Total Synthesis of (+)-Aculeatin D and (+)-6-*epi*-Aculeatin D

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Abstract: The stereoselective total synthesis of spiroketal natural product (+)-aculeatin D and unnatural (+)-6-*epi*-aculeatin D has been accomplished. Sharpless kinetic resolution of secondary allylic alcohol and phenyliodine(III) bis(trifluoroacetate) (PIFA)-mediated oxidative spirocyclization were used as key steps in this synthesis.

Key words: (+)-aculeatin D, (+)-6-*epi*-aculeatin D, Sharpless kinetic resolution, spirocylization

Spiroketal natural products such as aculeatin A–D (**1**–**4**, Figure 1) were recently isolated from *Amomum aculeatum* by Heilmann et al.[1] The *Amomum aculatum* (Zingiberaceae) is a herbaceous plant that is distributed throughout Malaysia, Indonesia and Papua New Guinea. It is traditionally used as a folk medicine to treat fever and malaria.[2] The aculeatins A–D represent a novel class of natural compounds that comprise an unusual 1,7-dioxadispiro[5.1.5.2]pentadecane spirocyclic system. These compounds have been found to exhibit antiprotozoal activity against some *Plasmodium* and *Trypanosoma* species. In addition, they also show antibacterial activity against the KB cell lines. The observed biological activity of the aculeatins may be attributed to the presence of the Michael acceptor moiety.[3] Due to their fascinating biological activities and novel structural features, these compounds have attracted the attention of several synthetic chemists.[4]

The presence of the hidden 1,3-dihydroxy units was the major concern in designing different synthetic routes to aculeatins. The majority of approaches utilize stepwise approaches to construct the 1,3-diol motif with the desired relative configuration, either by 1,3-induced asymmetric reduction or by intramolecular Michael addition and/or Chiron approach. In most of the approaches, phenyliodine(III) bis(trifluoroacetate) (PIFA)-mediated oxidative spirocyclization has been employed as a key step to construct the dispiroskeleton.[4] In recent years, Sharpless kinetic resolution has become one of the most valuable and versatile protocols for the synthesis of enantiomerically pure chiral secondary epoxy alcohols[5] because they readily undergo regioselective ring-opening reactions with various nucleophiles.[6] As a result, this reaction has found extensive use in the synthesis of various natural products.[7] Here we successfully employed this strategy to construct the *anti*-1,3-diol moiety for the synthesis of (+)-aculeatin D and its 6-epimer.

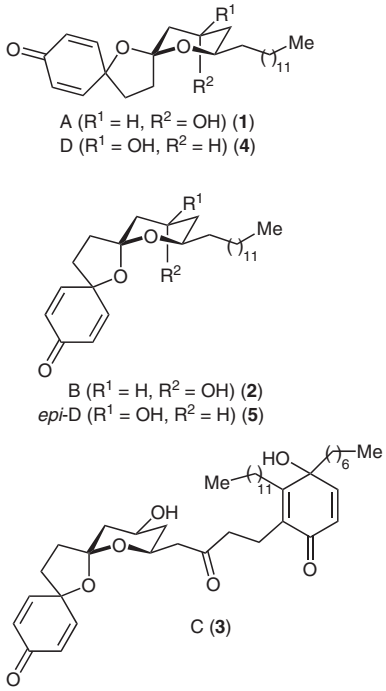

Figure 1 Aculeatins A–D and 6-*epi*-aculeatin D

In a continuation of our interest in the synthesis of biologically active natural products, we herein report an efficient and concise synthetic route for the total synthesis of the spiroketal natural product (+)-aculeatin D (**4**), which we chose because of its well-documented cytotoxicity (IC_{50} = 0.35 μg/mL), and the unnatural (+)-6-*epi*-aculeatin D (**5**), utilizing Sharpless kinetic resolution and PIFA-mediated oxidative spirocyclization as key steps.

