

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

Stuart J. Mickel,* Daniel Niederer, Robert Daeffler, Adnan Osmani, Ernst Kuesters, Emil Schmid, Karl Schaer, and Remo Gamboni

Chemical and Analytical Development, Novartis Pharma AG, CH 4002 Basel, Switzerland

Weichun Chen, Eric Loeser, Frederick R. Kinder, Jr., Kurt Konigsberger, Kapa Prasad, Timothy M. Ramsey, Oljan Repič, and Run-Ming Wang

Novartis Institutes for Biomedical Research, One Health Plaza, East Hanover, New Jersey 07936, U.S.A.

Gordon Florence, Isabelle Lyothier, and Ian Paterson

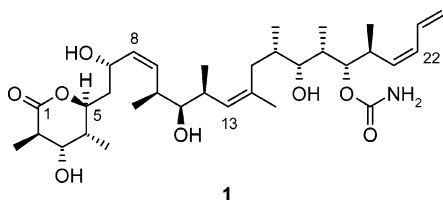
University of Cambridge, Chemical Laboratories Lensfield Road, Cambridge CB2 1EW, UK

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.



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-workers¹ for the controlled introduction of the C₇ 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, NEt₃, 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

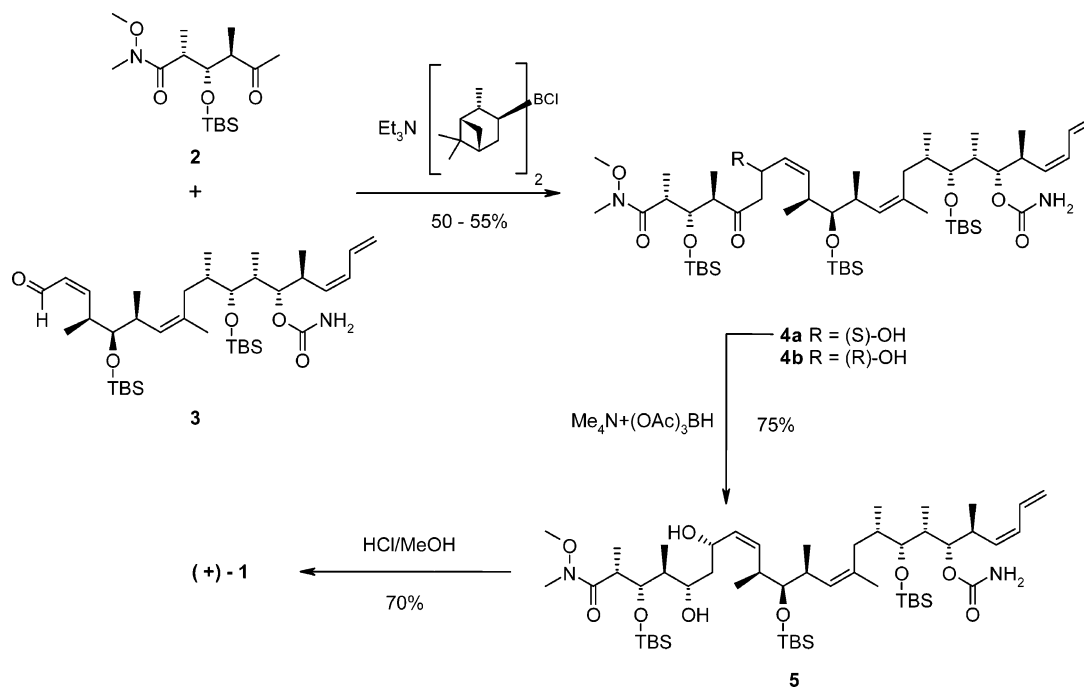
Aldol Coupling. Reaction of 6.6 equiv of the corresponding boron enolate of **2**, prepared by treatment of **2** with (+)-B-chlorodiisopinocampheylborane (DIP-Cl) and triethylamine in diethyl ether at 0 °C, followed by aldol addition, at –78 °C, with *cis*- α,β -unsaturated aldehyde **3** led to alcohol **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

* Author for correspondence. E-mail: stuart_john.mickel@pharma.novartis.com.

