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Total synthesis of aculeatins A and B via a tethered oxa-Michael approach☆

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Abstract—A stereocontrolled total synthesis of aculeatins A and B has been achieved in eight steps and in 15% overall yield. The key feature of this synthetic approach is the application of a Marouka allylation and tethered intramolecular oxa-Michael reaction to install the required stereocentres on the tetrahydropyran ring.

Spirocyclic natural products continue to fascinate synthetic organic chemists due to their challenging architecture, which has to be installed in a stereo- and enantioselective manner. Several spirocyclic natural products have been discovered which possess biological properties.[1] The isolation of aculeatins A **1** and B **2** (Fig. 1) as epimeric spiroacetals[2] followed by their racemic total synthesis[3] happened in quick succession. However, the only total synthesis of this rare natural product in optically pure form was reported very recently by Marco et al. involving asymmetric allylation using chiral diisocampheyl borane, Wacker oxidation and a boron aldol as key reactions.[4]

Our interest is designing strategies towards pyran-containing natural products[5] has culminated in a practical synthesis of both aculeatins A and B in good yields (overall yield of about 15%). Retrosynthesis revealed tetradecanal **6** and the known 4-benzyloxyphenyl acetylene **5** as starting materials (Scheme 1).

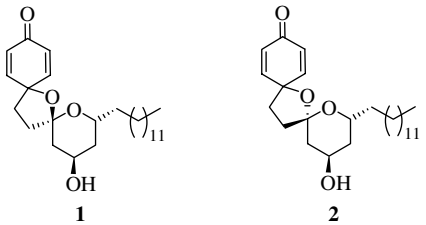

Figure 1.

The aldehyde **6** was subjected to an enantioselective Maruoka allylation[6] using titanium complex (***S*,*S***)-**I** and allyltri-*n*-butyltin to furnish the homoallylic alcohol **7** in 86% yield with excellent an enantioselectivity of 98% ee (determined by chiral HPLC).[7] A one-pot ozonolysis, followed by two-carbon homologation[8] using ethoxycarbonylmethylene triphenylphosphorane produced the δ-hydroxy-α,β-unsaturated ester **8**, which is set up for the tethered intramoleclar oxa-Michael reaction to install the second stereocentre. As anticipated, treatment of **8** with benzaldehyde and potassium *tert*-butoxide at 0 °C in anhydrous THF furnished benzylidene acetal **9** in good yield.[9] The diastereoselectivity was greater than 95% favouring the more stable *syn*-isomer. The conversion of the ester functionality in **9** to Weinreb amide **4** via acid **10** was uneventful. The addition of lithiated 4-benzyloxyphenyl acetylene[10] **5** furnished alkynone[11] **3**. Catalytic hydrogenolysis of the benzylidene, benzyloxy and acetylene groups gave **11** (not isolated) and further treatment with phenyliodonium(III) bis(trifluoroacetate) (PIFA)[12] in acetone–H_2O (9:1) yielded a mixture of aculeatins A and B in a ratio of 5:2, which were separated by column chromatography. All the compounds were fully characterized by NMR, mass and IR spectroscopy[13] and the spectral data of **1** and **2** were in full agreement with those reported in the literature[4] (Scheme 2).

In conclusion, a stereodivergent, short, high yielding synthesis of aculeatins A and B, which should be

