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Enantiospecific synthesis of the ABC and ABD ring systems of the marine diterpenes aberraranes

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Dedicated to Professor M. Nagarajan on the occasion of his 60th birthday

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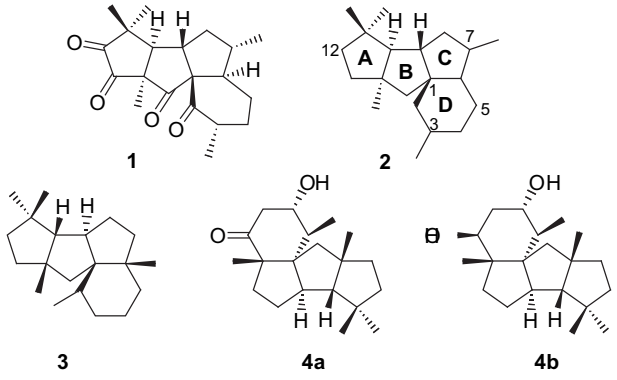
ABSTRACT

Enantiospecific synthesis of the ABC and ABD ring systems present in the marine diterpenes aberraranes, starting from the readily available (*S*)-campholenaldehyde, has been accomplished.

1. Introduction

The chemically most diverse West Indian gorgonian octocoral *Pseudopterogorgia elisabethae* is an exceptionally rich source of diterpene natural products, such as elisabethins, colombiasins, cumbiasins, pseudopterosins and elisapterosins, and some of them found to display significant anti-inflammatory and wound healing properties.[1a] In continuation of their search for bioactive natural products from marine sources, research group of Rodriguez recently reported[1b] the isolation of a new diterpene **1**, containing a new diterpene carbon framework named as 'aberrarane **2**', from the sea whip *P. elisabethae*. Aberrarone **1** displayed inhibitory activity against the chloroquine resistant strain protozoan parasite *Plasmodium falciparum*. The tetracyclic carbon system, a cyclohexane angularly fused to a linear *cis*, *anti*, *cis*-triquinane, was also encountered earlier in the diterpenes conidiogenanes **3**, which differ from aberraranes **2** in the location of two of the methyl groups on the C and D-rings, e.g., **4a**,**b**, isolated[2a] from the extracts of fermentation broth of *Penicillium cyclopium*, which were found to induce conidiogenesis in *P. cyclopium* in liquid culture, and also from a deep ocean sediment derived fungus[2b] *Penicillium* sp.



Presence of an interesting tetracyclic carbon framework **2**, coupled with potential biological properties made aberrarane system **2** attractive synthetic target. Although few model studies appeared in the literature (mostly in the context of the synthesis of

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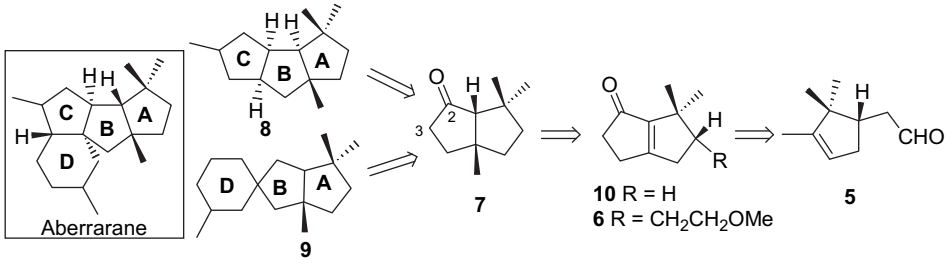
megallanane family of alkaloids) on the synthesis of conidiogenanes,[3] so far there is no report in the literature on the synthesis of aberraranes, either the total synthesis or the model studies (enantioselective or racemic). Recently, we have reported a convenient RCM based enantiospecific approach for the tricyclic ring system present in elisabethanes and related diterpenes starting from (*R*)-carvone.[4a] In continuation of our interest in the enantiospecific synthesis of polycyclic compounds employing chiral pool approach,[4] we have initiated an enantiospecific approach to the tetracyclic frameworks of the diterpenes aberrarane and conidiogenanes **2** and **3**. (*S*)-Campholenaldehyde **5** is a readily available cyclopentane based chiral starting material. Although, it has been employed in the synthesis of a variety of industrially (fragrance) important monocyclic compounds, its utility in the synthesis of polycyclic compounds was not explored to its potential.[5] Recently, we have reported an efficient route for the enantiospecific conversion of (*S*)-campholenaldehyde **5** into diquinanes, e.g., **6**, and triquinanes employing a Nazarov reaction as the key step.[6a] In continuation of our interest on the utility of (*S*)-campholenaldehyde in the synthesis of polycyclic compounds,[6] herein we wish to report the enantiospecific approach to the ABC and ABD tricyclic systems present in the aberrarane diterpenes.

