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A Formal Synthesis of (+)-Discodermolide

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Abstract:

Herein, we report the formal synthesis of (+)-discodermolide (1), a promising anticancer agent of sponge origin, in 24 linear steps, with 35 steps in total. The route proceeds from lactone 2, a building block containing the common 1,2-*anti*-2,3-*syn* stereotriad found in each of the three subunits, methyl ketone 4 (C_1-C_6), vinyl iodide 7 (C_9-C_{14}), and iodide 8 ($C_{15}-C_{24}$) utilized for the construction of 1. The key fragment union was achieved by a Suzuki cross-coupling between 7 and 8.

Introduction

Discodermolide (**1**, Figure 1) is a cytotoxic marine polyketide discovered in 1990 by Gunasekara and co-workers at the Harbor Branch Oceanographic Institution; it was isolated from the Caribbean deep-sea sponge *Discodermia dissoluta*.[1] Discodermolide is recognized as a member of a group of cell growth inhibitory agents including Taxol, known to arrest cell development at the boundary of the G2-M phase by binding and stabilizing mitotic spindle microtubules.[2] The remarkable biological profile of discodermolide has been recognized by Novartis Pharmaceutical Corporation who licensed discodermolide from the Harbor Branch Oceanographic Institution in 1998 to develop it as a new-generation anticancer drug, leading to discodermolide entering clinical trials. Extensive exploration of the efficacy of this compound has initially been hampered by the scarce supply of the material available from the natural source. The yield reported by Gunasekara in the isolation of discodermolide, following exhaustive extraction and purification, was 0.002% w/w from frozen sponge. Although it is likely that, as a polyketide, discodermolide is produced by a symbiotic microorganism associated with the sponge source, isolation of such a microorganism has thus far not been reported. Therefore, total synthesis remains the only means at present of providing the quantities of discodermolide required to support clinical development. This stands in contrast to Taxol, which is supplied by semi-synthesis and epothilone B, which is obtained by fermentation. Consequently, there has been considerable synthetic effort from academic groups directed towards providing a practical supply of discodermolide,[4−9] culminating in the preparation of one gram of material by Smith and co-workers[5b,c] and the report by Paterson and co-workers of two generations of practical syntheses.[8a,c,d] Within the pharmaceutical industry, the landmark synthesis of over 60 g of discodermolide for phase I clinical trials has been achieved by Novartis chemists, following a hybrid Smith−Paterson route.[10] Despite these impressive efforts, there is still a pressing demand for developing a more practical and efficient synthesis of discodermolide, particularly one that can be adapted to provide a manufacturing route. Our interest for the development of a process for discodermolide revolved first around the efficient access to the recurring 1,2-*anti*-2,3-*syn* stereotriad highlighted in Figure 1. The use of a common subunit containing this motif results in a significant reduction of complexity in the total synthesis of discodermolide by

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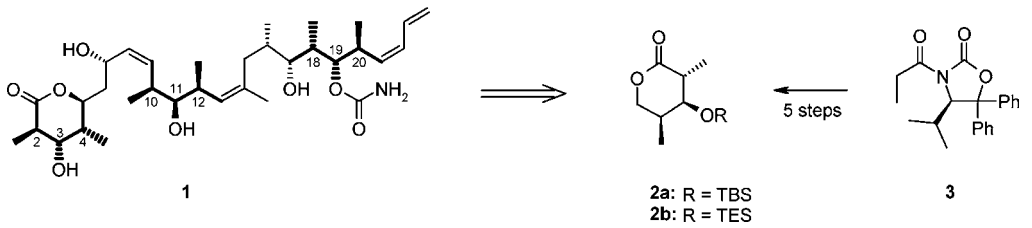
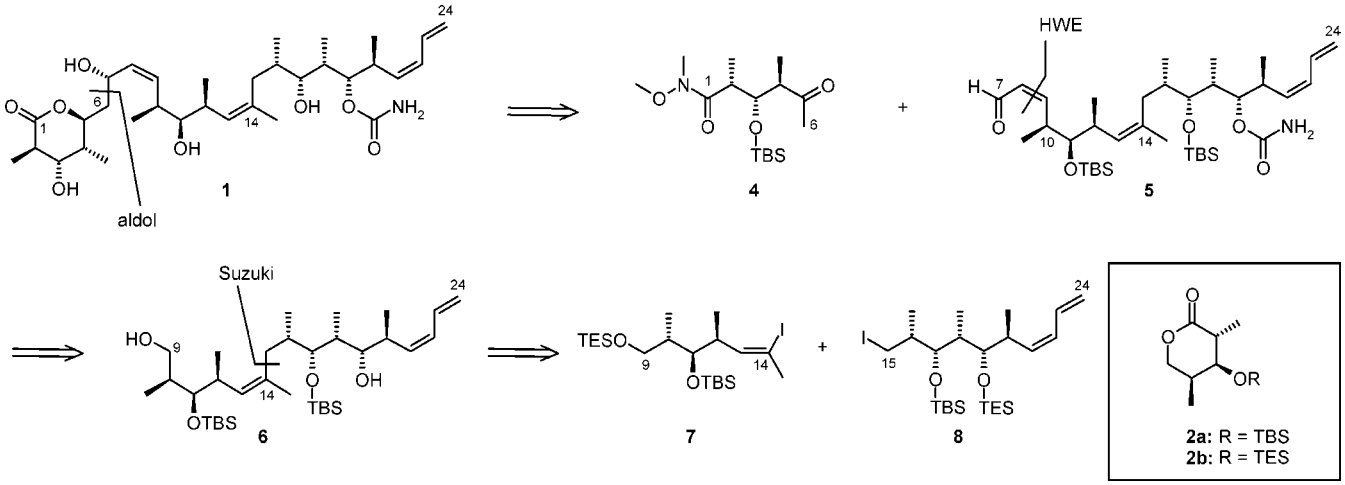


Figure 1. **Lactone 2 as a building block for the synthesis of discodermolide (1).**

Scheme 1. **Retrosynthesis of discodermolide based on C_6-C_7 aldol and $C_{14}-C_{15}$ Suzuki disconnections**

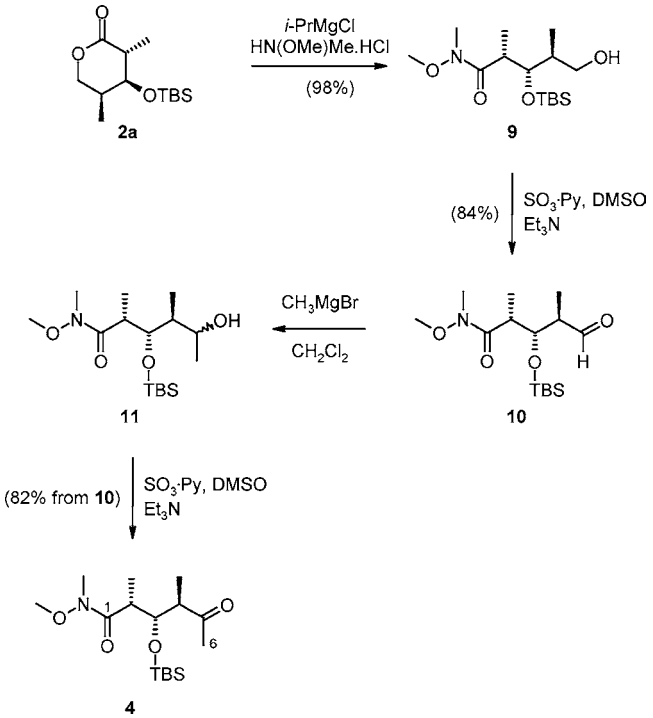


diminishing the total number of steps.[5a] For this purpose, we reported a practical route to the lactones **2a** and **2b** using chiral auxiliary (4*R*)-4-isopropyl-5,5-diphenyloxazolidin-2-one **3**.[11] Herein, we report full details of the utilization of **2** for a formal synthesis of discodermolide, which has the potential to be scaled up to provide significant quantities of discodermolide.[12]

Results and Discussion

Synthesis Plan. Analysis of discodermolide (**1**) suggests that convenient C−C bond disconnections may be made at C_6-C_7 and $C_{14}-C_{15}$, to divide **1** into three subunits, **4**, **7**, and **8**, of similar size, each having the common 1,2-*anti*-2,3-*syn* stereotriad derived from lactone **2**. The C_6-C_7 bond

Scheme 2. **Synthesis of C_1-C_6 subunit 4**



is forged via chiral boron-mediated aldol reaction with aldehyde **5** and ketone **4** as described by Paterson (also used in the Novartis large-scale synthesis of discodermolide).[10e] Further disconnection of **5** via a Horner−Wadsworth−Emmons olefination leads back to alcohol **6**, assembled by the Suzuki coupling, at $C_{14}-C_{15}$, of vinyl iodide **7** and iodide **8** (Scheme 1).

Synthesis of the C_1-C_6 Subunit 4. The synthesis of the C_1-C_6 ketone **4** (Scheme 2) began with the ring opening of

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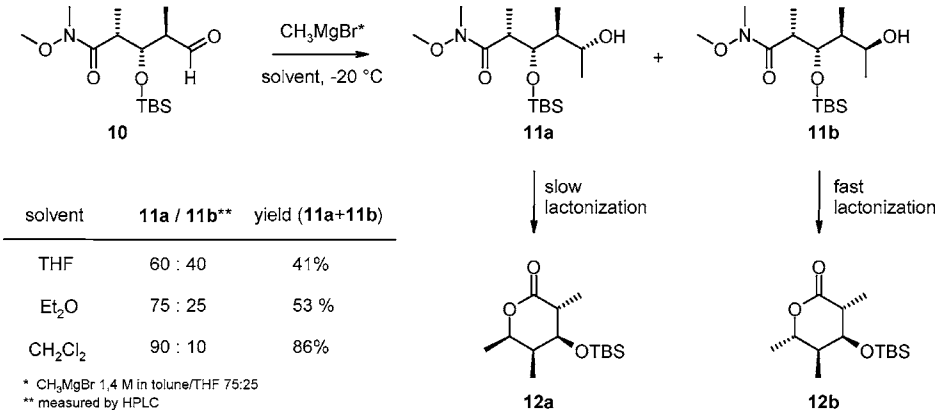
Scheme 3. **Solvent dependence of the Grignard reaction**



solvent	**11a / 11b****	yield (**11a+11b**)
THF	60 : 40	41%
Et_2O	75 : 25	53 %
CH_2Cl_2	90 : 10	86%

* CH_3MgBr 1,4 M in toluene/THF 75:25
** measured by HPLC

lactone **2a**, providing the Weinreb amide **9**,[13] followed by Parikh−Doering oxidation[14] to afford the aldehyde **10**. Reaction with a methyl Grignard reagent produced secondary alcohol **11** as a mixture of diastereomers. Subsequent oxidation yielded the methyl ketone **4** (C_1−C_6 subunit).

