First Stereocontrolled Synthesis of the (3*S*,5*R*,7*R*,10*R*,11*R*)-C1−C13 Fragment of Nystatin A_1

Guy Solladié,* Nicole Wilb, and Claude Bauder

Laboratoire de Stéréochimie associé au CNRS, Université Louis Pasteur, Ecole Européenne de Chimie, Polymères et Matériaux (ECPM). 25 rue Becquerel, 67087-Strasbourg-Cedex 2, France

Carlo Bonini,* Licia Viggiani, and Lucia Chiummiento

Dipartimento di Chimica, Università degli Studi della Basilicata, Via N. Sauro 85, 85100 Potenza, Italy

Received February 9, 1999

A convergent stereoselective synthesis of the (3*S*,5*R*,7*R*,10*R*,11*R*)-C1−C13 fragment of Nystatin A_1 is reported in this paper. This fragment contains an all-syn-1,3,5-triol subunit and a syn-1,2-diol moiety. The main features of the synthesis are the enzymatic desymmetrization of a *meso* diol to obtain an enantiomerically pure syn-4,6-dihydroxy-2-keto-phosphonate, chiral sulfoxide chemistry to prepare an α-(*R*)-hydroxyaldehyde and 2-trimethylsilyl thiazole reagent to synthesize a syn-α,*β*-(*R*,*S*)-dihydroxy aldehyde.

Nystatin A_1 is a macrolide antibiotic produced by *Streptomyces noursei* and was discovered in 1950.[1] It is one of the most commonly used in antifungal therapy. The molecular structure of this macrolide is an all-trans polyene part with six conjugated double bonds and a polyol moiety containing eight chiral hydroxylic centers. The gross structure of Nystatin A_1[2−4] was confirmed in 1970[5] and 1971,[6] and the absolute configuration of the chiral centers was assigned more recently by controlled degradation[7,8] and partial synthesis[9,10] (Figure 1).

Until now, only the synthesis of Nystatin A_1's C1−C10 fragment, containing three chiral hydroxylic centers, has been reported by Nicolaou[9] (via a Sharpless epoxidation) to confirm the absolute configuration and by Beau[10] from 6-O-silylated-D-glucal as the starting material. Bonini, after a preliminary work[11] to obtain the C1−C10 fragment in racemic form, reported a synthesis of the enantiomerically pure triol unit from 3-benzyloxypropanal using a chemioenzymatic approach.[12,13] More recently, Schneider[14] published the synthesis of the C1−C10 polyol fragment via a Cope rearrangement. We report in this paper the first convergent highly stereoselective synthesis of the C1−C13 fragment **1** in the natural configuration (3*S*, 5*R*, 7*R*, 10*R*, 11*R*).

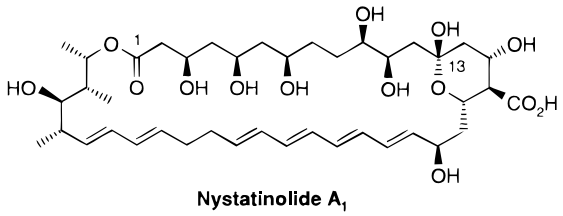


Figure 1.

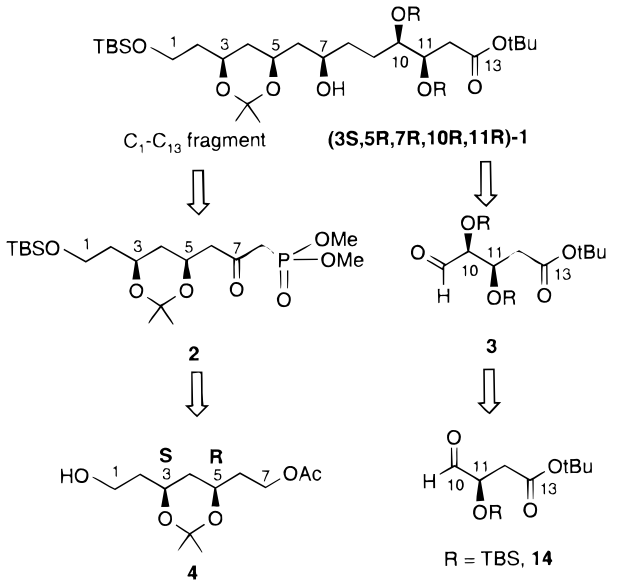
As shown in the retrosynthesis (Scheme 1), the C1−C13 fragment **1** (we used the atom numbering of the macrocycle for the synthesized fragments) can be disconnected in two parts: a chiral ketophosphonate **2** containing a 1,3-diol unit and a chiral aldehyde **3** with a 1,2-diol moiety. The phosphonate **2** could be obtained from the acetonide **4** we had already prepared[12] in high enantiomeric excess (>98%) by desymmetrization of the corresponding *meso*-3,5-O-isopropylidene-1,7-heptanediol by transesterification with vinyl acetate and PFL (*Pseudomonas fluorescens* lipase).[15] The aldehyde **3** can be prepared, according to Dondoni's methodology,[16] by condensation of 2-trimethylsilyl thiazole to the α-hydroxy-aldehyde **14**, which can be made by the use of chiral sulfoxides.[17]

