Organic Process Research & Development **2004**, *8*, 107–112

Large-Scale Synthesis of the Anti-Cancer Marine Natural Product (+)-Discodermolide. Part 3: Synthesis of Fragment C_{15-21}

Stuart J. Mickel,* Gottfried H. Sedelmeier, Daniel Niederer, Friedrich Schuerch, Guido Koch, E. Kuesters, Robert Daeffler, Adnan Osmani, Manuela Seeger-Weibel, E. Schmid, Alfred Hirni, Karl Schaer, and Remo Gamboni

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

Andrew Bach, Stephen Chen, Weichun Chen, Peng Geng, Christopher T. Jagoe, Frederick R. Kinder, Jr., George T. Lee, Joseph McKenna, Timothy M. Ramsey, Oljan Repič, Larry Rogers, Wen-Chung Shieh, Run-Ming Wang, and Liladhar Waykole

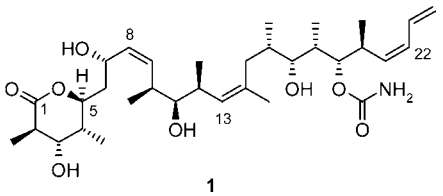
Novartis Institutes for Biomedical Research, One Health Plaza, East Hanover, New Jersey 07936, U.S.A.

Abstract:

Smith's procedure of preparing fragment C_{15-21} (5) from common precursor 3 was optimized. The ease of plant operations made this six-step route successful for the production of several kilograms of this fragment with high purity.

Introduction

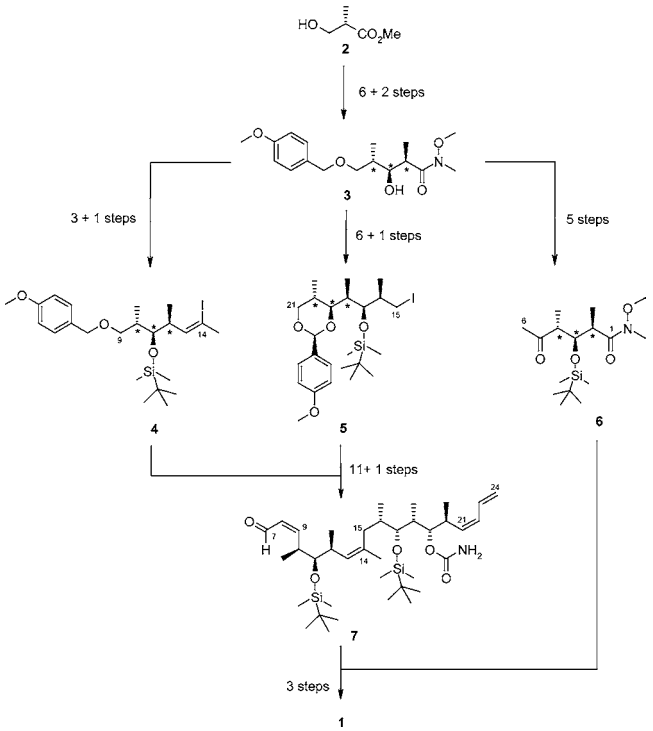
In the previous two parts of this series, large-scale preparations of two key fragments required for the total synthesis of (+)-discodermolide (**1**) are discussed.



1

In this contribution, the third part of the series, we present the route and results leading to the synthesis of fragment C_{15-21}. The strategy for the synthesis of this fragment (alkyl iodide **5**) from the common precursor **3** and its conversion to **1** is outlined in Scheme 1.

Scheme 1. **Synthetic strategy leading to fragment C_{15-21} (5) and (+)-discodermolide**



Results and Discussion

The published route[1] for the synthesis of fragment C_{15-21} (**5**) from the common precursor **3** was very attractive from the scale-up point of view, since all intermediates en route were reported as crystalline solids. We decided to further develop this six-step sequence for our multigram synthesis of (+)-discodermolide (Scheme 2).

Synthesis of PMP-Protected Aldehyde 9. Treatment of the Smith common precursor **3**[1] (described in Part 1) with a solution of DDQ[2] in toluene in the presence of 4-Å powdered molecular sieves furnished crystalline *p*-methoxybenzylidene (PMP) acetal **8** in 61% yield. This is one of several crystalline intermediates in the synthesis that can be purified easily by recrystallization of the crude material. Acetal **8** was produced presumably by an oxidative cyclization pathway via cations **3a** and **3b** as shown in Scheme 3. Anhydrous conditions are highly critical to obtain high yields of this reaction. If water is not excluded completely, some further oxidized *p*-methoxybenzyl cation **8a** can be captured by water, leading to benzoate **13** as a major byproduct (Scheme 4). Controlled reduction of the Weinreb amide **8** with $LiAlH_4$ provided another crystalline compound, aldehyde **9**, in high yield (91%). Intermediate **9** was isolated with high purity by crystallization and filtration.

Evans Aldol Reaction. To extend the carbon chain, the Evans aldol condensation protocol was employed. Coupling of aldehyde **9** with oxazolidinone **9a** at −78 to −10 °C

