Synthesis of Aculeatins A and B via Iterative Hydrolytic Kinetic Resolution

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Received 28 December 2009; revised 30 December 2009

Abstract: A simple and concise approach for the synthesis of aculeatins A and B starting from (±)-epichlorohydrin is described. The synthetic strategy features Jacobsen's hydrolytic kinetic resolution and a Linchpin coupling as key steps.

Key words: hydrolytic kinetic resolution, Linchpin coupling, epoxide, spirocyclization, aculeatins

Aculeatins A (**1**) and B (**2**) (Figure 1) were isolated by Heilmann and co-workers in 2000 from *Amomum Aculeatum* rhizomes.[1] They were found to inhibit the growth of human cancer KB cell lines and MFC-7 human breast cancer cells.[2]In addition, they display antiprotozoal activity against *Trypanosoma* and both the NF54 and chloroquine-resistant K1 strains of the malarial parasite *Plasmodium falciparum*. Interestingly, these compounds are endowed with an unprecedented 1,7-dioxadispiro[5.1.5.2]pentadecane tricyclic ring system which makes them attractive synthetic targets. In view of their important biological activity, and unusual and challenging structural features, the aculeatins have attracted considerable attention from synthetic organic chemists.

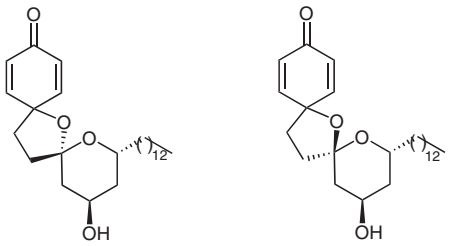


Figure 1 Aculeatins A (**1**) and B (**2**)

In 2002, Wong reported the first syntheses of racemic aculeatin A (**1**) and B (**2**) in which the spiroketal tricyclic framework was generated by intramolecular cyclization initiated by phenolic oxidation.[3] Marco and co-workers prepared **1** and **2** in enantiomerically pure form, for the first time, using an asymmetric allylation reaction.[4] Meanwhile, several other reported asymmetric syntheses of the aculeatins were based mainly on chiral pool starting materials, or via stereoselective methods to generate the stereogenic centers;[5] subsequent oxidative cyclization[6] was performed using phenyliodine bis(trifluoroacetate) (PIFA).

As part of our research program aimed at developing enantioselective syntheses of biologically active products based on hydrolytic kinetic resolution (HKR),[7] we became interested in devising a simple and concise route to aculeatins A and B. Herein, we report our successful endeavors toward the total syntheses of **1** and **2** employing HKR[8] and a Linchpin coupling[9] as the key steps.

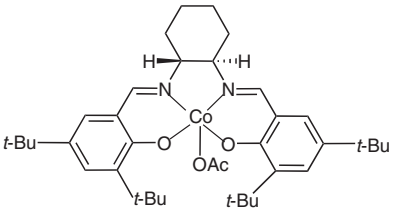


Figure 2 Structure of the (*R*,*R*)-(salen)Co(III)(OAc) catalyst

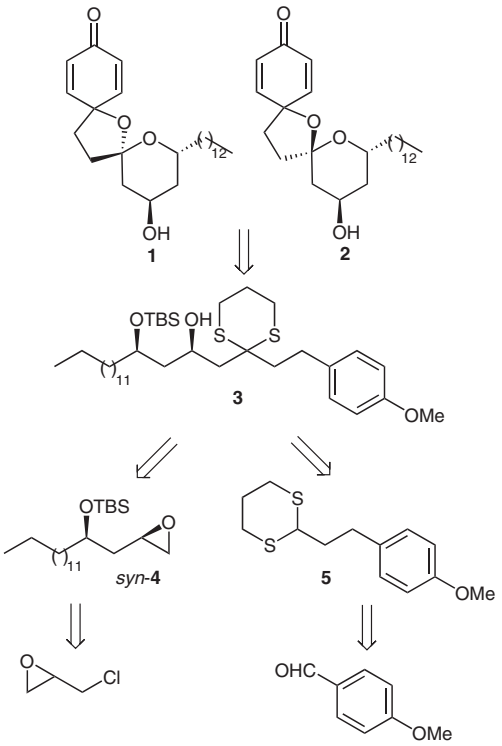
The HKR method involves a readily accessible cobalt-based chiral salen complex, (*R*,*R*)-(salen)Co(III)(OAc), as the catalyst (Figure 2), and water to resolve a racemic epoxide into an enantiomerically enriched epoxide and a diol. Typically, the products can serve as useful precursors for the synthesis of compounds of biological importance.[10]

Our retrosynthesis of the target compounds **1** and **2** is based on a convergent approach as delineated in Scheme 1. We envisioned that the common precursor **3** could be prepared via Linchpin coupling of epoxide *syn*-**4** and dithiane **5**. The epoxide *syn*-**4** could in turn be prepared from (±)-epichlorohydrin, while the dithiane fragment **5** could be obtained starting from *p*-anisaldehyde.

