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Stereoselective synthesis of bioactive natural spiroacetals aculeatins A and B ☆

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The paper is dedicated to Oishika (daughter of the senior author) on the occasion of her 15th birthday

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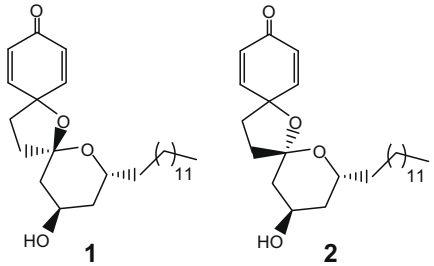
ABSTRACT

The stereoselective synthesis of two naturally occurring bioactive spiroacetals, aculeatins A and B has been accomplished using 1-tetradecanal as the starting material. The sequence introduces diastereoselective iodine-induced electrophilic cyclization and ring opening of epoxide with 1,3-dithiane as the key steps.

Aculeatins A and B, two epimeric spiroacetals, were isolated from the plant *Amomum aculeatum* (Zringiberaceae).[1] The compounds were found to be antiprotozoal against *Plasmodium* and *Trypanozoma* species. They also showed high cytotoxic activity against the KB cell line and several human cancer cell lines including Lu1 (human lung cancer) and MCF-7 (human breast cancer) cell lines.[1,2] Due to interesting structural pattern and impressive bioactivity the synthesis of aculeatins A and B is an important target to the organic chemists.[3] Here we would like to mention an alternative efficient approach for the synthesis of these two compounds.



The retrosynthetic analysis of **1** and **2** (depicted in Scheme 1) indicates that the key intermediate **3** can be prepared by diastereoselective iodine-induced electrophilic cyclization of **7** [derived from 1-tetradecanal (**8**)]. The cyclization product **6** can be converted into the epoxide **5** which can undergo ring opening with 1,3-dithiane and subsequently required alkylation.

The synthesis of aculeatins A and B (Scheme 2) was initiated from commercially available 1-tetradecanal (**8**) which on enantioselective Maruoka allylation[4] using titanium complex (*S,S*)-**I** and allyl tri-*n*-butyltin produced the homoallylic alcohol **9** in 82% yield with an enantioselectivity of 97% (determined by chiral HPLC).[3d] Compound **9** was treated with di-*tert*-butyl dicarbonate in the presence of DMAP in MeCN[5] to furnish the homoallylic *tert*-butyl carbonate **7** (88%) which was suitable for diastereoselective iodine-induced electrophilic cyclization to introduce the required stereogenic centre. The treatment of **7** with iodine in MeCN at −20 °C afforded the iodocarbonate **6** (73%) with high diastereoselectivity (de 95%) favouring *syn*-isomer.[6] The pure *syn*-isomer was separated by column chromatography. The compound was then treated with K_2CO_3 in MeOH to form the desired *syn*-epoxy alcohol **10** in 84% yield.[6a] The secondary hydroxyl group of the epoxide **10** was protected with $^tBuMe_2SiCl$ (TBS-Cl) to produce the TBS-protected epoxide **5** (89%). The epoxide ring of **5** was subsequently opened[7] with 1,3-dithiane using *n*-BuLi in THF at −78 °C to yield the product **11** (86%) which was again treated with TBS-Cl to form **4** in 89% yield. Compound **4** was then reacted with TBS-protected 4-hydroxyphenylethyl iodide (**A**) using *n*-BuLi at −78 °C to afford the required intermediate **3** (84%). The iodide **A** was prepared from TBS-protected 4-hydroxystilbene (**12**) by treatment with $DMSBH_3$ at room temperature and subsequently with

