Studies Towards the Total Synthesis of the Marine-derived Immunosuppressant Discodermolide; Asymmetric Synthesis of a C_1–C_8 δ-lactone Subunit

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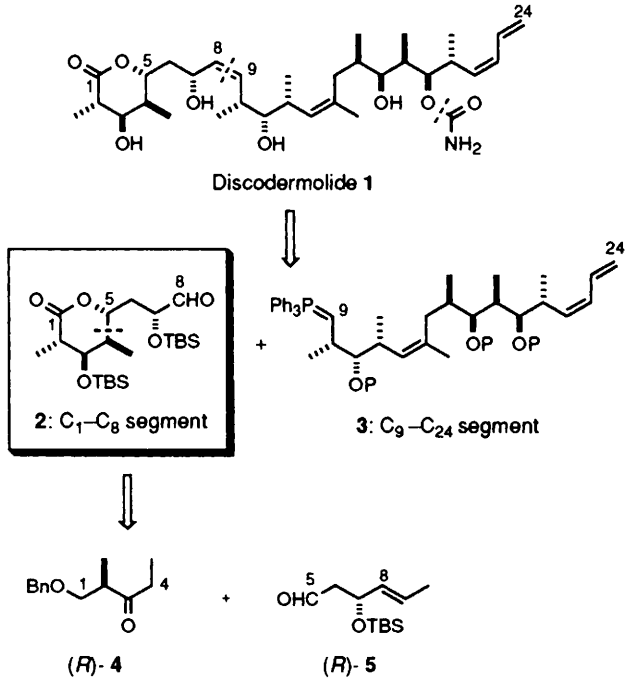
The stereoselective, boron-mediated, aldol/reduction sequence, **4** + **5** → **8** → **9**, allows an efficient asymmetric synthesis of the δ-lactone-containing, C_1–C_8 subunit **2** of discodermolide **1**.

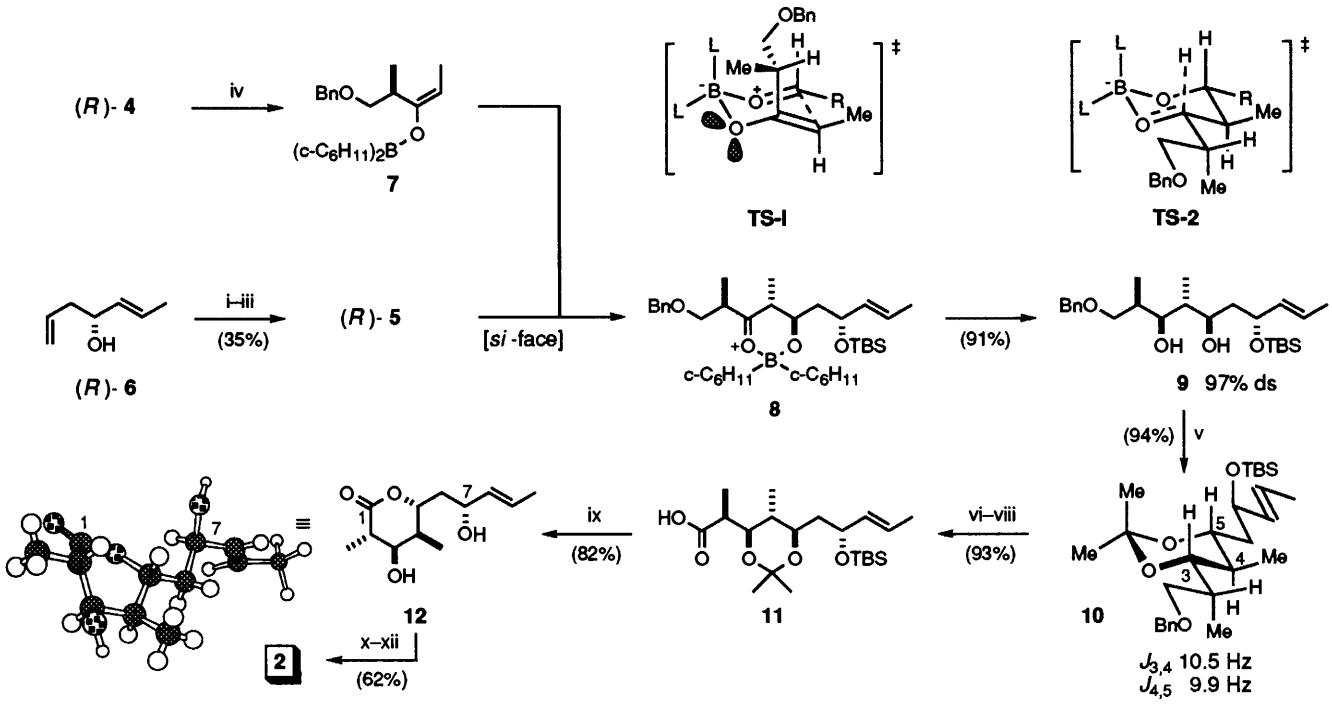
In 1990, Gunasekara *et al.* reported the isolation of the novel marine metabolite discodermolide **1** from the Caribbean sponge *Discodermia dissoluta*.[1a] Its structure was elucidated through a combination of spectroscopic techniques and X-ray crystallography, as having a tetrasubstituted δ-lactone ring, with a side-chain containing four double bonds, and a total of thirteen stereocentres. However, its absolute configuration has not yet been determined. This new bioactive polyhydroxylated δ-lactone was found to be a potent immunosuppressive compound both *in vitro*[1b] and *in vivo*.[1c] Discodermolide is also cytotoxic, inhibiting the *in vitro* proliferation of P388 leukaemia cells, and shows antifungal activity.[1a]

