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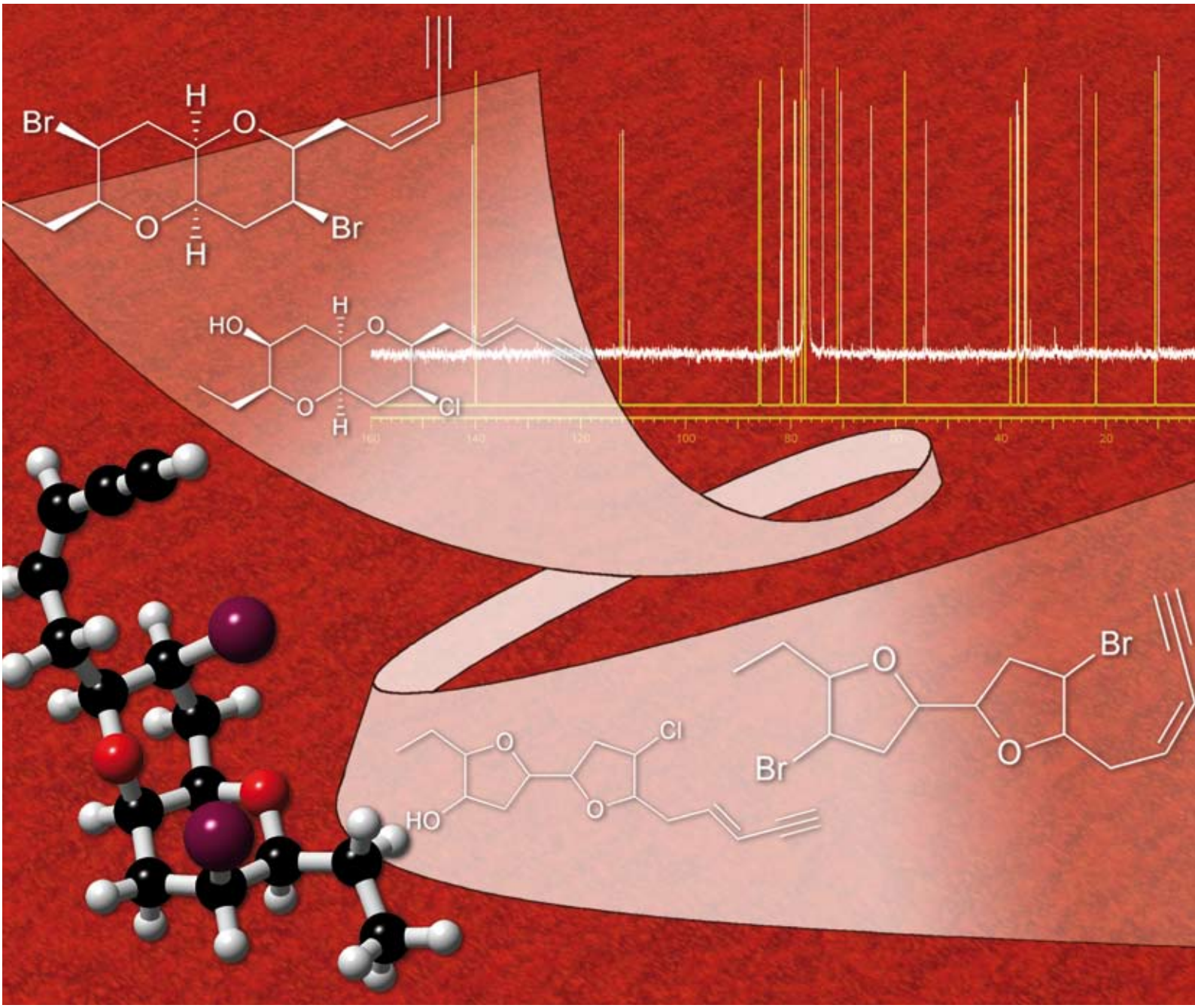

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FULL PAPER
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Synthesis of the originally proposed structures of elatenyne and an enyne from *Laurencia majuscula*†‡

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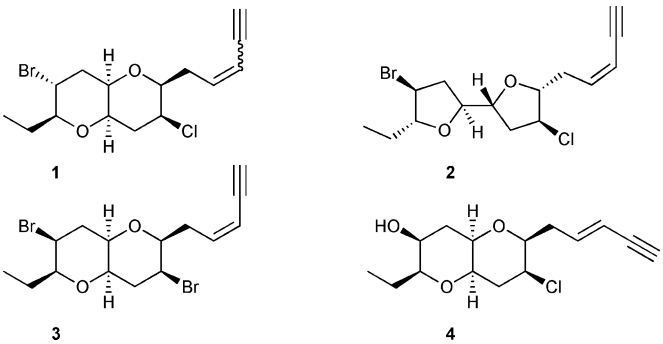
A bidirectional synthesis of the originally proposed structures for the natural products elatenyne and a chloroenyne from *Laurencia majuscula* is described along with a reassessment of the structures of the halogenated enynes based upon a ^{13}C NMR chemical shift/structure correlation.

Introduction

Until the advent of modern spectroscopic techniques in the later part of the 20th century, the structure determination of natural products was a time-consuming process that involved painstaking degradation and derivatisation of gram quantities of a natural product to provide structure information followed by total synthesis for structure confirmation. The development of a myriad of spectroscopic techniques (most notably NMR) now allows the structures of complex natural products to be determined routinely. Nevertheless, unambiguous structure assignment by NMR methods alone is not always straightforward especially in closely related molecules and total synthesis frequently still plays an important role in structure confirmation.[1] In particular through hetero-atom connectivity can still be a challenge to solve by NMR methods. For example, the two natural products (*Z*)-dactomelyne[2] (*Z*)-**1** and notoryne **2**[3] are constitutional isomers which both contain the same carbon and proton connectivity and hence unambiguous structure assignment would be challenging on the basis of NMR experiments alone.

The natural products **1** and **2** belong to a much wider group of C_{15} metabolites isolated from red algae and those marine organisms which feed on *Laurencia* species.[4] In 1986 the bis-brominated natural product elatenyne was isolated by Hall and Reiss and was assigned a pyrano[3,2-*b*]pyran structure **3** on the basis of extensive ^{1}H and ^{13}C NMR spectroscopic analysis.[5] More recently the structure of a halogenated C_{15} natural product isolated from *L. majuscula* was disclosed as the pyrano[3,2-*b*]pyran **4** again on the basis of extensive NMR spectroscopic analysis and by comparison with the structure **3** reported for elatenyne and with (*E*)-dactomelyne [(*E*)-**1**].[6]



Elatenyne and the *L. majuscula* enyne were attractive targets for total synthesis due to their unknown biological activity, densely functionalised pyrano[3,2-*b*]pyran cores and embedded C_2-symmetry.[7,8] We have previously demonstrated that the pyrano[3,2-*b*]pyran structures **3** and **4**, originally assigned to the natural products are incorrect, and proposed that the actual structures of the natural products are related to notoryne in having a core 2,2′-bifuranyl.[9,10] Herein we report the full details of the total synthesis of the halogenated pyrano[3,2-*b*]pyrans **3** and **4**. At the outset of the project we were unaware that the structures originally assigned to elatenyne and the chlorinated enyne from *L. majuscula* were incorrect. During these synthetic studies we uncovered a ^{13}C NMR chemical shift correlation which allows *cis*-fused pyrano[3,2-*b*]pyrans and 2,2′-bifuranyls, such as (*Z*)-dactomelyne [(*Z*)-**1**] and notoryne **2** to be readily distinguished and which ultimately led us to reassign the structures of elatenyne and the chloroenyne from *L. majuscula.*

Retrosynthetic analysis

We aimed to utilise a two-directional synthesis of the two targets **3** and **4**.[11] Thus, we envisaged that both halogenated pyrano[3,2-*b*]pyrans would be synthesised from the C_2-symmetric tetrol **5** (Fig. 1). Having had previous experience with the intramolecular hydrosilation of *exo*-cyclic enol ethers,[12,13] we postulated that the tetrol **5** would be available by intramolecular hydrosilation of the appropriately functionalised bis-*exo*-cyclic enol ether derived

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† Dedicated to Professor Andrew B. Holmes on the occasion of his 65th birthday, with respect and admiration.

‡ Electronic supplementary information (ESI) available: Experimental procedures for the preparation of a number of compounds including **8**, **16**, **26**, **29**, **31–34**, **37–46**, **55**, **58**, **59**, **68**, **76–78**, and ^{1}H NMR and ^{13}C NMR spectra of compounds **3**, **4**, **9**, **14**, **15**, **18**, **19**, **38**, **39**, **53**, **56**, **57**, **60–66**, **70–75** and **81–86**. CCDC reference number 698760. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b814953d

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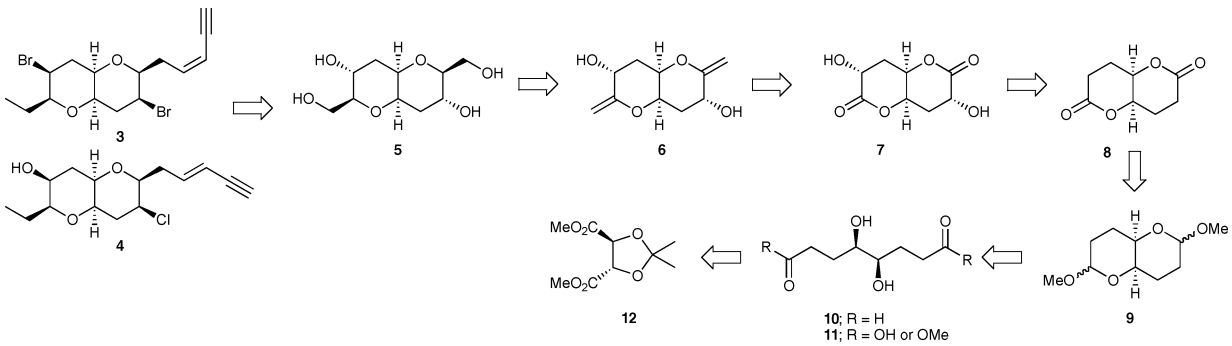


Fig. 1 Retrosynthetic analysis of the pyrano[3,2-*b*]pyrans **3** and **4**.

