

Article

Total Synthesis and Absolute Configuration of the Marine Norditerpenoid Xestenone

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Received: 2 November 2009; in revised form: 19 November 2009 / Accepted: 23 November 2009 /

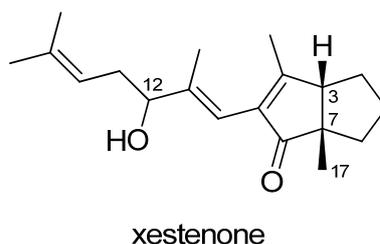
Published: 24 November 2009

Abstract: Xestenone is a marine norditerpenoid found in the northeastern Pacific sponge *Xestospongia vanilla*. The relative configuration of C-3 and C-7 in xestenone was determined by NOESY spectral analysis. However the relative configuration of C-12 and the absolute configuration of this compound were not determined. The authors have now achieved the total synthesis of xestenone using their developed one-pot synthesis of cyclopentane derivatives employing allyl phenyl sulfone and an epoxy iodide as a key step. The relative and absolute configurations of xestenone were thus successfully determined by this synthesis.

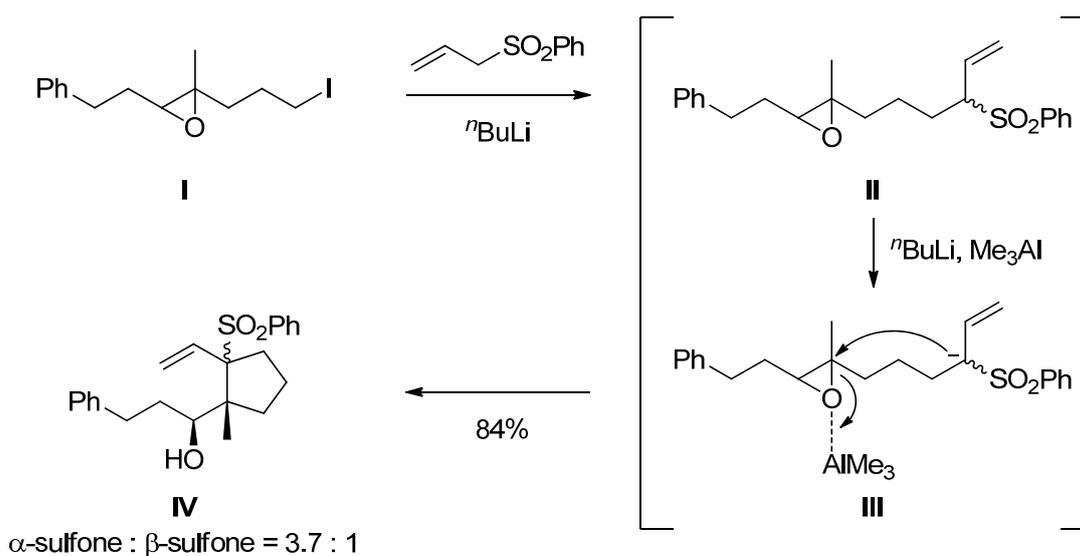
Keywords: xestenone; marine norditerpene; total synthesis; structural determination

1. Introduction

The norditerpenoid xestenone (Figure 1) was first isolated from the marine sponge *Xestospongia vanilla* in 1988 [1]. Its planar structure was determined by ¹H- and ¹³C-NMR and mass spectral analysis. The stereochemistry comprises two *cis* fused cyclopentane rings, as determined by the NOE correlation between the methyl protons at C-17 and the methine proton at C-3, although the relative configuration of C-12 and the absolute configuration were not determined. Moreover, no biological activity has been reported for xestenone, although various bioactive compounds that have been isolated from several *Xestospongia* sponges [2].

Figure 1. Structure of xestenone.

The authors recently reported a stereocontrolled one-pot synthesis of cyclopentane derivatives possessing a quaternary carbon, which involved: 1) reaction of an anion derived from allyl phenyl sulfone with epoxy iodide **I** to give epoxysulfone **II**; 2) *in situ* deprotonation of **II** to generate an epoxysulfone anion **III** and 3) intramolecular cyclization to give cyclopentane derivative **IV** (Scheme 1) [3]. This one-pot synthesis of cyclopentane derivatives has now been applied to the total synthesis of xestenone, and in this paper the authors wish to report on the successful total synthesis of xestenone and its complete structural determination.

Scheme 1. One-pot synthesis of cyclopentane derivatives.

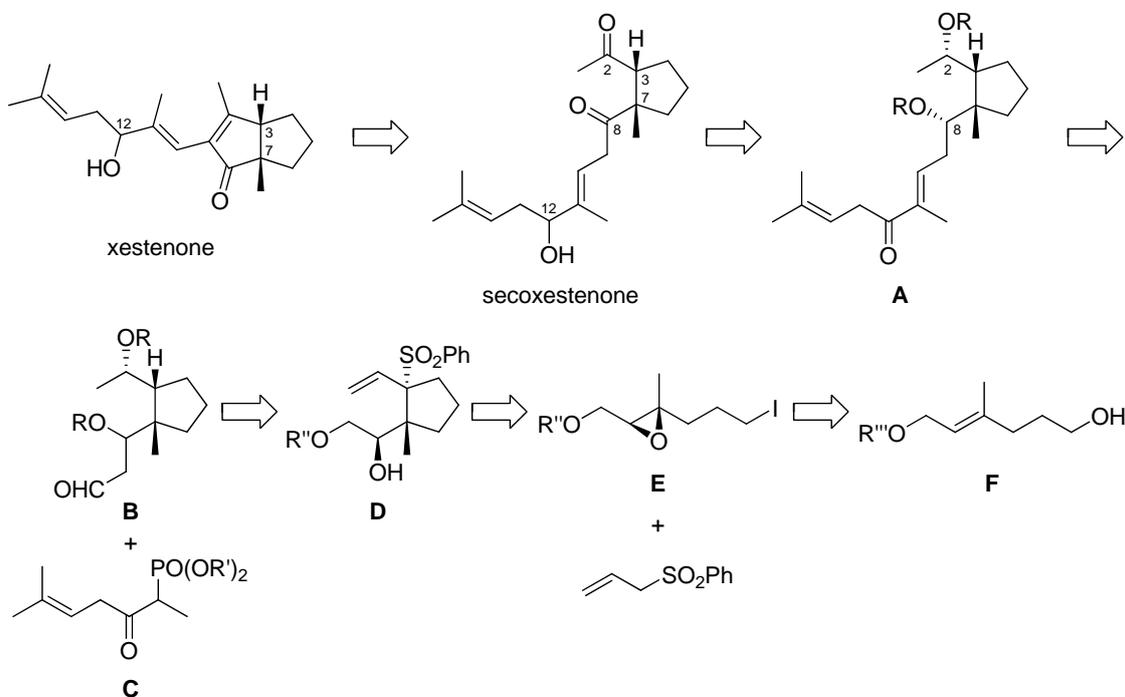
2. Results and Discussion

2.1. Retrosynthetic analysis

The authors planned to synthesize both xestenone and 12-*epi*-xestenone, since the relative configuration at C-12 of xestenone was unknown at the onset (Scheme 2). Xestenone was obtained from secoxestenone by intramolecular aldol condensation [4]. Secoxestenone would be obtained from α,β -unsaturated ketone **A** by 1,2-reduction of α,β -unsaturated ketone at C-12 and oxidation of the hydroxy group at C-2 and C-8. The α,β -unsaturated ketone **A** would be obtained from aldehyde **B** by the Horner-Wadsworth-Emmons reaction using known phosphonate **C** [5]. For the right hand fragment of xestenone, aldehyde **B** would be synthesized from cyclopentane **D** through various chemical

functionalizations. Cyclopentane **D** would be constructed by our developed stereocontrolled one-pot synthesis of cyclopentane derivatives using trisubstituted epoxy iodide **E** and allyl phenyl sulfone [3]. Epoxy iodide **E** would be obtained from alcohol **F**.

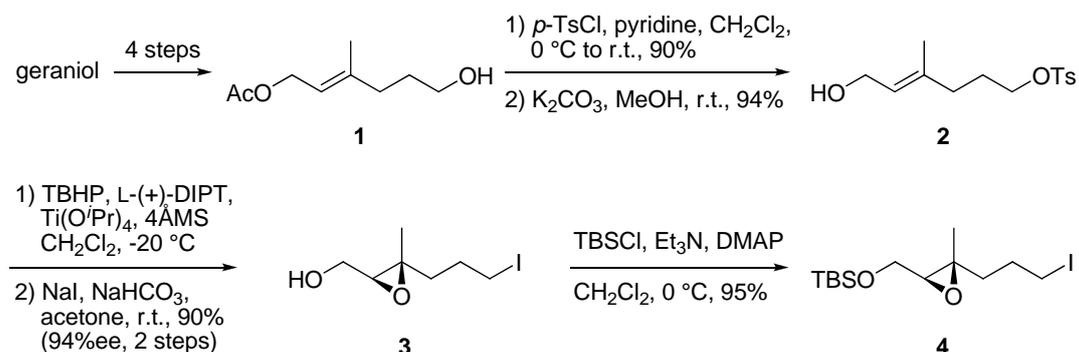
Scheme 2. Retrosynthetic analysis of xestenone.



2.2. Synthesis of xestenone

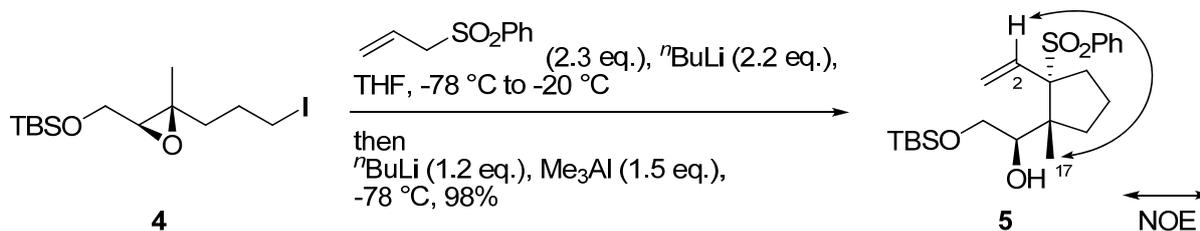
Geraniol was converted to alcohol **1** by known procedures [6]. Alcohol **1** was treated with *p*-TsCl and pyridine to give the corresponding tosylate (90%), which was deacetylated with K_2CO_3 in MeOH to furnish allylic alcohol **2** (94%; Scheme 3). Allylic alcohol **2** was converted to chiral β -epoxyalcohol using Sharpless asymmetric epoxidation under standard conditions [7] (94% ee). Iodination of the epoxy alcohol with NaI and $NaHCO_3$ furnished epoxy iodide **3** (90%, 2 steps). Protection of the primary hydroxy group in **3** as the TBS ether gave the desired chiral epoxy iodide **4** (95%).

