z* isomers (7:3). Moreover, our first unsuccessful attempts to extend this chemistry to other electron-deficient alkynes prompted us to improve our initial procedure.

In this paper, we described an optimized and more general procedure for a simple preparation of conjugated 1,3-dicarbonyl compounds starting from a variety of alkynes bearing electron-withdrawing groups.

2. Results and discussion

A series of new phosphine-catalyzed reactions on electron-deficient alkynes including isomerisation of carbon–carbon triple bonds, umpolung nucleophilic addition on alkynes and cycloadditions of substituted 2-alkynoates have been described.[10] The employed catalytic systems usually involved aryl or alkyl tertiary phosphines in the presence of a weak acid or weak acid and base mixtures as cocatalysts in benzene or toluene. We therefore looked at the influence of these parameters on the reaction of 1,3-dicarbonyl compounds on electron-deficient alkynes.

2.1. Screening of efficient catalysts

Our efforts to improve the procedure were first focused on the catalytic system nature. Since the first step of the mechanism involves a Michael addition of the catalyst on the alkyne, nucleophilic and steric characters of the catalyst should be of great importance in the efficiency of the process. As a model, we used phenyl-ethylpropiolate **1a** and acetylacetone **2a** as reactants. Reactions were conducted in a parallel manner using 20% of 19 different P, N and As nucleophiles as potent catalysts and acetic acid/sodium acetate as cocatalyst in refluxing toluene. Representative results are highlighted in Figure 1.

Diphenylmethylphosphine **C6** and tri-*n*butylphosphine **C9** were found much more active than other tested catalysts suggesting that nucleophilicity prevails in the catalytic activity and that the first step of the process was rate determining. Further experiments proved the superior catalytic activity of nBu_3P (**C9**) and showed that the reaction could occur under milder conditions and shorter time in high yields. This is shown by kinetic experiments conducted at 60 °C (Fig. 2).

In addition, it may also be worth noting that nBu_3P provided

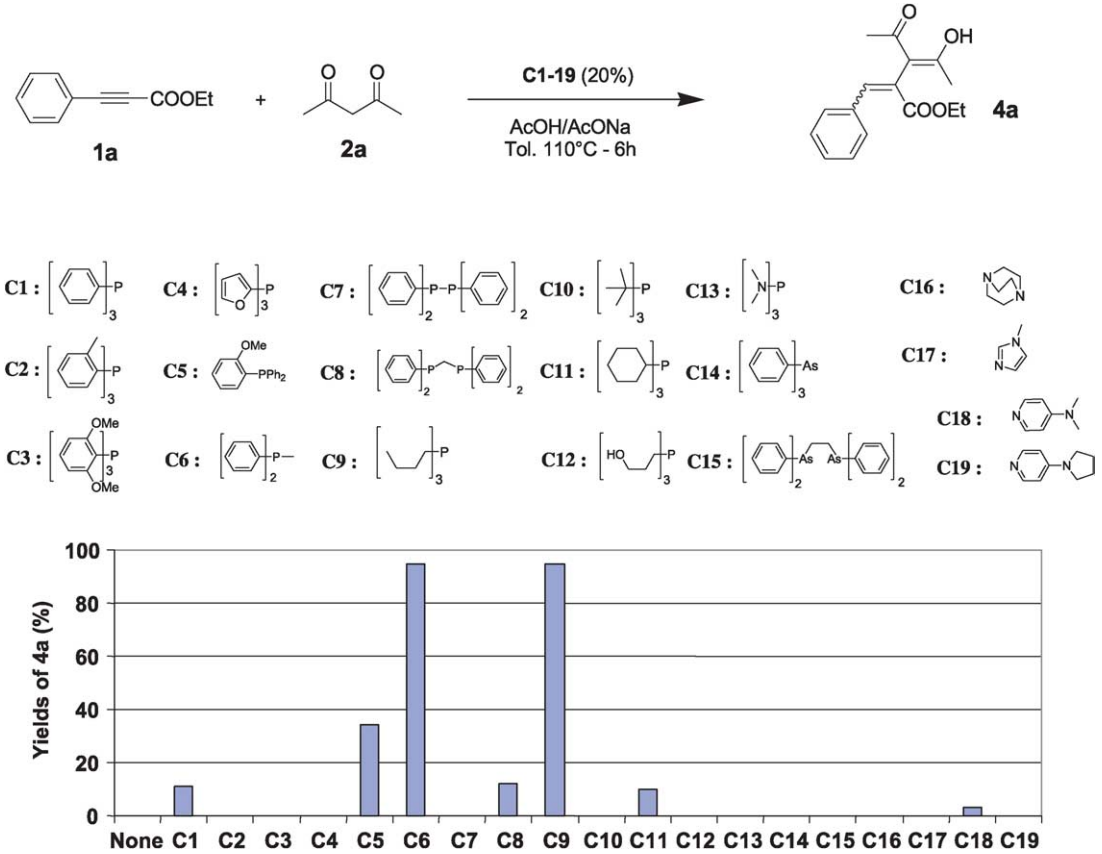


Figure 1. Screening of catalysts (**C1–19**) for the α-addition of acetylacetone **2a** on phenyl-ethylpropiolate **1a**. The mixture of phenyl-ethylpropiolate (0.045 mmol, 1 equiv), acetylacetone (0.050 mmol, 1.1 equiv), catalyst **C1–19** (9 μmol, 0.2 equiv) and cocatalyst (0.023 mmol, 0.5 equiv of NaOAc and AcOH) were stirred in 0.5 mL of toluene for 6 h at 110 °C. **4a** yields were determined by HPLC.

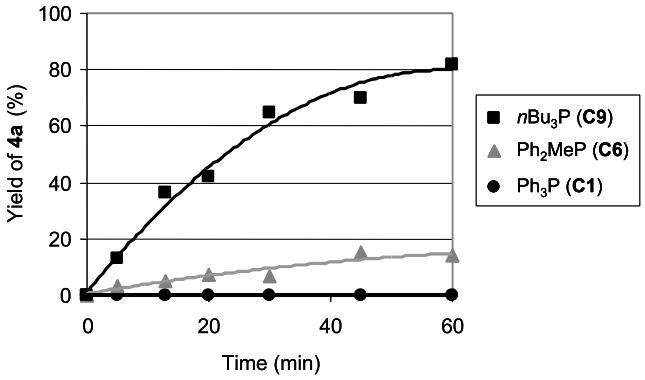


Figure 2. Comparative kinetics of the formation of **4a** catalyzed by phosphines **C1**, **C6** or **C9**. The mixture of phenyl-ethylpropiolate (0.360 mmol, 1 equiv), acetylacetone (0.396 mmol, 1.1 equiv) and catalyst **C1**, **C6** or **C9** (72 μmol, 0.2 equiv) were stirred in 4 mL of toluene for 1 h at 60 °C. **4a** yields were determined by HPLC.

product **4a** as pure *E*-isomer in contrast to other phosphines which produced mixtures of isomers.

2.2. Optimization of the reactions conditions

The influence of the cocatalyst was then investigated. Indeed, according to the proposed mechanism the reaction requires both general acid and base catalysis. We therefore carried out a series of nBu$_3$P catalyzed reactions varying the nature of the acid and base cocatalysts (Table 1).

Table 1. Optimization of the α-addition of acetylacetone on phenyl-ethylpropiolate reaction (influence of the cocatalyst)[a]

Entry	Cocatalyst	Yields of **4a** (%)[b]
1	None	70
2	AcOH/AcONa	77
3	PhOH/PhONa	71
4	HCOOH/HCOONa	42
5	H_2PO_4Na/HPO_4Na_2	67
6	*t*BuOH/*t*BuOK	67

[a] The mixture of phenyl-ethylpropiolate (0.045 mmol, 1 equiv), acetylacetone (0.050 mmol, 1.1 equiv), catalyst **C9** (9 μmol, 0.2 equiv) and cocatalyst (0.023 mmol, 0.5 equiv of a base/acid mixture) were stirred in 0.5 mL of toluene for 1 h at 60 °C.
[b] Yields determined by HPLC.

In our experimental conditions, the reaction occurred easily without the addition of cocatalyst (entry 1), therefore simplifying the experimental procedure. Similar results were described for the isomerisation reaction of carbon–carbon triple bounds.[11]

Finally we have undertaken the nBu$_3$P mediated reaction in several solvents to look at the influence of solvent polarity witch is known to change the ratio of keto/enol forms of 1,3-dicarbonyl compounds.[12] Certain solvents may also functioned as a proton source for the process. For instance, EtOH was found as an essential cocatalyst for the PPh_3 mediated isomerisation of alkynes.[10] The reaction proceeded well in a variety of solvents with no apparent relationship with the keto/enol ratio. However, the presence of by-products were observed in MeOH and water should be avoided in the reaction (Fig. 3).

2.3. α-*C*-Addition of 1,3-dicarbonyl compounds to electron-deficient alkynes

To demonstrate the usefulness of this phosphine-catalyzed reaction, a variety of 1,3-dicarbonyl compounds and electron-deficient alkynes were tested.

As shown in Table 2, various electron-deficient alkynes are suitable for this nBu$_3$P-catalyzed reaction to give the corresponding conjugated 1,3-diketones in good yields. In all cases, the products were isolated as *E* isomer (assignments were done on the basis of δ_{ppm} values of the olefin proton).[13]

The reaction proceeded at room temperature in high yields with alkynes bearing ketones as electron withdrawing groups and is compatible with the presence of hydroxyl function (entry 4). In solution, products **4** were observed exclusively as enolic form.

The nBu$_3$P mediated reaction was then successfully applied to a variety of open-chain 1,3 dicarbonyl compounds (Table 3).

β-Keto esters and malonates undergo smooth α-*C*-addition to phenyl-ethyl propiolate. Reactions with more hindered

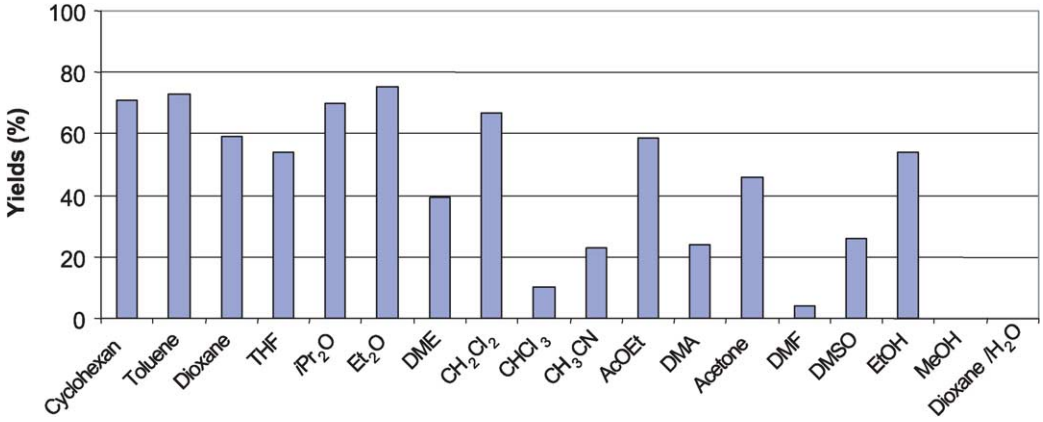
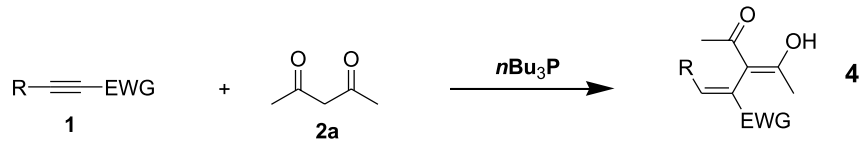
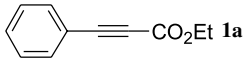
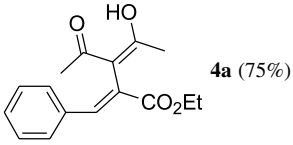
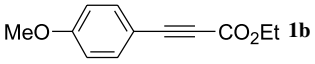
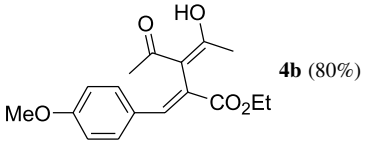
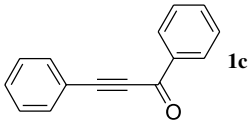
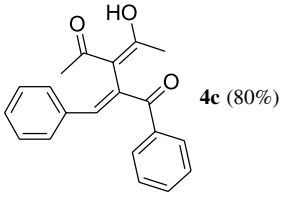
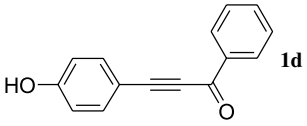
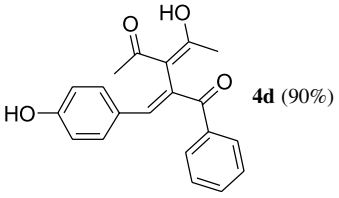
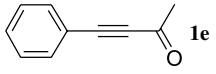
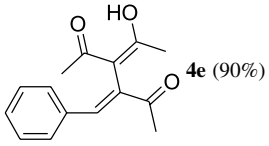


Figure 3. Optimization of the α-addition of acetylacetone on phenyl-ethylpropiolate. Influence of the solvent. The mixture of phenyl-ethylpropiolate (0.045 mmol, 1 equiv), acetylacetone (0.050 mmol, 1.1 equiv), catalyst **C9** (9 μmol, 0.2 equiv) were stirred in 0.5 mL of toluene at 60 °C for 1 h. Yields of **4a** were determined by HPLC.

Table 2. Synthesis of conjugated 1,3-diketones



Entry	Compound **1**	Conditions	Products[a] (yields)[b]
1		Tol., 60 °C, 1 h	 **4a** (75%)
2		Tol., 110 °C, 30 min	 **4b** (80%)
3		Tol., 25 °C, 1 h	 **4c** (80%)
4		Et_2O, 25 °C, 18 h	 **4d** (90%)
5		Tol., 25 °C, 12 h	 **4e** (90%)

[a] The reactions were carried out using alkynes bearing electron withdrawing groups (1 equiv), acetyl acetone (1.1 equiv) and nBu$_3$P (0.2 equiv. All compounds have been fully characterized by using ^{1}H, ^{13}C NMR, FT-IR and mass spectroscopy.
[b] Isolated yield.

1,3-dicarbonyl systems such as β-diketon **2d** or with acetoacetamide **2f** were less efficient and conducted to the formation of non-identified by-products.

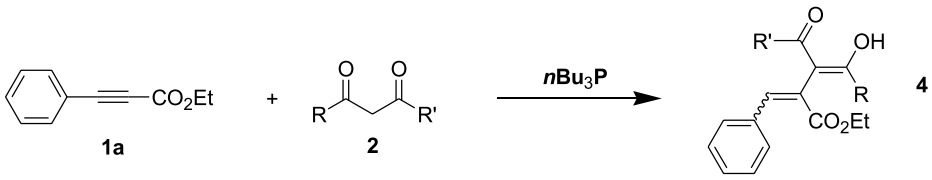
The reaction conducted with dibenzoylmethane **2g** afforded a mixture of products (inseparable by flash chromatography) which were identified by NMR and LC/MS as a 1:1 mixture of the expected cinnamate **4k** (mixture of *Z*/*E* isomers) and compound **5a** probably formed through lactonisation of **4k** (Scheme 2).

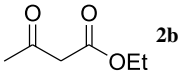
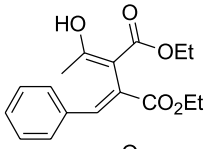
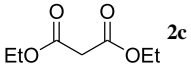
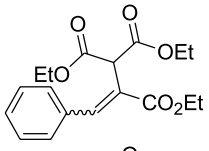
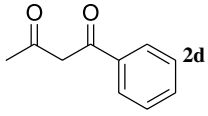
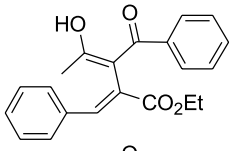
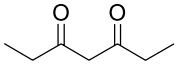
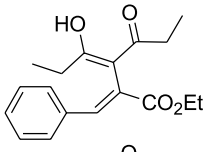
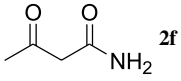
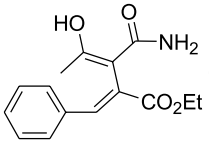
In contrast to open-chain 1,3 dicarbonyl substrates, the reactions involving cyclic 1,3 dicarbonyl pro-nucleophiles were globally more difficult. Thus, reactions required more drastic conditions and often produced by-products. For example, the reaction involving cyclohexane-dione **2h** yielded the expected cinnamate **4l** (mixture of a 8/2 *E*/*Z* isomers) in only 10% yield even after prolonged time of heating. Attempt to improve the yields by addition of co-catalysts were unsuccessful. This reaction conducted to the formation of two by-products ascribed as lactone **5b** and dihydrofuran **6** according to NMR and MS analysis. The later product corresponds to a cyclisation of **4l** through intramolecular Michael addition of the enolate to the vinyl ester moiety and subsequent migration of the double bound to afford 3,4-dihydrofuran derivative **6** (Scheme 3). Such behavior was not observed with open-chain 1,3 dicarbonyl pro-nucleophiles.

3. Conclusion

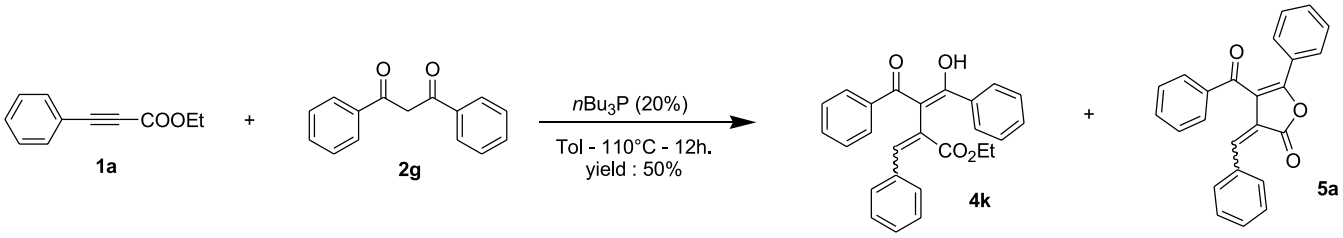
In summary, we have shown that nBu$_3$P was a preferable catalyst for the α-*C*-Addition of 1,3-dicarbonyl compounds to electron-deficient alkynes. The optimized procedure is straightforward, just mixing reactants with nBu$_3$P affords products in good yields. The reaction might be carried out in a variety of solvents on a panel of substrates. Some limitations of the process also occurred during this study. Reaction with non-substituted alkyl propiolates always gave

Table 3. Synthesis of functionalized cinnamates

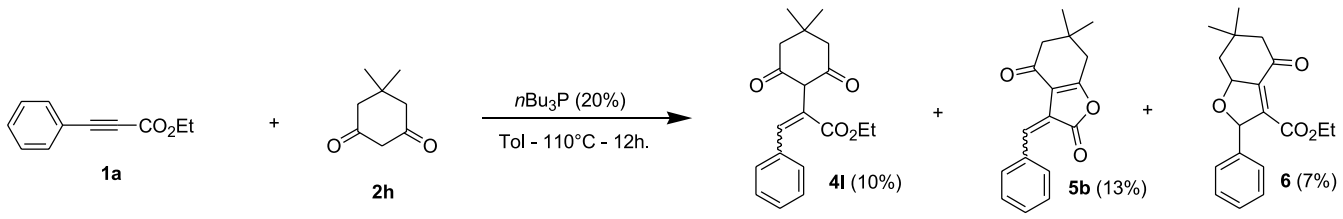


Entry	Activated methylene	Conditions	Products[a] (yields)[b]
1	 **2b**	Tol., 110 °C, 20 min	 **4f** (77%)
2	 **2c**	Tol., 110 °C, 2 h	 **4g** (78%)[c]
3	 **2d**	Tol.,110 °C, 2 h	 **4h** (40%)
4	 **2e**	Tol., 60 °C, 45 min	 **4i** (95%)
5	 **2f**	Tol.,110 °C, 12 h	 **4j** (30%)

[a] The reactions were run using phenyl-ethyl propiolate (1 equiv), activated methylenes (1.1 equiv) and nBu$_3$P (0.2 equiv). All compounds have been fully characterized by using ^{1}H, ^{13}C NMR, FT-IR and mass spectroscopy.
[b] Isolated yield.
[c] This product was obtained as a 8:2 mixture of *E*:*Z* isomers.



Scheme 2. Reaction of phenyl-ethyl propiolate **1a** with dibenzoylmethane **2g**.



Scheme 3. Reaction of phenyl-ethyl propiolate **1a** with cyclohexane-dione **2h**.

mixtures of products when nBu$_3$P was used as catalyst. For example, reaction of ethyl propiolate with acetylacetone in the presence of 10% of nBu$_3$P proceeded rapidly at room temperature to a transient formation of the attempted α-*C* adduct but then underwent decomposition. For this reaction, Ph$_3$P remains the catalyst of choice as we previously described.[8] Also observed were by-products with cyclic and hindered 1,3-dicarbonyls used as pro-nucleophiles.

Nevertheless the presented chemistry leads to unprecedented building blocks that should find broad applications in organic synthesis and in the design of new luminescent materials or antioxidants. Studies in these fields are undergoing in our laboratory.

4. Experimental

4.1. General

Unless otherwise stated, starting materials were obtained from commercial suppliers and used without purification. NMR spectra were recorded on Bruker instrument (AC300 and Avance 400), spectral data are reported in parts per million (δ). MS chromatograms were carried out on ESI/TOF Mariner spectrometer. IR spectra were recorded on NaCl or KBr plates as thin film on an FTIR instrument. LCMS chromatograms were carried out on Waters LC2525 with Micromasss ZQ; column: XTerra MS C18 5 μm, 4.6× 50 mm conditions 95% A: 5%B gradient to 0% A: 100%B (5 min), where A=(0.1% HCO_2H/H_2O) and B=MeCN; Flow: 1 mL min^{-1}. Elemental analyses were measured at the Service de Microanalyse de Gif sur Yvette (ICSN).

4.2. Typical procedure for the preparation of 4

To a mixture of 1,3-dicarbonyl compound (1.1 mmol, 1.1 equiv) and nBu$_3$P (41 mg; 0.2 mmol) in the appropriate solvent (Tol., Et$_2$O or EtOH, 3 mL), was added dropwise under argon an electron-deficient alkyne compound (1 mmol, 1 equiv). The resulting mixture was stirred under the conditions indicated in the tables. After concentrated under reduced pressure the residue was purified by flash chromatography on silica gel to afford pure product **4**. The reported yields are calculated from the ethyl phenyl propiolate.

4.2.1. 3-Acetyl-2-benzylidene-4-hydroxy-pent-3-enoic acid ethyl ester (4a). Flash chromatography performed on silica gel [diethyl ether/*n*-hexane (1:9)]. Colorless oil. (206 mg, 75%). IR (NaCl, cm^{-1}) 3410, 2983, 1702, 1633, 778, 692; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm)=1.32 (t, J=7.3 Hz, 3H, –O–CH_2CH_3), 1.90 (s, 6H, 2×CH_3), 4.28 (q, J=7.3 Hz, 2H, –O–CH_2CH_3), 7.35–7.33 (m, 3H, C_6H_5), 7.46–7.45 (m, 2H, C_6H_5), 7.86 (s, 1H, C_6H_5–CH=), 16.18 (s, 1H, –OH); ^{13}C NMR (J=75.47 Hz, $CDCl_3$) δ (ppm): 14.1, 23.0 (2C), 61.1, 107.8, 126.7, 128.7 (2C), 129.7, 129.8 (2C), 134.4, 142.6, 167.6, 190.7 (2C); MS (ESI/TOF) *m*/*z* 275 [M+1]$^+$, 297 [M+23]$^+$.

4.2.2. 3-Acethyl-4-hydroxy-2-(4-methoxy-benzylidene)-pent-3-enoic acid ethyl ester (4b). Flash chromatography performed on silica gel [diethyl ether/*n*-hexane (3:7)]. White solid. (182.6 mg, 80%).

Mp 66–68 °C. IR (KBr, cm^{-1}) 3631, 2964, 2841, 1705, 1603, 1511, 1254, 1173, 1029; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.29 (t, J=7.3 Hz, 3H, –O–CH_2CH_3), 1.89 (s, 6H, 2×CH_3), 3.79 (s, 3H, H_3C–O–), 4.25 (q, J=7.3 Hz, 2H, –O–CH_2CH_3), 6.85 (d, J=9.2 Hz, 2H, H_3C–O–C_6H_4–), 7.42 (d, J=9.2 Hz, 2H, H_3C–O–C_6H_4–), 7.80 (s, 1H, H_3C–O–C_6H_4–CH=), 16.20 (s, 1H, OH); ^{13}C NMR (J=75.47 Hz, $CDCl_3$) δ (ppm): 14.1, 23.0 (2C), 55.1, 60.9, 108,0, 114.2 (2C), 123.9, 127.0, 131.7 (2C), 142.2, 160.7, 167.8, 190.9 (2C); MS (ESI/TOF) *m*/*z* 305 [M+1]$^+$; Anal. calcd for $C_{17}H_{20}O_5$: C, 67.09; H, 6.62; Found: C, 67.03; H, 6.78.

4.2.3. 2-Benzylidene-3-(1-hydroxy-ethylidene)-1-phenyl-pentane-1,4-dione (4c). Flash chromatography performed on silica gel [AcOEt/*n*-hexane (2:8)]. White solid. (264 mg, 80%). Mp 123 °C. IR (KBr, cm^{-1}) 1646, 1597, 1575, 1250; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 1.95 (s, 6H, 2×–CH_3), 7.3–7.85 (m, 11H, 2×C_6H_5– and C_6H_5CH=), 16.06 (s, 1H, –OH); ^{13}C NMR (J=75.47 Hz, $CDCl_3$) δ (ppm): 23.3, 108.6, 128.4, 128.9, 129.3, 129.7, 130.0, 132.1, 134.4, 134.6, 137.9, 145.6, 190.8, 197.3; MS (ESI/TOF) *m*/*z* 329 [M+23(Na)]$^+$, 635 [2M+23(Na)]$^+$.

4.2.4. 2-(4-hydroxy-benzylidene)-3-(1-hydroxy-ethylidene)-1-phenyl-pentane-1,4-dione (4d). Flash chromatography performed on silica gel [diethyl ether/hexane (1:9)]. Yellow solid. (65 mg, 90%). Mp 142–144 °C. IR (KBr, cm^{-1}) 3321, 2961, 2925, 1641, 1595, 1577, 1260, 1170, 836, 732, 697; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm)=1.96 (s, 6H, 2×CH_3), 5.77 (br s, 1H, –OH phenol), 6.81 (d, J=9.2 Hz, 2H, HO–C_6H_5–), 7.36 (d, J=9.2 Hz, 2H, HO–C_6H_5–), 7.34 (s, 1H, HO–C_6H_5–CH=), 7.49 (t, J=7.32 Hz, 2H, –CO–C_6H_5), 7.58 (d, J=7.32 Hz, 1H, –CO–C_6H_5), 7.77 (d, J=7.32 Hz, 2H, –CO–C_6H_5), 16.11 (s, 1H, –OH *enol*); ^{13}C NMR (J=75.47 Hz, $CDCl_3$) δ (ppm): 23.2 (2C), 108.6, 115.9 (2C), 127.1, 128.2 (2C), 129.1 (2C), 131.2, 132.0 (2C), 132.4, 138.3, 145.7, 157.4, 191.0 (2C), 197.4; MS (ESI/TOF) *m*/*z* 323 [M+1]$^+$.

4.2.5. 3-Benzylidene-4-(1-hydroxy-ethylidene)-hexane-2,5-dione (4e). Flash chromatography performed on silica gel [diethyl ether/hexane (2:8)]. Yellow oil. (317 mg, 90%) IR (NaCl, cm^{-1}) 3513, 3055, 3002, 1711, 1667, 1615, 1231, 1000, 758, 693; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.77 (s, 6H, 2×$CH3$), 2.41 (s, 3H, H_3C–CO–), 7.32–7.28 (m, 3H, C_6H_5–), 7.42–7.39 (m, 2H, C_6H_5–), 7.64 (s, 1H, C_6H_5–CH=), 16.17 (s, 1H, OH); ^{13}C NMR (J=75.47 Hz, $CDCl_3$) δ (ppm): 23.0 (2C), 26.5, 107,9, 128.8 (2C), 129.4, 129.9 (2C), 134.4, 135.4, 142.3, 190.6 (2C), 199.2; MS (ESI/TOF) *m*/*z* 245 [M+1]$^+$, 267 [M+23]$^+$; Anal. calcd for $C_{15}H_{16}O_3$: C, 73.75; H, 6.60; Found: C, 74.12; H, 6.61.

4.2.6. 2-Benzylidene-3-(1-hydroxy-ethylidene)-succinic acid diethyl ester (4f). Flash chromatography performed on silica gel [AcOEt/*n*-hexane (1:9)]. Colorless oil. (244 mg, 77%). IR (neat; cm^{-1}) 2983, 1786, 1712, 1648, 1612, 1247; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 1.13 (t, J=7 Hz, 3H, –OCH_2CH_3), 1.3 (t, J=7 Hz, 3H, –OCH_2CH_3), 1.7 (s, 3H, =C(OH)CH_3), 4.05–4.35 (m,

4H, 2×–OCH_2CH$_3$), 7.2–7.45 (m, 5H,C$_6H_5$CH=), 7.74 (s, 1H, C$_6$H$_5$CH=), 13 (s, 1H, –OH); ^{13}C NMR (J=75.47 Hz, CDCl$_3$) δ (ppm) 13.9, 14.1, 19.0, 60.3, 60.8, 97.7, 125.8, 128.4 (2C), 129.0, 129.4 (2C), 135.0, 141.3, 167.7, 171.9, 173.7; MS (ESI/TOF) m/z 305 [M+1]$^+$.

4.2.7. 2,3-Bis-ethoxycarbonyl-4-phenyl-but-3-enoic acid ethyl ester (4g). Flash chromatography performed on silica gel [AcOEt/*n*-hexane (2:8)]. Yellow oil. (266 mg, 78%). IR (neat, cm^{-1}) 2983, 1749, 1733, 1639, 1255; ^{1}H NMR (300 MHz, CDCl$_3$) δ (ppm): 1.25 (t, J=7.3 Hz, 6H, 2×–OCH$_2$CH_3), 1.32 (t, J=7.3 Hz, 3H, –OCH$_2$CH_3), 4.19 (q, J=7.3 Hz, 4H, 2×–OCH_2CH$_3$),4.28 (q, J=7.3 Hz, 2H, –OCH_2CH$_3$), 4.49 (s, 1H, –O$_2$CCHCO$_2$– Z isomer (20%)), 4.69 (s, 1H, –O$_2$CCHCO$_2$– E isomer (80%)), 7.02 (s, 1H, C$_6$H$_5$CH= Z isomer (20%)), 7.2–7.45 (m, 5H, C$_6H_5$CH=), 7.95 (s, 1H, C$_6$H$_5$CH= E isomer (80%)); ^{13}C NMR (J= 75.47 Hz, CDCl$_3$) δ (ppm) 13.2 Z isomer, 13.7 E isomer, 13.8 E isomer, 50.6 E isomer, 56.6 Z isomer, 60.6 Z isomer, 61.0 E isomer, 61.4 E isomer, 61.6 Z isomer, 126.2, 126.6, 127.7, 128.1, 128.4, 128.5, 128.8, 132.3, 134.1, 135.2, 140.1 Z isomer, 142.4 E isomer, 166.1, 166.6, 167.2; MS (ESI/TOF) m/z 335 [M+1]$^+$; Anal. calcd for C$_{18}$H$_{22}$O$_6$: C, 64.66; H, 6.63; O, 28.71; Found C, 64.91; H, 6.73; O, 28.69.

4.2.8. 3-Benzoyl-2-benzylidene-4-hydroxy-pent-3-enoic acid ethyl ester (4h). Flash chromatography performed on silica gel [AcOEt/*n*-hexane (2:8)]. Yellow oil. (145 mg, 40%). IR (neat, cm^{-1}) 2981, 1785, 1709, 1621, 1243; ^{1}H NMR (300 MHz, CDCl$_3$) δ (ppm): 1.1 (t, J=7.3 Hz, –OCH$_2$CH_3), 1.25 (t, J=7.3 Hz, –OCH$_2$CH_3), 1.98 (s, –COCH_3), 2.03 (s, –COCH_3), 4.1 (m, –OCH_2CH$_3$), 7.15–7.5 (m, C$_6H_5$CH=), 7.73 (s, C$_6$H$_5$CH=), 15.57 (s, –OH); ^{13}C NMR (J=75.47 Hz, CDCl$_3$) δ (ppm): 13.9, 24.2, 61.0, 107.4, 127.3, 127.7, 128.7, 129.6, 129.7, 130.5, 134.7, 136.2, 142.6, 167.6, 184.7, 195.5; MS (ESI/TOF) m/z 337 [M+1]$^+$, 359 [M+23(Na)]$^+$, 695 [2M+23(Na)]$^+$.

4.2.9. 2-Benzylidene-4-hydroxy-3-propionyl-hex-3-enoic acid ethyl ester (4i). Flash chromatography performed on silica gel [diethyl ether/hexane (1:9)]. Colorless oil. (288 mg, 95%). IR (NaCl, cm^{-1}) 3057, 2981, 2940, 2880, 1709, 1620, 1595, 1240, 1194, 1030, 778, 692; ^{1}H NMR (300 MHz, CDCl$_3$) δ (ppm) 0.96 (t, J=7.3 Hz, 6H, 2× CH_3), 1.30 (t, J=7.3 Hz, 3H, –O–CH$_2$CH_3), 2,31–2,07 (m, 4H, 2×CH_2), 4.27 (q, J=7.3 Hz, 2H, –O–CH_2CH$_3$), 7.34–7.32 (m, 3H, C$_6H_5$), 7.47–7.43 (m, 2H, C$_6H_5$), 7.85 (s, 1H, C$_6$H$_5$–CH=), 16.05 (s, 1H, –OH); ^{13}C NMR (J=75.47 Hz, CDCl$_3$) δ (ppm): 8.6 (2C), 14,1, 28,9 (2C), 61.1, 106.6, 126.3, 128.6 (2C), 129.7, 130.0 (2C), 134.4, 142.7, 167.9, 193.7 (2C); MS: m/z (ESI/TOF) 303 [M+1]$^+$, 325 [M+ 23]$^+$.

4.2.10. 2-Benzylidene-3-carbamoyl-4-hydroxy-pent-3-enoic acid ethyl ester (4j). Flash chromatography performed on silica gel [AcOEt/*n*-hexane (2:8)]. White solid. Mp 119 °C. (96 mg, 30%). IR (KBr, cm^{-1}) 3464, 3419, 3329, 3262, 1769, 1713, 1692, 1674, 1637, 1571, 1429; ^{1}H NMR (300 MHz, CDCl$_3$) δ (ppm) 1.29 (t, J= 7 Hz, –OCH$_2$CH_3), 1.75 (s, =C(OH)CH_3), 4.25 (m, –OCH_2CH$_3$), 7.2–7.6 (m, C$_6H_5$CH=), 7.86 (s, C$_6$H$_5$CH=), 14.8 (s, –OH); ^{13}C NMR δ (ppm) 14.0, 19.3, 61.3, 97.0, 125.5, 128.7, 130.1, 133.9, 143.9, 167.7, 173.1, 173.6; MS (ESI/TOF) m/z 298 [M+23(Na)]$^+$, 314 [M+ 39(K)]$^+$, 573 [2M+23(Na)]$^+$.

4.2.11. 3-Benzoyl-2-benzylidene-4-hydroxy-4-phenyl-but-3-enoic acid ethyl ester (4k) and 4-benzoyl-3-benzylidene-5-phenyl-3H-furan-2-one (5a) mixture. Flash chromatography performed on silica gel [AcOEt/*n*-hexane (2:8)]. Yellow oil. 352 mg (212 mg **4k** and 140 mg **5a**). ^{1}H NMR (300 MHz, CDCl$_3$) δ (ppm) 0.97 (t, J=7 Hz, 3H, –OCH$_2$CH_3, **4k**), 3.96 (q, 2H, J=7 Hz, –OCH_2CH$_3$, **4k**), 7.05–8.25 (m, 6H, C$_6H_5$CH= and C$_6$H$_5$CH=, **4k** and **5a**), 15.3 (s, 1H, –OH, **4k**); MS (ESI/TOF) m/z 353 [M+1]$^+$ **5a**, 399 [M+1]$^+$ **4k**, 421 [M+ 23(Na)]$^+$ **4k**, 819 [2M+23(Na)]$^+$ **4k**; LC/MS: m/z 399 [M+1]$^+$ (8.80 min) **4k**; m/z 353 [M+1]$^+$ (8.25 min) **5a**.

4.2.12. 2-(2-Hydroxy-4,4-dimethyl-6-oxo-cyclohex-1-enyl)-3-phenyl-acrylic acid ethyl ester (4l). Flash chromatography performed on silica gel [diethyl ether/hexane(4:6)]. Colorless oil. (15 mg, 10%). ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 1.13 (s, 6H, 2×–CH_3), 1.32 (t, J=7.2 Hz, 3H, –O–CH$_2$CH_3), 2.36–2.32 (m, 4H, 2× CH_2), 4.23–4.20 (m, 2H, –O–CH_2CH$_3$), 4.28 (s, 1H, –(OC)–CH–(OC)–), 6.98 (s, 1H, C$_6$H$_5$–CH= (Z) isomer (23%)), 7.38–7.31 (m, 5H, –C$_6H_5$), 7.95 (s, 1H, C$_6$H$_5$–CH= (E) isomer (77%)); LC/MS m/z 315 [M+1]$^+$ (5.80 min).

4.2.13. 3-Benzylidene-6,6-dimethyl-3,5,6,7-tetrahydro-benzofuran-2,4-dione (5b). Flash chromatography performed on silica gel [diethyl ether/hexane (4:6)]. Colorless oil. (26 mg, 13%) ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 1.16 (s, 6H, 2×–CH_3), 2.41 (s, 2H, CH_2), 2.81 (s, 2H, CH_2), 6.08 (s, 1H, C$_6$H$_5$–CH–), 7.4–7.07 (m, 5H, C$_6$H$_5$–); LC/MS m/z 269 [M+1]$^+$ (6.40 min).

4.2.14. 6,6-Dimethyl-4-oxo-2-phenyl-2,4,5,6,7,7*a*-hexahydro-benzofuran-3-carboxylic acid ethyl ester (6). Flash chromatography performed on silica gel [diethyl ether/hexane (4:6)]. Colorless oil. (14 mg, 7%). ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 1.11 (s, 6H, 2×–CH_3), 1.29 (t, J=7.2 Hz, 3H, –O–CH$_2$CH_3), 2.21 (s, 2H, CH_2), 2.62 (s, 2H, CH_2), 4.19 (q, J=7.2 Hz, 2H, –O–CH_2CH$_3$), 5.26 (s, 1H, –O–CH–(CH$_2$–)–C=C–), 6.22 (s, 1H, C$_6H_5$–CH–(–O–)(C=C–)), 7.54–7.37 (m, 5H, C$_6$H$_5$–); ^{13}C NMR (J= 75.47 Hz, CDCl$_3$) δ (ppm) 14.2, 28.2 (2C), 41.8, 50.5, 60.3, 104.9, 106.7, 125.9 (2C), 128, 129.0 (2C), 131.3, 132.4, 159.7, 163.4, 174.7, 199.3 (2C); LC/MS m/z 315 [M+1]$^+$ (7.07 min).

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Total synthesis of four naturally occurring 2-azaanthraquinone antibiotics, 6-deoxy-8-methylbostrycoidin, 6-deoxybostrycoidin, 7-*O*-demethyl-6-deoxybostrycoidin and scorpinone

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Abstract—A total synthesis of four natural 2-azaanthraquinones, 6-deoxy-8-methylbostrycoidin, 6-deoxybostrycoidin, 7-*O*-demethyl-6-deoxybostrycoidin and scorpinone was accomplished using an optimized procedure for 2-azaanthraquinone synthesis, involving a [4+2]-cycloaddition protocol, of a polyoxygenated diene with a suitably functionalized benzoquinone, acetonylation with pyridinium ylids, cyclisation with ammonia and *O*-demethylation with boron(III) bromide. 2-Azaanthraquinones are rarely found in nature and reveal interesting physiological properties.

1. Introduction

Naturally occurring 2-azaanthraquinones are of special interest due to their important physiological properties.[1] Benz[*g*]isoquinoline-5,10-dione **1**, the unsubstituted azaanthraquinone, has been isolated from *Psychotricha camponutans* and *Mitracarpus scaber*, and exhibits growth inhibition against multi-drug resistant pathogens, for example, *Staphylococcus aureus* and *Plasmodium falciparum*.[1,2] This 2-azaanthraquinone **1** also revealed antimalarial activity, and recently, in vivo and in vitro trypanocidal activity against *Trypanosoma congolense* was discovered (Fig. 1).[2,3]

Besides the unsubstituted 2-azaanthraquinone **1**, also some oxygenated derivatives, for example, bostrycoidin **2** and analogues **3**–**8** as representative members, were found in nature and showed interesting activities. Bostrycoidin **2** and 9-*O*-methylbostrycoidin **3**, two metabolites of numerous *Fusarium* species, showed antibiotic activity against the tubercle bacil and G^+ bacteria, respectively.[4,5] Tolypocladin **4**, from the mycelium of *Tolypocladium inflatum*, displayed metal-chelating properties.[6] In addition, 2-azaanthraquinone derivatives interfere with the activity of DNA topoisomerases and attract considerable attention in cancer chemotherapy as intercalating DNA binding agents.[7] Recently, two new 2-azaanthraquinones, scorpinone **8** and 6-deoxy-8-methylbostrycoidin **5**, were identified in the mycelium of a Bispora-like tropical fungus and in the cultures of the mycobionts of the lichen *Haematomma* sp., respectively.[8,9] From a yellow strain mutant of *Nectria haematococca*, grown in a medium enriched with asparagin 6-deoxybostrycoidin **6**[10] and 7-*O*-demethyl-6-deoxybostrycoidin **7**[11] were isolated as intermediates in the bostrycoidin biosynthesis.

Because of the physiological importance of 2-azaanthraquinones, several methods have been developed for their synthesis. Most pathways deal with a Diels–Alder cyclization of appropriate building blocks, in which the nitrogen is already incorporated.[12–14] However, these methods suffer from the disadvantage of low yield and poor regioselectivity of the incorporation of the methoxy groups. The synthetic pathway used by Watanabe et al. was based on a condensation of C(4)-lithiated nicotinamide with a 2,3,5-trimethoxybenzamide as the key reaction for the construction of the azaanthraquinones.[14] The drawback of this regiospecific method is the low yield due to its multistep pathway, that is, condensation of aromatic rings, selective methylation at the pyridine ring, reduction, ring closure, oxidation and partial demethylation. Recently, we published a straightforward synthesis of 2-azaanthraquinones via an ammonia-induced cyclization of 2-acetonyl-3-bromomethyl-1,4-naphthoquinones.[15] An optimized procedure without the interference of side products, for example, naphtho[2,3-*c*]pyran-5,10-diones, was now developed to synthesize the natural product 6-deoxy-8-methylbostrycoidin **5** for the first time and to result in an improved

Keywords: 2-Azaanthraquinone; Natural products; Naphthoquinone.
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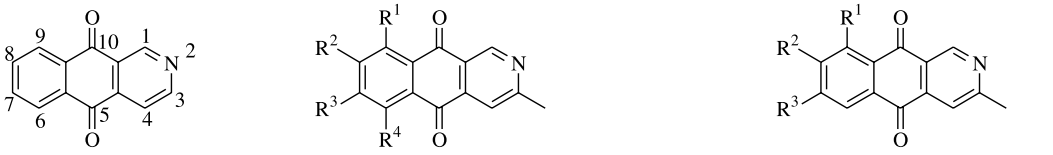


1

2 R^1=R^4=OH, R^2=H, R^3=OMe (bostrycoidin)
3 R^1=R^3=OMe, R^4=OH (9-*O*-methylbostrycoidin)
4 R^1=R^3=R^4=OH, R^2=H (tolypocladin)

5 R^1=OH, R^2=Me, R^3=OMe (6-deoxy-8-methylbostrycoidin)
6 R^1=OH, R^2=H, R^3=OMe (6-deoxybostrycoidin)
7 R^1=R^3=OH, R^2=H (7-*O*-demethyl-6-deoxybostrycoidin)
8 R^1=R^3= OMe, R^2=H (scorpinone)

Figure 1.

synthesis of three natural 2-azaanthraquinone antibiotics, 6-deoxybostrycoidin **6**, 7-*O*-demethyl-6-deoxybostrycoidin **7** and scorpinone **8**.

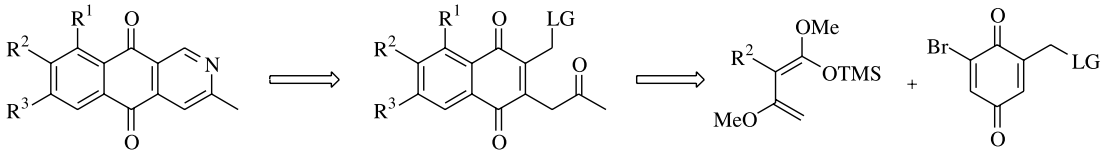
2. Results and discussion

The strategy for the synthetic pathway of the azaanthraquinones **5**–**8** consists of the synthesis of naphthoquinone **9** (LG, leaving group) which leads directly to the desired 2-azaanthraquinone system after treatment with ammonia via an intramolecular substitution (Scheme 1). The idea behind this approach was based on the hypothesis that naturally occurring 2-azaanthraquinones originate in vivo from the incorporation of ammonia into their *O*-analogues.[16] The naphthoquinone skeleton can be synthesized by a cycloaddition of an appropriate electron-rich and oxygenated diene **10** with the brominated benzoquinone **11**. In this strategy the choice of the leaving group in naphthoquinone **9** is determining the outcome of the cyclization reaction towards **5**–**8**. Earlier experiments showed that the use of a bromo atom as leaving group resulted in a mixture of pyranonaphthoquinones and 2-azaanthraquinones when treating naphthoquinones, analogous to **9**, with ammonia. However, when phenoxide was used as a leaving group, the reaction gave predominantly rise to 2-azaanthraquinones with almost no side products.[15,17]

For that reason 4,6-dibromo-2-(phenoxymethyl)phenol **14** was used as a starting material to synthesize 2-azaanthraquinones. The synthesis of **14** was accomplished by treating bromomethylphenol **13** with an excess of phenol under alkaline conditions. The latter brominated phenol **13** was synthesized by reacting *o*-cresol **12** with 3 equiv of bromine, first at 30 °C with 2 equiv of bromine to give the aromatic bromination, and afterwards at 120 °C with 1 equiv of bromine to introduce the bromine at the benzylic position.[18] The substitution reaction of **13** with phenoxide was carried out in good yield without the need for protection of the hydroxyl function of the brominated cresol **13**. Formation of byproducts was successfully suppressed by adding the brominated cresol to a refluxing solution of phenol in acetone in the presence of potassium carbonate (Scheme 2).

2,4-Dibromo-6-(phenoxymethyl)phenol **14** was oxidized by reaction with CrO_3 at room temperature to the benzoquinone **15**, which served as a dienophile in the subsequent regioselective cycloaddition. (1,3-Dimethoxy-1,3-butadien-1-yloxy)trimethylsilane **10a** was synthesized from methyl acetoacetate, while the analoguous 1,3-dimethoxy-2-methyl-1,3-butadien-1-yloxy)trimethylsilane **10b** was prepared from methyl 2-methylacetoacetate.[19] These dienes **10a** and **10b** were subsequently reacted with benzoquinone **15** to yield the substituted naphthoquinones **16a**–**b** in 62 and 55% yield, respectively. Dehydrobromination of the intermediate occurred spontaneously when treated with SiO_2 (during column chromatography). The naphthoquinones **16a**–**b**, bearing a free hydroxyl function, were protected as methyl ethers **17a** and **17b** by reaction with iodomethane and silver(I) oxide, prior to the introduction of an acetonyl group.

In this way, 6,8-dimethoxy-2-(phenoxymethyl)-1,4-naphthoquinones **17a**–**b** were reacted with *N*-(acetylmethyl)pyridinium ylide, formed in situ by reaction of *N*-acetonylpyridinium chloride and triethylamine



5 R^1=OH, R^2=Me, R^3=OMe
6 R^1=OH, R^2=H, R^3=OMe
7 R^1=R^3=OH, R^2=H
8 R^1=R^3=OMe, R^2=H

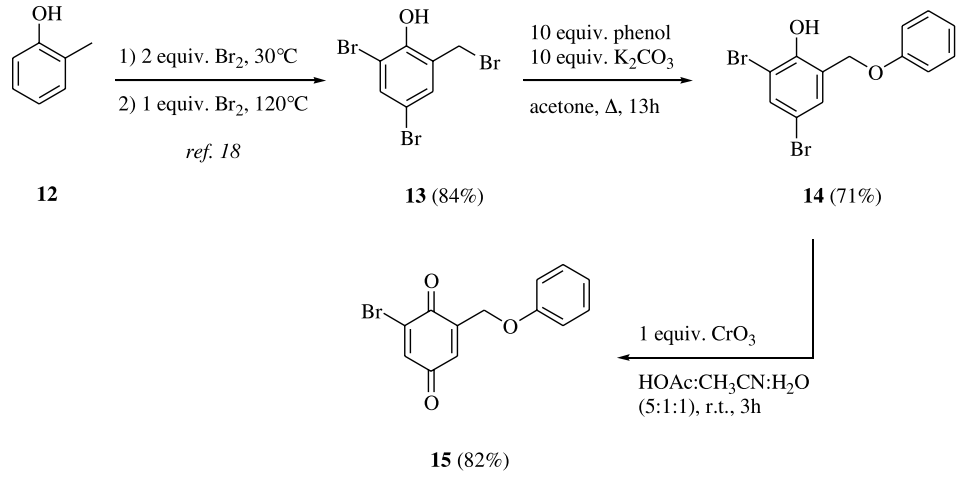
9

LG = Leaving group

10a R^2 = H
10b R^2 = Me

11

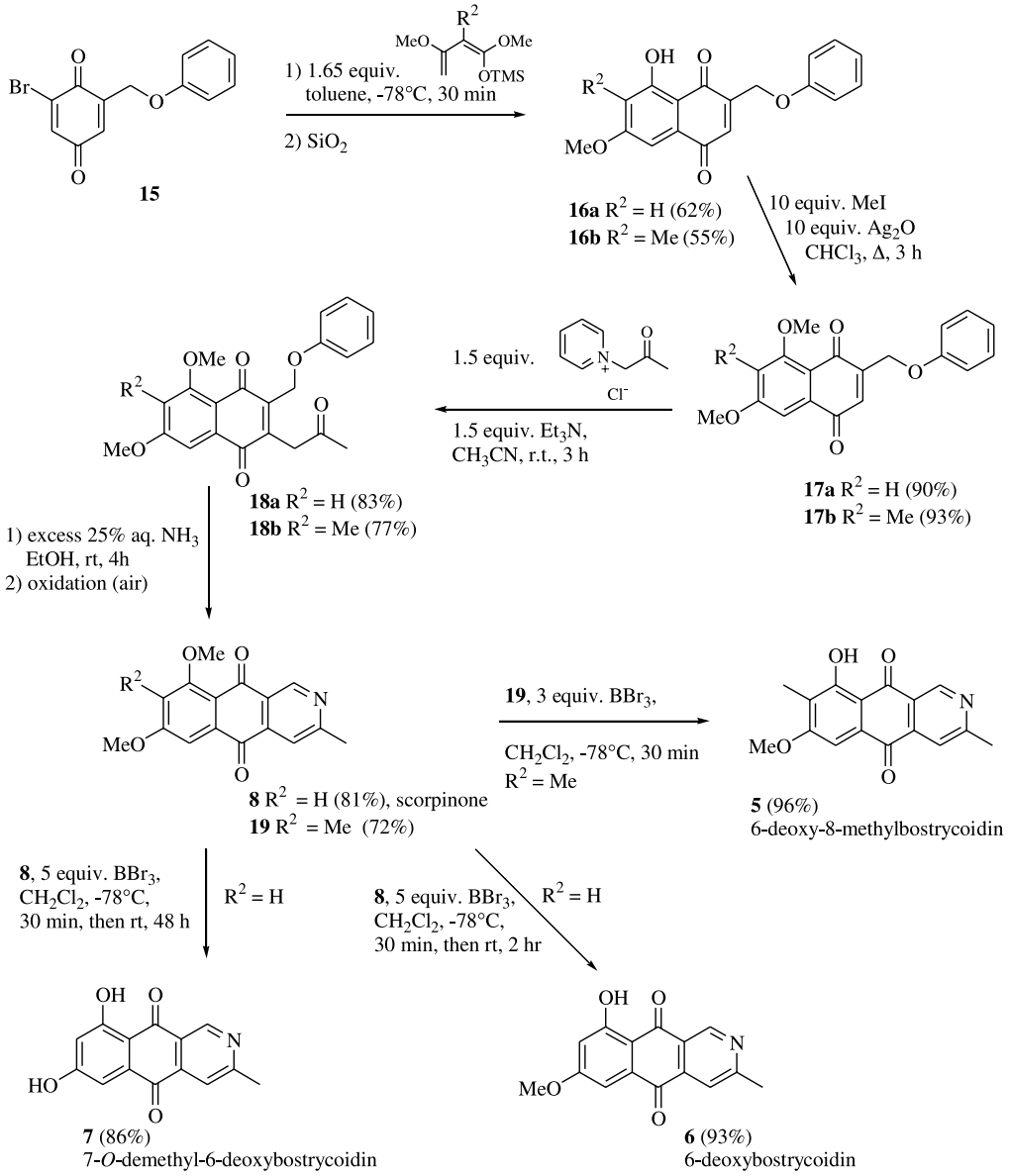
Scheme 1.



12 **13** (84%) **14** (71%)

15 (82%)

Scheme 2.



Scheme 3.

(Scheme 3).[20] The acetonylated products **18a–b** were treated with 10 equiv of ammonia resulting in a nucleophilic addition across the carbonyl of the acetonyl moiety and intramolecular substitution of the phenoxy group. The cyclized product oxidized spontaneously and afforded 2-azaanthraquinone **19** in 72% yield (from **18a**) and the natural product scorpinone **8** in 81% (from **18b**). No naphtho[2,3-*c*]pyran-5,10-dione was formed as side product, contrary to reactions of similar substrates with a bromine instead of a phenoxy group as leaving group. To obtain the recently discovered natural product 6-deoxy-8-methylbostrycoidin **5**, compound **19** was 9-*O*-demethylated using boron(III) bromide in dichloromethane in 96% yield in the final step (Scheme 3). In order to obtain the natural product 6-deoxybostrycoidin **6**, the natural product scorpinone **8** was selectively 9-*O*-demethylated by using 5 equiv of boron(III) bromide and stirring for 2 h at room temperature. A complete *O*-demethylation was obtained by reacting **8** with boron(III) tribromide in dichloromethane at room temperature for 48 h affording the natural product 7-*O*-demethyl-6-deoxybostrycoidin **7** in 86% yield.

In conclusion, using an optimized synthetic approach via dioxygenated 2-phenoxymethyl naphthoquinones, 2-aza-anthraquinones were synthesized by cyclization of 2-phenoxymethyl-3-acetonylnaphthoquinones with ammonia. This reaction pathway resulted in the first straightforward synthesis of the natural product 6-deoxy-8-methylbostrycoidin **5** and an optimized procedure for the natural products scorpinone **8**, 6-deoxybostrycoidin **6** and 7-*O*-demethyl-6-deoxybostrycoidin **7**.

3. Experimental

3.1. General methods

^{1}H NMR spectra (270 MHz) and ^{13}C NMR spectra (68 MHz) were run with a Jeol JNM-EX 270 NMR spectrometer. Peak assignments were performed with the aid of the DEPT technique, 2D-COSY spectra and HETCOR spectra. IR assignments were obtained from a Perkin Elmer Spectrum One spectrophotometer. Mass spectra were measured with an Agilent 1100 Series mass spectrometer (detector VL, 70 eV, ES 4000 V). Melting points were measured with a Buchi B-540 apparatus. The elemental analysis was performed on a Perkin Elmer 2400 Elemental Analyzer. Flash chromatography was carried out on a glass column with ACROS silica gel (particle size 0.035–0.07 mm, pore diameter ca. 6 nm). All solvents and reagents were obtained from commercial suppliers and were used without further purification.

3.1.1. 2,4-Dibromo-6-(phenoxymethyl)phenol (14). A solution of 2,4-dibromo-6-(bromomethyl)phenol **13**[15] (5 g, 14.5 mmol) in 50 ml of acetone was added dropwise to a refluxing mixture of phenol (13.6 g, 0.145 mol) and potassium carbonate (20 g, 0.145 mol) in 100 ml of acetone. After reflux overnight, the solvent was evaporated and the residue was redissolved in dichloromethane. After washing with water, the organic layer was dried over $MgSO_4$, filtered and evaporated in vacuo. Residual phenol was distilled off at high vacuum (0.5 mmHg, at 70 °C). To remove some minor impurities, **14** was purified by column chromatography with 5% ethyl acetate in hexane as eluent, yielding 3.7 g of white crystals (71%), mp 68–69 °C. ^{1}H NMR ($CDCl_3$): δ 5.12 (2H, s, CH_2), 6.10 (1H, s, OH), 6.98–7.03 (3H, m, 3×=CH), 7.26–7.35 (2H, m, 2×=CH), 7.50 (1H, d, J=2.3 Hz, =CH), 7.58 (1H, d, J=2.3 Hz, =CH). ^{13}C NMR ($CDCl_3$): δ 65.3 (CH_2O), 110.9 (C_{quat}), 112.7 (C_{quat}), 114.7 (2×=CH), 121.6 (=CH), 126.2 (C_{quat}), 129.6 (2×=CH), 130.6 (=CH), 133.5 (=CH), 149.2 (=C–O), 157.9 (=C–O). IR (KBr) ν 3408 (OH), 1598 (C=C), 1587 (C=C), 1497 (C=C), 1451 (C=C), 1245, 1222 cm^{-1}. MS *m/z* (%) 355/7/9 ($M-H^+$, 100). Anal. Calcd $C_{13}H_{10}Br_2O_2$: C 43.61%, H 2.82%; found: C 43.24%, H 2.93%.

3.1.2. 2-Bromo-6-(phenoxymethyl)benzo-1,4-quinone (15). To a solution of 2,4-dibromo-6-(phenoxymethyl)-phenol **14** (895 mg, 2.5 mmol) in 20 ml of HOAc:CH_3CN/4:1 was added CrO_3 (250 mg, 2.5 mmol) in 2 ml of aqueous HOAc (50%). The solution was stirred for 3 h at room temperature and, after completion of the oxidation, the mixture was poured in water and extracted with dichloromethane. Evaporation of the solvent in vacuo yielded 700 mg of crude benzoquinone **15**, which was recrystallised from hexane:EtOAc/70:30 (600 mg, 82%), mp 145–146 °C. ^{1}H NMR ($CDCl_3$): δ 4.92 (1H, d, J=2.0 Hz, CH_aH$_b$O), 4.96 (1H, d, J=2.0 Hz, CH$_a$$H_b$O), 6.94–7.05 (4H, m, 4×=CH), 7.26–7.35 (3H, m, 3×=CH). ^{13}C NMR ($CDCl_3$): δ 63.5 (CH_2), 114.6 (2×=CH), 121.9 (=CH), 129.7 (2×=CH), 132.0 (=CH), 137.1, 138.2 and 144.0 (2×C_{quat}, 1×=CH), 157.4 (C_{quat}), 178.9 and 184.4 (2×C=O). IR (KBr) ν 1674 (C=O), 1660 (C=O), 1634 (C=C), 1599 (C=C), 1498 (C=C), 1293, 1250 cm^{-1}. MS *m/z* (%) 293/5 ($M-H^+$, 100). Anal. Calcd $C_{13}H_7BrO_3$: C 53.27%, H 3.09%; found: C 53.41%, H 3.21%.

3.1.3. 8-Hydroxy-6-methoxy-2-(phenoxymethyl)-naphthoquinone (16a). To a solution of 2-bromo-6-(phenoxymethyl)benzo-1,4-quinone **15** (450 mg, 1.54 mmol) in 20 ml of dry toluene at −78 °C was added dropwise a solution of vinyl ketene acetal **10a**[17] (513 mg, 2.54 mmol) in 5 ml of toluene. The reaction was kept at this temperature for 30 min. Then, the resulting mixture was allowed to warm to room temperature and was stirred for 3 h. After the reaction mixture was filtered through silica gel, the filtrate was concentrated in vacuo and the resulting Diels–Alder adduct was recrystallized from ethanol to give 300 mg of the pure product **16a** (62%), mp 151–152 °C. ^{1}H NMR ($CDCl_3$): δ 3.90 (3H, s, CH_3O), 5.05 (2H, d, J=2.3 Hz, CH_2), 6.64 (1H, d, J=2.3 Hz, H-5), 7.00 (1H, s, H-3), 7.03–7.07 (2H, m, 2×=CH), 7.08 (1H, t, J=2.3 Hz, C_3–H), 7.17 (1H, d, J=2.3 Hz, H-7), 7.21–7.36 (2H, m, 2×=CH), 12.10 (1H, s, OH). ^{13}C NMR ($CDCl_3$): δ 53.1 (CH_3O), 63.2 (CH_2), 106.7 (C-7), 108.0 (C-5), 114.7 (2×=CH), 116.5 (C-9$_{quat}$), 121.7 (=CH), 129.7 (2×=CH), 132.6 (C-10$_{quat}$), 134.1 (C-3), 146.8 (C-2), 157.7 (=C–O),, 164.5 (=C–O), 166.4 (=C–O), 183.8 and 187.6 (2×C=O). IR (KBr) ν 1640 (C=O), 1620 (C=O), 1609 (C=C), 1588, 1388, 1311, 1241 cm^{-1}. MS *m/z* 497 (100), 311 ($M+H^+$, 50). Anal Calcd $C_{18}H_{14}O_5$: C 69.67%, H 5.55%; found: C 69.55%, H 5.42%.

3.1.4. 8-Hydroxy-6-methoxy-7-methyl-2-(phenoxy-methyl)naphthoquinone (16b). Mp 188–189 °C (55%).

^{1}H NMR ($CDCl_3$): δ 2.18 (3H, s, CH_3), 3.99 (3H, s, CH_3O), 5.07 (2H, d, J=2.0 Hz, CH_2O), 6.99–7.06 (3H, m, 3×=CH), 7.07 (1H, t, J=2 Hz, =CH), 7.21–7.36 (3H, m, 3×=CH), 12.21 (1H, s, OH). ^{13}C NMR ($CDCl_3$): δ 8.1 (CH_3), 53.4 (CH_3O), 63.2 (CH_2), 102.5 (C-5), 109.7 (C_{quat}), 114.6 (2×=CH), 120.3 (C_{quat}), 121.7 (=CH), 129.0 (C_{quat}), 129.7 (2×=CH), 133.9 (C-3), 146.4 (C-2), 157.7 (=C–O), 161.3 (=C–O), 163.5 (=C–O), 184.2 and 188.2 (2×C=O). IR (KBr) ν 1661 (C=O), 1638 (C=O), 1609 (C=C), 1598 (C=C), 1497 (C=C), 1323, 1248, 1120 cm^{-1}. MS m/z (%) 323 (M−H$^+$, 35), 309 (M−CH_3, 100).

3.1.5. 6,8-Dimethoxy-2-(phenoxymethyl)naphthoquinone (17a). To a solution of naphthoquinone **16a** (256 mg, 0.83 mmol) in 10 ml of chloroform was added iodomethane (1.17 g, 8.3 mmol) and silver(I) oxide (2.02 g, 8.3 mmol). The mixture was refluxed for 3 h, under protection from light by covering the flask with aluminum foil. After cooling, the reaction mixture was filtered over celite and evaporated in vacuo to give 240 mg of the pure naphthoquinone **17a**. The resulting product was pure and was used without further purification (90%), mp 176–177 °C. ^{1}H NMR ($CDCl_3$): δ 3.91 (3H, s, CH_3O), 3.94 (3H, s, CH_3O), 5.01 (2H, d, J=2.0 Hz, CH_2), 6.68 (1H, d, J=2.3 Hz, H-5), 6.94 (1H, s, H-3), 6.97–6.98 (2H, m, 2×=CH), 6.99 (1H, t, J=2.0 Hz, C_3-H), 7.19 (1H, d, J=2.3 Hz, H-7), 7.26–7.32 (2H, m, 2×=CH). ^{13}C NMR ($CDCl_3$): δ 56.3 and 56.7 (2×CH_3O), 64.2 (CH_2), 103.5 (CH-7), 104.4 (CH-5), 115.0 (2×=CH), 121.8 (=CH), 130.0 (2×=CH), 131.5 (C-3), 132.8 (C_{quat}), 136.3 (C_{quat}), 148.5 (C-2), 158.2, 162.4 and 165.2 (3×=C–O), 182.9 and 185.0 (2×C=O). IR (KBr) ν 1651 (C=O), 1633 (C=O), 1597, 1458, 1331, 1251, 1159 cm^{-1}. MS m/z 325 (M+H$^+$, 100). Anal. Calcd $C_{19}H_{16}O_5$: C 70.36%, H 4.79%; found: C 70.22%, H 5.18%.

3.1.6. 6,8-Dimethoxy-7-methyl-2-(phenoxymethyl)-naphthoquinone (17b). Mp 151–153 °C (93%). ^{1}H NMR ($CDCl_3$): δ 2.23 (3H, s, CH_3), 3.85 (3H, s, CH_3O), 3.99 (3H, s, CH_3O), 5.07 (2H, d, J=2.0 Hz, CH_2), 6.98–7.06 (3H, m, 3×=CH), 7.07 (1H, t, J=2.0 Hz, C_3-H), 7.26–7.41 (3H, m, 3×=CH). ^{13}C NMR ($CDCl_3$): δ 9.4 (CH_3), 56.5 and 61.4 (2×CH_3O), 64.2 (CH_2), 104.6 (CH-5), 115.0 (2×=CH), 118.6 (C_{quat}), 121.9 (=CH), 128.5 (C_{quat}), 130.0 (2×=CH), 132.0 (C-3), 133.2 (C_{quat}), 147.8 (C-2), 158.2, 160.4 and 163.1 (3×=C–O), 183.3 and 185.0 (2×C=O). IR (KBr) ν 1657 (C=O), 1634 (C=O), 1583, 1497, 1323, 1243, 1128 cm^{-1}. MS m/z (%) 339 (M+H$^+$, 100). Anal. Calcd $C_{20}H_{18}O_5$: C 70.99%, H 5.36%; found: C 70.63%, H 5.54%.

3.1.7. 2-Acetonyl-5,8-dimethoxy-3-(phenoxymethyl)-naphthoquinone (18a). To a solution of naphthoquinone **17a** (220 mg, 0.68 mmol) and acetonylpyridinium chloride (174 mg, 1.02 mmol) in 10 ml acetonitrile was added dropwise a solution of triethylamine (82 mg, 1.02 mmol) in 2 ml of acetonitrile. The resulting mixture was stirred for 3 h at room temperature under a nitrogen atmosphere and protected from light. After evaporation of the solvent, 5 ml of aq 2 M HCl was added and extracted with ethyl acetate. The combined organic phases were washed with saturated $NaHCO_3$, dried ($MgSO_4$) and evaporated in vacuo. Purification by flash chromatography with 30% EtOAc in hexane as eluent yielded 200 mg of naphthoquinone **18a** (83%), mp 146–147 °C. ^{1}H NMR ($CDCl_3$): δ 2.26 (3H, s, CH_3), 3.91 (3H, s, CH_3O), 3.92 (2H, s, CH_2C=O), 3.96 (3H, s, CH_3O), 5.08 (2H, s, CH_2O), 6.73 (1H, d, J=2.3 Hz, H-5), 6.90–6.98 (3H, m, 3×=CH), 7.22 (1H, d, J=2.3 Hz, H-7), 7.24–7.30 (2H, m, 2×=CH). ^{13}C NMR ($CDCl_3$): δ 30.1 (CH_3C=O), 41.2 (CH_2C=O), 55.8 (CH_3O), 56.4 (CH_3O), 61.3 (CH_2O), 103.2 (C-7), 104.3 (CH-5), 114.2 (C_{quat}), 114.5 (2×=CH), 121.3 (=CH), 129.5 (2×=CH), 132.3 (C_{quat}), 135.5 (C-3), 141.4 (C-2), 158.0, 161.9 and 164.6 (3×=C–O), 181.4 and 184.6 (2×C=O), 203.3 (CH_3C=O). IR (KBr) ν 1715 (C=O), 1663 (C=O), 1654 (C=O), 1597, 1556, 1354, 1334, 1273, 1164 cm^{-1}. MS m/z 381 (M+H$^+$, 100). Anal. Calcd $C_{22}H_{20}O_6$: C 69.46%, H 5.30%; found: C 69.52% H 5.42%.

3.1.8. 2-Acetonyl-5,7-dimethoxy-6-methyl-3-(phenoxymethyl)naphthoquinone (18b). Mp 162–163 °C (77%). ^{1}H NMR ($CDCl_3$): δ 2.22 (3H, s, CH_3), 2.29 (3H, s, CH_3), 3.83 (3H, s, CH_3O), 3.92 (2H, s, CH_2C=O), 3.96 (3H, s, CH_3O), 5.08 (2H, s, CH_2O), 6.91–7.00 (3H, m, 3×=CH), 7.25–7.31 (2H, m, 2×=CH), 7.38 (1H, s, C_5–H). ^{13}C NMR ($CDCl_3$): δ 9.0 (CH_3), 30.2 (CH_3C=O), 41.2 (CH_2C=O), 56.1 (CH_3O), 61.0 and 61.2 (CH_2O and CH_3O), 104.3 (CH-5), 114.5 (2×=CH), 118.1 (C_{quat}), 121.4 (=CH), 128.5 (C_{quat}), 129.5 (2×=CH), 132.4 (C_{quat}), 142.0 (C_{quat}), 143.0 (C_{quat}), 158.0, 159.6 and 162.5 (3×=C–O), 181.8 and 184.6 (2×C=O), 203.5 (CH_3C=O). IR (KBr) ν 1696 (C=O), 1670 (C=O), 1626, 1580, 1334, 1222, 1143 cm^{-1}. MS m/z (%) (M+H$^+$,100), 301 (M−C_6H_5O, 75). Anal. Calcd $C_{23}H_{22}O_6$: C 70.04%, H 5.62%; found: C 70.20%, H 5.48%.

3.1.9. 7,9-Dimethoxy-3-methylbenzo[*g*]isoquinoline-5,10-dione (8, scorpinone). To a solution of 3-acetonyl-5,7-dimethoxy-2-(phenoxymethyl)naphthoquinone **18a** (100 mg, 0.26 mmol) in 10 ml of ethanol was added dropwise a 25% aqueous solution of ammonia (0.43 ml, 5.2 mmol). The solution was protected from light and stirred at room temperature for 4 h in an open flask, allowing contact with air. After evaporation of the solvent, the residue was dissolved in CH_2Cl_2, washed with water, dried ($MgSO_4$) and evaporated. After recrystallization from ethanol 60 mg of 2-azaanthraquinone **8** was obtained (81%), mp 213–214 °C (lit. mp 195 °C).[1] Spectroscopic data (^{1}H NMR, ^{13}C NMR, IR, MS) were in accordance with those reported in literature.[1,8]

3.1.10. 7,9-Dimethoxy-3,8-dimethylbenzo[*g*]isoquinoline-5,10-dione (19). Mp 186–187 °C (72%). ^{1}H NMR ($CDCl_3$): δ 2.29 (3H, s, CH_3), 2.77 (3H, s, CH_3C=N), 3.93 (3H, s, CH_3O), 4.05 (3H, s, CH_3O), 7.60 (1H, s, =CH), 7.84 (1H, s, CH–C=N), 9.43 (1H, s, HC=N). ^{13}C NMR ($CDCl_3$): δ 9.3 (CH_3), 25.1 (CH_3C=N), 56.2 and 61.3 (2×CH_3O), 104.7 (HC-5), 117.5 (H*C*–C=N), 119.5, 125.2, 130.0, 133.9 and 137.7 (5×C_{quat}), 149.6 (HC=N), 160.3, 162.9 and 164.4 (3×C_{quat}), 180.8 and 183.2 (2×C=O). IR (KBr) ν 1674 (C=O), 1661 (C=O), 1579, 1319, 1229, 1127 cm^{-1}. MS m/z (%) 298 (M+H$^+$, 100). Anal. Calcd $C_{17}H_{15}NO_4$: C 68.68%, H 5.09%, N 4.71%; found: C 68.88%, H 4.96%, N 5.01%.

3.1.11. 6-Deoxy-8-methylbostrycoidin (6). To a solution of 2-azaanthraquinone **19** (120 mg, 0.4 mmol) in 10 ml of dry

dichloromethane was added dropwise boron(III) bromide (301 mg, 1.2 mmol) under a nitrogen atmosphere at −78 °C. After 30 min, the reaction was quenched with water and poured into 5 ml of 2 M NaOH. 1 M HCl was added in portions until the colour of the reaction mixture turned yellow. The resulting solution was extracted with dichloromethane, dried ($MgSO_4$) and evaporated. 6-Deoxy-8-methylbostrycoidin **6** was obtained as a pure product in almost quantitative yield (108 mg, 96%), mp 150–151 °C (decomposed, lit. mp[9] 149–153 °C). Spectroscopic data (^1H NMR, ^{13}C, IR, MS) were in accordance with those reported in literature.[9]

3.1.12. 7-Methoxy-9-hydroxy-3-methylbenzo[*g*]isoquinoline-5,10-dione (6-deoxybostrycoidin) (5). To a solution of 2-azaanthraquinone **8** (50 mg, 0.28 mmol) in 10 ml of dry dichloromethane was added dropwise boron(III) bromide (350 mg, 1.4 mmol) under a nitrogen atmosphere at −78 °C. After 30 min, the reaction was allowed to warm till room temperature. After stirring for 2 additional hours the reaction was quenched with water and poured into 5 ml 2 M NaOH. 1 M HCl was added in portions until the colour of the reaction mixture turned yellow. The resulting solution was extracted with dichloromethane, dried ($MgSO_4$) and evaporated. 6-Deoxybostrycoidin **7** was obtained as a pure product in good yield (45 mg, 93%), mp 193–194 °C (lit. mp 195–196 °C). Spectroscopic data (^1H NMR, IR, MS) were in accordance with those reported in literature.[10] ^{13}C NMR ($CDCl_3$): δ 25.3 (CH_3), 56.1 (CH_3O), 107.4 (C-8), 108.2 (C-6), 110.4 (C_{quat}), 118.5 (C-4), 124.1 (C_{quat}), 134.5 (C_{quat}), 138.6 (C_{quat}), 149.1 (C-1), 165.5 (C-3), 165.9 (=C–O), 166.4 (=C–O), 182.2 (C=O), 186.1 (C=O).

3.1.13. 7,9-Dihydroxy-3-methylbenzo[*g*]isoquinoline-5,10-dione (7-*O*-demethyl-6-deoxy-bostrycoidin) (7). To a solution of 2-azaanthraquinone **8** (30 mg, 0.1 mmol) in 10 ml of dry dichloromethane was added dropwise boron(III) bromide (125 mg, 0.5 mmol) under a nitrogen atmosphere at −78 °C. The reaction mixture was kept at this temperature for 30 min, then the mixture was allowed to warm to room temperature and stirred for 48 h. After the reaction was quenched with water and poured into 5 ml 2 M NaOH, 1 M HCl was added in portions until the colour of the reaction mixture turned yellow. The resulting solution was extracted with dichloromethane, dried ($MgSO_4$) and evaporated to give the crude compound **7**. This product was washed two times with dichloromethane and 7-*O*-demethyl-6-deoxybostrycoidin **7** was obtained as a pure product (22 mg, 86%), mp 291–292 °C (decomp.), lit.[1] mp 288–290 °C (decomp.) lit.[11] mp 300–305 °C (decomp.). Spectroscopic data (^1H NMR, ^{13}C NMR, IR, MS) were in accordance with those reported in literature.[11]

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An expedient synthesis of 3-acyltetramic acids of the melophlin family from α-aminoesters and immobilized Ph_3PCCO

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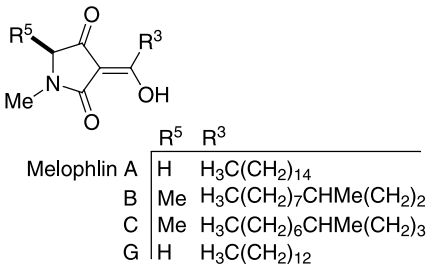
Abstract—The naturally occurring 3-acyltetramic acids (3-acylpyrrolidine-2,4-diones) melophlin A, B, C and G were prepared in few steps from α-aminoesters or their hydrochlorides by cyclization with Ph_3PCCO under mild conditions. The employment of immobilized, polystyrene-bound ylide greatly simplifies the removal of by-product Ph_3PO and of other impurities. Various 3-acylation methods were assessed.

1. Introduction

In recent years, the chemistry of tetramates has experienced a renaissance instigated by a steadily increasing number of isolated natural products of this type with distinct biological activities.[1,2] The structurally complex[3] 3-acyltetramic acids (3-acylpyrrolidine-2,4-diones) are among the most commonly found and pharmaceutically promising derivatives.[4–8] Hence, new synthetic routes were explored[9–16] that overcame drawbacks of earlier protocols such as limited scope and stereocontrol. For instance, enantioselective variants of the Lacey–Dieckmann cyclization[17] of *N*-(β-ketoacetyl)-α-amino esters, which emulates the biosynthesis of 3-acyltetramic acids, have been successfully employed.[18–20] However, complete or partial base-induced racemization at C-5 of the pyrrolin-2-one core still poses a problem and has been frequently observed.[21] Alternatively, 3-acyltetramic acids have been prepared by downstream acylation of preformed pyrrolidine-2,4-diones, for example, with the appropriate acid chloride in the presence of boron trifluoride-diethyl etherate.[22,23]

Herein we report an expeditious synthesis of the naturally occurring 3-acyltetramic acids melophlin A **1a**, B **1b**, C **1c** and G **1g** from α-aminoesters or their ammonium salts. Cyclization is brought about by a domino addition-Wittig alkenation reaction with the cumulated phosphorus ylide (triphenylphosphoranylidene)ketene, Ph_3PCCO, under neutral non-racemizing conditions. This parallels the conversion of α-hydroxyesters to the corresponding tetronates, developed and exploited by us previously.[24–26] Procedural advantages of using immobilized, resin-bound Ph_3PCCO are discussed.

The melophlins are a class of *N*-methyl-3-acyltetramic acids recently isolated from the marine sponge *Melophlus sarassinorum* (order Astrophorida, family Ancorinidae) and structurally differing only in the substituents at C-5 (R^5 = H or Me) and the chain length (C_{12} to C_{16}) and branching of the 3-acyl residue.[27,28] To date fifteen derivatives are known some of which show biological effects, such as general cytotoxic, antiproliferative, antifungal, antibacterial, and antiviral activity. Melophlins A and B displayed cytotoxic activity against HL60 cells at 0.2 and 0.4 μg/mL, respectively, and also arrested NIH3T3 cells in the G_1 phase of the cell cycle at 1–5 μg/mL. Melophlins C and G exerted no cytotoxicity but moderate activity against *B. subtilis* and *S. aureus*, against the brine shrimp *Artemia salina* and the larvae of the pest insect *Spodoptera littoralis*. Melophlin C is also quite active against *Candida albicans*.



	R^5	R^3
Melophlin A	H	$H_3C(CH_2)_{14}$
B	Me	$H_3C(CH_2)_7CHMe(CH_2)_2$
C	Me	$H_3C(CH_2)_6CHMe(CH_2)_3$
G	H	$H_3C(CH_2)_{12}$

Keywords: Tetramic acids; Phosphorus ylides; Solid phase organic synthesis; Immobilized reagents; Melophlins; Microwave.
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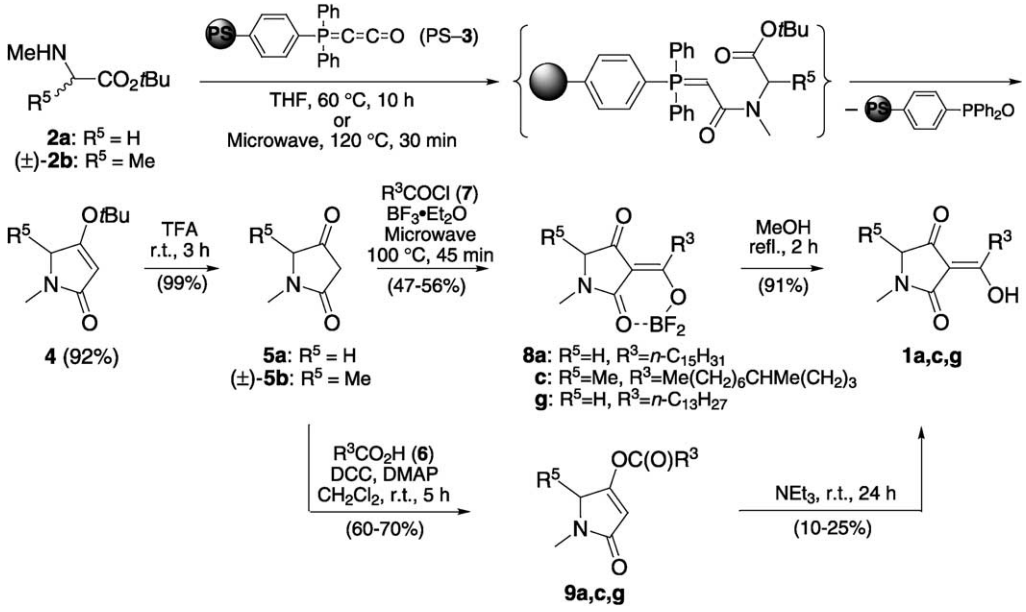


Scheme 1. Four-step syntheses of melophlins A, C, and G from sarcosine or methylalanine *t*-butyl esters **2**, immobilized (triphenylphosphoranylidene)ketene PS-**3** and carboxylic acids or chlorides.

2. Results and discussion

2.1. The melophlins A and G

The 5-unsubstituted melophlins A and G were prepared in just four steps from sarcosine *t*-butyl ester **2**. Treatment with Ph_3PCCO **3**,[29] immobilized by attachment to a polystyrene (PS) resin, gave the *N*-methyl-4-*t*-butoxypyrrolin-2-one **4a** ($R^5=H$) as product of a domino addition-intramolecular Wittig alkenation sequence. PS-**3** is a yellow air-stable free-running powder which is easy to prepare, dose and handle, and which furnishes olefins not contaminated with otherwise difficult to remove triphenylphosphane oxide.[30] Cleavage of **4a** with TFA quantitatively yielded *N*-methylpyrrolidine-2,4-dione **5a**.[31,32] Although Jones[23] reported that 5-unsubstituted tetramic acids may not be acylated at C-3 with acetyl chloride/BF_3-diethyl etherate due to side reactions such as rearrangements and condensations, we were able to attach myristoyl and palmitoyl residues to **5a** under these conditions. The intermediate BF_2-chelates **8** are isolable, fairly stable solids amenable even to chromatographical purification on silica gel. As described by Jones, these compounds were readily cleaved simply by heating with methanol to leave the respective melophlins **1a**,**g** in 40–47% overall yield (Scheme 1). This 3-acylation method has an edge over alternative procedures due to consistently greater chemical yields and its ease of work-up, especially when carried out under microwave irradiation. Yoshii's[33] base-induced (DBU/50 °C, or excess NEt_3, room temperature) Fries rearrangement of 4-*O*-acyl tetramates **9**, which are themselves available from **5** and the appropriate carboxylic acids **6** in the presence of DMAP and DCC, furnished **1** in poor yield and purity. A third alternative 3-acylation of **5** with the appropriate acid chloride **7** in the presence of $TiCl_4$ in nitrobenzene[34] performed slightly better, leading to **1a**,**g** in ca. 30% yield (see Table 1).

Table 1. Comparison of methods for the 3-acylation of tetramic acids **5** to give melophlins **1**

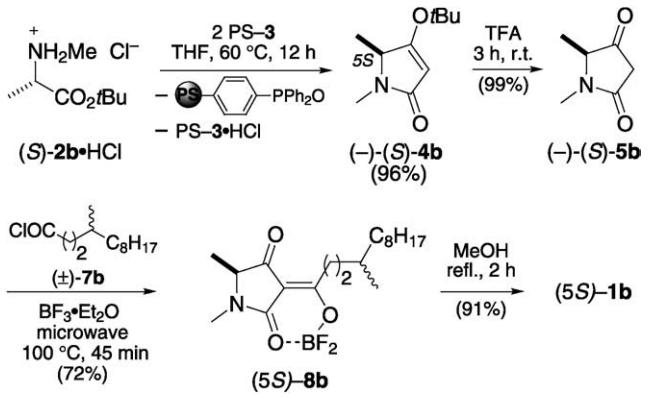
Melophlin	Acylation method	Yield (%)[a]	Purity (%)[b]
A (**1a**)	Jones[c]	39	99
	Jones/microwave[d]	47	99
	Yoshii[e]	9	20
B (**1b**)	Jones	35	99
	Jones/microwave	66	99
C (**1c**)	Jones	36	99
	Jones/microwave	43	99
	Yoshii	14	70
G (**1g**)	Jones/microwave	52	99
	Yoshii	6	18
	Jung[f]	30	90

[a] Overall yields; isolated for Jones and Jung, GC-% for Yoshii.
[b] By GC-MS; Yoshii products partly decomposed on columning.
[c] (i) $BF_3\cdot Et_2O$, R^3COCl, 80 °C, 8 h; (ii) MeOH, 50 °C, 2 h.
[d] As above but microwave, 100 °C, 45 min.
[e] (i) R^3CO_2H, CH_2Cl_2, DCC, DMAP, rt, 5 h; (ii) NEt_3, rt, 24 h.
[f] R^3COCl, $TiCl_4$, $PhNO_2$, 50 °C, 2 h, then H_2O.

2.2. 5-Methyl-3-acyltetramic acids; melophlins B and C

While natural melophlin C **1c** is known[27] to be a mixture of all four possible diastereoisomers, the absolute configuration at C-5 of melophlin B **1b** was shown to be *S* by oxidative degradation to *S*-alanine.[28] Regarding the configuration of the methyl substituted carbon atom C-4′ in the side-chain it remained unclear, whether natural **1b** is a single diastereoisomer or an unseparable mixture of the two possible diastereomers (5*S*,4′*S*) and (5*S*,4′*R*). We have now prepared (5*S*)-**1b** in analogy to the synthesis of melophlins A, C and G, only that we started from commercially available (*S*)-*N*-methylalanine *t*-butyl ester hydrochloride (*S*)-**2b**·HCl instead of the free aminoester (Scheme 2).

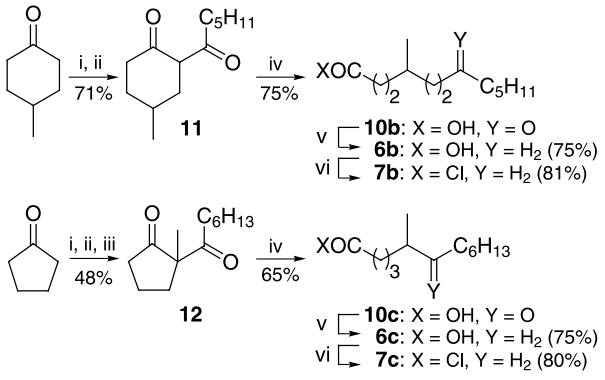
Treatment of this salt with 2 equiv of immobilized ylide PS-**3**, which conveniently acted both as a cumulene adding H–N across its C=C bond and as a base that deprotonated the intermediate acyl phosphonium salt, furnished *t*-butyl tetramate (−)-(*S*)-**4b** in 96% chemical yield and 99% ee



Scheme 2. Synthesis of melophlin B **1b**.

(GC; Lipodex-E, Macherey–Nagel; comparison with baseline separated authentic racemic samples). Quantitative cleavage of the ester with TFA gave 1,5-dimethylpyrrolidine-2,4-dione (−)-(*S*)-**5b**. This was 3-acylated, once more under Jones's conditions (BF_3–diethyl etherate),[23] with 4-methyldodecanoyl chloride (±)-**7b** to give the corresponding BF_2-adduct **8b** in a moderate 40% yield under classical thermal but in 72% yield under microwave irradiation conditions. Interestingly, **8b** could not be separated in two diastereoisomers like the BF_2-adduct **8c** which was obtained as a mixture of four stereoisomers from racemic (±)-**5b** and racemic acid chloride (±)-**7c**. The BF_2-chelate **8b** was finally converted to melophlin B (5*S*)-**1b** by boiling in methanol. The required carboxylic acids **6** and chlorides **7** were prepared via the keto acids **10**, following a modified procedure by Hünig[35] (Scheme 3). 4-Methyldodecanoic acid **6b** was obtained in four steps from 4-methylcyclohexanone, the enamine of which was first acylated with caproyl chloride to give **11** which in turn was ringopened with base to give **10b**. Wolff–Kishner reduction of **10b** eventually led to **6b**. The analogous reduction of keto acid **10c** as available from cyclopentanone via the acyl derivative **12** gave 5-methyldodecanoic acid **6c**.

Table 1 shows how the diverse methods for the 3-acylation of tetramic acids **5** performed in terms of yield and purity of products **1**.



Scheme 3. Synthesis of acids **6** and chlorides **7**. Reagents and conditions; (i) morpholine, pTSA (cat), toluene, reflux, 5 h; (ii) $C_5H_{11}COCl$ (for **11**) or $C_6H_{13}COCl$ (for **12**), NEt_3, $CHCl_3$, rt, 12 h, then aq. HCl, 90 °C, 5 h; (iii) *t*-BuOK, BuOH, then MeI; (iv) aq. KOH, 130 °C, 5 min, then aq. HCl; (v) N_2H_2, KOH, $N(CH_2CH_2OH)_3$, 150 °C, 1 h, then KOH (5 equiv), 205 °C, 4 h, Dean–Stark trap, then H_2O, HCl; (vi) $SOCl_2$, DMF, rt, 12 h.

In conclusion, we have demonstrated the versatility of immobilized Ph_3PCCO as an N-acylating C_2-building block for the construction of densely functionalized tetramic acids under mild conditions. It allows the direct cyclization of secondary α-ammonium esters to give pure tetramates devoid of triphenylphosphane oxide. The 3-acylation protocol by Jones carried out under microwave irradiation was found the method of choice, applicable also to the 5-unsubstituted tetramic acid **5a**.

3. Experimental

3.1. General

Microwave irradiations were carried out in sealed vials in an MLS Microchemist™ system. Melting points were recorded in a Gallenkamp apparatus and are uncorrected. Optical rotations were recorded at 589 nm with a Perkin–Elmer polarimeter 241. IR spectra were recorded on a Perkin–Elmer Spectrum One FT-IR spectrophotometer equipped with an ATR sampling unit. Nuclear magnetic resonance (NMR) spectra were recorded under conditions as indicated on a Bruker Avance 300 spectrometer. Chemical shifts are given in parts per million (δ) downfield from tetramethylsilane as internal standard. Mass spectra were recorded using a Varian MAT 311A (EI). Analytical HPLC was performed on a Beckman system with solvent module 126 and a diode array detector 168 equipped with a Nucleodex CD-β-PM column (Macherey–Nagel). Analytical GC was conducted on a Lipodex-E column (25 m, 0.25 mm; Macherey–Nagel). Micro-analyses were carried out with a Perkin–Elmer 2400 CHN elemental analyser. For flash chromatography Merck silica gel 60 (230–400 mesh) was used. PS-**3** (100–200 mesh, 1.20 g/mmol) was prepared as described previously,[30] all other starting compounds were purchased from Fluka and Bachem and used as such without further purification.

3.1.1. 4-*t*-Butoxy-1-methylpyrrolin-2-one 4a. PS-**3** (3.32 g, 4.0 mmol) was suspended in toluene (20 mL) and treated with sarcosine *t*-butylester **2a** (435 mg, 3.0 mmol). The mixture was shaken under gentle reflux for 10 h or irradiated in the microwave synthesizer at 120 °C for 30 min. After filtration and washing of the resin with 2× 15 mL each of THF, toluene, CH_2Cl_2, and diethyl ether, the combined filtrates were evaporated under reduced pressure and the crude product was purified by column chromatography (silica gel; ethyl acetate). Colourless oil (458 mg, 92%), R_f 0.26 (ethyl acetate) (Found: C, 64.1; H, 8.8; N, 8.5. $C_9H_{15}NO_2$ requires C, 63.9; H, 8.9; N, 8.3%). ν_{max}(ATR)/cm^{-1} 1680, 1604, 1344, 1168; δ_H (300 MHz; $CDCl_3$) 1.37 (9H, s, CMe_3), 2.86 (3H, s, NMe), 3.67 (2H, s, CH_2), 4.98 (1H, s, 3-H); δ_C (75 MHz; $CDCl_3$) 27.2 [$C(CH_3)_3$], 28.1 (NMe), 54.0 (C-5), 81.4 (CMe_3), 96.4 (C-3), 167.5 (C-2), 172.9 (C-4); *m*/*z* (EI, 70 eV) 169 (M^+, 10%), 154 (10%), 113 (100%).

3.1.2. (−)-(5*S*)-4-*t*-Butoxy-1,5-dimethylpyrrolin-2-one 4b. PS-**3** (1.66 g, 2.0 mmol) was suspended in THF (10 mL) and after 10 min swelling treated with (*S*)-*N*-methyl-L-alanine *t*-butyl ester hydrochloride **2b** (196 mg, 1.0 mmol). The mixture was either shaken at 60 °C for 12 h

or irradiated in the microwave synthesizer at 90 °C for 30 min. Work-up as described above for **4a**. Colourless oil (177 mg, 96%), R_f 0.31 (ethyl acetate), $[\alpha]_D^{25}$ −1.0 (*c* 0.5, $CHCl_3$) (Found: C, 65.4; H, 9.4; N, 7.8. $C_{10}H_{17}NO_2$ requires C, 65.5; H, 9.4; N, 7.6%). ν_{max}(ATR)/cm^{-1} 1656, 1608, 1340, 1168; δ_H (300 MHz; $CDCl_3$) 1.24 (3H, d, J=6.8 Hz, $CHCH_3$), 1.40 (9H, s, CMe_3), 2.85 (3H, s, NMe), 3.71 (1H, q, J=6.8 Hz, 5-H), 5.00 (1H, s, 3-H); δ_C (75 MHz; $CDCl_3$) 15.7 ($CHCH_3$), 25.8 (NCH_3), 27.1 [$C(CH_3)_3$], 60.0 (C-5), 81.0 (CMe_3), 94.9 (C-3), 171.5 (C-4), 171.8 (C-2); *m/z* (EI, 70 eV) 183 (M^+, 15%), 168 (5%), 127 (90%), 112 (80%), 57 (100%).

3.2. General procedure for the acidic cleavage of tetramates 4 to give tetramic acids 5

Tetramate **4** (2.0 mmol) was dissolved in dry TFA (10 mL) and stirred at rt for 3 h. *n*-Hexane was added and all volatiles were removed under reduced pressure on a rotary evaporator. The residue thus obtained was dried on an oil pump to leave sufficiently pure, bright yellow tetramic acids **5**.

3.2.1. 1-Methylpyrrolidine-2,4-dione 5a. Yellowish solid (228 mg, 99%) from **4a** (280 mg), R_f 0.20 (ethyl acetate), mp 49–51 °C (lit.,[31] 49–50 °C; lit.,[32] 48–51 °C). ν_{max}(ATR)/cm^{-1} 1779, 1636, 1615; δ_H (300 MHz; $CDCl_3$) 3.07 (3H, s, NMe), 3.19 (2H, s, 3-H), 3.97 (2H, s, 5-H); δ_C (75 MHz; $CDCl_3$) 29.8 (NMe), 41.2 (C-3), 59.7 (C-5), 171.8 (C-2), 201.7 (C-4); *m/z* (EI, 70 eV) 113 (M^+, 70%), 85 (95%), 42 (100%).

3.2.2. (−)-(5*S*)-1,5-Dimethylpyrrolidine-2,4-one 5b. Orange oil (250 mg, 99%), R_f 0.71 (ethyl acetate–ethanol, 1:1), $[\alpha]_D^{25}$ −8.2 (*c* 0.5, $CHCl_3$) (Found: C, 56.4; H, 7.0; N, 11.2. $C_6H_9NO_2$ requires C, 56.7; H, 7.1; N, 11.0%). ν_{max}(ATR)/cm^{-1} 1776, 1632, 1615, 1446, 1407; δ_H (300 MHz; $CDCl_3$) 1.37 (3H, d, J=7.0 Hz, 5-CH_3), 2.99 (3H, s, NCH_3), 3.11 (2H, s, CH_2), 3.93 (1H, q, J=7.0 Hz, 5-H); δ_C (75 MHz; $CDCl_3$) 14.9 (5-CH_3), 27.5 (NCH_3), 40.2 (C-3), 64.7 (C-5), 170.1 (C-2), 205.4 (C-4); *m/z* (EI, 70 eV) 127 (M^+, 10%), 112 (10%), 99 (10%), 56 (30%), 42 (100%).

3.3. Synthesis of 4-methyldodecanoic acid (±)-6b

3.3.1. 2-Hexanoyl-4-methylcyclohexanone 11. 4-Methylcyclohexanone (25 mL, 0.2 mol), morpholine (26.1 g, 0.3 mol), *p*-toluene sulfonic acid (100 mg) and toluene (100 mL) were heated under reflux at a Dean–Stark trap for 4 h. After removal of all volatiles the remainder was distilled in a Kugelrohr apparatus to give 4-methyl-1-morpholinocyclohex-1-ene (34.4 g, 95%) of bp 125 °C/11 Torr. This was dissolved in dry $CHCl_3$ (200 mL) and treated with NEt_3 (19.2 g, 190 mmol). To the resulting mixture kept at 40 °C was slowly added a solution of caproyl chloride (23.5 g, 175 mmol) in $CHCl_3$ (150 mL). After stirring at room temperature for a further 12 h, concentrated aqueous HCl (50 mL) and water (25 mL) were added, the mixture was refluxed for 5 h and the organic phase was washed with water (5×30 mL) until neutral. The combined aqueous phases were neutralized with NaOH and re-extracted with $CHCl_3$. The combined organic extracts were dried over Na_2SO_4, concentrated and distilled in a Kugelrohr apparatus to give sufficiently pure **11** (27.6 g, 75%) of bp 80–85 °C/1 Torr.

3.3.2. 4-Methyl-7-oxododecanoic acid 10b. 11 (21.3 g, 0.1 mol) at 100 °C was treated with a hot solution of KOH (16.8 g, 0.3 mol) in water (11 mL) while stirring to avoid temperature rising above 130 °C. After 5 min, water (200 mL) and then 10% aqueous HCl were added to adjust a slightly basic pH value. The mixture was extracted with $CHCl_3$ (2×30 mL), then acidified to pH 1 and finally extracted with further $CHCl_3$ (3×50 mL). The combined organic phases were dried over Na_2SO_4, concentrated and distilled to give colourless liquid **10b** (17 g, 75%); bp 115 °C/1 Torr (Found: C, 68.1; H, 10.2. $C_{13}H_{24}O_3$ requires C, 68.4; H, 10.6%). ν_{max}(ATR)/cm^{-1} 3100 (br), 2930, 1733, 1706, 1458; δ_H (300 MHz; $CDCl_3$) 0.79–0.86 (6H, m, CH_3), 1.19–1.53 (15H, m, CH, CH_2), 2.29–2.38 (6H, m, CH_2), 11.10 (1H, br, OH); δ_C (75 MHz; $CDCl_3$) 13.8 (CH_3), 18.9 (4-CH_3), 22.3, 23.4, 30.1, 31.1, 31.3, 31.5 (CH_2), 31.8 (C-4), 40.1, 42.7 (CH_2), 179.9 (C-1), 211.5 (C-7); *m/z* (EI, 70 eV) 228 (M^+, 10%), 182 (12%), 172 (80%), 157 (65%), 115 (20%), 43 (100%).

3.3.3. 4-Methyldodecanoic acid (±)-6b.[36] 10b (6.85 g, 30 mmol), hydrazine hydrate (100%, 10 mL), $N(CH_2CH_2OH)_3$ (30 mL) and KOH (1.68 g, 30 mmol) were mixed in a 1 L flask and kept at 150 °C for 1 h. The mixture was allowed to cool to room temperature, treated with KOH (8.4 g, 150 mmol) and $N(CH_2CH_2OH)_3$ (30 mL) and heated at a Dean–Stark trap to 205 °C for 4 h. It was cooled again, diluted with ice cold water (200 mL), acidified with conc. HCl to pH 1 and extracted with $CHCl_3$ (3×50 mL). The combined organic phases were dried over Na_2SO_4, concentrated and the residue thus obtained was bulb-to-bulb distilled to leave a colourless oil (7.4 g, 75%) of bp 174 °C/14 Torr (lit.,[36a] 130–134 °C/1.5 Torr). ν_{max}(ATR)/cm^{-1} 3091 (br), 2923, 2854, 1704; δ_H (300 MHz; $CDCl_3$) 0.81–0.88 (6H, m, CH_3), 1.14–1.44 (16H, m, CH_2), 1.58–1.67 (1H, m, C*H*-CH_3), 2.28–2.38 (2H, m, 2-H), 11.3 (1H, br, OH); δ_C (75 MHz; $CDCl_3$) 14.1 (CH_3), 19.2 (4-CH_3), 22.7, 26.9, 29.3, 29.6, 29.9, 31.6, 31.9 (CH_2), 32.3 (C-4), 34.1, 36.6 (CH_2), 180.9 (C-1); *m/z* (EI, 70 eV) 214 (M^+, 10%), 157 (30%), 113 (5%), 101 (15%), 85 (40%), 73 (100%).

3.4. Synthesis of 5-methyldodecanoic acid (±)-6c

3.4.1. 2-Heptanoyl-2-methylcyclopentanone 12. Analogously to **11** (see Section 3.3), crude 2-heptanoylcyclopentanone (10.1 g, 48%) was obtained via the corresponding enamine from cyclopentanone (8.4 g, 0.1 mol), morpholine (13.1 mL, 150 mmol), pTSA (20 mg), NEt_3 (12.5 mL, 90 mmol) and heptanoyl chloride (13.9 mL, 90 mmol). It was then added to a solution of *t*-BuOK (5.6 g, 50 mmol) in *t*-BuOH (100 mL) and the resulting mixture was treated with MeI (3.7 mL, 60 mmol) at room temperature. After stirring at for 12 h, the reaction mixture was filtered, the filtrate was concentrated on a rotary evaporator and the residue was purified by distillation to leave **12** (10.1 g, 48 mmol) as a sufficiently pure colourless oil of bp 105 °C/1 Torr.

3.4.2. 5-Methyl-6-oxododecanoic acid 10c. As described above for **10b**, **10c** (7.11 g, 65%) was obtained as a

colourless oil of bp 115 °C/1 Torr by basic cleavage of **12** (10.1 g, 48 mmol) (Found: C, 68.2; H, 10.3. $C_{13}H_{24}O_3$ requires C, 68.4; H, 10.6%). ν_{max}(ATR)/cm^{-1} 3100 (br), 2929, 1738, 1704, 1459; δ_H (300 MHz; $CDCl_3$) 0.81 (3H, t, J=5.85 Hz, CH_3), 1.02 (3H, d, J=7.05 Hz, 5-CH_3), 1.21–1.28 (6H, m, CH_2), 1.48–1.60 (6H, m, CH_2), 2.26–2.48 (5H, m, CH, CH_2), 11.31 (1H, br, OH); δ_C (75 MHz; $CDCl_3$) 13.8 (CH_3), 16.3 (5-CH_3), 22.3, 22.4, 23.7, 28.8, 31.7, 32.0, 33.8, 40.9 (CH_2), 45.8 (C-5), 180.0 (C-1), 214.5 (C-6); *m/z* (EI, 70 eV) 228 (M^+, 10%), 158 (10%), 113 (60%), 98 (15%), 85 (25%), 43 (100%).

3.4.3. 5-Methyldodecanoic acid (±)-6c.[37] **6c** (7.4 g, 75%) was prepared, as described for **6b**, from **10c** (6.84 g, 30 mmol); colourless oil of bp 174 °C/14 Torr (Found: C, 72.5; H, 14.7. $C_{13}H_{26}O_2$ requires C, 72.8; H, 14.9%). ν_{max}(ATR)/cm^{-1} 3100 (br), 2923, 1704, 1461; δ_H (300 MHz; $CDCl_3$) 0.82–0.88 (6H, m, CH_3), 1.14–1.35 (16H, m, CH_2), 1.58–1.63 (1H, m, 5-H), 2.27–2.33 (2H, m, 2-H), 11.7 (br, 1H, OH); δ_C (75 MHz; $CDCl_3$) 14.1 (CH_3), 19.5 (5-CH_3), 22.3, 22.7, 27.0, 29.3, 29.9, 31.9 (CH_2), 32.5 (C-5), 34.4, 36.4, 36.8 (CH_2), 180.6 (C-1); *m/z* (EI, 70 eV) 214 (M^+, 10%), 171 (25%), 152 (10%), 115 (50%), 97 (25%), 88 (20%), 69 (50%), 57 (50%), 43 (80%), 41 (100%).

3.5. Synthesis of methyldodecanoyl chlorides (±)-7

Under an atmosphere of dry argon, a mixture of the appropriate methyldodecanoic acid (±)-**6c** (2.14 g, 10 mmol), freshly distilled $SOCl_2$ (1.3 g, 11 mmol) and two drops of dry DMF was stirred at room temperature overnight. All volatiles were removed under reduced pressure, the crude product was purified by Kugelrohr (bulb-to-bulb) distillation and used right away.

3.5.1. 4-Methyldodecanoyl chloride (±)-7b. Colourless oil (1.89 g, 81%) of bp 110 °C/0.9 Torr (Found: C, 67.4; H, 11.0. $C_{13}H_{25}ClO$ requires C, 67.1; H, 10.8%). ν_{max}(ATR)/cm^{-1} 2924, 1795, 1465, 955, 710; δ_H (300 MHz; $CDCl_3$) 0.84–0.88 (6H, m, CH_3), 1.24–1.31 (14H, m, CH_2), 1.44–1.56 (2H, m, CH_2), 1.69–1.75 (1H, m, 4-H), 2.83–2.89 (2H, m, 2-H); δ_C (75 MHz; $CDCl_3$) 14.1 (C-12), 19.2 (4-CH_3), 22.7, 26.8, 29.3, 29.6, 29.8, 31.8 (CH_2), 31.9 (C-4), 36.5, 45.1 (C-2), 174.1 (C-1).

3.5.2. 5-Methyldodecanoyl chloride (±)-7c. Colourless oil (1.84 g, 80%) of bp 110 °C/0.9 Torr (Found: C, 67.3; H, 11.1. $C_{13}H_{25}ClO$ requires C, 67.1; H, 10.8%). ν_{max}(ATR)/cm^{-1} 2924, 1795, 1466, 954, 710; δ_H (300 MHz; $CDCl_3$) 0.83–0.88 (6H, m, CH_3), 1.10–1.19 (15H, m, 7×CH_2, 5-H), 1.24–1.35 (2H, m, CH_2), 2.82–2.88 (2H, m, 2-H); δ_C (75 MHz; $CDCl_3$) 14.1 (C-12), 19.4 (5-CH_3), 22.65, 22.7, 27.0, 29.3, 29.9, 31.9 (CH_2), 32.4 (C-4), 35.7, 36.7, 47.4 (C-2), 173.8 (C-1).

3.5.3. 1,5-Dimethyl-4-(5′-methyldodecanoyl)pyrrolin-2-one 9c—typical procedure for the 4-*O*-acylation of tetramic acids 5. A stirred solution of (±)-**5b** (130 mg, 1.0 mmol) in dry CH_2Cl_2 (6 mL) at 0 °C was treated with DMAP (24 mg, 0.2 mmol), (±)-**6c** (234 mg, 1.1 mmol) and finally with DCC (250 mg, 1.2 mmol). Stirring was continued for 10 min at 0 °C and for another 5 h at room temperature. The mixture was filtered through a short plug of celite to remove most of the by-product urea, the filtrate was concentrated on a rotary evaporator and the remainder was purified by chromatography on silica gel, deactivated with 5% water. White solid (194 mg, 60%), R_f 0.25 (ethyl acetate-*n*-hexane, 1:1), mp 56 °C (Found: C, 70.8; H, 10.4; N, 4.5. $C_{19}H_{33}NO_3$ requires C, 70.55; H, 10.3; N, 4.3%); ν_{max}(ATR)/cm^{-1} 2925, 1779, 1689, 1623; δ_H (300 MHz; $CDCl_3$) 0.81–0.88 (6H, m, CH_3), 1.07–1.32 (15H, m, CH_2, 5′-H), 1.33 (3H, d, J=6.86 Hz, CH_3CH$_2$), 1.55–1.69 (2H, m, 3′-H), 2.47 (2H, t, J=7.3 Hz, 2′-H), 2.91 (3H, s, NMe), 4.00 (1H, q, J=8.86 Hz, 5-H), 6.01 (1H, s, 3-H); δ_C (75 MHz; $CDCl_3$) 14.1, 15.5, 19.6 (CH_3), 22.2, 22.7, 27.1 (CH_2), 28.5 (CH_3), 29.4, 30.0, 32.0 (CH_2), 32.6 (C-5′), 34.7, 36.3, 36.9 (CH_2), 58.2 (C-5), 107.1 (C-3), 165.2 (C-4), 169.4 (CO), 170.3 (C-2).

3.6. Melophlin C—typical procedure for the synthesis of melophlins 1 from tetramates 9

Tetramate **9c** (323 mg, 1.0 mmol) was dissolved in anhydrous CH_2Cl_2 (5 mL) and NEt_3 (10 mL) and stirred at room temperature for 24 h. The solvent was evaporated under reduced pressure and the residue was taken up in $CHCl_3$ (40 mL) and extracted twice with 15 mL each of 10% aqueous HCl and brine. The organic phase was finally dried over Na_2SO_4 and evaporated under reduced pressure to leave **1c** as a yellowish oil (74 mg, 23%). For physical data see below (Section 3.8).

3.7. General procedures for the synthesis of boron difluoride complexes 8

Method A.[23] To a stirred solution of **5** (1.0 mmol) in ethereal boron trifluoride-diethyl ether (5 mL) was added methyldodecanoyl chloride **7** (711 mg, 3.0 mmol). After heating the mixture at 80 °C for 4 h, further **7** (237 mg, 1.0 mmol) was added and heating was continued for another 4 h at the same temperature. The cooled reaction mixture was then treated with saturated aqueous NH_4Cl (11 mL) and immediately extracted with ethyl acetate (3×20 mL). The combined extracts were dried over Na_2SO_4 and evaporated to yield a red oil, which was purified by column chromatography (silica gel; $CHCl_3$).

Method B. To a shaken solution of **5** (1.0 mmol) in 5 mL ethereal boron trifluoride-diethyl ether was added the appropriate acid chloride **7** (2 mmol). This mixture was then heated in a sealed tube under microwave irradiaton (330 W max) for 45 min at 100 °C. Workup as for method A. In the following, all yields of **8** refer to method B.

3.7.1. 3-[1′-(Difluoroboryloxy)-palmitoylidene]-1-methylpyrrolidine-2,4-dione 8a. White solid (208 mg, 52%) from **5a** (115 mg), R_f 0.36 ($CHCl_3$); mp 120–122 °C (Found: C, 62.9; H, 8.8; N, 3.6. $C_{21}H_{36}BF_2NO_3$ requires C, 63.2; H, 9.1; N, 3.5%). ν_{max}(ATR)/cm^{-1} 2954, 2917, 2850, 1733, 1655, 1570, 1538, 1018; δ_H (300 MHz; $CDCl_3$) 0.84 (3H, t, J=6.7 Hz, 16′-H), 1.15–1.40 (24H, m, CH_2), 1.57–1.65 (2H, m, 3′-H), 2.81 (2H, t, J=7.6 Hz, 2′-H), 3.19 (3H, s, NCH_3), 3.93 (2H, s, 5-H); δ_C (75 MHz; $CDCl_3$) 14.0 (C-16′), 22.6 (C-3′), 25.6, 29.0, 29.1 29.2, 29.3, 29.4, 29.5, 29.6, 30.2 (NCH_3), 31.82, 33.8 (C-2′), 59.1 (C-5), 99.8 (C-3), 171.8 (C-2), 186.9

(C-1′), 189.0 (C-4); *m/z* (EI, 70 eV) 399 (M^+, 30%), 379 (M^+-HF, 15%), 216 (45%), 203 (100%), 188 (15%), 161 (10%).

3.7.2. (5*S*)-3-[1′-(Difluoroboryloxy)-4′-methyldodecylidene]-1,5-dimethyl-pyrrolidine-2,4-dione 8b. Orange oil (267 mg, 72%) from (−)-**5b** (127 mg), R_f 0.27 ($CHCl_3$) (Found: C, 61.3; H, 8.5; N, 3.9. $C_{19}H_{32}BF_2NO_3$ requires C, 61.5; H, 8.7; N, 3.8%). ν_{max}(ATR)/cm^{-1} 2955, 2924, 2854, 1721, 1643, 1569, 1533, 1025; δ_H (300 MHz; $CDCl_3$) 0.83 (3H, t, J=6.96 Hz, 12′-H), 0.86 (3H, d, J=6.32 Hz, 4′-CH_3), 1.10–1.40 (14H, m, CH_2), 1.47 (3H, d, J=7.14 Hz, 5-CH_3) 1.41–1.49 (2H, m, CH_2), 1.57–1.68 (1H, m, 4′-H), 2.81 (2H, t, J=7.6 Hz, 2′-H), 3.12 (3H, s, NCH_3), 3.88 (1H, q, J=7.14 Hz, 5-H); δ_C (75 MHz; $CDCl_3$) 13.9 (C-12′), 14.1 (5-CH_3), 19.2 (4′-CH_3), 22.6, 26.8 (CH_2), 27.9 (NCH_3), 29.2, 29.5, 29.8, 31.7, 31.8 (CH_2), 32.5 (C-2′), 32.6 (C-4′), 36.4 (CH_2), 64.9 (C-5), 98.4 (C-3), 170.8 (C-2), 189.7 (C-1′), 190.4 (C-4); *m/z* (EI, 70 eV) 371 (M^+, 7%), 351 (M^+-HF, 5%), 244 (7%), 230 (40%), 217 (100%), 202 (20%).

3.7.3. 3-[1′-(Difluoroboryloxy)-5′-methyldodecylidene]-1,5-dimethyl-pyrrolidine-2,4-dione 8c. *Diastereomer α.* Orange oil (156 mg, 42%) from (±)-**5b** (127 mg), R_f 0.31 ($CHCl_3$) (Found: C, 61.2; H, 8.6; N, 4.1. $C_{19}H_{32}BF_2NO_3$ requires C, 61.5; H, 8.7; N, 3.8%). ν_{max}(ATR)/cm^{-1} 2955, 2925, 2856, 1721, 1644, 1570, 1533, 1019, 936; δ_H (300 MHz; $CDCl_3$) 0.78–0.86 (6H, m, 5′-CH_3, 12′-H), 1.10–1.40 (15H, m, 5′-H, CH_2), 1.41 (3H, d, J=7.14 Hz, 5-CH_3) 1.57–1.65 (2H, m, 3′-H), 2.78 (2H, t, J=7.61 Hz, 2′-H), 3.12 (3H, s, NCH_3), 3.88 (1H, q, J=7.14 Hz, 5-H); δ_C (75 MHz; $CDCl_3$) 13.9 (C-12′), 14.0 (5-CH_3), 19.3 (5′-CH_3), 22.6 (C-11′), 23.2 (C-3′), 26.8 (C-7′), 27.8 (NCH_3), 29.2 (C-8′), 29.8 (C-10′), 31.8 (C-9′), 32.4 (C-5′), 34.0 (C-2′), 36.3 (C-4′), 36.7 (C-6′), 64.9 (C-5), 98.5 (C-3), 170.8 (C-2), 189.2 (C-1′), 190.5 (C-4); *m/z* (EI, 70 eV) 371 (M^+, 10%), 351 (M^+-HF, 10%), 244 (7%), 233 (30%), 217 (100%), 202 (15%).

Diastereomer β Orange oil (17 mg, 5%) R_f 0.26 ($CHCl_3$). ν_{max}(ATR)/cm^{-1} 2955, 2925, 2856, 1721, 1644, 1570, 1533, 1019; δ_H (300 MHz; $CDCl_3$) 0.81–0.89 (6H, m, 5′-CH_3, 12′-H), 1.10–1.40 (15H, m, 5′-H, CH_2), 1.44 (3H, d, J=7.14 Hz, 5-CH_3) 1.60–1.71 (2H, m, 3′-H), 2.85 (2H, t, J=7.61 Hz, 2′-H), 3.14 (3H, s, NCH_3), 3.88 (1H, q, J=7.14 Hz, 5-H).

3.7.4. 3-[1′-(Difluoroboryloxy)-myristoylidene]-1-methyl-pyrrolidine-2,4-dione 8g. Yellow solid (207 mg, 56%) R_f 0.35 (hexane/ethyl acetate, 1:1); mp 114–116 °C (Found: C, 61.3; H, 8.7; N, 4.0. $C_{19}H_{32}BF_2NO_3$ requires C, 61.5; H, 8.7; N, 3.8%). ν_{max}(ATR)/cm^{-1} 2954, 2919, 2850, 1733, 1656, 1569, 1538, 1018; δ_H (300 MHz; $CDCl_3$) 0.82 (3H, t, J=6.9 Hz, 14′-H), 1.15–1.33 (20H, m, CH_2), 1.57–1.65 (2H, m, 3′-H), 2.79 (2H, t, J=7.6 Hz, 2′-H), 3.16 (3H, s, NCH_3), 3.91 (2H, s, 5-H); δ_C (75 MHz; $CDCl_3$) 14.0 (C-14′), 22.5 (C-3′), 25.5, 29.0, 29.1 29.2, 29.3, 29.4, 29.5, 29.6, 30.1 (NCH_3), 31.8, 33.8 (C-2′), 58.9 (C-5), 99.8 (C-3), 171.7 (C-2), 186.9 (C-1′), 189.0 (C-4); *m/z* (EI, 70 eV) 371 (M^+, 20%), 351 (M^+-HF, 20%), 216 (50%), 203 (100%), 188 (15%), 161 (10%).

3.8. Melophlins 1 from 8—general procedure

A stirred solution of the appropriate boron difluoride complex **8** (0.5 mmol) in MeOH (10 mL) was heated under reflux for 2 h. The cooled reaction mixture was diluted with ethyl acetate (10 mL) and evaporated under reduced pressure. The residue was taken up in ethyl acetate (25 mL), washed with water (10 mL), dried, and evaporated to yield the respective melophlin **1**.

3.8.1. Melophlin A 1a. Yellow oil (158 mg, 90%) from **8a** (200 mg), R_f 0.35 (CH_2Cl_2–MeOH, 19:1). ν_{max}(ATR)/cm^{-1} 2915, 2850, 1717, 1617, 1470, 1250, 948; δ_H (300 MHz; $CDCl_3$) 0.84 (3H, t, J=6.7 Hz, 16′-H), 1.18–1.39 (24H, m, CH_2), 1.54–1.66 (2H, m, 3′-H), 2.77 (2H, t, J=7.4 Hz, 2′-H), 2.98 (3H, s, NCH_3), 3.68 (2H, s, 5-H), 11.94 (br, 1H, OH); δ_C (75 MHz; $CDCl_3$) 14.1 (C-16′), 22.6 (C-15′), 25.9 (C-3′), 28.3 (NCH_3), 29.1, 29.2, 29.3, 29.4, 29.5, 29.6, 32.6 (C-2′), 57.6 (C-5), 101.6 (C-3), 173.5 (C-2), 187.5 (C-1′), 191.2 (C-4); *m/z* (EI, 70 eV) 351 (M^+, 10%), 182 (5%), 168 (30%), 155 (100%), 140 (40%); HR-EI MS; *m/z* 351.2773 calcd. for $C_{21}H_{37}NO_3$. Found: 351.2770.

3.8.2. Melophlin B 1b. Yellow oil (147 mg, 91%) from (5*S*)-**8b** (185 mg), R_f 0.37 (CH_2Cl_2–MeOH, 19:1). ν_{max}(ATR)/cm^{-1} 2924, 2854, 1712, 1613, 1448, 1369, 926; δ_H (300 MHz; $CDCl_3$) 0.83 (3H, t, J=6.9 Hz, 12′-H), 0.86 (3H, d, J=6.3 Hz, 4′-CH_3), 1.18–1.41 (16H, m, CH_2), 1.34 (3H, d, J=6.95 Hz, 5-CH_3), 1.51–1.59 (1H, m, 4′-H), 2.70–2.80 (2H, m, 2′-H), 2.93 (3H, s, NCH_3), 3.64 (1H, q, J=6.95 Hz, 5-H), 12.16 (br, 1H, OH); δ_C (75 MHz; $CDCl_3$) 14.0 (C-12′), 14.7 (5-CH_3), 19.2 (4′-CH_3), 22.6 (C-11′), 26.2 (NCH_3), 26.9 (C-3′), 29.3, 29.6, 29.8, 30.4 31.8 (C-6′ to C-10′), 32.6 (C-4′), 32.9 (C-2′), 36.6 (C-5′), 62.7 (C-5), 100.3 (C-3), 172.8 (C-2), 188.2 (C-1′), 194.6 (C-4);); *m/z* (EI, 70 eV) 323 (M^+, 10%), 305 (10%), 182 (35%), 169 (100%); HR-EI MS; *m/z* 323.2460 calcd. for $C_{19}H_{33}NO_3$. Found: 323.2461.

3.8.3. Melophlin C 1c. *Diastereomer α.* Yellow oil (160 mg, 91%) from **8c**$^{\alpha}$ (185 mg), R_f 0.29 (CH_2Cl_2–MeOH, 19:1). ν_{max}(ATR)/cm^{-1} 2925, 2854, 1712, 1618, 1452, 1371, 926; δ_H (300 MHz; $CDCl_3$) 0.79 (3H, d, J=6.9 Hz, 5′-CH_3), 0.82 (3H, t, J=6.9 Hz, 12′-CH_3), 1.18–1.41 (15H, m, CH_2), 1.34 (3H, d, J=6.9 Hz, 5-CH_3), 1.51–1.65 (2H, m, 3′-H), 2.70–2.76 (2H, m, 2′-H), 2.93 (3H, s, NCH_3), 3.64 (1H, q, J=6.9 Hz, 5-H), 11.60 (br, 1H, OH); δ_C (75 MHz; $CDCl_3$) 14.0 (C-12′), 14.8 (5-CH_3), 19.4 (5′-CH_3), 22.6 (C-11′), 23.5 (C-3′), 26.2 (NCH_3), 26.9 (C-7′), 29.3 (C-8′), 29.9 (C-10′), 31.8 (C-9′), 32.4 (C-5′), 32.7 (C-2′), 36.4 (C-4′), 36.8 (C-6′), 62.7 (C-5), 100.4 (C-3), 172.7 (C-2), 187.8 (C-1′), 194.6 (C-4); *m/z* (EI, 70 eV) 323 (M^+, 10%), 182 (30%), 169 (100%), 154 (60%); HR-EI MS; *m/z* 323.2460 calcd. for $C_{19}H_{33}NO_3$. Found: 323.2460.

Diastereomer β. Yellow oil (12 mg, 91%) from **8c**$^{\beta}$ (185 mg), R_f 0.24 (CH_2Cl_2–MeOH, 19:1).

3.8.4. Melophlin G 1g. Yellow oil (80 mg, 92%) from **8g** (100 mg), R_f 0.20 (CH_2Cl_2–MeOH, 19:1). ν_{max}(ATR)/cm^{-1} 2922, 2852, 1714, 1656, 1602, 1466, 1244; δ_H (300 MHz; $CDCl_3$) 0.80 (3H, t, J=6.8 Hz, CH_3), 1.18–1.37 (20H, m, CH_2), 1.51–1.65 (2H, m, CH_2), 2.74 (2H, t, J=7.55 Hz,

2′-H), 2.94 (3H, s, NCH_3), 3.65 (2H, s, 5-H), 10.71 (br, 1H, OH); δ_C (75 MHz; $CDCl_3$) 14.0 (CCH_3), 22.6 (CCH_3), 25.9 (CH_2), 28.4 (NCH_3), 24.7, 25.9, 29.3, 29.4, 29.6, 31.9 (CH_2), 32.7 (C-2′), 57.6 (C-5), 101.6 (C-3), 173.5 (C-2), 187.7 (C-1′), 191.3 (C-4); *m/z* (EI, 70 eV) 323 (M^+, 10%), 168 (30%), 155 (100%), 140 (35%); HR-EI MS; *m/z* 323.2460 calcd. for $C_{19}H_{33}NO_3$. Found: 323.2457.

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Total synthesis of marine bisindole alkaloids, (+)-hamacanthins A, B and (−)-antipode of *cis*-dihydrohamacanthin B

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Abstract—The total synthesis of the marine bisindole alkaloids, (+)-hamacanthins A (**2a**) and B (**2b**), and (−)-antipode of *cis*-dihydrohamacanthin B (**2e**) was achieved by transamidation–cyclization of *N*-(2-aminoethyl)-2-oxoethanamide **18** derived from (*S*)-indolylglycinol **10**.

1. Introduction

A growing number of bromoindole alkaloids are being discovered from a variety of marine invertebrates, including bryozoans, coelenterates, sponges and tunicates. Adding to their interest is the fact that they display a wide range of biological activity.[1] The dragmacidins **1**, 3,6-bisindole-piperazine and -pirazinone alkaloids, have been isolated from marine sponges *Dragmacidon*, *Halicortex*, *Hexadella* and *Spongosorites*, and tunicate *Didemmum candidum*.[1] A number of these metabolites were shown to possess a wide spectrum of pharmacological activities such as antifungal, antiinflammatory, antitumor, antiviral and cytotoxic activities, and inhibition of serine-threonine protain phosphatase and neural nitric synthetase.[1] The piperazinone alkaloid, hamacanthins **2**, found in marine sponges *Hamacantha* and *Rhaphisia* indicate significant antimicrobial activities against *C. albicans*, *C. neoformans* and *Bacillus subtilis*.[2] Hamacanthin A (**2a**) is a 3,6-bisindole derivative like dragmacidins **1**, but hamacanthin B (**2b**) is the 3,5-isomer, of which the substituent pattern is fairly unusual in these alkaloids (Fig. 1).

Since these alkaloids **1** and **2** are available from nature in only minute amounts, efficient methods for the total synthesis of **1** and **2** have been required to provide these alkaloids and the related compounds for launching a thorough biological investigation. Several groups have accomplished the total synthesis of (±)-dragmacidins **1**[3,4c] and (±)-hamacanthins **2**[4] and we also reported the synthesis of (±)-dragmacidins A–C (**1b–d**), (±)-*trans*- and *cis*-dihydrohamacanthin A (**2c**, **2d**) and (±)-hamacanthins (**2a**, **2b**).[5] However, there are few examples of the total synthesis of optical active alkaloids, namely (+)-dragmacidin F (**1g**) derived from (−)-quinic acid,[3e] (+)-dragmacidin A (**1b**), (+)-hamacanthin A (**2a**) and (−)-*trans*- and (−)-*cis*-dihydrohamacanthin A (**2c**, **2d**) as the antipode from (*S*)-indolylglycinol,[4c] and (+)-hamacanthin B (**2b**) from (*S*)-indolylethanediol.[4b] Herein, we describe the total synthesis of (+)-hamacanthins A (**2a**), (+)-B (**2b**) and (−)-antipode of *cis*-dihydrohamacanthin B (**2e**) via cyclization and transamidation of *N*-(2-aminoethyl)-2-oxoethanamide **18** derived from (*S*)-indolylglycinol **10**.

2. Results and discussion

There are two synthetic methods of (*S*)-6-bromoindolylglycinol **10**, one using asymmetric aminohydroxylation reported by Jiang's group[4c] and the other lipase-mediated resolution by us;[6] however, the optical purity of (*S*)-**10** obtained is insufficient for synthesis of optically pure natural products. Initially, we attempted a preparative method for optically pure (*S*)-**10** as follows. Reaction of readily available indolin-3-one **3**[7] with the optically active ylide **4**[8] in refluxing benzene smoothly proceeded with Wittig olefination to give a mixture (1:3) of the (*E*)- and (*Z*)-isomers of *N*-(3-indolylideneacety)oxazolidinone **5** in high yield (Scheme 1).[9] Since pure (*Z*)-olefin **5**, of which the configuration was confirmed by NOE experiment (Fig. 2), was obtained from the mixture by recrystallization (32%),[10] we attempted introduction of a nitrogen functional unit to (*Z*)-**5** through an indolenium intermediate **6**[5a,6] (Scheme 1, Table 1).

Keywords: Bromoindole; Indolylglycinol; Oxazolidin-2-one; Absolute configuration.
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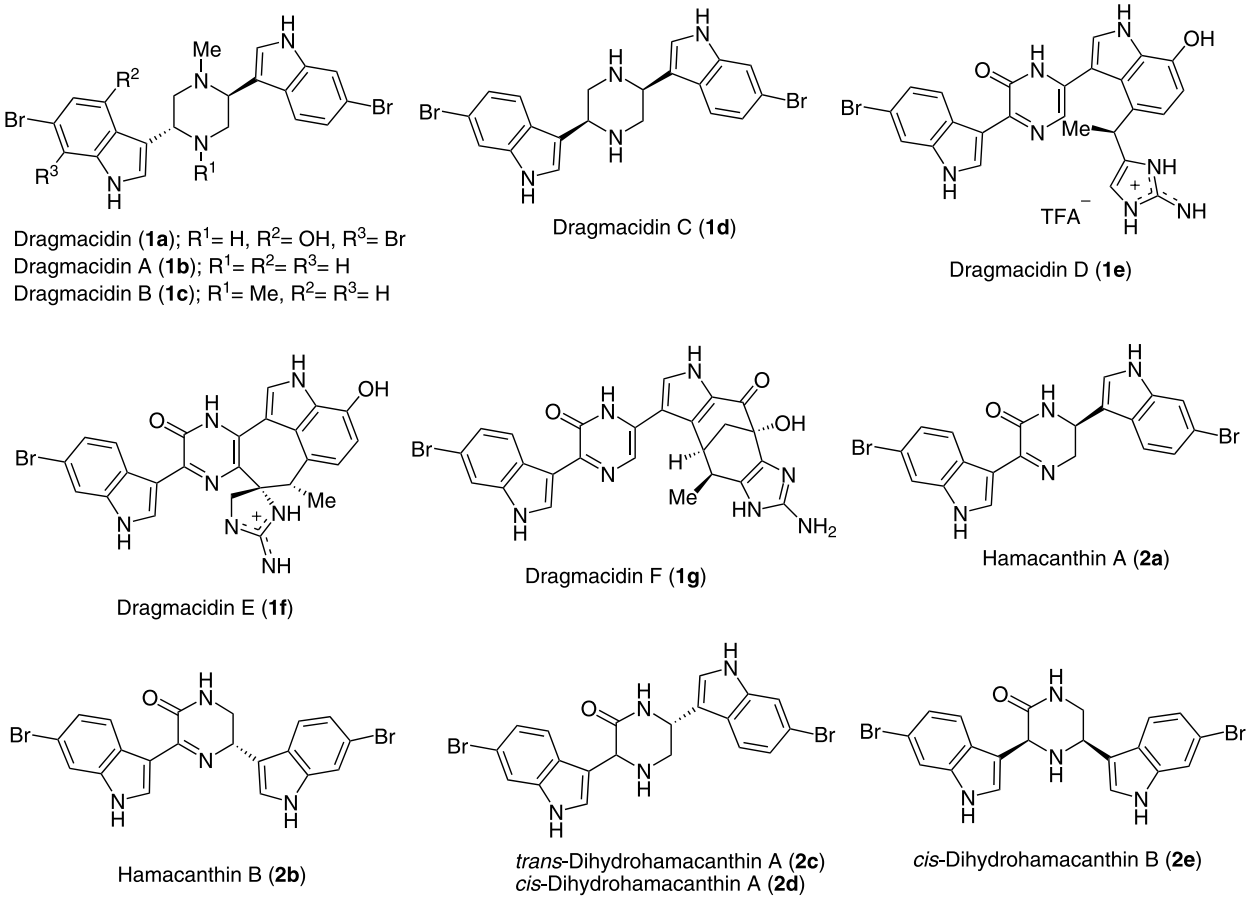
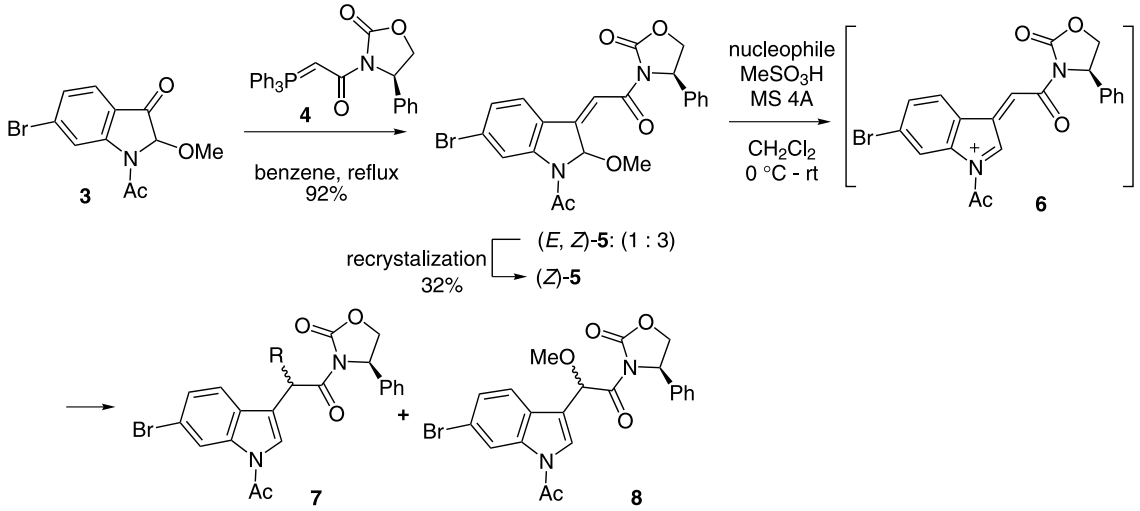


Figure 1. Marine bisindole alkaroids.

When (*Z*)-**5** was treated with benzamide or 1,1-dimethylurea in the presence of methanesulfonic acid, the desired indolylglycine **7** was not obtained at all but a diastereomeric mixture (1:2) of *N*-(2-indolyl-2-methoxyacetyl)oxazolidinone **8**, which was resulted from migration of the methoxy group via **6** (Table 1, entries 1 and 2). Similar treatment of (*Z*)-**5** with urethane produced the desired product **7a** (1:2.9) in 23% yield, but **8** as a main product was still formed (Table 1, entry 3). Reaction of (*Z*)-**5** with tosylamide proceeded stereoselectively to afford indolylglycine derivative **7b** in 47% yield as a diastereoisomeric mixture (1:7), of which separation was not easy (Table 1, entry 4). On treatment with $TMSN_3$, the desired reaction took place smoothly to give azide derivative **7c** in high yield, but with lower diastereoselectivity (1:1.3). Fortunately, the mixture could be easily separated on a normal column chromatography to obtain (2*S*)-2-azidoacetyloxazolidine **7c** and (2*R*)-epimer **7c** in 38 and 52% yields, respectively (Table 1, entry



Scheme 1. Addition of nitrogen nucleophiles into indolinium intermediate **6**.

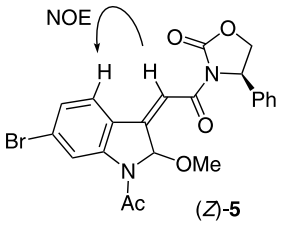


Figure 2. NOE experimental of (*Z*)-isomer **5**.

Table 1. Reaction of (*Z*)-**5** with nitrogen nucleophiles

Entry	Nucleophile	Yield (%)	
		7	**8**
1	$PhCONH_2$	—	80 (1:2.0)[a]
2	Me_2NCONH_2	—	86 (1:1.9)[a]
3	$EtOCONH_2$	**7a**:23 (1:2.9)[b]	63 (1:2.0)[a]
4	$TsNH_2$	**7b**:47 (1:7.0)[b]	—
5	$TMSN_3$	**7c**:90 (1:1.3)[a]	—

[a] The ratio of diastereoisomers was calculated with isolated yields.
[b] The ratio of diastereoisomers was determined by HPLC.

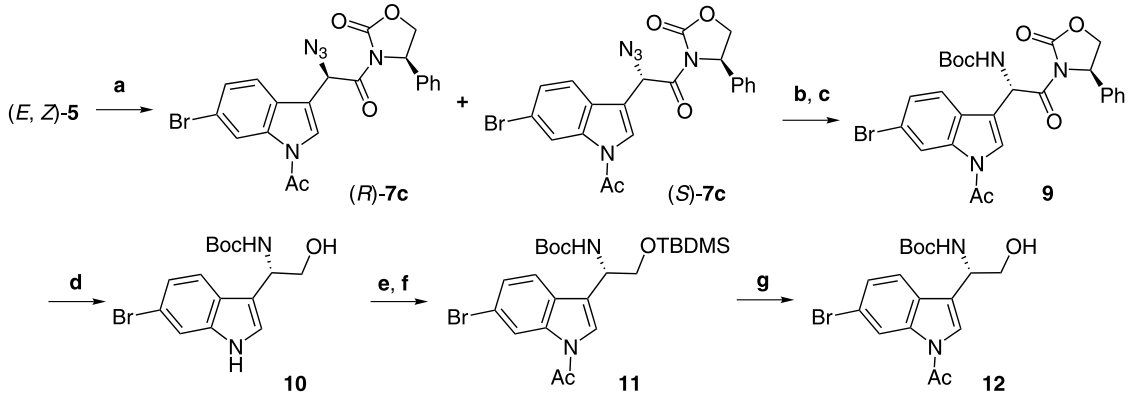
5). Due to the lower stereoselectivity of **7c**, we abandoned attempts for an asymmetrical method and turned to another measure to optically active 6-bromoindolylglycinol **10** using chemical resolution of **7c** for total synthesis of optically active hamacanthins **2**.

When the mixture of (*E*)- and (*Z*)-isomers **5** was treated with $TMSN_3$ in the presence of methanesulfonic acid followed by separation using column chromatography, (2*S*)- and (2*R*)-**7c** were obtained in 41 and 56% yields (Scheme 2). Azide (*S*)-**7c** was smoothly reduced with *n*-tributylphosphine in the presence of 10% HCl at 0 °C to a resulting amine, which was protected with Boc_2O to give oxazolidinylindolylglycine **9** (82% yield, 2 steps). The reductive removal of the oxazolidinyl group from **9** with sodium borohydride followed by hydrolysis with LiOH afforded (+)-indolylglycinol **10** in 85% yield without epimerization.[11] The absolute configuration of (+)-glycinol **10** was determined by transformation to known (+)-(*S*)-1-acetylindolylglycinol **12**,[6] which was prepared by *O*-silylation and *N*-acetylation of **10** followed by removal of the TBDMS group from **11** with concd HCl (32%, 3 steps).

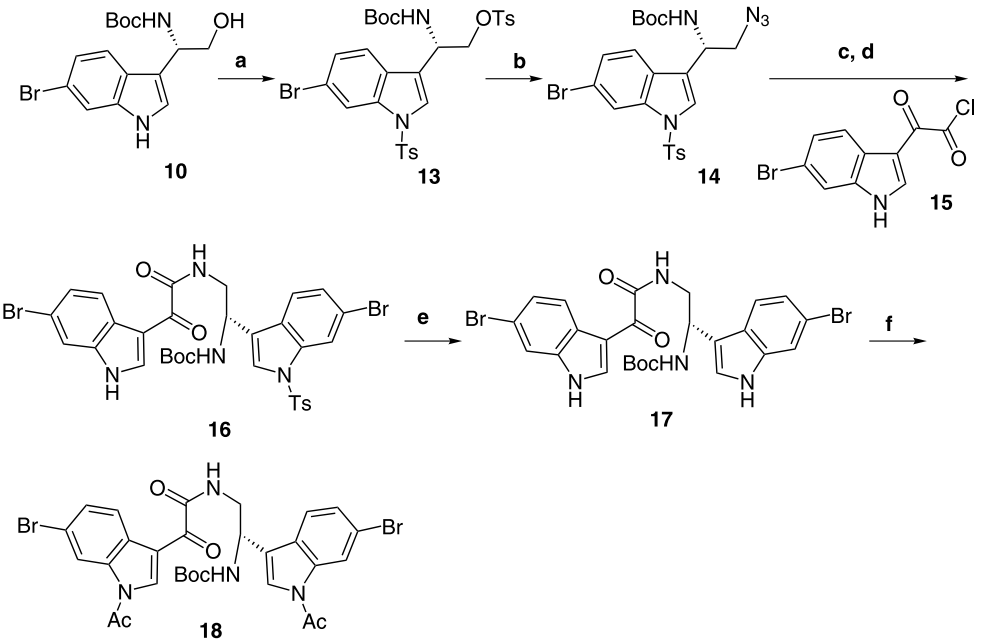
Next, we prepared (*S*)-*N*-(2-aminoethyl)-2-oxoethanamide **18** from (*S*)-glycinol **10** as a key synthetic intermediate for optically active hamacanthins **2** according to our synthetic method[5c] (Scheme 3). Tosylation of (*S*)-indolylglycinol **10** with *p*-toluenesulfonyl chloride at −20 °C provided *N*,*O*-ditosylate **13** (82%), which was displaced with NaN_3 at 80 °C leading to aminoazide **14** in 78% yield. Reduction of azide **14** with triphenylphosphine-H_2O followed by condensation with 6-bromoindol-3-yl-α-oxoacetyl chloride (**15**) afforded amide **16** (79%, 2 steps). After detosylation of **16** with 10% KOH in heating EtOH, a couple of indole nitrogens in **17** were re-protected by acetylation to *N*-(2-aminoethyl)-2-oxoethanamide **18** in 78% yield (2 steps).

We performed the total synthesis of optically active hamacanthins A (**2a**) and B (**2b**) via biomimetic transamidation–cyclization of **18** (Scheme 4). Removal of the Boc group in **18** followed by heating an intermediate **19** in dichloroethane provided 3,5-bisindolylpyrazinone **22** (65%) and its regio-isomer **23** (33%). The formation of **23** is explained in terms of intramolecular transamidation of **19** to a five membered ring intermediate **20** followed by cyclization of **21**. Deacetylation of **22** and **23** with ammonium hydroxide proceeded smoothly to afford optically pure (+)-hamacanthins A (**2a**) and B (**2b**) in 87 and 82% yields, respectively. The spectra data of synthetic products **2a** and **2b** are completely identical to those of natural (+)-hamacanthins A and B, respectively.[2a]

Finally, we tried to synthesize *cis*-dihydrohamacanthin B (**2e**), of which the absolute configuration was not yet determined. Namely, reaction of 3,5-bisindolylpyrazinone **22** with sodium cyanoborohydride in methanol took place with stereoselective reduction to give only (3*R*,5*S*)-isomer of *cis*-dihydrohamacanthin B (**2e**) in 73% yield,[12] whose relative configuration was determined by its NOE experiments (Fig. 3). The ^1H and ^{13}C NMR data of the resulting compound are identical to those of natural *cis*-dihydrohamacanthin B (**2e**).[2b] However, the specific rotation (−92.3) of the synthetic product was contrary to that (+98.7) of the natural product.[2b] This demonstrates that the



Scheme 2. Reagents and conditions: (a) $TMSN_3$, $MeSO_3H$, MS 4A, CH_2Cl_2, 0 °C-rt, (*S*)-**7c**: 41%, (*R*)-**7c**: 56%; (b) *n*-Bu_3P, 10% HCl, THF, 0 °C-rt; (c) Boc_2O, DMAP, CH_2Cl_2, 82% (2 steps); (d) $NaBH_4$, THF–H_2O, rt, then 10% LiOH, rt, 85%; (e) TBDMSCl, DMAP, Et_3N, CH_2Cl_2, rt; (f) Ac_2O, DMAP, CH_2Cl_2, rt, 51% (2 steps); (g) concd HCl, MeOH, rt, 62%.

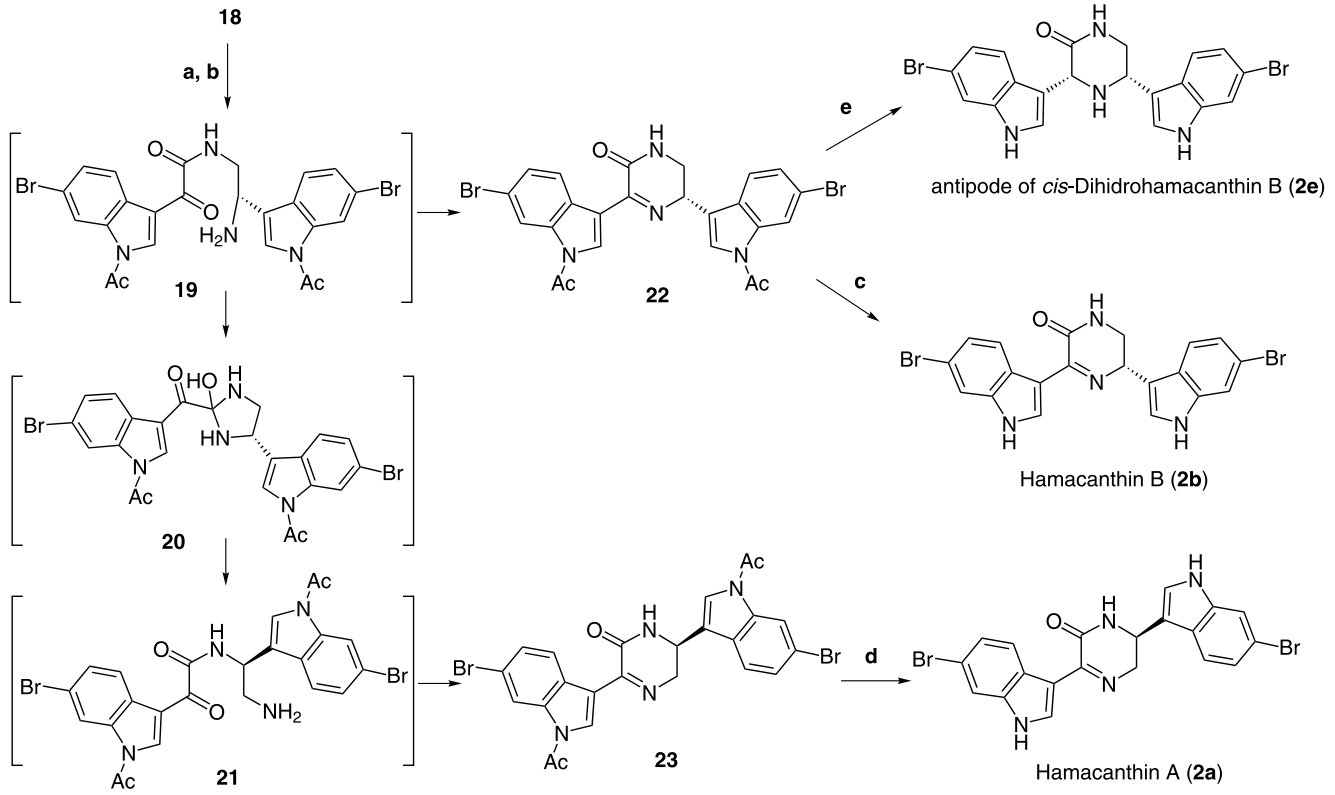


Scheme 3. Reagents and conditions: (a) TsCl, DMAP, Et_3N, CH_2Cl_2, −20 °C, 82%; (b) NaN_3, DMF, 80 °C, 78%; (c) Ph_3P, H_2O, THF, reflux; (d) 6-bromoindol-3-yl-α-oxoacetyl chloride **15**, Et_3N, THF, 0 °C-rt, 79% (2 steps); (e) 10% KOH, EtOH, reflux, 93%; (f) Ac_2O, DMAP, THF, rt, 84%.

natural (+)-*cis*-dihydrohamacanthin B (**2e**) has (3*S*,5*R*)-configuration.

3. Conclusion

In summary, we have demonstrated a synthetic method for (+)-hamacanthins A and B (**2a**, **2b**) and (−)-antipode of *cis*-dihydrohamacanthin B (**2e**) from the optically pure (*S*)-indolylglycinol **10** through intermolecular transamidation–cyclization. We also indicated that the configuration of natural (+)-*cis*-dihydrohamacanthin B (**1e**) is 3*S*,5*R*. Further work involving the synthesis of dihydrohamacanthins **2c**–**e** with natural configuration



Scheme 4. Reagents and conditions: (a) HCO_2H, CH_2Cl_2, rt; (b) pH=4, 1,2-dichloroethane, reflux, **22**: 65%, **23**: 33% (2 steps); (c) NH_4OH, THF–MeOH (3:1), rt, 82%; (d) NH_4OH, THF–MeOH (1:1), rt, 87%; (e) $NaBH_3CN$, MeOH, rt, 73%.

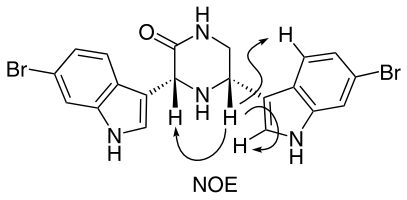


Figure 3. NOE experimental of antipode of *cis*-**2e**.

from (2*R*)-2-azidoacetyloxazolidine **7c** is now in progress.

4. Experimental

4.1. General

All melting points are uncorrected, and were measured on a Yanagimoto micromelting point apparatus. Optical rotations were obtained on a JASCO DIP-140 digital polarimeter. Optical purities were determined on a HPLC (JASCO UV-975) instrument equipped with AD (Daicel Chemical Ind., Ltd, Chiralpak®), OD (Daicel Chemical Ind., Ltd, Chiralcel®) or Finepak SIL-5 column (JASCO Corporation). IR spectra were recorded on a Shimadzu FTIR-8100 or Shimadzu FTIR-8400s spectrophotometer. ^{1}H and ^{13}C NMR spectra were measured on a JEOL JNM-AL 300 (300 MHz), JEOL JNM-GSX 400 (400 MHz) or JEOL JNM-LA 500 (500 MHz) spectrometer with tetramethylsilane as an internal standard. *J*-Values are given in Hertz. Mass spectra were recorded on a JEOL JMS-DX 302 or JEOL JMS 700 instrument with a direct inlet system operating at 70 eV. Elemental analyses were obtained using a Perkin–Elmer Model 240B elemental analyzer. Column chromatography was carried out on silica gel (Kanto Chemical Co. Inc, 230–400 mesh and Merck, 230–400 mesh).

4.1.1. (5″*R*)-(*Z*)-1-Acetyl-6-bromo-2-methoxy-3-(2′-oxo-2′-(2″-oxo-5″-phenyl-3″,1″-oxazolidinyl)ethylidene)indoline (5). A solution of indolin-3-one **3** (300 mg, 1.1 mmol) and (4*R*-phenyl-1,3-oxazolidine-2-one-3-yl)carbomethylenetriphenylphosphorane **4** (246 mg, 0.53 mmol) in benzene (9 mL) was heated under reflux for 6 h. After removal of the solvent, the residue was chromatographed on a silica gel column with AcOEt–hexane (1:2) as eluent to give indoline **5** (229 mg, 92%, *E*:*Z*=1:3) as a solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 2.36 (3H×0.5, s, CH_3–CO), 2.38 (3H×0.1, s, CH_3–CO), 2.39 (3H×0.1, s, CH_3–CO), 2.39 (3H×0.3, s, CH_3–CO), 2.93 (3H×0.5, s, CH_3–O–), 1.03 (3H×0.1, s, CH_3–O–), 3.08 (3H×0.3, s, CH_3–O–), 3.12 (3H×0.1, s, CH_3–O–), 4.23–4.37 (1H, m, –C*H*H–), 4.71–4.80 (1H, m, –C*H*H–), 5.54–5.63 (1H, m, –C*H*–CH_2–), 6.01 (1H×0.4, d, *J*=1.3 Hz, –C*H*–OMe), 6.65 (1H×0.5, d, *J*=2.0 Hz, –C*H*–OMe), 6.78 (1H×0.1, d, *J*=2.0 Hz, –C*H*–OMe), 7.11–7.53 (6.2H, m, Ar-H and =CH–), 7.87 (1H×0.5, d, *J*=2.0 Hz, =CH–), 8.25 (1H×0.3, d, *J*=8.6 Hz, Ar-H), 8.53 (1H, br, Ar-H). The *E*,*Z*-mixture of **5** was recrystalized with AcOEt–hexane to afford (*Z*)-**5** (73 mg, 32%) as yellow crystals. Mp 219 °C (AcOEt–hexane). IR ($CHCl_3$) cm^{-1}: 1778, 1682, 1628. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 2.36 (3H, s, CH_3–CO), 2.93 (3H, s, CH_3–O–), 4.31 (1H, dd, *J*=8.8, 3.4 Hz, –C*H*H–), 4.75 (1H, dd, *J*=8.8, 8.6 Hz, –C*H*H–), 5.56 (1H, dd, *J*=8.6, 3.4 Hz, –C*H*–CH_2–), 6.65 (1H, d, *J*=2.0 Hz, –C*H*–OMe), 7.24–7.42 (6H, m, Ar-H), 7.51 (1H, d, *J*=8.3 Hz, Ar-H), 7.88 (1H, d, *J*=2.0 Hz, =CH–), 8.52 (1H, br, Ar-H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 23.6, 50.4, 57.7, 70.3, 88.0, 111.6, 120.0, 122.3, 124.8, 125.4, 127.3, 127.8, 128.6, 129.1, 138.5, 146.0, 148.6, 153.5, 162.5, 169.5. MS (EI) *m*/*z* (%): 472 (M+2, 69), 470 (M$^+$, 70), 430 (19), 428 (20), 399 (20), 397 (21), 309 (43), 307 (42), 267 (99), 265 (100), 252 (29), 250 (31), 240 (29), 238 (32). HRMS (EI) *m*/*z* calcd for $C_{22}H_{19}BrN_2O_5$: 470.0477. Found: 470.0477. Anal. Calcd for $C_{22}H_{19}BrN_2O_5$: C, 56.07; H, 4.06; N, 5.94. Found: C, 55.86; H, 4.09; N, 5.90.

4.2. General procedure for addition of nitrogen function to olefin (*Z*)-5 and (*E*,*Z*)-5

Under nitrogen, methanesulfonic acid (139 μL, d 1.48, 2.1 mmol) was added to a mixture of (*Z*)-**5** or (*E*,*Z*)-**5** (100 mg, 0.21 mmol), nitrogen nucleophile (2.1 mmol) and MS 4A (100 mg) in dry CH_2Cl_2 (3.0 mL) at 0 °C. After stirring at room temperature for 1 h, the resulting mixture was filtered on Celite® 545 to remove MS 4A. The filtrate was washed with H_2O (10 mL) and satd $NaHCO_3$ (10 mL), dried over $MgSO_4$ and concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography with AcOEt–hexane (1:3) or benzene–hexane (1:1) as eluent to afford indolylglycine **7** or/and *N*-(2-indolyl-2-methoxyacetyl)oxazolidinone **8** as shown in Table 1.

4.2.1. (5″*R*)-1-Acetyl-6-bromo-3-{1′-methoxy-2′-oxo-2′-(2″-oxo-5″-phenyl-3″,1″-oxazolidinyl)ethyl}indole (8). *Major diasteroisomer*. Colorless crystals; Mp 160 °C (AcOEt–hexane). IR ($CHCl_3$) cm^{-1}: 1778, 1715. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 2.63 (3H, s, CH_3–CO), 3.29 (3H, s, CH_3–O), 4.31 (1H, dd, *J*=8.8, 3.3 Hz, –C*H*H–), 4.62 (1H, dd, *J*=8.8, 8.6 Hz, –C*H*H–), 5.33 (1H, dd, *J*=8.6, 3.3 Hz, –C*H*–CH_2–), 6.19 (1H, s, –C*H*–OMe), 7.32–7.45 (6H, m, Ar-H), 7.63 (1H, s, Ar-H), 7.73 (1H, d, *J*=8.5 Hz, Ar-H), 8.65 (1H, d, *J*=1.7 Hz, Ar-H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 24.0, 57.1, 58.0, 70.5, 74.9, 116.0, 119.4, 119.5, 122.1, 125.8, 126.5, 126.9, 127.2, 128.8, 129.1, 136.3, 138.4, 153.1, 168.2, 168.5. MS (EI) *m*/*z* (%): 472 (M+2, 13), 470 (M$^+$, 13), 282 (98), 280 (100), 240 (95), 238 (98). HRMS (EI) *m*/*z* calcd for $C_{22}H_{19}BrN_2O_5$: 470.0477. Found: 470.0473.

Minor diasteroisomer. Colorless crystals; Mp 75 °C (AcOEt–hexane). IR ($CHCl_3$) cm^{-1}: 1778, 1715. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 2.53 (3H, s, CH_3–CO), 3.41 (3H, s, CH_3–O–), 4.20 (1H, dd, *J*=9.3, 4.7 Hz, –C*H*H–), 4.73 (1H, dd, *J*=9.3, 9.0 Hz, –C*H*H–), 5.50 (1H, dd, *J*=9.0, 4.7 Hz, –C*H*–CH_2–), 6.13 (1H, s, –C*H*–OMe), 6.84 (2H, dd, *J*=7.6, 1.5 Hz, Ar-H), 7.02 (2H, t, *J*=7.6 Hz, Ar-H), 7.183 (1H, tt, *J*=7.6, 1.5 Hz, Ar-H), 7.184 (1H, dd, *J*=8.4, 1.5 Hz, Ar-H), 7.28 (1H, d, *J*=8.4 Hz, Ar-H), 7.35 (1H, s, Ar-H), 8.62 (1H, d, *J*=1.5 Hz, Ar-H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 23.9, 57.4, 57.6, 70.3, 74.9, 116.0, 119.3, 119.3, 121.3, 125.7, 126.2, 126.8, 127.1, 128.61, 128.63, 136.1, 137.1, 152.9, 168.2, 168.9. MS (EI) *m*/*z* (%): 472 (M+2, 14), 470 (M$^+$, 13), 282 (98), 280 (100), 240 (97),

238 (99). HRMS (EI) *m/z* calcd for $C_{22}H_{19}BrN_2O_5$: 470.0477. Found: 470.0476.

4.2.2. (5″*R*)-*N*-{1-(1′-Acetyl-6′-bromoindol-3-yl)-2-oxo-2-(2″-oxo-5″-phenyl-3″,1″-oxazolidinyl)ethyl}ethoxyformamide (7a) (Table 1, entry 3). Yellow viscous oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.14–1.31 (3H, m, C*H*$_3$–CH$_2$–), 2.47 (3H×0.75, s, CH$_3$–CO), 2.64 (3H×0.25, s, CH$_3$–CO), 4.02–4.31 (3H, m, –C*H*H– and –C*H*$_2$–CH$_3$), 4.59 (1H×0.25, dd, *J*=8.8, 8.6 Hz, –C*H*H–), 4.74 (1H×0.75, dd, *J*=9.0, 8.8 Hz, –C*H*H–), 5.32 (1H×0.25, dd, *J*=8.6, 3.5 Hz, –C*H*–CH$_2$–), 5.49 (1H×0.75, dd, *J*=8.8, 4.5 Hz, –C*H*–CH$_2$–), 5.56 (1H×0.75, br, –NH–), 5.80 (1H×0.25, br, –NH–), 6.83 (1H, d, *J*=8.1 Hz, –CH–CO), 6.96–7.61 (8H, m, Ar-H), 8.63 (1H×0.75, s, Ar-H), 8.68 (1H×0.25, d, *J*=1.5 Hz, Ar-H). HRMS (EI) *m/z* calcd for $C_{24}H_{22}BrN_3O_6$: 527.0692. Found: 527.0691. The ratio (1:2.9) of two diastereoisomers was determined by HPLC.

4.2.3. (5‴*R*)-1-Acetyl-6-bromo-3-(1′-[{(4″-methylphenyl)sulfonyl}amino]-2′-oxo-2′-{2‴-oxo-5‴-phenyl-3‴,1‴-oxazolidinyl}ethyl)indole (7b) (Table 1, entry 4). Colorless powder; Mp 232–235 °C (AcOEt–hexane). IR ($CHCl_3$) cm^{-1}: 1784, 1718. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 2.36 (3H, s, CH$_3$–), 2.39 (3H, s, CH$_3$–), 4.20 (1H, dd, *J*=9.2, 5.0 Hz, –C*H*H–), 4.67 (1H, dd, *J*=9.2, 9.0 Hz, –C*H*H–), 5.35 (1H, dd, *J*=9.0, 5.0 Hz, –C*H*–CH$_2$–), 5.78 (1H, d, *J*=8.8 Hz, –NH–), 6.57 (1H, d, *J*=8.8 Hz, –C*H*–NH–), 6.80 (1H, d, *J*=8.4 Hz, Ar-H), 6.92 (1H, s, Ar-H), 6.93 (2H, dd, *J*=7.8, 1.6 Hz, Ar-H), 7.07–7.13 (5H, m, Ar-H), 7.24 (1H, tt, *J*=7.8, 1.6 Hz, Ar-H), 7.54 (2H, d, *J*=8.5 Hz, Ar-H), 8.50 (1H, d, *J*=1.7 Hz, Ar-H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 21.6, 23.7, 51.4, 57.7, 70.2, 114.9, 119.3, 119.4, 120.4, 125.7, 125.9, 126.2, 127.0, 127.1, 128.8, 128.9, 129.0, 136.0, 136.4, 137.1, 143.5, 152.2, 167.9, 168.7. MS (EI) *m/z* (%): 611 (M+2, 51), 609 (M$^+$, 47), 456 (41), 454 (39), 421 (100), 419 (95), 382 (17), 380 (23), 379 (46), 377 (45), 251 (17), 249 (18), 224 (25), 222 (36), 155 (22), 132 (33), 91 (51). HRMS (EI) *m/z* calcd for $C_{28}H_{14}BrN_3O_6S$: 609.0569. Found: 609.0570. The ratio (1:7) of two diastereoisomers was determined by HPLC.

4.2.4. (1′*R*,5″*R*)-1-Acetyl-3-{1′-azido-2′-oxo-2′-(2″-oxo-5″-phenyl-3″,1″-oxazolidinyl)ethyl}-6-bromoindole [(*R*)-7c]. Yellow powder; Mp 148 °C (AcOEt–hexane). $[\alpha]_D$=−244.7 (*c* 0.37, $CHCl_3$). IR ($CHCl_3$) cm^{-1}: 2110, 1782, 1717. ^{1}H NMR ($CDCl_3$, 270 MHz) δ: 2.66 (3H, s, CH$_3$–), 4.34 (1H, dd, *J*=8.9, 3.6 Hz, –C*H*H–), 4.66 (1H, t, *J*=8.9 Hz, –C*H*H–), 5.40 (1H, dd, *J*=8.9, 3.6 Hz, –C*H*–CH$_2$–), 6.45 (1H, s, –CH–CO), 7.26–7.48 (6H, m, Ar-H), 7.58 (1H, s, Ar-H), 7.64 (1H, d, *J*=8.6 Hz, Ar-H), 8.68 (1H, d, *J*=1.7 Hz, Ar-H). ^{13}C NMR ($CDCl_3$, 68 MHz) δ: 23.9, 56.6, 58.1, 70.4, 114.0, 119.8, 120.1, 121.0, 125.9, 126.0, 126.8, 127.6, 129.2, 129.5, 136.5, 137.9, 152.9, 167.7, 168.4. MS (EI) *m/z* (%): 483 (M+2, 2), 481 (M$^+$, 2), 455 (18), 453 (18), 223 (34), 221 (35), 163 (81), 133 (95), 104 (100), 91 (34), 77 (22), 43 (19). Anal. Calcd for $C_{21}H_{16}BrN_5O_4$: C, 52.30; H, 3.34; N, 14.52. Found: C, 52.32; H, 3.45; N, 14.13.

4.2.5. (1′*S*,5″*R*)-1-Acetyl-3-{1′-azido-2′-oxo-2′-(2″-oxo-5″-phenyl-3″,1″-oxazolidinyl)ethyl}-6-bromoindole [(*S*)-7c]. Yellow powder; Mp 148 °C (AcOEt–hexane). $[\alpha]_D$=+120.9 (*c* 0.28, $CHCl_3$). IR ($CHCl_3$) cm^{-1}: 2110, 1784, 1717. ^{1}H NMR ($CDCl_3$, 270 MHz) δ: 2.42 (3H, s, CH$_3$–), 4.29 (1H, dd, *J*=8.9, 4.0 Hz, –C*H*H–), 4.76 (1H, t, *J*=8.9 Hz, –C*H*H–), 5.52 (1H, dd, *J*=8.9, 4.0 Hz, –C*H*–CH$_2$–), 6.40 (1H, s, –CH–CO), 7.00 (1H, s, Ar-H), 7.09 (1H, d, *J*=7.3 Hz, Ar-H), 7.23 (1H, t, *J*=7.3 Hz, Ar-H), 7.30–7.38 (5H, m, Ar-H), 8.65 (1H, d, *J*=1.3 Hz, Ar-H). ^{13}C NMR ($CDCl_3$, 68 MHz) δ: 23.7, 56.5, 57.7, 70.3, 113.9, 119.7, 120.0, 120.6, 125.3, 126.3, 126.7, 127.6, 129.1, 129.2, 136.4, 137.5, 152.7, 168.2, 168.3. MS (EI) *m/z* (%): 483 (M+2, 15), 481 (M$^+$, 17), 455 (28), 453 (28), 265 (34), 263 (35), 223 (99), 221 (100), 142 (34), 104 (57), 43 (37). HRMS (EI) *m/z* calcd for $C_{21}H_{16}BrN_5O_4$: 481.0386. Found: 481.0391. Anal. Calcd for $C_{21}H_{16}BrN_5O_4$: C, 52.30; H, 3.34; N, 14.52. Found: C, 52.26; H, 3.39; N, 14.43.

4.3. Preparation of optical pure indolylglycinol 10

4.3.1. *tert*-Butyl (1′*S*,5″*R*)-*N*-{1′-(1-Acetyl-6-bromoindol-3-yl)-2′-oxo-2′-(2″-oxo-5″-phenyl-3″,1″-oxazolidinyl)-ethylcarbamate (9). To a solution of azide (*S*)-**7c** (387 mg, 0.80 mmol) in THF (8 mL) and 10% HCl (0.3 mL), *n*-tributylphosphine (0.40 mL, d 0.81, 1.6 mmol) was added dropwise at 0 °C. The stirred reaction mixture was gradually warmed to ambient temperature over 12 h. After removal of the solvent, the residue was diluted with AcOEt (40 mL) and washed with satd NaCl (5 mL). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure to give a crude amine. A solution of the crude amine, DMAP (9.8 mg, 0.08 mmol) and di-*tert*-butyl dicarbonate (0.9 mL, d 0.95, 4.0 mmol) in CH_2Cl_2 (8 mL) was stirred at room temperature for 3 days. After removal of the solvent, the residue was purified by silica gel column chromatography with AcOEt–hexane (1:1) as eluent to afford indolylglycine **9** (366 mg, 82%) as a colorless powder. Mp 110–115 °C (AcOEt–hexane). $[\alpha]_D$=+121.0 (*c* 0.93, $CHCl_3$). IR ($CHCl_3$) cm^{-1}: 3495, 1786, 1713. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.42 (9H, s, *t*-Bu), 2.45 (3H, s, CH$_3$–CO), 4.22 (1H, dd, *J*=9.0, 4.4 Hz, –C*H*H–), 4.73 (1H, t, *J*=9.0 Hz, –C*H*H–), 5.37 (1H, br d, *J*=8.1 Hz, –NH–), 5.49 (1H, dd, *J*=9.0, 4.4 Hz, –C*H*–CH$_2$–), 6.79 (1H, d, *J*=8.1 Hz, –C*H*–NHBoc), 6.98 (2H, d, *J*=7.4 Hz, Ar-H), 7.11 (1H, s, Ar-H), 7.13 (2H, t, *J*=7.4 Hz, Ar-H), 7.22–7.28 (3H, m, Ar-H), 8.63 (1H, s, Ar-H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 23.8, 28.4, 49.9, 57.7, 70.1, 80.5, 116.3, 119.4, 119.5, 120.5, 125.3, 126.0, 126.6, 127.1, 128.8, 136.1, 137.6, 152.3, 154.7, 168.1, 169.7. MS (EI) *m/z* (%): 557 (M+2, 10), 555 (M$^+$, 10), 501 (15), 499 (15), 367 (28), 365 (28), 311 (99), 309 (100), 269 (24), 267 (56), 265 (35), 225 (33), 223 (45), 164 (25), 57 (41). HRMS (EI) *m/z* calcd for $C_{26}H_{26}BrN_3O_6$: 555.1005. Found: 555.1009. Anal. Calcd for $C_{26}H_{26}BrN_3O_6$: C, 56.12; H, 4.71; N, 7.55. Found: C, 56.11; H, 4.74; N, 7.36.

4.3.2. *tert*-Butyl (*S*)-*N*-[1-(6-bromoindol-3-yl)-2-hydroxy]-ethylcarbamate (10). Sodium borohydride (75 mg, 1.99 mmol) in water (0.45 mL) was added to a solution of indolylglycine **9** 276 mg, 0.50 mmol) in THF (10 mL) at room temperature. After stirring at the same temperature for 30 min, 10% LiOH (5 mL) was added. The reaction mixture was stirred under the same conditions for 30 min. The resulting mixture was concentrated under reduced pressure to give a residue, which was extracted with AcOEt (15 mL×2). The organic layer was washed with satd

NaCl, dried over $MgSO_4$ and evaporated to afford a residue. The residue was chromatographed on a silica gel column with AcOEt–hexane (2:1) as eluent to provide indolylglycinol **10** (149 mg, 85%) as colorless crystals. Mp 161–162 °C (acetone–hexane), >99%ee. $[\alpha]_D=+19.1$ (*c* 0.86, $CHCl_3$). IR (KBr) cm^{-1}: 3399, 3273, 1671, 1617. ^1H NMR (acetone-d_6, 300 Hz) δ: 1.40 (9H, s, *t*-Bu), 2.82 (1H, br, OH), 3.89 (2H, d, $J=4.2$ Hz, –CH_2–), 5.05 (1H, br, –C*H*–CH_2–), 6.05 (1H, br, –N*H*–Boc), 7.15 (1H, dd, $J=8.4$, 1.8 Hz, Ar-H), 7.36 (1H, d, $J=1.8$ Hz, Ar-H), 7.59 (1H, d, $J=1.5$ Hz, Ar-H), 7.65 (1H, d, $J=8.4$ Hz, Ar-H), 10.24 (1H, br, indole-NH). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 28.3, 50.1, 65.9, 79.9, 114.0, 114.4, 115.9, 120.0, 122.2, 123.0, 124.4, 136.8, 155.9. MS (EI) *m/z* (%): 356 (M+2, 13), 354 (M^+, 13), 325 (26), 323 (26), 269 (97), 267 (100), 225 (27), 223 (31), 210 (22), 208 (22), 57 (38). HRMS (EI) *m/z* calcd for $C_{15}H_{19}BrN_2O_3$: 354.0579. Found: 354.0584. Anal. Calcd for $C_{15}H_{19}BrN_2O_3$: C, 50.72; H, 5.39; N, 7.89. Found: C, 50.70; H, 5.37; N, 7.62.

4.3.3. *tert*-Butyl (*S*)-*N*-[1-(1-acetyl-6-bromoindol-3-yl)-2-(*tert*-butyldimethylsilyloxy)]ethylcarbamate (11). Under nitrogen, *tert*-butyldimethylsilyl chloride (739 mg, 4.91 mmol) was added in one portion to a solution of indolylglycinol **10** (871 mg, 2.45 mmol), DMAP (30 mg, 0.25 mmol) and triethylamine (0.7 mL, d 0.73, 4.91 mmol) in dry CH_2Cl_2 (25 mL) at room temperature. After stirring under the same conditions for 12 h, the excess silyl chloride was quenched with MeOH (12 mL). The solvent was removed by evaporation to give a residue, which was diluted with AcOEt (50 mL) followed by washing with water (10 mL) and satd NaCl (10 mL). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel chromatography with AcOEt–hexane (1:3) as eluent to give a crude product. A mixture of the crude, DMAP (299 mg, 2.45 mmol) and acetic anhydride (0.5 mL, d 1.08, 4.91 mmol) in dry CH_2Cl_2 (25 mL) was stirred at room temperature under nitrogen for 36 h. After removal of the solvent, the residue was chromatographed on a silica gel column with AcOEt–hexane (1:3) as eluent to obtain *O*-silyl-*N*-acetyl indolylglycinol **11** (632 mg, 51%) as colorless crystals. Mp 102–103 °C (CH_2Cl_2–hexane). $[\alpha]_D=+19.7$ (*c* 1.62, $CHCl_3$). IR (KBr) cm^{-1}: 3448, 1705. ^1H NMR ($CDCl_3$, 300 MHz) δ: 0.01 (3H, s, CH_3–Si–), 0.04 (3H, s, CH_3–Si–), 0.89 (9H, s, *t*–Bu–Si–), 1.45 (9H, s, *t*-Bu–O–), 2.59 (3H, s, CH_3–CO), 3.93 (1H, dd, $J=10.2$, 3.0 Hz, –C*H*H–), 4.01 (1H, dd, $J=10.2$, 3.8 Hz, –C*H*H–), 5.00 (1H, br, –C*H*–CH_2–), 5.08 (1H, d, $J=7.9$ Hz, –NH–), 7.40 (1H, dd, $J=8.5$, 1.7 Hz, Ar-H), 7.45 (1H, s, Ar-H), 7.49 (1H, d, $J=8.5$ Hz, Ar-H), 8.65 (1H, s, Ar-H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: −5.3, −5.2, 18.4, 23.9, 25.9, 28.5, 48.5, 65.0, 79.9, 119.0, 119.7, 120.3, 121.7, 123.3, 126.7, 127.8, 136.2, 155.1, 168.0. HRMS (FAB) *m/z* calcd for $C_{23}H_{36}BrN_2O_4Si$: 511.1628. Found: 511.1627.

4.3.4. *tert*-Butyl (*S*)-*N*-[1-(1-acetyl-6-bromoindol-3-yl)-2-hydroxy]ethylcarbamate (12). A solution of **11** (62 mg, 0.12 mmol) and concd HCl (12 μL) in MeOH (1.2 mL) was stirred at room temperature for 30 min. After removal of the solvent, the residue was diluted with water (5 mL) and extracted with AcOEt (10 mL×2). The organic layer was washed with satd NaCl (5 mL) and dried over $MgSO_4$. The extract was concentrated under reduced pressure to give a residue, which was purified by silica gel chromatography with AcOEt–hexane (1:1) as eluent to afford *N*-acetylaminoalcohol **12**[6] (28 mg, 62%) as colorless powder. Mp 143–145 °C (CH_2Cl_2–hexane); [lit.[6] mp 142–143 °C]. $[\alpha]_D=+38.3$ (*c* 1.51, $CHCl_3$); [lit.[6] $[\alpha]_D=+19.9$ (*c* 1.18, $CHCl_3$), 88.1%ee]. ^1H NMR ($CDCl_3$, 300 MHz) δ: 1.46 (9H, s, *t*-Bu), 2.61 (3H, s, CH_3–CO), 4.01 (2H, br s, –CH_2–), 5.06 (1H, br, –C*H*–CH_2–), 5.14 (1H, br, –NH–), 7.407 (1H, s, Ar-H), 7.412 (1H, dd, $J=8,4$, 1.7 Hz, Ar-H), 7.47 (1H, d, $J=8.4$ Hz, Ar-H), 8.65 (1H, br, Ar-H).

4.4. Synthesis of hamacanthins A, B (2a,b) and *cis*-dihydrohamacanthin B (2e)

4.4.1. *tert*-Butyl (*S*)-*N*-[1-{6-bromo-1-([4-methylphenyl]-sulfonyl)indol-3-yl}-2-(4-methylphenyl)sulfonyloxy]-ethylcarbamate (13). Under nitrogen atmosphere, a solution of indolylglycinol **10** (701 mg, 1.98 mmol), *p*-toluenesulfonyl chloride (3.76 g, 19.8 mmol), DMAP (241 mg, 1.98 mmol) and triethylamine (2.8 mL, d 0.726, 19.8 mmol) in dry CH_2Cl_2 (20 mL) was kept at −20° for 20 h. The resulting mixture was washed with water (5 mL) and satd NaCl (5 mL). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography with AcOEt–hexane (1:3) as eluent to afford tosylate **13** as colorless powder. Mp 197 °C (AcOEt–hexane); [lit.[4c] 190 °C dec]. IR ($CHCl_3$) cm^{-1}: 3441, 1713. ^1H NMR ($CDCl_3$, 300 MHz,) δ: 1.42 (9H, s, *t*-Bu), 2.35 (3H, s, CH_3–), 2.40 (3H, s, CH_3–), 4.24 (1H, dd, $J=10.0$, 3.9 Hz, –C*H*H–), 4.36 (1H, dd, $J=10.0$, 4.5 Hz, –C*H*H–), 5.11 (2H, br, –C*H*N*H*–), 7.14 (2H, d, $J=7.9$ Hz, Ar-H), 7.18 (1H, d, $J=8.7$ Hz, Ar-H), 7.26 (1H, dd, $J=8.7$, 1.5 Hz, Ar-H), 7.27 (2H, d, $J=7.9$ Hz, Ar-H), 7.44 (1H, d, $J=0.9$ Hz, Ar-H), 7.53 (2H, d, $J=8.3$ Hz, Ar-H), 7.75 (2H, d, $J=8.3$ Hz, Ar-H), 8.09 (1H, d, $J=1.5$ Hz, Ar-H).

4.4.2. *tert*-Butyl (*S*)-*N*-[2-Azido-1-{6-bromo-1-([4-meethylphenyl]sulfonyl)indol-3-yl}]ethylcarbamate (14). Under nitrogen atmosphere, a suspension of tosylate **13** (7.4 mg, 0.011 mmol) and sodium azide (7.3 mg, 0.11 mmol) in dry DMF (0.1 mL) was stirred at 80 °C for 1 h. After removal of the solvent, the residue was diluted with AcOEt (10 mL). The mixture was washed with water (5 mL) and satd NaCl (5 mL) and dried over $MgSO_4$. The organic layer was concentrated under reduced pressure to give a residue, which was chromatographed on a silica gel column with AcOEt–hexane (1:2) as eluent to afford *N*-Boc-aminoazide **14** (4.7 mg, 78%) as colorless powder. Mp 161–162 °C (AcOEt–hexane); [lit.[4c] 174–176 °C]. $[\alpha]_D=+4.6$ (*c* 0.95, $CHCl_3$); [lit.[4c] $[\alpha]_D=+4$ (*c* 1.67, $CHCl_3$)]. IR ($CHCl_3$) cm^{-1}: 3445, 2109, 1709. ^1H NMR ($CDCl_3$, 300 MHz) δ: 1.45 (9H, s, *t*-Bu), 2.32 (3H, s, CH_3–), 3.72 (1H, d, $J=12.1$, 4.2 Hz, –C*H*H–), 3.76 (1H, dd, $J=12.1$, 5.0 Hz, –C*H*H–), 4.92 (1H, br, –C*H*–CH_2–), 5.09 (1H, br, –N*H*-Boc), 7.27 (2H, d, $J=8.4$ Hz, Ar-H), 7.37 (1H, dd, $J=8.4$, 1.7 Hz, Ar-H), 7.41 (1H, d, $J=8.4$ Hz, Ar-H), 7.53 (1H, s, Ar-H), 7.77 (2H, d, $J=8.4$ Hz, Ar-H), 8.16 (1H, d, $J=1.7$ Hz, Ar-H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 21.7, 28.4, 46.8, 54.1, 80.5, 116.7, 118.9, 120.4, 120.7, 123.9, 126.7, 126.7, 127.7, 130.0, 134.7, 135.6, 145.3, 154.7. MS (EI) *m/z* (%): 535 (M+2, 1), 533 (M^+, 1), 479 (23), 477 (22), 423

(100), 421 (97), 379 (31), 377 (31), 155 (32), 92 (52), 57 (84). HRMS (EI) *m/z* calcd for $C_{22}H_{24}BrN_5O_4S$: 533.0732. Found: 533.0724. Anal. Calcd for $C_{22}H_{24}BrN_5O_4S$: C, 49.44; H, 4.53; N, 13.10. Found: C, 49.25; H, 4.55; N, 12.82.

4.4.3. (*S*)-*N*-[2-{6-bromo-1-([4-methylphenyl]sulfonyl)-indol-3-yl}-2-{(*tert*-butoxy)carbonylamino}ethyl]2-(6-bromoindol-3-yl)-2-oxoethanamide (16). A solution of *N*-Boc-aminoazide **14** (605 mg, 1.1 mmol), triphenylphosphine (594 mg, 2.3 mmol) and H_2O (0.4 mL, 22.7 mmol) in THF (11 mL) was heated under reflux for 1 h. After removal of the solvent, a solution of 6-bromoindol-3-yl-α-oxoacetyl chloride (**15**) (487 mg, 1.70 mmol) in dry THF (22 mL) was added to a solution of the residue and triethylamine (237 μL, d 0.73, 1.7 mmol) in dry THF (22 mL) under nitrogen at 0 °C. The reaction mixture was stirred at room temperature for 1 h and concentrated under reduced pressure to give a residue. AcOEt solution (50 mL) of the residue was washed with water (20 mL) and satd NaCl (20 mL). The organic layer was dried over $MgSO_4$ and evaporated to afford a crude product, which was chromatographed on a silica gel column with AcOEt–hexane (1:2) as eluent to provide amide **16** (677 mg, 79%) as a colorless powder. Mp 241–243 °C (AcOEt–hexane). $[\alpha]_D=-2.6$ (*c* 0.77, acetone). IR (KBr) cm^{-1}: 3378, 3247, 1688, 1624. ^1H NMR (acetone-d_6, 300 MHz) δ: 1.36 (9H, s, *t*-Bu), 2.20 (3H, s, CH_3–), 3.70 (1H, ddd, $J=13.4$, 7.3, 6.0 Hz, –C*H*H–), 4.01 (1H, dt, $J=13.4$, 6.8 Hz, –C*H*H–), 5.31 (1H, dd, $J=7.3$, 6.8 Hz, –C*H*–CH_2–), 6.57 (1H, br, –N*H*-Boc), 7.21 (2H, d, $J=8.0$ Hz, Ar-H), 7.421 (1H, dd, $J=8.4$, 1.7 Hz, Ar-H), 7.424 (1H, dd, $J=8.4$, 1.7 Hz, Ar-H), 7.74 (1H, d, $J=$ 8.4 Hz, Ar-H), 7.79 (1H, d, $J=1.7$ Hz, Ar-H), 7.81 (2H, d, $J=8.0$ Hz, Ar-H), 7.85 (1H, s, Ar-H), 8.12 (1H, d, $J=$ 1.7 Hz, Ar-H), 8.25 (1H, d, $J=8.4$ Hz, Ar-H), 8.40 (1H, br, –N*H*–CH_2–), 9.04 (1H, d, $J=3.1$ Hz, Ar-H), 11.37 (1H, br, indole-NH). ^{13}C NMR (acetone-d_6, 100 MHz) δ: 21.3, 28.5, 43.2, 47.6, 79.3, 113.4, 115.9, 116.9, 117.2, 118.5, 122.4, 123.1, 123.9, 125.1, 126.3, 126.5, 127.1, 127.4, 129.6, 130.8, 135.4, 136.5, 137.9, 140.0, 146.2, 155.9, 163.4, 181.3. Anal. Calcd for $C_{32}H_{30}Br_2N_4O_6S$: C, 50.67; H, 3.99; N, 7.39. Found: C, 50.63; H, 4.08; N, 7.07.

4.4.4. (*S*)-*N*-[2-(6-Bromoindol-3-yl)-2-{(*tert*-butoxy)carbonylamino}ethyl]2-(6-bromoindol-3-yl)-2-oxoethanamide (17). A solution of amide **16** (677 mg, 0.89 mmol) and 10% KOH (60 mL) in EtOH (88 mL) was heated under reflux for 1 h. The resulting mixture was concentrated under reduced pressure to give a residue, which was extracted with AcOEt (50 mL×2). The organic layer was washed with satd NaCl, dried over $MgSO_4$ and evaporated to afford a crude product. The crude product was purified by silica gel column chromatography with AcOEt–hexane (1:1) as eluent to afford detosylated oxoethanamide **17** (499 mg, 93%) as colorless powder. Mp 235–238 °C (AcOEt–hexane). $[\alpha]_D=+9.8$ (*c* 0.53, acetone). IR (KBr) cm^{-1}: 3378, 1674, 1634. ^1H NMR (acetone-d_6, 300 MHz) δ: 1.35 (9H, s, *t*-Bu), 3.71–3.81 (1H, m, –C*H*H–), 3.87–3.93 (1H, m, –C*H*H–), 5.33 (1H, br, –C*H*–CH_2–), 6.32 (1H, br, –N*H*-Boc), 7.18 (1H, dd, $J=8.4$, 1.8 Hz, Ar-H), 7.40 (1H, dd, $J=$ 8.4, 1.8 Hz, Ar-H), 7.44 (1H, d, $J=2.6$ Hz, Ar-H), 7.60 (1H, d, $J=1.8$ Hz, Ar-H), 7.75 (1H, d, $J=8.4$ Hz, Ar-H), 7.77 (1H, d, $J=1.8$ Hz, Ar-H), 8.23 (1H, d, $J=8.4$ Hz, Ar-H), 8.25 (1H, br, –NH–CO), 9.05 (1H, d, $J=2.0$ Hz, Ar-H), 10.31 (1H, br, indole-NH), 11.38 (1H, br, indole-NH). ^{13}C NMR (acetone-d_6, 100 MHz) $\delta=28.6$, 44.4, 48.2, 78.9, 113.4, 114.9, 115.3, 115.8, 116.1, 117.1, 121.2, 122.6, 123.8, 123.9, 126.1, 126.2, 126.5, 137.9, 138.3, 139.9, 156.2, 163.4, 181.6. Anal. Calcd for $C_{25}H_{24}Br_2N_4O_4$: C, 49.69; H, 4.00; N, 9.27. Found: C, 49.38; H, 4.09; N, 8.96.