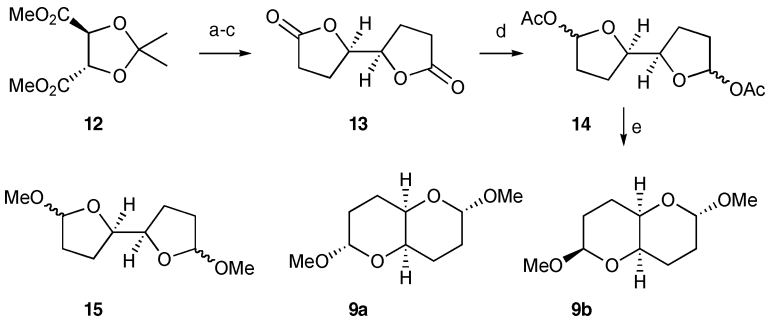
from **6**; an unstudied reaction with six-membered *exo*-cyclic enol ethers.[14] Alternatively the known hydroboration of α-oxygenated *exo*-cyclic enol ethers could also be used to convert **6** into the desired tetrol **5**.[15] The diol **6** would be prepared from the dihydroxy bis-δ-lactone **7** which would, in turn, be prepared by oxidation of the bis-δ-lactone **8**. To the best of our knowledge the bis-δ-lactone **8** has not been reported in the literature. The preparation of this bis-lactone would not be possible by cyclisation of an open chain intermediate diacid or diester (**11**) as under both kinetic and thermodynamic conditions this would give rise to the corresponding known bis-γ-lactone **13** (Scheme 1).[16] We therefore aimed to synthesise the bis-δ-lactone **8** by oxidation of the corresponding bis-methyl acetal **9**.[17] The bis-acetal **9** would be prepared from the corresponding dialdehyde **10** under equilibrating conditions with acid catalysis. Ultimately the dialdehyde would be synthesised from the commercially available tartrate-derived acetonide **12**.

Results and discussion

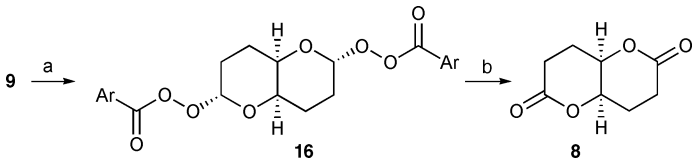
First generation route to the bis-*exo*-cyclic enol ether 6

Given the imbedded C_2-symmetry within the halogenated pyrano[3,2-*b*]pyrans **3** and **4** we restricted our synthetic plans to those which would result in a bidirectional synthesis of the target molecules starting from tartaric acid. The tartrate acetonide **12** was readily converted into the known bis-lactone **13**[18] (ν_{max} 1771 cm^{-1}) by an efficient 4 step procedure[19] (Scheme 1). Following the method of Rychnovsky,[20] the bis-lactone **13** was reduced with DIBAL and the intermediate alkoxides were acylated to give the anomeric acetates **14** as a mixture of 3 diastereomers. Treatment of the anomeric acetates **14** with methanolic hydrochloric acid at room temperature gave solely the three diastereomeric 2,2′-bifuranyls **15**. Use of methanolic hydrochloric acid at reflux provided a mixture of the two diastereomeric pyrano[3,2-*b*]pyrans **9** along with the 2,2′-bifuranyls **15**. The pyrano[3,2-*b*]pyrans **9** are present as a *ca.* 1.3 : 1 mixture of diastereomers (*ca.* 83% of the mixture at equilibrium) along with the 2,2′-bifuranyls **15** (*ca.* 17% of the mixture at equilibrium).[21–23] The five isomeric acetals could be separated by careful chromatography. The structures of the pyrano[3,2-*b*]pyrans **9** were tentatively assigned as follows. Due to reduced torsional strain it was expected that the pyrano[3,2-*b*]pyrans **9** would be thermodynamically more stable than the 2,2′-bifuranyls **15** and hence the major products in the equilibrium mixture should be the pyrano[3,2-*b*]pyrans **9**. Furthermore, the pyrano[3,2-*b*]pyrans **9** were readily oxidised to the bis-δ-lactone **8** (*vide infra*) which was spectroscopically distinct from the known bis-γ-lactone **13**.[18]

Having established a procedure for formation of the *cis*-fused pyrano[3,2-*b*]pyran **9** we required a method for oxidation of the methyl acetals directly to the corresponding bis-δ-lactone **8**. Following Grieco's procedure,[17] exposure of a mixture of the acetals **9** to *m*CPBA and $BF_3{\cdot}OEt_2$ followed by aqueous workup gave the bis-peroxyester **16** which on treatment with a solid supported guanidine base[24] gave the desired bis-δ-lactone **8** as a white crystalline solid in good yield (Scheme 2). The IR spectrum of the bis-δ-lactone was indicative of a 6-ring lactone (ν_{max} 1740 cm^{-1}) and was significantly different from the IR spectrum of the bis-γ-lactone **13** (ν_{max} 1771 cm^{-1}) thus confirming its structure. Disappointingly, it proved impossible to covert the bis-δ-lactone **8**



Scheme 1 Formation of the acetals **9** and **15**. *Reagents and conditions:* (a) DIBAL, toluene, −78 °C, then (carbethoxymethylene)triphenylphosphorane, MeOH, −78 °C → RT, 83%; (b) H_2, Pd/C, EtOH, 91%; (c) TFA, water, 100%; (d) DIBAL, CH_2Cl_2, −78 °C, then Ac_2O, pyridine, DMAP, CH_2Cl_2, −78 → −20 °C, 83%; (e) MeOH, HCl, 90%.



Scheme 2 Synthesis of the bis-δ-lactone **8**. *Reagents and conditions:* (a) *m*CPBA, $BF{\cdot}OEt_2$, 4 Å sieves, CH_2Cl_2; (b) 1,5,7-triazabicyclo[4.4.0]dec-5-ene on polystyrene.

into the corresponding hydroxylated bis-lactone **7**, or to form the enolate of **8** without decomposition.

Second generation route to the bis-*exo*-cyclic enol ether 6

Having been unable to oxidise the enolate derived from the bis-δ-lactone **8** we decided to approach the α,α′-dihydroxy bis-δ-lactone **7** by installation of the desired hydroxy groups prior to bis-lactone formation.

Thus, the α,α′-dihydroxy bis-δ-lactone **7** would be synthesised from the corresponding anomeric peracid ester **17** which, in turn, would be available by opening of the bis-epoxide **18** with *m*CPBA (Fig. 2). The bis-epoxide **18** would be prepared by epoxidation of *endo*-cyclic bis-enol ether **19**. We envisaged that the bis-enol ether would be formed by the elimination of two equivalents of methanol from the methoxy acetals **9**. Exposure of the pyrano[3,2-*b*]pyran **9a** to a large excess of iodotrimethylsilane followed by the addition of hexamethyldisilazane gave the bis-enol ether **19** in quantitative yield (Scheme 3)[25,26] which was used in the subsequent reactions without further purification. The structure of the bis-

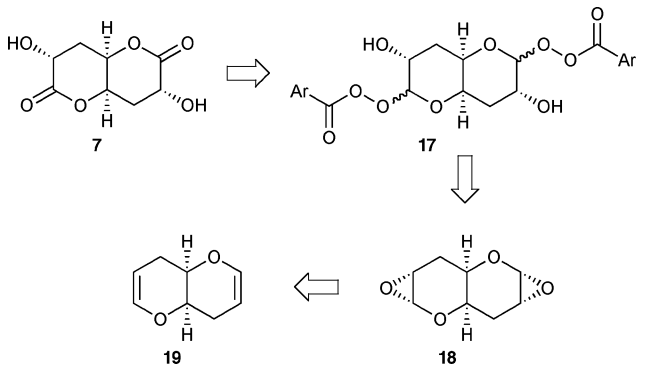
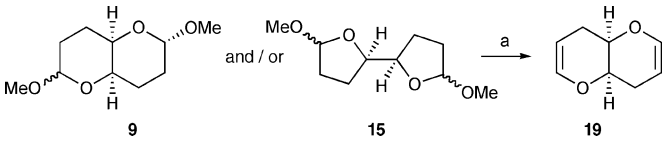


Fig. 2 Retrosynthesis of the α,α′-dihydroxy bis-δ-lactone **7**.



Scheme 3 Synthesis of the bis-enol ether **19**. *Reagents and conditions:* (a) NaI, TMSCl, MeCN, then hexamethyldisilazane.

enol ether was confirmed by X-ray crystallographic analysis of a later intermediate, the bis-epoxide **18**.

We subsequently discovered that subjection of any of the acetals **9**, **14** or **15** to the above reaction conditions gave the desired enol ether **19** as the sole product although the yield from the anomeric acetates **14** was considerably lower than from the acetals **9** or **15**. We postulate that the novel rearrangement of the 2,2′-bifuranyl acetals **15** to give the pyrano[3,2-*b*]pyran enol ether **19** proceeds as follows (Fig. 3). Silylation of the most sterically accessible oxygen lone pair in **15** occurs first which leads to the oxocarbenium ion **20**. The oxocarbenium ion **20** is trapped by the lone pair of the oxygen atom on the adjacent THF ring to give the tricyclic oxonium ion **21**, which fragments to give a second oxocarbenium ion **22**. This oxocarbenium ion is then captured by another oxygen atom lone pair to form the second tricyclic oxonium ion **23** which fragments to give the pyrano[3,2-*b*]-pyran system **24**. The resulting oxocarbenium ion can then be readily converted into the bis-anomeric iodide (**24**→**26**) which, on addition of base, gives the bis-enol ether **19**. We have briefly studied this reaction by ^{1}H NMR in d_3-MeCN. ^{1}H NMR analysis of a solution of the pyrano[3,2-*b*]pyran **9a** in d_3-MeCN immediately after the addition of iodotrimethylsilane shows the presence of a species we assigned to the bis-anomeric iodide **26**. Addition of HMDS to the above solution immediately results in the exclusive formation of the bis-enol ether **19** by ^{1}H NMR analysis. Exposure of one of the C_2-symmetric 2,2′-bifuranyl acetals **15** to iodotrimethylsilane followed by ^{1}H NMR analysis indicated the presence of the bis-anomeric iodide **26** and a second species which we assigned to the corresponding 2,2′-bifuranyl bis-anomeric iodide **29** (*ca.* 1 : 1 mixture of **26** and **29**).[27] Over many minutes the 2,2′-bifuranyl bis-anomeric iodides **29** were converted into the corresponding pyrano[3,2-*b*]pyran bis-anomeric iodides **26** presumably by way of the anomeric iodide **27** or equivalent intermediate. Exposure of the anomeric acetates **13** to the same reaction conditions followed by ^{1}H NMR gave the 2,2′-bifuranyl anomeric iodides **29** which slowly converted into the corresponding pyrano[3,2-*b*]pyran

