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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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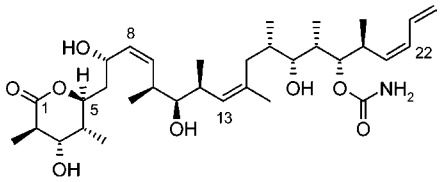
Abstract:

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.

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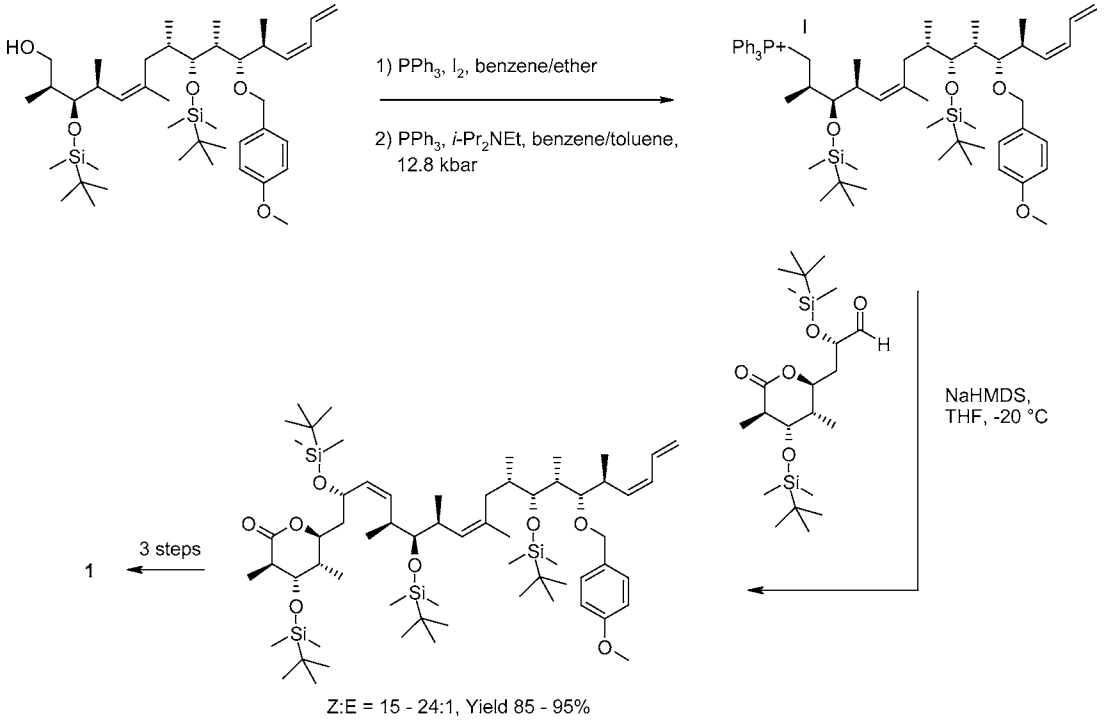
Scheme 1. **High-pressure phosphonium salt formation**



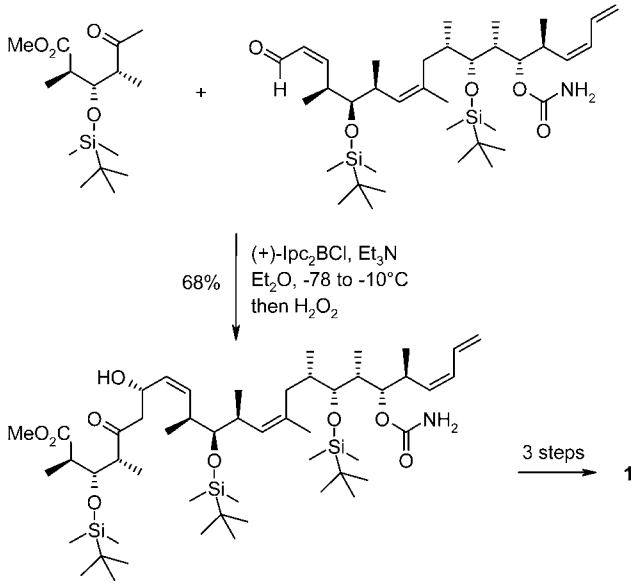
preparations of various discodermolide fragments[9] have appeared in the literature. A useful review of the available synthetic approaches has recently been published.[10]