As shown in Scheme 2, the synthesis of epoxide fragment *syn*-**4** started from commercially available (±)-epichlorohydrin which on ring-opening with dodecylmagnesium bromide gave alcohol **6**. Subsequent treatment with base gave the epoxide **7** in 92% yield. The *rac*-epoxide **7** was subjected to Jacobsen's HKR, using the (*R*,*R*)-(salen)Co(III)(OAc) catalyst, to give a mixture of enantiopure epoxide (*R*)-**8a**[11]in 46% yield along with diol **8b** in 45% yield, which were separated by silica gel column chromatography.

With enantiomerically pure epoxide (*R*)-**8a** in hand, our next task was to establish the second stereogenic center with the required stereochemistry. Thus epoxide **8a** was treated with vinylmagnesium bromide in the presence of copper(I) iodide to give the homoallylic alcohol **9** in 89%

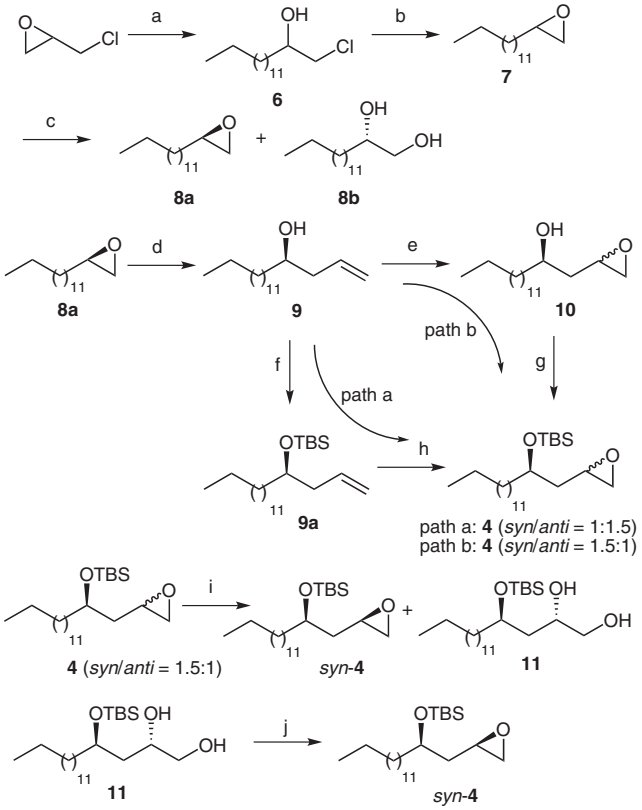
SYNTHESIS 2010, No. 9, pp 1479–1484
Advanced online publication: 24.02.2010
DOI: 10.1055/s-0029-1218687; Art ID: Z28109SS



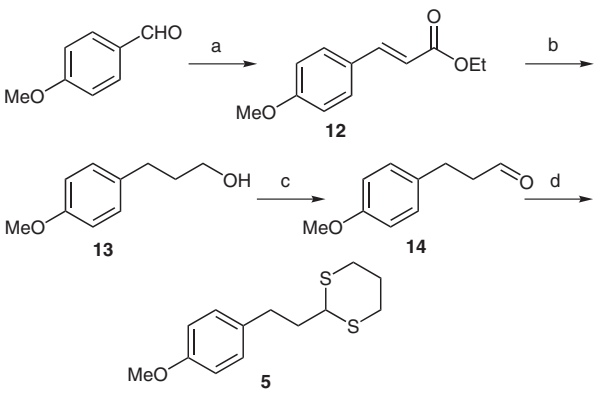
Scheme 1 Retrosynthesis of aculeatins A (**1**) and B (**2**)

yield. We next proceeded to explore the stereoselective outcome of the epoxidation reaction of **9** with and without protection of the hydroxy group. To this end, the hydroxy group of homoallylic alcohol **9** was protected as the *tert*-butyldimethylsilyl ether, followed by epoxidation with *m*-chloroperoxybenzoic acid (path a). The epoxide **4** thus obtained was found to be a mixture of two diastereomers (*syn*/*anti* = 1:1.5) with the desired *syn*-diastereomer present as the minor component. In contrast, epoxidation of unprotected homoallylic alcohol **9** gave compound **10** in favor of the desired *syn*-diastereomer (*syn*/*anti* = 1.5:1). Protection of the hydroxy group of epoxide **10** as the corresponding *tert*-butyldimethylsilyl ether gave epoxides *syn*-**4**/*anti*-**4** as a 1.5:1 diastereomeric mixture (path b). The two diastereomers could not be differentiated by thin layer chromatography. In order to improve the diastereoselectivity, the mixture of epoxides produced via path b was subjected to HKR using the (*R*,*R*)-(salen)Co(III)(OAc) complex (0.5 mol%) and water (0.55 equiv) to afford the diastereomerically pure epoxide *syn*-**4** in good yield.

