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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 chloroene from Laurencia majuscula is described along with a reassessment of the structures of the halogenated enynes based upon a 13C 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. In particular through hetero-atom connectivity can still be a challenge to solve by NMR methods. For example, the two natural products (Z)-dactomelyne (Z)-1 and notoryne 21 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 C15 metabolites isolated from red algae and those marine organisms which feed on Laurencia species. In 1986 the 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 1H and 13C NMR spectroscopic analysis. More recently the structure of a halogenated C15 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 with comparison with the structure 3 reported for elatenyne and with (E)-dactomelyne (E)-1.8

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 C2-symmetry.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’ve-bifuranyl10,11. 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 chloroene from L. majuscula were incorrect. During these synthetic studies we uncovered a 13C NMR chemical shift correlation which allows cis-fused pyrano[3,2-b]pyrans and 2,2’ve-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 chloroene 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 C2-symmetric tetroil (Fig. 1). Having had previous experience with the intramolecular hydrolysisation of exo-cyclic enol ethers,12,13 we postulated that the tetroil 5 would be available by intramolecular hydrolysisation of the appropriately functionalised bis-exo-cyclic enol ether derived...
from 6, an unstudied reaction with six-membered exo-cyclic enol ethers. Alternatively the known hydroboration of α-oxygenated exo-cyclic enol ethers could also be used to convert 6 into the desired tetrolic. 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). We therefore aimed to synthesise the bis-δ-lactone 8 by oxidation of the corresponding bis-methyl acetal 9. 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 acetone 12.

Results and discussion

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

Given the imbedded C2-symmetry within the halogenated pyranol[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 acetone 12 was readily converted into the known bis-lactone 13 (δmax 1771 cm⁻¹) by an efficient 4 step procedure (Scheme 1). Following the method of Rychnovsky, 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 pyranol[3,2-b]pyran 9 along with the 2,2'-bifuranyls 15. The pyranol[3,2-b]pyran 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). The five isomeric acetals could be separated by careful chromatography. The structures of the pyranol[3,2-b]pyrans 9 were tentatively assigned as follows. Due to reduced torsional strain it was expected that the pyranol[3,2-b]pyran 9 would be thermodynamically more stable than the 2,2'-bifuranyls 15 and hence the major products in the equilibrium mixture should be the pyranol[3,2-b]pyran 9. Furthermore, the pyranol[3,2-b]pyran 9 were readily oxidised to the bis-δ-lactone 8 (vide infra) which was spectroscopically distinct from the known bis-γ-lactone 13.

Having established a procedure for formation of the cis-fused pyranol[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, exposure of a mixture of the acetals 9 to mCPBA and BF₃·OEt₂ followed by aqueous workup gave the bis-peroxyester 16 which on treatment with a solid supported guanidine base 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 (δmax 1740 cm⁻¹) and was significantly different from the IR spectrum of the bis-γ-lactone 13 (δmax 1771 cm⁻¹) thus confirming its structure. Disappointingly, it proved impossible to covert the bis-δ-lactone 8

\[ \text{Scheme 1 Formation of the acetals 9 and 15. Reagents and conditions:} \text{(a) DIBAL, toluene, } -78 \, ^\circ \text{C, then (carbethoxymethylene)}\text{(triphenylphosphorane, MeOH, } -78 \, ^\circ \text{C } \rightarrow \text{ RT, 83%; (b) H}_2, \text{Pd/C, EtOH, 91%; (c) TFA, water, 100%; (d) DIBAL, CH}_3Cl, \text{ } -78 \rightarrow -20 \, ^\circ \text{C, 83%; (e) MeOH, HCl, 90%.} \]
Having been unable to oxidise the enolate derived from the bis-methanol from the methoxy acetals ether would be formed by the elimination of two equivalents of endo of quantitative yield (Scheme 3).

