Tetrahedron: *Asymmetry* 19 (2008) 1509–1513

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

Total synthesis of aculeatins A and B from D-glucose

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ARTICLE INFO

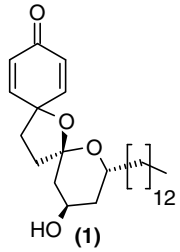
Article history:
Received 14 May 2008
Accepted 28 May 2008

ABSTRACT

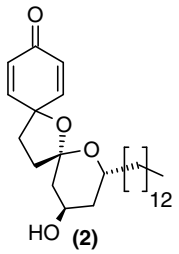
A simple and highly efficient total synthesis of cytotoxic dioxa-dispiroketals aculeatins A and B is disclosed. The key steps include alkynylation of a chiral aldehyde and in situ deprotection, spirocyclization of a 3,5-acetonide protected ketone.

1. Introduction

Several spirocyclic natural products possess interesting biological properties.[1] Among them epimeric dioxa-dispiroketals, aculeatins A–D[2,3] and aculeatols[4] isolated from the terrestrial plant species *Amomum aculeatum Roxb.* (Fam. Zingiberaceae) exhibited high cytotoxicity against the KB cancer cell lines as well as antiprotozoal activity against *Plasmodium falciparum* strains K1 and NF54. The observed biological activity of the aculeatins may be allied to the presence of a Michael acceptor moiety.[5] In addition, aculeatin A(1) was found to be active against MCF-7 (human breast cancer) cells.[6] The biological potential of these compounds has stimulated significant interest in the synthesis of aculeatins A and B. First, a synthesis of racemic aculeatins A **1** and B **2** was carried out by Wong et al.[7] Subsequently, these were synthesized in enantiomerically pure form by Marco et al.,[8] Chandrasekhar et al.[9a] and Peuchmaur and Wong.[9b]

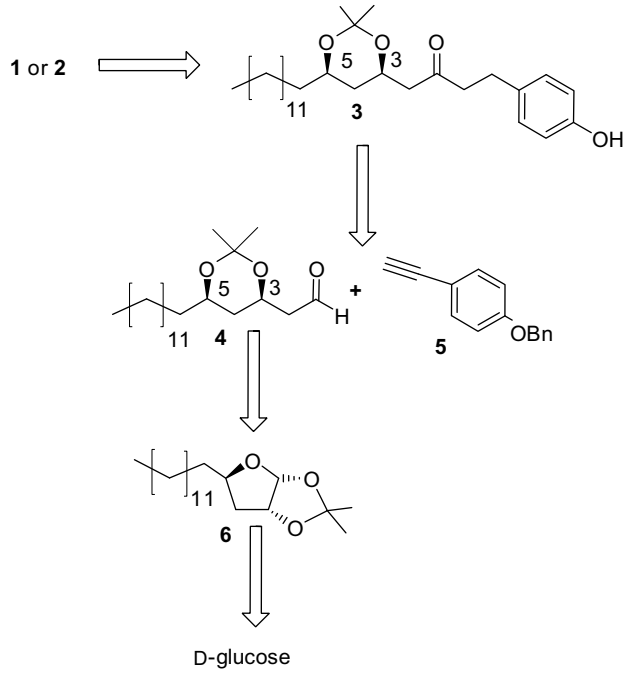


(1)



(2)

Herein, we report an efficient and practical total synthesis of the aculeatins A and B from commercially available D-glucose. From our retrosynthetic analysis of compound **1** (or) **2** (Scheme 1), we envisaged that the key intermediate **3** can be derived from modified D-glucose **6** and 4-benzyloxy phenyl acetylene **5**.



Scheme 1. Retrosynthesis of aculeatins A and B.

2. Results and discussion

Our synthesis (Scheme 2) started from 3-deoxy-1,2:5,6-di-*O*-isopropylidine-α-D-glucofuranose **7**, which was prepared from commercially available D-glucose following the reported procedure.[10] Regioselective deprotection of the 5,6-*O*-isopropylidene moiety of **7** with 0.8% H_2SO_4 in MeOH at ambient temperature afforded diol **8** in 85% yield. Introduction of the *n*-tridecyl group at the C-4 position was achieved in three steps: (i) oxidative

