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Development of a Third-Generation Total Synthesis of (+)-Discodermolide: An Expedient Still−Gennari-Type Fragment Coupling Utilizing an Advanced β-Ketophosphonate

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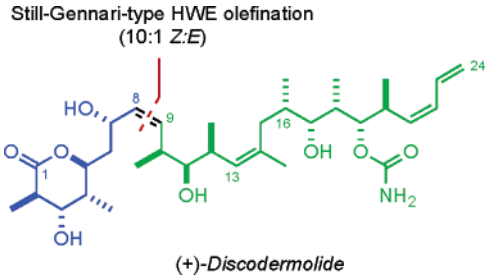
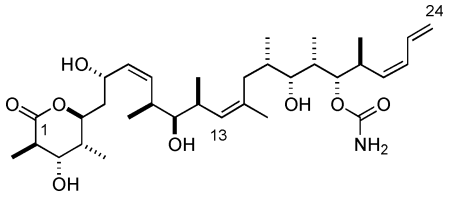


(+)-*Discodermolide*

A novel total synthesis of the complex polyketide discodermolide, a promising anticancer agent of marine sponge origin, has been completed in 11.1% overall yield over 21 linear steps. This third-generation approach features an unprecedented Still−Gennari-type HWE olefination reaction between advanced C1−C8 β-ketophosphonate **61** and C9−C24 aldehyde **7**, introducing the (8*Z*)-alkene with 10:1 selectivity. The stereotetrad found in the C1−C8 subunit **61** was established via a highly diastereoselective boron-mediated aldol reaction/in situ reduction between ketone (*S*)-**8** and 3-benzyloxypropanal. The (7*S*)-configuration was installed by the reduction of enone **73** with K-Selectride.

Introduction

In 1990, Gunasekera and co-workers at the Harbor Branch Oceanographic Institution in Florida reported the isolation of discodermolide (**1**, Figure 1), a polyketide metabolite obtained in low yields from the Caribbean deep-water sponge *Discodermia dissoluta* (0.002% w/w from the frozen sponge).[1] In preliminary biological studies, discodermolide was found to be an immunosuppressive agent, both in vitro and in vivo.[2] Further studies revealed discodermolide to be a potent microtubule-stabilizing agent that, like Taxol (paclitaxel), arrests cells at the G2/M boundary of the cell cycle.[3,4] This mechanism of action is shared by several other antimitotic agents, including the epothilones,[5] eleutherobin,[6] laulimalide,[7] peloruside A,[8] and most recently, dictyostatin.[9]



1: *(+)-Discodermolide*

FIGURE 1. Structure of discodermolide

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The IC_{50} values reported for discodermolide in breast, prostate, colon, lung, and ovarian cancer cell lines are generally in the low nanomolar range.[10] Comparative studies showed that discodermolide was 1000-fold more active than Taxol in promoting the same microtubule polymerization/bundling.[3] Of particular interest is the fact that multidrug-resistant human colon and ovarian cancer cells retained significant sensitivity to discodermolide.[10b] Cancers treated with Taxol or other hydrophobic antitumor drugs can become resistant to the drugs by acquiring the multidrug resistance (MDR) phenotype.[11] The expression of P-glycoprotein (P-gp), a transmembrane transporter protein that significantly reduces the intracellular concentration of these drugs, is associated with this phenotype. More recently, further studies regarding the precise mechanism by which discodermolide binds to β-tubulin and induces its polymerization have been performed.[12] These findings highlighted that binding of discodermolide and Taxol to β-tubulin are mutually exclusive, although it could not be ascertained whether they share the same or an overlapping binding site. This remarkable biological profile has been recognized by Novartis Pharmaceutical Corporation, leading to discodermolide entering clinical trials as a new-generation anticancer agent.

The supply problem for discodermolide is chronic and can be solved at present only by total synthesis. Consequently, because of the remarkable biological activity, there has been considerable synthetic effort directed toward providing a sustainable supply of discodermolide,[13] culminating in several total syntheses[14−18] and numerous fragment syntheses.[19] Notable contributions from academic groups achieving completed syntheses have come from Schreiber and co-workers,[14] followed by the groups of Smith,[15] Myles,[16] Marshall,[17] and Paterson.[18] The key bond disconnections and coupling reactions used in each of these syntheses are shown in Figure 2. All of the strategies coincide in the disassembly of the target molecule into three fragments of similar size and stereochemical complexity. Not surprisingly, the two internal (*Z*)-alkenes have been pivotal in the choice of disconnection strategies, either in Wittig-type olefination (Smith), Pd-catalyzed sp^2-sp^3 couplings (Smith and Marshall), enolate alkylations with allylic halides (Schreiber and Myles), Nozaki-−ishi couplings (Schreiber and Myles), or acetylide addition to aldehydes (Marshall). In contrast, the fragment coupling strategies developed in our group are entirely different, with stereocontrolled aldol reactions performed at C16−C17 and C6−C7 (first-generation route) or C5−C6 (second-generation route).[20] Within the pharmaceutical industry, over 60 g of discodermolide has recently been synthesized by Novartis chemists for Phase I clinical trials, following a hybrid Smith−Paterson route, and making use of our late-stage C6−C7 aldol coupling step.[21] Herein, we report full details of our third-generation total synthesis based on a novel C8−C9 fragment coupling using the Still−Gennari modification of the Horner−Wadsworth−Emmons olefination reaction.[18e] This improved synthesis has the potential to be scaled up to provide significant quantities of discodermolide and to provide novel structural analogues for SAR studies.

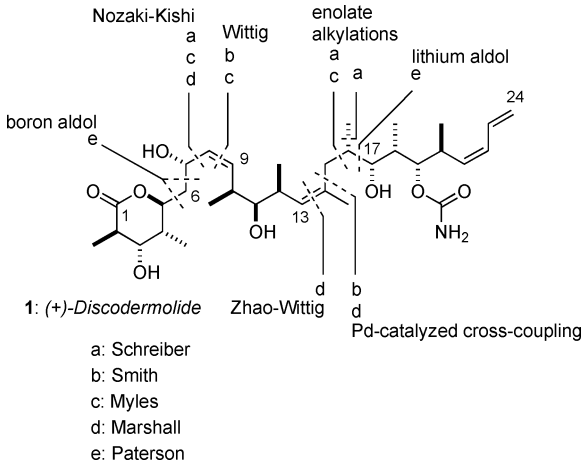

FIGURE 2. Previous coupling strategies employed for the total synthesis of discodermolide.

Results and Discussion

Synthesis Plan. In 2000, we reported an initial synthesis of discodermolide, based on the application of complex aldol reactions, that proceeded in 10.3% yield over 23 steps in the longest linear sequence with 42 steps in total.[18a−c] In 2003, we reported a second-generation

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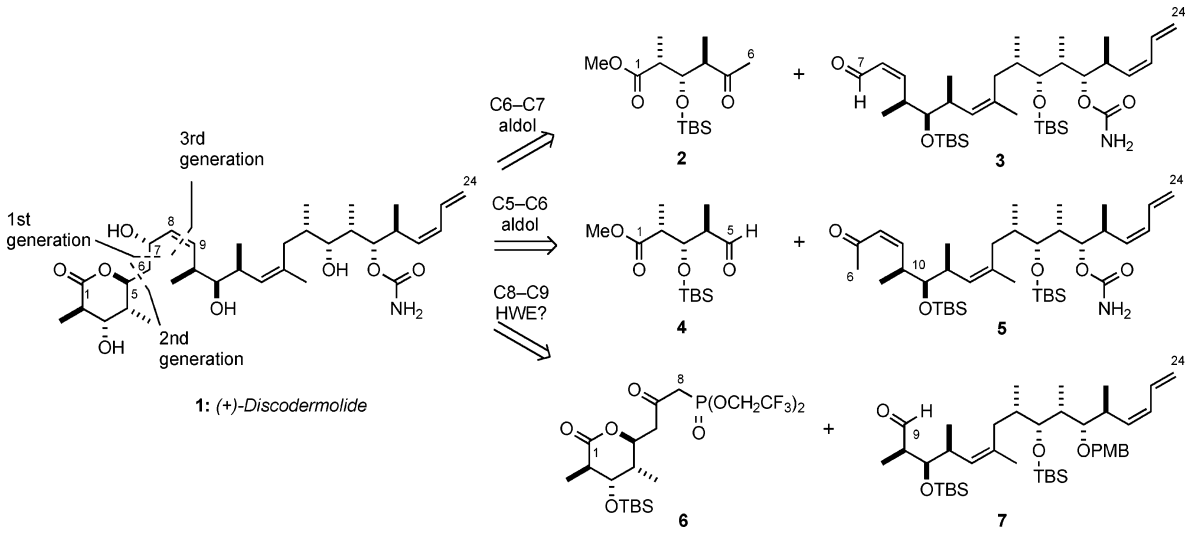
SCHEME 1. Summary of Fragment Coupling Strategies Investigated for Discodermolide



synthesis, relying solely upon substrate-based stereocontrol, which proceeded in 7.8% yield over 24 linear steps, with 35 steps in total.[18d,f] These two total syntheses were based on pivotal boron-mediated aldol coupling reactions performed, at a late stage, either at C6−C7 or at C5−C6 (Scheme 1).[20] In the former case using (+)-Ipc_2BCl/Et_3N,[18a−c] the reagent-controlled fragment union of ketone **2** and (*Z*)-enal **3** sets up the required (7*S*)-configuration, while in the second-generation route using *c*-Hex_2BCl/Et_3N,[18d,f] a reversed C5−C6 aldol coupling between aldehyde **4** and ketone **5**, exploiting 1,6-asymmetric induction from the remote C10 stereocenter, sets up the required (5*S*)-configuration under substrate control. In light of perceived technical difficulties in performing such complex aldol couplings on an industrial scale at a late stage with such valuable highly functionalized intermediates,[21e] where the quality of organoboron reagents from commercial suppliers is variable and arduous chromatographic isolation of the product is usually required, simplification of this key coupling step to complete the carbon skeleton was sought to further streamline the synthesis. To this end, we proposed a more convenient endgame, involving the use of an unprecedented Still−Gennari-type HWE olefination[22] at C8−C9 to couple the advanced β-ketophosphonate **6** with the aldehyde **7**, giving direct access to the entire carbon skeleton of discodermolide (Scheme 1).

Initial Attempts at Preparing the Advanced C1−C8 β-Ketophosphonate Subunit 6. The stereotetrad present in the C1−C8 β-ketophosphonate **6** was installed efficiently in one step, utilizing the highly diastereoselective *anti*-aldol reaction of ethyl ketone[23] **8** and 2-*tert*-butylsilyloxypropanal **9**, mediated by *c*-Hex_2BCl/Et_3N, followed by in situ reduction of the intermediate boron aldolate with $LiBH_4$ (Scheme 2).[24] This afforded 1,3-*syn* diol **10** in 84% yield after oxidative workup, where ^1H NMR analysis of the crude product indicated >97:3 dr, as expected from our earlier studies. Removal of the PMB group in diol **10** was performed by hydrogenolysis in EtOH using Pearlman's catalyst. The choice of solvent in this step was crucial to avoid any competing cleavage of the primary TBS ether. Oxidation of the resulting triol **11** with catalytic TEMPO and $PhI(OAc)_2$ afforded the δ-lactone **12** cleanly.[25] The C3-hydroxyl group was then protected as its TBS ether and the primary silyl group removed selectively by treatment with catalytic amounts of camphorsulfonic acid (CSA) in DCM and MeOH to afford alcohol **14**. Oxidation of **14**, using Dess−Martin periodinane,[26] provided aldehyde **15** in near-quantitative yield.[27]

To install the required phosphonate moiety, aldehyde **15** was first transformed into the corresponding acid

