Synthetic study of marine lobane diterpenes. Enantioselective syntheses of lobatrienolide and lobatrientriol from (+)-nopinone

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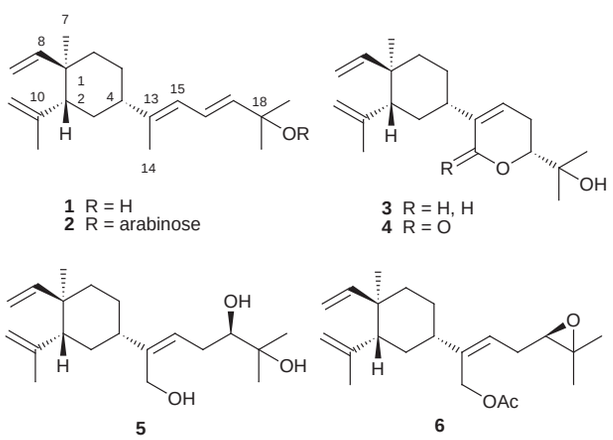
The first enantioselective syntheses of highly oxygenated lobane diterpenes, (+)-lobatrienolide **4** and (+)-lobatrientriol **5**, have been achieved, starting with (4*R*,5*R*)-1-acetoxy-4-isopropenyl-5-methyl-5-vinylcyclohex-1-ene **10b** which itself has been prepared from (+)-nopinone **7** as a versatile building block toward the asymmetric synthesis of natural products.

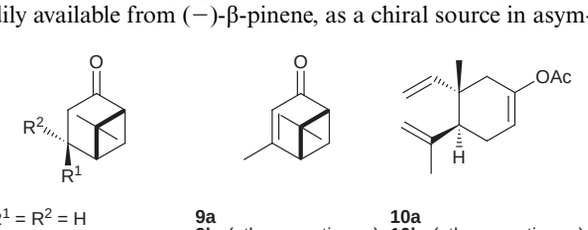
Introduction

Marine lobane natural products are the first diterpenes possessing a unique prenylated elemane carbon skeleton.[1,2] Fuscol **1**,



isolated from the Gorgonian *Eunicea fusca* by Schmitz *et al.*,[3] is representative, and its arabinose glycoside, fuscoside B **2**, isolated from *E. fusca* by Fenical *et al.*, is known as a promising lead compound for new antiinflammatory agents, and as a selective inhibitor of leukotriene synthesis.[4] Enantioselective total synthesis of **1** has been accomplished by Yamada *et al.*[5] and recently by our group.[6] More highly oxygenated congeners, lobatriene **3**,[2,7] lobatrienolide **4**,[8] lobatrientriol **5**[8] and acetoxylobaoxide **6**[8] were recently isolated from the Okinawan soft coral *Sinularia flexibilis* by Kusumi and Kakisawa *et al.*, and their structural elucidations were carried out mainly by use of ^{1}H NMR studies.[8] The absolute configuration of **3** and **4** were elucidated by use of the modified Mosher method for the former, and chemical correlations with **3** for the latter.[8] Synthetic studies of these natural products have not been reported yet.

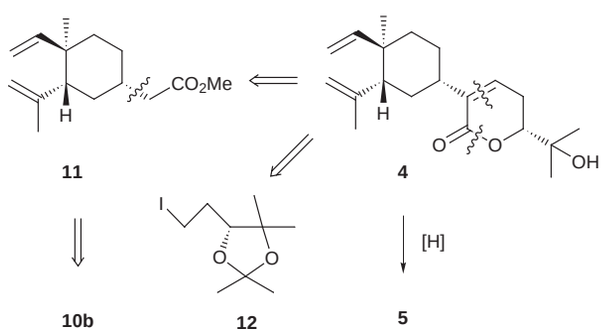
We have been studying the utility of (1*S*,5*S*)-(+)-nopinone **7**, readily available from (−)-β-pinene, as a chiral source in asymmetric synthesis, and reported the effective transformation of **7** into (1*R*,4*S*,5*S*)-(+)-4,7,7-trimethyl-4-vinylnopinone **8** *via* (1*R*,5*R*)-(+)-verbenone **9a**, followed by BF_3-promoted cyclobutane opening[9] to give (4*S*,5*S*)-(−)-1-acetoxy-4-isopropenyl-5-methyl-5-vinylcyclohex-1-ene **10a**.[10,11] Furthermore, we have developed a general transformation of **7** into (1*S*,5*S*)-(−)-verbenone **9b**.[11] This made it possible to prepare (4*R*,5*R*)-(+)-**10b** from **7** as the common starting material. Both enol acetates **10a**,**b** are obtainable in more than 40% overall yield from **7** and its enantiomer, respectively.