Scheme 3. Synthesis of epoxy iodide **4**.



The sulfonyl carbanion prepared from allyl phenyl sulfone (2.3 eq.) and n BuLi (2.2 eq.) was reacted with epoxy iodide **4** at -20 °C. Following confirmation of the disappearance of **4** by TLC, n BuLi (1.2 eq.) and Me_3Al (1.5 eq.) were added at -78 °C to give cyclopentane **5** as the sole product (98%; Scheme 4). The *trans*-configuration of the vinyl and 1-hydroxy-2-silyloxyethyl groups in cyclopentane **5** was determined by NOE correlation between the vinyl proton at C-2 and methyl protons at C-17. The stereoselectivity of this reaction is presumably the result of steric hindrance between the phenyl sulfonyl group and the 1-hydroxy-2-silyloxyethyl group in the intermediate sulfonyl carbanion.

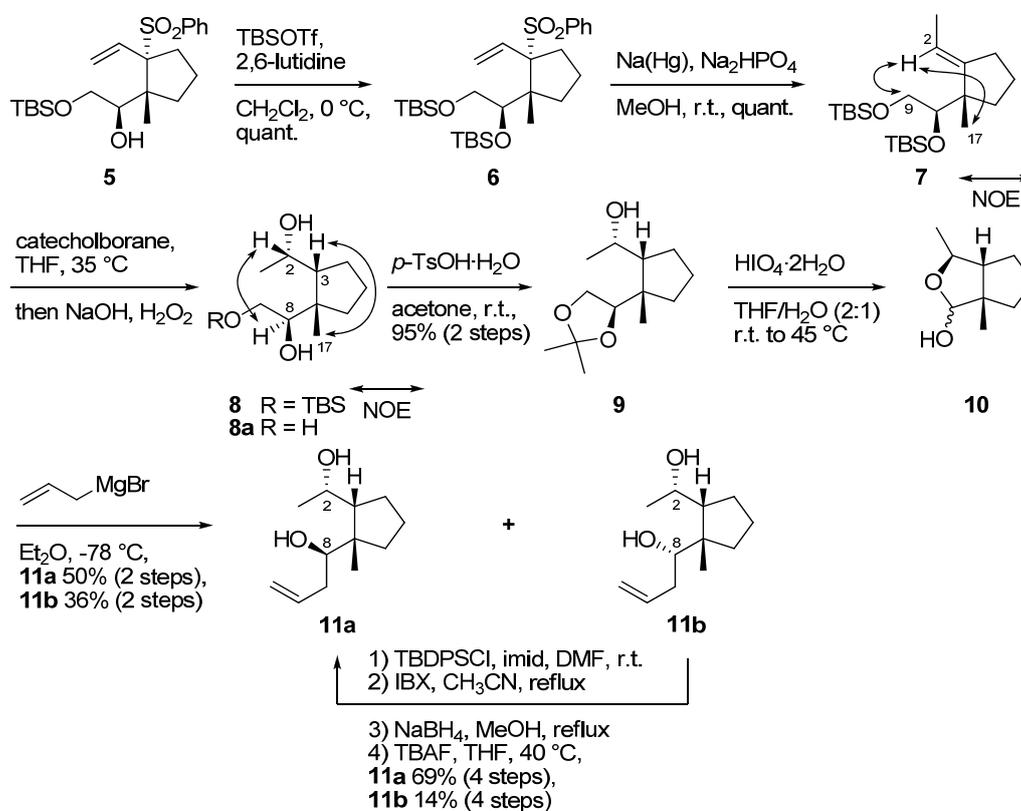
Scheme 4. Synthesis of intermediate **5**.



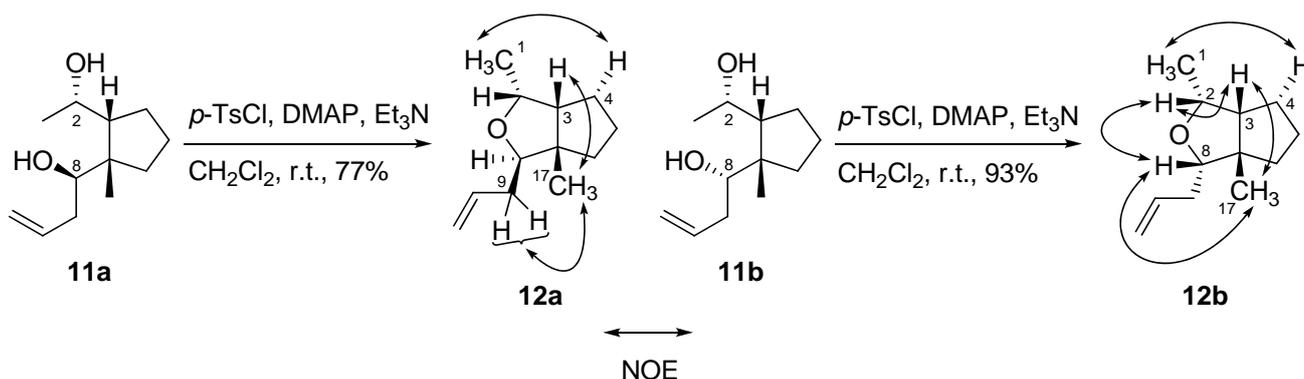
Protection of the secondary hydroxy group of **5** with TBSOTf and 2,6-lutidine (Scheme 5) furnished bis-silyl ether **6** (quant.). The phenylsulfonyl group in **6** was removed by treatment with Na(Hg) and Na_2HPO_4 to give trisubstituted (*E*)-olefin **7** as a sole product (quant.). The *E*-configuration of the trisubstituted olefin in **7** was determined by NOE correlation between the vinyl proton at C-2 and methyl protons at C-17, and the vinyl proton at C-2 and methylene protons at C-9. Diastereoselective hydroboration-oxidation of *E*-olefin **7** with catecholborane furnished a mixture of diol **8** and triol **8a**. The stereochemistry of diol **8** was elucidated by NOESY spectral analysis. The NOE correlation between the methyl protons at C-17 and methine proton at C-3, and the methine proton at C-2 and methine proton at C-8 in diol **8** suggested that the methyl group and methine proton of cyclopentane were oriented in the same β -configuration. The mixture of diol **8** and triol **8a** was treated with *p*-TsOH \cdot H_2O in acetone to give acetonide **9** (95%, 2 steps). Subsequent deprotection of the acetonide group in **9** and oxidative cleavage of the 1,2-diol with $\text{HIO}_4 \cdot 2\text{H}_2\text{O}$ afforded hemiacetal **10**, which was converted to homoallylic alcohols **11a** (50%, 2 steps) and **11b** (36%, 2 steps). These alcohols were easily separated by silica gel chromatography. The relative configurations of these homoallylic alcohols **11a** and **11b** were determined by chemical conversion and NOESY spectral analysis. Compounds **11a** and **11b** were converted to tetrahydrofurans **12a** and **12b** by treatment with *p*-TsCl, DMAP and Et_3N (Scheme 6). The NOE correlations of **12a** between the methylene protons at C-9 and methyl protons at C-17, and one of the methylene protons at C-4 and methyl protons at C-1 suggested that the C-1 methyl group and allyl group were oriented on different faces of the tetrahydrofuran ring, therefore, the stereochemistry of the hydroxy group at C-8 in homoallylic alcohol **11a** was found to adopt a β -configuration. The NOE correlations of **12b** between the methine proton at C-2 and methine proton at C-3, the methine proton at C-2 and methine proton at C-8, the methine proton at C-8 and methyl protons at C-17, the methine proton at C-3 and methyl protons at C-17, and the methyl protons at C-1 and one of the methylene protons at C-4 were observed. The results suggested that the C-1 methyl group and allyl group were oriented on the same face of the

tetrahydrofuran ring. Therefore, the stereochemistry of the hydroxy group at C-8 in homoallylic alcohol **11b** was found to adopt an α -configuration. Both homoallylic alcohols **11a** and **11b** could be converted to xestenone. However, the chemical yield of the later steps in this synthesis from α -alcohol **11b** was low. Therefore, α -alcohol **11b** was converted into β -alcohol **11a** by inversion of the C-8 stereocenter. The hydroxy group at C-2 in α -alcohol **11b** was protected with TBDPSCI and imidazole to give TBDPS ether, which was oxidized with IBX [8] to afford the ketone. Diastereoselective reduction of the ketone with NaBH_4 to the alcohol, followed by deprotection of the TBDPS group with TBAF furnished a mixture of the desired β -alcohol **11a** (69%, 4 steps) and α -alcohol **11b** (14%, 4 steps).