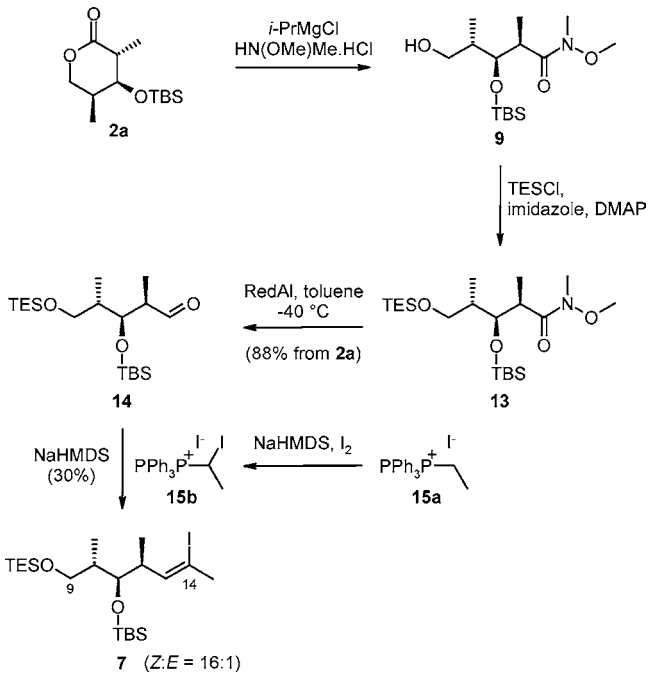
The Grignard reaction run initially in THF was troublesome due to the propensity of the secondary alcohol **11** for lactonization, resulting in poor yields of desired material (Scheme 3). The diastereoselectivity observed for the addition of methylmagnesium bromide onto aldehyde **10** was 60:40, as measured from the reaction mixture by HPLC at the end of reagent addition. Interestingly, whereas the minor diastereomer lactonized rapidly to **12b** upon work-up, the major diastereomer proved to be much more stable, converting slowly to **12a** after isolation. Assignment of the structures of **12a** and **12b** allowed the determination of the stereochemical outcome of the Grignard addition. Thus, the major diastereomer **11a** was the expected Felkin−Ahn product. The slow lactonization of **11a** was exploited to our advantage. Indeed, the Felkin−Ahn selectivity of the Grignard reaction was solvent dependent. It increased to 75:25 when switching from THF to Et_2O and to 90:10 in CH_2Cl_2. Accordingly, when the Grignard reaction was performed in CH_2Cl_2, the secondary alcohol was isolated in 86% yield as a mixture of diastereomers consisting predominantly of **11a**. In practice, the crude reaction mixture was not purified but oxidized directly to give **4**.

Overall, the synthesis of the C_1−C_6 methyl ketone **4** was completed in four steps and 68% yield to provide multigram quantities when required.

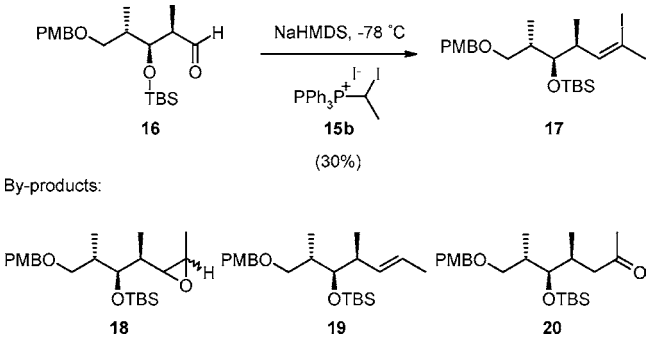
Synthesis of the C_9−C_{14} Subunit 7. The second key subunit **7** was accessed utilizing the alcohol **9** (Scheme 4). TES protection followed by reduction of the Weinreb amide with RedAl in toluene at −40 °C afforded **14**, the substrate for the olefination step utilizing the Zhao protocol,[15] also used by Smith[5] and Marshall.[7b] The desired (*Z*)-vinyl olefin **7** was obtained in 30% yield after chromatographic purification. Only small amounts of the undesired trans isomer were detected (*Z*:*E* = 16:1).

This olefination step, which allows concise access to **7**, was one of the most challenging reactions in terms of

Scheme 4. **Synthesis of C_9−C_{14} subunit 7**



Scheme 5. **Zhao-olefination in the phase I Novartis synthesis of discodermolide**



reproducibility and scale-up. We were exposed for the first time to the Zhao Wittig reaction during the synthesis of intermediate **17**, in the campaign providing discodermolide for phase I clinical trials at Novartis (Scheme 5).[10b] We consistently obtained a 25−35% yield on a lab scale. In addition to the expected olefin **17**, the reaction of **15b** with **16** afforded the cis epoxide **18** as a major byproduct.[16] Difficult work-up and instability of **17** also contributed to

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(14) Parikh, J. R.; Doering, W. v. E. *J. Am. Chem. Soc.* **1967**, *89*, 5505.
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the low yield. Moreover, the *Z*:*E* selectivity was poorly reproducible, ranging from 6:1 to up to 17:1. Reaction parameters were screened and alternative approaches were investigated to minimize the formation of **18**, with limited success. Replacing BuLi, used in the original procedure to deprotonate ethyltriphenylphosphonium iodide, by NaHMDS did improve the yield by a moderate percentage. Addition of TMEDA had no effect. A protocol developed by Shen, where the initially formed betaine intermediate is deprotonated with a second equivalent of base and then iodinated led to the des-iodo olefin **19**.[17]

However, while investigating the process, we found that the quenching and the work-up had a profound effect on the *Z*:*E* ratio of **17**. With a methanol quench and an aqueous work-up, the reaction product was isolated as a mixture of (*Z*) and (*E*) isomers in an irreproducible ratio ranging from 6:1 to 17:1. When the reaction mixture was quenched, using no more than a stoichiometric amount of aqueous saturated ammonium chloride, followed by a nonaqueous work-up, **17** was reproducibly obtained in 28−30% yield with a high *Z*:*E* ratio of 16:1 to 19:1. The formation of ketone **20**, another byproduct in the process,[16] was completely suppressed under these conditions. This optimized protocol was applied to our benefit for the olefination of aldehyde **14** delivering the C_9−C_{14} subunit **7** in 26% yield from **2a**.

Synthesis of the C_{15}−C_{24} Subunit 8. Synthesis of the third key subunit started with the ring opening of lactone **2b**, giving **21**, which underwent Parikh−Doering oxidation to aldehyde **22**, the substrate for the installation of the terminal *(Z)*-diene moiety. Following the methodology developed by Paterson and co-workers,[18] this was introduced efficiently by Nozaki−Hiyama allylation[19] and subsequent Peterson-type elimination.[20] Addition of aldehyde **22** and 1-bromo-1-trimethylsilyl-2-propene (**23**) to chromium (II) chloride in THF followed by direct treatment with KH, afforded the requisite (*Z*)-diene **25** exclusively in 77% yield over three steps. Subsequent conversion of the Weinreb amide functionality with DIBAL-H gave aldehyde **26**, setting the stage for a diastereoselective syn boron aldol. Thus, treatment of **26** with the in situ generated boron enolate of the D-phenylalanine-derived Evans auxiliary **27** gave the aldol product **28** as a single diastereomer in 85% yield.[21] TBS protection of the newly created hydroxyl group, followed by a two-step reductive removal of the Evans auxiliary via the thiobenzyl ester **30** provided alcohol **31**.[22] Conversion of the primary hydroxyl to the iodide via the Karady/Seebach protocol completed the synthesis of **8**.[23] In summary, the C_{15}−C_{24} subunit **8** was synthesized from **2b** in 34% yield over nine steps (Scheme 6).

C_{14}−C_{15} Suzuki Cross-Coupling. The key C_{14}−C_{15} bond construction was now addressed. We initially examined the reported fragment connections in the C_{13}−C_{18} region, compatible with the utilization of a common precursor strategy (Figure 2). Among several alternatives, the palladium-catalyzed cross-couplings pioneered by Smith and Marshall at C_{14}−C_{15} appeared to be reasonably practical and prone to scaling-up.

We investigated first the variation of the Negishi coupling[24] as described by Smith (Scheme 7).[5c] While the yield was satisfactory (up to 55%), this process produced several side products, including des-iodo compounds **33** and **34**, which were not easily separable from the desired product **32**. Whereas **33**, the classical byproduct of lithiation of an alkyl iodide with *t*-BuLi was expected at the outset of our investigations,[25a,b] the presence of **34** in the reaction mixture after work-up was more problematical. It appeared that a quantity of organolithium species derived from the three equivalents of *t*-BuLi necessary to generate the reactive organozinc intermediate was occasionally carried over in the palladium-catalysed coupling reaction where it triggered a partial des-iodination of **7** through lithium−iodine exchange.[25c] The inherent sensitivity of the Negishi coupling to moisture and air was also a problem. Consequently, we felt that switching to the Suzuki reaction, notorious for its tolerance to water and air, could present some advantages.

Marshall described a Suzuki-type cross-coupling step in his approach to discodermolide.[7b,26] Employing his protocol for our coupling reaction, [**8**/*t*-BuLi/9-methoxy-9-borabicyclo-[3,3,1]nonane (9-MeOBBN) added to **7**/K_3PO_4/Pd(dppf)Cl_2] resulted in a much cleaner reaction mixture and provided **32** in up to 65% yield. The only byproduct generated was the des-iodo compound **33**. Some C_{13}−C_{14} trans isomer of **32**, carried over from the trans impurity in **7**, was also observed but could be easily separated by chromatography in the next step. However, whereas the Smith procedure called for an efficient 1:1.15 ratio of educts **7** and **8**, the Suzuki coupling as practiced by Marshall utilized a 1:2.20 ratio making it a costly alternative in terms of consumption of the elaborate building block **8**. Reducing the equivalents of **8** to less than two, while keeping the other reaction parameters unchanged, resulted in significantly lower yields.

To improve the efficiency of the Suzuki procedure in terms of the amounts of **8** necessary, we investigated the process (Scheme 8), concentrating our efforts on two main aspects: the generation of the organoborane intermediate and

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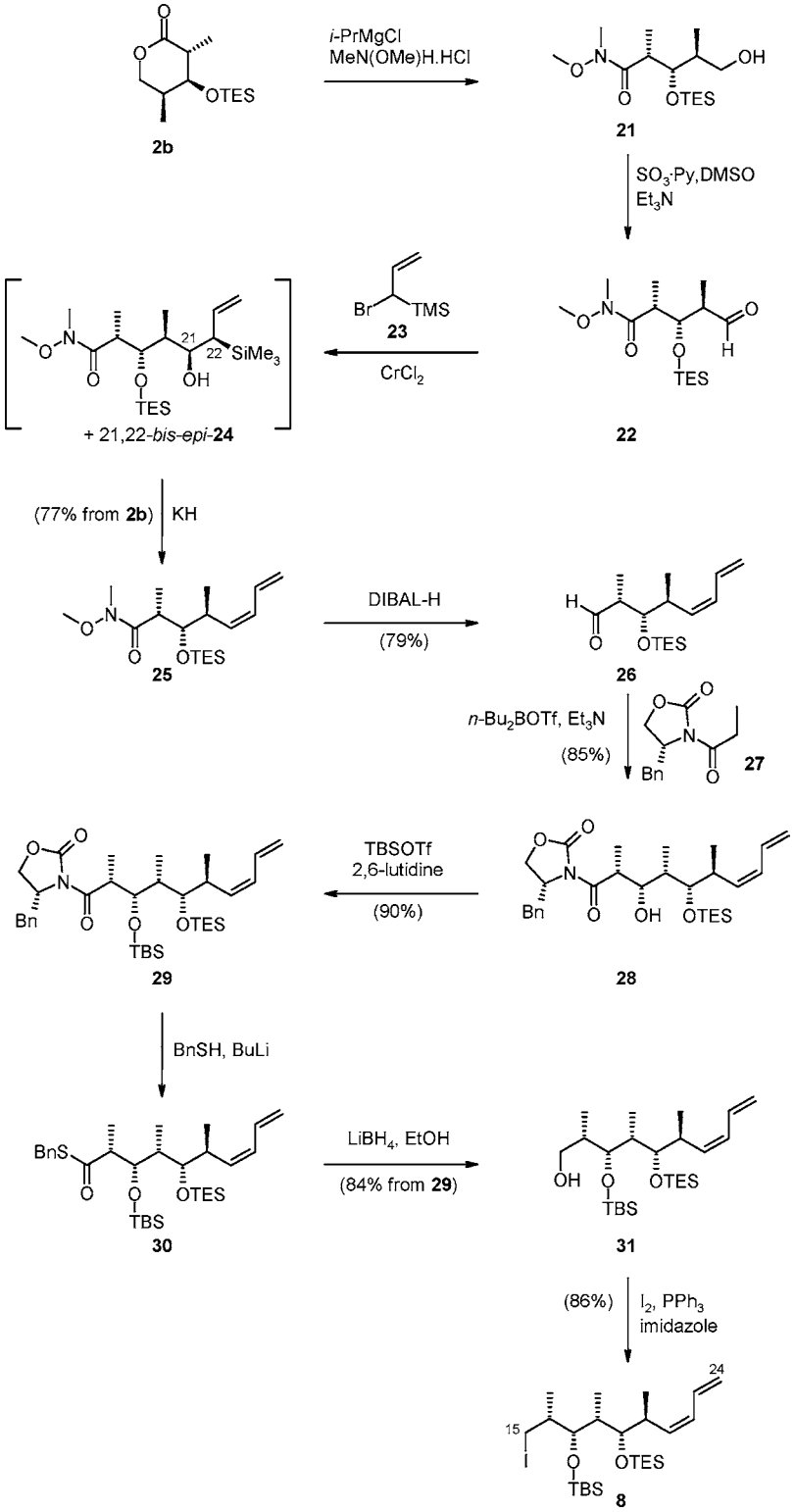
Scheme 6. **Synthesis of $C_{15}-C_{24}$ subunit 8**