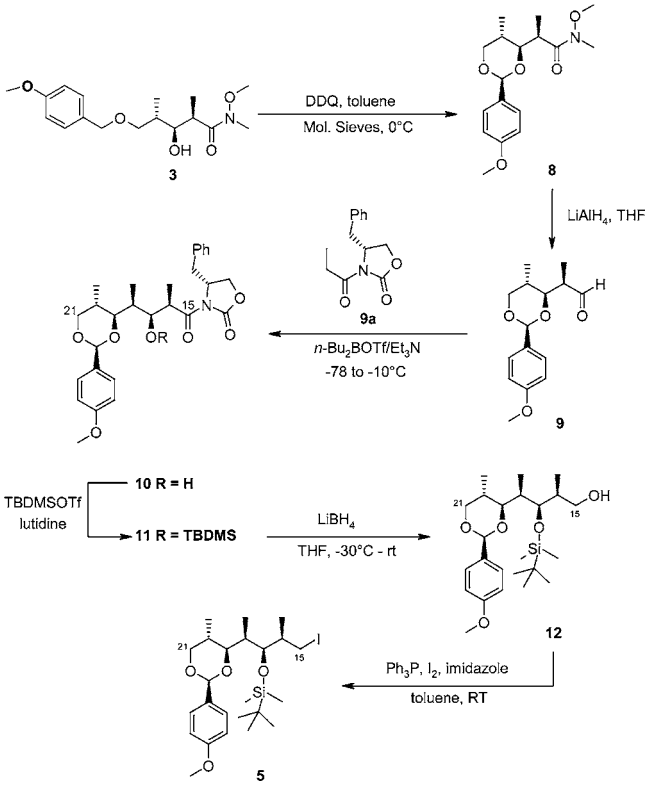
* Corresponding author. E-mail: stuart_john.mickel@pharma.novartis.com.

(1) (a) 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. (b) Smith, A. B.; Kaufman, M. D.; Beauchamp, T. J.; LaMarche, M. J.; Arimoto, H. *Org. Lett.* **1999**, *1*, 1823.

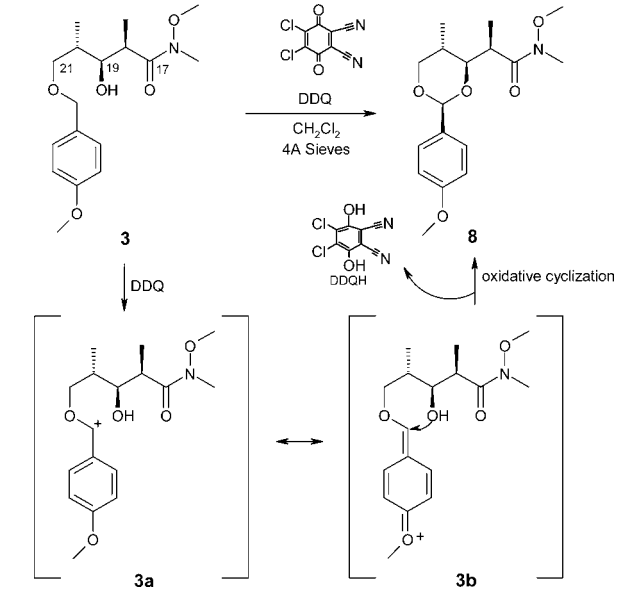
(2) Oikawa, Y.; Yoshioka, T.; Yonemitsu, O. *Tetrahedron Lett*. **1982**, *23*, 889.

10.1021/op034132z CCC: $27.50
Published on Web 12/04/2003

Scheme 2. **Synthesis of fragment C_{15-21} from the common precursor**



Scheme 3. **Oxidative cyclization**



mediated by di-*n*-butylboron triflate afforded the desired C_{15-21} backbone. The success of the aldol reaction was dependent largely on the quality of the di-*n*-butylboron triflate, as previously discussed (see Part 1 in this series). Gratifyingly, intermediate **10** was also a crystalline solid and could be readily isolated from the reaction mixture after workup, crystallization, and filtration in 85% yield. The diastereomeric excess of this compound was so high that none of the undesired diastereoisomer was detected. However, when the same reaction was carried out either at room temperature or allowed to warm to room temperature before

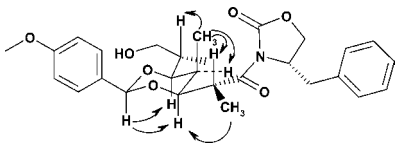
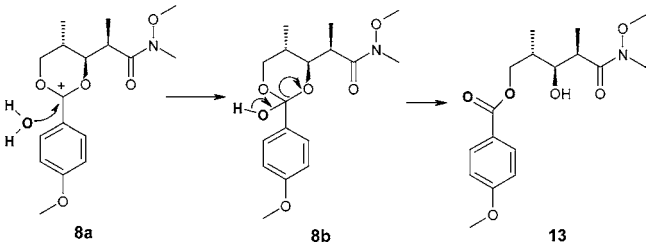
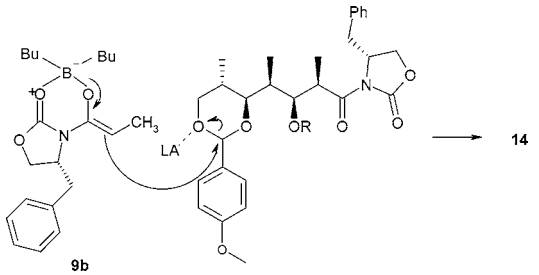


Figure 1. **NOE of 15.**

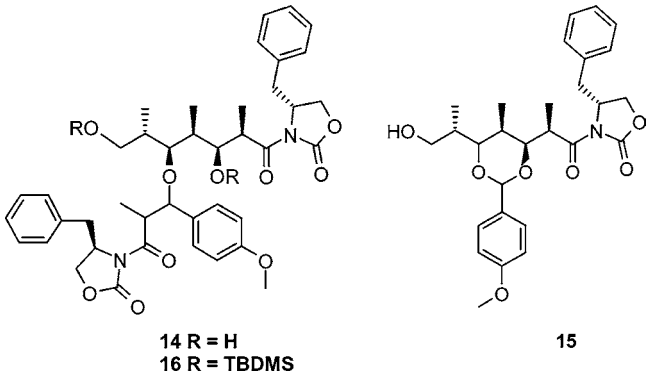
Scheme 4. **Formation of benzoate byproduct**



Scheme 5. **Formation of byproduct 14**



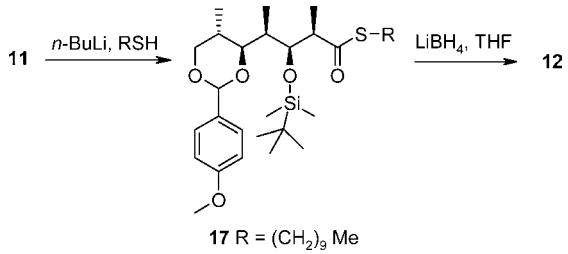
quench, significant amounts of byproducts (**14**, major, and **15,** minor) formed. Removal of byproduct **14** from the desired product **10** by crystallization was difficult, since it cocrystallized with the product. As a result, it was important to keep the reaction mixture below 0 °C to suppress the formation of these byproducts.



