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Total synthesis and structural confirmation of the antibacterial diterpene leubethanol

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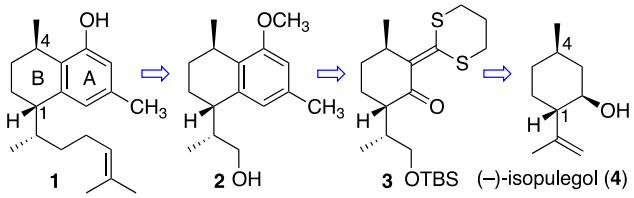
ABSTRACT

We report the total synthesis of leubethanol (**1**), a serrulatane compound that has recently been reported as having considerable antibacterial activity against multidrug-resistant bacteria, such as *Staphylococcus aureus*, and is of interest for applications in the control of bacterial biofilms in human medicine. Our synthetic route begins with (−)-isopulegol (**4**) and key steps include substrate directed hydroboration to generate the C1′ stereocentre and formation of the aromatic ring via the α-oxoketene-*S*,*S*-acetal intermediate **3**. Overall the conversion of (−)-isopulegol (**4**) to leubethanol was achieved in 13 steps and an overall yield of 7%. Comparison of our spectroscopic data with those reported for leubethanol (**1**), isolated from *Leucophyllum frutescens*, verified the structure of the natural product.

1. Introduction

The serrulatanes are a class of diterpenes that have been extracted from the leaves of a wide variety of Australian-native *Eremophila* plants.[1–5] In addition, the serrulatane natural product leubethanol (**1**) was recently isolated[6] from the root bark of the evergreen shrub *Leucophyllum frutescens* used in Mexican traditional medicine. These natural products are part of a new class of antimicrobial compounds that possess interesting biological activity against *Mycobacterium tuberculosis*,[6] *Staphylococci*[2–4] and *Streptococci*[2–4] bacteria as well as anti-inflammatory properties.[5] All biological studies to date involving serrulatanes have required the compounds to be extracted from the plants. These desert plants are not readily accessible and may not allow cropping of usable material in drought years; moreover, extraction and purification are tedious and provide only small amounts. This necessarily limits the amounts of serrulatane compound that are available for the study of biological activities and for the development of potential practical applications, such as antibacterial coatings to protect biomedical devices and implants from bacterial biofilm formation.[7]

The structure, including stereochemistry, of the methyl serrulatane leubethanol (**1**) was determined[6] by extensive NMR spectroscopy. Despite being one of the simplest serrulatanes it has recently been shown to display potent antibacterial action against multi-drug resistant *M. tuberculosis*.[6] As part of our investigations into the synthesis of various serrulatanes for biological evaluation and future medical use we targeted leubethanol (**1**) as one of the simpler structures of this class. Our proposed route (Scheme 1), as well as confirming the structure of leubethanol (**1**), also enables ready preparation of side-chain analogues.



Scheme 1. Retrosynthetic analysis of leubethanol (**1**).

A major challenge in the synthesis of the serrulatanes lies in the control of all three stereocentres, especially considering the absence of functional groups near the stereocentres.[8,9] Stereocontrol in the synthesis of the closely-related pseudopterosins and seco-pseudopterosins has been achieved using: a rhodium catalyzed hydroboration,[10] a rhodium catalyzed C–H activation/Cope rearrangement,[9] an enantioselective copper catalyzed conjugate addition of an alkylzinc[11] and conjugate addition to arene-$Cr(CO)_3$ complexes.[8,12] In contrast, our approach to the total synthesis of leubethanol (**1**) utilized the inexpensive and readily available chiral

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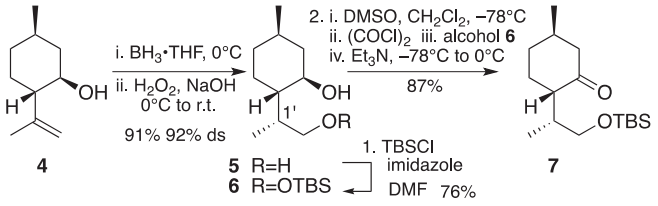
pool starting material (−)-isopulegol (**4**) to provide two of the three required stereocentres.

The retrosynthetic analysis is depicted in Scheme 1, highlighting the proposed annulation of the aromatic ring onto (−)-isopulegol (**4**) via the key α-oxoketene-*S*,*S*-acetal intermediate **3**. The commercially available monoterpene (−)-isopulegol (**4**) bears two stereocentres in common with leubethanol (C1 and C4) and the hydroxyl group can be used to direct hydroboration and thus generate the required configuration of the remaining methyl stereocentre.

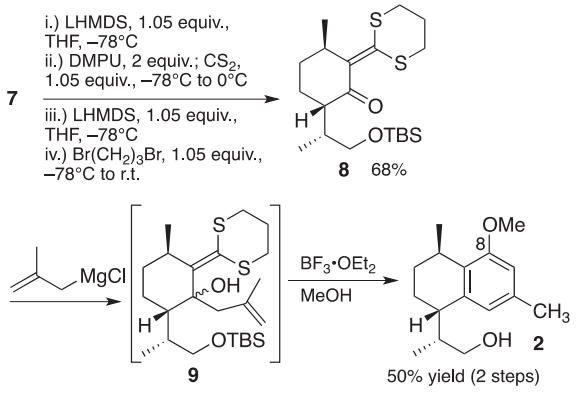
2. Results and discussion

In the first step of the synthesis of leubethanol (**1**) (−)-isopulegol (**4**) was treated with $BH_3 \cdot THF$ to give the diol **5** with good stereoselectivity[13] and the diastereomeric ratio (C1′ epimer) was determined from the ^1H NMR spectrum to be 12:1 (Scheme 2). The diol **5** was purified by recrystallization and the hydroboration was readily conducted on up to 15 g of starting material. The recrystallization of diol **5** did not separate the minor isomer but after selective TBS protection of the primary hydroxyl the minor isomer was readily removed by column chromatography to give pure TBS ether **6**. Swern oxidation of the TBS ether **6** gave ketone **7,** providing opportunity for functionalisation at the position alpha to the ketone.