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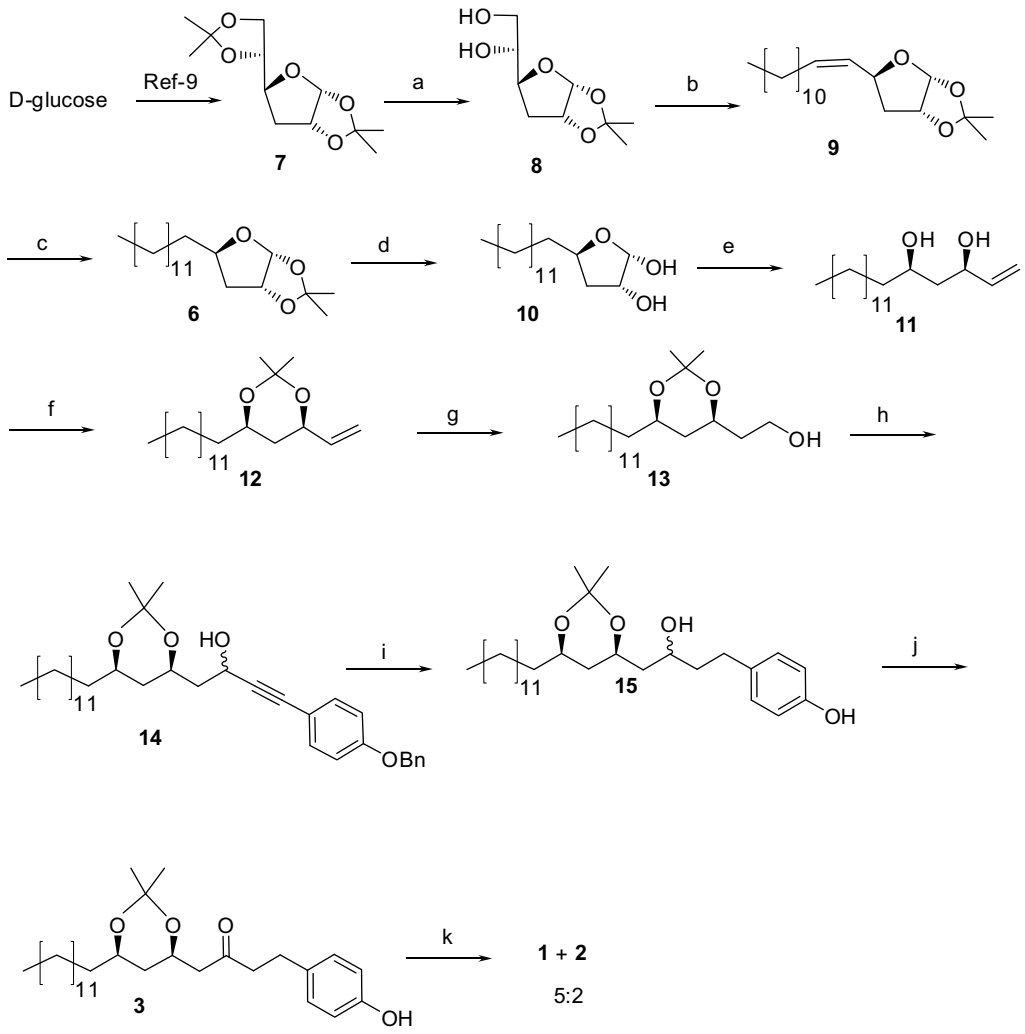
doi:10.1016/j.tetasy.2008.05.028



Scheme 2. Reagents and conditions: (a) 0.8% aq H_2SO_4, MeOH, rt, 85%; (b) (i) $NaIO_4$ on silica gel, CH_2Cl_2, 96%; (ii) *n*-$C_{12}H_{25}P^+Ph_3Br^-$, KO*t*Bu, THF, 0 °C to rt, 75%; (c) 10% Pd–C, H_2, EtOAc, rt, 1 h, 98%; (d) (i) 4% aq H_2SO_4, THF, 60 °C, 4 h, 92%; (e) CH_3PPh_3I, KO*t*Bu, THF, 0 °C, 5 h, 80%; (f) PTSA (cat), 2,2-dimethoxypropane, acetone, rt, 0.5 h, 98%; (g) $(Cy)_2BH$, THF, 0 °C, 97%; (h) (i) IBX, DMSO, CH_2Cl_2, rt, 4 h, 95%; (ii) 4-benzyloxyphenyl acetylene, *n*-BuLi, THF, −78 °C, 2 h, 85%; (i) 10% Pd–C, H_2, EtOAc, rt, 5 h, 88%; (j) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, then Et_3N, −78 to 0 °C, 89%; (k) $PhI(OOCCF_3)_2$, 5 mol % CF_3COOH, Me_2CO/H_2O (9:1), rt, 4 h, 72% overall, 5:2 mixture of aculeatins A and B.