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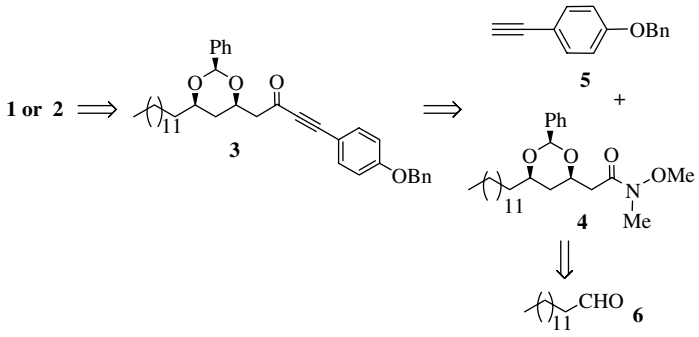
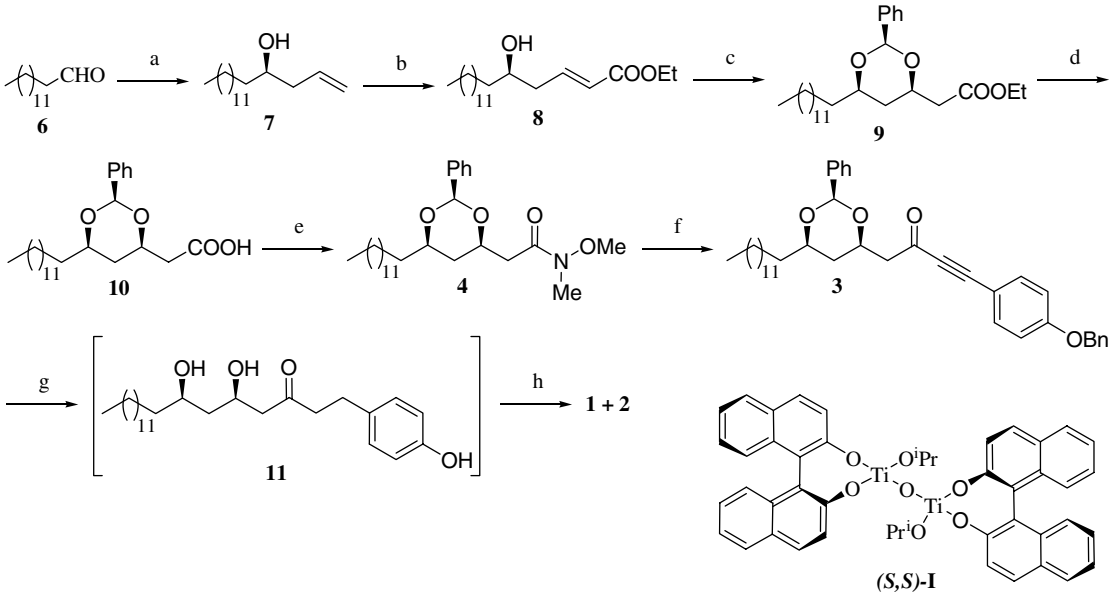


Scheme 1.



Scheme 2. Reagents and conditions: (a) (***S,S***)-**I** (10 mol %), $Bu_3SnCH_2CH{=}CH_2$, CH_2Cl_2, −15 °C to 0 °C, 24 h, 86%; (b) (i) O_3, CH_2Cl_2, −78 °C, 45 min, then PPh_3; (ii) $Ph_3P{=}CHCO_2Et$, CH_2Cl_2, rt, 2 h, 80% (for two steps); (c) PhCHO, *t*-BuOK, THF, 0 °C, 45 min, 69%; (d) LiOH, THF–H_2O (3:1) 0 °C to rt, 4 h, 91%; (e) NH(Me)(OMe)·HCl, DCC, Et_3N, DMAP, CH_2Cl_2, 0 °C to rt, 90%; (f) *n*-BuLi, **5**, THF, −78 °C to −22 °C, 75%; (g) Pd–C, H_2, EtOAc, rt; (h) $PhI(OOCCF_3)_2$, Me_2CO–H_2O (9:1), rt, 10 min, 52 (two steps), 2.5:1 mixture of aculeatins A and B.

amenable to scale up, has been achieved in an overall yield of 15%.

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13. Representative analytical data: Compound **7**: Waxy white solid; $[\alpha]_D^{25}$ +5.00 (*c* 1, $CHCl_3$); IR (KBr): *v* 3346 (br,OH), 2924, 2852 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 5.86–5.72 (m, 1H), 5.13–5.07 (m, 2H), 3.63–3.55 (m, 1H), 2.31–2.23 (m, 1H), 2.15–2.05 (m, 1H), 1.43–1.37 (m, 2H), 1.35–1.25 (m, 22H), 0.88 (t, 3H, $J = 6.7$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 134.9, 118.0, 70.6, 41.9, 36.8, 31.9, 29.6–29.3 (br, several overlapped signals), 25.6, 22.6, 14.1. (ESI-MS): *m*/*z* 277 [M+Na]. Compound **9**: Waxy white solid; $[\alpha]_D^{25}$ +1.50 (*c* 1, $CHCl_3$); IR (KBr): *v* 2924, 2852, 1727 (ketone C=O), 1106, 1025, 751, 728, 696; ^1H NMR (200 MHz, $CDCl_3$): δ 7.39–7.34 (m, 2H), 7.27–7.18 (m, 3H), 5.43 (s, 1H), 4.23–4.12 (m, 1H), 4.05 (q, 2H, $J = 6.9$ Hz), 3.75–3.67 (m, 1H), 2.61 (dd, 1H, $J = 15.6$, 6.0 Hz), 2.37 (dd, 1H, $J = 15.6$, 6.0 Hz), 1.65–1.35 (m, 4H), 1.28–1.159 (m, 25H), 0.81 (t, 3H, $J = 6.9$ Hz) ^{13}C NMR (50 MHz, $CDCl_3$): δ 170.4, 138.6, 127.9, 126.1, 100.5, 96.2, 76.6, 73.2, 60.3, 40.9, 36.6, 35.9, 32.0, 29.7 (br, several overlapped signals), 29.4, 25.4, 25.1, 22.7, 14.3, 14.2. (ESI-MS): *m*/*z* 455.3 [M+Na].