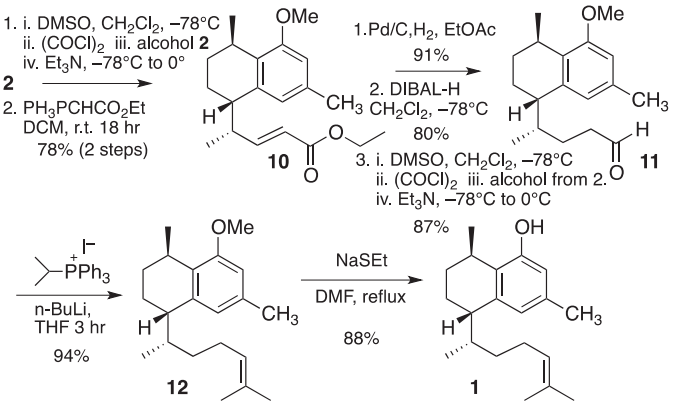
Scheme 2. Formation of the methyl stereocentre.

A careful modification of the method of Kocienski et al.[14] gave the α-oxoketene-*S*,*S*-akcetal **8** as shown in Scheme 3. It was found that the enolate needed to be initially formed in THF at −78 °C and the DMPU added immediately before addition of the CS_2. The reaction was then warmed to 0 °C to allow reaction with the CS_2 to proceed before re-cooling to −78 °C prior to the addition of the second equivalent of base (LHMDS) and 1,3-dibromopropane. Using these optimized conditions the one-pot, multistep reaction gave compound **8** in 68% yield.



Scheme 3. Construction of the keteneacetal **8** followed by benzannulation.

The 1,2-addition to the carbonyl of α-oxoketene-*S*,*S*-acetals followed by treatment with a Lewis acid has been reported as a controlled method for achieving benzannulation.[14–16] Thus, methallylmagnesium chloride was added to the keteneacetal **8**, giving the sensitive intermediate carbinol **9**. Exposure of **9** to $BF_3 \cdot OEt_2$ in the presence of methanol leads to the annulated product **2**, complete with both the required oxygen functionality at C8 and the methyl substituent on the aromatic ring. Conveniently, the Lewis acid treatment removes the TBS protecting group, giving the C2′ alcohol and allowing for direct extension of the hydrocarbon tail.The final phase of the synthesis involves building the hydrocarbon tail (Scheme 4). Oxidation of the methoxy arene **2** gave the corresponding aldehyde, which was immediately reacted with (carbethoxymethylene)triphenylphosphorane in a Wittig reaction to afford the unsaturated ester **10**. Hydrogenation with Pd/C and H_2 followed by reduction of the ester to the alcohol with DIBAL-H and re-oxidation to the aldehyde gave the saturated aldehyde **11**.



Scheme 4. Assembly of the hydrocarbon tail followed by demethylation.

The completion of the hydrocarbon tail was achieved through another Wittig olefination, in this instance with the ylide derived from isopropyltriphenyl phosphonium iodide, to install the isoprene moiety, thereby producing the methoxy serrulatane **12**. Finally, demethylation[17] of the methoxy serrulatane **12** with NaSEt in DMF afforded compound **1**. The ^1H and ^{13}C NMR spectroscopic data (Table 1) and optical rotation ($[\alpha]_D^{25}$ −32 (*c* 0.15, $CHCl_3$)) for synthetic **1** were essentially identical to that reported ($[\alpha]_D$ −32 (*c* 0.15, $CHCl_3$))[6] for the natural product leubethanol. This total chemical synthesis thus offers definitive verification of the structural configuration of leubethanol provided in the report of its isolation from the natural source.[6]

3. Conclusions

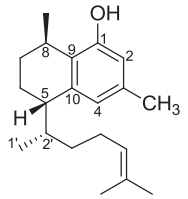
We have synthesised the naturally occurring antimicrobial compound leubethanol in 13 steps from commercially available (−)-isopulegol with an overall yield of 7%. This total chemical synthesis establishes a route for the preparation of larger amounts of this compound for studies of its antimicrobial properties and potential applications, and confirms the stereochemical configuration of this natural product, as reported in its isolation[6] from *L. frutescens*.