(3*S*,5*R*)-7-Acetoxy-1-hydroxy-3,5-O-isopropylidene-heptane (**4**), readily obtained from *meso*-3,5-O-isopropylidene-1,7-heptanediol with lipase,[12,15] was protected by a TBS group to afford the compound **5**, and then the acetate was hydrolyzed with Na/MeOH. The resulting primary alcohol **6** was oxidized to the corresponding acid, which was then immediately esterified with diazomethane to give the ester **7** with an overall yield of 82% from **4** (Scheme 2). The phosphonate **2** was then obtained in 65%

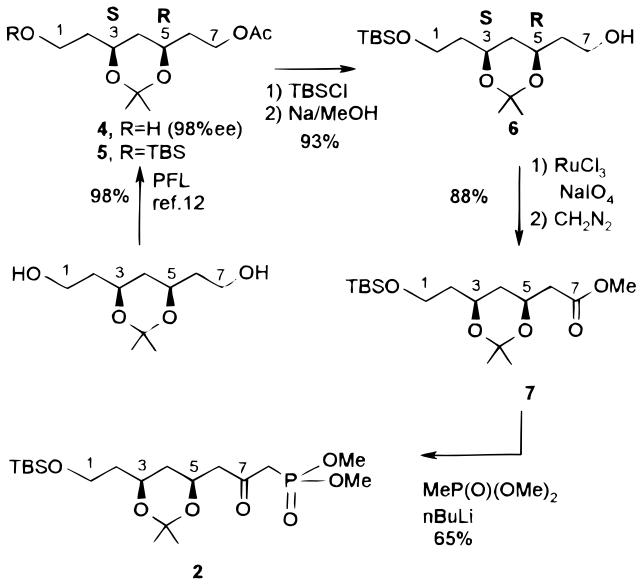
(1) Hazen, E. L.; Brown, R. *Science* **1950**, *112*, 423.
(2) Dutcher, J. D.; Walters, D. R.; Wintersteiner, O. *J. Org. Chem.* **1963**, *28*, 995.
(3) Saltza, M.; Dutcher, J. D.; Reid, J.; Wintersteiner, O. *J. Org. Chem.* **1963**, *28*, 999.
(4) Manwaring, D. G.; Rickard, R. W.; Golding, B. T. *Tetrahedron Lett.* **1969**, 5319.
(5) Chong, C. N.; Rickard, R. W. *Tetrahedron Lett.* **1970**, 5145.
(6) Borowski, E.; Zielinski, J.; Falkowski, L.; Ziminski, T.; Golik, J.; Kolodziejczyk, P.; Jereczek, E.; Gdulewicz, M.; Shenin, Y.; Kotienko, T. *Tetrahedron Lett.* **1971**, 685.
(7) Lancelin, J.-M.; Paquet, F.; Beau, J.-M. *Tetrahedron Lett.* **1988**, *29*, 2827.
(8) Lancelin, J.-M.; Beau, J.-M. *Tetrahedron Lett.* **1989**, *30*, 4521.
(9) Nicolaou, K. C.; Ahn, K. H. *Tetrahedron Lett.* **1989**, *30*, 1217.
(10) Prandi, J.; Beau, J.-M. *Tetrahedron Lett.* **1989**, *30*, 4517.
(11) Bonini, C.; Righi, G.; Rossi, L. *Tetrahedron* **1992**, *48*, 9801.
(12) Bonini, C.; Racioppi, R.; Viggiani, L., Righi, G.; Rossi, L. *Tetrahedron: Asymmetry* **1993**, *4*, 793.
(13) Bonini, C.; Giugliano, A.; Racioppi, R.; Righi, G. *Tetrahedron Lett.* **1996**, *37*, 2487.
(14) Schneider, C.; Rehfeuter, M. *Tetrahedron Lett.* **1998**, *39*, 9.
(15) The transesterification reaction with PPL has been greatly improved with a chemical yield of 96 to 98%, manuscript in prepration.
(16) (a) Dondoni, A.; Fogagnolo, M., Medici, A.; Pedrini, P. *Tetrahedron Lett.* **1985**, *26*, 5477. Dondoni, A.; Fantin, G.; Fogagnolo, M., Pedrini, P. *J. Org. Chem.* **1990**, *55*, 1439. (b) Dondoni, A.; Orduna, J.; Merino, P. *Synthesis* **1992**, 201.
(17) Solladié, G.; Almario, A. *Tetrahedron: Asymmetry* **1994**, *5*, 1717.

