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Total synthesis of aculeatins A and B from (*S*)-malic acid

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ABSTRACT

A simple convergent approach towards the total synthesis of bioactive spiroacetals aculeatins A and B is described. The key features of the synthetic strategy include a *syn*-stereoselective 1,3-asymmetric reduction, epoxide ring opening and oxidative spirocyclization reaction by employing (*S*)-malic acid as the starting material.

1. Introduction

There has been considerable interest in spirocyclic natural products from synthetic as well as bioorganic chemists, due to their unique structural properties and promising biological activities. In particular, the epimeric dioxa-dispiroketals and aculeatins A–D which were isolated[1] from the petroleum ether extract of the rhizomes of species *Amomum aculeatum Roxb*. (Fam Zingiberaceae), exhibit high cytotoxicity against the KB cancer cell lines as well as antiprotozoal activity against *Plasmodium falciparum* strains K1 and NF54. It is believed that the presence of a Michael acceptor moiety in the aculeatins structure is responsible for their biological activity.[2] Aculeatin **A 1** has been found to be active against MCF-7 (human breast cancer) cells.[3] In view of these interesting biological activities, efforts have been made to develop some new synthetic approaches for the preparation of these spirocyclic natural products (Fig. 1).[4]

As part of our studies directed towards the synthesis of biologically active molecules,[5] we herein report an efficient and practical approach for the total synthesis of aculeatins **A 1** and **B 2** by employing (*S*)-malic acid; an inexpensive and readily available starting material. The retrosynthetic concept is outlined in Scheme 1. Thus, the dispirocyclic framework of the aculeatins can be created via phenolic oxidation of intermediate ketone **15**, which in turn can be obtained by the condensation of the aldehyde of **11** and 4-benzyloxy-phenyl acetylene. Compound **11** can be formed by the *syn*-stereoselective 1,3-asymmetric reduction of ketone **5**, which in turn can be obtained from *S*-malic acid.

2. Results and discussion

The synthesis of aculeatins **A 1** and **B 2** utilizes the known alcohol **3**, which was derived from (*S*)-malic acid according to a literature procedure.[6] The primary alcohol **3** was subjected to a Swern's oxidation[7] to afford the aldehyde, which was taken up for the Barbier reaction (Zn/allylbromide/aq NH_4Cl/THF) to provide the diastereomeric homoallyl alcohol **4** in 88% yields (Scheme 2).

The diastereomeric ratio of the required compound **6** could be improved upon by subjecting the diastereomeric homoallyl alcohol **4** to an oxidation and reduction protocol to provide the desired diasteriomer **6**. For this purpose compound **4** was subjected to

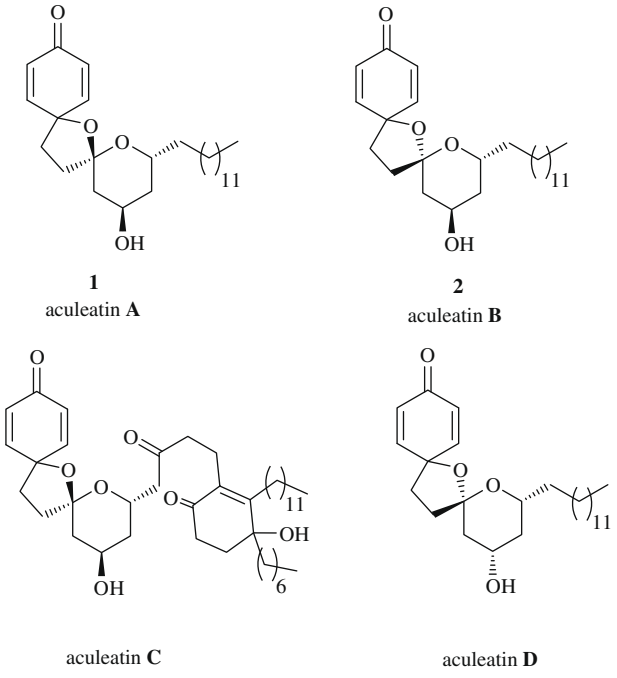

Figure 1. Chemical structures of the aculeatins.