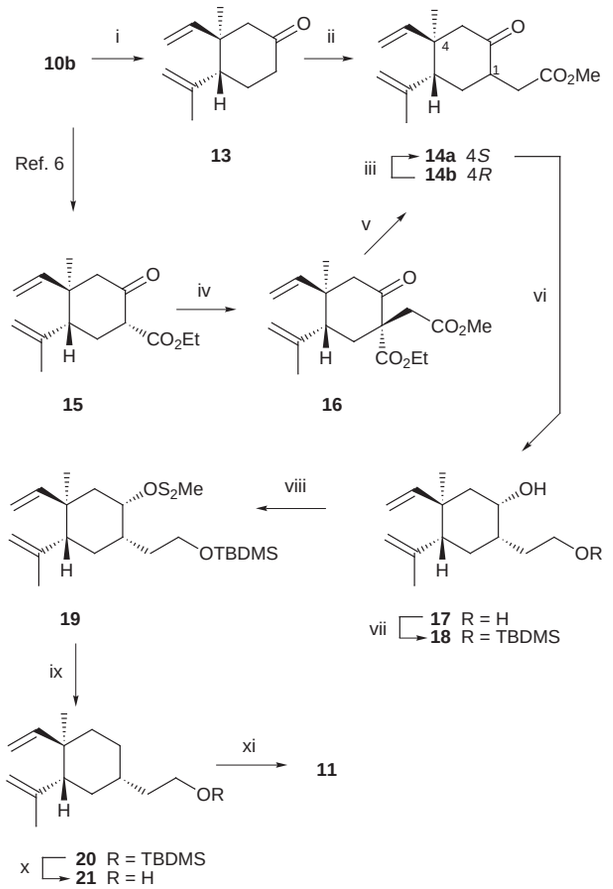
The enol acetates **10a**,**b** could serve as promising chiral templates for the asymmetric synthesis of elemane sesqui- and lobane diterpenoids, since these natural products possess, as their major framework, the same carbon skeleton as that of **10a**,**b**. In fact, the usefulness of **10a** has been demonstrated by the synthesis of (+)-eleman-8β,12-olide,[10] and that of **10b** was recently demonstrated by the efficient synthesis of (+)-fuscol **1** (*vide ante*).[6] As part of a synthetic study on lobane diterpenes, the present paper describes the effective application of **10b** in the synthesis of lobatrienolide **4** and lobatrientriol **5**.

Results and discussion

We chose lobatrienolide **4** as the first synthetic target among the two mentioned above, since lobatrientriol **5** could be derived by reduction of **4**. Lobatrienolide **4** is regarded as 2-substituted pent-2-en-5-olide possessing a (1,1-dimethylmethanol) function at the C(5) position, so this view led us to consider an enantioselective synthesis of **4** by the combination of two fragments, ester **11** which could be obtained from **10b** and the known (5*R*)-5-(2′-iodoethyl)-2,2,4,4-tetramethyl-1,3-dioxolane **12**,[12] as shown in the retrosynthetic disconnections in Scheme 1.

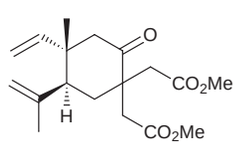


Scheme 1



Scheme 2 *Reagents and conditions*: i, K_2CO_3, MeOH (98%); ii, LDA, $BrCH_2CO_2Me$, THF, HMPA, −78 to −40 °C; iii, K_2CO_3, MeOH, room temp. (60% from **13**); iv, NaH, $BrCH_2CO_2Me$, THF, HMPA, 0 °C to room temp. (95%); v, (1) NaOH, DMSO, H_2O then aqueous HCl, (2) CH_2N_2, ether (81% from **15**); vi, $LiAlH_4$, THF (81%); vii, TBDMSCl, imidazole, DMF (87%); viii, BuLi, CS_2, MeI, THF (quant.); ix, Bu_3SnH, AIBN, toluene, 90 °C (quant.); x, Bu_4NF, THF (90%); xi, (1) Jones reagent, acetone, (2) CH_2Cl_2, ether (73%).

To prepare compound **11**, our synthesis started with the chemical transformation of **10b** into keto ester **14a** (Scheme 2). In the synthesis of (+)-β-elemenone,[10] we have prepared the enantiomer of **14a** by treatment of **10a** with MeLi (2 equiv.) in THF followed by addition of methyl bromoacetate. However, the reproducibility of this reaction was poor, and the dialkylation product **22** was invariably produced as a by-product,



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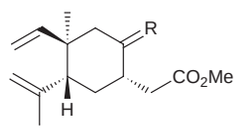
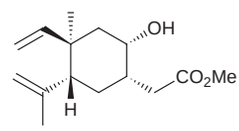
probably because of the action of the concomitantly produced lithium *tert*-butoxide. In the present synthesis, compound **10b** was first converted into ketone **13** by hydrolysis. Treatment of **13** with LDA in THF and HMPA followed by addition of methyl bromoacetate provided a mixture (*ca.* 1 : 9 ratio) of keto esters **14a** and **b** in 60% yield with no formation of **22**. From ^{1}H NMR studies, the stereochemistry of the acetate moiety at the C(1) position† in **14a** and **b** were assigned to be axial and equatorial, respectively, on the basis of a multiplet (half band width 21.8 Hz) at δ 2.89 for the former and that (half band width, 14.4 Hz) at δ 3.02 for the latter. Compound **14b** was smoothly isomerised into thermodynamically stable **14a** upon treatment with K_2CO_3 in methanol. On the other hand, the sodium salt of the keto ester **15**, which had been prepared from **10b** in the synthesis of fuscol **1**,[6] was treated with methyl bromoacetate to give diester **16** as the sole product. The stereochemistry of **16** was tentatively assigned as depicted in Scheme 2, from an analysis of the stereoelectronic effects governing the approach of the nucleophile, away from the axially oriented angular methyl group. Hydrolysis of **16** with concomitant decarboxylation followed by esterification of the resulting carboxylic acid with diazomethane afforded **14a** in 61% overall yield.

In order to remove the ketone carbonyl group in **14a**, two kinds of derivatives, thio acetal **23** and tosyl hydrazone **24**, were



23 R = SCH_2CH_2S
24 R = NNH-*p*-Ts



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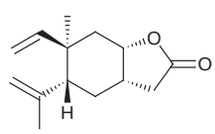

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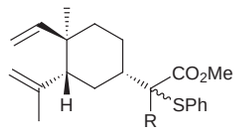
prepared from **14a**. However, attempted desulfurisation of **23** with Raney nickel (W-4) proved to be fruitless, because the reaction provided a mixture of products arising from concomitant reduction of the double bonds, from which the desired ester **11** could not be isolated. In addition, reduction of **24** with sodium cyanoborohydride in the presence of toluene-*p*-sulfonic acid under the standard reaction conditions[13] resulted in recovery of the starting material. Stereoselective reduction of **14a** with lithium tri-*tert*-butoxyaluminium hydride in THF at low temperature provided hydroxy ester **25** in quantitative yield. It is worth mentioning that **25** was unstable and easily lactonised, mostly in the work-up process, to lead to *cis*-fused γ-lactone **26**.