As the HKR method provided the desired epoxide *syn*-**4** along with unwanted diol **11** in similar amounts, we decided to convert diol **11** into the required epoxide *syn*-**4** via internal nucleophilic substitution of a secondary mesylate.[12] Accordingly, chemoselective pivalation of diol **11** with pivaloyl chloride was followed by mesylation of the secondary hydroxy group. Treatment of the crude mesylate with potassium carbonate in methanol led to deprotection of the pivaloyl ester and concomitant ring closure via intramolecular S_N2 displacement of the mesyl group to furnish epoxide *syn*-**4** in 61% overall yield.

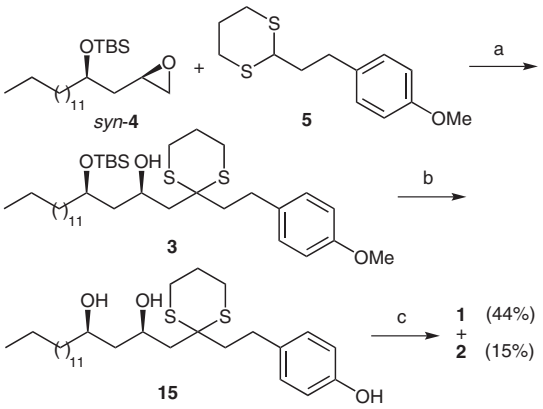


Scheme 2 Synthesis of epoxide *syn*-**4**. *Reagents and conditions*: (a) dodecylmagnesium bromide, THF, CuI, –40 °C, 12 h, 84%; (b) KOH, Et_2O, r.t., 1 h, 92%; (c) (*R*,*R*)-(salen)Co(III)(OAc) (0.5 mol%), THF, H_2O (0.55 equiv), 0 °C, 14 h (46% for **8a**, 45% for **8b**); (d) vinylmagnesium bromide, THF, CuI, –20 °C, 12 h, 89%; (e) MCPBA, CH_2Cl_2, 0 °C to r.t., 10 h, 96%; (f) TBDMSCl, imidazole, CH_2Cl_2, 0 °C to r.t., 3 h, 92%; (g) TBDMSCl, imidazole, CH_2Cl_2, 0 °C to r.t., 4 h, 95%; (h) MCPBA, CH_2Cl_2, 0 °C to r.t., 8 h, 95%; (i) (*R*,*R*)-(salen)Co(III)(OAc) (0.5 mol%), THF, H_2O (0.55 equiv), 0 °C, 24 h (49% for *syn*-**4**, 37% for **11**); (j) (i) PivCl, Et_3N, cat. DMAP, r.t., 2 h; (ii) MsCl, Et_3N, DMAP, 0 °C to r.t., 1 h; (iii) K_2CO_3, MeOH, r.t., overnight (61% over 3 steps).



Scheme 3 Synthesis of dithiane **5**. *Reagents and conditions*: (a) Ph_3PCHCO_2Et, toluene, reflux, 6 h, 86%; (b) (i) 10% Pd/C, H_2 (60 psi), EtOAc, r.t., 1 h; (ii) $LiAlH_4$, THF, r.t. to reflux, 12 h, (81% over 2 steps); (c) IBX, DMSO–THF (1:1), 0 °C to r.t., 6 h, 84%; (d) 1,3-propanedithiol, cat. $BF_3{\cdot}OEt_2$, CH_2Cl_2, 0 °C, 12 h, 88%.

The synthesis of dithiane fragment **5** (Scheme 3) started from commercially available *p*-anisaldehyde which on two carbon homologation via Wittig reaction provided the olefin **12** as a *cis*/*trans* mixture. Reduction of the double bond was carried out under hydrogenation conditions using 10% palladium on charcoal. This was followed by ester reduction with lithium aluminum hydride to afford the alcohol **13** in 81% overall yield. The alcohol **13** was oxidized using 2-iodoxybenzoic acid (IBX) to give the corresponding aldehyde **14**, which on subsequent treatment with 1,3-propanedithiol in the presence of a catalytic amount of boron trifluoride–diethyl ether complex,[13] at room temperature, furnished the dithiane fragment **5** in excellent yield.



Scheme 4 Synthesis of aculeatin A (**1**) and B (**2**). *Reagents and conditions*: (a) *n*-BuLi, HMPA, THF, –78 °C, 1 h, 87%; (b) BBr_3, CH_2Cl_2, r.t. to –78 °C, 4 h; (c) $PhI(O_2CCF_3)_2$, Me_2CO–H_2O (9:1), r.t., 4 h, 64% (over 2 steps), 2.93:1 diastereomeric mixture of **1** and **2**.