10.1021/jo990245y CCC: $18.00
Published on Web 06/26/1999

Scheme 1



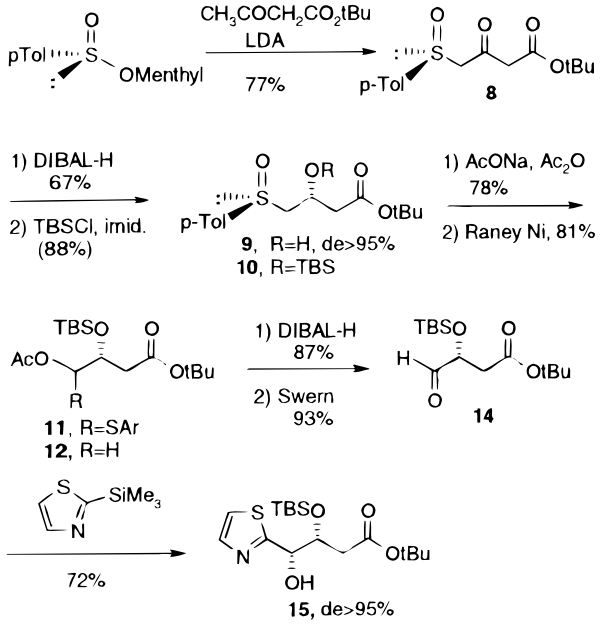
Scheme 2



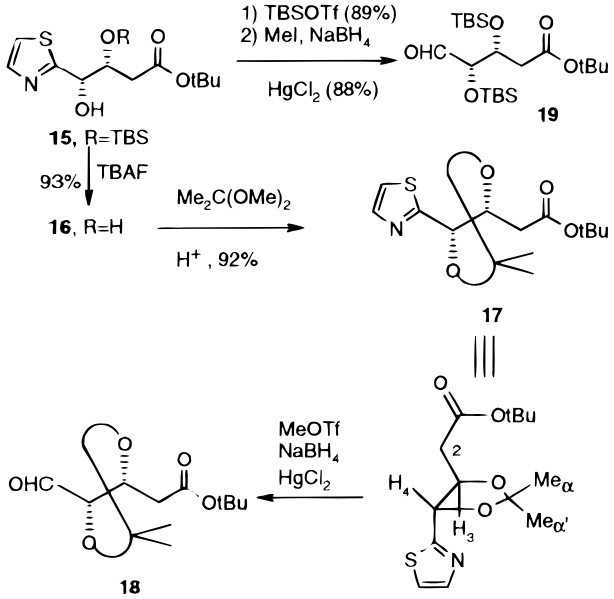
yield by condensation of the dimethyl methylphosphonate anion to the methyl ester **7** (we observed the formation, in 25 to 30% yield of the α,β-unsaturated ester resulting from the elimination of the β-oxygen and the acetonide opening in a basic medium).

