ORGANIC LETTERS

2005
Vol. 7, No. 21
4613−4616

Design, Total Synthesis, and Evaluation of C(13)–C(14) Cyclopropane Analogues of (+)-Discodermolide

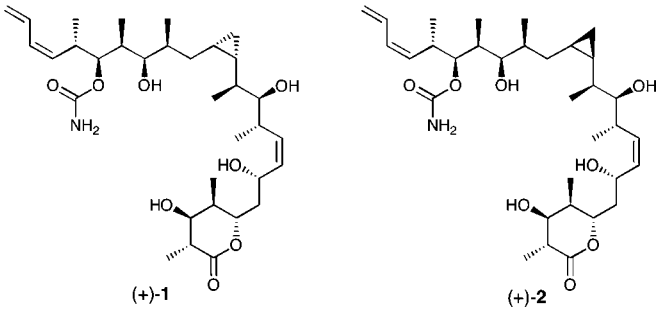
Amos B. Smith, III,*,† Ming Xian,† and Fenghua Liu‡

Department of Chemistry, Monell Chemical Senses Center, and Laboratory for Research on the Structure of Matter, University of Pennsylvania, Philadelphia, Pennsylvania 19104, and Kosan Bioscience, Inc., 3832 Bay Center Place, Hayward, California 94545

smithab@sas.upenn.edu

Received July 18, 2005

ABSTRACT



The design, total synthesis, and biological evaluation of two C(13)–C(14)-cyclopropyl analogues [(+)-1 and (+)-2] of (+)-discodermolide have been achieved. Key features of the syntheses include highly stereoselective, hydroxyl-directed cyclopropanations of vinyl iodides and higher order cuprate-mediated cross-coupling reactions between cyclopropyl iodides and alkyl iodides. Biological evaluation revealed that neither orientation of the cyclopropyl methylene completely substitutes for the C(14) methyl found in (+)-discodermolide (3).

(+)-Discodermolide (**3**, Figure 1), a potent antitumor polyketide natural product first isolated in 1990 by Gunasekera et al. at the Harbor Branch Oceanographic Institute from extracts of the rare Caribbean marine sponge *Discodermia dissoluta*,[1] comprises a linear 24-membered polyketide backbone punctuated by 13 stereogenic centers. The pioneering syntheses of both the (+)- and (−)-antipodes by Schreiber and co-workers permitted assignment of the absolute stereochemistry of **3**.[2]

Discodermolide was initially reported to be a potent immunosuppressive agent, both in vivo and in vitro;[3] this activity was subsequently recognized to be due to the potent microtubule-stabilizing antimitotic activity.[4] Importantly, discodermolide displays not only significant tumor cell growth inhibitory activity against a wide panel of human cancel cell lines including paclitaxel-resistant cells[5] but also cytotoxic synergy with paclitaxel in a variety of cell lines[6] as well as the induction of accelerated cell senescence.[7] The remarkable, wide-ranging biological activity, in conjunction with both the challenging architecture and the growing interest in providing useful quantities of (+)-discodermolide for clinical development, has stimulated considerable chemi-

† University of Pennsylvania.
‡ Kosan Bioscience, Inc.

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10.1021/ol051691c CCC: $30.25
Published on Web 09/20/2005

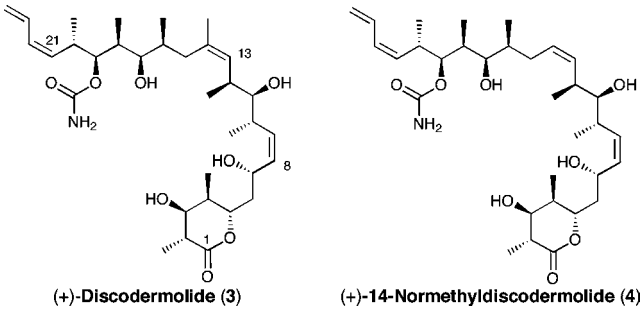


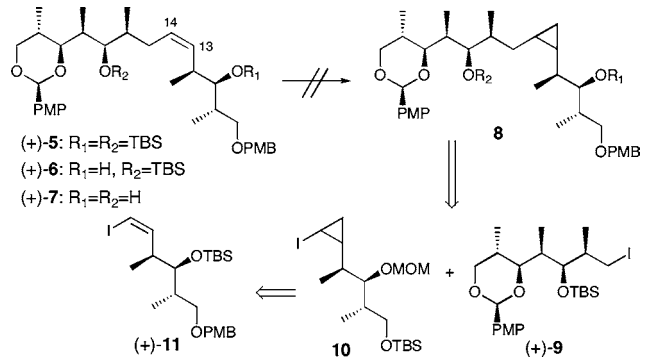
Figure 1. (+)-Discodermolide (**3**) and the (+)-14-normethyl congener (**4**).