Formation of these byproducts suggested instability of the *p*-methoxybenzyl protecting group. Formation of **14** was attributed to the presence of excess di-*n*-butylboron triflate and enolate **9b**, which could open the acetal ring mediated by the boron (Lewis acid) (Scheme 5). The structure of byproduct **14** was supported by NMR spectroscopy. The structure of **15** was also supported by NMR experiments (NOE indicated by arrows) as shown in Figure 1.

Intermediate **10** was unstable at ambient temperature and underwent epimerization at the C_{16} position. This can be completely suppressed by storing it at temperatures below −10 °C. Thus, rapid workup and isolation were essential to achieve a higher yield. Epimerization was most likely caused

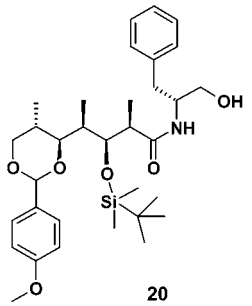
Scheme 6. **Reduction via a thio ester**

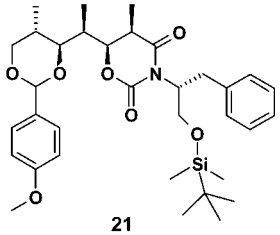


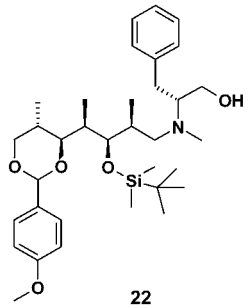
by retro-aldol/aldol reactions initiated by the unprotected hydroxy group. This was supported by the fact that silyl ether **11**, formed by silylation of **10** with TBDMSOTf/lutidine in quantitative yield, was found to be stable at ambient temperature. Both hydroxyl groups of byproduct **14** were also silylated to furnish bis-silyl ether **16** as a stable reference sample.

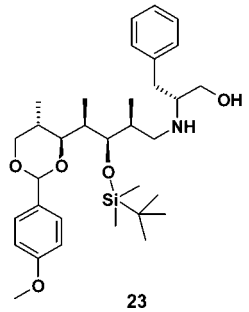
Conversion to the Iodo Intermediate 5. Reductive removal of the oxazolidinone chiral auxiliary from **11** leading to an alcohol was required. Treatment of **11** with a solution of lithium borohydride in THF/EtOH[3] gave an average yield of 60% of the desired alcohol **12** after chromatography on silica gel. We were unable to reproduce the high yields (>80%) reported in the literature,[1] despite examining various other reducing agents, solvents, etc. For example, reduction of **11** with sodium borohydride[4] was very slow and resulted in a very messy reaction. Another alternative approach, where **11** was converted into a thio ester **17**[5] followed by reduction,[6] did not improve the yield (Scheme 6). Attempts to reduce **11** to the corresponding aldehyde with the Schwartz reagent, according to a recently described procedure,[7] were also unsuccessful.

We found the lower yield was caused by several competing reactions that led to four byproducts **20**−**23**; **20** was the major byproduct. It is obvious that **20**, **22**, and **23** were generated by uncontrolled reductions of the carbonyl groups internal and external to the oxazolidinone ring. The exact pathway for the formation of **21** was unclear.

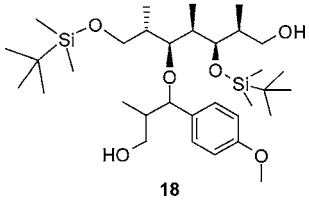


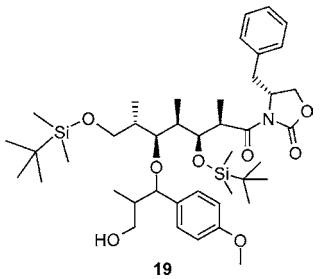






Silyl ether **16** was also reduced under the same conditions to furnish diol **18** as an analytical reference. Interestingly, the partially reduced, mono-oxazolidinone **19** was also isolated.





Finally, conversion of alcohol **12** into the desired alkyl iodide **5** was accomplished by employing Ph_3P/I_2/imidazole. The desired product was isolated as an oil in 90% yield without chromatography. Iodide **5** is light sensitive and forms a low-melting crystalline solid.

In conclusion, fragment C_{15-21} (**5**) was produced in six steps from the common precursor **3** with an overall yield of 24%. Although the yield was about half of what was reported by Smith (56%),[1a] the ease of plant operations made this route successful for the production of several kilograms of this fragment with high purity.