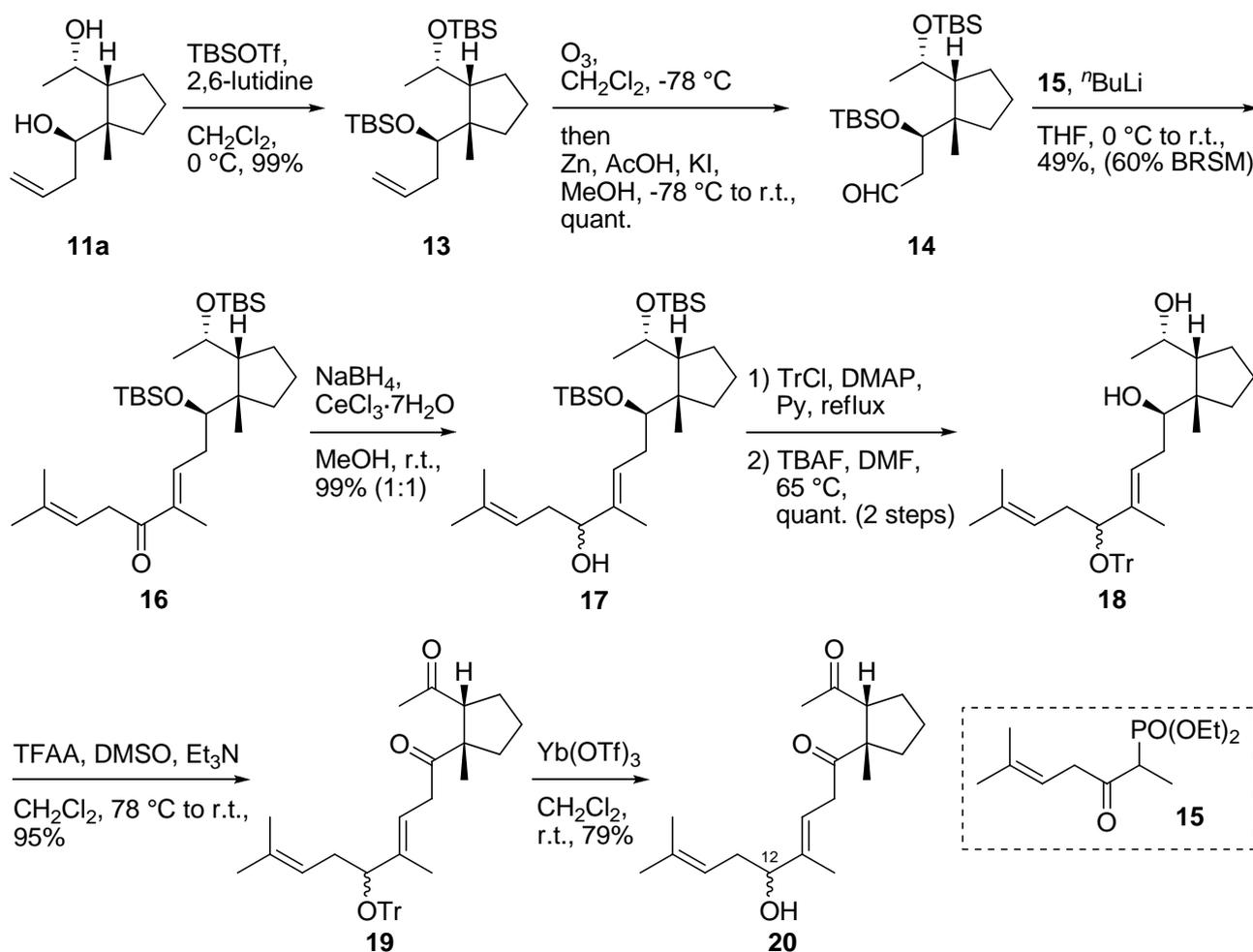
Scheme 5. Synthesis of diols **11a** and **11b**.



Scheme 6. Determination of the relative configuration of **11a** and **11b**.



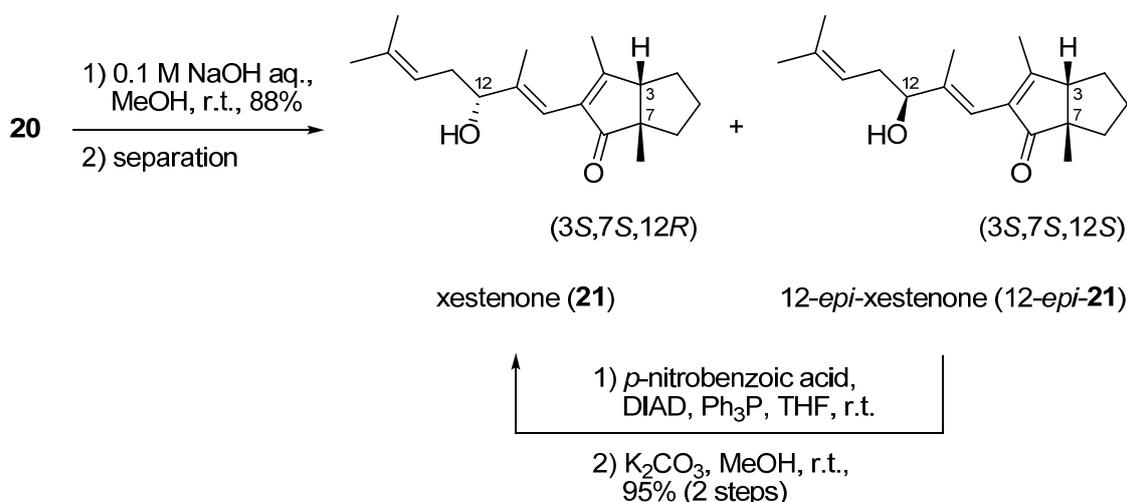
β -Alcohol **11a** was converted to bis-silyl ether **13** by treatment with TBSOTf and 2,6-lutidine (99%), and was followed by ozonolysis to give aldehyde **14** (quant.), thereby completing the synthesis of the right hand fragment of xestenone in 14 steps from known alcohol **1** [6] (Scheme 7). Treatment of aldehyde **14** with the anion of phosphonate **15** [5] in THF at r.t. provided α,β -unsaturated ketone **16** (49%). 1,2-Reduction of the α,β -unsaturated ketone **16** with NaBH₄ in the presence of CeCl₃·7H₂O in MeOH [9] furnished allylic alcohol **17** as an inseparable mixture (99%, 1:1). Protection of the hydroxy group in allylic alcohol **17** with TrCl and DMAP in pyridine provided the trityl ether, and was followed by desilylation with TBAF to give diol **18** (quant., 2 steps). Oxidation of two hydroxy groups in diol **18** with TFAA, DMSO and Et₃N generated diketone **19** (95%). Lewis acid-mediated deprotection of the trityl group in diketone **19** with Yb(OTf)₃ furnished diketone **20** as an inseparable diastereomeric mixture of the hydroxy group at C-12 (79%). Diketone **20** corresponds to secoxestenone.

Scheme 7. Synthesis of diketone **20**.

Finally, intramolecular aldol condensation of diketone **20** was achieved by treatment with 0.1 M NaOH aq. to furnish a diastereomeric mixture of xestenone **21** and 12-*epi*-**21** (88%; Scheme 8). Separation of the diastereomeric mixture using a chiral HPLC column gave **21** {[α]_D²⁵ +2.2° (*c* 0.08, MeOH)}, and 12-*epi*-**21** {[α]_D²⁵ -113.7° (*c* 0.09, MeOH)}. The optical rotation of synthetic **21** is not

identical, but very close to the value obtained for the natural product $\{[\alpha]_D^{20} (c\ 1.00, \text{MeOH})\}$ [1]. Moreover, the CD spectrum of the synthetic **21** matched that of the natural product [1]. The CD spectrum of the synthetic **21** showed a positive Cotton effect at 323 nm and a negative Cotton effect at 258 nm. The absolute configuration of the hydroxy group at C-12 in **21** was determined by comparing the $^1\text{H-NMR}$ data of the two diastereomeric esters (MPA esters) [10]. The absolute configuration of the hydroxy group at C-12 in 12-*epi*-**21** was determined by the same method. As a result, the absolute stereochemistry of the three chiral centers in xestenone was determined to be 3*S*, 7*S* and 12*R*. 12-*epi*-xestenone (12-*epi*-**21**) was converted to xestenone (**21**) by a Mitsunobu reaction.

Scheme 8. Synthesis of xestenone (**21**).



3. Experimental Section

3.1. General

Optical rotations were measured using a Jasco P-1030 polarimeter. Melting points (mp) were measured using a Yazawa melting point apparatus BY-2 and are uncorrected. IR spectra were recorded using a Jasco FT-IR/620 spectrometer. UV spectra were recorded using a Jasco V-550 spectrophotometer. Circular dichroism (CD) spectra were measured with a Jasco J-720 spectropolarimeter. $^1\text{H-}$ and $^{13}\text{C-NMR}$ spectra were recorded on a Bruker DRX-400 or a Bruker Biospin AV-600 spectrometer. Chemical shifts are given on the δ (ppm) scale using tetramethylsilane (TMS) as the internal standard (s, singlet; d, doublet; t, triplet; q, quartet; quint, quintet; m, multiplet; br, broad). High resolution ESIMS (HRESIMS) spectra were obtained using a Micromass LCT spectrometer. Elemental analysis data were obtained using an Elemental Vavio EL. Flash column chromatography was performed using Kanto Chemical Silica Gel 60N (spherical, neutral) 40–50 μm .

3.2. (*E*)-6-Hydroxy-4-methylhex-4-enyl 4-methylbenzenesulfonate (**2**)

To a solution of (*E*)-6-hydroxy-3-methylhex-2-enyl acetate [6] (**1**, 530 mg, 3.08 mmol) in CH₂Cl₂ (10.3 mL) were added pyridine (374 μL , 4.62 mmol) and *p*-toluenesulfonyl chloride (705 mg,

3.70 mmol) at 0 °C. After stirring for 5 hr at r.t., the mixture was diluted with Et₂O, washed with H₂O and brine, and then dried. Removal of the solvent gave a residue which was then purified by silica gel column chromatography (hexane/AcOEt = 2:1) to generate tosylate (905 mg, 90% yield) as a colorless oil. IR (neat) 2924, 1733, 1359 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃) δ ppm: 7.77 (2H, d, *J* = 8.2 Hz), 7.33 (2H, d, *J* = 8.2 Hz), 5.25 (1H, m), 4.52 (2H, d, *J* = 7.2 Hz), 4.01 (2H, t, *J* = 6.4 Hz), 2.44 (3H, s), 2.05 (2H, t, *J* = 7.2 Hz), 2.03 (3H, s), 1.77 (2H, m), 1.64 (3H, s); ¹³C-NMR (100 MHz, CDCl₃) δ ppm: 170.9, 144.7, 133.3, 129.8, 127.8, 119.6, 69.8, 61.0, 35.0, 26.8, 21.5, 20.9, 16.2; HRESIMS (*m/z*) calcd. for C₁₆H₂₃O₅S (M+H)⁺ 349.1086, found 349.1086; Anal. Calcd. for C₁₆H₂₂O₅S: C, 58.87; H, 6.79. Found: C, 58.94; H, 6.75.