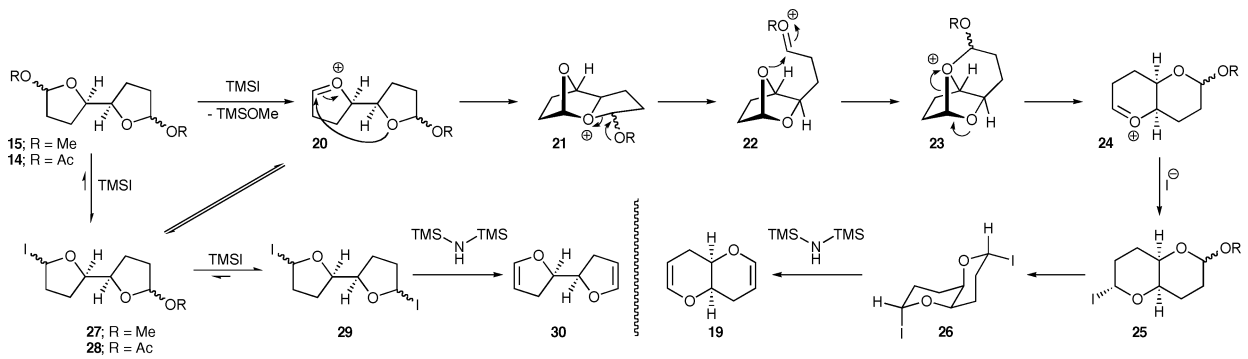


Fig. 3 Proposed mechanism for the formation of the bis-enol ether **19**.

bis-anomeric iodides **26** over a number of hours. In a separate experiment, treatment of a solution of the bis-anomeric acetates **13** in toluene with TMSI followed by the addition of HMDS gave the known 2,2′-bifuranyl bis-enol ether **30**.[28] These results are in accord with the proposed mechanism. The 2,2′-bifuranyl bis-methyl acetals **15** are rapidly converted into a mixture of the bis-anomeric iodides **26** and **29**. The 2,2′-bifuranyl anomeric iodides then rearrange to the pyrano[3,2-*b*]pyran anomeric iodides **26** as shown in Fig. 3. This rearrangement involves a number of charged intermediates and therefore proceeds readily in acetonitrile. With the bis-anomeric acetates **13** the conversion of the 2,2′-bifuranyl anomeric iodides **29** into corresponding pyrano[3,2-*b*]pyran **26** is slower than with the bis-methyl acetals **15**. This is probably due to a methoxy group being a better electron donor than an acetoxy group and hence intermediates such as **22** are formed more rapidly when R = Me than when R = Ac. Hence in toluene the rearrangement of the bis-anomeric acetates **13** is far slower and as a result the 2,2′-bifuranyl bis-enol ether **30** is the ultimate product. The driving force for the rearrangement of the acetals **15** to give the pyrano[3,2-*b*]pyran **19** may arise from the release of torsional strain in moving from a 2,2-bifuranyl to a pyrano[3,2-*b*]pyran.

Having developed an efficient synthesis of the bis-enol ether **19** from a mixture of the acetals **9** and **15**, we aimed directly to form the corresponding anomeric peracid esters **17** by treatment of the bis-enol ether **19** with excess *m*CPBA. In practice, this strategy was not effective. However, epoxidation of the bis-enol ether **19** with *m*CPBA in CH_2Cl_2 and methanol[29] delivered the bis-methyl acetals **31** as an inseparable mixture of anomers (Scheme 4).[30]

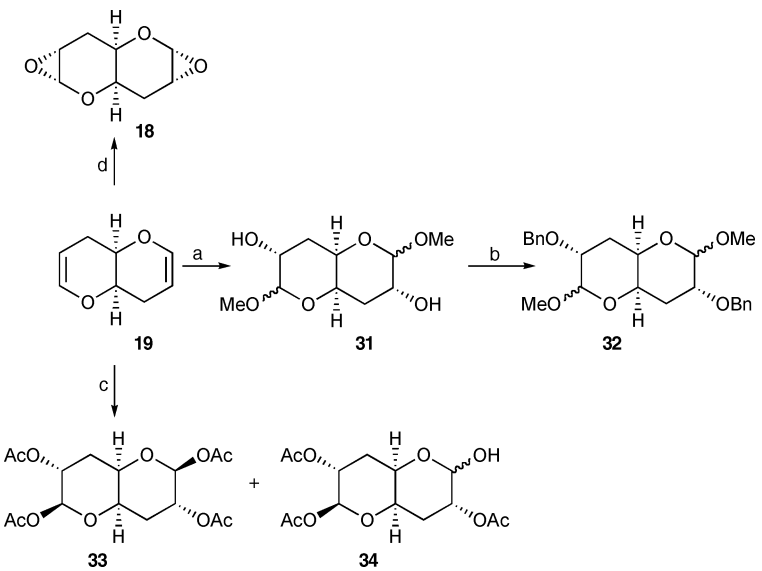
The free hydroxy groups in the acetals **31** were protected as benzyl ethers (**32**) to avoid water solubility issues which we had encountered with the lactone **8**. Disappointingly, the oxidation of the bis-methyl acetals **32** under Grieco's conditions[17] failed to deliver any of the desired bis-δ-lactone. Similarly attempted oxidation of the anomeric acetates **33**[31] under the same conditions, following precedent from the work of Hoppe,[32] was also unsuccessful resulting in substrate decomposition. We therefore sought to isolate the pure bis-epoxide **18** before exploring further routes towards **7**.

The bis-epoxide **18** was readily synthesised by treatment of the bis-enol ether **19** with dimethyldioxirane in acetone,[33,34] and was isolated as a white crystalline solid which was characterised crystallographically.[9] Disappointingly, attempted formation of the α-hydroxy anomeric peroxyesters **17** by opening of the bis-epoxide **18** with *m*CPBA was not successful. We attempted to convert the epoxide into the desired bis-δ-lactone **7** from the corresponding anomeric sulfides by Pummerer rearrangement[35] which was also unsuccessful (see ESI for substrate preparation‡). We also attempted to open the bis-epoxide **18** with iodomethyllithium[36] or dimethylsulfonium methylide[37] which would have given us direct access to the *exo*-cyclic bis-enol ether **6**, but again these reactions were unsuccessful.

Third generation route to the bis-*exo*-cyclic enol ether 6

Due to the failure of the epoxide-opening reactions and subsequent synthetic manipulations, we turned our attention to the direct functionalisation of enol ethers. We planned to convert the bis-*endo* cyclic enol ether **19** into the hydroxymethyl substituted bis-enol ether **35** which could be converted into the desired intermediate **6** by Evans–Mislow rearrangement of the corresponding sulfoxides **36**, or undergo intramolecular hydrosilation or hydroboration itself (Fig. 4).[38]

In the event, this plan was unsuccessful; attempted metallation of the enol ether **19** with *t*BuLi resulted in decomposition of the substrate. Ley has shown that anomeric sulfones undergo lithiation at the anomeric position and react with a wide variety of electrophiles.[39,40] Furthermore, in many cases, spontaneous elimination of benzenesulfinic acid occurs to give a functionalised *endo*-cyclic enol ether (such as **35**).[40] We therefore investigated this methodology for the synthesis of **35**. Exposure of the bis-*endo*-cyclic enol ether **19** to freshly prepared benzenesulfinic acid[39–41] gave the desired anomeric bis-sulfone **37a** in poor yield



Scheme 4 Elaboration of the enol ether **19**. *Reagents and conditions:* (a) *m*CPBA, MeOH, CH_2Cl_2, 74%; (b) NaH, BnBr, DMF, 39–54%; (c) $PhI(OAc)_2$, $BF_3{\cdot}OEt_2$, CH_2Cl_2 then Et_3N, **33** 15%, **34** 19%; (d) DMDO, acetone, $NaHCO_3$, 98%.

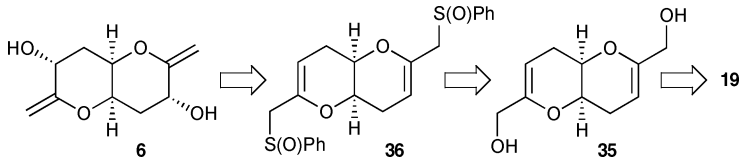
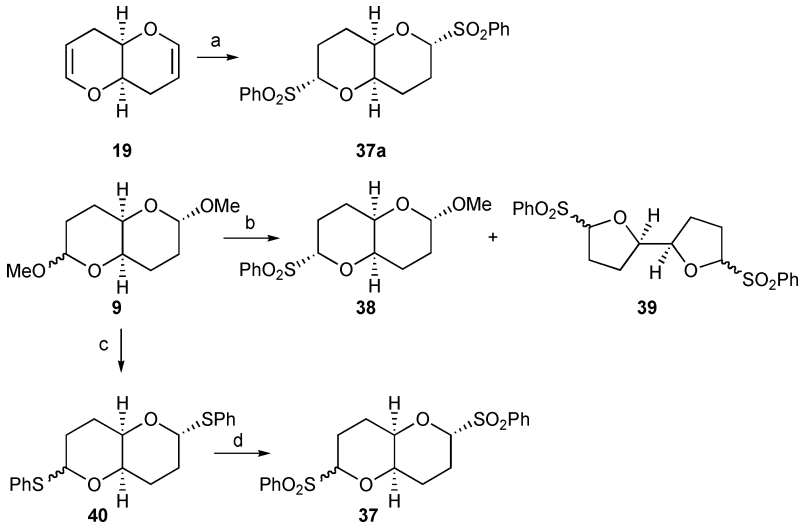


Fig. 4 Retrosynthesis of the bis-enol ether **6**.



Scheme 5 Synthesis of anomeric sulfones. *Reagents and conditions:* (a) $PhSO_2H$, 4 Å molecular sieves, CH_2Cl_2, 4–10%; (b) $PhSO_2H$, $CaCl_2$, CH_2Cl_2, **38** 27%, **39** 10%; (c) PhSH, $BF_3{\cdot}OEt_2$, CH_2Cl_2, 87%; (d) *m*CPBA, $NaHCO_3$, EtOAc, 100%.