the Suzuki coupling itself. Iodide **8** is consumed by *t*-BuLi through two pathways: a productive one leading to the methoxyborate **36**, which is the reactive alkyl donor in the subsequent coupling step, and an unproductive one affording des-iodo **33** (Scheme 9).[25a,b] The latter pathway is an unavoidable consequence of the use of *t*-BuLi in the lithium−iodine exchange protocol and accounts for 2−10% of the material balance on a gram scale. On a larger scale, however, with longer times for reagent transfer, generation of **33** becomes more important. We anticipated that limitation of **33** might be possible by inversion of the order of addition of reagents, that is by treatment of the solution of **8** with pre-cooled *t*-BuLi. Being able to monitor the generation of **36** against **33** in the process was a prerequisite, and a control procedure was developed. Thus, after addition of 9-MeOBBN to the reaction mixture, a sample was collected and treated with H_2O_2/THF/EtOH/pH 7 buffer, which quantitatively oxidized **36** to the alcohol **31**, while having no effect on the

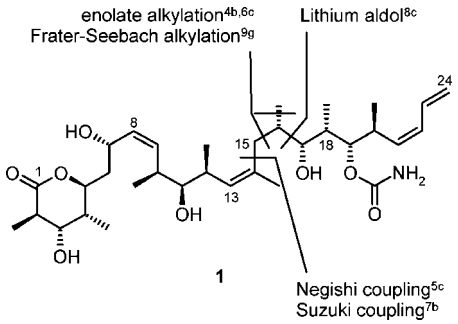


Figure 2. **Strategic fragment connections in the $C_{13}-C_{18}$ region in total syntheses of discodermolide.**

undesired **33**. HPLC analysis of the mixture of **31** and **33** provided the ratio between the desired and the undesired consumption pathways of iodide **8** prior to cross-coupling. This control showed that, on a multigram scale, the ratio **31**/**33** increased from 75:25 to 94:6 upon reversal of the order of addition of **8** and *t*-BuLi.

The presence of THF is also of paramount importance for the overall efficacy of the Suzuki reaction. Indeed, during the warm-up to room temperature, this solvent stabilizes the "ate" complex **36**, which is the reactive alkyl donor in the coupling process (Scheme 8).[27] In the absence of THF, **36** decomposes to the poorly reactive borane **37**, diverting a significant amount of **36** from the productive pathway. Dioxane was found to have the same stabilizing effect, but not the other commonly used ethers such as dibutyl ether or TBME. Finally, the quality of 9-MeOBBN played also a role, and best results were obtained using freshly distilled reagent.[28] A slight excess of this reagent was used to quench any excess of *t*-BuLi (deleterious for vinyl iodide **7** in the subsequent coupling reaction).

We next turned our attention to the Suzuki coupling itself. The mild reaction medium was beneficial to the sensitive vinyl iodide **7**. Changing the base from K_3PO_4 to the more reactive Cs_2CO_3 dramatically accelerated the reaction.[29] Completion was reached within less than 1 h, with a reduced catalyst loading of 4 mol % instead of the 10 mol % used initially.

Overall, these modifications improved greatly the efficacy of the Suzuki process. The reaction was rapid and clean. The stoichiometry of **8** was reduced to 1.2 equiv, and the yield increased to 81% (from **7**). The work-up was also simplified, and the overall process could be easily reproduced on a larger scale.

Completion of the Synthesis. TES deprotection of **32** afforded the diol **38**, which was converted to the C_7-C_{24} aldehyde **39** using procedures described by Paterson and co-workers (Scheme 10). Completion of the total synthesis of **1** using intermediates **39** and **4** has been reported elsewhere.[10d,e]

(27) (a) Fürstner, A.; Seidel, G. *Tetrahedron* **1995**, *41*, 11165. (b) Aliprantis, A. O.; Canary, J. W. *J. Am. Chem. Soc.* **1994**, *116*, 6985. (c) Smith, G. B.; Dezeny, G. C.; Hughes, D. L.; King, A. O.; Verhoeven, T. R. *J. Org. Chem.* **1994**, *59*, 8151.

(28) 9-MeOBBN is readily prepared from 9-H-9-BBN dimer and MeOH, see: Brown, H. C.; Knights, E. F.; Scouten, C. G. *J. Am. Chem. Soc.* **1974**, *96*, 7765.

(29) Harris, C. R.; Danishefsky, S. J. *J. Org. Chem.* **1999**, *64*, 8434.

Conclusions

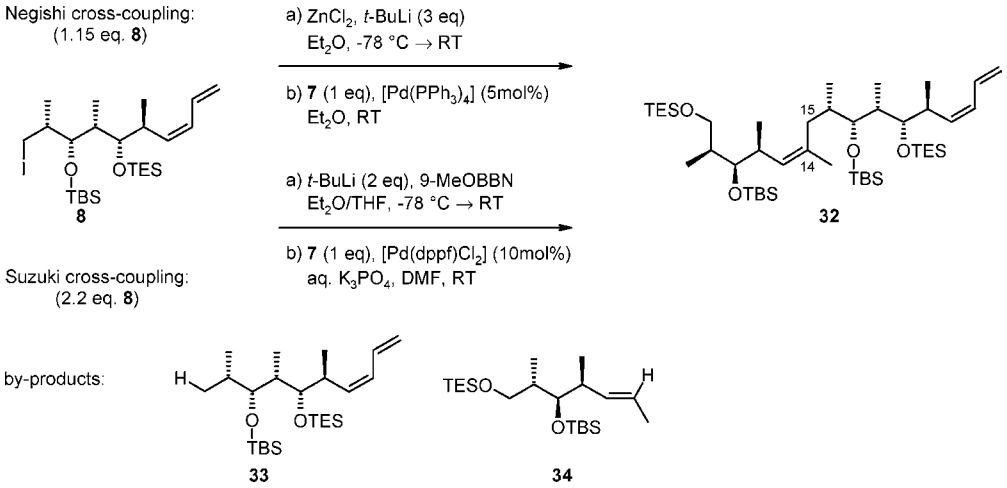
We have described a highly convergent and practical formal synthesis of (+)-discodermolide **1** that features *Z*:*E* selectivity improvements in the Zhao olefination procedure and increase in the efficiency of the key Suzuki cross-coupling. This route proceeds in 24 linear steps, with 35 steps in total. This approach substantially reduces the total number of steps required to complete discodermolide, by utilizing the lactone **2a**/**b** as a building block for the synthesis of the three key subunits **4**, **7**, and **8**.

Experimental Section

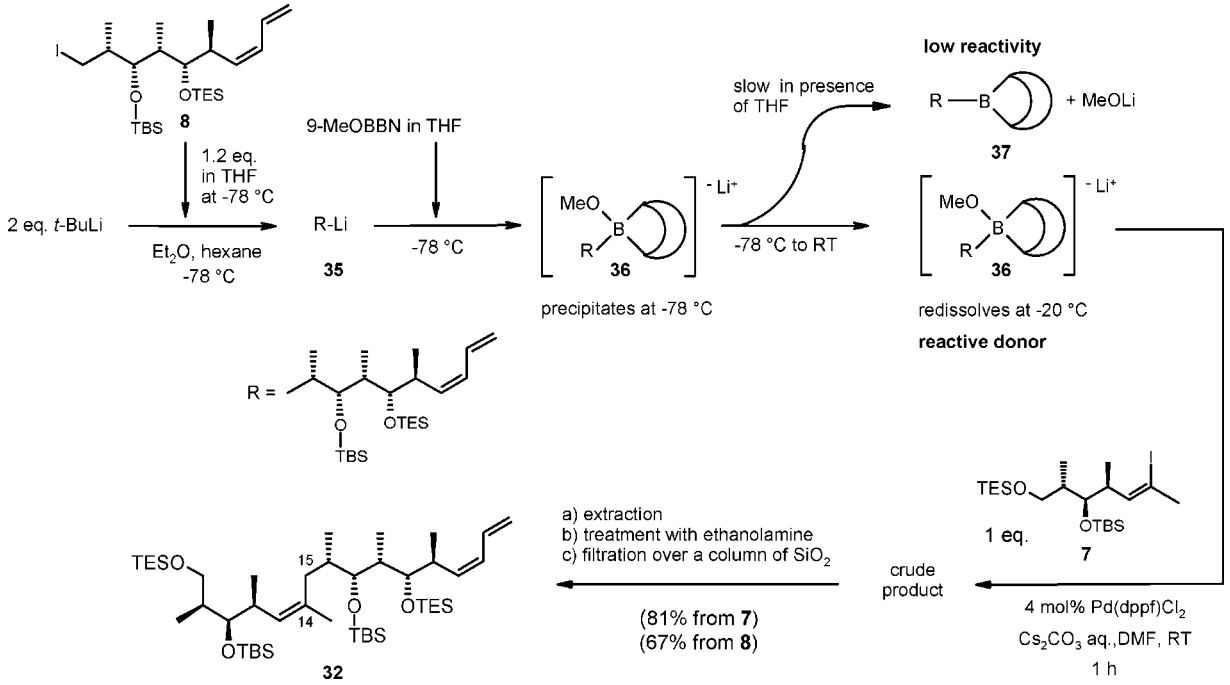
(2*R*,3*S*,4*S*)-3-(*tert*-Butyldimethyl-silanyloxy)-5-hydroxy-2,4-dimethyl-pentanoic Acid Methoxymethylamide (9). A solution of **2a** (1.80 g, 6.96 mmol) in THF (23 mL) at 23 °C under an atmosphere of argon was treated with *N*,*O*-dimethylhydroxylamine hydrochloride (1.05 g, 10.79 mmol), and the resulting suspension was cooled at −15 °C. A solution of isopropylmagnesium chloride in THF (2 M, 10.5 mL, 20.9 mmol) was added dropwise over a period of 40 min (exothermic), after which the reaction mixture became a clear gray-colored solution, which was further stirred between −15 and −10 °C for 1 h and 20 min before being worked up by dilution with TBME (20 mL) followed by addition of 1:1 v/v mixture of saturated aqueous NH_4Cl and water (40 mL). The mixture was allowed to warm-up at 23 °C and stirred until the salts had dissolved. The layers were separated, and the aqueous layer was extracted with TBME (15 mL). The organic extracts were washed with saturated aqueous NaCl (3 × 25 mL), combined, dried ($MgSO_4$), and concentrated in vacuo to give the crude alcohol **9** (2.18 g, 98%) as colorless crystals, which did not require further purification. Mp 28.9−29.8 °C; $R_f = 0.18$ (SiO_2, 1:1 heptane/AcOEt); ^{1}H NMR (DMSO, 500 MHz, 300 K): δ 4.29 (dd, $J = 5.1$, 4.7. Hz, 1H), 3.87 (dd, $J = 5.5$, 5.2 Hz, 1H), 3.67 (s, 3H), 3.46 (m, 1H), 3.16−3.07 (m, 1H), 3.07 (s, 3H), 3.08−2.97 (br m, 1H), 1.70−1.59 (br m, 1H), 0.99 (d, $J =$ 6.9 Hz, 3H), 0.89 (d, $J = 7.0$ Hz, 3H), 0.88 (s, 9H,), 0.04 (s, 3H), −0.01 (s, 3H); ^{13}C NMR (DMSO-d_6 125 MHz, 300 K): δ 175.3, 74.7, 62.5, 61.1, 41.0, 37.9, 31.8, 26.0, 18.1, 14.1, 13.4, −4.1, −4.2; IR (film): ν_{max} 3450m, 2956s, 2938s, 2885m, 2857m, 1634m, 1463m, 1386m, 1255s, 1102m, 1073m, 1050m, 1004m, 869m, 837s, 775s cm^{-1}; MS (ES^+) *m*/*z* (%) 661 (40, $[2\ M + Na]^+$), 499 (23, $[3\ M + Ca]^{2+}$), 491 (8, $[3\ M + Na + H]^{2+}$), 342 (100, $[M + Na]^+$), 320 (57, $[M + H]^+$).