4. Experimental section

4.1. General experimental procedures

All reactions were carried out using anhydrous solvents under a nitrogen atmosphere and performed in oven dried round bottom flasks fitted with a rubber Suba Seal unless otherwise stated. Organic solutions were concentrated via rotary evaporation under reduced pressure. Thin Layer Chromatography (TLC) was executed with the indicated mobile phase solvents on silica gel plates (E. Merck, 60 F254, 0.25 mm) with compounds visualised by exposure to a UV lamp (λ=254 nm) and developed by dipping in a $KMnO_4$ solution or anisaldehyde solution, followed by rapid heating using

Table 1
Comparison of the ^{1}H and ^{13}C NMR data for natural leubethanol and synthesised **1**



Position	Natural product[a]		Synthesised product **1**[b]		
	δ_H (m, *J*[Hz])[c]	δ_C[c]	δ_H (m, *J*[Hz])[c]	δ_C[c]	$\Delta\delta$[d]
C1		153.01		152.99	0.02
C2	6.448 (br d, 1.6, <0.20)	113.25	6.42 (s)	113.19	0.06
C3		134.83		135.02	−0.19
C3Me	2.270 (s)	20.96	2.24	21.05	−0.09
C4	6.615 (dq, 1.64, <0.20)	122.30	6.59 (s)	122.44	−0.14
C5	2.59 (ddd, 6.23,5.21, 2.95)	42.37	2.58	42.38	0.01
C6	a: 1.74 (ddd, 13.84, 5.00, 3.37, 2.95); b: 1.870 (dddd, 13.84, 13.30, 6.23, 3.52)	19.43	a: 1.72 (m); b: 1.92–1.85 (m)	19.41	0.02
C7	a: 1.520 (dddd, 13.35, 5.20, 3.52, 2.58); b: 1.967 (dddd, 13.25, 13.25, 6.16, 3.37)	27.47	a: 1.49–1.56 (m); b: 1.96 (m)	27.46	0.01
C8	3.078 (ddq, 6.97, 6.16, 2.58)	26.56	3.06 (m)	26.57	−0.01
C8Me	1.224 (d, 6.97)	21.13	1.20 (d, 6.9)	21.16	−0.03
9		126.38		126.31	0.07
10		140.81		140.99	−0.18
C1′	0.984 (d, 6.84)	18.64	0.96 (d, 6.9)	18.72	−0.08
C2′	1.902 (dddq, 10.02, 6.84, 5.21, 2.96)	37.74	1.92–1.85 (m)	37.80	−0.06
C3′	a: 1.107 (dddd, 13.19, 10.02, 9.28, 4.86); b: 1.314 (dddd, 13.9, 9.63, 6.94, 2.96)	33.33	a: 1.06 (m); b: 1.27–1.31 (m)	33.39	−0.06
C4′	a: 2.010 (ddddqq, 14.37, 9.63, 6.76, 4.86, 1.17, 0.89); b: 1.834 (ddddq, 14.37, 9.28, 7.60, 6.94, 1.14, 0)	26.16	a: 1.98 (m); b: 1.84–1.80 (m)	26.23	−0.07
C5′	5.018 (ddqq, 7.60, 6.76, 1.38, 1.36)	124.91	5.00 (t, 7.0)	124.92	−0.01
C6′		130.95		131.11	−0.16
C6′Me	1.582 (dd/br s, 1.36, 0.89, 0)	17.49	1.55 (d, 1.3)	17.61	−0.12
C7′	1.683 (ddd, 1.38, 1.18, 1.14)	25.59	1.68 (d, 1.3)	25.70	−0.11

[a] Chemical shifts and coupling constants as reported in Molina-Salinas et al.[6] (900 MHz).
[b] Bruker 600 MHz NMR Spectrometer ($CDCl_3$). Assignments assisted by $^{1}H-^{13}C$ HMBC, $^{1}H-^{13}C$ HMQC, $^{1}H-^{1}H$ COSY.
[c] Chemical shifts in ppm referenced to $CHCl_3$ at 7.26 ppm and to $CDCl_3$ at 77.00 ppm.
[d] This is the difference in the ^{13}C chemical shift of the isomer and that reported for the natural product.

a heat gun. Silica chromatography was performed using silica gel (EM Merck, 230–400 mesh). When purifying compounds with acid sensitivity, column chromatography was performed on buffered silica as indicated. Buffered silica was prepared by spinning 100 g of silica gel 60 (mesh size 0.040–0.063 mm) with 10 mL of pH 7 phosphate buffer on a rotary evaporator overnight at atmospheric pressure.

^{1}H NMR spectra were recorded on a Bruker Avance III 600 or 400 MHz as indicated. Chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane and referenced to residual protonium in the NMR solvent ($CHCl_3$, δ=7.26). Data are reported as follows: chemical shift, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, qt=quintet, sx=sextet, m=multiplet, br=broad, app=apparent), integration and coupling constant *J* (Hertz). ^{13}C NMR spectra were recorded on a Bruker Avance III 600 or 400 MHz as indicated. Chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane and referenced to the carbon resonances in the NMR solvent ($CDCl_3$, δ=77.0, centre line). Optical rotations were obtained using a PolAAR 21 polarimeter, referenced to the sodium D line (589 nm) at 20 °C, using the spectroscopic grade solvents specified and at concentrations (*c*, g/100 mL) as indicated in a cell with a 100 mm path length. High resolution mass spectra were acquired with a Water Synapt HDMS unit in either positive or negative ion mode.