(Scheme 5).[30] Attempted preparation of the bis-sulfones **37** from the corresponding bis-methyl acetals **9** using benzenesulfinic acid and calcium chloride[39,40] gave the 2,2′-bifuranyl anomeric sulfones **39** (mixture of 3 diastereomers) and the pyrano[3,2-*b*]pyran **38**. Ultimately we found that the anomeric sulfones **37** could be prepared in good yield from the bis-methyl acetals **9** by way of the corresponding anomeric sulfides **40**. Thus, exposure of the bis-methylacetals **9** to thiophenol in the presence of a Lewis acid delivered the anomeric sulfides **40** as an inseparable 2 : 1 mixture of diastereomers in good yield.[30] The anomeric sulfides were readily oxidised to the corresponding inseparable mixture of anomeric sulfones **37**.

Yet again we were frustrated by our inability to convert the anomeric sulfones **37** into the bis-enol ether **35**. Attempted lithiation of the sulfones with BuLi or LDA followed by addition of trioxane failed to give the desired product. Use of D_2O as the electrophile did not result in any deuterium incorporation. In all of the attempted lithiations, only varying levels of decomposition of the starting material were observed.

Fourth generation route to the bis-*exo*-cyclic enol ether 6

Our final approach to the hydrosilation substrate is illustrated in Fig. 5. Thus, we proposed to synthesise the desired bis-*exo*-cyclic enol ether **6** by rearrangement of the bis-epoxide **41**. The bis-epoxide **41** would be made from the bis-*endo*-cyclic enol ether **42** which we proposed to synthesise by elimination of two equivalents of methanol from the bis-methyl-acetal **43**, analogous to the preparation of the bis-enol-ether **19**.

The diketone **44** required for the synthesis of the acetal **43** was readily prepared from the tartrate acetonide **12** (Scheme 6).

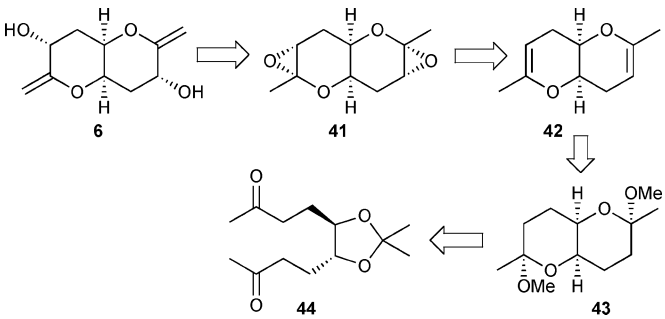
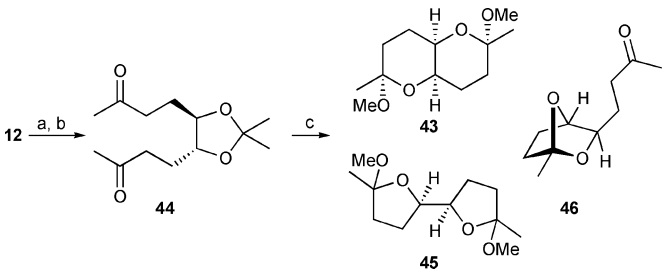


Fig. 5 Retrosynthetic analysis of the bis-enol ether **6**.

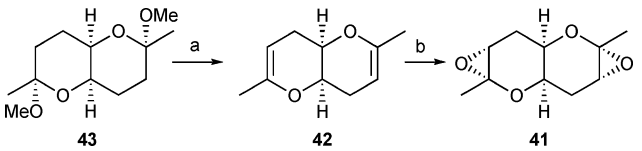


Scheme 6 Synthesis of the bis-acetal **43**. *Reagents and conditions:* (a) DIBAL, toluene, −78 °C, then (acetylmethylene)triphenylphosphorane, MeOH, −78 °C → RT, 80%; (b) H_2, Pd/C, EtOH, 99%; (c) $BF_3{\cdot}OEt_2$, CH_2Cl_2, MeOH, water, **43**, 50%.

After screening a wide range of protic and Lewis acids, we found that stirring the diketone **44** with $BF_3{\cdot}OEt_2$ in methanol gave the desired pyrano[3,2-*b*]pyran **43** identical with the previously prepared racemic sample.[22] Also isolated from the reaction mixture

was a single diastereomer of the 2,2′-bifuranyl **45** which rapidly decomposed; the dioxabicyclic[2.2.1]heptane **46** was formed in varying amounts when other acid catalysts were used. The next step in the proposed synthesis of the bis-enol ether **42** required the elimination of two equivalents of methanol from the bis-methyl acetal **43**.

Disappointingly, the conditions used for the formation of the bis-enol ether **19** from the bis-acetal **9** gave the desired enol ether in reasonable yield (50%) but contaminated with a number of inseparable impurities. A range of reaction conditions were screened; however, many of these resulted in formation of significant quantities of the bicyclic ketone **46**. Ultimately we found that exposure of the bis-methyl acetal **43** to bromotrimethylsilane followed by addition of DBU gave the desired bis-enol ether **42** in 55% yield (Scheme 7). The bis-epoxide **41** was readily formed from the bis-enol ether **42** on exposure to dimethyl-dioxirane in dichloromethane.[42]



Scheme 7 Synthesis of the epoxide **41**. *Reagents and conditions:* (a) TMSBr, DBU, 55%; (b) DMDO, CH_2Cl_2, 100%.

There is considerable precedent for the rearrangement of epoxides to give allylic alcohols, including those with an *exo*-cyclic olefin; however, we again were thwarted in our attempts to synthesise the bis-enol ether **6** from the bis-epoxide **41**. Exposure to the epoxide to a wide range of reagents and conditions [$Al(OiPr)_3$ in toluene;[43] Al_2O_3,[44] TMSBr/DBU;[45,46] LDA;[47] $Li/H_2NCH_2CH_2NH_2$;[47] MeMgNCy*i*Pr;[48] PhSeH, oxidative workup;[49] KO*t*Bu] did not give any of the desired product.

We had invested considerable synthetic effort in trying to make the bis-*exo*-cyclic enol ether **6** precursor for the proposed hydroboration or intramolecular hydrosilation reaction to give the tetrol **5**. All of the routes which we investigated towards **6** involved two-directional synthesis. While this can be a very efficient strategy for the synthesis of complex natural products,[11] it has so far proved unsuccessful in our case. This may be in part due to the bowl shaped conformation of the *cis*-fused pyrano[3,2-*b*]pyran intermediates which can result in the reaction on one side of the molecule having considerable influence on the reactivity of the opposite side of the molecule. Indeed, it might well have proved possible to synthesise the bis-enol ether **6** if a two-directional approach had not been used.

Structure determination

Our failure to synthesise the bis-enol ether **6** was most disappointing; however, this failure had resulted in the synthesis of a large number of 2,2′-bifuranyls and *cis*-fused pyrano[3,2-*b*]pyrans. Careful analysis of all of these compounds revealed that the ^{13}C NMR chemical shifts of the central oxygen-bearing carbons fell into two distinct groups: for the pyrano[3,2-*b*]pyrans, the ^{13}C NMR chemical shifts of the central oxygen-bearing carbons C-8a and C-4a resonate at less then $\delta = 76$ ppm, whereas the corresponding carbon atoms in the 2,2′-bifuranyls (C-2 and C-2′) resonate at greater than $\delta = 76$ ppm. We were alerted to this chemical shift pattern by the vastly different chemical shifts of the central oxygen bearing carbons in the various anomeric sulfones (Fig. 6). In this paper we report the synthesis of a large number of *cis*-fused pyrano[3,2-*b*]pyrans and 2,2′-bifuranyls and >98% of these fit this pattern.

In order to be able to put forward such a chemical shift correlation, it is imperative that the structures of all of the pyrano[3,2-*b*]pyrans and 2,2′-bifuranyls have been assigned correctly. Hoffmann has used ^1H NMR to investigate the conformation of the *cis*-fused pyrano[3,2-*b*]pyran skeleton **47**[50] and the related tetraoxadecalin **48** (TOD) system[51] which has also been extensively studied by Fuchs.[52–56] *cis*-Fused pyrano[3,2-*b*]-pyrans and TODs are conformationally flexible and may exist in the O-proximal or O-distal conformations (Fig. 7). The ^1H NMR vicinal coupling constants $J_{8ax,8a} = J_{4ax,4a}$ are characteristically large in the O-distal conformer with the corresponding coupling constants being small in the O-proximal conformer ($J_{8eq,8a} = J_{4eq,4a}$); in the analysis of equilibrating mixtures of conformers in solution, reference values

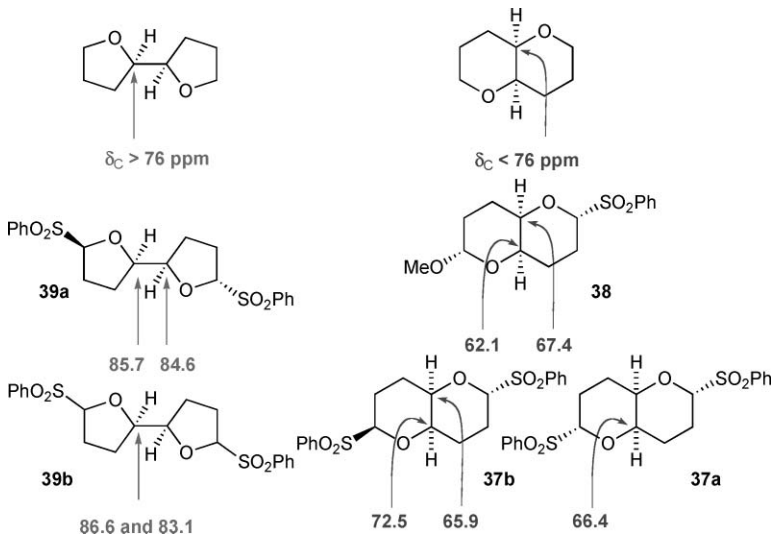


Fig. 6 ^{13}C NMR chemical shifts for 2,2′-bifuranyls and pyrano[3,2-*b*]pyrans.

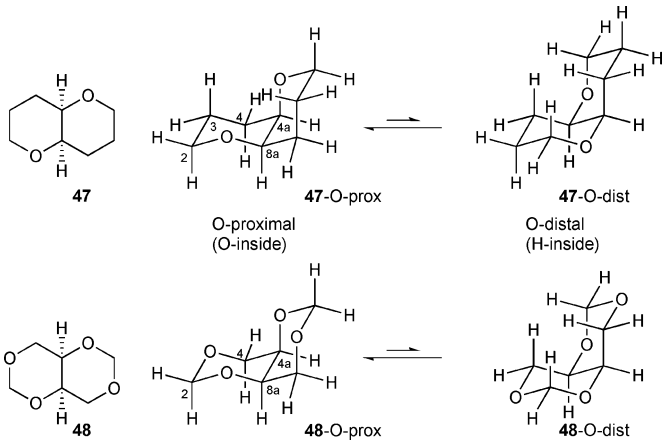


Fig. 7 Conformations of the *cis*-fused pyrano[3,2-*b*]pyran **47** and the tetraoxadecalin **48**.