A conventional method frequently employed for removal of a ketone function, *i.e.* chemical transformation into a double bond and subsequent catalytic hydrogenation, is not applicable in our synthesis, so instead **14a** was reduced with excess $LiAlH_4$ to give diol **17**;[14] regioselective protection of the primary hydroxy group provided silyl ether **18**. Chemical transformation of **18** into the alcohol **21** was carried out by a sequence of reactions; (1) preparation of xanthate **19**, (2) reductive removal of the xanthate ester group with formation of **20**, and (3) deprotection to give **21**. Finally, Jones oxidation of **21** followed by esterification of the resulting carboxylic acid with diazomethane provided, in *ca.* 35% overall yield from **10b**, the requisite ester **11** whose ^{1}H NMR, and HPLC analyses proved to be homogeneous.

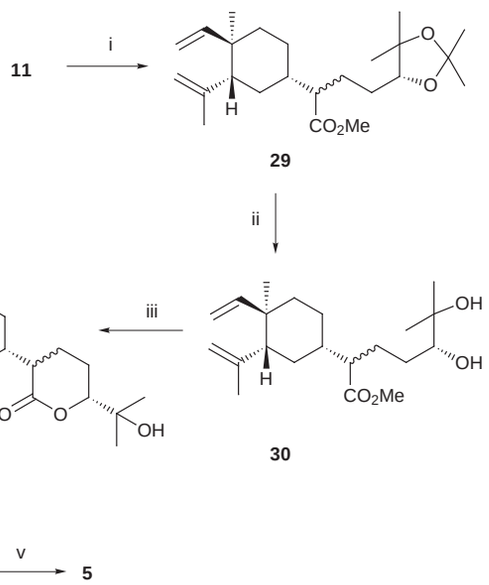
The alkylating agent, (5*R*)-5-(2′-iodoethyl)-2,2,4,4-tetramethyl-1,3-dioxolane **12**, necessary for construction of the oxygenated side-chain at the C(1) position, was prepared from (+)-malic acid (100% ee) according to the procedures reported by Serra *et al.*[12] First, we attempted to use α-phenylthio ester **27**, which is available from **11** by phenylsulfenylation, because not only would **27** be more reactive in the alkylation reaction than **11** itself, but also the phenylthio group would serve as a means for introduction of an enone function into the product. Compound **27** was readily prepared by treatment of the lithium salt of **11** with *S*-phenyl benzenethiosulfonate (LDA, THF, 70%).[15] However, attempted alkylation of **27** with **12** (NaH,

† The numbering system used here and in the Experimental Section follows IUPAC rules, and is different from the natural product numbering used for fuscol **1**.



27 R = H
28 R = Et

THF or DMF,[16] rt) proved to be fruitless, because the reaction was sluggish and a large proportion of **27** was recovered unchanged, although the reaction of **27** with ethyl iodide as a model produced smoothly the ethylated compound **28** (NaH, DMF, rt, 66%).

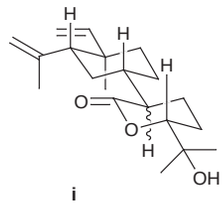


Scheme 3 *Reagents and conditions*: i, **12**, LDA, THF–HMPA (3:1), −78 to 0 °C (98%); ii, PPTS, MeOH (quant.); iii, *p*-TsOH, CH_2Cl_2 (80%); iv, (1) LDA, PhSeCl, THF, HMPA, (2) 30% H_2O_2, THF (44% from **31**); v, (1) DIBALH, toluene, −78 °C, (2) $NaBH_4$, MeOH, 0 °C (80%).

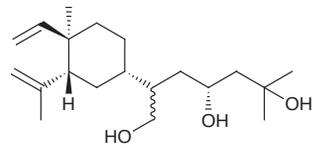
The alkylation reaction of **11** with **12** was examined next in some detail (Scheme 3). We conducted reactions of **11** with LDA in THF (−78→0 °C) followed by addition of **12** in the presence and absence of additives [HMPA and 12-crown-4]. No reactions occurred in THF in the presence or absence of 12-crown-4 (2 equiv.). Many of the reactions in the presence of HMPA (2–10 equiv.) proceeded very slowly and were incomplete after 20 h (0 °C to rt; trace–16% yield of **29**). After considerable experimentation, the reaction conditions using a large excess of HMPA (THF–HMPA, 3:1) resulted in complete alkylation, giving **29** in a shorter reaction time (2 h) and 98% isolated yield.

Deprotection of the acetal function in **29** was effected by heating gently with PPTS in aqueous methanol to give diol **30** in 82% isolated yield, along with a trace amount of a lactone product **31**. Upon treatment of **30** with a catalytic amount of toluene-*p*-sulfonic acid in CH_2Cl_2, dihydrolobatrienolide **31**, the key synthetic intermediate, was successfully produced in 80% isolated yield (65% overall yield from **29**) as a separable mixture of two diastereomers (a 2:1 ratio) with respect to the substituent at the α position of the δ-lactone ring. This was evidenced by the ^{1}H NMR (400 MHz, C_6D_6) analysis; the stereochemistry of both of the hydrogen atoms on the carbon flanking the 1,1-dimethylmethanol group in diastereomers **31** was established to be axial, on the basis of the chemical shifts and coupling constants at δ 3.58 (dd, J 11.0, 3.4) for the major product and at δ 3.65 (dd, J 11.5, 3.2) for the minor one. These findings suggest the stereostructure of diastereomers **31** as depicted in **i**.