cal efforts resulting in seven total syntheses.[2,8] Additional endeavors have focused on the design and synthesis of structurally simplified analogues of this potentially important chemotherapeutic agent.[9]

In parallel with our efforts to develop an ever more practical total synthesis of discodermolide to provide material for clinical development,[10] we broadened our program in collaboration with Kosan Bioscience, Inc., to include the production of analogues designed to probe the structure−activity relationship (SAR), as well as to define the critical minimum structural element necessary for tumor cell growth inhibition.[11] In conjunction with this effort, we assigned the solution conformation, similar to the solid-state structure, on the basis of a combination of 1- and 2-D NMR techniques and computational studies.[12,13] A combination of $A^{1,3}$ and *syn*-pentane nonbonded interactions along the carbon backbone appears to play a major role in defining the observed turn conformation.[12,13] From the SAR perspective, our initial results indicate that congeners of discodermolide lacking the C(14) methyl substituent, as in the (+)-14-normethyl congener (**4**), demonstrate a general trend of relative inactivity against the NCI/ADR multidrug-resistant cell line,[11b] despite retaining nanomolar cytotoxicity against a wide variety of drug-sensitive cell lines.[11b] The underlying nature of these results involving the subtle interplay between structure and function in the C(13)−C(14) region of discodermolide continues to be the subject of active investigation in our laboratory. In this paper, we disclose the design, total synthesis, and biological evaluation of two cyclopropyl congeners of discodermolide: (+)-13*S*,14*S*-cyclopropyldiscodermolide (**1**) and (+)-13*R*,14*R*-cyclopropyldiscodermolide (**2**).

Initial efforts focused on the direct cyclopropanation of the known advanced olefin (+)-**5**[11a] to install the cyclopropane functionality at C(13)−C(14) as required for an advanced recursor such as **8** (Scheme 1).

Scheme 1



All attempts, however, employing a variety of cyclopropanation conditions provided only trace amounts of the desired cyclopropanes, and then only as mixtures of diastereomers. The related secondary alcohols (+)-**6** and (+)-**7** were likewise unreactive.

Attention therefore quickly shifted to an alternative strategy to construct **8**. We reasoned that introduction of the cyclopropane moiety prior to elaboration of the C(14)−C(15) bond, employing intermediates such as (+)-**9** and (+)-**11** readily available in our laboratory, might be feasible. This synthetic plan called for construction of cyclopropyl iodide **10** (Scheme 1).

Not entirely unexpectedly, direct cyclopropanation of known vinyl iodide (+)-**11**[11a] again proved unsuccessful, given the electron-deficient nature of the olefin. Literature[14] precedent, however, suggested that an allylic hydroxyl group might significantly augment the chance for successful cyclopropanation. With this scenario in mind, removal of the TBS group in (+)-**11** and cyclopropanation employing the conditions of Denmark and co-workers (Scheme 2)

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(9) (a) Hung, D. T.; Nerenberg, J. B.; Schreiber, S. L. *Chem. Biol.* **1994**, *1*, 67−71. (b) Choy, N.; Shin, Y.; Nguyen, P. Q.; Curran, D. P.; Balachandran, R.; Madiraju, C.; Day, B. W. *J. Med. Chem.* **2003**, *46*, 2846−2864.

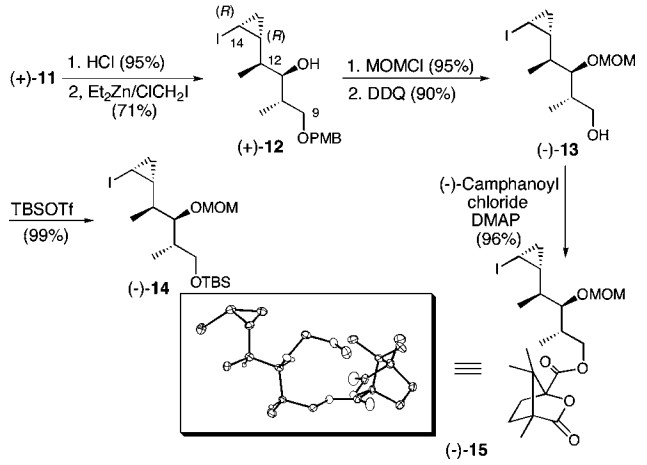
(10) Recently, we reported a fourth-generation synthesis comprised of a longest linear sequence of 17 steps and proceeded in 9% overall yield; see: Smith, A. B., III; Freeze, B. S.; Xian, M.; Hirose, T. *Org. Lett.* **2005**, *7*, 1825−1828. Also see: Paterson, I.; Lyothier, I. *Org. Lett.* **2004**, *6*, 4933−4936.