The enantiomerically pure aldehyde **14** was prepared by a method we already reported[17] in seven steps with 25% overall yield from the dianion of *tert*-butyl acetoacetate and (+)-menthyl-(*R*)-*p*-toluenesulfinate (Scheme 3). The β-ketosulfoxide **8** was first stereoselectively reduced to the (*R*)-configuration[17] with DIBAL in 67% (de >98%), and the resulting alcohol **9** was protected by a TBS group to give the compound **10** in 88% yield. After a Pummerer rearrangement, the product **11** was subjected to desulfurization with Raney Nickel to get the compound **12** in 63% overall yield. We finally reduced the acetate with DIBAL and oxidized the resulting primary alcohol **13** by a Swern oxidation to the aldehyde **14** in 81% overall yield (during the reduction of **12** with DIBAL, it was important to neutralize and hydrolyze the reaction medium as

Scheme 3



Scheme 4



quickly as possible to prevent the migration of the silyl group from the secondary to the primary alcohol).

The crucial point at this stage was to prepare a pure syn-1,2-diol from **14**. The known Dondoni's method,[16a] using the addition of 2-trimethylsilyl thiazole (2-TST) to α-hydroxyaldehyde usually gives mainly the anti-1,2-diol. However, previous work in our laboratory[18] as well as a more recent report from Dondoni[16b] showed indeed that mainly the syn-1,2-diol could be also obtained. When we treated the aldehyde **14** with 2-TST, we got only the pure syn-1,2-diol **15** in 72% yield (Scheme 3).

The relative configuration of **15** was assigned by removing the silyl-protecting group with TBAF (93%) in THF and preparing the acetonide **17** (dimethoxypropane, acetone, pTsOH cat., 92%) (Scheme 4). In ^{1}H NMR, the coupling constants H4−H3 (J = 8 Hz) as well as the chemical shift in ^{13}C NMR of the two methyl groups α

(18) Almario, A. Thesis, Université Louis Pasteur, Strasbourg, 1994.

Scheme 5

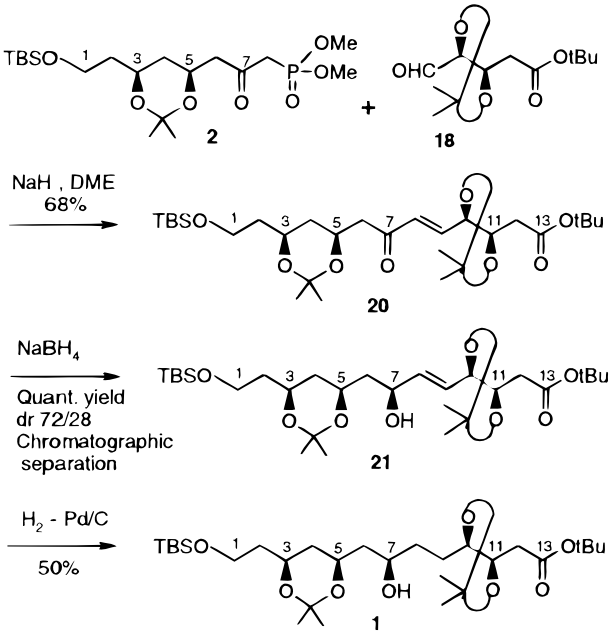


Table 1. Reduction Conditions of the Carbonyl of Compound 20

entry	hydride	solvent	temperature (°C)	syn:anti[a]	conversion (%)
1	$LiAlH_4$−LiI	Et_2O	−100	77:23	50
2	L-Selectride	THF	−78	66:34	100
3	L-Selectride	THF	−100	65:35	100
4	Super-Hydride	THF	−78	53:47	100
5	$NaBH_4$	MeOH	0	72:28	100

[a] Syn:anti ratios were determined by ^{1}H NMR (200 MHz, $CDCl_3$) analysis.

and α′ (27.9 and 27.3 ppm, respectively) are characteristic of a trans configuration for **17**.[19] Finally, we observed an NOE between H_4 and H_2. These results confirmed a syn relative configuration for the diol **15**, which is, therefore, the (*RS*) enantiomer.

The free hydroxylic function in **15** was then protected by TBS in 89% yield (with *tert*-butyl dimethylsilyl triflate; no reaction was observed with TBDMSCl), and the thiazole group was hydrolyzed in the usual conditions[16] in 88% yield to get the pure aldehyde **19** in 78% overall yield from **15** (Scheme 4).

Unfortunately, the Horner−Wadsworth−Emmons coupling between the phosphonate **2** and the aldehyde **19** gave only 12% yield in the desired product and important degradation products. The lack of reactivity was probably due to the bulky TBS group in **19**. So, we hydrolyzed the thiazole group in the acetonide **17** to obtain the aldehyde **18** in 50% yield. This time, the Horner−Wadsworth−Emmons reaction between the phosphonate **2** and the aldehyde **18** gave, in 68% yield, the protected polyol **20** (Scheme 5).