4.4.5. (*S*)-*N*-[2-(1-Acetyl-6-bromoindol-3-yl)-2-{(*tert*-butoxy)carbonylamino}ethyl]-2-(1-acetyl-6-bromoindol-3-yl)-2-oxoethanamide (18). A solution of **17** (499 mg, 0.83 mmol), DMAP (101 mg, 0.83 mmol) and acetic anhydride (0.4 mL, d 1.082, 4.13 mmol) in dry THF (8.3 mL) was stirred at room temperature under nitrogen for 12 h. The resulting mixture was evaporated to give a residue, which was chromatographed on a silica gel column with AcOEt–hexane (1:2) as eluent to afford acetate **18** (478 mg, 84%) as colorless powder. Mp 217–219 °C (AcOEt–hexane). $[\alpha]_D=-5.0$ (*c* 0.12, DMSO). IR (KBr) cm^{-1}: 3345, 3310, 1732, 1700, 1676, 1647. ^1H NMR (DMSO-d_6, 400 MHz) δ: 1.33 (9H, s, *t*-Bu), 2.61 (3H, s, CH_3–), 2.75 (3H, s, CH_3–), 3.50 (1H, dt, $J=13.3$, 6.7 Hz, –C*H*H–), 3.71 (1H, dt, $J=13.3$, 6.2 Hz, –C*H*H–), 5.19 (1H, dd, $J=6.7$, 6.2 Hz, –C*H*–CH_2–), 7.38 (1H, d, $J=9.0$ Hz, –N*H*-Boc), 7.44 (1H, d, $J=8.4$ Hz, Ar-H), 7.60 (1H, d, $J=$ 8.6 Hz, Ar-H), 7.70 (1H, d, $J=8.4$ Hz, Ar-H), 7.87 (1H, s, Ar-H), 8.16 (1H, d, $J=8.6$ Hz, Ar-H), 8.46 (1H, s, Ar-H), 8.51 (1H, s, Ar-H), 8.97 (1H, s, Ar-H), 9.09 (1H, br, –N*H*–CH_2–). ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 23.6, 23.7, 28.1, 43.1, 45.8, 78.1, 114.7, 117.3, 118.2, 118.4, 118.5, 120.8, 120.9, 122.8, 124.4, 125.9, 126.0, 127.8, 127.9, 135.2, 135.4, 138.4, 154.9, 162.1, 169.1, 169.9, 182.6. Anal. Calcd for $C_{29}H_{28}Br_2N_4O_6$: C, 50.60; H, 4.10; N, 8.14. Found: C, 50.65; H, 4.19; N, 8.14.

4.5. Preparation of pyrazinones 22 and 23 through transamidation–cyclization

A solution of **18** (170 mg, 0.25 mmol) and HCO_2H (14 mL) in CH_2Cl_2 (14 mL) was stirred at room temperature for 16 h. After removal of the solvent and excess HCO_2H, the residue was diluted with 1,2-dichroloethane (41 mL). The solution was adjusted to pH 4 by adding dropwise HCO_2H. The solution was heated under reflux for 1 h and concentrated under reduced pressure to give a residue. The residue was chromatographed on a silica gel column with AcOEt–hexane (2:1) as eluent to afford 3,5-pyrazinone **22** (92 mg, 65%) and 2,5-isomer **23** (47 mg, 33%), respectively.

4.5.1. (*S*)-3,5-Bis(1-acetyl-6-bromoindol-3-yl)-1*H*,2*H*,3*H*-diazin-6-one (22). Colorless powder; Mp >300 °C (THF–hexane). $[\alpha]_D=+177.6$ (*c* 0.13, DMSO). IR (KBr) cm^{-1}: 3234, 1717, 1697. ^1H NMR (DMSO-d_6, 300 MHz) δ: 2.65 (3H, s, CH_3–), 2.71 (3H, s, CH_3–), 3.57–3.66 (2H, m, –CH_2–), 5.35 (1H, dd, $J=10.5$, 5.9 Hz, –C*H*–CH_2–), 7.43 (1H, dd, $J=8.6$, 1.8 Hz, Ar-H), 7.47 (1H, dd, $J=8.4$, 1.8 Hz, Ar-H), 7.75 (1H, d, $J=8.4$ Hz, Ar-H), 7.84 (1H, s, Ar-H), 8.27 (1H, d, $J=8.6$ Hz, Ar-H), 8.53 (1H, d, $J=$ 1.8 Hz, Ar-H), 8.54 (1H, d, $J=1.8$ Hz, Ar-H), 8.78 (1H, s, Ar-H), 8.84 (1H, br, –NH–). MS (EI) *m/z*: 572 (M+4, 29), 570 (M+2, 51), 568 (M^+, 30), 291 (26), 289 (25), 223 (24), 221 (25), 197 (42), 195 (40), 43 (100). HRMS (EI) *m/z* calcd for $C_{24}H_{18}Br_2N_4O_3$: 567.9746. Found: 567.9746.

4.5.2. (*S*)-2,5-Bis(1-acetyl-6-bromoindol-3-yl)-1*H*,2*H*,3*H*-diazin-6-one (23). Colorless powder; Mp 288–291 °C (THF–hexane). $[\alpha]_D=+76.2$ (*c* 0.35, DMSO). IR (KBr) cm^{-1}: 3230, 1717, 1694. ^1H NMR (acetone-d_6, 300 MHz): $\delta=2.66$ (3H, s, CH_3–), 2.75 (3H, s, CH_3–), 4.25 (1H, dd, $J=16.7$, 9.9 Hz, –C*H*H–), 4.42 (1H, dd, $J=16.7$, 4.4 Hz, –C*H*H–), 5.24 (1H, dd, $J=9.9$, 4.4 Hz, –C*H*–CH_2–), 7.47 (1H, dd, $J=8.6$, 2.0 Hz, Ar-H), 7.48 (1H, dd, $J=8.4$, 1.8 Hz, Ar-H), 7.82 (1H, d, $J=8.4$ Hz, Ar-H), 7.93 (1H, s, Ar-H), 7.98 (1H, br, –NH–), 8.44 (1H, d, $J=8.6$ Hz, Ar-H), 8.63 (1H, d, $J=1.8$ Hz, Ar-H), 8.64 (1H, d, $J=2.0$ Hz, Ar-H), 8.85 (1H, s, Ar-H). MS (EI) *m/z*: 572 (M+4, 50), 570 (M+2, 99), 568 (M^+, 51), 278 (89), 276 (86), 236 (89), 234 (86), 223 (44), 221 (40), 43 (100). HRMS (EI) *m/z* calcd for $C_{24}H_{18}Br_2N_4O_3$: 567.9746. Found: 567.9747. Anal. Calcd for $C_{24}H_{18}Br_2N_4O_3$: C, 50.55; H, 3.18; N, 9.83. Found: C, 50.36; H, 3.25; N, 9.44.

4.5.3. (*S*)-3,5-Bis(6-bromoindol-3-yl)-1*H*,2*H*,3*H*-diazin-6-one (2b): hamacanthin B. A solution of 3,5-pyrazinone **22** (19 mg, 0.034 mmol) and NH_4OH (0.7 mL) in THF–MeOH (10 mL, 3:1) was stirred at room temperature for 10 h. After removal of the solvent, the residue was extracted with AcOEt (5 mL×2). The organic layer was washed with satd NaCl (5 mL) and dried over $MgSO_4$. The extract was concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography with AcOEt–hexane (3:1) as eluent to afford hamacanthin B (**2b**) (13 mg, 82%) as yellow powder. Mp 167–169 °C dec (Et_2O–hexane). $[\alpha]_D=+170.1$ (*c*=0.49, MeOH); [lit.[2a] $[\alpha]_D=+172$ (*c* 0.1, MeOH)]. IR (KBr) cm^{-1}: 1672, 1580, 1447. ^1H NMR (DMSO-d_6, 300 MHz) δ: 3.46 (1H, ddd, $J=12.4$, 9.5, 1.9 Hz, –C*H*H–), 3.61 (1H, dt, $J=12.4$, 4.8 Hz, –C*H*H–), 5.24 (1H, dd, $J=9.5$, 4.8 Hz, –C*H*–CH_2–), 7.12 (1H, dd, $J=8.4$, 1.6 Hz, Ar-H), 7.17 (1H, dd, $J=8.6$, 1.6 Hz, Ar-H), 7.27 (1H, d, $J=2.4$ Hz, Ar-H), 7.58 (1H, d, $J=1.6$ Hz, Ar-H), 7.62 (1H, d, $J=1.6$ Hz, Ar-H), 7.65 (1H, d, $J=8.6$ Hz, Ar-H), 8.29 (1H, d, $J=8.4$ Hz, Ar-H), 8.41 (1H, d, $J=2.6$ Hz, Ar-H), 8.51 (1H, br, –NH–CO), 11.14 (1H, br, indole-NH), 11.63 (1H, br, indole-NH). ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 43.2, 53.6, 110.9, 113.7, 113.9, 114.1, 114.6, 114.7, 120.7, 121.1, 123.1, 123.6, 123.9, 124.79, 124.81, 132.6, 136.8, 137.1, 156.8, 156.9. MS (EI) *m/z*: 488 (M+4, 5), 486 (M+2, 10), 484 (M^+, 5), 291 (28), 289 (25), 223 (21), 221 (20), 197 (97), 195 (100), 116 (89), 89 (38). HRMS (EI) *m/z* calcd for $C_{20}H_{14}Br_2N_4O$: 483.9534. Found: 483.9540.

4.5.4. (*S*)-2,5-Bis(6-bromoindol-3-yl)-1*H*,2*H*,3*H*-diazin-6-one (2a): hamacanthin A. A solution of 2,5-pyrazinone **23** (34 mg, 0.059 mmol) and NH_4OH (0.5 mL) in THF–MeOH (15 mL, 1:1) was stirred at room temperature for 10 h. After removal of the solvent, the residue was extracted with AcOEt (5 mL×2). The organic layer was washed with satd NaCl (5 mL) and dried over $MgSO_4$. The extract was concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography with AcOEt–hexane (3:1) as eluent to afford hamacanthin A (**2a**) (25 mg, 87%) as yellow powder. Mp 289 °C (acetone–hexane); [lit.[4c] mp 270–271 °C]. $[\alpha]_D=+83.7$ (*c* 0.47, MeOH); [lit.[2a] $[\alpha]_D=+84$ (*c* 0.1, MeOH)]. IR (KBr) cm^{-1}: 3439, 3191, 1669, 1586, 1445. ^1H NMR (DMSO-d_6, 300 MHz) δ: 4.05 (1H, dd, $J=16.2$, 8.2 Hz, –C*H*H–), 4.13 (1H, dd, $J=16.2$, 5.0 Hz, –C*H*H–), 4.98 (1H, ddd, $J=16.2$, 5.0 2.0 Hz, –C*H*–CH_2–), 7.14 (1H, dd, $J=8.4$, 1.8 Hz, Ar-H), 7.20 (1H, dd, $J=8.6$, 1.8 Hz, Ar-H), 7.31 (1H, d, $J=2.4$ Hz, Ar-H), 7.56 (1H, d, $J=1.8$ Hz, Ar-H), 7.62 (1H, d, $J=1.8$ Hz, Ar-H), 7.66 (1H, d, $J=8.4$ Hz, Ar-H), 8.29 (1H, d, $J=8.6$ Hz, Ar-H), 8.41 (1H, d, $J=2.4$ Hz, Ar-H), 8.79 (1H, br, –N*H*–CO), 11.16 (1H, br, indole-NH), 11.59 (1H, br, indole-NH). ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 46.1, 53.4, 110.8, 113.0, 113.8, 113.96, 114.00, 114.5, 120.5, 121.3, 123.0, 123.9, 124.3, 124.4, 124.8, 132.4, 136.8, 137.0, 157.1, 157.2. MS (EI) *m/z*: 488 (M+4, 40), 486 (M+2, 80), 484 (M^+, 42), 236 (100), 234 (93), 225 (43), 223 (70), 221 (28), 197 (27), 195 (28). HRMS (EI) *m/z* calcd for $C_{20}H_{14}Br_2N_4O$: 483.9535. Found: 483.9529.

4.5.5. (3*S*,5*R*)-3,5-Bis(6-bromoindol-3-yl)piperazinone-2-one (2e): (−)-antiporde of *cis*-dihydrohamacanthin B. A solution of 3,5-pyrazinone **22** (37.3 mg, 0.065 mmol) and sodium cyanoborohydride (412 mg, 6.5 mmol) in MeOH (4.3 mL) was stirred at room temperature for 2 days. The excess reductant in the resulting mixture was quenched with water (1 mL). After removal of the solvent, the residue was extracted with AcOEt (5 mL×3). The combined organic layer was washed with satd NaCl (3 mL), dried over $MgSO_4$ and concentrated under reduced pressure to give a crude product. The crude was purified by silica gel column chromatography with MeOH–CH_2Cl_2 (1:5) as an eluent to afford *cis*-dihydrohamacanthin B (**2e**) (23.4 mg, 73%) as a yellow powder. Mp 168–172 °C (AcOEt–hexane). $[\alpha]_D=-92.3$ (*c* 0.66, acetone); [lit.[2b] $[\alpha]_D=+98.7$ (*c* 0.2, acetone)]. ^1H NMR (acetone-d_6, 300 MHz) δ: 3.53 (1H, dt, $J=11.0$, 3.7 Hz, –C*H*H–), 3.73 (1H, t, $J=11.0$ Hz, –C*H*H–), 4.67 (1H, dd, $J=11.0$, 3.7 Hz, –C*H*–CH_2–), 5.03 (1H, s, –CH–CO), 7.14 (1H, dd, $J=8.4$, 1.8 Hz, Ar-H), 7.16 (1H, dd, $J=8.4$, 1.8 Hz, Ar-H), 7.38 (1H, d, $J=2.4$ Hz, Ar-H), 7.41 (1H, d, $J=2.4$ Hz, Ar-H), 7.53 (1H, d, $J=1.8$ Hz, Ar-H), 7.59 (1H, d, $J=1.8$ Hz, Ar-H), 7.78 (1H, d, $J=8.4$ Hz, Ar-H), 7.83 (1H, d, $J=8.4$ Hz, Ar-H), 10.23 (1H, br, indole-NH), 10.37 (1H, br, indole-NH). ^{13}C NMR (acetone-d_6, 100 MHz) δ: 49.8, 52.3, 58.9, 114.6, 114.9, 115.0, 115.2, 115.9, 116.1, 121.7, 122.1, 122.5, 122.7, 124.0, 125.7, 125.9, 126.8, 138.27, 138.32, 170.1. HRMS (FAB) *m/z* calcd for $C_{20}H_{15}Br_2N_4O$: 484.9614. Found: 484.9609.

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9. The ratio of *E*- and *Z*-isomers **5** was determined by its ^{1}H NMR spectrum.
10. Attempted separation of the *E*-, *Z*-mixture using column chromatography was unsuccessful.
11. Prashad, M.; Har, D.; Kim, H.-Y.; Repic, O. *Tetrahedron Lett.* **1998**, *39*, 7067–7070. Since an inseparable mixture of **9** and its 1-acetyl derivative **12** was obtained, deacetylation was carried out in a one-pot procedure.
12. The 2,5-pyrazinone **23** was treated with sodium cyanoborohydride to convert into *trans*- and *cis*-dihydrohamacanthins A (**1c**,**d**) as an inseparable mixture, whose ratio was ca. 1:1.

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Diastereoselective synthesis of α,β-unsaturated systems

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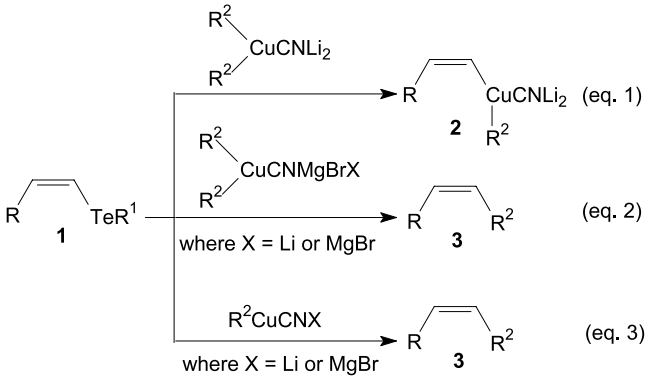
Abstract—Functionalized *Z*-vinylic tellurides were used in substitution reactions with lower order cyanocuprates leading to α,β-unsaturated ketones and esters in good yields. In the case of acyclic tellurides, the product was obtained in high diastereoselectivity. The control of the stereoselectivity was achieved by simple change of the reaction temperature.

1. Introduction

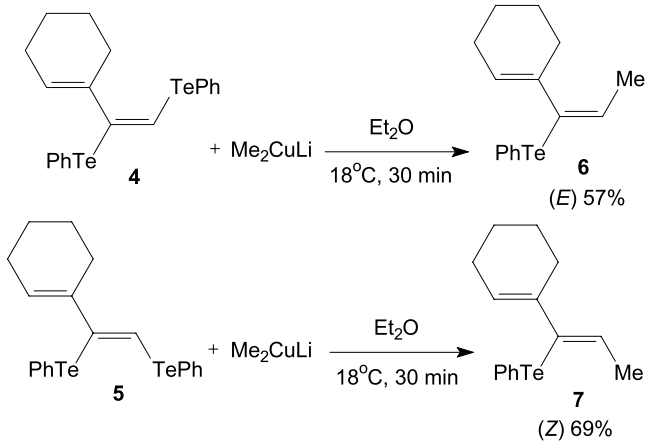
Z-Vinylic tellurides **1** have been extensively explored by us[1–3] and others[4,5] due to their synthetic potencial to perform cross-coupling reactions[2,4] and to generate other organometallic reagents through transmetallation with commercially available alkyllithium[6] or with other organometallic species,[5] mainly organocopper reagents.[3] We found that the reactivity of vinylic tellurides with organocuprates is affected by the counterion present in the cyanocuprate.[7]

Transmetallation of *Z*-vinylic tellurides **1** takes place with higher order cyanocuprates when both cations are lithium, leading to *Z*-vinylic cyanocuprates **2** used in further transformations (Scheme 1—Eq. (1)).[3] On the contrary, substitution of the tellanyl group occurs when at least one gegenion in the higher order cyanocuprate is magnesium[7] or when lithium or magnesium lower order cyanocuprates are used,[8] affording disubstituted olefins **3** (Scheme 1—Eq. (2) and (3)). An important feature of all these reactions is that the *Z* double bond stereochemistry of the starting telluride is maintained.

Substitution reactions involving vinylic tellurides were also explored by other research groups.[9,10] In 1994, Sonoda et al. also reported the alkylation of *vic*-bis(phenyltelluro)alkenes **4** and **5** with lithium dialkylcuprates, yielding the corresponding 1-alkyl-2-phenyltelluroalkenes **6** and **7** respectively, with retention of the double bond geometry (Scheme 2).[9]



Scheme 1.



Scheme 2.

Keywords: Functionalized tellurides; Cyanocuprates; α,β-Unsaturated esters; α,β-Unsaturated ketones; Diastereoselective synthesis.
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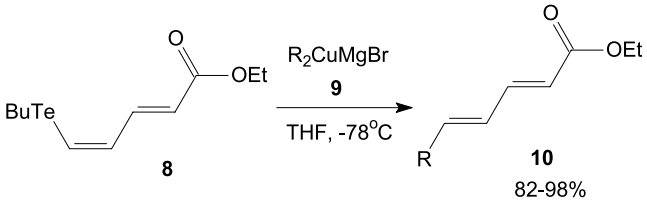
On the other hand, Huang et al. investigated the substitution of functionalized *Z*-vinylic telluride **8** with several organocuprates.[10] In these studies, a high diastereoselectivity (>99%) was achieved with magnesium Gilman cuprates **9**, leading to the detellurolated products **10** with *E* configuration (Scheme 3). Other cuprates led to isomeric mixtures of *Z* and *E* products and the total retention of the *Z* configuration was not observed in any case.



Scheme 3.

In this way, β-functionalized *Z*-vinylic tellurides could be interesting precursors of α,β-unsaturated systems with defined stereochemistry. Preliminary results from our laboratory also support this idea.[11]

The diastereoselective synthesis of α,β-unsaturated ketones and esters has constantly attracted the attention of organic chemists since these structural units are found in pheromones and other natural compounds.[12] In addition, they are important building blocks for the synthesis of more complex molecules.[13] Several procedures have been reported for the synthesis of these compounds such as condensation,[14] oxidation,[15] elimination[16] and acylation[17] reactions, but a convenient access to these compounds is still desirable.

In this work, we report a new methodology aiming the diastereoselective synthesis of such systems through substitution reaction between functionalized tellurides and lower order cyanocuprates.

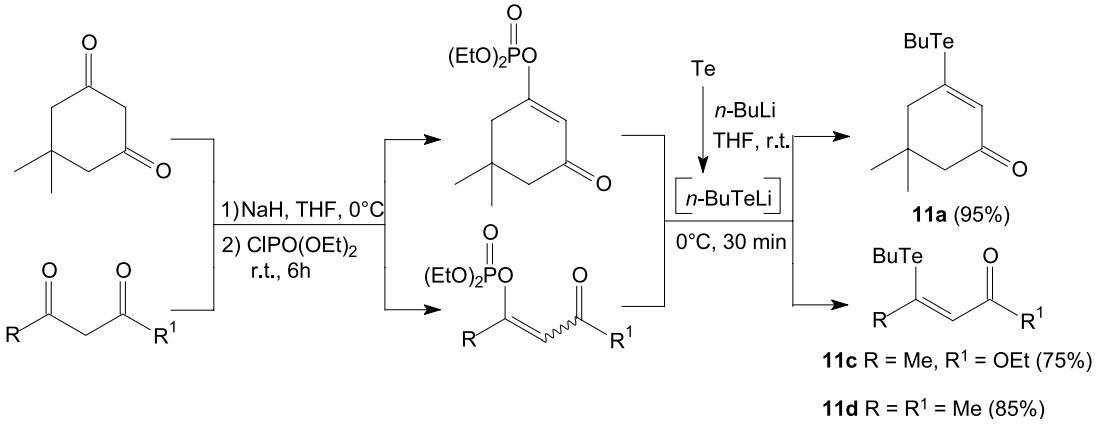
Recently, the toxicity of organotellurium compounds has been discussed in the literature,[18] although data on this topic are still scarce. In addition, it is known that some of these compounds, usually the species with low molecular mass, present a persistent bad smell.[1] In this way, the manipulation of these compounds must be carried out in appropriate hoods using disposable gloves and all the glassware used must be immersed into a solution of sodium hypochlorite immediately after use.

2. Results and discussion

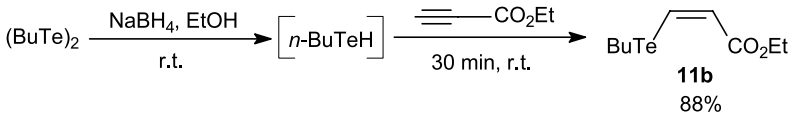
Recently, a convenient route to synthesize functionalized *Z*-vinylic tellurides was developed by our group, which consisted in the nucleophilic vinylic substitution of enol phosphates, tosylates, acetates or triflates by lithium butyltellurolate.[19] Using this protocol, functionalized *Z*-vinylic tellurides **11a**, **11c** and **11d** were synthesized from the corresponding enol phosphate, previously prepared from the commercially available β-dicarbonylic compound (Scheme 4).[20] On the other hand, telluride **11b** was obtained from hydrotelluration[21] of ethyl propiolate (Scheme 5).[22]

The substitution reactions were performed by the addition at room temperature of *Z*-vinylic tellurides **11** to a solution of the corresponding lower order cyanocuprate **12**, previously prepared by the slow addition of the corresponding alkyllithium over a CuCN suspension in THF at −78 °C. The detellurolated products **13–16** were obtained in good yields after purification through silica gel column chromatography (Table 1).

The stereochemistry assignment of products **14** was made on the basis of the coupling constants of the vinylic hydrogen atoms measured by ^{1}H NMR. On the other hand, the olefin stereochemistry of the products **15** and **16** was determined by differential NOE and NOESY experiments.

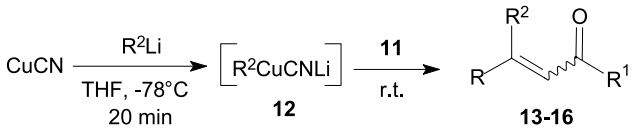


Scheme 4.



Scheme 5.

Table 1. Results obtained when the substitution reaction was performed at room temperature[a]



Telluride	Cyanocuprate		
	n-BuCuCNLi	*s*-BuCuCNLi	*t*-BuCuCNLi
	12a	**12b**	**12c**
n-BuTe **11a**	*n*-Bu **13a** (85%)	*s*-Bu **13b** (83%)	*t*-Bu **13c** (97%)
n-BuTe O OEt **11b**	*n*-Bu OEt **14a** (73%) 4:1 (*E*:*Z*)	*s*-Bu OEt **14b** (79%) *E*	*t*-Bu OEt **14c** (85%) *E*
n-BuTe O OEt **11c**	*n*-Bu O OEt **15a** (79%) 10:1 (*Z*:*E*)	*s*-Bu O OEt **15b** (81%) *Z*[b]	*t*-Bu O OEt **15c** (85%) *Z*[b]
n-BuTe O **11d**	*n*-Bu O **16a**[c] (70%) 2:1 (*E*:*Z*)	*s*-Bu O **16b**[c] (68%) 5:1 (*E*:*Z*)	*t*-Bu O **16c**[c] (65%) *E*[d]

[a] The isomer ratios were determined by GC and GC-MS.
[b] Traces of the *E* isomer were detected by GC-MS.
[c] 1.1 equiv of cuprate was used.
[d] Traces of the *Z* isomer were detected by GC-MS.

The reaction was fast for all substrates, varying from 5 to 30 min, depending on the starting telluride. In the case of the cyclic telluride **11a**, its total consumption occurred in only 5 min. However, tellurides **11b**, **11c** and **11d** were consumed in approximately 10, 20 and 30 min, respectively. In the last case, the reaction time using equimolar amounts of telluride **11d** and cyanocuprate was longer than 40 min, time enough to initiate the decomposition of the starting cuprate at room temperature and, consequently, to prevent the total consumption of the telluride. In order to make the procedure reproducible, a small excess of cuprate was used and, in this way, the total consumption of the telluride took place in 30 min.

Analyzing Table 1, it is worth of note that products **14b**, **14c**, **15b**, **15c** and **16c** were obtained in high diastereoselectivity. Esters **14b** and **14c** were obtained as single isomers of *E* configuration and no traces of the *Z* isomer were detected by GC-MS, indicating a total inversion of configuration of the starting telluride **11b**. In the same way, ketone **16c**, generated by reaction between *t*-BuCuCNLi **12c** and telluride **11d**, presented *E* configuration but traces of the *Z* isomer were detected. On the other hand, retention of the *Z* stereochemistry of the starting telluride **11c** was observed in the products **15b** and **15c**, with traces of the *E* isomer.

Distinctly, products **14a**, **15a**, **16a** and **16b** were obtained as isomeric mixtures. The reaction between *n*-BuCuCNLi **12a** and telluride **11b** gave the α,β-unsaturated ester **14a** as a 4:1 mixture of *E* and *Z* diastereoisomers. In the same way, ketones **16a** and **16b** were afforded in poor diastereoselectivity, as 2:1 and 5:1 mixtures of *E* and *Z* isomers, respectively. Moreover, product **15a** was obtained as a 10:1 mixture, with the *Z* olefin as the major isomer.

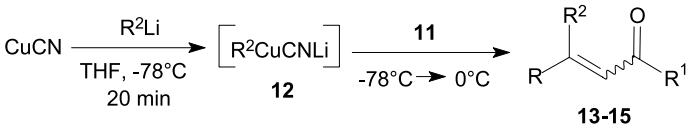
These results showed that all the reactions carried out between *n*-BuCuCNLi **12a** and acyclic tellurides led to isomeric mixtures of products, while the reactions performed with *t*-BuCuCNLi **12c** and *s*-BuCuCNLi **12b**, with the exception of product **16b**, exhibited the best results in terms of diastereoselectivity.

It is also noteworthy that all α,β-unsaturated ketones **16** as well as all esters **14** were volatile and had a pleasant smell.

Aiming to increase the reaction diastereoselectivity, the influence of the temperature of the telluride addition was investigated. In this way, tellurides **11** were added at −78 °C over a solution of the corresponding lower order cyanocuprate **12** and the reaction was allowed to reach 0 °C. After silica gel column chromatography, the products were obtained in good yields (Table 2).

As expected with the decrease of the temperature, the reaction time increased for all tellurides, except for telluride **11d**, that was not completely consumed under these conditions. The consumption of telluride **11d** was not completely observed at any temperature lower than room temperature, even using excess of cuprate. At low temperatures, tellurides **11b**, **11c** and **11d** were consumed

Table 2. Results obtained when the substitution reaction was performed at low temperatures[a]



Telluride	Cyanocuprate		
	n-BuCuCNLi	*s*-BuCuCNLi	*t*-BuCuCNLi
	12a	**12b**	**12c**
n-BuTe **11a**	*n*-Bu **13a** (81%)	*s*-Bu **13b** (78%)	*t*-Bu **13c** (93%)
n-BuTe O OEt **11b**	*n*-Bu O OEt **14a**[b] (70%) Z	*s*-Bu O OEt **14d** (72%) Z[c]	*t*-Bu O OEt **14e** (81%) Z[c]
n-BuTe O OEt **11c**	*n*-Bu O OEt **15a**[d] (82%) Z[c]	*s*-Bu O OEt **15b** (77%) Z	*t*-Bu O OEt **15c** (75%) Z

[a] The isomers ratios were determined by GC and GC-MS.
[b] After the telluride addition at −78 °C, the reaction temperature was allowed to reach 0 °C.
[c] Traces of the *E* isomer were detected by GC-MS.
[d] After the telluride addition at −78 °C, the reaction temperature was allowed to reach the room temperature and 1.1 equiv of cuprate was used.

in 15, 30 and 40 min respectively, in accordance to the observed reaction times when the reaction was carried out at room temperature.

The results presented in Table 2 showed that the reactions performed with telluride **11b** as well as with telluride **11c** were highly diastereoselective, leading, in all cases, to the corresponding products **14** and **15** with *Z* configuration, maintaining the initial configuration of the starting olefin. In the case of products **14a**, **15b** e **15c**, it was observed the exclusive formation of the *Z* isomers, since no traces of the other isomers were detected by GC–MS.

In these temperature studies, the results obtained with telluride **11b** are remarkable. As shown in Tables 1 and 2, when the reaction was performed at room temperature with the cyanocuprates *s*-BuCuCNLi **12b** e *t*-BuCuCNLi **12c**, the products **14b** and **14c** presented exclusively the *E* configuration. When the reaction was carried out at low temperature the stereochemistry of the starting telluride was retained yielding the products **14d** e **14e** of *Z* configuration. These results demonstrated the likelihood of a kinetic control of this substitution reaction by changing the temperature, allowing the possibility of synthesis of the *Z* or the *E* isomer from the same Z vinylic telluride **11b**.

In addition, when the reaction between telluride **11b** and *n*-BuCuCNLi **12a** was performed at low temperatures, ester **14a** was obtained as a single *Z* isomer. This result showed that the reaction exhibited a higher diastereoselectivity with the decrease of reaction temperature, since at room temperature, product **14a** had already been obtained as a 4:1 (*E*:*Z*) mixture.

Similarly to the results obtained for telluride **11b**, the diastereoselectivity of the substitution reaction was also slightly better when the reaction was carried out at low temperatures with telluride **11c**. Under these conditions, α,β-unsaturated esters **15b** and **15c** were synthesized as pure *Z* diastereoisomers, while traces of the *E* isomer were detected by GC–MS at room temperature. In the same way, a high selectivity was observed in the reaction with cuprate *n*-BuCuCNLi **12a**, giving the *Z* product **15a** with only traces of the *E* isomer, while at room temperature a considerable amount of the *E* isomer was present in the product (10:1, *Z*:*E*).

Moreover, the treatment of β-functionalized vinylic tellurides with cuprates gave better diastereoselective results than the direct substitution reaction between cuprates and β-keto enolphosphates. The latter reaction was already investigated and the esters were obtained in good yields, but moderate selectivity was observed.[23]

Another interesting fact that should be pointed out is that ester **15a** is the formal precursor of the (*Z*)-3-methyl-2-heptenoic acid, a molecule that has been identified as a component of the female sex pheromone of the Bruchid pest *Callosobruchus analis*.[24]

3. Conclusion

In conclusion, this methodology showed to be a convenient route to afford α,β-unsaturated compounds that are useful building blocks for organic synthesis.[13,14] The diastereoselectivity of the reaction was controlled by the reaction

temperature, the best results being achieved at low temperatures.

4. Experimental

4.1. General

All solvents used were previously dried and distilled according to the usual methods.[25] THF was distilled from sodium/benzophenone under N_2, immediately before use. All organolithium were titrated using 1,10-phenanthroline as indicator prior to use.[26] Elemental tellurium (200 mesh) was purchased from Aldrich and dried overnight in an oven at 100 °C. CuCN was dried under vacuum in an *Abderhalden* apparatus over P_2O_5, at 70 °C. The following reagents were prepared according to the literature procedures: diethyl 5,5-dimethyl-3-oxocyclohex-1-enyl phosphate,[20] (*Z*)-ethyl 3-(butyltellanyl)-acrylate,[22] ethyl (*Z*)-3-(butyltellanyl)-2-butenoate[19] and (*Z*)-4-(butyltellanyl)-3-penten-2-one.[19] The remaining chemicals were obtained from commercial sources. All operations were carried out in dried glassware, under an inert atmosphere of dry and deoxygenated N_2. Column chromatography was carried out with Merck silica gel (230–400 Mesh). Thin Layer Chromatography (TLC) was performed on silica gel 60 F_{254} on aluminium sheets. ^1H and ^{13}C NMR spectra were recorded on either a Varian DPX-300, Bruker DRX-500 or a Bruker AC-200 spectrometers using as internal standard tetramethylsilane and the central peak of $CDCl_3$ (77 ppm), respectively. Chemical shifts (δ) are given in ppm, coupling constants (J) in Hz and multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), qn (quintet), sext (sextet), m (multiplet) and br (broad). Infrared spectra were recorded on a Bomem MB-100 spectrophotometer. Low resolution mass spectra were obtained on a Shimadzu CGMS-17A/QP5050A instrument operating at 70 eV. Elemental analysis were performed at the Microanalytical Laboratory of the Chemistry Institute—University of São Paulo. The IUPAC names were obtained using the software ChemDraw® Ultra, version 7.0.1.

4.1.1. Preparation of 3-(butyltellanyl)-5,5-dimethylcyclohex-2-enone (11a). To a suspension of elemental tellurium (0.38 g, 3 mmol) in THF (4 mL) under nitrogen at room temperature was slowly added *n*-butyllithium (from a 1.4 M solution in hexanes, 2.1 mL, 3 mmol). A clear yellow solution was formed. Then diethyl 5,5-dimethyl-3-oxocyclohex-1-enyl phosphate was added (0.83 g, 3 mmol) at 0 °C and the reaction was stirred at this temperature for 20 min. The resulting mixture was diluted with ethyl acetate (50 mL) and washed with brine (3× 50 mL). The organic phase was dried over magnesium sulfate and the solvents were evaporated. The residue was purified by silica gel column chromatography eluting with hexane:ethyl acetate (9:1). (0.840 g, 91%) IR ν_{max}/cm^{-1} 2957, 2930, 2871, 1658, 1574, 1464, 1368, 1342, 1297, 1271, 1245, 1141, 1002, 859 (neat). ^1H NMR (200 MHz, $CDCl_3$) δ 6.33 (t, J=1.6 Hz, 1H), 2.82 (t, J=7.7 Hz, 2H), 2.45 (d, J=1.8 Hz, 2H), 2.24 (s, 2H), 1.82 (qn, J=7.7 Hz, 2H), 1.39 (sext, J=7.7 Hz, 2H), 1.04 (s, 6H), 0.91 (t, J=7.4 Hz, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 194.6, 149.4, 132.1, 51.1, 49.2, 35.1, 33.0, 27.9, 25.2, 13.4, 8.8. LRMS *m/z* (rel. int.) 310 (24), 308 (M^+, 22), 306 (13), 254 (12), 252 (12), 123 (38), 109 (23), 95 (13), 79 (21), 67 (100), 57 (24), 55 (19). Anal. calcd for $C_{12}H_{20}OTe$: C, 46.81, H, 6.55; Found: C, 46.84, H, 6.41.

4.2. General procedure for substitution reactions between functionalized tellurides and lower order cyanocuprates at room temperature

To a suspension of dry CuCN (0,089 g; 1 mmol) in THF (10 mL), under nitrogen at −78 °C was slowly added alkyllithium (1 mmol). The reaction was stirred at this temperature for 20 min and a limpid and clear solution was obtained. The mixture was allowed to reach room temperature and the corresponding telluride (1 mmol) was added. The reaction was monitored by TLC, until the consumption of the telluride. The reaction mixture was diluted with ethyl acetate (50 mL) and washed with a 1:1 solution of saturated aqueous NH_4Cl and NH_4OH (4× 50 mL). The organic phase was dried with magnesium sulfate and the solvents were evaporated. The residue was purified by silica gel column chromatography eluting with hexane:ethyl acetate (9:1).

4.2.1. 3-Butyl-5,5-dimethylcyclohex-2-enone (13a). (0.153 g, 85%) [56745-22-3]. IR ν_{max}/cm^{-1} 2958, 2933, 2872, 1669, 1629, 1468, 1386, 1369, 1299, 1279, 1246 (neat). ^1H NMR (500 MHz, $CDCl_3$) δ 5.87 (t, J=1.1 Hz, 1H), 2.21–2.17 (m, 6H), 1.48 (qn, J=7.4 Hz, 2H), 1.34 (sext, J=7.3 Hz, 3H), 1.03 (s, 6H), 0.92 (t, J=7.3 Hz, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 200.0, 164.2, 124.4, 51.0, 43.8, 37.6, 33.5, 28.9, 28.2, 22.2, 13.7. LRMS *m/z* (rel. int.) 180 (M^+, 7), 138 (8), 124 (3), 109 (2), 95 (6), 83 (14), 82 (100), 67 (6); 55 (7).

4.2.2. 3-*sec*-Butyl-5,5-dimethylcyclohex-2-enone (13b). (0.150 g, 83%) [93136-18-6]. IR ν_{max}/cm^{-1} 2961, 2935, 2874, 1669, 1625, 1462, 1368, 1301, 1280 (neat). ^1H NMR (300 MHz, $CDCl_3$) δ 5.87 (s, 1H), 2.22 (s, 2H), 2.21–2.14 (m, 2H), 1.53–1.37 (m, 3H), 1.07 (d, J=6.8 Hz, 3H), 1.03 (s, 6H), 0.86 (t, J=7.4 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.2, 168.2, 124.1, 53.4, 51.3, 43.1, 41.2, 33.5, 28.2, 27.3, 18.3, 11.9. LRMS *m/z* (rel. int.) 180 (M^+, 4), 138 (7), 124 (2), 96 (5), 82 (100), 55 (6).

4.2.3. 3-*terc*-Butyl-5,5-dimethylcyclohex-2-enone (13c). (0.175 g, 97%) [28017-80-3]. IR ν_{max}/cm^{-1} 2962, 2872, 1668, 1617, 1467, 1365, 1302, 1249 (neat). ^1H NMR (500 MHz, $CDCl_3$) δ 5.95 (s, 1H), 2.22 (s, 2H), 2.21 (s, 2H), 1.12 (s, 9H), 1.03 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.8, 171.0, 121.7, 50.8, 40.0, 36.3, 33.5, 27.9. LRMS *m/z* (rel. int.) 180 (M^+, 29), 165 (19), 137 (21), 124 (86), 123 (18), 109 (100), 96 (36), 95 (23), 81 (36), 67 (22), 57 (22).

4.2.4. Ethyl hept-2-enoate (14a). (0.114 g, 73%, 4:1 mixture (*E*:*Z*)). IR ν_{max}/cm^{-1} 2961, 2930, 2869, 1721, 1644, 1462, 1416, 1206, 1180, 1036, 824 (neat).

E isomer [54340-72-6]. ^1H NMR (500 MHz, $CDCl_3$) δ 6.96 (dt, J=15.5, 7.0 Hz, 1H), 5.81 (dt, J=15.7, 1.5 Hz, 1H), 4.19 (q, J=7.0 Hz, 2H), 2.19 (dq, J=7.5, 1.5 Hz, 2H), 1,67–1,61 (m, 2H), 1.47–1.22 (m, 5H), 0.94 (t, J=7.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.9, 149.4, 121.2,

64.0, 31.8, 30.1, 22.2, 19.1, 13.7. LRMS *m/z* (rel. int.) 156 (M^+, 6), 127 (12), 111 (45), 101 (19), 99 (44), 86 (16), 82 (12), 73 (45), 68 (30), 55 (100).

Z isomer [35066-42-3]. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.21 (dt, J=11.5, 7.5 Hz, 1H), 5.75 (dt, J=11.5, 1.6 Hz, 1H), 4.16 (q, J=7.1 Hz, 2H), 2.65 (dq, J=7.5, 1.5 Hz, 2H), 1.47–1.33 (m, 4H), 1.28 (t, J=7.2 Hz, 3H), 0.91 (t, J=7.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.6; 150.4; 119.6; 63.7; 31.1; 30.7; 22.3; 19.2; 13.8. LRMS *m/z* (rel. int.) 156 (M^+, 20), 127 (48), 111 (31), 99 (100), 81 (24), 68 (26), 55 (63).

4.2.5. Ethyl (*E*)-4-methylhex-2-enoate (14b). (0.123 g, 79%) [78023-52-6]. IR ν_{max}/cm^{-1} 2965, 2932, 2877, 1721, 1653, 1461, 1369, 1308, 1269, 1243, 1186, 1159, 1136, 1042 (neat). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.86 (dd, J=15.7, 7.8 Hz, 1H), 5.78 (dd, J=15.7, 1.2 Hz, 1H), 4.18 (q, J=7.1 Hz, 2H), 2.24–2.19 (m, 1H), 1.40–1.34 (m, 2H), 1.29 (t, J=7.1 Hz, 3H), 1.04 (d, J=6.7 Hz, 3H), 0.88 (t, J=7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.0, 154.4, 119.8, 60.2, 38.2, 28.9, 19.2, 14.3, 11.6. LRMS *m/z* (rel. int.) 156 (M^+, 10), 128 (10), 111 (37), 110 (29), 95 (34), 82 (40), 73 (26), 69 (28), 56 (27), 55 (100).

4.2.6. Ethyl (*E*)-4,4-dimethyl-pent-2-enoate (14c). (0.132 g, 85%) [22147-62-2]. IR ν_{max}/cm^{-1} 2959, 2926, 1712, 1682, 1556, 1332, 1207, 1145, 1033 (neat). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.97 (d, J=15.8 Hz, 1H), 5.73 (d, J=15.8 Hz, 1H), 4.19 (q, J=7.1 Hz, 2H), 1.29 (t, J=7.1 Hz, 3H), 1.08 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.3, 159.0, 116.7, 60.1, 33.7, 28.6, 14.3. LRMS *m/z* (rel. int.) 156 (M^+, 16), 141 (51), 113 (42), 111 (57), 95 (41), 83 (100), 69 (29), 67 (52), 55 (78).

4.2.7. Ethyl 3-methyl-hept-2-enoate (15a). (0.134 g, 79%, 10:1 mixture (*Z*:*E*)). IR ν_{max}/cm^{-1} 2963, 2932, 2867, 1716, 1648, 1453, 1378, 1241, 1193, 1149, 1042, 858 (neat).

Z isomer [42778-40-5]. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.65–5.64 (m, 1H), 4.13 (q, J=7.1 Hz, 2H), 2.64–2.60 (m, 2H), 1.87 (d, J=1.4 Hz, 3H), 1.47–1.42 (m, 2H), 1.40–1.34 (m, 2H), 1.27 (t, J=7.1 Hz, 3H), 0.92 (t, J=7.2 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.4, 160.7, 116.0, 59.4, 33.2, 30.4, 25.2, 22.9, 14.3, 14.0. LRMS *m/z* (rel. int.) 170 (M^+, 43), 141 (62), 128 (26), 125 (80), 113 (100), 100 (27), 96 (28), 95 (77), 82 (57), 69 (52), 67 (42), 56 (33), 55 (97).

E isomer [42778-90-5]. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.66–5.65 (m, 1H), 4.14 (q, J=7.1 Hz, 2H), 2.64–2.60 (m, 2H), 2.15 (d, J=1.3 Hz, 3H), 1.47–1.42 (m, 2H), 1.40–1.34 (m, 2H), 1.28 (t, J=7.1 Hz, 3H), 0.90 (t, J=7.1 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.0, 160.1, 115.5, 60.4, 40.7, 29.6, 22.3, 18.7, 14.3, 13.9. LRMS *m/z* (rel. int.) 170 (M^+, 4), 128 (100), 125 (66), 113 (46), 100 (49), 95 (31), 83 (26), 82 (47), 69 (44), 67 (23), 56 (39), 55 (75).

4.2.8. Ethyl (*Z*)-3,4-dimethyl-hex-2-enoate (15b). (0.138 g, 81%). IR ν_{max}/cm^{-1} 2962, 2929, 2869, 1715, 1642, 1455, 1378, 1222, 1154, 1039 (neat). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.64 (q, J=1.2 Hz, 1H), 4.13 (q, J=7.1 Hz, 2H), 3.78 (sext, J=7.1 Hz, 1H), 1.76 (d, J=1.3 Hz, 3H), 1.39 (qn, J=7.4 Hz, 2H), 1.27 (t, J=7.1 Hz, 3H), 1.02 (d, J=6.9 Hz, 3H), 0.85 (t, J=7.4 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.1, 147.7, 120.9, 60.3, 33.5, 27.3, 25.3, 14.4, 13.5, 5.7. LRMS *m/z* (rel. int.) 170 (M^+, 62), 155 (24), 127 (24), 125 (82), 124 (20), 113 (20), 109 (50), 97 (57), 96 (71), 95 (66), 83 (46), 82 (28), 81 (43), 69 (55), 67 (50), 55 (100), 53 (25). Anal. calcd for $C_{10}H_{18}O_2$: C, 70.55, H, 10.66; Found: C, 70.37, H, 10.68.

4.2.9. Ethyl (*Z*)-3,4,4-trimethyl-pent-2-enoate (15c). (0.144 g, 85%) [21016-48-8]. IR ν_{max}/cm^{-1} 2972, 2873, 1724, 1623, 1457, 1444, 1372, 1245, 1179, 1055, 1027 (neat). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.62 (q, J=1.3 Hz, 1H), 4.14 (q, J=7.1 Hz, 2H), 1.84 (d, J=1.3 Hz, 3H), 1.28 (t, J=7.1 Hz, 3H), 1.20 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.0, 158.5, 116.6, 60.1, 36.4, 29.1, 24.0, 14.2. LRMS *m/z* (rel. int.) 170 (M^+, 2), 155 (72), 127 (51), 125 (63), 109 (53), 97 (99), 83 (31), 81 (47), 69 (31), 57 (36), 55 (100), 43 (41), 41 (76).

4.2.10. 4-Methyl-oct-3-en-2-one (16a). (0.097 g, 70%, 2:1 mixture (*E*:*Z*)). IR ν_{max}/cm^{-1} 2959, 2932, 2870, 1689, 1617, 1441, 1380, 1355, 1166, 961 (neat).

E isomer [23732-25-4]. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.07 (s, 1H), 2.17 (s, 3H), 2.16–2.10 (m, 2H), 2.12 (d, J=0.9 Hz, 3H), 1.47–1.30 (m, 4H), 0.88–0.86 (t, J=6.8 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.2, 159.5, 124.0, 33.3, 32.4, 30.3, 25.3, 22.8, 13.4. LRMS *m/z* (rel. int.) 140 (M^+, 2), 125 (2), 111 (4), 97 (9), 82 (4), 69 (8), 55 (46), 43 (100).

Z isomer [36219-17-7]. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.05 (s, 1H), 2.58 (t, J=7.3 Hz, 2H), 2.15 (s, 3H), 1.86 (d, J=1.1 Hz, 3H), 1.47–1.30 (m, 4H), 0.92 (t, J=7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.8, 158.9, 123.5, 40.9, 31.7, 29.7, 22.3, 19.2, 13.8. LRMS *m/z* (rel. int.) 140 (M^+, 12), 125 (15), 111 (41), 83 (22), 69 (16), 55 (43), 43 (100).

4.2.11. 4,5-Dimethyl-hept-3-en-2-one (16b). (0.095 g, 68%, 5:1 mixture (*E*:*Z*)). IR ν_{max}/cm^{-1} 2965, 2931, 2876, 1687, 1615, 1459, 1377, 1356, 1216, 1174 (neat).

E isomer [104664-46-2]. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.99 (s, 1H), 2.08–1.98 (m, 1H), 2.11 (s, 3H), 1.98 (d, J=1.2 Hz, 3H), 1.34–1.26 (m, 2H), 0.97 (d, J=6.8 Hz, 3H), 0.76 (t, J=7.4 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.2, 163.0, 123.3, 46.1, 32.1, 27.8, 19.1, 16.1, 12.2. LRMS *m/z* (rel. int.) 140 (M^+, 5), 125 (27), 112 (18), 97 (20), 83 (12), 69 (28), 67 (10), 55 (58), 43 (100).

Z isomer [104664-56-4]. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.97 (s, 1H), 3.68 (sext, J=7.2 Hz, 1H), 2.08 (s, 3H), 1.68 (d, J=1.3 Hz, 3H), 1.34–1.26 (m, 2H), 0.92 (d, J=6.8 Hz, 3H), 0.76 (t, J=7.4 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.7, 162.4, 125.1, 36.1, 32.2, 28.0, 19.4, 18.8, 11.8. LRMS *m/z* (rel. int.) 140 (M^+, 21), 125 (28), 111 (6), 97 (24), 83 (11), 69 (23), 67 (12), 55 (57), 43 (100).

4.2.12. (*E*)-4,5,5-Trimethyl-hex-3-en-2-one (16c). (0.091 g, 65%) [23732-21-0]. IR ν_{max}/cm^{-1} 2965, 2913, 2873, 1687, 1605, 1467, 1366, 1261, 1214, 1185. ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.13 (s, 1H), 2.20 (s, 3H), 2.11 (d, J=1.1 Hz, 3H), 1.10 (s, 9H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 199.7, 165.6, 120.5, 37.8, 32.0, 28.5, 15.6. LRMS *m/z* (rel.

int.) 140 (M^+, 11), 125 (50), 97 (16), 83 (12), 69 (15), 67 (11), 57 (19), 55 (50), 43 (100).

4.3. General procedure for substitution reactions between functionalized tellurides and lower order cyanocuprates at low temperatures

To a suspension of dry CuCN (0.089 g; 1 mmol) in THF (10 mL), under nitrogen at −78 °C was slowly added alkyllithium (1 mmol). The reaction was stirred at this temperature for 20 min and a limpid and clear solution was obtained. Then the corresponding telluride (1 mmol) was added and the reaction was warmed up to 0 °C. The reaction was maintained at this temperature and monitored by TLC, until the consumption of the telluride. The reaction mixture was diluted with ethyl acetate (50 mL) and washed with a 1:1 solution of saturated aqueous NH_4Cl and NH_4OH (4× 50 mL). The organic phase was dried with magnesium sulfate and the solvents were evaporated. The residue was purified by silica gel column chromatography eluting with hexane:ethyl acetate (9:1).

4.3.1. (*Z*)-Ethyl 4-methylhex-2-enoate (14d). (0.112 g, 72%) [169735-64-2]. IR ν_{max}/cm^{-1} 2966, 2933, 1723, 1645, 1416, 1188, 1131, 1035 (neat). ^1H NMR (300 MHz, $CDCl_3$) δ 5.95 (dd, J=11.5, 10.2 Hz, 1H), 5.71 (dd, J=11.5, 0.8 Hz, 1H), 4.16 (q, J=7.1 Hz, 2H), 3.45–3.35 (m, 1H), 1.44–1.31 (m, 2H), 1.28 (t, J=7.1 Hz, 3H), 1.00 (d, J=6.6 Hz, 3H), 0.87 (t, J=7.4 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.4, 155.9, 118.6, 59.8, 34.3, 29.8, 19.9, 14.2, 11.7. LRMS *m/z* (rel. int.) 156 (M^+, 28), 128 (22), 113 (30), 111 (44), 110 (26), 99 (25), 95 (33), 82 (40), 81 (33), 73 (34), 69 (37), 67 (30), 56 (40), 55 (100).

4.3.2. (*Z*)-Ethyl 4,4-dimethyl-pent-2-enoate (14e). (0.126 g, 81%) [136265-15-1]. IR ν_{max}/cm^{-1} 2960, 2908, 2872, 1728, 1638, 1385, 1363, 1203, 1179, 1032 (neat). ^1H NMR (300 MHz, $CDCl_3$) δ 5.98 (d, J=12.9 Hz, 1H), 5.64 (d, J=12.9 Hz, 1H), 4.16 (q, J=7.1 Hz, 2H), 1.29 (t, J=7.1 Hz, 3H), 1.19 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.8, 154.7, 118.7, 60.1, 33.8, 29.6, 14.2. LRMS *m/z* (rel. int.) 156 (M^+, 9), 141 (49), 113 (57), 111 (55), 95 (52), 83 (100), 69 (28), 67 (59), 59 (21), 55 (88).

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Activation of chlorine and fluorine by a phenylazo group towards nucleophilic aromatic substitution. Regioselective preparation of polysubstituted anilines

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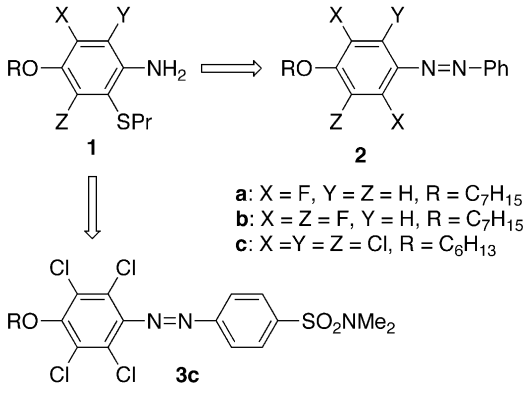
Abstract—A phenylazo group was used for selective activation of *ortho* fluorine and chlorine atoms towards nucleophilic aromatic substitution with the propanethiolate anion. This enabled a regioselective synthesis of three substituted 4-alkoxyanilines. The regioselectivity of substitution was confirmed by comparison of experimental NMR chemical shifts with empirically predicted values. The observed reactivity of the substrates is discussed in the context of the substituent effect.

1. Introduction

Recently, we demonstrated[1] that a phenylazo group moderately activates *ortho* fluorine atoms towards nucleophilic aromatic substitution (NAS)[2] and therefore is an effective and attractive alternative to the nitro group in the preparation of substituted anilines. Using this methodology, we prepared[1] a series of anilines required for the synthesis of polyfunctionalized biphenyls.[3] We also developed synthetic access to benzo[1,2,4]thiadiazines using 2-alkylthioanilines as the staring materials.[4] The preparation of partially halogenated 7-alkoxybenzo[1,2,4]-thiadiazines,[5] requires *p*-alkoxyanilines **1a–c**, which, in principle, can be derived from the corresponding polyhalogenated azo derivatives **2a–c** (Scheme 1).

Here we describe the application of the phenylazo group as an activator of *ortho* F and Cl atoms towards NAS with a thiolate anion, and also as a mask for an amino group in regioselective preparation of anilines **1**. We also briefly investigate the activating ability of the arylazo group substituted in the *para* position by the strongly electron-withdrawing sulfonyl group in **3c**.



Scheme 1.

2. Results

The key step in the synthesis of anilines **1** is the regioselective introduction of the propylthio substituent. Following an earlier established protocol,[1] the fluoro derivatives **2a** and **2b** were reacted with 1.1 equiv of the propanethiolate in boiling ethanol. Substrate **2b** was completely consumed after 4 h and the corresponding product **4b** was isolated in 75% yield (Scheme 2). In contrast, only about half of fluoride **2a** reacted after 8 h under the same conditions to give **4a** in 41% isolated yield. In both reactions, the formation of about 15% of ethoxy derivatives **5a** and **5b** was observed. Approximately the same amounts of **5** were observed when excess PrSH (1.6 equiv) was used with the same amount of base

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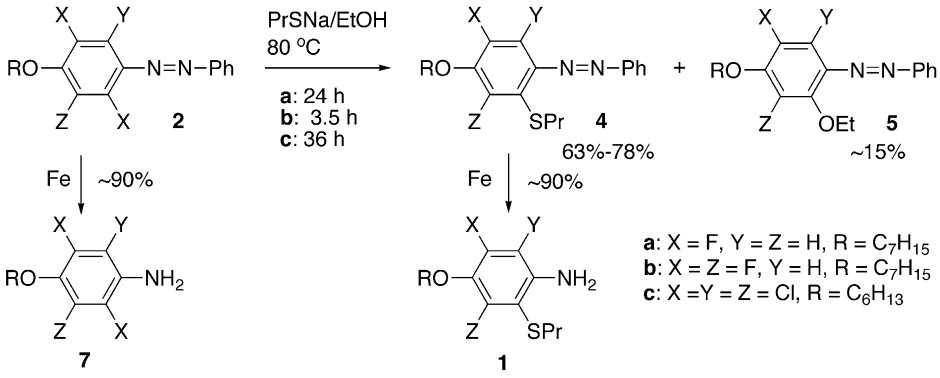


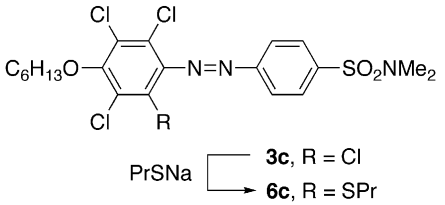
Scheme 2.

(1.1 equiv). This suggests that low concentration of the nucleophile and equilibrium with the solvent (EtOH) are responsible for the appearance of the side product **5**, rather than partial loss of the thiolate due to air oxidation. The formation of **5b** was almost completely suppressed and the reaction time was shortened when 2.2 equiv of the thiolate and 1 equiv of PrSH were used, and the desired product **4b** was isolated in 75% yield. Thus, higher concentrations of the nucleophile are needed for selective substitution.

A similar thiolation reaction of the tetrachloro derivative **2c** with 1.6 equiv of PrSNa in ethanol gave about 80% yield of an 8:1 mixture of monosubstituted product **4c** and presumably the ethoxy side product **5c**. No 2,6-bispropane-thiolated product was found despite a 60% excess of the nucleophile. Complete conversion of the starting **2c** was observed after 36 h, which compares to 3.5 h for **2b** and 24 h for **2a** under similar conditions. No reaction of 2,3,5,6-tetrachloroanisole (lacking the azo group) with PrSNa was detected by GC–MS after 48 h under similar conditions.

In order to increase the rate of replacement of the Cl atom in **2c** by stabilization of the negative charge on the nitrogen atoms, a strongly electron-withdrawing sulfonamido group was introduced in substrate **3c**. A small-scale reaction demonstrated that after 18 h about half of **3c** was consumed, but NMR analysis of the crude and complex reaction mixture showed only traces of the desired product **6c** (Scheme 3). This poor selectivity for **6c** presumably resulted from removing the electron density from the azo group in **3c** and activating it towards reduction by the thiolate anion.

Alternatively, the thiolation of the tetrachloro derivatives **2c** and **3c** was conducted under PTC conditions, as reported for non-activated polychlorinated substrates.[6] Each substrate was consumed within 3 h, which is comparable to the reaction times reported for some non-activated chloroarenes under analogous conditions.[6] Compound **2c** produced pure



Scheme 3.

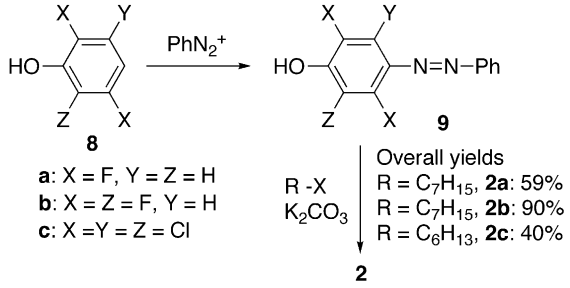
4c in a 78% isolated yield. In contrast, **3c** formed a complex mixture of products, from which **6c** was obtained in about 60% yield or $<10\%$ of analytically pure sample.

The resulting substituted azo compounds **4** were reduced to the desired amines **1** using iron powder. For comparison, the starting azo compounds **2a** and **2b** were also converted to amines **7a** and **7b**, respectively, and both series of amines were generally obtained in about 90% isolated yields (Scheme 2).

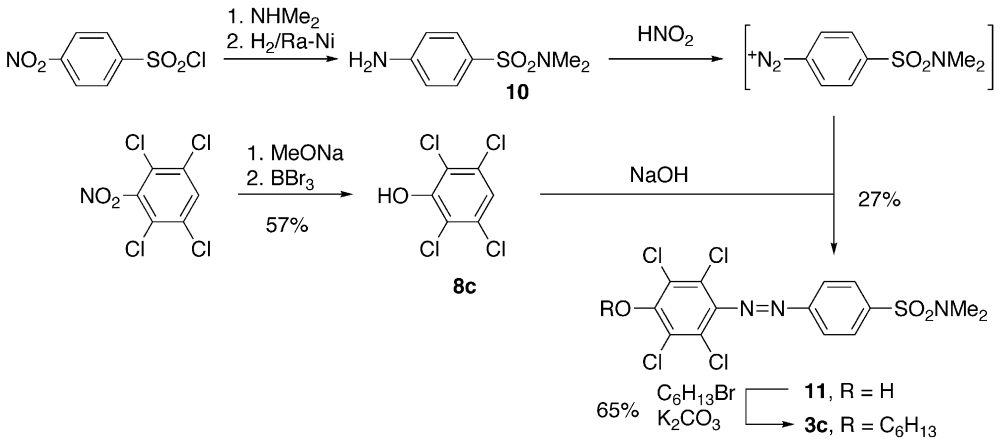
The required azo compounds **2** were prepared by a diazo coupling reaction of the appropriate phenols **8** and benzenediazonium chloride followed by alkylation of the resulting crude azophenols **9** with either *n*-heptyl iodide (**9a** and **9b**) or *n*-hexyl bromide (**9c**, Scheme 4). The yields of azophenols **9a** and **9b** were above 70%. In contrast, **9c** was isolated in only 44% yield, which is consistent with the results for the tetrafluoro analog.[7] Generally, the crude phenols were pure enough for subsequent O-alkylation under PTC conditions. This was demonstrated on 2,3,6-trifluorophenol (**8b**), which gave a 90% overall yield of **2b** in two steps.

The sulfonamide **3c** was prepared in a similar manner in about 20% overall yield by diazo coupling of 2,3,5,6-tetrachlorophenol (**8c**) with a diazonium salt derived from amine **10** followed by alkylation of the resulting phenol **11** (Scheme 5).

Azo compounds that are exposed to sunlight partially isomerize to form *cis*/*trans* mixtures, as evident from the NMR spectra. For instance, spectra of **2b** and **4b** show significantly shielded aromatic hydrogen atoms in the *cis* isomer up to 1 ppm relative to those in the *trans* isomers. At



Scheme 4.



Scheme 5.

a photochemical equilibrium, the ratio of the *trans* and *cis* isomers of **2b** was 3:1 in a chloroform solution. Pure *trans* isomers were obtained by heating samples above 80 °C for 1 h.

2,3,5,6-Tetrachlorophenol (**8c**) was obtained in two steps in 57% overall yield by nucleophilic displacement of the nitro group in 2,3,5,6-tetrachloronitrobenzene with the methoxy group,[8] followed by demethylation of the resulting 2,3,5,6-tetrachloroanisole with BBr_3 (Scheme 5). The original methoxylation procedure[8] was modified by using THF to increase solubility of the starting nitro compound. *p*-Aminobenzenesulfonamide **10** was prepared from 4-nitrobenzenesulfonyl chloride with aqueous $NHMe_2$ followed by catalytic reduction of the resulting nitro amide (Scheme 5).[9]

3. Discussion and conclusions

Results show that the phenylazo group effectively activates both fluorine and chlorine towards nucleophilic substitution and tolerates the reaction conditions. Considering the ready accessibility of the azo precursors through diazo coupling either to phenols or metalloarenes,[1] the method is synthetically useful for the preparation of *ortho*-substituted anilines. If general, the method may be particularly valuable for substitution of chlorine in NAS reactions, since the most common activating group NO_2 is replaced preferentially or exclusively by nucleophiles in many polychlorinated nitroarenes.[1,10] An alternative approach to substitution of halogen in chloroaniline derivatives requires high temperatures and long reaction times.[11] In contrast, NAS in chloroazobenzenes, such as **2c**, can be accomplished selectively under mild conditions and short reaction times (PTC).

The phenylazo group appears to be an optimum substituent for NAS reactions due to its activating ability and synthetic simplicity. The previously investigated 4-Me_2N substituent appears to completely compensate the moderate activating effect of the PhN_2 group,[1] presumably due to the strong donating character of the amino group. In the current study, the 4-sulfonyl group in **3c** activates other undesired reaction pathways, which result in complex reaction mixtures.

Based on the observed reaction times, the reactivity of the haloarenes follows the order **2b** > **2a** > **2c**. The significantly higher mobility of fluorine in **2b** than in **2a** (c.f. 3.5 h vs 24 h reaction time) results from the activating effect of the *ortho* fluorine atom in the former, which is absent in **2a**. According to a comparative study of penta- and hexafluorobenzenes,[12] *ortho* substitution with fluorine, as in **2b**, may increase the NAS rate by a factor of about 30, while fluorine in the *para* position, as in **2a**, is expected to be modestly deactivating. Thus, fluorine atoms in **2b** and those studied before[1] are additionally activated by *ortho* halogens and show significantly enhanced reactivity (shorter reaction times).

The lowest reactivity in the series is exhibited by the chloroarene **2c** (36 h reaction time), which reflects the generally observed[13] 2–3 order-of-magnitude lower mobility of Cl than F in NAS reactions. However, the mobility of chlorine in **2c** is increased by the presence of three other Cl atoms exerting strong *ortho*, and moderate *meta* and *para* activating effects.[12,14] Therefore, it is conceivable that a precursor lacking the additional Cl atoms, e.g. the hypothetical chloro analog of **2a**, would exhibit low reactivity and a synthetically useful NAS reaction would have to be performed under the PTC conditions.[6] Support for this expectation is provided by the high selectivity for monosubstituted product **4c**, which results from lower activation of the mobile chlorine atom (*ortho* to the azo group) by the SPr group in **4c** than by the Cl in the same position in **2c**. According to the results for substituted 2- and 4-chloroquinolines,[14] the change of Cl to a SMe group retards the NAS rate by a factor >20, which is consistent with the trends in the σ_m values (0.37 and 0.15, respectively).[15] Interestingly, these studies found the SMe substituent to be even less effective than H in activation of the *meta* chlorine towards NAS.[14]

Nucleophilic substitution in **2** occurs regioselectively, which is expected based on the small *ortho* deactivating effect of the alkoxy group[16] and the moderately *ortho* activating ability of the azo group. Proton NMR analysis of the azo compounds **4** and the amines **1**, combined with the results for unsubstituted derivatives **2** and **7**, shows a good correlation between the predicted and experimental chemical shifts (Fig. 1). The plot reflects stronger solvent-solute

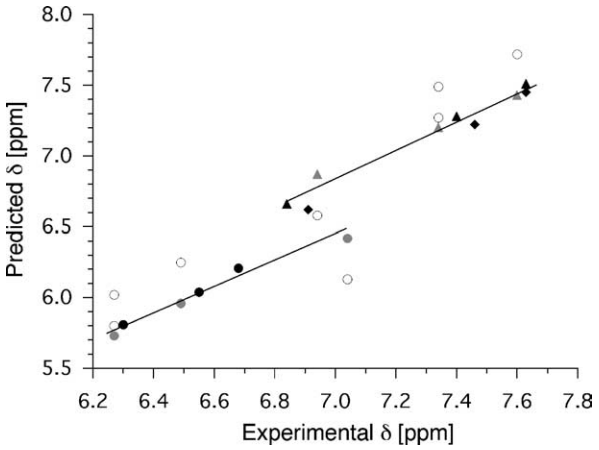


Figure 1. Correlation between experimental and predicted (ChemDraw 8.0 Ultra) chemical shifts for fluorinated anilines **1** (black dots) and **7** (gray dots), azo compounds **2** (black triangles) and **4** (gray triangles) and phenols **9** (black diamonds). Best fit lines: $y=0.92x$ ($R^2=0.97$) for **1** and **7**, and $y=0.98x$ ($R^2=0.96$) for **4** and **9**. Open circles represent the calculated chemical shift for other regioisomers of **1** and **4**.

interactions for anilines **1** and **7**, which are deshielded relative to the predicted values (slope 0.92), than observed for azo compounds **2** and **4** (slope 0.98). In contrast, chemical shifts predicted for other regioisomers of **4** and **1** lie outside the correlation. The magnitude of the ^1H–^{19}F coupling constants (J_{HF}) in the NMR spectra is also consistent with the assigned structures. For instance, in **1a** the more shielded proton adjacent to the amino group is more strongly coupled to the ^{19}F nucleus ($J_{HF}=12.6$ Hz) than the downfield hydrogen atom ($J_{HF}=9.0$ Hz).

Although the main focus of this work was the introduction of an alkylthio substituent through the NAS process, the isolation of the ethoxy derivatives **5** as side products suggests a more general application of the PhN_2 group as an activating mask for the NH_2 group in other NAS reactions.

4. Experimental

4.1. General

Melting points are uncorrected. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 300 and 75.5 MHz, respectively, and referenced to the solvent, unless specified otherwise. ^{19}F NMR spectra were recorded at 282.4 MHz and referenced to CF_3COOH (external standard). IR spectra were recorded by deposition of a thin film from solution on sodium chloride plates or as KBr pellets.

4.1.1. 5-Fluoro-4-heptyloxy-2-propylthioaniline (1a). Azo compound **4a** (89 mg, 0.23 mmol) was added in one portion to a vigorously stirred suspension of iron dust (130 mg, 2.32 mmol) in water (3 mL) and acetic acid (0.1 mL) at 100 °C and stirred for 1 h. The reaction mixture was cooled down, poured into satd $NaHCO_3$ and extracted with diethyl ether. Combined organic layers were dried ($MgSO_4$) and concentrated to give an oily residue which was short-path distilled (bp 185 °C/0.15 Torr) to give 63 mg (90% yield) of amine **1a** as a transparent oil: ^1H NMR δ 0.89 (t, $J=6.6$ Hz, 3H), 0.99 (t, $J=7.2$ Hz, 3H), 1.25–1.49 (m, 8H), 1.53 (sextet, $J=7.3$ Hz, 2H), 1.75 (quintet, $J=6.6$ Hz, 2H), 2.66 (t, $J=7.2$ Hz, 2H), 3.93 (t, $J=6.6$ Hz, 2H), 4.2 (brs, 2H), 6.49 (d, $J=12.6$ Hz, 1H), 7.04 (d, $J=9.0$ Hz, 1H); ^{13}C NMR δ 13.2, 14.0, 22.6, 22.9, 25.8, 29.0, 29.4, 31.7, 37.3, 71.0, 103.2 (d, $J=22.2$ Hz), 112.5 (d, $J=3.4$ Hz), 124.4 (d, $J=3.6$ Hz), 139.9 (d, $J=11.8$ Hz), 143.3 (d, $J=9.9$ Hz); 154.3 (d, $J=246.8$ Hz); ^{19}F NMR δ −132.34 (s, 1F); IR (neat) ν_{max} 3460 and 3360 (NH_2), 1497 cm^{-1}; MS, *m/e* (relative intensity) 299 (M^+, 45), 159 (100). HR-FABMS, calcd for $C_{16}H_{26}FNOS$ ($[M]^+$): *m/e* 299.1719; found: *m/e* 299.1704. Anal. Calcd for $C_{16}H_{26}FNOS$: C, 64.18; H, 8.75; N, 4.68. Found: C, 64.80; H, 8.84; N, 4.92.

4.1.2. 3,5-Difluoro-4-heptyloxy-2-propylthioaniline (1b). The amine **1b** was obtained in 94% yield according to the procedure described for **1a** and purified by chromatography (CH_2Cl_2–hexane, 3:1) to give a transparent quickly darkening in air oil: ^1H NMR δ 0.89 (t, $J=6.9$ Hz, 3H), 0.98 (t, $J=7.4$ Hz, 3H), 1.26–1.49 (m, 8H), 1.55 (sextet, $J=7.4$ Hz, 2H), 1.72 (quintet, $J=7.2$ Hz, 2H), 2.65 (t, $J=7.2$ Hz, 2H), 3.96 (t, $J=6.6$ Hz, 2H), 4.45 (brs, 2H), 6.27 (dd, $J_1=12.3$ Hz, $J_2=2.0$ Hz, 1H); ^{19}F NMR δ −127.32 (d, $J=10.4$ Hz, 1F), −120.18 (d, $J=10.4$ Hz, 1F); IR (neat) ν_{max} 3470 and 3371 (NH_2), 1493 cm^{-1}; MS, *m/e* (relative intensity) 317 (M^+, 25), 177 (100). HR-FABMS, calcd for $C_{16}H_{25}F_2NOS$ ($[M]^+$): *m/e* 317.1625; found: *m/e* 317.1599.

4.1.3. 3,5,6-Trichloro-4-hexyloxy-2-propylthioaniline (1c). The amine **1c** was obtained in 65% yield as a transparent oil according to the procedure described for **1a** and purified by column chromatography (CH_2Cl_2–hexanes, 1:1): ^1H NMR δ 0.91 (t, $J=7.1$ Hz, 3H), 0.99 (t, $J=7.4$ Hz, 3H), 1.32–1.38 (m, 4H), 1.46–1.53 (m, 2H), 1.57 (sextet, $J=7.3$ Hz, 2H), 1.82 (quintet, $J=7.1$ Hz, 2H), 2.75 (t, $J=7.4$ Hz, 2H), 3.92 (t, $J=6.6$ Hz, 2H), 5.0 (brs, 2H); ^{13}C NMR δ 13.4, 14.0, 22.6, 23.2, 25.5, 29.9, 31.6, 36.7, 73.7, 115.8, 116.1, 129.6, 134.2, 143.7, 144.2; IR (neat) ν_{max} 3480 and 3368 (NH_2), 1586, 1431 cm^{-1}. Anal. Calcd for $C_{15}H_{22}Cl_3NOS$: C, 48.59; H, 5.98; N, 3.78. Found: C, 48.74; H, 5.98; N, 3.76.

4.1.4. 2,5-Difluoro-4-(heptyloxy)azobenzene (2a). A mixture of 2,5-difluoro-4-phenylazophenol (**9a**, 4.70 g, 20.1 mmol), anhydrous K_2CO_3 (3.60 g, 26 mmol), *n*-heptyl iodide (4.70 g, 20.8 mmol), Aliquat®336 (0.2 mL) and acetone (30 mL) was stirred and refluxed overnight. Hexane (30 mL) was added and the mixture was filtered through a silica gel plug and washed with CH_2Cl_2. The filtrate was concentrated, the residue dissolved in hexanes and filtered again through a silica gel plug with warm hexanes as the eluent. The orange filtrate was evaporated to give a solid, which was recrystallized from pentane to yield 5.25 g (79% yield) of **2a** as orange crystals: mp 80–81 °C; bp 220 °C/0.2 Torr (short path); ^1H NMR δ 0.90 (t, $J=6.6$ Hz, 3H), 1.31–1.51 (m, 8H), 1.88 (quintet, $J=7.0$ Hz, 2H), 4.08 (t, $J=6.6$ Hz, 2H), 6.84 (dd, $J_1=11.7$ Hz, $J_2=7.2$ Hz, 1H), 7.45–7.54 (m, 3H), 7.63 (dd, $J_1=11.7$ Hz, $J_2=7.2$ Hz, 1H), 7.88–7.94 (m, 2H); ^{19}F NMR δ −139.32 (d, $J=13.6$ Hz, 1F), −126.85 (d, $J=13.6$ Hz, 1F); IR (KBr) ν_{max} 1623, 1503, 1282 cm^{-1}; MS, *m/e* (relative intensity) 332 (M^+, 30), 77 (100). Anal. Calcd for $C_{19}H_{22}F_2N_2O$: C, 68.66; H, 6.67; N, 8.43. Found: C, 68.69; H, 6.67; N, 8.44.

4.1.5. 2,3,5-Trifluoro-4-(heptyloxy)azobenzene (2b). The compound **2b** was synthesized in 90% overall yield based on **8b** according to the procedure described for **2a** as an orange oily mixture of *trans–cis* isomers in a 5:1 ratio that solidified upon standing: bp 210 °C/0.2 Torr (short path); mp 36–37 °C; ^{1}H NMR (major isomer) δ 0.90 (t, J=6.6 Hz, 3H), 1.31–1.55 (m, 8H), 1.81 (quintet, J=7.0 Hz, 2H), 4.29 (t, J=6.6 Hz, 2H), 7.40 (ddd, J_1=11.7 Hz, J_2=3.0 Hz, J=0.9 Hz, 1H), 7.50–7.55 (m, 3H), 7.91–7.96 (m, 2H); (minor isomer, selected signals) δ 1.73 (quintet, J=7.0 Hz, 2H), 4.13 (t, J=6.6 Hz, 2H), 6.48 (ddd, J_1=10.2 Hz, J_2=6.0 Hz, J_3=2.4 Hz, 1H), 6.88–6.92 (m, 2H), 7.29–7.34 (m, 2H); ^{19}F NMR (major isomer) δ −151.83 (d, J=7.6 Hz, 2F), −133.46 (t, J=7.7 Hz, 1F); (minor isomer) δ −149.91 (dd, J_1=21.7 Hz, J_2=5.0 Hz, 1F), −147.86 (dd, J_1=21.7 Hz, J_2=11.9 Hz, 1F), −132.40 (dd, J_1=11.9 Hz, J_2=5.1 Hz, 1F); IR (KBr) ν_{max} 1493, 1347 cm^{-1}; MS, *m/e* (relative intensity) 350 (M^+, 15), 77 (100). Anal. Calcd for $C_{19}H_{21}F_3N_2O$: C, 65.13; H, 6.04; N, 8.00. Found: C, 65.21; H, 6.08; N, 8.11.

4.1.6. 2,3,5,6-Tetrachloro-4-(hexyloxy)azobenzene (2c). The compound **2c** was synthesized in 91% yield according to the procedure described for **2a** using *n*-hexyl bromide and acetonitrile as a solvent: mp 64–65 °C; ^{1}H NMR δ 0.93 (t, J=7.0 Hz, 3H), 1.34–1.42 (m, 4H), 1.50–1.60 (m, 2H), 1.89 (quintet, J=7.0 Hz, 2H), 4.06 (t, J=6.5 Hz, 2H), 7.53–7.60 (m, 3H), 7.94–7.99 (m, 2H); ^{13}C NMR δ 14.0, 22.6, 25.4, 29.9, 31.5, 74.2, 119.5, 123.2, 124.1, 128.5, 129.3, 132.9, 146.5, 152.0; IR (KBr) ν_{max} 1371 cm^{-1}. Anal. Calcd for $C_{18}H_{18}Cl_4N_2O$: C, 51.46; H, 4.32; N, 6.67. Found: C, 51.36; H, 4.32; N, 6.65.

4.1.7. *N,N*-Dimethyl-4-[2,3,5,6-tetrachloro-4-hexyloxyphenyl(azo)]benzene-sulfonamide (3c). Compound **3c** was synthesized in 65% yield as a 6:1 mixture of *trans–cis* isomers according to the procedure described for **2a** using *n*-hexyl bromide and acetonitrile as a solvent and recrystallized from *i*-octane: mp 100–101 °C; ^{1}H NMR δ (major isomer) 0.92 (t, J=7.2 Hz, 3H), 1.32–1.41 (m, 4H), 1.50–1.60 (m, 2H), 1.90 (quintet, J=6.9 Hz, 2H), 2.79 (s, 6H), 4.08 (t, J=6.5 Hz, 2H), 7.98 (d, J=8.4 Hz, 2H), 8.08 (d, J=8.4 Hz, 2H); (minor isomer, selected signals) δ 2.70 (s, 6H), 4.00 (t, J=6.6 Hz, 2H), 7.13 (d, J=8.7 Hz, 2H), 7.73 (d, J=8.4 Hz, 2H); ^{13}C NMR δ 14.1, 22.6, 25.4, 30.0, 31.6, 37.9, 74.4, 123.6, 124.3, 128.5, 128.9, 139.1, 145.9, 152.7, 153.8; IR (KBr) ν_{max} 1351, 1167 cm^{-1}. HR-FABMS, calcd for $C_{20}H_{24}Cl_4N_3O_3S$ ($[M+H]^+$): *m/e* 526.0292; found: *m/e* 526.0278. Anal. Calcd for $C_{20}H_{23}Cl_4N_3O_3S$; C, 45.56; H, 4.40; N, 7.97. Found: C, 45.93; H, 4.49; N, 7.85.

4.1.8. 5-Fluoro-4-heptyloxy-2-(propylthio)azobenzene (4a). Compound **2a** (112 mg, 0.34 mmol) was suspended in ethanol (3 mL, 95%), then a solution of NaOH (15 mg, 0.375 mmol in 1.5 mL EtOH) was added, followed by propanethiol (50 μL, 0.552 mmol) at rt under N_2. The mixture was stirred at 90 °C for 10 h, more propanethiol (50 μL, 0.552 mmol) was added and the stirring was continued overnight. When the TLC analysis showed absence of the starting **2a** (about 24 h) the reaction mixture was evaporated to dryness. The product was purified by flash chromatography (CH_2Cl_2–hexanes, 1:5) followed by recrystallization from EtOH to give 82 mg (63% yield) of **4a** as orange needles: mp 66–67 °C; ^{1}H NMR δ 0.91 (t, J=6.6 Hz, 3H), 1.09 (t, J=7.3 Hz, 3H), 1.28–1.54 (m, 8H), 1.78 (sextet, J=7.4 Hz, 2H), 1.87 (quintet, J=7.2 Hz, 2H), 2.97 (t, J=7.2 Hz, 2H), 4.11 (t, J=6.6 Hz, 2H), 6.94 (d, J=7.8 Hz, 1H), 7.41–7.51 (m, 3H), 7.60 (d, J=12.0 Hz, 1H), 7.90–7.95 (m, 2H); ^{13}C NMR δ 13.7, 14.1, 22.2, 22.6, 25.9, 29.0, 29.1, 31.7, 35.1, 69.6, 104.4 (d, J_{CF}=20.1 Hz), 112.6 (br), 123.1 129.1, 130.8, 136.7 (d, J_{CF}=2.6 Hz), 143.3 (d, J_{CF}=4.1 Hz), 150.0 (d, J_{CF}=12.2 Hz), 151.3 (d, J_{CF}=248.2 Hz), 152.7. ^{19}F NMR δ −138.1 (s, 1F); IR (KBr) ν_{max} 1600, 1503, 1267 cm^{-1}. Anal. Calcd for $C_{22}H_{29}FN_2OS$: C, 68.01; H, 7.52; N, 7.21. Found: C, 67.87; H, 7.54; N, 7.15.

4.1.9. 3,5-Difluoro-4-heptyloxy-2-(propylthio)azobenzene (4b). Compound **4b** was prepared in 69% yield according to the procedure described for **4a** and without using additional PrSH. Full conversion of **2b** was achieved after 3.5 h. When double the amount of NaOH and PrSH was used, the reaction was completed after 2 h and compound **4b** was isolated in 75% yield. The product was purified by PTLC (hexanes) to give a red oil of **4b** as a 6:1 mixture of *trans–cis* isomers: ^{1}H NMR (major isomer) δ 0.90 (t, J=6.6 Hz, 3H), 0.98 (t, J=7.3 Hz, 3H), 1.25–1.50 (m, 8H), 1.59 (sextet, J=7.3 Hz, 2H), 1.80 (quintet, J=7.1 Hz, 2H), 2.94 (t, J=7.2 Hz, 2H), 4.22 (t, J=6.6 Hz, 2H), 7.34 (dd, J_1=11.7 Hz, J_2=2.1 Hz, 1H), 7.49–7.57 (m, 3H), 7.93–7.98 (m, 2H); (minor isomer, selected signals) δ 2.88 (t, J=7.2 Hz, 2H), 4.07 (t, J=6.6 Hz, 2H), 5.96 (dd, J_1=10.2 Hz, J_2=1.8 Hz, 1H), 6.86–6.90 (m, 2H); ^{19}F NMR (major isomer) δ −127.65 (d, J=9.4 Hz, 1F), −121.17 (d, J=9.5 Hz, 1F); (minor isomer) δ −126.16 (d, J=10.5 Hz, 1F), −121.25 (d, J=10.6 Hz, 1F); IR (neat) ν_{max} 1481 cm^{-1}; FAB, *m/e* (relative intensity) 407 (MH^+, 52) 363 (M^+-C_3H_7, 100). HR-FABMS, calcd for $C_{22}H_{29}F_2N_2OS$ ($[M+H]^+$): *m/e* 407.1969; found: *m/e* 407.1975.

4.1.10. 2,3,5-Trichloro-4-hexyloxy-6-(propylthio)azobenzene (4c). *Method A*. Compound **2c** was reacted with sodium propanethiolate in EtOH as described for **4a**. When TLC analysis showed full conversion of the substrate after 36 h, the reaction mixture was worked up and product **4c** contaminated with small amounts of the presumably ethoxy derivative **5c** was isolated in 78% yield.

Method B. Compound **2c** (1800 mg, 4.29 mmol), powdered KOH (317 mg, 0.76 mmol), and hexadecyltributylphosphonium bromide (109 mg, 0.215 mmol) were stirred in toluene (8 mL) under nitrogen. Propanethiol (343 mg, 4.51 mmol) was added via syringe, and the syringe was washed with toluene (3 mL). The reaction was monitored by TLC. Upon total conversion of the starting material (~3 h), the reaction mixture was passed through a silica gel plug using first pure hexanes and proceeding up to CH_2Cl_2–hexanes in 1:1 ratio, to afford 1.54 g (78% yield) of **4c** as a dark red oil: ^{1}H NMR δ 0.87 (t, J=7.2 Hz, 3H), 0.93 (t, J=7.0 Hz, 3H), 1.36–1.41 (m, 4H), 1.46 (sextet, J=7.3 Hz, 2H), 1.51–1.59 (m, 2H), 1.89 (quintet, J=6.9 Hz, 2H), 2.70 (t, J=7.2 Hz, 2H), 4.05 (t, J=6.6 Hz, 2H), 7.56–7.59 (m, 3H), 7.94–7.97 (m, 2H); ^{13}C NMR δ 13.2, 14.0, 22.6, 22.8, 25.5, 30.0, 31.6, 38.2, 73.9, 123.1, 123.2, 126.4, 129.3, 130.0, 132.4, 134.2, 151.5, 152.0, 152.3; IR (KBr) ν_{max}

1363 cm^{-1}. Anal. Calcd for $C_{21}H_{25}Cl_4N_2OS$: C, 54.85; H, 5.48; N, 6.09. Found: C, 55.22; H, 5.62; N, 5.77.

4.1.11. 2-Ethoxy-5-fluoro-4-(heptyloxy)azobenzene (5a). The ethoxy derivative **5a** was isolated in about 10% yield and ~95% purity as a second fraction in chromatographic purification of **4a** (CH_2Cl_2–hexanes, 1:1) in the form of a red oil: ^{1}H NMR δ 0.90 (t, J=6.6 Hz, 3H), 1.25–1.50 (m, 8H), 1.52 (t, J=7.1 Hz, 3H), 1.87 (quintet, J=7.0 Hz, 2H), 4.09 (t, J=6.6 Hz, 2H), 4.28 (q, J=7.0 Hz, 2H), 6.67 (d, J=7.2 Hz, 1H), 7.41–7.54 (m, 3H), 7.62 (d, J=12.3 Hz, 1H), 7.85–7.92 (m, 2H); ^{19}F NMR δ −143.53 (s, 1F); FAB, *m/e* (relative intensity) 359 (MH+, 100). HR-FABMS, calcd for $C_{21}H_{28}FN_2O_2$ ($[M+H]^+$): *m/e* 359.2135; found: *m/e* 359.2146.

4.1.12. 2-Ethoxy-3,5-difluoro-4-(heptyloxy)azobenzene (5b). The ethoxy derivative **5b** was isolated in about 10% yield and ~90% purity as a second fraction in chromatographic purification of **4b** (CH_2Cl_2–hexanes, 1:1) in the form of a red oil: ^{1}H NMR δ 0.89 (t, J=6.6 Hz, 3H), 1.23–1.40 (m, 8H), 1.46 (t, J=7.0 Hz, 3H), 1.80 (quintet, J=7.2 Hz, 2H), 4.25 (t, J=6.6 Hz, 2H), 4.36 (q, J=7.0 Hz, 2H), 7.36 (dd, J_1=12.0 Hz, J_2=2.1 Hz, 1H), 7.47–7.56 (m, 3H), 7.88–7.95 (m, 2H); ^{19}F NMR δ −145.32 (d, J=4.5 Hz, 1F); −134.27 (d, J=4.5 Hz, 1F); FAB, *m/e* (relative intensity) 377 (MH+, 100). HR-FABMS, calcd for $C_{21}H_{27}F_2N_2O_2$ ($[M+H]^+$): *m/e* 377.2041; found: *m/e* 377.2017.

4.1.13. *N*,*N*-Dimethyl-4-[4-hexyloxy-2,3,5-trichloro-6-propylthiophenyl(azo)]benzenesulfonamide (6c). Following Method B described for **4c**, compound **6c** was obtained from **3c** in 63% yield and about 75% purity after chromatography (CH_2Cl_2). An analytical sample was obtained by recrystallization from Et_2O–heptane mixture: mp 100–101 °C; ^{1}H NMR δ 0.88 (t, J=7.2 Hz, 3H), 0.93 (t, J=6.9 Hz, 3H), 1.33–1.44 (m, 6H), 1.47 (sextet, J=7.0 Hz, 2H), 1.90 (quintet, J=7.0 Hz, 2H), 2.74 (t, J=7.2 Hz, 2H), 2.80 (s, 6H), 4.07 (t, J=6.6 Hz, 2H), AA′MM′ 7.98 and 8.07 (d, J=8.7 Hz, 4H); IR (KBr) ν_{max} 1352, 1169 cm^{-1}. HR-FABMS, calcd for $C_{23}H_{31}Cl_3N_3O_3S_2$ ($[M+H]^+$): *m/e* 566.0872; found: *m/e* 566.0858.

4.1.14. 2,5-Difluoro-4-heptyloxyaniline (7a). The amine **7a** was synthesized in 91% yield according to the procedure described for **1a** using 4.5 g of **2a**, 5.0 g of iron 60 mL of water and 8 mL acetic acid: bp 150 °C/0.1 Torr (short path); mp 45–46 °C; ^{1}H NMR δ 0.89 (t, J=6.8 Hz, 3H), 1.29–1.45 (m, 8H), 1.76 (quintet, J=7.0 Hz, 2H), 3.5 (bs, 2H), 3.91 (t, J=6.6 Hz, 2H), 6.55 (dd, J_1=12.0 Hz, J_2=8.4 Hz, 1H), 6.68 (dd, J_1=11.7 Hz, J_2=7.5 Hz, 1H); ^{13}C NMR δ 14.1, 22.6, 25.8 29.0, 29.3, 31.8, 70.9, 104.6 (dd, J_1=23.9 Hz, J_1=2.8 Hz), 105.2 (dd, J_1=23.9 Hz, J_1=4.4 Hz), 127.7 (dd, J_1=15.2 Hz, J_1=9.6 Hz), 138.8 (dd, J_1=12.6 Hz, J_1=9.1 Hz), 147.0 (d, J=232.1 Hz), 149.4 (d, J=239.6 Hz); ^{19}F NMR δ −139.69 (d, J=13.8 Hz, 1F), −139.26 (d, J=13.8 Hz, 1F); IR (KBr) ν_{max} 3411, 3307 and 3207 (NH_2), 1537 cm^{-1}; MS, *m/e* (relative intensity) 243 (M^+, 5), 145 (100). Anal. Calcd for $C_{13}H_{19}F_2N_2O$: C, 64.18; H, 7.87; N, 5.76. Found: C, 64.37; H, 7.89; N, 5.79.

4.1.15. 2,3,5-Trifluoro-4-heptyloxyaniline (7b). The amine **7b** was synthesized in 94% yield according to the procedure described for **1a** and purified by distillation (150–151 °C/0.1 Torr) to give a light yellow oil: ^{1}H NMR δ 0.88 (t, J=6.6 Hz, 3H), 1.25–1.48 (m, 8H), 1.72 (quintet, J=7.0 Hz, 2H), 3.7 (brs, 2H), 4.00 (t, J=6.6 Hz, 2H), 6.30 (ddd, J_1=10.3 Hz, J_2=7.8 Hz, J_3=2.5 Hz, 1H); ^{19}F NMR δ −163.80 (dd, J_1=19.5 Hz, J_2=10.2 Hz, 1F), −152.86 (d, J=19.5 Hz, 1F), −135.17 (d, J=10.2 Hz, 1F); IR (KBr) ν_{max} 3485 and 3390 (NH_2), 1522, 1490 cm^{-1}; MS *m/e* (relative intensity) 261 (M^+, 5), 163 (100). Anal. Calcd for $C_{13}H_{18}F_3N_2O$: C, 59.76; H, 6.94; N, 5.36. Found: C, 60.17; H, 7.09; N, 5.37.

4.1.16. 2,3,5,6-Tetrachlorophenol.[17](8c) A solution sodium metal (2.72 g, 120 mmol) in methanol (100 mL) was added to 2,3,5,6-tetrachloronitrobenzene (26.18 g, 100 mmol) in dry THF (75 mL) at rt. The reaction mixture was stirred for 4 h at 60 °C, filtered and solvents evaporated. The residue was treated with water and extracted with CH_2Cl_2. Combined organic layers were dried ($MgSO_4$) and evaporated. The residue was recrystallized from EtOH to give 17.34 g (71% yield) of pure 2,3,5,6-tetrachloroanisole: mp 88–89 °C (lit.[8] mp 89–90 °C); ^{1}H NMR δ 3.92 (s, 3H), 7.41 (s, 1H).

A 1.0 M solution of BBr_3 in CH_2Cl_2 (10 mL) was added to the anisole solution (2.46 g, 10 mmol) in CH_2Cl_2 (100 mL) under inert atmosphere at 0 °C. The reaction mixture was allowed to warm up to rt, stirred overnight, poured into water and extracted with CH_2Cl_2. Combined organic layers were dried ($MgSO_4$) and evaporated. The crude product was recrystallized from *i*-octane to give 1.86 g (80% yield or 57% overall) of phenol **8c** as pale yellow crystals: mp 115–116 °C (lit.[18] mp 115 °C); ^{1}H NMR δ 6.10 (s, 1H), 7.23 (s, 1H). Anal. Calcd for $C_6H_2Cl_4O$: C, 31.08; H, 0.87. Found: C, 30.97; H, 0.89.

4.1.17. 2,5-Difluoro-4-phenylazophenol (9a). A solution of benzenediazonium chloride prepared from aniline (4.80 g, 51.6 mmol), 3 M HCl (65 mL) and a solution of $NaNO_2$ (4.80 g, 69.5 mmol, in 60 mL of water) and treated with urea (0.4 g) was added dropwise to a stirred solution of 2,5-difluorophenol (**8a**, 5.00 g, 38.5 mmol) and NaOH (5.40 g, 135 mmol) in water (90 mL) at 0 °C. After 30 min, the reaction mixture was allowed to warm up to rt and was stirred for another 1 h. Diluted HCl was added and the resulting precipitation was filtered and recrystallized from aqueous acetic acid to give 6.70 g (74% yield) of phenol **9a** as brown crystals: mp 126–128 °C; ^{1}H NMR δ 6.91 (dd, J_1=10.2 Hz, J_2=7.5 Hz, 1H), 7.45–7.55 (m, 3H), 7.63 (dd, J_1=11.1 Hz, J_2=6.6 Hz, 1H), 7.88–7.94 (m, 2H); ^{19}F NMR δ −144.74 (d, J=14.0 Hz, 1F), −126.89 (d, J=14.0 Hz, 1F); IR (KBr) ν_{max} 3504, 1623, 1506, 1303 cm^{-1}. HR-FABMS, calcd for $C_{12}H_9F_2N_2O$ ($[M+H]^+$): *m/e* 235.0683; found: *m/e* 235.0692.

4.1.18. 2,3,6-Trifluoro-4-phenylazophenol (9b). The compound **9b** was obtained as a crude brown powder according to the procedure described for **9a** and was used without further purification: mp 117–119 °C; ^{1}H NMR δ 2.7 (br s, 1H), 7.46 (ddd, J_1=11.1 Hz, J_2=6.3 Hz, J_3=2.4 Hz, 1H), 7.50–7.57 (m, 3H), 7.89–7.96 (m, 2H); ^{19}F NMR δ −157.86 (dd, J_1=19.5 Hz, J_2=6.0 Hz, 1F), −151.70 (dd,

$J_1=19.5$ Hz, $J_2=11.1$ Hz, 1F), −140.74 (dd, $J_1=11.1$ Hz, $J_2=6.2$ Hz, 1F); IR (KBr) ν_{max} 3535, 1518, 1333 cm^{-1}. HR-FABMS, calcd for $C_{12}H_8F_3N_2O$ ($[M+H]^+$): *m/e* 253.0589; found: *m/e* 253.0596.

4.1.19. 2,3,5,6-Tetrachloro-4-phenylazophenol (9c). Phenol **9c** was obtained according to procedure described for **9a** in 44% yield after recrystallization from aqueous acetic acid as orange microcrystals: mp 144–148 °C; ^1H NMR δ 6.15 (s, 1H), 7.54–7.59 (m, 3H), 7.94–7.97 (m, 2H); ^{13}C NMR δ 119.9, 123.2, 124.6, 129.3, 132.7, 143.2, 148.3, 152.0; IR (KBr) ν_{max} 3100 (br, OH), 1385 cm^{-1}. Anal. Calcd for $C_{12}H_6Cl_4N_2O$: C, 42.90; H, 1.80; N, 8.34. Found: C, 42.65; H, 1.69; N, 8.09.

4.1.20. *N,N*-Dimethyl-4-[2,3,5,6-tetrachloro-4-hydroxyphenyl(azo)]benzene-sulfonamide (11). Compound **11** was obtained as orange microcrystals according to the procedure described for **9a** in 27% yield after recrystallization from aqueous acetic acid: mp 235–236 °C; ^1H NMR (acetone-d_6) δ 2.73 (s, 6H), 7.66 (s, 1H), AA′MM′ 7.94 and 8.05 (d, $J=8.4$ Hz, 4H); IR (KBr) ν_{max} 3308, 1379, 1331, 1159, 1147 cm^{-1}. Anal. Calcd for $C_{14}H_{11}Cl_4N_3O_3S$: C, 37.95; H, 2.50; N, 9.48. Found: C, 37.95; H, 2.52; N, 9.14.

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Synthesis of the B-ring of FR182877. Investigation of the reactions of 6-fumaryl 1,3,8-nonatrienes☆

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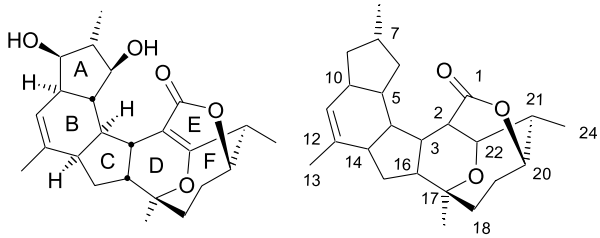
Abstract—Investigation of the intramolecular Diels–Alder reactions of 6-fumaryl 1,3,8-nonatrienes, substituted at the C5 by a vinyl group, to afford the B-ring of FR182877 are reported. The synthesis of the required 1,3,8-nonatriene was achieved quickly and in high yield. 6-Fumaryl 1,3,8-nonatrienes substituted at the C5 by a vinyl group were found to undergo competing tandem sigmatropic rearrangement/Diels–Alder cyclisation when heated under standard Diels–Alder cyclisation conditions. This rearrangement became the exclusive pathway when the reaction was performed in the presence of a Lewis acid. As expected from modeling studies, the major intramolecular Diels–Alder cyclisation product was the desired *exo-trans* adduct, which was required for the synthesis of FR182877. Intrigued by the rearrangements, a number of alterations were made to the 1,3,8-nonatriene. Replacement of the fumaryl group by an acetyl group resulted in the diminished reactivity of the 1,3,8-nonatriene with neither rearrangements nor cycloadditions observed. Variation of the C5 substituent was found to be very important in determining the π-diastereoselectivity of the Diels–Alder cyclisation.

1. Introduction

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

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



FR182877 **1**

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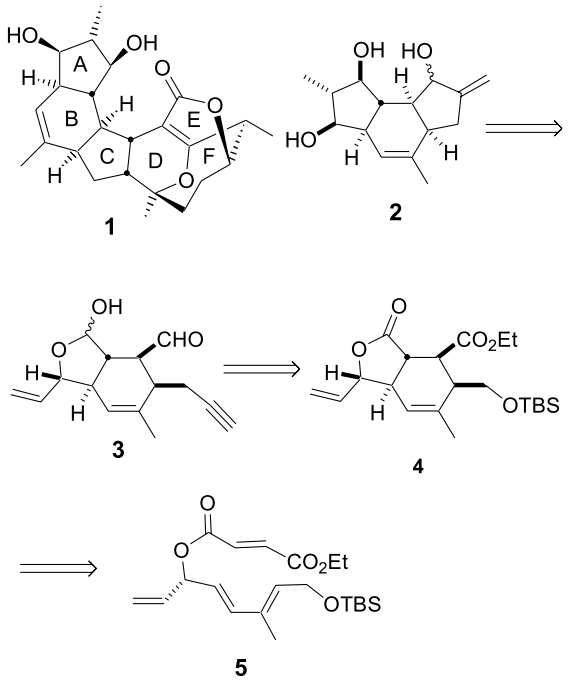
Armstrong reporting a procedure for the synthesis of a number of DE-ring analogues,[10] and ourselves reporting the synthesis of the DEF-rings of both FR182877[11,12] and of the related natural product hexacyclinic acid.[12,13]

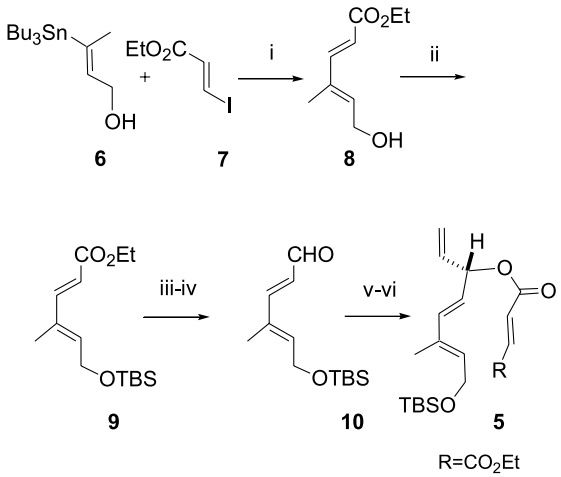
2. Results and discussion

Our strategy for the synthesis of the ABC-rings of **1** was to employ an ester tethered intramolecular Diels–Alder reaction to form the B-ring with appropriate functionality to allow for the synthesis of the A- and C-rings via a reductive annulation protocol. Such a route would install the desired stereochemical triad of the A-ring in one step and form the C-ring with functionality suitable to expedite its union with a DEF-ring precursor unit (Scheme 1).[14]



Scheme 1.

Our initial target was the Diels–Alder precursor **5**. This was prepared in six steps from known vinyl stannane **6**[15] and vinyl iodide **7**[16] via a Stille reaction.[17] Protection of the hydroxyl group of **8** as a TBS ether followed by a $LiAlH_4$ reduction and a subsequent Swern re-oxidation afforded dienal **10**. Attempts to partially reduce the ester **9** to the aldehyde with DIBAL-H were unsuccessful as mixtures of starting ester **9**, aldehyde **10**, and the over reduced alcohol were always obtained. Aldehyde **10** was treated with vinyl magnesiumbromide to afford the alcohol in quantitative yield, which was esterified with monoethyl fumaryl chloride to provide the intramolecular Diels–Alder (IMDA) precursor **5** (Scheme 2). Compound **5** was unstable to purification on silica gel[14] and there was a need to generate it cleanly and use it immediately in the Diels–Alder cycloaddition. A number of conditions were investigated



Scheme 2. Reagents and conditions: (i) $(MeCN)_2PdCl_2$, DMF, 84%; (ii) TBSCl, imidazole, DMF, 100%; (iii) $LiAlH_4$, Et_2O, 0 °C, 82%; (iv) DMSO, $(COCl)_2$, CH_2Cl_2, Et_3N, −78 °C, 75%; (v) vinyl magnesiumbromide, THF, rt, 99%; (vi) $EtO_2CCH{=}CHCOCl$, Et_3N, Et_2O, 0 °C–rt, 95%.

of which only the use of Et_3N in ether at 0 °C gave **5** cleanly. The problems encountered with other conditions were slow formation of Diels–Alder precursor **5** and decomposition products (probably from polymerisation of the starting material) alongside product formation.

With quantities of **5** in hand we were now in a position to consider the intramolecular Diels–Alder reaction we hoped to use to set up the stereochemical relationships of the substituents around the B-ring. There are, however, a few drawbacks of using ester tethered IMDA reactions: they often require more forcing conditions to effect cyclisation than the carbon-based counterparts, which has been

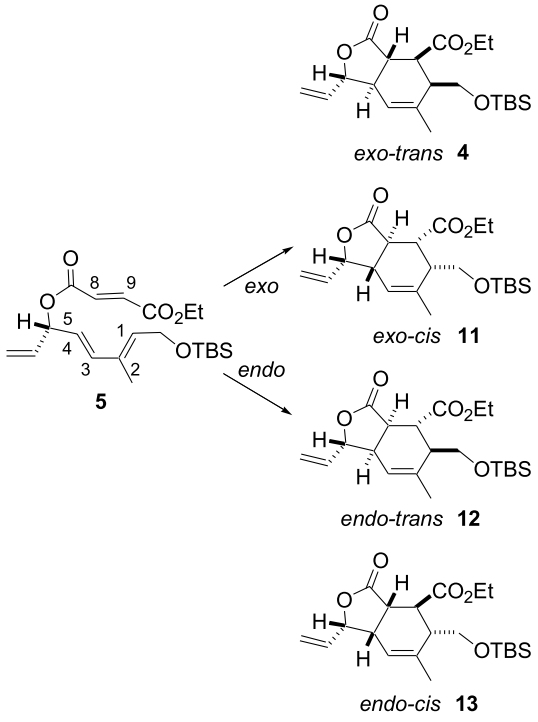


Figure 1.

attributed to an equilibrium disfavouring the *s-cis* conformation of the connecting ester tether. Another problem is susceptibility to polymerisation under the reaction conditions. Despite these potential problems, the IMDA reaction remains an attractive option for forming hydroisobenzofuranone units.[18]

If **5** were to undergo an IMDA reaction then four Diels–Alder adducts are possible (Fig. 1). These products arise from both *exo* and *endo* cyclisation; *exo* cyclisation gives the protons across the ring junction in a *trans* orientation and *endo* cyclisation gives the same protons in a *cis* orientation. For IMDA cyclisations of this type where the tether consists of just three atoms linking the diene to the dienophile, *exo* cyclisation is generally favoured due to a reduced torsional strain compared to that encountered in the *endo* transition state. In this system cyclisation is further complicated by whether the dienophile approaches the diene on the α-face (the same face as the vinyl moiety) or the β-face (the opposite face to the vinyl moiety). Approach from the α-face would result in the *exo-cis* and *endo-cis* adducts being formed and the approach from the β-face in the *exo-trans* and *endo-trans* adducts. The *cis* and *trans* labelling refers to the relationship between the protons at C4 and C5 in the products. The stereochemistry dictated by the synthesis of FR182877 requires *exo*-cyclisation with approach from the β-face of the diene unit, (i.e., the *exo-trans* adduct **4**).

The lack of precedent in the literature for predicting the diastereoselectivities of these ester tethered Diels–Alder reactions was a cause of some concern, and this led us to conduct some MM2 molecular modeling calculations on the various transition states leading to the possible Diels–Alder adducts. Our calculations indicated that β-attack of the dienophile via an *exo*-transition state would be favoured by approx. 1.32 kcal mol^{-1}. Contemporaneously to our own studies Sherburn and Paddon-Row reported a comprehensive computational and synthetic study on the Diels–Alder reactions of ester tethered 1,3,8-nonatrienes.[19] They reported that for C9-substituted trienes the *endo*/*exo* selectivity was strongly dependent on the stereochemistry of the dienophile, (*Z*)-dienophiles showing significant *exo*-selectivity and (*E*)-dienophiles showing a less pronounced *exo*-selectivity. All IMDA transition states displayed a substantial bond forming asynchronicity.[20] The bond forming process is more advanced between C4 and C8 than C1 and C9 in the transition state due to the connecting tether forcing C4 and C8 into close proximity. Strain builds up in the developing lactone ring in the transition state and is alleviated by twisting the transition state about the C4–C8 bond. The twisting involved is more facile for the *exo* transition state than the *endo* transition state explaining to the higher *exo* selectivity they observed. The presence of additional C5 substitution led to enhanced *exo*/*endo* selectivity and influenced the π-diastereofacial selectivity of the IMDA cyclisation. The increased *exo*/*endo* selectivity was explained by additional steric interactions and torsional strain between the C5 substituent and the C4 proton in the *endo* transition states. The π-diastereofacial selectivity of the IMDA cyclisation has been attributed to the minimisation of developing $A^{1,3}$-strain during the intramolecular process. The dienophile approach to the α-face of the diene causes a destabilising eclipsing interaction between the C5 substituent and the H3 visible leading to the *exo-cis* and *endo-cis* products, respectively. The *exo-trans* transition state lacks these destabilising interactions and can therefore be predicted as the major product. Combined with our own calculations, the reports of Sherburn and Paddon-Row gave us confidence that the desired Diels–Alder adduct would predominate.

The IMDA precursor **5** was subjected to Sherburn's reaction conditions[21] and after 24 h, six new products were generated. These were separated by silica gel chromatography and characterised individually by ^{1}H and ^{13}C NMR spectroscopy and identified as **4**, **11**, **12**, **14**, **15** and **16** (Fig. 2). As predicted by ourselves and Sherburn, the major

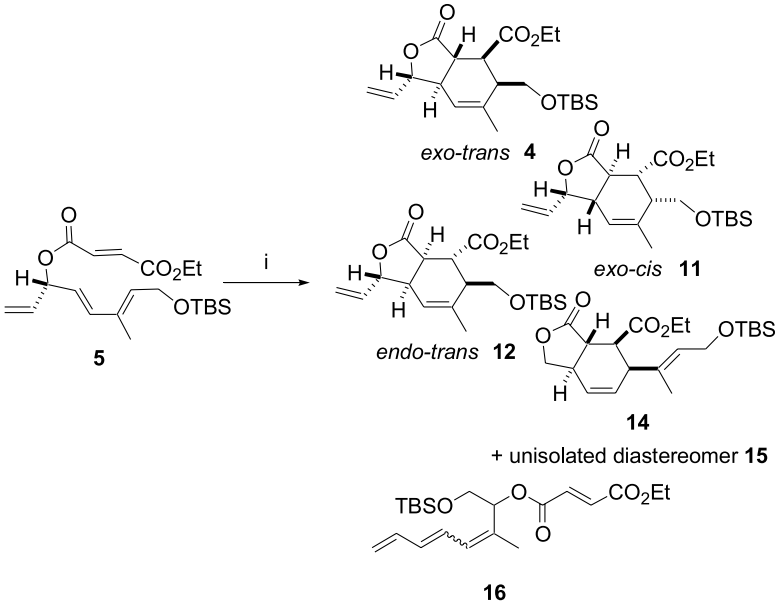


Figure 2. Reagents and conditions: (i) PhMe, BHT, 110 °C, **4** (43%), **11** (8%), **12** (4%), **14** and **15** (6%) and **16** (12%).

Diels–Alder product was the desired *exo-trans* isomer **4** obtained in 43% yield, with the *exo-cis* isomer **11** in 8% yield and an *endo* isomer **12** in 4% yield. The stereochemistry for *exo*-cycloadducts **4** and **11** were determined by NOE studies (Fig. 3) but unfortunately the stereochemistry of the *endo*-adduct could not be determined due to inconclusive results. However, due to the precedent set by the work of Sherburn we tentatively assigned **12** as the *endo-trans* adduct. Three other products were also produced, one of which (**16**) still contained the characteristic peaks in the ^{1}H NMR spectrum of a highly unsaturated system. Products **14** and **15** were isolated as a mixture after repeated flash chromatography. The major component **14** was finally isolated after extensive chiral HPLC separations.[22] Unfortunately **15**, which looked like the diastereomer of **14**, from the NMR spectrum of the product mixture, could not be isolated in this manner. The structure of **16** was assigned by 2D-correlation NMR spectroscopy and ^{13}C NMR data was in agreement. Compound **14** was assigned by 2D-correlation NMR spectroscopic and gradient NOE experiments (Fig. 3).

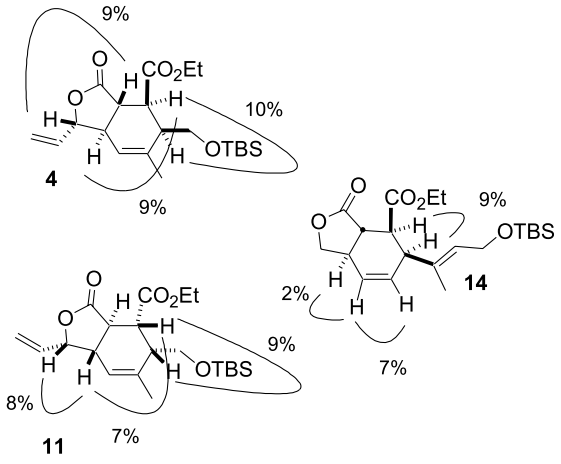
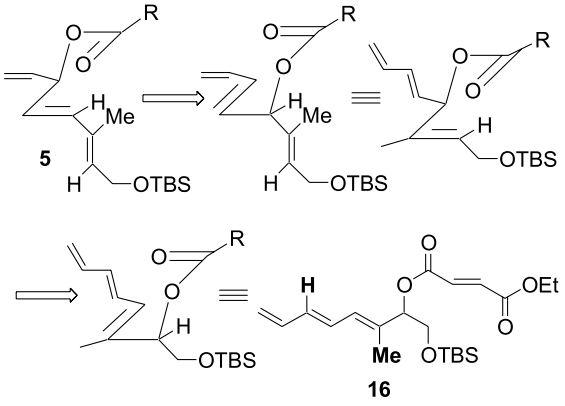


Figure 3.

Products **14**, **15** and **16** appear to be the result of rearrangement of the IMDA precursor with subsequent IMDA cyclisation in the case of products **14** and **15**. These rearrangements could occur via three possible mechanisms: ionic transposition; [3,3]-sigmatropic rearrangement of the fumarate group along the carbon chain or direct [1,5] migration. If the rearrangements occurred via an ionic transposition, scrambling of the double bond geometry might be expected. In the case of product **16** only one isomer was isolated, detected by the presence of a single set of signals in the ^{13}C NMR spectrum. However, the double bond geometry could not be determined due to overlapping signals in the ^{1}H NMR spectrum. Based on literature precedent for sigmatropic rearrangements on similar systems, and because only one stereoisomer of **14** was observed, rearrangement by [3,3]-sigmatropic transposition of the fumarate group is favoured. Two consecutive [3,3]-sigmatropic rearrangements of **5** via the proposed chair-like transition states shown in Scheme 3 result in the *trans,trans*-conjugated triene of **16**. Interestingly, when **16** was resubjected to Diels–Alder cyclisation conditions, no further reaction was observed. This finding may be attributed to the anticipated steric clash between the proton H5 and the methyl group in compound **16** disfavouring the adoption of a *s-cis* conformation required for Diels–Alder reaction.



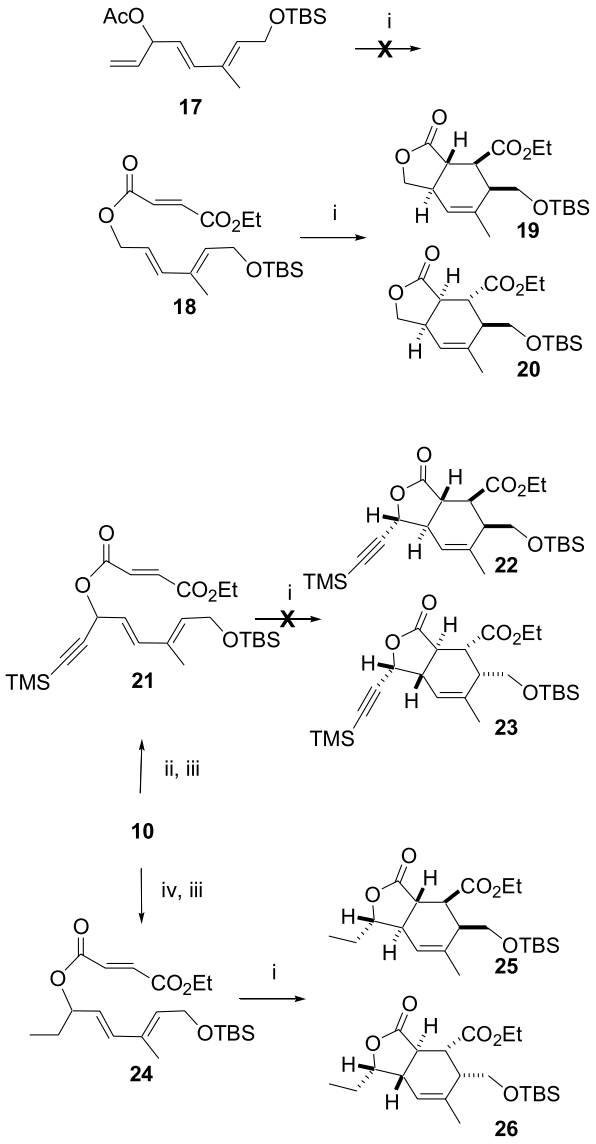
Scheme 3.

A single [3,3]-sigmatropic rearrangement of **5** with the fumarate moving in the opposite direction, towards the vinyl group affords an appropriate IMDA precursor. As this precursor was not observed in the reaction it suggested that its IMDA cyclisation is very facile. When the Diels–Alder cyclisation of **5** was attempted using diethylaluminium chloride as a Lewis acid catalyst, **14** and **15** were the only identifiable products albeit in only a combined 41% yield.

Similar rearrangements to this have been previously reported by Eberle in his study on the thermal reactions of monoethyl fumarates and acetates of 1-phenyl-2,4-hexadiene-1-ol.[23] In the case of the acetates [3,3]-sigmatropic rearrangements took place to give the fully conjugated allylic alcohol. When the monoethyl fumarates were used rearrangement took place followed by a Diels–Alder cyclisation to give a bicyclic lactone. Eberle suggested that the driving force for this facile rearrangement was the formation of a system with extended conjugation.

Intrigued by these rearrangements, of which the driving force appeared to be the formation of a conjugated triene, we made a number of alterations to precursor **5** and examined the effect on the rearrangements. Firstly, acetate **17** was synthesised by acylation of the precursor to **5** with acetyl chloride, and subjected to the rearrangement conditions. Somewhat surprisingly, after 3 days and contrary to the studies by Eberle, only starting acetate **17** was observed (Scheme 4).

Next, the C5 substituents were varied to include both saturated and alternative unsaturated groups. The unsaturated group chosen for the C5 substituent was TMS-acetylene, selected as a possible masking group for the vinyl functionality. If the product ratio favoured the *exo-trans* cyclisation product it could be incorporated into the synthesis of FR182877 and then later removed to reveal the vinyl moiety. A proton **18** and an ethyl group **24** were selected as the saturated substituent. The requisite IMDA precursors were prepared from **10** via addition of lithium TMS-acetylide or ethyl magnesiumbromide, and esterified

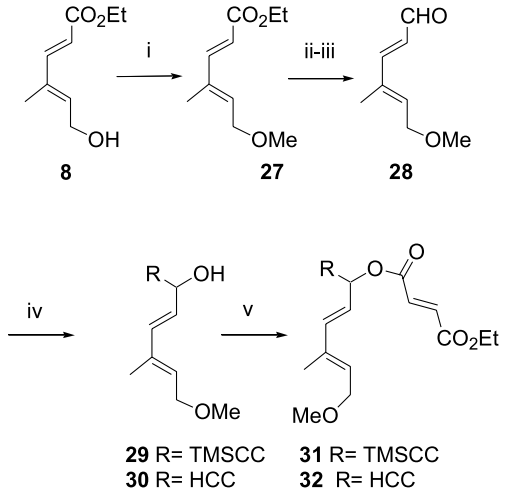


Scheme 4. Reagents and conditions: (i) PhMe, BHT, 110 °C, **19** 42%, **20** 21%, **25**:**26** 7:1 (52%); (ii) Lithium TMS-acetylide, THF, −20 °C–rt, 86%; (iii) $EtO_2CCH{=}CHCOCl$, Et_3N, Et_2O, 0 °C–rt, **21** 87%, **24** 89%; (iv) Ethyl magnesiumbromide, THF, rt, 85%.

with monoethyl fumaryl chloride, in the manner previously employed for the synthesis of **5**. This afford Diels–Alder precursors **18**, **21** and **24**.

The partition between Diels–Alder cyclisation and the rearrangement process was examined. Compounds **18**, **21** and **24** were heated individually to 110 °C in toluene in the presence of BHT. Triene **18** only underwent Diels–Alder cyclisation generating the *exo*-cycloadduct **19** as the major product in 42% yield with the *endo*-cycloadduct **20** in 21% yield. Rearrangement also failed to occur when triene **24** bearing an ethyl group at C5 was heated under the reaction conditions. In this case Diels–Alder cyclisation furnished a mixture of *exo-trans* (**25**) and *exo-cis* (**26**) in a 7:1 ratio and a combined yield of 52%. No *endo* products were observed by 400 MHz ^{1}H NMR spectroscopy. Unfortunately only the major *exo-trans* adduct was isolated in pure form. Neither the Diels–Alder cycloadducts nor the rearrangement products were isolated from the reaction involving the TMS-acetylene bearing substrate **21**. The ^{1}H NMR spectrum of the crude reaction mixture was rather complicated showing some starting material peaks and a lot of silyl residue. We believe that the complex nature of this spectrum is due to decomposition under the reaction conditions.

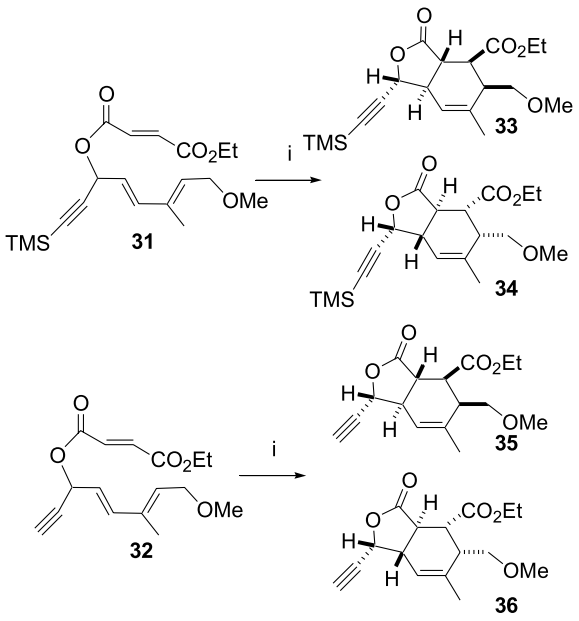
Due to this apparent decomposition it was decided to investigate the effect of changing the alcohol protecting group from a TBS ether to a methyl ether. To this end, the hydroxyl in compound **8** was protected as its methyl ether **27** using a silver(I) oxide-mediated reaction in quantitative yield. Traditional ether formation using sodium hydride to deprotonate the alcohol **8** resulted in polymerisation. The ester was then converted to the aldehyde via complete reduction to the alcohol and Swern re-oxidation (Scheme 5). Both lithium TMS-acetylide and ethynyl magnesium-bromide were added to aldehyde **28** to furnish alcohols **29** and **30**, respectively (Scheme 5). Alcohols **29** and **30** were esterified with monoethyl fumaryl chloride to afford IMDA precursors **31** and **32**, respectively.



Scheme 5. Reagents and conditions: (i) Ag_2O, MeI, rt, 99%; (ii) $LiAlH_4$, Et_2O, 0 °C, 78%; (iii) $(COCl)_2$, DMSO, CH_2Cl_2, Et_3N, −78 °C, 90%; (iv) For **29**: Lithium TMS-acetylide, THF, −20 °C–rt, 91%. For **30**: ethynyl magnesiumbromide, THF, rt, 75%; (v) $EtO_2CCH{=}CHCOCl$, Et_3N, Et_2O, 0 °C–rt, **31** 92%, **32** 85%.

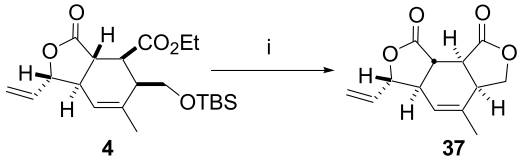
Upon heating under our now standard conditions it was found that both **31** and **32** only underwent Diels–Alder cyclisations. Triene **31** provided a mixture of *exo* adducts **33** and **34** in a 3:1 ratio and a combined yield of 46%, while triene **32** afforded a mixture of *exo* adducts **35** and **36** in a 3:1 ratio and a combined yield of 56% (Scheme 6). Unfortunately, all attempts to separate **33** from **34** and **35** from **36** failed, this combined with the low yields halted further investigation of these substrates. We therefore turned our attention to the conversion of **4** to **3**, the substrate required for reductive annulation of the A- and C-rings (Scheme 1).

Our plan was to deprotect the TBS ether to reveal the hydroxyl group, which could be converted to a leaving group and subsequently displaced with acetylide. To this end **4** was treated with TBAF in THF which resulted in loss



Scheme 6. Reagents and conditions: (i) PhMe, BHT, 110 °C, **33** and **34** 3:1 ratio (46%), **35** and **36** 3:1 ratio (56%).

of the TBS group and spontaneous lactonisation to afford *bis*-lactone **37** (Scheme 7). Attempts to buffer the reaction with NH_4Cl did not alleviate the problem. The deprotection was also attempted with DDQ,[24] hydrogen fluoride amine complexes buffered with pyridine[25] and triethylamine,[26] however, only starting material was isolated in these cases.



Scheme 7. Reagents and conditions: (i) TBAF, THF, NH_4Cl, rt, 52%.

Due to the extreme difficulty in manipulating the *cis*-lactone in the presence of the *trans*-lactone, it was decided to synthesise a homologated series, with an extra methylene group between the B-ring and the silyl ether to give **38**. It was hoped that **38** would not lactonise upon deprotection, as six-membered lactones usually form at a slower rate than analogous five-membered lactones, due to a greater loss of entropy.[27] If lactonisation were to occur, the product would contain both a five- and six-membered lactone **39** (Fig. 4). It may, therefore, be possible to open the unsubstituted six-membered lactone in the presence of the substituted five-membered lactone.

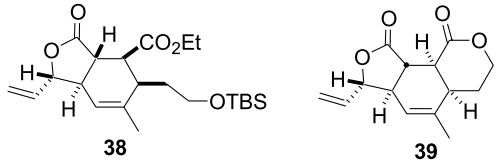
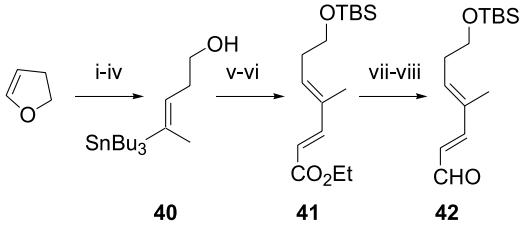


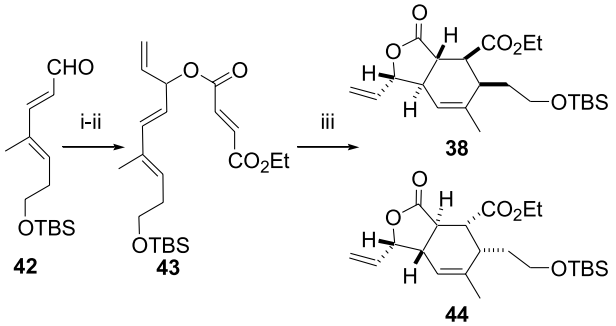
Figure 4.

The homologated analogue **38** was to be synthesised via a Diels–Alder cyclisations by installing the extra methylene group in the diene portion of the Diels–Alder precursor prior to IMDA cyclisation. Stannyl alcohol **40** was prepared from 2,3-dihydrofuran via a copper-mediated 1,2-metallate rearrangement.[28] The resultant cuprate was reacted with methyl iodide to afford the (*E*)-stannyl alcohol **40** as a single isomer by ^1H and ^{13}C NMR spectroscopy. Stille coupling of **40** with (*E*)-ethyl 3-iodoacrylate followed by TBS protection affored **41**. A sequence of $LiAlH_4$ reduction and Swern re-oxidation provided quantities of **42** (Scheme 8).



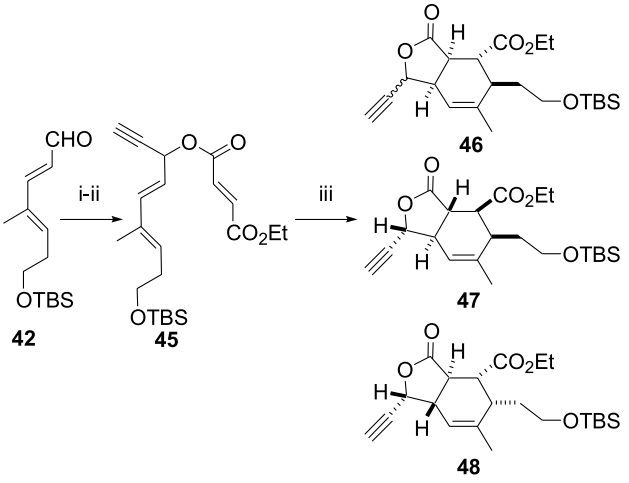
Scheme 8. Reagents and conditions: (i) ^{t}BuLi, THF, −78–0 °C, 1 h; (ii) CuCN, Et_2O:THF (1.6:1), ^{n}BuLi, Bu_3SnH, −35 °C, 1 h, then added to lithiated dihydrofuran, −35–0 °C, 2 h; (iii) MeI, −30 °C–rt, 3.5 h; (iv) saturated aqueous NH_4Cl and concentrated ammonia solution (4:1), 0 °C–rt, 85%; (v) (*E*)-ethyl 3-iodoacrylate, DMF, $Pd(MeCN)_2Cl_2$, rt, 90%; (vi) TBSCl, DMF, imidazole, rt, 94%; (vii) $LiAlH_4$, Et_2O, 0 °C, 93%; (viii) DMSO, $(COCl)_2$, CH_2Cl_2, Et_3N, −78 °C, 84%.

Vinyl magnesiumbromide was added to aldehyde **42** to afford the alcohol, which was subsequently treated with monoethyl fumaryl chloride to provide the IMDA precursor **43** in an isolated yield of 57% (Scheme 9). The Diels–Alder precursor **43** was subjected to the standard cyclisation conditions to generate two Diels–Alder cycloadducts **38** and **44** which were isolated in a combined yield of only 13% (ratio 3:1). The remaining material could not be identified, but was probably the result of polymerisation of the starting material, a problem that has been previously reported on similar substrates.[29] Repeated flash chromatography of the two cycloadducts afforded only the major adduct in pure form. A coupling constant of 13.4 Hz for the protons across the ring junction revealed an *exo*-cycloadduct. The stereochemical relationship between the protons at H4 and H5 of **38** could not be conclusively assigned, due to overlapping peaks in NOE NMR studies. Due to the absence of a NOE signal between H4 and H5, it was tentatively concluded that the major cycloadduct from the cyclisation of **43** was the *exo-trans* adduct **38**.



Scheme 9. Reagents and conditions: (i) vinyl magnesiumbromide, THF, rt, 92%; (ii) monoethyl fumaryl chloride, Et_2O, Et_3N, 0 °C–rt, 57%; (iii) PhMe, catalytic BHT, reflux, **38** (10%), **44** (3%).

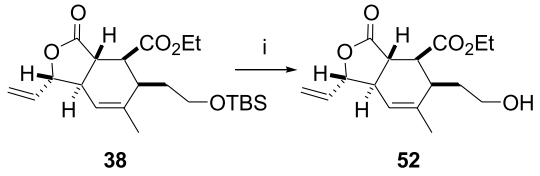
Masking the vinyl group as an acetylene was investigated to see whether an improvement in yield of the *exo-trans* cycloadduct could be obtained. Ethynyl magnesiumbromide was added to aldehyde **42** and the resultant alcohol esterified with monoethyl fumaryl chloride to afford IMDA precursor **45** (Scheme 10). Diels–Alder cyclisation of **45** afforded three cycloadducts. Flash chromatography provided pure samples of all three adducts whose structures were assigned from coupling constants of the ring junction protons, and in the case of **48** by NOE studies, as the *endo* adduct **46** (4%) ($J=8.4$ Hz), and two *exo*-cycloadducts *exo-trans* **47** (10%) and *exo-cis* **48** (38%) ($J=13.7$ Hz). The reversal in selectivity from *exo-trans* to *exo-cis* is probably due to the reduced steric clash between the alkyne substituent and H3 and H8 in the transition state. Unfortunately the relative stereochemistry of H4 and H5 in the *endo* adduct could not be determined in this manner.



Scheme 10. Reagents and conditions: (i) ethynyl magnesiumbromide, THF, rt, 88%; (ii) monoethyl fumaryl chloride, Et_2O, Et_3N, 0 °C–rt, 65%; (iii) PhMe, reflux, **46** (4%), **47** (10%), **48** (38%).

Intrigued by the reversal of selectivity in the IMDA cyclisation, we decided to see what effect, if any, a TMS-acetylene would have on the selectivity. TMS-acetylene was deprotonated with *n*-butyllithium and added to aldehyde **42** (Scheme 11). The resultant alcohol was esterified with monoethyl fumaryl chloride to afford the IMDA precursor **49**. The Diels–Alder precursor **49** was subjected to the standard cyclisation conditions to provide two cycloadducts **50** and **51** which were easily separated. The major adduct **50** was isolated in 39% yield and the minor adduct **51** was isolated in 10% yield. Subsequent ^{1}H NMR spectroscopy revealed both to be *exo*-adducts with coupling constants of 13.6 Hz for the protons across the ring junction. The NOE NMR spectroscopic studies were carried out on the minor product **51**, which revealed better separation of peaks in the ^{1}H NMR spectrum. The minor product was confirmed as the *exo-trans* adduct, as NOE signals were observed between H1 and H9 7%, between H4 and H9 8%, and H5 and H8 7%.

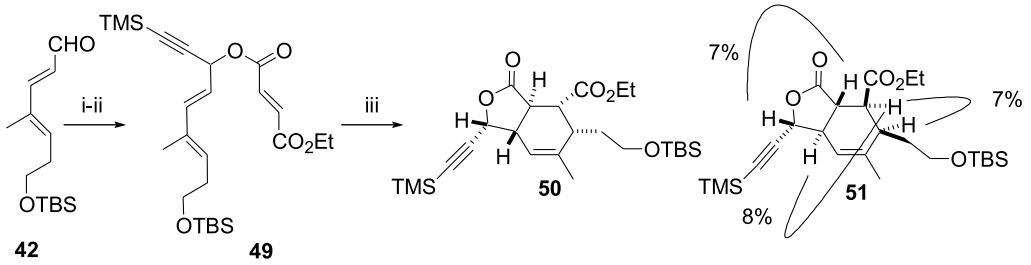
Despite the disappointing yields and selectivities in the homologated series we attempted the removal of the TBS group in **38** with TBAF buffered with NH_4Cl and gratifyingly no lactonisation occurred, yielding the free alcohol **52** in 54% (Scheme 12). Unfortunately, due to the poor yields in the Diels–Alder reaction of the homologated series and the reversal in selectivity when an acetylene group was substituted at C5 we were unable to progress further with the synthesis of the ABC-rings of FR182877 using this strategy.



Scheme 12. Reagents and conditions: (i) TBAF, THF, NH_4Cl, 0 °C–rt, 54%.

3. Conclusions

Diels–Alder reactions of C5 substituted 6-fumaryl 1,3,8-nonatrienes have been studied with an aim to synthesise the ABC-rings of FR182877. While the desired *exo-trans* stereoisomer for the synthesis of the ABC-rings of FR182877 predominated in our initial investigations, progress towards the ABC-rings were hampered and ultimately abandoned due to unexpected competing [3,3]-sigmatropic rearrangements of the Diels–Alder precursors and low yields. This [3,3]-sigmatropic rearrangement seems to be driven by the formation of a thermodynamically more stable conjugated triene unit. Interestingly, when the C5 substituent is changed from a vinyl unit to an acetylene unit a reversal of the stereoselectivity occurs, favouring the undesired *exo-cis* diastereomer. We propose that this change in stereoselectivity is a result of a minimization of a transannular interaction between the C5 substituent and H8 in the transition states of the cyclisation reaction. To our knowledge this is the first time that such a switch in diastereoselectivity has been noted in the Diels–Alder



Scheme 11. Reagents and conditions: (i) lithium TMS-acetylide, THF, 0 °C–rt, 80%; (ii) monoethyl fumaryl chloride, Et_2O, Et_3N, 0 °C–rt, 79%; (c) PhMe, catalytic BHT, reflux, **50** (39%) **51** (10%).

reactions of C5 substituted 6-fumaryl 1,3,8-nonatrienes. As such these observations compliment the previous studies by Sherburn and Paddon-Row and will be of use to those seeking to use the Diels–Alder reactions of C5 substituted 6-fumaryl 1,3,8-nonatrienes in synthesis.

4. Experimental

4.1. General

All melting points are uncorrected. Reaction progress was monitored using glass-backed TLC plates pre-coated with silica UV_{254} and visualized by using either UV radiation (254 nm), ceric ammonium molybdate or anisaldehyde stains. Column chromatography was performed using silica gel 60 (220–240 mesh), with the solvent systems indicated in the relevant experimental procedures. Dichloromethane was distilled from calcium hydride; tetrahydrofuran and diethyl ether were distilled from sodium/benzophenone ketyl, dimethyl formamide was stirred with calcium hydride and distilled prior to use. Benzene, DMSO and MeCN were all distilled from calcium hydride prior to use. Hexane was distilled prior to use. All other reagents were used as received from commercial suppliers unless stated otherwise in the appropriate text.

4.1.1. Ethyl (*E*,*E*)-6-hydroxy-4-methylhexa-2,4-dienoate (8). Reaction of stannyl alcohol **6** (5.80 g, 16.1 mmol) with (*E*)-ethyliodoacrylate **7** (3.81 g, 16.9 mmol) in *N*,*N*-dimethylformamide (20 mL) and a substoichiometric amount of dichloro-*bis*-acetonitrile palladium(II) (0.21 g, 0.80 mmol) was carried out under the conditions described in the literature.[17] The crude oil was purified by flash chromatography on silica (silica treated with 1% triethylamine, 3:1 petroleum ether–ethyl acetate) to afford alcohol **8** as a pale yellow oil (2.38 g, 87%). R_f (silica): 0.20 (2:1 petroleum ether–ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31 (1H, d, J=15.8 Hz), 6.02 (1H, t, J=6.4 Hz), 5.89 (1H, d, J=15.8 Hz), 4.36 (2H, d, J=6.4 Hz), 4.22 (2H, q, J=7.1 Hz), 1.81 (3H, s), 1.31 (3H, t, J=7.1 Hz); ^{13}C NMR (67.8 MHz, $CDCl_3$): δ 167.4 (C), 148.5 (CH), 139.1 (CH), 133.8 (C), 117.5 (CH), 60.4 (CH_2), 59.4 (CH_2), 14.2 (CH_3), 12.4 (CH_3); IR (ν_{max} cm^{-1}): 3425 (*O–H*), 2952 (*C–H*), 1717 (*C=O*); LRMS (CI, CH_4) *m/z* 341 [2×M+H]$^+$ (30%), 171 [M+H]$^+$ (100), 153 (50); HRMS (CI, CH_4) *m/z*. Found: [M+H]$^+$ 171.1021, $C_9H_{15}O_3$ requires: 171.1021.

4.1.2. Ethyl (*E*,*E*)-6-(*tert*-butyldimethylsilanyloxy)-4-methylhexa-2,4-dienoate (9). Precursor alcohol (0.20 g, 1.2 mmol) was protected as the silyl ether using chloro-*tert*-butyldimethylsilane (0.18 g, 1.2 mmol) and imidazole (0.12 g, 1.8 mmol) dissolved in the minimum amount of *N*,*N*-dimethylformamide (3 mL). When complete the reaction mixture was diluted with diethyl ether, and washed with saturated aqueous solutions of copper sulphate (×2), sodium hydrogen carbonate and finally brine (×2), then dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography on silica gel using a gradient elution system (silica treated with 1% triethylamine, 19:1 petroleum ether–ethyl acetate to 2:1 petroleum ether–ethyl acetate) to afford **9** as a yellow oil (0.31 g, 93%). R_f (silica): 0.75 (2:1 petroleum ether–ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32 (1H, d, J=15.9 Hz), 5.87 (1H, t, J=6.0 Hz), 5.83 (1H, d, J=15.9 Hz), 4.37 (2H, d, J=6.0 Hz), 4.22 (2H, q, J=7.1 Hz), 1.77 (3H, s), 1.31 (3H, t, J=7.1 Hz), 0.91 (9H, s), 0.08 (6H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.3 (C), 148.6 (CH), 140.4 (CH), 132.5 (C), 117.1 (CH), 60.4 (CH_2), 60.3 (CH_2), 25.9 (CH_3), 18.3 (C), 14.3 (CH_3), 12.4 (CH_3), −5.1 (CH_3), −5.2 (CH_3); IR (ν_{max} cm^{-1}): 2955 (*C–H*), 2930 (*C–H*), 2885 (*C–H*), 2857 (*C–H*), 1714 (*C=O*); LRMS (CI, CH_4): *m/z* 285 [M+H]$^+$ (67%), 227 (100), 211 (52), 153 (56); HRMS (CI, CH_4) *m/z*. Found: [M+H]$^+$ 285.1876, $C_{15}H_{29}O_3Si$ requires: 285.1886.

4.1.3. Reduction of 9 to give (*E*,*E*)-6-(*tert*-butyldimethylsilanyloxy)-4-methylhexa-2,4-dien-1-ol. Ester **9** (3.09 g, 10.9 mmol) was reduced with lithium aluminium hydride (0.630 g, 16.3 mmol) in diethyl ether (80 mL). The reaction mixture was stirred for 30 min and then quenched with water (1.0 mL), an aqueous solution of sodium hydroxide (1.0 mL, 2 M) and again with water (2.9 mL). The resultant suspension was diluted with diethyl ether (250 mL) and filtered through celite. The filtrate was dried ($MgSO_4$), and the solvent evaporated to give a yellow oil. The crude material was purified by flash chromatography on silica gel (4:1 petroleum ether–ethyl acetate) to afford the title compound as a colourless oil (2.15 g, 82%). R_f (silica): 0.60 (2:1 petroleum ether–ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.26 (1H, d, J=15.7 Hz), 5.79 (1H, dt, J=15.7, 5.8 Hz), 5.59 (1H, t, J=6.2 Hz), 4.32 (2H, d, J=6.2 Hz), 4.20 (2H, t, J=5.8 Hz), 1.75 (3H, s), 0.90 (9H, s), 0.07 (6H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 135.7 (CH), 133.4 (C), 132.0 (CH), 128.3 (C), 127.1 (CH), 63.7 (CH_2), 60.3 (CH_2), 26.0 (CH_3), 18.4 (C), 12.7 (CH_3), −5.0 (CH_3); IR (ν_{max} cm^{-1}): 3509 (*O–H*), 3444 (*O–H*), 2952 (*C–H*), 2929 (*C–H*), 2857 (*C–H*); LRMS (CI, CH_4): *m/z* 225 (100%), 93 (60%); HRMS (CI, CH_4) *m/z*. Found: [M+H]$^+$ 243.1775, $C_{13}H_{27}O_2Si$ requires: 243.1780.

4.1.4. (*E*,*E*)-6-(*tert*-Butyldimethylsilanyloxy)-4-methylhexa-2,4-dienal (10). Dry dimethyl sulphoxide (0.53 mL, 7.5 mmol) diluted in dichloromethane (11 mL) was added to oxalyl chloride (0.33 mL, 3.8 mmol) in dichloromethane (11 mL) over 10 min at −78 °C. and stirred for 45 min. The alcohol (*E*,*E*)-6-(*tert*-Butyldimethylsilanyloxy)-4-methylhexa-2,4-dien-1-ol (0.45 g, 1.9 mmol) in dichloromethane (5.5 mL) was added over a 10 min period and stirred for 1 h at −78 °C, after which triethylamine (3 mL, 20 mmol) was added over a 15 min period and reaction mixture allowed to warm slowly to rt. The product was extracted with dichloromethane, washed with aqueous solutions of hydrochloric acid (1 M), saturated sodium hydrogen carbonate, and brine (×2), dried ($MgSO_4$) and concentrated. The oil was purified by flash chromatography on silica gel (silica treated with 1% triethylamine, 19:1 petroleum ether–ethyl acetate) to afford aldehyde **10** as a yellow oil (0.34 g, 75%). R_f (silica): 0.75 (2:1 petroleum ether–ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.58 (1H, d, J=7.8 Hz), 7.12 (1H, d, J=15.6 Hz), 6.15 (1H, dd, J=15.6, 7.8 Hz), 6.09 (1H, t, J=5.9 Hz), 4.40 (2H, d, J=5.9 Hz), 1.81 (3H, s), 0.91 (9H, s), 0.08 (6H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.6, 156.4, 142.5, 132.6, 127.7, 60.3, 25.7, 18.1, 12.4, −5.4; IR (ν_{max} cm^{-1}): 2954 (*C–H*), 2926 (*C–H*), 2856

(*C–H*), 1679 (*C=O*); LRMS (CH_4): *m/z* 240 $[M]^+$ (70%), 223 (83), 183 (100), 109 (47), 81 (37); HRMS (CH_4) *m/z*. Found: $[M]^+$ 240.1547, $C_{13}H_{24}O_2Si$ requires: 240.1546.

4.1.5. (*E,E*)-8-(*tert*-Butyldimethylsilanyloxy)-6-methylocta-1,4,6-trien-3-ol. Vinyl magnesiumbromide (1.7 mL, 1 M in THF, 1.7 mmol) was added to aldehyde **10** (0.33 g, 1.4 mmol) in THF (10 mL). When complete the reaction was quenched with a saturated solution of ammonium chloride, and diluted with ethyl acetate. The organic layer was washed with 1 M aqueous hydrochloric acid (×2) and the aqueous layers were back extracted with ethyl acetate. The combined organics were washed with saturated aqueous sodium hydrogen carbonate and brine, dried ($MgSO_4$) and concentrated to give the crude alcohol which was purified by flash chromatography on silica gel (silica treated with 1% triethylamine, 9:1 petroleum ether–ethyl acetate) to afford a pale yellow oil (0.37 g, 99%). R_f (silica): 0.65 (2:1 petroleum ether–ethyl acetate); ^1H NMR (400 MHz, $CDCl_3$): δ 6.27 (1H, d, $J=15.8$ Hz), 5.92 (1H, ddd, $J=17.2$, 10.4, 5.9 Hz), 5.66 (1H, dd, $J=15.8$, 6.7 Hz), 5.61 (1H, t, $J=6.2$ Hz), 5.28 (1H, ddd, $J=17.2$, 1.4, 1.4 Hz), 5.15 (1H, ddd, $J=10.3$, 1.4, 1.4 Hz), 4.70 (1H, dd, $J=6.7$, 5.9 Hz), 4.32 (2H, d, $J=6.2$ Hz), 1.75 (3H, s), 0.91 (9H, s), 0.08 (6H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.6 (CH), 135.4 (CH), 133.4 (C), 132.5 (CH), 128.9 (CH), 115.1 (CH_2), 73.9 (CH), 60.3 (CH_2), 26.0 (CH_3), 18.4 (C), 12.7 (CH_3), 1.07 (CH_3), −5.0 (CH_3); IR (ν_{max} cm^{-1}): 3600 (*O–H*), 2954 (*C–H*), 2929 (*C–H*), 2884 (*C–H*), 2857 (*C–H*); LRMS (CI, CH_4): *m/z* 267 $[M-H]^+$ (20%), 251 (100), 252 (35), 253 (30), 137 (35), 132 (20), 121 (53), 119 (48); HRMS (CI, CH_4) *m/z*. Found: $[M-H]^+$ 267.1778, $C_{15}H_{28}O_2Si$ requires: 267.1780.

4.1.6. Ethyl (*E,E*)-6-(*tert*-butyldimethylsilanyloxy)-4-methyl-1-vinylhexa-2,4-dienyl fumarate (5). To (*E,E*)-8-(*tert*-butyldimethylsilanyloxy)-6-methylocta-1,4,6-trien-3-ol (93 mg, 0.35 mmol) in diethyl ether (8 mL) was added triethylamine (0.10 mL, 0.70 mmol) and stirred for 10 min at 0 °C before ethyl fumaryl chloride (64 mg, 0.39 mmol) was added diluted in diethyl ether (0.5 mL). The reaction was stirred for a further 10 min at 0 °C and then warmed to rt and stirred for 18 h. The reaction was quenched with a saturated aqueous solution of sodium hydrogen carbonate and stirred for 1 h. The reaction mixture was diluted with ethyl acetate and washed sequentially with saturated aqueous solutions of copper sulphate, sodium hydrogen carbonate and brine. The organic layer was dried (Na_2SO_4) and concentrated to afford a yellow oil (0.13 g, 95%). R_f (silica): 0.80 (2:1 petroleum ether–ethyl acetate); ^1H NMR (400 MHz, C_6D_6): δ 7.06–6.90 (2H, m), 6.29 (1H, d, $J=16.8$ Hz), 5.95 (1H, t, $J=7.1$ Hz), 5.74 (1H, ddd, $J=17.2$, 10.5, 6.1 Hz), 5.68 (1H, t, $J=6.0$ Hz), 5.57 (1H, dd, $J=15.7$, 7.1 Hz), 5.18 (1H, ddd, $J=17.2$, 1.2, 1.2 Hz), 4.99 (1H, ddd, $J=10.5$, 1.2, 1.2 Hz), 4.19 (2H, d, $J=6.2$ Hz), 3.84 (2H, q, $J=7.1$ Hz), 1.50 (3H, d, $J=0.8$ Hz), 0.97 (9H, s), 0.84 (3H, t, $J=7.1$ Hz), 0.05 (6H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.0 (C), 164.0 (C), 138.1 (CH), 135.0 (CH), 133.9 (CH), 133.7 (CH), 132.9 (C), 123.9 (CH), 117.7 (CH_2), 77.3 (CH), 76.3 (CH), 60.4 (CH_2), 60.2 (CH_2), 26.0 (CH_3), 18.4 (C), 14.2 (CH_3), 12.6 (CH_3), 1.1 (CH_3), −5.1 (CH_3). IR (ν_{max} cm^{-1}): 2918 (*C–H*), 2897 (*C–H*), 2862 (*C–H*), 2801 (*C–H*), 1725 (*C=O*), 1708 (*C=O*).

4.1.7. Diels–Alder cyclisation of ethyl (*E,E*)-6-(*tert*-butyldimethylsilanyloxy)-4-methyl-1-vinylhexa-2,4-dienyl fumarate (5). Fumarate ester **5** (0.10 g, 0.25 mmol) was heated under reflux in toluene (35 mL) in the presence of BHT (3.0 mg, 13 μmol) to afford an orange residue after removal of solvent. Repeated flash chromatography on silica gel using a gradient elution system (silica treated with 1% triethylamine, 9:1 petroleum ether–diethyl ether to 1:1 petroleum ether–diethyl ether) afforded pure samples of an *exo-cis* adduct **11** (7.4 mg, 7%), an *exo-trans* adduct **4** (39.0 mg, 39%), an *endo* adduct **12** (3.8 mg, 4%), an acyclic rearrangement product **16** (11.0 mg, 11%) and a mixture of cyclised rearrangement products **14** and **15** (6.2 mg, 6%). The mixture of cyclised rearrangement products were separated using chiral HPLC and the major diastereomeric product **14** isolated and partially characterised before it decomposed.

4.1.8. Ethyl (1*R,2*R**,3*S**,6*S**,7*S**)-3-(*tert*-butyldimethylsilanyloxymethyl)-4-methyl-9-oxo-7-vinyl-8-oxabicyclo-[4.3.0]-non-4-ene-2-carboxylate (11).** R_f (silica): 0.40 (2:1 petroleum ether–diethyl ether). ^1H NMR (400 MHz, C_6D_6): δ 5.53 (1H, ddd, $J=15.8$, 10.7, 5.1 Hz) 5.20 (1H, ddd, $J=17.1$, 1.5, 1.5 Hz), 5.08 (1H, dd, $J=1.4$, 1.4 Hz), 5.01 (1H, ddd, $J=10.7$, 1.5, 1.5 Hz), 4.44 (1H, dd, $J=5.1$, 1.6 Hz), 4.27–4.09 (2H, m), 3.59 (1H, dd, $J=10.9$, 4.4 Hz), 3.46 (1H, dd, $J=13.0$, 2.1 Hz), 3.18 (1H, dd, $J=14.0$, 11.7 Hz), 2.74 (1H, dd, $J=11.7$, 6.9 Hz), 2.30 (1H, m), 2.21 (1H, m), 1.44 (3H, s), 1.15 (3H, t, $J=7.2$ Hz), 0.89 (9H, s), 0.02 (6H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.3 (C), 171.0 (C), 137.3 (C), 131.3 (CH), 120.6 (CH), 119.3 (CH_2), 80.2 (CH), 61.6 (CH_2), 60.8 (CH_2), 45.4 (CH), 44.3 (CH), 37.3 (CH), 25.9 (CH), 21.9 (CH_3), 18.4 (C), 14.2 (CH_3), −5.5 (CH_3), −5.7 (CH_3). IR (ν_{max} cm^{-1}): 2990 (*C–H*), 2946 (*C–H*), 2885 (*C–H*), 2858 (*C–H*), 1779 (*lactone C=O*), 1731 (*ester C=O*); LRMS (CI, NH_3): *m/z* 395 $[M+H]^+$ (60%), 369 (35), 132 (50), 123 (40), 109 (100), 92 (60), 91 (75), 90 (40), 84 (40), 74 (45), 72 (55), 68 (35), 60 (35); HRMS (ES) *m/z*. Found: $[M+H]^+$ 395.2241, $C_{21}H_{35}O_5Si$ requires: 395.2248.

4.1.9. Ethyl (1*S,2*S**,3*R**,6*R**,7*S**)-3-(*tert*-butyldimethylsilanyloxymethyl)-4-methyl-9-oxo-7-vinyl-8-oxabicyclo-[4.3.0]-non-4-ene-2-carboxylate (4).** R_f (silica): 0.40 (2:1 petroleum ether–diethyl ether). ^1H NMR (400 MHz, $CDCl_3$): δ 5.86 (1H, ddd, $J=17.3$, 10.5, 7.1 Hz), 5.61 (1H, d, $J=1.4$ Hz), 5.46 (1H, ddd, $J=17.3$, 1.0 Hz), 5.36 (1H, ddd, $J=10.5$, 1.0, 1.0 Hz), 4.38 (1H, dd, $J=10.4$, 7.1 Hz), 4.31–4.15 (2H, m), 3.85 (1H, dd, $J=11.0$, 4.4 Hz), 3.60 (1H, dd, $J=11.0$, 2.0 Hz), 3.24 (1H, dd, $J=13.7$, 11.6 Hz), 2.90 (1H, dd, $J=11.6$, 6.7 Hz), 2.56 (1H, m), 2.45 (1H, m), 1.79 (3H, s), 1.30 (3H, t, $J=7.0$, Hz), 0.92 (3H, s), 0.92 (3H, s), 0.08 (3H, s), 0.05 (3H, s), 0.02 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.6 (C), 170.8 (C), 137.5 (C), 133.8 (CH), 119.9 (CH_2), 119.7 (CH), 83.5 (CH), 61.3 (CH_2), 60.8 (CH_2), 47.5 (CH), 45.4 (CH), 43.9 (CH), 41.9 (CH), 25.9 (CH_3), 21.8 (CH_3), 18.2 (C), 14.2 (CH_3), −5.6 (CH_3); IR (ν_{max} cm^{-1}): 3003 (*C–H*), 2942 (*C–H*), 2851 (*C–H*), 1748 (*lactone C=O*), 1714 (*ester C=O*); LRMS (CI, NH_3): *m/z* 395 $[M+H]^+$ (60%), 228 (30), 132 (100), 112 (35), 109 (30), 108 (50), 106 (50), 98 (45), 94 (40), 92 (85), 91 (100), 86 (35), 84 (50), 75 (35), 74 (60), 72 (80), 70

(40), 61 (50); HRMS (ES) *m/z*. Found: $[M+H]^+$ 395.2264, $C_{21}H_{35}O_5Si$ requires: 395.2248.

4.1.10. Ethyl (1*R,2*R**,3*R**,6*R**)-3-(*tert*-butyldimethylsilanyloxymethyl)-4-methyl-9-oxo-7-vinyl-8-oxabicyclo-[4.3.0]-non-4-ene-2-carboxylate (12).** R_f (silica): 0.45 (2:1 petroleum ether–diethyl ether). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.92 (1H, ddd, $J=17.0$, 10.5, 5.9 Hz), 5.45 (1H, ddd, $J=4.0$, 1.5, 1.5 Hz), 5.39 (1H, ddd, $J=17.0$, 1.0, 1.0 Hz), 5.30 (1H, ddd, $J=10.5$, 1.0, 1.0 Hz), 4.57 (1H, dd, $J=5.9$, 5.9 Hz), 4.30–4.15 (2H, m), 3.64 (2H, dd, $J=5.0$, 2.0 Hz), 3.30 (1H, dd, $J=7.2$, 5.7 Hz), 3.13 (1H, dd, $J=8.3$, 7.2 Hz), 2.90 (1H, m), 2.62 (1H, m), 1.80 (3H, s), 1.28 (3H, t, $J=7.1$ Hz), 0.91 (9H, s), 0.08 (3H, s), 0.07 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.7, 173.9, 136.5, 134.8, 84.4, 62.3, 61.6, 43.4, 40.5, 39.6, 25.8, 22.2, 18.2, 14.1, −5.6; IR (ν_{max} cm^{-1}): 2929 (*C–H*), 2857 (*C–H*), 1770 (*lactone C=O*), 1724 (*ester C=O*); LRMS (CI, NH_3): *m/z* 412 $[M+Na]^+$ (90%), 395 $[M+H]^+$ (100), 239 (40), 222 (70); HRMS (ES) *m/z*. Found: $[M+H]^+$ 395.2250, $C_{21}H_{35}O_5Si$ requires: 395.2248.

4.1.11. Ethyl 1-(*tert*-butyldimethylsilanyloxymethyl)-2-methylhepta-2,4,6-trienyl fumarate (16). R_f (silica): 0.50 (2:1 petroleum ether–diethyl ether). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.90 (1H, d, $J=15.8$ Hz), 6.85 (1H, d, $J=15.8$ Hz), 6.45–6.35 (2H, m), 6.25 (1H, dd, $J=15.0$, 10.5 Hz), 6.13 (1H, d, $J=11.0$ Hz), 5.35 (1H, t, $J=6.5$ Hz), 5.24 (1H, dd, $J=16.1$, 1.5 Hz), 5.11 (1H, dd, $J=10.9$, 1.5 Hz), 4.27 (2H, q, $J=7.1$ Hz), 3.76 (1H, dd, $J=6.5$, 3.3 Hz), 1.84 (3H, s), 1.31 (3H, t, $J=7.1$ Hz), 0.88 (9H, s), 0.08 (3H, s), 0.06 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.1 (C), 164.2 (C), 137.1 (CH), 134.5 (CH), 133.9 (CH), 133.7 (CH), 133.5 (C), 128.2 (CH), 128.1 (CH), 117.8 (CH_2), 80.2 (CH), 63.9 (CH_2), 61.4 (CH_2), 25.8 (CH_3), 18.3 (C), 14.2 (CH_3), 13.8 (CH_3), −5.3 (CH_3); IR (ν_{max} cm^{-1}): 2941 (*C–H*), 2862 (*C–H*), 2740 (*C–H*), 1704 (*C=O*).

4.1.12. Ethyl (1*S,2*S**,3*S**,6*R**)-3-[3-(*tert*-butyldimethylsilanyloxy)-1-methylpropenyl]-9-oxo-8-oxabiccyclo-[4.3.0]-non-4-ene-2-carboxylate (14).** R_f (silica): 0.40 (2:1 petroleum ether–diethyl ether); HPLC conditions: Chiralpak AD 95:5 (heptanes: ethanol), at 1 mL/min. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.96 (1H, ddd, $J=9.9$, 1.9, 1.9 Hz), 5.63 (1H, ddd, $J=9.9$, 3.2, 3.2 Hz), 5.42 (1H, t, $J=5.4$ Hz), 4.49 (1H, dd, $J=8.1$, 6.3 Hz), 4.24–4.12 (4H, m), 3.97 (1H, dd, $J=11.0$, 8.1 Hz), 3.41 (1H, m), 2.99 (1H, dd, $J=11.6$, 8.1 Hz), 2.80 (1H, m), 2.73 (1H, dd, $J=13.4$, 11.6 Hz), 1.62 (3H, d, $J=0.9$ Hz), 1.27 (3H, t, $J=7.2$ Hz), 0.91 (9H, s), 0.07 (6H, s); IR (ν_{max} cm^{-1}): 3003 (*C–H*), 2942 (*C–H*), 2851 (*C–H*), 1748 (*lactone C=O*), 1714 (*ester C=O*).

4.1.13. (*E*,*E*)-3-Acetoxy-8-(*tert*-butyldimethylsilanyloxy)-6-methylocta-1,4,6-triene (17). To (*E*,*E*)-8-(*tert*-butyldimethylsilanyloxy)-6-methylocta-1,4,6-trien-3-ol (0.20 g, 0.75 mmol) in dichloromethane (2 mL) was added *N*,*N*−4-dimethylaminopyridine (DMAP) (2.0 mg, 15 μmol) and triethylamine (0.28 mL, 2.0 mmol) and the mixture stirred at rt for 20 min, then cooled to 0 °C and acetic anhydride (90 μL, 0.90 mmol) added over 5 min. When complete, the reaction mixture was diluted with ethyl acetate and washed sequentially with saturated solutions of aqueous copper sulphate, sodium hydrogen carbonate and brine. The organic layer was dried ($MgSO_4$), filtered through celite and concentrated to give acetate **17** as a yellow oil (0.20 g, 87%). R_f (silica): 0.90 (2:1 petroleum ether–ethyl acetate); ^{1}H NMR (400 MHz, $CHCl_3$): δ 6.30 (1H, d, $J=15.7$ Hz), 5.87 (1H, ddd, $J=16.9$, 10.4, 6.1 Hz), 5.77 (1H, t, $J=6.4$ Hz), 5.64 (1H, m), 5.60 (1H, dd, $J=15.7$, 7.0 Hz), 5.29 (1H, ddd, $J=16.9$, 1.2, 1.2 Hz), 5.22 (1H, ddd, $J=10.4$, 1.2, 1.2 Hz), 4.32 (2H, d, $J=6.4$ Hz), 2.09 (3H, s), 1.74 (3H, s), 0.91 (9H, s), 0.08 (6H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.8 (C), 137.5 (CH), 135.6 (CH), 133.4 (CH), 133.0 (C), 124.6 (CH), 117.1 (CH_2), 75.1 (CH), 60.2 (CH_2), 26.0 (CH_3), 25.9 (CH_3), 21.4 (CH_3), 18.7 (C), 12.6 (CH_3), −5.1 (CH_3); IR (ν_{max} cm^{-1}): 2954 (*C–H*), 2930 (*C–H*), 2885 (*C–H*), 2857 (*C–H*), 1737 (*C=O*).

4.1.14. Ethyl (*E*,*E*)-6-(*tert*-butyldimethylsilanyloxy)-4-methylhexa-2,4-dienyl fumarate (18). (*E*,*E*)-6-(*tert*-Butyldimethylsilanyloxy)-4-methylhexa-2,4-dien-1-ol (0.25 g, 1.0 mmol) was esterified with monoethyl fumaryl chloride (0.18 g, 1.1 mmol) in diethyl ether (23 mL) in the presence of triethylamine (0.30 mL, 2.1 mmol) to afford a pale yellow oil (0.38 g, quantitative). R_f (silica): 0.75 (2:1 petroleum ether–diethyl ether); ^{1}H NMR (400 MHz, $CHCl_3$): δ 6.86 (2H, s), 6.34 (1H, d, $J=15.6$ Hz), 5.72 (1H, dt, $J=15.6$, 6.6 Hz), 5.64 (1H, t, $J=5.8$ Hz), 4.75 (2H, d, $J=6.6$ Hz), 4.32 (2H, d, $J=5.8$ Hz), 4.26 (2H, q, $J=7.0$ Hz), 1.74 (3H, s), 1.32 (3H, t, $J=7.0$ Hz), 0.90 (9H, s), 0.07 (6H, s); ^{13}C NMR (100 MHz, $CHCl_3$): δ 164.9 (C), 164.8 (C), 139.3 (CH), 133.9 (CH), 133.6 (CH), 133.4 (CH), 132.9 (C), 120.8 (CH), 66.0 (CH_2), 61.3 (CH_2), 60.2 (CH_2), 25.9 (CH_3), 18.4 (C), 14.1 (CH_3), 12.6 (CH_3), 1.0 (CH_3), −5.2 (CH_3); IR (ν_{max} cm^{-1}): 2955 (*C–H*), 2930 (*C–H*), 2857 (*C–H*), 1723 (*C=O*).

4.1.15. (*E*,*E*)-8-(*tert*-Butyldimethylsilanyloxy)-6-methylocta-4,6-diene-3-ol. Ethyl magnesiumbromide (1.5 mL, 1 M in THF, 1.5 mmol) was added to aldehyde **10** (0.30 g, 1.3 mmol) in THF (9 mL) yielding a yellow oil that was purified by flash chromatography on silica gel (silica treated with 1% triethylamine, 19:1 petroleum ether–ethyl acetate) to afford a pale yellow oil (0.29 g, 85%). R_f (silica): 0.30 (2:1 petroleum ether–diethyl ether); ^{1}H NMR (400 MHz, $CHCl_3$): δ 6.19 (1H, d, $J=15.5$ Hz), 5.59 (1H, dd, $J=15.5$, 7.0 Hz), 5.56 (1H, t, $J=6.7$ Hz), 4.29 (2H, d, $J=6.7$ Hz,), 4.04 (1H, dt, $J=7.0$, 7.0 Hz), 2.12 (1H, br s), 1.71 (3H, d, $J=1.2$ Hz), 1.61–1.51 (2H, m), 0.91–0.86 (3H, m), 0.88 (9H, s), 0.05 (6H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 135.0 (CH), 133.5 (C), 131.9 (CH), 130.9 (CH), 74.5 (CH), 60.3 (CH_2), 30.4 (CH_2), 26.0 (CH_3), 18.4 (C), 12.7 (CH_3), 9.8 (CH_3), −5.1 (CH_3); IR (ν_{max} cm^{-1}): 3606 (*O–H*), 2929 (*C–H*), 2882 (*C–H*), 2857 (*C–H*).

4.1.16. (*E*,*E*)-8-(*tert*-Butyldimethylsilanyloxy)-6-methyl-1-(trimethylsilanyl)octa-4,6-dien-1-yn-3-ol. *n*-Butyllithium (3.0 mL, 7.6 mmol) was added to a solution of trimethylsilylacetylene (1.1 mL, 7.9 mmol) in THF (33 mL) at −20 °C and the stirred for 1 h. Aldehyde **10** (1.72 g, 7.20 mmol) in THF (2 mL) was added to the reaction mixture at −20 °C then warmed to rt and stirred for 3 h. The reaction mixture was quenched with saturated aqueous ammonium chloride (3 mL) and then diluted with ethyl acetate (100 mL). The organic layer was washed with dilute hydrochloric acid (5 mL, 1 M) and the aqueous layers were

back extracted with ethyl acetate (2×25 mL). The combined organics were washed with a saturated aqueous solution of sodium hydrogen carbonate (20 mL) and brine (50 mL), dried ($MgSO_4$) and concentrated to afford a pale yellow oil, which was purified by flash chromatography on silica gel (silica treated with 1% triethylamine, 4:1 petroleum ether–ethyl acetate) to give the acetylene alcohol (2.10 g, 86%). R_f (silica): 0.60 (2:1 petroleum ether–ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.42 (1H, d, J=15.6 Hz), 5.72 (1H, ddd, J=15.6, 6.2, 0.5 Hz), 5.65 (1H, t, J=6.2 Hz), 4.93 (1H, br m), 4.33 (2H, d, J=6.2 Hz), 2.07 (1H, br s), 1.76 (3H, d, J=1.1 Hz), 0.93–0.89 (9H, m), 0.20–0.19 (6H, m), 0.17–0.16 (9H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 136.6, 133.6, 133.0, 126.5, 104.6, 91.1, 63.4, 60.3, 18.5, 12.8, 0.0, −5.1; IR (ν_{max} cm^{-1}): 3592 (*O–H*), 2956 (*C–H*), 2929 (*C–H*), 2857 (*C–H*); LRMS (CI, CH_4): *m/z* 322 [M−OH]$^+$ (35%), 321 (100), 211 (35), 189 (30), 147 (30), 73 (68).

4.1.17. Ethyl (*E*,*E*)-6-(*tert*-butyldimethylsilanyloxy)-4-methyl-1-(trimethylsilanylethynyl) hexa-2,4-dienyl fumarate (21). (*E*,*E*)-8-(*tert*-Butyldimethylsilanyloxy)-6-methyl-1-(trimethylsilanyl)octa-4,6-dien-1-yn-3-ol (1.85 g, 5.64 mmol) was esterified with monoethyl fumaryl chloride (1.01 g, 6.20 mmol) in diethyl ether (127 mL) in the presence of triethylamine (1.6 mL, 11 mmol) to afford a yellow oil (2.21 g, 87%). R_f (silica): 0.65 (4:1 petroleum ether–ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.91 (1H, d, J=15.6 Hz), 6.87 (1H, d, J=15.6 Hz), 6.53 (1H, d, J=15.5 Hz), 6.12 (1H, d, J=6.7 Hz), 5.72 (1H, m), 5.66 (1H, dd, J=15.5, 6.7 Hz), 4.33 (2H, d, J=6.1 Hz), 4.26 (2H, q, J=7.0 Hz), 1.75 (3H, d, J=0.7 Hz), 1.32 (3H, t, J=7.0 Hz), 0.91 (9H, s), 0.20 (9H, s), 0.08 (3H, s), 0.08 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.8, 163.7, 139.6, 135.2, 134.9, 134.4, 133.2, 121.8, 100.1, 92.9, 65.7, 61.4, 60.2, 41.6, 32.2, 26.0, 18.4, 14.1, 12.7, 1.1, −0.2, −5.1; IR (ν_{max} cm^{-1}): 2957 (*C–H*), 2929 (*C–H*), 2857 (*C–H*), 1721 (*C=O*).

4.1.18. Ethyl (*E*,*E*)-6-(*tert*-butyldimethylsilanyloxy)-1-ethyl-4-methylhexa-2,4-dienyl fumarate (24). (*E*,*E*)-8-(*tert*-Butyldimethylsilanyloxy)-6-methylocta-4,6-diene-3-ol (0.30 g, 1.1 mmol) was esterified with monoethyl fumaryl chloride (0.20 g, 1.2 mmol) in diethyl ether (25 mL) in the presence of triethylamine (0.31 mL, 2.2 mmol) to afford **24** as a yellow oil (0.39 g, 89%). R_f (silica): 0.85 (4:1 petroleum ether–ethyl acetate); ^{1}H NMR (400 MHz, $CHCl_3$): δ 6.86 (1H, d, J=16.5 Hz), 6.82 (1H, d, J=16.5 Hz), 6.28 (1H, d, J=15.7 Hz), 5.61 (1H, t, J=6.1 Hz), 5.53 (1H, dd, J=15.7, 7.1 Hz), 5.31 (1H, dt, J=7.1, 7.1 Hz), 4.29 (2H, d, J=6.1 Hz), 4.24 (2H, q, J=7.2 Hz), 1.78–1.66 (2H, m), 1.71 (3H, s), 1.30 (3H, t, J=7.2 Hz), 0.92–0.85 (3H, m), 0.88 (9H, s), 0.10 (6H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.1 (C), 164.4 (C), 137.6 (CH), 134.1 (CH), 133.5 (CH), 133.3 (CH), 133.0 (C),125.4 (CH), 77.4 (CH), 61.4 (CH_2), 60.3 (CH_2), 27.8 (CH_2), 26.0 (CH_3), 21.5 (CH_3), 18.5 (C), 14.2 (CH_3), 12.6 (CH_3), 9.6 (CH_3), −5.1 (CH_3); IR (ν_{max} cm^{-1}): 2929 (*C–H*), 2856 (*C–H*), 1721 (*C=O*); LRMS (CH_4): *m/z* 397 (16%), 201 (57), 127 (67), 121 (45), 117 (60), 103 (30), 89 (56), 75 (100), 73 (70); HRMS (CH_4) *m/z*. Found: [M+H]$^+$ 397.2400, $C_{21}H_{37}O_5Si$ requires: 397.2410.

4.1.19. Diels–Alder cyclisation of ethyl (*E*,*E*)-6-(*tert*-butyldimethylsilanyloxy)-4-methylhexa-2,4-dienyl fumarate (18). Fumarate ester **18** (77 mg, 0.21 mmol) was heated under reflux in toluene (30 mL) in the presence of BHT (2.5 mg, 11 μmol) to afford a brown residue. The residue was purified by flash chromatography on silica gel using a gradient elution system (silica treated with 1% triethylamine, 19:1 petroleum ether–diethyl ether to 4:1 petroleum ether–diethyl ether) to afford two Diels–Alder products, the minor *endo* adduct **20** (17 mg, 21%) and the major *exo* product **19** (32 mg, 42%).

4.1.20. Ethyl (1*S,2*S**,3*R**,6*R**)-3-(*tert*-butyldimethylsilanyloxymethyl)-4-methyl-9-oxo-8-oxabicyclo-[4.3.0]-non-4-ene-2-carboxylate (19).** R_f (silica): 0.75 (2:1 petroleum ether–ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.63 (1H, d, J=1.4 Hz), 4.37 (1H, dd, J=7.9, 6.4 Hz), 4.31–4.13 (2H, m), 3.83 (1H, dd, J=11.0, 2.1 Hz), 3.81 (1H, dd, J=11.4, 7.9 Hz), 3.58 (1H, dd, J=11.0, 2.0 Hz), 3.10 (1H, dd, J=13.7, 11.5 Hz), 2.88 (1H, dd, J=11.5, 6.6 Hz), 2.75 (1H, m), 2.56 (1H, m), 1.77 (3H, s), 1.29 (3H, t, J=7.1 Hz), 0.89 (3H, m), 0.85 (6H, s), 0.02 (3H, s), 0.00 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.4 (C), 170.9 (C), 137.2 (C), 120.5 (CH), 70.6 (CH_2), 61.3 (CH_2), 60.7 (CH_2), 45.5 (CH), 43.8 (CH), 42.0 (CH), 41.2 (CH), 25.8 (CH_3), 21.8 (CH_3), 18.2 (C), 14.2 (CH_3), −5.6 (CH_3), −5.8 (CH_3); IR (ν_{max} cm^{-1}): 2953 (*C–H*), 2929 (*C–H*), 2884 (*C–H*), 2857 (*C–H*), 1770 (*lactone C=O*), 1732 (*ester C=O*); LRMS: (CI, NH_3): *m/z* 369 [M+H]$^+$ (100%); HRMS: (ES) *m/z*. Found: [M+H]$^+$ 369.2091, $C_{19}H_{33}O_5Si$ requires: 369.2097.

4.1.21. Ethyl (1*R,2*R**,3*R**,6*R**)-3-(*tert*-butyldimethylsilanyloxymethyl)-4-methyl-9-oxo-8-oxabicyclo-[4.3.0]-non-4-ene-2-carboxylate (20).** R_f (silica): 0.75 (2:1 petroleum ether–ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.42 (1H, d, J=1.4 Hz), 4.41 (1H, dd, J=8.8, 6.9 Hz), 4.24–4.11 (2H, m), 4.04 (1H, dd, J=8.8, 3.2 Hz), 3.65 (1H, dd, J=10.2, 4.8 Hz), 3.50 (1H, dd, J=10.2, 7.8 Hz), 3.46 (1H, dd, J=7.8, 4.1 Hz), 3.19 (1H, m), 3.16 (1H, dd, J=8.4, 4.1 Hz), 2.65 (1H, m), 1.79 (3H, s), 1.27 (3H, t, J=7.1 Hz), 0.92 (9H, s), 0.09 (3H, s), 0.07 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.6, 174.1, 135.9, 121.6, 72.1, 63.2, 61.1, 43.3, 39.1, 38.4, 34.2, 25.9, 22.8, 18.2, 14.2, −5.5; IR (ν_{max} cm^{-1}): 2955 (*C–H*), 2929 (*C–H*), 2857 (*C–H*), 1772 (*lactone C=O*), 1725 (*ester C=O*); LRMS: (APcI) *m/z* 369 (100%); HRMS: (APcI) *m/z*. Found: [M+H]$^+$ 369.2083, $C_{19}H_{33}O_5Si$ requires: 369.2097.

4.1.22. Diels–Alder cyclisation of ethyl (*E*,*E*)-6-(*tert*-butyldimethylsilanyloxy)-1-ethyl-4-methylhexa-2,4-dienyl fumarate (24). Fumarate ester **24** (0.31 g, 0.78 mmol) was heated under reflux in toluene (110 mL) in the presence of BHT (9.0 mg, 39 μmol) to afford a brown residue. Purified by flash chromatography on silica gel using a gradient elution system (silica treated with 1% triethylamine, 9:1 petroleum ether–diethyl ether to 2:1 petroleum ether–diethyl ether) to afford a mixture of Diels–Alder products (7:1 ratio) (0.15 g, 52%). The *exo-trans* product **25**, the major adduct was isolated cleanly however, the *exo-cis* adduct **26** could not be isolated in pure form.

4.1.23. Ethyl (1*S,2*S**,3*R**,6*R**,7*S**)-3-(*tert*-butyldimethylsilanyloxymethyl)-7-ethyl-4-methyl-9-oxo-8-oxabicyclo-[4.3.0]-non-4-ene-2-carboxylate (25).** R_f (silica): 0.50 (4:1 petroleum ether–ethyl acetate); ^{1}H NMR

(400 MHz, $CDCl_3$): δ 5.63 (1H, d, $J=1.1$ Hz), 4.30–4.11 (2H, m), 3.95 (1H, ddd, $J=10.3$, 7.8, 4.0 Hz), 3.82 (1H, dd, $J=11.0$, 4.4 Hz), 3.57 (1H, dd, $J=11.0$, 2.0 Hz), 3.18 (1H, dd, $J=13.6$, 11.6 Hz), 2.87 (1H, dd, $J=11.6$, 6.7 Hz), 2.54 (1H, m), 2.33 (1H, m), 1.79–1.63 (2H, m), 1.76 (3H, s), 1.28 (3H, t, $J=7.1$ Hz), 1.05 (3H, t, $J=7.4$ Hz), 0.85 (9H, s), 0.02 (3H, s), 0.00 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.1 (C), 171.0 (C), 137.2 (C), 120.5 (CH), 84.2 (CH), 61.3 (CH_2), 60.7 (CH_2), 46.8 (CH), 45.4 (CH), 43.9 (CH), 42.4 (CH), 26.2 (CH_2), 25.8 (CH_3), 21.9 (CH_3), 18.2 (C), 14.2 (CH_3), 9.8 (CH_3), -5.6 (CH_3), -5.8 (CH_3); IR (ν_{max} cm^{-1}): 2930 (*C–H*), 2884 (*C–H*), 2857 (*C–H*), 1778 (*lactone C=O*), 1725 (*ester C=O*); LRMS: (CI, CH_4) *m/z* 397 $[M+H]^+$ (100%); HRMS: (ES) *m/z*. Found: $[M+H]^+$ 397.2408, $C_{21}H_{37}O_5Si$ requires: 397.2410.

4.1.24. Ethyl (*E,E*)-6-methoxy-4-methylhexa-2,4-dienoate (27). To alcohol **8** (0.50 g, 2.9 mmol) in methyl iodide (4.50 mL, 70.6 mmol) was added silver(I) oxide (1.09 g, 4.70 mmol) and the resultant mixture stirred at rt for 17 h. The reaction mixture was diluted with dichloromethane (35 mL) and filtered through celite. The filtrate was washed with brine (20 mL), dried ($MgSO_4$) and concentrated to afford a yellow oil (0.54 g, 99%). R_f (silica): 0.80 (2:1 petroleum ether–ethyl acetate); ^{1}H NMR (400 MHz, $CHCl_3$): δ 7.30 (1H, d, $J=15.7$ Hz), 5.96 (1H, t, $J=6.3$ Hz), 5.86 (1H, d, $J=15.7$ Hz), 4.19 (2H, q, $J=7.1$ Hz,), 4.10 (2H, d, $J=6.3$ Hz), 3.34 (3H, s), 1.79 (3H, s), 1.28 (3H, t, $J=7.1$ Hz); ^{13}C NMR (67.5 MHz, $CDCl_3$): δ 157.3 (C), 148.3 (CH), 136.5 (CH), 134.8 (C), 117.6 (CH), 69.1 (CH_2), 60.4 (CH_2), 58.4 (CH_2), 14.3 (CH_3), 12.6 (CH_3); IR (ν_{max} cm^{-1}): 2955 (*C–H*), 2930 (*C–H*), 2844 (*C–H*), 2857 (*C–H*), 1715 (*C=O*); LRMS: (CI, CH_4) *m/z* 369 $[2M+H]^+$ (39%), 185 $[M+H]^+$ (100), 184 $[M]^+$ (41), 155 (48), 153 (76), 111 (63); HRMS: (CI, CH_4) *m/z*. Found: $[M+H]^+$ 185.1180, $C_{10}H_{17}O_3$ requires: 185.1178.

4.1.25. (*E,E*)-6-Methoxy-4-methylhexa-2,4-dien-1-ol. Ester **27** (4.70 g, 16.5 mmol) was reduced with lithium aluminium hydride (0.950 g, 24.8 mmol) in diethyl ether (120 mL) to yield a yellow oil. The crude material was purified by flash chromatography on silica gel (4:1 petroleum ether–ethyl acetate) to afford the title compound as a colourless oil (3.13 g, 78%). R_f (silica): 0.25 (4:1 petroleum ether–ethyl acetate); ^{1}H NMR (400 MHz, $CHCl_3$): δ 6.27 (1H, d, $J=15.7$ Hz), 5.81 (1H, dt, $J=15.7$, 5.4 Hz), 5.59 (1H, t, $J=6.7$ Hz), 4.19 (2H, d, $J=5.4$ Hz), 4.05 (2H, d, $J=6.7$ Hz), 3.32 (3H, s), 1.78 (3H, s); ^{13}C NMR (67.5 MHz, $CDCl_3$): δ 136.2 (C), 135.3 (CH), 128.1 (CH), 127.7 (CH), 68.9 (CH_2), 63.6 (CH_2), 58.1 (CH_3), 12.8 (CH_3); IR (ν_{max} cm^{-1}): 3610 (*O–H*), 3445 (*O–H*), 2992 (*C–H*), 2928 (*C–H*), 2875 (*C–H*), 2823 (*C–H*).

4.1.26. (*E,E*)-6-Methoxy-4-methylhexa-2,4-dienal (28). (*E,E*)-6-Methoxy-4-methylhexa-2,4-dien-1-ol (1.37 g, 12.2 mmol) was oxidised using a Swern procedure using dimethyl sulphoxide (3.47 mL, 49.0 mmol) and oxalyl chloride (2.15 mL, 24.5 mmol) to give an orange oil. The oil was purified by passing through a plug of silica (2:1 petroleum ether–diethyl ether) to afford aldehyde **28** as a yellow oil (1.21 g, 90%). R_f (silica): 0.35 (2:1 petroleum ether–diethyl ether); ^{1}H NMR (400 MHz, $CHCl_3$): δ 9.58 (1H, d, $J=7.8$ Hz), 7.12 (1H, d, $J=15.7$ Hz), 6.15 (1H, dd, $J=15.7$, 7.8 Hz), 6.09 (1H, t, $J=6.2$ Hz), 4.14 (2H, d, $J=6.2$ Hz), 3.37 (3H, s), 1.83 (3H, t, $J=0.8$ Hz); ^{13}C NMR (67.5 MHz, $CDCl_3$): δ 194.1 (CH), 156.3 (CH), 139.0 (CH), 135.0 (C), 128.3 (CH), 69.2 (CH_2), 58.6 (CH_3), 12.8 (CH_3); IR (ν_{max} cm^{-1}): 3689 (*O–H*), 3336 (*O–H*), 2993 (*C–H*), 2929 (*C–H*), 2824 (*C–H*), 2736 (*C–H*); LRMS: (CI, CH_4) *m/z* 141 $[M+H]^+$ (22%), 123 (32), 109 (37), 95 (39), 81 (100); HRMS: (CI, CH_4) *m/z*. Found: $[M+H]^+$ 141.0917, $C_8H_{13}O_2$ requires: 141.0916.