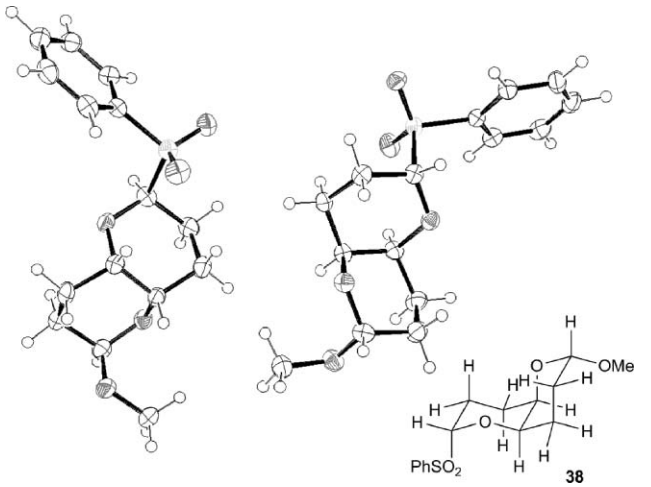


Fig. 9 X-Ray crystal structure of the anomeric sulfone **38** showing two molecules in the unit cell (50% probability ellipsoids).

of 1.2 Hz (O-proximal) and 10.6 Hz (O-distal) have been used for these coupling constants in TODs.[51,57] In the unfunctionalised pyrano[3,2-*b*]pyran **47**, H-4a and H-8a appear in the ^{1}H NMR spectrum as a narrow triplet (J 2.9 Hz) due to small axial–axial and axial–equatorial couplings to H-4$_{ax}$ and H-4$_{eq}$,[50] a feature that was characteristic of the pyrano[3,2-*b*]pyrans synthesised in this work.[50,58] Furthermore, in TODs which exist in the O-proximal conformation **48**-O-prox, $J_{4a,8a}$ is ~1.6 Hz,[53] but in the O-distal conformation, $J_{4a,8a}$ is ~6 Hz.[51] The ^{13}C shift of C-4a and C-8a in a wide range of TODs has been reported to fall in the range 69–70 ppm.[52,53]

The characteristic ^{1}H NMR coupling constants (small $J_{4,4a}$, $J_{8,8a}$ and $J_{4a,8a}$, and large $J_{3,4ax}$) along with ^{13}C NMR chemical shifts, coupled with X-ray crystallographic analysis of certain intermediates allowed the confident assignment of the structure and conformation of the pyrano[3,2-*b*]pyrans described in this paper. Furthermore, as alluded to above, the line shape of H-4a/8a was highly indicative of a pyrano[3,2-*b*]pyran and became a useful structure assignment tool. For example, in the sulfone **38**, H-8a and H-4a were narrow triplets with the typical line shape of a pyrano[3,2-*b*]pyran and ~3 Hz coupling to their vicinal neighbours H-8 and H-4 respectively indicating **38** was a pyrano[3,2-*b*]pyran predominantly in the O-proximal conformation (Fig. 8); $J_{4a,8a}$ was too small to be resolved. The anomeric protons H-2 and H-6 appeared as doublets, indicating they were in equatorial positions, coupling to one of the vicinal protons being too small to be resolved. In the ^{13}C NMR C-4a and C-8a resonated at (interchangeably) $\delta = 67.4$ and $\delta = 62.1$ ppm which also suggested a pyrano[3,2-*b*]pyran structure. The X-ray crystal structure of the sulfone **38**[59–61] (Fig. 9) obtained subsequently completely confirmed the NMR structural assignment. The asymmetric unit contains two molecules, both with pyrano[3,2-*b*]pyran rings in the O-proximal chair–chair conformation and the anomeric substituents axial as required for maximum anomeric stabilisation.

The 2,2′-bifuranyls were characterised by the ^{13}C NMR chemical shift of C-2 and C-2′ being $> \delta = 76$ ppm. The 2,2′-bifuranyls showed a larger ^{1}H–^{1}H coupling constant between the H-2 and H-2′ and one of their vicinal neighbours. Furthermore, these protons appeared as a well defined multiplet in the ^{1}H NMR spectrum. Additionally, the H-2/2′ multiplets were typically more complex and wider than the corresponding mutliplets in the pyrano[3,2-*b*]pyrans. For example, in the ^{13}C NMR of the sulfone **39a** C-2 and C-2′ resonated at $\delta = 85.7$ and $\delta = 84.6$ ppm whereas in the ^{1}H NMR spectrum, the corresponding protons had large couplings between them and to their vicinal neighbours ($J_{2,2'}$ 7.0 Hz, $J_{2,3}$ 7.0 Hz, $J_{2',3'}$ 9.1 Hz).

Reassessment of the structures of elatenyne and the chloroenyne from *L. majuscula*

The ^{13}C NMR chemical shifts of the central oxygen-bearing carbons in elatenyne[5] and the chloroenyne from *L. majuscula*[6] resonate at δ = 79.5 and 80 ppm, and δ = 77.9 and 79.2 respectively, outside the range for a pyrano[3,2-*b*]pyran. This initial discrepancy of the ^{13}C NMR chemical shifts alerted us to the possibility that the structures of elatenyne and the *L. majuscula* enyne had been incorrectly assigned. Comparison of the ^{1}H NMR coupling constants of both the *L. majuscula* enyne and elatenyne and closely related derivatives,[5] with that of (*E*)- and (*Z*)-dactomelyne led further weight to this proposal (Fig. 10). In particular, comparison of the ^{1}H NMR coupling constants of the axial chlorine-containing pyran ring in (*E*)-dactomelyne with the corresponding protons in both elatenyne and the *L. majuscula*

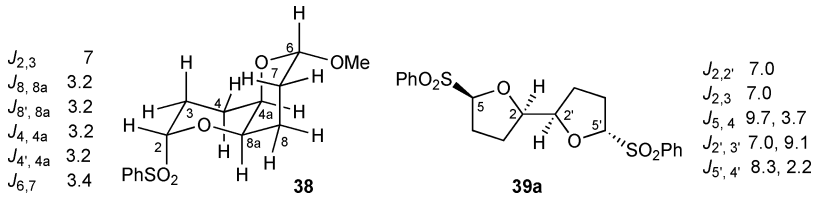


Fig. 8 Structure assignment of the anomeric sulfones by ^{1}H NMR.

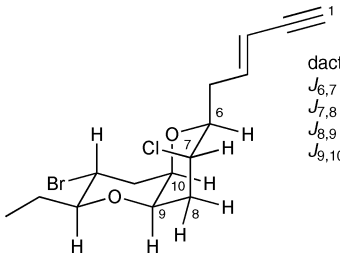


Fig. 10 Comparison of dactomelyne with the *L. majuscula* enyne and elatenyne (natural product numbering). *Coupling constants are a combination of those for elatenyne and from closely related derivatives.[5]

enyne showed considerable differences in the magnitude of the vicinal couplings.

The ^{13}C NMR chemical shift pattern we had uncovered and the ^{1}H NMR coupling constants of H-9 and H-10 (natural product numbering corresponding to H-4a and H-8a in a pyrano[3,2-*b*] pyran, and H-2 and H-2′ in a 2,2′-bifuranyl) led us to believe that the correct structures of elatenyne and the chloroenyne from *L. majuscula* were the 2,2′-bifuranyls **50** and **51** respectively (Fig. 11) related to the natural product notoryne **2**.

Notoryne **2**[3] was isolated by Suzuki and co-workers and was shown to have a 2,2′-bifuranyl skeleton by chemical correlation and analysis of fragmentation patterns in the FI and EI mass spectra. Thus, the EI mass spectrum of notoryne has fragments at *m/z* 177/179, 133, 97 and 69 which were assigned to furan fragments arising from fission of the inter-ring C–C bond (Fig. 11). Furthermore, the dibrominated 2,2′-bifuranyl **49**, a degradation product of laurefucin,[3,62] shows similar fragmentation under EI conditions. The EI mass spectra of both elatenyne[5] and the chloroenyne from *L. majuscula*[6] both have ions which can be readily explained as occurring by the same fragmentation of a 2,2′-bifuranyl skeleton.

In 1989 Erickson and co-workers reported the isolation and partial structure determination of a dibrominated 2,2′-bifuranyl from *L. majuscula*.[63] On the basis of ^{1}H NMR and ^{13}C NMR *J*-value analysis, they proposed a 2,2′-bifuranyl core structure and assigned the relative intra-ring stereochemistry but not the relative inter-ring stereochemistry. The proposed structures (**52**) are shown (Fig. 12). There are striking similarities between the ^{13}C NMR spectra of elatenyne and the dibromoenyne **52** and we propose that it is possible that elatenyne is the double bond isomer of the enyne **52**.

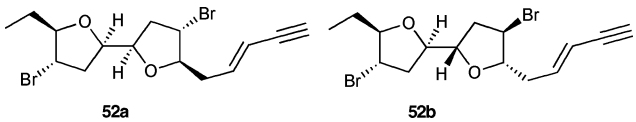


Fig. 12 Proposed structures of a dibromo-enyne from *L. majuscula*..

We had amassed considerable evidence that the structures originally proposed for elatenyne and the chlorinated enyne from *L. majuscula* were incorrect. However, in order to confirm these structure misassignments it was necessary to undertake the total synthesis of the originally proposed structures of these natural products namely the halogenated pyrano[3,2-*b*]pyrans **3** and **4**.

