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

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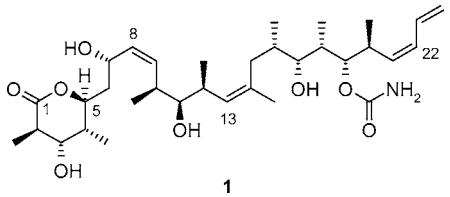
Abstract:

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

Introduction

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



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

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

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

Results and Discussion

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

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

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

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

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

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

(5) Critcher, D. J.; Connolly, S.; Wills, M. *J. Org. Chem.* **1997**, *62*, 6638.

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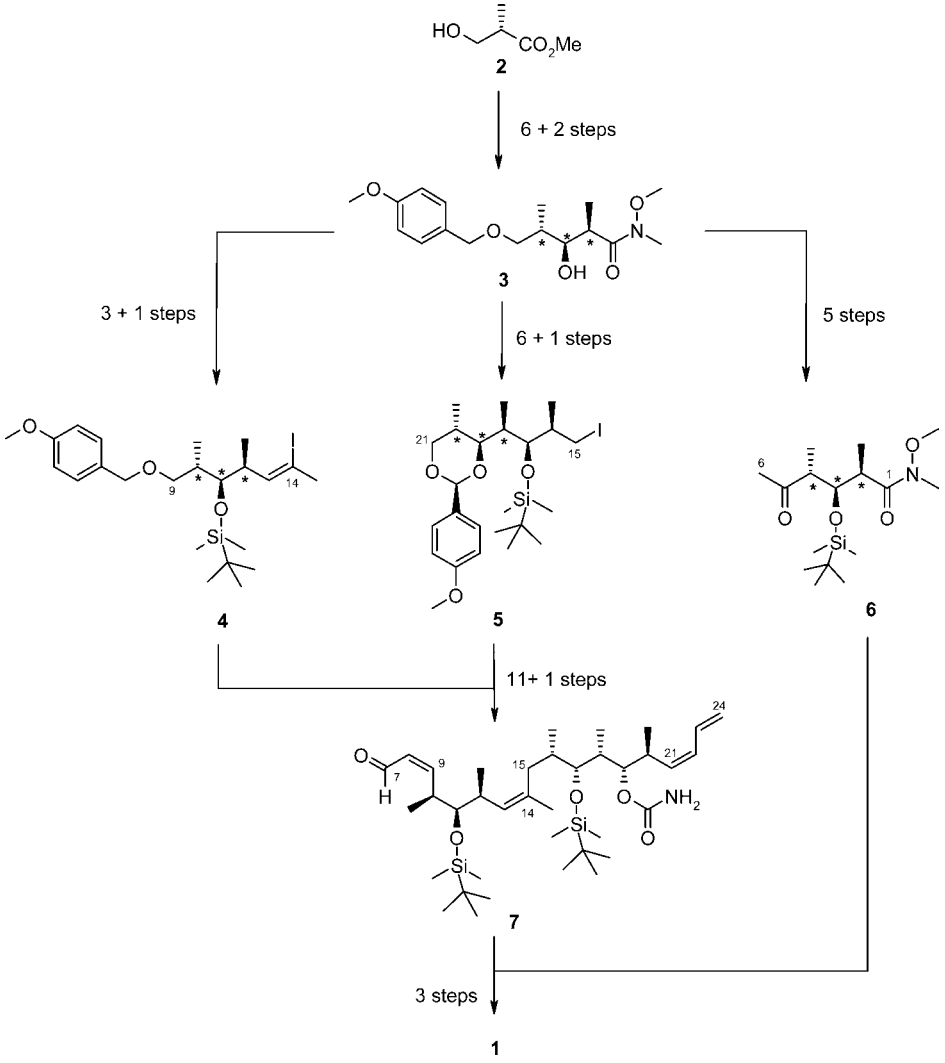
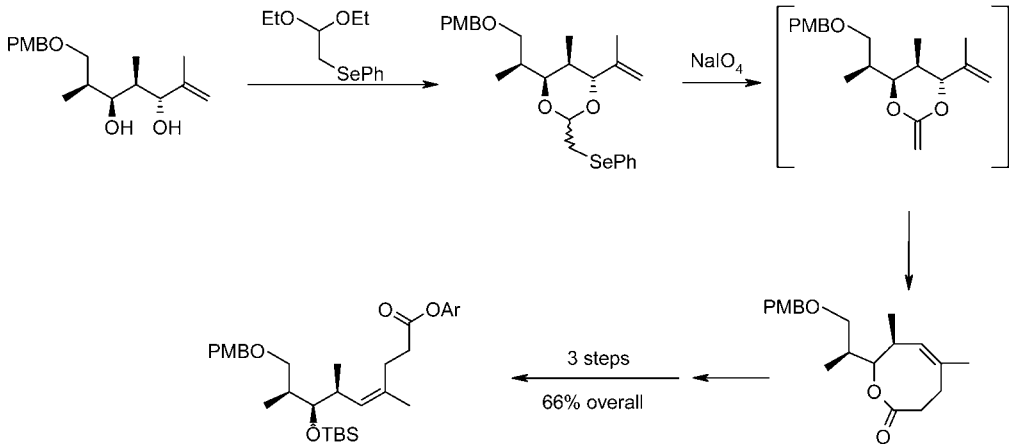
Scheme 1. **Synthetic strategy leading to fragment C_1-_6 (6) and C_9-_{14} (4)**