4.1.27. (*E,E*)-8-Methoxy-6-methyl-1-(trimethylsilanyl)-octa-4,6-dien-1-yn-3-ol (29). *n*-Butyllithium (4.4 mL, 9.6 mmol) was added to a solution of trimethylsilylacetylene (1.64 mL, 11.6 mmol) in THF (15 mL) at -20 °C and stirred for 1 h. Aldehyde **28** (1.35 g, 9.63 mmol) in THF (40 mL) was added to the above solution at -20 °C then warmed to rt and stirred for 3 h. The reaction mixture was quenched with a solution of saturated aqueous ammonium chloride (2 mL) and then diluted with ethyl acetate (100 mL). The organic layer was washed with aqueous hydrochloric acid (20 mL, 1 M) and the aqueous layers were back extracted with ethyl acetate (25 mL). The combined organics were washed with a solution of saturated aqueous sodium hydrogen carbonate (50 mL) and brine (50 mL), dried ($MgSO_4$) and concentrated to afford a pale yellow oil. This oil was purified by flash chromatography on silica gel (silica treated with 1% triethylamine, 4:1 petroleum ether–ethyl acetate) to give the acetylene alcohol (2.09 g, 91%). R_f (silica): 0.45 (3:1 petroleum ether–ethyl acetate); ^{1}H NMR (400 MHz $CDCl_3$): δ (1H, d, $J=15.6$ Hz), 5.76 (1H, dd, $J=15.6$, 6.1 Hz), 5.66 (1H, t, $J=6.6$ Hz), 4.93 (1H, d, $J=6.1$ Hz), 4.08 (2H, d, $J=6.6$ Hz), 3.34 (3H, s), 2.23 (1H, br s, *OH*), 1.79 (3H, s), 0.19 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 136.3 (CH), 135.7 (C), 129.7 (CH), 127.1 (CH), 104.5 (C), 91.1 (C), 69.0 (CH_2), 63.3 (CH), 58.1 (CH_3), 12.9 (CH_3), -0.10 (CH_3); IR (ν_{max} cm^{-1}): 3393 (*O–H*), 2961 (*C–H*), 2926 (*C–H*); LRMS (EI): *m/z* 238 (6%), 125 (68), 111 (52), 73 (100); HRMS (EI) *m/z*. Found: $[M]^+$ 238.1382, $C_{13}H_{22}O_2Si$ requires: 238.1389.

4.1.28. (*E,E*)-8-Methoxy-6-methylocta-4,6-dien-1-yn-3-ol (30). Ethynyl magnesiumbromide (17 mL, 0.5 M in THF, 8.6 mmol) was added to aldehyde **28** (1.70 g, 7.13 mmol) in THF (25 mL) giving a brown oil. The crude oil was filtered through a plug of silica (eluting with diethyl ether) and the solvent was then evaporated leaving an orange oil (0.89 g, 75%). R_f (silica): 0.30 (3:1 petroleum ether–ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.48 (1H, d, $J=15.6$ Hz), 5.79 (1H, ddd, $J=15.6$, 6.1, 0.4 Hz), 5.70 (1H, t, $J=6.5$ Hz), 4.97 (1H, m), 4.08 (2H, d, $J=6.5$ Hz), 3.35 (3H, s), 2.61 (1H, d, $J=2.2$ Hz), 1.81 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 135.6, 129.1, 127.1, 83.3, 73.9, 68.6, 62.0, 57.7, 25.4, 12.6; IR (ν_{max} cm^{-1}): 3592 (*O–H*), 3305 (*O–H*), 2928 (*C–H*), 2823 (*C–H*), 2253 (*C≡C*).

4.1.29. Ethyl (*E,E*)-6-methoxy-4-methyl-1-(trimethylsilanylethynyl)hexa-2,4-dienyl fumarate (31). Alcohol **29** (0.40 g, 1.7 mmol) was esterified with monoethyl fumaryl chloride (0.30 g, 1.8 mmol) in diethyl ether (38 mL) in the presence of triethylamine (0.47 mL, 3.3 mmol) to afford a yellow oil (0.56 g, 92%). R_f (silica): 0.50 (2:1 petroleum ether–diethyl ether); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.90 (1H, d, $J=15.8$ Hz), 6.86 (1H,

d, $J=15.8$ Hz), 6.55 (1H, d, $J=15.6$ Hz), 6.05 (1H, dd, $J=6.6$, 0.8 Hz), 5.70 (1H, dd, $J=15.6$, 6.6 Hz), 5.71 (1H, t, $J=6.6$ Hz), 4.26 (2H, q, $J=7.1$ Hz), 4.08 (2H, d, $J=6.6$ Hz), 3.35 (3H, s), 1.79 (3H, d, $J=1.1$ Hz), 1.31 (3H, t, $J=7.1$ Hz), 0.20 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.9 (C), 163.8 (C), 139.3 (CH), 135.2 (C), 134.5 (CH), 133.2 (CH), 131.2 (CH), 122.4 (CH), 99.9 (C), 93.1 (C), 68.9 (CH_2), 65.7 (CH), 61.4 (CH_2), 58.2 (CH_3), 14.2 (CH_3), 12.8 (CH_3), −0.2 (CH_3); IR (ν_{max} cm^{-1}): 2962 (*C–H*), 1725 (*C=O*); LRMS (EI): *m/z* 364 $[M]^+$ (25%), 221 (36), 220 (51), 207 (33), 205 (41), 201 (49), 175 (32), 173 (37),128 (40), 127 (100), 117 (46), 116 (44), 113 (31), 111 (74), 103 (31), 99 (99), 98 (32), 89 (73); HRMS (EI) *m/z*. Found: $[M]^+$ 364.1706, $C_{19}H_{28}O_5Si$ requires: 364.1708.

4.1.30. Diels–Alder cyclisation of ethyl (*E,E*)-6-methoxy-4-methyl-1-(trimethylsilanylethynyl)hexa-2,4-dienyl fumarate (31). Fumarate ester **31** (0.27 g, 0.74 mmol) was heated under reflux in toluene (104 mL) in the presence of BHT (8.0 mg, 37 μmol) to afford a brown residue. Purified by flash chromatography on silica gel using a gradient elution system (silica treated with 1% triethylamine, 9:1 petroleum ether–diethyl ether to 2:1 petroleum ether–diethyl ether) to afford a mixture of *exo-cis* and *exo-trans* Diels Alder products (3:1 ratio) (0.12 g, 46%). Unfortunately neither adduct could be isolated in pure form.

4.1.31. Ethyl (*E,E*)-1-ethynyl-6-methoxy-4-methylhexa-2,4-dienyl fumarate (32). Alcohol **28** (97 mg, 0.58 mmol) was esterified with monoethyl fumaryl chloride (0.10 g, 0.64 mmol) in diethyl ether (13 mL) in the presence of triethylamine (0.16 mL, 1.2 mmol) to afford **32** as a yellow oil (0.14 g, 85%). R_f (silica): 0.65 (2:1 petroleum ether–diethyl ether); ^{1}H NMR (400 MHz, $CHCl_3$): δ 6.91 (1H, d, $J=15.8$ Hz), 6.87 (1H, d, $J=15.8$ Hz), 6.57 (1H, d, $J=15.4$ Hz), 6.03 (1H, dd, $J=6.8$, 2.1 Hz), 5.74 (1H, t, $J=6.5$ Hz), 5.72 (1H, dd, $J=15.4$, 6.8 Hz), 4.26 (2H, q, $J=7.1$ Hz), 4.08 (2H, d, $J=6.5$ Hz), 3.34 (3H, s), 2.64 (1H, d, $J=2.1$ Hz), 1.79 (3H, s), 1.31 (3H, t, $J=7.1$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 164.7, 163.7, 139.4, 135.0, 134.7, 132.8, 131.5, 121.8, 78.9, 75.8, 68.8, 65.0, 61.4, 58.1, 14.1, 12.7; IR (ν_{max} cm^{-1}): 2985 (*C–H*), 2902 (*C–H*), 2823 (*C–H*), 2253 (*C≡C*), 1722 (*C=O*).

4.1.32. Diels–Alder cyclisation of ethyl (*E,E*)-1-ethynyl-6-methoxy-4-methylhexa-2,4-dienyl fumarate (32). Fumarate ester **32** (0.13 g, 0.49 mmol) was heated under reflux in toluene (70 mL) in the presence of BHT (5.5 mg, 25 μmol) to afford a brown residue that was purified by flash chromatography on silica gel using a gradient elution system (silica treated with 1% triethylamine, 9:1 petroleum ether–diethyl ether to 2:1 petroleum ether–diethyl ether) to afford a mixture of *exo-cis* and *exo-trans* Diels–Alder products (3:1 ratio) (77 mg, 56%). Unfortunately neither product could be isolated in pure form. R_f (silica): 0.65 (2:1 petroleum ether–ethyl acetate).

4.1.33. (3*S,3a*R**,5a*R**,8a*S**,8b*S**)-5-Methyl-3-vinyl-3,3a,5a,6,8a,8b-hexahydro-2,7-dioxa-*as*-indacene-1,8-dione (37).** To the *exo-trans* adduct **4** (0.20 g, 0.51 mmol), in THF (10 mL) was added ammonium chloride (33 mg, 0.61 mmol), followed by TBAF (0.61 mL, 1 M in THF, 0.61 mmol) and the mixture stirred at rt for 4 h. The reaction mixture was partitioned between ethyl acetate (20 mL) and brine (10 mL) and washed with a saturated solution of copper sulphate (12 mL). The aqueous layer was further extracted with ethyl acetate and the combined organics washed with brine (15 mL) and dried ($MgSO_4$). The crude oil was purified by passing through a plug of silica (silica treated with 1% triethylamine) to afford **37** as a colourless oil (62 mg, 52%). R_f (silica): 0.60 (2:1 petroleum ether–ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.94 (1H, ddd, $J=17.1$, 10.6, 5.3 Hz), 5.56 (1H, d, $J=1.2$ Hz), 5.43 (1H, ddd, $J=17.1$, 1.5, 0.9 Hz), 5.36 (1H, ddd, $J=10.6$, 0.9, 0.9 Hz), 4.70 (1H, ddd, $J=5.3$, 3.4, 1.5 Hz), 4.53 (1H, ddd, $J=7.7$, 7.7, 1.5 Hz), 4.08 (1H, ddd, $J=7.7$, 5.1, 3.3 Hz), 3.25 (1H, m), 3.10–3.06 (2H, m), 2.93 (1H, m), 1.80 (3H, t, $J=1.5$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.4 (C), 175.4 (C), 134.3 (C), 133.8 (CH), 122.4 (CH), 118.4 (CH_2), 83.5 (CH), 70.5 (CH_2), 41.2 (CH), 38.8 (CH), 37.1 (CH), 36.1 (CH), 21.4 (CH_3); IR (ν_{max} cm^{-1}): 3037 (*C–H*), 2918 (*C–H*), 1777 (*C=O*); LRMS (EI): *m/z* 179 (31%), 178 (54), 152 (35), 151 (73), 150 (87), 107 (64), 106 (87), 105 (30), 93 (49), 92 (92), 91 (100), 79 (50), 78 (30), 77 (35), 57 (64); HRMS (ES) *m/z*. Found: $[M]^+$ 234.0897, $C_{13}H_{14}O_4$ requires: 234.0892.

4.1.34. Ethyl (1*S,2*S**,3*R**,6*R**,7*S**)-3-(*tert*-butyldimethylsilanyloxyethyl)-4-methyl-9-oxo-7-vinyl-8-oxa-bicyclo-[4.3.0]-non-4-ene-2-carboxylate (38).** R_f (silica): 0.45 (2:1 petroleum ether–ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.85 (1H, ddd, $J=17.4$, 10.4, 7.2 Hz), 5.46 (1H, d, $J=17.4$ Hz), 5.44 (1H, s), 5.37 (1H, d, $J=10.4$ Hz), 4.44 (1H, dd, $J=10.1$, 7.2 Hz), 4.29 (1H, m), 4.17 (1H, m), 3.59 (1H, m), 3.40 (1H, m), 2.87 (1H, dd, $J=11.4$, 6.1 Hz), 2.63 (1H, m), 2.61 (1H, dd, $J=13.4$, 11.4 Hz), 2.46 (1H, dd, $J=13.4$, 10.1 Hz), 1.93 (1H, m), 1.78 (3H, s), 1.58 (1H, m), 1.31 (3H, t, $J=7.2$ Hz), 0.89 (9H, s), 0.04 (6H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.5, 171.3, 141.7, 133.7, 120.1, 117.0, 83.6, 61.6, 60.9, 47.7, 43.6, 42.1, 39.1, 33.4, 26.0, 21.9, 18.3, 14.2, −5.3; IR (ν_{max} cm^{-1}): 2954 (*C–H*), 2929 (*C–H*), 2857 (*C–H*), 1769 (*lactone C=O*), 1722 (*ester C=O*); LRMS: (ES) *m/z* 409 $[M+H]^+$ (100%), 363 (32), 277 (70), 231 (84); HRMS: (ES) *m/z*. Found: $[M+H]^+$ 409.2384, $C_{22}H_{37}O_5Si$ requires: 409.2410.

4.1.35. Ethyl (*E,E*)-7-(*tert*-butyldimethylsilanyloxy)-4-methyl-1-vinylhepta-2,4-dienyl fumarate (43). (*E,E*)-9-(*tert*-Butyldimethylsilanyloxy)-6-methylnona-1,4,6-trien-3-ol (0.40 g, 1.4 mmol) was esterified with monoethyl fumaryl chloride (0.25 g, 1.6 mmol) in diethyl ether (32 mL) in the presence of triethylamine (0.40 mL, 2.83 mmol) to afford a yellow oil. The crude material was purified by flash chromatography on silica gel (silica treated with 1% triethylamine, 19:1 petroleum ether–diethyl ether to 2:1 petroleum ether–diethyl ether) to afford the Diels–Alder precursor as a colourless oil (0.32 g, 57%). R_f (silica): 0.40 (2:1 petroleum ether–diethyl ether); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.84 (2H, s), 6.31 (1H, d, $J=15.8$ Hz), 5.91–5.81 (2H, m) 5.55–5.50 (2H, m), 5.29 (1H, dd, $J=17.1$, 1.3 Hz), 5.20 (1H, dd, $J=10.5$, 1.3 Hz), 4.22 (2H, q, $J=7.1$ Hz), 3.60 (2H, t, $J=7.0$ Hz), 2.34 (2H, dt, $J=7.1$, 7.0 Hz), 1.72 (3H, s), 1.28 (3H, t, $J=7.1$ Hz), 0.86 (9H, s), 0.02 (6H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.8, 163.8, 138.8, 135.2, 134.1, 133.8, 131.0, 122.5, 117.3, 76.4,

62.4, 61.2, 32.1, 25.9, 18.3, 14.1, 12.4, −5.3, −5.5; IR (ν_{max} cm^{-1}): 2955 (*C–H*), 2929 (*C–H*), 2857 (*C–H*), 1717 (*C=O*); LRMS: (ES) *m/z* 409 (100%); HRMS: (ES) *m/z*. Found: $[M+H]^+$ 409.2417, $C_{22}H_{37}O_5Si$ requires: 409.2410.

4.1.36. Ethyl (*E*,*E*)-7-hydroxy-4-methylhepta-2,4-dienoate. Reaction of alcohol **40** (14.0 g, 37.3 mmol) with (*E*)-ethyliodoacrylate (8.86 g, 39.2 mmol) in *N*,*N*-dimethylformamide (47 mL) and a catalytic amount of dichloro-*bis*-acetonitrile palladium(II) (0.48 g, 1.9 mmol) afforded a pale yellow oil. Flash chromatography on silica using a gradient elution system (9:1 petroleum ether–ethyl acetate to 2:1 petroleum ether–ethyl acetate) yielded coupled product (6.19 g, 90%) as a colourless oil. R_f (silica): 0.20 (2:1 petroleum ether–ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34 (1H, d, J=15.8 Hz), 5.93 (1H, t, J=7.4 Hz), 5.83 (1H, d, J=15.8 Hz), 4.21 (2H, q, J=7.1 Hz), 3.74 (2H, dt, J=6.6, 5.8 Hz), 2.50 (2H, dt, J=7.4, 6.6 Hz), 1.82 (3H, s), 1.30 (3H, t, J=7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.4, 149.1, 137.7, 134.4, 115.7, 61.2, 60.0, 32.1, 20.7, 14.1, 12.1; IR (ν_{max} cm^{-1}): 3622 (*O–H*), 3491 (*O–H*), 2938 (*C–H*), 2882 (*C–H*), 1697 (*C=O*); LRMS: (CI, CH_4) *m/z* 185 $[M+H]^+$ (100%), 154 (60), 139 (97), 121 (39), 111 (40), 93 (46), 81 (62); HRMS: (CI, CH_4) *m/z*. Found: $[M]^+$184.1099, $C_{10}H_{16}O_3$ requires: 184.1099.

4.1.37. Ethyl (*E*,*E*)-7-(*tert*-butyldimethylsilanyloxy)-4-methylhepta-2,4-dienoate (41). Ethyl (*E*,*E*)-7-hydroxy-4-methylhepta-2,4-dienoate (3.29 g, 17.9 mmol) was protected as the silyl ether using chloro-*tert*-butyldimethylsilane (2.69 g, 17.9 mmol) and imidazole (1.82 g, 26.8 mmol) dissolved in the minimum amount of *N*,*N*-dimethylformamide (40 mL) and stirred at rt for 16 h. The crude product was purified by flash chromatography on silica gel using a gradient elution system (19:1 petroleum ether–ethyl acetate to 9:1 petroleum ether–ethyl acetate) to afford silyl ether **41** as a colourless oil (5.02 g, 94%). R_f (silica): 0.40 (9:1 petroleum ether–ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53 (1H, d, J=15.7 Hz), 5.92 (1H, t, J=7.4 Hz), 5.81 (1H, d, J=15.7 Hz), 4.22 (2H, q, J=7.1 Hz), 3.68 (2H, t, J=6.8 Hz), 2.44 (2H, dt, J=7.4, 6.8 Hz), 1.79 (3H, s), 1.31 (3H, t, J=7.1 Hz), 0.89 (9H, s), 0.08 (6H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.5 (C), 149.3 (CH), 138.0 (CH), 134.3 (C), 115.8 (CH), 62.0 (CH_2), 60.1 (CH_2), 32.5 (CH_2), 25.8 (CH_3), 18.2 (C), 14.3 (CH_3), 12.2 (CH_3), −5.4 (CH_3); IR (ν_{max} cm^{-1}): 2928 (*C–H*), 2857 (*C–H*), 1698 (*C=O*); LRMS: (ES) *m/z* 300 (30%), 299 $[M+H]^+$ (100); HRMS: (ES) *m/z*. Found: $[M+H]^+$ 299.2030, $C_{16}H_{31}O_3Si$ requires: 299.2043.

4.1.38. (*E*,*E*)-7-(*tert*-Butyldimethylsilanyloxy)-4-methylhepta-2,4-dien-1-ol. Ester **41** (5.02 g, 16.8 mmol) was reduced with lithium aluminium hydride (0.960 g, 25.2 mmol) in diethyl ether (125 mL) to give a yellow oil. The crude material was passed through a plug of silica gel (4:1 petroleum ether–ethyl acetate) to afford the title compound (4.01 g, 93%). R_f (silica): 0.45 (2:1 petroleum ether–ethyl acetate); ^{1}H NMR (400 MHz, $CHCl_3$): δ 6.27 (1H, d, J=15.7 Hz), 5.76 (1H, dt, J=15.7, 5.9 Hz), 5.51 (1H, t, J=7.1 Hz), 4.21 (2H, t, J=5.9 Hz), 3.64 (2H, t, J=6.8 Hz), 2.38 (2H, dt, J=7.1, 6.8 Hz), 1.77 (3H, s), 0.90 (9H, s), 0.06 (6H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 136.5 (CH), 135.0 (C), 129.2 (CH), 125.5 (CH), 63.9 (CH_2), 62.6 (CH_2), 32.1 (CH_2), 25.9 (CH_3), 18.3 (C), 12.5 (CH_3), −5.3 (CH_3); IR (ν_{max} cm^{-1}): 3609 (*O–H*), 2953 (*C–H*), 2929 (*C–H*), 2857 (*C–H*); LRMS: (CI, CH_4) *m/z* 257 $[M+H]^+$ (20%), 199 (37), 131 (50), 101 (38), 89 (43), 75 (100); HRMS: (CI, CH_4) *m/z*. Found: $[M+H]^+$ 257.1534, $C_{14}H_{29}O_2Si$ requires: 257.1542.

4.1.39. (*E*,*E*)-7-(*tert*-Butyldimethylsilanyloxy)-4-methylhepta-2,4-dienal (42). (*E*,*E*)-7-(*tert*-Butyldimethylsilanyloxy)-4-methylhepta-2,4-dien-1-ol (4.00 g, 15.6 mmol) was oxidised via a Swern procedure using dimethyl sulphoxide (4.6 mL, 64 mmol) and oxalyl chloride (2.7 mL, 31 mmol) to afford an orange oil. The orange residue was subjected to flash chromatography on silica gel (silica treated with 1% triethylamine, 19:1 petroleum ether–ethyl acetate) to afford the aldehyde as a yellow oil (3.33 g, 84%). R_f (silica): 0.30 (19:1 petroleum ether–ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.56 (1H, d, J=7.8 Hz), 7.12 (1H, d, J=15.6 Hz), 6.11 (1H, dd, J=15.6, 7.8 Hz), 6.06 (1H, t, J=7.3 Hz), 3.71 (2H, t, J=6.5 Hz), 2.47 (2H, dt, J=7.3, 6.5 Hz), 1.83 (3H, s), 0.88 (9H, s), 0.05 (6H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 194.1 (CH), 157.4 (CH), 140.7 (CH), 134.8 (C), 127.0 (CH), 61.9 (CH_2), 32.7 (CH_2), 25.9 (CH_3), 18.3 (C), 12.5 (CH_3), −5.4 (CH_3); IR (ν_{max} cm^{-1}): 2954 (*C–H*), 2929 (*C–H*), 2844 (*C–H*), 2857 (*C–H*), 1673 (*C=O*); LRMS: (ES) *m/z* 509 $[2\times M]^+$, (10%), 296 (80), 255 $[M]^+$ (100), 123 (100); HRMS: (CI, CH_4) *m/z*. Found: $[M+H]^+$ 255.1779, $C_{14}H_{27}O_2Si$ requires: 255.1780.

4.1.40. (*E*,*E*)-9-(*tert*-Butyldimethylsilanyloxy)-6-methylnona-1,4,6-trien-3-ol. Vinyl magnesiumbromide (6.4 mL, 1 M in THF, 6.4 mmol) was added to aldehyde **42** (1.36 g, 5.34 mmol) in THF (40 mL) yielding a yellow oil, which was purified by flash chromatography on silica gel (silica treated with 1% triethylamine, 2:1 petroleum ether–ethyl acetate) to afford a colourless oil (1.39 g, 92%). R_f (silica): 0.35 (2:1 petroleum ether–ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.26 (1H, d, J=15.7 Hz), 5.92 (1H, ddd, J=17.2, 10.4, 5.8 Hz), 5.60 (1H, dd, J=15.7, 6.3 Hz), 5.51 (1H, t, J=7.2 Hz), 5.27 (1H, dd, J=17.2, 1.3 Hz), 5.14 (1H, dd, J=10.4, 1.3 Hz), 4.68 (1H, dd, J=6.3, 5.8 Hz), 3.63 (2H, t, J=7.1 Hz), 2.37 (2H, dt, J=7.2, 7.1 Hz), 1.76 (3H, s), 0.89 (9H, s), −0.05 (3H, s), −0.05 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.8, 136.1, 134.6, 129.6, 127.6, 114.9, 74.1, 62.7, 32.2, 26.0, 18.4, 12.6, −5.2; IR (ν_{max} cm^{-1}): 3599 (*O–H*), 2928 (*C–H*), 2884 (*C–H*), 2857 (*C–H*), 2738 (*C–H*); LRMS: (CI, CH_4) *m/z* 265 (30%), 133 (100), 105 (25), 92 (20); HRMS: (CI, CH_4) *m/z* Found $[M-H]^+$ 281.1933, $C_{16}H_{29}O_2Si$ requires 281.1937.

4.1.41. Diels–Alder cyclisation of ethyl (*E*,*E*)-7-(*tert*-butyldimethylsilanyloxy)-4-methyl-1-vinylhepta-2,4-dienyl fumarate (43). Fumarate ester **43** (0.33 g, 0.81 mmol) was heated under reflux in toluene (115 mL) in the presence of BHT (9.0 mg, 41 μmol) to afford a brown residue. The residue was purified by flash chromatography on silica gel using a gradient elution system (silica treated with 1% triethylamine, 19:1 petroleum ether–diethyl ether to 1:1 petroleum ether–diethyl ether) to afford a two Diels–Alder adducts. The *exo-trans* adduct **38** (38 mg, 10%), and the *exo-cis* adduct **44** (11 mg, 3%).

4.1.42. (*E,E*)-9-(*tert*-Butyldimethylsilanyloxy)-6-methylnona-4,6-dien-1-yn-3-ol. Ethynyl magnesiumbromide (11.2 mL, 5.62 mmol, 0.5 M in THF) was added to aldehyde **42** (1.19 g, 4.68 mmol) in THF (41 mL) yielding a yellow oil, which was purified by flash chromatography on silica gel using a gradient elution system (silica treated with 1% triethylamine, 6:1 petroleum ether–ethyl acetate to 2:1 petroleum ether–ethyl acetate) to afford a colourless oil (1.15 g, 88%). R_f (silica): 0.40 (2:1 petroleum ether–ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.46 (1H, d, J=15.6 Hz), 5.70 (1H, dd, J=15.6, 6.4 Hz), 5.59 (1H, t, J=7.3 Hz), 4.95 (1H, dd, J=6.4, 6.4 Hz), 3.64 (2H, t, J=7.0 Hz), 2.61 (1H, d, J=2.2 Hz), 2.39 (2H, dt, J=7.3, 7.0 Hz), 1.78 (3H, s), 0.90 (9H, s), 0.06 (6H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ?137.5, 134.1, 131.1, 124.8, 83.3, 74.3, 63.0, 62.6, 32.3, 26.0, 18.4, 12.6, −5.2; IR (ν_{max} cm^{-1}): 3593 (*O–H*), 3305 (*O–H*), 2954 (*C–H*), 2928 (*C–H*), 2884 (*C–H*), 2857 (*C–H*); LRMS: (CI, CH_4) *m/z* 131 (42%), 75 (100); HRMS: (CI, CH_4) *m/z*. Found: $[M-H]^+$ 279.1769, $C_{16}H_{27}O_2Si$ requires: 279.1780.

4.1.43. Ethyl (*E,E*)-7-(*tert*-butyldimethylsilanyloxy)-1-ethynyl-4-methylhepta-2,4-dienyl fumarate (45). (*E,E*)-9-(*tert*-Butyldimethylsilanyloxy)-6-methylnona-4,6-dien-1-yn-3-ol (0.97 g, 3.5 mmol) was esterified with monoethyl fumaryl chloride (0.62 g, 3.8 mmol) in diethyl ether (78 mL) in the presence of triethylamine (0.97 mL, 6.9 mmol) to afford a yellow oil. The crude oil was purified by flash chromatography on silica gel (silica treated with 1% triethylamine, 19:1 petroleum ether–diethyl ether to 2:1 petroleum ether–diethyl ether) to afford **45** as a colourless oil (0.92 g, 65%). R_f (silica): 0.80 (2:1 petroleum ether–ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.92 (1H, d, J=15.8 Hz), 6.87 (1H, d, J=15.8 Hz), 6.56 (1H, d, J=15.5 Hz), 6.02 (1H, d, J=7.1 Hz), 5.64 (1H, t, J=7.1 Hz), 5.63 (1H, dd, J=15.7, 7.1 Hz), 4.27 (2H, q, J=7.1 Hz), 3.65 (2H, t, J=7.1 Hz), 2.63 (1H, d, J=2.2 Hz), 2.40 (2H, dt, J=7.1, 7.1 Hz), 1.77 (3H, s), 1.32 (3H, t, J=7.1 Hz), 0.90 (9H, s), 0.06 (3H, s), 0.01 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.7 (C), 163.7 (C), 140.4 (CH), 134.5 (CH), 133.8 (C), 132.9 (CH), 132.4 (CH), 119.9 (CH), 77.2 (C), 65.3 (CH), 62.4 (CH_2), 61.4 (CH_2), 32.2 (CH_2), 25.9 (CH_3), 18.3 (C), 14.1 (CH_3), 12.4 (CH_3), −5.3 (CH_3); IR (ν_{max} cm^{-1}): 2954 (*C–H*), 2929 (*C–H*), 2857 (*C–H*), 1720 (*C=O*).

4.1.44. Diels–Alder cyclisation of ethyl (*E,E*)-7-(*tert*-butyldimethylsilanyloxy)-1-ethynyl-4-methylhepta-2,4-dienyl fumarate (45). Fumarate ester **45** (1.00 g, 2.46 mmol) was heated under reflux in toluene (200 mL) for 18 h then concentrated in vacuo to leave a brown residue. The residue was purified by flash chromatography on silica gel (silica treated with 1% triethylamine, 19:1 petroleum ether–ethyl acetate to 4:1 petroleum ether–ethyl acetate) to afford three Diels–Alder products, an *endo* adduct **46** (42 mg, 4%), an *exo-trans* adduct **47** (0.10 g, 10%) and an *exo-cis* adduct **48** (0.38 g, 38%).

4.1.45. Ethyl (1*R,2*R**,3*R**,6*R**)-3-(*tert*-Butyldimethylsilanyloxyethyl)-7-ethynyl-4-methyl-9-oxo-8-oxabicyclo-[4.3.0]-non-4-ene-2-carboxylate (46).** R_f (silica): 0.15 (19:1 petroleum ether–ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.40 (1H, s), 4.83 (1H, dd, J=2.6, 2.6 Hz), 4.17 (2H, q, J=7.1 Hz), 3.80–3.70 (2H, m), 3.46 (1H, dd, J=8.4, 2.6 Hz), 3.38–3.30 (2H, m), 2.78 (1H, br, d, J=9.5 Hz), 2.67 (1H, d, J=2.6 Hz), 1.78 (1H, m), 1.75 (3H, s), 1.38 (1H, m), 1.26 (3H, t, J=7.1 Hz), 0.91 (9H, s), 0.08 (3H, s), 0.07 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.3, 173.6, 140.3, 119.0, 76.2, 72.8, 61.3, 60.2, 41.5, 40.0, 37.1, 36.0, 34.7, 29.8, 26.0, 22.8, 18.3, 14.3, −5.2; IR (ν_{max} cm^{-1}): 2976 (*C–H*), 2954 (*C–H*), 2930 (*C–H*), 2858 (*C–H*), 1778 (*lactone C=O*), 1724 (*ester C=O*); LRMS: (ES) *m/z* 408 $[M+H]^+$ (40%), 407 (100).

4.1.46. Ethyl (1*S,2*S**,3*R**,6*R**,7*R**)-3-(*tert*-butyldimethylsilanyloxyethyl)-7-ethynyl-4-methyl-9-oxo-8-oxabicyclo-[4.3.0]-non-4-ene-2-carboxylate (47).** R_f (silica): 0.10 (19:1 petroleum ether–ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.57 (1H, s), 4.60 (1H, dd, J=10.6, 2.0 Hz), 4.33–4.12 (2H, m), 3.56 (1H, m), 3.35 (1H, m), 2.87 (1H, dd, J=11.5, 6.1 Hz), 2.76 (1H, br m), 2.67 (1H, dd, J=2.0 Hz), 2.65 (1H, br m), 2.54 (1H, dd, J=13.7, 11.5 Hz), 1.90 (1H, m), 1.79 (3H, s), 1.57 (1H, m), 1.30 (3H, t, J=7.0 Hz), 0.89 (9H, s), 0.03 (6H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.0 (C), 170.8 (C), 142.2 (C), 116.4 (CH), 77.8 (C), 76.5 (CH), 70.9 (CH), 61.4 (CH_2), 60.9 (CH_2), 48.5 (CH), 43.3 (CH), 41.4 (CH), 38.9 (CH), 33.3 (CH_2), 25.8 (CH_3), 21.7 (CH_3),18.2 (C), 14.0 (CH_3), −5.5 (CH_3); IR (ν_{max} cm^{-1}): 2954 (*C–H*), 2930 (*C–H*), 2857 (*C–H*), 1791 (*lactone C=O*), 1730 (*ester C=O*); LRMS: (EI) *m/z* 350 (71%), 349 (100), 275 (30), 229 (53), 201 (44), 157 (65), 142 (36), 129 (33), 103 (31), 73 (74); HRMS: (EI) *m/z*. Found: $[M]^+$ 406.2180, $C_{22}H_{34}O_5Si$ requires: 406.2176.

4.1.47. Ethyl (1*R,2*R**,3*S**,6*S**,7*R**)-3-(*tert*-butyldimethylsilanyloxyethyl)-7-ethynyl-4-methyl-9-oxo-8-oxabicyclo-[4.3.0]-non-4-ene-2-carboxylate (48).** R_f (silica): 0.10 (19:1 petroleum ether–ethyl acetate); ^{1}H NMR (400 MHz, CD_3OD): δ 5.45 (1H, d, J=1.1 Hz), 5.17 (1H, dd, J=6.5, 2.1 Hz), 4.20–4.02 (2H, m), 3.48–3.37 (2H, m), 3.08 (1H, d, J=2.1 Hz,), 2.93 (1H, m), 2.85 (1H, dd, J=11.6, 6.3 Hz), 2.71 (1H, dd, J=13.7, 11.6 Hz), 2.56 (1H, unresolved dd, J=6.1 Hz), 1.82 (1H, m), 1.70 (3H, s), 1.50 (1H, m), 1.21 (3H, t, J=7.2 Hz), 0.80 (9H, s), 0.04 (6H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.1 (C), 171.0 (C), 141.9 (C), 117.2 (CH), 77.2 (C), 76.8 (CH), 69.8 (CH), 61.3 (CH_2), 60.9 (CH_2), 45.2 (CH), 43.5 (CH), 39.0 (CH), 38.5 (CH), 33.3 (CH_2), 25.9 (CH_3), 21.8 (CH_3),18.2 (C), 14.0 (CH_3), −5.4 (CH_3); IR (ν_{max} cm^{-1}): 2953 (*C–H*), 2929 (*C–H*), 2857 (*C–H*), 1795 (*lactone C=O*), 1731 (*ester C=O*); LRMS: (ES) *m/z* 408 $[M+H]^+$ (50%), 407 (100); *Microanalysis*: Found: C 65.06%, H 8.35%, $C_{22}H_{34}O_5Si$ requires: C 64.99%, H 8.43%.

4.1.48. Ethyl (1*R,2*R**,3*S**,6*S**,7*R**)-7-ethynyl-3-(2-hydroxyethyl)-4-methyl-9-oxo-8-oxabicyclo-[4.3.0]-non-4-ene-2-carboxylate (52).** To Diels-Alder adduct **38** (0.10 g, 0.25 mmol) in THF (2 mL) at 0 °C was added ammonium chloride (90 mg, 1.7 mmol) and tetrabutylammonium fluoride (0.5 mL, 0.5 mmol, 1 M in THF). The reaction was allowed to warm to rt and was stirred for 6 h. After this time the reaction was diluted with ethyl acetate (10 mL) and washed with saturated aqueous copper sulphate (5 mL) and brine (2×5 mL), and then dried ($MgSO_4$). The organic layer was concentrated to give alcohol **52** as a brown oil. The residue was purified by flash

chromatography on silica gel (silica treated with 1% triethylamine, 2:1 petroleum ether–ethyl acetate) to afford the title compound as a colourless oil (54 mg, 54%). R_f (silica): 0.25 (2:1 petroleum ether–ethyl acetate); ^{1}H NMR (400 MHz, CD_3OD): δ 5.55 (1H, s), 5.15 (1H, dd, J=6.4, 2.1 Hz), 4.34–4.18 (2H, m), 3.60 (2H, t, J=7.0 Hz), 3.04 (1H, dd, J=13.2, 11.7 Hz,), 2.95 (1H, m), 2.91 (1H, dd, J=11.7, 6.4 Hz), 2.67 (1H, br s), 2.62 (1H, d, J=2.1 Hz), 2.02 (1H, m), 1.82 (3H, s), 1.65 (1H, m), 1.32 (3H, t, J=7.2 Hz); IR (ν_{max} cm^{-1}): 3622 (*O–H*), 3305 (*O–H*), 2939 (*C–H*), 1790 (*lactone C=O*), 1730 (*ester C=O*); LRMS: (ES) *m/z* 293 $[M+H]^+$ (40%), 247 (100); HRMS: (ES) *m/z*. Found: $[M+H]^+$ 293.1414, $C_{16}H_{21}O_5$ requires: 293.1389.

4.1.49. (*E,E*)-9-(*tert*-Butyldimethylsilanyloxy)-6-methyl-1-(trimethylsilanyl)nona-4,6-dien-1-yn-3-ol. *n*-Butyllithium (0.11 mL, 0.28 mmol, 2.5 M in hexanes) was added to trimethylsilyl acetylene (45 μL, 0.32 mmol) in THF (1.5 mL) at 0 °C. After 20 min a solution of aldehyde 289 (50 mg, 0.20 mmol) in THF (0.5 mL) was added over 5 min and stirred for 10 min at 0 °C, then 30 min at rt. The reaction was quenched with a saturated aqueous solution of ammonium chloride (1 mL), which was then diluted with ethyl acetate (7 mL). The organic layer was separated and washed with aqueous hydrochloric acid (1 M, 2×1 mL), saturated aqueous sodium hydrogen carbonate (5 mL) and brine (5 mL), dried ($MgSO_4$) and concentrated to afford a yellow oil. The oil was purified by flash chromatography on silica gel (9:1 petroleum ether–ethyl acetate to 2:1 petroleum ether–ethyl acetate) to afford the product alcohol as a colourless oil (55 mg, 80%). R_f (silica): 0.45 (2:1 petroleum ether–ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.43 (1H, d, J=15.4 Hz), 5.68 (1H, dd, J=15.4, 6.3 Hz), 5.57 (1H, t, J=7.6 Hz), 4.93 (1H, dd, J=6.3, 6.3 Hz), 3.65 (2H, t, J=7.0 Hz), 2.39 (2H, dt, J=7.6, 7.0 Hz), 1.78 (3H, s), 0.90 (9H, s), 0.20 (9H, s), 0.04 (3H, s), 0.01 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.3, 134.1, 130.8, 125.1, 104.7, 90.9, 77.2, 63.5, 62.5, 32.1, 25.9, 18.3, 12.6, −0.2, −5.3; IR (ν_{max} cm^{-1}): 3584 (*O–H*), 2956 (*C–H*), 2929 (*C–H*), 2857 (*C–H*); LRMS: (ES) *m/z* 335 (100%), 203 (30); HRMS: (CI, CH_4) *m/z* Found $[M-H]^+$ 351.2156, $C_{19}H_{37}O_2Si_2$ requires 351.2176.

4.1.50. Ethyl (*E,E*)-7-(*tert*-butyldimethylsilanyloxy)-4-methyl-1-(trimethylsilanylethynyl) hepta-2,4-dienyl fumarate (49). (*E,E*)-9-(*tert*-Butyldimethylsilanyloxy)-6-methyl-1-(trimethylsilanyl)nona-4,6-dien-1-yn-3-ol (0.19 g, 0.53 mmol) was esterified with monoethyl fumaryl chloride (94 mg, 0.58 mmol) in diethyl ether (12 mL) in the presence of triethylamine (0.15 mL, 1.1 mmol) to afford a yellow oil. The crude oil was purified by flash chromatography on silica gel (silica treated with 1% triethylamine, 19:1 petroleum ether–diethyl ether to 2:1 petroleum ether–diethyl ether) to afford the Diels–Alder precursor as a colourless oil (0.20 g, 79%). R_f (silica): 0.85 (4:1 petroleum ether–ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.90 (1H, d, J=15.8 Hz), 6.86 (1H, d, J=15.8 Hz), 6.54 (1H, d, J=15.6 Hz), 6.05 (1H, d, J=6.5 Hz), 5.62 (1H, t, J=6.7 Hz), 5.60 (1H, dd, J=15.6, 6.5 Hz), 4.26 (2H, q, J=7.1 Hz), 3.65 (2H, t, J=7.1 Hz), 2.39 (2H, dt, J=7.1, 6.7 Hz), 1.77 (3H, s), 1.32 (3H, t, J=7.1 Hz), 0.90 (9H, s), 0.20 (9H, s), 0.06 (6H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.9, 163.8, 140.4, 134.4, 134.0, 133.3, 132.2, 120.5, 116.3, 100.3, 92.8, 66.0, 62.5, 61.4, 32.3, 26.0, 18.4, 14.2, 12.6, −0.2, −5.2; IR (ν_{max} cm^{-1}): 2956 (*C–H*), 2929 (*C–H*), 2900 (*C–H*), 2857 (*C–H*), 1719 (*C=O*).

4.1.51. Diels–Alder cyclisation of ethyl (*E,E*)-7-(*tert*-butyldimethylsilanyloxy)-4-methyl-1-(trimethylsilanylethynyl)hepta-2,4-dienyl fumarate (49). Fumarate ester **49** (0.24 g, 0.50 mmol) was heated under reflux in toluene (70 mL) in the presence of BHT (5.5 mg, 25 μmol) to afford an orange residue. The crude residue was purified by flash chromatography on silica gel using a gradient elution system (silica treated with 1% triethylamine, 19:1 petroleum ether–ethyl acetate to 1:1 petroleum ether–ethyl acetate) to afford two Diels–Alder adducts. The *exo-trans* adduct **51** (24 mg, 10%), and the *exo-cis* adduct **50** (93 mg, 39%).

4.1.52. Ethyl (1*S,2*S**,3*R**,6*R**,7*R**)-3-(*tert*-butyldimethylsilanyloxyethyl)-4-methyl-9-oxo-7-(trimethylsilanylethynyl)-8-oxabicyclo-[4.3.0]-non-4-ene-2-carboxylate (51).** R_f (silica): 0.20 (9:1 petroleum ether–ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.58 (1H, s), 4.60 (1H, d, J=10.0 Hz), 4.29 (1H, m), 4.16 (1H, m), 3.56 (1H, m), 3.38 (1H, m), 2.86 (1H, dd, J=11.4, 6.1 Hz), 2.74 (1H, tq, J=13.6, 11.0 Hz), 2.64 (1H, br t, J=6.1 Hz), 2.53 (1H, dd, J=13.6, 11.4 Hz), 1.90 (1H, m), 1.81 (3H, s), 1.58 (1H, m), 1.31 (3H, t, J=7.1 Hz), 0.89 (9H, s), 0.20 (9H, s), 0.03 (6H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.4, 171.0, 142.0, 116.8, 98.8, 94.2, 71.8, 61.5, 61.0, 48.7, 43.5, 41.6, 39.0, 33.4, 26.0, 21.8, 18.3, 14.2, −0.3, −5.3; IR (ν_{max} cm^{-1}): 2955 (*C–H*), 2930 (*C–H*), 2900 (*C–H*), 2857 (*C–H*), 1794 (*lactone C=O*), 1731 (*ester C=O*); LRMS: (ES) *m/z* 479 $[M+H]^+$ (100%), 433 (85), 347 (90), 301 (50), 273 (48); HRMS: (ES) *m/z*. Found: $[M+H]^+$ 479.2615, $C_{25}H_{43}O_5Si_2$ requires: 479.2649.

4.1.53. Ethyl (1*R,2*R**,3*S**,6*S**,7*R**)-3-(2-*tert*-butyldimethylsilanyloxyethyl)-4-methyl-9-oxo-7-(trimethylsilanylethynyl)-8-oxabicyclo-[4.3.0]-non-4-ene-2-carboxylate (50).** R_f (silica): 0.20 (9:1 petroleum ether–ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.46 (1H, d, J=1.1 Hz), 5.10 (1H, d, J=5.9 Hz), 4.30 (1H, m), 4.17 (1H, m), 3.56 (1H, m), 3.42 (1H, m), 2.95–2.83 (3H, m), 2.64 (1H, br s), 1.94 (1H, m), 1.8 (3H, s), 1.58 (1H, m), 1.32 (3H, t, J=7.1 Hz), 0.88 (9H, s), 0.17 (9H, s), 0.04 (6H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.5, 171.2, 141.8, 117.5, 98.0, 94.9, 70.7, 61.4, 60.9, 45.6, 43.5, 39.1, 38.6, 33.6, 25.9, 21.8, 18.2, 14.2, −0.3, −5.3; IR (ν_{max} cm^{-1}): 2955 (*C–H*), 2930 (*C–H*), 2884 (*C–H*), 2857 (*C–H*), 1791 (*lactone C=O*), 1731 (*ester C=O*); LRMS: (ES) *m/z* 479 $[M+H]^+$ (100%), 433 (54), 347 (47), 273 (41); HRMS: (ES) *m/z*. Found: $[M+H]^+$ 479.2662, $C_{25}H_{43}O_5Si_2$ requires: 479.2649; *Microanalysis*: Found: C 62.71%, H 8.80%, $C_{25}H_{42}O_5Si_2$ requires: C 62.72%, H 8.84%.

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Biomimetic synthesis of (±)-aculeatin D

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Abstract—A practical, efficient and diastereoselective synthesis of the cytotoxic and antiprotozoal compound aculeatin D (**1**) is described, employing a biomimetic oxidative cyclisation cascade reaction to generate the tricyclic system of the natural product. The synthesis proceeds in ten steps from commercially available 1-tetradecanol.

1. Introduction

During the course of research on novel cytotoxic and antiprotozoal comounds derived from plants, three novel compounds, named aculeatins A **1**, B **2** and C **3** (Fig. 1) were isolated by Heilmann and co-workers from the petroleum ether extracts of the rhizomes of *Amomum aculeatum*.[1] Further investigation of these extracts led to the isolation of a fourth member, named aculeatin D **4**, of this small class of natural products.[2] Common to all four metabolites is the presence of a unique 1,7-dioxa-dispiro[5.1.5.2]-9,12-dien-11-one tricyclic ring system, which is without precedent in the literature, while aculeatin C **3** also contains an additional cyclohexadienone unit. All four compounds were found to display optical activity, however, the absolute configuration of these compounds remains unknown.

The plant from which the aculeatin class of compounds has been isolated, *A. aculeatum*, has traditionally been used by the indigenous people of Papau New Guinea as a folk medicine against fever and malaria.[3] Initial studies have shown the aculeatin compounds to display an impressive range of biological effects, including antibacterial activity against *Bacillus cereus* and *Escherichia coli*, and potent antiprotozoal activity against both the NF54 and the chloroquine-resistant K1 strains of the malarial parasite *Plasmodium falciparum*. Most intriguingly, all four compounds were found to display potent cytotoxicity against a KB carcinoma cell line (ATCC CCL 17). The relative stereochemistry of the C-2, C-4 and C-6 tetrahydropyran ring substituents was found to be important in determining the relative potency of the compounds; aculeatin D **4** was found to be the most active in the cytotoxicity assay, with an

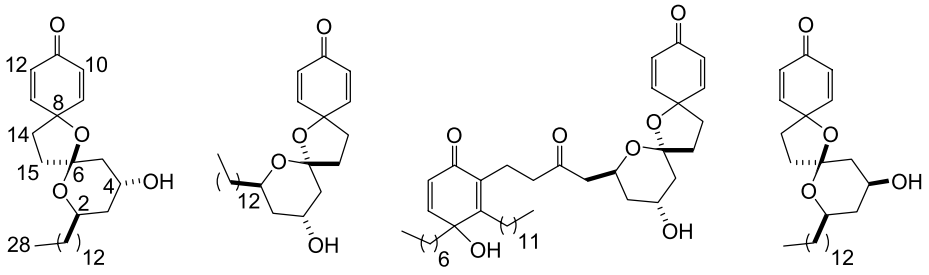

Figure 1.

Keywords: Biomimetic synthesis; Aculeatin D; Oxidative cyclisation; Hypervalent iodine reagents.
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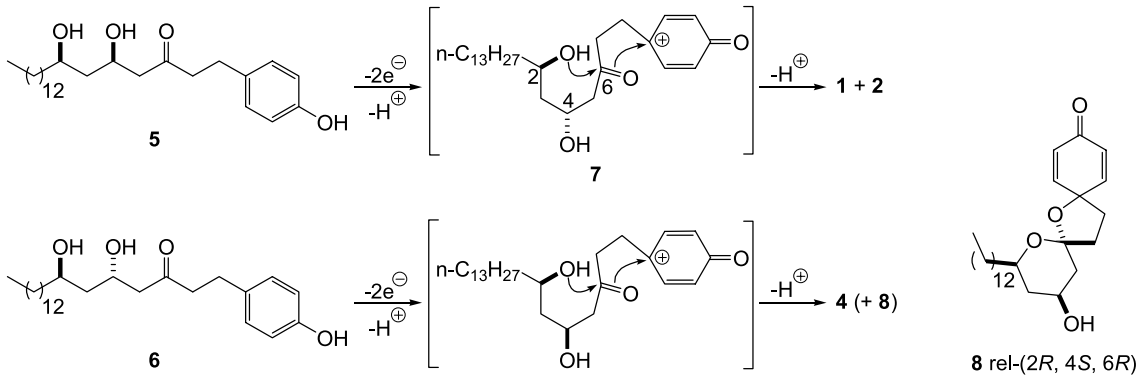


Scheme 1.

IC_{50} value of 0.38 μg/mL.[2] The structural novelty of these compounds potentially indicates a hitherto unknown mode of cytotoxicity.

A key consideration in designing a synthesis of the generic aculeatin compound structure involves the stereoselective construction of the tricyclic spiroketal-containing ring system. Spiroketal units occur as substructures of a wide variety of biologically active natural products, and there has been considerable interest in the synthesis and chemical reactivity of spiroketal ring systems.[4,5] A potentially rapid biomimetic approach to the synthesis of the aculeatin class of compounds would involve a formal two-electron oxidation of the phenol ring in precursors **5** or **6** (Scheme 1) being followed by tandem cationic based intramolecular cyclisations, to generate the core tricyclic ring system in a single step from an open chain precursor.

The oxidative double cyclisation of the *syn*-1,3-diol **5** would be expected to generate aculeatins A **1** and B **2**, which would arise as the result of cyclisation of the C-2 hydroxyl group (aculeatin numbering) onto the *Re* and *Si* diastereotopic faces of the C-6 ketone group in intermediate **7** respectively. By analogy, the oxidative cyclisation of the *anti*-1,3-diol **6** would be expected to generate aculeatin D **4**, as well as, potentially, the corresponding C-6 diastereoisomer **8**. Following a report by Wong of the synthesis of racemic aculeatins A **1** and B **2** (Scheme 2),[6] in which a phenolic dithioketal **9** was similarly oxidized, we now disclose the results of our studies on the synthesis and oxidative cyclisation of the 1,3-*anti* diol **6**, which has culminated in the first total synthesis of racemic aculeatin D **4**.

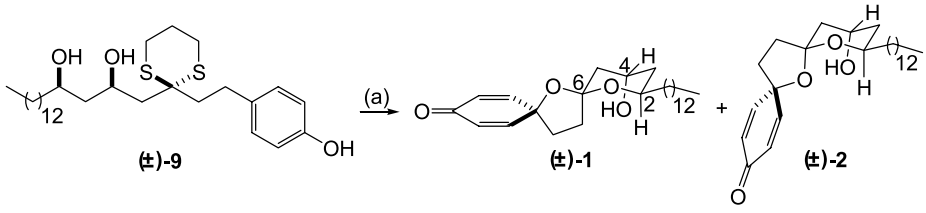
2. Results and discussion

We initially decided to pursue a simple model system to investigate the viability of the tandem oxidation/double cyclisation reaction, as at that time there were few reports in the literature of the intra-molecular oxidative cyclisation of phenolic compounds employing aliphatic hydroxyl groups as the capturing nucleophile,[7,8] and no examples of tandem oxidative cyclisations to generate a tricyclic ring system.

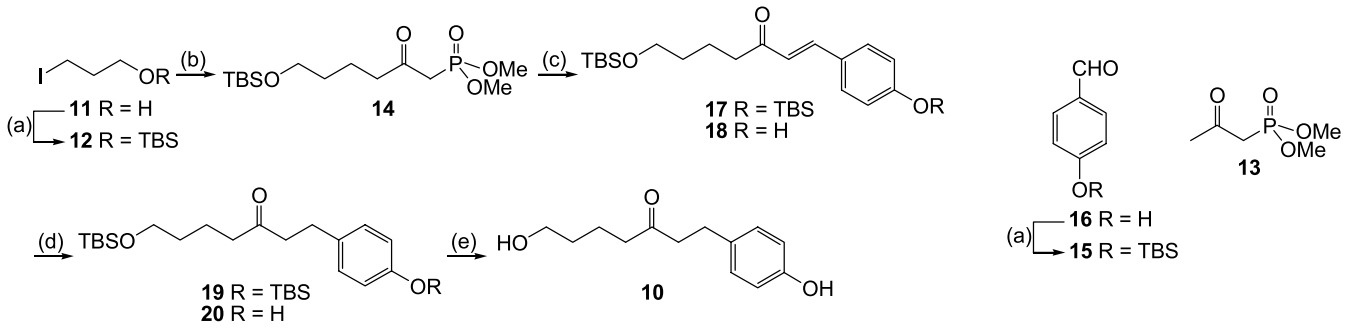
To this end, ketone **10** was prepared from 3-iodo-1-propanol **11**, which was initially protected as the corresponding TBS ether **12** (Scheme 3).[9] Selective γ-alkylation of the dianion derived from phosphonate **13** with iodide **12**, under the conditions reported for the corresponding diethyl phosphonate homologue,[10] then gave β-ketophosphonate **14**. The Wadsworth-Emmons reaction of phosphonate **14** with aldehyde **15** (readily prepared in one step via the protection of 4-hydroxybenzaldehyde **16**[11]) then gave alkene **17**. A second product was isolated from this reaction, and this was determined to be the unexpected desilylated phenol **18**. Optimisation of the reaction conditions revealed that the yield of the desired alkene **17** was maximised at 74%, together with 14% of the mono-deprotected side product **18**, if the reaction was quenched 4 h after the addition of aldehyde **15**.

While the lability of aryl silyl ethers relative to alkyl silyl ethers under basic conditions has been documented,[12] it was nevertheless suprising to find that the phenolic silyl ether could be cleaved under the relatively mild conditions of the reaction. However, after chromatographic separation, both the di- and mono-protected compounds **17** and **18** could be carried through to the next stages of the synthesis. Alkenes **17** and **18** were then separately hydrogenated to give ketones **19** and **20** respectively; deprotection of either compound **19** or **20** then gave the desired model cyclisation precursor **10** in moderate yield.

It was decided to employ hypervalent iodine(III) based reagents to effect the oxidative cyclisation of the model



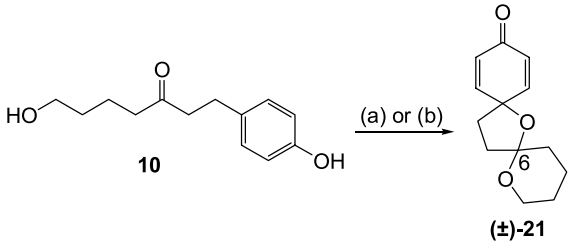
Scheme 2. Reagents and conditions: (a) $PhI(O_2CCF_3)_2$, $MeCN/H_2O$ (6:1 v/v), 0 °C, 5 min (44% (±)-**1**+15% (±)-**2**).



Scheme 3. Reagents and conditions: (a) TBSCl, imidazole, THF, rt, 2 h (91% for **11**→**12**, 90% for **16**→**15**), (b) **13**, NaH, THF, 0 °C, 1.5 h then *n*-BuLi, 0 °C, 20 min then **12**, 0 °C, 1 h (71%), (c) NaH, THF, rt, 1.5 h then **15**, rt, 4 h (72% **17**+14% **18**), (d) H_2 (1 atm), cat. Pd/C, EtOAc, rt, 16 h (65% for **17**→**19**, 82% for **18**→**20**), (e) TBAF, THF, 0 °C→rt, 2 h (48% for **19**→**10**, 25% for **20**→**10**).

compound **10**, as such iodine reagents are a convenient alternative to the use of toxic heavy-metal based reagents (e.g. $Pb(OAc)_4$) for activating hydroxylated aromatic rings towards oxidative nucleophilic substitution reactions.[13,14] Treatment of ketone **10** with $PhI(OAc)_2$ in MeCN led to clean consumption of starting material and formation of a single new product, albeit in moderate (unoptimised) yield, which was shown to be the desired tricyclic compound (±)-**21** (Scheme 4). It was subsequently found that the reaction yield could be increased dramatically if $PhI(O_2CCF_3)_2$ was used as the oxidant.

Due to the presence of the newly formed anomeric centre at the C-6 position, the product (±)-**21** could potentially exist in two favoured conformations, (±)-**21**-**A** and (±)-**21**-**B**



Scheme 4. Reagents and conditions: (a) $PhI(OAc)_2$, MeCN, rt, 1 h (43%), (b) $PhI(O_2CCF_3)_2$, MeCN, rt, 2 h (66%).

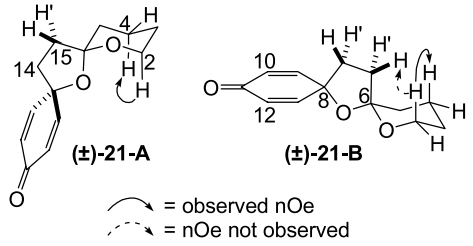


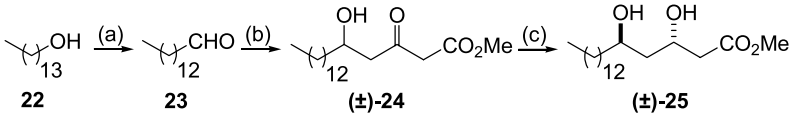
Figure 2.

(Fig. 2). However, the ^1H and ^{13}C NMR spectra of the product (±)-**21** clearly indicated that, in deuterated chloroform solution, the compound existed in a single conformation, which was proposed to be (±)-**21**-**A** on the basis of the absence of an observable NOE between the axial C-2 proton and the C-15 methylene protons.

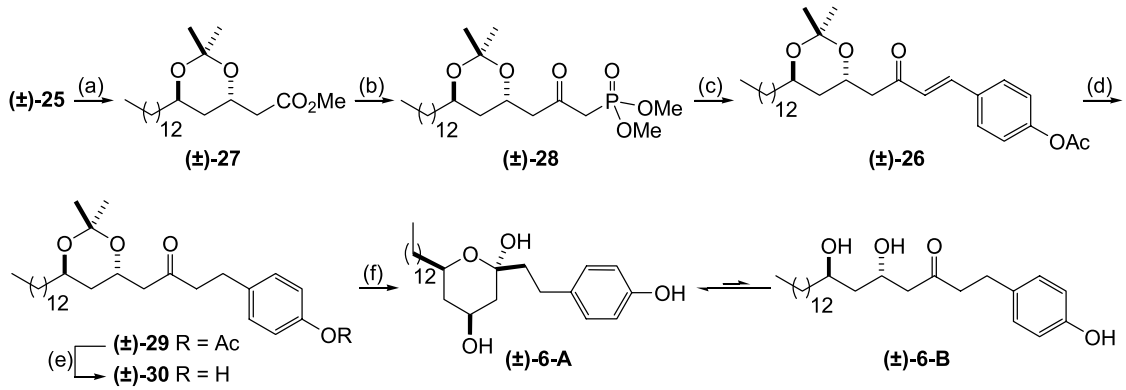
Encouraged by the facile oxidative conversion of ketone **10** to tricyclic compound **21**, we then focused our efforts on the synthesis of the diol **6** required for the formation of aculeatin D **4**. Thus, oxidation of commercially available 1-tetradecanol **22** using PCC afforded the corresponding aldehyde **23** (Scheme 5),[15] then selective γ-alkylation of the dianion of methyl acetoacetate gave racemic alcohol (±)-**24** in good overall yield. Following the Evans' protocol, treatment of compound (±)-**24** with tetramethylammonium triacetoxyborohydride resulted in a chemo- and diastereoselective reduction of the ketone group;[16] 500 MHz NMR analysis of the crude product mixture indicated the formation of a 95:5 mixture of 1,3-*anti*-:1,3-*syn*-diol products, and a single recrystallisation gave the pure 1,3-*anti* product (±)-**25** in excellent yield.

Based upon earlier failures to obtain alkene **26** (Scheme 6) without hydroxyl group protection, diol (±)-**25** was converted into the acetonide derivative **27** in excellent yield; analysis of the ^{13}C NMR spectrum of acetonide (±)-**27** confirmed the relative stereochemistry of the 1,3-*anti*-diol unit, through the application of the Rychnovsky protocol for the configurational assignment of 1,3-polyol chains.[17] Treatment of acetonide (±)-**27** with α-lithio methyl phosphonoacetate then gave phosphonate (±)-**28**.

Gratifyingly, the Wadsworth–Emmons olefination between phosphonate (±)-**28** and commercially available 4-acetoxybenzaldehyde proceeded efficiently at room temperature to afford alkene (±)-**26** in good yield (Scheme 6), and exclusively as the (*E*)-isomer (confirmed by the measured coupling constant between the alkene



Scheme 5. Reagents and conditions: (a) PCC, DCM, rt, 2 h (85%), (b) methyl acetoacetate, NaH, THF, 0 °C, 10 min then *n*-BuLi, 0 °C, 10 min then **23**, 20 min (84%), (c) $Me_4NBH(OAc)_3$, MeCN/AcOH (1:1 v/v), −25 °C, 2 h then 0 °C, 3 h (89%).



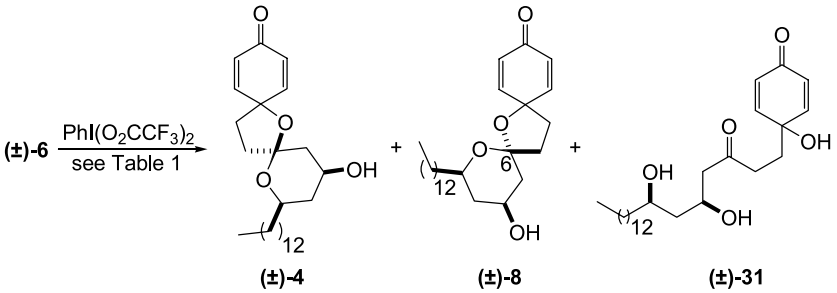
Scheme 6. Reagents and conditions: (a) 2,2-dimethoxypropane, CSA, 0 °C, 3 h (98%), (b) dimethyl methylphosphonate, *n*-BuLi, THF, −78 °C, 30 min then (±)-**27**, −78 °C, 20 min (65%), (c) NaH, THF, 0 °C→rt, 40 min then 4-acetoxybenzaldehyde, rt, 24 h (82%), (d) H_2 (1 atm), cat. Pd/C, EtOAc, rt, 16 h (76%), (e) K_2CO_3, MeOH, rt, 45 min (89%), (f) 0.5 M aq. HCl, THF, 0 °C→rt, 1 h (83%).

protons of 16 Hz). The palladium-catalysed hydrogenation of alkene (±)-**26** then afforded ketone (±)-**29**, and subsequent basic cleavage of the acetate group then gave phenol (±)-**30**. The acetonide protecting group was then cleanly removed from ketone (±)-**30** under aqueous acidic conditions. The product was formed as a white solid in good yield, and was shown to be the cyclic compound (±)-**6-A**, however, in solution this material was found to equilibrate to a mixture of cyclic compound (±)-**6-A** and the open-chain derivative (±)-**6-B**; in deuterated acetone a 2:1 equilibrium mixture of compounds (±)-**6-A**:(±)-**6-B** was formed within 3 h at room temperature.

The oxidative cyclisation of ketone (±)-**6** was first attempted under the conditions that were successful for the conversion of model precursor **10** into tricyclic compound (±)-**21**. Treatment of ketone (±)-**6** with $PhI(O_2CCF_3)_2$ in MeCN at 0 °C led to the rapid consumption of the starting material, and the formation of two new products in moderate yield (Scheme 7 and Table 1); spectroscopic analysis revealed that these two compounds were tricyclic compound (±)-**8** and ketone (±)-**31**. Extensive NOE analysis indicated that compound (±)-**8** was the C-6 epimer of aculeatin D **4**; particularly indicative of the stereochemistry at the C-6 position in compound (±)-**8** was the absence of observable NOEs between the C-15 methylene group and the C-2 and C-4 hydrogens (enhancements which are observed in aculeatin D **4**[2]), and the observation of an NOE between one of the C-15 methylene protons and the axial methylene proton at the C-5 position (Fig. 3). The formation of ketone **31** is likely to be due to the presence of adventitious water in the reaction mixture, which intercepts the putative phenoxenium cation[18] before the intramolecular cyclisation can occur.

The next conditions attempted were those used by Wong in the conversion of dithiane (±)-**9** to a mixture of racemic aculeatins A (±)-**1** and B (±)-**2** (cf. Scheme 2);[6] however, the use of aqueous acetonitrile as the solvent for the oxidation of phenol (±)-**6** did not produce any of the desired aculeatin D (±)-**4**, but instead merely increased the yield of ketone (±)-**31** (Table 1).

After extensive variation of the reaction conditions, it was found that performing the oxidation in acetone resulted in the formation of an additional third product, isolated in 11% yield, which was found to be the desired racemic aculeatin D (±)-**4** (Table 1). The NMR and mass spectrometry data



Scheme 7.

Table 1

Conditions	Yield of (±)-**4** (%)	Yield of (±)-**8** (%)	Yield of (±)-**31** (%)
MeCN, 0 °C, 1 h	0	33	15
MeCN/H_2O (6:1 v/v), 0 °C, 1 h[6]	0	29	44
Acetone, rt, 20 min	11	40	20
Acetone/H_2O (9:1 v/v), rt, 20 min	19	43	27

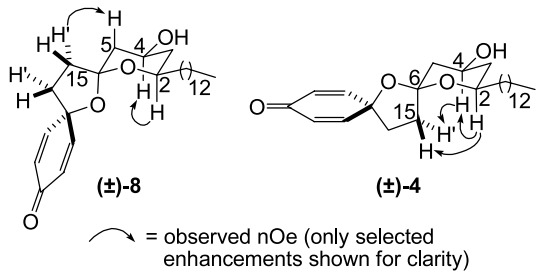


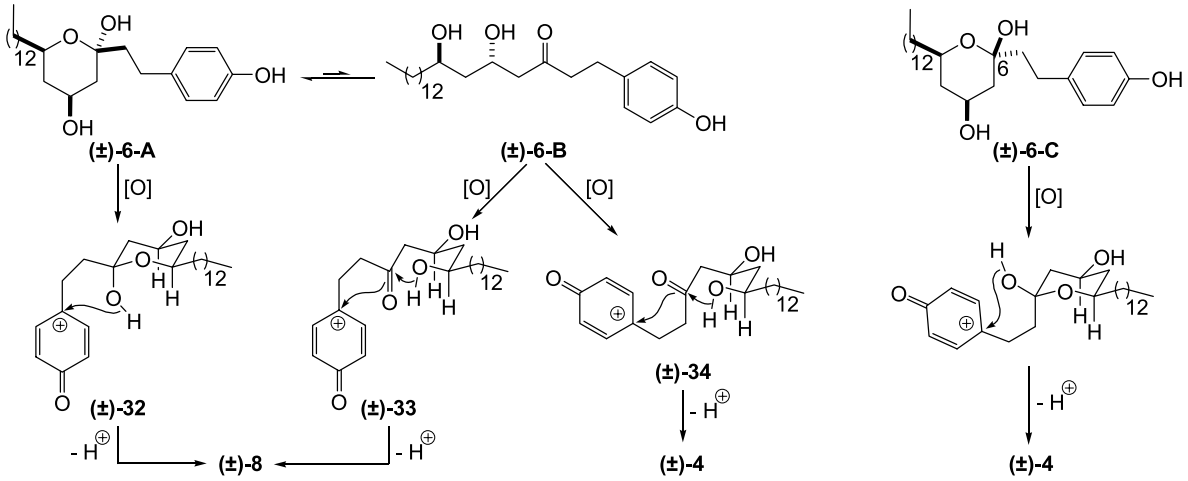
Figure 3.

of compound (±)-**4** were found to be in excellent agreement with those reported for the natural product,[2] and co-chromatography (TLC) of the synthetic material with an authentic sample of the natural product revealed that the two compounds were identical.[19] The relative stereochemistry of the spiroacetal ring system in (±)-**4** was confirmed by NOE analysis (Fig. 3). After further optimization, it was found that using an acetone/water (9:1 v/v) solvent system for the reaction maximised the yield of aculeatin D (±)-**4** (18%), the proportion of the desired product (±)-**4** ((±)-**4**:(±)-**8**:(±)-**31** 1.0:2.4:1.5) and also the overall yield of the reaction (88%). It is interesting to note that the ratio of C-6 anomers **4**:(±)-**8** obtained under these conditions is almost exactly opposite the ratio of anomers (±)-**1**:(±)-**2** obtained by Wong in the deprotection/oxidative cyclisation reaction of dithiane (±)-**9**.[6]

It is possible to propose a mechanistic rationale for the dramatic influence of the nature of the solvent on the product distribution on the oxidative cyclisation (Scheme 8). The cyclisation precursor was found to exist as an equilibrium mixture of the cyclic compound (±)-**6**-**A** and the open-chain compound (±)-**6**-**B** in solution (vide supra). In deuterated acetone the equilibrium ratio of (±)-**6**-**A**: (±)-**6**-**B** was shown to be 2:1 (by 500 MHz NMR analysis), whereas in deuterated acetonitrile compound (±)-**6**-**A** was present almost exclusively ((±)-**6**-**A**: (±)-**6**-**B** >95:5); this suggests that the partitioning between (±)-**6**-**A** and (±)-**6**-**B** is likely to be due to hydrogen-bonding effects, since acetone would be expected to stabilize intermolecular hydrogen bonds (and thus favour the open-chain compound (±)-**6**-**B**) to a greater extent than would acetonitrile. A two-electron oxidation of the phenol ring in compound (±)-**6**-**A** would generate cation **32**, which is suitably positioned to undergo a rapid cyclisation to generate product (±)-**8**. The oxidation of compound (±)-**6**-**B**, however, could be expected to lead to both products (±)-**4** and (±)-**8**, via the double cyclisation of the intermediate cations (±)-**33** and (±)-**34** respectively. Greater solvent polarity would thus be expected to increase the proportion of (±)-**4** formed in the reaction, as is observed experimentally. An alternative pathway for the formation of (±)-**4** would be from compound (±)-**6**-**C** (Scheme 8), in a manner analogous to the proposed formation of (±)-**8** from (±)-**6**-**A**. However, this pathway appears to be less likely on the basis of the fact that compound (±)-**6**-**C** (the C-6 epimer of compound (±)-**6**-**A**) could not be detected at any point by NMR analysis of solutions of the cyclisation precursor, even after three weeks in deuterated acetone at room temperature. As an aside, it is possible to speculate that metal ion coordination could favour the open-chain structure (±)-**6**-**B** (required for formation of aculeatin D (±)-**4**) over the cyclic compound (±)-**6**-**A**, thus increasing the proportion of (±)-**4** formed during the oxidative cyclisation; however, this was not investigated experimentally.

3. Conclusions

The first total synthesis of racemic aculeatin D (±)-**4** has therefore been completed in ten steps from 1-tetradecanol **22**, thus confirming the structure and relative stereochemistry of this novel natural product. A number of analogues and derivatives of the natural product are potentially available through minor modifications of this flexible synthetic route. The key feature of the synthesis is the rapid construction of the tricyclic ring system via an oxidative cyclisation cascade in the last step. It is intriguing to speculate as to whether a similar cyclisation pathway is followed in the biosynthesis of these metabolites within the producing plant *A. aculeatum*, and as to whether compound **8** is co-produced with the other aculeatins, but has not been isolated yet.



Scheme 8.

4. Experimental

4.1. General procedures

All reactions were performed in oven-dried (24 h at 110 °C) glassware under an argon atmosphere. THF and DCM were distilled before use. Anhydrous DCM was obtained by refluxing over calcium hydride for 1 h, followed by distillation under argon. Anhydrous THF was obtained by refluxing over sodium-benzophenone for 1 h, followed by distillation under argon. All reagents were used as received, unless otherwise stated. Solvents were evaporated under reduced pressure at 40 °C using a Buchi Rotavapor RE111. Melting points were obtained using a Cambridge Instruments microscope with a Reichert–Jung heating mantle, and are uncorrected.

Flash chromatography was performed using silica gel (Prolabo Silica Gel 60, 200–400 mesh) as the stationary phase. TLC was performed on aluminium sheets pre-coated with silica (Merck Silica Gel 60 F_{254}), which were visualised by the quenching of UV fluorescence (λ_{max} 254 nm) and/or by staining with 5% w/v phosphomolybdic acid in EtOH followed by heating. Retention factor (R_f) values are quoted to ± 0.05.

IR spectra were recorded either as thin films on NaCl plates, as KBr discs or as solutions in $CHCl_3$ using a Perkin–Elmer Paragon 1000 Fourier Transform spectrometer. Only significant absorptions (ν_{max}) are reported, and all absorptions are reported in wavenumbers (cm^{-1}). The following abbreviations are used to describe absorption intensity: w, weak; m, medium; s, strong and br, broad.

Proton magnetic resonance spectra (^1H NMR) were recorded at 200, 400 or 500 MHz using Bruker DPX200, Bruker DQX400, Bruker DPX400, Bruker DRX500 or Bruker AMX500 spectrometers. Chemical shifts (δ_H) are reported in parts per million (ppm), and are referenced to the residual protonated solvent peak. COSY, NOE or NOESY experiments were used in selected cases to aid assignment. The order of citation in parentheses is (1) number of equivalent nuclei (by integration), (2) multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, m = multiplet, br = broad), (3) coupling constant (J) quoted in Hertz to the nearest 0.5 Hz, and (4) assignment. Carbon magnetic resonance spectra (^{13}C) were recorded at 100.6 or 125.7 MHz using Bruker DQX400, Bruker DPX400, Bruker DRX500 or Bruker AMX500 spectrometers. DEPT-135, HMBC, HMQC or HSQC experiments were used in selected cases to aid assignment. Chemical shifts (δ_C) are quoted in parts per million (ppm) and are referenced to the appropriate solvent peak. The assignment is quoted in parentheses.

Low resolution mass spectra (m/z) were recorded on Micromass Platform ES (ES) or VG Mass Lab Trio-1 (CI and EI) spectrometers. Only molecular ions and selected fragments of molecular ions are reported, with intensities quoted as percentages of the base peak. High resolution mass spectra were recorded on a VG AutoSpec spectrometer by chemical ionisation or on a Micromass LCT electrospray ionisation mass spectrometer operating at a resolution of 5000 full width at half height. Positive ion spectra were calibrated relative to poly(ethyleneglycol), with tetraoctylammonium bromide as the internal lock mass.

4.2. Experimental details

4.2.1. *tert*-Butyl-(3-iodopropoxy)dimethylsilane 12.[9] To a stirred solution of 1-iodopropan-3-ol **11** (1.00 g, 5.38 mmol) in THF (15 ml) was added imidazole (1.10 g, 16.12 mmol, 3.0 equiv) and TBSCl (1.05 g, 7.00 mmol, 1.3 equiv) at rt. After 2 h H_2O (20 ml) was added, and the mixture was diluted with DCM (20 ml). The layers were separated, and the aqueous layer was extracted with DCM (3×20 ml). The combined organic layers were washed with brine (1× 50 ml), dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography (Petrol) gave the title compound (1.47 g, 91%) as a pale yellow oil: R_f 0.15 (Petrol), δ_H (200 MHz; $CDCl_3$) 0.03 (6H, s, Si(CH_3)$_2$), 0.88 (9H, s, SiC(CH_3)$_3$), 1.88–2.04 (2H, m, CH_2CH_2OTBS), 3.25 (2H, t, J=6.5 Hz, CH_2I), 3.63 (2H, t, J=5.5 Hz, CH_2OTBS).

4.2.2. Dimethyl [6-(*tert*-butyldimethylsilanyloxy-2-oxohexyl)phosphonate 14. To a stirred suspension of NaH (101 mg of a 60% w/w suspension in mineral oil, 2.52 mmol, 1.8 equiv) in THF (30 ml) was added dimethyl (2-oxopropyl)phosphonate **13** (233 mg, 1.41 mmol) dropwise at 0 °C. The mixture was warmed to rt, stirred for 1.5 h, then re-cooled to 0 °C, before the addition of *n*-BuLi (0.62 ml of a 2.5 M solution in hexanes, 1.55 mmol, 1.1 equiv). After 20 min a solution of iodide **12** (506 mg, 1.68 mmol, 1.2 equiv) in THF (2 ml) was added, and the mixture was stirred at 0 °C for 1 h, before being quenched by the cautious addition of sat. aq. NH_4Cl (10 ml). The layers were separated, and the aqueous layer was extracted with EtOAc (3×20 ml). The combined organic layers were washed with brine (1×40 ml), dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography (EtOAc) gave the title compound (339 mg, 71%) as a pale yellow oil: R_f 0.2 (EtOAc); ν_{max} (film)/cm^{-1} 2955 (s), 2857 (m), 1716 (s), 1471 (m); δ_H (400M Hz; $CDCl_3$) −0.09 (6H, s, Si(CH_3)$_2$), 0.76 (9H, s, SiC(CH_3)$_3$), 1.37–1.42 (2H, m, CH_2CH_2OTBS), 1.48–1.56 (2H, m, CH_2CH_2C(=O)), 2.52 (2H, t, J=7.0 Hz, CH_2CH_2C(=O)), 2.97 (2H, d, J= 122.5 Hz, CH_2P(=O)(OCH$_3$)$_2$), 3.48 (2H, t, J=6.0 Hz, CH_2OTBS), 3.66 (6H, d, J=11.0 Hz, P(=O)(OCH_3)$_2$); δ_C(100.6 MHz; $CDCl_3$) −5.5 (Si(CH_3)$_2$), 18.2 (SiC(CH$_3$)$_3$), 19.7 (CH_2CH_2C(=O)), 25.8 (SiC(CH_3)$_3$), 31.8 (CH_2CH_2-OTBS), 41.1 (d, $^1J_{13C-31P}$=128.0 Hz, CH_2P(=O)(OCH$_3$)$_2$), 43.7 (d, $^3J_{13C-31P}$=2.0 Hz, CH_2CH_2C(=O)), 52.8 (d, $^2J_{13C-31P}$=3.0 Hz, P(=O)(OCH_3)$_2$), 62.6 (CH_2OTBS), 201.6 (d, $^2J_{13C-31P}$=6.0 Hz, C=O); m/z(ES$^+$) 361 (100%, MNa$^+$), 339 (15, MH$^+$); HRMS: Found 339.1757 (MH$^+$); $C_{14}H_{32}O_5PSi$ requires 339.1757.

4.2.3. 4-(*tert*-Butyldimethylsilanyloxy)benzaldehyde 15.[11] To a stirred solution of 4-hydroxybenzaldehyde **16** (2.00 g, 16.35 mmol) in THF (40 ml) was added imidazole (2.45 g, 36.03 mmol, 2.2 equiv) and TBSCl (3.70 g, 24.54 mmol, 1.5 equiv) at rt. After 2 h H_2O (40 ml) was added, and the mixture was diluted with DCM (40 ml). The layers were separated, and the aqueous layer was extracted with DCM (3×40 ml). The combined organic layers were

washed with brine (1×50 ml), dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography (20:1 petrol/EtOAc) gave the title compound (3.48 g, 90%) as a pale yellow oil: R_f 0.1 (4:1 petrol/EtOAc); δ_H (200 MHz; $CDCl_3$) 0.19 (6H, s, $Si(CH_3)_2$), 0.92 (9H, s, $SiC(CH_3)_3$), 6.87 (2H, d, $J=8.5$ Hz, Ar*H*), 7.72 (2H, d, $J=8.5$ Hz, Ar*H*), 9.81 (1H, s, C*H*O).

4.2.4. 7-(*tert*-Butyldimethylsilanyloxy)-1-[4-(*tert*-butyldimethylsilanyloxy)phenyl]hept-1-en-3-one 17 and 7-(*tert*-butyldimethylsilanyloxy)-1-(4-hydroxyphenyl)-hept-1-en-3-one 18. To a stirred suspension of NaH (0.47 g of a 60% w/w suspension in mineral oil, 11.80 mmol, 1.4 equiv) in THF (40 ml) was added a solution of phosphonate **14** (3.74 g, 11.05 mmol, 1.3 equiv) in THF (5 ml) dropwise at rt. After 1.5 h a solution of aldehyde **15** (2.01 g, 8.50 mmol) in THF (5 ml) was added dropwise. After a further 4 h H_2O (30 ml) was cautiously added, the layers were separated, and the aqueous layer was extracted with Et_2O (2×50 ml). The combined organic layers were washed with brine (1×40 ml), dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography (25:1 petrol/EtOAc) gave the title compounds **17** (2.76 g, 72%) followed by **18** (0.39 g, 14%) as colourless oils.

Data for compound **17**: R_f 0.65 (22:3 petrol/EtOAc); ν_{max} (film)/cm^{-1} 2935 (m), 2910 (s), 1663 (s), 1600 (w), 1508 (m); δ_H (400 MHz; $CDCl_3$) 0.05 (6H, s, $Si(CH_3)_2$), 0.22 (6H, s, $Si(CH_3)_2$), 0.90 (9H, s, $SiC(CH_3)_3$), 0.98 (9H, s, $SiC(CH_3)_3$), 1.54–1.61 (2H, m, CH_2CH_2OTBS), 1.68–1.77 (2H, m, $CH_2CH_2C(=O)$), 2.67 (2H, t, $J=7.5$ Hz, CH_2CH_2-C(=O)), 3.64 (2H, t, $J=6.5$ Hz, CH_2OTBS), 6.60 (1H, d, $J=16.0$ Hz, ArCH=C*H*C(=O)), 6.83–6.87 (2H, m, Ar*H*), 7.44–7.46 (2H, m, Ar*H*), 7.50 (1H, d, $J=16.0$ Hz, ArC*H*=CHC(=O)); δ_C(100.6 MHz; $CDCl_3$) −5.3 ($Si(CH_3)_2$), −4.4 ($Si(CH_3)_2$), 18.2 ($SiC(CH_3)_3$), 18.3 ($SiC(CH_3)_3$), 20.9 ($CH_2CH_2C(=O)$), 25.6 ($SiC(CH_3)_3$), 26.0 ($SiC(CH_3)_3$), 32.4 (CH_2CH_2OTBS), 40.5 (CH_2CH_2-C(=O)), 62.9 (CH_2OTBS), 120.5 (Ar*C*), 124.4 (ArCH=*C*HC(=O)), 127.8 (Ar*C*), 129.8 (Ar*C*), 142.2 (Ar*C*H=CHC(=O)), 158.0 (Ar*C*), 200.3 (*C*=O); *m*/*z* (CI^+) 449 (100%, MH^+), 391 (52), 317 (69); HRMS: Found 449.2889 (MH^+); $C_{25}H_{45}O_3Si_2$ requires 449.2907.

Data for compound **18**: R_f 0.15 (22:3 petrol/EtOAc); ν_{max} (film)/cm^{-1} 3266 (br s), 2950 (s), 1589 (s), 1512 (m); δ_H (400 MHz; $CDCl_3$) 0.06 (6H, s, $Si(CH_3)_2$), 0.90 (9H, s, $SiC(CH_3)_3$), 1.56–1.63 (2H, m, CH_2CH_2OTBS), 1.71–1.79 (2H, m, $CH_2CH_2C(=O)$), 2.70 (2H, t, $J=7.5$ Hz, CH_2CH_2-C(=O)), 3.66 (2H, t, $J=6.5$ Hz, CH_2OTBS), 6.62 (1H, d, $J=16.0$ Hz, ArCH=C*H*C(=O)), 6.80–6.84 (2H, m, Ar*H*), 7.42–7.46 (2H, m, Ar*H*), 7.55 (1H, d, $J=16.0$ Hz, ArC*H*=CHC(=O)); δ_C(100.6 MHz; $CDCl_3$) −5.3 ($Si(CH_3)_2$), 18.4 ($SiC(CH_3)_3$), 21.1 ($CH_2CH_2C(=O)$), 26.0 ($SiC(CH_3)_3$), 32.2 (CH_2CH_2OTBS), 40.3 (CH_2CH_2-C(=O)), 63.0 (CH_2OTBS), 116.2 (Ar*C*), 123.2 (ArCH=*C*HC(=O)), 126.3 (Ar*C*), 130.4 (Ar*C*), 143.9 (Ar*C*H=CHC(=O)), 159.3 (Ar*C*), 202.2 (*C*=O); *m*/*z* (ES^+) 335 (100%, MH^+), 203 (20); HRMS: Found 335.2055 (MH^+); $C_{19}H_{31}O_3Si$ requires 335.2042.

4.2.5. 7-(*tert*-Butyldimethylsilanyloxy)-1-[4-(*tert*-butyldimethylsilanyloxy)phenyl]heptan-3-one 19. To a stirred solution of alkene **17** (2.76 g, 6.15 mmol) in EtOAc (50 ml) was added 10% Pd/C (ca. 100 mg) at rt. The flask was evacuated (water aspirator) and pressurized with H_2 (balloon) three time, and the mixture was then stirred for 16 h under H_2 (balloon). The mixture was then filtered through a pad of Celite®, washing thoroughly with EtOAc, and the filtrate was concentrated. Purification by flash chromatography (9:1 petrol/EtOAc) gave the title compound (1.81 g, 65%) as a colourless oil: R_f 0.65 (22:3 petrol/EtOAc); ν_{max} (film)/cm^{-1} 2933 (s), 2859 (m), 1714 (s), 1609 (w), 1567 (m); δ_H (400 MHz; $CDCl_3$) 0.04 (6H, s, $Si(CH_3)_2$), 0.17 (6H, s, $Si(CH_3)_2$), 0.89 (9H, s, $SiC(CH_3)_3$), 0.97 (9H, s, $SiC(CH_3)_3$), 1.43–1.50 (2H, m, CH_2CH_2-OTBS), 1.57–1.64 (2H, m, $CH_2CH_2CH_2$OTBS, 2.37 (2H, t, $J=7.5$ Hz, $CH_2CH_2CH_2CH_2$OTBS), 2.66 (2H, t, $J=7.5$ Hz, $ArCH_2CH_2C(=O)$), 2.80 (2H, t, $J=7.5$ Hz, $ArCH_2$-$CH_2C(=O)$), 3.59 (2H, t, $J=6.0$ Hz, CH_2OTBS), 6.73 (2H, d, $J=8.0$ Hz, Ar*H*), 7.00 (2H, d, $J=8.0$ Hz, Ar*H*); δ_C (100.6 MHz; $CDCl_3$) −5.3 ($Si(CH_3)_2$), −4.5 ($Si(CH_3)_2$), 18.1 ($SiC(CH_3)_3$), 18.3 ($SiC(CH_3)_3$), 20.8 ($CH_2CH_2CH_2$-OTBS), 25.7 ($SiC(CH_3)_3$), 25.9 ($SiC(CH_3)_3$), 29.0 ($ArCH_2CH_2C(=O)$), 32.2 (CH_2CH_2OTBS), 42.7 (CH_2-$CH_2CH_2CH_2$OTBS), 44.4 ($ArCH_2CH_2C(=O)$), 62.7 (CH_2-OTBS), 129.1 (Ar*C*), 129.9 (Ar*C*), 133.7 (Ar*C*), 153.8 (Ar*C*), 209.8 (*C*=O); *m*/*z*(ES^+) 468 (100%, MNH_4^+), 451 (57, MH^+); HRMS: Found 451.3058 (MH^+); $C_{25}H_{47}O_3Si_2$ requires 451.3064.

4.2.6. 7-(*tert*-Butyldimethylsilanyloxy)-1-(4-hydroxyphenyl)hept-1-en-3-one 20. To a stirred solution of alkene **18** (150 mg, 0.45 mmol) in EtOAc (10 ml) was added 10% Pd/C (ca. 10 mg) at rt. The flask was evacuated (water aspirator) and pressurized with H_2 (balloon) three time, and the mixture was then stirred for 16 h under H_2 (balloon). The mixture was then filtered through a pad of Celite®, washing thoroughly with EtOAc, and the filtrate was concentrated. Purification by flash chromatography (9:1 petrol/EtOAc) gave the title compound (124 mg, 82%) as a colourless oil: R_f 0.35 (7:3 petrol/EtOAc); ν_{max} (film)/cm^{-1} 3386 (br s), 2933 (s), 1705 (s), 1613 (m), 1514 (m); δ_H (400 MHz; $CDCl_3$) 0.04 (6H, s, $Si(CH_3)_2$), 0.89 (9H, s, $SiC(CH_3)_3$), 1.43–1.50 (2H, m, CH_2CH_2OTBS), 1.57–1.64 (2H, m, $CH_2CH_2CH_2$OTBS), 2.36 (2H, t, $J=7.5$ Hz, $CH_2CH_2CH_2CH_2$OTBS), 2.66 (2H, t, 7.5 Hz, $ArCH_2CH_2$-C(=O)), 2.80 (2H, t, $J=7.5$ Hz, $ArCH_2CH_2C(=O)$), 3.58 (2H, t, $J=6.0$ Hz, CH_2OTBS), 6.73 (2H, d, $J=8.5$ Hz, Ar*H*), 7.00 (2H, d, $J=8.5$ Hz, Ar*H*); δ_C (100.6 MHz; $CDCl_3$) −5.3 ($Si(CH_3)_2$), 18.3 ($SiC(CH_3)_3$), 20.2 (CH_2-CH_2CH_2OTBS), 26.0 ($SiC(CH_3)_3$), 29.0 ($ArCH_2CH_2$-C(=O)), 32.1 (CH_2CH_2OTBS), 42.8 ($CH_2CH_2CH_2$-CH_2OTBS), 44.5 ($ArCH_2CH_2C(=O)$), 62.9 (CH_2OTBS), 115.4 (Ar*C*), 129.5 (Ar*C*), 132.8 (Ar*C*), 154.2 (Ar*C*), 211.2 (*C*=O); *m*/*z*(ES^+) 337 (84%, MH^+), 224 (100); HRMS: Found 337.2195 (MH^+); $C_{19}H_{33}O_3Si$ requires 337.2199.

4.2.7. 7-Hydroxy-1-(4-hydroxyphenyl)heptan-3-one 10. Method A—from ketone **19**. To a stirred solution of ketone **19** (1.80 g, 4.0 mmol) in THF (20 ml) was added TBAF (12.0 ml of a 1 M solution in THF, 12.0 mmol, 3.0 equiv) at 0 °C. The mixture was warmed to rt, stirred for 2 h, then quenched by the addition of H_2O (10 ml). The mixture was partitioned between EtOAc (20 ml) and H_2O (20 ml), the layers were separated, and the aqueous layer was extracted

with EtOAc (2×30 ml). The combined organic layers were dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography (7:3 EtOAc/petrol) gave the title compound (0.43 g, 48%) as a white solid.

Method B—from ketone **20**. To a stirred solution of ketone **20** (150 mg, 0.45 mmol) in THF (30 ml) was added TBAF (1.34 ml of a 1 M solution in THF, 1.34 mmol, 3.0 equiv) at 0 °C. The reaction mixture was warmed to rt, stirred for 2 h, then quenched by the addition of H_2O (5 ml). The mixture was partitioned between EtOAc (10 ml) and H_2O (10 ml), the layers were separated, and the aqueous layer was extracted with EtOAc (3×10 ml). The combined organic layers were dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography (7:3 EtOAc/petrol) gave the title compound (25 mg, 25%) as a white solid.

Data for compound **10**. R_f 0.25 (7:3 EtOAc/petrol); mp 75–76 °C; ν_{max} (KBr)/cm^{-1} 3427 (br s), 1699 (m); δ_H (400 MHz; $CDCl_3$) 1.52–1.62 (2H, m, C*H*$_2$CH$_2$CH$_2$OH), 1.63–1.73 (2H, m, C*H*$_2$CH$_2$OH), 2.43 (2H, t, J=7.0 Hz, C*H*$_2$CH$_2$CH$_2$CH$_2$OH), 2.67–2.72 (2H, m, ArCH$_2$C*H*$_2$-C(=O)), 2.82–2.85 (2H, m, ArC*H*$_2$CH$_2$C(=O)), 3.61 (2H, t, J=6.5 Hz, C*H*$_2$OH), 6.75 (2H, d, J=8.5 Hz, Ar*H*), 7.45 (2H, d, J=8.5 Hz, Ar*H*); δ_C(100.6 MHz; $CDCl_3$) 19.6 (*C*H$_2$CH$_2$CH$_2$OH), 29.7 (Ar*C*H$_2$CH$_2$C(=O)), 32.0 (*C*H$_2$-CH$_2$OH), 42.5 (*C*H$_2$CH$_2$CH$_2$CH$_2$OH), 44.5 (ArCH$_2$*C*H$_2$-C(=O)), 62.3 (*C*H$_2$OH), 115.3 (Ar*C*), 129.4 (Ar*C*), 133.0 (Ar*C*), 154.0 (Ar*C*), 210.5 (*C*=O); *m*/*z*(CI$^+$) 223 (70%, MH$^+$), 205 (73), 107 (100); HRMS: Found 223.1337 (MH$^+$); $C_{13}H_{19}O_3$ requires 223.1334.

4.2.8. 1,7-Dioxadispiro[5.1.5.2]pentadeca-9,12-dien-11-one (±)-21. Method A—using PhI(OAc)$_2$. To a stirred solution of iodobenzene diacetate (218 mg, 0.68 mmol, 1.51 equiv) in MeCN (15 ml) was added a solution of ketone **10** (100 mg, 0.45 mmol) in MeCN (3 ml) at rt. After 2 h the reaction was quenched by the addition of sat. aq. $NaHCO_3$ (20 ml). The layers were separated, and the aqueous layer was extracted with EtOAc (3×20 ml). The combined organic layers were dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography (2:1 petrol/EtOAc) gave the title compound (43 mg, 43%) as a colourless oil.

Method B—using PhI(O$_2$CCF$_3$)$_2$. To a stirred solution of [bis(trifluoroacetoxy)iodo]benzene (126 mg, 0.29 mmol, 1.3 equiv) in MeCN (8 ml) was added a solution of ketone **10** (50 mg, 0.225 mmol) in MeCN (1 ml) at rt. After 2 h the reaction was quenched by the addition of sat. aq. $NaHCO_3$ (10 ml). The layers were separated, and the aqueous layer was extracted with EtOAc (3×10 ml). The combined organic layers were dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography (2:1 petrol/EtOAc) gave the title compound (33 mg, 66%) as a colourless oil.

Data for compound (±)-**21**. R_f 0.65 (7:3 EtOAc/petrol); ν_{max} (film)/cm^{-1} 3584 (br s), 2945 (s), 1671 (s), 1632 (w); δ_H (500 MHz; $CDCl_3$) 1.53–1.62 (1H, m, *H*-3$_{equiv}$), 1.63–1.70 (1H, m, *H*-3$_{ax}$), 1.71–1.89 (4H, m, *H*-4$_{ax}$, *H*-5$_{ax}$, *H*-14′ and *H*-15′), 1.91–2.03 (2H, m, *H*-4$_{equiv}$ and *H*-5$_{equiv}$), 2.14–2.18 (1H, m, *H*-15), 2.34–2.42 (1H, m *H*-14), 3.65–3.69 (1H, m, *H*-2$_{equiv}$), 3.91 (1H, dt, J=11.5, 3.0 Hz, *H*-2$_{ax}$), 6.08–6.13 (2H, m, *H*-10 and *H*-12), 6.77 (1H, dd, J=10.0, 3.0 Hz, *H*-9), 6.91 (1H, dd, J=10.0, 3.0 Hz, *H*-13); δ_C(125.7 MHz; $CDCl_3$) 19.9 (*C*-4), 25.0 (*C*-3), 33.7 (*C*-5), 34.5 (*C*-15), 38.6 (*C*-14), 61.7 (*C*-2), 78.6 (*C*-8), 107.9 (*C*-6), 126.9 (*C*-10 and *C*-12), 152.0 (*C*-9), 155.3 (*C*-13), 185.6 (*C*-11); *m*/*z* (CI$^+$) 221 (70%, MH$^+$), 205 (15), 148 (100); HRMS: Found 221.1168 (MH$^+$); $C_{13}H_{17}O_3$ requires 221.1178.

4.2.9. 1-Tetradecanal 23.[15] To a stirred suspension of PCC (15.00 g, 70.0 mmol, 1.5 equiv) in DCM (250 ml) was added 1-tetradecanol **22** (10.00 g, 46.6 mmol) in one portion at rt. After 2 h the mixture was diluted with Et_2O (400 ml), and filtered through a pad of Florisil, washing the cake thoroughly with Et_2O. The filtrate was concentrated, dissolved in Et_2O (50 ml), and filtered through a pad of silica, washing thoroughly with Et_2O. The filtrate was concentrated to afford the title compound (8.43 g, 85%) as a colourless oil, which was used without further purification in the next step: R_f 0.45 (23:2 petrol/Et_2O).

4.2.10. (±)-Methyl 5-hydroxy-3-oxo-octadecanoate (±)-24. To a stirred suspension of NaH (1.73 g of a 60% w/w suspension in mineral oil, 43.2 mmol, 1.2 equiv) in THF (80 ml) was added methyl acetoacetate (3.90 ml, 36.1 mmol) dropwise at 0 °C. After 10 min *n*-BuLi (15.10 ml of a 2.5 M solution in hexanes, 37.8 mmol, 1.05 equiv) was added dropwise. After a further 10 min a solution of aldehyde **23** (8.40 g, 39.6 mmol, 1.1 equiv) in THF (25 ml) was added dropwise. After 20 min the reaction was quenched by the cautious addition of 1 M aq. HCl (80 ml). The mixture was partitioned between EtOAc (50 ml) and 1 M aq. HCl (50 ml). The layers were separated, and the aqueous layer was extracted with EtOAc (2×70 ml). The combined organic layers were washed with brine (1×50 ml), dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography (18:7 petrol/EtOAc) gave the title compound (9.94 g, 84%) as an off-white powder: R_f 0.25 (7:3 petrol/EtOAc); mp 51–53 °C; ν_{max} (KBr)/cm^{-1} 3401 (s), 2917 (m), 1747 (m), 1709 (m); δ_H (400 MHz; $CDCl_3$) 0.88 (3H, t, J=7.0 Hz, CH$_2$C*H*$_3$), 1.21–1.54 (24H, m, CH(OH)(C*H*$_2$)$_{12}$CH$_3$), 2.65 (1H, dd, J=17.5, 9.0 Hz, CH(OH)C*H*(H)C(=O)), 2.74 (1H, dd, J=17.5, 3.0 Hz, CH(OH)CH(*H*)C(=O)), 3.50 (2H, s, C*H*$_2$CO$_2$CH$_3$), 3.75 (3H, s, CO$_2$C*H*$_3$), 4.04–4.11 (1H, m, C*H*(OH)); δ_C(100.6 MHz; $CDCl_3$) 14.1 (CH$_2$*C*H$_3$), 29.3, 29.4, 29.5, 29.6, 31.9 (all CH(OH)(*C*H$_2$)$_{12}$CH$_3$), 36.4 (CH(OH)*C*H$_2$-C(=O)), 49.7 (*C*H$_2$CO$_2$CH$_3$), 52.5 (CO$_2$*C*H$_3$), 67.5 (*C*H(OH)), 167.4 (*C*O$_2$CH$_3$), 203.7 (CH(OH)CH$_2$*C*(=O)); *m*/*z*(CI$^+$) 329 (8%, MH$^+$), 311 (100), 253 (80); HRMS: Found 329.2701 (MH$^+$); $C_{19}H_{37}O_4$ requires 329.2692.

4.2.11. (3*S*,5*R*)- and (3*R*,5*S*)-Methyl 3,5-dihydroxyoctadecanoate (±)-25. Tetramethylammonium triacetoxyborohydride (4.70 g, 17.9 mmol, 5.0 equiv) was added to a mixture of MeCN (15 ml) and AcOH (15 ml) at rt. After 10 min the solution was cooled to −25 °C, and a solution of ketone (±)-**24** (1.17 g, 3.6 mmol) in MeCN (8 ml) was added dropwise. The mixture was stirred at −25 °C for 2 h, then warmed to 0 °C. After a further 3 h the reaction was quenched by the addition of 0.5 M aq. sodium potassium tartrate tetrahydrate (50 ml), then the mixture was poured

into EtOAc (650 ml). The mixture was washed with sat. aq. Na_2CO_3 (2×300 ml), brine (1×200 ml), and the organic layer was dried ($MgSO_4$), filtered and concentrated to afford a yellow solid. Purification by recrystallisation from (4:1 hexane/Et_2O) gave the title compound (1.05 g, 89%) as a white powder in two crops: R_f 0.35 (1:1 petrol/EtOAc); mp 63–65 °C; ν_{max} (KBr)/cm^{-1} 3381 (br s), 2917 (m), 1724 (s); δ_H (400 MHz; $CDCl_3$) 0.88 (3H, t, J=7.0 Hz, CH_2CH_3), 1.26–1.52 (24H, m, $CH(OH)(CH_2)_{12}CH_3$), 1.54–1.71 (2H, m, $CH(OH)CH_2CH(OH)$), 2.38 (1H, d, J=2.5 Hz, $CH(OH)(CH_2)_{12}CH_3$), 2.52–2.55 (2H, m, $CH_2CO_2CH_3$), 3.43 (1H, d, J=3.5 Hz, $CH(OH)CH_2CO_2CH_3$), 3.73 (3H, s, CO_2CH_3), 3.92–3.95 (1H, m, $CH(OH)(CH_2)_{12}CH_3$), 4.35–4.40 (1H, m, $CH(OH)CH_2CO_2CH_3$); δ_C (100.6 MHz; $CDCl_3$) 14.1 (CH_2CH_3), 29.3, 29.4, 29.6, 29.7, 31.9, 37.5 (all $CH(OH)(CH_2)_{12}CH_3$), 41.0 ($CH(OH)CH_2CH(OH)$), 41.9 ($CH_2CO_2CH_3$), 51.8 (CO_2CH_3), 65.7 ($CH(OH)(CH_2)_{12}CH_3$), 69.0 ($CH(OH)CH_2CO_2CH_3$), 173.3 (CO_2CH_3); m/z (ES^+) 353 (38%, MNa^+), 331 (28, MH^+), 248 (100); HRMS: Found 353.2656 (MNa^+); $C_{19}H_{38}NaO_4$ requires 353.2668.

4.2.12. (4*S*,6*R*)- and (4*R*,6*S*)-Methyl 4-[4-(2,2-dimethyl-6-tridecyl-[1,3]dioxan-4-yl)-3-oxo-butyl-1-ene]phenyl acetate (±)-26. To a stirred solution of phosphonate (±)-**28** (2.00 g, 4.32 mmol, 1.1 equiv) in THF (20 ml) was added NaH (0.17 g of a 60% w/w suspension in mineral oil, 4.25 mmol, 1.1 equiv) at 0 °C. The mixture was warmed to rt and stirred for 40 min, before the addition of 4-acetoxybenzaldehyde (0.55 ml, 3.91 mmol). After 24 h the reaction was quenched by the cautious addition of H_2O (10 ml), and the mixture was partitioned between Et_2O (20 mL) and brine (20 ml). The layers were separated, and the aqueous layer was extracted with Et_2O (2×20 ml). The combined organic layers were dried ($MgSO_4$), filtered and concentrated to afford a white solid. Purification by recrystallisation (22:3 hexane/EtOAc) gave the title compound (1.61 g, 82%) as a white powder in two crops: R_f 0.4 (22:3 heaxane/EtOAc); mp 85–86 °C; ν_{max} ($CHCl_3$)/cm^{-1} 2928 (s), 2855 (m), 1764 (s), 1686 (m), 1602 (w); δ_H (500 MHz; $CDCl_3$) 0.93 (3H, t, J=7.0 Hz, CH_2CH_3), 1.31–1.58 (24H, m, $CH(CH_2)_{12}CH_3$), 1.38 (3H, s, $C(CH_3)(CH_3)$), 1.41 (3H, s, $C(CH_3)(CH_3)$), 1.69–1.81 (2H, m, $CH_2CHCH_2C(=O)$), 2.36 (3H, s, O_2CCH_3), 2.74 (1H, dd, J=16.0, 5.0 Hz, $CHCH(H)C(=O)$), 3.01 (1H, dd, J=16.0, 7.5 Hz, $CHCH(H)C(=O)$), 3.82–3.86 (1H, m, $CHCH_2C(=O)$), 4.42–4.44 (1H, m, $CH(CH_2)_{12}CH_3$), 6.77 (1H, d, J=16.0 Hz, $ArCH=CHC(=O)$), 7.18 (2H, d, J=8.5 Hz, ArH), 7.59 (1H, d, J=16.0 Hz, $ArCH=CHC(=O)$), 7.61 (2H, d, J=8.5 Hz, ArH); δ_C (125.7 MHz; $CDCl_3$) 14.5 (CH_2CH_3), 23.1 (O_2CCH_3), 25.2 ($C(CH_3)(CH_3)$), 25.8 ($C(CH_3)(CH_3)$), 29.8, 30.0, 30.1, 32.4, 36.3 (all $CH(CH_2)_{12}CH_3$), 38.9 ($CH_2CHCH_2C(=O)$), 47.5 ($CHCH_2C(=O)$), 63.9 ($CH(CH_2)_{12}CH_3$), 67.0 ($CHCH_2C(=O)$), 100.9 ($C(CH_3)_2$), 122.6 (ArC), 127.8 ($ArCH=CHC(=O)$), 129.9 (ArC), 132.7 (ArC), 142.4 ($ArCH=CHC(=O)$), 152.7 (ArC), 169.2 (O_2CCH_3), 198.2 ($CHCH_2C(=O)$); m/z(CI^+) 443 (100%, $[MH-C_3H_6O]^+$). Molecular ion intensities were too weak to record accurate HRMS data.

4.2.13. (4*S*,6*R*)- and (4*R*,6*S*)-Methyl (2,2-dimethyl-6-tridecyl-[1,3]dioxan-4-yl]acetate (±)-27. To a stirred solution of diol (±)-**25** (0.91 g, 2.75 mmol) in 2,2-dimethoxypropane (15 ml) was added CSA (ca. 40 mg) at 0 °C. After 3 h the mixture was partitioned between EtOAc (20 ml) and sat. aq. $NaHCO_3$ (20 ml). The layers were separated, and the aqueous layer was extracted with EtOAc (2×20 ml). The combined organic layers were dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography (23:2 petrol/EtOAc) gave the title compound (1.00 g, 98%) as a colourless oil: R_f 0.7 (1:1 petrol/EtOAc); ν_{max} (film)/cm^{-1} 2925 (s), 1746 (s), 1437 (w); δ_H (500 MHz; $CDCl_3$) 0.93 (3H, t, J=6.5 Hz, CH_2CH_3), 1.34–1.58 (22H, $CHCH_2(CH_2)_{11}CH_3$), 1.46 (3H, s, $C(CH_3)(CH_3)$), 1.48 (3H, s, $C(CH_3)(CH_3)$), 1.65–1.67 (2H, m, $CHCH_2(CH_2)_{11}CH_3$), 1.68–1.71 (2H, m, $CH_2CHCH_2CO_2CH_3$), 2.48 (1H, dd, J=8.0, 3.0 Hz, $CH(H)CO_2CH_3$), 2.59 (1H, dd, J=8.0, 4.5 Hz, $CH(H)CO_2CH_3$), 3.73 (3H, s, CO_2CH_3), 3.81–3.83 (1H, m, $CH(CH_2)_{12}CH_3$), 4.28–4.33 (1H, m, $CHCH_2CO_2CH_3$); δ_C (125.7 MHz; $CDCl_3$) 14.5 (CH_2CH_3), 25.1 ($C(CH_3)(CH_3)$), 25.7 ($C(CH_3)(CH_3)$), 29.8, 30.0, 30.1, 32.3, 36.3 (all $CH(CH_2)_{12}CH_3$), 38.5 ($CH_2CHCH_2CO_2CH_3$), 41.1 ($CH_2CO_2CH_3$), 52.0 (CO_2CH_3), 63.9 ($CHCH_2CO_2CH_3$), 66.9 ($CH(CH_2)_{12}CH_3$), 100.9 ($C(CH_3)_2$), 171.8 (CO_2CH_3); m/z(CI^+) 371 (20%, MH^+), 355 (90), 313 (100); HRMS: Found 371.3159 (MH^+); $C_{22}H_{43}O_4$ requires 371.3161.

4.2.14. (4*S*,6*R*)- and (4*R*,6*S*)-Dimethyl [3-(2,2-dimethyl-6-tridecyl-[1,3]dioxan-4-yl)-2-oxo-propyl]phosphate (±)-28. To a stirred solution of dimethyl methylphosphonate (2.16 ml, 20.0 mmol, 3.0 equiv) in THF (40 ml) was added *n*-BuLi (8.00 ml of a 2.5 M solution in hexanes, 20.0 mmol, 3.0 equiv) dropwise at −78 °C. After 30 min a solution of ester (±)-**27** (2.47 g, 6.67 mmol) in THF (15 ml) was added dropwise. After 20 min the reaction was quenched by the addition of sat. aq. NH_4Cl (40 ml). The mixture was warmed to rt, and then partitioned between EtOAc (50 ml) and brine (50 ml). The layers were separated, and the aqueous layer was extracted with EtOAc (2×50 ml). The combined organic layers were dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography (5:1 petrol/EtOAc) gave the title compound (2.01 g, 65%) as a colourless oil: R_f 0.20 (5:1 petrol/EtOAc); ν_{max} (film)/cm^{-1} 2924 (m), 2854 (s), 1717 (s), 1260 (m); δ_H (500 MHz; $CDCl_3$) 0.91 (3H, t, J=6.5 Hz, CH_2CH_3), 1.33 (3H, s, $C(CH_3)(CH_3)$), 1.28–1.53 (24H, m, $CH(CH_2)_{12}CH_3$), 1.37 (3H, s, $C(CH_3)(CH_3)$), 1.61–1.69 (2H, m, $CH_2CHCH_2C(=O)$), 2.72 (1H, dd, J=8.5, 2.5 Hz, $CHCH(H)C(=O)$), 2.84 (1H, dd, J=8.5, 4.5 Hz, $CHCH(H)C(=O)$), 3.10–3.24 (2H, m, $CH_2P(=O)(OCH_3)_2$), 3.77–3.78 (3H, m, $P(=O)(OCH_3)(OCH_3)$), 3.80–3.83 (4H, m, $P(=O)(OCH_3)(OCH_3)$ and $CHCH_2(CH_2)_{12}CH_3$), 4.21–4.39 (1H, m, $CHCH_2C(=O)$); δ_C (125.7 MHz; $CDCl_3$) 14.5 (CH_2CH_3), 25.2 ($C(CH_3)(CH_3)$), 25.7 ($C(CH_3)(CH_3)$), 29.8, 29.9, 30.0, 30.1, 32.3, 36.2 (all $CH(CH_2)_{12}CH_3$), 38.4 ($CH_2CHCH_2C(=O)$), 42.4 (d, $^1J_{13C-31P}$=106.0 Hz, $CH_2P(=O)(OCH_3)_2$), 50.2 ($CHCH_2C(=O)$), 53.4 ($P(=O)(OCH_3)_2$), 63.5 ($CHCH_2C(=O)$), 66.9 ($CH(CH_2)_{12}CH_3$), 100.8 ($C(CH_3)_2$), 200.4 ($C=O$); m/z(ES^+) 480 (75%, MNH_4^+), 463 (37, MH^+), 148 (100); HRMS: Found 485.3008 (MNa^+); $C_{24}H_{47}NaO_6P$ requires 485.3008.

4.2.15. (4*S*,6*R*)- and (4*R*,6*S*)-Methyl 4-[4-(2,2-dimethyl-6-tridecyl-[1,3]dioxan-4-yl)-3-oxo-butyl]phenylacetate

(±)-29. To a stirred solution of alkene (±)-**26** (1.60 g, 3.20 mmol) in EtOAc (40 ml) was added 10% Pd/C (ca. 100 mg) at rt. The flask was evacuated (water aspirator) and pressurized with H_2 (balloon) three time, and the mixture was then stirred for 16 h under H_2 (balloon). The mixture was then filtered through a pad of Celite®, washing thoroughly with EtOAc, and the filtrate was concentrated. Purification by flash chromatography (22:3 petrol/EtOAc) gave the title compound (1.22 g, 76%) as a colourless oil: R_f 0.45 (22:3 petrol/EtOAc); ν_{max} (film)/cm^{-1} 2925 (s), 2854 (s), 1766 (s), 1717 (s); δ_H (500 MHz; $CDCl_3$) 0.87 (3H, t, J=6.5 Hz, CH_2CH_3), 1.19–1.42 (24H, m, $CH(CH_2)_{12}CH_3$), 1.38 (3H, s, $C(CH_3)(CH_3)$), 1.41 (3H, s, $C(CH_3)(CH_3)$), 1.52–1.62 (2H, m, $CH_2CHCH_2C(=O)$), 2.24 (3H, s, O_2CCH_3), 2.39 (1H, dd, J=15.5, 5.0 Hz, $CHCH(H)C(=O)$), 2.62–2.68 (2H, m, $ArCH_2CH_2C(=O)$), 2.64 (1H, dd, J=15.5, 8.5 Hz, $CHCH(H)C(=O)$), 2.73–2.76 (2H, m, $ArCH_2CH_2C(=O)$), 3.70–3.73 (1H, m, $CHCH_2C(=O)$), 4.22–4.29 (1H, m, $CH(CH_2)_{12}CH_3$) 6.76 (2H, d, J=7.5 Hz, Ar*H*), 7.03 (2H, d, J=7.5 Hz, Ar*H*); δ_C (125.7 MHz; $CDCl_3$) 14.5 (CH_2CH_3), 23.3 (O_2CCH_3), 25.0 ($C(CH_3)(CH_3)$), 25.7 ($C(CH_3)(CH_3)$), 29.1, 29.8, 30.0, 30.1 (all $CHCH_2(CH_2)_{11}CH_3$), 30.0 ($ArCH_2CH_2C(=O)$), 32.2 ($ArCH_2CH_2C(=O)$), 36.2 ($CHCH_2(CH_2)_{11}CH_3$), 38.7 ($CH_2CHCH_2C(=O)$), 49.2 ($CHCH_2C(=O)$), 63.6 ($CH(CH_2)_{12}CH_3$), 66.8 ($CHCH_2C(=O)$), 100.7 ($C(CH_3)_2$), 121.8 (Ar*C*), 129.7 (Ar*C*), 139.0 (Ar*C*), 149.3 (Ar*C*), 169.8 (O_2CCH_3), 207.9 ($CHCH_2C(=O)$); m/z(ES$^+$) 520 (80%, MNH_4^+), 148 (100); HRMS: Found 525.3551 (MNa^+); $C_{31}H_{50}NaO_5$ requires 525.3556.

4.2.16. (4*S*,6*R*)- and (4*R*,6*S*)-1-(2,2-Dimethyl-6-tridecyl-[1,3]dioxan-4-yl)-4-(4-hydroxyphenyl)butan-2-one (±)-30. To a stirred solution of acetate (±)-**29** (1.00 g, 1.99 mmol) in MeOH (40 ml) was added K_2CO_3 (0.36 g, 2.61 mmol, 1.3 equiv) in one portion at rt. After 45 min the mixture was partitioned between 50% sat. aq. NH_4Cl (100 ml) and EtOAc (100 ml). The layers were separated, and the aqueous layer was extracted with EtOAc (3× 100 ml). The combined organic layers were dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography (4:1 petrol/EtOAc) gave the title compound (0.82 g, 89%) as a white solid: R_f 0.25 (2:1 petrol/EtOAc); mp 54–55 °C, ν_{max} ($CHCl_3$)/cm^{-1} 3597 (br s), 2928 (m), 2855 (s), 1714 (s), 1612 (w); δ_H (500 MHz; $CDCl_3$) 0.91 (3H, t, J=6.5 Hz, CH_2CH_3), 1.28–1.42 (24H, m, $CH(CH_2)_{12}CH_3$), 1.34 (3H, s, $C(CH_3)(CH_3)$), 1.35 (3H, s, $C(CH_3)(CH_3)$), 1.57–1.64 (2H, m, $CH_2CHCH_2C(=O)$), 2.44 (1H, dd, J=16.0, 5.0 Hz, $CHCH(H)C(=O)$), 2.71 (1H, dd, J=16.0, 8.0 Hz, $CHCH(H)C(=O)$), 2.74–2.78 (2H, m, $ArCH_2CH_2C(=O)$), 2.81–2.84 (2H, m, $ArCH_2CH_2C(=O)$), 3.72–3.78 (1H, m, $CHCH_2C(=O)$), 4.27–4.37 (1H, m, $CH(CH_2)_{12}CH_3$), 5.50 (1H, s, O*H*), 6.73–6.79 (2H, m, Ar*H*), 7.02–7.07 (2H, m, Ar*H*); δ_C (125.7 MHz; $CDCl_3$) 14.6 (CH_2CH_3), 25.1 ($C(CH_3)(CH_3)$), 25.7 ($C(CH_3)(CH_3)$), 29.0, 29.8, 30.0, 30.1 (all $CHCH_2(CH_2)_{11}CH_3$), 30.1 ($ArCH_2CH_2C(=O)$), 32.3 ($ArCH_2CH_2C(=O)$), 36.2 ($CHCH_2(CH_2)_{11}CH_3$), 38.7 ($CH_2CHCH_2C(=O)$), 49.3 ($CHCH_2C(=O)$), 63.7 ($CHCH_2C(=O)$), 67.0 ($CH(CH_2)_{12}CH_3$), 101.0 ($C(CH_3)_2$), 115.7 (Ar*C*), 129.8 (Ar*C*), 133.3 (Ar*C*), 154.5 (Ar*C*), 209.0 (C=O); m/z(CI^+) 403 (100%, $[MH-C_3H_6O]^+$). Molecular ion intensities were too weak to record accurate HRMS data.

4.2.17. (2*S*,4*S*,6*R*)- and (2*R*,4*R*,6*S*)-2-[2-(4-Hydroxyphenyl)ethyl]-6-tridecyl-tetrahydropyran-2,4-diol (±)-6-A and (5*S*,7*R*)- and (5*R*,7*S*)-dihydroxy-1-(4-hydroxyphenyl)icosan-3-one (±)-6-B. To a stirred solution of acetonide (±)-**30** (314 mg, 0.68 mmol) in THF (25 ml) was added 0.5 M aq. HCl (10 ml) at 0 °C. The mixture was warmed to rt, stirred for 1 h, then partitioned between EtOAc (70 ml) and sat. aq. $NaHCO_3$ (70 ml). The layers were separated, and the aqueous layer was extracted with EtOAc (3×50 ml). The combined organic layers were washed with brine (1×50 ml), dried ($MgSO_4$), filtered and concentrated to afford a white solid. Purification by recrystallisation (21:4 hexane/EtOAc) gave the title compound (238 mg, 83%) as a white powder: R_f 0.2 (1:1 petrol/EtOAc); mp 97–98 °C; ν_{max} ($CDCl_3$)/cm^{-1} 3599 (br m), 2928 (m), 2855 (m), 1705 (s), 1612 (w), 1515 (s); NMR data: If the product was dissolved in acetone-d_6, and the spectra recorded immediately, a single compound ((±)-**6-A**) was observed: δ_H (500 MHz; acetone-d_6) 0.90 (3H, t, J=6.0 Hz, CH_2CH_3), 1.07–1.09 1H, m, $CH(H)CH(CH_2)_{12}CH_3$), 1.22–1.31 (23H, m, $CCH(H)CH(OH)$ and $CHCH_2(CH_2)_{11}CH_3$), 1.45–1.47 (2H, m, $CHCH_2(CH_2)_{11}CH_3$), 1.86–1.87 (2H, m, $ArCH_2CH_2C$), 1.89–1.91 (1H, m, $CH(H)CH(CH_2)_{12}CH_3$), 2.05–2.07 (1H, m, $CCH(H)CH(OH)$), 2.68–2.71 (2H, m, $ArCH_2CH_2C$), 3.61 (1H, d, J=5.0 Hz, $CCH_2CH(OH)$), 3.87–3.97 (1H, m, $CH(CH_2)_{12}CH_3$), 4.05–4.15 (1H, m, $CCH_2CH(OH)$), 4.18 (1H, s, $ArCH_2CH_2C(OH)$), 6.75 (2H, d, J=8.0 Hz, Ar*H*), 7.05 (2H, d, J=8.0 Hz, Ar*H*), 7.99 (1H, s, ArO*H*); δ_C (125.7 MHz; acetone-d_6) 13.8 (CH_2CH_3), 28.9 ($ArCH_2CH_2C$), 29.0, 29.2, 30.0, 32.1 (all $CHCH_2(CH_2)_{11}CH_3$), 36.4 ($CHCH_2(CH_2)_{11}CH_3$), 41.9 (CH_2 $CH(CH_2)_{12}CH_3$), 43.3 ($CCH_2CH(OH)$), 45.9 ($ArCH_2CH_2C$), 64.6 ($CCH_2CH(OH)$), 68.5 ($CH(CH_2)_{12}CH_3$), 97.8 ($ArCH_2CH_2C$), 115.5 (Ar*C*), 129.5 (Ar*C*), 133.7 (Ar*C*), 155.7 (Ar*C*). Within 3hr at rt, the same sample had equilibrated to form a 2:1 mixture of (±)-**6-A** and (±)-**6-B**. Although the complete assignment of the ^1H NMR spectrum was not possible due to considerable peak overlap, the ^{13}C NMR spectra could be completely assigned: ^{13}C NMR data for (±)-**6-B**: δ_C (125.7 MHz; acetone-d_6) 13.9 (CH_2CH_3), 28.9 ($ArCH_2CH_2C(=O)$), 29.0, 29.2, 30.0 (all $CHCH_2(CH_2)_{11}CH_3$), 38.4 ($CHCH_2(CH_2)_{11}CH_3$), 44.2 ($CH_2CH(CH_2)_{12}CH_3$), 45.4 ($CH(OH)CH_2C(=O)$), 50.7 ($ArCH_2CH_2C(=O)$), 65.5 ($CH(OH)CH_2C(=O)$), 68.2 ($CH(CH_2)_{12}CH_3$), 115.5 (Ar*C*), 129.5 (Ar*C*), 132.5 (Ar*C*), 156.0 (Ar*C*), 209.4 (C=O); m/z(ES$^+$) 443 (85%, MNa^+), 438 (35, MNH_4^+), 421 (28, MH^+), 229 (100); HRMS: Found 443.3140 (MNa^+); $C_{26}H_{44}NaO_4$ requires 443.3137.

4.2.18. Aculeatin D (±)-4, (2*R*,4*S*,6*R*)- and (2*S*,4*R*,6*S*)-4-hydroxy-2-tridecyl-1,7-dioxadispiro[5.1.5.2]pentadeca-9,12-dien-11-one (±)-8 and (5*S*,7*R*)- and (5*R*,7*S*)-4-(5,7-dihydroxy-3-oxo-icosyl)-4-hydroxycyclohexa-2,5-dienone (±)-31. To a stirred solution of compound (±)-**6** (216 mg, 0.51 mmol) in acetone/H_2O (40 ml of a 9:1 v/v solution) was added $PhI(O_2CCF_3)_2$ (258 mg, 0.60 mmol, 1.2 equiv) in one portion at rt. The mixture was stirred for 20 min in the dark, then partitioned between EtOAc (30 ml) and sat. aq. $NaHCO_3$ (30 ml). The layers were separated, and the aqueous layer was extracted with EtOAc (2× 20 ml). The combined organic layers were washed with brine (1×20 ml), dried ($MgSO_4$), filtered and concentrated.

Purification by flash chromatography (5:4 petrol/EtOAc) gave the title compounds (±)-**8** (92 mg, 43%) followed by (±)-**4** (40 mg, 19%) followed by (±)-**31** (60 mg, 27%), all as colorless oils.

Data for compound (±)-**8**. R_f 0.3 (5:4 petrol/EtOAc); ν_{max} (film)/cm^{-1} 3400 (br s), 2926 (s), 2854 (m), 1671 (s), 1630 (s), 1457 (m), 1389 (m); δ_H (500 MHz; $CDCl_3$) 0.91 (3H, t, J=7.0 Hz, CH_2CH_3), 1.05–1.07 (1H, m, *H-3*$_{ax}$), 1.33–1.40 (24H, $CH(CH_2)_{12}CH_3$), 1.40–1.45 (3H, m, *H-5*$_{ax}$, *H-14′* and *H-15′*), 1.53–1.62 (1H, m, *H-3*$_{equiv}$), 1.85–1.87 (2H, m, *H-5*$_{equiv}$ and *H-15*), 2.00–2.12 (1H, m, *H-14*), 3.68–3.72 (1H, m, *H-2*), 3.87–3.94 (1H, m, *H-4*), 6.02 (1H, dd, J=8.0, 2.0 Hz, *H-12*), 6.10–6.15 (2H, m, *H-10* and *H-13*), 6.68 (1H, dd, J=10.0, 3.0 Hz, *H-9*); δ_C (125.7 MHz; C_6D_6) 14.6 (CH_2CH_3), 26.3, 30.1, 30.3, 30.4, 32.6 (all $CHCH_2(CH_2)_{11}CH_3$), 35.1 (*C-14*), 36.6 ($CHCH_2(CH_2)_{10}CH_3$), 39.1 (*C-15*), 41.5 (*C-3*), 43.7 (*C-5*), 65.4 (*C-4*), 69.5 (*C-2*), 79.4 (*C-8*), 109.3 (*C-6*), 127.2 (*C-13*), 127.6 (*C-10*), 149.0 (*C-12*), 151.3 (*C-9*), 185.0 (*C-11*); *m/z*(EI+) 418 (2%, M^+), 401(100); HRMS: Found 419.3171 (MH^+); $C_{26}H_{43}O_4$ requires 419.3161.

Data for compound (±)-**4**. R_f 0.2 (5:4 petrol/EtOAc); ν_{max} (film)/cm^{-1} 3418 (br s), 2922 (m), 2853 (s), 1668 (s), 1632 (w), 1455 (s), 1010 (s); δ_H (500 MHz; C_6D_6) 0.91 (3H, t, J=7.0 Hz, CH_2CH_3), 1.07–1.14 (1H, m, *H-3*$_{ax}$), 1.17–1.23 (1H, m, *H-15′*), 1.25–1.36 (22H, m, $CHCH(H)(CH_2)_{11}CH_3$, $CHCH_2CH(H)(CH_2)_{10}CH_3$ and $CHCH_2CH_2(CH_2)_{10}CH_3$) 1.42–1.50 (2H, m, *H-14′* and $CHCH_2CH(H)(CH_2)_{10}CH_3$), 1.52–1.58 (1H, m, $CHCH(H)(CH_2)_{11}CH_3$), 1.66–1.69 (1H, m, *H-3*$_{equiv}$), 1.78–1.84 (2H, m, *H-5*$_{ax}$ and *H-15*), 1.87–1.94 (2H, m, *H-5*$_{equiv}$ and *H-14*), 2.96–3.01 (1H, m, *H-2*), 3.45–3.51 (1H, m, *H-4*), 6.04 (1H, dd, J=9.5, 2.0 Hz, *H-12*), 6.07 (1H, dd, J=9.5, 2.0 Hz, *H-10*), 6.25 (1H, dd, J=10.0, 3.0 Hz, *H-13*), 6.90 (1H, dd, J=10.0, 3.0 Hz, *H-9*); δ_C (125.7 MHz; C_6D_6) 14.3 (CH_2CH_3), 23.1 (CH_2CH_3), 26.2, ($CHCH_2CH_2(CH_2)_{10}CH_3$), 29.8, 29.9, 30.1, 30.1, 30.1, 32.3 (all $CHCH_2CH_2(CH_2)_9CH_2CH_3$), 33.1 (*C-15*), 35.2 (*C-14*), 36.2 ($CHCH_2(CH_2)_{11}CH_3$), 41.3 (*C-3*), 44.1 (*C-5*), 66.6 (*C-4*), 71.6 (*C-2*), 78.1 (*C-8*), 109.3 (*C-6*), 127.1 (*C-10*), 127.3 (*C-12*), 148.9 (*C-13*), 151.9 (*C-9*), 184.9 (*C-11*); *m/z* (CI^+) 436 (3%, MNH_4^+), 419 (12, MH^+), 401 (14), 163 (48), 155 (100), 107 (58); HRMS: Found 419.3156 (MH^+); $C_{26}H_{43}O_4$ requires 419.3161.

Data for compound (±)-**31**. R_f 0.10 (5:4 petrol/EtOAc); ν_{max} ($CHCl_3$)/cm^{-1} 3394 (br m), 2924 (m), 2854 (m), 1720 (s), 1670 (m), 1513 (m); δ_H (500 MHz; C_6D_6) 0.91 (3H, t, J=7.0 Hz, CH_2CH_3), 1.07–1.09 (1H, m, $CHCH(H)(CH_2)_{11}CH_3$), 1.13–1.23 (1H, m, $C(OH)CH(H)CH_2C(=O)$), 1.32–1.39 (23H, m, $CHCH(H)(CH_2)_{11}CH_3$ and $CHCH_2(CH_2)_{11}CH_3$), 1.54–1.66 (2H, m, $CH_2CH(OH)CH_2C(=O)$), 1.72–1.77 (1H, m, $C(OH)CH_2CH(H)C(=O)$), 1.91–1.97 (1H, m, $C(OH)CH_2CH(H)C(=O)$), 2.08–2.16 (1H, m, $C(OH)CH(H)CH_2C(=O)$), 2.34–2.38 (1H, m, $CH(OH)CH(H)C(=O)$), 2.54–2.58 (1H, m, $CH(OH)CH(H)C(=O)$), 3.31–3.35 (1H, m, $CH(CH_2)_{12}CH_3$), 4.03–4.07 (1H, m, $CH(OH)CH_2C(=O)$), 5.93 (1H, dd, J=10.0, 1.0 Hz, $CCH=CHC(=O)$), 6.14 (1H, dd, J=10.5, 1.0 Hz, $CCH=CHC(=O)$), 6.24 (1H, dd, J=10.0, 3.0 Hz, $CCH=CHC(=O)$), 6.50 (1H, dd, J=10.5, 3.0 Hz, $CCH=CHC(=O)$); δ_C (125.7 MHz; C_6D_6) 14.6 (CH_2CH_3), 24.6, 30.1, 30.3, 30.4, 32.6, 34.6 (all $CHCH_2(CH_2)_{11}CH_3$), 36.0 ($CHCH_2(CH_2)_{11}CH_3$), 37.4 ($C(OH)CH_2CH_2C(=O)$), 39.6 ($C(OH)CH_2CH_2C(=O)$), 43.2 ($CH_2CH(OH)CH_2C(=O)$), 53.7 ($CH(OH)CH_2C(=O)$), 69.3 ($CH(OH)CH_2C(=O)$), 73.0 ($C(OH)CH_2CH_2C(=O)$), 75.7 ($CH(CH_2)_{12}CH_3$), 128.1 ($CCH=CHC(=O)$), 131.5 ($CCH=CHC(=O)$), 145.9 ($CCH=CHC(=O)$), 153.0 ($CCH=CHC(=O)$), 184.3 ($CCH=CHC(=O)$), 206.5 ($C(OH)CH_2CH_2C(=O)$); *m/z*(CI^+) 418(100%, $[M-H_2O]^+$). Molecular ion intensities were too weak to record accurate HRMS data.

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19. We are indebted to Prof. Heilmann for performing the TLC comparisons, and for kindly supplying copies of the spectra of natural (−)-aculeatin D **4**.

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Cryoelectrochemistry: electrochemical reduction of 2(*RS*)-methyl 1-(*tert*-butoxycarbonyl)-2-iodomethyl-2,5-dihydropyrrole-2-carboxylate

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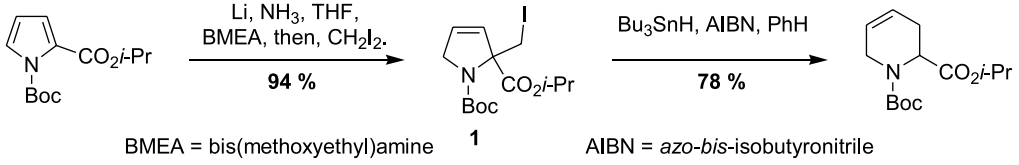
Abstract—Cryoelectrochemisty with cyclic voltammetry and chronoamperometry has been applied to give an insight into a reductive pyrroline ring opening reaction, and has allowed the number of electrons participating in the reaction to be deduced from potential step experiments.

1. Introduction

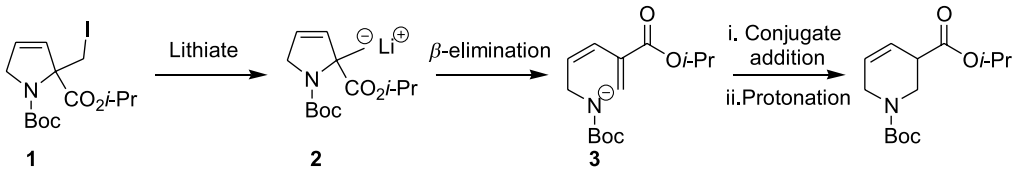
The recent discovery that the Birch-reduction of electron-deficient pyrroles[1,2] is compatible with the use of 1,1-dihaloalkanes as an electrophile, has allowed access to synthetically useful α-iodomethyl pyrrolines (such as **1**) in excellent yields (Scheme 1). It has been successfully demonstrated that these versatile pyrrolines undergo a one-carbon radical ring-expansion to yield tetrahydropyridines.[3]

With a continued interest in the stereoselective formation of tetrahydropyridines,[4–6] it was envisaged that α-iodomethyl pyrrolines (**1**) could be lithiated to produce reactive intermediate **2**. β-Elimination to form enone **3**, followed by conjugate addition and protonation could yield synthetically useful tetrahydropyridines with the ester functionality on C-3 as opposed to C-2 (Scheme 2).

However, initial attempts to transmetallate the primary iodide unit within pyrroline **1** with *n*-BuLi, *sec*-BuLi and



Scheme 1.



Scheme 2.

Keywords: Reductive elimination; Cryoelectrochemisty; Cyclic voltammetry and chronoamperometry.
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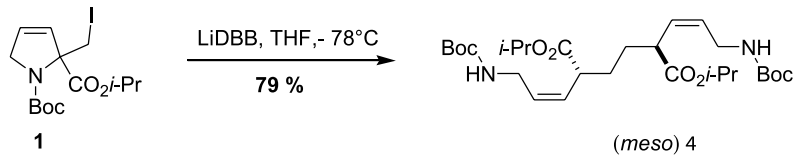


Scheme 3.

tert-BuLi were all unsuccessful and returned only starting material. The steric demands of this centre were considered too great and, therefore, formation of the anion via single electron transfer was explored. With the literature precedent of using lithium di-*tert*-butyldihphenyl (LiDBB) as a reagent for single electron transfer to form anions from halides,[7] pyrroline **1** was treated with LiDBB in THF at −78 °C for 2 h. A single crystalline product was obtained in 79% yield; however, ^{1}H NMR and ^{13}C NMR spectroscopy both ruled out the formation of a tetrahydropyridine. Instead the product was identified as the dimerised adduct **4**, formed as a single diastereoisomer† (Scheme 3). Dimer **4** was thought to result from the dimerisation of enone **3** through the β-position. Mechanistically, enone **3** can arise by two different routes (Scheme 4). In Route A, a ketyl radical **5** is formed and then collapses by cleaving the carbon–nitrogen bond. Route B involves reductive cleavage of the carbon–iodine bond, whereby the intermediate radical anion **6** accepts a second electron to give anion **7** and then undergoes ring opening. Enone **3** can accept an electron to form radical anion **8** which dimerises to furnish **4**. In theory both pathways consume three electrons to form **8**.

This paper describes our electrochemical studies of pyrroline **1**, in an attempt to verify the reaction pathway envisaged for the formation of enone **3**. Pyrroline **1** contains three electroactive groups; the halogen, ester and carbamate units and was thus judged too unwieldy for initial electrochemical studies. A series of simple compounds were chosen to model the different functional groups present in pyrroline **1** allowing their electrochemical response to be observed individually (Fig. 1). Pyrroline **9** was also synthesised as a molecule analogous to pyrroline **1** on which the final electrochemical experiments would be performed. In these experiments we aimed to determine the relative reactivity of the three electroactive groups (and, therefore, predict the likely route to compound **3**). We also sought to use chronoamperometry experiments to determine the number of electrons involved in the dimerisation reaction.

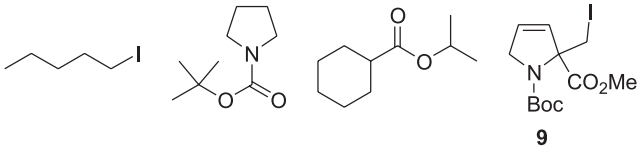
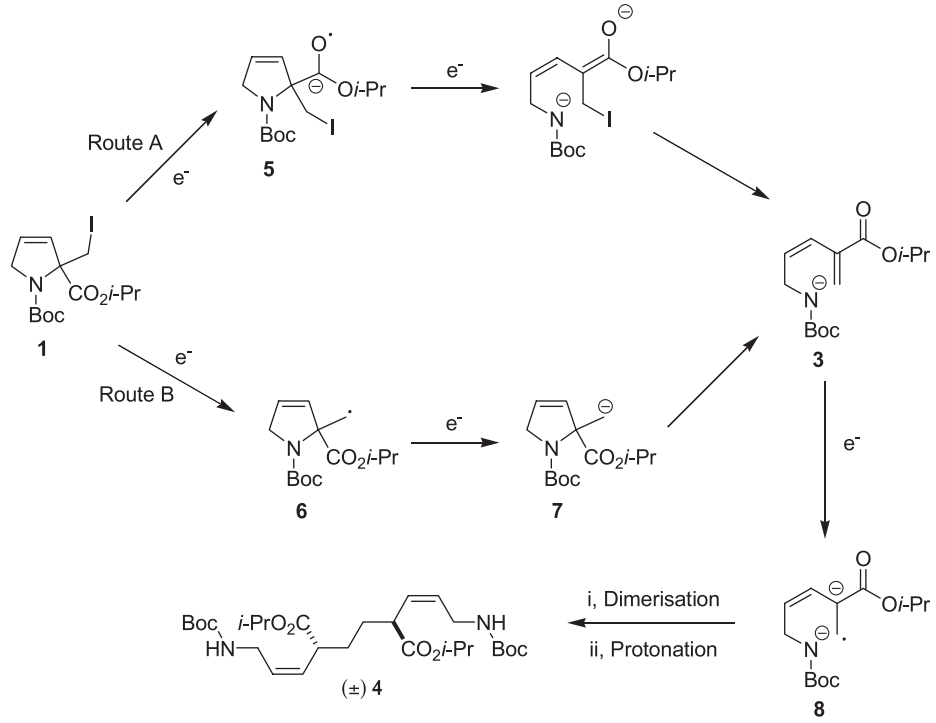


Figure 1.



Scheme 4.

† As determined by X-ray crystallography.

2. Theory

Chronoamperometry permits the simultaneous determination of the diffusion coefficient, D, and n, the number of electrons transferred to the electroactive species of interest. The time dependent current response, I, resulting from a diffusion-controlled reductive current after a potential step at a microdisc electrode is given in Eq. 1 below:

$$I = -4nFDCrf(\tau) \quad (1)$$

where Eq. 2 defines $f(\tau)$:

$$f(\tau) = 0.7854 + 0.8862\tau^{-1/2} + 0.2146e^{-0.7823\tau^{-1/2}} \quad (2)$$

and Eq. 3 defines τ:

$$\tau = 4Dt/r^2 \quad (3)$$

F is the Faraday constant, r is the radius of the disc electrode and t the time. The above approximation (Eqs. 1–3) were derived by Shoup and Szabo,[8] and describes the current response to within an accuracy of 0.6% over all τ. Experimentally, the chronoamperometric experiment is run over a time scale incorporating a transition from transient, with a $I \propto D^{1/2}$ dependence, to steady-state with a $I \propto D$ dependence behaviour. Accordingly deconvolution of the parameters D and n is possible from a single scan. Fitting was achieved via ORGIN 6.0 (Microcal Software Inc.) where, having input accurate value for r and C, the software iterates through values of D and n until the fit of the experimental data had been optimised.

3. Results and discussion

3.1. Electrochemical reduction of 1-iodopentane

A 3.14 mM solution of 1-iodopentane in THF (0.1 M TBAP) was prepared and cooled to −72 °C. A platinum microelectrode was used to record the voltammetric response (Fig. 2). A reduction wave is observed at ca. −2.9 V (vs Ag wire) which is just before the on-set of solvent breakdown. No corresponding oxidation wave was observed in the potential window studied, suggesting a chemically irreversible process. A mass transport corrected Tafel plot (Fig. 3) of the voltammogram from Figure 2 (corresponding to the reduction of iodopentane) was constructed, the gradient of which produced an alpha value of 0.26. This relatively small value is perhaps not unexpected since Andrieux and co-workers observed low alpha values (ca. 0.3) for the reduction of butyl iodide in DMF and interpreted the low values as resulting from a dissymmetry of the potential energy curves of the reactant and products in the context of Butler-Volmer kinetics.[9]

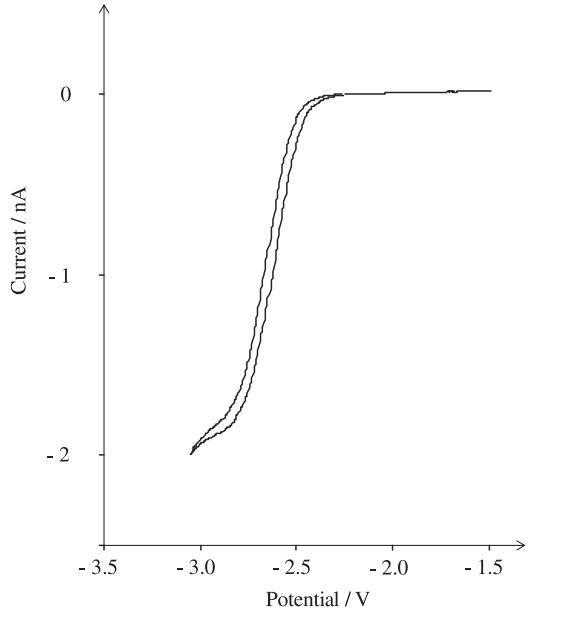


Figure 2. Voltammetric response of iodopentane (3.14 mM) in THF (0.1 M TBAP) using a 5 μm (radius) platinum microelectrode recorded at a scan rate of 20 mV s^{-1} at −72 °C (vs Ag wire).

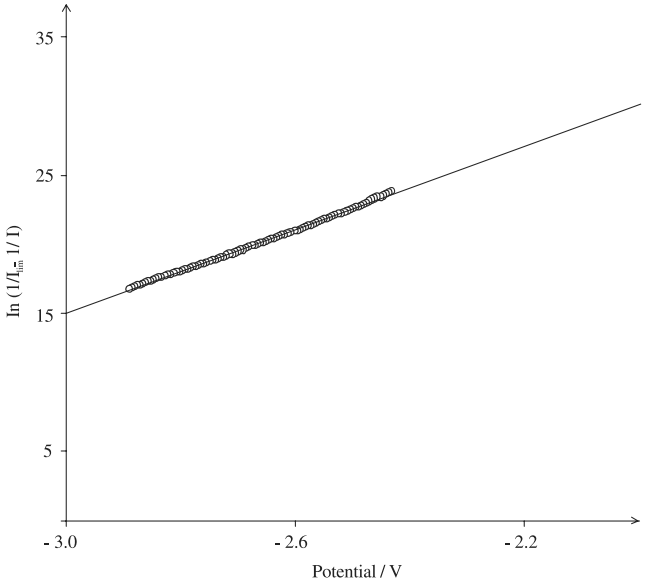


Figure 3. Mass transport corrected Tafel plot from the voltammetry presented in Figure 1.

The change in the limiting current was measured as the temperature of the solution was increased. It was found that the voltammetric wave shifted to less negative potentials as the temperature was increased, and above −40 °C moved beyond the solvent window. Accordingly, voltammetry of 1-iodopentane was impossible at or near room temperature. A 0.1 M TBAP solution in THF was prepared in which a 5 μm (radius) platinum microelectrode was used to examine the magnitude of the solvent window as a function of temperature over the range of +16 to −71 °C. The voltammetric responses are shown in Figure 4A. It can be seen that as the temperature decreased, the cathodic potential window widened to more negative potentials. This is emphasised in Figure 4B which clearly shows the onset of solvent breakdown, (taken at the point which the current rapidly drops off) is shifted from −2.8 V at +16 °C to −3.3 V at −71 °C. Clearly, there is an advantage to using cryoelectrochemistry to study the kinetics and reaction mechanism of room temperature electrochemically 'invisible' processes. We now turned to investigating the diffusion coefficient and number of electrons transferred for iodopentane using chronoamperometry.

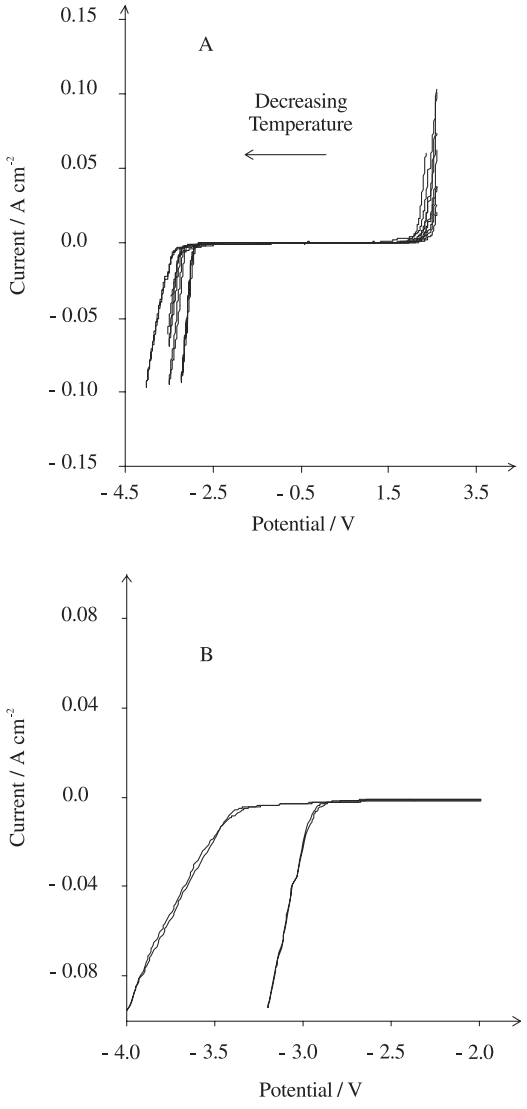


Figure 4. Solvent window of THF containing 0.1 M TBAP recorded at a range of temperatures (A) with (B) highlighting the extent of changing the temperature on the electrochemical window.

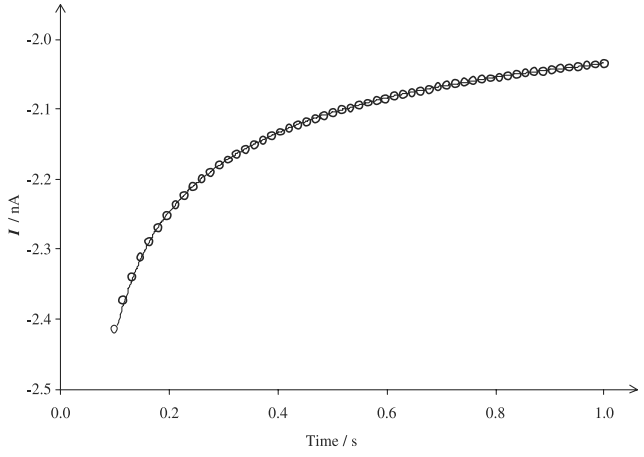


Figure 5. Experimental (solid line) and fitted theoretical (circles) chronoamperometric curve, for the reduction of 3.14 mM iodopentane in THF (0.1 M TBAP) at a 5 μm platinum electrode.

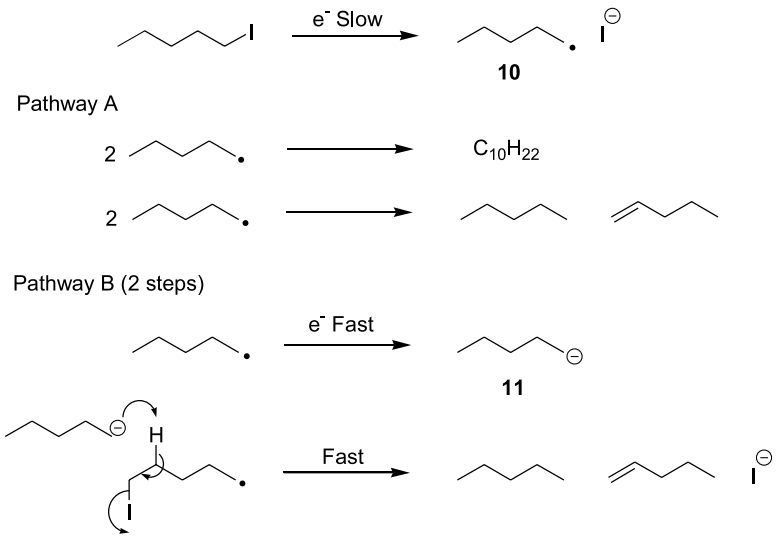
A chronoamperometric method was applied to deduce the diffusion coefficient, D, and number of electrons transferred, n, to the electroactive species. To ensure that the electrochemical system was initially at equilibrium, the potential was held at a point corresponding to the passage of no Faradaic current for a period of 20 s before being instantaneously stepped to a potential in the plateau region of the reductive wave. Analysis via the Shoup and Szabo[8] expression was then employed to yield n and D in THF at −72 °C. Figure 5 depicts a typical chronoamperometric curve with the corresponding fitting applied to deduce the required parameters. The chronoamperometric experiments were performed at both 5 and 25 μm (radii) platinum electrodes with the average D and n of the two taken. The diffusion coefficient was found to be $2.84(\pm 0.38)\times 10^{-6}$ $cm^2\ s^{-1}$ with the number of electrons transferred per molecules found to correspond to 1. This is in agreement with the estimation produced from the Wilke–Chang equation[10] that predicts 3.2×10^{-6} $cm^2\ s^{-1}$.

The result of $n=1$ for the reduction of iodopentane is surprising given that the formation of the alkyl anion ($n=2$) has been reported using similar, shorter chain alkyl halides.[11] The result that $n=1$ implies that one electron is transferred per molecule of substrate. There are two possible explanations for this observation (Scheme 5), both have an identical first step with the heterogeneous electron transfer and concomitant C–I bond cleavage to yield the alkyl radical species (**10**) and iodide anion. Previous studies in DMF indicated no radical anion intermediate.[12]

The electrochemically produced radical is a reactive species and can either disproportionate or dimerise (Pathway A, Scheme 5), or accept a second electron to form the anion **11** which then performs an efficient elimination on 1-iodopentane (Pathway B). Pathway B results in a 1:1 production of pentane and 1-pentene with (in total) one electron transferred per molecule of iodopentane consumed. Route B implies that the second electron reduction to form the anion proceeds at a more positive potential than the C–I cleavage. The voltammogram only shows one peak (Fig. 2) indicating instantaneous reduction of the radical species. The existence of radicals, as suggested by Route A, seems unlikely as previous studies performed on 1-iodobutane have shown that no octane (dimerised product) was formed, only a ~1:1 mixture of butane and butene.[13] The results support Pathway B given that the rate of dimerisation is much faster than disproportionation.

3.2. Electrochemical reduction of 1-(*tert*-butoxycarbonyl)-pyrrolidine and cyclohexanecarboxylic acid isopropyl ester

1-(*tert*-Butoxycarbonyl)-pyrrolidine and cyclohexanecarboxylic acid isopropyl ester were investigated since they isolate two of the potential electroactive sites on pyrroline **1**. Cyclic voltammetry was recorded at −72 °C using two different sizes of platinum electrode. The voltammetric response confirmed that the carbamate functionality was electro-inactive over the potential range studied with only a background response (scan in the absence of any electroactive species) observed; it can be assumed that this molecule has a reduction potential greater

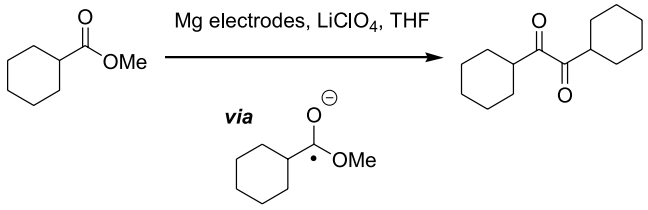


Scheme 5.

than −3.0 V (vs silver wire). This however, may not be surprising since Boc protecting groups are regularly used in Birch-type reactions without undergoing chemical reduction.

Following on, the cyclohexanecarboxylic acid isopropyl ester was analysed by cyclic voltammetry. No voltammetric responses were observed in the potential range studied (0 to −3.0 V).

The fact that no obvious reduction peak was measured for the ester in the cyclic voltammetric experiment was a surprise as electrochemical procedures for acyloin-type reactions are known at potentials approximately −2.7 V (vs SCE) as developed by Kashimura and Shono et al.[14] The reaction proceeds through the dimerisation of a ketyl radical species which is generated electrochemically (Scheme 6). This result, however, was dependent of the use of magnesium electrodes which may provide some electrophilic activation of the carbonyl group.



Scheme 6.

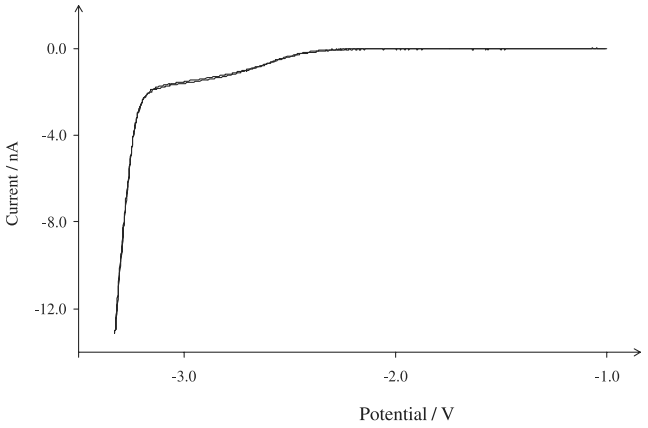


Figure 6. Voltammetric response of (2*RS*)-1-(*tert*-butoxycarbonyl)-2-iodomethyl-2,5-dihydropyrrole-2-carboxylic acid methyl ester in THF (0.1 M TBAP) recorded at −72 °C using a 5 μm platnium microelectrode (vs Ag wire) at a scan rate of 20 mV s^{-1}.

3.3. Electrochemical reduction of 2(*RS*)-methyl 1-(*tert*-butoxycarbonyl)-2-iodomethyl-2,5-dihydropyrrole-2-carboxylate

A 0.99 mM solution of pyrroline **9** was dissolved in THF also containing 0.1 M TBAP. Figure 6 shows the voltammetric response using a platinum microelectrode at −72 °C recorded at a scan rate of 20 mV s^{-1}. A limiting current is clearly observed at ca. −3.0 V which again is close to solvent breakdown as observed for the reduction of iodopentane.

Given the reduction potential of iodopentane, the electroactive site within the electrochemical cell is likely to be the carbon iodine bond, favouring Route B (Scheme 4). However, the reductive ring opening reaction is performed with the presence of lithium ions (from LiDBB) and it is not yet possible to determine the relative activation that the lithium ions provide to the three electroactive functional groups.

Chronoamperometry was applied to deduce the values of n and D. A typical experimental transient and corresponding fit is shown in Figure 7. Consequently the diffusion coefficient was found to be $2.78(\pm 0.15)\times 10^{-6}$ cm s^{-1} (at −71 °C) with the number of electrons transferred per molecule found to correspond to three.

Following Route B (Scheme 4) it appears that alkyl radical **6** immediately accepts a second electron to give **7**, which ring opens to furnish an enone intermediate **3** (Scheme 4). Enone **3** is either as susceptible or more susceptible to electrochemical reduction as **1** and accepts a third electron to

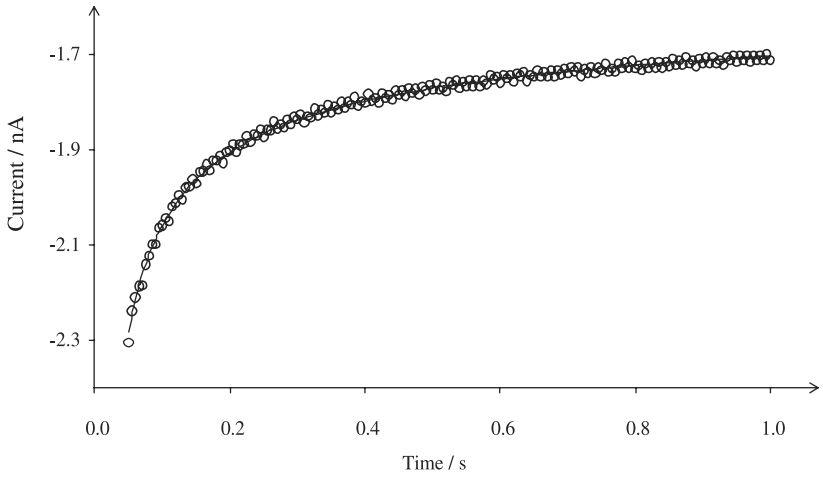


Figure 7. Experimental (circles) and fitted theoretical (solid line) chronoamperometric curves, for the reduction of (2*RS*)-1-(*tert*-butoxycarbonyl)-2-iodomethyl-2,5-dihydropyrrole-2-carboxylic acid methyl ester in THF (0.1 M TBAP) at a 5 μm platinum electrode.

produce the radical anion **8**, the species that dimerises. The rapid reduction of **6** and **3** at the potential required to reduce the C–I bond is implied by the presence of only a 'single step' in the voltammogram (Fig. 6).

The results of chronoamperometry do not allow the distinction between Routes A and B as both consume three electrons. However, as there is only a single peak in the voltagramm of **9** at a potential similar to that of 1-iodopentane (Fig. 6), the electrochemical data is most consistent with Route B for ring opening. This result further corroborates our supposition that the electrochemical reaction in the case of iodopentane is best modelled by the formation of an anion rather than a radical species.

4. Conclusions

It has been demonstrated that pyrroline **1** accepts three electrons in the ring-opening dimerisation reaction to form **4**. Within the electrochemical cell, the measured potential of **9** indicates that pyrroline **1** accepts an electron into the carbon–iodine bond first, eventually leading to dimerisation. It is worth noting that, in the synthetic reaction, the effect of lithium ions in solution is unknown and they may alter the relative reactivity of the electroactive functionalised group. More study is required to address this question.

Cryoelectrochemisty with cyclic voltammetry and chronoamperometry has been applied to give an insight into an organic mechanism at low temperature which has allowed the number of electrons participating in the reaction to be deduced from potential step experiments without recourse to bulk chrono-coulometery while the low temperature allows otherwise voltammetry invisible molecules such as iodopentane to be studied.

5. Experimental

5.1. Electrochemistry

All reagents were used as received without any further purification. Voltammetric measurements were carried out on a μ-Autolab (Eco-Chemie, Utrecht, Netherlands) potentiostat. A three-electrode arrangement was used in an airtight electrochemical cell (ca. 50 mL). The working electrodes employed were a 1 mm (diameter) platinum electrode (housed in a Teflon insulating case), 5 μm (radius) and 25 μm (radius) platinum microdisc electrodes (Cypress Systems Inc., Kansas, US) with a large area bright platinum wire (Goodfellow Cambridge Ltd, Cambridge, UK) used as the counter electrode. A silver wire was used as the quasi-reference electrode (Goodfellow Cambridge Ltd, Cambridge, UK). The working electrodes were polished using alumina of decreasing sizes on soft lapping pads. Before carrying out electrochemical experiments, the microdisc radii were electrochemically calibrated using a literature methodology.[15] Tetra-*n*-butylammonium perchlorate was added to freshly distilled THF with all experiments undertaken in an acetone/dry ice bath thermostatted at -74 ± 2 °C. Typically the solutions were degassed for 30 min using impurity-free nitrogen (BOC Gases, Guildford, Surrey, UK) to remove any trace oxygen.

5.2. General

Tetrahydrofuran was distilled before use from sodium-benzophenone ketyl radical under an argon atmosphere. All reactions were carried out under argon using oven-dried glassware. Proton and carbon NMR spectra were recorded on Fourier transform spectrometers using an internal deuterium lock. Chemical shifts are quoted in parts per million (ppm) downfield of tetramethylsilane. Coupling constants *J* are quoted in hertz. Both the proton and carbon NMR spectra of compound **1** and **9** exhibit doubling of some signals because of the presence of Boc group rotamers. Infrared spectra were recorded on an FTIR spectrophotometer. Electrospay ionization (ESI) and chemical ionization (CI) mass spectra and accurate mass data were recorded.

5.2.1. 2(*RS*)-Isopropyl 1-(*tert*-butoxycarbonyl)-2-iodomethyl-2,5-dihydropyrrole-2-carboxylate 1. Ammonia (250 mL) was freshly distilled onto cut lithium wire (111 mg, 16.0 mmol, 4.0 equiv) under an atmosphere of

argon at −78 °C. The resulting dark blue solution was stirred for 1 h before the addition of bis(methoxyethyl)-amine (5.90 mL, 40.0 mmol, 10.0 equiv) and dry tetrahydrofuran (20 mL). After 5 min isopropyl 1-(*tert*-butoxycarbonyl)pyrrole-2-carboxylate[2] (1.01 g, 4.0 mmol) dissolved in dry tetrahydrofuran (30 mL) was added dropwise over 5 min and stirred for a further 55 min, the dark blue colour persisting throughout. Isoprene (~0.25 mL) was added until the dark blue colour disappeared. On addition of diiodomethane (2.26 cm^3, 28.0 mmol, 7.0 equiv) the rapidly stirring solution turned dark brown and was allowed to stir for 15 min before the addition of saturated ammonium chloride (5 mL). The reaction was allowed to warm to ambient temperature and ammonia evaporated. Aqueous citric acid (1.0 mol dm^{-3}, 125 mL) was added and the solution stirred for 5 min before being separated. The aqueous layer was extracted with ether (4×150 mL), the combined organic extracts were dried (anhydrous magnesium sulfate) and evaporated under reduced pressure. The residue was chromatographed [SiO_2, ethyl acetate-light petroleum (bp 40–60 °C), 5:95], to give the dihydropyrrole **1** (1.49 g, 94%) as an oil; R_f [ethyl acetate-light petroleum (bp 40–60 °C), 5:95] 0.11; ν_{max} (thin film)/cm^{-1} 2978 (CH), 2933 (CH), 2866, 1727 (CO), 1704 (NCO), 1550 (C=C), 1258 (COC), and 1177 (COC); δ_H (400 MHz; $CDCl_3$) 6.11, 6.05 (1H, dt, J=6.1, 2.0 Hz, CH=CH–C), 5.42, 5.38 (1H, dt, J=6.1, 2.0 Hz, CH_2CH=CH), 4.99 (1H, sep, J=6.3 Hz, OCH), 4.40, 4.12 (1H, d, J=10.6 Hz, CH_AH_BI), 4.31–4.12 (2H, m, NCH_2), 3.85, 3.83 (1H, d, J=10.6 Hz, CH_AH_BI), 1.47, 1.45 (9H, s, CMe_3) and 1.25–1.19 (6H, m, $CHMe_2$); δ_C (100.6 MHz; $CDCl_3$) 168.0, 167.7, 153.1, 152.7, 130.4, 130.2, 129.4, 129.1, 80.9, 80.1, 75.1, 74.4, 69.8, 69.6, 55.4, 55.2, 28.4, 21.7, 21.6, 13.7, 13.4; *m/z* (+ESI) 417 (23, MNa^+) and 396 (MH^+); (Found MNa^+, 418.0482. $C_{14}H_{22}NO_4INa$ requires MNa, 418.0491).

5.2.2. (*meso*)-Diisopropyl 2,5-bis-(3-*tert*-butoxycarbonyl-amino-propenyl)-hex-*cis*-enedioic-1-carboxylate 4. Freshly cut lithium wire (20.8 mg, 3.00 mmol, 3.0 equiv) was hammered out into a foil, cut into several small strips, and placed in a Schlenk tube containing DBB (798 mg, 3.00 mmol, 3.0 equiv) and some glass 'antibumping' granules. The tube was evacuated and purged with argon several times. The contents of the Schlenk tube were then stirred vigorously until the lithium foil had been completely reduced to a powder (typically 0.5–2 h) under an atmosphere of argon. The Schlenk tube was cooled to −78 °C under an atmosphere of argon, and tetrahydrofuran (25 mL) added, immediately resulting in a dark turquoise solution. Pyrroline **1** (394 mg, 1.00 mmol) dissolved in dry tetrahydrofuran (30 mL) were added dropwise over a period of 2–5 min. The turquoise colour persisted throughout the course of the substrate addition. The reaction mixture was stirred at −78 °C for a further 2 h and saturated ammonium chloride (5 mL) was added. The reaction mixture was separated and the aqueous layer extracted with ethyl acetate (3×15 cm^3). The combined organic extracts were dried (anhydrous magnesium sulfate) and evaporated under reduced pressure. The residue was chromatographed [SiO_2, light petroleum (bp 40–60 °C), then ethyl acetate-light petroleum (bp 40–60 °C), 10:90], to give the carbamate **4** (198 mg, 79%) as needles, mp 87–90 °C [(from dichloromethane-light petroleum (bp 40–60 °C)]; R_f [ethyl acetate-light petroleum (bp 40–60 °C) 20:80] 0.50; ν_{max} (solution cell)/cm^{-1} 3370 (NH), 2978 (CH), 2936 (CCH_3), 1713 (CO), 1457 (CH_2), 1441 (CH_3), 1420 (CH_2), 1250 (COC), 1043 (COC) and 1021 (COC); δ_H (400 MHz; $CDCl_3$) 5.63–5.60 (2H, m, NCH_2CH=CH), 4.46–5.40 (2H, m, NCH_2CH=CH), 4.97 (2H, sep, J=6.3 Hz, OCH), 4.73–4.69 (2H, br m, NH), 3.86–3.69 (4H, dm, NCH_2), 3.27–3.52 (2H, m, $CHCO_2$), 1.78–1.66 (2H, m, $CHCH_AH_B$), 1.43 (20H, apparent s, CMe_3 and $CHCH_AH_B$) and 1.22–1.19 (12H, m, $CHMe_2$); δ_C (100.6 MHz; $CDCl_3$) 172.7, 155.7, 130.1, 129.2, 79.3, 68.2, 44.0, 37.7, 29.6, 28.4, 21.7 and 21.6; δ_H (400 MHz; C_6D_6) 5.46–5.36 (4H, m, CH=CH), 4.97, 4.96 (2H, sep, J=6.3 Hz, OCH), 4.55, 4.45 (2H, s, NH), 3.90–3.79 (2H, NCH_AH_B), 3.66–3.60 (2H, m, NCH_ACH_B), 3.33 (2H, s, $CHCO_2$), 1.84–1.80 (2H, m, $CHCH_AH_B$), 1.58–1.49 (2H, m, $CHCH_AH_B$), 1.44, 1.43 (18H, s, CMe_3) and 1.02, 1.00 (12H, d, J=6.3 Hz, $CHMe_2$); δ_C (100.6 MHz; C_6D_6) 172.8, 155.9, 130.5, 130.4, 78.9, 68.1, 44.4, 38.3, 30.2, 28.7, 22.0 and 21.9; *m/z* (+ESI) 563 (100%, MNa^+), 542 (1, MH^+) and 442 (100, MH^+–CO_2CMe_3); (Found MH^+, 541.3488. $C_{28}H_{49}N_2O_8$ requires MH, 541.3489).

5.2.3. 1-(*tert*-Butoxycarbonyl)-pyrrolidine. Pyrrolidine (372 mg, 5.23 mmol) was dissolved in dichloromethane (50 mL) and stirred at ambient temperature. Di-*tert*-butyl dicarbonate (1.24 g, 5.69 mmol, 1.1 equiv) dissolved in dichloromethane (10 mL) was added dropwise and the reaction stirred under an atmosphere of argon for 2 h. The mixture was evaporated under reduced pressure. The residue was chromatographed [SiO_2, ether-light petroleum (bp 40–60 °C), 10:90], to give the carbamate (604 mg, 68%) as an oil; δ_H (400 MHz; $CDCl_3$) 3.30 (4H, d, J=9.6 Hz, NCH_2), 1.83 (4H, m, CH_2) and 1.46 (9H, s, CMe_3). δ_C (100.6 MHz; $CDCl_3$) 154.7, 78.8, 45.9, 28.5 and 25.0. All data agreed with that previously published.[16]

5.2.4. Isopropyl cyclohexanecarboxylate. Isopropyl alcohol (0.38 mL, 4.97 mmol) was dissolved in dichloromethane (30 mL) and triethylamine (2.20 mL, 15.8 mmol, 3.2 equiv) added. The reaction was cooled to 0 °C under an atmosphere of argon and cyclohexane carbonyl chloride (0.91 mL, 6.80 mmol, 1.4 equiv) was added dropwise and allowed to warm to room temperature. After 4 h of stirring the mixture was poured into saturated ammonium chloride (50 mL) and the layers separated. The aqueous layer was extracted with ether (3×50 cm^3), the combined organic extracts were dried (anhydrous magnesium sulphate) and evaporated under reduced pressure. The residue was chromatographed [SiO_2, ethyl acetate-light petroleum (bp 40–60 °C), 2:98], to give the ester (651 mg, 77%) as a liquid; δ_H (400 MHz; $CDCl_3$) 4.99 (1H, hp, J=6.3 Hz, OCH), 2.24 (1H, tt, J=11.2, 3.6 Hz, CHCO), 1.94–1.84 (2H, m, $C_2H_AH_B$, $C_6H_AH_B$), 1.82–1.69 (2H, m, $C_3H_AH_B$, $C_5H_AH_B$), 1.49–1.35 (2H, m, $C_2H_AH_B$, $C_6H_AH_B$), 1.34–1.12 (4H, m, $C_3H_AH_B$, $C_5H_AH_B$, and CH_2), 1.66 (6H, d, J=6.3 Hz, $OCHMe_2$). δ_C (100.6 MHz; $CDCl_3$) 175.6, 67.0, 43.4, 29.0, 25.8, 25.4 and 21.8. All data agreed with that previously published.[17]

5.2.5. 2(*RS*)-Methyl 1-(*tert*-butoxycarbonyl)-2-iodomethyl-2,5-dihydropyrrole-2-carboxylate 9. Ammonia

(150 mL) was freshly distilled onto cut lithium wire (55.2 mg, 8.00 mmol, 4.0 equiv) under an atmosphere of argon at −78 °C. The resulting dark blue solution was stirred for 1 h before the addition of bis(methoxyethyl)-amine (1.48 mL, 10.0 mmol, 5.0 equiv) and dry tetrahydrofuran (20 mL). After 5 min methyl 1-(*tert*-butoxycarbonyl)-pyrrole-2-carboxylate (452 mg, 2.0 mmol) dissolved in dry tetrahydrofuran (30 mL) was added dropwise over 5 min and stirred for a further 55 min, the dark blue colour persisting throughout. Isoprene (~0.25 mL) was added until the dark blue colour disappeared. On addition of diiodomethane (0.83 mL, 8.00 mmol, 4.0 equiv) the rapidly stirring solution turned dark brown and was allowed to stir for 15 min before the addition of saturated ammonium chloride (5 mL). The reaction was allowed to warm to ambient temperature and ammonia evaporated. Aqueous citric acid (1.0 mol dm^{-3}, 125 mL) was added and the solution stirred for 5 min before being separated. The aqueous layer was extracted with ether (4×150 mL), the combined organic extracts were dried (anhydrous magnesium sulfate) and evaporated under reduced pressure. The residue was chromatographed [SiO_2, ethyl acetate-light petroleum (bp 40–60 °C), 5:95], to give the dihydropyrrole **6** (134 mg, 18%) as an oil; R_f [ethyl acetate-light petroleum (bp 40–60 °C), 4:96] 0.11; ν_{max} (thin film)/cm^{-1} 2980, 1730, 1703, 1393, 1258, 1176, 1106 and 973; δ_H (400 MHz; $CDCl_3$) 6.19–6.07 (1H, m, CH=CH–C), 5.49–5.39 (1H, m, CH_2CH=CH), 4.43, 4.12 (1H, d, J=10.9 Hz, CH_AH_BI), 4.37–4.12 (2H, m, NCH_2), 3.82, 3.79 (1H, d, J=10.9 Hz, CH_AH_BI), 3.74 (3H, s, OMe) and 1.40, 1.45 (9H, s, CMe_3); δ_C (100.6 MHz; $CDCl_3$) 169.3, 168.8, 153.2, 152.6, 130.7, 130.4, 129.2, 128.9, 80.9, 80.4, 75.0, 74.3, 55.2, 55.1, 53.0, 52.9, 28.4, 28.3, 13.5 and 13.1; *m/z* (+CI) 368 (1, MH^+); (Found MNa^+, 368.0364. $C_{12}H_{19}NO_4INa$ requires MH, 368.0359).

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Quinoxalines XIV.† Synthesis, ^{1}H, ^{13}C, ^{15}N NMR spectroscopic, and quantum chemical study of 1*H*-pyrazolo[3,4-*b*]quinoxalines (flavazoles)

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Abstract—The synthesis of a series of 1*H*-pyrazolo[3,4-*b*]quinoxalines (flavazoles) by acylation, alkylation, halogenation, and aminomethylation of the parent compound is reported and their structure is investigated by ^{1}H, ^{13}C, and ^{15}N NMR spectroscopy. The restricted rotation about the partial C, N double bond of the N-acyl derivatives **7**–**10** is studied by dynamic NMR spectroscopy and the barriers to rotation are determined. In order to assign unequivocally the ^{15}N chemical shifts of N-4 and N-9, in case of 3-substituted flavazoles, exemplary the ^{1}H, ^{13}C, and ^{15}N NMR chemical shifts of **34**, **35**, and **39** are also theoretically calculated by quantum chemical methods [ab initio at different levels of theory (HF/6-31G* and B3LYP/6-31G*)].

1. Introduction

Previously, we reported a new and convenient synthesis of 1*H*-pyrazolo[3,4-*b*]quinoxalines (flavazoles) by reacting quinoxaline-2-aldoximes and -ketoximes with hydrazine, alkylhydrazines or arylhydrazines under acidic conditions to afford unsubstituted, 1- and/or 3-substituted flavazoles; various other substituents could be introduced by acylation and alkylation of the 1-unsubstituted compounds.[2]

It is the major objective of the present paper to continue these studies and to further investigate substitution possibilities by acylation, alkylation, halogenation, and Mannich reaction. Beside synthesis, NMR spectroscopic properties of the flavazoles (cf. Fig. 1) were studied in detail by employing the whole arsenal of 1D and 2D NMR spectroscopy and also theoretical methods. The restricted rotation about the exocyclic partial C, N double bond in the N-acyl compounds **7**, **8**, **9**, and **10**, respectively, was studied by dynamic NMR.

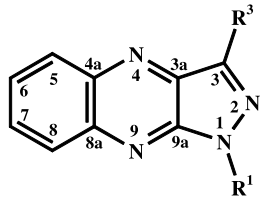

Figure 1. Investigated 1*H*-pyrazolo[3,4-*b*]quinoxalines (flavazoles) (**1**–**48**), R^1 and R^3 are given in Schemes 1–4.

2. Results and discussion

2.1. Syntheses

1*H*-Pyrazolo[3,4-*b*]quinoxalines were acylated only in position 1 by applying aroyl chlorides in the presence of pyridine.[2] When employing acetic anhydride instead, also the nonsubstituted flavazole (**1**), the 3-methyl substituted analogue **2**, and the 3-chloro- and 3-bromo-substituted compounds (**5** and **6**), could be acylated. If acetic anhydride is applied in 25-fold excess and as solvent too, **7**–**10** could be also obtained (cf. Scheme 1).

1*H*-Pyrazolo[3,4-*b*]quinoxaline (**1**) can be readily halogenated, but the reaction product proved to be dependent on the substituent pattern: nonsubstituted flavazole is halogenated in position 3, thus, with trichloroisocyanuric acid (TCC) 3-chloro-1*H*-pyrazolo[3,4-*b*]quinoxaline (**5**) was obtained which is described as cytotoxic and was already synthesized from 3-amino-1*H*-pyrazolo[3,4-*b*]quinoxaline.[3] The reaction of **1** with *N*-bromosuccinimide yielded 3-bromo-1*H*-pyrazolo[3,4-*b*]quinoxaline (**6**).

The 3-halogeno substituted reaction products **5** and **6** can be

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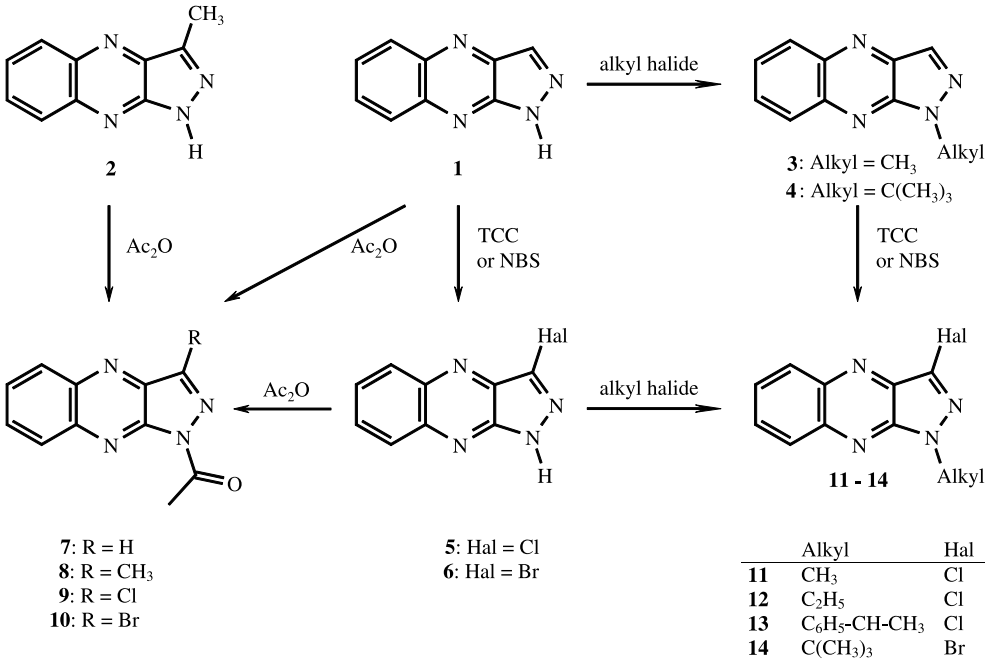
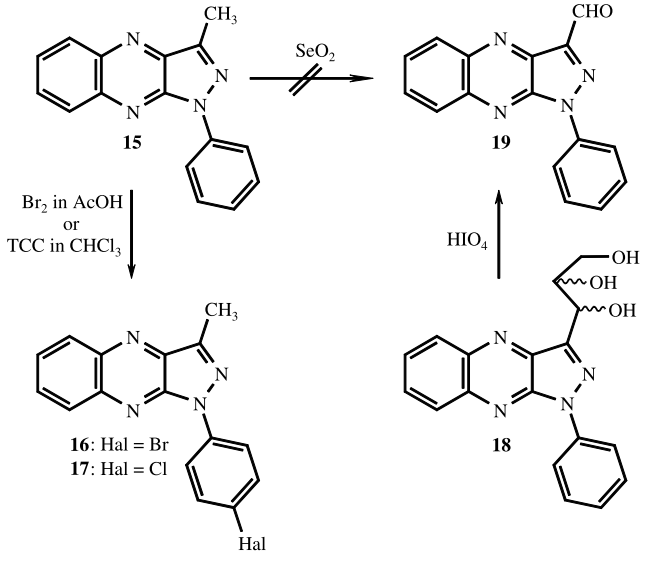


Scheme 1.

further acylated and alkylated in position 1; thus, the reaction of **5** with methyl iodide yielded 3-chloro-1-methyl-1*H*-pyrazolo[3,4-*b*]quinoxaline (**11**), with ethyl iodide 3-chloro-1-ethyl-1*H*-pyrazolo[3,4-*b*]quinoxaline (**12**) was obtained and with 1-bromo-1-phenylethane the corresponding 3-chloro-1-(1-phenylethyl-1*H*-pyrazolo[3,4-*b*]quinoxaline (**13**) was synthesized (cf. Scheme 1).

As seen in Scheme 1 there is a second path of reaction from the nonsubstituted flavazole (**1**) to the 1-alkyl-3-halogeno-1*H*-pyrazolo[3,4-*b*]quinoxalines via the alkyl substituted derivatives (e.g., **3**, **4**): first, **1** is alkylated to **3** and, then, chlorinated employing TCC. Along this path, the methyl group remains in the molecule and the reaction product **11** obtained proved to be identical to the reaction product of the alkylation reaction of **5**. Similarly, halogenation of 1-*tert*-butyl-1*H*-pyrazolo[3,4-*b*]quinoxaline (**4**) with NBS led to 3-bromo-1-*tert*-butyl-1*H*-pyrazolo[3,4-*b*]quinoxaline (**14**).



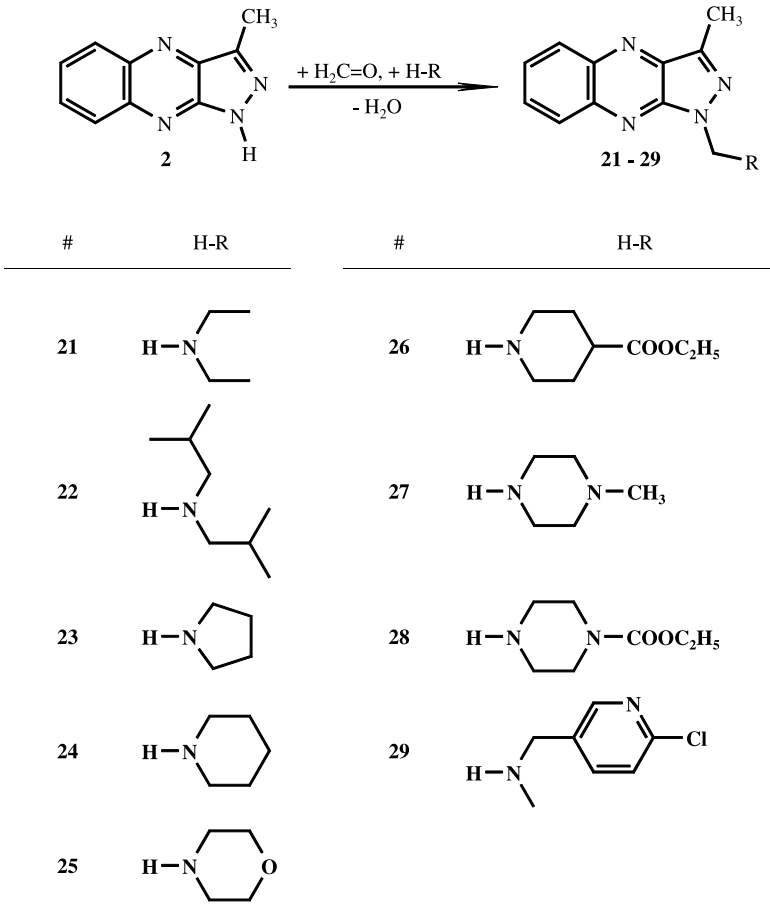
Scheme 2.

The halogenation of 3-methylflavazole (**2**) and 1,3-dimethylflavazole (**33**) under the same conditions was useless, the unsuccessful bromination of **15** (cf. Scheme 2) was already reported previously.[4] However, if elemental bromine in glacial acetic acid at room temperature is used, the *p*-substituted product **16** could be isolated. The corresponding chloro compound **17** could be synthesized with TCC. **17** was already obtained from the reaction of 2-acetylquinoxaline oxime with 4-chlorophenylhydrazine.[2]

Generally, the chemical reactivity of the methyl group in position 3 of the 1*H*-pyrazolo[3,4-*b*]quinoxalines proved to be very weak. Experiments to oxidize **15** by $KMnO_4$, CrO_3, SeO_2, and CrO_2Cl_2 were unsuccessful.[4] Otherwise, El-Maghraby et al. report the oxidation of **15** with SeO_2 in ethanol to the corresponding aldehyde.[5] This procedure could not be reproduced in our investigations, even when replacing ethanol by other solvents as dioxane/water, toluene, xylene, mesitylene, diethyleneglycol diethylether, or at their reflux temperature. On the other hand, 1-phenyl-1*H*-pyrazolo[3,4-*b*]quinoxalin-3-carbaldehyde (**19**)[6] can be synthesized by oxidation of 1-phenyl-3-(D-*erythro*-trihydroxypropyl)-1*H*-pyrazolo[3,4-*b*]quinoxaline (**18**) with potassium periodate.[7]

The aldehyde **19** reacted with *p*-toluenesulfonyl hydrazide giving the corresponding tosylhydrazone **20**.

