

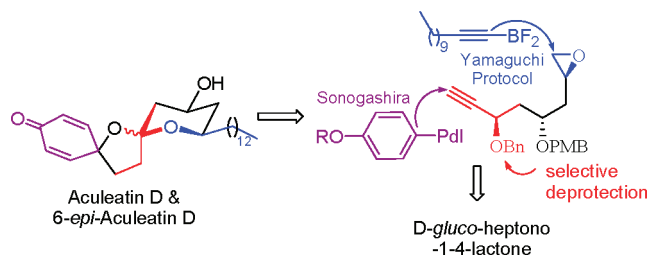
# A Carbohydrate-Based Approach for the Total Synthesis of Aculeatin D and 6-*epi*-Aculeatin D

C. V. Ramana\* and Burgula Srinivas

Division of Organic Chemistry, National Chemical Laboratory, Dr. Homi Bhabha Road, Pune 411 008, India

vr.chepuri@ncl.res.in

Received January 4, 2008

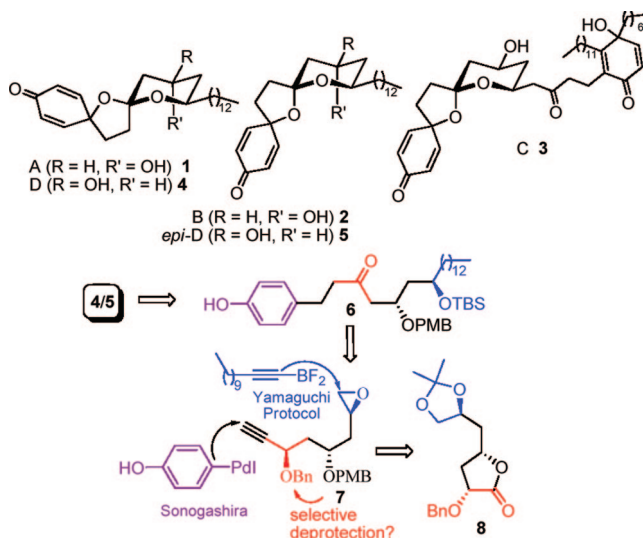


A concise approach for the total synthesis of aculeatin D and 6-*epi*-aculeatin D employing differentially protected *anti,anti*-1,3,5-triol alkyne prepared from  $\alpha$ -D-glucioheptonic- $\gamma$ -lactone derivative is documented. Phenol protecting group manipulation for selective *O*-debenzylolation 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).<sup>1,2</sup> 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.<sup>3–7</sup>

The syntheses reported for aculeatins<sup>3–7</sup> 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  $\mu$ g/mL).



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

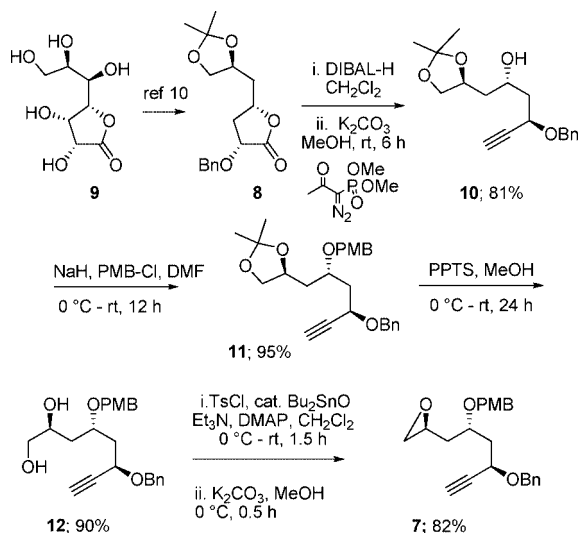
As outlined in Figure 1, our retrosynthetic disconnection identified an alkyne epoxide 7 as the key intermediate which can be extended to the advanced keto 3,5-diol unit 6 by the Yamaguchi protocol<sup>8</sup> at one end and the Sonogashira coupling<sup>9</sup> on the alkyne end, thus keeping flexibility 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.<sup>10,11</sup> 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 glucioheptono-1,4-lactone (9) was advanced to the key intermediate