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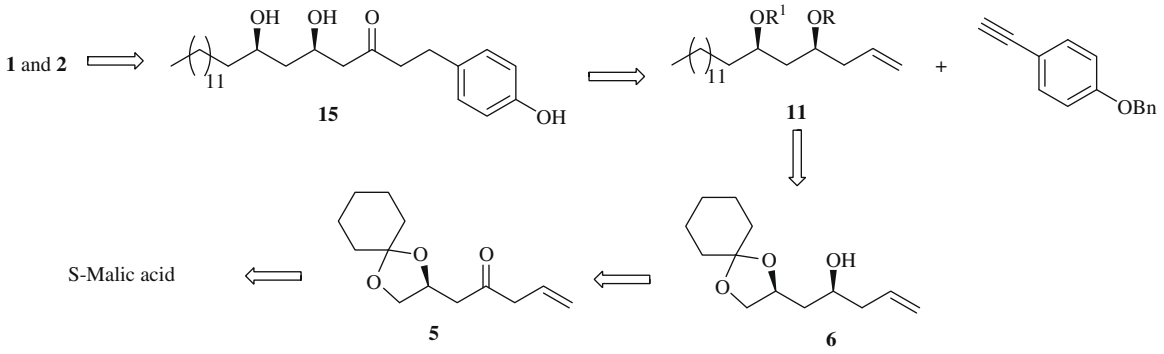
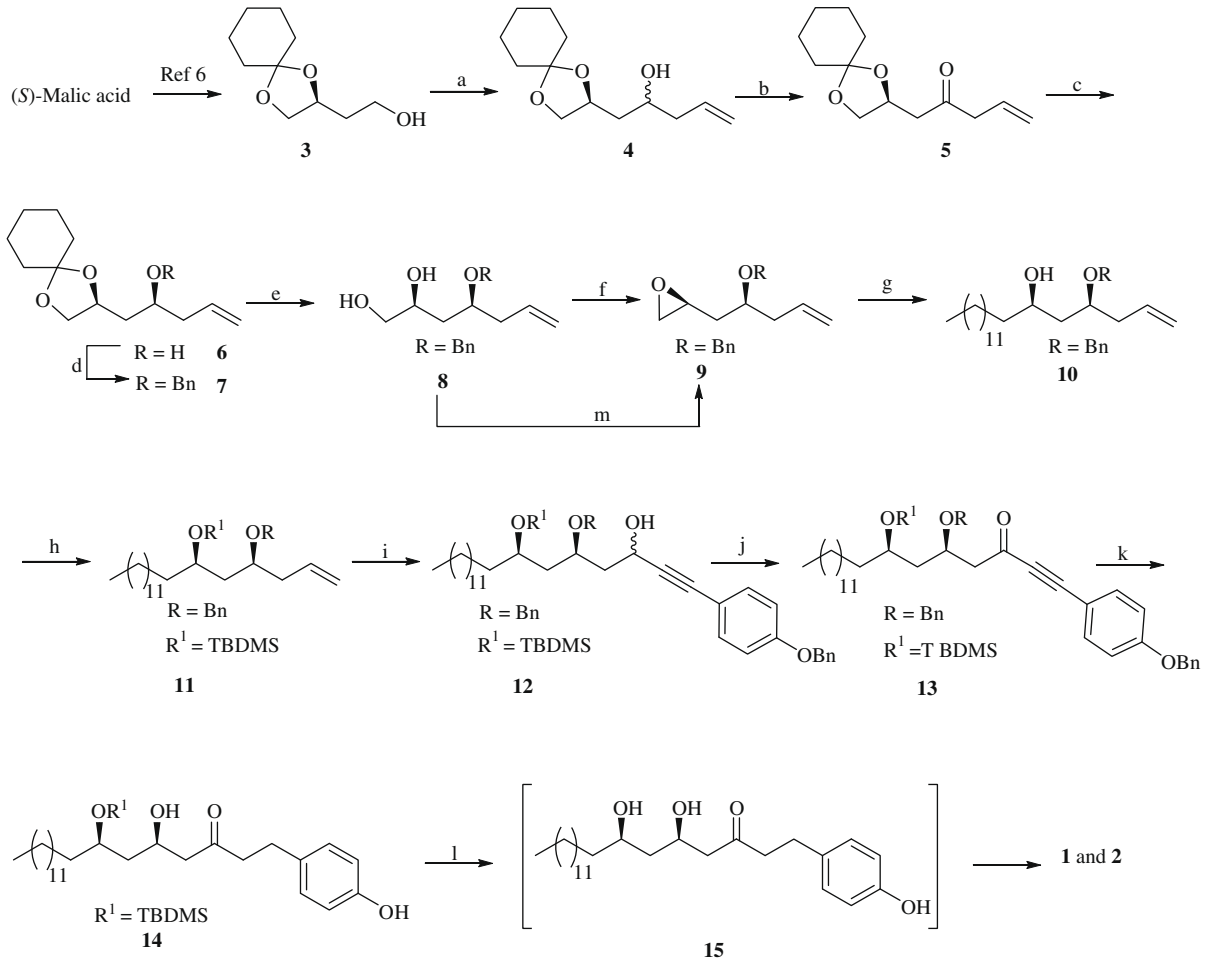