To a solution of the above tosylate (9.47 g, 29.0 mmol) in MeOH (290 mL) was added K₂CO₃ (4.81 g, 34.8 mmol) at r.t. After stirring for 30 min at the same temperature, the mixture was diluted with Et₂O and then filtered through a silica gel pad. Removal of the solvent gave a residue which was then purified by silica gel column chromatography (hexane/AcOEt = 2:1) to generate allylic alcohol **2** (7.74 g, 94% yield) as a colorless oil. IR (neat) 3387, 2923, 1354 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃) δ ppm: 7.75 (2H, d, *J* = 8.2 Hz), 7.32 (2H, d, *J* = 8.2 Hz), 5.31 (1H, m), 4.07 (2H, d, *J* = 6.5 Hz), 4.00 (2H, t, *J* = 6.5 Hz), 2.42 (3H, s), 2.02 (2H, t, *J* = 7.8 Hz), 1.76 (2H, m), 1.59 (3H, s), 1.52 (1H, br s); ¹³C-NMR (100 MHz, CDCl₃) δ ppm: 144.7, 137.2, 133.2, 129.8, 127.8, 124.7, 69.8, 59.0, 35.0, 26.6, 21.5, 15.9; HRESIMS (*m/z*) calcd. for C₁₄H₂₁O₄S (M+H)⁺ 307.0980, found 307.0994; Anal. Calcd. for C₁₄H₂₀O₄S: C, 59.13; H, 7.09. Found: C, 59.07; H, 7.06.

3.3. ((2*S*,3*S*)-3-(3-Iodopropyl)-3-methyloxiran-2-yl)methanol (**3**)

To a cold (-20 °C) suspension of 4Å molecular sieves (114 mg) in CH₂Cl₂ (1.6 mL) were added L-(+)-DIPT (5.2 μL, 24.8 μmol), Ti(O^{*i*}Pr)₄ (6.2 μL, 21.0 μmol) and TBHP (164 μL, 101 mmol, 6.17 M in CH₂Cl₂ solution). After stirring for 30 min at the same temperature, a solution of allylic alcohol **2** (54.4 mg, 191 μmol) in CH₂Cl₂ (500 μL) was added over 5 min. After stirring at -20 °C for 15 min, NaOH (13.0 μL, 30% in saturated aqueous NaCl) was added. The mixture was diluted with Et₂O, warmed to r.t. and stirred for 10 min. MgSO₄ (11.6 mg) and Celite (1.4 mg) were then added and after stirring for 15 min, the mixture was filtered through a Celite pad and the filtrate was concentrated under reduced pressure to afford the crude epoxide. To a solution of the crude epoxide in acetone (1.9 mL) were added NaHCO₃ (17.7 mg, 210 μmol) and NaI (286 mg, 1.91 mmol) at r.t. After stirring for 8 hr at the same temperature, the mixture was diluted with Et₂O and then filtered through a silica gel pad. Removal of the solvent gave a residue which was then purified by silica gel column chromatography (hexane/AcOEt = 1:2) to generate epoxy iodide **3** (44.0 mg, 90% yield) as a yellow oil. [α]_D²⁸ -10.0 (*c* 1.03, CHCl₃); IR (neat) 3418, 2929 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃) δ ppm: 3.79 (1H, m), 3.68 (1H, m), 3.18 (2H, m), 2.97 (2H, t, *J* = 5.4 Hz), 1.99 (1H, br s), 1.93 (2H, m), 1.64 (2H, m), 1.29 (3H, s); ¹³C-NMR (100 MHz, CDCl₃) δ ppm: 62.6, 61.2, 60.3, 39.0, 29.0, 16.8, 5.8; HRESIMS (*m/z*) calcd. for C₇H₁₂IO (M-OH)⁺ 238.9933, found 238.9930; Anal. Calcd. for C₇H₁₃IO₂: C, 32.83; H, 5.12. Found: C, 33.06; H, 5.26.

3.4. *tert*-Butyl(((2*S*,3*S*)-3-(3-iodopropyl)-3-methyloxiran-2-yl)methoxy)dimethylsilane (**4**)

To a solution of epoxy iodide **3** (387 mg, 1.51 mmol) in CH₂Cl₂ (1.5 mL) were added Et₃N (253 mg, 1.82 mmol), DMAP (185 mg, 1.51 mmol) and TBSCl (251 mg, 1.82 mmol) and the mixture was stirred at r.t. for 30 min. The mixture was diluted with Et₂O, washed with saturated aqueous NaHCO₃ solution, H₂O and brine, and then dried. Removal of the solvent gave a residue which was then purified by silica gel column chromatography (hexane/AcOEt = 7:1) to generate epoxy iodide **4** (530 mg, 95% yield) as a colorless oil. $[\alpha]_D^{25} +6.9$ (*c* 1.06, CHCl₃); IR (neat) 2929 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃) δ ppm: 3.76 (1H, dd, *J* = 11.5, 5.5 Hz), 3.69 (1H, dd, *J* = 11.5, 5.5 Hz), 3.19 (2H, t, *J* = 7.0 Hz), 2.91 (1H, t, *J* = 5.5 Hz), 1.95 (2H, m), 1.64 (2H, m), 1.26 (3H, s), 0.91 (9H, s), 0.07 (6H, s); ¹³C-NMR (100 MHz, CDCl₃) δ ppm: 62.8, 62.0, 59.5, 39.0, 29.2, 25.9, 18.3, 16.7, 5.8, -5.2, -5.4; HRESIMS (*m/z*) calcd. for C₁₃H₂₈IO₂Si (M+H)⁺ 371.0903, found 371.0921; Anal. Calcd. for C₁₃H₂₇IO₂Si: C, 42.16; H, 7.35. Found: C, 42.37; H, 7.23.

3.5. (*R*)-1-[(1*R*,2*S*)-2-Benzenesulfonyl-1-methyl-2-vinylcyclopentyl]-2-(*tert*-butyldimethylsiloxy)ethanol (**5**)

To a solution of allyl phenyl sulfone (95.2 mg, 0.552 mmol) in THF (3.0 mL) was added ⁿBuLi (317 μL, 0.500 mmol, 1.58 M in hexane solution) at -78 °C and the mixture was warmed to 0 °C. The mixture was stirred for 30 min at the same temperature. After cooling to -78 °C, a solution of epoxy iodide **4** (84.1 mg, 0.227 mmol) in THF (1.6 mL) was added and the mixture was warmed to -20 °C. The mixture was stirred for 30 min at the same temperature. After cooling to -78 °C, ⁿBuLi (173 μL, 0.273 mmol, 1.58 M in hexane solution) was added and the mixture was warmed to -20 °C. The mixture was stirred for 30 min at the same temperature. After cooling to -78 °C, Me₃Al (331 μL, 0.341 mmol, 1.03 M in hexane) was added. After stirring for 1 hr at the same temperature, the mixture was diluted with Et₂O, washed with saturated aqueous NH₄Cl solution, H₂O and brine, and then dried. Removal of the solvent gave a residue which was then purified by silica gel column chromatography (hexane/AcOEt = 10:1) to generate cyclopentane **5** (94.4 mg, 98% yield) as a white solid. mp 125–126 °C; $[\alpha]_D^{25} -114$ (*c* 0.81, CHCl₃); IR (KBr) 3560, 2952 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃) δ ppm: 7.78 (2H, m), 7.57 (1H, m), 7.45 (2H, m), 6.19 (1H, dd, *J* = 17.4, 10.9 Hz), 5.25 (1H, d, *J* = 10.9 Hz), 4.73 (1H, d, *J* = 17.4 Hz), 4.56 (1H, dt, *J* = 6.2, 2.9 Hz), 4.29 (1H, dd, *J* = 9.5, 3.5 Hz), 3.67 (1H, t, *J* = 8.8 Hz), 3.23 (1H, d, *J* = 2.9 Hz), 2.57 (1H, m), 2.06 (3H, m), 1.73 (2H, m), 0.99 (3H, s), 0.93 (9H, s), 0.14 (6H, s); ¹³C-NMR (100 MHz, CDCl₃) δ ppm: 137.4, 135.3, 133.3, 130.6, 127.9, 120.3, 81.0, 74.3, 64.2, 54.6, 37.2, 30.8, 25.9, 20.0, 19.6, 18.2, -5.1, -5.3; HRESIMS (*m/z*) calcd. for C₂₂H₃₇O₄SSi (M+H)⁺ 425.2182, found 425.2179; Anal. Calcd. for C₂₂H₃₆O₄SSi: C, 62.22; H, 8.54. Found: C, 62.11; H, 8.41.

3.6. {(1*S*,2*R*)-2-[(*R*)-1,2-Bis(*tert*-butyldimethylsiloxy)ethyl]-2-methyl-1-vinylcyclopentanesulfonyl}benzene (**6**)

To a solution of cyclopentane **5** (7.01 g, 16.5 mmol) in CH₂Cl₂ (16.5 mL) were added 2,6-lutidine (17.7 g, 165 mmol) and TBSOTf (7.02 g, 26.6 mmol) and the mixture was stirred at 0 °C for 30 min.

The mixture was diluted with Et₂O, washed with saturated aqueous NaHCO₃ solution, H₂O and brine, and then dried. Removal of the solvent gave a residue which was then purified by silica gel column chromatography (hexane/AcOEt = 5:1) to generate bis-silyl ether **6** (8.89 g, quantitative yield) as a colorless oil. $[\alpha]_D^{25}$ -77.9 (*c* 1.62, CHCl₃); IR (neat) 2954, 1133 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃) δ ppm: 7.78 (2H, m), 7.57 (1H, m), 7.45 (2H, m), 6.37 (1H, dd, *J* = 17.4, 10.9 Hz), 5.27 (1H, d, *J* = 10.9), 4.72 (1H, d, *J* = 17.4 Hz), 4.63 (1H, dd, *J* = 5.9, 1.8 Hz), 4.15 (1H, dd, *J* = 10.5, 1.8 Hz), 3.87 (1H, dd, *J* = 10.5, 5.9), 2.51 (1H, m), 2.12 (1H, m), 2.01 (1H, m), 1.90 (3H, m), 0.92 (21H, m), 0.16 (12H, m); ¹³C-NMR (100 MHz, CDCl₃) δ ppm: 137.3, 135.3, 133.2, 130.7, 127.9, 120.7, 81.1, 77.2, 66.5, 56.3, 40.0, 31.6, 26.3, 26.2, 19.8, 19.0, 18.5, -3.3, -4.6, -5.1, -5.4; HRESIMS (*m/z*) calcd. for C₂₈H₅₁O₄SSi₂ (M+H)⁺ 539.3047, found 539.3086; Anal. Calcd. for C₂₈H₅₀O₄SSi₂: C, 62.40; H, 9.35. Found: C, 62.37; H, 9.11.