Also the Mannich reaction of 3-methyl flavazoles was studied: the electron withdrawing effect of the nitrogen atoms in the 1*H*-pyrazolo[3,4-*b*]quinoxaline ring system should accelerate the elimination of the proton and, thus, from 3-methyl-1*H*-pyrazolo[3,4-*b*]quinoxaline (**2**) with



Scheme 3.

formaldehyde and a number of different secondary amines the corresponding Mannich bases (**21**–**29**) were synthesized in mostly good or very good yields (cf. Scheme 3).

2.2. General assignment of the chemical shifts and coupling constants

For NMR analysis additional compounds (**30**–**48**) were taken into account for which the syntheses were already described in a previous paper.[2] Their substitution pattern is given in Scheme 4.

The unequivocal assignment of the chemical shifts of both proton and carbon atoms of the pyrazole ring of the compounds **1**–**4**, **7**, and **30**–**32** proved unequivocal. The HMQC and HMBC experiments (starting from $R^3=H$) show all connectivities which are needed to assign also nitrogen chemical shifts. To get an impression about the value of the long-range coupling constants selective long-range[8] and *J*-HMBC-1[9] experiments for ^nJ(C,H) and *J*-HMBC-2 experiments[9] for ^nJ(N,H) were proceeded exemplary at compound **4**. The corresponding values thus obtained are given in Table 1.

The difference in the value of ^2J(C-3a, H-3) between the two experiments may be due to a relatively bad digital resolution of about 3.6 Hz in the *J*-HMBC-1 experiment. Recently it was shown that both experiments agree well.[10]

In cases where $R^3=CH_3$ or CHO, long-range connectivities from the corresponding substituent protons to C-3a, N-2, and N-1, respectively, were used to assign unequivocally the latter chemical shifts. The chemical shift of C-9a was then assigned by long-range connectivities to substituent protons in R^1, or, if this was not possible, using the rule that this carbon is the only one in the whole molecule who gives no HMBC signals to any of the hydrogen atoms. To know something about the long-range coupling constants ^nJ(C, H)

R^3 = H: R^1 = Ph (**30**), *o*-Cl-Ph (**31**), *m*-Cl-Ph (**32**);

R^3 = Me: R^1 = Me (**33**), Et (**34**), *i*-Pr (**35**), *n*-Bu (**36**), $CH_2CH(CH_3)_2$ (**37**), *t*-Bu (**38**), CH_2-CH=CH_2 (**39**), CH_2COOEt (**40**), *p*-Cl-C_6H_4-CH_2- (**41**), $CH(CH_3)$Ph (**42**), *o*-Cl-Ph (**43**), *m*-Cl-Ph (**44**), *p*-NO_2-Ph (**45**), COPh (**46**), *m*-Cl-C_6H_4-C(O)- (**47**), *p*-Cl-C_6H_4-C(O)- (**48**).

Scheme 4.

Table 1. Long-range coupling constants in compound **4** (Hz); signs not estimated

^nJ(X,H)	N-1, *t*-Bu	N-1, H-3	N-4, H-3	N-4, H-5	N-9, H-8	C-3a, H-3	C-4a, H-6	C-4a, H-8	C-5, H-7	C-6, H-8	C-7, H-5	C-8, H-5	C-8, H-6	C-8a, H-5	C-8a, H-7	C-9a, H-3
Sellr[a]						10.0					9.5	1.8		5.5		3.7
HMBC[b]	2.4	6.6	13.4	1.1	1.2	13.4	9.9	5.1	7.4	9.4	9.4	≈0	7.5	5.1	9.9	3.4

[a] Selective long-range experiment according to Ref. 8. Not all possible long-range couplings were determined; only two hydrogens (H-3 and H-5) were selected for irradiation.
[b] *J*-HMBC experiments according to Ref. 9.

in these compounds exemplary a *J*-HMBC-2 experiment on compound **40** was carried out. The detected coupling constants are given in Table 2.

The compounds **9**–**14** contain no protons in position 3, therefore, the corresponding long-range couplings cannot be taken to assign unequivocally C-3a. Here, the assignments given in Table 3 are in analogy with the other compounds studied.

The chemical shifts of N-4 and N-9 were assigned by HMBC measurements corroborated by theoretical calculations (vide infra). Each of them were found for the compounds studied in a relatively narrow range (−67 to −57 ppm for N-4, and −116.6 to −97.5 ppm for N-9). These two absorption ranges are considered to be large enough to assign the two ^{15}N chemical shifts unequivocally. These different chemical shifts of the nitrogen atoms N-4 and N-9 are thus the key to assign the chemical shifts of the phenylene ring atoms. The long-range connectivities in the H,N-HMBC from H-5 to N-4 and H-8 to N-9 are marking the beginning and the end of the four-spin system H-5–H-8, which can be assigned unequivocally furthermore by H,H-COSY experiments. Direct C–H correlation NMR experiments (HMQC) yield the ^{13}C chemical shifts of C-5–C-8, and the corresponding values of C-4a and C-8a are accessible via long-range connectivities from the H,C-HMBC spectra.

2.2.1. ^{1}H NMR chemical shifts. The experimentally detected ^{1}H NMR chemical shifts of the investigated compounds are given in Table 3.

In the compounds **1**, **3**, **4**, **7**, and **30**–**32** (cf. Tables 3 and 4) position 3 is nonsubstituted: the H-3 protons were found to be in the range of 8.40–8.79 ppm. All attempts to correlate their chemical shifts with electronic substituent parameters (σ_m, σ_p, σ_I, and σ_R, respectively) failed. In cases of R^3 = Me the range of the chemical shifts of the methyl protons was determined to be even more narrow (2.66–2.89 ppm). An influence of the different substituents in R^1 is again not perceptible.

The ranges of the chemical shifts of the phenylene protons are as follows: 8.03–8.35 ppm for H-5, 7.52–7.91 ppm for H-6, 7.60–7.98 ppm for H-7, and 7.92–8.35 ppm for H-8, respectively. In all compounds having no carbonyl function directly bound to positions 1 or 3, H-5 is always downfield with respect to H-8, and H-6 is upfield with respect to H-7 (with the exception of **31**: here is δ[H-6] ≈ δ[H-7]). Introducing an aldehyde group into position 3 (**19**) reverses this rule. Carbonyl functions at position 1 reduce at least the difference between H-5 and H-8 (**47**) up to zero (**9**, **10**) or even below zero (**7**, **8**, **46**, **48**). As to H-6 and H-7 of the carbonyl containing compounds, however, they follow (with the exception of **19**) the rule given above.

Table 2. Long-range C,H coupling constants as determined in compound **40** (Hz); sign not estimated

	CH_3–CH_2	CH_2–CH_3	CH_2–OCO	CH_3–*C*-3a	CH_3–*C*-3	CH_2–*C*-9a	CH_2–*C*O
^nJ(C,H)	4.2	2.1	2.6	2.7	7.2	2.1	5.4

Table 3. ^{1}H NMR chemical shifts (ppm) and H,H-coupling constants (Hz) of some selected compounds studied

Compound	R^1	R^3	5	6	7	8
1	14.15 (br)	8.79 (s)	8.27 (d, 8.0)	7.86 (t, 8.3)	7.95 (t, 8.3)	8.18 (d, 8.5)
2	11.23 (br)	2.85 (s)	8.32 (d, 8.6)	7.76 (t, 8.3)	7.87 (t, 8.3)	8.19 (d, 8.5)
3	4.18 (s)	8.40 (s)	8.13 (d, 8.5)	7.63 (t, 8.3)	7.73 (t, 8.5)	8.01 (d, 8.6)
4	1.92 (s)	8.43 (s)	8.15 (d, 8.3)	7.63 (t, 8.2)	7.70 (t, 8.5)	8.09 (d, 8.5)
7	2.94 (s)	8.56 (s)	8.17 (d, 8.4)	7.80 (t, 8.3)	7.88 (t, 8.4)	8.25 (d, 8.7)
9	2.93 (s)	–	8.35 (d, 8.5)	7.91 (t, 8.2)	7.98 (t, 8.4)	8.35 (d, 8.5)
15	*o*: 8.30 (d, 8.3); *m*: 7.44 (t, 8.6); *p*: 7.20 (t, 8.3)	2.72 (s)	8.03 (d, 8.5)	7.52 (t, 8.3)	7.60 (t, 8.5)	7.92 (d, 8.5)
19	*o*: 8.35 (m); *m*: 7.53 (t, 7.4); *p*: 7.36 (t, 7.4)	10.38 (s)	8.05 (d, 8.7)	7.81 (t, 8.3)	7.75 (t, 8.3)	8.35 (m)
30	*o*: 8.37 (d, 8.7); *m*: 7.50 (t, 8.5); *p*: 7.27 (t, 7.4)	8.54 (s)	8.12 (d, 8.3)	7.63 (t, 8.5)	7.71 (t, 8.3)	8.06 (d, 8.7)
33	4.01 (s)	2.66 (s)	8.04 (d, 8.6)	7.54 (t, 7.7)	7.64 (t, 8.0)	7.89 (d, 8.6)
34	4.53 (q, 7.3); 1.56 (t, 7.3)	2.75 (s)	8.12 (d, 8.6)	7.58 (t, 8.0)	7.68 (t, 8.3)	7.98 (d, 8.5)
40	5.30 (s); 4.22 (q, 7.2); 1.23 (t, 7.2)	2.80 (s)	8.23 (d, 8.5)	7.67 (t, 8.3)	7.76 (t, 8.4)	8.06 (d, 8.7)
47	4′, 5′: 7.50 (m); 6′: 7.44 (m); 7′: 7.64 (d, 7.0)	2.74 (s)	8.26 (d, 8.1)	7.83 (t, 8.2)	7.89 (t, 8.3)	8.25 (d, 8.1)

A complete table containing data of all measured compounds is included in the Supplementary material.

Table 4. ^{13}C and ^{15}N NMR chemical shifts (ppm) of some of the selected compounds studied

Compound	1	2	3	3a	4	4a	5	6	7	8	8a	9	9a	Others
1	−202.0 $^{1}J_{N,H}$: 106.7 Hz	−42.6	134.4	136.4	−62.9	140.6	129.9	127.8	130.8	128.4	141.0	−113.4	143.1	
2	−209.5 $^{1}J_{N,H}$: 105.8 Hz	−51.8	144.7	136.6	−64.7	141.0	130.4	127.8	131.1	128.2	141.3	−114.5	144.0	CH_3: 11.8
3	−210.2	−37.8	132.8	136.4	−63.0	140.8	129.9	127.3	130.3	128.3	141.2	−114.3	141.7	CH_3: 33.9
4	−182.8	−39.7	131.6	137.3	−67.0	140.4	129.7[a]	127.2	129.8[a]	128.9	140.6	−106.7	142.0	*t*-Bu: 60.5; 28.8
7	−167.2	−45.2	141.5	138.1	−60.0	141.5	129.8	129.3	131.5	129.3	141.3	−99.5	142.6	C═O: 168.1; CH_3: 23.5
9	−172.0	−60.7	140.9	134.4	−64.3	142.1	130.4	130.4	132.7	129.7	142.5	−97.9	143.4	$COCH_3$: 167.6; 23.7
15	−198.8	−52.8	143.9	137.3	−63.5	140.2	129.8	127.5	130.4	128.7	141.0	−109.8	142.0	CH_3: 11.5; *i*: 129.2; *o*: 119.0; *m*: 128.8; *p*: 124.9
19	−185.8	−29.4	140.7	134.1	−59.0	142.4	130.3	129.3	131.5	128.8	140.7	−103.7	142.2	CHO: 184.3; *i*: 138.0; *o*: 120.2; *m*: 129.0; *p*: 127.0
30	−192.4	−44.2	135.0	137.8	−62.7	141.1	130.0	128.2	130.8	129.0	141.3	−108.5	141.7	*i*: 139.2; *o*: 119.7; *m*: 129.0; *p*: 125.7
33	−217.9	−46.0	141.3	135.5	−63.7	139.8	129.8	126.5	129.9	127.9	140.9	−116.3	142.1	CH_3: 11.2; NCH_3: 33.2
34	−204.2	−48.7	141.5	136.0	−64.1	140.2	129.9	126.6	130.0	128.1	141.1	−116.6	141.9	CH_3: 11.4; Et: 41.6; 14.5
40	−217.2	−47.6	143.6	136.5	−62.3	140.8	130.2	127.3	130.6	128.3	141.5	−115.9	143.3	CH_3: 11.6; 1′: 47.9; 2′: 167.9; 3′: 61.6; 4′: 14.0
47	−172.9	−53.8	149.8	138.6	−60.3	141.5	130.0	131.5	129.5	129.6	141.7	−98.1	143.8	CH_3: 11.7; C═O: 164.6; 1′: 134.4; 2′: 131.7; 3′: 129.5; 4′:131.6; 5′: 126.6; 6′: 129.3

A complete table containing data of all measured compounds is included in the Supplementary material.

[a] Or reversed.

Table 5. Qualitative correlation between δ^{15}N-1 and E_s

R^1 (compound)	δ^{15}N (ppm)	E_s
Me (**33**)	−217.9	0
Et (**34**)	−204.2	−0.07
i-Pr (**35**)	−194.3	−0.47
t-Bu (**38**)	−188.8	−1.54

2.2.2. ^{13}C NMR chemical shifts. In general, the ^{13}C NMR chemical shifts of the carbon atoms of the flavazole ring system are observed mostly in very narrow ranges for each position. These values are listed in Table 4.

The widest range is shown by C-3. However, its chemical shifts can be grouped in different sets depending on the nature of the substituents in positions 3 and 1. If R^3=H, the values were found between 131.6 and 135.7 ppm for **3**, **4**, and **30**–**32**; introducing a carbonyl function into R^1 (**7**) increases the chemical shift to 141.5 ppm. Compounds with R^3=Me and no carbonyl function in R^1 show values in the range of 140.4–146.9 ppm; the carbonyl function in R^1 again increases the value to 148.5–149.8 ppm. If chlorine is introduced into position 3, the chemical shifts of this carbon atom were observed in the range of 132.4–133.0 ppm (without a carbonyl containing substituent R^1); the corresponding carbonyl compound (**9**) shows again an increased value of 140.9 ppm. The chemical shifts of C-3 in compounds **10** and **19**, having bromine and CHO at position 3, respectively, were determined to be 130.4 and 140.7 ppm.

The chemical shifts of the carbon atoms in position 3a are in the range of 135.8–138.6 ppm for R^3=H; halogen or CHO substitution in position 3 changes it to 132.2–136.2 ppm. The influence of the character of the substituent R^1 is not significant.

Both the quarternary carbons of the phenylene moiety were found to resonate in very narrow ranges: 139.8–142.4 ppm for C-4a, and 140.6–142.5 ppm for C-8a. However, the other carbons of this ring are more separated and resonate in the ranges of 129.7–130.4 ppm for C-5, 126.5–130.4 ppm for C-6, 129.8–132.7 ppm for C-7, and 127.3–129.9 ppm for C-8, respectively. Interestingly, in all investigated compounds the chemical shift of C-5 is downfield from C-8 and that of C-6 is highfield shifted from C-7.

The chemical shifts of C-9a show only a small influence of the substituents R^1 and R^3, all signals are in the range 141.7–144.7 ppm.

2.2.3. ^{15}N NMR chemical shifts. All measured ^{15}N NMR chemical shifts are given in Table 4.

Due to the varying substitution in position 1 the chemical shift of N-1 shows the widest range (−222.2 to −166.8 ppm). All available substituent constants were tried to be correlated with the N-1 chemical shifts, however only a qualitative correlation between the steric substituent parameter E_s[11] and δ^{15}N in the series **33**, **34**, **35**, and **38**, where R^3=Me and R^1= Me, Et, *i*-Pr, and *t*-Bu, respectively, were found (Table 5).

The ^{15}N chemical shifts of N-2 were found in the range of

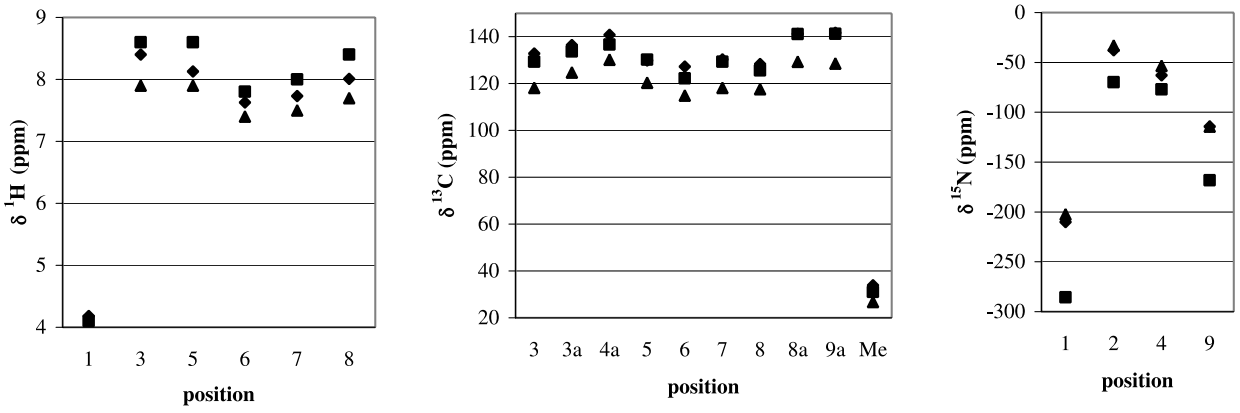


Figure 2. Experimental (♦) and calculated (HF/6-31G*: ■; B3LYP/6-31G*: ▲) ^{1}H, ^{13}C, and ^{15}N chemical shifts of **3**.

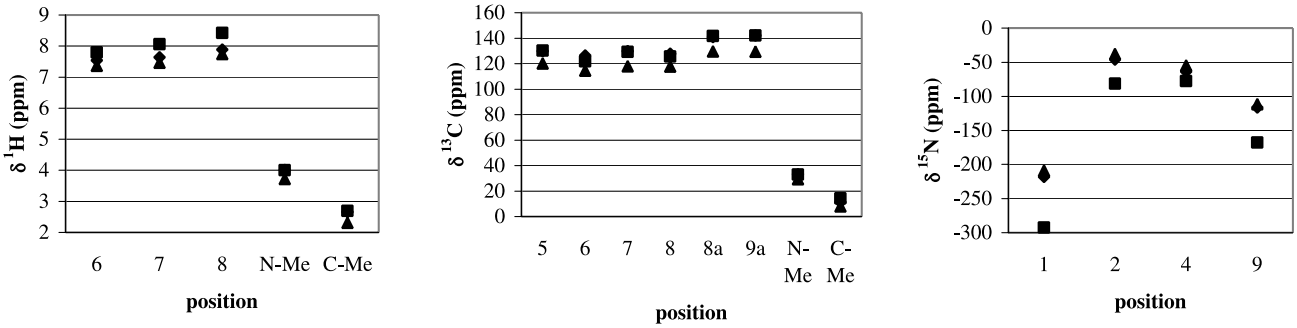


Figure 3. Experimental (♦) and calculated (HF/6-31G*: ■; B3LYP/6-31G*: ▲) ^{1}H, ^{13}C, and ^{15}N chemical shifts of **33**.

Table 6. Calculated and experimental chemical shifts of compounds **34**, **35** and **39**, respectively (ppm)

Atom	Exp.	HF/6-31G*	B3LYP/6-31G*
Compound **34**			
H-5	8.12	8.66	7.88
H-6	7.58	7.79	7.36
H-7	7.68	8.05	7.46
H-8	7.98	8.41	7.74
CH_2	4.53	4.18	4.13
CH_3-1	1.56	1.85	1.52
CH_3-3	2.75	2.72	2.36
C-3	141.5	139.82	130.27
C-3a	136.0	135.62	125.71
C-4a	140.2	136.16	129.67
C-5	129.9	130.20	120.17
C-6	126.6	121.88	114.58
C-7	130.0	129.11	117.83
C-8	128.1	125.76	117.83
C-8a	141.1	141.48	129.48
C-9a	141.9	142.13	129.48
CH_2	41.6	37.80	37.06
CH_3-1	14.5	12.77	6.93
CH_3-3	11.4	14.33	8.34
N-1	−204.2	−283.56	−198.21
N-2	−48.7	−88.00	−46.08
N-4	−64.1	−77.94	−54.91
N-9	−116.6	−167.52	−112.03
Compound **35**			
H-5	8.18	8.64	7.87
H-6	7.60	7.77	7.35
H-7	7.71	8.04	7.43
H-8	8.05	8.37	7.70
CH	5.32	5.00	5.04
CH_3-1	1.65	1.56	1.30
CH_3-3	2.81	2.74	2.38
C-3	141.5	141.21	131.37
C-3a	136.4	134.76	124.89
C-4a	140.5	135.92	129.79
C-5	130.1	130.30	120.16
C-6	126.8	121.61	114.36
C-7	130.1	129.28	117.91
C-8	128.3	125.53	117.61
C-8a	141.3	141.44	129.52
C-9a	141.9	141.49	128.57
CH	48.4	41.63	60.10
CH_3-1	21.7	21.92	34.94
CH_3-3	11.6	14.49	26.05
N-1	−194.3	−273.16	−188.53
N-2	−52.1	−90.19	−48.39
N-4	−64.1	−77.23	−54.85
N-9	−115.7	−171.25	−115.02
Compound **39**			
H-5	8.19	8.65	7.88
H-6	7.63	7.79	7.35
H-7	7.74	8.06	7.46
H-8	8.05	8.38	7.70
$-CH_2-$	5.14	4.82	4.70
–CH=	6.12	6.16	5.75
$=CH_2$	5.27	5.52	5.08
CH_3-3	2.78	2.70	2.34
C-3	142.5	141.68	132.07
C-3a	136.2	135.22	125.07
C-4a	140.5	135.87	129.58
C-5	130.1	130.30	120.22
C-6	127.0	121.79	114.52
C-7	130.3	129.37	118.04
C-8	128.3	125.50	117.55
C-8a	141.4	141.32	129.49
C-9a	142.4	142.04	129.21
$-CH_2-$	49.1	45.25	44.27
–CH=	132.6	131.48	122.77
$=CH_2$	118.0	116.23	107.62
CH_3-3	11.5	14.35	8.32
N-1	−208.6	−282.80	−198.62
N-2	−48.0	−83.49	−40.21
N-4	−63.3	−77.05	−54.48
N-9	−115.5	−171.60	−115.44

Table 6 (*continued*)

−60.7 to −37.1 ppm, whereby the compounds with R^3= H are situated at the lowfield end, the compounds with R^3= Me more in the middle, and the compounds with R^3= halogen at the highfield end of this absorption range. Only **19** with R^3=CHO is highfield shifted to −29.4 ppm. Successful correlation with common substituent parameters was not observed.

Both, the chemical shifts of N-1 and N-2 are in a comparable range as those found for (substituted) indazoles.[12]

The chemical shifts of N-4 and N-9 show two well separated ranges, which can be used successfully for the unambiguous assignment of the proton and carbon chemical shifts of the phenylene moiety. These ranges are −67.0 to −59.0 ppm for N-4 and −116.6 to −97.9 ppm for N-9. However, an ab initio assignment was only possible for compounds with R^3=H, using the long-range connectivity from H-3 to N-4 from the HMBC experiments. This was corroborated by quantum chemical calculations (see below), which gave also different well separated ranges of the chemical shifts of N-4 and N-9, respectively. Accordingly, it was concluded that where R^3 is other than hydrogen, the chemical shift ranges of N-4 and N-9 do not overlap (Fig. 1).

2.2.4. Quantum chemical calculations. For some of the compounds the ^{1}H, ^{13}C and ^{15}N chemical shifts were calculated theoretically at different levels of theory (HF/6-31G* and B3LYP/6-31G*). From Figures 2 and 3 and Table 6 it can be concluded that for the ^{1}H NMR chemical shifts neither of these methods gave significantly better results. In contrast, in case of the ^{13}C NMR chemical shifts the HF/6-31G* method and in case of the ^{15}N NMR chemical shifts the B3LYP/6-31G* method supplied the best results.

The ^{1}H NMR chemical shifts, especially for the protons of the phenylene moiety, should be influenced by the aromaticity of the flavazole ring system. Therefore, the aromaticity of the different rings were calculated exemplarily for compounds **3**, **4**, **7**–**10**, **19**, and **33**–**36**. However, the aromaticity (Table 7) as judged from the calculated chemical shielding of a ghost atom situated 2 Å above the corresponding ring did not show significant differences for the phenyl ring and for the six-membered heterocyclic ring system in the centre of the compounds. The only remarkable deviation was found for the five-membered pyrazole ring system. In this case, the chemical shielding (which was used as an indication of aromaticity) is lowered due to the acetyl group in position 3. However, no significant correlation with the experimental data could be obtained.

Decisive for the unambiguous assignment of the chemical shifts of the phenylene ring nuclei is the unequivocal

Table 7. Calculated chemical shieldings (ppm) of a ghost atom situated 2 Å above the centre of the corresponding ring (A, five-membered pyrazole ring; B, six-membered heterocyclic ring; C, phenylene ring)

Ring	**3**	**4**	**7**-*E*	**7**-*Z*	**8**-*E*	**8**-*Z*	**9**-*E*	**9**-*Z*	**10**-*E*	**10**-*Z*	**19**-*E*	**19**-*Z*	**33**	**34**	**35**	**38**
A	4.49	4.52	3.91	3.86	3.72	3.68	3.85	3.80	3.83	3.78	4.12	4.25	4.59	4.50	4.41	4.50
B	6.68	6.69	6.57	6.41	6.48	6.31	6.64	6.48	6.62	6.46	6.49	6.49	6.74	6.69	6.64	6.69
C	5.55	5.56	5.62	5.69	5.63	5.70	5.61	5.69	5.61	5.68	5.44	5.45	5.70	5.56	5.61	5.56

knowledge of the chemical shifts of N-4 and N-9. As already mentioned they could be determined experimentally only for compounds with R^3 = H. Therefore, special attention was paid to the exact calculation of these chemical shifts. The ^{15}N chemical shifts, thus calculated for **34**, **35**, and **39** (as examples for the whole variety), proved to be different sufficiently to distinguish unequivocally the two nitrogen atoms in the compounds studied. This is surprising because they seem to be very similar. This is why an natural chemical shift (NCS) analysis[13] was carried out for one case (**35**) which gives the different partitions to the shielding constants from the different chemical bonds, lone pairs, and core electrons. Contributions to the shielding of N-4 and N-9 of major importance are given in Table 8.

Table 8. Most important partitions to the isotropic chemical shielding (ppm) of the nitrogen atoms N-4 and N-9 of **35** as calculated by the NCS analysis

Bond/electron	N-4	Bond/electron	N-9
Core	239.66	Core	239.62
Lone pair N-4	−184.14	Lone pair N-9	−130.2
N-4–C-3a	−60.2	N-9–C-9a	−54.66
N-4–C-4a	−50.2	N-9–C-8a	−48.22
C-3a–C-3	−3.05	C-9a–N-1	−2.65
C-3a–C-9a	−3.46	C-9a–C-3a	−2.74
C-4a–C-5	−2.34	C-8a–C-8	−1.48
C-4a–C-8a	−0.1	C-8a–C-4a	−0.35
Total[a]	−62.96	Total[a]	−2.79

Lewis and non-Lewis contributions are added.
[a] Total means of the sum of all partitions to the chemical shieldings of N-4 and N-9, respectively.

As a whole it is found that N-4 is less shielded by about 60 ppm as compared with N-9. This is in good agreement with the experimentally determined values of compound **35** (ca. 52 ppm). From Table 8 it can be seen that the reason for the different chemical shifts of the two nitrogen atoms are the very different contributions of their corresponding N-lone pairs to the shieldings; the other contributions are much more the same.

2.2.5. Restricted rotation about the amide bond. The compounds with R^1 = COMe show a splitting of the COMe proton signal at low temperature. This is due to the restricted rotation of the amide bond. Calculated and experimentally detected values of the free energy difference of the rotamers (ΔG°) and the free energy of activation ($\Delta G^\#$) are given in Table 9. The calculated and experimentally determined values of $\Delta G^\#$ agree very well; small differences may be due to the inaccuracy of the calculation method. These inaccuracies are probably also the reason for the differences in ΔG° values, which are, however, in this case of higher significance because of their much smaller values compared to $\Delta G^\#$ of the rotational isomers.

The rotational barriers ($\Delta G^\#$) for **7**–**10** are located at the lower end of the range of the free energy of rotation of the amide bond in common amides. Lowering of the barrier in these cases can be caused by a weak basic character of N-1 and by a steric hindrance of the annelated ring system.[14] The theoretical calculations showed that in all cases the (*Z*)-configuration is more stable than the (*E*)-analogue. The strong steric hindrance in this part of the molecule should

Table 9. Coalescence temperatures (T_c), free energies (ΔG°), and free energies of activation ($\Delta G^\#$) of the restricted rotation about the amide partial double bond (kJ/mol)

Compound	T_c (K)	$\Delta G^\#$ (kJ/mol)[a]	$\Delta G^\#$ (kJ/mol)[b,c]	ΔG° (kJ/mol)[a]	ΔG° (kJ/mol)[b]
7	235	54.6 and 50.7	46.2	3.43	4.26
8	250	52.9 and 50.0	48.4	2.34	3.76
9	240	48.9 and 46.5	47.5	3.16	3.85
10	240	51.0 and 47.7	47.3	3.52	3.97

Experimental ΔG° was determined at $T=203$ K.
[a] Experimental.
[b] Calculated with DFT (B3LYP/6-31G*) under consideration of solvent (CD_2Cl_2).
[c] Rotation from (*E*) to (*Z*).

also be the reason that no dynamic phenomena of other amidic compounds with a (substituted) benzoyl group at R^1 (**46**, **47**, and **48**, respectively) could be observed. In these cases, obviously one of the two ground states is energetically too unstable to be experimentally detected.

In contrast to the restricted rotation about the amide bond the hindrance of the rotation of the C(O)–C-3 bond in compound **19** could not be observed. The theoretical calculations show a $\Delta G^\#$ of 36.3 kJ/mol as barrier of this rotation. Thus, it is much smaller than the energy barrier for the restricted rotation about the amide bond.

2.2.6. Conjugation within 1-phenyl substituted flavazoles. If $R^1=$Ph, delocalisation of the π electrons of this phenyl ring at N-1 and the flavazole ring system can be expected. As a measure for this conjugation the torsional angle between the two planes of the both aromatic moieties can be considered. For compound **19** it was found by the theoretical calculations to be 0.9 and 2.1° for (*E*) and (*Z*), respectively; so it is more or less planar. The ^{13}C NMR chemical shifts of the *o*-carbons and the difference of ^{13}C NMR chemical shifts of the *m*- and *o*-carbons of the phenyl moiety were used to assess this interannular conjugation. For an unhindered conjugation in 1-phenyl pyrazoles δ(*o*-C) proved to be 118.5–118.8 and the δ(*m*-C)–δ(*o*-C) 10.5 ppm.[15] The detected values for compounds **15**, **19**, and **30** [δ(*o*-C) 119.0–120.2 and δ(*m*-C)–δ(*o*-C) 8.8–9.8] are much closer to the values of 1-phenyl pyrazole than to the given values obtained in cases of hindered conjugation [δ(*o*-C) 124.6–125.4 and δ(*m*-C)–δ(*o*-C) 3.3–4.0]. Together with the results of the theoretical calculation a non-hindered conjugation along the two aromatic moieties in **15**, **19**, and **30** can be concluded.

3. Experimental

All melting points were determined on a Boetius micro hotstage microscope (Fa. Analytik Dresden). The IR spectra (potassium bromide) were recorded with a Perkin Elmer FTIR 1600 spectrometer (cm^{-1}). The mass spectra were obtained on a Finnigan-MAT SSQ 710 (70 eV). Elemental analyses were performed on the autanalyser CHNS-932 (Fa. Leco Instruments GmbH); reliable microanalyses were obtained for all substances (C, H, N, S $\pm$0.3%).

3.1. Syntheses

Compounds **1**–**4**, **15**–**17**, and **30**–**48** were synthesized according to literature.[2]

3.1.1. General procedure for the synthesis of 3-halo-1*H*-pyrazolo[3,4-*b*]quinoxalines (5–6). The N-Hal-compound was added slowly to a solution of **1** (50 mmol, 8.50 g) in *N*,*N*-dimethylformamide (300 mL) at room temperature with stirring. The mixture was heated at 80 °C for 10 min and then 220 mL of the solvent were removed in vacuo. After cooling down to 15 °C the residue was treated with water (100 mL) and kept overnight in the refrigerator. The solid was collected by filtration, washed twice with methanol and recrystallized from xylene or dioxane.

3.1.1.1. 3-Chloro-1*H*-pyrazolo[3,4-*b*]quinoxaline (5). From trichloroisocyanuric acid (TCC) (20 mmol, 4.65 g) in 72% yield as yellow prisms, mp 280–281 °C; ms: *m*/*z* (%) 207 (20) $(M+3)^+$, 206 (36) $(M+2)^+$, 205 (60) $(M+1)^+$, 204 (100) M^+, 169 (10) $(M-Cl)^+$, 143 (30) (169–CN)$^+$, 116 (37) (143–HCN)$^+$, 102 (17), 90 (52), 75 (24), 63 (55); IR: 3126, 3038, 2918, 2817, 1716, 1594, 1500, 1480, 1462, 1342, 1294, 1274, 1240, 1202, 1132, 1090, 1036, 968, 916, 852, 800, 768, 728, 606, 544, 460, 436, 420. Elemental analysis (%) for $C_9H_5ClN_4$: calcd C 52.87, H 2.46, N 27.38; found C 53.11, H 2.50, N 27.40. Because of its extremely low solubility in common solvents no NMR spectra could be taken.

3.1.1.2. 3-Bromo-1*H*-pyrazolo[3,4-*b*]quinoxaline (6). From *N*-bromosuccinimide (NBS) (55 mmol, 9.75 g) in 83% yield as yellow as prisms, mp 283–284 °C; ms: *m*/*z* (%) 251 (11) $(M+3)^+$, 250 (83) $(M+2)^+$, 249 (12) $(M+1)^+$, 248 (96) M^+, 169 (50) $(M-Br)^+$, 143 (14) (169–CN)$^+$, 117 (32) (143–HCN)$^+$, 90 (100), 85 (16), 76 (14), 64 (31), 63 (39); IR: 3112, 3022, 2896, 2776, 1716, 1622, 1582, 1500, 1478, 1458, 1424, 1346, 1288, 1270, 1206, 1134, 1086, 1016, 1000, 916, 784, 758, 732, 606, 594, 544, 516, 426. Elemental analysis (%) for $C_9H_5BrN_4$: calcd C 43.40, H 2.02, N 22.50; found C 43.65, H 2.12, N 22.74. Because of its extremely low solubility in common solvents no NMR spectra could be taken.

3.1.2. General procedure for the acetylation of 1-unsubstituted flavazoles (7–10). The mixture of the appropriate 1-unsubstituted flavazole (10 mmol) and acetic anhydride (25 mL, 265 mmol) was heated under reflux for 30 min and kept overnight in the refrigerator. The solid was collected by filtration under suction, washed with 50% aqueous ethanol and recrystallized.

3.1.2.1. 1-Acetyl-1*H*-pyrazolo[3,4-*b*]quinoxaline (7). From **1** in 45% yield as colourless needles (hexane), mp 162–164 °C; ms: *m*/*z* (%) 212 (22) M^+, 211 (100) $(M-1)^+$, 210 (95) $(M-2)^+$, 169 (20), 168 (85) $(M-CH_3CO, -H)^+$,

141 (20) $(M-CH_3CON_2)^+$, 115 (31) (141–CHCH), 74 (6), 62 (8); IR: 3082, 1738, 1577, 1501, 1406, 1380, 1350, 1298, 1256, 1213, 1176, 1134, 1084, 1024, 969, 939, 907, 881, 840, 808, 763, 733, 738, 610, 584, 419. Elemental analysis (%) for $C_{11}H_8N_4O$: calcd C 62.26, H 3.80, N, 26.40; found C 62.45, H 3.82, N 26.52.

3.1.2.2. 1-Acetyl-3-methyl-1*H*-pyrazolo[3,4-*b*]quinoxaline (8). From **2** in 88% yield as colorless needles (toluene), mp 191–193 °C; ms: *m/z* (%) 226 (9) M^+, 185 (10), 184 (78) $(M-CH_2CO)$, 183 (13), 155 (10) (184–HN_2), 143 (54), 116 (18), 102 (17), 90 (10), 76 (11); IR: 3016, 2928, 1846, 1722, 1618, 1580, 1542, 1500, 1446, 1418, 1364, 1312, 1290, 1260, 1246, 1232, 1202, 1148, 1122, 1096, 1038, 1010, 978., 924, 892, 834, 772, 730, 678, 634, 602, 578, 462, 420. Elemental analysis (%) for $C_{12}H_{10}N_4O$: calcd C 63.71, H 4.46, N 24.77; found C 63.56, H 4.48, N 24.56.

3.1.2.3. 1-Acetyl-3-chloro-1*H*-pyrazolo[3,4-*b*]quinoxaline (9). From **5** in 62% yield as light brown needles (ethanol), mp 220.5–221.5 °C; ms: *m/z* (%) 248 (8) $(M+2)^+$, 247 (7) $(M+1)^+$, 246 (16) M^+, 206 (32), 205 (12), 204 (100) $(M-CH_2CO)^+$, 169 (17) (204–Cl)$^+$, 143 (34), 116 (17), 102 (8), 90 (17), 76 (11), 63 (11); IR: 3062, 2888, 1852, 1747, 1619, 1572, 1498, 1468, 1408, 1374, 1351, 1301, 1281, 1250, 1222, 1188, 1151, 1131, 1066, 969, 918, 873, 836, 775, 725, 663, 630, 602, 571, 547, 420. Elemental analysis (%) for $C_{11}H_7ClN_4O$: calcd C 53.56, H 2.86, N 22.72; found C 53.61, H 2.86, N 23.01.

3.1.2.4. 1-Acetyl-3-bromo-1*H*-pyrazolo[3,4-*b*]quinoxaline (10). From **6** in 69% yield as light brown needles (ethanol), mp 220–221 °C; ms: *m/z* (%) 293 (8) $(M+3)^+$, 292 (21) $(M+2)^+$, 291 (8) $(M+1)^+$, 290 (21) M^+, 251 (9), 250 (100), 248 (84) $(M-CH_2CO)$, 169 (42) (248–Br)$^+$, 143 (12), 117 (12) (143–CN)$^+$, 90 (22); IR: 3063, 2934, 1978, 1744, 1565, 1496, 1459, 1409, 1372, 1351, 1296, 1276, 1250, 1216, 1190, 1128, 1058, 964, 916, 858, 835, 761, 727, 627, 573, 520, 419. Elemental analysis (%) for $C_{11}H_7BrN_4O$: calcd C 45.38, H 2.43, N 19.25. Found C 45.62, H 2.45, N 19.35.

3.1.3. General procedure of alkylation of 3-halo-1*H*-pyrazolo[3,4-*b*]quinoxalines (11–13). To a solution of 3-halo-1*H*-pyrazolo[3,4-*b*]quinoxaline (10 mmol) in *N*,*N*-dimethylformamide (30 mL) the alkylating agent (15 mmol) and powdered anhydrous potassium carbonate (20 mmol, 2.76 g) were added. The mixture was stirred over 24 h at 50 °C and then diluted with water (50 mL). The precipitate was collected by filtration, treated with cold 2 N NaOH, washed with water until neutral and dried.

3.1.3.1. 3-Chloro-1-methyl-1*H*-pyrazolo[3,4-*b*]quinoxaline (11). From **5** (2.04 g) and methyl iodide (2.13 g) in 57% yield as yellow prisms (dioxane), mp 200–201 °C; ms: *m/z* 220 (26) $(M+2)^+$, 219 (16) $(M+1)^+$, 218 (76) M^+, 217 (19) $(M-1)^+$, 183 (15) $(M-Cl)^+$, 129 (33), 102 (18), 90 (14), 76 (11), 63 (11); IR: 3047, 2940, 1978, 1732, 1574, 1488, 1462, 1400, 1352, 1302, 1242, 1208, 1166, 1116, 1022, 940, 892, 846, 818, 768, 722, 658, 626, 602, 552, 528, 488, 424. Elemental analysis (%) for $C_{10}H_7ClN_4$: calcd C 54.94, H 3.22, N 25.63; found C 54.93, H 3.19, N 25.81.

3.1.3.2. 3-Chloro-1-ethyl-1*H*-pyrazolo[3,4-*b*]quinoxaline (12). From **5** (2.04 g) and ethyl iodide (2.33 g) in 56% yield as yellow prisms (hexane), mp 97–99 °C; ms: *m/z* (%) 234 (30) $(M+2)^+$, 233 (25) $(M+1)^+$, 232 (100) M^+, 219 (23), 217 (70) $(M-CH_3)^+$, 206 (14), 204 (38) $(M-CH_2{=}CH_2)^+$, 154 (8), 129 (35), 102 (23), 90 (14); IR: 2986, 2942, 1716, 1652, 1574, 1486, 1460, 1436, 1402, 1378, 1352, 1296, 1238, 1224, 1194, 1166, 1116, 1086, 1046, 982, 928, 882, 846, 794, 764, 724, 650, 618, 602, 554, 488, 424. Elemental analysis (%) for $C_{11}H_9ClN_4$: calcd C 56.78, H 3.90, N 24.08; found C 56.77, H 4.06, N 24.30.

3.1.3.3. 3-Chloro-1-(1-phenylethyl)-1*H*-pyrazolo[3,4-*b*]-quinoxaline (13). From **5** (2.04 g) and (1-bromoethyl)-benzene (2.78 g) in 89% yield as yellow prisms (heptane), mp 128–130 °C; ms: *m/z* (%) 310 (9) $(M+2)^+$, 309 (5) $(M+1)^+$, 308 (19) M^+, 293 (8) $(M-CH_3)$, 207 (5), 206 (28), 205 (19), 204 (100) $(M-C_6H_5CHCH_2)^+$, 177 (8), 175 (10) $(M-C_6H_5CHCH_2N_2)^+$, 169 (12) (204–Cl)$^+$, 154 (10) (169–NH)$^+$, 143 (22), 129 (16), 116 (23); IR: 3060, 2976, 2930, 2870, 1962, 1716, 1618, 1570, 1496, 1480, 1442, 1404, 1378, 1350, 1298, 1228, 1206, 1176, 1144, 1132, 1118, 1080, 1056, 1030, 1004, 982, 956, 934, 884, 850, 774, 758, 728, 716, 700, 624, 616, 602, 556, 546, 534, 490, 422. Elemental analysis (%) for $C_{17}H_{13}ClN_4$: calcd C 66.13, H 4.24, N 18.15; found C 66.30, H 4.51, N 18.38.

3.1.4. General procedure of halogenation of substituted 1*H*-pyrazolo[3,4-*b*]quinoxalines (11, 14, 16, 17). The N-Hal-compound was added slowly to a solution of the substituted 1*H*-pyrazolo [3,4-*b*]-quinoxaline (3 mmol) in *N*,*N*-dimethylformamide (5 mL) at room temperature with stirring. The mixture was heated up to 80 °C and stirred at this temperature for 10 min. After cooling the mixture was diluted with water (5–20 mL). The solid was collected by filtration, washed with a little amount of cold methanol and recrystallized.

3.1.4.1. 3-Chloro-1-methyl-1*H*-pyrazolo[3,4-*b*]quinoxaline (11). From TCC (1 mmol, 0.23 g) and **3** (0.55 g) in 53% yield as yellow prisms (dioxane), mp 200–201 °C, IR to be identical to the product **11** obtained from 3-chloroflavazole.

3.1.4.2. 3-Bromo-1-*tert*-butyl-1*H*-pyrazolo[3,4-*b*]-quinoxaline (14). From NBS (3.4 mmol, 0.60 g) and **4** (0.68 g) in 48% yield as yellow needles (ethanol), mp 192–193.5 °C; ms: *m/z* (%) 307 (30) $(M+3)^+$, 306 (100) $(M+2)^+$, 305 (30) $(M+1)^+$, 304 (100) M^+, 291 (15), 289 (15) $(M-CH_3)^+$, 250 (50), 248 (48) $(M-C_4H_8)^+$, 169 (30) (248–Br)$^+$, 143 (20), 102 (22), 90 (25); IR: 3068, 2975, 2933, 2683, 1967, 1715, 1622, 1565, 1494, 1477, 1436, 1414, 1388, 1368, 1348, 1292, 1258, 1233, 1198, 1148, 1122, 1068, 1025, 928, 871, 803, 759, 728, 606, 589, 496, 425. Elemental analysis (%) for $C_{13}H_{13}BrN_4$: calcd C 51.16, H 4.29, N 18.36; found C 50.93, H 4.41, N 18.65.

3.1.4.3. 1-(4-Bromophenyl)-3-methyl-1*H*-pyrazolo-[3,4-*b*]quinoxaline (16). Solutions of **15** (2.60 g, 10 mmol) in acetic acid (400 mL) and bromine (1.76 g,

11 mmol) in acetic acid (30 mL) were mixed and kept in a closed bottle for 3 days at room temperature. Thereafter, the mixture was diluted with water (700 mL) and kept in the refrigerator for 24 h. The solid was collected by filtration, washed with water and recrystallized twice from acetic acid. The compound was obtained in 75% yield as yellow needles, mp 241–242°, and found to be identical to the product from 2-acetylquinoxaline oxime and 4-bromophenylhydrazine.[2] Because of its extreme bad solubility in common solvents no NMR spectra could be recorded.

3.1.4.4. 1-(4-Chlorophenyl)-3-methyl-1*H*-pyrazolo-[3,4-*b*]quinoxaline (17). From TCC (1 mmol, 0.23 g) and **15** (0.78 g) in 50% yield as yellow needles (toluene), mp 234–236 °C, IR is identically with the product from 2-acetylquinoxaline oxime and 4-chlorophenylhydrazine.[2] Because of its extreme bad solubility in common solvents no NMR spectra could be recorded.

3.1.4.5. 1-Phenyl-1*H*-pyrazolo[3,4-*b*]quinoxalin-3-carbaldehyde (19). A solution of **18**[16] (10 mmol, 3.36 g) in hot dioxane (200 mL) was slowly poured into a suspension of KIO_4 (25 mmol, 5.75 g) and $NaHCO_3$ (30 mmol, 2.52 g) in 1 kg ice-water under vigorous stirring. The mixture was allowed to warm up to room temperature in 1 h and stirring was continued for 2–4 h. The mixture was kept overnight in the refrigerator. The solid was collected by filtration and washed with water. The crude product was considerably pure. The yield was 2.60 g (95%) yellow–brown prisms, mp 143.5–144.5 °C, after recrystallization from ethanol 2.10 g (77%) golden prisms, mp 145–146 °C; ms: *m/z* (%) 276 (12) $(M+2)^+$, 275 (65) $(M+1)^+$, 274 (100) M^+, 246 (14), 245 (64) (M−CHO), 219 (6), 218 (9) $(245–HCN)^+$, 77 (7) C_6H_5; IR: 3043, 3063, 2867, 2829, 1939, 1793, 1699, 1593, 1568, 1498, 1465, 1430, 1397, 1375, 1359, 1331, 1322, 1292, 1237, 1205, 1149, 1069, 1027, 1008, 996, 959, 934, 901, 891, 856, 847, 834, 802, 767, 743, 688, 669, 648, 614, 600, 536, 506, 481, 425. Elemental analysis (%) for $C_{16}H_{10}N_4O$: calcd C 70.06, H 3.67, N 20.43; found C 70.22, H 3.59, N 20.27.

3.1.4.6. (1-Phenyl-1*H*-pyrazolo[3,4-*b*]quinoxalin-3-carbaldehyde)-(*p*-tolylsulfonyl)hydrazone (20). A mixture of the carbaldehyde **19** (2.74 g, 10 mmol), *p*-toluenesulfonyl hydrazide (2.05 g, 11 mmol) and ethanol (300 mL) was heated under reflux for 30 min, in which time the hydrazone began to crystallize. The product was allowed to stand overnight in the refrigerator. The solid was collected by suction filtration. The compound was obtained in 56% yield after recrystallization as orange prisms (1-butanol), mp 205–207 °C (dec.); ms: *m/z* (%) 443 $(M+1)^+$, 287 (19) $(M-CH_3C_6H_4SO_2)$, 260 (20), 259 (100) $(287–N_2)^+$, 258 (13), 156 (17) $(M-287+H)^+$, 139 (15) $(156–OH)^+$, 102 (12), 92 (17), 91 (31), 77 (36), 65 (18); IR: 3442, 3190, 3046, 2923, 2860, 2794, 1936, 1597, 1567, 1499, 1450, 1425, 1349, 1303, 1293, 1242, 1207, 1184, 1165, 1092, 1078, 1041, 967, 920, 910, 885, 852, 818, 801, 784, 759, 706, 690, 673, 658, 595, 566, 546, 531, 498, 475, 421. Elemental analysis (%) for $C_{23}H_{18}N_6O_2S$: calcd C 62.43, H 4.10, N 18.99; found C 62.25, H 4.01, N 19.18. Because of its extremely low solubility in common solvents no NMR spectra could be taken.

3.1.5. General procedure for aminomethylation of 1*H*-pyrazolo[3,4-*b*]quinoxalines (21–29). To a suspension of **2** (10 mmol, 1.84 g) in ethanol (20 mL), an appropriate amine (12 mmol) and finally formalin (1.2 mL, 16 mmol) [solution of 37% CH_2=O in water] were added under stirring. The reaction was weakly exothermic (the temperature increased from 25 °C until 29 °C). The mixture was then heated under reflux for 2–5 min till the product began to crystallize. The mixture was kept overnight in the refrigerator. The solid was collected by filtration, washed with cold 2 N NaOH (if not esters), and with water or diluted ethanol. The products were purified by recrystallization.

3.1.5.1. 1-Diethylaminomethyl-3-methyl-1*H*-pyrazolo[3,4-*b*]quinoxaline (21). From diethyl amine in 48% yield as yellow needles (hexane), mp 75.5–76.5 °C; ms: *m/z* (%) 270 (6) $(M+1)^+$, 269 (1.5) M^+, 213 (21), 212 (86) $(M-C_2H_5–C_2H_4)^+$, 197 (29) $(M-Et_2N)^+$, 129 (30) $(C_6H_4NC_3H_3)^+$, 102 (24), 87 (35), 86 (100) $(Et_2NCH_2)^+$, 58 (31); IR: 3066, 2964, 2926, 2822, 1958, 1576, 1498, 1480, 1476, 1380, 1350, 1334, 1308, 1240, 1216, 1200, 1172, 1134, 1118, 1090, 1062, 1022, 996, 978, 952, 898, 842, 802, 758, 730, 708, 640, 616, 602, 554, 424. Elemental analysis (%) for $C_{15}H_{19}N_5$: calcd C 66.89, H 7.11, N 26.00; found C 66.75, H 6.98, N 25.92.

3.1.5.2. 1-Diisobutylaminomethyl-3-methyl-1*H*-pyrazolo[3,4-*b*]quinoxaline (22). From diisobutyl amine in 75% yield as yellow needles (heptane), mp 101.5–102.5 °C; ms: *m/z* (%) 326 (5) $(M+1)^+$, 282 (21) $(M-CH_3CHCH_3)$, 241 (20), 240 (82) $(M-CH_2=C–CH_3)$, 198 (29), 197 (91), 143 (55), 142 (100) $(M-CH_3CN: 2=C_8H_4N_3+C_9H_{20}N)^+$, 129 (70), 128 (23), 102 (31), 100 (20), 98 (19), 86 (37), 57 (54) $(CH_2CH(CH_3)_2)^+$; IR: 3040, 2964, 2866, 2826, 1946, 1728, 1632, 1578, 1498, 1482, 1466, 1404, 1382, 1356, 1352, 1308, 1282, 1244, 1204, 1170, 1120, 1078, 1018, 970, 954, 930, 900, 848, 822, 766, 726, 706, 646, 616, 602, 558, 424. Elemental analysis (%) for $C_{19}H_{27}N_5$: calcd C 70.12, H 8.36, N 21.57; found C 70.05, H 8.30, N 21.44.

3.1.5.3. 3-Methyl-1-pyrrolidinomethyl-1*H*-pyrazolo[3,4-*b*]quinoxaline (23). From pyrrolidine in 83% yield as yellow needles (heptane), mp 137–139 °C; ms: *m/z* (%) 268 (21) $(M+1)^+$, 267 (41) M^+, 199 (13), 198 (71), 197 (22) $(M-pyrrolidino)^+$, 129 (23), 102 (19), 85 (32), 84 (100), 83 (18), 70 (47) $pyrrolidino^+$, 55 (27); IR: 3064, 2938, 2874, 2830, 1938, 1716, 1576, 1498, 1478, 1458, 1386, 1344, 1310, 1272, 1242, 1150, 1116, 1084, 1024, 980, 962, 900, 842, 754, 722, 648, 606, 588, 520, 420. Elemental analysis (%) for $C_{15}H_{17}N_5$: calcd C 67.39, H 6.41, N 26.20; found C 67.47, H 6.44, N 26.48.

3.1.5.4. 3-Methyl-1-piperidinomethyl-1*H*-pyrazolo-[3,4-*b*]quinoxaline (24). From piperidine in 87% yield as yellow needles (heptane), mp 120–121 °C; ms: *m/z* (%) 282 (23) $(M+1)^+$, 281 (66) M^+, 198 (58), 197 (55) $(M-piperidino)^+$, 185 (42), 155 (17), 143 (10), 129 (55), 128 (10), 102 (27), 98 (100) $[CH_2N(CH_2)_5]^+$, 96 (27), 84 (10) $piperidino^+$, 55 (20); IR: 3040, 2936, 2852, 2810, 2762, 1618, 1580, 1558, 1514, 1498, 1480, 1452, 1404, 1386, 1348, 1328, 1310, 1285, 1248, 1170, 1136, 1118, 1062, 1022, 996, 978, 948, 902, 852, 842, 764, 728, 716, 648, 618, 604, 584, 552, 520, 482, 424. Elemental analysis (%) for

$C_{16}H_{19}N_5$: calcd C 68.30, H 6.81, N 24.89; found C 68.52, H 6.93, N 25.12.

3.1.5.5. 3-Methyl-1-morpholinomethyl-1*H*-pyrazolo-[3,4-*b*]quinoxaline (25). From morpholine in 60% yield as yellow needles (ethanol), mp 186.5–187.5 °C; ms: *m/z* (%) 284 (3.4) $(M+1)^+$, 283 (17) M^+,199 (17), 198 (61), 197 (13) $(M-\text{morpholino})^+$, 129 (13), 101 (16), 100 (100) $[CH_2N(C_2H_4)_2O]^+$, 86 (15) morpholino$^+$, 56 (34); IR: 3062, 2968, 2938, 2914, 2853, 2826, 1918, 1806, 1700, 1612, 1578, 1498, 1478, 1448, 1434, 1384, 1366, 1338, 1310, 1264, 1240, 1208, 1170, 1150, 1138, 1116, 1100, 1070, 1006, 976, 892, 862, 842, 798, 774, 754, 726, 650, 618, 608, 556, 528, 502, 424. Elemental analysis (%) for $C_{15}H_{17}N_5O$: calcd C 63.59, H 6.05, N 24.72; found C 63.33, H 6.16, N 24.17.

3.1.5.6. Ethyl 1-(3-methyl-1*H*-pyrazolo[3,4-*b*]quinoxalin-1-ylmethyl)piperidin-4-carboxylate (26). From ethyl piperidin-4-carboxylate in 91% yield as golden needles (heptane), mp 133–134 °C; ms: *m/z* (%) 354 (7) $(M+1)^+$, 353 (16) M^+, 308 (10) $(M-C_2H_5O)^+$, 198 (25), 197 (22) $(M-156)^+$, 171 (31), 170 (100) (197–HCN)$^+$, 169 (10), 157 (11), 156 (87) (M − 197 or 170–CH_2 or 197–CH_3CN)$^+$, 142 (35) (170–CH_2N or 170–$CH_2{=}CH_2$), 129 (21), 99 (23), 97 (12), 96 (20); IR: 2940, 2804, 2764, 1724, 1580, 1556, 1510, 1496, 1480, 1444, 1402, 1370, 1348, 1326, 1308, 1268, 1254, 1244, 1176, 1144, 1198, 1044, 1024, 998, 968, 952, 902, 864. 840, 766, 714, 648, 620, 602, 584, 552, 422. Elemental analysis (%) for $C_{19}H_{23}N_5O_2$: calcd C 64.57, H 6.56, N 19.82; found C 64.41, H 6.47, N 19.95.

3.1.5.7. 3-Methyl-1-(4-methylpiperazin-1-yl)methyl-1*H*-pyrazolo[3,4-*b*]quinoxaline (27). From 1-methylpiperazine in 62% yield as yellow needles (heptane), mp 143–144 °C; ms: *m/z* (%) 298 (6) $(M+2)^+$, 297 (20) $(M+1)^+$, 296 (13) M^+, 197 (18) $(M-\text{methylpiperazine})^+$, 129 (15), 114 (15), 113 (89) $[CH_2N(C_2H_4)_2NCH_3]^+$, 112 (36), 111 (100) (113–2H), 102 (16); IR: 3052, 2962, 2938, 2880, 2828, 2794, 2764, 1580, 1514, 1500, 1450, 1406, 1386, 1350, 1326, 1312, 1286, 1234, 1200, 1170, 1146, 1120, 1072, 1052, 1010, 976, 902, 800, 768, 736, 724, 654, 618, 554, 526, 424. Elemental analysis (%) for $C_{16}H_{20}N_6$: calcd C 64.84, H 6.80, N 28.36; found: C 64.71, H 6.53, N 28.18.

3.1.5.8. Ethyl 4-(3-methyl-1*H*-pyrazolo[3,4-*b*]quinoxalin-1-ylmethyl)piperazin-1-carboxylate (28). From ethyl piperazin-1-carboxylate in 81% yield as yellow needles (heptane), mp 165–166 °C; ms: *m/z* (%) 355 (3.9) $(M+1)^+$, 354 (11) M^+, 199 (10), 198 (50), 197 (19) $[M-N(C_2H_4)_2\text{-}NCOOEt]^+$, 172 (21), 171 (100) $[CH_2N(C_2H_4)_2N\,COOEt]^+$, 170 (11), 169 (32), 157 (39) (M-197), 143 (28), 129 (40), 102 (24), 98 (14), 97 (29), 70 (28), 56 (41), 55 (13); IR: 3060, 2978, 2952, 2832, 1682, 1580, 1516, 1498, 1480, 1460, 1432, 1386, 1374, 1362, 1340, 1310, 1282, 1244, 1211, 1176, 1156, 1118, 1100, 1080, 1028, 1004, 962, 876, 842, 766, 732, 722, 654, 618, 602, 590, 554, 540, 422. Elemental analysis (%) for $C_{18}H_{22}N_6O_2$: calcd C 61.00, H 6.26, N 23.71; found C 60.87, H 6.22, N 23.52.

3.1.5.9. 1-[*N*-(2-Chlorpyrid-5-ylmethyl)-*N*-methylamino]methyl-3-methyl-1*H*-pyrazolo-[3,4-*b*]-quinoxaline (29). From 2-chloro-5-(*N*-methylaminomethyl)pyridine as yellow needles (ethanol), mp 113–115 °C; ms:*m/z* (%) 354 (1.9) $(M+2)^+$, 353 (4.2) $(M+1)^+$, 352 (3.8) M^+, 309 (13), 199 (13), 198 (95) $(M-CH_3NCHPyCl)^+$, 197 (16), 171 (90) $(CH_3N(CH_2)CH_2Py^{37}Cl)^+$, 169 (100) $(CH_3\text{-}N(CH_2)CH_2Py^{35}Cl)^+$, 155 (13) $(M-198)^+$, 129 (25), 128 (65), 126 (95), 102 (24), 99 (11), 90 (20); IR: 3050, 2982, 2946, 2846, 2814, 1626, 1590, 1584, 1516, 1494, 1458, 1384, 1358, 1322, 1308, 1224, 1168, 1134, 1106, 1040, 1016, 974, 948, 916, 850, 816, 758, 720, 682, 640, 616, 602, 558, 494, 452, 420. Elemental analysis (%) for $C_{18}H_{17}ClN_6$: calcd C 61.28, H 4.86, N 23.82; found C 61.42, H 5.08, N 24.05.

3.2. NMR measurements

NMR spectra were recorded using Bruker Avance 500 or Avance 300 spectrometers. For preparing the solutions 130–160 mg (in case of good solubility) were dissolved in 0.7 mL of chloroform-d. If the solubility was not good enough saturated solutions were used. Chemical shifts were referenced to TMS (for ^1H), to the solvent (^{13}C), or to external CH_3NO_2 (=0 ppm for ^{15}N). In some cases it was not possible to get 1D ^{15}N spectra, here the chemical shifts were extracted from the 2D ^1H,^{15}N-gs-HMBC spectra. All 1D and 2D COSY, HMQC, and HMBC experiments were taken from the standard Bruker software. To measure heteronuclear long-range J couplings pulse sequences described in literature[8,9] were used.

Low-temperature ^1H NMR measurements were done on solutions of ca. 20 mg in 0.7 mL of CD_2Cl_2. The free energies of rotation ($\Delta G^{\#}$) were calculated by the method of Shanan-Atidi and Bar-Eli[17] using the methyl signals of the acetyl group.

3.3. Quantum chemical calculations

The ab initio program package GAUSSIAN 98[18] was used for all calculations which were carried out at the Hartree-Fock and DFT-B3LYP[19] level by means of 6-31G* split-valence basis set.[20] The geometry optimization of selected compounds was performed without restrictions. The quantum-chemical calculations were processed on SGI Octane and a Linux cluster at Potsdam University.

The magnetic shieldings of all nuclei were calculated using the GIAO method[21] implemented in GAUSSIAN 98 at the theory level mentioned above. The chemical shifts are differences in magnetic shielding of atoms and references. As references for ^{13}C and ^1H TMS, for ^{15}N chemical shifts nitromethane were employed.

The NBO 5.0[13] was used to link the GAUSSIAN 98 program. The natural chemical shielding (NCS)-NBO analysis partitions quantitatively the magnetic shielding of a certain nucleus into magnetic contributions from core orbitals (major), chemical bond and lone pair orbitals. The shielding and deshielding contributions are divided into Lewis and non-Lewis parts. Non-Lewis parts are connected with electron density in antibonding orbitals.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2005.01.013; or is available on request.

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New intra–intermolecular criss-cross cycloaddition of unsymmetrical allenylazines with alkynes leading to three fused five-membered heterocycles

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Abstract—This report describes a new type of intra–intermolecular criss-cross cycloadditions. Thermal reactions of unsymmetrical allenylazines in the presence of alkynes led to three fused five-membered heterocycles in some cases. In the case of unsymmetrical substituted alkynes, a regioselectivity was observed. The molecular structures of all products are discussed. One X-ray crystal structure is also reported.

1. Introduction

Criss-cross cycloaddition reaction was described in 1917 as intermolecular reaction of benzaldazine with 2 equiv of isothiocyanate affording a heterocyclic compound having two fused five-membered rings.[1] The reaction was named in the subsequent paper.[2] Criss-cross cycloadditions may be classified as a special type of [2+3] cycloaddition,[3] or 1,3-dipolar cycloaddition, respectively. The formation of their products was explained in 1963 by Huisgen[4] as a success of two succesive 1,3-dipolar cycloadditions. This assumption was proved in 1973 when a stable 1,3-dipole was identified by X-ray crystallographic analysis.[5]

Later, besides intermolecular criss-cross cycloadditions intramolecular reactions were also observed. In such a reaction depending on regioselectivity, two types of fused heterocyclic compounds could be formed. Central[6] and lateral[7,8] connections of the rings were observed. A combination of both approaches gave rise an intra–intermolecular criss-cross cycloaddition reaction.[9,10] It was found that the unsymmetrical allenylazine firstly reacts intramolecularly affording a 1,3-dipole intermediate that in the following intermolecular reaction reacts with submitted dipolarophile phenylisocyanate. The mechanism of the reaction and the order of the steps were supported by ab initio calculations[11] and by the identification of the product formed in the reaction without the presence of a dipolarophile.[9]

In this paper, we study the reactivity of aldazines **1** with alkynes **3** (Scheme 1) in connection with our previous results concerning alkyne reactions with fluorinated unsymmetrical allenylazine[10] and other investigations dealing with their reactions in intramolecular[7,8] and intermolecular reactions.[12,13]

2. Results and discussion

The reactivity of alkynes **3** (Table 1) was initially tested on allenylazine **1a**. When the reactivity of an alkyne was low a transformation of intermediate **2** into product **5** was observed. The same product **5** is also formed when any dipolarophile is missing in the reaction mixture. The alkynes **3a–c**, they underwent criss-cross cycloaddition were then used also with the other azines **1b** and **c**.

Keywords: Criss-cross; Cycloaddition; 1,3-Dipolar; Unsymmetrical azine; Allene; Alkyne; 1,10-Diazatricyclo[5.2.1.0^{4,10}]deca-2,6-diene.
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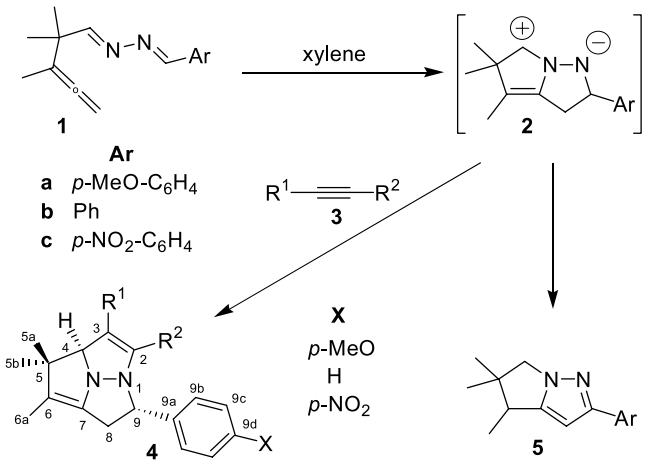

Scheme 1. General scheme of criss-cross cycloadditions.

Table 1. List of alkynes **3**

Cpd	Structure of alkynes
3a	MeOOC–C≡C–COOMe
3b	H–C≡C–COOEt
3c	F_3C–C≡C–COOEt
3d	H_3C–C≡C–COOEt
3e	Me_3Si–C≡C–COOEt
3f	Ph–C≡C–COOEt
3g	Ph–C≡C–H

X-ray analysis (Fig. 1) enabled us to determine the configuration of the synthesized products. In the asymmetric part of the unit cell, two molecules are present, both possessing the same configuration at their stereogenic centers (C4 and C9). As a whole however, the crystal is a racemate, due to the presence of the crystallographic inversion center.

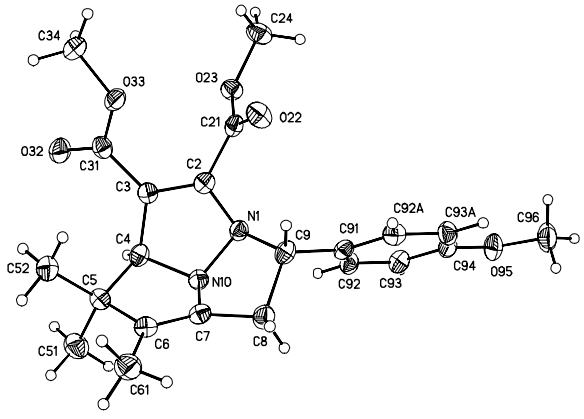

Figure 1. X-ray structure of compound **4a**.

The comparison to the related derivative (Fig. 2), differing in C2, C3, and C9 substitutions,[10] even strongly demonstrates the rigidity of the heterocycle. The r.m.s. deviation of the superimposition is naturally higher (0.0702 Å), yet reasonable with respect to the number of atoms to be fitted.

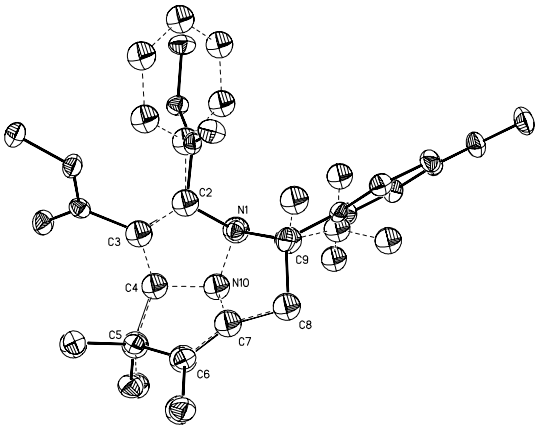

Figure 2. Superimposition of the molecular structures of **4a** and **6**.

With very few exceptions, the analogous bond distances within the heterocycles differ no more than 0.017(4) Å, thus confirming their low sensitivity to the variations in substituents.

When the symmetrical alkyne **3a** reacted with the azines **1a–c** only one stereoisomer was formed (Table 2). In the case of unsymmetrical alkynes **3b** and **c** both possible regioisomers were formed. The ratio of isomers was estimated by ^{1}H NMR spectroscopy, after removal of the solvent, in the case of fluorinated derivatives from alkyne **3c** by ^{19}F NMR spectroscopy. Reaction of alkyne **3b** was accompanied by the formation of product **5**. On the other hand, when dipolarophiles **3a** and **c** were used, no product **5** was found. We suppose that the main reason for the formation of the side product **5** is the low reactivity of alkyne **3b** and the fact that at higher temperature the acidic proton on the carbon bound with the triple bond could take part in the transformation of intermediate **2** even in anhydrous xylene.

Regioselectivity of alkyne **3c** is the highest of all the used alkynes and appeared independent upon the substitution of the phenyl (Table 2). The isomer with COOEt at carbon atom 3 (compounds **4j**, **4l** and **4n**) prevails (about 80%). On the other hand reactions with alkyne **3b** are characterized by a low regioselectivity (about 60/40 = **4e/4d**, **4g/4f** and **4i/4h**), with preferred stereoisomer containing COOEt group at C2. Regioselectivity is only moderately increasing from electron-donating to electron-withdrawing substitution on the phenyl group.

The structure of criss-cross cycloaddition products **4** was assigned using IR, GC/MS, ^{1}H, ^{13}C, DEPT135 and ^{19}F NMR spectra, respectively. The interactions between protons and carbons were assigned by 2D NMR spectra (COSY, HMQC and HMBC). The molecular weights of all the products were confirmed by GC/MS by the presence of their molecular ion-peaks. In the IR spectra, adducts **4d–o** were characterized by one carbonyl vibration, whereas compounds **4a–c** showed two esters groups. All adducts **4** showed similar value of chemical shifts for protons 5a ($\delta \sim 1.1$), 5b ($\delta \sim 1.3$), 4 ($\delta \sim 4.3$) as well as similar system of multiplets for protons 8a ($\delta \sim 2.4$, ddq), 8b ($\delta \sim 3.1$, dd), 9

Table 2. The overview of criss-cross cycloaddition products **4**

Cpd	R^1	R^2	Ar	Yield[a] (%)	Ratio[b] (%)
4a	CO_2Me	CO_2Me	*p*-MeO–C_6H_4	83	–
4b	CO_2Me	CO_2Me	Ph	89	–
4c	CO_2Me	CO_2Me	*p*-NO_2–C_6H_4	77	–
4d	CO_2Et	H	*p*-MeO–C_6H_4	28	46
4e	H	CO_2Et	*p*-MeO–C_6H_4	26	54
4f	CO_2Et	H	Ph	35	41
4g	H	CO_2Et	Ph	49	59
4h	CO_2Et	H	*p*-NO_2–C_6H_4	18	34
4i	H	CO_2Et	*p*-NO_2–C_6H_4	37	66
4j	CO_2Et	CF_3	*p*-MeO–C_6H_4	73	81
4k	CF_3	CO_2Et	*p*-MeO–C_6H_4	18	19
4l	CO_2Et	CF_3	Ph	74	81
4m	CF_3	CO_2Et	Ph	15	19
4n	CO_2Et	CF_3	*p*-NO_2–C_6H_4	70	82
4o	CF_3	CO_2Et	*p*-NO_2–C_6H_4	17	18

[a] Yield of isolated product.
[b] Ratio of regioisomers determined by ^{19}F or ^1H NMR spectra in the crude reaction mixture.

Table 3. Selected proton and carbon chemical shifts of compounds **4a–o**

Cpd	H-4	H-8a	H-8b	H-9	C-4	C-8	C-9
4a	4.46	2.48	3.06	4.84	76.7	32.8	65.2
4b	4.47	2.40	3.02	4.80	77.0	33.0	65.7
4c	4.44	2.37	3.15	5.01	77.3	32.7	64.9
4d	4.41	2.43	3.05	4.69	76.4	33.4	65.8
4e	4.19	2.42	2.90	4.84	78.5	32.1	66.5
4f	4.42	2.44	3.08	4.73	76.5	33.4	66.2
4g	4.20	2.42	2.92	4.88	78.5	32.1	67.0
4h	4.43	2.39	3.17	4.84	76.7	33.2	65.4
4i	4.21	2.35	3.00	4.99	78.6	31.8	66.0
4j	4.54	2.46	3.04	4.76	78.0	33.2	67.1
4k	4.37	2.48	3.03	4.64	78.9	32.6	66.4
4l	4.55	2.46	3.07	4.80	78.0	33.2	67.4
4m	4.36	2.49	3.06	4.70	78.9	32.6	66.8
4n	4.57	2.40	3.15	4.88	78.2	32.9	66.5
4o	4.47	2.35	3.07	4.73	79.0	32.3	65.8

($\delta \sim 4.8$, dd), 6a ($\delta \sim 1.6$, q) (Table 3). The same type of observations could be found also for carbon and fluorine atoms in NMR spectra. Those observations correlate well with the proposed stereochemistry and observations of related products of the criss-cross cycloadditions with phenyl isocyanate.[9]

Compound **4a** was analyzed more carefully. The structure was determined by X-ray diffraction analysis (Fig. 1) and quantitative NOE experiments. The *cis*-relative configuration of H-4 and C-5b was assigned using 2D NOESY experiment. On the other hand, the *cis* relationship between H-8b and H-9 was found using 1D NOE experiments. Irradiation of H-8b at δ 3.10 induced a 16% NOE effect on H-9 and 30% NOE on H-8a. Moreover, irradiation of the H-9 at δ 4.88 induced a 5% NOE on H-8b (Fig. 3). These results and the similarity of all the spectra for compounds **4** allowed us to assign the stereochemistry of each product **4**.

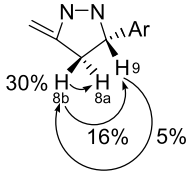

Figure 3. NOE effects in ^1H NMR spectrum.

The relative configurations on stereogenic centers are 4*S**,9*S** and 4*R**,9*R** for all products **4**, except **4e**,**g**,**i** with configuration 4*R**,9*S** and 4*S**,9*R**.

The structure of regioisomers **4e**,**g**,**i** and **4d**,**f**,**h** was assigned using ^1H and ^{13}C NMR data. The presence of a coupling constant between H-3 and H-4 ($^3J_{H\text{-}3,H\text{-}4} = 2.2$ Hz) indicated the close proximity of these two protons for regioisomer **4e**. No such a coupling constant was observed in the proton NMR spectra of the other regioisomer **4d**. On the other hand, the very close value of $^3J_{H\text{-}3,H\text{-}4}$ was obtained from trifluoromethylated analogue **6** for which we obtained an X-ray diffraction analysis.[10] We observed similar chemical shifts for protons H-2 (in compounds **4d**, **f**, **h**) and H-3 (in compounds **4e**, **g**, **i**) and for carbons C-2 and C-3, respectively (Table 4). The connectivity between protons and carbon atoms was also confirmed by DEPT135 experiments. All the data allowed us to assign the regiochemistry of each type of isomers starting from propiolate **3b**.

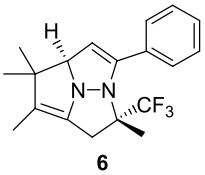

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Table 4. Selected proton and carbon chemical shifts of **4d–i**

Cpd	H-2	H-3	C-2	C-3
4d	7.08		149.4	107.9
4e		5.72	142.0	117.1
4f	7.07		149.4	108.1
4g		5.73	145.0	117.2
4h	7.07		148.7	109.3
4i		5.76	141.3	117.7

Table 5. Selected carbon chemical shifts of **4**, Ar=*p*-MeO–C_6H_4

Cpd	C-2	C-3
4a	150.1	107.3
4d	149.4	107.9
4e	143.1	117.1
4j	144.2 q, $^2J_{C,F}$=34.8	112.4 q, $^3J_{C,F}$=2.1
4k	147.0 q, $^3J_{C,F}$=4.1	110.5 q, $^2J_{C,F}$=35.3

The structure of trifluoromethyl substituted regioisomers **4j**,**l**,**n** and **4k**,**m**,**o** was assigned using ^{19}F, ^1H and ^{13}C NMR data. First of all, in the ^{13}C NMR spectra, the coupling constant ($J_{C\text{-}5a,F}$=3.2 Hz) observed for compounds **4k** and **4m** indicated the close proximity of methyl C-5a and trifluoromethyl groups. No similar observations were made for compounds **4j** and **4l**. Similar chemical shifts were obtained for carbon C-2 ($\delta_{C\text{-}2}\sim$145 ppm) and C-3 ($\delta_{C\text{-}3}\sim$112 ppm) for each regioisomer of *p*-methoxy substituted derivatives (Table 5). The $^2J_{C,F}\sim$35 Hz and $^3J_{C,F}\sim$3 Hz coupling constants showed also the position of trifluoromethyl substituent attached to C-2 and C-3, respectively.

The fluorine NMR spectra were also very helpful: δ_{CF3} −59.6 can be assigned to one isomer, whereas δ_{CF3} −54.0 to the other (Table 6). Finally, in the proton NMR spectra, compounds **4j**,**l** and **n** clearly showed allylic coupling between proton H-4 and fluorine ($^5J_{H\text{-}4,F}$=2.4 Hz).

3. Conclusion

The method of intra–intermolecular criss-cross cycloaddition was successfully applied to the preparation of new substituted 1,10-diazatricyclo[5.2.1.0^{4,10}]deca-2,6-dienes **4** in high yields (Table 2). Products were characterized by NMR and mass spectrometry (Tables 6–8). Besides, compound **4a** was characterized by X-ray diffraction analysis. In the series of substituted alkynes **3** (Table 1), the reaction occurred only in the case of reactive species such as **3a–c**. In all this cases, the reaction is diastereoselective. For unsymmetrically substituted alkynes **3b–c**, formation of both regioisomers was observed. Alkyne **3c** was characterized by high regioselectivity at C2 and C3 independent upon the substitution in the position 4 of the phenyl at allenylazine **1**. Just the opposite was observed for the reaction with alkyne **3b**: the regioselectivity was very low.

4. Experimental

4.1. General

Melting points are uncorrected. FT-IR spectra were recorded with a MIDAC Corporation Spectrafile IR apparatus. ^1H, ^{13}C and ^{19}F spectra were recorded on a Bruker AC-250 or AC-500 spectrometer with $CDCl_3$ as the solvent. Tetramethylsilane (δ 0.00) or $CHCl_3$ (δ 7.27) were

Table 6. ^{19}F NMR chemical shifts of products **4j–o**

Cpd	**4j**	**4k**	**4l**	**4m**	**4n**	**4o**
δ^a	−59.6	−54.0	−59.6	−54.0	−59.6	−54.0

[a] NMR solvent: $CDCl_3$.

Table 7. Elemental analyses or HRMS of products **4a–o**

Cpd	Formula	Calcd	Found
4a	$C_{22}H_{26}N_2O_5$	C, 66.32;H, 6.58; N, 7.03	C, 65.91;H, 6.75; N, 6.74
4b	$C_{21}H_{25}N_2O_4^+$	369.1814	369.1804
4c	$C_{21}H_{23}N_3O_6$	C, 61.01;H, 5.61; N, 10.16	C, 61.15;H, 5.57; N, 9.82
4d	$C_{21}H_{27}N_2O_3^+$	355.2022	355.2011
4e	$C_{21}H_{27}N_2O_3^+$	355.2022	355.2030
4f	$C_{20}H_{25}N_2O_2^+$	325.1916	325.1910
4g	$C_{20}H_{25}N_2O_2^+$	325.1916	325.1927
4h	$C_{20}H_{24}N_3O_4^+$	370.1767	370.1773
4i	$C_{20}H_{24}N_3O_4^+$	370.1767	370.1765
4j	$C_{22}H_{26}F_3N_2O_3^+$	423.1896	423.1879
4k	$C_{22}H_{26}F_3N_2O_3^+$	423.1896	423.1882
4l	$C_{21}H_{24}F_3N_2O_2^+$	393.1790	393.1794
4m	$C_{21}H_{24}F_3N_2O_2^+$	393.1790	393.1801
4n	$C_{21}H_{23}F_3N_3O_4^+$	438.1641	438.1636
4o	$C_{21}H_{23}F_3N_3O_4^+$	438.1641	438.1631

Table 8. Spectroscopic data of criss-cross cycloaddition products **4**

Cpd	Solvents[a]	mp (°C)	IR (cm^{-1})	GC-MS *m/z* (%)	^1H NMR[b] δ, *J* (Hz)	^{13}C NMR[b] δ, *J* (Hz)
4a	AcOEt/PE (30/70)	78–80	1129, 1247, 1436, 1514, 1611, 1704 (C=O), 1742 (C=O), 2836, 2904, 2954	398 (M^+; 35), 277 (50), 245 (22), 199 (44), 121 (100), 91 (33)	1.06 (s, 3H, H-5a), 1.32 (s, 3H, H-5b), 1.56 (d, $^5J_{H,H}$=1.8, 3H, H-6a), 2.48 (ddq, $^2J_{H,H}$=14.4, $^3J_{H,H}$=6.3, $^5J_{H,H}$=1.8, 1H, H-8a), 3.06 (dd, $^2J_{H,H}$=14.4, $^3J_{H,H}$=8.6, 1H, H-8b), 3.70 (s, 3H, $COOCH_3$), 3.79 (s, 3H, OCH_3), 3.80 (s, 3H, $COOCH_3$), 4.46 (s, 1H, H-4), 4.84 (dd, $^3J_{H,H}$=8.6, $^3J_{H,H}$=6.3, 1H, H-9), 6.87 (d, $^3J_{H,H}$=8.8, 2H, H-9c), 7.31 (d, $^3J_{H,H}$=8.8, 2H, H-9b)	8.2 (C-6a), 21.1 (C-5a), 27.5 (C-5b), 32.8 (C-8), 51.1 ($COOCH_3$), 52.7 ($COOCH_3$), 54.7 (C-5), 55.0 (OCH_3), 65.2 (C-9), 76.7 (C-4), 107.3 (C-3), 113.8 (C-9c), 116.1 (C-6), 127.0 (C-9b), 134.6 (C-9a), 141.5 (C-7), 150.1 (C-2), 158.7 (C-9d), 163.3 (C=O), 164.1 (C=O)
4b	CH_2Cl_2	101–104	1130, 1209, 1347, 1436, 1620, 1705 (C=O), 1743 (C=O), 2861, 2954	368 (M^+; 35), 277 (31), 245 (25), 184 (41), 169 (90), 153 (52), 121 (100), 91 (91)	1.06 (s, 3H, H-5a), 1.31 (s, 3H, H-5b), 1.48 (d, $^5J_{H,H}$=1.4, 3H, H-6a), 2.40 (ddq, $^2J_{H,H}$=14.4, $^3J_{H,H}$=6.1, $^5J_{H,H}$=1.4, 1H, H-8a), 3.02 (dd, $^2J_{H,H}$=14.4, $^3J_{H,H}$=8.7, 1H, H-8b), 3.70 (s, 3H, $COOCH_3$), 3.77 (s, 3H, $COOCH_3$), 4.47 (s, 1H, H-4), 4.80 (dd, $^3J_{H,H}$=8.7, $^3J_{H,H}$=6.1, 1H, H-9), 7.2-7.4 (m, 5H, Ph)	8.5 (C-6a), 21.4 (C-5a), 27.8 (C-5b), 33.0 (C-8), 51.5 (OCH_3), 53.1 (OCH_3), 55.0 (C-5), 65.7 (C-9), 77.0 (C-4), 108.0 (C-3), 116.6 (C-6), 126.1 (C-9b), 127.4 (C-9d), 128.8 (C-9c), 141.6 (C-7), 142.7 (C-9a), 150.2 (C-2), 163.6 (C=O), 164.5 (C=O)
4c	AcOEt/PE (35/65)	71–75	1125, 1210, 1347, 1438, 1522, 1606, 1713 (C=O), 1742 (C=O), 2862, 2955	413 (M^+; 44), 277 (33), 245 (42), 229 (98), 166 (56), 153 (100), 95 (75)	1.01 (s, 3H, H-5a), 1.27 (s, 3H, H-5b), 1.53 (d, $^5J_{H,H}$=1.6, 3H, H-6a), 2.37 (ddq, $^2J_{H,H}$=14.5, $^3J_{H,H}$=6.0, $^5J_{H,H}$=1.6, 1H, H-8a), 3.15 (dd, $^2J_{H,H}$=14.5, $^3J_{H,H}$=8.9, 1H, H-8b), 3.68 (s, 3H, $COOCH_3$), 3.75 (s, 3H, $COOCH_3$), 4.44 (s, 1H, H-4), 5.01 (dd, $^3J_{H,H}$=8.9, $^3J_{H,H}$=6.0, 1H, H-9), 7.55 (d, $^3J_{H,H}$=8.8, 2H, H-9b), 8.14 (d, $^3J_{H,H}$=8.8, 2H, H-9c)	8.5 (C-6a), 21.3 (C-5a), 27.6 (C-5b), 32.7 (C-8), 51.6 (OCH_3), 53.1 (OCH_3), 55.0 (C-5), 64.9 (C-9), 77.3 (C-4), 109.9 (C-3), 117.3 (C-6), 124.0 (C-9c), 127.0 (C-9b), 140.9 (C-7), 147.1 (C-9d), 148.5 (C-2), 150.2 (C-9a), 163.2 (C=O), 164.3 (C=O)
4d	AcOEt/PE (30/70)	[c]	1113, 1248, 1331, 1513, 1586, 1694 (C=O), 2836, 2960	354 (M^+; 46), 339 (30), 259 (27), 233 (40), 121 (100)	1.07 (s, 3H, H-5a), 1.26 (t, $^3J_{H,H}$=7.1, 3H, CH_2–CH_3), 1.32 (s, 3H, H-5b), 1.55 (d, $^5J_{H,H}$=1.5, 3H, H-6a), 2.43 (ddq, $^2J_{H,H}$=14.5, $^3J_{H,H}$=6.1, $^5J_{H,H}$=1.5, 1H, H-8a), 3.05 (dd, $^2J_{H,H}$=14.5, $^3J_{H,H}$=8.6, 1H, H-8b), 3.80 (s, 3H, OCH_3), 4.15 (q, $^3J_{H,H}$=7.1, 2H, CH_2–CH_3), 4.41 (s, 1H, H-4), 4.69 (dd, $^3J_{H,H}$=8.6, $^3J_{H,H}$=6.1, 1H, H-9), 7.08 (s, 1H, H-2), 6.88 (d, $^3J_{H,H}$=8.7, 2H, H-9c), 7.33 (d, $^3J_{H,H}$=8.7, 2H, H-9b)	8.5 (C-6a), 14.5 (CH_2–CH_3), 21.7 (C-5a), 27.7 (C-5b), 33.4 (C-8), 54.8 (C-5), 55.4 (OCH_3), 59.6 (CH_2–CH_3), 65.8 (C-9), 76.4 (C-4), 107.9 (C-3), 114.1 (C-9c), 116.0 (C-6), 127.1 (C-9b), 135.4 (C-9a), 142.0 (C-7), 149.4 (C-2), 158.9 (C-9d), 165.4 (C=O)
4e	AcOEt/PE (30/70)	[c]	1032, 1242, 1515, 1708 (C=O), 2836, 2930, 2956	354 (M^+; 61), 339 (42), 259 (36), 233 (71), 199 (54), 121 (100)	1.08 (s, 3H, H-5a), 1.21 (t, $^3J_{H,H}$=7.1, 3H, CH_2–CH_3), 1.29 (s, 3H, H-5b), 1.56 (d, $^5J_{H,H}$=1.8, 3H, H-6a), 2.42 (ddq, $^2J_{H,H}$=14.7, $^3J_{H,H}$=6.2, $^5J_{H,H}$=1.8, 1H, H-8a), 2.90 (dd, $^2J_{H,H}$=14.7, $^3J_{H,H}$=8.8, 1H, H-8b), 3.79 (s, 3H, OCH_3), 4.0-4.3 (m, 2H, CH_2–CH_3), 4.19 (d, $^3J_{H,H}$=2.2, 1H, H-4), 4.84 (dd, $^3J_{H,H}$=8.8, $^3J_{H,H}$=6.2, 1H, H-9), 5.72 (d, $^3J_{H,H}$=2.2, 1H, H-3), 6.88 (d, $^3J_{H,H}$=8.6, 2H, H-9c), 7.43 (d, $^3J_{H,H}$=8.6, 2H, H-9b)	8.6 (C-6a), 14.2 (CH_2–CH_3), 22.0 (C-5a), 27.1 (C-5b), 32.1 (C-8), 52.9 (C-5), 55.4 (OCH_3), 61.0 (CH_2–CH_3), 66.5 (C-9), 78.5 (C-4), 113.9 (C-9c), 115.5 (C-6), 117.1 (C-3), 127.7 (C-9b), 137.3 (C-9a), 142.0 (C-2), 143.1 (C-7), 158.5 (C-9d), 162.0 (C=O)
4f	AcOEt/PE (10/90)	[c]	1114, 1189, 1265, 1331, 1455, 1589, 1694 (C=O), 2861, 2930, 2960	324 (M^+; 80), 309 (55), 233 (49), 229 (100), 184 (51), 91 (83)	1.07 (s, 3H, H-5a), 1.26 (t, $^3J_{H,H}$=7.1, 3H, CH_2–CH_3), 1.32 (s, 3H, H-5b), 1.54 (d, $^5J_{H,H}$=1.7, 3H, H-6a), 2.44 (ddq, $^2J_{H,H}$=14.5, $^3J_{H,H}$=6.0, $^5J_{H,H}$=1.7, 1H, H-8a), 3.08 (dd, $^2J_{H,H}$=14.5, $^3J_{H,H}$=8.8, 1H, H-8b), 4.15 (q, $^3J_{H,H}$=7.1, 2H, CH_2–CH_3), 4.42 (s, 1H, H-4), 4.73 (dd, $^3J_{H,H}$=8.8, $^3J_{H,H}$=6.0, 1H, H-9), 7.07 (s, 1H, H-2), 7.2-7.4 (m, 5H, Ph)	8.5 (C-6a), 14.5 (CH_2–CH_3), 21.7 (C-5a), 27.7 (C-5b), 33.4 (C-8), 54.9 (C-5), 59.7 (CH_2–CH_3), 66.2 (C-9), 76.5 (C-4), 108.1 (C-3), 116.1 (C-6), 126.0 (C-9b), 127.4 (C-9d), 128.8 (C-9c), 142.0 (C-7), 143.3 (C-9a), 149.4 (C-2), 165.4 (C=O)
4g	AcOEt/PE (10/90) then CH_2Cl_2[d]	[c]	1029, 1128, 1218, 1370, 1455, 1605, 1716 (C=O), 2931, 2960	324 (M^+; 65), 229 (82), 184 (44), 169 (100), 135 (71), 91 (77)	1.08 (s, 3H, H-5a), 1.17 (t, $^3J_{H,H}$=7.2, 3H, CH_2–CH_3), 1.29 (s, 3H, H-5b), 1.55 (d, $^5J_{H,H}$=1.8, 3H, H-6a), 2.42 (ddq, $^2J_{H,H}$=14.5, $^3J_{H,H}$=6.3, $^5J_{H,H}$=1.8, 1H, H-8a), 2.92 (dd, $^2J_{H,H}$=14.5, $^3J_{H,H}$=8.9, 1H, H-8b), 4.0-4.3 (m, 2H, CH_2–CH_3), 4.20 (d, $^3J_{H,H}$=2.3, 1H, H-4), 4.88 (dd, $^3J_{H,H}$=8.9, $^3J_{H,H}$=6.3, 1H, H-9), 5.73 (d, $^3J_{H,H}$=2.3, 1H, H-3), 7.21 (tm, $^3J_{H,H}$=7.3, 1H, H-9d), 7.33 (tm, $^3J_{H,H}$=7.5, 2H, H-9c), 7.50 (dm, $^3J_{H,H}$=7.3, 2H, H-9b)	8.6 (C-6a), 14.1 (CH_2–CH_3), 22.0 (C-5a), 27.1 (C-5b), 32.1 (C-8), 53.0 (C-5), 61.0 (CH_2–CH_3), 67.0 (C-9), 78.5 (C-4), 115.6 (C-6), 117.2 (C-3), 126.5 (C-9b), 126.8 (C-9d), 128.5 (C-9c), 142.0 (C-7), 143.0 (C-9a), 145.0 (C-2), 161.9 (C=O)
4h	Et_2O/PE (50/50) then CH_2Cl_2[d]	148–155	1142, 1359, 1511, 1597, 1692 (C=O), 2859, 2923, 2959	369 (M^+; 83), 352 (66), 322 (49), 255 (67), 207 (100), 135 (77), 106 (58)	1.07 (s, 3H, H-5a), 1.27 (t, $^3J_{H,H}$=7.1, 3H, CH_2–CH_3), 1.32 (s, 3H, H-5b), 1.55 (d, $^5J_{H,H}$=1.5, 3H, H-6a), 2.39 (ddq, $^2J_{H,H}$=14.6, $^3J_{H,H}$=5.7, $^5J_{H,H}$=1.5, 1H, H-8a), 3.17 (dd, $^2J_{H,H}$=14.6, $^3J_{H,H}$=8.9, 1H, H-8b), 4.16 (q, $^3J_{H,H}$=7.1, 2H, CH_2–CH_3), 4.43 (s, 1H, H-4), 4.84 (dd, $^3J_{H,H}$=8.9, $^3J_{H,H}$=5.7, 1H, H-9), 7.07 (s, 1H, H-2), 7.60 (d, $^3J_{H,H}$=8.7, 2H, H-9b), 8.20 (d, $^3J_{H,H}$=8.7, 2H, H-9c)	8.6 (C-6a), 14.5 (CH_2–CH_3), 21.8 (C-5a), 27.7 (C-5b), 33.2 (C-8), 55.0 (C-5), 60.0 (CH_2–CH_3), 65.4 (C-9), 76.7 (C-4), 109.3 (C-3), 117.2 (C-6), 124.2 (C-9c), 127.0 (C-9b), 141.2 (C-7), 147.3 (C-9d), 148.7 (C-2), 150.7 (C-9a), 165.2 (C=O)

Table 8 (*continued*)

Cpd	Solvents[a]	mp (°C)	IR (cm^{-1})	GC-MS *m/z* (%)	^1H NMR[b] δ, *J* (Hz)	^{13}C NMR[b] δ, *J* (Hz)
4i	Et_2O/PE (50/50)	[c]	1129, 1219, 1346, 1519, 1606, 1720 (C=O), 2869, 2932, 2961	369 (M^+; 48), 274 (40), 229 (83), 214 (70), 95 (100)	1.08 (s, 3H, H-5a), 1.19 (t, $^3J_{H,H}$=7.1, 3H, CH_2–CH_3), 1.28 (s, 3H, H-5b), 1.56 (d, $^5J_{H,H}$=1.7, 3H, H-6a), 2.35 (ddq, $^2J_{H,H}$=14.4, $^3J_{H,H}$=6.3, $^5J_{H,H}$=1.7, 1H, H-8a), 3.00 (dd, $^2J_{H,H}$=14.4, $^3J_{H,H}$=9.0, 1H, H-8b), 4.0-4.3 (m, 2H, CH_2–CH_3), 4.21 (d, $^3J_{H,H}$=2.1, 1H, H-4), 4.99 (dd, $^3J_{H,H}$=9.0, $^3J_{H,H}$=6.3, 1H, H-9), 5.76 (d, $^3J_{H,H}$=2.1, 1H, H-3), 7.68 (d, $^3J_{H,H}$=8.7, 2H, H-9b), 8.19 (d, $^3J_{H,H}$=8.7, 2H, H-9c)	8.6 (C-6a), 14.2 (CH_2–CH_3), 22.0 (C-5a), 27.1 (C-5b), 31.8 (C-8), 53.1 (C-5), 61.2 (CH_2–CH_3), 66.0 (C-9), 78.6 (C-4), 116.7 (C-6), 117.7 (C-3), 123.9 (C-9c), 127.4 (C-9b), 141.3 (C-2), 142.1 (C-7), 146.9 (C-9d), 152.4 (C-9a), 161.8 (C=O)
4j	CH_2Cl_2	[c]	1175, 1212, 1317, 1513, 1603, 1728 (C=O), 2842, 2938, 2983	422 (M^+; 37), 407 (47), 301 (26), 199 (84), 121 (100). 91 (30)	1.02 (s, 3H, H-5a), 1.30 (t, $^3J_{H,H}$=7.1, 3H, CH_2–CH_3), 1.31 (s, 3H, H-5b), 1.58 (d, $^5J_{H,H}$=1.8, 3H, H-6a), 2.46 (ddq, $^2J_{H,H}$=14.6, $^3J_{H,H}$=5.9, $^5J_{H,H}$=1.8, 1H, H-8a), 3.04 (dd, $^2J_{H,H}$=14.6, $^3J_{H,H}$=8.8, 1H, H-8b), 3.80 (s, 3H, OCH_3), 4.22 (q, $^3J_{H,H}$=7.1, 2H, CH_2–CH_3), 4.54 (q, $^5J_{H,F}$=2.4, 1H, H-4), 4.76 (dd, $^3J_{H,H}$=8.8, $^3J_{H,H}$=5.9, 1H, H-9), 6.88 (d, $^3J_{H,H}$=8.7, 2H, H-9c), 7.34 (d, $^3J_{H,H}$=8.7, 2H, H-9b)	8.5 (C-6a), 14.0 (CH_2–CH_3), 21.2 (C-5a), 27.5 (C-5b), 33.2 (C-8), 54.9 (C-5), 55.4 (OCH_3), 61.1 (CH_2–CH_3), 67.1 (C-9), 78.0 (C-4), 112.4 (q, $^3J_{C,F}$=2.1, C-3), 114.1 (C-9c), 116.0 (C-6), 120.3 (q, $^1J_{C,F}$=274.2, CF_3), 127.3 (C-9b), 135.3 (C-9a), 141.8 (C-7), 144. 2 (q, $^2J_{C,F}$=34.8, C-2), 159.0 (C-9d), 164.0 (C=O)
4k	CH_2Cl_2	129–131	1107, 1148, 1241, 1321, 1509, 1617, 1731 (C=O), 2857, 2948, 2986	422 (M^+; 73), 407 (100), 361 (89), 241 (25), 226 (29), 121 (49)	1.15 (s, 3H, H-5a), 1.19 (t, $^3J_{H,H}$=7.3, 3H, CH_2–CH_3), 1.30 (s, 3H, H-5b), 1.59 (d, $^5J_{H,H}$=1.8, 3H, H-6a), 2.48 (ddq, $^2J_{H,H}$=14.7, $^3J_{H,H}$=6.1, $^5J_{H,H}$=1.8, 1H, H-8a), 3.03 (dd, $^2J_{H,H}$=14.7, $^3J_{H,H}$=8.8, 1H, H-8b), 3.80 (s, 3H, OCH_3), 4.1-4.4 (m, 2H, CH_2–CH_3), 4.37 (brs, 1H, H-4), 4.64 (dd, $^3J_{H,H}$=8.8, $^3J_{H,H}$=6.1, 1H, H-9), 6.89 (d, $^3J_{H,H}$=8.7, 2H, H-9c), 7.36 (d, $^3J_{H,H}$=8.7, 2H, H-9b)	8.6 (C-6a), 13.8 (CH_2–CH_3), 21.2 (q, $J_{C,F}$=3.2, C-5a), 27.9 (C-5b), 32.6 (C-8), 55.46 (C-5), 55.52 (OCH_3), 62.3 (CH_2–CH_3), 66.4 (C-9), 78.9 (m, C-4), 110.5 (q, $^2J_{C,F}$=35.3, C-3), 114.1 (C-9c), 115.7 (C-6), 123.2 (q, $^1J_{C,F}$=268.8, CF_3), 127.4 (C-9b), 135.5 (C-9a), 141.9 (C-7), 147.0 (q, $^3J_{C,F}$=4.1, C-2), 159.0 (C-9d), 161.0 (C=O)
4l	CH_2Cl_2	[c]	1152, 1302, 1354, 1620, 1701(C=O), 2868, 2914, 2964	392 (M^+; 72), 377 (74), 301 (70), 169 (100), 141 (53), 91 (82)	1.02 (s, 3H, H-5a), 1.29 (t, $^3J_{H,H}$=7.1, 3H, CH_2–CH_3), 1.31 (s, 3H, H-5b), 1.57 (d, $^5J_{H,H}$=1.8, 3H, H-6a), 2.46 (ddq, $^2J_{H,H}$=14.6, $^3J_{H,H}$=5.8, $^5J_{H,H}$=1.8, 1H, H-8a), 3.07 (dd, $^2J_{H,H}$=14.6, $^3J_{H,H}$=8.8, 1H, H-8b), 4.22 (q, $^3J_{H,H}$=7.1, 2H, CH_2–CH_3), 4.55 (q, $^5J_{H,F}$=2.3, 1H, H-4), 4.80 (dd, $^3J_{H,H}$=8.8, $^3J_{H,H}$=5.8, 1H, H-9), 7.2-7.4 (m, 5H, Ph)	8.5 (C-6a), 14.0 (CH_2–CH_3), 21.2 (C-5a), 27.5 (C-5b), 33.2 (C-8), 54.9 (C-5), 61.1 (CH_2–CH_3), 67.4 (C-9), 78.0 (C-4), 112.5 (q, $^3J_{C,F}$=2.6, C-3), 116.1 (C-6), 120.3 (q, $^1J_{C,F}$=273.9, CF_3), 126.1 (C-9b), 127.5 (C-9d), 128.8 (C-9c), 141.7 (C-7), 143.1 (C-9a), 144.2 (q, $^2J_{C,F}$=34.8, C-2), 163.3 (C=O)
4m	CH_2Cl_2	107–109	1106, 1144, 1214, 1258, 1319, 1615, 1729 (C=O), 2860, 2911	392 (M^+; 16), 301 (18), 184 (48), 169 (100), 135 (45), 91 (73)	1.15 (s, 3H, H-5a), 1.15 (t, $^3J_{H,H}$=7.2, 3H, CH_2–CH_3), 1.30 (s, 3H, H-5b), 1.59 (d, $^5J_{H,H}$=1.8, 3H, H-6a), 2.49 (ddq, $^2J_{H,H}$=14.7, $^3J_{H,H}$=6.2, $^5J_{H,H}$=1.8, 1H, H-8a), 3.06 (dd, $^2J_{H,H}$=14.7, $^3J_{H,H}$=8.2, 1H, H-8b), 4.1-4.4 (m, 2H, CH_2–CH_3), 4.36 (brs, 1H, H-4), 4.70 (dd, $^3J_{H,H}$=8.2, $^3J_{H,H}$=6.2, 1H, H-9), 7.2-7.5 (m, 5H, Ph)	8.6 (C-6a), 13.8 (CH_2–CH_3), 21.2 (q, $J_{C,F}$=3.2, C-5a), 27.9 (C-5b), 32.6 (C-8), 55.5 (C-5), 62.3 (CH_2–CH_3), 66.8 (C-9), 78.9 (m, C-4), 110.7 (q, $^2J_{C,F}$=35.3, C-3), 115.8 (C-6), 123.2 (q, $^1J_{C,F}$=268.8, CF_3), 126.1 (C-9b), 127.4 (C-9d), 128.8 (C-9c), 141.8 (C-7), 143.3 (C-9a), 147.0 (q, $^3J_{C,F}$=4.3, C-2), 160.9 (C=O)
4n	CH_2Cl_2	[c]	1150, 1348, 1524, 1720 (C=O), 2868, 2934, 2969	437 (M^+; 34), 422 (65), 301 (83), 214 (82), 168 (100), 167 (80), 153 (68), 91 (65)	1.03 (s, 3H, H-5a), 1.31 (t, $^3J_{H,H}$=7.1, 3H, CH_2–CH_3), 1.32 (s, 3H, H-5b), 1.59 (d, $^5J_{H,H}$=1.8, 3H, H-6a), 2.40 (ddq, $^2J_{H,H}$=14.5, $^3J_{H,H}$=6.1, $^5J_{H,H}$=1.8, 1H, H-8a), 3.15 (dd, $^2J_{H,H}$=14.5, $^3J_{H,H}$=8.8, 1H, H-8b), 4.24 (q, $^3J_{H,H}$=7.1, 2H, CH_2–CH_3), 4.57 (q, $^5J_{H,F}$=2.4, 1H, H-4), 4.88 (dd, $^3J_{H,H}$=8.8, $^3J_{H,H}$=6.1, 1H, H-9), 7.60 (d, $^3J_{H,H}$=8.8, 2H, H-9b), 8.22 (d, $^3J_{H,H}$=8.8, 2H, H-9c)	8.5 (C-6a), 14.0 (CH_2–CH_3), 21.1 (C-5a), 27.5 (C-5b), 32.9 (C-8), 55.0 (C-5), 61.3 (CH_2–CH_3), 66.5 (C-9), 78.2 (C-4), 113.6 (q, $^3J_{C,F}$=2.6, C-3), 117.1 (C-6), 119.9 (q, $^1J_{C,F}$=273.6, CF_3), 124.1 (C-9c), 127.0 (C-9b), 140.9 (C-7), 143.1 (q, $^2J_{C,F}$=34.9, C-2), 147.3 (C-9d), 150.2 (C-9a), 163.3 (C=O)
4o	CH_2Cl_2	[c]	1127, 1212, 1347, 1521, 1734 (C=O), 2860, 2928, 2966	437 (M^+; 21), 301 (34), 229 (63), 214 (81), 168 (61), 167 (56), 95 (100)	1.11 (t, $^3J_{H,H}$=7.1, 3H, CH_2–CH_3), 1.16 (s, 3H, H-5a), 1.30 (s, 3H, H-5b), 1.53 (d, $^5J_{H,H}$=1.8, 3H, H-6a), 2.35 (ddq, $^2J_{H,H}$=14.7, $^3J_{H,H}$=6.0, $^5J_{H,H}$=1.8, 1H, H-8a), 3.07 (dd, $^2J_{H,H}$=14.7, $^3J_{H,H}$=9.0, 1H, H-8b), 4.1-4.4 (m, 2H, CH_2–CH_3), 4.47 (brs, 1H, H-4), 4.73 (dd, $^3J_{H,H}$=9.0, $^3J_{H,H}$=6.0, 1H, H-9), 7.56 (d, $^3J_{H,H}$=8.6, 2H, H-9b), 8.15 (d, $^3J_{H,H}$=8.8, 2H, H-9c)	8.6 (C-6a), 13.8 (CH_2–CH_3), 21.1 (m, C-5a), 27.9 (C-5b), 32.3 (C-8), 55.7 (C-5), 62.5 (CH_2–CH_3), 65.8 (C-9), 79.0 (m, C-4), 112.2 (q, $^2J_{C,F}$=35.3, C-3), 116.7 (C-6), 123.2 (q, $^1J_{C,F}$=267.0, CF_3), 124.1 (C-9c), 127.1 (C-9b), 141.0 (C-7), 146.0 (q, $^3J_{C,F}$=4.5, C-2), 147.3 (C-9d), 150.6 (C-9a), 160.6 (C=O)

[a] Solvents used for chromatographic separations.
[b] NMR solvent: $CDCl_3$.
[c] Oil.
[d] First purification using AcOEt/PE or Et_2O/PE followed by second purification using CH_2Cl_2.

used as internal standards for ^{1}H, $CDCl_3$ (δ 77.23) for ^{13}C NMR spectra, and $CFCl_3$ (δ 0.0) for ^{19}F NMR spectra. MS data were obtained on Trace MS Thermoquest apparatus (GC-MS) 70 eV in electron impact mode. Elemental analyses were performed with a Perkin–Elmer CHN 2400 apparatus. High Resolution Mass Spectra (HRMS) were performed on Q-TOF Micro micromass positive ESI (CV = 30 V). All reactions were monitored by TLC (Merck F 254 silica gel). All reactions were carried out under dry argon. Products were separated by preparative TLC. Xylene (mixture of isomers) was dried and distilled from sodium/benzophenone and stored over dry molecular sieve 4 Å. Alkynes were commercially available and used after a purification by distillation. Ethyl 4,4,4-trifluoro-2-butynoate **3c** was prepared according to literature.[14] Unsymmetrical azines **1a–c** were prepared according to the general method.[15,16] Diffraction data were collected on a Kuma KM-4 four-circle CCD diffractometer and corrected for Lorentz and polarization effects. The structure was solved by direct methods and refined using SHELXTL.[17] The hydrogen atoms were placed in idealized calculated positions and refined (riding). Crystallographic data for compound **4a** have been deposited with the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK, under No. CCDC 250533.

4.2. General procedure for criss-cross cycloaddition reactions—preparation of compounds 4

An unsymmetrical azine **1a–b** (0.250 mmol) was mixed with alkyne **3a** (0.275 mmol), **3c** (0.300 mmol), or **3b**, **d–g** (0.500 mmol) in dry xylene (10 ml). The mixture was heated under reflux (3.0 h for **1a**, 2.5 h for **1b**, 0.5 h for **1c**), then xylene was removed under vacuum (~1 Torr). All products **4** were purified by preparative TLC (see Table 8).

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Desymmetrization by direct cross-metathesis producing hitherto unreachable P-stereogenic phosphine oxides

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Abstract—Desymmetrization of prochiral di- and trialkenyl phosphine oxides by cross-metathesis with various olefinic partners allowed direct access to novel racemic P-stereogenic products featuring two or three different alkenyl groups. The excellent control of product selectivity and *E*/*Z* selectivity allowed the preparation of desymmetrized products in good yields from readily available precursors. These are the first examples of desymmetrization of prochiral substrates by direct cross-metathesis.

1. Introduction

With the appearance of functional group-compatible transition-metal catalysts over the past decade, olefin metathesis has rapidly become a powerful transformation widely used in organic synthesis.[1] Recently, we have shown that ring closing metathesis (RCM) and cross-metathesis (CM) are effective methods for the construction of various phosphine oxides and borane-stabilized phosphines.[2] As part of our program aimed at developing transition metal-catalyzed transformations for the construction of diverse phosphorus-containing compounds, we herein report how the cross-metathesis reaction can provide a direct entry to structurally diverse P-stereogenic phosphine oxides featuring two or three different alkenyl groups. These compounds could be regarded as valuable building blocks for the preparation of numerous targets upon functional group manipulation of the double bonds. These targets could include mixed phosphine–phosphine oxide ligands that seem to hold special promise for a wide variety of reactions catalyzed by late transition metals.[3] A survey of the literature revealed that, in contrast to α,β-unsaturated monoalkenyl analogues, phosphine oxides possessing two or three different alkenyl groups are virtually unknown, probably due to the lack of general synthetic methodologies for their preparation.[4] Herein we disclose a conceptually novel approach toward the preparation of unsymmetrical racemic P-stereogenic dienes and trienes, a desymmetrization process that relies upon the cross-metathesis coupling of prochiral phosphine oxides with various olefinic partners.

Keywords: Cross-Metathesis; Desymmetrization; Phosphine oxide.
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2. Results and discussion

The desymmetrization of prochiral phosphine oxides by cross-metathesis with an olefinic partner is a complex problem as one needs to control selectivity at different levels. Indeed, the challenge is to achieve high yield of the cross-product with minimal amounts of competing self-metathesis product. In addition, the methodology should favor the formation of the product resulting from a single cross-metathesis reaction, minimizing as much as possible the formation of achiral products resulting from a double cross-metathesis. Finally, *E*/*Z* selectivity is also a critical issue particularly if the newly formed double bond requires further stereoselective manipulation. Therefore, it is not surprising that the possibility to use a cross-metathesis reaction for the desymmetrization of a prochiral diene has hardly been investigated[5] and to the best of our knowledge, trienes have never been desymmetrized using this technology (Eqs. 1 and 2, Fig. 1).

The unprecedented activity of catalyst **1**[6] in the presence of conjugated electron-deficient olefins including α,β-unsaturated phosphine oxides has allowed the formation of products with high CM selectivity and excellent *E*/*Z* selectivity.[2d,7] The high cross-product/dimer ratio is due to the slow rate of dimerization of these substrates with these catalysts. It was therefore anticipated that phenyldivinylphosphine oxide **3** and trivinylphosphine oxide **4** were ideal candidates for desymmetrization (Eqs. 1 and 2, Fig. 1). They were easily prepared by treatment of the commercially available $PhPOCl_2$ or $POCl_3$ with vinylmagnesium bromide in good isolated yields (76 and 70%, respectively). A preliminary study revealed that compounds **3** and **4** are reluctant to homodimerize in the presence of up to 4 mol%

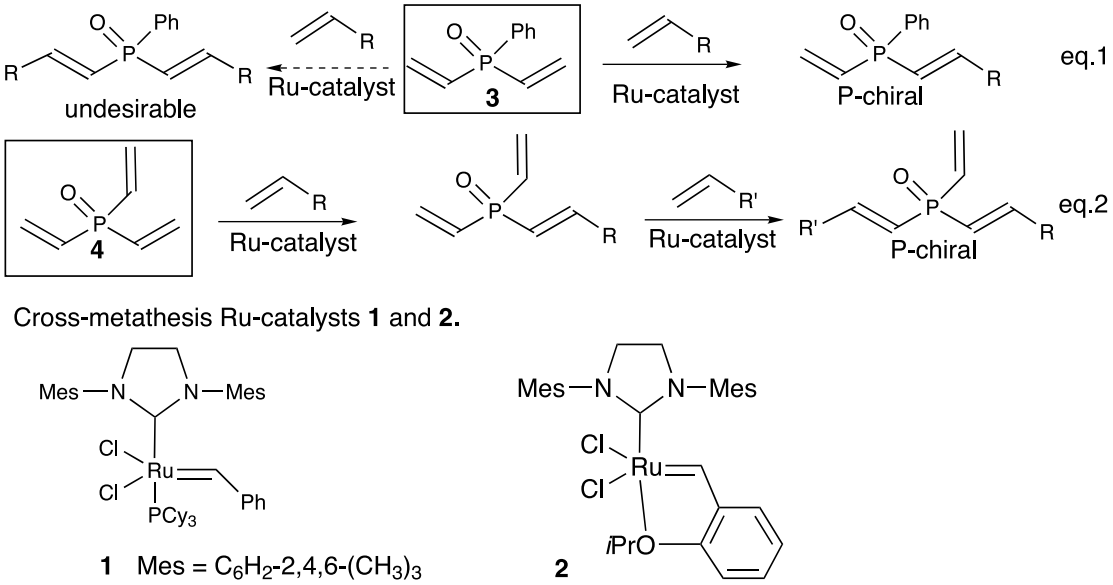


Figure 1. Desymmetrization of P-templates by CM.

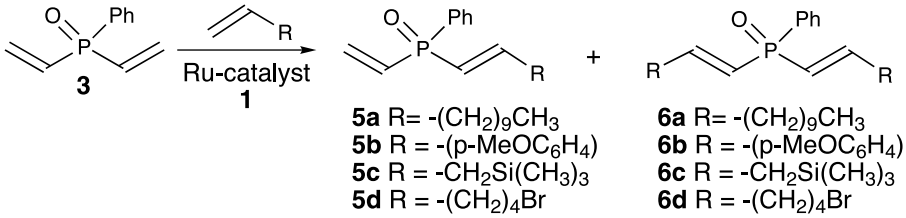
of catalysts **1** or **2**[6] in DCM at reflux (**3** and **4** are therefore type III olefins, according to the classification of Grubbs[8]), auguring high CM selectivity in the presence of olefinic partners of type I or type II.

In the exploration of a variety of reaction conditions to optimize the metathesis of diene **3** with dodecene, a representative type I olefin, we discovered that the best product distribution was obtained using 1 equiv of the olefinic partner (0.3 M) and 3 equiv of the diene in DCM under reflux in the presence of 2 mol% of catalyst **1** (Table 1, entries 1 and 2). Under these conditions, the crude mixture revealed the presence of products **5a** and **6a** in a 4:1 ratio with the exclusive formation of *E*-isomers. No trace of product resulting from a homodimerization process of the diene **3** was detected in the reaction mixture, confirming that the combination of olefinic partners of type I and type III led to selective CM reactions. Clearly, the use of an excess of the diene minimizes the formation of the undesired achiral product **6a**. Under these conditions, the desired desymmetrized P-stereogenic phosphine oxide **5a** was isolated as a pure compound in 79% yield. It should be noted that the excess diene **3** was recovered for recycling after purification.

This positive result led us to examine the cross-metathesis of **3** with various olefinic partners including 4-methoxystyrene, trimethylallylsilane and 6-bromohexene in the presence of 2 mol% of **1** (Table 1, entries 3–5). Particularly, noteworthy are the good yields attained for these reactions reflecting good control of selectivities under these conditions. The stereoselectivity of these transformations in favor of the *E*-isomer is excellent making them synthetically practical. Indeed, no trace of the *Z*-isomer could be detected in the crude reaction mixtures except for product **5d**. For this compound, less than 10% of the minor *Z*-isomer was formed.

Further functionalization of compound **5a** by CM with styrene in the presence of 5 mol% of **1** afforded (*E*,*E*)-**7** in up to 69% isolated yield (Table 2). This reaction is best performed in the presence of 3 equiv of **5a**. The crude mixture of this reaction revealed the formation of several side products identified as compounds **8**, **6a** and **3** in

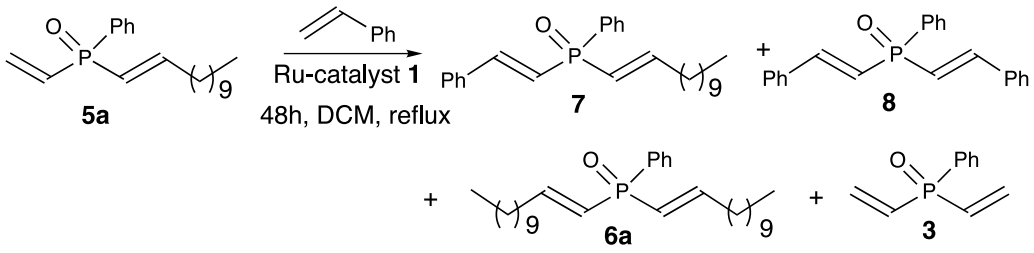
Table 1. Desymmetrization of the prochiral diene **3**



Entry	Conditions	Yield **5** (%)	Yield **6** (%)
1	1 equiv **3**, 1 equiv dodecene, 2 mol% **1**, 24 h	**5a** 47	**6a** 23
2	3 equiv **3**, 1 equiv dodecene, 2 mol% **1**, 24 h	**5a** 79	**6a** 14
3	3 equiv **3**, 4-methoxystyrene, 2 mol% **1**, 24 h	**5b** 68	**6b** —[a]
4	3 equiv **3**, CH_2=$CHCH_2Si(CH_3)_3$, 2 mol% **1**, 24 h	**5c** 72	**6c** —[a]
5	3 equiv **3**, CH_2=$CH(CH_2)_4Br$, 2 mol% **1**, 24 h	**5d** 86	**6d** —[a]

[a] Less than 5% of this product was detected in the crude mixture.

Table 2. Optimization of the CM of **5a** with styrene



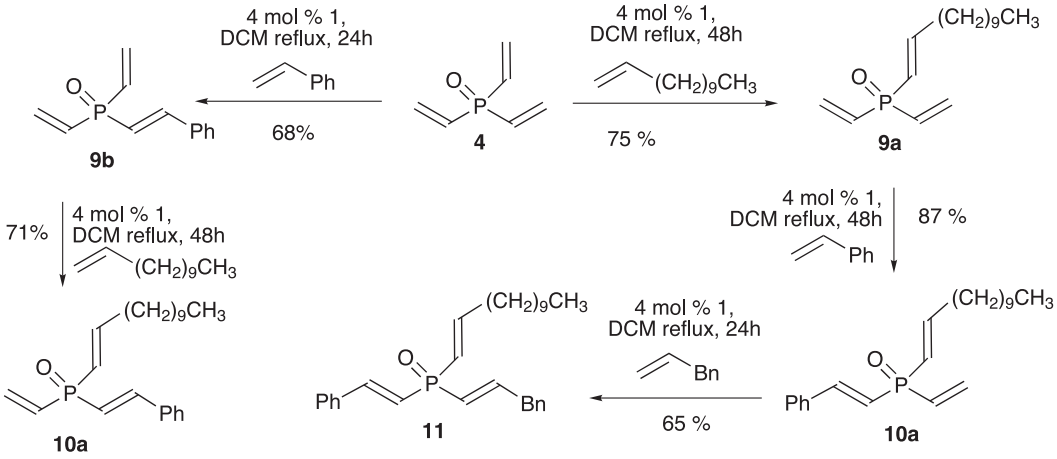
Reaction conditlions	Ratio **5a/7/8/6a/3**	Isolated yield **7** (%)
1 equiv **5a**, 3 equiv styrene	0:4:4:1:0	36
1 equiv **5a**, 1 equiv styrene	0:2:1:1:0	47
2 equiv **5a**, 1 equiv styrene	8:6:1:3:2	59
3 equiv **5a**, 1 equiv styrene	15:8:1:5:4	69

addition to unreacted starting material **5a**. All these side-products could be separated from the desired desymmetrized phosphine oxide **7** by silica gel chromatography. The formation of compound **8** suggests that capping one of the double bond with an alkyl chain was not sufficient to prevent its reaction with styrene upon CM. In this process, the resulting Ru-carbenoid species bearing the alkyl chain can further react to afford minor quantities of **6a**. The presence of these side products demonstrated that alkene group exchange is possible under these conditions.

The possibility to desymmetrize the triene **4** was investigated next. This overall process involves two or three sequential cross-metathesis reactions as illustrated in Scheme 1. Triene **4** (3 equiv) was firstly reacted with dodecene (1 equiv) in the presence of 4 mol % of catalyst **1** to afford 75% of the triene **9a** as a single *E*-isomer. We were pleased to discover that triene **9a** (3 equiv) reacted further in the presence of styrene (1 equiv) and this CM reaction allowed the formation of 87% of compound **10a** and only traces of the undesired product resulting from a double cross-metathesis reaction. In addition, compound **10a** was formed as the sole *E*-isomer. By reversing the order of the two CM reactions, **10a** could be obtained with an overall chemical yield of 48% instead of 65%, suggesting that the order of introduction of the two olefinic partners is important. Finally, the phosphine oxide **11** substituted by three different *E*-alkenyl groups was successfully prepared in 65% by reacting **10a** (3 equiv) with 3-phenylpropene (1 equiv) for 24 h in CH_2Cl_2 at reflux with 4 mol% of catalyst **1**. If this reaction is left stirring for extended reaction time (up to 48 h), only 32% of the desired product could be isolated suggesting that the catalyst mediated alkene group exchanges leading to mixture of products, as previously observed with substrate **5a** (Scheme 1).

3. Conclusion

In conclusion, we have demonstrated that phosphine oxides **3** and **4** could be successfully desymmetrized using CM leading to a series of P-stereogenic phosphine oxides. This unprecedented strategy allows direct access to these compounds that were never prepared before, probably due to the difficulties associated with their syntheses using more traditional synthetic strategies. This novel desymmetrization process on phosphorus templates illustrates how molecular symmetry can be exploited for the construction of P-stereogenic compounds that are not heterocyclic. Current efforts aimed at studying the reactivity of these novel compounds and at developing an enantioselective desymmetrization process for the preparation of nonracemic P-stereogenic targets are underway in our laboratory.



Scheme 1. Desymmetrization of the pro-prochiral triene **4**.

4. Experimental

4.1. General procedures

^{1}H NMR spectra were recorded at 400 and 500 MHz on a Bruker DPX400 and Bruker AMX500 spectrometers, respectively. ^{13}C NMR spectra were recorded on the same spectrometers at 100 and 125 MHz respecively. Proton decoupled ^{31}P NMR spectra were recorded on a Bruker AMX500 spectrometer at 202 MHz. Chemical shifts (δ) are quoted in parts per million (ppm) and are referenced to the residual solvent peak. Multiplicities are reported as broad (br), singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), or as a combination of these. Coupling constants (J) are reported to the nearest 0.1 Hertz (Hz). Infra-red spectra were recorded as thin films using a Perkin–Elmer Paragon 1000FT-IR spectrometer. Absorption peaks are reported in wavenumbers (cm^{-1}). High resolution mass spectra (m/z) were recorded on micro-mass GCT in chemical ionisation (NH_3, CI+) or on a AutoSpec-oaTof instruments (CI+). Melting points (mp) were obtained using standard melting point apparatus and are uncorrected. Flash chromatography was accomplished on silica gel using Merck silica gel C60 (40–60μ). The solvents were dried before use; tetrahydrofuran (THF) by distillation over sodium/benzophenone ketyl; dichloromethane (DCM) over calcium hydride. All other reagents were purified in accordance with the instructions in 'Purification of Laboratory Chemicals', D.D. Perrin and W.L.F. Armarego, Pergamon Press, Third Edition, 1998, or used as obtained from chemical sources.

4.1.1. (Divinyl-phosphinoyl)-benzene 3. A solution of phenylphosphonic dichloride (1 mL, 7.07 mmol) in a mixture of THF (35 mL) and ether (35 mL) was cooled to −70 °C and vinylmagnesium bromide (1 M in THF, 14.1 mL, 14.1 mmol) was then added slowly. The solution was stirred at −70 °C for 3 h then poured into a mixture of HCl 12 M (21 mL) and ice water (140 mL). The mixture was extracted with DCM, dried over $MgSO_4$ and concentrated in vacuo. Purification of this residue by silica gel chromatography (98/02: AcOEt/MeOH) allowed isolation of 960 mg of a white solid (5.39 mmol, yield=76%). ^{1}H NMR (400.2 MHz, $CDCl_3$, ppm): δ 7.62–7.67 (2H, m), 7.38–7.49 (3H, m), 6.46–6.10 (6H, system $(ABC)_2X$). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm): δ 134.2 (s), 131.9 (d, J_P= 2.4 Hz), 131.5 (d, J_P=105.5 Hz), 130.7 (d, J_P=99.1 Hz), 130.7 (d, J_P=9.6 Hz), 128.6 (d, J_P=12.0 Hz). ^{31}P NMR (162.0 MHz, $CDCl_3$, ppm): δ 20.4 (s). IR (film, cm^{-1}): 1180, 1392, 1438, 1603, 3000, 3027, 3056, 3078. Mp=48–49 °C (lit.,[9] mp=50–51 °C). HRMS: (CI+) $C_{10}H_{12}OP$ ($M+H^+$), calcd 179.0626, found 179.0626.

4.1.2. (Divinyl-phosphinoyl)-ethene 4. A solution of phosphorus oxychloride (1 mL, 10.7 mmol) in a mixture of THF (50 mL) and ether (50 mL) was cooled to −70 °C and vinylmagnesium bromide (1 M in THF, 32.2 mL, 32.2 mmol) was added slowly. The solution was stirred at −70 °C for 3 h then poured into a mixture of HCl 12 M (30 mL) and ice water (200 mL). The mixture was extracted with DCM, dried over $MgSO_4$ and concentrated in vacuo. Purification of this residue by silica gel chromatography (98/02: AcOEt/MeOH) allowed isolation of 961 mg of a white solid (7.51 mmol, yield=70%). ^{1}H NMR (400.2 MHz, $CDCl_3$, ppm): δ 6.10–6.34 (9H, system $(ABC)_3X$). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm): δ 134.0 (s), 130.4 (d, J_P= 99.9 Hz). ^{31}P NMR (162.0 MHz, $CDCl_3$, ppm): δ 17.6 Hz. IR (film, cm^{-1}): 1169, 1396, 1601, 2962, 3003, 3031, 3082. Mp=96–98 °C (lit.,[10] mp=99–101 °C). HRMS: (CI+) $C_6H_{10}OP$ ($M+H^+$), calcd 129.0469, found 129.0467.

4.2. General procedure for cross-metathesis between two alkenes a and b using catalyst 1

A solution of alkenes **a** and **b** in DCM was heated to reflux under argon. Catalyst **1** (2 mol%) was then added as a solid every 24 h. The reaction was followed by TLC. The mixture was then concentrated in vacuo and the product purified by silica gel chromatography.

4.2.1. (Dodec-1-enyl-vinyl-phosphinoyl)-benzene 5a. General procedure with **3** (200 mg, 1.12 mmol) and dodecene (83 μL, 0.375 mmol, c=0.3 M) in DCM (1.25 mL) using 2 mol% of catalyst **1** (6.3 mg, 7.49 μmol) for 24 h. Purification of the residue by silica gel chromatography (98/01/01: chloroform/AcOEt/MeOH) allowed isolation of 94.5 mg of **5a** as a colourless oil (0.297 mmol, yield=79%), and 12.2 mg of (di-dodec-1-enyl-phosphinoyl)-benzene **6a** as a colourless oil (0.027 mmol, yield=14%). **5a**: ^{1}H NMR (400.1 MHz, $CDCl_3$, ppm): δ 7.64–7.70 (2H, m), 7.39–7.48 (3H, m), 6.67 (1H, ddt, ^3J= 6.7, 17.1 Hz, J_P=19.5 Hz), 6.07–6.47 (3H, system ABCX), 5.97 (1H, ddt, ^4J=1.5 Hz, ^3J=17.1 Hz, J_P=24.2 Hz), 2.19–2.25 (2H, m), 1.38–1.45 (2H, m), 1.15–1.30 (14H, m), 0.83 (3H, t, ^3J=6.8 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm): δ 152.3 (d, J_P=2.0 Hz), 133.2 (s), 132.6 (d, J_P= 105.4 Hz), 131.7 (d, J_P=98.9 Hz), 131.6 (d, J_P=2.7 Hz), 130.6 (d, J_P=9.8 Hz), 128.5 (d, J_P=12.0 Hz), 121.3 (d, J_P=104.1 Hz), 34.4 (d, J_P=16.9 Hz), 31.8 (s), 29.5 (s), 29.4 (s), 29.3 (s), 29.2 (s), 29.0 (s), 27.8 (d, J_P=1.2 Hz), 22.6 (s), 14.0 (s). ^{31}P NMR (202.4 MHz, $CDCl_3$, ppm): 21.2 (s). IR (film, cm^{-1}): 1185, 1437, 1465, 1630, 2854, 2925. HRMS: (CI+) $C_{20}H_{32}OP$ ($M+H^+$), calcd 319.2191, found 319.2190. **6a**: ^{1}H NMR (400.2 MHz, $CDCl_3$, ppm): δ 7.67–7.72 (2H, m), 7.43–7.52 (3H, m), 6.67 (2H, ddt, ^3J=6.6, 16.9 Hz, J_P=19.7 Hz), 5.98 (2H, ddt, ^4J=1.5 Hz, ^3J= 16.9 Hz, J_P=24.0 Hz), 2.27–2.22 (2H, m), 1.49–1.42 (2H, m), 1.20–1.35 (2H,m), 0.88 (6H, t, ^3J=6.9 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm): δ 151.6 (d, J_P=2.4 Hz), 133.6 (d, J_P=104.7 Hz), 131.4 (d, J_P=2.4 Hz), 130.7 (d, J_P= 9.6 Hz), 128.4 (d, J_P=12.0 Hz), 122.2 (d, J_P=103.9 Hz), 34.4 (d, J_P=16.8 Hz), 31,9 (s), 29.6 (s), 29,5 (s), 29.4 (s), 29.3 (s), 29.1 (s), 27.9 (d, J_P=1.2 Hz), 22.7 (s), 14.1 (s). ^{31}P NMR (162.0 MHz, $CDCl_3$, ppm): 20.0 (s). IR (film, cm^{-1}): 1176, 1442, 1470, 1635, 2849, 2913. HRMS: (CI+) $C_{30}H_{52}OP$ ($M+H^+$), Calcd. 459.3756, found 459.3757.

4.2.2. 1-Methoxy-4-[2-(phenyl-vinyl-phosphinoyl)-vinyl]-benzene 5b. General procedure with **3** (200 mg, 1.12 mmol), and *p*-methoxystyrene (50 μL, 0.375 mmol, c=0.3 M) in DCM (1.25 mL) using 2 mol% catalyst **1** (6.3 mg, 7.49 μmol) for 24 h. Purification of the residue by silica gel chromatography (98/02: AcOEt/MeOH) allowed isolation of 72.0 mg of **5b** as a yellow oil (0.254 mmol, yield=68%). **5b**: ^{1}H NMR (400.1 MHz, $CDCl_3$, ppm): δ 7.72–7.78 (2, m), 7.34–7.52 (6H, m), 6.87 (2H, d, ^3J= 8.5 Hz), 6.14–6.58 (4H, m) which could be described as

6.14–6.58 (3H, system ABCX) overlapping with 6.44 (1H, dd, $^3J=17.4$ Hz, $J_P=22.2$ Hz), 3.79 (3H, s). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm): 161.1 (s), 146.6 (d, $J_P=4.0$ Hz), 133.6, (s), 132.7 (d, $J_P=105.8$ Hz), 131.7 (d, $J_P=2.7$ Hz), 131.7 (d, $J_P=99.7$ Hz), 130.7 (d, $J_P=9.9$ Hz), 129.2 (d, $J_P=1.0$ Hz), 128.6 (d, $J_P=12.1$ Hz), 127.9 (d, $J_P=18.4$ Hz), 115.8 (d, $J_P=107.1$ Hz), 114.2 (s), 55.3 (s). ^{31}P NMR (162.0 MHz, $CDCl_3$, ppm): 22.5 (s). IR (film, cm^{-1}): 1174, 1398, 1421, 1438, 1464, 1604, 2838, 2960. HRMS: (CI+) $C_{17}H_{18}O_2P$ ($M+H^+$), calcd 285.1044, found 285.1043.

4.2.3. Trimethyl-[3-(phenyl-vinyl-phosphinoyl)-allyl]-silane 5c. General procedure using **3** (200 mg, 1.12 mmol) and allyltrimethylsilane (59 μL, 0.375 mmol, $c=0.3$ M) in DCM (1.25 mL) with 2 mol% of catalyst **1** (6.3 mg, 7.49 μmol) for 24 h. Purification of the residue by silica gel chromatography (98/01/01: chloroform/AcOEt/MeOH) allowed isolation of 71.0 mg of **5c** as a colourless oil (0.269 mmol, yield 72%). **5c** ^1H NMR (400.1 MHz, $CDCl_3$, ppm): δ 7.66–7.72 (2H, m), 7.40–7.51 (3H,m), 6.69 (1H, ddt, $^3J=8.5$, 16.9 Hz, $J_P=19.3$ Hz), 6.49–6.08 (3H, system ABCX), 5.78 (1H, ddt, $^4J=1.2$ Hz, $^3J=16.9$ Hz, $J_P=24.4$ Hz), 1.80–1.82 (2H, m), 0.03 (9H, s). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm): δ 150.3 (d, $J_P=2.4$ Hz), 133.1 (d, $J_P=105.5$ Hz), 132.9 (s), 132.2 (d, $J_P=99.0$ Hz), 131.5 (d, $J_P=2.4$ Hz), 130.7 (d, $J_P=9.7$ Hz), 128.4 (d, $J_P=11.4$ Hz), 118.7 (d, $J_P=107.1$ Hz), 27.4 (d, $J_P=16.2$ Hz), −1.9 (s). ^{31}P NMR (202.4 MHz, $CDCl_3$, ppm): 21.3 (s). IR (film, cm^{-1}): 1170, 1393, 1438, 1637, 2853, 2925, 3058.

4.2.4. [(6-Bromo-hex-1-enyl)-vinyl-phosphinoyl]-benzene 5d. General procedure with **3** (200 mg, 1.12 mmol) and bromohexene (50 μL, 0.375 mmol, c = 0.3 M) in DCM (1.25 mL) using 2 mol% of catalyst **1** (6.3 mg, 7.49 μmol) for 24 h. Purification of the residue by silica gel chromatography (98/02: AcOEt/MeOH) allowed isolation of 101.0 mg of **5d** as a brown oil (0.323 mmol, yield = 86%). **5d**: ^1H NMR (400.1 MHz, $CDCl_3$, ppm): δ 7.64–7.69 (2H, m), 7.41–7.50 (3H, m), 6.67 (1H, ddt, $^3J=6.5$, 17.1 Hz, $J_P=19.5$ Hz), 6.10–6.48 (3H, system ABCX), 6.02 (1H, ddt, $^2J=1.4$ Hz, $^3J=17.1$ Hz, $J_P=24.2$ Hz), 3.36 (2H, t, $^3J=6.7$ Hz), 2.24–2.30 (2H, m), 1.81–1.88 (2H–m), 1.56–1.64 (2H, m). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm): δ 153.7 (d, $J_P=1.7$ Hz), 136.3 (s), 135.1 (d, $J_P=105.5$ Hz), 134.4 (d, $J_P=2.4$ Hz), 134.3 (d, $J_P=99.0$ Hz), 133.4 (d, $J_P=9.7$ Hz), 131.3 (d, $J_P=12.2$ Hz), 124.9 (d, $J_P=103.1$ Hz), 36.1 (d, $J_P=17.0$ Hz), 35.9 (s), 34.7 (s), 29.1 (s). ^{31}P NMR (202.4 MHz, $CDCl_3$, ppm): 20.9 (s). IR (film, cm^{-1}): 1173, 1397, 1437, 1623, 2860, 2933. HRMS: (CI+) $C_{14}H_{19}OPBr$ ($M+H^+$), calcd 313.0357, found 313.0360.

4.2.5. [(2-Phenyl-vinyl)-dodec-1-enyl-phosphinoyl]-benzene 7. General procedure with **5a** (154.2 mg, 0.485 mmol) and styrene (18 μL, 0.162 mmol, $c=0.3$ M) in DCM (0.5 mL) using 5 mol% of catalyst **1** (6.8 mg, 8.08 μmol) for 48 h. Purification of the residue by silica gel chromatography (90/10: chloroform/AcOEt) allowed isolation of 44.0 mg of **7** as a colourless oil (0.112 mmol, yield = 69%), as well as 28.4 mg of **6a**, 5.0 mg of [bis-(2-phenyl-vinyl)-phosphinoyl]-benzene **8**, 63.7 mg of **5a** and 10.0 mg of **3**. **7** ^1H NMR (400.2 MHz, $CDCl_3$, ppm): δ 7.74–7.79 (2H, m), 7.35–7.52 (9H, m), 6.76 (1H, ddt, $^3J=6.6$, 16.9 Hz, $J_P=19.7$ Hz), 6.61 (1H, dd, $^3J=17.4$ Hz, $J_P=22.0$ Hz), 6.09 (1H, dd, $^3J=17.1$ Hz, $J_P=24.4$ Hz), 2.26–2.31 (2H, m), 1.44–1.51 (2H, m), 1.24–1.35 (14H, m), 0.87 (3H, t, $^3J=6.8$ Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm): δ 152.3 (d, $J_P=2.0$ Hz), 146.4 (d, $J_P=3.8$ Hz), 135.2 (d, $J_P=17.8$ Hz), 133.3 (d, $J_P=106.6$ Hz), 131.6 (d, $J_P=2.7$ Hz), 130.7 (d, $J_P=9.8$ Hz), 129.9 (s), 128.8 (s), 128.6 (d, $J_P=12.0$ Hz), 127.6 (d, $J_P=0.8$ Hz), 121.8 (d, $J_P=105.2$ Hz), 119.8 (d, $J_P=105.1$ Hz), 34.5 (d, $J_P=17.0$ Hz), 31.9 (s), 29.6 (s), 29.5 (s), 29.4 (s), 29.3 (s), 29.1 (s), 27.9 (d, $J_P=1.1$ Hz), 22.7 (s), 14.1 (s). ^{31}P NMR (162.0 MHz, $CDCl_3$, ppm): 20.9 (s). IR (film, cm^{-1}): 1179, 1437, 1612, 2854, 2926. HRMS: (CI+) $C_{26}H_{36}OP$ ($M+H^+$), calcd 395. 2504, found 395.2513. **8**: ^1H NMR (400.2 MHz, $CDCl_3$, ppm): δ 7.27–7.86 (17H, m), 6.72 (2H, dd, $^3J=17.4$ Hz, $J_P=22.2$ Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm): δ 146.9 (d, $J_P=3.7$ Hz), 135.2 (d, $J_P=18.0$ Hz), 133.1 (d, $J_P=107.7$ Hz), 131.9 (d, $J_P=2.6$ Hz), 130.8 (d, $J_P=10.0$ Hz), 130.1 (s), 128.9 (s), 128.8 (d, $J_P=12.1$ Hz), 127.7 (s), 119.4 (d, $J_P=106.2$ Hz). ^{31}P NMR (162.0 MHz, $CDCl_3$, ppm): 21.7 (s). IR (film, cm^{-1}): 1169, 1216, 1438, 1493, 1574, 1608, 2993. HRMS: (CI+) $C_{22}H_{20}OP$ ($M+H^+$), calcd 331.1252, found 331.1256.

4.2.6. 1-(Divinyl-phosphinoyl)-dodec-1-ene 9a. General procedure with **4** (200 mg, 1.56 mmol) and dodecene (116 μL, 0.521 mmol, $c=0.3$ M) in DCM (1.74 mL) using 5 mol% of catalyst **1** (22.1 mg, 26.0 μmol) for 48 h. Purification of the residue by silica gel chromatography (90/10: chloroform/AcOEt) allowed isolation of 105.0 mg of **9a** as a colourless oil (0.392 mmol, yield = 75%). **9a**: ^1H NMR (400.2 MHz, $CDCl_3$, ppm): δ 6.69 (1H, ddt, $^3J=6.6$, 17.2 Hz, $J_P=20.0$ Hz), 6.08–6.35 (6H, system $(ABC)_2X$), 5.83 (1H, ddt, $^4J=1.5$ Hz, $^3J=17.2$ Hz, $J_P=24.5$ Hz), 2.21–2.27 (2H, m), 1.41–1.49 (2H, m), 1.20–1.35 (14H, m), 0.9 (3H, t, $^3J=6.8$ Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm): δ 152.2 (d, $J_P=1.9$ Hz), 133.2 (s), 131.2 (d, $J_P=99.8$ Hz), 120.7 (d, $J_P=105.2$ Hz), 34.5 (d, $J_P=16.8$ Hz), 31.9 (s), 29.6 (s), 29.5 (s), 29.4 (s), 29.3 (s), 29.1 (s), 27.8 (d, $J_P=1.2$ Hz), 22.7 (s), 14.1 (s). ^{31}P NMR (162.0 MHz, $CDCl_3$, ppm): 17.6 (s). IR (film, cm^{-1}): 1173, 1392, 1466, 1603, 1638, 2851, 2922. HRMS: (CI+) $C_{16}H_{30}OP$ ($M+H^+$), calcd 269.2034, found 269.2029.

4.2.7. [2-(Divinyl-phosphinoyl)-vinyl]-benzene 9b. General procedure starting from **4** (160 mg, 0.125 mmol) and styrene (48 μL, 0.417 mmol, $c=0.3$ M) in DCM (1.4 mL) using 5 mol% catalyst **1** (17.6 mg, 20.8 μmol) for 24 h. Purification of the residue by silica gel chromatography (98/02: AcOEt/MeOH) allowed isolation of 57.6 mg of **9b** as a colourless oil (0.282 mmol, yield = 68%). **9b**: ^1H NMR (400.2 MHz, $CDCl_3$, ppm): δ 7.35–7.50 (6H, m), 6.12–6.49 (7H, m which could be analysed as 6.44 (1H, dd, $^3J=17.4$ Hz, $J_P=22.2$ Hz) overlapping with 6.12–6.42 (6H, system $(ABC)_2X$). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm): δ 147,0 (d, $J_P=3.2$ Hz), 135.0 (d, $J_P=18.4$ Hz), 133.7 (s), 130.9 (d, $J_P=100.7$ Hz), 130.1 (s), 128.8 (s), 127.6 (s), 118.2 (d, $J_P=106.3$ Hz). ^{31}P NMR (162.0 MHz, $CDCl_3$, ppm): 18.5 (s). IR (film, cm^{-1}): 1171, 1393, 1449, 1495, 1604, 2853, 2924, 3000, 3026. HRMS: (CI+) $C_{12}H_{14}OP$ ($M+H^+$), calcd 205.0782, found 205.0787.

4.2.8. [2-(Dodec-1-enyl-vinyl-phosphinoyl)-vinyl]-benzene 10a. General procedure starting from **9b** (45.0 mg, 0.221 mmol) and dodecene (16 μL, 0.074 mmol, $c=0.3$ M)

in DCM (0.25 mL) using 5 mol% of catalyst **1** (3.1 mg, 3.68 μmol) for 48 h. Purification of the residue by silica gel chromatography (98/02: AcOEt/MeOH) allowed isolation of 18.0 mg of **10a** as a colourless oil (0.052 mmol, yield = 71%). **10a**: ^{1}H NMR (400.2 MHz, $CDCl_3$, ppm): δ 7.31–7.49 (6H, m), 6.70 (1H, ddt, ^{3}J = 6.6, 17.1 Hz, J_P = 20.0 Hz), 6.50–6.07 (4H, m which could be analysed as 6.43 (1H, ^{3}J = 17.4 Hz, J_P = 22.0 Hz) overlapping with 6.41–6.07 (3H, system ABCX)), 5.89 (1H, ddt, ^{4}J = 1.5 Hz, ^{3}J = 17.1 Hz, J_P = 24.4 Hz), 2.21–2.27 (2H, m), 1.41–1.48 (2H, m), 1.18–1.35 (14H, m), 0.86 (3H, t, ^{3}J = 6.8 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm): δ 151.9 (d, J_P = 2.4 Hz), 146.2 (d, J_P = 4.0 Hz), 135.2 (d, J_P = 17.6 Hz), 132.9 (s), 131.7 (d, J_P = 100.7 Hz), 129.9 (s), 128.8 (s), 127.5 (s), 121.3 (d, J_P = 105.5 Hz), 119.2 (d, J_P = 105.5 Hz), 34.5 (d, J_P = 16.8 Hz), 31.8 (s), 29.6 (s), 29.5 (s), 29.4 (s), 29.3 (s), 29.1 (s), 27.8 (d, J_P = 1.6 Hz), 22.6 (s), 14.1 (s). ^{31}P NMR (162.0 MHz, $CDCl_3$, ppm): 18.3 (s). IR (film, cm^{-1}): 1174, 1449, 1465, 1625, 2854, 2925. HRMS: (CI+) $C_{22}H_{34}OP$ ($M+H^+$), calcd 345.2347, found 345.2351. **10a** was also synthesized using the general procedure starting from **9a** (118 mg, 0.440 mmol) and styrene (17 μL, 0.147 mmol, c = 0.3 M) in DCM (0.5 mL) using 5 mol% catalyst **1** (6.2 mg, 7.34 μmol) for 48 h. Purification of the residue by silica gel chromatography (98/02: AcOEt/MeOH) allowed isolation of 44.0 mg of **10a** as a colourless oil (0.128 mmol, yield = 87%).

4.2.9. {2-[(3-Phenyl-propenyl)-dodec-1-enyl-phosphinoyl]-vinyl}-benzene 11. General procedure starting from **10a** (56.5 mg, 0.164 mmol) and 3-phenylpropene (7 μL, 0.055 mmol, c = 0.3 M) in DCM (0.2 mL) using 5 mol% catalyst **1** (2.3 mg, 2.74 μmol) for 24 h. Purification of the residue by silica gel chromatography (90/10: chloroform/AcOEt) allowed isolation of 15.5 mg of **11** as a colourless oil (0.036 mmol, yield = 65%). **11**: ^{1}H NMR (500.0 MHz, $CDCl_3$, ppm): δ 7.22–7.54 (11H, m), 6.87 (1H, ddt, ^{3}J = 6.2, 17.0 Hz, J_P = 19.2 Hz), 6.72 (1H, ddt, ^{3}J = 6.5, 17.1 Hz, J_P = 19.8 Hz), 6.47 (1H, dd, ^{3}J = 17.5 Hz, J_P = 21.8 Hz), 5,89–5.97 (2H, m), 3.63 (2H, d, ^{3}J = 6.2 Hz), 2.27–2.31 (2H, m), 1.47–1.53 (2H, m), 1;29–1.38 (14H, m), 0.93 (3H, t; ^{3}J = 7.0 Hz). ^{13}C NMR (125.7 MHz, $CDCl_3$, ppm): δ 151.4 (s), 148.9 (s), 145.8 (s), 137.5 (s), 135.2 (d, J_P = 18.9 Hz), 129.7 (s), 128.8 (s), 128.7 (s), 128.5 (s), 127.5 (s), 126.5 (s), 123.7 (d, J_P = 105.6 Hz), 121.7 (d, J_P = 106.9 Hz), 119.7 (d, J_P = 110.6 Hz), 40.5 (d, J_P = 17.6 Hz), 34.4 (d, J_P = 16.3 Hz), 31.7 (s), 29.4 (s), 29.3 (s), 29.2 (s), 29.0 (s), 27.8 (s), 22.5 (s), 14.0 (s). ^{31}P NMR (202.4 MHz, $CDCl_3$, ppm): 19.1 (s). IR (film, cm^{-1}): 1170, 1452, 1495, 1576, 1624, 2855, 2926. HRMS: (CI+) $C_{29}H_{40}OP$ ($M+H^+$), calcd 435.2817, found 435.2824.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2005.01.019

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A new approach for the synthesis of 2-substituted indole derivatives via Michael type adducts

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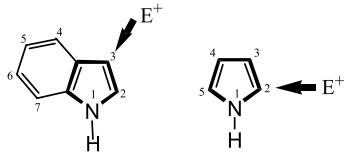
Abstract—4,7-Dihydroindole undergoes regioselective alkylation at the 2-position of the indole nucleus through conjugate addition with α,β-unsaturated carbonyl compounds. The oxidation of the Michael adducts affords the corresponding 2-substituted indole derivatives which were characterized by spectroscopic methods.

1. Introduction

The chemistry of indole is one of the most active areas of heterocyclic chemistry. The indole moiety remains at the forefront of biological and medicinal chemistry. The most ubiquitous of the bioactive alkaloids known are based on the indole nucleus.[1] Since the 3-position of indole is the preferred site for electrophilic substitution reaction, 3-alkyl or acyl indoles are versatile intermediates for the synthesis of a wide range of indole derivatives.[2] The simple and direct method for the synthesis of 3-alkylated indoles involve the conjugate addition of indoles to α,β-unsaturated compounds. 2-Substituted indoles are also potential intermediates for many alkaloids and pharmacologically important substances.[3] While the methods for the preparation of 3-substituted indoles are well established, there is a need for yet easier access to 2-substituted indoles. Generally restricted methods have been reported for the preparation of 2-substituted indoles. α-Lithioindoles have been used to prepare 2-haloindoles and to introduce a variety of substituents by the reaction with appropriate electrophiles such as aldehydes, ketones and chloformates.[4] Another method for the synthesis of 2-substituted indoles involves α-palladation at moderate temperature if C-3 is occupied. The metallated products are allowed to react with acrylates, other alkenes (Heck reaction) or carbon monoxide in situ.[5] Additionally, 2-methylindoles have been elaborated into many 2-substituted indole derivatives using an allylic bromination reaction.[6] However, most of these methods involve protection of the indole 3-position with an ester or benzoyl group and masking the indole nitrogen as a phenyl sulfonyl or acyl.



1 **2**

Indole (**1**) undergoes electrophilic substitution preferentially at β(C3)-position whereas pyrrole (**2**) gives reaction at α(C2)-position.[7] The positional selectivity in these five-membered systems is well explained by the stability of the Wheland intermediates for electrophilic substitution. The intermediate cations from β- for indole (**1**) and α- for pyrrole (**2**) are the more stabilized. Michael reactions are one of the most important carbon–carbon bond-forming reactions in organic synthesis.[8,9] We would like to disclose herein our approach for synthesis of 2-substituted indole derivatives with Michael type adducts. Our synthetic strategy is based on a dipole change by transforming the indole ring into a pyrrole derivative.

2. Results and discussion

Firstly, we carried out Birch reduction reaction of indole with Li in liquid ammonia, which is a very powerful reducing system, and which reduces the benzene ring but not the pyrrole ring to form 4,7-dihydroindole (**3**) and 4,5,6,7-tetrahydroindole (**4**) (Scheme 1).[10] We obtained a mixture consisting of **3** and **4** in a 4:1 ratio, which could be best separated by recrystallization, respectively. Since the

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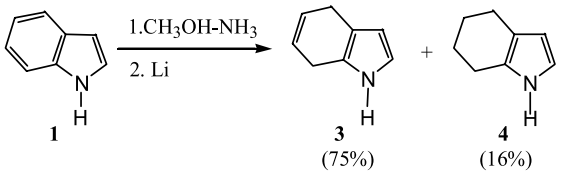


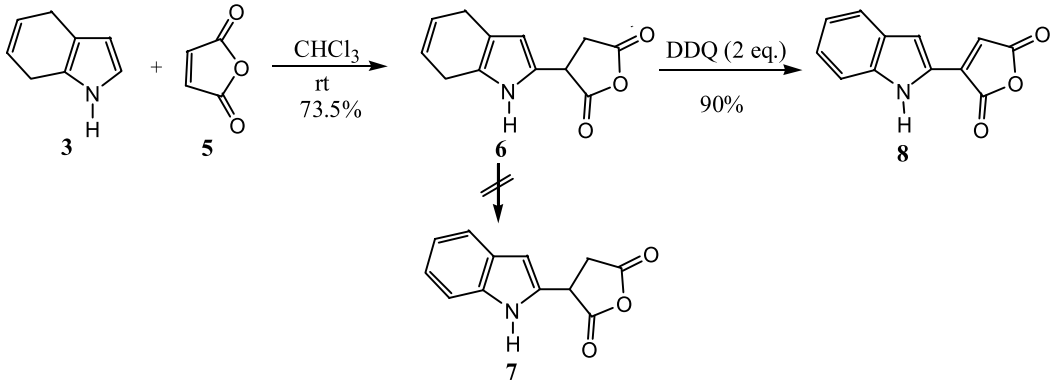
Scheme 1.

reduction products are now pyrrole derivatives, we investigated the Michael reaction of 4,7-dihydroindole (**3**) with α,β-unsaturated carbonyl compounds (Table 1). The reaction of **3** with maleic anhydride (**5**) in $CHCl_3$ gave 3-(4,7-dihydro-1*H*-indol-2-yl)-dihydro-furan-2,5-dione (**6**) in a 73.5% (Scheme 2). For the next step, we attempted the aromatization of the cyclohexadiene ring in **6** to obtain the indole derivative **7**. Whereas, the oxidation of **6** with 1 equiv of 1,2-dicyano-4,5-dichloroquinone (DDQ) gave a complex reaction mixture, the indole derivative **8** was obtained by reaction of **6** with 2 equiv of DDQ in a 90%. Similarly, various α,β-unsaturated carbonyl compounds such as diethyl azodicarboxylate (**9**), 1,3-diphenyl-propenone (**10**),[11] 2-cyclohexenone (**11**)[11] and 2-cyclopentenone (**12**)[11] were reacted with 4,7-dihydroindole (**3**) in order to

Table 1. Michael addition of 4,7-dihydroindole (**3**) with some α,β-unsaturated compounds

Entry	Nucleophile	Electrophile	Catalyst	Oxidant	Product	Yield (%)[a]
1	**3**	**5**	–		**8**	90
2[b]	**3**	**9**	$Bi(NO_3)_3$		**13**	45
3	**3**	**10**	$Bi(NO_3)_3$		**15**	30
4	**3**	**11**	$Bi(NO_3)_3$		**16**	49
5	**3**	**12**	$Bi(NO_3)_3$		**17**	45

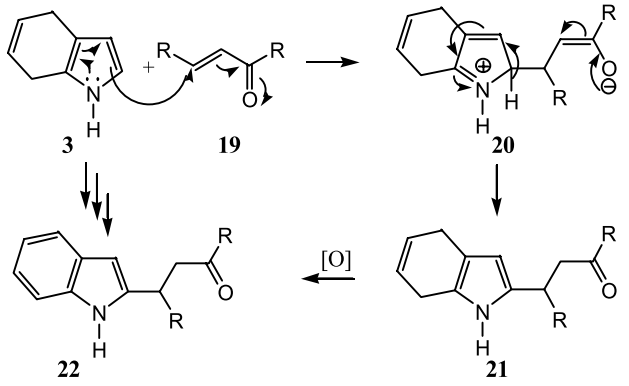
[a] Isolated yield.
[b] $EtO_2C–NH–NH–CO_2Et$ (**14**)[12] forms at entry 2.



Scheme 2.

synthesize the corresponding indole derivatives. The Michael acceptors **9**–**12** failed to react with dihydroindole **3** under the present reaction conditions. Compound **3** was treated with 1 mol of diethyl azodicarboxylate (**9**) in the presence of a catalytic amount of $Bi(NO_3)_3$[9] as mild reagent in CH_2Cl_2 to give a mixture of the corresponding Michael adduct, indole derivative **13**, reduction product **14**[12] of diethyl azodicarboxylate (**9**) and the unreacted **3**. Therefore, the dihydroindole **3** reacted with 2 equiv of diethyl azodicarboxylate (**9**) in the presence of $Bi(NO_3)_3$ to furnish **13** and **14** in moderate yield. While 1 equiv of the diethyl azodicarboxylate (**9**) is used as the Michael acceptor, the rest serves as oxidation reagent. Next, the indole derivatives **15**–**17** were synthesized from the reaction of **3** with the enones **10**–**12** in the presence of $Bi(NO_3)_3$ followed by the oxidation of these formed Michael adducts with *p*-benzoquinone (**18**) as the oxidation agent.

The structures of the products were determined by ^1H NMR, ^{13}C NMR, IR and elemental analysis. The Michael addition product **6** was characterized by the presence of NH signals at δ 8.38 ppm, olefinic protons and C3-H in pyrrole ring at 5.88–5.32 ppm (3H), allylic proton at 4.39 ppm (dd, $J=9.4$, 7.7 Hz). Furthermore CH_2 protons in the anhydride ring gave rise to a resolved the AB system. While the A part (low field) of the AB system showed at 3.43 ppm (dd, $J=18.7$, 9.4 Hz), the B part of the system and the CH_2 protons in the cyclohexadiene ring coincided at 3.33–3.15 ppm. Notably, NOE experiments for C3-H in all indole derivatives (**8**, **13**, **15**, **16**, **17**) showed that a NOE between the aromatic C4-H and C3-H in the five-membered ring but not observed NOE between the C3-H and the NH protons. Thus, the reaction of the dihydroindole **3** with the Michael acceptors results in 2-substitution of the indole nucleus. This observed regioselectivity shows that the attack of the dihydroindole **3** to the unsaturated compound occurs at the C-2 position. The reaction of the dihydroindole **3** with the α,β-unsaturated compounds probably proceeds through an intermediate **20** as depicted in Scheme 3. In the last step, the oxidation of the Michael addition products gives the corresponding indole derivatives.



Scheme 3.

In summary, we have developed an efficient strategy to access 2-substituted indole derivatives starting from indole. Further applications of this chemistry are currently in progress.

3. Experimental

3.1. General methods

Solvents were concentrated at reduced pressure. Melting points were determined on Buchi 539 capillary melting apparatus and uncorrected. Infrared spectra were obtained from KBr pellets or film on a Mattson 1000 FT-IR spectrophotometer. ^1H NMR and ^{13}C NMR spectra were recorded on 200 (50) and 400 (100)-MHz Varian spectrometer and are reported in δ units with $SiMe_4$ as internal standard. Elemental analyses were carried out on a Carlo Erba 1108 model CHNS-O analyser.

3.1.1. Birch reduction reaction of the indole (1). Liquid ammonia (500 mL) was distilled under N_2 into a predried, three-necked flask. Then, the solution of the indole (**1**) (25 g, 0.21 mol) in dry methanole (128 g, 4 mol) was added, and the resulting solution was cooled to -35 ± 5 °C and stirred as mechanical. The resulting solution was treated with Lithium metal (6 g, 0.84 mol) added in small pieces for 5–10 min, which reacted very rapidly. The resulting deep blue solution was stirred at the same temperature for 60 min and then the resulting mixture was allowed to warm to rt. After the excess ammonia had evaporated, Et_2O (200 mL), NH_4Cl (5 g) and H_2O (300 mL) were carefully added to the reaction mixture. The layers were separated, the aqueous layer was extracted with Et_2O (2×200 mL), and the combined organic layers were washed with $NaHCO_3$ ($2\times$ 100 mL), dried ($MgSO_4$), filtered, and concentrated. The ^1H NMR of the residue showed that the formation of **3** and **4** in a 4:1 ratio. The residue (23 g) was recrystallized with CH_2Cl_2/hexane to give the dihydroindole **3** (19 g, 75%) as a colourless crystals, mp: 35–36 °C (lit.[10] mp 37–39 °C). Further the recrystalliztion of the residue furnished the tetrahydroindole **4** (4.10 g, 16%) as a pale yellow crystals from hexane; mp 53–54 °C (lit.[10] mp 54–55 °C); For 4,7-dihydro-1*H*-indole (**3**): ^1H NMR (200 MHz, $CDCl_3$): δ 7.70 (m, NH, 1H), 6.72 (t, $J=2.5$ Hz, A part of AB system, =CH, H-2, 1H), 6.07 (t, $J=2.5$ Hz, B part of AB system, =CH, H-3, 1H), 5.95 (bd, $J=10.1$ Hz, A part of AB system, =CH, H-5 or H-6, 1H), 5.87 (bd, $J=10.1$ Hz, B part of AB system, =CH, H-5 or H-6, 1H), 3.30 (bs, H-4 and H-7, CH_2, 4H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 128.00, 127.93, 125.98, 118.28, 115.88, 108.77, 27.01, 26.02; IR (CH_2Cl_2, cm^{-1}): 3364, 3018, 2856, 2825, 1651, 1555, 1362, 1324, 1208, 1150, 1085, 958. For 4,5,6,7-tetrahydro-1*H*-indole (**4**): ^1H NMR (200 MHz, $CDCl_3$): δ 7.72 (m, NH, 1H), 6.66 (t, $J=2.6$ Hz, A part of AB system, =CH, H-2, 1H), 6.03 (t, $J=2.6$ Hz, B part of AB system, =CH, H-3, 1H), 2.64–2.55 (m, CH_2, 4H), 1.93–1.73 (m, CH_2, 4H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 128.97, 118.90, 117.73, 109.44, 26.02, 25.61, 25.04, 24.88; IR (CH_2Cl_2, cm^{-1}): 3370, 3093, 2923, 2846, 1673, 1596, 1542, 1442, 1311, 1203, 1133, 1079, 1056, 910, 833.

3.1.2. 3-(4,7-Dihydro-1*H*-indol-2-yl)-dihydro-furan-2,5-dione (6). A solution of 4,7-dihydroindole (**3**) (300 mg, 2.50 mmol) and freshly sublimed maleic anhydride (247 mg, 2.50 mmol) in 20 mL $CHCl_3$ was stirred at room temperature for 2 days. After removal of the solvent, the residue was filtered on a short silica gel column (5 g) eluting with $CHCl_3$ (200 mL) to give 400 mg (73.5%) of the title

compound **6**. The crystallization of the residue from $CHCl_3$/hexane gave dark yellow powder; mp 145–146 °C: ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.38 (m, NH, 1H), 5.88–5.82 (m, =CH, pyrrole and cyclohexadiene ring, 3H), 4.39 (dd, J= 9.4, 7.7 Hz, CH, 1H), 3.43 (dd, J=18.7, 9.4 Hz, A part of AB system, CH_2, 1H), 3.33–3.15 (m, CH_2, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 173.51, 170.95, 128.11, 127.55, 124.56, 123.23, 116.57, 107.16, 41.78, 36.29, 26.65, 25.81; IR (CH_2Cl_2, cm^{-1}): 3401, 3031, 2861, 2831, 1859, 1774, 1604, 1411, 1272, 1234, 1149, 1072, 1002. Anal. calcd for $C_{12}H_{11}NO_3$: C, 66.35; H, 5.10; N, 6.45. Found: C, 67.03; H, 5.04; N, 6.39.

3.1.3. 3-(1*H*-Indol-2-yl)-furan-2,5-dione (8). To a stirred solution of **6** (152 mg, 0.71 mmol) in 10 mL of dry benzene (CAUTION-CARCINOGENIC) was added a solution of DDQ (355 mg, 1.54 mmol). After the addition was complete, stirring was continued for 1 h at room temperature. The solvent was evaporated and residue was filtered on a short silica gel column (5 g) eluting with CH_2Cl_2 (100 mL). The residue (148 mg, 99%) was recrystallized from ethyl acetate/hexane to give **8** as dark brown powder (135 mg, 90%); mp 223–224 °C: ^{1}H NMR (200 MHz, CD_3COCD_3): δ 11.00 (m, NH, 1H), 7.71 (d, J=7.7 Hz, A part of AB system, 1H), 7.55 (d, J=1.5 Hz, H-3, 1H), 7.48 (d, J=7.7 Hz, A part of AB system, 1H), 7.31 (bt, J= 7.7 Hz, A part of AB system, 1H), 7.12 (s, 1H), 7.11 (d, J= 7.7 Hz, B part of AB system, 1H); ^{13}C NMR (50 MHz, CD_3COCD_3): δ 167.61, 167.25, 142.13, 141.26, 131.02, 129.94, 128.94, 125.20, 123.74, 123.45, 121.40, 116.35, 114.76, 114.06; IR (CH_2Cl_2, cm^{-1}): 3394, 1835, 1766, 1619, 1511, 1411, 1280, 1241, 1141, 910. Anal. calcd for $C_{12}H_7NO_3$: C, 67.61; H, 3.31; N, 6.57. Found: C, 67.04; H, 3.26; N, 6.69.

3.1.4. Reaction of 4,7-dihydroindole (3) diethyl azodicarboxylate (9). A solution of 4,7-dihydroindole (**3**) (179 mg, 1.50 mmol), diethyl azodicarboxylate (**9**) (502 mg, 3.01 mmol) and $Bi(NO_3)_3$ (117 mg, 0.24 mmol) in 2 mL CH_2Cl_2 was stirred at room temperature for 16 h. The residue was filtered on a silica gel column (60 g) eluting with ethyl acetate/hexane (5%) to give the indole derivative **13**, which was crystallized from CH_2Cl_2/hexane (140 mg, 45%, dark grey powders, mp: 115–116 °C. Further elution with ethyl acetate/hexane (40%) furnished the product **14**: (140 mg, 40%) colourless powder from CH_2Cl_2/hexane; mp 119–120 °C (lit.[12] mp 128–130 °C); For **13**: ^{1}H NMR (200 MHz, $CDCl_3$): δ 9.76 (m, NH, 1H), 7.51 (bd, J= 6.6 Hz, 1H), 7.31 (bd, J=7.7 Hz, 1H), 7.26–7.06 (m, 2H), 6.12 (m, =CH, H-3, 1H), 4.37–4.15 (m, CH_2, 4H), 1.36–1.17 (m, CH_3, 6H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 157.75, 156.08, 135.26, 129.07, 123.36, 123.22, 122.11, 121.91, 121.83, 112.86, 65.64, 64.70, 16.38 (2C); IR (CH_2Cl_2, cm^{-1}): 3324, 3062, 2993, 2931, 1720, 1627, 1604, 1558, 1465, 1380, 1319, 1249, 1172, 1072, 1010. Anal. calcd for $C_{14}H_{17}N_3O_4$: C, 57.72; H, 5.88; N, 14.42. Found: C, 57.56; H, 5.97; N, 14.30. For **14**: ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.62 (m, NH, 2H), 4.20 (q, J=7.1 Hz, OCH_2, 4H), 1.27 (t, J=7.1 Hz, CH_3, 6H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 158.73, 64.25, 16.39; IR (CH_2Cl_2, cm^{-1}): 3301, 2993, 1712, 1519, 1380, 1326, 1241, 1072.

3.1.5. 3-(1*H*-Indol-2-yl)-1,3-diphenyl-propan-1-one (15). A solution of 4,7-dihydroindole (**3**) (300 mg, 2.52 mmol), 1,3-diphenyl-propenone (**10**) (132 mg, 0.63 mmol) and $Bi(NO_3)_3$ (219 mg, 0.45 mmol) in 2 mL CH_2Cl_2 was stirred at room temperature for 16 h. After the solvent was evaporated, the residue was filtered on a short silica gel column (5 g) eluting with CH_2Cl_2 (100 mL). The crude product (432 mg, 1.32 mmol) and 147 mg (1.32 mmol) *p*-benzoquinone were dissolved in CH_2Cl_2 (20 mL) and stirred at room temperature for 24 h. Reaction mixture was diluted with CH_2Cl_2 (100 mL), and the organic phase was washed with NaOH (2×50 mL, 10%), washed with water (2×50 mL) and dried over $MgSO_4$. After removal of the solvent, the residue was purified on a silica gel column (50 g) eluting with ethyl acetate/hexane (5%) to give 40 mg of unreacted 1,3-diphenyl-propenone (**10**) as the first fraction. Further elution with ethyl acetate/hexane (5%) furnished the product **15**: (242 mg, 30%) yellow crystals from CH_2Cl_2/hexane; mp 124–125 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.23 (m, NH, 1H), 8.02–7.97 (m, 2H), 7.63–7.50 (m, 4H), 7.48–7.23 (m, 6H), 7.15–7.00 (m, 2H), 6.20 (m, =CH, H_3, 1H), 4.96 (dd, J=7.7 Hz, 5.5 Hz, CH, 1H), 3.92 (dd, J=17.7, 7.7 Hz, A part of AB system, CH_2, 1H), 3.70 (dd, J=17.7, 5.5 Hz, B part of AB system, CH_2, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 200.56, 144.26, 143.66, 138.80, 138.14, 135.41, 130.81, 130.69, 130.17, 130.12, 129.13, 123.51, 122.07, 121.63, 114.63, 112,62, 101.96, 46.92, 41.76; IR (CH_2Cl_2, cm^{-1}): 3392, 3046, 2923, 2869, 1684, 1600, 1458, 1346, 1292, 1253, 1223, 992, 753, 700. Anal. calcd for $C_{23}H_{19}NO$: C, 84.89; H, 5.89; N, 4.30. Found: C, 85.01; H, 5.74; N, 4.41.

3.1.6. 3-(1*H*-Indol-2-yl)-cyclohexanone (16). A solution of 4,7-dihydroindole (**3**) (100 mg, 0.84 mmol), 2-cyclohexenone (**11**) (81 mg, 0.84 mmol) and $Bi(NO_3)_3$ (73 mg, 0.30 mmol) in 2 mL CH_2Cl_2 was stirred at room temperature for 16 h. After the solvent was evaporated, the residue was filtered on a short silica gel column (5 g) eluting with CH_2Cl_2 (100 mL). The crude product (181 mg, 0.82 mmol) and *p*-benzoquinone (98 mg, 0.90 mmol) were dissolved in CH_2Cl_2 (20 mL) and stirred at room temperature for 24 h. Reaction mixture was diluted with CH_2Cl_2 (100 mL), and the organic phase was washed with NaOH (2×50 mL, 10%), washed with water (2×50 mL) and dried over $MgSO_4$. After removal of the solvent, the residue was filtered on a silica gel column (45 g) eluting with ethyl acetate/hexane (20%) to give 90 mg (49%) as a dark brown powder which was recrystallized from CH_2Cl_2/hexane; mp 148–149 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.10 (m, NH, 1H), 7.56 (bd, J=6.5 Hz, 1H), 7.32 (bd, J=8.0 Hz, 1H), 7.20–7.05 (m, 2H), 6.28 (bs, =CH, H_3, 1H), 3.26 (pentet, J=4.8 Hz, CH, 1H), 2.85–1.75 (m, CH_2, 8H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 212.26, 143.32, 137.84, 130.35, 123.66, 122.19, 121.90, 112.57, 100.86, 49.06, 43.28, 39.73, 33.23, 26.67; IR (CH_2Cl_2, cm^{-1}): 3340, 3054, 2939, 2861, 1704, 1643, 1596, 1550, 1457, 1419, 1349, 1311, 1234, 1172, 1141. Anal. calcd for $C_{14}H_{15}NO$: C, 78.84; H, 7.09; N, 6.57. Found: C, 79.01; H, 6.97; N, 6.71.

3.1.7. 3-(1*H*-Indol-2-yl)-cyclopentanone (17). A solution of 4,7-dihydroindole (**3**) (200 mg, 1.68 mmol), 2-cyclopentenone (**12**) (146 mg, 1.68 mmol) and $Bi(NO_3)_3$ (146 mg, 0.37 mmol) in 2 mL CH_2Cl_2 was stirred at room temperature for 16 h. After the solvent was evaporated, the

residue was filtered on a short silica gel column (5 g) eluting with CH_2Cl_2 (100 mL). The crude product (350 mg, 1.74 mmol) and *p*-benzoquinone (206 mg, 1.91 mmol) were dissolved in CH_2Cl_2 (20 mL) and stirred at room temperature for 24 h. Reaction mixture was diluted with CH_2Cl_2 (100 mL), and the organic phase was washed with NaOH (2×50 mL, 10%), washed with water (2×50 mL) and dried over $MgSO_4$. After removal of the solvent, the residue was filtered on a silica gel column (45 g) eluting with ethyl acetate/hexane (20%) gave 150 mg (45%) as a dark brown powder which was recrystallized from CH_2Cl_2/hexane; mp 100–101 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.21 (bs, NH, 1H), 7.58 (bd, J=8.2 Hz, 1H), 7.33 (bd, J=7.4 Hz, 1H), 7.23–7.08 (m, 2H), 6.30 (bs, =CH, H_3, 1H), 3.59–3.51 (m, CH, 1H), 2.77–2.05 (m, CH_2, 6H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 219.82, 142.69, 138.18, 130.34, 123.71, 122.19, 121.96, 112.59, 100.78, 46.56, 40.00, 37.58, 31.54; IR (CH_2Cl_2, cm^{-1}): 3384, 3061, 2961, 2906, 1738, 1630, 1461, 1407, 1300, 1246, 1153, 1015. Anal. calcd for $C_{13}H_{13}NO$: C, 78.36; H, 6.58; N 7.03. Found: C, 78.48; H, 6.44; 6.90.

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Synthesis of a new class of keto-linked bis heterocycles

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Abstract—A new class of keto-linked bis heterocycles have been prepared by 1,3-dipolar cycloaddition of tosyl methyl isocyanide, nitrile imines and nitrile oxides to unsymmetrical bischalcones.

1. Introduction

The development of simple, facile and efficient synthetic methods for the synthesis of five-membered heterocycles from readily available reagents is one of the major challenges in organic synthesis. Amongst five-membered heterocycles, pyrroles, pyrazoles and isoxazoles have gained importance because of their varied physiological activities. 4-Aminopyrrole-2-carboxylates exhibit antibiotic, antiviral and oncolytic properties.[1] Celecoxib, a pyrazole derivative and Valdecoxib, an isoxazole derivative are now widely used in the market as anti-inflammatory drugs.[2] Hence, it is thought that a worthwhile programme would be to prepare molecules having both pyrrole and pyrazole/isoxazole rings. In the literature, multistep synthetic routes of 3,4-disubstituted pyrroles have been reported either by coupling of imines and nitroalkanes, or using Friedel-Crafts acylation with an electron-withdrawing group on the pyrrole nitrogen or 3,4-silylated precursors.[3] 3,4-Disubstituted pyrroles have also been synthesized from Michael acceptors with tosyl methyl isocyanide (TosMIC).[4,5]

Similarly, amongst different methods for the synthesis of pyrazolines and isoxazolines, 1,3-dipolar cycloaddition of an ylide onto an alkene in a 3+2 manner is a facile one.[6]

Among the ylides, diazomethane, nitrile imines and nitrile oxides have been used extensively as reactive intermediates. The nitrile imines and nitrile oxides can be generated by dehydrogenation of aryl aldehyde phenylhydrazones and aryl aldoximes with lead tetraacetate,[7] mercuric acetate,[8] 1-chlorobenzotriazole,[9] chloramine-T[10] etc. However, use of the latter for the in situ generation of dipolar reagents has enthused many organic chemists. In fact, we have reported the 1,3-dipolar cycloaddition reaction of chloramine-T catalysed dipolar reagents with different activated mono and bis olefins.[11] The present communication deals with the synthesis of hitherto unknown keto-linked bis heterocycles having a pyrrole in combination with a pyrazole or isoxazole unit, adopting 1,3-dipolar cycloadditions onto activated olefins.

2. Results and discussion

The synthetic scheme is based on the reactivity of 2-methyl-1-phenyl-5-aryl-1,4-pentadien-3-one **1** towards 1,3-dipolar reagents viz., TosMIC, diazomethane, nitrile imines and nitrile oxides. When **1** is treated with TosMIC in the presence of sodium hydride in a mixture of ether and DMSO, a solid is obtained which is identified as 4-aryl-3-(3′-phenyl-2′-methyl-2′-propenone)-1*H*-pyrrole **2** by ^{1}H NMR spectroscopy. Compound **2a** exhibited two singlets at δ 7.12 and 7.15 ppm due to the C_2–H and C_5–H of the pyrrole ring protons. A singlet is observed at δ 6.75 ppm for the olefinic proton, and another singlet at 2.10 ppm for the methyl protons, as well as signals due to aromatic protons, and the ^{13}C NMR spectra showed signals at δ 135.2 and 138.5 ppm for the olefinic carbons, C-2′ and C-3′. The formation of **2** indicates that the reaction proceeds in a regiospecific manner. Attempts were made to prepare (3-methyl-4-phenyl-3*H*-pyrrolyl)-(4-phenyl-1*H*-pyrrol-3-yl) methanone either by treating **1** with 2 equiv of TosMIC, or **2** with 1 equiv of TosMIC but did not succeed (Scheme 1).

The olefin in **2** is utilized in the synthesis of pyrazolines and isoxazolines. When **2** is subjected to 1,3-dipolar cycloaddition reaction with diazomethane, (3′-methyl-4′-phenyl-3′,4′-dihydro-2′*H*-pyrazol-3′-yl)-(4-aryl-1*H*-pyrrol-3-yl)-methanone (**3**) is obtained. The ^{1}H NMR spectrum of **3a**

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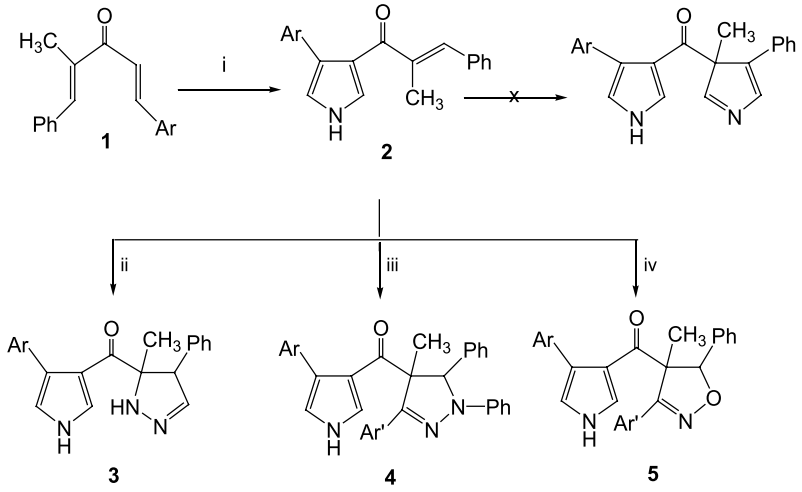

i) TosMIC, NaH, Et_2O + DMSO ii) CH_2N_2 / Et_2O / Et_3N
iii) Ar'-CH=NNHPh / Chloramine-T.$3H_2O$/MeOH
iv) Ar'-CH=NOH / Chloramine-T.$3H_2O$ / MeOH

	Ar	Ar'
2a,3a	C_6H_5	-
2b,3b	4-$MeOC_6H_4$	-
2c,3c	4-ClC_6H_4	-
4a,5a	C_6H_5	C_6H_5
4b,5b	4-$MeOC_6H_4$	C_6H_5
4c,5c	C_6H_5	4-ClC_6H_4
4d,5d	4-ClC_6H_4	4-ClC_6H_4

Scheme 1.

showed a doublet at δ 4.65 ppm for $C_{4'}$–H and a singlet at 1.18 ppm for methyl protons. The signals due to $C_{5'}$–H are appearing at downfield and are merged with the aromatic protons. The ^{13}C NMR spectrum of **3a** exhibited signals at δ 44.9, 81.4, 100.2, 118.1, 122.2, 125.3, 126.2 and 195.3 ppm for the carbons, C-4′, C-3′, C-5′, C-3, C-5, C-2, C-4 and CO, respectively.

In addition, the reaction of **2** with nitrile imines and nitrile oxides produced (4′-methyl-3′-aryl-1′,5′-diphenyl-4′,5′-dihydro-1′*H*-pyrazol-4′-yl)-(4-aryl-1*H*-pyrrol-3-yl)-methanone (**4**) and (4′-methyl-3′-aryl-5′-phenyl-4′,5′-dihydro-isoxazol-4′-yl)-(4-aryl-1*H*-pyrrol-3-yl)-methanone (**5**). The ^1H NMR spectra of **4a** and **5a** exhibited singlets at δ 5.31 and 5.41 ppm for the $C_{5'}$–H of the pyrazoline and isoxazoline rings, respectively. The ^{13}C NMR spectra of these compounds displayed signals at δ 64.6, 63.2 (C-4′), 85.9, 84.3 (C-5′), 159.2, 159.5 (C-3′), 118.1, 118.1 (C-3), 122.1, 122.2 (C-5), 125.3, 125.3 (C-2), 126.2, 126.2 (C-4), 195.2, 195.3 (C═O), respectively.

3. Conclusion

Thus, the 1,3-dipolar cycloaddition of dipolar reagents viz., TosMIC, diazomethane, nitrile imines and nitrile oxides to unsymmetrical bischalcones provides a simple, elegant and well-versed methodology to develop a new and novel keto-linked bis heterocycles having two different heterocyclic rings.

4. Experimental

4.1. General

Melting points were determined in open capillaries on a Mel-Temp apparatus and are uncorrected. The purity of the compounds were checked by TLC (silica gel H, BDH, ethyl acetate/hexane, 1:3). IR spectra were recorded on a Perkin-Elmer grating infrared spectrophotometer, model 337 in KBr pellets. ^1H NMR spectra were recorded at 300 MHz on a Varian EM-360 spectrometer. ^{13}C NMR spectra were run on a Varian VXR spectrometer operating at 75.5 MHz. All chemical shifts were reported in ppm from TMS as an internal standard. Elemental analyses were obtained from the University of Pune, Pune, India.

The starting substrates unsymmetrical bischalcones were prepared according to the literature procedure.[12] Aryl aldehyde phenylhydrazones and Aryl aldoximes were prepared by standard procedures.[13]

4.1.1. 4-Aryl-3-(3′-phenyl-2′-methyl-2′-propenone)-1*H*-pyrrole (2)—General procedure. An equimolar (5 mmol) mixture of TosMIC and 2-methyl-1-phenyl-5-aryl-1,4-pentadien-3-one **1** in Et_2O–DMSO (2:1) was added dropwise while stirring to a suspension of sodium hydride (50 mg) in Et_2O (10 mL) at room temperature. Stirring was continued for about 5 h and diluted with water. It was extracted with ether and dried over anhyd. Na_2SO_4. The solvent was removed in vacuo. The resultant solid was purified by recrystallization from methanol.

4.1.2. 4-Phenyl-3-(3′-phenyl-2′-methyl-2′-propenone)-1*H*-pyrrole (2a). Pale-yellow solid, (0.88 g, 61%); mp 165–170 °C; [Found: C, 83.67; H, 6.02; N, 4.95. $C_{20}H_{17}NO$ requires C, 83.59; H, 5.96; N, 4.87%]; ν_{max} (KBr): 1584 (C=C), 1612 (C=O), 3171 (NH) cm^{-1}; δ_H (MHz, $CDCl_3$) 2.10 (3H, s, CH_3), 6.75 (1H, s, $C_{3'}$–H), 7.12 (1H, s, C_2–H), 7.15 (1H, s, C_5–H), 7.23–7.32 (10H, m, Ph), 9.17 (1H, bs, NH); δ_C ($CDCl_3$) 14.3 (CH_3), 118.1 (C-3), 122.2 (C-5), 125.3 (C-2), 126.2 (C-4), 135.2 (C-2′), 138.5 (C-3′), 195.2 (C=O), 126.8, 127.6, 128.1, 128.7, 129.2, 129.6, 134.5, 136.8 (aromatic carbons).

4.1.3. 4-(4-Methoxyphenyl)-3-(3′-phenyl-2′-methyl-2′-propenone)-1*H*-pyrrole (2b). Pale-yellow solid, (1.15 g, 72%); mp 179–181 °C; [Found: C, 79.56; H, 5.97; N, 4.45. $C_{21}H_{19}NO_2$ requires C, 79.47; H, 6.03; N, 4.41%]; ν_{max} (KBr): 1582 (C=C), 1615 (C=O), 3212 (NH) cm^{-1}; δ_H ($CDCl_3$) 2.18 (3H, s, CH_3), 3.72 (3H, s, Ph–OCH_3), 6.69 (1H, s, $C_{3'}$–H), 7.08 (1H, s, C_2–H), 7.11 (1H, s, C_5–H), 7.12–7.34 (9H, m, Ph), 9.18 (1H, bs, NH); δ_C ($CDCl_3$) 14.5 (CH_3), 55.2 (OCH_3), 117.5 (C-3), 121.9 (C-5), 124.7 (C-2), 126.5 (C-4), 136.4 (C-2′), 137.9 (C-3′), 193.8 (C=O), 115.2, 125.2, 126.7, 127.8, 128.6, 129.2, 133.9, 159.8 (aromatic carbons).