Scheme 1. Retrosynthetic analysis of **1** and **2**.



Scheme 2. Reagents and conditions: (a) (i) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C, 3 h, (ii) Zn, allyl bromide, NH_4Cl, THF, 0 °C to rt, 4 h; (b) IBX, DMSO, CH_2Cl_2, 3 h; (c) LiI–$LiAlH_4$, diethyl ether, −78 °C to −100 °C, 1 h; (d) NaH, BnBr, THF, 0 °C to rt, 8 h; (e) TFA (THF/H_2O 9:1) 0 °C to rt, 6 h; (f) TsCl, Bu_2SnO, Et_3N, CH_2Cl_2, 0 °C to rt, 5 h then K_2CO_3, MeOH, 0 °C, 1 h; (g) $C_{12}H_{25}MgBr$, CuI (cat), THF, −35 °C, 3 h; (h) TBDMSCl, imidazole, CH_2Cl_2, 0 °C to rt, 12 h; (i) (i) OsO_4–$NaIO_4$, 2,6-lutidine, dioxane/water (3:1), 0 °C to rt, 12 h, (ii) *n*-BuLi, 4-benzyloxyphenyl acetylene, THF, −78 °C, 4 h; (j) Dess–Martin periodinate, CH_2Cl_2, 0 °C to rt, 2 h; (k) Pd–C, H_2, EtOAc, rt, 12 h; (l) (i) TBAF, THF, 0 °C to rt, 1 h, (ii) $PhI(OOCCF_3)_2$, Me_2CO–H_2O (9:1), rt, 15 min, 5:2 mixture of aculeatins A and B; (m) NaH, TsCl, THF, 0 °C, 2 h.

oxidation with IBX and DMSO in CH_2Cl_2 to afford ketone **5**, which was taken up for the *syn*-stereoselective 1,3-asymmetric reduction with LiI–$LiAlH_4$ in ether at −100 °C to give the *syn* alcohol **6** in 75% yield (95% de).[8] Protection of the resulting secondary alcohol with BnBr and NaH, in THF afforded **7**, which upon subsequent cyclohexylidene deprotection with TFA (THF/H_2O 9:1) gave diol **8**. Oxirane formation can be achieved by two approaches. In the first method, the selective tosylation of the primary hydroxyl group in **8** using standard conditions TsCl, Bu_2SnO and trimethylamine[9] in CH_2Cl_2 affords an unstable monoprotected tosylated compound, which without further purification was taken up for the cyclization using K_2CO_3 in methanol to afford epoxide **9**. In the second method, to the diol **8** (taken in THF) were added NaH and TsCl as described in the previous one-pot method.[10] The regioselective ring opening of the epoxide with *n*-dodecyl magnesium bromide in the presence of cuprous iodide in dry THF at −35 °C afforded the

secondary alcohol **10** in 79%. Then the hydroxyl group of compound **10** was protected as the TBDMS ether using TBDMSCl and imidazole to afford **11**. The TBDMS ether was selected for the protection of this hydroxyl as it could be easily cleaved before the spiroacetalization step. The one-pot oxidative cleavage of the terminal alkene in **11** using OsO_4–$NaIO_4$, 2,6-lutidine and dioxane/water (3:1) afforded the aldehedye,[11] which was reacted with lithiated 4-benzyloxyphenyl acetylene to give the corresponding diastereomeric alkynol **12**. Compound **12** upon oxidation using Dess–Martin periodinate in CH_2Cl_2 afforded alkynone **13**, which underwent catalytic hydrogenation by using 10% Pd–C in EtOAc to result in debenzylation as well as triple bond reduction to produce **14**. Treatment of **14** with TBAF in THF formed keto-triol **15** (not isolated) and subsequent treatment with phenyliodonium(III)bis(trifluoroacetate) (PIFA) in acetone/water (9:1) resulted in phenolic oxidation as well as spiroacetalization[12] to yield aculeatins **A 1** and **B 2** in a 5:2 ratio in about 15 min, these were separated by column chromatography. The spectroscopic and analytical data were comparable to the previously reported data in the literature.[4b–f]

