Total Synthesis of Aculeatins A and B from L-Malic Acid

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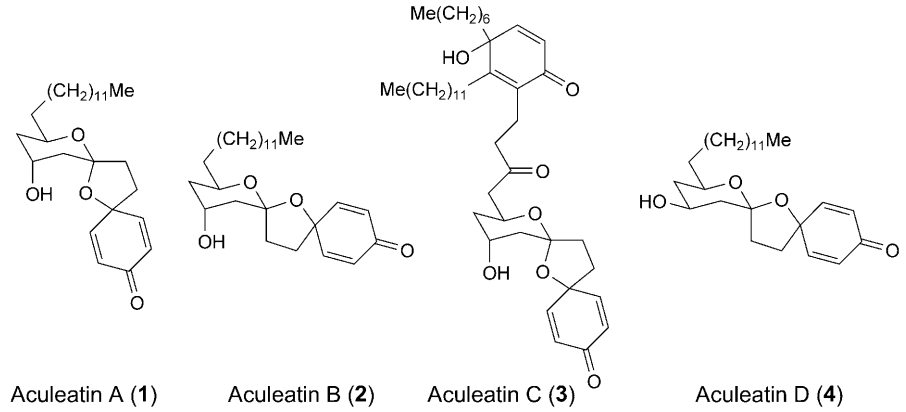
An efficient total synthesis of the cytotoxic spiroketal natural products aculeatin A and B is described. The synthesis of the 1,3,5-triol moiety with appropriate configuration was accomplished from the commercially available L-malic acid. The key steps in this synthesis are the *Barbier* allylation, $LiAlH_4$/LiI-mediated *syn*-stereoselective 1,3-asymmetric reduction, and phenyliodine bis(trifluoroacetate) (= [bis(trifluoroacetoxy)iodo]benzene; PIFA) mediated oxidative spirocyclization.

Introduction. – In 2000, *Heilmann et al.* reported the isolation of the three biologically active spiroketals aculeatins A – C (**1** – **3**, resp.) from the extract of *Amomum aculeatum* (Zingiberaceae) [1]. *Amomum aculatum* is a herbaceous plant distributed in Malaysia, Indonesia, and Papua New Guinea. It is used as a folk medicine to treat fever and malaria [2], *etc*. The aculeatins A – C (**1** – **3**, resp.) were identified as potent inhibitors of the human tumor KB cell line, and they also displayed promising activity against the *Plasmodium falciparum* strains K1 and NF 54. The same group discovered aculeatin D (**4**) from the same family, and reported its remarkably high cytotoxic, antibacterial, and antiprotozoal activities [2]. The observed biological activities of the aculeatins may be related to the presence of the *Michael*-acceptor moiety[1]). Aculeatins A – D (**1** – **4**, resp.) represent a novel kind of natural compounds, which display the unprecedented spirocyclic 1,7-dioxadispiro[5.1.5.2]pentadecane system. The first total synthesis of racemic aculeatins A and B has been reported by *Wong* [4] in 2002. Subsequently, the enantioselective synthesis of aculeatins A and B has been accomplished by *Marco* and co-workers in 2005 [5]. Recently, *Baldwin et al.* have reported for the first time the total synthesis of aculeatin D [6]. Later, a number of other syntheses have also been appeared in literature. Many of these approaches utilize phenol oxidation as a final step to construct the spirocyclic system [7].