4.1.4. 4-(4-Chlorophenyl)-3-(3′-phenyl-2′-methyl-2′-propenone)-1*H*-pyrrole (2c). Pale-yellow solid, (1.11 g, 69%); mp 202–204 °C; [Found: C, 74.74; H, 5.06; N, 4.41. $C_{20}H_{16}ClNO$ requires C, 74.65; H, 5.01; N, 4.35%]; ν_{max} (KBr): 1585 (C=C), 1613 (C=O), 3194 (NH) cm^{-1}; δ_H ($CDCl_3$) 2.24 (3H, s, CH_3), 6.79 (1H, s, $C_{3'}$–H), 7.14 (1H, s, C_2–H), 7.18 (1H, s, C_5–H), 7.24–7.35 (9H, m, Ph), 9.21 (1H, bs, NH); δ_C ($CDCl_3$) 14.7 (CH_3), 118.6 (C-3), 123.4 (C-5), 126.1 (C-2), 127.8 (C-4), 134.9 (C-2′), 137.6 (C-3′), 196.4 (C=O), 125.8, 126.7, 127.6, 129.3, 131.7, 132.6, 134.7 (aromatic carbons).

4.1.5. (3′-Methyl-4′-phenyl-3′,4′-dihydro-2′*H*-pyrazol-3′-yl)-(4-aryl-1*H*-pyrrol-3-yl)-methanone (3)—General procedure. To a well cooled solution of 4-aryl-3-(3′-phenyl-2′-methyl-2′-propenone)-1*H*-pyrrole **2** (5 mmol) in dichloromethane (20 mL), an ethereal solution of diazomethane (40 mL, 0.4 M) and triethylamine (0.12 g) were added. The reaction mixture was kept at −20 to −15 °C for 40–48 h. The solvent was removed under reduced pressure, then purified by recrystallization from methanol.

4.1.6. (3′-Methyl-4′-phenyl-3′,4′-dihydro-2′*H*-pyrazol-3′-yl)-(4-phenyl-1*H*-pyrrol-3-yl)-methanone (3a). Yellow solid, (1.22 g, 74%); mp 194–196 °C; [Found: C, 76.49; H, 5.85; N, 12.83. $C_{21}H_{19}N_3O$ requires C, 76.57; H, 5.81; N, 12.76%]; ν_{max} (KBr): 1560 (C=N), 1660 (C=O), 3370 (NH) cm^{-1}; δ_H ($CDCl_3$) 1.18 (3H, s, CH_3), 4.65 (1H, d, $C_{4'}$–H), 6.53 (1H, bs, NH), 7.10 (1H, s, C_2–H), 7.14 (1H, s, C_5–H), 7.21–7.30 (11H, m, Ph and $C_{5'}$–H), 9.15 (1H, bs, NH); δ_C ($CDCl_3$) 17.1 (CH_3), 44.9 (C-4′), 81.4 (C-3′), 100.2 (C-5′), 118.1 (C-3), 122.2 (C-5), 125.3 (C-2), 126.2 (C-4), 195.3 (C=O), 125.9, 126.7, 128.6, 128.9, 129.2, 129.7, 136.4, 137.6 (aromatic carbons).

4.1.7. (3′-Methyl-4′-phenyl-3′,4′-dihydro-2′*H*-pyrazol-3′-yl)-[4-(4-methoxyphenyl)-1*H*-pyrrol-3-yl]-methanone (3b). Yellow solid, (1.4 g, 78%); mp 206–208 °C; [Found: C, 73.59; H, 5.93; N, 11.75. $C_{22}H_{21}N_3O_2$ requires C, 73.52; H, 5.89; N, 11.69%]; ν_{max} (KBr): 1563 (C=N), 1664 (C=O), 3374 (NH) cm^{-1}; δ_H ($CDCl_3$) 1.21 (3H, s, CH_3), 3.75 (3H, s, Ph–OCH_3), 4.62 (1H, d, $C_{4'}$–H), 6.49 (1H, bs, NH), 7.05 (1H, s, C_2–H), 7.09 (1H, s, C_5–H), 7.14–7.30 (10H, m, Ph and $C_{5'}$–H), 9.16 (1H, bs, NH); δ_C ($CDCl_3$) 16.9 (CH_3), 55.6 (OCH_3), 43.8 (C-4′), 82.4 (C-3′), 101.3 (C-5′), 117.6 (C-3), 123.1 (C-5), 124.8 (C-2), 126.5 (C-4), 194.6 (C=O), 114.2, 125.7, 126.3, 128.2, 128.7, 129.1, 136.8, 160.4 (aromatic carbons).

4.1.8. (3′-Methyl-4′-phenyl-3′,4′-dihydro-2′*H*-pyrazol-3′-yl)-[4-(4-chlorophenyl)-1*H*-pyrrol-3-yl]-methanone (3c). Yellow solid, (1.44 g, 79%); mp 212–214 °C; [Found: C, 69.27; H, 4.93; N, 11.64. $C_{21}H_{18}ClN_3O$ requires C, 69.32; H, 4.99; N, 11.55%]; ν_{max} (KBr): 1559 (C=N), 1658 (C=O), 3368 (NH) cm^{-1}; δ_H ($CDCl_3$) 1.19 (3H, s, CH_3), 4.68 (1H, d, $C_{4'}$–H), 6.65 (1H, bs, NH), 7.14 (1H, s, C_2–H), 7.17 (1H, s, C_5–H), 7.25–7.36 (10H, m, Ph and $C_{5'}$–H), 9.17 (1H, bs, NH); δ_C ($CDCl_3$) 17.3 (CH_3), 50.2 (C-4′), 80.9 (C-3′), 99.8 (C-5′), 119.4 (C-3), 123.6 (C-5), 126.4 (C-2), 127.8 (C-4), 196.6 (C=O), 126.4, 127.0, 128.1, 128.3, 129.1, 132.8, 133.5, 137.9 (aromatic carbons).

4.1.9. (4′-Methyl-3′-aryl-1′,5′-diphenyl-4′,5′-dihydro-1′*H*-pyrazol-4′-yl)-(4-aryl-1*H*-pyrrol-3-yl)-methanone (4)—General procedure. A mixture of 4-aryl-3-(3′-phenyl-2′-methyl-2′-propenone)-1*H*-pyrrole **2** (1 mmol), aryl aldehyde phenylhydrazone (2 mmol) and chloramine-T (2 mmol) in methanol (20 mL) was heated under reflux for 18–20 h on a water bath. The precipitated inorganic salts were filtered off, then the filtrate concentrated and the residue extracted with dichloromethane. The organic extract was washed with water, brine and dried (anhyd. Na_2SO_4). Evaporation of the solvent under vacuum gave the crude product, which was recrystallized from ethanol.

4.1.10. (4′-Methyl-1′,3′,5′-triphenyl-4′,5′-dihydro-1′*H*-pyrazol-4′-yl)-(4-phenyl-1*H*-pyrrol-3-yl)-methanone (4a). White solid (0.32 g, 65%); mp 179–181 °C; [Found: C, 82.37; H, 5.64; N, 8.80. $C_{33}H_{27}N_3O$ requires C, 82.30; H, 5.65; N, 8.73%]; ν_{max} (KBr): 1575 (C=N), 1658 (C=O), 3176 (NH) cm^{-1}; δ_H ($CDCl_3$) 1.19 (3H, s, CH_3), 5.31 (1H, s, $C_{5'}$–H), 7.12 (1H, s, C_2–H), 7.17 (1H, s, C_5–H), 7.25–7.34 (20H, m, Ph), 9.25 (1H, bs, NH); δ_C ($CDCl_3$) 16.9 (CH_3), 64.6 (C-4′), 85.9 (C-5′), 159.2 (C-3′), 118.1 (C-3), 122.1 (C-5), 125.3 (C-2), 126.2 (C-4), 195.2 (C=O), 112.8, 117.5, 126.8, 127.2, 128.3, 128.6, 128.9, 129.2, 129.5, 130.4, 132.2, 136.6, 138.8, 143.7 (aromatic carbons).

4.1.11. (4′-Methyl-1′,3′,5′-triphenyl-4′,5′-dihydro-1′*H*-pyrazol-4′-yl)-[4-(4-methoxy-phenyl)-1*H*-pyrrol-3-yl]-methanone (4b). White solid, (0.36 g, 69%); mp 193–195 °C; [Found: C, 79.74; H, 5.74; N, 8.30. $C_{34}H_{29}N_3O_2$ requires C, 79.82; H, 5.71; N, 8.21%]; ν_{max} (KBr): 1558 (C=N), 1662 (C=O), 3178 (NH) cm^{-1}; δ_H ($CDCl_3$) 1.16 (3H, s, CH_3), 3.78 (3H, s, Ph–OCH_3), 5.29 (1H, s, $C_{5'}$–H), 7.05 (1H, s, C_2–H), 7.15 (1H, s, C_5–H), 7.18–7.29 (19H, m, Ph), 9.27 (1H, bs, NH); δ_C ($CDCl_3$) 17.2 (CH_3), 55.5 (OCH_3), 63.9 (C-4′), 84.6 (C-5′), 160.4 (C-3′), 118.3 (C-3), 121.7 (C-5), 126.2 (C-2), 127.4 (C-4), 196.4 (C=O), 113.3, 114.8, 117.9, 126.2, 128.4, 128.9, 129.1, 129.4, 129.8, 130.1, 130.6, 131.5, 137.8, 143.6, 161.8 (aromatic carbons).

4.1.12. [4′-Methyl-3′-(4-chlorophenyl)-1′,5′-diphenyl-4′,5′-dihydro-1′*H*-pyrazol-4′-yl]-(4-phenyl-1*H*-pyrrol-3-yl)-methanone (4c). White solid, (0.37 g, 71%); mp 210–212 °C; [Found: C, 76.72; H, 5.15; N, 8.19. $C_{33}H_{26}ClN_3O$ requires C, 76.81; H, 5.08; N, 8.14%]; ν_{max} (KBr): 1564 (C=N), 1666 (C=O), 3184 (NH) cm^{-1}; δ_H ($CDCl_3$) 1.19 (3H, s, CH_3), 5.30 (1H, s, $C_{5'}$–H), 7.10 (1H, s, C_2–H), 7.18 (1H, s, C_5–H), 7.29–7.42 (19H, m, Ph), 9.32 (1H, bs, NH); δ_C ($CDCl_3$) 17.4 (CH_3), 64.8 (C-4′), 85.8 (C-5′), 158.3 (C-3′), 119.4 (C-3), 123.4 (C-5), 125.8 (C-2), 126.6 (C-4), 194.3 (C=O), 112.6, 115.8, 125.5, 126.3, 128.2, 128.6, 128.8, 129.3, 129.6, 130.2, 135.8, 136.2, 137.8, 143.5 (aromatic carbons).

4.1.13. [4′-Methyl-3′-(4-chlorophenyl)-1′,5′-diphenyl-4′,5′-dihydro-1′*H*-pyrazol-4′-yl]-[4-(4-chlorophenyl)-1*H*-pyrrol-3-yl]-methanone (4d). White solid, (0.41 g, 74%); mp 204–206 °C; [Found: C, 71.92; H, 4.62; N, 7.71. $C_{33}H_{25}Cl_2N_3O$ requires C, 72.00; H, 4.58; N, 7.63%]; ν_{max} (KBr): 1572 (C=N), 1657 (C=O), 3180 (NH) cm^{-1}; δ_H ($CDCl_3$) 1.18 (3H, s, CH_3), 5.31 (1H, s, $C_{5'}$–H), 7.09 (1H, s, C_2–H), 7.22 (1H, s, C_5–H), 7.25–7.34 (18H, m, Ph), 9.27 (1H, bs, NH); δ_C ($CDCl_3$) 16.9 (CH_3), 64.9 (C-4′), 86.2 (C-5′), 159.6 (C-3′), 118.9 (C-3), 123.9 (C-5), 126.8 (C-2), 127.3 (C-4), 195.8 (C=O), 112.5, 115.6, 125.6, 127.8, 128.1, 128.7, 129.2, 129.6, 129.8, 131.2, 133.6, 134.8, 135.9, 138.6, 142.6 (aromatic carbons).

4.1.14. (4′-Methyl-3′-aryl-5′-phenyl-4′,5′-dihydro-isoxazol-4′-yl)-(4-aryl-1*H*-pyrrol-3-yl)-methanone (5)—General procedure. A mixture of 4-aryl-3-(3′-phenyl-2′-methyl-2′-propenone)-1*H*-pyrrole **2** (1 mmol), aryl aldoxime (2 mmol) and chloramine-T (2 mmol) in methanol (20 mL) was heated under reflux for 16–18 h on a water bath. The precipitated inorganic salts were filtered off, the filtrate concentrated and the residue extracted with dichloromethane. The organic extract was washed with water, brine and dried (anhyd. Na_2SO_4). The solvent was removed under reduced pressure. Recrystallization of the crude product from ethanol gave pure **5**.

4.1.15. (4′-Methyl-3′,5′-diphenyl-4′,5′-dihydro-isoxazol-4′-yl)-(4-phenyl-1*H*-pyrrol-3-yl)-methanone (5a). Colorless solid, (0.27 g, 65%); mp 172–174 °C; [Found: C, 79.85; H, 5.41; N, 6.95. $C_{27}H_{22}N_2O_2$ requires C, 79.78; H, 5.46; N, 6.89%]; ν_{max} (KBr): 1578 (C=N), 1664 (C=O), 3170 (NH) cm^{-1}; δ_H ($CDCl_3$) 1.16 (3H, s, CH_3), 5.41 (1H, s, $C_{5'}$–H), 7.09 (1H, s, C_2–H), 7.17 (1H, s, C_5–H), 7.25–7.40 (15H, m, Ph), 9.20 (1H, bs, NH); δ_C ($CDCl_3$) 14.3 (CH_3), 63.2 (C-4′), 84.3 (C-5′), 159.5 (C-3′), 118.1 (C-3), 122.2 (C-5), 125.3 (C-2), 126.2 (C-4), 195.3 (C=O), 125.5, 126.6, 127.9, 128.3, 128.9, 129.6, 131.2, 131.6, 136.4, 137.7 (aromatic carbons).

4.1.16. (4′-Methyl-3′,5′-diphenyl-4′,5′-dihydro-isoxazol-4′-yl)-[4-(4-methoxyphenyl)-1*H*-pyrrol-3-yl]-methanone (5b). Colorless solid, (0.29 g, 68%); mp 187–189 °C; [Found: C, 77.10; H, 5.61; N, 6.48. $C_{28}H_{24}N_2O_3$ requires C, 77.04; H, 5.54; N, 6.42%]; ν_{max} (KBr): 1574 (C=N), 1665 (C=O), 3175 (NH) cm^{-1}; δ_H ($CDCl_3$) 1.19 (3H, s, CH_3), 3.80 (3H, s, Ph–OCH_3), 5.36 (1H, s, $C_{5'}$–H), 7.05 (1H, s, C_2–H), 7.15 (1H, s, C_5–H), 7.19–7.39 (14H, m, Ph), 9.22 (1H, bs, NH); δ_C ($CDCl_3$) 13.9 (CH_3), 55.7 (OCH_3), 63.8 (C-4′), 84.8 (C-5′), 158.7 (C-3′), 117.9 (C-3), 121.6 (C-5), 124.9 (C-2), 126.8 (C-4), 197.4 (C=O), 114.5, 124.6, 127.3, 127.8, 128.2, 128.4, 129.3, 131.0, 131.6, 136.7, 161.4 (aromatic carbons).

4.1.17. [4′-Methyl-3′-(4-chlorophenyl)-5′-phenyl-4′,5′-dihydro-isoxazol-4′-yl]-(4-phenyl-1*H*-pyrrol-3-yl)-methanone (5c). Colorless solid, (0.29 g, 66%); mp 212–214 °C; [Found: C, 73.47; H, 4.85; N, 6.42. $C_{27}H_{21}ClN_2O_2$ requires C, 73.55; H, 4.80; N, 6.35%]; ν_{max} (KBr): 1565 (C=N), 1658 (C=O), 3180 (NH) cm^{-1}; δ_H ($CDCl_3$) 1.18 (3H, s, CH_3), 5.42 (1H, s, $C_{5'}$–H), 7.10 (1H, s, C_2–H), 7.19 (1H, s, C_5–H), 7.24–7.42 (14H, m, Ph), 9.27 (1H, bs, NH); δ_C ($CDCl_3$) 14.2 (CH_3), 62.9 (C-4′), 84.6 (C-5′), 160.2 (C-3′), 119.4 (C-3), 123.4 (C-5), 125.2 (C-2), 126.3 (C-4), 196.9 (C=O), 124.6, 126.2, 127.9, 128.2, 128.4, 128.9, 129.1, 131.6, 136.2, 136.8, 137.5 (aromatic carbons).

4.1.18. [4′-Methyl-3′-(4-chlorophenyl)-5′-phenyl-4′,5′-dihydro-isoxazol-4′-yl]-[4-(4-chlorophenyl)-1*H*-pyrrol-3-yl]-methanone (5d). Colorless solid, (0.34 g, 71%); mp 200–202 °C; [Found: C, 68.14; H, 4.28; N, 5.95. $C_{27}H_{20}Cl_2N_2O_2$ requires C, 68.22; H, 4.24; N, 5.89%]; ν_{max} (KBr): 1572 (C=N), 1649 (C=O), 3172 (NH) cm^{-1}; δ_H ($CDCl_3$) 1.19 (3H, s, CH_3), 5.44 (1H, s, $C_{5'}$–H), 7.09 (1H, s, C_2–H), 7.19 (1H, s, C_5–H), 7.26–7.40 (13H, m, Ph), 9.26 (1H, bs, NH); δ_C ($CDCl_3$) 14.5 (CH_3), 63.7 (C-4′), 85.6 (C-5′), 159.8 (C-3′), 118.6 (C-3), 122.8 (C-5), 125.7 (C-2), 127.2 (C-4), 197.3 (C=O), 123.7, 126.2, 127.1, 128.2, 128.8, 129.4, 129.8, 130.6, 132.8, 135.6, 136.7, 138.2 (aromatic carbons).

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Nitrilimine cycloaddition onto 2-azetidinones bearing alkenyl dipolarophile(s)

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Abstract—Silver acetate-promoted nitrilimines cycloaddition onto 3(*R**)-phenyl-4(*R**)-cinnamoyl-2-azetidinone **1** were highly stereoselective giving 4-(4,5-dihydropyrazol-5-yl) carbonyl-2-azetidinones **5** as the major products and regioisomeric 4-(4,5-dihydropyrazol-4-yl) carbonyl-2-azetidinones **6** as the minor one. When the same protocol was applied to the novel 3(*R**)-phenyl-4(*S**)-(4-benzoyl-*E*,*E*-1,3-butadienyl)-2-azetidinone **2** it resulted in site- and regioselective but not stereoselective cycloaddition, involving the formation of the four cycloadducts **10**–**13**.

1. Introduction

Since the discovery of penicillin in 1928, 2-azetidinone-based heterocycles have become one of the most widely used class of drugs for the systematic treatment of bacterial infections.[1] Due to their relevance in both clinic and economic fields, variously substituted 2-azetidinones represent a very attractive target for contemporary organic synthesis.[2] As a result, considerable efforts have been concerned with the design of new β-lactam antibiotics which cover a wide spectrum of antibacterial activity.[3] This scenario was further substantiated by the discovery that β-lactamases caused resistance against some penicillins and cephalosporins, thus stimulating the search for new drugs which should display enhanced stability towards the β-lactamases.[4] In a recent communication,[5] we presented the first stereoselective synthesis of a 4-(4,5-dihydropyrazol-5-yl)carbonyl-2-azetidinone and the regioisomeric 4-(4,5-dihydropyrazol-4-yl)carbonyl-2-azetidinone. We were intrigued by the chance to incorporate in the same molecule the 2-azetidinone and the pyrazole rings, the latter being found in several compounds which display biological activity as antinflammatory[6] and anti-coagulating[7] factors. As a good way to bring together the above-mentioned fragments we exploited nitrilimine 1,3-dipolar cycloaddition onto the 2-azetidinone bearing an ethylenic dipolarophile bond. To gain better insight about the site-, regio- and stereoselectivity outcome of this methodology, we decided to investigate further the behaviour of 3(*R**)-phenyl-4(*R**)-cinnamoyl-2-azetidinone **1**[5] towards nitrilimines and to undertake the study of the novel 3(*R**)-phenyl-4(*S**)-(4-benzoyl-*E*,*E*-1,3-butadienyl)-2-azetidinone **2** as dipolarophile (Fig. 1).

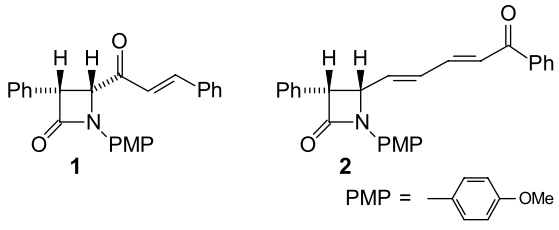

Figure 1.

2. Results and discussion

2.1. Nitrilimine cycloadditions to 3(*R**)-phenyl-4(*R**)-cinnamoyl-2-azetidinone 1

The generation of nitrilimine intermediate **4** was accomplished in situ by treatment of the corresponding hydrazonoyl chloride **3**[8] with an equimolecular amount of silver acetate in dry dioxane at room temperature in the presence of **1**[5]. Besides the recovery of some quantity of unreacted **1**, regioisomeric cycloadducts (4*R**,5′*S**)-**5** and (4*R**,4′*R**)-**6** were obtained (Scheme 1). Reaction times, overall product yields and regioisomeric ratio data are summarised in Table 1. Product separation was achieved by simple silica

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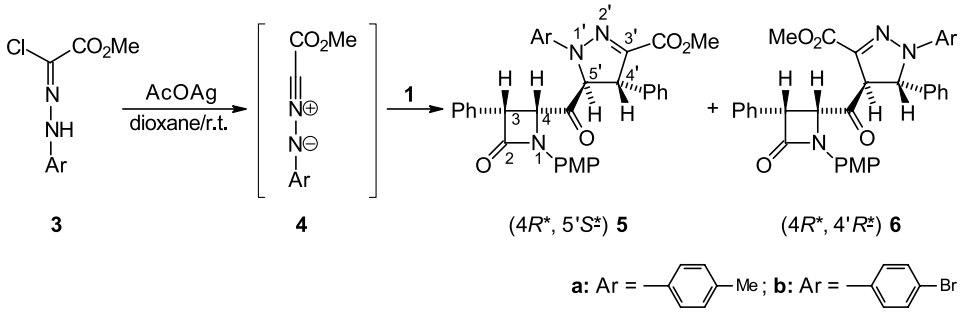


Scheme 1.

Table 1. Cycloadditions between hydrazonoyl chlorides **3** and azetidinone **1**

Reactant	Time (h)	Product and yields (%)[a]			Product ratio[b]
		1	**5**	**6**	**5**:**6**
3a	30	15	56	14	80:20
3b	100	5	71	14	83:17

[a] Isolation yields.
[b] Deduced from ^{1}H NMR analysis of reaction crudes.

gel column chromatography, while analytical and spectroscopic data of the cycloadducts are in full agreement with the structures depicted. As far as cycloaddition regiochemistry is concerned, it reflects that observed in the reaction between nitrilimines and α,β-unsaturated carbonyls.[9] On the other hand, the stereochemical outcome of the cycloaddition deserves some comments. Both major product (4*R**,5′*S**)-**5** and minor product (4*R**,4′*R**)-**6** were detected as single stereoisomers thus making the cycloaddition fully stereoselective. This fact can be understood by close inspection of Dreiding stereomodels of **1**, which clearly shows that the phenyl ring in the 3-position of the 2-azetidinone moiety effectively hinders one of the two diastereofaces of the alkenyl dipolarophile. It needs to be added that the relative configurations of the newly-formed stereocentres of major **5** and minor **6** is dependent upon the conformation of **1**. In our preceding paper[5] we assumed that the free interchange between the four possible conformations of the cinnamoyl fragment in the 4-position of the 2-azetidinone ring of **1** is precluded by severe steric repulsion (Fig. 2), and we concluded that only the *syn* s-*cis* conformation should be the reasonable candidate describing the ground state conformation of **1**. Here, these assumptions find confirmation on the grounds of diffractometric analysis of the novel major cycloadduct (4*R**,5′*S**)-**5b** (Fig. 3).[10]

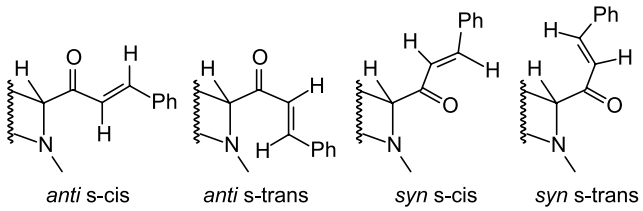


Figure 2.

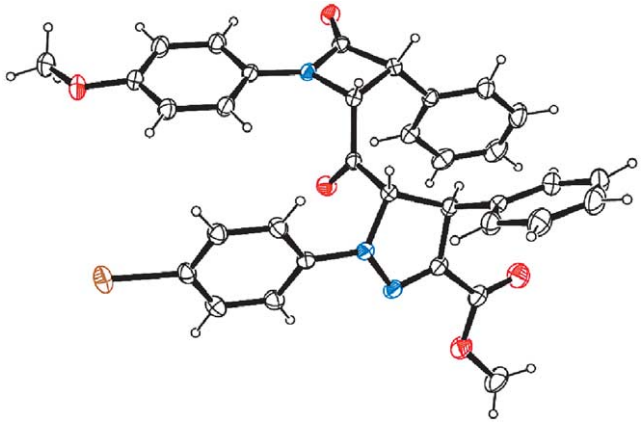
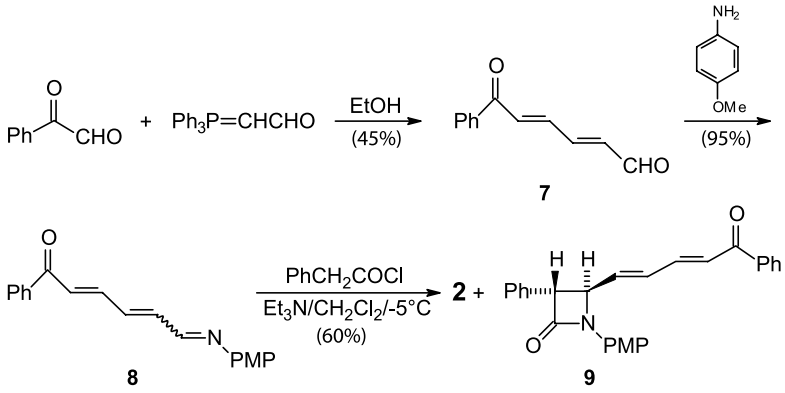


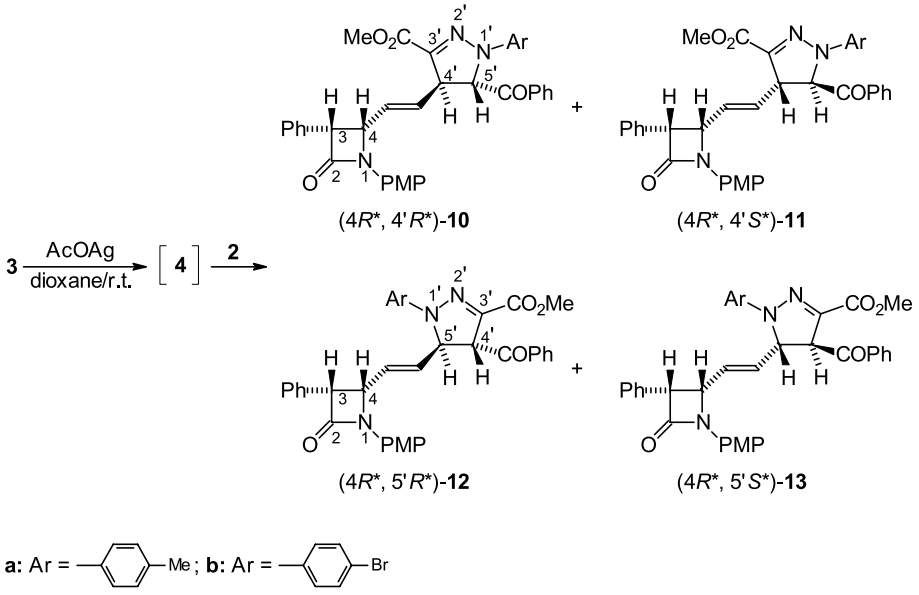
Figure 3. ORTEP plot of (4*R**,5′*S**)-**5b**. Ellipsoid at 20% of probability level; H atoms not to scale. Black=C,H; red=O; blue=N; brown=Br.

2.2. Nitrilimine cycloadditions to 3(*R**)-phenyl-4(*S**)-(4-benzoyl-*E*,*E*-1,3-butadienyl)-2-azetidinone 2

In order to obtain the 2-azetidinone derivative **2**, we followed the three-step synthetic sequence outlined in the Scheme 2. First, phenylglyoxal was submitted to Wittig reaction in the presence of (triphenylphosphoranylidene)-acetaldehyde. The resulting dienal **7**, which was obtained as the only isolable product, was readily converted to the imine derivative **8** which was then reacted with phenylacetyl chloride in the presence of triethylamine, thus following the Staudinger [2+2] cycloaddition protocol. Compound **2** was obtained as the major one (48%) and isolated in the analytically pure state after chromatographic separation from isomeric 3,4-*trans* **9** (12%). Next, 2-azetidinone **2** was treated with hydrazonoyl chlorides **3** as described before with **1**. Since both of the conjugated olefins of **2** are suitable position for dipolar attack, which can proceed with two opposite orientations, both site-, regio- and stereoselectivity phenomena can be involved in their cycloadditions. In fact,



Scheme 2.



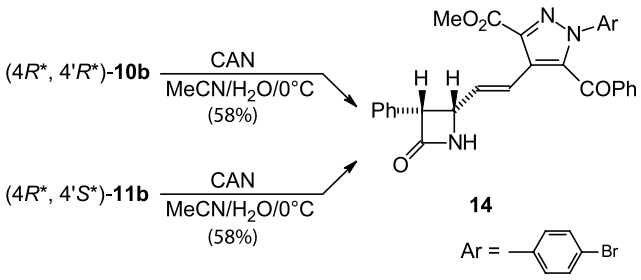
Scheme 3.

Table 2. Cycloadditions between hydrazonoyl chlorides **6** and azetidinone **2**

Reactant	Time (h)	Product and yields (%)[a]				Product ratio[b]
		10	**11**	**12**	**13**	**10**:**11**:**12**:**13**
6a	48	31	31	13	13	35:35:15:15
6b	190	25	25	9	9	37:37:13:13

[a] Isolation yields.
[b] Deduced from ^{1}H NMR analysis of reaction crudes.

1,3-dipolar cycloaddition of nitrilimine **4** gave a complex mixture of the four cycloadducts **10**–**13** (Scheme 3). Reaction times, product yields and product ratio data are given in Table 2. Structural assignment of cycloadducts **10**–**13** was somewhat laborious. ^{1}H NMR spectroscopy of crude reaction products showed the disappearance of the signal due to the α-hydrogen to the benzoyl group of **2**, which resonates as a doublet at 6.91 δ. This indicates that only the activated alkenyl dipolarophile of **2** is involved in cycloaddition, thus making the process fully site-selective. To this point, due to the stereoconservativity typical of 1,3-dipolar cycloadditions, it is possible envisage the formation of up to four regio- and stereoisomeric cycloadducts. After laborious chromatographic separation, the two major products **10b** and **11b** were isolated in the pure state. The latter products were submitted to oxidation with cerium (IV) ammonium nitrate giving the same pyrazole derivative, namely *E*-1-(azetidin-4-yl)-2-(pyrazol-4-yl)-ethylene **14** (Scheme 4). Following this chemical correlation experiment, it can be argued that: (i) major cycloadducts **10** and **11** must be stereoisomers, and (ii) minor cycloadducts **12** and **13** also must be stereoisomers and regioisomeric with



Scheme 4.

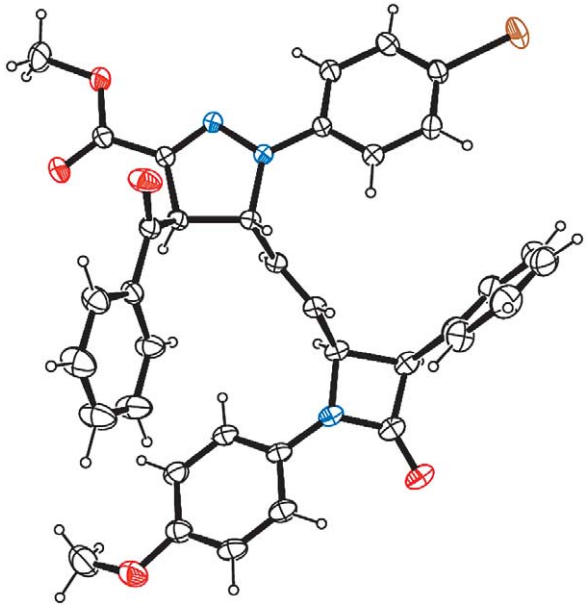


Figure 4. ORTEP plot of (4*R**,5′*R**)-**12b**. Ellipsoid at 20% of probability level; H atoms not to scale. Black = C,H; red = O; blue = N; brown = Br.

respect to **10** and **11**. Slow evaporation of a chloroformic solution of **12b** gave crystals suitable for X-ray diffractometric analysis (Fig. 4)[10] thus enabling us to the unequivocal assignment of structures (4*R**,5′*R**)-**12** and (4*R**,5′*S**)-**13** to the two minor cycloadducts. Structural assignment of major **10** and **11** rely upon NOE experiment. As can be seen from Figure 5, NOE enhancements between H_A–H_B and H_C–H_D occurs in the case of (4*R**,4′*R**)-**10b**, while (4*R**,4′*S**)-**11b** did not show any NOE enhancement. This picture is consistent with the ground state conformations of both major cycloadducts optimised at the AM1[11]

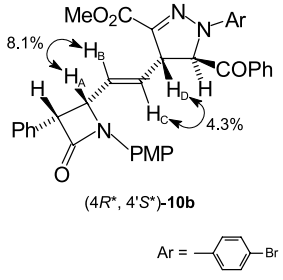


Figure 5.

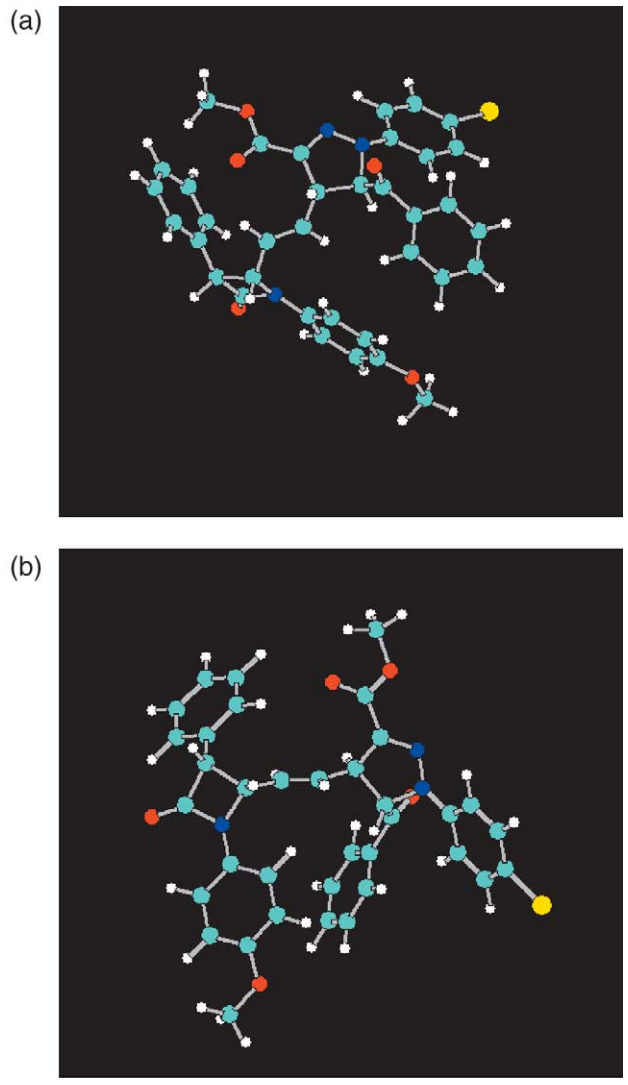


Figure 6. AM1 optimised ground state conformations of the two major cycloadducts: (a) (4*R**,4′*R**)-**10b**; (b) (4*R**,4′*S**)-**11b**.

Table 3. AM1 computed distances H_A–H_B, H_C–H_D of major cycloadducts (4*R**,4′*R**)-**10b** and (4*R**,4′*S**)-**11b**

Product	Distance (Å)	
	H_A–H_B	H_C–H_D
(4*R**,4′*R**)-**10b**	2.56	2.87
(4*R**,4′*S**)-**11b**	3.12	3.13

level (Fig. 6),[12] while H_A–H_B and H_C–H_D computed distances are given in Table 3. As can be inferred from Table 2, nitrilimine cycloaddition to 4-butadienyl-2-azetidinone **2** occurs with a moderate degree of regioselectivity but was not stereoselective. A comparison with the behaviour of 4-cinnamoyl-2-azetidinone **1** suggest that the distance between the reactive dipolarophile and the 2-azetidinone core is critical in determining cycloaddition stereoselectivity. The phenyl ring in the 3-position of the 2-azetidinone ring of **2** cannot hinder one of the two diastereofaces of the outer alkenyl dipolarophile thus causing the lack of stereoselectivity.

3. Conclusions

The site-, regio- and stereoselectivity involved in nitrilimine 1,3-dipolar cycloaddition to highly-functionalised 2-azetidinones have been studied. Although regioselectivities obeys the known rules dictated from FMO theory, stereoselectivies depend upon the length of the tether joining the reactive dipolarophile to the 2-azetidinone core.

4. Experimental

4.1. General

Melting points were determined with a Büchi apparatus in open tubes and are uncorrected. IR spectra were recorded with a Perkin–Elmer 1725× spectrophotometer. Mass spectra were determined with a VG-70EQ apparatus. ^{1}H NMR (300 MHz) spectra were taken with a Bruker AC 300 or a Bruker AMX 300 instrument (in $CDCl_3$ solutions at room temperature). Chemical shifts are given as ppm from tetramethylsilane and *J* values are given in Hz. The NOESY experiments were acquired with 1024 data points for 512 increments, without zero-filling. A relaxation delay (d1) of 2 s and a mixing time (d8) of 800 ms (compound **10b**) or 700 ms (compound **11b**) was used.

4.1.1. 6-Oxo-6-phenyl-hexa-2,4-*E*,*E*-dien-1-al 7. A suspension of methyltriphenylphosphonium chloride (3.64 g, 10.7 mmol) in ethanol (16 mL) was warmed to 50 °C to obtain a clear solution. Triethylamine (1.23 g, 12.2 mmol) was added and the resulting dark solution was warmed to 50 °C for 0.5 h. The mixture was added dropwise to a stirred solution of phenylglyoxal monohydrate (0.74 g, 4.9 mmol) in ethanol (16 mL) under nitrogen athmosphere and then warmed to 70 °C for 1.5 h. The reaction was monitored by TLC (eluent: dichloromethane/ethyl acetate 95:5). Brine (20 mL) was added and the resulting mixture was extracted with dichloromethane (4×20 mL). The organic layer was dried over sodium sulfate and evaporated under reduced pressure giving 6-oxo-6-phenyl-hexa-2,4-*E*,*E*-dien-1-al **7** (0.41 g, 45%) as pale yellow powder, mp 86 °C (from diisopropyl ether). IR (nujol) 1690, 1660, 1615 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.51 (1H, dd, J=15.3, 7.7 Hz), 7.32 (1H, dd, J=15.3, 7.9 Hz), 7.37 (1H, d, J=15.0 Hz), 7.51 (1H, dd, J=15.0, 7.9 Hz), 7.5–7.8 (5H, m), 9.72 (1H, d, J=7.7 Hz); MS *m*/*z* 186 (M^+). Anal. Calcd for $C_{12}H_{10}O_2$: C, 77.40; H, 5.41. Found: C, 77.46; H, 5.46.

4.1.2. *N*-(4-Methoxyphenyl)-1-(5-oxo-5-phenyl-penta-1,3-*E*,*E*-dienyl)methanimine 8. A solution of 4-methoxyaniline (0.30 g, 2.5 mmol) in ethanol (0.75 mL) was added dropwise to **7** (0.46 g, 2.5 mmol) in ethanol (5.0 mL). The mixture was stirred at room temperature for 5 min and the solid material was filtered off giving **8** as yellow powder, mp 108 °C (from ethanol). IR (nujol) 1650, 1590, 1560 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.86 (3H, s), 6.9–7.1 (4H, m), 7.21 (1H, d, J=14.6 Hz), 7.25–7.60 (8H, m), 8.30 (1H, d, J=8.1 Hz); MS *m*/*z* 291 (M^+). Anal. Calcd for $C_{19}H_{17}NO_2$: C, 78.32; H, 5.88; N, 4.81. Found: C, 78.27; H, 5.84; N, 4.75.

4.1.3. 3(*R)-Phenyl-4(*S**)-(4-benzoyl-*E*,*E*−1,3-butadienyl)-2-azetidinone 2 and 3(*R**)-phenyl-4(*R**)-(4-benzoyl-*E*,*E*-1,3-butadienyl)-2-azetidinone 9.** A solution of **8** (0.40 g, 1.4 mmol) and triethylamine (0.61 g, 6.0 mmol) in dry dichloromethane (25 mL) was cooled to −5 °C. Phenylacetyl chloride (0.70 g, 4.5 mmol) in dry dichloromethane (13 mL) was added under nitrogen athmosphere and the resulting mixture was stirred and cooled to 0 °C for 1 h, then at room temperature for 6 h. The reaction was monitored by TLC (eluent: dichloromethane/ethyl acetate 95:5). Brine (20 mL) was added and the resulting mixture was extracted with dichloromethane (2×20 mL). The organic layer was washed with water, dried over sodium sulfate and evaporated under reduced pressure giving a solid. The residue was chromatographed on a silica gel column with *t*-butylmethyl ether/light petroleum 3:2. First fractions gave 3,4-*cis* **2**, further elution gave isomeric 3,4-*trans* **9**.

Compound **2**. (0.27 g, 48%). IR (nujol) 1745, 1660 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.80 (3H, s), 4.86 (1H, d, J=6.0 Hz), 4.93 (1H, dd, J=7.5, 6.0 Hz), 5.81 (1H, dd, J=15.2, 7.5 Hz), 6.55 (1H, dd, J=15.2, 10.7 Hz), 6.8–6.9 (2H, m), 6.92 (1H, d, J=15.0 Hz), 7.14 (1H, dd, J=15.0, 10.7 Hz), 7.4–7.9 (12H, m); MS *m*/*z* 409 (M^+). Anal. Calcd for $C_{27}H_{23}NO_3$: C, 79.19; H, 5.66; N, 3.42. Found: C, 79.15; H, 5.63; N, 3.38.

Compound **9**. (70 mg, 12%). IR (nujol) 1745, 1660 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.79 (3H, s), 4.26 (1H, d, J=2.5 Hz), 4.54 (1H, dd, J=7.7, 2.5 Hz), 6.42 (1H, dd, J=15.2, 7.7 Hz), 6.69 (1H, dd, J=15.2, 10.8 Hz), 6.8–6.9 (4H, m), 7.03 (1H, d, J=15.0 Hz), 7.32 (1H, dd, J=15.0, 10.8 Hz), 7.40–7.95 (10H, m); MS *m*/*z* 409 (M^+). Anal. Calcd for $C_{27}H_{23}NO_3$: C, 79.19; H, 5.66; N, 3.42. Found: C, 79.26; H, 5.70; N, 3.47.

4.1.4. Nitrilimine cycloadditions to 3(*R)-phenyl-4(*R**)-cinnamoyl-2-azetidinone 1 and 3(*R**)-phenyl-4(*S**)-(4-benzoyl-*E*,*E*-1,3-butadienyl)-2-azetidinone 2.** To a solution of **1**[5] or **2** (1.0 mmol) and the appropriate hydrazonoyl chloride **3** (2.0 mmol) in dry dioxane (25 mL) was added silver acetate (0.17 g, 1.0 mmol). The mixture was kept under vigorous stirring in the dark for 24 h at room temperature. Hydrazonoyl chloride **3** (1.0 mmol) and silver acetate (0.5 mmol) were added again, and the mixture was stirred for further 24 h. The reaction was monitored by TLC (eluent: light petroleum/ethyl acetate 65:35). The undissolved material was filtered off and dichloromethane (40 mL) was added. The organic layer was washed firstly with 5% aqueous sodium hydrogencarbonate, then with water (25 mL), dried over sodium sulfate and evaporated under reduced pressure. The residue was chromatographed on a silica gel column with *t*-butylmethyl ether/light petroleum 65:35.

In the case of compounds **5** and **6** (from 2-azetidinone **1**) first fractions gave major **5**, further elution gave minor **6**.

Compounds (4*R**,5′*S**)-**5b** and (4*R**,4′*R**)-**6b** were obtained as previously described.[5]

Compound (4*R**,5′*S**)-**5b**. (0.45 g, 71%) as yellow prisms, mp 203 °C (from diisopropyl ether). IR (nujol) 1750, 1735 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.67 (3H, s), 3.81 (3H,

s), 4.05 (1H, d, $J=3.3$ Hz), 4.65 (1H, d, $J=3.3$ Hz), 4.84 (1H, d, $J=6.3$ Hz), 5.09 (1H, d, $J=6.3$ Hz), 6.8–7.5 (18H, m); MS *m/z* 638 (M^+). Anal. Calcd for $C_{34}H_{28}BrN_3O_5$: C, 63.96; H, 4.42; N, 6.58. Found: C, 64.01; H, 4.45; N, 6.63.

Compound (4*R**,4′*R**)-**6b**. (0.09 g, 14%) as pale yellow powder, mp 182 °C (from diisopropyl ether). IR (nujol) 1745, 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.73 (3H, s), 3.80 (3H, s), 4.95 (1H, d, $J=6.6$ Hz), 5.31 (1H, d, $J=4.1$ Hz), 5.86 (1H, d, $J=6.6$ Hz), 6.32 (1H, d, $J=4.1$ Hz), 6.8–7.5 (18H, m); MS *m/z* 638 (M^+). Anal. Calcd for $C_{34}H_{28}BrN_3O_5$: C, 63.96; H, 4.42; N, 6.58. Found: C, 63.91; H, 4.46; N, 6.52.

In the case of compounds **10a**–**13a** (from 2-azetidinone **2**), first fractions gave major **10a**, further elution gave a mixture of **11a**–**13a**.

Compound (4*R**,4′*R**)-**10a**. (0.19 g, 31%). IR (nujol) 1740, 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.29 (3H, s), 3.74 (3H, s), 3.82 (3H, s), 3.85 (1H, dd, $J=8.5$, 4.4 Hz), 4.82–4.88 (2H, m), 5.12 (1H, d, $J=4.4$ Hz), 5.45 (1H, dd, $J=15.7$, 5.0 Hz), 6.02 (1H, dd, $J=15.7$, 8.5 Hz), 6.8–7.6 (18H, m); MS *m/z* 599 (M^+). Anal. Calcd for $C_{37}H_{33}N_3O_5$: C, 74.11; H, 5.55; N, 7.01. Found: C, 74.16; H, 5.58; N, 7.08.

The mixture of compounds **11a**–**13a** was chromatographed on a silica gel column with ethyl acetate/light petroleum 3:2. First fractions gave major **11a**, further elution gave a mixture of minor **12a** and **13a**.

Compound (4*R**,4′*S**)-**11a**. (0.19 g, 31%). IR (nujol) 1750, 1735 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.30 (3H, s), 3.72 (3H, s), 3.81 (3H, s), 3.89 (1H, dd, $J=8.0$, 4.0 Hz), 4.80–4.86 (2H, m), 5.19 (1H, d, $J=4.0$ Hz), 5.50 (1H, dd, $J=15.6$, 5.3 Hz), 6.01 (1H, dd, $J=15.6$, 8.0 Hz), 6.7–7.8 (18H, m); MS *m/z* 599 (M^+). Anal. Calcd for $C_{37}H_{33}N_3O_5$: C, 74.11; H, 5.55; N, 7.01. Found: C, 74.08; H, 5.51; N, 6.94.

Compounds (4*R**,5′*R**)-**12a** and (4*R**,5′*S**)-**13a** (156 mg, 26%) were as 1:1 mixture on the basis of ^1H NMR spectrum. Diagnostic signals were at δ 4.42 (1H, d, $J=5.0$ Hz), first minor diastereoisomer, and at δ 4.57 (1H, d, $J=5.5$ Hz), second minor diastereoisomer.

In the case of compounds **10b**–**13b** (from 2-azetidinone **2**), first fractions gave a mixture of major **10b** and minor **13b**, further elution gave a mixture of major **11b** and minor **12b**.

The mixture of compounds **10b** and **13b** was chromatographed on a silica gel column with dichloromethane/light petroleum 9:1. First fractions gave major **10b**, further elution gave minor **13b**.

Compound (4*R**,4′*R**)-**10b**. (0.17 g, 25%). IR (nujol) 1745, 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.81 (3H, s), 3.84 (3H, s), 3.87 (1H, dd, $J=7.9$, 3.9 Hz), 4.82–4.88 (2H, m), 5.14 (1H, d, $J=3.9$ Hz), 5.50 (1H, dd, $J=15.7$, 5.2 Hz), 6.01 (1H, dd, $J=15.7$, 7.9 Hz), 6.9–7.7 (18H, m); MS *m/z* 664 (M^+). Anal. Calcd for $C_{36}H_{30}BrN_3O_5$: C, 65.07; H, 4.55; N, 6.32. Found: C, 65.12; H, 4.59; N, 6.39.

Compound (4*R**,5′*S**)-**13b**. (60 mg, 9%). IR (nujol) 1740, 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.73 (6H, s), 4.50 (1H, d, $J=4.9$ Hz), 4.79 (1H, dd, $J=7.5$, 4.9 Hz), 4.80–4.85 (2H, m), 5.50 (1H, dd, $J=15.7$, 3.8 Hz), 5.84 (1H, dd, $J=15.7$, 7.5 Hz), 6.9–7.7 (18H, m); MS *m/z* 664 (M^+). Anal. Calcd for $C_{36}H_{30}BrN_3O_5$: C, 65.07; H, 4.55; N, 6.32. Found: C, 65.10; H, 4.51; N, 6.27.

The mixture of compounds **11b** and **12b** was crystallised with chloroform. Minor **12b** was obtained as a crystalline solid while the mother liquor contained major **11b**.

Compound (4*R**,4′*S**)-**11b**. (0.17 g, 25%). IR (nujol) 1745, 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.74 (3H, s), 3.82 (3H, s), 3.86 (1H, dd, $J=8.5$, 4.3 Hz), 4.85–4.90 (2H, m), 5.07 (1H, d, $J=4.3$ Hz), 5.45 (1H, dd, $J=15.7$, 4.9 Hz), 6.02 (1H, dd, $J=15.7$, 8.5 Hz), 6.9–7.6 (18H, m); MS *m/z* 664 (M^+). Anal. Calcd for $C_{36}H_{30}BrN_3O_5$: C, 65.07; H, 4.55; N, 6.32. Found: C, 65.14; H, 4.58; N, 6.37.

Compound (4*R**,5′*R**)-**12b**. (60 mg, 9%). Mp 186 °C (from chloroform). IR (nujol) 1750, 1735 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.83 (6H, s), 4.58 (1H, d, $J=5.2$ Hz), 4.75 (1H, dd, $J=7.9$, 5.2 Hz), 4.80–4.85 (2H, m), 5.48 (1H, dd, $J=15.7$, 3.5 Hz), 5.83 (1H, dd, $J=15.7$, 7.9 Hz), 6.8–7.7 (18H, m); MS *m/z* 664 (M^+). Anal. Calcd for $C_{36}H_{30}BrN_3O_5$: C, 65.07; H, 4.55; N, 6.32. Found: C, 65.03; H, 4.55; N, 6.36.

4.1.5. Cerium(IV) ammonium nitrate oxidation of major cycloadducts 10b and 11b. A solution of **10b** or **11b** (0.17 g, 0.26 mmol) in acetonitrile (15 mL) was cooled to 0 °C. Cerium(IV) ammonium nitrate (0.55 g, 1.0 mmol) in water (8.0 mL) was added dropwise under vigorous stirring and ice-cooling. The reaction was monitored by TLC (eluent: light petroleum/ethyl acetate 3:2). After 2 h water (15 mL) and saturated aqueous sodium dithionite (10 mL) were added. The resulting mixture was extracted with ethyl acetate (4×25 mL), the organic layer was washed with water (2×25 mL) and dried over sodium sulfate. Evaporation of the solvent under reduced pressure gave **14** as a dark oil.

Compound **14**. (85 mg, 58%). IR (nujol) 1750, 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.99 (3H, s), 4.47 (1H, dd, $J=7.7$, 5.2 Hz), 4.62 (1H, d, $J=5.2$ Hz), 5.50 (1H, dd, $J=16.2$, 7.7 Hz), 5.73 (1H, br s), 6.95 (1H, d, $J=16.2$ Hz), 7.1–7.1 (14H, m); MS *m/z* 572 (M^+). Anal. Calcd for $C_{29}H_{22}BrN_3O_4$: C, 62.60; H, 3.99; N, 7.55. Found: C, 62.58; H, 3.97; N, 7.58.

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2-Bromoethyl glycosides for synthesis of glycoconjugates on solid support

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Abstract—2-Bromoethyl glycosides can easily and in high yields be transformed into sulfones by treatment with a suitable thiol followed by oxidation with *m*CPBA. The observation that the so formed sulfones were cleaved by treatment with NaOMe/MeOH was used to design a new safety catch linker for synthesis of glycoconjugates on solid support.

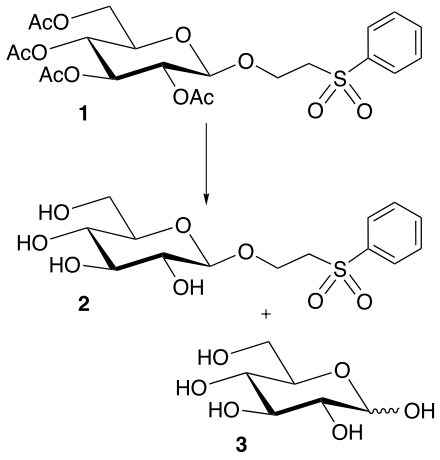
1. Introduction

Since the introduction of solid phase peptide synthesis by Merrifield in 1963,[1] polymer-supported synthesis has become the method of choice for synthesis of peptides and oligonucleotides. The first investigations into solid-phase oligosaccharide synthesis were conducted in the early 1970s and, whilst some groundbreaking work was done, progress was halted by the lack of powerful glycosylating agents, diverse protecting groups and on-bead analytical techniques.[2] As advances were made in the solution phase synthesis of complex carbohydrates, new protecting groups, and selective glycosylating agents became available during the 1990s thus fuelling the interest in solid phase oligosaccharide synthesis. Also, on-bead analytical techniques such as high-resolution magic angle spinning NMR and FT-IR became widely available.

Presently, complex oligosaccharides are synthesized on solid phase using a wide variety of linker systems, glycosyl donors and acceptors, promoter systems and strategies.[2] A number of different linker systems suitable for solid phase oligosaccharide synthesis are available with differences in stability, cleavage reagents and the group introduced upon cleavage. Notable examples are silyl ether linkers,[3,4] acid- and base-labile linkers such as amino-functionalized Rink resin[5] and a benzylidene acetal-type linker to Wang aldehyde resin.[6] Also, thioglycoside linkers have been used, as well as linkers cleaved by oxidation, hydrogenation, photocleavage and even olefin metathesis.[2] Even though solid phase oligosaccharide synthesis is becoming more advanced and automated synthesis is becoming a realistic goal[2,7] further linker systems are needed. Especially attractive are safety-catch linkers, that is, linkers that are stable to most conditions until activated by, for example, oxidation or reduction.[8,9]

2-Bromoethyl was introduced as an anomeric protecting group that can be transformed into a spacer for glycoconjugates.[10] The 2-bromoethyl group is easily introduced by normal glycosylation of 2-bromoethanol and is stable towards standard reagents used in carbohydrate synthesis.[11] It shows unusual stability towards anomerization.[12]

The formed glycosides can then be alkylated using different thiols by treatment with, for example, Cs_2CO_3 in DMF.[13]



Scheme 1. Deprotection of **1** under basic conditions (0.05 M NaOMe–MeOH) gave the desired product **2** as well as glucose (**3**).

Keywords: Solid support; Glycoconjugates; Safety catch linker.
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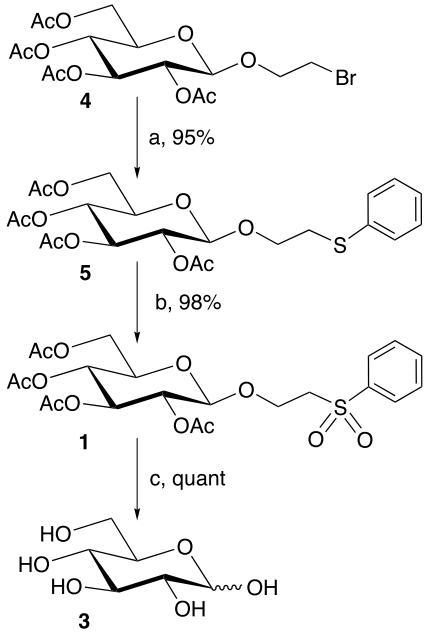
These thioethers are easily oxidized to sulfones using *m*-chloroperbenzoic acid (*m*CPBA). An attempt to deacetylate the sulfone **1** (Scheme 1) under basic conditions (0.05 M NaOMe–MeOH) gave the desired product **2** as well as a small amount of free glucose (**3**), that is, the aglycon was cleaved off. We realized that 2-bromoethyl glycosides can be coupled to solid supported thiols and thereby be used for solid phase glycoside synthesis.

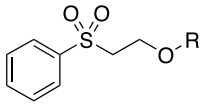
2. Cleavage of bromoethyl glycosides in solution

Before performing the reaction on solid support, an investigation of the system was performed in solution. As a model for the linker, compound **1** was chosen. The model compound was synthesized from 2-bromoethyl tetra-*O*-acetyl-β-D-glucopyranoside **4**[14,15] in two steps (Scheme 2). Treatment of **4** with thiophenol and Cs_2CO_3 gave **5** in 95% yield. The sulfide **5** was then oxidized to the corresponding sulfone **1** in 98% yield using *m*CPBA.



Scheme 2. (a) Thiophenol, Cs_2CO_3, DMF, 2 h. (b) *m*CPBA, EtOAc, 30 min. (c) NaOMe–MeOH, 4–56 h.

It was anticipated that basic treatment of compound **1** would result in abstraction of an α-proton (α relative to the sulfone), leading to an elimination reaction with concomitant expulsion of the glucoside. Thus, treatment of **1** with NaOMe–MeOH (1.0 M) smoothly furnished an α/β-mixture of D-glucose in quantitative yield within 4 h. Complete cleavage was likewise obtained with lower concentrations of NaOMe, although requiring longer reaction times. As a lower limit a 0.05 M solution was used, resulting in a reaction time of 56 h. However, investigation of the cleavage products showed that compound **6**[16] (Fig. 1) was formed instead of the expected alkene.



6: R = CH_3
7: R = CH_2CH_3

Figure 1. Cleavage products formed during alkoxide treatment of **1**.

Performing the reaction in NaOEt–EtOH (1.0 M) similarly gave D-glucose in quantitative yield, along with compound **7**[16] (Fig. 1). An NMR-study was performed in order to elucidate the reaction mechanism. The model compound **1** was thus treated with a 0.7 M $NaOCD_3$–CD_3OD-solution and NMR-spectra were recorded over a period of 300 min. After 1 min complete deacetylation was observed along with about 50% exchange of the protons in α-position to the sulfone. The exchange of α-protons was complete within 5 min. The ratio of the integral of the anomeric NMR-signals for the formed glucose compared to the total integral of the anomeric protons of glucose (**3**) and deacetylated bromoethyl glucoside (**2**) was measured and is shown in Figure 2. About 10% glucose was formed within 5 min, whereas complete conversion required 300 min. During the experiment no signals corresponding to alkene protons were observed.

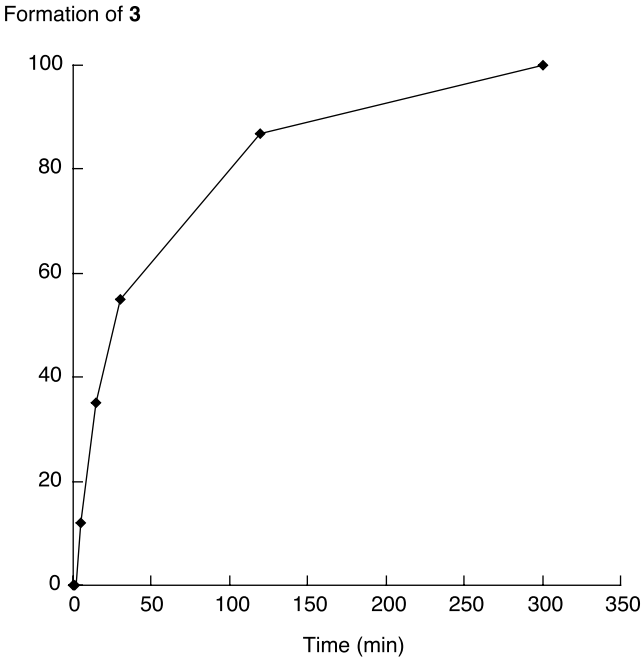
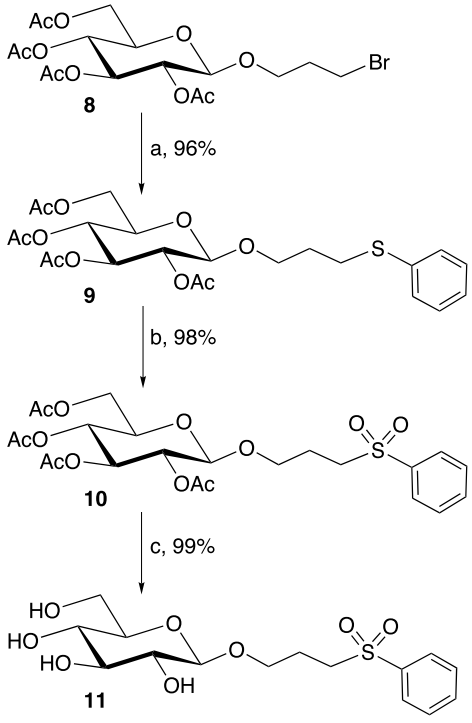


Figure 2. Formation of glucose (**3**) by treating the sulfone **1** with 0.7 M $NaOCD_3$–CD_3OD. The graph shows the percentage of the integral for the NMR-signals of the anomeric protons of glucose (**3**) compared to the total integral for the anomeric protons of glucose (**3**) and deacetylated bromoethyl glycoside (**2**).

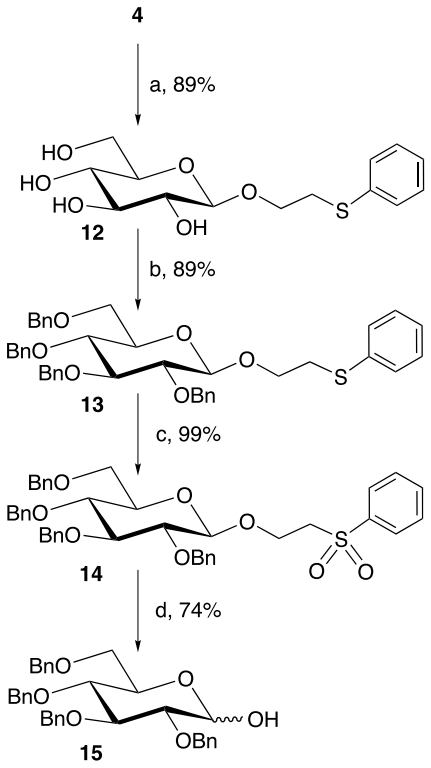
The fact that the deuterium–hydrogen exchange of the protons in α-position to the sulfone is much faster than formation of glucose indicates that the reaction follows a reversible carbanion elimination $(E1cB)_R$, followed by a fast addition of the nucleophile (methoxide or ethoxide). This is supported by observations in similar systems, $PhSO_2CH_2CH_2Z$, with leaving groups (Z) other than carbohydrates.[16]

However, to disprove an S_N2-mechanism, we performed a second experiment where a glucoside carrying a propyl linker (compound **10**) was synthesized in two steps from the known 2-bromopropyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside[15] (**8**, Scheme 3), in a manner similar to that described for compound **1**. Treatment of **10** with NaOMe–MeOH (1.0 M) gave an almost quantitative yield of compound **11**; hence no cleavage product was observed.



Scheme 3. (a) Thiophenol, Cs_2CO_3, DMF, 1 h. (b) *m*CPBA, EtOAc, 0.5 h. (c) NaOMe–MeOH, CH_2Cl_2, 24 h.

As a final experiment compound **15** was synthesized from **4** in four steps, in order to verify the generality of the cleavage reaction. Compound **4** was deacetylated and subsequently benzylated under basic conditions to give **13**. The sulfide **13** was then oxidized to the sulfone **14**. Treatment of **14** with NaOMe–MeOH (1.0 M) gave compound **15** in 74% yield together with compound **6** (Scheme 4).

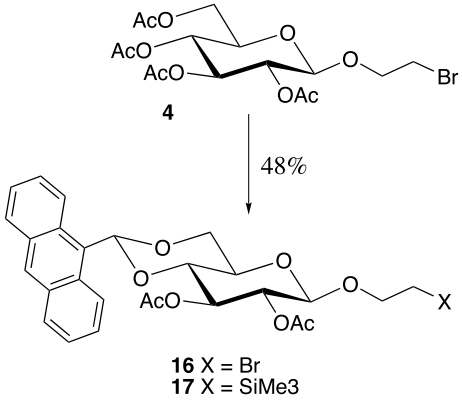


Scheme 4. (a) NaOMe-MeOH, 45 min. (b) DMF, NaH, BnBr, 1 h. (c) *m*CPBA, EtOAc, 0.5 h. (d) NaOMe–MeOH, 22 h.

3. Use of 2-bromoethyl glycosides on solid support

To evaluate the bromoethyl group as a linker for solid phase carbohydrate synthesis we performed a series of experiments in order to optimize the coupling of the glycosides to thiol resin. Cesium carbonate was used as base in solution phase but the poor solubility in DMF makes it less suitable for solid phase reactions. Instead the non-nucleophilic base 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) was investigated and turned out to work well.

To follow the reactions we used the newly developed anthraldehyde protective group which shows a strong UV-absorbance at around 365 nm and also a strong fluorescence.[17] Compound **4** was deprotected using NaOMe–MeOH, transformed into the fluorescent acetal by treatment with anthraldehyde dimethyl acetal, and then acetylated using standard conditions to give compound **16** (Scheme 5).



Scheme 5. (i) NaOMe–MeOH–CH_2Cl_2, 20 min. (ii) Anthraldehyde dimethyl acetal, MeCN, *p*TSA, overnight. (iii) Pyridine, Ac_2O, overnight.

We decided to use a relatively inexpensive scavenger resin, 3-(3-mercaptophenyl)propanamidomethylpolystyrene resin, as solid support. The resin was first treated with tributyl phosphine (0.7 M in THF–H_2O 95:5) to reduce any disulfides and then swelled in DMF. DBU (1 equiv to resin substitution) was then added followed by different equivalents of compound **16**. Samples were taken from the solution at various time intervals, diluted with MeCN and the absorbance measured at 364 nm. Treatment with 0.5 equiv (to resin substitution) of **16** resulted in an almost complete loss of absorbance in about 10 min, indicating that all material was coupled to the resin. Addition of 1.0 equiv of **16** resulted in about 70% reduction of the original

absorbance, which gives an indication of the practically useful loading of the resin for this coupling (Fig. 3).

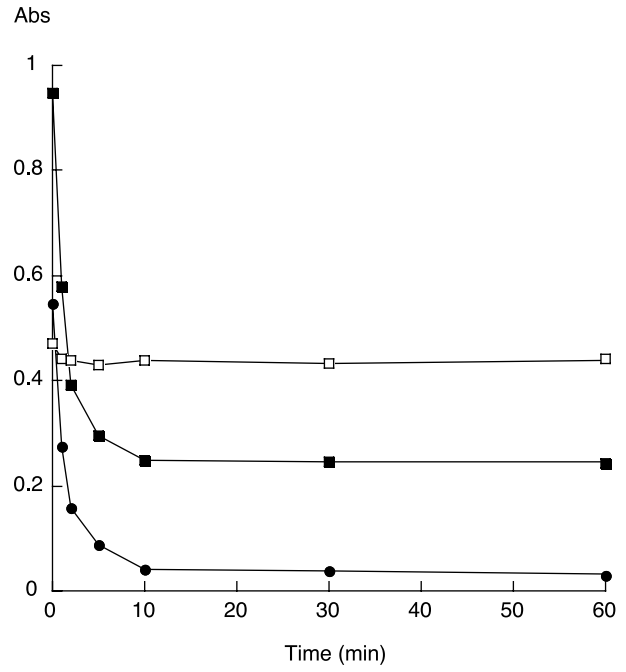


Figure 3. Coupling of **16** to thiophenyl resin using 0.5 equiv (●) and 1.0 equiv (■). As a control the resin was treated with 0.5 equiv of the unreactive **17** (□). Samples were taken from the solution at various time intervals and diluted with acetonitrile and the absorbance measured at 364 nm.

As a control, compound **17**[17] with an unreactive trimethylsilylethyl group was subjected to the same conditions and showed, as expected, only a minute drop in absorbance due to dilution but no coupling.

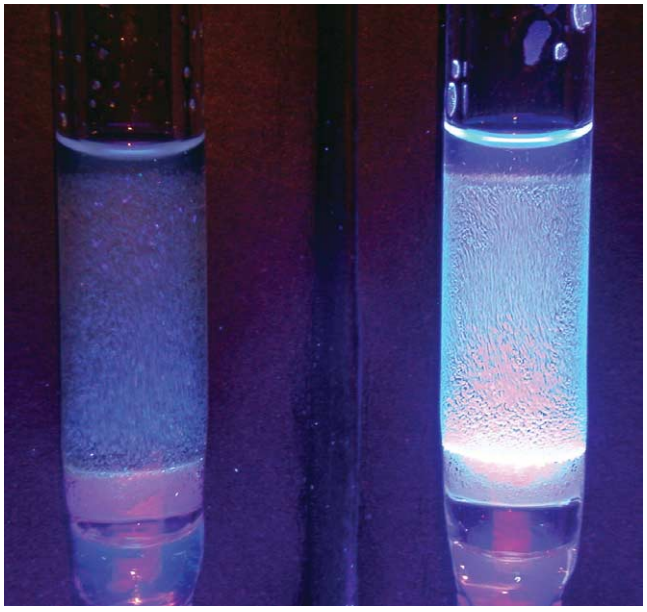


Figure 4. Visual comparison between resin treated with the unreactive compound **17** (left) and the reactive **16** (right) illuminated with long wave UV-radiation (365 nm). The resin treated with **16** shows a strong fluorescence.

To verify that compound **16** had been coupled to the resin the two samples, treated with 0.5 equiv of **16** and **17**, respectively, were washed with several volumes of DMF and CH_2Cl_2 and then swelled in a mixture of MeOH and CH_2Cl_2 and illuminated with long wave UV-radiation (365 nm). As expected, only the resin treated with **16** showed a strong fluorescence (Fig. 4).

The stability of the thioethyl linker was investigated by subjecting compound **5** or **12** to standard conditions used in synthetic carbohydrate chemistry, such as basic, acidic or reductive protective group manipulations as well as typical glycosylation conditions (NIS–TfOH or $BF_3 \cdot OEt_2$). The results, summarized in Table 1, show that the thioethyl linker is stable to typical conditions. However, treatment with $BF_3 \cdot OEt_2$ caused anomerization (16%).

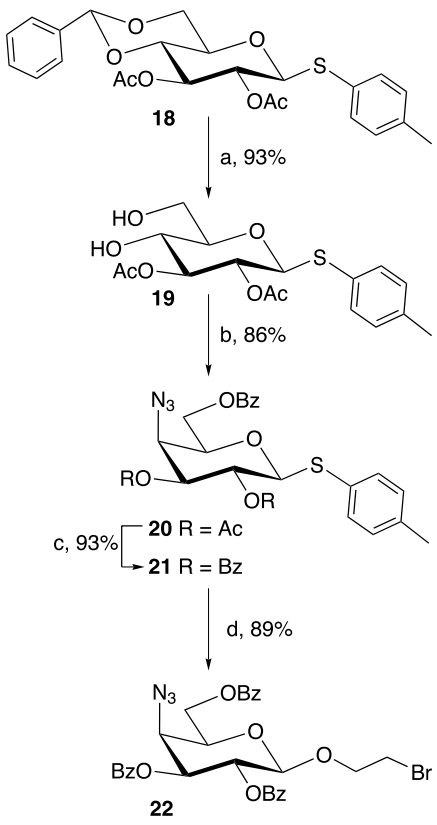
Table 1. Stability of the thioethyl linker. Compound **5** or **12** was subjected to the conditions below. The samples were purified and analyzed using NMR

Reaction	Conditions	Product
Acylation	Pyridine, Ac_2O, 16 h	**5**
Deacylation	NaOMe-MeOH (0.05 M), 1 h	**12**
	HCl-MeOH, 16 h	**12**
Acetal formation	$PhCH(OMe)_2$, *p*TsOH, CH_3CN, 3 h	**5**
Acetal cleavage	AcOH (80%), 90 °C, 3 h	**5**
Benzylation	BnBr, NaH, DMF, 16 h	**13**
Debenzylation	Pd-C (10%), AcOH, H_2 (500 psi), 2 h	**5**
Glycosylation	NIS, TfOH, MS-AW 300, CH_2Cl_2, 0 °C, 30 min	**5**
	BF_3OEt_2, CH_2Cl_2, 1 h	**5** (α/β 1:5)

To estimate the possible overall yield using the bromoethyl linker we coupled compound **4** (0.5 equiv to resin substitution) to the resin using DBU as base. Methyl iodide was then added to cap the residual thiol groups and the resin was washed and the sulfide oxidized to sulfone using *m*CPBA. The resin was again washed and then cleaved by treatment with 0.2 M NaOMe–MeOH–CH_2Cl_2 overnight to give glucose in an excellent 55% yield after purification.

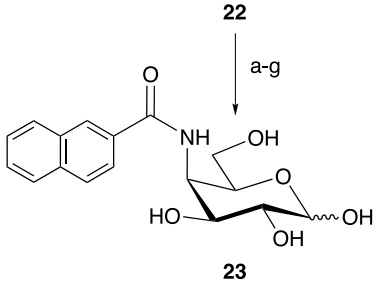
With a working protocol for using bromoethyl glycosides on solid support we decided to illustrate the usefulness of this novel linker with a more advanced compound. Compound **22** was synthesized in four steps from the known compound **18**[18] (Scheme 6). The benzylidene acetal protecting group of compound **18** was cleaved off using 80% AcOH at 90 °C. In a one-pot procedure the primary hydroxyl group of the formed diol **19** was selectively benzoylated at −78 °C and the secondary hydroxyl group was then transformed into a trifluoromethanesulfonate and consecutively inverted using NaN_3 in DMF. The total yield for this conversion was 86%. All attempts to glycosylate compound **20** using 2-bromoethanol resulted either in de-O-acetylation of position 2 (using NIS and TMSOTf) or formation of the chloro sugar (using ICl and AgOTf).[19] Instead compound **20** was de-O-acetylated and then O-benzoylated. The benzoylated compound was easily glycosylated using NIS and TMSOTf to give **22** in 89% yield.[20]

Compound **22** was coupled to the thiol resin by the standard procedure. The benzoyl protecting groups were removed by



Scheme 6. (a) AcOH (80%, aq), 90 °C. (b) CH_2Cl_2, pyridine, BzCl, Tf_2O, then NaN_3, DMF. (c) NaOMe-MeOH, 2 h, then BzCl, pyridine, DMAP overnight. (d) CH_2Cl_2, 2-bromoethanol, NIS, TMSOTf, MS AW-300.

treatment with NaOMe–MeOH (0.05 M) for 1 h. The azide was then reduced using DTT–DBU–DMF[21] and condensed with 2-naphthoyl chloride. The sulfide was then oxidized to the sulfone and treated with NaOMe–MeOH–CH_2Cl_2 to give compound **23** as an anomeric mixture in 27% yield after purification, a recovery comparable to other methods for synthesis of glycoconjugates on solid support (Scheme 7).[2]



Scheme 7. (a) DMF, DBU, thiol resin. (b) DMF, DBU, MeI. (c) NaOMe-MeOH-CH_2Cl_2 (0.05 M). (d) DTT, DMF, DBU. (e) DMF, pyridine, 2-naphthoyl chloride. (f) *m*CPBA, CH_2Cl_2. (g) NaOMe-MeOH, CH_2Cl_2 (0.2 M).

4. Conclusion

We have shown that 2-bromoethyl glycosides can easily be transformed into sulfones which can be cleaved by treatment with NaOMe–MeOH to yield hemiacetals. We propose that the reaction follows a reversible carbanion elimination $(E1cB)_R$, followed by a fast addition of the nucleophile. We have also shown that 2-bromoethyl glycosides can be coupled to solid supported thiols and thereby be used for synthesis of glycoconjugates on solid support.

5. Experimental

5.1. General

The structures of all new compounds were determined by careful NMR analysis, including COSY, NOESY, HETCOR, and long-range HETCOR. NMR-spectra were recorded with 300 and 400 MHz instruments. Chemical shifts are given in ppm downfield from the signal for Me_4Si, with reference to internal $CHCl_3$ or MeOH. All new compounds were determined to be >95% pure by ^1H NMR spectroscopy. Molecular sieves were activated by heating under vacuum. CH_2Cl_2 and MeCN were dried by distillation from CaH_2, DMF was distilled. Column chromatography was performed on SiO_2 (Matrex LC-gel; 60A, 35-70 MY, Grace), and TLC on Merck SiO_2 60 F_{256}. 3-(3-Mercaptophenyl)propanamidomethylpolystyrene was purchased from Argonaut Technologies. Compounds **4**,[15] **8**,[15] **17**,[17] and **18**[18] were prepared as described in the literature. Compounds **3** and **15** are commercially available.

5.1.1. 2-(Phenylsulfonyl)ethyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (1). To a solution of **5** (490 mg, 0.93 mmol) in EtOAc (32 mL) was added *m*CPBA (60%, 590 mg) and the resulting mixture was stirred at room temperature. After 30 min, the mixture was filtered through a short column of alumina, concentrated, and chromatographed (SiO_2, heptane–EtOAc, 1:2) to give **1** as a white solid (512 mg, 98%). $[\alpha]_D^{20} = -9.4$ (*c* 1.2, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 7.55–8.00 (m, 5H, Ar), 5.17 (t, 1H, $J=9.5$ Hz, H-3), 5.01 (t, 1H, $J=9.8$ Hz, H-4), 4.83 (dd, 1H, $J=9.6$, 8.0 Hz, H-2), 4.51 (d, 1H, $J=8.0$ Hz, H-1), 4.23 (dd, 1H, $J=12.3$, 5.0 Hz, H-6), 4.09–4.16 (m, 2H, H-6, CH_2), 3.98–4.06 (m, 1H, CH_2), 3.68 (ddd, 1H, $J=10.0$, 5.0, 2.4 Hz, H-5), 3.35–3.50 (m, 2H, CH_2), 2.10, 2.04, 2.03, 1.99 (s, 3H each, OAc). ^{13}C NMR ($CDCl_3$): δ 170.79, 170.37, 169.60, 169.58, 139.71, 134.15, 129.52, 128.24, 72.79, 72.12, 71.05, 68.39, 63.28, 62.01, 56.38, 20.94, 20.89, 20.78. HRMS calcd for $C_{22}H_{28}O_{12}S$ (M+Na) 539.1199, found 539.1206.

5.1.2. D-Glucose (3). To a solution of **1** (15 mg, 0.029 mmol) in MeOH (1.28 mL) was added NaOMe (0.067 mL, 1 M in MeOH) and the resulting mixture was stirred at room temperature. After 56 h AcOH (5% in MeOH) was added until neutral solution (moist pH-paper). The mixture was concentrated and chromatographed (SiO_2, CH_2Cl_2–MeOH–H_2O, 66:33:4→10:20:1) to give **3** as a white solid (4.9 mg, 94%) and **6** as a clear oil (5.8 mg, 99%).

5.1.3. 2-(Phenylthio)ethyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (5). To a solution of 2-bromoethyl-2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (**4**) (92 mg, 0.20 mmol) in DMF (4 mL) were added thiophenol (0.038 mL,

0.36 mmol) and Cs_2CO_3 (120 mg, 0.36 mmol) and the resulting mixture was stirred at room temperature. After 2 h the reaction mixture was diluted with CH_2Cl_2, washed with water, dried ($MgSO_4$), concentrated, co-concentrated with toluene and chromatographed (SiO_2, toluene–acetone, 10:1) to give **5** as a white solid (93 mg, 95%). $[\alpha]_D^{20} = -9.1$ (*c* 1.1, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 7.10–7.30 (m, 5H, Ar), 5.13 (t, 1H, $J=9.5$ Hz, H-3), 5.01 (t, 1H, $J=9.8$ Hz, H-4), 4.93 (dd, 1H, $J=9.6$, 8.0 Hz, H-2), 4.45 (d, 1H, $J=8.0$ Hz, H-1), 4.17 (dd, 1H, $J=12.3$, 4.8 Hz, H-6), 4.05 (dd, 1H, $J=12.3$, 2.4 Hz, H-6), 3.94 (ddd, 1H, $J=10.4$, 7.7, 5.5 Hz, CH_2), 3.57–3.65 (m, 2H, H-5, CH_2), 2.97–3.07 (m, 2H, CH_2), 2.00, 1.98, 1.95, 1.94 (s, 3H each, OAc). ^{13}C NMR ($CDCl_3$): δ 170.86, 170.49, 169.60, 135.67, 129.84, 129.25, 126.65, 101.22, 72.93, 72.06, 71.35, 68.87, 68.54, 62.09, 33.45, 20.94, 20.82, 20.80. HRMS calcd for $C_{22}H_{28}O_{10}S$ (M+Na) 507.1301, found 507.1300.

5.1.4. Deprotection study of 2-(phenylsulfonyl)ethyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (1). Compound **1** (10 mg, 0.019 mmol) was dissolved in CD_3OD (1.0 mL) and the mixture was added to an NMR-tube and an NMR-spectrum was recorded. CD_3ONa (0.075 mL, 1 M in CD_3OD) was added and NMR-spectra were recorded after 1, 15, 30, 120, and 300 min, respectively. After 1 min, **1** was completely deacylated and the shift of the anomeric proton was 4.23 ppm. The amount cleaved product was determined as the percentage of the integral for the NMR-signals of the anomeric protons of **3** (5.18 and 4.62 ppm) compared to the total integral for the anomeric protons of glucose and deacetylated bromoethyl glycoside.

5.1.5. 3-(Phenylthio)propyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (9). Thiophenol (0.055 mL, 0.38 mmol) and Cs_2CO_3 (124 mg, 0.38 mmol) were added to a solution of **8** (120 mg, 0.26 mmol) in DMF (5 mL) and the resulting mixture was stirred at room temperature. After 1 h the reaction mixture was diluted with CH_2Cl_2, washed with water, dried ($MgSO_4$), concentrated, co-concentrated with toluene and chromatographed (SiO_2, heptane–EtOAc, 3:1) to give **9** as a pale yellow oil (135 mg, 96%). $[\alpha]_D^{20} = +3.4$ (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 7.08–7.26 (m, 5H, Ar), 5.13 (t, 1H, $J=9.5$ Hz, H-3), 5.02 (t, 1H, $J=9.8$ Hz, H-4), 4.93 (dd, 1H, $J=9.6$, 8.0 Hz, H-2), 4.42 (d, 1H, $J=8.0$ Hz, H-1), 4.19 (dd, 1H, $J=12.3$, 4.7 Hz, H-6), 4.06 (dd, 1H, $J=12.3$, 2.4 Hz, H-6), 3.88 (dt, 1H, $J=9.7$, 5.5 Hz, CH_2), 3.55–3.65 (m, 2H, H-5, CH_2), 2.85–3.95 (m, 2H, CH_2), 2.01, 1.95 (s, 3H each, OAc), 1.93 (s, 6H, OAc), 1.75–1.90 (m, 2H, CH_2). ^{13}C NMR ($CDCl_3$): δ 171.11, 170.71, 169.83, 169.75, 136.57, 129.45, 129.37, 126.38, 101.34, 73.22, 72.22, 71.70, 68.82, 68.35, 30.17, 29.26, 21.18, 21.05, 21.03. HRMS calcd for $C_{23}H_{30}O_{10}S$ (M+Na) 521.1457, found 521.1455.

5.1.6. 3-(Phenylsulfonyl)propyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (10). To a solution of **9** (45 mg, 0.083 mmol) in EtOAc (2.5 mL) was added *m*CPBA (53 mg, 0.18 mmol, 60%) and the resulting mixture was stirred at room temperature. After 30 min, the mixture was filtered through a short column of alumina, concentrated, and chromatographed (SiO_2, heptane–EtOAc, 1:2) to give **10** as a clear oil (46 mg, 97%). $[\alpha]_D^{20} = -12.4$ (*c* 1.3, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 7.50–8.00 (m, 5H, Ar), 5.19 (t, 1H, $J=9.5$ Hz, H-3), 5.06 (t, 1H, $J=9.8$ Hz, H-4), 4.95 (dd, 1H, $J=9.6$, 8.0 Hz, H-2), 4.47 (d, 1H, $J=8.0$ Hz, H-1), 4.24 (dd, 1H, $J=12.3$, 4.8 Hz, H-6), 4.12 (dd, 1H, $J=12.3$, 2.3 Hz, H-6), 3.88–3.95 (m, 1H, CH_2), 3.65–3.70 (m, 2H, H-5, CH_2), 3.10–3.25 (m, 2H, CH_2), 2.09, 2.03, 2.02, 2.00 (s, 3H each, OAc), 2.00–2.05 (m, 2H, CH_2). ^{13}C NMR ($CDCl_3$): δ 170.86, 170.43, 169.61, 169.54, 133.99, 129.57, 128.18, 100.90, 72.89, 72.08, 71.36, 68.48, 67.70, 62.03, 53.06, 23.34, 20.95, 20.87, 20.80. HRMS calcd for $C_{23}H_{30}O_{12}S$ (M+Na) 553.1356, found 553.1346.

5.1.7. 3-Phenylsulfonyl-propyl β-D-glucopyranoside (11). Compound **10** (23 mg, 0.040 mmol) was dissolved in NaOMe–MeOH (1 M, 1 mL) and the resulting mixture was stirred at room temperature. After 24 h, AcOH (5% in MeOH) was added until neutral solution (moist pH-paper). The mixture was concentrated and chromatographed (SiO_2, CH_2Cl_2–MeOH–H_2O, 66:33:4) to give **11** as a clear oil (16 mg, 99%). $[\alpha]_D^{20} = -14.2$ (*c* 0.5, MeOH). ^{1}H NMR (CD_3OD): δ 7.60–7.95 (m, 5H, Ar), 4.19 (d, 1H, $J=7.8$ Hz, H-1), 3.94 (dt, 1H, $J=10.1$, 5.9 Hz, CH_2), 3.84 (dd, 1H, $J=12.0$, 2.0 Hz, H-6), 3.60–3.67 (m, 2H, H-6, CH_2), 3.20–3.45 (m, 5H, H-3, H-4, H-5, CH_2), 3.14 (dd, 1H, $J=9.0$, 7.9 Hz, H-2), 1.92–2.00 (m, 2H, CH_2). ^{13}C NMR (CD_3OD): δ 140.65, 135.17, 130.69, 129.27, 101.45, 78.11, 75.14, 71.71, 68.48, 62.87, 54.10, 24.69. HRMS calcd for $C_{15}H_{22}O_8S$ (M+Na) 385.0933, found 385.0928.

5.1.8. 2-(Phenylthio)ethyl β-D-glucopyranoside (12). Compound **4** (120 mg, 0.25 mmol) was dissolved in NaOMe–MeOH (0.05 M, 5 mL) and stirred for 45 min at room temperature and then neutralized using Amberlite IR-120 H+. The mixture was concentrated and chromatographed (SiO_2, CH_2Cl_2–MeOH 5:1) to give **12** as a white solid (78 mg, 89%). $[\alpha]_D^{20} = -24.8$ (*c* 0.9, MeOH). ^{1}H NMR (CD_3OD): δ 7.15–7.41 (m, 5H, Ar), 4.28 (d, 1H, $J=7.8$ Hz, H-1), 3.97 (ddd, 1H, $J=10.4$, 8.2, 6.4 Hz, CH_2), 3.85 (dd, 1H, $J=10.0$, 2.1 Hz, H-6), 3.75 (ddd, 1H, $J=10.4$, 8.2, 6.5 Hz, CH_2), 3.66 (dd, 1H, $J=11.9$, 5.3 Hz, H-6), 3.23–3.37 (m, 3H, H-3, H-4, H-5), 3.15–3.21 (m, 3H, H-2, CH_2). ^{13}C NMR (CD_3OD): δ 137.42, 130.46, 130.21, 127.34, 104.69, 78.13, 75.18, 71.67, 69.73, 62.80, 33.91. HRMS calcd for $C_{14}H_{20}O_6S$ (M+Na) 339.0878, found 339.0864.

5.1.9. 2-(Phenylthio)ethyl 2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranoside (13). To a solution of **12** (69 mg, 0.22 mmol) in DMF (distilled, 3 mL) was added NaH (60%, 90 mg) and BnBr (0.15 mL). The reaction mixture was stirred for 1 h and then quenched by addition of MeOH (1 mL). The mixture was then diluted with CH_2Cl_2, washed with water, dried (Na_2SO_4), concentrated and chromatographed (SiO_2, heptane–EtOAc, 1:1) to give **13** as a white waxy solid (131 mg, 89%). $[\alpha]_D^{20} = +15.9$ (*c* 1.7, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 7.10–7.35 (m, 25H, Ar), 4.95, 4.68 (ABq, ^{1}H each, $J=11.0$ Hz, OBn), 4.90, 4.76 (ABq, ^{1}H each, $J=11.0$ Hz, OBn), 4.79, 4.50 (ABq, ^{1}H each, $J=11.1$ Hz, OBn), 4.57, 4.52 (ABq, ^{1}H each, $J=12.1$ Hz, OBn), 4.35 (d, 1H, $J=7.8$ Hz, H-1), 4.07 (ddd, 1H, $J=10.2$, 7.7, 5.7 Hz, CH_2), 3.55–3.75 (m, 5H, H-3, H-5, H-6, CH_2), 3.38–3.45 (m, 2H, H-2, H-4), 3.10–3.21 (m, 2H, CH_2). ^{13}C NMR ($CDCl_3$): δ 138.78, 138.68, 138.30, 138.27, 135.27, 129.59, 129.19, 128.58, 128.42, 128.18, 128.08, 127.99, 127.87, 127.84, 126.40, 104.01, 84.82, 82.39, 77.94, 75.91, 75.22 75.08, 75.06, 73.70, 72.32, 69.03, 68.71, 33.49.

HRMS calcd for $C_{42}H_{44}O_6S$ (M+Na) 699.2756, found 699.2723.

5.1.10. 2-(Phenylsulfonyl)ethyl 2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranoside (14). To a solution of **13** (73 mg, 0.11 mmol) in EtOAc (4 mL) was added *m*CPBA (60%, 70 mg) and the resulting mixture was stirred at room temperature. After 30 min, the mixture was filtered through a short column of alumina to give **14** as a white solid (75 mg, 99%). $[\alpha]_D^{20}=+14.5$ (*c* 1.6, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 7.82 (dd, 2H, $J=8.6$, 1.3 Hz, Ar), 7.53 (dt, 1H, $J=7.4$ Hz, Ar), 7.41 (t, 1H, $J=7.7$ Hz, Ar), 7.00–7.30 (m, 20H, Ar), 4.80, 4.67 (ABq, ^1H each, $J=10.9$ Hz, OBn), 4.73, 4.45 (ABq, ^1H each, $J=11.2$ Hz, OBn), 4.56, 4.47 (ABq, ^1H each, $J=11.3$ Hz, OBn), 4.52, 4.44 (ABq, ^1H each, $J=12.1$ Hz, OBn), 4.21 (d, 1H, $J=7.8$ Hz, H-1), 4.12 (dt, 1H, $J=10.9$, 6.6 Hz, CH_2), 3.85 (dt, 1H, $J=10.9$, 6.6 Hz, CH_2), 3.61, 3.56 (dABq, ^1H each, $J=10.7$, 4.4, 2.1 Hz, H-6), 3.28–3.52 (m, 5H, H-3, H-4, H-5, CH_2), 3.10 (t, 1H, $J=8.0$ Hz, H-2). ^{13}C NMR ($CDCl_3$): δ 138.62, 138.56, 138.20, 133.92, 129.36, 128.65, 128.62, 128.59, 128.57, 128.47, 128.15, 128.11, 128.09, 128.00, 127.94, 127.88, 103.84, 84.62, 82.31, 77.74, 76.91, 75.93, 75.22, 75.00, 73.72, 72.31, 68.87, 63.26, 56.69. HRMS calcd for $C_{42}H_{44}O_8S$ (M+Na) 731.2655, found 731.2606.

5.1.11. 2,3,4,6-Tetra-*O*-benzyl-D-glucose (15). To a solution of **14** (58 mg, 0.082 mmol) in CH_2Cl_2 (2 mL) was added NaOMe–MeOH (1 M, 2 mL) and the mixture was stirred for 22 h and then neutralized using Amberlite IR-120 H+. The mixture was concentrated and purified on Sephadex LH-20 (CH_2Cl_2–MeOH 1:1) to give **15** as a white solid (33 mg, 74%) and **6** as a clear oil (7 mg, 43%).

5.1.12. 2-Bromoethyl 2,3-di-*O*-acetyl-4,6-*O*-(9-anthracenyl)methylene-β-D-glucopyranoside (16). To a solution of **4** (600 mg, 1.32 mmol) in MeOH (10 mL) and CH_2Cl_2 (5 mL) was added NaOMe–MeOH (1 M, 0.45 mL). The mixture was stirred for 20 min and then neutralized by addition of AcOH (1 mL). The mixture was concentrated and filtered through a column of SiO_2 (CH_2Cl_2–MeOH 5:1). The residue was then dissolved in MeCN (10 mL) and anthraldehyde dimethyl acetal (323 mg, 1.65 mmol) and *p*TSA (5 mg) were added and the mixture was stirred at room temperature overnight protected from light and then neutralized by addition of Et_3N (1 mL) and co-concentrated with toluene 3 times. The residue was chromatographed (SiO_2, toluene→6:1 toluene–acetone) and the crude product was then dissolved in pyridine (5 mL) and acetic anhydride (4 mL) was added. The mixture was stirred overnight and then co-concentrated with toluene 3 times and the residue was chromatographed (SiO_2, heptane–EtOAc 1:1) to give **16** as a white solid (354 mg, 48%). $[\alpha]_D^{20}=-70.7$ (*c* 1.2, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 8.60 (d, 2H, $J=9.2$ Hz, Ar), 8.51 (s, 1H, Ar), 8.01 (d, 2H, $J=8.3$ Hz, Ar), 7.45–7.55 (m, 4H, Ar), 6.90 (s, 1H, ArCH), 5.45 (t, 1H, $J=9.3$ Hz, H-3), 5.10 (dd, 1H, $J=9.1$, 7.9 Hz, H-2), 4.83 (d, 1H, $J=7.8$ Hz, H-1), 4.55–4.60 (m, 1H, H-6), 4.23 (p, 1H, $J=5.6$ Hz, CH_2), 3.85–4.15 (m, 4H, H-4, H-5, H-6, CH_2), 3.50 (t, 2H, $J=5.6$ Hz, CH_2), 2.10, 1.90 (s, 3H each, OAc*2). ^{13}C NMR ($CDCl_3$): δ 170.31, 169.96, 131.65, 130.25, 129.89, 129.24, 126.51, 126.46, 125.13, 124.97, 101.84, 100.99, 79.52, 72.66, 71.90, 70.19, 69.80, 66.97, 30.10, 21.02, 20.97. HRMS calcd for $C_{27}H_{27}BrO_8$ (M+Na) 581.0787, found 581.0781.

5.1.13. Coupling of 2-bromoethyl 2,3-di-*O*-acetyl-4,6-*O*-(9-anthracenyl)methylene-β-D-glucopyranoside (4) or 2-(trimethylsilyl)ethyl 2,3-di-*O*-acetyl-4,6-*O*-(9-anthracenyl)methylene-β-D-glucopyranoside (17) to thiol scavenger resin. 3-(3-Mercaptophenyl)propanamidomethylpolystyrene resin (1.54 mmol/g, 50 mg) was swelled in DMF (0.480 mL) for 5 min and then DBU (0.020 mL) was added and the resin was shaken for another 5 min. Compound **16** (20 mg or 40 mg) or **17** (20 mg) was dissolved in DMF (0.700 mL) and added to the resin. Samples (0.010 mL) were taken from the solution at different times and added to MeCN (0.990 mL). The samples (0.500 mL) were diluted with MeCN (2.000 mL) and the UV-absorbance measured at 364 nm.

5.1.14. Stability of 2-(phenylthio)ethyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (5). Compound **5** (24 mg, 0.05 mmol) was subjected to the following conditions: (a) **5** was dissolved in pyridine (1.0 mL) and acetic anhydride (0.8 mL) was added. The mixture was stirred for 22 h and then co-concentrated with toluene and chromatographed (SiO_2, heptane–EtOAc, 1:1) to give **5** (24 mg, quant). (b) **5** was dissolved in NaOMe–MeOH (0.05 M, 1 mL) and stirred for 1 h. The mixture was neutralized by addition of Amberlite IR-120 H+ and then concentrated to give **12** (16 mg, quant). (c) **5** was dissolved in MeOH saturated with HCl and stirred for 17 h. The mixture was concentrated and chromatographed (SiO_2, CH_2Cl_2–MeOH, 5:1) to give **12** (15 mg, 94%). (d) **5** was dissolved in MeCN (1 mL, filtered through Al_2O_3) and α,α-dimethoxytoluene (0.10 mL) and *p*TSA (cat) were added. The mixture was stirred for 17 h, Et_3N (0.050 mL) was added and the mixture was co-concentrated with toluene and chromatographed (SiO_2, heptane–EtOAc, 1:1) to give **5** (24 mg, quant). (e) **5** was dissolved in AcOH (80%, 3 mL) and stirred at 90 °C for 3 h. The mixture was co-concentrated with toluene to give **5** (23 mg, 95%). (f) **5** was dissolved in AcOH (3 mL) and Pd–C (10%, 25 mg) was added. The mixture was pressurized with H_2 (500 psi) for 2 h and then filtered through Celite and concentrated to give **5** (20 mg, 84%). (g) **5** was dissolved in CH_2Cl_2 (2 mL) and $BF_3\cdot OEt_2$ (0.019 mL, 3 equiv) was added. The mixture was stirred for 1 h, then quenched by addition of Et_3N (0.040 mL). The mixture was then co-concentrated with toluene and chromatographed (SiO_2, heptane–EtOAc, 1:1) to give **5** (24 mg, quant, α–β 1:5). (h) **5** was dissolved in CH_2Cl_2 (2 mL) and MS AW-300 (50 mg) was added and the mixture was cooled down to 0 °C, under Ar. NIS (16 mg) was added, the mixture was stirred for 10 min and then TfOH (cat) was added. The mixture was stirred for another 10 min at 0 °C and then quenched by addition of Et_3N (0.10 mL), concentrated and chromatographed (SiO_2, heptane–EtOAc, 1:1) to give **5** (24 mg, quant).

5.1.15. Coupling and deprotection of 2-bromoethyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (4) to thiol scavenger resin. 3-(3-Mercaptophenyl)propanamidomethylpolystyrene resin (1.54 mmol/g, 100 mg) was swelled in DMF (1.0 mL) for 5 min and then DBU (0.040 mL) was added and the resin was shaken for another 5 min. Compound **4** (35 mg, 0.5 equiv to resin substitution)

was dissolved in DMF (1.0 mL) and added to the resin. After 1 h MeI (0.010 mL) was added and the resin shaken for another 10 min and then washed with DMF, CH_2Cl_2, MeOH and diethyl ether and dried under vacuum. To the dried resin was added CH_2Cl_2 (2 mL) and *m*CPBA (70%, 70 mg) and the mixture was shaken for 30 min and then washed with CH_2Cl_2, MeOH and diethyl ether and dried under vacuum. To the dried resin were added CH_2Cl_2 (1 mL), MeOH (1 mL) and NaOMe–MeOH (1 M, 0.40 mL) and the mixture was shaken overnight and then neutralized with Amberlite IR-120 H+, filtered and washed with MeOH. The residue was purified on Sephadex (LH-20, CH_2Cl_2–MeOH, 1:1) to give **3** as a white solid (7.6 mg, α–β 1:1, 55%).

5.1.16. 4-Methylphenyl 2,3-di-*O*-acetyl-1-thio-β-D-glucopyranoside (19). Compound **18** (2.63 g, 5.74 mmol) was dissolved in AcOH (80%, aq 70 mL) and stirred at 90 °C for 2.5 h and then co-concentrated with toluene. The residue was chromatographed (SiO_2, toluene–acetone, 2:1) to give **19** as a white solid (1.98 g, 93%). $[\alpha]_D^{20} = -33.5$ (*c* 1.2, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 7.40 (bd, 2H, *J*=8.1 Hz, Ar), 7.17 (bd, 2H, *J*=7.9 Hz, Ar), 5.06 (t, 1H, *J*=9.3 Hz, H-3), 4.95 (dd, 1H, *J*=9.9, 9.3 Hz, H-2), 4.72 (d, 1H, *J*=10.0 Hz, H-1), 3.97, 3.85 (dddABq, ^{1}H each, *J*=12.4, 6.0, 3.4 Hz, H-6), 3.75 (dt, 1H, *J*=9.5, 4.9 Hz, H-4), 3.47 (ddd, 1H, *J*=9.6, 4.7, 3.4 Hz, H-5), 2.75 (d, 1H, *J*=4.9 Hz, HO-4), 2.38 (s, 3H, $ArCH_3$), 2.15, 2.12 (s, 3H each, OAc), 2.05 (dd, 1H, *J*=7.3, 6.1 Hz, HO-6). ^{13}C NMR ($CDCl_3$): δ 172.10, 169.95, 139.17, 133.82, 130.26, 128.32, 86.33, 79.99, 70.34, 69.73, 62.73, 21.61, 21.30, 21.27. HRMS calcd for $C_{17}H_{22}O_7S$ (M+Na) 393.0984, found 393.0984.

5.1.17. 4-Methylphenyl 2,3-di-*O*-acetyl-4-azido-6-*O*-benzoyl-4-deoxy-1-thio-β-D-galactopyranoside (20). Compound **19** (1.00 g, 2.70 mmol) was dissolved in CH_2Cl_2 (5 mL) and pyridine (0.87 mL) and cooled to −78 °C under Ar. Benzoyl chloride (0.329 mL, 2.84 mmol) was added dropwise and the mixture was stirred at −78 °C for 30 min and then left to retain room temperature during 60 min. The mixture was then again cooled to −78 °C and trifluoromethanesulphonic anhydride (0.89 mL, 5.40 mmol) was added dropwise. After 30 min at −78 °C the mixture was allowed to retain room temperature during 60 min and then diluted with CH_2Cl_2 and washed with satd aq $NaHCO_3$, dried and concentrated. The residue was dissolved in DMF (18 mL) and NaN_3 (3.60 g) was added and the mixture was stirred overnight and then filtered (SiO_2, heptane–EtOAc, 2:1) and chromatographed (SiO_2, heptane–EtOAc 2:1) to give **20** as a white solid (1.16 g, 86%). $[\alpha]_D^{20} = -50.2$ (*c* 1.3, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 6.97–8.02 (m, 9H, Ar), 5.26 (t, 1H, *J*=9.8 Hz, H-2), 5.12 (dd, 1H, *J*=9.7, 3.7 Hz, H-3), 4.58 (d, 1H, *J*=10.0 Hz, H-1), 4.54, 4.45 (ABq, ^{1}H each, *J*=11.5, 5.4 Hz, H-6), 4.05–4.12 (m, 1H, H-4), 3.93 (dt, 1H, *J*=5.7, 1.3 Hz, H-5), 2.27 (s, 3H, $ArCH_3$), 2.09, 2.08 (s, 3H each, OAc). ^{13}C NMR ($CDCl_3$): δ 170.57, 169.80, 166.47, 138.81, 133.86, 133.43, 130.22, 130.12, 129.81, 128.94, 87.48, 74.85, 74.51, 67.79, 63.74, 60.71, 21.60, 21.28, 20.43. HRMS calcd for $C_{24}H_{25}N_3O_7S$ (M+Na) 522.1311, found 522.1308.

5.1.18. 4-Methylphenyl 4-azido-2,3,6-tri-*O*-benzoyl-4-deoxy-1-thio-β-D-galactopyranoside (21). To a mixture of **20** (530 mg, 1.06 mmol) in MeOH (25 mL) was added NaOMe–MeOH (0.25 mL, 1 M) and the resulting mixture was stirred for 5 h and then neutralized using Amberlite IR-120 H+. The residue was dissolved in pyridine (30 mL) and benzoyl chloride (0.45 mL, 3.88 mmol) and a catalytic amount of DMAP was added and the solution was stirred overnight. MeOH was added and the mixture was concentrated and flash chromatographed (SiO_2, heptane–EtOAc, 2:1) to give **21** as a white solid (615 mg, 93%). $[\alpha]_D^{21} = -28.3$ (*c* 1.2, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 8.10–8.15 (m, 6H, Ar), 7.40–7.70 (m, 11H, Ar), 7.04 (d, 2H, *J*=8.0 Hz, Ar), (5.77 (t, 1H, *J*=9.9 Hz, H-2), 5.61 (dd, 1H, *J*=9.8, 3.6 Hz, H-3), 4.91 (d, 1H, *J*=10.0 Hz, H-1), 4.70, 4.68 (ABq, ^{1}H each, *J*=11.5, 7.0 Hz, H-6), 4.38 (dd, 1H, *J*=3.6, 1.2 Hz, H-4), 4.17 (dt, 1H, *J*=7.0, 1.2 Hz, H-5), 2.34 (s, 3H, $ArCH_3$). ^{13}C NMR ($CDCl_3$): δ 166.51, 166.12, 165.57, 138.87, 134.22, 133.85, 133.76, 133.68, 130.50, 130.27, 130.25, 130.11, 129.86, 129.71, 128.98, 128.96, 128.91, 128.84, 128.64, 87.72, 75.13, 75.08, 68.32, 63.79, 61.02, 21.61. HRMS calcd for $C_{34}H_{29}N_3O_7S$ (M+Na) 646.1624, found 646.1617.

5.1.19. 2-Bromoethyl 2,3,6-tri-*O*-benzoyl-4-azido-4-deoxy-β-D-galactopyranoside (22). Compound **21** (388 mg, 0.62 mmol) was dissolved in CH_2Cl_2 (20 mL) and MS AW-300 (600 mg) was added and the resulting mixture was stirred for 30 min and then cooled to 0 °C. 2-Bromoethanol (0.070 mL, 1.00 mmol), *N*-iodosuccinimide (196 mg, 0.87 mmol) and a catalytic amount of trimethylsilyl trifluoromethanesulfonate were added and the mixture was stirred for 10 min, then Et_3N (1.0 mL) was added. The mixture was filtered through a short SiO_2-column and then chromatographed (SiO_2, heptane–EtOAc, 4:1) to give **22** as a white solid (345 mg, 89%). $[\alpha]_D^{21} = -53.0$ (*c* 1.3, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 8.11–7.96 m, 6H, Ar), 7.65–7.37 (m, 9H, Ar), 5.79 (dd, 1H, *J*=10.3, 7.8 Hz, H-2), 5.59 (dd, 1H, *J*=10.3, 3.7 Hz, H-3), 4.82 (d, 1H, *J*=7.9 Hz, H-1), 4.67, 4.58 (dABq, ^{1}H each, *J*=11.4, 6.4 Hz, H-6), 4.35 (dd, 1H, *J*=3.7, 1.2 Hz, H-4), 4.16 (m, 2H, H-5, CH_2), 3.90 (m, 1H, CH_2), 3.45 (m, 2H, CH_2). ^{13}C NMR ($CDCl_3$): δ 166.05, 165.70, 165.17, 133.81, 133.49, 133.24, 130.06, 129.77, 129.72, 129.26, 128.58, 128.56, 128.33, 128.13, 101.60, 73.31, 70.96, 69.59, 69.14, 62.82, 60.28, 29.57. HRMS calcd for $C_{29}H_{26}BrN_3O_8$ (M+Na) 646.0801, found 646.0775.

5.1.20. 4-Deoxy-4-(2-naphthoyl)-amido-D-galactose (23). 3-(3-Mercaptophenyl)propanamidomethylpolystyrene resin (1.54 mmol/g, 100 mg) was swelled in DMF (1.0 mL) for 5 min and then DBU (0.040 mL) was added and the resin was shaken for another 5 min. Compound **22** (48 mg, 0.5 equiv to resin substitution) was dissolved in DMF (1.0 mL) and added to the resin. After 1 h MeI (0.050 mL) was added and the resin shaken for another 10 min and then washed with DMF, CH_2Cl_2, MeOH and diethyl ether and dried under vacuum. The dried resin was swelled in CH_2Cl_2 (1 mL) and MeOH (1 mL) and NaOMe–MeOH (1 M, 0.10 mL) were added. The resin was shaken for 1 h and then washed with MeOH and CH_2Cl_2. DTT (76 mg) in DMF (1 mL) was added followed by DBU (0.010 mL) and the resin was shaken overnight and then washed with DMF, CH_2Cl_2, MeOH and diethyl ether and dried under vacuum. The dried resin was swelled in DMF (2 mL) and pyridine

(0.20 mL) and 2-naphthoyl chloride (50 mg) were added. The resin was shaken for 4 h and then washed with DMF, CH_2Cl_2, MeOH and diethyl ether and dried under vacuum. To the dried resin were added CH_2Cl_2 (4 mL) and *m*CPBA (70%, 70 mg) and the mixture was shaken for 30 min and then washed with CH_2Cl_2, MeOH and diethyl ether and dried under vacuum. To the dried resin was added CH_2Cl_2 (2 mL), MeOH (2 mL) and NaOMe–MeOH (1 M, 0.80 mL) and the mixture was shaken overnight and then neutralized with acetic acid and washed with MeOH. The residue was chromatographed (SiO_2, CH_2Cl_2–MeOH 5:1) to give **23** as a complex anomeric and rotameric mixture (6.8 mg, 27%). HRMS calcd for $C_{17}H_{19}NO_6$ (M+Na) 356.1110, found 356.1123. ^{1}H NMR can be found as Supplementary Material. ^{13}C NMR (CD_3OD): δ 170.80, 136.43, 134.22, 130.17, 192.72, 129.35, 129.10, 128.96, 128.92, 128.76, 128.12, 127.94, 125.30, 124.60, 99.71, 98.49, 71.22, 70.04, 66.41, 66.22, 65.94, 64.89, 63.43, 62.11, 55.54, 55.37.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2005.01.015

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Conformational behavior of dithia[n.3.3](1,3,5)cyclophanes and dithia[n.3.3](1,2,6)cyclophanes

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Abstract—The conformational behavior of a series of crown-fused dithia[n.3.3](1,2,6)cyclophanes (**126-CPs**) and dithia[n.3.3](1,3,5)-cyclophanes (**135-CPs**) was investigated by variable-temperature ^{1}H and ^{13}C NMR spectroscopy, X-ray crystallography and density functional theory (DFT) calculations. Single crystal X-ray structure analysis showed that two thia-bridges in **126-CPs** adopted a *pseudochair–pseudochair* (*cc*) conformation and the cyclophane decks underwent a ring-tilting motion in the case of [10.3.3](1,2,6)cyclophane (**1a**). In contrast, the thia-bridges in **135-CPs** took both *cc* and *pseudoboat–pseudochair* (*bc*) conformations, and the ring-tilting process was also found in [10.3.3](1,3,5)cyclophane (**2a**). Variable temperature ^{1}H NMR study revealed that there was no wobbling-motion for two thia-bridges in **126-CPs** while thia-bridges in **135-CPs** experienced a wobbling-process with a conformational barrier of 9.21 and 8.80 kcal mol^{-1}, respectively, for **2a** and [13.3.3](1,3,5)cyclophane (**2b**). DFT calculations for the two cyclophanes series revealed that **126-CPs** preferred a *cc* conformation which was consistent with the experimental observation; similarly, **135-CPs** took a preferential *cc* conformation, agreeing with **2a** having a predominant *cc* conformer (*cc*:*bc* ratio = 70:30), but not **2b** having a predominant *bc* conformer (*cc*:*bc* ratio = 15:85) in the solid state.

1. Introduction

Conformational analysis plays an important role in cyclophane chemistry.[1] The understanding of preferred conformations in cyclophane (**CP**) is of importance in the design of various supramolecular systems. Small-sized **CP** molecules, such as, 2,11-dithia[3.3]metacyclophane (**MCP**)[2–6] frequently act as a model to explore the mobility of such **CPs** due to the presence of a variety of conformational processes including ring-flipping, ring-tilting, bridge-wobbling and *syn-anti* isomerization. It is well understood that the conformational characteristics of [3.3]**MCP** are dependent particularly upon the 'internal' (9, 18-position) substitution, the attribute of the 'internal' atom and the nature of the bridge heteroatoms (Chart 1).[7–10] The 'internal' substituents in [3.3]**MCP** are able to direct its conformation preference when non-covalent interaction such as hydrogen bonding between substituents and bridges is present.[8] For example, 9-amino-2,11-dithia[3.3]**MCP**, being different from its precursor *syn*-9-nitro-2,11-dithia[3.3]**MCP**, is *anti*. However, 9-18-diamino-2,11-dithia[3.3]**MCP** shows *syn* and its thia-bridges adopt a *pseudoboat–pseudoboat* (*bb*) conformation as a result of the formation of an intramolecular hydrogen-bonding network. Likewise, 9-amino-18-nitro-2,11-dithia[3.3]**MCP** takes a *pseudoboat–pseudochair* (*bc*) conformation due to the presence of an intramolecular S···H–N hydrogen bonding. Other factors such as the dipole moment of a molecule sometimes may have an effect on the predominant conformation.[11]

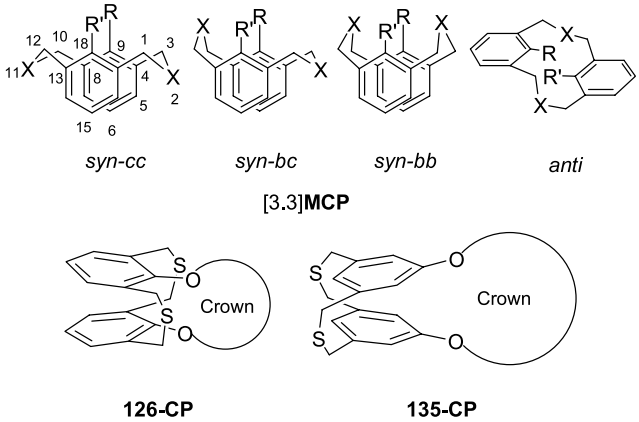

Chart 1.

Keywords: Conformation; (1,3,5)Cyclophane; (1,2,6)Cyclophane.
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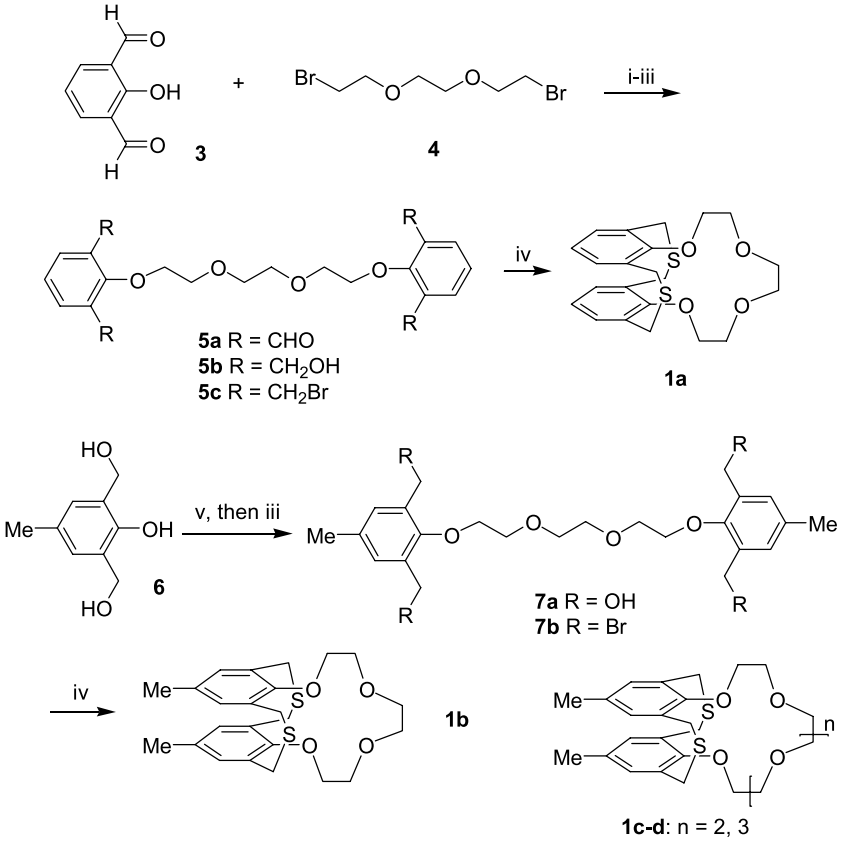
On the other hand, examples of the synthesis and conformational analysis of multibridged cyclophanes were studied 30 years ago. Boekelheide first reported the synthesis of 2,11,20-trithia[3_3](1,3,5)**CP**[12] in which one thia-bridge underwent a wobbling-process in the solid state.[13] Shinmyozu studied the synthesis and conformational behavior of [3_3](1,3,5)**CP**, in which one bridge experienced a wobbling-process with an activation energy barrier of 12.4 kcal mol^{-1}.[14] Fluorine-substituted [3_3](1,3,5)**CP** whose π–π absorption bands correlate to the number of fluorine atoms were also investigated.[15] Bodwell reported the synthesis of [n.3.3](1,3,5)**CPs** as tethered [2.2]**MCPs** precursors with various lengths of alkyl tether.[16,17] Recently, our interest has focused on the synthesis and complexation properties of crown-fused dithia[n.3.3](1,2,6)**CPs** (**126-CPs**) and dithia[n.3.3]-(1,3,5)**CPs** (**135-CPs**) (Chart 1).[18–20] Their binding properties towards alkali metal ions largely relate to the ring-tilting motion of two aromatic rings. Herein we wish to further report the syntheses, X-ray crystal structure and the conformational analysis of crown-fused **126-CPs** and **135-CPs** in solution by variable-temperature ^{1}H and ^{13}C NMR spectroscopy. The energy-minimized structures based on the DFT calculations are presented and compared with those from the X-ray crystallography and variable-temperature NMR spectroscopy.

2. Results and discussion

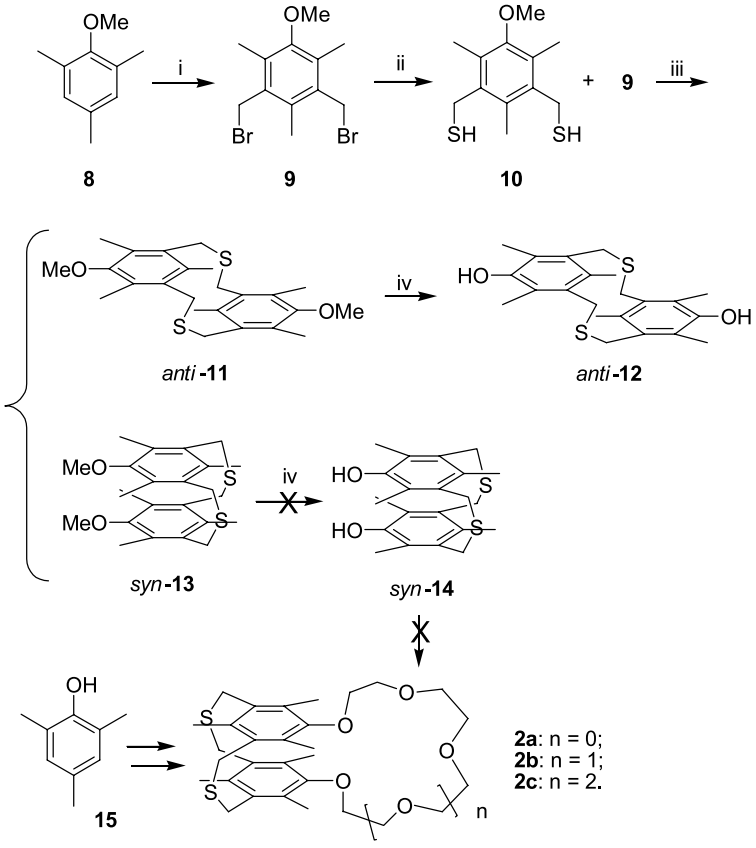
2.1. Synthesis of 126-CPs and 135-CPs

First, **1a** and **1b** were synthesized as shown in Scheme 1. Compound 2,6-diformylphenol **3**, which was prepared by tetrabromination of 2,6-dimethylphenol acetate followed by hydrolysis in NaOAc/HOAc,[21] was used as a starting material. Compound **5a** was obtained in a 48% yield when the reaction temperature was maintained at 60–70 °C and the mixture stirred for 24 h. A near quantitative yield of tetrol **5b** was obtained by reducing **5a** with $NaBH_4$ in refluxing THF. Treatment of **5b** with phosphorus tribromide in dry CH_2Cl_2 readily gave tetrabromide **5c** in 80% yield. Finally **1a** was obtained by intramolecular cyclization of **5c** with Na_2S under high dilution conditions. The method of preparation of **1b** was the same as that of other analogs **1c–d**.[18,19]

The synthesis of **2a–c** was attempted (Scheme 2). First, compound **9** was prepared from bromomethylation of 2,4,6-trimethylanisole in 47% HBr/HOAc in the presence of a phase transfer catalyst *N*,*N*,*N*-trimethyltetradecyl ammonium bromide.[22] Compound **9** was converted to **10** by reacting with thiourea followed by hydrolysis in refluxing 10% KOH aqueous solution. The compound



Scheme 1. The synthetic route for **1a–b**. Reagents and conditions: (i) K_2CO_3, DMF, 60–70 °C; (ii) $NaBH_4$, THF, reflux; (iii) PBr_3, CH_2Cl_2, 0 °C; (iv) Na_2S, ethanol/benzene, high dilution conditions, rt; (v) $Br(CH_2CH_2O)_2CH_2CH_2Br$, K_2CO_3, acetone, reflux.



Scheme 2. The synthetic route for **2a**–**c**. Reagents and conditions: (i) 1,3,5-trioxane, HOAc, aq HBr (48%), 95 °C; (ii) $(NH_2)_2CS$, aq KOH, reflux, 9 M H_2SO_4; (iii) KOH, benzene, ethanol, high dilution conditions, rt; (iv) BBr_3, CH_2Cl_2.

syn-**13**, together with its isomer *anti*-**11** was prepared from the cross-coupling reaction of dibromide **9** and dithiol **10** under high dilution conditions. The two isomers could be readily separated by column chromatography. Demethylation of *anti*-**11** was carried out using BBr_3 in CH_2Cl_2 to afford *anti*-**12**. A similar reaction attempted using the isomer *syn*-**13** however was unsuccessful. The significant steric hindrance of the *ortho*-methyl and opposite aryl groups might have discouraged the reaction. An alternative synthesis of **2a**–**c** was achieved starting from 2,4,6-trimethylphenol **15** which reacted with polyethylene glycol dibromide, followed by tetrabromomethylation and intramolecular cyclization with sodium sulfide to afforded **2a**–**c**.[20]

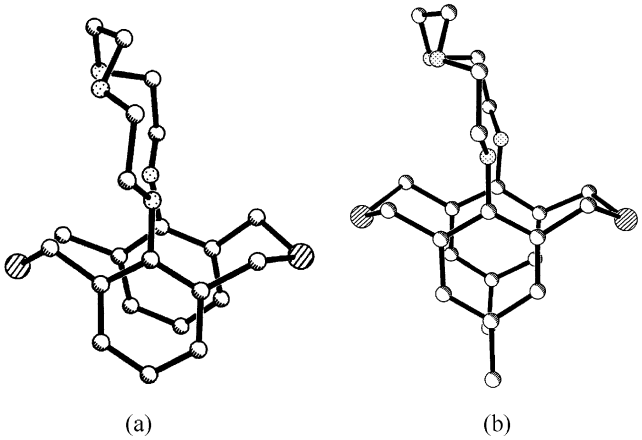


Figure 1. ORTEP drawings of (a) **1a**-(**I**) and (b) **1b**.

2.2. Crystal structures of 126-CPs and 135-CPs

The X-ray single crystal structures of **1a**–**d** and **2a**–**b** were determined. All the single crystal structures of **1a**–**d** clearly showed a *pseudochair–pseudochair* (*cc*) conformation for both thia-bridges. Their normal C–S bond lengths and C–S–C bond angles were similar and close to expected values.[23–26] It was noteworthy that **1a** showed that there were two different non-interconverting structures **1a**-(**I**) and **1a**-(**II**) in the crystalline state. The ORTEP drawings of **1a**-(**I**) and **1b** are illustrated in Figure 1. However, **1a**(**I**) and **1a**(**II**) did not exhibit significant differences between their bond lengths, bond angles and thia-bridge conformations. Figure 2 clearly manifests the ring-tilting process in **1a**. Analysis of other single crystal structures of **1c**–**d** showed the same *cc* conformation for thia-bridges and no disorder of thia-bridges was observed.[18,19] This appears to indicate that the wobbling process of thia-bridges is restricted by the 'internal' substitution for **126-CPs** series.

Similar to **1a**, two independent conformers (**2a**-(**I**) and **2a**-(**II**)) of **2a** were also found in the crystalline state and one of the two thia-bridges in a conformer (**2a**-(**II**)) was triply disordered.[20] Both thia-bridges in **2a**-(**II**) adopted the *pseudochair* conformation with C–S bond lengths and C–S–C bond angles very close to those observed in **1a**. Nevertheless, in conformer **2a**-(**I**), one thia bridge was

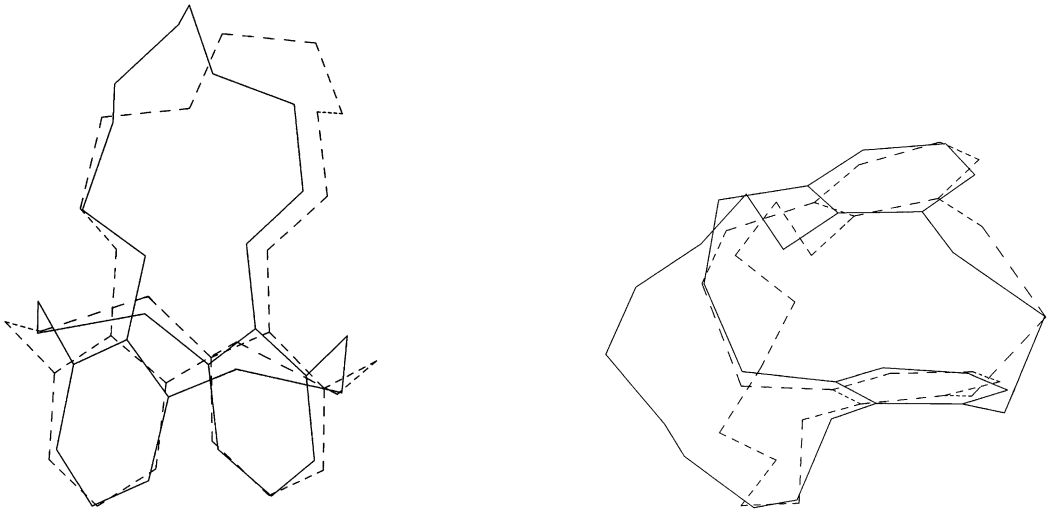


Figure 2. A diagram illustrating the tilting motion in the two conformers of **1a**-(**I**) and **1a**-(**II**). Two independent structures are indicated by solid line and dashed line, respectively.

Table 1. A comparison of the dihedral angles of two aryl rings and the centroid–centroid distances of aromatic rings in **1a–d**, **2a–b** and compound **16**

CP	Dihedral angle of two aryl rings (°)	Centroid–centroid distance of two aryl rings (Å)
1a-(**I**)	16.2	3.50
1a-(**II**)	15.5	3.49
1b	14.2	3.49
1c	13.4	3.45
1d	12.8	3.43
2a-(**I**)	16.1	3.59
2a-(**II**)	13.6	3.55
2b	12.9	3.56
16	<1	3.19

'normal' but the sulfur atom in the second was triply disordered with an occupancy ratio of 0.4:0.3:0.3. The observation indicates a possible inter-conversion among *bc* and *cc* conformations in the solid state. Similarly, one of thia-bridges in **2b** was disordered, resulting in a **2b**-*bc* conformation as a major component (85%). The coexistence of *bc* and *cc* conformers has also been found previously[12,13] except that the *cc* conformation was the predominant isomer (80%). In comparison to the conformers in **2a** with a ratio of 70:30 (*cc*:*bc*, inclusive of **2a**(**I**) and **2a**(**II**)), **2b** with a ratio of 15:85 (*cc*:*bc*) has significantly more preference for the *bc* conformer. In addition to the probable effect of crystal packing, we believe this is in part as a result of the great difference in their ground state energies, that is, an increase in ground state energy going from *bc* to *cc*.

There is a possible explanation why a wobbling-process in one of the thia-bridges was only observed for **2a** and **2b** but not in the series of **126-CPs**. In **1a**, for example, the *bc* conformation would experience a significant steric repulsion between the *pseudo-boat* sulfur atom and the central phenolic oxygen atom in the crown ether moiety and thus the strong preference for only the *cc* conformer. In contrast, in **2a–b** a pair of similar steric interactions would be experienced in both the *cc* and *bc* conformations, thus the

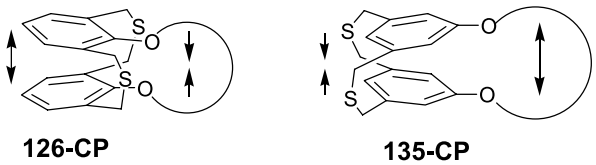


Figure 3. The tilting process of **126-CPs** and **135-CPs**.

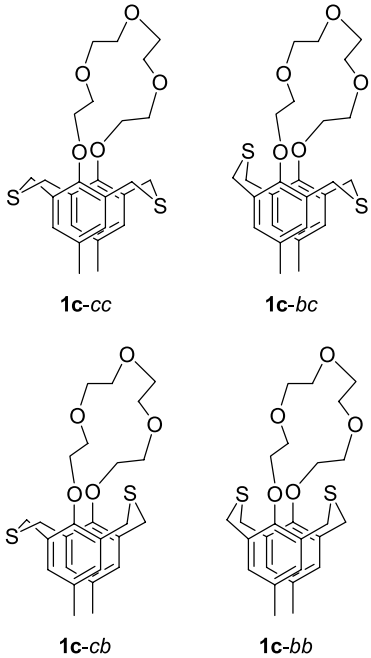


Figure 4. The possible conformation of **1c** in solution.

disorder in one of the thia-bridges even in the solid state was observed. On the basis of a buttressing effect, the *cc* conformation would be relatively less stable, and thus **135-CPs** have a preference to the propelling *bc* conformation similar to that observed[13] of which one of the sulfur bridges experiences rapid wobbling.

The benzene rings in all **126-CPs** and **135-CPs** in the solid state were not parallel to each other. The centroid arene–arene stacking (interplanar) distances and dihedral angles (tilting angle) for aromatic rings are summarized in Table 1. The interplanar distances were slightly larger than the normal arene–arene stacking distance of 3.4 Å. Unlike 2,11,20-trithia[3_3](1,3,5)**CP**[12] (**16**) in which two benzene rings are nearly parallel, the two benzene rings in each of **2a** and **2b** were tilted at an angle in the range of 12.9–16.1° in the reverse manner to **126-CPs** (Fig. 3). There was also a decreasing trend in dihedral angle going from **2a** to **2b**. The decrease in tilting dihedral angle following an increase in chain length of the crown ether link could be explained by an increasing demand for a larger cavity size of the crown ether. A smaller dihedral angle going from **1a** to **1b** is however not understood. If the steric demand of the methyl groups in **1b** is taken into consideration, the dihedral angle in **1b** would be expected to be larger. In this series of **126-CPs**, an identical transannular distance accompanied by a varying dihedral angle of two aryl rings indirectly supports a breathing mechanism (in solution)[19] of the crown ether unit

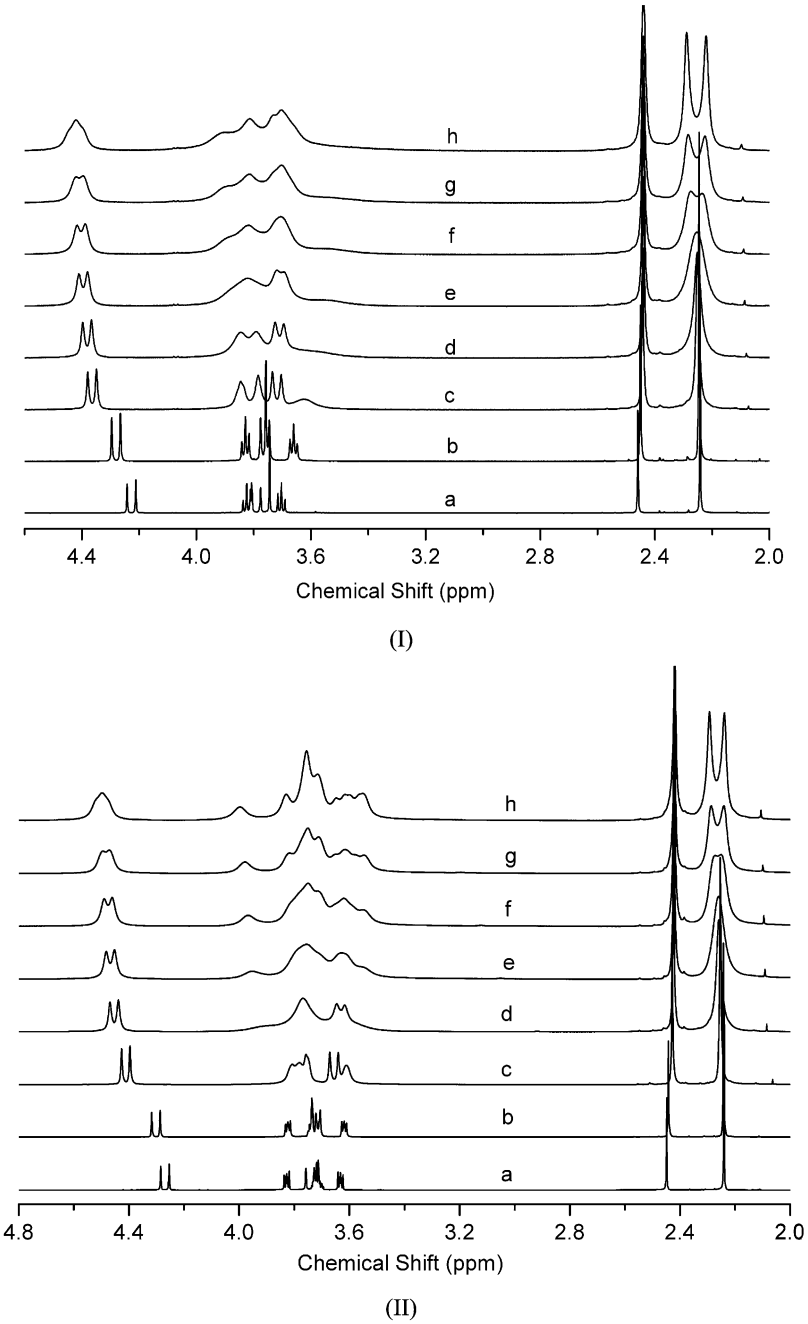


Figure 5. The variable temperature ^{1}H NMR spectra of (I) **2a**: (a) 300, (b) 253, (c) 203, (d) 193, (e) 188, (f) 185, (g) 183 and (h) 178 K; and (II) **2b**: (a) 300 K, (b) 273 K, (c) 213 K, (d) 193 K, (e) 188 K, (f) 185 K, (g) 183 K and (h) 178 K in CD_2Cl_2.

as described. The change in dihedral angle would result in a change in the conformation and cavity size of the crown ether and thus its complexation ability.

2.3. Dynamic NMR spectroscopy study

Although **1a**–**d** take the *cc* conformations as observed in the solid state, it is not possible to rule out the wobbling processes *cc* ⇔ *bc* ⇔ *cb* ⇔ *bb* as well as their diastereotopic conformers of thia-bridges in solution as illustrated in Figure 4 using **1c** as an example. Therefore we examined the dynamic NMR (500 MHz) spectra of **1a**–**d** over the temperature range from 298 to 178 K, however we did not observe the freezing of this wobbling process of the thia-bridges indicating either a relatively low energy conversion barrier or less opportunity to adopt *bc*, *cb*, or *bb* due to the electronic repulsion between sulfur and phenolic oxygen. Thus, it would be more interesting to find out whether the bridge wobbling processes of the thia-bridges in **135-CPs** series could be observed. The aryl rings in **135-CPs** are hexa-substituted and thus the relatively higher steric demand might allow observation of the freezing of the bridge wobbling processes at a reasonable temperature within the experimental limitations.

The temperature-dependent ^{1}H NMR (500 MHz) spectra of **2a** were recorded in CD_2Cl_2 in the temperature range of 178–300 K (Fig. 5(I)). In general the NMR signals broadened significantly as the temperature was lowered from 300 to 178 K. Although the oxyethylene protons in the crown unit were clearly resolved at 300 K, broadening of these signals upon cooling led to weak and overlapped signals. This phenomenon is however consistent with a slowing down of the conformational processes in the macroring. The diastereotopic bridge methylene protons (–CH_2SCH_2–) also appeared clearly as an AB quartet at δ 4.23 and 3.79 at room temperature. These signals broadened and finally coalesced at about 180 K. They were expected to reappear as two separate AB quartets at the low temperature limit, but in our study, the limitation of the temperature was near 175 K at which these signals were not fully resolved. Actually, a broad incipient triplet was observed in both spectra of **2a** and **2b** at 178 K.

The methyl protons in **2a** appeared as two singlets at δ 2.46 and 2.24 in an integration ratio of 1:2 at room temperature. Thus, the latter could be readily assigned to the two methyl groups adjacent to the crown ether unit. The two methyl groups were certainly also adjacent to the two thia-bridges and thus could be used as proton probes for the conformational analysis of the bridge wobbling processes by dynamic ^{1}H NMR spectroscopy. As the temperature was lowered, the signals corresponding to this pair of methyl groups (at δ 2.24 at 300 K) broadened and coalesced at 186 K. This signal became gradually resolved again as the temperature was further lowered and reappeared as two singlets at δ 2.26 and 2.22 at 178 K. This in fact indicates the freezing out of the wobbling processes of the thia-bridges, leading to a conformation in which the two initially (room temperature) identical methyl groups are now magnetically non-equivalent. The dynamic NMR study of **2b** revealed a similar phenomenon (Fig. 5(II)). An analysis of the general conformational behavior will be discussed using **2b** as an example.

In the analysis of a conformational process using dynamic NMR spectroscopy the free energy of activation ($\Delta G_c^{\neq}$), which represents the conformational barrier, could be estimated by the coalescence temperature method. Employing a pair of non-coupled signals as the probe for conformational analysis, the value of $\Delta G_c^{\neq}$ could be derived from the Eyring equation:[27]

$$k_c = 0.707\pi\Delta\nu$$

$$\Delta G_c^{\neq} = 2.303RT_c(10.319 + \log T_c - \log k_c)$$

Where $\Delta\nu$ is the frequency difference at the low temperature limit, T_c is the coalescence temperature and $\Delta G_c^{\neq}$ is the transition state free energy at coalescence temperature.

Although the crown ether link in **2b** is relatively longer than that in **2a** their conformational barriers for the thia-bridge wobbling processes seem to be very similar (Table 2). These barriers are in fact relatively lower than that observed for a similar wobbling process in [3.3]-**MCP** (10.8 kcal mol^{-1}).[5] In contrast, similar bridge wobbling processes of aza-bridges in *N*,*N*,*N*-tritosyl-2,11,20-triaza[3$_3$](1,3,5)**CP** (13.6 kcal mol^{-1})[28] and [3$_3$](1,3,5)**CP** (12.4 kcal mol^{-1})[14] however, involved a higher energy barrier.

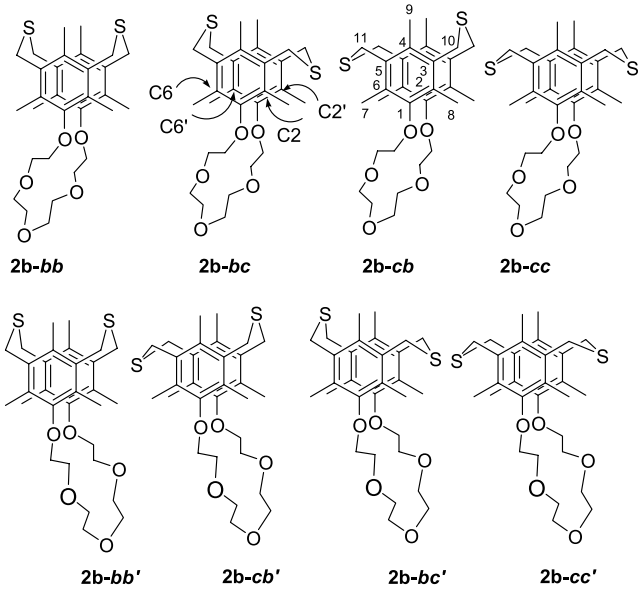


Figure 6. Possible conformations of **2b** in solution.

Table 2. The coalescence temperature and activation energy of **2a**–**b**

	T_c (K)	$\Delta\nu$ (Hz)	k_c (Hz)	$\Delta G_c^{\neq}$ (kcal mol^{-1})
2a	186	30	60	9.21
2b	186	34	76	8.80

Possible conformational processes of the three bridges in **2b** are illustrated in Figure 6. The large crown ether unit is expected to undergo the extreme 'left to right' swing resulting in the two series of conformers **2b**-*bb*–**2b**-*cc* and **2b**-*bb*′–**2b**-*cc*′ (**2b**-*bb* is equivalent to **2b**-*bb*′, **2b**-*bc* to **2b**-*cb*′, **2b**-*cb* to **2b**-*bc*′ and **2b**-*cc* to **2b**-*cc*′). The crown ether link is relatively longer and more flexible and thus would involve a much lower energy barrier. On the other hand, it could be assumed that the resolution of the proton signals of methyl groups at aromatic C2/C2′ and C6/C6′ is dependent only on the restricted conformational changes of the thia-bridges. There should be no resolution of these methyl proton signals if the frozen conformation is either **2b**-*bb* ⇔ **2b**-*bb*′ or **2b**-*cc* ⇔ **2b**-*cc*′ due to their symmetry. Thus, it could be concluded that the experimentally observed frozen conformer of **2b** in the dynamic NMR study was **2b**-*bc* ⇔ **2b**-*cb*′ and **2b**-*cb* ⇔ **2b**-*bc*′ (**2b**-*cb* ⇔ **2b**-*bc*′ is not identical to **2b**-*bc* ⇔ **2b**-*cb*′ and the two pairs are not inter-converting). In fact a crystallographic structure of **2b** also indicates the same conformational preference in the solid state. The two resolved methyl proton signals for **2b** at the low temperature limit appeared at δ 2.29 and 2.24, respectively. In **2b**-*bc* ⇔ **2b**-*cb*′ or **2b**-*cb* ⇔ **2b**-*bc*′, one of the sulfur atoms is in close proximity to the methyl groups attached to aromatic C2/C2′ and C6/C6′ for **2b**-*bc*, **2b**-*cb*′, **2b**-*cb* and **2b**-*bc*′, (the methyl groups at C6/C6′ and C2/C2′). The anisotropic effect of this sulfur atom might induce a small downfield shift of the methyl signal concerned, thus resulting in its resolution from the signal of the methyl groups at C2/C2′ and C6/C6′ for **2b**-*bc*/**2b**-*cb*′ or **2b**-*cb*/**2b**-*bc*′, respectively, in **2b**-*bc* ⇔ **2b**-*cb*′ or **2b**-*cb* ⇔ **2b**-*bc*′.

Table 3. The selected chemical shifts of **2b**[a] at 298 and at 178 K

	Chemical shift	
	298 K	178 K
C(1)	152.55	155.98, 149.95
C(3,5)	132.09	131.01, 130.45
C(4)	130.24	129.09, 128.43
C(2,6)	127.44	126.35
C(10,11)	30.83	29.75, 29.56, 29.49, 29.35
C(9)	17.80	17.26, 17.05
C(7,8)	12.31	11.97, 11.86, 11.16, 11.02

[a] The numbering of carbon atoms is shown in Figure 6.

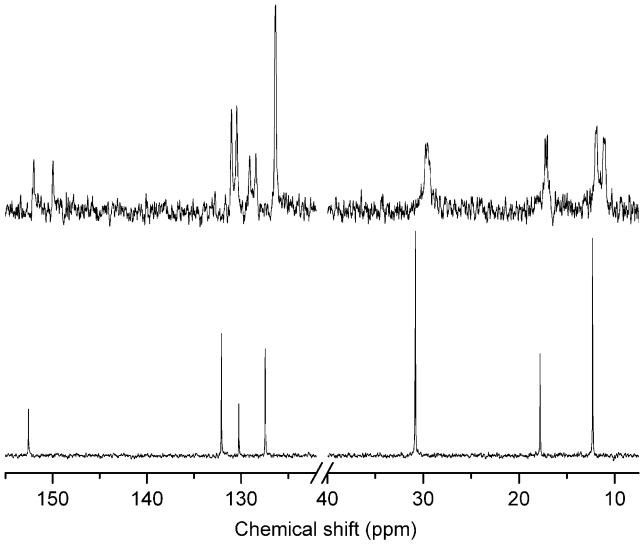


Figure 7. ^{13}C NMR spectra of **2b** (a) at 298 K and (b) at 178 K in CD_2Cl_2.

^{13}C NMR spectrum of **2b** was measured at 178 K and the assignment of selected carbon signals is listed in Table 3 It was worthy to note that while only an averaged singlet at δ 12.31 was observed at room temperature for the methyl carbons attached to C2, 2′, 6 and 6′, however, four singlets with a 1:1 ratio appeared in the spectrum taken at 178 K at δ 11.97, 11.86, 11.16 and 11.02, respectively. Simultaneously, the singlet at 30.83 corresponding to the bridge carbon emerged as four singlets. Moreover, three aromatic carbon signals were separated to two sets of singlets in a 1:1 ratio (Fig. 7). It implies that two conformers (**2b**-*bc* or **2b**-*cb*′ and **2b**-*cb* or **2b**-*bc*′) exist at this temperature. It is clear that there are two pairs of relatively well-resolved ($\Delta\delta \approx 0.8$ ppm) methyl signals. This is also consistent with the argument that the anisotropic effect of sulfur results in the deshielding of the carbons in close proximity.

2.4. Computational study of conformers

A series of DFT calculations (BLYP/DNP) were performed to determine the relative energy for the different conformers of **126-CPs** and **135-CPs** together with *syn*-9,18-dimethoxy[3.3]**MCP** (**17**) for comparison, and the results are summarized in Table 4. For both series, all *cc* conformers had the global minimum energy. The *bc*, *cb* and *bb* conformers of **126-CPs** series had a higher energy by 4.30–11.91 kcal mol^{-1} than their corresponding *cc* conformers. The electronic repulsion and steric hindrance between sulfur and phenolic oxygen accounts for the high-energy difference among conformers in **126-CPs** series. The global energy minimum conformers of **126-CPs** exactly responded to the structures in solution and in the solid state. In contrast, the differences (0.89–3.69 kcal mol^{-1}) between *cc* and other conformers in **135-CPs** series were much less than those in **126-CPs** series. The relative population of these conformers (Table 5) was thus estimated based on the data of Table 4. It was shown that the total population of *bb*, *bc* and *cb* conformers was found to be negligible for **126-CPs**. In contrast, there were more than totally 37 and 36% of *bc* and *cb* conformers, for example, for **2a** and **2b**, respectively. The calculated ratio of *cc*:(*bc*/*cb*) (63:37) for **2a** is approximately close to the experimental value (70:30) in the solid state, however, the order of conformers ratio of *cc*:(*bc*/*cb*) (63:36) for **2b** was reversed when compared to

Table 4. The relative energy (kcal mol^{-1}) of conformers of **1a–d**, **2a–c** and compound **17** (BLYP/DNP)

CP	**1a**	**1b**	**1c**	**1d**	**2a**	**2b**	**2c**	**17**
bb	11.24	11.91	9.23	8.50	2.90	2.51	3.69	10.28
bc	7.37	5.22	5.19	4.30	0.89	1.09	1.60	5.65
cb	5.69	5.10	4.93	4.36	1.60	1.24	2.02	
cc	0	0	0	0	0	0	0	0

Table 5. The population of conformers of **1a–d** and **2a–c** at 298 K[a]

CP	1a	1b	1c	1d	2a	2b	2c
bb	0	0	0	0	0	1	0
bc	0	0	0	0	28	20	11
cb	0	0	0	0	9	16	6
cc	100	100	100	100	63	63	83

[a] The population was calculated based on the data of Table 4.

the experimental values (15:85). The discrepancy in calculated and experimental population may be a consequence of the effect of crystal packing as mentioned above.

3. Conclusions

We have demonstrated that the preferential conformations of **126-CPs** were *cc* as a result of the electronic repulsion between sulfur and internal phenolic oxygen, while **135-CPs** had a tendency to take *cc* and *bc* conformations. Dynamic NMR analyses in solution were in agreement with the analyses of conformation by X-ray crystallography. The conformational barriers for the wobbling-process estimated by variable-temperature ^{1}H NMR, were 9.21 and 8.80 kcal mol^{-1}, respectively, for **2a** and **2b**, less than that of [3$_3$](1,3,5)**CP**. The ^{13}C NMR spectra at low temperature suggested two conformers with a 1:1 ratio coexisted, corresponding to the results in the solid state. The DFT calculations provided the evidence on the conformational analysis of **126-CPs** and **135-CPs**.

4. Experimental

4.1. General

The NMR spectra were determined on a Bruker ACF (300 MHz) FT-NMR spectrometer, operating at 300.13 and 75.47 MHz for ^{1}H and ^{13}C, respectively in $CDCl_3$ at room temperature. The temperature-dependent NMR experiments were performed on a Bruker AMX (500 MHz) NMR spectrometer in CD_2Cl_2. All chemical shifts are reported in ppm downfield from tetramethylsilane as an internal standard. Infrared spectra were recorded on a Perkin–Elmer 1310 infrared spectrometer. Mass spectra were determined on a VG Micromass 7035 mass spectrometer at 70 eV with electron impact or on a Finnegan TSQ mass spectrometer with electrospraying ionization (ESI). Relative intensities are given in parenthesis. Microanalysis was performed by the Microanalytical Laboratory of the Department of Chemistry, National University of Singapore.

4.2. Calculation method

The structures of **135-CPs** and **126-CPs** series were optimized using the density functional theory electronic structure program-DMol^3 available as part of Materials Studio (Accelrys Inc).[29,30] In this code electronic wave function is expanded in a localized atom-centered basis set with each basis function defined numerically on a dense radial grid. All-electron calculations were performed with a double numeric polarized (DNP) basis set (which is analogous to the Gaussian 6-31(d,p) basis set), the most complete set available in the code. The gradient-corrected BLYP functional,[31,32] a finite basis-set cutoff of 4.0 Å and a 'fine' quality (convergence tolerances: energy 1.0×10^{-5} Ha; maximum force 0.002 Ha/Å; maximum displacement 0.005 Å. SCF tolerance: 1.0×10^{-6}) were used. During modeling, the crown moiety in cyclophane was maintained to tilt to one side and two thia-bridges took *cc*, *bc* or *bb* conformation during the calculation.

4.2.1. 1,8-Bis(2,6-diformylphenoxyl)-3,6-dioxaoctane (5a). A mixture of 2,6-diformylphenol (300 mg, 2.0 mmol), triethylene glycol dibromide (276 mg, 1.0 mmol) and anhydrous K_2CO_3 (500 mg) was stirred in dry DMF (10 mL) at 60–70 °C under nitrogen for 24 h. The reaction mixture was poured into ice water (50 mL) and stirred for 30 min. The resulting precipitate was collected by filtration and washed with water. The crude product was purified by chromatography on silica gel using ethyl acetate and hexane (2:3) as eluent to give **5a** (210 mg, 51%) as a light yellow solid: mp 120–121.5 °C; ^{1}H NMR 3.64 (oxyethylene, s, 4H), 3.83 (oxyethylene, m, 4H), 4.33 (oxyethylene, m, 4H), 7.34 (aromatic, t, 2H, J=7.6 Hz), 8.59 (aromatic, d, 4H, J=7.6 Hz), 10.44 (–C*H*O, s, 4H); IR (KBr) 1676 cm^{-1} (–CHO); MS (ESI) (*m*/*z*) 437.2 (M+ Na$^+$, 93); Anal. Calcd for $C_{22}H_{22}O_8$: C, 63.76; H, 5.35. Found: C, 63.89; H, 5.55.

4.2.2. 1,8-Bis(2,6-dihydroxyphenoxyl)-3,6-dioxaoctane (5b). A mixture of compound **5a** (150 mg, 3.62 mmol) and sodium borohydride (100 mg) in THF (10 mL) was heated at reflux for 1 h. The mixture was cooled and the THF was removed under reduced pressure. The residue was extracted with $CHCl_3$ and the organic layer was washed, dried and evaporated to afford tetrol **5b** (145 mg, 95%) as a colorless oil: ^{1}H NMR δ 3.42 (–O*H*, br. s, 4H), 3.69 (oxyethylene, s, 4H), 3.73–3.76 (oxyethylene, m, 4H), 4.03–4.06 (oxyethylene, m, 4H), 4.58 (–C*H*$_2$OH, s, 8H), 6.98 (aromatic, t, 2H, J=7.6 Hz), 7.18 (aromatic, d, 4H, J= 7.6 Hz); MS (EI) (*m*/*z*) 368.1 (M$^+$ −3H$_2$O, 12); IR (KBr) 3364 cm^{-1} (–OH); Anal. Calcd for $C_{22}H_{30}O_8$: C, 62.55; H, 7.16. Found: C, 62.30; H, 7.30.

4.2.3. 1,8-Bis(2,6-dibromomethylphenoxyl)-3,6-dioxaoctane (5c). PBr_3 (1.0 g, 3.7 mmol) was added to a solution of **5b** (0.20 g, 0.47 mmol) in dry 1,4-dioxane (10 mL) at 0 °C. The mixture was further stirred for 5 h at 0 °C, and then the mixture was poured into ice water/dichloromethane. The organic layer was separated and the water layer was extracted three times with dichloromethane. All organic layers were combined and washed with 10% $NaHCO_3$, water, and then evaporated. The residue was chromatographed on silica gel using ethyl acetate/hexane (9:1) as eluent to yield the product **5c** (0.24 g, 75%) as a white solid: mp 115–116 °C (lit.: 116–117 °C[33]); ^{1}H NMR δ

3.87 (oxyethylene, s, 4H), 3.95–3.98 (oxyethylene, m, 4H), 4.30–4.33 (oxyethylene, m, 4H), 4.64 (–CH_2Br, s, 8H), 7.11 (aromatic, t, 2H, J=7.6 Hz), 7.41 (aromatic, H, d, 4H, J=7.6 Hz).

4.2.4. 18,27-Dithia-1,4,7,10-tetraoxa-[10.3.3](1,2,6)cyclophane (1a). A solution of 95% sodium sulfide nonahydrate (480 mg, 2.0 mmol) in 95% ethanol (300 mL) and a solution of **5c** (674 mg, 1.0 mmol) in benzene (300 mL) in separate rotaflow dropping funnels were added dropwise simultaneously at the same rate to nitrogen purged 95% ethanol (1 L). After the addition, the mixture was stirred for another 15 h and the bulk of the solvent was removed under reduced pressure. Water and dichloromethane were added to the residue, and the mixture was stirred until all solids dissolved. The organic layer was separated, dried, and evaporated. The residue was chromatographed on silica gel using ethyl acetate/dichloromethane (1:40) as eluent to yield **1a** (140 mg, 33%) as colorless crystals: mp 213–215 °C; ^{1}H NMR ($CDCl_3$) δ 3.34 (–CH_2SCH_2–, d, 4H, J=14.5 Hz), 3.66–3.69 (oxyethylene, m, 4H), 3.92–3.95 (oxyethylene, m, 8H), 4.55 (–CH_2SCH_2–, d, 4H, J=14.5 Hz), 6.64 (aromatic, t, 2H, J=7.6 Hz), 6.97 (aromatic, d, 4H, J=7.6 Hz); ^{13}C NMR δ 155.28, 131.09, 129.19, 123.99, 73.15, 69.85, 69.24, 30.35; MS (EI) (*m*/*z*) 418 (M^+, 77); Anal. Calcd for $C_{22}H_{26}O_4S_2$: C, 63.13; H, 6.26; Found: C, 63.30; H, 6.30.

4.2.5. 1,8-Bis(4-methyl-2,6-dihydroxymethylphenoxyl)-3,6-dioxaoctane (7a). Triethylene glycol dibromide (4.92 g, 17.8 mmol) was added under nitrogen to a suspension of anhydrous K_2CO_3 (10 g, 72.4 mmol) and 2,6-dihydroxymethylphenol (6.0 g, 35.7 mmol) in acetone (70 mL). The mixture was maintained at gentle reflux for 5 days and the acetone was then removed under reduced pressure. The residue was poured into a mixture of water and dichloromethane. The organic layer was washed, dried, and then evaporated. The residue was chromatographed on silica gel using ethyl acetate/dichloromethane (15:85, then 40:60) as eluent to yield **7a** (5.35 g, 67%) as a colorless oil which crystallized on long standing when kept at 0 °C: mp 93–96 °C; ^{1}H NMR δ 2.28 (methyl, s, 6H), 3.78 (oxyethylene, s, 4H), 3.82–3.86 (oxyethylene, m, 4H), 4.12–4.15 (oxyethylene, m, 4H), 4.64 (–CH_2OH, s, 8H), 7.07 (aromatic, s, 4H); IR (KBr) 3387 cm^{-1} (–OH); MS (EI) (*m*/*z*) 414 (M^+-2H_2O, 7), 396 (M^+-3H_2O, 48). Anal. Calcd for $C_{24}H_{34}O_8$: C, 63.98; H, 7.61, 28.41. Found: C, 63.75; H, 7.77.

4.2.6. 1,8-Bis(4-methyl-2,6-dibromomethylphenoxyl)-3,6-dioxaoctane (7b). The preparation of **7b** follows the similar synthetic procedure of **5b**: mp 97–98 °C; ^{1}H NMR δ 2.29 (methyl, s, 6H), 3.86 (oxyethylene, s, 4H), 3.93–3.96 (oxyethylene, m, 4H), 4.26–4.28 (oxyethylene, m, 4H), 4.60 (–CH_2Br, s, 8H), 7.16 (aromatic, s, 4H); MS (EI) (*m*/*z*) 698 (M^+, 1), 700 (M^++2, 4), 702 (M^++4, 5.4), 704 (M^++6, 4), 706 (M^++8, 1); Anal. Calcd for $C_{24}H_{30}Br_4O_4$: C, 41.06; H, 4.31. Found: C, 40.90; H, 4.50.

4.2.7. 18,27-Dithia-14,22-dimethyl-1,4,7,10-tetraoxa-[10.3.3](1.2.6)cyclophane (1b). The preparation of **1b** follows the similar synthetic procedure of **1a**. Tetrabromide **7b** (700 mg, 1.0 mmol) reacted with sodium sulfide nonahydrate (480 mg, 2.0 mmol) to yield **1b** (140 mg, 31%) as colorless crystals: mp 223–225 °C; ^{1}H NMR δ 2.11 (methyl, s, 6H), 3.29 (–CH_2SCH_2–, d, 4H, J=14.5 Hz), 3.63–3.66 (oxyethylene, m, 4H), 3.90–3.92 (oxyethylene, m, 4H), 3.96 (oxyethylene, s, 4H), 4.51 (–CH_2SCH_2–, d, 4H, J=14.5 Hz), 6.80 (aromatic, s, 4H); ^{13}C NMR δ 153.34, 133.01, 130.52, 129.74, 73.26, 69.95, 69.39, 30.29, 20.57; MS (EI) (*m*/*z*) 446 (M^+, 23); Anal Calcd for $C_{24}H_{30}O_4S_2$: C, 64.54; H, 6.77. Found: C, 64.70; H, 6.50.

4.2.8. 2,4,6-Trimethyl-3,5-bis(bromomethyl)anisole (9). 2,4,6-Trimethylanisole (10 g, 66.6 mmol) was added to a mixture of 47% aq HBr (40 mL) and glacial acetic acid (180 mL), followed by 1,3,5-trioxane (18.0 g, 0.20 mol) and tetradecyltrimethyl ammonium bromide (0.50 g). The mixture was heated up and the temperature kept at 95 °C for 5 h (thin layer chromatography (TLC) was performed to monitor the completeness of the reaction). After cooling to room temperature, the white precipitate was filtered, washed with plenty of water and then dissolved in dichloromethane. The organic layer was washed with 5% bicarbonate, water and dried. The organic solvent was removed under the reduced pressure and residue was chromatographed on silica gel using ethyl acetate and hexane (10:90) as eluent to afford the pure **9** (8.3 g, 31%) as a white solid: mp 137–138.5 °C; ^{1}H NMR δ 2.36 (methyl, s, 6H), 2.42 (methyl, s, 3H), 3.67 (methoxy, s, 3H), 4.57 (–CH_2Br, s, 4H); MS (EI) (*m*/*z*) 338 (M^++4, 70), 336 (M^++2, 83), 334 (M^+, 72), 176 (M^+-2^{79}Br); Anal. Calcd for $C_{12}H_{16}Br_2O$: C, 42.89; H, 4.80. Found: C, 43.10; H, 4.65.

4.2.9. 2,4,6-Trimethyl-3,5-bis(mercaptomethyl)anisole (10). Compound **9** (3.63 g, 10.9 mmol) was added to a stirred solution of thiourea (1.65 g, 23.6 mmol) in absolute ethanol (40 mL). After addition, the mixture was continued to reflux for another 2 h, and then the mixture was cooled to room temperature, filtered and dried under vacuum to give 2,4,6-trimethyl-3,5-bis(isothioureamethyl)anisole dibromide crude salt (5.0 g). The salt was used in the next step without further purification. A solution of 5.0 g of salt in 20% KOH (50 mL) was boiled under reflux for 5 h. After the mixture was cooled to room temperature, 9 M aqueous H_2SO_4 was added to neutralize the alkaline solution until pH to 7. The neutralized mixture was extracted with dichloromethane. The organic layer was washed with water, dried and concentrated. The residue was chromatographed on silica gel using ethyl acetate and hexane as eluent (1:9) to give **10** (2.17 g, 83%) as a pale yellowish solid: mp 109–110 °C; ^{1}H NMR δ 1.59 (–SH, t, 2H, J=6.4 Hz), 2.34 (methyl, s, 6H), 2.40 (methyl, s, 3H) 3.66 (methoxy, s, 3H), 3.77 (–CH_2SH, d, 4H, J=6.4 Hz); MS (EI) (*m*/*z*) 242 (M^+, 87); Anal. Calcd for $C_{12}H_{18}OS_2$: C, 59.46; H, 7.48. Found: C, 59.70; H, 7.30.

4.2.10. 2,11-Dithia-5,7,9,14,16,18-hexamethyl-6,15-dimethoxy[3.3](1,3)cyclophane (11/13). A solution of dibromide **9** (3.00 g, 8.93 mmol) and dithiol **10** (2.16 g, 8.93 mmol) dissolving in benzene (500 mL) were slowly added dropwise to 95% ethanol (1500 mL) over 8 h. The resulting solution was stirred for another 16 h, and then the bulky solvent was removed under the reduced pressure. Dichloromethane was added to the residue and stirred. The organic solvent was washed with dilute hydrochloric acid

and water. The dichloromethane was removed and the residue was chromatographed on silica gel using dichloromethane and hexane (1:1) to give *anti*-isomer (1.83 g, 49%) and *syn*-isomer (0.363 g, 10%) as colorless crystals and white solid, respectively.

4.2.11. *anti*-2,11-Dithia-5,7,9,14,16,18-hexamethyl-6,15-dimethoxy[3.3](1,3)cyclophane (11). Mp >240 °C (decomposed); ^{1}H NMR δ 1.21 (methyl, s, 6H), 2.44 (methyl, s, 12H), 3.69 (methoxy, s, 6H), 3.67 (–C*H*$_2$SC*H*$_2$–, d, 4H, J=13.7 Hz), 3.78 (–C*H*$_2$SC*H*$_2$–, d, 4H, J=13.7 Hz); MS (ESI) no molecular ion peak was observed MS (EI) (*m*/*z*) 416 (M^+, 75); Anal. Calcd for $C_{24}H_{32}O_2S_2$: C, 69.19; H, 7.74. Found: C, 69.33; H, 7.64.

4.2.12. *syn*-2,11-Dithia-5,7,9,14,16,18-hexamethyl-6,15-dimethoxy[3.3](1,3)cyclophane (13). Mp >240 °C (decomposed); ^{1}H NMR δ 2.07 (methyl, s, 6H), 2.34 (methyl, s, 12H), 3.61 (methoxy, s, 6H), 3.70 (–C*H*$_2$SC*H*$_2$–, s, 8H); MS (EI) (*m*/*z*) no molecular ion peak was observed; Anal. Calcd for $C_{24}H_{32}O_2S_2$: C, 69.19; H, 7.74. Found: C, 69.50; H, 7.90.

4.2.13. *anti*-2,11-Dithia-5,7,9,14,16,18-hexamethyl-6,15-dihydroxy[3.3](1,3)cyclophane (12). 1 M BBr_3/CH_2Cl_2 (2.0 mL, 2.0 mmol) was added to the solution of anti-**11** (100 mg, 0.24 mmol) in $CHCl_3$ (5 mL) at −78 °C. The mixture was stirred at −78 °C for 3 h, and then stirred overnight at room temperature. The water was added to the mixture, and then extracted with CH_2Cl_2. The organic layer was washed with water, dried and filtered. CH_2Cl_2 was removed and the residue was chromatographed on silica gel using dichloromethane and acetone (3:1) as eluent to give **12** (10 mg, 11%) as a white solid: mp 250 °C (decomposed); ^{1}H NMR δ 1.21 (methyl, s, 6H), 2.38 (methyl, s, 12H), 3.67 (–CH_2SCH_2–, d, 4H, J=13.8 Hz), 3.78 (–CH_2SCH_2–, d, 4H, J=13.8 Hz) 4.55 (–OH, s, 2H); IR (KBr) 3545 cm^{-1} (–OH); MS (EI) (*m*/*z*) 388 (M^+, 66); Anal. Calcd $C_{22}H_{28}O_2S_2$ for: C, 68.00; H, 7.26. Found: C, 67.90; H, 7.41.

5. Supporting materials

Crystallographic data for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publication numbers CCDC-245673 (**1a**) and 245672 (**1b**). Copies of the data can be obtained free of charge upon application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 1223 33603; e-mail: deposit@ccdc.cam.ac.uk).

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Synthesis of *cis* bis-β-lactams via Staudinger cycloaddition reaction using C_2-symmetric 1,2-diamines

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Abstract—An efficient stereoselective synthesis of bis-β-lactams via cycloaddition reaction (Staudinger reaction) of ketenes with bisimines derived from C_2-symmetric 1, 2-diamines is described. The reaction provided diastereomeric mixture of *meso* and C_2-symmetric *cis*-bis-β-lactams with higher selectivity for *meso*-bis-β-lactams.

1. Introduction

The β-lactam skeleton is the key structural unit of the most widely employed β-lactam antibiotics.[1] The constant need for new drugs displaying broader antibacterial activity and the necessity for new β-lactam antibiotics to combat the microorganisms that have built up resistance against the most traditional drugs,[2] have maintained the interest of organic chemists in β-lactams for decades. In addition to its use in the synthesis of variety of β-lactam antibiotics, the β-lactam skeleton has been recognized as a useful building block by exploiting its strain energy associated with four-member ring.[3] Efforts have been made in exploring such new aspects of β-lactam chemistry using enantiomerically pure β-lactams as versatile intermediates for organic syntheses.[3c,g–h,4] Ojima et al.[5] have shown the utility of bis-β-lactams for the synthesis of peptides. The synthesis of bis-β-lactams, in general, has been reported by a step-wise construction of β-lactam rings.[6]

In continuation of our work on synthesis of bis-β-lactams,[7] we were interested in building bis-β-lactams from C_2-symmetric vicinal bisimines using the Staudinger cycloaddition reaction. Among the various methods available for the synthesis of β-lactams, the Staudinger cycloaddition reaction (ketene–imine cycloaddition reaction) is the most widely used,[8] mainly because of the simplicity in reaction procedures and predictability of stereochemical output. We have been studying the Staudinger cycloaddition reaction for the diastereoselective construction of the β-lactam ring for several years.[9] In this publication, we wish to report our work on the synthesis of bis-β-lactams from bisimines and ketenes using the Staudinger cycloaddition reaction.

2. Results and discussion

We selected *trans*-1,2-diaminocyclohexane for the preparation of various bisimines from different aldehydes and these imines were used for the stereoselective construction of bis-β-lactams. *trans*-1,2-Diaminocyclohexane is one of a few vicinal diamines commercially available in both the enantiomeric forms with wide applications in stereoselective synthesis[10] and chemotherapy.[11] Bisimines derived from *trans*-1,2-diaminocyclohexane have been used as chiral ligands for asymmetric epoxidation,[12] cyclopropanation,[13] Diels–Alder reaction,[14] asymmetric alkylation[15] and several other asymmetric reactions.[16] Gawronski et al.[17] have shown that out of four different conformations of *N*,*N*-dibenzylidine-1, 2-diaminocyclohexane, *syn–syn*-bisimine **A** is the most favored conformation (Fig. 1). We were interested in studying the effect of this conformational preference on the product formation during [2+2] cycloaddition reaction of bisimine and ketene.

The bisimines **3a–c** were prepared by stirring (±) *trans*-1,2-diaminocyclohexane with freshly distilled excess aldehydes (benzaldehyde, 4-methoxybenzaldehyde and cinnamaldehyde) in the presence of anhydrous $MgSO_4$ or anhydrous K_2CO_3 in dry dichloromethane for about 15 h at room temperature. The unreacted aldehyde was removed by washing the crude reaction product with 10% ethyl

Keywords: Stereoselective synthesis; Ketenes; Imines; Staudinger cycloaddition reaction.
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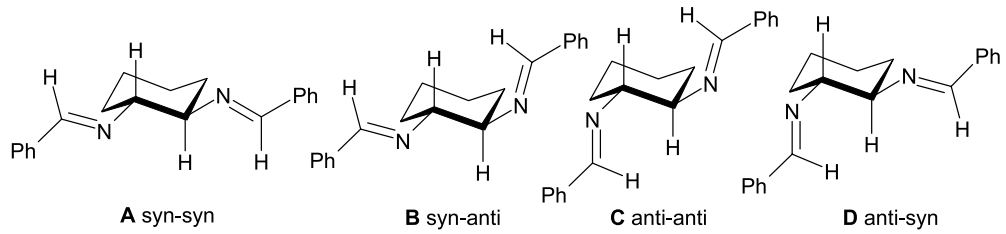
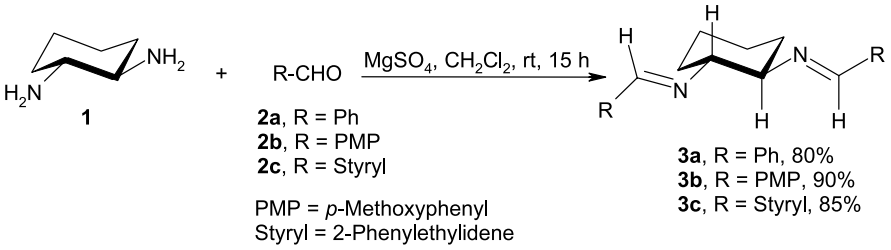


Figure 1. Conformations of *N*,*N*′-dibenzylidinecyclohexane-1,2-diamine.

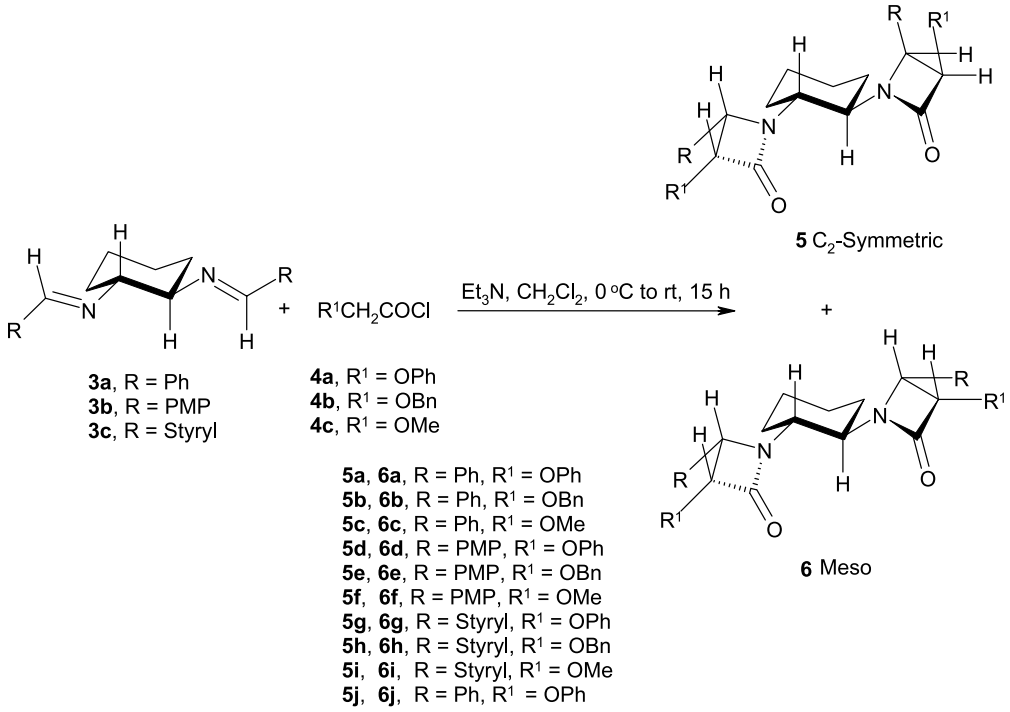


Scheme 1.

acetate–pet ether solution to get bisimines **3a–c** (Scheme 1) in very good yields.

Bisimines **3a–c** on cycloaddition reaction (Staudinger reaction) with ketenes generated from various acid chlorides (phenoxyacetyl chloride, benzyloxyacetyl chloride and methoxyacetyl chloride) in the presence of triethylamine gave diastereomeric mixtures of *cis*-bis-β-lactams **5a–g** and **6a–g** in good to excellent yields (Scheme 2, Table 1). The TLC and ^{1}H NMR spectra of the crude reaction mixture showed the presence of two diastereomers. These diastereomers were separated by flash column chromatography. The C_2-symmetric structure for bis-β-lactam **5a** was assigned on the basis of ^{1}H NMR spectral analysis. The ^{1}H NMR spectra showed two doublets at δ 5.27 and 5.39 for *cis*-β-lactam ring protons (J=4.7 Hz for *cis* β-lactam protons). A single broad doublet at δ 3.97 for both the methyne protons of cyclohexane ring with J=9 Hz was observed. ^{13}C NMR spectra also showed a single peak for both the methyne carbons of cyclohexane ring at 53.91 ppm; two peaks for β-lactam carbons of both the rings at 61.4 ppm (*C*–4H) and 81.6 ppm (*C*–3H); and a single peak for both the carbonyl carbons at 167.7 ppm. This was further confirmed by single crystal X-ray spectroscopic analysis of **5a** (Fig. 2).[18]

The *meso* structure was assigned to the other diastereomer **6a** as ^{1}H NMR spectra showed two doublets at δ 5.05 and 5.40 (J=4.7 Hz) for one *cis*-β-lactam ring protons; and two



Scheme 2.

Table 1. Synthesis of bis-β-lactams **5a–i** and **6a–i**

β-Lactams	R[a]	R[1]	Ratio of **5** and **6**[b]	Yield (%)[c]	Mp of **5** (°C)[d]	Mp of **6** (°C)[d]
5a, **6a**	–Ph	–OPh	34:66	90	231–232	82–83
5b, **6b**	–Ph	–OBn	34:66	87	111–112	72–73
5c, **6c**	–Ph	–OMe	23:77	86	247–248	191–192
5d, **6d**	–PMP	–OPh	22:78	93	158–159	209–210
5e, **6e**	–PMP	–OBn	28:72	80	194–195	123–124
5f, **6f**	–PMP	–OMe	24:76	73	229–230	84–85
5g, **6g**	–Styryl	–OPh	36:64	88	245–246	175–176
5h, **6h**	–Styryl	–OBn	46:54	81	179–180	61–62
5i, **6i**	–Styryl	–OMe	42:56	86	211–212	79–80

[a] PMP=*p*-methoxyphenyl; Bn= benzyl.
[b] The ratio of the diastereomers **5** and **6** was determined by ^{1}H NMR.
[c] Isolated yields of the diastereomeric mixture of **5** and **6**.
[d] Pure diastereomers were obtained by flash column chromatography.

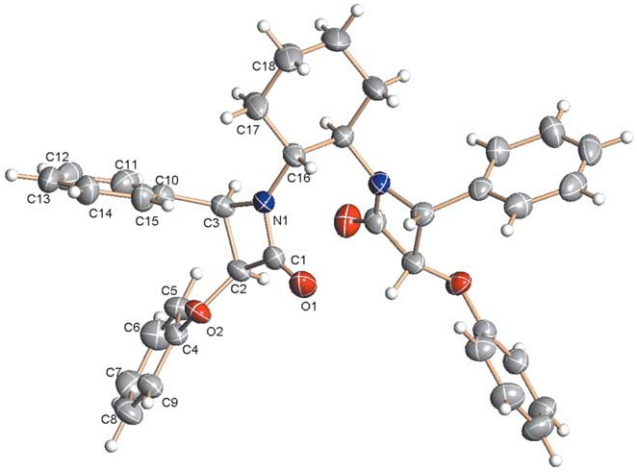


Figure 2. ORTEP diagram of **5a**.

doublets at δ 5.47 and 5.56 (J=4.6 Hz) for other *cis*-β-lactam ring protons due to non-equivalence of both the β-lactam rings. Two multiplets at δ 3.55–3.60 and 3.71–3.76 for two non-equivalent methyne protons of cyclohexane ring were observed for *meso* bis-β-lactam **6a**. Similarly ^{13}C NMR spectra showed two sets of carbon signals for both the azetidin-2-one rings as well as carbonyl carbons. The structure was further confirmed by single crystal X-ray analysis (Fig. 3).[18] The structures for other C_2-symmetric bis-β-lactams **5b–i** and *meso* bis-β-lactams **6b–i** were assigned by correlating the spectral data with that of **5a** and **6a**, respectively. Higher selectivity for *meso* bis-β-lactam formation was observed in the cycloaddition reaction (Table 1).

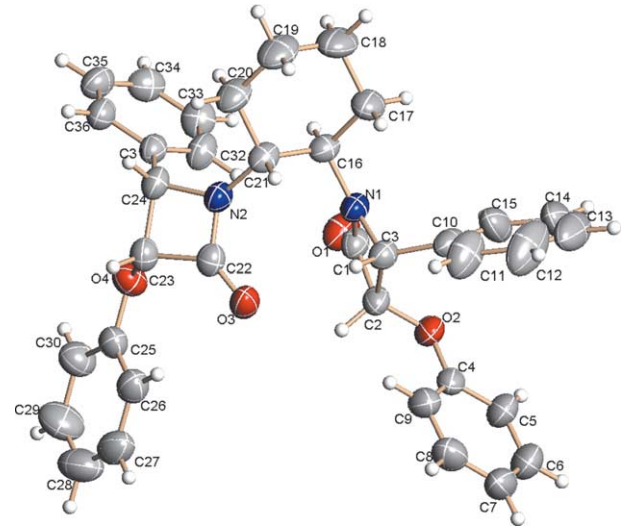
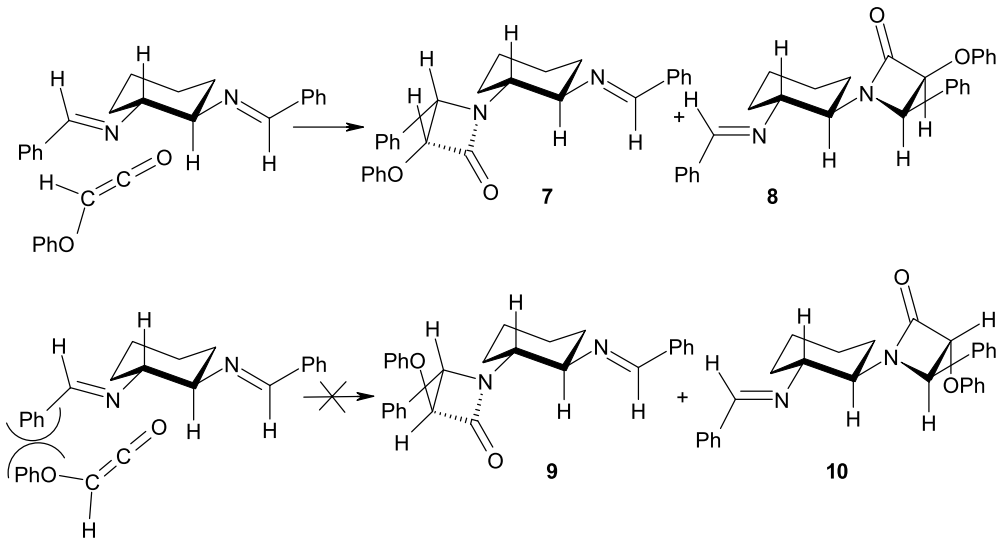


Figure 3. ORTEP diagram of **6a**.

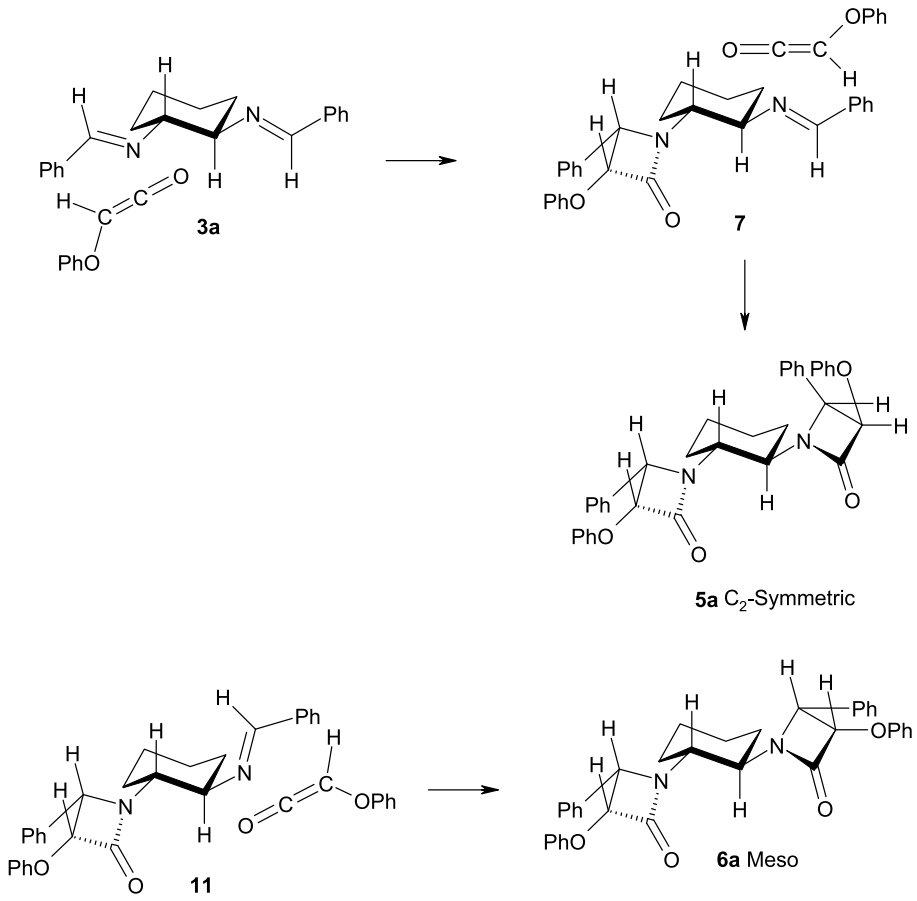
We believe that mono-β-lactam is initially formed by the reaction of the most stable *syn–syn* bis-imine conformer **A** with ketene. The approach of the ketene in the Staudinger cycloaddition reaction is such that the steric interaction between the aryl group of the imine and phenoxy group of the ketene is minimum in the transition state (Scheme 3) resulting in the formation of *cis*-β-lactam. However, the formation of *trans*-β-lactam is unfavorable due to severe steric interaction between the aryl group of imine and phenoxy group of ketene in the transition state. The mono-β-lactam **7** further undergoes cycloaddition reaction with the second molecule of ketene to give bis-β-lactam (Scheme 4). The approach of the second ketene towards the *syn*-imine **7** is from the opposite site of the preformed azetidinone ring to give C_2-symmetric bis-β-lactam **5a**. However, *meso* bis-β-lactam **6a** is formed by the cycloaddition of *anti*-imine **11** with the second molecule of ketene from opposite site of the preformed β-lactam ring as shown in Scheme 4. To substantiate this, cycloaddition reaction of bis-imine **3a** with 1 equiv of phenoxyketene, generated in situ from phenoxyacetyl chloride and triethylamine, was carried out. The ^{1}H NMR of the crude reaction product showed the formation of two diastereomers of mono-β-lactams **7** and **8** in equal amount along with traces of bis-β-lactams **5a** and **6a**. However, all our attempts to separate the diastereomers were unsuccessful. This mixture was further subjected to Staudinger reaction with 1 equiv of phenoxyketene to get mixture of bis-β-lactams **5a** and **6a** in good yield.