The retrosynthetic analysis of (+)-aculeatin D (**4**) and its 6-epimer (+)-*epi*-aculeatin D (**5**) is depicted in Scheme 1. Accordingly, the spiroketal system could be generated via phenolic oxidation of an appropriate ketone **6**, which, in turn, could be prepared from protected *anti*-1,3-diol **7**. The key intermediate **7** could be synthesized from epoxyalcohol **8** by regioselective reductive ring-opening. The starting epoxyalcohol **8** could be prepared from allylic alcohol **9** using Sharpless kinetic resolution.

The synthesis of (+)-aculeatin D began with the commercially available 1-tetradecanol (**10**), which was oxidized under Swern conditions and subsequently converted into α,β- unsaturated ester **11** using Wittig olefination in 86%

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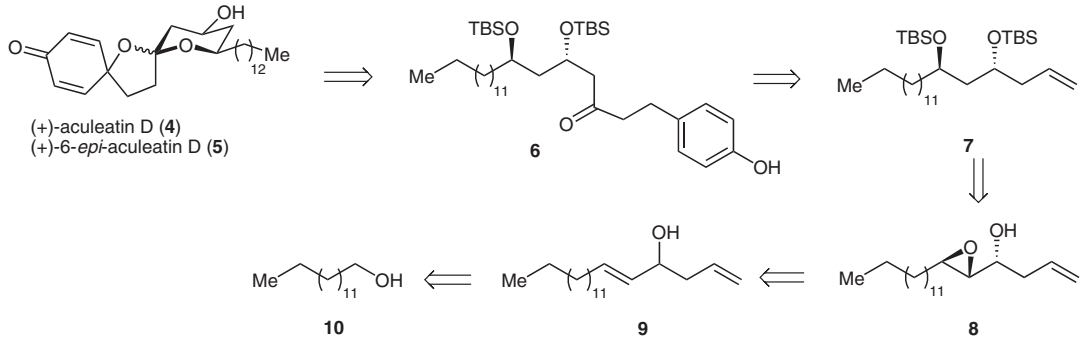


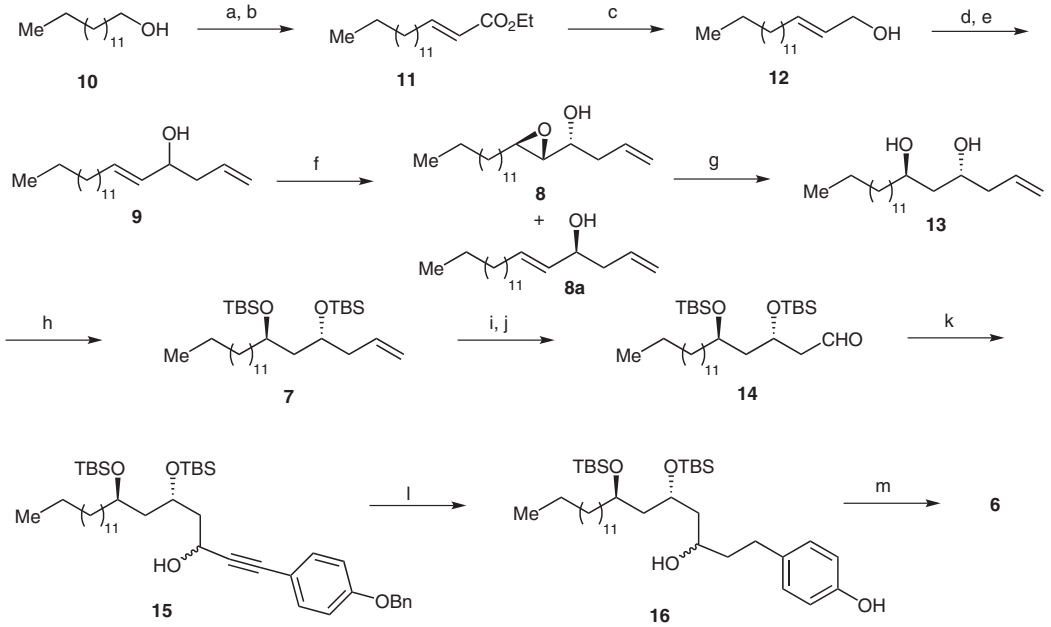
Scheme 1 Retrosynthetic analysis of (+)-aculeatin D and (+)-6-*epi*-aculeatin D

