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Towards the synthesis of (+)-discodermolide†

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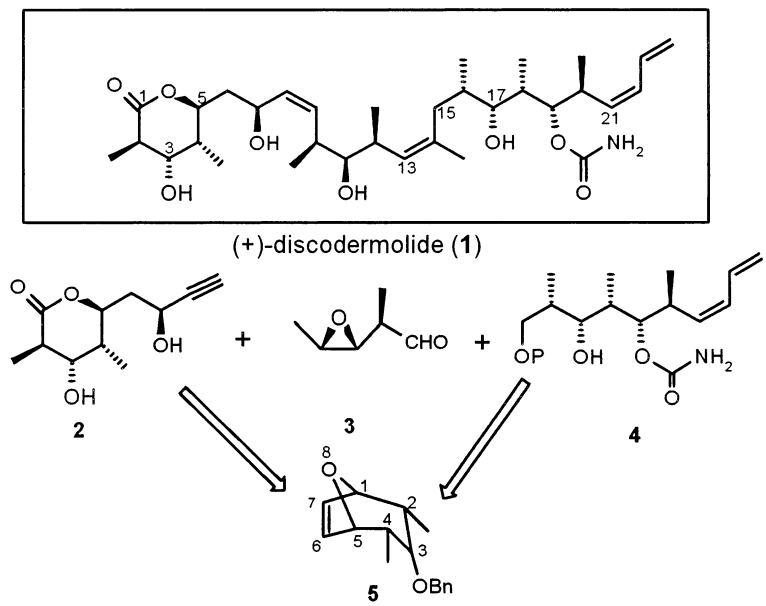
Abstract—An approach to the asymmetric synthesis of fragments corresponding to C1–C7 and C15–C24 of (+)-discodermolide is reported. Key elements of the successful strategy include elaboration of two advanced fragments from a common precursor.

(+)-Discodermolide **1** was isolated from the Caribbean sponge *Discodermia dissoluta* by Gunasekera and co-workers.[1] The structure of (+)-discodermolide comprises a linear polypropionate backbone punctuated by (*Z*)-olefinic linkages at C(8–9), C(13–14) and C(21–22). By virtue of its potent immunosuppressive and potential antitumor activity and in view of its limited availability, interest in the chemical synthesis of this natural product continues unabated.[1,2]

Several synthetic approaches towards discodermolide have been disclosed.[3,4] We chose to adopt a highly convergent strategy to the synthesis of (+)-discodermolide (**1**), disconnecting the carbon backbone at C(8–9) and C(13–14) *Z* alkenes thus dividing the target into three key subunits, **2**, **3** and **4**. In this letter we detail our efforts towards the enantio- and diastereoselective synthesis of **2** and **4** from a common precursor **5**. The advantages of making use of such a common bicyclic



Scheme 1.