As with the macrolide immunosuppressant agents, FK506 and rapamycin, the specific mechanism of action of discodermolide, along with associated SAR studies, are of significant interest.[1b,c,2] These studies promise to lead to the development of alternative drugs to cyclosporin A for use in transplant surgery and for the treatment of autoimmune disease, where toxicity and undesirable side-effects are minimised. In contrast to FK506 and rapamycin, which are produced by fermentation, discodermolide is in very scarce supply (0.002% yield from rare sponge). Hence, total synthesis is attractive for producing sufficient quantitites for full evaluation of its immunosuppressant action, as well as for determining its absolute configuration and providing structural analogues.

The polypropionate-like structure of discodermolide should be readily accessible using the aldol chemistry[3] of the versatile dipropionate reagent (*R*)-**4** (or its enantiomer) to quickly



Scheme 1 Principal bond disconnections and identity of key segments (TBS = *tert*-butyldimethylsilyl)



Scheme 2 Synthesis of C_1–C_8 segment **2**; *Reagents and conditions*: i, TBSCl (1.1 equiv.), imidazole (1.21 equiv.), CH_2Cl_2, 25 °C, 4.5 h; ii, OsO_4 (0.5 mol%), NMO (1.0 equiv.), 10:3:1 Bu^tOH:THF:H_2O, 25 °C, 21 h; iii, $NaIO_4$ (4.5 equiv.), 4:1 acetone:H_2O, 25 °C, 1.5 h; iv, $(c\text{-Hex})_2BCl$ (1.5 equiv.) Et_3N (1.6 equiv.), Et_2O −15 °C, 2 h; **5**, −78 °C, 35 min; $LiBH_4$ (5.0 equiv.), −78 °C, 2 h; H_2O_2, MeOH, 10% NaOH; v, 2,2-dimethoxypropane, CH_2Cl_2, PPTS, 25 °C, 3.5 h; vi, LiDBB (4 equiv.), THF, −78 °C, 1 min; vii, Dess–Martin periodinane (1.12 equiv.), CH_2Cl_2, 10 min; viii, $NaClO_2$ (10.9 equiv.) NaH_2PO_4, Bu^tOH, 2-methyl-but-2-ene, 25 °C, 1.5 h; ix, 1:2 HCl (0.5 mol dm^{-3}):THF, 25 °C, 38 h; x, TBSCl (4.4 equiv.), imidazole (5 equiv.), DMF, 19 h, 25 °C; xi, TBSOTf (1.2 equiv.), 2,6-lutidine (1.5 equiv.), CH_2Cl_2, −78 °C, 20 min; xii, O_3, CH_2Cl_2, −78 °C, 15 min; Me_2S, −78 → 25 °C. (NMO = *N*-methylmorpholine-*N*-oxide; DIPT = diisopropyl tartrate; DMAP = 4-dimethylaminopyridine; LiDBB = lithium di-*tert*-butylbiphenyl; PPTS = pyridinium *p*-toluenesulfonate; DMF = dimethylformamide; Bn = benzyl; ds = diastereoselectivity)