yield (two steps).[8] The chemoselective reduction of **11** using DIBAL-H in CH_2Cl_2 gave the allylic alcohol **12** in 95% yield.[9] The allylic alcohol **12** was then oxidized to the corresponding aldehyde in 90% yield using IBX in DMSO and subsequently subjected to zinc-mediated allylation to furnish the secondary allylic alcohol **9** in 75% yield.[10] Racemic allylic alcohol **9** was subjected to Sharpless kinetic resolution using (–)-DIPT and Ti(O*i*-Pr)$_4$ to achieve the chiral epoxy alcohol **8** and allylic alcohol **8a** (Scheme 2).

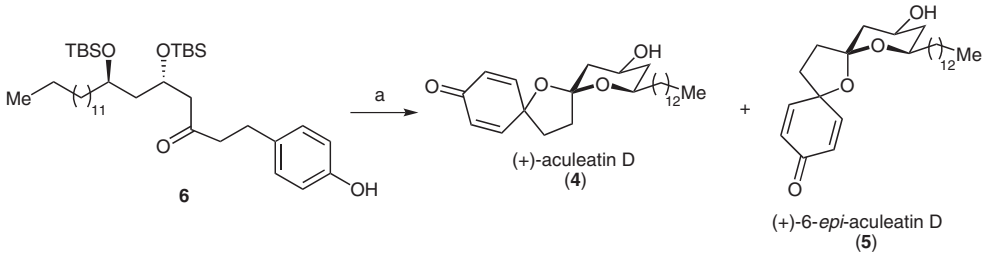
The resulting epoxyalcohol **8** was subjected to regioselective reductive ring-opening with Red-Al® to provide the *anti*-1,3-diol fragment **13**.[11] The diol **13** was then protected as its di-TBS ether using TBSOTf and 2,6-lutidine to give **7** in 95% yield. The terminal olefin **7** was then subjected to OsO_4-catalyzed dihydroxylation and $NaIO_4$-mediated cleavage to give the aldehyde **14**, which was further treated with *n*-BuLi and *p*-benzyloxyphenylacetylene in THF to afford the secondary alcohol **15** as a mixture of diastereomers.[12] Debenzylation and alkyne reduction of alcohol **15** was achieved in a single step using Pd/C under a hydrogen atmosphere, to provide the diol **16** in 92% yield.[13] Secondary alcohol **16** was then converted into the corresponding ketone **6** under Swern oxidation conditions (Scheme 2).[14]

Cleavage of the TBS-ethers from compound **6** with TBAF in THF gave the corresponding diol, which was used without further purification for the oxidative spirocyclization using PIFA in acetone–water (10:1, v/v solution) to furnish the (+)-aculeatin D (**4**) and its thermodynamically more stable 6-epimer (+)-6-*epi*-aculeatin D (**5**; which is stabilized by a favorable anomeric effect),[15] in good yield (Scheme 3). The physical and spectral data of these compounds were in agreement with those reported in the literature.[4,16]

In conclusion, we have accomplished an efficient and short total synthesis of naturally occurring biologically active spiroketal natural product (+)-aculeatin D and its