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**

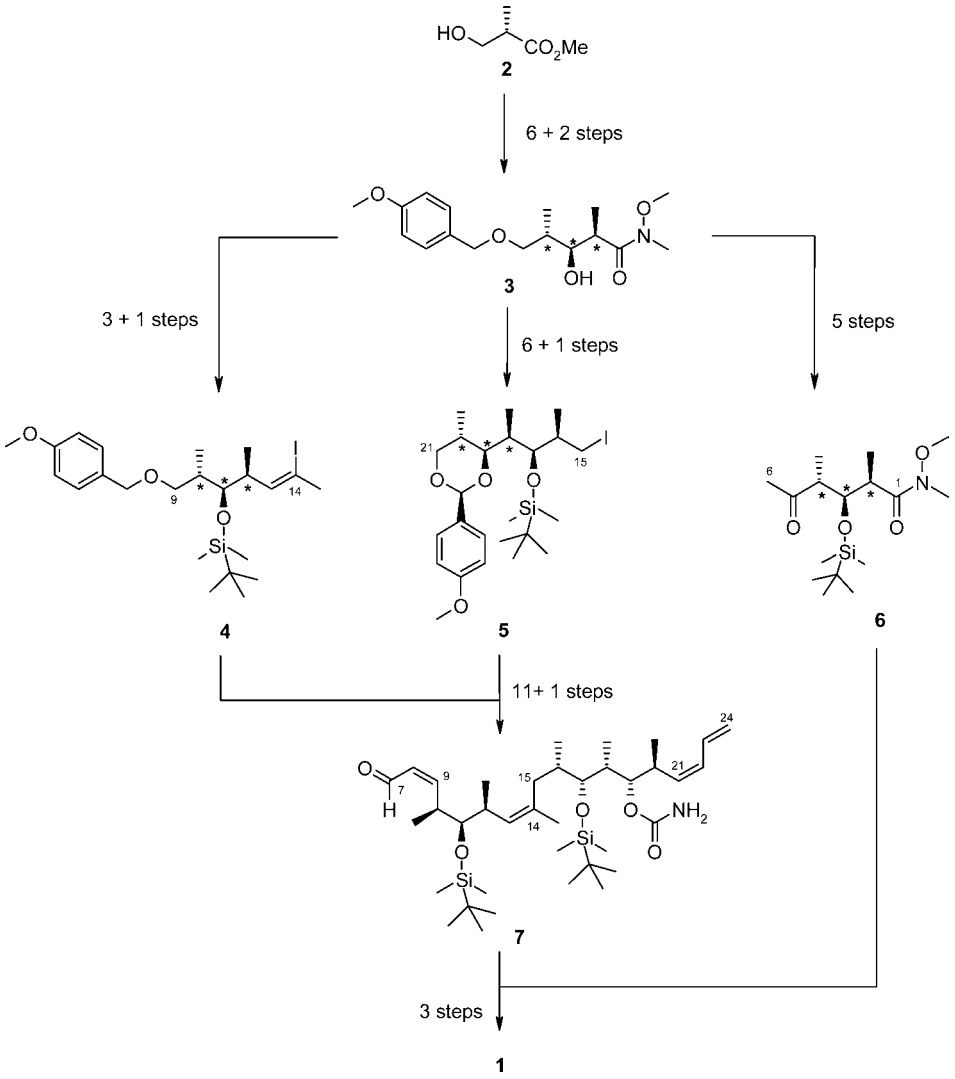


2] for this approach was readily available. It was clear from the beginning of this venture that there was a need for changing some chemistry in the late steps; for example, the high-pressure reaction (12.8 kbar) used for introducing the C_{8-9} *cis*-double bond (Scheme 1) was not practicable on large 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**.