Experimental Section

(*R*)-*N*-Methoxy-2-[(4*S*,5*S*)-2-(4-methoxyphenyl)-5-methyl-1-[1,3]dioxin-4-yl]-*N*-methyl- propionamide (8). To a solution of common precursor **3** (18.1 kg, 77% purity, 42.83 mol) in toluene (260 kg) was added powdered 4-Å molecular sieves (18.1 kg). The suspension was cooled to 0 °C, and a solution of DDQ (15.0 kg, 66.1 mol) in toluene (90.4 kg) was added over 60 min. The addition equipment was washed with toluene (17 kg). The suspension was stirred overnight at 0 °C. Cellflock (filter aid) (18.1 kg) was added and the suspension filtered. The solid was washed with toluene (1 × 175 kg, followed by 2 × 36.4 kg). The combined filtrates were washed with 2 M aqueous sodium hydroxide solution (92.1 kg). The organic phase was then washed with four times with water (128 kg) containing 15% aqueous NaCl (26.8 kg) and concentrated under vacuum at 45 °C to about one-third of the original volume. The residue was filtered, and the solid was rinsed with toluene (2 × 9.1 kg). The combined filtrate was concentrated under vacuum at 45 °C to give an oil. The oily residue was dissolved in diisopropyl ether (15.8 kg), and the resulting solution was stirred for 60 min at room temperature after which time crystallization began. The suspension was cooled to 0 °C, and stirred for an additional 2.5 h. The product was isolated by filtration, washed with 10 kg of a 2/1 diisopropyl ether/heptane mixture

(3) Penning, T. D.; Djuric, S. W.; Haack, R. A.; Kalish, V. J.; Miyashiro, J. M.; Rowell, B. W.; Yu, S. S. *Synth. Commun.* **1990**, *20*, 307.
(4) Prashad, M.; Har, D.; Kim, Hong-Yong; Repič, O. *Tetrahedron Lett.* **1998**, *39*, 7067.
(5) Evans, D. A.; Wu, L. D.; Wiener, J. J. M.; Johnson, J. S.; Ripin, D. H. B.; Tedrow, J. S. *J. Org. Chem.* **1999**, *64*, 6411.
(6) Liu, H. J.; Bukownik, R.; Pednekar, P. R. *Synth. Commun.* **1981**, *11*, 599.
(7) White, J. M.; Ashok, R T.; Georg, G. I. *J. Am. Chem. Soc.* **2000**, *122*, 11995.

and dried at 30 °C to give **8** (6.9 kg, 50%) as a white crystalline solid: ^{1}H NMR ($CDCl_3$) δ 7.40 (m, 2H), 6.86 (m, 2H), 5.46 (s, 1H), 4.40 (dd, J = 11.6, 4.0 Hz, 1H), 3.90−3.76 (m, 4H), 3.51 (pseudo t, J = 10.9 Hz, 1H), 3.22−3.11 (m, 4H), 1.95 (m, 1H), 1.26 (d, J = 6.9 Hz, 3H), 0.75 (d, J = 6.9 Hz, 3H). The following compound (**13**) was also isolated by chromatography from the mother liquors.

4-Methoxybenzoic acid (2*S*,3*S*,4*R*)-3-hydroxy-4-(methoxymethylcarbamoyl)-2-methyl-pentyl ester (13): ^{1}H NMR ($CDCl_3$) δ 7.92 (m, 2H), 6.84 (m, 2H), 4.48 (A part of ABq, J = 11.7, 3.7 Hz, 1H), 4.30 (B part of ABq, J = 11.7, 6.7 Hz, 1H), 4.10 (br s, exch D_2O, 1H), 3.79 (s, 3H), 3.76−3.70 (m, 1H), 3.20−2.98 (m, 4H), 1.99 (m, 1H), 1.12 (d, J = 6.7 Hz, 3H), 0.94 (d, J = 7.5 Hz, 3H).

2-[(4*R*,5*S*,6*S*)-2-(4-Methoxyphenyl)-5-methyl-[1,3]dioxin-4-yl]-propionaldehyde (9). A solution of amide **8** (1.953 kg, 6.04 mol) in anhydrous THF (16 L) was cooled to −75 °C. A solution of lithium aluminum hydride (1.2 kg of a 10 wt/wt % solution in THF, 3.16 mol) was added dropwise over 30 min. The reaction mixture was warmed to −20 °C, and ethyl acetate (0.58 kg, 6.6 mol) was added dropwise over 15 min. The mixture was treated with 50% (w/v) aqueous solution of sodium potassium tartrate (16 L) and stirred for 60 min. The organic layer was separated, and the aqueous phase was re-extracted with THF (7 L). The organic layers were concentrated under vacuum, and toluene (10 L) was added to the residue. The toluene solution was extracted with 20% aqueous solution of citric acid (2 × 3 L), followed by washing with water (3 × 3 L). The organic phase was concentrated under vacuum at 40 °C, and heptane (6 L) was added to the residue. Crystallization began immediately. The suspension was cooled to 4 °C and stirred for 3.5 h. The solid was collected by filtration, rinsed with heptane (2 × 500 mL), and dried to give aldehyde **9** (1.455 kg, 91%) as a white crystalline solid: $[\alpha]^{25}_D$ +10.3 (c = 1, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 9.74 (d, J = 0.61 Hz, 1H), 7.32 (m, 2H), 6.84 (m, 2H), 5.47 (s, 1H), 4.13 (dd, J = 11.3, 4.7 Hz, 1H), 4.05 (dd, J = 9.7, 2.8 Hz, 1H), 3.77 (s, 3H), 3.56 (pseudo t, J = 11.7 Hz, 1H), 2.56 (qd, J = 7.21, 2.8 Hz, 1H), 2.09 (m, 1H), 1.22 (d, J = 7.2 Hz, 3H), 0.79 (d, J = 6.6 Hz, 3H).