With substantial amounts of both the required fragments in hand the coupling of epoxide *syn*-**4** and dithiane **5** was accomplished via the Linchpin protocol (Scheme 4). Toward this end, the lithiated anion of dithiane **5** was prepared using *n*-butyllithium in tetrahydrofuran at –78 °C, and then quenched with epoxide *syn*-**4** to afford the coupled product **3**. One-pot cleavage of the methyl and *tert*-butyldimethylsilyl groups using boron tribromide[14] gave triol **15**. Finally, spirocyclization of crude **15** with phenyliodine bis(trifluoroacetate) in acetone–water (9:1 v/v),[6] at room temperature, furnished a diastereoisomeric mixture of aculeatins A (**1**) and B (**2**) in the ratio 2.93:1; these were separated by silica gel column chromatography. Compounds **1** and **2** were fully characterized by IR, NMR and mass spectroscopy data which were in accord with those reported in the literature.[4,5]

In conclusion, a short and efficient total synthesis of aculeatins A (**1**) and B (**2**) in high enantioselectivities and 11.5% overall yield has been accomplished. The stereocenters were installed by means of iterative Jacobsen's hydrolytic kinetic resolution, and the final oxidative spirocyclization step was achieved using phenyliodine bis(trifluoroacetate). It is expected that this approach would be suitable for the synthesis of other aculeatins, and we are currently working toward this objective.

All reactions were carried out under an inert atmosphere, unless otherwise stated, following standard syringe–septa techniques. Solvents were dried and purified by conventional methods prior to use. The progress of all the reactions was monitored by TLC using glass plates precoated with silica gel 60 F254 to a thickness of 0.25 mm (Merck). Column chromatography was performed on silica gel (60 and 230 mesh) using PE or a PE–EtOAc mixture as the eluent. Petroleum ether (PE) refers to the fraction boiling in the 60–80 °C range. Optical rotations were measured on a JASCO DIP-360 digital polarimeter at 25 °C. IR spectra were recorded on a Perkin-Elmer FT-IR spectrophotometer. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ using Bruker AC-200 and AC-400 spectrometers at 200 MHz or 400 MHz (^1H) and 50 MHz or 100 MHz (^{13}C); TMS was used as the internal standard. ESI-MS were obtained using an API-Q-Star Applied Biosystems spectrometer. Elemental analyses were carried out on a Carlo Erba CHNS-O analyzer.

1-Chloropentadecan-2-ol (6)

To a stirred soln of (±)-epichlorohydrin (14.00 g, 152.3 mmol) and CuI (2.90 g, 15.2 mmol) in anhyd THF (150 mL) was added dropwise, at –40 °C, a soln of dodecylmagnesium bromide, itself prepared from dodecyl bromide (113.12 g, 453.9 mmol) and Mg turnings (7.40 g, 304.6 mmol) in anhyd THF. The mixture was warmed to –20 °C over 12 h and then poured onto sat. aq NH_4Cl soln. The organic layer was separated and the aqueous layer was extracted with EtOAc (3 × 100 mL). The combined solvent extract was dried over Na_2SO_4, concd and purified by silica gel column chromatography (EtOAc–PE, 1:9) to give **6**; yield: 9.06 g (84%), as a colorless oil.

IR (neat): 3409, 2955, 1467, 1216 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 0.89 (t, *J* = 3.0 Hz, 3 H), 1.26 (s, 20 H), 1.43–1.64 (m, 4 H), 2.02 (s, 1 H), 3.75–3.89 (m, 1 H), 3.40–3.55 (m, 1 H), 3.57–3.77 (m, 1 H), 3.75–3.89 (m, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.0, 22.6, 25.4, 29.3–29.6 (br, several overlapping signals), 31.8, 34.1, 50.4, 71.4.

ESI–MS: *m*/*z* = 285 [M + Na^+].

2-Tridecyloxirane (7)

To a soln of crude **6** (8 g, 30.43 mmol) in Et_2O (50 mL) was added finely powdered KOH (5.12 g, 91.3 mmol). The mixture was stirred vigorously for 6 h and then poured onto H_2O (50 mL). The aqueous layer was extracted with Et_2O (3 × 150 mL) and the combined organic layers dried over Na_2SO_4. Evaporation of the solvent and silica gel column chromatographic purification (PE) of the residue gave epoxide **7**; yield: 6.35 g (92%), as a colorless liquid.

IR ($CHCl_3$): 3018, 2952, 2929, 2862, 1472, 1466, 1379, 1260, 1022, 916, 828 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 6.6 Hz, 3 H), 1.26 (s, 20 H), 1.42–1.59 (m, 4 H), 2.46 (dd, *J* = 5.0, 2.8 Hz, 1 H), 2.75 (dd, *J* = 5.0, 4.0 Hz, 1 H), 2.87–2.95 (m, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.1, 22.6, 25.9, 29.3–29.6 (br, several overlapping signals), 31.9, 32.5, 47.0, 52.3.