- (1) Heilmann, J.; Mayr, S.; Brun, R.; Rali, T.; Sticher, O. *Helv. Chim. Acta* **2000**, *83*, 2939–2945.
- (2) Heilmann, J.; Brun, R.; Mayr, S.; Rali, T.; Sticher, O. *Phytochemistry* **2001**, *57*, 1281–1285.
- (3) (a) Wong, Y.-S. *Chem. Commun.* **2002**, 686–687. (b) Peuchmaur, M.; Wong, Y.-S. *J. Org. Chem.* **2007**, *72*, 5374–5379. (c) Peuchmaur, M.; Wong, Y.-S. *Synlett* **2007**, 2902–2906.
- (4) Falomir, E.; Álvarez-Bercedo, P.; Carda, M.; Marco, J. A. *Tetrahedron Lett.* **2005**, *46*, 8407–8410.
- (5) Baldwin, J. E.; Adlington, R. M.; Sham, V. W.-W.; Marquez, R.; Bulger, P. G. *Tetrahedron* **2005**, *61*, 2353–2363.
- (6) Álvarez-Bercedo, P.; Falomir, E.; Carda, M.; Marco, J. A. *Tetrahedron* **2006**, *62*, 9641–9649.
- (7) Chandrasekhar, S.; Rambabu, C.; Shyamsunder, T. *Tetrahedron Lett.* **2007**, *48*, 4683–4685.

- (8) Yamaguchi, M.; Hirao, I. *Tetrahedron Lett.* **1983**, *24*, 391–394.
- (9) (a) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467–4470. (b) Nguefack, J.-F.; Bolitt, V.; Sinou, D. *Tetrahedron Lett.* **1996**, *31*, 5527–5530. (c) Hundertmark, T.; Littke, A. F.; Buchwald, S. L.; Fu, G. C. *Org. Lett.* **2000**, *2*, 1729–1731. (d) Witulski, B.; Alayrac, C.; Arnaut, A.; Collot, V.; Rault, S.; Azcon, J. R. *Synthesis* **2005**, 771–780.
- (10) Ramana, C. V.; Srinivas, B.; Puranik, V. G.; Gurjar, M. K. *J. Org. Chem.* **2005**, *70*, 8216–8219.
- (11) (a) Oikawa, Y.; Tanaka, T.; Horita, K.; Yonemitsu, O. *Tetrahedron Lett.* **1984**, *25*, 5397–5400. (b) Horita, K.; Yoshioka, T.; Tanaka, T.; Oikawa, Y.; Yonemitsu, O. *Tetrahedron* **1986**, *42*, 3021–3028. (c) Perosa, A.; Tundo, P.; Zinoviyev, S. *Green Chem.* **2002**, *4*, 492–494. (d) Weissman, S. A.; Zewge, D. *Tetrahedron* **2005**, *61*, 7833–7863. (e) Llaser, E.; Romea, P.; Urpí, F. *Tetrahedron Lett.* **2006**, *47*, 5815–5818. (f) Vincent, A.; Prunet, J. *Tetrahedron Lett.* **2006**, *47*, 4075–4077.

## SCHEME 1. Synthesis of Epoxide 7



lactone **8** following our established procedure (Scheme 1).<sup>10</sup> Controlled reduction of lactone **8** with DIBAL-H and subsequent Ohira–Bestmann alkynylation<sup>12</sup> of intermediate lactol afforded the alkyne **10**.

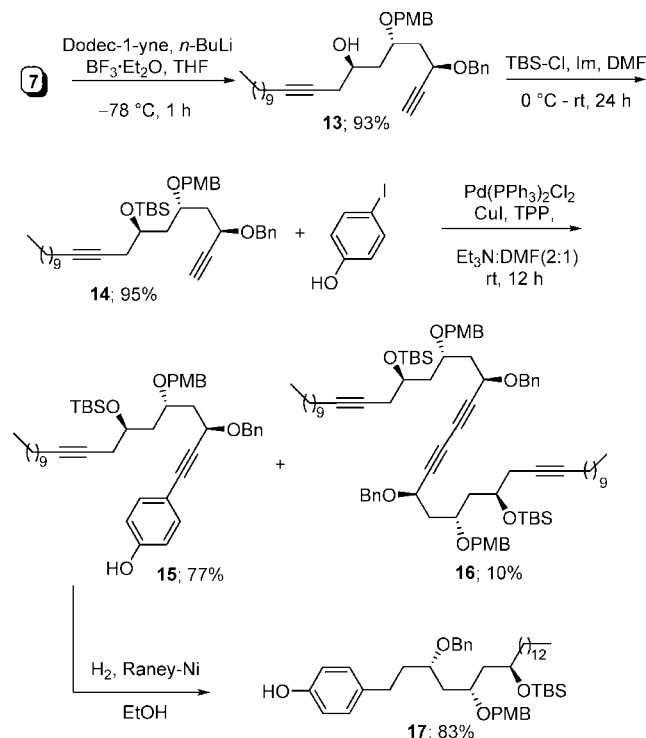
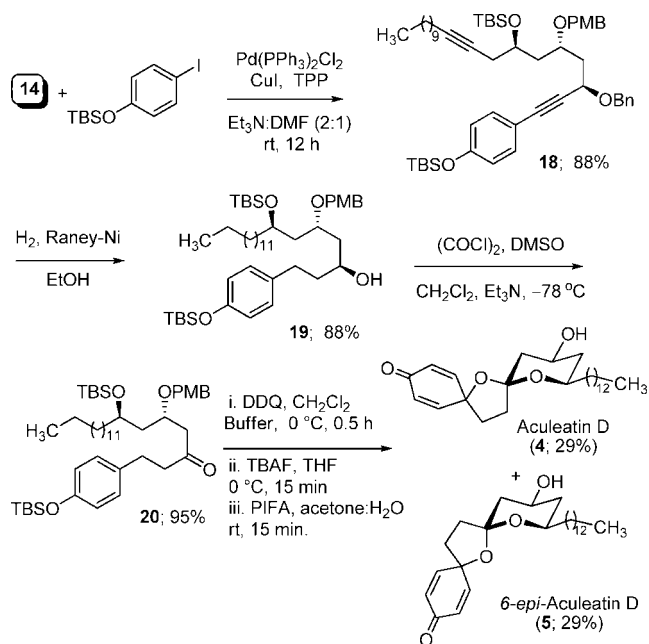
Treatment of **10** with *p*-methoxybenzyl chloride in the presence of NaH in DMF followed by acetonide hydrolysis of resulting product **11** by using PPTS in MeOH afforded the diol **12**. The diol **12** was transformed to the oxirane **7** by selective primary OH tosylation using TsCl, Bu<sub>2</sub>SnO, and triethylamine in dichloromethane followed by cyclization with K<sub>2</sub>CO<sub>3</sub> 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<sub>3</sub>·Et<sub>2</sub>O delivered the diyne **13** in near quantitative yields (Scheme 2).<sup>8</sup> 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**.<sup>9</sup> Our next concern was the hydrogenation of diyne **15** along with the desired selective propargyl-*O*-debenzylation.<sup>10</sup> 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 ketodiols by using phenyliodi-