The crucial step was the reduction of the carbonyl function C7 of **20** with a syn selectivity. We tried several reaction conditions (Table 1) with different reducing agents. In the conditions developed by Suzuki[20] (lithium aluminum hydride−lithium iodide, entry 1), we observed good syn selectivity (77:23) but only a 50% conversion. With L-Selectride or Super-Hydride,[21] we had a moderate syn selectivity and a good yield. Finally, the use of $NaBH_4$ at 0 °C afforded compound **21** with good syn selectivity (72:28) and a complete conversion. This diastereofacial selectivity, in nonchelating hydride addition on a carbonyl β to a chiral center, can be explained by a preferential conformation in an open chain model.[21,22]

After separation of the two diastereomers of **21**, the absolute configuration of the C7 center was determined by Mosher's ester using MTPA-Cl in pyridine;[23] the (*S*)- and (*R*)-MTPA esters were prepared from the main diastereomer **21**, and the ^{1}H NMR spectra were recorded. The $\Delta\delta$ values for the vinylic signals were characteristic of an S configuration at C7 in the isomer **21**.

Finally, the fragment C1−C13 **1** of Nystatin was obtained by double bond hydrogenation of **21** over palladium on charcoal.

In conclusion, we have reported the first stereocontrolled synthesis of the C1−C13 polyol moiety of Nystatin in the natural (3*S*,5*R*,7*R*,10*R*,11*R*) configuration, using a convergent synthesis with a combination of biocatalytic chemistry and sulfoxide-mediated asymmetric induction to create the chiral centers.

Experimental Section

(−)-(3*S*,5*R*)-7-Acetoxy-1-O-(*tert*-butyldimethylsilyl)-3,5-O-isopropylidene-heptane (5). In a two-necked round-bottomed flask with a nitrogen inlet and while stirring, compound **4**[12] (0.1 g, 0.41 mmol) and imidazole (0.041 g, 0.6 mmol) were added to freshly distilled CH_2Cl_2 (25 mL). The reaction mixture was cooled in ice for 20 min and TBDMSCl (0.09 g, 0.60 mmol) and catalytic DMAP (4-(dimethylamino)-pyridine) were added. After 20 h (TLC monitoring), the mixture was diluted with CH_2Cl_2 and washed with brine. The organic layers are dried on Na_2SO_4 and evaporated in vacuo, affording pure compound **5** (0.148 g, 0.41 mmol; 100%): $[\alpha]^{20}_D = -1.7$ ($c = 1.00$, $CHCl_3$); ^{1}H NMR ($CDCl_3$) $\delta = 4.30-4.15$ (m, 2H), 4.14−3.90 (m, 2H), 3.80−3.60 (m, 2H), 2.09 (s, 3H), 1.85−1.70 (m, 2H), 1.70−1.60 (m, 2H), 1.40 (s, 3H), 1.38 (s, 3H), 1.30−1.10 (m, 2H), 0.90 (s, 9H), 0.00 (s, 6H); ^{13}C NMR ($CDCl_3$) $\delta = 171.3$, 99.7, 65.9, 65.5, 60.9, 58.7, 39.4, 37.1, 35.3, 30.1, 25.9, 20.9, 19.7, −5.4. Anal. Calcd for $C_{18}H_{36}O_5Si$ (360.21): C, 60.01; H, 9.99. Found: C, 60.12; H, 9.87.

(−)-(3*S*,5*R*)-1-O-(*tert*-Butyldimethylsilyl)-3,5-O-isopropylidene-heptanol (6). Compound **5** (0.148 g, 0.41 mmol) was dissolved in MeOH (20 mL) with a catalytic amount of Na. After the mixture was stirred for 4 h, the solvent was evaporated. The crude mixture was diluted with $CHCl_3$ and was filtered on Celite. After evaporation of the solvent, the crude product was chromatographed on silica gel (petroleum ether/EtOAc 75:25 as eluent) to afford pure **6** (0.121 g; 93%): $[\alpha]^{20}_D = -8.2$ ($c = 1.10$, $CHCl_3$); ^{1}H NMR ($CDCl_3$) $\delta = 4.15-4.00$ (m, 2H), 3.80−3.70 (m, 2H), 3.68−3.58 (m, 2H), 2.60 (bs, 1H), 1.80−1.70 (m, 2H), 1.70−1.61 (m, 2H), 1.45 (s, 3H), 1.37 (s, 3H), 1.40−1.28 (m, 2H), 0.89 (s, 9H), 0.00 (s, 6H); ^{13}C NMR ($CDCl_3$) $\delta = 98.6$, 65.5, 60.9, 58.7, 39.4, 38.1, 36.9, 30.2, 25.9, 19.9, 18.3, −5.4. Anal. Calcd for $C_{16}H_{34}O_4Si$ (318.2): C, 60.39; H, 10.68. Found: C, 60.52; H, 11.01.