ESI–MS: *m*/*z* = 249 [M + Na^+].

(2*R*)-2-Tridecyloxirane (8a)

A soln of epoxide **7** (7.5 g, 33.13 mmol) and (*R*,*R*)-(salen)Co(III)(OAc) (0.109 g, 0.17 mmol) in THF (0.5 mL) was stirred at 0 °C for 5 min, and then distilled H_2O (327 μL, 18.22 mmol) was added. After stirring for 24 h, the mixture was concd and purified by silica gel column chromatography (PE) to afford **8a**; yield: 3.45 g (46%), as a yellow liquid. Further chromatographic purification (PE–EtOAc, 4:1) provided diol **8b**; yield: 3.64 g (45%), brown liquid, as a single diastereomer.

$[\alpha]_D^{25}$ +6.54 (*c* 1.0, $CHCl_3$).

IR (neat): 3018, 2869, 1736, 1467, 1216, 915, 828 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 6.6 Hz, 3 H), 1.26 (s, 20 H), 1.42–1.59 (m, 4 H), 2.45 (dd, *J* = 5.1, 2.8 Hz, 1 H), 2.77 (dd, *J* = 5.1, 4.0 Hz, 1 H), 2.84–2.93 (m, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.0, 22.6, 25.9, 29.3–29.6 (br, several overlapping signals), 31.9, 32.4, 46.9, 52.1.

ESI–MS: *m*/*z* = 249 [M + Na^+].

(4*R*)-Heptadec-1-en-4-ol (9)

To a stirred soln of **8a** (3.25 g, 14.36 mmol) and CuI (274 mg, 1.44 mmol) in anhyd THF (30 mL) was added dropwise a soln of vinylmagnesium bromide (3.07 g, 28.72 mmol, 28.72 mL, 1 M soln in THF) over a period of 30 min at –20 °C. The resulting mixture was stirred for 12 h and then allowed to warm to 0 °C before being quenched with sat. aq NH_4Cl soln (20 mL). The aqueous layer was extracted with Et_2O (3 × 50 mL), and the combined extracts washed with brine (20 mL) and dried (Na_2SO_4). Evaporation of the solvent and silica gel column chromatographic purification (EtOAc–PE, 1:19) of the residue gave alkene **9**; yield: 3.24 g (89%), as a colorless oil.

$[\alpha]_D^{25}$ +4.92 (*c* 1.0, $CHCl_3$) [Lit.[5e] $[\alpha]_D^{25}$ +5.0 (*c* 1.0, $CHCl_3$)].

IR ($CHCl_3$): 3372, 2955, 1640, 1467, 1216 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 6.7 Hz, 3 H), 1.26 (s, 22 H), 1.44–1.46 (m, 2 H), 1.65 (s, 1 H), 2.05–2.21 (m, 1 H), 2.24–2.38 (m, 1 H), 3.57–3.70 (m, 1 H), 5.08–5.19 (m, 2 H), 5.73–5.94 (m, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.1, 22.7, 25.7, 29.3–29.6 (br, several overlapping signals), 31.9, 36.8, 41.9, 70.7, 118.0, 134.9.

ESI–MS: *m*/*z* = 277 [M + Na^+].

(2*R*)-1-(Oxiran-2-yl)pentadecan-2-ol (10)

To a stirred soln of alkene **9** (2.5 g, 87.08 mmol) in CH_2Cl_2 (30 mL) at 0 °C was added 50% MCPBA (5.10 g, 14.75 mmol). The reaction mixture was stirred at r.t. for 10 h, quenched with sat. aq $NaHCO_3$ soln and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layer was washed with sat. aq $NaHCO_3$ soln (3 × 10 mL) and brine (3 × 10 mL), dried over Na_2SO_4, concentrated and purified by silica gel column chromatography (PE–EtOAc, 9:1) to afford a diastereomeric mixture (1.5:1) of epoxide **10**; yield: 2.55 g (96%), as a white solid.

IR ($CHCl_3$): 3436, 3192, 2968, 2932, 2852, 1471, 1379, 1265, 1206, 1101, 944, 878 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ (1.5:1 mixture of diastereomers) = 0.88 (t, *J* = 6.8 Hz, 3 H), 1.26 (s, 22 H), 1.50–1.68 (m, 2 H), 1.79–1.94 (m, 1 H), 2.52 (dd, *J* = 4.9, 2.8 Hz, 0.4 H), 2.64 (dd, *J* = 4.9, 2.9 Hz, 0.6 H), 2.79–2.87 (m, 1 H), 3.07–3.23 (m, 1 H), 3.78–3.97 (m, 1 H), 4.52 (br s, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ (1.5:1 mixture of diastereomers) = 14.1, 22.6, 25.4, 25.5, 29.3, 29.6 (br, several overlapping signals), 31.9, 37.4, 37.5, 38.8, 39.6, 46.6, 46.9, 50.3, 50.7, 69.3, 70.6.

