Stereoselective Syntheses of the C1-C5, C7-C15 and C17-C24 Fragments of (+)-Discodermolide Using a Catalytic and Asymmetric Vinylogous Mukaiyama Reaction

Belén Bazán-Tejeda, Marie Georgy, Jean-Marc Campagne*

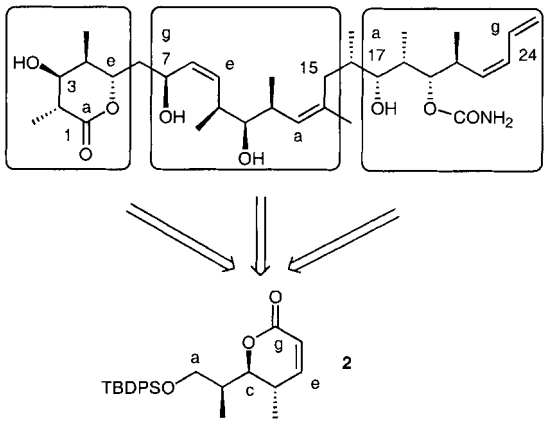
ICSN-CNRS, Avenue de la Terrasse, 91198 Gif sur Yvette, France
Fax +33(1)69077247; E-mail: campagne@icsn.cnrs-gif.fr

Received 10 November 2003

Abstract: The stereoselective syntheses of C1-C5, C7-C15 and C17-C24 fragments of (+)-discodermolide are described from a common intermediate: an α,β-unsaturated six-membered lactone obtained in one step using a catalytic and asymmetric vinylogous Mukaiyama (CAVM) reaction.

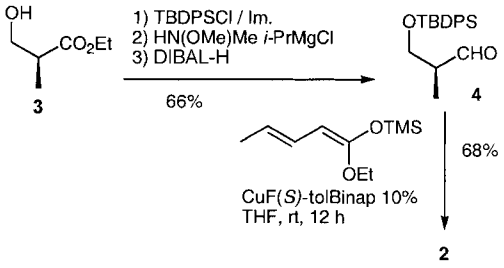
Key words: asymmetric, lactones, stereoselectivity, catalysis, copper

Discodermolide (**1**), isolated in 1990, by Gunasekera[1] from the marine sponge *Discodermia dissoluta*, is a potential anti-cancer agent. Discodermolide was found to bind to tubulin with a 100 fold greater affinity than taxol and also to act synergistically with taxol.[2,3] This natural product also possesses an original structure bearing 13 stereogenic centers and 3 *Z*-double bonds. Owing to its biological properties, original structure and scarcity from the natural source (0.002% w/w from frozen sponges), considerable synthetic efforts have been undertaken culminating in 5 total syntheses,[4–8] a formal synthesis,[9] a great number of different synthetic approaches,[10] and the design[11] of simplified potent analogues.[2,3]



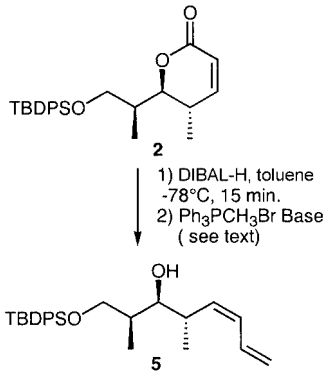
Scheme 1

From a retrosynthetic point of view, it has been previously shown that discodermolide could be divided in three main fragments possessing the same *syn*/*anti* stereotriad. Different accesses to this stereotriad have been developed using efficient asymmetric aldol,[5,8,9] crotylation,[4,10] or allenylmetal[7] methodologies. We have recently reported[12] a stereoselective access to lactone **2**, which possesses the correct *syn*/*anti* stereotriad and interestingly, a well-positioned *Z*-double bond (Scheme 1). We thus embarked on a total synthesis of (+)-discodermolide. In this communication, we would like to disclose the syntheses of C1-C5, C7-C15 and C17-C24 fragments of (+)-discodermolide starting from lactone **2**.



Scheme 2

Lactone **2** was synthesized in four steps starting from commercially available enantiomerically pure ester **3** (Scheme 2). Aldehyde **4** was first obtained using standard procedures[13] in three steps and 66% overall yield.

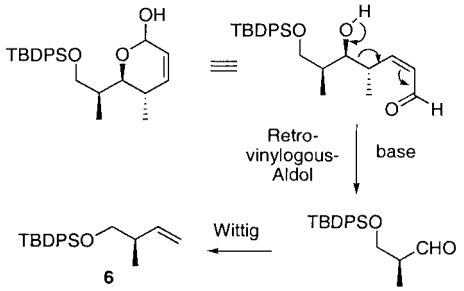


Scheme 3

Starting from aldehyde **4**, a catalytic and asymmetric vinylogous Mukaiyama (CAVM) reaction in the presence of Carreira's catalyst[14] (10%) led to lactone **2** as a single diastereoisomer in a 68% yield.