4.2. Preparative procedures

*4.2.1. (1R,2S,5R)-2-[(R)-2′-Hydroxy-1′-methylethyl]-5-methylcyclohexan-1-ol (**5**).* $BH_3\cdot THF$ (1 M solution in THF, 107 mL, 107 mmol) was added dropwise to a stirred solution of (−)-isopulegol (15 g, 16.5 mL, 97 mmol) in THF (390 mL) at 0 °C. After stirring for 3 h, H_2O (14 mL) was slowly added to the reaction flask, followed by H_2O_2 (30 wt %, 21 mL) and NaOH (30 wt %, 21 mL) and the flask was allowed to warm to room temperature over 30 min. The volume was reduced by half, the product extracted with Et_2O (3×55 mL) and the organic layers were washed with brine (37 mL), dried over $MgSO_4$ and concentrated in vacuo to give the crude diol (**5**). The crude diol was recrystallised with cyclohexane to give a mixture of diol (**5**) and its C1′ epimer (ratio 12:1) (15 g, 88 mmol, 91% yield) as low melting white crystals. The spectroscopic data obtained for the major isomer is consistent with that previously reported.[13] Discernible signals attributed to the minor epimer are marked with an asterisk (*). IR (ν_{max} film/cm^{-1}) 3234, 2960, 2945, 2912, 1450, 1037; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.60 (1H, dd, *J*=10.5 and 3.4 Hz, C2′H_A), 3.54 (1H, dd, *J*=10.6 and 4.3 Hz, C2′H_B), 3.42 (1H, app. quintet, *J*=10.4 and 4.3 Hz, C1*H*), 2.04–1.99 (1H, m), 1.93 (1H, dd, *J*=12.0 Hz), 1.81 (1H, br s, O*H*), 1.61 (1H, d, *J*=12.3 Hz), 1.53 (1H, q, *J*=13.0 and 3.3 Hz), 1.41–1.38 (1H, m), 1.32 (1H, dd, *J*=9.7 and 3.1 Hz), 1.21 (1H, dq, *J*=12.2 and 3.4 Hz), 0.94 (3H, d, *J*=7.3 Hz, C5H_3) 0.89 (3H, d, *J*=6.5 Hz, C1′CH_3), 0.98–0.81 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 71.5*, 69.9, 66.8, 66.4*, 48.5, 44.4, 45.5*, 45.0*, 38.5, 34.6, 31.4, 31.5*, 29.5, 22.1*, 22.0, 12.5*, 12.0.

*4.2.2. (1R,2S,5R)-2-[((R)-2′-tert-Butyldimethylsilyloxy)-1′-methylethyl]-5-methylcyclohexan-1-ol (**6**).* To a solution of diol **5** (12: 1 mixture of the two isomers, 15 g, 87 mmol) and imidazole (13.8 g, 203 mmol, 2.3 equiv) in dry DMF (65 mL) was added *tert*-butyldimethylsilyl chloride (TBSCl, 14 g, 97 mmol). After 15 min, the reaction

mixture was quenched with saturated aqueous NH_4Cl (100 mL) and the product extracted into hexanes (3×100 mL). The combined organic layers were washed with brine (100 mL), dried over $MgSO_4$ and concentrated in vacuo. The crude oil was purified by column chromatography (SiO_2, hexanes/EtOAc 6:1) to give the stereochemically pure TBS ether **6** (19 g, 66 mmol, 76% yield) as a colourless oil. $[\alpha]_D^{25}$ −28.9 (*c* 2.3, MeOH); IR (ν_{max} film/cm^{-1}) 3440, 2927, 2858, 1472, 1461; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.90 (1H, br s, O*H*), 3.42 (1H, dd, A portion of an ABX system, J_{AB}=9.9 Hz, J_{Bx}=5.4 Hz, C2′H_A), 3.36 (1H, dd, B portion of an ABX system, J_{AB}=9.9 Hz, J_{Bx}=3.8 Hz, C2′H_B), 3.17 (1H, m, C1H), 1.76–1.73 (1H, m), 1.66 (1H, m), 1.42–1.31 (2H, m), 1.19–1.16 (3H, m), 0.94–0.84 (2H, m), 0.75 (3H, d, *J*=6.5 Hz, C5H_3), 0.67 (12H, overlapping s, *t*-Bu and d, *J*=6.5 Hz, C1′H_3) −0.16 (6H, s, $SiMe_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 69.7, 67.7, 49.2, 43.8, 38.3, 34.7, 31.4, 29.1, 25.8, 22.1, 18.3, 12.3, −5.61, −5.65. HRESIMS *m*/*z* 309.2220 (M+Na) (calcd for $C_{16}H_{34}O_2SiNa$, 309.2226).

*4.2.3. (2S,5R)-2-[(R)-2′-tert-Butyldimethylsilyloxy)-1′-methylethyl]-5-methylcyclohexan-1-one (**7**).* To a solution of DMSO (2.9 g, 2.6 mL, 37 mmol, 3 equiv) in CH_2Cl_2 (65 mL) at −78 °C was added oxalyl chloride (2.0 M solution in CH_2Cl_2, 9.3 mL, 18.6 mmol, 1.5 equiv). After 10 min, the alcohol **6** (3.56 g, 12.4 mmol) in CH_2Cl_2 (15 mL) was added via cannula. After 1 h, Et_3N (7.5 g, 10.4 mL, 75 mmol, 6 equiv) was added and the reaction mixture was warmed to room temperature over 2 h. Saturated aqueous NH_4Cl (65) was added to the vigorously stirred suspension and the product extracted into hexanes (3×40 mL). The combined organic layers were washed successively with HCl (1.5 M, 25 mL) and brine (25 mL). The residue obtained on concentration in vacuo was purified by column chromatography (SiO_2, CH_2Cl_2) to give the ketone **7** (3.07 g, 10.8 mmol, 87%) as a pale yellow oil. $[\alpha]_D^{25}$−8.2 (*c* 1.5, MeOH); IR (ν_{max} film/cm^{-1}) 2955, 2857, 1642, 1462, 1382, 1251, 1084, 845, 774; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.62 (1H, dd, A portion of an ABX system, J_{AB}=9.4 Hz, J_{Bx}=5.4 Hz, C2′H_A) 3.58 (1H, dd, B portion of an ABX system, J_{AB}=9.4 Hz, J_{Bx}=3.2 Hz, C2′H_B), 2.34–2.26 (3H, m), 2.10–2.05 (2H, m) 2.04–1.95 (2H, m), 1.94–1.80 (2H, m), 1.01 (3H, d, *J*=6.2 Hz, C5H_3), 0.94 (3H, d, *J*=6.7 Hz, C1′H_3), 0.87 (9H, s, *t*-Bu), 0.02 (6H, s, $SiMe_2$); ^{13}C NMR δ_C (100 MHz, $CDCl_3$) 212.0, 65.4, 52.1, 51.1, 35.6, 34.8, 34.2, 29.6, 25.9, 22.3, 18.2, 15.1, −5.5.