2. Results and discussion

It was contemplated (Scheme 1) that a cyclopentannulation at the C-2–C-3 bond of the diquinane **7** would lead to the ABC ring system **8** of aberrarane **2**. On the other hand, a spirocyclohexannulation at the C-3 carbon of the diquinane **7** would lead to the ABD ring system **9** of aberrarane **2**. The trimethylated diquinane **7** could be obtained from the enone **10**. Synthesis of an analogue **6** from (*S*)-campholenaldehyde **5** employing a Nazarov reaction has already been developed earlier in our laboratory.[6a]



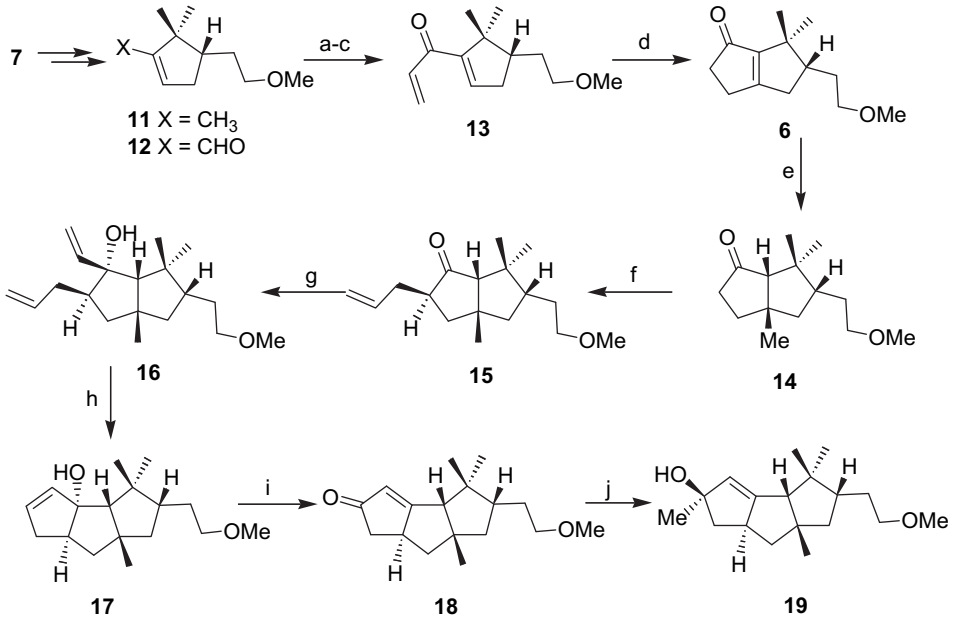
Scheme 1. Retrosynthetic analysis of ABC and ABD rings of aberraranes.

The synthetic sequence starting from the campholenyl methyl ether **11**, readily available from (*S*)-campholenaldehyde **5** in two steps,[7] is depicted in Scheme 2. To begin with the ether **11** was converted in to the diquinane enone **6** employing the strategy developed earlier in our laboratory.[6a] Thus, selenium dioxide mediated allylic oxidation of the ether **11** generated the aldehyde **12**, which on coupling with vinylmagnesium bromide followed by oxidation of the resultant alcohol with IBX in DMSO furnished the cross conjugated dienone **13**. Nazarov cyclisation[8] of the dienone **13** with methanesulfonic acid and phosphorus pentoxide in methylene chloride generated the diquinane enone **6**. Reaction of the enone **6** with the cuprate derived from methylmagnesium chloride and copper iodide in ether/THF at low temperature furnished the key intermediate of the sequence, the diquinane **14** in a highly stereoselective manner, in 79% yield. The stereochemistry of the newly created quaternary carbon atom was assigned on the basis of the well established[6d] approach of the reagent from the less hindered face of the diquinane system, i.e., anti to the side chain on C-7 carbon.