(2*R*,3*S*,4*R*)-3-(*tert*-Butyldimethyl-silanyloxy)-2,4-dimethyl-5-oxo-pentanoic Acid Methoxymethylamide (10). A solution of crude **9** (2.18 g, 6.8 mmol) in CH_2Cl_2 (6.5 mL) at 0 °C under an atmosphere of argon was treated sequentially with triethylamine (3.8 mL, 27.3 mmol), DMSO (2.4 mL), and a solution of sulfur trioxide·pyridine complex (3.26 g, 20.5 mmol) in DMSO (11.2 mL), which was added dropwise over a period of 10 min (exothermic). After stirring at 0 °C for 1 h and 30 min, the reaction mixture was diluted with TBME (50 mL) and worked up. A mixture of aqueous $NaHSO_4$ (1 M, 25 mL) and H_2O (7 mL) was added dropwise at 0 °C over a period of 5 min (exothermic, ice−salt cooling bath), and the resulting mixture was stirred for 10 min. The

Scheme 7. **Palladium-catalyzed $C_{14}-C_{15}$ bond formations**



Scheme 8. **$C_{14}-C_{15}$ Suzuki cross-coupling process**

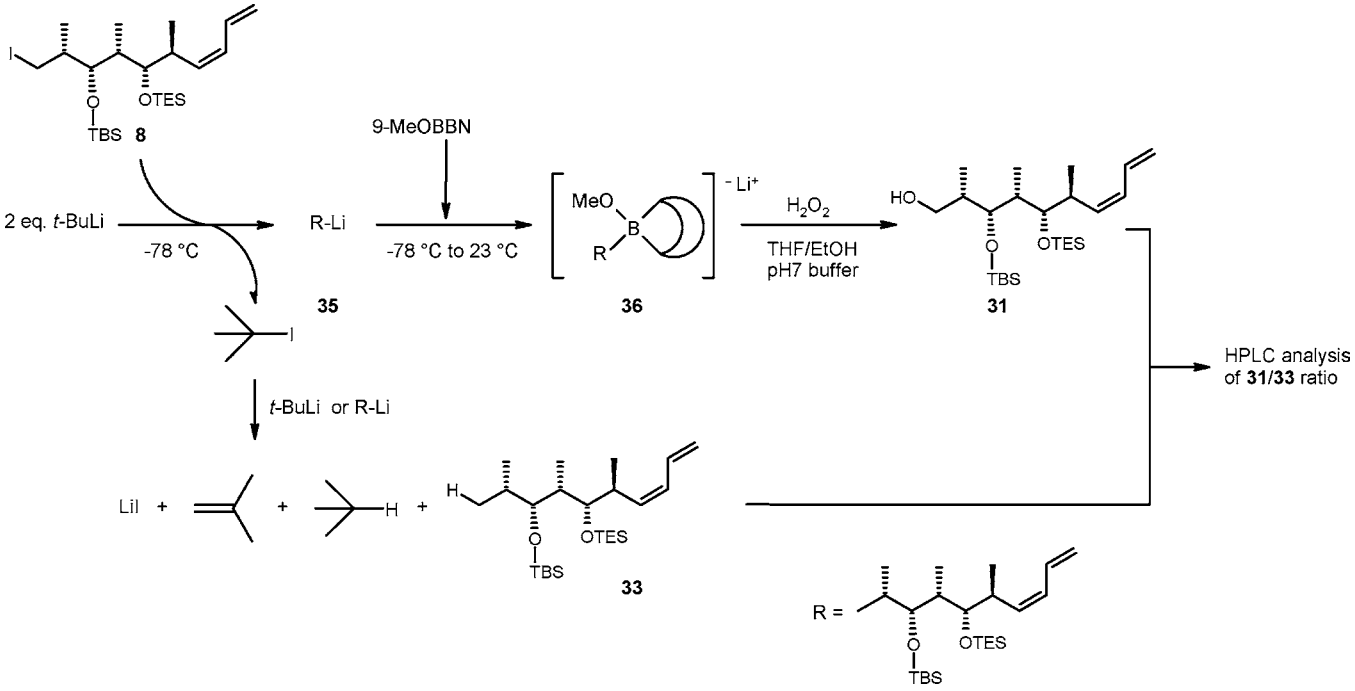


layers were separated, and the aqueous layer was extracted with TBME (50 mL). The organic extracts were washed with aqueous $NaHCO_3$ (8% m/m solution, 40 mL) and saturated aqueous NaCl (60 mL) and were combined, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by flash chromatography (100 g of SiO_2, 3:1 hexane/AcOEt) to give the aldehyde **10** as a pale yellowish oil (1.82 g, 84%), which crystallized upon conservation at 4 °C. $R_f = 0.32$ (SiO_2, 6:4 heptane/AcOEt); ^{1}H NMR (DMSO, 500 MHz, 300 K): δ 9.58 (d, $J = 1.2$ Hz, 1H), 4.21 (dd, $J = 7.6$, 3.6 Hz, 1H), 3.68 (s, 3H), 3.14−3.03 (dq, $J = 7.6$, 6.9 Hz, 1H), 3.04 (s, 3H), 2.52 (qdd, $J = 7.0$, 3.6, 1.2 Hz, 1H), 1.08 (d, $J = 6.9$ Hz, 3H), 0.99 (d, $J = 7.0$ Hz, 3H), 0.85 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (DMSO-d_6 125 MHz, 300 K): δ 202.6, 174.3, 74.1, 61.4, 51.3, 38.4, 31.7, 26.0, 17.8, 14.3, 9.6, −4.41, −4.45; IR (KBr): ν_{max} 2956m, 2937m, 2743w, 1719m, 1645s, 1470m, 1461m, 1470m, 1464m, 1386m, 1258m, 1102m, 1083m, 1065m, 988m, 865m, 839s, 776s cm^{-1}; MS (ES$^+$) *m*/*z* (%) 657 (4, [2 M + Na]$^+$), 496 (8, [3 M + Ca]$^{2+}$), 340 (100, [M + Na]$^+$), 337 (12, [2 M + Ca]$^{2+}$), 318 (10, [M + H]$^+$).

(2*R*,3*S*,4*R*)-3-(*tert*-Butyldimethyl-silanyloxy)-5-hydroxy-2,4-dimethylhexanoic Acid Methoxymethylamide (11). The aldehyde **10** (1.40 g, 4.20 mmol) was dissolved in CH_2Cl_2 (15 mL) and cooled to −20 °C. A solution of methylmagnesium bromide (5.3 mL, 1.4 M in toluene/THF 75:25, 7.4 mmol) was added dropwise, maintaining the temperature at −20 °C. The reaction mixture was quenched with 10% aqueous solution of NH_4Cl (50 mL) and allowed to warm to 5 °C. The CH_2Cl_2 phase was separated and washed with water (2 × 10 mL). The solvent was concentrated in vacuo to give 1.62 g of crude alcohol **11** as an oil, which was used without further purification. HPLC in process control (Nucleosil 100−5 CIB AB CC250 4 mm; H_2O/CH_3CN 80:20−0:100 gradient, 1.0 mL/min, oven 60 °C, detection 210 nm): **11b**: 20.5 min, **10**: 22.0 min, **11a**: 22.9 min.

(2*R*,3*S*,4*R*)-3-(*tert*-Butyldimethyl-silanyloxy)-2,4-dimethyl-5-oxo-hexanoic Acid Methoxymethylamide (4). The

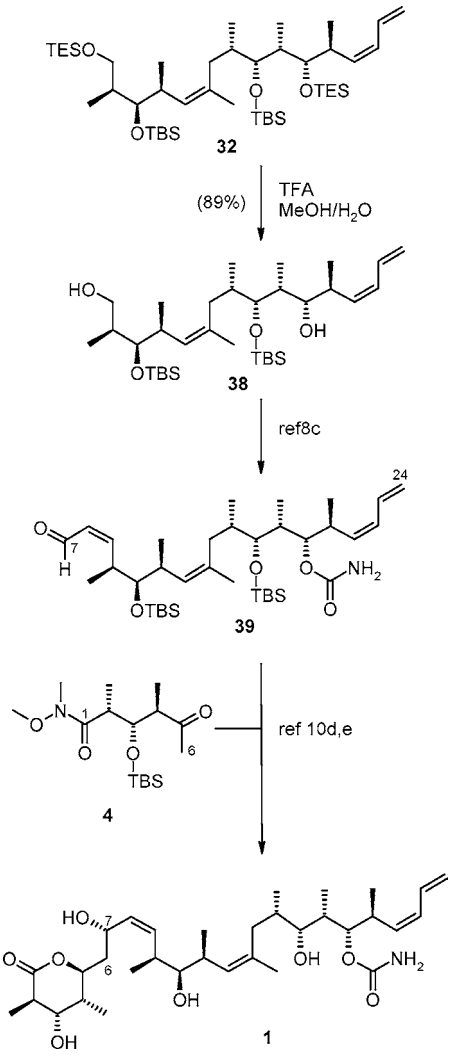
Scheme 9. **Control procedure for the generation of 36**



crude alcohol **11** (1.35 g) was dissolved in CH_2Cl_2 (4 mL) and cooled to 0 °C. Triethylamine (3.0 mL, 22 mmol) and DMSO (1.6 mL) were added. The mixture was cooled to −20 °C and a solution of sulfur trioxide·pyridine complex (2.73 g, 17.2 mmol) in DMSO (8 mL) was added dropwise. The mixture was warmed to 0 °C and stirred for an additional 2 h. The mixture was diluted with TBME (30 mL) and treated with a solution of $NaHSO_4$ (1.9 g) in water (20 mL). The organic phase was separated and washed sequentially with aqueous saturated $NaHCO_3$ (20 mL) and H_2O (20 mL). The solvents were removed in vacuo to give crude **4** as an oil. Purification by chromatography (SiO_2, 10:1 hexane/TBME) gave 1.10 g (82% yield from **10**) of pure compound **4** as a colorless oil. R_f = 0.50, (SiO_2, 20% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.28 (dd, J = 7.8, 4.1, 1H), 3.67 (s, 3H), 3.10−2.93 (br m, 4H), 1.09 (d, J = 6.8, 3H), 1.03 (d, J = 6.9, 3H), 0.86 (s, 9H), 0.06 (s, 6H);^{13}C NMR ($CDCl_3$, 125 MHz, 300 K): δ 210.2, 76.6, 74.1, 61.3, 53.3, 38.2, 30.2, 26.0, 18.2, 14.8, 14.2, 11.0, −4.2, −4.4. IR (neat): ν_{max} 2956, 2931, 2857, 1713, 1658 cm^{-1}.