*4.2.4. (2S,5R)-2-[(R)-2′-tert-Butyldimethylsilyloxy)-1′-methylethyl]-6-(1,3-dithian-2-ylidene)-5-methylcyclohexan-1-one (**8**).* To a solution of lithium bis(trimethylsilyl)amide (LHMDS, 1.0 M solution in THF, 1.11 mL, 1.11 mmol, 1.05 equiv) at −78 °C was added the ketone **7** (0.30 g, 1.05 mmol) in THF (1.6 mL) via cannulation. After 30 min, 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU, 0.27 g, 0.26 mL, 2.11 mmol, 2 equiv) was added to the reaction flask, followed by rapid addition of CS_2 (84 mg, 67 μL, 1.11 mmol, 1.05 equiv). The reaction mixture was allowed to warm to 0 °C over 1.5 h, stirred at this temperature for an additional 1 h before returning to −78 °C. A second portion of LHMDS (1.0 M solution in THF, 1.11 mL, 1.11 mmol, 1.05 equiv) was added dropwise. After a further 30 min, 1,3 dibromopropane (0.22 g, 0.11 mL, 1.11 mmol, 1.05 equiv) in THF (3.3 mL) was added and the solution was warmed to room temperature overnight, then poured into saturated aqueous NH_4Cl (10 mL). The product was extracted with Et_2O (3×5 mL) and the combined organic layers were washed with brine (10 mL) and dried over Na_2SO_4. The residue obtained upon concentration in vacuo was purified by column chromatography (buffered SiO_2, CH_2Cl_2) to afford the ketene-*S*,*S*-acetal **8** (0.284 g, 0.71 mmol, 68% yield) as a pale yellow oil. $[\alpha]_D^{25}$ +92.8 (*c* 0.7, MeOH); IR (ν_{max} film/cm^{-1}) 2928, 2856, 1643, 1471, 1418, 1281, 1257, 1089, 836, 775, 668; ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.51 (2H, dd, A portion of an ABX system, J_{AB}=7.1 Hz, C2′H_A), 3.21 (1H, app. sextet, *J*=5.9 Hz, C5*H*), 3.02 (1H, ddd, *J*=12.3, 8.3 and 4.3 Hz, SCH_A), 2.1 (2H, ddd, *J*=14.9, 12.6 and 4.7 Hz, SCH_2), 2.72 (1H, ddd, *J*=13.9, 6.9 and 4.6 Hz, SCH_B), 2.30 (1H, dd, *J*=12.5 and 6.2 Hz), 2.15 (2H, m), 2.09 (1H, m), 2.00 (1H, m), 1.90 (1H, m), 1.69 (1H, m), 1.39 (1H, m), 1.10 (3H, d, *J*=6.9 Hz, C5H_3), 0.90 (3H, d, *J*=7.0 Hz, C1′H_3), 0.87 (s, 9H, *t*-Bu), 0.02 and 0.01 (s, 3H each, $SiMe_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.2, 149.9, 137.1, 65.8, 50.2, 37.1, 34.0, 28.9, 28.6, 28.5, 25.9, 25.8, 23.7, 19.9, 18.2, 15.1, −5.4, −5.5.

*4.2.5. 2-(R)-(1S,4R,5-Methoxy-7-methyl-1,2,3,4-tetrahydronaphthalen-1-yl)-propan-1-ol (**2**).* Methallylmagnesium chloride (105 mmol, 7 equiv) was prepared by the dropwise addition of methallyl chloride (3.18 g, 3.43 mL, 35 mmol) in THF (140 mL) to Mg turnings (2.56 g, 105 mmol) in the presence of I_2. The reaction was refluxed for 1 h and cooled prior to cannulation of oxo-ketene *S*,*S* acetal **8** (2.01 g, 5.01 mmol) in THF (59 mL) at 0 °C. The ice bath was removed and the reaction continued at room temperature for 90 min before quenching with saturated aqueous NH_4Cl (100 mL). The product was extracted with Et_2O (3×30 mL) and the combined organic layers dried over Na_2SO_4 then concentrated in vacuo to give the crude alcohol as an orange oil. The crude alcohol, used without purification, was dissolved in THF (6 mL) and added via cannula to a stirred solution of $BF_3{\cdot}OEt_2$ (5 g, 4.95 mL, 35 mmol, 7 equiv) in MeOH (20 mL) at −40 °C. The reaction was left overnight then worked up with saturated aqueous $NaHCO_3$ (30 mL) diluted with brine (20 mL) and the product extracted with Et_2O (3×40 mL), dried over Na_2SO_4. The oil obtained upon concentration in vacuo was purified by column chromatography (buffered SiO_2, CH_2Cl_2/hexanes 12:1) to give the methoxy arene **2** (616 mg, 2.5 mmol, 50% yield). $[\alpha]_D^{25}$ −3.1 (*c* 55.6, $CHCl_3$); IR (ν_{max} film/cm^{-1}) 2928, 2856, 1643, 1472, 1418, 1281, 1255, 1087, 837, 775, 668; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.63 (1H, s, C8*H*), 6.53 (1H, s, C6*H*), 3.82 (3H, s, OCH_3), 3.53 (1H, dd, *J*=10.7 and 5.7 Hz, C1H_A), 3.45 (1H, dd, *J*=10.7 and 5.9 Hz, C1H_B), 3.17–3.20 (1H, m, C4CH_3), 2.72 (1H, m, C1′*H*), 2.32 (3H, s, C7CH_3), 1.94–1.91 (1H, m), 1.89–1.87 (1H, m), 1.77–1.75 (1H, m), 1.58–1.55 (1H, m), 1.54–1.51 (1H, m), 1.17 (3H, d, *J*=6.9 Hz, C4CH_3), 1.01 (3H, d, *J*=6.9 Hz, C3H_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.1, 139.3, 135.0, 128.4, 122.4, 108.8, 66.3, 55.1, 41.8, 39.7, 27.0, 26.3, 21.5, 21.2, 19.6, 16.7. HRESIMS *m*/*z* 271.1674 (M+Na) (calcd for $C_{16}H_{24}O_2Na$, 271.1674).