SYNLETT 2004, No. 4, pp 0720–0722
Advanced online publication: 29.01.2004
DOI: 10.1055/s-2004-817744; Art ID: G30103ST

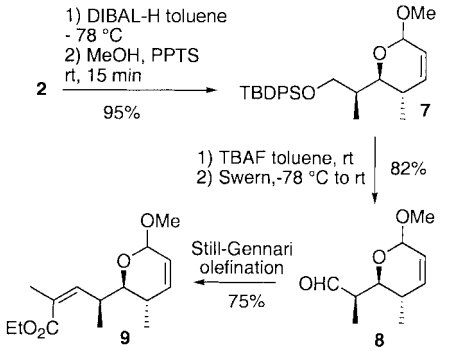
In order to construct fragment C17-C24, lactone **2** was first partially reduced to the corresponding lactol, which was not purified but directly engaged in a Wittig reaction with methyl(triphenyl)phosphonium bromide (Scheme 3). Initial attempts (using different amounts of phosphonium bromide and NaHMDS in THF) were quite disappointing leading to the expected diene **5** in low yields (18–26%).



Scheme 4

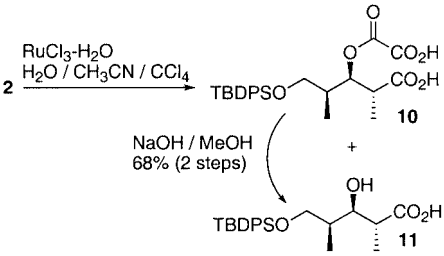
Careful examination of the by-products generated in the Wittig reaction led us to isolate compound **6**,[15] which is probably resulting from a Wittig reaction on the retro-vinylogous-aldol product of the lactol (Scheme 4). This observation led us to reconsider the amount of base in this reaction. Indeed, using 2.5 equivalents of phosphonium bromide and 2 equivalents of NaHMDS in THF, compound **5**[16] could be isolated in 70% yield (2 steps). Fragment C17-C24 **5** was thus obtained in two steps and 70% yield from lactone **2**.

The synthesis of fragment C7-C15 (Scheme 5) started with the partial reduction of the lactone to the corresponding lactol, followed by its protection as acetal **7**.



Scheme 5

Treatment of the silylether with TBAF, which after subsequent oxidation using a Swern reaction led to aldehyde **8** in 82% yield. Olefination using the Still–Gennari[17,18] modification of the Horner–Wadsworth–Emmons reaction ultimately led (75% yield) to the selective formation of **9**[19] with the requisite C13-C14 *Z*-trisubstituted double bond. Fragment C7-C15[19] was thus obtained in 5 steps (55% overall yield from **2**).



Scheme 6

Fragment C1-C5 (Scheme 6) was finally obtained in two steps by oxidative cleavage[20] of the double bond in lactone **2**. A mixture of compounds **10** and **11**[21] was obtained. Further basic treatment of the crude mixture led to fragment C1-C5[21] in 68% yield (2 steps).

In conclusion, we have developed short accesses to C1-C5, C7-C15 and C17-C24 fragments of (+)-discodermolide in 2, 5 and 2 steps, respectively, starting from a common intermediate: the lactone **2**. Our current work on assembling these fragments will be reported in due course.

Acknowledgment

We thank CNRS and CONACYT-Mexico (fellowship to B. B.-T.) for financial support.

References

(1) Gunasereka, S. P.; Gunasereka, M.; Schulte, G. K. *J. Org. Chem.* **1990**, *55*, 4912; corrigendum: *J. Org. Chem.* **1991**, *56*, 1346.
(2) For a review, see: Kalesse, M. *ChemBioChem* **2000**, *1*, 171.
(3) For a review, see: Paterson, I.; Florence, G. J. *Eur. J. Org. Chem.* **2003**, 2193.
(4) Hung, D. T.; Nerenberg, J. B.; Schreiber, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 11054.
(5) Smith, A. B. III; Beauchamp, T. J.; LaMarche, M. J.; Kaufman, M. D.; Qiu, Y. P.; Arimoto, H.; Jones, D. R.; Kobayashi, K. *J. Am. Chem. Soc.* **2000**, *122*, 8654.
(6) (a) Harried, S. S.; Yang, G.; Strawn, M. A.; Myles, D. C. *J. Org. Chem.* **1997**, *62*, 6098. (b) Harried, S. S.; Lee, C. P.; Yang, G.; Lee, T. I. H.; Myles, D. C. *J. Org. Chem.* **2003**, *68*, 6646.
(7) (a) Marshall, J. A.; Johns, B. A. *J. Org. Chem.* **1998**, *63*, 7885. (b) Marshall, J. A.; Lu, Z. H.; Johns, B. A. *J. Org. Chem.* **1998**, *63*, 817.
(8) (a) Paterson, I.; Florence, G. J.; Gerlach, K.; Scott, J. P.; Sereining, N. *J. Am. Chem. Soc.* **2001**, *123*, 9535. (b) Paterson, I.; Delgado, O.; Florence, G. J.; Lyothier, I.; Scott, J. P.; Sereining, N. *Org. Lett.* **2003**, *5*, 35.
(9) Francavilla, C.; Chen, W.; Kinder, F. R. Jr. *Org. Lett.* **2003**, *5*, 1233.
(10) Bouzbouz, S.; Cossy, J. *Org. Lett.* **2003**, *5*, 3029; and references cited therein.
(11) Choy, N.; Shin, Y.; Nguyen, P. Q.; Curran, D. P.; Balachandran, R.; Madiraju, C.; Day, B. W. *J. Med. Chem.* **2003**, *46*, 2846; and references cited therein.
(12) Bluet, G.; Bazan-Tejeda, B.; Campagne, J. M. *Org. Lett.* **2001**, *3*, 3807.