ESI–MS: *m*/*z* = 293 [M + Na^+].

(4*R*)-4-[(*tert*-Butyldimethylsilyl)oxy]heptadec-1-ene (9a)

To a stirred soln of alcohol **9** (1 g, 3.93 mmol) in CH_2Cl_2 (15 mL) was added imidazole (0.53 g, 7.86 mmol). TBDMSCl (0.77 g, 5.10 mmol) was added at 0 °C and the reaction was stirred at r.t. for 3 h. The reaction mixture was quenched with sat. aq NH_4Cl soln and extracted with CH_2Cl_2 (3 × 20 mL). The organic extract was washed with brine (3 × 10 mL), dried over Na_2SO_4 and concentrated. Silica gel column chromatography (PE) of the residue provided silyl ether **9a**; yield: 1.33 g (92%), as a colorless liquid.

$[\alpha]_D^{25}$ +5.37 (*c* 1.0, $CHCl_3$).

IR ($CHCl_3$): 3088, 2929, 2896, 1642, 1255, 1129 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 0.06 (s, 6 H), 0.90 (s, 9 H), 0.90 (merged t, 3 H), 1.27 (s, 22 H), 1.36–1.43 (m, 2 H), 2.18–2.25 (m, 2 H), 3.69 (quin, *J* = 5.7 Hz, 1 H), 4.99–5.01 (m, 1 H), 5.05–5.09 (m, 1 H), 5.73–5.93 (m, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = –4.5, –4.3, 14.1, 18.1, 22.7, 25.3, 25.9, 29.4, 29.7, 31.9, 36.8, 41.9, 72.0, 116.4, 135.5.

ESI–MS: *m*/*z* = 391 [M + Na^+].

(2*R*)-2-[(*tert*-Butyldimethylsilyl)oxy]-1-[(2*R*/*S*)-oxiran-2-yl]pentadecane (*syn*-4/*anti*-4)

Path a: To a stirred soln of alcohol **10** (2 g, 7.40 mmol) in CH_2Cl_2 (25 mL) was added imidazole (1.00 g, 14.81 mmol). TBDMSCl (1.45 g, 9.63 mmol) was added at 0 °C and the reaction was stirred at r.t. for 4 h. The reaction mixture was quenched with sat. aq NH_4Cl soln and extracted with CH_2Cl_2 (3 × 20 mL). The organic extract was washed with brine (3 × 10 mL), dried over Na_2SO_4 and concentrated. Silica gel column chromatography (PE–EtOAc, 19:1) of the residue provided *syn*-**4**/*anti*-**4**; yield: 2.72 g (95%), as a colorless liquid.

***Path b*: *syn*-4/*anti*-4**

IR ($CHCl_3$): 3041, 2926, 2854, 1465, 1255, 1070, 835, 773 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ (1.5:1 mixture of diastereomers) = 0.06, 0.07 (2 s, 3.6 H), 0.09 (s, 2.4 H), 0.89 (t, *J* = 7.1 Hz, 3 H), 0.90 (s, 9 H), 1.26 (s, 22 H), 1.48–1.55 (m, 2 H), 1.60–1.64 (m, 1 H), 1.70–1.76 (m, 1 H), 2.46 (dd, *J* = 5.1, 2.7 Hz, 0.43 H), 2.48 (dd, *J* = 5.1, 2.7 Hz, 0.57 H), 2.76 (t, *J* = 4.5 Hz, 0.43 H), 2.80 (t, *J* = 4.9 Hz, 0.57 H), 3.01–3.07 (m, 1 H), 3.84–3.91 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ (1.5:1 mixture of diastereomers) = –4.7, –4.6, –4.5, –4.4, 14.9, 18.0, 22.7, 25.0, 25.4, 25.8, 29.3, 29.6 (br, several overlapping signals), 31.9, 37.1, 37.9, 40.1, 40.2, 46.8, 47.7, 49.5, 50.0, 70.1, 70.4.

ESI–MS: *m*/*z* = 407 [M + Na^+].

(2*R*)-2-[(*tert*-Butyldimethylsilyl)oxy]-1-[(2*R*)-oxiran-2-yl]pentadecane (*syn*-4)

A soln of epoxide *syn*-**4**/*anti*-**4** (prepared via path b) (2.5 g, 6.49 mmol) and (*R*,*R*)-(salen)Co(III)(OAc) (0.021 g, 0.32 mmol) in THF (0.3 mL) was stirred at 0 °C for 5 min, and then distilled H_2O (64 L, 3.57 mmol) was added. After stirring for 24 h, the reaction mixture was concentrated and purified by silica gel column chromatography (PE–EtOAc, 19:1) to afford *syn*-**4**; yield: 1.23 g (49%), as a yellow liquid. Further chromatographic purification (PE–EtOAc, 3:2) provided diol **11**; yield: 0.969 g (37%), brown liquid, as a single diastereomer. The diastereoselectivity was determined from ^1H and ^{13}C NMR spectral data.

