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A Carbohydrate-Based Approach for the Total Synthesis of Aculeatin D and 6-*epi*-Aculeatin D

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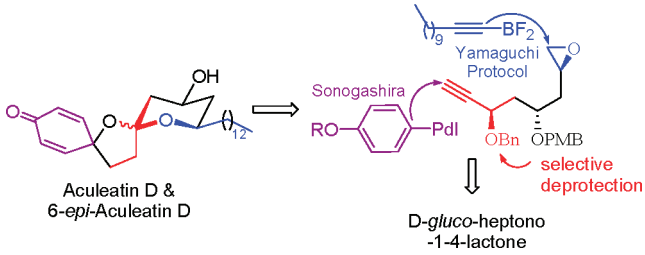

A concise approach for the total synthesis of aculeatin D and 6-*epi*-aculeatin D employing differentially protected *anti*,*anti*-1,3,5-triol alkyne prepared from α-D-glucoheptonic-γ-lactone derivative is documented. Phenol protecting group manipulation for selective *O*-debenzylation during the hydrogenation of the diyne intermediate and one-pot phenolic oxidation with concomitant spiroketalization highlight the accomplished total synthesis.

Aculeatins A−D are the spiroketals isolated from the terrestrial plant species *Amomum aculeatum*. They were assigned structures **1**−**4**, respectively (Figure 1).[1,2] Aculeatins were found to display antiprotozoal activity against some *Plasmodium* and *Trypanosoma* species. In addition, they showed potential antibacterial activity and cytotoxicity against the KB cell line. Because of their promising biological activity taken together with the presence of structurally fascinating 1,7-dioxadispiro[5.1.5.2]pentadecane spirocyclic architecture, aculeatins A−D aroused substantial interest culminating in several total syntheses.[3–7]

The syntheses reported for aculeatins[3–7] in general are linear in nature and involve a stepwise construction of each chiral center present by either asymmetric aldol or chiral allylation protocols and finally phenolic oxidation of a 3,5-*syn*- or *anti*-diol ketone. A flexible total synthesis that would allow access to modified aculeatins like functional group addition to the cyclohexadienone unit and/or alterations on the aliphatic side chain should give access to various synthetic analogues for structure-activity studies. It was reasoned that addition of these units at a late stage in the synthesis would support this criteria. Herein we report a concise approach by selecting aculeatin D (**4**) as a target considering its documented superior cytotoxicity (IC_{50} = 0.38 μg/mL).

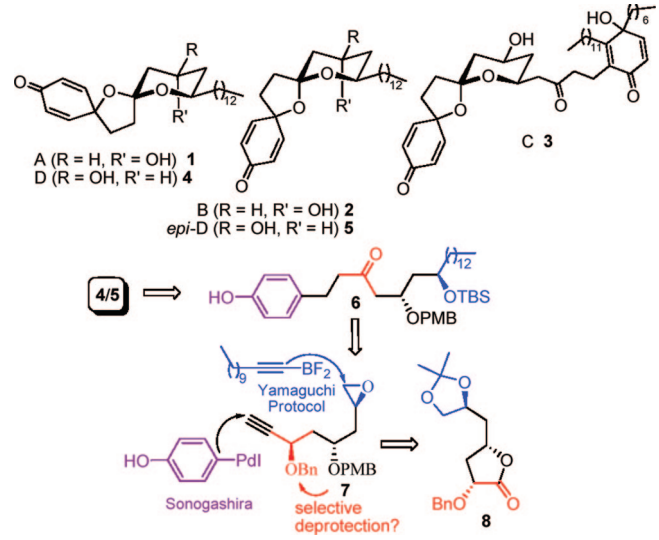

FIGURE 1. Aculeatins A−D and 6-*epi*-aculeatin D and retrosynthetic strategy for aculeatin D.

As outlined in Figure 1, our retrosynthetic disconnection identified an alkyne epoxide **7** as the key intermediate which can be extended to the advanced keto 3,5-diol unit **6** by the Yamaguchi protocol[8] at one end and the Sonogashira coupling[9] on the alkyne end, thus keeping flexibility at both sides. In agreement with our previous observation, we hypothesized a selective propargylic-OBn cleavage during the Raney Ni hydrogenation of the alkyne units.[10,11] Oxidation of the released free C6-OH and subsequent global deprotection and phenolic oxidation should complete the total synthesis of aculeatin D (**4**) and its 6-epimer (**5**).