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

Having been unable to oxidise the enolate derived from the bis-δ-lactone 9 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 anomic peracid ester 17 which, in turn, would be available by opening of the bis-epoxide 18 with mCPBA (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) and which was used in the subsequent reactions without further purification. The structure of the bis-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 anomic acetates 14 was considerably lower than from the acetals 9 or 15. We postulate that the novel rearrangement of the 2,2′-bifuranyl acetics 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 1H NMR in d6-MeCN. 1H NMR analysis of a solution of the pyrano[3,2-b]pyran 9a in d6-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 1H NMR analysis. Exposure of one of the C2-symmetric 2,2′-bifuranyl acetics 15 to iodotrimethylsilane followed by 1H 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). 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 anomic acetates 13 to the same reaction conditions followed by 1H NMR gave the 2,2′-bifuranyl anomic iodides 29 which slowly converted into the corresponding pyrano[3,2-b]pyran.
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. 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 mCPBA. In practice, this strategy was not effective. However, epoxidation of the bis-enol ether 19 with mCPBA in CH2Cl2 and methanol30 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 conditions37 failed to deliver any of the desired bis-δ-lactone. Similarly attempted oxidation of the anomeric acetates 33 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. Disappointingly, attempted formation of the α-hydroxy anionic peroxyesters 17 by opening of the bis-epoxide 18 with mCPBA was not successful. We attempted to convert the epoxide into the desired bis-δ-lactone 7 from the corresponding anomeric sulfides by Pummerer rearrangement35 which was also unsuccessful (see ESI for substrate preparation†). We also attempted to open the bis-epoxide 18 with iodomethyllithium36 or dimethylsulfonylmethylid 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 tBuLi 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 acid39–41 gave the desired anomeric bis-sulfone 37a in poor yield.

![Scheme 4](image-url)

Scheme 4  Elaboration of the enol ether 19. Reagents and conditions: (a) mCPBA, MeOH, CH2Cl2, 74%; (b) NaH, BnBr, DMF, 39–54%; (c) PhI(OAc)2, BF3·OEt2, CH2Cl2 then Et3N, 33 15%, 34 19%; (d) DMDO, acetone, NaHCO3, 98%.
Scheme 5 Synthesis of anomeric sulfones. Reagents and conditions: (a) PhSO2H, 4 Å molecular sieves, CH2Cl2, 4–10%; (b) PhSO2H, CaCl2, CH2Cl2, 38 27%, 39 10%; (c) PhSH, BF3 · OEt2, CH2Cl2, 87%; (d) mCPBA, NaHCO3, EtOAc, 100%.

(Scheme 5). Attempted preparation of the bis-sulfones 37 from the corresponding bis-methyl acetals 9 using benzenesulfinic acid and calcium chloride 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. 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 D2O 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).
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

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 42. Exposure to a wide range of reagents and conditions [Al(OiPr)3 in toluene;43 Al2O3,44 TMSBr/DBU;45,46 LDA,47 Li/H2NCH2CH2NH2;48 MeMgNCY3Pr;49 PhSeH, oxidative workup;50 KOiBu] 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 pyran[3,2-¢]-pyrans 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 pyran[3,2-b]pyrans. Careful analysis of all of these compounds revealed that the 13C NMR chemical shifts of the central oxygen-bearing carbons fell into two distinct groups: for the pyran[3,2-b]pyrans, the 13C NMR chemical shifts of the central oxygen-bearing carbons C-8a and C-4a resonate at less than δ = 76 ppm, whereas the corresponding carbon atoms in the 2,2¢-bifuranyls (C-2 and C-2¢) resonate at greater than δ = 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 pyran[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 pyran[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 pyran[3,2-b]pyran skeleton 4710 and the related tetraoxadecaline 48 (TOD) system14 which has also been extensively studied by Fuchs.12–16 cis-Fused pyran[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 Jax,ax = Jax,ax are characteristically large in the O-distal conformer with the corresponding coupling constants being small in the O-proximal conformer (Jax,ax = Jax,ax); in the analysis of equilibrating mixtures of conformers in solution, reference values

