

Stereoselective Synthesis of the C₁-C₇ Segment of (+)-Discodermolide

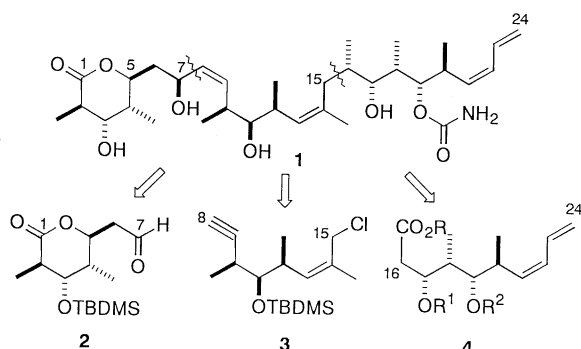
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A new and highly stereoselective synthesis of the C₁-C₇ segment of (+)-discodermolide, the marine natural product having the potent immunosuppressive activity, is described in which the stereospecific methylation of γ,δ -epoxy acrylate with trimethylaluminum and the intramolecular conjugate addition of an acetal alkoxide anion are involved as key steps.

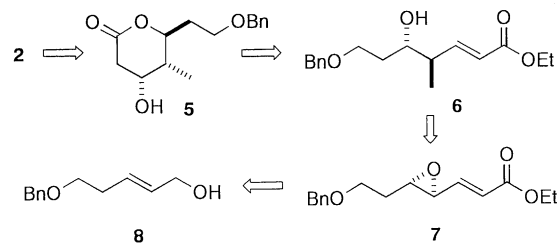
Discodermolide (**1**) is the polypropionate-derived marine natural product recently isolated from the Caribbean sponge *Discodermia dissoluta*,¹ which has been revealed to be an extremely potent immunosuppressive agent comparable with FK506 and rapamycin.^{1,2} The absolute stereochemistry of **1** 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 Schreiber³ 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 C₇-C₈ and C₁₅-C₁₆ 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 C₁-C₇ 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.

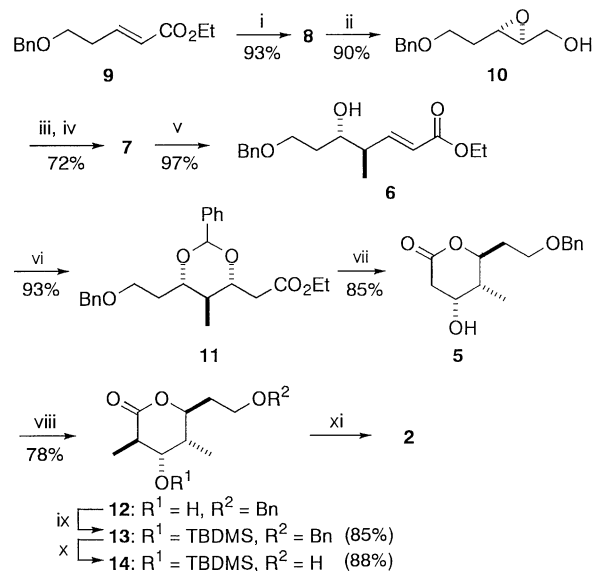
Retrosynthesis of the C₁-C₇ segment **2** was outlined in Scheme 2. The β -methyl group at C₂ position in **2** may be stereoselectively introduced by the simple methylation reaction via a lactone enolate derived from the β -hydroxy lactone **5**. The key compound **5** is presumably constructed from **6** by the use of an intramolecular conjugate addition of a benzyl acetal alkoxide anion based on the Evans protocol⁶ and subsequent lactonization of the resulting benzylidene acetal. The anti alcohol **6** having the C₄ and C₅ 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 epoxidation⁹ followed by a Wittig reaction.