$[\alpha]_D^{25}$ –8.42 (*c* 1.0, $CHCl_3$).

IR ($CHCl_3$): 3041, 2926, 2854, 1465, 1255, 1070, 835, 773 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.05 (s, 3 H), 0.06 (s, 3 H), 0.88 (t, *J* = 7.0 Hz, 3 H), 0.90 (s, 9 H), 1.26 (s, 22 H), 1.51–1.54 (m, 2 H), 1.61 (dt, *J* = 13.8, 5.8 Hz, 1 H), 1.73 (dt, *J* = 13.8, 5.8 Hz, 1 H), 2.46 (dd, *J* = 5.0, 2.8 Hz, 1 H), 2.76 (t, *J* = 4.5 Hz, 1 H), 3.02–3.07 (m, 1 H), 3.85 (quin, *J* = 5.8 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.5, –4.6, 14.1, 18.0, 22.7, 25.8, 29.4, 29.6, 29.7, 31.9, 37.2, 40.1, 46.8, 49.6, 70.4.

ESI–MS: *m*/*z* = 407 [M + Na^+].

Anal. Calcd for $C_{23}H_{48}O_2Si$: C, 71.81; H, 12.58. Found: C, 71.78; H, 12.53.

2-[2-(4-Methoxyphenyl)ethyl]-1,3-dithiane (5)

To a soln of aldehyde **14** (4.0 g, 24.09 mmol) in anhyd CH_2Cl_2 (40 mL) at 0 °C was added 1,3-propanedithiol (2.93 mL, 28.90 mmol)

and a cat. amount of $BF_3{\cdot}OEt_2$, and the reaction stirred at r.t. for 12 h. After completion (TLC), the reaction was quenched with sat. aq $NaHCO_3$ soln, diluted with H_2O and extracted with EtOAc (3 × 30 mL). The combined organic layer was washed with brine (3 × 10 mL), dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel column chromatography (PE–EtOAc, 1:4) to afford dithiane **5**; yield: 5.46 g (88%), as a white liquid.

IR ($CHCl_3$): 2995, 2904, 2831, 1654, 1610, 1512, 1438, 1246, 1176, 1035, 908, 827 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.82–1.93 (m, 1 H), 2.04 (q, *J* = 7.3 Hz, 2 H), 2.09–2.15 (m, 1 H), 2.78 (t, *J* = 7.7 Hz, 2 H), 2.83–2.86 (m, 4 H), 3.80 (s, 3 H), 3.98 (t, *J* = 7.0 Hz, 1 H), 6.84 (d, *J* = 8.8 Hz, 2 H), 7.14 (d, *J* = 8.8 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.9, 30.2, 31.5, 37.0, 46.4, 55.1, 113.7, 129.4, 132.8, 157.8.

(2*R*,4*R*)-4-[(*tert*-Butyldimethylsilyl)oxy]-1-{[2-(4-methoxyphenyl)ethyl]-1,3-dithian-2-yl}heptadecan-2-ol (3)

A flame-dried round bottom flask was charged with dithiane **5** (0.71 g, 2.81 mmol), followed by anhyd THF (10 mL) and HMPA (1 mL). The resulting soln was cooled to –78 °C and treated dropwise with *n*-BuLi (0.24g, 3.74 mmol, 2.34 mL, 1.6 M soln in hexane). The dark-brown reaction mixture was stirred for 30 min after which was added dropwise, epoxide *syn*-**4** (0.70 g, 1.87 mmol) in anhyd THF (5 mL) containing HMPA (0.5 mL). The reaction mixture was stirred for an additional 30 min, then quenched with sat. aq NH_4Cl soln, diluted with H_2O (5 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layer was washed with brine (3 × 10 mL), dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel column chromatography (gradient: 10–20% EtOAc–PE) to afford coupled product **3**; yield: 1.25g (87%), as a thick syrup.

$[\alpha]_D^{25}$ –3.10 (*c* 1.0, $CHCl_3$).

IR ($CHCl_3$): 3485, 2987, 2924, 2852, 2360, 1612, 1512, 1448, 1246, 1055, 813, 767 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 0.09 (s, 3 H), 0.11 (s, 3 H), 0.09 (t, *J* = 3.5 Hz, 3 H), 0.91 (s, 9 H), 1.26 (s, 22 H), 1.42–1.76 (m, 4 H), 1.90–2.12 (m, 3 H), 2.17–2.39 (m, 3 H), 2.59–2.99 (m, 6 H), 3.79 (s, 3 H), 3.88–4.00 (m, 1 H), 4.07–4.35 (m, 1 H), 6.83 (d, *J* = 8.7 Hz, 2 H), 7.14 (d, *J* = 8.7 Hz, 2 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = –4.5, –4.2, 14.1, 18.0, 22.7, 24.9, 25.1, 25.3, 25.9, 26.1, 26.2, 29.3, 29.6, 29.7, 29.8, 31.9, 37.2, 41.8, 44.7, 45.8, 52.1, 55.2, 66.9, 71.4, 113.8, 129.3, 133.9, 157.8.