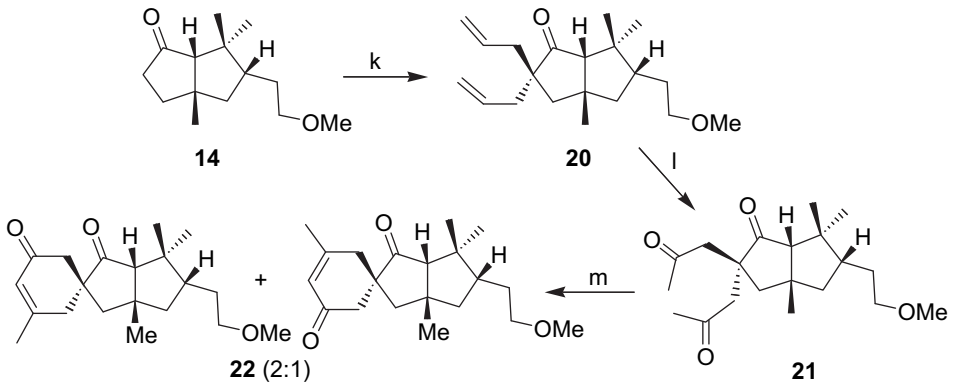
For the generation of the third cyclopentane ring of the ABC ring system of aberrarane system, a ring closing metathesis reaction[9] (RCM) based cyclopentannulation strategy was investigated by introducing an allyl and a vinyl group at the C-3 and C-2 carbons, respectively, of the diquinane **14**. Reaction of the diquinane **14** with lithium diisopropylamide (LDA) followed by treatment of the resultant enolate with allyl bromide furnished, exclusively, the *exo* allylated diquinane **15**, in 75% yield, via the approach of the electrophile from the less hindered *exo* face of the diquinane **14**, which has enough precedent in the literature.[10] Grignard reaction of the diquinane **15** with vinylmagnesium bromide generated the allyl alcohol **16** in a highly stereoselective manner, whose stereochemistry was tentatively assigned and was confirmed later by the facile RCM reaction. Refluxing a 0.05 M benzene solution of the alcohol **16** with 5 mol % of Grubbs' first generation catalyst for 5 h cleanly generated the triquinane **17** in 75% yield. Oxidation with pyridinium chlorochromate (PCC) and silica gel in methylene chloride at rt transformed the triquinane alcohol **17** in to the enone **18**, whose structure was deduced from its spectral data. Presence of a carbonyl absorption band at 1709 cm^{-1} due to a typical cyclopentenone in the IR spectrum, a singlet at δ 5.81 ppm due to the olefinic proton in the ^1H NMR spectrum and in particular presence of two quaternary carbon resonances at δ 210.3 and 191.0 and a methine at 126.3 ppm due to the cyclopentenone system in the ^{13}C NMR spectrum[11,6a] confirmed the structure of the enone **18**. A Grignard reaction on the enone **18** with methylmagnesium chloride introduced the requisite additional carbon on the third cyclopentane ring to furnish the ABC ring system **19** of aberrarane **2**.

For the construction of the ABD tricyclic ring system of aberraranes **2**, a Wacker reaction[12] followed by an intramolecular aldol condensation was investigated for the spirocyclohexannulation at the C-3 carbon of the diquinane **14**. Thus, reaction of the diquinane **14** with an excess of sodium hydride and allyl bromide furnished the bisallylated diquinane **20** in 74% yield. Wacker reaction of the bisallylated diquinane **20** with palladium chloride and copper chloride in *N*,*N*-dimethylformamide (DMF) and water in an oxygen atmosphere for 4 h furnished the triketone **21** in 85% yield. Intramolecular aldol condensation of the triketone **21** with 1 M potassium hydroxide in methanol at rt furnished a 2:1 mixture of the spiroenone **22**, which was found to be inseparable by chromatography. The structure of the spiroenone **22** was established from its spectral data. Presence of carbonyl absorption bands at 1725 cm^{-1} due to cyclopentanone and at 1668 cm^{-1} due to cyclohexenone in the IR spectrum, a singlet at δ 5.82 ppm in the ^1H NMR spectrum and in particular presence of two quaternary carbon resonances at δ 220.6 and 195.3 due to typical cyclopentanone and cyclohexenone ketone carbons, respectively, and a quaternary carbon resonance at 158.9 and a methine at 126.0 ppm due to the β and α carbons, respectively, of the cyclohexenone moiety for the major isomer in the ^{13}C NMR spectrum confirmed the structure of the spiroenone **22**. The spiroenone **22** represents the ABD ring system of aberraranes **2** (Scheme 3).

In summary, we have accomplished enantiospecific syntheses of the ABC and ABD tricyclic ring systems present in the new diterpene group aberrarane **2**, employing (*S*)-campholenaldehyde **5** as



Scheme 2. Reagents: (a) SeO_2, dioxane, H_2O; (b) CH_2=CHMgBr, THF; (c) IBX, DMSO; (d) P_2O_5, CH_3SO_3H, CH_2Cl_2; (e) MeMgCl, CuI, Et_2O, THF; (f) LDA, THF; CH_2=$CHCH_2Br$; (g) CH_2=CHMgBr, THF; (h) $Cl_2(Cy_3P)_2Ru$=CHPh, C_6H_6; (i) PCC, silica gel, CH_2Cl_2; (j) MeMgCl, THF.



Scheme 3. Reagents: (k) NaH, THF, CH_2=$CHCH_2Br$; (l) $PdCl_2$, CuCl, DMF, H_2O, O_2; (m) KOH, MeOH.

the starting material and the diquinane **6** as the key intermediate. An RCM based cyclopentannulation was employed for the synthesis of the ABC ring system, whereas a combination of Wacker reaction and intramolecular aldol condensation was utilized for the construction of the ABD ring system. Investigations on the degradation of the two additional carbons[6d] present on the A-ring and extrapolation of the methodology for the synthesis of the tetracyclic systems **2** and **3** of aberraranes and conidiogenanes are currently in progress.