Phenylselenenylation of **31** at the 2-position of the lactone



i



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ring provided the selenide as a mixture of diastereomers in 63% yield (73% yield from the consumed **31**). Oxidation of the selenide with 30% H_2O_2 followed by elimination of the selenoxide gave the target lobatrienolide **4** in 70% yield. It is interesting to note that, in the selenoxide elimination, no regioisomer with respect to the newly formed double bond could be detected in spite of a careful inspection of the reaction mixture. The ^{1}H and ^{13}C NMR, IR and mass spectral data of the synthetic **4**, $[\alpha]_D^{26}$ +81.0 (*c* 0.30, $CHCl_3$) {lit., $[\alpha]_D^{25}$ +89.3 (*c* 0.63, $CHCl_3$)[7]}, including the sign of optical rotation, were identical with those of the authentic sample.[7] Since the absolute configuration of lobatrienolide **4** has been assigned in chemical correlation with lobatriene **6** whose absolute configuration was elucidated by use of the modified Mosher method,[8] the present study also supports the absolute stereostructure of **4** by a synthetic means.

Lobatrientriol **5** could be derived from **4** by reduction of the δ-lactone ring. However, reduction of **4** with lithium aluminium hydride produced the desired **5** only in 11% yield, and the major product obtained in 29% yield was surmised to be an over-reduction product **32** by the ^{1}H NMR analysis. Then, a stepwise method; reduction of **4** with DIBALH, followed by reduction of the resulting hemiacetal with $NaBH_4$, was employed, thus giving, in more than 80% overall yield, lobatrientriol **5**, $[\alpha]_D^{26}$ +14.9 (*c* 0.22, $CHCl_3$) {lit., $[\alpha]_D^{25}$ +15.0 (*c* 0.20, $CHCl_3$)[5]}. Spectral data of synthetic **5** were identical with those of natural **5**,[5] indicating the absolute configuration of **5** to be (1*S*,2*R*,4*S*,17*R*).

In summary, as part of the enantioselective synthesis of lobane diterpenes from (+)-nopinone **7**, the first syntheses of (+)-lobatrienolide **4** and (+)-lobatrientriol **5** from the enol acetate **10b** were accomplished in 14 and 17 steps and *ca.* 7 and 6% overall yield, respectively, thus synthetically supporting their absolute configurations which were elucidated by ^{1}H NMR studies and chemical correlations. Since all of the lobane natural products possess commonly an oxygenated eight-carbon side chain at the C(4) position, the present study demonstrates that compound **10b** could serve as a versatile building block for the enantioselective synthesis of lobane natural products.

Experimental

^{1}H NMR spectra were recorded at 400 MHz. *J* Values are given in Hz. $[\alpha]_D$ Values are given in units of 10^{-1} deg cm^2 g^{-1}. All reactions were carried out under dry N_2 or Ar atmosphere. Extracts obtained on aqueous work-up of the reaction mixtures were washed successively with water and brine, and dried over Na_2SO_4. Column chromatography was performed on 70–230 mesh silica gel (Merck). Medium pressure chromatography (MPLC) utilised a 22 i.d. × 300 mm silica gel (10 μm) column. Solvents for elution are shown in parentheses. Ether refers to diethyl ether.

(3*R*,4*R*)-3-Methyl-4-isopropenyl-3-vinylcyclohexanone 13

The compound **13**, $[\alpha]_D$ +30.0 (*c* 0.54, in $CHCl_3$), was prepared from **10b**[6] according to the procedure described for preparation of its enantiomer reported earlier.[10]

Methyl 2-[(1*S*,4*R*,5*R*)-5-isopropenyl-4-methyl-4-vinyl-2-oxocyclohexyl]acetate 14a

Method 1. To a stirred solution of diisopropylamine (0.35 ml,

2.49 mmol) in THF (3 ml) was added dropwise at −78 °C a 1.61 M solution of BuLi in hexane (1.55 ml, 2.48 mmol). After being stirred for 20 min, a solution of **13** (362 mg, 2.04 mmol) in THF (2 ml) was added dropwise and stirring was continued for an additional 30 min. To the reaction mixture was added a solution of methyl bromoacetate (1.09 g, 7.14 mmol) and HMPA (408 mg, 2.48 mmol) in THF (2 ml). The reaction mixture was stirred for 4 h, during which the reaction temperature rose slowly to −40 °C, quenched by addition of aqueous NH_4Cl, and extracted with EtOAc. Removal of the solvent followed by filtration of the residue through a short silica gel column (hexane–EtOAc, 9:1) gave a mixture of **14a** and **b** as an oil. A mixture of the oil and K_2CO_3 (280 mg, 2.0 mmol) in methanol (5 ml) was stirred at room temperature for 20 h, and concentrated. Water was added to the residue, and the product was extracted into EtOAc. Evaporation of the solvent followed by purification of the residue with MPLC (hexane–EtOAc, 9:1) gave the title compound **14a** (306 mg, 60%) as an oil, $[\alpha]_D$ +3.35 (*c* 0.34, in $CHCl_3$). The IR and ^1H NMR spectra of **14a** were identical with those of its enantiomer prepared earlier.[10]