To explore in this direction, commercially available glucoheptono-1,4-lactone (**9**) was advanced to the key intermediate

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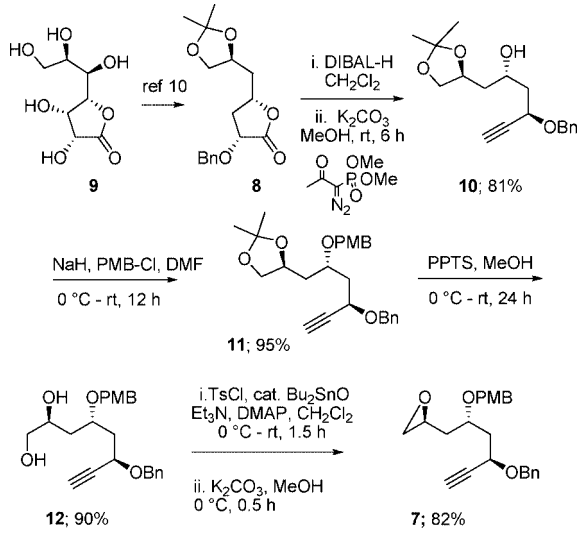
SCHEME 1. Synthesis of Epoxide 7



lactone **8** following our established procedure (Scheme 1).[10] Controlled reduction of lactone **8** with DIBAL-H and subsequent Ohira−Bestmann alkynylation[12] of intermediate lactol afforded the alkyne **10**.

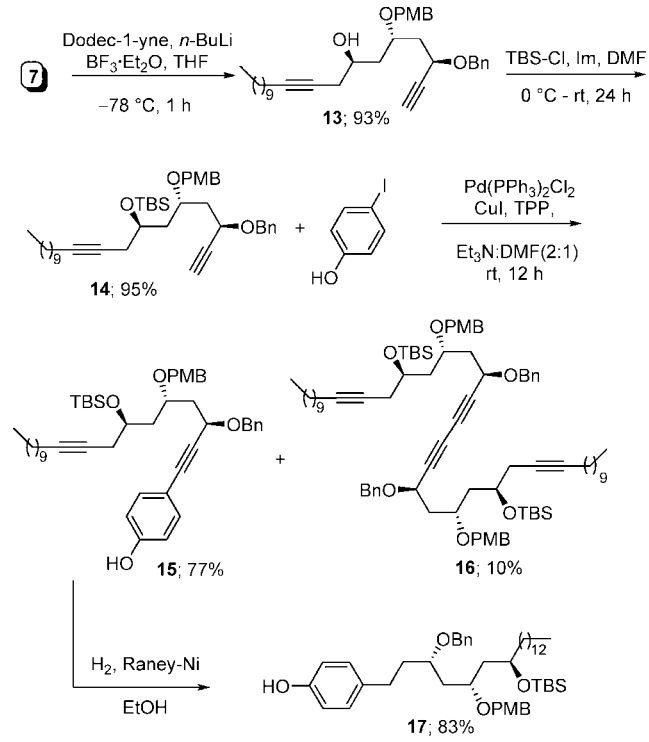
Treatment of **10** with *p*-methoxybenzyl chloride in the presence of NaH in DMF followed by acetonide hydrolysis of resulting product **11** by using PPTS in MeOH afforded the diol **12**. The diol **12** was transformed to the oxirane **7** by selective primary OH tosylation using TsCl, Bu_2SnO, and triethylamine in dichloromethane followed by cyclization with K_2CO_3 in methanol.

After having the epoxide **7**, we next focused our efforts on the synthesis of the keto-3,5-diol unit **6**. Thus, the projected opening of **7** with dodec-1-nyllithium in the presence of $BF_3 \cdot Et_2O$ delivered the diyne **13** in near quantitative yields (Scheme 2).[8] Protection of the free hydroxyl group in **13** as its TBS ether followed by Sonogashira coupling of resulting **14** with *p*-iodophenol gave the required coupling product **15** along with small amounts of self-dimerized product **16**.[9] Our next concern was the hydrogenation of diyne **15** along with the desired selective propargyl-*O*-debenzylation.[10] To our surprise, hydrogenation of **15** was facile, but resulted exclusively in diyne reduction to afford product **17**.