(13) Trost, B. M.; Gunzner, J. L.; Dirat, O.; Rhee, Y. H. *J. Am. Chem. Soc.* **2002**, *124*, 10396.
(14) Kruger, J.; Carreira, E. M. *J. Am. Chem. Soc.* **1998**, *120*, 837.
(15) Konno, K.; Fujishima, T.; Maki, S.; Liu, Z.; Miura, D.; Chokki, M.; Ishizuka, S.; Yamaguchi, K.; Kan, Y.; Kurihara, M.; Miyata, N.; Smith, C.; DeLuca, H. F.; Takayama, H. *J. Med. Chem.* **2000**, *43*, 4247.
(16) **Experimental Procedure for Fragment C17-C24 5.** DIBAL-H (0.55 mL, 1 M in hexanes) is added to a solution of **2** (200 mg, 0,49 mmol) in toluene (6 mL) at –78 °C. After 15 min at –78 °C, sat. NH_4Cl (10 mL) is added and the reaction mixture is allowed to warm up to r.t. After extraction with CH_2Cl_2 and classical work-up, lactol (196 mg) is obtained without further purification as a colorless oil. Triphenylmethylphosphonium bromide (59 mg, 0,16 mmol) is suspended in THF (0.5 mL) at 0 °C. NaHMDS (63 μL, 0,127 mmol, 2 M in THF) is then added dropwise. After 2.5 h at 0 °C, the reaction mixture is cooled to –78 °C and a solution of crude lactol (26 mg, 0.063 mmol) in THF (0.6 mL) is added. The reaction mixture is allowed to warm up to r.t. and after 15 h the solvent is evaporated. The crude residue is purified by column chromatography (pentane/CH_2Cl_2 8:2 to 6:4). Diene **5** is obtained (18 mg, 70% yield) as a colorless oil.
Analytical data: R_f = 0.38 (heptane/EtOAc 9:1). IR: 3503, 3071, 3049, 2999, 2961, 2930, 2858 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 0.95 (3 H, d, *J* = 6.7 Hz, H10), 0.97 (3 H, d, *J* = 7.0 Hz, H9), 1.07 (9 H, s, *t*- Bu), 1.81–1.93 (1 H, m, H7), 2.27 (1 H, d, *J* = 2.6 Hz, OH), 2.73–2.85 (1 H, m, H5), 3.63 (1 H, dt, *J* = 2.5 and 8.1 Hz, H6), 3.72 (2 H, d, *J* = 2 Hz, H8), 5.12 (1 H, d, *J* = 10.1 Hz, H1), 5.22 (1 H, d, *J* = 16.8 Hz, H1′), 5.42 (1 H, t, *J* = 10.4 Hz, H4), 6.12 (1 H, d, *J* = 11 Hz, H3), 6.61 (1 H, dt, *J* = 10.4 and 16.8 Hz, H2), 7.36–7.46 (6 H, m, Ph), 7.66–7.72 (4 H, m, Ph). ^{13}C RMN ($CDCl_3$): δ = 9.67 (C9), 17.41 (C10), 19.20 (*t*-Bu), 26.98 (3 C, *t*-Bu), 35.79 (C5), 36,82 (C7), 68.12 (C8), 76.38 (C6), 117.89 (C1), 127.64 (4 C, Ph), 129.65 (2 C, Ph), 130.20 (C3), 132.25 (C2), 133.31 (Ph), 133.45 (Ph), 135.50 (C4), 135.67 (4 C, Ph). $[\alpha]_D^{25}$ +43.5 (*c* 1, $CHCl_3$). HRMS (ESI+) $[MNa]^+$: calcd *m/z* = 431.2382, found *m/z* = 431.2379.
(17) Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405.
(18) The same reaction carried out under 'regular' HWE conditions led to a 95:5 *Z*/*E* mixture.
(19) **Experimental Procedure for Fragment C7-C15 9.** To a solution of fluorophosphonate[22] (70 mg, 0.2 mmol) and 18-C-6 (64 mg, 0.24 mmol) at –78 °C, is added KHMDS (0.4 mL, 0.5 M in toluene). After 15 min, a solution of aldehyde **8** (18 mg, 0.1 mmol) in THF (0.2 mL) is added. After 8 min, in an ice-water bath, starting aldehyde has disappeared (CCM monitoring). After quenching using sat. NH_4Cl (15 min) and classical work-up, the crude residue is purified by column chromatography (heptane/EtOAc 7:3) to give **9** (20 mg, 75%) as a colorless oil.