Method 2. To a stirred mixture of NaH (715 mg, 0.85 mmol) in THF (20 ml) was added dropwise at 0 °C a solution of **15** (3.38 g, 13.5 mmol) in THF (20 ml). After being stirred for 30 min, HMPA (2.5 ml, 13.8 mmol) followed by methyl bromoacetate (2.2 ml, 16.7 mmol) was added dropwise, and the reaction mixture was stirred for 4 h, during which the reaction temperature rose slowly to room temperature. The reaction mixture was quenched with aqueous NH_4Cl, and extracted with ether. Concentration of the extract gave an oil which was filtered through a short silica gel column (hexane–ether, 3:1) to give diester **16** (4.13 g, 95%) as an oil (Found: C, 66.69; H, 8.17. $C_{18}H_{26}O_5$ requires C, 67.06; H, 8.13%); ν_{max}(neat)/cm^{-1} 3085, 1747, 1739, 1714, 911, 862; δ_H($CDCl_3$) 1.05 (3H, s), 1.27 (3H, t, *J* 7.0), 1.77 (3H, s), 2.04 (1H, br s), 2.06 (1H, dd, *J* 13.4, 3.2), 2.22 (1H, d, *J* 13.4), 2.43 (1H, dd, *J* 13.4, 3.2), 2.67 (1H, d, *J* 13.4), 2.80 (1H, d, *J* 16.4), 3.09 (1H, d, *J* 16.4), 3.63 (3H, s), 4.23 (2H, q with fine splitting, *J* 7.0), 4.76 and 4.96 (1H, s each), 4.94 (1H, d, *J* 17.8), 5.00 (1H, d, *J* 10.8), 5.84 (1H, dd, *J* 17.8, 10.8).

A mixture of **16** (4.10 g, 12.7 mmol), DMSO (20 ml) and aqueous NaOH (20%, 20 ml) was stirred at 50 °C for 12 h. After cooling at 0 °C, the reaction mixture was acidified by addition of aqueous HCl and saturated with brine. The product was extracted with EtOAc, and the residue obtained by concentration of the extracts was filtered through a short silica gel column (EtOAc). Concentration of the eluate left an oil, which was dissolved in ether (100 ml). The ethereal solution was treated at 0 °C with a diazomethane–ether solution and concentrated. An oily residue was chromatographed on silica gel (hexane–EtOAc, 12:1) to give the title compound **14a** (2.73 g, 81% from **15**).

(1*S*,2*S*,4*R*,5*R*)-2-[2-(*tert*-Butyldimethylsilyloxy)ethyl]-4-isopropenyl-5-methyl-5-vinylcyclohexanol 18

To a stirred mixture of lithium aluminium hydride (507 mg, 13.4 mmol) in THF (25 ml) was added dropwise at −50 °C a solution of **14a** (3.37 g, 13.4 mmol) in THF (20 ml). The reaction mixture was stirred for 2 h, quenched carefully by addition of aqueous NH_4Cl, and filtered. The solid was washed with ether, and the combined filtrates were dried. Evaporation of the solvent left an oil which was chromatographed on silica gel (hexane–AcOEt, 1:1) to give diol **17** (2.46 g, 81%) as an oil, $[\alpha]_D$ +41.6 (*c* 0.03, in $CHCl_3$); ν_{max}(neat)/cm^{-1} 3355, 1446, 1006, 891; δ_H($CDCl_3$) 1.17 (3H, s), 1.24–1.32 (2H, m), 1.60–2.04 (8H, m), 1.72 (3H, s), 3.69 and 3.76 (1H, m each), 4.03 (1H, br s, 1/2H = 8.3‡), 4.62 and 4.82 (1H, s each), 4.90 (1H, d, *J* 17.3), 4.90 (1H, d, *J* 11.0), 5.76 (1H, dd, *J* 17.3, 11.0); *m*/*z* (EI) 206 ($M^+ - H_2O$, 25), 191 (12), 175 (18), 161 (30), 93 (100).

To a solution of **17** (2.41 g, 10.7 mmol) and imidazole (2.19 g, 32.2 mmol) in DMF (20 ml) was added a solution of TBDMSCl (1.68 g, 11.2 mmol) in DMF (10 ml) with stirring. The reaction mixture was stirred for 1 h, quenched by addition of aqueous $NaHCO_3$, and extracted with ether–hexane (1:1). Concentration of the extract followed by purification of the residue with chromatography on silica gel (hexane–AcOEt, 12:1) gave the title compound **18** (3.15 g, 87%) as an oil (Found: C, 70.89; H, 11.48. $C_{20}H_{38}O_2Si$ requires C, 70.94; H, 11.31%); $[\alpha]_D$ +18.3 (*c* 0.35, in $CHCl_3$); ν_{max}(neat)/cm^{-1} 3510, 1250, 1093, 836; δ_H($CDCl_3$) 0.07 (6H, s), 0.90 (9H, s), 1.17 (3H, s), 1.22–1.27 (2H, m), 1.57–1.87 (5H, m), 1.71 (3H, s), 1.99 (1H, m), 2.67 (1H, br s, OH), 3.59 and 3.69 (1H, m each), 4.02 (1H, br s, 1/2H = 8.5‡), 4.62 and 4.81 (1H, s each), 4.87 (1H, d, *J* 17.5), 4.90 (1H, d, *J* 10.5), 5.77 (1H, dd, *J* 17.5, 10.5).