(2*R*,3*S*,4*S*)-3-(*tert*-Butyldimethyl-silanyloxy)-2,4-dimethyl-5-triethyl-silanyloxypentanoic Acid Methoxymethyl-amide (13). A slightly turbid solution of crude **9** (39.90 g, 125 mmol), imidazole (9.6 g, 141 mmol), and DMAP (1.45 g, 12 mmol) in DMF (110 mL) at 0 °C under an atmosphere of argon was treated dropwise over a period of 20 min with TESCl (19.2 g, 127 mmol). After stirring at 23 °C for 3 h, the reaction mixture was poured in H_2O (200 mL). Concentrated HCl (5 mL) was added followed by hexane (250 mL). The layers were separated, and the aqueous layer was extracted with hexane (200 mL). The organic extracts were washed with 0.1 N aqueous HCl (150 mL) and saturated aqueous $NaHCO_3$ (150 mL) and were combined, dried ($MgSO_4$), and concentrated in vacuo to give the crude bis-silyl ether **13** (50 g) as a pale yellowish oil, which did not

Scheme 10. **Completion of the synthesis following published procedures**



require further purification. R_f = 0.39 (SiO_2, 3:1 hexane/AcOEt); ^{1}H NMR (DMSO-d_6, 400 MHz, 300 K): δ 3.86 (t, J = 5.4 Hz, 1H), 3.66 (dd, J = 9.6, 4.6 Hz, 1H), 3.65 (s, 3H), 3.27 (dd, J = 9.6, 8.6 Hz, 1H), 3.06 (s, 3H), 3.05−2.95 (br m, 1H), 1.72−1.61 (br m, 1H), 0.99 (d, J = 6.9 Hz, 3H), 0.900 (d, J = 6.8 Hz, 3H), 0.898 (t, J = 7.9 Hz, 9H), 0.86 (s, 9H), 0.53 (q, J = 7.9 Hz, 6H), 0.02 (s, 3H), −0.02 (s, 3H); ^{13}C NMR (DMSO-d_6, 125 MHz, 300 K): δ 74.5, 64.1, 61.0, 40.9, 38.1, 32.0, 26.0, 18.0, 14.1, 12.9, 6.7, 4.0, −4.16, −4.23; MS (ES$^+$) m/z (%) 889 (10, [2 M + Na]$^+$), 456 (95, [M + Na]$^+$), 434 (100, [M + H]$^+$).

(2*R*,3*S*,4*S*)-3-(*tert*-Butyldimethyl-silanyloxy)-2,4-dimethyl-5-triethyl-silanyloxypentanal (14). A solution of Red-Al (3.5 M in toluene, 13.2 mL, 46 mmol) in toluene (30 mL) at −40 °C under an atmosphere of argon was treated dropwise over a period of 20 min with a solution of **13** (10.0 g, 23 mmol) in toluene (30 mL). After stirring at −40 °C for 1 h and 15 min, the reaction was quenched by adding dropwise over a period of 15 min saturated aqueous potassium sodium tartrate (50 mL). The resultant mixture was stirred for 3 h at 23 °C. The layers were separated, and the aqueous layer was extracted with toluene (30 mL). The organic extracts were washed with saturated aqueous $NaHCO_3$ (50 mL) and H_2O (2 × 50 mL) and were combined, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by filtration (80 g of SiO_2, 9.5 × 3 cm, elution with 2 L of 100:1.5 hexane/AcOEt) to give the aldehyde **14** (7.56 g, 88% over three steps based on **2a**) as a colorless oil. R_f = 0.75 (SiO_2, 3:1 hexane/AcOEt); ^{1}H NMR (DMSO-d_6, 400 MHz, 300 K): δ 9.63 (s, 1H), 4.22 (dd, J = 7.4, 2.4 Hz, 1H), 3.65 (dd, J = 9.8, 4.7 Hz, 1H), 3.44 (dd, J = 9.8, 6.8 Hz, 1H), 2.56 (qd, J = 6.9, 2.4 Hz, 1H), 1.75 (d quint d, J = 7.4, 6.8, 4.7 Hz, 1H), 0.97 (d, J = 6.9 Hz, 3H), 0.91 (t, J = 7.9 Hz, 9H), 0.87 (d, J = 6.8 Hz, 3H), 0.81 (s, 9H), 0.55 (q, J = 7.9 Hz, 6H), 0.04 (s, 3H), −0.08 (s, 3H);^{13}C NMR (DMSO-d_6, 125 MHz, 300 K): δ 205.3, 71.3, 64.2, 49.2, 40.0, 25.8, 18.0, 13.8, 6.9, 6.8, 4.0, −4.2, −4.4; IR (film): ν_{max} 2957s, 2937s, 2878s, 2859s, 2710w, 1729s, 1472m, 1463m, 1389w, 1253m, 1091s, 1030s, 837s, 813m, 776s, 744s cm^{-1}; MS (EI) m/z (%) 345 (5, [M − C_2H_5]$^+$), 317 (19, [M − C_4H_9]$^+$), 145 (100, [Et_3SiOCH_2]$^+$).

(*Z*)-(4*S*,5*R*,6*S*)-5-(*tert*-Butyldimethyl-silanyloxy)-2-iodo-4,6-dimethyl-7-triethyl-silanyloxyhept-2-ene (7). A suspension of ethyltriphenylphosphonium iodide **15a** (10.06 g, 24.0 mmol) in THF (100 mL) at 23 °C under an atmosphere of argon was treated dropwise with NaHMDS (2 M in THF, 12.5 mL, 25 mmol) after which the suspension immediately developed an intense orange color and dissolved gradually. After stirring at 23 °C for 30 min, the resulting deep-orange solution was added dropwise to a solution of iodine (6.05 g, 24.0 mmol) in THF (200 mL) at −78 °C over a period of 1 h and 15 min. (1-Iodoethyl)-triphenylphosphonium iodide **15b** precipitated as a brown solid. After stirring the resulting suspension at −78 °C for 15 min, NaHMDS (2 M in THF, 12.0 mL, 24.0 mmol) was added dropwise at −78 °C within 10 min, after which the reaction mixture cleared gradually to become a red solution. After stirring at −78 °C for 30 min, a solution of **13** (5.00 g, 13.3 mmol) in THF (15 mL) was added at −78 °C within 5 min. The resulting reaction mixture was stirred for 1 h and 30 min at −78 °C. Triphenylphosphine oxide precipitated gradually. Thereupon the reaction mixture was allowed to warm to −20 °C and was quenched with saturated aqueous NH_4Cl (1.10 mL). The beige suspension was partially concentrated under reduced pressure (300 mL of distillate). Heptane (100 mL) was added and the suspension was concentrated again under reduced pressure (100 mL of distillate). The residual suspension was filtrated and the filtercake was washed with 50 mL of heptane. The filtrate was collected and concentrated in vacuo. Purification of the residue by flash chromatography (350 g of SiO_2, 99:1 to 98:2 hexane/AcOEt, gradient) afforded the vinyl iodide **7** contaminated with 6 mol % of the *E*-isomer as a colorless oil (1.82 g, 30%). R_f = 0.77 (SiO_2, 9:1 heptane/AcOEt);^{1}H NMR (DMSO-d_6, 400 MHz, 300 K): δ 5.41 (dd, J = 8.7, 1.3 Hz, 1H), 3.65−3.60 (m, 2H), 3.35 (dd, J = 9.6, 8.2 Hz, 1H), 2.43 (d, J = 1.3 Hz, 3H), 2.45−2.31 (m, 1H), 1.79−1.68 (m, 1H), 0.92 (d, $J \approx$ 7 Hz, 3H), 0.908 (t, J = 7.8 Hz, 9H), 0.909 (d, J = 6.9 Hz, 3H), 0.87 (s, 9H), 0.55 (q, J = 7.8 Hz, 6H), 0.03 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (DMSO-d_6, 125 MHz, 300 K): δ 139.1, 99.6, 75.8, 64.1, 44.1, 40.4, 33.2, 26.0, 18.1, 14.7, 13.9, 6.8, 4.0, −4.01, −4.04; IR (film): ν_{max} 2957s, 2934s, 2877s, 2858m, 1472m, 1462m, 1257m, 1087s, 1022s, 1006s, 860m, 837s, 813m, 774s, 743s cm^{-1}; MS (EI) m/z (%) 513 (100, [M + H]$^+$).

(2*R*,3*S*,4*S*)-3-(*tert*-Butyldimethyl-silanyloxy)-5-hydroxy-2,4-dimethylpentanoic Acid Methoxymethylamide (21). A solution of **2b** (14.21 g) in THF (100 mL) at 23 °C under an atmosphere of argon was treated with *N*,*O*-dimethylhydroxylamine hydrochloride (9.14 g, 94 mmol), and the resulting suspension was cooled at −20 °C. A 2 M solution of isopropylmagnesium chloride in THF (85.5 mL, 171 mmol) was then added dropwise over a period of 30 min (exothermic) after which the reaction mixture became a clear gray-colored solution, which was further stirred at −20 °C for 15 min before being worked up by dilution with TBME (500 mL) followed by addition of 1:1 v/v mixture of saturated aqueous NH_4Cl and water (350 mL). The mixture was allowed to warm to 23 °C and stirred until the salts had dissolved. The layers were separated, and the aqueous layer was extracted with TBME (2 × 250 mL). The organic extracts were washed with saturated aqueous NaCl (2 × 200 mL), combined, dried ($MgSO_4$), and concentrated in vacuo to give the crude alcohol **21** (17.79 g) as a pale yellowish oil, which did not require further purification and was subjected directly to the next step. R_f = 0.24 (SiO_2, 1:1 heptane/AcOEt); MS (ES$^+$) m/z (%) 342 (100, [M + Na]$^+$).

