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Chiral cyclopropanes: asymmetric synthesis of constanolactones A and B

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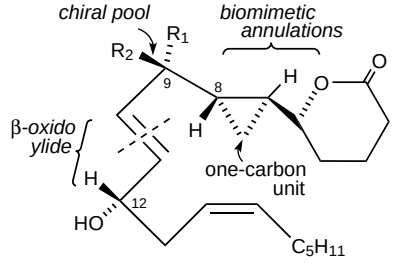
Abstract—The title marine eicosanoids were prepared using a novel, stereoselective bis-annulation to create the characteristic cyclopropane-δ-lactone motif.

Constanolactones A (**1**) and B (**2**) were isolated[1] by Nagle and Gerwick in 1990 from the temperate red alga *Constantinea simplex* where together they accounted for 3–4% of the organic extractable lipids.[2] In common with a few other marine fatty acid metabolites,[3–5] **1** and **2** incorporate a characteristic cyclopropane–lactone motif as well as intriguing biological activities that have provoked considerable synthetic interest.[6–8] To expedite current pharmaceutical evaluations of this family, we describe herein a convergent, asymmetric total synthesis of **1** and **2**. The key transformations in our strategy exploit (i) introduction of a one-carbon unit by dehydrative alkylation;[9] (ii) a stereospecific, one-pot bis-annulation to create the cyclopropane-δ-lactone substructure;[10] and (iii) a β-oxido ylide homologation.[11]



Constanolactones A/B

1: R_1 = OH, R_2 = H
2: R_1 = H, R_2 = OH

The synthesis commenced with the addition of the lithium salt of 6-(*tert*-butyldiphenylsilyloxy)hexyne[12] (**11**) to the readily available chiral aldehyde[13] **3**, providing a chromatographically separable mixture (45:55) of alcohols **4** and **6** (Scheme 1).[14,15] The undesired isomer, **4**, was inverted to **6** via Mitsunobu adduct **5** and saponification. Dehydrative alkylation[9] of **6** with bis(phenylsulphonyl)methane proceeded with inversion of configuration and served to introduce the C(7)-cyclopropyl methylene.[16] To set the stage for the bis-annulation, the bis-sulphonyl adduct was uneventfully converted to carboxylic acid **7** by sequential chromium(II) reduction of the acetylene,[17] fluoride mediated desilylation, and PDC oxidation. Exposure of **7** to iodine and NaH in refluxing THF smoothly generated cyclopropyl-δ-lactone **8** as the sole product.[18]

Following desulphonylation of **8** using magnesium[9] in aqueous THF, the resultant *seco*-acid was utilized to adjust the C(5)-stereochemistry via intramolecular Mitsunobu inversion. Acetonide hydrolysis then led to diol-**9**. Primary selective tosylation of **9** and displacement with Ph_3P furnished the corresponding β-hydroxy phosphonium salt which was converted to its β-oxido ylide using 2 equiv. of base at low temperature.[11] Subsequent condensation with 2(*S*)-(4-methoxybenzyloxy)-4(*Z*)-decenal[19] (**12**) afforded **10** embodying the complete carbon framework of the constanolactones. Mild MPM cleavage of **10** using Cr(II)/LiI[20] evolved constanolactone B (**2**). Alternatively, **10** gave rise to constanolactone A (**1**) via sequential Mitsunobu inversion of the C(9)-alcohol, saponification with subsequent re-lactonization upon acidification, and Cr(II)/LiI de-

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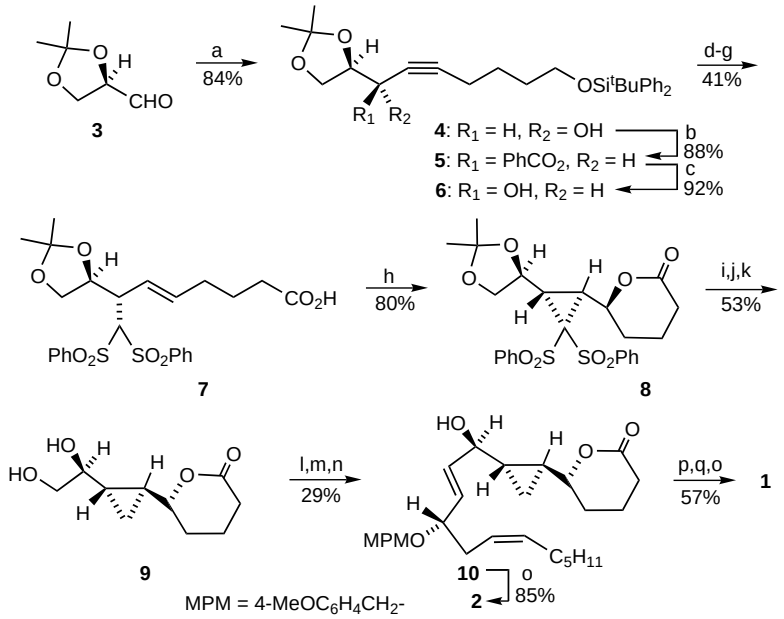