*4.2.6. Ethyl 4-(R)-(1S,4R,5-methoxy-7-methyl-1,2,3,4-tetrahydronaphthalen-1-yl)-pent-2-enoate (**10**).* DMSO (1.02 g, 0.93 mL, 3 equiv) in CH_2Cl_2 (20 mL) was stirred at −78 °C and oxalyl chloride (2.0 M in CH_2Cl_2, 3.27 mL, 6.54 mmol, 1.5 equiv) was added dropwise. The reaction mixture was stirred for 10 min prior to cannulation of the alcohol **2** (1.08 g, 4.3 mmol) in CH_2Cl_2 (5 mL). After 1.5 h, Et_3N (3.64 mL, 26.2 mmol, 6 equiv) was added dropwise and the flask warmed to room temperature over 1 h. The mixture was diluted with CH_2Cl_2 (50 mL) then washed successively with water (2×25 mL) and brine (50 mL). The organic layers were combined and dried over Na_2SO_4, and filtered into a round bottom flask. Carbethoxymethylene triphenylphosphorane (3.13 g, 8.72 mmol, 2 equiv) was added into the solution of crude aldehyde. The reaction was monitored by TLC. The CH_2Cl_2 was evaporated and the crude reaction mixture was purified by column chromatography (buffered SiO_2, CH_2Cl_2/hexanes 4:1) to give the unsaturated ester **10** as an oil (1.06 g, 3.35 mmol, 78% yield). $[\alpha]_D^{25}$ −82.1 (*c* 2.9, $CHCl_3$); IR (ν_{max} film/cm^{-1}) 2936, 2870, 1717, 1649, 1613, 1579, 1463, 1274, 1232, 1212, 1148, 1095, 1037, 998, 866, 833, 730; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.87 (1H, dd, *J*=10.5 and 4.8 Hz, C3*H*), 6.56 (1H, s, C8*H*), 6.50 (1H, s, C6*H*), 5.69 (1H, d, *J*=15.6 Hz, C2*H*), 4.13 (2H, *q*, *J*=7.1 Hz, OCH_2CH$_3$), 3.80 (3H, s, OCH_3), 3.13–3.10 (1H, m, C4′*H*), 2.65 (1H, m, C1′*H*), 2.40 (1H, m), 2.31 (3H, s, C7CH_3) 1.87–1.80 (2H, m), 1.69–1.66 (1H, m), 1.44–1.40 (1H, m), 1.27 (3H, t, *J*=7.1 Hz, OCH$_2$CH_3), 1.11 (3H, d, *J*=6.9 Hz, C4′CH_3), 1.08 (3H, d, *J*=6.9 Hz, C5CH_3); ^{13}C NMR (151 MHz, $CDCl_3$) δ 168.9, 157.1, 153.3, 138.3, 134.8, 128.4, 122.7, 119.7, 109.1, 60.1, 55.0, 50.3, 42.3, 26.1, 26.0, 21.4, 21.2, 19.6, 18.4, 14.1. HRESIMS *m*/*z* 339.1931 (M+Na) (calcd for $C_{20}H_{28}O_3Na$, 339.1936).

*4.2.7. Ethyl 4-(R)-(1S,4R,5-methoxy-7-methyl-1,2,3,4-tetrahydronaphthalen-1-yl)-pentanoate (**13**).* The unsaturated ester **10** (450 mg, 1.49 mmol)

