Synthesis of the C_8-C_{15} Segment of (+)-Discodermolide

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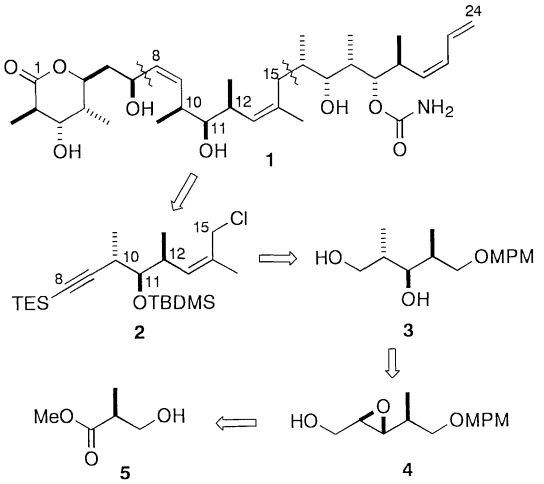
Succeeding to the preceding paper, stereoselective synthesis of the C_8-C_{15} segment of (+)-discodermolide (**1**), the marine natural product having the potent immunosuppressive activity, is described in which the contiguous asymmetric centers at C_{11} and C_{12} positions were stereospecifically constructed via the methylation of an epoxy alcohol with lithium dimethylcuprate.

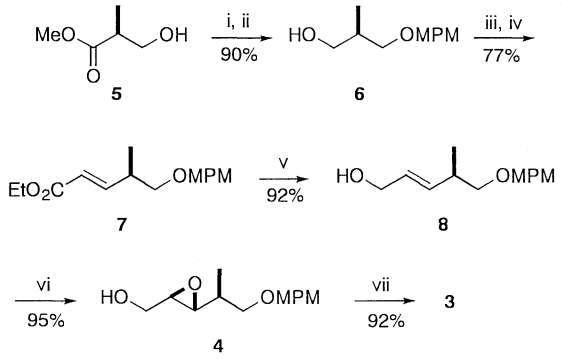
In the preceding paper,[1] we reported the stereoselective synthesis of the C_1-C_7 segment of (+)-discodermolide (**1**) by the use of the stereospecific methylation of γ,δ-epoxy acrylate with trimethylaluminum and the intramolecular conjugate addition of an acetal alkoxide anion as key steps. We report here an elaboration of the C_8-C_{15} segment **2** of **1** which involves a regiospecific methylation of an epoxy alcohol with lithium dimethylcuprate and the *Z*-selective Horner-Emmons reaction using methyl 2-[bis(2-methylphenyl)phosphono]propionate as key steps.



Scheme 1.

We designed the acetylenic compound **2** as the C_8-C_{15} segment of (+)-discodermolide (**1**) and its retrosynthesis was outlined in Scheme 1. The terminal carbon-carbon triple bond and another terminus (*Z*)-allyl chloride moiety may be regioselectively introduced from diol **3**. The anti alcohol **3** bearing the C_{10}, C_{11}, and C_{12} stereogenic centers, a key intermediate in the present synthesis, will be derivable from β-epoxy alcohol **4** by the regioselective methylation with lithium dimethylcuprate. The β-epoxy alcohol **4** should be prepared from the commercially available hydroxy ester **5**.

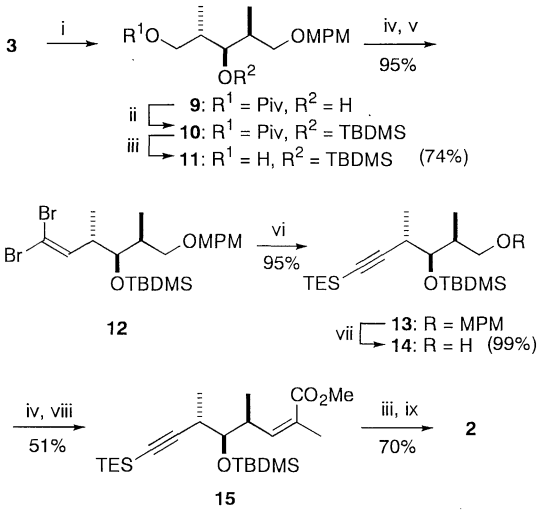
The key intermediate **3** was straightforwardly synthesized starting from methyl (*S*)-3-hydroxy-2-methylpropionate (**5**) according to the reaction path shown in Scheme 2. Thus protection of the hydroxyl group in **5** with *p*-methoxybenzyl trichloroacetamide[2] followed by reduction of the resulting ester



Scheme 2. *Reagents and conditions*: i. $MPMOC(=NH)CCl_3$, PPTS, CH_2Cl_2; ii. $LiAlH_4$, THF; iii. $(COCl)_2$, Me_2SO, CH_2Cl_2, -70 °C, then Et_3N; iv. $(EtO)_2P(O)CH_2CO_2Et$, NaH, THF, 0 °C; v. DIBAL-H, CH_2Cl_2, 0 °C; vi. (-)-DIPT, $Ti(O^iPr)_4$, TBHP, MS-4A, CH_2Cl_2, 0 °C; vii. $(CH_3)_2CuLi$, Et_2O, -40°C.