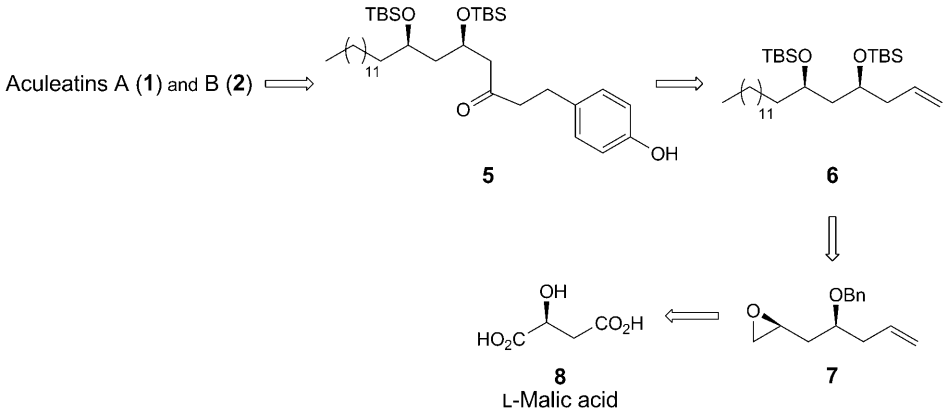
The potent cytotoxicity together with the novel structural features of aculeatins A and B make them attractive synthetic targets. In this article, we wish to disclose the total synthesis of aculeatin A (**1**) and its spiro-epimer aculeatin B (**2**) from the commercially available and inexpensive starting material L-malic acid. This strategy mainly relies on the *Barbier* allylation, *syn*-stereoselective 1,3-asymmetric reduction, and phenyliodine(III) bis(trifluoroacetate) (PIFA)-mediated oxidative phenol spirocyclization.

[1]) For the importance of *Michael* acceptor moieties for cytotoxicity, see, *e.g.*, [3].



The retrosynthetic analysis for **1** and **2** is depicted in *Scheme 1*. The spiroketal system could be generated *via* phenol oxidation of the appropriate intermediate ketone **5**, which can be prepared from the terminal epoxide **7** *via* alkene **6**. From epoxide **7**, one can access their functionalized analogs very easily by the late-stage introduction of the alkyl chain and aromatic segments. The epoxide **7** could be easily prepared from L-malic acid.

Scheme 1. *Retrosynthetic Analysis of Aculeatin A* (**1**) *and Aculeatin B* (**2**)

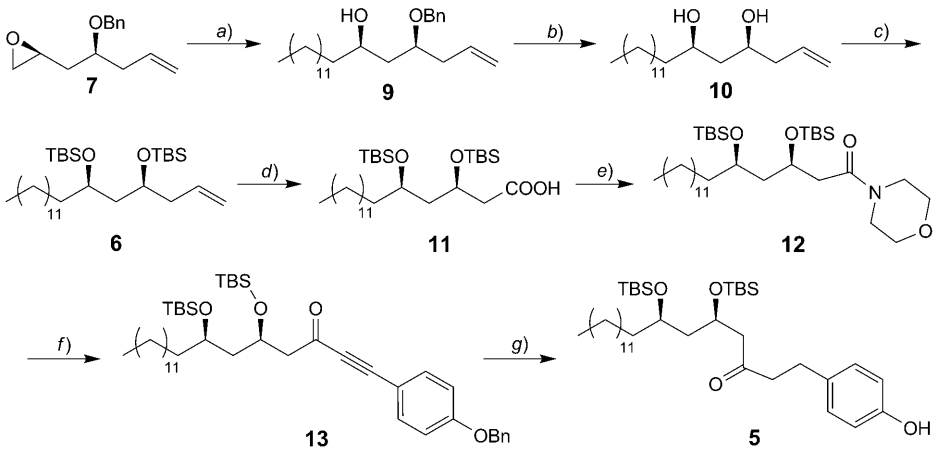


Results and Discussion. – The synthesis of aculeatins started from epoxide **7**, which was easily prepared from L-malic acid according to known procedures [8].