cleavage of diol **8** using silica gel-supported $NaIO_4$;[11] (ii) a twelve carbon homologation using *n*-dodecayltriphenylphosphonium bromide and KO*t*Bu in THF at 0 °C and (iii) followed by hydrogenation using 10% Pd–C to afford **6** in 87% overall yield. Deprotection of the 1,2-*O*-isopropylidine group[12] of **6** with 4% aqueous sulfuric acid in THF at 60 °C gave the epimeric lactols **10** in 90% yield. This was subjected to a Wittig olefination[13] with in situ generated methylene triphenyl phosphorane to afford 3,5-*syn* diol olefinic intermediate **11**. Protection of the 1,3-*syn* diol intermediate **11** using 2,2-dimethoxy propane, in acetone using *p*-TSA afforded **12** in 98% yield, followed by selective hydroboration using dicyclohexyl borane in THF yielded alcohol **13** in 97% yield. This alcohol was oxidized using IBX to furnish aldehyde **4** (not isolated), which was subjected to reaction with lithiated 4-benzyloxyphenyl acetylene[14] to yield the corresponding alkynols[15] **11** in 85% yield. Benzyl deprotection of alkynols **11** using 10% Pd–C/H_2 in ethyl acetate gave a mixture of **12** in 88% yield. Alcohol **12** was oxidized under Swern conditions to afford **3**. In a previous report, the prolonged reaction time of secondary acetonide deprotection and subsequent phenolic oxidation and spiro acetalization[16] of **3**[7] using phenyliodonium(III) bis (trifluoroacetate) in acetone–H_2O (9:1) gave aculeatins A and B in a 5.5: 1 ratio in 24 h. Here we reduced this reaction time to 4 h by the addition of 5 mol % of CF_3COOH and produced, in almost equal selectivity, aculeatins A and B (5:2) in 70% yield. The physical and spectroscopic data of compounds **1** and **2** were in good agreement with the reported data of natural aculeatins A **1** and B **2**.[1] All the compounds were fully characterized by ^1H NMR, ^{13}C NMR, mass and IR spectroscopy.

3. Conclusion

In conclusion, a simple, highly efficient and chiral pool approach towards the total synthesis of aculeatins A and B has been developed using the alkynylation of a chiral aldehyde and rapid in situ deprotection and phenolic oxidative spiroacetylation. In our synthesis, 3,5-*syn* diols are taken from the chiron D-glucose.

4. Experimental

4.1. General methods

Solvents were dried over standard drying agents and freshly distilled prior to use. Chemicals were purchased and used without further purification. All column chromatographic separations were

performed using silica gel (Acme's, 60–120 mesh). Organic solutions were dried over anhydrous Na_2SO_4 and concentrated below 40 °C in vacuo. ^1H NMR (200 MHz and 300 MHz) and ^{13}C NMR (50 MHz and 75 MHz) spectra were measured with a Varian Gemini FT-200 MHz spectrometer and Bruker Avance 300 MHz with tetramethylsilane as the internal standard for solutions in deuteriochloroform. *J* values are given in Hertz. IR spectra were recorded on Perkin–Elmer IR-683 spectrophotometer with NaCl optics. Optical rotations were measured with JASCO DIP 300 digital polarimeter at 25 °C. Mass spectra were recorded on CEC-21-11013 or Fannigan Mat 1210 double focusing mass spectrometers operating at a direct inlet system or LC/MSD Trap SL (Agilent Technologies).

4.1.1. (1*S*)-1-[(3a*R*,5*R*,6a*R*)-2,2-Dimethylperhydrofuro[2,3-*d*]-[1,3]dioxol-5-yl] ethane-1,2-diol 8

To a stirred solution of compound **7** (1.44 g, 5.90 mmol) in methanol (20 mL) was added 0.8% H_2SO_4 solution (5 mL). After completion of the reaction, methanol was removed under reduced pressure after which was added a saturated $NaHCO_3$ (20 mL) solution. It was extracted into chloroform (5 × 50 mL) and dried over anhydrous Na_2SO_4. The solvent was removed under vacuum, and the residue purified by flash column chromatography (silica gel, 60–120 mesh; hexane/ethyl acetate = 1:9) to afford compound **8** as a white solid (1 g, 83% yield): IR (neat): 3423, 2985, 2934, 1641, 1377, 1016 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 5.73 (d, 1H, J = 3.77 Hz), 4.68 (m, 1H), 4.15 (m, 1H), 4.13 (td, 1H, J = 4.53, 5.28 Hz), 3.82 (m, 1H), 3.64 (dd, 1H, J = 3.02 Hz), 3.53 (dd, 1H, J = 6.79 Hz), 3.18 (br s, 1H), 2.92 (br s, 1H), 2.02(dd, 1H, J = 4.53, 13.59 Hz), 1.79 (dd, 1H, J = 4.53, 3.02, 10.57, 6.04 Hz), 1.47 (s, 3H), 1.29 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 111.55, 105.0, 80.4, 78.3, 72.2, 64.1, 33.6, 26.4, 25.9; ESI-MS: m/z 227 $[M+Na]^+$.