3. Conclusion

In conclusion, we have developed a simple, convenient and efficient convergent approach for the synthesis of naturally occurring aculeatins **A** and **B** by using a *syn*-stereoselective 1,3-asymmetric reduction and an oxidative spirocyclization reaction. Interestingly, (*S*)-malic acid has been used as the starting material in this protocol.

4. Experimental

4.1. General experimental

Reagents and chemicals were purchased from Aldrich. All solvents and reagents were purified by standard techniques. THF was freshly distilled from $LiAlH_4$. Crude products were purified by column chromatography on 60–120 silica gel. IR spectra were recorded on Perkin–Elmer 683 spectrometer. Optical rotations were obtained on a Horiba 360 digital polarimeter. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution on a Varian Gemini 200, Bruker Avance 300. Chemical shifts are reported in ppm with respect to the internal TMS. Mass spectra were recorded on VG micromass-7070H (70 Ev)

4.2. (2*S*)-2-[(2*S*)-2-(Benzyloxy)-4-pentenyl]-1,4-dioxaspiro[4.5]-decane 7

To a stirred solution of the compound **6** (2.5 g, 11.0 mmol) in dry THF (25 mL) were added sodium hydride (0.52 g, 13.3 mmol, 60%) and benzyl bromide (1.44 mL, 12.1 mmol) at 0 °C, and allowed to stir at room temperature for 8 h. After completion of the reaction, it was quenched with saturated NH_4Cl solution (20 mL). Next, the THF was evaporated, extracted with $CHCl_3$ (2×40 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, 60–120 mesh, EtOAc/hexane 5:95) to afford **7** (3.03 g, 86%) as a yellow oil. $[\alpha]_D^{25} = +4.5$ (*c* 1.1, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ = 1.38 (m, 2H), 1.56 (m, 8H), 1.66 (m, 1H), 1.92 (m, 1H), 2.36 (t, 2H), 3.43 (t, 1H), 3.51 (m, 1H), 3.89 (t, 1H), 4.16 (m, 1H), 4.49 (dd, 2H), 5.07 (m, 2H), 5.8 (m, 1H), 7.28 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): 23.9, 24.0, 25.2, 35.3, 36.65, 37.5, 38.1, 69.1, 70.7, 72.5, 75.5, 108.95, 117.3, 127.4, 127.6, 128.2, 134.3, 138.3; MS–EIMS: *m/z* 339 $(M+Na)^+$; HR ESIMS: *m/z* calcd for $C_{20}H_{28}O_3Na$: 339.1936; found: 339.1945.

4.3. (2*S*,4*S*)-4-(Benzyloxy)-6-heptene-1,2-diol 8

To a stirred solution of the compound **7** (2.7 g, 8.5 mmol) in THF/H_2O (9:1; 30 mL), trifluoroacetic acid (1.26 mL, 17.0 mmol) was added slowly at 0 °C and stirred for an additional 6 h at room temperature. After completion of the reaction, it was quenched with aqueous sodium bicarbonate solution. Next, the THF was evaporated, extracted with EtOAc (2×25 mL), dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography (silica gel, 60–120 mesh, EtOAc/hexane 45:55) to afford **8** (1.63 g, 81%) as a colourless syrup. $[\alpha]_D^{25} = +77.5$ (*c* 1.1, $CHCl_3$); IR (neat): γ_{max}: 3403, 2926, 2870, 1452, 1063, 741, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.55–1.77 (m, 2H), 2.17 (br s, 1H), 2.33–2.41 (m, 2H), 3.36 (m, 1H), 3.48–3.56 (m, 2H), 3.7–3.84 (m, 2H), 4.55 (dd, *J* = 11.3 Hz, 2H), 5.11 (m, 2H), 5.71–5.84 (m, 1H), 7.29 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): 36.8, 37.8, 66.5, 70.7, 71.4, 78.3, 117.9, 127.9, 128.5, 133.5, 137.6; MS–EIMS: *m/z* 237 $(M+H)^+$; HR ESIMS: *m/z* calcd for $C_{14}H_{20}O_3Na$: 259.1310; found: 259.1311.