with $LiAlH_4$ gave rise to the alcohol **6** in 90% overall yield. In order to evaluate the enantiomeric excess of the product, a part of **6** was transformed into the corresponding (*S*)-α-methoxyphenylacetic acid ester and the enantiomeric excess of **6** was found to be >95% by its ^1H NMR analysis. Swern oxidation of the alcohol **6** followed by the Horner-Emmons reaction with triethyl phosphonoacetate gave the (*E*)-α,β-unsaturated ester **7** in 77% yield after purification by silica gel chromatography. The unsaturated ester **7** was then reduced with DIBAL-H in CH_2Cl_2 to afford the alcohol **8** in 92% yield. The Katsuki-Sharpless asymmetric epoxidation[3] of the resulting alcohol **8** with D-(-)-diethyl tartrate furnished the desired β-epoxy alcohol **4** as a single product in 95% yield. The reaction of the epoxy alcohol **4** with lithium dimethylcuprate cleanly proceeded in Et_2O at -23 °C[4] giving rise to the desired diol **3** as the sole product in 92% yield, though a large excess of the cuprate reagent (15 equiv.) was required for completion of the reaction.[5]

With the key intermediate **3** in hand, we focused on the elaboration of the fully functionalized C_8-C_{15} segment **2**. Initially, the diol **3** was converted to **11** by a three step reaction sequence: 1) regioselective protection of the primary hydroxyl group with pivaloyl chloride, 2) subsequent protection of the secondary hydroxyl group with *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBDMSOTf), 3) reduction of the resulting pivalate ester with DIBAL-H, in 74% overall yield (Scheme 3). Dess-Martin oxidation[6,7] of the alcohol **11** obtained and the subsequent Wittig reaction with CBr_4 and HMPT[8] produced the methylene dibromide **12** in 95% yield. Treatment of the dibromide **12** with BuLi (2.2 equiv.) in THF at -78 °C followed by trapping the resulting lithium acetylide with triethylsilyl chloride furnished the silyl acetylene **13** in 95% yield. Removal of the MPM group of **13** with DDQ in CH_2Cl_2 afforded the alcohol **14** in nearly quantitative yield. The alcohol



Scheme 3. *Reagents and conditions*: i. $(CH_3)_3CCOCl$, pyridine, CH_2Cl_2, 0 °C; ii. TBDMSOTf, pyridine, CH_2Cl_2, 0 °C; iii. DIBAL-H, CH_2Cl_2, -78 °C; iv. Dess-Martin periodinane, CH_2Cl_2; v. CBr_4, HMPT, THF, 0 °C; vi. BuLi (2.2 equiv.), THF, -78 °C, then TESCl; vii. DDQ, H_2O, CH_2Cl_2; viii. $(o\text{-}C_7H_7O)_2P(O)CHMeCO_2Me$, NaH, THF, -78 °C to 0 °C; ix. CH_3SO_2Cl, Et_3N, CH_2Cl_2, 0 °C then LiCl, rt.

14 thus obtained was further transformed into the *Z*-unsaturated ester **15** by Dess-Martin oxidation followed by the Horner-Emmons reaction with methyl 2-[bis(2-methylphenyl)phosphono]-propionate[9] in THF, whereupon the desired *Z*-unsaturated ester **15** and the *E*-isomer were obtained in 51% and 5% yields, respectively, after purification by silica gel chromatography. Finally, the *Z*-unsaturated ester **15** was converted to the fully functionalized C_8-C_{15} segment **2**[10] by the following reaction sequence: 1) reduction of the ester group with DIBAL-H, 2) treatment of the resulting allylic alcohol with methanesulfonyl chloride followed by LiCl, in 70% overall yield.

Thus a new and stereoselective synthetic route to the C_8-C_{15} segment of discodermolide (**1**) was developed. The synthesis of the remaining C_{16}-C_{24} segment of discodermolide is progress in our laboratory.

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References and Notes

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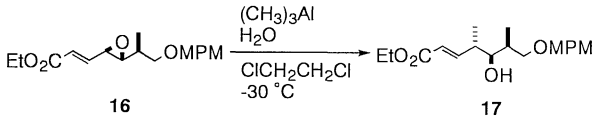
5 As an alternative route for construction of the asymmetric centers at C_{11} and C_{12} positions, the methylation of **16** with trimethylaluminum (10 equiv.) in dichloroethane in the presence of water (6 equiv.) was examined and the desired product **17** was obtained as a single product.



6 Oxidation of **11** with Swern oxidation resulted in poor yield of the product.

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10 ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.06 (s, 3H), 0.07 (s, 3H), 0.57 (q, *J* = 7.9 Hz, 6H), 0.92 (s, 9H), 0.99 (t, *J* = 7.9 Hz, 9H), 1.00 (d, *J* = 6.9 Hz, 3H), 1.17 (d, *J* = 7.3 Hz, 3H), 1.81 (d, *J* = 1.2 Hz, 3H), 2.64 (dq, *J* = 2.6, 7.3 Hz, 1H), 2.84 (ddq, *J* = 10.6, 6.9, 6.9 Hz, 1H), 3.31 (dd, *J* = 2.6, 7.2 Hz, 1H), 3.97 (d, *J* = 10.9 Hz, 1H), 4.35 (d, *J* = 10.9 Hz, 1H), 5.21 (dq, *J* = 10.6, 1.2 Hz, 1H).