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Large-Scale Synthesis of the Anti-Cancer Marine Natural Product (+)-Discodermolide. Part 1: Synthetic Strategy and Preparation of a Common Precursor

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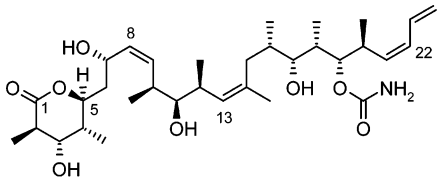
Abstract:

The synthetic strategy for producing multigram quantities of (+)-discodermolide (1) using a hybridized Novartis−Smith−Paterson synthetic route via common precursor 3 is described. In the first part of this five-part series, we present a multikilogram preparation of α-methyl aldehyde 10 from Roche ester, its *syn*-aldol reaction with Evans boron enolate, removal of the chiral auxiliary, and the preparation of Weinreb amide 3 (Smith common precursor). The common precursor was produced without any chromatography.

Introduction

A small, but structurally diverse collection of naturally occurring non-taxane microtubule-stabilizing agents (MTS) has been discovered over the past decade. These include the epothilones (EPO), eleutherobin, laulimalide, and discodermolide. (+)-Discodermolide (**1**) is a novel polyketide natural product first isolated from extracts of the marine sponge *Discodermia dissoluta* by researchers at Harbor Branch Oceanographic Institution (HBOI).[1] Discodermolide stabilizes microtubules faster and more potently than any of the other known MTS agents and is a potent inhibitor of tumor cell growth in vitro, including paclitaxel (PTX)- and EPO-resistant cells.[2] Discodermolide also demonstrates significant human tumor growth inhibition in hollow fiber and xenograft mouse models (including PTX-resistant tumors).[3] Discodermolide is currently undergoing phase I clinical trials.



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Structurally, discodermolide consists of a linear polypropionate chain containing 13 stereocentres, six of which are hydroxyl-bearing, with one of these esterified as a δ-lactone (C5) with another as a carbamate (C19). It also features seven methyl-bearing stereocentres and three *Z*-configured alkenes, one of these being part of the terminal diene unit. Also present in the structure is a common stereo triad (methyl, hydroxyl, and methyl) that is repeated three times. The Schreiber group has synthesized both antipodes, thus establishing the absolute configuration of **1**.[4] Since the publications of Schreiber's synthesis, several total syntheses[5−8] and

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(1) (a) Gunasekera, S. P.; Gunasekera, M.; Longley, R. E.; Schulte, G. K. *J. Org. Chem*. **1990**, *55*, 4912, Correction *J. Org. Chem*. **1991**, *56*, 1346. (b) Gunasekera, S. P.; Pomponi, S. A.; Longley, R. E.; U. S. Patent 5,840,750, November 24, 1998. (c) Gunasekera, S. P.; Paul, G. K.; Longley, R. E.; Isbrucker, R. A.; Pomponi, S. A. *J. Nat. Prod*. **2002**, *65*, 1643.

(2) (a) Jordan, M. A. *Curr. Med. Chem.: Anti-Cancer Agents* **2002**, *2*, 1. (b) Altmann, K. H. *Curr. Opin. Chem. Biol*. **2001**, *5*, 424. (c) He, L. F.; Orr, G. A.; Horwitz, S. B. *Drug Discovery Today* **2001**, *6*, 1153. (d) He, L.; Chia-Ping, H. Y.; Horwitz, S. B. *Mol. Cancer Ther*. **2001**, *1*, 3. (e) Kowalsky, R. J.; Giannakakou, P.; Gunasekera, S. P.; Longley, R. E.; Day, B. W.; Hamel, E. *Mol. Pharmacol*. **1997**, *52*, 613. (f) Kalesse, M. *ChemBiochem*. **2000**, *1*, 171. (g) Longley, R. E.; Caddigan, D.; Harmody, D.; Gunasekra, M.; Gunasekra, S. P. *Transplantation* **1991**, *52*, 650. (h) Longley, R. E.; Caddigan, D.; Harmody, D.; Gunasekra, M.; Gunasekra, S. P. *Transplantation* **1991**, *52*, 656. (i) Martello, L. A.; LaMarche, M. J.; He, L.; Beauchamp, T. J.; Smith, A. B.; Horwitz, S. B. *Chem. Biol*. **2001**, *8*, 843.

(3) Kinder, F. R., Jr.; Bair, K. W.; Chen, W.; Florence, G.; Francavilla, C.; Geng, P.; Gunasekera, S.; Guo, Q.; Lassota, P. T.; Longley, R. E.; Palermo, M. G.; Paterson, I.; Pomponi, S.; Ramsey, T. M.; Rogers, L.; Sabio, M.; Sereinig, N.; Sorensen, E.; Wang, R. M.; Wright, A. Synthesis and Antitumor Activity of Analogues of the Novel Microtubule Stabilizing Agent Discodermolide. In *Abstracts of Papers*; 224th American Chemical Society National Meeting, Boston, MA, August 18−22, 2002; American Chemical Society: Washington, DC, 2002; MEDI-236.

(4) (a) Nerenberg, J. B.; Hung, D. T.; Sommers, P. K.; Schreiber, S. L. *J. Am. Chem. Soc*. **1993**, *115*, 12621. (b) Hung, D. T.; Nerenber, J. B.; Schreiber, S. L. *J. Am. Chem. Soc*. **1996**, *118*, 11054.

(5) (a) Smith, A. B.; Qui, Y.; Jones, D. R.; Kobayashi, K. *J. Am. Chem. Soc*. **1995**, *117*, 12011. (b) Smith, A. B.; Kaufmann, M. D.; Beauchamp, T. J.; LaMarche, M. J.; Arimoto, H. *Org. Lett*. **1999**, *1*, 1823; Additions and corrections *Org. Lett*. **2000**, *2*, 1983. (c) Smith, A. B.; Beauchamp, T. J.; LaMarche, M. J.; Kaufmann, M. D.; Qui, Y.; Arimoto, H.; Jones, D. R.; Kobayashi, K. *J. Am. Chem. Soc*. **2000**, *112*, 8654.

(6) Harried, S. S.; Yang, G.; Strawn, M. A.; Myles, D. C. *J. Org. Chem*. **1997**, *62*, 6098.

(7) Marshall, J. A.; Johns, B. A. *J. Org. Chem*. **1998**, *63*, 7885.

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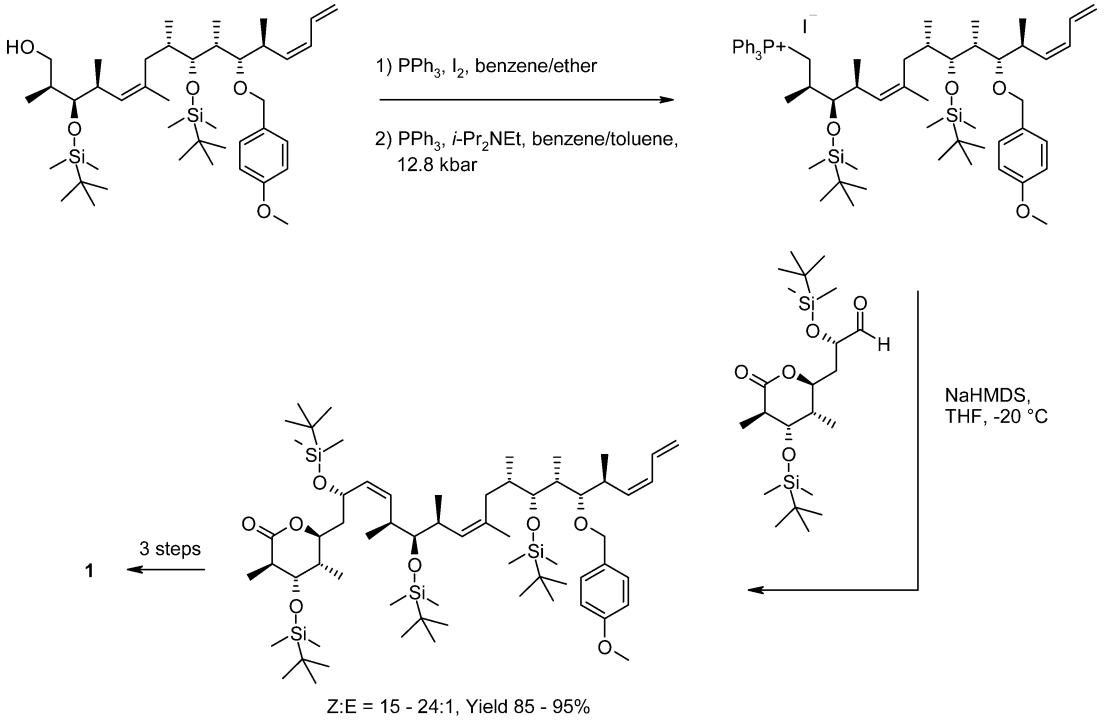
Scheme 1. **High-pressure phosphonium salt formation**



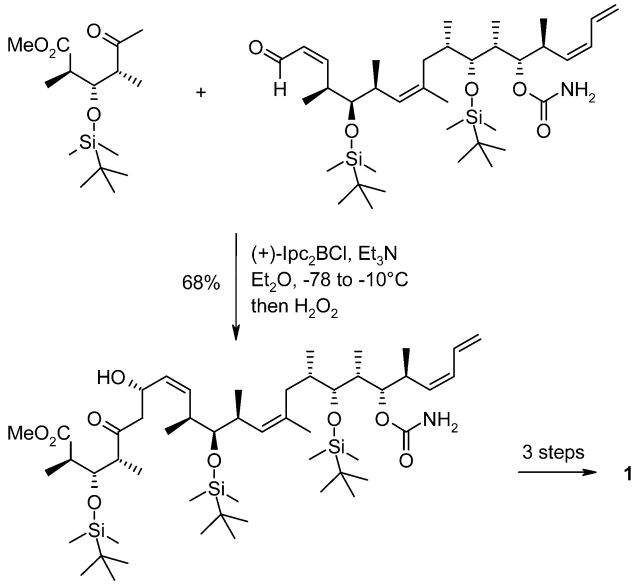
preparations of various discodermolide fragments[9] have appeared in the literature. A useful review of the available synthetic approaches has recently been published.[10]

The compound supply for development cannot be met through the isolation and purification of discodermolide from *Discodermia* sp. (which must be harvested using manned submersibles). Attempts to reproducibly isolate a discodermolide-producing microorganism for fermentation have not been successful to date. Therefore, all discodermolide used for late preclinical research and development activities as well as for the ongoing clinical trial has been supplied by total synthesis.

The synthetic route used for the preparation of multigram amounts of discodermolide was envisaged as a hybrid synthesis which advantageously incorporated the best features of the published syntheses by Smith and Paterson (vide infra). Selection of these two syntheses was made after a detailed analysis of every publication on discodermolide and related syntheses.

Smith's publication of the one-gram synthesis of discodermolide predisposed our selection, and we started practicing this route because the starting material [(*S*)-Roche ester

Scheme 2. **Last steps of Paterson's route**

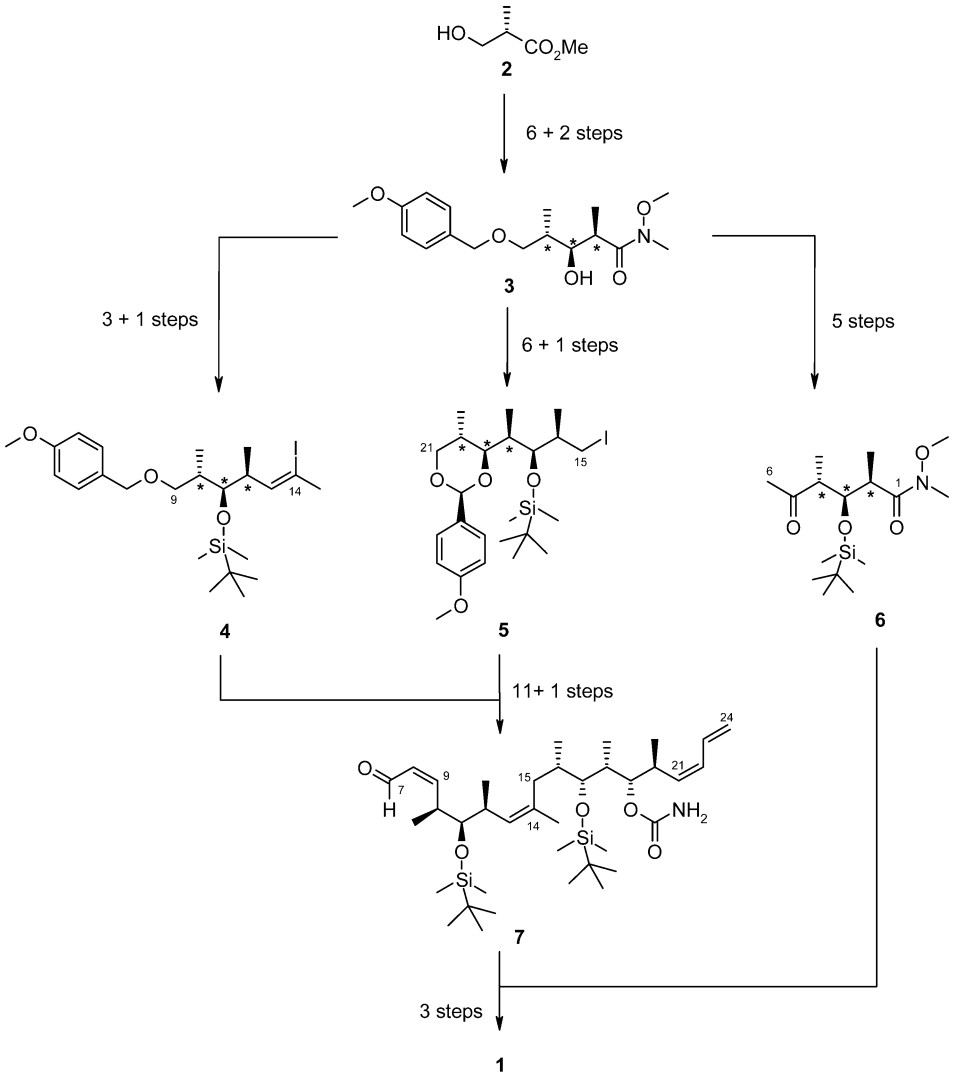


2] for this approach was readily available. It was clear from the beginning of this venture that there was a need for changing some chemistry in the late steps; for example, the high-pressure reaction (12.8 kbar) used for introducing the C_{8-9} *cis*-double bond (Scheme 1) was not practicable on large scale (added in revision: Professor Smith has recognized this limitation of his synthesis and has recently described a solution to this problem. Smith, A. B.; Freeze, B. Scott; Brouard, I.; Hirose, T. *Org. Lett*. **2003**, *5*, 4405−4408). On the other hand, Paterson's reagent-controlled, chiral boron enolate methodology (Scheme 2) fit into our strategy. The Paterson aldehyde **7** could be obtained via an advanced intermediate that was described by Smith.[5c] Thus, it seemed logical to us that a combination of these two approaches

(9) For examples, see: (a) Francavilla, C.; Chen, W.; Kinder, F. R., Jr. *Org. Lett.* **2003**, *5*, 1233−1236. (b) Arefolov, A.; Panek, J. S. *Org. Lett*. **2002**, *4*, 2397. (c) Shahid, K. A.; Mursheda, J.; Okazaki, M.; Shuto, Y.; Goto, F.; Kiyooka, S. *Tetrahedron Lett.* **2002**, *43*, 6377. (d) Shahid, K. A.; Li, Y. N.; Okazaki, M.; Shuto, Y.; Goto, F.; Kiyooka, S. *Tetrahedron Lett*. **2002**, *43*, 6373. (e) Miyazawa, M.; Oonuma, S.; Maruyama, K.; Miyashita, M. *Chem. Lett*. **1997**, 1191. (f) Miyazawa, M.; Oonuma, S.; Maruyama, K.; Miyashita, M. *Chem. Lett.* **1997**, 1193. (g) BouzBouz, S.; Cossy, J. *Org. Lett.* **2001**, *3*, 3995. (h) Golec, J. M. C.; Jones, S. *Tetrahedron Lett*. **1993**, *34*, 8159. (i) Evans, P. L.; Golec, J. M. C.; Gillespie, R. J. *Tetrahedron Lett*. **1993**, *34*, 8163. (j) Golec, J. M. C.; Gillespie, R. J. *Tetrahedron Lett*. **1993**, *34*, 8167. (k) Marshall, J. A.; Lu, Z. H.; Johns, B. A. *J. Org. Chem*. **1998**, *63*, 817. (l) Yang, G.; Myles, D. C. *Tetrahedron Lett.* **1994**, *35*, 1313. (m) Yang, G.; Myles, D. C. *Tetrahedron Lett*. **1994**, *35*, 2503. (n) Paterson, I.; Schlapbach, A. *Synlett* **1995**, 498.

(10) Paterson, I.; Florence, G. J. *Eur. J. Org. Chem*. **2003**, *12*, 2193.

Scheme 3. **Novartis synthetic route to (+)-discodermolide**



could offer a viable opportunity to scale up the synthesis of **1**. The resulting hybridized synthetic approach for producing **1** is outlined in Scheme 3.

Our work progressed in three stages: proof of synthesis, preparation of a 6-g batch, and production of 60 g of (+)-discodermolide. The present five-part publication describes our experience with large-scale preparation of **1**. In Part 1, we discuss some of the problems we encountered, and the solutions we found in scaling up the preparation of **3**. In Part 2, we describe the conversion of this common intermediate into fragments C_{1-6} (**6**) and C_{9-14} (**4**). Part 3 describes the preparation of the C_{15-21} fragment (**5**). Part 4 relates to the preparation of fragment $C_{7-}C_{24}$ (**7**). Part 5 illustrates the linkage of fragments C_{1-6} and C_{7-24} and the final steps leading to the production of 60 g of **1**.

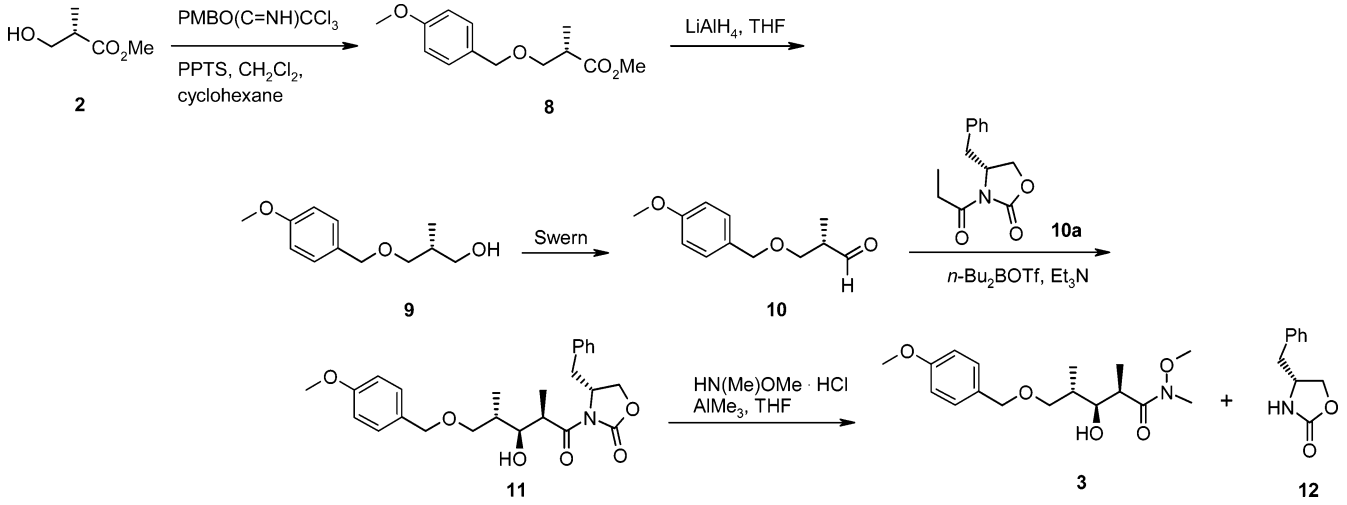
Results and Discussion

Smith's approach[5c] to **3** from Roche ester **2** is outlined in Scheme 4. This pathway was optimized by us into a more efficient route for the large-scale production of **3**.

Chiral Aldehyde. The formation of the 4-methoxybenzyl ether **8** from Roche ester **2** proceeded in > 98% yield, employing Smith's protocol. Reduction of **8** with lithium aluminium hydride was efficient; however, the workup proved problematic. Large quantities of aluminum salts were formed, which did not allow for efficient filtration (it required >24 h). Switching the reducing agent to lithium borohydride solved this problem and furnished alcohol **9** in >98% yield after acetic acid quench and extractive isolation. Conversion of **9** to **10** called for a Swern oxidation. This was not an option for us on large scale, since the formation of methyl sulfide (stench) as a byproduct was not environmentally friendly. This reagent was replaced by a simple, two-phase, TEMPO/bleach oxidation in dichloromethane, which afforded aldehyde **10** in quantitative yield. However, **10** was not stable for extended storage. Racemization of the stereogenic centre was observed within 2 days of storage, even at 0 °C. To overcome this hurdle, crude **10** was subjected to Evans' *syn*-aldol reaction without further purification.

Evans' *syn*-Aldol Reaction. Enolization of 3-propionyl-(*R*)-4-benzyloxazolidinone (**10a**) with dibutylboron triflate in the presence of triethylamine at 0 °C, followed by treatment of the resulting enolate with crude **10** at −78 °C, furnished alcohol **11** in 46−55% yield on a 20−25-kg scale. The success of this reaction was largely dependent on the quality of dibutylboron triflate. Aged reagent did not perform

Scheme 4. **Smith's synthesis of the common precursor**



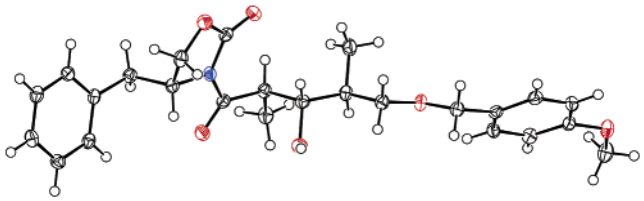


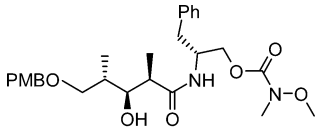
Figure 1. **Single-crystal X-ray structure of 11.**

well and resulted in low yield (<35%). This may be overcome by distillation of the reagent; however, a distillation is not practical for large-scale operation. On a 20−50-g scale in the lab, we routinely achieved yields of >75% for this aldol reaction, but we were unable to replicate it in the pilot plant. The reasons for this are still unclear. More work is required to achieve a completely robust and reproducible process. The acceptable quality of dibutylboron triflate especially needs to be better defined. A recent publication may be able to assist in solving this quality definition.[11]

The aldol reaction was completely stereoselective, and none of the undesired diastereoisomer was ever detected by us. The reaction can also be run at room temperature without detriment to the selectivity. In contrast to the published procedure, which purified **11** by chromatography, we were able to crystallize the aldol product **11** with 80% recovery. This was accomplished by dissolving the crude aldol adduct in a mixture of *n*-butanol and diisopropyl ether, followed by careful addition of heptane over an extended period of time to afford crystalline **11** of high purity; the structure was confirmed by single-crystal X-ray analysis (Figure 1).

Transamidation. The Smith approach employed trimethylaluminum-promoted transamidation of **11** into Weinreb amide **3**, which was a nice one-step conversion. However, trimethylaluminum was not an ideal choice of reagent for a large-scale plant operation due to its pyrophoric properties. We decided to replace it with triisobutylaluminum, which was safer and which had been utilized on an industrial scale in Ziegler−Natta processes. We found that the *N*,*O*-dimethylhydroxylamine/triisobutylaluminum complex (3.5 equiv) had reacted efficiently with **11** (1 equiv) at room temperature and produced the desired **3** in 75−80% yield, depending on the purity of **11**. Two-thirds of 4-benzyloxazolidinone **12** could be recovered by crystallization from the reaction mixture after workup. The purity of **3** obtained by this protocol was 85%. The remaining 15% was a series of minor byproducts: one being generated in this reaction (compound **13**), and the rest were impurities carried through the synthesis from preceding steps.

We studied this reaction by calorimetry and found that the addition of triisobutylaluminum to a suspension of *N*,*O*-dimethylhydroxylamine hydrochloride in THF was highly exothermic. It was noted that the resulting complex of triisobutylaluminum/*N*,*O*-dimethylhydroxylamine/THF was thermally unstable. According to DSC, this complex started to give off heat at 30 °C and reached the maximum at 140 °C, resulting in the release of a total of −406 kJ/kg of energy. The instability is presumably due to an aluminum-catalyzed polymerization reaction of tetrahydrofuran. Thus, in case of a cooling failure in the plant, the chance of a thermal runaway could be very high. The high risk in process safety made this process unfeasible for scale-up. To make this chemistry more amenable to the pilot plant, we investigated the following variations: inverse addition, alternative solvents, extending the addition times, and lowering the temperature. In all cases, we observed the formation of significant amount of byproduct **13**, attributed to the opening of the oxazolidinone ring. We were unable to define conditions which could minimize this competitive ring-opening reaction.



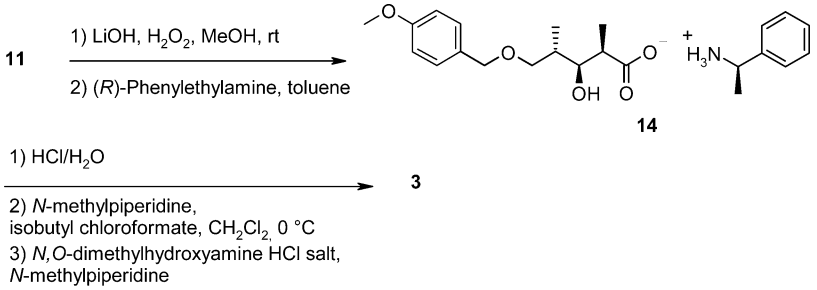
13

In view of these results, we decided to abandon the transamidation protocol and to investigate two other methods.

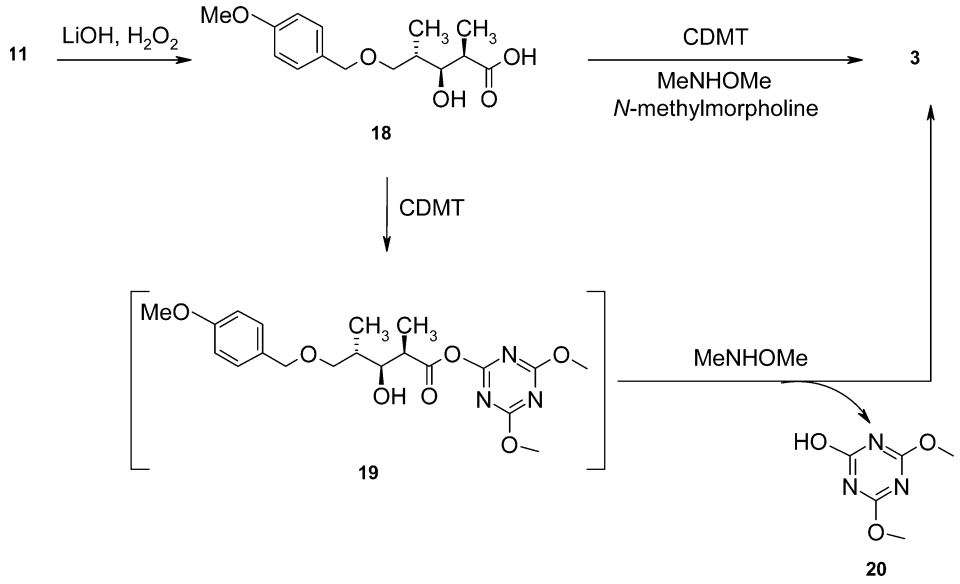
Amide Formation Employing Chloroformate. Formation of an amide bond from a carboxylic acid via a mixed anhydride was investigated as the first alternative (Scheme 5).

(11) Medina, J. R.; Cruz, G.; Cabrera, C. R.; Soderquist, J. A. *J. Org. Chem.* **2003**, *68*, 4631.

Scheme 5. **Synthetic route to 3 using isobutyl chloroformate**

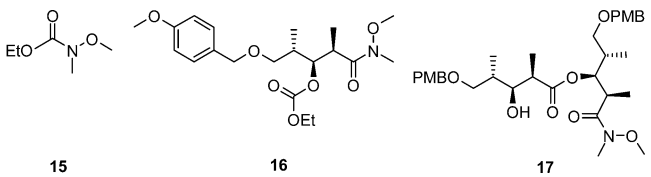


Scheme 6. **Alternative route to 3 using CDMT**

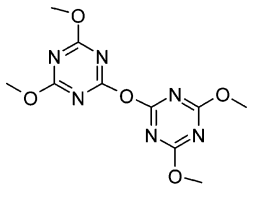


Without further purification, we proceeded to cleave the oxazolidinone by treating it sequentially with hydrogen peroxide and lithium hydroxide in a mixture of water and methanol. After workup, the resulting acid was isolated as a crystalline salt of (*R*)-2-phenylethylamine (**14)** in 84% yield from **11**. Crystallisation of the salt at this stage is the first purification carried out thus far in the synthesis and also serves to protect the rather unstable acid from decomposition. Chiral auxiliary **12** was easily recovered by crystallization without degradation of either chemical or enantiomeric purity (see Experimental Section).

After liberation of the acid, by treatment of the salt **14** with hydrochloric acid and extractive isolation, formation of a mixed anhydride with isobutyl chloroformate followed by reaction with *N*,*O*-dimethylhydroxylamine afforded Weinreb amide **3** in 75−80% yield. The choice of chloroformate was an important factor for the success of this process. The use of ethyl chloroformate resulted in the formation of several byproducts (**15**, **16**, and **17**). Replacing ethyl chloroformate with isobutyl chloroformate minimized the byproducts.



Amide Formation Employing CDMT. An alternative strategy of amide bond formation utilizing 2-chloro-4,6-dimethoxy-1,3,5-triazine (CDMT) as the coupling reagent was investigated (Scheme 6). CDMT had been used to activate a carboxylic acid by forming an activated triazine ester, which was subsequently coupled with an amine in the same pot to generate an amide.[12] Treating **11** with hydrogen peroxide and lithium hydroxide furnished acid **18** as an oil in 71% yield. After activation of **18** with CDMT in the presence of *N*-methylmorpholine, we found the resulting triazine ester **19** to be quite stable, and its formation could be monitored by HPLC. As soon as the formation of **19** had been completed, the amine (MeNHOMe) was added to afford **3** in good yield. A large batch of **3** (1.34 kg) was produced in 85% yield and with high purity (95.8% HPLC) without chromatography. The major triazine byproduct **20** generated during this reaction was easily removed from the product during aqueous acid and base workup. Another minor byproduct, **21**, was identified.



To ensure total conversion of **19** to **3**, the reaction vessel

(12) (a) Kaminski, Z. J. *Synthesis* **1987**, *10*, 917−920. (b) Kaminski, Z. J.; Paneth, P.; Rudzinski, J. *J. Org. Chem.* **1998**, *63*, 4248.

must be kept closed so that no volatile *N*,*O*-dimethylhydroxylamine escapes from the reaction medium.

With the common precursor in hand, we were ready to proceed to the next stage of discodermolide synthesis, which is described in the following contributions.

Conclusions

In summary, Smith's procedure for the preparation of common precursor **3** from Roche ester **2** was modified to facilitate large-scale production in the pilot plant. Evan's *syn*-aldol reaction product was crystallized, and the structure was confirmed by X-ray. Kilogram quantities of Weinreb amide **3** were prepared using two peptide synthesis protocols, which eliminated the use of trialkylaluminum. Intermediate **3** was thus prepared in six steps without chromatography.

Experimental Section

For this five-part series the following general experimental details apply: Reagents and solvents were obtained from commercial sources and used as received. Proton and carbon-13 NMR data were recorded on a Brucker SP 400 instrument at 400.1 and 100.2 MHz, respectively. Melting points were determined on an Electrothermal 8101 apparatus and are uncorrected. IR spectra were recorded with a NICOLET Magna 550 instrument. Optical rotations were measured with a JASCO-P 1030 polarimeter.

(*S*)-3-(4-Methoxybenzyloxy)-2-methylpropionic Acid Methyl Ester (8). To a stirred suspension of sodium hydride (1.31 kg of a 60% suspension in mineral oil, 32.75 mol) in 67.5 kg of *tert*-butyl methyl ether was added a solution of 4-methoxybenzyl alcohol (45 kg, 325.69 mol) in *tert*-butyl methyl ether (15 kg) over a period of 30 min, maintaining the temperature at 20−22 °C. The addition equipment was washed with 10 kg of *tert*-butyl methyl ether, and the resulting reaction mixture was stirred for a further 90 min at 20−22 °C. The mixture was cooled to 0−4 °C, and trichloroacetonitrile (50.3 kg, 348.36 mol) was added over 100 min. The reaction mixture was stirred for 90 min, warmed to room temperature, and concentrated under vacuum to a final volume of about 100 L. At room temperature, the concentrate was treated sequentially with heptane (143 kg) and methanol (1.05 kg) containing 25 g of an antistatic agent. To the resulting suspension was added Cellflock filter aid (5 kg); the mixture was stirred for 30 min at room temperature and filtered. The solid was rinsed with heptane (2 × 25 kg), and the combined filtrate was concentrated under vacuum to a final volume of about 85 L at a maximum temperature of 30 °C to produce 97.2 kg of the intermediate trichloroimidate as an oil.

A solution of (*S*)-3-hydroxy-2-methyl propionic acid methyl ester (33.3 kg, 281.89 mol) in a mixture of 118 kg of dichloromethane and 132 kg of cyclohexane was cooled to 0 °C, and the trichloroimidate (89.9 kg, corresponding to 79.7 kg of trichloroimidate with 100% purity, 282.06 mol), prepared as described above, was added over 45 min, maintaining the temperature between 0 and 5 °C. The addition funnel was rinsed with a mixture of dichloromethane (59 kg) and cyclohexane (68.8 kg). Solid pyridine *p*-toluenesulphonate (3.79 kg, 15 mol) was added in one portion and the reaction mixture stirred for 3 h at 0 to 5 °C. After this time a suspension formed, and the temperature of the mixture was raised to 24 °C and stirred for a further 18 h. The suspension was filtered and the solid rinsed with heptane (3 × 20 kg). The combined filtrate was concentrated under vacuum at 25 °C to a volume of about 71 L. Heptane (379 kg) was added to the oily residue, followed by Cellflock (17.9 kg). The suspension was stirred for 30 min at room temperature and filtered. The solid was rinsed with heptane (3 × 35 kg), and the combined filtrate was evaporated under vacuum at 30 °C to give **8** (69.6 kg) as an oil (GC, 96.5 area %, corrected to 67.16 kg, 100% yield): $[\alpha]^{25}_{D}$ −12.0 (c = 1, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 7.28 (m, 2H), 6.84 (m, 2H), 4.45 (s, 2H), 3.81 (s, 3H), 3.70 (s, 3H), 3.65 (dd, J = 12.0, 6.0 Hz, 1H), 3.45 (dd, J = 12.0, 6.0 Hz, 1H), 2.75(m, 1H), 1.15 (d, J = 10.0 Hz, 3H).

(*R*)-3-(4-Methoxybenzyloxy)-2-methylpropan-1-ol (9). *(A) Reduction with Lithium Aluminium Hydride.* Lithium aluminium hydride (32.1 kg of a 10% solution) was diluted with anhydrous THF (179.2 kg) and cooled to 0 °C. A solution of ester **(8)** (18.6 kg, 100%, 77.73 mol) in THF (54.1 L) was added over 60 min. The reaction was exothermic, and gas evolution was observed. After the addition was complete, the reaction mixture was stirred for another 2 h at 0 °C. After this time, a solution of potassium sodium tartrate (14.8 kg, 54.45 mol) in water (23 L) was added slowly. During the initial phase of the addition, this quench was very exothermic, and vigorous gas evolution was observed. Finally, the gray suspension was stirred overnight at room temperature. The suspension was filtered (filtration was extremely slow) and the solid rinsed with THF (2 × 18 kg). The combined filtrate was evaporated to dryness under vacuum at 25 °C to give alcohol **9** (16.49 kg, 100%) as an oil, which was used without further purification: $[\alpha]_{D}$ +14.6 (c = 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.23 (m, 2H), 6.86 (m, 2H), 4.43 (ABq, J = 12 Hz, 2H), 3.79 (s, 3H), 3.64−3.49 (m, 3H), 3.37 (dd, J = 9.57, 8.17 Hz, 1H), 2.60 (br m, 1H), 2.05 (m, 1H), 0.85 (d, J = 6.9 Hz, 3H).

(B) Reduction with Lithium Borohydride. To a solution of lithium borohydride (172 kg of a 10% w/w solution in THF) was added dropwise a solution of ester **8** (65 kg, 272.81 mol, as obtained) in THF (133 kg) and ethanol (42.4 kg) over 3 h, maintaining the temperature at 20 °C. After the addition was complete, the mixture was stirred at 20 °C for a further 2 h. After this time the reaction mixture was diluted with *tert*-butyl methyl ether (79.5 kg) and acetic acid (398 kg of a 2 M solution) was added within 5 h. Vigorous gas evolution was noted, and the reaction was exothermic. When the addition was completed, the two-phase mixture was stirred for 15 min at room temperature and the organic layer separated. The organic layer was washed with aqueous sodium hydroxide solution (212 kg, 2 M). The organic layer was separated and washed with brine (192 kg), dried over Na_2SO_4 (11 kg), and filtered. The solid was rinsed with *tert*-butyl methyl ether (2 × 20 kg), and the combined filtrate was evaporated under vacuum at 25 °C to yield product **9** (50 kg, 100%).

(*S*)-3-(4-Methoxybenzyloxy)-2-methylpropionaldehyde (10). A solution of alcohol **(9)** (29 kg, 137.85 mol) in dichloromethane (470 kg) was cooled to 0 °C. TEMPO (210 g, 1.34 mol) was added followed by a 2.75 M aqueous solution of potassium bromide (34.9 kg) and a 1.6 M aqueous solution of potassium hydrogen carbonate (152 kg). To the rapidly stirred two-phase mixture was added a solution of bleach (126 kg of a 11% solution, 185.5 mol) over 90 min. The resulting mixture was stirred for a further 40 min at 0 to 5 °C. A 1.0 M aqueous solution of sodium thiosulphate (79.9 kg) was added. The mixture was then warmed to room temperature within 15 min, and the layers were separated. The organic layer was washed with water (2 × 184 kg). Sodium sulphate (7.5 kg) was added, and the suspension was stirred for 10 min at room temperature and filtered. The solid was rinsed with dichloromethane (2 × 22 kg), and the combined filtrate was concentrated under vacuum at 20−25 °C to afford aldehyde **10** (28.6 kg) as an oil, which was used immediately in the next step: $[\alpha]^{25}_D$ +30.7 (c = 1, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 9.64 (d, J = 1.5 Hz, 1H), 7.19 (m, 2H), 6.83 (m, 2H), 4.40 (s, 2H), 3.75 (s, 3H), 3.62−3.53 (m, 2H), 2.60 (m, 1H), 1.10 (d, J = 7.3 Hz, 3H).

(*R*)-4-Benzyl-3-[(2*R*,3*S*,4*S*)-3-hydroxy-5-(4-methoxybenzyloxy)-2,4-dimethyl-pentanoyl]-oxazolidin-2-one (11). A solution of (*R*)-4-benzyl-3-propionyloxazolidin-2-one (30.0 kg, 128.61 mol) in dichloromethane (233 kg) was cooled to 0 °C and treated with dibutylboron triflate (193 kg, 1.0 M in dichloromethane). The solution was stirred for 10 min at 0−5 °C, and triethylamine (22.1 kg, 218 mol) was added dropwise. The addition funnel was rinsed with dichloromethane (67 kg), and the reaction mixture was stirred for 45 min at 0−5 °C. The resulting enolate solution was cooled to −80 to −75 °C. A solution of **10** (24.3 kg, 116.68 mol) in dichloromethane (72.5 kg) was added over 60 min. The addition funnel was rinsed with dichloromethane (15 kg), and the reaction mixture was stirred for 60 min at −75 °C. The reaction mixture was warmed to −45 °C over 30 min and stirred for 60 min. Finally the reaction was warmed to 0 °C within 30 min and stirred for a further 60 min. Water (100 kg) was added, and the two-phase system was stirred for 10 min. The organic phase was separated, treated with a pH 7 phosphate buffer solution (242 kg), and cooled to 0 to 5 °C. Hydrogen peroxide (28.8 kg of 35% w/w solution, 317.6 mol) was added slowly, and the mixture was stirred for 60 min at 0−5 °C. Excess peroxide was destroyed by the addition of a 2.0 M aqueous solution of sodium sulphite (213 kg) over 30 min (exothermic). The mixture was warmed to room temperature, and the organic phase was separated, washed with water (2 × 350 kg), and treated with Na_2SO_4 (20 kg). The suspension was filtered and the solid rinsed with dichloromethane (2 × 30 kg). The filtrate was evaporated under vacuum at 35 °C to a final volume of 65 L. To remove butanol formed by the oxidation process, toluene (409 kg) was added to the residue and evaporated at 45 °C under vacuum. This procedure was repeated once more and delivered aldol product **11 (**68.4 kg, 62% by HPLC, corrected yield 82%) as an oil.

Example of Crystallization of 11. The crude aldol product (53.8 kg) containing ∼44 area % by HPLC of **11** was dissolved in butanol (26.1 kg), and diisopropyl ether (39.0 kg) and heptane (76.4 kg) were added. The solution was seeded with pure **11** (10 g) and stirred for 22 h at 22 °C. The thin suspension was cooled in a linear manner to 8−12 °C over 2 h and stirred for 6.5 h. The suspension was warmed to 20 °C over 30 min and stirred for 16 h. The suspension was cooled to 8−12 °C over 1 h in a linear fashion, and heptane (75.6 kg) was added over 6 h. After the addition was completed, stirring was continued for a further 1 h and the suspension warmed to 20 °C. Finally the suspension was stirred for 20 h at 20 °C, filtered, and rinsed three times with a mixture of heptane (34 kg) and butanol (4.3 kg). The solid was dried under vacuum at 30 °C for 24 h to yield **11** (19.0 kg, 80%): mp 69−70 °C; $[\alpha]^{25}_D$ −35.6 (c = 1, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 7.35−7.10 (m, 7H), 6.80 (m, 2H), 4.61 (m, 1H), 4.38 (s, 2H), 4.12 (m, 2H), 3.88 (m, 1H), 3.80 (m, 1H), 3.74 (s, 3H), 3.50−3.40 (m, 2H), 3.27 (dd, J = 13, 3.0 Hz, 1H), 2.70 (dd, J = 13.6, 9.7 Hz, 1H), 1.91 (m, 1H), 1.52 (br s, exch D_2O, 1H), 1.19 (d, J = 6.7 Hz, 3H), 0.88 (d, J = 6.93 Hz, 3H).