The known ester **9**¹⁰ was reduced with DIBAL-H in CH₂Cl₂ 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, CH₂Cl₂, 0 °C; ii. Ti(OⁱPr)₄, (+)-DIPT, TBHP, 4A-MS, CH₂Cl₂, -23 °C; iii. (COCl)₂, DMSO, CH₂Cl₂, -78 °C then Et₃N; iv. (EtO)₂P(O)CH₂CO₂Et, NaH, THF, 0 °C; v. (CH₃)₃Al, H₂O, ClCH₂CH₂Cl, -30 °C; vi. PhCHO, ^tBuOK, THF, 0 °C; vii. AcOH, H₂O, THF, 90 °C; viii. LDA, MeI, THF, -50 °C; ix. TBDMSiCl, DMAP, imidazole, DMF; x. H₂, Pd / C, ether; xi. PCC, CH₂Cl₂.

phosphonoacetate in THF in 78% overall yield. The methylation of **7** with $(\text{CH}_3)_3\text{Al}$ (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.

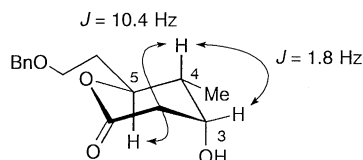


Figure 1.

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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References and Notes

- S. P. Gunasekera, M. Gunasekera, R. E. Longley, and G. K. Schulte, *J. Org. Chem.*, **55**, 4912 (1990).
Corrections: *Ibid.* **56**, 1346 (1991).
- S. L. Schreiber, *Science*, **251**, 283 (1991); M. K. Rosen and S. L. Schreiber, *Angew. Chem. Int. Ed. Engl.*, **31**, 384 (1992).
- a) J. B. Nerenberg, D. T. Hung, P. K. Somers, and S. L. Schreiber, *J. Am. Chem. Soc.*, **115**, 12621 (1993). b) D. T. Hung, J. B. Nerenberg, and S. L. Schreiber, *J. Am. Chem. Soc.*, **118**, 11054 (1996).
- D. L. Clark and C. H. Heathcock, *J. Org. Chem.*, **58**, 5878 (1993); J. M. C. Golec and S. D. Jones, *Tetrahedron Lett.*, **34**, 8159 (1993); P. L. Evans, J. M. C. Golec, and R. J. Gillespie, *Tetrahedron Lett.*, **34**, 8163 (1993); J. M. C. Golec and R. J. Gillespie, *Tetrahedron Lett.*, **34**, 8167 (1993); I. Paterson and S. P. Wren, *J. Chem. Soc., Chem. Commun.*, **1993**, 1790; G. Yang and D. C. Myles, *Tetrahedron Lett.*, **35**, 1313 (1994); G. Yang and D. C. Myles, *Tetrahedron Lett.*, **35**, 2503 (1994); I. Paterson and A. Schlapbach, *Synlett*, **1995**, 498.
- A. B. Smith, III, Y. Qiu, D. R. Jones, and K. Kobayashi, *J. Am. Chem. Soc.*, **117**, 12011 (1995).
- D. A. Evans and J. A. Gaucht-Prunet, *J. Org. Chem.*, **58**, 2446 (1993).
- M. Miyashita, M. Hoshino, and A. Yoshikoshi, *J. Org. Chem.*, **56**, 6483 (1991).
- M. Miyashita, K. Yoshihara, K. Kawamine, M. Hoshino, and H. Irie, *Tetrahedron Lett.*, **34**, 6285 (1993); T. Shiratani, K. Kimura, K. Yoshihara, S. Hatakeyama, H. Irie, and M. Miyashita, *J. Chem. Soc., Chem. Commun.*, **1996**, 21; M. Miyashita, T. Shiratani, K. Kawamine, S. Hatakeyama, and H. Irie, *J. Chem. Soc., Chem. Commun.*, **1996**, 1027.
- T. Katsuki and K. B. Sharpless, *J. Am. Chem. Soc.*, **102**, 5974 (1980).
- M. J. Martinell, *J. Org. Chem.*, **55**, 5065 (1990).
- The enantiomeric purity of **6** was found to be 94% by ^1H NMR analysis of the corresponding (*S*)- α -methoxyphenylacetic 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).
- 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}
- $[\alpha]_D^{20}$ -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.