Scheme 2 *Reagents and conditions*: (a) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, –78 to –40 °C, 85%; (b) PPh_3=$CHCO_2Et$, benzene, reflux; (c) DIBAL-H, CH_2Cl_2, 0 °C→r.t., 2 h, 95%; (d) IBX, DMSO, CH_2Cl_2, r.t., 5 h, 90%; (e) Zn, allyl bromide, sat. NH_4Cl, 2 h, 75%; (f) (–)-DIPT, Ti(O*i*-Pr)$_4$, TBHP, CH_2Cl_2, –20 °C, 48 h, 43% (isolated yield of epoxyalcohol **8**); (g) Red-Al, THF, 0 °C, 1 h, 82%; (h) TBSOTf, 2,6-lutidine, CH_2Cl_2, 5 h, 95%; (i) OsO_4, NMO, acetone–H_2O (4:1), 90%; (j) $NaIO_4$, THF–H_2O (3:1), 88%; (k) *p*-benzyloxyphenylacetylene, *n*-BuLi, THF, –78 °C, 1 h, 92%; (l) H_2 (1 atm), 10% Pd-C, EtOAc, r.t., 5 h, 92%; (m) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, –78 to –40 °C, 86%.



Scheme 3 *Reagents and conditions*: (a) TBAF, THF, 0 °C, 30 min, and $PhI(O_2CCF_3)_2$, acetone–H_2O (10:1), r.t., 4 h, 60% (each isomer in 30% yield).

6-epimer. Highlights of this synthetic venture includes the Sharpless kinetic resolution of the secondary allylic alcohol, which was successfully employed for the construction of the *anti*-1,3-diol system, and PIFA-mediated spiroketalization. The present strategy employs a minimal use of protecting groups and the introduction of the aromatic system towards the end of the synthesis provides sufficient flexibility for the construction of various analogues.

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(16) **(1*R*)-1-[(2*R*,3*R*)-3-Tridecyloxiran-2-yl]-3-buten-1-ol** (**8**): colorless oil; $[\alpha]_D^{25}$ +5.8 (*c* 1.0, $CHCl_3$); IR (neat): 3384, 2919, 2850, 1639, 1464, 1283, 1066, 883 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 5.90–5.74 (m, 1 H), 5.18–5.08 (m, 2 H), 3.56–3.47 (m, 1 H), 2.88–2.83 (t, *J* = 2.2 Hz, 1 H), 2.72–2.68, (q, *J* = 2.2 Hz, 1 H), 2.38–2.31 (m, 2 H), 1.88 (br s, 1 H), 1.30–1.24 (m, 24 H), 0.88 (t, *J* = 6.6 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 133.6, 118.1, 68.1, 60.4, 55.4, 38.1, 31.9, 31.5, 29.7, 29.6 (× 2), 29.5 (× 2), 29.4, 29.3 (× 2), 25.9, 22.6, 14.1; ESI-MS: *m*/*z* = 319 $[M + Na]^+$; HRMS: *m*/*z* $[M + Na]^+$ calcd for $C_{19}H_{36}O_2Na$: 319.2613; found: 319.2599.
(4*R*,6*R*)-1-Nonadecene-4,6-diol (**13**): white solid; mp 83–85 °C, $[\alpha]_D^{25}$ –10.7 (*c* 1.0, $CHCl_3$); IR (neat): 3507, 3354, 2918, 2849, 1643, 1467, 1356, 1069 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 5.86–5.74 (m, 1 H), 5.18–5.08 (m, 2 H), 3.99–3.84 (m, 2 H), 2.28–2.21 (m, 2 H), 1.59–1.56 (m, 2 H), 1.33–1.23 (m, 24 H), 0.88 (t, *J* = 6.5 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 134.6, 118.1, 69.2, 68.1, 42.0, 41.8, 37.4, 31.9, 29.7–29.5 (× 7), 29.3, 25.7, 22.6, 14.1; ESI-MS: *m*/*z* = 321 $[M + Na]^+$; HRMS: *m*/*z* $[M + Na]^+$ calcd for $C_{19}H_{38}O_2Na$: 321.2769; found: 321.2773.
***tert*-Butyl({(1*R*,3*R*)-3-[1-(*tert*-butyl)-1,1-dimethylsilyl]oxy-1-tridecyl-5-hexenyl}oxy)-dimethylsilane** (**7**): colorless oil; $[\alpha]_D^{25}$ –15.0 (*c* 1.0, $CHCl_3$); IR (neat): 2927, 2856, 1636, 1464, 1253, 1075, 833 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 5.85–5.70 (m, 1 H), 5.07–4.98 (m, 2 H), 3.85–3.69 (m, 2 H), 2.24–2.17 (m, 2 H), 1.57–1.48 (m, 2 H), 1.33–1.22 (m, 24 H), 0.92–0.81 (m, 21 H), 0.09–0.06 (m, 12 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 135.0, 116.7, 70.1, 69.8, 45.0, 42.5, 37.8, 31.9, 30.9, 29.7 (× 6), 29.6, 29.3, 25.9 (× 6), 25.6, 25.0, 22.6, 14.1, –3.9, –4.0, –4.1, –4.3; ESI-MS: *m*/*z* = 527 $[M + H]^+$; HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{31}H_{67}O_2Si_2$: 527.4679; found: 527.4668.
(5*R*,7*R*)-1-[4-(Benzyloxy)phenyl]-5,7-di[1-(*tert*-butyl)-1,1-dimethylsilyl]oxy-1-icosyn-3-ol (**15**): colorless oil; $[\alpha]_D^{25}$ +11.2 (*c* 1.0, $CHCl_3$); IR (neat): 3450, 2926, 2854, 1608, 1507, 1462, 1249 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.45–7.32 (m, 7 H), 6.90 (d, *J* = 8.8 Hz, 2 H), 5.06 (s, 2 H), 4.84 (d, *J* = 3.2 Hz, 1 H), 4.16 (br s, 1 H), 3.74–3.65 (m, 1 H), 2.11–1.86 (m, 3 H), 1.78–1.70 (m, 2 H), 1.33–1.21 (m, 24 H), 0.94–0.83 (m, 21 H), 0.07 (s, 6 H), 0.06 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.8, 136.6, 135.2, 133.0,