(2*R*,3*S*,4*S*)-3-Hydroxy-5-(4-methoxybenzyloxy)-2,4-dimethylpentanoic Acid Methoxymethylamide (3). *(A) Triisobutylaluminum-Promoted Amide Formation.* A suspension of *N*,*O*-dimethylhydroxylamine hydrochloride (13 g, 133.35 mmol) in THF (97 mL) was cooled to 0 °C and treated with triisobutylaluminum (133.35 mL, 1.0 M in hexane). The suspension slowly turned into a solution as the mixture was warmed to room temperature over 15 min. The solution of the aluminum complex was stirred for 60 min at room temperature and a solution of **11** (16.84 g, 38.14 mmol) in THF (30 mL) was added over 45−60 min. The reaction mixture was stirred for 3 h at room temperature, cooled to 0 °C, and quenched carefully with a 2.0 M aqueous hydrochloric acid (194 mL). The mixture was warmed to room temperature and stirred for 30 min. The phases were separated, and the organic layer was washed with a saturated solution of sodium bicarbonate (194 mL), followed by brine (194 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated under vacuum to give crude product **3** (25.4 g) as an oil. This oil was dissolved in a mixture of *tert*-butyl methyl ether (21.2 mL) and heptane (6.8 mL) and seeded with (*R*)-4-benzyloxazolidin-2-one **(12)**. The suspension was stirred for 60 min at room temperature. Heptane (6.8 mL) was added dropwise, and the mixture was cooled to 0 °C and stirred for an additional 60 min. The mixture was treated with heptane (3.4 mL) and stirred for 2 h at 0 °C. The solid was isolated by filtration to recover **12** (5.22 g, 77%). The filtrate was evaporated to dryness to give **3** (17.6 g, contaminated with **12)** as an oil, which was utilized without further purification. Chromatography on silica gel eluting with heptane/ethyl acetate, 2/1, afforded a pure sample: ^{1}H NMR ($CDCl_3$) δ 7.25 (m, 2H), 6.85 (m, 2H), 4.43 (s, 2H), 3.75 (s, 3H), 3.70−3.50 (m, 7H), 3.18 (s, 3H), 3.05 (br s exch D_2O, 1H), 1.89 (m, 1H), 1.15 (d, J = 7.0 Hz, 3H), 0.0.97 (d, J = 6.8 Hz, 3H).

Also isolated was 1.5 g of byproduct **13**: ^{1}H NMR ($CDCl_3$) δ 7.30−7.10 (m, 7H), 6.82 (m, 2H), 5.21 (br s, exch D_2O, 1H), 4.40 (m, 3H), 4.05 (m, 3H), 3.75 (s, 3H), 3.60−3.40 (m, 5H), 3.05 (s, 3H), 2.87−2.70 (m, 3H), 2.35 (m, 1H), 1.85 (m, 1H), 1.05 (d, J = 7.0 Hz, 3H), 0.76 (d, J = 7.1 Hz, 3H).

(2*R*,3*S*,4*S*)-3-Hydroxy-5-(4-methoxybenzyloxy)-2,4-dimethylpentanoic Acid (*R*)-1-Phenylethylamine Salt (14). To a solution of crude **11** (25 kg, 56.6 mol) in methanol (167.2 kg) was added water (105.6 kg) and hydrogen peroxide (24.6 kg of 35% w/w solution, 253.24 mol). A 2 M aqueous solution of lithium hydroxide (60.8 kg) was added over 2 h (oxygen was evolved), and the mixture was stirred for 2 h at room temperature. A 2.0 M aqueous solution of sodium sulphite (52.0 kg) was added slowly (exothermic). The mixture was stirred for 10 min at room temperature and extracted with toluene (102.6 kg). The aqueous phase was re-extracted with toluene (2 × 102.6 kg). The combined toluene phases contained **12,** which could be recovered according to the procedure described below.

Toluene (77 kg) was added to the aqueous phase, and the two-phase mixture was treated with concentrated hydrochloric acid until the pH reached 2.0−2.5 (ca. 15.8 kg of 37% HCl required). More toluene (70 kg) was added, and the mixture was stirred for 15 min at room temperature. The organic phase was separated, and the aqueous phase was extracted with toluene (140 kg). The combined toluene extracts were washed with water (176 kg) and concentrated under vacuum at 35 °C to a volume of about 124 L, which was filtered, and the solid (inorganic salts) was washed with toluene (2 × 40 kg). The combined filtrate containing acid **18** was transferred to a second reactor containing toluene (22 kg). The concentration of acid **18** was determined by titration of the toluene solution. The toluene solution was treated with (*R*)-1-phenylethylamine (7.14 kg, 59 mol) and stirred for 1 h at room temperature (crystallization began towards the end of the amine addition). The suspension was cooled to 0 °C, stirred for 2.5 h, filtered, and the solid was rinsed with toluene (3 × 25 kg). The solid was dried under vacuum at 30 °C to give salt **14** (19.13 kg, 84%)**:** $[\alpha]_D$ +16.9 (c = 1, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 7.40−7.20 (m, 7H), 7.15−6.80 (br m, 6H becomes 2H on D_2O exch), 4.40 (s, 2H), 4.18 (q, J = 7.0 Hz, 1H), 3.78 (s, 3H), 3.65 (br m, 1H), 3.55 (Br m, 1H), 3.42 (br m, 1H), 2.30 (br m, 1H), 1.80 (br m, 1H), 1.50 (d, J = 8.0 Hz, 3H), 0.95 (d, J = 8.5 Hz, 3H), 0.80 (d, J = 8.0 Hz, 3H).

Recovery of 12. The toluene extracts from several reactions were combined to give a total volume of 2000 L. This was evaporated under vacuum at 35 °C to a final volume of about 200 L, cooled to 20 °C, and seeded with commercial **12** (10 g). The resulting suspension was cooled to 0 °C, stirred for 1 h, and filtered. The solid was rinsed with a mixture (9/1) of heptane/ethyl acetate (60 kg) and dried under vacuum at 40 °C to recover **12 (**47.7 kg). Chiral HPLC, (Chiralcel-OD column, 250 mm × 4.6 mm, eluting with *n*-hexane/ethanol, 75/25, flow rate 0.7 mL/min, at 15 °C and 215 nM detection) showed none (<0.1%) of the antipode to be present. The chemical purity was determined by HPLC (as previously) to be >99.8% (m/m).

(2*R*,3*S*,4*S*)-3-Hydroxy-5-(4-methoxybenzyloxy)-2,4-dimethylpentanoic Acid (18). A solution of **11** (2980 g, 6.75 mol) in THF (14.5 L) was cooled to 0 °C, and then H_2O (3.6 L) was added, while maintaining the temperature at 0 °C. The solution was cooled to −5 °C, and a 30% aqueous solution of H_2O_2 (2493 g, 22.0 mol) was added dropwise, maintaining the temperature at 0 °C. A solution of lithium hydroxide monohydrate (354.1 g, 8.44 mol) in H_2O (3.6 L) was added, while maintaining the temperature 0 °C. The reaction was stirred for 30 min at 0 °C. The reaction was quenched by adding a solution of Na_2SO_3 (2600 g, 20.63 mol) in H_2O (16 L), maintaining the temperature at 0 °C. The mixture was concentrated under vacuum at 25 °C, and the residual mixture was washed with *tert*-butyl methyl ether (3 × 2 L). The aqueous layer was cooled to 3 °C and adjusted to pH 2 with 12 M HCl (750 mL). The oily precipitate was extracted with *tert*-butyl methyl ether (2 × 4 L). The combined organic layers (containing product) were washed with H_2O (2 × 2 L) and saturated NaCl (2 L) and concentrated under vacuum at 25 °C. The residual oil was cooled to 5 °C and dissolved in saturated $NaHCO_3$ (10 L). The resulting aqueous solution was washed with ethyl acetate (2 × 8 L) and *tert*-butyl methyl ether (2 × 2 L). The pH of the aqueous layer was adjusted to 2 with 12 M HCl (600 mL), while maintaining the temperature at 0 °C. The oily precipitate was extracted into *tert*-butyl methyl ether (3 × 3 L). The combined extracts (containing product) were washed with H_2O (2 × 2 L) and brine (2 L), dried over $MgSO_4$ (500 g), and filtered. The filter cake was rinsed with *tert*-butyl methyl ether (2 × 1 L). The combined filtrates were concentrated to afford **18** (1342 g, 71%) as a viscous colorless oil: IR ($CHCl_3$) 3010.6, 1747.2, 1612.7, 1514.0 cm^{-1}; ^{1}H NMR 300 MHz ($CDCl_3$) δ 7.23 (d, J = 8.5 Hz, 2H), 6.88 (d, J = 8.5 Hz, 2H), 4.45 (s, 2H), 3.92 (dd, J = 8.5, 3.3 Hz, 1H), 3.79 (s, 3H), 3.63 (dd, J = 9.2, 4.1 Hz, 1H), 3.50 (apparent t, J = 8.5 Hz, 1H), 2.64−2.61 (m, 1H), 2.05 (s, 1H), 1.21−1.14 (m, 1H), 1.17 (d, J = 7.0 Hz, 3H), 0.89 (d, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.0, 129.5, 129.3, 113.0, 76.0, 74.0, 73.0, 55.0, 42.0, 35.0, 13.0, 9.0. Anal. Calcd for $C_{15}H_{22}O_5$: C, 63.81; H, 7.86. Found: C, 63.43; H, 7.90.

(2*R*,3*S*,4*S*)-3-Hydroxy-5-(4-methoxybenzyloxy)-2,4-dimethylpentanoic Acid Methoxymethyl Amide (3). *(A) Isobutyl Chloroformate Procedure.* A suspension of salt **14** (34.0 kg, 84.26 mol) in water (63 L) and dichloromethane (168 kg) was cooled to 0 °C. A 1.0 M aqueous solution of hydrochloric acid (87.3 kg) was added over 15 min and stirred for an additional 20 min at 0 °C. The phases were separated, and the aqueous layer was extracted with dichloromethane (112 kg). The combined organic phases were washed with brine (50 kg) and dried over Na_2SO_4 (11 kg). The suspension was filtered, and the solid was rinsed with dichloromethane (2 × 25 kg). The combined filtrate containing the acid **18** was concentrated under vacuum at 35 °C to a volume of about 84 L, which was then cooled to 0 °C. *N*-Methylpiperidine (8.76 kg, 88.48 mol) was charged,

followed by dropwise addition of isobutyl chloroformate (11.5 kg, 84.25 mol). The mixture was stirred at 0 °C for another 20 min. To the resulting mixed anhydride solution was added a 103-kg of a mixture of *N*,*O*-dimethylhydroxylamine hydrochloride (10.4 kg, 106.72 mol) and *N*-methylpiperidine (11.1 kg, 112.1 mol) in dichloromethane (96.6 kg) within 20 min. The reaction mixture was stirred for another 30 min at 0 °C and treated with *N*-methylpiperidine (0.876 kg, 8.85 mol), followed by a second portion of isobutyl chloroformate (1.16 kg, 8.5 mol). The reaction was stirred for 15 min at 0 °C, and a second portion (10.3 kg) of the mixture of *N*,*O*-dimethylhydroxylamine hydrochloride and *N*-methylpiperidine in dichloromethane, from above, was added over 15 min at 0 °C. The reaction was stirred for 30 min at 0 °C and warmed to 20°C, and 1.0 M hydrochloric acid (147 kg) was added. The phases were separated, and the aqueous phase was extracted with dichloromethane (140 kg). The combined dichloromethane phases were washed with saturated aqueous solution of sodium bicarbonate (130 kg) and water (2 × 105 L). The organic phase was dried over Na_2SO_4 (11 kg) and concentrated under vacuum at 35 °C to give crude **3** (28.62 kg, HPLC purity 76.7%, corrected yield 80%).

(B) CDMT Procedure. A cold (3 °C) solution of acid **18** (1340 g, 4.75 mol) in THF (12 L) was charged with CDMT (915 g, 5.22 mol). To the resulting solution, *N*-methylmorpholine (528.3 g, 5.22 mol) was added dropwise, while maintaining the temperature at 0 °C. The reaction was stirred for an additional 1 h at 3 °C. Next, *N*,*O*-dimethylhydroxylamine hydrochloride (926.5 g, 9.5 mol) was added to the cold suspension (3 °C), followed by dropwise addition of *N*-methylmorpholine (961.1 g, 9.5 mol), while maintaining the temperature at 0 °C. The nitrogen purge was discontinued, and the reaction flask was sealed. The reaction was allowed to warm to 23 °C and stirred for 18 h. The suspension was cooled to 10 °C, and *N*,*O*-dimethylhydroxylamine hydrochloride (449.8 g, 4.61 mol) was added. Next, *N*-methylmorpholine (466.5 g, 4.61 mol) was added dropwise, while maintaining the temperature at 10 ° C. The resulting heavy suspension was stirred for 24 h at 18 °C. The suspension was filtered, and the filter cake was rinsed with *tert*-butyl methyl ether (2 × 1 L). The combined filtrate was concentrated under vacuum at 25 °C. The residual oil was dissolved in *tert*-butyl methyl ether (6 L) and washed with H_2O (2 × 2 L), 1 M HCl (3 × 2 L), H_2O (2 × 2 L), saturated $NaHCO_3$ (2 × 2 L), H_2O (2 × 2 L), and brine (1 × 2 L). The organic layer was dried over $MgSO_4$ (500 g), filtered, and rinsed with *tert*-butyl methyl ether (2 × 500 mL). The combined filtrate was concentrated under vacuum at 20 °C to afford **3** (1309 g, 85%) as a colorless oil: $[\alpha]^{25}_D$ −10.8 (c = 1.0, $CHCl_3$); IR (film) 3459, 2964, 2936, 1612, 1585, 1513, 1461, 1421, 1385, 1301, 1247 cm^{-1}; ^1H NMR (C_6D_6) δ 7.25 (d, J = 8.6 Hz, 2H), 6.85 (d, J = 8.6 Hz, 2H), 4.44 (AB_q, J_{AB} = 11.6 Hz, $\Delta\delta_{AB}$ = 17 Hz, 2H), 3.79 (s, 3H), 3.7 (ddd, J = 8.2, 3.2, 2.2 Hz, 1H), 3.66 (s, 3H), 3.62 (dd, J = 9.0, 4.0 Hz, 1H), 3.53 (dd, J = 9.1, 5.9 Hz, 1H), 3.17 (s, 3H), 3.07−3.01 (m, 1H), 1.91−1.84 (m, 1H), 1.17 (d, J = 7.0 Hz, 3H), 0.98 (d, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 174.9, 159.3, 130.7, 126.1, 113.7, 76.3, 73.2, 71.6, 61.2, 55.2, 39.0, 38.9, 37.8, 14.4, 12.9. Anal. Calcd for $C_{17}H_{27}NO_5$: C, 62.74; H, 8.37; N,4.31. Found: C, 62.58; H, 8.07; N, 4.22.

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This five-part series is dedicated to the memory of Professor Malcolm M. Campbell, University of Bath, England.

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Large-Scale Synthesis of the Anti-Cancer Marine Natural Product (+)-Discodermolide. Part 2: Synthesis of Fragments C_{1-6} and C_{9-14}

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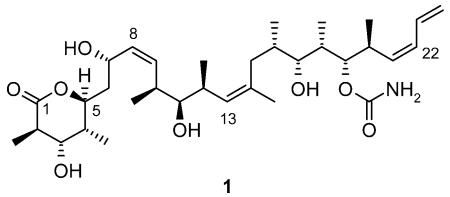
Abstract:

Kilogram-scale syntheses of fragments C_{1-6} (6) and C_{9-14} (4) of (+)-discodermolide from common precursor 3 are described. Improved procedures for each step of both fragments were developed by minimizing or eliminating the formation of byproducts that were isolated and characterized in Smith's synthesis.

Introduction

The marine natural product (+)-discodermolide[1] (**1**) contains a stereo triad that repeats itself three times (C_{2-4}, C_{10-12}, C_{18-20}).



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These fragments can, therefore, be made conveniently from a common precursor **3**, as described by Smith.[2] In Part 2 of this series, we discuss the large-scale preparation of intermediates C_{9-14} (**4**) and C_{1-6} (**6**) from the common precursor **3** (Scheme 1).

Fragment C_{9-14} (**4**) contains a *cis*-trisubstituted double bond at C_{13-14} and offers a synthetic challenge in controlling the stereochemistry. Numerous approaches for the construction of this trisubstituted *cis* double bond have been described, some of which were quite ingenious. For example, Paterson[3] described a route leading to a trisubstituted olefin via a Claisen rearrangement (Scheme 2). Panek[4] utilized a strategy involving acetylene chemistry, followed by a Negishi coupling, and introduction of the vinyl iodide at the end (Scheme 3). Unfortunately neither of these elegant routes was deemed suitable for scale-up primarily because (1) the selenium chemistry utilized by Paterson is highly toxic and (2) in the Panek approach, the use of large excesses of the Schwarz reagent combined with the uncertain stability of the *p*-methoxybenzyl group in **4** (despite literature reports that this group would survive the chemistry).[5] Therefore, the original procedure starting with **3** described by Smith[2] was developed for our multikilogram production of fragment **4**.

Similarly, fragment C_{1-6} (**6**), required for the construction of the lactone ring of (+)-discodermolide, can also be synthesized from **3**. As a result, there would be a synergy in preparing both fragments **4**, **5**, and **6** from the same precursor **3** for our multigram synthesis of (+)-discodermolide. The preparation of fragment **5** is discussed in part 3 of this series.

Results and Discussion

Synthesis of Fragment C_{9-14} (4). The four-step route that we employed for the preparation of fragment **4** from the common precursor **3** (obtained from **2**, as described in part 1 of this series) is shown in Scheme 4.

Silylation of **3** with *tert*-butyldimethylsilyl triflate afforded TBDMS ether **8** in excellent yield (90%) after chromatography on silica gel. Smith's procedure employed DIBAL-H for the reduction of Weinreb amide **8** at −78 °C to produce the desired aldehyde **9**. However, it also generated an alcohol byproduct due to the uncontrolled over-reduction of the resulting aldehyde. We developed an alternative process for the reduction employing Red-Al at −20 °C, a temperature that is easier for pilot-plant operation. It was equally effective and avoided tedious low-temperature operations in our plant. The isolated yield of **9** as an oil was also high (68%) after chromatography on silica gel.

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(1) (a) Gunasekera, S. P.; Gunasekera, M.; Longley, R. E.; Schulte, G. K. *J. Org. Chem*. **1990**, *55*, 4912; correction *J. Org. Chem.* **1991**, *56*, 1346. (b) Gunasekera, S. P.; Paul, G. K.; Longley, R. E.; Isbrucker, R. A.; Pomponi, S. A. *J. Nat. Prod*. **2002**, *65*, 1643.

(2) Smith, A. B.; Beauchamp, T. J.; LaMarche, M. J.; Kaufman, M. D.; Qiu, Y.; Arimoto, H.; Jones, D. R.; Kobayashi, K. *J. Am. Chem. Soc.* **2000**, *122*, 8654.

(3) Paterson, I; Florence, G. J.; Gerlach, K.; Scott, J. P. *Angew. Chem., Int. Ed.* **2000**, *39*, 377.

(4) (a) Panek, J. S.; Hu, T. *J. Org. Chem*. **1997**, *62*, 4912. (b) Arefolov, A.; Langille, N. F.; Panek, J. S. *Org. Lett*. **2001**, *3*, 3281. (c) Arefolov, A.; Panek, J. S. *Org. Lett*. **2002**, *4*, 2397.

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10.1021/op0341317 CCC: $27.50
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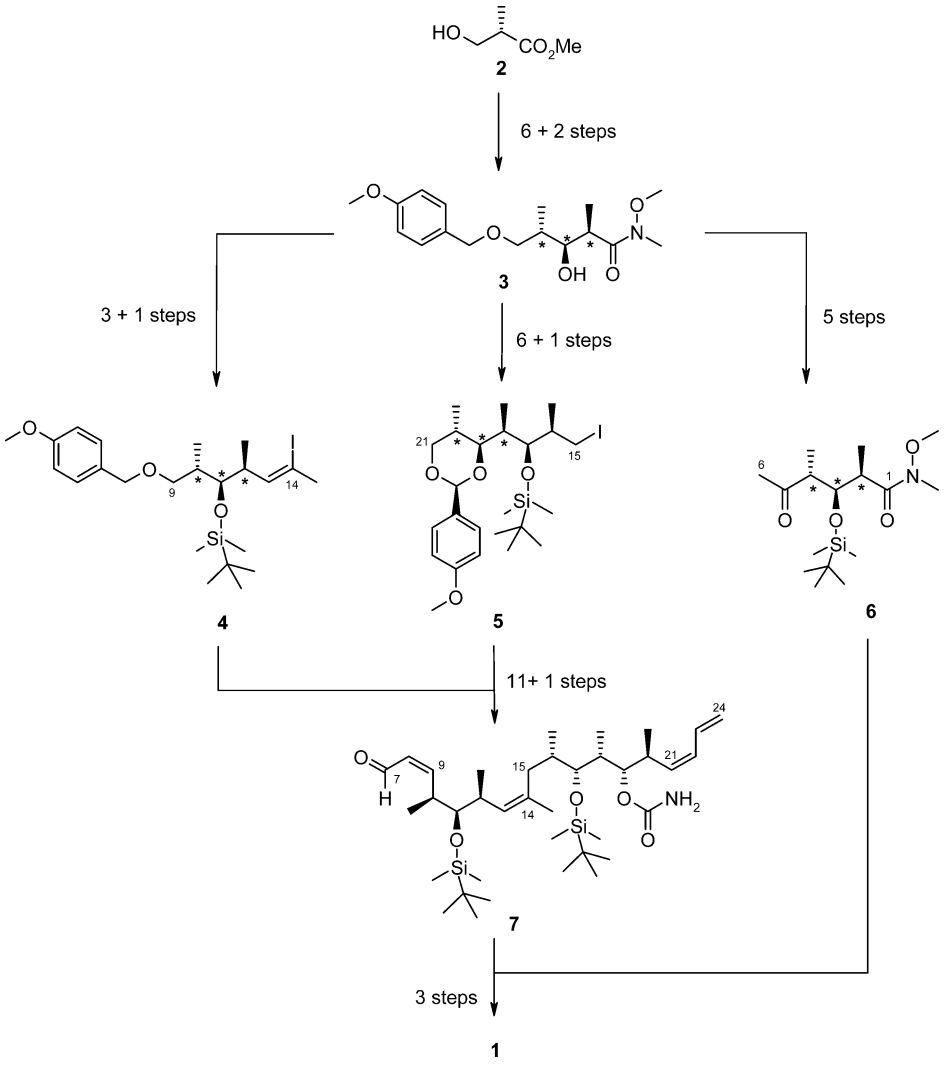
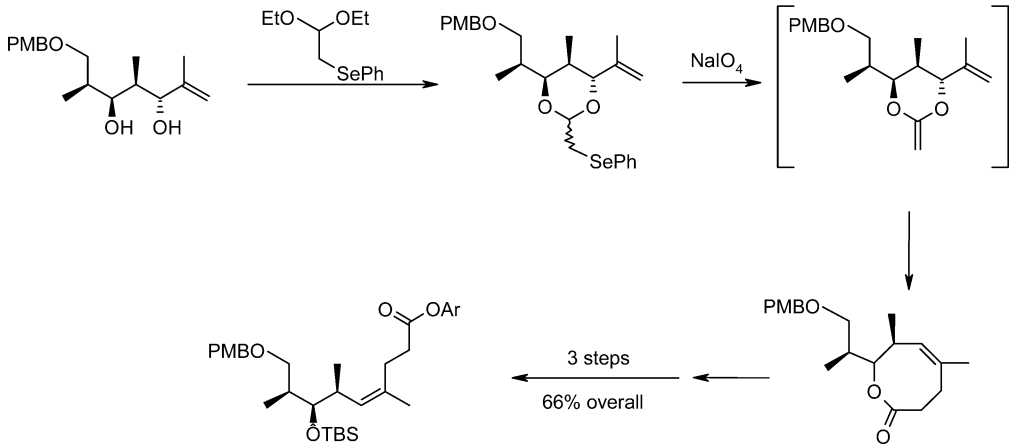
Scheme 1. **Synthetic strategy leading to fragment C_1-_6 (6) and C_9-_{14} (4)**

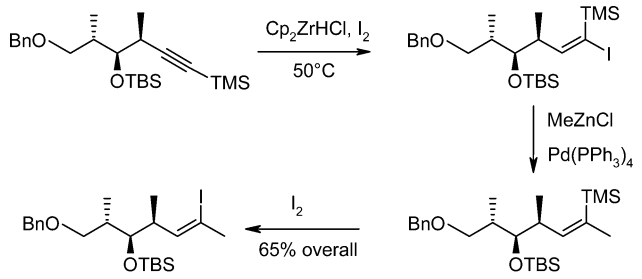


Scheme 2. **Paterson's approach to $C_{13,14}$-*cis*-trisubstituted double bond**

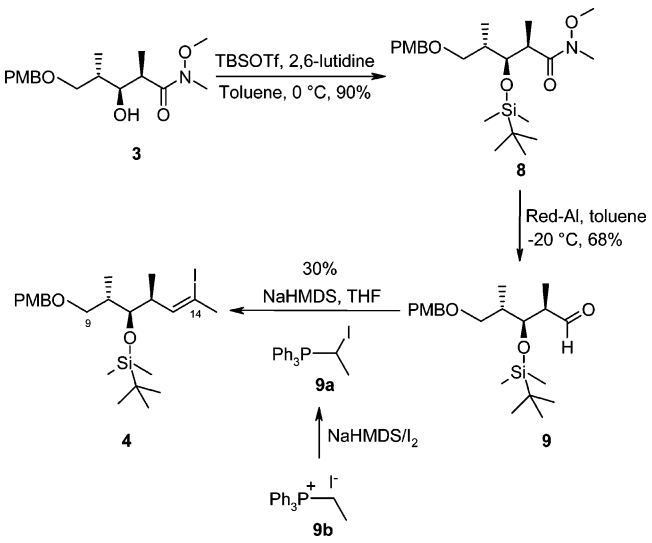


The success of converting amide **8** into aldehyde **9** was very dependent on the quality of silyl ether **8**. If **8** was not pure, the yield of aldehyde would drop to below 60%. The reaction time and temperature were also found to be critical. When the reaction was held too long at 0 °C, a competing de-silylation reaction occurred that led to the formation of significant amounts of hydroxy aldehyde **10**. If necessary, however, aldehyde **10** can easily be isolated and subjected to the standard silylation conditions to regenerate **9**. By maintaining the reaction temperature between −5 to 0 °C, formation of **10** was also minimized. Another byproduct (olefin **11)** was isolated in small quantity, which was formed by β-elimination either of silyl alcohol from **9** or of water from **10**. Attempts to convert all of **8** into **9** were unsuc-

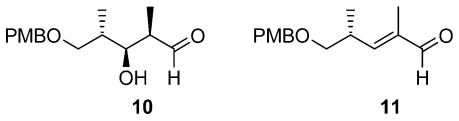
Scheme 3. **Panek's approach to $C_{13,14}$-*cis*-trisubstituted double bond**



Scheme 4. **Synthesis of fragment C_{9-14}**



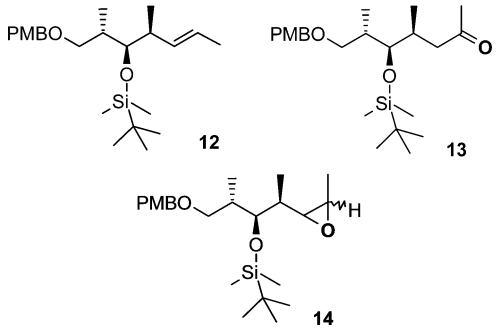
cessful. The final reaction conditions were a compromise to minimize byproduct formation. Aldehyde **9** was stable if stored at <-10 °C.



Utilizing the Zhao olefination procedure,[6] also used by Smith[2] and Marshall,[7] we obtained the desired *cis*-vinyl iodide **4** in 31% yield after chromatography purification on silica gel. Only small amounts of the undesired *trans* isomer were detected (*cis*:*trans* = 15:1). We did not observe any *des*-iodo olefin **12**, suggesting that the formation of **9a** from **9b** via ylide iodination (Scheme 4) had been completed before it was added to aldehyde **9**.

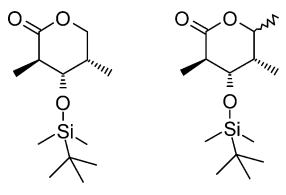
This olefination step was one of the most difficult reactions for scale-up. We consistently obtained 25−31% yield on the maximum scale of 2.5 kg of aldehyde **9**. Complicated workup procedures and instability of **4** contributed to low yield. Smith utilized iodine for the conversion of ethyltriphenylphosphonium iodide (**9b**) into the iodo ylide (**9a**).[2] We found that *N*-iodosuccinimide can be used to replace iodine without detriment. While this makes the reaction easier to handle, it did not contribute to an increase in yield. Initially, we observed the formation of the methyl ketone **13**[8] during the workup. This byproduct can be avoided by using nonaqueous workup.

Smith[8] reported that the reaction of **9a** with **9** afforded epoxide **14** in addition to the desired **4** in a 1:1 ratio. Alternative approaches were investigated to minimize this major byproduct; however, they were unsuccessful. For example employing a method described by Shen,[9] where the initially formed betaine intermediate was deprotonated with a second equivalent of base and then iodinated, produced des-iodo olefin **12**. Utilizing Hanessian's phosphonates[10] in this process also resulted in only des-iodo olefin **12**.



Synthesis of Fragment C_{1-6} (6). The five-step synthesis of fragment **6** from common precursor **3** is outlined in Scheme 5.

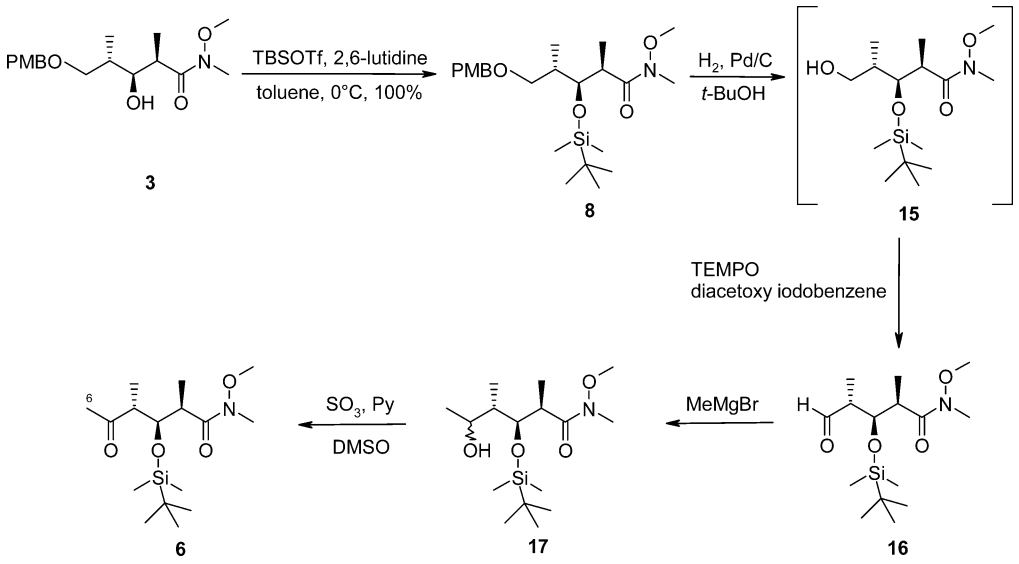
The published approach[2] to aldehyde **16** from **3** was followed. Hydrogenolysis of PMB ether **8** (same intermediate as for fragment **4** synthesis) with palladium on carbon in *tert*-butyl alcohol afforded alcohol **15**. Due to its propensity for lactonisation to **18**, **15** was used as a *tert*-butyl alcohol solution immediately for the next step without isolation or purification. Oxidation of **15** with TEMPO (2,2,6,6-tetramethylpiperidine-1-oxy radical) and diacetoxy iodobenzene furnished aldehyde **16** as an oil**,** which was again used for the next step without purification. Further elaboration of **16** to the analogous Paterson fragment[3] **6** needed for the final aldol coupling (see Part 5 of this series) proceeded by utilising a methyl Grignard reagent and produced secondary alcohol **17** as a mixture of diastereoisomers. Since **17** also lactonized readily to **19**, it was oxidized immediately with SO_3/pydridine in DMSO to yield pure methyl ketone **6** (fragment C_{1-6}) after chromatography. By following these continuous operations, the amounts of both lactones (**18** and **19**) were minimized. The overall yield for the five-step sequence was 66% on a routine scale of several kilograms.



Having prepared both fragments C_{9-14} (**4**) and C_{1-6} (**6**) in large quantities from common precursor **3,** synthesis of

(6) Chen, J.; Zhao, K. *Tetrahedron Lett.* **1994**, *35*, 2827.
(7) Marshall, J. A.; Johns, B. A. *J. Org. Chem.* **1998**, *63*, 7885.
(8) Arimoto, H.; Kaufmann, M. D.; Kobayashi, K.; Qiu, Y.; Smith, A. B. *Synlett* **1998**, 765.
(9) Shen, Y.; Gao, S. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1331.

Scheme 5. **Synthesis of fragment C_1-_6 (6)**



the third structural segment (Fragment C_{15-21}) will be undertaken next (Part 3).

Experimental Section

(2*R*,3*S*,4*S*)-3-(*tert*-Butyldimethylsilanyloxy)-5-(4-methoxybenzyloxy)-2,4-dimethylpentanoic acid methoxymethyl amide (8). To a cooled (0−5 °C) solution of amide **3** (25 kg, 76.8 mol) in toluene (84.0 kg), 2,6-lutidine (10.7 kg, 99.9 mol) was added *tert*-butyldimethylsilyl triflate (24.4 kg, 92.3 mol) dropwise over a period of 30 min, maintaining the temperature between 0 and 5 °C. The reaction mixture was stirred for 30−60 min at 0−5 °C and treated with 10% aqueous solution of sodium hydrogen sulphate (120 kg). The phases were separated, and the aqueous phase was re-extracted with toluene (63 kg). The combined organic phases were washed twice with water (2 × 120 kg) and concentrated under vacuum at 40 °C to give crude silyl ether **8** (37 kg) as an oil. This crude material was chromatographed in two portions of 18 kg over silica gel (150 kg) eluting initially with heptane/ethyl acetate 15/1 followed by ethyl acetate to give the purified **8** (30.4 kg, 90%) as an oil: ^{1}H NMR ($CDCl_3$) δ 7.18 (m, 2H), 6.80 (m, 2H), 4.32 (ABq, J = 11.5 Hz, 2H), 3.86 (dd, J = 8.17, 2.53 Hz, 1H), 3.74(s, 3H), 3.54−3.48 (m, 4H), 3.09 (dd, J = 9.8, 8.2 Hz, 1H), 3.05 (m, 4H), 1.84 (br m, 1H), 1.05 (d, J = 7 Hz, 3H), 0.94 (d, J = 6.6 Hz, 3H), 0.83 (s, 9H), 0.00 (s, 6H).

(2*R*,3*S*,4*S*)-3-(*tert*-Butyldimethylsilanyloxy)-5-(4-methoxybenzyloxy)-2,4-dimethylpentanal (9). A solution of amide **8** (14.1 kg, 32.07 mol) in toluene (78 kg) was cooled to an internal temperature of −20 °C. Red-Al (14.0 kg, 70% solution in toluene, 48.48 mol) was added dropwise over 60 min, maintaining the temperature at −20 °C. After the addition was completed, the reaction was stirred for 60 min and the cooling bath temperature adjusted to 0 °C. The reaction mixture was quenched by the portionwise addition of 10% aqueous solution of citric acid (initially 4 × 0.6 kg portions followed by one portion of 139 kg, total 141.4 kg). The mixture was allowed to warm to room temperature, and the two-phase system was stirred for an additional 20 min. The organic phase was separated and washed with 10% citric acid solution (141 kg) and twice with diluted brine (111 kg water plus 34 kg of saturated sodium chloride solution). The organic phase was dried over Na_2SO_4 (3 kg), filtered, and concentrated under vacuum to give crude **9 (**11.76 kg) as an oil. Chromatography on silica gel, eluting with heptane/ethyl acetate, 9/1, delivered pure aldehyde **9** (8.30 kg, 68%): ^{1}H NMR ($CDCl_3$) δ 9.70 (d, J = 2 Hz, 1H), 7.25 (m, 2H), 6.85 (m, 2H), 4.40 (ABq, J = 13 Hz, 2H), 4.20 (m, 1H), 3.81 (s, 3H), 3.40 (m, 1H), 3.38 (m, 1H), 2.50 (m, 1H), 2.05 (m, 1H), 1.13 (d, J = 6 Hz, 3H), 0.95 (d, J = 6 Hz, 3H), 0.85 (s, 9H), 0.05 (s, 3H), 0.00 (s, 3H).

Also isolated were the following two byproducts.

Desilylated aldehyde 10: ^{1}H NMR ($CDCl_3$) δ 9.69 (s, 1H), 7.19 (m, 2H), 6.83 (m, 2H), 4.40 (s, 2H), 4.03 (dt, J = 9.0, 2.0 Hz, exch D_2O, 1H), 3.75 (s, 3H), 3.58 (dd, J = 9.13, 3.2 Hz, 1H), 3.45 (pseudo t, J = 8.41 Hz, 1H), 2.38 (m, 1H), 1.94 (m, 1H), 1.08 (d, J = 6.9 Hz, 3H), 0.79 (d, J = 6.5 Hz, 3H).

α,β-Unsaturated aldehyde 11: ^{1}H NMR ($CDCl_3$) δ 9.31 (s, 1H), 7.18 (m, 2H), 6.80 (m, 2H), 6.25 (d, J = 15 Hz, 1H), 4.35 (s, 2H), 3.75 (s, 3H), 3.31 (m, 2H), 2.95 (m, 1H), 1.73 (s, 3H), 1.05 (d, J = 6 Hz, 3H).

***tert*-Butyl-{(*Z*)-(1*R*,2*S*)-4-iodo-1-[(S)-2-(4-methoxybenzyloxy)-1-methylethyl]-2-methylpent-3-enyloxy}-dimethylsilane (4).** *(A) Procedure Utilizing Iodine.* A suspension of ethyltriphenylphosphonium iodide (4.44 kg, 10.62 mol) in dry THF (40 L) was treated with a 40% solution of sodium hexamethyldisilazane in THF (4.87 kg, 10.6 mol) at room temperature. The resulting red solution was added dropwise within 30 min to a cold (−78 °C) solution of iodine (2.7 kg, 10.6 mol) in THF. The resulting dark red suspension was

(10) (a) Stowell, M. H. B.; Ueland, J. M.; McClard, R. W. *Tetrahedron Lett*. **1990**, *31*, 3261. (b) Patois, C.; Savignac, P. *Tetrahedron Lett*. **1991**, *32*, 1317. (c) Hanessian, S.; Bennani, Y. L.; Delorne, D. *Tetrahedron Lett*. **1990**, *31*, 6461. (d) Hanessian, S.; Bennani, Y. L. *Tetrahedron Lett*. **1990**, *31*, 6465.

stirred for an additional 15 min at −78 °C, and a 40% solution of sodium hexamethyldisilazane in THF (4.6 kg, 9.56 mol) was added over 10 min. The slightly turbid red solution was then treated with a solution of **9** (2.55 kg, 6.7 mol) in THF (10 L). The reaction mixture was warmed to −20 °C and stirred for 20 min. A solution of ammonium chloride (12 kg) in water (70 L) was added. The organic layer was separated and the aqueous layer re-extracted with THF (20 L). The combined organic layers were washed with brine (50 L), dried over $MgSO_4$ and filtered. The filtrate was concentrated under vacuum at 30 °C to a volume of about 35 L. Heptane was added, followed by Cellflock filter aid (12 kg). The mixture was filtered and the solid rinsed with heptane (70 L) in three portions. The combined filtrates were concentrated under vacuum to give crude iodide **4 (**22.3 kg). This material was chromatographed over 50 kg of silica gel eluting initially with heptane/TBME, 99/1 (37 L), followed by heptane/TBME, 97/3 (14 L), to give pure **4** (1.08 kg, 31%) after evaporation of the solvents: ^{1}H NMR ($CDCl_3$) δ 7.25 (m, 2H), 6.86 (m, 2H), 5.27 (dq, J = 8.8, 1.5 Hz, 1H) [Note: containing < 1.0% of *trans* C═CH signal at δ 6.0 as a dq], 4.40 (ABq, J = 11.7 Hz, 2H), 3.80 (s, 3H), 3.58 (pseudo t, J = 6 Hz, 1H), 3.50 (dd, J = 9.0, 4.8 Hz, 1H), 3.22 (dd, J = 9.25, 8 Hz, 1H), 2.50−2.40 (m, 4H, CHMe + Me), 1.95 (m, 1H), 0.99 (d, J = 6.85 Hz, 3H), 0.94 (d, J = 6.86 Hz, 3H), 0.88 (s, 9H), 0.03 (s, 3H), 0.00 (s, 3H). Further elution yielded both *cis*- and *trans*-epoxide **14** as well as small amounts of ketone **13.**

***cis*-Epoxide 14:** ^{1}H NMR ($CDCl_3$) δ 7.21 (m, 2H), 6.81 (m, 2H), 4.37 (ABq, J = 11.5 Hz, 2H), 3.75 (s, 3H), 3.72 (dd, J = 6.5, 2.9 Hz, 1H), 3.51 (dd, J = 9.0, 4.6 Hz, 1H), 3.19 (dd, J = 9.05, 7.85 Hz), 3.03 (dq, J = 5.88, 1.33 Hz, 1H), 2.72 (dd, J = 9.41, 4.2 Hz, 1H), 1.96 (m, 1H), 1.43 (m, 1H), 1.20 (d, J = 5.4 Hz, 3H), 0.89 (d, J = 7 Hz, 3H), 0.86 (d, J = 7 Hz, 3H), 0.84 (s, 9H), 0.02 (s, 3H), 0.00 (s, 3H).

***trans*-Epoxide 14:** ^{1}H NMR ($CDCl_3$) δ 7.21 (m, 2H), 6.81 (m, 2H), 4.37 (ABq, J = 11.6 Hz, 2H), 3.78 (s, 3H), 3.61 (dd, J = 6.6, 2.8 Hz, 1H), 3.42 (dd, J = 9.0, 5 Hz, 1H), 3.23 (dd, J = 9.3, 7.1 Hz, 1H), 3.02 (dq, J = 5.7, 1.4 Hz, 1H), 2.79 (dd, J = 9.5, 4.0 Hz, 1H), 1.96 (m, 1H), 1.55 (m, 1H), 1.23 (d, J = 5.5 Hz, 3H), 1.07 (d, J = 6.6 HZ, 3H), 0.91 (d, J = 6.9 Hz, 3H), 0.91 (s, 9H), 0.02 (s, 6H).