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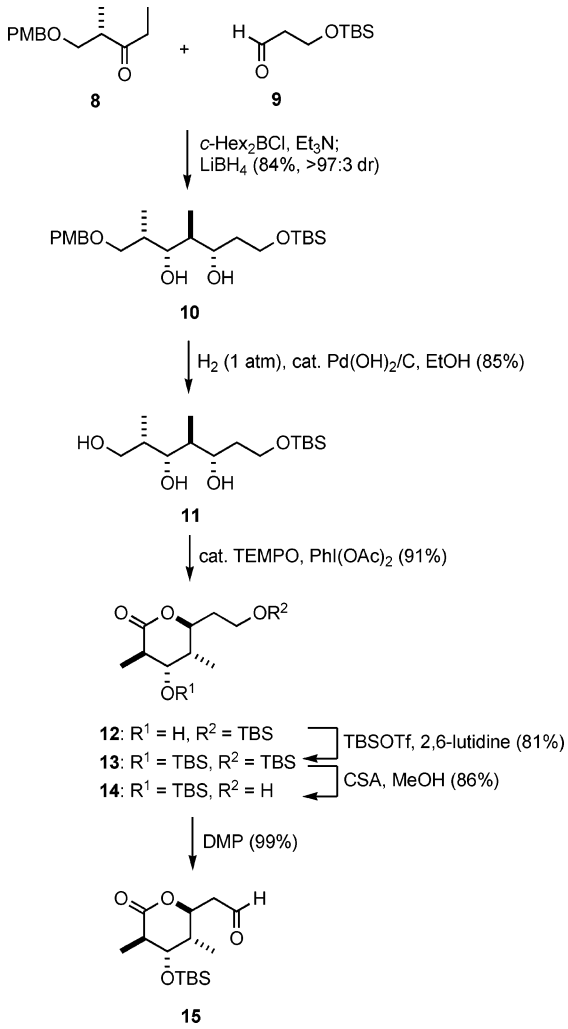
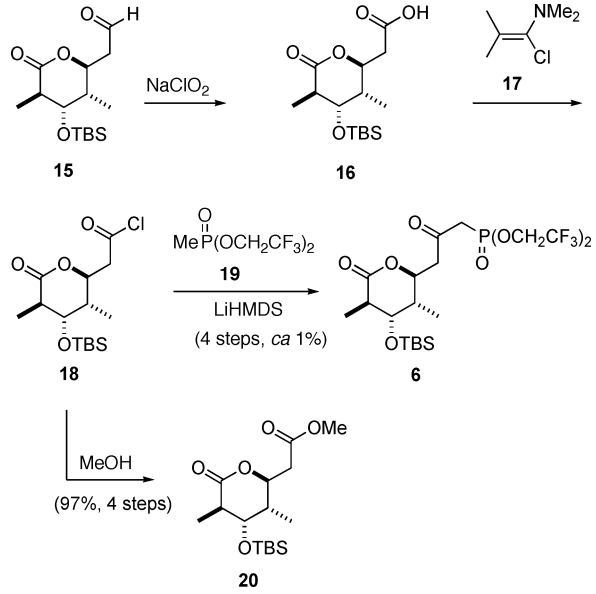
(27) It should be noted that aldehyde **15** could not be purified by flash chromatography on silica gel, as it undergoes partial decomposition by β-elimination and ring-opening of the δ-lactone ring.

SCHEME 2. Synthesis of C1−C7 Aldehyde 15



chloride (Scheme 3).[28] Oxidation of **15** with $NaClO_2$ provided carboxylic acid **16**,[29] which was treated immediately with the Ghosez chloroenamine reagent **17**,[30]

SCHEME 3. Attempted Synthesis of *β*-Ketophosphonate 6

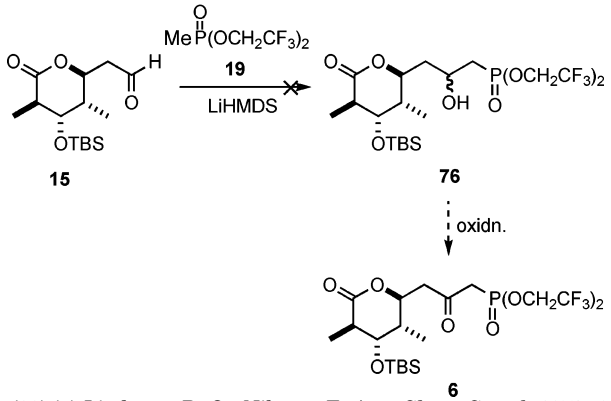


to form acid chloride **18**. The latter was added to a solution of the lithiated methyl phosphonate **19**.[31] Unfortunately, only trace quantities of the desired phosphonate **6** could be isolated, after extensive chromatographic purification, and characterized. To ascertain that acid chloride **18** was indeed formed, it was quenched with an excess of methanol, and the corresponding methyl ester **20** was isolated in 97% yield from the alcohol **14**, confirming that **18** was generated in essentially quantitative yield. However, all efforts to improve the synthesis of phosphonate **6** failed. This setback was attributed to the substrate undergoing facile decomposition by *β*-elimination and ring-opening of the *δ*-lactone ring. We therefore proposed a new strategy, making use of linear *β*-ketophosphonate **21**, which should be accessible from acid chloride **22** (Scheme 4), with the objective of investigating its HWE olefination reaction with aldehydes to give enone **23** under Still−Gennari-type conditions.

Synthesis of Linear *β*-Ketophosphonate 21. The synthesis of the revised phosphonate **21** started out with the bis-TBS protection of the 1,3-*syn*-diol **10** (Scheme 5). Removal of the PMB protecting group was then best achieved here by treatment of **24** with DDQ, to afford alcohol **25** in 80% yield. In contrast to the situation encountered with **10** (Scheme 3), hydrogenolysis of the PMB group in **24** failed to provide **25** in satisfactory yield when using Pearlman's catalyst with a variety of solvents, due to unavoidable competing cleavage of the primary TBS ether. The primary hydroxyl in **25** was next oxidized to the aldehyde **26**, using TEMPO and PhI(OAc)$_2$, in 83% yield.[32] Further oxidation with $NaClO_2$ provided the corresponding carboxylic acid **27**,[29] which was esterified with an ethereal solution of $TMSCHN_2$, affording methyl ester **28** in 84% yield.

With the desired stereochemistry and oxidation states in place for the C1−C7 region, the next objective was to install the *β*-ketophosphonate moiety in order to reach

(28) The initial plan was to react aldehyde **15** with lithiated methyl phosphonate **19**, however this failed to produce the desired adduct **76**. 1H NMR analysis of the crude product indicated the presence of a *trans* double bond, which was attributed to partial *β*-elimination and ring-opening of the lactone. Also a substantial amount of unreacted aldehyde **15** was present in the crude product mixture.



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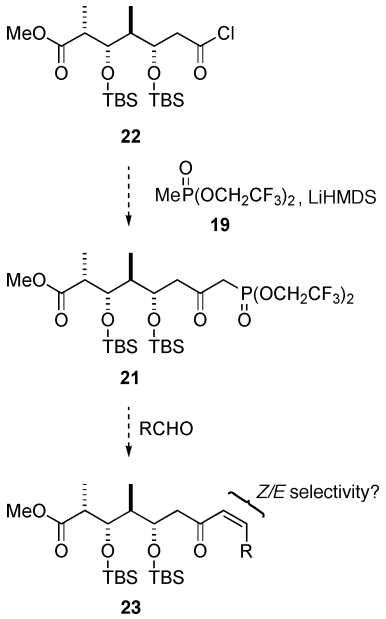
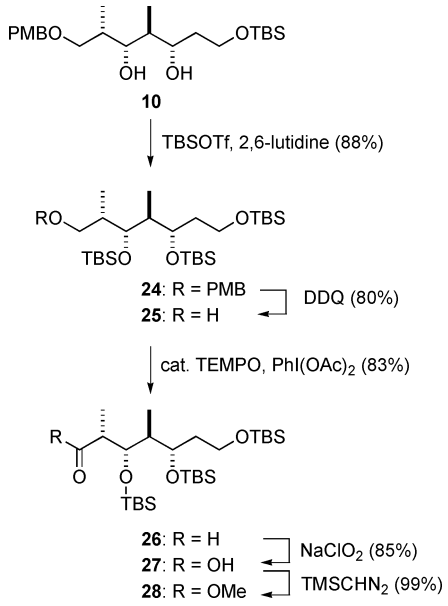
SCHEME 4. Revised Strategy Utilizing Phosphonate 21

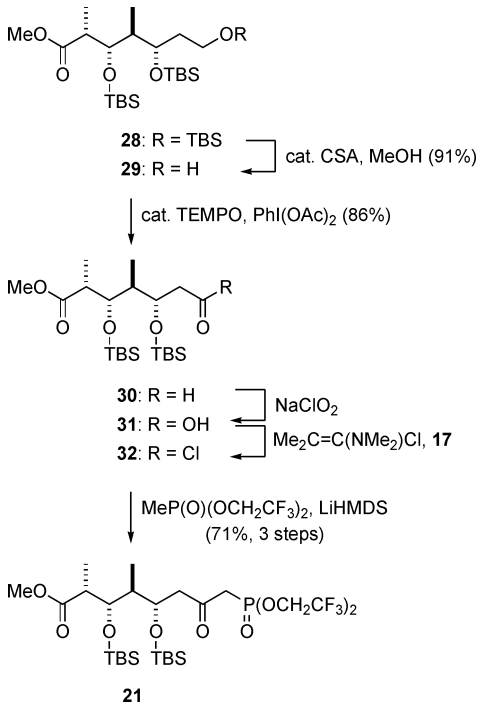


SCHEME 5. Synthesis of C1−C7 Ester 28



the desired C1−C8 segment **21** (Scheme 6). Thus, **28** was treated with a catalytic amount of CSA in DCM and MeOH to cleave selectively the primary TBS ether. The resulting primary alcohol **29** was oxidized to the aldehyde **30** with TEMPO and $PhI(OAc)_2$.[32] Further oxidation with $NaClO_2$ provided crude carboxylic acid **31**.[29] Acid **31** was then treated with the Ghosez reagent **17**,[30] providing the corresponding acid chloride **32**, which was reacted immediately with the lithium anion of methyl phosphonate **19** at −100 °C (external bath temperature).[31] Pleasingly, this reaction proceeded smoothly to provide β-ketophosphonate **21** in 71% yield over three steps. In contrast to the instability experienced with δ-lactone **6**, the phosphonate **21** could be isolated easily by flash chromatography on silica gel and was amenable to long-term storage without any degradation.

SCHEME 6. Synthesis of β-Ketophosphonate 21

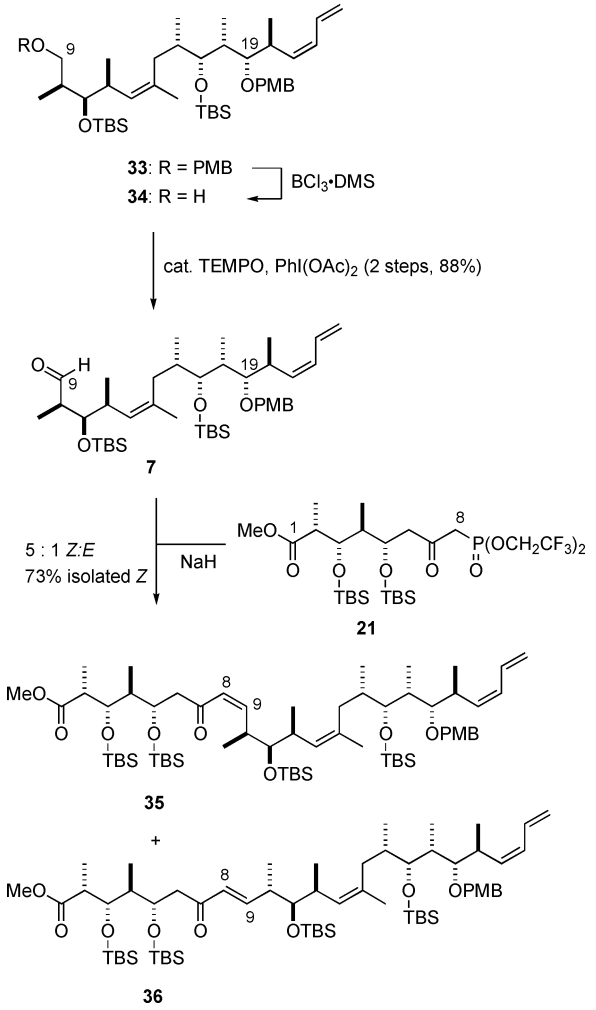


Implementing the C8−C9 Still−Gennari-Type HWE Coupling. With the advanced phosphonate **21** in hand, its HWE olefination reaction with the C9−C24 aldehyde **7** was then investigated. Aldehyde **7** was readily prepared in two steps and 85% yield from the known bis-PMB ether **33**, by selective deprotection of the primary PMB group, with BCl_3·DMS in DCM at 0 °C,[33] and oxidation of the resulting alcohol **34** using either the TEMPO/$PhI(OAc)_2$ system[32] or Swern conditions[34] (Scheme 7). Phosphonate **21** was treated with NaH in THF at 0 °C for 30 min prior to the addition of aldehyde **7**. Analysis of the crude product by ^1H NMR spectroscopy showed a mixture of *Z* and *E* olefins in a 5:1 ratio. Gratifyingly, the desired (*Z*)-isomer **35** could be isolated by flash chromatography in 73% yield.[35] Notably, this coupling proceeds satisfactorily employing NaH under experimentally undemanding conditions, without resorting to expensive crown ether additives, which is of prime importance for minimizing the cost of goods in scaling up. As such, this represents a major improvement over the endgames used in our first and second generation routes, which rely on the availability of good quality boron reagents for performing the late-stage aldol coupling steps.[21e] Moreover, this constitutes one of the first examples of a (*Z*)-selective intermolecular Still−Gennari-type HWE olefination employing such an elaborate β-ketophosphonate.[36]

Further Elaboration of (*Z*)-Enone 35. Following the successful HWE olefination reaction performed between phosphonate **21** and aldehyde **7**, the full C1−C24 carbon skeleton of discodermolide was now in place. The completion of the synthesis now required installation of the carbamate moiety at C19, selective reduction at C7, and

(33) Congreve, M. S.; Davison, E. C.; Fuhry, M. A.; Holmes, A. B.; Payne, A. N.; Robinson, A.; Ward, S. E. *Synlett* **1993**, 663.
(34) (a) Omura, K.; Swern, D. *Tetrahedron Lett.* **1978**, *34*, 1651. (b) Mancuso, A. J.; Huang, S. L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2231.