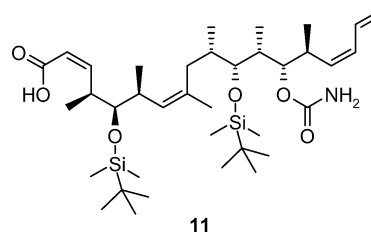
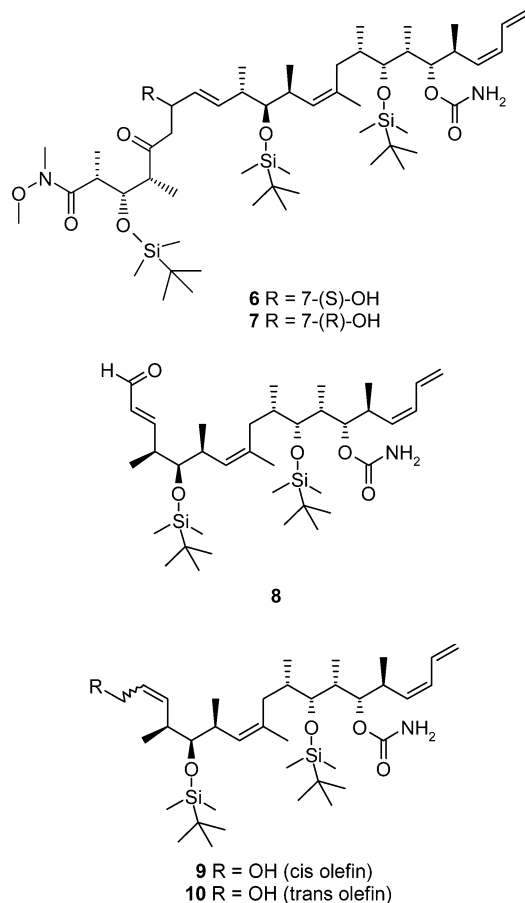
(1) (a) Paterson, I.; Florence, G. J.; Gerlach, K.; Scott, J. P. *Angew. Chem., Int. Ed.* 2000, 39, 377. (b) Cowden, C. J.; Paterson, I. *Org. React.* 1997, 51, 1.

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

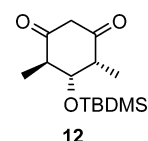


of the aldehyde **8** (see part 4 for NMR data). The mechanism of this double bond isomerization is not clear. It occurs at -78°C even before the aldol reaction and may be the consequence of an addition/elimination process of chloride or triethylamine induced by boron coordination to the aldehyde oxygen 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-dimethylsilyloxy)-4,6-dimethylcyclohexane-1,3-dione (**12**).

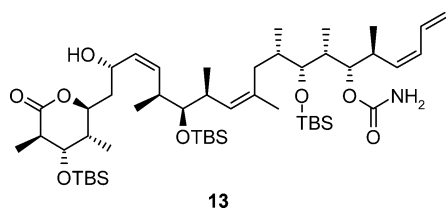


On large scale, we were still unable to reproduce the result of the small-scale experiment although the reduction was

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 reduction² 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.



Final Step and Isolation. With the diol **5** in hand, the stage was set for the cleavage of silyl groups⁴ 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

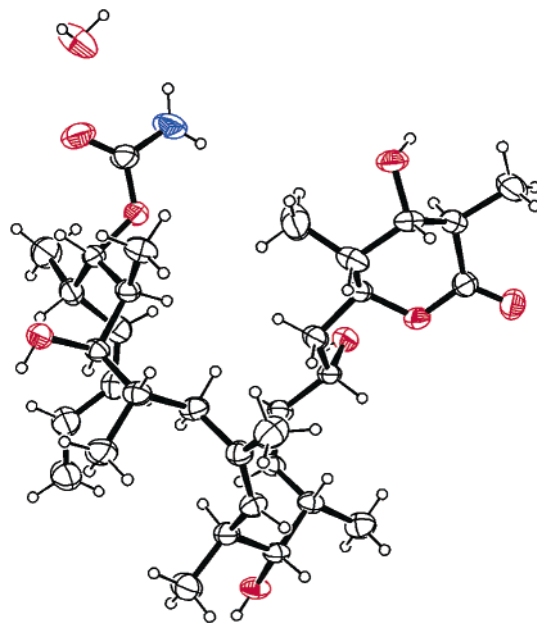
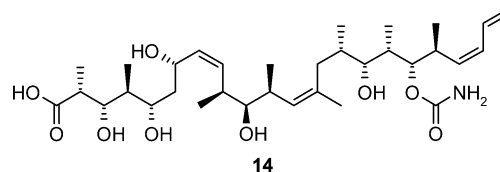


Figure 1. Single-crystal X-ray structure of (+)-discodermolide.

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.



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 literature³ (Figure 1).

Recycling of Byproducts from the Desilylation Step.