4.4. (2*S*)-2-[(2*S*)-2-(Benzyloxy)-4-pentenyl]oxirane 9

To a stirred solution of diol **8** (1.4 g, 5.9 mmol) in dry CH_2Cl_2 (25 mL), were added Bu_2SnO (catalytic), *p*-TsCl (1.13 g, 5.9 mmol) and Et_3N (0.99 mL, 7.1 mmol) at 0 °C and allowed to stir at room temperature for 5 h. Later, the reaction mixture was extracted with CH_2Cl_2 (2×25 mL), dried over anhydrous Na_2SO_4 and concentrated in vacuo to afford monotosylated product. This was used for the next step. To a stirred solution of this monotosylated compound taken in dry methanol (20 mL), was added solid K_2CO_3 (1.63 g, 11.8 mmol) at 0 °C and stirred at the same temperature for 1 h. After completion of the reaction, K_2CO_3 was filtered through a Celite pad. Methanol was evaporated and extracted with $CHCl_3$ (2×20 mL). The combined organic phases were dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography (silica gel, 60–120 mesh, EtOAc/hexane 5:95) to afford the compound **9** (0.95 g, 73%, over two steps) as a liquid. $[\alpha]_D^{25} = +25.5$ (*c* 1.1, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 1.69–1.81 (m, 2H), 2.36–2.42 (m, 3H), 2.69 (t, 1H), 3.01 (m, 1H), 3.62 (m, 1H), 4.55 (dd, *J* = 12.1 Hz, 2H), 5.102 (m, 2H), 5.79–5.89 (m, 1H), 7.24–7.32 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$): 36.5, 38.2, 46.65, 49.4, 70.7, 76.2, 117.4, 127.4, 127.5, 128.2, 134.2, 138.4. MS–EIMS: *m/z* 219 $(M+H)^+$; HR ESIMS: *m/z* calcd for $C_{14}H_{18}O_2Na$: 241.1204; found: 241.1203.

4.5. (4*S*,6*R*)-4-(Benzyloxy)-1-nonadecen-6-ol 10

To a stirred solution of **9** (0.85 g, 3.89 mmol) and CuI (catalytic amount) in dry THF (20 mL) was added slowly *n*-dodecyl magnesium bromide {freshly prepared with Mg (0.280 mg, 11.67 mmol), dodecyl bromide (3.08 mL, 12.83 mmol) and I_2 (5 mg) in dry THF (20 mL)} at −35 °C under a nitrogen atmosphere. Then the reaction mixture was stirred for 3 h at the same temperature. After 3 h the reaction was quenched with saturated NH_4Cl solution (20 mL) at 0 °C, after which the THF was evaporated and extracted with ethyl acetate (2×30 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography (silica gel, 60–120 mesh, EtOAc/hexane 10:90) to afford compound **10** (1.2 g, 79%) as a liquid. $[\alpha]_D^{25} = +53.5$ (*c* 1.1, $CHCl_3$); IR (neat): γ_{max}: 3449, 2924, 2853, 1460, 1068, 738, 697 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.88 (t, *J* = 6.8 Hz, 3H), 1.206 (m, 22H), 1.33–1.34 (m, 2H), 1.50–1.57 (m, 2H), 2.32 (m, 2H), 3.26 (br s, 1H), 3.59–3.65 (m, 1H), 4.54 (dd, *J* = 11.3 Hz, 2H), 5.06 (m, 2H), 5.72 (m, 1H), 7.25 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): 14.1, 22.7, 25.4, 29.3, 29.64 (br, several overlapped signals), 31.9,

37.7, 37.9, 40.8, 70.7, 71.6, 79.4, 117.7, 127.8, 128.5, 133.7, 137.7; MS–EIMS: *m/z* 389 $(M+H)^+$; HR ESIMS: *m/z* calcd for $C_{26}H_{44}O_2Na$: 411.3239; found: 411.3230.