Ketone 13: ^{1}H NMR ($CDCl_3$) δ 7.27 (m, 2H), 6.85 (m, 2H), 4.39 (ABq, J = 11.5 Hz, 2H), 3.78 (s, 3H), 3.50 (dd, J = 9.1, 4.5 Hz, 1H), 3.47 (dd, J = 6.16, 3 Hz, 1H), 3.21 (dd, J = 9.1, 7.4 Hz, 1H), 2.48 (dd, J = 16.3, 4.4 Hz, 1H), 2.28 (dd, J = 16.2, 8.0 Hz, 1H), 2.21 (m, 1H), 1.89 (m, 1H), 0.96 (d, J = 7 Hz, 3H), 0.86 (s, 9H), 0.86 (d, J = 6.6 Hz, 3H), 0.01 (s, 3H), 0.00 (s, 3H).

(B) Procedure Utilizing N-Iodosuccinimide. This was performed exactly the same as the above Procedure A, except that *N*-iodosuccinimide was used to replace iodine. The workup was simplified as follows: sodium sulfate decahydrate was added to the reaction mixture and the suspension stirred for 10 min at −20 °C. The resulting light-yellow suspension was treated with heptane and Cellflock (filter aid) and filtered. The solid was washed with heptane, and the combined filtrates were evaporated under vacuum to give the crude product. Chromatography, as described above, yielded pure **4 (**956 g, 27.5%).

Des-iodo olefin 12 (Obtained by the Procedure Described by Shen[9]): ^{1}H NMR ($CDCl_3$) δ 7.21 (m, 2H), 6.83 (m, 2H), 5.31 (m, 1H), 5.19 (m, 1H), 4.36 (s, 2H), 3.77 (s, 3H), 3.50 (dd, J = 9.2, 4.9 Hz, 1H), 3.40 (dd, J = 7.3, 3.9 Hz, 1H), 3.20 (dd, J = 10.3, 8.5 Hz, 1H), 2.62 (m, 1H), 1.97 (m, 1H), 1.54 (dd, J = 6.7 & 1.5 Hz, 3H), 0.93 (d, J = 7.1 Hz, 3H), 0.88 (d, J = 6.7 Hz, 3H), 0.83 (s, 9H), 0.01 (s, 3H), 0.00 (s, 3H).

(2*R*,3*S*,4*S*)-3-(*tert*-Butyldimethylsilanyloxy)-5-hydroxy-2,4-dimethylpentanoic Acid Methoxymethyl Amide (15). A 51.3% water suspension of palladium on charcoal (1.11 kg, 20%) was diluted with *tert*-butyl alcohol (11.8 kg). This suspension was added to a solution of **8** (2.78 kg, 6.32 mol) in *tert*-butyl alcohol (10 kg). The suspension was hydrogenated under H_2 (9 bar) for 35 min at room temperature. The reaction mixture was filtered and the catalyst rinsed with *tert*-butyl alcohol (4 kg). The *tert*-butyl alcohol solution of **15** was used immediately in the next step.

(2*R*,3*S*,4*R*)-3-(*tert*-Butyl-dimethylsilanyloxy)-2,4-dimethyl-5-oxo-pentanoic Acid Methoxymethyl Amide (16). To the *tert*-butyl alcohol solution of **15** were added TEMPO (2,2,6,6-tetramethylpiperidin-1-oxy radical, 146.6 g, 0.94 mol) and solid diacetoxy iodobenzene (4.13 kg, 12.8 mol) at room temperature. The suspension was stirred for 75 min at room temperature and diluted with toluene (13.7 L) and 10% aqueous solution of sodium thiosulfate (23 L). The two-phase system was stirred for 10 min at room temperature, and the phases were separated. The organic phase was concentrated to about one-third of its original volume and filtered. The solid was rinsed with toluene (1 L), and the combined filtrates were concentrated under vacuum at 45 °C to give 2.27 kg of crude aldehyde **16** as an oil, which was used without further purification.

(2*R*,3*S*,4*S*)-3-(*tert*-Butyl-dimethylsilanyloxy)-5-hydroxy-2,4-dimethylhexananoic Acid Methoxymethyl Amide (17). The crude aldehyde **16** (1.4 kg) was dissolved in dichloromethane (16 L) and cooled to −20 °C. A solution of methylmagnesium bromide (5.3 L, 1.4 M) was added dropwise within 90−100 min, maintaining the temperature at −20 °C. The reaction mixture was quenched with 10% aqueous solution of ammonium chloride (44 L) and allowed to warm to 5 °C. The dichloromethane phase was separated and washed with water (2 × 10 L). The solvent was concentrated under vacuum to give 1.61 kg of crude alcohol **17** as an oil, which was used without further purification.

(2*R*,3*S*,4*R*)-3-(*tert*-Butyldimethylsilanyloxy)-2,4-dimethyl-5-oxo-hexananoic acid methoxymethyl amide (6). The crude alcohol **17** (1.35 kg) was dissolved in dichloromethane (4 L) and cooled to 0 °C. Triethylamine (3.0 L) and DMSO (1.6 L) were added. The mixture was cooled to −20 °C, and a solution of the sulphur trioxide pyridine complex (2.73 kg) in DMSO (8 L) was added over 20 min. The mixture was warmed to 0 °C and stirred for an additional 2 h. The mixture was diluted with *tert*-butyl methyl ether (27.4 L) and treated with a solution of sodium hydrogen sulfate (1.86

kg) in water (17 L). The organic phase was separated and washed sequentially with sodium bicarbonate (20 L) and water (20 L). The solvent was concentrated under vacuum to give crude **6** (1.26 kg) as an oil. Chromatography on silica gel (25 kg) eluting with heptane/*tert*-butyl methyl ether 10/1 gave, after removal of solvents, 0.94 kg (73% overall yield from **8**) of pure compound **6**: ^{1}H NMR ($CDCl_3$) δ 4.28 (dd, J = 7.8, 4.2 Hz, 1H), 3.67 (s, 3H), 3.10−2.93 (br m, 4H), 2.69 (s, 3H), 1.09 (d, J = 6.8 Hz, 3H), 1.03 (d, J = 6.9 Hz, 3H), 0.86 (s, 9H), 0.06 (s, 6H). Also isolated were the following compounds:

(3*R*,4*S*,5*S*)-4-(*tert*-Butyldimethylsilanyloxy)-3,5-dimethyltetrahydropyran-2-one (18): ^{1}H NMR ($CDCl_3$) δ 4.19 (dd, J = 11.2, 9.9 Hz, 1H), 4.06 (ddd, J = 10.9, 4.7, 0.8 Hz, 1H), 3.62 (m, 1H), 2.55 (qd, J = 7.7, 3.9 Hz 1H), 2.13 (m, 1H), 1.23 (d, J = 7.5 Hz, 3H), 0.90 (d, J = 7.4 Hz, 3H), 0.83 (s, 9H), 0.01 (s, 3H), 0.00 (s, 3H).

(3*R*,4*S*,5*S*)-4-(*tert*-Butyldimethylsilanyloxy)-3,5,6-trimethyltetrahydropyran-2-one (19) (1:1 mixture of diastereoisomers): ^{1}H NMR ($CDCl_3$) δ 4.33 (dd, J = 6.8, 2.7 Hz, 2H), 3.66 (dd, J = 9.9, 4.1 Hz, 2H), 2.37 (qd, J = 11.2, 7.0 Hz, 2H), 1.88 (m, 2H), 1.26 (d, J = 6.6 Hz, 3H), 1.22 (d, J = 6.9 Hz, 3H), 0.89 (d, J = 7.4 Hz, 3H), 0.85−0.82 (m, 21H), 0.01 (m, 12H).

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Large-Scale Synthesis of the Anti-Cancer Marine Natural Product (+)-Discodermolide. Part 3: Synthesis of Fragment C_{15-21}

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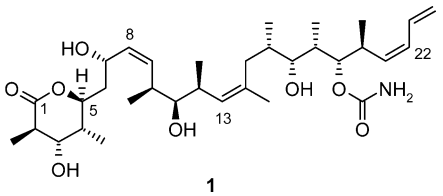
Abstract:

Smith's procedure of preparing fragment C_{15-21} (5) from common precursor 3 was optimized. The ease of plant operations made this six-step route successful for the production of several kilograms of this fragment with high purity.

Introduction

In the previous two parts of this series, large-scale preparations of two key fragments required for the total synthesis of (+)-discodermolide (**1**) are discussed.



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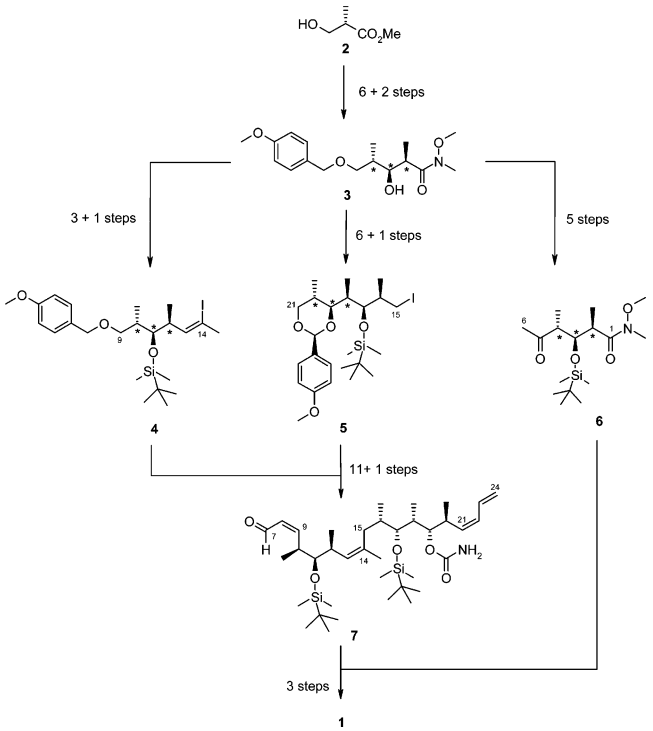
In this contribution, the third part of the series, we present the route and results leading to the synthesis of fragment C_{15-21}. The strategy for the synthesis of this fragment (alkyl iodide **5**) from the common precursor **3** and its conversion to **1** is outlined in Scheme 1.

Scheme 1. **Synthetic strategy leading to fragment C_{15-21} (5) and (+)-discodermolide**



Results and Discussion

The published route[1] for the synthesis of fragment C_{15-21} (**5**) from the common precursor **3** was very attractive from the scale-up point of view, since all intermediates en route were reported as crystalline solids. We decided to further develop this six-step sequence for our multigram synthesis of (+)-discodermolide (Scheme 2).

Synthesis of PMP-Protected Aldehyde 9. Treatment of the Smith common precursor **3**[1] (described in Part 1) with a solution of DDQ[2] in toluene in the presence of 4-Å powdered molecular sieves furnished crystalline *p*-methoxybenzylidene (PMP) acetal **8** in 61% yield. This is one of several crystalline intermediates in the synthesis that can be purified easily by recrystallization of the crude material. Acetal **8** was produced presumably by an oxidative cyclization pathway via cations **3a** and **3b** as shown in Scheme 3. Anhydrous conditions are highly critical to obtain high yields of this reaction. If water is not excluded completely, some further oxidized *p*-methoxybenzyl cation **8a** can be captured by water, leading to benzoate **13** as a major byproduct (Scheme 4). Controlled reduction of the Weinreb amide **8** with $LiAlH_4$ provided another crystalline compound, aldehyde **9**, in high yield (91%). Intermediate **9** was isolated with high purity by crystallization and filtration.

Evans Aldol Reaction. To extend the carbon chain, the Evans aldol condensation protocol was employed. Coupling of aldehyde **9** with oxazolidinone **9a** at −78 to −10 °C

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(1) (a) Smith, A. B.; Beauchamp, T. J.; LaMarche, M. J.; Kaufman, M. D.; Qiu, Y.; Arimoto, H.; Jones, D. R.; Kobayashi, K. *J. Am. Chem. Soc.* **2000**, *122*, 8654. (b) Smith, A. B.; Kaufman, M. D.; Beauchamp, T. J.; LaMarche, M. J.; Arimoto, H. *Org. Lett.* **1999**, *1*, 1823.

(2) Oikawa, Y.; Yoshioka, T.; Yonemitsu, O. *Tetrahedron Lett.* **1982**, *23*, 889.

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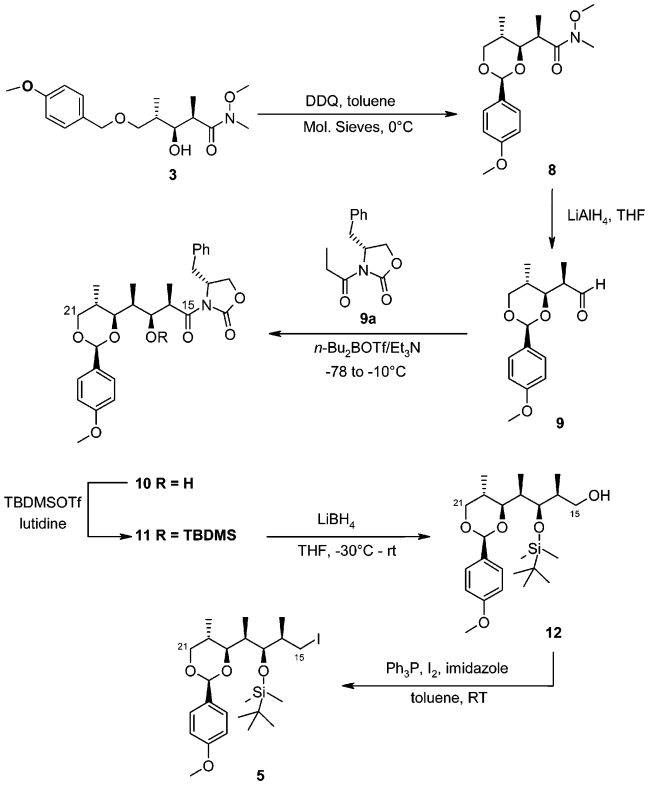
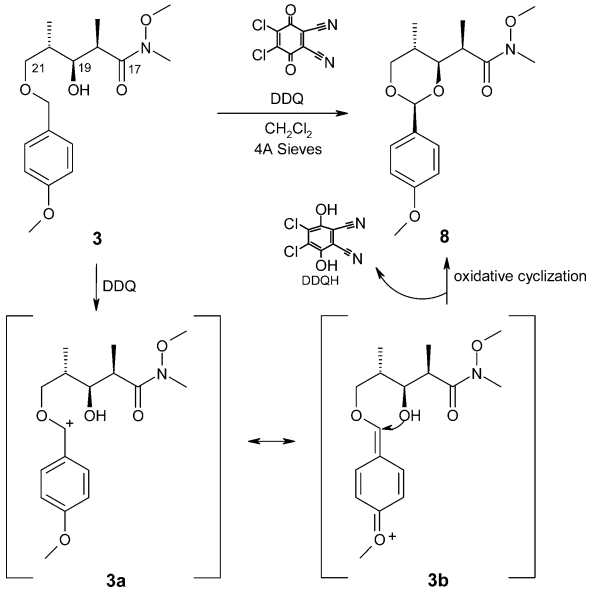
Scheme 2. **Synthesis of fragment C_{15-21} from the common precursor**



Scheme 3. **Oxidative cyclization**



mediated by di-*n*-butylboron triflate afforded the desired C_{15-21} backbone. The success of the aldol reaction was dependent largely on the quality of the di-*n*-butylboron triflate, as previously discussed (see Part 1 in this series). Gratifyingly, intermediate **10** was also a crystalline solid and could be readily isolated from the reaction mixture after workup, crystallization, and filtration in 85% yield. The diastereomeric excess of this compound was so high that none of the undesired diastereoisomer was detected. However, when the same reaction was carried out either at room temperature or allowed to warm to room temperature before

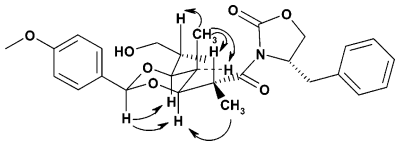
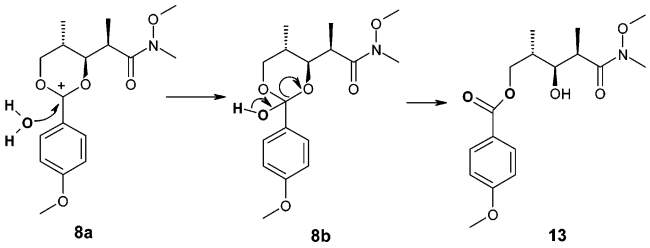
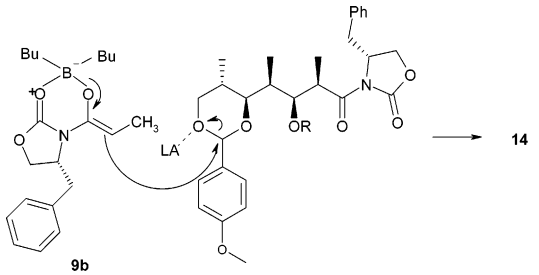


Figure 1. **NOE of 15.**

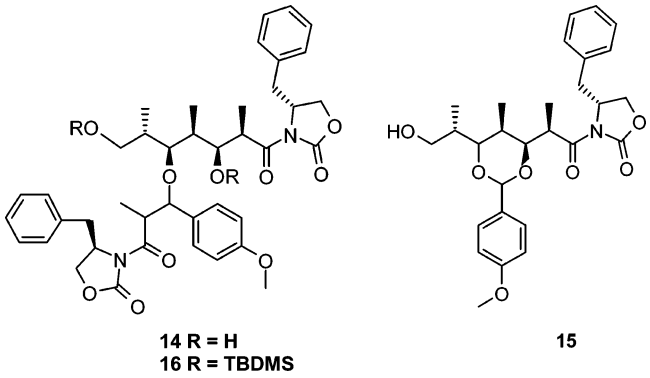
Scheme 4. **Formation of benzoate byproduct**



Scheme 5. **Formation of byproduct 14**



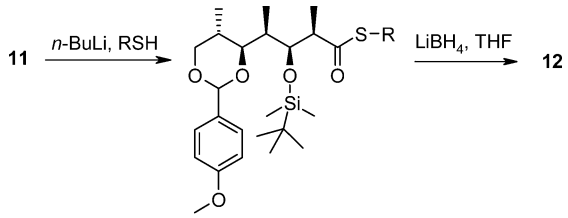
quench, significant amounts of byproducts (**14**, major, and **15,** minor) formed. Removal of byproduct **14** from the desired product **10** by crystallization was difficult, since it cocrystallized with the product. As a result, it was important to keep the reaction mixture below 0 °C to suppress the formation of these byproducts.



Formation of these byproducts suggested instability of the *p*-methoxybenzyl protecting group. Formation of **14** was attributed to the presence of excess di-*n*-butylboron triflate and enolate **9b**, which could open the acetal ring mediated by the boron (Lewis acid) (Scheme 5). The structure of byproduct **14** was supported by NMR spectroscopy. The structure of **15** was also supported by NMR experiments (NOE indicated by arrows) as shown in Figure 1.

Intermediate **10** was unstable at ambient temperature and underwent epimerization at the C_{16} position. This can be completely suppressed by storing it at temperatures below −10 °C. Thus, rapid workup and isolation were essential to achieve a higher yield. Epimerization was most likely caused

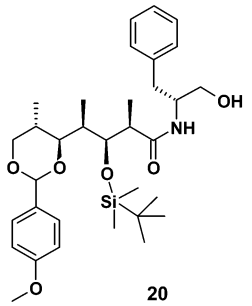
Scheme 6. **Reduction via a thio ester**

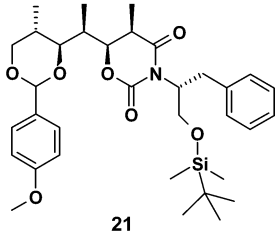


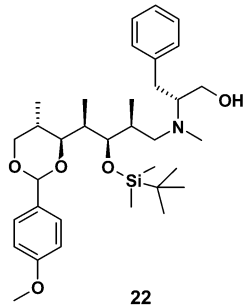
by retro-aldol/aldol reactions initiated by the unprotected hydroxy group. This was supported by the fact that silyl ether **11**, formed by silylation of **10** with TBDMSOTf/lutidine in quantitative yield, was found to be stable at ambient temperature. Both hydroxyl groups of byproduct **14** were also silylated to furnish bis-silyl ether **16** as a stable reference sample.

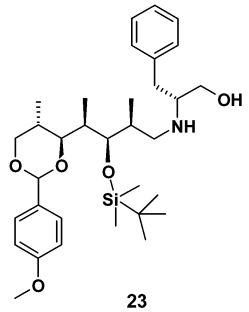
Conversion to the Iodo Intermediate 5. Reductive removal of the oxazolidinone chiral auxiliary from **11** leading to an alcohol was required. Treatment of **11** with a solution of lithium borohydride in THF/EtOH[3] gave an average yield of 60% of the desired alcohol **12** after chromatography on silica gel. We were unable to reproduce the high yields (>80%) reported in the literature,[1] despite examining various other reducing agents, solvents, etc. For example, reduction of **11** with sodium borohydride[4] was very slow and resulted in a very messy reaction. Another alternative approach, where **11** was converted into a thio ester **17**[5] followed by reduction,[6] did not improve the yield (Scheme 6). Attempts to reduce **11** to the corresponding aldehyde with the Schwartz reagent, according to a recently described procedure,[7] were also unsuccessful.

We found the lower yield was caused by several competing reactions that led to four byproducts **20**−**23**; **20** was the major byproduct. It is obvious that **20**, **22**, and **23** were generated by uncontrolled reductions of the carbonyl groups internal and external to the oxazolidinone ring. The exact pathway for the formation of **21** was unclear.

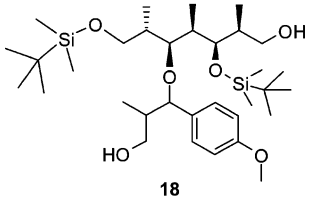


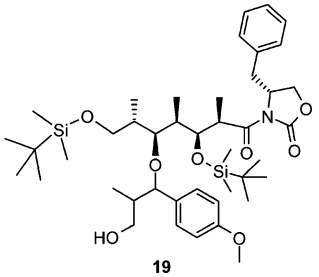






Silyl ether **16** was also reduced under the same conditions to furnish diol **18** as an analytical reference. Interestingly, the partially reduced, mono-oxazolidinone **19** was also isolated.





Finally, conversion of alcohol **12** into the desired alkyl iodide **5** was accomplished by employing Ph_3P/I_2/imidazole. The desired product was isolated as an oil in 90% yield without chromatography. Iodide **5** is light sensitive and forms a low-melting crystalline solid.

In conclusion, fragment C_{15-21} (**5**) was produced in six steps from the common precursor **3** with an overall yield of 24%. Although the yield was about half of what was reported by Smith (56%),[1a] the ease of plant operations made this route successful for the production of several kilograms of this fragment with high purity.

Experimental Section

(*R*)-*N*-Methoxy-2-[(4*S*,5*S*)-2-(4-methoxyphenyl)-5-methyl-1-[1,3]dioxin-4-yl]-*N*-methyl- propionamide (8). To a solution of common precursor **3** (18.1 kg, 77% purity, 42.83 mol) in toluene (260 kg) was added powdered 4-Å molecular sieves (18.1 kg). The suspension was cooled to 0 °C, and a solution of DDQ (15.0 kg, 66.1 mol) in toluene (90.4 kg) was added over 60 min. The addition equipment was washed with toluene (17 kg). The suspension was stirred overnight at 0 °C. Cellflock (filter aid) (18.1 kg) was added and the suspension filtered. The solid was washed with toluene (1 × 175 kg, followed by 2 × 36.4 kg). The combined filtrates were washed with 2 M aqueous sodium hydroxide solution (92.1 kg). The organic phase was then washed with four times with water (128 kg) containing 15% aqueous NaCl (26.8 kg) and concentrated under vacuum at 45 °C to about one-third of the original volume. The residue was filtered, and the solid was rinsed with toluene (2 × 9.1 kg). The combined filtrate was concentrated under vacuum at 45 °C to give an oil. The oily residue was dissolved in diisopropyl ether (15.8 kg), and the resulting solution was stirred for 60 min at room temperature after which time crystallization began. The suspension was cooled to 0 °C, and stirred for an additional 2.5 h. The product was isolated by filtration, washed with 10 kg of a 2/1 diisopropyl ether/heptane mixture

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(5) Evans, D. A.; Wu, L. D.; Wiener, J. J. M.; Johnson, J. S.; Ripin, D. H. B.; Tedrow, J. S. *J. Org. Chem.* **1999**, *64*, 6411.
(6) Liu, H. J.; Bukownik, R.; Pednekar, P. R. *Synth. Commun.* **1981**, *11*, 599.
(7) White, J. M.; Ashok, R T.; Georg, G. I. *J. Am. Chem. Soc.* **2000**, *122*, 11995.

and dried at 30 °C to give **8** (6.9 kg, 50%) as a white crystalline solid: ^{1}H NMR ($CDCl_3$) δ 7.40 (m, 2H), 6.86 (m, 2H), 5.46 (s, 1H), 4.40 (dd, J = 11.6, 4.0 Hz, 1H), 3.90−3.76 (m, 4H), 3.51 (pseudo t, J = 10.9 Hz, 1H), 3.22−3.11 (m, 4H), 1.95 (m, 1H), 1.26 (d, J = 6.9 Hz, 3H), 0.75 (d, J = 6.9 Hz, 3H). The following compound (**13**) was also isolated by chromatography from the mother liquors.

4-Methoxybenzoic acid (2*S*,3*S*,4*R*)-3-hydroxy-4-(methoxymethylcarbamoyl)-2-methyl-pentyl ester (13): ^{1}H NMR ($CDCl_3$) δ 7.92 (m, 2H), 6.84 (m, 2H), 4.48 (A part of ABq, J = 11.7, 3.7 Hz, 1H), 4.30 (B part of ABq, J = 11.7, 6.7 Hz, 1H), 4.10 (br s, exch D_2O, 1H), 3.79 (s, 3H), 3.76−3.70 (m, 1H), 3.20−2.98 (m, 4H), 1.99 (m, 1H), 1.12 (d, J = 6.7 Hz, 3H), 0.94 (d, J = 7.5 Hz, 3H).

2-[(4*R*,5*S*,6*S*)-2-(4-Methoxyphenyl)-5-methyl-[1,3]dioxin-4-yl]-propionaldehyde (9). A solution of amide **8** (1.953 kg, 6.04 mol) in anhydrous THF (16 L) was cooled to −75 °C. A solution of lithium aluminum hydride (1.2 kg of a 10 wt/wt % solution in THF, 3.16 mol) was added dropwise over 30 min. The reaction mixture was warmed to −20 °C, and ethyl acetate (0.58 kg, 6.6 mol) was added dropwise over 15 min. The mixture was treated with 50% (w/v) aqueous solution of sodium potassium tartrate (16 L) and stirred for 60 min. The organic layer was separated, and the aqueous phase was re-extracted with THF (7 L). The organic layers were concentrated under vacuum, and toluene (10 L) was added to the residue. The toluene solution was extracted with 20% aqueous solution of citric acid (2 × 3 L), followed by washing with water (3 × 3 L). The organic phase was concentrated under vacuum at 40 °C, and heptane (6 L) was added to the residue. Crystallization began immediately. The suspension was cooled to 4 °C and stirred for 3.5 h. The solid was collected by filtration, rinsed with heptane (2 × 500 mL), and dried to give aldehyde **9** (1.455 kg, 91%) as a white crystalline solid: $[\alpha]^{25}_D$ +10.3 (c = 1, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 9.74 (d, J = 0.61 Hz, 1H), 7.32 (m, 2H), 6.84 (m, 2H), 5.47 (s, 1H), 4.13 (dd, J = 11.3, 4.7 Hz, 1H), 4.05 (dd, J = 9.7, 2.8 Hz, 1H), 3.77 (s, 3H), 3.56 (pseudo t, J = 11.7 Hz, 1H), 2.56 (qd, J = 7.21, 2.8 Hz, 1H), 2.09 (m, 1H), 1.22 (d, J = 7.2 Hz, 3H), 0.79 (d, J = 6.6 Hz, 3H).

(*R*)-4-Benzyl-3-{(2*R*,3*S*,4*S*)-3-hydroxy-4-[(4*S*,5*S*)-2-(4-methoxyphenyl)-5-methyl-[1,3]dioxin-4-yl]-2-methylpentanoyl}-oxazolidin-2-one (10). A solution of (*R*)-4-benzyl-3-propionyloxazolidin-2-one **9a** (1.81 kg, 7.76 mol) in dichloromethane (6.5 L) was cooled to −2 to 0 °C. A 26 wt % solution of di-*n*-butylboron triflate (2.44 kg, 8.54 mol) was added within 20 min. Triethylamine (995 g, 9.85 mol) was added within 20 min, and the mixture was stirred for 60 min at 0 °C. The resulting enolate solution was cooled to −78 °C, and a solution of aldehyde **9** (1.3 kg, 4.92 mol) was added dropwise within 15 min. The mixture was stirred for an additional 1 h at this temperature. The reaction mixture was warmed stepwise to 0 °C by holding at −50 °C for 1 h and at −22 °C for 16 h. Upon reaching 0 °C, aqueous phosphate buffer solution (6.5 L, pH 7.0) was added, followed by dropwise addition of aqueous hydrogen peroxide (1.52 kg, 35% solution) over 45 min, maintaining the temperature at 0 °C. The reaction mixture was stirred for 60 min at 0 °C, and a 50% aqueous solution of sodium thiosulphate (10 kg) was added slowly (very exothermic for the addition of the first 2−3 kg). The mixture was stirred for 30 min at 5 °C, and the organic phase was separated, washed with water (13 L), dried over $MgSO_4$, and filtered. The solvent was concentrated under vacuum at 30 °C to give the crude product as an oil. This oil was dissolved in 2-propanol (2.6 L), and heptane (6.5 L) was added dropwise. The solution was seeded and stirred at room temperature for 60 min. More heptane (5.2 L) was added to the suspension and stirred for 20 h at 20 °C. The solid was collected by filtration, rinsed, and dried at 20 °C to afford **10** (2.066 kg, 85%) as a white crystalline solid: $[\alpha]^{25}_D$ −16.3 (c = 1, $CHCl_3$); ^{1}H NMR (CD_3OD) δ 7.41−7.23 (m, 7H), 6.90 (m, 2H), 5.51 (s, 1H), 4.69 (m, 1H), 4.27−4.07 (m, 4H), 4.01 (dd, J = 6.9, 4.9 Hz, 1H), 3.81 (s, 3H), 3.67 (dd, J = 10.0, 1.7 Hz, 1H), 3.57 (pseudo t, J = 11.0 Hz, 1H), 3.16 (A part of ABq, J = 13.5, 3.5 Hz, 1H), 2.95 (B part of ABq, J = 13.5, 7.9 Hz, 1H), 2.13−1.94 (m, 2H), 1.27 (d, J = 6.93 Hz, 3H), 1.09 (d, J = 7.3 Hz, 3H), 0.82 (d, J = 6.6 Hz, 3H).

Chromatography of mother liquors on silica gel allowed the isolation of byproducts **14** and **15**.

Compound 14: ^{1}H NMR (C_6D_6) δ 7.50 (m, 2H), 7.20−7.00 (m, 8H), 6.88 (m, 2H), 6.71 (m, 2H), 5.01−4.87 (m, 2H), 4.32 (m, 2H), 3.89 (m, 1H), 3.75−3.40 (m, 10H), 3.32 (m, 1H), 3.28 (s, 3H), 3.17 (t, J = 6.5 Hz, exch D_2O, primary OH, 1H), 2.88 (A part of ABq, J = 13.5, 3.5 Hz, 1H), 2.64 (B part of ABq, J = 13.5, 7.9 Hz, 1H), 2.32−2.16 (m, 2H), 1.45−1.35 (m, 7H, becomes 6H on D_2O exch), 1.04 (d, J = 6.7 Hz, 3H), 0.98 (d, J = 7.2 Hz, 3H). After derivitization with trichloroacetyl isocyanate, the following spectrum was obtained: ^{1}H NMR (C_6D_6) δ 7.45 (m, 2H), 7.20−6.95 (m, 8H), 6.82 (m, 2H), 6.76 (m, 2H), 5.23 (dd, J = 9.0, 4.0 Hz, 1H, CHOH), 4.85 (d, J = 11.0 Hz, 1H, OCHPhOMe), 4.75 (qd, J = 11.0, 4.0 Hz, OCCH(CH3)OCHPhOMe), 4.50 (dd, J = 10.2, 5.0 Hz, 1H), 4.40 (m, 1H), 4.30 (m, 1H), 3.43 (m, 1H), 3.72 (pseudo t, J = 10 Hz, 1H), 3.60−3.45 (m, 4H), 3.30−3.18 (m, 5H), 2.83−2.67 (m, 3H), 2.35 (B part of ABq, J = 13.5, 8.4 Hz, 1H), 1.86 (m, 1H), 1.30−1.20 (m, 6H), 0.98 (d, J = 6.7 Hz, 3H), 0.89 (d, J = 7.0 Hz, 3H).

(*R*)-4-Benzyl-3-{(*R*)-2-[4*S*,5*R*]-6-((*S*)-2-hydroxy-1-methylethyl)-2-(4-methoxyphenyl)-5-methyl[1,3]dioxin-4-yl]-propionyl}-oxazolidin-2-one (15): ^{1}H NMR (C_6D_6) δ 7.52 (m, 2H), 7.05 (m, 3H), 6.83 (m, 4H, 5.50 (s, 1H), 4.56 (m, 1H), 4.31 (dd, J = 10.0, 2.1 Hz, 1H), 4.20 (m, 1H), 3.70−3.58 (m, 3H), 3.44 (dd, J = 10.5, 4.3 Hz, 1H), 3.31 (s, 3H), 3.15 (pseudo t, J = 9.5 Hz, 1H), 2.94 (dd, J = 12.5, 4.1 Hz, 1H), 2.25 (dd, J = 12.2, 8.2 Hz, 1H), 2.06−1.90 (m, 2H), 1.56 (d, J = 6.8 Hz, 3H), 1.13 (d, J = 6.9 Hz, 3H), 0.66 (d, J = 7.4 Hz, 3H).

(*R*)-4-Benzyl-3-{(2*R*,3*S*,4*R*)-3-(*tert*-butyl-dimethylsilanyloxy)-4-[(4*S*,5*S*)-2-(4-methoxyphenyl)-5-methyl-[1,3]-dioxin-4-yl]-2-methylpentanoyl}-oxazolidin-2-one (11). Compound **10** (2.05 kg, 4.12 mol) was dissolved in dichloromethane (15 L) and treated with 2,6-lutidine (850 g, 7.93 mol). The solution was cooled to −10 °C, and *tert*-butyldimethylsilyl triflate (1.8 kg, 6.81 mol) was added

dropwise over 15 min. The reaction mixture was stirred at −10 °C for a further 30 min and warmed to 0 °C. The mixture was diluted with *tert*-butyl methyl ether (24 L) and washed with 10% aqueous solution of sodium hydrogen sulphate (15 L). The organic phase was separated and washed with brine, dried over $MgSO_4$, filtered, and concentrated under vacuum to give silyl ether **11** as an oil (2.881 kg, 114%), which was used without further purification: ^{1}H NMR ($CDCl_3$) δ 7.38 (m, 2H), 7.25 (m, 3H), 7.15 (m, 2H), 6.81 (m, 2H), 5.45 (s, 1H), 4.27 (m, 1H), 4.10 (dd, J = 6.8, 4.5 Hz, 1H), 4.05−3.90 (m, 2H), 3.80−3.70 (m, 4H), 3.48 (pseudo t, J = 10.6 Hz, 1H), 3.08 (A part of ABq, J = 13.5, 3.5 Hz, 1H), 2.58 (B part of ABq, J = 13.5, 7.9 Hz, 1H), 2.10−1.90 (m, 2H), 1.18 (d, J = 6.8 Hz, 3H), 1.05 (d, J = 7.4 Hz, 3H), 0.9 (s, 9H), 0.71 (d, J = 6.7 Hz, 3H), 0.02 (s, 6H).

Compound 16. Compound **14** (0.46 g, 0.63 mmol) was silylated in the same fashion as **11** to produce 0.95 g of **16**: ^{1}H NMR ($CDCl_3$) δ 7.40−7.20 (m, 10H), 7.15 (m, 2H), 6.86 (m, 2H), 4.80−4.65 (m, 2H), 4.45 (m, 2H), 4.18−3.90 (m, 4H), 3.80 (s, 3H), 3.66 (m, 1H), 3.63−3.52 (m, 3H), 3.30 (m, 1H), 2.95 (m, 2H), 3.16 (A part of ABq, J = 13.5, 3.5 Hz, 1H), 2.63 (B part of ABq, J = 13.5, 7.9 Hz, 1H), 2.10 (m, 1H), 1.61 (m, 1H), 1.05 (m, 6H), 1.00−0.78 (m, 22H), 0.08−0.00 (m, 12H).

(2*S*,3*R*,4*R*)-3-(*tert*-butyldimethylsilanyloxy)-4-[(4*S*,5*S*)-2-(4-methoxyphenyl)-5-methyl-[1,3]dioxin-4-yl]-2-methylpentan-1-ol (12). Silyl ether **11** (5.0 kg, 8.17 mol) was dissolved in THF (50.0 kg), and the solution was cooled to −35 °C. Ethanol (0.957 kg) was added, followed by dropwise addition of a 10 wt % solution of lithium borohydride in THF (4.52 kg, 20.75 mol) over a period of 35 min. The mixture was warmed to 23 °C within 60 min and stirred for 2 h. A 1.0 M aqueous solution of sodium hydroxide (44.4 kg) was added slowly, and the mixture was stirred for 2 h at 20 °C. *tert*-Butyl methyl ether (31.6 kg) was added. The organic layer was separated, washed with brine (50 kg), dried over Na_2SO_4, and concentrated under vacuum at 25 °C to give the crude product as an oil (4.72 kg, 131%). The crude material was dissolved in a mixture of cyclohexane (32.8 kg) and methanol (7.46 kg). Water (2.36 kg) was added, and the two-phase mixture was stirred for 10 min. The organic phase was separated and concentrated under vacuum to give an oil (3.39 kg). This material was divided into three portions, and each (1.13 kg) was chromatographed over 25 kg of silica gel eluting with hexane/ethyl acetate mixtures (starting with 15% of ethyl acetate, followed by 20, 30, and finally 75% of ethyl acetate). The fractions containing the desired product from all three chromatographies were combined and concentrated under vacuum to give alcohol **12** (1.989 kg, 56%) as an oil: $[\alpha]^{25}_D$ +38.6 (c = 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.34 (m, 2H), 6.83 (m, 2H), 5.36 (s, 1H), 4.06 (dd, J = 8.1, 4.7 Hz, 1H), 3.81 (dd, J = 7.0, 2.4 Hz, 1H), 3.76 (s, 3H), 3.36−3.38 (m, 3H), 2.10−1.85 (m, 2H), 1.70 (br t, exch D_2O, 1H), 0.99 (d, J = 7.0 Hz, 3H), 0.85 (s, 9H), 0.81 (d, J = 6.7 Hz, 3H), 0.71 (d, J = 7.1 Hz, 3H), 0.00 (s, 3H), −0.03 (s, 3H). The following byproducts (**20**−**23)** were also isolated by chromatography on further elution.

(2*R*,3*S*,4*R*)-3-(*tert*-Butyldimethylsilanyloxy)-4-[(4*S*,5*S*)-2-(4-methoxyphenyl)-5-methyl-[1,3]dioxan-4-yl]-2-methylpentanoic acid ((*R*)-1-benzyl-2-hydroxyethyl)-amide (20): ^{1}H NMR ($CDCl_3$) δ 7.47 (m, 2H), 7.22 (m, 3H), 7.01 (m, 2H), 6.95 (m, 2H), 5.54−5.49 (m, 2H), 4.12 (m, 2H), 3.96 (m, 1H), 3.86 (m, 2H), 3.79 (s, 3H), 3.51 (pseudo t, J = 11.5 Hz, 1H), 3.44 (dd, J = 10.9, 3.6, 1H), 3.16 (dd, J = 11.5, 6.7 Hz, 1H), 2.71−2.57 (br s, 1H), 2.55−2.45 (m, 2H), 2.23 (dd, J = 13.9, 7.3 Hz, 1H), 2.11−1.96 (m, 2H), 1.02−0.97 (m, 6H), 0.92 (s, 9H), 0.73 (d, J = 6.7 Hz, 3H), 0.08 (s, 3H), 0.04 (s, 3H).

(5*R*,6*S*)-3-[(*R*)-1-Benzyl-2-(*tert*-Butyldimethylsilanyloxy)-ethyl]-6-{(*R*)-1-[(4*S*,5*S*)-2-(4-methoxyphenyl)-5-methyl-[1,3]dioxan-4-yl]ethyl}-5-methyl-[1,3]oxazinane-2,4-dione (21): ^{1}H NMR ($CDCl_3$) δ 7.40 (m, 2H), 7.34−7.22 (m, 5H), 6.90 (m, 2H), 5.44 (s, 1H), 4.64 (m, 2H), 4.14 (m, 2H), 4.03 (pseudo t, J = 8.6 Hz, 1H), 3.95 (dd, J = 8.43, 3.7 Hz, 1H), 3.84 (s, 3H), 3.55 (m, 1H), 3.45 (dd, J = 10.4, 2.5 Hz, 1H), 3.34 (m, 1H), 2.82 (dd, J = 13.6, 11.1 Hz, 1H), 2.66 (qd, J = 7.4, 3.3 Hz, 1H), 2.18 (m, 2H), 1.27 (d, J = 7.2 Hz, 3H), 1.24 (d, J = 6.5 Hz, 3H), 0.95 (s, 9H), 0.81 (d, J = 6.5 Hz, 3H), 0.33 (m, 6H).

(*R*)-2-({(2*S*,3*R*,4*R*)-3-(*tert*-Butyldimethylsilanyloxy)-4-[(4*S*,5*S*)-2-(4-methoxyphenyl)-5-methyl[1,3]dioxan-4-yl]-2-methylpentyl}-methylamino)-3-phenylpropan-1-ol (22): ^{1}H NMR ($CDCl_3$) δ 7.41 (m, 2H), 7.23 (m, 3H), 7.08 (m, 2H), 6.90 (m, 2H), 5.44 (s, 1H), 4.13 (d, J = 11.4, 4.7 Hz, 1H), 3.82 (s, 3H), 3.69 (d, J = 7.1 Hz, 1H), 3.61 (d, J = 9.4 Hz, 1H), 3.54 (pseudo t, J = 11.4 Hz, 1H), 3.40−3.30 (m, 2H), 2.98−2.87 (m, 2H), 2.43 (dd, J = 12.6, 8.3 Hz, 1H), 2.35−2.24 (m, 6H, becomes 5H on D^2O exch), 2.15−2.01 (m, 2H), 1.92 (m, 1H), 1.05 (d, J = 7.4 Hz, 3H), 0.95 (s, 9H), 0.90 (d, J = 6.8 Hz, 3H), 0.77 (d, J = 6.8 Hz, 3H), 0.07 (m, 6H).