The regioselective opening of epoxide **7** with $C_{12}H_{25}MgBr$ (prepared from $C_{12}H_{25}Br$ and Mg in Et_2O) in the presence of CuI in THF gave the secondary alcohol **9** in good yield (*Scheme 2*). Deprotection of **9** using Li-naphthalene in THF gave the diol **10**, which was further converted into its TBSO derivative **6** in 90% yield using TBSOTf and 2,6-lutidine. The terminal alkene **6** was subjected to ozonolytic cleavage, followed by oxidation with $NaClO_2/NaH_2PO_4$ to afford the acid **11**, which was further converted

into the amide **12** by treatment with morpholine and diisopropylcarbodiimide (DIC). Treatment of **12** with lithiated [4-(benzyloxy)phenyl]acetylene in THF [9] afforded the alkynone **13**. Debenzylation and a subsequent alkyne reduction of **13** were achieved in a single step using Pd/C under H_2 atmosphere to provide compound **5** in 90% yield [10] (*Scheme 2*). In a synthesis reported in [7f], 1,3-diol was protected as acetonide, and then the terminal olefin was subjected to hydroboration, a reaction which was well studied by *Gurjar* and co-workers [11]. The resulting alcohol was converted into an aldehyde, and then treated with lithiated [4-(benzyloxy)phenyl]acetylene to yield the corresponding alkynol, which was subsequently converted into the corresponding ketone. In the present protocol, the key intermediate was synthesized *via* the substitution of morpholinamide with lithiated [4-(benzyloxy)phenyl]acetylene to accomplish alkynone **13** directly as described in *Scheme 2*.

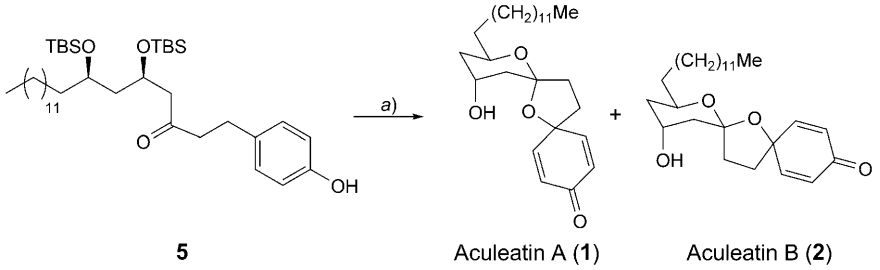
Scheme 2



a) $C_{12}H_{25}MgBr$, CuI, THF, 0° → r.t., 2 h; 80%. *b*) Li, naphthalene, THF, –78°, 1 h; 90%. *c*) TBSOTf (TBS = (*t*-Bu)Me_2Si, Tf = CF_3SO_2), 2,6-lutidine, CH_2Cl_2, 0° → r.t., 4 h; 90%. *d*) 1. O_3, Ph_3P, CH_2Cl_2, – 78°; 2. $NaClO_4$, NaH_2PO_4. *e*) Morpholine, diisopropylcarbodiimide (DIC), 4-(dimethylamino)pyridine (DMAP), CH_2Cl_2, 0° → r.t., 3 h; 85%. *f*) [4-(Benzyloxy)phenyl]acetylene, BuLi, THF, – 78°, 1 h; 92%. *g*) H_2 (1 atm), 10% Pd/C, AcOEt, r.t., 5 h; 90%.

The deprotection of the TBS ethers in **5** with TBAF in THF afforded the corresponding diol, which was used as such (without further purification) for the oxidative spirocyclization using PIFA (phenyliodine(III) bis(trifluoroacetate)) in acetone/H_2O 10 : 1 (*v*/*v*) to furnish a mixture of aculeatin A (**1**), which is thermodynamically more stable (stabilized by a favorable anomeric effect) [12] and its spiroepimer aculeatin B (**2**) in 64% overall yield in a ratio of 5 : 2. These stereoisomers were smoothly separated by column chromatography. Aculeatin A (**1**) was obtained in 46% and aculeatin B (**2**) in 18% yield. The physical and spectroscopic data of compounds **1** and **2** were in good agreement with the data reported in [7] (*Scheme 3*).

Scheme 3



a) Bu_4NF (TBAF), THF, 0°, 30 min, then $PhI(OC(O)CF_3)_2$, acetone/H_2O 10:1, r.t., 4 h; 64% (aculeatin A (**1**; 46%) and aculeatin B (**2**; 18%)).