(2*R*,3*S*,4*R*)-2,4-Dimethyl-5-oxo-3-triethyl-silanyloxypentanoic Acid Methoxymethylamide (22). A solution of crude **21** (17.79 g) in CH_2Cl_2 (60 mL) at 0 °C under an atmosphere of argon was treated sequentially with triethylamine (31.0 mL, 223 mmol), DMSO (20 mL), and a solution of sulfur trioxide·pyridine complex (26.6 g, 167 mmol) in DMSO (90 mL), which was added dropwise over a period of 30 min (exothermic). After stirring at 0 °C for 30 min, the reaction mixture was diluted with TBME (500 mL) and worked up. An aqueous solution of $NaHSO_4$ (26 g in 250

mL) was added dropwise at 0 °C over a period of 30 min (exothermic, salt-ice cooling bath). The layers were separated and the aqueous layer was extracted with TBME (2 × 250 mL). The organic extracts were washed with aqueous $NaHCO_3$ (8% m/m solution, 400 mL) and saturated aqueous NaCl (400 mL) and were combined, dried ($MgSO_4$), and concentrated in vacuo to give the crude aldehyde **22** (17.39 g) as a yellowish oil, which did not require further purification. R_f = 0.41 (SiO_2, 1:1 heptane/AcOEt); MS (ES^+) *m*/*z* (%) 657 (80, $[2\ M + Na]^+$), 512 (30, $[3\ M + CH_3OH + Ca]^{2+}$), 496 (36, $[3\ M + Ca]^{2+}$), 340 (100, $[M + Na]^+$), 318 (90, $[M + H]^+$).

(*Z*)-(2*R*,3*S*,4*S*)-2,4-Dimethyl-3-triethyl-silanyloxyocta-5,7-dienoic Acid Methoxymethylamide (25). A green-colored suspension of $CrCl_2$ (32.45 g, 265.8 mmol) in THF (200 mL) (exothermic) at 0 °C under an atmosphere of argon was treated sequentially with a solution of crude **22** (14.07 g, 44.3 mmol) in THF (60 mL, exothermic) and (1-bromo-allyl)-trimethylsilane (**23**) (34.22 g, 177.2 mmol, rinsed with 10 mL of THF), the resultant mixture was stirred at 0 °C for 4 h, at which time it had become a reddish-colored suspension and the reaction was judged complete by TLC. The reaction was then worked up by addition of phosphate buffer (pH 7, 400 mL, exothermic) along with TBME (700 mL). The layers were separated and the aqueous layer was extracted with TBME (2 × 400 mL). The organic extracts were washed with saturated aqueous NaCl (2 × 400 mL), combined, dried ($MgSO_4$), and concentrated in vacuo to give crude intermediate **24** as a green oil (35.59 g). To a suspension of KH (1.95 g, 48.6 mmol, from 5.59 g of a 35% suspension of KH in oil) in THF (80 mL) at 0 °C under an atmosphere of argon was added dropwise over a period of 25 min, **24** dissolved in THF (40 mL). After stirring at 0 °C overnight, the reaction mixture was diluted with hexane (300 mL) and poured onto saturated aqueous NH_4Cl (500 mL) at 0 °C. The pH during the addition was carefully controlled and maintained between 5 and 7 by addition of additional 1 N HCl (33 mL). The layers were then separated, and the aqueous layer was extracted with hexane (2 × 300 mL). The organic extracts were washed with saturated aqueous NaCl (2 × 300 mL), combined, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by flash chromatography (225 g of SiO_2, 9:1 hexane/AcOEt) to give the diene **25** as a pale yellowish oil (11.63 g, 77% over three steps based on **2b**). R_f = 0.36 (SiO_2, 3:1 heptane/AcOEt); ^{1}H NMR (DMSO-d_6, 400 MHz, 300 K): δ 6.49 (dt, J = 16.8, 10.6 Hz, Hz, 1H), 6.03 (t, J = 11.0 Hz, 1H), 5.48 (t, J = 10.6 Hz, 1H), 5.21 (dd, J = 16.8, 1.8 Hz, 1H), 5.13 (br d, J = 10.2 Hz, 1H), 3.86 (dd, J = 7.8, 4.1 Hz, 1H), 3.71−3.62 (m, 1H), 3.61 (s, 3H), 3.07 (s, 3H), 2.83−2.71 (m, 1H), 1.06 (d, J = 7.0 Hz, 3H), 0.97 (t, J = 7.9 Hz, 9H), 0.96 (d, J = 6.8 Hz, 3H), 0.62 (q, J = 7.9 Hz, 6H); ^{13}C NMR (DMSO-d_6, 125 MHz, 300 K): δ 175.1, 133.5, 132.3, 129.6, 117.9, 77.3, 67.0, 60.9, 36.0, 31.8, 18.7, 14.1, 7.0, 5.1; IR (film): ν_{max} 3083w, 2958s, 2912s, 2877s, 2733w, 1661s, 1460s, 1414m, 1383m, 1286w, 1239m, 1122s, 1072s, 1054s, 1000s, 901w, 859m, 840w, 810w, 738m cm^{-1}; MS (ES^+) *m*/*z* (%) 705 (13, $[2\ M + Na]^+$), 532 (27, $[3\ M + Ca]^{2+}$), 364 (49, $[M + Na]^+$), 342 (100, $[M + H]^+$).

(*Z*)-(2*R*,3*S*,4*S*)-2,4-Dimethyl-3-triethyl-silanyloxyocta-5,7-dienal (26). A solution of **25** (5.123 g, 15.0 mmol) in THF (14 mL) at −30 °C under an atmosphere of argon was treated dropwise with a 1.5 M solution of DIBAL-H in toluene (10.5 mL, 15.8 mmol). After stirring at −30 °C for 40 min, the reaction was judged complete by disappearance of the starting material (TLC) and quenched with methanol (3 mL, exothermic). The mixture was then worked up by addition of saturated aqueous potassium sodium tartrate (200 mL) and hexane (200 mL). The layers were separated, and the aqueous layer was extracted with hexane (2 × 100 mL). The organic extracts were washed with saturated aqueous $NaHCO_3$ (2 × 100 mL) and saturated aqueous NaCl (100 mL) and were combined, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by flash chromatography (200 g of SiO_2, 19:1 hexane/AcOEt) to give the aldehyde **26** as a colorless oil (3.347 g, 79%). R_f = 0.61 (SiO_2, 3:1 heptane/AcOEt); ^{1}H NMR (DMSO-d_6, 400 MHz, 300 K): δ 9.66 (s, 1H), 6.57 (dt, J = 16.8, 10.6 Hz, Hz, 1H), 5.99 (t, J = 11.0 Hz, 1H), 5.40 (t, J = 10.6 Hz, 1H), 5.20 (dd, J = 16.8, 1.8 Hz, 1H), 5.12 (br d, J = 10.2 Hz, 1H), 4.09 (dd, J = 5.1, 4.1 Hz, 1H), 2.90−2.80 (m, 1H), 2.58−2.51 (m, 1H, partially obscured by DMSO), 0.99 (d, J = 7.0 Hz, 3H), 0.95 (d, J = 6.8 Hz, 3H), 0.89 (t, J = 7.9 Hz, 9H), 0.55 (q, J = 7.9 Hz, 6H); ^{13}C NMR (DMSO-d_6, 125 MHz, 300 K): δ 204.8, 134.8, 132.8, 130.1, 118.5, 75.4, 50.7, 36.4, 18.7, 8.4, 7.3, 5.3; IR (film): ν_{max} 3086w, 2959s, 2912s, 2877s, 2709w, 1723s, 1463w, 1593w, 1458m, 1414m, 1379m, 1347w, 1239m, 1148m, 1135m, 1108s, 1082s, 1046m, 1018s, 964m, 904m, 852m, 793m, 740s cm^{-1}; MS (EI) *m*/*z* (%) 253 (21, $[M - CHO]^+$), 201 (43, $[M - C_6H_9]^+$), 115 (100, $[Si(CH_2CH_3)_3]^+$).

(*R*)-4′-Benzyl-3′-[(*Z*)-(2*R*,3*S*,4*S*,5*S*,6*S*)-3-hydroxy-2,4,6-trimethyl-5-triethyl-silanyloxydeca-7,9-dienoyl]-oxazolidin-2′-one (28). A solution of (*R*)-4-benzyl-3-propionyloxazolidin-2-one **27** (1.33 g, 5.70 mmol) in CH_2Cl_2 (6.0 mL) at 0 °C under an atmosphere of argon was treated sequentially with *n*-Bu_2BOTf (1 M in CH_2Cl_2, 5.40 mL, 5.40 mmol) and triethylamine (1.00 mL, 7.17 mmol). After stirring at 0 °C for 1 h, the resulting yellow solution was cooled to −78 °C and treated with a solution of **26** (1.13 g, 4.00 mmol) in CH_2Cl_2 (4.0 mL). Thereupon, the reaction solution was stirred successively at −78 °C for 15 min and at 0 °C for 30 min. Phosphate buffer (pH 7, 6.0 mL), MeOH (9.0 mL), and MeOH/35% H_2O_2 (6:1 v/v, 7.0 mL) were then added sequentially at 0 °C. After stirring for 1 h at 0 °C, the resulting biphasic mixture was treated with 40% aqueous $Na_2S_2O_3$ (6.0 mL). The volatiles were removed in vacuo and the residual aqueous phase was diluted with H_2O (20 mL) and extracted with AcOEt (2 × 40 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (20 mL) and saturated aqueous NaCl (20 mL) and were dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification of the residue by flash chromatography (200 g of SiO_2, 9:1 hexane/AcOEt) afforded the aldol product **28** as a colorless oil (1.74 g, 85%). R_f = 0.29 (SiO_2, 3:1 heptane/AcOEt); ^{1}H NMR ($CDCl_3$, 500 MHz, 300 K): δ 7.37−7.22 (m, 5H),

6.65 (dt, $J = 16.8$, 10.6 Hz, 1H), 6.01 (t, $J = 11.0$ Hz, 1H), 5.53 (t, $J = 10.4$ Hz, 1H), 5.21 (dd, $J = 16.8$, 1.8 Hz, 1H), 5.14 (br d, $J = 10.2$ Hz, 1H), 4.68 (ddd, $J = 9.5$, 5.1, 3.2 Hz, 1H), 4.20 (d, $J = 5.1$ Hz, 2H), 4.02−3.93 (m, 2H), 3.68 (t, $J = 4.3$ Hz, 1H), 3.26 (dd, $J = 13.4$, 3.2 Hz, 1H), 2.88 (br dqd, $J = 10.4$, 6.9, 4.3 Hz, 1H), 2.79 (dd, $J = 13.4$, 9.5 Hz, 1H), 2.72 (br s, 1H), 1.78−1.70 (m, 1H), 1.32 (d, $J = 6.5$ Hz, 3H), 1.02 (d, $J = 6.9$ Hz, 3H), 1.00 (d, $J = 7.0$ Hz, 3H), 0.98 (t, $J = 7.9$ Hz, 9H), 0.64 (q, $J = 7.9$ Hz, 6H); ^{13}C NMR (DMSO-d_6, 125 MHz, 300 K): δ 177.1, 152.7, 135.2, 135.1, 132.5, 129.4, 129.3, 128.9, 127.4, 117.4, 78.7, 73.2, 66.1, 55.1, 40.8, 39.6, 37.7, 36.5, 18.8, 13.0, 9.4, 7.0, 5.5; IR (film): ν_{max} 3540m (br), 2959s, 2877s, 1785s, 1695m, 1455m, 1382s, 1352m, 1237m, 1209s, 1110m, 1076m, 1011s, 969m, 737s, 702m cm^{-1}; MS (ES$^+$) *m*/*z* (%) 1053 (40, [2 M + Na]$^+$), 1050 (15, [4 M + Ca]$^{2+}$), 793 (27, [3 M + Ca]$^{2+}$), 785 (13, [3 M + Na + H]$^{2+}$), 538 (100, [M + Na]$^+$), 535 (18, [2 M + Ca]$^{2+}$).