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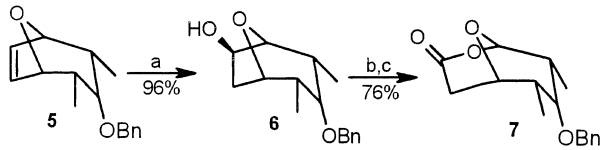
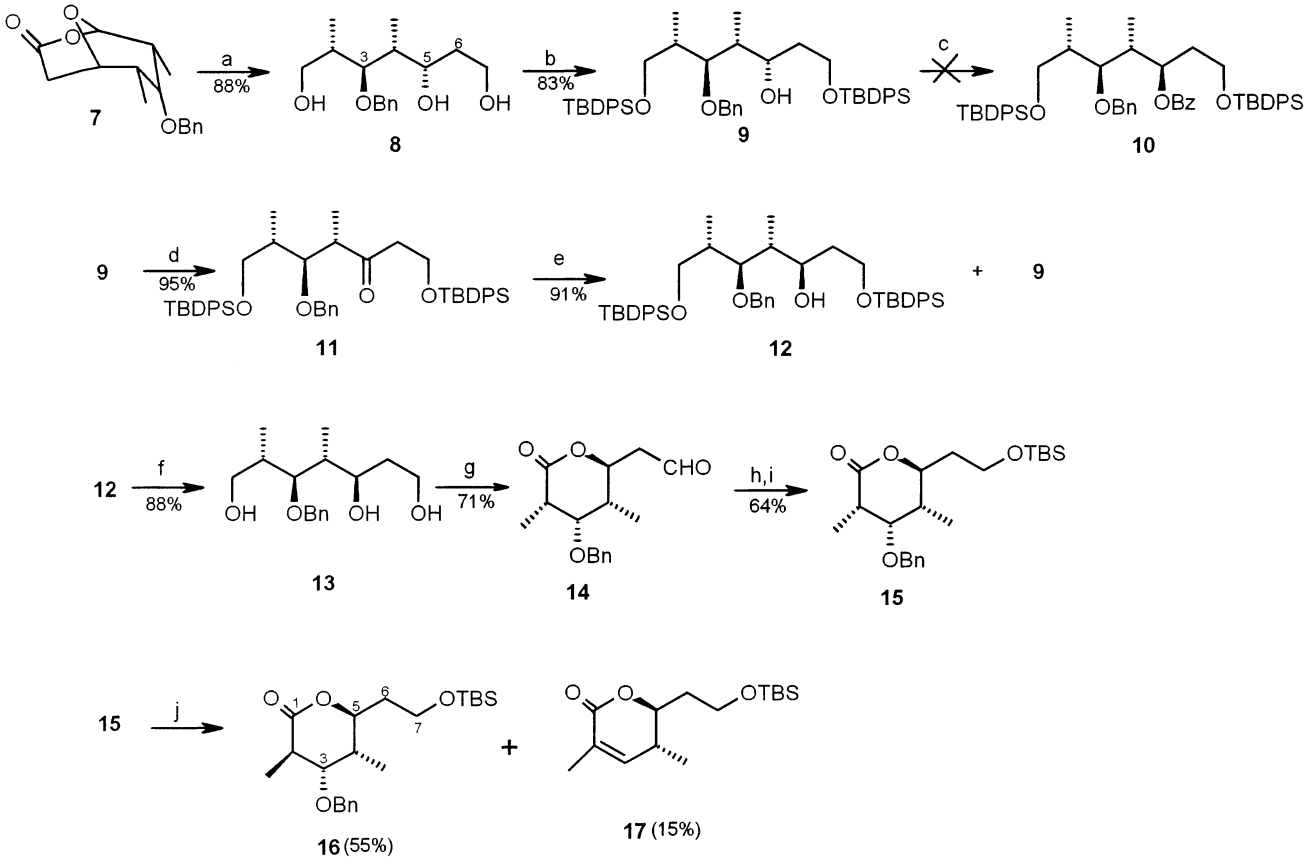


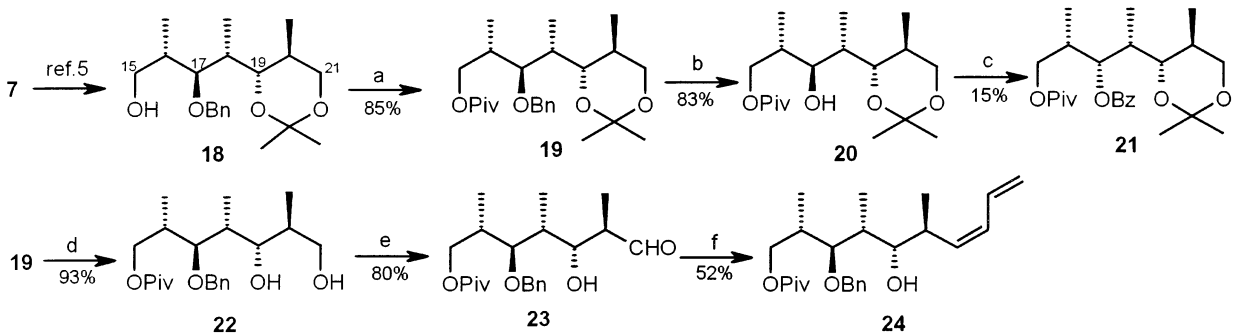
Scheme 2. (a) (+)-Ipc_2BH, −23°C, 24 h, 3N NaOH, 30% H_2O_2, rt, 6 h; (b) PCC, DCM, rt, 3 h; (c) *m*-CPBA, $NaHCO_3$, DCM, rt, 10 h.

precursor are manifold. The relative stereochemistry at C-4 of the precursor **5** can be correlated to C-4 of **1**, while C-2 and C-4 of **5** can be correlated to C-16 and C-18 of **1**. The bicyclic compound **5** has five stereogenic centres and two prostereogenic *sp*2 sites, which could facilitate further functionalization (Scheme 1).