In conclusion, we have accomplished an efficient total synthesis of the naturally occurring cytotoxic spiroketals aculeatin A (**1**) and its spiroepimer aculeatin B (**2**). The synthesis of the 1,3,5-triol core has been achieved starting from the commercially available and inexpensive L-malic acid. The synthesis involves *Barbier* allylation, $LiAlH_4$/LiI-mediated *syn*-stereoselective 1,3-asymmetric reduction [8a], and PIFA-mediated oxidative spirocyclization as key steps. This approach employs the late-stage introduction of the alkyl chain and aromatic segments which provides sufficient flexibility for the synthesis of various analogs of aculeatins.

Experimental Part

General. The solvents were dried over standard drying agents and freshly distilled prior to use. The reagents were purchased from *Aldrich* and *Acros*, and were used without further purification unless otherwise stated. The preparation of epoxide **7** was described in [8a]. All moisture-sensitive reactions were carried out under N_2. Org. solns. were dried over anh. Na_2SO_4 and concentrated *in vacuo* below 40°. Column chromatography (CC): silica gel (SiO_2; *Acme*'s 60–120 mesh). Optical rotations: *Horiba* high-sensitive polarimeter *SEPA-300* at 25°. IR Spectra: *Perkin-Elmer IR-683* spectrophotometer with NaCl optics. ^{1}H- (200 and 300 MHz) and ^{13}C-NMR (50 and 75 MHz) spectra: *Varian Gemini FT-200* and *Bruker Avance 300* instruments with TMS as internal standard in $CDCl_3$; *J* values are given in Hz. MS: *Agilent Technologies 1100 Series* (*Agilent* ChemStation software).

Synthesis. (4S,6R)-4-(Benzyloxy)nonadec-1-en-6-ol (**9**). A 50-ml three-necked flask containing Mg turnings (484 mg, 20.18 mmol) and a stirring bar were dried in an oven at 100° for 2 h and cooled to r.t. under a stream of dry N_2. A portion of 1-bromododecane (4.56 g, 18.34 mmol) in anh. THF (20 ml) was introduced, the reaction was initiated with a small crystal of I_2, and the remaining soln. was added within 10 min at 0°. The stirring was continued for another 2 h at r.t., and the mixture was cooled to −40°. Then, CuI (173.3 mg, 0.917 mmol) was added, the mixture was allowed to stir for 30 min, and then a soln. of epoxide **7** [8a] (2.0 g, 9.17 mmol) in dry THF was added dropwise within 10 min. The resulting mixture was stirred at −40° for 1 h and at r.t. for 2 h. After completion, the reaction was quenched by addition of sat. NH_4Cl soln., and the mixture was extracted with Et_2O, washed with H_2O and brine, and dried (Na_2SO_4). Removal of the solvent, followed by purification on SiO_2, gave pure **9** (2.85 g, 80%). Pale yellow liquid. $[\alpha]_D^{20} = +49.8$ ($c = 1.5$, $CHCl_3$). IR (KBr): 3429, 3070, 2926, 2859, 1715, 1640, 1495, 1450, 1351, 1275, 1069, 916, 742, 698, 665. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.36–7.24 (*m*, 5 H); 5.86–5.71 (*m*, 1 H); 5.15–5.05 (*m*, 2 H); 4.56 (*dd*, *J* = 11.3, 5.3, 2 H); 3.84–3.71 (*m*, 1 H); 3.63–3.57 (*m*, 2 H); 3.43–3.29 (*m*, 1 H); 3.26–3.14 (*m*, 1 H); 2.48–2.27 (*m*, 2 H); 1.77–1.66 (*m*, 2 H); 1.59–1.49 (*m*, 2 H); 1.39–1.20 (*m*, 20 H); 0.89 (*t*, *J* = 6.0, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 137.9; 133.8; 128.4; 127.8; 117.7; 79.5;

71.3; 68.9; 40.9; 38.5; 37.9; 31.8; 29.5 (br., several overlapped signals); 29.3; 25.6; 22.6; 14.9. LC/MS: 389 ($[M+H]^+$).