128.6 (× 2), 128.0, 127.4 (× 2), 124.9, 114.7 (× 2), 88.5, 85.0, 69.9, 69.3, 61.5, 46.1, 45.2, 37.3, 32.1, 31.9, 29.7 (× 8), 29.6, 29.3, 26.4, 25.9, 25.8, 24.9, 23.4, 22.6, 18.0, 17.9, 14.1, –3.8, –4.1 (× 2), –4.4; ESI-MS: *m/z* = 737 $[M + H]^+$; HRMS: *m/z* $[M + Na]^+$ calcd for $C_{45}H_{76}O_4NaSi_2$: 759.5054; found: 759.5068.

(5*R*,7*R*)-5,7-Di[1-(*tert*-butyl)-1,1-dimethylsilyl]oxy-1-(4-hydroxyphenyl)icosan-3-ol (**16**): colorless oil; $[\alpha]_D^{25}$ +8.2 (*c* 1.0, $CHCl_3$); IR (neat): 3440, 2926, 2855, 1621, 1463, 1254, 1077 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.05 (d, *J* = 8.4 Hz, 2 H), 6.74 (d, *J* = 8.3 Hz, 2 H), 5.40 (br s, 1 H), 3.94–3.60 (m, 3 H), 2.76–2.54 (m, 2 H), 1.80–1.51 (m, 6 H), 1.41–1.21 (m, 24 H), 0.93–0.84 (m, 21 H), 0.11 (s, 6 H), 0.04 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 153.7, 134.1, 129.4, 115.1, 71.7, 70.2, 70.0, 48.9, 46.4, 44.1, 39.5, 37.3, 31.9, 30.7, 29.6 (× 8), 29.3, 25.9 (× 5), 25.8, 24.9, 22.6, 18.0, 17.8, 14.1, –3.8, –4.2 (× 2), –4.4; ESI-MS: *m/z* = 651 $[M + H]^+$; HRMS: *m/z* $[M + Na]^+$ calcd for $C_{38}H_{74}O_4NaSi_2$: 673.5023; found: 673.4998.