4.6. [(1*R*,3*S*)-3-(Benzyloxy)-1-tridecyl-5-hexenyl]oxy(*tert*-butyl)dimethylsilane 11

To a cooled (0 °C) solution of **10** (0.98 g, 2.31 mmol) in CH_2Cl_2 (15 mL), was added imidazole (0.19 g, 2.8 mmol) followed by TBDMSCl (0.38 g, 2.5 mmol) and then stirred for 12 h at room temperature. The reaction mixture was treated with saturated aqueous NH_4Cl solution (15 mL) and extracted with CH_2Cl_2 (2×20 mL), dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography (silica gel, 60–120 mesh, EtOAc/hexane 5:95) to afford **11** (1.03 g, 81%) as a liquid. $[\alpha]_D^{25} = +14.5$ (*c* 1.1, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 0.011 (s, 3H), 0.021 (s, 3H), 0.86–0.90 (m, 12H), 1.25–1.35 (m, 24H), 1.48–1.56 (m, 1H) 1.69–1.76 (m, 1H), 2.25–2.35 (m, 2H), 3.5 (m, 1H), 3.72 (m, 1H), 4.48 (dd, *J* = 11.9 Hz, 2H) 5.06 (m, 2H), 5.81 (m, 1H), 7.19–7.31 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): −4.42, −4.32, 14.1, 18.1, 22.7, 25.1, 25.9, 29.3, 29.66 (br, several overlapped signals), 29.78, 31.9, 37.2, 38.4, 41.5, 69.5, 70.6, 75.6, 117.1, 127.4, 127.7, 128.2, 134.8, 138.8; MS–EIMS: *m/z* 503 $(M+H)^+$; HR ESIMS: *m/z* calcd for $C_{32}H_{58}O_2NaSi$: 525.4103; found: 525.41.

4.7. (5*S*,7*R*)-5-(Benzyloxy)-1-[4-(benzyloxy)phenyl]-7-[1-(*tert*-butyl)-1,1dimethylsilyl]oxy-1-icosyn-3-ol 12

To a stirred solution of compound **11** (0.5 g, 0.99 mmol) in dioxane/water (5 mL, 3:1) were added 2,6-lutidine (0.23 mL, 1.98 mmol), OsO_4 (5 mL in toluene) and $NaIO_4$ (0.426 g, 1.98 mmol) at 0 °C and then the reaction mixture was stirred at room temperature for 12 h. After completion of the reaction, water and CH_2Cl_2 were added. The organic layer was separated and the water layer was extracted by CH_2Cl_2 (2×20 mL). The combined organic phases were dried over anhydrous Na_2SO_4 and concentrated in vacuo to afford the aldehyde, which were used for the next step without further purification. To a stirred solution of 1-(benzyloxy)-4-(1-ethynyl)benzene (0.62 g, 2.9 mmol) in dry THF (10 mL) was added *n*-BuLi (1.55 mL of a 1.6 M solution in hexanes, 2.5 mmol) at −78 °C and stirred for 45 min for the anion generation. To this lithiated 4-benzyloxyphenyl acetylene solution, the above crude aldehyde taken in THF (2 mL) was added dropwise and stirred for 4 h at the same temperature. The reaction was then quenched by the addition of saturated NH_4Cl solution (5 mL). Next, the THF was evaporated and extracted with ethyl acetate (2×15 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography (silica gel, 60–120 mesh, EtOAc/hexane 10:90) to afford compound **12** (0.51 g, 72%, over two steps) as a yellow liquid. $[\alpha]_D^{25} = -39.5$ (*c* 1.1, $CHCl_3$); IR (neat): γ_{max}: 3425, 2926, 2854, 1507, 1461, 1247, 1060, 833, 774, 737, 697 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.044 (s, 3H), 0.049 (s, 3H), 0.865–0.906 (m, 12 H), 1.25 (br s, 22 H) 1.42–1.46 (m, 2H), 1.59–1.68 (m, 2H), 1.90–2.16 (m, 2H), 3.55 (d, *J* = 7.5 Hz, 1H), 3.68–3.78 (m, 1H), 4.04–4.17 (m, 1H), 4.45–4.64 (m, 2H), 4.81 (td, *J* = 3.8, 7.5 Hz, 1H), 5.06 (s, 2H), 6.9 (d, 2H), 7.25–7.43 (m, 12H). ^{13}C NMR (75 MHz, $CDCl_3$): −4.4, −4.2, 14.0, 17.98, 22.7, 25.0, 25.9, 29.3, 29.64 (br, several overlapped signals), 29.78, 31.9, 37.7, 41.1, 41.2, 60.0, 69.3, 69.9, 71.2, 75.1, 84.7, 88.7, 114.7, 127.4, 127.7, 127.8, 127.9, 128.04, 128.09, 128.47, 128.57, 133.1, 136.5, 137.99,158.7; MS–EIMS: *m/z* 713 $(M+H)^+$; HR ESIMS: *m/z* calcd for $C_{46}H_{68}O_4NaSi$: 735.4784; found: 735.4803.