(*R*)-2-({(2*S*,3*R*,4*R*)-3-(*tert*-Butyldimethylsilanyloxy)-4-[(4*S*,5*S*)-2-(4-methoxyphenyl)-5-methyl[1,3]dioxan-4-yl]-2-methylpentylamino}-3-phenylpropan-1-ol (23): ^{1}H NMR ($CDCl_3$) δ 7.44 (m, 2H), 7.33 (m, 2H), 7.27 (m, 1H), 7.22 (m, 2H), 6.89 (m, 2H), 5.44 (s, 1H), 4.10 (dd, J = 10.9, 4.1 Hz, 1H), 3.83−3.31 (m, 6H, becomes 5H on D_2O exch), 3.53 (d, J = 8.2 Hz, 1H), 3.50−3.44 (m, 2H), 3.33 (dd, J = 14.5, 7.6 Hz, 1H), 3.13 (m, 1H), 2.72 (td, J = 10.6, 4.0 Hz, 1H), 2.55 (td, J = 11.2, 2.3 Hz, 1H), 2.52−2.44 (m, 2H), 2.15−2.00 (br m, 2H, becomes 1H on D_2O exch), 1.80 (m, 1H), 0.96 (d, J = 6.8 Hz, 3H), 0.89 (s, 9H), 0.72 (d, J = 6.7 Hz, 3H), 0.63 (d, J = 6.5 Hz, 3H), 0.00 (s, 3H), −0.04 (s, 3H).

(2*R*,3*S*,4*R*)-3-(*tert*-Butyldimethylsilanyloxy)-4-[(4*S*,5*S*)-2-(4-methoxyphenyl)-5-methyl-[1,3]dioxin-4-yl]-2-methylpentanethioic acid *S*-decyl ester (17). A solution of 1-decanethiol (89.7 mg, 0.48 mmol) in THF (3 mL) was cooled to −78 °C and treated with *n*-butyllithium (0.739 mL, 1.18 mmol). The solution was stirred for 5 min, and a solution of **11** (0.3 g, 0.47 mmol) in THF (5 mL) was added dropwise. The mixture was stirred at −78 °C for 10 min, warmed to 0 °C, and stirred for 30 min. The reaction was quenched by the addition of saturated aqueous ammonium chloride solution (20 mL) and diluted with *tert*-butyl methyl

ether (10 mL). The organic layer was separated, washed with water, dried over Na_2SO_4, and concentrated under vacuum at 30 °C to give an oil (0.35 g). Chromatography on silica gel gave thio ester **17** (0.188 g, 66%) as a waxy solid: ^{1}H NMR ($CDCl_3$) δ 7.41 (m, 2H), 6.86 (m, 2H), 5.43 (s, 1H), 4.19 (dd, J = 6.8, 3.6 Hz, 1H), 4.09 (dd, J = 11.3, 4.54 Hz, 1H), 3.79 (s, 3H), 3.61 (dd, J = 10.5, 1.9 Hz, 1H), 3.49 (pseudo t, J = 11.0 Hz, 1H), 2.98 (qd, J = 6.8, 3.3 Hz, 1H), 2.79 (td, J = 7.8, 2.3 Hz, 2H), 2.02−1.90 (m, 2H), 1.51 (m, 1H), 1.36−1.20 (m, 16H), 1.12 (d, J = 7.1 Hz, 3H), 1.01 (d, J = 7.1 Hz, 3H), 0.89−0.87 (m, 12H), 0.71 (d, J = 6.7 Hz, 3H), 0.00 (s, 3H), −0.04 (s, 3H).

Silyl ether **16** was reduced using the same procedure as described for the conversion of **11** to **12**. The following two compounds (**18** and **19**) were isolated.

(2*S*,3*R*,4*R*,5*S*,6*S*)-3,7-Bis-(*tert*-butyldimethylsilanyloxy)-5-[3-hydroxy-1-(4-methoxyphenyl)-2-methylpropoxy]-2,4,6-trimethylheptan-1-ol (18): ^{1}H NMR ($CDCl_3$) δ 7.20 (m, 2H), 6.85 (m, 2H), 4.15 (d, J = 10 Hz, 1H), 3.85 (br m, 1H), 3.75 (s, 3H), 3.70−3.50 (m, 4H), 3.37 (dd, J = 11.0, 8.0 Hz, 1H), 3.20 (d, J = 6.0 Hz, 1H), 3.05−2.90 (m, 3H), 2.25−2.05 (m, 2H), 1.60 (m, 2H), 0.96 (d, J = 7.0 Hz, 3H), 0.90 (m, 12H), 0.80 (s, 9H), 0.60 (d, J = 6.5 Hz, 3H), 0.52 (d, J = 6.8 Hz, 3H), 0.02 to −0.04 (m, 12H).

(*R*)-4-Benzyl-3-{(2*R*,3*S*,4*R*,5*S*,6*S*)-3,7-bis-(*tert*-butyldimethylsilanyloxy)-5-[3-hydroxy-1-(4-methoxyphenyl)-2-methylpropoxy]-2,4,6-trimethylheptanoly}-oxazolidin-2-one (19): ^{1}H NMR ($CDCl_3$) δ 7.20 (m, 7H), 6.82 (m, 2H), 6.02 (br m, exch D_2O, 1H), 4.30 (d, J = 10 Hz, 1H), 4.20 (m, 2H), 3.85 (s, 3H), 3.80−3.30 (m, 8H), 2.90 (A part of ABq, J = 13.5, 3.5 Hz, 1H), 2.60 (B part of ABq, J = 13.5, 7.9 Hz, 1H), 2.40−2.20 (m, 2H), 1.60 (m, 4H), 1.00 (d, J = 7.2 Hz, 3H), 0.95−0.75 (m, 15H), 0.70 (s, 9H), 0.58 (d, J = 6.5 Hz, 3H), 0.02 to −0.05 (m, 12H).

***tert*-Butyl-((1*S*,2*R*)-3-iodo-1-{(*R*)-1-[(4*S*,5*S*)-2-(4-methoxyphenyl)-5-methyl-[1,3]dioxin-4-yl]-ethyl}-2-methylpropoxy)-dimethylsilane (5).** Alcohol **12** (2.75 kg, 6.27 mol) was dissolved in a mixture of toluene (30 kg) and acetonitrile (4.77 kg). Imidazole (1.37 kg, 20.13 mol) and triphenylphosphine (2.70 kg, 10.3 mol) were added, and the solution was cooled to 10−15 °C. A solution of iodine (2.59 kg, 10.2 mol) in toluene (24.5 kg) containing acetonitrile (3.89 kg) was added dropwise over 25 min. The mixture was warmed to room temperature within 30 min and stirred for 3 h. A 5% aqueous solution of sodium thiosulphate (58 kg) was added, and the reaction mixture was stirred for 10 min. The organic phase was separated and washed sequentially with 5% aqueous sodium thiosulphate (58 kg) and brine (66 kg). The organic phase was dried over Na_2SO_4 and concentrated under vacuum at 40 °C until a final volume of 10 L was reached. Hexane (37.4 kg) was added, and the suspension was stirred for 10 min. The solid was filtered and rinsed with heptane (2 × 10 kg). The combined filtrates were cooled to 2 °C and stirred for 8 h. The solid was filtered and rinsed with heptane (4 kg). The combined filtrates were charged with methanol (17.4 kg) and water (5.5 kg). The resulting two-phase system was stirred for 10 min, and the organic phase was separated. This procedure was repeated once more. The combined organic layers were dried over Na_2SO_4 and concentrated under vacuum at 30 °C to give iodo compound **5 (**3.11 kg 90%) as a light-sensitive oil. If required, this material may be purified by chromatography on silica gel eluting with hexane/*tert*-butyl methyl ether: ^{1}H NMR ($CDCl_3$) δ 7.36 (m, 2H), 6.83 (m, 2H), 5.37 (s, 1H), 4.05 (dd, J = 11.0, 4.7 Hz, 1H), 3.81 (dd, J = 7.2, 2.1 Hz, 1H), 3.75 (s, 3H), 3.48−3.40 (m, 2H), 3.10 (dd, J = 7.2, 2.0 Hz, 1H), 2.10−1.95 (m, 2H), 1.80 (m, 1H), 0.97 (d, J = 7.0 Hz, 3H), 0.93 (d, J = 6.8 Hz, 3H), 0.85 (s, 9H), 0.68 (d, J = 6.7 Hz, 3H), 0.02 (s, 3H), 0.00 (s, 3H).

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Large-Scale Synthesis of the Anti-Cancer Marine Natural Product (+)-Discodermolide. Part 4: Preparation of Fragment C_{7-24}

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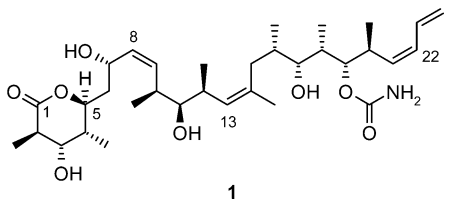
Abstract:

Coupling of C_{9-14} (4) and C_{15-21} (5a) fragments to produce the *cis*-trisubstituted olefin was achieved using Suzuki-type coupling conditions employed by Marshall (5a/*tert*-BuLi/B-OMe-9-BBN added to 4/Cs_2CO_3/Pd(dppf)$_2$). The terminal (*Z*)-diene moiety was attached to aldehyde 10 by using a sequential Nozaki−Hiyama allylation and Peterson olefination sequence; careful monitoring of the disappearance of both diastereomeric *β*-hydroxysilanes was found to be essential for achieving a high yield. In the oxidation of alcohols 12 and 16 to 13 and 7, respectively, using iodobenzene diacetate and TEMPO, addition of a trace of water was found to be crucial for complete conversion. The C_{8-9} (*Z*)-olefin functionality was introduced on to aldehyde 13 using a Still−Gennari HWE reaction. Subsequent carbamate installation at C-19 followed by a reduction/oxidation sequence gave the title fragment C_{7-24} (7) ready to be coupled with the C_{1-6} fragment, which is described in Part 2 of this series.

Introduction

In the preceding contributions of this five-part series, the large-scale preparations of the C_{1-6}, C_{9-14}, and C_{15-21} fragments that are required for the total synthesis of (+)-discodermolide (**1**) are discussed.



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In this contribution we present the results of coupling the key C_{9-14} (**4**) and C_{15-21} (**5**) fragments and further chain elaboration to afford an advanced intermediate C_{7-24} (**7**) that is needed for the final stage of the discodermolide synthesis. This required the construction of the synthetically challenging *Z*-trisubstituted double bond via sp^3-sp^2 cross coupling of an alkyl iodide and a vinyl iodide and subsequent elaboration of the product to the target aldehyde **7**. In the course of this synthetic sequence we smoothly make the transition from the Smith strategy[1] to the attractive end game approach of Paterson[2] (Scheme 1).

Results and Discussion

Coupling of Fragments C_{9-14} and C_{15-21}. The coupling of C_{9-14} (**4**) and C_{15-21} (**5a**) fragments to produce the (Z)-trisubstituted olefin **8** is shown in Scheme 2. We initially examined a variation of the Negishi coupling[3] as practiced by Smith.[1] This process produced several side products, as indicated by the NMR spectrum of the crude reaction mixture after workup, which were not separable from the desired product. Marshall described[4] an alternative Suzuki-type[5] cross-coupling step in his approach to discodermolide. Employing this protocol for our coupling reaction, [**5a**/*tert*-BuLi/9-methoxy-9-borabicyclo[3.3.1]nonane added to **4**/Cs_2CO_3/Pd(dppf)Cl_2, resulted in a much cleaner reaction mixture. The only byproduct generated was des-iodo compound **5b**. Some *trans* isomer of **8**, carried over from the *trans* impurity in **4**, was also observed. Pure **8** was easily obtained from the crude product in good yield (73%) by crystallization from acetonitrile. The structure and absolute configuration of **8**

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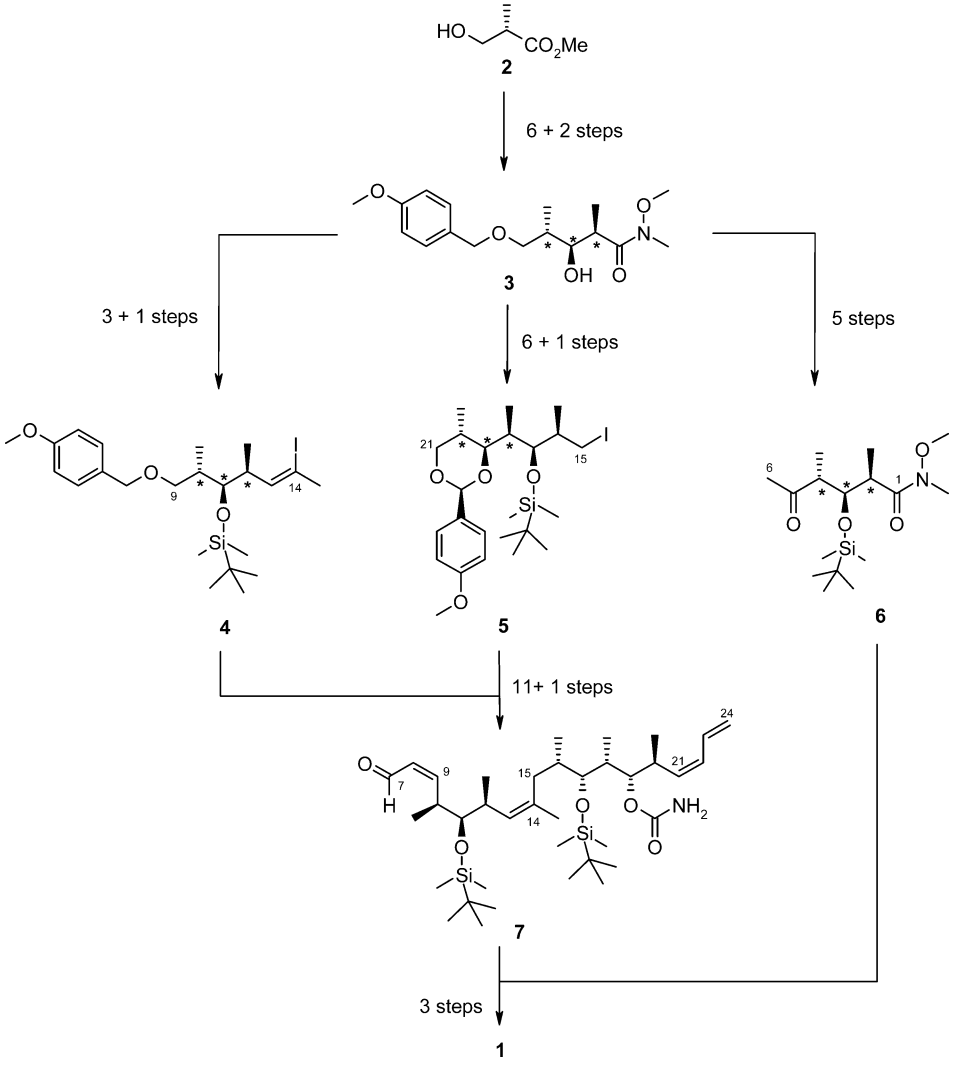
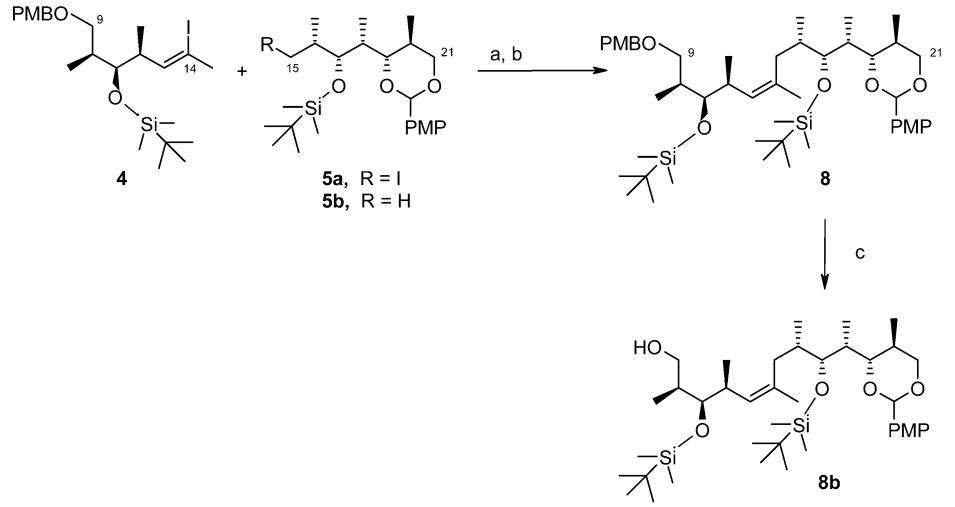
Scheme 1. **Synthetic strategy leading to the advanced fragment C_{7-24} (7) and (+)-discodermolide (1)**



Scheme 2. **Coupling of C_{9-14} and C_{15-21} fragments**[a]



[a] Reagents: a) *t*-BuLi. 9-MeOBBN, THF, −78 °C; b) Cs_2CO_3, DMF, $Pd(dppf)_2Cl_2$, 20 °C; c) DDQ.

was confirmed by single-crystal X-ray analysis of **8b** (Figure 1), obtained by removal of the *p*-methoxybenzyl protecting group of **8** with DDQ.

With the first fragment union successfully completed, the transition from the Smith approach to the Paterson route was now required to arrive at the final C_{7-24} coupling partner. This necessitates the elaboration of both termini to introduce the (*Z*)-enal and the terminal (*Z*)-diene unit and introduction of the pendant carbamate moiety as detailed in Scheme 3.

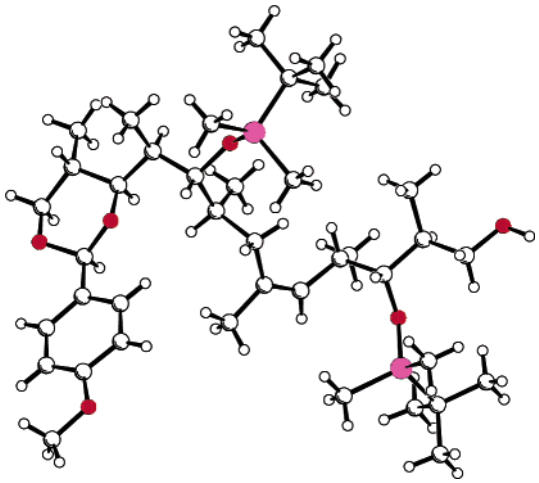
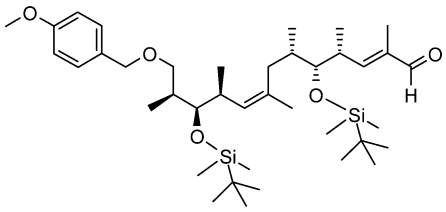


Figure 1. **Single-crystal X-ray structure of fragment 8b.**

Installation of the Terminal Diene. The elaboration of intermediate **8** to the advanced C_{7-24} fragment (**7**) is described in Scheme 3. Cleavage of the *p*-methoxyphenyl (PMP) acetal with DIBAL[6] afforded alcohol **9** in high yield (92%). Oxidation of **9** under Parikh−Doering conditions with SO_3/pyridine in DMSO gave aldehyde **10** in 93% yield. A cautious workup of the reaction mixture was critical for a high yield. If the reaction mixture was not rendered slightly basic, significant amounts (up to 20%) of the, β-unsaturated aldehyde **17** could be generated via elimination of *p*-methoxybenzyl alcohol.

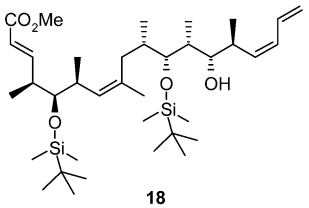


17

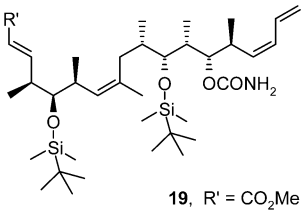
With the aldehyde **10** in hand, we departed from Smith's approach and turned our attention to the installation of the terminal diene. Numerous strategies have been employed for the introduction of this motif within the context of discodermolide syntheses. We chose to adopt the highly attractive Paterson two-step, one-pot protocol.[7] This was achieved by first employing Nozaki−Hiyama allylation conditions, whereby aldehyde **10** and allyl bromide **10b** were added to a suspension of $CrCl_2$ in dry THF to yield a β-hydroxysilane intermediate, which on treatment with KH underwent a Peterson *syn*-elimination to afford the required (*Z*)-diene. Reproducibility of this protocol was initially problematic after we had replaced KH with KOH as the base for reasons of safety and ease of operation. We observed that diene **11** was consistently contaminated with significant amounts of an impurity as shown by NMR. Further investigation suggested that a mixture of diastereomeric β-hydroxysilanes **11a** and **11b** was generated under our modified conditions (Scheme 4). Whether conversion of **11a** to **11** was completed could not be determined by TLC analysis since TLC could not separate these two compounds. This was overcome by developing an HPLC method to monitor the Peterson elimination reaction. Aided by HPLC, we observed that diastereomers **11a** and **11b** underwent *syn*-elimination at different rates. As a result, it was important to ensure that both β-hydroxysilanes were consumed before work up and isolation. This made the conversion of aldehyde **10** to diene **11** reproducible and afforded the latter as an oil in 81% yield after chromatography.

Conversion of C9 Alcohol to (*Z*)-Enal. Oxidative removal of the two *p*-methoxybenzyl protecting groups of diene **11** with DDQ/H_2O gave diol **12** as a foam in high yield (88%) after chromatography. Oxidation of diol **12** with iodobenzene diacetate and TEMPO produced aldehyde **13** as a red oil in 91% yield. Attempts to directly oxidize **11** to **13** were unsuccessful.[8] Aldehyde **13** thus generated was used without purification, since the iodobenzene generated from the reduction was judged not to interfere in the next step. It should be noted that traces of water have a dramatic effect on this reaction. This oxidation when performed on a 300-mg to 1-g scale with 2,2,6,6,-tetramethyl-1-piperidinyloxy (TEMPO, 0.1 equiv) and iodobenzene diacetate (DAIB, 1.2 equiv) gave a good yield of **13**. However, this reaction was not reproducible on scale-up, and the yield dropped to 10%. As the original report by Piancatelli[9] mentioned that the reaction "...can be performed in an open flask without any particular precautions, e.g., inert atmosphere or dry solvent...", we felt that these factors may be crucial for the progress of the reaction. This conclusion led to the addition of water (0.1 equiv) and resulted in a dramatic acceleration of the oxidation reaction.

Introduction of the *cis*-double bond C_{8-9} was accomplished utilizing the Still−Gennari variation of the Horner−Wadsworth−Emmons reaction.[10] Thus, generation of the anion of bis-2,2,2-trifluoroethylphosphonoacetic acid methyl ester with potassium hexamethyldisilazide in the presence of 18-crown-6 and reaction with crude aldehyde **13** gave *cis*-olefin **14** in 76% yield from **12**. About 2.5% of the *trans*-olefin **18** was formed under these conditions. The *trans*-isomer was separated by chromatography on silica gel, since we felt that purification at this stage was appropriate. Compound **18** was used to make the corresponding *trans*-isomers **19**−**21** for reference.



18



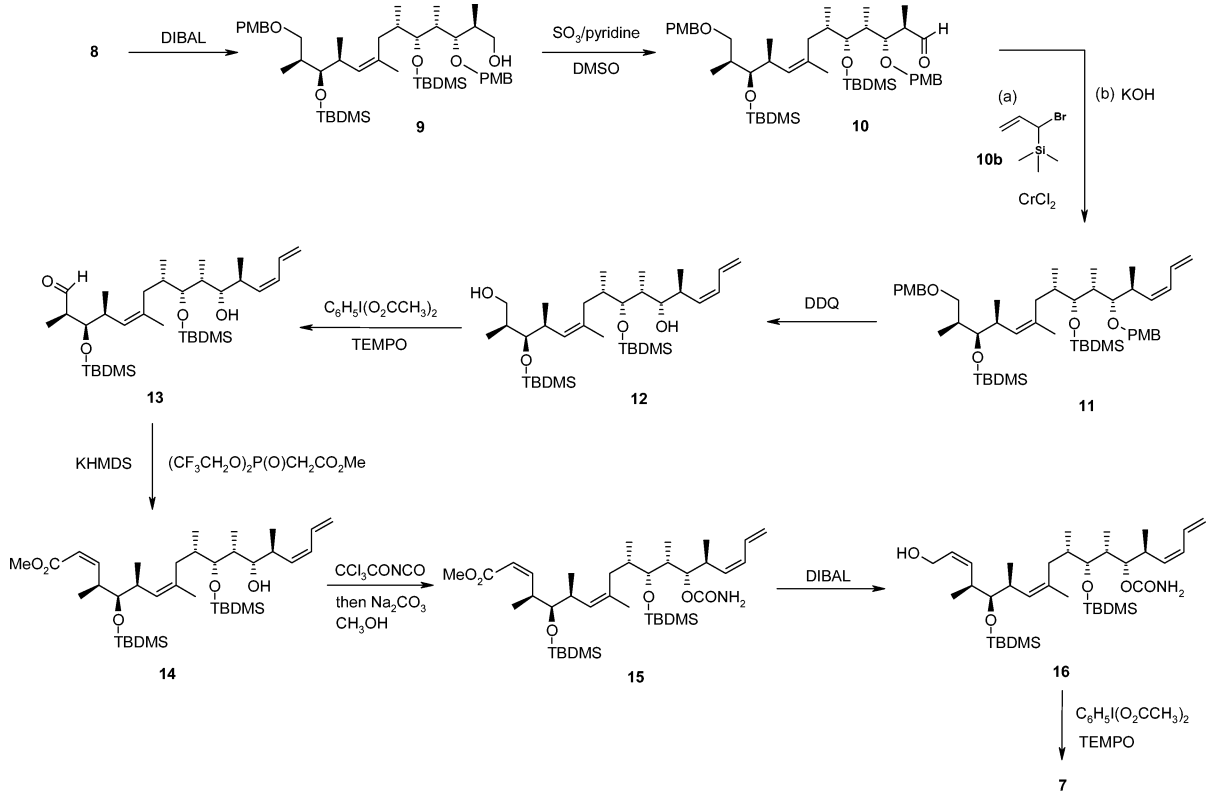
19, R' = CO_2Me
20, R' = CH_2OH
21, R' = CHO

Formation of carbamate **15** proceeded in quantitative yield by reaction of **14** with trichloroacetyl isocyanate followed

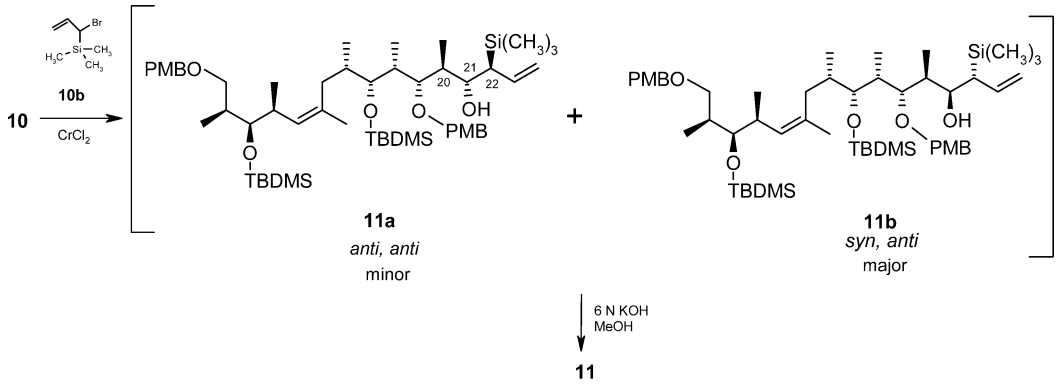
(6) (a) Takano, S.; Akiyama, M.; Sano, S.; Ogasawara, K. *Chem. Lett*. **1983**, 1593. (b) Evans, D. A.; Ng, H. P. *Tetrahedron Lett*. **1993**, *34*, 2229.
(7) Paterson, I.; Schlapbach, A. *Synlett* **1995**, 498.

(8) (a) Nakajima, N.; Uoto, K.; Yonemitsu, O. *Heterocycles* **1990**, *31*, 5. (b) McDonald, C. E.; Nice, L. E.; Kennedy, K. E. *Tetrahedron Lett*. **1994**, *35*, 57. (c) Organ, M. G.; Bilokin, Y. V.; Bratovanov, S. *J. Org. Chem*. **2002**, *67*, 5176.

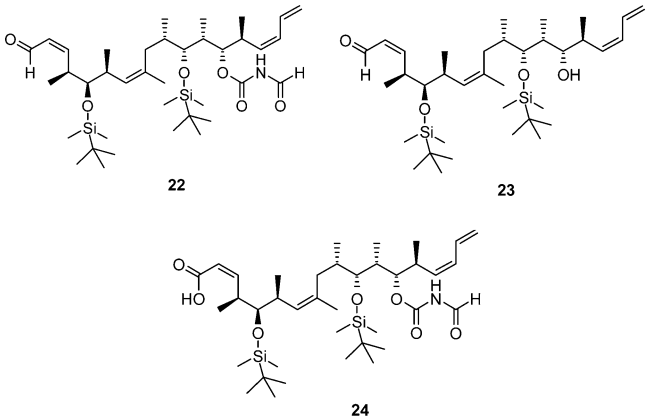
Scheme 3. **Synthesis of fragment C_7-_{24} (7)**



Scheme 4. **Installation of the terminal diene unit**



by methanolysis as described by Paterson[2] in his modification of the Kocovsky procedure.[11] Reduction of the ester group **15** with DIBAL in dichloromethane at −78 °C yielded a mixture of alcohol **16** and aldehyde **7 (**10−20%, depending on the reaction time). Attempts to reduce ester **15** exclusively to aldehyde **7** were unsuccessful, since the latter was easily reduced to alcohol **16**. This mixture was used in the next step without further purification. Oxidation of **16** with iodobenzene diacetate and TEMPO in the presence of traces of water afforded **7** as a white foam in 80% yield (two steps from **15**) after chromatography. Three byproducts (**22, 23**, and **24**) were also isolated during the purification. Their origin could be attributed to byproducts present in the previous steps.



Having successfully assembled the pivotal fragment C_{7-24}, we were ready to address the most challenging phase of the entire campaign, the finale based on the C_6-C_7 coupling. The following contribution describes the chemistry involved

(9) De Mico, A.; Margarita, R.; Parlanti, L.; Vescovi, A.; Piancatelli, G. *J. Org. Chem*. **1997**, *62*, 6974.
(10) Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405.
(11) Kocovsky, P. *Tetrahedron Lett*. **1986**, *27*, 5521.

and the problems encountered in the large-scale synthesis of (+)-discodermolide.

Experimental Section

(4*S*,5*S*)-4-[(*Z*)-(1*R*,2*R*,3*S*,7*S*,8*R*,9*S*)-2,8-bis-(*tert*-butyldimethylsilanyloxy)-10-(4-methoxybenzyloxy)-1,3,5,7,9-pentamethyldec-5-enyl]-2-(4-methoxyphenyl)-5-methyl-[1,3]dioxane (8). *(A) Suzuki Procedure.* A solution of *tert*-butyllithium (2.4 kg, 15%, 5.63 mol) in diethyl ether was diluted with 3 L of hexane and cooled to an internal temperature of −80 °C. To this solution was added a pre-cooled (−40 °C) solution of iodide **5a** (1.58 kg, 2.91 mol) in 16 L of tetrahydrofuran in 30 min, followed by the addition of a pre-cooled (−40 °C) solution of 9-methoxy-BBN (530 g, 3.49 mol) in tetrahydrofuran (5 L) in 15 min. A suspension formed after the addition. The cooling bath was removed, and this borane intermediate was added to a mixture of vinyl iodide **4** (1.1 kg, 2.12 mol) in DMF (19 L) containing Pd(dppf)Cl_2 (78 g, 0.10 mol) and cesium carbonate (2.4 kg, 7.37 mol, predissolved in 2 L of water) within 2.5 h. The resulting mixture was allowed to warm to 25 °C and stirred for an additional 20 h. The mixture was filtered through Cellflock (filter aid). The solid was rinsed with heptane, and the combined heptane filtrates were evaporated to a volume of about 12 L. Ethanolamine (235 g, 3.85 mol) was added, and the mixture was stirred for 15 min and filtered through Cellflock. The solids were rinsed with heptane (3 × 3 L). The combined heptane filtrates were evaporated to a volume of about 3 L. This concentrate was chromatographed on silica gel eluting with a mixture of heptane/*tert*-butyl methyl ether to give, after evaporation of the solvent, 2.07 kg of a light-orange oil. This oil was redissolved in a mixture of 8 L of acetonitrile and 2 L of heptane and warmed to 30 °C. About 2.5 L of the solvent was removed by distillation at 30 °C (mainly heptane), and the product began to crystallize. The suspension was cooled to room temperature, and the thick suspension was diluted with 3.5 L of acetonitrile. The suspension was cooled to 0 °C, stirred for 30 min, and filtered. The solid was rinsed with cold acetonitrile (1 L) and dried in a vacuum to give olefin **8** (1.26 kg, 73% based on **4**): $[\alpha]_D$ +27.7 (c = 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.36 (m, 2H), 7.22 (m, 2H), 6.85 (m, 4H), 5.37 (s, 1H), 4.99 (d, J = 9.97 Hz, 1H), 4.36 (ABq, J = 11.8 Hz, 2H), 4.09 (dd, J = 11.0 4.8 Hz, 1H), 3.78 (s, 3H), 3.77 (s, 3H), 3.60 (dd, J = 7.0 & 1.9 Hz, 1H), 3.50−3.40 (m, 3H), 3.37 (dd, J = 6.3 4.8 Hz, 1H), 3.18 (pseudo t, J = 8.9 Hz, 1H), 2.50 (m, 1H), 2.31 (m, 1H), 2.11−1.82 (m, 4H), 1.65 (m, 1H), 1.54 (s, 3H), 1.04 (d, J = 6.9 Hz, 3H), 0.93 (d, J = 7.7 Hz, 3H), 0.89 (s, 9H), 0.87 (s, 9H), 0.72 (d, J = 6.2 Hz, 3H), 0.02 (s, 3H), 0.00 (s, 9H). Note: The mother liquors were concentrated and chromatographed on silica gel to yield an additional 60−80 g of **8.** Further elution of the chromatography column led to the isolation of **5b**.

***tert*-Butyl-((*R*)-1-{(*R*)-1-[(4*S*,5*S*)-2-(4-methoxyphenyl)-5-methyl-[1,3]dioxan-4-yl]-ethyl}-2-methylpropoxy)-dimethylsilane (5b):** ^{1}H NMR (d_6-DMSO) δ 7.30 (m, 2H), 6.92 (m, 2H), 5.45 (s, 1H), 4.02 (dd, J = 11.9 5.5 Hz, 1H), 3.78 (s, 3H), 3.60−3.45 (m, 3H), 2.0−1.80 (m, 3H), 1.00−0.88 (m, 15H), 0.85 (d, J = 6.3 Hz, 3H), 0.62 (d, J = 6.5 Hz, 3H), 0.05 (s, 3H), 0.00 (s, 3H).

(B) Negishi Procedure. A solution of **5** (13.7 g, 25 mmol) in 400 mL of diethyl ether was treated with 26 mL of a 1.0 M solution of zinc chloride (1.0 M in diethyl ether), and the resulting thin suspension was cooled to an internal temperature of −75 °C. A solution of *tert*-butyllithium (40 mL, 1.7 M solution in pentane, 65 mmol) was added dropwise over 60 min. The solution was stirred for 30 min at −75 °C and slowly warmed to 20 °C within 60 min. The resulting white suspension was stirred for 60 min at 20 °C and treated with a solution of **4** (10.4 g, 20 mmol) in diethyl ether (140 mL). Tetrakis(triphenylphosphine)palladium(0) (1.0 g) was added, and the suspension was stirred for 3 h at 20 °C. The reaction mixture was treated with water (250 mL) and stirred for 30 min at 20 °C. The mixture was then filtered through Cellflock, and the solids were rinsed with 300 mL of *tert*-butyl methyl ether. The organic phase was separated and washed with brine (200 mL). The solvent was removed in vacuo at 30 °C to give 21.5 g of an oil. This oil was purified by silica gel chromatography eluting with hexane/ethyl acetate mixtures (1.5 L, 98/2 then 2 L, 94/6). The appropriate fractions were combined and evaporated to dryness to give 12.5 g, 76.8%, of **8** as a pink oil. This oil was dissolved in acetonitrile (200 mL) containing 10% hexane. The mixture was concentrated at 30 °C in vacuo (ca. 60 mL distilled) and cooled to 20 °C to induce crystallization. The suspension was stirred for 60 min at 25 °C and cooled to 0 °C, stirred for 60 min, and filtered. The solid was rinsed with 35 mL of cold acetonitrile, dried in vacuo at 20 °C to give **8** (10.0 g, 62% based on **4**): mp 79−80.5 °C; NMR identical to that above.

Alcohol 8b Crystal for X-ray. To a solution of olefin **8** (1.33 g, 1.6 mmol) in 16 mL of dichloromethane under a nitrogen atmosphere at 0 °C was added water (75 mg, 4.1 mmol). To this solution was added solid DDQ (387 mg, 1.7 mmol). The red-brown suspension was stirred at 0 °C for 4 h. The mixture was dried over $MgSO_4$, diluted with 20 mL of dichloromethane, and filtered. The filtrate was passed through a 1-in. thick pad of silica gel that was pre-wetted with ethyl acetate/hexane (1:1). The pad was rinsed with 25 mL of ethyl acetate/hexane (1:1). The filtrate was evaporated under vacuo to give an off-white solid (1.2 g). This solid was partially dissolved in 50 mL of ethanol at 23 °C. To the suspension was added solid sodium borohydride (250 mg, 6.7 mmol) at 23 °C. The resulting suspension was stirred for 20 min at 23 °C. The mixture was cooled to 0 °C, and quenched with saturated aqueous ammonium chloride (50 mL). The mixture was concentrated under vacuum to remove the ethanol. The residue was partitioned between dichloromethane (200 mL) and water (100 mL). The dichloromethane layer was separated, washed with water (100 mL), dried over $MgSO_4$, filtered, and evaporated under vacuum to give a crude white solid (1.1 g, 100%). A single crystal of suitable size was grown for X-ray studies by dissolving 20 mg of this solid in 2-propanol and allowing the solvent to evaporate slowly under ambient conditions.

(*Z*)-(2*S*,3*S*,4*R*,5*R*,6*S*,10*S*,11*R*,12*S*)-5,11-Bis-(*tert*-butyldimethylsilanyloxy)-3,13-bis-(4-methoxybenzyloxy)-2,4,6,8,10,12-hexamethyltridec-8-en-1-ol (9). A solution of olefin **8** (1.92 kg, 2.36 mol) in toluene (17 L) was cooled to an internal temperature of −15 to −20 °C. A solution of DIBAL in toluene (10.9 kg of a 1.0 M solution, 10.9 mol) was added dropwise within 60 min. The reaction mixture was warmed to 0−5 °C and stirred for 60 min. Ethyl acetate (15 L) was then added within 45 min, maintaining the temperature at 0 °C, followed by a solution of saturated sodium potassium tartrate (60 L). The mixture was warmed to 25 °C and stirred for an additional 60 min. The organic layer was separated. The aqueous phase was re-extracted with ethyl acetate (12 L). The combined organic phases were washed with 10 L of water. The organic layer was dried with $MgSO_4$ and filtered, and the solvent was removed in vacuo at 50 °C to give 1.91 kg of an oil. This oil was chromatographed on silica gel eluting with heptane/ethyl acetate, 3/1. The appropriate fractions were combined and concentrated to give **9** as an oil (1.78 kg, 92%): ^{1}H NMR ($CDCl_3$) δ 7.32 (m, 4H), 6.85 (m, 4H), 5.01 (d, J = 10.5 Hz, 1H), 4.49 (ABq, J = 9.2 Hz, 2H), 4.36 (ABq, J = 11.7 Hz, 2H), 3.78 (s, 3H), 3.77 (s, 3H), 3.73 (dd, J = 11.3 & 2.9 Hz, 1H), 3.60−3.43 (m, 4H), 3.35 (m, 1H), 3.19 (pseudo t, J = 8.8 Hz, 1H), 2.80−2.67 (br s, exch D_2O, 1H), 2.49 (m, 1H), 2.22 (pseudo t, J = 12.0 Hz, 1H), 2.01−1.84 (m, 4H), 1.73 (m, 1H), 1.57 (s, 3H), 1.03 (m, 6H), 0.92 (m, 12H), 0.86 (m, 12H), 0.72 (d, J = 6 Hz, 3H), 0.06 (s, 6H), 0.00 (s, 6H).

(*Z*)-(2*R*,3*R*,4*R*,5*R*,6*S*,10*S*,11*R*,12*S*)-5,11-Bis-(*tert*-butyldimethylsilanyloxy)-3,13-bis-(4-methoxybenzyloxy)-2,4,6,8,10,12-hexamethyltridec-8-enal (10). A solution of alcohol **9** (1.64 kg, 2.01 mol) in 10.5 L of dichloromethane containing 5.8 L of dimethyl sulfoxide was treated with 660 g, (6.52 mol) of triethylamine. The mixture was cooled to −5 °C, and a solution of sulfur trioxide/pyridine complex (768 g, 4.83 mol) in 9 L of dimethyl sulfoxide was added dropwise within 30 min. The mixture was stirred for 60 min at 0 °C, and heptane (30 L) was added followed by water (20 L). The organic phase was separated and washed sequentially with water (10 L), saturated sodium bicarbonate (10 L), and finally water (4 × 10 L). The organic phase was dried with $MgSO_4$ and filtered, and the solvent was removed to give an oil. This oil was purified by chromatography on silica gel to give **10** as an oil (1.53 kg, 93%): ^{1}H NMR ($CDCl_3$) δ 9.79 (d, J = 2.4 Hz, 1H), 7.21 (m, 4H), 6.84 (m, 4H), 5.01 (d, J = 10.2 Hz, 1H), 4.45 (ABq, J = 11.2 Hz, 2H), 4.35 (ABq, J = 11.9 Hz, 2H), 3.76 (s, 6H), 3.57−3.52 (m, 2H), 3.45 (dd, J = 9.2, 4.4 Hz, 1H), 3.36 (dd, J = 6.5, 4.8 Hz, 1H), 3.19 (pseudo t, J = 9.2 Hz, 1H), 2.73 (m, 1H), 2.49 (m, 1H), 2.23 (pseudo t, J = 12.3 Hz, 1H), 1.93 (m, 3H), 1.64 (m, 1H), 1.56 (s, 3H), 1.10 (d, J = 7.1 Hz, 3H), 1.01 (d, J = 6.8 Hz, 3H), 0.94−0.89 (m, 12H), 0.88−0.83 (m, 12H), 0.71 (d, J = 6.5 Hz, 3H), 0.05 (s, 3H), 0.04 (s, 3H), 0.00 (s, 6H). The following compound (**17**) was also isolated from the chromatography.