## 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**)

ne(III) bis(trifluoroacetate) (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<sup>4</sup> and synthetic 6-*epi*-aculeatin D,<sup>5</sup> respectively.

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

(12) (a) Ohira, S. *Synth. Commun.* **1989**, *19*, 561–564. (b) Roth, G. J.; Liepold, B.; Müller, S. G.; Bestmann, H. J. *Synlett* **1996**, 521–522.

units (phenol and side chain) at the late stage of the synthesis thus provide sufficient flexibility for related analogues synthesis.<sup>13</sup>

## Experimental Section

**Preparation of Epoxide (7).** To a solution of diol **12** (600 mg, 1.56 mmol) in dry  $\text{CH}_2\text{Cl}_2$  (15 mL) were added  $\text{Bu}_2\text{SnO}$  (7 mg) and *p*-TsCl (327 mg, 1.71 mmol) followed by triethylamine (435  $\mu\text{L}$ , 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  $\text{CH}_2\text{Cl}_2$  and extracted. The combined organic phases were washed with water and brine, dried ( $\text{Na}_2\text{SO}_4$ ), and concentrated. The crude tosylate (840 mg) was dissolved in methanol (20 mL) and stirred with anhydrous  $\text{K}_2\text{CO}_3$  (270 mg) for 30 min at 0 °C and concentrated. The crude was dissolved in ethyl acetate, washed with water and brine, dried ( $\text{Na}_2\text{SO}_4$ ), 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.  $[\alpha]_D^{25} = +86.9$  ( $c = 1$ ,  $\text{CHCl}_3$ ). IR ( $\text{CHCl}_3$ ):  $\nu$  3432, 3289, 2927, 2110, 1612, 1513, 1248, 1069, 753, 699  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (200 MHz,  $\text{CDCl}_3$ ):  $\delta$  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).  $^{13}\text{C}$  NMR (50 MHz,  $\text{CDCl}_3$ ):  $\delta$  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,  $[\text{M} + \text{Na}]^+$ ). Anal. Calcd for  $\text{C}_{23}\text{H}_{26}\text{O}_4$ : C, 75.38; H, 7.15. Found: C, 75.30; H, 7.08.

**(3S,5R,7R)-3-O-Benzyl-5-O-(4-methoxybenzyl)-7-O-tert-butyl-dimethylsilyl-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 ( $5 \times 10$  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.  $[\alpha]_D^{25} = +14.9$  ( $c = 1$ ,  $\text{CHCl}_3$ ). IR ( $\text{CHCl}_3$ ):  $\nu$  3368, 2854, 1613, 1514, 1216, 1039, 834, 758, 697  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  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).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  –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,  $[\text{M} + \text{Na}]^+$ ). Anal. Calcd for  $\text{C}_{47}\text{H}_{74}\text{O}_5\text{Si}$ : C, 75.55; H, 9.98. Found: C, 75.48; H, 9.90.