2-[(1*S*,3*R*,4*R*)-(3-Isopropenyl-4-methyl-4-vinylcyclohexyl)]-ethanol 21

To a stirred solution of **18** (4.55 g, 13.4 mmol) in THF (50 ml) at −78 °C was added dropwise a 1.54 M solution of BuLi in hexane (13.0 ml, 20.0 mmol). After being stirred for 30 min, CS_2 (1.6 ml, 26.7 mmol) was added, and after being stirred for an additional 30 min, MeI (1.7 ml, 27.3 mmol) was added dropwise. Stirring was continued for an additional 50 min, the reaction mixture was quenched by addition of aqueous NH_4Cl, and the product was extracted with ether. Removal of the solvent left an oil which was chromatographed on silica gel (hexane–AcOEt, 50:1) to give **19** (5.70 g, quant.), $[\alpha]_D$ −11.5 (*c* 0.60, in $CHCl_3$); ν_{max}(neat)/cm^{-1} 1231, 1216, 1050, 835; δ_H($CDCl_3$) 0.04 (6H, s), 0.89 (9H, s), 1.06 (3H, s), 1.51–1.63 (5H, m), 1.75 (3H, s), 1.79–1.95 (2H, m), 2.03–2.11 (2H, m), 2.59 (3H, s), 3.64 (2H, td, *J* 6.1, 1.2), 4.67 (1H, s), 4.87 (1H, d, *J* 17.3), 4.91 (1H, d, *J* 10.7), 4.93 (1H, s), 5.78 (1H, dd, *J* 17.3, 10.7).

To a stirred solution of **19** (6.15 g, 14.3 mmol) in toluene (40 ml) at 90 °C was added dropwise a solution of AIBN (449 mg, 2.73 mmol) and tributyltin hydride (11.2 ml, 40.2 mmol) in toluene (20 ml), and stirring was continued for an additional 30 min. After being cooled at room temperature, the reaction mixture was added to a silica gel column. Toluene and organic tin compounds were removed by use of hexane as an eluent, then the product was eluted with hexane–AcOEt (50:1), giving **20** (4.50 g, quant.) as an oil, $[\alpha]_D$ +9.30 (*c* 0.60, in $CHCl_3$); ν_{max}(neat)/cm^{-1} 1254, 1100, 835, 775; δ_H($CDCl_3$) 0.05 (6H, s), 0.90 (9H, s), 0.95 (3H, s), 1.02–1.17 (2H, m), 1.70 (3H, s), 1.26–1.61 (7H, m), 1.96 (1H, dd, *J* 12.4, 3.0), 3.68 (2H, t, *J* 7.1), 4.57 (1H, s), 4.85 (1H, s), 4.87 (1H, d, *J* 10.4), 4.90 (1H, d, *J* 17.8), 5.81 (1H, dd, *J* 17.8, 10.4).

To a stirred solution of **20** (4.50 g) in THF (30 ml) was added dropwise a 1.0 M solution of Bu_4NF in THF (16.1 ml, 16.1 mmol), and stirring was continued for an additional 6 h. The reaction mixture was quenched by addition of aqueous $NaHCO_3$, and extracted with ether. Removal of the solvent followed by chromatography of the residue on silica gel gave the title compound **21** (2.52 g, 90% from **19**) as an oil (Found: C, 80.39; H, 11.70. $C_{14}H_{24}O$ requires C, 80.71; H, 11.61%); ν_{max}(neat)/cm^{-1} 3332, 1375, 1045, 890; δ_H($CDCl_3$) 0.98 (3H, s), 1.12–1.65 (10H, m), 1.70 (3H, s), 1.97 (1H, dd, *J* 12.4, 2.4), 3.71 (2H, br s), 4.57 and 4.81 (1H, s each), 4.88 (1H, d, *J* 10.5), 4.89 (1H, d, *J* 17.8), 5.81 (1H, dd, *J* 17.8, 10.5); *m*/*z* (EI) 208 (M^+, 12%), 193 (34), 163 (59), 121 (60), 107 (100).

Methyl 2-[(1*S*,3*R*,4*R*)-3-isopropenyl-4-methyl-4-vinylcyclohexyl]acetate 11

To a stirred solution of **21** (650 mg, 3.12 mmol) in acetone (10 ml) at 0 °C was added Jones reagent dropwise, prepared from CrO_3 (13.4 g), concentrated H_2SO_4 (12 ml) and water (25 ml), until the orange colour of the reagent persisted for a few minutes.

‡ 1/2H Refers to the half band width, with values given in Hz.

The excess reagent was destroyed by addition of a small quantity of isopropyl alcohol. Saturated brine was added to the reaction mixture, and the product was extracted with ether. Removal of the solvent left an oil, which was dissolved in ether (10 ml). To this ethereal solution, an ethereal diazomethane solution was added at 0 °C dropwise, until the yellow colour of diazomethane persisted. Concentration followed by chromatography of the residue on silica gel gave the title compound **11** (539 mg, 73%) as an oil (Found: C, 75.98; H, 10.15. $C_{15}H_{24}O_2$ requires C, 76.23; H, 10.23%); $[a]_D$ +66.7 (*c* 0.54, $CHCl_3$); ν_{max}(neat)/cm^{-1} 1740, 1151, 1045, 891; δ_H($CDCl_3$) 0.98 (3H, s), 1.16–1.62 (6H, m), 1.69 (3H, s), 1.77–1.90 (1H, m), 2.00 (1H, dd, *J* 12.8, 3.3), 2.26 (2H, d, *J* 7.0), 3.67 (3H, s), 4.56 and 4.81 (1H, s each), 4.87 (1H, d, *J* 10.5), 4.89 (1H, d, *J* 17.8), 5.80 (1H, dd, *J* 17.8, 10.5); *m*/*z* (EI) 236 (M^+, 3%), 221 (10), 162 (97), 147 (52), 106 (100).