3. Experimental section

3.1. General

IR spectra were recorded on Perkin–Elmer Spectrum BX FTIR spectrophotometer. ^1H (400 MHz) and ^{13}C (100 MHz) NMR spectra were recorded on a Brucker Avance 400 spectrometer. The chemical shifts (δ ppm) and coupling constants (Hz) are reported in the standard fashion with reference to either internal tetramethylsilane (for ^1H) or the central line (77.0 ppm) of $CDCl_3$ (for ^{13}C). In the ^{13}C NMR, nature of the carbons (C, CH, CH_2, CH_3) was determined by recording the DEPT-135 spectra, and is given in parentheses. High-resolution mass spectra were recorded using Micromass Q-TOF micro mass spectrometer using electron spray ionization mode. Optical rotations were measured using a Jasco P-1020 digital polarimeter and $[\alpha]_D$ values are given in units of 10^{-1} deg cm^2 g^{-1}. Thin-layer chromatographies (TLC) were performed on glass plates (7.5×2.5 and 7.5×5.0 cm) coated with Acme's silica gel G containing 13% calcium sulfate as binder and various combinations of ethyl acetate and hexane were used as eluent. Visualization of spots was accomplished by exposure to iodine vapour or anisaldehyde/H_2SO_4 or MeOH/H_2SO_4 spray followed by heating. Acme's silica gel (100–200 mesh) was used for column chromatography (approximately 15–20 g per 1 g of the crude product).

*3.1.1. (1S,5S,7S)-7-(2-Methoxyethyl)-5,8,8-trimethyltricyclo[3.3.0]bicyclooctan-2-one **14**.* To a magnetically stirred suspension of CuI (913 mg, 4.8 mmol) in ether (5 mL) was added a solution of methylmagnesium chloride (2.0 M in THF, 4.8 mL, 9.6 mmol) and stirred for 1 h at rt to give bright yellow coloured methyl cuprate reagent. A solution of the enone[6a] **6** (340 mg, 1.6 mmol) in ether (2 mL) was added drop wise to the reagent at −30 °C and stirred at the same temperature for 1 h. The reaction was then quenched with aq NH_4Cl solution (5 mL) and extracted with ether (3×5 mL). The combined organic extract was washed with brine (5 mL) and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue over a silica gel column using ethyl acetate/hexane (1:20) as eluent

furnished the ketone **14** (300 mg, 79%) as oil. R_f (5% EtOAc/hexane) 0.45; $[\alpha]_D^{25}$ −80.9 (*c* 3.0, $CHCl_3$); IR (neat): ν_{max}/cm^{-1} 1731 (C=O), 1386, 1366, 1263, 1173, 1148, 1119; ^1H NMR (400 MHz, $CDCl_3$+CCl_4): δ 3.45–3.30 (2H, m), 3.28 (3H, s, OCH_3), 2.30 (2H, t, *J* 8.0 Hz), 2.00–1.73 (5H, m), 1.75–1.56 (1H, m), 1.49 (1H, t, *J* 11.6 Hz), 1.34–1.20 (1H, m), 1.17 (3H, s), 1.11 (3H, s) and 0.71 (3H, s) [3× *tert*-CH_3]; ^{13}C NMR (100 MHz, $CDCl_3$+CCl_4): δ 220.6 (C, C=O), 72.0 (CH_2, C-2′), 70.8 (CH, C-1), 58.4 (CH_3, OCH_3), 48.5 (CH, C-7), 46.5 (CH_2, C-3), 45.7 (C), 45.6 (C), 40.4 (CH_2), 37.0 (CH_2), 30.1 (CH_3), 28.9 (CH_3), 28.8 (CH_2), 17.7 (CH_3); HRMS: *m*/*z* calcd for $C_{14}H_{24}O_2$ (M+Na): 247.1674; Found: 247.1672.