4.1.2. (3a*R*,5*S*,6a*R*)-2,2-Dimethyl-5-[(*Z*)-1-tridecenyl]perhydrofuro[2,3-*d*][1,3]dioxole 9. Preparation of silica gel-supported $NaIO_4$ reagent

$NaIO_4$ (2.57 g, 12.0 mmol) was dissolved in 5 mL of hot water (70 °C) in a 25 mL round-bottomed flask. To the hot solution was added silica gel (230–400 mesh, 10 g) with vigorous swirling and shaking. The resultant silica gel coated with $NaIO_4$ was in powder form and free-flowing.

To a solution of the vicinol diol **8** (926 mg, 4.54 mmol) in CH_2Cl_2 (30 mL) was added this silica gel-supported $NaIO_4$ reagent (9.0 g). After completion of the reaction, the silica gel was filtered and washed with dichloromethane (5 × 10 mL). Removal of the solvent afforded the aldehyde (960 mg, 96% yield), which was used for the next reaction without purification. To a stirred suspension of *n*-dodecyl phosphonium bromide (6.12 g, 12.2 mmol) in dry THF (50 mL) at 0 °C was added *t*-BuOK (1.15 g, 10.28 mmol) and the solution was stirred for 2 h. To this, a solution of aldehyde (642 mg, 4.11 mmol) in dry THF (10 mL) was added dropwise at 0 °C and slowly warmed to room temperature and stirred for 4 h. After completion of the reaction, it was quenched with saturated aq ammonium chloride (20 mL), extracted into ethyl acetate (3 × 60 mL), washed with brine, dried over anhydrous $Na_2S_2O_4$ and concentrated under reduced pressure. The crude product **9** was purified on silica gel column chromatography (silica gel, 60–120 mesh; hexane/ethyl acetate = 9:1) to obtain pure compound **9** (1.0 g) in 75% yield as a colourless syrup. $[\alpha]_D^{25} = -10.5$ (*c* 0.82, $CHCl_3$); IR (film): 2925, 2854, 1459, 1375, 1019, 847, 759 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 5.73 (d, 1H, J = 3.77), 5.49 (m, 1H), 5.29 (m, 1H), 4.87 (td, 1H J = 3.77, 4.53), 4.65 (t, 1H, J = 3.77), 2.06 (m, 3H), 1.49 (br s, 4H), 1.27 (br s, 7H), 1.24 (br s, 16H), 0.86 (t, 3H, J = 6.79); ^{13}C NMR (75 MHz, $CDCl_3$): δ 134.1, 127.9, 111.85, 105.2, 80.6, 73.3, 39.7, 31.8, 29.5 (br, several overlapped signals), 29.3, 29.1, 27.8, 26.7, 26.1, 22.6, 14.1 (br, several overlapped signals), 29, 25, 22.5, 20, 14; ESI-MS: m/z 284, 325 $[M+1]^+$.

4.1.3. (3a*R*,5*R*,6a*R*)-2,2-Dimethyl-5-tridecylperhydrofuro[2,3-*d*][1,3]dioxole 6

To a stirred solution of olefin **9** (932 mg, 2.88 mmol) in ethyl acetate (5 mL) was added 10% Pd/C (50 mg) under hydrogen atmosphere. After 1 h, the catalyst was filtered and removal of solvent afforded **6**, which was purified on silica gel column chromatography (silica gel, 60–120 mesh; hexane/ethyl acetate = 9:1) to obtain compound **6** (918 mg, 98% yield) as a yellow syrup; $[\alpha]_D^{25} = -12.3$ (*c* 1.7, $CHCl_3$); IR (neat): 2925, 2854, and 1021 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 5.72 (1H, d, J = 3.7), 4.64 (1H, td, J = 4.53, 3.77), 4.1 (1H, m), 2.02–2.06 (1H, dd, J = 12.8, 3.7), 1.6 (1H, m), 1.47 (3H, s), 1.34–1.42 (2H, m), 1.28 (3H, s), 1.26 (19H, br s), 0.893 (3H, t, J = 7.5); ^{13}C NMR (75 MHz, $CDCl_3$): δ 111, 106, 81, 78, 40, 35, 32, 30 (br, several overlapped signals), 27.5, 27, 23, 14; ESI-MS: m/z 344 $[M+Na^+]$.