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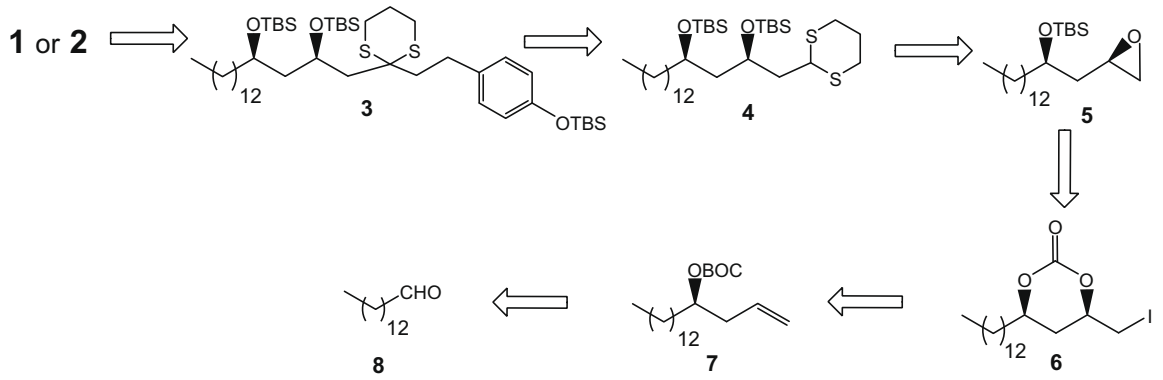
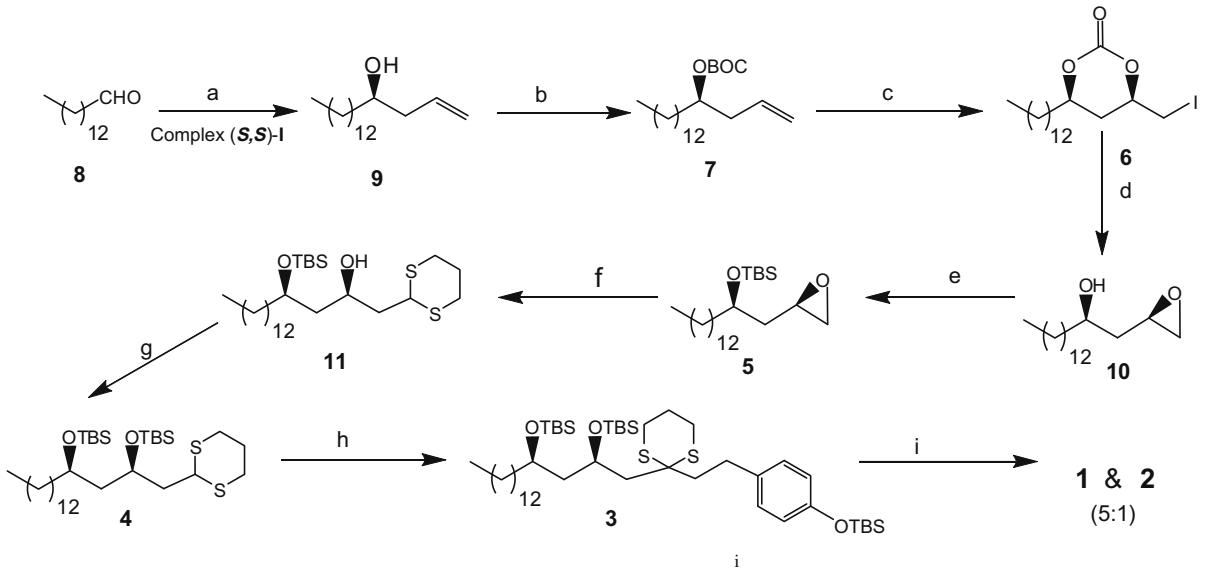


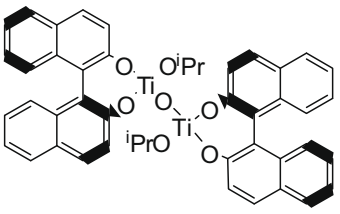
Scheme 1. Retrosynthetic analysis.