Analytical data: R_f = 0,66 (heptane/EtOAc 7:3). IR: 2965, 2930, 2865, 2821, 1705, 1602 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 0.98 (3 H, d, *J* = 7.2 Hz, H12). 1.03 (3 H, d, *J* = 6.8 Hz, H13), 1,07 (3 H, dd, *J* = 1.6 and 6.7 Hz, H11), 1.30 (3 H, t, *J* = 7.2 Hz, H16), 2.24–2.35 (1 H, m, H5), 3.38 (3 H, s, H14), 3.45–3.61 (2 H, m, H6-H7), 4.20 (2 H, q, *J* = 7.2 Hz, H15), 4.85 (1 H, bs, H2), 5.68 (1 H, dt, *J* = 2.6 and 10 Hz, H3), 5.79 (1 H, bd, *J* = 10 Hz, H4), 6.14 (1 H, dd, *J* = 1.4 and 8.4 Hz, H8). ^{13}C NMR ($CDCl_3$): δ = 13.05 (C12), 14.2 (C16), 16.3 (C13), 20.8 (C11), 30.9 (C5), 33.3 (C7), 55.0 (C14), 60.0 (C15), 75.3 (C6), 95.4 (C2), 124.0 (C3), 136.2 (C4), 140.5 (C9), 146.6 (C8), 167.7 (C10), $[\alpha]_D^{25}$ +138.9 (*c* 0.58, $CHCl_3$). Anal. Calcd for (%): C, (67.14); H, (9.01). Found (%): C, (67.23); H (9.11).
(20) Carlsen, H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936.
(21) **Experimental Procedure for Fragment C1-C5 11.** To a solution of lactone **2** (60 mg, 0.15 mmol) in CCl_4 (0.15 mL), CH_3CN (0.15 mL) and H_2O (0.27 mL) are added. $RuCl_3 \cdot H_2O$ (15 μL, 6% in H_2O) and $NaIO_4$ (135 mg, 0.6 mmol) are then added and the reaction is stirred at r.t. for 24 h. The reaction mixture is diluted with H_2O (1 mL) and extracted with CH_2Cl_2. Organic phases are discarded and the aqueous phase is acidified with 1 N HCl and extracted with CH_2Cl_2. Organic phases are dried over $MgSO_4$, filtered and evaporated to give a mixture of compounds **10** and **11**. The crude product is dissolved in MeOH (2 mL) and a solution of NaOH (2 mL) is then added. After 1 h stirring at r.t., the reaction mixture is evaporated. The residue is taken up in H_2O and then acidified (1 N HCl). Extraction with CH_2Cl_2 and classical work-up gave acid **11** (42 mg, 68%).
Analytical data: IR: 3435, 2929, 1713, 1112 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 0.95 (3 H, d, *J* = 7.0 Hz, H6), 1.07 (9 H, s, *t*-Bu), 1.15 (3 H, d, *J* = 7.1 Hz, H7), 1.73–1.84 (1 H, m, H4), 2.61 (1 H, m H2), 3.60 (1 H, dd, *J* = 5.7 and 10 Hz, H5), 3.82 (1 H, dd, *J* = 3.9 and 10 Hz, H5′), 4.12 (1 H, d, *J* = 10.1 Hz, H3), 7.36–7.46 (6 H, m, Ph), 7.66–7.72 (4 H, m, Ph). ^{13}C NMR ($CDCl_3$): δ = 9.3 (C6), 17.4 (C7), 19.2 (1 C, *t*-Bu), 26.9 (3 C, *t*-Bu), 36.8 (C4), 43.7 (C2), 68.3 (C5), 74.8 (C3), 127.7 (4 C, Ph), 129.7 (2 C, Ph), 133.3 (1 C, Ph), 134.7 (1 C, Ph), 135.6 (4 C, Ph), 179.0 (C=O). HRMS (ESI+) $[MNa]^+$: calcd *m/z* = 423.197, found *m/z* = 423.200.
(22) Patois, C.; Savignac, P. *Synth. Commun.* **1991**, *21*, 2391.