build up the carbon and oxygen skeleton with control of the sp^3 stereochemistry. This methodology is highly flexible and essentially any stereoisomer can be selectively prepared at will.[3a,b] Thus, our synthetic plan for discodermolide (Scheme 1) is based on the Wittig coupling of the two advanced segments **2** and **3**. For access to the former, an *anti–anti* aldol reaction[3c] of the chiral ketone (*R*)-**4**[3d] with a suitable aldehyde partner is required. Herein, we report an efficient asymmetric synthesis of this C_1–C_8 subunit **2** from (*R*)-**4** and (*R*)-**5**, as summarised in Scheme 2.

The aldehyde (*R*)-**5** was prepared† in three steps from the allylic alcohol **6**, which was obtained[4] by kinetic resolution using Sharpless asymmetric epoxidation mediated by (+)-diisopropyl tartrate.[5] Hydroxyl protection as its *tert*-butyldimethylsilyl (TBS) ether was followed by regioselective dihydroxylation of the terminal alkene and periodate glycol cleavage to give enantiomerically pure (*R*)-**5**, $[\alpha]_D^{20}$ + 14.0 (*c* 2.0, $CHCl_3$). Using our standard conditions,[3c] enolisation[6] of the ketone (*R*)-**4**[3d] by $(c\text{-}C_6H_{11})_2BCl$–$Et_3N$ and addition of the derived *E* enol borinate **7** to the aldehyde (*R*)-**5** gave the intermediate dicyclohexylboron aldolate **8** (*i.e. si*-face attack *via* preferred[7] transition state **TS-1**). This aldolate was reduced *in situ* by addition of $LiBH_4$ (axial attack *via* preferred[8] transition state **TS-2**) to give directly the *syn* 1,3-diol **9**, $[\alpha]_D^{20}$ +11.0 (*c* 3.6, $CHCl_3$), in 91% yield with 97% diastereoselectivity. The indicated stereochemistry was confirmed by ^1H and ^{13}C NMR analysis‡[9] of the derived acetonide **10**. This one-pot, boron-mediated, aldol/reduction sequence seems to be generally useful for the expedient synthesis of such stereotetrads.[3b,8]

The acetonide **10** was next converted into the acid **11** in 93% yield in three straightforward steps: (*i*) debenzylation by lithium di-*tert*-butylbiphenyl; (*ii*) Dess–Martin oxidation[10] to the aldehdye; (*iii*) sodium chlorite oxidation.[11] Treatment of **11** with HCl in aqueous tetrahydrofuran (THF) gave the δ-lactone **12**, $[\alpha]_D^{20}$ +36.7 (*c* 5.12, $CHCl_3$), in 82% yield. At this stage, comparisons of the ^1H and ^{13}C NMR spectra§ with that reported[1a] for the C_1–C_7 section of discodermolide,

† All yields are for isolated material. All new compounds gave spectroscopic data in agreement with the assigned structures.