Scheme 1. *Reagents and conditions*: (a) acetylene **11**, *n*-BuLi, THF, −78°C, 1 h; add **3**, −78°C, 3 h, then rt, 2 h. (b) $PhCO_2H$, PPh_3/DEAD, C_6H_6, 23°C, 12 h. (c) NaOH, MeOH, 23°C, 12 h. (d) $(PhO_2S)_2CH_2$, PPh_3/DEAD, C_6H_6, 23°C, 3 h. (e) $CrSO_4$, DMF/H_2O, 23°C, 2 h. (f) *n*-Bu_4NF, THF, 23°C, 18 h. (g) PDC, DMF, 23°C, 40 h. (h) NaH, I_2, THF, 68°C, 44 h. (i) Mg, cat. $HgCl_2$, THF/H_2O (2:1), 23°C, 12 h. (j) PPh_3/DEAD, C_6H_6, 23°C, 7 h. (k) CF_3CO_2H, THF/H_2O (4:1), 40°C, 10 h. (l) TsCl, py, 4°C, 36 h. (m) Ph_3P, CH_3CN, 80°C, 40 h. (n) Wittig salt, *sec*-BuLi (2 equiv.), THF, −78°C, 1.5 h; add **12**, −78 to −20°C, 2 h. (o) $CrCl_2$/LiI, moist EtOAc, 45°C, 2 h. (p) 4-$(O_2N)C_6H_4CO_2H$, PPh_3/DEAD, C_6H_6, 23°C, 10 h. (q) NaOH, THF/H_2O, 23°C, 15 h; PhH, 4 Å mol. sieves, 80°C, 5 h.

protection. The spectral and physical data for **1** and **2** were identical with published values.

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15. Spectral/physical data for key intermediates: TLC (SiO_2, Et_2O/hexane 1:3): **4**, $R_f \sim 0.51$; **6**, $R_f \sim 0.46$. **4**: ^1H NMR (250 MHz, $CDCl_3$) δ 7.65–7.70 (m, 4H), 7.35–7.50 (m, 6H), 4.48 (ddd, 1H, $J=2$, 4, 6 Hz), 4.17–4.24 (m, 1H), 4.00–4.10 (m, 2H), 3.66 (t, 2H, $J=5.9$ Hz), 2.20–2.28 (m, 2H), 2.12 (d, 1H, $J=4.2$ Hz), 1.55–1.70 (m, 4H), 1.46 (s, 3H), 1.37 (s, 3H), 1.04 (s, 9H). **6**: ^1H NMR (250 MHz, $CDCl_3$) δ 7.65–7.70 (m, 4H), 7.35–7.50 (m, 6H), 4.25–4.31 (m, 1H), 4.04–4.16 (m, 2H), 3.83–3.89 (m, 1H), 3.66 (t, 2H, $J=5.9$ Hz), 2.31 (d, 1H, $J=4.2$ Hz), 2.20–2.25 (m, 2H), 1.57–1.60 (m, 4H), 1.45 (s, 3H), 1.37 (s, 3H), 1.05 (s, 9H); ^{13}C NMR: δ 135.54, 133.92, 129.56, 127.61, 110.37, 87.15, 79.19, 66.26, 64.62, 63.27, 31.63, 26.85, 25.30, 24.93, 19.21, 18.47. **7**: ^1H NMR (250 MHz, $CDCl_3$) δ 7.80–7.90 (m, 4H), 7.62–7.70 (m, 2H), 7.48–7.55 (m, 4H), 5.70 (dd, 1H, $J=10.6$ Hz), 5.58 (dt, 1H, $J=11.1$, 7.2 Hz), 4.71 (d, 1H, $J=2.4$ Hz), 4.56 (dt, $J=6.5$ Hz), 4.11 (dd, 1H, $J=6.4$, 8.5 Hz), 3.91 (dd, 1H, $J=6.4$, 8.5 Hz), 3.75 (ddd, 1H, $J=2.2$, 7.0, 10.8 Hz), 2.37 (t, 2H, $J=7.5$ Hz), 2.08 (quintet, 2H, $J=7.2$ Hz), 1.72 (q, 2H, $J=7.4$ Hz), 1.33 (s, 3H), 1.32 (s, 3H); ^{13}C NMR: δ 178.33, 140.14, 138.64, 134.85, 134.33, 129.35, 129.15, 123.50, 109.45, 84.23, 77.20, 76.17, 67.20, 40.24, 33.33, 27.01, 26.39, 25.04, 24.13. **8**: ^1H NMR (250 MHz, $CDCl_3$) δ 7.82–7.90 (m, 4H), 7.62–7.70 (m, 2H), 7.48–7.60 (m, 4H), 5.14 (ddd, 1H, $J=3.3$, 9.9, 9.9 Hz), 4.73 (ddd, 1H, $J=9.2$, 4.4, 6.0 Hz), 4.06 (dd, 1H, $J=9.1$, 6.0 Hz), 3.59 (dd, 1H, $J=4.4$, 9.1 Hz), 3.06 (dd, 1H, $J=9.5$, 9.5 Hz), 2.67 (dd, 1H, $J=9.4$ Hz), 2.45–2.70 (m, 2H), 1.80–2.25 (m, 4H), 1.53 (s, 3H), 1.27 (s, 3H); ^{13}C NMR: δ 169.84, 139.12, 138.78, 134.60, 134.37, 128.59, 128.87, 110.10, 75.83, 73.31, 68.80, 65.69, 42.57, 36.16, 29.38, 28.02, 27.37, 25.26, 18.24. **9**: ^1H NMR (250 MHz, $CDCl_3$) δ 0.15–0.36 (m, 3H), 0.64–0.75 (m, 1H), 1.60–2.08 (m, 4H), 2.25–2.36 (m, 2H), 3.19 (ddd, $J=3.1$, 3.2, 13.8 Hz, 1H), 3.72–3.82 (m, 3H), 4.22–4.35 (m, 1H).
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18. Interestingly, the *cis*-olefinic analog of **7** also gave **8** as the only stereoisomer, albeit in much lower yield (40–45%). In this case the presumed C(5)-iodo intermediate could be isolated (80%) when the annulation was conducted at room temperature. When the cyclopropyl-iodide was warmed with base, it was completely converted to *trans*-**7**. This suggests that *cis*-**7** leads to an intermediate that preferentially undergoes in situ E2-elimination to *trans*-**7** which is the ultimate source of **8**.
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