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A Strategy for Exploiting the Pseudosymmetry of the C1–C13 Stretch of Discodermolide

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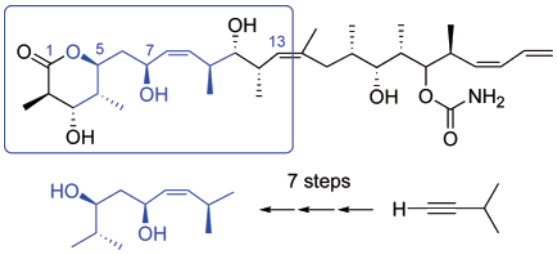
ABSTRACT



The pseudo-C_2 symmetry of the C1 to C13 stretch of the discodermolide structure offers a potential strategic advantage for synthetic design. Two approaches based on this recognition were devised, and one was shown to be effective in a model series.

Discodermolide (**1**), a natural product isolated from the Caribbean sponge *Discodermia dissoluta* in 0.002% yield, originally attracted attention because of its immunosuppressive and antileukemic activities.[1] Subsequent studies revealed that it stabilizes microtubules, promoting cell cycle arrest.[2] The activity of the microtubule-stabilizing drugs taxol, the epothilones, and discodermolide has been attributed to concentration-dependent aneuploidy associated with aberrant mitosis.[3] Of the microtubule-binding drugs, discodermolide is particularly interesting because it maintains activity against multidrug resistant (MDR) cell lines including those of the breast, ovary, and colon.[4] Because of its unique tubulin binding properties that suggest a future role in cancer therapy and because it is available only in minute quantities from the sea sponge, (+)-discodermolide (**1**) has become an important target for total synthesis.

To date, seven groups have reported the completion of discodermolide syntheses,[5,6] and other groups have described significant progress en route to the target. All of the syntheses

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are remarkable for providing solutions to the multiple problems presented by the structure.

Although at least two of the total syntheses have provided (+)-discodermolide for testing and are described as practical, all require more than 20 steps in the longest linear sequence and more than 30 steps in total. Partial syntheses from other groups are of lengths suggesting comparable total numbers of steps at completion.[7] A "hybrid synthesis," carried out on a 60-g scale, demonstrates both the power of modern methodology and the formidable demands of a large-scale preparation.[8]

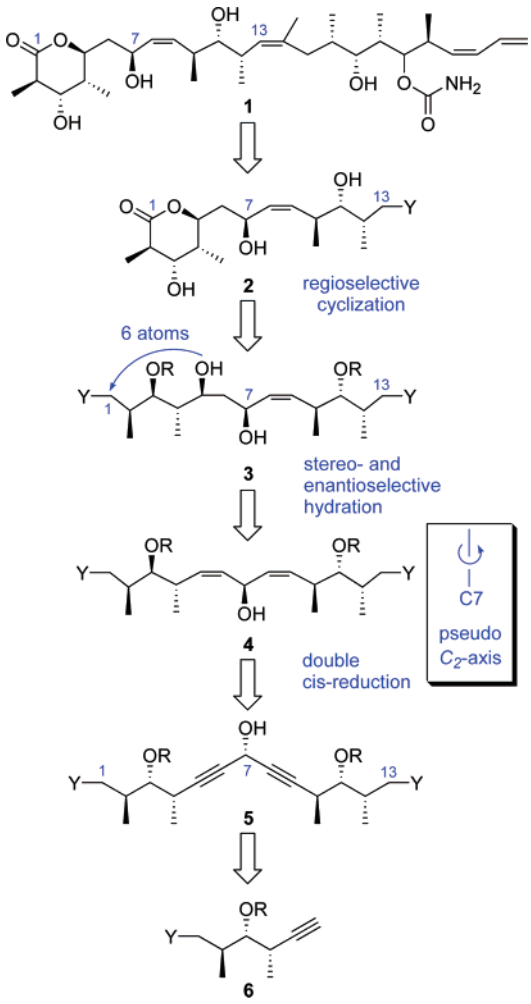
Solving a problem of the complexity of (+)-discodermolide in more than 20 steps is not inconsistent with the state of the art. Indeed the reported total syntheses and approaches are elegant in concept, and they have served as the basis for the development of several innovative and generally useful methods. Nevertheless, in light of the importance of the target as a potential drug and its scarcity, as well as the continuing challenge to develop new and better strategies and methods, we contemplated the discovery of a route that might contribute to improvements in the overall efficiency of a chemical synthesis.