(2*E*,8*Z*)-(4*R*,5*R*,6*S*,10*S*,11*R*,12*S*))-5,11-Bis-(*tert*-butyldimethylsilanyloxy)-13-(4-methoxybenzyloxy)-2,4,6,8,10,12-hexamethyltrideca-2,8-dienal (17): ^{1}H NMR ($CDCl_3$) δ 9.37 (s, 1H), 7.22 (m, 2H), 6.84 (m, 2H), 6.36 (d, J = 9.5 Hz, 1H), 5.00 (d, J = 10.3 Hz), 4.36 (ABq, J = 12.7 Hz, 2H), 3.78 (s, 3H), 3.45 (m, 2H), 3.35 (dd, J = 4.83, 4.2 Hz, 1H), 3.19 (pseudo t, J = 7.8 Hz, 1H), 2.87 (m, 1H), 2.46 (m, 1H), 1.94 (m, 1H), 1.74 (s, 3H), 1.54 (s, 3H), 1.05 (d, J = 6.6 Hz, 3H), 0.91 (m, 12H), 0.86 (m, 12H), 0.72 (d, J = 6.6 Hz, 3H), 0.06 (s, 3H), 0.05 (s, 3H), 0.00 (s, 6H).

***β*-Hydroxysilanes 11a and 11b.** A dried 5-L, four-necked, round-bottomed flask equipped with paddle stirrer, rubber septum, thermometer, and a glass stopper was filled with argon and placed in a dry bag under nitrogen purge. Chromium(II) chloride (23.1 g, 0.19 mol) was transferred to the flask in the dry bag under nitrogen purge. The flask was sealed and placed on a mechanical stirrer. Anhydrous, degassed THF (1.0 L, inhibited with 250 ppm of 2,6-di-*tert*-butyl-4-methylphenol) was added via cannula, and the green suspension was cooled to 0 °C under argon purge. A solution of aldehyde **10** (34.0 g, 0.04 mol) in anhydrous, degassed THF (2.2 L) was further degassed with argon for 30 min and transferred via cannula to the reaction flask. Allyl bromide **10b** (40.4 g, 0.21 mol) was added via syringe. With cooling bath in place and positive argon pressure applied, the reaction mixture was allowed to warm to 25 °C and stirred for an additional 16 h. Analytical samples for **11a** and **11b** were obtained by flash chromatography on SiO_2 (hexanes/ethyl acetate, 95/5, for **11a** and hexanes/ethyl acetate, 90/10, for **11b**).

***β*-Hydroxysilane 11a:** colorless oil; R_f 0.35 (toluene); $[\alpha]^{25}_D$ −3.3 (c = 0.5, $CHCl_3$); IR (KBr) 3496, 2957, 2930, 2856, 1613, 1514, 1463, 1360, 1302, 1172 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.28−7.21 (m, 4H), 6.90−6.82 (m, 4H), 5.98 (ddd, J = 17.4, 10.4, 10.4 Hz, 1H), 5.03 (d, J = 10.2 Hz, 1H), 4.95 (dd, J = 10.2, 2.1 Hz, 1H), 4.83 (dd, J = 17.3, 2.1 Hz, 1H), 4.52 (ABq, J_{AB} = 10.8 Hz, $\Delta\delta_{AB}$ = 29.3 Hz, 2H), 4.38 (ABq, J_{AB} = 11.6 Hz, $\Delta\delta_{AB}$ = 19.4 Hz, 2H), 3.86 (b, 1H), 3.80 (s, 3H), 3.79 (s, 3H), 3.76−3.71 (m, 1H), 3.52 (dd, J = 6.6, 2.0, 1H), 3.48 (dd, J = 9.2, 4.9 Hz, 1H), 3.39 (dd, J = 6.3, 4.7 Hz, 1H), 3.34 (dd, J = 6.4, 3.5 Hz, 1H), 3.21(dd, J = 8.7, 8.7 Hz, 1H), 2.57−2.44(m, 1H), 2.32 (dd, J = 12.4, 12.4, 1H), 2.01−1.79 (m, 4H), 1.73 (bd, J = 10.7, 1H), 1.68 (bd, J = 11.3, 1H), 1.59 (s, 3H), 0.97 (d, J = 7.0, 3H), 0.93 (d, J = 7.5, 3H), 0.92 (s, 9H), 0.89 (d, J = 7.5, 3H), 0.88 (s, 9H), 0.77 (d, J = 6.9, 3H), 0.74 (d, J = 6.7, 3H), 0.068 (s, 3H), 0.062 (s, 3H), 0.037 (s, 9H), 0.029 (s, 3H), 0.023 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 159.8, 159.4, 136.3, 132.0, 131.9, 131.4, 130.5, 129.9, 129.4, 114.3, 114.1, 113.8, 87.4, 78.8, 77.9, 75.3, 75.0, 73.1, 72.9, 55.7, 42.0, 41.3, 39.9, 39.2, 37.8, 36.1, 35.3, 32.0, 26.7, 26.5, 23.6, 23.0, 18.9, 18.8, 17.5, 16.2, 14.9, 14.5, 13.0, 12.2, −1.8, −2.8, −2.9, −3.4, −3.5. Anal. Calcd for $C_{53}H_{94}O_7Si_3$: C, 68.63; H, 10.21; Si, 9.08. Found: C, 68.74; H, 10.02; Si, 9.03.

***β*-Hydroxysilane 11b:** colorless oil; R_f 0.07 (toluene); $[\alpha]^{25}_D$ +3.2 (c = 0.8, $CHCl_3$); IR (KBr) 2957, 2931, 2856, 1613, 1513, 1463, 1376, 1312, 1249, 1080, 1039 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.25 (d, J = 5.65, 2 H), 7.24 (d, J = 5.8 Hz, 2H), 6.90−6.82 (m, 4H), 5.82 (ddd, J = 17.1, 10.4, 10.4 Hz, 1H), 5.04 (d, J = 10.2 Hz, 1H), 5.00 (dd, J = 10.4, 2.0

Hz, 1H), 4.91 (dd, J = 17.1, 1.8 Hz, 1H), 4.54 (ABq, J_{AB} = 10.8 Hz, $\Delta\delta_{AB}$ = 25.9 Hz, 2H), 4.38 (ABq, J_{AB} = 11.6 Hz, $\Delta\delta_{AB}$ = 17.9 Hz, 2H), 4.16−4.10 (m, 1H), 3.79 (s, 3H), 3.78 (s, 3H), 3.52 (dd, J = 5.6, 3.4 Hz, 1H), 3.48 (dd, J = 9.2, 4.9 Hz, 1H), 3.43 (dd, J = 5.6, 5.6 Hz, 1H), 3.40 (dd, J = 6.1, 4.7 Hz, 1H), 3.21 (dd, J = 8.8, 8.8 Hz, 1H), 2.62 (b, 1H), 2.56−2.46 (m, 1H), 2.28 (dd, J = 12.4, 12.4 Hz, 1H), 2.01−1.88 (m, 3H), 1.88−1.74 (m, 2H), 1.71 (bd, J = 12.1 Hz, 1H), 1.60 (s, 3H), 1.01 (d, J = 7.0 Hz, 3H), 0.99 (d, J = 7.0 Hz, 3H), 0.95 (d, J = 6.6 Hz, 3H), 0.94 (s, 9H), 0.89 (s, 9H), 0.88 (d, J = 7.3 Hz, 3H), 0.76 (d, J = 6.7 Hz, 3H), 0.071 (s, 3H), 0.068 (s, 3H), 0.03 (s, 3H), 0.025 (s, 3H), 0.021 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 159.1, 159.0, 138.0, 131.54, 131.49, 131.0, 130.9, 129.0, 114.0, 113.77, 113.68, 85.0, 78.4, 77.6, 75.2, 72.7, 72.5, 69.7, 55.3, 42.1, 40.2, 39.3, 38.8, 36.8, 35.7, 35.1, 26.3, 26.1, 23.1, 22.7, 18.5, 18.4, 17.1, 14.1, 13.4, 11.7, 10.8, −1.9, −3.2, −3.8, −3.9. Anal. Calcd for $C_{53}H_{94}O_7Si_3$: C, 68.45; H, 9.84; Si, 9.13. Found: C, 68.57; H, 10.20; Si, 9.06.

1-[(5*Z*,13*Z*)-(2*S*,3*R*,4*S*,8*S*,9*R*,10*R*,11*S*,12*S*)-11-(4-Methoxybenzoxy)-3,9-bis-(*tert*-butyldimethylsilanyloxy)-2,4,6,8,-10,12-hexamethylhexadeca-5,13,15-trienyloxymethyl]-4-methoxybenzene (11). A suspension of chromium(II) chloride (980 g, 7.97 mol) in tetrahydrofuran (90 L) was cooled to 0 °C and treated with a solution of aldehyde **10** (1.52 kg, 1.87 mol) in tetrahydrofuran (20 L). To the suspension was added a solution of 1-bromoallyltrimethylsilane (2.0 kg, 10.4 mol) in tetrahydrofuran (10 L). The mixture was stirred for 15 min at 0 °C and warmed to 15 °C, stirred for 60 min, and recooled to 0 °C. Methanol (7.5 L) was added followed by 15 L of a 6 M solution of potassium hydroxide. The mixture was warmed to 25 °C and stirred for 16 h. The organic phase was separated and the aqueous phase re-extracted with 30 L of tetrahydrofuran. The combined organic layers were washed with brine (10 L) and concentrated to give 1.71 kg of an oil. The oil was purified by chromatography on silica gel eluting with heptane/isopropyl alcohol mixtures to give *cis*-diene **11** as an oil (1.27 kg, 81%): ^{1}H NMR ($CDCl_3$) δ 7.24 (m, 4H), 6.84 (m, 4H), 6.57 (dt, J = 16.5, 10.5 Hz, 1H), 5.99 (pseudo t, J = 10.6 Hz, 1H), 5.55 (pseudo t, J = 10.4 Hz, 1H), 5.18 (d, J = 16 Hz, 1H), 5.09 (d, J = 9.0 Hz, 1H), 4.94 (d, J = 10 Hz, 1H), 4.50 (ABq, J = 9.6 Hz, 2H), 4.35 (ABq, J = 11.2 Hz, 2H), 3.77 (s, 3H), 3.76 (2, 3H), 3.42 (m, 2H), 3.34 (m, 1H), 3.26−3.14 (m, 2H) 2.98 (m, 1H), 2.43 (m, 1H), 2.06−1.89 (m, 2H), 1.85−1.69 (m, 2H), 1.51 (s, 3H), 1.09 (d, J = 6.9 Hz, 3H), 0.98 (d, J = 6.9 Hz, 3H), 0.93 (m, 9H), 0.90 (d, J = 6.4 Hz, 3H), 0.86 (m, 9H), 0.84 (d, J = 6.9 Hz, 3H), 0.69 (d, J = 6.9 Hz, 3H), 0.08 (s, 6H), 0.00 (s, 6H).

(5*Z*,13*Z*)-(2*S*,3*R*,4*S*,8*S*,9*R*,10*R*,11*S*,12*S*)-3,9-Bis-(*tert*-butyldimethylsilanyloxy)-2,4,6,8,10,12-hexamethylhexadeca-5,13,15-triene-1, 11-diol (12). To a solution of diene **11** (1.28 kg, 1.51 mol) in 20 L of dichloromethane was added solid DDQ (983 g, 4.33 mol). The red-brown suspension was stirred for 75 min at 25 °C and filtered through Cellflock. The solid was rinsed with 20 L of dichloromethane in two portions, and the solvent was concentrated to give 1.41 kg of a red oil. This was purified by chromatography over silica gel eluting with toluene/ethyl acetate mixtures (initially 97.5/2.5, finally 90/10). The fractions containing product were combined and concentrated to afford diol **12** as a foam (792 g, 88%): ^{1}H NMR ($CDCl_3$) δ 6.62 (dtd, J = 16.8, 11.7, 1.09 Hz, 1H), 6.13 (pseudo t, J = 10.9 Hz, 1H), 5.32 (pseudo t, J = 10.4 Hz, 1H), 5.22 (d, J = 16.7 Hz, 1H), 5.14 (d, J = 10.1 Hz, 1H), 4.99 (d, J = 10.4 Hz, 1H), 3.66 (dd, J = 10.9, 4.5 Hz, 1H), 3.61 (dd, J = 5.8, 3.3 Hz, 1H), 3.39 (dd, J = 6.9, 3.8 Hz, 1H), 3.33 (dd, J = 8.1, 3.0 Hz, 1H), 2.80 (m, 1H), 2.57 (m, 1H), 2.17 (pseudo t, J = 11.7 Hz, 1H), 1.95−1.75 (m, 7H, becomes 5H on D_2O), 1.62 (s, 3H), 1.00−0.88 (m, 30H), 0.75 (d, J = 6.6 Hz, 3H), 0.09 (s, 6H), 0.08 (s, 6H).

(5*Z*,13*Z*)-(2*R*,3*R*,4*S*,8*S*,9*R*,10*R*,11*S*,12*S*)-3,9-Bis-(*tert*-butyldimethylsilanyloxy)-11-hydroxy-2,4,6,8,10,12-hexamethylhexadeca-5,13,15-trienal (13). To a solution of alcohol **12** (782 g, 1.31 mol) in dichloromethane (4 L) was added water (2.4 g). A mixture of iodobenzene diacetate (620 g, 1.92 mol) and TEMPO (40.1 g) was added in five portions over a period of 30 min with vigorous stirring. The orange reaction mixture was stirred for an additional 60 min at 25 °C and a 25% solution of sodium thiosulphate was added. The mixture was stirred for 15 min, and the organic phase was separated. The aqueous phase was re-extracted with dichloromethane (5 L), and the combined organic phases were treated with solid sodium bicarbonate (400 g). The suspension was filtered. The filtrate was washed with water (2 L) and evaporated in vacuo at 20 °C to give aldehyde **13** as a red oil (1.10 kg): ^{1}H NMR ($CDCl_3$) δ 9.63 (s, 1H), 6.64 (dt, J = 16.8, 11.7 Hz, 1H), 6.15 (pseudo t, J = 10.9 Hz, 1H), 5.35 (pseudo t, J = 10.2 Hz, 1H), 5.25 (d, J = 16.7 Hz, 1H), 5.17 (d, J = 9.8 Hz, 1H), 4.83 (d, J = 10.5 Hz, 1H), 3.76 (dd, J = 8, 3.6 Hz, 1H), 3.62 (dd, J = 5.8, 3.3 Hz, 1H), 3.36 (dd, J = 7.6, 3.3 Hz, 1H), 2.83 (m, 1H), 2.54 (m, 1H), 2.19 (pseudo t, J = 12.4 Hz, 1H), 1.96−1.72 (m, 4H), 1.60 (s, 3H), 1.08 (d, J = 7.1 Hz, 3H), 1.01−0.86 (m, 27H), 0.74 (d, J = 6.5 Hz, 3H), 0.10 (s, 9H), 0.07 (s, 3H). This oil was used without further purification.

(2*Z*,7*Z*,15*Z*)-(4*S*,5*S*,6*S*,10*S*,11*R*,12*R*,13*S*,14*S*)-5,11-Bis-(*tert*-butyldimethylsilanyloxy)-13-hydroxy-4,6,8,10,12,14-hexamethyloctadeca-2,7,15,17-tetraenoic Acid Methyl Ester (14). A solution of 18-crown-6 (315 g), and bis-2,2,2-trifluoroethylphosphonoacetic acid methyl ester (570 g, 1.8 mol) in 10.3 L of toluene was cooled to 0 °C and treated with a solution of potassium hexamethyldisilazide in toluene (3 kg, 0.5 M solution, 1.72 mol). The red solution was stirred for 45 min at 0 °C and cooled to −20 °C. A solution of crude aldehyde **13** (1.05 kg, 1.76 mol) in toluene (3 L) was added within 15 min. The reaction mixture was stirred for 10 min, warmed to 0 °C, and stirred for an additional 90 min. The reaction was quenched with saturated aqueous ammonium chloride solution (10 L). The organic phase was separated, washed with brine (10 L), dried over $MgSO_4$, filtered, and concentrated to produce a yellow oil. Chromatography over silica gel eluting with hexane/ethyl acetate, 15/1, afforded ester **14** (622 g, 76% from **12**): $[\alpha]^{20}_D$ +53.7 (c = 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 6.64 (dtd, J = 16.9, 10.6, 1.0 Hz, 1H), 6.36 (dd, J = 11.9, 9.7 Hz, 1H), 6.12

(pseudo t, J = 11.1 Hz, 1H), 5.70 (d, J = 11.4 Hz, 1H), 5.33 (pseudo t, J = 10.6 Hz, 1H), 5.23 (dd, J = 16.8, 2.0 Hz, 1H), 5.14 (d, J = 9.8 Hz, 1H), 4.90 (d, J = 10.6 Hz, 1H), 3.71−3.61 (m, 4H), 3.57 (dd, J = 5.7, 3.5 Hz, 1H), 3.38−3.29 (m, 2H), 2.80 (m, 1H), 2.31 (m, 1H), 2.09 (pseudo t, J = 12.4 Hz, 1H), 1.89−1.73 (m, 2H), 1.64 (d, J = 11.6, 1H), 1.55 (s, 3H), 1.00 (d, J = 6.9 Hz, 3H), 0.96 (d, J = 6.4 Hz, 3H), 0.93 (d, J = 6.7 Hz, 3H), 0.91−0.89 (m, 18H), 0.81 (d, J = 6.9 Hz, 3H), 0.69 (d, J = 6.6 Hz, 3H), 0.07 (s, 3H), 0.05 (s, 9H). Further elution of the chromatography column led to the isolation of **18**.

(2*E*,7*Z*,15*Z*)-(4*S*,5*S*,6*S*,10*S*,11*R*,12*R*,13*S*,14*S*)-5,11-Bis-(*tert*-butyldimethylsilanyloxy)-13-hydroxy-4,6,8,10,12,14-hexamethyloctadeca-2,7,15,17-tetraenoic acid methyl ester (18): ^{1}H NMR ($CDCl_3$) δ 6.94 (dd, J = 15.3, 7.4 Hz, 1H), 6.59 (dtd, J = 16.8, 10.65, 1.1 Hz, 1H), 6.10 (pseudo t, J = 11.9 Hz, 1H), 5.64 (dd, J = 15.9, 1.7 Hz, 1H), 5.30 (pseudo t, J = 10.8 Hz, 1H), 5.20 (dd, J = 16.5, 2.3 Hz, 1H), 5.12 (d, J = 10.2 Hz, 1H), 4.88 (d, J = 10.3 Hz, 1H), 3.74−3.53 (m, 5H), 3.51−3.26 (m, 2H), 2.77 (m, 1H), 2.55−2.33 (m, 2H), 2.10 (pseudo t, J = 12.5 Hz, 1H), 1.90−1.77 (m, 4H), 1.54 (s, 3H), 0.99 (d, J = 7 Hz, 3H), 0.95−0.78 (m, 27H), 0.68 (d, J = 6.7 Hz, 3H), 0.04 (s, 3H), 0.00 (s, 9H).

(2*Z*,7*Z*,15*Z*)-(4*S*,5*S*,6*S*,10*S*,11*R*,12*R*,13*S*,14*S*)-5,11-Bis-(*tert*-butyldimethylsilanyloxy)-13-carbamoyloxy-4,6,8,10,-12,14-hexamethyloctadeca-2,7,15,17-tetraenoic Acid Methyl Ester (15). To a solution of ester **14** (739 g, 1.14 mol) in dichloromethane (5 L) was added dropwise trichloroacetyl isocyanate (332 g, 1.76 mol) over a period of 30 min. The reaction mixture was stirred for 90 min, and methanol (3 L) was added. The mixture was concentrated in vacuo at 20 °C until no more solvent distilled. Methanol (7.5 L) was added to the residue followed by solid sodium carbonate (365 g). The suspension was stirred at 25 °C for 2 h, and water (10 L) and *tert*-butyl methyl ether (10 L) were added. The organic phase was separated, and the aqueous phase was re-extracted with *tert*-butyl methyl ether (7.5 L). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to give carbamate **15** (789 g, 100%) as a foam: $[\alpha]^{20}_D$ +76.3 (c = 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 6.58 (dtd, J = 17, 10.6, 1.0 Hz, 1H), 6.36 (dd, J = 11.6, 9.79 Hz, 1H), 6.01 (pseudo t, J = 11.4 Hz, 1H), 5.69 (dd, J = 11.6, 0.8 Hz, 1H), 5.37 (pseudo t, J = 10.8 Hz, 1H), 5.20 (dd, J = 17, 1.8 Hz, 1H), 5.12 (d, J = 10.1 Hz, 1H), 4.87 (d, J = 10.3 Hz, 1H), 4.71 (pseudo t, J = 5.9 Hz, 1H), 4.51 (s, 2H, NH_2), 3.71−3.61 (m, 4H), 3.39 (pseudo t, J = 4.5 Hz, 1H), 3.33 (dd, J = 7.2, 2.8 Hz, 1H), 2.97 (m, 1H), 2.27 (m, 1H), 1.99 (pseudo t, J = 12.8 Hz, 1H), 1.91−1.74 (m, 2H), 1.54 (s, 3H), 1.00 (d, J = 7.2 Hz, 3H), 0.98 (d, J = 7.0 Hz, 3H), 0.91 (m, 21H), 0.86 (d, J = 7.0 Hz, 3H), 0.67 (d, J = 6.9 Hz, 3H), 0.07 (s, 3H), 0.06 (s, 6H), 0.05 (s, 3H). This was used without further purification.

(2*E*,7*Z*,15*Z*)-(4*S*,5*S*,6*S*,10*S*,11*R*,12*R*,13*S*,14*S*)-5,11-Bis-(*tert*-butyldimethylsilanyloxy)-13-carbamoyloxy-4,6,8,10,-12,14-hexamethyloctadeca-2,7,15,17-tetraenoic Acid Methyl Ester (19). Employing the same procedure for converting **14** to **15**, the *trans*-carbamate **19** can be obtained from the corresponding *trans*-ester **18** in a similar manner: ^{1}H NMR ($CDCl_3$) δ 6.93 (dd, J = 15.9, 7.2 Hz, 1H), 6.59 (dt, J = 16.9, 10.6 Hz, 1H), 5.99 (pseudo t, J = 11.1 Hz, 1H), 5.63 (dd, J = 15.5, 2.4 Hz, 1H), 5.33 (pseudo t, J = 10.2 Hz, 1H), 5.23−5.06 (m, 2H), 4.85 (d, J = 4.8 Hz, 1H), 4.69 (pseudo t, J = 6.3 Hz, 1H), 4.51 (s, 2H, NH_2), 3.74−3.53 (m, 5H), 3.51−3.26 (m, 2H), 2.77 (m, 1H), 2.55−2.33 (m, 2H), 2.10 (pseudo t, J = 12.5 Hz, 1H), 1.90−1.07 (m, 4H), 1.54 (s, 3H), 0.99 (d, J = 7 Hz, 3H), 0.95−0.78 (m, 27H), 0.68 (d, J = 6.7 Hz, 3H), 0.04 (s, 3H), 0.00 (s, 9H).

Carbamic Acid (6*Z*,11*Z*)-(1*S*,2*R*,3*R*,4*S*,8*S*,9*S*,10*S*)-3,9-Bis-(*tert*-butyl-dimethylsilanyloxy)-13-hydroxy-2,4,6,8,10-pentamethyl-1-((*Z*)-(*S*)-1-methylpenta-2,4-dienyl)-trideca-6,11-dienyl Ester (16). A solution of carbamate **15** (789 g, 1.14 mol) in dichloromethane (15 L) was cooled to −78 °C. A solution of DIBAL (5.6 L, 1.0 M solution in dichloromethane) was added dropwise over 60 min. The mixture was stirred for an additional 60 min at −78 °C and quenched with 12 L of a saturated aqueous solution of sodium potassium tartrate. Water (10 L) was added followed by *tert*-butyl methyl ether (10 L). The mixture was stirred vigorously for 15 min. The organic layer was separated and washed with water (2 × 7 L). The solvent was concentrated in vacuo at 20 °C to give crude alcohol **16** (810 g): $[\alpha]^{20}_D$ +76.3 (c = 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 6.56 (dtd, J = 16.8, 10.6, 1.1 Hz, 1H), 5.99 (pseudo t, J = 11.0 Hz, 1H), 5.59−5.67 (m, 2H), 5.32 (pseudo t, J = 10.6 Hz, 1H), 5.18 (dd, J = 16.8, 2 Hz, 1H), 5.09 (d, J = 10.3 Hz, 1H), 4.92 (d, J = 10.3 Hz, 1H), 4.67 (pseudo t, J = 6.1 Hz, 1H), 4.57−4.65 (s, 2H, NH_2), 4.04 (dd, J = 10.8, 3 Hz, 2H), 3.35 (dd, J = 5.7, 3.6 Hz, 1H), 3.21 (dd, J = 7.2, 3.4 Hz, 1H), 2.94 (m, 1H), 2.60 (m, 1H), 2.33 (m, 1H), 1.83 (m, 1H), 1.63−1.53 (m, 6H), 0.95 (d, J = 6.6 Hz, 3H), 0.92−0.86 (m, 24H), 0.84 (d, J = 6.6 Hz, 3H), 0.66 (d, J = 6.8 Hz, 3H), 0.05 (s, 3H), 0.04 (s, 3H), 0.01 (s, 3H), 0.00 (s, 3H). This was used without further purification.

Carbamic Acid (6*Z*,11*E*)-(1*S*,2*R*,3*R*,4*S*,8*S*,9*S*,10*S*)-3,9-Bis-(*tert*-butyl-dimethylsilanyloxy)-13-hydroxy-2,4,6,8,10-pentamethyl-1-((*Z*)-(*S*)-1-methylpenta-2,4-dienyl)-trideca-6,11-dienyl Ester (20). Employing the same procedure for converting **15** to **16**, the *trans*-allyl alcohol **20** can be obtained from the corresponding *trans*-ester **19** in a similar manner**:** ^{1}H NMR ($CDCl_3$) δ 6.57 (dt, J = 16.9, 0.5 Hz, 1H), 6.00 (pseudo t, J = 10.8 Hz, 1H), 5.65 (d, J = 7.4 Hz, 1H), 5.61 (d, J = 7.9 Hz, 1H), 5.52 (m, 1H), 5.34 (pseudo t, J = 10.5 Hz, 1H), 5.19 (d, J = 10.5 Hz, 1H), 5.10 (d, J = 10.1 Hz, 1H), 4.91 (d, J = 10.16 Hz, 1H), 4.69 (pseudo t, J = 6.1 Hz, 1H), 4.55−4.45 (s, 2H, NH_2), 4.05 (m, 1H), 3.31 (m, 2H), 3.24 (m, 1H), 2.90 (m, 1H), 2.55−2.33 (m, 2H), 2.10 (pseudo t, J = 12.5 Hz, 1H), 1.90−1.77 (m, 4H), 1.54 (s, 3H), 0.99 (d, J = 7 Hz, 3H), 0.95−0.78 (m, 27H), 0.68 (d, J = 6.7 Hz, 3H), 0.04 (s, 3H), 0.00 (s, 9H).

Carbamic Acid (6*Z*,11*Z*)-(1*S*,2*R*,3*R*,4*S*,8*S*,9*S*,10*S*)-3,9-Bis-(*tert*-butyl-dimethylsilanyloxy)-2,4,6,8,10-pentamethyl-1-((*Z*)-(*S*)-1-methylpenta-2,4-dienyl)-13-oxo-trideca-6,11-dienyl Ester (7). A solution of crude alcohol **16** (810 g, 1.22 mol) in dichloromethane (5 L) was charged with water (1.8 g). A mixture of iodobenzene diacetate (478 g, 1.5 mol) and TEMPO (31 g) was added in five portions over a period of

30 min with vigorous stirring. The orange reaction mixture was stirred for 60 min at 25°C, and a 25% solution of sodium thiosulphate was added. The mixture was stirred for 15 min, and the organic phase was separated. The aqueous phase was re-extracted with dichloromethane (5 L). The combined organic phases were treated with solid sodium bicarbonate (400 g). The suspension was filtered, and the filtrate was washed with water (2 L) and concentrated in a vacuum at 20 °C to give 1.04 kg of a red oil. This was purified by chromatography over silica gel eluting sequentially with mixtures of hexane/ethyl acetate, 12/1, 10/1, 8/1, and finally 4/1. The product fractions were combined, and the solvent was concentrated to give aldehyde **7** (647 g, 80%) as a white foam: $[\alpha]^{20}_D$ +84.9 (c = 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 9.78 (d, J = 8.1 Hz, 1H), 6.67 (pseudo t, J = 11.0 Hz, 1H), 6.54 (dtd, J = 17.0, 10.4 Hz, 0.95H, 1H), 5.94 (pseudo t, J = 10.7 Hz, 1H), 5.84 (dd, J = 11.3 & 8.5 Hz, 1H), 5.32 (pseudo t, J = 10.7 Hz, 1H), 5.16 (dd, J = 17.0, 2.0 Hz, 1H), 5.08 (d, J = 10.4 Hz, 1H), 4.87 (d, J = 10.4 Hz, 1H), 4.67 (pseudo t, J = 4.4 Hz, 1H), 4.56−4.41 (s, 2H, NH_2), 3.42−3.27 (m, 2H), 2.92 (m, 1H), 2.24 (m, 1H), 1.79 (m, 2H), 1.53 (s, 3H), 1.04 (d, J = 6.9 Hz, 3H), 0.96 (d, J = 6.9 Hz, 3H), 0.90−0.78 (m, 24H), 0.63 (d, J = 7.3 Hz, 3H), 0.04 (s, 3H), 0.03 (s, 6H), 0.00 (s, 3H). The following byproducts (**22** and **23**) were also isolated by chromatography.

Formyl carbamate 22: ^{1}H NMR (d_6-DMSO) δ 10.91 (d, J = 9.2 Hz, 1H), 9.78 (d, J = 8.1 Hz, 1H), 8.87 (d, J = 8.5 Hz, 1H), 6.67−6.56 (m, 2H), 6.05 (pseudo t, J = 10.7 Hz, 1H), 5.83 (dd, J = 11.3, 8.5 Hz, 1H), 5.39 (pseudo t, J = 10.7 Hz, 1H), 5.25 (d, J = 17 Hz, 1H), 5.17 (d, J = 11.3 Hz, 1H), 5.00 (d, J = 10.4 Hz, 1H), 4.82 (pseudo t, J = 5.1 Hz, 1H), 3.55−3.20 (m, 4H [partially obscured by solvent]), 3.06 (m, 1H), 2.24 (m, 1H), 1.79 (m, 2H), 1.53 (s, 3H), 1.04 (d, J = 6.9 Hz, 3H), 0.96 (d, J = 6.9 Hz, 3H), 0.90−0.78 (m, 24H), 0.63 (d, J = 7.3 Hz, 3H), 0.04 (s, 3H), 0.03 (s, 6H), 0.00 (s, 3H); MS (Na^+) 714.4.

Alcohol 23: ^{1}H NMR ($CDCl_3$) δ 9.75 (d, J = 7.9 Hz, 1H), 6.86 (pseudo t, J = 10.9 Hz, 1H), 6.54 (dt, J = 16.6, 10.3 Hz, 1H), 5.98 (pseudo t, J = 10.9 Hz, 1H), 5.84 (dd, J = 10.3, 8.0 Hz, 1H), 5.28−5.09 (m, 2H), 4.86 (m, 1H), 3.39−3.04 (m, 3H), 2.98 (m, 1H), 2.20 (m, 1H), 1.94−1.62 (m, 7H), 1.04 (d, J = 6.9 Hz, 3H), 0.965 (d, J = 6.9 Hz, 3H), 0.90−0.79 (m, 24H), 0.62 (d, J = 7.3 Hz, 3H), 0.04−0.00 (m, 12H).

Carbamic Acid (6*Z*,11*E*)-(1*S*,2*R*,3*R*,4*S*,8*S*,9*S*,10*S*)-3,9-Bis-(*tert*-butyldimethylsilanyloxy)-2,4,6,8,10-pentamethyl-1-((*Z*)-(*S*)-1-methylpenta-2,4-dienyl)-13-oxo-trideca-6,11-dienyl Ester (21). Employing the same procedure for converting **16** to **7**, *trans*-aldehyde **21** can be obtained from the corresponding *trans*-alcohol **20** in a similar manner: ^{1}H NMR ($CDCl_3$) δ 9.42 (d, J = 7.6 Hz, 1H), 6.83 (dd, J = 16.3, 7.0 Hz, 1H), 6.57 (dt, J = 16.7, 10.8 Hz, 1H), 6.01−5.89 (m, 2H), 5.31 (pseudo t, J = 10.8 Hz, 1H), 5.16 (d, J = 16.7 Hz, 1H), 5.08 (d, J = 10.1 Hz, 1H), 4.92 (d, J = 10.1 Hz, 1H), 4.66 (pseudo t, J = 5.9 Hz, 1H), 4.55−4.38 (s, 2H, NH_2), 3.42−3.29 (m, 2H), 2.93 (m, 1H), 2.61 (m, 1H), 2.35 (m, 1H), 1.81 (m, 2H), 1.57−1.49 (m, 5H), 1.03 (d, J = 6.9 Hz, 3H), 0.94 (d, J = 6.9 Hz, 3H), 0.89−0.78 (m, 24H), 0.64 (d, J = 7.3 Hz, 3H), 0.04 (s, 3H), 0.00 (s, 9H).

Acknowledgment

We thank Dr. Grety Rihs for performing the X-ray analysis of compound **8b**. We appreciate Mr. Karl Gunderson's assistance in analyzing the NMR spectra of compounds **11a** and **11b**.

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Large-Scale Synthesis of the Anti-Cancer Marine Natural Product (+)-Discodermolide. Part 5: Linkage of Fragments C_{1-6} and C_{7-24} and Finale

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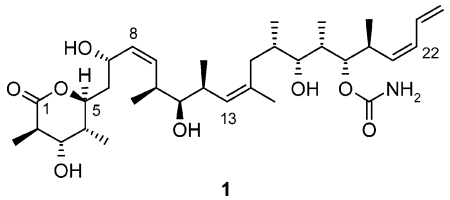
Abstract:

The finale of the large-scale preparation of 60 g of the highly complex marine natural product, (+)-discodermolide (1), using a hybridized Novartis−Smith−Paterson synthetic route is presented. This contribution, which is the concluding part of a five-part series, highlights a reagent-controlled stereoselective boron enolate aldol reaction between 2 and 3 forming the C7 hydroxyl-bearing stereocenter, selective reduction of 4a to generate the 1,3-*anti*-diol 5, and a global deprotection and concomitant lactonization leading to (+)-discodermolide (1). A novel procedure for converting the minor epimeric aldol adduct 4b into discodermolide using a five-step sequence is also described. This large-scale synthesis of discodermolide involved 39 steps (26 steps in the longest linear sequence) and several chromatographic purifications and delivered sufficient material for early-stage human clinical trials.

Introduction

After 36 chemical steps and a gallant effort by many dedicated scientists, we now describe the finale that resulted in the delivery of 60 g of (+)-discodermolide (**1**), attesting to the power of contemporary organic synthesis in making available sufficient quantities of a highly complex organic molecule, sourced from nature in submilligram quantities, for a thorough evaluation of its therapeutic potential.



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Having described the synthesis of fragments C_{1-6} and C_{7-24} in the preceding contributions in this series, the final coupling of these two fragments was foreseen as proceeding via a mismatched chiral boron enolate aldol reaction. This key step was in analogy with the corresponding methyl ester of **2** that was used by Paterson and co-workers[1] for the controlled introduction of the C_7 hydroxyl-bearing stereocenter in their recent discodermolide total synthesis. This complex aldol coupling requires the use of reagent-control to reverse the intrinsic substrate selectivity, i.e. it is a mismatched reaction. Initial screening of these conditions [(+)-DIP-chloride, NEt_3, ether] for the aldol reaction of ketone **2** with aldehyde **3** were encouraging. However, on large scale this reaction proved to be much more complex than we expected, and the solution presented here is by no means optimal but sufficient to achieve our objective. The details of the steps leading to the production of (+)-discodermolide are outlined in Scheme 1.

Results and Discussion

Aldol Coupling. Reaction of 6.6 equiv of the corresponding boron enolate of **2**, prepared by treatment of **2** with (+)-B-chlorodiisopinocampheylborane (DIP-Cl) and triethylamine in diethyl ether at 0 °C, followed by aldol addition, at −78 °C, with *cis*-α,β-unsaturated aldehyde **3** led to alcohol **4a** in 55−60% yield after chromatography on reverse-phase silica gel, together with its epimer **4b** in a ratio of ∼4:1.

The quality of commercial (+)-DIP-Cl was capricious. We used commercially available solid (+)-DIP-Cl initially. This reagent is difficult to obtain and to handle in large quantity as it is hygroscopic and inherently unstable. On storage it eliminates pinene, which reduces the quality of the reagent. Obtaining a well-defined quality reagent on a large scale from a commercial supplier was problematic. Routine analytical methods are not really suitable for monitoring the quality of this boron reagent. On several occasions we did not obtain the desired **4a** but the *trans*-aldol **6** together with its epimer **7** in a 3:1 ratio together with isomerized aldehyde **8**. Also obtained were significant amounts of allyl alcohol **9** and its *trans*-isomer **10** resulting from the reduction

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(1) (a) Paterson, I.; Florence, G. J.; Gerlach, K.; Scott, J. P. *Angew. Chem., Int. Ed.* **2000**, *39*, 377. (b) Cowden, C. J.; Paterson, I. *Org. React.* **1997**, *51*, 1.

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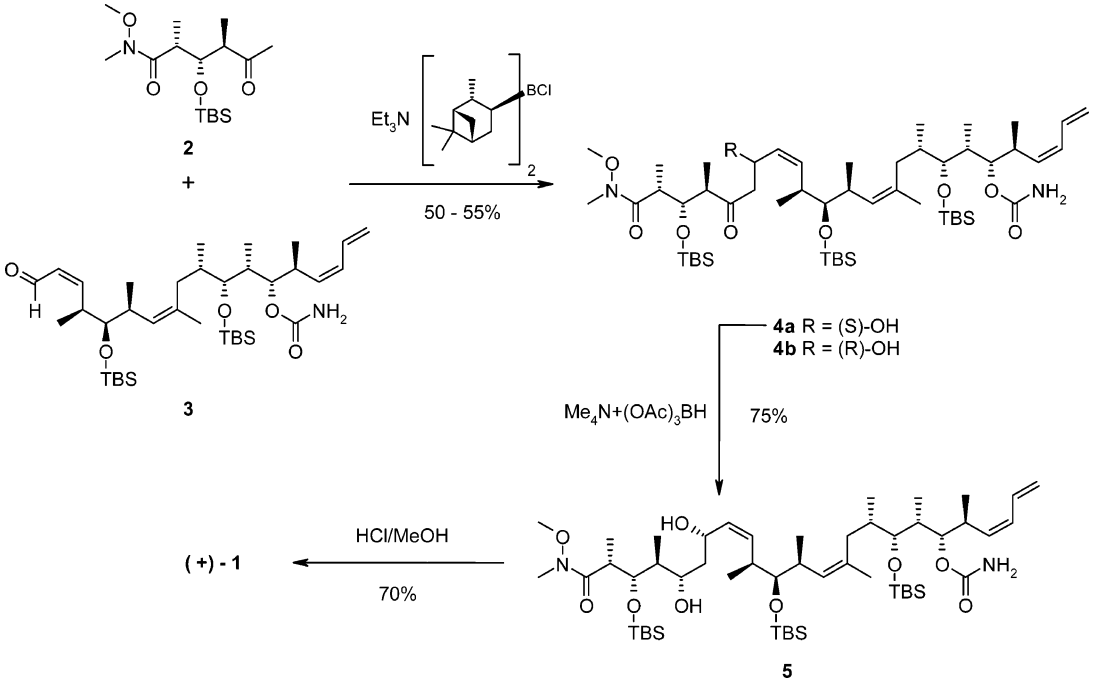
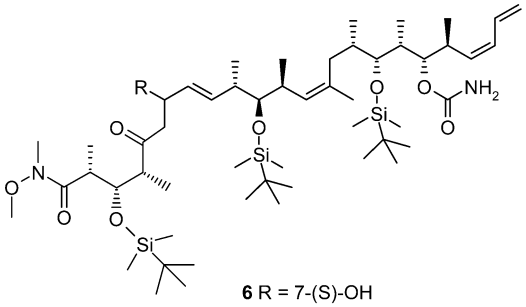
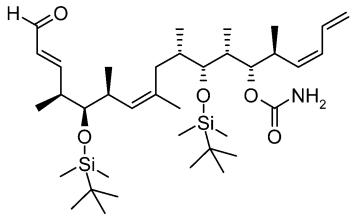
10.1021/op034134j CCC: $27.50

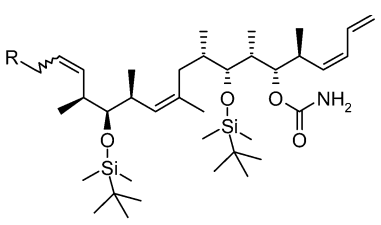
Scheme 1. **Linkage of fragments 2 and 3 and the end game**



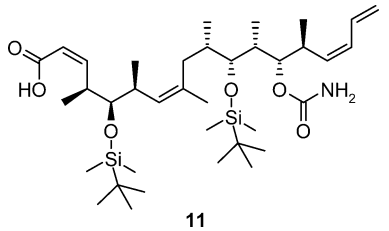
of the aldehyde **8** (see part 4 for NMR data). The mechanism of this double bond isomerization is not clear. It occurs at −78 °C even before the aldol reaction and may be the consequence of an addition/elimination process of chloride or triethylamine induced by boron coordination to the aldehyde oxygen atom, but this is speculative.



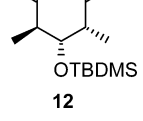




This reagent problem was solved by utilizing a 70% solution of (+)-DIP-Cl in hexane, which is, according to the manufacturer, indefinitely stable at room temperature. A solution is also more amenable to scale-up, eliminating the problems associated with handling the solid reagent. When carried out on a 250-mg scale, the reagent immediately brought about the formation of the correct product **4a** and its epimer **4b** (4:1) in around 45% yield after chromatography on reverse-phase silica gel. Also isolated from this chromatography were small quantities of acid **11**. This most probably arises from peroxide oxidation of **3**. However, on scale-up



(50 g of **3**) the yield of the desired product **4a** was reduced to 23%. What actually happened was the reduction of **3** to **9**, and unfortunately **9** was not recoverable from the complex reaction mixture. We surmised that the probable cause was incomplete enolization. Extending the time for enolate formation to 24 h at 0 °C on a small scale provided a yield of 50% yield of **4a** together with significant amounts of the Claisen condensation product (4*R*,6*R*)-5-(*tert*-butyl-dimethylsilanyloxy)-4,6-dimethylcyclohexane-1,3-dione (**12**).

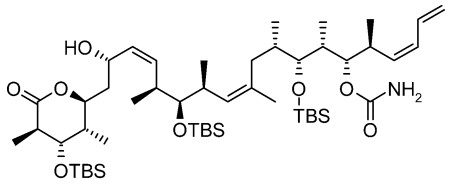


On large scale, we were still unable to reproduce the result of the small-scale experiment although the reduction was

no longer a problem. After investigating the fate of the desired aldol intermediate throughout the entire process, we determined the reason for the low yield was due to the apparent instability of the aldol adduct (or its boron complex) to the workup conditions. Prior to the peroxide treatment, quenching of the reaction mixture with water followed by phase separation and evaporation of the ether led to a reduction in yield of around 15%. A further reduction of 15−20% of the yield occurred after the peroxide workup. The reason for this instability is still unclear as we could not isolate any byproducts containing any of the structural features of the reactants. Some loss of product also occurred when the reaction mixture was purified on normal-phase silica gel.

