Stereoselective Synthesis of the C_1-C_7 Segment of (+)-Discodermolide

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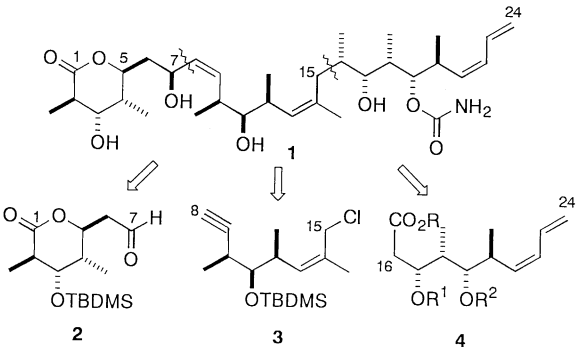
A new and highly stereoselective synthesis of the C_1-C_7 segment of (+)-discodermolide, the marine natural product having the potent immunosuppressive activity, is described in which the stereospecific methylation of γ,δ-epoxy acrylate with trimethylaluminum and the intramolecular conjugate addition of an acetal alkoxide anion are involved as key steps.

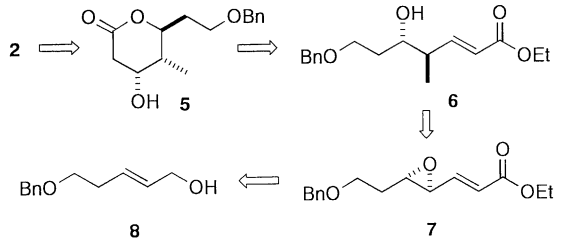
Discodermolide (**1**) is the polypropionate-derived marine natural product recently isolated from the Caribbean sponge *Discodermia dissoluta*,[1] which has been revealed to be an extremely potent immunosuppressive agent comparable with FK506 and rapamycin.[1,2] The absolute stereochemistry of **1** has been elucidated by Schreiber and co-workers in 1993 by the total synthesis of its antipode.[3a] The pharmacological evaluation and extremely scarcity of the natural material have stimulated intensive synthetic effort,[4] including total syntheses by Schreiber[3] and Smith.[5]

We independently designed a synthetic strategy toward the total synthesis of discodermolide (**1**), in which the carbon backbone of **1** was disconnected between the C_7-C_8 and C_{15}-C_{16} bonds dividing into the three segments **2**, **3**, and **4** (Scheme 1). In this paper, we report an efficient and highly stereoselective synthesis of the C_1-C_7 segment of **1** which involves the stereospecific methylation of γ,δ-epoxy acrylate with trimethylaluminum and the subsequent intramolecular conjugate addition of an acetal alkoxide anion as key steps.



Scheme 1.

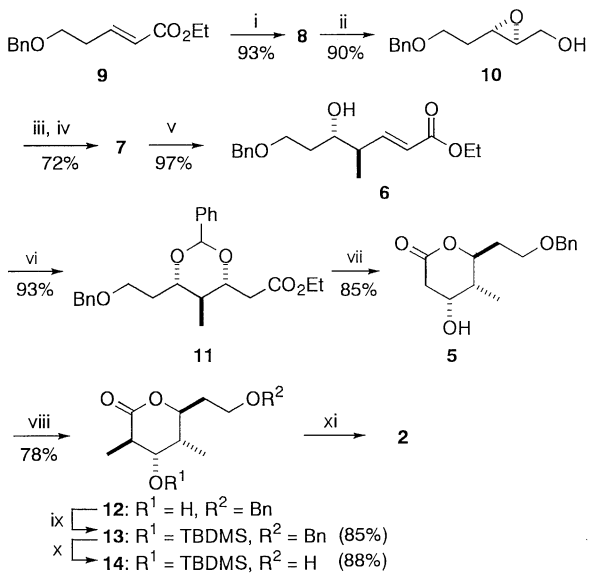
Retrosynthesis of the C_1-C_7 segment **2** was outlined in Scheme 2. The β-methyl group at C_2 position in **2** may be stereoselectively introduced by the simple methylation reaction via a lactone enolate derived from the β-hydroxy lactone **5**. The key compound **5** is presumably constructed from **6** by the use of an intramolecular conjugate addition of an benzyl acetal alkoxide anion based on the Evans protocol[6] and subsequent lactonization of the resulting benzylidene acetal. The anti alcohol **6** having the C_4 and C_5 stereogenic centers is readily obtainable by using the stereospecific methylation reaction of the γ,δ-epoxy acrylate **7**



Scheme 2.

with trimethylaluminum in the presence of water which was recently developed by us.[7,8] The chiral epoxy acrylate **7** is readily accessible from the *trans*-5-benzyloxy-2-penten-1-ol (**8**) via the Katsuki-Sharpless asymmetric epoxidation[9] followed by a Wittig reaction.