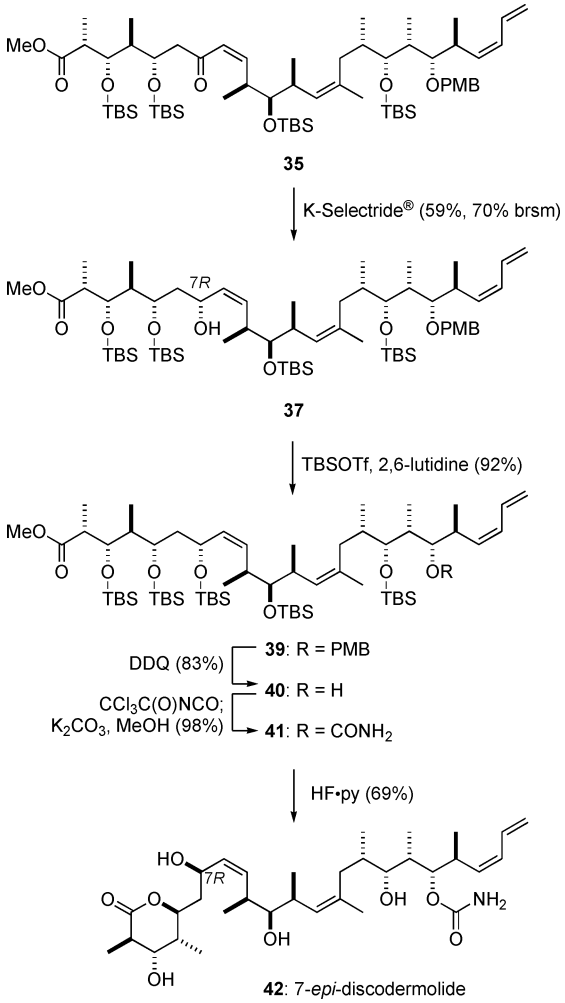
SCHEME 7. Still–Gennari-Type HWE Olefination of Aldehyde 7 and Phosphonate 21



global TBS deprotection with concomitant δ-lactonization. Due to problems encountered with performing the reduction at C7 when the C19 carbamate moiety was already installed, it was envisaged to conduct the reduction step first (Scheme 8). This reduction step proved to be unexpectedly troublesome. A range of reducing agents were screened, including (*R*)- and (*S*)-CBS·BH_3,[37] $NaBH_4$/$CeCl_3$,[38] $LiBH_4$, and L-Selectride. However, these experiments all resulted either in poor diastereoselectivities or no reaction. Hoping to build on the results obtained in our second-generation route,[18d,f] the reduction of **35** was next attempted with K-Selectride. Under suitable reaction conditions (−25 °C, 24 h), a single diastereomeric alcohol **37** was formed selectively and isolated in 59% yield (70% based on recovered starting material). By analogy with the results obtained for a similar substrate (**38**, Scheme 9) employed in our second-generation route,[18d,f] this alcohol **37** was tentatively assigned as having the desired (7*S*)-configuration. However, after DDQ deprotection of the PMB ether at C19 in **39** to give alcohol **40**, and installation of the carbamate moiety,[39] treatment with HF·py provided 7-*epi*-discodermolide (**42**) rather than discodermolide (Scheme 8)!

This complete reversal in the sense of stereoinduction obtained by the reduction of enone **35** at C7 with K-Selectride was totally unexpected. When the C1–C5

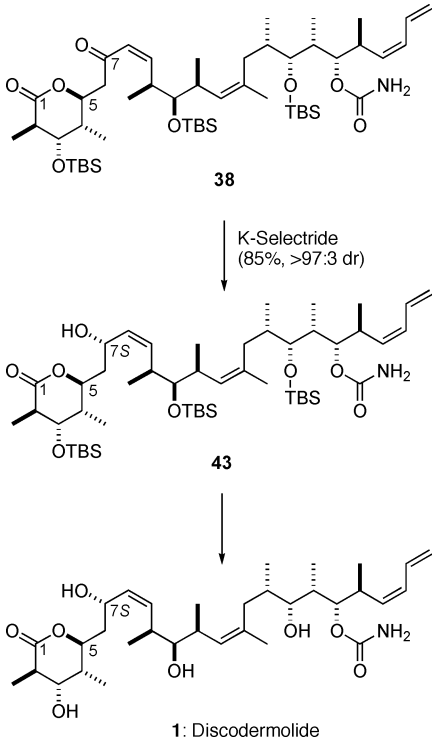
SCHEME 8. Synthesis of 7-*epi*-Discodermolide



δ-lactone was already in place, as in **38** (Scheme 9), reduction of the C7 ketone with K-Selectride proceeded smoothly at −78 °C to provide the desired (7*S*)-alcohol **43** (85%, >97:3 dr).[18d,f] However, with the linear C1–C6 side chain, bearing TBS ethers at C3 and C5, the reduction facial selectivity is overturned with use of K-Selectride under more forcing conditions, affording only the undesired (7*R*)-alcohol **37**. These findings suggest that the conformational preference of the C1–C6 region plays a controlling role in determining the facial selectivity of reduction of the C7 ketone, while the influence of the C9–C24 region is apparently less important.

Achieving Selective C7 Reduction by Adjustment of Protecting Groups. As mentioned previously, a variety of other reducing agents were screened for the reduction of enone **35**. However, there was either no reaction or poor diastereoselectivity was observed. Efforts were therefore directed toward converging with the second-generation endgame, where the aim was to lactonize first and then use K-Selectride to reduce **38** at C7 in the desired stereochemical sense for discodermolide (Scheme 9).[18d,f] As the TBS ether at C5 in our most advanced intermediate **35** could not be cleaved selectively, the protecting group strategy required revision. Two strategies were considered—protecting the C3- and C5-hydroxyl groups either as their TES ethers, as in **44**,

SCHEME 9. Endgame for the Second-Generation Synthesis of Discodermolide

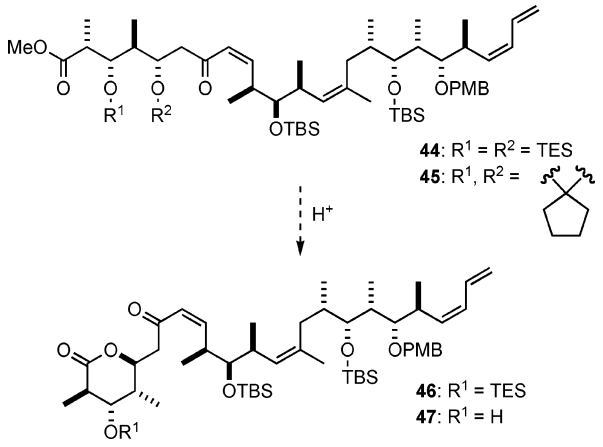


or as a cyclic cyclopentylidene acetal,[40] as in **45** (Scheme 10).

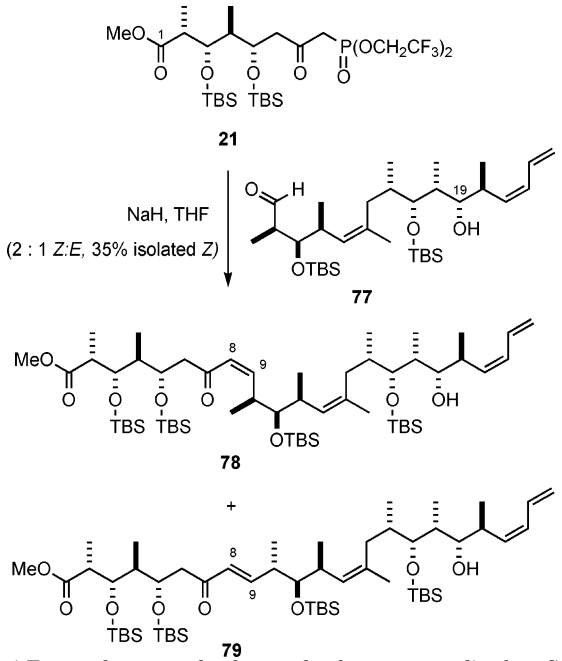
Initial efforts were directed toward the synthesis of the revised phosphonate **48**, bearing TES ethers at C3 and C5 (Scheme 11). The chemistry already developed for the synthesis of phosphonate **21** needed some modification. A benzyl ether at C7 was introduced to allow its cleavage in the presence of the two TES ethers. The *anti*-aldol reaction between ethyl ketone **8** and 3-benzyloxypropanal **49**, mediated by *c*-Hex_2BCl and Et_3N, followed by an in situ reduction with $LiBH_4$ afforded *syn*-diol **50**, in 84% yield and >97:3 dr (Scheme 11).[23,24] Treatment of diol **50** with TESOTf and 2,6-lutidine afforded bis-TES ether **51** in 80% yield. Oxidative cleavage of the PMB group with DDQ provided alcohol **52**, which was oxidized to the corresponding aldehyde **53** under Swern conditions.[34] Treatment with $NaClO_2$ provided the corresponding carboxylic acid **54** in 98% yield.[29] Esterification was achieved by treatment of **54** with $TMSCHN_2$ in excellent yield. The resulting methyl ester **55** was used as a model for studying the possibility of cleaving the TES group at C5 and inducing δ-lactonization under mild acidic conditions. Gratifyingly, treatment of **55** with CSA (1 equiv) in DCM proceeded smoothly to provide δ-lactone **56** in 91% yield. At this point, the prospect of obtaining the ketolactone **46**, after treatment of **44** with CSA, was good, as too was the opportunity to converge with our second-generation synthesis of discodermolide (see Scheme 10).[18d,f]

Attention was now focused on the installation of the phosphonate moiety. Hydrogenolysis of the benzyl ether **55** in THF, using $Pd(OH)_2/C$ as the catalyst, provided alcohol **57**. The choice of solvent was found to be crucial to avoid any competing TES deprotection. Swern oxidation of alcohol **57** afforded the corresponding aldehyde **58** in 94% yield over the two steps.[34] Oxidation of **58** to the corresponding carboxylic acid was achieved with $NaClO_2$ in 69% yield.[28] Acid **59** was then treated with the Ghosez chloroenamine **17**,[30] affording the acid chloride **60**, which was reacted immediately with a solution of $(CF_3CH_2O)_2P(O)CH_2Li$ at −100 °C.[31] Unfortunately, this reaction failed to produce the desired phosphonate **48**, even though no starting acid **59** was recovered after aqueous workup. The presence of olefinic signals in the ^1H NMR spectrum of the crude product was evident, and loss of the TES group at C5, with partial δ-lactonization,

SCHEME 10. Revised Protecting Group Strategies



(35) To shorten the synthesis by one step, the olefination reaction with the aldehyde **77**, having a free hydroxyl group at C19, was attempted. Unexpectedly, this led to a diminished selectivity (*Z*/*E* = 2:1) and a reduced 35% yield.



(36) For another example of a complex fragment coupling by a Still−Gennari-type HWE olefination, see: Paterson, I.; Britton, R.; Delgado, O.; Meyer, A.; Poullennec, K. *Angew. Chem., Int. Ed.* **2004**, *43*, 4629.