and catalytic amount of Pd/C (15 mg) were stirred in EtOAc (9 mL) under H_2 for 7 days, after which, the reaction mixture was filtered through Celite© and the solvent evaporated to give the crude oil. Purification was achieved with column chromatography (buffered SiO_2, CH_2Cl_2) to afford the saturated ester **13** (412 mg, 1.35 mmol, 91% yield). $[\alpha]_D^{25}$ −41.2 (*c* 2.6, $CHCl_3$); IR (ν_{max} film/cm^{-1}) 2955, 2870, 1735, 1612, 1578, 1462, 1272, 1173, 1097, 1035, 832; ^1H NMR (400 MHz, $CDCl_3$) δ 6.57 (1H, s, C8*H*) 6.50 (1H, s, C6*H*), 4.07 (2H, q, *J*=7.1 Hz, OCH_2CH_3), 3.80 (3H, s, OCH_3), 3.15–3.13 (1H, m, C4′*H*), 2.58 (2H, m), 2.30 (3H, s, C7CH_3), 2.17 (1H, m), 2.17 (C1′*H*), 1.90–1.85 (2H, m), 1.71–1.74 (2H, m), 1.50–1.42 (1H, m), 1.13 (3H, t, *J*=7.1 Hz, CH_2CH_3), 0.96 (3H, d, *J*=6.9 Hz, C4′CH_3), 0.94 (3H, d, *J*=6.9 Hz, C5CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.9, 157.0, 139.7, 134.7, 128.6, 122.2, 108.6, 60.1, 55.1, 42.2, 38.1, 33.0, 28.8, 27.2, 26.4, 21.3, 21.2, 19.3, 18.6, 14.2.

*4.2.8. 4-(R)-(1S,4R,5-Methoxy-7-methyl-1,2,3,4-tetrahydronaphthalen-1-yl)-pentan-1ol (**14**).* To a stirred solution of the saturated ester **13** (300 mg, 0.99 mmol) in CH_2Cl_2 (10 mL) was added DIBAL-H (1 M in toluene, 4.00 mL, 4.00 mmol, 4 equiv) at −78 °C. After 1 h, sodium potassium tartarate (15 mL) was added and the solution warmed to room temperature. The product was extracted with CH_2Cl_2 (3×15 mL), the combined organic layers washed with brine (5 mL) and dried over Na_2SO_4 and concentrated in vacuo. The crude oil was purified by column chromatography (buffered SiO_2, CH_2Cl_2/Et_2O 10:1) to give the alcohol **14** (220 mg, 0.79 mmol, 80%). $[\alpha]_D^{25}$ −52.2 (*c* 0.9, $CHCl_3$); IR (ν_{max} film/cm^{-1} 3424, 2955, 2870, 1724, 1612, 1578, 1462, 1343, 1272, 1097, 832); ^1H NMR (400 MHz, $CDCl_3$) δ 6.60 (1H, s, C8*H*), 6.51 (1H, s, C6*H*), 3.81 (3H, s, OCH_3), 3.53 (2H, dd, *J*=10.7 and 4.4 Hz, CH_2OH), 3.14 (1H, m, C4′*H*), 2.60 (1H, m, C1′*H*), 2.30 (3H, s, C7CH_3), 1.89–1.83 (3H, m), 1.74 (1H, m), 1.68–1.63 (1H, m), 1.47 (1H, m), 1.33–1.30 (3H, m), 1.13 (3H, d, *J*=6.9 Hz, C4′CH_3), 0.98 (3H, d, *J*=6.9 Hz, C5H_3); ^{13}C NMR (151 MHz, $CDCl_3$) δ 157.0, 140.3, 134.8, 128.7, 122.0, 108.5, 63.4, 55.2, 42.3, 41.2, 31.2, 29.2, 27.4, 26.5, 21.7, 21.6, 20.3, 19.2. HRESIMS *m*/*z* 299.1990 (M+Na) (calcd for $C_{18}H_{28}O_2Na$, 299.1987).

*4.2.9. 4-(R)-(1S,4R,5-Methoxy-7-methyl-1,2,3,4-tetrahydronaphthalen-1-yl)-pentanal (**11**).* DMSO (79 mg, 72 μL, 1.01 mmol, 3 equiv) in CH_2Cl_2 (2 mL) was stirred at −78 °C and oxalyl chloride (2.0 M in CH_2Cl_2, 253 μL, 0.50 mmol, 1.5 equiv) was added dropwise. The reaction mixture was stirred for 10 min prior to cannulation of the alcohol **14** (93 mg, 0.33 mmol) in CH_2Cl_2 (1.5 mL). After 1.5 h, Et_3N (282 μL, 2.02 mmol, 6 equiv) was added dropwise and the flask warmed to room temperature over 1 h. The mixture was quenched with saturated aqueous NH_4Cl (5 mL) and the product extracted with Et_2O (3×15 mL). The combined organic layers were washed successively with HCl (1.5 M, 5 mL) and brine (5 mL). The residue obtained on concentration in vacuo was purified by column chromatography (SiO_2, CH_2Cl_2) to give the aldehyde **11** (80 mg, 0.29 mmol, 87%). $[\alpha]_D^{25}$ −54.3 (*c* 1.1, $CHCl_3$); IR (ν_{max} film/cm^{-1}) 2955, 2870, 1724, 1612, 1579, 1462, 1343, 1271, 1097, 832; ^1H NMR (400 MHz, $CDCl_3$) δ 9.63 (1H, s, C1*H*O), 6.57 (1H, s, C8*H*), 6.51 (1H, s, C6*H*), 3.80 (3H, s, OCH_3), 3.15–3.13 (1H, m, C4′*H*), 2.61 (1H, m, C1′*H*), 2.30 (3H, s, C7CH_3), 2.17–2.16 (2H, m), 1.90–1.85 (2H, m), 1.71–1.74 (3H, m) 1.50–1.42 (2H, m), 1.13 (3H, d, *J*=6.9 Hz, C4′CH_3), 0.97 (3H, d, *J*=6.9 Hz, C5H_3); ^{13}C NMR (151 MHz, $CDCl_3$) δ 203.2, 157.0, 140.3, 135.0, 128.7, 122.0, 108.6, 55.1, 42.5, 41.2, 38.4, 27.3, 27.2, 26.5, 21.6, 21.5, 20.3, 18.7.