(*R*)-4-Benzyl-3-{(2*R*,3*S*,4*S*)-3-hydroxy-4-[(4*S*,5*S*)-2-(4-methoxyphenyl)-5-methyl-[1,3]dioxin-4-yl]-2-methylpentanoyl}-oxazolidin-2-one (10). A solution of (*R*)-4-benzyl-3-propionyloxazolidin-2-one **9a** (1.81 kg, 7.76 mol) in dichloromethane (6.5 L) was cooled to −2 to 0 °C. A 26 wt % solution of di-*n*-butylboron triflate (2.44 kg, 8.54 mol) was added within 20 min. Triethylamine (995 g, 9.85 mol) was added within 20 min, and the mixture was stirred for 60 min at 0 °C. The resulting enolate solution was cooled to −78 °C, and a solution of aldehyde **9** (1.3 kg, 4.92 mol) was added dropwise within 15 min. The mixture was stirred for an additional 1 h at this temperature. The reaction mixture was warmed stepwise to 0 °C by holding at −50 °C for 1 h and at −22 °C for 16 h. Upon reaching 0 °C, aqueous phosphate buffer solution (6.5 L, pH 7.0) was added, followed by dropwise addition of aqueous hydrogen peroxide (1.52 kg, 35% solution) over 45 min, maintaining the temperature at 0 °C. The reaction mixture was stirred for 60 min at 0 °C, and a 50% aqueous solution of sodium thiosulphate (10 kg) was added slowly (very exothermic for the addition of the first 2−3 kg). The mixture was stirred for 30 min at 5 °C, and the organic phase was separated, washed with water (13 L), dried over $MgSO_4$, and filtered. The solvent was concentrated under vacuum at 30 °C to give the crude product as an oil. This oil was dissolved in 2-propanol (2.6 L), and heptane (6.5 L) was added dropwise. The solution was seeded and stirred at room temperature for 60 min. More heptane (5.2 L) was added to the suspension and stirred for 20 h at 20 °C. The solid was collected by filtration, rinsed, and dried at 20 °C to afford **10** (2.066 kg, 85%) as a white crystalline solid: $[\alpha]^{25}_D$ −16.3 (c = 1, $CHCl_3$); ^{1}H NMR (CD_3OD) δ 7.41−7.23 (m, 7H), 6.90 (m, 2H), 5.51 (s, 1H), 4.69 (m, 1H), 4.27−4.07 (m, 4H), 4.01 (dd, J = 6.9, 4.9 Hz, 1H), 3.81 (s, 3H), 3.67 (dd, J = 10.0, 1.7 Hz, 1H), 3.57 (pseudo t, J = 11.0 Hz, 1H), 3.16 (A part of ABq, J = 13.5, 3.5 Hz, 1H), 2.95 (B part of ABq, J = 13.5, 7.9 Hz, 1H), 2.13−1.94 (m, 2H), 1.27 (d, J = 6.93 Hz, 3H), 1.09 (d, J = 7.3 Hz, 3H), 0.82 (d, J = 6.6 Hz, 3H).

Chromatography of mother liquors on silica gel allowed the isolation of byproducts **14** and **15**.

Compound 14: ^{1}H NMR (C_6D_6) δ 7.50 (m, 2H), 7.20−7.00 (m, 8H), 6.88 (m, 2H), 6.71 (m, 2H), 5.01−4.87 (m, 2H), 4.32 (m, 2H), 3.89 (m, 1H), 3.75−3.40 (m, 10H), 3.32 (m, 1H), 3.28 (s, 3H), 3.17 (t, J = 6.5 Hz, exch D_2O, primary OH, 1H), 2.88 (A part of ABq, J = 13.5, 3.5 Hz, 1H), 2.64 (B part of ABq, J = 13.5, 7.9 Hz, 1H), 2.32−2.16 (m, 2H), 1.45−1.35 (m, 7H, becomes 6H on D_2O exch), 1.04 (d, J = 6.7 Hz, 3H), 0.98 (d, J = 7.2 Hz, 3H). After derivitization with trichloroacetyl isocyanate, the following spectrum was obtained: ^{1}H NMR (C_6D_6) δ 7.45 (m, 2H), 7.20−6.95 (m, 8H), 6.82 (m, 2H), 6.76 (m, 2H), 5.23 (dd, J = 9.0, 4.0 Hz, 1H, CHOH), 4.85 (d, J = 11.0 Hz, 1H, OCHPhOMe), 4.75 (qd, J = 11.0, 4.0 Hz, OCCH(CH3)OCHPhOMe), 4.50 (dd, J = 10.2, 5.0 Hz, 1H), 4.40 (m, 1H), 4.30 (m, 1H), 3.43 (m, 1H), 3.72 (pseudo t, J = 10 Hz, 1H), 3.60−3.45 (m, 4H), 3.30−3.18 (m, 5H), 2.83−2.67 (m, 3H), 2.35 (B part of ABq, J = 13.5, 8.4 Hz, 1H), 1.86 (m, 1H), 1.30−1.20 (m, 6H), 0.98 (d, J = 6.7 Hz, 3H), 0.89 (d, J = 7.0 Hz, 3H).

(*R*)-4-Benzyl-3-{(*R*)-2-[4*S*,5*R*]-6-((*S*)-2-hydroxy-1-methylethyl)-2-(4-methoxyphenyl)-5-methyl[1,3]dioxin-4-yl]-propionyl}-oxazolidin-2-one (15): ^{1}H NMR (C_6D_6) δ 7.52 (m, 2H), 7.05 (m, 3H), 6.83 (m, 4H, 5.50 (s, 1H), 4.56 (m, 1H), 4.31 (dd, J = 10.0, 2.1 Hz, 1H), 4.20 (m, 1H), 3.70−3.58 (m, 3H), 3.44 (dd, J = 10.5, 4.3 Hz, 1H), 3.31 (s, 3H), 3.15 (pseudo t, J = 9.5 Hz, 1H), 2.94 (dd, J = 12.5, 4.1 Hz, 1H), 2.25 (dd, J = 12.2, 8.2 Hz, 1H), 2.06−1.90 (m, 2H), 1.56 (d, J = 6.8 Hz, 3H), 1.13 (d, J = 6.9 Hz, 3H), 0.66 (d, J = 7.4 Hz, 3H).