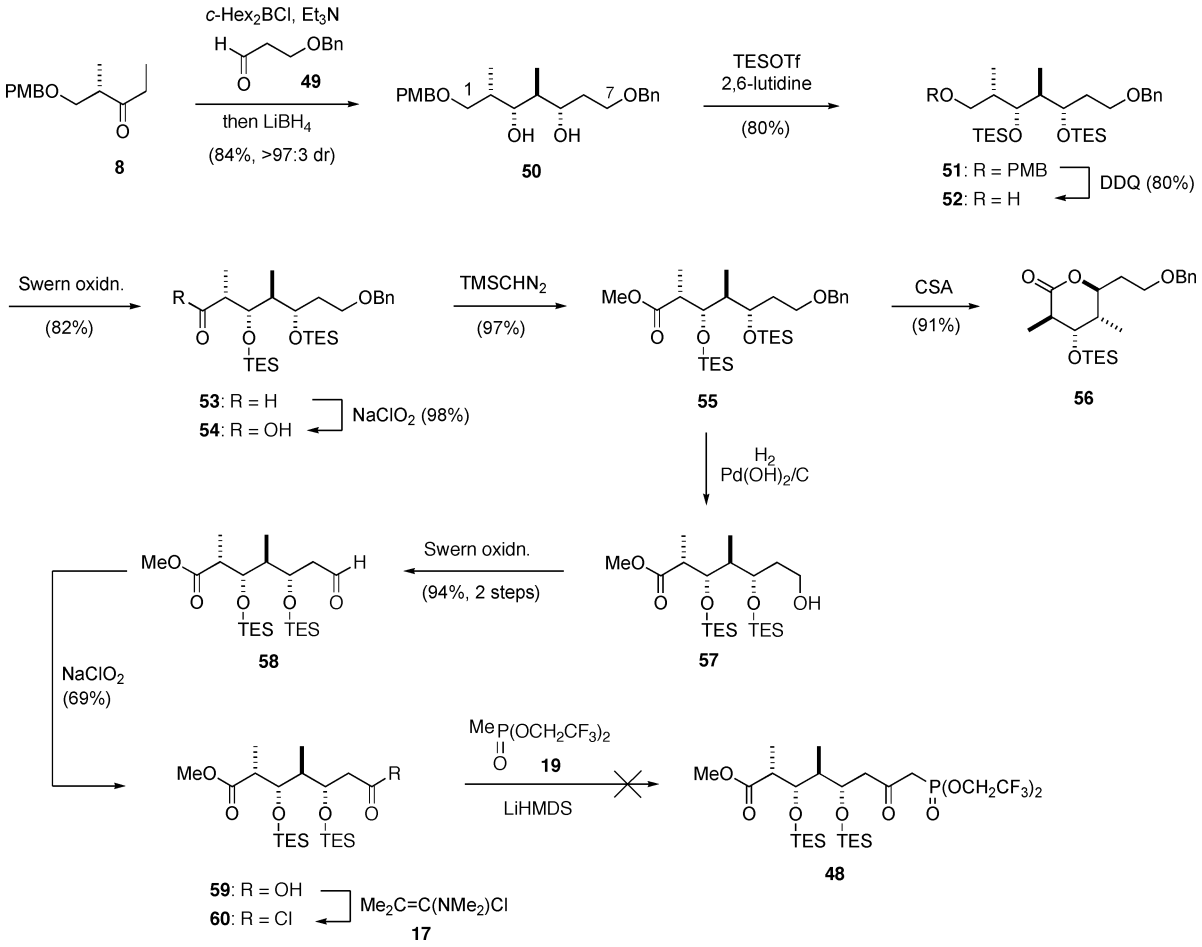
(37) Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 9, 5551.

(38) (a) Luche, J. L.; Gemal, A. L. *J. Am. Chem. Soc.* **1979**, *101*, 5848. (b) Gemal, A. L.; Luche, L. *J. Am. Chem. Soc.* **1981**, *103*, 5454.

(39) Kocovsky, P. *Tetrahedron Lett.* **1986**, *27*, 5521.

(40) Evans, D. A.; Connell, B. T. *J. Am. Chem. Soc.* **2003**, *125*, 10899.

SCHEME 11. Attempted Synthesis of Phosphonate 48



was suspected. As it was unlikely that the cleavage of the TES ether had occurred under the reaction conditions to install the phosphonate moiety (LiHMDS, −100 °C), it was therefore reasoned that this had happened either on the acid **59** or on the acid chloride **60**, leading to partial δ-lactonization and inducing decomposition by β-elimination. At this stage, the TES protecting group strategy was abandoned in favor of the cyclopentylidene acetal alternative.

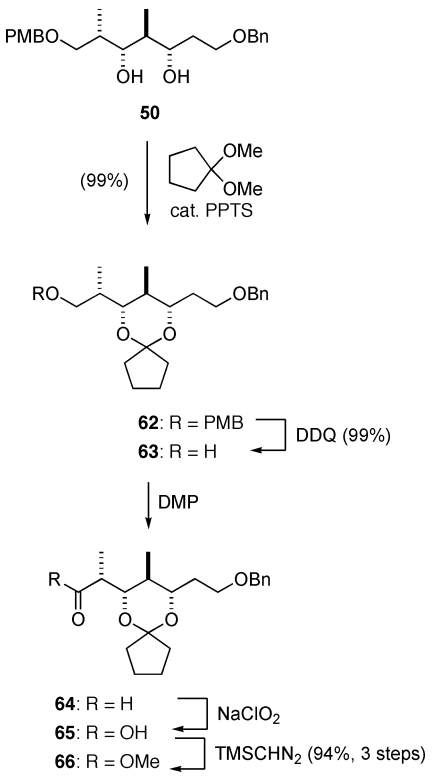
The synthesis of the revised phosphonate **61** was performed in a fashion similar to that of its TBS-protected analogue **21** (Schemes 12 and 13). Diol **50** was converted in near-quantitative yield into cyclopentylidene acetal **62** by treatment with cyclopentanone dimethyl acetal,[41] under mild acid catalysis with PPTS. PMB ether cleavage in **62** with DDQ was followed by Dess−Martin oxidation of the resulting alcohol **63** to provide the aldehyde **64**.[26] Subsequent oxidation to the corresponding acid **65** ($NaClO_2$),[29] and treatment with $TMSCHN_2$, afforded methyl ester **66** in a high-yielding sequence (four steps, 93%).

Ester **66** was further elaborated into the desired phosphonate **61** using chemistry similar to that described previously (Scheme 13). Hydrogenolysis of the benzyl ether was followed by stepwise oxidation to the carboxylic acid **69** (Dess−Martin periodinane, followed by $NaClO_2$).[26,29] The crude acid **69** was treated with the Ghosez reagent **17**[30] to generate acid chloride **70**, which was reacted immediately with $(CF_3CH_2O)P(O)CH_2Li$.[31] Pleasingly, this acylation reaction proceeded smoothly, providing β-ketophosphonate **61** in 70% yield from aldehyde **68**. Starting from ketone (*S*)-**8**, this sequence can be performed conveniently on a multigram scale in 45% overall yield.

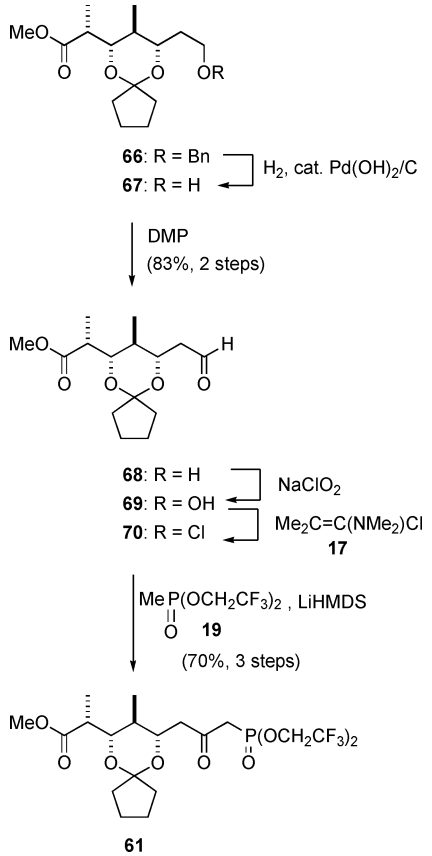
Completion of the Total Synthesis of Discodermolide. With the new phosphonate **61** in hand, the stage was now set to again investigate the Still−Gennari HWE olefination with aldehyde **7**.[22,31] Utilizing the optimized conditions developed previously, phosphonate **61** was treated with NaH in THF at −10 °C for 30 min and then reacted with aldehyde **7** (Scheme 14). A clean olefination reaction occurred that was now more selective than obtained with bis-TBS-protected phosphonate **21** (*Z*/*E* = 10:1, compared to 5:1 for **21**), with the (*Z*)-enone **71** isolated by simple flash chromatography on silica gel in 74% yield. With the carbon backbone of discodermolide now in place, the carbamate moiety at C19 needed to be installed. First, the PMB ether was cleaved oxidatively with DDQ in essentially quantitative yield. Subsequent treatment of the resulting alcohol **72** with trichloroacetyl isocyanate and methanolysis of the intermediate trichloroacetyl adduct (K_2CO_3, MeOH) provided **73** in 98% yield.[39] With compound **73** in hand, the original plan was to treat it with a mild acid to cleave the cyclopentylidene acetal, and then reduce at C7 with K-Selectride (vide supra). However, to minimize the total number of steps,

(41) Clerici, A.; Pastori, N.; Porta, O. *Tetrahedron* **2001**, *57*, 217.

SCHEME 12. Synthesis of Ester 66



SCHEME 13. Synthesis of Phosphonate 61



the selective reduction of **73** was attempted first. Enone **73** was therefore treated with K-Selectride in toluene at −78 °C (Scheme 15). Gratifyingly, the reduction proved to be clean and efficient, going to completion within 3 h at −78 °C, and provided a single diastereomeric alcohol, **74**, in 90% yield. The desired (7*S*)-configuration in **74** was easily established by carrying out the final global deprotection. This proceeded cleanly using HF·py, with concomitant δ-lactonization, providing (+)-discodermolide in 84% yield, which was identical to an authentic sample in all respects. The similar stereochemical outcome for the reduction of the δ-lactone containing enone **38** and the cyclopentylidene acetal-protected enone **73** is attributed to their both having restricted conformational flexibility in the C1−C6 region, which serves to direct the bulky hydride reagent to the same face of the C7 ketone.

Conclusions. In summary, a highly convergent, third-generation synthesis of discodermolide has been completed. It proceeds in seven steps and 47% yield from the advanced C9−C24 intermediate **33**, which was also used in the two previous synthetic routes to discodermolide developed in our group. In the first-generation route, compound **33** was converted into discodermolide in nine steps and 42% yield,[18a−c] whereas eight steps were required following the second-generation endgame (Scheme 15).[18d,f] Overall, this represents a significant improvement in terms of efficiency, together with the ease of performing the final fragment coupling step and purification of the coupled product, which are key criteria for developing an industrial synthesis.[21,13b]

This third-generation synthesis exploits a late-stage Still−Gennari-type HWE coupling using phosphonate **61** under experimentally undemanding conditions, both in terms of reaction conditions and isolation protocols. Notably, this coupling proceeds satisfactorily by simply using NaH as a base, without resorting to expensive crown ether additives, important for minimizing the cost of goods in scaling up.[42] As such, this new endgame represents a major advance over our first and second generation routes. The overall stereocontrol has also been improved, as the C5 stereocenter is now set up at an early stage via an expedient in situ aldol reaction/reduction (>97:3 dr), while the C7 stereocenter is installed by reduction of enone **73** by K-Selectride (>97:3 dr). This new synthesis of discodermolide proceeds in 11.3% yield over 21 steps (longest linear sequence) from the Roche ester **75**, based on our first-generation synthesis of intermediate **33** followed by the revised endgame reported herein.[43] By avoiding some of the experimentally challenging steps associated with earlier syntheses,[21e] this new route should be more applicable to the preparation of larger quantities of discodermolide as required for clinical development, as well as being amenable to the synthesis of novel structural analogues for further SAR studies.