We initiated our synthesis from precursor **5**, which we had developed and utilized for the synthesis of a rifamycin-S fragment wherein, we had exploited the desymmetrization approach to create six stereogenic centres at once.[5] Asymmetric hydroboration of the olefin **5** using (+)-diisopinocampheylborane gave **6** (96%) in high optical purity as reported by us.[5] By



Scheme 3. (a) LAH, THF, 0°C–rt, 4 h; (b) TBDPS-Cl, imidazole, DCM, 0°C–rt, 2 h; (c) DEAD, TPP, *p*-$NO_2C_6H_4$-COOH, THF, 0°C–rt; (d) Dess–Martin periodinane, DCM, rt, 2 h; (e) $NaBH_4$, MeOH/THF, 0°C–rt, 1 h; (f) TBAF, THF, rt, 1.5 h; (g) IBX, DMSO/DCM, rt, 6 h; (h) $NaCNBH_3$, MeOH/AcOH, pH 5.5, rt, 1 h; (i) TBDMS-Cl, imidazole, DCM, 0°C–rt, 1.5 h; (j) 1% NaOH, THF, 3 h, H^+, CH_3COONa, Ac_2O, warm, 5 min.



Scheme 4. (a) Me_3CCOCl, Py, DCM, 0°C–rt, 4 h; (b) 10% Pd-C/H_2, rt, EtOH, 5 h; (c) DEAD, TPP, *p*-$NO_2C_6H_4$-COOH, THF, rt; (d) acetone, PTSA, rt, 2 h; (e) IBX, DMSO/DCM, rt, 1 h; (f) allyl triphenylphosphonium bromide salt, *n*-BuLi, −78°C, 45 min.

modifying our earlier conditions, the alcohol **6** was converted to the lactone **7** by a two-step sequence, PCC oxidation followed by Baeyer–Villiger oxidation of the resulting ketone as shown in Scheme 2.[6]

Synthesis of the C1–C7 fragment

Having obtained the bicyclic lactone **7** with all the functionality for elaboration of the C1–C7 fragment of **2**, our attention was directed to the opening of the bicyclic ring. It was felt that reduction of the lactone with LAH would be the most ideal route to obtain the triol **8**. The primary hydroxyl groups of the triol **8** were then protected as their TBDPS ethers (83%). Inversion of the hydroxyl group configuration at C-5 of the intermediate **9** to obtain the stereochemistry for C-5 of (+)-discodermolide employing the Mitsunobu protocol[7] failed. Alternatively, we explored an oxidation reduction strategy. Oxidation using Dess–Martin periodinane gave the corresponding keto compound **11** in 95% yield. It was found that reduction of the keto group of **11** using $NaBH_4$ in MeOH:THF (4:1) afforded the required β isomer **12** as the major isomer (**12:9** = 9:1, 91%). That the alcohol **12** was the C-5 epimer of alcohol **9** was unambiguously shown by oxidation of **12** to afford **11**. It is pertinent to note that the C5-H of **12** resonated upfield (δ 3.85) relative to C5-H of **9** (δ 4.15) indicating an *anti* relationship between the CH_3 group at C-4 and OH at C-5. The required β isomer **12** was separated by column chromatography. This was followed by deprotection of the TBDPS ethers using TBAF, to afford the triol **13** in 88% yield. It was then proposed to transform the triol to the lactone **14**. Towards this end, oxidation of the triol **13** using IBX resulted in the lactone **14** (71%) via the lactol. The next step called for epimerization of the C-2 methyl group. To circumvent the possibility of unwanted side reactions involving the reactive aldehyde group, we reduced it with $NaCNBH_3$ followed by protection of the resulting alcohol as a TBS ether **15**. Epimerization of **15** using 1% NaOH in tetrahydrofuran afforded the required product **16**[8] in 55% yield along with minor amounts of the α,β-unsaturated analogue **17** (15%) arising from 1,2-elimination (Scheme 3).

Synthesis of C-15–C-24 fragment

For the synthesis of the C-15–C-24 fragment we prepared the precursor **18** by our earlier method.[5] The primary hydroxyl of the compound **18** was protected as its pivalate ester (85%). The steps required for the elaboration of **18** to the target fragment **4** included an inversion at C-17 and elaboration of the diene moiety. For the inversion at C-17 we deprotected the benzyl ether of compound **19** by Pd-C/H_2, followed by a Mitsunobu reaction. The yield of Mitsunobu reaction to invert the sterically hindered hydroxy stereochemistry was only 15%. We therefore changed our strategy and initially explored elaboration of the diene moiety that is the C-21–C-24 fragment of (+)-discodermolide. Acetonide deprotection of compound **19** gave the diol **22** in 93% yield. Selective oxidation of the primary hydroxyl group using IBX afforded the aldehyde **23** in 80% yield, which was characterized by the presence of an aldehyde proton at δ 9.79 in the ^{1}H NMR spectrum. The IR spectrum revealed absorption bands at 3400 cm^{-1} for the hydroxyl group and 1730 cm^{-1} for the carbonyl group. The terminal *Z*-diene was installed via Wittig olefination of the aldehyde **23** using the ylide generated from allyltriphenylphosphonium bromide salt and *n*-BuLi in anhydrous THF at −78°C to afford compound **24** and its *trans* isomer in the ratio 73:27, which was determined from ^{1}H NMR spectrum[9] (Scheme 4).