(*R*)-4-Benzyl-3-{(2*R*,3*S*,4*R*)-3-(*tert*-butyl-dimethylsilanyloxy)-4-[(4*S*,5*S*)-2-(4-methoxyphenyl)-5-methyl-[1,3]-dioxin-4-yl]-2-methylpentanoyl}-oxazolidin-2-one (11). Compound **10** (2.05 kg, 4.12 mol) was dissolved in dichloromethane (15 L) and treated with 2,6-lutidine (850 g, 7.93 mol). The solution was cooled to −10 °C, and *tert*-butyldimethylsilyl triflate (1.8 kg, 6.81 mol) was added

dropwise over 15 min. The reaction mixture was stirred at −10 °C for a further 30 min and warmed to 0 °C. The mixture was diluted with *tert*-butyl methyl ether (24 L) and washed with 10% aqueous solution of sodium hydrogen sulphate (15 L). The organic phase was separated and washed with brine, dried over $MgSO_4$, filtered, and concentrated under vacuum to give silyl ether **11** as an oil (2.881 kg, 114%), which was used without further purification: ^{1}H NMR ($CDCl_3$) δ 7.38 (m, 2H), 7.25 (m, 3H), 7.15 (m, 2H), 6.81 (m, 2H), 5.45 (s, 1H), 4.27 (m, 1H), 4.10 (dd, J = 6.8, 4.5 Hz, 1H), 4.05−3.90 (m, 2H), 3.80−3.70 (m, 4H), 3.48 (pseudo t, J = 10.6 Hz, 1H), 3.08 (A part of ABq, J = 13.5, 3.5 Hz, 1H), 2.58 (B part of ABq, J = 13.5, 7.9 Hz, 1H), 2.10−1.90 (m, 2H), 1.18 (d, J = 6.8 Hz, 3H), 1.05 (d, J = 7.4 Hz, 3H), 0.9 (s, 9H), 0.71 (d, J = 6.7 Hz, 3H), 0.02 (s, 6H).

Compound 16. Compound **14** (0.46 g, 0.63 mmol) was silylated in the same fashion as **11** to produce 0.95 g of **16**: ^{1}H NMR ($CDCl_3$) δ 7.40−7.20 (m, 10H), 7.15 (m, 2H), 6.86 (m, 2H), 4.80−4.65 (m, 2H), 4.45 (m, 2H), 4.18−3.90 (m, 4H), 3.80 (s, 3H), 3.66 (m, 1H), 3.63−3.52 (m, 3H), 3.30 (m, 1H), 2.95 (m, 2H), 3.16 (A part of ABq, J = 13.5, 3.5 Hz, 1H), 2.63 (B part of ABq, J = 13.5, 7.9 Hz, 1H), 2.10 (m, 1H), 1.61 (m, 1H), 1.05 (m, 6H), 1.00−0.78 (m, 22H), 0.08−0.00 (m, 12H).

(2*S*,3*R*,4*R*)-3-(*tert*-butyldimethylsilanyloxy)-4-[(4*S*,5*S*)-2-(4-methoxyphenyl)-5-methyl-[1,3]dioxin-4-yl]-2-methylpentan-1-ol (12). Silyl ether **11** (5.0 kg, 8.17 mol) was dissolved in THF (50.0 kg), and the solution was cooled to −35 °C. Ethanol (0.957 kg) was added, followed by dropwise addition of a 10 wt % solution of lithium borohydride in THF (4.52 kg, 20.75 mol) over a period of 35 min. The mixture was warmed to 23 °C within 60 min and stirred for 2 h. A 1.0 M aqueous solution of sodium hydroxide (44.4 kg) was added slowly, and the mixture was stirred for 2 h at 20 °C. *tert*-Butyl methyl ether (31.6 kg) was added. The organic layer was separated, washed with brine (50 kg), dried over Na_2SO_4, and concentrated under vacuum at 25 °C to give the crude product as an oil (4.72 kg, 131%). The crude material was dissolved in a mixture of cyclohexane (32.8 kg) and methanol (7.46 kg). Water (2.36 kg) was added, and the two-phase mixture was stirred for 10 min. The organic phase was separated and concentrated under vacuum to give an oil (3.39 kg). This material was divided into three portions, and each (1.13 kg) was chromatographed over 25 kg of silica gel eluting with hexane/ethyl acetate mixtures (starting with 15% of ethyl acetate, followed by 20, 30, and finally 75% of ethyl acetate). The fractions containing the desired product from all three chromatographies were combined and concentrated under vacuum to give alcohol **12** (1.989 kg, 56%) as an oil: $[\alpha]^{25}_D$ +38.6 (c = 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.34 (m, 2H), 6.83 (m, 2H), 5.36 (s, 1H), 4.06 (dd, J = 8.1, 4.7 Hz, 1H), 3.81 (dd, J = 7.0, 2.4 Hz, 1H), 3.76 (s, 3H), 3.36−3.38 (m, 3H), 2.10−1.85 (m, 2H), 1.70 (br t, exch D_2O, 1H), 0.99 (d, J = 7.0 Hz, 3H), 0.85 (s, 9H), 0.81 (d, J = 6.7 Hz, 3H), 0.71 (d, J = 7.1 Hz, 3H), 0.00 (s, 3H), −0.03 (s, 3H). The following byproducts (**20**−**23)** were also isolated by chromatography on further elution.

(2*R*,3*S*,4*R*)-3-(*tert*-Butyldimethylsilanyloxy)-4-[(4*S*,5*S*)-2-(4-methoxyphenyl)-5-methyl-[1,3]dioxan-4-yl]-2-methylpentanoic acid ((*R*)-1-benzyl-2-hydroxyethyl)-amide (20): ^{1}H NMR ($CDCl_3$) δ 7.47 (m, 2H), 7.22 (m, 3H), 7.01 (m, 2H), 6.95 (m, 2H), 5.54−5.49 (m, 2H), 4.12 (m, 2H), 3.96 (m, 1H), 3.86 (m, 2H), 3.79 (s, 3H), 3.51 (pseudo t, J = 11.5 Hz, 1H), 3.44 (dd, J = 10.9, 3.6, 1H), 3.16 (dd, J = 11.5, 6.7 Hz, 1H), 2.71−2.57 (br s, 1H), 2.55−2.45 (m, 2H), 2.23 (dd, J = 13.9, 7.3 Hz, 1H), 2.11−1.96 (m, 2H), 1.02−0.97 (m, 6H), 0.92 (s, 9H), 0.73 (d, J = 6.7 Hz, 3H), 0.08 (s, 3H), 0.04 (s, 3H).