(11) (a) Martello, L. A.; LaMarche, M. J.; He, L.; Beauchamp, T. J.; Smith, A. B., III; Horwitz, S. B. *Chem. Biol.* **2001**, *8*, 843−855. (b) Smith, A. B., III; Freeze, B. S.; LaMarche, M.; Hirose, T.; Brouard, I.; Xian, M.; Sundermann, K. F.; Shaw, S. J.; Burlingame, M. A.; Horwitz, S. B.; Myles, D. C. *Org. Lett.* **2005**, *7*, 315−318. (c) Smith, A. B., III; Freeze, B. S.; LaMarche, M.; Hirose, T.; Brouard, I.; Xian, M.; Sundermann, K. F.; Shaw, S. J.; Burlingame, M. A.; Horwitz, S. B.; Myles, D. C. *Org. Lett.* **2005**, *7*, 311−314. (d) Shaw, S. J.; Sundermann, K. F.; Burlingame, M. A.; Myles, D. C.; Freeze, B. S.; Xian, M.; Brouard, I.; Smith, A. B., III. *J. Am. Chem. Soc.* **2005**, *127*, 6532−6533.

(12) Smith, A. B., III; LaMarche, M.; Falcone-Hindley, M. *Org. Lett.* **2001**, *3*, 695−698.

(13) A similar, albeit not identical solution conformation of (+)-discodermolide has been proposed by Synder et al.; see: Synder, J. P.; Nevins, N.; Cicero, D. O. *J. Am. Chem. Soc.* **2000**, *122*, 724−725.

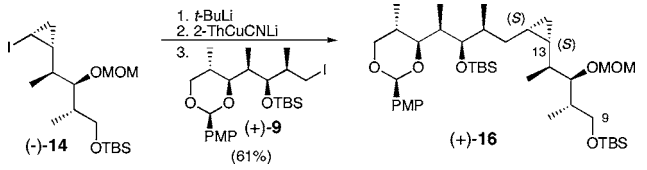
Scheme 2



gratifyingly furnished a single cyclopropyl iodide (+)-**12** in 71% yield.[15,16] The stereochemical outcome was tentatively assigned as 13*R*,14*R*, based on a likely reactive conformation imposed by $A^{1,3}$ interactions, in conjunction with the stereogenicity at C(12). Protection of the secondary hydroxyl as the MOM ether, followed by DDQ removal of the PMB moiety and reprotection of the primary hydroxyl as the TBS ether, furnished cyclopropyl iodide (−)-**14** in excellent overall yield. To verify the stereochemistry, camphanic ester (−)-**15** was prepared, crystallized, and analyzed by X-ray diffraction (see ORTEP in Scheme 2).

With (+)-**9**[10] and (−)-**14** in hand, we explored their union initially by palladium(0)-catalyzed cross-coupling. To this end, alkyl iodide (+)-**9** was converted to the trialkyl boronate by lithiation, followed by addition of *B*-methoxy-9-BBN.[10] Treatment with the cyclopropyl iodide (−)-**14**, under the modified Suzuki conditions developed by Charette,[17] however, resulted in none of the desired product. Traditional alkylation methods likewise proved unsuccessful; only complex product mixtures were obtained. Ultimately, we discovered that the 2-thienyl cyanocuprate derived from (−)-**14**[18] underwent clean alkylation to provide (+)-**16** in 61% yield (Scheme 3). Success with this transformation was

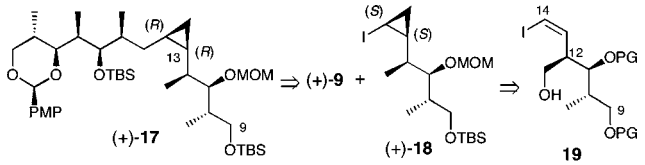
Scheme 3



critically dependent upon rigorous removal of oxygen to avoid oxidative coupling products.