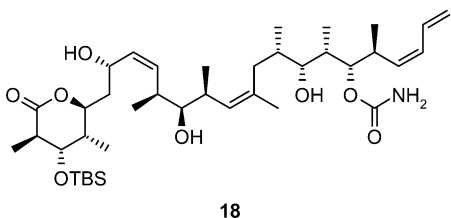
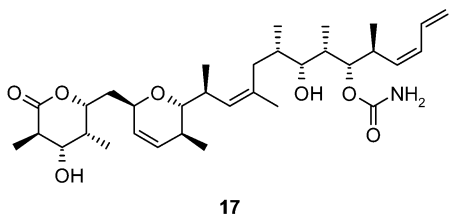
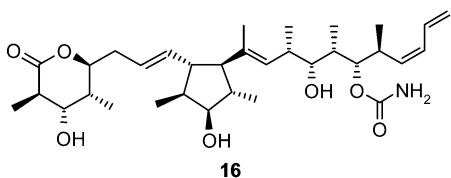
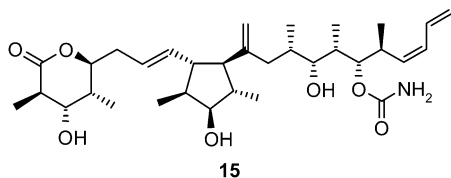
In the desilylation step there are several intermediates formed which eventually convert to the final product. After the isolation of **1** in pure form from the reverse-phase column, the combined remaining fractions indicated the following % area composition by HPLC: 5.56% discodermolide, 5.68% 3-*tert*-butyldimethylsilyl 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.

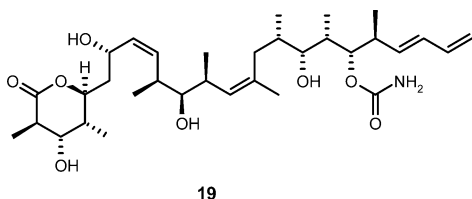
(3) Smith, A. B.; Beauchamp, T. J.; LaMarche, M. J.; Kaufman, M. D.; Qiu, Y. P.; Arimoto, H.; Jones, D. R.; Kobayashi, K. *J. Am. Chem. Soc.* **2000**, *122*, 8654 and references therein.

(4) Gunasekera, S. P.; Mickel, S. J.; Daeflfer, 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/H₂O.



We also noticed the presence of a trace of *trans*-diene **19** under these desilylation conditions. As the Nozaki–Hiyama–Peterson sequence⁶ of generating the *cis*-diene is clean, the formation of *trans*-diene was attributed to subsequent acid-catalyzed isomerization.



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/SO₃ complex in DMSO with an excess of Et₃N 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 (7*S*)-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.

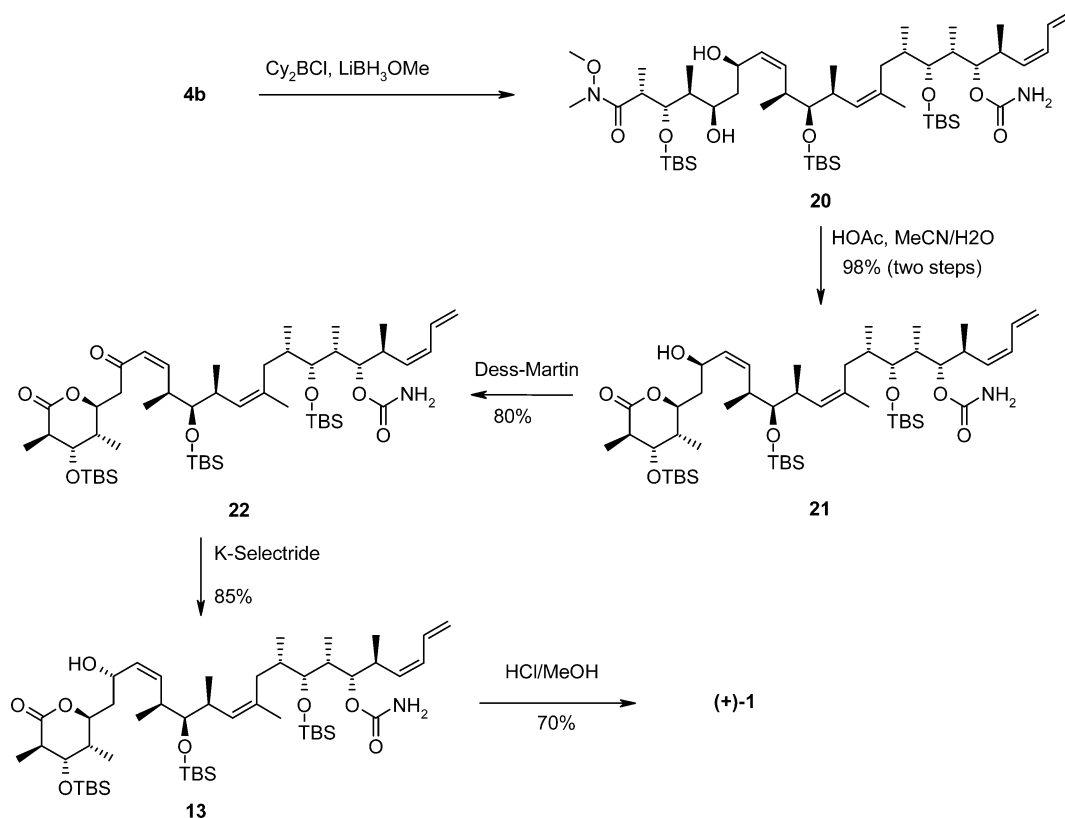
(6) Paterson, I.; Schlapbach, A. *Synlett* **1995**, 498.