(4S,6R)-Nonadec-1-ene-4,6-diol (**10**). To a soln. of naphthalene (4.61 g, 36 mmol) in dry THF (30 ml) was added Li (253 mg, 36 mmol) at r.t. The resulting mixture was stirred for 1 h at the same temp. and then cooled to $-78°$. Later, a soln. of **9** (2.8 g, 7.21 mmol) in dry THF was added slowly, and the stirring was continued at the same temp. for 1 h. Then, the reaction was quenched with solid NH_4Cl, and the mixture was extracted with AcOEt (2×20 ml), washed with H_2O (2×10 ml) and brine (1×20 ml), and dried (Na_2SO_4). Evaporation of the solvent, followed by purification on CC, afforded **10**. Semi-solid. $[\alpha]_D^{25}=+16.9$ ($c=1.3$, $CHCl_3$); IR (neat): 3507, 3360, 2918, 2860, 1647, 1467, 1356, 1070. ^{1}H-NMR (400 MHz, $CDCl_3$): 5.88–5.73 (*m*, 1 H); 5.18–5.07 (*m*, 2 H); 4.01–3.85 (*m*, 2 H); 2.32–2.21 (*m*, 2 H); 1.62–1.54 (*m*, 2 H); 1.53–1.37 (*m*, 2 H); 1.36–1.23 (*m*, 24 H); 0.88 (*t*, $J=6.4$, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 134.6; 118.1; 69.2; 68.0; 42.1; 41.9; 37.4; 31.9; 29.7–29.5 (br., several overlapped signals); 29.3; 25.9; 22.6; 14.0. ESI-MS: 321 ($[M+Na]^+$).

(5S,7R)-2,2,3,3,9,9,10,10-Octamethyl-5-(prop-2-en-1-yl)-7-tridecyl-4,8-dioxa-3,9-disilaundecane (**6**). To a stirred soln. of **10** (2.0 g, 6.71 mmol) in anh. CH_2Cl_2 (20 ml) at 0° were added TBSOTf (3.90 ml, 14.76 mmol) and 2,6-lutidine (2.16 ml, 20.13 mmol) successively, and the mixture was stirred for 4 h at 25°. Then, the reaction was quenched with H_2O (10 ml), and the mixture was extracted with CH_2Cl_2 ($3\times$ 20 ml). The org. extracts were washed with brine (10 ml), dried (Na_2SO_4), and concentrated *in vacuo*. The crude product was further purified by CC to afford pure **6** (3.15 g, 90%). Colorless liquid. $[\alpha]_D^{20}=-3.9$ ($c=0.8$, $CHCl_3$). IR (KBr): 3483, 2967, 2885, 1640, 1030. ^{1}H-NMR (300 MHz, $CDCl_3$): 5.92–5.62 (*m*, 1 H); 5.10–4.90 (*m*, 2 H); 3.86–3.63 (*m*, 2 H); 2.30–2.14 (*m*, 2 H); 1.67–1.45 (*m*, 2 H); 1.44–1.05 (*m*, 27 H); 0.85 (*s*, 18 H); 0.06 (*s*, 6 H); 0.04 (*s*, 6 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 135.0; 116.2; 70.1; 69.8; 44.9; 42.2; 37.8; 31.9; 29.5 (br., several overlapped signals); 25.9; 25.6; 25.86; 22.6; 18.0; 14.1; −4.0; −4.1. LC-MS: 550 ($[M+Na]^+$).