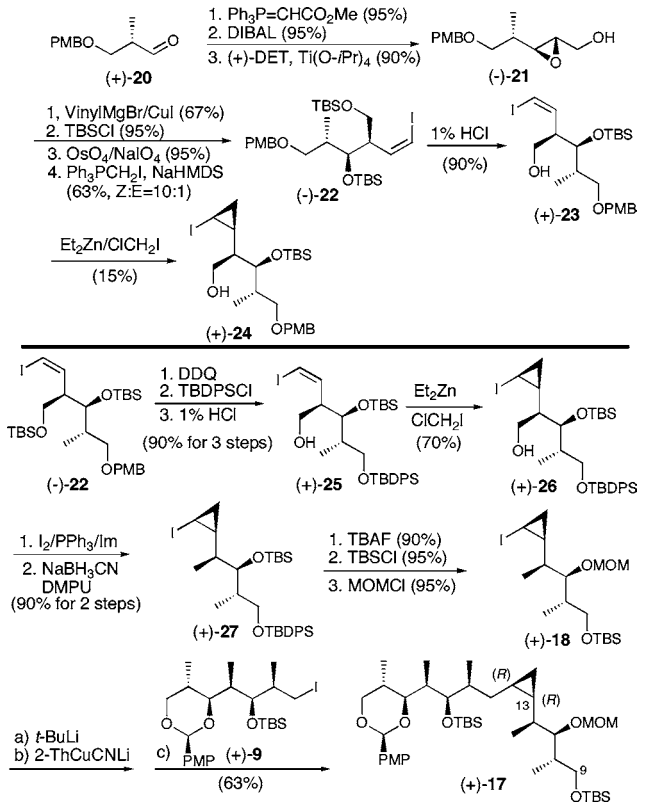
Having successfully constructed the C(13,*S*)-C(14,*S*) cyclopropyl fragment (+)-**16**, we turned to the synthesis of the diastereomer (+)-**17** (Scheme 4). Based on our experience with (+)-**16**, we reasoned that (+)-**17** should be available from (+)-**9** and the C(13,*S*)-C(14,*S*) cyclopropyl iodide (+)-**18**. To introduce the requisite cyclopropane configuration, vinyl iodide **19**, bearing a hydroxymethyl group at C(12), was selected as the precursor.

Scheme 4



Toward this end, known aldehyde (+)-**20**[8a] (Scheme 5) was converted to epoxy alcohol (−)-**21** according to a known three-step sequence.[19] Conversion to vinyl iodide (−)-**22** then entailed treatment with vinylmagnesium bromide in the presence of CuI, followed by bis-TBS protection, oxidative-

Scheme 5



was converted to epoxy alcohol (−)-**21** according to a known three-step sequence.[19] Conversion to vinyl iodide (−)-**22** then entailed treatment with vinylmagnesium bromide in the presence of CuI, followed by bis-TBS protection, oxidative-

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(15) Denmark, S. E.; Edwards, J. P. *J. Org. Chem.* **1991**, *56*, 6974−6981.

(16) Other conditions (cf. Simmons−Smith reaction employing the Furukawa or Shi variants) led either to no reaction or to low yields; see: (a) Furukawa, J.; Kawabata, N.; Nishimura, J. *Tetrahedron* **1968**, *24*, 53−58. (b) Yang, Z.; Lorenz, J. C.; Shi, Y. *Tetrahedron Lett.* **1998**, *39*, 8621−8624.

(17) (a) Charette, A. B.; Giroux, A. *J. Org. Chem.* **1996**, *61*, 8718−8719. (b) Charette, A. B.; De Freitas-Gil, R. P. *Tetrahedron Lett.* **1997**, *38*, 2809−2812.

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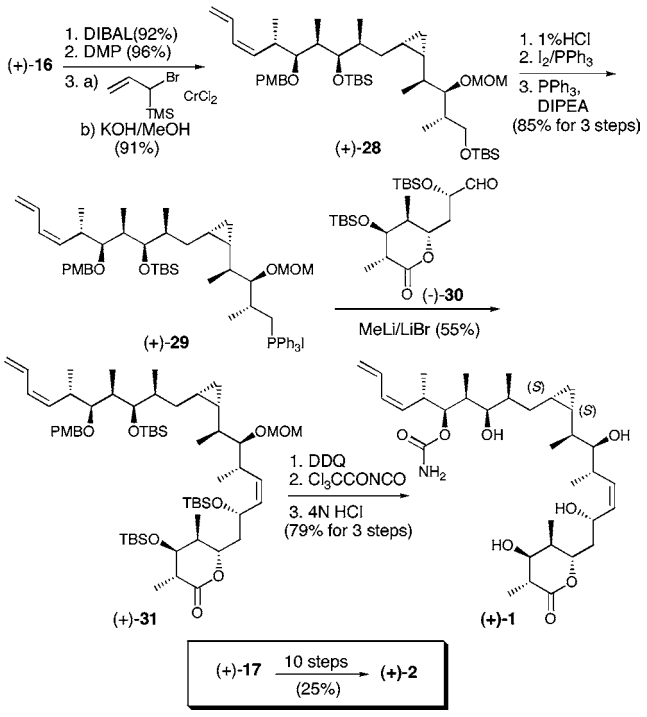
cleavage of the terminal olefin, and Wittig reaction using the Zhao protocol;[20] (−)-**22** was obtained in 38% yield (four steps) with a *Z*/*E* selectivity of 10:1. Selective removal of the primary TBS group next furnished (+)-**23**, which was subjected to cyclopropanation to afford the desired product (+)-**24**, albeit in low yield (~15%).