(5*S*,7*R*)-5,7-Di[1-(*tert*-butyl)-1,1-dimethylsilyl]oxy-1-(4-hydroxyphenyl)icosan-3-one (**6**): colorless oil; $[\alpha]_D^{25}$ +8.0 (*c* 1.0, $CHCl_3$); IR (neat): 3449, 2925, 2853, 1724 (keto), 1637, 1442, 1260, 1082 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.03 (d, *J* = 8.3 Hz, 2 H), 6.73 (d, *J* = 8.4 Hz, 2 H), 5.12 (br s, 1 H), 4.24–4.15 (m, 1 H), 3.69–3.62 (m, 1 H), 2.85–2.41 (m, 6 H), 1.69–1.66 (m, 2 H), 1.33–1.21 (m, 24 H), 0.90–0.86 (s, 12 H), 0.84 (s, 9 H), 0.07 (s, 12 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 208.6, 135.1, 129.4, 125.0, 115.2 (× 2), 70.0, 67.4, 51.1, 46.3, 45.7, 37.6, 32.1, 31.9, 29.6 (× 6), 29.3, 28.5, 26.3, 25.9 (× 7), 25.0, 23.4, 22.6, 14.1, –4.1, –4.2, –4.3, –4.4; ESI-MS: *m/z* = 649 $[M + H]^+$; HRMS: *m/z* $[M + H]^+$ calcd for $C_{38}H_{73}O_4Si_2$: 649.5047; found: 649.5041.

Aculeatin D: colorless oil; $[\alpha]_D^{25}$ +40.0 (*c* 1.0, $CHCl_3$); IR (neat): 3426, 2923, 2853, 1660 (keto), 1628, 1459, 1061, 1013 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 6.90 (dd, *J* = 10.5, 3.2 Hz, 1 H), 6.77 (dd, *J* = 10.5, 3.2 Hz, 1 H), 6.07 (dd, *J* = 10.0, 1.5 Hz, 1 H), 6.03 (dd, *J* = 10.0, 1.5 Hz, 1 H), 4.05–3.96 (m, 1 H), 3.77–3.62 (m, 1 H), 2.20 (m, 1 H), 1.97 (m, 1 H), 1.73 (m, 1 H), 1.45–1.35 (m, 2 H), 1.31–1.06 (m, 28 H), 0.81 (t, *J* = 6.9 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 185.6, 151.5, 149.2, 127.0, 126.8, 108.9, 82.8, 69.0, 68.1, 43.9, 42.8, 35.8, 34.5, 32.1, 31.9, 30.3, 29.8–29.5 (× 4), 29.3, 28.9, 28.8, 28.5, 25.7, 21.7; ESI-MS: *m/z* = 419 $[M + H]^+$, 441 $[M + Na]^+$; HRMS: *m/z* $[M + Na]^+$ calcd for $C_{26}H_{42}O_4Na$: 441.2980; found: 441.2970.

6-*epi*-Aculeatin D: colorless oil; $[\alpha]_D^{25}$ +5.0 (*c* 1.0, $CHCl_3$); IR (neat): 3426, 2923, 2853, 1660 (keto) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 6.77 (dd, *J* = 10.5, 3.2 Hz, 1 H), 6.72 (dd, *J* = 10.5, 3.2 Hz, 1 H), 6.06 (dd, *J* = 10.0, 1.9 Hz, 1 H), 6.03 (dd, *J* = 10.0, 1.9 Hz, 1 H), 4.04–3.90 (m, 1 H), 3.75–3.67 (m, 1 H), 2.37–2.15 (m, 3 H), 2.01–1.93 (m, 3 H), 1.86–1.56 (m, 3 H), 1.35–1.15 (m, 24 H), 0.83 (t, *J* = 7.3 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 185.3, 151.4, 149.8, 128.7, 128.6, 109.6, 79.5, 68.1, 63.9, 41.4, 40.5, 38.7, 35.8, 34.6, 31.9, 30.3, 29.6 (× 4), 29.5, 29.3, 28.9, 23.7, 22.9, 14.0; ESI-MS: *m/z* = 419 $[M + H]^+$.