3.7. (S)-1-[(R)-1,2-Bis(tert-butyl dimethylsiloxy)ethyl]-2-ethylidene-1-methylcyclopentane (**7**)

To a solution of bis-silyl ether **6** (9.29 g, 17.2 mmol) in MeOH (344 mL) were added Na₂HPO₄ (17.1 g, 120.5 mmol) and 5% Na(Hg) (31.6 g). After stirring for 1 hr at r.t., the mixture was diluted with Et₂O and filtered through silica gel. The filtrate was then concentrated under reduced pressure. The resultant residue was then purified by silica gel column chromatography (hexane only) to generate *E*-olefin **7** (6.86 g, quantitative yield) as a colorless oil. $[\alpha]_D^{25}$ +19.0 (*c* 1.35, CHCl₃); IR (neat) 2955 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃) δ ppm: 5.17 (1H, m), 3.78 (1H, dd, *J* = 10.3, 2.8 Hz), 3.52 (1H, dd, *J* = 9.2, 1.8 Hz), 3.46 (1H, dd, *J* = 10.3, 5.8 Hz), 2.35 (1H, m), 2.08 (2H, m), 1.67 (1H, m), 1.58 (3H, d, *J* = 6.7 Hz), 1.53 (2H, m), 1.22 (1H, m), 0.97 (3H, s), 0.88 (9H, s), 0.86 (9H, s), 0.07 (3H, s), 0.03 (3H, s), 0.03 (3H, s), 0.00 (3H, s); ¹³C-NMR (100 MHz, CDCl₃) δ ppm: 150.2, 114.1, 79.1, 66.3, 49.5, 35.7, 30.0, 26.1, 26.0, 23.9, 22.5, 18.4, 18.3, 14.7, -3.9, -5.0, -5.3; HRESIMS (*m/z*) calcd. for C₂₂H₄₆O₂Si₂Na (M+Na)⁺ 421.2934, found 421.2914; Anal. Calcd. for C₂₂H₄₆O₂Si₂: C, 66.26; H, 11.63. Found: C, 66.36; H, 11.50.

3.8. (S)-1-[(1R,2S)-2-[(R)-2,2-Dimethyl-[1,3]dioxolan-4-yl]-2-methylcyclopentyl]ethanol (**9**)

To a solution of *E*-olefin **7** (3.86 g, 9.69 mmol) in THF (19.4 mL) was added catecholborane (6.40 mL, 60.1 mmol) dropwise at 0 °C. After stirring for 12 hr at the same temperature, 1M NaOH solution (12.9 mL) and 35% aqueous H₂O₂ solution (36.9 mL) were added to the mixture at r.t. After stirring for 2 hr, the resultant mixture was diluted with CHCl₃, washed with H₂O and brine, dried and then concentrated to afford a mixture of diol **8** and triol **8a**. To a solution of the crude alcohols in acetone (96.9 mL) was added *p*-TsOH·H₂O (735 mg, 3.88 mmol) at r.t. After stirring for 2 hr at the same temperature, the mixture was diluted with Et₂O, washed with saturated aqueous NaHCO₃ solution, H₂O and brine, and then dried. Removal of the solvent gave a residue which was then purified by silica gel column chromatography (hexane/acetone = 4:1) to generate acetone **9** (2.11 g, 95% yield) as a colorless oil. $[\alpha]_D^{25}$ +4.0 (*c* 0.58, CHCl₃); IR (neat) 3443, 2956 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃) δ ppm: 4.42 (1H, dd, *J* = 8.5, 6.5 Hz), 4.01 (1H, m), 3.96 (1H, dd, *J* = 7.8, 6.5 Hz), 3.66 (1H, t, *J* = 8.2 Hz), 2.07 (1H, s), 1.89 (1H, m), 1.69–1.50 (4H, m), 1.41 (3H, s), 1.35 (3H, s), 1.37–1.33 (2H, m), 1.20 (3H, d, *J* = 6.2 Hz), 1.07 (3H, s); ¹³C-NMR (100 MHz, CDCl₃) δ ppm: 108.5, 79.9, 69.3,

66.9, 59.1, 45.1, 35.0, 31.2, 27.8, 26.5, 25.3, 24.2, 23.3; HRESIMS (m/z) calcd. for $C_{13}H_{25}O_3$ ($M+H$)⁺ 229.1804, found 229.1810; Anal. Calcd. for $C_{13}H_{24}O_3$: C, 68.38; H, 10.59. Found: C, 68.43; H, 10.59.

3.9. (*R*)-1-[(1*S*,2*R*)-2-((*S*)-1-Hydroxyethyl)-1-methylcyclopentyl]but-3-en-1-ol (**11a**) and (*S*)-1-[(1*S*,2*R*)-2-((*S*)-1-hydroxyethyl)-1-methylcyclopentyl]but-3-en-1-ol (**11b**)

To a solution of acetonide **9** (2.11 g, 9.24 mmol) in THF was added a solution of $HIO_4 \cdot 2H_2O$ (12.6 g, 55.4 mmol) in H_2O (93.0 mL) at r.t. After stirring for 3 hr at 45 °C, the mixture was diluted with Et_2O , washed with H_2O and brine, dried and then concentrated to afford crude hemiacetal **10**. To a solution of crude hemiacetal **10** in Et_2O (93.0 mL) was added allyl magnesium bromide (33.0 mL, 32.3 mmol, 1.0 M in Et_2O solution) at -78 °C. After stirring for 1 hr at 0 °C, the mixture was diluted with Et_2O , washed with saturated aqueous NH_4Cl solution, H_2O and brine, and then dried. Removal of the solvent gave a residue which was then purified by silica gel column chromatography (hexane/ $AcOEt$ = 8:1) to generate diol **11a** (914 mg, 50% yield) as a colorless oil and diol **11b** (650 mg, 36 % yield) as a white solid. Compound **11a**: $[\alpha]_D^{25}$ -5.0 (c 0.39, $CHCl_3$); IR (neat) 3306, 2955 cm^{-1} ; 1H -NMR (400 MHz, $CDCl_3$) δ ppm: 5.87 (1H, m), 5.19 (1H, d, J = 10.4 Hz), 5.18 (1H, d, J = 16.8 Hz), 3.86 (1H, m), 3.68 (1H, dd, J = 10.5, 2.3 Hz), 3.18 (2H, br s), 2.34 (1H, m), 2.13 (1H, m), 1.80 (1H, m), 1.62–1.34 (5H, m), 1.22 (1H, m), 1.17 (3H, d, J = 6.2 Hz), 1.09 (3H, s); ^{13}C -NMR (100 MHz, $CDCl_3$) δ ppm: 136.1, 118.7, 72.5, 69.2, 58.8, 47.8, 39.5, 37.1, 30.2, 22.7, 22.5, 22.4; HRESIMS (m/z) calcd. for $C_{12}H_{23}O_2$ ($M+H$)⁺ 199.1698, found 199.1713; Anal. Calcd. for $C_{12}H_{22}O_2$: C, 72.68; H, 11.18. Found: C, 72.40; H, 10.99. Compound **11b**: mp 93–95 °C; $[\alpha]_D^{25}$ -35.0 (c 0.20, $CHCl_3$); IR (KBr) 3351, 2953 cm^{-1} ; 1H -NMR (400 MHz, $CDCl_3$) δ ppm: 5.30 (1H, m), 5.18 (1H, d, J = 10.2 Hz), 5.17 (1H, d, J = 16.9 Hz), 4.11 (1H, m), 3.76 (1H, dd, J = 10.8, 2.1 Hz), 2.48 (1H, m), 2.27 (2H, br s), 2.13 (1H, m), 1.85 (1H, m), 1.67 (2H, m), 1.60 (2H, m), 1.45 (2H, m), 1.22 (3H, d, J = 6.2 Hz), 1.19 (3H, s); ^{13}C -NMR (100 MHz, $CDCl_3$) δ ppm: 136.2, 118.6, 75.7, 69.5, 59.5, 47.5, 37.8, 36.5, 32.0, 29.5, 23.9, 23.4; HRESIMS (m/z) calcd. for $C_{12}H_{23}O_2$ ($M+H$)⁺ 199.1698, found 199.1681; Anal. Calcd. for $C_{12}H_{22}O_2$: C, 72.68; H, 11.18. Found: C, 72.65; H, 10.91.

3.10. (1*R*,2*R*,3*aS*,3*R*)-3-Allyl-1,3*a*-dimethylhexahydrocyclopenta[*c*]furan (**12a**)

To a solution of diol **11a** (34.4 mg, 0.174 mmol) in CH_2Cl_2 (1.7 mL) were added Et_3N (105 mg, 1.04 mmol), DMAP (106 mg, 0.868 mmol) and *p*-toluenesulfonyl chloride (132 mg, 0.694 mmol) at r.t. The mixture was stirred for two days at the same temperature. The mixture was diluted with Et_2O , washed with saturated aqueous NH_4Cl solution, H_2O and brine, and then dried. Removal of the solvent gave a residue which was then purified by silica gel column chromatography (hexane/ $AcOEt$ = 10:1) to generate tetrahydrofuran **12a** (24.1 mg, 77% yield) as a colorless oil. $[\alpha]_D^{26}$ +21.5 (c 1.58, $CHCl_3$); IR (neat) 2953, 2870 cm^{-1} ; 1H -NMR (400 MHz, $CDCl_3$) δ ppm: 5.84 (1H, m), 5.09 (1H, m), 5.03 (1H, m), 4.25 (1H, quint., J = 6.5 Hz), 3.64 (1H, dd, J = 9.0, 4.8 Hz), 2.30–2.15 (2H, m), 2.07 (1H, m), 1.68–1.59 (5H, m), 1.46 (1H, m), 1.16 (3H, d, J = 6.5 Hz), 1.07 (3H, s); NOESY correlations (H/H): H-1/H-4; H-3/H-17; H-9/H-17; ^{13}C -NMR (100 MHz, $CDCl_3$) δ ppm: 136.7, 116.4, 85.0, 74.5, 57.0, 39.1, 35.4, 27.3, 26.5, 22.1, 17.3; HRESIMS (m/z) calcd. for $C_{12}H_{21}O$ ($M+H$)⁺ 181.1592, found 181.1590; Anal. Calcd. for $C_{12}H_{20}O$: C, 79.94; H, 11.18. Found: C, 80.11; H, 11.10.