*(3R,5R)-3,5-Bis{[(*tert*-butyl)(dimethyl)silyl]oxy}octadecanoic Acid* (**11**). A stirred soln. of **6** (2.0 g, 3.78 mmol) in CH_2Cl_2 (5 ml) at $-78°$ was subjected to ozonolysis by passing O_3 gas until no starting material was observed on TLC. The soln. was purged with N_2 to remove the excess of O_3 and cooled to 0°; then, Ph_3P (1.95 g, 7.57 mmol) was added, and the resulting mixture was stirred for 2.5 h at 0° and then concentrated *in vacuo*. The resulting crude product was diluted with hexane (10 ml) and filtered through a *Celite* pad, and the residue was further washed with hexane (50 ml), and the filtrate was dried (Na_2SO_4). The solvent was removed under reduced pressure, and the resulting aldehyde was subjected to oxidation without further purification. To a stirred soln. of the crude aldehyde in *t*-BuOH (4 ml) was added 2-methylbut-2-ene (1 ml) in *t*-BuOH (1 ml). The soln. was cooled to 0° and then treated with a soln. of $NaClO_2$ (0.11 g, 1.25 mmol) and NaH_2PO_4 (0.455 g, 3.8 mmol) in H_2O (2 ml). After 2 h, the mixture was partitioned between brine (5 ml) and Et_2O (5 ml). The org. phase was separated, and the aq. phase was extracted with Et_2O (3×10 ml). The combined org. phases were washed with brine (10 ml), dried (Na_2SO_4), concentrated *in vacuo*, and purified by flash chromatography (Et_2O) to afford pure **11** (1.82 g, 90%). R_f (SiO_2; 30% AcOEt in hexane) 0.25. $[\alpha]_D^{20}=-22.9$ ($c=1.5$, $CHCl_3$). IR (KBr): 3460, 2989, 2855, 1710, 1055. ^{1}H-NMR (300 MHz, $CDCl_3$): 4.26–4.10 (*m*, 1 H); 3.81–3.66 (*m*, 1 H); 2.66–2.39 (*m*, 2 H); 1.76–1.58 (*m*, 2 H); 1.41–1.17 (*m*, 29 H); 0.89 (*s*, 18 H); 0.08 (*d*, $J=3.6$, 6 H); 0.06 (*d*, $J=1.4$, 6 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 176.3; 70.1; 67.5; 45.2; 43.0; 37.2; 32.0; 29.4 (br., several overlapped signals); 22.6; 24.8; 25.8; 25.7; 18.0; 17.8; 14.1; −4.0; −4.5; −4.2; −4.3. LC/MS: 545 ($[M+H]^+$).

*(3R,5R)-3,5-Bis{[(*tert*-butyl)(dimethyl)silyl]oxy}-1-(morpholin-4-yl)octadecan-1-one* (**12**). To a stirred soln. of morpholine (0.30 g, 1.6 mmol) in CH_2Cl_2 (10 ml) were added **11** (1.5 g, 1.74 mmol) and diisopropylcarbodiimide (0.36 g, 1.74 mmol) at r.t. After stirring the mixture for 10 min, DMAP (0.1 g, 0.8 mmol) was added, and the mixture was stirred for 4 h. After completion, the reaction was quenched with H_2O (8 ml) and extracted with CH_2Cl_2 (2×10 ml). The org. layer was dried (Na_2SO_4), concentrated *in vacuo*, and purified by CC to afford **12** (1.32 g, 85%). Colorless oil. $[\alpha]_D^{20}=-79.9$ ($c=0.9$, $CHCl_3$). IR (KBr): 3170, 2928, 1630, 1385, 1250, 1160. ^{1}H-NMR (200 MHz, $CDCl_3$): 4.36–4.14 (*m*, 1 H); 3.84–3.42 (*m*, 9 H); 2.59–2.24 (*m*, 2 H); 1.70–1.55 (*m*, 2 H); 1.50–1.12 (*m*, 27 H); 0.87 (*s*, 9 H); 0.85 (*s*, 9 H); 0.07 (*d*, $J=3.6$, 6 H); 0.03 (*d*, $J=5.0$, 6 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 169.3; 154.0; 70.0; 69.4; 46.5; 43.9; 37.0; 31.9; 29.6 (br., several overlapped signals); 25.8; 25.0; 22.8; 21.7; 18.0; 14.0; −4.3; −4.2. ESI-MS: 568 ($[M+H]^+$).