Total synthesis of the pyrano[3,2-*b*]pyrans 3 and 4

Having established that the originally proposed structures for the natural products elatenyne and the chloroenyne from *L. majuscula* (**3** and **4**) were likely to be incorrect, we sought further confirmation of this by undertaking the total synthesis of these two halogenated pyrano[3,2-*b*]pyrans. Given the difficulty we encountered in preparing the *exo*-cyclic enol ether **6** we aimed to synthesise both molecules by using appropriate organometallic

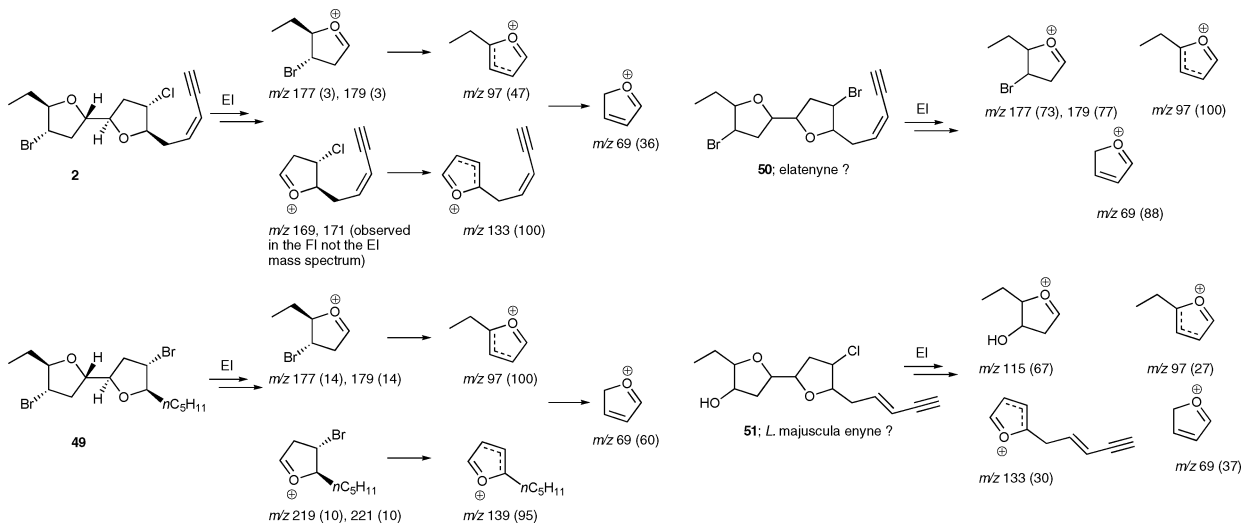
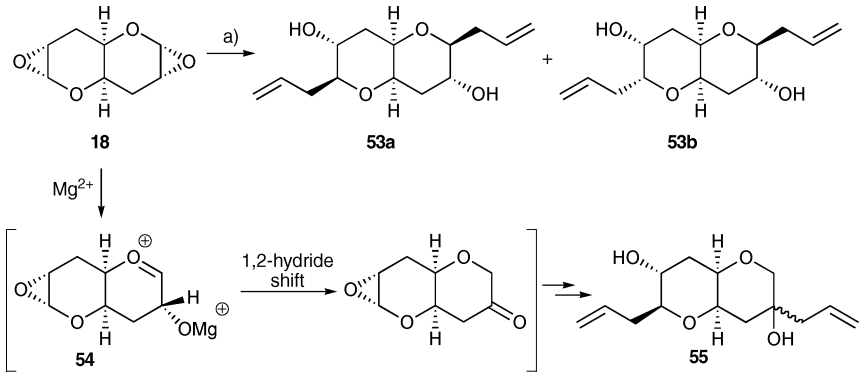


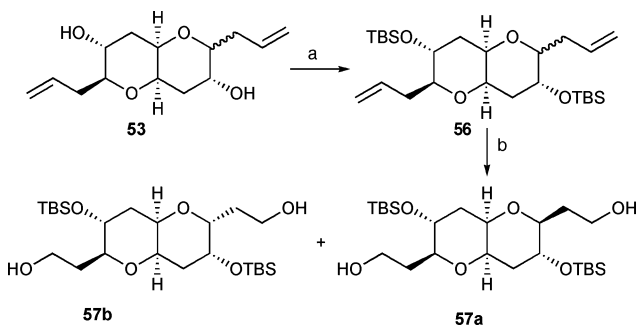
Fig. 11 Fragmentation patterns for a number of halogenated 2,2′-bifuranyls.



Scheme 8 Opening of the epoxide **18**. *Reagents and conditions:* (a) diallylmagnesium, THF, Et_2O, 57%.

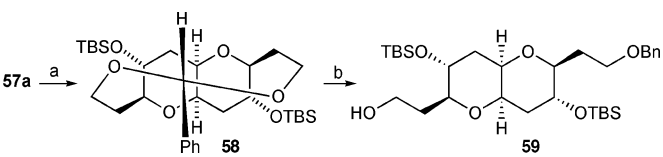
reagents to open the bis-epoxide **18** at the anomeric centres with inversion of configuration thus setting the required stereochemistry for the synthesis of **3** and **4**. The synthesis of *C*-glycosides by the opening of 1,2-anhydrosugars with organometallic reagents is well precedented[64–68] and treatment of the epoxide **18** with allylmagnesium chloride or bromide gave the desired pyrano[3,2-*b*]pyran **53a** in moderate yields along with the inseparable diastereomer **53b** (Scheme 8).[30] The highest yields were obtained using diallylmagnesium which Rainier has used extensively for the opening of similar epoxides in the synthesis of the ladder toxins.[67] The improved yields using diallylmagnesium may be due to the removal of Lewis acidic magnesium bromide or chloride from the reaction mixture where it may catalyse side reactions of **18**. If the epoxide was not purified by crystallisation prior to treatment with the organomagnesium reagents, then the tertiary alcohols **55** were formed as a side product as a 4 : 1 mixture of inseparable diastereomers. Such products have previously been observed by Rainer who proposed that they arise from opening of the epoxide to give an oxocarbenium ion (*e.g.* **54**) followed by 1,2-hydride shift, to give a ketone which is then attacked by the allylmagnesium reagent.[69]

The diols **53** were persilylated and the terminal alkenes cleaved by ozonolysis of the mixture of silylethers **56** with a reductive workup (PPh_3 and $NaBH_4$) to give the separable diols **57** in excellent overall yield (Scheme 9).[30] Use of other methods of double bond cleavage ($RuCl_3/NaIO_4$[70] or $OsO_4/NaIO_4$[71]) was far less satisfactory.



Scheme 9 Synthesis of the diols **57**. *Reagents and conditions:* (a) TBSOTf, Et_3N, CH_2Cl_2, 99%; (b) O_3/O_2, CH_2Cl_2, MeOH, –78 °C, then PPh_3, –78 °C, 2 h, then $NaBH_4$, –78 °C → RT, 2 h, 82%.

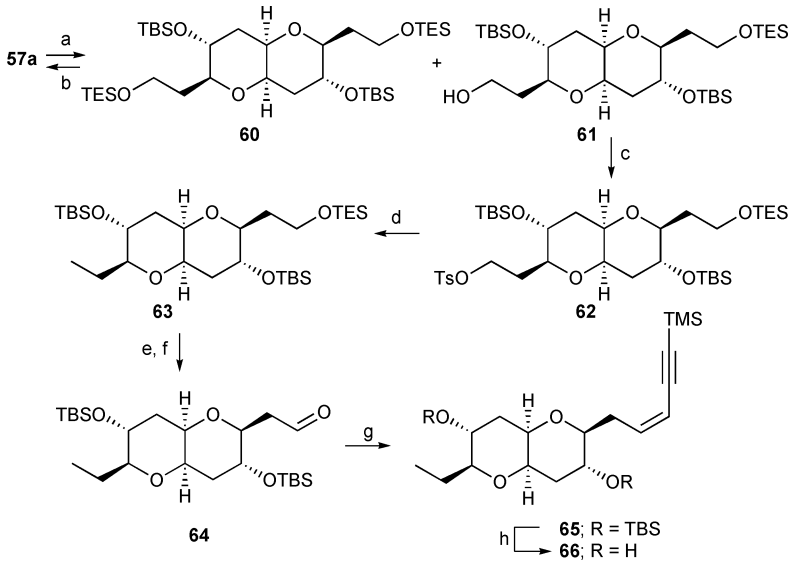
Having developed an efficient synthesis of the C_2-symmetric diol **57a** it was necessary to introduce the two side chains which required the differentiation of the two primary alcohols. Our first approach towards this goal was to convert the alcohols into the corresponding benzylidene acetal and then cleave the resulting acetal with DIBAL-H.[72] Exposure of the diol **57a** to benzaldehyde dimethylacetal with PPTS as the acid catalyst, delivered the desired benzylidene acetal **58** in low yield (Scheme 10).[73] The use of stronger acids such as PTSA resulted in extensive silyl group migration and cleavage. Disappointingly, treatment of the acetal **58** with DIBAL-H gave a very poor yield of the desired differentially protected tetrol derivative **59** and hence this method of desymmetrising the diol **57a** was not pursued further.



Scheme 10 Synthesis of the benzyl ether **59**. *Reagents and conditions:* (a) $PhCH(OMe)_2$, PTSA, 4 Å molecular sieves, toluene, reflux, 41%; (b) DIBAL, toluene, 0 °C, 17%.

Our next approach to desymmetrising the diol **57a** involved monotosylation or monoiodination such that the resulting products could be reduced to install the necessary ethyl side chain of **3** and **4**. Unfortunately, under a large number of reaction conditions neither monotosylation nor monoiodination of the diol **57a** could be achieved in yields above 30%. Furthermore, we could only oxidise the diol **57a** to the monoaldehyde in sub-statistical yield and further functionalisation of the monoaldehyde was low yielding (see ESI‡). The low efficiency of these transformations led us to investigate an alternative desymmetrisation procedure.

Schreiber has shown that mono-silylation is an efficient method for desymmetrising C_2-symmetric intermediates and this procedure proved effective in our system.[74] Thus, treatment of diol **57a** with 1 equivalent of chlorotriethylsilane gave 48% of the desired alcohol **61**, along with 17% of the bis-triethylsilyl ether **60** and 35% recovered starting material **57a** (Scheme 11). Selective deprotection of the two triethylsilyl groups in **60** by treatment with K_2CO_3 in methanol gave quantitative recovery of the diol **57a**, which was combined with the diol recovered from the initial



Scheme 11 Synthesis of the pyrano[3,2-*b*]pyran **66**. *Reagents and conditions:* (a) TESCl, Et_3N, CH_2Cl_2, **61** 48%, **57a** 35%, **60** 17%; (b) K_2CO_3, MeOH, 100%; (c) TsCl, Et_3N, DMAP, CH_2Cl_2, 93%; (d) Et_3BHLi, Et_2O, 91%; (e) K_2CO_3, MeOH, 98%; (f) TPAP, NMO, 4 Å molecular sieves, CH_2Cl_2, 95%; (g) $Me_3SiC{\equiv}CCH_2SiMe_2tBu$, *t*BuLi, $Ti(OiPr)_4$, THF, −78 °C, add **64**, −78 °C → RT, 0.5 h, then $(Me_3Si)_2NK$, 75%; (h) TsOH, MeOH, 22 h, 75%.

silylation reaction and resubjected to the silylation conditions to provide a further 22% of **61** (total 70% of **61** after one recycle).