3.11. (1R,2R,3aS,3S)-3-Allyl-1,3a-dimethylhexahydrocyclopenta[c]furan (**12b**)

To a solution of diol **11b** (32.4 mg, 0.163 mmol) in CH₂Cl₂ (1.6 mL) were added Et₃N (82.8 mg, 0.817 mmol), DMAP (79.9 mg, 0.654 mmol) and *p*-toluenesulfonyl chloride (93.5 mg, 0.490 mmol) at r.t. The mixture was stirred for 2 days at the same temperature. The mixture was diluted with Et₂O, washed with saturated aqueous NH₄Cl solution, H₂O and brine, and then dried. Removal of the solvent gave a residue which was then purified by silica gel column chromatography (hexane/AcOEt = 5:1) to generate tetrahydrofuran **12b** (27.1 mg, 93% yield) as a colorless oil. $[\alpha]_D^{26}$ -35.1 (*c* 1.14, CHCl₃); IR (neat) 2951, 2866 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃) δ ppm: 5.87 (1H, m), 5.12 (1H, m), 5.04 (1H, m), 3.84 (1H, quint., *J* = 6.4 Hz), 3.32 (1H, dd, *J* = 8.4, 4.9 Hz), 2.36–2.23 (2H, m), 1.97 (1H, m), 1.63–1.59 (6H, m), 1.19 (3H, d, *J* = 6.5 Hz), 1.07 (3H, s); NOESY correlations (H/H): H-1/H-4; H-2/H-3; H-2/H-8; H-3/H-17; H-8/H-17; ¹³C-NMR (100 MHz, CDCl₃) δ ppm: 136.1, 116.3, 86.9, 75.4, 56.1, 35.1, 34.7, 30.0, 27.7, 26.8, 25.9, 15.5; HRESIMS (*m/z*) calcd. for C₁₂H₂₁O (M+H)⁺ 181.1592, found 181.1577; Anal. Calcd. for C₁₂H₂₀O: C, 79.94; H, 11.18. Found: C, 79.91; H, 11.14.

3.12. Conversion from diol **11b** to diol **11a**

To a solution of diol **11b** (50.0 mg, 0.252 mmol) in DMF (252 μL) were added imidazole (21.0 mg, 0.308 mmol) and TBDPSCl (83.5 mg, 0.304 mmol) and the mixture was stirred at r.t. for 1 hr. The mixture was diluted with Et₂O, washed with saturated aqueous NaHCO₃ solution, H₂O and brine and then dried. The crude mixture was diluted with Et₂O and filtered through a silica gel pad. The filtrate was concentrated to afford the crude alcohol. To a solution of the crude alcohol in CH₃CN (2.5 mL) was added IBX (212 mg, 0.757 mmol) at r.t. After stirring for 30 min at 80 °C, the mixture was diluted with Et₂O and then filtered through a Celite pad. Removal of the solvent gave a residue which was filtered through a silica gel pad to afford the crude ketone. To a solution of the crude ketone in MeOH (2.5 mL) was added NaBH₄ (28.6 mg, 0.756 mmol) at r.t. After stirring for 2 hr under reflux, the mixture was diluted with Et₂O, washed with H₂O and brine and then dried. Removal of the solvent gave a residue which was then filtered through a silica gel pad to afford the crude alcohols. To a solution of the crude alcohols in THF (2.5 mL) was added TBAF (760 μL, 0.760 mmol, 1.0 M in THF solution) at r.t. After stirring for 12 hr at 40 °C, the mixture was diluted with Et₂O, washed with H₂O and brine and then dried. Removal of the solvent gave a residue which was then purified by silica gel column chromatography (hexane/AcOEt = 4:1) to generate diol **11a** (34.6 mg, 69%) and diol **11b** (6.9 mg, 14 %).

3.13. (1S,2R)-1-[(R)-1-(tert-Butyldimethylsiloxy)but-3-enyl]-2-[(S)-1-(tert-butyldimethylsiloxy)ethyl]-1-methylcyclopentane (**13**)

To a solution of diol **11a** (988 mg, 4.98 mmol) in CH₂Cl₂ (2.7 mL) were added 2,6-lutidine (2.67 g, 24.9 mmol) and TBSOTf (3.95 g, 14.9 mmol) and the mixture was stirred at 0 °C for 30 min. The mixture was diluted with Et₂O, washed with saturated aqueous NaHCO₃ solution, H₂O and brine, and then dried. Removal of the solvent gave a residue which was then purified by silica gel column chromatography (hexane only) to generate bis-silyl ether **13** (2.11 g, 99% yield) as a colorless oil.

$[\alpha]_D^{25} +0.97$ (*c* 1.07, CHCl₃); IR (neat) 2956, 2885, 1471 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃) δ ppm: 5.90 (1H, m), 5.00 (2H, m), 4.13 (1H, quint, *J* = 6.1 Hz), 3.80 (1H, dd, *J* = 6.5, 3.7 Hz), 2.38 (1H, m), 2.22 (1H, m), 1.85–1.57 (6H, m), 1.19 (1H, m), 1.09 (3H, d, *J* = 6.1 Hz), 1.04 (3H, s), 0.89 (9H, s), 0.88 (9H, s), 0.06 (12H, m); ¹³C-NMR (100 MHz, CDCl₃) δ ppm: 137.7, 115.8, 77.2, 76.8, 69.1, 56.6, 50.1, 40.3, 35.1, 27.4, 27.1, 26.2, 26.0, 22.5, 18.4, 18.1, -3.0, -3.4, -3.6, -4.0; HRESIMS (*m/z*) calcd. for C₂₄H₅₁O₂Si₂ (M+H)⁺ 427.3428, found 427.3437; Anal. Calcd. for C₂₄H₅₀O₂Si₂: C, 67.54; H, 11.81. Found: C, 67.44; H, 11.66.

3.14. (R)-3-(tert-Butyldimethylsiloxy)-3-((1S,2R)-2-[(S)-1-(tert-butyldimethylsiloxy)ethyl]-1-methylcyclopentyl)propionaldehyde (14)

A cold (-78 °C) solution of bis-silyl ether **13** (482 mg, 1.13 mmol) in CH₂Cl₂ (56.5 mL) was treated with ozone until the blue color generated persisted for more than 15 min. Excess ozone was removed using an argon flow. To the mixture were then added MeOH (56.5 mL), Zn powder (739 mg, 11.3 mmol), KI (1.88 g, 11.3 mmol) and AcOH (682 mg, 11.4 mmol). The mixture was allowed to warm to r.t., stirred for 1 hr at the same temperature and then concentrated under reduced pressure. The resultant residue was diluted with Et₂O, washed with saturated aqueous NaHCO₃ solution, H₂O and brine and then dried. Removal of the solvent gave a residue which was then purified by silica gel column chromatography (hexane/AcOEt = 20:1) to generate aldehyde **14** (484 mg, quantitative yield) as a colorless oil. $[\alpha]_D^{25} -0.56$ (*c* 1.08, CHCl₃); IR (neat) 2955, 2857, 1727 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃) δ ppm: 9.85 (1H, dd, *J* = 2.7, 1.3 Hz), 4.42 (1H, dd, *J* = 6.0, 4.1 Hz), 4.10 (1H, quint, *J* = 6.1 Hz), 2.67 (2H, m), 1.84 (1H, m), 1.74 (2H, m), 1.61 (3H, m), 1.23 (1H, m), 1.12 (3H, d, *J* = 6.1 Hz), 1.05 (3H, s), 0.88 (9H, s), 0.88 (9H, s), 0.06 (12H, m); ¹³C-NMR (100 MHz, CDCl₃) δ ppm: 201.9, 70.9, 69.0, 56.3, 50.5, 49.6, 35.4, 27.3, 26.7, 26.0, 22.4, 22.3, -3.4, -3.7, -4.0, -4.1; HRESIMS (*m/z*) calcd. for C₂₃H₄₈O₃Si₂Na (M+Na)⁺ 451.3040, found 451.3052; Anal. Calcd. for C₂₃H₄₈O₃Si₂: C, 64.42; H, 11.28. Found: C, 64.40; H, 11.10.

3.15. (6E,9R)-9-(tert-Butyldimethylsiloxy)-9-((1R,2S)-2-[(S)-1-(tert-butyldimethylsiloxy)ethyl]-1-methylcyclopentyl)-2,6-dimethylnona-2,6-dien-5-one (16)

To a solution of phosphonate **15** [5] (306 mg, 1.17 mmol) in THF (700 μ L) was added ⁿBuLi (591 μ L, 0.935 mmol, 1.58 M in hexane solution) at 0 °C. The mixture was stirred for 1 hr at the same temperature and a solution of aldehyde **14** (200 mg, 0.467 mmol) in THF (4.0 mL) was added dropwise at r.t. After stirring for 5 hr, the mixture was diluted with Et₂O, washed with saturated aqueous NH₄Cl solution, H₂O and brine, and then dried. Removal of the solvent gave a residue which was then purified by silica gel column chromatography (hexane/benzene = 4:1) to generate α,β -unsaturated ketone **16** (123 mg, 49% yield) as a white solid and recovered aldehyde **14** (36.5 mg, 18% yield). Compound **16**: mp 55–58 °C; $[\alpha]_D^{25} +11.2$ (*c* 0.57, CHCl₃); UV (MeOH) λ_{\max} (ϵ) nm: 234 (18800); IR (KBr) 2956, 2931, 2856, 1674 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃) δ ppm: 6.83 (1H, t, *J* = 6.1 Hz), 5.34 (1H, m), 4.10 (1H, quint, *J* = 6.2 Hz), 3.97 (1H, t, *J* = 5.6 Hz), 3.38 (2H, d, *J* = 7.0 Hz), 2.49 (2H, m), 1.85 (1H, m), 1.78 (3H, s), 1.74 (3H, s), 1.80–1.74 (2H, m), 1.64 (3H, s), 1.64–1.57 (4H, m), 1.11 (3H, d, *J* = 6.1 Hz), 1.06 (3H, s), 0.90 (9H, s), 0.88 (9H, s), 0.08 (6H, d,

$J = 12.6$ Hz), 0.06 (6H, d, $J = 6.5$ Hz); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ ppm: 199.9, 141.5, 136.9, 134.6, 117.1, 77.2, 75.9, 69.1, 56.5, 50.1, 37.1, 35.6, 35.1, 27.2, 27.1, 26.1, 26.0, 25.7, 22.5, 22.4, 18.3, 18.1, 11.9, -3.2, -3.4, -3.8, -3.9; HRESIMS (m/z) calcd. for $\text{C}_{31}\text{H}_{61}\text{O}_3\text{Si}_2$ ($\text{M}+\text{H}$) $^+$ 537.4159, found 537.4168; Anal. Calcd. for $\text{C}_{31}\text{H}_{60}\text{O}_3\text{Si}_2$: C, 69.34; H, 11.26. Found: C, 69.40; H, 11.05.