4.1.4. (3*R*,5*R*)-5-Tridecyltetrahydro-2,3-furandiol 10

To a solution of **6** (868 mg, 2.67 mmol) in tetrahydrofuran (20 mL) was added 4% aq H_2SO_4 solution (2 mL) and then stirred at 70 °C temperature for 6 h. After completion of the reaction, the reaction mass was extracted into ethyl acetate (4 × 25 mL). The combined organic layer was washed with saturated aq $NaHCO_3$, brine solution, and the organic layer dried over anhydrous Na_2SO_4. Removal of the solvent gave epimeric lactols **10**, which was purified on silica gel column chromatography (silica gel, 60–120 mesh; hexane/ethyl acetate = 1:1) to obtain compound **10** (700 mg, 92% yield) as a white solid. $[\alpha]_D^{25} = +5$ (*c* 0.5, $CHCl_3$); IR (neat): 3423, 3353, 2919, 2848, 1460, 1081 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 5.27(d, 1H, J = 3.7), 4.2 (m, 2H), 1.92–1.60 (m, 2H), 1.26 (br s, 20H), 0.89 (t, 3H, J = 6,79); ^{13}C NMR (75 MHz, $CDCl_3$): δ 102.7, 76.4, 71.9, 38.7, 37.8, 35.9, 31.9, 29.65, 29.62 (br, several overlapped signals), 26.21, 25.8, 22.69, 14.17; ESI-MS: m/z 286 [M], 304 $[M+18]^+$.

4.1.5. (3*R*,5*R*)-1-Octadecene-3,5-diol 11

To a mixture of methyl triphenylphosphonium iodide (2.76 g, 6.84 mmol) and potassium *tert*-butoxide (639 mg, 5.69 mmol) was added dry THF (50 mL) at room temperature and stirred under N_2 for 4 h, after which stirring was stopped and the solid was allowed to settle. The clear supernatant orange-yellow liquid was cannulated into the solution of compound **10** (650 mg, 2.28 mmol) in dry THF (10 mL) at −78 °C. The reaction mixture was brought to room temperature and stirred for 3 h. After completion of the reaction, the reaction was quenched with saturated aq ammonium chloride solution and extracted into ethyl acetate (3 × 40 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and the removal of solvent under reduced pressure gave crude product **11** as a pale yellow syrup which was purified on silica gel column chromatography (hexane/ethyl acetate = 1.2:1) to obtain pure diol **11** (518 mg, 80% yield) as a white solid. $[\alpha]_D^{25} = -3.2$ (*c* 0.87, $CHCl_3$); IR (neat): 3281, 2919, 2849, 1465, 1317, 1073 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 5.8 (m, 1H), 5.26 (dt, 1H, J = 17.18, 1.56), 5.03–5.18 (dt, 1H, J = 10.15), 4.33 (m, 1H), 3.83 (q, 1H, J = 2.34), 3.24 (br s, 2H), 1.59 (m, 2H), 1.25 (br s, 24H), 0.88 (t, 3H, J = 7.03); ^{13}C NMR (75 MHz, $CDCl_3$): δ 141.1, 114.5, 96.5, 74.1, 72.7, 43.3, 38.5, 32.3, 30.0 (br, several overlapped signals), 29.7, 25.7, 23.0, 14.5; ESI-MS: m/z 285, 307, 363 $[M+39]^+$.

4.1.6. (4*R*,6*R*)-2,2-Dimethyl-4-tridecyl-6-vinyl-1,3-dioxane 12

To a solution of compound **11** (500 mg, 1.76 mmol) in dry acetone (15 mL) and 2,2-dimethoxypropane (0.36 mL, 3.52 mmol) were added *p*-toluenesulfonic acid (30 mg, 0.17 mmol) and activated 3 Å molecular sieves (0.5 g) after which the reaction was stirred for 30 min at room temperature. After completion of the reaction, the molecular sieves were filtered and aq saturated $NaHCO_3$ solution (10 mL) was added and extracted into CH_2Cl_2