(*R*)-4-Benzyl-3-[(*Z*)-(2*R*,3*S*,4*R*,5*S*,6*S*)-3-(*tert*-butyldimethyl-silanyloxy)-2,4,6-trimethyl-5-triethyl-silanyloxydeca-7,9-dienoyl]-oxazolidin-2-one (29). A solution of **28** (1.74 g, 3.37 mmol) and 2,6-lutidine (1.03 mL, 8.87 mmol) in CH_2Cl_2 (16 mL) at −20 °C under an atmosphere of argon was treated dropwise with TBSOTf (1.83 mL, 8.00 mmol). The resulting reaction mixture was allowed to warm-up at 0 °C within 30 min and was stirred for an additional 2.5 h before being worked up. TBME (50 mL) and 1 N HCl (30 mL) were added sequentially, and the layers were separated. The aqueous layer was extracted with TBME (50 mL). The organic layers were washed with 1 N HCl (30 mL), saturated aqueous $NaHCO_3$ (30 mL), and saturated aqueous NaCl (30 mL) and were combined, dried over $MgSO_4$, and concentrated in vacuo. Purification of the residue by flash chromatography (200 g of SiO_2, 95:5 hexane/AcOEt) afforded the silyl-ether product **29** as a colorless oil (1.91 g, 90%). $R_f = 0.52$ (SiO_2, 3:1 heptane/AcOEt). ^{1}H NMR (DMSO-d_6, 500 MHz, 300 K): δ 7.37−7.19 (m, 5H), 6.71 (m, 1H), 5.99 (t, $J = 11.1$ Hz, 1H), 5.68 (t, $J = 10.2$ Hz, 1H), 5.19 (m, 2H), 4.58 (ddd, $J = 9.8$, 4.7, 3.2 Hz, 1H), 4.13 (d, $J = 4.7$ Hz, 2H), 4.08 (dd, $J = 7.4$, 1.6 Hz, 1H), 4.04 (dq, $J = 7.4$, 6.7 Hz, 1H), 3.59 (dd, $J = 9.0$, 1.3 Hz, 1H), 3.24 (dd, $J = 13.3$, 3.2 Hz, 1H), 2.95 (br dqd, $J = 10.2$, 7.0, 1.3 Hz, 1H), 2.72 (dd, $J = 13.3$, 9.8, Hz, 1H), 1.47−1.39 (m, 1H), 1.24 (d, $J = 6.7$ Hz, 3H), 1.06 (d, $J = 7.0$ Hz, 3H), 1.00 (t, $J = 8.0$ Hz, 9H), 0.97 (s, 9H), 0.95 (d, $J = 6.8$ Hz, 3H), 0.67 (q, $J = 8.0$ Hz, 6H), 0.18 (s, 3H), 0.15 (s, 3H); ^{13}C NMR (DMSO-d_6, 125 MHz, 300 K): δ 175.8, 152.8, 135.4, 133.7, 133.4, 129.4, 128.8, 127.2, 116.5, 72.9, 65.9, 55.4, 43.8, 42.4, 37.7, 35.5, 26.2, 19.5, 18.5, 15.0, 10.9, 7.1, 5.6, −3.4; IR (film): ν_{max} 2957s, 2878s, 1785s, 1697s, 1455m, 1382s, 1210s, 1120s, 1078m, 1048m, 1020s, 969m, 835s, 774m, 739s, 702m cm^{-1}; MS (ES$^+$) *m*/*z* (%) 964 (25, [3 M + Ca]$^{2+}$), 956 (7, [3 M + Na + H]$^{2+}$), 652 (100, [M + Na]$^+$), 649 (38, [2 M + Ca]$^{2+}$).

(*Z*)-(2*R*,3*S*,4*R*,5*S*,6*S*)-3-(*tert*-Butyldimethyl-silanyloxy)-2,4,6-trimethyl-5-triethyl-silanyloxydeca-7,9-dienethioic Acid *S*-Benzyl Ester (30). A solution of benzyl mercaptan (0.80 mL, 6.8 mmol) in THF (20 mL) at 0 °C under an atmosphere of argon was treated dropwise over a period of 15 min with *n*-BuLi (1.6 M in hexanes, 3.12 mL, 5.0 mmol). After stirring at 0 °C for 15 min, a solution of **29** (1.10 g, 1.75 mmol) in THF (10 mL) was added dropwise. Thereupon, the reaction mixture was stirred at 0 °C for 1 h and worked up; 1 N NaOH (40 mL) and TBME (40 mL) were added sequentially, and the layers were separated. The organic layer was washed with 1 N NaOH (40 mL) and saturated aqueous NaCl (2 × 40 mL), dried over $MgSO_4$, and concentrated in vacuo to give the crude thioester **30** (1.28 g) as a gel, which did not require further purification. An analytical sample was obtained by purification with flash chromatography (SiO_2, 95:5 hexane/AcOEt). $R_f = 0.77$ (SiO_2, 9:1 heptane/AcOEt); ^{1}H NMR ($CDCl_3$, 500 MHz, 300 K): δ 7.34−7.23 (m, 5H), 6.64 (dt, $J = 16.8$, 10.6 Hz, 1H), 6.02 (t, $J = 11.0$ Hz, 1H), 5.52 (t, $J = 10.3$ Hz, 1H), 5.22 (d, $J = 16.8$ Hz, 1H), 5.14 (d, $J = 10.2$ Hz, 1H), 4.11 (s, 2H), 4.09 (t, $J = 4.8$ Hz, 1H), 3.58 (dd, $J = 5.9$, 3.6 Hz, 1H), 2.94−2.86 (m, 1H), 2.80−2.88 (m, 1H), 1.73−1.56 (m, 1H), 1.20 (d, $J = 7.0$ Hz, 3H), 1.05 (d, $J = 6.9$ Hz, 3H), 1.01 (t, $J = 8.0$ Hz, 9H), 0.96 (d, $J = 6.9$ Hz, 3H), 0.94 (s, 9H), 0.69 (q, $J = 8.0$ Hz, 6H), 0.10 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (DMSO-d_6, 125 MHz, 300 K): δ 201.2, 137.5, 134.1, 129.4, 128.9, 128.5, 127.1, 117.3, 73.7, 52.8, 41.8, 36.5, 33.2, 26.2, 18.7, 18.5, 12.4, 11.6, 7.1, 5.6, −3.7, −3.8; IR (film): ν_{max} 2957s, 2877s, 2857s, 1789s, 1472m, 1455s, 1252s, 1121s, 1075s, 1006s, 1020s, 958s, 837s, 775s, 738s, 700 m cm^{-1}; MS (ES$^+$) *m*/*z* (%) 561 (13, [M − CH_3]$^+$), 547 (56, [M − C_2H_5]$^+$), 519 (32, [M − C_4H_9]$^+$), 363 (100, [M − $C_{11}H_{23}OSi$]$^+$).

(*Z*)-(2*S*,3*R*,4*R*,5*S*,6*S*)-3-(*tert*-Butyldimethyl-silanyloxy)-2,4,6-trimethyl-5-triethyl-silanyloxydeca-7,9-dien-1-ol (31). To a solution of crude **30** (1.28 g) in THF (20 mL) at 0 °C under an atmosphere of argon were sequentially added $LiBH_4$ (300 mg 14 mmol) and EtOH (0.80 mL, 14 mmol)). The resulting mixture was stirred at 23 °C overnight and then worked up; 1 N NaOH (30 mL) was added. After stirring for 1 h at 23 °C, TBME (40 mL) was added, and the layers were separated. The aqueous layer was extracted with TBME (2 × 40 mL). The organic layers were washed with 1 N NaOH (30 mL) and saturated aqueous NaCl (2 × 40 mL) and were combined, dried over $MgSO_4$, and concentrated in vacuo. Purification of the residue by flash chromatography (200 g of SiO_2, 95:5 hexane/AcOEt) afforded the alcohol **31** as a colorless oil (670 mg, 84% over two steps based on **29**). $R_f = 0.27$ (SiO_2, 9:1 heptane/AcOEt). ^{1}H NMR ($CDCl_3$, 500 MHz, 300 K): δ 6.60 (dt, $J = 16.8$, 10.6 Hz, 1H), 6.04 (t, $J = 11.0$ Hz, 1H), 5.60 (t, $J = 10.4$ Hz, 1H), 5.22 (dd, $J = 16.8$, 1.8 Hz, 1H), 5.14 (d, $J = 10.1$ Hz, 1H), 3.71 (t, $J = 4.1$ Hz, 1H), 3.61 (br dd, $J = 10.6$, 7.0 Hz, 1H), 3.56 (dd, $J = 7.0$, 3.3 Hz, 1H), 3.44 (br dd, $J = 10.6$, 6.4 Hz, 1H), 2.94−2.86 (m, 1H), 1.91−1.82 (m, 1H), 1.72 (br t, 1H), 1.73−1.66 (m, 1H), 1.05 (d, $J = 6.9$ Hz, 3H), 1.00 (t, $J = 8.0$ Hz, 9H), 0.97 (d, $J = 6.9$ Hz, 3H), 0.94 (s, 9H), 0.85 (d, $J = 6.9$ Hz, 3H), 0.67 (q, $J = 8.0$ Hz, 6H), 0.12 (s, 3H), 0.10 (s, 3H); ^{13}C NMR (DMSO-d_6, 125 MHz, 300 K): δ 134.5, 132.4, 129.0, 117.4, 77.8, 73.5, 65.9, 40.7, 40.2, 35.9, 26.1, 19.0, 18.4, 12.2, 11.7, 7.1, 5.7, −3.6, −3.9; IR (film):

ν_{max} 3400br, 2958s, 2878s, 2858s, 1472m, 1462s, 1252s, 1097s, 1076s, 1028s, 970m, 903m, 837s, 810m, 773s, 738s, cm^{-1}; MS (ES^+) *m/z* (%) 427 (11, $[M - C_2H_5]^+$), 399 (10, $[M - C_4H_9]^+$), 373 (8, $[M - C_6H_9]^+$), 243 (100, $[M - C_{11}H_{23}OSi]^+$).