3.1.2. (1S,3R,5R,7S)-7-(2-Methoxyethyl)-5,8,8-trimethyl-3-allylbicyclo[3.3.0]octan-2-one ***15****.* To a cold (−70 °C), magnetically stirred solution of diisopropylamine (0.38 mL, 2.75 mmol) in anhydrous THF (2 mL) was added slowly a solution of *n*-BuLi (2.0 M in hexane, 0.8 mL, 1.6 mmol) over a period of 5 min and stirred for 10 min. To the LDA thus formed was added drop wise a solution of the ketone **14** (240 mg, 1.1 mmol) in anhydrous THF (2 mL) at −70 °C over a period of 5 min and stirred for 30 min at the same temperature. The enolate was then treated with allyl bromide (0.14 mL, 1.65 mmol) and stirred for 3 h at rt. The reaction mixture was diluted with water (5 mL) and extracted with ether (2× 5 mL). The combined organic extract was washed with brine (5 mL) and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue over a silica gel column using ethyl acetate/hexane (1:20) as eluent furnished the ketone **15** (200 mg, 75%) as oil. R_f (5% EtOAc/hexane) 0.5; $[\alpha]_D^{25}$ −114.1 (*c* 4.8, $CHCl_3$); IR (neat): ν_{max}/cm^{-1} 3077, 1729 (C=O), 1641, 1386, 1292, 1191, 1154, 1119, 999, 912; ^1H NMR (400 MHz, $CDCl_3$+CCl_4): δ 5.85–5.65 (1H, m, C*H*=CH_2), 5.02 (1H, d, *J* 18.4 Hz) and 4.97 (1H, d, *J* 10.9 Hz) [CH=C*H*$_2$], 3.55–3.30 (2H, m), 3.31 (3H, s, OCH_3), 2.55–2.25 (2H, m), 2.24–1.25 (9H, m), 1.19 (3H, s), 1.16 (3H, s) and 0.72 (3H, s) [3× *tert*-CH_3]; ^{13}C NMR (100 MHz, $CDCl_3$+CCl_4): δ 219.7 (C, C=O), 136.2 (CH, *C*H=CH_2), 116.0 (CH_2, C=*C*H$_2$), 72.3 (CH_2, OCH_2), 70.6 (CH, C-1), 58.4 (CH_3, OCH_3), 48.8 (CH), 47.6 (CH), 45.6 (CH_2), 45.5 (C), 43.0 (C), 40.6 (CH_2), 33.6 (CH_2), 30.7 (CH_3), 30.6 (CH_2), 29.0 (CH_3), 18.7 (CH_3); HRMS: *m*/*z* calcd for $C_{17}H_{28}O_2$ (M+Na): 287.1987; Found: 247.1981.

3.1.3. (1S,2S,3R,5R,7S)-3-Allyl-7-(2-methoxyethyl)-2-vinyl-5,8,8-trimethylbicyclo[3.3.0]octan-2-ol ***16****.* To a cold (0–5 °C), magnetically stirred solution of the ketone **15** (30 mg, 0.12 mmol) in anhydrous THF (0.5 mL) was added a solution of vinylmagnesium bromide (1.0 M, 0.3 mL, 0.3 mmol) and stirred for 1 h at 0 °C. The reaction was then quenched with aq NH_4Cl (3 mL) and extracted with ether (2× 5 mL). The combined organic extract was washed with brine (5 mL) and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue over a silica gel column using ethyl acetate/hexane (1:20) as eluent furnished the alcohol 16 (25 mg, 75%) as oil. R_f (5% EtOAc/hexane) 0.55; $[\alpha]_D^{25}$ −89.3 (*c* 3.0, $CHCl_3$); IR (neat): ν_{max}/cm^{-1} 3460 (OH), 1586, 1086, 1051, 875, 823, 623; ^1H NMR (400 MHz, $CDCl_3$+CCl_4): δ 6.04 (1H, dd, *J* 17.2 and 10.8 Hz, C*H*=CH_2), 5.85–5.65 (1H, m), 5.21 (1H, d, *J* 17.2 Hz), 5.05 (1H, d, *J* 10.8 Hz), 4.96 (1H, d, *J* 16.8 Hz), 4.92 (1H, d, *J* 10.0 Hz), 3.50–3.20 (2H, m, OCH_2), 3.01 (3H, s, OCH_3) 2.60–1.20 (12H, m), 1.16 (3H, s), 1.13 (3H, s) and 1.05 (3H, s) [3× *tert*-CH_3]; ^{13}C NMR (100 MHz, $CDCl_3$+CCl_4): δ 143.6 (CH, *C*H=CH_2), 138.2 (CH, CH_2*C*H=CH_2), 115.3 (CH_2, CH_2CH=CH_2), 110.5 (CH_2, CH=*C*H$_2$), 84.6 (C, C-2), 72.6 (CH_2, OCH_2), 71.0 (CH, C-1), 58.4 (CH_3, OCH_3), 47.8 (CH_2), 47.5 (CH), 47.1 (CH), 46.1 (C), 44.6 (CH_2), 43.4 (C), 34.8 (CH_2), 32.4 (CH_3), 30.2 (CH_3), 28.1 (CH_2), 18.2 (CH_3); HRMS: *m*/*z* calcd for $C_{19}H_{32}O_2$ (M+Na): 315.2300; Found: 315.2299.