(3 × 30 mL). The combined organic layer was dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to afford crude compound **12** as a colourless syrup. Purification of the crude product on silica gel column chromatography (hexane/ethyl acetate = 9:1) gave **12** (559 mg, 98% yield) as a colourless liquid. $[\alpha]_D^{25} = +1.25$ (*c* 1.2, $CHCl_3$); IR (neat): 3050, 2925, 2854, 1646, 1462 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 5.8 (m, 1H), 5.1–5.3 (m, 2H), 4.28 (m, 1H), 3.85 (m, 1H), 1.53 (s, 3H), 1.41 (s, 3H), 1.25 (br s, 26H), 0.88 (t, 3H, *J* = 7.05); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.9, 115.1, 98.5, 70.3, 68.7, 36.8, 36.4, 31.9, 30.2, 29.6 (br, several overlapped signals), 29.3, 24.9, 22.6, 19.7, 14.0; ESI-MS: *m*/*z* 325 $[M+1]^+$.

4.1.7. 2-[(4*S*,6*R*)-2,2-Dimethyl-6-tridecyl-1,3-dioxane-4-yl]-1-ethanol 13

To a solution of cyclohexene (0.435 mL, 4.62 mmol) in THF (20 mL) at 0 °C was added BH_3–DMS (0.212 mL, 2.31 mmol). The reaction mixture was warmed to room temperature and stirred for 1 h at rt. To this, olefin **12** (500 mg, 1.54 mmol) in THF (5 mL) was added at 0 °C and then stirred at 0 °C for 12 h. The reaction mixture was oxidized by the addition of methanol (0.5 mL), 3 M aq NaOH solution (1 mL) and 30% aq H_2O_2 solution (0.9 mL). After stirring at room temperature for 10 h, water was added and the organic layer was extracted into ethyl acetate (4 × l30 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure to give crude product **13**. The resulting crude product was purified on silica gel column chromatography (hexane/ethyl acetate = 4:1) to afford pure compound **13** (511 mg, 97% yield) as a colourless liquid. $[\alpha]_D^{25} = -25$ (*c* 0.68, $CHCl_3$); IR (neat): 3314 (OH), 2919, 2850, 1196 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 4.08 (1H, m), 3.73 (3H, m), 2.4 (1H, br s, –OH), 1.69 (2H, m), 1.45 (3H, s), 1.37 (3H, s), 1.27 (26H, br s), 0.90 (3H, *J* = 7.55); ^{13}C NMR (75 MHz, $CDCl_3$): δ 96.0, 69.7, 69.5, 61, 39, 37, 36, 32, 30.5, 29.5 (br, several overlapped signals), 29, 25, 22.5, 20, 14; ESI-MS: *m*/*z* 365.3 $[M+Na]^+$.

4.1.8. 4-[4-(Benzyloxy)phenyl]-1-[(4*S*,6*R*)-2,2-dimethyl-6-tridecyl-1,3-dioxan-4-yl]-3-butyn-2-ol 14

To a stirred solution of 2-iodoxybenzoic acid (IBX) (573 mg, 2.04 mmol) in DMSO (2 mL) was added a solution of **13** (500 mg, 1.46 mmol) in THF (10 mL) at room temperature and stirred for 4 h. After completion of the reaction as monitored by TLC, water (10 mL) was added to the reaction mixture, and the precipitated solid was filtered off and the filtrate diluted with water (50 mL) and extracted into ether (4 × 50 mL). The combined organic layer was washed with aqueous $NaHCO_3$, water, brine and dried over Na_2SO_4. Removal of the solvent afforded aldehyde **4** (472 mg, 95% yield), which was used for the next reaction without purification. To a solution of 1-(benzyloxy)-4-(1-ethynyl)benzene **5** (406 mg, 1.94 mmol) in THF (20 mL) at −78 °C was added *n*-BuLi (1.21 mL of a 1.6 M solution in hexanes, 1.94 mmol) and stirred 20 min for anion generation. To this anion solution, aldehyde **4** (472 mg, 1.29 mmol) in THF (5 mL) was added slowly. The resulting solution was slowly warmed to ambient temperature over 2 h, and quenched by the addition of saturated aq ammonium chloride solution (20 mL). The organic layer was extracted into ethyl acetate (3 × 30 mL), and the combined organic layer was washed with brine, and dried over anhydrous Na_2SO_4. Removal of solvent under reduced pressure afforded the mixture of crude products **14**. The resulting syrup was purified on silica gel column chromatography (hexane/ethyl acetate = 9:1) and gave racemic alkynols in the ratio of 1:2 (from ^1H NMR without separation) **14** (600 mg, 84% yield) as a colourless liquid. $[\alpha]_D^{25} = -28$ (*c* 0.68, $CHCl_3$); IR (neat): 3435 (OH), 2924, 2853, 1507, 1243 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.40 (5H, m), 7.32–7.35 (2H, d, *J* = 9.0), 6.86–6.89 (2H, d, *J* = 9.0), 5.06 (2H,s), 4.77 (1H, t, *J* = 6.7), 4.15 (1H, m), 3.81 (1H, m), 2.78 (OH, br s), 2.04 (1H, m), 1.86 (1H, m), 1.46 (3H, s), 1.39 (3H, s), 1.28 (27H, br s), 3.73 (3H), 2.4 (1H, br s), 1.69 (2H, m), 1.45 (3H, s), 1.37 (3H, s), 1.27 (27 H, br s), 0.91 (3H, t, *J* = 6.7); ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.7, 136.6, 133.0, 128.5, 127.9, 127.2, 114.7, 98.4, 96.1, 88.5, 84.5, 69.85, 68.80, 68.16, 61.27, 44.10, 37.03, 36.39, 31.94, 30.26, 29.67 (several overlapped signals), 29.38, 22.69, 19.81, 14.20; EIMS: *m*/*z* 548 (M−1), 530 (M−18).