4.8. (5*R*,7*R*)-5-(Benzyloxy)-1-[4-(benzyloxy)phenyl]-7-[1-(*tert*-butyl)-1,1 dimethylsilyl]oxy-1-icosyn-3-one 13

To a stirred solution of compound **12** (0.4 g, 0.56 mmol) in CH_2Cl_2 (10 mL), Dess–Martin periodinate (0.26 g, 0.62 mmol) was added at 0 °C and stirred for 2 h. After completion of the reaction, it was quenched with aqueous sodium thiosulfate solution (5 mL) and saturated aqueous sodium bicarbonate solution (2 mL). The reaction mixture was extracted with CH_2Cl_2 (2×10 mL), dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography (silica gel, 60–120 mesh, EtOAc/hexane 7:93) to afford **13** (0.35 g, 87%) as a yellow liquid. $[\alpha]_D^{25} = +4.5$ (*c* 1.1, $CHCl_3$); IR (neat): γ_{max}: 2926.4, 2854.8, 2196.5, 1665.0, 1251.4, 1072.2, 834.4, 736.6, 697.6 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 0.032 (s, 3H), 0.045 (s, 3H), 0.857–0.926 (m, 12 H), 1.17–1.34 (m, 22 H), 1.36–1.45 (m, 2H) 1.54–1.65 (m, 1 H), 1.79–1.89 (m, 1 H), 2.8 (dd, *J* = 15.8 Hz, 1H), 2.92 (dd, *J* = 15.8 Hz, 1H), 3.74 (m, 1H), 4.12 (m, 1H), 4.52 (dd, *J* = 11.3 Hz, 2H), 5.08 (s, 2H), 6.91 (d, *J* = 9.1 Hz, 2H), 7.17–7.41 (m, 10 H), 7.44 (d, *J* = 9.1 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): −4.4, −4.3, 14.1, 18.0, 22.7, 25.1, 25.9, 29.3, 29.6 (br, several overlapped signals), 29.76, 31.9, 37.1, 41.7, 50.8, 69.4, 70.1, 71.4, 72.9, 88.2, 92.2, 111.95, 115.1, 127.4, 127.5, 127.8, 128.2, 128.6, 135.1, 136.05, 138.3, 160.9, 185.9; MS–EIMS: *m/z* 711 $(M+H)^+$; HR ESIMS: *m/z* calcd for $C_{46}H_{66}O_4NaSi$: 733.4628; found: 733.4618

4.9. (5*R*,7*R*)-7-[1-(*tert*-Butyl)-1,1-dimethylsilyl]oxy-5-hydroxy-1-(4-hydroxyphenyl)icosan-3-one 14

To a stirred solution of compound **13** (0.3 g, 0.42 mmol) in ethyl acetate (5 mL) was added Pd-C (10%) (catalytic amount) under a hydrogen atmosphere and stirred for 12 h. After completion of the reaction, it was filtered through a Celite pad. Concentration of the filtrate gives the crude product, which was purified by column chromatography (silica gel, 60–120 mesh, EtOAc/hexane 35:65) to afford **14** (0.18 g, 80%) as a yellow syrup. $[\alpha]_D^{25} = -4.5$ (*c* 1.1, $CHCl_3$); IR (neat): γ_{max}: 3385, 2926, 2855, 1706, 1515, 1254, 1079, 834, 720, 665 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.068 (s, 3H), 0.073 (s, 3H), 0.861–0.903 (m, 12 H), 1.25 (m, 22H), 1.41–1.57 (m, 4H), 2.48 (t, *J* = 6.8 Hz, 2H), 2.67 (m, 2H), 2.79 (m, 2H), 3.38 (d, 1H), 3.88 (m, 1H), 4.1 (m, 1H), 4.9 (s, 1H), 6.67 (d, *J* = 8.3 Hz, 2H), 6.98 (d, *J* = 8.3 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): −4.6, −4.1, 14.1, 17.9, 22.6, 24.7, 25.8, 28.6, 29.3 (br, several overlapped signals), 29.6, 31.9, 37.5, 42.4, 45.4, 49.8, 66.98, 72.2, 115.3, 129.3, 132.4, 154.4, 210.4; MS–EIMS: *m/z* 535 $(M+H)^+$; HR ESIMS: *m/z* calcd for $C_{32}H_{58}O_4NaSi$: 557.4002; found: 557.4001.