3.1.4. (1S,2S,4S,6R,8R)-4-(2-Methoxyethyl)-3,3,6-trimethyltricyclo[6.3.0.0^{2,6}*]undec-10-en-1-ol* ***17****.* To a magnetically stirred solution of the alcohol **16** (30 mg, 0.1 mmol) in dry benzene (2 mL, 0.05 M) was added Grubb's first generation catalyst (4 mg, 5 mol %). The reaction mixture was refluxed for 5 h and the catalyst was filtered off through a short silica gel column. Evaporation of the solvent and purification of the residue on a silica gel column using ethyl acetate/hexane (1:20) as eluent furnished the triquinane 17 (21 mg, 75%) as oil. R_f (5% EtOAc/hexane) 0.5; $[\alpha]_D^{25}$ −33.1 (*c* 1.7, $CHCl_3$); IR (neat): ν_{max}/cm^{-1} 3458 (OH), 3046, 1378, 1370, 1361, 1190, 1116, 1080, 1033, 786, 732; ^1H NMR (400 MHz, $CDCl_3$+CCl_4): δ 5.80 (1H, br s), 5.69 (1H, br s), 3.45–3.30 (2H, m, H-2′), 3.30 (3H, s, OCH_3), 2.70 (1H, d, *J* 16.8 Hz), 2.56 (1H, dt, *J* 10.8 and 6.6 Hz), 2.16 (1H, t, *J* 12.9 Hz), 2.02 (1H, d, *J* 16.8 Hz), 1.75 (1H, s), 1.74–1.24 (9H, m), 1.10 (3H, s), 1.05 (3H, s) and 0.98 (3H, s) [3× *tert*-CH_3]; ^{13}C NMR (100 MHz, $CDCl_3$+CCl_4): δ 140.0 (CH, C-11), 132.4 (CH, C-10), 95.3 (C, C-1), 72.5 (CH_2, C-2′), 70.0 (CH, C-2), 58.4 (CH_3, OCH_3), 52.2 (CH_2), 49.2 (CH_2), 49.0 (CH), 48.3 (CH), 46.5 (C), 45.6 (C), 40.6 (CH_2), 32.3 (CH_3), 28.6 (CH_2), 28.2 (CH_3), 17.3 (CH_3); HRMS: *m*/*z* calcd for $C_{17}H_{28}O_2$ (M+Na): 287.1987; Found: 287.1988.

3.1.5. (1S,6S,8R,10S)-10-(2-Methoxyethyl)-8,11,11-trimethyltricyclo[6.3.0.0^{2,6}*]undec-2-en-4-one* ***18****.* To a magnetically stirred suspension of PCC (77 mg, 0.36 mmol) and silica gel (77 mg) in CH_2Cl_2 (0.5 mL) was added a solution of the alcohol **17** (25 mg, 0.1 mmol) in CH_2Cl_2 (1 mL) and stirred for 30 min. The reaction mixture was then filtered through a small silica gel column with CH_2Cl_2. Evaporation of the solvent and purification of the residue on a silica gel column using ethyl acetate/hexane (1:20) as eluent furnished the enone 18 (16 mg, 67%) as oil. R_f (10% EtOAc/hexane) 0.5; $[\alpha]_D^{25}$ −111.0 (*c* 1.5, $CHCl_3$); IR (neat): ν_{max}/cm^{-1} 1709 (C=O), 1627, 1387, 1296, 1261, 1235, 1186, 1154, 1119, 959, 848, 814; ^1H NMR (400 MHz, $CDCl_3$+CCl_4): δ 5.81 (1H, s, H-3), 3.50–3.30 (2H, m, H-2′), 3.31 (3H, s, OCH_3), 3.06 (1H, br s), 2.57 (1H, dd, *J* 18.0 and 6.4 Hz), 2.46 (1H, s, H-1), 2.15–1.50 (7H, m), 1.50–1.25 (6H, m), 1.15 (6H, s) and 0.67 (3H, s) [3× *tert*-CH_3]; ^{13}C NMR (100 MHz, $CDCl_3$+CCl_4): δ 210.3 (C, C=O), 191.0 (C, C-2), 126.3 (CH_2, C-3), 72.3 (CH_2, C-2′), 64.3 (CH, C-1), 58.5 (CH_3, OCH_3), 51.7 (C), 47.2 (CH), 45.5 (C), 45.3 (CH), 45.1 (CH_2), 44.3 (CH_2), 42.6 (CH_2), 30.7 (CH_3), 30.1 (CH_3), 29.1 (CH_2), 19.4 (CH_3); HRMS: *m*/*z* calcd for $C_{17}H_{26}O_2$ (M+Na): 285.1830; Found: 285.1820.