The alcohol **61** was readily converted into the corresponding tosylate **62** which was reduced with lithium triethylborohydride[75,76] to give the ethyl-substituted pyrano[3,2-*b*]pyran **63** in excellent overall yield. The primary silyl protecting group of **63** was removed under basic conditions and the resulting alcohol oxidised to the corresponding aldehyde **64** using TPAP and NMO.[77] The (*Z*)-enyne was introduced in a highly selective manner using a Yamamoto–Peterson reaction.[78,79] Thus, addition of the allenyltitanium reagent derived from 3-(*t*butyldimethylsilyl)-1-trimethylsilylpropyne to the aldehyde **64** gave an intermediate silanol which, on the addition of a potassium base, was readily converted into the desired (*Z*)-enyne **65** in good yield and selectivity (>10 : 1, (*Z*) : (*E*)). The remaining oxygen protecting groups were removed under acidic conditions to give the diol **66** in readiness for the proposed double bromination for the synthesis of **3**.

The introduction of bromine atoms with inversion of configuration to the more hindered face of the pyrano[3,2-*b*]pyran **66** was expected to prove challenging and we first investigated this transformation on the allyl-substituted pyrano[3,2-*b*]pyrans **53**.[80] S_N2 reaction of the activated hydroxyl groups would be impossible in the ground state O-proximal conformation of **53a**-O-prox since the trajectory for backside attack is completely blocked (Fig. 13). The reactive O-distal conformation **53a**-O-dist would place all the substituents in axial positions, and furthermore, in this conformation the nucleophilic bromide ion must attack a secondary centre past an axial substituent. In addition, the S_N2 reaction is at a carbon atom bearing a β-oxygen substituent, a situation which is known to yield slow rates of S_N2 reactions.[81] Kozikowski's synthesis of the dactomelynes stalled at the introduction of the corresponding chlorine substituent[8] and Murai has implied that the halogen substituents in molecules such as the dactylenes are best introduced prior to ring-formation.[82]

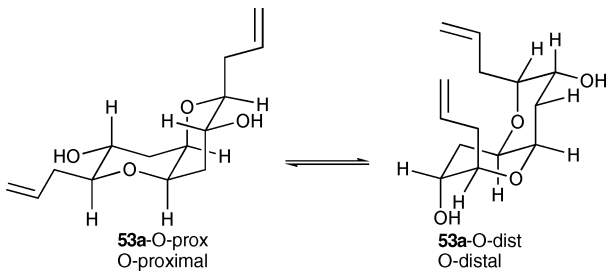
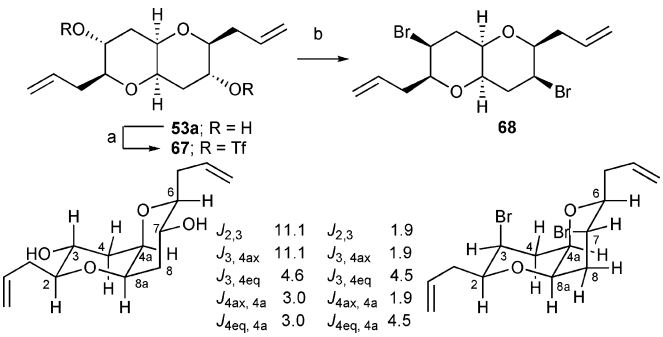


Fig. 13 Conformations of the diol **53a**.

A variety of methods ($CBr_4/P(oct)_3$,[83] PBr_3,[84] the Ghosez reagent,[85] $SOBr_2$,[8,86] Mitsunobu reaction with $ZnBr_2$,[87] triflate with LiBr in HMPA,[88] imidazolylsulfonate with TBABr in toluene[89]) failed to give the desired dibromide **68**. Ultimately, we found that heating the bis-triflate **67** with tetrabutylammonium bromide in toluene under reflux gave the desired dibromide **68** in low yield (Scheme 12). Proof that the installation of the bromine atoms in **68** had occurred with inversion of configuration followed from

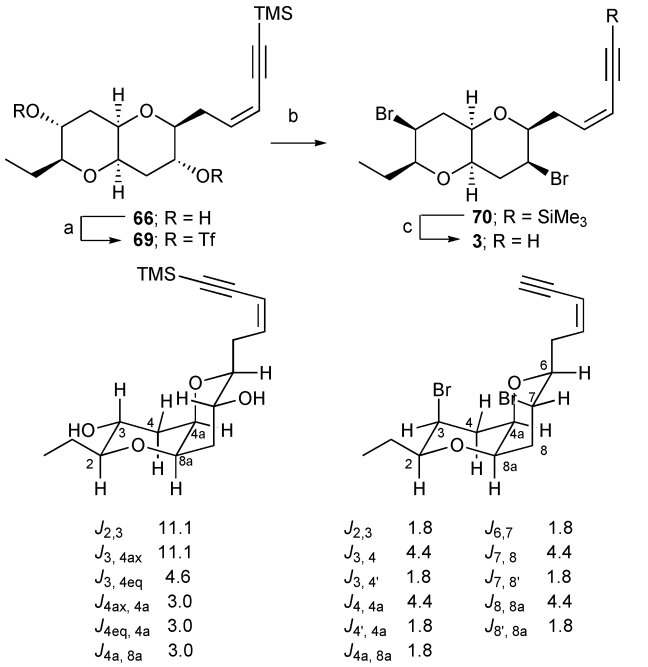


Scheme 12 Synthesis of the dibromide **68**. *Reagents and conditions:* (a) Tf_2O, pyridine, CH_2Cl_2; (b) nBu_4NBr, toluene, reflux 2 h, 17% from **53**.

J-value analysis. Furthermore, H-4a and H-8a in **68** appeared as a multiplet with the typical line shape for a pyrano[3,2-*b*]pyran with the ^{13}C NMR chemical shift of C-4a,8a being 71.4 ppm, consistent with the pyrano[3,2-*b*]pyran structure.

Mixtures of other unidentifiable compounds were also isolated from the reaction mixture which had NMR spectra consistent with elimination and/or rearranged products, however, pure material could never be obtained. Attempts at optimising the reaction did not prove fruitful. Extended reaction times resulted in decomposition of the product dibromide. Use of more polar solvents such as DMF in place of toluene gave the formate ester of the starting material and elimination products in low yield and purity.

Pleasingly, treatment of the triflate **69** derived from the diol **66** under the same reaction conditions (tetrabutylammonium bromide in toluene at reflux) delivered the corresponding dibromide **70** again in low yield (14%) (Scheme 13). The dibromide was relatively unstable, however, deprotection with TBAF gave the stable enyne **3** in quantitative yield. The $^{3}J_{H,H}$ coupling constants between the ring protons in **70** and synthetic **3** were very similar to those observed in the model brominated compound **68** (*vide supra*) which strongly suggested that bromination with inversion of configuration had occurred to give a pyrano[3,2-*b*]pyran with the desired stereochemistry. The ^{1}H NMR coupling constant between the bridgehead protons H-4a and H-8a in synthetic **3** was 1.8 Hz (in **70** it was also 1.8 Hz), which is in excellent agreement with a pyrano[3,2-*b*]pyran in the O-proximal conformation. The ^{13}C NMR chemical shifts of C-4a and C-8a in **3** were 71.4 and 71.2 ppm again consistent with a pyrano[3,2-*b*]pyran structure. Thus, we are confident that the synthetic enyne **3** had the structure and conformation shown in Scheme 13. The ^{1}H NMR and ^{13}C NMR chemical shifts and $^{3}J_{H\text{-}H}$ coupling constants were compared with those reported for elatenyne[5] and many discrepancies were noted. In particular, the ^{1}H NMR chemical shifts for H-6 and H-7, and H-2 and H-3 were different by >0.2 ppm between the synthetic and natural material with differences in the ^{13}C NMR chemical shifts of up to 8 ppm.[90] Thus, we have confirmed that **3** is not the structure of natural elatenyne.

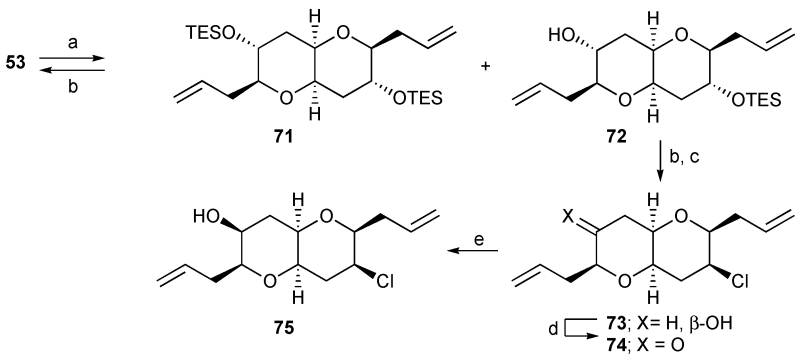


Scheme 13 Synthesis of the dibromide **3**. *Reagents and conditions:* (a) Tf_2O, pyridine, CH_2Cl_2; (b) nBu$_4$NBr, toluene, reflux 2 h, 14% from **66**; (c) TBAF, THF, 100%.