4.1.9. (4*S*,6*R*)-4-[(*R*)-2-Hydroxy-4-(4-hydroxyphenyl)butyl]-2,2-dimethyl-6-tridecyl-[1,3]dioxane 15

To a solution of compound **14** (300 mg, 0.54 mmol) in EtOAc (10 mL) was added Pd–C 10% (50 mg) and stirred under an H_2 atmosphere for 7 h. After completion, the reaction mass was filtered through Celite and the solvent was removed under reduced pressure to give crude product **15.** Purification of the crude product using column chromatography on silica gel (hexane–EtOAc, 4:1) gave a mixture of alcohols **15** (222 mg, 88% yield) as a colourless solid; $[\alpha]_D^{25} = -25$ (*c* 0.4, $CHCl_3$). IR (film): 3386 (OH), 2929, 1724, 1257, 1076 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 6.95 (d, 2H, *J* = 8.59), 6.69 (d, 2H, *J* = 8.59), 4.06 (m, 1H), 3.81 (m, 2H), 2.61 (t, 2H, *J* = 8.59), 1.46–1.82 (m, 4H), 1,45 (s, 3H), 1.37 (s, 3H), 1.26 (br s, 28H), 0.89 (t, 3H, *J* = 7.03); ^{13}C NMR (75 MHz, $CDCl_3$): δ 154.0, 133.6, 129.3, 115.2, 98.6, 71.1, 70.5, 68.8, 42.9, 39.5, 37.3, 36.2, 31.9, 30.7, 30.2, 29.6 (br, several overlapped signals), 29.5, 29.3, 24.9, 22.6, 19.9, 14.1; ESI-MS: *m*/*z* 485.4 $[M+Na]^+$.

4.1.10. 1-[(4*R*,6*R*)-2,2-Dimethyl-6-tridecyl-[1,3]dioxan-4-yl]-4-(4-hydroxyphenyl)-butane-2-one 3

To a solution of oxalyl chloride (73.2 μL, 0.86 mmol) in dry CH_2Cl_2 (3 mL) under N_2 was added DMSO (141 μL, 1.29 mmol) at −78 °C. After 10 min, a solution of alcohol **15** (200 mg, 0.43 mmol) in dry CH_2Cl_2 (5 mL) was added dropwise. The addition of Et_3N (0.3 mL, 2.15 mmol) was followed by stirring for 15 min at −78 °C and for a further 1 h at 0 °C. After completion of the reaction, the resulting mixture was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and evaporated to give crude product **3** and the resulting syrup was purified on silica gel column chromatography (hexane/ethyl acetate = 7:3) to obtain the pure ketone **3** (177 mg, 89% yield) as a colourless solid; $[\alpha]_D^{25} = -4.0$ (*c* 0.55, $CHCl_3$). IR (film): 3395 (OH), 2919, 2851, 1703, 1614, 1514, 1381 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 6.98 (d, 2H, *J* = 8.30), 6.69 (d, 2H, *J* = 8.30), 5.19 (br s, 1H), 4.24 (m, 1H), 3.76 (m, 1H), 2.82–2.68 (br m, 4H), 2.63 (dd, 1H, *J* = 15.86, 7.55), 2.35 (dd, 1H, *J* = 15.8, 5.28), 1.49 (m, 1H), 1.39 (s, 3H), 1.31 (s, 3H), 1.26 (br m, 24H), 1.11 (q, 1H, *J* = 11.33), 0.89 (t, 3H, *J* = 6.79); ^{13}C NMR (75 MHz, $CDCl_3$): δ 208.5, 153.9, 133.0, 129.4, 115.2, 98.6, 68.8, 65.8, 49.4, 46.6, 36.8, 36.3, 31.9, 30.1, 29.6 (br, several overlapped signals), 29.5, 29.3, 28.6, 24.9, 22.6, 19.7, 14.1; HR EIMS *m*/*z* (rel. int.) 483.34 [M+Na].