All these problems were overcome by simply omitting these workup steps. After washing with water, the mixture was directly applied to a reverse-phase silica gel column, and elution with acetonitrile/*tert*-butyl methyl ether/water removed all the "reactive components". The product **4a** was obtained by further elution with acetonitrile/*tert*-butyl methyl ether (1:1) followed by evaporation of the product-containing fractions, extraction of the residue with *tert*-butyl methyl ether, and re-evaporation, in 50−55% yield in a reproducible manner. The epimer **4b** is easily isolated by further elution from the column and may be recycled to **(+)-1** as described below. We also examined other bases for enolate formation, e.g., diisopropylamine, 2,6-lutidine, as well as increasing[2a] or decreasing the excesses of **2**. No positive effects were noted, and we settled on the conditions described above.

Evans−Saksena reduction[2] of **4a** with tetramethylammonium triacetoxyborohydride delivered the 1,3-*anti*-diol **5** in high stereoselectivity and reasonable yield after chromatography. Contrary to the corresponding methyl ester used by Paterson[1a] where the product from the reduction was, on some occasions, formed as a mixture of *anti*-diol and the corresponding lactone in a ratio of 85:15, no lactone **13** derived from *anti*-diol **5** was observed.



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Final Step and Isolation. With the diol **5** in hand, the stage was set for the cleavage of silyl groups[4] and lactonization leading to **1**. This cleavage reaction required carefully controlled reaction conditions. Hydrochloric acid must be added to **5** in portions during a period of around 10 h. Careful washing of the reactor walls with portions of methanol was necessary to keep **13** and other partially desilylated intermediates in solution, otherwise these intermediates oil out of the reaction mixture, play no further part in the reaction, and decrease the overall yield of **1**. If this occurs they may be readily isolated from the reaction mixture and recycled. Neutralization of the reaction mixture followed by extractive workup afforded crude **1**. Chromatography on reverse-phase silica gel with an acetonitrile/water mixture delivered **(+)-1** in 70% yield. The compound thus isolated was shown by HPLC to be a mixture of lactone and hydroxy acid **14** (92:8). This equilibrium was readjusted completely to the lactone side by lowering the pH with hydrochloric acid.

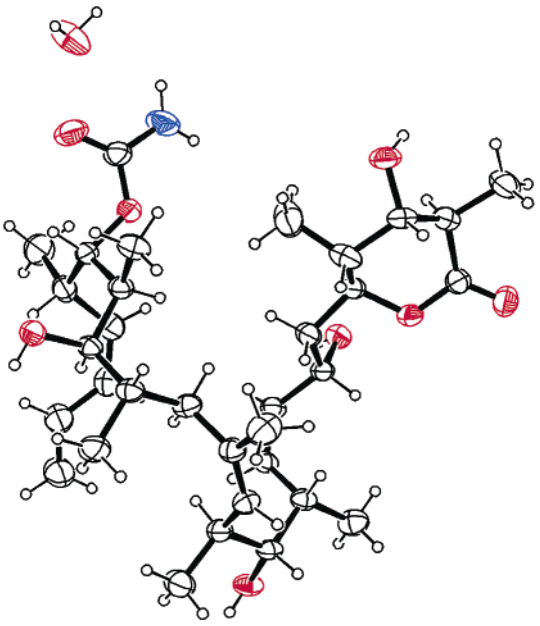
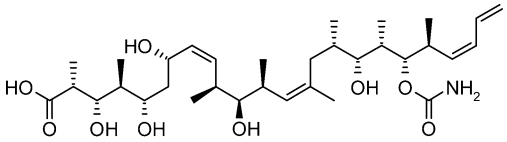


Figure 1. **Single-crystal X-ray structure of (+)-discodermolide.**



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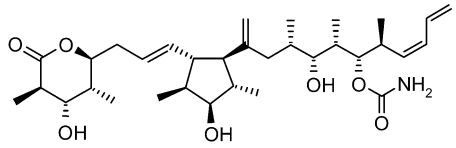
Thus, on crystallization from acetonitrile/water (85:15) at pH 4 the lactone was the only product isolated as sandy crystals in 95% yield. The polymorphic form (monohydrate) that was obtained by the above recrystallization method was highly reproducible. Discodermolide **1** is known to exist in several other polymorphic forms depending on the method of isolation. All spectroscopic data, the single-crystal X-ray structure, and optical rotation are in full agreement with the data reported in the literature[3] (Figure 1).

Recycling of Byproducts from the Desilylation Step. In the desilylation step there are several intermediates formed which eventually convert to the final product. After the isolation of **1** in pure form from the reverse-phase column, the combined remaining fractions indicated the following % area composition by HPLC: 5.56% discodermolide, 5.68% 3-*tert*-butyldimethylsilyl discodermolide, 9.83% of a bis-silylated discodermolide, and 78.92% of 3,11,17-tris-*tert*-butyldimethylsilyl discodermolide **13**. Treatment of this mixture with 37% hydrochloric acid in acetonitrile/water (9/1)

(2) Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560.
(3) Smith, A. B.; 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 and references therein.
(4) Gunasekera, S. P.; Mickel, S. J.; Daeffler, R.; Niederer, D.; Wright, A. E.; Linley, P.; Pitts, T. *J. Nat. Prod.* Submitted November 2003.

at 0 °C, workup, and crystallization from acetonitrile/water gave discodermolide of around 90−95% purity (by HPLC). Analysis of the mother liquors from this crystallization revealed the presence of other side products. Extensive chromatography on silica gel with dichloromethane/methanol mixtures enabled their isolation in pure state and characterization with the following proposed structures **16**−**18**. Their detailed isolation and spectral characteristics will be described elsewhere.[4] These compounds are also formed in small amounts by treatment of discodermolide itself with HCl/H_2O.



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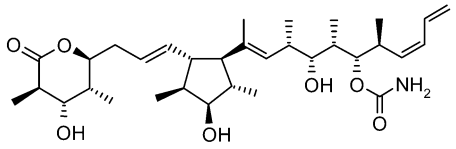

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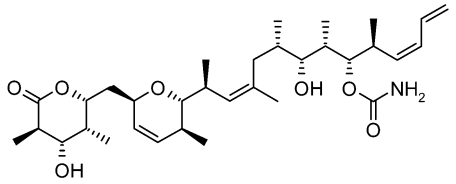

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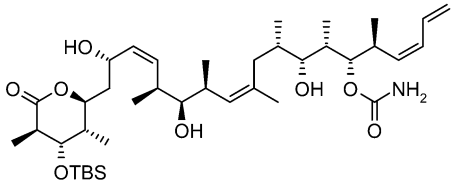

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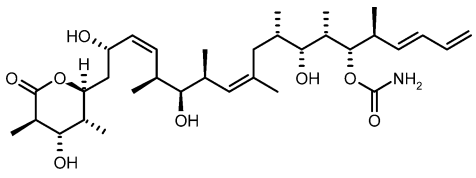
We also noticed the presence of a trace of *trans*-diene **19** under these desilylation conditions. As the Nozaki−Hiyama−Peterson sequence[6] of generating the *cis*-diene is clean, the formation of *trans*-diene was attributed to subsequent acid-catalyzed isomerization.



19

Conversion of the Epimeric Aldol Adduct 4b to Discodermolide. The undesired aldol epimer **4b** was converted to **1** following the five-step process shown in Scheme 2. Stereocontrolled 1,3-*syn*-reduction of **4b** was accomplished by utilizing modified Narasaka−Prasad conditions.[5] Treatment of **4b** with dicyclohexylchloroborane−triethylamine complex generated the corresponding boron aldolate that was then reduced in situ with LiBH3OMe, which, after an oxidative workup, afforded the expected 1,3-*syn*-diol **20** with >97% diastereoselectivity.[5] 1,3-*Syn*-diol **20** was then converted to 7-epi-TBS-discodermolide **21** in 98% yield by treatment with acetic acid in MeCN and water.

With **21** in hand stereochemical correction of C7 was now required. This would involve oxidation of the C7−OH to the corresponding ketone followed by substrate controlled reduction to the known keto-lactone **22**.

A range of oxidants was investigated. Dess−Martin periodinane gave the best result (80% yield), while a Swern oxidation was not as clean, and the recovery was very poor. Pyridine/SO_3 complex in DMSO with an excess of Et_3N gave no reaction. Oxidation with TPAP, NMO, and 4-Å molecular sieves seemed at first very clean; however, only 50% of the desired product was isolated. The stereocontrolled reduction of **22** was then investigated. Gratifyingly, reduction with K-Selectride in toluene proceeded cleanly in favor of the desired (*7S*)-configuration in **13** (85%, 97:3 dr).[7] On scaling up, the recovery of **13** decreased to around 60−70% yield. Two factors were attributed to the significant loss in yield: (1) the sensitivity of the substrate to the oxidative workup employed and (2) chromatography on "normal phase" silica gel. Finally, global deprotection as described earlier led to **(+)-1**. This efficient five-step sequence recycles the C7 epimer **4b** to the target drug substance with complete stereocontrol; as a result, the byproduct proves to be highly valuable rather than an inconvenience.

Conclusions

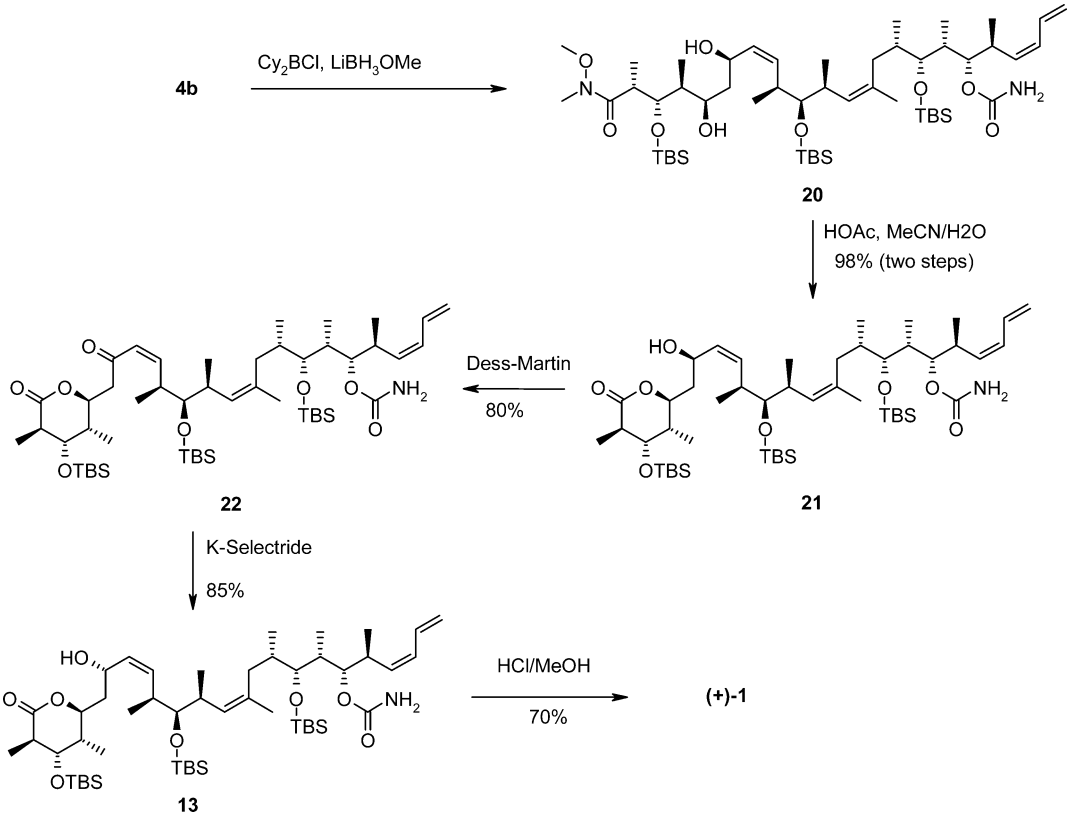
Over 60 g of (+)-discodermolide (Figure 2) was prepared in 39 steps and required 17 chromatographic purifications. The entire process took some 20 months to complete, an average of one step per fortnight. Surprisingly, the majority of the steps were transferred to larger scale without any great problems. We identified around seven problematic steps, of which three occur early in the route. Clearly, improving the yields of these problematic areas would be highly beneficial, especially at the beginning of the synthesis, to reduce the quantities of early intermediates. An improved route to the common intermediate would be an advantageous, one avoiding the difficult boron aldol (part 1), as reagent quality was suboptimal. The end game is far from ideal; after such a synthetic sequence the final few steps leading to the final drug substance need to be kept "simple". The arduous chromatography of the final aldol coupling product (part 5) is clearly not practical to move into production; fortunately, the predicted low dosage levels should keep the yearly manufacturing requirements to a minimum.

One major problem associated with a synthesis of this length is the proper laboratory examination of the later reactions in a sequence. Initially, there are no answers to

(5) Paterson, I.; Florence, G. J.; Gerlach, K.; Scott, J. P.; Sereinig, N. *J. Am. Chem. Soc*. **2001**, *123*, 9535.
(6) Paterson, I.; Schlapbach, A. *Synlett* **1995**, 498.
(7) Paterson, I.; Delgado, O.; Florence, G. J.; Lyothier, I.; Scott, J. P.; Sereinig, N. *Org. Lett*. **2003**, *5*, 35.

Figure 2. **(+)-Discodermolide.**

Scheme 2. **Epimer 4b to 1**



these supply problems; one just has to run the small-scale reaction and hope that on transfer to larger scale the reaction proceeds as expected. We certainly stumbled over this exact point during the final aldol coupling, and as a result the project very nearly ended in failure, or at least the required amount of discodermolide would not have been able to be delivered. On a positive note, this project was a first for Novartis, and its progress was avidly followed by the entire department who were all interested in the "disco". The success of this project and its chemistry paves the way for other, perhaps even more complex, natural products to be prepared for early-phase clinical evaluations and sends a positive message to the both the isolation and synthetic academic community and possibly other pharmaceutical com-

panies that: "your work need not just be of academic interest" and it may be worth taking a few risks.

A total of over 43 chemists participated in the concept of the synthesis, experimental design, and execution. Several early steps were carried out in our pilot plant. The hybridized Novartis−Smith−Paterson synthetic route that resulted from this exercise, and the preparation of 60 g of a structurally complex molecule containing 13 stereogenic centers is a crowning achievement to all those who participated in this endeavor. The option of optimizing the present synthesis further or replacing with a better one is a topic of our ongoing studies, and we are confident of climbing this mountain as the situation demands.

Experimental Section

Coupling of 2 with 3. *(a) With Solid (+)-DIP-Cl.* A solution of (+)-DIP-Cl (0.99 g, of 95% purity, 0.94 g, 2.93 mmol) in diethyl ether (10 mL) was cooled to 0−3 °C, and triethylamine (0.3 g, 2.93 mmol) was added. The resulting suspension was stirred for 5 min at 0 °C, and a solution of **2** (0.96 g, 2.89 mmol) in diethyl ether (2 mL) was added within 10 min. The enolate was allowed to form over 2 h at 0 °C, cooled to −78 °C, and **3** (1.28 g, 1.93 mmol) in diethyl ether (2 mL) was added within 20 min. The mixture was warmed slowly to −7 °C and stirred overnight. The reaction was quenched with methanol (20 mL) and the solvent evaporated to give an oil. This was redissolved in methylene chloride, and 50 mL of pH 7 phosphate buffer was added. The two-phase system was treated with hydrogen peroxide solution (0.41 g of a 30% solution) and stirred for 10 min. The organic layer was separated and washed with 20 mL of a 50% solution of sodium thiosulfate followed by 50 mL of water. The organic solution was dried over sodium sulphate and filtered, and the solvent was removed to give 2.17 g of an oil. This oil was purified by filtration over 40 g of reverse-phase silica gel initially eluting with acetonitrile, then acetonitrile/*tert*-butyl methyl ether (85/15), and finally with acetonitrile/ *tert*-butyl methyl ether (80/20) to give 0.44 g (23% yield) of **6**. Also isolated was an inseparable mixture of **3**, **8**, **9**, and **10**.

Carbamic acid (6*Z*,11*E*)-(1*S*,2*R*,3*R*,4*S*,8*S*,9*S*,10*S*,13*S*,-16*R*,17*S*,18R)-3,9,17-tris-(*tert*-butyldimethylsilanyloxy)-13-hydroxy-18-(methoxymethylcarbamoyl)-2,4,6,8,10,16-hexamethyl-1-((*Z*)-(*S*)-1-methylpenta-2,4-dienyl)-15-oxo-nonadeca-6,11-dienyl ester (6): ^{1}H NMR ($CDCl_3$) δ 6.57 (dt, J = 16.7 10.3 Hz, 1H), 6.01 (pseudo t, J = 10.6 Hz, 1H), 5.63 (dd, J = 15.7 7.7 Hz, 1H), 5.50−5.25 (m, 2H), 5.20 (d, J = 17.5 Hz, 1H), 5.10 (d, J = 10.6 Hz, 1H), 4.90 (d, J = 11.0 Hz, 1H), 4.82−4.42 (m, 4H), 4.27 (dd, J = 7.7 3.5 Hz, 1H), 3.68 (s, 3H), 3.37 (m, 1H), 3.26 (m, 1H), 3.13−2.88 (m, 5H), 2.81−2.25 (m, 6H), 2.09−1.47 (m, 10H), 1.10 (d, J = 6.8 Hz, 3H), 1.04 (d, J = 7.2 Hz, 3H), 0.99−0.80 (m, 39H), 0.68 (d, J = 6.5 Hz, 3H), 0.13 to −0.03 (m, 18H).

Further elution provided small quantities of **(2*Z*,7*Z*,-15*Z*)-(4*S*,5*S*,6*S*,10*S*,11*R*,12*R*,13*S*,14*S*)-5,11-bis-(*tert*-butyl-dimethylsilanyloxy)-13-carbamoyloxy-4,6,8,10,12,14-hex-amethyloctadeca-2,7,15,17-tetraenoic acid (11).** ^{1}H NMR ($CDCl_3$) δ 12.5−12.0 (br s, exch D_2O, 1H), 6.61 (dtd, J = 16.6, 10.5 1.0 Hz, 1H), 6.44 (dd, J = 11.9 9.9 Hz, 1H), 6.12 (pseudo t, J = 10.9 Hz, 1H), 5,72 (d, J = 11.7 Hz, 1H), 5.33 (pseudo t, J = 10.3 Hz, 1H), 5.22 (dd, J = 16.8 2.0 Hz, 1H), 5.14 (d, J = 10.6 Hz, 1H), 4.33−4.20 (br s, 2H), 3.68−3.55 (m, 2H), 3.38 (dd, J = 7.4 2.8 Hz, 1H), 3.33 (dd, J = 7.6 3.5 Hz, 1H), 2.80 (m, 1H), 2.33 (m, 1H), 2.11 (pseudo t, J = 12.5 Hz, 1H), 1.89−1.65 (m, 3H), 1.56 (s, 3H), 1.00 (d, J = 7.3 Hz, 3H), 0.96 (d, J = 6.3 Hz, 3H), 0.93 (d, J = 7.1 Hz, 3H), 0.91−0.88 (m, 21H), 0.69 (d, J = 6.7 Hz, 3H), 0.07 (s, 6H), 0.06 (s, 6H). (M^+ + Na) = 703, (M^+ − H) = 679.

(b) With (+)-Dip-Cl 70% in Hexane (Aldol Reaction Final Conditions). A solution of (+)-DIP-Cl in hexane (263 g, 70% in hexane, 0.574 mol) was diluted with diethyl ether (453 g) and the resulting solution cooled to 0−3 °C. Triethylamine (71.4 g, 0.71 mol) was added within 5 min. The addition funnel was washed with diethyl ether (14.2 mL) and the suspension stirred at 0 °C for 5 min. A solution of **2** (234 g, 0.706 mol) in diethyl ether (305 mL) was added within 22 min, and the addition funnel was washed with diethyl ether (122 mL). The resulting suspension was stirred at 0 °C for at least 10 h and cooled to an internal temperature of −78 °C. A solution of **3** (71 g, 0.107 mol) in diethyl ether (305 mL) was added within 30 min. The addition funnel was washed with diethyl ether (122 mL) and the reaction mixture stirred at −78 °C for 1 h. After this time the reaction mixture was warmed to −65 °C over 15 min and stirred for 3 h. Warming was then continued until −55 °C was reached within 15 min and the mixture stirred at −55 °C for 3.75 h. After further warming to −45 °C over 15 min and stirring for 105 min, the reaction mixture was warmed to −30 °C within 15 min and stirred for 55 min. Water (1530 g) was added followed by *tert*-butyl methyl ether (305 mL). The mixture was stirred for 5 min and the organic layer separated. The aqueous layer was re-extracted with *tert*-butyl methyl ether (1220 mL), and the organic layers were combined (1525 mL total volume). This product solution was chromatographed on reverse-phase silica gel (20 kg, LiChroprep PR-18) eluting with 584 kg of a mixture of acetonitrile/*tert*-butyl methyl ether/water (75/12.5/12.5) followed by 152 kg of an acetonitrile/*tert*-butyl methyl ether mixture (51.5/48.5). The product-containing fractions were combined, and the solvent was removed by distillation until a volume of around 35 L was obtained. *tert*-Butyl methyl ether (23 L) was added, the mixture was stirred for 10 min, and the organic phase was separated. The lower phase was re-extracted with *tert*-butyl methyl ether (5 L), and the organic extracts were combined. The solvent was removed in vacuo at a temperature of 30 °C. *tert*-Butyl methyl ether (1 L) was added, the mixture was stirred for 10 min, and the organic phase was separated. The lower phase was re-extracted with *tert*-butyl methyl ether (1 L), and the organic extracts were combined. The solvent was removed in vacuo at a temperature of 30 °C to give 66.9 g, 62.8%, of the desired **4a** as a nonhygroscopic foam. ^{1}H NMR ($CDCl_3$) δ 6.53 (dt, J = 16.8 10.1 Hz, 1H), 5.96 (pseudo t, J = 10.7 Hz, 1H), 5.43 (pseudo t, J = 10.7 Hz, 1H), 5.35−5.24 (m, 2H), 5.15 (d, J = 16.8 Hz, 1H), 5.06 (d, J = 10.1 Hz, 1H), 4.98 (d, J = 10.1 Hz, 1H), 4.72 (td, J = 8.0 2.1 Hz, 1H), 4.65 (pseudo t, J = 6.06

Hz, 1H), 4.55−4.41 (br s, 2H), 4.25 (dd, J = 7.8 4.3 Hz, 1H), 3.66 (s, 3H), 3.35 (pseudo t, J = 3.35 Hz, 1H), 3.23 (pseudo t, J = 10.8 Hz, 1H), 3.03 (s, 3H), 2.93 (m, 2H), 2.76−2.62 (m, 3H), 2.40 (m, 1H), 1.94−1.75 (m, 2H), 1.65−1.48 (m, 5H), 1.21 (d, J = 6.8 Hz, 3H), 1.15 (d, J = 7.3 Hz, 3H), 1.07 (d, J = 6.5 Hz, 3H), 1.04 (d, J = 6.7 Hz, 3H), 0.90−0.77 (m, 30H), 0.65 (d, J = 6.8 Hz, 3H), 0.06 to −0.05 (m, 18H).

Further elution provided the 7-epi isomer **4b**. ^{1}H NMR ($CDCl_3$) δ 6.55 (dt, J = 16.6 10.1 Hz, 1H), 5.98 (pseudo t, J = 10.5 Hz, 1H), 5.50−5.24 (m, 4H), 5.17 (d, J = 16.2 Hz, 1H), 5.07 (d, J = 9.1 Hz, 1H), 4.89 (d, J = 8.8 Hz, 1H), 4.82−4.57 (m, 4H), 4.25 (dd, J = 8.8 3.4 Hz, 1H), 3.70 (s, 3H), 3.35 (m, 1H), 3.24 (dd, J = 7.8 2.7 Hz, 1H), 3.16 (s, 3H), 3.05−2.85 (m, 2H), 2.70 (m, 1H), 2.42−2.25 (m, 2H), 2.05 (pseudo t, J = 11.8 Hz, 1H), 1.94−1.73 (m, 3H), 1.58 (s, 3H), 1.08 (d, J = 6.8 Hz, 3H), 1.03 (d, J = 7.3 Hz, 3H), 0.94 (d, J = 6.7 Hz, 3H), 0.90−0.80 (m, 39H), 0.65 (d, J = 6.8 Hz, 3H), 0.10 to −0.05 (m, 18H).

Carbamic Acid (6*Z*,11*Z*)-(1*S*,2*R*,3*R*,4*S*,8*S*,9*S*,10*S*,-13*S*,15*S*,16*S*,17*S*,18R)-3,9,17-Tris-(*tert*-butyldimethyl-silanyloxy)-13,15-dihydroxy-18-(methoxymethylcarbamoyl)-2,4,6,8,10,16-hexamethyl-1-((*Z*)-(*S*)-1-methyl-penta-2,4-dienyl)-nonadeca-6,11-dienyl Ester (5). A solution of tetramethylammonium triacetoxy borohydride (385 g, 1.46 mol) in 410 g of tetrahydrofuran was treated with glacial acetic acid (972 g). The mixture was stirred for 20−30 min at room temperature and cooled to −25 °C. A solution of **4a** (103 g, 0.103 mol) in tetrahydrofuran (343 g) was added within 30 min. The addition funnel was rinsed with 104 mL of tetrahydrofuran and the reaction mixture stirred for 30 min at −25 °C. The mixture was warmed within 30 min to 0 °C and stirred at that temperature for 18 h. The reaction was quenched with a sodium−potassium tartrate solution (462 mL of a 50% solution), allowing the temperature to rise to 20 °C. Water (4.6 L) was added followed by *tert*-butyl methyl ether (1.03 kg). The two-phase mixture was vigorously stirred during the addition of sodium hydroxide solution until a pH of 6.5−7.5 was reached (around 2.6 kg of a 30% solution required). The organic phase was separated and the aqueous phase re-extracted with *tert*-butyl methyl ether (1.03 kg). The organic phase was separated and combined with the first extract. The combined organic phases were washed sequentially with brine (1.66 kg) and saturated sodium bicarbonate solution (1.47 kg). The organic phases were dried with sodium sulfate and filtered, and the solvent was removed to give the crude product as an oil (101.3 g). This was purified by chromatography on silica gel eluting with heptane/ethyl acetate mixtures to produce 76 g, 73.3% of **5** as a nonhygroscopic foam. ^{1}H NMR ($CDCl_3$) δ 6.52 (dt, J = 16.5 10.3 Hz, 1H), 5.95 (pseudo t, J = 11.1 Hz, 1H), 5.55−5.24 (m, 2H), 5.15 (d, J = 16.9 Hz, 1H), 5.05 (d, J = 10.7 Hz, 1H), 4.91 (d, J = 9.8 Hz, 1H), 4.64 (pseudo t, J = 6.2 Hz, 1H), 4.61−4.49 (m, 3H), 4.10 (d, J = 8.9 Hz, 1H), 3.91−3.82 (br s, 2H), 3.66 (s, 3H), 3.33 (m, 1H), 3.19 (pseudo t, J = 6.2 Hz, 1H), 3.13 (s, 3H), 3.07−3.00 (m, 1H), 2.91 (m, 1H), 2.59 (m, 1H), 2.34 (m, 1H), 2.03 (m, 1H), 1.89−1.45 (m, 7H), 0.95−0.75 (m, 45H), 0.63 (d, J = 6.8 Hz, 3H), 0.06 to −0.07 (m, 18H). $[\alpha]_D$ +37.8, (c = 1 in $CHCl_3$).

(+)-Discodermolide (1). *(Note: discodermolide is a cytotoxic agent, and appropriate measures must be taken to ensure safe handling and nonexposure of personnel.)* To a solution of **5** (77.5 g, 77.7 mmol) in methanol (22 kg) was added every 15 min a 1.02-kg portion of 3 M hydrochloric acid. This was repeated 16 times. Finally four portions of 2.03 kg of 3 M hydrochloric acid were added every 15 min. The reactor walls were washed with 2.4 kg of methanol and the reaction mixture stirred for 3 h at room temperature. A further portion of hydrochloric acid (8.13 kg, 3 M) was added, and stirring continued for a further 2 h. A solution of saturated sodium bicarbonate (144 kg) was added slowly (gas evolution) followed by 5.54 kg of a pH 7 phosphate buffer solution. The methanol was removed by distillation in vacuo at 30 °C until 33 L had been collected. (pH control is necessary; the pH may rise above 7; if that is the case, it may be adjusted by the addition of small portions of 3 M hydrochloric acid until a value of 6.5 is obtained.) Ethyl acetate (16.0 kg) and *tert*-butyl methyl ether (20.7 kg) were added, and the mixture was extracted. The organic phase was separated and the aqueous phase re-extracted with the ethyl acetate (16.0 kg) and *tert*-butyl methyl ether (20.7 kg) mixture. The organic phase was separated and combined with the first extract. The combined extracts were dried over magnesium sulphate and filtered, and the solid was washed with *tert*-butyl methyl ether (13.2 kg). The solvent was removed in vacuo at 30 °C to give 38 g, 82.4%, of crude **1**. This material was redissolved in 2-propanol (8.81 kg), and water (78.4 kg) was added. This solution was passed through a filter onto a column containing 15 kg of ODS-RP-18 reverse-phase silica gel and eluted with acetonitrile/water (25/75). The product-containing fractions were combined and evaporated to around 66% of the original volume. The remaining aqueous phase was extracted twice with ethyl acetate (2 × 30 kg). The ethyl acetate was removed in vacuo to give 28.0 g, 60.6% of **(+)-1** as a foam, which was crystallized as described below. The filter was washed with 2-propanol and the solvent removed to give an oil. This oil mostly contained the fully protected discodermolide **13** which was hydrolyzed according to ref 4.

(+)-Discodermolide Monohydrate (1). The material (65 g) obtained from several chromatographies, as described earlier, was redissolved in 8.73 kg of a mixture of acetonitrile/water (85/15) at pH 4. The solution was concentrated in vacuo to a volume of 3.3 L. Water (1.27 kg) was added and the resulting thin suspension concentrated in vacuo to a volume of 1.4 L. The resulting suspension was cooled to 0 °C and stirred for 2 h. The product was collected by filtration, thoroughly washed with water, and dried in a vacuum at 35 °C for 16 h to give 61.7 g (95% yield) of (+)-discodermolide monohydrate. ^{1}H NMR (CD_3CN) δ 6.58 (dtd, J = 16.73, 10.5 0.89 Hz, 1H), 5.99 (pseudo t, J = 11.1 Hz, 1H), 5.46 (pseudo t, J = 10.5 Hz, 1H), 5.38−5.25 (m, 2H), 5.17 (dd, J = 17.1 2.0 Hz, 1H), 5.10−4.92 (br m, 3H), 4.88 (d, J = 10.1 Hz, 1H), 4.63 (dd, J = 7.99 3.85 Hz, 1H), 4.48−4.30 (m, 2H), 3.54 (pseudo q, J = 5.18 Hz, 1H), 3.25 (d, J =

4.88 Hz, 1H), 3.10−2.94 (m, 3H), 2.74 (d, J = 5.33 Hz, 1H), 2.62 (d, J = 5.33 Hz, 1H), 3.57 (d, J = 6.8 Hz, 1H), 2.55−2.44 (m, 2H), 2.18 (m, 1H), 1.80−1.46 (m, 8H), 1.38 (ddd, J = 14.5, 10.7 2.2 Hz, 1H), 1.10 (d, J = 7.3 Hz, 3H), 0.92 (d, J = 6.8 Hz, 3H), 0.90 (d, J = 7.0 Hz, 3H), 0.86 (d, J = 6.8 Hz, 3H), 0.80 (d, J = 5.8 Hz, 3H), 0.71 (d, J = 7.0 Hz, 3H). ^{13}C NMR (CD_3CN) δ 173.4, 157, 132.9, 132.5, 132.4, 131.9, 129.8, 127.2, 116.9, 78.5, 77.9, 76.1, 74.7, 71.9, 62.0, 42.7, 40.9, 37.2, 35.7, 35.3, 35.0, 33.3, 32.9, 22.0, 18.4, 16.9, 16.3, 14.5, 14.3, 11.8, 7.9. $[\alpha]_D$ = +20.1 (c = 1 in MeOH).

Also isolated from the column was the *trans*-diene **19**. ^{1}H NMR (d_6-DMSO) δ 6.58 (dtd, J = 16.73, 10.5 0.89 Hz, 1H), 5.99 (pseudo t, J = 11.1 Hz, 1H), 5.46 (pseudo t, J = 10.5 Hz, 1H), 5.38−5.25 (m, 2H), 5.17 (dd, J = 17.1 2.0 Hz, 1H), 5.10−4.92 (br m, 3H), 4.88 (d, J = 10.1 Hz, 1H), 4.63 (dd, J = 7.99 3.85 Hz, 1H), 4.48−4.30 (m, 2H), 3.54 (pseudo q, J = 5.18 Hz, 1H), 3.25 (d, J = 4.88 Hz, 1H), 3.10−2.94 (m, 3H), 2.74 (d, J = 5.33 Hz, 1H), 2.62 (d, J = 5.33 Hz, 1H), 3.57 (d, J = 6.8 Hz, 1H), 2.55−2.44 (m, 2H), 2.18 (m, 1H), 1.80−1.46 (m, 8H), 1.38 (ddd, J = 14.5, 10.7 2.2 Hz, 1H), 1.10 (d, J = 7.3 Hz, 3H), 0.92 (d, J = 6.8 Hz, 3H), 0.90 (d, J = 7.0 Hz, 3H), 0.86 (d, J = 6.8 Hz, 3H), 0.80 (d, J = 5.8 Hz, 3H), 0.71 (d, J = 7.0 Hz, 3H).

Conversion of 4b to 1. (2*R*,3*S*,4*S*,5*S*,7*R*,8*Z*,10*S*,11*S*,-12*S*,13*Z*,16*S*,17*R*,18*S*,19*S*,20*S*,21*Z*)-3,11,17-Tris-(*tert*-butyldimethylsilyloxy)-5,7-dihydroxy-19-carbamoyloxy-*N*,2,4,-10,12,14,16,18,20-nonamethyl-*N*-methoxy-tetracosa-8,13,21,23-tetranamide (20). Aldol adduct **4b** (1 g, 1.004 mmol) was dissolved in THF (20 mL) and cooled to −78 °C. $cHex_2BCl/Et_3N$ mixture, freshly prepared from $cHex_2BCl$ (2.07 mL, 10 mmol) and Et_3N (1.32 mL, 18 mmol) in THF (5 mL) at 0°C, (2 M solution, 3.01 mL, 6.02 mmol, 6 equiv) was added, and the reaction mixture was stirred at −78 °C for 40 min. A freshly prepared [by adding at 0 °C MeOH (0.9 mL, 22 mmol) to a suspension of $LiBH_4$ (440 mg, 20 mmol) in THF (20 mL) and stirring at room temperature for 1.5 h] 1 M solution of $LiBH_3OMe$ (15.06 mL, 15.06 mmol, 15 equiv) was added slowly, and the mixture was stirred at −78 °C for 1 h. It was allowed to warm very slowly (up to −10 °C over 2 h) and was then stirred at 0 °C for 3 h. A pH 7 buffer (10 mL) was added very slowly, followed by MeOH (5 mL) and 30% aqueous H_2O_2 (2 mL), dropwise, and the reaction mixture was stirred at room temperature for 40 min. After dilution with water (200 mL), the aqueous layer was extracted with dichloromethane (4 × 50 mL) and ethyl acetate (2 × 50 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated under vacuum. The cyclohexanol was removed by Kugelrohr distillation (50 °C, 0.5 mmHg). Purification by flash chromatography on silica gel (petroleum ether/ethyl acetate, 4:1) then afforded the desired *syn*-diol **19** (1.01 g, quantitative yield).

R_f 0.25 (20% AcOEt/PE); $[\alpha]_D$ +30.4 (c = 0.20, $CHCl_3$); IR (thin film) 3450, 2958, 2928, 1663, 1252, 1093, 1037, 834, 774 cm^{-1}; ^{1}H NMR (CDCl3) δ_H: 6.60 (ddd, J = 16.8, 10.9, 10.4 Hz, 1H), 6.03 (dd, J = 11.0, 11.0 Hz,1H), 5.44−5.29 (m, 3H), 5.21 (dd, J = 16.8, 1.5 Hz, 1H), 5.12 (d, J = 10.1 Hz,1H), 4.99 (d, J = 10.1 Hz,1H), 4.73 (dd, J = 6.1, 6.1,), 4.58 (br s, 2H), 4.57−4.50 (m, 1H), 4.15 (dd, J = 9.7, 2.6 Hz, 1H), 4.00 (br s, 1H), 3.74 (s, 3H), 3.52 (s, 1H), 3.41 (dd, J = 4.8, 4.3 Hz, 1H), 3.32 (dd, J = 6.9, 3.6 Hz, 1H), 3.30−3.05 (m, 5H), 2.99 (m, 1H), 2.69−2.59 (m, 1H), 2.49−2.39 (m, 1H), 2.11 (dd, J = 12.5, 12.4 Hz, 1H), 1.96−1.82 (m, 2H), 1.80−1.50 (m, 4H), 1.59 (s, 3H), 1.16 (3H, d, J = 6.9 Hz, Me_2); 0.99 (3H, d, J = 6.8 Hz, Me_{20}), 0.96−0.89 (m, 36H), 0.85 (d, J = 7.0 Hz, 3H), 0.11−0.04 (m, 18H); ^{13}C NMR ($CDCl_3$): δ_C 177.8, 157.0, 133.7, 133.6, 132.5, 132.3, 132.1, 130.9, 129.7, 117.8, 80.7, 78.6, 77.1, 74.2, 73.9, 68.2, 61.7, 46.5, 41.8, 38.4, 38.1, 37.4, 36.5, 36.2, 34.8, 34.5, 32.4, 26.2 (2 signals), 26.0, 22.8, 18.5, 18.4, 18.3, 18.1, 17.8, 17.4, 16.5, 13.5, 12.4, 10.2, −3.3, −3.4 (2C), −3.9, −4.2, −4.4; HRMS (ES$^+$) calcd for $C_{53}H_{104}N_2O_9Si_3Na$ [M + Na]$^+$ 1019.6947, found 1019.6993.

3,11,17-Tris-(*tert*-butyldimethylsilyl)-7-epi-discodermolide (21). Diol **19** (1 g, 1.004 mmol) was dissolved in acetonitrile (10 mL), water (10 mL), and acetic acid (10 mL). The reaction mixture was stirred at 50 °C for 5 h and then at room temperature for 20 h, before being quenched with saturated aqueous sodium bicarbonate (50 mL). The aqueous layer was extracted with ethyl acetate (5 × 50 mL). The combined extracts were dried (sodium sulfate) and concentrated under reduced pressure. Purification by flash chromatograph on silica gel (hexane/ethyl acetate, 6:1) afforded the title compound **20** (920 mg, 98%).

R_f 0.45 (35% EtOAc/Hexane); $[\alpha]_D$ +20.0 (c = 0.33, $CHCl_3$); IR (thin film) 3460, 2958, 2930, 2857, 1726, 1600, 1462, 1385 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ_H 6.60 (ddd, J = 16.8, 10.7, 10.6 Hz, 1H), 6.03 (dd, J = 11.0, 11.0 Hz, 1H), 5.59 (dd, J = 10.7, 10.6 Hz, 1H), 5.42−5.28 (m, 2H), 5.22 (d, J = 16.7 Hz, 1H), 5.13 (d, J = 10.2 Hz, 1H), 5.04 (d, J = 9.7 Hz, 1H), 4.72 (dd, J = 6.0, 5.8 Hz, 1H), 4.71−4.63 (m, 1H), 4.56 (br s, 2H), 4.32 (dd, J = 9.2, 8.5 Hz, 1H), 3.65 (br s, 1H), 3.41 (dd, J = 4.3, 4.1 Hz, 1H), 3.29 (dd, J = 5.9, 3.8 Hz, 1H), 3.02−2.98 (m, 1H), 2.78−2.69 (m, 1H), 2.65−2.57 (m, 1H), 2.47−2.38 (m, 1H), 2.14 (dd, J = 12.5, 12.5 Hz, 1H), 2.05−1.95 (m, 1H), 1.95−1.84 (m, 4H), 1.77−1.66 (m, 1H), 1.62 (s, 3H), 1.26 (d, J = 7.1 Hz, 3H), 0.99 (d, J = 6.1 Hz, 3H), 0.98 (d, J = 6.1 Hz, 3H), 0.96−0.83 (m, 36H), 0.71 (d, J = 6.6 Hz, 3H), 0.10−0.04 (m, 18H); ^{13}C NMR ($CDCl_3$) δ_C 173.6, 156.9, 135.7, 133.8, 132.5, 132.1, 131.4, 131.0, 129.8, 117.9, 80.8, 79.2, 78.6, 76.1, 74.3, 64.9, 43.8, 40.7, 38.1, 36.7, 36.6, 36.4, 34.8, 34.5, 33.9, 26.3, 26.2, 25.7, 22.7, 19.4, 18.5, 18.4, 17.9, 17.4 (2C), 16.2, 14.0, 13.3, 10.2, −3.3, −3.5 (2C), −3.7, −4.5, −4.8; m/z (ES$^+$) 958 (100, [M + Na]$^+$); HRMS (ES$^+$) calcd for $C_{51}H_{97}O_8NSi_3Na$ [M + Na]$^+$ 958.6420, found 958.6449.

3,11,17-Tris-(*tert*-butyldimethylsilyl)-7-oxo-discodermolide (22). Compound **21** (125 mg, 0.133 mmol) was dissolved in dichloromethane (5 mL), and Dess−Martin periodinane (113 mg, 0.266 mmol, 2 equiv) was added. The reaction mixture was stirred at room temperature for 4 h. Purification by flash chromatography on silica gel (petroleum ether/ethyl acetate, 4:1) afforded the title compound (100 mg, 80%) as a white solid.