3.1.6. (1R,4S,6R,8R,10S)-10-(2-Methoxyethyl)-4,8,11,11-tetramethylbicyclo[6.3.0.0^{2,6}*]undec-2-en-4-ol* ***19****.* To a magnetically stirred solution of the enone **18** (15 mg, 0.05 mmol) in anhydrous THF (0.2 mL) was added a solution of methylmagnesium chloride (2.5 M, 0.08 mL, 0.2 mmol) and stirred for 1 h at 0 °C. The reaction was then quenched with aq NH_4Cl (0.5 mL) and extracted with ether (2×3 mL). The combined organic extract was washed with brine (1 mL) and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue over a silica gel column using ethyl acetate/hexane (1:9) as eluent furnished the alcohol **19** (10 mg, 63%), containing varying amount (5–10%) of its hydroxy epimer, as oil. R_f (20% EtOAc/hexane) 0.5; $[\alpha]_D^{25}$ −60.3 (*c* 0.5, $CHCl_3$); IR (neat): ν_{max}/cm^{-1} 3417 (OH), 1365, 1269, 1119, 935; ^1H NMR (400 MHz, $CDCl_3$+CCl_4): δ 5.25 (1H, s, H-3), 3.50–3.25 (2H, m, H-2′), 3.32 (3H, s, OCH_3), 2.95–2.75 (1H, m), 2.27 (1H, dd, *J* 12.2 and 6.9 Hz), 2.12 (1H, s, H-1), 1.95–1.40 (5H, m), 1.34 (3H, s, *tert*-CH_3), 1.30–1.20 (3H, m), 1.12 (3H, s) and 1.04 (3H, s) [2× *tert*-CH_3], 0.90 (1H, t, *J* 10.8 Hz), 0.60 (3H, s, *tert*-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$+CCl_4): δ 154.2 (C, C-2), 128.2 (CH, C-3), 88.4 (C, C-4), 72.6 (CH_2, OCH_2), 62.2 (CH), 58.5 (CH_3, OCH_3), 52.2 (C), 50.6 (CH_2), 48.8 (CH), 46.9 (CH_2), 46.6 (CH), 45.3 (CH_2), 44.5 (C), 30.7 (CH_3), 30.3 (CH_3), 29.4 (CH_2), 27.3 (CH_3), 18.7 (CH_3); HRMS: *m*/*z* calcd for $C_{18}H_{30}O_2Na$ (M+Na): 301.2144; Found: 301.2144.

3.1.7. (1S,5R,7S)-3,3-Diallyl-7-(2-methoxyethyl)-5,8,8-trimethylbicyclo[3.3.0]octan-2-one ***20****.* To a magnetically stirred suspension of NaH (60% dispersion in oil, 208 mg, 5.2 mmol, washed with dry hexanes) in THF (1 mL) was added a solution of

the ketone **14** (280 mg, 1.3 mmol) in THF (1 mL) and stirred for 30 min at rt. Allyl bromide (0.4 mL, 5.2 mmol) was added to the reaction mixture and stirred for 5 h at rt. It was then quenched with water (3 mL) and extracted with ether (2×5 mL). The combined organic extract was washed with brine (5 mL) and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue over a silica gel column using ethyl acetate/hexane (1:20) as eluent furnished the ketone 20 (280 mg, 74%) as oil. R_f (5% EtOAc/hexane) 0.55; $[\alpha]_D^{27}$ −23.8 (*c* 2.3, $CHCl_3$); IR (neat): ν_{max}/cm^{-1} 3077, 1723 (C=O), 1639, 1385, 1366, 1291, 1252, 1184, 1120, 997, 959, 914; ^{1}H NMR (400 MHz, $CDCl_3$+CCl_4): δ 5.66 (2H, ddt, *J* 17.1, 9.1 and 7.4 Hz, 2× C*H*=CH_2), 5.25–4.65 (4H, m, 2× CH=C*H*$_2$), 3.50–3.25 (2H, m), 3.28 (3H, s, OCH_3), 2.35–1.95 (5H, m), 1.95–1.50 (6H, m), 1.43 (1H, t, *J* 12.2 Hz), 1.25 (3H, s), 1.14 (3H, s) and 0.68 (3H, s) [3× *tert*-CH_3]; ^{13}C NMR (100 MHz, $CDCl_3$+CCl_4): δ 222.7 (C, C=O), 134.2 (CH) and 133.4 (CH) [2× *C*H=CH_2], 118.4 (CH_2) and 118.0 (CH_2) [2× CH=*C*H_2], 72.1 (CH_2, OCH_2), 71.5 (CH, C-1), 58.4 (CH_3, OCH_3), 56.0 (C, C-3), 49.3 (CH_2), 48.5 (CH), 47.8 (CH_2), 46.2 (C), 42.0 (C), 41.4 (CH_2), 39.8 (CH_2), 32.5 (CH_3), 29.1 (CH_3), 28.6 (CH_2), 18.6 (CH_3); HRMS: *m*/*z* calcd for $C_{20}H_{32}O_2$ (M+Na): 327.2300; Found: 327.2300.