‡ For **10** ^1H NMR δ (400 MHz, $CDCl_3$) 7.24–7.34 (5 H, m), 5.54 (1 H, dqd, *J* 15.4, 6.5, 1.5 Hz), 5.39 (1 H, dd, *J* 15.4, 7.1, 1.5 Hz), 4.51 (1 H, d, *J* 12.1 Hz), 4.46 (1 H, d, *J* 12.1 Hz), 4.24 (1 H, m), 3.68 (1 H, dd, *J* 10.5, 2.0 Hz), 3.63 (1 H, dt, *J* 9.9, 1.3 Hz), 3.46 (1 H, d, *J* 8.3, 8.3 Hz), 3.28 (1 H, m), 2.06 (1 H, m), 1.76 (1 H, m), 1.63 (3 H, br, d, *J* 6.3 Hz), 1.29–1.40 (2 H, m), 1.39 (3 H, s), 1.30 (3 H, s), 0.87 (9 H, s), 0.83 (3 H, d, *J* 7.0 Hz), 0.73 (3 H, d, *J* 7.0 Hz), 0.02 (3 H, s), −0.01 (3 H, s); ^{13}C NMR δ (100.6 MHz, $CDCl_3$) 138.8, 135.5, 128.3, 127.6, 127.4, 124.7, 97.6, 73.3, 73.1, 73.0, 70.8, 69.4, 43.2, 35.1, 34.1, 30.2, 26.0, 20.1, 18.1, 17.6, 11.8, 9.6, −3.7, −4.7.

§ For **12** ^1H NMR δ (400 MHz, $CDCl_3$) 5.65 (1 H, dqd, *J* 15.3, 6.3, 1.3 Hz), 5.46 (1 H, ddd, *J* 15.3, 6.3, 1.3 Hz), 4.59 (1 H, dt, *J* 10.1, 2.2 Hz), 4.39 (1 H, m), 3.65 (1 H, t, *J* 3.7 Hz), 3.49 (1 H, br s), 3.09 (1 H, br s), 2.68 (1 H, dq, *J* 3.7, 7.4 Hz), 1.52–1.89 (3 H, m), 1.65 (3 H, d, *J* 6.3 Hz), 1.26 (3 H, d, *J* 7.4 Hz), 1.01 (3 H, d, *J* 6.9 Hz); ^{13}C NMR δ (100.6 MHz, $CDCl_3$) 174.7, 133.6, 126.4, 77.2, 73.1, 67.7, 43.2, 40.9, 35.4, 17.6, 15.7, 12.7.

indicated an almost exact match. As with discodermolide,[1a] the δ-lactone ring in **12** adopts a boat conformation. Finally, TBS protection of the hydroxy groups and ozonolysis of the olefinic side-chain in **12** gave a 62% yield of the required aldehyde **2**,¶ $[\alpha]_D^{20}$ +51.6 (*c* 0.93, $CHCl_3$).

In summary, this synthesis of the C_1-C_8 subunit **2** proceeds in nine steps (41% yield) from the chiral ethyl ketone (*R*)-**4** with 97% overall diastereoselectivity. This work further demonstrates the general applicability of our dipropionate reagent to the stereocontrolled synthesis of polypropionate natural products.[3] Studies directed towards the total synthesis of the novel immunosuppressant discodermolide *via* the Wittig coupling of subunits **2** and **3** are underway.

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¶ For **2** ^{1}H NMR δ (400 MHz, $CDCl_3$) 9.66 (1 H, s), 4.51 (1 H, dt, *J* 10.5, 2.1 Hz), 4.45 (1 H, dd, *J* 10.5, 2.3 Hz), 3.66 (1 H, t, *J* 2.3 Hz), 2.65 (1 H, dq, *J* 7.6, 2.3 Hz), 1.73–1.95 (3 H, m), 1.26 (3 H, d, *J* 7.6 Hz), 0.98 (3 H, d, *J* 6.7 Hz), 0.91 (9 H, s), 0.88 (9 H, s), 0.12 (3 H, s), 0.10 (3 H, s), 0.07 (3 H, s), 0.06 (3 H, s); ^{13}C NMR δ (100.6 MHz, $CDCl_3$) 203.3, 173.1, 76.0, 74.7, 73.7, 44.2, 36.2, 34.2, 25.7, 16.5, 14.0, −4.5, −4.6, −4.9, −5.2.

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