4.1.11. (2*R*,4*R*,6*R*)-4-Hydroxy-2-tridecyl-1,7-dioxadispiro-[5.1.5.2]pentadeca-9,12-dien-11-one (aculeatin A) 1 and (2*R*,4*R*,6*S*)-4-hydroxy-2-tridecyl-1,7-dioxadispiro-[5.1.5.2]pentadeca-9,12-dien-11-one (aculeatin B) 2

To a solution of ketone **3** (150 mg, 0.32 mmol) in an acetone–water mixture (9:1, 10 mL) was added $PhI(OCOCF_3)_2$ (412 mg, 0.96 mmol) in a single portion followed by the dropwise addition of CF_3COOH (1.2 μL, 0.0161 mmol). The reaction mixture was stirred for 4 h at room temperature in the dark. After completion of the reaction, water was added and extracted into ethyl acetate (3 × 25 mL). The combined organic layer was dried over anhydrous sodium sulfate and concentrated to give crude mixture of aculeatin A **1** and aculeatin B **2** which was purified on silica column eluting with hexane–EtOAc to yield **1** (70 mg) and **2** (28 mg). Aculeatin A **1**: Oil; $[\alpha]_D^{25} = -5.2$ (*c* 0.73, $CHCl_3$); IR (neat): 3417 (OH), 2925,

2854, 1671, 1630, 1512, 1461, 1099 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 6.85 (dd, 1H, J = 9.82, 3.02),6.78 (dd, 1H, J = 9.82, 3.02), 6.14 (dd, 1H, J = 9.82, 1.51), 6.09 (dd, 1H, J = 10.5, 2.26), 4.05–4.15 (m, 2H), 3.32 (br s, 1H), 2.38 (m, 1H), 2.24 (m, 1H), 1.93–2.04 (m, 3H), 1.94 (br d, 1H, J = 14.3), 1.76 (br d, 1H, J = 13.5), 1.60–1.40 (br m, 4H), 1.21–1.37 (br m, 21H), 0.87 (t, 3H, J = 6.79); ^{13}C NMR (75 MHz, $CDCl_3$): δ 185.3, 150.9, 148.8, 127.4, 127.2, 109.1, 79.8, 65.4, 64.9, 39.2, 38.0, 35.9, 34.2, 32.0, 29.7 (br, several overlapped signals), 29.6, 29.4, 25.7, 22.7, 14.1; HR EIMS m/z (rel. int.) 441.29 [M+Na].

AculeatinB **2**: Oil; $[\alpha]_D^{25} = +54$ (c 0.2, $CHCl_3$); IR (neat): 3417(OH), 2925, 2854, 1671, 1630, 1512, 1461, 1099 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 6.99 (dd, 1H, J = 9.80, 3.02), 6.78 (dd, 1H, J = 9.80, 3.02), 6.14 (dd, 1H, J = 9.82, 1.61), 6.09 (dd, 1H, J = 9.82, 1.61), 4.36 (apparent quintuplet, J = 3.1), 3.87 (m, 1H), 2.68 (br dd, 1H, J = 12.8, 7.2 Hz), 2.30 (td, 1H, J = 12.3, 7.2), 2.10–2.00 (m, 2H), 1.95–1.84 (m, 2H), 1.60–1.40 (br m, 8H), 1.40–1.20 (br m, 19H), 0.88 (t, 3H, J = 6.9); ^{13}C NMR (75 MHz, $CDCl_3$): δ 185.5, 151.0, 148.5, 127.5, 127.3, 109.3, 79.9, 65.5, 65.0, 39.3, 38.2, 36.1, 34.4, 32.1, 29.9 (br, several overlapped signals), 29.8, 29.5, 25.8, 22.9, 14.3; HR EIMS m/z (rel. int.) 441.29 [M+Na].

Acknowledgements

The authors are thankful to UGC, CSIR, New Delhi, Ministry of Earth Sciences (MoES), and Department of Biotechnology (DBT), New Delhi, India, respectively, for financial support and Dr. J. S. Yadav, Director, Indian Institute of Chemical Technology (IICT), for his encouragement.

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