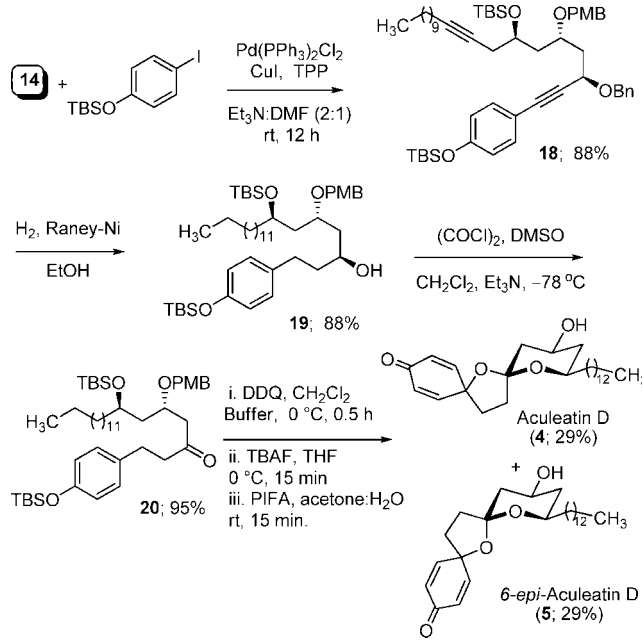
After careful experimentation by employing protected *p*-iodophenol derivatives for Sonogashira coupling and subsequent Raney Ni hydrogenation, we concluded that TBS was the optimal protecting group that improved the yield in Sonogashira coupling and, to our delight, the anticipated *O*-debenzylation during the hydrogenation of respective intermediate **18** affording **19**. Oxidation of **19** under Swern conditions afforded the keto-3,5-diol unit **20**.

Having the keto-3,5-*anti*-diol **20**, the stage was set for the global deprotection and subsequent phenol oxidation. Attempted global deprotection of PMB, TBS-ethers in acidic conditions (TFA, PTSA, or PPTS) in solvents like methanol or dichloromethane yielded an unidentified complex mixture. Sequential deprotection of PMB-ether by using DDQ in dichloromethane under buffered conditions followed by, TBS-ether deprotection in presence of TBAF in THF produced the free diol. Oxidative spiroacetalization of intermediate ketodiol by using phenyliodine(III) bis(trifluroacetate) (PIFA) in acetone/water (10:1, v/v solution) completed the synthesis of epimeric aculeatins **4** and **5**. Physical and spectral data of these compounds were in agreement with the data reported for natural aculeatin D[4] and synthetic 6-*epi*-aculeatin D,[5] respectively.

SCHEME 2. Yamaguchi Protocol, Sonogashira Coupling, and Hydrogenation with Raney Ni



SCHEME 3. Total Synthesis of Aculeatin D (4) and 6-*epi*-Aculeatin D (5)



In conclusion, a chiral pool approach employing an easily accessible 1,3-polyol unit for the total synthesis of naturally occurring aculeatin D and its 6-epimer was documented. As such, this route employs the addition of the both the terminal

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units (phenol and side chain) at the late stage of the synthesis thus provide sufficient flexibility for related analogues synthesis.[13]