4.10. (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

Compound **14** (0.14 g, 0.26 mmol) was dissolved in dry THF (10 mL), cooled to 0 °C and TBAF (0.86 mL, 0.86 mmol, 1 M in THF) was slowly added. The reaction mixture was stirred for 1 h at room temperature. After completion of the reaction, it was quenched with water, then THF was evaporated, extracted with $CHCl_3$ (2×10 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure affords an oily compound **15**, which was used directly in the next step without purification. The above crude material was dissolved in a 9:1 acetone/water (10 mL) system and $PhI(OOCCF_3)_2$ (0.225 g, 0.52 mmol) was added. The reaction mixture was stirred at room temperature for 15 min in the dark. After completion of the reaction, water was added and extracted with ethyl acetate. The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography (silica gel, 60–120 mesh, EtOAc/hexane 25:75) to yield **1** (0.049 g, 45%) and **2** (0.019 g, 17%).

4.10.1. Aculeatin A 1

$[\alpha]_D^{25} = -5.3$ (*c* 1.1, $CHCl_3$); IR (neat): γ_{max}: 3552, 2925.2, 2853.8, 1673.0, 1632.7, 1099.3, 1000.8 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.88 (t, *J* = 6.8 Hz, 3H), 1.22–1.36 (br m, 21H), 1.39–1.47 (br m, 4H), 1.75 (br d, *J* = 14.3 Hz, 1H), 1.93 (br m, *J* = 14.3 Hz, 1H), 1.94–2.03 (m, 3H), 2.22 (m, 1H), 2.36 (m, 1H), 3.2 (br s, 1H), 4.06–4.09 (m, 2H), 6.09 (dd, *J* = 2.26, 10.04 Hz, 1H), 6.13 (dd, *J* = 2.26, 10.04 Hz, 1H), 6.75 (dd, *J* = 3.02, 10.57 Hz, 1H), 6.82 (dd, *J* = 3.02, 10.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): 14.07, 22.63, 25.59, 29.4, 29.7 (br, several overlapped signals), 31.9, 34.1, 35.84, 37.9, 39.04, 64.8, 65.4, 79.78, 109.0, 127.01, 127.3, 148.7, 150.8, 185.3; MS–EIMS: *m/z* 419 $(M+H)^+$; HR ESIMS: *m/z* calcd for $C_{26}H_{42}O_4Na$: 441.2980; found: 441.2961.

4.10.2. Aculeatin B 2

$[\alpha]_D^{25} = +53.5$ (*c* 1.1, $CHCl_3$); IR (neat): γ_{max}: 3552, 2925.2, 2853.8, 1673.0, 1632.7, 1099.3, 1000.8 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.88 (7, *J* = 6.7 Hz, 3H), 1.25–1.35 (br m, 19H), 1.42–1.66 (br m, 8H), 1.85–1.95 (m, 2H), 2.01–2.09 (m, 2H), 2.29 (td, *J* = 7.3, 12.4 Hz, 1H), 2.67, (br dd, *J* = 7.3, 13.1 Hz, 1H), 3.8 (m, 1H), 4.36 (apparent quintuplet, *J* = 3.1, 6.4 Hz, 1H), 6.1 (dd, *J* = 9.7, 2.0 Hz, 1H), 6.13 (dd, *J* = 9.7, 2.0 Hz, 1H), 6.77 (dd, *J* = 2.9, 10.2 Hz, 1H), 6.98 (dd, *J* = 2.9, 10.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): 14.08, 22.8, 25.9, 29.32, 29.5, 29.8, (br, several overlapped signals), 31.9, 35.26, 35.7, 37.9, 40.56, 65.08, 69.44, 77.54, 108.67, 127.1 (two signals), 149.4, 152.28, 185.66; MS–EIMS: *m/z* 419 $(M+H)^+$; HR ESIMS: *m/z* calcd for $C_{26}H_{42}O_4Na$: 441.2980; found: 441.2961.

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