We recognized that a short synthesis of a molecule as complex as (+)-discodermolide would require a convergent strategy based on large building blocks. Like other researchers, we found the C13−C14 double bond to be an attractive disconnect (Scheme 1). Thus, we hoped to construct a synthon equivalent to species **2** by a short scheme. In contemplating this C1 to C13 moiety, we perceived the existence of C_2 symmetry of equivalent functional group patterns. This recognition has not been noted previously.

The large building block **2** could be the product of a cyclization that differentiated equivalent functional groups Y at the termini of the linear **3** (i.e., **2** → **3**). Furthermore, in diol **3**, the functionality at C5/C6 is the result of "hydration" of an olefinic bond, related by symmetry to the C8/C9 olefinic bond (i.e., **3** → **4**). The C2/C3/C4 stereotriad in dienol **4** or its precursor diynol **5** is related by a rotation to the C12/C11/C10 triad. Aside from the C7 chiral center, diynol **5** has a C_2 axis; diynol **5** and its C7 epimer are the same compound. We imagined that diynol **5** might be obtained from the chiral triad **6**, readily available by the method of Marshall.[9]

To establish the feasibility of elaborating diol **3** from the pseudosymmetric **5**, we examined possible sequences in a

Scheme 1. Hidden Symmetry in the C1 to C13 Stretch of Discodermolide Suggests a Synthetic Strategy



truncated, model series. Thus we prepared diynol **10** and tested methods for its conversion to chiral, anti diol **7**. Initially, we considered extending the catalytic, asymmetric intramolecular hydrosilation/oxidation methodology of Tamao[10] to the desymmetrization of dienol **10** (Scheme 2).

Substrates for the hydrosilation experiments were prepared by the three-step sequence shown (Scheme 2). Lithiated 3-methyl-1-butyne added to methyl formate to give the key model diynol **11**. Lindlar hydrogenation gave the *cis,cis*-dienol **10**, which was readily derivatized to the desired substrates. In experiments with four silyl ethers **9a**−**d** and three hydrosilation catalysts,[11] we recovered either starting material or, after extended times, material in which one of the cis double bonds had isomerized. In light of the reactivity of related systems,[12] the stability of our substrate is surprising.

(6) For a review of five of these, see: Paterson, I.; Florence, G. J. *Eur. J. Org. Chem.* **2003**, 2193−2208.

(7) (a) BouzBouz, S.; Cossy, J. *Org. Lett.* **2003**, *5*, 3029−3031 and **2001**, *3*, 3995−3998. (b) Arefolov, A.; Panek, J. S. *Org. Lett.* **2002**, *4*, 2397−2400. (c) Kiyooka, S.-i.; Shahid, K. A.; Goto, F.; Okazaki, M.; Shuto, Y. *J. Org. Chem.* **2003**, 68, 7967−7978.

(8) A remarkable "large-scale synthesis" of (+)-discodermolide monohydrate has been reported by a Novartis group. This preparation, termed a "hybridized Novartis−Smith−Paterson" route, requires 39 steps (26 steps in the longest linear sequence) and 17 chromatographic purifications. Material obtained from this scheme is said to be sufficient for early-stage human clinical trials. See: Mickel, S. J.; Niederer, D.; Daeffler, R.; Osmani, A.; Kuesters, E.; Schmid, E.; Schaer, K.; Gamboni, R.; Chen, W.; Loeser, E.; Kinder, F. R., Jr.; K., K.; Prasad, K.; Ramsey, T. M.; Repic, O.; Wang, R.-M.; Florence, G.; Lyothier, I.; Paterson, I. *Org. Process Res. Dev.* **2004**, *8*, 122−130 and previous papers in the series.

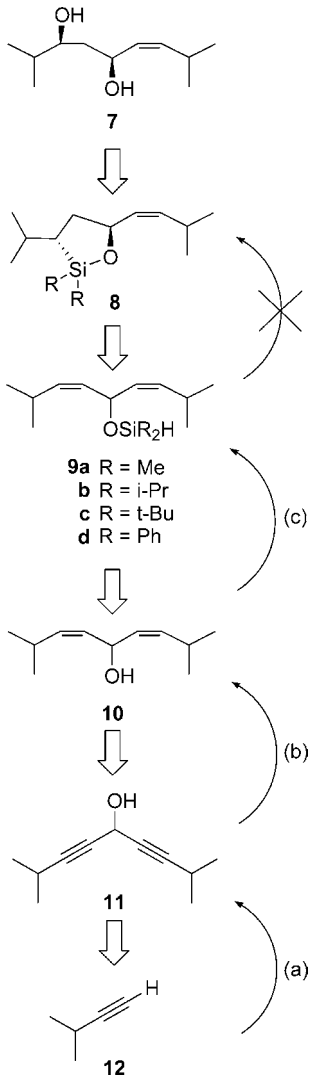
(9) Marshall, J. A.; Johns, B. A. *J. Org. Chem.* **2000**, *65*, 1501−1510.