R_f 0.21 (20% EtOAc/Hexane); $[\alpha]_D$+77.8 (c = 1.3, $CHCl_3$); IR (thin film) 3372, 2958, 2931, 2857, 1732, 1606, 1472, 1385 cm^{-1}; ^1H NMR ($CDCl_3$) δ_H 6.60 (ddd, J = 16.6, 10.7, 10.6 Hz, 1H), 6.25 (dd, J = 11.3, 9.8 Hz, 1H), 6.10 (d, J = 11.5 Hz, 1H), 6.03 (dd, J = 11.1, 11.0 Hz, 1H), 5.39 (dd, J = 10.6, 10.5 Hz, 1H), 5.22 (d, J = 16.2 Hz, 1H), 5.14 (d, J = 10.2 Hz, 1H), 4.86 (d, J = 10.2 Hz, 1H), 4.77 (ddd, J = 9.7, 5.0, 5.0 Hz, 1H), 4.74 (dd, J = 6.2, 6.0 Hz, 1H), 4.61 (br s, 2H), 3.66 (dd, J = 2.8, 2.8 Hz, 1H), 3.63−3.54 (m, 1H), 3.45−3.35 (m, 2H), 2.99 (ddq, J = 10.0, 6.6, 6.0 Hz, 1H), 2.86 (dd, J = 16.1, 5.4 Hz, 1H), 2.70 (dd, J = 16.1, 5.0 Hz, 1H), 2.63 (qd, J = 7.4, 3.6 Hz, 1H), 2.38−2.27 (m, 1H), 2.20−2.08 (m, 1H), 2.08−2.00 (m, 1H), 1.90−1.80 (m, 2H), 1.65−1.57 (m, 1H), 1.57 (s, 3H), 1.30−1.20 (m, 3H), 1.08−0.95 (3 × d, J = 6.0, 6.6, 7.0 Hz, 9H), 0.95−0.80 (m, 33H), 0.69 (d, J = 6.8 Hz, 3H), 0.15−0.05 (m, 18H); ^{13}C NMR ($CDCl_3$) δ_C 196.8, 173.7, 157.0, 152.4, 133.7, 132.7, 132.1, 130.3, 129.8, 125.4, 117.9, 80.5, 78.7, 77.8, 77.2, 74.1, 46.8, 43.7, 38.1, 38.0, 37.7, 36.2, 34.9, 34.4, 33.5, 26.2, 26.1, 25.7, 22.7, 18.5, 18.4, 18.2, 18.0, 17.5 (2C), 16.0, 13.8, 13.7, 10.1, −3.3, −3.5 (2C), −3.9, −4.5, −4.8; m/z (ES^+) 956 (100, $[M + Na]^+$); HRMS (ES^+) calcd for $C_{51}H_{95}O_8NSi_3Na$ $[M + Na]^+$ 956.6263, found 956.6279.

Ketolactone **22** (10 mg, 0.0107 mmol) was dissolved in toluene (1 mL) and cooled to −78 °C. K-Selectride (1 M in THF, 32 L, 0.032 mmol, 3 equiv) was added, and the reaction mixture was stirred at −78 °C for 6 h. It was quenched with 1 drop of acetic acid and allowed to warm to room temperature. The reaction mixture was directly purified by flash chromatography on silica gel (20−50% ethyl acetate in hexane) to yield compound 1**3** (8.5 mg, 85%) as a white solid.

R_f 0.39 (33% AcOEt in hexane); $[\alpha]_D$ +42 (c = 0.167, $CHCl_3$); IR (thin film) 3354, 2959, 2931, 2880, 1727, 1598, 1253, 1037, 836 cm^{-1}; ^1H NMR ($CDCl_3$) δ_H 6.60 (ddd, J = 17.1, 10.7, 10.2 Hz, 1H), 6.03 (dd, J = 11.0, 10.7 Hz, 1H), 5.51 (dd, J = 10.6, 10.2 Hz, 1H), 5.40−5.30 (m, 2H), 5.22 (d, J = 16.6 Hz, 1H), 5.13 (d, J = 10.3 Hz, 1H), 5.01 (d br, J = 9.8 Hz, 1H), 4.80−4.70 (m, 1H), 4.72 (dd, J = 6.2, 5.6 Hz, 1H), 4.68−4.58 (m, 1H), 4.49 (s br, 2H), 3.70 (m, 1H), 3.50−3.45 (m, 1H), 3.27 (dd, J = 5.0, 4.7 Hz, 1H), 3.05−2.95 (m, 1H), 2.80−2.70 (m, 1H), 2.70−2.60 (m, 1H), 2.48−2.39 (m, 1H), 2.09 (dd, J = 12.6, 11.9 Hz, 1H), 1.98−1.75 (m, 5H), 1.68−1.50 (m, 5H), 1.26 (d, J = 7.5 Hz, 3H), 1.03−0.80 (m, 39H), 0.71 (d, J = 6.5 Hz, 3H), 0.62 (t, J = 7.9 Hz, 3H), 0.60 (t, J = 7.9 Hz, 3H), 0.11 (s, 3H), 0.08 (s, 3H), 0.05 (s, 3H), 0.03 (s, 3H); ^{13}C NMR ($CDCl_3$) δ C 173.9, 156.9, 134.8, 133.6, 132.1, 132.0, 131.4, 131.2, 129.8, 118.0, 80.6, 78.8, 77.2, 76.9, 74.5, 63.9, 44.1, 41.2, 37.9, 37.0, 36.3, 36.2, 35.1, 34.5, 34.4, 26.3, 26.2, 22.9, 19.1, 18.5 (2C), 17.5, 17.1, 16.3, 13.8, 13.7, 10.1, 6.8, 4.9, −3.1, −3.4, −3.5, −3.9; m/z (CI^+) 958.8 (100, $[M + Na]^+$); HRMS (ES^+) Calcd for $C_{51}H_{98}O_8NSi_3$ $[M + H]^+$ 936.6595, Found: 936.6592.

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The Development of a Practical Total Synthesis of Discodermolide, a Promising Microtubule-Stabilizing Anticancer Agent

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Dedicated to the memory of D. John Faulkner[‡]

Keywords: Antitumor agents / Cytotoxic / Marine polyketides / Total synthesis / Tubulin

Marine organisms provide an important source of natural product diversity with an associated range of significant biological activities. Discodermolide, isolated in microscopic quantities from a deep-water sponge, shares the same microtubule-stabilizing mechanism as Taxol and has a promising antitumor profile. There is, however, a chronic supply problem hampering clinical development and so a practical total synthesis of discodermolide is an important goal. This review highlights the completed total syntheses of discodermolide, focusing on the various methods and strategies employed for achieving stereocontrol and realising the pivotal fragment couplings.

1. Introduction

The vast ecosystem in our oceans provides a practically unlimited reservoir of structurally diverse secondary metabolites.[1,2] The biological activity of these marine natural products is often startling, demonstrating, for example, potent cytotoxic properties.[3,4] The low natural abundance, however, of many of these compounds, as isolated from sponges, corals and other marine organisms, dictates that alternative means of supply are usually required to further investigate and exploit their biological activities. These factors, coupled with their often complex molecular architectures and elaborate stereochemistry, offer compelling challenges for contemporary organic synthesis.[5,6] Along with other synthetic groups, we have sought innovative strategies and methods to deliver these precious compounds and their analogues for further biological studies and preclinical de-

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Ian Paterson was born in Dundee, Scotland. He received his B.Sc. degree in Chemistry from St. Andrews University. In 1979, he obtained his PhD from Cambridge University, working with Professor Ian Fleming on the development of new synthetic methods using allylsilanes and silyl enol ethers. After spending a postdoctoral year with Professor Gilbert Stork at Columbia University, working on the total synthesis of erythromycin A, he joined the faculty at University College London. In 1983, he moved back to Cambridge University, where he is now Professor of Organic Chemistry and a Professorial Fellow of Jesus College. His research interests are centred on the design and development of new synthetic methods for the control of stereochemistry and their application to the total synthesis of a range of biologically active compounds. He has developed novel strategies and general methods for the asymmetric synthesis of polyol building blocks, particularly by using substrate- and reagent-controlled aldol reactions, which facilitate the practical synthesis of structurally complex, polyketide natural products. Within his group, this research has enabled the total synthesis of rare anticancer agents, including spongistatin 1 (altohyrtin A), swinholide A and discodermolide, as well as antibiotics, such as concanamycin F and oleandolide.

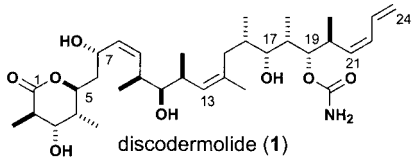
Gordon J. Florence was born in Manchester, England, in 1975. He gained a B.A. degree in Natural Sciences from Cambridge University in 1997. He received his PhD from Cambridge University in 2001, under the supervision of Professor Ian Paterson, working on the total synthesis of discodermolide, which included the development and application of new asymmetric aldol methodology. From 2001 to 2002, he was a Postdoctoral Research Associate with Professor Craig J. Forsyth at the University of Minnesota, working toward the synthesis of azaspiracid. In 2002, he returned to Cambridge as a Research Fellow of Emmanuel College and is currently focussing on the development of new stereoselective methods and their application to the total synthesis of several marine macrolides.

MICROREVIEWS: This feature introduces the readers to the authors' research through a concise overview of the selected topic. Reference to important work from others in the field is included.

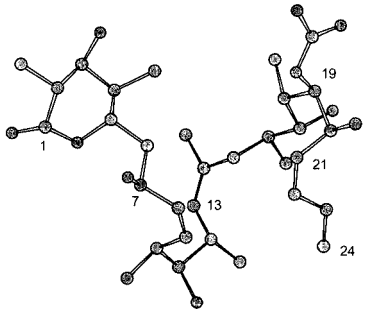
velopment. A notable example, and a primary focus of our group's research over the past decade, is discodermolide, a promising microtubule-stabilizing anticancer agent of sponge origin.[7−9]

2. Isolation and Biological Activity of Discodermolide

Discodermolide (**1**, Figure 1) is a unique polyketide that was isolated by Gunasekera and co-workers at the Harbor Branch Oceanographic Institution in 1990 from the Caribbean deep-sea sponge *Discodermia dissoluta*.[10−12] Initially, the sponge was collected off the Bahamas by manned submersibles at a depth in excess of 33 m.[11] These samples were exhaustively extracted and purified to provide crystalline discodermolide, $C_{33}H_{55}NO_8$, in 0.002% w/w isolation yield from the frozen sponge. Discodermolide's structure, as determined by extensive spectroscopic studies and single-crystal X-ray crystallography, features 13 stereogenic centres, a tetrasubstituted δ-lactone, one di- and one trisubstituted (*Z*)-alkene, a carbamate moiety and a terminal (*Z*)-diene. Discodermolide adopts a U-shaped conformation, where the internal (*Z*)-alkenes act as conformational locks by minimising 1,3-allylic strain between their respective substituents and *syn*-pentane interactions along the backbone are avoided, while the δ-lactone is held in a boat-like conformation.



discodermolide (**1**)



X-ray structure of discodermolide (**1**);
hydrogen atoms omitted for clarity

Figure 1. Structure and conformation of discodermolide (**1**)

Discodermolide was found initially to be a potent immunosuppressive agent,[13,14] similar to FK-506 and rapamycin, as well as displaying antifungal activity. Further biological screening revealed striking cytotoxicity in a variety of human and murine cell lines (IC_{50} 3−80 nM), causing cell cycle arrest at the G2/M phase boundary and subsequent cell death by apoptosis.[15,16] Discodermolide is a member of an elite group of natural products (Figure 2) that act as microtubule-stabilizing agents and mitotic spindle poisons,[7−9,17] which currently include Taxol® (paclitaxel) (**2**),[18] epothilones A (**3**) and B (**4**),[19] sarcodictyin A (**5**),[20] eleutherobin (**6**),[21] laulimalide (**7**),[22] FR182877 (**8**),[23] peloruside A (**9**),[24] and dictyostatin (**10**).[25] Despite showing no apparent structural similarities, discodermolide stabilizes microtubules more potently than the clinically important anticancer drug Taxol® and competitively inhibits the binding of radiolabelled Taxol to microtubules, suggesting that it occupies the same or an overlapping binding site on β-tubulin.[15,26]

Notwithstanding the general resemblance in mechanism of action to Taxol® and its analogues, such as Taxotere® (**11**),[27] discodermolide has some unique activities. Notably, the growth of Taxol-resistant ovarian and colon carcinoma cells that overexpress P-glycoprotein are inhibited by discodermolide at low-nanomolar concentrations.[28] Furthermore, unlike the epothilones and eleutherobin, discodermolide cannot substitute for Taxol in a Taxol-resistant carcinoma cell line that requires low concentrations of Taxol for normal growth.[29] Significantly, the presence of low concentrations of Taxol amplified the toxicity of discodermolide by 20-fold against this cell line, a feature that was not observed with the epothilones or eleutherobin. Hence, the combination of discodermolide with Taxol and other anticancer drugs may offer potential synergies. Moreover, in hollow fiber and xenograft mouse models, discodermolide demonstrates significant growth inhibition of human tumors in vivo, including those that are Taxol-resistant.[30]

The highly encouraging biological profile of discodermolide makes it a promising candidate for clinical development as a chemotherapeutic agent for the treatment of breast cancer and other drug-resistant solid tumors. This feature has been recognised by Novartis Pharmaceuticals Corporation, who licensed discodermolide from the Harbor Branch Oceanographic Institution in 1998 to develop it as a new-generation anticancer drug.

3. Total Synthesis

While the early clinical development of Taxol (**2**) was severely hampered by its supply, this problem was eventually resolved by semi-synthesis from 10-deacetylbaccatin III, which is obtained by extracting the needles of the European Yew tree.[31] In comparison, the epothilones, which are currently in clinical trials as anticancer agents, can be obtained by fermentation.[32] Unfortunately, this approach is not possible for discodermolide as yet, even though as a polyketide it is likely to be produced by a symbiotic microorganism associated with the sponge source. Therefore, the supply problem for discodermolide is chronic and can be solved at present only by total synthesis, rather than semi-synthesis as with Taxol. Consequently, there has been considerable synthetic effort directed towards discodermolide, culminating in several total syntheses[33−37] and numerous fragment

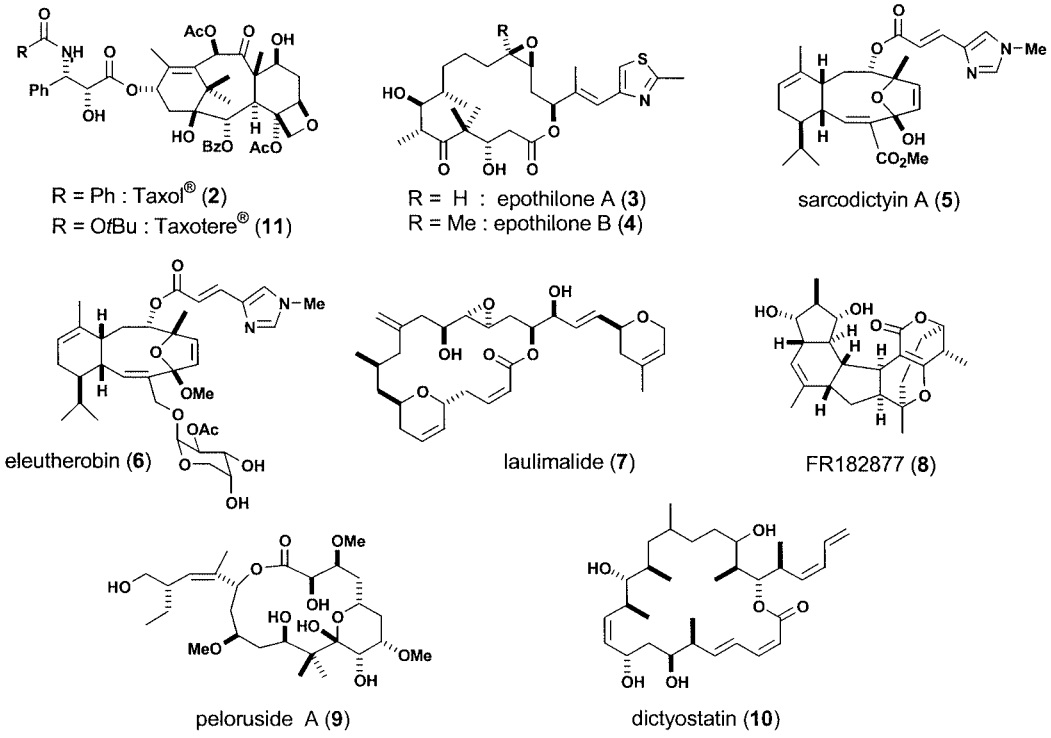


Figure 2. Microtubule-stabilizing agents; the configurational assignments of peloruside A and dictyostatin have not been rigorously established

syntheses.[38] This Microreview highlights the completed syntheses of discodermolide by ourselves and the groups of Schreiber, Smith, Myles and Marshall. In particular, we focus on the strategies employed to configure the multiple stereogenic centres and (*Z*)-alkenes, and the pivotal fragment coupling steps.

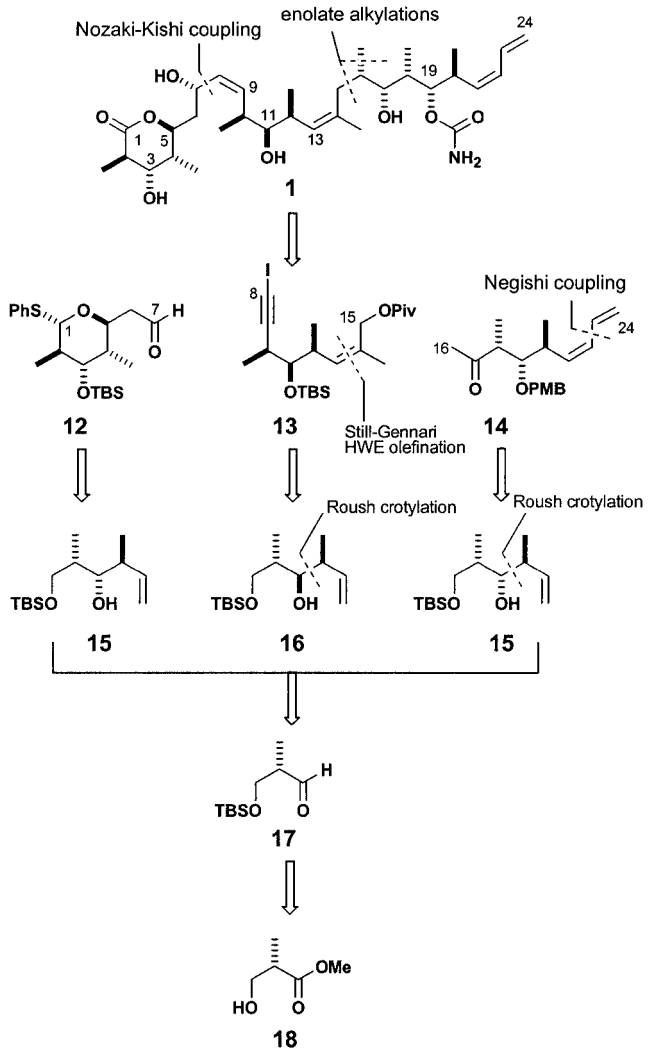
3.1 Schreiber Syntheses of Discodermolide[33]

Schreiber and co-workers disclosed their total synthesis of *ent*-discodermolide (*ent*-**1**) in 1993, which served to establish the absolute configuration.[33b] In 1996, they reported the first synthesis of the natural antipode (+)-discodermolide (**1**), essentially using the same route performed in the correct enantiomeric series (Scheme 1), along with several analogues designed to study their tubulin-binding and microtubule-stabilizing properties.[33a] Their synthetic route to (+)-discodermolide involved two key fragment couplings at C7−C8 and C15−C16, based on a Nozaki−Kishi addition[39] and an enolate alkylation, respectively. This approach relied on the use of three subunits **12** (C1−C7), **13** (C8−C15) and **14** (C16−C24) that were accessed from the homoallylic alcohols **15** and **16**, where the characteristic stereotriads were configured by two separate Roush asymmetric crotylation reactions[40] performed on the chiral aldehyde **17**, derived from the Roche ester **18**.

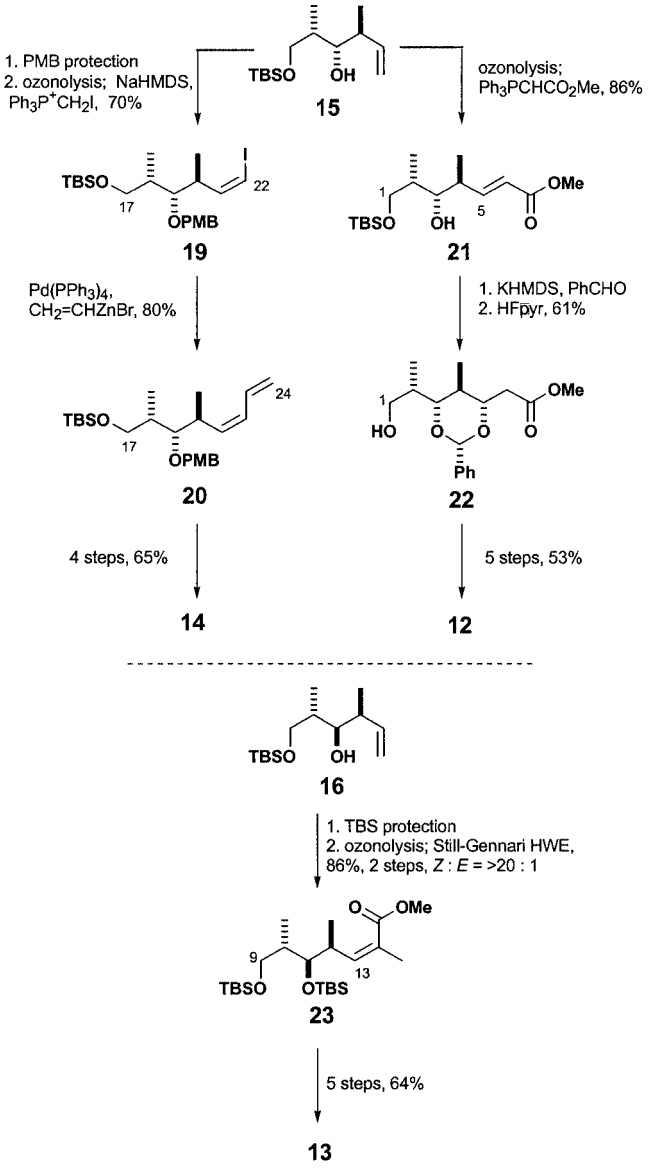
The C16−C24 segment **14** was synthesised in seven steps from homoallylic alcohol **15** (Scheme 2), in which the terminal (*Z*)-diene unit was introduced by a palladium-catalysed Negishi coupling[41] of vinyl iodide **19** with vinylzinc bromide to give **20**. The C1−C7 aldehyde **12**, as precursor to the δ-lactone, was prepared in eight steps from homoallylic alcohol **15**. The sequence included an intramolecular Michael addition of a hemiacetal to the (*E*)-enoate **21**, which proceeded with complete stereoselectivity at C5.[42] A further five-step sequence, performed on the acetal **22**, completed the synthesis of the thioacetal **12**. The trisubstituted (*Z*)-alkene was introduced efficiently by Still−Gennari HWE olefination [(*Z*)/(*E*) > 20:1], following silyl protection and ozonolysis of **16**. The resulting (*Z*)-enoate **23** was then converted into iodoacetylene **13** in a further five steps.

The Nozaki−Kishi coupling reaction of iodoacetylene **13** and aldehyde **12**, in the presence of $CrCl_2$/$NiCl_2$, gave propargylic alcohol **24** with *dr* = 2:1 at C7 (Scheme 3).[39] The low level of stereocontrol in this addition represents a disadvantage of this disconnection. The minor, undesired epimer can be recycled, however, by an oxidation/CBS reduction[43] protocol. Following elaboration, the resulting bromide **25** was coupled to the methyl ketone **14** via the lithium enolate. Further alkylation of the lithium (*Z*)-enolate of **26** with methyl iodide gave **27**, introducing the C16 stereocentre with *dr* = 3:1. Installation of the carbamate was followed by the presumed chelation-controlled reduction of the ketone **28** to introduce the OH group at C17 with *dr* = 30:1. Global deprotection completed the synthesis of discodermolide (**1**), with an overall yield of 4.3% achieved over 24 steps in the longest linear sequence.

The Schreiber synthesis is particularly noteworthy in that the absolute stereochemistry of discodermolide was assigned unambiguously, and through the preparation of nu-



Scheme 1. Strategy for the total synthesis of discodermolide developed by Schreiber et al.



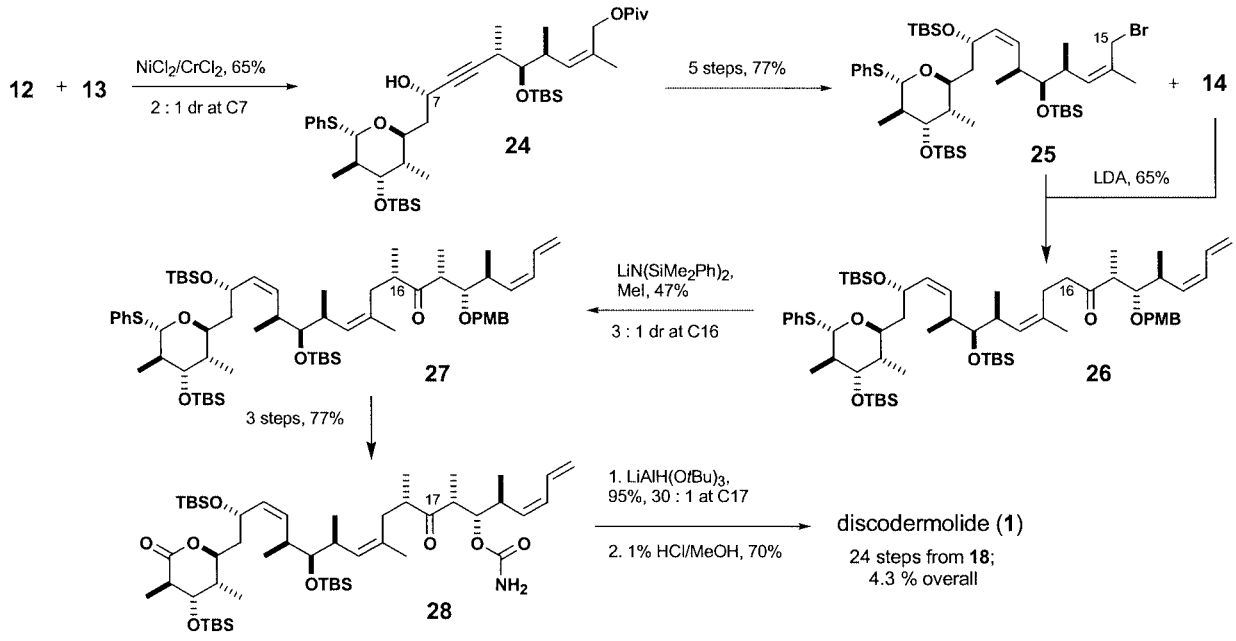
Scheme 2. Synthesis of the C1−C7, C8−C15 and C16−C24 segments of discodermolide according to Schreiber et al.

merous analogues the first structure−activity relationship study was possible.[33a] Perhaps most surprising was the discovery that the unnatural antipode (*ent*-**1**) is also cytotoxic and causes cell cycle arrest in the S-phase.[44]

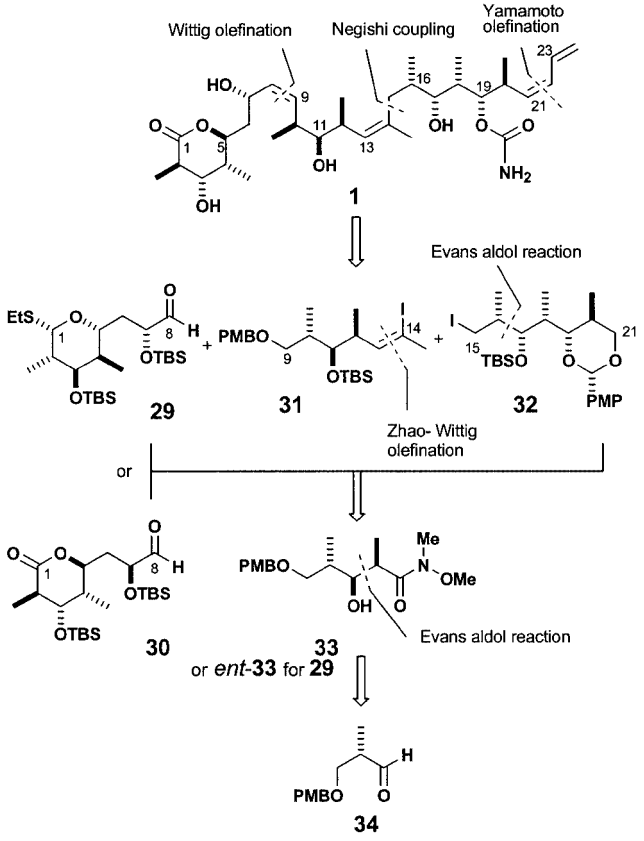
3.2 Smith Syntheses of Discodermolide[34]

Smith and co-workers first achieved the total synthesis of *ent*-discodermolide (*ent*-**1**) and subsequently developed a second-generation approach to provide discodermolide itself.[34] Their strategy involved key fragment couplings at C8−C9 and C14−C15 using a Wittig olefination and a Negishi[41] cross-coupling reaction, respectively (Scheme 4). The modifications to their original route involved the earlier introduction of the terminal (*Z*)-diene unit by a Yamamoto olefination[45] and the replacement of thioacetal aldehyde **29** with δ-lactone aldehyde **30** for the C1−C8 subunit. The segments **31** (C9−C14) and **32** (C15−C21) were used in both syntheses in the appropriate enantiomeric series. In their second-generation route, all three segments were derived from the common precursor **33**, which incorporates the repeating stereotriad sequence of discodermolide.

The common precursor **33** was configured using the *syn*-aldol reaction of the α-chiral aldehyde **34**, which is derived in three steps from Roche ester **18**, with the Evans propionimide **35** (Scheme 5).[46] The (*Z*)-alkenyl iodide at C14 was introduced directly in moderate yield and variable selectivity [(*Z*)/(*E*) = 8:1−17:1] by the Zhao−Wittig olefination protocol[47,48] performed on aldehyde **36**, following silyl protection and DIBAL reduction of **33**. The synthesis of C15−C21 segment **32** utilised a second Evans-aldol reaction to configure the *syn* relationship of C16−C17 to provide **37** and was completed in a further three steps. Palladium-catalysed cross-coupling of the zincate derived from the vinyl iodide **31** with primary iodide **32** then gave the C9−C21 segment **38**.[41]



Scheme 3. Total synthesis of discodermolide according to Schreiber et al.



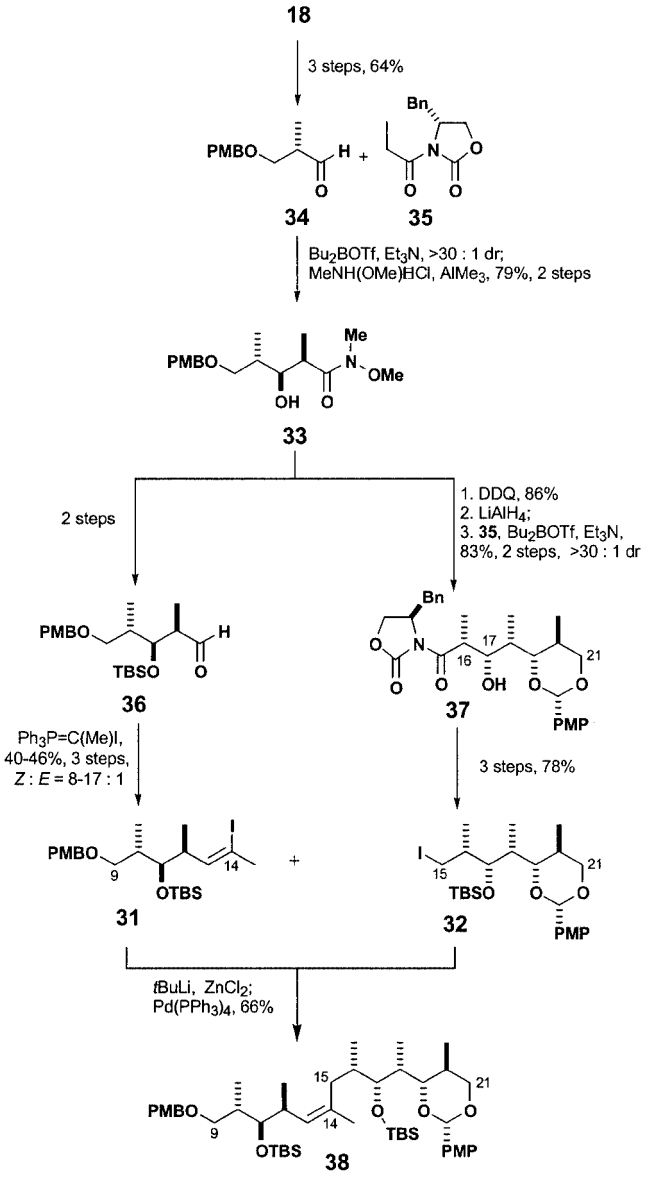
Scheme 4. Strategy for the total synthesis of discodermolide developed by Smith et al.

In the initial Smith synthesis of *ent*-discodermolide,[34c] the C1−C8 thioacetal aldehyde **29** was prepared in 14 steps from *ent*-**33**, exploiting the coupling of dithiane **39** with epoxide **40**, derived from (*R*)-glycidol, to complete the carbon skeleton in **41** (Scheme 6).

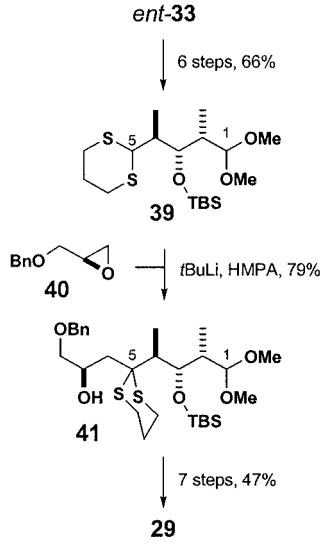
The elaboration of the C9−C21 fragment *ent*-**38** to phosphonium salt **42** proved troublesome and required the treatment of intermediate iodide **43** with triphenylphosphane at ultrahigh pressure (12.8 kbar = 12.6 × 10^3 atm) for 6 d using a specialised reactor (Scheme 7).[49,50] Subsequent (*Z*)-selective Wittig coupling of aldehyde **29** and phosphonium salt **42** gave the advanced C1−C21 intermediate **44**. The terminal (*Z*)-diene unit was then introduced by a three-step sequence utilising the Yamamoto olefination protocol to give **45**.[45] A further five-step sequence was required to complete the synthesis of *ent*-discodermolide (*ent*-**1**), with 2.2% overall yield obtained over 28 steps (longest linear sequence).

The Smith second-generation approach was designed both to reduce the number of steps and to generate a gram of the natural (+)-enantiomer of discodermolide (**1**), and the common-precursor strategy was used to access the δ-lactone aldehyde **30** that now replaced **29** (Scheme 4). The synthesis of the aldehyde **30** was achieved in eight steps from the Weinreb amide **33** (Scheme 8). A remarkable non-Felkin-selective addition of silyl enol ether **46** to aldehyde **47** gave ketone **48**, after acid-catalysed δ-lactonisation, followed by K-Selectride reduction at C7 to give alcohol **49** with *dr* = 9:1. The sequence was completed by TBS protection and ozonolysis to produce **30**, corresponding to a total of 13 steps in 21% yield. In comparison, *ent*-**30** was synthesised earlier by the Paterson group in 12 steps and 29% yield when a similar Wittig strategy was employed.[38a]

The earlier installation of the terminal diene unit was addressed with the C9−C21 fragment **38** (Scheme 9). The diene was installed in a five-step sequence to give the C9−C24 intermediate **50**, with a (*Z*)/(*E*) ratio of 8:1−12:1,



Scheme 5. Synthesis of the C9−C21 segment of discodermolide according to Smith et al.



Scheme 6. Synthesis of the C1−C8 segment of *ent*-discodermolide according to Smith et al.

again utilising the Yamamoto olefination.[45] The phosphonium salt **51** was prepared from **50** in a further two steps, again requiring ultrahigh-pressure conditions. The key Wittig coupling of phosphonium salt **51** and aldehyde **30** gave **52** with a (*Z*)/(*E*) ratio of 15:1−24:1. A further three steps were required to complete this second-generation synthesis of discodermolide, which proceeded in an improved 6% yield over 24 steps (longest linear sequence).

The Smith synthesis is notable in that it provided an impressive 1.043 g of discodermolide, which was considerably more than had ever been isolated from the sponge source, and this synthesis proved to be timely to enable further biological and preclinical evaluation. Further scale-up of this route, however, would pose significant technical challenges, in particular because of the limited availability of ultrahigh-pressure reactors for performing large-scale preparations of the phosphonium salt **51**, as required for the late-stage fragment coupling.

3.3 Myles Synthesis of *ent*-Discodermolide[35]

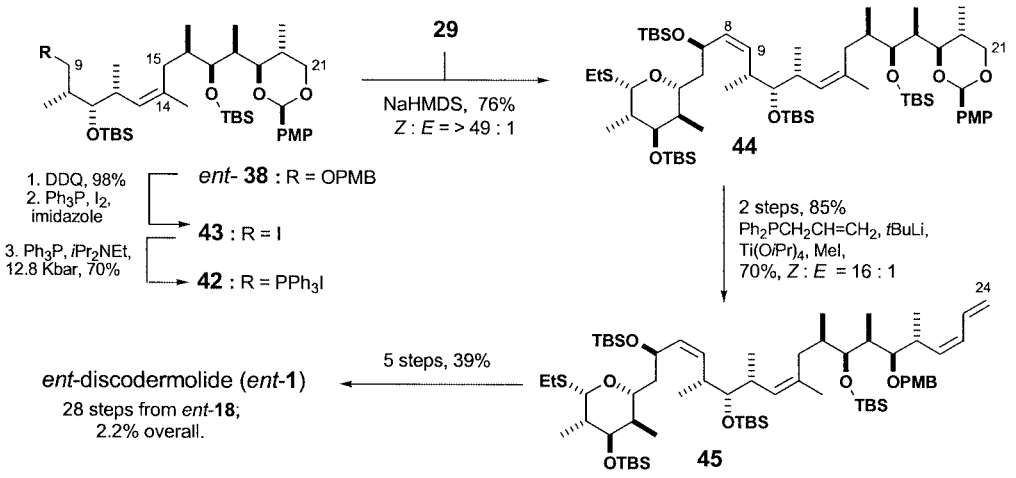
In the total synthesis of *ent*-discodermolide (*ent*-**1**) reported by Myles and co-workers,[35] the three segments **53** (C1−C7), **54** (C9−C15) and **55** (C16−C21) were employed, as shown in Scheme 10, with key couplings performed at C7−C8 based on a Nozaki−Kishi addition[39] and C15−C16 relying on an ambitious enolate alkylation step.

The synthesis of the C9−C15 segment **54** exploited methodology developed in the Danishefsky group[51] to introduce the trisubstituted (*Z*)-olefin (Scheme 11), where $TiCl_4$-mediated cyclocondensation of the chiral aldehyde **56** and diene **57**, gave the dihydropyrone **58**.[35b]

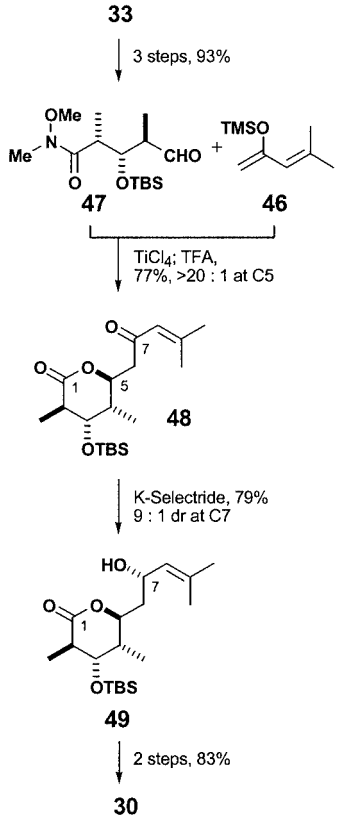
Subsequent Luche reduction and Ferrier rearrangement provided the lactol **59**, which was then converted into the iodide **54** in five further steps. The lithium-mediated aldol reaction of pentan-3-one and the Roche ester derived aldehyde *ent*-**34**, followed by hydroxy protection, allowed access to the C16−C21 segment **55**.[35c]

The C1−C7 aldehyde **53** was prepared in 10 steps from homoallylic alcohol **60**, where the C5-OH group was introduced by a Brown asymmetric allylation on aldehyde **61**. The resulting alcohol **62** was then converted into **53** by a five-step sequence.

The adventurous ethyl ketone alkylation strategy to form the C15−C16 bond had also been explored by Schreiber[33] and Heathcock.[38b] Both of these groups, however, were unable to obtain the C16 configuration of discodermolide with useful selectivity using the ethyl ketone. In contrast, Myles found that in the alkylation of **54** with the lithium (*Z*)-enolate of **55**, the MOM protection of the C19-OH group and the judicious choice of lithium base and solvent system were critical to provide the desired C9−C21 segment **63** with *dr* = 6:1 (Scheme 12).[35a] Subsequent manipu-



Scheme 7. Total synthesis of *ent*-discodermolide according to Smith et al.



Scheme 8. Synthesis of the C1−C8 segment of discodermolide according to Smith et al.

lations, including reduction at C17 (*dr* = 8:1), and a Stork−Wittig olefination gave the C8−C21 vinyl iodide **64**.[52] Following PMB deprotection and oxidation, the terminal diene unit was installed using the modified Roush allylation reagent **65** with subsequent Peterson-type *syn* elimination.[53,54] Introduction of the carbamate followed to afford the vinyl iodide **66**. In a manner similar to the Schreiber synthesis,[33] the Nozaki−Kishi coupling to form the C7−C8 bond through addition of iodide **64** to aldehyde **53** proceeded, at best, in moderate yield to give **67** with *dr* = 2:1 at C7. Global deprotection and concomitant δ-lactonisation of **67** gave *ent*-discodermolide (*ent*-**1**) in a synthesis that proceeded in ca. 1.4% overall yield from iodide **54** (the yields and full details of this synthesis are not available in the literature).