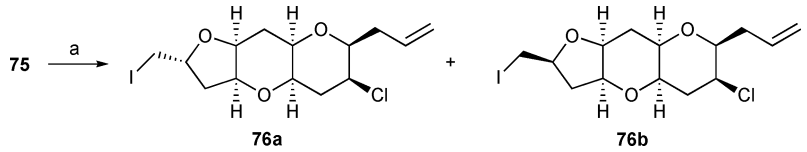
Synthesis of the proposed structure of the enyne from *L. majuscula*

We aimed to synthesise the chlorinated enyne from *L. majuscula* from the diols **53**. The diols **53** were desymmetrised by the silylation procedure we had used previously[74] to give the mono-protected alcohol **72** in 64% yield after one recycling sequence (Scheme 14).[91] The required chlorine atom was readily introduced by conversion of the alcohol **72** to the corresponding triflate followed by heating with tetrabutylammonium chloride in toluene under reflux to give the desired chloride **73** in 43% yield after complete removal of the silyl protecting group. It is interesting to note that the attempted replacement of an axial hydroxy group by a chlorine atom in studies towards the synthesis of the dactomelynes failed completely.[8] The remaining secondary hydroxy group in **73** was inverted by an oxidation[77]/reduction sequence to give the alcohol **75** as a single diastereomer; the stereochemistry of **75** was confirmed by X-ray crystal structure analysis.[9]

Differentiation of the two terminal alkenes was now required such that the C-2 and C-6 side chains of **4** could be introduced selectively. Exposure of the alcohol **75** to iodine gave the



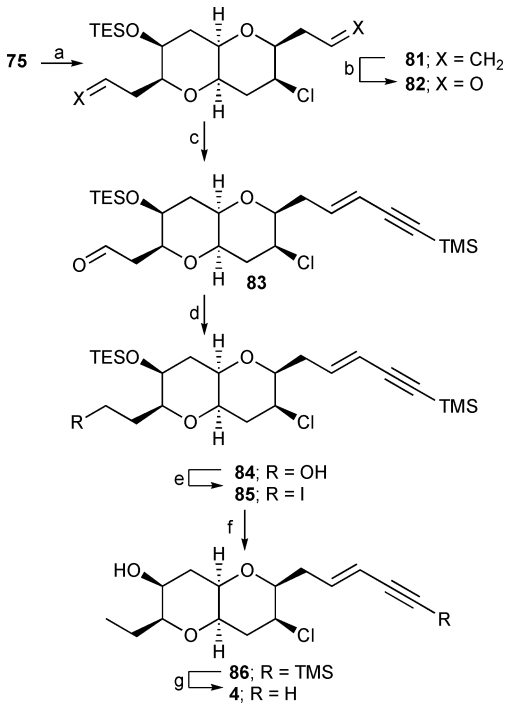
Scheme 14 Synthesis of the pyrano[3,2-*b*]pyran **75**. *Reagents and conditions:* (a) TESCl, Et_3N, CH_2Cl_2, **72** 42%, **71** 38%, **53a** 20%; (b) Tf_2O, pyridine, CH_2Cl_2; (c) nBu$_4$NCl, toluene, reflux, 2 h, then Amberlite™ resin IR-120, MeOH, 43% from **72**; (d) nPr$_4$NRuO$_4$, NMO, CH_2Cl_2, 4 Å molecular sieves, 65%; (e) $NaBH_4$, MeOH, 87%.



Scheme 15 Iodoetherification of the alcohol **75**. *Reagents and conditions:* (a) I_2, CH_2Cl_2, $NaHCO_3$; **76a** 85%, **76b** 11%.

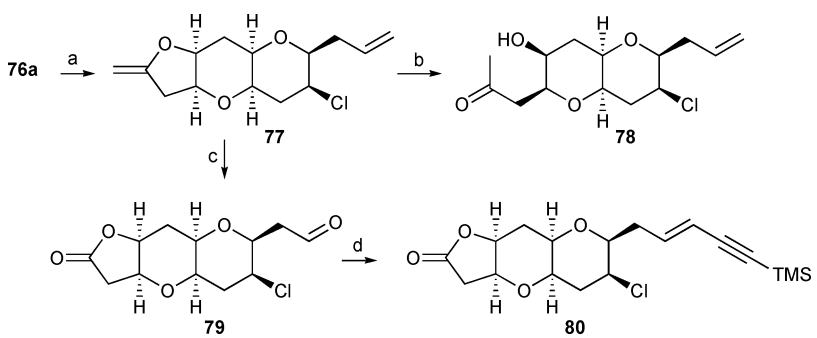
corresponding tricyclic iodides **76** in 96% yield as an 8 : 1 mixture of diastereomers (Scheme 15). The configuration at the iodomethyl bearing stereocentre was tentatively assigned on the basis of ^{1}H NMR NOESY experiments.[30]

Having successfully differentiated the two terminal alkenes in **75** we aimed to eliminate HI from the iodides **76** to give an enol ether which on ozonolysis would deliver a lactone aldehyde in readiness for introduction of the enyne side chain. We conducted a number of exploratory experiments to test the validity of this approach. On a small scale, exposure of the major diastereomer of the iodides **76a** to DBU in toluene at reflux gave the unstable enol ether **77** which readily hydrolysed to the keto alcohol **78** on silica gel (Scheme 16). Disappointingly, the elimination reaction to form the enol ether was somewhat capricious. Furthermore, although ozonolysis of the enol ether **77** did generate the lactone aldehyde **79** (ν_{max} 1775, 1723 cm^{-1}), the reaction was not clean even under a number of reaction conditions. We were able to conduct a Wittig reaction on <1 mg of the lactone aldehyde **79** which did give rise to material with a ^{1}H NMR in accord with the desired enyne **80**; however, given the capricious nature of both the formation of the enol ether **77** from the iodide **76a** and its subsequent ozonolysis, this route was not going to be able to supply sufficient quantities of material for completion of the synthesis. Having demonstrated that the Wittig reaction on the lactone aldehyde **79** was indeed possible, we proposed to synthesise this intermediate from the chloride **75** by ozonolysis of the terminal olefins followed by oxidation of the intermediate lactol to the corresponding γ-lactone **79**. We were disappointed to discover that ozonolysis of the chloride **75** under a range of conditions destroyed the substrate and gave unidentifiable material. The use of potassium osmate and sodium periodate were equally ineffective.[71] We suspected that the axial alcohol in **75** might be interfering with the cleavage of the olefins. Indeed exposure of the alcohol **75** to triethylsilyl triflate gave the corresponding silyl ether **81** which on ozonolysis under standard conditions gave the dialdehyde **82** in excellent yield after reductive workup with triphenylphosphine (Scheme 17).



Scheme 17 Completion of the synthesis of **4**. *Reagents and conditions:* (a) Et_3SiOTf, Et_3N, CH_2Cl_2, 99%, (b) O_3/O_2, CH_2Cl_2, −78 °C, then Ph_3P, −78 °C, 0.5 h, then RT, 8 h, 99%; (c) $Ph_3P^+CH_2C{\equiv}C\text{-}SiMe_3$ Br^-, *n*BuLi, THF, add **82**, −78 → 0 °C, 45%, (15% recovered **82**); (d) $NaBH_4$, MeOH, 100%; (e) I_2, PPh_3, imidazole, Et_2O, MeCN, RT, 72%; (f) Zn, AcOH, MeOH, Et_2O, RT, then HCl, 96%; (g) nBu_4NF, THF, RT, 92%.

We were delighted to find that addition of one equivalent of the ylide derived from (3-trimethylsilyl-2-propynyl)-triphenylphosphonium bromide to a cold solution of the dialdehyde **82** delivered the desired enyne **83** with high *E*-selectivity (*E*/*Z* > 7 : 1). A small quantity of the bis-enyne was also formed in the reaction and 25% of the dialdehyde **82** was recovered; however,



Scheme 16 Exploratory transformations of the iodide **76a**. *Reagents and conditions:* (a) DBU, toluene, reflux; (b) SiO_2; (c) O_3/O_2, CH_2Cl_2, −78 °C, then PPh_3, −78 °C → RT; (d) $Ph_3P^+CH_2C{\equiv}C\text{-}SiMe_3$ Br^-, *n*BuLi, THF, add **79**, −78 → 0 °C.

we were unable to find any of the mono-enyne corresponding to reaction of the aldehyde proximal to the silyl protecting group. The origin of the regioselectivity of this Wittig reaction may be steric in nature due to the larger volume of an OTES group compared with a chlorine atom. Reduction of the remaining aldehyde in **83** gave the alcohol **84**. The alcohol was converted into the corresponding iodide **85** which on treatment with zinc dust and a small quantity of acetic acid,[92] followed by the addition of aqueous hydrochloric acid gave the ethyl-substituted pyrano[3,2-*b*]pyran **86** in excellent yield. The acetylene protecting group was removed with TBAF to complete the synthesis of the originally proposed structure (**4**) of the enyne from *L. majuscula.*

The ^{1}H and ^{13}C NMR chemical shifts and $^{3}J_{H,H}$ coupling constants of the enyne **4** were compared with this reported for the chloroenyne from *L. majuscula*, and many discrepancies were observed. In particular, in the ^{1}H NMR of the *L. majuscula enyne*, the resonances corresponding to H-6, H-8a, H-4a and H-12 were all at $>\delta = 4$ ppm whereas the corresponding protons in the synthetic material were all well below $<\delta = 4$ ppm. For the synthetic material, the central oxygen-bearing carbons resonated at $\delta = 70.5$ and 73.9 ppm whereas for the natural product these carbons resonated at $\delta = 79.2$ and 77.9. It was clear that the spectroscopic data for the natural material did not match that of the synthetic pyrano[3,2-*b*]pyran confirming that the structure of the natural product had been originally misassigned.

Conclusions

In this study we explored a number of routes for the preparation of the bis-*exo*-cyclic enol ether **6** *en route* to the synthesis of the originally proposed structures of elatenyne **3** and the chloroenyne from *L. majuscula* **4**. This resulted in the preparation of a large number of *cis*-fused pyrano[3,2-*b*]pyrans and 2,2′-bifuranyls. Although we ultimately did not synthesise the desired *exo*-cyclic enol ether **6** the large number of pyrano[3,2-*b*]pyrans and 2,2′-bifuranyls we had made led to us uncovering a ^{13}C NMR chemical shift/structure correlation and to postulate that the originally proposed structure for elatenyne and the chloroenyne from *L. majuscula* were incorrect. This proposal was confirmed by the two-directional total synthesis of both of these halogenated pyrano[3,2-*b*]pyrans. On the basis of our chemical shift model and reanalysis of all of the spectroscopic data of both natural products, we have proposed that the gross structures of the natural products is based upon a central 2,2′-bifuranyl core (the 2,2′-bifuranyls **50** and **51**). Reisolation of the natural products would allow further spectroscopic analysis to aid full structure determination. In the meantime, work is underway to predict the structures of elatenyne and the chloroenyne from *L. majuscula* on the basis of DFT calculations of ^{13}C NMR chemical shifts[93] and using a rational biosynthetic pathway,[3,94] and to confirm the stereochemistry of the natural products by stereoselective total synthesis.

Experimental

See ESI.‡

Acknowledgements

We thank Prof. James Reiss (La Trobe University) and Prof. Gabriele König (Universität Bonn) for supplying spectral data for elatenyne and the enyne isolated from *L. majuscula* respectively; Dr David Fox for helpful discussions; GlaxoSmithKline (CASE award to HMS), the Royal Society (University Research Fellowships to JWB and SIP) and the EPSRC for funding. AstraZeneca UK are gratefully acknowledged for some unrestricted funds.

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