Reasoning that the low efficiency was due to the PMB group, vinyl iodide (−)-**22** was converted to the corresponding TBDPS ether (+)-**25** via an efficient (90%) three-step sequence (DDQ, TBDPSCl/imidazole, 1% HCl/EtOH). Hydroxyl-directed cyclopropanation, again employing the conditions of Denmark et al.,[15] provided (+)-**26** as a single diastereomer in 70% yield. To complete construction of cyclopropyl iodide (+)-**18**, removal of the primary hydroxyl group was now required. We immediately ruled out the Barton−McCombie or related radical-based protocols given the likely effect on the cyclopropyl iodide functionality. After some effort, we were pleased to uncover a high-yielding, two-step deoxygenation protocol entailing iodination (I_2/Ph_3P, 95% yield) followed by selective deiodination using a combination of $NaBH_3CN$ and DMPU[21] (95% yield). Attempts to couple (+)-**27** with (+)-**9,** however, employing the same higher order cuprate as for (+)-**16**, proved unsuccessful. Reasoning that the difference in the two systems was the pattern of protecting groups, (+)-**27** was converted to (+)-**18** and then subjected to the same cuprate-coupling protocol. Cyclopropane (+)-**17** was obtained in 63% yield.

Having assembled both diastereomeric cyclopropanes (+)-**16** and (+)-**17**, we were poised to complete the synthesis of **1** and **2** (Scheme 6). Reduction of the acetal in (+)-**16** with DIBAL furnished the corresponding primary alcohol, which in turn was subjected to Dess−Martin periodinane oxidation[22] and installation of the terminal diene via the Paterson two-step, one-pot protocol.[23] The desired TBS ether (+)-**28** was then further elaborated to the corresponding Wittig salt (+)-**29** employing conditions similar to that reported in our fourth-generation total synthesis of (+)-discodermolide.[10] Wittig union with aldehyde (−)-**30**, removal of the secondary PMB group, and installation of the carbamate at C(19), followed by global deprotection completed construction of (+)-13*S*,14*S*-cyclopropyldiscodermolide (**1**). In a similar fashion, (+)-**17** was advanced through the same synthetic sequence to furnish (+)-13*R*,14*R*-cyclopropyldiscodermolide (**2**) with a similar overall yield (see the Supporting Information for experimental details).

Scheme 6



Biological evaluation of (+)-**1** and (+)-**2** revealed the general trend, as observed for 14-normethyldiscodermolide analogues, of relative inactivity against the NCI/ADR multidrug-resistant cell line (Table 1). However, the cytotoxicities in the MCF-7 and SKOV-3 lines proved comparable to that of (+)-14-normethyldiscodermolide (**4**), while activity in the A549 cell line was somewhat reduced. Taken together, these results suggest that the relative geometry of the cyclopropane ring appears to have little impact on bioactivity vis-à-vis (+)-14-normethyldiscodermolide (**4**).

Table 1. Cytotoxicity Observed for Analogues (+)-**1** and (+)-**2**

	cytotoxicity IC_{50}, nM			
	MCF-7	NCI/ADR	A549	SKOV-3
(+)-**1**	46	4000	320	110
(+)-**2**	38	4000	210	70
(+)-**3**	14	180	29	54
(+)-**4**	34	>1000	94	84

In summary, we have achieved the total synthesis of two C(13)−C(14) cyclopropane analogues of discodermolide. Highlights of the syntheses include highly stereoselective, hydroxyl-directed cyclopropanations of vinyl iodide substrates and efficient higher order cuprate-mediated cross-coupling reactions between cyclopropyl iodides and alkyl iodides. The cell growth inhibitory activities of (+)-**1** and (+)-**2** imply that neither orientation of the cyclopropane ring completely substitutes for the C(14) methyl found in (+)-discodermolide, suggesting further that the bioactive conformation is governed, at least in part, by $A^{1,3}$-strain.

Acknowledgment. Financial support was provided by the National Institutes of Health (Institute of General Medical Sciences) through Grant No. GM-29028.

Supporting Information Available: Representative procedures, spectral data, and analytical data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL051691C

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