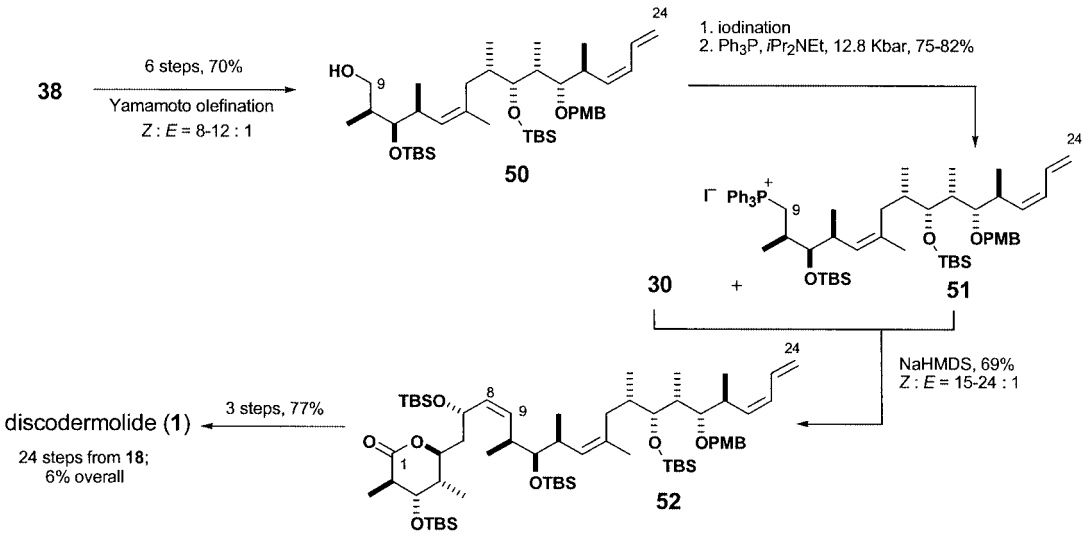
3.4 Marshall Synthesis of Discodermolide[36]

The synthetic plan adopted by Marshall and co-workers[36] for (+)-discodermolide involved the three segments **68** (C1−C7), **69** (C8−C13) and **70** (C15−C24), with key coupling steps performed at C7−C8 by lithium acetylide addition to an aldehyde and C14−C15 using a novel Suzuki cross-coupling reaction (Scheme 13).[55]

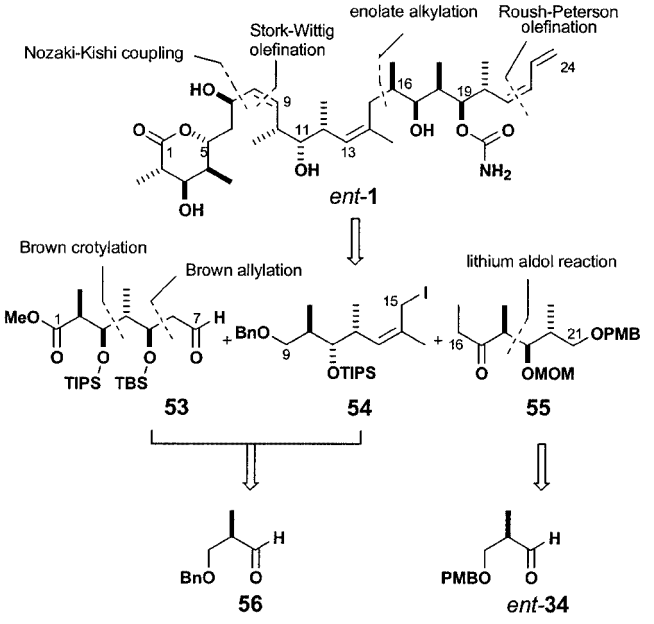
The stereopentad found in the C15−C24 segment **70** was built using methodology developed within the Marshall group,[56] involving the addition of chiral allenylstannane **71** to the Roche ester derived aldehyde **17** to give **72** with *dr* > 20:1 (Scheme 14). Introduction of the C19 and C20 stereocentres utilised a sequence of reduction, Sharpless epoxidation, and methyl cuprate opening of the resulting epoxide to afford diol **73**.[36b]

Installation of the terminal diene unit was performed using the Nozaki−Hiyama/Peterson protocol developed in the Paterson group,[38f] and protecting group transformations completed the synthesis of the iodide **70** in a further eight steps.

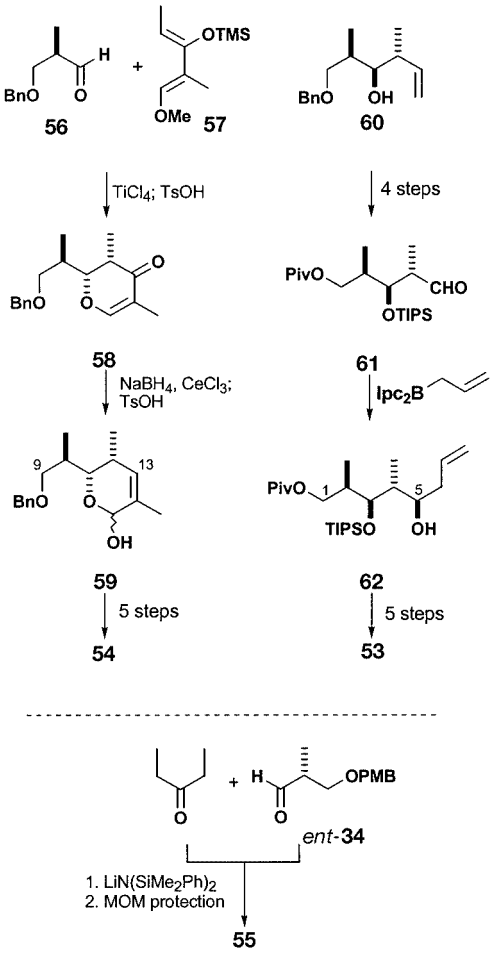
The common stereotriad found in **68** (C1−C7) and **69** (C8−C13) was accessed with *dr* = 9:1 by the addition of a chiral allenylzinc species, prepared in situ from the treatment of propargylic mesylate **74** with Et_2Zn and catalytic Pd^0, to the α-chiral aldehyde **75**. Protection of the resulting alcohol **76** as the MOM ether gave the C8−C13 segment **69**. A further nine-step sequence performed on **76** provided the C1−C7 segment **68**, which involved Red-Al reduction, Sharpless epoxidation, and hydride opening of the resulting epoxide to introduce the C5-OH group.[36b]



Scheme 9. Total synthesis of discodermolide according to Smith et al.

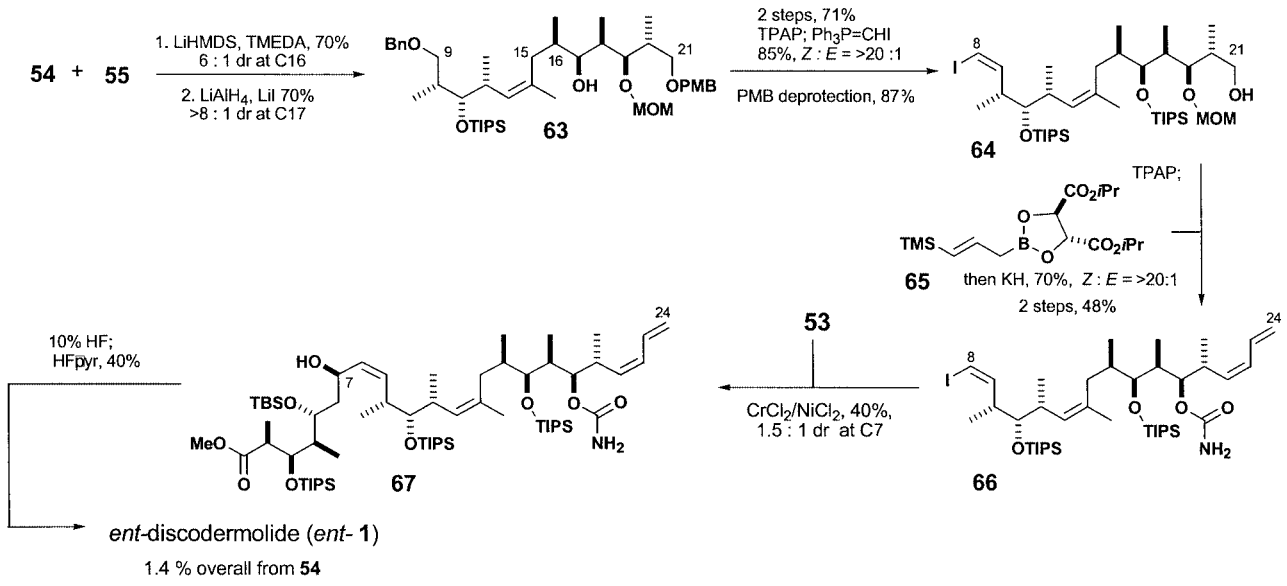


Scheme 10. Strategy for the total synthesis of *ent*-discodermolide developed by Myles et al.

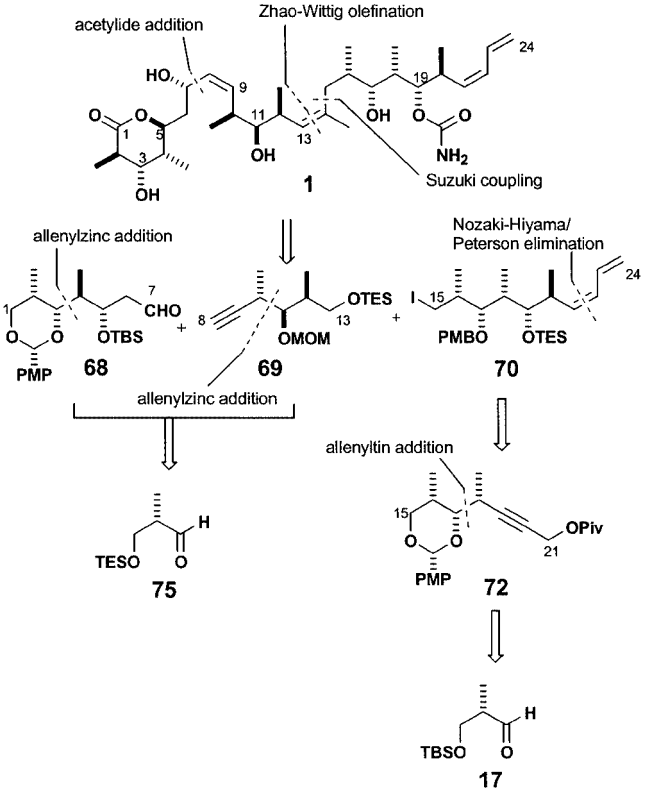


Scheme 11. Synthesis of the C1−C7, C9−C15 and C16−C21 segments of discodermolide according to Myles et al.

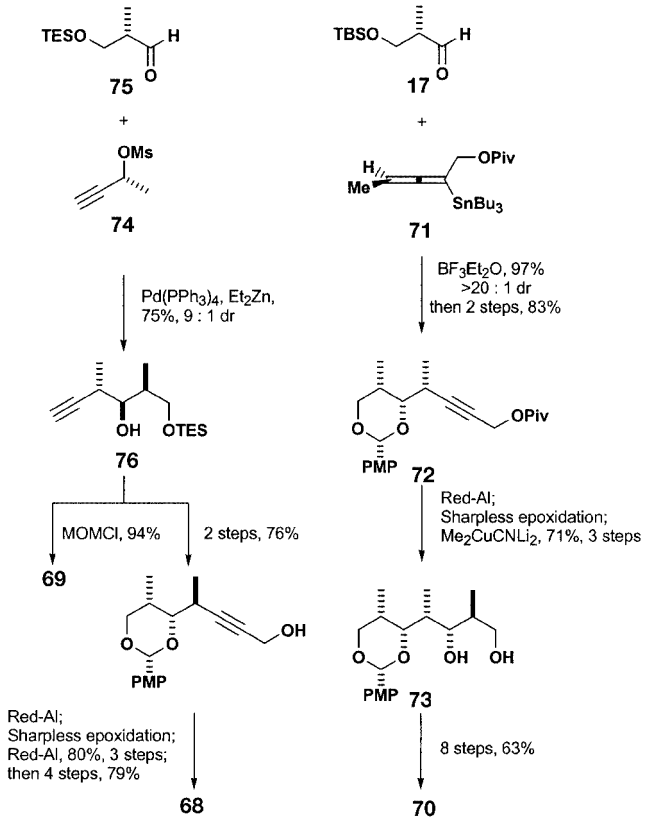
As shown in Scheme 15, the addition of the lithium acetylide derivative of alkyne **69** to the aldehyde **68** proceeded in high yield to give alcohol **77** as a 6:1 ratio of epimers at C7 (where the minor epimer could be recycled by Mitsunobu inversion). Following the Lindlar hydrogenation of the alkyne moiety and protecting group manipulations, the Zhao−Wittig protocol was employed on **78** to introduce the (*Z*)-alkenyl iodide,[47] which was characterised by variable yields and selectivity [(*Z*)/(*E*) = 1.3:1−9:1). The efficient Suzuki cross-coupling[55] of vinyl iodide **79** and C15−C24 boronate **80**, derived from primary iodide **70**, facilitated the assembly of the advanced C1−C24 intermediate **81**. After a series of manipulations and deprotections, the synthesis of discodermolide (**1**) was completed in 2.2% overall yield achieved over 29 steps (longest linear sequence). The Marshall synthesis clearly demonstrated the



Scheme 12. Total synthesis of *ent*-discodermolide according to Myles et al.



Scheme 13. Strategy for the total synthesis of discodermolide developed by Marshall et al.

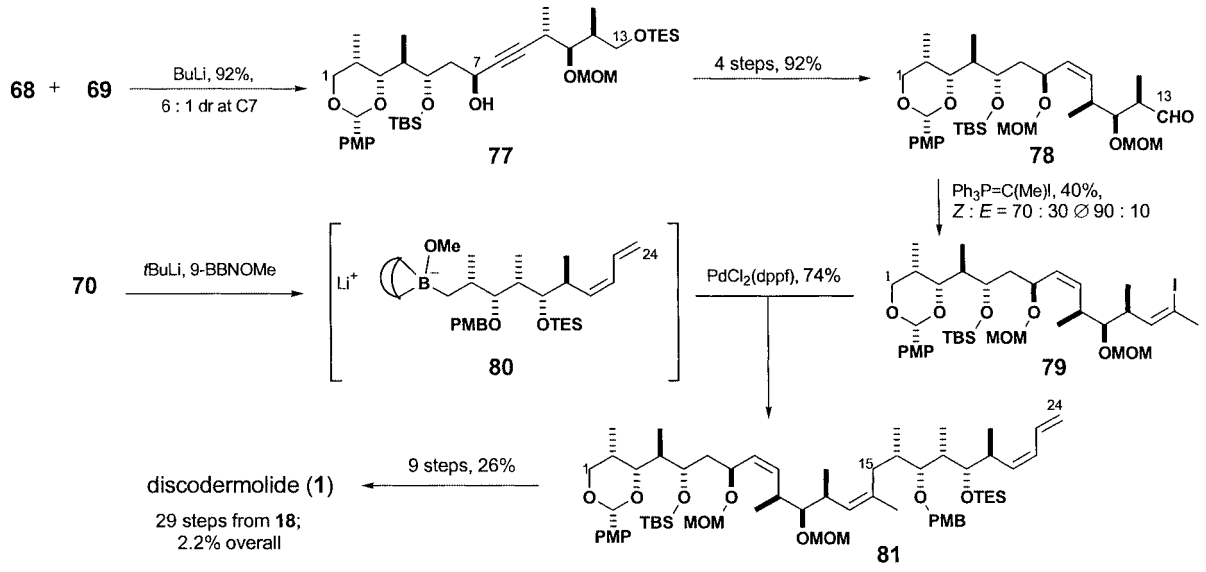


Scheme 14. Synthesis of the C1−C7, C8−C13 and C15−C24 segments of discodermolide according to Marshall et al.

versatility of their chiral allenylmetal methodology for the preparation of polypropionate arrays and the utility of the Suzuki cross-coupling for complex fragments.

3.5 Paterson Syntheses of Discodermolide[37]

The synthesis of discodermolide and structural analogues has been the subject of extensive effort within our grou-

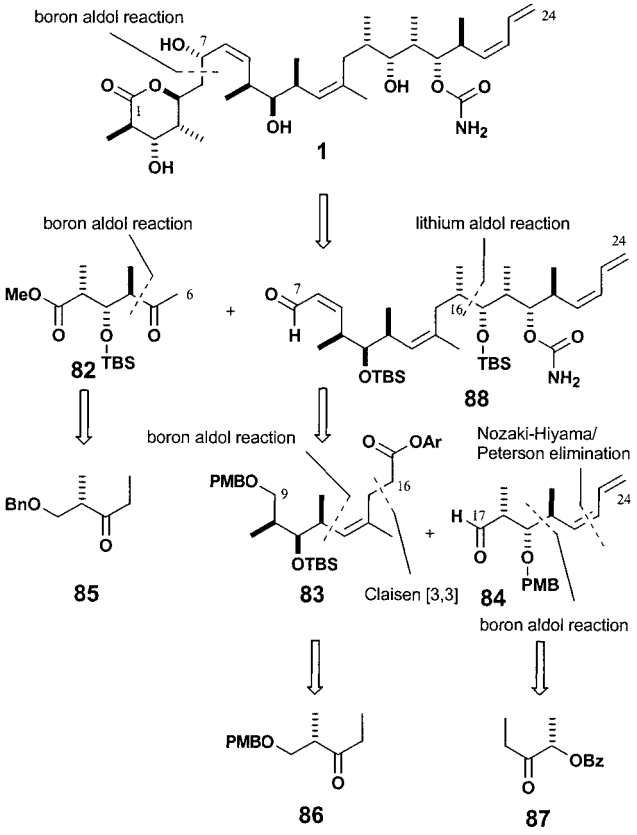


Scheme 15. Total synthesis of discodermolide according to Marshall et al.

p.[37][38a][38f] The construction of the requisite polypropionate arrays found in discodermolide was accomplished, at an early stage,[38a][38f] with relative ease using our aldol-based methodology.[57–59] Problems were encountered, however, in the fragment-coupling steps and introducing the trisubstituted (*Z*)-olefin, such that a revised strategy was designed to circumvent these difficulties. As shown in Scheme 16, this approach was based on the application of two aldol reactions to unite three subunits **82** (C1–C6), **83** (C9–C16) and **84** (C17–C24).[37a–37c] The stereochemical motifs present in each of these compounds were configured, utilising our group's methodology, by employing the ethyl ketones **85**, **86** and **87** as chiral building blocks.[58][59] The full carbon backbone was completed by an adventurous aldol coupling reaction at C6–C7 between methyl ketone **82** and the advanced (*Z*)-enal **88**. The latter compound was assembled by a lithium-mediated aldol reaction at C16–C17 between aryl ester **83** and aldehyde **84**. This approach constituted a novel construction of the carbon skeleton of (+)-discodermolide by installing three stereogenic centres in two fragment-coupling steps, while the trisubstituted (*Z*)-alkene was installed efficiently by a Claisen rearrangement using Holmes methodology.[60]

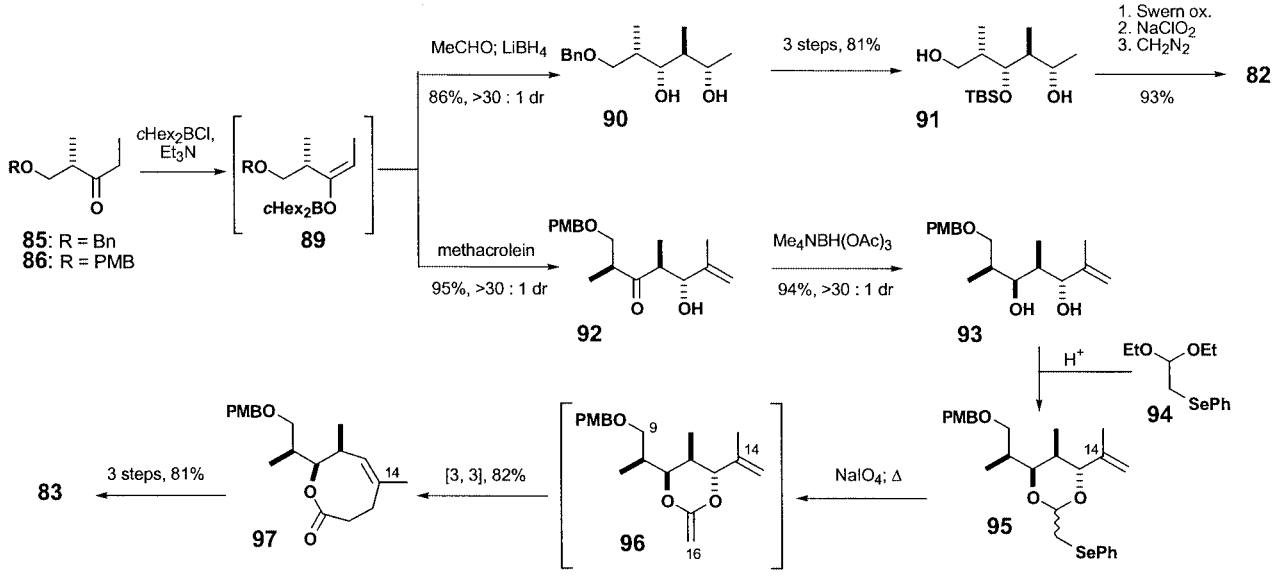
Our synthesis of the C1–C6 methyl ketone **82** started with an *anti*-aldol reaction between the ethyl ketone **85**, prepared in three steps from Roche ester **18**, and acetaldehyde (Scheme 17).[58] Enolization with *c*Hex$_2$BCl/Et$_3$N and addition of acetaldehyde to enolate **89** provided the intermediate aldolate, where an in situ reduction with LiBH$_4$ gave diol **90** (*dr* > 30:1).[61] Subsequent protecting group manipulations provided **91** and the synthesis of **82** was completed through oxidation at C1 and C5, and subsequent methyl ester formation.

Our synthesis of the C9–C16 aryl ester **83** began with the *anti*-aldol reaction of ethyl ketone **86** with methacrolein to provide **92** with *dr* > 30:1 (Scheme 17). An Evans *anti*



Scheme 16. Strategy for the first-generation synthesis of discodermolide developed by Paterson et al.; Ar = 2,6-dimethylphenyl

reduction provided diol **93** (*dr* > 30:1),[62] which then underwent transacetalisation with **94** to give acetal **95**. Following the Holmes protocol,[60] oxidation and thermal elimination of the phenyl selenoxide gave the intermediate ketene acetal **96**, which in turn underwent Claisen [3,3] re-

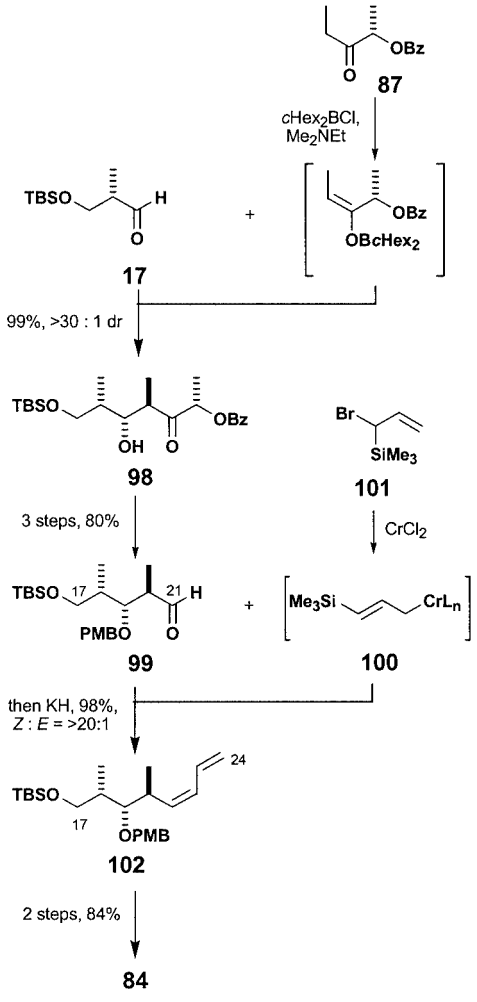


Scheme 17. Synthesis of the C1−C6 and C9−C16 segments of discodermolide according to Paterson et al.

arrangement to afford the lactone **97**, leading to complete selectivity for introduction of the trisubstituted (*Z*)-alkene. A further three-step sequence was then required to complete the ester **83**.

As shown in Scheme 18, our synthesis of the C17−C24 aldehyde **84** began with the boron-mediated aldol reaction of the lactate-derived ethyl ketone **87** with the α-chiral aldehyde **17** to give the *anti* adduct **98** exclusively.[59] Subsequent protecting group manipulations and oxidative cleavage gave aldehyde **99**. Following the protocol that we had developed earlier, the terminal (*Z*)-diene moiety was introduced efficiently by sequential Nozaki−Hiyama allylation and Peterson elimination reactions.[38f] Addition of the allylchromium compound **100**, generated from bromide **101**, to aldehyde **99**, provided the (*Z*)-diene **102** after *syn* elimination of the intermediate adducts. Silyl deprotection and oxidation completed the synthesis of **84**.

As shown in Scheme 19, the lithium-mediated *anti*-aldol reaction of the Heathcock-type aryl ester **83** with aldehyde **84** gave the expected adduct **103** with *dr* = 30:1 based on Felkin−Anh stereoinduction.[63] Following ester reduction, either in situ or after isolation of **103**, a two-step deoxygenation sequence was performed on **104**, to introduce the C16-CH_3 group. TBS protection of the C17-OH group and subsequent PMB deprotection gave diol **105**. Following selective primary oxidation with TEMPO,[64] the C8−C9 (*Z*)-olefin was introduced efficiently by a Still−Gennari HWE reaction to give **106** with (*Z*)/(*E*) > 30:1. Subsequent carbamate installation at C19 and a reduction/oxidation sequence at the C7 terminus gave enal **88** in readiness for the pivotal C6−C7 aldol coupling. This step proved to be particularly challenging and required considerable effort to secure the desired C7 configuration.[37a−37c] Enolization of **82** with *c*Hex_2BCl/Et_3N provided the boron enolate **107**, which on addition to **88** gave the undesired (7*R*) adduct



Scheme 18. Synthesis of the C17−C24 segment of discodermolide according to Paterson et al.

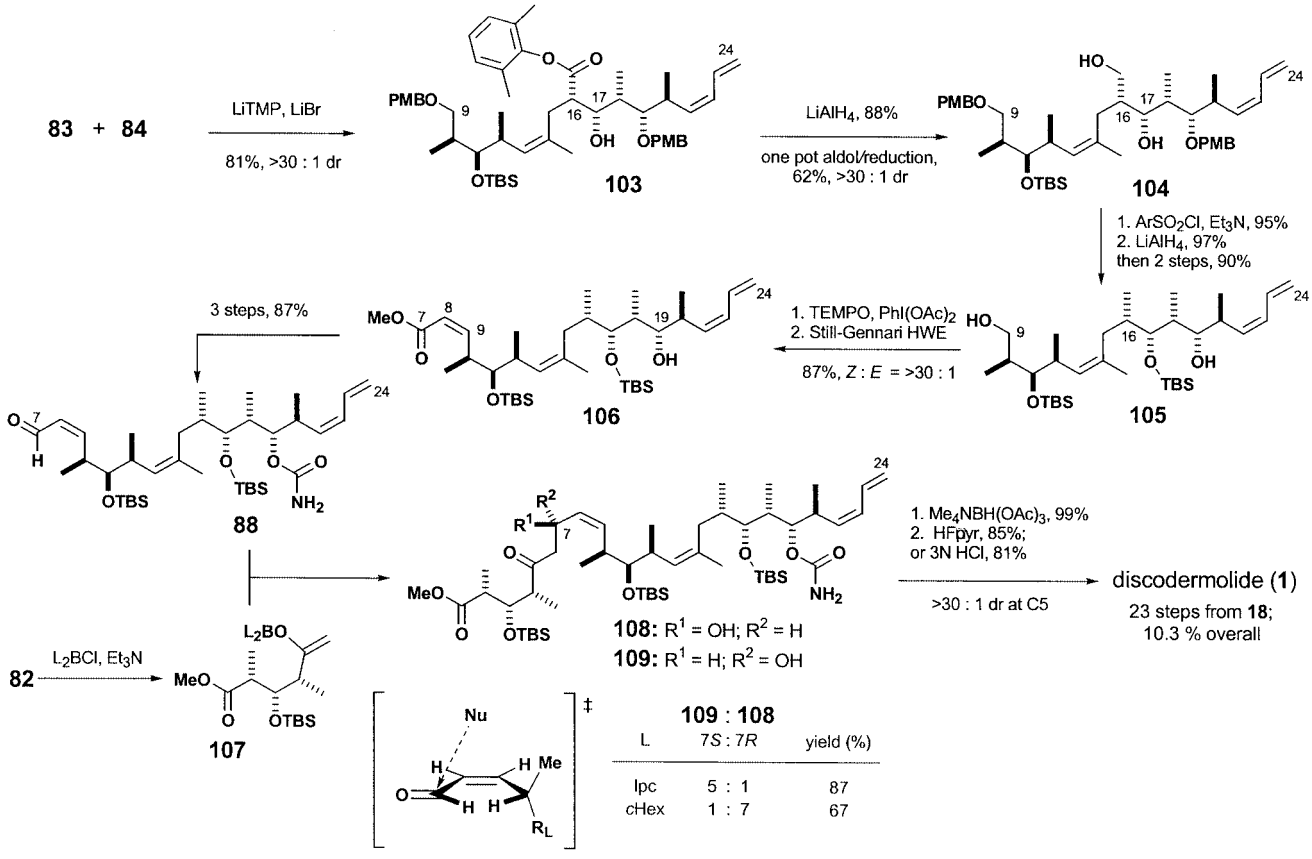
108 with *dr* = 7:1, arising from high levels of remote 1,4-stereoinduction from the (*Z*)-enal with preferred attack on the sterically less congested *re* face as indicated. Therefore, to obtain the desired (7*S*) adduct **109**, it was necessary to employ a chiral boron reagent to overturn the π-facial bias of aldehyde **88**. Gratifyingly, enolisation of **82** with (+)-Ipc_2BCl/Et_3N and addition of **107** to enal **88** gave the desired aldol adduct **109** with *dr* = 5:1.[65] This result represents a rare example of the use of reagent control to reverse the intrinsic substrate selectivity successfully in a complex aldol coupling of two chiral carbonyl components. An Evans 1,3-*anti* reduction on **109** introduced the final stereogenic centre at C5 with *dr* > 30:1. Global deprotection and δ-lactonisation then completed our synthesis of discodermolide (**1**) in 10.3% yield over 23 steps (longest linear sequence).

This first-generation synthesis of discodermolide demonstrated the novel application of complex aldol reactions in key fragment unions and achieved essentially complete control over the double-bond geometry. The only step that proceeded with less-than-perfect stereocontrol was the final aldol coupling, but we have since developed an effective sequence to convert also the minor (7*R*) adduct **108** into discodermolide.[66]

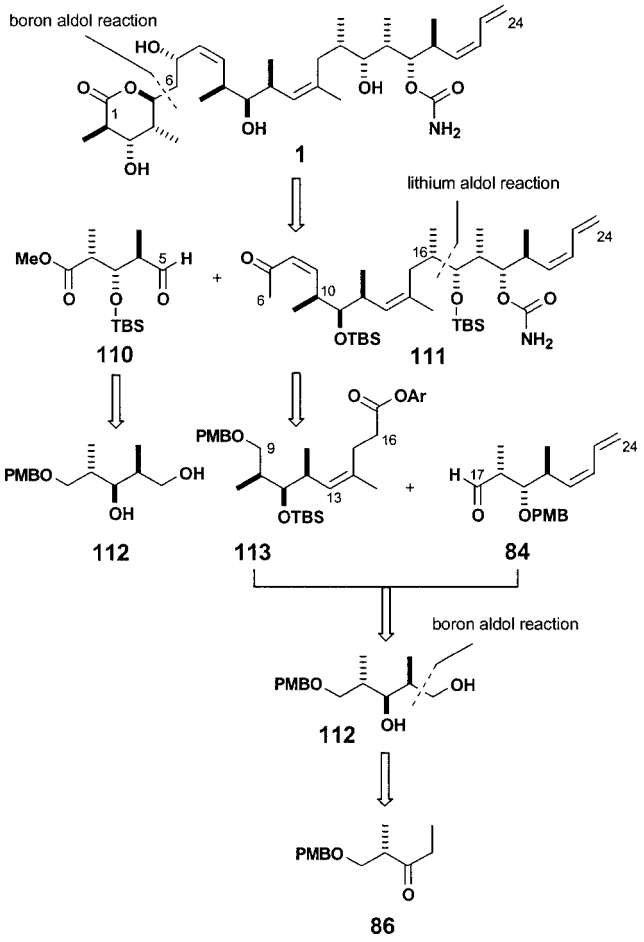
Following our first-generation synthesis, a revised strategy towards discodermolide was devised (Scheme 20) both to eliminate the use of all chiral reagents and auxiliaries, thus relying solely on substrate control, and to reduce the total number of steps.[37d] To achieve these specific goals, a novel aldol coupling across C5−C6 was employed between aldehyde **110** and methyl ketone **111**, relying on long-range asymmetric induction from the C10 γ-stereocenter. The use of a common building block **112**, containing the repeating *anti-syn* stereotriad found in the three subunits **110**, **113** and **84**, helped to reduce the total number of steps.

Our synthesis of the common building block **112** started with the boron-mediated aldol reaction of ethyl ketone **86** with formaldehyde to give adduct **114** with *dr* = 20:1, containing the required 1,3-*anti*-configured methyl groups (Scheme 21).[58] A hydroxy-directed reduction then gave diol **112** with *dr* = 10:1, which was isolated conveniently in stereochemically pure form by recrystallization. Notably, the five-step synthesis of **112**, starting from Roche ester **18**, can be performed on a large scale without recourse to chromatographic purification.

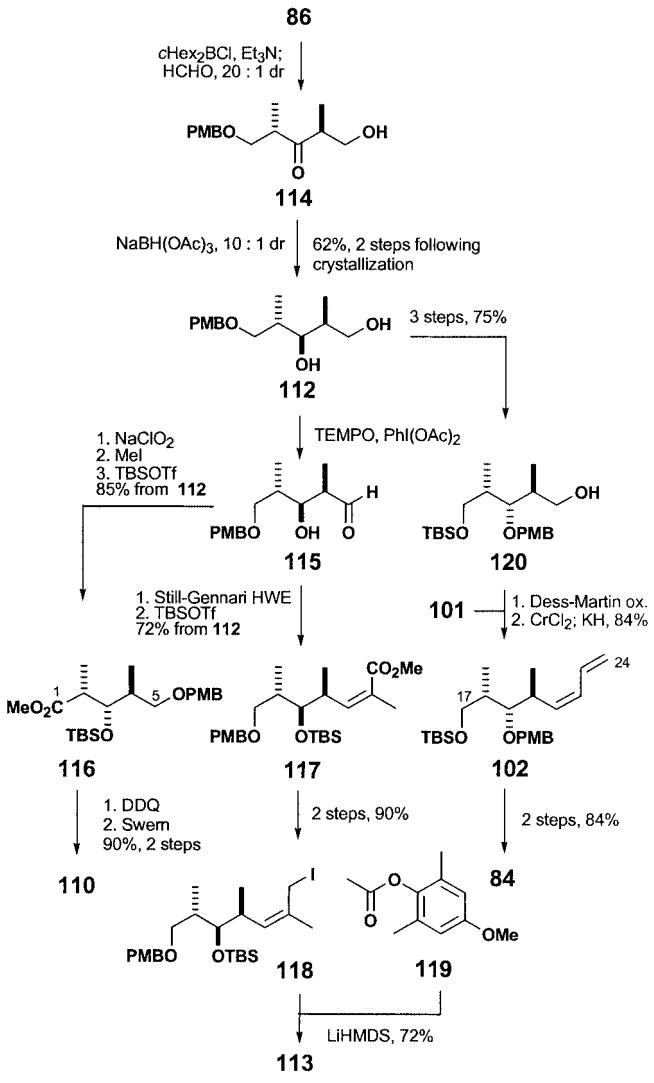
Our synthesis of the C1−C5 subunit **110** from the common precursor **112** began with a selective TEMPO oxidation of the C1−OH group to give **115**. Further oxidation to the carboxylic acid and conversion into the methyl ester was followed by TBS protection. Deprotection of **116** at the C5 terminus and oxidation completed the C1−C5 aldehyde **110** in six steps. In parallel, the C9−C16 subunit **113** was accessed in five steps utilising aldehyde **115**. The trisubstituted (*Z*)-olefin was introduced by Still−Gennari HWE olefination, as used in the Schreiber synthesis,[33] and TBS protection of the C11-OH group then provided **117**. Re-



Scheme 19. Completion of first-generation synthesis of discodermolide according to Paterson et al.; Ar = 2,4,6-trimethylphenyl



Scheme 20. Strategy for the second-generation synthesis of discodermolide developed by Paterson et al.; Ar = 4-methoxy-2,6-dimethylphenyl

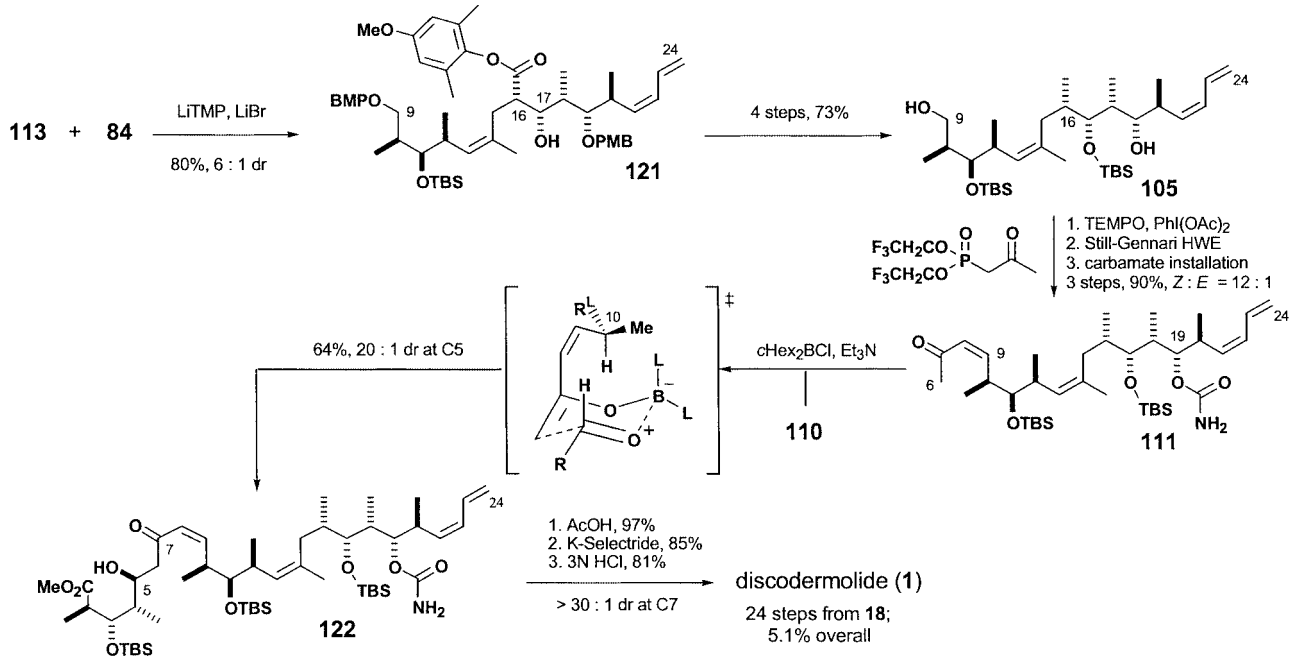


Scheme 21. Synthesis of the C1−C5, C9−C16 and C17−C24 segments of discodermolide according to Paterson et al.

duction of the methyl ester and conversion into the iodide **118** was followed by alkylation with the lithium enolate of the novel aryl ester **119**, to complete the C9−C16 subunit **113**. The revised synthesis of the C17−C24 subunit **84** from the common precursor **112** began with a three-step sequence of protecting group manipulation to give **120**. Oxidation of the primary hydroxy group was followed by installation of the terminal (*Z*)-diene by our usual method[38f] to provide the known intermediate **102**, which was converted into **84** as before.[37a]

The lithium-mediated aldol coupling of **113** and **84** provided **121** with *dr* = 6:1,[63] which was then converted into alcohol **105** (Scheme 22) by following our previously established route.[37a,37b] Selective primary oxidation of **105** and introduction of the (*Z*)-enone moiety under modified Still−Gennari HWE conditions provided **111** with (*Z*)/(*E*) = 12:1,[67] following carbamate installation at C19. The novel boron-mediated aldol reaction of methyl ketone **111** and aldehyde **110** exploited remote 1,6-asymmetric induction from C10 as in the indicated transition state. Enolisation of **111** with *c*Hex_2BCl/Et_3N and reaction with **110** gave the desired (5*S*) adduct **122** with *dr* = 20:1. In contrast, the analogous lithium-mediated reaction gave the (5*R*) adduct exclusively, as expected from Felkin−Anh control. Acid-promoted δ-lactonisation of **122** was followed by K-Selectride reduction at C7,[34a] introducing the final stereogenic centre with *dr* > 30:1. Global deprotection then completed our second-generation synthesis of discodermolide (**1**), which proceeded in 5.1% yield over a 24-step longest linear sequence (35 total steps).

In comparison with our original route, this second-generation approach reduced substantially the total number of steps required to complete discodermolide. The use of chiral reagents and auxiliaries was eliminated, altogether achieving a more cost-effective route. In contrast to the earlier syntheses of discodermolide by the groups of Schreiber, Smith, Myles and Marshall, which start out from the ubiquitous Roche ester **18**, our second route relies solely on substrate control to configure all the remaining stereocentres.



Scheme 22. Completion of second-generation synthesis of discodermolide according to Paterson et al.

4. Outlook

The different synthetic approaches developed to date clearly demonstrate the feasibility of chemical synthesis providing useful quantities of discodermolide, and this feature has enabled further biological and preclinical evaluation of this potent microtubule-stabilizing antimitotic agent, as well as inspiring the development and application of new methods for acyclic stereocontrol. It is evident that lengthy total syntheses of such complex natural products are no longer limited to delivering milligrams of product.[68] The prospect of realising the crossover of discodermolide from laboratory to clinic as a new-generation anticancer agent will require a practical and scaleable synthesis that can ultimately deliver kilogram quantities. Rising to this challenge, the Chemical Development Group of Novartis Pharma AG in Basel has recently succeeded in synthesising discodermolide on a sufficiently large scale for Phase I clinical trials. Thanks to the power of modern organic synthesis, the problem of discodermolide supply is certainly not insurmountable!

Abbreviations

Ac: acetyl; Ar: unspecified aryl group; 9-BBNOMe: 9-borabicyclo[3.3.1]nonyl methoxide; Bn: benzyl; Bz: benzoyl; DDQ: 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; DIBAL: diisobutylaluminium hydride; dppf: 1,1′-bis(diphenylphophino)ferrocene; *dr*: diastereomeric ratio; HMPA: hexamethylphosphoramide; HWE: Horner−Wadsworth−Emmons; Ipc: isopinocampheyl; KHMDS: potassium bis(trimethylsilyl)amide; L: unspecified ligand; LiHMDS: lithium bis(trimethylsilyl)amide; LDA: lithium diisopropylamide; MOM: methoxymethyl; Ms: methylsulfonyl; NaHMDS: sodium bis(trimethylsilyl)amide; OTf: trifluoromethanesulfonate; PMB: *p*-methoxybenzyl; PMP: *p*-methoxyphenyl; PPTS: pyridinium *p*-toluenesulfonate; Piv: pivaloyl; pyr: pyridine; TBS: *tert*-butyldimethylsilyl; TES: triethylsilyl; TFA: trifluoroacetic acid; TIPS: triisopropylsilyl; TMEDA: *N*,*N*,*N*′,*N*′-tetramethylethylenediamine; TMS: trimethylsilyl; TMP: 2,2,6,6-tetramethylpiperidine; TPAP: tetrapropylammonium perruthenate; TsOH: *p*-toluenesulfonic acid.

Acknowledgments

We thank the EPSRC, EC (Network HPRN-CT-2000-00018), Emmanuel College, Cambridge (G. J. F.), and Novartis Pharma AG for support.

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