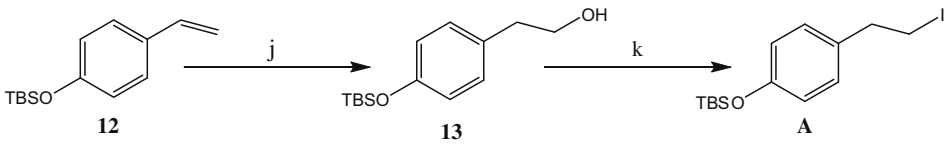
Scheme 2. Reagents and conditions: yields: (a) $TiCl_4$ (5 mol %), $Ti(O^iPr)_4$ (15 mol %), rt, 1 h, Ag_2O (10 mol %), rt, 5 h, (*S*,*S*)-**I** (20 mol %), rt, 2 h, allyl tri-*n*-butyltin, 0 °C, 12 h, 82%; (b) BOC_2O, DMAP, CH_3CN, 0 °C to rt, 10 h, 89%; (c) I_2, CH_3CN, −20 °C, 6 h, 72%; (d) K_2CO_3, MeOH, rt, 30 min, 81%; (e) TBS-Cl, Imidazole, DCM, 0 °C to rt, 5 h, 89%; (f) 1,3-dithiane, *n*-BuLi, THF–HMPA (9:1), −78 °C, 1 h, 86%; (g) TBS-Cl, imidazole, DCM, 0 °C to rt, 5 h, 89%; (h) compound **A**, *n*-BuLi, THF–HMPA (9:1), −78 °C, 84%; (i) *p*-TSA-MeOH, 0 °C and PIFA, $MeCN/H_2O$ (6:1), 0 °C, 5 min.

$NaBH_4$ and H_2O_2 at 0 °C[8] followed by iodination[9] (Scheme 3). The intermediate **3** was then treated with *p*-TSA at 0 °C to room temperature and finally with phenyliodonium (III) bis (trifloroacetate) (PIFA) at 0 °C[3a] to afford aculeatins A (**1**) and B (**2**) (5:1) (Scheme 2). Which were separated by column chromatography. The physical and spectral properties of **1** and **2** were found to be identical to those of the naturally occurring compounds.[1]

In the present synthesis two key steps involving diastereoselective iodine-induced electrophilic cyclization and ring opening of epoxide with 1,3-dithiane have been introduced for the synthesis



Complex (***S,S***)-**I**



Scheme 3. Reagents and conditions: yields: (j) BH_3·DMS, THF, 0 °C to rt, H_2O_2, NaOAc, 85%; (k) I_2, Ph_3P, imidazole, ether/acetonitrile (3:1), 0 °C to rt, 1 h, 90%.

of aculeatins A and B.[10] This protocol has not been used earlier for the synthesis of aculeatins to install a new chiral centre with *syn*-selectivity.[3] All the steps involved in the present synthesis are high-yielding and the applied reagents are readily available. The overall process is simple and straightforward. The ease of synthesis that this strategy offers is impressive. In some of the earlier methods (i) the reactions steps were comparatively larger,[3f] (ii) the intermediates were obtained in unsatisfactory yields[3e] and (iii) larger reaction times were required.[3b,c] Thus the present method is a new and efficient advantageous route to the stereoselective synthesis of aculeatins A and B.

Acknowledgements

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10. The spectral data of two new important intermediates **6** and **10** are given below.
Compound **6**: IR 1722, 1402, 1261 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 4.52–4.41 (2H, m), 3.42 (1H, dd, J = 9.0, 4.0 Hz), 3.30 (1H, dd, J = 9.0, 7.0 Hz), 2.42–2.32 (2H, m), 1.81–1.62 (2H, m), 1.44–1.21 (22H, m), 0.89 (3H, t, J = 7.0 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 148.7, 78.5 75.4, 34.5, 31.8, 31.2, 29.9, 29.6, 29.2, 22.5,14.2, 4.8; MS (ESI): m/z 447 $[M+Na]^+$, 425$[M+H]^+$; HRMS (ESI): m/z 447.1380 $[M+Na]^+$. Calcd for $C_{18}H_{33}I\,O_3Na$; m/z 447.1372.
Compound **10**: IR 3419, 1462, 1269 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 3.84 (1H, m), 3.04 (1H, m), 2.72 (1H, t, J = 5.0 Hz), 2.45 (1H, dd, J = 5.0, 4.0 Hz), 2.02 (1H, br s), 1.82 (1H, m), 1.49–1.40 (5H, m), 1.36–1.20 (20H, m), 0.88 (3H, t, J = 7.0 Hz) ^{13}C NMR (50 MHz, $CDCl_3$): δ 70.0, 50.6, 46.2, 39.9, 37.8, 32.0, 29.8, 29.7, 29.0, 25.6, 22.4, 20.8, 14.1; MS (ESI): m/z 293 $[M+Na]^+$; HRMS (ESI): m/z 293.1356 $[M+Na]^+$. Calcd for $C_{18}H_{33}I\,O_3Na$; m/z 293.1347.