3.16. (5R,6E,9R)-9-(tert-Butyldimethylsiloxy)-9-[(1R,2S)-2-[(S)-1-(tert-butyldimethylsiloxy)ethyl]-1-methylcyclopentyl]-2,6-dimethylnona-2,6-dien-5-ol and (5S,6E,9R)-9-(tert-butyldimethylsiloxy)-9-[(1R,2S)-2-[(S)-1-(tert-butyldimethylsiloxy)ethyl]-1-methylcyclopentyl]-2,6-dimethylnona-2,6-dien-5-ol (17)

To a solution of $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ (144 mg, 0.386 mmol) in MeOH (9.3 mL) was added NaBH_4 (11.0 mg, 0.290 mmol) at 0 °C. The mixture was then added to a solution of α,β -unsaturated ketone **16** (104 mg, 0.193 mmol) in MeOH (10.0 mL) at 0 °C and stirred for 30 min at the same temperature. The mixture was diluted with Et_2O , washed with H_2O and brine, and then dried. Removal of the solvent gave a residue which was then purified by silica gel column chromatography (CHCl_3 only) to generate a diastereomeric mixture of allylic alcohol **17** (103 mg, 99% yield) as a colorless oil. IR (neat) 3353, 2957 cm^{-1} ; $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ ppm: 5.54 (1H, m), 5.11 (1H, m), 4.14 (1H, m), 4.00 (1H, m), 3.80 (1H, m), 2.42–2.14 (4H, m), 1.86 (1H, m), 1.80–1.57 (5H, m), 1.72 (3H, s), 1.64 (3H, s), 1.62 (3H, s), 1.15 (1H, m), 1.09 (3H, d, $J = 6.1$ Hz), 1.02 (1.5 H, s), 1.02 (1.5H, s), 0.88 (9H, d, $J = 6.9$ Hz), 0.88 (9H, d, $J = 5.4$ Hz), 0.06 (12H, m); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ ppm: 136.6, 136.5, 134.8, 134.7, 125.6, 125.5, 120.2, 120.2, 77.2, 77.2, 68.9, 68.9, 56.2, 56.2, 50.2, 50.2, 35.1, 35.0, 34.1, 34.0, 26.7, 26.6, 26.5, 26.3, 26.2, 26.0, 25.9, 22.5, 22.1, 22.1, 22.1, 18.4, 18.1, 18.0, 12.1, 12.1, -3.1, -3.2, -3.4, -3.5, -3.7, -3.7, -4.0, -4.0; HRESIMS (m/z) calcd. for $\text{C}_{31}\text{H}_{62}\text{O}_3\text{Si}_2\text{Na}$ ($\text{M}+\text{Na}$) $^+$ 561.4135, found 561.4156; Anal. Calcd. for $\text{C}_{31}\text{H}_{62}\text{O}_3\text{Si}_2$: C, 69.08; H, 11.59. Found: C, 68.92; H, 11.30.

3.17. (1R,3E,5R)-1-[(1S,2R)-2-((S)-1-Hydroxyethyl)-1-methylcyclopentyl]-4,8-dimethyl-5-trityloxy-nona-3,7-dien-1-ol and (1R,3E,5S)-1-[(1S,2R)-2-((S)-1-hydroxyethyl)-1-methylcyclopentyl]-4,8-dimethyl-5-trityloxy-nona-3,7-dien-1-ol (18)

To a solution of the diastereomeric mixture of allylic alcohol **17** (40.0 mg, 0.074 mmol) in pyridine (740 μL) were added DMAP (5.0 mg, 0.041 mmol) and TrCl (103 mg, 0.395 mmol) at r.t. After stirring for 4 days at 80 °C, the mixture was diluted with Et_2O , washed with H_2O and brine, and then dried. Removal of the solvent gave a residue which was filtered through a short-path silica gel pad (hexane/AcOEt = 20:1). The filtrate was then concentrated to afford the crude trityl ether. To a solution of the crude trityl ether in DMF (1.5 mL) was added TBAF (1.5 mL, 0.150 mmol, 1.0 M in THF solution) at r.t. After stirring for 2 days at 50 °C, the mixture was diluted with Et_2O , washed with H_2O and brine and then dried. Removal of the solvent gave a residue which was then purified by silica gel column chromatography (hexane/AcOEt = 10:1) to generate a diastereomeric mixture of diol **18** (40.9 mg, quantitative yield) as a colorless oil. IR (neat) 3344, 2961 cm^{-1} ; $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ ppm: 7.51 (6H, m), 7.30–7.20 (9H, m), 4.93 (1H, t, $J = 6.6$ Hz), 4.77 (0.5H, dd, $J = 6.7, 6.7$ Hz), 4.68 (0.5H, dd, $J = 9.0, 5.5$ Hz), 4.00 (1H, dd, $J = 5.7, 5.7$ Hz), 3.79 (0.5H, m), 3.73 (0.5H, m), 3.47–3.36 (1H, m), 2.31 (0.5H, m), 2.12–1.88 (3.5 H, m), 1.82–1.73 (2.5H, m), 1.63 (3H, m), 1.54 (3H, m), 1.48

(3H, m), 1.57–1.43 (2.5H, m), 1.41–1.31 (2H, m), 1.17 (1.5H, m), 1.14 (1.5H, m), 1.07 (3H, m); ^{13}C -NMR (100 MHz, CDCl_3) δ ppm: 145.1, 140.4, 140.3, 133.7, 133.2, 129.0, 127.5, 127.5, 126.9, 126.9, 122.1, 121.4, 120.6, 120.4, 87.2, 87.2, 79.5, 78.5, 77.2, 72.6, 72.3, 69.0, 68.9, 59.1, 47.3, 47.2, 39.6, 33.1, 33.0, 30.3, 30.1, 30.1, 29.6, 29.2, 26.1, 25.8, 25.7, 22.4, 22.4, 22.3, 22.3, 22.2, 17.7, 12.7, 11.6; HRESIMS (m/z) calcd. for $\text{C}_{38}\text{H}_{48}\text{O}_3\text{Na}$ ($\text{M}+\text{Na}$) $^+$ 575.3501, found 575.3522; Anal. Calcd. for $\text{C}_{38}\text{H}_{48}\text{O}_3$: C, 82.56; H, 8.75. Found: C, 82.52; H, 8.60.

3.18. (3*E*,5*R*)-1-((1*S*,2*R*)-2-Acetyl-1-methylcyclopentyl)-4,8-dimethyl-5-trityloxynona-3,7-dien-1-one and (3*E*,5*S*)-1-((1*S*,2*R*)-2-acetyl-1-methylcyclopentyl)-4,8-dimethyl-5-trityloxynona-3,7-dien-1-one (19)

To a cold ($-78\text{ }^\circ\text{C}$) solution of TFAA (67.6 mg, 0.322 mmol) in CH_2Cl_2 (100 μL) was added DMSO (33.6 mg, 0.430 mmol) in CH_2Cl_2 (100 μL). The mixture was stirred at $-78\text{ }^\circ\text{C}$ for 30 min, treated with a solution of the diastereomeric mixture of diol **18** (29.6 mg, 0.054 mmol) in CH_2Cl_2 (340 μL), stirred for 2 hr and then Et_3N (54.3 mg, 0.537 mmol) was added. The mixture was warmed to r.t. and stirred for 30 min. The mixture was diluted with Et_2O , washed with saturated aqueous NaHCO_3 solution, H_2O and brine and then dried. Removal of the solvent gave a residue which was then purified by silica gel column chromatography (hexane/ AcOEt = 6:1) to generate a diastereomeric mixture of diketone **19** (27.9 mg, 95% yield) as a colorless oil. IR (neat) 2965, 1705 cm^{-1} ; ^1H -NMR (400 MHz, CDCl_3) δ ppm: 7.49 (6H, m), 7.26–7.16 (9H, m), 4.95 (1H, t, J = 6.1 Hz), 4.81 (1H, t, J = 7.3 Hz), 3.92 (1H, dd, J = 8.8, 4.7 Hz), 2.92 (2H, m), 2.78 (1H, dd, J = 8.6, 5.0 Hz), 2.23–1.72 (6H, m), 2.15 (3H, s), 1.63–1.55 (2H, m), 1.58 (3H, s), 1.48 (3H, s), 1.42 (3H, s), 1.21 (3H, s); ^{13}C -NMR (100 MHz, CDCl_3) δ ppm: 212.2, 210.7, 145.2, 137.6, 132.4, 129.2, 127.5, 126.8, 120.5, 118.7, 87.2, 79.3, 77.2, 60.9, 59.8, 37.9, 35.4, 33.5, 29.9, 27.6, 25.8, 25.2, 22.4, 17.8, 12.1; HRESIMS (m/z) calcd. for $\text{C}_{38}\text{H}_{44}\text{O}_3\text{Na}$ ($\text{M}+\text{Na}$) $^+$ 571.3188, found 571.3196. Anal. Calcd. for $\text{C}_{38}\text{H}_{44}\text{O}_3$: C, 83.17; H, 8.08. Found: C, 83.12; H, 8.21.