Methyl 2-[(1*S*,3*R*,4*R*)-3-isopropenyl-4-methyl-4-vinylcyclohexyl]-4-[(5*R*)-2,2,4,4-tetramethyl-1,3-dioxalan-5-yl]butanoate 29

To a stirred solution of diisopropylamine (0.35 ml, 2.50 mmol) in THF (1 ml) at 0 °C was added dropwise a 1.59 M solution of BuLi in hexane (1.26 ml, 2.00 mmol). The reaction mixture was stirred for 30 min, and then cooled at −78 °C. A solution of **11** (237 mg, 1.00 mmol) in THF (2 ml) followed by HMPA (1.6 ml) was added dropwise, and stirring was continued at −78 to 0 °C for 2 h. The reaction mixture was recooled at −78 °C, and a solution of iodide **12** [12] (860 mg, 3.03 mmol) in THF (2 ml) was added dropwise. After being stirred for 2 h, the reaction mixture was quenched by addition of aqueous NH_4Cl, and extracted with ether. Removal of the solvent left the residue which was chromatographed on silica gel (hexane–AcOEt, 12:1) to give the title compound **29** (387 mg, 98%) as an oil (Found: C, 73.27; H, 10.47. $C_{24}H_{40}O_4$ requires C, 73.43; H, 10.27%); ν_{max}(neat)/cm^{-1} 1733, 1371, 1217, 909; δ_H($CDCl_3$) 0.97 (3H, s), 1.07 (3H, s), 1.14–1.70 (10H, m), 1.24 (3H, s), 1.33 (3H, s), 1.41 (3H, s), 1.69 (3H, s), 1.78–1.87 (1H, m), 1.95 (1H, dd, *J* 12.4, 3.3), 2.25 (1H, m), 3.69 (3H, s), 3.70 (1H, m), 4.56 and 4.81 (1H, s each), 4.87 (1H, d, *J* 17.8), 4.89 (1H, d, *J* 10.5), 5.79 (1H, dd, *J* 17.8, 10.5).

Methyl (5*R*)-2-[(1*S*,3*R*,4*R*)-3-isopropenyl-4-methyl-4-vinylcyclohexyl]-5,6-dihydroxy-6-methylheptanoate 30

A mixture of **29** (207 mg, 0.53 mmol), PPTS (20 mg) and methanol (3 ml) was gently refluxed for 5 h. To the reaction mixture, water (1 ml) and PPTS (10 mg) were added, and stirring was continued for an additional 4 h. After being cooled to room temperature, water was added, and the product was extracted with AcOEt. Removal of the solvent left an oily residue which was chromatographed on silica gel (hexane–AcOEt, 2:1) to give the title compound **30** (186 mg, quant.) as an oil (Found: C, 71.28; H, 10.45. $C_{21}H_{36}O_4$ requires C, 71.55; H, 10.29%); ν_{max}(neat)/cm^{-1} 3411, 1734, 1374, 1157, 891; δ_H($CDCl_3$) 0.96 (3H, s), 1.14 (3H, s), 1.16–1.52 (6H, m), 1.20 (3H, s), 1.57–1.70 (3H, m), 1.68 (3H, s), 1.80–1.88 (2H, m), 1.95 (1H, dd, *J* 12.4, 3.4), 2.05 (1H, s, OH), 2.17 and 2.35 (1H in total, a 1:2 ratio, d, *J* 5.1, OH), 2.21–2.31 (1H, m), 3.31 and 3.38 (1H in total, a 1:2 ratio, ddd, *J* 10.5, 4.6, 2.2), 3.68 (3H, s), 4.56 and 4.81 (1H, s each), 4.86 (1H, d, *J* 17.8), 4.89 (1H, d, *J* 10.5), 5.79 (1H, dd, *J* 17.8, 10.5).

(2*R*,5*R*)-2-[(1*S*,3*R*,4*R*)-3-Isopropenyl-4-methyl-4-vinylcyclohexyl]-5-(1-hydroxy-1-methylethyl)-5-pentanolide (dihydrolobatrienolide) 31

A mixture of **30** (145 mg, 0.42 mmol), toluene-*p*-sulfonic acid (*ca.* 10 mg) and CH_2Cl_2 (3 ml) was gently refluxed for 8 h. After being cooled to room temperature, the reaction mixture was washed with water. Removal of the solvent followed by purification of the residue with MPLC (hexane–AcOEt, 1:1) gave the title compound **31** (106 mg, 80%) as an oil (Found: C, 74.77; H, 10.09. $C_{20}H_{32}O_3$ requires C, 74.96; H, 10.06%); ν_{max}(neat)/cm^{-1} 3446, 1734, 1372, 1181, 1083, 890; δ_H($CDCl_3$) 0.99 (3H, s), 1.21 and 1.22 (3H in total, a 1:2 ratio, s each), 1.27 and 1.28 (3H in total, a 1:2 ratio, s each), 1.30–1.81 (8H, m), 1.70 (3H, s), 1.86–2.08 (4H, m), 2.21 and 2.27 (1H in total, a 2:1 ratio, s each, OH), 2.35–2.46 (1H, m), 4.57 and 4.58 (1H in total, a 2:1 ratio, s each), 4.82 (1H, s), 4.89 (1H, d, *J* 17.8), 4.90 (1H, d, *J* 10.5), 5.79 and 5.81 (1H in total, a 1:2 ratio, dd, *J* 17.8, 10.5 each); δ_H(C_6D_6) 1.01 and 1.04 (3H in total, a 1:2 ratio, s each), 1.03 and 1.05 (3H in total, a 1:2 ratio, s each), 1.06–1.68 (11H, m), 1.11 and 1.14 (3H in total, a 2:1 ratio, s each), 1.74 and 1.75 (3H, in total, a 2:1 ratio, s each), 1.79–2.22 (2H, m), 2.32 and 2.35 (1H in total, s each, OH), 3.58 and 3.65 (1H in total, a 1:2 ratio, dd each, *J* 11.0, 3.4 and 11.5, 3.2, respectively), 4.69 and 4.73 (1H in total, a 1:2 ratio, s each), 4.92–4.99 (3H, m), 5.77 and 5.82 (1H in total, a 1:2 ratio, dd, *J* 17.8, 10.5 each); *m*/*z* (EI) 320 (M^+, 4%), 162 (100), 158 (37), 147 (41), 107 (43).