The known ester **9**[10] was reduced with DIBAL-H in CH_2Cl_2 to give the allyl alcohol **8** in 93% yield which was then subjected to the Katsuki-Sharpless asymmetric epoxidation with (+)-DIPT resulting in formation of the α-epoxy alcohol **10** in 90% yield (Scheme 3). The α-epoxy alcohol **10** thus obtained was transformed into the *trans*-γ,δ-epoxy acrylate **7** by Swern oxidation followed by the Horner-Emmons reaction with triethyl



Scheme 3. *Reagents and conditions*: i. DIBAL-H, CH_2Cl_2, 0 °C; ii. $Ti(O^iPr)_4$, (+)-DIPT, TBHP, 4A-MS, CH_2Cl_2, -23 °C; iii. $(COCl)_2$, DMSO, CH_2Cl_2, -78 °C then Et_3N; iv. $(EtO)_2P(O)CH_2CO_2Et$, NaH, THF, 0 °C; v. $(CH_3)_3Al$, H_2O, $ClCH_2CH_2Cl$, -30 °C; vi. PhCHO, ^tBuOK, THF, 0 °C; vii. AcOH, H_2O, THF, 90 °C; viii. LDA, MeI, THF, -50 °C; ix. TBDMSiCl, DMAP, imidazole, DMF; x. H_2, Pd / C, ether; xi. PCC, CH_2Cl_2.

phosphonoacetate in THF in 78% overall yield. The methylation of **7** with $(CH_3)_3Al$ (10 equiv.) cleanly proceeded in 1,2-dichloroethane in the presence of water (6 equiv.) at -30 °C giving the anti compound **6** as the sole product in 97% yield.[11] No other stereoisomers were detected. According to the Evans protocol,[6] treatment of **6** with excess benzaldehyde and potassium *tert*-butoxide in THF at 0 °C produced the benzylidene acetal **11** in 93% yield,[12] which was then treated with 70% aqueous acetic acid in THF at 90 °C giving rise to the δ-lactone **5** in 85% yield. The stereochemistry of the lactone **5** was confirmed by coupling constants between H_3, H_4 and H_5 protons in its ^1H NMR spectrum as shown in Figure 1.

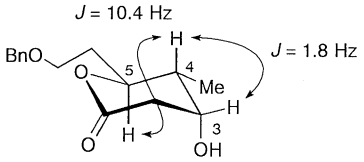


Figure 1.

With the key compound **5** in hand, the crucial methylation reaction was examined. Thus the dianion generated from **5** by treatment with lithium diisopropylamide (LDA, 2.5 equiv.) in THF at -78 °C was conducted with methyl iodide (6 equiv.) to give the single product in 78% yield. The stereochemistry of a newly introduced methyl group was assigned to β, namely the structure of **12**, by the NOE measurement of the product. In addition, the chemical shifts of two methyl groups at C_2 and C_4 positions (1.32 and 1.09 ppm, respectively) in **12** were in well agreement with those of discodermolide (**1**) (1.22 and 0.97 ppm), respectively.[13] The exclusive formation of **12** can be rationalized assuming that the methylation took place from the less-hindered and stereoelectronically preferable axial face with high stereoselectivity. The compound **12** having all the requisite stereogenic centers was transformed into the target molecule **2** by the following reaction sequence: (1) Silylation of the secondary hydroxyl group with *tert*-butyldimethylsilyl chloride in DMF (**13**, 85%); (2) removal of the benzyl group by catalytic hydrogenation over 10% Pd/C in ether (**14**, 88%); (3) PCC oxidation of the resulting primary alcohol in CH_2Cl_2 (nearly quantitative yield). Thus a new and efficient synthetic route to the C_1-C_7 segment of discodermolide (**1**) was established. The overall yield of **2** was 34.5% starting from **9**.

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11 The enantiomeric purity of **6** was found to be 94% by ^1H NMR analysis of the corresponding (*S*)-α-methoxy-phenylacetic acid ester. B. M. Trost, J. L. Belletire, S. Godleski, P. G. McDougal, J. M. Balkovec, J. J. Baldwin, M. E. Christy, G. S Ponticello, S. L. Varga, and J. P. Springer, *J. Org. Chem.*, **51**, 2370 (1986).

12 Schreiber and co-workers have successfully used the Evans protocol for introduction of the stereogenic center at C_5 in their total synthesis of (-)-discodermolide.[3a]

13 $[\alpha]_D^{20}$ -37.8 (*c* 0.83, $CHCl_3$); IR ($CHCl_3$) 3618, 3460, 2977, 2895, 2434, 1718, 1521, 1475, 1423, 1338, 1116, 1091, 1047, 1029, 964, 929, 877, 669, and 624 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.07 (d, *J* = 6.9 Hz, 3H), 1.30 (d, *J* = 7.4 Hz, 3H),1.81 (ddt, J = 9.2, 14.5, 5.3 Hz, 1H), 1.88-2.01 (m, 1H), 2.05 (ddt, J = 2.8, 7.3, 14.5 Hz, 1H), 2.66 (dq, *J* = 4.3, 7.4 Hz, 1H), 3.69 (dd, *J* = 5.4, 7.3 Hz, 2H), 3.65-3.75 (m, 1H), 4.50 (d, *J* = 11.7 Hz, 1H), 4.52 (d, *J* = 11.7 Hz, 1H), 4.45-4.55 (m, 1H), and 7.24-7.39 (m, 5H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 12.7, 14.3, 33.8, 38.7, 42.5, 66.2, 72.9, 73.2, 78.7, 127.5, 127.6, 128.3, 138.3, and 173.3 ppm.