ESI–MS: *m*/*z* = 661 [M + Na^+].

Anal. Calcd for $C_{36}H_{66}O_3S_2Si$: C, 67.65; H, 10.41; S, 10.03. Found: C, 67.58; H, 10.39; S, 10.01.

(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)

A soln of compound **3** (0.50 g, 0.78 mmol) in anhyd CH_2Cl_2 (5 mL) at –78 °C was added to a soln of BBr_3 (0.79 g, 3.14 mmol, 3.14 mL, 1.0 M soln in CH_2Cl_2). After 2 h, the mixture was warmed to –25 °C. The reaction progress was monitored by TLC and was found to be complete after 2 h. The reaction mixture was quenched with sat. aq $NaHCO_3$ soln (3 × 10 mL), extracted with CH_2Cl_2 (3 × 20 mL) and washed with brine (3 × 10 mL), then the organic layer was dried over Na_2SO_4 and concentrated in vacuo to yield crude **15**. To a soln of crude **15** (0.10 g, 0.196 mmol) in acetone–H_2O (9:1, 5 mL) was added $PhI(O_2CCF_3)_2$ (0.21 g, 0.489 mmol) in one portion, and the reaction mixture stirred for 4 h at r.t. After completion of the reaction, sat. aq $NaHCO_3$ soln was added and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic layer was dried over Na_2SO_4 and concentrated to give a crude mixture of aculeatins A (**1**) and B (**2**) which was purified by flash silica gel column chromatography (gradient: 25–40% EtOAc–PE) to afford aculeatin A (**1**); yield: 0.039 g (44%), and aculeatin B (**2**); yield: 0.013 g (15%).

Aculeatin A (1)

$[\alpha]_D^{25}$ –5.3 (*c* 0.9, $CHCl_3$).

IR (neat): 3491, 2934, 1673, 1622, 1516, 1463, 1099, 1053, 949, 846 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 6.6 Hz, 3 H), 1.27 (s, 21 H), 1.40–1.52 (m, 4 H), 1.80 (d, *J* = 14.0 Hz, 1 H), 1.93 (d, *J* = 14.0 Hz, 1 H), 1.98–2.04 (m, 3 H), 2.24 (dd, *J* = 10.3, 7.3 Hz, 1 H), 2.33–2.43 (m, 1 H), 3.37 (d, *J* = 9.8 Hz, 1 H), 4.08–4.13 (m, 2 H), 6.11 (dd, *J* = 10.5, 1.9 Hz, 1 H), 6.15 (dd, *J* = 10.5, 1.9 Hz, 1 H), 6.76 (dd, *J* = 10.0, 3.1 Hz, 1 H), 6.85 (dd, *J* = 10.0, 2.9 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1, 22.6, 25.6, 29.3, 29.6 (br, several overlapping signals), 31.9, 34.1, 35.8, 37.9, 39.0, 64.8, 65.3, 79.7, 109.0, 127.0, 127.3, 148.7, 150.8, 185.3.

ESI–MS: *m*/*z* = 441 [M + Na^+].

Aculeatin B (2)

$[\alpha]_D^{25}$ +47.2 (*c* 0.2, $CHCl_3$).

IR (neat): 3486, 2952, 1671, 1635, 1461, 1078, 980, 868 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.89 (t, *J* = 6.5 Hz, 3 H), 1.26 (s, 21 H), 1.41–1.52 (m, 4 H), 1.56–1.64 (m, 2 H), 1.87–1.97 (m, 2 H), 2.01–2.11 (m, 2 H), 2.33 (td, *J* = 12.4, 7.4 Hz, 1 H), 2.69 (dd, *J* = 13.1, 7.1 Hz, 1 H), 3.85–3.89 (m, 1 H), 4.37–4.39 (m, 1 H), 6.11 (dd, *J* = 10.5, 1.9 Hz, 1 H), 6.15 (dd, *J* = 10.5, 1.9 Hz, 1 H), 6.77 (dd, *J* = 10.5, 3.0 Hz, 1 H), 6.99 (dd, *J* = 10.5, 2.9 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1, 22.6, 25.9, 29.3, 29.4, 29.6 (br, several overlapping signals), 31.9, 35.2, 35.3, 35.7, 37.9, 40.5, 65.1, 69.4, 77.5, 108.4, 127.1, 149.1, 152.2, 185.6.

ESI–MS: *m*/*z* = 441 [M + Na^+].

Acknowledgment

A.H. thanks UGC, New Delhi for financial support in the form of a SRF.

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