(10) Tamao, K.; Tohma, T.; Inui, N.; Nakayama, O.; Ito, Y. *Tetrahedron Lett.* **1990**, *31*, 7333−7336.

(11) (a) [(*R*,*R*)-Me-DUPHOS-Rh]BF_4: see ref 12, below. (b) $[RhCl(nbd)]_2$ + (*S*,*S*)-DIOP: see ref 10, above. (c) $(Ph_3P)_3RhCl$.

(12) Bergens, S. H.; Noheda, P.; Whelan, J.; Bosnich, B. *J. Am. Chem. Soc.* **1992**, *114*, 2121−2128. (b) Bergens, S. H.; Noheda, P.; Whelan, J.; Bosnich, B. *J. Am. Chem. Soc.* **1992**, *114*, 2128−2135. (c) Bosnich, B. *Acc. Chem. Res.* **1998**, *31*, 667−674.

Scheme 2. Attempted Desymmetrization of Dienol **10** Based on Intramolecular Hydrosilation[a]



[a] Reagents and conditions: (a) MeLi, THF, HCO_2Me, 88%; (b) H_2, Lindlar cat., quinoline, 99%; (c) DMAP, $ClSiR_2H$, CH_2Cl_2, 2 days, 75%−quantitative.

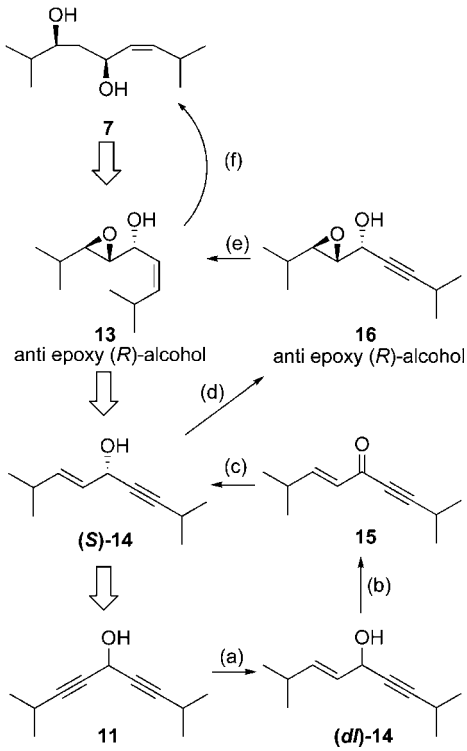
However, in any event, isomerization[13] of the olefinic bond abrogates the stereoselectivity of this approach.

Variations on our original design were therefore entertained. Regio- and stereospecific hydration of trans allylic alcohols to anti 1,3-diols can be accomplished by Sharpless asymmetric epoxidation (SAE) followed by Red-Al epoxide-opening (see **7** → **13** → (*S*)-**14**). One can therefore consider the preparation of diol **7** from diynol **11** via chiral enynol (*S*)-**14**. We have now demonstrated this model desymmetrization (Scheme 3).

Achiral diynol **11** was converted to the chiral trans enynol (*S*)-**14** in three steps. Monoreduction of the symmetric diynol **11** with Red-Al afforded (*dl*)-enynol **14**. PDC oxidation to

(13) In his mechanistic studies[12] Bosnich had found that cis/trans isomerization of 4-phenyl-2-propen-1-ol was more rapid than intramolecular silylation with the $[Rh(binap)]^+$ catalyst.

Scheme 3. Desymmetrization of Achiral Alcohol **11** to Chiral Diol **7**[a]



[a] Reagents and conditions: (a) Red-Al (2 equiv), THF, 90%; (b) PDC, 4 Å molecular sieves, CH_2Cl_2, 76%; (b) (*S*)-CBS, $BH_3{\cdot}SMe_2$, THF, 85%; (d) $Ti(OiPr)_4$, D-(−)-diisopropyl tartrate, *t*-BuOOH, 4 Å molecular sieves, CH_2Cl_2, 92%; (e) H_2, Lindlar cat., quinoline, MeOH, 78%; (f) Red-Al, THF, 70%.

the volatile enynone **15** followed by reduction with the (*S*)-CBS reagent and borane dimethyl sulfide[14] provided the chiral enynol (*S*)-**14** with 86% ee.[15] In early experiments, yields for individual steps applied in the model sequence were highly variable, a quality attributed to the volatility and water solubility of the low molecular weight intermediates. However, optimized procedures afforded good to excellent yields for each step (see Supporting Information).