**(3S,5R,7R)-5-O-(4-Methoxybenzyl)-7-O-tert-butyl-dimethylsilyl-1-(4-tert-butyl-dimethylsilyloxyphenyl)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 ( $5 \times 20$  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.  $[\alpha]_D^{25} = -5.1$  ( $c = 1$ ,  $\text{CHCl}_3$ ). IR ( $\text{CHCl}_3$ ):  $\nu$  3480, 2855, 1611, 1510, 1252, 1039, 836, 758, 692  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  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).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  –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,  $[\text{M} + \text{Na}]^+$ ). Anal. Calcd for  $\text{C}_{46}\text{H}_{82}\text{O}_5\text{Si}_2$ : C, 71.63; H, 10.72. Found: C, 71.58; H, 10.60.

**(5S,7R) 5-(4-Methoxybenzyloxy)-7-(tert-butyl-dimethylsilyloxy)-1-(4-tert-butyl-dimethylsilyloxyphenyl)icosan-3-one (20).** In a flame-dried, two necked, round-bottom flask (25 mL) was dissolved oxalyl chloride (67  $\mu\text{L}$ , 0.77 mmol) under  $\text{N}_2$  in dry  $\text{CH}_2\text{Cl}_2$  (5 mL). After the solution was cooled to –78 °C, dry DMSO (100  $\mu\text{L}$ , 1.42 mmol) was added dropwise with stirring for 15 min. A solution of alcohol **19** (200 mg, 0.25 mmol) in dry  $\text{CH}_2\text{Cl}_2$  (5 mL) was added dropwise and stirred for 30 min. To this was added  $\text{Et}_3\text{N}$  (216  $\mu\text{L}$ , 1.55 mmol) and stirring continued for 15 min at –78 °C. The reaction mixture was partitioned between  $\text{CH}_2\text{Cl}_2$  and water, the organic phase was separated, and the aqueous phase was extracted with  $\text{CH}_2\text{Cl}_2$ . Combined organic phases were washed with brine, dried ( $\text{Na}_2\text{SO}_4$ ), 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.  $[\alpha]_D^{25} = -4.5$  ( $c = 1$ ,  $\text{CHCl}_3$ ). IR ( $\text{CHCl}_3$ ):  $\nu$  3415, 2927, 1715, 1612, 1511, 1252, 1040, 836, 759, 686  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  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).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  –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,  $[\text{M} + \text{K}]^+$ ). Anal. Calcd for  $\text{C}_{46}\text{H}_{80}\text{O}_5\text{Si}_2$ : 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  $\text{CH}_2\text{Cl}_2$  (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  $\text{CH}_2\text{Cl}_2$ . The organic phase was washed with water and brine, dried ( $\text{Na}_2\text{SO}_4$ ), and concentrated. The crude (84 mg) was dissolved in dry THF (5 mL) and treated with TBAF (250  $\mu\text{L}$  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<sub>2</sub>O (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<sub>3</sub> (4 mL) was added and the resulting mixture extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried (Na<sub>2</sub>SO<sub>4</sub>), 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.** [ $\alpha$ ]<sub>D</sub><sup>25</sup> = +47.7 (*c* = 0.2, CHCl<sub>3</sub>) [lit. [ $\alpha$ ]<sub>D</sub><sup>23</sup> = +46.5 (*c* = 1, CHCl<sub>3</sub>)]. IR (neat):  $\nu$  3410, 2916, 2849, 1665, 1628, 1057, 1009 cm<sup>-1</sup>. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  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). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  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]<sup>+</sup>, 441.4 [M + Na]<sup>+</sup>. Anal. Calcd for C<sub>26</sub>H<sub>42</sub>O<sub>4</sub>: C, 74.60; H, 10.11. Found: C, 74.48; H, 10.00.

**(+)-6-*epi*-Aculeatin D.** [ $\alpha$ ]<sub>D</sub><sup>25</sup> = +14.6 (*c* = 0.2, CHCl<sub>3</sub>) [lit. [ $\alpha$ ]<sub>D</sub><sup>26</sup> = +15.0 (*c* = 1, CHCl<sub>3</sub>)]. IR (neat):  $\nu$  3410, 2916, 2849, 1664, 1628, 1053, 1005 cm<sup>-1</sup>. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  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). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  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]<sup>+</sup>, 441.4 [M + Na]<sup>+</sup>. Anal. Calcd for C<sub>26</sub>H<sub>42</sub>O<sub>4</sub>: C, 74.60; H, 10.11. Found: C, 74.51; H, 10.02.

**Acknowledgment.** B.S. thanks CSIR (New Delhi) for financial assistance in the form of a research fellowship.

**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>.

JO800026N