*4.2.10. (5S,8R)-3,8-Dimethyl-5-[6-methylhept-5-en-2-(R)-yl]-1-methoxy-5,6,7,8-tetrahydronaphthalene (**12**).* To a stirred suspension of isopropyltriphenyl phosphonium iodide (111 mg, 0.26 mmol, 1.5 equiv) in THF (2 mL) at 0 °C was added *n*-BuLi (1.24 M in hexanes, 195 μL, 1.4 equiv). The deep orange solution was aged for 30 min prior to the cannulation of the aldehyde **11** (47 mg, 0.17 mmol) in THF (1 mL). The reaction was kept at 0 °C for 1 h then warmed to room temperature and stirred for a further 1 h. The reaction mixture was diluted with pentane (5 mL) then quenched with saturated aqueous NH_4Cl (5 mL), the product extracted with pentane (3×5 mL), the combined organic layers washed with brine (5 mL) and concentrated in vacuo. The crude oil was purified by column chromatography (buffered SiO_2, pentane/Et_2O 20:1) to afford the pure olefin **12** (48 mg, 0.16 mmol, 94%). $[\alpha]_D^{25}$ −42.5 (*c* 0.4, MeOH), ^1H NMR (600 MHz, $CDCl_3$) δ 6.61 (1H, s, C4*H*), 6.51 (1H, s, C2*H*), 5.01 (1H, t, *J*=7.0 Hz, C5′*H*), 3.81 (3H, s, OCH_3), 3.14 (1H, m, C8*H*), 2.58 (1H, m, C5*H*), 2.31 (3H, s, C3CH_3), 2.18–1.92 (2H, m), 1.91–1.87 (2H, m), 1.84–1.80 (1H, m), 1.72 (1H, m), [1.68 (3H, d, *J*=1.3 Hz) and 1.56 (3H, d, *J*=1.3 Hz) C7′H_3 and C6′CH_3], 1.49–1.46 (1H, m), 1.31–1.27 (1H, m), 1.15 (3H, d, *J*=6.9 Hz, C8CH_3), 1.09 (1H, m), 0.97 (3H, d, *J*=6.9 Hz, C1′H_3); ^{13}C NMR (151 MHz, $CDCl_3$) δ 157.0, 140.4, 134.6, 130.9, 128.6, 125.0, 122.1, 108.4, 53.5 42.4, 37.9, 33.4, 27.5, 26.5, 26.3, 25.7, 21.5, 21.4, 19.5, 18.8, 17.6.

*4.2.11. (5S,8R)-3,8-Dimethyl-5-[6′-methylhept-5′-en-2′-(R)-yl]-5,6,7,8-tetrahydronaphthalen-1-ol (**1**).* A solution of the methoxy serrulatane **12** (88 mg, 0.29 mmol) in DMF (3 mL) was degassed by stirring under N_2 for 30 min prior to the addition of NaSEt (246 mg, 2.9 mmol, 10 equiv). The mixture was refluxed for 2 h, cooled to room temperature and a second portion of NaSEt (123 mg, 1.45 mmol, 5 equiv) added. The mixture was returned to reflux for a further 3 h. After cooling to room temperature, the reaction was quenched with HCl (1 M, 2 mL) and the product extracted in Et_2O (3×5 mL). The combined organic layers were washed with brine (2×2 mL), dried over Na_2SO_4 and the solvent removed in vacuo. The crude oil was purified by column chromatography (buffered SiO_2, CH_2Cl_2/MeOH 9:1) to afford leubethanol (**1**) (73 mg, 0.24 mmol, 88%). $[\alpha]_D^{25}$ −32 (*c* 0.15, $CHCl_3$); IR ν_{max} film/cm^{-1} 3461, 2925, 1618, 1580, 1456; ^1H NMR (600 MHz, $CDCl_3$) δ 6.59 (1H, s, C4*H*), 6.42 (1H, s, C2*H*), 5.00 (1H, t, *J*=7.0 Hz, C5′*H*), 4.63 (1H, br s, O*H*), 3.06 (1H, m, C8*H*), 2.58 (1H, m, C5*H*), 2.24 (3H, s, C3CH_3), 1.98–1.95 (2H, m), 1.92–1.85 (2H, m), 1.84–1.80 (1H, m), 1.72 (1H, m), [1.68 (3H, d, *J*=1.3 Hz) and 1.55 (3H, d, *J*=1.3 Hz) C7′CH_3 and C6′CH_3], 1.49–1.46 (1H, m), 1.31–1.27 (1H, m), 1.20 (3H, d, *J*=6.9 Hz, C8CH_3), 1.06 (1H, m), 0.96 (3H, d, *J* 6.9, C1′H_3); ^{13}C NMR (151 MHz, $CDCl_3$) δ 153.0, 141.0, 135.0, 131.1, 126.3, 124.9, 122.4, 113.2, 42.4, 37.8, 33.4, 27.5, 26.6, 26.2, 25.7, 21.2, 21.1, 19.4, 18.7, 17.6. HRESIMS *m*/*z* 285.2220 (M−H) (calcd for $C_{20}H_{29}O$, 285.2212).

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Supplementary data

Copies of the ^1H NMR, ^{13}C NMR and Accurate Mass Spectra are available for compounds **6**, **2**, **10** & **1**. Copies of the ^1H NMR and ^{13}C NMR spectra are available for compounds **5**, **7**, **8**, **14** & **12** and the ^1H NMR spectrum for compound **13** is available. Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2013.05.082.

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