3.19. Diastereomeric mixture of secoxestonone (20)

To a solution of the diastereomeric mixture of diketone **19** (76.2 mg, 0.139 mmol) in CH_2Cl_2 (14 mL) was added $\text{Yb}(\text{OTf})_3$ (172 mg, 0.277 mmol) at r.t. After stirring for 30 min, the mixture was diluted with Et_2O . To this was added NaHCO_3 and the mixture was then filtered through a silica gel pad. Removal of the solvent gave a residue which was then purified by silica gel column chromatography (hexane/ AcOEt = 1:1) to generate a diastereomeric mixture of secoxestonone **20** (33.5 mg, 79% yield) as a colorless oil. IR (neat) 3448, 2965, 1706 cm^{-1} ; ^1H -NMR (400 MHz, CDCl_3) δ ppm: 5.60 (1H, m), 5.10 (1H, m), 4.05 (1H, m), 3.27 (2H, m), 2.85 (1H, m), 2.27 (3H, m), 2.16 (3H, m), 2.09 (1H, m), 1.91–1.75 (3H, m), 1.71 (3H, s), 1.66 (1H, m), 1.63 (3H, s), 1.63 (3H, s), 1.28 (3H, m); ^{13}C -NMR (100 MHz, CDCl_3) δ ppm: 212.8, 210.8, 148.5, 141.9, 134.7, 120.8, 120.1, 118.2, 77.2, 76.9, 61.3, 60.4, 59.7, 37.8, 35.9, 35.5, 34.0, 30.2, 29.8, 27.8, 27.7, 25.9, 25.7, 25.6, 25.3, 22.4, 18.0, 12.3, 12.1; HRESIMS (m/z) calcd. for $\text{C}_{19}\text{H}_{30}\text{O}_3\text{Na}$ ($\text{M}+\text{Na}$) $^+$ 329.2093, found 329.2085. Anal. Calcd. for $\text{C}_{19}\text{H}_{30}\text{O}_3$: C, 74.47; H, 9.87. Found: C, 74.29; H, 9.85.

3.20. Xestenone (**21**) and 12-*epi*-xestenone (12-*epi*-**21**)

To a solution of the diastereomeric mixture of secoxestenone **20** (26.5 mg, 0.087 mmol) in MeOH (6.7 mL) was added 0.1 M NaOH aqueous solution (21.6 mL) at r.t. The mixture was stirred for 30 min, neutralized with 1.0 M HCl aqueous solution, diluted with Et₂O, washed with H₂O and brine, dried and then concentrated under reduced pressure. The resultant residue was purified by silica gel column chromatography (hexane/AcOEt = 4:1) to give a mixture of **21** and 12-*epi*-**21** (22.0 mg, 88% yield) as a colorless oil. The above mixture was subjected to HPLC (CHIRALPAK IA, 1.0 cm × 25 cm, hexane/EtOH = 95:5, flow rate: 1.0 mL/min) to give xestenone **21** (*t*_R = 12.0 min) and 12-*epi*-**21** (*t*_R = 15.0 min); **21**: [α]_D²⁵ +2.2 (*c* 0.075, MeOH); UV (sh, MeOH) λ_{max} nm (ε): 257 (6100); CD (MeOH) λ_{ext} nm [θ]: 323 (+87,000), 258 (-129,000); IR (neat) 3419, 1685 cm⁻¹; ¹H-NMR (600 MHz, CDCl₃) δ ppm: 5.93 (1H, s), 5.18 (1H, br t, *J* = 6.9 Hz), 4.18 (1H, t, *J* = 6.4 Hz), 2.71 (1H, d, *J* = 9.1 Hz), 2.35 (2H, m), 1.96 (3H, s), 1.93 (1H, m), 1.90 (1H, br s), 1.82 (1H, m), 1.75 (3H, s), 1.69 (1H, m), 1.67 (3H, s), 1.64 (1H, m), 1.55 (3H, s), 1.35 (1H, m), 1.25 (1H, m), 1.21 (3H, s); ¹³C-NMR (150 MHz, CDCl₃) δ ppm: 212.7, 172.2, 144.3, 137.4, 134.9, 119.9, 115.6, 76.4, 56.7, 54.8, 37.5, 34.2, 28.9, 25.9, 24.8, 22.5, 18.0, 16.7, 14.4; HRESIMS (*m/z*) calcd. for C₁₉H₂₈O₂Na (M+Na)⁺ 311.1987, found 311.1981. Anal. Calcd. for C₁₉H₂₈O₂: C, 79.12; H, 9.78. Found: C, 78.97; H, 9.74. 12-*epi*-**21**: [α]_D²⁵ -113.7 (*c* 0.085, MeOH); UV (sh, MeOH) λ_{max} nm (ε): 254 (2,100); CD (MeOH) λ_{ext} nm [θ]: 320 (+116,000), 256 (-104,000); IR (neat) 3418, 1686 cm⁻¹; ¹H-NMR (600 MHz, CDCl₃) δ ppm: 5.92 (1H, s), 5.16 (1H, t, *J* = 7.2 Hz), 4.19 (1H, t, *J* = 6.3 Hz), 2.71 (1H, d, *J* = 9.1 Hz), 2.35 (2H, m), 1.96 (3H, s), 1.93 (1H, m), 1.81 (1H, m), 1.74 (3H, s), 1.69 (1H, m), 1.67 (3H, s), 1.62 (1H, m), 1.55 (3H, s), 1.35 (1H, m), 1.25 (1H, m), 1.22 (3H, s); ¹³C-NMR (150 MHz, CDCl₃) δ ppm: 212.8, 172.2, 144.3, 137.4, 134.8, 119.9, 115.9, 76.5, 56.7, 54.7, 37.5, 34.1, 28.9, 25.9, 24.8, 22.5, 18.0, 16.7, 14.1; HRESIMS (*m/z*) calcd. for C₁₉H₂₈O₂Na (M+Na)⁺ 311.1987, found 311.1975. Anal. Calcd. for C₁₉H₂₈O₂: C, 79.12; H, 9.78. Found: C, 79.03; H, 9.88.

3.21. General procedure for the synthesis of MPA ester

To a solution of xestenone (**21**) in CH₂Cl₂ were added DCC, DMAP and (*S*)-(+)- or (*R*)-(-)- α -methoxyphenylacetic acid at r.t. After stirring for 30 min at 40 °C the mixture was concentrated. Removal of the solvent gave a residue which was then purified by silica gel column chromatography (hexane/AcOEt = 6:1) to generate (*S*)- or (*R*)-MPA ester. (*S*)-MPA ester: ¹H-NMR (400 MHz, CDCl₃) δ ppm: 7.44–7.27 (5H, m), 5.66 (1H, s), 5.26 (1H, dd, *J* = 7.9, 5.7 Hz), 5.06 (1H, m), 4.75 (1H, s), 3.43 (3H, s), 2.62 (1H, d, *J* = 9.2 Hz), 2.39 (2H, m), 1.88 (1H, m), 1.76 (1H, m), 1.70 (3H, s), 1.68 (3H, s), 1.61 (3H, s), 1.59 (2H, m), 1.30 (1H, m), 1.26 (3H, br s), 1.19 (1H, m), 1.15 (3H, s); ¹³C-NMR (150 MHz, CDCl₃) δ ppm: 211.9, 169.8, 139.2, 137.0, 134.6, 128.8, 128.5, 128.2, 127.2, 119.0, 118.1, 117.8, 82.6, 79.0, 56.6, 54.7, 37.4, 31.8, 29.7, 28.8, 25.8, 24.7, 22.5, 18.0, 16.5, 14.4; HRESIMS (*m/z*) calcd. for C₂₈H₃₆O₄Na (M+Na)⁺ 459.2511, found 459.2521; (*R*)-MPA ester: ¹H-NMR (400 MHz, CDCl₃) δ ppm: 7.45–7.29 (5H, m), 5.88 (1H, s), 5.24 (1H, dd, *J* = 7.7, 5.7 Hz), 4.80 (1H, m), 4.77 (1H, s), 3.43 (3H, s), 2.67 (1H, d, *J* = 9.0 Hz), 2.28 (2H, m), 1.91 (1H, m), 1.85 (3H, s), 1.81–1.59 (3H, m), 1.53 (3H, s), 1.48 (3H, br s), 1.47 (3H, s), 1.33 (1H, m), 1.22 (1H, m), 1.19 (3H, s); ¹³C-NMR (150 MHz, CDCl₃) δ ppm: 212.1, 170.0, 139.5, 137.0, 134.4, 128.8, 128.5, 128.2, 127.2, 119.0, 118.7,

117.8, 82.6, 79.0, 56.7, 54.7, 37.5, 31.9, 29.7, 28.9, 25.6, 24.8, 22.5, 17.8, 16.6, 16.5; HRESIMS (m/z) calcd. for $C_{28}H_{36}O_4Na$ ($M+Na$)⁺ 459.2511, found 459.2501.

3.22. Conversion of 12-*epi*-21 to 21

To a solution of 12-*epi*-21 (1.7 mg, 0.006 mmol) in THF (59 μ L) were added Ph_3P (2.3 mg, 0.009 mmol) and *p*-NO₂BzOH (1.5 mg, 0.009 mmol) at r.t. After stirring for 10 min, DIAD (1.8 mg, 0.009 mmol) was added and the mixture was stirred for an additional 2 hr. The crude mixture was diluted with Et₂O and filtered through a silica gel pad. The filtrate was then concentrated to afford the crude ester. To a solution of the crude ester in MeOH (200 μ L) was added K₂CO₃ (12.2 mg, 0.088 mmol) at r.t. After stirring for 30 min at the same temperature, the mixture was diluted with Et₂O and then filtered through a silica gel pad. Removal of the solvent gave a residue which was then purified by silica gel column chromatography (hexane/AcOEt = 2:1) to generate xestenone (21, 1.6 mg, 95% yield).

4. Conclusions

The first total synthesis of xestenone has been accomplished *via* the stereocontrolled one-pot synthesis of cyclopentane derivatives using allyl phenyl sulfone as the key step. Moreover, the authors have determined that the absolute configuration of xestenone is 3*S*, 7*S* and 12*R*.

Acknowledgements

The authors are grateful to Prof. Raymond J. Andersen of the University of British Columbia for providing the NMR spectra of xestenone.

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