![Fig. 6](https://www.org-biomol-chem.org/7/238-252/article-pdf/243/243/32009.pdf)
of 1.2 Hz (O-proximal) and 10.6 Hz (O-distal) have been used for these coupling constants in TODs. In the unfunctionalised pyrano[3,2-b]pyran 47, H-4a and H-8a appear in the 1H NMR spectrum as a narrow triplet (J 2.9 Hz) due to small axial–axial and axial–equatorial couplings to H-4ax and H-4eq, a feature that was characteristic of the pyrano[3,2-b]pyrans synthesised in this work. Furthermore, in TODs which exist in the O-proximal conformation 48-O-prox, J4a,8a is ~1.6 Hz but in the O-distal conformation, J4a,8a is ~6 Hz. The 13C shift of C-4a and C-8a in a wide range of TODs has been reported to fall in the range 69–70 ppm.

The characteristic 1H NMR coupling constants (small J4a,8a, J3,4ax, and J6,7a, and large J2,3ax) along with 13C 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); J4a,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 13C NMR C-4a and C-8a resonated at (interchangeably) δ = 67.4 and δ = 62.1 ppm which also suggested a pyrano[3,2-b]pyran structure. The X-ray crystal structure of the sulfone 38 showed two molecules in the unit cell (50% probability ellipsoids) 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 13C NMR chemical shift of C-2 and C-2′ being >δ = 76 ppm. The 2,2′-bifuranyls showed a larger 1H–1H 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 1H NMR spectrum. Additionally, the H-2/H-2′ multiplets were typically more complex and wider than the corresponding multiplets in the pyrano[3,2-b]pyrans. For example, in the 13C NMR of the sulfone 39a C-2 and C-2′ resonated at δ = 85.7 and δ = 84.6 ppm whereas in the 1H NMR spectrum, the corresponding protons had large couplings between them and to their vicinal neighbours (J2,2′ 7.0 Hz, J2,3 7.0 Hz, J2,9 9.1 Hz).

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

The 13C NMR chemical shifts of the central oxygen-bearing carbons in elatényne4 and the chloroenyne from L. majuscula6 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 13C 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 1H NMR coupling constants of both the L. majuscula enyne and elatényne and closely related derivatives, with that of (E)- and (Z)-dactomelyne led further weight to this proposal (Fig. 10). In particular, comparison of the 1H NMR coupling constants of the axial chlorine-containing pyran ring in (E)-dactomelyne with the corresponding protons in both elatenyne and the L. majuscula
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 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 EI and FI 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 3 and the chloroenyne from L. majuscula 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.

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 these 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
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-anhydro sugars with organometallic reagents is well preceded\textsuperscript{44-48} and treatment of the epoxide 18 with allylmagnesium chloride or bromide gave the desired pyran[3,2-b]pyran 53\textsubscript{a} in moderate yields along with the inseparable diastereomer 53\textsubscript{b} (Scheme 8).\textsuperscript{49} 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.\textsuperscript{50}

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.\textsuperscript{51}

The diols 53 were persilylated and the terminal alkenes cleaved by ozonolysis of the mixture of silyl ethers 56 with a reductive workup (PPh\textsubscript{3} and NaBH\textsubscript{4}) to give the separable diols 57 in excellent overall yield (Scheme 9).\textsuperscript{49} Use of other methods of double bond cleavage (RuCl\textsubscript{3}/NaIO\textsubscript{4}\textsuperscript{70} or OsO\textsubscript{4}/NaIO\textsubscript{4}\textsuperscript{71}) was far less satisfactory.

Having developed an efficient synthesis of the C\textsubscript{2}-symmetric diol 57\textsubscript{a} 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.\textsuperscript{72} Exposure of the diol 57\textsubscript{a} to benzaldehyde dimethylacetal with PPTS as the acid catalyst, delivered the desired benzylidene acetal 58 in low yield (Scheme 10).\textsuperscript{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 57\textsubscript{a} was not pursued further.