Further functionalization was initiated by SAE. Treatment of alcohol (*S*)-**14** with the reagent from D-(−)-diisopropyl tartrate provided epoxy alcohol **16** in 92% yield with an expected enrichment of the ee % of the major anti epoxy diastereomer.[16] In addition to containing a small amount of

(14) (a) Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551−5553. (b) Parker, K. A.; Ledeboer, M. W. *J. Org. Chem.* **1996**, *61*, 3214−3217. (c) Garcia, J.; Lopez, M.; Romeu, J. *Synlett* **1999**, *4*, 429−431.

(15) *S*)-2-Methyl-CBS-oxaborolidine (from Aldrich) has a ≥94% enantiomeric purity.

(16) On the basis of enantiomeric and diastereomeric ratios reported by McDonald for epoxidation of a similar enynol prepared from the (*R*)-CBS reagent, we expected Sharpless oxidation of our alcohol (*S*)-**14** (93% of the CBS product) with the reagent from D-(−)-diisopropyl tartrate to provide a mixture of anti epoxy alcohol **16** and its syn diastereomer in a ratio close to 99:1. We expected these conditions to convert (*R*)-**14**, 7% of the CBS product, to a 1:1 mixture of the syn epoxy alcohol and the enantiomer of **16**. See: McDonald, F. E.; Reddy, K. S.; Diaz, Y. *J. Am. Chem. Soc.* **2000**, *122*, 4304−4309 and Supporting Information.

its enantiomer, the alcohol **16** was presumed to contain small amounts of its diastereomers. Diastereomers were not easily removed at this stage. However, *syn*- and *anti*-epoxy allylic alcohols were readily separated after the next step of the sequence.

Hydrogenation of the Sharpless product under Lindlar conditions gave a mixture of allylic alcohols. The major anti epoxy alcohol, **13**, separated from the minor syn product[17] (presumably both enantiomers; see Supporting Information) and from residual quinoline by chromatography on silica gel, was obtained in 78% yield. A Mosher ester analysis showed this material to be a single enantiomer within the limits of detection by analysis with ^{1}H NMR at 600 MHz.[18,19]

Completion of the model sequence was effected by treatment of epoxy alcohol **13** with Red-Al. Regiospecific opening of the epoxide provided a single diasteromeric diol, chiral **7**, in 70% yield.[20]

(17) The low field region of the ^{1}H NMR spectrum of epoxy alcohol **13** exhibited signals at 5.45 (t, J = 10.3 Hz, 1H), 5.18 (t, J = 10.3 Hz, 1H), 4.65 (d, J = 8.3 Hz, 1 H). In the same region, its syn diastereomer showed 5.42 (t, J = 10.5 Hz, 1H), 5.36 (t, J = 10.5 Hz, 1H), 4.26 (bs, 1H).

(18) The low field region of the ^{1}H NMR spectrum of the (*R*)-Mosher ester of **13** (from the (*S*)-Mosher acid chloride) exhibited clear signals at 5.82 (dd, J = 9.5, 4.2 Hz, 1H), 5.57 (t, J = 10.5 Hz, 1H), 5.15 (t, J = 10.3 Hz, 1H). This pattern was resolved from and easily distinguished from that of the (*S*)-Mosher ester of **13**: 5.79 (dd, J = 9.8, 4.8 Hz, 1H), 5.57 (dd, J = 10.7, 9.8 Hz, 1H), 5.27 (t, J = 10.7 Hz, 1H).

(19) The anti epoxy alcohol **13** was contaminated with a small amount of an impurity that appeared to contain a trans olefin.

The sequence from alkyne **12** to the chiral diol **7** represents a concise construction of the C5 to C9 functional group display of (+)-discodermolide. It establishes the groundwork for the conversion of a simple stereotriad-bearing alkyne (general structure **6**) to an advanced intermediate for discodermolide synthesis (general structure **3**) in seven steps. We are continuing to investigate the potential advantages of a desymmetrization approach to the synthesis of valuable polyketide building blocks.

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Supporting Information Available: Experimental procedures and spectroscopic and analytical data for all new compounds; structure proof for diol **7** and its diastereomers. This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) Full details of structure assignment and characterization of anti diol **7** are contained in Supporting Information.