*(5*R*,7*R*)-1-[4-(Benzyloxy)phenyl]-5,7-bis{[(*tert*-butyl)(dimethyl)silyl]oxy}icos-1-yn-3-one* (**13**). To a stirred soln. of 1-(benzyloxy)-4-ethynylbenzene (0.37 g, 8.8 mmol) in THF (30 ml) was added BuLi (5.5 ml; 1.6M soln. in hexane, 8.8 mmol) at $-78°$, and the mixture was stirred for 20 min. Then, $BF_3 \cdot Et_2O$ was added, stirring was continued for 30 min, and then a soln. of **12** (2.0 g, 4.4 mmol) in THF (10 ml) was added at $-78°$. The resulting mixture was warmed to 0° and allowed to stir for 1 h, then the reaction was quenched with aq. NH_4Cl (40 ml), and the mixture was extracted with Et_2O (3×50 ml). The combined org. extracts were washed with brine (60 ml), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by CC to afford **13** (0.36 g, 77%). $[\alpha]_D^{20} = -11.8$ ($c = 1.1$, $CHCl_3$). IR (KBr): 3059, 2926, 2855, 2201, 1731, 1678, 1125. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.40–7.22 (*m*, 7 H); 6.89–6.80 (*d*, $J = 8.3$, 2 H); 5.04 (*s*, 2 H); 4.21–4.10 (*m*, 1 H); 3.75–3.61 (*m*, 1 H); 2.54–2.90 (*m*, 3 H); 1.60–1.45 (*m*, 3 H); 1.40–1.16 (*m*, 23 H); 0.85 (*s*, 18 H); 0.08 (*d*, $J = 5.6$, 6 H); 0.07 (*d*, $J = 1.4$, 6 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 209.6; 127.5; 127.8; 128.5; 128.7; 128.6; 114.7; 70.0; 67.3; 51.0; 45.7; 44.1; 37.6; 31.8; 29.6 (br., several overlapped signals); 27.8; 25.7; 25.8; 25.5; 24.9; 22.7; 22.25; 14.0; 13.8; −4.13; −4.5. LC/MS: 736 ($[M+H[^+$).

*(5*R*,7*R*)-5,7-Bis{[(*tert*-butyl)(dimethyl)silyl]oxy}-1-(4-hydroxyphenyl)icosan-3-one* (**5**). To a stirred soln. of **13** (350 mg, 0.62 mmol) in AcOEt (10 ml) was added 10% Pd/C (40 mg). The mixture was stirred under H_2 atmosphere for 8 h. After completion, the mixture was filtered through *Celite*, and the solvent was removed under reduced pressure to give the crude product, which was purified by CC on SiO_2 (hexane/AcOEt 4:1) to afford pure **5** (260 mg, 88%). Colorless solid. $[\alpha]_D^{20} = -4.8$ ($c = 1.5$, $CHCl_3$). IR (KBr): 3388 (OH), 2929, 1720, 1258, 1075. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.05 (*d*, $J = 8.4$, 2 H); 6.74 (*d*, $J = 8.6$, 2 H); 4.24–4.13 (*m*, 1 H); 3.74–3.59 (*m*, 1 H); 2.86–2.64 (*m*, 4 H); 2.60–2.42 (*m*, 2 H); 1.70–1.50 (*m*, 7 H); 1.34–1.20 (*m*, 27 H); 0.86 (*s*, 9 H); 0.85 (*s*, 9 H); 0.07 (*s*, 6 H); 0.04 (*s*, 6 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 208.6; 154.0; 133.7; 129.3; 115.2; 71.0; 70.5; 42.9; 39.6; 37.4; 36.3; 31.9; 30.7; 30.2; 29.6 (br., several overlapped signals); 29.3; 24.9; 22.6; −4.16; −4.28. ESI-MS: 649 ($[M+H]^+$).