Experimental Section

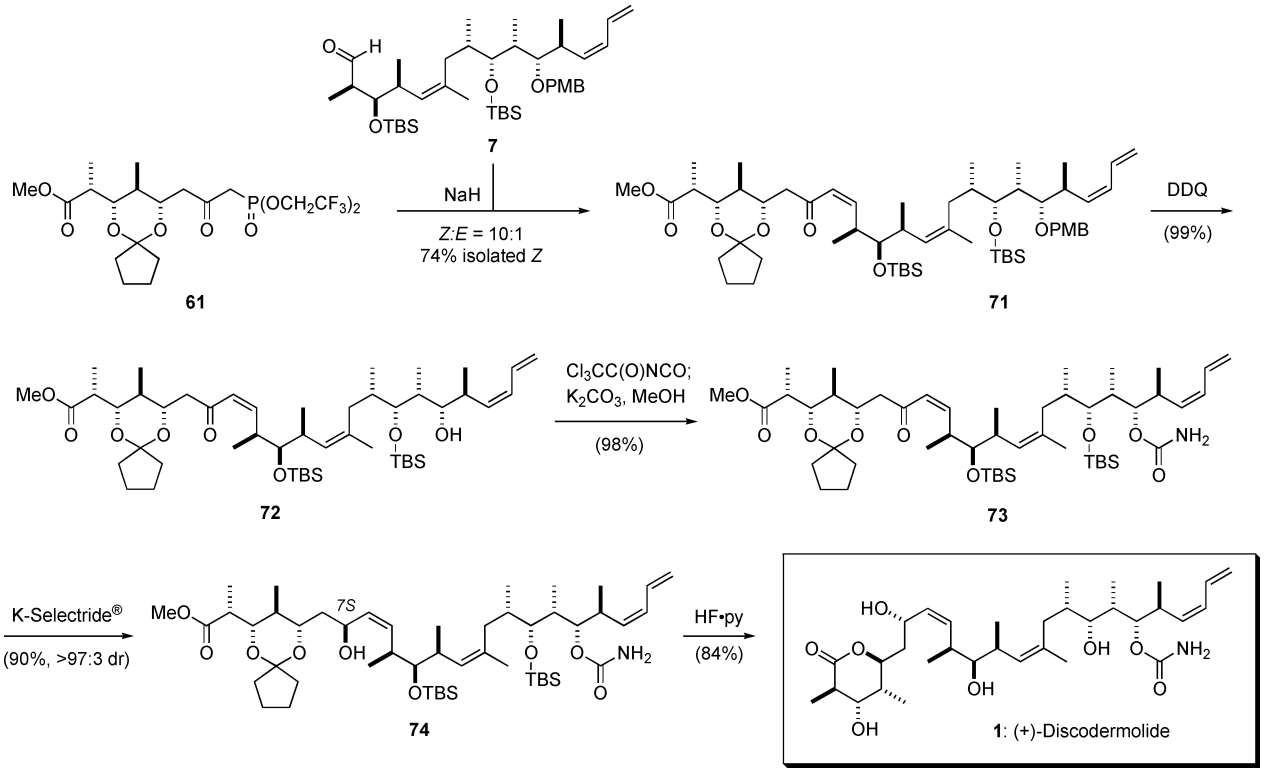
General experimental methods can be found in the Supporting Information.

(2*S*,3*R*,4*S*,5*S*)-1-(4-Methoxybenzyloxy)-7-benzyloxy-2,4-dimethylheptane-3,5-diol (50). To a stirred solution of *c*-Hex$_2$BCl (920 μL, 4.20 mmol) in Et$_2$O (10 mL) at 0 °C was

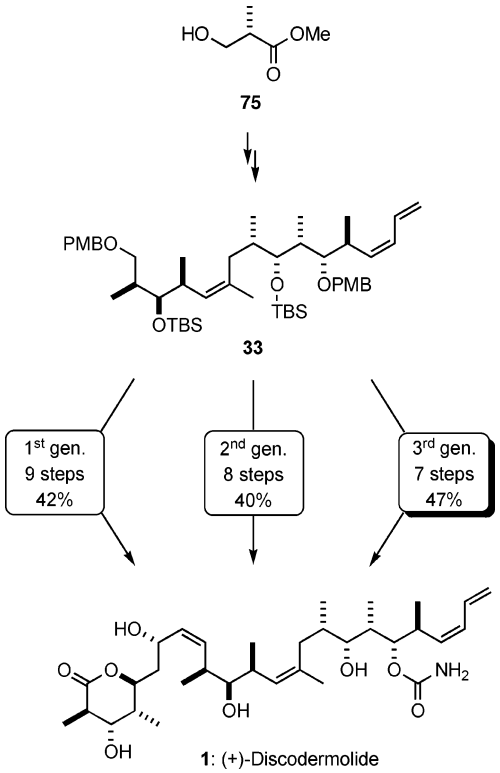
(42) To drive the olefination reaction to completion, an excess of either the aldehyde or the phosphonate was used. However, these can be recovered readily by flash chromatography and recycled.

(43) The overall yield would be 9.5% over 23 steps based on the second-generation synthesis of **33**. See ref 18d,f.

SCHEME 14. Completion of the Third-Generation Total Synthesis of Discodermolide



SCHEME 15. Comparison of the Three Different Synthetic Routes to Discodermolide from Advanced Intermediate 33



added Et_3N (675 μL, 4.84 mmol), followed by a solution of ketone **8**[18c] (763 mg, 3.23 mmol) in Et_2O (5 mL). The reaction mixture was stirred at 0 °C for 2 h and was then cooled to −78 °C. A solution of 3-benzyloxypropanal (530 mg, 3.23 mmol) in Et_2O (8 mL) was cannulated in the reaction mixture, which was stirred for 3 h at −78 °C. $LiBH_4$ (2 M in THF) was added, and the mixture was stirred at −78 °C for 3 h and then transferred to a freezer (−23 °C, 20 h). Aqueous NH_4Cl (20 mL) was added to the cold (−20 °C) mixture, which was then allowed to warm to rt and extracted with Et_2O (3 × 20 mL). The combined organic extracts were concentrated under vacuum, redissolved in MeOH (10 mL), and cooled to 0 °C. NaOH (10%, 10 mL) was added, followed by H_2O_2 (30%, 10 mL). The mixture was stirred at rt for 3 h, diluted with H_2O (20 mL), and extracted with Et_2O (3 × 20 mL). The combined organic extracts were dried (Na_2SO_4), concentrated under vacuum, and purified by flash chromatography (20 to 50% Et_2O in hexane) to afford diol **50** as a colorless oil (1.09 g, 84%): R_f 0.45 (50% AcOEt in hexane); $[\alpha]^{20}_D$ −3.0 (*c* 0.85, $CHCl_3$); IR (thin film) 3428 (br, s), 2964 (s), 2861 (s), 1613, 1514, 1248, 1092, 699 (s); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.36−7.27 (5H, m), 7.26−7.23 (2H, m), 6.90−6.86 (2H, m), 4.53 (2H, s), 4.45 (2H, s), 3.87−3.83 (1H, m), 3.80 (3H, s), 3.77−3.66 (3H, m), 3.53 (2H, qd, J = 9.0, 5.4 Hz), 1.93−1.88 (2H, m), 1.78−1.72 (1H, m), 1.70−1.64 (1H, m), 1.43 (1H), 1.21 (1H), 0.95 (3H, d, J = 7.0 Hz), 0.75 (3H, d, J = 6.9 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 159.2, 138.0, 130.3, 129.2, 128.4, 127.7, 113.8, 77.9, 75.7, 75.1, 73.3, 73.1, 70.0, 55.3, 40.9, 35.2, 33.8, 30.3, 12.7, 9.3; *m/z* (CI+) 403.3 (40, $[M + H]^+$), 210.1 (50), 182.1 (55), 154.1 (85), 138.2 (70), 121.1 (100); HRMS (+ESI) calcd for $C_{24}H_{35}O_5$ $[M + H]^+$ 403.2479, found 403.2475.

(2*S*,3*R*,4*S*,5*S*)-1-(4-Methoxybenzyloxy)-7-benzyloxy-3,5-cyclopentylidene acetal-2,4-dimethylheptane (62). Diol **50** (900 mg, 2.23 mmol) was dissolved in DCM (5 mL) and cyclopentylidene dimethyl acetal (10 mL, contaminated with 25% of cyclopentanone).[41] A catalytic amount of PPTS (10 mg) was added, and the reaction mixture was stirred for 1.5 h at 50 °C. The mixture was cooled to rt, and the solvents were removed under reduced pressure. Purification by flash chromatography (33% Et_2O in hexane) afforded **62** (1.05 g, 100%) as a colorless oil: R_f 0.75 (33% AcOEt in hexane); $[\alpha]^{20}_D$ −6.8 (*c* 0.50, $CHCl_3$); IR (thin film) 2963 (s), 2856 (s), 1613 (s), 1513 (s), 1247 (s), 1095 (s), 698 (s); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.39−7.35 (4H, m), 7.33−7.27 (3H, m), 6.92−6.88 (2H, m), 4.56 (1H, d, J = 12.0 Hz), 4.50 (1H, d, J = 12.0 Hz), 4.47 (1H, d, J

= 5.1 Hz), 4.43 (1H, d, J = 5.1 Hz), 3.83 (3H, s), 3.67−3.59 (3H, m), 3.56 (1H, dt, J = 9.8, 2.2 Hz), 3.48 (1H, dd, J = 8.6, 8.6 Hz), 3.30 (1H, dd, J = 8.8, 6.1 Hz), 2.09−2.05 (2H, m), 1.90−1.78 (4H, m), 1.66−1.52 (6H, m), 0.88 (3H, d, J = 7.0 Hz), 0.78 (3H, d, J = 6.7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 159.1, 138.7, 130.8, 129.2, 128.3, 127.6, 127.4, 113.7, 109.7, 74.5, 73.2, 73.0, 72.8, 72.7, 66.7, 55.2, 40.2, 35.6, 33.8, 33.4, 31.1, 24.4, 22.6, 11.5, 9.7; *m/z* (CI+) 486.4 (100, $[M + NH_4]^+$), 469.4 (95, $[M + H]^+$); HRMS (+ESI) calcd for $C_{29}H_{41}O_5$ $[M + H]^+$ 469.2949, found 469.2925.

(2*S*,3*R*,4*S*,5*S*)-7-Benzyloxy-3,5-cyclopentylidene acetal-2,4-dimethylheptan-1-ol (63). Compound **62** (90 mg, 0.192 mmol) was dissolved in DCM (5 mL) and pH 7 buffer (0.5 mL). The mixture was stirred vigorously, and DDQ (66 mg, 0.288 mmol) was added. After 45 min, the reaction mixture was diluted with pH 7 buffer (25 mL) and extracted with DCM (3 × 10 mL). The combined organic extracts were dried (Na_2SO_4), concentrated under reduced pressure, and purified by flash chromatography (10% Et_2O in hexane), to afford alcohol **63** as a colorless oil (66 mg, 99%): R_f 0.44 (33% AcOEt in hexane); $[\alpha]^{20}_D$ −17.6 (*c* 0.60, $CHCl_3$); IR (thin film) 3449 (br, m), 2966 (s), 2872 (s), 1099 (s), 1000 (s), 698 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.37−7.26 (5H, m), 4.53 (1H, d, J = 12.0 Hz), 4.47 (1H, d, J = 12.0 Hz), 3.73 (1H, dd, J = 10.6, 3.4 Hz), 3.68−3.47 (5H, m), 2.06−1.99 (1H, m), 1.94−1.70 (5H, m), 1.69−1.53 (6H, m), 0.98 (3H, d, J = 7.1 Hz), 0.75 (3H, d, J = 6.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 138.6, 128.3, 127.6, 127.5, 109.8, 78.9, 73.1, 73.0, 67.8, 66.5, 40.2, 35.7, 34.8, 33.3, 31.2, 24.3, 22.4, 11.6, 9.2; *m/z* (CI+) 349.3 (100, $[M + H]^+$), 265.2 (97); HRMS (+ESI) calcd for $C_{21}H_{33}O_4$ $[M + H]^+$ 349.2373, found 349.2372.

(2*S*,3*R*,4*S*,5*S*)-7-Benzyloxy-3, 5-cyclopentylidene acetal-2,4-dimethylheptanal (64). Alcohol **63** (600 mg, 1.72 mmol) was dissolved in DCM (10 mL). $NaHCO_3$ (1.46 g, 17.2 mmol) was added, followed by Dess−Martin periodinane (1.46 g, 3.44 mmol). The reaction mixture was stirred for 3 h and then diluted with Et_2O (20 mL), aq $Na_2S_2O_3$ (20 mL), and aq $NaHCO_3$ (20 mL). After 30 min of vigorous stirring, the layers were separated, the aqueous phase was extracted with Et_2O (3 × 20 mL), and the combined organic extracts were washed with aq $NaHCO_3$ (2 × 40 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The crude aldehyde **64** was used without any further purification. For characterization purposes, a sample was purified by flash chromatography (20% Et_2O in hexane): colorless oil; R_f 0.68 (33% AcOEt in hexane); $[\alpha]^{20}_D$ −54.4 (*c* 0.50, $CHCl_3$); IR (thin film) 2968 (s), 2871 (s), 1734 (s), 1079 (s), 1001 (s); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 9.64 (1H, s), 7.36−7.26 (5H, m), 4.53 (1H, d, J = 12.0 Hz), 4.47 (1H, d, J = 12.0 Hz), 4.02 (1H, dd, J = 10.3, 2.6 Hz), 3.65−3.54 (3H, m), 2.47 (1H, dq, J = 7.0, 2.6 Hz), 2.06−2.01 (1H, m), 1.98−1.70 (4H, m), 1.64−1.42 (6H, m), 1.14 (3H, d, J = 7.0 Hz), 0.80 (3H, d, J = 6.7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 204.6, 138.6, 128.3, 127.6, 127.5, 110.0, 75.1, 73.1, 73.0, 66.4, 47.1, 39.9, 35.3, 33.3, 31.2, 24.3, 22.3, 11.7, 6.5; HRMS (+ESI) calcd for $C_{21}H_{30}O_4Na$ $[M + Na]^+$ 369.2054, found 369.2052.