Other C_2-symmetric vicinal diamines, such as 1,2-diphenylethylenediamine (**12a**)[20] and 2,3-diaminobutane (**12b**),[21] were also used for the preparation of bis-imines **13a**,**b**. These imines were used for the Staudinger reaction (Scheme 5). Here too, a mixture of C_2-symmetric **14a–d** and *meso* bis-β-lactams **15a–d**, with higher selectivity for meso isomer, was obtained in very good yields (Table 2). The diastereomers **14a–d** and **15a–d** were separated by flash column chromatography and characterized by spectral analyses.

The Staudinger cycloaddition reaction conditions were also



Scheme 3.

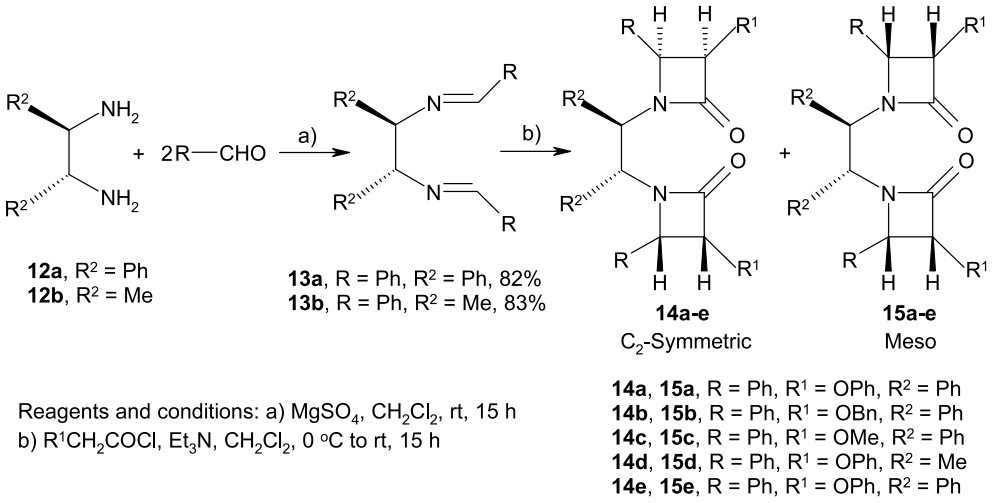


Scheme 4.

employed for the asymmetric synthesis of bis-β-lactams (**5j**, **6j** Scheme 2 and **14e**, **15e** Scheme 5) from chiral bis-imine derived from optically pure (+)-1*R*,2*R*-*trans*-1,2-diaminocyclohexane,[22] (−)-1*S*,2*S*-diphenylethylenediamine[23] and benzaldehyde; and in situ generated phenoxyketene from phenoxyacetyl chloride. The cycloaddition reaction gave a mixture of C_2-symmetric **5j**, **14e** and *meso* **6j**, **15e** bis-β-lactams (Table 3). Both C_2-symmetric and *meso* β-lactams were separated by careful flash column chromatography and characterized by spectral analyses.

3. Conclusion

In conclusion we have shown the application of Staudinger cycloaddition reaction for the synthesis of bis-β-lactams



Scheme 5.

Table 2. Synthesis of bis-β-lactams **14a–d** and **15a–d**

Compounds	R	R^1	R^2	Ratio of **14** and **15**[a]	Yield (%)[b]	Mp of **14** (°C)[c]	Mp of **15** (°C)[c]
14a, **15a**	–Ph	–OPh	–Ph	42:58	81	197–198	201–202
14b, **15b**	–Ph	–OBn	–Ph	44:56	84	190–191	79–80
14c, **15c**	–Ph	–OMe	–Ph	40:60	88	194–195	201–202
14d, **15d**	–Ph	–OPh	–Me	30:70	91	69–70	175–176

[a] The ratio of the diastereomers **14** and **15** was determined by ^{1}H NMR.
[b] Isolated yields of the diastereomeric mixture of **14** and **15**.
[c] Pure diastereomers were obtained by flash column chromatography.

Table 3. Asymmetric synthesis of bis-β-lactams **5j**, **6j**, **14e** and **15e**

Compound	R	R^1	R^2	Ratio[a]	Yield (%)[b]	$[\alpha]_D$ ($CHCl_3$)[c]	Configuration
5j	–Ph	–OPh		**5j/6j** 40:60	76	−146.9 (*c*, 0.80)	1*R*,2*R*,3′*S*,4′*R* 3″*S*,4″*R*
6j	–Ph	–OPh				−53.83 (*c*, 1.00)	1*R*,2*R*,3′*S*,4′*R* 3″*R*,4″*S*
14e	–Ph	–OPh	–Ph	**14e/15e** 36:64	80	+3.03 (*c*, 0.99)	1*S*,2*S*,3′*R*,4′*S* 3″*R*,4″*S*
15e	–Ph	–OPh	–Ph			+6.15 (*c*, 0.65)	1*S*,2*S*,3′*R*,4′*S* 3″*S*,4″*R*

[a] The ratio of the diastereomers **5j/6j** and **14e/15e** was determined by ^{1}H NMR.
[b] Isolated yields of the diastereomeric mixture.
[c] Pure diastereomers were obtained by flash column chromatography.

from C_2-symmetric 1,2-diamines in excellent yields. Both C_2-symmetric as well as *meso* bis-β-lactams were formed in the reaction, which could be easily separated. The reaction was also employed for asymmetric synthesis of bis-β-lactams using enantiomerically pure (+)-1*R*,2*R*-*trans*-1,2-diaminocyclohexane and (−)-1*S*,2*S*-1,2-diphenylethylenediamine.

4. Experimental

4.1. General

^{1}H NMR and ^{13}C NMR Spectra were recorded in $CDCl_3$ solution on a Bruker AC 200 or Bruker MSL 300 spectrometers and chemical shifts are reported in ppm downfield from tetramethylsilane for ^{1}H NMR. Infrared spectra were recorded on Perkin–Elmer Infrared Spectrophotometer, Model 599-B or Shimadzu FTIR-8400 using sodium chloride optics. Melting points were determined on a Thermonik Campbell melting point apparatus and were uncorrected. The microanalyses were performed on a Carlo-Erba, CHNS-O EA 1108 elemental analyzer. Optical rotations were recorded on a JASCO-181 digital polarimeter under standard conditions.

4.2. General procedure for the preparation of imines 3a–c

A mixture of freshly distilled aldehyde (2.78 g, 26.3 mmol), (±) *trans*-1,2-diaminocyclohexane (1.0 g, 8.8 mmol) and anhydrous $MgSO_4$ or anhydrous K_2CO_3 (2.20 g, 17.5 mmol) in dry dichloromethane (30 mL) was stirred for 15 h at room temperature. The reaction mixture was then filtered through a bed of celite and solvent was removed under reduced pressure. The residue was then treated with 10% solution of ethyl acetate in pet ether to remove unreacted aldehyde and filtered to give required bis-imine (2.00 g, 80%). Following this procedure bisimines **3a–c** were prepared in excellent yield.

4.2.1. *N*,*N*′-Dibenzylidenecyclohexane-1,2-diamine (3a). It was obtained as a white solid, recrystallized from EtOAc–petroleum ether (90:10) as needles, yield 80%; mp 129–130 °C; [found C, 82.58; H, 7.54; N, 9.53 $C_{20}H_{22}N_2$ requires C, 82.72; H, 7.63; N, 9.64]; ν_{max} (Nujol) 1462, 1578, 1641 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 1.03–2.07 (m, 8H, C*H*$_2$, Cyclohexane), 3.21–3.45 (m, 2H, C*H*, Cyclohexane), 7.12–7.64 (m, 10H, Ar), 8.15 (s, 2H, –N=C*H*); δ_C (75.48 MHz, $CDCl_3$) 24.5, 32.9, 73.7, 127.9, 128.2, 130.0, 136.5, 160.8; MS (*m*/*z*): 290 (M^+).

4.2.2. *N*,*N*′-Bis (4-methoxybenzylidene)cyclohexane-1,2-diamine (3b). It was isolated as a white solid and recrystallized from EtOAc–petroleum ether (90:10) to give white needles; yield 90%; mp 166–167°C; [found C, 75.36; H, 7.38; N, 7.86 $C_{22}H_{26}N_2O_2$ requires C, 75.48; H, 7.49; N, 8.00]; ν_{max} ($CHCl_3$) 1253, 1512, 1606, 1643 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 1.20–1.97 (m, 8H, C*H*$_2$, Cyclohexane), 3.27–3.42 (m, 2H, C*H*, Cyclohexane), 3.78 (s, 6H, OC*H*$_3$), 6.82 (d, J=9 Hz, 4H, Ar), 7.54 (d, J=9 Hz, 4H, Ar), 8.13 (s, 2H, –N=C*H*); δ_C (75.48 MHz, $CDCl_3$) 24.5, 33.0, 55.2, 73.7, 113.7, 129.2, 129.4, 160.3, 161.2; MS (*m*/*z*): 352 (M^+).

4.2.3. *N*,*N*′-Bis (styrylmethylene)cyclohexane-1,2-diamine (3c). It was isolated as a brown oil; yield 85%; [found C, 84.08; H, 7.57; N, 8.04 $C_{24}H_{26}N_2$ requires C, 84.17; H, 7.65; N, 8.18]; ν_{max} (neat) 1253, 1448, 1632, 1677, 2854, 2929 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 1.22–1.84 (m, 8H, C*H*$_2$, Cyclohexane), 3.06–3.23 (m, 2H, C*H*, Cyclohexane), 6.70–6.80 (m, 4H, C*H*-olefin), 7.05–7.55 (m, 10H, Ar), 7.80–7.90 (m, 2H, –N=C*H*); δ_C (75.48 MHz, $CDCl_3$) 24.3, 33.0, 73.7, 127.0, 127.9, 128.3, 128.9, 131.0, 135.7, 141.3, 152.4, 162.4; MS (*m*/*z*): 342 (M^+).

4.3. A typical procedure for the preparation of β-lactams 5a and 6a

A solution of the phenoxyacetyl chloride **4a** (0.350 g, 3.0 mmol) in dry methylene chloride (10 mL) was added slowly to a solution of the imine **3a** (0.200 g, 1.0 mmol) and triethylamine (0.96 mL, 10.0 mmol) in CH_2Cl_2 (10 mL) at 0 °C. After the addition was complete, the reaction mixture was allowed to warm up to room temperature and stirred for 15 h. The reaction mixture was then washed with water (2× 10 mL), saturated sodium bicarbonate solution (10 mL) and saturated brine solution (10 mL). The organic layer was then dried over anhydrous Na_2SO_4, and concentrated to give the crude diastereomeric mixture (0.350 g, 90%) The diastereomers were separated by flash column chromatography (petroleum ether–ethyl acetate 7:3) to give pure diastereomer of β-lactams (**5a** and **6a**). Following this procedure other β-lactams **5b–i** and **6b–i** were also prepared.

4.3.1. 1,2-Bis (3′-phenoxy-4′-phenylazetidin-2′-one-1′-yl)cyclohexane (5a). It was isolated as a white solid from diastereomeric mixture by flash column chromatography and recrystallized from dichloromethane–petroleum ether, white crystalline solid, mp 231–232 °C; [found C, 77.19; H, 5.88; N, 4.84 $C_{36}H_{34}N_2O_4$ requires C, 77.39, H, 6.13; N, 5.01]; R_f (30% ethyl acetate/pet ether) 0.42; ν_{max} ($CHCl_3$) 1745 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 0.69–1.80 (m, 8H, C*H*$_2$, Cyclohexane), 3.97 (br d, J=9 Hz, 2H, C*H*, Cyclohexane), 5.27 (d, J=4.7 Hz, 2H, C4*H*), 5.39 (d, J=4.7 Hz, 2H, C3*H*), 6.48–7.73 (m, 20H, Ar); δ_C (75.48 MHz) 24.4, 30.1, 54.0, 61.4, 81.6, 115.7, 121.9, 128.0, 128.6, 128.9, 129.1, 134. 9, 156.8, 167.7; MS (*m*/*z*): 588 (M^+).

4.3.2. 1-(3′-Phenoxy-4′-phenylazetidin-2′-one-1′-yl)-2-(3″-phenoxy-4″-phenylazetidin-2″-one-1″-yl)cyclohexane (6a). It was obtained as a white solid, which was recrystallized from methanol, white needles, mp 82–83 °C; [found C, 77.23; H, 5.96; N, 4.78 $C_{36}H_{34}N_2O_4$ requires C, 77.39, H, 6.13; N, 5.01]; R_f (30% ethyl acetate/pet ether) 0.25; ν_{max} ($CHCl_3$) 1753 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 0.83–2.06 (m, 8H, C*H*$_2$, Cyclohexane), 3.55–3.60 (m, 1H, C*H*, Cyclohexane), 3.71–3.76 (m, 1H, C*H*, Cyclohexane), 5.05 (d, J=4.7 Hz, 1H, C4*H*), 5.40 (d, J=4.7 Hz, 1H, C4′*H*), 5.47 (d, J=4.6 Hz, 1H, C3*H*), 5.56 (d, J=4.6 Hz, 1H, C3′*H*), 6.72–7.55 (m, 20H, Ar); δ_C (125 MHz) 24.1, 29.2, 31.3, 53.4, 55.2, 61.2, 62.2, 81.1, 81.3, 115.7, 121.8, 122.0, 128.0, 128.4, 128.6, 129.0, 129.1, 133.6, 134.8, 157.0, 166.4, 166.5; MS (*m*/*z*): 588 (M^+).

4.3.3. 1,2-Bis (3′-benzyloxy-4′-phenylazetidin-2′-one-1′-yl)cyclohexane (5b). It was obtained as a white solid, which was recrystallized from dichloromethane–methanol, white crystalline solid, mp 111–112 °C; [found C, 77.56; H, 6.35; N, 4.87 $C_{38}H_{38}N_2O_4$ requires C, 77.79, H, 6.53; N, 4.77]; R_f (30% ethyl acetate/pet ether) 0.48; ν_{max} ($CHCl_3$) 1747 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 0.72–1.84 (m, 8H, C*H*$_2$, Cyclohexane), 3.92 (br d, J=9 Hz, 2H, C*H*, Cyclohexane), 4.01 (d, J=10.9 Hz, 2H, CH_2Ph), 4.31 (d, J=10.9 Hz, 2H, CH_2Ph), 4.89 (d, J=4.3 Hz, 2H, C4*H*), 5.11 (d, J=4.3 Hz, 2H, C3*H*), 6.81–7.68 (m, 20H, Ar); δ_C (75.48 MHz) 24.0, 24.4, 29.7, 30.1, 53.4, 61.0, 72.3, 72.5, 83.8, 81.6, 127.8, 128.1, 128.2, 128.5, 128.8, 129.3, 135.6, 136.3, 167.5, 168.3; MS (*m*/*z*): 586 (M^+).

4.3.4. 1-(3′-Benzyloxy-4′-phenylazetidin-2′-one-1′-yl)-2-(3″-benzyloxy-4″-phenylazetidin-2″-one-1″-yl)cyclohexane (6b). It was obtained as a white solid, which was recrystallized from methanol, white needles, mp 72–73 °C; [found C, 77.62; H, 5.40; N, 4.65 $C_{38}H_{38}N_2O_4$ requires C, 77.79, H, 5.33; N, 4.77]; R_f (30% ethyl acetate/pet ether) 0.35; ν_{max} ($CHCl_3$) 1749 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 0.82–2.0 (m, 8H, C*H*$_2$, Cyclohexane), 3.41–3.73 (m, 2H, C*H*, Cyclohexane), 4.07 (d, J=11.0 Hz, 1H, C*H*Ph), 4.16 (d, J=11.0 Hz, 1H, C*H*Ph), 4.27 (d, J=7.8 Hz, 1H, C*H*Ph), 4.33 (d, J=7.8 Hz, 1H, C*H*Ph), 4.85 (d, J=4.7 Hz, 1H, C4*H*), 4.88 (d, J=4.7 Hz, 1H, C4′*H*), 4.98 (d, J=4.3 Hz, 1H, C3*H*), 5.29 (d, J=4.3 Hz, 1H, C3′*H*), 6.88–7.66 (m, 20H, Ar); δ_C (125 MHz) 24.0, 29.3, 31.4, 52.9, 54.7, 60.7, 61.7, 72.3, 82.4, 83.0, 128.2, 128.5, 129.0, 129.2, 134.2, 135.4, 136.2, 136.4, 167.2, 167.5; MS (*m*/*z*): 586 (M^+).

4.3.5. 1,2-Bis (3′-methoxy-4′-phenylazetidin-2′-one-1′-yl)cyclohexane (5c). It was obtained as a white solid, which was recrystallized from methanol, white crystalline solid, mp 247–248 °C; [found C, 71.59; H, 6.71; N, 6.22 $C_{26}H_{30}N_2O_4$ requires C, 71.86, H, 6.96; N, 6.45]; R_f (30% ethyl acetate/pet ether) 0.44; ν_{max} ($CHCl_3$) 1743 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 0.52–1.95 (m, 8H, C*H*$_2$, Cyclohexane), 3.01 (s, 6H, OC*H*$_3$), 3.73 (br d, J=9 Hz, 2H, C*H*, Cyclohexane), 4.49 (d, J=4.3 Hz, 2H, C4*H*), 4.92 (d, J=

4.3 Hz, 2H, C3*H*), 7.16–7.42 (m, 10H, Ar); δ_C (50.32 MHz) 24.3, 29.9, 53.4, 58.0, 60.8, 85.1, 123.3, 128.1, 128.7, 135.4, 168.5; MS (*m*/*z*): 434 (M^+).

4.3.6. 1-(3′-Methoxy-4′-phenylazetidin-2′-one-1′-yl)-2-(3″-methoxy-4″-phenylazetidin-2″-one-1″-yl)cyclohexane (6c). It was obtained as a white solid, which was recrystallized from methanol, white needles, mp 191–192 °C; [found C, 71.63; H, 6.73; N, 6.33 $C_{26}H_{30}N_2O_4$ requires C, 71.86, H, 6.96; N, 6.45]; R_f (30% ethyl acetate/pet ether) 0.33; ν_{max} ($CHCl_3$) 1747 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 0.45–1.91 (m, 8H, CH_2, Cyclohexane), 3.01 (s, 6H, OCH_3), 3.18–3.54 (m, 2H, C*H*, Cyclohexane), 4.47 (d, *J*=4.3 Hz, 1H, C4*H*), 4.56 (d, *J*=4.3 Hz, 1H, C4′*H*), 4.64 (d, *J*=4.7 Hz, 1H, C3*H*), 5.06 (d, *J*=4.7 Hz, 1H, C3′*H*), 7.04–7.42 (m, 10H, Ar); δ_C (75.48 MHz) 24.0, 29.2, 31.3, 53.1, 55.0, 58.0, 60.5, 61.8, 84.6, 84.8, 128.0, 128.4, 128.8, 128.8, 129.0, 134.1, 135.4, 167.4; MS (*m*/*z*): 434 (M^+).

4.3.7. 1,2-Bis [3′-phenoxy-4′-(*p*-methoxyphenyl)azetidin-2′-one-1′-yl]cyclohexane (5d). It was obtained as a white solid, which was recrystallized from dichloromethane–methanol, white needles, mp 158–159 °C; [found C, 73.71; H, 6.03; N, 4.52 $C_{38}H_{38}N_2O_6$ requires C, 73.77, H, 6.19; N, 4.52]; R_f (30% ethyl acetate/pet ether) 0.59; ν_{max} ($CHCl_3$) 1747 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 0.67–1.82 (m, 8H, CH_2, Cyclohexane), 3.93 (br d, *J*=9 Hz, 2H, C*H*, Cyclohexane), 3.76 (s, 6H, OCH_3), 5.22 (d, *J*=4.7 Hz, 2H, C4*H*), 5.34 (d, *J*=4.7 Hz, 2H, C3*H*), 6.54–7.47 (m, 18H, Ar); δ_C (50.32 MHz) 24.3, 29.9, 29.7, 30.1, 53.7, 55.0, 60.9, 81.4, 113.3, 114.6, 115.5, 121.8, 126.5, 129.1, 129.5, 129.9, 156.7, 159.7, 167.6; MS (*m*/*z*): 620 (M^+).

4.3.8. 1-[3′-Phenoxy-4′-(*p*-methoxyphenyl)azetidin-2′-one-1′-yl]-2-[3″-phenoxy-4″- (*p*-methoxyphenyl)azetidin-2″-one-1″-yl]cyclohexane (6d). It was obtained as a white solid, which was recrystallized from dichloromethane–methanol, white needles, mp 209–210 °C; [found C, 73.59; H, 6.07; N, 4.28 $C_{38}H_{38}N_2O_6$ requires C, 73.77, H, 6.19; N, 4.52]; R_f (30% ethyl acetate/pet ether) 0.47; ν_{max} ($CHCl_3$) 1753 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 0.83–2.06 (m, 8H, CH_2, Cyclohexane), 3.49–3.71 (m, 2H, C*H*, Cyclohexane), 3.75, 3.79 (s, 6H, OCH_3), 5.01 (d, *J*=4.7 Hz, 1H, C4*H*), 5.37 (d, *J*=4.7 Hz, 1H, C4′*H*), 5.46 (d, *J*=4.3 Hz, 1H, C3*H*), 5.50 (d, *J*=4.3 Hz, 1H, C3′*H*), 6.70–7.55 (m, 18H, Ar); δ_C (50.32 MHz) 23.9, 29.0, 31.4, 53.0, 55.0, 55.1, 60.7, 61.5, 81.0, 81.1, 113.4, 113.8, 115.6, 121.7, 121.9, 125.2, 126.6, 129.1, 130.4, 157.0, 159.7, 160.0, 166.4, 166.5; MS (*m*/*z*): 620 (M^+).

4.3.9. 1,2-Bis [3′-benzyloxy-4′-(*p*-methoxyphenyl)azetidin-2′-one-1′-yl]cyclohexane (5e). It was obtained as a white solid, which was recrystallized from dichloromethane–methanol, white needles, mp 194–195 °C; [found C, 74.14; H, 6.38; N, 4.15 $C_{40}H_{42}N_2O_6$ requires C, 74.28, H, 6.54; N, 4.33]; R_f (30% ethyl acetate/pet ether) 0.40; ν_{max} ($CHCl_3$) 1755 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 0.68–1.81 (m, 8H, CH_2, Cyclohexane), 3.79 (br d, *J*=9 Hz, 2H, C*H*, Cyclohexane), 3.83 (s, 6H, OCH_3), 3.98 (d, *J*=10.9 Hz, 2H, CH_2Ph), 4.24 (d, *J*=10.9 Hz, 2H, CH_2Ph), 4.78 (d, *J*=4.3 Hz, 2H, C4*H*), 5.01 (d, *J*=4.3 Hz, 2H, C3*H*), 6.83–7.47 (m, 18H, Ar); δ_C (50.32 MHz) 24.4, 30.1, 53.3, 55.3, 60.5, 72.4, 83.6, 113.5, 127.5, 127.8, 128.2, 129.9, 136.4, 159.8, 168.3; MS (*m*/*z*): 648 (M^+).

4.3.10. 1-[3′-Benzyloxy-4′-(*p*-methoxyphenyl)azetidin-2′-one-1′-yl]-2-[3″-benzyloxy-4″-(*p*-methoxyphenyl)azetidin-2″-one-1″-yl]cyclohexane (6e). It was obtained as a white solid, which was recrystallized from dichloromethane–methanol, white crystalline solid, mp 123–124 °C; [found C, 74.17; H, 6.45; N, 4.28 $C_{40}H_{42}N_2O_6$ requires C, 74.28, H, 6.54; N, 4.33]; R_f (30% ethyl acetate/pet ether) 0.24; ν_{max} ($CHCl_3$) 1751 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 0.77–1.92 (m, 8H, CH_2, Cyclohexane), 3.72–3.86 (m, 2H, C*H*, Cyclohexane), 3.83, 3.85 (s, 6H, OCH_3), 4.01–4.33 (m, 4H, CH_2Ph), 4.76 (d, *J*=4.7 Hz, 1H, C4*H*), 4.89 (d, *J*=4.7 Hz, 1H, C4′*H*), 4.91 (d, *J*=4.3 Hz, 1H, C3*H*), 5.21 (d, *J*=4.3 Hz, 1H, C3′*H*), 6.80–7.49 (m, 18H, Ar); δ_C (125 MHz) 24.0, 29.1, 31.4, 52.6, 54.6, 55.2, 60.2, 61.1, 72.2, 82.3, 82.8, 113.5, 113.9, 125.9, 127.2, 127.7, 127.8, 128.2, 130.2, 130.4, 136.3, 136.5, 159.7, 160.1, 167.3, 167.5; MS (*m*/*z*): 648 (M^+).

4.3.11. 1,2-Bis [3′-methoxy-4′-(*p*-methoxyphenyl) azetidine-2′-one-1′-yl]cyclohexane (5f). It was obtained as a white solid, which was recrystallized from methanol to get white crystalline solid, mp 229–230 °C; [found C, 67.88; H, 6.83; N, 5.56 $C_{28}H_{34}N_2O_6$ requires C, 67.99, H, 6.92; N, 5.66]; R_f (60% ethyl acetate/pet ether) 0.52; ν_{max} ($CHCl_3$) 1743 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 0.60–1.94 (m, 8H, CH_2, Cyclohexane), 3.03 (s, 6H, OCH_3), 3.79 (br d, *J*=9 Hz, 2H, C*H*, Cyclohexane), 3.82 (s, 6H, PhOCH_3), 4.55 (d, *J*=4.3 Hz, 2H, C4*H*), 4.96 (d, *J*=4.3 Hz, 2H, C3*H*), 6.89 (d, *J*=8.6 Hz, 4H, Ar), 7.34 (d, *J*=8.6 Hz, 4H, Ar); δ_C (125.76 MHz) 24.5, 30.2, 53.3, 55.2, 58.0, 60.4, 85.2, 113.6, 127.5, 129.8, 159.9, 167.9; MS (*m*/*z*): 496 (M^+).

4.3.12. 1-[3′-Methoxy-4′-(*p*-methoxyphenyl)azetidin-2′-one-1′-yl]-2-[3″-methoxy-4″-(*p*- ethoxyphenyl)azetidin-2″-one-1″-yl]cyclohexane (6f). It was obtained as a white solid, which was recrystallized from methanol to get white crystalline solid, mp 84–85 °C; [found C, 67.86; H, 6.85; N, 5.49 $C_{28}H_{34}N_2O_6$ requires C, 67.99, H, 6.92; N, 5.66]; R_f (60% ethyl acetate/pet ether) 0.44; ν_{max} ($CHCl_3$) 1745 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 0.72–1.93 (m, 8H, CH_2, Cyclohexane), 3.09 (s, 6H, OCH_3), 3.35–3.65 (m, 2H, C*H*, Cyclohexane), 3.82, 3.84 (s, 6H, PhOCH_3), 4.60 (d, *J*=4.7 Hz, 1H, C4*H*), 4.70 (d, *J*=4.7 Hz, 1H, C4′*H*), 4.76 (d, *J*=4.3 Hz, 1H, C3*H*), 5.22 (d, *J*=4.3 Hz, 1H, C3′*H*), 6.85–7.01 (m, 4H, Ar), 7.34–7.48 (m, 4H, Ar); δ_C (75 MHz) 23.9, 24.0, 28.9, 31.3, 52.7, 54.7, 55.1, 55.2, 57.92, 59.9, 61.0, 84.4, 84.5, 113.4, 113.9, 125.7, 127.1, 130.2, 159.7, 160.0, 167.3, 167.5; MS (*m*/*z*): 496 (M^+).

4.3.13. 1-(3′-Phenoxy-4′-styrylazetidin-2′-one-1′-yl)-2-(3″-phenoxy-4″-styrylazetidin-2″-one-1″-yl)cyclohexane (5g). It was obtained as a white solid, which on recrystallization from methanol gave white needles, mp 245–246 °C; [found C, 78.57; H, 6.16; N, 4.51 $C_{40}H_{38}N_2O_4$ requires C, 78.66, H, 6.27; N, 4.58]; R_f (30% ethyl acetate/pet ether) 0.68; ν_{max} ($CHCl_3$) 1747 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 1.07–2.01 (m, 8H, CH_2, Cyclohexane), 3.83–3.95 (m, 2H, C*H*, Cyclohexane), 4.88 (dd, *J*=4.7, 8.2 Hz, 2H, C4*H*), 5.29 (d, *J*=4.7 Hz, 2H, C3*H*), 6.28 (dd, *J*=8.2, 16 Hz, 2H, *H*C=CH), 6.77 (d, *J*=16 Hz, 2H, =C*H*Ph),

6.91–7.44 (m, 20H, Ar); δ_C (75.48 MHz) 24.7, 30.2, 53.5, 60.5, 82.0, 115.8, 122.2, 125.0, 126.7, 128.2, 128.6, 129.4, 136.0, 136.2, 157.4, 166.6; MS (*m/z*): 610 (M^+).

4.3.14. 1-(3′-Phenoxy-4′-styrylazetidin-2′-one-1′-yl)-2-(3″-phenoxy-4″-styrylazetidin-2″-one-1″-yl)cyclohexane (6g). It was obtained as a white solid, which was recrystallized from methanol to get white crystalline solid, mp 175–176 °C; [found C, 78.49; H, 6.27; N, 4.58 $C_{40}H_{38}N_2O_4$ requires C, 78.66, H, 6.27; N, 4.58]; R_f (30% ethyl acetate/pet ether) 0.40; ν_{max} ($CHCl_3$) 1753 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 1.05–2.09 (m, 8H, C*H*$_2$, Cyclohexane), 3.72–3.93 (m, 2H, C*H*, Cyclohexane), 4.67 (dd, *J*=4.4, 9.4 Hz, 1H, C4*H*), 5.16 (dd, *J*=4.4, 9.4 Hz, 1H, C4′*H*), 5.38 (dd, *J*=4.7, 9.4 Hz, 2H, C3*H* and C3′*H*), 6.27 (dd, *J*=9.4, 16 Hz, 1H, *H*C=CH), 6.67–6.87 (m, 3H, *H*C=CH and =C*H*Ph), 6.89–7.70 (m, 20H, Ar); δ_C (75.48 MHz) 24.2, 24.4, 28.4, 31.1, 52.2, 54.8, 60.3, 60.6, 81.6, 81.7, 115.6, 115.8, 121.8, 122.0, 124.0, 125.3, 126.6, 127.0, 128.0, 128.2, 128.5, 129.2, 135.8, 136.0, 136.2, 136.5, 157.4, 165.7, 166.2; MS (*m/z*): 610 (M^+).

4.3.15. 1-(3′-Benzyloxy-4′-styrylazetidin-2′-one-1′-yl)-2-(3″-benzylxy-4″-styrylazetidin-2″-one-1″-yl)cyclohexane (5h). It was obtained as a white solid, which was recrystallized from methanol to get white crystalline solid, mp 179–180 °C; [found C, 78.86; H, 6.55; N, 4.29 $C_{42}H_{42}N_2O_4$ requires C, 78.97, H, 6.63; N, 4.39]; R_f (20% ethyl acetate/pet ether) 0.54; ν_{max} ($CHCl_3$) 1743 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 1.01–1.91 (m, 8H, C*H*$_2$, Cyclohexane), 3.71–3.82 (m, 2H, C*H*, Cyclohexane), 4.58 (d, *J*=10.2 Hz, 2H, C*H*$_2$Ph), 4.63 (d, *J*=10.2 Hz, 2H, C*H*$_2$Ph), 4.65 (dd, *J*=4.3, 9.4 Hz, 2H, C4*H*), 4.73 (d, *J*=4.3 Hz, 2H, C3*H*), 6.31 (dd, *J*=9.4, 16 Hz, 2H, *H*C=CH), 6.72 (d, *J*=16 Hz, 2H, =C*H*Ph), 7.15–7.51 (m, 20H, Ar); δ_C (75.48 MHz) 24.6, 30.3, 52.9, 60.3, 73.0, 83.7, 126.0, 126.7, 127.9, 128.2, 128.3, 128.6, 135.1, 136.2, 136.8, 167.5; MS (*m/z*): 638 (M^+).

4.3.16. 1-(3′-Benzyloxy-4′-styrylazetidin-2′-one-1′-yl)-2-(3″-benzylxy-4″-styrylazetidin-2″-one-1″-yl)cyclohexane (6h). It was obtained as a white solid, which on recrystallization from methanol gave white crystalline solid, mp 61–62 °C; [found C, 78.91; H, 6.48; N, 4.32 $C_{42}H_{42}N_2O_4$ requires C, 78.97, H, 6.63; N, 4.39]; R_f (20% ethyl acetate/pet ether) 0.44; ν_{max} ($CHCl_3$) 1745 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 1.00–2.10 (m, 8H, C*H*$_2$, Cyclohexane), 3.62–3.73 (m, 2H, C*H*, Cyclohexane), 4.32–4.41 (m, 1H, C4*H*), 4.60 (d, *J*=11.3 Hz, 2H, C*H*$_2$Ph), 4.66 (d, *J*=11.3 Hz, 2H, C*H*$_2$Ph), 4.76 (d, *J*=4.7 Hz, 1H, C4′*H*), 4.86 (d, *J*=4.3 Hz, 1H, C3*H*), 4.93 (dd, *J*=4.7, 9.4 Hz, 1H, C3′*H*), 6.31 (dd, *J*=9.4, 15.7 Hz, 1H, *H*C=CH), 6.62–6.85 (m, 3H, *H*C=CH and =C*H*Ph), 7.18–7.65 (m, 20H, Ar); δ_C (75.48 MHz) 24.3, 24.4, 28.6, 31.3, 51.8, 54.4, 60.1, 60.5, 72.5, 72.8, 82.7, 83.5, 124.9, 126.7, 127.5, 127.9, 128.2, 128.3, 128.6, 135.0, 135.7, 136.2, 136.4, 137.0, 166.9, 167.2; MS (*m/z*): 638 (M^+).

4.3.17. 1-(3′-Methoxy-4′-styrylazetidin-2′-one-1′-yl)-2-(3″-methoxy-4″-styrylazetidin-2″-one-1″-yl)cyclohexane (5i). It was obtained as a white solid, which was recrystallized from methanol to get white crystalline solid, mp 211–212 °C; [found C, 73.92; H, 6.95; N, 5.68 $C_{30}H_{34}N_2O_4$ requires C, 74.05, H, 7.04; N, 5.75]; R_f (40% ethyl acetate/pet ether) 0.49; ν_{max} ($CHCl_3$) 1741 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 1.01–1.96 (m, 8H, C*H*$_2$, Cyclohexane), 3.41 (s, 6H, OC*H*$_3$), 3.78–3.81 (m, 2H, C*H*, Cyclohexane), 4.49 (d, *J*=4.3 Hz, 2H, C4*H*), 4.62 (dd, *J*=4.3, 9.4 Hz, 2H, C3*H*), 6.27 (dd, *J*=9.4, 16 Hz, 2H, *H*C=CH), 6.77 (d, *J*=16 Hz, 2H, =C*H*Ph), 7.25–7.50 (m, 10H, Ar); δ_C (75.48 MHz) 24.6, 30.3, 52.9, 58.6, 60.0, 85.3, 125.7, 126.6, 128.2, 128.6, 135.2, 136.2, 167.5; MS (*m/z*): 486 (M^+).

4.3.18. 1-(3′-Methoxy-4′-styrylazetidin-2′-one-1′-yl)-2-(3″-methoxy-4″-styrylazetidin-2″-one-1″-yl)cyclohexane (6i). It was obtained as a white solid, which was recrystallized from methanol to get white needles, mp 79–80 °C; [found C, 73.88; H, 6.92; N, 5.65 $C_{30}H_{34}N_2O_4$ requires C, 74.05, H, 7.04; N, 5.75]; R_f (40% ethyl acetate/pet ether) 0.38; ν_{max} ($CHCl_3$) 1749 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 1.01–1.99 (m, 8H, C*H*$_2$, Cyclohexane), 3.43, 3.44 (s, 6H, OC*H*$_3$), 3.60–3.73 (m, 2H, C*H*, Cyclohexane), 4.34–4.45 (m, 1H, C4*H*), 4.60 (dd, *J*=4.7, 9.4 Hz, 2H, C4′*H* and C3*H*), 4.92 (dd, *J*=4.7, 9.4 Hz, 1H, C3′*H*), 6.28 (dd, *J*=9.4, 16 Hz, 1H, *H*C=CH), 6.62–6.89 (m, 3H, *H*C=CH and=C*H*Ph), 7.24–7.67 (m, 10H, Ar); δ_C (75.48 MHz) 24.3, 24.4, 28.5, 31.2, 51.8, 54.3, 58.4, 58.5, 59.9, 60.3, 84.8, 85.1, 124.6, 126.1, 126.6, 127.1, 128.0, 128.1, 128.6, 135.1, 135.8, 136.1, 136.3, 166.6, 167.3; MS (*m/z*): 486 (M^+).

4.3.19. Procedure for the preparation of mono-β-lactams (7 and 8). Phenoxy acetyl chloride **4a** (0.1 mL, 1.0 mmol) in dry methylene chloride (10 mL) was added slowly to a solution of the bis-imine **3a** (0.20 g, 1.0 mmol) and triethylamine (0.96 mL, 10.0 mmol) in CH_2Cl_2 (10 mL) at 0 °C. After the addition was complete, the reaction mixture was allowed to warm up to room temperature and stirred for 15 h. The reaction mixture was then washed with water (2× 10 mL), saturated sodium bicarbonate solution (10 mL) and saturated brine solution (10 mL). The organic layer was then dried over anhydrous Na_2SO_4 and concentrated to give the crude diastereomeric mixture **7** and **8** (0.22 g).

Data for diastereomeric mixture of mono-β-lactams **7** and **8**. White solid; ν_{max} ($CHCl_3$) 1645, 1749 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 1.28–2.25 (m, 16H), 3.10–3.95 (m, 4H), 4.73 (d, *J*=4.7 Hz, 2H), 4.83 (d, *J*=4.3 Hz, 1H), 5.04 (d, *J*=4.3 Hz, 2H), 5.18 (d, *J*=4.7 Hz, 1H), 6.58–7.83 (m, 30H), 8.33 (s, 1H), 8.45 (s, 1H); δ_C (125 MHz) 23.9, 24.3, 24.7, 25.2, 29.7, 29.9, 33.5, 33.8, 53.8, 58.2, 59.4, 61.3, 64.1, 69.9, 72.2, 96.0, 115.5, 121.7, 127.9, 128.0, 128.2, 128.6, 128.8, 129.0, 130.8, 131.0, 133.9, 136.1, 156.8, 161.4, 165.5, 167.6.

4.3.20. *N,N′*-Dibenzylidene-1,2-diphenylethane-1,2-diamine (13a). This bis-imine **13a** was prepared from (±)1,2-diphenylethylenediamine and benzaldehyde following the same procedure as described for **3a–c**. It was isolated as a white solid and recrystallized from EtOAc–petroleum ether (10:90). White needles; yield 82%; mp 158–159 °C; [found C, 86.43; H, 6.13; N, 7.06 $C_{28}H_{24}N_2$ requires C, 86.56; H, 6.22; N, 7.21] ν_{max} ($CHCl_3$) 1643 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 4.67 (s, 2H, C*H*Ph), 7.03–7.90 (m, 20H, Ar), 8.22 (s, 2H, –N=C*H*) δ_C (75.48 MHz, $CDCl_3$) 81.3,

126.8, 127.8, 128.1, 128.3, 128.4, 130.3, 136.4, 141.1, 161.7; MS (*m*/*z*): 388 (M^+).

Following the typical procedure described for **5a**, **6a** bis-β-lactams **14a–c** and **15a–c** were prepared.

4.3.21. 1,2-Diphenyl-1,2-bis(3′-phenoxy-4′-phenylazetidin-2′-one-1′-yl)ethane (14a). It was obtained as a white solid, which was recrystallized from methanol to get white crystalline solid, mp 197–198 °C; [found C, 78.81; H, 5.78; N, 4.50 $C_{40}H_{36}N_2O_4$ requires C, 78.92, H, 5.96; N, 4.60]; R_f (30% ethyl acetate/pet ether) 0.63; ν_{max} ($CHCl_3$) 1757 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 5.19 (s, 2H, C*H*Ph), 5.34 (d, *J*= 4.1 Hz, 2H, C4*H*), 5.55 (d, *J*=4.1 Hz, 2H, C3*H*), 6.69–7.30 (m, 30H, Ar); δ_C (125 MHz) 59.9, 60.9, 73.1, 111.5, 118.0, 123.3, 123.6, 124.0, 124.1, 124.2, 125.0, 125.1, 125.7, 125.8, 125.9, 152.7, 167.2; MS (*m*/*z*): 608 (M^+).

4.3.22. 1,2-Diphenyl-1-(3′-phenoxy-4′-phenylazetidin-2′-one-1′-yl)-2-(3″-phenoxy-4″-phenylazetidin-2″-one-1″-yl)ethane (15a). It was obtained as a white solid, which was recrystallized from methanol to get white crystalline solid, mp 209–210 °C; [found C, 78.85; H, 5.74; N, 4.53 $C_{40}H_{36}N_2O_4$ requires C, 78.92, H, 5.96; N, 4.60]; R_f (30% ethyl acetate/pet ether) 0.52; ν_{max} ($CHCl_3$) 1751 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 5.24–5.34 (m, 2H, C*H*Ph), 4.85 (d, *J*= 4.7 Hz, 1H, C4*H*), 5.43 (d, *J*=4.7 Hz, 1H, C4′*H*), 5.33 (d, *J*=4.3 Hz, 1H, C3*H*), 5.57 (d, *J*=4.3 Hz, 1H, C3′*H*), 6.67–7.40 (m, 30H, Ar); δ_C (75 MHz) 61.0, 61.8, 61.9, 64.0, 81.2, 81.6, 115.6, 115.8, 121.8, 122.0, 127.2, 127.6, 127.9, 128.3, 128.5, 128.6, 129.1, 129.2, 129.4, 132.4, 133.2, 136.4, 137.2, 157.0, 157.1, 165.8, 166.9; MS (*m*/*z*): 608 (M^+).

4.3.23. 1,2-Diphenyl-1,2-bis(3′-benzyloxy-4′-phenylazetidin-2′-one-1′-yl)ethane (14b). It was obtained as a white solid, which was recrystallized from methanol to get white crystalline solid, mp 190–191 °C; [found C, 79.05; H, 6.23; N, 4.28 $C_{42}H_{40}N_2O_4$ requires C, 79.21, H, 6.33; N, 4.39]; R_f (20% ethyl acetate/pet ether) 0.56; ν_{max} ($CHCl_3$) 1741 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 4.11 (d, *J*=10.3 Hz, 2H, C*H*Ph), 4.54 (d, *J*=4.3 Hz, 2H, C4*H*), 4.70 (d, *J*=4.7 Hz, 2H, C3*H*), 5.63 (d, *J*=11 Hz, 4H, CH_2Ph), 6.98–7.62 (m, 30H, Ar); δ_C (50 MHz) 59.2, 61.5, 62.9, 63.8, 72.2, 72.8, 82.2, 82.8, 127.7, 127.9, 128.0, 128.1, 128.2, 128.3, 128.4, 128.5, 128.6, 129.2, 130.7, 136.0, 136.4, 138.0, 138.3, 138.6, 139.5, 141.0, 166.8; MS (*m*/*z*): 636 (M^+).

4.3.24. 1,2 Diphenyl-1-(3′-benzyloxy-4′-phenylazetidin-2′-one-1′-yl)-2-(3″-benzyloxy-4″-phenylazetidin-2″-one-1″-yl)ethane (15b). It was obtained as a white solid, which on recrystallization from methanol gave white crystalline solid, mp 79–80 °C; [found C, 79.09; H, 6.20; N, 4.30 $C_{42}H_{40}N_2O_4$ requires C, 79.21, H, 6.33; N, 4.39]; R_f (20% ethyl acetate/pet ether) 0.44; ν_{max} ($CHCl_3$) 1753 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 4.02–4.32 (m, 2H, C*H*Ph), 4.61 (d, *J*= 4.3 Hz, 1H, C4*H*), 4.84 (d, *J*=4.3 Hz, 1H, C4′*H*), 4.98 (d, *J*=4.7 Hz, 1H, C3*H*), 5.12 (d, *J*=4.7 Hz, 1H, C3′*H*), 5.14–5.23 (q, *J*=11.8 Hz, 4H, CH_2Ph), 6.72–7.55 (m, 30H, Ar); δ_C (75 MHz) 60.8, 61.5, 63.8, 63.9, 72.2, 72.3, 82.9, 83.1, 127.5, 127.6, 127.7, 127.8, 127.9, 128.0, 128.1, 128.2, 128.3, 128.7, 128.9, 129.1, 129.4, 133.3, 134.1, 136.4, 136.8, 137.5, 167.0, 167.8; MS (*m*/*z*): 636 (M^+).

4.3.25. 1,2-Diphenyl-1,2-bis(3′-methoxy-4′-phenylazetidin-2′-one-1′-yl)ethane (14c). It was obtained as a white solid, which was recrystallized from methanol to get white crystalline solid, mp 194–195 °C; [found C, 76.49; H, 5.88; N, 5.10 $C_{34}H_{32}N_2O_4$ requires C, 76.67, H, 6.05; N, 5.26]; R_f (30% ethyl acetate/pet ether) 0.55; ν_{max} ($CHCl_3$) 1747 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 3.01 (s, 6H, OCH_3), 4.47 (d, *J*= 5.1 Hz, 2H, C4*H*), 4.53 (d, *J*=5.1 Hz, 2H, C3*H*), 5.60 (d, *J*=10.3 Hz, 2H, C*H*Ph), 7.00–7.68 (m, 20H, Ar); δ_C (50 MHz) 57.9, 61.3, 67.2, 85.0, 127.2, 127.7, 127.9, 128.0, 128.2, 128.3, 128.5, 128.6, 129.1, 130.7, 133.6, 136.4, 138.2, 140.9, 162.3; MS (*m*/*z*): 532 (M^+).

4.3.26. 1,2-Diphenyl-1-(3′-methoxy-4′-phenylazetidin-2′-one-1′-yl)-2-(3″-methoxy-4″-phenylazetidin-2″-one-1″-yl)ethane (15c). It was obtained as a white solid, which was recrystallized from methanol to get white crystalline solid, mp 201–202 °C; [found C, 76.53; H, 5.83; N, 5.07 $C_{34}H_{32}N_2O_4$ requires C, 76.67, H, 6.05; N, 5.26]; R_f (30% ethyl acetate/pet ether) 0.47; ν_{max} ($CHCl_3$) 1743 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 3.06, 3.09 (s, 6H, OCH_3), 4.66 (d, *J*= 4.3 Hz, 2H, C4*H* and C4′*H*), 4.80 (d, *J*=4.7 Hz, 1H, C3*H*), 5.08 (d, *J*=4.7 Hz, 1H, C3′*H*), 5.22 (q, *J*=11.8 Hz, 2H, C*H*Ph), 6.76–7.47 (m, 20H, Ar); δ_C (50 MHz) 57.9, 58.1, 60.6, 61.2, 61.4, 63.4, 84.7, 85.0, 127.5, 127.8, 127.9, 128.1, 128.3, 128.5, 128.8, 129.1, 132.8, 133.7, 136.5, 137.2, 167.0, 167.8; MS (*m*/*z*): 532 (M^+).

4.3.27. *N*,*N*′-Dibenylidenebutane-2, 3-diamine (13b). This bis-imine **13b** was prepared from (±) 2,3-diaminobutane and benzaldehyde following the same procedure as described for **3a–c**. It was isolated as an oil; yield 83%; ν_{max} ($CHCl_3$) 1583, 1596, 1643 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 1.30 (d, *J*=5.8 Hz, 6H, CH_3), 3.38–3.53 (m, 2H, C*H*), 7.17–7.92 (m, 10H, Ar), 8.16 (s, 2H, –N=C*H*).

Following the typical procedure described for **5a**, **6a** bis-β-lactams **14d** and **15d** were prepared from bisimine **13b** and phenoxyacetyl chloride.

4.3.28. 2,3-Bis [3′-Phenoxy-4′-phenylazetidin-2′-one-1′-yl]butane (14d). It was obtained as a white solid, which was recrystallized from methanol to get white crystalline solid, mp 69–70 °C; [found C, 76.55; H, 6.05; N, 5.16 $C_{34}H_{32}N_2O_4$ requires C, 76.67, H, 6.05; N, 5.26]; R_f (30% ethyl acetate/pet ether) 0.50; ν_{max} ($CHCl_3$) 1755 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 0.81 (d, *J*=6.6 Hz, 6H, CH_3), 4.08–4.17 (m, 2H, C*H*CH_3), 5.26 (d, *J*=4.7 Hz, 2H, C4*H*), 5.40 (d, *J*=4.7 Hz, 2H, C3*H*), 6.62–7.52 (m, 20H, Ar); δ_C (125 MHz) 15.9, 51.2, 61.3, 81.3, 111.5, 127.9, 128.0, 128.6, 128.9, 129.1, 134.4, 156.6, 167.4; MS (*m*/*z*): 532 (M^+).

4.3.29. 2-(3′-Phenoxy-4′-phenylazetidin-2′-one-1′-yl)-3-(3″-phenoxy-4″-phenylazetidin-2″-one-1″-yl)butane (15d). It was obtained as a white solid, which was crystallized from methanol to get white crystalline solid, mp 175–176 °C; [found C, 76.48; H, 6.03; N, 5.08 $C_{34}H_{32}N_2O_4$ requires C, 76.67, H, 6.05; N, 5.26]; R_f (30% ethyl acetate/pet ether) 0.35; ν_{max} ($CHCl_3$) 1755 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 0.88 (d, *J*=6.6 Hz, 3H, CH_3), 1.32 (d, *J*=6.6 Hz, 3H, CH_3), 3.71–3.90 (m, 2H, C*H*CH_3), 4.95 (d, *J*=4.7 Hz, 1H, C4*H*), 5.37 (d, *J*=4.7 Hz, 1H, C4′*H*), 5.40

(d, $J=4.3$ Hz, 1H, C3*H*), 5.50 (d, $J=4.3$ Hz, 1H, C3′*H*), 6.60–7.57 (m, 20H, Ar); δ_C (125 MHz) 15.8, 17.1, 51.7, 52.4, 61.5, 62.6, 80.9, 115.6, 121.8, 122.0, 128.0, 128.4, 128.7, 129.2, 133.0, 134.4, 156.8, 166.3, 166.4; MS (*m*/*z*): 532 (M^+).

4.3.30. Procedure for asymmetric synthesis of bis-β-lactams (5j, 6j, 14e and 15e). Following the typical procedure described for **5a**, **6a** the bis-β-lactams **5j**, **6j**, **14e** and **15e** were prepared from chiral bis-imines derived from optically pure (+)-1*R*,2*R*-*trans*-1, 2-diaminocyclohexane, (−)-1*S*,2*S*-diphenylethylenediamine and benzaldehyde; and phenoxyacetyl chloride.

4.3.30.1. (1*R*,2*R*,3′*S*,4′*R*,3″*S*,4″*R*)-1,2-Bis (3′-phenoxy-4′-phenylazetidin-2′-one-1′-yl)cyclohexane (5j). It was obtained as a white crystalline solid; mp 231–232 °C; $[\alpha]_D^{25}=-146.9$ (*c*, 0.80, $CHCl_3$); spectral data same as for **5a**.

4.3.30.2. (1*R*,2*R*,3′*S*,4′*R*,3″*R*,4″*S*)-1-(3′-Phenoxy-4′-phenylazetidin-2′-one-1′-yl)-2-(3″-phenoxy-4″-phenylazetidin-2″-one-1″-yl)cyclohexane (6j). It was obtained as a white crystalline solid, mp 82–83 °C; $[\alpha]_D^{25}=-53.83$ (*c*, 1.00, $CHCl_3$); spectral data same as for **6a**.

4.3.30.3. (1*S*,2*S*,3′*R*,4′*S*,3″*R*,4″*S*)-1,2-Diphenyl-(3′-phenoxy-4′-phenylazetidin-2′-one-1′-yl)ethane (14e). It was obtained as a white amorphous solid, mp 197–198 °C; $[\alpha]_D^{25}=+3.03$ (*c*, 0.99, $CHCl_3$); spectral data same as for **14a**.

4.3.30.4. (1*S*,2*S*,3′*R*,4′*S*,3″*S*,4″*R*)-1,2-Diphenyl-1-(3′-phenoxy-4′-phenylazetidin-2′-one-1′-yl)-2-(3″-phenoxy-4″-phenylazetidin-2″-one-1″-yl)ethane (15e). It was obtained as a white amorphous solid, mp 209–210 °C; $[\alpha]_D^{25}=+6.15$ (*c*, 0.80, $CHCl_3$); spectral data same as for **15a**.

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Photo-irradiation of α-halo carbonyl compounds: a novel synthesis of α-hydroxy- and α,α′-dihydroxyketones

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Abstract—The reaction of α-halo ketones (α-iodocycloalkanones, α-bromocycloalkanones, α-iodo-β-alkoxy esters, and α-iodoacyclic-ketones) with irradiation under a high-pressure mercury lamp gave the corresponding α-hydroxyketones in good yields. For α-bromoketones, it was found that α-hydroxylation does not occur. However, α-bromoketones were converted into α-hydroxyketones in the presence of KI. In the case of α,α′-diiodo ketones, α,α′-dihydroxyketones, which up to now have scarcely been reported, were obtained. This reaction affords a new, clean and convenient synthetic method for α-hydroxy- and α,α′-dihydroxyketones.

1. Introduction

In the synthesis of various natural products and pharmacologically active compounds, α-hydroxycarbonyl compounds are potential intermediates. Accordingly, α-hydroxyketones synthesis is an important reaction. α-Hydroxyketones are usually prepared by one of the following methods: α-hydroxylation by treatment of their enolate forms with a molybdenum peroxide reagent in THF–hexane at −70 °C;[1] transformation of the enamine derivatives of ketones to α-hydroxy derivatives by molecular oxygen;[2] α-hydroxylation of silyl enol ethers with *m*-chloroperbenzoic acid,[3] or with certain other oxidizing agents;[4] reaction of an alkyllithium reagent with carbon monoxide in the presence of dichloroarylmethane;[5] and direct air oxidation of ketones with a bimetallic palladium (II) complex in aqueous THF.[6]

It is known that there has been considerable interest in the development of direct methods for the synthesis of α-hydroxyketones using non-toxic hypervalent iodine reagents, which involve the following methods: reaction of ketones with iodobenzene diacetate in the presence of potassium hydroxide in methanol and then hydrolysis of the dimethylacetals;[7] oxidation of enol silyl ether of acetophenone using the system iodosobenzene/boron trifluoride etherate/water in methylene chloride at −40 °C;[8] reaction of ketones with [bis(trifluoroacetoxy)] iodobenzene and trifluoroacetic acid in acetonitrile–water under acidic conditions;[9] and α-hydroxylation by treatment of their enolate forms with [hydroxy(tosyloxy)iodo]benzene in aqueous dimethyl sulfoxide at room temperature.[10]

During the course of our studies, we investigated some novel photosynthetic reactions to transform ketone derivatives into useful compounds. For example, the self-coupling reaction of cyclic ketones gives the corresponding pinacol-type compounds in good yields with a high-pressure mercury lamp.[11] α-Iodocycloalkanones, which were synthesized by our laboratory by a new method, are important as intermediates in organic synthesis.[12] For these iodo ketones which are unstable and sensitive to light, we have already shown that the photo-dehydroiodination from α-iodocycloalkanones in hexane affords α,β-unsaturated ketones as major products, accompanied by photoreduced products as by-products. In hexane containing a small amount of water, the substituted product 2-hydroxycycloalkanone was also obtained.[13] In our previous paper, we found that photo-cleavage of the carbon–carbon bond of α-iodocycloalkanones giving ω,ω-dialkoxyalkanoic esters in alcohol gave α-hydroxyketones as intermediates.[14] In order to increase the yield of α-hydroxyketones, we undertook a closer inquiry into the reaction conditions. Still earlier, we described that the irradiation of α-iodo- and α,α′-diiodo ketones in solvents containing a small amount of air gave the α-hydroxy- and α,α′-hydroxyketones under a high-pressure mercury lamp.[15,16] Herein, we report details concerning a novel synthesis of α-hydroxy- and α,α′-dihydroxyketones.

Keywords: Hydroxylation; Cyclododecanone; Halo ketone; α,α′-Dihydroxyketone.
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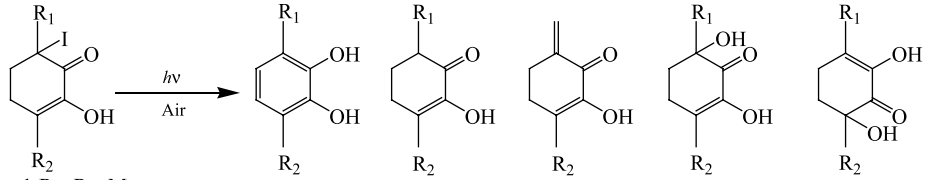
Table 1. Photochemical reaction of 3-iodo-3,6-dialkylcyclohexane-1,2-diones (**1–2**) under air



Run	Substrate	Solvent	Time/h	Product (%)[a]				
				a	**b**	**c**	**d**	**d′**
1	**1**	MeOH	4	0	0	0	t	
2	**1**	EtOH	4	0	0	0	42	
3	**1**	1-PrOH	4	0	t	4	35	
4	**1**	2-PrOH	4	0	2	5	34	
5	**1**	*n*-Hex	4	0	0	0	56	
6	**2**	MeOH	2	0	0	0	28	6
7	**2**	EtOH	2	0	0	10	47	23
8	**2**	1-PrOH	2	25	0	13	31	16
9	**2**	2-PrOH	2	19	0	16	34	16
10	**2**	*n*-Hex	2	0	0	14	41	18

Reaction conditions: substrate (15.7 mmol) in solvent (10 ml) was irradiated by a high-pressure mercury lamp (400 W) under air.
[a] Yields were determined from GLC.

2. Results and discussion

The irradiation of 3-iodo-3,6-dialkylcyclohexanediones (**1–2**) in a solvent at room temperature under air atmosphere with a 400 W mercury lamp for 2–4 h gave the corresponding 3-hydroxy-3,6-dialkylcyclohexanediones (**1d**-**2d**) as major products. These results are summarized in Table 1. From these results, it was found that this reaction afforded hydroxydiosphenol[17,18] in buchu oil from the leaves of *Barosma betulina Bartl.* (mountain buchu). The reaction exhibits the possibility of a new synthetic method of α-hydroxyketones from α-iodoketones. We investigated the photo-irradiation of 2-iodocycloketones (**3–8**), and 2-iodo cyclododecanone (**7**) was selected as a model compound to investigate the synthesis of α-hydroxyketones from α-iodoketones. These results are summarized in Table 2.

Table 2. Effects of some amines on photochemical reaction of α-iodoketone **7**

Run	Solvent	Base (molar equivalent)	Time/h	Product (%)[a]				
				a	**b**	**c**	**d**	**e**
1	Me_2CO	0	10	3	50	t	5	42
2	*n*-Hex	0	10	8	t	6	5	41
3	*c*-Hex	0	10	4	3	15	9	45
4	PhH	0	10	5	2	9	2	52
5	Et_2O	0	10	4	t	8	13	53
6	EtOAc	0	10	5	t	2	8	28
7	MeCN	0	10	17	t	3	3	59
8	THF	0	10	13	t	2	12	70
9	Me_2CO	*i*-Pr_2NH (1)	10	t	4	t	95	0
10	Me_2CO	*n*-Pr_3N (1)	10	t	2	t	95	0
11	Me_2CO	Et_2NH (1)	43	t	4	t	90	0
12	Me_2CO	$PhNMe_2$ (1)	50	10	4	t	85	0
13	Me_2CO	C_5H_5N (1)	10	16	13	t	17	45
14	Me_2CO	C_5H_5N (10)	10	16	10	t	24	43
15	Me_2CO	C_5H_5N (50)	15	11	11	t	43	30
16	Me_2CO	C_4H_5NH (1)	40	9	6	t	30	46
17	Me_2CO	C_4H_5NH (10)	40	7	22	t	37	0
18	Me_2CO	*t*-BuOK (1)	10	t	58	t	33	0
19	Me_2CO	NaOH (1)	20	t	93	t	2	0
20	Me_2CO	NH_3 (1)	20	4	5	t	90	0
21	Me_2CO	Et_3N (1)	10	t	t	t	95	0
22	*n*-Hex	Et_3N (1)	15	3	t	2	68	0
23	*c*-Hex	Et_3N (1)	15	9	t	7	63	0
24	PhH	Et_3N (1)	25	t	t	t	83	0
25	Et_2O	Et_3N (1)	62	2	t	t	87	0
26	EtOAc	Et_3N (1)	17	t	t	t	90	0
27	MeCN	Et_3N (1)	17	t	7	t	77	0
28	THF	Et_3N (1)	18	12	t	t	77	0

Reaction conditions: substrate (0.1 mmol) in solvent (10 ml) was irradiated by a high-pressure mercury lamp (400 W) under air.
[a] Yields were determined by GLC. t=trace.

From runs 1–8, it was found that 2-hydroxycyclododecanone (**7d**) was obtained as a by-product. In the presence of triethylamine (run 21), ω-formylcarboxylic acid (**7e**) was not obtained, and 2-hydroxycyclododecanone (**7d**) was formed as the only product. From the results mentioned above, we investigated the photo-irradiation of some α-iodoketones. These results are summarized in Table 3. The irradiation of α-iodo ketones (**3**–**14**) gave the corresponding α-hydroxyketones (**3d**-**14d**) in good yields (Scheme 1).

As can be seen from Table 3, it was found that the reaction containing triethylamine (molar equivalent) gave preferentially the α-hydroxyketones. Thus, in order to discuss the reactivity of the α-iodocyclicketones, it was compared with that of the bromo derivatives. Under the some reaction conditions as that of α-iodocyclicketones, the reaction of α-bromo ketones did not give α-hydroxyketones, but the irradiation of α-bromo ketones in the presence of KI (0.1 mmol) gave the corresponding α-hydroxyketones as major products (runs 3, 5, 8, 12, and 14). It was found that the yields of α-hydroxy ketones were lower in the case of the bromo ketones with KI. However, in the case of non-occurrence of α-iodination, that is, α-iodocamphor, this reaction cannot be applied to the synthesis of α-hydroxycamphor. In order to overcome this problem, we tried the reaction of α-bromocamphor (**28′**) with KI. As can be seen from Table 3 (runs 18–22), it was found that α-hydroxycamphor was obtained in good yields.

In order to investigate the reaction pathway of the hydroxylation for α-iodocycloalkanones in acetone containing triethylamine, photo-irradiation of **7** was carried out. From runs 1–8 of Table 2, it was found that the ring-opening product **7e** was obtained as the major product. Kropp has reported that the photobehaviors of alkyl iodides are competing ionic and radical photobehaviors.[19] In line with the conception of Kropp, the irradiation of **7** gave not only the reduced ketone **7b** and the eliminated product **7c** as the products of radical photobehavior, but also the α-hydroxyketone **7d** and the ring-opening product **7e** as the products of ionic photobehavior (Fig. 1). In the case of photo-irradiation in acetone (run 1, Table 2), the radical products are obtained in much the same ratio as the ionic products. So, the photo-irradiation of **7** in acetone is an ideal reaction to investigate how to decrease the reduced ketone **7b** and the ring-opening product **7e**.

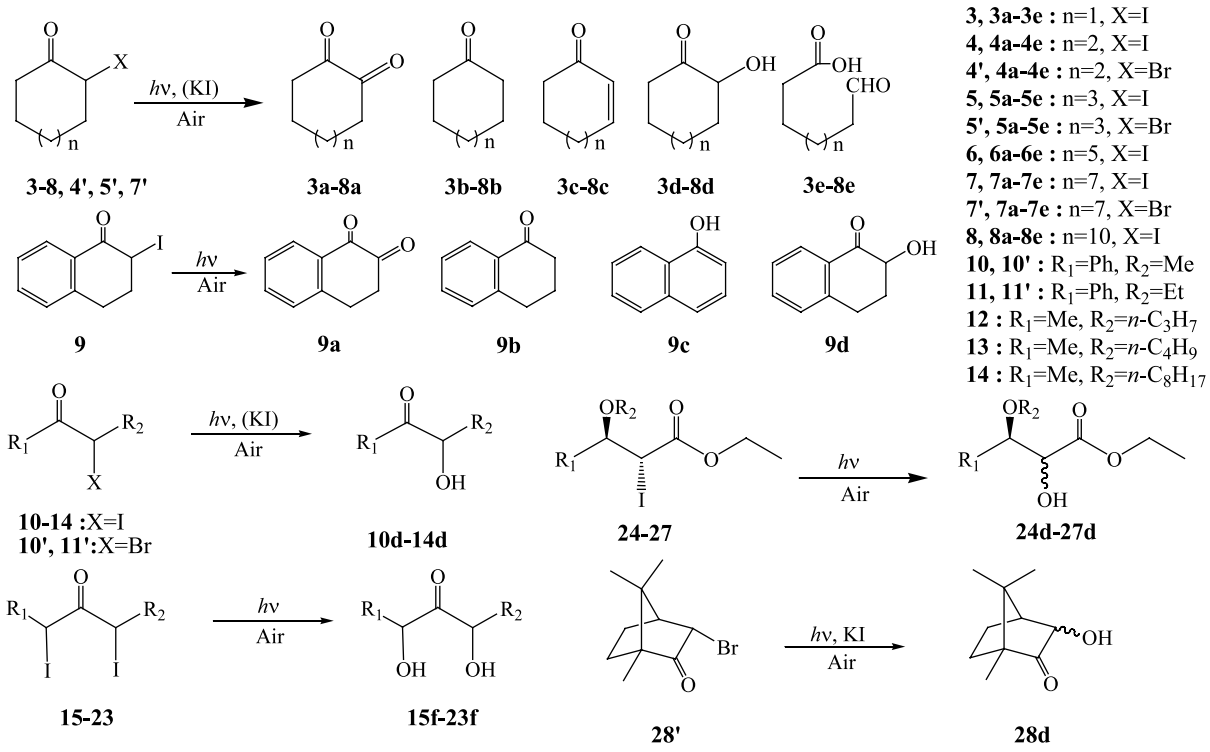
On the other hand, the ring-opening product **7e** was obtained as the final product of ionic photobehavior (Fig. 1). It is considered that the α-hydroxyketone **7d** is an intermediate of the ionic photobehavior, and we investigated the irradiation of **7d** in acetone by a high-pressure mercury lamp (400 W) under air. The reaction resulted in the recovery of substrate **7d**, and the ring-opening product **7e** was not obtained (Scheme 2). The result suggests that the presence of HI is vital to give the ring-opening product **7e** via α-hydroxyketone **7d**. It seems that the irradiation of **7** gave **7d** as the final product of the ionic photobehavior instead of **7e** in the presence of an HI scavenger.

According to Kropp's report, it is noted that bases such as Et_3N or NH_4OH are used as an HX scavenger in photo-irradiation of alkyl halides.[19] Based on the views of Kropp, we investigated the reaction in the presence of various bases to decrease the ring-opening product **7e** (runs

Table 3. Photochemical reaction of α-halo ketones in the presence of Et_3N

Run	Substrate	X	*n*	Solvent	Et_3N (molar equivalent)	Time/h	Product (%)[a]					
							a	**b**	**c**	**d**	**e**	
1	**3**	I	1	Me_2CO	1	10	10	4	t	49	0	
2	**4**	I	2	Me_2CO	1	10	41	t	t	56	0	
3	**4**[b]	Br	2	MeOH	1	12	t	4	t	42	0	
4	**5**	I	3	Me_2CO	1	10	35	t	t	60	0	
5	**5**[b]	Br	3	MeOH	1	12	t	3	t	35	0	
6	**6**	I	5	Me_2CO	1	10	24	t	t	70	0	
7	**7**	I	7	Me_2CO	1	10	t	t	t	95	0	
8	**7**[b]	Br	7	MeOH	1	12	t	3	7	47	0	
9	**8**	I	10	Me_2CO	1	10	t	t	t	95	0	
10	**9**	I		Me_2CO	1	12	t	5	15	70	0	
11	**10**	I		Me_2CO	1	10	t	t	t	81	0	
12	**10**[b]	Br		Me_2CO	1	12	t	t	t	30	0	
13	**11**	I		Me_2CO	1	10	t	t	t	87	0	
14	**11**[b]	Br		Me_2CO	1	12	t	t	t	31	0	
15	**12**	I		Me_2CO	1	10	t	t	t	89[c]	0	
16	**13**	I		Me_2CO	1	10	t	t	t	92[c]	0	
17	**14**	I		Me_2CO	1	10	t	t	t	94[c]	0	
18	**28**[b]	Br		MeOH	1	48	t	t	t	85	0	(*exo*/*endo*=40:60)[c]
19	**28**[b]	Br		MeOH	2	12	t	t	t	62	0	(*exo*/*endo*=40:60)[c]
20	**28**[b]	Br		EtOH	2	24	t	t	t	52	0	(*exo*/*endo*=33:67)[c]
21	**28**[b]	Br		Me_2CO	2	72	t	t	t	86	0	(*exo*/*endo*=43:57)[c]
22	**28**[b]	Br		MeCN	2	68	t	t	t	85	0	(*exo*/*endo*=43:57)[c]

Reaction conditions: substrate (0.1 mmol) in solvent (10 ml) was irradiated by a high-pressure mercury lamp (400 W) under air.
[a] Yields were determined by GLC.
[b] KI (0.1 mmol) was used.
[c] Product ratio was determined from the peak area ratio of the NMR spectrum. t=trace.



Scheme 1. Photo-irradiation of α-halo carbonyl compounds.

9–21, Table 2). It was found that amine bases such as *i*-Pr_2NH, Et_2NH, $PhNMe_2$, NH_3, Et_3N, and *n*-Pr_3N were effective. In the presence of Et_3N (run 21), ω-formylcarboxylic acid (**7e**) was not obtained, and 2-hydroxycyclododecanone (**7d**) was formed as the only product. In the presence of oxide bases, the radical product **7b** was obtained as the major product (runs 18 and 19). From these results, it is believed that the radical photo-behavior is preferentially carried out in the presence of a strong base such as NaOH (Scheme 3).

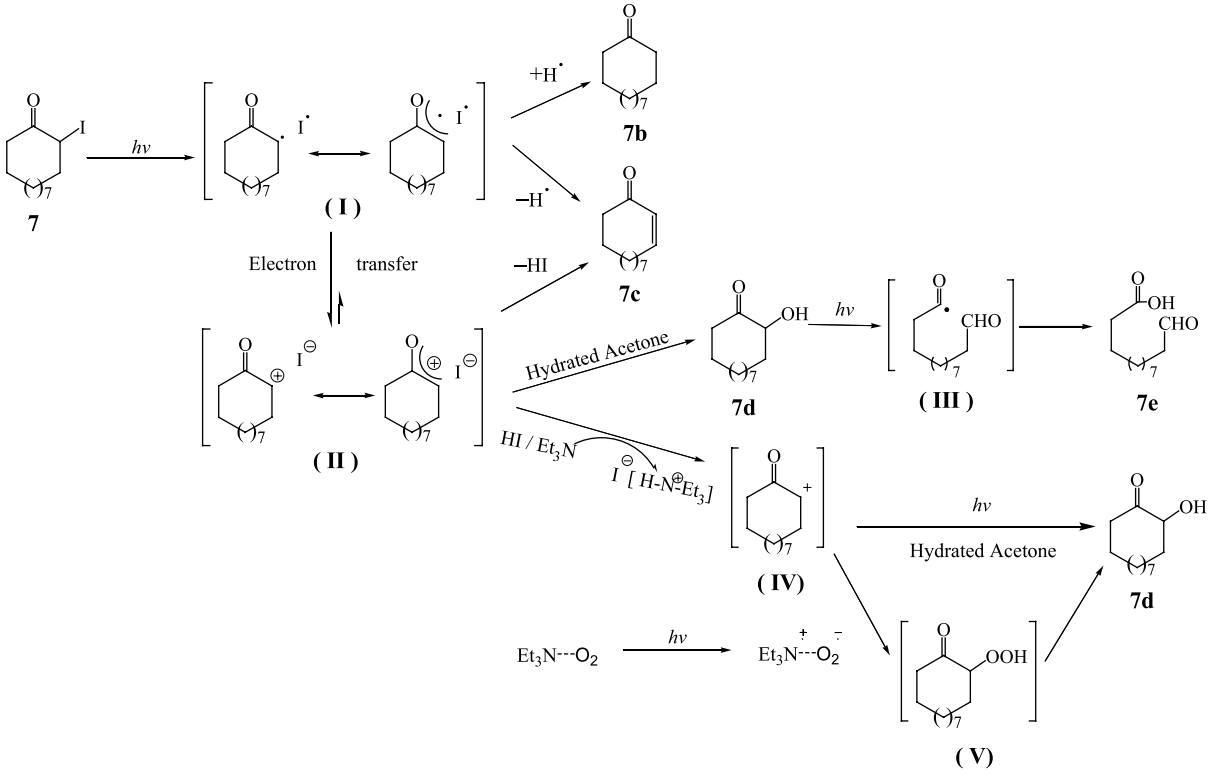
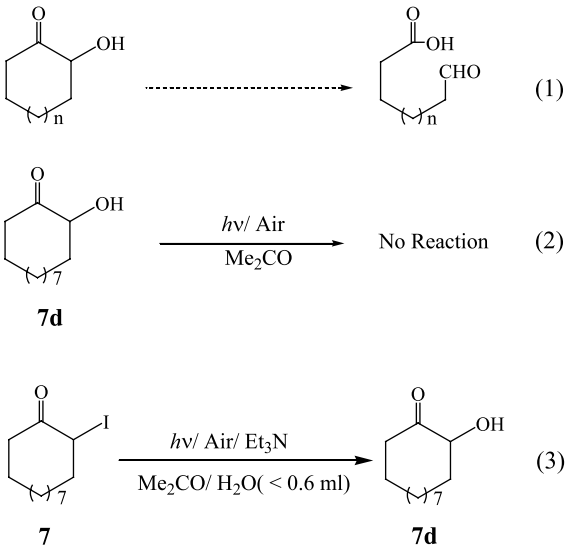
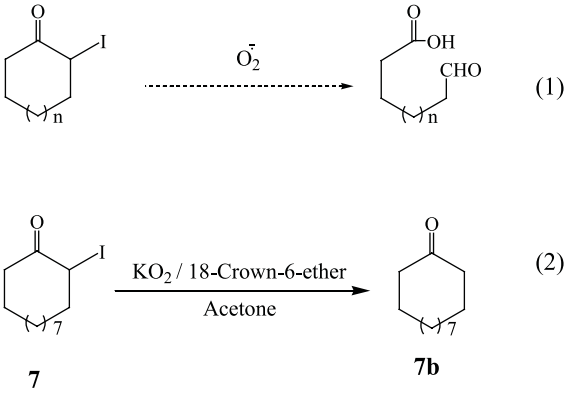


Figure 1. The photo-irradiation pathway of α-iodocyclododecanone (**7**).



Scheme 2.



Scheme 3.

For the results mentioned above, it was found that Et_3N is the best HX scavenger to give α-hydroxyketone derivatives. In order to investigate the relationship between the yields of products (**7b**, **7d**, and **7e**) and the equivalent of Et_3N, the irradiation of 2-iodocyclododecanone (**7**) in the presence of Et_3N was carried out (Fig. 2). It was found that the yield of α-hydroxyketone **7d** depended on the quantity of Et_3N. In the absence of Et_3N, α-hydroxyketone **7d** was not obtained; the reduced ketone **7b** and ring-opening product **7e** were formed in 50 and 42% yields, respectively. As the equivalent of Et_3N increased, the reduced ketone **7b** decreased. When the reduced ketone **7b** disappeared, the ring-opening product **7e** stated decreasing. Finally, α-hydro-hydroxyketone **7d** was formed as the only product (95%) in the presence of above 1 molar equivalent of Et_3N. It is believed that Et_3N has two important roles in this photo-irradiation: first, Et_3N makes the ionic photobehavior become the main pathway; second, Et_3N is an HI scavenger to stop the synthetic process of the ring-opening product **7e**.

To discuss the pathway from the caged cation **IV** to hydroxyketone **7d** in Figure 1, we consulted the experimental results regarding the effect of water in our previous paper. In Ji's paper, it was found that a small amount of water in alcohol is absolutely essential for forming the ring-opening product, and hydroxyketone is a reactive intermediate.[14] In the irradiation of **7** in acetone containing Et_3N, it was found that the yield of hydroxyketone **7d** did not decrease in the presence of 0.6 ml H_2O (Scheme 2). It is believed that the water contained in acetone is a very important agent to form hydroxyketones.

On the other hand, the direct photo-oxidation of triethylamine with molecular oxygen[20] is well known. Therefore, we discussed the possibility of the electron transfer between molecular oxygen and triethylamine in the photobehavior of hydroxyketones (Fig. 1). In order to clarify this pathway, oxidation of **7** with superoxide anion was carried out. In the oxidation of **7** in acetone containing KO_2 and 18-crown-6-ether, hydroxyketone **7d** was not obtained (Scheme 2). This result denies for the direct attack of superoxide anion to give hydroxyketone **7d**. However, the result is not rule out the attack of the ion-pair formation of molecular oxygen and triethylamine. Therefore, the pathway from the caged cation **V** to hydroxyketone **7d** is possible.

In order to investigate the reaction of α,α′-diiodo ketones, the irradiation of α,α′-diiodo ketones (**15**–**19**, **22**–**23**) was carried out with a 400 W mercury lamp under air

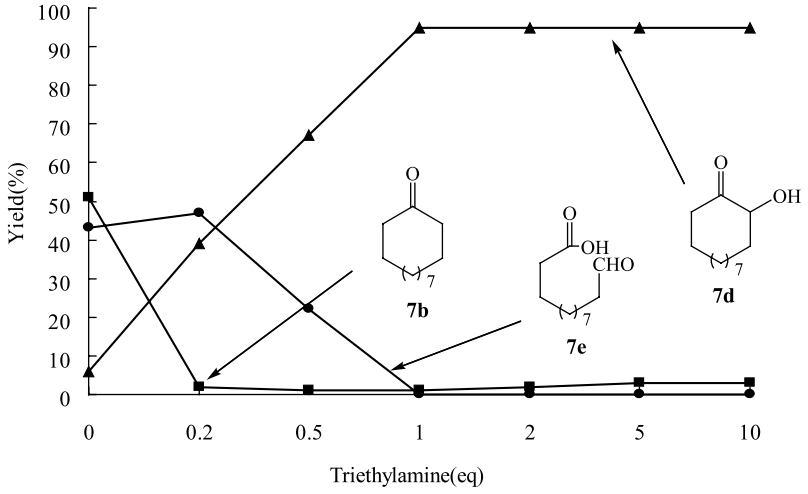


Figure 2. Relation between molar equivalent of triethylamine and yields of products.

Table 4. Photochemical reaction of α-iodo- and α,α′-diiodoacyclicketone

Run	Substrate	R_1	R_2	Time (h)	Product (%)
1	**15** (*cis*/*trans*=95/5)	Me	Me	5	**15f** (47,*cis*/*trans*=50/50)[a]
2	**16** (*cis*/*trans*=90/10)	Et	Et	6	**16f** (58,*cis*/*trans*=50/50)[a]
3	**17** (*cis*/*trans*=75/25)	n-C_3H_7	n-C_3H_7	6	**17f** (65,*cis*/*trans*=50/50)[a]
4	**18** (*cis*/*trans*=62/38)	n-C_4H_9	n-C_4H_9	6	**18f** (73,*cis*/*trans*=50/50)[a]
5	**19** (*cis*/*trans*=54/46)	Me	n-C_7H_{15}	5	**19f** (70,*cis*/*trans*=50/50)[a]
6	**20**	H_2	n-C_3H_7	3	**20f** (t)
7	**21**	H_2	n-C_4H_9	3	**21f** (t)
8	**22**	CH_2–$(CH_2)_2$–CH_2		5	**22f** (82,*cis*/*trans*=87/13)[a]
9	**23**	CH_2–$(CH_2)_7$–CH_2		5	**23f** (54,*cis*/*trans*=90/10)[a]
10	**24**	Me	Me	10	**24d** (65,*syn*/*anti*=81/19)[a]
11	**25**	Me	Et	10	**25d** (62,*syn*/*anti*=80/20)[a]
12	**26**	Ph	Me	8	**26d** (72,*syn*/*anti*=84/16)[a]
13	**27**	Ph	Et	8	**27d** (75,*syn*/*anti*=81/10)[a]

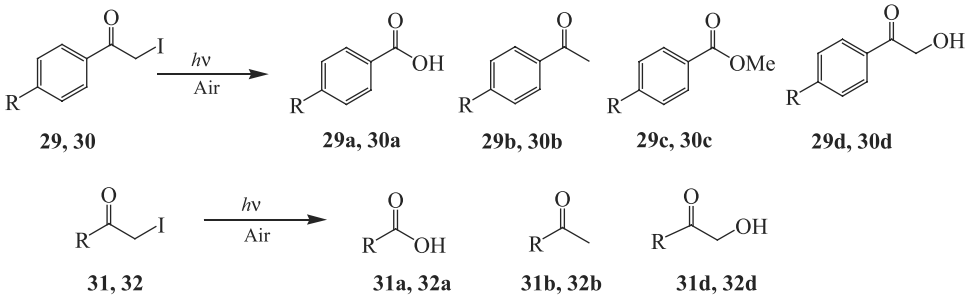
Reaction conditions: substrate (0.1 mmol) in acetone (10 ml) containing triethylamine (0.2 mmol) was irradiated by a high-pressure mercury lamp (400 W) under air. Yields were determined by GLC.
[a] Isolated yields. Product ratio was determined from the peak area ratio of the NMR spectrum.

atmosphere in acetone containing Et_3N (Table 4). It was found that the corresponding α,α′-dihydroxy ketones (**15f**-**19f**, **22f**-**23f**) were obtained in good yields. In the case of α-iodo-β-alkoxy esters (**24**–**27**), α-hydroxy-β-alkoxy esters (**24d**-**27d**) were also obtained in good yields (runs 10–13). However, the irradiation of the primary α-iodo ketones (**20**, **21**) did not give α,α′-dihydroxyketones (**20f**, **21f**) as major products.

Moreover, the irradiation of primary α-iodo ketone derivatives (**29**–**32**) was carried out in acetone containing Et_3N (Table 5). It was found that the corresponding α-hydroxycarbonyl compounds (**29d**–**32d**) were formed in low yields (5–10%). From these results, it is considered that the synthetic method is not applicable to form primary α-hydroxyketones. Also, the photo-irradiation was investigated using α-iodo-β-alkoxy alkanoic esters (**33**–**40**) as secondary α-iodo carbonyl compounds or tertiary α-iodo carbonyl compounds (Table 6). The secondary α-iodo carbonyl compounds (**33**–**38**) gave the corresponding α-hydroxy-β-alkoxy alkanoic esters (**33d**–**38d**) in good yields. As tertiary α-iodo carbonyl compounds, α-iodo-β-alkoxy alkanoic esters **39** and **40** gave the corresponding tertiary α-hydroxy carbonyl compounds **39d** and **40d** in 42 and 40% yield, respectively. On the basis of these results, it was found that the yields of tertiary α-hydroxy carbonyl compounds were lower than the yields of secondary α-hydroxy carbonyl compounds.

In conclusion, this method is very clean, simple, and convenient for the synthesis of secondary α-hydroxy carbonyl compounds and tertiary α-hydroxy carbonyl compounds. It is particularly noteworthy that this reaction affords a new synthetic method for α-hydroxyketones, α,α′-dihydroxyketones and α-hydroxy-β-alkoxy ester derivatives.

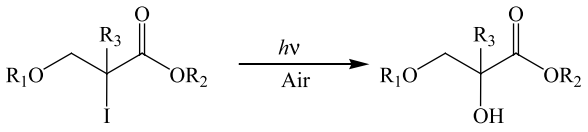
Table 5. Photochemical reaction of primary α-iodoketone derivatives (**29**–**32**)



Run	Substrate	Solvent	Et_3N (equiv)	R	Time/h	Product (%)[a]			
						a	**b**	**c**	**d**
1	**29**	Acetone	0	H	3	45	25	0	6
2	**29**	MeOH	0	H	3	0	20	67	5
3	**29**	Et_2O	0	H	3	0	90	0	5
4	**29**	Acetone	1	H	5	0	20	0	10
5	**29**	MeOH	1	H	5	0	10	20	5
6	**29**	Et_2O	1	H	5	0	5	0	5
7	**30**	An	1	OMe	5	0	30	0	10
8	**31**	An	1	n-C_4H_9	5	0	5	0	5
9	**32**	An	1	n-C_5H_{11}	5	0	5	0	5

Reaction conditions: substrate (0.1 mmol) in solvent (10 ml) was irradiated by a high-pressure mercury lamp (400 W) under air.
[a] Yields were determined from GLC.

Table 6. Photochemical reaction of α-iodo-β-alkoxyl alkanoic ester (**33–40**)



33-40 **33d-40d**

Run	Substrate	R_1	R_2	R_3	Time/h	Product (%)[a]
1	**33**	Me	Me	H	10	**33d** (52)
2	**34**	Et	Me	H	10	**34d** (56)
3	**35**	*n*-Pr	Me	H	12	**35d** (61)
4	**36**	Me	Et	H	10	**36d** (60)
5	**37**	Et	Et	H	10	**37d** (62)
6	**38**	*n*-Pr	Et	H	10	**38d** (71)
7	**39**	Me	Et	Me	8	**39d** (42)
8	**40**	Et	Et	Me	8	**40d** (40)

Reaction conditions: substrate (0.1 mmol) in acetone (10 ml) containing triethylamine (0.1 mmol) was irradiated by a high-pressure mercury lamp (400 W) under air.
[a] Isolated yields.

3. Experimental

3.1. General procedure

IR spectra were recorded on a Jasco FT-IR 230 spectrometer. ^{1}H and ^{13}C NMR spectra were measured using a JEOL GSX 400 Model spectrometer in deuteriochloroform solutions with tetramethylsilane used as an internal standard.

GC–MS (EI) analyses were performed on a Shimazu GCMS-QP5050 with an ionizing energy of 70 eV. CIMS (*i*-butane reagent gas) were recorded on a Shimazu GCMS-QP5050 with an ionizing energy of 300 eV. The high-resolution mass spectra (EI) were performed on a JEOL JMS-GCMATE II with an ionizing energy of 70 eV.

3.2. Photo-irradiation of α-halo ketones (1–14, 28)

Typical procedure for the irradiation of α-iodo ketones. A mixture of α-iodo ketone (0.10 mmol) and acetone (10 ml) containing triethylamine (0.10 mmol) was irradiated by a 400 W high-pressure mercury lamp under air for 10 h. After the irradiation was completed, the mixture was concentrated, poured into water, and extracted with diethyl ether (30 ml). The ethereal solution was washed with a saturated solution of sodium thiosulfate (2×2.0 ml), saturated aq NaCl (2×2.0 ml) and water (2×2.0 ml). The ethereal solutions were dried over Na_2SO_4 and concentrated in a vacuum. The resulting oil was chromatographed on silica gel. Elution with hexane–ether (3:1) gave isolated compounds. These compounds were identified by ^{1}H NMR, ^{13}C NMR, IR and GC–MS.

Typical procedure for the irradiation of α-bromo ketones. A mixture of α-bromo ketone (0.10 mmol), KI (0.10 mmol) and triethylamine (0.10 mmol) in acetone (10 ml) was irradiated by a 400 W high-pressure mercury lamp in the presence of air for 12 h.

3.2.1. 3-Hydroxy-3,6-dimethylcyclohexane-1,2-dione (1d). Pale-yellow oil; IR (NaCl)=3447, 1675 and 1647 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ(ppm)=5.78 (s, 1H), 3.18 (s, 1H), 2.64–2.41 (m, 1H), 2.35 (t, 1H), 2.09-2.04 (m, 2H), 1.95 (s, 3H) and 1.26 (d, 3H); ^{13}C NMR ($CDCl_3$) δ(ppm)=197.3, 141.2, 131.8, 72.7, 35.3, 29.7, 27.7 and 17.1; MS (EI) *m/z* 156 (M^+), 138 ($[M-H_2O]^+$), 125, 113, 98, 95, 70, 58 and 43; MS (CI) *m/z* 157 ($[M+H]^+$).

3.2.2. 3-Hydroxy-3-methyl-6-isopropylcyclohexane-1,2-dione (2d). Colorless needles; mp 71–72 °C; IR (KBr)=3447, 1670 and 1637 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ(ppm)=5.28 (s, 1H), 3.23 (s, 1H), 3.19–3.11 (m, 1H), 2.40–2.31 (m, 2H), 2.13–1.95 (m, 2H), 1.34 (s, 3H) and 1.07 (dd, 6H); ^{13}C NMR ($CDCl_3$) δ(ppm)=197.9, 140.6, 139.7, 72.6, 35.3, 28.1, 24.3, 20.7 and 19.5; MS (EI) *m/z* 184 (M^+), 166 ($[M-H_2O]^+$), 124, 123, 109, 83, 69, 55 and 43; MS (CI) *m/z* 185 ($[M+H]^+$). Found: *m/z* 184.110. Calcd for $C_{10}H_{16}O_3$: M, 184.110.

3.2.3. 2-Hydroxycycloheptanone (4d).[21] Pale-yellow oil; IR (NaCl)=3469 (O–H) and 1699 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ(ppm)=4.29 (dt, 1H, *J*=6.2, 2.1 Hz, C*H*OH), 3.86 (brd, 1H, CHO*H*), 2.72 (dddd, 1H, *J*=0.9, 2.2, 4.8, 7.1 Hz, C(O)C*H*H), 2.47 (ddd, 1H, *J*=3.8, 11.3, 18.2 Hz, C(O)CH*H*), 2.01–2.09 (m, 1H), 1.74–1.93 (m, 3H), 1.54–1.73 (m, 3H) and 1.29–1.40 (m, 1H); ^{13}C NMR ($CDCl_3$) δ(ppm)=213.2, 77.2, 40.0, 33.6, 29.4, 26.5 and 23.2; MS (EI) *m/z* 128 (M^+), 110 ($[M-H_2O]^+$), 99, 81, 57 and 44; MS (CI) *m/z* 129 ($[M+H]^+$).

3.2.4. 2-Hydroxycyclooctanone (5d).[21] Pale-yellow oil; IR (NaCl)=3475 (O–H) and 1701 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ(ppm)=4.19 (dd, 1H, *J*=1.9, 4.3 Hz, C*H*OH), 3.79 (brs, 1H, CHO*H*), 2.71 (dt, 1H, *J*=2.6, 8.5 Hz, C(O)C*H*H), 2.30–2.45 (m, 2H), 1.91–2.08 (m, 2H), 1.62–1.87 (m, 4H), 1.32–1.45 (m, 2H) and 0.85–0.97 (m, 1H); ^{13}C NMR ($CDCl_3$) δ(ppm)=217.6, 76.1, 37.4, 29.2, 28.3, 25.7, 24.8 and 22.1; MS (EI) *m/z* 142 (M^+), 124 ($[M-H_2O]^+$), 113, 98, 81, 57 and 41; MS (CI) *m/z* 143 ($[M+H]^+$).

3.2.5. 2-Hydroxycyclodecanone (6d).[21] Pale-yellow oil; IR (NaCl)=3463 (O–H) and 1699 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ(ppm)=4.23 (d, 1H, *J*=4.0 Hz, C*H*OH), 3.94 (brs, 1H, CHO*H*), 3.15 (ddd, 1H, *J*=3.6, 8.1, 12.2 Hz, C(O)C*H*H), 2.29 (dt, 1H, *J*=1.1, 4.6 Hz, C(O)CH*H*),

2.04–2.27 (m, 3H), 1.21–1.72 (m, 10H) and 0.98–1.15 (m, 1H); ^{13}C NMR ($CDCl_3$) δ(ppm)=214.5, 76.8, 35.2, 29.3, 26.1, 25.0, 23.3, 22.9, 22.5 and 20.7; MS (EI) *m/z* 170 (M^+), 152 ([M−H_2O]$^+$), 134 ([M−H_2O]$^+$), 111, 98, 81, 57 and 41; MS (CI) *m/z* 171 ([M+H]$^+$).

3.2.6. 2-Hydroxycyclododecanone (7d).[21] Pale-yellow oil; IR (NaCl) 3418 (O–H) and 1714 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ(ppm)=4.23 (brs, 1H), 3.94 (brs, 1H), 3.01 (m, 1H), 2.05–2.31 (m, 2H), 1.48–1.68 (m, 1H), 1.05–1.45 (m, 15H) and 0.73–0.91 (m, 1H); ^{13}C NMR ($CDCl_3$) δ(ppm)= 212.9, 76.6, 34.3, 30.7, 26.1, 24.9, 22.6, 22.5, 21.9, 21.6, 18.8 and 15.6; MS (EI) *m/z* 198 (M^+), 180, 162, 149, 133, 111, 95, 82 and 55; MS (CI) *m/z* 199 ([M+1]$^+$).

3.2.7. 2-Hydroxycyclopentadecanone (8d). Pale-yellow oil; IR (NaCl)=3477 (O–H) and 1708 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ(ppm)=4.25 (q, 1H, *J*=1.9 Hz, C*H*OH), 3.62 (d, 1H, *J*=2.3 Hz, CHO*H*), 2.61 (dt, 1H, *J*=8.2, 3.9 Hz, C(O)C*H*H), 2.33 (dt, 1H, *J*=6.4, 3.0 Hz, C(O)CH*H*), 1.54–1.93 (m, 3H) and 1.12–1.49 (m, 21H); ^{13}C NMR ($CDCl_3$) δ(ppm)=212.7, 76.0, 36.8 (2C), 32.6, 27.2, 26.5, 26.4, 26.1 (2C), 25.9 (2C), 25.8, 22.2 and 21.9; MS (EI) *m/z* 240 (M^+), 222 ([M−H_2O]$^+$), 166, 152, 138, 124, 110, 96, 82 and 55; HRMS found: *m/z* 240.2119 [M]$^+$. Calcd for $C_{15}H_{28}O_2$: M, 240.2089.

3.2.8. 2-Hydroxytetralone (9d).[22] Pale-yellow oil; IR (NaCl)=3476 (O–H), 1685 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ(ppm)=8.04 (dd, 1H, *J*=1.3, 5.3 Hz), 7.51 (dt, 1H, *J*=1.0, 5.2 Hz), 7.33 (t, 1H, *J*=5.6 Hz), 7.26 (d, 1H, *J*=5.5 Hz), 4.38 (dd, 1H, *J*=4.0, 9.5 Hz, C*H*OH), 4.05 (brs, 1H, CHO*H*), 3.14 (ddd, 1H, *J*=3.9, 8.8, 11.8 Hz, CH(OH)C*H*H), 3.02 (ddd, 1H, *J*=1.8, 3.1, 11.7 Hz, CH(OH)CH*H*), 2.52 (dddd, 1H, *J*=1.9, 3.1, 3.9, 5.2 Hz, C(OH)CH_2C*H*H) and 2.03 (dq, 1H, *J*=3.4, 9.2 Hz, C(OH)CH_2CH*H*); ^{13}C NMR ($CDCl_3$) δ(ppm)=199.8, 144.3, 134.5, 130.8, 129.0, 127.8, 127.0, 74.1, 32.0 and 27.9; MS (EI) *m/z* 162 (M^+), 144 ([M−H_2O]$^+$), 133, 118, 103, 90, 77, 63 and 51; MS (CI) *m/z* 163 ([M+H]$^+$).

3.2.9. 2-Hydroxy-1-phenyl-1-propanone (10d).[10] Pale-yellow oil; IR (NaCl)=3448 (O–H), 1685 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ(ppm)=7.93 (dt, 2H, *J*=6.5, 1.3 Hz), 7.62 (tt, 1H, *J*=1.2, 12.6 Hz), 7.51 (tt, 2H, *J*=1.3, 12.8 Hz), 5.17 (dq, 1H, *J*=3.6, 7.0 Hz, C*H*OH), 3.80 (brd, 1H, CHO*H*), 1.46 (d, 3H, *J*=7.0 Hz, CH(OH)CH_3); ^{13}C NMR ($CDCl_3$) δ(ppm)=202.4, 134.0, 133.2, 128.9 (2C), 128.6 (2C), 69.3 and 22.3; MS (EI) *m/z* 135 ([M−CH_3]$^+$), 115, 105 ([M−C(OH)CH_3]$^+$), 91, 77, 63 and 51.

3.2.10. 2-Hydroxy-1-phenyl-1-butanone (11d).[23] Pale-yellow oil; IR (NaCl)=3475 (O–H), 1685 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ(ppm)=7.91 (dt, 2H, *J*=7.4, 1.6 Hz), 7.62 (tt, 1H, *J*=1.1, 7.7 Hz), 7.51 (tt, 2H, *J*=2.6, 11.5 Hz), 5.07 (dt, 1H, *J*=3.9, 7.6 Hz, C*H*OH), 3.72 (d, 1H, *J*= 6.0 Hz, CHO*H*), 1.56–1.69 (m, 2H, CH(OH)CH_2) and 0.94 (t, 3H, *J*=7.2 Hz, CH_2CH_3); ^{13}C NMR ($CDCl_3$) δ(ppm)= 202.1, 133.9, 133.7, 128.9 (2C), 128.5 (2C), 73.9, 28.8 and 8.8; MS (EI) *m/z* 135 ([M−CH_2CH_3]$^+$), 115, 105 ([M−C(OH)CH_2CH_3]$^+$), 91, 77, 59 and 51.

3.2.11. 3-Hydroxy-2-hexanone (12d).[6] Pale-yellow oil; IR (NaCl)=3415 (O–H), 1718 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ(ppm)=4.22 (dd, 1H, *J*=3.9, 7.2 Hz, C*H*OH), 2.21 (s, 3H, C(O)CH_3), 1.35–1.86 (m, 4H) and 0.96 (t, 3H, *J*=7.5 Hz, CH_2CH_3); ^{13}C NMR ($CDCl_3$) δ(ppm)=210.5, 76.8, 35.5, 25.2, 17.8 and 13.6; MS (EI) *m/z* 117 ([M+H]$^+$), 97, 87, 73, 55 and 43.

3.2.12. 3-Hydroxy-2-heptanone (13d).[24] Pale-yellow oil; IR (NaCl)=3421 (O–H), 1718 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ(ppm)=4.18 (dd, 1H, *J*=4.4, 7.3 Hz, C*H*OH), 3.70 (brs, 1H, CHO*H*), 2.20 (s, 3H, C(O)CH_3), 1.78–1.88 (m, 1H), 1.51–1.61 (m, 1H), 1.29–1.48 (m, 2H) and 0.92 (t, 3H, *J*=6.8 Hz, CH_2CH_3); ^{13}C NMR ($CDCl_3$) δ(ppm)= 210.4, 77.0, 33.3, 28.6, 25.2, 22.6 and 13.9; MS (EI) *m/z* 130 (M^+), 112 ([M−H_2O]$^+$), 97 ([M−CH_3]$^+$), 87, 69, 57 and 41.

3.2.13. 3-Hydroxy-2-undecanone (14d).[25] Pale-yellow oil; IR (NaCl)=3475 (O–H), 1718 (C=O) cm^{-1}, ^{1}H NMR ($CDCl_3$) δ(ppm)=4.19 (dt, 1H, *J*=7.2, 4.7 Hz, C*H*OH), 3.53 (d, 1H, *J*=4.3 Hz, CHO*H*), 2.20 (s, 3H, C(O)CH_3), 1.78–1.88 (m, 1H), 1.41–1.60 (m, 2H), 1.24–1.37 (m, 11H) and 0.88 (t, 3H, *J*=6.9 Hz, CH_2CH_3); ^{13}C NMR ($CDCl_3$) δ(ppm)=210.0, 76.7, 33.5, 31.8, 29.4, 29.3, 29.1, 25.1, 24.7, 22.6 and 14.0; MS (EI) *m/z* 186 (M^+), 143, 125, 111, 97, 83, 69, 55 and 43.

3.3. Photo-irradiation of α,α′-diiodo ketones (15–23)

Typical procedures. A mixture of α,α′-diiodo ketone (0.10 mmol) and triethylamine (0.20 mmol) in acetone (10 ml) was irradiated by a high-pressure mercury lamp in the presence of air. After the irradiation was completed, the mixture was concentrated, poured into water, and extracted with diethyl ether (30 ml). The ethereal solution was washed with a saturated solution of sodium thiosulfate (2×2.0 ml), saturated aq NaCl (2×2.0 ml) and water (2×2.0 ml). The ethereal solution was dried over Na_2SO_4 and concentrated in a vacuum. The resulting oil was chromatographed on silica gel. Elution with hexane–ether (3:1) gave isolated compounds. These compounds were identified by ^{1}H NMR, ^{13}C NMR, IR and GC–MS.

3.3.1. 3,5-Dihydroxy-4-heptanone (*cis*/*trans*=50/50, 16f). Colorless oil, IR (NaCl)=3397 (O–H), 1718 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ(ppm)=4.41 (dd, 2H, *J*=4.0, 6.9 Hz, C*H*OH), 4.37 (dd, 2H, *J*=3.9, 7.9 Hz, C*H*OH), 3.33 (brs, 2H×2, CHO*H*), 1.85–1.99 (m, 2H×2), 1.65 (dquint, 2H, *J*=14.7, 6.9 Hz), 1.63 (dquint, 2H, *J*=14.2, 7.0 Hz), 0.98 (t, 6H, *J*=7.0 Hz, CH_2CH_3) and 0.97 (t, 6H, *J*=7.0 Hz, CH_2CH_3); ^{13}C NMR ($CDCl_3$) δ(ppm)=214.3, 213.9, 75.8, 74.6, 27.4, 26.7, 9.3 and 8.8; MS (EI) *m/z* 128 ([M−H_2O]$^+$), 117, 100, 88, 70, 59 and 41; HRMS found: *m/z* 147.0987 [M+H]$^+$. Calcd for $C_7H_{15}O_3$: M+H, 147.1021.

3.3.2. 4,6-Dihydroxy-5-nonanone (*cis*/*trans*=50/50, 17f).[26] Colorless oil, IR (NaCl)=3421 (O–H), 1718 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ(ppm)=4.37 (dd, 2H, *J*=3.1, 6.4 Hz, C*H*OH), 4.35 (dd, 2H, *J*=3.9, 7.8 Hz, C*H*OH), 3.38 (brs, 2H×2, CHO*H*), 1.64–1.81 (m, 2H×2), 1.27–1.54 (m, 2H×2), 0.88 (t, 6H, *J*=6.2 Hz, CH_2CH_3) and 0.87 (t, 6H, *J*=6.9 Hz, CH_2CH_3), ^{13}C NMR ($CDCl_3$) δ(ppm)=214.7, 214.2, 74.5, 73.6, 36.2, 35.6, 18.3, 18.1,

13.7 and 13.6; MS (EI) *m/z* 156 ([M−H_2O]$^+$), 145, 114, 102, 84, 73, 55 and 43; HRMS found: *m/z* 175.1292 [M+H]$^+$. Calcd for $C_9H_{19}O_3$: M+H, 175.1334.

3.3.3. 5,7-Dihydroxy-6-undecanone (*cis/trans*=50/50, 18f). Colorless oil, IR (NaCl)=3421 (O–H), 1718 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ(ppm)=4.44 (dd, 2H, *J*=3.6, 8.5 Hz, C*H*OH), 4.41 (dd, 2H, *J*=3.8, 8.0 Hz, C*H*OH), 3.42 (brs, 2H, CHO*H*), 3.23 (brs, 2H, CHO*H*), 1.77–1.92 (m, 2H×2), 1.51–1.61 (m, 2H×2), 1.30–1.48 (m, 2H×2) and 0.92 (t, 6H, *J*=7.0 Hz, CH_2CH_3); ^{13}C NMR ($CDCl_3$) δ(ppm)=214.7, 214.2, 74.8, 73.8, 34.1, 33.4, 27.2, 26.7, 22.4, 21.1, 14.2 and 13.9; MS (EI) *m/z* 184 ([M−H_2O]$^+$), 173 ([M−CH_2CH_3]$^+$), 128, 116, 98, 87, 69, 57 and 41; HRMS found: *m/z* 203.1757 [M+H]$^+$. Calcd for $C_{11}H_{23}O_3$: M+H, 203.1647.

3.3.4. 2,4-Dihydroxy-3-undecanone (*cis/trans*=50/50, 19f). Pale-yellow oil, IR (NaCl)=3409 (O–H), 1718 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ(ppm)=4.52 (dd, 2H, *J*=7.2, 3.2 Hz, C*H*OH); 4.47 (dd, 2H, *J*=3.8, 7.9 Hz, C*H*OH), 3.99 (brs, 2H×2, CHO*H*), 1.76–1.90 (m, 1H×2), 1.51–1.67 (m, 1H×2), 1.41 (d, 3H×2, *J*=6.5 Hz, CH_3-CH(OH)), 1.22–1.35 (m, 10H×2) and 0.88 (t, 3H×2, *J*=7.4 Hz, CH_2CH_3); ^{13}C NMR ($CDCl_3$) δ(ppm)=214.8, 214.5, 74.6, 73.7, 70.9, 70.2, 34.2, 33.7, 31.8, 31.7, 29.3 (2C), 29.2 (2C), 25.1, 24.9, 22.7, 22.6, 20.3, 19.8, 14.2 and 14.1; MS (EI) *m/z* 173 ([M−CH_2CH_3]$^+$), 158, 141, 129, 111, 98, 83, 69, 55 and 43; HRMS found: *m/z* 203.1650 [M+H]$^+$. Calcd for $C_{11}H_{23}O_3$: M+H, 203.1647.

3.3.5. *cis*-2,7-Dihydroxycycloheptanone (22f).[27] Colorless needles; mp 83–85 °C; IR (KBr)=3413 (O–H), 1708 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ(ppm)=4.28 (dd, 2H, *J*=3.9, 9.6 Hz, C*H*OH), 3.45 (brs, 2H, CHO*H*), 2.04–2.18 (m, 2H), 1.87–1.96 (m, 2H), 1.69–1.79 (m, 2H) and 1.56–1.66 (m, 2H); ^{13}C NMR ($CDCl_3$) δ(ppm)=214.6, 76.7 (2C), 32.5 (2C) and 27.1 (2C); MS (EI) *m/z* 144 (M$^+$), 126 ([M−H_2O]$^+$), 115, 97, 85, 70, 57 and 41; HRMS found: *m/z* 144.0763 [M]$^+$. Calcd for $C_7H_{12}O_3$: M, 144.0789.

3.3.6. *cis*-2,12-Dihydroxycyclododecanone (23f). Colorless oil, IR (NaCl)=3384 (O–H), 1718 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ(ppm)=4.59 (ddd, 2H, *J*=4.7, 7.2, 10.2 Hz, C*H*OH), 3.37 (brs, 2H, CHO*H*), 1.86–2.06 (m, 2H), 1.58–1.83 (m, 2H), 1.23–1.53 (m, 10H), 1.06–1.17 (m, 2H) and 0.92–1.03 (m, 2H); ^{13}C NMR ($CDCl_3$) δ(ppm)=212.7, 73.3, 72.6, 32.0, 30.7, 25.1, 23.4, 23.1, 22.8, 22.4, 21.7 and 19.8; MS (EI) *m/z* 214 (M$^+$), 183, 155, 147, 135, 112, 98, 95, 81, 55 and 41; CI-MS (*m/z*): 215 ([M+H]$^+$); HRMS found: *m/z* 214.1597 [M]$^+$. Calcd for $C_{12}H_{22}O_3$: M, 214.1569.

3.4. Photo-irradiation of α-iodo-β-alkoxy alkanoic ester (24–27, 33–40)

Typical procedures. A mixture of α-iodo-β-alkoxy alkanoic ester (0.10 mmol) and triethylamine (0.10 mmol) in acetone (10 ml) was irradiated by a high-pressure mercury lamp in the presence of air for 10 h. After the irradiation was completed, the mixture was concentrated, poured into water, and extracted with diethyl ether (30 ml). The ethereal solution was washed with a saturated solution of sodium thiosulfate (2×2.0 ml), saturated aq NaCl (2×2.0 ml) and water (2×2.0 ml). The ethereal solution was dried over Na_2SO_4 and concentrated in a vacuum. The resulting oil was chromatographed on silica gel. Elution with hexane–ether (3:1) gave isolated compounds. These compounds were identified by ^{1}H NMR, ^{13}C NMR, IR and GC–MS.

3.4.1. Ethyl *syn*-3-methoxy-2-hydroxy butanonate (24d). Pale-yellow oil, IR (NaCl)=3482 (O–H), 1735 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ(ppm)=4.31 (dq, 1H, *J*=10.1, 7.1 Hz, C(O)OC*H*HCH_3), 4.25 (dq, 1H, *J*=10.1, 7.1 Hz, C(O)OCH*H*CH_3), 4.03 (dd, 1H, *J*=2.1, 7.7 Hz, CHO*H*), 3.73 (dq, 1H, *J*=2.1, 6.1 Hz, CH(OH)C*H*), 3.32 (s, 3H, CH_3O), 2.95 (d, 1H, *J*=7.7 Hz, CHO*H*), 1.31 (t, 3H, *J*=7.1 Hz, C(O)OCH_2CH_3), 1.28 (d, 3H, *J*=6.1 Hz, CH(OH)CHCH_3); ^{13}C NMR ($CDCl_3$) δ(ppm)=173.0, 77.3, 74.1, 61.5, 56.9, 14.8 and 14.2; MS (EI) *m/z* 163 ([M+H]$^+$), 147, 131, 119, 104, 89, 76, 59 and 43; HRMS found: *m/z* 162.0809 [M]$^+$. Calcd for $C_7H_{14}O_4$: M, 162.0892.

3.4.2. Ethyl *anti*-3-methoxy-2-hydroxy butanonate (24d). Pale-yellow oil, IR (NaCl)=3463 (O–H), 1735 (C=O) cm^{-1}: ^{1}H NMR ($CDCl_3$) δ(ppm)=4.32 (dd, 1H, *J*=3.8, 5.6 Hz, C*H*OH), 4.27 (dq, 2H, *J*=3.5, 7.1 Hz, C(O)OCH_2CH_3), 3.65 (dq, 1H, *J*=3.9, 6.5 Hz, CH(OH)C*H*), 3.41 (s, 3H, CH_3O), 2.98 (brd, 1H, CHO*H*), 1.32 (t, 3H, *J*=7.1 Hz, C(O)OCH_2CH_3), 1.17 (d, 3H, *J*=6.5 Hz, CH(OH)CHCH_3); ^{13}C NMR ($CDCl_3$) δ(ppm)=172.6, 78.2, 72.6, 61.7, 56.9, 14.2 and 14.0, MS (EI) *m/z* 162 (M$^+$), 147, 131, 119, 104, 89, 76, 59 and 43. HRMS found: *m/z* 162.0809 [M]$^+$. Calcd for $C_7H_{14}O_4$: M, 162.0892.

3.4.3. Ethyl *syn*-3-ethoxy-2-hydroxy butanonate (25d). Pale-yellow oil, IR (NaCl)=3504 (O–H), 1735 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ(ppm)=4.29 (dq, 1H, *J*=10.1, 7.0 Hz, C(O)OC*H*HCH_3), 4.25 (dq, 1H, *J*=10.1, 7.0 Hz, C(O)OCH*H*CH_3), 4.03 (d, 1H, *J*=3.5, 6.2 Hz, C*H*OH), 3.83 (dq, 1H, *J*=3.5, 6.2 Hz, CH(OH)C*H*), 3.60 (dq, 1H, *J*=9.0, 7.0 Hz, CH_3CH*H*O), 3.36 (dq, 1H, *J*=9.0, 7.0 Hz, CH_3C*H*HO), 2.98 (brs, 1H, CHO*H*), 1.31 (t, 3H, *J*=7.0 Hz, C(O)OCH_2CH_3), 1.28 (d, 3H, *J*=6.2 Hz, CH(OH)CHCH_3), 1.14 (t, 3H, *J*=7.0 Hz, CH_3CH_2O); ^{13}C NMR ($CDCl_3$) δ(ppm)=173.0, 75.5, 74.2, 64.6, 61.4, 15.7, 15.2 and 14.1; MS (EI) *m/z* 151, 131, 121, 105, 91, 77, 65 and 51; HRMS found: *m/z* 176.1016 [M]$^+$. Calcd for $C_8H_{16}O_4$: M, 176.1049.

3.4.4. Ethyl *anti*-3-ethoxy-2-hydroxy butanonate (25d). Pale-yellow oil, IR (NaCl)=3461 (O–H), 1735 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ(ppm)=4.29–4.33 (m, 1H, C*H*OH), 4.27 (dq, 2H, *J*=1.9, 7.2 Hz, C(O)OCH_2CH_3), 3.74 (dq, 1H, *J*=3.1, 6.5 Hz, CH(OH)C*H*), 3.59 (dq, 1H, *J*=9.1, 7.0 Hz, CH_3C*H*HO), 3.54 (dq, 1H, *J*=9.1, 7.0 Hz, CH_3CH*H*O), 2.90 (brd, 1H, *J*=5.6 Hz, CHO*H*), 1.31 (t, 3H, *J*=7.2 Hz, C(O)OCH_2CH_3), 1.21 (t, 3H, *J*=7.0 Hz, CH_3CH_2O), 1.16 (d, 3H, *J*=6.5 Hz, CH(OH)CHCH_3); ^{13}C NMR ($CDCl_3$) δ(ppm)=172.6, 76.4, 72.9, 64.6, 61.6, 15.4, 14.7 and 14.2; MS (EI) *m/z* 151, 131, 121, 105, 91, 77, 65 and 51.

3.4.5. Ethyl *syn*-3-phenyl-3-methoxy-2-hydroxy propionate (26d). Pale-yellow oil, IR (NaCl)=3488 (O–H), 1735

(C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ(ppm)=7.31–7.39 (m, 5H, C_6H_5), 4.55 (d, 1H, J=3.2 Hz, C*H*OH), 4.28 (dq, 1H, J=10.6, 7.0 Hz, C(O)OC*H*HCH$_3$), 4.25 (d, 1H, J=3.2 Hz, CH(OH)C*H*OCH$_3$), 4.22 (dq, 1H, J=10.6, 7.0 Hz, C(O)OCH*H*CH$_3$), 3.28 (s, 3H, CH_3O), 3.02 (d, 1H, J=7.5 Hz, CHO*H*) and 1.27 (t, 3H, J=7.0 Hz, C(O)OCH$_2$-CH_3); ^{13}C NMR ($CDCl_3$) δ(ppm)=172.1, 137.0, 128.3 (2C), 128.2, 127.3 (2C), 83.9, 74.9, 61.7, 57.4 and 14.1; MS (EI) m/z 176 ([M−OCH$_3$−OH]$^+$), 151, 131, 121, 105, 91, 77, 65 and 51; MS (CI) m/z 225 ([M+H]$^+$).

3.4.6. Ethyl *anti*-3-phenyl-3-methoxy-2-hydroxy propionate (26d). Pale-yellow oil, IR (NaCl)=3482 (O–H), 1735 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ(ppm)=7.27–7.38 (m, 5H, C_6H_5), 4.53 (d, 1H, J=4.4 Hz, C*H*OH), 4.23 (d, 1H, J=4.4 Hz, CH(OH)C*H*), 4.19 (dq, 1H, J=12.7, 7.0 Hz, C(O)OC*H*HCH$_3$), 4.11 (dq, 1H, J=12.7, 7.0 Hz, C(O)OCH*H*CH$_3$), 3.31 (s, 3H, CH_3O), 3.17 (d, 1H, J=7.5 Hz, CHO*H*), 1.17 (t, 3H, J=6.8 Hz, C(O)OCH$_2$CH_3); ^{13}C NMR ($CDCl_3$) δ(ppm)=171.6, 136.1, 128.1 (2C), 128.0, 127.2 (2C), 84.3, 74.0, 61.2, 57.2 and 13.8; MS (EI) m/z 192 ([M−OCH$_3$]$^+$), 176 ([M−OCH$_3$−OH]$^+$), 151, 131, 121, 105, 91, 77, 65 and 51; MS (CI) m/z 225 ([M+H]$^+$).

3.4.7. Ethyl *syn*-3-phenyl-3-ethoxy-2-hydroxy propionate (27d). Pale-yellow oil, IR (NaCl)=3496 (O–H), 1735 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ(ppm)=7.34–7.41 (m, 5H, C_6H_5), 4.67 (d, 1H, J=3.2 Hz, C*H*OH), 4.26 (dq, J=10.6, 7.0 Hz, C(O)OC*H*HCH$_3$), 4.23 (d, 1H, J=3.2 Hz, CH(OH)C*H*), 4.22 (dq, 1H, J=10.6, 7.0 Hz, C(O)OCH*H*CH$_3$), 3.50 (dq, 2H, J=9.5, 7.0 Hz, CH$_3$CH_2O), 3.09 (d, 1H, J=7.3 Hz, CHO*H*), 1.27 (t, 3H, J=7.0 Hz, C(O)OCH$_2$CH_3), 1.16 (t, 3H, J=7.1 Hz, CH_3CH$_2$O); ^{13}C NMR ($CDCl_3$) δ(ppm)=172.1, 137.8, 128.2 (2C), 128.1, 127.3 (2C), 127.2, 81.8, 75.1, 64.9, 61.5, 14.9 and 14.1; MS (EI) m/z 193, 165, 147, 135, 119, 107, 91, 79, 65 and 51.

3.4.8. Ethyl *anti*-3-phenyl-3-ethoxy-2-hydroxy propionate (27d). Pale-yellow oil, IR (NaCl)=3496 (O–H), 1735 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ(ppm)=7.25–7.35 (m, 5H, C_6H_5), 4.62 (d, 1H, J=4.2 Hz, C*H*OH), 4.08–4.19 (m, 3H), 3.34 (dq, 2H, J=9.6, 7.0 Hz, CH$_3$CH_2O), 2.96 (d, 1H, J=7.6 Hz, CHO*H*), 1.21 (t, 3H, J=7.1 Hz, CH_3CH$_2$O) and 1.19 (t, 3H, J=7.0 Hz, C(O)OCH$_2$CH_3); ^{13}C NMR ($CDCl_3$) δ(ppm)=171.8, 136.9, 128.1 (2C), 128.0, 127.3 (2C), 127.1, 82.5, 74.3, 65.0, 61.3, 15.1 and 13.9; MS (EI) m/z 193, 165, 147, 135, 119, 107, 91, 79, 65 and 51.

3.4.9. Methyl 3-methoxy-2-hydroxy propionate (33d). Pale-yellow oil, IR (NaCl)=3430 (O–H), 1737 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ(ppm)=4.32 (t, 1H, J=3.2 Hz, C*H*OH), 3.82 (s, 3H, C(O)CH_3), 3.69 (dt, 2H, J=4.1, 9.9 Hz, CH(OH)CH_2), 3.40 (s, 3H, CH_3O) and 3.12 (brs, 1H, CHO*H*); ^{13}C NMR ($CDCl_3$) δ(ppm)=173.1, 73.9, 70.7, 59.5 and 52.7; MS (EI) m/z 134 (M$^+$), 116 ([M−H$_2$O]$^+$), 104, 91, 75, 59 and 45; HRMS found: m/z 134.0583 [M]$^+$. Calcd for $C_5H_{10}O_4$: M, 134.0579.

3.4.10. Methyl 3-ethoxy-2-hydroxy propionate (34d). Pale-yellow oil, IR (NaCl)=3442 (O–H), 1735 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ(ppm)=4.32 (brs, 1H, C*H*OH), 3.81 (s, 3H, C(O)OCH_3), 3.72 (d, 2H, J=3.8 Hz, CH(OH)CH_2), 3.57 (dq, 1H, J=9.6, 7.0 Hz, CH$_3$C*H*HO), 3.53 (dq, 1H, J=9.6, 7.0 Hz, CH$_3$CH*H*O), 3.05 (brs, 1H, CHO*H*) and 1.19 (t, 3H, J=7.0 Hz, CH_3CH$_2$O); ^{13}C NMR ($CDCl_3$) δ(ppm)=173.1, 71.6, 70.8, 67.2, 52.6 and 14.9; MS (EI) m/z 115 ([M−OCH$_3$]$^+$), 105, 90, 71, 59 and 43; HRMS found: m/z 148.0733 [M]$^+$. Calcd for $C_6H_{12}O_4$: M, 148.0736.

3.4.11. Methyl 3-*n*-propyroxy-2-hydroxy propionate (35d). Pale-yellow oil, IR (NaCl)=3475 (O–H), 1751 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ(ppm)=4.32 (brs, 1H, C*H*OH), 3.80 (s, 3H, C(O)OCH_3), 3.72 (d, 2H, J=3.8 Hz, CH(OH)CH_2), 3.47 (dt, 1H, J=9.3, 7.5 Hz, CH$_3$CH$_2$-C*H*HO), 3.41 (dt, 1H, J=9.3, 7.5 Hz, CH$_3$CH$_2$CH*H*O), 3.09 (brd, 1H, CHO*H*), 1.58 (sextet, 2H, J=7.5 Hz, CH$_3$CH_2CH$_2$O) and 0.89 (t, 3H, J=7.5 Hz, CH_3CH$_2$CH$_2$-O); ^{13}C NMR ($CDCl_3$) δ(ppm)=173.1, 73.4, 71.8, 70.8, 52.5, 22.6 and 10.4; MS (EI) m/z 133 ([M−CH$_2$CH$_3$]$^+$), 119 ([M−(CH$_2$)$_2$CH$_3$]$^+$), 103, 90, 73, 61 and 43; HRMS found: m/z 162.0863 [M]$^+$. Calcd for $C_7H_{14}O_4$: M, 162.0892.

3.4.12. Ethyl 3-methoxy-2-hydroxy propionate (36d). Pale-yellow oil, IR (NaCl)=3461 (O–H), 1739 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ(ppm)=4.30 (t, 1H, J=3.6 Hz, C*H*OH), 4.27 (dq, 2H, J=1.1, 7.0 Hz, C(O)OCH_2CH$_3$), 3.69 (dd, 2H, J=1.1, 3.8 Hz, CH(OH)CH_2), 3.39 (s, 3H, CH_3O), 3.25 (brs, 1H, CHO*H*) and 1.31 (t, 3H, J=7.0 Hz, C(O)OCH$_2$CH_3); ^{13}C NMR ($CDCl_3$) δ(ppm)=172.7, 74.0, 70.7, 61.8, 59.5 and 14.2; MS (EI) m/z 148 (M$^+$), 130 ([M−H$_2$O]$^+$), 118, 105, 85, 75, 59 and 45; HRMS found: m/z 148.0735 [M]$^+$. Calcd for $C_6H_{12}O_4$: M, 148.0736.

3.4.13. Ethyl 3-ethoxy-2-hydroxy propionate (37d). Pale-yellow oil, IR (NaCl)=3482 (O–H), 1735 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ(ppm)=4.31 (t, 1H, J=4.8 Hz, C*H*OH), 4.27 (dq, 2H, J=5.0, 7.2 Hz, C(O)OCH_2CH$_3$), 3.72 (d, 2H, J=3.4 Hz, CH(OH)CH_2), 3.57 (dq, 1H, J=8.9, 7.1 Hz, CH$_3$C*H*HO), 3.52 (dq, 1H, J=8.9, 7.1 Hz, CH$_3$CH*H*O), 3.16 (brd, 1H, CHO*H*), 1.31 (t, 3H, J=7.1 Hz, C(O)OCH$_2$-CH_3) and 1.19 (t, 3H, J=7.0 Hz, CH_3CH$_2$O); ^{13}C NMR ($CDCl_3$) δ(ppm)=172.6, 71.7, 70.7, 67.0, 61.7, 14.9 and 14.1; MS (EI) m/z 129, 119, 104, 89, 76, 59 and 43; HRMS found: m/z 162.0885 [M]$^+$. Calcd for $C_7H_{14}O_4$: M, 162.0892.

3.4.14. Ethyl 3-*n*-propyroxy-2-hydroxy propionate (38d). Pale-yellow oil, IR (NaCl)=3504 (O–H), 1735 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ(ppm)=4.30 (t, 1H, J=3.6 Hz, C*H*OH), 4.26 (dq, 2H, J=3.9, 7.1 Hz, C(O)OCH_2-CH$_3$), 3.72 (d, 2H, J=3.1 Hz, CH(OH)CH_2), 3.48 (dt, 1H, J=9.1, 6.8 Hz, CH$_2$C*H*HO), 3.40 (dt, 1H, J=9.1, 6.8 Hz, CH$_2$CH*H*O), 3.23 (brs, 1H, CHO*H*), 1.58 (sextet, 2H, J=7.1 Hz, CH$_3$CH_2CH$_2$O), 1.31 (t, 3H, J=7.1 Hz, C(O)OCH$_2$CH_3) and 0.89 (t, 3H, J=7.1 Hz, CH_3CH$_2$CH$_2$-O); ^{13}C NMR ($CDCl_3$) δ(ppm)=172.6, 73.2, 71.9, 70.7, 61.5, 22.5, 14.1, 10.3 and 10.2; MS (EI) m/z 177 ([M+H]$^+$), 147 ([M−CH$_2$CH$_3$]$^+$), 133, 119, 104, 89, 73, 61 and 43; HRMS found: m/z 176.1009 [M]$^+$. Calcd for $C_8H_{16}O_4$: M, 176.1049.

3.4.15. Ethyl 3-methoxy-2-methyl-2-hydroxy propionate (39d). Pale-yellow oil, IR (NaCl)=3504 (O–H), 1735 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ(ppm)=4.25 (dq, 2H, J=2.3, 7.2 Hz, C(O)OCH_2), 3.65 (d, 2H, J=9.3 Hz, CH(OH)CH_2), 3.46 (brs, 1H, CHO*H*), 3.37 (s, 3H, CH_3O), 1.36 (s, 3H, C(O)CCH_3), 1.30 (t, 3H, J=7.1 Hz, C(O)OCH$_2$CH_3); ^{13}C NMR ($CDCl_3$) δ(ppm)=175.0, 78.4, 74.7, 61.8, 59.5, 21.8 and 14.1; MS (EI) m/z 162 (M^+), 144 ([M−H_2O]$^+$), 130, 117, 99, 89, 71, 57 and 43; HRMS found: m/z 162.0896 [M]$^+$. Calcd for $C_7H_{14}O_4$: M, 162.0892.

3.4.16. Ethyl 3-ethoxy-2-methyl-2-hydroxy propionate (40d). Pale-yellow oil, IR (NaCl)=3504 (O–H), 1733 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ(ppm)=4.18–4.33 (m, 2H, C(O)OCH_2CH$_3$), 3.68 (d, 1H, J=9.1 Hz, CH(OH)CH*H*), 3.55 (dq, 1H, J=9.6, 7.0 Hz, CH$_3$C*H*HO), 3.49 (dq, 1H, J=9.6, 7.0 Hz, CH$_3$CH*H*O), 3.45 (brs, 1H, CHO*H*), 3.42 (d, 1H, J=9.1 Hz, CH(OH)C*H*H), 1.36 (s, 3H, C(O)CCH_3), 1.30 (t, 3H, J=7.0 Hz, C(O)OCH$_2$CH_3) and 1.16 (t, 3H, J=7.1 Hz, CH_3CH$_2$O), ^{13}C NMR ($CDCl_3$) δ(ppm)=175.1, 76.2, 75.9, 67.0, 61.7, 21.7, 14.9 and 14.1; MS (EI) m/z 176 (M^+), 158 ([M−H_2O]$^+$), 146, 133, 117, 103, 90, 75, 59 and 43; HRMS found: m/z 176.1070 [M]$^+$. Calcd for $C_8H_{16}O_4$: M, 176.1049.

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A new protocol to synthesize 1,4-dihydropyridines by using 3,4,5-trifluorobenzeneboronic acid as a catalyst in ionic liquid: synthesis of novel 4-(3-carboxyl-1*H*-pyrazol-4-yl)-1,4-dihydropyridines

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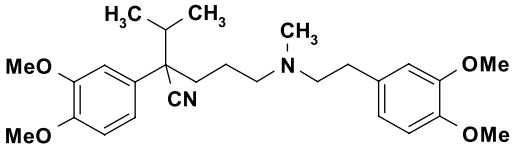
Abstract—3,4,5-Trifluorobenzeneboronic acid catalysed, ionic liquid mediated facile synthesis of 4-pyrazolyl 1,4-dihydropyridines at room temperature by the cyclocondensation of ethyl 3-aminocrotonate, pyrazole aldehyde and a β-keto ester is reported. The procedure adopted was found to be eco-benign, facile at room temperature and better than the conventional, [bmim]Cl mediated and $InCl_3$ catalysed, [bmim]Cl mediated 1,4-dihydropyridine syntheses.

1. Introduction

4-Aryl-l,4-dihydropyridines form a major class of drugs used in the management of cardiovascular diseases.[1,2] Baraldi et al. have explored the less common hetero aryl dihydropyridines for the calcium channel activity.[3,4]

Development of drug resistance, both intrinsic drug resistance and acquired drug resistance, remains a clinical obstacle in the chemotherapy of many cancers.[5,6] Among the possible resistance modifiers, the dihydropyridines (DHPs), calcium antagonists, have been studied extensively as the analogue of verapamil (VP) **1**.[7] The finding that the enantiomer of verapamil and nigludipine lacks calcium antagonistic activity but still has MDR reversal activity indicated that the MDR reversal activity is independent of the calcium antagonistic activity.[8,9] It was proposed by Tanabe et al. that NIK-250, **2** which possess a heterocyclic ring at the 4-postion can overcome MDR and has moderate calcium antagonistic activity in vitro without optical resolution.[10–14] Further, it was observed that imidazothiazole derivatives could potentiate the MDR reversal activity without significant side effects observed for 1,4-dihydropyridine derivatives.[15] Baraldi et al. during their exploration on the calcium antagonist activity revealed that pyrazolyl and imidazolyl 1,4-dihydropyridines exhibit weak calcium antagonist activity.[16] Manfredini et al.[17] have shown pyrazole nucleosides as potential analogues of ribavirin[18] in antitumor activity.



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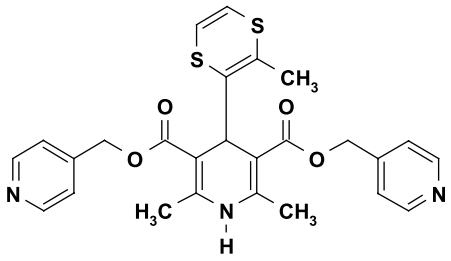

2

Our interest was to synthesize 4-[3-ethoxycarbonyl-1*H*-pyrazol-4-yl]-1,4-dihydro-pyridine dicarboxylates in which the pyrazole-3-ester moiety mimic the one in pyrazole nucleoside reported by Manfredini et al. We expect these compounds to show weak calcium antagonist but high MDR

Keywords: 1,4-Dihydropyridines; 3,4,5-Trifluorobenzeneboronic acid; Ionic liquid; 4-(3-Carboxyl-1H-pyrazol-4-yl)-1,4-dihydropyridines; Vilsmeier reagent.
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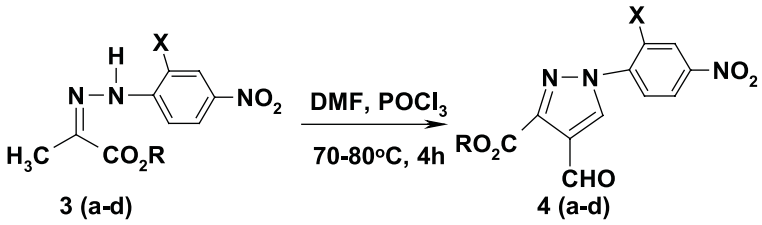


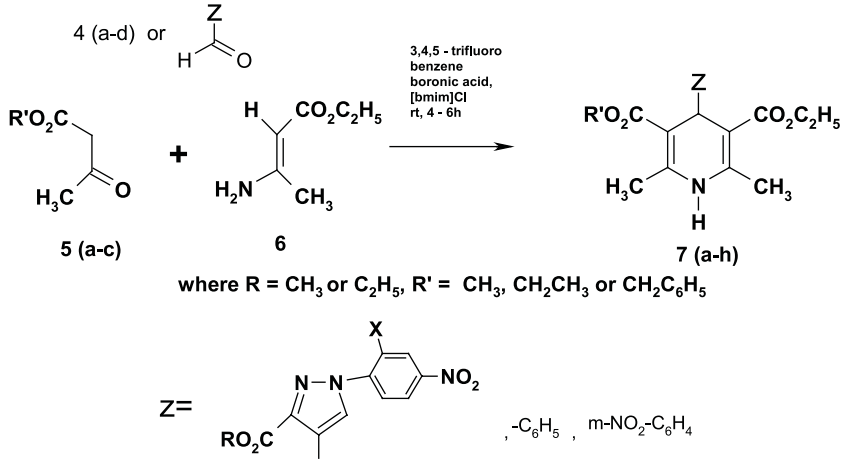
Scheme 1. Synthesis of alkyl-1(2,4-dinitrophenyl)-4-formyl-1*H*-pyrazole-3-carboxylate.

Table 1. Synthesis of 1*H*-pyrazole-3-carboxylic acid esters

Entry	X	R	Time (h)	Yield (%)
4a	H	CH_3	4	85
4b	NO_2	CH_3	4	79
4c	H	C_2H_5	4	88
4d	NO_2	C_2H_5	4	80

reversal activity. The original Hantzsch[19] dihydropyridine synthesis consisted of the reaction of ethyl acetoacetate (2 equiv) with an aldehyde and ammonia. This method has been widely used for the preparation of the 1,4-dihydropyridine where the substitution at the fourth position is an aliphatic,[20] aromatic[21] or heterocyclic[22] residue. Enamines could replace ethyl acetoacetate and could serve as an ammonia source paving way to a series of 1,4-dihydropyridines of medicinal interest.[23] Microwave-assisted synthesis of dihydropyridines[24] was reported advantageous since it accelerates the reaction rate. A solid-phase synthesis of dihydropyridines was also demonstrated.[25] Conventional Hantzsch dihydropyridine syntheses generally involve organic solvents like methanol and acetic acid. Ionic liquid because of its polarity, negligible vapor pressure, recyclability, high thermal stability and immiscibility with a number of organic solvents has attracted much interest from synthetic chemists.[26] In continuation of our work on the synthesis of 1*H*-Pyrazole-4-carboxylates[27] using Vilsmeier methodology, we synthesized 4-formyl-1*H*-pyrazole-3-carboxylates[17b] **4**(**a**–**d**) (Scheme 1) from alkyl pyruvate 4-nitro or 2,4-dinitro phenyl hydrazones **3**(**a**–**d**) upon treatment with 8 equiv of DMF/$POCl_3$ (Table 1).

We have attempted the pyrazolyl dihydropyridines synthesis by using ionic liquid medium at room temperature. During the earlier attempts[28] to synthesise dihydropyridines by condensing an aldehyde, β-ketoester and methyl 3-aminocrotonate using [bmim]PF_6 and [bmim]BF_4 as the reaction media, it was observed that [bmim]Cl was unsuccessful. When we attempted the synthesis of 4-[3-ethoxycarbonyl-1H-pyrazol-4-yl]-1,4-dihydro-pyridine dicarboxylates in [bmim]Cl the reaction was facile with ethyl 3-aminocrotonate, pyrazole aldehydes and a β-keto ester. The reason may be attributed to the substrate effect that can contribute to the formation of the product dihydropyridine in moderate to good yields. The remaining ionic liquid was thoroughly washed with ethyl acetate after completion of the reaction (monitored by TLC) and recycled in subsequent reactions. Second and third reactions using recovered ionic liquid afforded similar yields to those obtained in the first run. In the fourth and fifth runs, the yields steadily decreased. That is in the case of pyrazole aldehyde **4d**, ethyl acetoacetate and ethyl 3-aminocrotonate in [bmim]Cl, the yields of **7e** obtained were 51, 50, 50, 48, 47 in five successive runs. However, the activity of ionic liquid was consistent and no decrease in yield was observed when the recycled ionic liquid was activated at 80 °C under vacuum in each cycle. In order to increase the yield of the dihydropyridine obtained through [bmim]Cl mediated synthesis we added 5 mol% of $InCl_3$ or 5 mol% of 3,4,5-trifluorobenzeneboronic acid (Scheme 2) to the reaction



Scheme 2. Synthesis of pyrazolyl dihydropyridines.

Table 2. Ionic liquid mediated synthesis of symmetrical and unsymmetrical dihydropyridines catalysed by 3,4,5-trifluorobenzene boronic acid

Entry	Aldehyde (Z-CHO)	Ester (R′)	Product	Time (h)	Yield (%)
1	**4a**	$-CH_3$	**7a**	6	92
2	**4a**	$-CH_2\ CH_3$	**7b**[31]	5	86
3	**4c**	$-CH_3$	**7c**	4	87
4	**4c**	$-CH_2\ CH_3$	**7d**	4	91
5	**4d**	$-CH_2\ CH_3$	**7e**	5	85
6	**4c**	$-CH_2\ C_6H_5$	**7f**	4	87
7	Benzaldehyde	$-CH_2\ CH_3$	**7g**	4	90
8	*m*-Nitro-benzaldehyde	$-CH_2\ CH_3$	**7h**	5	93

The compounds gave satisfactory spectral and elemental analysis value. Furthermore the structure of compound **7b** was confirmed by X-ray crystallographic study (Fig. 1).[31]

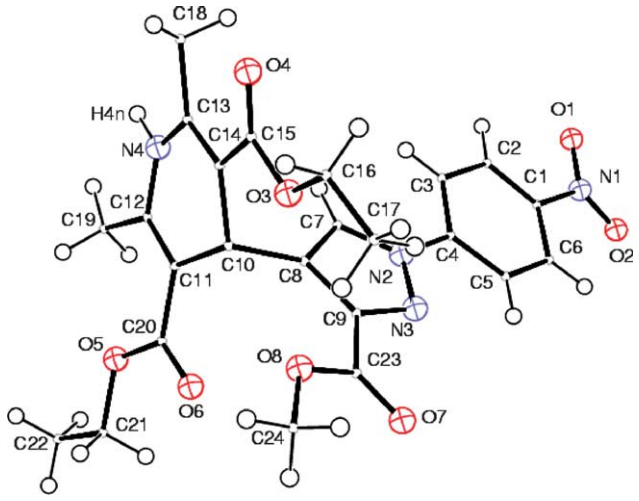


Figure 1. The ORTEP[31] view of 4-[3-methoxycarbonyl-1-(4-nitrophenyl)-1*H*-pyrazol-4-yl]-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylic acid diethyl ester, **7b** showing 30% probability displacement ellipsoids and the atom numbering scheme.

mixture and found that the yield obtained increased considerably (Table 2).

The stability of boronic acids to air and moisture and their relatively low toxicity (benzeneboronic acid:[29] LD_{50}, oral-rat = 740 mg/kg), have enthused us to employ 3,4,5-trifluorobenzeneboronic acid[30] as a catalyst in dihydropyridine synthesis.

The increase in yield might be due to increase in the acidity of the reaction mixture, which contributes to the product yield. Both the catalyst and [bmim]Cl recovered after the reaction are recyclable. The yield decreases during successive runs with the recovered ionic liquid-catalyst mixture but further addition of 5 mol% of catalyst to the reaction mixture ensures excellent yield of the product. Further we found that the formation of dihydropyridine in exceptional yields was feasible with other aromatic aldehydes also. The following comparison (Table 3) clearly indicates the versatility of 3,4,5-trifluorobenzeneboronic acid catalysed [bmim]Cl mediated synthesis over the other methods adopted for the synthesis of dihydropyridines.

Table 3. Comparison of dihydropyridine syntheses (synthesis of 7e)

Reaction condition	Time (h)	Yield (%)
Reflux in ethanol (Δ)	8	48
[bmim]Cl (rt)	6	51
[bmim]Cl + boronic acid	5	85
[bmim]Cl + $InCl_3$	6	80

In summary, we have developed a mild, simple and environmentally benign protocol for the synthesis of dihydropyridines in ionic liquid media using 3,4,5-trifluorobenzeneboronic acid as catalyst. We hope the pyrazolyl dihydropyidines we have synthesized to show MDR reversal activity, exploration of which would be our ultimate goal.

2. Experimental

2.1. General procedure for the preparation 1*H*-pyrazole-3-carboxylates

1.4 g of $POCl_3$ (0.008 mol) was added drop wise to an ice-cold stirred solution of ethyl pyruvate 2,4-dinitrophenyl hydrazone (0.001 mol) in 10 mL dry DMF. The reaction mixture was allowed to attain room temperature and then refluxed at 70–80 °C for about 4 h. The resulting mixture was poured onto crushed ice, neutralized with sodium acetate and left standing overnight. The pale yellow precipitate obtained was purified by silica gel (60–120 mesh) column chromatography with ethyl acetate–petroleum ether mixture (15:85) to yield the product.

2.1.1. Methyl-1(4-nitrophenyl)-4-formyl-1H-pyrazole-3-carboxylate, 4a. Yellow crystals (15% ethyl acetate: petroleum ether); mp 214 °C; IR (KBr) cm^{-1}: 3123, 2919, 2882, 1716, 1677, 1595, 1529, 1340, 1262, 857; ^1H NMR (500 MHz, $CDCl_3$) δ: 10.46 (s, 1H, formyl –CH), 8.62 (s, 1H Pyrazole –CH), 8.40–8.42 (d, J = 9.2 Hz, 2H), 7.99–8.01 (d, J = 9.2 Hz, 2H), 4.06 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$, ppm): δ 186.2, 161.5, 147.4, 145.1, 142.8, 130.5, 126.6, 125.6, 120.6, 53.1; MS (*m*/*z*): 275 (M^+); Anal. Calcd for $C_{12}H_9N_3O_5$: C, 52.37; H, 3.30; N, 15.27; Found: C, 52.42; H, 3.28; N, 15.38.

2.1.2. Methyl-1(2,4-dinitrophenyl)-4-formyl-1H-pyrazole-3-carboxylate, 4b. Yellow crystals (15% ethyl acetate: petroleum ether); mp 138 °C; IR (KBr) cm^{-1}: 3120, 2958, 2888, 1727, 1684, 1611, 1541, 1348, 1257, 836, 743; ^1H NMR (500 MHz, $CDCl_3$) δ: 10.43 (s, 1H, formyl –CH), 8.87–8.88 (d, J_1 = 2.3 Hz, 1H), 8.61–8.63 (dd, J_1 = 2.3 Hz, J_2 = 8.6 Hz, 1H), 8.39 (s, 1H, Pyrazole –CH), 7.92–7.93 (d, J_2 = 8.6 Hz, 1H), 4.01 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$, ppm): δ 185.9, 161.1, 144.3, 147.8, 145.7, 136.5, 134.1,

128.7, 128.4, 126.5, 121.6, 53.1; MS (*m/z*): 320 (M^+); Anal. Calcd for $C_{12}H_8N_4O_7$: C, 45.01; H, 2.52; N, 17.50; Found: C, 44.92; H, 2.58; N, 17.56.

2.1.3. Ethyl-1(4-nitrophenyl)-4-formyl-1H-pyrazole-3-carboxylate, 4c. Yellow crystals (15% ethyl acetate: petroleum ether); mp 148 °C; IR (KBr) cm^{-1}: 3130, 2992, 2889, 1714, 1681, 1596, 1528, 1342, 1258, 856, 750; ^1H NMR (500 MHz, $CDCl_3$) δ: 10.45 (s, 1H, formyl –CH), 8.62 (s, 1H, Pyrazole –CH), 8.39–8.41 (d, $J=9.2$ Hz, 2H), 8.00–8.01 (d, $J=9.2$ Hz, 2H), 4.51–4.55 (q, $J=7.5$ Hz, 2H), 1.46–1.49 (t, $J=7.5$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$, ppm): δ 186.3, 161.1, 147.3, 145.5, 142.8, 130.5, 126.5, 125.6, 120.6, 62.4, 14.4; MS (*m/z*): 289 (M^+); Anal. Calcd for $C_{13}H_{11}N_3O_5$: C, 53.98; H, 3.83; N, 14.53; Found: C, 53.92; H, 3.81; N, 14.64.

2.1.4. Ethyl-1(2,4-dinitrophenyl)-4-formyl-1*H*-pyrazole-3-carboxylate, 4d. Yellow crystals (15% ethyl acetate: petroleum ether); mp 130 °C; IR (KBr) cm^{-1}: 3330, 3122, 3079, 2999, 2890, 1734, 1686, 1610, 1551, 1351, 1268, 1242, 1109, 742, 629; ^1H NMR (500 MHz, $CDCl_3$) δ: 10.45 (s, 1H, formyl –CH), 8.87–8.88 (d, $J_1=2.3$ Hz, 1H), 8.61–8.63 (dd, $J_1=2.3$ Hz, $J_2=8.6$ Hz, 1H), 8.36 (s, 1H Pyrazole –CH), 7.91–7.93 (d, $J_2=8.6$ Hz, 1H), 4.47–4.51 (q, $J=7.5$ Hz, 2H), 1.42–1.45 (t, $J=7.5$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$, ppm): δ 186.0, 160.6, 147.7, 146.1, 144.3, 136.6, 134.0, 128.7, 128.3, 126.5, 121.6, 62.6, 14.3; MS (*m/z*): 334 (M^+); Anal. Calcd for $C_{13}H_{10}N_4O_7$: C, 46.70; H, 3.02; N, 16.77; Found: C, 46.75; H, 3.06; N, 16.58.

2.2. General procedure for $InCl_3$ or 3,4,5-trifluorobenzeneboronic acid catalyzed synthesis of symmetrical and unsymmetrical dihydropyridines in ionic liquid at room temperature

0.72 g (2.5 mmol, 1 equiv) of pyrazole aldehyde **4c**, 0.33 g (2.5 mmol, 1 equiv) of ethyl acetoacetate, 0.32 g (2.5 mmol, 1 equiv) of ethyl 3-aminocrotonate were mixed with 2 grams of bmimCl and stirred after adding 5 mol% of $InCl_3$ or 5 mol% 3,4,5-trifluorobenzeneboronic acid for about six hours. Then the mixture was extracted with ethyl acetate and column chromatographed with 15% ethyl acetate–petroleum ether (bp. 60–80 °C) mixture to get pure yellow colored 4-[3-ethoxycarbonyl-1-(4-nitrophenyl)-1H-pyrazol-4-yl]-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylic acid diethyl ester **7d** in excellent yield. The remaining ionic liquid-catalyst mix was thoroughly washed with ethyl acetate and recycled for subsequent reactions.

2.2.1. 4-[3-Methoxycarbonyl-1-(4-nitrophenyl)-1*H*-pyrazol-4-yl]-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylic acid 3-ethyl ester 5-methyl ester, 7a. Yellow crystals (15% ethyl acetate:petroleum ether); mp 228 °C; IR (KBr) cm^{-1}: 3318, 2986, 1707, 1650, 1494, 1340, 1221, 855, 749; ^1H NMR (500 MHz, $CDCl_3$, ppm): δ 8.28–8.30 (d, $J=9.2$ Hz, 2H), 7.86–7.87 (d, $J=9.2$ Hz, 2H), 7.83 (s, 1H, pyrazole –CH), 5.83 (brs, 1H), 5.58 (s, 1H), 4.03–4.09 (m, 2H), 3.98 (s, 3H), 3.59 (s, 3H), 2.33 (s, 3H), 2.30 (s, 3H), 1.16–1.19 (t, $J=8.0$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$, ppm): δ 167.9, 167.5, 162.6, 146.1, 144.0, 143.9, 143.8, 143.3, 135.2, 128.6, 125.3, 119.5, 104.3, 104.1, 60.1, 52.1, 51.1, 29.7, 19.7, 19.6, 14.3; MS (*m/z*): 484 (M^+); Anal. Calcd for $C_{23}H_{24}N_4O_8$: C, 57.02; H, 4.99; N, 11.56; Found: C, 57.12; H, 5.04; N, 11.58.

2.2.2. 4-[3-Methoxycarbonyl-1-(4-nitrophenyl)-1*H*-pyrazol-4-yl]-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylic acid diethyl ester, 7b. Yellow crystals (15% ethyl acetate:petroleum ether); mp 212 °C; IR (KBr) cm^{-1}: 3338, 3093, 2982, 1728, 1689, 1494, 1339, 1216, 1099, 854, 750; ^1H NMR (500 MHz, $CDCl_3$, ppm): δ 8.27–8.29 (d, $J=9.2$ Hz, 2H), 7.86–7.88 (d, $J=9.2$ Hz, 2H), 7.86 (s, 1H, pyrazole –CH), 5.83 (brs, 1H), 5.61 (s, 1H), 4.03–4.09 (m, 4H), 3.97 (s, 3H), 2.31 (s, 6H), 1.16–1.19 (t, $J=7.5$ Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$, ppm): δ 167.5, 162.5, 146.0, 143.9, 143.8, 143.3, 135.3, 128.7, 125.3, 119.4, 104.3, 60.0, 52.1, 29.7, 19.7, 14.3; MS (*m/z*): 498 (M^+); Anal. Calcd for $C_{24}H_{26}N_4O_8$: C, 57.83; H, 5.26; N, 11.24; Found: C, 57.94; H, 5.31; N, 11.13.

2.2.3. 4-[3-Ethoxycarbonyl-1-(4-nitrophenyl)-1*H*-pyrazol-4-yl]-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylic acid 3-ethyl ester 5-methyl ester, 7c. Yellow crystals (15% ethyl acetate:petroleum ether); mp 202 °C; IR (KBr) cm^{-1}: 3336, 3094, 2982, 1720, 1690, 1495, 1339, 1217, 1098, 855, 750; ^1H NMR (500 MHz, $CDCl_3$, ppm): δ 8.27–8.29 (d, $J=9.2$ Hz, 2H), 7.86–7.88 (d, $J=9.2$ Hz, 2H), 7.82 (s, 1H, pyrazole –CH), 5.79 (brs, 1H), 5.59 (s, 1H), 4.44–4.48 (q, $J=7.5$ Hz, 2H), 4.05–4.09 (q, $J=7.5$ Hz, 2H), 3.59 (s, 3H), 2.32 (s, 3H), 2.30 (s, 3H), 1.44–1.47 (t, $J=7.5$ Hz, 3H), 1.15–1.18 (t, $J=7.5$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$, ppm): δ 167.9, 167.5, 162.3, 146.0, 144.0, 143.8, 143.7, 143.6, 135.1, 128.5, 125.3, 119.4, 104.4, 104.2, 61.2, 60.0, 51.1, 29.7, 19.7, 19.6, 14.5, 14.4; MS (*m/z*): 498 (M^+); Anal. Calcd for $C_{24}H_{26}N_4O_8$: C, 57.83; H, 5.26; N, 11.24; Found: C, 57.88; H, 5.11; N, 11.29.

2.2.4. 4-[3-Ethoxycarbonyl-1-(4-nitrophenyl)-1*H*-pyrazol-4-yl]-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylic acid diethyl ester, 7d. Yellow crystals (15% ethyl acetate:petroleum ether); mp 224 °C; IR (KBr) cm^{-1}: 3334, 3090, 2990, 1722, 1693, 1492; ^1H NMR (500 MHz, $CDCl_3$, ppm): δ 8.26–8.28 (d, $J=9.2$ Hz, 2H), 7.86–7.88 (d, $J=9.2$ Hz, 2H), 7.85 (s, 1H, pyrazole –CH), 5.83 (brs, 1H), 5.61 (s, 1H), 4.42–4.47 (q, $J=7.5$ Hz, 2H), 4.04–4.09 (q, $J=7.5$ Hz, 4H), 2.30 (s, 6H), 1.43–1.46 (t, $J=7.5$ Hz, 3H), 1.15–1.18 (t, $J=7.5$ Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$, ppm): δ 167.6, 162.2, 146.0, 143.9, 143.7, 143.7, 135.2, 128.6, 125.3, 119.4, 104.3, 61.1, 60.0, 29.7, 19.7, 14.4, 14.4; MS (*m/z*): 513 (M^+); Anal. Calcd for $C_{25}H_{28}N_4O_8$: C, 58.59; H, 5.51; N, 10.93; Found: C, 58.54; H, 5.48; N, 11.02.

2.2.5. 4-[3-Ethoxycarbonyl-1-(2,4-dinitrophenyl)-1*H*-pyrazol-4-yl]-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylic acid diethyl ester, 7e. Yellow crystals (15% ethyl acetate:petroleum ether); mp 88 °C; IR (KBr) cm^{-1}: 3344, 3092, 2984, 1726, 1690, 1545, 1348, 1216, 1098, 912, 739; ^1H NMR (500 MHz, $CDCl_3$, ppm): δ 8.63–8.64 (d, $J_1=2.3$ Hz, 1H), 8.43–8.45 (dd, $J_1=2.3$ Hz, $J_2=8.6$ Hz, 1H), 7.86–7.88 (d, $J_2=8.6$ Hz, 1H), 7.60 (s, 1H, pyrazole –CH), 6.32 (brs, 1H), 5.49 (s, 1H), 4.35–4.39 (q, $J=7.5$ Hz, 2H), 3.98–4.09 (m, 4H), 2.22 (s, 6H), 1.36–1.39 (t, $J=7.5$ Hz, 3H), 1.12–1.15 (t, $J=7.5$ Hz, 6H); ^{13}C NMR (125 MHz,

$CDCl_3$, ppm): δ 167.6, 161.9, 146.1, 144.7, 144.3, 143.4, 137.2, 135.5, 131.3, 127.6, 127.1, 121.1, 103.7, 61.2, 59.9, 29.7, 19.3, 18.4, 14.3; MS (*m*/*z*): 558 (M^+); Anal. Calcd for $C_{25}H_{27}N_5O_{10}$: C, 53.86; H, 4.88; N, 12.56; Found: C, 53.80; H, 4.92; N, 12.62.

2.2.6. 4-[3-Ethoxycarbonyl-1-(4-nitrophenyl)-1*H*-pyrazol-4-yl]-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylic acid 3-benzyl ester 5-ethyl ester, 7f. Yellow crystals (15% ethyl acetate:petroleum ether); mp 138 °C; IR (KBr) cm^{-1}: 3337, 3093, 2981, 1725, 1694, 1494, 1216, 1113, 855, 749; ^1H NMR (500 MHz, $CDCl_3$, ppm): δ 8.26–8.28 (d, $J=9.2$ Hz, 2H), 7.77–7.79 (d, $J=9.2$ Hz, 2H), 7.74 (s, 1H, pyrazole –CH), 7.21–7.27 (m, 5H), 5.80 (brs, 1H), 5.60 (s, 1H), 5.02–5.11 (q, $J=16.0$ Hz, 2H), 4.35–4.26 (m, 2H), 4.03–4.07 (q, $J=7.5$ Hz, 2H), 2.30 (s, 3H), 2.29 (s, 3H), 1.33–1.36 (t, $J=7.5$ Hz, 3H), 1.14–1.17 (t, $J=7.5$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$, ppm): δ 167.5, 167.3, 162.2, 146.0, 144.6, 143.9, 143.6, 136.7, 134.3, 128.7, 128.5, 128.1, 127.9, 125.2, 119.4, 104.0, 103.3, 65.7, 61.1, 60.0, 30.2, 19.9, 19.8, 14.4; MS (*m*/*z*): 575 (M^+); Anal. Calcd for $C_{30}H_{30}N_4O_8$: C, 62.71; H, 5.26; N, 9.75; Found: C, 62.63; H, 5.32; N, 9.65.

2.2.7. 2,6-Dimethyl-3,5-dicarboethoxy-4-phenyl-1,4-dihydropyridine,[32] 7g. Yellow crystals (15% ethyl acetate: petroleum ether); mp 158 °C (lit. mp 158–159)[32b]; IR (KBr) cm^{-1}: 3322, 1676, 1633, 1595, 1529, 1102, 851; ^1H NMR (500 MHz, $CDCl_3$, ppm): δ 7.01–7.26 (m, 5H), 6.00 (brs, 1H), 4.98 (s, 1H), 4.08 (q, $J=8.2$ Hz, 4H), 2.29 (s, 6H), 1.21 (t, $J=7.7$ Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$, ppm): δ 168.2, 152.2, 148.3, 144.9, 128.6, 126.2, 103.8, 59.6, 39.5, 19.3, 14.3; MS (*m*/*z*): 329 (M^+); Anal. Calcd for $C_{19}H_{23}NO_4$: C, 69.28; H, 7.04; N, 4.25; Found: C, 69.21; H, 7.07; N, 4.31.

2.2.8. 2,6-Dimethyl-3,5-dicarboethoxy-4-(3-nitrophenyl)-1,4-dihydropyridine,[32] 7h. Yellow crystals (15% ethyl acetate:petroleum ether); mp 164 °C (lit. mp 162–163);[32b] IR (KBr) cm^{-1}: 3328, 1674, 1633, 1590, 1529, 1105, 857; ^1H NMR (500 MHz, $CDCl_3$, ppm): δ 8.13 (s, 1H), 8.02 (d, $J=7.5$ Hz, 1H), 7.66 (d, $J=7.5$ Hz, 1H), 7.38 (d, $J=8.6$ Hz, 1H), 6.16 (brs, 1H), 5.10 (s, 1H), 4.10 (q, $J=7.8$ Hz, 4H), 2.36 (s, 6H), 1.24 (t, 6H); ^{13}C NMR (125 MHz, $CDCl_3$, ppm): δ 167.2, 150.0, 148.1, 145.0, 134.5, 128.6, 123.1, 121.3, 103.2, 60.0, 40.0, 19.5, 14.2; MS (*m*/*z*): 374 (M^+); Anal. Calcd for $C_{19}H_{22}N_2O_6$: C, 60.95; H, 5.92; N, 7.48; Found: C, 60.81; H, 5.88; N, 7.62.

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31. The pyrazole ring is planar and the 1,4-dihydropyridine attached to it adopts intermediate boat conformation (CCDC 247509).
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Synthesis of (+)-goniothalesdiol and (+)-7-*epi*-goniothalesdiol

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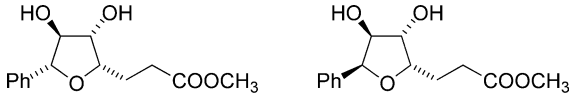
Dedicated to Prof. Peter Stanetty on his 60th birthday.

Abstract—A total synthesis of (+)-goniothalesdiol, a 3,4-dihydroxy-2,5-disubstituted tetrahydrofuran isolated from *Goniothalamus borneensis* (Annonaceae), and its 7-epimer is reported using oxycarbonylation methodology for construction of polyhydroxylated substituted heterocycles. Diastereoselectivity of addition of organometallic reagents to 2,3-*O*-isopropylidene-D-threose derivatives using theoretical calculations based on the semiempirical PM5 was studied.

1. Introduction

The palladium(II)-catalysed oxycarbonylation[1] of unsaturated polyols[2] or/and aminopolyols[3] represents a powerful methodology[4] for construction of 5-/6-membered saturated oxa/azaheterocycles. In our long term program directed towards the application of carbonylation methodology to natural product synthesis, we have described the syntheses of both enantiomers of cytotoxic styryl-lactones goniofufurone,[5a,b] 7-*epi*-goniofufurone,[5a,b] erythro-skyrine,[5c] homo-DLX,[5d] homo-DMDP,[5d] homo-DNJ[5e,f] and homo-L-ido-DNJ.[5e,f] Herein, we report experimental details of the optimised synthesis of goniothalesdiol **1** and 7-*epi*-goniothalesdiol **2** (Fig. 1) starting with D-mannitol.[6]



1 **2**

Figure 1. Goniothalesdiol **1** and 7-*epi*-goniothalesdiol **2**.

Goniothalesdiol was isolated from the bark of the Malaysian tree *Goniothalamus borneensis* (Annonaceae), and has been revealed to have significant cytotoxicity against P388 mouse leukaemia cells, and insecticidal activities.[7] The structure and relative stereochemistry of **1** was assigned on the basis of ^{1}H, ^{13}C NMR spectroscopy and the absolute configuration was confirmed by semi-synthesis from natural (+)-goniothalenol (altholactone).

Meanwhile, growing attention is given to this class of compounds, as demonstrated by development of new syntheses of unnatural enantiomer of goniothalesdiol (−)-**1**,[8] and its 7-epimer (+)-**2**.[9] Both syntheses started from chiral pool, D-glucuronolactone or D-tartaric acid, respectively, using Grignard addition followed by Lewis acid promoted hydrogenation of the corresponding lactone, the latter setting the *cis* configuration at C_6-C_7 of the epimer, and thus were not applicable for natural goniothalesdiol. Recently, preparation of 3,6-anhydro-2-deoxy-6-*C*-phenyl-D-*gluco*-1,4-hexonolactone **9**, an intermediate in our synthetic route,[6] was described from an erythrulose derivate[10] via an aldol reaction.

2. Results and discussion

We report herein details of the optimised synthesis[6] of natural goniothalesdiol (+)-**1** and its 7-epimer (+)-**2**. The strategy followed is shown in Scheme 1. In both routes the phenyl moiety is introduced by diastereoselective addition of organometallic reagents at C_1 of the aldose **6**, to allow for an entry into both diastereomers. For the second crucial step, oxycarbonylating bicyclisation of pentenitols, advantage is taken of recent progress in Pd(II)-catalysed carbonylations of unsaturated polyols or aminopolyols, that have turned out bicyclic lactones/lactams with high regio-control and excellent stereoselectivity, without necessity of OH-protection.[4,5]

Keywords: Palladium(II) catalysis; Stereoselective oxycarbonylation; Diastereoselective addition to carbonyl; Goniothalesdiol; Natural products; PM5 calculations.
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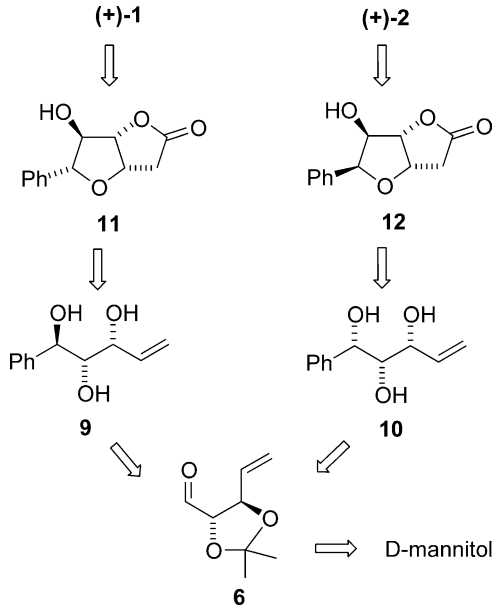
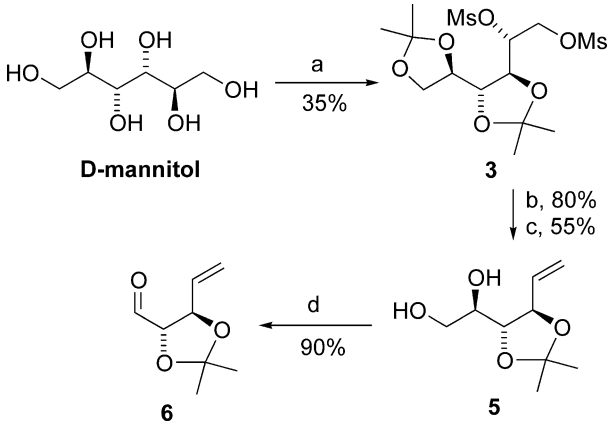


Scheme 1. Retrosynthetic analysis of **1** and **2**.

The first key intermediate, aldose **6**, was obtained from D-mannitol by a standard carbohydrate chemistry procedure.[11,12] Following the reaction sequence, acetonisation of D-mannitol,[13] selective hydrolysis of the terminal acetonide,[13] *O*-mesylation of both unprotected hydroxyl groups, reductive elimination with sodium iodide[14] and subsequent selective hydrolysis of the next terminal acetonide with HCl in ethanol, the diol **5** was readily prepared, however, in poor yield (3% overall[4a,6]).

In order to improve the efficiency of the synthesis of the requisite aldose **6** various reaction conditions for dioxolane ring hydrolysis and work up of reactions were examined. An effort that culminated in development of a four-step protocol for synthesis of C_5-aldose **6** with 14% yield, starting from cheap D-mannitol. (Scheme 2). The major improvement is the one pot conversion of D-mannitol to bismesylate **3**, which was isolated by simple crystallisation in 35% yield together with 30% of tris-*O*-acetonide-D-mannitol; the latter can be recycled. A selective hydrolysis

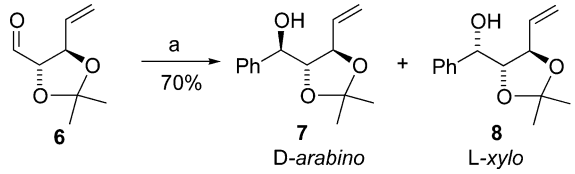


Scheme 2. Reagents and conditions: (a) 1, H_2SO_4, acetone; 2, H_2O; 3, NaOH; 4, MsCl, pyridine; (b) Lit.[14] NaI, acetone; (c) Lit.[15] $Zn(NO_3)_2 \cdot 6H_2O$, acetonitrile; (d) $NaIO_4$, H_2O.

of the second terminal acetonide was achieved with $Zn(NO_3)_2 \cdot 6H_2O$ in acetonitrile.[15]

With aldose **6** in our hands the synthesis was set up for the first key reaction of the sequence—Grignard addition with phenylmagnesium bromide (Scheme 3). A diastereomeric mixture of D-*arabino* **7** and L-*xylo* **8** partially protected pentenitols in the ratio 50:50 and 70% yield was obtained. The diastereomers could be readily separated by flash chromatography.

The unexpected lack of diastereocontrol observed in the



Scheme 3. Reagents and conditions: (a) PhMgBr, THF.

addition led us to study the reactions of organometallic reagents with aldehyde **6** in more detail.[16]

Generally, the design of addition of *C*-nucleophiles to aldehyde **6** could be based on models of either chelation-control: 1,2- (Cram) versus 1,3-asymmetric induction (Reetz) or non-chelation-control (Felkin-Anh), leading to alcohols **8** (1,2-*syn*, Cram) or **7** (1,2-*anti*, Reetz and Felkin-Anh).

Table 1 summarises the results of a series of micro scale experiments with several organometallics. The best results were noted with the Seebach reagent (entry 6, non-chelation control) and with $PhCeCl_2$ in diethyl ether at $-10\,^{\circ}C$, affording the requisite D-*arabino* diastereomer (1,2-*anti*) in 62% de (entry 1, chelation control). General *anti*-diastereoselectivity, observed in this set of reactions, in concert with literary references,[16] called for a new model of the transition state for these reactions. In the case of hard Lewis acids, such as $MgBr_2$ (entry 4), the convenient Cram's chelating model favored 1,2-*syn*-diastereomer (L-*xylo*, **8**), whereas dominance of 1,2-*anti*-diastereomer was found in practice. Our model considers a 1,2-chelation of the subsidiary Lewis acid along with the chelation of organometallic reagent, causing the *Re* face of carbonyl group to be the preferred one for a nucleophilic attack (model B, Fig. 2). The activation energy for this model of TS (model B, 4 kcal/mol), was considerably lower, than that predicted by the modified Cram's model (model A, ~8 kcal/mol) or classical Cram's model (15 kcal/mol). Transition state candidates were determined using saddle-point calculations and potential energy surfaces. PM5 semiempirical method was chosen as well balanced compromise between speed and accurancy,[17] even though it is still a novelty in the field of metal complex calculations.[18] Transition states were subsequently verified by vibrational and IRC analysis.

Predictions made by the suggested bis-chelation model of the transition state for addition of organometallic reagents to 2,3-*O*-isopropylidene-D-threose derivatives matched the

Table 1. Addition of organometallics to aldehyde **6**

Entry	Reagent	Temp °C	Solvent	*anti*-**7**:*syn*-**8**
1	$PhCeCl_2$	−10	Et_2O	81:19
2	PhMgBr/18-crown-6	rt	CH_2Cl_2	79:21
3	PhMgBr/LiCl	−80	THF	72:28
4	$PhMgBr/MgBr_2$	−80	THF	69:31
5	PhLi	rt	Et_2O	79:21
6	$PhTi(OiPr)_3$[a]	−80	CH_2Cl_2	>98:<2
7	$PhMgBr/SnCl_4$	−80	THF	68:32
8	$PhMgBr/TiCl_4$	−80	THF	44:56
9	$PhMgBr/ZnBr_2$	−80	THF	63:37
10	$PhMgBr/ZnBr_2$	−80	Et_2O	52:48

[a] Low conversion.

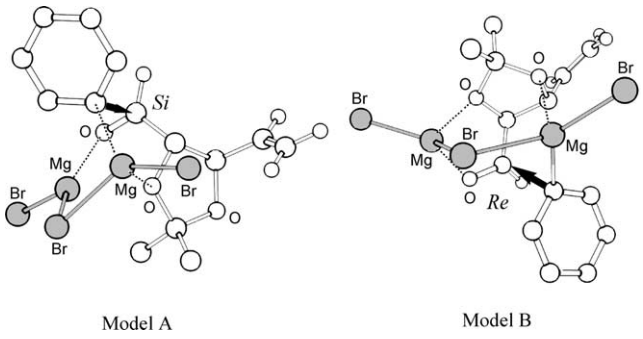


Figure 2. Models of transition states, calculated by PM5 method.

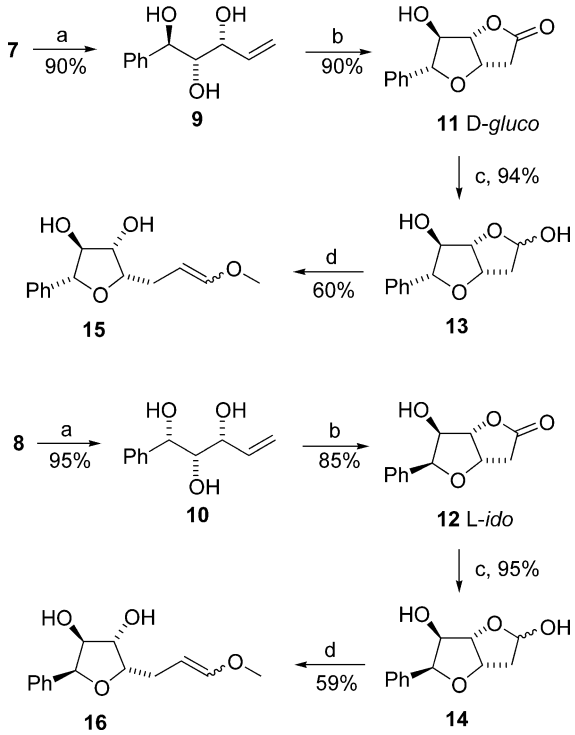
experimental results and clarified the discrepancies in stereochemical outcomes of additions to *erythro*-[19] versus *threo*-[16] configured aldehydes. In fact, the goniothalesdiol-precursor **7** was obtained by the addition of $PhCeCl_2$ to aldehyde **6** in 55% yield.

The second crucial step of both syntheses, which were run in parallel with the pure diastereomers **7** (D-*arabino*) and **8** (L-*xylo*) is oxycarbonylating bicyclisation. Firstly, the acetonide group was removed in acidic ethanol and pentenitols **9** and **10** were exposed to oxycarbonylation conditions (Scheme 4). The reaction was carried out under standard conditions with palladium(II) chloride as catalyst (0.1 equiv), copper(II) chloride as oxidant (3 equiv), sodium acetate (3 equiv) in acetic acid as buffer under a carbon monoxide atmosphere (balloon) at room temperature. As expected only the required lactones **11** and **12**, were formed with high regio- and *threo*-selectivity.[4,5] After work-up of the reaction mixture and flash chromatography the key intermediates were isolated, **11** in 90% and **12** in 85% yield, after recrystallisation. The configuration of both lactones, D-*gluco* for **11** (intermediate with correct stereochemistry for the natural product) and L-*ido* for **12** (precursor of **2**) was established by comparison of ^1H NMR data with the literature data of 3,6-anhydro-2-deoxy-1,4-heptonolactones of the same configuration.[4a] The final confirmation of the absolute stereochemistry came from the single crystal X-ray analysis of **12**.[20]

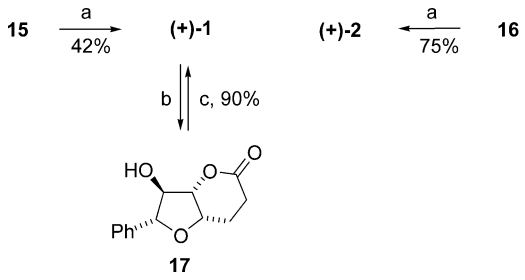
The syntheses continued with smooth partial reduction of the lactones using diisobutylaluminium hydride in CH_2Cl_2 affording a mixture of anomeric lactols **13** and **14** (*exo*:*endo*, 75:25) in very good yields, which were transformed to tetrahydrofuran derivatives **15** and **16** by the Wittig reaction with (methoxymethylene)-triphenylphosphonium chloride and *tert*-butyllithium in THF (60 and 59% as the mixtures of *E/Z*-isomers, 60:40).

Finally, the *E/Z*-isomeric mixtures of **15** and **16** were subjected to a three-step, in one-pot sequence to convert the vinyl ether to the methyl carboxylate (Scheme 5). Ether cleavage with sulphuric acid in THF–H_2O, followed by Ag_2O oxidation of the aldehyde and an acidic esterification with methanol afforded target compounds (+)-**1** and (+)-**2**, respectively. Final purification by Kugelrohr-distillation in vacuo (190 °C, 0.05 Torr), followed by repeated treatment with acidic Amberlyst in the case of (+)-**1**, because of lactonisation by heating to **17**, provided the target goniothalesdiol (+)-**1** and its 7-epimer (+)-**2** in 42 and 75% yields, respectively over three steps.

The NMR data, mp, and specific rotations of (+)-**1** and (+)-**2** were in good agreement with the reported data for the



Scheme 4. Reagents and conditions: (a) HCl, aqueous EtOH; (b) $PdCl_2$, $CuCl_2$, AcONa, AcOH, CO; (c) DIBAL-H, CH_2Cl_2; (d) $Ph_3PCH_2OCH_3Cl$, ^tBuLi, THF.



Scheme 5. Reagents and conditions: (a) 1, H_2SO_4, THF–H_2O; 2, Ag_2O, NaOH, THF–H_2O; 3, Amberlyst 15, MeOH; (b) distillation, 190 °C/0.05 Torr; (c) Amberlyst 15, MeOH.

natural product,[7] and/or unnatural antipode[8] {$[\alpha]_D^{27} = -7.1$ (*c* 0.15, EtOH)} and its 7-epimer.[9]

3. Conclusions

In conclusion, (+)-goniothalesdiol and (+)-7-*epi*-goniothalesdiol have been synthesised in 10 steps from cheap D-mannitol using an oxycarbonylation strategy for construction of tetrahydrofuran ring in two key steps, namely diastereoselective addition of organometallics to aldose **6** followed by a palladium(II)-catalysed oxycarbonylation of the appropriate unsaturated triols **9**, **10**. The synthesis of D-threose derivative, a very useful C_5-chiron, was developed from D-mannitol.

The diastereoselectivity of addition of organometallic reagent to aldose **6** was studied and model for transition state was designed using theoretical calculations based on the semiempirical PM5.

4. Experimental

4.1. General methods

Commercial reagents were used without further purification. All solvents were distilled before use. Hexanes refer to the fraction boiling at 60–65 °C. Lewis acids for diastereoselectivity studies were prepared as follows: $CeCl_3$, $ZnBr_2$ and LiCl as commercial hydrates (Fluka) were heated in tube oven at 150 °C under pressure of 2 Torr for 5 h, then stored under argon gas. $MgBr_2 \cdot THF$: 1 equiv of Mg turnings and few crystals of iodine were heated in the flask covered with reflux condenser and dropping funnel, cooled, charged with Ar and under vigorous stirring solution 1.05 equiv of 1,2-dibromoethane in THF was added and refluxed until no Mg remained. $Ti(O^iPr)_3Cl$: at −10 °C, 1 equiv of $TiCl_4$ was added dropwise to 3 equiv of $Ti(O^iPr)_4$ and stirred for 2 h, then distilled under reduced pressure (bp 65–70 °C/0.1 Torr). $TiCl_4$ and $SnCl_4$ were used without further treatment. Flash column liquid chromatography (FLC) was performed on silica gel Kieselgel 60 (40–63 μm, 230–400 mesh) and analytical thin-layer chromatography (TLC) was performed on aluminum plates pre-coated with either 0.2 mm (DC-Alufolien, Merck) or 0.25 mm silica gel 60 F_{254} (ALUGRAM® SIL G/UV$_{254}$, Macherey-Nagel). The compounds were visualised by UV fluorescence and by dipping the plates in an aqueous H_2SO_4 solution of cerium sulphate/ammonium molybdate followed by charring with a heat-gun. HPLC analyses were performed on Varian Dynamax system with variable wavelength UV detector. Melting points were obtained using a Boecius apparatus and are uncorrected. Optical rotations were measured with a POLAR L-μP polarimeter (IBZ Messtechnik) with a water-jacketed 10,000 cm cell at the wavelength of sodium line D ($\lambda = 589$ nm). Specific rotations are given in units of 10^{-1} deg cm^2 g^{-1} and concentrations are given in g/100 mL. Elemental analyses were run on FISONS EA1108 instrument, HRMS on Finnigan MAT 8230. Infrared spectra were recorded either on a Philips Analytical PU9800 FTIR spectrometer or a Perkin–Elmer 1750 FTIR spectrophotometer as KBr discs (KBr) or as thin films on KBr plates (film). NMR spectra were recorded on a Tesla BS 487 (80 MHz) and a Varian VXR-300 spectrometers. Chemical shifts (δ) are quoted in ppm and are either referenced to the tetramethylsilane (TMS) as internal standard. Compounds are numbered according to carbohydrate naming scheme.

4.1.1. 1,2:3,4-Di-*O*-isopropylidene-5,6-di-*O*-mesyl-D-mannitol (3). To the suspension of D-mannitol (25 g, 0.137 mol) in dry acetone (300 mL) was concd H_2SO_4 (3.5 mL) added dropwise and the mixture was stirred for 6 h at room temperature. At this point, the reaction could be scaled up by addition of discretionary amount of acetone solution of 1,2:3,4:5,6-tri-*O*-isopropylidene-D-mannitol (*c*, 13.8 g/100 mL). Water was added (3.3 mL/100 mL of reaction solution) and the mixture was additionally stirred for 1 h (TLC monitoring). The mixture was neutralised with 10% aqueous sol NaOH and boiled-down to half of volume in vacuo. Resulting aqueous slurry was extracted with CH_2Cl_2 (4×50 mL) and combined extracts were dried over Na_2CO_3 and evaporated in vacuo. Oily residue, containing mixture of 1,2:3,4-di-*O*-isopropylidene-D-mannitol and 1,2:3,4:5,6-tri-*O*-isopropylidene-D-mannitol was dissolved in pyridine (35 mL) and cooled to 0 °C. A solution of MsCl (6.4 mL, 9.6 g, 82 mmol) in pyridine (15 mL) was added dropwise with vigorous stirring, keeping the reaction temperature below 10 °C. After 10 h stirring at rt the mixture was poured on ice/water (350 mL) to form a brown-yellow precipitate, which was filtered and dissolved in boiling AcOEt (150 mL). The solution was dried over Na_2SO_4 an concentrated in vacuo. The residue was slurried in cold hexanes (100 mL) and filtered to provide crude product. The procedure was repeated twice and obtained white powder was recrystallised from MeOH; yield 20 g (35%) of **3**, colourless crystals, mp 120–122 °C, $[\alpha]_D^{25} = +22.5$ (*c* 2.3, CH_2Cl_2); {lit.[14]: mp 118–120 °C, $[\alpha]_D^{20} = +25.1$ (*c* 2.0, $CHCl_3$); lit.[4a]: mp 117–118 °C, $[\alpha]_D^{23} = +24.7$ (*c* 2.18, $CHCl_3$)}. Combined hexanes extracts were evaporated and the solid residue crystallised from Et_2O to give 1,2:3,4:5,6-tri-*O*-isopropylidene-D-mannitol (12 g, 30%), mp 68–70 °C, $[\alpha]_D^{25} = +16$ (*c* 1.4, MeOH); {lit.[4a]: mp 66–67 °C, $[\alpha]_D^{23} = +16.5$ (*c* 1.395, MeOH)}.

4.1.2. 3,4:5,6-Di-*O*-isopropylidene-D-*arabino*-1-hexenitol (4).[14] The dimesylate **3** (8 g, 16.6 mmol) and dry NaI (24 g, 160 mmol were dissolved in dry acetone (100 mL) and heated at 100 °C for 6 h in an autoclave. The resulting

brown suspension was distributed between $Na_2S_2O_3$ solution (10% in H_2O, 100 mL) and AcOEt (100 mL). Inorganic phase was extracted with AcOEt (3×50 mL) and combined organic phases were dried over Na_2SO_4. Concentrated crude mixture was distilled under reduced pressure on a microscale distillation apparatus equipped with 15 cm Vigreux column. Analytically pure product **4** was isolated (3.52 g, 80%) as a colourless oil, bp 40–45 °C/0.05 Torr, $[\alpha]_D^{25}=-4.8$ (*c* 3.25, CH_2Cl_2); {lit.[12]: $[\alpha]_D^{23}=-3.6$ (*c* 4.23, $CHCl_3$); lit.[14]: $[\alpha]_D^{21}=-5.5$ (*c* 2.4, $CHCl_3$); lit.[4a]: bp 70–80 °C/1 mbar, $[\alpha]_D^{21}=-5.3$ (*c* 2.98, $CHCl_3$)}.

4.1.3. 3,4-*O*-isoPropylidene-D-*arabino*-1-hexenitol (5). According to lit.[15] a solution of bisacetonide **4** (5 g, 26.6 mmol) and $Zn(NO_3)_2\cdot 6H_2O$ (39 g, 133 mmol) in acetonitrile (30 mL) was stirred at rt for 24 h. After concentration in vacuo the remainder was distributed between CH_2Cl_2 (200 mL) and water (200 mL) and separated water layer was extracted with CH_2Cl_2 (2× 50 mL). Combined organic extracts were dried over Na_2CO_3 and after solvent removal separated by flash column chromatography on silica (50% AcOEt in hexanes). Yield of **5** as a colourless oil: 2.3 g (55%), R_f 0.21 (50% AcOEt in hexanes), $[\alpha]_D^{25}=+6.4$ (*c* 0.47, CH_2Cl_2); {lit.[12]: $[\alpha]_D^{23}=+16.1$ (*c* 3.25, EtOH)}. IR (film, cm^{-1}): ν 3391 (bs), 2936 (s), 2985 (s), 1732 (s), 1647, 1559 (all m); ^1H NMR (300 MHz, $CDCl_3$): δ 1.42, 1.43 (2× s, 6H, $C(CH_3)_2$), 3.25 (broad s, 2H, OH), 3.64–3.90 (m, 4H, H-1, H-2, H-3), 4.42 ('t', 1H, $J_{4,5}=7$ Hz, $J_{3,4}=7$ Hz, H-4), 5.25 (d, 1H, $J_{5,6Z}=10.3$ Hz, H-6Z) 5.41 (d, 1H, $J_{5,6E}=17.5$ Hz, H-6E), 5.88 (ddd, 1H, $J_{4,5}=7$ Hz, $J_{5,6Z}=10.3$ Hz, $J_{5,6E}=17.5$ Hz, H-5); ^{13}C NMR (75 MHz, $CDCl_3$): δ 26.9, 27.0 (all q, $C(CH_3)_2$), 63.5 (t, C-1), 72.1, 79.3, 81.0 (all d, C-2, C-3, C-4), 109.4 (s, $C(CH_3)_2$), 118.6 (t, C-6), 135.9 (d, C-5). Anal. calcd for $C_9H_{16}O_4$ (188.2): C, 57.43; H, 8.57. Found: C, 57.72; H, 8.55.

4.1.4. 2,3-*O*-isoPropylidene-D-*threo*-4-pentenose (6). A solution of $NaIO_4$ (3.4 g, 14.6 mmol) in water (35 mL) was added dropwise to the suspension of **5** (2.3 g, 12.2 mmol) in water (9 mL) at 0 °C. After 90 min (TLC monitoring) of vigorous stirring (white precipitate had been created) NaCl (3 g) was added and mixture was extracted with AcOEt (4× 50 mL). Extracts were dried over K_2CO_3 and concentrated. After removal of the traces of solvent (0.05 Torr for 30 min at rt) a colourless viscous oil of **6** (1.7 g, 90%) was obtained in satisfactory purity for the next reaction step. R_f 0.58 (50% AcOEt in hexanes), $[\alpha]_D^{25}=-24.1$ (*c* 0.21, $CHCl_3$). ^1H NMR (80 MHz, $CDCl_3$): δ 1.46 (s, 6H, $C(CH_3)_2$), 3.80–4.48 (m, 2H, H-2, H-3), 5.00–5.50 (m, 2H, H-5E, H-5Z), 5.65–6.20 (m, 1H, H-4), 9.72 (d, 1H, $J_{1,2}=2$ Hz, H-1). The aldose **6** can be stored for 1 month at 0–10 °C without loss of quality.