(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 (6Z,11E)-(1S,2R,3R,4S,8S,9S,10S,13S,-16R,17S,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-oxononadeca-6,11-dienyl ester (6**):** ¹H NMR (CDCl₃) 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 (**2Z,7Z,-15Z**)-(4S,5S,6S,10S,11R,12R,13S,14S)-5,11-bis-(*tert*-butyldimethylsilanyloxy)-13-carbamoyloxy-4,6,8,10,12,14-hexamethyloctadeca-2,7,15,17-tetraenoic acid (**11**). ¹H NMR (CDCl₃) δ 12.5–12.0 (br s, exch D₂O, 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. ¹H NMR (CDCl₃) 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**. ^1H 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 (6Z,11Z)-(1S,2R,3R,4S,8S,9S,10S,-13S,15S,16S,17S,18R)-3,9,17-Tris-(tert-butyl-dimethyl-silyloxy)-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 triacetoxymethylborohydride (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. ^1H 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 \times 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. ^1H 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. $[\alpha]_{\text{D}} = +20.1$ ($c = 1$ in MeOH).

Also isolated from the column was the *trans*-diene **19**.

^1H 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. (2R,3S,4S,5S,7R,8Z,10S,11S,12S,13Z,16S,17R,18S,19S,20S,21Z)-3,11,17-Tris-(tert-butyltrimethylsilyloxy)-5,7-dihydroxy-19-carbamoyloxy-N,2,4,10,12,14,16,18,20-nonamethyl-N-methoxy-tetracosal, 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 . $\text{cHex}_2\text{BCl}/\text{Et}_3\text{N}$ 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); $[\alpha]_{\text{D}} +30.4$ ($c = 0.20$, CHCl_3); IR (thin film) 3450, 2958, 2928, 1663, 1252, 1093, 1037, 834, 774 cm^{-1} ; ^1H NMR (CDCl_3) 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 $\text{C}_{53}\text{H}_{104}\text{N}_2\text{O}_9\text{Si}_3\text{Na}$ [$\text{M} + \text{Na}$] $^+$ 1019.6947, found 1019.6993.

3,11,17-Tris-(tert-butyltrimethylsilyl)-7-epi-discoder-molide (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 chromatography on silica gel (hexane/ethyl acetate, 6:1) afforded the title compound **20** (920 mg, 98%).

R_f 0.45 (35% EtOAc/Hexane); $[\alpha]_{\text{D}} +20.0$ ($c = 0.33$, CHCl_3); IR (thin film) 3460, 2958, 2930, 2857, 1726, 1600, 1462, 1385 cm^{-1} ; ^1H 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, [$\text{M} + \text{Na}$] $^+$); HRMS (ES^+) calcd for $\text{C}_{51}\text{H}_{97}\text{O}_8\text{-NSi}_3\text{Na}$ [$\text{M} + \text{Na}$] $^+$ 958.6420, found 958.6449.

3,11,17-Tris-(tert-butyltrimethylsilyl)-7-oxo-discoder-molide (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 ($3 \times$ 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, $[\text{M} + \text{Na}]^+$); HRMS (ES^+) calcd for $\text{C}_{51}\text{H}_{95}\text{O}_8\text{NSi}_3\text{Na}$ $[\text{M} + \text{Na}]^+$ 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 **13** (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, $[\text{M} + \text{Na}]^+$); HRMS (ES^+) Calcd for $\text{C}_{51}\text{H}_{98}\text{O}_8\text{NSi}_3$ $[\text{M} + \text{H}]^+$ 936.6595, Found: 936.6592.

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