(2*S*,3*R*,4*S*,5*S*)-7-Benzyloxy-3,5-cyclopentylidene acetal-2,4-dimethylheptanoic Acid (65). Crude aldehyde **64** (max 1.72 mmol) was dissolved in *t*-BuOH (10 mL) and a few drops of 2-methyl-2-butene. A solution of $NaClO_2$ (390 mg, 3.44 mmol) and $NaH_2PO_4 \cdot 2\ H_2O$ (1.61 g, 10.32 mmol) in water (10 mL) was added dropwise, and the reaction mixture was stirred for 1 h before being partitioned between brine (50 mL) and DCM (20 mL). The aqueous layer was re-extracted with DCM (2 × 20 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. The crude acid **65** was used without any further purification. For characterization purposes, a sample was purified by flash chromatography (25% Et_2O in hexane): colorless oil; R_f 0.38 (33% AcOEt in hexane); $[\alpha]^{20}_D$ −27.8 (*c* 0.90, $CHCl_3$); IR (thin film) 2958, 2873 (s, CH), 1711 (s), 1336, 1195, 1098, 999 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.37−7.26 (5H, m), 4.54 (1H, d, J = 12.0 Hz), 4.48 (1H, d, J = 12.0 Hz), 3.99 (1H, dd, J = 10.4, 2.2 Hz), 3.65−3.57 (3H, m), 2.74 (1H, dq, J = 7.1, 2.3 Hz), 2.06−2.01 (1H, m), 1.96−1.74 (4H, m), 1.64−1.53 (6H, m), 1.16 (3H, d, J = 7.0 Hz), 0.80 (3H, d, J = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 180.2, 138.5, 128.3, 127.6, 127.5, 110.1, 76.0, 73.0, 72.9, 66.4, 40.7, 39.9, 35.7, 33.2, 30.8, 24.2, 22.3, 11.5, 8.4; HRMS (+ESI) calcd for $C_{21}H_{31}O_5$ $[M + H]^+$ 363.2166, found 363.2170.

Methyl (2*S*,3*R*,4*S*,5*S*)-7-Benzyloxy-3, 5-cyclopentylidene acetal-2,4-dimethylheptanoate (66). Crude acid **65** (max = 1.72 mmol) was dissolved in hexane (16 mL) and MeOH (2 mL). TMS-CHN_2 (2 M in hexane) was added dropwise until the yellow color persisted. The reaction mixture was then stirred for 30 min, quenched with 1 drop of AcOH, and concentrated under reduced pressure. Purification by flash chromatography (10−33% Et_2O in hexane) afforded ester **66** as a colorless oil (608 mg, 94% over three steps): R_f 0.67 (33% AcOEt in hexane); $[\alpha]^{20}_D$ −37.0 (*c* 0.60, $CHCl_3$); IR (thin film) 2950 (s), 2873 (s), 1744 (s), 1197 (s), 1111 (s), 699 (s); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.35−7.26 (5H, m), 4.53 (1H, d, J = 12.0 Hz), 4.47 (1H, d, J = 12.0 Hz), 3.95 (1H, dd, J = 10.4, 3.1 Hz), 3.68 (3H, s), 3.62−3.53 (3H, m), 2.69 (1H, dq, J = 7.1, 3.1 Hz), 2.06−1.98 (1H, m), 1.95−1.72 (4H, m), 1.65−1.48 (6H, m), 1.14 (3H, d, J = 7.1 Hz), 0.78 (3H, d, J = 6.7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 174.9, 138.6, 128.3, 127.6, 127.5, 109.9, 76.2, 73.1 (2C), 66.5, 51.6, 40.8, 39.9, 35.9, 33.3, 30.9, 24.2, 22.4, 11.6, 8.7; *m/z* (CI+) 394.3 (90, $[M + NH_4]^+$), 377.3 (80, $[M + H]+$), 293.2 (100); HRMS (+ESI) calcd for $C_{22}H_{33}O_5$ $[M + H]^+$ 377.2323, found 377.2321.

Methyl (2*S*,3*R*,4*S*,5*S*)-3,5-Cyclopentylidene acetal-7-hydroxy-2,4-dimethylheptanoate (67). Compound **66** (200 mg, 0.53 mmol) was dissolved in THF (10 mL). $Pd(OH)_2$ (10% on C, 20 mg) was added, and the reaction system was purged three times with H_2 and then stirred under an atmosphere of H_2 for 20 min. Filtration through Celite and removal of solvents in vacuo afforded alcohol **67**, which was used without any further purification. For characterization purposes, a sample was purified by flash chromatography (20% Et_2O in hexane): colorless oil; R_f 0.29 (33% AcOEt in hexane); $[\alpha]^{20}_D$ −13.2 (*c* 1.40, $CHCl_3$); IR (thin film) 3452 (br m), 2952 (s), 2877 (s), 1733 (s), 1197 (s), 1109 (s), 986 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 3.97 (1H, dd, J = 10.4, 2.9 Hz), 3.82−3.70 (2H, m), 3.67 (3H, s), 3.64 (1H, dd, J = 9.5, 2.3 Hz), 2.68 (1H, dq, J = 7.0, 3.0 Hz), 2.60−2.10 (1H, br s), 1.95−1.52 (11H, m), 1.14 (3H, d, J = 7.1 Hz), 0.76 (3H, d, J = 6.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 174.7, 110.1, 76.9, 76.1, 61.1, 51.7, 40.8, 40.0, 35.6, 34.7, 30.9, 24.2, 22.3, 11.6, 8.6; *m/z* (CI+) 287.2 (60, $[M + H]^+$), 203.1 (100); HRMS (+ESI) calcd for $C_{15}H_{27}O_5$ $[M + H]^+$ 287.1853, found 287.1854.

Methyl (2*S*,3*R*,4*S*,5*S*)-3,5-Cyclopentylidene acetal-2,4-dimethyl-7-oxoheptanoate (68). Crude alcohol **67** (max = 0.53 mmol) was dissolved in DCM (5 mL). $NaHCO_3$ (451 mg, 5.30 mmol) was added, followed by Dess−Martin periodinane (452 mg, 1.06 mmol). The reaction mixture was stirred for 30 min, hexane (3 mL) was then added, and the precipitate was filtered through a pad of silica and concentrated in vacuo. Purification by flash chromatography (10−33% Et_2O in hexane) provided aldehyde **68** as a colorless oil (125 mg, 83% over 2 steps): R_f 0.50 (33% AcOEt in hexane); $[\alpha]^{20}_D$ −18.0 (*c* 0.65, $CHCl_3$); IR (thin film) 2954 (s), 2877 (s), 1730 (s), 1201 (s), 1110 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 9.77 (1H, s), 4.03−3.93 (2H, m), 3.68 (3H, s), 2.69 (1H, dq, J = 7.0, 3.1 Hz), 2.61 (1H, dd, J = 15.8, 1.5 Hz), 2.52 (1H, ddd, J = 16.0, 8.5, 2.6 Hz), 1.98−1.71 (4H, m), 1.68−1.51 (5H, m), 1.14 (3H, d, J = 7.1 Hz), 0.78 (3H, d, J = 6.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 201.4, 174.6, 110.3, 76.0, 72.3, 51.7, 46.9, 40.8, 39.7, 35.6, 30.9, 24.3, 22.3, 11.5, 8.7; *m/z* (CI+) 302.2 (100, $[M + NH_4]^+$), 285.2 (40, $[M + H]^+$), 201.1 (37), 90.1 (60); HRMS (+ESI) calcd for $C_{15}H_{26}O_5$ $[M + H]^+$ 285.1697, found 285.1699.

(2*S*,3*R*,4*S*,5*S*)-3,5-Cyclopentylidene acetal-2,4-dimethylheptanedioic Acid 1-Methyl Ester (69). Aldehyde **68** (120 mg, 0.42 mmol) was dissolved in *t*-BuOH (5 mL) and 2-methyl-2-butene (a few drops). A solution of $NaClO_2$ (80%, 104 mg,

0.91 mmol) and $NaH_2PO_4 \cdot 2H_2O$ (428 mg, 2.74 mmol) in water (5 mL) was added dropwise, and the reaction mixture was stirred at rt for 45 min. The mixture was diluted with brine (50 mL) and extracted with DCM (3 × 20 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. The resulting acid was used without any further purification. For characterization purposes, **69** was purified by flash chromatography (20% Et_2O in hexane): colorless oil; R_f 0.12 (33% AcOEt in hexane); $[\alpha]^{20}_D$ −12.5 (*c* 0.90, $CHCl_3$); IR (thin film) 2952 (s), 2880 (s), 1740 (s, C=O), 1717 (s), 1198 (s), 1111 (s), 986 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 3.98 (1H, dd, J = 10.3, 2.6 Hz), 3.89 (1H, dt, J = 9.1, 2.5 Hz), 3.66 (3H, s), 2.68−2.64 (2H, m), 2.42 (1H, dd, J = 15.6, 9.0 Hz), 1.89 − 1.72 (4H, m), 1.60−1.50 (5H, m), 1.11 (3H, d, J = 7.1 Hz), 0.77 (3H, d, J = 6.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 176.5, 174.6, 110.3, 75.9, 73.2, 51.7, 40.7, 39.6, 38.7, 35.4, 30.7, 24.1, 22.2, 11.5, 8.6; HRMS (+ESI) calcd for $C_{15}H_{25}O_6$ $[M + H]^+$ 301.1646, found 301.1641.

Methyl (2*S*,3*R*,4*S*,5*S*)-3,5-cyclopentylidene acetal-2,4-dimethyl-7-oxo-8-[bis(2,2,2-trifluoroethoxy)phosporyl]-octanoate (61). Acid **69** (max 0.42 mmol) was dissolved in DCM (5 mL). 1-Chloro-*N*,*N*,2-trimethyl-1-propenylamine (121 μL, 0.914 mmol) was added, and the reaction mixture was stirred at rt for 1 h before being concentrated under reduced pressure. The crude acid chloride was dried under high vacuum for 30 min. In the meantime, methylphosphonic acid bis(2,2,2-trifluoroethyl) ester[31] **19** (357 mg, 1.37 mmol) was dissolved in THF (1 mL) and cooled to −98 °C. LiHMDS (1 M in THF, 1.36 mL, 1.36 mmol) was added, and the reaction mixture was stirred at −98 °C for 10 min before the addition of the crude acid chloride in solution in THF (3 mL). The mixture was stirred for 1 h at −98 °C, quenched with aq NH_4Cl (5 mL), and allowed to warm to rt. After dilution with more aq NH_4Cl (20 mL), the mixture was extracted with DCM (3 × 10 mL), and the combined organic extracts were dried ($MgSO_4$), concentrated under reduced pressure, and purified by flash chromatography (25−50% AcOEt in hexane), affording β-ketophosphonate **61** as a viscous colorless oil (160 mg, 70% over three steps): R_f 0.36 (50% AcOEt in hexane); $[\alpha]^{20}_D$ −28.8 (*c* 0.70, $CHCl_3$); IR (thin film) 2968 (m), 2876 (m), 1727 (s), 1263 (s), 1171 (s), 1072 (s); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 4.48−4.38 (4H, m), 3.98 (1H, dd, J = 10.3, 3.1 Hz), 3.89 (1H, ddd, J = 12.1, 8.5, 3.6 Hz), 3.68 (3H, s), 3.35 (2H, d, J_{PH} = 21.1 Hz), 2.76−2.65 (3H, m), 1.92−1.61 (4H, m), 1.60−1.49 (5H, m), 1.13 (3H, d, J = 7.1 Hz), 0.77 (3H, d, J = 6.7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 200.1 (d, J = 7.0 Hz), 174.5, 122.5 (qdd, J = 276.2, 7.0, 1.6 Hz), 110.4, 75.9, 73.5, 62.3 (qdd, J = 53.2, 15.0, 5.4 Hz), 51.7, 47.7 (d, J = 5.4 Hz), 43.2, 42.1, 40.8, 39.7, 35.6, 30.8, 24.2, 22.3, 11.5, 8.7; *m/z* (CI$^+$) 560 ($[M + NH_4]^+$), 543 (20, $[M + H]^+$); HRMS (+ESI) calcd for $C_{20}H_{30}O_8F_6P$ $[M + H]^+$ 543.1583, found 543.1582.