Experimental Section

Preparation of Epoxide (7). To a solution of diol **12** (600 mg, 1.56 mmol) in dry CH_2Cl_2 (15 mL) were added Bu_2SnO (7 mg) and *p*-TsCl (327 mg, 1.71 mmol) followed by triethylamine (435 μL, 3.12 mmol) and DMAP (20 mg) at 0 °C. The reaction mixture was slowly warmed to rt and stirred for 1.5 h. The reaction mixture was diluted with CH_2Cl_2 and extracted. The combined organic phases were washed with water and brine, dried (Na_2SO_4), and concentrated. The crude tosylate (840 mg) was dissolved in methanol (20 mL) and stirred with anhydrous K_2CO_3 (270 mg) for 30 min at 0 °C and concentrated. The crude was dissolved in ethyl acetate, washed with water and brine, dried (Na_2SO_4), and concentrated. Purification of the crude by column chromatography (15% ethyl acetate in petroleum ether) gave the epoxide **7** (470 mg, 82% for two steps) as a colorless oil. $[\alpha]^{25}_D = +86.9$ ($c = 1$, $CHCl_3$). IR ($CHCl_3$): ν 3432, 3289, 2927, 2110, 1612, 1513, 1248, 1069, 753, 699 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 7.36−7.27 (m, 5H), 7.14 (dt, $J = 8.7$, 2.8 Hz, 2H), 6.82 (dt, $J = 8.7$, 2.8 Hz, 2H), 4.79 (d, $J = 11.4$ Hz, 1H), 4.48 (d, $J = 10.8$ Hz, 1H), 4.39 (d, $J = 11.4$ Hz, 1H), 4.28 (d, $J = 10.8$ Hz, 1H), 4.34−4.25 (m, 1H), 3.86 (ddd, $J = 12.7$, 11.9, 5.9 Hz, 1H), 3.76 (s, 3H), 3.03 (ddt, $J = 5.8$, 3.9, 2.7 Hz, 1H), 2.78 (dd, $J = 5.0$, 4.0 Hz, 1H), 2.49 (dd, $J = 5.0$, 2.7 Hz, 1H), 2.47 (d, $J = 2.1$ Hz, 1H), 2.01 (dd, $J = 7.0$, 5.9 Hz, 2H), 1.74 (t, $J = 5.8$ Hz, 2H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 37.6 (t), 41.7 (t), 47.3 (t), 49.2 (d), 55.1 (q), 64.8 (d), 70.5 (t), 71.4 (t), 72.6 (d), 73.9 (d), 82.7 (s), 113.6 (d, 2C), 127.7 (d), 128.1 (d, 2C), 128.3 (d, 2C), 129.4 (d, 2C), 130.3 (s), 137.5 (s), 159.1 (s) ppm. ESI-MS: *m/z* 389.22 (100, $[M + Na]^+$). Anal. Calcd for $C_{23}H_{26}O_4$: C, 75.38; H, 7.15. Found: C, 75.30; H, 7.08.

(3*S*,5*R*,7*R*)-3-*O*-Benzyl-5-*O*-(4-methoxybenzyl)-7-*O*-*tert*-butyldimethylsilyl-1-(4-hydroxyphenyl)icosane-3,5,7-triol (17). A suspension of dialkyne **15** (200 mg, 0.27 mmol) and Raney-Ni (20 mg) in ethanol (10 mL) was flushed with hydrogen gas and stirred under hydrogen (20 psi) atmosphere for 10 h at rt. The reaction mixture was filtered through a plug of filter aid, washed with methanol thoroughly (5 × 10 mL), and concentrated. Purification of the crude product by column chromatography (10% ethyl acetate in petroleum ether) yielded hydrogenated product **17** (168 mg, 83%) as a colorless oil. $[\alpha]^{25}_D = +14.9$ ($c = 1$, $CHCl_3$). IR ($CHCl_3$): ν 3368, 2854, 1613, 1514, 1216, 1039, 834, 758, 697 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.34−7.24 (m, 5H), 7.17 (dt, $J = 8.6$, 2.8 Hz, 2H), 7.01 (dt, $J = 8.4$, 3.0 Hz, 2H), 6.83 (dt, $J = 8.6$, 2.8 Hz, 2H), 6.72 (dt, $J = 8.4$, 2.9 Hz, 2H), 5.00 (br.s, 1H), 4.49 (d, $J = 11.4$ Hz, 1H), 4.41 (d, $J = 10.9$ Hz, 1H), 4.34 (d, $J = 11.4$ Hz, 1H), 4.27 (d, $J = 10.9$ Hz, 1H), 3.83 (dt, $J = 12.2$, 5.5 Hz, 1H), 3.77 (s, 3H), 3.70 (dt, $J = 12.2$, 6.3 Hz, 1H), 3.60 (dt, $J = 11.7$, 5.8 Hz, 1H), 2.61 (t, $J = 8.0$ Hz, 2H), 1.90−1.76 (m, 3H), 1.74 (t, $J = 6.2$ Hz, 2H), 1.55 (ddd, $J = 13.4$, 6.8, 6.0 Hz, 1H), 1.46−1.39 (m, 2H), 1.31−1.25 (m, 22H), 0.88 (s, 9H), 0.87 (t, $J = 7.0$ Hz, 3H), 0.05 (s, 3H), 0.04 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.3 (q), −4.1 (q), 14.1 (q), 18.1 (s), 22.7 (t), 24.7 (t), 26.0 (q, 3C), 29.3 (t), 29.6 (t), 29.7 (t), 29.7 (t), 29.9 (t), 30.4 (t), 31.9 (t), 36.1 (t), 37.6 (t), 40.4 (t), 42.6 (t), 55.2 (q), 69.5 (d), 70.3 (t), 70.8 (t), 73.3 (d), 75.3 (d), 113.7 (d, 2C), 115.2 (d, 2C), 127.4 (d), 127.8 (d, 2C), 128.3 (d, 2C), 129.3 (d, 2C), 129.4 (d, 2C), 130.9 (s), 134.3 (s), 138.8 (s), 153.6 (s), 159.0 (s) ppm. ESI-MS: *m/z* 770.04 (100, $[M + Na]^+$). Anal. Calcd for $C_{47}H_{74}O_5Si$: C, 75.55; H, 9.98. Found: C, 75.48; H, 9.90.