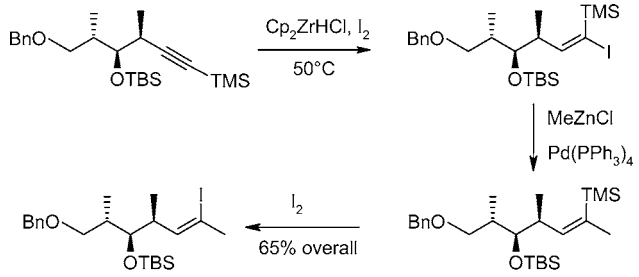


Scheme 2. **Paterson's approach to $C_{13,14}$-*cis*-trisubstituted double bond**

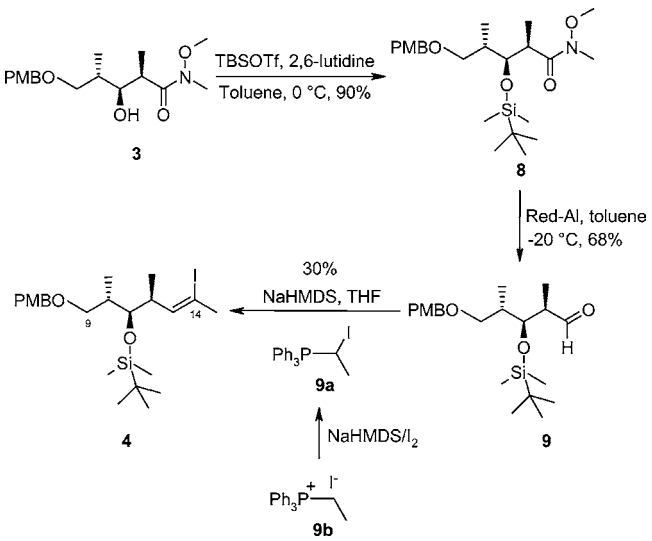


The success of converting amide **8** into aldehyde **9** was very dependent on the quality of silyl ether **8**. If **8** was not pure, the yield of aldehyde would drop to below 60%. The reaction time and temperature were also found to be critical. When the reaction was held too long at 0 °C, a competing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

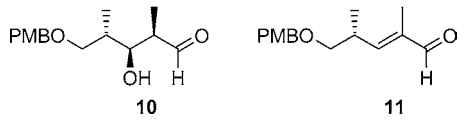
Scheme 3. **Panek's approach to $C_{13,14}$-*cis*-trisubstituted double bond**



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



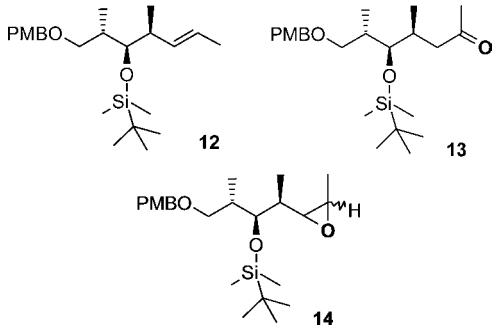
cessful. The final reaction conditions were a compromise to minimize byproduct formation. Aldehyde **9** was stable if stored at <-10 °C.



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

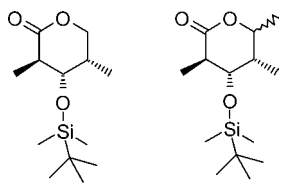
This olefination step was one of the most difficult reactions for scale-up. We consistently obtained 25−31% yield on the maximum scale of 2.5 kg of aldehyde **9**. Complicated workup procedures and instability of **4** contributed to low yield. Smith utilized iodine for the conversion of ethyltriphenylphosphonium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

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



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

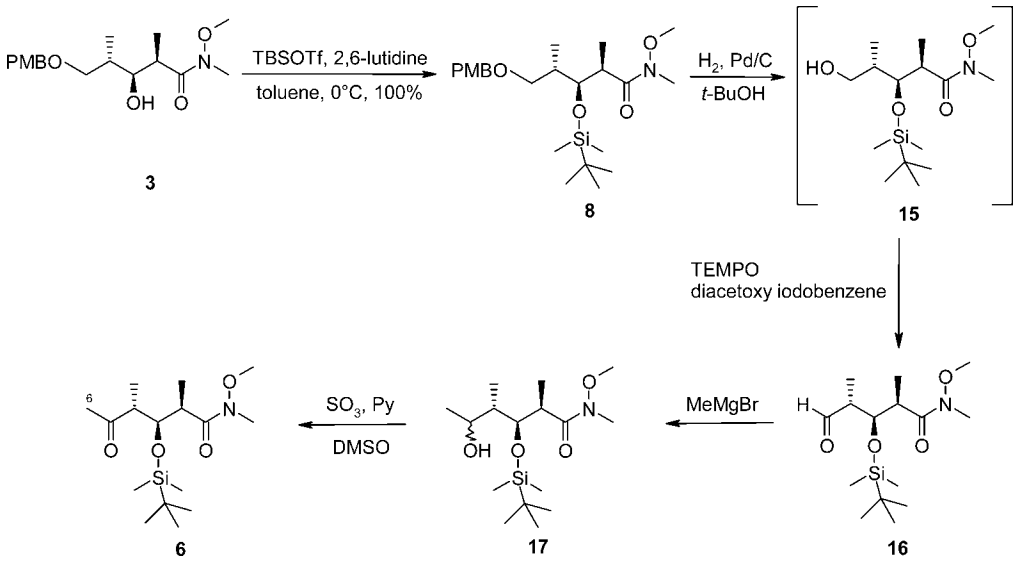
The published approach[2] to aldehyde **16** from **3** was followed. Hydrogenolysis of PMB ether **8** (same intermediate as for fragment **4** synthesis) with palladium on carbon in *tert*-butyl alcohol afforded alcohol **15**. Due to its propensity for lactonisation to **18**, **15** was used as a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



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

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

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



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

Experimental Section

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

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

Also isolated were the following two byproducts.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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