In summary we have completed the highly stereocontrolled synthesis of the C1–C7 and C15–C24 fragments of (+) discodermolide. Studies towards completing the total synthesis of discodermolide using the subunits **16** and **24** are now underway.

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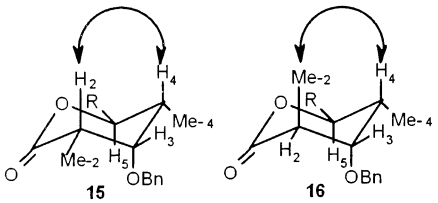

NMR studies of the compound **16** showed NOEs between Me-2 and H4. This observation confirmed the configuration at C2 centre of **16** as '*R*'. ^{1}H NMR of compound **16** (500 MHz, $CDCl_3$): δ 0.050 (s, 3H, Si-Me), 0.052 (s, 3H, Si–Me), 0.88 (s, 9H, $C(CH_3)_3$), 1.07 (d, $J=6.6$ Hz, 3H, C4-CH_3), 1.30 (d, $J=7.5$ Hz, 3H, C2-CH_3), 1.73 (m, 1H, H6), 1.91 (m, 1H, H6), 2.07 (ddq, $J=9.5$, 3.3, 6.6 Hz, 1H, H-4), 2.88 (dq, $J=3.8$, 7.5 Hz, 1H, H-2), 3.41 (dd, $J=3.3$, 3.8 Hz, 1H, H-3), 3.80 (m, 2H, H7), 4.53 (ddd, $J=9.5$, 9.1, 2.8 Hz, 1H, H-5), 4.48 (d, $J=11.6$ Hz, 1H, -OCH_2), 4.64 (d, $J=11.6$ Hz, 1H, -OCH_2), 7.28–7.37 (m, 5H, ArH). $[\alpha]_{20}^{D}$ +12.10 ($c=0.40$, $CHCl_3$).

9. ^{1}H NMR of compound **24** (500 MHz, $CDCl_3$): δ 0.91 (d, $J=6.7$ Hz, 3H), 1.02 (d, $J=7.1$ Hz, 3H), 1.10 (d, $J=6.7$ Hz, 3H), 1.23 (s, 9H), 1.98 (m, 1H), 2.23 (m, 1H), 2.31 (m, 1H) 3.44 (dd, $J=2.7$, 9.6 Hz, 1H), 3.66 (t, $J=4.2$ Hz, 1H), 4.10 (dd, $J=3.2$, 6.0 Hz, 1H), 4.25 (dd, $J=3.4$, 5.2 Hz, 1H), 4.58 (d, $J=10.6$ Hz, 1H), 4.65 (d, $J=10.6$ Hz, 1H), 5.14 (ddd, $J=2.1$, 10.3, 1.1 Hz, 1H), 5.21 (ddd, $J=2.1$, 16.9, 1.1 Hz, 1H), 5.37 (ddd, $J=10.1$, 11.2, 1.1 Hz, -C<u>H</u>=CH-CH=), 6.10 (ddd, $J=11.2$, 11.3, 1.1 Hz, -CH=C<u>H</u>-CH=), 6.65 (dddd, $J=10.3$, 11.3, 16.9, 1.1 Hz, -CH=CH-C<u>H</u>=), 7.3–7.4 (m, 5H, ArH). $[\alpha]_{20}^{D}$ −11.8 ($c=0.12$, $CHCl_3$). The olefinic protons for the '*E*' isomer of the compound **24** appeared at δ 5.45 (ddd, $J=9.3$, 15.3, 0.70 Hz, -C<u>H</u>=CH-CH=), 6.13 (ddd, $J=10.3$, 15.3, 0.70 Hz, -CH=C<u>H</u>-CH=), 6.28 (dddd, $J=10.3$, 10.9, 16.95, 0.70 Hz, -CH=CH-C<u>H</u>=).