(5*R*,6*S*)-3-[(*R*)-1-Benzyl-2-(*tert*-Butyldimethylsilanyloxy)-ethyl]-6-{(*R*)-1-[(4*S*,5*S*)-2-(4-methoxyphenyl)-5-methyl-[1,3]dioxan-4-yl]ethyl}-5-methyl-[1,3]oxazinane-2,4-dione (21): ^{1}H NMR ($CDCl_3$) δ 7.40 (m, 2H), 7.34−7.22 (m, 5H), 6.90 (m, 2H), 5.44 (s, 1H), 4.64 (m, 2H), 4.14 (m, 2H), 4.03 (pseudo t, J = 8.6 Hz, 1H), 3.95 (dd, J = 8.43, 3.7 Hz, 1H), 3.84 (s, 3H), 3.55 (m, 1H), 3.45 (dd, J = 10.4, 2.5 Hz, 1H), 3.34 (m, 1H), 2.82 (dd, J = 13.6, 11.1 Hz, 1H), 2.66 (qd, J = 7.4, 3.3 Hz, 1H), 2.18 (m, 2H), 1.27 (d, J = 7.2 Hz, 3H), 1.24 (d, J = 6.5 Hz, 3H), 0.95 (s, 9H), 0.81 (d, J = 6.5 Hz, 3H), 0.33 (m, 6H).

(*R*)-2-({(2*S*,3*R*,4*R*)-3-(*tert*-Butyldimethylsilanyloxy)-4-[(4*S*,5*S*)-2-(4-methoxyphenyl)-5-methyl[1,3]dioxan-4-yl]-2-methylpentyl}-methylamino)-3-phenylpropan-1-ol (22): ^{1}H NMR ($CDCl_3$) δ 7.41 (m, 2H), 7.23 (m, 3H), 7.08 (m, 2H), 6.90 (m, 2H), 5.44 (s, 1H), 4.13 (d, J = 11.4, 4.7 Hz, 1H), 3.82 (s, 3H), 3.69 (d, J = 7.1 Hz, 1H), 3.61 (d, J = 9.4 Hz, 1H), 3.54 (pseudo t, J = 11.4 Hz, 1H), 3.40−3.30 (m, 2H), 2.98−2.87 (m, 2H), 2.43 (dd, J = 12.6, 8.3 Hz, 1H), 2.35−2.24 (m, 6H, becomes 5H on D^2O exch), 2.15−2.01 (m, 2H), 1.92 (m, 1H), 1.05 (d, J = 7.4 Hz, 3H), 0.95 (s, 9H), 0.90 (d, J = 6.8 Hz, 3H), 0.77 (d, J = 6.8 Hz, 3H), 0.07 (m, 6H).

(*R*)-2-({(2*S*,3*R*,4*R*)-3-(*tert*-Butyldimethylsilanyloxy)-4-[(4*S*,5*S*)-2-(4-methoxyphenyl)-5-methyl[1,3]dioxan-4-yl]-2-methylpentylamino}-3-phenylpropan-1-ol (23): ^{1}H NMR ($CDCl_3$) δ 7.44 (m, 2H), 7.33 (m, 2H), 7.27 (m, 1H), 7.22 (m, 2H), 6.89 (m, 2H), 5.44 (s, 1H), 4.10 (dd, J = 10.9, 4.1 Hz, 1H), 3.83−3.31 (m, 6H, becomes 5H on D_2O exch), 3.53 (d, J = 8.2 Hz, 1H), 3.50−3.44 (m, 2H), 3.33 (dd, J = 14.5, 7.6 Hz, 1H), 3.13 (m, 1H), 2.72 (td, J = 10.6, 4.0 Hz, 1H), 2.55 (td, J = 11.2, 2.3 Hz, 1H), 2.52−2.44 (m, 2H), 2.15−2.00 (br m, 2H, becomes 1H on D_2O exch), 1.80 (m, 1H), 0.96 (d, J = 6.8 Hz, 3H), 0.89 (s, 9H), 0.72 (d, J = 6.7 Hz, 3H), 0.63 (d, J = 6.5 Hz, 3H), 0.00 (s, 3H), −0.04 (s, 3H).

(2*R*,3*S*,4*R*)-3-(*tert*-Butyldimethylsilanyloxy)-4-[(4*S*,5*S*)-2-(4-methoxyphenyl)-5-methyl-[1,3]dioxin-4-yl]-2-methylpentanethioic acid *S*-decyl ester (17). A solution of 1-decanethiol (89.7 mg, 0.48 mmol) in THF (3 mL) was cooled to −78 °C and treated with *n*-butyllithium (0.739 mL, 1.18 mmol). The solution was stirred for 5 min, and a solution of **11** (0.3 g, 0.47 mmol) in THF (5 mL) was added dropwise. The mixture was stirred at −78 °C for 10 min, warmed to 0 °C, and stirred for 30 min. The reaction was quenched by the addition of saturated aqueous ammonium chloride solution (20 mL) and diluted with *tert*-butyl methyl

ether (10 mL). The organic layer was separated, washed with water, dried over Na_2SO_4, and concentrated under vacuum at 30 °C to give an oil (0.35 g). Chromatography on silica gel gave thio ester **17** (0.188 g, 66%) as a waxy solid: ^{1}H NMR ($CDCl_3$) δ 7.41 (m, 2H), 6.86 (m, 2H), 5.43 (s, 1H), 4.19 (dd, J = 6.8, 3.6 Hz, 1H), 4.09 (dd, J = 11.3, 4.54 Hz, 1H), 3.79 (s, 3H), 3.61 (dd, J = 10.5, 1.9 Hz, 1H), 3.49 (pseudo t, J = 11.0 Hz, 1H), 2.98 (qd, J = 6.8, 3.3 Hz, 1H), 2.79 (td, J = 7.8, 2.3 Hz, 2H), 2.02−1.90 (m, 2H), 1.51 (m, 1H), 1.36−1.20 (m, 16H), 1.12 (d, J = 7.1 Hz, 3H), 1.01 (d, J = 7.1 Hz, 3H), 0.89−0.87 (m, 12H), 0.71 (d, J = 6.7 Hz, 3H), 0.00 (s, 3H), −0.04 (s, 3H).