(3*S*,5*R*,7*R*)-5-*O*-(4-Methoxybenzyl)-7-*O*-*tert*-butyldimethylsilyl-1-(4-*tert*-butyldimethylsilyloxyphenyl)icosane-3,5,7-triol (19). A suspension of di-TBS derivative **18** (1 g, 1.17 mmol) and Raney-Ni (100 mg) in ethanol (30 mL) was flushed with hydrogen gas and stirred under hydrogen (20 psi) atmosphere at 55 °C for 18 h. The reaction mixture was filtered through a plug of filter aid, washed with methanol thoroughly (5 × 20 mL), and concentrated. Purification of crude product by column chromatography (10% ethyl acetate in petroleum ether) yielded hydrogenated product **19** (800 mg, 88%) as a colorless oil. $[\alpha]^{25}_D = -5.1$ ($c = 1$, $CHCl_3$). IR ($CHCl_3$): ν 3480, 2855, 1611, 1510, 1252, 1039, 836, 758, 692 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.23 (dt, $J = 8.6$, 2.9 Hz, 2H), 7.03 (dt, $J = 8.4$, 2.9 Hz, 2H), 6.86 (dt, $J = 8.6$, 2.9 Hz, 2H), 6.73 (dt, $J = 8.4$, 2.9 Hz, 2H), 4.51 (d, $J = 10.9$ Hz, 1H), 4.42 (d, $J = 10.9$ Hz, 1H), 3.93−3.90 (m, 1H), 3.84−3.79 (m, 1H), 3.79 (s, 3H), 3.77−3.71 (m, 1H), 3.11 (br.s, 1H), 2.73−2.67 (m, 1H), 2.60−2.54 (m, 1H), 1.90−1.83 (m, 2H), 1.78−1.71 (m, 1H), 1.68−1.59 (m, 3H), 1.56−1.51 (m, 2H), 1.44−1.40 (m, 2H), 1.28−1.25 (m, 20H), 0.97 (s, 9H), 0.87 (s, 9H), 0.87 (t, $J = 7.0$ Hz, 3H), 0.17 (s, 6H), 0.03 (s, 3H), 0.02 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ −4.4 (q, 2C), −4.4 (q), −4.0 (q), 14.1 (q), 18.1 (s), 18.2 (s), 22.7 (t), 24.7 (t), 25.7 (q, 3C), 25.9 (q, 3C), 29.3 (t), 29.7 (t), 29.7 (t), 29.9 (t), 31.1 (t), 31.9 (t), 37.7 (t), 39.5 (t), 39.8 (t), 41.5 (t), 55.3 (q), 68.1 (d), 69.8 (d), 70.6 (t), 74.9 (d), 113.9 (d, 2C), 119.8 (d, 2C), 129.2 (d, 2C), 129.4 (d, 2C), 130.2 (s), 134.9 (s), 153.6 (s), 159.3 (s) ppm. ESI-MS: *m/z* 793.98 (100, $[M + Na]^+$). Anal. Calcd for $C_{46}H_{82}O_5Si_2$: C, 71.63; H, 10.72. Found: C, 71.58; H, 10.60.