Methyl (−)-(3*S*,5*R*)-1-O-(*tert*-Butyldimethylsilyl)-3,5-O-isopropylidene-heptan-7-oate (7). $NaIO_4$ (1.21 g, 5.66 mmol) was added to a biphasic solution of compound **6** (0.6 g, 1.89 mmol) in CCl_4 (9 mL), MeCN (9 mL), and phosphate buffer (pH 7, 0.4 M, 13.5 mL). After the mixture was stirred

(19) (a) Rychnovsky, S. D.; Skalitzky, D. J. *Tetrahedron Lett.* **1990**, *31*, 945. (b) Dana, G.; Danechpajouh, H. *Bull. Soc. Chim. Fr.* **1980**, 395.

(20) (a) Mori, Y.; Kuhara, M.; Takeuchi, A.; Suzuki, M. *Tetrahedron Lett.* **1988**, *29*, 5419. (b) Mori, Y.; Kuhara, M.; Takeuchi, A.; Kageyama, H.; Suzuki, M. *Tetrahedron Lett.* **1988**, 29, 5423.

(21) Evans, D. A.; Dart, M. J.; Duffy, J. L. *Tetrahedron Lett.* **1994**, *35*, 8541.

(22) Bonini, C.; Esposito, V.; D'Auria, M.; Righi, G. *Tetrahedron* **1997**, *53*, 13419 and references therein.

(23) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512.

for 5 min, $RuCl_3 \cdot 3H_2O$ (10.5 mg, 4.7 mmol) was added to the mixture, which was vigorously stirred for 6 h at room temperature. Then, CH_2Cl_2 (30 mL) was added, and the organic layer was separated. After drying on Na_2SO_4, the organic solution was concentrated in vacuo, diluted with ether, filtered through a Celite pad, and concentrated in vacuo, affording the crude acid (0.6 g). The acid was then diluted in ether (30 mL) and treated with CH_2N_2 in ether, until the solution became yellow. The solution was then evaporated in vacuo with a trap of acetic acid; the crude residue was then purified by flash chromatography (petroleum ether/EtOAc 75:25 as eluent), affording pure compound **7** (0.580 g; 88%): $[\alpha]^{20}_D = -13.3$ ($c = 0.98$, $CHCl_3$); ^{1}H NMR ($CDCl_3$) $\delta = 4.40-4.28$ (m, 1H, X part of an ABX syst), 4.10−4.00 (m, 1H), 3.70 (s, 3H), 3.80−3.60 (m, 2H), 2.46 (AB part of an ABX syst, 2H, $J_{AB} = 15.5$ Hz, $J_{AX} = 6.9$ Hz, $J_{BX} = 6.2$ Hz, $\Delta\nu = 39.9$ Hz), 1.70−1.60 (m, 2H), 1.46 (s, 3H), 1.38 (s, 3H), 1.30−1.15 (m, 2H), 0.90 (s, 9H), 0.05 (s, 6H); ^{13}C NMR ($CDCl_3$) $\delta = 173.0$, 99.0, 66.5, 65.5, 58.0, 51.5, 41.5, 39.5, 37.0, 31.0, 26.0, 20.0, 18.5, −5.0. Anal. Calcd for $C_{17}H_{34}O_5Si$ (346.20): C, 58.97; H, 9.8. Found: C, 59.12; H, 10.12.