(10*S*,11*S*,12*S*,13*Z*,16*S*,17*R*,18*S*,19*S*,20*S*,21*Z*)-11,17-Bis-(*tert*-butyldimethylsilyloxy)-19-(4-methoxybenzyloxy)-10,12,14,16,18,20-hexamethylhexadeca-13,21, 23-trien-9-ol (34). PMB ether **33** (100 mg, 0.119 mmol) was dissolved in DCM (10 mL) and cooled to 0 °C. $BCl_3 \cdot$DMS (2 M in DCM, 60 μL, 0.119 mmol) was added dropwise, and the reaction mixture was stirred for 20 min at 0 °C before being partitioned between aq $NaHCO_3$ (20 mL) and DCM (10 mL). The aqueous phase was re-extracted with DCM (3 × 10 mL), and the combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure. Purification by flash chromatography (10% Et_2O in hexane) afforded alcohol **34** as a colorless oil (680 mg, 95%): R_f 0.30 (20% AcOEt in hexane); $[\alpha]^{20}_D$ +32.7 (*c* 0.95, $CHCl_3$); IR (thin film) 3448 (br w), 2958 (s), 2856 (s), 1613 (s), 1514 (s), 1250 (s), 1031 (s); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.27 (2H, d, J = 8.6 Hz), 6.87 (2H, d, J = 8.6 Hz), 6.60 (1H, ddd, J = 16.9, 10.7, 10.5 Hz), 6.05 (1H, dd, J = 11.1, 11.0 Hz), 5.58 (1H, dd, J = 10.6, 10.6 Hz), 5.23 (1H, d, J = 16.8 Hz), 5.12 (1H, d, J = 10.2 Hz), 4.97 (1H, d, J = 10.2 Hz), 4.56 (1H, d, J = 10.6 Hz), 4.47 (1H, d, J = 10.6 Hz), 3.80 (3H, s), 3.68−3.64 (1H, m), 3.52−3.48 (1H, m), 3.44 (1H, dd, J = 4.8, 3.9 Hz), 3.39 (1H, dd, J = 6.9, 3.7 Hz), 3.25 (1H, dd, J = 7.4, 3.6 Hz), 3.03−2.97 (1H, m), 2.54 (1H, m), 2.35 (1H, br s), 2.05 (1H, dd, J = 12.5, 12.4 Hz), 1.85−1.77 (3H, m), 1.76−1.61 (1H, m), 1.57 (3H, s), 1.11 (3H, d, J = 6.8 Hz), 1.01 (3H, d, J = 6.9 Hz), 0.99 (3H, d, J = 7.2 Hz), 0.96−0.90 (21H, m), 0.72 (3H, d, J = 6.7 Hz), 0.11−0.06 (12H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 159.1, 134.5, 132.8, 132.3, 131.2, 130.4, 129.2 (2C), 129.0, 117.5, 113.7 (2C), 84.5, 81.7, 77.0, 75.0, 65.3, 55.3, 40.1, 38.4, 36.8, 36.0, 35.3, 35.2, 26.3, 26.2, 23.0, 18.7, 18.6, 18.3, 17.6, 15.8, 14.7, 10.6, −3.2, −3.4, −3.6, −3.9; *m/z* (+ESI) 734.6 (100, $[M + H_2O]^+$), 717.6 (80, $[M + H]^+$); HRMS (+ESI) calcd for $C_{42}H_{77}O_5Si_2$ $[M + H]^+$ 717.5304, found 717.5298.

(10*S*,11*S*,12*S*,13*Z*,16*S*,17*R*,18*S*,19*S*,20*S*,21*Z*)-11,17-Bis-(*tert*-butyldimethylsilyloxy)-19-(4-methoxybenzyloxy)-10,12,14,16,18,20-hexamethylhexadeca-13,21, 23-trienal (7). Alcohol **34** (300 mg, 0.418 mmol) was dissolved in DCM (5 mL). $PhI(OAc)_2$ (162 mg, 0.502 mmol) was added, followed by TEMPO (13.1 mg, 0.084 mmol), and the reaction mixture was stirred at rt for 8 h. Aqueous $Na_2S_2O_3$ (10 mL) was added, and the mixture was vigorously stirred for a further 20 min before being extracted with DCM (3 × 10 mL). The combined organic extracts were dried (Na_2SO_4), concentrated under reduced pressure, and purified by flash chromatography (10% Et_2O in hexane) to afford the desired aldehyde **7** as a colorless oil (266 mg, 89%): R_f 0.53 (20% AcOEt in hexane); $[\alpha]^{20}_D$ +22.8 (*c* 1.25, $CHCl_3$); IR (thin film) 2957 (s), 2930 (s), 2857 (s), 1721 (s), 1372, 1248 (s); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 9.59 (1H, s), 7.28 (2H, d, J = 8.5 Hz), 6.88 (2H, d, J = 8.5 Hz), 6.60 (1H, ddd, J = 16.8, 10.6, 10.6 Hz), 6.03 (1H, dd, J = 11.0, 11.0 Hz), 5.58 (1H, dd, J = 10.6, 10.6 Hz), 5.22 (1H, d, J = 16.9 Hz), 5.13 (1H, d, J = 10.2 Hz), 4.79 (1H, d, J = 10.6 Hz), 4.57 (1H, d, J = 10.6 Hz), 4.48 (1H, d, J = 10.6 Hz), 3.80 (3H, s), 3.75 (1H, dd, J = 8.2, 3.5 Hz), 3.43 (1H, dd, J = 4.7, 3.9 Hz), 3.26 (1H, dd, J = 7.5, 3.5 Hz), 3.04−2.98 (1H, m), 2.55−2.46 (2H, m), 2.01 (1H, dd, J = 12.4, 12.4 Hz), 1.85−1.75 (2H, m), 1.63 (1H, app br d, J = 10.6 Hz), 1.54 (3H, s), 1.12 (3H, d, J = 6.8 Hz), 1.06 (3H, d, J = 6.9 Hz), 1.03 (3H, d, J = 6.8 Hz), 0.96 (9H, s), 0.94 (3H, d, J = 6.6 Hz), 0.91 (9H, s), 0.71 (3H, d, J = 6.6 Hz), 0.12 (3H, s), 0.11 (3H, s), 0.09 (3H, s), 0.07 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 202.8, 159.0, 135.2, 134.4, 132.1, 131.1, 129.1 (2C), 128.9, 117.5, 113.7 (2C), 84.5, 78.3, 77.1, 75.0, 55.2, 52.1, 40.0, 36.4, 36.3, 35.3, 35.1, 26.2, 25.8, 22.8, 18.6, 18.1, 17.9, 14.7, 10.5, 9.5, −3.1, −3.5, −4.3, −4.4; *m/z* (+ESI) 739.5 (100, $[M + Na]^+$); HRMS (+ESI) calcd for $C_{42}H_{76}O_5Si_2Na$ $[M + Na]^+$ 739.51184, found 739.512347.

Methyl (2*R*,3*S*,4*S*,5*S*,8*Z*,10*S*,11*S*,12*S*,13*Z*,16*S*,17*R*,18*S*,-19*S*,20*S*,21*Z*)-11,17-Bis(*tert*-butyldimethylsilyloxy)-3,5-cyclopentylidene acetal-19-(4-methoxybenzyloxy)-2,4,-10,12,14,16,18,20-octamethyl-7-oxotetracosa-8,13,21,23-tetraenoate (71). Phosphonate **61** (10 mg, 18.4 μmol) was dissolved in THF (1 mL) and cooled to −10 °C. Sodium hydride (60% in oil, 0.8 mg, 19 μmol) was added, and the reaction mixture was stirred at −10 °C for 30 min. Aldehyde **7** (40 mg, 55.3 μmol) was added in solution in THF (2 mL), and the reaction mixture was allowed to warm to rt slowly and stirred for 2.5 d. Aqueous NH_4Cl (10 mL) was added, the mixture was extracted with DCM (4 × 5 mL), and the combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. The *Z*/*E* ratio was determined by ^{1}H NMR spectroscopy as being 10:1. Purification by flash chromatography (10% AcOEt in hexane) afforded the *Z*-enone **71** as a colorless oil (13.5 mg, 74%): R_f 0.75 (33% AcOEt in hexane); $[\alpha]^{20}_D$ +57.4 (*c* 0.35, $CHCl_3$); IR (thin film) 2958 (s), 2932 (s), 2857 (s), 1747 (s), 1250 (s), 1039 (s), 836 (s); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.27 (2H, d, J = 8.6 Hz), 6.86 (2H, d, J = 8.6 Hz), 6.59 (1H, ddd, J = 16.8, 10.6, 10.4 Hz), 6.13−6.00 (3H, m), 5.57 (1H, dd, J = 10.6, 10.5 Hz), 5.21 (1H, d, J = 16.9 Hz), 5.12 (1H, d, J = 10.1 Hz), 4.85 (1H, d, J = 10.3 Hz), 4.55 (1H, d, J = 10.5 Hz), 4.47 (1H, d, J = 10.6 Hz), 3.98−3.93 (2H, m), 3.79 (3H, s), 3.67 (3H, s), 3.60−3.57 (1H, m), 3.44−3.40 (2H, m), 3.24 (1H, dd, J = 7.5, 3.5 Hz), 3.05−2.95 (1H, m), 2.65 (1H, dq, J = 7.0, 3.2 Hz), 2.62 (1H, dd, J = 15.6, 3.3 Hz), 2.62 (1H, dd, J

= 15.5, 8.2 Hz), 2.38 − 2.30 (1H, m), 1.97 (1H, dd, J = 12.4, 12.4 Hz), 1.90−1−61 (6H, m), 1.60−1.48 (6H, m), 1.51 (3H, s), 1.11 (3H, d, J = 7.1 Hz), 1.10 (3H, d, J = 6.8 Hz), 1.05−0.87 (24H, m), 0.86 (3H, d, J = 6.6 Hz), 0.73 (3H, d, J = 6.6 Hz), 0.68 (3H, d, J = 6.6 Hz), 0.10−0.01 (12H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 198.4, 174.8, 159.0, 151.2, 134.4, 132.3, 132.2, 131.2, 130.7, 129.1, 129.0, 125.4, 117.6, 113.7, 110.1, 84.7, 80.4, 76.1, 75.0, 73.1, 55.3, 51.7, 48.1, 40.8, 40.1, 39.8, 38.2, 37.1, 35.9, 35.8, 35.3 (2C), 30.8, 26.3, 26.2, 24.3, 22.8, 22.4, 18.7, 18.6, 18.4, 18.0, 17.1, 14.8, 11.6, 10.5, 8.7, −3.1, −3.3, −3.6, −4.0; HRMS (+ESI) calcd for $C_{58}H_{102}O_9Si_2N$ $[M + NH_4]^+$ 1012.7088, found 1012.7081.