(5*S*,7*R*) 5-(4-Methoxybenzyloxy)-7-(*tert*-butyldimethylsilyloxy-1-(4-*tert*-butyldimethylsilyloxyphenyl)icosan-3-one (20). In a flame-dried, two necked, round-bottom flask (25 mL) was dissolved oxalyl chloride (67 μL, 0.77 mmol) under N_2 in dry CH_2Cl_2 (5 mL). After the solution was cooled to −78 °C, dry DMSO (100 μL, 1.42 mmol) was added dropwise with stirring for 15 min. A solution of alcohol **19** (200 mg, 0.25 mmol) in dry CH_2Cl_2 (5 mL) was added dropwise and stirred for 30 min. To this was added Et_3N (216 μL, 1.55 mmol) and stirring continued for 15 min at −78 °C. The reaction mixture was partitioned between CH_2Cl_2 and water, the organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2. Combined organic phases were washed with brine, dried (Na_2SO_4), and concentrated. Purification of the crude by column chromatography (5% ethyl acetate in petroleum ether) afforded ketone **20** (190 mg, 95%) as a colorless oil. $[\alpha]^{25}_D = -4.5$ ($c = 1$, $CHCl_3$). IR ($CHCl_3$): ν 3415, 2927, 1715, 1612, 1511, 1252, 1040, 836, 759, 686 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.19 (dt, $J = 8.6$, 2.9 Hz, 2H), 6.99 (dt, $J = 8.4$, 2.9 Hz, 2H), 6.85 (dt, $J = 8.6$, 2.9 Hz, 2H), 6.72 (dt, $J = 8.4$, 2.9 Hz, 2H), 4.42 (d, $J = 10.9$ Hz, 1H), 4.39 (d, $J = 10.9$ Hz, 1H), 4.09−4.02 (m, 1H), 3.84−3.79 (m, 1H), 3.78 (s, 3H), 2.80 (t, $J = 7.4$ Hz, 2H), 2.71 (dd, $J = 15.5$, 7.1 Hz, 1H), 2.69 (t, $J = 7.4$ Hz, 2H), 2.49 (dd, $J = 15.6$, 5.0 Hz, 1H), 1.76−1.69 (m, 1H), 1.51−1.41 (m, 3H), 1.25 (m, 22H), 0.97 (s, 9H), 0.88 (s, 9H), 0.87 (t, $J = 7.18$ Hz, 3H), 0.17 (s, 6H), 0.04 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ −4.5 (q, 2C), −4.4 (q), −4.0 (q), 14.1 (q), 18.1 (s), 18.2 (s), 22.7 (t, 24.7 (t), 25.7 (q, 3C), 25.9 (q, 3C), 28.7 (t), 29.3 (t), 29.6 (t), 29.7 (t), 29.8 (t), 31.9 (t), 37.9 (t), 42.7 (t), 45.6 (t), 48.8 (t), 55.2 (q), 69.5 (d), 71.1 (t), 73.1 (d), 113.8 (d, 2C), 119.9 (d, 2C), 129.1 (d, 2C), 129.2 (d, 2C), 130.7 (s), 133.6 (s), 153.8 (s), 159.1 (s), 208.6 (s) ppm. ESI-MS: *m/z* 807.83 (100, $[M + K]^+$). Anal. Calcd for $C_{46}H_{80}O_5Si_2$: C, 71.82; H, 10.48. Found: C, 71.78; H, 10.40.

Synthesis of Aculeatin D (4) and 6-*epi*-Aculeatin D (5). To a solution of PMB ether **20** (100 mg, 0.2 mmol) in CH_2Cl_2 (10 mL) and buffer (2 mL) was added DDQ (45 mg, 0.18 mmol) portionwise at 0 °C and stirring continued for another 30 min at the same temperature. The reaction mixture was filtered through a plug of filter aid and washed with CH_2Cl_2. The organic phase was washed with water and brine, dried (Na_2SO_4), and concentrated. The crude (84 mg) was dissolved in dry THF (5 mL) and treated with TBAF (250 μL of 1 M solution in THF, 0.25 mmol) at 0 °C. After the mixture was stirred for 15 min at the same temperature, solvent

(13) For isolation of truncated aculeatins A and B, see: Chin, Y.-W.; Salim, A. A.; Su, B.-N.; Mi, Q.; Chai, H.-B.; Riswan, S.; Kardono, L. B. S.; Ruskandi, A.; Farnsworth, N. R.; Swanson, S. M.; Kinghorn, A. D. *J. Nat. Prod.* **2008**, *71*, 390–395.

was evaporated under reduced pressure. The crude ketal (50 mg) was dissolved in acetone/H_2O (2.5 mL, 10:1 v/v solution), and PIFA (68 mg, 0.16 mmol) was added in one portion at room temperature. After the mixture was stirred for 15 min in darkness, a saturated aqueous solution of $NaHCO_3$ (4 mL) was added and the resulting mixture extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The crude product was purified by flash column chromatography (30% and 35% ethyl acetate in petroleum ether) to afford **5** (16 mg, 30%) and **4** (15 mg, 28%) as colorless oils.