Aculeatin A (=*(2*R*,4*R*,6*R*)-4-Hydroxy-2-tridecyl-1,7-dioxadispiro[5.1.5.2]pentadeca-9,12-dien-11-one*; **1**) *and Aculeatin B* (=*(2*R*,4*R*,6*S*)-4-Hydroxy-2-tridecyl-1,7-dioxadispiro[5.1.5.2]pentadeca-9,12-dien-11-one*; **2**). To a stirred soln. of **5** (75 mg, 0.16 mmol) in anh. THF (2 ml) was added TBAF (0.2 ml, 0.2 mmol), and the mixture was stirred for 3 h at 0°. Then, the reaction was quenched with H_2O (3 ml), and the mixture was extracted with AcOEt (2×2 ml). The combined org. extracts were dried (Na_2SO_4) and concentrated *in vacuo*. To a soln. of crude product in acetone/H_2O mixture (9:1, 10 ml) was added $PhI(OCOCF_3)_2$ (206 mg, 0.48 mmol) in one portion. The resulting mixture was stirred for 5 h at 25° in the dark. After completion, the reaction was quenched with H_2O (2 ml), and the mixture was extracted with AcOEt (3×4 ml). The combined org. layers were dried (Na_2SO_4) and concentrated *in vacuo* to give a mixture **1**/**2**, which was separated by CC to afford pure **1** (24 mg, 46%) and **2** (13 mg, 18%).

Data of **1**. See [7]. Oil. $[\alpha]_D^{20} = -52.3$ ($c = 1.0$, $CHCl_3$). IR (KBr): 3416 (OH), 2926, 1671, 1630, 1512, 1459, 1102. ^{1}H-NMR (300 MHz, $CDCl_3$): 6.85 (*dd*, $J = 9.8, 3.0$, 1 H); 6.78 (*dd*, $J = 9.8, 3.0$, 1 H); 6.14 (*dd*, $J = 9.8, 1.5$, 1 H); 6.09 (*dd*, $J = 10.5, 2.2$, 1 H); 4.05–4.15 (*m*, 2 H); 3.31 (br. *s*, 1 H); 2.38 (*m*, 1 H); 2.23 (*m*, 1 H); 1.94–2.03 (*m*, 3 H); 1.95 (br. *d*, $J = 14.2$, 1 H); 1.75 (br. *d*, $J = 13.5$, 1 H); 1.60–1.39 (*m*, 4 H); 1.21–1.36 (*m*, 21 H); 0.87 (*t*, $J = 6.7$, 3 H). ^{13}C-NMR (75 M, $CDCl_3$): 185.3; 150.9; 148.9; 127.4; 127.1; 109.1; 79.6; 65.4; 64.8; 39.1; 38.0; 35.9; 34.2; 32.1; 29.7 (br., several overlapped signals); 29.6; 29.4; 25.7; 22.8; 14.1. EI-MS: 441.29 ($[M+Na]^+$).

Data of **2**. See [7]. Oil. $[\alpha]_D^{20} = 54.5$ ($c = 0.7$, $CHCl_3$). IR (KBr): 3416 (OH), 2926, 2854, 1671, 1630, 1510, 1459, 1102. ^{1}H-NMR (300 MHz, $CDCl_3$): 6.99 (*dd*, $J = 9.8, 3.0$, 1 H); 6.78 (*dd*, $J = 9.8, 3.0$, 1 H); 6.14 (*dd*, $J = 9.8, 1.6$, 1 H); 6.09 (*dd*, $J = 9.8, 1.6$, 1 H); 4.36 (*quint.*, $J = 3.1$, 1 H); 3.87 (*m*, 1 H); 2.68 (*dd*, $J = 12.8, 7.2$, 1 H); 2.30 (*td*, $J = 12.3, 7.2$, 1 H); 2.10–2.01 (*m*, 2 H); 1.95–1.83 (*m*, 2 H); 1.60–1.39 (*m*, 8 H); 1.40–1.19 (*m*, 19 H); 0.88 (*t*, $J = 6.9$, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 185.5; 151.0; 148.6; 127.5; 127.3; 109.3; 79.8; 65.5; 65.0; 39.3; 38.3; 36.1; 34.4; 32.0; 29.9 (br., several overlapped signals); 29.8; 29.5; 25.8; 22.9; 14.3. EI-MS: 441.29 ($[M+Na]^+$).

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Received March 2, 2010