Methyl (2*R*,3*S*,4*S*,5*S*,8*Z*,10*S*,11*S*,12*S*,13*Z*,16*S*,17*R*,18*S*,-19*S*,20*S*,21*Z*)-11,17-Bis(*tert*-butyldimethylsilyloxy)-3,5-cyclopentylidene acetal-19-hydoxy-2,4,10,12,14,16,18,20-octamethyl-7-oxotetracosa-8,13,21,23-tetraenoate (72). Compound **71** (40 mg, 40.1 μmol) was dissolved in DCM (2 mL) and pH 7 buffer (0.2 mL) and cooled to 0 °C. DDQ (18.3 mg, 80.3 μmol) was added, and the reaction mixture was stirred at 0 °C for 30 min and then at rt for 45 min. The mixture was partitioned between pH 7 buffer (20 mL) and DCM (10 mL). The aqueous phase was re-extracted with DCM (3 × 10 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash chromatography (20−50% AcOEt in hexane) afforded alcohol **72** as a colorless oil (35 mg, 99%): R_f 0.56 (20% AcOEt in hexane); $[\alpha]^{20}_D$ +51.6 (c 0.60, $CHCl_3$); IR (thin film) 2958 (s), 2932 (s), 1735 (s), 1087 (s), 1022 (s), 773 (s); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 6.63 (1H, ddd, J = 16.8, 10.7, 10.4 Hz), 6.19−6.08 (2H, m), 6.07 (1H, d, J = 11.6 Hz), 5.34 (1H, dd, J = 10.4, 10.4 Hz), 5.24 (1H, d, J = 16.7 Hz), 5.15 (1H, d, J = 10.1 Hz), 4.90 (1H, d, J = 10.3 Hz), 4.00−3.95 (2H, m), 3.68 (3H, s), 3.63−3.59 (2H, m), 3.42 (1H, dd, J = 6.8, 3.1 Hz), 3.33 (1H, dd, J = 7.4, 2.9 Hz), 2.82−2.78 (1H, m), 2.68 (1H, dq, J = 7.0, 3.1 Hz), 2.65 (1H, dd, J = 15.6, 3.5 Hz), 2.60 (1H, dd, J = 15.5, 7.9 Hz), 2.40−2.36 (1H, m), 2.16 (1H, dd, J = 12.4, 12.4 Hz), 1.92−1.67 (7H, m), 1.66−1.48 (5H, m), 1.60 (3H, s), 1.14 (3H, d, J = 7.1 Hz), 0.98−0.87 (30H, m), 0.75 (3H, d, J = 6.7 Hz), 0.71 (3H, d, J = 6.8 Hz), 0.09−0.01 (12H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 198.5, 174.7, 151.1, 134.7, 132.5, 132.1, 131.0, 130.7, 125.6, 118.4, 110.2, 80.5, 78.8, 76.3, 76.2, 73.1, 51.6, 48.1, 40.9, 39.8, 38.3, 38.0, 37.4, 36.4, 36.3, 35.8, 34.9, 30.8, 26.23, 26.19, 24.3, 23.1, 22.4, 18.5, 18.4, 17.8, 17.5, 17.2, 13.4, 11.7, 9.5, 8.7, −3.4, −3.5 (2C), −4.0; HRMS (+ESI) calcd for $C_{50}H_{90}O_8Si_2Na$ $[M + H]^+$ 897.6066, found 897.6087.

Methyl (2*R*,3*S*,4*S*,5*S*,8*Z*,10*S*,11*S*,12*S*,13*Z*,16*S*,17*R*,18*S*,-19*S*,20*S*,21*Z*)-11,17-Bis-(*tert*-butyldimethylsilyloxy)-19-carbamoyloxy-3, 5-cyclopentylidene acetal-2,4,10,12,14,-16,18,20-octamethyl-7-oxotetracosa-8,13,21,23-tetraenoate (73). Alcohol **72** (10 mg, 11.4 μmol) was dissolved in DCM (1 mL). Trichloroacetyl isocyanate (6.8 μL, 57.1 μmol) was added, and the reaction mixture was stirred for 1.5 h. The mixture was loaded onto the top of a plug of neutral alumina and left there for 2 h. Elution with AcOEt, concentration under reduced pressure, and purification by flash chromatography (10−20% AcOEt in hexane) afforded carbamate **73** as a colorless oil (9.9 mg, 95%): R_f 0.47 (33% AcOEt in hexane); $[\alpha]^{20}_D$ +63.3 (c 0.15, $CHCl_3$); IR (thin film) 2958 (s), 2932 (s), 2857 (s), 1732 (s), 1037 (s), 836 (s), 773 (s); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 6.60 (1H, ddd, J = 16.8, 10.7, 10.6 Hz), 6.15 (1H, dd, J = 11.6, 9.3 Hz), 6.08−6.01 (2H, m), 5.38 (1H, dd, J = 10.7, 10.5 Hz), 5.22 (1H, d, J = 16.8 Hz), 5.14 (1H, d, J = 10.0 Hz), 4.87 (1H, d, J = 10.4 Hz), 4.73 (1H, dd, J = 6.1, 6.1 Hz), 4.52 (2H, br s), 4.00−3.96 (2H, m), 3.68 (3H, s), 3.60−3.52 (1H, m), 3.45−3.40 (2H, m), 3.08−2.96 (1H, m), 2.68 (1H, dq, J = 7.1, 3.1 Hz), 2.62 (1H, dd, J = 15.5, 3.8 Hz), 2.57 (1H, dd, J = 15.5, 7.7 Hz), 2.40−2.30 (1H, m), 2.07 (1H, dd, J = 12.5, 12.3 Hz), 1.92−1.67 (7H, m), 1.66−1.48 (5H, m), 1.57 (3H, s), 1.13 (3H, d, J = 7.1 Hz), 0.99 (3H, d, J = 6.8 Hz), 0.96 (3H, d, J = 7.0 Hz), 0.95−0.88 (21H, m), 0.87 (3H, d, J = 6.6 Hz), 0.75 (3H, d, J = 6.7 Hz), 0.69 (3H, d, J = 6.7 Hz), 0.11−0.02 (12H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 198.4, 174.8, 156.9, 151.4, 133.6, 132.4, 132.1, 130.6, 129.8, 125.5, 118.0, 110.2, 80.4, 78.9, 76.1, 73.2, 51.7, 48.2, 40.9, 39.8, 38.1, 38.0, 37.3, 36.1, 36.0, 35.1, 34.5, 30.8, 26.23, 26.19, 25.9, 24.3, 22.8, 22.4, 18.5, 18.4, 18.0, 17.5, 17.3, 13.7, 11.7, 10.2, 8.7, −3.43, −3.45, −3.5, −4.0; HRMS (+ESI) calcd for $C_{51}H_{91}O_9Si_2Na$ $[M + Na]^+$ 940.6125, found 940.6149.

Methyl (2*R*,3*S*,4*S*,5*S*,7*S*,8*Z*,10*S*,11*S*,12*S*,13*Z*,16*S*,17*R*,-18*S*,19*S*,20*S*,21*Z*)-11,17-Bis(*tert*-butyldimethylsilyloxy)-19-carbamoyloxy-3,5-cyclopentylidene acetal-7-hydroxy-2,4,10,12,14,16,18,20-octamethyltetracosa-8,13,21,23-tetraenoate (74). Ketone **73** (7 mg, 7.6 μmol) was dissolved in toluene (1 mL) and cooled to −78 °C. K-Selectride (1 M in THF, 23 μL, 23 μmol) was added, and the reaction mixture was stirred for 6 h, allowing the temperature to warm slowly up to −40 °C. The mixture was quenched with aq NH_4Cl (10 mL) and extracted with AcOEt (3 × 10 mL). The organic extracts were stirred vigorously with a solution of sodium perborate (120 mg, 0.76 mmol) in water (20 mL). After 2 h, the layers were separated, and the aqueous phase was reextracted with AcOEt (10 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash chromatography (15−20% AcOEt in hexane) afforded alcohol **74** as a colorless oil (6.3 mg, 90%): R_f 0.30 (33% AcOEt in hexane); $[\alpha]^{20}_D$ +43.4 (c 0.35, $CHCl_3$); IR (thin film) 3355 (br, m), 2958 (s), 2930 (s), 2857 (s), 1726 (s), 1038 (s), 836 (s), 773 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 6.60 (1H, ddd, J = 16.8, 10.5, 10.3 Hz), 6.03 (1H, dd, J = 11.0, 11.0 Hz), 5.48 (1H, dd, J = 10.7, 9.8 Hz), 5.42−5.34 (2H, m), 5.22 (1H, d, J = 17.2 Hz), 5.13 (1H, d, J = 10.2 Hz), 5.00 (1H, d, J = 10.0 Hz), 3.97 (1H, dd, J = 6.1, 6.0 Hz), 4.73 (1H, t, J = 7.7 Hz), 4.54 (2H, br s), 3.97 (1H, dd, J = 10.3, 3.2 Hz), 3.81−3.72 (1H, m), 3.68 (3H, s), 3.42 (1H, dd, J = 4.6, 4.4 Hz), 3.28 (1H, dd, J = 5.7, 4.6 Hz), 3.03−2.95 (1H, m), 2.79 (1H, br s), 2.75−2.62 (2H, m), 2.49−2.38 (1H, m), 2.04 (1H, dd, J = 12.8, 12.4 Hz), 1.92−1.70 (8H, m), 1.70−1.49 (6H, m), 1.59 (3H, s), 1.15 (3H, d, J = 7.1 Hz), 0.99 (3H, d, J = 6.8 Hz), 0.94−0.90 (24H, m), 0.86 (3H, d, J = 6.6 Hz), 0.76 (3H, d, J = 6.7 Hz), 0.71 (3H, d, J = 6.7 Hz), 0.11−0.02 (12H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 174.9, 156.9, 134.7, 133.6, 132.1, 131.9, 131.2, 131.1, 129.8, 118.0, 110.2, 80.6, 78.7, 77.2, 76.9, 76.2, 74.1, 65.0, 51.7, 40.9, 40.1, 39.4, 37.9, 37.3, 36.2, 36.1, 35.5, 35.1, 34.5, 30.9, 26.2 (2C), 24.3, 22.9, 22.4, 18.5, 18.4, 17.5, 17.1, 13.6, 11.6, 10.1, 8.8, −3.2, −3.4, −3.5, −4.0; HRMS (+ESI) calcd for $C_{51}H_{93}O_9Si_2Na$ $[M + Na]+$ 942.6281, found 942.6304.

(+)-Discodermolide (1). To a stirred solution of **74** (6 mg, 6.5 μmol) in THF (1 mL) at 0 °C was added HF·py (0.2 mL). The reaction mixture was stirred at rt for 3 h and recooled to 0 °C, and a second aliquot of HF·py (0.2 mL) was added. After 16 h at rt, the mixture was cooled to 0 °C, and a final aliquot of HF·py (0.1 mL) was added. After 6 h at rt, the mixture was carefully quenched at 0 °C with aq $NaHCO_3$ (20 mL). Extraction with AcOEt (5 × 10 mL), drying ($MgSO_4$), and concentration under vacuum afforded the crude product, which was purified by flash chromatography (5−10% MeOH in DCM) to give (+)-discodermolide **1** as a white solid (3.0 mg, 84%): R_f 0.20 (10% MeOH in DCM); $[\alpha]^{20}_D$ +13.2 (c 1.1, MeOH), Lit.[17] +7.2 (c 0.7, MeOH); IR (thin film) 3429 (br), 2966 (s), 2929 (s), 1729 (s), 1602 (m), 1265 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 6.62 (1H, ddd, J = 16.8, 10.6, 10.6 Hz), 6.03 (1H, dd, J = 11.0, 11.0 Hz), 5.53 (1H, dd, J = 11.1, 7.9 Hz), 5.43 (1H, dd, J = 10.7, 10.3 Hz), 5.36 (1H, dd, J = 10.5, 10.2 Hz), 5.22 (1H, d, J = 16.8 Hz), 5.17 (1H, d, J = 9.7 Hz), 5.13 (1H, d, J = 10.1 Hz), 4.75 (1H, ddd, J = 7.5, 7.5, 2.6 Hz), 4.71 (1H, dd, J = 7.2, 4.2 Hz), 4.63 (1H, ddd, J = 10.0, 9.8, 2.1 Hz), 4.61 (2H, br s), 3.75 (1H, dd, J = 4.0, 4.0 Hz), 3.29 (1H, dd, J = 4.9, 4.5 Hz), 3.20 (1H, dd, J = 6.6, 4.9 Hz), 3.00 (1H, ddq, J = 9.9, 6.9, 6.9 Hz), 2.80 (1H, ddq, J = 9.7, 6.8, 6.8 Hz), 2.68 (1H, dq, J = 7.3, 4.5 Hz), 2.65−2.53 (1H, m), 2.10−1.80 (10H, m), 1.74−1.67 (1H, m), 1.65 (3H, s), 1.32 (3H, d, J = 7.3 Hz), 1.08 (3H, d, J = 6.9 Hz), 1.02 (3H, d, J = 6.8 Hz), 1.00 (3H, d, J = 5.9 Hz), 0.99 (3H, d, J = 6.3 Hz), 0.95 (3H, d, J = 6.8 Hz), 0.83 (3H, d,

J = 5.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 173.7, 157.1, 134.4, 133.7, 133.4, 132.9, 132.1, 129.9, 129.7, 117.9, 79.0, 78.9, 77.2, 75.7, 73.2, 64.4, 43.1, 41.0, 37.4, 36.1, 36.0, 35.7, 35.3, 34.8, 33.1, 23.3, 18.4, 17.5, 15.6, 15.5, 13.7, 12.5, 9.0; HRMS (+ESI) calcd for $C_{33}H_{55}O_8NNa$ $[M + Na]^+$ 616.3825, found 616.3839.

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Supporting Information Available: General experimental methods, detailed experimental procedures, and spectroscopic data for compounds **6**, **10**−**16**, **20**, **21**, **24**−**32**, **35**−**37**, **39**−**42**, and **51**−**59** and selected NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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