4.2. 2,3-*O*-isoPropylidene-5-*C*-phenyl-D-*arabino*-1-pentenitol (7) and 2,3-*O*-isopropylidene-5-*C*-phenyl-L-*xylo*-1-pentenitol (8)

Preparative procedure with PhMgBr: a dry flask was charged with Mg turnings (260 mg, 10.7 mmol) and a few particles of iodine, heated under Ar until the iodine started to sublime. The solution of PhBr (1.7 g, 10.8 mmol) in dry THF (20 mL) was added dropwise to start a vigorous exothermic reaction. Reaction was left to reflux for 1 h, until no Mg particles remained in the flask, and subsequently cooled to 0 °C. Aldehyde **6** (1.5 g, 9.6 mmol) in THF (15 mL) was added and solution was left to stand overnight (12 h), and then quenched with saturated solution of NH_4Cl (20 mL), Et_2O (30 mL) was added and the separated aqueous phase extracted with AcOEt (4×30 mL). Organic phases were dried over Na_2SO_4 and concentrated. Crude oil was separated on silica gel column (100 g, 4 cm i.d. of column, 4% AcOEt and 0.3% THF in hexanes) to afford **7** (750 mg, 33%), **8** (600 mg, 27%) and 200 mg fraction containing both isomers. Overall yield of isolated products was 70%.

Preparative procedure with $PhCeCl_2\cdot MgBrCl$: The aldehyde **6** (500 mg, 3.21 mmol) in Et_2O (10 mL) was added to the freshly prepared reagent [875 mg, 2.35 mmol of dry $CeCl_3$ was sonicated for 10 min in dry Et_2O (10 mL), then 2.35 mmol of freshly prepared PhMgBr in Et_2O (10 mL) was added and suspension was stirred for 2 h at −10 °C and the resulting suspension was left to stir overnight. Reaction was quenched by addition of 5% HCl (15 mL) and extracted with Et_2O. Organic phases were dried over Na_2SO_4 and concentrated. Crude oil was separated on silica gel column (25 g, 2.5 cm i.d. of column, 4% AcOEt and 0.3% THF in hexanes) to afford **7** (410 mg, 55%), **8** (105 mg, 14%) and 80 mg fraction containing both isomers. Overall yield of isolated products was 79%.

4.2.1. Compound 7. R_f 0.49 (23% AcOEt in hexanes), $[\alpha]_D^{21}=+4.4$ (*c* 0.21, CH_2Cl_2). IR (film, cm^{-1}): ν 3467 (s), 2987 (s), 1455, 1381, 1240, 1217, 1167, 1057, 701 (all s). ^1H NMR (300 MHz, $CDCl_3$): δ 1.43, 1.45 (all s, 6H, $C(CH_3)_2$), 2.68 (broad s, 2H, OH), 4.02 (dd, 1H, $J_{4,5}=4.0$ Hz, $J_{3,4}=8.1$ Hz, H-4), 4.42 (dd, 1H, $J_{2,3}=6.2$ Hz, $J_{3,4}=8.1$ Hz, H-3), 4.88 (ddd, 1H, $J_{1Z,2}=10.5$ Hz, H-1Z), 4.99 (d, 1H, $J_{1E,2}=17.3$ Hz, H-1E), 5.03 (bd, 1H, $J_{4,5}=4.0$ Hz, H-5), 5.28 (ddd, 1H, $J_{2,3}=6.2$ Hz, $J_{1Z,2}=10.5$ Hz, $J_{1E,2}=17.3$ Hz, H-2), 7.20–7.40 (m, 5H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$): δ 26.9 ('q', 2× q $C(CH_3)_2$), 71.8, 77.0, 84.2 (all d, C-3, C-4, C-5), 109.4 (s, $C(CH_3)_2$), 117.1 (t, C-1), 126.1, 128.3, 129.7 (all d, Ph), 135.7 (d, C-2), 138.5 (s, Ph). Anal. calcd for $C_{14}H_{18}O_3$ (234.3): C, 71.77; H, 7.74; Found: C, 72.12; H, 7.55.

4.2.2. Compound 8. R_f 0.57 (23% AcOEt/hexanes), $[\alpha]_D^{21}=+14.4$ (*c* 0.25, CH_2Cl_2). IR (film, cm^{-1}): ν 3466 (s), 2987 (s), 1458, 1381, 1240, 1218, 1166, 701 (all s). ^1H NMR (300 MHz, $CDCl_3$): δ 1.44, 1.48 (2× s, 6H, $C(CH_3)_2$), 2.81 (broad s, OH), 3.93 (dd, 1H, $J_{4,5}=5.3$ Hz, $J_{3,4}=8.1$ Hz, H-4), 4.31 (dd, 1H, $J_{2,3}=6.8$ Hz, $J_{3,4}=8.1$ Hz, H-3), 4.62 (bd, 1H, $J_{4,5}=5.3$ Hz, H-5), 5.00 (d, 1H, $J_{1Z,2}=10.5$ Hz, H-1Z), 5.08 (d, 1H, $J_{1E,2}=17.3$ Hz, H-1E), 5.44 (ddd, 1H, $J_{2,3}=6.2$ Hz, $J_{1Z,2}=10.5$ Hz, $J_{1E,2}=17.3$ Hz, H-2), 7.26–7.29 (m, 5H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.2, 27.1 (both q, $C(CH_3)_2$), 74.0, 79.1, 84.5 (all d, C-3, C-4, C-5), 109.7 (s, $C(CH_3)_2$), 118.1 (t, C-1), 125.3, 126.8, 128.4 (all d, Ph), 134.7 (d, C-2), 139.8 (s, Ph). Anal. calcd for $C_{14}H_{18}O_3$ (234.3): C, 71.77; H, 7.74; Found: C, 71.92; H, 7.95.

4.3. Typical procedure for addition of organometallics to aldehyde 6

Freshly prepared phenylating reagent (1.1 mmol PhMgBr, PhLi, $PhCeCl_2$) in 10 mL of corresponding solvent was set up to chosen temperature. Aldehyde **6** (156 mg, 1 mmol) was added dropwise in solvent (5 mL) and mixture was kept at initial temperature for additional 3 h, then kept to reach rt. Reaction was left until no **6** was observed, but no longer than 24 h (Table 1).

4.4. Typical procedure for addition of organometallics to aldehyde 6 in the presence of Lewis acid

Lewis acid (1.1 mmol) was dissolved or suspended in corresponding solvent (10 mL) and cooled to chosen temperature. Aldehyde **6** (156 mg, 1 mmol) in solvent (5 mL) was added and mixture was left to stir for 30 min. Phenylating agent (1.1 mL, 1.1 mmol PhLi or PhMgBr, 1 M soln) was added dropwise within 10 min, and mixture was stirred at initial temperature for 2 h, then left to reach rt; until no **6** was observed, but no longer than 24 h.

4.5. Procedure for addition of organometallics to aldehyde 6 in the presence of crown-ether

Freshly prepared PhMgBr in Et_2O (1.2 mmol in 10 mL) was concentrated under Ar. Syrupy brown residue was dissolved in CH_2Cl_2 (10 mL), 18-crown-6 (4 equiv) was added and mixture was left to stir until all crown-ether dissolved. Aldehyde **6** (156 mg, 1 mmol) in CH_2Cl_2 (5 mL) was added during 10 min and mixture was left overnight.

4.6. General workup procedure for all reactions above

Reactions were quenched with satd NH_4Cl (10 mL), extracted with Et_2O and dried over Na_2SO_4. Crude oils were analysed on *n*-phase HPLC (Separon SGX 250×4 mm column, $\lambda=254$ nm, 17% AcOEt in *i*-hexane, flow rate 0.7 mL/min, 25 °C); $T_r=7.8$ min for **7** and 11.7 min for **8**.

4.6.1. 5-*C*-Phenyl-D-*arabino*-1-pentenitol; [(1*R*, 2*S*, 3*R*)-1-phenyl-pent-4-ene-1,2,3-triol] (9). A suspension of protected triol **7** (600 mg, 2.56 mmol) in 70% EtOH (10 mL) and concd HCl (1 mL) was stirred for 3 h at rt. Solvents were removed in vacuo and residue was purified by flash chromatography on silica (50% AcOEt in hexanes). Yield of **9** (450 mg, 90%), colourless crystals; mp 143–144 °C, R_f 0.21 (50% AcOEt/hexanes), $[\alpha]_D^{21}=+11.9$ (*c* 0.08, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.46 (broad s, 3H, OH), 3.67 (dd, 1H, $J_{3,4}=2.6$ Hz, $J_{4,5}=5.4$ Hz, H-4), 4.28 (dd, 1H, $J_{3,4}=2.6$ Hz, $J_{2,3}=5.4$ Hz, H-3), 4.88 (d, 1H, $J_{4,5}=5.4$ Hz, H-5), 5.21 (d, 1H, $J_{1Z,2}=10.6$ Hz, H-1Z), 5.30 (d, 1H, $J_{1E,2}=17.2$ Hz, H-1E), 5.90 (ddd, 1H, $J_{2,3}=5.4$ Hz, $J_{1Z,2}=10.6$ Hz, $J_{1E,2}=17.2$ Hz, H-2), 7.27–7.43 (m, 5H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$): δ 71.4, 75.7, 75.9 (all d, C-3, C-4, C-5), 116.2 (t, C-1), 126.4, 127.7, 128.4 (all d, Ph), 137.4 (d, C-2), 140.8 (s, Ph). Anal. calcd for $C_{11}H_{14}O_3$ (194.2): C, 68.02; H, 7.27. Found: C, 68.22; H, 7.31.

4.6.2. 5-*C*-Phenyl-L-*xylo*-1-pentenitol; [(1*S*, 2*S*, 3*R*)-1-phenyl-pent-4-ene-1,2,3-triol] (10). Procedure as above; protected triol **8** (600 mg, 2.56 mmol). Flash column chromatography (50% AcOEt in hexanes) afforded pure **10** (472 mg, 95%) as colourless oil, R_f 0.15 (50% AcOEt/hexanes), $[\alpha]_D^{21}=+29.4$ (*c* 0.35, MeOH). IR (film, cm^{-1}): ν 3386 (s), 3064, 3032, 2914, 1718 (all m), 1494, 1454, 1401 (all s), 1198, 1042 (all m). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.96 (broad s, 3H, OH), 3.59 (dd, 1H, $J_{3,4}=3.3$ Hz, $J_{4,5}=5.5$ Hz, H-4), 4.04 (dd, 1H, $J_{3,4}=3.3$ Hz, $J_{2,3}=5.5$ Hz, H-3), 4.79 (d, 1H, $J_{4,5}=5.5$ Hz, H-5), 5.20 (d, 1H, $J_{1Z,2}=10.5$ Hz, H-1Z), 5.29 (d, 1H, $J_{1E,2}=17.2$ Hz, H-1E), 5.87 (ddd, 1H, $J_{2,3}=5.5$ Hz, $J_{1Z,2}=10.5$ Hz, $J_{1E,2}=17.2$ Hz, H-2), 7.26–7.40 (m, 5H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$): δ 72.6, 74.5, 77.4 (all d, C-3, C-4, C-5), 116.8 (t, C-1), 126.6, 128.0, 128.5 (all d, Ph), 137.6 (d, C-2), 140.7 (s, Ph). Anal. calcd for $C_{11}H_{14}O_3$ (194.2): C, 68.02; H, 7.27. Found: C, 68.31; H, 7.52.

4.6.3. 3,6-Anhydro-2-deoxy-6-*C*-phenyl-D-*gluco*-1,4-hexonolactone; [(1*S*, 5*S*, 7*R*, 8*R*)-8-hydroxy-7-phenyl-2,6-dioxabicyclo[3.3.0]octan-3-one] (11). A 25 mL-flask with stopcock equipped side inlet was charged with $PdCl_2$ (9 mg, 0.05 mmol, 0.1 equiv), $CuCl_2$ (207 mg, 1.55 mmol, 3 equiv) and AcONa (127 mg, 1.55 mmol, 3 equiv). Alkenol **9** (100 mg, 0.52 mmol) in AcOH (10 mL) was added and the flask was purged with CO from balloon (residual air was removed through side inlet with water aspirator). The mixture was vigorously stirred at rt until colour of the mixture changed from green to pale brown (approx. 10 h). Inorganic material was removed on Cellite® pad and the filtrate was concentrated in vacuo. Residue was dissolved in AcOEt (25 mL) and washed with 10% $NaHCO_3$ (10 mL). Separated organic phase was dried over Na_2SO_4 and concentrated. Crude product was purified on silica gel column (50% AcOEt in hexanes). Spectroscopically pure lactone **11** was isolated as pale brown oil (102 mg, 90%), R_f 0.44 (50% AcOEt/hexanes), $[\alpha]_D^{21}=-75$ (*c* 0.38, CH_2Cl_2). IR (film, cm^{-1}) ν 3438, 2930, 1782, 1194, 1154, 1048, 1003, 760, 701. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.64 (d, 1H, $J_{2A,2B}=18$ Hz, H-2), 2.97 (dd, 1H, $J_{2A,2B}=18$ Hz, $J_{2,3}=2.7$ Hz, H-2), 4.06 (dd, 1H, $J_{5,OH}=5.1$ Hz, $J_{4,5}=5.4$ Hz, H-5), 4.66 (d, 1H, $J_{4,5}=5.7$ Hz, H-4), 4.87 (bs, 2H, H-3, H-6), 5.97 (d, 1H, $J_{5,OH}=5.1$ Hz, OH), 7.26–7.40 (m, 5H, Ph); ^{13}C NMR (75 MHz, DMSO-d_6): δ 35.7 (t, C-2), 77.4 (d, C-5), 81.8 (d, C-3), 86.8 (d, C-4), 90.1 (d, C-6), 125.8, 127.7, 128.3 (all d, Ph), 139.4 (s, Ph), 175.5 (s, C-1). HR MS: 220.0733±5 ppm (calcd 220.0736 for $C_{12}H_{12}O_4$).

4.6.4. 3,6-Anhydro-2-deoxy-6-*C*-phenyl-L-*ido*-1,4-hexonolactone; [(1*S*, 5*S*, 7*S*, 8*R*)-8-hydroxy-7-phenyl-2,6-dioxabicyclo[3.3.0]octan-3-one] (12). Procedure as above; alkenol **10** (100 mg, 0.52 mmol). Lactone **12** was obtained in pure form by crystallisation of the crude product from AcOEt. Yield of **12** (97 mg, 85%), as colourless crystals, mp 177–180 °C, R_f 0.44 (50% AcOEt/hexanes), $[\alpha]_D^{21}=+38$ (*c* 0.31, CH_2Cl_2). IR (KBr, cm^{-1}): ν 3499, 1774, 1188, 1158, 1052, 1037, 742. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.47 (d, 1H, $J_{2A,2B}=18.3$ Hz, H-2), 2.86 (dd, 1H, $J_{2A,2B}=18.3$ Hz, $J_{2,3}=6.6$ Hz, H-2), 4.20 (dd, 1H, $J_{5,OH}=5.1$ Hz, $J_{5,6}=3.6$ Hz, H-5), 4.88 (2× d, 2H, $J_{3,4}=3.8$ Hz, $J_{5,6}=3.6$ Hz, H-4, H-6), 4.94 (dd, 1H, $J_{2,3}=6.0$ Hz, $J_{3,4}=3.8$ Hz, H-3), 5.19 (d, 1H, $J_{5,OH}=5.4$ Hz, OH), 7.15–7.32 (m, 5H, Ph)); ^{13}C NMR (75 MHz, DMSO-d_6): δ 35.7 (t, C-2), 74.4 (d, C-5), 76.4 (d, C-3), 82.2 (d, C-4), 88.1 (d, C-6) 127.1, 127.3, 127.4 (all d, Ph), 136.7 (s, Ph), 176 (s, C-1)).

Anal. calcd for $C_{12}H_{12}O_4$ (220.2): C, 65.45; H, 5.49. Found: C, 65.28; H, 5.50.

4.6.5. 3,6-Anhydro-2-deoxy-6-*C*-phenyl-α/β-D-glucofuranose (13). A flame dried 25 mL-flask with stopcock equipped side inlet was flushed with Ar, charged with lactone **11** (130 mg, 0.6 mmol) in dry CH_2Cl_2 (5 mL) and cooled to −80 °C. Diisobutylaluminiumhydride solution (0.8 mL, 1.2 mmol, 2 equiv, 1.5 M soln in toluene) was added dropwise under vigorous stirring. The mixture was kept at −80 °C for 90 min and subsequently quenched with 1 M HCl (5 mL). Water phase was separated and extracted with AcOEt (3×10 mL). Combined organic extracts were washed with satd NaCl, dried over Na_2SO_4 and evaporated. Crude aldose **13** was isolated in 95% purity as colourless oil (125 mg, 94%) and therefore no purification was necessary, R_f 0.24 (50% AcOEt/hexanes). IR (KBr, cm^{-1}): ν 3455, 3410, 2938, 1247, 1101, 1074, 1059, 996, 958 (all s). ^{1}H NMR (300 MHz, DMSO-d_6, mixture of anomers in 1:8 ratio, following spectra are for major anomer): δ 2.03 (dd, 2H, $J_{1,2}$=3.6 Hz, $J_{2,3}$=4.5 Hz, H-2), 4.02 (dd, 1H, $J_{5,6}$=2.5 Hz, $J_{5,OH}$=5.1 Hz, H-5), 4.47 (d, 1H, $J_{3,4}$=4.5 Hz, H-4), 4.81 (d, 1H, $J_{5,6}$=2.4 Hz, H-6), 4.85 (d, 1H, $J_{5,OH}$=5.4 Hz, OH), 4.98 ('q', 1H, $J_{2,3}$=4.8 Hz, $J_{3,4}$=4.5 Hz, H-3), 5.51 ('q', 1H, $J_{1,2}$=3.6 Hz, $J_{1,OH}$=4.3 Hz, H-1), 6.24 (d, 1H, $J_{1,OH}$=4.8 Hz, OH), 7.14–7.37 (m, 5H, Ph); ^{13}C NMR (75 MHz, DMSO-d_6): δ 41.5 (t, C-2), 76.2 (d, C-5), 80.7 (d, C-3), 81.7 (d, C-6), 87.0 (d, C-4), 98.8 (d, C-1), 126.8, 127.3, 127.5 (3× d, Ph), 137.6 (s, Ph).

4.6.6. 3,6-Anhydro-2-deoxy-6-*C*-phenyl-α/β-D-idofuranose (14). The same procedure as above was used for the preparation of idofuranose **14** (127 mg, 95%), colourless oil, R_f 0.24 (50% AcOEt/hexanes). ^{1}H NMR (300 MHz, DMSO-d_6, only one anomer was detected): δ 1.85 (dt, 1H, $J_{2A,2B}$=9.0 Hz, $J_{1,2}$=$J_{2,3}$=4.5 Hz, H-2A), 2.23 (d, 1H, $J_{2A,2B}$=9.0 Hz, H-2B), 3.87 (dd, 1H, $J_{5,OH}$=5.1 Hz, H-5), 4.42 (d, 1H, $J_{5,6}$=2.4 Hz, H-6), 4.54 (d, 1H, $J_{3,4}$=5.7 Hz, H-4), 4.73 (dd, 1H, $J_{2,3}$=4.5 Hz, $J_{3,4}$=5.1 Hz, H-3), 5.49 (dd, 1H, $J_{1,2}$=4.5 Hz, $J_{1,OH}$=5.1 Hz, H-1), 5.61 (d, 1H, $J_{5,OH}$=5.1 Hz, OH), 6.25 (d, 1H, $J_{1,OH}$=5.4 Hz, OH), 7.14–7.38 (m, 5H, Ph); ^{13}C NMR (75 MHz, DMSO-d_6): δ 40.8 (t, C-2), 81.8 (d, C-5), 82.9 (d, C-3), 87.9 (d, C-6), 89.0 (d, C-4), 99.1 (d, C-1), 125.9, 127.4, 128.1 (3× d, Ph), 140.6 (s, Ph).

4.6.7. (*E*/*Z*)-4,7-Anhydro-2,3-dideoxy-1-*O*-methyl-7-*C*-phenyl-D-*gluco*-1-heptenitol (15). A flame dried 100 mL-flask with stopcock equipped side inlet was flushed with Ar, charged with methoxymethylene–triphenyl–phosphonium chloride (1.27 g, 3.78 mmol, 7 equiv) in dry THF (20 mL) and cooled to −80 °C. *tert*-Butyllithium (2.5 mL, 3.75 mmol, 6.9 equiv, 1.5 M in pentane) was added in two portions and the mixture was stirred at −80 °C for 1 h. Properly prepared reagent has bright red colour. Furanose **13** (120 mg, 0.54 mmol) in THF (5 mL) was added and the temperature was kept under −60 °C for additional 2 h. After overnight stirring at rt water (20 mL) and diethyl ether (50 mL) was added and separated water layer was extracted with diethyl ether. Combined organic layers were washed with water (30 mL) and dried over Na_2SO_4. Crude brown oil was purified by flash chromatography (20 g of silica-gel, 20%, then 35% and 50% ethyl acetate in toluene as eluent) to afford **15** (81 mg, 60%, pale yellow oil), as a mixture of *E*/*Z* isomers (*E*: *Z*=60:40).

E-**15**: ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.20 (dd, 2H, $J_{2,3}$=5.9 Hz, $J_{3,4}$=7.5 Hz, H-3), 3.45 (s, 3H, Me), 3.90–4.02 (m, 2H, H-5, H-6), 4.10 (dd, 1H, $J_{3,4}$=7.5 Hz, $J_{4,5}$=4.1 Hz, H-4), 4.38 (dd, 1H, $J_{1,2}$=13.0 Hz, $J_{2,3}$=5.9 Hz, H-2), 4.74 (s, 1H, H-7), 5.01 (d, 1H, $J_{5,OH}$=3.6 Hz, OH), 5.15 (d, 1H, $J_{6,OH}$=4.2 Hz, OH), 6.43 (d, 1H, $J_{1,2}$=12.9 Hz, H-1), 7.16–7.35 (m, 5H, Ph); ^{13}C NMR (75 MHz, DMSO-d_6): δ 27.2 (t, C-3), 55.5 (q, Me), 76.7 (d, C-5), 78.3 (d, C-6), 81.6 (d, C-4), 81.7 (d, C-7), 99.0 (d, C-2), 126.5, 127.2, 127.3 (all d, Ph), 139.3 (s, Ph), 148.2 (d, C-1).

Z-**15**: ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.15–2.26 (m, 2H, H-3), 3.55 (s, 3H, Me), 3.92 (m, 2H, H-5, H-6), 4.05–4.14 (m, 1H, $J_{6,7}$=7.5 Hz, H-7), 4.77 (d, 1H, $J_{4,5}$=4.2 Hz, H-4), 4.79 (d, 1H, $J_{1,2}$=6.3 Hz, H-2), 5.00 (d, 1H, $J_{5,OH}$=3.6 Hz, OH), 5.09 (d, 1H, $J_{6,OH}$=4.5 Hz, OH), 6.03 (d, 1H, $J_{1,2}$=6.3 Hz, H-1), 7.16–7.35 (m, 5H, Ph); ^{13}C NMR (75 MHz, DMSO-d_6): δ 23.9 (t, C-3), 59.0 (q, Me), 77.0 (d, C-5), 78.3 (d, C-6), 80.6 (d, C-4), 81.6 (d, C-7), 102.2 (d, C-2), 126.5, 127.2, 127.3 (3× d, Ph), 139.3 (s, Ph), 147.3 (d, C-1).

4.6.8. (*E*/*Z*)-4,7-Anhydro-2,3-dideoxy-1-*O*-methyl-7-*C*-phenyl-L-*ido*-1-heptenitol (16). Following the above procedure heptenitol **16** was obtained (80 mg, 59%) as a mixture of *E*/*Z* isomers (*E*: *Z*=62:38 by NMR) from idofuranose **14** (120 mg, 0.54 mmol).

E-**16**: ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.20–2.35 (m, 2H, H-3), 3.44 (s, 3H, Me), 3.80 (dd, 1H, $J_{5,OH}$=4.5 Hz, $J_{4,5}$=4.8 Hz, H-5), 3.84 (2× d, 2H, $J_{6,OH}$=3.6 Hz, $J_{6,7}$=3.6 Hz, H-6, H-7), 4.46 (d, 1H, $J_{3,4}$=5.7 Hz, $J_{4,5}$=4.2 Hz, H-4), 4.76 (dd, 1H, $J_{1,2}$=12.9 Hz, H-2), 4.90 (d, 1H, $J_{6,OH}$=3.6 Hz, OH), 5.40 (d, 1H, $J_{5,OH}$=4.5 Hz, OH), 6.43 (d, 1H, $J_{1,2}$=12.9 Hz, H-1), 7.20–7.44 (m, 5H, Ph); ^{13}C NMR (75 MHz, DMSO-d_6): δ 27.0 (t, C-3), 55.4 (q, Me), 77.9 (d, C-5), 82.0 (d, C-6), 84.8 (d, C-4), 86.7 (d, C-7), 99.0 (d, C-2), 126.4, 128.7, 128.8 (all d, Ph), 141.1 (s, Ph), 148.2 (d, C-1).

Z-**16**: ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.30–2.40 (m, 2H, H-3), 3.55 (s, 3H, Me), 3.80 (t, 1H, $J_{5,OH}$=4.5 Hz, $J_{4,5}$=4.8 Hz, H-5), 3.84 (2× d, 2H, $J_{6,OH}$=3.6 Hz, $J_{6,7}$=3.6 Hz, H-6, H-7), 4.46 (dd, 1H, $J_{3,4}$=5.7 Hz, $J_{4,5}$=4.2 Hz, H-4), 4.76 (d, 1H, $J_{1,2}$=6.3 Hz, H-2), 4.90 (d, 1H, $J_{6,OH}$=4.2 Hz, OH), 5.40 (d, 1H, $J_{5,OH}$=4.5 Hz, OH), 6.02 (d, 1H, $J_{1,2}$=6.3 Hz, H-1), 7.20–7.44 (m, 5H, Ph); ^{13}C NMR (75 MHz, DMSO-d_6): δ 23.7 (t, C-3), 59.1 (q, Me), 77.6 (d, C-5), 81.0 (d, C-6), 84.7 (d, C-4), 86.5 (d, C-7), 102.2 (d, C-2), 126.4, 127.9, 128.8 (all d, Ph), 141.7 (s, Ph), 147.4 (d, C-1).

4.6.9. (+)-Goniothalesdiol (1). A solution of D-*gluco*-heptenitol **15** (100 mg, 0.4 mmol) in THF (7 mL) and water (3 mL) was acidified with H_2SO_4 (96%, 1 mL) and left to stir at rt, until no starting material was detected by TLC (approx. 3 h). The mixture was carefully neutralised with 10% NaOH solution (pH=8) and the entire content of the reaction flask was introduced into the freshly prepared suspension of Ag_2O (250 mg, 1.5 mmol of $AgNO_3$ and 130 mg, 3.25 mmol of NaOH in 5 mL of deionised water, stirred for 30 min to prepare brown suspension). After 1 h of

vigorous stirring colour of the suspension turned to black and TLC detected no spots with Rf > 0.05 (50% AcOEt in hexanes). The precipitate of Ag/Ag_2O was filtered off (Cellite pad) and the filtrate neutralised with 1 M HCl. Solvents were replaced with dry MeOH (25 ml) and acidic catex (1 g, Amberlyst 15, previously washed three times with MeOH) was added. After 1 h of stirring at rt, catex and inorganic salts were removed by filtration on Celite® and the filtrate was concentrated. Crude yellow oil (100 mg), containing mixture of methylester **1**, nonesterified acid and impurities, was distilled on Kugelrohr apparatus (190 °C/ 0.05 Torr) to provide colourless oil (50 mg), a mixture of required product **1** and lactone **17** (50:50, determined by ^{1}H NMR). Another esterification this mixture (10 mL of dry MeOH, 300 mg of Amberlyst 15, 1 h at rt) afforded analytically pure goniothalesdiol **1** (45 mg, 42%) as a colourless oil, R_f 0.20 (50% AcOEt/hexanes), $[\alpha]_D^{21} = +6.9$ (*c* 0.38, MeOH) {lit.[7]:$[\alpha]_D^{25} = +7.5$ (*c* 0.23, EtOH), (−)-goniothalesdiol lit.[8]: $[\alpha]_D^{27} = -7.1$ (*c* 0.15, EtOH)}. IR (film, cm^{-1}): ν 3448 (bs), 2956 (m), 2929 (m), 1736, 1449, 1375, 1236, 1176, 1070, 757, 700 (all s). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.03–2.15 (m, 2H, H-3), 2.42–2.70 (m, 2H, H-2), 3.68 (s, 3H, OMe), 4.03–4.07 (m, 3H, H-4, H-5, H-6), 4.59 (d, 1H, $J_{6,7}$ = 4.5 Hz, H-7), 7.25 (d, 1H, J = 7.0 Hz, H-4′), 7.33 (t, 2H, J = 7.0 Hz, H-3′, H-5′), 7.41 (d, 2H, J = 7.0 Hz, H-2′, H-6′); ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.7 (t, C-3), 30.6 (t, C-2), 51.9 (q, OMe), 79.0 (d, C-5), 80.7 (d, C-4), 85.3 (d, C-6), 86.1 (d, C-7), 126.1 (d, C-3′, C-5′), 127.9 (d, C-4′), 128.7 (d, C-2′, C-6′), 139.9 (s, C-1′), 174.7 (s, C-1). Anal. calcd for $C_{14}H_{18}O_5$ (266.3): C, 63.15; H, 6.81. Found: C, 63.38; H, 6.60.

4.6.10. (+)-7-*epi*-Goniothalesdiol (2). Prepared as above from **16** (100 mg, 0.4 mmol). In this case the second esterification was not needed, because Kugelrohr distillation afforded pure target compound **2** (80 mg, 75%) as colourless oil, R_f 0.21 (50% AcOEt/hexanes), $[\alpha]_D^{21} = +70.3$ (*c* 0.23, EtOH) {lit.[9]:$[\alpha]_D^{25} = +66.6$ (*c* 0.74, EtOH)}. IR (film, cm^{-1}): ν 3456 (s), 2926 (m), 1717 (s), 1452, 1369, 1253, 1173, 1067, 742, 704 (all s). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.07 (dd, 2H, $J_{2,3} = J_{3,4}$ = 7.2 Hz, H-3), 2.40–2.65 (m, 2H, H-2), 3.70 (s, 3H, OMe), 4.16 (d, 1H, $J_{6,7}$ = 3.0 Hz, H-6), 4.21 (d, 1H, $J_{4,5}$ = 2.9 Hz, H-5), 4.31 (dt, 1H, $J_{3,4}$ = 7.2 Hz, $J_{4,5}$ = 2.9 Hz, H-4), 5.32 (d, 1H, $J_{6,7}$ = 3.0 Hz, H-7), 7.25–7.43 (m, 5H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.5 (t, C-3), 30.6 (t, C-2), 52.0 (q, OMe), 76.9 (d, C-5), 79.1 (d, C-4), 81.4 (d, C-6), 82.3 (d, C-7), 126.7 (d, C-3′, C-5′), 127.9 (d, C-4′), 128.6 (d, C-2′, C-6′), 136.8 (s, C-1′), 175.1 (s, C-1). Anal. calcd for $C_{14}H_{18}O_5$ (266.3): C, 63.15; H, 6.81. Found: C, 63.42; H, 6.93.

Acknowledgements

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An efficient construction of bridged chiral tetracyclic indolidines, a core structure of asperparaline, via stereocontrolled catalytic Pauson–Khand reaction

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Abstract—A reaction of chiral enyne **22** derived from L-proline with a catalytic amount of cobalt (0) octacarbonyl in the presence of *N*-methylmorphorine *N*-oxide gave tricyclic enone **24** in 54% yield (73% based on consumed starting material). Treatment of enone **11** with aqueous methylamine followed by silica gel afforded bridged tetracyclic indolidine **1**, a common structural motif of natural metabolites, an asperparaline series of compounds and also a potential intermediate for the synthesis of a paralytic alkaloid, asperparaline C (**4**), in 70% yield.

1. Introduction

In our previous report,[1] we briefly communicated the racemic synthesis of tetracyclic indolidine **1**, which constitutes the C3 and C10–C25 portions of a paralytic alkaloid, asperparaline C (**4**) (Fig. 1),[2] via Pauson–Khand cycloaddition reaction[3] mediated by a stoichiometric amount of cobalt (0) octacarbonyl. In this paper, we wish to describe full details of the work which includes additional new work such as a catalytic version of the key Pauson–Khand reaction,[4] chiral synthesis of **1** starting from L-proline using Seebach's protocol[5] and also improvement of the yield of each step to result in a concise, enantio- and stereo-controlled synthesis of **1**.

The indolidine alkaloids, asperparalines A to C (**2** to **4**), were discovered by Hayashi and co-workers from 'okara' (the insoluble residue of whole soybeans) that has been fermented with *Aspergillus japonicus* JV-23.[2] Asperparalines showed interesting paralytic activity within 1 h against silkworms at a dose of 10 μg of diet which lasted for 7 to 10 h upon oral administration. On the other hand, Everett and co-workers also isolated the same compound as asperparaline A (**2**) named aspergillimide (VM55598) along with SB202327 (**5**) possessing anthelmintic activity.[6] There are numerous other structurally related natural methabolites including brevinamides **6**,[7] paraherquamides **7**,[8] macrofortine **8**,[9] and sclerotamide **9**,[10] which have a variety of biological activities such as anthelmintic,[6] antinematodal,[8] and antiinsectant[10] activities.

Asperparalines and related compounds have a common unique diazabicyclo[2.2.2]octane skeleton formed from biosynthetic intramolecular [4+2] cycloaddition.[11] Asperparalines and asperdillimides have also 3-*spiro*-succinimide which is rare in naturally occurring products.[12] Previously, we reported the model studies for constructing spirosuccinimide from 2,2-dimethylcyclopentanone as shown in Scheme 1.[13]

Our retro-synthetic plan for asperparaline C (**4**) is shown in Figure 2. Following the results of our previous model studies for the construction of spirosuccinimide from cyclopentanone (Scheme 1),[13] tetracyclic ketone **1** could be a precursor for introducing the spirosuccinimide. The energy minimized 3D-structure of α,β-unsaturated dinitrile **10**,[14] which would be derived from ketone **1** by Knoevenagel condensation based on the model study,[13] indicated that a Michael-type nucleophilic attack such as the cyanide anion to the β-position of an unsaturated system would occur from the convex face to produce the corresponding trinitrile possessing the correct stereochemistry at C-3 (asperparaline numbering) in accord with asperparaline. The ketone **1** could be transformed from enone **11** by stereoselective 1,4-addition of methylamine

Keywords: Asperparaline; Pauson–Khand reaction; Indolidine alkaloid; Paralytic activity; Spiro-succinimide.
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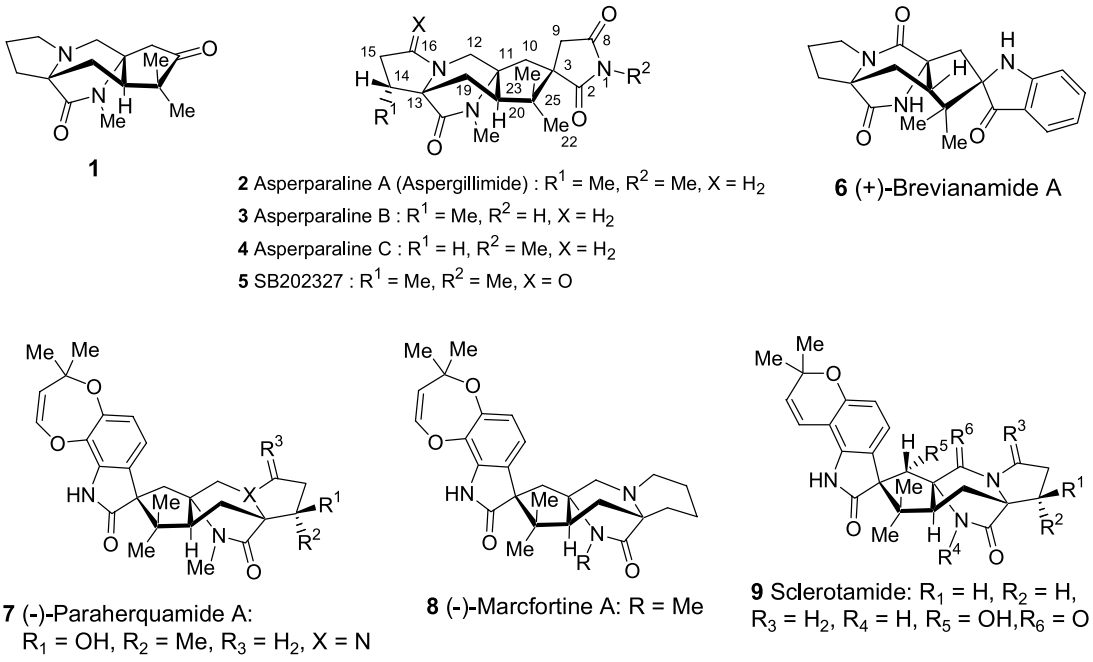
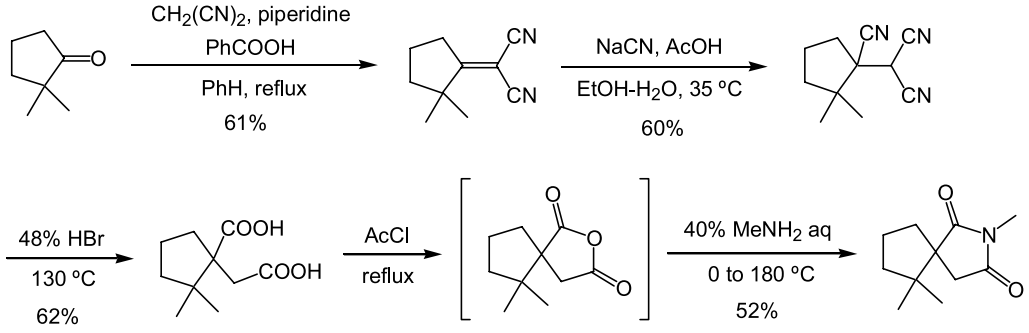


Figure 1. Asperparaline and related methabolites.



Scheme 1. Model studies for the synthesis of 3-spiro-succinimide.[13]

followed by intramolecular amide formation with an ester. The 3D structure of enone **11** suggested that the amine would attack from the same face with the ester group at C-13 (asperparaline numbering) to produce the desired stereochemistry at C-11. The precursor of **11** would be enyne **12** by the transformation using Pauson–Khand [2+2+1] cycloaddition reaction. The reaction would proceed via the stable conformer **13** other than **14** to produce **11**, as a major product. Enyne **12** could be prepared starting from L-proline as a chiral form by the use of Seebach's protocol[5] for synthesizing chiral α-substituted proline.

2. Results and discussion

We initially intended to establish the synthetic route by the use of readily available racemic material. The racemic enyne **12** was prepared from *N*-Cbz-proline by the standard method involving the sequential alkylation of ester enolate, deprotection, followed by *N*-alkylation via **15** and **18** (Scheme 2). Disappointingly, the Pauson–Khand reaction of **12** under various conditions (Table 1) gave no desired product **11**. Probably, the approach of the cobalt complex formed on alkyne to alkene would be prevented due to the steric bulk of the terminal geminal dimethy group. To confirm this speculation, two enynes, allyl proline **21** and crotyl proline **22**, were synthesized along the same reaction sequences. Indeed, as shown in Table 2, allyl proline **21** yielded tricyclic enone **23** in high yield by the use of a stoichiometric amount of cobalt (0) octacarbonyl in THF in the presence of DMSO as promoter[15] as a single stereoisomer. At this point, the stereochemistry of the newly produced C-20 position (asperparaline numbering) of enone **23** was tentatively estimated by molecular calculation as follows. A plausible mechanism of the Pauson–Khand reaction is shown in Scheme 3.[3] The stereo-discrimination step should be the stage from complex **25** to metallacycle **26**. Although the best way to predict the stereochemical outcome would be to calculate the transition state energy of every possible conformer of **25**, it is necessary to use an accurate molecular calculation program. We conducted the calculation with **26** instead of transition state **25** based upon the hypothesis that the steric energy of **26** would reflect that

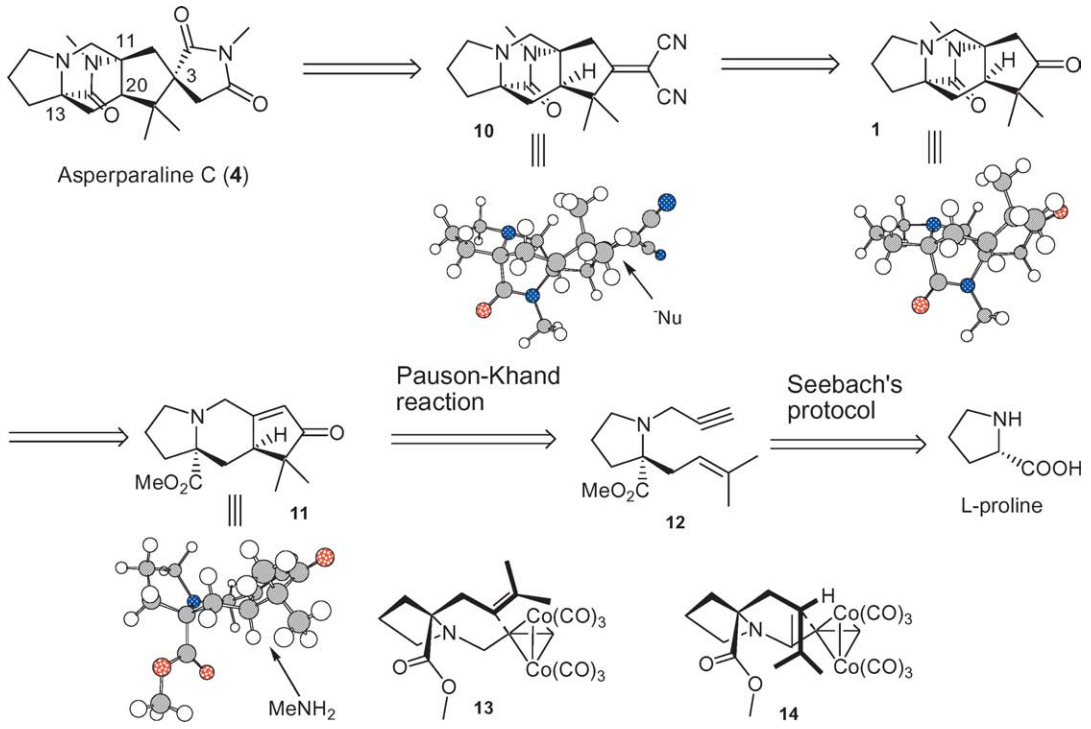
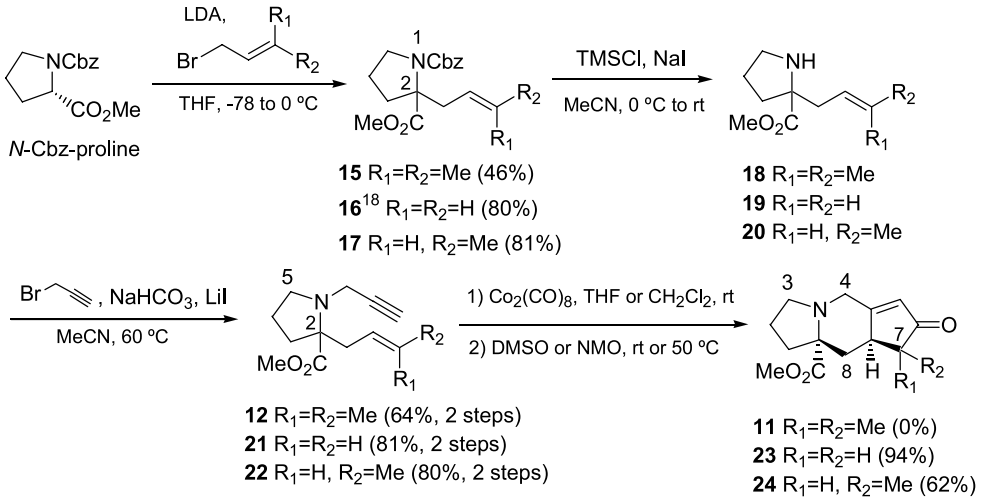
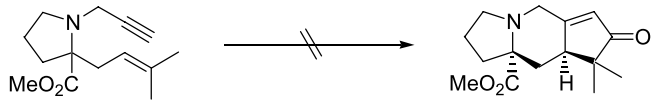


Figure 2. Retro-synthetic approach to asperparaline C.



Scheme 2. Synthesis of racemic enone **11**, **23** and **24**.

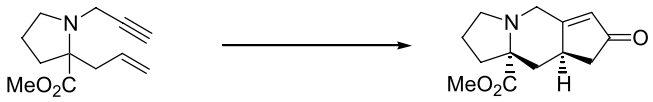
Table 1. Reaction condition from enyne **12** to enone **11**



12 **11**

Entry	$Co_2(CO)_8$ (equiv)	Solvent	Conditions for the formation of cobalt–alkyne complex	Promoter	Conditions for the reaction of cobalt–alkyne complex with alkene	Yield (%)
1	1.05	THF	Ar, rt, 2 h	DMSO (6 equiv)	Ar, 50 °C, 72 h	0
2	1.05	CH_2Cl_2	Ar, rt, 2 h	NMO (9 equiv)	Ar, rt, 96 h	0
3	1.0	THF	Ar, rt, 2 h	NMO (6 equiv)	Ar, rt, 15 h	0
4	1.05	THF	Ar, rt, 2 h	TMANO·$2H_2O$ (6 equiv)	Ar, rt, 12 h	0
5	1.0	THF	Ar, rt, 2 h	TMANO (6 equiv)	Ar, rt, 24 h	0

Table 2. Reaction conditions for the synthesis of enone **23**



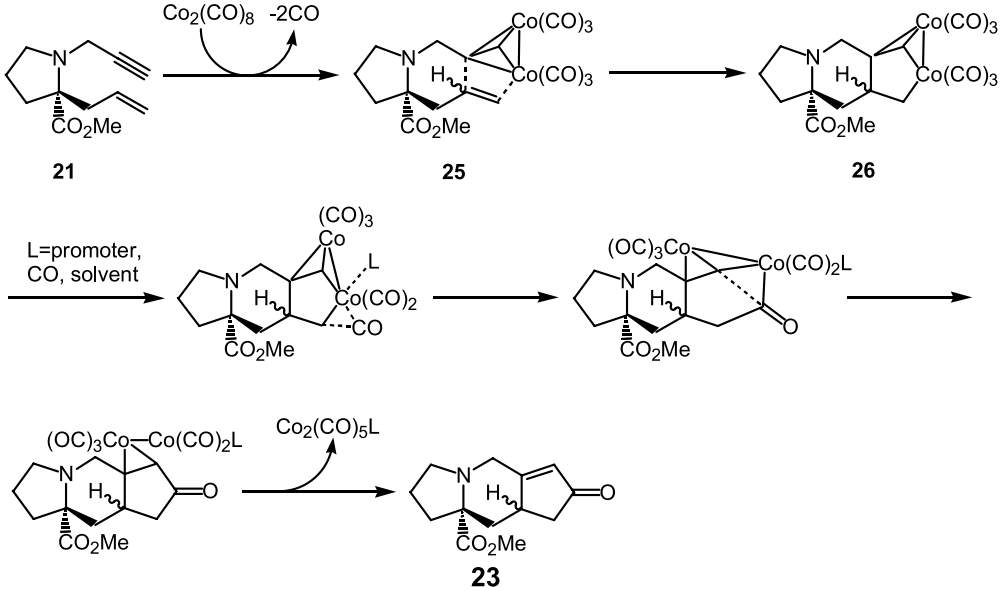
21 **23**

Entry	$Co_2(CO)_8$ (equiv)	Solvent	Conditions for the formation of cobalt–alkyne complex	Promoter	Conditions for the reaction of cobalt–alkyne complex with alkene	Isolated yield (%)
1	1.2	CH_2Cl_2	CO, rt, 2 h	NMO (6 equiv)	CO, rt, 22 h	72
2	1.1	PhH	Ar, rt, 2 h	DMSO (0.1 equiv)	O_2, 50 °C, 72 h	46
3	1.05	THF	Ar, rt, 2 h	DMSO (6 equiv)	Ar, 50 °C, 26 h	94
4	0.1	DME	CO, rt, 10 min	CO	CO, 60 °C, 42 h	6

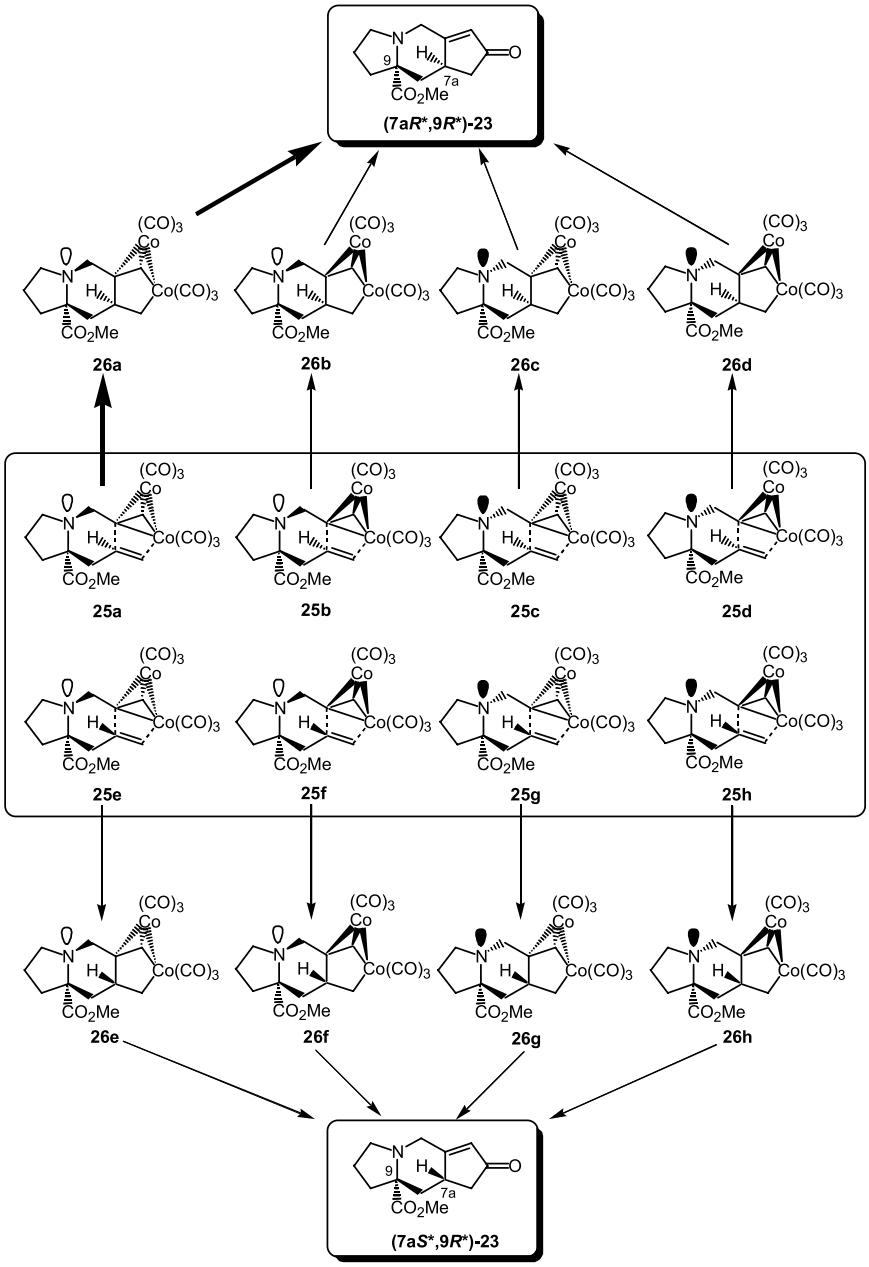
of **25**. The possible conformer of transition state **25** would be **25a** to **25h** (Scheme 4) and the corresponding metallacycle **26a** to **26d** should afford enone (7a*R**,9*R**)-**23**; on the other hand, **26e** to **26h** from **25e** to **25h** should provide diastereomer (7a*S**,9*R**)-**23**. Table 3 shows the calculated steric energy of **26a** to **26h**, the difference in energy between **26b** to **26h** and the most stable conformer **26a**, the equilibrium constants based on Boltzmann equation, the calculated distribution of **26a** to **26h**, and the ratio of formation on (7a*R**,9*R**)-**23** and (7a*S**,9*R**)-**23** based on the MM2 calculation composed in Chem3D program.[14] The carbonyl group on cobalt was replaced to hydrogen to simplify the calculation. These results well reflected the experimental results.

The formation of bridged lactam was studied using enone **23** (Table 4). Thus, enone **23** was treated with methyl amine in the presence of additives followed by acidic treatment to produce lactam **27** in excellent yield as a single diastereomer. The reaction pathway was assumed as follows shown in Scheme 5. The first Michael-type addition of methylamine to enone **23** would give intermediate **28** stereoselectively (not isolated), then spontaneous intramolecular lactam formation afforded imine **29**. Acidic treatment to hydrolyze imine **29** would produce the desired lactam **27**. Especially, silica gel in aqueous methanol was extremely effective (Table 4, entry 5). The relative stereochemistry of **27** and also the precursor enone **23** became undoubtedly apparent by this transformation, because another Michael adduct **30** from stereoisomer 7a-*epi*-**23** could not cyclyze to lactam as shown in Scheme 5. It was assumed that the attack of methylamine to enone **23** would occur from the convex face of the molecule, predominantly. Consequently, the chirality of the quaternary carbon of enyne **21** was effectively transformed into C-1 and C-5 of the product **27** via the Pauson–Khand reaction followed by Michael-type addition.

Unfortunately, introduction of a geminal dimethyl group on enone **23** at C7 position was ineffective to yield the desired **11** in only 3% yield along with mono methylated **24** (14%) and recovered **23** (28%) by treatment of **23** with LDA and MeI in the presence of HMPA at −78 °C (Scheme 6). We next examined the cycloaddition of enyne **22** possessing a crotyl side chain. Although the efficiency rather declined in comparison to **21**, the enone **24** was obtained in 62% yield in a ratio of 4:1 based on the stereochemistry of the secondary methyl group at C7 (Table 5). Introduction of a lacked



Scheme 3. Plausible mechanism of Pauson–Khand reaction.

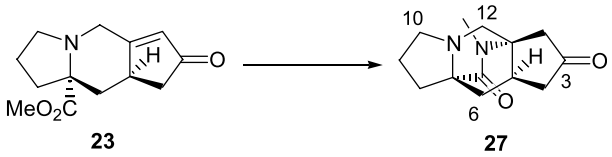


Scheme 4. Reaction pathway from transition state **25** to enone **23** via metallacycle **26**.

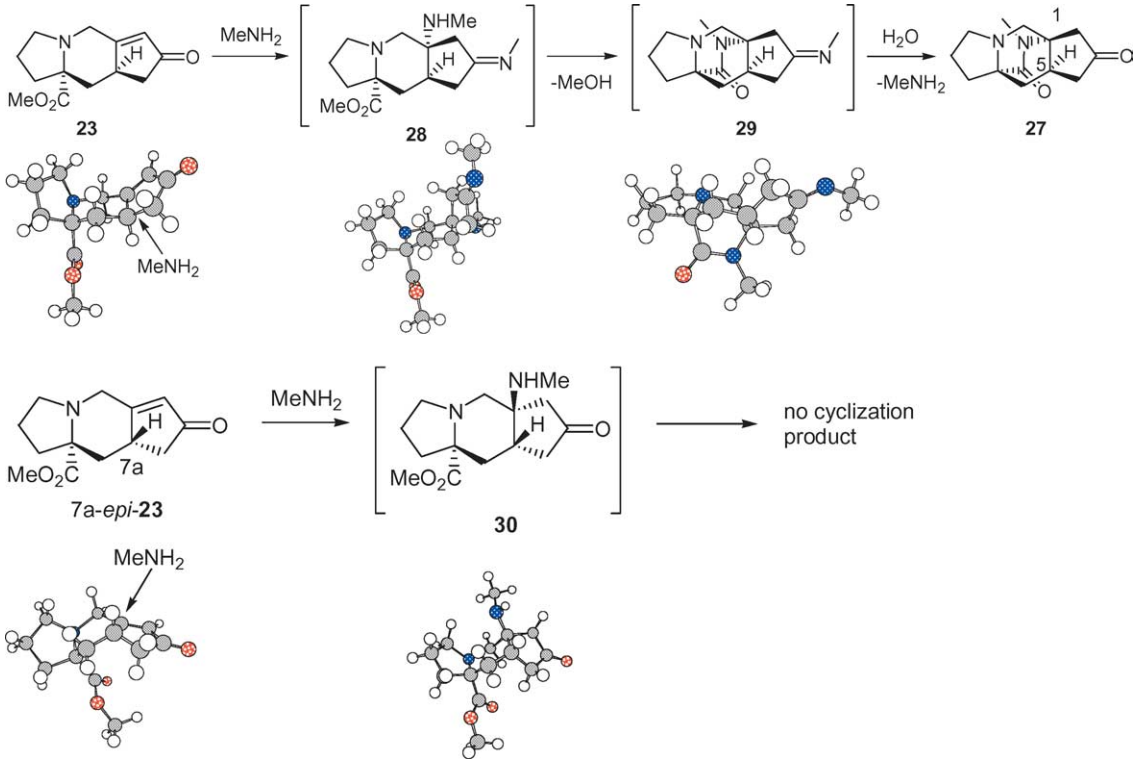
Table 3. Calculated product distribution based on steric energy of metallacycle **26**

	26a	**26b**	**26c**	**26d**
Steric energy (kcal/mol)	299.55	301.62	300.97	302.66
Difference of steric energy to **26a** (kcal/mol)	0	2.07	1.42	3.11
Equilibrium constant	1	3.97×10^{-2}	1.09×10^{-1}	7.90×10^{-3}
Calculated distribution	85.8	3.41	9.35	6.78×10^{-1}
Total distribution of (7a*R**,9*R**)-**23** (%)			99	
	26e	**26f**	**26g**	**26h**
Steric energy (kcal/mol)	302.58	304.63	307.35	305.54
Difference of steric energy to **26a** (kcal/mol)	3.03	5.08	7.80	5.99
Equilibrium constant	8.87×10^{-3}	3.67×10^{-4}	5.28×10^{-6}	8.92×10^{-5}
Calculated distribution	7.61×10^{-1}	3.15×10^{-2}	4.53×10^{-4}	7.65×10^{-3}
Total distribution of (7a*S**,9*R**)-**23** (%)			1	

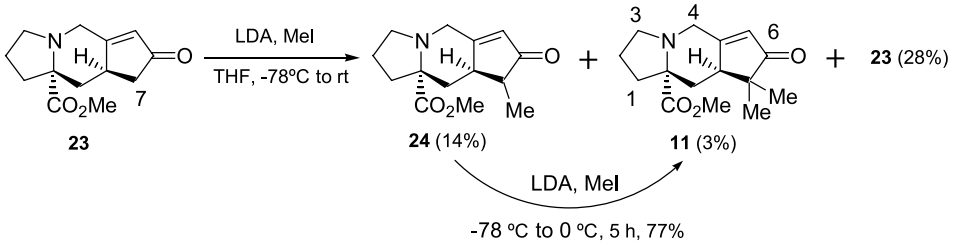
Table 4. Reaction conditions for the synthesis of lactam **27** from enone **23**



Entry	Conditions	Isolated yield (%)
1	(1) 40% $MeNH_2$ aq (20 equiv), Na_2CO_3 (0.2 equiv), rt, 24 h (2) Concd HCl, rt, 24 h→40 °C, 3 h	52
2	(1) 40% $MeNH_2$ aq (20 equiv), Na_2CO_3 (0.05 equiv), rt, 15 h (2) Concd HCl, 45 °C, 24 h	57
3	(1) 40% $MeNH_2$ aq (20 equiv), $NaHCO_3$ (0.1 equiv), rt, 13 h (2) Concd HCl, rt, 7 h	60
4	(1) 40% $MeNH_2$ aq (20 equiv), $MeNH_3Cl$ (0.2 equiv), rt, 21 h (2) Concd HCl, 45 °C, 13 h	69
5	(1) 40% $MeNH_2$ aq (20 equiv), $MeNH_3Cl$ (0.2 equiv), rt, 16 h (2) SiO_2, MeOH–H_2O, rt–45 °C, 7 h	95

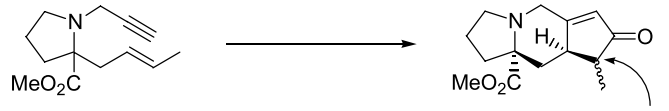


Scheme 5. Reaction pathway from enone **23** to lactam **27**.



Scheme 6. Introduction of methyl group at C7 of enone **23**.

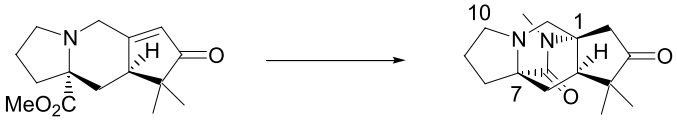
Table 5. Reaction conditions for the synthesis of enone **24** from enyne **22**



22 **24**

Entry	$Co_2(CO)_8$ (equiv)	Solvent	Conditions for the formation of cobalt–alkyne complex	Promoter	Conditions for the reaction of cobalt–alkyne complex with alkene	Isolated yield (%)
1	1.0	THF	Ar, rt, 2 h	DMSO (6 equiv)	Ar, 50 °C, 35 h	34
2	1.0	THF	Ar, rt, 2 h	DMSO (12 equiv)	Ar, 50 °C, 72 h	48
3	1.0	CH_2Cl_2	Ar, rt, 2 h	TMANO (9 equiv)	Ar, rt, 21 h	53
4	1.0	CH_2Cl_2	Ar, rt, 2 h	NMO (9 equiv)	Ar, rt, 15 h	53
5	1.0	CH_2Cl_2	Ar, rt, 2 h	NMO (9 equiv)	Ar, rt, 24 h→O_2, 1 h	62

Table 6. Reaction conditions for the synthesis of lactam **1** from enone **11**



11 **1**

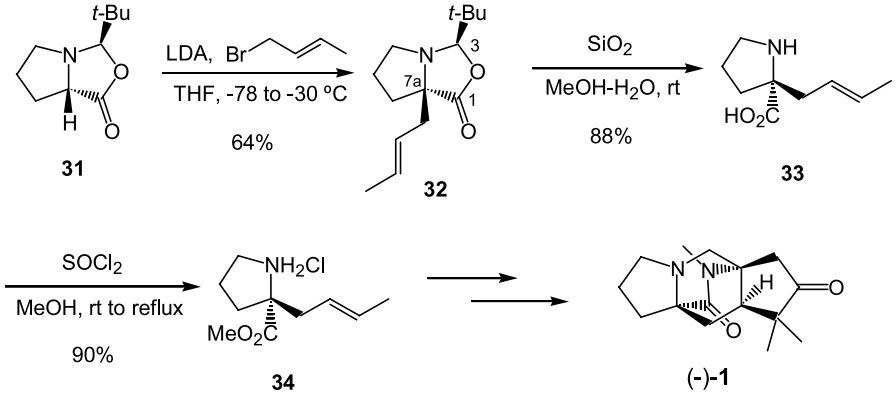
Entry	Conditions	Isolated yield (%)
1	(1) 40% $MeNH_2$ aq (20 equiv), $MeNH_3Cl$ (0.2 equiv), rt, 16 h (2) Concd HCl, 45 °C, 18 h→rt, 41 h	28
2	(1) 40% $MeNH_2$ aq (20 equiv), $MeNH_3Cl$ (0.5 equiv), rt, 96 h (2) SiO_2, MeOH, H_2O, reflux, 4 h	39
3	(1) 40% $MeNH_2$ aq (20 equiv), $MeNH_3Cl$ (0.5 equiv), rt, 48 h (2) SiO_2, MeOH, H_2O, rt, 18 h→reflux, 1 h	39
4	(1) 40% $MeNH_2$ aq (40 equiv), rt, 48 h→reflux, 4 h (2) SiO_2, MeOH, H_2O, rt, 18 h	70

methyl group on **24** was successfully accomplished to give enone **11** in 77% yield by treatment with LDA and MeI (Scheme 6). The lactam formation of **11** needed stronger conditions (Table 6) to produce racemic lactam **1** in 70% yield again as a single diastereomer.

As the synthetic route to **1** was established as racemic form, we next examined the chiral synthesis of **1** and also a catalytic approach for the key Pauson–Khand reaction.

The optically active indolidine **1** was synthesized starting from chiral crotyl proline **34**, prepared from bicyclic compound **31**[5] via **32** and **33** by the stereoselective crotylation, hydrolysis, followed by esterification (Scheme 7), by the same reaction sequence as the racemic series.

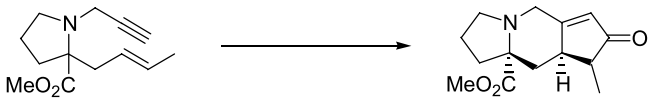
The catalytic Pauson–Khand reaction[4] was successively introduced as shown in Table 7. The reaction was undertaken under a carbon monoxide atmosphere using a catalytic amount of $Co_2(CO)_8$ and NMO as promoter to yield **24** in moderate yield. The efficiency was almost the same as that of the stoichiometric series (see Table 5).



31 **32** **33** **34** **(-)-1**

Scheme 7. Synthesis of chiral indolidine (−)-**1**.

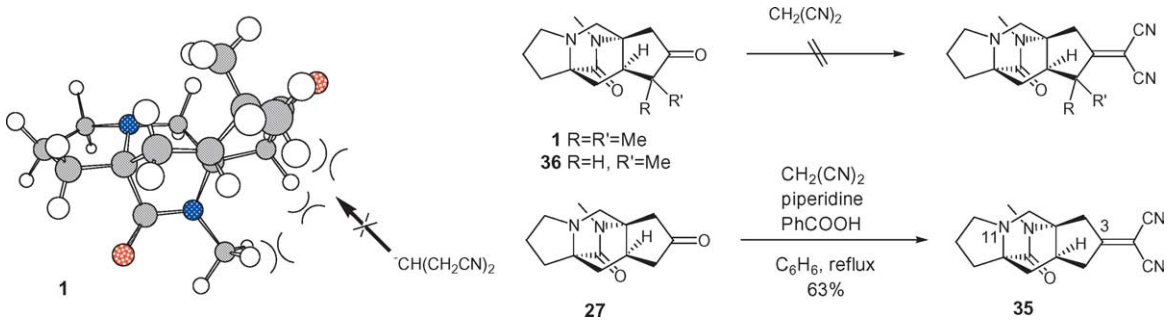
Table 7. Catalytic Pauson–Khand reaction of enyne **22** to enone **24**



22 **24**

Entry	$Co_2(CO)_8$ (equiv)	Solvent	Conditions	Promoter (equiv)	Isolated yield (%)
1	0.05	CH_2Cl_2	CO, 22 h, rt	NMO (0.05)	23 (76)[a]
2	0.05	Benzene	CO, 22 h, 70 °C	NMO (0.05)	54 (26)[a]
3	0.05	Toluene	CO, 22 h, 120 °C	NMO (0.05)	49 (33)[a]

[a] Values in parentheses represent recovery yields of compound **22**.



Scheme 8. Knoevenagel reaction of lactams.

The next stage was set for the construction of 3-*spiro*-succinimide relying on our earlier study (Scheme 1).[13] Unfortunately, the Knoevenagel reaction of ketone **1** with malononitrile under the same reaction condition as the model studies and also stronger conditions such as heating and using a Lewis acid catalyst[16] gave no desired product.[17] The results would be attributed to the additional steric bulk by the bridged lactam on the convex face from which the nucleophile would approach and also the neighboring geminal dimethyl group and hydrogens, one of which would occupy pseudo axial position, respectively, to carbonyl group. Energy minimized conformation of **1** suggested that the *N*-methyl group would shield the convex face of the molecule and the pseudo axial methyl group and hydrogen would also prevent the nucleophilic attack (Scheme 8). To confirm this point, the Knoevenagel reaction of **27** and **36**, derived from enone **24** in 73% yield by the same procedure as the synthesis of **1** and **27**, was examined. Although unsaturated dinitrile **35** was obtained in 63% yield, **36** gave no condensed product.

3. Conclusion

In summary, a concise and stereocontrolled approach for the construction of tetracyclic indolidine **1**, a common structural motif for the biologically active alkaloid asperparaline series of natural products and a potential intermediate for asperparaline C (**4**), has been demonstrated in 8 steps in 12% overall yield starting from L-proline as a chiral process. This protocol constitutes the following three key features: (i) an efficient synthesis of chiral enyne **22** using Seebach's protocol from L-proline; (ii) a stereocontrolled catalytic Pauson–Khand cycloaddition reaction (from **22** to **24**); (iii) a novel facile formation of bridged lactam (from **11** to **1**). The molecular modeling calculation using a popular program (Chem3D) satisfactorily predicted the stereochemical outcome in the key metal-mediated cycloaddition step (from **21** to **23**) and this assumption was confirmed later by the chemical transformation (from **23** to **27**). Further study directed toward the total synthesis of asperparaline C (**4**) from tetracycle **1** by another approach is currently under investigation.

In addition, biological tests for most of the synthetic compounds described in this paper were conducted. As a result, all compounds have not revealed remarkable paralysis against silkworms at a dose of 0.1 mg of diet and also agrochemical profiles on the usual random screening program such as antifungal, insecticidal, and herbicidal activity at 100 ppm. The results suggested that the whole molecular architecture of asperparaline should be essential for exhibiting biological activities.

4. Experimental

4.1. General

Infrared (IR) spectra were recorded on a Perkin–Elmer FT-IR 1760X spectrometer. NMR spectra were recorded on a JEOL JNM-GX 270 spectrometer, operating at 270 MHz for ^{1}H NMR and 67.5 MHz for ^{13}C NMR. Chemical shifts in $CDCl_3$ are reported on the δ scale relative to $CHCl_3$ (7.26 ppm for ^{1}H NMR and 77.00 ppm for ^{13}C NMR) as an internal reference. The following abbreviations are used to multiplicities: 's' (singlet), 'd' (doublet), 't' (triplet), 'm' (multiplet), 'br' (broad). Optical rotations were measured on a JASCO DIP-360 polarimeter. Mass spectra were measured on a JEOL JNM-AX 500 mass spectrometer. Column chromatography was carried out with silica gel Merck 60 (230–400 mesh ASTM). Reactions were carried out in dry solvents under an argon atmosphere. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl.

Dichloromethane (CH_2Cl_2) was distilled from calcium hydride. Other reagents were purified by usual methods.

4.1.1. 2-(3-Methyl-but-2-enyl)-pyrrolidine-1,2-dicarboxylic acid 1-benzyl ester 2-methyl ester (15), 2-allyl-pyrrolidine-1,2-dicarboxylic acid 1-benzyl ester 2-methyl ester (16), and 2-but-2-enyl-pyrrolidine-1,2-dicarboxylic acid 1-benzyl ester 2-methyl ester (17). 15% *n*-BuLi in hexane (18.8 mL, 30.4 mmol) was added slowly to a solution of diisopropylamine (3.08 g, 4.27 mL, 30.4 mmol) in anhydrous THF (100 mL) at −78 °C under nitrogen atmosphere and stirred for 30 min at 0 °C. After cooling to −78 °C, *N*-Cbz-proline methyl ester (5.0 g, 19.0 mmol) in anhydrous THF (25 mL) was added over 20 min. After stirring for 1 h, HMPA (6.81 g, 6.61 mL, 38.0 mmol) was added dropwise over 5 min and stirred for 10 min. Crotyl bromide (3.13 mL, 30.4 mmol) in anhydrous THF (25 mL) was added over 1 h and warmed to 0 °C over 30 min and stirred for 1 h at 0 °C. 1 N HCl solution (50 mL) was added to the reaction mixture and the organic layer was separated. The water layer was extracted with ethyl acetate (50 mL) and the combined organic layer was washed with satd aq $NaHCO_3$ (30 mL) and brine (30 mL) and dried over $MgSO_4$. Concentration in vacuo gave a crude product, which was purified by silica gel column chromatography (eluting with EtOAc–hexane=1:9) to give crotyl proline methyl ester **17** (4.88 g, 81%) as a pale yellow oil. R_f=0.67 (EtOAc–hexane=1:2, I_2). IR (NaCl, film) ν_{max} cm^{-1}: 2954, 2881, 1742 (ester C=O), 1704 (carbamate C=O), 1408, 1357, 1169, 1120, 1025, 699. ^1H NMR δ ($CDCl_3$): 1.64 (3H, d, J=6.4 Hz, CH=CH–CH_3), 1.77–2.15 (4H, m), 2.48–3.07 (2H, m, CH_2–CH=CH), 3.47 (2H, s, O–CH_2–Ph), 3.70 (3H, s, O–CH_3), 5.11 (1H, dd, J=12.2, 47.3 Hz), 5.14 (1H, br s), 5.23–5.38 (1H, m), 5.38–5.58 (1H, m), 7.32–7.37 (5H, m, Ph). ^{13}C NMR δ ($CDCl_3$): 18.2, 18.7, 23.3, 36.6, 48.3, 52.1, 67.0, 68.2, 125.0, 127.5, 127.5, 127.7, 127.8, 128.0, 130.3, 136.9, 154.0, 174.6. FAB MS *m/z* (%):318 (MH^+, 19), 274 ($[M-CO_2]^+$, 9), 182 ($[M-Cbz]^+$, 16). HRMS (FAB) *m/z* (MH^+): calcd for $C_{18}H_{24}NO_4$, 318.1705; found, 318.1694.

Compound **15**. Pale yellow oil. R_f=0.61 (EtOAc–hexane=1:2, I_2). IR (NaCl, film) ν_{max} cm^{-1}:2955, 2880, 1742 (ester C=O), 1705 (carbamate C=O), 1409, 1355, 1127, 1028, 699. ^1H NMR δ ($CDCl_3$): 1.58 (3H, s), 1.70 (3H, s), 1.74–2.08 (4H, m), 2.58–3.05 (2H, m, CH_2–CH=C(CH_3)$_2$), 3.46 (2H, s, O–CH_2–Ph), 3.71 (3H, s, O–CH_3), 4.97–5.24 (3H, m), 7.26–7.36 (5H, m, Ph). ^{13}C NMR δ ($CDCl_3$) *cis*+*trans* rotamers: 18.1, 18.1, 22.8, 23.3, 26.1, 26.2, 31.9, 33.2, 35.7, 37.1, 48.4, 49.2, 52.1, 52.4, 66.6, 67.0, 68.0, 68.8, 118.3, 118.5, 127.5, 127.7, 127.8, 128.0, 128.3, 128.3, 135.1, 135.3, 136.3, 136.9, 154.0, 154.2, 174.7, 174.8. FAB MS *m/z* (%): 332 (MH^+, 15), 288 ($[M-CO_2]^+$, 10), 196 ($[M-Cbz]^+$, 8). HRMS (FAB) *m/z* (MH^+): calcd for $C_{19}H_{26}NO_4$, 332.1862; found, 332.1850.

Compound **16**.[18] Pale yellow oil. R_f=0.59 (EtOAc–hexane=1:2, I_2).IR (NaCl, film) ν_{max} cm^{-1}: 2954, 2880, 1742 (ester C=O), 1704 (carbamate C=O), 1408, 1357, 1170, 1119, 1026, 699. ^1H NMR δ ($CDCl_3$): 1.82–2.16 (4H, m), 2.56–2.72 (1H, m, *H*–CH–CH=CH_2), 2.88–3.17 (1H, m, *H*–CH–CH=CH_2), 3.47 (2H, s, O–CH_2–Ph), 3.71 (3H, s, O–CH_3), 5.00–5.23 (4H, m), 5.62–5.80 (1H, m, C*H*=CH_2), 7.27–7.37 (5H, m, Ph). ^{13}C NMR δ ($CDCl_3$): 18.0, 28.5, 35.3, 43.0, 50.7, 66.1, 69.0, 117.3, 127.3, 127.6, 128.1, 128.5, 128.6, 140.6, 140.9, 159.3, 174.1.

4.1.2. 2-(3-Methyl-but-2-enyl)-1-prop-2-ynyl-pyrrolidine-2-carboxylic acid methyl ester (12), 2-allyl-1-prop-2-ynyl-pyrrolidine-2-carboxylic acid methyl ester (21), and 2-but-2-enyl-1-prop-2-ynyl-pyrrolidine-2-carboxylic acid methyl ester (22). Under nitrogen atmosphere, sodium iodide (7.36 g, 49.1 mmol) was added to a solution of *N*-Cbz-crotyl proline 17 (2.0 g, 6.3 mmol) in anhydrous MeCN (20 mL) and cooled to 0 °C. TMSCl (3.20 mL, 25.2 mmol) was added to the mixture and the mixture was stirred for 6 h at room temperature. After cooling to 0 °C, 1 N HCl (20 mL) was added to the mixture. After stirring for 30 min, the phases were separaterd and the water layer was washed with hexane (20 mL×2). The water layer was converted to pH 9–10 by adding 50% K_2CO_3 and extracted with methylene chloride (20 mL×3). The organic phase was washed with brine, dried over $MgSO_4$, and concentrated in vacuo to give free amine **20**.

A mixture of the above amine **20**, propargyl bromide (0.71 mL, 9.4 mmol), sodium bicarbonate (1.59 g, 18.9 mmol), LiI (84.3 mg, 0.63 mmol) in MeCN (20 mL) was heated at 60 °C with stirring for 14 h. After cooling, water (20 mL) was added to the mixture and the two layers were separated. The water layer was extracted with ether (20 mL×2) and the combined organic phase was washed with brine, dried ($MgSO_4$) and evaporated. The residue was purified by silica gel column chromatography (EtOAc–hexane=1:19) to give enyne **22** (1.12 g, 80%) as a colorless oil. R_f=0.72 (EtOAc–hexane=1:2, I_2). IR (NaCl, film) ν_{max} cm^{-1}: 3300 (C≡*C*–*H*), 2950, 2856, 1728 (C=O), 1435, 1195, 970, 651. ^1H NMR δ ($CDCl_3$): 1.65 (3H, d, J=7.1 Hz, CH=CH–CH_3), 1.72–1.90 (3H, m), 2.16–2.26 (3H, m), 2.60 (1H, dd, J=7.0, 13.7 Hz, *H*–CH–CH=CH–CH_3), 2.72–2.84 (1H, m), 3.16–3.22 (1H, m), 3.34 (1H, dd, J=2.4, 16.8 Hz, *H*–CH–C≡CH), 3.61 (1H, dd, J=2.4, 16.8 Hz, *H*–CH–C≡CH), 3.68 (3H, s, O–CH_3), 5.30–5.41 (1H, m, CH=C*H*–CH_3), 5.46–5.59 (1H, m, C*H*=CH–CH_3). ^{13}C NMR δ ($CDCl_3$): 18.2, 21.4, 33.9, 37.7, 38.2, 51.2, 51.3, 69.7, 71.3 (C≡*C*H), 80.9 (*C*≡CH), 125.8 (CH=*C*H–CH_3), 128.7 (*C*H=CH–CH_3), 173.7. FAB MS *m/z* (%): 222 (MH^+, 13), 190 ($[M-OMe]^+$, 56), 162 ($[M-CO_2Me]^+$, 100). HRMS (FAB) *m/z* (MH^+): calcd for $C_{13}H_{20}NO_2$, 222.1494; found, 222.1499.

Compound **12**. R_f=0.79 (EtOAc–hexane=1:2, I_2). IR (NaCl, film) ν_{max} cm^{-1}: 3298 (C≡*C*–*H*), 2951, 1727 (C=O), 1435, 1195, 1175, 647. ^1H NMR δ ($CDCl_3$): 1.63 (3H, s), 1.70 (3H, s), 1.58–1.86 (3H, m), 2.19–2.24 (3H, m), 2.65 (1H, dd, J=7.6, 14.3 Hz, *H*–CH–CH=C(CH_3)$_2$), 2.74–2.83 (1H, m, H–C5), 3.17–3.24 (1H, m, H–C5), 3.34 (1H, dd, J=2.4, 16.8 Hz, *H*–CH–C≡CH), 3.67 (3H, s, O–CH_3), 3.60–3.68 (1H, m), 5.02–5.08 (1H, m, C*H*=C(CH_3)$_2$). ^{13}C NMR δ ($CDCl_3$):18.1, 21.4, 26.1, 33.6, 34.0, 37.8, 51.2, 51.3, 70.0 (C2), 71.3 (C≡*C*H), 81.0 (*C*≡CH), 119.0 (*C*H=C(CH_3)$_2$), 134.2 (CH=*C*(CH_3)$_2$), 173.7 (C=O). FAB MS *m/z* (%): 236 (MH^+, 31), 176 ($[M-CO_2Me]^+$, 38), 166 ($[M-CH_2CH=C(CH_3)_2]^+$, 100). HRMS (FAB) *m/z* (MH^+): calcd for $C_{14}H_{22}NO_2$, 236.1651; found, 236.1628.

Compound **21**. R_f=0.72 (EtOAc–hexane=1:2, I_2). IR (NaCl, film) ν_{max} cm^{-1}: 3299, 2952, 2837, 1727 (C=O), 1641 (C=C), 1433, 1197, 1171, 989, 918, 649. ^1H NMR δ ($CDCl_3$): 1.81–1.88 (3H, m), 2.18–2.23 (2H, m), 2.32 (1H, dd, J=7.1, 14.3 Hz, *H*–CH–CH=CH_2), 2.65 (1H, dd, J=7.3, 14.6 Hz, *H*–CH–CH=CH_2), 2.77–2.85 (1H, m), 3.17–3.23 (1H, m), 3.35 (1H, dd, J=7.6, 15.6 Hz, *H*–CH–C≡CH), 3.61 (1H, dd, J=7.4, 15.4 Hz, *H*–CH–C≡CH), 3.68 (3H, s, O–CH_3), 5.06–5.13 (2H, m, CH=CH_2), 5.69–5.85 (1H, m, C*H*=CH_2). ^{13}C NMR δ ($CDCl_3$): 21.4, 33.9, 37.6, 39.3, 51.2, 51.3, 69.2, 71.3 (C≡*C*H), 80.8 (*C*≡CH), 118.0 (CH=*C*H_2), 133.5 (*C*H=CH_2), 173.6.

4.1.3. 6-Oxo-2,3,6,7,7a,8-hexahydro-1*H*,4*H*-3a-aza-s-indacene-8a-carboxylic acid methyl ester (23) and 7-methyl-6-oxo-2,3,6,7,7a,8-hexahydro-1*H*,4*H*-3a-aza-s-indacene-8a-carboxylic acid methyl ester (24).

4.1.3.1. Synthesis of 23 by a stoichiometric Pauson–Khand reaction (Table 2, entry 3). To a stirred solution of $Co_2(CO)_8$ (0.31 g, 0.91 mmol) in dry THF (9 mL) under Ar at room temperature was added dropwise a solution of enyne **21** (0.19 g, 0.91 mmol) in THF (1 mL). After 2 h of stirring at room temperature, DMSO (0.39 mL, 5.46 mmol) was added in one portion. The reaction mixture was stirred for 26 h at 50 °C. After cooling, the mixture was filtered through Celite, which was thoroughly washed with acetone. The solvent was eliminated under reduced pressure, and the crude product was purified by silica gel column chromatography (eluting with hexane: EtOAc=1:1) to give enone **23** (201 mg, 94%) as a pale yellow crystal. R_f=0.25 (EtOAc). Mp 80.2–81.1 °C. $[\alpha]_D^{18}$ +34.1° (*c* 1.9, $CHCl_3$). IR (NaCl, film) ν_{max} cm^{-1}:2954, 1713 (C=O), 1630 (C=C), 1445, 1198, 1152. ^1H NMR δ ($CDCl_3$): 1.37 (1H, t, J=12.5 Hz, H–C8), 1.73–2.19 (5H, m), 2.57–2.66 (2H, m, H_2–C7), 2.70–2.77 (1H, m, H–C7a), 2.91 (1H, dd, J=7.3, 16.5 Hz, H–C3), 3.09–3.17 (1H, m, H–C3), 3.79 (3H, s, O–CH_3), 3.79–3.94 (2H, m, H_2–C4), 5.98 (1H, br s, H–C5). ^{13}C NMR δ ($CDCl_3$): 21.0, 36.5, 38.1, 38.7, 42.0, 47.8, 49.9, 52.1, 67.3 (C8a), 128.4 (C5), 174.5 (C4a), 176.4 (*C*O_2Me), 207.7 (C6). FAB MS *m*/*z* (%): 236 (MH^+, 69), 176 ($[M-CO_2Me]^+$, 100). HRMS (EI) *m*/*z* (M^+): calcd for $C_{13}H_{17}O_3N$, 235.1209; found, 235.1220.

4.1.3.2. Synthesis of 24 by a catalytic Pauson–Khand reaction (Table 7, entry 2). To a stirred solution of $Co_2(CO)_8$ (37 mg, 0.11 mmol) in dry benzene (50 mL) under CO atmosphere at room temperature was added dropwise a solution of enyne **22** (500 mg, 2.26 mmol) in benzene (5 mL). After 2 h of stirring at room temperature, NMO (50% in water, 0.028 mL, 0.11 mmol) was added in one portion. The reaction mixture was stirred for 22 h at 70 °C. After cooling, the mixture was filtered through Celite, which was thoroughly washed with acetone. The solvent was eliminated under reduced pressure, and the crude product was purified by silica gel column chromatography (eluting with hexane–EtOAc=1:1) to give enone **24** (304 mg, 54%) as a brown oil and recovered enyne **22** (130 mg, 26%). R_f=0.30 (EtOAc, I_2). $[\alpha]_D^{22}$ +44.9°(*c* 1.0, $CHCl_3$). IR (NaCl, film) ν_{max} cm^{-1}: 2957, 2878, 1728 (ester C=O), 1708 (ketone C=O), 1632 (C=C), 1449, 1176. ^1H NMR δ ($CDCl_3$): 1.07 (3H, d, J=7.3 Hz, CH_3–C7), 1.36 (1H, t, J=12.9 Hz, H-8), 1.73–1.85 (1H, m, H–C1), 1.85–1.95 (2H, m, H_2–C2), 1.99 (1H, dq, J=2.9, 7.3 Hz, H–C7), 2.16 (1H, dt, J=12.2, 7.1 Hz, H–C1), 2.27–2.36 (1H, m, H–C7a), 2.67 (1H, dd, J=5.6, 12.9 Hz, H–C8), 2.93 (1H, dd, J=8.5, 15.3 Hz, H–C3), 3.12 (1H, dd, J=8.5, 15.3 Hz, H–C3), 3.68–3.92 (2H, m, H_2–C4), 3.79 (3H, s, O–CH_3), 5.95 (1H, br s, H–C5); ^{13}C NMR δ ($CDCl_3$): 14.2, 21.0, 36.5, 37.8, 46.4, 47.8, 47.9, 50.0, 52.1, 67.3 (C8a), 127.2 (C5), 174.0 (C4a), 174.5 (*C*O_2Me), 209.9 (C6). EI-MS *m*/*z* (%): 249 (M^+, 39), 190 ($[M-CO_2Me]^+$, 32), 154 (100), 136 (83). HRMS (EI) *m*/*z* (M^+): calcd for $C_{14}H_{19}NO_3$, 249.1365; found, 249.1382.

4.1.4. 7,7-Dimethyl-6-oxo-2,3,6,7,7a,8-hexahydro-1*H*,4*H*-3a-aza-s-indacene-8a-carboxylic acid methyl ester (11).

15% *n*-BuLi in hexane (2.61 mL, 4.21 mmol) was added slowly to a solution of diisopropylamine (0.43 g, 0.59 mL, 4.21 mmol) in anhydrous THF (15 mL) at −78 °C under nitrogen atmosphere and stirred for 30 min at 0 °C. After cooling to −78 °C, enone **24** (350 mg, 1.40 mmol) in anhydrous THF (1.5 mL) was added to the above solution over 5 min. After stirring for 5 min, HMPA (0.50 g, 0.49 mL, 2.81 mmol) was added dropwise and stirred for 10 min. MeI (0.80 g, 0.35 mL, 5.61 mmol) was added and stirred for 1 h at −78 °C. Saturated aqueous NaCl (15 mL) was added and the organic layer was separated. The water layer was extracted with ethyl acetate (30 mL) and the combined organic layer was washed with brine (30 mL) and dried over $MgSO_4$. Concentration in vacuo gave a residue, which was purified by silica gel column chromatography (hexane–EtOAc=3:2) to give enone **11** (285 mg, 77%) as a pale yellow oil. R_f=0.30 (EtOAc, I_2). $[\alpha]_D^{22}$ +18.1° (*c* 0.65, $CHCl_3$); IR (NaCl, film) ν_{max} cm^{-1}: 2965, 2869, 1729 (ester C=O), 1708 (ketone C=O), 1633 (C=C), 1449, 1191, 1152. ^1H NMR δ ($CDCl_3$): 0.92 (3H, s, CH_3–C6), 1.03 (3H, s, CH_3–C6), 1.26–1.38 (1H, m, H–C8), 1.71–1.88 (3H, m), 2.04–2.13 (1H, m), 2.27–2.39 (2H, m), 2.92 (1H, dd, J=7.6, 15.6 Hz, H–C12), 3.12 (1H, dd, J=7.5, 15.4 Hz, H–C12), 3.72 (3H, s, O–CH_3), 3.79–3.87 (2H, m, H_2–C2), 5.83 (1H, br s, H–C4). ^{13}C NMR δ ($CDCl_3$): 20.4, 21.0, 25.2, 33.8, 36.7, 46.3, 48.0, 49.7, 50.0, 52.1, 67.2, (C8a), 125.3 (C5), 174.0 (C4a), 174.5 (*C*O_2Me), 209.9 (C6). EI-MS *m*/*z* (%): 263 (M^+, 100), 204 ($[M-CO_2Me]^+$, 82), 154 (62), 136 (43). HRMS (EI) *m*/*z* (M^+): calcd for $C_{15}H_{21}NO_3$, 263.1521; found, 263.1544.

4.1.5. 11,13-Diaza-4,4,13-trimethyltetracyclo-[5.5.2.0^{1,5}.0^{7,11}]tetradecane-3,14-dione (1), 11,13-diaza-13-methyltetracyclo[5.5.2.0^{1,5}.0^{7,11}]tetradecane-3,14-dione (27), and 11,13-diaza-4,13-dimethyltetracyclo-[5.5.2.0^{1,5}.0^{7,11}]tetradecane-3,4-dione (36).

A solution of enone **11** (0.2 g, 0.76 mmol) in 40% aqueous methylamine (2.62 mL, 30.4 mmol) was stirred for 48 h at room temperature. Water (10 mL) was added to the mixture and the solution was heated at reflux for 4 h. After cooling, the mixture was concentrated in vacuo, the residue was dissolved in MeOH (6 mL) and water (1.2 mL), and SiO_2 (0.8 g) was added. The mixture was stirred for 18 h at room temperature. After cooling, the mixture was filterd and the filtrate was washed with methanol, and the solvent was concentrated in vacuo. The residue was purified by silica gel column chromatography (eluting with EtOAc–acetone=1:1) to give lactam **1** (140 mg, 70%) as a brown oil. R_f=0.7 (acetone, I_2). $[\alpha]_D^{22}$ −43.6°(*c* 0.96, $CHCl_3$). IR (NaCl, film) ν_{max} cm^{-1}: 2991, 2887, 1766

(ketone C=O), 1660, (lactam C=O), 1650, 1388, 1095. ^{1}H NMR δ ($CDCl_3$): 0.97 (3H, s, CH_3–C4), 1.07 (3H, s, CH_3–C4), 1.38–1.49 (1H, m, H–C6), 1.65–1.74 (1H, m, H–C6), 1.83–1.99 (2H, m), 2.15–2.44 (4H, m), 2.47 (1H, dd, J=1.5, 2.0 Hz), 2.53–2.67 (2H, m), 2.99 (3H, s, CH_3–N13), 3.05–3.13 (1H, m, H–C10), 3.24 (1H, d, J=11.3 Hz, H–C12). ^{13}C NMR δ ($CDCl_3$): 17.7, 20.9, 22.2, 23.1, 27.9, 29.8, 36.5, 43.9, 46.2, 52.2, 54.0, 56.0, 61.2, 173.0 (C14), 217.6 (C3). EI-MS m/z (%): 262 (M^+, 1), 247 (1), 234 (1), 219 (8), 203 (80), 190 (6), 176 (7), 165 (8), 138 (17), 133 (33), 120 (13), 96 (27), 83 (12), 68 (15), 55 (25), 41 (100). HRMS (EI) m/z (M^+): calcd for $C_{15}H_{22}N_2O_2$, 262.1681; found, 262.1679.

Compound **27**. R_f=0.43 (acetone). $[\alpha]_D^{20}$ −149.6° (c 1.1, $CHCl_3$). IR (KBr, disk) ν_{max} cm^{-1}:3440 (br), 2923, 1750 (ketone C=O), 1666 (lactam C=O), 1651, 1390, 1097. ^{1}H NMR δ ($CDCl_3$): 1.35–1.46 (1H, m, H–C6), 1.69 (1H, dd, J=5.5, 12.5 Hz, H–C6), 1.82–1.95 (2H, m), 2.16–2.36 (5H, m), 2.48–2.68 (4H, m), 2.98 (3H, s, CH_3–N13), 3.06–3.13 (1H, m, H–C10), 3.18–3.22 (1H, d, J=11.6 Hz, H–C12). ^{13}C NMR δ ($CDCl_3$): 22.2, 26.9, 27.8, 34.3, 40.9, 42.6, 45.5, 53.7, 53.8, 62.8, 66.0 (C7), 172.8 (C14), 211.4 (C3). EI MS m/z (%): 234 (M^+, 5), 206 (3), 175 (100), 149 (51), 137 (21), 108 (12), 96 (20). HRMS (EI) m/z (M^+): calcd for $C_{13}H_{18}N_2O_2$, 234.1368; found, 234.1349.

Compound **36**. R_f=0.49 (acetone, I_2). Mp 116–118.2 °C. IR (KBr, disk) ν_{max} cm^{-1}: 2980, 2875, 2798, 1746 (ketone C=O), 1662 (lactam C=O), 1651, 1390, 1324, 1098. ^{1}H NMR δ ($CDCl_3$): 1.15 (3H, d, J=7.0 Hz, CH_3–C4), 1.36–1.48 (1H, m, H–C6), 1.64–1.73 (1H, m, H–C6), 1.84–1.96 (3H, m), 2.18–2.39 (4H, m), 2.51–2.64 (3H, m), 2.98 (3H, s, CH_3–N13), 3.05–3.13 (1H, m, H–C10), 3.24 (1H, d, J=11.3 Hz, H–C12). ^{13}C NMR δ ($CDCl_3$): 12.8, 22.1, 26.6, 27.6, 33.4, 44.1, 47.9, 48.3, 53.7, 54.7, 60.9, 65.8, 172.6 (C14), 213.4 (C3). EI-MS m/z (%): 249 (MH^+, 56), 189 (37), 154 (100), 136 (89). HRMS (EI) m/z (M^+): calcd for $C_{14}H_{20}N_2O_2$, 248.1525; found, 248.1521.

4.1.6. 7a-But-2-enyl-3-*tert*-butyl-tetrahydro-pyrrolo-[1,2-*c*]oxazol-1-one (32). 15% n-BuLi in hexane (28.71 mL, 46.4 mmol) was added slowly to a solution of diisopropylamine (6.52 mL, 46.4 mmol) in anhydrous THF (100 mL) at −78 °C under nitrogen atmosphere and stirred for 30 min at 0 °C. After cooling to −78 °C, oxazolidone **31** (5.00 g, 27.3 mmol) in anhydrous THF (25 mL) was added over 20 min. After stirring for 1 h, HMPA (9.49 mL, 54.6 mmol) was added dropwise over 5 min and stirred for 10 min. Crotyl bromide (4.77 mL, 46.4 mmol) in anhydrous THF (25 mL) was added over 1 h and stirred for 1 h at −78 °C. The mixture was warmed to −30 °C over 1 h and saturated aqueous $NaHCO_3$ (50 mL) was added. The organic layer was separated. The water layer was extracted with ethyl acetate (50 mL) and the combined organic layer was washed with satd aq $NaHCO_3$ (50 mL) and brine (50 mL) and dried over $MgSO_4$. Concentration in vacuo gave a residue, which was purified by distillation under reduced pressure to give crotyl Oxazolidinone **32** (3.78 g, 64%) as a pale yellow oil. R_f=0.60 (EtOAc–C_6H_6=1:200). Bp$_3$: 85–90 °C. $[\alpha]_D^{22}$ +13.5°(c 1.0, $CHCl_3$). IR (NaCl, film) ν_{max} cm^{-1}: 2963, 2871, 1780 (C=O), 1633, 1191. ^{1}H NMR δ ($CDCl_3$): 0.92 (9H, s), 1.64 (3H, d, J=7.1 Hz, CH=CH–CH_3), 1.73–1.90 (4H, m), 2.35 (2H, d, J=7.4 Hz, CH_2–CH=CH), 2.74–2.99 (2H, m), 4.24 (1H, s), 5.46–5.58 (2H, m). ^{13}C NMR δ ($CDCl_3$): 17.3, 21.1, 21.2, 21.3, 28.8, 34.3, 36.8, 49.5, 107.1, 124.8, 133.1, 174.5 (C=O). FAB MS m/z (%): 238 (MH^+, 4), 180 ([M−t-Bu]$^+$,100), 135 (89). HRMS (FAB) m/z (MH^+): calcd for $C_{14}H_{24}NO_2$, 238.1807; found, 238.1834.

4.1.7. 2-But-2-enyl-pyrrolidine-2-carboxylic acid (33). A mixture of crotyl oxazolidone **32** (3.0 g, 13.4 mmol) and silica gel (SiO_2, 3.0 g) in MeOH/H_2O (6:1, 30 mL) was stirred for 48 h at room temperature. After filtration, the residue was washed with MeOH and the filtrate was concentrated in vacuo. The residue was dissolved in $CHCl_3$/MeOH (20:1, 30 mL) and again filtered. The residue was washed with $CHCl_3$/MeOH (20:1) and the filtrate was concentrated in vacuo. The residue was washed with ether and dried over P_2O_5 under reduced pressure to give carboxylic acid **33** (2.0 g, 88%) as a colorless crystal. R_f=0.23 (MeOH–$CHCl_3$=1:4, ninhydrin).Mp 280–285 °C. $[\alpha]_D^{20}$ −70.4°(c 1.0, CH_3OH). IR (KBr, disk) ν_{max} cm^{-1}: 3085, 1628 (C=O), 1390, 933. ^{1}H NMR δ (D_2O): 1.64 (3H, d, J=6.4 Hz, CH=CH–CH_3), 1.73–1.90 (4H, m), 2.24 (1H, dd, J=7.1, 14.6 Hz, H–CH–CH=CH), 2.69 (1H, dd, J=7.3, 14.6 Hz, H–CH–CH=CH), 2.88–3.03 (2H, m), 5.46–5.58 (2H, m). ^{13}C NMR δ (D_2O): 17.3, 22.6, 31.3, 37.8, 42.5, 77.1, 123.8, 133.2, 179.5 (CO_2H). FAB MS m/z (%):170 (MH^+, 100), 124 ([M−CO_2H]$^+$, 100). HRMS (FAB) m/z (MH^+): calcd for $C_9H_{16}NO_2$, 170.1181; found, 170.1100.

4.1.8. (*R*)-2-(−)-Crotylproline methyl ester hydrochloride (34). Thionyl chloride (4.31 mL, 59.1 mmol) was added dropwise to a solution of α-crotyl proline **33** (2.00 g, 11.82 mmol) in anhydrous MeOH (50 mL) at 0 °C and the mixture was stirred for 48 h at room temperature. After refluxing for 1 h, the mixture was concentrated in vacuo. The residue was crystallized in MeOH/EtOAc followed by drying over P_2O_5 under reduced pressure to give methyl ester **34** (2.34 g, 90%) as a colorless crystal. R_f=0.74 (MeOH–$CHCl_3$=1:4, ninhydrin). Mp 166.5–170.0 °C. $[\alpha]_D^{22}$ −48.7°(c 1.0, CH_3OH). IR (KBr, disk) ν_{max} cm^{-1}: 2880, 2711, 2490, 1759 (C=O), 1644 (C=C), 1588, 1341, 1220, 1154, 946. ^{1}H NMR δ (CD_3OD): 1.73 (3H, d, J=6.4 Hz, CH=CH–CH_3), 1.88–2.50 (4H, m), 2.71 (1H, dd, J=7.1, 14.6 Hz, H–CH–CH=CH), 2.93 (1H, dd, J=7.1, 14.6 Hz, H–CH–CH=CH), 3.40–3.48 (2H, m), 3.89, (3H, s, O–CH_3), 5.55–5.78 (2H, m). ^{13}C NMR δ (CD_3OD): 17.6, 20.8, 31.3, 37.8, 42.2, 50.7, 67.7, 123.1, 133.0, 174.5.

4.1.9. 11,13-Diaza-3-(dicyanomethylene)-13-methyl-tetracyclo-[5.5.2.0^{1,5}.0^{7,11}]tetradecan-14-one (35). The lactam **27** (90.3 mg, 0.385 mmol) and malononitrile (51 mg, 0.77 mmol) were added to benzene (10 mL) containing piperidine (7.99 mg, 0.039 mmol) and benzoic acid (18.8 mg, 0.154 mmol), and the mixture was heated to reflux with azeotropic removal of water by Dean–Stark trap for 28 h. After cooling, the mixture was diluted with diethyl ether (20 mL), and successively washed with water (10 mL), a 10% $NaHCO_3$ solution (10 mL) and brine (10 mL). The organic phase was dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by flash chromatography over silica gel (eluting with EtOAc) to give unsaturated dinitrile **35** (68.5 mg, 63%) as an pale yellow

crystal. $R_f = 0.70$ (acetone, I_2). Mp 151.6–153.0 °C. IR (KBr, disk) ν_{max} cm^{-1}:3437 (br), 2946, 2806, 2234 (C≡N), 1661 (amide C=O), 1620 (C=C), 1386, 1320, 1103. ^1H NMR δ ($CDCl_3$): 1.34–1.46 (1H, m, H–C6), 1.68 (1H, dd, $J = 6.3$, 13.2 Hz, H–C6), 1.80-1.92 (2H, m), 2.13–2.39 (5H, m), 2.48–2.72 (4H, m), 2.96 (3H, s, CH_3–N13), 3.01–3.15 (1H, m, H–C10), 3.21 (1H, dd, $J = 7.8$, 20.0 Hz, H–C12). ^{13}C NMR δ ($CDCl_3$): 22.3, 27.0, 27.7, 33.2, 37.9, 40.3, 43.0, 53.6, 53.7, 64.7, 66.0, 84.9 ($C(CN)_2$), 110.5 (CN), 110.9 (CN), 172.5 (C14), 184.4 (C3). FAB MS *m/z* (%): 283 (MH^+, 100), 223 (53). HRMS (FAB) *m/z* (MH^+): calcd for $C_{16}H_{19}N_4O$, 283.1559; found, 283.1548.

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Orthogonality and compatibility between Tsc and Fmoc amino-protecting groups

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Abstract—New deprotection conditions that provide a complete orthogonality between Tsc and Fmoc amino-protecting groups are described. The potential of these orthogonal deprotection conditions was then demonstrated by the efficient solid-phase synthesis of branched peptides **20** and **21** using doubly protected amino acids such as Tsc-Lys(Fmoc)-OH **4c** and Fmoc-Lys(Tsc)-OH **4d**.

1. Introduction

Recently, we reported the 2-(4-trifluoromethylphenylsulfonyl)ethoxycarbonyl (Tsc) function as a novel base-labile amino-protecting group (Fig. 1).[1] The Tsc group differs from the 9-fluorenylmethoxycarbonyl (Fmoc) group regarding its less sensitivity to premature deprotection when installed on the exocyclic amino group of the heteroaromatic pyrrole (Py) and imidazole (Im) amino acids. The higher efficiency of Tsc compared to Fmoc in the solid-phase synthesis of pyrrole-imidazole polyamides envisions its promising use for protecting numerous amines.

The development of orthogonal amino-protecting groups or deprotection conditions allows new strategies for the solid- and solution-phase syntheses of more complex peptides and scaffolds.[2] Although a large number of orthogonal strategies are available, a combination of amino-protecting groups both orthogonal and compatible under basic deprotection conditions is rare.[3] Here, we report a dual Tsc/Fmoc strategy that provides a convenient procedure for both the orthogonal and compatible use of such amino-protecting groups under basic deprotection conditions. Our Tsc/Fmoc strategy was successfully applied to the synthesis of branched peptides by use of amino acids bearing the Tsc/Fmoc dyad.

2. Results and discussion

2.1. Synthesis of Tsc- and Fmoc-protected amino acids and esters

In order to develop orthogonal deprotection conditions required for the Tsc/Fmoc strategy, Tsc- and Fmoc-protected amino acids and esters were prepared (Fig. 1 and Scheme 1). Tsc- and Fmoc-protected pyrrole (**1a**, **1b**), imidazole (**2a**, **2b**), and phenylalanine (**3a**, **3b**) amino esters were synthesized by direct introduction of Tsc and Fmoc into the corresponding amino esters **13**, **14**, and **15**, respectively. Tsc-protected pyrrole **1c** and imidazole **2c** amino acids were prepared from esters **13** and **14**, respectively via base-resistant 2-(4-trifluoromethylphenylthio)ethoxycarbonyl (Ttc) protection.[1] Basic ester hydrolysis of Ttc-protected esters followed by subsequent oxidative conversion of Ttc into Tsc afforded the desired amino acids **1c** and **2c**. An alternative preparation of Tsc-Phe-OEt **3a** from Ttc-Phe-OEt was performed in a similar manner. Fmoc-protected pyrrole **1d** and imidazole **2d** amino acids were synthesized as described.[4] Lysine amino esters (**4a**, **4b**) and acids (**4c**, **4d**) with N^{α}-Tsc/N^{ε}-Fmoc or N^{α}-Fmoc/N^{ε}-Tsc protecting groups were prepared by direct introduction of Tsc into H-Lys(Fmoc)-OMe **16** and Fmoc-Lys-OMe **17b** amino esters and H-Lys(Fmoc)-OH and Fmoc-Lys-OH amino acids. It is noteworthy that Tsc-protected amino acids could be prepared using Tsc-Cl or convertible Ttc-Cl.

2.2. Chemical and thermal stability of Tsc and Fmoc in the presence of *N*,*N*-diisopropylethylamine

In order to implement the Tsc/Fmoc strategy, orthogonal deprotection conditions were required. We reasoned that this should be possible given the different deprotection rates

Keywords: Tsc; Fmoc; Amino-protecting group; Orthogonal deprotection; Branched peptide.
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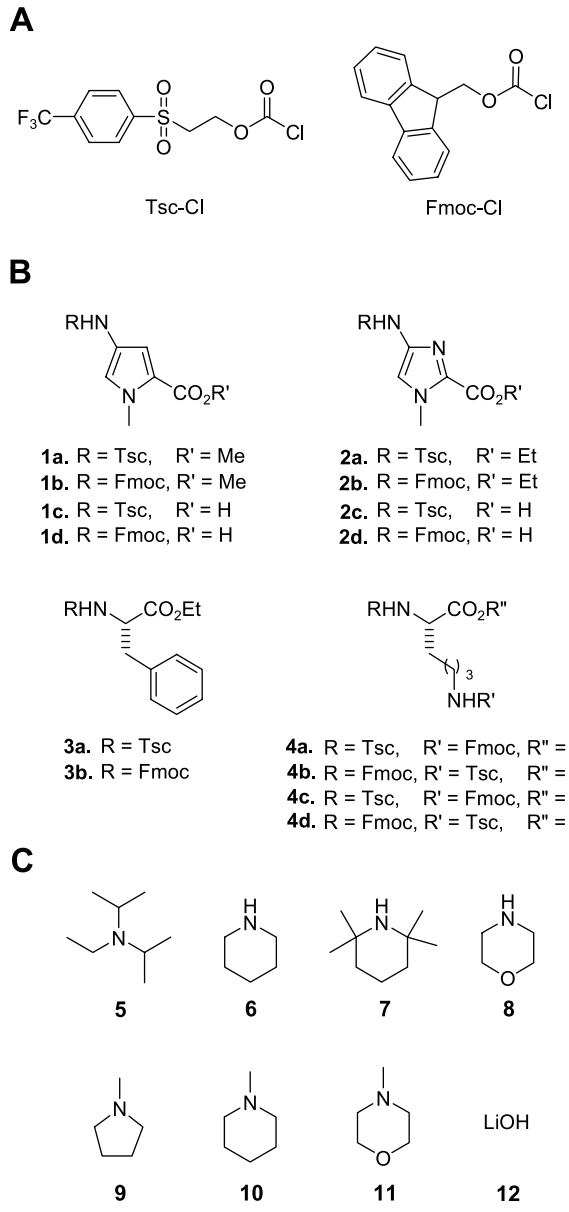
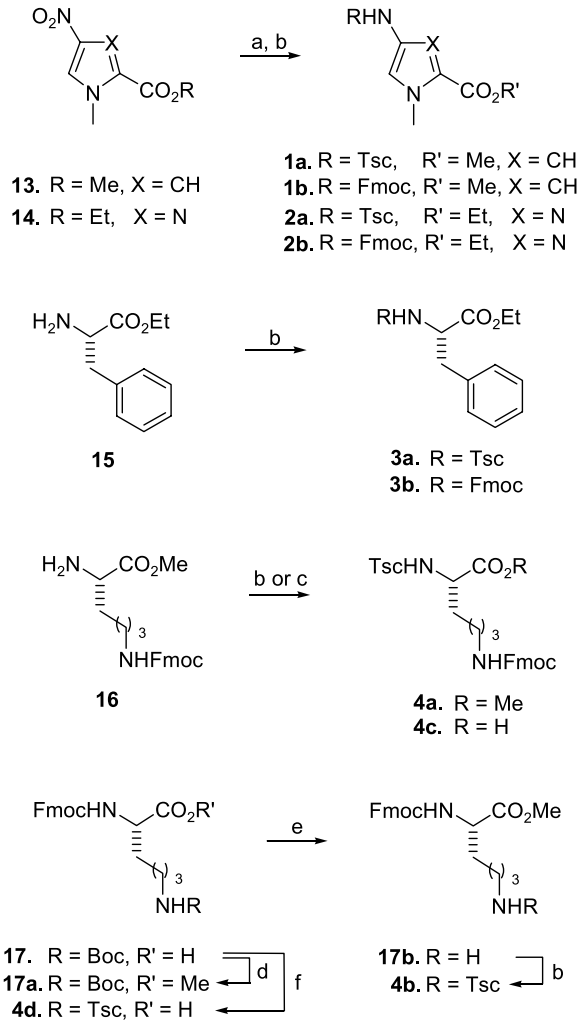


Figure 1. Structure of Tsc-Cl and Fmoc-Cl (A), Tsc- and Fmoc-protected amino acids and esters (B), and various bases tested for deprotecting Tsc and Fmoc groups (C).



Scheme 1. Reagents and conditions: (a) 10% Pd/C, 40 psi H_2, EtOAc (**13**) or DMF (**14**), rt; (b) Tsc-Cl (**1a**, 69%; **2a**, 82%; **3a**, 88%; **4a**, 92%; **4b**, 69%) or Fmoc-Cl (**1b**, 88%; **2b**, 83%; **3b**, 77%), DIEA, CH_2Cl_2, rt; (c) (i) 0.1 N LiOH, THF/H_2O (1:1), 0 °C, (ii) Tsc-Cl, $NaHCO_3$, 1,4-dioxane, rt, (**4c**, 85%); (d) CH_2N_2, CH_2Cl_2, rt, 74%; (e) 20% TFA, CH_2Cl_2, rt, (**17b** from **17a**, 88%); (f) (i) 9% TFA, CH_2Cl_2, rt, (ii) Tsc-Cl, $NaHCO_3$, 1,4-dioxane, rt, (**4d**, 38%).

of Tsc and Fmoc under basic conditions. To test such a possibility, we examined the premature deprotection of Tsc- and Fmoc-protected pyrrole and imidazole amino acids **1c**, **1d**, **2c**, and **2d** in the presence of *N*,*N*-diisopropylethylamine (DIEA, **5**) as a mild base (Fig. 2).[1,5] While both Tsc and Fmoc were completely cleaved within 5 min at room temperature by treatment with 20% (v/v) piperidine in DMF, their cleavage by 0.5 M DIEA in DMF proceeded much slower. Intriguingly, moreover, the difference in their deprotection rates is clearly significant. Careful HPLC monitoring of the decomposition of Tsc-Py-OH **1c** and Tsc-Im-OH **2c** in the presence of DIEA at 25 °C revealed that >98% of the Tsc group remained intact even after 4 h, whereas about 60 and 10% of the Fmoc groups were eliminated from Fmoc-Py-OH **1d** and Fmoc-Im-OH **2d**, respectively. Tsc-Py-OH and Tsc-Im-OH were also less prone to premature deprotection than their Fmoc analogs at higher temperature (>95% versus <50% intact after 2 h at 50 °C). Therefore, Tsc is superior to Fmoc in chemical and thermal stability when used to protect the exocyclic amino group of heteroaromatic amino acids. The higher stability of Tsc-Py-OH compared to Tsc-Im-OH is reversed in the case of Fmoc-Py-OH and Fmoc-Im-OH. Taken together, all these results indicate that the deprotection rates of Tsc and Fmoc are dependent on bases, temperature, and amino acids. Therefore, proper choice of deprotection conditions would permit the orthogonality between Tsc and Fmoc in addition to their compatibility affordable by piperidine treatment.

2.3. Orthogonal deprotection conditions for Tsc and Fmoc groups

To develop orthogonal deprotection conditions for Tsc and Fmoc, a set of deprotection conditions were evaluated using

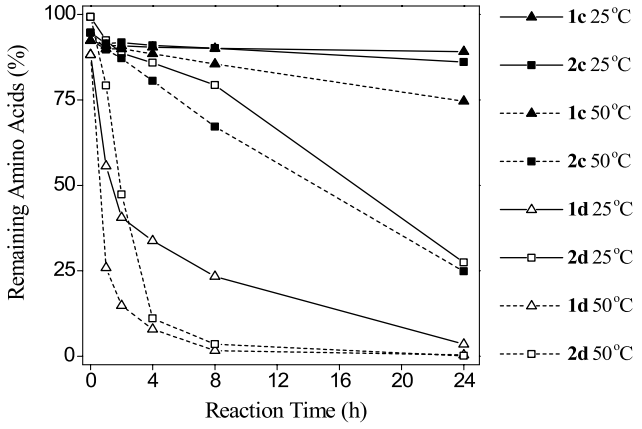
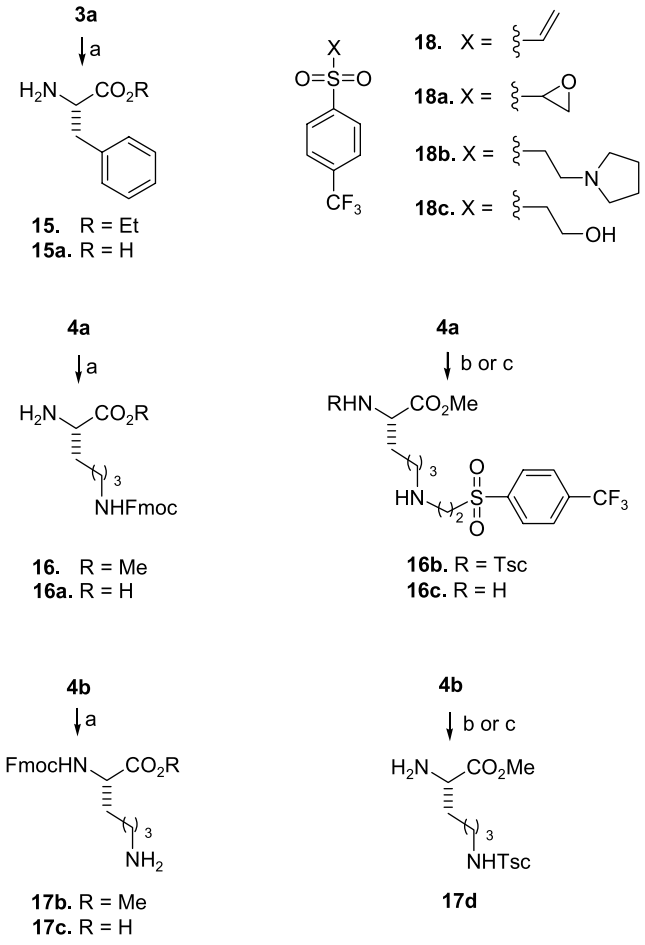


Figure 2. Effect of DIEA (**5**) on the chemical stability of amino acids at 25 or 50 °C. Time courses for the premature deprotection of amino-protecting groups in Tsc-Py-OH **1c** (▲), Tsc-Im-OH **2c** (■), Fmoc-Py-OH **1d** (△), and Fmoc-Im-OH **2d** (□) amino acids (0.1 M) were performed by their treatment with DIEA (0.5 M) in DMF at 25 °C (solid lines) or 50 °C (dashed lines). The amount of intact amino acids was determined by analytical HPLC on a Nova-Pak® C_{18} reverse-phase column (3.9×150 mm, 4 μm, Waters, Milford, MA) with UV monitoring at 280 nm under gradient conditions: 0–20 min, 5% MeCN/min, 1 mL/min flow rate.

the Tsc- (**1a**–**3a**) and Fmoc-protected (**1b**–**3b**) amino esters and basic reagents **6**–**12** (Table 1 and Scheme 2).[6] Among secondary and tertiary amines **6**–**11**, 1-methylpyrrolidine (**9**) showed a selective preference for the deprotection of Fmoc-protected amino esters **1b**–**3b** (Table 1). Complete and selective removal of Fmoc while maintaining Tsc in both heteroaromatic and aliphatic amino esters **1b**–**3b** was accomplished by using 50% 1-methylpyrrolidine in DMF for 1 h at 25 °C. We then attempted to develop conditions for the deprotection of Tsc without removing Fmoc. We found that LiOH is the reagent of choice for such purposes (Scheme 2). Fast cleavage of Tsc-protected amino ester **3a** was achieved in high yield (>99%) using 0.1 N aqueous



Scheme 2. Reagents and conditions: (a) 0.1 N LiOH, THF/H_2O (1:1), 0 °C, 5 min, (**15**, 85%, **15a**, 15%, **18a**, 77% from **3a**; **16**, 92%, **16a**, 8% from **4a**; **17b**, 75%, **17c**, 20% from **4b**); (b) 50% 1-methylpyrrolidine, DMF, 25 °C, 1 h, (**16b**, >95%; **17d**, >98%); (c) 0.5 M DIEA, DMF, 50 °C, 4 h, (**16c**, 82%; **17d**, 87%).

Table 1. Base sensitivities of the amino-protecting groups in Tsc-protected (**1a**, **2a**, and **3a**) and Fmoc-protected (**1b**, **2b**, and **3b**) amino esters[a]

		1a	2a	3a	1b	2b	3b
6	5%	H	H	H	H	H	H
	20%	H	H	H	H	H	H
	50%	H	H	H	H	H	H
7	5%	L	*M*	*L*	*M*	*M*	*L*
	20%	L	M	*L*	M	M	L
	50%	*M*	M	L	M	M	L
8	5%	*L*	*L*	*L*	*H*	*H*	M
	20%	L	L	L	H	*H*	*H*
	50%	L	L	M	H	H	*H*
9	5%	*L*	*L*	*L*	*H*	*H*	*L*
	20%	*L*	*L*	*L*	*H*	*H*	M
	50%	*L*	*L*	*L*	*H*	*H*	*H*
10	5%	*L*	*L*	*L*	M	M	M
	20%	*L*	*L*	*L*	M	M	M
	50%	*L*	*L*	*L*	M	M	M
11	5%	*L*	*L*	*L*	*L*	*L*	*L*
	20%	*L*	*L*	*L*	*L*	*L*	*L*
	50%	*L*	*L*	*L*	*L*	L	*L*

[a] Deprotection of amino esters **1a**–**3a** and **1b**–**3b** by various bases **6**–**11** was detected by HPLC monitoring of intact amino esters at 254 nm. Base sensitivity was classified based on the % amount of decomposed amino esters after their treatment (0.1 M) with bases (5, 20, and 50%) in DMF at room temperature for the indicated time: H (>90%, 5 min), *H* (>90%, 30 min), M (>90%, 2 h), *M* (>50%/<90%, 2 h), L (>10%/<50%, 2 h), *L* (<10%, 2 h).

LiOH/THF at 0 °C for 5 min wherein the occurrence of epimerization is negligible.[6a–d] Consequently, the best orthogonality between Tsc and Fmoc in terms of reactivity and selectivity in solution could therefore be achieved if Fmoc is deprotected with 50% 1-methylpyrrolidine in DMF at 25 °C for 1 h whereas Tsc is deprotected with 0.1 N LiOH in THF/H_2O (1:1) at 0 °C for 5 min.

The orthogonality of such conditions for Tsc/Fmoc deprotection was further demonstrated using doubly protected amino esters such as Tsc-Lys(Fmoc)-OMe **4a** and Fmoc-Lys(Tsc)-OMe **4b** (Scheme 2). Complete and selective cleavage of Tsc in the presence of Fmoc occurred in their treatment with LiOH/THF (Fig. 3). In addition, the selectivity of 1-methylpyrrolidine for complete Fmoc cleavage in the presence of Tsc proved to be excellent in both **4a** and **4b**. In the case of **4a**, however, **16b** rather than the desired Tsc-Lys-OMe was obtained as a major product. Presumably, the initially formed Tsc-Lys-OMe underwent the rapid conversion to **16b** by intermolecular Michael-like addition,[3j,7] which would occur more slowly in the solid-phase synthesis. Formation of free amines was accompanied by concomitant release of **18a** upon treatment of **3a** with LiOH. However, the negligible amount (<1%) of **18b** and **18c** was detected in the treatment of **4a** and **4b** with 1-methylpyrrolidine, respectively.[8]

The deprotection of Tsc with LiOH proceeded faster than ester hydrolysis. Thus, when **3a** was treated with 0.1 N LiOH, we obtained a product mixture of ethyl ester **15** (85%) and carboxylic acid **15a** (15%). The same thing happened with **4a** and **4b** that were treated with 0.1 N LiOH: 92% of ester **16** and 8% of acid **16a** from **4a**; 75% of ester **17b** and 20% of acid **17c** from **4b** (Scheme 2, and Fig. 3a and d). However, ester hydrolysis by LiOH is not expected to cause a problem in its usage for Tsc deprotection in the solid-phase peptide synthesis unless the Tsc/Fmoc/ester triad is needed due to ester groups in the side chain and/or resin linkage. In addition, it is unlikely that ester groups in the side chain limit the use of Tsc/Fmoc in tandem for preparing the Tsc/Fmoc/ester triad since base-labile Tsc could be introduced directly or via base-resistant Ttc.[9]

2.4. Synthesis of branched peptides using the Tsc/Fmoc strategy

The potential of these orthogonal deprotection conditions was then demonstrated by their use for the solid-phase synthesis of branched peptides (Scheme 3). First, the branched peptide **20** was synthesized on the Fmoc-Rink Amide MBHA resin through two methods A and B via **19a** and **19b**. Resin-bound peptides **19a** and **19b** can be branched off due to the presence of Tsc-Lys(Fmoc)-OH **4c** and Fmoc-Lys(Tsc)-OH **4d** at their N-terminus, respectively. Methods A and B differ in the order of applying Tsc and Fmoc deprotection conditions. Tsc deprotection

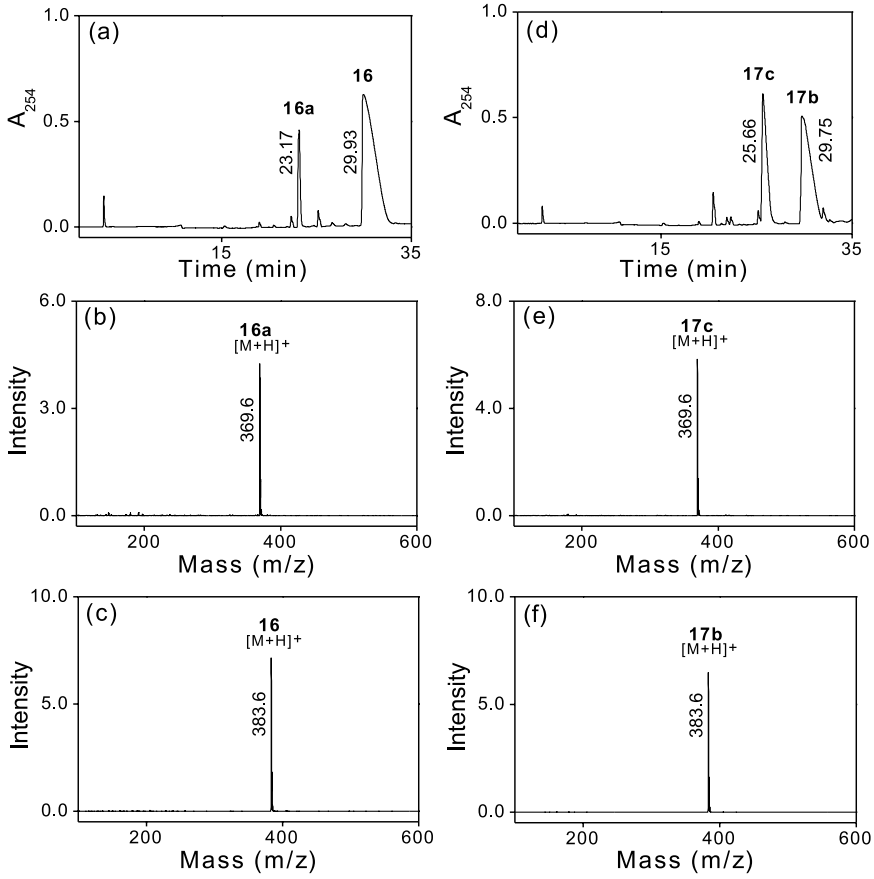
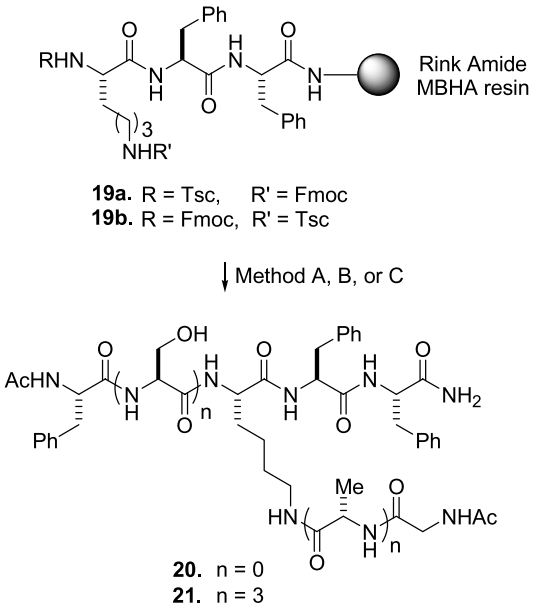


Figure 3. LC-MS analysis of a reaction mixture containing acid **16a** (23.17 min, b) and ester **16** (29.93 min, c) from **4a** (a) or acid **17c** (25.66 min, e) and ester **17b** (29.75 min, f) from **4b** (d). The reaction mixture was prepared by treating **4a** (a) or **4b** (d) with 0.1 N LiOH in THF/H_2O (1:1) at 0 °C for 5 min according to Scheme 2 and experimental 3.1.16 and 3.1.19.



Scheme 3. Reagents and conditions of method A: (a) 0.1 N LiOH, THF/H_2O (1:1), 0 °C, 10 min (LiOH); (b) Ac-Phe-OH for **19a** or Ac-Gly-OH for **19b**, PyBOP, DIEA, DMF, rt (coupling); (c) Ac_2O, DIEA, CH_2Cl_2, rt (capping); (d) 50% 1-methylpyrrolidine, DMF, rt, 1 h (MP); (e) Ac-Gly-OH for **19a** or Ac-Phe-OH for **19b**, coupling; (f) capping; (g) TFA, rt, (**20** via **19a**, 18%; **20** via **19b**, 15%). Method B: (a) MP; (b) Ac-Gly-OH for **19a** or Ac-Phe-OH for **19b**, coupling; (c) capping; (d) LiOH; (e) Ac-Phe-OH for **19a** or Ac-Gly-OH for **19b**, coupling; (f) capping; (g) TFA, rt, (**20** via **19a**, 29%; **20** via **19b**, 17%). Method C: (a) **19b**, MP; (b) Fmoc-Ser(But)-OH, coupling; (c) capping and then two repeats of (a)–(c); (d) MP; (e) Fmoc-Phe-OH, coupling; (f) capping; (g) MP; (h) capping; (i) LiOH×2 or 50% piperidine, rt, 10 min; (j) Tsc-Ala-OH, coupling; (k) capping and then two repeats of (i)–(k); (l) LiOH×2 or 50% piperidine, rt, 10 min; (m) Fmoc-Gly-OH, coupling; (n) capping; (o) 50% piperidine, rt, 10 min; (p) capping; (q) TFA, rt, (**21** via **19b**, 40% (LiOH) and 63% (piperidine)).

followed by Fmoc deprotection was carried out in method A whereas their deprotection order was reversed in method B. Peptides thus prepared were purified by reverse-phase HPLC. All the conditions afforded peptide **20** in >98% yield of each coupling step and overall recoveries between 15 and 29%. All observed molecular masses characterized by MALDI-TOF mass spectrometry agreed to within 0.1% of the calculated peptide mass. These results indicate that our Tsc/Fmoc orthogonal strategy is suitable for the preparation of branched peptides regardless of the position of Tsc and Fmoc on two amino groups of lysine and their deprotecting order.

HPLC and MALDI-TOF analyses showed that the cleaner preparation of the crude peptides was achieved using **4d** (via **19b**) compared to **4c** (via **19a**) at the branched position of **20** (Fig. 4, I, II versus III, IV). However, the crude peptide mixture prepared with **4d** (via **19b**) contained greater amounts of the Tsc-containing byproduct **20c** than the desired **20** (Fig. 4, III and IV). This result indicates that treatment of **4d** in **19b** with 0.1 N LiOH for 10 min at 0 °C is not efficient enough to give the complete deprotection of Tsc in the solid-phase peptide synthesis. Based on these results, Tsc deprotection twice with LiOH or once with piperidine was used in conjunction with **4d** for the efficient synthesis of the longer branched peptide **21**. As expected, such choices afforded peptide **21** in high isolated yield (up to 63%) (Scheme 3, Method C and Fig. 5).

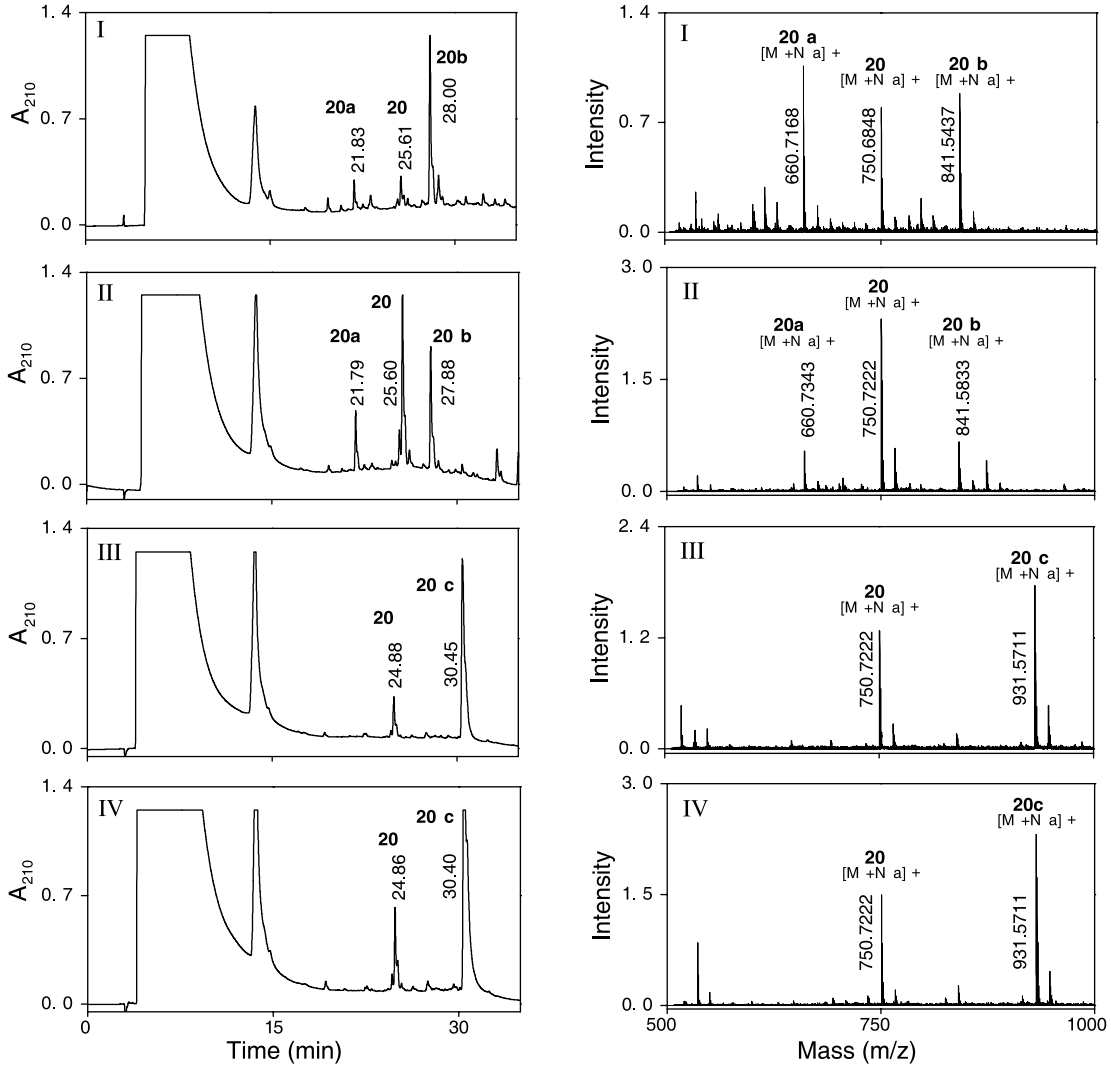
In conclusion, we have shown that 1-methylpyrrolidine and LiOH are the reagents of choice for mild and orthogonal deprotection of Fmoc and Tsc, respectively. The suitability of such conditions was demonstrated by their use for the efficient synthesis of branched peptides. Our new Tsc/Fmoc strategy should therefore greatly extend the scope of the Tsc group to dual protections under mild basic conditions. We anticipate that Tsc/Fmoc will be a potential alternative to standard Dde/Fmoc, particularly where use of the Dde amino-protecting group is not possible.[3d–f]

3. Experimental

3.1. General

^1H and ^{13}C NMR spectra were recorded on a Varian Mercury 300 or a Bruker Avance 500 NMR spectrometer. Chemical shifts (δ) are reported in parts per million (ppm) with reference to tetramethylsilane or solvent and coupling constants (J) are reported in hertz (Hz). High-resolution mass spectra (HRMS) were recorded on a JEOL JMS-AM505WA mass spectrometer using fast atom bombardment (FAB) or chemical ionization (CI) techniques. Matrix-assisted laser desorption ionization time-of-flight (MALDI-TOF) mass spectra were recorded on an Applied Biosystems Voyager-DE™ STR mass spectrometer. HPLC analysis was performed on a Waters 600 HPLC system equipped with a 2487 dual λ absorbance detector. LC-MS analysis was performed on a Hewlett-Packard HP-1100 HPLC system and a Micromass QUATTRO LC triple quadrupole tandem mass spectrometer. Thin-layer chromatography (TLC) was performed on silica gel 60 F_{254} precoated plates (0.25 mm thickness, Merck). Flash chromatography was carried out on silica gel 60 (230–400 mesh, Merck). Reagent-grade chemicals were purchased from Aldrich, Fluka, Junsei, and TCI and used as received unless otherwise specified. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl under N_2. *N*,*N*-Dimethylformamide (DMF) was distilled from calcium hydride in vacuo. Dichloromethane was distilled from calcium hydride under N_2.

3.1.1. Tsc-Py-OMe (1a). To a solution of **13** (3 g, 16.3 mmol) in EtOAc (40 mL) was added 10% Pd/C (50 mg). After stirring at room temperature for 10 h under 40 psi H_2, 10% Pd/C was removed by filtration through Celite 545 followed by washing with EtOAc and MeOH and then solvent evaporation. To a stirred solution of the resulting amine in dry CH_2Cl_2 (20 mL) was added *N*,*N*-diisopropylethylamine (DIEA, 4.11 mL, 23.6 mmol) and then Tsc-Cl[1] (5.67 g, 17.9 mmol) at 0 °C. After stirring at room temperature for 7 h, the reaction mixture was quenched with H_2O and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography (EtOAc/*n*-hexane=1:1) to give **1a** (4.90 g, 69%) as a white solid. TLC (EtOAc/*n*-hexane=1:1) R_f=0.33; ^1H NMR (300 MHz, DMSO-d_6) δ 9.30 (brs, 1H), 8.15 (d, J=8.1 Hz, 2H), 8.01 (d, J=8.4 Hz, 2H), 7.02 (d, J=2.1 Hz, 1H), 6.61 (d, J=1.8 Hz, 1H), 4.36 (t, J=5.6 Hz,



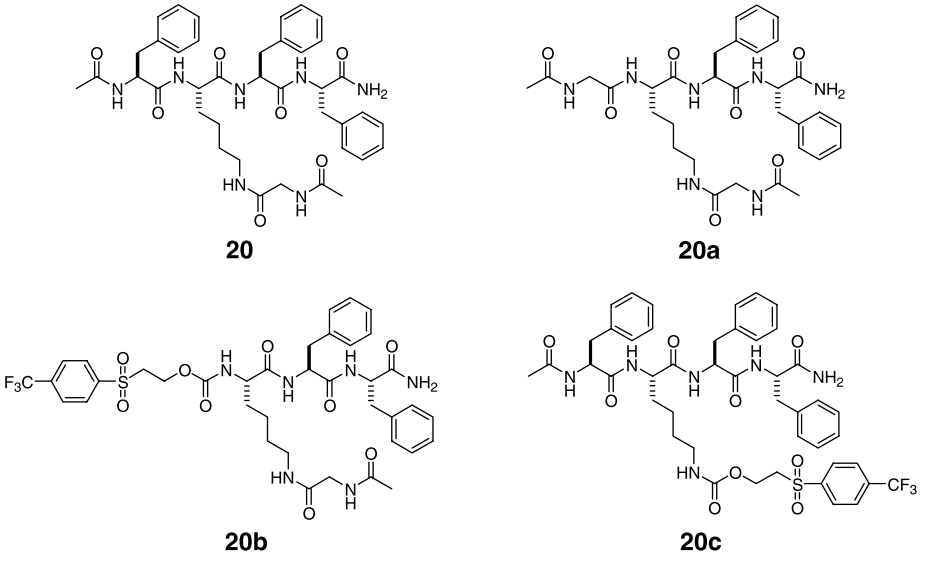


Figure 4. HPLC (left) and MALDI-TOF (right) analyses of a crude mixture containing peptide **20** (24.86–25.61 min in left) and byproducts **20a–c**. The crude mixture was prepared with **4c** (via **19a**) using method A (I) or B (II) or **4d** (via **19b**) using method A (III) or B (IV). HPLC analysis was performed on a C_{18} reverse-phase column (4.6×250 mm, 5 μm particle size, TP silica, Vydac, Hesperia, CA) with a linear H_2O/MeCN gradient containing 0.1% (v/v) TFA: 0–5 min 100% H_2O, 5–35 min 2.67% MeCN/min, 1 mL/min flow rate, 210 nm.

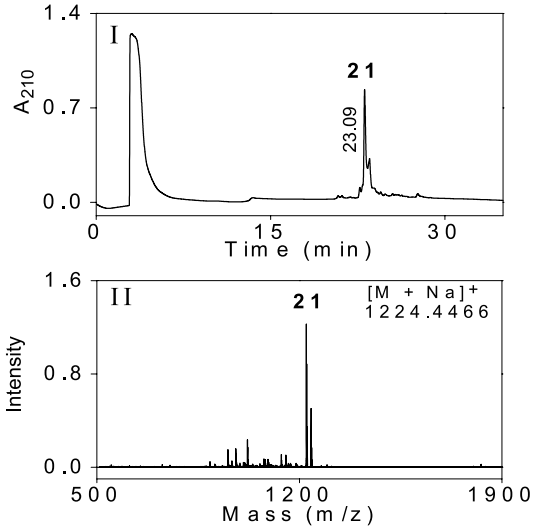


Figure 5. HPLC (I) and MALDI-TOF (II) analyses of a crude mixture containing peptide **21**. The crude mixture was prepared with **4d** (via **19b**) using method C (piperidine). The HPLC condition is identical to that of Fig. 4 except for using a linear gradient of 3.33% rather than 2.67% MeCN/min during 5–35 min.

2H), 3.86 (t, J=5.7 Hz, 2H), 3.80 (s, 3H), 3.72 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 160.68, 152.45, 143.23, 133.48 (q, J=32.3 Hz), 128.80, 126.61 (q, J=3.6 Hz), 123.35 (q, J=273.5 Hz), 122.32, 119.28, 118.82, 107.53, 57.52, 54.21, 50.92, 36.16; HRMS (FAB+) for $C_{17}H_{17}F_3N_2O_6S$ (M^+), calcd 434.0759, found 434.0765.

3.1.2. Fmoc-Py-OMe (1b). To a solution of **13** (3 g, 16.3 mmol) in EtOAc (40 mL) was added 10% Pd/C (50 mg). After stirring at room temperature for 10 h under 40 psi H_2, 10% Pd/C was removed by filtration through Celite 545 followed by washing with EtOAc and MeOH and then solvent evaporation. To a stirred solution of the resulting amine in dry CH_2Cl_2 (20 mL) was added *N*,*N*-diisopropylethylamine (4.11 mL, 23.6 mmol) and then Fmoc-Cl (4.64 g, 17.9 mmol) at 0 °C. After stirring at room temperature for 4 h, the reaction mixture was quenched with H_2O and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography (EtOAc/*n*-hexane=1:3) to give **1b** (5.41 g, 88%) as a white solid. TLC (EtOAc/*n*-hexane=1:1) R_f=0.62; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.51 (brs, 1H), 7.90 (d, J=7.5 Hz, 2H), 7.73 (d, J=7.5 Hz, 2H), 7.43 (td, J=7.2, 0.6 Hz, 2H), 7.35 (td, J=7.4, 1.1 Hz, 2H), 7.12 (d, J=1.5 Hz, 1H), 6.69 (d, J=1.8 Hz, 1H), 4.48 (d, J=6.6 Hz, 2H), 4.28 (t, J=6.3 Hz, 1H), 3.81 (s, 3H), 3.72 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 160.67, 153.28, 143.81, 140.81, 127.63, 127.10, 125.03, 122.71, 120.16, 119.28, 118.82, 107.45, 65.37, 50.91, 46.70, 36.17; HRMS (FAB+) for $C_{22}H_{20}N_2O_4$ (M^+), calcd 376.1423, found 376.1414.

3.1.3. Tsc-Im-OEt (2a). To a solution of **14** (2 g, 10.1 mmol) in DMF (20 mL) was added 10% Pd/C (45 mg). After stirring at room temperature for 10 h under 40 psi H_2, 10% Pd/C was removed by filtration through Celite 545 followed by washing with EtOAc and MeOH and then solvent evaporation. To a stirred solution of the resulting amine in dry CH_2Cl_2 (30 mL) was added *N*,*N*-diisopropylethylamine (1.93 mL, 11.1 mmol) and then Tsc-Cl (3.52 g, 11.1 mmol) at 0 °C. After stirring at room temperature for 7 h, the reaction mixture was quenched with H_2O and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography (EtOAc/*n*-hexane=3:1) to give **2a** (3.7 g, 82%) as a white solid. TLC (EtOAc/*n*-hexane=3:1) R_f=0.40; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.99 (brs, 1H), 8.12 (d, J=8.1 Hz, 2H), 7.97 (d, J=8.1 Hz, 2H), 7.20 (s, 1H), 4.34 (brt, 2H), 4.24 (q, J=7.2 Hz, 2H), 3.87 (brs, 5H), 1.27 (t, J=7.1 Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 158.37, 152.46, 143.20, 137.42, 133.40 (q, J=31.8 Hz), 131.01, 128.85, 126.54, 123.30 (q, J=272.3 Hz), 113.59, 60.46, 57.79, 54.14, 35.42, 14.08; HRMS (FAB+) for $C_{17}H_{19}F_3N_3O_6S$ (MH$^+$), calcd 450.0947, found 450.0957.

3.1.4. Fmoc-Im-OEt (2b). To a solution of **14** (2 g, 10.1 mmol) in DMF (20 mL) was added 10% Pd/C (45 mg). After stirring at room temperature for 10 h under 40 psi H_2, 10% Pd/C was removed by filtration through Celite 545 followed by washing with EtOAc and MeOH and then solvent evaporation. To a stirred solution of the resulting amine in dry CH_2Cl_2 (20 mL) was added *N*,*N*-diisopropylethylamine (1.93 mL, 11.1 mmol) and then Fmoc-Cl (2.87 g, 11.1 mmol) at 0 °C. After stirring at room temperature for 4 h, the reaction mixture was quenched with H_2O and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography (EtOAc/*n*-hexane=1:2) to give **2b** (3.27 g, 83%) as a white solid. TLC (EtOAc/*n*-hexane=1:1) R_f=0.39; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.41 (brs, 1H), 7.89 (d, J=7.5 Hz, 2H), 7.76 (d, J=6.6 Hz, 2H), 7.41 (t, J=7.4 Hz, 2H), 7.32 (t, J=7.4 Hz, 3H), 4.26 (m, 5H), 3.89 (s, 3H), 1.28 (t, J=6.8 Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 158.38, 153.27, 143.70, 140.72, 137.78, 131.10, 127.70, 127.11, 125.44, 120.12, 113.62, 66.13, 60.51, 46.45, 35.43, 14.07; HRMS (FAB+) for $C_{22}H_{22}N_3O_4$ (MH$^+$), calcd 392.1610, found 392.1605.

3.1.5. Ttc-Phe-OEt. To a stirred solution of **15**-HCl (0.5 g, 2.18 mmol) in dry CH_2Cl_2 (15 mL) was added *N*,*N*-diisopropylethylamine (0.55 mL, 3.16 mmol) and then Ttc-Cl[1] (0.93 g, 3.27 mmol) at 0 °C. After stirring at room temperature for 4 h, the reaction mixture was quenched with H_2O and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography (EtOAc/*n*-hexane=1:1) to give the title compound (778 mg, 81%) as a white solid. TLC (EtOAc/*n*-hexane=1:2) R_f=0.52; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 (d, J=8.1 Hz, 2H), 7.41 (d, J=8.4 Hz, 2H), 7.27 (m, 3H), 7.13 (dd, J=7.8, 1.8 Hz, 2H), 5.20 (d, J=8.1 Hz, 1H), 4.61 (dt, J=8.0, 6.1 Hz, 1H), 4.23 (t, J=6.8 Hz, 2H), 4.17 (q, J=7.1 Hz, 2H), 3.17 (t, J=7.1 Hz, 2H), 3.13 (dd, J=13.5, 5.4 Hz, 1H), 3.07 (dd, J=13.8, 5.7 Hz, 1H), 1.24 (t, J=7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.37, 155.24, 140.86 (q, J=1.4 Hz), 135.65, 129.28, 128.54, 127.87, 127.79 (q, J=32.6 Hz), 127.11, 125.77 (q, J=3.8 Hz), 124.04 (q, J=271.8 Hz), 63.00, 61.54, 54.73, 38.26, 31.24, 14.07; HRMS (FAB+)

for $C_{21}H_{23}F_3NO_4S$ (MH^+), calcd 442.1300, found 442.1294.

3.1.6. Tsc-Phe-OEt (3a). To a stirred solution of **15**-HCl (1.5 g, 6.53 mmol) in dry CH_2Cl_2 (20 mL) was added *N*,*N*-diisopropylethylamine (1.69 mL, 9.70 mmol) and then Tsc-Cl (2.27 g, 7.18 mmol) at 0 °C. After stirring at room temperature for 7 h, the reaction mixture was quenched with H_2O and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography (EtOAc/*n*-hexane=1:1) to give **3a** (2.72 g, 88%) as a white solid. Alternatively, **3a** was synthesized by oxidation of Ttc-Phe-OEt with H_2O_2/$NaMoO_4$ in acetone.[1] To a solution of Ttc-Phe-OEt (1.2 g, 2.71 mmol) in acetone (30 mL) was added 0.3 M aqueous Na_2MoO_4 (0.8 mL, 0.24 mmol) and 30% aqueous H_2O_2 (1.5 mL). After stirring at room temperature for 18 h, the reaction mixture was extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography (EtOAc/*n*-hexane=1:1) to give **3a** (1.18 g, 91%) as a white solid. TLC (EtOAc/*n*-hexane=1:1) R_f=0.51; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03 (d, J=8.4 Hz, 2H), 7.79 (d, J=8.4 Hz, 2H), 7.26 (m, 3H), 7.09 (dd, J=7.8, 1.5 Hz, 2H), 5.09 (d, J=8.1 Hz, 1H), 4.48 (dt, J=8.2, 6.2 Hz, 1H), 4.38 (t, J=5.9 Hz, 2H), 4.15 (q, J=7.1 Hz, 2H), 3.47 (td, J=5.9, 1.8 Hz, 2H), 3.08 (dd, J=14.1, 6.0 Hz, 1H), 3.00 (dd, J=13.7, 6.5 Hz, 1H), 1.22 (t, J=7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.01, 154.38, 142.86 (q, J=1.2 Hz), 135.50, 135.34 (q, J=33.2 Hz), 129.10, 128.72, 128.45, 127.04, 126.32 (q, J=3.7 Hz), 122.95 (q, J=273.2 Hz), 61.48, 58.08, 55.23, 54.59, 37.91, 13.92; HRMS (FAB+) for $C_{21}H_{23}F_3NO_6S$ (MH^+), calcd 474.1198, found 474.1213.

3.1.7. Fmoc-Phe-OEt (3b). To a stirred solution of **15**-HCl (1.5 g, 6.53 mmol) in dry CH_2Cl_2 (20 mL) was added *N*,*N*-diisopropylethylamine (1.69 mL, 9.70 mmol) and then Fmoc-Cl (1.86 g, 7.18 mmol) at 0 °C. After stirring at room temperature for 4 h, the reaction mixture was quenched with H_2O and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography (EtOAc/*n*-hexane=1:3) to give **3b** (2.1 g, 77%) as a white solid. TLC (EtOAc/*n*-hexane=1:2) R_f=0.45; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75 (d, J=7.2 Hz, 2H), 7.55 (dd, J=6.8, 5.0 Hz, 2H), 7.38 (t, J=7.2 Hz, 2H), 7.29 (td, J=7.4, 1.2 Hz, 2H), 7.25 (m, 3H), 7.10 (dd, J=6.6, 1.2 Hz, 2H), 5.35 (d, J=7.8 Hz, 1H), 4.65 (dt, J=8.2, 6.0 Hz, 1H), 4.43 (dd, J=10.4, 7.1 Hz, 1H), 4.32 (dd, J=10.4, 6.8 Hz, 1H), 4.19 (t, J=6.6 Hz, 1H), 4.16 (q, J=7.2 Hz, 2H), 3.14 (dd, J=13.4, 5.6 Hz, 1H), 3.08 (dd, J=13.5, 5.7 Hz, 1H), 1.22 (t, J=7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.40, 155.46, 143.76, 143.65, 141.20, 135.71, 129.28, 128.45, 127.61, 127.00, 126.96, 125.04, 124.97, 119.90, 119.88, 66.81, 61.44, 54.72, 47.05, 38.18, 14.04; HRMS (FAB+) for $C_{22}H_{26}NO_4$ (MH^+), calcd 416.1862, found 416.1856.

3.1.8. Tsc-Lys(Fmoc)-OMe (4a). To a stirred solution of **16**-HCl (200 mg, 0.477 mmol, Novabiochem, La Jolla, CA) in dry CH_2Cl_2 (20 mL) was added triethylamine (73 μL, 0.525 mmol) and then Tsc-Cl (181 mg, 0.573 mmol) at 0 °C. After stirring at room temperature for 3 h, the reaction mixture was quenched with H_2O and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography (EtOAc/*n*-hexane=1:1) to give **4a** (290 mg, 92%) as a white solid. TLC (EtOAc/*n*-hexane=2:1) R_f=0.29; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.12 (d, J=8.0 Hz, 2H), 8.01 (d, J=8.0 Hz, 2H), 7.87 (d, J=7.5 Hz, 2H), 7.66 (d, J=7.5 Hz, 2H), 7.49 (d, J=7.5 Hz, 1H), 7.40 (t, J=7.3 Hz, 2H), 7.31 (t, J=7.3 Hz, 2H), 7.24 (t, J=5.3 Hz, 1H), 4.27 (m, 3H), 4.22 (dd, J=12.5, 6.0 Hz, 1H), 4.19 (t, J=6.8 Hz, 1H), 3.88 (td, J=8.0, 5.2 Hz, 1H), 3.77 (t, J=5.3 Hz, 2H), 3.59 (s, 3H), 2.93 (q, J=6.3 Hz, 2H), 1.64–1.47 (m, 2H), 1.38–1.30 (m, 2H), 1.25–1.18 (m, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 172.58, 156.02, 155.22, 143.88, 143.26, 140.68, 133.41 (q, J=32.4 Hz), 128.79, 127.52, 126.97, 126.55 (q, J=3.4 Hz), 125.05, 123.34 (q, J=272.8 Hz), 120.05, 65.10, 57.53, 54.19, 53.74, 51.74, 46.73, 39.66, 30.18, 28.79, 22.54; HRMS (FAB+) for $C_{32}H_{34}F_3N_2O_8S$ (MH^+), calcd 663.1988, found 663.1979.

3.1.9. Fmoc-Lys(Boc)-OMe (17a). To a stirred solution of **17** (500 mg, 1.07 mmol) in dry CH_2Cl_2 (15 mL) was added diazomethane (0.8 M in dry diethyl ether) at 0 °C. After stirring at room temperature for 2 h, the reaction mixture was quenched with MeOH and extracted with CH_2Cl_2/H_2O. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography (EtOAc/*n*-hexane=2:1) to give **17a** (380 mg, 74%) as a white solid. TLC (EtOAc/*n*-hexane=2:1) R_f=0.58; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.88 (d, J=7.5 Hz, 2H), 7.74 (d, J=7.5 Hz, 1H), 7.71 (dd, J=7.5, 3.0 Hz, 2H), 7.41 (t, J=7.5 Hz, 2H), 7.32 (t, J=7.5 Hz, 2H), 6.76 (t, J=5.5 Hz, 1H), 4.29 (m, 2H), 4.22 (t, J=7.0 Hz, 1H), 3.99 (td, J=8.5, 5.0 Hz, 1H), 3.61 (s, 3H), 2.89 (q, J=4.5 Hz, 2H), 1.70–1.56 (m, 2H), 1.36 (s, 9H), 1.32–1.23 (m, 4H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 172.89, 156.07, 155.53, 143.76, 143.72, 140.69, 127.58, 127.00, 125.18, 120.05, 77.30, 65.57, 53.82, 51.75, 46.63, 39.67, 30.32, 28.97, 28.22, 22.76; HRMS (FAB+) for $C_{27}H_{35}N_2O_6$ (MH^+), calcd 483.2495, found 483.2498.

3.1.10. Fmoc-Lys-OMe (17b). To a solution of **17a** (300 mg, 0.622 mmol) in CH_2Cl_2 (16 mL) was added trifluoroacetic acid (TFA, 4.0 mL) in one portion. After stirring at room temperature for 3 h, the reaction mixture was concentrated at 30 °C in vacuo to give **17b** (210 mg, 88%) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.89 (d, J=7.5 Hz, 2H), 7.74 (m, 3H), 7.70 (t, J=6.5 Hz, 2H), 7.41 (t, J=7.3 Hz, 2H), 7.33 (t, J=7.5 Hz, 2H), 4.34 (dd, J=10.5, 7.0 Hz, 1H), 4.29 (dd, J=10.5, 7.0 Hz, 1H), 4.22 (t, J=7.0 Hz, 1H), 4.00 (td, J=8.5, 5.0 Hz, 1H), 3.62 (s, 3H), 2.75 (q, J=5.5 Hz, 2H), 1.72–1.57 (m, 2H), 1.56–1.47 (m, 2H), 1.39–1.29 (m, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 172.77, 156.10, 143.75, 143.72, 140.72, 127.61, 127.02, 125.16, 125.13, 120.10, 65.55, 53.60, 51.85, 46.63, 38.52, 30.04, 26.42, 22.36; HRMS (FAB+) for $C_{22}H_{27}N_2O_4$ (MH^+), calcd 383.1971, found 383.1976.

3.1.11. Fmoc-Lys(Tsc)-OMe (4b). To a stirred solution of **17b** (600 mg, 1.57 mmol) in dry CH_2Cl_2 (20 mL) was added *N*,*N*-diisopropylethylamine (272 μL, 1.57 mmol) and then

Tsc-Cl (596 mg, 1.88 mmol) at 0 °C. After stirring at room temperature for 4 h, the reaction mixture was quenched with H_2O and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography (EtOAc/*n*-hexane=1:1) to give **4b** (715 mg, 69%) as a white solid. TLC (EtOAc/*n*-hexane=2:1) R_f=0.29; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.11 (d, J=8.0 Hz, 2H), 8.01 (d, J=8.0 Hz, 2H), 7.88 (d, J=7.5 Hz, 2H), 7.73 (d, J=7.5 Hz, 1H), 7.70 (dd, J=6.8, 1.8 Hz, 2H), 7.41 (t, J=7.5 Hz, 2H), 7.32 (t, J=7.5 Hz, 2H), 6.93 (t, J=5.3 Hz, 1H), 4.32–4.20 (m, 5H), 3.97 (td, J=8.1, 5.0 Hz, 1H), 3.76 (t, J=5.5 Hz, 2H), 3.61 (s, 3H), 2.82 (q, J=6.0 Hz, 2H), 1.67–1.54 (m, 2H), 1.29–1.22 (m, 4H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 172.86, 156.05, 155.09, 143.75, 143.72, 143.38, 140.69, 133.32 (q, J=32.0 Hz), 128.75, 127.58, 126.99, 126.51 (q, J=3.7 Hz), 125.16, 123.36 (q, J=272.8 Hz), 120.06, 65.56, 57.16, 54.35, 53.76, 51.76, 46.61, 39.67, 30.21, 28.71, 22.62; HRMS (FAB+) for $C_{32}H_{34}F_3N_2O_8S$ (MH$^+$), calcd 663.1988, found 663.1998.

3.1.12. Tsc-Lys(Fmoc)-OH (4c).[10] To a cooled (0 °C) solution of **16**-HCl (302 mg, 0.72 mmol) in THF (7 mL) was added dropwise over 3 min a solution of LiOH (56 mg, 2.34 mmol) in H_2O (7 mL). After stirring at 0 °C for 50 min (the time for complete reaction as judged by TLC (MeOH/CH_2Cl_2=1:9)), the reaction mixture was adjusted to pH 7 by adding saturated aqueous NH_4Cl. To the resulting suspension was added 1,4-dioxane (20 mL), 1 M aqueous $NaHCO_3$ (0.86 mL, 0.86 mmol), and then Tsc-Cl (273.6 mg, 0.864 mmol) at 0 °C. After stirring at room temperature overnight, the reaction mixture was quenched with 1 N aqueous HCl and extracted with EtOAc. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash chromatography (MeOH/CH_2Cl_2=1:9) to give **4c** (397 mg, 85%) as a white solid. TLC (MeOH/CH_2Cl_2=1:8) R_f=0.31; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.12 (d, J=8.5 Hz, 2H), 8.01 (d, J=9.0 Hz, 2H), 7.87 (d, J=7.5 Hz, 2H), 7.66 (d, J=7.5 Hz, 2H), 7.40 (t, J=7.5 Hz, 2H), 7.31 (t, J=7.3 Hz, 2H), 7.27 (d, J=8.0 Hz, 1H), 7.25 (t, J=5.8 Hz, 1H), 4.27 (m, 3H), 4.21 (dd, J=12.5, 5.5 Hz, 1H), 4.18 (t, J=5.8 Hz, 1H), 3.78 (td, J=9.0, 5.3 Hz, 1H), 3.75 (t, J=6.0 Hz, 2H), 2.94 (q, J=6.3 Hz, 2H), 1.65–1.46 (m, 2H), 1.40–1.30 (m, 2H), 1.26–1.18 (m, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 173.63, 156.05, 155.25, 143.91, 143.30, 140.71, 133.40 (q, J=32.4 Hz), 128.83, 127.56, 127.01, 126.58 (q, J=3.7 Hz), 125.10, 123.40 (q, J=273.0 Hz), 120.08, 65.15, 57.46, 54.27, 53.79, 46.76, 39.67, 30.35, 28.88, 22.70; HRMS (FAB+) for $C_{31}H_{32}F_3N_2O_8S$ (MH$^+$), calcd 649.1831, found 649.1844.

3.1.13. Fmoc-Lys(Tsc)-OH (4d).[10] To a solution of **17** (1.39 g, 2.96 mmol) in CH_2Cl_2 (40 mL) was added trifluoroacetic acid (4.0 mL) in one portion. After stirring at room temperature for 3 h, the reaction mixture was concentrated at 30 °C in vacuo to give Fmoc-Lys-OH (1.09 g, >99%) as a white solid. To a stirred solution of crude Fmoc-Lys-OH in 1,4-dioxane (40 mL) was added 1 M aqueous $NaHCO_3$ (3.55 mL, 3.55 mmol) and then Tsc-Cl (1.12 g, 3.55 mmol) at 0 °C. After stirring at room temperature for 8 h, the reaction mixture was quenched with 1 N aqueous HCl and extracted with EtOAc. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash chromatography (MeOH/CH_2Cl_2=1:9) to give **4d** (720 mg, 38%) as a white solid. TLC (MeOH/CH_2Cl_2=1:9) R_f=0.28; ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.54 (brs, 1H), 8.11 (d, J=8.0 Hz, 2H), 8.01 (d, J=8.0 Hz, 2H), 7.88 (d, J=7.0 Hz, 2H), 7.71 (d, J=7.5 Hz, 2H), 7.57 (d, J=8.0 Hz, 1H), 7.40 (t, J=7.5 Hz, 2H), 7.31 (t, J=7.0 Hz, 2H), 6.93 (t, J=5.8 Hz, 1H), 4.27–4.19 (m, 5H), 3.88 (td, J=8.5, 4.0 Hz, 1H), 3.76 (t, J=5.5 Hz, 2H), 2.82 (q, J=6.0 Hz, 2H), 1.68–1.53 (m, 2H), 1.29–1.22 (m, 4H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 173.90, 156.11, 155.10, 143.80, 143.77, 143.41, 140.69, 140.67, 133.33 (q, J=32.1 Hz), 128.77, 127.60, 127.03, 126.53 (q, J=3.4 Hz), 125.24, 125.22, 123.37 (q, J=272.8 Hz), 120.06, 65.55, 57.17, 54.36, 53.76, 46.63, 39.67, 30.35, 28.79, 22.79; HRMS (FAB+) for $C_{31}H_{32}F_3N_2O_8S$ (MH$^+$), calcd 649.1831, found 649.1822.

3.1.14. Tsc-Ala-OH. To a solution of H-Ala-OH (250 mg, 2.81 mmol) in 1 M aqueous $NaHCO_3$ (20 mL) was added 1,4-dioxane (20 mL) and then Tsc-Cl (1.07 g, 3.37 mmol) at 0°C. After stirring at room temperature for 2 h, the reaction mixture was quenched with 1 N aqueous HCl and extracted with EtOAc. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The residue was recrystallized from diethyl ether and *n*-hexane to afford the title compound (515 mg, 50%) as a white solid. TLC (MeOH/CH_2Cl_2=1:9) R_f=0.34; ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.52 (brs, 1H), 8.12 (d, J=8.5 Hz, 2H), 8.02 (d, J=8.0 Hz, 2H), 7.29 (d, J=7.5 Hz, 1H), 4.29 (m, 1H), 4.20 (m, 1H), 3.86 (m, 1H), 3.77 (m, 2H), 1.17 (d, J=7.0 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 174.03, 154.86, 143.36, 133.42 (q, J=32.4 Hz), 128.83, 126.58 (q, J=3.7 Hz), 123.39 (q, J=273.3 Hz), 57.48, 54.32, 49.07, 16.88; HRMS (FAB+) for $C_{13}H_{15}F_3NO_6S$ (MH$^+$), calcd 370.0572, found 370.0571.

3.1.15. Deprotection of Tsc-Phe-OEt with LiOH. To a cooled (0 °C) solution of **3a** (17.0 mg, 0.036 mmol) in THF (0.35 mL) was added dropwise over 1 min 0.2 N aqueous LiOH (0.35 mL, 0.070 mmol). After stirring at 0 °C for 10 min (the time for complete reaction as judged by TLC (EtOAc/*n*-hexane=1:5)), the reaction mixture was adjusted to pH 7 by adding saturated aqueous NH_4Cl and then extracted with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (EtOAc/*n*-hexane=1:5) to give **18a** (7.0 mg, 77%) as a white solid. TLC (EtOAc/*n*-hexane=1:4) R_f=0.27; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10 (d, J=8.4 Hz, 2H), 7.89 (d, J=8.1 Hz, 2H), 4.17 (dd, J=3.8, 2.3 Hz, 1H), 3.49 (dd, J=5.4, 2.1 Hz, 1H), 3.19 (dd, J=5.4, 3.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.30 (q, J=1.2 Hz), 136.05 (q, J=33.2 Hz), 129.42, 126.53 (q, J=3.6 Hz), 122.97 (q, J=273.2 Hz), 63.05, 45.43; HRMS (CI+) for $C_9H_8F_3O_3S$ (MH$^+$), calcd 253.0146, found 253.0142.

3.1.16. Deprotection of Tsc-Lys(Fmoc)-OMe with LiOH. To a cooled (0 °C) solution of **4a** (5.9 mg, 9 μmol) in THF (87 μL) was added dropwise over 1 min 0.2 N aqueous LiOH (87 μL, 17.4 μmol). After stirring at 0 °C for 5 min, the reaction mixture (50 μL) was adjusted to pH 1 by adding

1 N aqueous HCl (100 μL) and then analyzed on a LC-MS using a C_{18} reverse-phase column (4.6×250 mm, 5 μm particle size, TP silica, Vydac, Hesperia, CA) with a linear H_2O/MeCN gradient containing 0.1% (v/v) AcOH: 0–5 min 100% H_2O, 5–35 min 2.67% MeCN/min, 1 mL/min flow rate, 254 nm, R_v=23.17 mL (**16a**, 8%) and 29.93 mL (**16**, 92%) (Fig. 3).

3.1.17. Deprotection of Tsc-Lys(Fmoc)-OMe with 1-methylpyrrolidine. To a stirred solution of **4a** (50.0 mg, 75.4 μmol) in dry DMF (189 μL) was added 1-methylpyrrolidine (189 μL, 1.82 mmol) at room temperature. After stirring at 25 °C for 1 h, the reaction mixture was directly purified by flash chromatography (MeOH/CH_2Cl_2=1:30 and then MeOH/CH_2Cl_2=1:9) to give **16b** (48.4 mg, 95%) and **18b**. **16b**: TLC (MeOH/CH_2Cl_2=1:9) R_f=0.43; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.08 (d, J=8.1 Hz, 2H), 8.07 (d, J=8.1 Hz, 2H), 7.87 (d, J=8.1 Hz, 2H), 7.86 (d, J=8.4 Hz, 2H), 5.11 (d, J=8.4 Hz, 1H), 4.43 (t, J=5.8 Hz, 2H), 4.21 (td, J=7.8, 5.3 Hz, 1H), 3.74 (s, 3H), 3.50 (t, J=5.9 Hz, 2H), 3.32 (t, J=6.3 Hz, 2H), 3.03 (t, J=6.3 Hz, 2H), 2.56 (t, J=6.9 Hz, 2H), 1.83–1.72 (m, 2H), 1.65–1.53 (m, 2H), 1.50–1.41 (m, 2H); HRMS (FAB+) for $C_{26}H_{31}F_6N_2O_8S_2$ (MH^+), calcd 677.1426, found 677.1425. **18b**: TLC (MeOH/CH_2Cl_2=1:9) R_f=0.33; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07 (d, J=8.7 Hz, 2H), 7.83 (d, J=8.4 Hz, 2H), 3.35 (t, J=7.5 Hz, 2H), 2.87 (t, J=7.4 Hz, 2H), 2.39 (m, 4H), 1.65 (m, 4H); HRMS (FAB+) for $C_{13}H_{16}F_3NO_2S$ (M^+), calcd 307.0854, found 307.0866.

3.1.18. Deprotection of Tsc-Lys(Fmoc)-OMe with DIEA. To a solution of **4a** (66.3 mg, 0.10 mmol) in dry DMF (1 mL) was added *N*,*N*-diisopropylethylamine (87.1 μL, 0.50 mmol) at room temperature. After heating at 50 °C for 4 h, the reaction mixture was quenched with H_2O and extracted with EtOAc. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography (MeOH/CH_2Cl_2=1:9) to give **16c** (32.5 mg, 82%) as a white solid. TLC (MeOH/CH_2Cl_2=1:9) R_f=0.27; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07 (d, J=8.1 Hz, 2H), 7.86 (d, J=8.7 Hz, 2H), 3.72 (s, 3H), 3.44 (dd, J=7.5, 5.4 Hz, 1H), 3.32 (t, J=6.5 Hz, 2H), 3.04 (t, J=6.5 Hz, 2H), 2.57 (t, J=6.9 Hz, 2H), 1.61–1.38 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.47, 142.90 (q, J=1.3 Hz), 135.53 (q, J=33.3 Hz), 128.65, 126.48 (q, J=3.7 Hz), 123.05 (q, J=273.5 Hz), 56.01, 54.26, 51.97, 49.21, 42.90, 34.59, 29.54, 23.24; HRMS (FAB+) for $C_{16}H_{24}F_3N_2O_4S$ (MH^+), calcd 397.1409, found 397.1395.

3.1.19. Deprotection of Fmoc-Lys(Tsc)-OMe with LiOH. To a cooled (0 °C) solution of **4b** (5.9 mg, 9 μmol) in THF (87 μL) was added dropwise over 1 min 0.2 N aqueous LiOH (87 μL, 17.4 μmol). After stirring at 0 °C for 5 min, the reaction mixture (50 μL) was adjusted to pH 1 by adding 1 N aqueous HCl (100 μL) and then analyzed on a LC-MS using a C_{18} reverse-phase column (4.6×250 mm, 5 μm particle size, TP silica, Vydac, Hesperia, CA) with a linear H_2O/MeCN gradient containing 0.1% (v/v) AcOH: 0–5 min 100% H_2O, 5–35 min 2.67% MeCN/min, 1 mL/min flow rate, 254 nm, R_v=25.66 mL (**17c**, 20%) and 29.75 mL (**17b**, 75%) (Fig. 3).

3.1.20. Deprotection of Fmoc-Lys(Tsc)-OMe with 1-methylpyrrolidine. To a stirred solution of **4b** (50.0 mg, 75.4 μmol) in dry DMF (189 μL) was added 1-methylpyrrolidine (189 μL, 1.82 mmol) at room temperature. After stirring at 25 °C for 1 h, the reaction mixture was directly purified by flash chromatography (EtOAc/*n*-hexane=2:1 and then MeOH/CH_2Cl_2=1:9) to give **17d** (32.5 mg, 98%) and **18c**. **17d**: TLC (MeOH/CH_2Cl_2=1:9) R_f=0.39; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.08 (d, J=8.1 Hz, 2H), 7.86 (d, J=8.4 Hz, 2H), 4.54 (t, J=5.7 Hz, 1H), 4.41 (t, J=5.7 Hz, 2H), 3.72 (s, 3H), 3.50 (t, J=5.9 Hz, 2H), 3.43 (dd, J=7.5, 5.3 Hz, 1H), 3.06 (q, J=6.5 Hz, 2H), 1.78–1.30 (m, 6H); HRMS (FAB+) for $C_{17}H_{24}F_3N_2O_6S$ (MH^+), calcd 441.1307, found 441.1321. **18c**: TLC (EtOAc/*n*-hexane=2:1) R_f=0.30; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10 (d, J=8.4 Hz, 2H), 7.88 (d, J=8.4 Hz, 2H), 4.06 (t, J=5.4 Hz, 2H), 3.40 (t, J=5.3 Hz, 2H); HRMS (FAB+) for $C_9H_{10}F_3O_3S$ (MH^+), calcd 255.0303, found 255.0303.

3.1.21. Deprotection of Fmoc-Lys(Tsc)-OMe with DIEA. To a solution of **4b** (66.3 mg, 0.10 mmol) in dry DMF (1 mL) was added *N*,*N*-diisopropylethylamine (87.1 μL, 0.50 mmol) at room temperature. After heating at 50 °C for 4 h, the reaction mixture was quenched with H_2O and extracted with EtOAc. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography (MeOH/CH_2Cl_2=1:9) to give **17d** as a white solid (38.3 mg, 87%). TLC (MeOH/CH_2Cl_2=1:9) R_f=0.39; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.08 (d, J=8.1 Hz, 2H), 7.86 (d, J=8.4 Hz, 2H), 4.47 (t, J=5.4 Hz, 1H), 4.41 (t, J=5.9 Hz, 2H), 3.73 (s, 3H), 3.50 (t, J=5.9 Hz, 2H), 3.43 (dd, J=7.5, 5.4 Hz, 1H), 3.06 (q, J=6.5 Hz, 2H), 1.78–1.38 (m, 6H); HRMS (FAB+) for $C_{17}H_{24}F_3N_2O_6S$ (MH^+), calcd 441.1307, found 441.1305.

3.2. Peptide synthesis

Peptides **20** and **21** were synthesized on the Fmoc-Rink Amide MBHA resin in a stepwise fashion by a manual solid-phase method as described.[1,11] Fmoc-Rink Amide MBHA resin (loading 0.64 mmol/g resin, copolystyrene-1% DVB, 100–200 mesh, 31.3 mg, 20 μmol, Novabiochem, La Jolla, CA) was placed in a glass reaction vessel (5 mL, fitted with a glass frit (G3, 20–30 μm, Iwaki)) and swollen in CH_2Cl_2 for 5 min followed by drainage for use with standard Fmoc chemistry. Amino acids (50 μmol for **4c**, **4d**, and Tsc-Ala-OH or 60 μmol for other amino acids) were activated with PyBOP (31.2 mg, 60 μmol) in DMF (2 mL) and coupled in the presence of *N*,*N*-diisopropylethylamine (DIEA, 13.9 μL, 80 μmol) with shaking (wrist action shaker, Burrell) at room temperature for 3 h. Deprotection of the Fmoc group was performed using 50% (v/v) piperidine for 10 min or 50% (v/v) 1-methylpyrrolidine for 1 h in DMF with shaking at room temperature. Deprotection of the Tsc group was performed using 50% (v/v) piperidine for 10 min or 0.1 N LiOH in cooled (4 °C) THF/H_2O (1:1) for 10 min (or ×2) with shaking at room temperature. Unreacted free amines were capped by acetylation with acetic anhydride (9.4 μL, 100 μmol) and DIEA (17.4 μL, 100 μmol) in CH_2Cl_2 (2 mL) with shaking at room temperature for 15 min. All peptides were

acetylated at the N terminus and amidated at the C terminus. All couplings were monitored using a ninhydrin assay. A solvent wash (5 mL×3) with DMF, MeOH, CH_2Cl_2, and then DMF was performed right after deprotection, coupling, and capping. An additional CH_2Cl_2 wash was employed right before and after capping. Peptide resin cleavage and side-chain deprotection were performed in a single step using trifluoroacetic acid (TFA, 1 mL) at room temperature for 2 h. After evaporation of the solvent or precipitation with ether followed by centrifugation, crude peptides were dissolved in DMF (1 mL). HPLC purification was achieved using a C_{18} reverse-phase column (10×250 mm, 5 μm particle size, TP silica, Vydac, Hesperia, CA) with a linear H_2O/MeCN gradient containing 0.1% (v/v) TFA: 0–5 min 100% H_2O, 5–35 min 3.33% MeCN/min, 3 mL/min flow rate, 210/254 nm. Peptides were recovered upon lyophilization of the appropriate fractions as a solid (Scheme 3 and Figs. 4 and 5): **20** via **19a**, method A, 2.6 mg, 18% recovery; **20** via **19a**, method B, 4.2 mg, 29%; **20** via **19b**, method A, 2.3 mg, 15%; **20** via **19b**, method B, 2.5 mg, 17%; **21** via **19b**, method C, 9.6 mg, 40% (LiOH for Tsc deprotection) and 15.1 mg, 63% (piperidine for Tsc deprotection, Fig. 5). Purity of the peptide was determined to be >98% by analytical HPLC on a C_{18} reverse-phase column (4.6×250 mm, 5 μm particle size, TP silica, Vydac, Hesperia, CA) with a linear H_2O/MeCN gradient containing 0.1% (v/v) TFA: 0–5 min 100% H_2O, 5–35 min 3.33% MeCN/min, 1 mL/min flow rate, 210/254 nm, R_v=22.50 mL (**20**) and 23.09 mL (**21**). The molecular mass of each peptide was measured using MALDI-TOF mass spectrometry: **20**, $C_{39}H_{49}N_7O_7Na/C_{39}H_{49}N_7O_7K$ (MNa$^+$)/(MK$^+$), calcd 750.3586/766.3325, found 750.8125/766.7810; **21**, $C_{57}H_{79}N_{13}O_{16}Na/C_{57}H_{79}N_{13}O_{16}K$ (MNa$^+$/MK$^+$), calcd 1224.5660/1240.5399, found 1224.4465/1240.4049.

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Synthesis and structural revision of naturally occurring ayapin derivatives

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Abstract—The synthesis of three highly oxygenated naturally occurring coumarins, 8-methoxy-6,7-methylenedioxycoumarin, 5-methoxy-6,7-methylenedioxycoumarin and 5,8-dimethoxy-6,7-methylenedioxycoumarin is described for the first time, together with a new method for the preparation of ayapin (6,7-methylenedioxycoumarin). Comparison of the spectroscopic data of the synthetic tetraoxygenated coumarin 5,8-dimethoxy-6,7-methylenedioxycoumarin with literature reports resulted in the structural revision of several natural coumarins. Two coumarins, both identified as 5,8-dimethoxy-6,7-methylenedioxycoumarin must have other structures, while the structure of another coumarin, described as the isomeric 7,8-dimethoxy-5,6-methylenedioxycoumarin has to be revised to 5,8-dimethoxy-6,7-methylenedioxycoumarin.

1. Introduction

In the last decade, a large number of tri- and tetraoxygenated coumarins have been isolated from plants. Examples include purpurenol,[1] purpurasol,[2] purpurasolol,[3] isopurpurasol,[4] 8-methoxy-6,7-methylenedioxycoumarin **2**,[5] 5-methoxy-6,7-methylenedioxycoumarin **3**[6,7] and 5,8-dimethoxy-6,7-methylenedioxycoumarin **4** (Fig. 1). In this article we report the synthesis of four coumarins bearing a methylenedioxy substituent at C6 and C7. Hence they are all derivatives of 6,7-methylenedioxycoumarin **1** (ayapin). 6,7-Methylenedioxycoumarin **1** was first isolated from *Eupatorium ayapana* (Asteraceae)[8] and was given the trivial name ayapin. Later, ayapin **1** was also isolated from a number of other plants, including *Helianthus annuus*,[9] *Artemisia apiacea*,[10] *Pterocaulon virgatum*[11] and *P. polystachyum*.[12]

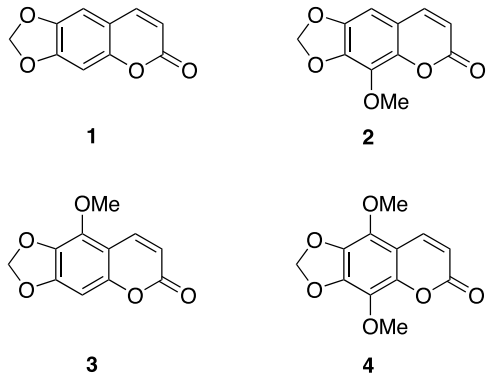

Figure 1.

2. Results and discussion

Different methods for the synthesis of coumarins from *o*-hydroxybenzaldehydes were described in the literature. A convenient way for the synthesis of coumarins is the reaction of salicylaldehydes with alkoxycarbonylmethylenephosphorane in *N*,*N*-diethylaniline under reflux.[13–16] Although this method has been successfully applied for the synthesis of simple mono- and dioxygenated coumarins,[13–16] this is the first report on its application on tri- and tetraoxygenated coumarins. The key feature of the synthetic pathway was the synthesis of suitable *o*-hydroxybenzaldehydes which then are transformed to the corresponding coumarins via the Wittig reaction.

2-Hydroxy-4,5-methylenedioxybenzaldehyde **6** was

Keywords: Coumarins; *o*-Hydroxybenzaldehydes; Wittig reaction; Natural products; Structural revision; 6*H*-[1,3]Dioxolo[4,5-*g*]chromen-6-ones.
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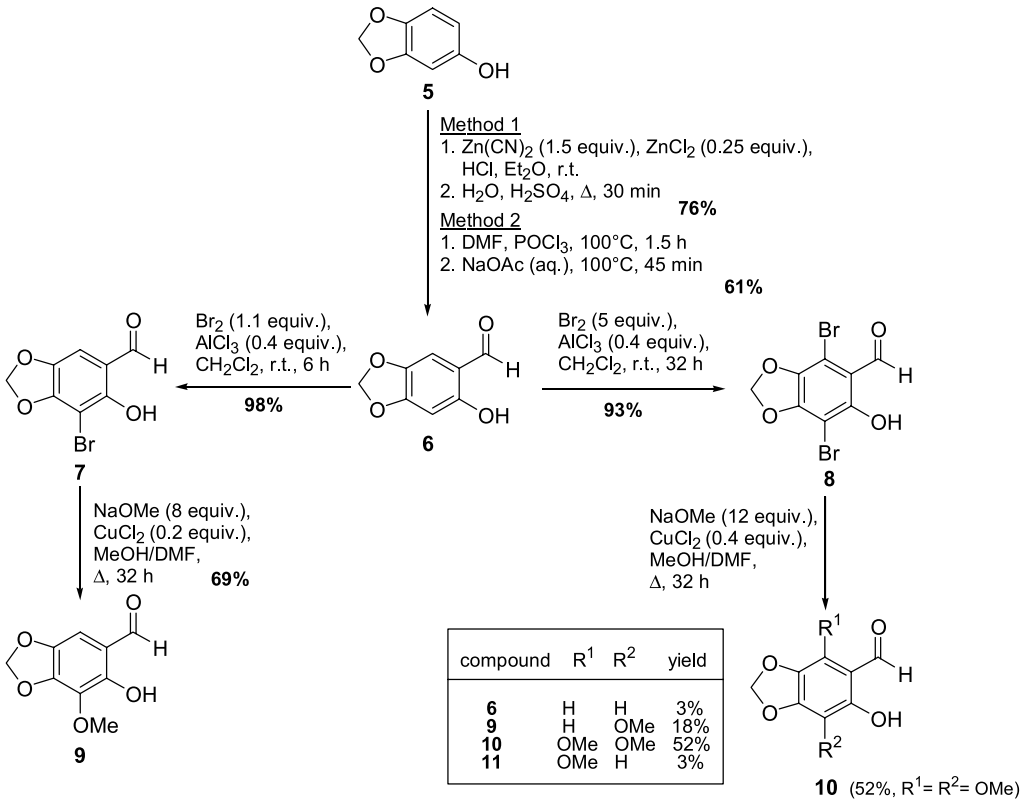


Scheme 1.

synthesized from sesamol **5** in two different ways (Scheme 1).[18] Using the Gattermann formylation,[17,18] 2-hydroxy-4,5-methylenedioxybenzaldehyde **6** was obtained in 76% yield. The Villsmeier–Haack reaction[18,19] yielded 61% of the desired aldehyde **6**. Different conditions for the bromination of compound **6** were evaluated. Treatment of 2-hydroxy-4,5-methylenedioxybenzaldehyde **6** with 2 equiv of bromine in dichloromethane resulted in no reaction. Low yields of 3-bromo-2-hydroxy-4,5-methylenedioxybenzaldehyde **7** were obtained using bromine in acetic acid. Best results were obtained when the reaction was performed in dichloromethane with aluminium(III) chloride as a Lewis catalyst. Thus, when 2-hydroxy-4,5-methylenedioxybenzaldehyde **6** was stirred for 6 h with 1.1 equiv of bromine and 0.4 equiv of aluminium(III) chloride, 3-bromo-2-hydroxy-4,5-methylenedioxybenzaldehyde **7** was obtained in excellent yield (98%). Interestingly, it was found that when more equivalents of bromine were used and longer reaction times were applied, also the dibrominated benzaldehyde **8** was present in the reaction mixture. This was remarkable since it involved bromination at the deactivated *ortho* position to the carbonyl. Optimization of the latter side reaction by applying a large excess of bromine (5 equiv), 0.4 equiv of aluminium(III) chloride and an extended reaction time of 32 h resulted in a high yielding procedure for the synthesis of 3,5-dibromo-2-hydroxy-4,5-methylenedioxybenzaldehyde **8** (93%).