(*Z*)-(5*S*,6*S*,7*R*,8*S*,9*R*)-8-(*tert*-Butyldimethyl-silanyloxy)-10-iodo-5,7,9-trimethyl-6-triethyl-silanyloxydeca-1,3-diene (8). A solution of **31** (553 mg, 1.21 mmol) in ether (25 mL) and acetonitrile (7.5 mL) at 0 °C under an atmosphere of argon was treated with triphenylphosphine (542 mg, 2.07 mmol) and imidazole (124 mg, 1.82 mmol) and the resulting solution was stirred at 0 °C for 15 min. Thereupon, iodine (460 mg, 1.81 mmol) was added, after which a brown precipitate formed immediately. The suspension was stirred at 0 °C for 1 h and then worked up. Aqueous $Na_2S_2O_3$ (10% m/m, 10 mL) was added dropwise over a period of 10 min and the resulting colorless biphasic mixture was stirred for a further 10 min. TBME (100 mL) was then added, and the layers were separated. The organic layer was washed with saturated aqueous NaCl (2 × 25 mL), dried over $MgSO_4$, and concentrated in vacuo. Purification of the residue by flash chromatography (60 g of SiO_2, 98:2 hexane/AcOEt) afforded the alcohol **8** as a pale yellowish oil (686 mg, 86%). R_f = 0.69 (SiO_2, 9:1 heptane/AcOEt); ^{1}H NMR ($CDCl_3$, 500 MHz, 300 K): δ 6.61 (dt, J = 16.8, 10.6 Hz, 1H), 6.04 (t, J = 11.0 Hz, 1H), 5.56 (t, J = 10.4 Hz, 1H), 5.23 (dd, J = 16.8, 1.8 Hz, 1H), 5.14 (d, J = 10.1 Hz, 1H), 3.62 (t, J = 4.2 Hz, 1H), 3.54 (dd, J = 6.0, 3.5 Hz, 1H), 3.35 (dd, J = 9.4, 4.3 Hz, 1H), 3.00 (t, J = 9.3 Hz, 1H), 2.90−2.80 (m, 1H), 2.05−1.95 (m, 1H), 1.75−1.65 (m, 1H), 1.04 (d, J = 6.9 Hz, 3H), 1.08−0.95 (two t, 6H, obscured), 1.00 (t, J = 8.0 Hz, 9H), 0.94 (s, 9H), 0.66 (q, J = 8.0 Hz, 6H), 0.12 (s, 3H), 0.10 (s, 3H); ^{13}C NMR (DMSO-d_6, 125 MHz, 300 K): δ 134.3, 132.4, 129.2, 117.5, 77.7, 75.1, 42.1, 40.7, 36.1, 26.1, 18.9, 18.5, 15.2, 13.4, 12.0, 7.1, 5.7, −3.55, −3.56; IR (film): ν_{max} 2956s, 2934s, 2878s, 2858m, 1472m, 1462s, 1252s, 1100s, 1030s, 1005s, 971m, 836s, 812m, 773s, 739s, cm^{-1}; MS (ES^+) *m/z* (%) 537 (7, $[M - C_2H_5]^+$), 485 (55, $[M - C_6H_9]^+$), 313 (100, $[M - C_{15}H_{29}OSi]^+$).

(3*Z*,11*Z*)-(5*S*,6*S*,7*S*,8*R*,9*S*,13*S*,14*R*,15*S*)-8,14-Bis-(*tert*-butyldimethyl-silanyloxy)-5,7,9,11,13,15-hexamethyl-6,16-bis-triethyl-silanyloxyhexadeca-1,3,11-triene (32). A dried reactor (50 mL) equipped with a magnetic stirring bar and under an atmosphere of argon was charged sequentially with hexane (4 mL) and a solution of *tert*-BuLi in Et_2O (3.30 mL, 5.61 mmol, 1.7 M). The solution was cooled to −80 °C. To this solution was added a pre-cooled (−40 °C) solution of **8** (1.59 g, 2.80 mmol) in THF (15 mL) in 5 min, followed by a pre-cooled (−40 °C) solution of 9-methoxy-BBN (553 mg, 3.64 mmol) in THF (5 mL) in 5 min. The internal temperature of the reaction mixture did not exceed −75 °C. A white suspension formed after the addition. The temperature was allowed to return to 23 °C within 1.5 h. At ca. −20 to −10 °C, the white suspension dissolved and the reaction mixture was a clear, slightly yellowish solution at 23 °C. While the methoxyborate solution was warming up, a solution of **7** (1.18 g, 2.30 mmol) in DMF (20 mL) was added at room temperature into a reactor equipped with a propeller stirrer. To this solution, Cs_2CO_3 (2.62 g, 8.05 mmol) predissolved in water (2.2 mL) was added. The solution turned from dark yellowish to slightly brownish. The catalyst [Pd(dppf)Cl_2·CH_2Cl_2] (66 mg, 0.09 mmol, 4 mol %) was added as a solid in one portion. The solution turned reddish. The methoxyborate solution, warmed-up at room temperature, was then added via a dropping funnel over a period of 30 min. The reaction mixture became a brown turbid solution containing white solid. During the addition of the methoxyborate, a small portion of MeOLi flocculated slowly out of solution in the dropping funnel. The reaction mixture turned dark 30 min after the end of addition of the methoxyborate. This was due to the precipitation of metallic palladium and indicated the end of the reaction through full consumption of **7** as shown by TLC. The heterogeneous mixture was filtrated over a pad of Cellflock (filter aide). The filtrate was extracted with heptane (2 × 50 mL). The heptane fractions were back-extracted with brine (2 × 30 mL), combined, dried over $MgSO_4$, and concentrated in vacuo to a volume of about 12 mL. To this residual turbid solution containing a dark-brownish precipitate was added ethanolamine (245 mg, 4.00 mmol, 1.1 eq. per eq 9-methoxy-9-BBN utilized). The resulting mixture was stirred for 1 h at 23 °C before being treated with Cellflock and filtrated over a filter coated with Cellflock. The filtercake was rinsed with heptane (3 × 5 mL). The filtrate was concentrated in vacuo. Purification of the residue by flash chromatography (100 g of SiO_2, 0.5−1.0% AcOEt/hexane, gradient elution) afforded **31** as a pale yellowish oil (1.54 g, 81%). R_f = 0.31 (SiO_2, 99:1 hexane/AcOEt); ^{1}H NMR ($CDCL_3$, 500 MHz, 300 K): δ 6.62 (dt, J = 16.8, 10.6 Hz, Hz, 1H, C_2−H), 6.05 (t, J = 11.1 Hz, 1H, C_3−H), 5.58 (t, J = 10.4 Hz, 1H, C_4−H), 5.24 (dd, J = 16.8, 1.8 Hz, 1H, C_1−H_a), 5.15 (br d, J = 10.2 Hz, 1H, C_1−H_b), 5.07 (d, J = 10.2 Hz, 1H, C_{12}−H), 3.68 (dd, J = 9.7, 5.1 Hz, 1H, C_{16}−H_a), 3.60 (dd, J = 6.6, 3.5 Hz, 1H, C_6−H), 3.51 (t, J = 4.5 Hz, 1H, C_8−H), 3.42 (dd, J = 6.2, 4.8 Hz, 1H, C_{14}−H), 3.38 (t, J = 9.2 Hz, 1H, C_{16}−H_b), 2.97−2.88 (m, 1H, C_5−H), 2.55−2.45 (m, 1H, C_{13}−H), 2.16 (t, J = 12.3 Hz, 1H, C_{10}−H_a), 1.92−1.78 (m, 2H, C_9−H and C_{15}−H), 1.78−1.72 (m, 2H, C_7−H and C_{10}−H_b), 1.63 (s, 3H, C_{11}−CH_3), 1.06 (d, J = 6.9 Hz, 3H, C_5−CH_3), 1.05−0.97 (two d, 6H, C_7−CH_3 and C_{13}−CH_3), 1.03 (t, J = 8.0 Hz, 9H, Si($CH_2C\mathit{H}_3$)$_3$), 1.00 (t, J = 8.0 Hz, 9H, Si($CH_2C\mathit{H}_3$)$_3$), 0.97 (s, 9H, SiC(CH_3)$_3$), 0.95 (s, 9H, SiC(CH_3)$_3$), 0.91 (d, J = 6.6 Hz, 3H, C_{15}−CH_3), 0.74 (d, J = 6.6 Hz, 3H, C_9−CH_3), 0.68 (q, J = 8.0 Hz, 6H, Si($C\mathit{H}_2$-CH_3)$_3$), 0.62 (q, J = 8.0 Hz, 6H, Si($C\mathit{H}_2CH_3$)$_3$), 0.14 (s, 3H, Si(CH_3)), 0.11 (s, 3H, Si(CH_3)), 0.09 (s, 3H, Si(CH_3)), 0.07 (s, 3H, Si(CH_3)); ^{13}C NMR (DMSO-d_6, 125 MHz, 300 K): δ 134.6, 132.3, 131.7, 131.3, 128.9, 117.4, 78.2, 77.9, 77.0, 64.9, 41.4, 40.3, 36.1, 35.9, 35.4, 35.0, 26.2, 26.1, 22.9, 18.8, 18.5, 18.4, 17.2, 14.0, 13.8, 7.1, 6.8, 5.7, 4.4, −3.1, −3.4, −3.8, −4.0; IR (film): ν_{max} 2958s, 2935s, 2878s, 2858s, 1473m, 1462m, 1377m, 1252m, 1080s, 1029s, 1006s, 836s, 806m, 773s, 740m cm^{-1}; MS (AP+) *m/z* (%) 825 (17, $[M + H]^+$), 693 (41, $[M - HOSiC_6H_{15}]^+$).

(3*Z*,11*Z*)-(5*S*,6*S*,7*S*,8*R*,9*S*,13*S*,14*R*,15*S*)-8,14-Bis-(*tert*-butyldimethyl-silanyloxy)-5,7,9,11,13,15-hexamethyl-6,16-

bis-triethyl-silanyloxyhexadeca-1,3,11-triene (38). To a solution of **32** (130 mg, 0.16 mmol) in THF/H_2O 5:1 v/v (4.8 mL) at 23 °C was added trifluoroacetic acid (130 mg, 1.14 mmol). The resulting reaction solution was stirred at ambient temperature for 17 h, at which time the reaction was judged complete (TLC). The reaction mixture was diluted with hexane (20 mL), washed successively with $NaHCO_3$ (15 mL) and saturated aqueous NaCl (15 mL), and was dried ($MgSO_4$) and concentrated under reduced pressure. Purification of the residue by flash chromatography (50 g of SiO_2, 85:15 hexane/AcOEt) afforded diol **38** as a colorless oil (72 mg, 77%). R_f = 0.16 (SiO_2, 85:15 hexane/AcOEt); ^{1}H NMR ($CDCL_3$, 500 MHz, 300 K): δ 6.66 (dt, J = 16.8, 10.6 Hz, Hz, 1H), 6.17 (t, J = 11.0 Hz, 1H), 5.36 (t, J = 10.5 Hz, 1H), 5.26 (dd, J = 16.8, 1.8 Hz, 1H), 5.17 (br d, J = 10.2 Hz, 1H), 5.03 (d, J = 10.0 Hz, 1H), 3.68 (dd, J = 10.9, 4.6 Hz, 1H), 3.65 (dd, J = 5.6, 3.3 Hz, 1H), 3.56 (dd, J = 10.9, 5.4 Hz, 1H), 3.44 (dd, J = 6.5, 4.0 Hz, 1H), 3.38 (dd, J = 7.6, 3.3 Hz, 1H), 2.88−2.78 (m, 1H), 2.66−2.57 (m, 1H), 2.47−2.36 (br s, 2H), 2.21 (t, J = 12.2 Hz, 1H), 1.96−1.89 (m, 1H), 1.87−1.85 (1H), 1.86−1.80 (m, 2H), 1.65 (s, 3H), 1.02−0.96 (four d, 12H), 0.95 (s, 9H), 0.94 (s, 9H), 0.79 (d, J = 6.7 Hz, 3H), 0.13 (s, 6H), 0.12 (s, 3H), 0.10 (s, 3H); ^{13}C NMR (DMSO-d_6, 125 MHz, 300 K): δ 134.7, 133.2, 132.1, 130.9, 130.4, 118.3, 81.5, 78.7, 76.1, 65.4, 38.4, 38.2, 37.0, 36.5, 36.3, 34.9, 26.2, 26.1, 23.5, 17.4, 17.2, 15.8, 13.5, 9,5, −3.4, −3.6, −3.9; IR (film): ν_{max} 3450m (br), 2959s, 2930s, 2885s, 2857s, 1472s, 1463s, 1377m, 1257s, 1080s, 1022s, 1005s, 983m, 836s, 807m, 773m cm^{-1}; MS (ES$^+$) m/z (%) 914 (5, $[3\ M + Ca]^{2+}$), 619 (100, $[M + Na]^+$), 597 (6, $[M + H]^+$).

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