Lobatrienolide 4

To a stirred solution of diisopropylamine (122 mg, 1.21 mmol) in THF (2 ml) was added dropwise at −78 °C a 1.54 M solution of BuLi in hexane (0.71 ml, 1.11 mmol). After being stirred for 20 min, a solution of **31** (155 mg, 0.48 mmol) in THF (2 ml) was added dropwise and stirring was continued for an additional 1 h. To the reaction mixture was added over a period of 30 min a solution of benzeneselenenyl chloride (230 mg, 1.20 mmol) and HMPA (2 ml) in THF (2 ml). The reaction mixture was stirred for 3 h, during which the reaction temperature rose to −30 °C, quenched with aqueous NH_4Cl, and extracted with EtOAc. Removal of solvent left the residue which was purified by MPLC (hexane–EtOAc, 2:1) to give the selenide (145 mg, 63%) as a mixture of diastereomers; δ_H($CDCl_3$) 0.97 and 0.98 (3H in total, *ca.* 9:1 ratio, s each), 1.21 and 1.24 (3H, s each), 1.32–1.49 (6H, m), 1.74–1.89 (3H, m), 1.75 (3H, s), 1.95–2.15 (2H, m), 2.17 (1H, m), 2.35 (1H, m), 4.06 and 4.20 (1H in total, *ca.* 9:1 ratio, dd, *J* 12.0, 3.2 and 11.0, 2.2, respectively), 4.61 and 4.64 (1H in total, *ca.* 9:1 ratio, s each), 4.84–4.93 (3H, m), 5.73 (1H, dd with fine splittings, *J* 16.8, 10.5 each), 7.3–7.7 (5H, m).

A solution of the selenide (144 mg, 0.3 mmol) in THF (6 ml) was stirred and cooled at 0 °C as 30% H_2O_2 (3 drops) was added, and the resulting solution was stirred for 12 h. The reaction mixture was filtered through a short silica gel column, and the filtrate was concentrated. Purification of the residue by MPLC (hexane–EtOAc, 1:1) gave the title compound **4** (68 mg, 70%) as an oil, $[a]_D^{26}$ +81.0 (*c* 0.30, $CHCl_3$) {lit., $[a]_D^{25}$ +89.3 ($CHCl_3$) [7]}, whose ^{1}H NMR, IR and MS data were identical with those of the authentic sample.[7]

Lobatrientriol 5

With DIBALH followed by $NaBH_4$. To a stirred solution of **4** (67 mg, 0.21 mmol) in toluene (2 ml) was added at −78 °C a 0.95 M solution of DIBALH in toluene (0.66 ml, 0.63 mmol), and stirring was continued for 3 h. The reaction mixture was quenched by addition of phosphoric acid buffer solution (pH 7.0), and filtered through a short silica gel column with toluene. Concentration of the filtrate left an oil, which was dissolved in methanol (1 ml). The methanol solution was cooled at 0 °C, and $NaBH_4$ (18 mg, 0.46 mmol) was added portion by portion with stirring. After being stirred for 2 h, most of the methanol was removed, and aqueous HCl was added to the oily residue. The product was extracted with EtOAc and the combined extracts were concentrated. Purification of the residue with MPLC (hexane–EtOAc, 1:2) gave **5** (55 mg, 80%) as an oil, $[a]_D^{26}$ +14.9 (*c* 0.22, $CHCl_3$) {lit., $[a]_D^{25}$ +15.0 (*c* 0.20, $CHCl_3$) [5]}, whose spectral data (^{1}H NMR and IR) were identical with those of natural **5**.[5]

With $LiAlH_4$. A mixture of **4** (50 mg, 0.16 mmol) and lithium aluminium hydride (28.8 mg, 0.76 mmol) in THF (1 ml) was stirred at 0 °C for 4 h, and quenched by addition of aqueous NH_4Cl. Extraction with EtOAc followed by concentration of the combined extracts left the residue which was purified by MPLC (hexane–EtAOc, 1:2) gave **5** (6 mg, 11%) and **32a**,**b** (15 mg, 29%) as a separable mixture of diastereomers (*ca.* 2:1 ratio).

32a (Major): $\delta_H(CDCl_3)$ 0.98, 1.17, 1.22 and 1.70 (3H, s each), 1.13–2.45 (16H, m), 3.38 (1H, d, *J* 10.0), 3.58 (1H, dd, *J* 10.7, 5.7), 3.72 (1H, dd, *J* 10.7, 4.9), 4.57 (1H, m), 4.82 (1H, m), 4.87 (1H, m), 4.92 (1H, m), 5.80 (1H, dd, *J* 17.8, 10.5).

32b (Minor): $\delta_H(CDCl_3)$: 0.98, 1.13, 1.21 and 1.67 (3H, s each), 1.10–2.40 (15 H, m), 3.37 (1H, dd, *J* 10.2, 1.8), 3.64 (1H, dd, *J* 10.8, 6.1), 3.70 (1H, dd, *J* 10.8, 4.2), 4.57 (1H, m), 4.81 (1H, m), 4.82 (1H, m), 4.90 (1H, m), 5.80 (1H, dd, *J* 17.8, 10.5).

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