The next step involved the nucleophilic aromatic substitution of these arylbromides with sodium methoxide. The reaction of arylhalides with sodium methoxide in the presence of copper(I) halides or pseudohalides as a catalyst has been described and different mechanisms have been postulated.[20–22] A problem that often occurs in this reaction is that not only the substitution reaction takes place but also the undesired reductive dehalogenation. This reductive dehalogenation is probably due to the formation of copper(0) in the reaction mixture.[21] It has been proven that polar co-solvents can improve the rate as well as the final yield of the reaction, most probably because these solvents increase the stability and solubility of the copper salts, which have poor solubility in pure methanol.[21–22] Amides such as *N*,*N*-dimethylformamide are sometimes used as co-solvents and have been useful in the substitution of aromatic aldehydes.[23,24] In order to optimize the reaction, the catalytic influence of different copper salts under the same reaction conditions was compared (Table 1). When no catalyst was added, no reaction could be observed (Table 1, entry 1). Different copper(I) salts such as copper(I) iodide, copper(I) bromide and copper(I) cyanide gave comparable results (Table 1, entries 2–4). Copper(II) hydroxide and basic copper(II) carbonate gave only complex reaction mixtures. Copper(II) acetoacetate an copper(II) acetate were lacking any catalytic activity (Table 1, entries 5 and 6). Good results were obtained using copper(II) chloride as a catalyst (Table 1, entry 9). Under the given circumstances, after 14 h, 60% of the desired 2-hydroxy-3-methoxy-4,5-methylenedioxybenzaldehyde **9** was formed in the reaction mixture. Further optimization of the reaction procedure by using 8 equiv of sodium methoxide, 0.2 equiv of catalyst and a reaction time of 32 h gave 2-hydroxy-3-methoxy-4,5-methylenedioxybenzaldehyde **9** in 69% isolated yield (Table 1, entry 10).

Table 1. Comparison of the catalytic activity of different copper salts for the synthesis of 2-hydroxy-3-methoxy-4,5-methylenedioxybenzaldehyde **9** from 3-bromo-2-hydroxy-4,5-methylenedioxybenzaldehyde **7** (analysis of the reaction mixture based on ^{1}H NMR)

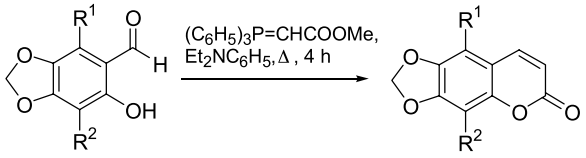
Entry		**7**	**6**	**9**
1[a]	No catalyst	100	0	0
2[a]	CuI	60	7	33
3[a]	CuBr	62	6	32
4[a]	CuCN	66	6	28
5[a]	$Cu(OH)_2$	Complex reaction mixture		
6[a]	$Cu_2CO_3(OH)_2$	Complex reaction mixture		
7[a]	$Cu(CH_3COO)_2$	100	0	0
8[a]	$Cu(acac)_2$	100	0	0
9[a]	$CuCl_2$	35	5	60
10[b]	$CuCl_2$	6	17	77 (69[c])

[a] Reaction conditions: 2 N NaOMe (20 equiv), catalyst (0.5 equiv), MeOH/DMF (3/1), △, 14 h.
[b] Reaction conditions: 2 N NaOMe (8 equiv), catalyst (0.2 equiv), MeOH/DMF (3/1), △, 32 h.
[c] Isolated yield after purification of the reaction mixture by column chromatography.

In a similar way 2-hydroxy-3,6-dimethoxy-4,5-methylenedioxybenzaldehyde **10** was synthesized in 52% isolated yield from 3,6-dibromo-2-hydroxy-4,5-methylenedioxybenzaldehyde **8** and sodium methoxide in MeOH/DMF in the presence of copper(II) chloride under reflux for 32 h. 2-Hydroxy-4,5-methylenedioxybenzaldehyde **6** (3%), 2-hydroxy-3-methoxy-4,5-methylenedioxybenzaldehyde **9** (18%) and 2-hydroxy-6-methoxy-4,5-methylenedioxybenzaldehyde **11** (3%) were isolated as side products in this reaction (Scheme 1).

The *o*-hydroxybenzaldehydes **6**, **9**, **10** and **11** were converted to the corresponding coumarins using the Wittig reaction of methoxycarbonylmethylenetriphenylphosphorane in *N*,*N*-diethylaniline.[13–16] In this way ayapin **1**, 8-methoxyayapin **2**, 5-methoxyayapin **3** and 5,8-dimethoxyayapin **4** were synthesized in high yields (77–82%, Scheme 2). Special attention was paid to the optimization of the workup procedure. In an earlier report we described a workup procedure that involved a crystallization from the reaction mixture.[25] An improved method involved the removal of the solvent through distillation under reduced pressure, followed by chromatography of the residue over silica gel. In this way high yields of the corresponding coumarins were obtained, as outlined in Scheme 2.

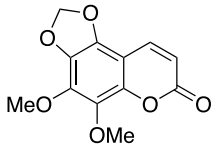
8-Methoxy-6,7-methylenedioxycoumarin **2** is a naturally occurring coumarin identified in *Asterolasia trymalioides* (Rutaceae), a shrub from South-East Australia.[5] Although the synthesis of 8-methoxy-6,7-methylenedioxycoumarin **2** from 6,7-dihydroxy-8-methoxycoumarin has been reported,[26] the published data for 8-methoxy-6,7-methylenedioxycoumarin do not correspond with those reported for the natural coumarin, nor with our own findings. However, the spectroscopic data we obtained for this coumarin are in full agreement with those published for the natural coumarin.[5]



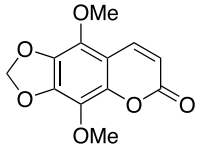
R^1	R^2	starting product	coumarin	yield
H	H	**6**	**1**	78 %
H	OMe	**9**	**2**	77 %
OMe	H	**11**	**3**	79 %
OMe	OMe	**10**	**4**	82 %

Scheme 2.

The isomeric 5-methoxy-6,7-methylenedioxycoumarin **3** was first isolated from *Simsia cronquistii* (Asteracea),[6] and from two *Pterocaulon* species, *P. virgatum* and *P. polystachyum*.[7] Very recently, it was found that 5-methoxy-6,7-methylenedioxycoumarin **3** is an inhibitor of cellular proliferation in human promyelocytic leukemia U-937 cells, and could therefore be a promising option for the treatment of several forms of leukemia.[27,28] 5,8-Dimethoxy-6,7-methylenedioxycoumarin **4** was reported twice in the literature.[29,31] Based on ^{1}H NMR and mass spectrometric data, 5,8-dimethoxy-6,7-methylenedioxycoumarin **4** was proposed as the structure of sabandin, a natural coumarin isolated from *Ruta pinnata* (Rutaceae).[29,30] Recently, structure **4** was also assigned to artemicapin A, a coumarin from *Artemisia capillaris* (Asteraceae) based on ^{1}H NMR, ^{13}C NMR, NOESY and HMBC experiments.[31] Since the spectroscopic data from both references differ substantially, an unambiguous synthesis of this compound was desirable. The spectroscopic data for the synthesized 5,8-dimethoxy-6,7-methylenedioxycoumarin **4** do not match with those reported for sabandin[29,30] or artemicapin A.[31] Moreover, the ^{13}C NMR and ^{1}H NMR correspond very well with those reported for a coumarin isolated from a Brazilian plant, *Metreodorea flavida* (Rutaceae).[32] This coumarin was identified as the regioisomeric structure 7,8-dimethoxy-5,6-methylenedioxycoumarin **12** (Fig. 2). Because no NOE correlation was found between the hydrogen at position 4 and the methoxy protons, the authors concluded that the methylenedioxy substituent was positioned at carbons 5 and 6.[32] Our own findings with the natural compound 5-methoxy-6,7-methylenedioxycoumarin **3**[6,7] revealed the absence of NOE correlation between H4



12



4

Figure 2.

Table 2. ^{1}H and ^{13}C NMR data for the natural coumarin from *Metreodorea flavida* and for 5,8-dimethoxy-6,7-methylenedioxycoumarin **4**

	Coumarin from *Metreodorea flavida*[32]	5,8-Dimethoxy-6,7-methylenedioxycoumarin
^{1}H NMR ($CDCl_3$)	3.99 (3H, s)	4.02 (3H, s)
	4.04 (3H, s)	4.06 (3H, s)
	6.01 (2H, s)	6.03 (2H, s)
	6.20 (1H, d, $J=9.7$ Hz)	6.22 (1H, d, $J=9.7$ Hz)
	7.91 (1H, d, $J=9.7$ Hz)	7.93 (1H, d, $J=9.7$ Hz)
^{13}C NMR ($CDCl_3$)	61.1 (–O*C*H_3)	60.3 (–O*C*H_3)
	61.1 (–O*C*H_3)	61.2 (–O*C*H_3)
	102.1 (–O*C*H_2O–)	102.2 (–O*C*H_2O–)
	107.0 (*C*q)	107.1 (*C*q)
	112.0 (*C*H)	112.2 (*C*H)
	126.9 (*C*q)	127.0 (*C*q)
	132.8 (*C*q)	132.9 (*C*q)
	133.4 (*C*q)	133.5 (*C*q)
	138.8 (*C*H)	138.9 (*C*H)
	142.9 (*C*q)	143.1 (*C*q)
	143.7 (*C*q)	143.8 (*C*q)
	160.5 (*C*=O)	160.6 (*C*=O)

and the protons of the methoxy substituent at C5. This was confirmed by the fact that no NOE correlation could be found between the H4 proton of the synthesized 5,8-dimethoxy-6,7-methylenedioxycoumarin **4** and any of the methoxy groups. These observations prove that the presence or absence of a methoxy substituent at C5 cannot be derived from the results of NOE experiments.

Based on the spectroscopic evidence the structure of the natural coumarin from *M. flavida* has to be revised to 5,8-dimethoxy-6,7-methylenedioxycoumarin **4**. The ^{1}H NMR data for both the synthesized 5,8-dimethoxy-6,7-methylenedioxycoumarin **4** and the natural coumarin from *M. flavida* are given in table 2. These data show clearly that the natural product from *M. flavida* is identical to 5,8-dimethoxy-6,7-methylenedioxycoumarin **4**.

3. Conclusion

Four natural coumarins were synthesized (of which three for the first time) from the corresponding *o*-hydroxybenzaldehydes using the Wittig reaction. Comparison of the spectroscopic data of the synthetic coumarins with literature data led to the structural revision of a tetraoxygenated coumarin from *M. flavida* and unequivocally proved the structure of a trioxygenated coumarin from *A. trymalioides*.

4. Experimental

4.1. General

^{1}H NMR spectra (270 or 300 MHz) and ^{13}C NMR spectra (68 or 75 MHz) were recorded on a Joel JNM-EX 270 NMR spectrometer or a Joel Eclipse FT 300 NMR spectrometer, respectively. IR spectra were recorded on a Perkin–Elmer Spectrum One spectrophotometer. Mass spectra were recorded on an Agilent 1100 Series VL mass spectrometer (ES 70 eV) or on a Varian MAT 112 mass spectrometer (EI 70 eV). Melting points were measured with a Büchi B-450 apparatus. Elemental analyses were measured with a Perkin–Elmer 2400 Elemental Analyzer. Flash chromatography was performed with ACROS silica gel (particle size 0.035–0.070 mm, pore diameter ca. 6 nm) using a glass column.

4.2. Synthetic procedures

4.2.1. 2-Hydroxy-4,5-methylenedioxybenzaldehyde 6. *Gattermann procedure*. Dry hydrogen chloride was bubbled through a stirred suspension of sesamol **5** (4.14 g; 30 mmol), zinc(II) cyanide (5.28 g, 45 mmol), zinc(II) chloride (1.02 g; 7.5 mmol) and a trace of sodium chloride in 100 ml of diethyl ether. To prevent the in situ formed hydrogen cyanide from escaping, the flask was connected to a condenser, cooled with ice water. After the formation of a green precipitate the solution is additionally treated with dry hydrogen chloride gas for 30 min. The ether was decanted and the precipitate was rinsed thoroughly with ether. The formed iminium salt was dissolved in 75 ml of water. A few drops of concentrated sulfuric acid were added and the resulting mixture was heated to 100 °C for 30 min. The reaction mixture was cooled to room temperature and the formed crystals were filtered off. The crystals were dissolved in dichloromethane and the solution was dried over magnesium sulfate. After filtration and evaporation of the solvent 3.76 g (76%) of pure 2-hydroxy-4,5-methylenedioxybenzaldehyde **6** was obtained.

Vilsmeier procedure. Sesamol (4.14 g, 30 mmol) was dissolved in *N*,*N*-dimethylformamide (24 ml). At 0 °C 16 ml of phosphoroxytrichloride was added. The resulting mixture was stirred for 1 h at 100 °C. After cooling, the reaction mixture was poured into 250 ml of a saturated sodium acetate solution and heated for 45 min at 100 °C. The reaction mixture was cooled down again and the precipitate was filtered off. The precipitate was recrystallized from ethanol, giving 3.02 g (61%) of pure 2-hydroxy-4,5-methylenedioxybenzaldehyde **6** as white needles.

Mp (°C): 127 (lit. 125–126[18]). IR (KBr, cm^{-1}): 3500 (broad, OH); 1605 (broad, C=O). ^{1}H NMR (270 MHz, $CDCl_3$): δ 6.02 (2H, s, O*C*H_2O); 6.46 (1H, s, 3-C*H*); 6.85 (1H, s, 6-C*H*); 9.62 (1H, s, C*H*O); 11.78 (O*H*). ^{13}C NMR (68 MHz, $CDCl_3$): δ 98.33 (3-*C*H); 102.19 (O*C*H_2O); 109.34 (6-*C*H); 113.64 (1-C_q); 141.33 (5-C_q); 155.18 (2- or 4-C_q); 161.51 ((2- or 4-C_q); 193.71 (*C*HO). MS (70 eV,

EI, *m/z* (%)): 166 (M^+, 100); 165 (90); 107 (15); 79 (11); 69 (11); 53 (24); 52 (14); 51 (13). Anal. Calcd for $C_8H_6O_4$: C, 57.84%; H, 3.64%. Found: C, 57.99%; H, 3.49%.

4.2.2. 3-Bromo-2-hydroxy-4,5-methylenedioxybenzaldehyde 7. To a solution of 2-hydroxy-4,5-methylenedioxybenzaldehyde **6** (0.83 g; 5 mmol) and aluminium(III) chloride (0.27 g; 2 mmol) in dichloromethane (50 ml), bromine (0.88 g; 5.5 mmol) was added dropwise. After 6 h of stirring at room temperature the reaction mixture was poured into a saturated aqueous sodium metabisulfite solution (50 ml) and extracted three times with dichloromethane (50 ml). The combined organic layers were washed with 50 ml of a saturated sodium bicarbonate solution and 50 ml of water. The organic layer was dried over magnesium sulfate. After filtration and evaporation of the solvent 1.2 g (98%) of 3-bromo-2-hydroxy-4,5-methylenedioxybenzaldehyde **7** was obtained.

Mp (°C): 141 (light yellow solid). IR (KBr, cm^{-1}): 3440 (broad, OH); 1632 (C=O). ^1H NMR (270 MHz, $CDCl_3$): δ 6.12 (2H, s, OCH_2O); 6.87 (1H, s, 6-C*H*); 9.61 (1H, s, C*H*O); 12.36 (O*H*). ^{13}C NMR (75 MHz, $CDCl_3$): δ 91.22 (*C*Br); 102.67 (O*C*H_2O); 108.59 (6-*C*H); 113.80 (1-C_q); 141.08 (5-C_q); 153.34 (2- or 4-C_q); 157.99 (2- or 4-C_q); 193.58 (*C*HO). MS (70 eV, EI, *m/z* (%)): 244/6 (M^+, 100); 243/5 (70); 131/3 (17); 79 (20); 77 (20); 55 (16); 53 (54); 51 (38); 50 (31); 49 (15); 44 (10). Anal. Calcd for $C_8H_5O_4Br$: C, 39.21%; H, 2.06%. Found: C, 39.37%; H, 2.15%.

4.2.3. 3,6-Dibromo-2-hydroxy-4,5-methylenedioxybenzaldehyde 8. To a solution of 2-hydroxy-4,5-methylenedioxybenzaldehyde **6** (0.83 g; 5 mmol) and aluminium(III) chloride (0.27 g; 2 mmol) in dichloromethane (50 ml) bromine (4 g; 25 mmol) was added dropwise. After 32 h of stirring at room temperature the reaction mixture was poured into a saturated sodium metabisulfite solution (50 ml) and extracted three times with dichloromethane (50 ml). The combined organic layers were washed with 50 ml of a saturated sodium bicarbonate solution and 50 ml of water. The organic layer was dried over magnesium sulfate. After filtration and evaporation of the solvent 1.51 g (93%) of 3,6-dibromo-2-hydroxy-4,5-methylenedioxybenzaldehyde **8** was obtained.

Mp (°C): 198 (light yellow solid). IR (KBr, cm^{-1}): 3446 (broad, OH); 1627 (C=O). ^1H NMR (270 MHz, $CDCl_3$): δ 6.18 (2H, s, OCH_2O); 10.00 (1H, s, C*H*O); 13.42 (O*H*). ^{13}C NMR (68 MHz, $CDCl_3$): δ 90.49 (3-*C*Br); 101.58 (6-*C*Br); 102.82 (O*C*H_2O); 110.83 (1-C_q); 139.85 (5-C_q); 152.83 (2- or 4-C_q); 160.27 (2- or 4-C_q); 194.37 (*C*HO). MS (70 eV, ES^-, *m/z* (%)): 321/323/325 ($M-H^+$). Anal. Calcd for $C_8H_4O_4Br_2$: C, 29.66%; H, 1.24%. Found: C, 29.79%; H, 1.32%.

4.2.4. 2-Hydroxy-3-methoxy-4,5-methylenedioxybenzaldehyde 9. 3-Bromo-2-hydroxy-4,5-methylenedioxybenzaldehyde **7** (245 mg; 1 mmol) and copper(II) chloride (27 mg; 0.2 mmol) were dissolved in a mixture of 2 ml of methanol and 2 ml of *N*,*N*-dimethylformamide. To this solution 4 ml of a 2 N sodium methoxide solution in methanol was slowly added. The reaction mixture was stirred for 32 h at 100 °C. The solvent was removed under reduced pressure. The precipitate was dissolved in ether (20 ml), poured into 20 ml of a 2 N hydrogen chloride solution and extracted with diethyl ether (3×20 ml). The combined organic layers were washed with a 2 N hydrogen chloride solution (10 ml) and water (10 ml). The organic layer was dried over magnesium sulfate. After filtration and evaporation of the solvent the residue was chromatographed over silica gel (20% ethyl acetate/80% hexane), giving 136 mg (69%) of pure 2-hydroxy-3-methoxy-4,5-methylenedioxybenzaldehyde **9**.

Mp (°C): 97.9–98.2 (white powder). IR (KBr, cm^{-1}): 3420 (broad, OH); 1620 (C=O). ^1H NMR (270 MHz, $CDCl_3$): δ 4.05 (3H, s, OCH_3); 6.02 (2H, s, OCH_2O); 6.65 (1H, s, 6-C*H*); 9.65 (1H, s, C*H*O); 11.73 (1H, s, O*H*). ^{13}C NMR (68 MHz, $CDCl_3$): δ 60.50 (O*C*H_3); 102.32 (O*C*H_2O); 103.72 (6-*C*H); 114.03 (1-C_q); 141.92 (C_q); 144.63 (C_q); 144.96 (C_q); 153.55 (C_q); 194.16 (*C*HO). MS (70 eV, EI, *m/z* (%)): 196 (M^+, 100); 195 (19); 181 (11); 165 (16); 150 (16); 123 (10); 120 (13); 95 (13); 69 (13); 66 (11); 55 (24); 53 (21); 44 (10). Anal. Calcd for $C_9H_8O_5$: C, 55.11%; H, 4.11%. Found: C, 55.32%; H, 3.98%.

4.2.5. 2-Hydroxy-3,6-dimethoxy-4,5-methylenedioxybenzaldehyde 10. 3,6-Dibromo-2-hydroxy-4,5-methylenedioxybenzaldehyde **8** (0.97 g; 3 mmol) and copper(II) chloride (0.16 g; 1.2 mmol) were dissolved in a mixture of 12 ml of methanol and 12 ml of *N*,*N*-dimethylformamide. To this solution 24 ml of 2 N sodium methoxide in methanol was added dropwise. The reaction mixture was stirred for 32 h at 100 °C. The solvent was evaporated and the residue was dissolved in diethyl ether (120 ml), poured into 120 ml of 2 N hydrogen chloride solution and extracted with diethyl ether (3×100 ml). The combined extracts were washed with 2 N hydrogen chloride solution (60 ml) and water (60 ml). The organic layers were dried on magnesium sulfate. After filtration and evaporation of the solvent the residue was separated by chromatography over silica (20% ethyl acetate, 80% hexane). This procedure yielded 508 mg (52%) of 2-hydroxy-3,6-dimethoxy-4,5-methylenedioxybenzaldehyde **10**, 106 mg (18%) of 2-hydroxy-3-methoxy-4,5-methylenedioxybenzaldehyde **9**, 18 mg (3%) of 2-hydroxy-6-methoxy-4,5-methylenedioxybenzaldehyde **11**, and 15 mg (3%) of 2-hydroxy-4,5-methylenedioxybenzaldehyde **6**.

2-Hydroxy-3,6-dimethoxy-4,5-methylenedioxybenzaldehyde **10**. Mp (°C): 121.4 (white powder). IR (KBr, cm^{-1}): 3447 (broad, OH); 1625 (C=O). ^1H NMR (270 MHz, $CDCl_3$): δ 3.94 (3H, s, 6-OCH_3); 4.07 (3H, s, 3-OCH_3); 5.97 (2H, s, OCH_2O); 10.04 (1H, s, C*H*O); 12.59 (1H, s, O*H*). ^{13}C NMR (68 MHz, $CDCl_3$): δ 60.22 (O*C*H_3); 60.90 (O*C*H_3); 102.01 (O*C*H_2O); 107.46 (1-C_q); 126.72 (3-C_q or 5-C_q); 128.07 (3-C_q or 5-C_q); 139.53 (6-C_q); 147.78 (2-C_q or 4-C_q); 154.59 (2-C_q or 4-C_q); 192.52 (*C*HO). MS (70 eV, ES^+, *m/z* (%)): 227 ($M+H^+$). Anal. Calcd for $C_{10}H_{10}O_6$: C, 53.10%; H, 4.46%. Found: C, 52.91%; H, 4.33%.

2-Hydroxy-6-methoxy-4,5-methylenedioxybenzaldehyde **11**. Mp (°C): 121 (white powder). IR (KBr, cm^{-1}): 3435 (broad, OH); 1633 (C=O). ^1H NMR (270 MHz, $CDCl_3$): δ 4.12 (3H, s, OCH_3); 5.93 (2H, s, OCH_2O); 6.12 (1H, s, 3-C*H*); 10.03 (1H, s, C*H*O); 12.56 (1H, s, O*H*). ^{13}C NMR (68 MHz, $CDCl_3$): δ 60.03 (O*C*H_3); 92.14 (3-*C*H); 101.60 (O*C*H_2O);

107.24 (1-C_q); 127.41 (C_q); 143.79 (C_q); 157.27 (C_q); 162.49 (C_q); 191.99 (*C*HO). MS (70 eV, ES^+, *m/z* (%)): 197 ($M+H^+$). Anal. Calcd for $C_9H_8O_5$: C, 55.11%; H, 4.11%. Found: C, 55.37%; H, 4.19%.

4.2.6. Ayapin (6,7-methylenedioxycoumarin) 1. *6H-[1,3]Dioxolo[4,5-g]chromen-6-one*. 2-Hydroxy-4,5-methylenedioxybenzaldehyde **6** (166 mg; 1 mmol) and methoxycarbonyltriphenylphosphorane (401 mg; 1.2 mmol) were dissolved in 5 ml of *N*,*N*-diethylaniline. The reaction mixture was stirred for 4 h at 220 °C under nitrogen atmosphere. The reaction mixture was cooled down to room temperature. The solvent was removed by vacuum distillation (0.01 mmHg/40–50 °C). After chromatography (50% diethyl ether, 50% hexane), 148 mg (78%) of pure ayapin **1** was obtained (white solid).

Mp (°C): 229–230 (lit. 231–232[26]). IR (KBr, cm^{-1}): 1705 (C=O), 1620, 1575. ^1H NMR (270 MHz, $CDCl_3$): δ 6.07 (2H, s, OCH_2O); 6.28 (1H, d, $J=9.6$ Hz, 3-C*H*); 6.82 and 6.83 (each 1H, each s, 5-C*H* and 8-C*H*); 7.58 (1H, d, $J=9.6$ Hz, 4-C*H*). ^{13}C NMR (68 MHz, $CDCl_3$): δ 98.42 (8-*C*H); 102.35 (O*C*H_2O); 105.03 (5-*C*H); 112.68 (4a-C_q); 113.40 (3-*C*H);143.50 (4-*C*H); 144.92 (6-C_q); 151.25 (7- or 8a-C_q); 151.28 (7- or 8a-C_q); 161.26 (*C*=O). MS (70 eV, EI, *m/z* (%)): 191 (M+1, 14); 190 (M^+, 100); 162 (60); 161 (37); 81 (12); 79 (12); 76 (17); 53 (12); 51 (14). Anal. Calcd for $C_{10}H_6O_4$: C, 63.16%; H, 3.18%. Found: C, 63.36%; H, 3.28%.

4.2.7. 8-Methoxy-6,7-methylenedioxycoumarin 2. *4-Methoxy-6H-[1,3]dioxolo[4,5-g]chromen-6-one*. The synthesis of 8-methoxy-6,7-methylenedioxycoumarin **2** (169 mg; 0.77 mmol) from 2-hydroxy-3-methoxy-4,5-methylenedioxybenzaldehyde **9** (196 mg; 1.00 mmol) was analogous to the synthesis of ayapin **1**. Yield: 77% (white solid).

Mp (°C): 148–150 °C (lit. mp not reported[5]). IR (KBr, cm^{-1}): 1705 (C=O), 1585. ^1H NMR (270 MHz, $CDCl_3$): δ 4.12 (3H, s, OCH_3); 6.05 (2H, s, OCH_2O); 6.29 (1H, d, $J=9.6$ Hz, 3-C*H*); 6.57 (1H, s, 5-C*H*); 7.56 (1H, d, $J=9.6$ Hz, 4-C*H*). ^{13}C NMR (68 MHz, $CDCl_3$): δ 60.70 (O*C*H_3); 99.33 (5-*C*H); 102.30 (O*C*H_2O); 113.30 (4a-C_q); 113.89 (3-*C*H); 131.91 (7- or 8a-C_q); 140.63 (7- or 8a-C_q); 143.47 (8-*C*H); 143.66 (4-*C*H); 145.60 (6-C_q); 160.59 (*C*=O). MS (70 eV, EI, *m/z* (%)): 220 (M^+, 100); 192 (51); 190 (32); 162 (22); 147 (22); 79 (26); 63 (21); 53 (19); 51 (29); 44 (27). Anal. Calcd for $C_{11}H_8O_5$: C, 60.01%; H, 3.66%. Found: C, 59.95%; H, 3.48%.

4.2.8. 5-Methoxy-6,7-methylenedioxycoumarin 3. *9-Methoxy-6H-[1,3]dioxolo[4,5-g]chromen-6-one*. The synthesis of 5-methoxy-6,7-methylenedioxycoumarin **3** (8.7 mg; 0.04 mmol) from 2-hydroxy-6-methoxy-4,5-methylenedioxybenzaldehyde **11** (9.8 mg; 0.05 mmol) was analogous to the synthesis of ayapin **1**. Yield: 79% (white solid).

Mp (°C): 192 (lit. 200–202,[6] 192–194[7]). IR (KBr, cm^{-1}): 1740 (C=O), 1627 (C=C). ^1H NMR (270 MHz, $CDCl_3$): δ 4.14 (3H, s, OCH_3); 6.01 (2H, s, OCH_2O); 6.21 (1H, d, $J=9.9$ Hz, 3-C*H*); 6.54 (1H, s, 8-C*H*); 7.95 (1H, d, $J=9.9$ Hz, 4-C*H*). ^{13}C NMR (68 MHz, $CDCl_3$): δ 59.99 (*C*H_3O); 92.50 (8-*C*H); 101.83 (O*C*H_2O); 106.63 (4a-C_q); 111.74 (3-*C*H); 131.76 (6-C_q); 138.05 (5-C_q); 138.84 (4-*C*H); 151.56 (7- or 8a-C_q); 152.67 (7- or 8a-C_q); 161.33 (*C*=O). MS (70 eV, ES^+, *m/z* (%)): 221 ($M+H^+$). Anal. Calcd for $C_{11}H_8O_5$: C, 60.01%; H, 3.66%. Found: C, 60.23%; H, 3.51%.

4.2.9. 5,8-Dimethoxy-6,7-methylenedioxycoumarin 4. *4,9-Dimethoxy-6H-[1,3]dioxolo[4,5-g]chromen-6-one*. The synthesis of 5,8-dimethoxy-6,7-methylenedioxycoumarin **4** (41 mg; 0.16 mmol) out of 2-hydroxy-3,5-dimethoxy-4,5-methylenedioxybenzaldehyde **9** (45.2 mg; 0.2 mmol) was analogous to the synthesis of ayapin **1**. Yield: 82% (yellow solid).

Mp (°C): 131–133 (lit. mp not reported[32]). IR (KBr, cm^{-1}): 1724 (C=O), 1620, 1590. ^1H NMR (270 MHz, $CDCl_3$): δ 4.02 (3H, s, 5-OCH_3); 4.06 (3H, s, 8-OCH_3) 6.03 (2H, s, OCH_2O); 6.22 (1H, d, $J=9.7$ Hz, 3-C*H*); 7.93 (1H, d, $J=9.7$ Hz, 4-C*H*). ^{13}C NMR (68 MHz, $CDCl_3$): δ 60.22 (8-O*C*H_3); 61.25 (5-O*C*H_3); 102.21 (O*C*H_2O); 107.10 (4a-C_q); 112.24 (3-*C*H); 127.04 (C_q); 132.92 (C_q); 133.48 (C_q); 138.92 (4-*C*H); 143.07 (7- or 8a-C_q); 143.83 (7- or 8a-C_q); 160.59 (*C*=O). MS (70 eV, ES^+, *m/z* (%)): 251 ($M+H^+$). Anal. Calcd for $C_{12}H_{10}O_6$: C, 57.60%; H, 4.03%. Found: C, 57.50%; H, 4.20%.

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New phenolic triterpenes from *Maytenus blepharodes*. Semisynthesis of 6-deoxoblepharodol from pristimerin

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Abstract—Four new phenolic triterpenes with a 24-*nor*-D:A-friedoleane skeleton, isoblepharodol, 7-oxoblepharodol, blepharotriol and 6-deoxoblepharodol, were isolated from *Maytenus blepharodes*. Their structures were elucidated on the basis of spectroscopic analysis, including homo and heteronuclear correlation NMR experiments (COSY, ROESY, HSQC, and HMBC). The semisynthesis of 6-deoxoblepharodol and its epimer at C-8 was achieved by catalytic reduction of pristimerin, a quinone-methide triterpene present in the plant. The biosynthetic formation of the phenolic triterpenes isolated from this species is also discussed. The compounds were assayed for antimicrobial and cytotoxic activities.

1. Introduction

The aromatic and quinoid triterpenoids constitute a small group of unsaturated and oxygenated D:A-friedo-*nor*-oleananes, and in nature these pigments are restricted to the plant families Celastraceae and Hyppocrataceae.[1] This type of triterpenoids are of medical interest since they tend to exhibit antibiotic[2] and anticancer activities.[3] As part of our studies on medicinal plants belonging to the Celastraceae family, which are widely used as folk medicines in South and Central America,[4] we had previously reported phenolic triterpenes,[5] triterpene dimers,[6,7] and dihydro-β-agarofuran sesquiterpenes[6] from *Maytenus blepharodes* Lundell, a species that grows in Panama.

A further search for structurally interesting and bioactive compounds from this plant resulted in the isolation of the new phenolic triterpenes isoblepharodol (**1**), 7-oxo blepharodol (**2**), blepharotriol (**3**), and 6-deoxoblepharodol (**4**), together with the known phenolic triterpenes 6-oxo-pristimerol,[8] 7-hydroxy-6-oxopristimerol,[9] demethyl zeyl-asteral and demethylzeylasterone.[10] Their structures were determined by spectroscopic methods, including ^{1}H–^{13}C heteronuclear correlation (HSQC), long-range correlation with inverse detection (HMBC), and ROESY NMR experiments. Catalytic reduction of pristimerin,[11] a quinone-methide triterpene present in the plant, yielded **4** and its epimer at C-8 (**5**), in addition to pristimerol, a known synthetic compound.[12] We put forth a biosynthetic route to the phenolic triterpenes isolated from *M. blepharodes*, deriving from pristimerin, the most abundant secondary metabolite.[5] Their antimicrobial activity was tested against Gram-positive and Gram-negative bacteria and the yeast *Candida albicans*, while the cytotoxic activity was assayed against HeLa (human cervix carcinoma), Hep-2 (human larynx carcinoma), and Vero (African green monkey kidney) cell lines.

2. Results and discussion

Compound **1** was isolated as a pale yellow amorphous solid with the molecular formula $C_{30}H_{42}O_5$ determined by HREIMS. Its IR spectrum showed absorption bands for hydroxyl (3396 cm^{-1}), ester carbonyl (1713 cm^{-1}) and carbonyl (1627 cm^{-1}) groups, and the UV spectrum revealed la presence of a non-conjugated aromatic system (287 and 320 nm). The ^{1}H NMR spectrum (Table 1) showed signals for six methyl groups, one of them on an aromatic ring at δ 2.09, a methoxy group at δ 3.60, an aromatic proton

Keywords: Phenolic triterpenes; Semisynthesis; *Maytenus blepharodes*; Celastraceae.
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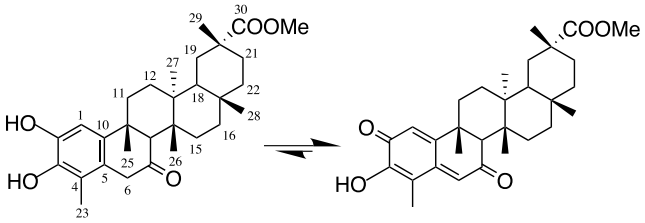
Table 1. ^{1}H and ^{13}C NMR data of compounds **1–7**

	1		**2**		**3**		**4**		**5**		**6**		**7**	
	δ_H[a]	δ_C[b]	δ_H[a]	δ_C[b]	δ_H[a]	δ_C[b]	δ_H[a]	δ_C[b]	δ_H[a]	δ_C[b]	δ_H[a]	δ_C[b]	δ_H[a]	δ_C[b]
1	6.90 s	107.8 d	6.99 s	107.9 d	6.55 s	103.2 d	6.67 s	108.4 d	6.75 s	111.5 d	6.79 s	102.5 d	6.47 s	99.3 d
2		141.7 s		150.0 s		149.5 s		140.9 s		141.2 s		150.5 s		157.9 s
3		140.4 s		141.4 s		128.5 s		139.7 s		139.5 s		142 4 s		134.1 s
4		122.0 s		129.1 s		148.8 s		122.0 s		120.3 s		128.9 s		155.5 s
5		123.9 s		122.8 s		108.7 s		126.6 s		129.6 s		123.7 s		110.2 s
6	3.36 d_{AB} (8.4)	43.9 t		182.0 s		189.3 s	2.56, 2.72	28.3 t	2.66 br d (14.7)	29.5 t		181.0 s	2.66 s	189.2 s
7		209.8 s		197.0 s	6.28 s	123.4 d	1.68, 1.79	18.5 t		30.0 t		196.6 s	6.29 s	123.7 d
8	2.84 s	58.3 d	3.20 s	60.3 d		178.1 s	1.69	44.1 d	1.40 m	56.2 d	3.19 s	60.3 d		177.7 s
9		38.8 s		38.7 s		40.5 s		36.8 s		38.3 s		38.7 s		40.8 s
10		142.4 s		153.6 s		150.0 s		143.8 s		142.1 s		152.3 s		153.2 s
11	1.40, 2.15	33.7 t	0.99, 2.05	33.5 t	2.20	33.7 t	1.70, 1.90	34.1 t		33.6 t	0.97, 2.05	33.4 t	2.23	33.9 t
12	1.30, 1.82	29.4 t	1.55, 1.64	27.8 t	1.36, 2.18	29.8 t		30.2 t		27.0 t	1.52, 1.68	27.8 t		29.7 t
13		39.1 s		39.5 s		39.5 s		38.9 s		40.3 s		39.2 s		39.4 s
14		38.7 s		39.2 s		45.4 s		39.4 s		38.2 s		39.4 s		45.4 s
15	1.21, 1.82	28.4 t	1.90, 2.15	38.7 t		28.8 t		29.0 t		30.8 t	2.17	38.7 t		28.8 t
16	1.46, 1.56	36.1 t	1.33, 1.85	35.8 t	0.90, 2.05	34.8 t		36.5 t	0.92, 2.08	37.1 t	1.33, 1.85	35.8 t		34.8 t
17		30.3 s		30.2 s		30.5 s		30.3 s		31.0 s		30.3 s		30.5 s
18		43.6 d	1.65	43.6 d	1.58[c]	44.3 d	1.58	44.5 d	1.49	46.6 d	1.64	43.5 d		44.3 d
19α	2.35	30.6 t	2.35	30.6 t	2.43 d (15.5)	30.8 t		30.6 t	2.35 br d (15.3)	30.5 t	2.35	30.5 t		30.9 t
19β	1.62		1.62		1.70				1.59		1.63			
20		40.6 s		40.7 s		40.4 s		40.6 s		40.6 s		40.5 s		40.5 s
21	1.91, 2.05	29.8 t	2.02	30.3 t		29.3 t		30.0 t		30.1 t	2.03	30.2 t		29.7 t
22	1.98	35.9 t	2.17	35.8 t	1.58[c], 1.90	36.3 t	2.09 s	36.2 t	0.83, 2.21	35.6 t	1.99, 2.16	35.7 t		36.3 t
23	2.09 s	11.5 q	2.61 s	13.8 q				11.3 q	2.11 s	11.2 q	2.56 s	13.2 q		
25	1.34 s	27.9 q	1.28 s	31.5 q	1.54 s	37.6 q	1.18 s	27.4 q	1.42 s	36.9 q	1.30 s	31.6 q	1.57 s	37.7 q
26	1.12 s	15.1 q	1.36 s	14.7 q	1.30 s	18.2 q	0.94 s	15.9 q	1.19 s	25.8 q	1.36 s	14.7 q	1.31 s	18.3 q
27	0.73 s	16.8 q	0.79 s	16.9 q	0.56 s	14.1 q	0.78 s	17.3 q	0.67 s	18.9 q	0.79 s	16.8 q	0.58 s	20.8 q
28	1.08 s	31.5 q	1.11 s	31.5 q	1.10 s	31.6 q	1.10 s	31.8 q	1.07 s	31.3 q	1.11 s	29.0 q	1.11 s	31.6 q
29		179.4 s		180.0 s		178.8 s		179.3 s		179.4 s		179.4 s		178.9 s
30	1.18 s	32.3 q	1.21 s	32.5 q	1.17 s	32.7 q	1.19 s	31.9 q	1.16 s	32.9 q	1.20 s	32.4 q	1.18 s	32.8 q
OMe-29	3.60 s	51.6 q	3.63 s	51.8 q	3.54 s	51.5 q	3.59 s	51.5 q	3.56 s	51.4 q	3.62 s	51.4 q	3.54 s	51.5 q
OMe-2											4.02 s	55.9 q	3.94 s	56.0 q
OMe-3													3.90 s	60.6 q

[a] δ, $CDCl_3$, J are given in Hz in brackets.
[b] Data are based on DEPT and HSQC experiments.
[c] Overlapping signals.

at δ 6.90 and a signal at δ 5.19, exchangeable with D_2O. The signals at δ 3.36 d_{AB} and 2.84 s were assigned to the α protons to a carbonyl group, which was in agreement with the ^{13}CNMR spectrum (Table 1). The full assignments and connectivities were determined by its COSY, HSQC and HMBC spectra. Thus, the carbonyl group was located at C-7 from the HMBC correlations, which linked the signals at δ_H 2.84 (H-8) and 3.36 (H-6) to the signal at δ_C 209.8. All these data suggested that **1** was an isomer of the previously reported phenolic triterpene, blepharodol,[5] that we named isoblepharodol. Upon standing for a few days in the laboratory at room temperature, this compound was oxidized into a yellow solid, the spectroscopic data of which were identical to those of the known quinone-methide, dispermoquinone[13] (Fig. 1).



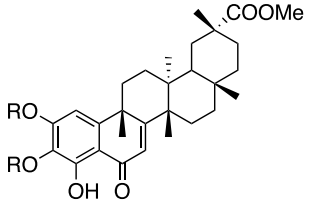
1 Isoblepharodol — Dispermoquinone

Figure 1. Structure of isoblepharodol (**1**) and its quinone-methide form, dispermoquinone.

Compound **2** has the molecular formula $C_{30}H_{40}O_6$ by HREIMS and ^{13}C NMR data. Its IR spectrum indicated the presence of hydroxyl (3413 cm^{-1}) and carbonyl (1720 and 1650 cm^{-1}) groups, and the UV spectrum showed absorption maxima at 284 and 314 nm, characteristic of an aromatic ring and a conjugated diketone. The NMR data (Table 1) were similar to those of **1**, the main differences being the disappearance of the signal at δ_H 3.36 (H-6) and the presence of an additional carbonyl group at δ_C 182.0. The position of this second carbonyl group has been assigned to C-6 due to the downfield chemical shift for the Me-23 at δ_H 2.61, suggesting that it is in a periplanar position to a carbonyl group,[5] and confirmed by a HMBC experiment, where a three-bond coupling between the signals at δ_C 182.0 and δ_H 3.20 (H-8), was observed.

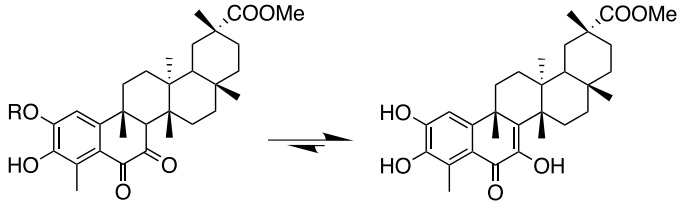
Therefore, the structure of **2** was determined as 7-oxo-blepharodol, which is in a tautomeric keto-enolic equilibrium with 7-hydroxy-6-oxopristimerol, also isolated from the plant (Fig. 2). Compound **2** was methylated with diazomethane, affording 2-*O*-methyl-7-oxoblepharodol (**6**), which structure was confirmed by a NOE effect observed between the methoxyl group (δ 4.02) and H-1 (δ 6.79) in a ROESY experiment.

Compound **3** was assigned the molecular formula $C_{29}H_{38}O_6$ (HREIMS). The IR spectrum showed absorption bands of hydroxyl (3368 cm^{-1}), carboxyl (1723 cm^{-1}) and α,β-unsaturated carbonyl (1645 cm^{-1}) groups, which was confirmed by its UV spectrum showing absorption maxima at 332 and 245 nm, characteristic of a pyrogallol-type system. Its ^{1}H NMR spectrum (Table 1) showed signals for five angular methyls, a methoxy group at δ 3.54 and two singlets at δ 6.55 and 6.28, characteristic of an aromatic proton and a proton in α position to a conjugated ketone, respectively. A signal at δ 13.11, exchangeable with D_2O, was also observed, and its downfield chemical shift suggested that it is a hydroxyl proton engaged in an hydrogen-bond with the carbonyl group in a stable 6-membered ring system. These data were confirmed by its ^{13}C NMR spectrum (Table 1), with signals at δ 123.4 (C-7), 178.1 (C-8) and 189.3 (C-6); in addition, signals for six aromatic carbons, three of which are linked to oxygen at δ 128.5 (C-3),[5] 148.8 (C-4), and 149.5 (C-2), were observed. All these data indicated that **3** is 4-hydroxy-23-*nor*-6-oxopristimerol, that we named blepharotriol, representing the first example of a phenolic triterpene with three vicinal phenolic groups on A ring. When **3** was treated with diazomethane, the derivative 2,3-*O*-dimethyl-blepharotriol (**7**) was obtained; the 4-OH group resists methylation due to it being engaged in a stabilized hydrogen-bond. Its structure was confirmed by a ROESY experiment, showing a NOE effect between the methoxy group at C-2 (δ 3.94) and H-1 (δ 6.47), and by a HMBC experiment, linking the signal at δ_H 6.47 and those at δ_C 134.1 (C-3) and δ_C 157.9 (C-2), which in turn correlated with the signals at δ_H 3.90 and 3.94, assigned to methoxy groups.



3 R = H Blepharotriol
7 R = CH_3 2,3-*O*-Dimethoxy-blepharotriol

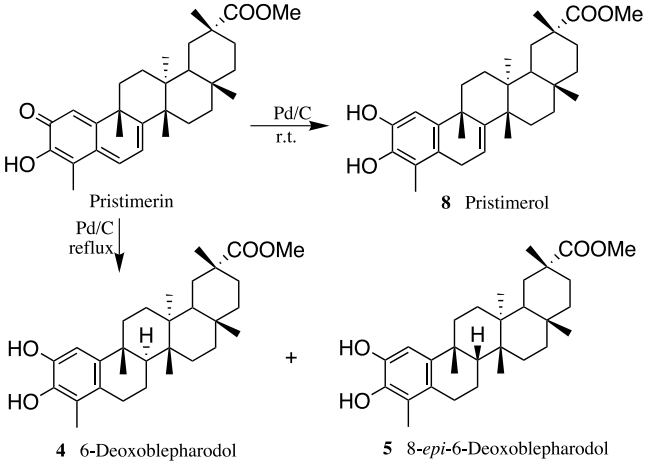
Compound **4**, with a molecular formula $C_{30}H_{44}O_4$ established by HREIMS, was obtained as a minor component. Its IR spectrum showed absorption bands for hydroxyl



2 R = H 7-Oxoblepharodol
6 R = CH_3 2-*O*-Methoxy-7-oxoblepharodol
7-Hydroxy-6-oxopristimerol

Figure 2. Tautomeric equilibrium between 7-oxoblepharodol (**2**) and 7-hydroxy-6-oxopristimerol.

(3417 cm^{-1}) and carboxyl (1729 cm^{-1}) groups, and the UV spectrum showed an absorption maximum at 277 nm, characteristic of an aromatic ring. Its ^1H NMR (Table 1) spectrum showed signals for six methyl groups, one of them on an aromatic ring at δ 2.09, a methoxy at δ 3.59, a singlet at δ 5.05 exchangeable with D_2O, and an aromatic proton at δ 6.67. These data indicated that **4** was related to **1**, the most notable differences being the downfield displacement of the Me-25 (δ_H 1.18) and H-1 (δ_H 6.67), and the absence of a carbonyl carbon (Table 1). All these data established the structure of **4** as 6-deoxoblepharodol (Scheme 1).



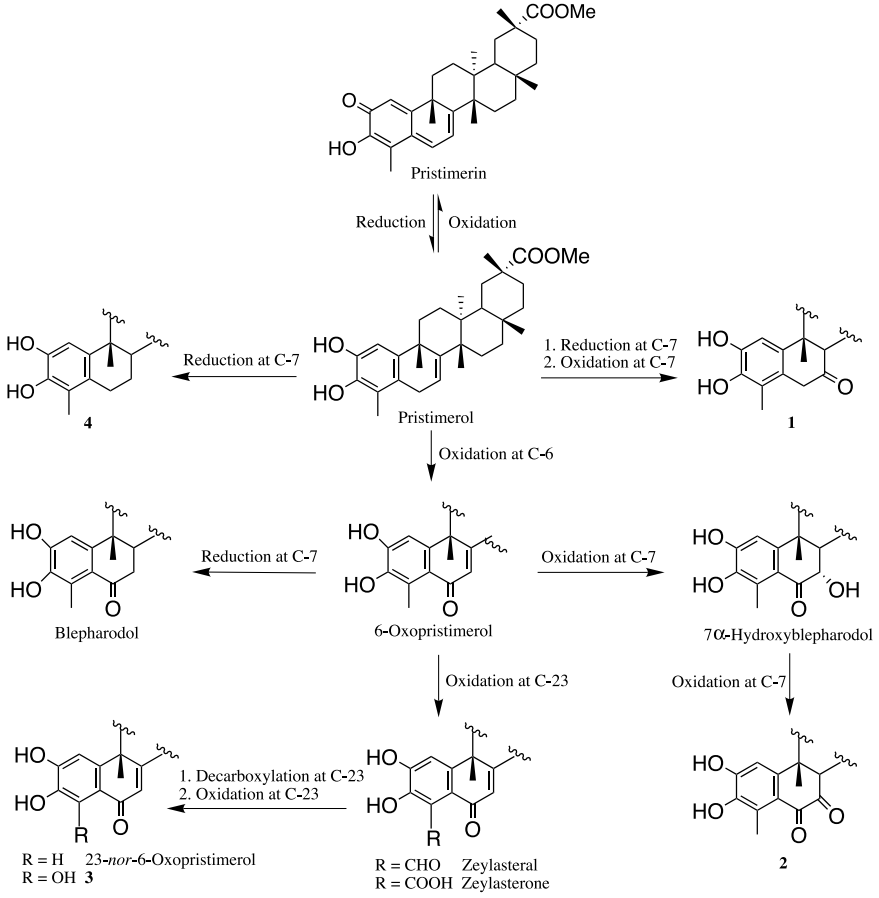
Scheme 1. Synthesis of **4**, **5** and **8** from pristimerin.

In an attempt to obtain a greater amount of compound **4** for biological assays, we decided to synthesize it from pristimerin,[11] a *nor*-quinonemethide triterpenenoid also present in the plant.[5] Thus, treatment of pristimerin, dissolved in glacial acetic acid, with 5% Pd/C under an atmosphere of hydrogen at reflux, afforded a mixture of **4** and **5** (Scheme 1). When the reaction was achieved at room temperature, pristimerol (**8**),[12] a known synthetic compound whose ^1H and ^{13}C NMR data have not been previously assigned, was obtained.

Compound **5**, according to its spectroscopic data, proved to be the isomer at C8 of **4** (Scheme 1). The most noteworthy differences were the signals assigned to H-8 (δ_H 1.69 in **4** and δ_H 1.40 in **5**), as well as the Me-25 and Me-26 which their chemical shifts increased by about 0.2 ppm. The ^{13}C NMR spectrum (Table 1) shows significant differences for the chemical shifts of C-7, C-8, Me-25 and Me-26. These data indicated a β-axial stereochemistry at H-8, which was confirmed by a ROESY experiment, showing a NOE effect between the signals at δ_H 1.40 (H-8) and δ_H 1.19 (Me-26).

The formation of the phenolic triterpenes, isolated from *M. blepharodes*, from pristimerin (the most abundant secondary metabolite), can be explained on the basis of simple transformations such as ring A aromatizations, oxidations, decarboxylations and reductions (Scheme 2).

Compounds **2**–**8** were tested on Gram-positive and Gram-negative bacteria, and the yeast *Candida albicans*. Due to



Scheme 2. Biosynthetic proposal for phenolic triterpenes isolated from *Maytenus blepharodes*.

Table 2. Minimal inhibitory concentrations (MIC, μg/ml) of **2–5** and **8** against the susceptible Gram-positive bacteria[a]

Bacteria	**2**	**3**	**4**	**5**	**8**	Control[b]
S. aureus	30	>40	>40	>40	>40	5–2
S. epidermidis	>40	>40	20–10	2	0.6	5
S. saprophyticus	>40	>40	>40	20–10	10–5	4
E. faecalis	>40	>40	>40	>40	>40	40–20
B. subtilis	8–4	8–4	10–5	5–2.5	1–0.5	2–5
B. cereus	10	>40	20–10	10–5	2.5	n.a.[c]

[a] All assays were carried out in triplicate.
[b] Cephotaxime was used as positive control.
[c] n.a.: not assayed.

Table 3. Cytotoxic activity[a] of **2–5** and **8**

	IC_{50} (μg/mL)					
Cell line	**2**	**3**	**4**	**5**	**8**	Control[b]
HeLa	19.6	12.2	13.5	1.6	0.5	0.6
Hep-2	>20	>20	>20	5.9	2.8	>20
Vero	n.a.[c]	>20	12.6	2.2	1.4	10.6

[a] All assays were carried out in triplicate.
[b] Mercaptopurine was used as positive control.
[c] n.a.: not assayed.

the scarcity of compound **1**, its biological activities were not determined. All the compounds assayed were inactive (MIC>40 μg/mL) against the Gram-negative bacteria and the yeast. The results (Table 2) showed that compound **8** was the most active compound against Gram-positive bacteria, including *E. faecalis*, a multidrug-resistant bacterium.[14] Compounds with extended conjugation to the B-ring showed a broader spectrum of activity (**8**, **5** and **4** versus **2** and **3**); the results also suggest the relevance of the configuration at C-8 (**5** vs **4**) and of the phenolic ring (**2** and **3** vs **6** and **7**) for the activity.

The cytotoxic activity (Table 3) showed that **5** and **8** were even more active against the two tumor cell lines (HeLa and Hep-2) used, than mercaptopurine used as control, while **2–4** were slightly active against HeLa, the other assayed compounds being inactive (IC_{50}>20 μg/mL).

3. Experimental

3.1. General

IR spectra were recorded in $CHCl_3$ on a Bruker IFS 55 spectrophotometer and UV spectra were collected in absolute EtOH on a Jasco V-560. ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance at 400 and 100 MHz, respectively. Optical rotations were measured on a Perkin–Elmer 241 automatic polarimeter and CD spectra on a Jasco J-600 spectropolarimeter. EIMS and HR-EIMS were recorded on a Micromass Autospec spectrometer. TLC 1500/LS 25 Schleicher and Schuell foils were used for thin layer chromatography. Purification was performed using silica gel (particle size 40–63 μM, Merck, and HPTLC-Platten-Sil 20 UV_{254}, Panreac) and Sephadex LH-20 (Pharmacia).

3.2. Plant

Maytenus blepharodes was collected at Baru volcano, Chirique, Panama, in August 1991, and a voucher specimen is on file in the Department of Medicinal Chemistry and Pharmacognosy, University of Panama.

3.3. Extraction and isolation

The root bark of the plant (0.5 kg) was extracted with *n*-hexane-Et_2O (1:1) (4 L) in a Soxhlet apparatus. The extract (10 g) was chromatographed on Sephadex LH-20, using *n*-hexane–$CHCl_3$–MeOH (2:1:1) as eluant, followed by repeated chromatographies on silica gel with *n*-hexane–EtOAc mixtures of increasing polarity and preparative HPTLC (*n*-hexane–$CHCl_3$–acetone, 6:3:1) to yield **1** (9.0 mg), **2** (31.5 mg), **3** (43.6 mg), **4** (1.2 mg), 6-oxopristimerol (77.0 mg), 7-hydroxy-6-oxopristimerol (3.0 mg), demethylzeylasteral (7.0 mg) and demethylzeylasterone (53.0 mg).

3.3.1. Isoblepharodol (1). Pale yellow amorphous solid; $[\alpha]_D^{20}$ −63.8° (*c* 0.21, MeOH); UV (EtOH) λ_{max} (log ε) 320 (3.5), 287 (3.7), 204 (2.5) nm; IR ν_{max} (film) 3396, 2896, 2856, 1713, 1627, 1463, 1384, 1309, 1215, 1095, 758 cm^{-1}; ^1H NMR δ 5.19 (1H, br s, OH), for other signals, see Table 1; ^{13}C NMR, see Table 1; EIMS *m*/*z* 482 (M^+, 100), 467 (7), 422 (4), 407 (4), 314 (2), 299 (3), 259 (17), 243 (12), 231 (15), 217 (28), 205 (32), 203 (54), 135 (13), 121 (15), 109 (24), 95 (23); HR-EIMS *m*/*z* $[M]^+$ 482.3025 (calcd for $C_{30}H_{42}O_5$, 482.3032).

3.3.2. 7-Oxoblepharodol (2). Yellow amorphous solid; $[\alpha]_D^{20}$ −76.2° (*c* 0.38, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 314 (3.5), 284 (3.6), 205 (3.2) nm; IR ν_{max} (film) 3413, 1720, 1650, 1583, 1450, 1370, 1293, 1257, 1044, 750 cm^{-1}; ^1H and ^{13}C NMR, see Table 1; EIMS *m*/*z* 496 (M^+, 14), 453 (5), 437 (5), 263 (19), 234 (89), 203 (100), 147 (14), 121

(17), 95 (32); HR-EIMS *m/z* $[M]^+$ 496.2810 (calcd for $C_{30}H_{40}O_6$, 496.2825).

3.3.3. Blepharotriol (3). Yellow amorphous solid; $[\alpha]_D^{20}$ −31.6° (*c* 0.31, MeOH); UV (EtOH) λ_{max} (log ε) 332 (3.9), 245 (4.3), 210 (4.0) nm; IR ν_{max} (film) 3368, 2927, 2885, 1723, 1645, 1594, 1462, 885, 757 cm^{-1}; ^1H NMR δ 13.11 (1H, s, OH-4, exchangeable with D_2O), for other signals, see Table 1; ^{13}C NMR, see Table 1; EIMS *m/z* 482 (M^+, 100), 467 [M^+-15, 10), 428 (8), 294 (2), 287 (3), 271 (6), 259 (9), 236 (14), 233 (11), 219 (49), 203 (41); HR-EIMS *m/z* $[M]^+$ 482.2656 (calcd for $C_{29}H_{38}O_6$, 482.2668).

3.3.4. 6-Deoxoblepharodol (4). Pale yellow amorphous solid; $[\alpha]_D^{20}$ −9.47° (*c* 0.19, MeOH); UV (EtOH) λ_{max} (log ε) 277 (5.8), 202 (6.5), 191 (5.8) nm; IR ν_{max} (film) 3417, 2924, 2855, 1729, 1693, 1454, 1289, 756 cm^{-1}; ^1H NMR δ 5.05 (1H, br s, OH), for other signals, see Table 1; ^{13}C NMR, see Table 1; EIMS *m/z* 468 (M^+, 91), 453 (27), 263 (11), 249 (64), 217 (22), 204 (40), 203 (100); HR-EIMS *m/z* $[M]^+$ 468.3244 (calcd for $C_{30}H_{44}O_4$, 468.3240).

3.3.5. 2-*O*-Methoxy-7-oxoblepharodol (6). Compound **2** (7.0 mg) was treated with CH_2N_2 and purified by preparative TLC to give compound **6** (4.5 mg, 62.5%) as a pale yellow amorphous solid; $[\alpha]_D^{20}$ −41.1° (*c* 0.42, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 315 (3.5), 284 (3.6), 2.05 (3.2) nm; IR ν_{max} (film) 3421, 2925, 2854, 2360, 1728, 1599, 1462, 1377, 1296, 1215, 1154, 758 cm^{-1}; NMR ^1H δ 5.76 (1H, br s, OH), for other signals, see Table 1; ^{13}C NMR, see Table 1; EIMS *m/z* 510 (M^+, 28), 494 (9), 467 (14), 435 (4), 325 (3), 311 (4), 299 (5), 263 (20), 248 (99), 219 (23), 203 (100), 95 (85); HR-EIMS *m/z* $[M]^+$ 510.2972 (calcd for $C_{31}H_{42}O_6$, 510.2981).

3.3.6. 2,3-*O*-Dimethoxy-blepharotriol (7). Compound **3** (9.0 mg) was treated with CH_2N_2 and purified by preparative TLC to give compound **7** (7.2 mg, 75.8%) as a pale yellow amorphous solid; $[\alpha]_D^{20}$ +12.5° (*c* 0.80, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 331 (3.9), 282 (3.6), 205 (3.2) nm; IR ν_{max} (film) 3449, 2920, 2850, 2360, 2342, 1638, 1541, 1458, 1319, 1261, 1215, 1120, 756 cm^{-1}; ^1H and ^{13}C NMR, see Table 1; EIMS *m/z* 510 [M^+, 100), 495 (46), 451 (2), 299 (4), 247 (7), 119 (5), 97 (18), 71 (22), 57 (31); HR-EIMS *m/z* $[M]^+$ 510.3017 (calcd for $C_{31}H_{42}O_6$, 510.2981).

3.4. Reduction of pristimerin

Pd/C 5% (100.0 mg) was added to a solution of pristimerin (279.0 mg) dissolved in glacial acetic acid (7 mL), and the resulting solution was stirred at reflux under hydrogen atmosphere for 3 h. The solution was then filtered through celite, quenches by addition of a saturated aqueous sodium bicarbonate solution, and the aqueous residue extracted three times with dichloromethane. The combined organic layers were washed with brine water, dried over magnesium sulfate and concentrated on a rotovapor. The crude obtained was purified by preparative TLC with hexane-diethyl ether (6:4) to afford compounds **4** (6.4 mg), and **5** (17.0 mg). Reduction of pristimerin (111.0 mg) at room temperature, following the same procedure as above, gave pristimerol (**8**, 27.7 mg).

3.4.1. 8-*epi*-6-Deoxoblepharodol (5). Pale yellow amorphous solid; $[\alpha]_D^{20}$ −6.0° (*c* 1.08, MeOH); UV (EtOH) λ_{max} (log ε) 281 (3.3) nm; IR ν_{max} (film) 3550, 3427, 2928, 2857, 1729, 1618, 1455, 1289, 1213, 759 cm^{-1}; ^1H NMR δ 5.76 (1H, br s, OH), for other signals, see Table 1; ^{13}C NMR, see Table 1; EIMS *m/z* 468 (M^+, 100), 453 (34), 261 (4), 249 (47), 245 (16), 217 (16), 203 (58), 189 (53), 177 (16), 149 (28), 121 (27), 109 (54); HR-EIMS *m/z* $[M]^+$ 468.3208 (calcd for $C_{30}H_{44}O_4$, 468.3240).

3.4.2. Pristimerol (8). Pale yellow amorphous solid; $[\alpha]_D^{20}$ −7.7° (*c* 0.13, MeOH); UV (EtOH) λ_{max} (log ε) 421 (3.0), 323 (3.4); IR ν_{max} (film) 3407, 2924, 2361, 1691, 1461, 758 cm^{-1}; ^1H NMR δ 0.59 (3H, s, Me-27), 1.09 (3H, s, Me-28), 1.14 (3H, s, Me-30), 1.23 (3H, s, Me-26), 1.29 (3H, s, Me-25), 1.65 (1H, m, H19β), 2.10 (3H, s, Me-23), 2.21 (1H, d, J=15.8 Hz, H-19α), 2.99 (1H, br d, J=20.8 Hz, H-6), 3.24 (1H, dd, J=6.1, 20.8 Hz, H-6), 3.52 (3H, s, OMe-29), 5.78 (1H, d, J=5.9 Hz, H-7), 6.73 (1H, s, H-1), 6.83 (1H, br s, H-OH), 7.99 (1H, br s, H-OH); ^{13}C NMR δ 10.7 (q, C-24), 17.8 (q, C-27), 22.3 (q, C-26), 27.5 (t, C-6), 28.8 (t, C-15), 29.7 (t, C-12), 30.2 (t, C-22), 30.3 (s, C-18), 30.5 (t, C-20), 31.0 (q, C-28), 32.1 (q, C-30), 33.8 (q, C-25), 34.4 (t, C-11), 34.6 (t, C-23), 36.5 (s, C-9), 36.8 (t, C-16), 37.5 (s, C-13), 40.1 (s, C-21), 43.7 (s, C-14), 44.4 (d, C-19), 50.8 (q, OMe-29), 108.3 (d, C-1), 117.9 (d, C-7), 119.9 (s, C-4), 124.0 (s, C-5), 140.2 (s, C-10), 140.7 (s, C-3), 142.8 (s, C-2), 149.3 (s, C-8), 178.1 (s, C-29); EIMS *m/z* 466 (M^+, 8) 451 (18), 391 (5), 243 (10), 227 (8), 201 (15), 187 (100); HR-EIMS *m/z* $[M]^+$ 466.3045 (calcd for $C_{30}H_{42}O_4$, 466.3083).

3.5. Bioassays

3.5.1. Antimicrobial activity. Activity was tested against Gram-positive (*Staphylococcus aureus* ATCC 6538, *S. epidermidis* CECT 232, *S. saprophyticus* CECT 235, *Enterococcus faecalis* CECT 481, *Bacillus subtilis* CECT 39, *B. cereus* CECT 496, *Mycobacterium smegmati* CECT 3032) and Gram-negative (*Escherichia coli* CECT 99, *Proteus mirabilis* CECT 170, *Salmonella* sp CECT 456, and *Pseudomonas aeruginosa* AK 958) bacteria and a yeast (*Candida albicans* UBC 1). The bacteria were maintained on Nutrient Agar (Oxoid or Brain Heart infusion agar, in the case of *E. faecalis* and *M. smegmati*) and the yeast on Sabouraud Agar (Oxoid) at 37 °C. The minimal inhibitory concentration (MIC) of compounds previously dissolved in DMSO (dimethyl sulfoxide) was estimated by the microdilution method.[15]

3.5.2. Cytotoxic activity. HeLa (human carcinoma of the cervix), Hep-2 (human carcinoma of the larynx), and Vero (african green monkey kidney) cell lines were each grown as a monolayer in Dulbecco's modified Eagle's medium, DMEM (Sigma), supplemented with 5% fetal calf serum (Gibco), and 1% of penicillin–streptomycin mixture (10.000 UI/mL). The cells were maintained at 37 °C in 5% CO_2 and 90% humidity. Cytotoxicity was assessed using the colorimetric MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide] reduction assay.[16] 2×10^4 cells in 50 μL were added to each well. After 48 h the optical density was measured using a microELISA reader

(multiscan Plus II) at 550 nm after dissolving the MTT formazan with DMSO (100 mL).[16]

Acknowledgements

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Barbier-type reaction mediated with tin nano-particles in water

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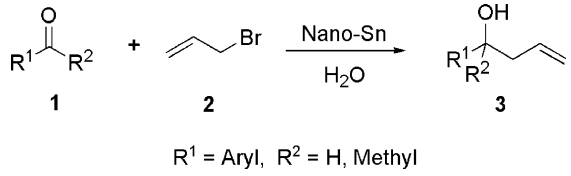
Abstract—Tin nano-particles are employed in the Barbier-type allylation reaction of carbonyl compounds in water to afford the corresponding homoallylic alcohols in good yields. The in situ generated allylation intermediates, allyltin(II) bromide and diallyltin dibromide, have been directly observed by using ^{1}H NMR. A mechanism is proposed based on this observation.

1. Introduction

The classical Barbier-type reaction has not been used as extensively as Grignard-type reaction even though the latter involves an extra step to prepare the organometallic reagents.[1] This is because many side reactions can also be mediated by the metal at the same condition. In order to extend the application of Barbier-type reactions and fully take its advantage, Barbier-type reactions in aqueous media were developed in the recent years.[2] The importance of this type of reaction has been gradually recognized not only because the tedious protection–deprotection processes can be simplified for certain functional groups containing acidic hydrogen atoms, but also because there is a growing public interest in Green Chemistry.[3] Many metal mediators as well as their salts[4] have been used in the Barbier-type allylation reactions to enhance the reaction yield and improve the stereoselectivity.[5] The dimension of metal particles should affect on metal-mediated allylation of carbonyl compounds in aqueous media because the key intermediate is believed to be generated on the metal surface.[2b] However, the metal particles smaller than the regular powder, for example, nanometer-scale particles,[6] have been not been well studied as a reagent in organic reactions.[7,8] As suggested by our previous study,[7] the yield of the Barbier-type allylation reaction can be improved by applying nano-scale metal particles. In order to further test this idea and explore the mechanism of Barbier-type reactions in water, we recently studied the allylation mediated by tin nano-particles with different sizes (Scheme 1). The details of this study are described below.



Scheme 1.

2. Results and discussion

2.1. TEM and XRD of 20-nm and 100-nm tin particles

In order to further study the mechanism of Barbier-type allylation reaction mediated by metal nano-particles and the effect of the size of nano-particles on this reaction, tin nano-particles with different sizes were prepared. Tin nano-particles with an average diameter of 20-nm were prepared by γ-radiation (method A), and tin nano-particles with an average diameter of 100-nm were prepared conveniently by reduction of $SnCl_2$ with KBH_4 in water at the presence of cetyl trimethylaminoium bromide (CTAB) (method B). Both of the two kinds of tin nano-particles were characterized by transmission electron microscopy (TEM) and X-ray powder diffraction (XRD). The average size of two kinds of nano-particles is illustrated by the TEM images (Fig. 1). As shown in Figure 2, both 20- and 100-nm tin particles are polycrystalline and their XRD patterns are consistent with that of metallic tin.[9]

Keywords: Tin; Nano-particles; Barbier-type reaction; Mechanism; Water.
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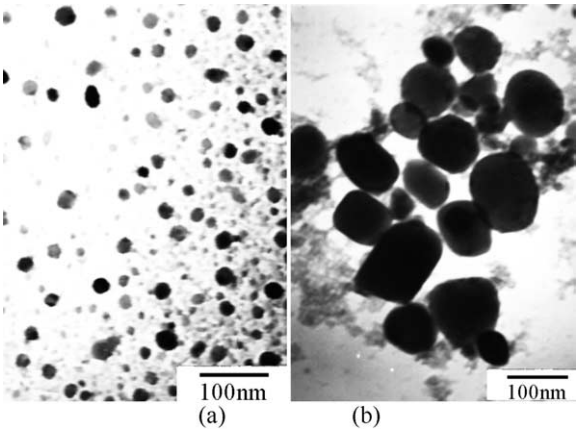


Figure 1. (a) A TEM image of 20-nm tin particles prepared with method A; (b) A TEM image of 100-nm tin particles prepared with method B.

the aldehydes (entries 1–11 in Table 2) and ketones (entries 12–14 in Table 4) can be allylated in this reaction. Furthermore, both aromatic (entries 1–9 and 14 in Table 2) and aliphatic (entries 10–13 in Table 2) carbonyl compounds are reactive. The ketone with hydroxyl group is successfully employed in this reaction without protection (entry 13 in Table 2), yielding the corresponding homoallylic alcohol. Interestingly, the allylation of 4-nitrobenzaldehyde mediated by 20 nm tin particles generates the corresponding homoallylic alcohol in an excellent yield (entry 9 in Table 2). In comparison, the reaction between 4-nitrobenzaldehyde and allyl bromide usually only yields N-alkylation products[10] when mediated by metals in aqueous media. 20-nm particles usually give rise to a higher yield of the homoallylic alcohol than 100-nm tin particles do. But the difference is small.

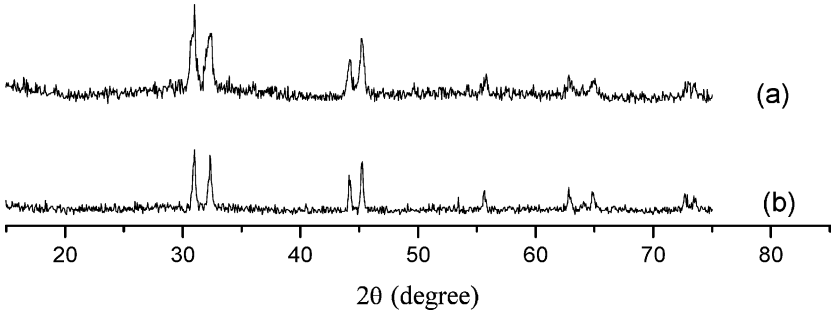


Figure 2. (a) XRD pattern of 20-nm tin particles; (b) XRD pattern of 100-nm tin particles.

2.2. Allylation reaction mediated by tin nano-particles in water

As shown in Table 1, tin nano-particles were found to be more effective than regular tin in mediating the allylation reaction.[7a] When 100-nm tin particles were employed the corresponding homoallylic alcohol was obtained in a yield of 98% (entry 7 in Table 1). When 20-nm tin nano-particles were used, the corresponding homoallylic alcohol was yielded quantitatively (entry 6 in Table 1).

Table 1. Allylation of benzaldehyde mediated by various metals in water

Entry	Metal	Size	Yield (%)[a]/ Time (h)
1	Fe	Regular[b]	Polymerization
2	Mg	Regular	—
3	Al	Regular	—
4	Zn	Regular	20/24
5	Sn	Regular	93/15
6	Sn	20-nm	95/1.5 (100/6.0)
7	Sn	100-nm	90/1.5 (98/9.0)

[a] Determined by ^{1}H NMR.
[b] The diameter of regular tin is about 80 μm.

Subsequently, tin nano-particles with average diameters of 20- and 100-nm were employed in the allylations of various aldehydes and ketones. As summarized in Table 2, this reaction usually generates the corresponding homoallylic alcohol in a high yield (mostly higher than 90%). Both of

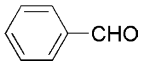
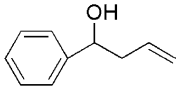
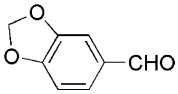
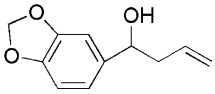
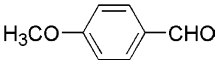
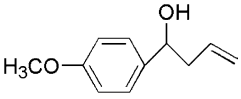
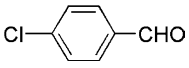
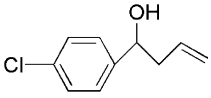
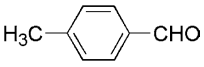
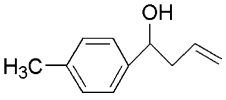
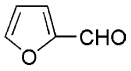
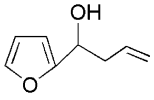
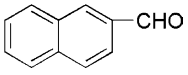
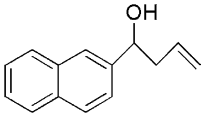
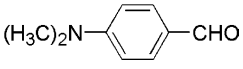
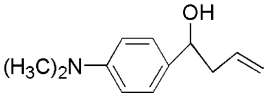
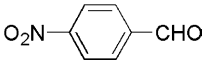
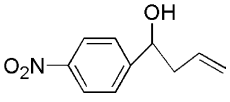
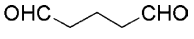
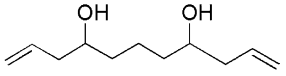
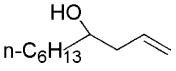
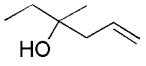
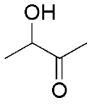
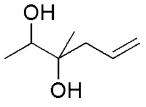
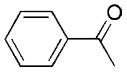
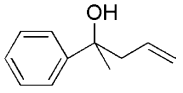
2.3. Regioselectivity and diastereoselectivity of the allylation reaction mediated by tin nano-particles

Additionally the regioselectivity and diastereoselectivity were studied for the nanometer-sized tin mediated allylation in the reaction of benzaldehyde and substituted allyl bromide (Scheme 2). As indicated in Table 3, the reaction between benzaldehyde and ethyl 4-bromo-2-butenate exclusively affords γ-adduct no matter whether tin is regular or nanometer sized (entries 1–3 in Table 4). The *syn* product is more favored by smaller tin particles. When 20-nm tin particles mediates the allylation reaction, the ratio of *syn* to *anti* homoallylic alcohol is as high as 94:6. The regular tin mediated reaction between benzaldehyde and crotyl bromide favors α-adduct (entry 4 in Table 4). On the other hand, the reaction mediated by tin nano-particles affords γ-adduct with a high selectivity (entries 5 and 6 in Table 3, 90% for 100 nm tin particles and almost 100% for 20 nm tin particles). Interestingly, when 20-nm diameter tin aggregates into bigger particles, both α- and γ-products are yielded in a ratio of 33:52 (entry 7 in Table 3).

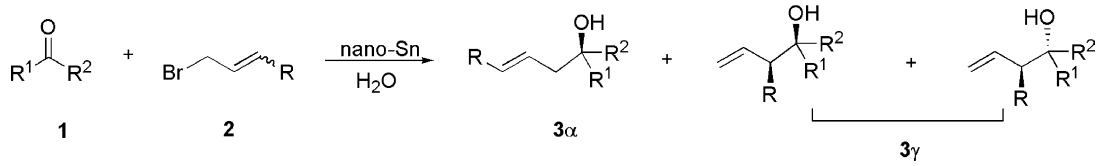
2.4. The detection of the intermediates and a proposed mechanism

Different mechanisms have been proposed for the aqueous Barbier type reactions involving the intermediates of a radical,[2b] a radical anion,[11] and an allylmetal species.[12] Direct observation of an intermediate is obviously important to establish a specific mechanism. However, as we know, no

Table 2. Allylation reactions mediated by tin nano-particles in water

Entries	Substrates	Products	Diameter of nano-Sn	Yield (%)[a]/Time (h)
1			20-nm 100-nm	95/1.5 90/1.5
2			20-nm 100-nm	99/3.0 96/3.0
3			20-nm 100-nm	99/2.0 95/2.0
4			20-nm 100-nm	99/2.0 95/2.0
5			20-nm 100-nm	96/3.0 89/3.0
6			20-nm 100-nm	96/3.0 92/3.0
7			20-nm 100-nm	99/3.0 96/3.0
8			20-nm 100-nm	95/3.0 81/3.0
9			20-nm 100-nm	95/3.0 86/3.0
10			20-nm 100-nm	90/1.5 90/1.5
11	*n*-C6H13CHO		20-nm 100-nm	99/1.5 99/1.5
12			20-nm 100-nm	85/1.5 81/1.5
13			20-nm 100-nm	81/3.0 79/3.0
14			20-nm 100-nm	65/4.0 59/4.0

[a] The yield was determined by ^{1}H NMR.



Scheme 2.

Table 3. Regioselectivity and diastereoselectivity of the allylation reaction mediated by tin nano-particles in water

Entry	R_1	R_2	R	Av size of Sn	Time (h)	Yield (%)[a]	α(*Z*/*E*)	γ(*anti*/*syn*)[b]
1	Ph	H	$COOCH_2CH_3$	Regular	24	58	—	(26:74)
2	Ph	H	$COOCH_2CH_3$	100-nm	12	55	—	(19:81)
3	Ph	H	$COOCH_2CH_3$	20-nm	12	61	—	(6:94)
4	Ph	H	CH_3	Regular	24	76	54(53:47)	22(37:63)
5	Ph	H	CH_3	100-nm	12	70	7(60:40)	63(49:51)
6	Ph	H	CH_3	20-nm	12	80	Trace	(44:56)
7	Ph	H	CH_3	20-nm	24	85	33(74:26)	52(33:67)[c]

[a] Isolated yield.
[b] The ratio of *syn* isomer to *anti* isomer (E isomer to Z isomer) was determined by ^{1}H NMR, ^{13}C NMR and isolation.
[c] The reaction was mediated by aggregated tin nano-particle.

Table 4. Allylation of carbonyl compounds by tin nano-particles in different solvent

Entry	Solvent	Metal	Yield (%)
1	—	Regular	0
2	—	20-nm	0
3	—	100-nm	0
4	CH_3OH	20-nm	0
5	CH_3OH	100-nm	0
6	Ethyl ether	20-nm	0
7	Ethyl ether	100-nm	0
8	H_2O	20-nm	95
9	H_2O	100-nm	90

Determined by ^{1}H NMR.

in situ allylation intermediate was reported to be observed in distilled water at room temperature in the allylation reaction mediated by metal tin. The following experiment was designed to search for the intermediate. 100-nm tin particles (178 mg, 1.5 mmol) and allyl bromide (0.18 mL, 2 mmol) were mixed in water (2–4 mL) at room temperature. After stirring for 15 min, the black mixture changed to milk-white. Then benzaldehyde was added to this mixture and the corresponding homoallylic alcohol was obtained in a good yield. This result implies that the milk-white substance should be the intermediate of the allylation. To identify the structure of the white substance, allyl bromide and the tin nano-particles (20 or 100 nm) were stirred in D_2O at room temperature and then monitored by using ^{1}H NMR. In the ^{1}H NMR spectrum two doublets at 2.16 and 2.48 ppm were observed (Fig. 3A, a), which are assigned to be the signals due to allyltin (II) bromide (**4**) and diallyltin dibromide (**5**), respectively.[12] The interconversion between allyltin (II) bromide (**4**) and diallyltin dibromide (**5**) was further studied by using tin nano-particles of different sizes. When a mixture of 1 mmol of allyl bromide and 0.5 mmol of 20-nm tin particles was stirred in D_2O at room temperature the ratios of **4** to **5** were 42/58 (0.5 h), 28/72 (1 h), 16/84 (1.5 h) and 8/92 (24 h), respectively (Fig. 3A, b–e). The ratio of **4** to **5** decreased due to the transformation of **4** to **5**. When 1 mmol of allyl bromide and 0.5 mmol of 100-nm tin were stirred in D_2O at room temperature, two intermediates, **4** and **5**, were generated immediately as indicated by the appearance of two doublets at 2.16 ppm and at 2.48 ppm in the ^{1}H NMR spectrum. The ratio of **4** to **5** were 1/99 (10 min) (Fig. 3A, f) and 0/100 (25 min) (Fig. 3A, g). After addition of another 1 mmol of 100-nm tin particles, the ratios of **4** to **5** were 55/45 (35 min), 36/64 (60 min) and 0/100 (15 h), respectively, as shown in Figure 3A, h–j. This indicates **5** can be converted to **4** by the addition of tin metal and also suggests that **5** is more stable in the aqueous solution.[12d] In comparison, when regular tin was stirred with allyl bromide in D_2O at room temperature, neither **4** nor **5** was observed in ^{1}H NMR spectrum. The absence of allyltin intermediates suggests that the mechanism of allylation reaction mediated by regular tin at neutral condition and room temperature involves not an allyltin intermediate but a radical or a radical anion.[2b] In fact, the allylation reaction mediated by regular tin requires heat (or ultrasonic irradiation) or the use of catalyst (HBr or Al) to promote the formation of covalent organometallic intermediates.[12d,13] Compared with regular tin, nanometer sized tin particles have a higher surface energy, which favors the formation of allyltin intermediates.

It is noted that water plays an important role in the allylation reaction. The reaction occurs only when water is used as solvent or as a catalyst regardless of the presence of organic solvent (entries 8 and 9 in Table 4). In anhydrous methanol or diethyl ether, or in a solvent-free condition,[14] no allylation product is yielded (entries 1–7 in Table 4). However, it is still not clear how water molecules participate in the reaction.

As shown in Figure 3B, when allyl bromide is replaced with crotyl bromide, two peaks are observed at 2.16 and 2.46 ppm, respectively in the ^{1}H NMR spectrum. The two peaks split into asymmetric multiplets rather than doublets, which are observed in the ^{1}H NMR spectrum of the reaction mixture of allyl bromide and tin nano-particles. This indicates that a covalent bond is formed between tin atom and γ-C when crotyltin (II) bromide and dicrotyltin dibromide are generated.[15]

As shown in Scheme 3, the formation of a γ-C–Sn bond can be explained by assuming that a π complex (**I**) is formed as a transition state. In this mechanism, allyl bromide binds the surface of tin nano-particles and generates the π-complex (**I**) first. Then the π electrons delocalize toward the γ-C and give rise to the formation of γ-C–Sn bond. Quantum chemistry calculation also indicates that the π complex transition state (**I**) is favored in energy.[16] Intermediate **4** can be further converted to **5** in the presence allylic bromide, and intermediate **5** can be converted to **4** in the presence of excessive tin. Both intermediate **4** and **5** can react with a carbonyl compound to give the corresponding homoallylic alcohol.

Most of experimental results can be explained based on this mechanism. For example, the allylation of 4-nitrobenzaldehyde yields reduction or polymerization products instead of

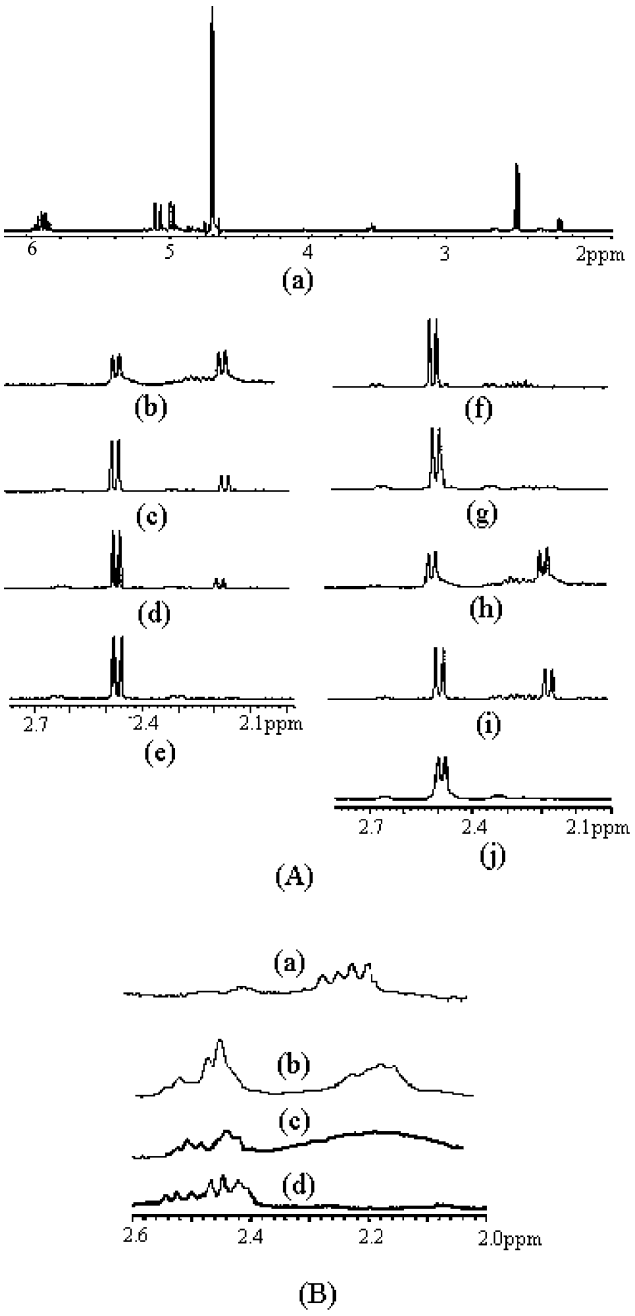


Figure 3. (A). Partial ^{1}H NMR spectra for the mixture of allyl bromide and nano-tin stirred in D_2O solution for different periods of time. (a–e) for 20-nm: (a) 1.5 h; (b) 0.5 h; (c) 1 h; (d) 1.5 h; (e) 24 h. (f–j) for 100-nm: (f) 15 min; (g) 25 min; (h) 35 min; (i) 60 min; (j) 15 h). (B) Partial ^{1}H NMR spectra of for the mixture of crotyl bromide and tin nano-particles stirred in D_2O solution for different periods of time. (a) 15 min; (b) 45 min; (c) 1.5 h; (d) 6 h.

homoallylic alcohol when mediated with regular tin[10] since the formation of allyltin intermediates is too slow to compete with the side reactions. When mediated with tin nano-particles, the allyltin intermediates are generated faster. Therefore the corresponding homoallylic alcohol is obtained in a high yield.

The selective formation of γ-addition product in the allylation reaction mediated with tin nano-particles (entries 5 and 6 in Table 3) can be explained by a γ-C bonded crotyltin (II) bromide intermediate (**4** in Scheme 3), which should be more stable than the α-C bonded crotyltin bromide because the γ-C is a secondary carbon. On the other hand, α-addition product is the major in the allylation reaction mediated by regular tin. This suggests again that the mechanism of allylation reaction mediated by regular tin at neutral condition and room temperature involves an intermediate rather than allyltin.[17] However, the allylation of benzaldehyde with ethyl-4-bromo-2-butenate only yields the γ-addition products no matter whether regular tin or nanometer-sized tin is used as a mediator (entries 1–3 in Table 3). This implies that γ-C bonded allyltin intermediates are formed when allyl group is conjugated with an electron-withdrawing group (such as an ester) regardless of the dimension of metallic tin (regular powder or nano-particles). The exclusive formation of γ-C bonded allyltin intermediates is due to the electron-withdrawing character of ester group, which can stabilize the high electron density on the Sn-bonded carbon.[18]

3. Conclusion

In conclusion, the allylation reaction mediated with tin nano-particles of different size in water has been systematically investigated. More importantly, the in situ generated allylation intermediates (**4** and **5** in Scheme 3) have been directly observed using ^{1}H NMR. A mechanism involving the allyltin intermediates is proposed. Further research is in progress in our laboratory to control the regioselectivity and stereoselectivity in allylation reactions by adjusting the dimension of the metal nano-particles.

4. Experimental

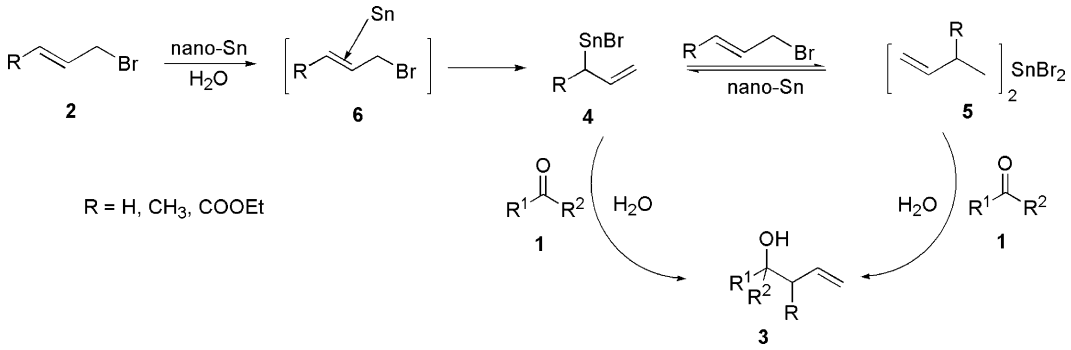
Analytical thin-layer chromatography (TLC) plates were commercially available. Solvents were reagent grade unless otherwise noted. Tin powder (150 mesh, 99.99%, 100 g packing) was freshly opened for use. Carbonyl compounds were further purified by redistillation or recrystallization from commercial chemicals when necessary.

4.1. General method for preparation of 20-nm tin particles

Method A. To 1L of a solution of 2-propanol in water (2.0 mol/L) were added 2.25 g (0.01 mol) of $SnCl_2\cdot 2H_2O$ and 20 g (0.5 mol) of NaOH. The reaction mixture was stirred until $SnCl_2$ and NaOH were dissolved. The solution was bubbled with nitrogen over 20 min and then irradiated with a γ-ray (^{60}Co) source for about 12 h (2.5×10^4 Gy). The 20-nm tin particles were obtained from the solution by centrifugation. The tin nano-particles were washed with water and alcohol, respectively, and dried under vacuum.

4.2. General method for preparation of 100-nm tin particles

Method B. A solution of potassium borohydride (0.80, 15 mmol) in water (20 mL) was slowly added to a stirred solution of $SnCl_2\cdot 2H_2O$ (2.25 g, 10 mmol) and cetyl-trimethylaminoium bromide (0.36 g, 2 mmol) in 100 mL



Scheme 3. A proposed mechanism for the allylation reaction mediated by tin nano-particles.

of water. The mixture was stirred at room temperature for 15 min and in-situ tin nano-particles were yielded. The mixture of in-situ tin nano-particles was centrifuged to give 100-nm tin particles. The tin nano-particles were washed with water and alcohol, respectively, and dried under vacuum.

4.3. Details of in situ NMR experiments

In a typical procedure, tin nano-particles (178 mg, 1.5 mmol) and allyl bromide (0.14 mL, 1.5 mmol) were added into 2 mL of D_2O at room temperature. After the mixture was stirred for 10 min, the solution turned milky white. The milky white solution was briefly evacuated, purged with nitrogen, and transferred via cannula to a NMR tube.

4.4. General method for allylation of carbonyl compounds in aqueous media

To a mixture of carbonyl compound (1 mmol) in water (4 mL) was added tin nano-particles (0.118 g 1 mmol–0.177 g 1.5 mmol) and allyl bromide (0.14 mL 1.5 mmol) at room temperature. The mixture was stirred for 0.5–4 h and quenched with 1 N HCl (1 mL) solution. The mixture was extracted with ether (3×10 mL), and the combined organic layer was washed with saturated aqueous $NaHCO_3$ solution and dried over magnesium sulfate. The organic solvent was evaporated, and the corresponding homoallylic alcohol was yielded. The product was usually pure enough without further purification according to the ^1H NMR spectrum, and was further purified by flash chromatography on silica gel only when necessary.

4.5. Spectroscopic data

IR (Perkin–Elmer, 2000FTIR), ^1H NMR (CD_3Cl, 500 or 400 MHz), ^{13}C NMR ($CDCl_3$, 125.7 or 100 MHz) and MS–GC (HP 5890(II)/HP5972, EI.

4.5.1. *syn*-Ethyl-2-[hydroxy(phenyl)methyl]but-3-enoate (entry 1, Table 3). IR(NaCl, cm^{-1}): 3482, 1728, 1638, 1318, 1176, 1027, 765, 701. ^1H NMR ($CDCl_3$, 400 MHz, ppm) δ: 7.17–7.33 (m, 5H), 5.75–6.90 (m, 1H), 5.06–5.25 (m, 2H), 4.91 (d, J=6.4 Hz, 1H), 3.95 (q, J=7.0 Hz, 2H), 3.22–3.41 (m, 1H), 3.10 (s, 1H), 1.02 (t, J=7.0 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ: 172.5, 140.7, 132.0, 128.2, 127.9, 126.5, 120.5, 74.0, 60.9, 58.4, 14.0. HRMS (EI) m/z calcd for $C_{13}H_{16}O_3$: 220.1099. Found: 220.1052.

4.5.2. *anti*-Ethyl-2-[hydroxy(phenyl)methyl]but-3-enoate (entry 1, Table 3). IR(NaCl, cm^{-1}): 3450, 1731, 1635, 1304, 1176, 1035, 760, 700; ^1H NMR ($CDCl_3$, 400 MHz, ppm) δ: 7.17–7.26 (m, 5H), 5.51–5.67 (m, 1H), 4.90–5.02 (m, 2H), 4.84 (d, J=8.4 Hz, 1H), 4.10 (q, J=7.2 Hz, 2H), 3.31–3.38 (m, 1H), 2.35–2.2.68 (br, 1H), 1.16 (t, J=7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 173.0, 141.2, 132.2, 128.4, 128.0, 126.7 119.5, 75.3, 61.1, 57.9, 14.1. HRMS (EI) m/z calcd for $C_{13}H_{16}O_3$: 202.0994 (M−18). Found: 202.0996 (M−18).

4.5.3. Phenyl-3-penten-1-ol (mixture of *Z* and *E*) (entry 4, Table 3). IR (film, cm^{-1}): 3432, 3083, 1644. ^1H NMR ($CDCl_3$, 400 MHz, ppm) δ: 7.29–7.39 (m, 5H), 5.53–5.72 (m, 1H), 5.40–5.50 (m, 1H), 4.65–4.72 (m, 1H), 2.42–2.65 (m, 3H), 1.61–1.73 (m, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 144.2, 144.1, 129.2, 128.4, 127.5, 127.4, 126.9, 126.0, 125.9, 125.8, 73.9, 73.6, 42.7, 36.9, 18.1, 13.0. HRMS (EI) m/z calcd for $C_{11}H_{14}O$: 162.1045. Found: 162.1049.

4.5.4. 2-Methyl-1-phenyl-3-buten-1-ol (mixture of *syn* and *anti*) (entry 4, Table 3). IR (film, cm^{-1}): 3417, 3080, 1640. ^1H NMR ($CDCl_3$, 400 MHz, ppm) δ: 7.27–7.39 (m, 5H), 5.64–5.88 (m, 1H), 5.13–5.23 (m, 2×0.37H) (*anti*), 4.99–5.09 (m, 2×0.63H) (*syn*), 4.57 (d, J=5.84 Hz, 1×0.63H) (*syn*), 4.32 (d J=7.64 Hz, 1×0.37H) (*anti*), 2.35–2.62 (m, 1H), 1.99–2.19 (br, 1H), 1.02 (q, J=6.87 Hz, 3×0.63H) (*syn*), 0.90 (d, J=6.83 Hz, 3×0.37H) (*anti*). ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ: 14.1 (*syn*), 16.5 (*anti*), 44.6 (*syn*), 46.2 (*anti*), 77.1 (*syn*), 77.4 (*anti*), 115.5 (*syn*), 116.8 (*anti*), 126.5 (*syn*), 126.9 (*anti*), 127.4 (*syn*), 127.7 (*anti*), 128.1 (*syn*), 128.3 (*anti*), 140.3 (*syn*), 140.6 (*anti*), 142.4 (*anti*), 142.6 (*syn*). HRMS (EI) m/z calcd for $C_{11}H_{14}O$: 162.1045. Found: 162.1042.

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meso-Tetraaryl-7,8-diol-21,23-dithiachlorins and their pyrrole-modified derivatives: a spectroscopic comparison to their aza-analogues

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Abstract—Osmium tetraoxide-mediated dihydroxylation of *meso*-tetraaryl-21,23-dithiaporphyrins generates the corresponding *meso*-tetraaryl-7,8-dihydroxy-21,23-dithiachlorins and *meso*-tetraaryl-7,8,17,18-tetrahydroxy-21,23-dithiabacteriochlorins. Oxidative diol cleavage reactions of the *meso*-tetraaryldithia-7,8-dihydroxychlorin generate, depending on the conditions chosen, the corresponding *meso*-tetraaryldithia-7-oxa-8-oxo-21,23-dithiaporphyrin (dithiaporpholactone) or *meso*-tetraaryl-7,8-ethoxy-7a-oxa-7a-homo-21,23-dithiaporphyrin (morpholinodithiachlorin), respectively. The UV–vis spectra of the heterochlorins and pyrrole-modified dithiaporphyrins are compared to those of the corresponding all-aza homologues. In general, the trends which distinguish the spectra of dithiaporphyrins from those of all-azaporphyrins are preserved. Thus, the spectra of the dioldithiachlorins tetraoldithiabacteriochlorins are chlorin- and bacteriochlorin-like and bathochromically shifted as compared to the all-azaanalogues, respectively. Also, the dithiaporpholactone spectrum is porphyrin-like. However, the UV–vis spectrum of the morpholinodithiachlorin is uncharacteristic for a morpholinochlorin spectrum. The derivatives described are the first examples of heterochlorins and pyrrole-modified dithiaporphyrins.

1. Introduction

One of the driving forces in contemporary porphyrin chemistry is the modulation of the optical properties of porphyrins and chlorins with the aim of generating long-wavelength absorbing and fluorescing molecules. Chromophores with these characteristics possess potential use as fluorescence imaging[1] or phototherapeutic agents.[2] This is because regular porphyrins do not, with respect to their longest wavelengths of absorption, fulfill the ideal photophysical requirements for these applications. They generally do not absorb light within the 'photo-therapeutic window' of tissue, that is, the range of ~680–850 nm in which tissue has minimal absorbance. This has led to extensive efforts to convert porphyrins to chlorins,[3] as chlorins generally have a longer wavelength of absorbance.[4] The search for alternative long-wavelength absorbing chromophores has led to the synthesis of porphyrin isomers,[5] heteroporphyrins,[6–8] expanded porphyrins[5] and pyrrole-modified porphyrins, that is, porphyrins in which at least one of the pyrrolic subunit of a porphyrins was replaced by a non-pyrrolic heterocycle.[9–13]

The dihydroxylation of porphyrins is a well known reaction for the modification of β-octaalkylporphyrins.[14] The corresponding derivatization of *meso*-tetraaryporphyrins was developed much later. We reported the OsO_4-mediated dihydroxylation of *meso*-tetraaryl-porphyrin (**1**) to generate dihydroxychlorin **2**[10,15] and the corresponding tetrahydroxybacteriochlorins,[3] **3**[16] (Scheme 1). This reaction was employed in the synthesis of photosensitizers.[17] The 1,2-*vic*-diol moiety was also demonstrated to be a versatile synthetic handle in the synthesis of a number of pyrrole-modified porphyrins and secochlorins[3] (Scheme 1). Some of these derivatives possess significantly bathochromically shifted optical spectra while others have been used in molecular recognition devices.[10–12,18,19]

One class of porphyrin derivatives, the heteroporphyrins, incorporate other heteroatoms than nitrogen into the porphyrinic macrocycle.[6,20] *meso*-Tetraaryl-21,23-dithiaporphyrins (**6**), porphyrins in which the two pyrrole-type nitrogens are replaced by sulfur atoms, possess significantly longer wavelengths of absorption (λ_{max} (log ε) = 699 (3.67) nm)[21] as compared to all-aza porphyrin **1** (λ_{max} (log ε) = 647 (3.59) nm).[22] Furthermore, their photo-therapeutic efficacy was demonstrated.[7,8] The *meso*-aryl groups allow for the introduction of a wide variety of substituents to adjust the solubility and biodistribution properties of the potential pharmaceutical agent.

Keywords: Chlorins; Dithiaporphyrins; Pyrrole-modified porphyrins.
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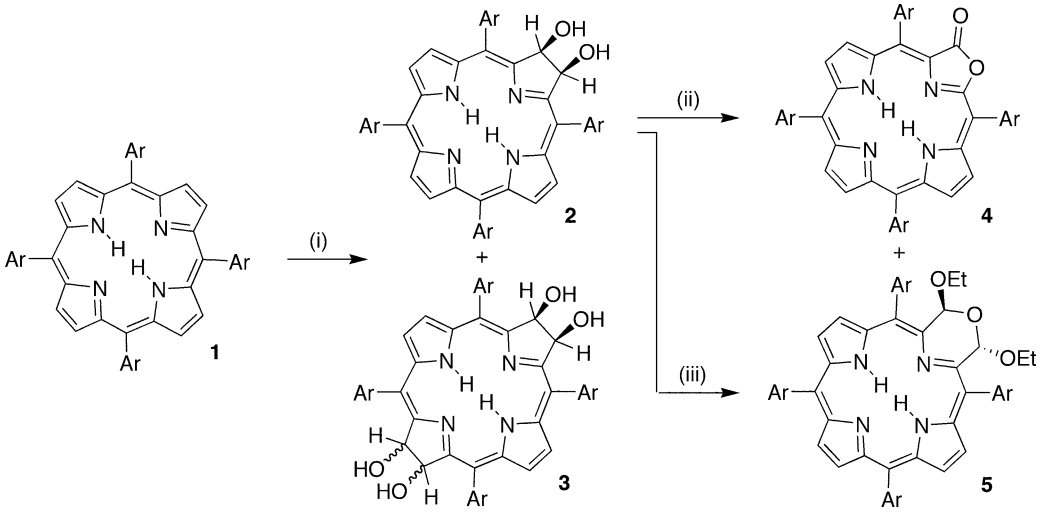
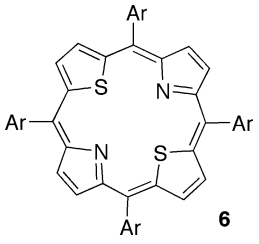


Scheme 1. Reaction conditions: (i) 1. OsO_4/pyridine, 2. H_2S, 3. chromatography;[10,16,17] (ii) 1. $KMnO_4$/18-crown-6, THF 2. chromatography;[11] (iii) 1. $NaIO_4$/silica gel, EtOH, 2. chromatography.[11]



Several questions arise: Is the OsO_4-mediated dihydroxylation of dithiaporphyrins possible? What are the photophysical properties of the resulting dithiachlorins? The answers to these questions are particularly interesting as we are not aware of any examples of heterochlorins. Further, are the dihydroxyheterochlorins also susceptible to modifications of the dihydroxylated β,β′-bond, and are the resulting chromophores also characterized by the same, often surprising, photophysical properties as their aza-analogues? This contribution follows up on our preliminary communication and investigates these questions in detail.[23] In doing so, we expand the knowledge of heterochlorins and pyrrole-modified pyrrolic molecules. We also detail the scopes and limits of the use of dithiaporphyrins in the creation of long-wavelength absorbing chromophores using the methods previously shown to be successful in the all-aza chlorin series.

2. Results and discussion

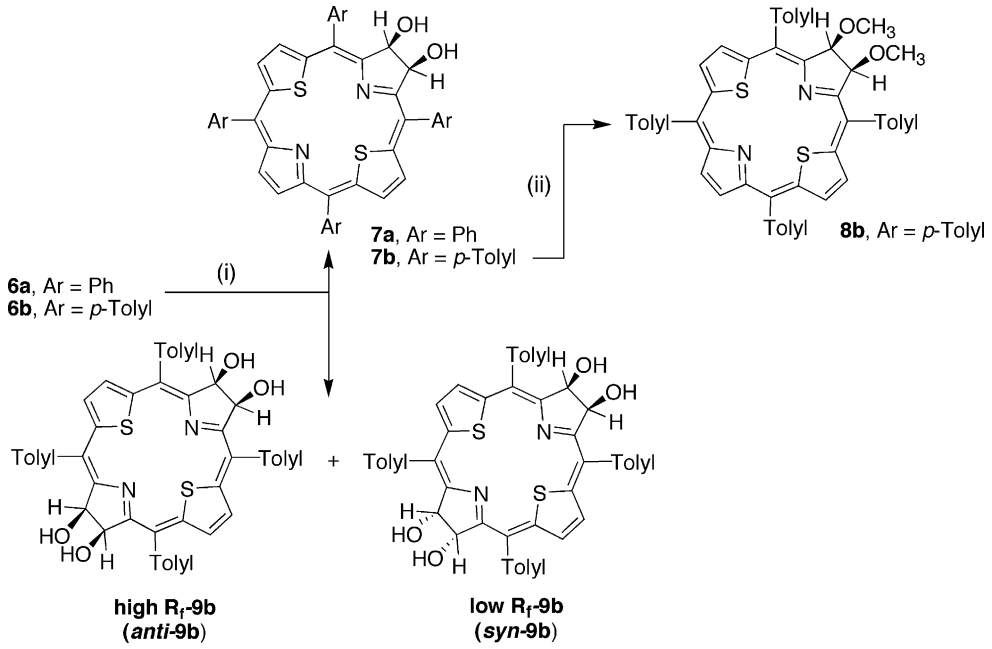
2.1. OsO_4-mediated dihydroxylation of dithiaporphyrins

Reaction of the bright orange dithiaporphyrins **6** with a 1.2-fold stoichiometric excess OsO_4 in $CHCl_3$/pyridine generated, over a period of several days, one more polar dark orange major product, **7**, and to a much lesser degree, two more polar pink products, **9** (Scheme 2). Quenching of the reaction mixture with H_2S, followed by filtration and chromatographic separation of the products, recovered ~60% of the starting material **6**, and produced the orange product **7** in 20% yield, and the two minor products **9** in low yields (<5%).

The general appearance of the UV–vis spectrum (for a detailed discussion of the optical properties of **7**, see below) and the high-resolution mass (e.g., for **7b**: $m/z=739.2453$, MH^+, FAB-PEG, corresponding to $C_{48}H_{39}N_2O_2S_2$, that is, the starting material **6b**+2 OH) of the dark orange products **7** identify them as the expected dihydroxychlorins **7**. Likewise, the identical UV–vis and the identical masses of the two high polarity products (e.g., for **9b** of 772.2469, corresponding to $C_{48}H_{40}N_2O_4S_2$, i.e., starting material **6b**+4 OH) identify these products as the tetrahydroxybacteriochlorins **9**. Methylation of the 1,2-diol moiety of **7b** using a Williamson ether synthesis generates the low polarity dimethoxychlorin **8b**.

In principle, the diol moiety can be located at the thiophene- or the pyrrole-type building blocks. The ^1H NMR of the chlorins **7** (and **8**), however, provide unequivocal evidence for their location on the pyrrole-type units (Fig. 1). Three signals, a singlet and two doublets at the low-field edge of the spectrum, are characteristic for the β-hydrogen region of symmetrically β,β′-modified porphyrins. The singlet at 8.54 ppm is found at a comparable position to that of the all-aza diolchlorin **2** (8.48 ppm).[10] The doublets at 9.18 and 9.50 ppm ($^3J=5$ Hz) are about 0.9 ppm low-field-shifted and in the region characteristic for the thiophene β-hydrogens (the signal for the β_S-hydrogens at 9.69 ppm for **6a**).[7] This places the diol moiety unequivocally onto a pyrrolic subunit. All other signals, notably the split signals for the *o*-hydrogens of one tolyl group, reflect the face differentiation of the *cis*-diol moiety. The singlet at 6.17 ppm is characteristic for the pyrrolidine moiety and is analogous to the corresponding signal found in the all-aza diolchlorin **2**.[10]

The spectroscopically derived assignment of the position of the diol moiety is, in fact, the only reasonable position considering that OsO_4 is expected to react with the double bond that, once removed, results in the least



Scheme 2. Reaction conditions: (i) 1. OsO_4/pyridine, 2. H_2S, 3. chromatography;[23] (ii) 1. NaH, MeI, THF 2. chromatography.

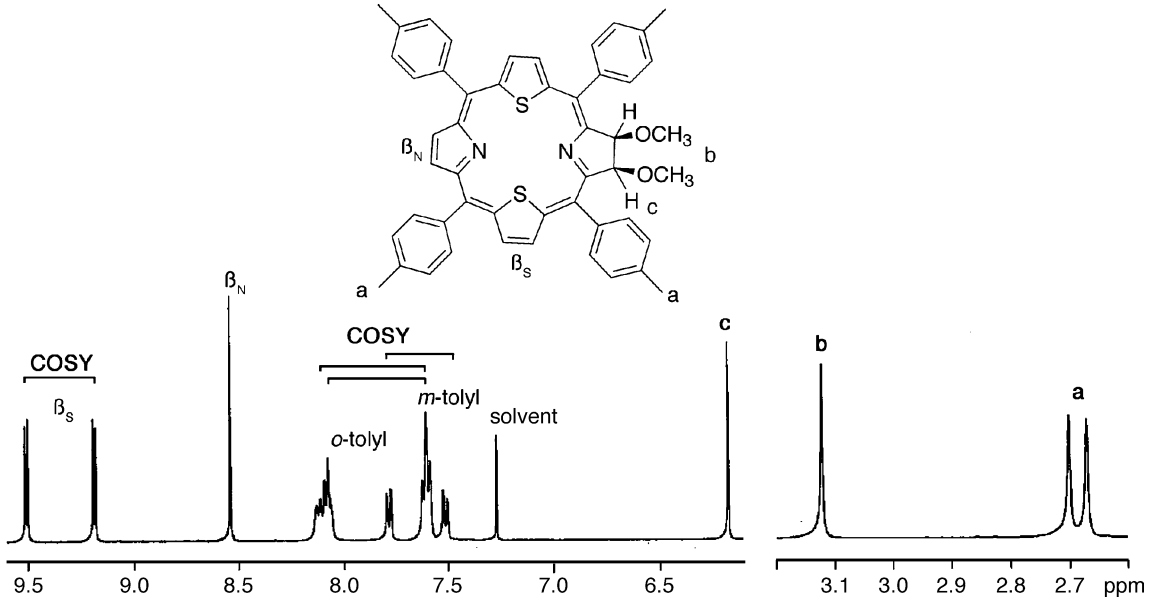


Figure 1. ^1H (400 MHz, $CDCl_3$, 25 °C) of dimethoxydithiachlorin **8b**, including the couplings as observed by H,H-COSY spectroscopy.

loss of resonance energy.[24] Like all-azaporphyrins, dithiaporphyrins contain 22 conjugated π-electrons of which 18 maintain a closed aromatic system, with two 'cross-conjugated', pseudo-olefinic β,β′-double bonds (Fig. 2A).

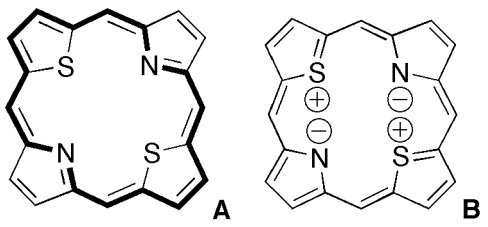


Figure 2. π-Conjugation pathways of dithiaporphyrins.

In regular porphyrins, tautomeric exchange of the inner hydrogens interchanges the core nitrogens between amine and imine nitrogens, and therefore also the position of the cross-conjugated β,β′-bonds. On the contrary, in dithiaporphyrins, any other resonance structure than the one shown in Figure 2A leads to high-energy, charged species, as shown in Figure 2B. In effect, this fixes the position of the double bond accessible for dihydroxylation on the pyrrolic subunit. This fixing of the position of the pseudo-olefinic bond, however, does not result in a dramatic acceleration of the dihydroxylation reaction rate as compared to all-azaporphyrins.[10,15] The reaction times in both cases stretch over several days. This analysis also allows the projection that, unlike for the all-azaporphyrins,[16] the corresponding

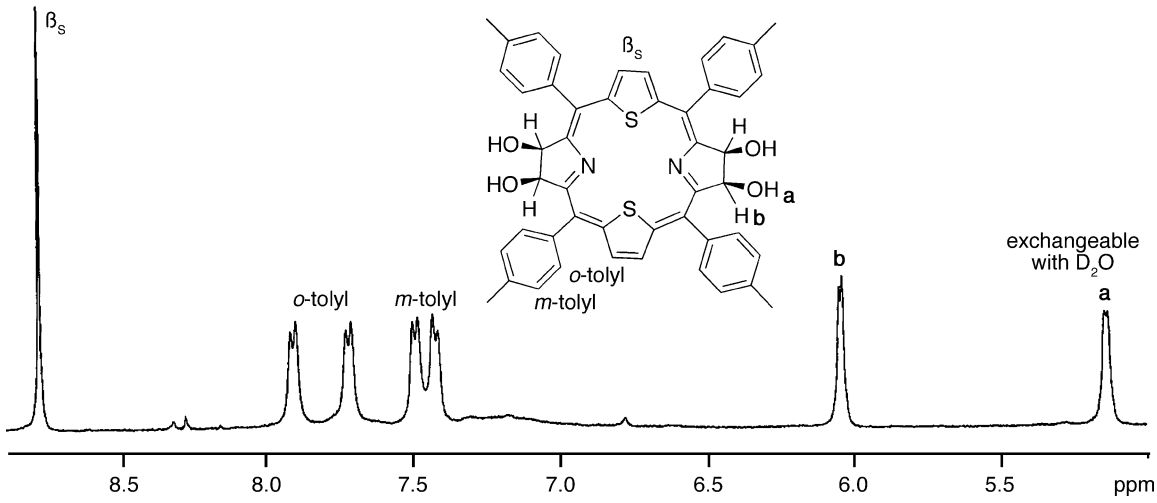


Figure 3. ^{1}H NMR (400 MHz, DMSO-d_6, 100 °C) of *meso*-tetratolyl-2,3,17,18-tetrahydroxy-21,23-dithiabacteriochlorin (high R_f-**9b**). An additional signal for the *p*-methyl groups are visible as a singlet at 2.50 ppm.

tetrahydroxyisobacteriochlorin series of the dithiaporphyrins cannot be formed.

Analogously to the all-aza-porphyrins,[16] however, bis-dihydroxylation of dithiaporphyrins **6** leads to the formation of tetrahydroxydithiabacteriochlorins **9**. The two pigments of identical mass and optical (see also below) properties are the two isomeric structures in which the 1,2-*cis*-diol functionalities are arranged *syn* and *anti* toward each other. The polarities of the two isomers are vastly different. We assigned the lower polarity compound (with a R_f value of 0.74 vs 0.85 for dihydroxychlorin **7b**, both on silica, 3% MeOH in $CHCl_3$) to the *anti* isomer (*anti*-**9b**) and the high polarity compound (R_f value of 0.18, silica, 3% MeOH in $CHCl_3$) to the *syn* isomer (*syn*-**9b**). This is because, idealized, the *syn* isomer can interact simultaneously with both diol functionalities with a (planar) silica gel matrix, whereas sterics allow the *anti*-isomer to interact with the matrix with only one diol moiety at a time. Thus, its R_f value is very similar to that of the mono-diol **7b**. We are reporting NMR data only for the *syn* isomer of **9b** as we failed to obtain a clean sample of the *anti*-isomer. Relative to *syn*-**9b**, much less of the *anti*-**9b** is produced and it is difficult to separate it cleanly from the diol **7b**. In general, the tetraol compounds are only sparingly soluble (note that the NMR data reported were recorded at 100 °C in DMSO-d_6), an observation also noted for the all-aza compounds **3**.[16] This also hindered the preparation of **9b** by osmylation of **7b**.

Figure 3 shows the ^{1}H NMR of the high polarity isomer of **9b**. The spectrum is much simplified compared to the spectrum of **7b**, reflecting the higher symmetry of the dithiabacteriochlorin as compared to the dithiachlorin. The thiophene β-signal is shifted toward higher field. A comparable shift for the pyrrolic β-hydrogens was also observed in the all-aza series.[25] The four doublets assigned to the tolyl-*ortho* and -*meta* protons reflect the face differentiation of the *cis*-diol moieties.

2.2. UV–vis and fluorescence spectroscopic comparison of dithiaporphyrin 6, dithiadihydroxychlorin 7, and all-aza-dihydroxychlorin 2

Dihydroxylation of *meso*-tetraphenylporphyrin **1** generates diolchlorin **2** which possesses a chlorin-type spectrum that, however, is not bathochromically shifted as compared to the parent porphyrin spectrum. The λ_{max} is, in fact, 7 nm hypsochromically shifted.[26] Figure 4 shows a comparison of the UV–vis and fluorescence spectra of dithiaporphyrin **6b** and two dihydroxychlorins, all-aza diolchlorin **2** and dihydroxydithiachlorin **7b**. Dihydroxylation of dithiaporphyrin **6b** also generates a chlorin-type spectrum with a

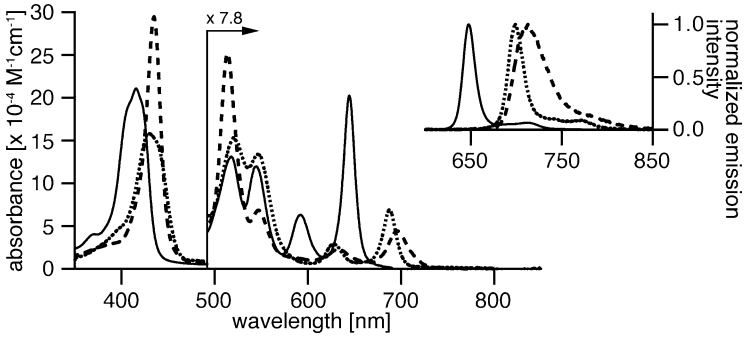


Figure 4. UV–vis spectra (CH_2Cl_2) of **2** (R = –Ph) (—); **6b** (– – –) and **7b** (···). Insert: normalized fluorescence spectra (CH_2Cl_2) of **2** (R = –Ph) (—); **6b** (– – –) and **7b** (···), excitation at their respective $\lambda_{max\text{-}Soret}$. The UV–vis data are summarized in Table 1.

slightly hypsochromically shifted λ_{max} as compared to dithiaporphyrin **6b**. As compared to the spectrum of the dihydroxychlorin **2**, the spectrum of **7b** is well red-shifted ($\Delta\lambda_{max}=40$ nm), thus mirroring the differences of the optical properties of the parent porphyrins (λ_{max} for **6a** at 434 nm).[21] One difference to the outcome of the dihydroxylation in the all-aza series is of note. The absorption intensity of λ_{max} of the most red-shifted side band of dithiachlorin **7b** is much lower, both relative to the intensity of the other side bands and in absolute terms as compared to that of the spectrum of **2**. The emission wavelength shifts in the fluorescence spectra of the dihydroxydithiachlorins reflect the trends seen in $\lambda_{max\text{-}absorption}$.

The UV–vis spectra of the dithiabacteriochlorins **9** are typical bacteriochlorin spectra (Fig. 5). Compared to the spectrum of the all-azabacteriochlorin **3**, the Soret band and the longest wavelength absorption band of dithiabacteriochlorin low-R_f-**9b** are significantly bathochromically shifted (378 and 399, and 707 and 734 nm, respectively), mirroring qualitatively the bathochromic shift of the dithiaporphyrin as compared to the all-azaporphyrin. As was also observed in the chlorin spectrum, the relative absorption intensity of the longest wavelength absorption band with respect to the Soret band is relatively lower as compared to the all-aza pigment.

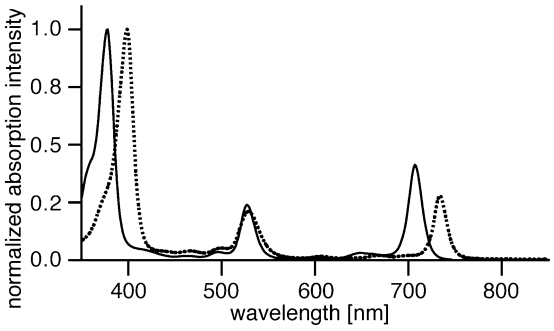
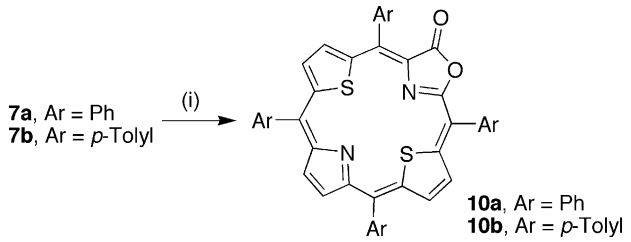


Figure 5. UV–vis spectra (CH_2Cl_2) of **3** (high R_f-isomer, R=–Ph) (—) and low-R_f-**9b** (···). The UV–vis data are summarized in Table 1.



Scheme 3. Reaction conditions: (i) 1. aq $KMnO_4$/18-crown-6/$CHCl_3$, 2. chromatography.[23]

2.3. MnO_4^--mediated diol cleavage of dihydroxydithiachlorin 7

Porpholactones are porphyrin-like derivatives in which one peripheral double bond of a porphyrin is replaced with a lactone moiety. First reported by Crossley,[27] porpholactones have generated interest for their use as chlorin model compounds,[28] and their Pt-complexes have found use in oxygen partial pressure-sensitive paints.[29] Porpholactones are generated by oxidation of β-activated porphyrins or chlorins.[27–29] We recently introduced a convenient synthesis of porpholactone **4** by MnO_4^--induced cleavage of diol **2** under phase transfer catalysis conditions (Scheme 1).[11] This reaction is also applicable to dihydroxydithiachlorins **7**. Thus, reaction of a $CHCl_3$ solution of **7b** with an aqueous solution of $KMnO_4$ in the presence of the phase transfer catalysts 18-crown-6 produced within minutes one main non-polar ($R_f=0.80$, silica/$CHCl_3$), dark orange product, **10b**. Its HR-MS (FAB+, PEG) showed the expected composition $C_{47}H_{34}N_2O_2S_2$. This composition indicated the characteristic loss of one framework carbon and four hydrogens from the diol dithiachlorin **7b**, and indicates the successful formation of dithiaporpholactone **10b** (Scheme 3). A $\nu_{C=O}$ band at 1773 cm^{-1} in the IR spectrum of **10** identifies the functional group ($\nu_{C=O}=$ 1760 cm^{-1} for porpholactone **4**).[27]

The ^1H NMR of **10b** is shown in Figure 6. The β-region of the spectrum displays six doublets corresponding to the expected six non-equivalent peripheral protons. The six signals can be distinguished into two groups, the two doublets at 8.51 ppm ($^3J=4.5$ Hz) and 8.58 ppm ($^3J=$

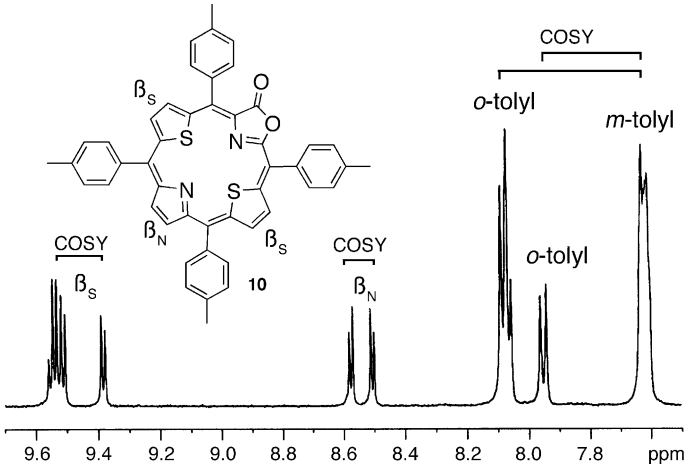


Figure 6. ^1H NMR (400 MHz, $CDCl_3$, 25 °C) spectrum, including the couplings as observed by H,H-COSY spectroscopy of porphodithialactone **10b**. Additional signals for the tolylmethyl groups are visible in the high-field region of the spectrum.

4.5 Hz) belonging to the pyrrolic protons and the four (partially overlaying doublets) in the region above 9.3 ppm are assigned to the thiophene protons. In comparison, all β-signals for the all-aza porpholactone are found between 8.5 and 8.8 ppm.

2.4. UV–vis and fluorescence spectroscopical comparison of the dithiaporpholactone 10 to its all-aza-analogue 4

The UV–vis and fluorescence spectra of **10b** in comparison to those of the all-aza analogue **4** are shown in Figure 7. Both spectra are very much like the spectra of their respective parent porphyrins, with all bands essentially unshifted.[29] Thus, as was observed before for **4**, the lactone moiety closely mimics the electronic influence of a β,β′-double bond.

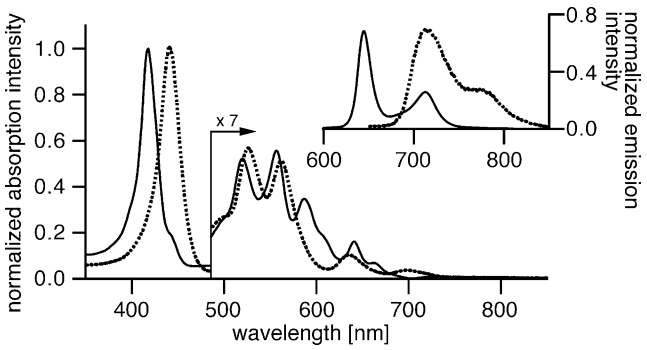
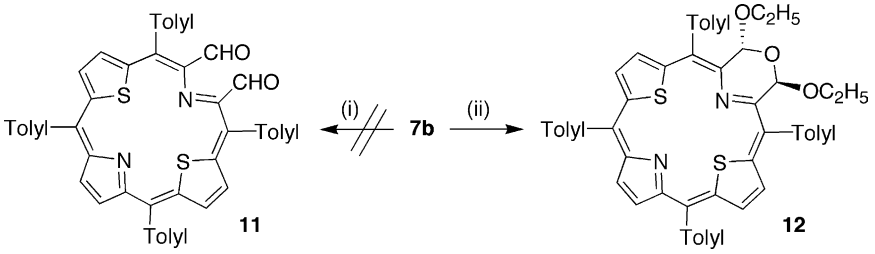


Figure 7. UV–vis spectra (CH_2Cl_2) of **4** (R=–Ph) (—) and **10b** (···). Insert: Normalized fluorescence spectra (CH_2Cl_2) of **4** (R=–Ph) (—) and **10b** (···), excitation at their respective $\lambda_{max\text{-}Soret}$. The UV–vis data are summarized in Table 1.

2.5. IO_4^--mediated diol cleavage of dihydroxydithiachlorin 7b

We have shown that the Ni^{2+} complex of dihydroxychlorin **2** can be subjected to diol cleavage, generating a corresponding bisaldehyde secochlorin Ni^{2+} complex in which a β,β′-pyrrole bond of the porphyrin framework is cleaved.[10,12] While the bisaldehyde secochlorin Ni^{2+} complex can be isolated and crystallized,[10,12] we have also shown that the corresponding reaction using free base **2** solely leads to decomposition.[10] Dithiasecochlorin **11** also remained elusive. Diol cleavage of dihydroxydithiachlorin **7b** under oxidative conditions (Pb^{IV} acetate or $NaIO_4$-silica gel) leads to extensive decomposition. Other than a small amount of porpholactone **10**, no product could be identified. This further underlines the stabilizing effect of the templating central metal. It also characterizes, parallel to the all-aza case, porphodithialactone **10** as the



Scheme 4. Reaction conditions: (i) Pb^{IV} acetate, THF or $NaIO_4$–silica gel, $CHCl_3$; (ii) 1. $NaIO_4$–silica gel, $CHCl_3$, EtOH, 2. chromatography.

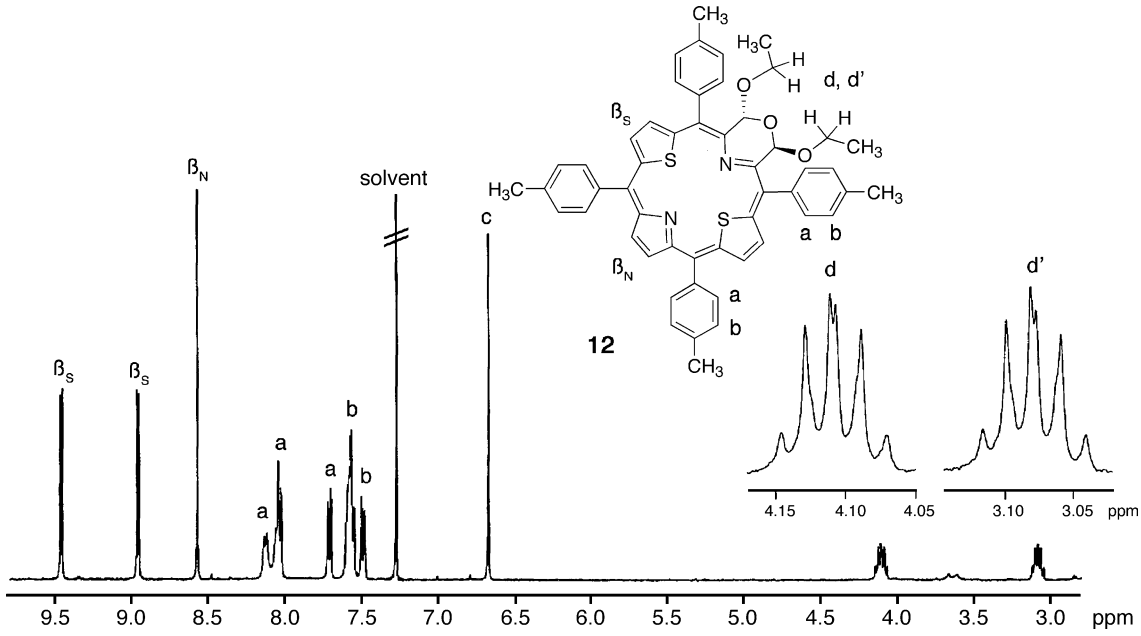


Figure 8. ^1H NMR spectrum (400 MHz, $CDCl_3$, 25 °C) of *meso*-tetratolylithiamorpholinochlorin **12**. The signals attributed to the two (equivalent) methyl carbons of the ethoxy side chains are found at 1.22 ppm and two singlets at 2.68 and 2.67 ppm are assigned the tolyl methyl groups.

'thermodynamic sink' in the oxidative degradation of dithiachlorins.

Indirect evidence for the in situ formation of dithiaseco-chlorin **11**, however, could be gathered. Diol cleavage of **7b** in the presence of EtOH produced a brown non-polar (R_f= 0.44, silica–CH_2Cl_2) product (Scheme 4). The HR-mass (MH^+, FAB-PEG) of this product indicated the composition $C_{52}H_{46}N_2O_3S_2$, as expected for morpholinodithia-chlorin **12**. Thus, in situ formation of **11** was followed by nucleophile-induced ring closure to establish the morpholino subunit, followed by double acetalization. An analogous reaction sequence was also shown to be applicable to all-aza diol **2** to produce the morpholinochlorin **5** (Scheme 1).[11]

The ^{1}H NMR spectrum of **12** gave further evidence for the confirmation of its identity (Fig. 8). Two doublets, each integrating for one hydrogen, are observed at 9.46 and 8.95 ppm. These are assigned to the two non-equivalent thiophene hydrogens in this 2-fold symmetric pyrrole-modified dithiaporphyrin. The pyrrolic hydrogens located opposite of the morpholine ring are found as a singlet at 8.56 ppm. The aryl group proton signals split into three groups, again a feature seen in the all-aza case. A feature very characteristic for the morpholinochlorins can be detected in the upfield region of the spectrum: the two doublets of quartets at 4.12 and 3.08 ppm. They are assigned to the methylene hydrogens of the ethoxy groups. Sterics (interaction with the flanking *meso*-aryl groups) and stereoelectronics (equivalent to the anomeric control in glycoside formation) arrange the ethoxy groups *anti* toward each other. Both ethoxy groups are in equivalent positions (the molecule possesses C_2-symmetry) but the two hydrogen of each methylene group are diastereotopic.[10,11,13] Thus, the methylene signal is split. Their significant chemical shift difference finds its explanation in the proximity of one of the methylene hydrogens to the diatopic ring current of the porphyrinic chromophore.

2.6. UV–vis and fluorescence spectroscopical comparison of the dithiamorpholinochlorin 12 to its all-azaanalogue 5

The UV–vis spectra of the dithiaderivatives discussed thus far were, apart from certain minor intensity variations, significantly red-shifted compared to the spectra of the all-aza derivatives. In light of this, the comparison of the spectra of the corresponding morpholino derivatives **5** and **12** is surprising (Fig. 9). The Soret band in the dithiamorpholinochlorin is only 10 nm bathochromically shifted, the longest wavelength absorption band only 8 nm. Moreover, the spectrum of the all-aza compound is a typical chlorin-type spectrum, with the λ_{max} band the most intense of the side band. In contrast, the λ_{max} band of the dithiamorpholinochlorin is not more intense than any of the side bands. With the side band furthest to the blue being most intense, it provides an almost porphyrin-like spectrum. The much lesser relative intensity enhancement of the dithiachlorin-type derivatives compared to the all-azachlorin derivatives was pointed out in the foregoing but it has reached an extreme here. We cannot offer an explanation for this observation.

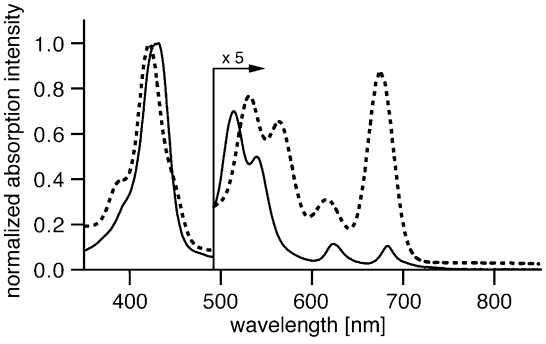


Figure 9. UV–vis spectra (CH_2Cl_2) of **5** (R=–Ph) (···) and **12** (—). The UV–vis data are summarized in Table 1.

3. Conclusions

In conclusion, we have prepared a series of novel dithiachlorin- and dithiaporphyrin-type derivatives. The UV-spectra of these derivatives do not always follow expectations. While the formal replacement of two of the pyrrolic nitrogens of these porphyrinic macrocycles with sulfur atoms generally leads to a significant bathochromic shift, most prominent in the parent dithiaporphyrin, this is not always the case. This underlines the unique properties of these heteroanalogs of porphyrins. This work implies for the practitioner searching for long-wavelength absorbing materials that the replacement of pyrrolic nitrogens for sulfur atoms is not a general principle for the generation of long wavelength absorbing chromophores. Further, the findings call for an in depth theoretical investigation of the electronic properties of dithiaporphyrins and -chlorins.

4. Experimental

4.1. Materials and instrumentation

All solvents and reagents used were reagent grade or better and were used as received. The analytical TLC plates were Silicycle ultra pure silica gel 60 (aluminum backed, 250 μm); preparative TLC plates (20×20 cm, 500 μm silica gel on glass) and the flash column silica gel (standard grade, 60 Å, 32–63 μm) used were provided by Sorbent Technologies, Atlanta, GA. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DRX400 and were referenced to residual solvent peaks. UV–vis spectra were recorded on a Cary 50 spectrophotometer, fluorescence spectra on a Cary Eclipse (5 nm excitation and emission slit width; reproduced uncorrected). The UV–vis data not listed in the spectroscopic data section are tabulated in Table 1. The IR spectra were recorded on a Perkin-Elmer Model 834 FT-IR. ESI mass spectra were recorded on a Micromass Quattro II at the conditions indicated. High resolution FAB mass spectra were provided by the Mass Spectrometry Facility, Department of Chemistry and Biochemistry, University of Notre-Dame (Bill Boggess). Elemental analyses were provided by Numega Resonance Labs Inc., San Diego, CA.

The silica gel-supported $NaIO_4$ was prepared according to a procedure adopted from the literature:[30] $NaIO_4$ (2.57 g,

Table 1. UV–vis absorption data of the compounds investigated and their all-aza analogues (all in $CHCl_3$ or CH_2Cl_2)

Compound	Soret $-\lambda_{max}$, nm (log ε) or (rel. $I \equiv 1.0$)	Q bands $-\lambda_{max}$, nm (log ε) or (intensity rel. to Soret band)				Ref.
		IV	III	II	I	
6 (Ar=–Ph)	435 (5.47)	515 (4.47)	548 (3.86)	635 (3.35)	699 (3.67)	21a
1 (Ar=–Ph)	418 (5.67)	515 (4.27)	548 (3.93)	592 (3.74)	647 (3.59)	22
8b[a]	433 (5.20)	520 (4.34)	545 (4.23)	627 (3.60)	687 (3.91)	This work
Low-R_f-**9b**	399 (1.00)	528 (0.21)		735 (0.27)		This work
3 (Ar=–Ph)	376 (5.42)	528 (5.08)		708 (4.89)		16
10b	440 (1.00)	526 (0.08)	561 (0.07)	633 (0.02)	699 (0.01)	This work
4 (Ar=–Ph)	419 (5.30)	532 (4.04)	564 (3.99)	618 (3.60)	678 (4.11)	11
12	433 (1.00)	514 (0.14)	540 (0.10)	623 (0.023)	683 (0.021)	This work
5 (Ar=–*p*-Tol)	419 (5.30)	532 (4.04)	564 (3.99)	618 (3.60)	678 (4.11)	11

[a] Dimethoxy derivative chosen over the dihydroxy compounds **7a/b** because of its proven purity.

12.0 mmol) was dissolved in hot H_2O (5 mL, ~70 °C) in a 25 mL round-bottom flask. To the hot solution was added silica gel (10 g, 40 μm flash grade) under vigorous swirling. The resulting product was dried in an open vessel at 50 °C for 12 h, resulting in a free flowing powder.

The dithiaporphyrins **6a–b** were prepared as described by Detty and co-workers,[8] whereby we simplified the workup of the final products by reduction of the oxidant prior to the chromatographic workup, adopting a method reported by Bonnett.[31]

The purity of the compounds, for which no elemental analysis is available, was judged by tlc and their ^1H and ^{13}C NMR spectra to be ≧97%. In particular, no other porphyrinic products were detected.

4.2. General procedure for the OsO_4-mediated dihydroxylation of *meso*-tetraaryl-21,23-dithiachlorins 6a–b

Dithiaporphyrins **6a–b** (42×10^{-5} mol) were dissolved/suspended in the least amount of slightly warmed EtOH-stabilized $CHCl_3$:pyridine (1:3, ~100 mL) and was treated with OsO_4 (1.2 equiv) (CAUTION: Fume hood and eye protection!). The reaction flask was stoppered and stirred at ambient temperature for 3 days, and shielded from light with aluminum foil. The reaction was monitored by TLC and UV–vis spectroscopy. The reaction was quenched by purging with H_2S for 5 min (CAUTION: Fume hood, trapping of excess H_2S!). The solution was then filtered through a plug of Celite to remove the precipitated OsS. The filtrate was evaporated to dryness by a stream of N_2 or using rotary evaporation (Fume hood!). The resulting residue was loaded onto a silica gel column (20×5 cm) and eluted with CH_2Cl_2. The first fraction recovered was starting material (~30% after recrystallization). An eluent mixture of 1% MeOH in CH_2Cl_2 then eluted the dioldithiachlorins **7a–c**, respectively. A mixture of 3% MeOH in CH_2Cl_2 then eluted the low polarity isomer low R_f-**9**, followed by the high polarity isomer high R_f-**9**. All products were further purified by preparative TLC.

4.2.1. *meso*-Tetraphenyl-7,8-dihydroxy-21,23-dithiachlorin (7a).

This compound was prepared according to the general procedure. Purification of the compound was accomplished by preparative TLC (silica–3% MeOH in CH_2Cl_2), followed by slow solvent exchange from CH_2Cl_2 to MeOH to yield **7a** as a micro-crystalline, purple material in 18% yield (52 mg). R_f (silica–5% MeOH in CH_2Cl_2)=0.40; UV–vis ($CHCl_3$): λ_{max} (log ε) 408 (5.27), 518 (4.19), 544 (4.19), 592 (3.85), 644 (4.38) nm; fluorescence ($CHCl_3$, $\lambda_{excitation}$=408 nm) $\lambda_{max\text{-}emission}$ 692, 733 (sh) nm; ^1H NMR (400 MHz, $CDCl_3$): δ 9.46 (d, J=5.0 Hz, 1H), 9.10 (d, J=5.0 Hz, 1H), 8.40 (s, 1H), 8.21 (d, J=6.7 Hz, 1H), 8.14 (d, J=7.0 Hz, 2H), 7.97 (d, J=6.5 Hz, 1H), 7.78 (m, 6H), 6.26 (m, 1H), 5.41 (dd, J=5.5, 1.6 Hz, 1H, exchangeable with D_2O) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.9, 153.2, 150.3, 141.3, 140.7, 140.4, 135.7, 135.2, 133.5, 133.3, 133.0, 132.1, 131.2, 128.4, 127.8, 127.6, 127.5, 73.5 ppm; HR-MS (MH^+, FAB-PEG): calcd for $C_{44}H_{31}N_2O_2S_2$, 683.1827, found: 683.1830.

4.2.2. *meso*-Tetratolyl-7,8-dihydroxy-21,23-dithiachlorin (7b).

This compound was prepared according to the general procedure. Purification was accomplished by preparative TLC (silica–1% MeOH in CH_2Cl_2), followed by slow solvent exchange from CH_2Cl_2 to MeOH to yield **7b** as a micro-crystalline, purple material in 20% yield (58 mg). R_f (silica–3% MeOH in $CHCl_3$)=0.85; UV–vis ($CHCl_3$): λ_{max} (log ε) 430 (5.20), 521 (4.33), 547 (4.27), 627 (3.59), 688 (3.98) nm; fluorescence ($CHCl_3$, $\lambda_{excitation}$=430 nm) $\lambda_{max\text{-}emission}$ 692, 735 (sh) nm; ^1H NMR (400 MHz, $CDCl_3$): δ 9.50 (d, J=4.8 Hz, 1H), 9.16 (d, J=4.8 Hz, 1H), 8.51 (s, 1H), 8.09 (m, 3H), 7.84 (m, 1H), 7.61 (m, 4H), 6.47 (s, 1H), 3.2 (br s, 1H), 2.46 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.9, 149.6, 136.6, 136.4, 135.4, 133.6, 132.6, 132.0, 131.9, 131.6, 130.9, 130.7, 130.2, 127.6, 127.1, 126.9, 72.6, 19.5 ppm; IR (KBr): 3427 (br), 2919, 2365, 1729 cm^{-1}; HR-MS (M^+, FAB-PEG): calcd for $C_{48}H_{40}N_2O_2S_2$, 690.2375, found: 690.2370.

4.2.3. *meso*-Tetratolyl-7,8,17,18-tetrahydroxy-21,23-dithiabacteriochlorin (high R_f-9b).

The compound was prepared according to the general procedure. Purification was accomplished by preparative TLC (silica–1% MeOH in CH_2Cl_2), followed by slow solvent exchange from CH_2Cl_2 to EtOH to yield **9b** as a powdery material in 5% yield (16 mg). R_f (silica–3% MeOH in $CHCl_3$)=0.18; UV–vis ($CHCl_3$) λ_{max} (rel. intensity): 399 (1.00), 528 (0.21), 735 (0.27) nm; fluorescence (CH_2Cl_2, $\lambda_{excitation}$ at 399 nm): $\lambda_{max\text{-}emission}$ 749, 768 (sh) nm; ^1H NMR (400 MHz, DMSO-d_6, 100 °C): δ 8.78 (s, 1H), 7.91 (d, J=7.0 Hz, 1H), 7.72 (d, J=7.1 Hz, 1H), 7.50 (d, J=6.9 Hz, 1H), 7.43

(d, J=7.0 Hz, 1H), 6.05 (d, J=4.5 Hz, 1H), 5.14 (d, J=4.5 Hz, 1H), 2.53 (s, 3H), 2.46 (s, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6, 100 °C): δ 143.8, 138.0, 136.5, 130.9, 130.8, 128.9, 128.5, 128.2, 69.8, 21.2 ppm; IR (KBr): 3418 (br), 2921, 1097 cm^{-1}; HR-MS (M^+, FAB-PEG): calcd for $C_{48}H_{40}N_2O_4S_2$, 772.2429, found: 772.2469.

4.2.4. *meso*-Tetratolyl-7,8,17,18-tetrahydroxy-21,23-dithiabacteriochlorin (low R_f-9b). The compound was isolated in <5% yield according to general procedure, followed by preparative plate chromatography (silica–2% MeOH in $CHCl_3$). R_f (silica–3% MeOH in $CHCl_3$)=0.74; fluorescence (CH_2Cl_2, $\lambda_{excitation}$ at 399 nm): $\lambda_{max\text{-}emission}$ 749, 768 (sh) nm; HR-MS (M^+, FAB-PEG): calcd for $C_{48}H_{40}N_2O_4S_2$, 772.2429, found: 772.2444.

4.2.5. *meso*-Tetratolyl-7,8-dimethoxy-21,23-dithiachlorin (8b). In a two neck round bottom flask, **7b** (28 mg, 4.1×10^{-5} mol) were dissolved in dry THF (20 mL) and placed under N_2. To the stirring mixture, NaH (~0.50 g, 60% emulsion in oil, briefly washed with THF) was added slowly. MeI (70 μL) was added via syringe, and reaction was allowed to stir for 19 h. The reaction carefully quenched with water. The reaction mixture was then partitioned between $CHCl_3$ (25 mL) and H_2O (25 mL) and washed several times with H_2O. The product was isolated by preparative TLC (silica–$CHCl_3$) and recrystallized by slow solvent exchange from $CHCl_3$ to EtOH to provide a 40% (11 mg) yield of crystalline material. R_f (silica–$CHCl_3$)=0.72; fluorescence (CH_2Cl_2, $\lambda_{excitation}$ at 433 nm): $\lambda_{max\text{-}emission}$ 691, 733 (sh) nm; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.50 (d, J=5.0 Hz, 1H), 9.18 (d, J=5.0 Hz, 1H), 8.54 (s, 1H), 8.09 (m, 3H), 7.78 (dd, J=6.5, 1.7 Hz, 1H), 7.60 (m, 3H), 7.51 (br d, J=7.7 Hz, 1H), 6.17 (s, 1H), 3.12 (s, 3H), 2.70 (s, 3H), 2.67 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.0, 154.7, 151.0, 142.8, 138.6, 138.5, 138.0, 137.4, 136.1, 135.8, 134.0, 133.3, 132.2, 130.8, 128.5, 128.4, 128.2, 82.0, 58.5, 21.8, 21.7 ppm; IR (KBr): 2917, 1508, 1448, 1132 cm^{-1}; HR-MS (FAB-PEG MH^+): calcd for $C_{50}H_{43}N_2O_2S_2$, 767.2766; found: 767.2742. Anal. Calcd for $C_{50}H_{42}N_2O_2S_2$ (%): C, 78.30; H, 5.52; N, 3.65. Found: C, 78.10; H, 5.49; N, 3.60.

4.3. Dithiaporpholactones 10 via MnO_4^--induced oxidation of dihydroxydithiachlorins 7 (general procedure)

To a stirring solution of **7** (2.2×10^{-5} mol) in THF (20 mL) was added 18-crown-6 (2.0 mg, 7.8×10^{-6} mol, 0.33 equiv), followed by $KMnO_4$ (17 mg, 11×10^{-5} mol, 5 equiv), and the mixture was allowed to react for 12 h at ambient temperature. The solution was filtered through a short plug of silica. The filter cake was washed with CH_2Cl_2 until the filtrate was colorless. The resulting solution was evaporated to dryness. The product was purified by column or preparative plate chromatography (silica–$CHCl_3$), eluted with $CHCl_3$, and recrystallized by solvent exchange into EtOH.

4.3.1. *meso*-Tetraphenyldithia-7-oxa-8-oxo-21,23-dithiaporphyrin (porphodithialactone, 10a). This compound was prepared in 61% yield (8.9 mg) according to the general procedure. R_f (silica–$CHCl_3$)=0.78; UV–vis ($CHCl_3$) λ_{max} (rel. intensity): 437 (1.00), 522 (0.09), 558 (0.07), 631 (0.01), 691 (0.005) nm; fluorescence (CH_2Cl_2, $\lambda_{excitation}$ at 437 nm): $\lambda_{max\text{-}emission}$ 716, 750 (sh) nm; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.54 (m, 3H), 9.38 (d, J=4.9 Hz, 1H), 8.57 (d, J=4.5 Hz, 1H), 8.50 (d, J=4.5 Hz, 1H), 8.19 (d, J=6.1 Hz, 6H), 8.06 (m, 2H), 7.78 (m, 12H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.4, 158.5, 155.4, 155.2, 152.1, 150.3, 146.0, 145.7, 140.6, 138.2, 137.7, 137.4, 137.0, 136.2, 135.6, 135.5, 134.8, 134.1, 134.0, 133.8, 132.8, 132.5, 132.3, 132.0, 129.0, 128.8, 128.7, 128.6, 128.3, 127.9, 127.8, 118.2 ppm; HR-MS (MH^+, FAB-PEG): calcd for $C_{43}H_{27}N_2O_2S_2$, 667.1514, found: 667.1536.

4.3.2. *meso*-Tetratolyl-7-oxa-8-oxo-21,23-dithiaporpholactone (10b)

This derivative was prepared in 54% yield (9.2 mg) according to the general procedure. R_f=0.8 (silica–$CHCl_3$); fluorescence (CH_2Cl_2, $\lambda_{excitation}$ at 437 nm): $\lambda_{max\text{-}emission}$ 717, 748 (sh) nm; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.53 (m, 3H), 9.38 (d, J=4.9 Hz, 1H), 8.58 (d, J=4.5 Hz, 1H), 8.51 (d, J=4.5 Hz, 1H), 8.07 (m, 6H), 7.95 (d, J=7.8 Hz, 2H), 7.62 (m, 8H), 2.71 (s, 6H), 2.68 (s, 3H), 2.67 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.8, 158.7, 155.6, 155.4, 152.2, 150.6 146.2, 146.0, 138.9, 138.8, 138.6, 138.5, 138.1, 137.8, 136.3, 135.7, 134.93, 134.9, 134.7, 134.4, 134.4, 134.1, 134.0, 132.7, 132.6, 132.2, 129.6, 129.4, 128.9, 128.8, 118.3, 22.2, 22.03, 22.02, 21.9 ppm; IR (KBr): 3429 (br), 2958, 2923, 2855, 1773 cm^{-1}; HR-MS (MH^+, FAB-PEG): calcd for $C_{47}H_{35}N_2O_2S_2$, 723.2140, found: 723.2146.

4.4. *meso*-Tetratolyl-7,8-ethoxy-7a-oxa-2a-homo-21,23-dithiaporphyrin (morpholino-dithiachlorin, 12)

meso-Tetratolyl-2,3-dihydroxy-21,23-dithiachlorin (**7b**) (20 mg, 3.0×10^{-5} mol) was dissolved in $CHCl_3$ (10 mL) at ambient temperature in a round-bottom flask equipped with a magnetic stirring bar, a N_2 inlet and bubbler, and was shielded from ambient light with aluminum foil. Excess EtOH (~0.5 mL) was added to the solution and the flask purged with N_2. Silica gel-supported $NaIO_4$ (~0.25 g, preparation see above) was added to the vigorously stirring reaction mixture and allowed to react for ~12 h. Additional oxidant (~0.20 g) was added until all starting material was consumed (reaction control by TLC). Upon completion, the mixture was filtered (glass frit M) and the filter cake washed with $CHCl_3$. The filtrate was evaporated to dryness by rotary evaporation. The products were purified by preparative TLC (silica–$CHCl_3$). The main orange product was eluted with $CHCl_3$ and crystallized by slow solvent exchange with EtOH to yield **12** in 28% yield (5.8 mg) in microcrystalline form. R_f (silica–1% EtOH in CH_2Cl_2): 0.44; fluorescence (CH_2Cl_2, $\lambda_{excitation}$ at 433 nm): $\lambda_{max\text{-}emission}$ 693 nm; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.46 (d, J=5.0 Hz, 1H), 8.95 (d, J=5.0 Hz, 1H), 8.56 (s, 1H), 8.07 (m, 3H), 7.71 (dd, J=7.6, 1.8 Hz, 1H), 7.52 (m, 4H), 6.67 (s, 1H), 4.12 (dq, J=7.9, 7.1 Hz, 1H), 3.08 (dq, J=7.9, 7.1 Hz, 1H), 2.68 (s, 3H), 2.67 (s, 3H), 1.22 (t, J=7.1 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.4, 148.2, 146.2, 143.7, 139.8, 138.6, 137.9, 137.5, 135.5, 134.9, 134.4, 134.1, 133.5,

131.9, 130.9, 128.3, 128.1, 128.0, 95.6, 64.4, 21.8, 21.7, 15.4

4.5. Tabulation of the optical data of the dithiachromophores

See Table 1.

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Novel synthesis of 4-halo-3-hydroxy-2-pyrone: one pot rearrangement–cyclization reaction by magnesium halide

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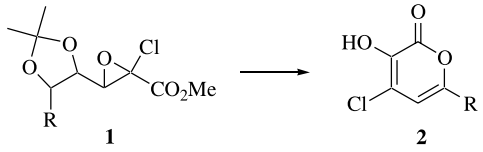
Abstract—Treatment of acetonide protected 4,5-dihydroxy-2-chloroglycidic ester or its rearrangement product, the acetonide protected 4,5-dihydroxy-3-chloro-2-oxo ester, with magnesium halides gave 4-halo-3-hydroxy-2-pyrone in excellent to reasonable yields in one pot. The mechanism of this novel one pot rearrangement–cyclization reaction is also proposed.

1. Introduction

The 2-pyrone moiety is an important constituent of a large number of natural products which exhibits a wide range of biological activity.[1] Recently, it has been discovered that phenyl substituted 2-pyrone has potent activity as HIV-1 protease inhibitors.[2] Besides, 2-pyrones have also been used for the syntheses of many useful molecules. For example, it is used as a diene component in Diels–Alder reactions[3] and also as a precursor to other heterocyclic compounds.[4] One group has reported the efficient asymmetric base-catalyzed Diels–Alder reaction of 3-hydroxy-2-pyrone.[5] As mentioned above, the 2-pyrone unite is very useful and have drawn much attention for its synthesis. Though a number of methods have been reported for the synthesis of 2-pyrone,[6] only a few works concerning the synthesis of 3-hydroxy-2-pyrone have been known.[7] Moreover, there is no report about synthesis of 6-substituted 4-halo-3-hydroxy-2-pyrone so far. But if there is an efficient procedure for the preparation of highly substituted 2-pyrone like 6-substituted 4-halo-3-hydroxy-2-pyrone, it is a powerful tool for the synthesis of various molecules and natural products. Furthermore this class compound can be expected as regards application to flavoring agents and perfumes itself.[8]

During some other researches in our group, we have unexpectedly discovered that 4-chloro-3-hydroxy-2-pyrone **2a** (R=H) could be obtained in one pot by treating acetonide protected glycidic ester **1a** (R=H) with magnesium chloride (Scheme 1). This reaction was completed very smoothly under mild condition and the yield was also excellent. As far as we know, this kind of one pot rearrangement–cyclization reaction has not been reported, and this reaction is not only unique but also very effective protocol for the preparation of 4-halo-3-hydroxy-2-pyrone **2**. Here, in this paper we demonstrate the novel synthesis of 4-halo-3-hydroxy-2-pyrone **2** by the reaction of acetonide protected 4,5-dihydroxy-2-chloroglycidic ester **1** with magnesium halides.



Scheme 1.

2. Result and discussion

First, we investigated the solvent effect on the reaction of synthesis of 2-pyrone **2a** from glycidic ester **1a** (Table 1). The starting material, 2-chloroglycidic ester **1a** was prepared from acetonide protected glyceraldehyde[9] via Darzens condensation reaction with dichloroacetate. When EtOAc was used as a solvent, desired 2-pyrone **2a** was obtained in good yield (entry 1). In case of toluene, the yield

Keywords: 3-Hydroxy-2-pyrone; Magnesium halide; Darzens condensation; Dichloroacetate; Cyclization.
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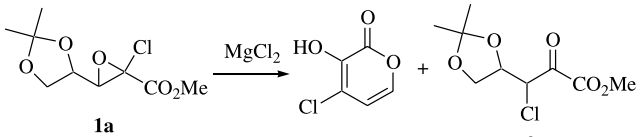
Table 1. Synthesis of 4-chloro-3-hydroxy-2-pyrone **2a** by the reaction of acetonide protected 4,5-dihydroxy-2-chloroglycidic ester **1a** with magnesium chloride



1a **2a** **3a**

Entry	$MgCl_2$ (equiv)	Solvent	Temperature (°C)	Time (h)	Product/Yield (%)
1	4.0	EtOAc	60	3	**2a**/81, **3a**/7
2	4.0	Toluene	Reflux	23	**2a**/49, **3a**/26[a]
3	4.0	Et_2O	Reflux	60	**3a**/75[a]
4	4.0	THF	Reflux	2	**2a**/97
5	4.0	DME	60 to reflux	15[b]	**2a**/92
6	4.0	Benzene	Reflux	8	0[a]
7	4.0	CH_2Cl_2	Reflux	8	0[a]
8	1.0	THF	Reflux	5	**2a**/97
9	0.5	THF	Reflux	15	**2a**/94
10	0.2	THF	Reflux	29	**2a**/91

[a] Starting material **1a** was recovered: 20, 15, 100, 100% yields (entries 2, 3, 6, 7), respectively.
[b] Reaction time and temprature were 7 h at 60 °C and then 8 h at reflux.

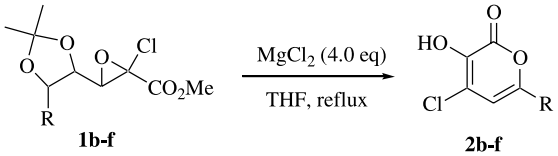
became moderate and the reaction was not completed even after 23 h (entry 2). Furthermore in case of Et_2O, only rearrangement product, 3-chloro-2-keto ester **3a** was furnished (entry 3). And then, we found that THF and DME were suitable solvents for this reaction and the yield was also excellent (entries 4, 5). On the contrary, benzene and CH_2Cl_2 gave no desired product and only starting material was recovered (entries 6, 7). Next, we optimized the amount of magnesium chloride, and its quantity was reduced to 0.2 equiv (entries 8–10). In these cases all reactions gave 2-pyrone **2a** in high yields (91–97%), though it took longer time to complete the reaction. These result shows that the reaction actually proceeds by the catalytic amount of magnesium chloride.

Then we also tried to apply this reaction to 5-substituted 2-chloroglycidic ester for the synthesis of the 6-substituted 2-pyrone. In the presence of $MgCl_2$, 5-substituted glycidic esters **1b–f** were also converted to corresponding 2-pyrones **2a–f** in good yields (Table 2). These glycidic esters **1b–f** were prepared from Darzens condensation reactions of synthesized aldehydes with dichloroacetate in our original reported procedure.[10] Treatment of glycidic ester **1b** with 4 equiv of $MgCl_2$ in THF under refluxing condition for 11 h provided 4-chloro-3-hydroxy-6-methyl-2-pyrone (**2b**) in 98% yield after purification by silica gel flash chromatography (entry 1). And other 5-substituted 2-chloroglycidic esters were also converted to 6-substituted 2-pyrone in good yields. But in this case, some diastereomers (entries 2, 3 for **1c** and entries 6, 7 for **1f**) showed different reactivity in this reaction and the starting material was recovered (entries 3, 6). This difference of reactivity is probably due to the bulkiness of the substituent R which prevents the attack of magnesium chloride on the epoxide and the rearrangement of substrate **1**.

Next, we carried out the investigation of other magnesium halide for this reaction (Table 3). At first, we attempt to try same reaction condition as entry 4 in Table 1, which gave good result in case of magnesium chloride. Glycidic ester **1a** was treated with 4 equiv $MgBr_2 \cdot 6H_2O$ in THF under refluxing condition for 4 h (entry 1). But, this time desired 2-pyrone **2g** was not obtained, and only rearrangement product **3g** was formed in 92% yield. Even if the reaction time was prolonged, the result did not change and only **3g** was obtained again (entry 2). On the contrary, when $MgBr_2 \cdot Et_2O$ was used at rt, desired bromine substituted 2-pyrone **2g** could be obtained in 22% yield (entry 3). And when the solvent was changed to toluene, the yield of desired compound **2g** was improved (entries 4, 5). At this time, the reaction with $MgBr_2 \cdot 6H_2O$ gave the product in better yield than that with $MgBr_2 \cdot Et_2O$. The reaction in EtOAc also furnished desired 2-pyrone **2g** in reasonable yield (entries 6–8). And in all these cases, chlorine substituted 2-pyrone **2a** was also obtained as a by-product. Furthermore, attempted reaction with MgF_2 resulted in the recovery of the starting material (entries 9–11).

And then, for the purpose of investigation of this reaction

Table 2. Synthesis of 6-substituted 4-chloro-3-hydroxy-2-pyrones **2b–f** by the reaction of acetonide protected 4,5-dihydroxy-2-chloroglycidic esters **1b–f** with magnesium chloride



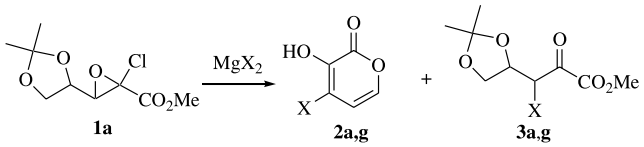
1b-f **2b-f**

b: R = Me
c: R = Pr
d: R = 4-$MeOC_6H_4$
e: R = C_6H_5
f: R = 1-naphthyl

Entry	Substrate[a]	Time (h)	Product/Yield (%)
1	**1b**	11	**2b**/98
2	**1c**	16	**2c**/83
3	**1c**	68	**2c**/69 (92)[b]
4	**1d**	20	**2d**/92
5	**1e**	20	**2e**/94
6	**1f**	94	**2f**/27 (83)[b]
7	**1f**	20	**2f**/89

[a] Major isomers, which were obtained from reported procedure[10] were used as a substrate (entries 1, 3–6). Minor isomers were used as a substrate (entries 2, 7).
[b] Based on consumed **1**.

Table 3. Synthesis of 4-halo-3-hydroxy-2-pyrone **2** by the reaction of acetonide protected 4,5-dihydroxy-2-chloroglycidic ester **1a** with magnesium halide



1a **2a,g** **3a,g**

a: X = Cl, **g**: X = Br

Entry	MgX_2[a]	Solvent	Temp.	Time (h)	Product/Yield (%)
1	$MgBr_2 \cdot 6H_2O$	THF	Reflux	4	**3g**/92
2	$MgBr_2 \cdot 6H_2O$	THF	Reflux	17	**3g**/71
3	$MgBr_2 \cdot Et_2O$ (2.0 equiv)	THF	rt	12	**2g**/22, **2a**/2 **3g**/58, **3a**/3
4	$MgBr_2 \cdot Et_2O$	Toluene	Reflux	25	**2g**/49, **2a**/7
5	$MgBr_2 \cdot 6H_2O$	Toluene	Reflux	25	**2g**/59, **2a**/5
6	$MgBr_2 \cdot Et_2O$ (2.0 equiv)	EtOAc	rt	12	**2g**/58, **2a**/9
7	$MgBr_2 \cdot Et_2O$	EtOAc	Reflux	0.5	**2g**/45, **2a**/2
8	$MgBr_2 \cdot 6H_2O$	EtOAc	Reflux	19	**2g**53, **2a**/18
9	MgF_2	THF	Reflux	19	**3a**/5[b]
10	MgF_2	EtOAc	Reflux	21	0[b]
11	MgF_2	Toluene	Reflux	21	0[b]

[a] Four equivalents of MgX_2 were used in each case if not mentioned.
[b] Starting material **1a** was recovered: 90, 95, 91% yields (entries 9–11), respectively.

mechanism, we followed the reaction of the glycidic ester **1a** with $MgCl_2$ by the ^1H NMR analysis (Fig. 1). The reaction condition is taken to be the same as that of entry 8 in Table 1. A proper analysis of the ^1H NMR reveals the formation of three products in this reaction, in addition to the desired 2-pyrone **2a**. From the ^1H NMR chart, one of the compounds was identified to be the rearrangement product **3a** and 5-membered ring compound **4a** was also verified. Furthermore there was another peak shown as H_d in Figure 1. We suppose this is the enolic proton of **3a**′, because it was also observed by ^1H NMR after isolation of **3a**. From this ^1H NMR chart, it seems that these compound **3a** (**3a**′) and **4a** are intermediates of this reaction. And we could suppose the following mechanism. The starting

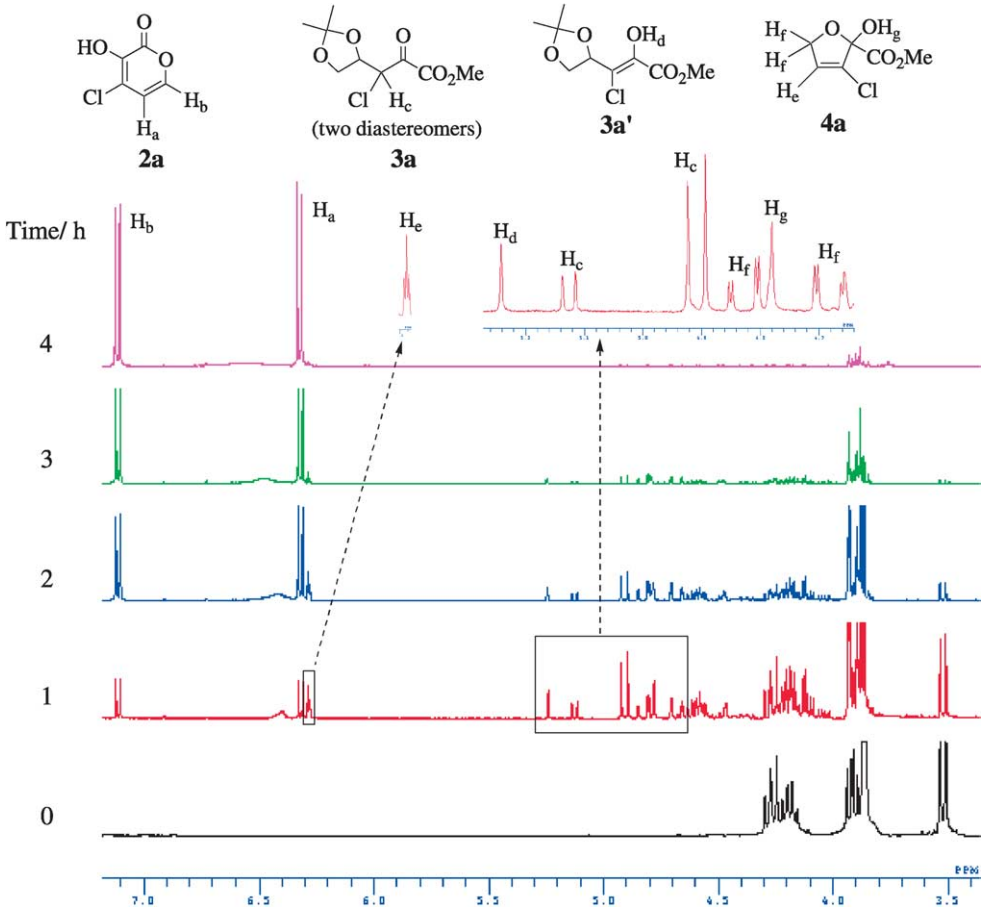


Figure 1. ^1H NMR spectra (300 MHz) of the reaction mixture under the same condition of Table 1 (entry 8) between 0 and 4 h.

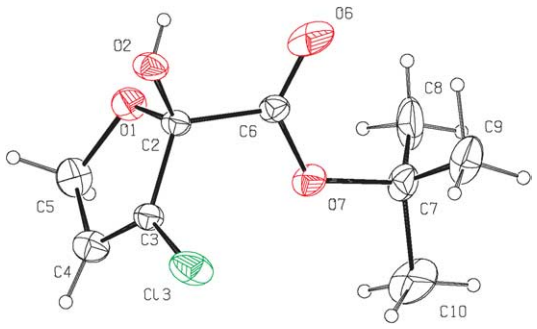
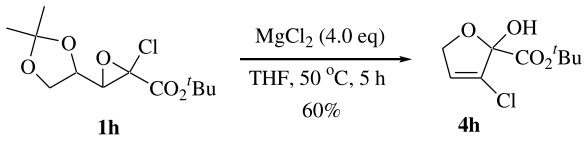


Figure 2. ORTEP view of the compound **4h**.



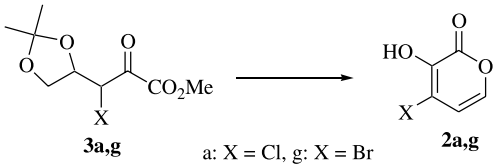
Scheme 2.

material, glycidic ester **1a** was first transformed to the rearrangement product **3a**. And then, the compound **3a** (**3a′**) was converted to the compound **4a**, which was finally transformed to 2-pyrone **2a**. Unfortunately, we could not isolate the pure compound **4a**, but its structure was confirmed by the X-ray analysis of the crystal compound **4h** (Fig. 2), which has the same feature in ^{1}H NMR data of compound **4a**.[11] The compound **4h** was obtained from the reaction of *t*-Bu ester **1h** with $MgCl_2$ as shown in Scheme 2. Interestingly, this time we could not obtained 2-pyrone **2a** which may be due to the bulkiness of the ester group.

In order to confirm our proposed mechanism, we also investigated the next reaction (Table 4). The rearrangement product **3a** (from Tables 1 and 3) was treated with 4.0 equiv of $MgCl_2$ in THF under refluxing condition, and furnished 2-pyrone **2a** in almost quantitative yield (entry 2). The bromine substituted ester **3g** also gave the 4-bromo-2-pyrone **2g** (entries 3, 4). Thus, these results are in agreement with the proposed mechanism mentioned above. Moreover, when the rearrangement product **3a** was treated without $MgCl_2$ in THF under refluxing condition, no desired compound was formed and only starting material was recovered (entry 1). This result prompted us to investigate the effect of $MgCl_2$ in this reaction, and thus further study was carried out (Scheme 3). Treatment of glycidic ester **1a** with $MgCl_2$ under the same reaction condition as Table 1 (entry 8) for 1 h provided a mixture of compounds **3a**, **3a′**, **4a** and recovered **1a**. And this crude product was treated without $MgCl_2$ in THF under refluxing condition again for 4 h, but in this time the reaction did not proceed and compound **3a**, **3a′**, **4a** and **1a** still remained as it was. Thus, these results indicated that $MgCl_2$ played a vital role not only in the rearrangement of glycidic ester **1a** to keto ester **3a**, but also in the conversion of keto ester **3a** (**3a′**) to compound **4a** and compound **4a** to 2-pyrone **2a**.

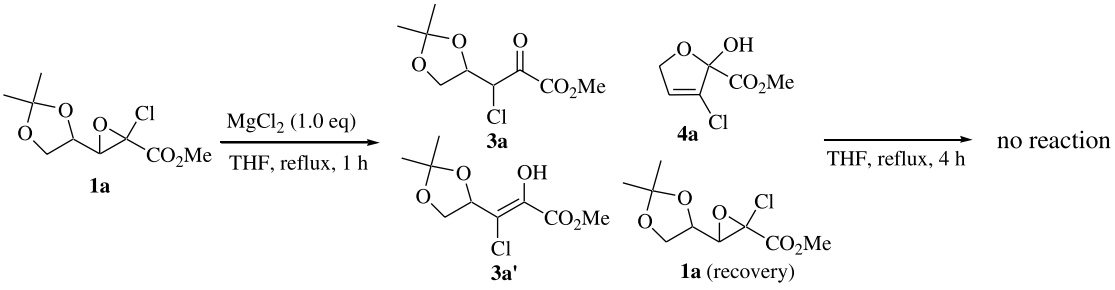
From the above results, a plausible mechanism for furnishing 2-pyrone **2a** from glycidic ester **1a** can be summarized as shown in Scheme 4. The first step of the reaction is the conversion of glycidic ester **1a** to keto ester **3a** in the presence of magnesium chloride as reported.[12] Then, acetone is eliminated via keto–enol tautomerism form product **3a′**, which thereby converts into intermediate compound **5**. In this step, if nucleophilic addition of hydroxyl group occurs to keto carbonyl carbon (path A),

Table 4. Synthesis of 4-halo-3-hydroxy-2-pyrone **2** by the reaction of acetonide protected 4,5-dihydroxy-2-oxo-3-halopentanoic ester **3** with magnesium halide

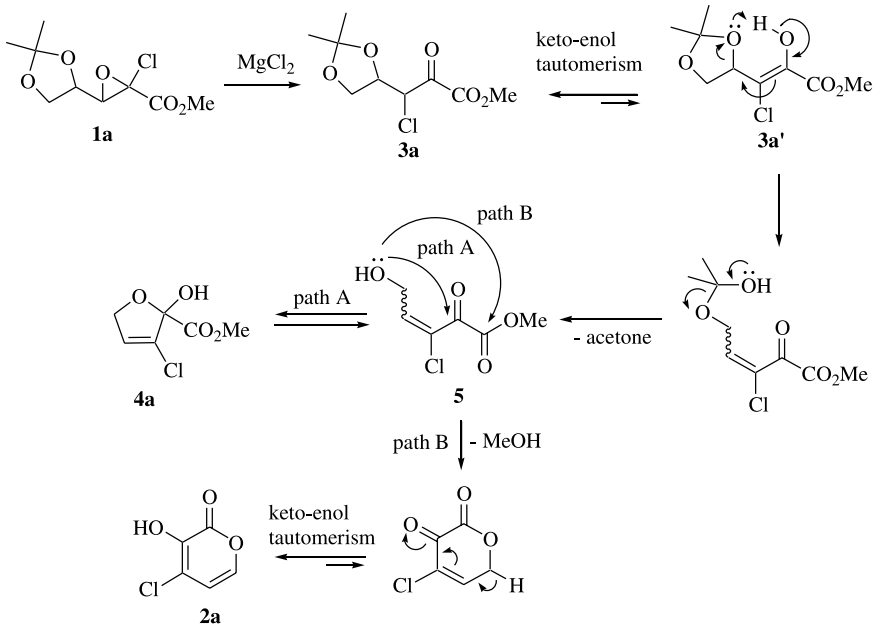


Entry	Substrate	X	Conditions	Product/Yield (%)
1	**3a**	Cl	THF, reflux, 3 h	0[a]
2	**3a**	Cl	$MgCl_2$ (4.0 equiv), THF, reflux, 1 h	**2a**/99
3	**3g**	Br	$MgBr_2 \cdot Et_2O$ (4.0 equiv), EtOAc, reflux, 45 min.	**2g**/52
4	**3g**	Br	$MgBr_2 \cdot 6H_2O$ (4.0 equiv), EtOAc, reflux, 12 h	**2g**/52

[a] Starting material was recovered quantitatively.



Scheme 3.



Scheme 4.

compound **4a** would be formed, which is in equilibrium with the intermediate compound **5**. On the contrary, if nucleophilic attack occurs at ester carbonyl carbon (path B), it would furnish the 4-chloro-3-hydroxy-2-pyrone (**2a**) after elimination of MeOH. Thus, this proposed mechanism is well accordance with and very well explains our results, which have given only the 6-membered ring 2-pyrone compound.

3. Conclusion

In conclusion, we have developed an efficient and novel protocol for the synthesis of 4-halo-3-hydroxy-2-pyrone by the reaction of acetonide protected 4,5-dihydroxy-2-chloroglycidic ester with magnesium halide in excellent to reasonable yields. And a variety of 6-substituted 4-halo-3-hydroxy-2-pyrones can also be prepared from commercially available or synthesized aldehydes by this method. The mechanism of this novel one pot rearrangement–cyclization reaction was also proposed. With a careful investigation of this reaction, we have discovered that magnesium halide has a crucial and novel role in many steps in this reaction for furnishing the 3-hydroxy-2-pyrone. Further exploitation of this strategy towards the synthesis of biologically active compound and applying this novel reaction to other cyclic compounds are in progress and will be reported in a future.

4. Experimental

NMR spectra were recorded on JEOL JNM-AL300 instrument and calibrated using residual undeuterated solvent as an internal reference. IR spectra were recorded on a Thermo Nicolet Avatar 360T2 infrared spectrophotometer. Elemental analyses were performed on Perkin–Elmer 2400 series II CHNS/O analyzer. For thin layer chromatography, aluminum sheets Merk silica gel coated 60 F254 plates were used and the plates were visualized with UV light and phosphomolybdic acid (5% in EtOH). Merck silica gel 60 N (spherical, neutral) (40–50 μm) was used for the flash chromatography. Melting points were obtained in open capillary tubes on a Mel-Temp-II hot stage microscope. THF was distilled from sodium wire/benzophenone before use. All other chemicals were used as received.

4.1. General procedure for the synthesis of 2a–g, 3a, g and 4h

To a stirred solution of α-chloroglycidic ester **1a** (50 mg, 0.21 mmol) in THF (2 mL) was added magnesium chloride (80 mg, 0.84 mmol), and the reaction mixture was heated to reflux for 2 h. Then the reaction mixture was allowed to cool to room temperature. Distilled water (2 mL) was added and the organic layer was extracted three times with EtOAc. The combined organic layer was dried over $MgSO_4$ and concentrated. The crude product was purified by column-chromatography (hexane/EtOAc 5:1 to 2:1) to give 4-chloro-3-hydroxy-2-pyrone (**2a**) in 97% yield. Other compounds were also obtained by this method.

4.1.1. 4-Chloro-3-hydroxy-2-pyrone (2a).[13] Pale yellow crystal; mp 166–167 °C (*i*-PrOH) [lit.[13] mp 125–135 °C ($CHCl_3$)]; R_f 0.23 (hexane/EtOAc, 2:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.32 (d, J=5.7 Hz, 1H), 6.56 (br, 1H), 7.12 (d, J=5.7 Hz, 1H); IR (neat): 3321, 1683, 1349, 1112, 779 cm^{-1}. Spectral data were identical with those of the authentic sample.

4.1.2. 4-Chloro-3-hydroxy-6-methyl-2-pyrone (2b). White crystal; mp 136–137 °C (hexane); R_f 0.15 (hexane/EtOAc, 2:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.23 (s, 3H), 6.04 (s, 1H), 6.16 (br, 1H); IR (neat): 3344, 1699, 1652, 1357, 1218 cm^{-1}. Anal. Calcd for $C_6H_5ClO_3$: C, 44.88; H, 3.14. Found C, 44.57; H, 3.22.

4.1.3. 4-Chloro-3-hydroxy-6-propyl-2-pyrone (2c). Colorless oil; R_f 0.31 (hexane/EtOAc, 2:1); ^{1}H NMR

(300 MHz, $CDCl_3$) δ 0.96 (t, $J=7.5$ Hz, 3H), 1.67 (m, 2H), 2.44 (t, $J=7.5$ Hz, 2H), 6.05 (s, 1H), 6.59 (br, 1H); IR (neat): 3317, 1685, 1648, 1366, 1206 cm^{-1}. Anal. Calcd for $C_8H_9ClO_3$: C, 50.94; H, 4.81. Found C, 50.98; H, 5.15.

4.1.4. 4-Chloro-3-hydroxy-6-(4-methoxyphenyl)-2-pyrone (2d). White crystal; mp 154–156 °C (*i*-PrOH); R_f 0.27 (hexane/EtOAc, 2:1); ^1H NMR (300 MHz, $CDCl_3$) δ 3.85 (s, 3H), 6.23 (br, 1H), 6.59 (s, 1H), 6.95 (d, 2H, $J=$ 9.0 Hz); 7.66 (d, 2H, $J=9.0$ Hz); IR (neat): 3282, 1699, 1639, 1512, 1368, 1174 cm^{-1}. Anal. Calcd for $C_{12}H_9ClO_4$: C, 57.05; H, 3.59. Found C, 56.65; H, 3.90.

4.1.5. 4-Chloro-3-hydroxy-6-phenyl-2-pyrone (2e). Red crystal; mp 195–198 °C (*i*-PrOH); R_f 0.11 (hexane/EtOAc, 2:1); ^1H NMR (300 MHz, $CDCl_3$) δ 6.33 (br, 1H), 6.72 (s, 1H), 7.45 (m, 3H), 7.72 (m, 2H); IR (neat): 3297, 1683, 1635, 1371, 1181 cm^{-1}. Anal. Calcd for $C_{11}H_7ClO_3$: C, 59.35; H, 3.17. Found C, 59.66; H, 3.48.

4.1.6. 4-Chloro-3-hydroxy-6-(1-naphtyl)-2-pyrone (2f). Gray crystal; mp 169–171 °C (benzene); R_f 0.26 (hexane/EtOAc, 2:1); ^1H NMR (300 MHz, $CDCl_3$) δ 6.50 (br, 1H), 6.62 (s, 1H), 7.55 (m, 4H), 7.93 (m, 2H), 8.11 (m, 1H); IR (neat): 3277, 1699, 1362, 1200, 1179 cm^{-1}. Anal. Calcd for $C_{15}H_9ClO_3$: C, 66.07; H, 3.33. Found C, 65.97; H, 3.47.

4.1.7. 4-Bromo-3-hydroxy-2-pyrone (2g). Pale yellow crystal; mp 171–172 °C (*i*-PrOH); R_f 0.16 (hexane/EtOAc, 2:1); ^1H NMR (300 MHz, $CDCl_3$) δ 6.42 (d, $J=5.7$ Hz, 1H), 6.47 (br, 1H), 7.04 (d, $J=5.7$ Hz, 1H); IR (neat): 3170, 1672, 1631, 1345, 1191, 775 cm^{-1}. Anal. Calcd for $C_5H_3BrO_3$: C, 31.44; H, 1.58. Found C, 31.82; H, 1.75.

4.1.8. Methyl 3-chloro-2-oxo-4,5-*O*-isopropylidene-pentanoate (3a). Yellow oil; R_f 0.20 (hexane/EtOAc, 2:1); main isomer: ^1H NMR (300 MHz, $CDCl_3$) δ 1.34 (s, 3H), 1.44 (s, 3H), 3.93 (s, 3H), 4.10 (dd, $J=3.6$, 9.3 Hz, 1H), 4.20 (dd, $J=6.0$, 9.3 Hz, 1H), 4.58 (ddd, $J=3.6$, 6.0, 9.0 Hz, 1H), 4.91 (d, $J=9.0$ Hz, 1H); IR (neat): 1736, 1255, 1067, 835 cm^{-1}. Anal. Calcd for $C_9H_{13}ClO_5$: C, 45.68; H, 5.54. Found C, 46.01; H, 5.70.

4.1.9. Methyl 3-bromo-2-oxo-4,5-*O*-isopropylidene-pentanoate (3g). Pale yellow oil; R_f 0.35 (hexane/EtOAc, 2:1); main isomer: ^1H NMR (300 MHz, $CDCl_3$) δ 1.34 (s, 3H), 1.44 (s, 3H), 3.93 (s, 3H), 4.10 (dd, $J=4.2$, 9.3 Hz, 1H), 4.23 (dd, $J=6.0$, 9.3 Hz, 1H), 4.68 (ddd, $J=4.2$, 6.0, 9.0 Hz, 1H), 4.97 (d, $J=9.0$ Hz, 1H); IR (neat): 1734, 1251, 1060, 840 cm^{-1}. Anal. Calcd for $C_9H_{13}BrO_5$: C, 38.45; H, 4.66. Found C, 38.18; H, 4.63.

4.1.10. *t*-Butyl 3-chloro-2-hydroxy-2,5-dihydrofuran-2-carboxylate (4h). Colorless crystal; mp 85–87 °C (toluene); R_f 0.39 (hexane/EtOAc, 2:1); ^1H NMR (300 MHz, $CDCl_3$) δ 1.51 (s, 9H), 4.64 (dd, $J=1.8$, 13.5 Hz, 1H), 4.80 (dd, $J=$ 1.8, 13.5 Hz, 1H), 4.89 (br, 1H), 6.23 (t, $J=1.8$ Hz, 1H); IR (neat): 3441, 1720, 1370, 1146, 1061 cm^{-1}. Anal. Calcd for $C_9H_{13}ClO_4$: C, 48.99; H, 5.94. Found C, 48.63; H, 5.68.

4.2. X-ray structure determination of 4h

The X-ray diffraction data for crystal **4h** were collected on a CAD4 Enraf-Nonius automatic four-circle difractometer (graphite monochromator, Cu K_α radiation (1.54184 Å), $\omega/2\theta$ scan method, $\theta \leq 74.11°$). Twenty five centered reflections gave a refined unit cell of dimensions $a=$ 8.543(1) Å, $b=12.736(2)$ Å, $c=11.451(1)$ Å, $\beta=$ 111.68(6)°, $V=1157.8(5)$ $Å^3$, $Z=4$, $\rho=1.27$ (g cm^{-3}). A total of 2243 reflections were measured, of which 1442 were unique with $I>3\sigma$. The stability of crystals and of experimental conditions was checked every 2 h using three control reflections, while the orientation was monitored every 200 reflections by centering two standards. Corrections for Lorentz and polarization effects were applied. The structure was solved in the uniquely assignable space group $P2_1/c$ by direct methods and difference Fourier syntheses using SIR program[14] and MolEN package[15]. All non-hydrogen atoms were refined anisotropically, H-atoms were located in ΔF maps and were refined isotropically. The final R values were $R=0.043$, $R_\omega=0.059$ for 1442 unique reflections with $F^2 \geq 3\sigma$. All calculations were carried out on a DEC Alpha Station 200 computer, all figures were made using the program PLATON.[16]

Crystallographic data (excluding structure factors) for the structure **4h** in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 244262. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0) 1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

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11. The NMR data of the compound **4a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.88 (s, 3H), 4.68 (dd, $J=1.8$, 13.5 Hz, 1H), 4.78 (br, 1H), 4.83 (dd, $J=1.8$, 13.5 Hz, 1H), 6.28 (t, $J=1.8$ Hz, 1H).
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