(+)-Aculeatin D. $[\alpha]^{25}_D = +47.7$ ($c = 0.2$, $CHCl_3$) [lit. $[\alpha]^{23}_D = +46.5$ ($c = 1$, $CHCl_3$)]. IR (neat): ν 3410, 2916, 2849, 1665, 1628, 1057, 1009 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 6.98 (dd, $J = 10.5$, 3.2 Hz, 1H), 6.77 (dd, $J = 10.5$, 3.2 Hz, 1H), 6.13 (dd, $J = 10.3$, 1.9 Hz, 1H), 6.12 (dd, $J = 10.3$, 1.9 Hz, 1H), 3.88−3.80 (m, 1H), 3.40−3.32 (m, 1H), 2.39 (ddd, $J = 12.7$, 7.4, 2.0 Hz, 1H), 2.26 (ddd, $J = 12.5$, 11.3, 7.3 Hz, 1H), 2.12 (ddd, $J = 12.1$, 4.4, 1.6 Hz, 1H), 2.06 (ddd, $J = 12.7$, 8.4, 2.0 Hz, 1H), 1.95 (m, 1H), 1.87−1.75 (m, 2H), 1.69−1.57 (m, 1H), 1.53−1.43 (m, 2H), 1.35−1.23 (m, 22H), 0.87 (t, $J = 6.7$ Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1 (q), 22.7 (t), 25.9 (t), 29.3 (t), 29.4 (t), 29.6 (t), 29.6 (t), 29.7 (t), 31.9 (t), 33.4 (t), 34.9 (t), 35.7 (t), 40.8 (t), 43.6 (t), 66.8 (d), 71.6 (d), 78.1 (s), 109.2 (s), 127.2 (d), 127.4 (d), 148.8 (d), 151.5 (d), 185.5 (s) ppm. ESI-MS: m/z 419.4 $[M + H]^+$, 441.4 $[M + Na]^+$. Anal. Calcd for $C_{26}H_{42}O_4$: C, 74.60; H, 10.11. Found: C, 74.48; H, 10.00.

(+)-6-*epi*-Aculeatin D. $[\alpha]^{25}_D = +14.6$ ($c = 0.2$, $CHCl_3$) [lit. $[\alpha]^{26}_D = +15.0$ ($c = 1$, $CHCl_3$)]. IR (neat): ν 3410, 2916, 2849, 1664, 1628, 1053, 1005 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 6.81 (dd, $J = 10.4$, 3.2 Hz, 1H), 6.76 (dd, $J = 10.4$, 3.2 Hz, 1H), 6.11 (dd, $J = 10.1$, 1.9 Hz, 1H), 6.10 (dd, $J = 10.1$, 1.9 Hz, 1H), 4.15−4.02 (m, 1H), 3.83−3.75 (m, 1H), 2.42−2.32 (m, 1H), 2.24 (dd, $J = 10.3$, 8.2 Hz, 1H), 2.08 (ddd, $J = 12.4$, 4.7, 1.6 Hz, 1H), 2.04−1.94 (m, 3H), 1.62 (dd, $J = 11.8$, 11.8 Hz, 1H), 1.52−1.41 (m, 2H), 1.32−1.22 (m, 22H), 1.18 (ddd, $J = 11.6$, 11.6, 11.6 Hz, 1H), 0.87 (t, $J = 7.0$ Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1 (q), 22.7 (t), 25.7 (t), 29.3 (t), 29.7 (t), 31.9 (t), 34.6 (t), 35.9 (t), 38.8 (t), 40.6 (t), 43.0 (t), 65.3 (d), 69.1 (d), 79.0 (s), 108.9 (s), 127.0 (d), 127.1 (d), 149.2 (d), 151.4 (d), 185.5 (s) ppm. ESI-MS: m/z 419.4 $[M + H]^+$, 441.4 $[M + Na]^+$. Anal. Calcd for $C_{26}H_{42}O_4$: C, 74.60; H, 10.11. Found: C, 74.51; H, 10.02.

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Supporting Information Available: General Experimental Methods and experimental procedures for preparation and compound characterization data of **10**−**16** and **18** and copies of NMR spectra of compounds **7**, **13**, **16**−**20**, **4**, and **5**. This material is available free of charge via the Internet at http://pubs.acs.org.

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