3.1.8. (1S,5R,7S)-7-(2-Methoxyethyl)-3,3-bis(2-oxopropyl)-5,8,8-trimethylbicyclo[3.3.0]octan-2-one ***21****.* A suspension of palladium chloride (13 mg, 0.08 mmol) and cuprous chloride (107 mg, 0.80 mmol) in DMF (2 mL) and water (1 mL) was magnetically stirred in an oxygen atmosphere, created by evacuative displacement of air (balloon), for 1 h at rt. A solution of the diallylated ketone **20** (50 mg, 0.16 mmol) in DMF (2 mL) was added to the reaction mixture and stirred for 4 h at rt in oxygen atmosphere. 1 N aq HCl (2 mL) was then added to the reaction mixture and extracted with ether (2×5 mL). The combined organic extract was washed with brine (5 mL) and dried (Na_2SO_4). Evaporation of the solvent and purification of the product over a silica gel column using ethyl acetate/hexane (1:20) as eluent furnished the triketone 21 (48 mg, 85%) as oil. R_f (10% EtOAc/hexane) 0.5; $[\alpha]_D^{25}$ −19.2 (*c* 1.4, $CHCl_3$); IR (neat): ν_{max}/cm^{-1} 1716 (C=O), 1385, 1362, 1157, 1119; ^{1}H NMR (400 MHz, $CDCl_3$+CCl_4): δ 3.50–3.30 (2H, m, OCH_2), 3.30 (3H, s, OCH_3), 3.08 and 2.65 (2H, 2× d, *J* 17.6 Hz), 2.60 and 2.48 (2H, 2× d, *J* 17.6 Hz), 2.43 (1H, s, H-1), 2.11 (3H, s) and 2.05 (3H, s) [2× CH_3C=O], 1.98 and 1.91 (2H, 2× d, *J* 14.6 Hz, H-4), 1.85–1.50 (6H, m), 1.28 (3H, s), 1.18 (3H, s), 0.74 (3H, s) [3× *tert*-CH_3]; ^{13}C NMR (100 MHz, $CDCl_3$+CCl_4): δ 222.8 (C, C-2), 206.0 (C) and 205.9 (C) [2× CH_3*C*=O], 72.3 (CH_2, OCH_2), 70.7 (CH, C-1), 58.5 (CH_3, OCH_3), 51.6 (C, C-3), 50.6 (CH_2), 48.6 (CH_2), 48.5 (CH_2), 47.9 (CH), 47.0 (CH_2), 45.1 (C), 43.1 (C), 31.5 (CH_3), 31.3 (CH_3), 30.7 (CH_3), 30.3 (CH_3), 29.0 (CH_2), 19.8 (CH_3); HRMS: *m*/*z* calcd for $C_{20}H_{32}O_4$ (M+Na): 359.2198; Found: 359.2196.

3.1.9. (1S,5R,7S)-7-(2-Methoxyethyl)-2′,5,8,8-tetramethylbicyclo[3.3.0]octane-spiro[3.1′]cyclo-hex-4′-en-2,3′-diones ***22****.* To a magnetically stirred solution of the trione **21** (40 mg, 0.13 mmol) in THF (2 mL) was added 1 M KOH in MeOH (0.26 mL, 0.26 mmol), and the reaction mixture was stirred for 15 min. Solvent was then evaporated under reduced pressure. The residue was taken in ether (5 mL), washed with brine (3 mL) and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue over a silica gel column using ethyl acetate/hexane (1:4) as eluent furnished a 1:2 mixture of the spiro enedione 22 (20 mg, 53%) as oil. R_f (20% EtOAc/hexane) 0.55; $[\alpha]_D^{26}$ −5.7 (1.5 *c*, $CHCl_3$); IR (neat): ν_{max}/cm^{-1} 1725 (C=O), 1668 (C=O), 1380, 1366, 1319, 1288, 1249, 1157, 1119; ^{1}H NMR (400 MHz, $CDCl_3$+CCl_4): 2:1 mixture of spiroenones **22**, important signals δ 5.82 and 5.86 (1H, s), 3.50–3.30 (2H, m, OCH_2), 3.29 (3H, s), 1.27 (3H, s), 1.16 and 1.15 (3H, s), 0.69 and 0.67 (3H, s) [3× *tert*-CH_3]; ^{13}C NMR (100 MHz, $CDCl_3$+CCl_4): 2:1 mixture of spiroenones **22**: signals due to the major spiroenone: δ 220.6 (C, C-2), 195.9 (C, C-3′), 158.9 (C, C-5′), 126.0 (CH, C-4′), 71.9 (CH_2, OCH_2), 71.6 (CH), 58.5 (CH_3, OCH_3), 55.5 (C), 50.9 (CH_2), 49.6 (CH_2), 48.8 (CH), 47.0 (C), 45.3 (CH_2), 42.4 (C), 39.8 (CH_2), 32.5 (CH_3), 28.7 (CH_2), 28.2 (CH_3), 24.5 (CH_3), 18.3 (CH_3); Signals due to the minor spiroenone: δ 220.8 (C, C-2), 196.8 (C, C-3′), 157.1 (C, C-5′), 126.4 (CH, C-4′), 71.8 (CH_2, OCH_2), 72.0 (CH), 58.5 (CH_3, OCH_3), 55.3 (C), 50.5 (CH_2), 49.2 (CH_2), 48.8 (CH), 47.0 (C), 44.6 (CH_2), 42.4 (C), 40.6 (CH_2), 32.7 (CH_3), 28.6 (CH_2), 28.3 (CH_3), 24.5 (CH_3), 18.3 (CH_3); HRMS: *m*/*z* calcd for $C_{20}H_{30}O_3$ (M+Na): 341.2093; Found: 341.2091.

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