Our next approach to desymmetrising the diol 57\textsubscript{a} involved monotosylation or monoiiodination 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 monoiiodination of the diol 57\textsubscript{a} could be achieved in yields above 30\%. Furthermore, we could only oxidise the diol 57\textsubscript{a} to the monoaldehyde in sub-statistical yield and further functionalisation of the monoaldehyde was low yielding (see ESI\textsuperscript{1}). 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\textsubscript{2}-symmetric intermediates and this procedure proved effective in our system.\textsuperscript{74} Thus, treatment of diol 57\textsubscript{a} 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 57\textsubscript{a} (Scheme 11). Selective deprotection of the two triethylsilyl groups in 60 by treatment with K\textsubscript{2}CO\textsubscript{3} in methanol gave quantitative recovery of the diol 57\textsubscript{a}, which was combined with the diol recovered from the initial
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\textsuperscript{75,76} to give the ethyl-substituted pyrano[3,2-\textit{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.\textsuperscript{77} The (\textit{Z})-enyne was introduced in a highly selective manner using a Yamamoto–Peterson reaction.\textsuperscript{78,79} Thus, addition of the allenyltitanium reagent derived from 3-(\textit{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 (\textit{Z})-enyne 65 in good yield and selectivity (\textgreater\textit{10} : \textit{1} (\textit{Z}) : (\textit{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-\textit{b}]pyran 66 was expected to prove challenging and we first investigated this transformation on the allyl-substituted pyrano[3,2-\textit{b}]pyrans 53.\textsuperscript{80} \textit{Sn}2 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 \textit{Sn}2 reaction is at a carbon atom bearing a \textit{\beta}-oxygen substituent, a situation which is known to yield slow rates of \textit{Sn}2 reactions.\textsuperscript{81} Kozikowski’s synthesis of the dactomelynes stalled at the introduction of the corresponding chlorine substituent\textsuperscript{8} and Murai has implied that the halogen substituents in molecules such as the dactylene are best introduced prior to ring-formation.\textsuperscript{82}

\textbf{Scheme 11} Synthesis of the pyrano[3,2-\textit{b}]pyran 66. \textit{Reagents and conditions:} (a) TESCl, Et3N, CH2Cl2, 61 48%, 57a 35%, 60 17%; (b) K2CO3, MeOH, 100%; (c) TsCl, Et3N, DMAP, CH2Cl2, 93%; (d) Et3BHLi, Et2O, 91%; (e) K2CO3, MeOH, 98%; (f) TPAP, NMO, 4 Å molecular sieves, CH2Cl2, 95%; (g) Me3SiC\textright\textleft CCH2SiMe3Bu, \textit{t}BuLi, Ti(O\textit{i}Pr)4, THF, \textt{\textminus}78 \degree \text{C}, add 64, \textt{\textminus}78 \degree \text{C} \rightarrow \text{RT}, 0.5 h, then (Me3Si)2NK, 75%; (h) TsOH, MeOH, 22 h, 75%.

A variety of methods (CBr4/P(oct),\textsuperscript{83} PBr3,\textsuperscript{84} the Ghosez reagent,\textsuperscript{85} SOBr2,\textsuperscript{8,86} Mitsunobu reaction with ZnBr2,\textsuperscript{87} triflate with LiBr in HMPA,\textsuperscript{88} imidazolylsulfonate with TBABr in toluene\textsuperscript{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

\textbf{Scheme 12} Synthesis of the dibromide 68. \textit{Reagents and conditions:} (a) Ti\textt{\textit{t}}O, pyridine, CH3Cl; (b) \textit{n}Bu3NBr, toluene, reflux 2 h, 17% from 53.
to those observed in the model brominated compound desired stereochemistry. The 1H NMR coupling constant between configuration had occurred to give a pyrano[3,2-

In particular, the 1H NMR chemical shifts for H-6 and H-7, and 13C NMR chemical shifts and 3b coupling constants were compared with those reported for elatenyne and many discrepancies were noted. In particular, the 1H 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 13C NMR chemical shifts of up to 8 ppm. Thus, we have confirmed that 3 is not the structure of natural elatenyne.