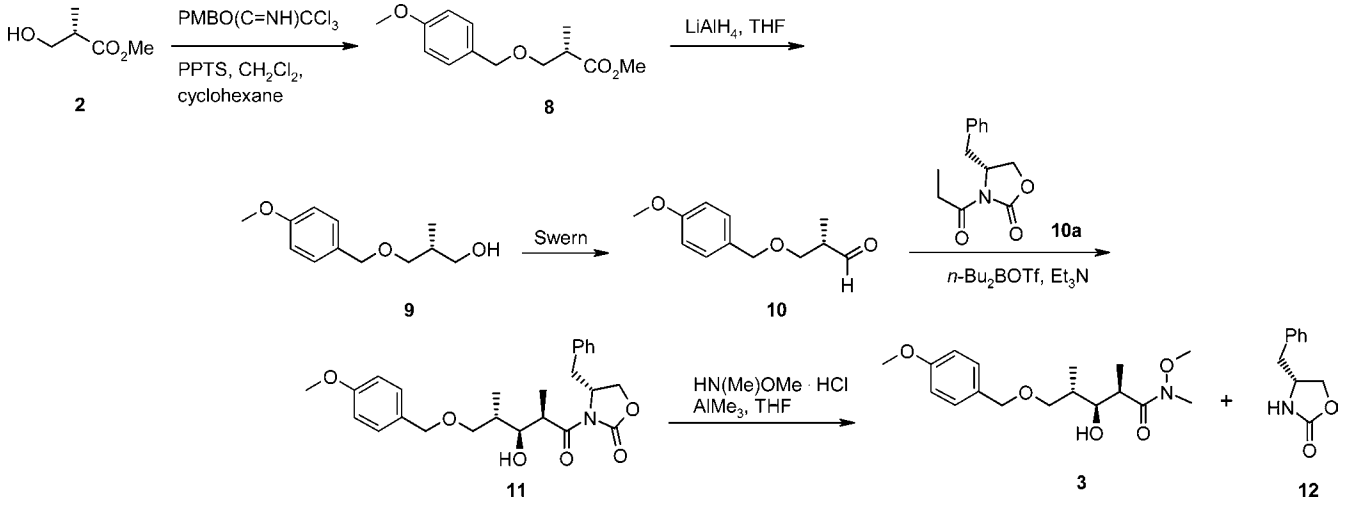
Results and Discussion

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**



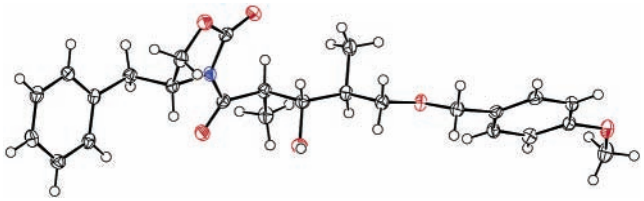


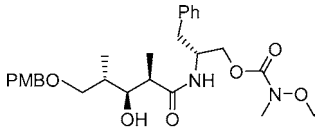
Figure 1. **Single-crystal X-ray structure of 11.**

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.



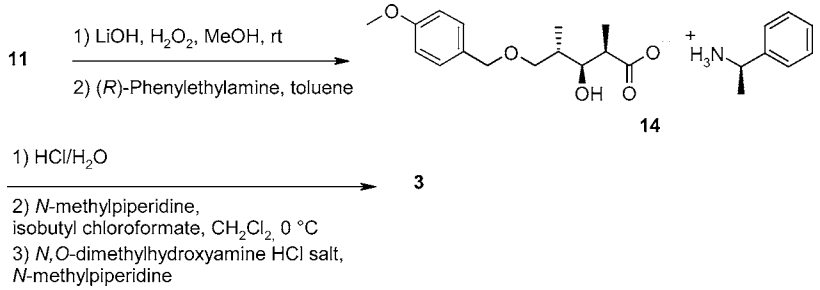
13

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

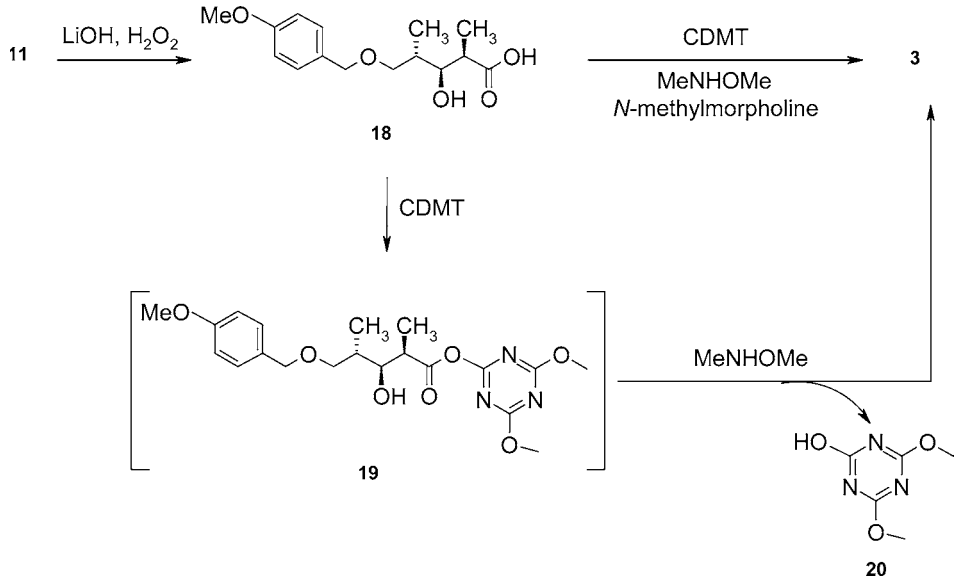
Amide Formation Employing Chloroformate. Formation of an amide bond from a carboxylic acid via a mixed anhydride was investigated as the first alternative (Scheme 5).

(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**

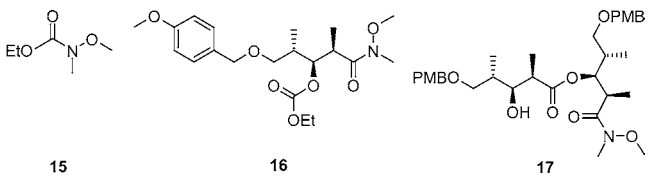


Scheme 6. **Alternative route to 3 using CDMT**

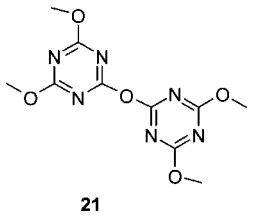


Without further purification, we proceeded to cleave the oxazolidinone by treating it sequentially with hydrogen peroxide and lithium hydroxide in a mixture of water and methanol. After workup, the resulting acid was isolated as a crystalline salt of (*R*)-2-phenylethylamine (**14)** in 84% yield from **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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