Silyl ether **16** was reduced using the same procedure as described for the conversion of **11** to **12**. The following two compounds (**18** and **19**) were isolated.

(2*S*,3*R*,4*R*,5*S*,6*S*)-3,7-Bis-(*tert*-butyldimethylsilanyloxy)-5-[3-hydroxy-1-(4-methoxyphenyl)-2-methylpropoxy]-2,4,6-trimethylheptan-1-ol (18): ^{1}H NMR ($CDCl_3$) δ 7.20 (m, 2H), 6.85 (m, 2H), 4.15 (d, J = 10 Hz, 1H), 3.85 (br m, 1H), 3.75 (s, 3H), 3.70−3.50 (m, 4H), 3.37 (dd, J = 11.0, 8.0 Hz, 1H), 3.20 (d, J = 6.0 Hz, 1H), 3.05−2.90 (m, 3H), 2.25−2.05 (m, 2H), 1.60 (m, 2H), 0.96 (d, J = 7.0 Hz, 3H), 0.90 (m, 12H), 0.80 (s, 9H), 0.60 (d, J = 6.5 Hz, 3H), 0.52 (d, J = 6.8 Hz, 3H), 0.02 to −0.04 (m, 12H).

(*R*)-4-Benzyl-3-{(2*R*,3*S*,4*R*,5*S*,6*S*)-3,7-bis-(*tert*-butyldimethylsilanyloxy)-5-[3-hydroxy-1-(4-methoxyphenyl)-2-methylpropoxy]-2,4,6-trimethylheptanoly}-oxazolidin-2-one (19): ^{1}H NMR ($CDCl_3$) δ 7.20 (m, 7H), 6.82 (m, 2H), 6.02 (br m, exch D_2O, 1H), 4.30 (d, J = 10 Hz, 1H), 4.20 (m, 2H), 3.85 (s, 3H), 3.80−3.30 (m, 8H), 2.90 (A part of ABq, J = 13.5, 3.5 Hz, 1H), 2.60 (B part of ABq, J = 13.5, 7.9 Hz, 1H), 2.40−2.20 (m, 2H), 1.60 (m, 4H), 1.00 (d, J = 7.2 Hz, 3H), 0.95−0.75 (m, 15H), 0.70 (s, 9H), 0.58 (d, J = 6.5 Hz, 3H), 0.02 to −0.05 (m, 12H).

***tert*-Butyl-((1*S*,2*R*)-3-iodo-1-{(*R*)-1-[(4*S*,5*S*)-2-(4-methoxyphenyl)-5-methyl-[1,3]dioxin-4-yl]-ethyl}-2-methylpropoxy)-dimethylsilane (5).** Alcohol **12** (2.75 kg, 6.27 mol) was dissolved in a mixture of toluene (30 kg) and acetonitrile (4.77 kg). Imidazole (1.37 kg, 20.13 mol) and triphenylphosphine (2.70 kg, 10.3 mol) were added, and the solution was cooled to 10−15 °C. A solution of iodine (2.59 kg, 10.2 mol) in toluene (24.5 kg) containing acetonitrile (3.89 kg) was added dropwise over 25 min. The mixture was warmed to room temperature within 30 min and stirred for 3 h. A 5% aqueous solution of sodium thiosulphate (58 kg) was added, and the reaction mixture was stirred for 10 min. The organic phase was separated and washed sequentially with 5% aqueous sodium thiosulphate (58 kg) and brine (66 kg). The organic phase was dried over Na_2SO_4 and concentrated under vacuum at 40 °C until a final volume of 10 L was reached. Hexane (37.4 kg) was added, and the suspension was stirred for 10 min. The solid was filtered and rinsed with heptane (2 × 10 kg). The combined filtrates were cooled to 2 °C and stirred for 8 h. The solid was filtered and rinsed with heptane (4 kg). The combined filtrates were charged with methanol (17.4 kg) and water (5.5 kg). The resulting two-phase system was stirred for 10 min, and the organic phase was separated. This procedure was repeated once more. The combined organic layers were dried over Na_2SO_4 and concentrated under vacuum at 30 °C to give iodo compound **5 (**3.11 kg 90%) as a light-sensitive oil. If required, this material may be purified by chromatography on silica gel eluting with hexane/*tert*-butyl methyl ether: ^{1}H NMR ($CDCl_3$) δ 7.36 (m, 2H), 6.83 (m, 2H), 5.37 (s, 1H), 4.05 (dd, J = 11.0, 4.7 Hz, 1H), 3.81 (dd, J = 7.2, 2.1 Hz, 1H), 3.75 (s, 3H), 3.48−3.40 (m, 2H), 3.10 (dd, J = 7.2, 2.0 Hz, 1H), 2.10−1.95 (m, 2H), 1.80 (m, 1H), 0.97 (d, J = 7.0 Hz, 3H), 0.93 (d, J = 6.8 Hz, 3H), 0.85 (s, 9H), 0.68 (d, J = 6.7 Hz, 3H), 0.02 (s, 3H), 0.00 (s, 3H).

Received for review September 16, 2003.

OP034132Z