Scheme 13 Synthesis of the dibromide 3. Reagents and conditions: (a) Tf2O, pyridine, CH2Cl2; (b) nBu4NBr, toluene, reflux 2 h, 14% from 66; (c) TBAF, THF, 100%.

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 to give the mono-protected alcohol 72 in 64% yield after one recycling sequence (Scheme 14). 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. The remaining secondary hydroxy group in 73 was inverted by an oxidation/reduction sequence to give the alcohol 75 as a single diastereomer; the stereochemistry of 75 was confirmed by X-ray crystal structure analysis.

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, Et3N, CH2Cl2, 72 42%, 71 38%, 53a 20%; (b) Tf2O, pyridine, CH2Cl2; (c) nBu4NCl, toluene, reflux, 2 h, then Amberlite™ resin IR-120, MeOH, 43% from 72; (d) nPrNRuO4, NMO, CH2Cl2, 4 Å molecular sieves, 65%; (e) NaBH4, MeOH, 87%.

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 13C 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 1H NMR coupling constant 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 1H 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 13C 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 1H NMR and 13C NMR chemical shifts and 1H coupling constants were compared with those reported for elatenyne and many discrepancies were noted. In particular, the 1H 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 13C NMR chemical shifts of up to 8 ppm. Thus, we have confirmed that 3 is not the structure of natural elatenyne.

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
corresponding tricyclic iodoethers 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 1H NMR NOESY experiments.\textsuperscript{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 ($\nu_{\text{max}}$ 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 1H 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 y-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.\textsuperscript{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).

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-enzyme was also formed in the reaction and 25% of the dialdehyde 82 was recovered; however,
we were unable to find any of the mono-enzyme 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,42 followed by the addition of aqueous hydrochloric acid gave the ethyl-substituted pyran[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 1H and 13C NMR chemical shifts and 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 1H NMR of the *L. majuscula* enyne, the resonances corresponding to H-6, H-8a, H-4a and H-12 were all at >δ = 4 ppm whereas the corresponding protons in the synthetic material were all well below <δ = 4 ppm. For the synthetic material, the central oxygen-bearing carbons resonated at δ = 70.5 and 73.9 ppm whereas for the natural product these carbons resonated at δ = 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 missassigned.

**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 elatyne 3 and the chloroenyne from *L. majuscula* 4. This resulted in the preparation of a large number of cis-fused pyran[3,2-b]pyrans and 2,2′-bifuranlyls. Although we ultimately did not synthesise the desired exo-cyclic enol ether 6 the large number of pyran[3,2-b]pyrans and 2,2′-bifuranlyls we had made led us to uncovering a 13C NMR chemical shift/structure correlation and to postulate that the originally proposed structure for elatyne and the chloroenyne from *L. majuscula* were incorrect. This proposal was confirmed by the two-directional total synthesis of both of these halogenated pyran[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′-bifuranylic core (the 2,2′-bifuranlyls 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 elatyne and the chloroenyne from *L. majuscula* on the basis of DFT calculations of 13C NMR chemical shifts49 and using a rational biosynthetic pathway,119 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 elatyne 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 JW and SIP) and the EPSRC for funding. AstraZeneca UK are gratefully acknowledged for some unrestricted funds.

**Notes and references**


10 It should be noted that at the time of the isolation of elatyne, no C55, halogenated 2,2′-bifuranyl natural products had been reported. A 2,2′-bifuranyl structure for elatyne was considered less likely than the corresponding pyran[3,2-b]pyran: J. G. Hall, Ph. D. Thesis, La Trobe University (Australia), 1984.


14 In model studies related to this project we have demonstrated that the intramolecular hydrosilation of glucose and galactose-derived exo-cyclic enol ethers gives rise to the corresponding 1,3-diols.


The equilibrium position was readily determined by 1H NMR by allowing various mixtures of 15 and 9 to equilibrate in d6-methanol to which 10 mol% acetyl chloride had been added. Beginning either with a mixture of the 2,2′-bifuranyl 15 or a 1:1 mixture of 15:9 gave the equilibrium ratios after 10 hours at room temperature which did not change after one week. In a separate experiment, a mixture of the pyran[3,2-b]pyrans 9 also readily equilibrated to the same mixture of 15:9 on standing in acidic methanol. The pyranol[3,2-b]pyran 9 exist as a 1:1 mixture of diastereomers at equilibrium which is in keeping with the magnitude of the anomic effect for 2-methoxetylthiophryran in methanol see: R. U. Limieux, A. A. Pavia, J. C. Martin and K. A. Watanabe, Can. J. Chem., 1969, 47, 4427.


For full structure determination see ESI.

The validity of this assumption was confirmed by simulating the 1H NMR spectra of a number of the C7-symmetric pyran[3,2-b]pyrans synthesised in this work implies that they exist predominantly in the O-proximal conformation and hence Jαβ is small. Because Jαβ is small the 1H NMR spectra of these pyran[3,2-b]pyrans is pseudo-first order and meaningful coupling constants can be extracted. The validity of this assumption was confirmed by simulating the 1H NMR spectra of a number of the C7-symmetric pyran[3,2-b]pyrans reported in this work (see ESI).

Crystal structure determination: crystallographic data of sulfone 38 was collected on the synchrotron radiation source at Station 9.8, Daresbury SRS, UK, on a Bruker SMART CCD diffractometer. The structures were solved by direct methods using the program SIR92 (ref. 65). The refinement (on F2) and graphical calculations were performed using the CRYSTALS (ref. 66) suite program. Crystal data: C15H20O5S, 3 symbols, monoclinic, space group P21/a, a = 5.5615(17) Å, b = 27.699(8) Å, c = 10.094(3) Å, β = 105.644(6)°, V = 1497.48(8) Å3, T = 293 K, μ = 0.235 mm−1. Of 10048 reflections measured, 6771 were independent (Rint = 0.02). Final R = 0.0464 (4429 reflections with I > 3σ(I)) and wR = 0.0493. Crystallographic data (excluding structure factors) for this structure have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 69760. Copies of the data can be obtained free of charge on application to the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK. [Fax: (internat.) + 44-1223/363-033; E-mail: deposit@ccdc.cam.ac.uk].

We attempted to convert the asymmetric diol 53b into the symmetric diol 53a by an oxidation, epimerisation, reduction sequence. Treatment of the mixture of diols 53 with Jones’ reagent gave the corresponding separable diketones. Disappointingly, attempted epimerisation of the resulting diketones under basic conditions resulted in decomposition (see ESI).

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80 The model bromination studies were conducted on the inseparable 5 : 1 mixture of diastereomers 60a : 60b.
81 A. Streitwieser, Chem. Rev., 1956, 56, 571.
84 N. Petragnani, H. M. C. Ferraz and M. Yonashiro, Synthesis, 1985, 27.
90 For a side by side comparison of the 'H NMR and 13C NMR chemical shifts for the natural and synthetic material see the ESI.
91 Compounds 71 and 72 were formed as mixtures (and yields are for the mixture) along with their corresponding diastereomers arising from silylation of the diol 53b. The minor diastereomer was removed after chlorination to give 73.
92 The reported conditions were particularly effective: Z. H. Peng and K. A. Woerpel, J. Am. Chem. Soc., 2003, 125, 6018.