Dimethyl (+)-(3*S*,5*S*)-1-*tert*-Butyldimethylsilyloxy-3,5-isopropylidenedioxy-7-oxo-octyl-8-phosphonate (2). A 1.5 M solution of n-BuLi in hexane (0.5 mL; 2.0 equiv) was added at −78 °C to dimethyl methyl phosphonate (0.1 mL; 2.5 equiv) in dry THF (2 mL). After 50 min, the ester **7** (129.7 mg; 0.373 mmol) in dry THF (2 mL) was dropwise added to the solution. Two hours later, the colorless mixture was hydrolyzed with a saturated solution of NH_4Cl (10 mL) and stirred at room temperature for 1 h. Water (10 mL) and CH_2Cl_2 (15 mL) were added, and the solution was acidified to pH 4 with HCl 10% (1 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL), and the organic layers were dried over $MgSO_4$ and concentrated. The crude product was then purified by chromatography on silica gel (AcOEt/CH_2Cl_2 1:1) to afford **2** as a colorless liquid (106 mg; 64.7%): $[\alpha]^{20}_D = +4.5$ ($c = 0.88$, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) $\delta = 4.39-4.26$ (m, 1H, X part of an ABX syst), 4.10−3.95 (m, 1H), 3.795 (d, 3H, P−O*Me*, $J = 11$ Hz), 3.792 (d, 3H, P−O*Me*, $J = 11$ Hz), 3.70−3.55 (m, 2H), 3.22, 3.14, 3.11 and 3.03 (AB syst coupled with P, 2H, $J_{AB} = 14$ Hz, $J_{H-P} = 22.5$ Hz, $\Delta\nu = 8$ Hz), 2.70 (AB part of an ABX syst, 2H, $J_{AB} = 16$ Hz, $J_{AX} = 7$ Hz, $J_{BX} = 5$ Hz, $\Delta\nu = 37.5$ Hz), 1.65−1.56 (m, 2H), 1.58 (dt, $1H_{éq}$, $J = 2.5$ Hz, $J = 12.5$ Hz), 1.24−1.06 (m, $1H_{ax}$), 0.86 (s, 9H, Si−C(CH_3)$_3$), 0.02 (s, 6H, Si−CH_3); ^{13}C NMR ($CDCl_3$) $\delta = 200.9$ (d, CO, $J_{C-P} = 6.5$ Hz), 99.4 (*C*(Me)$_2$), 66.0 (CH−O), 66.3 (CH−O), 59.3 (CH_2), 53.7 (d, P−O*CH*$_3$, $J_{C-P} = 6.5$ Hz), 51.0 (CH_2), 44.1 (d, P-*CH*$_2$, $J_{C-P} = 127.6$ Hz), 40.0 (CH_2), 37.3 (CH_2), 30.7 (C(*Me*)$_2$), 26.6 (Si−C(*CH*$_3$)$_3$), 20.4 (C(*Me*)$_2$), 18.9 (Si-*C*(CH_3)$_3$), −4.7 (Si−CH_3). Anal. Calcd for $C_{19}H_{39}O_7SiP$ (438.57): C, 52.03; H, 8.96. Found: C, 52.16; H, 9.22.

***tert*-Butyl (−)-(S_S)-3-Oxo-4-p-tolylsulfinyl Butanoate (8).** To a solution of diisopropylamine (29.7 mL; 0.226 mmol; 2.17 equiv) in THF (400 mL) was added n-BuLi (1.42 M in hexane; 148 mL; 2.1 equiv) at −40 °C. After 30 min, *tert*-butyl acetoacetate (17.2 mL; 0.104 mol) was added slowly via cannula at −65 °C. The cold bath was removed, and the solution was stirred for 1 h before adding a solution of (+)-menthyl-(S_R)-*p*-toluenesulfinate (15.37 g; 0.0522 mol; 0.5 equiv) in THF (120 mL) at −75 °C. When the reaction was completed (TLC), saturated NH_4Cl (100 mL) was added, and the pH was adjusted to 1 with diluted HCl. The aqueous layer was extracted with AcOEt (3 × 100 mL). The combined organic layers were washed with brine (100 mL), dried over $MgSO_4$, filtered, and concentrated to a deep yellow oil. This crude unstable product was purified by rapid chromatography on silica gel to afford a clear yellow unstable oil **8** (11.93 g; 77%), which must be immediately used in the next reaction: $[\alpha]^{20}_D = -204$ ($c = 1.4$, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) ketone/enol (70: 30), $\delta = 12.10$ (broad s, 0.3H, enol), 7.52 (A part of an $(AB)_2$ system, 0.7H, $J_{AB} = 6.5$ Hz, $\Delta\nu = 39$ Hz), 7.32 (B part of an $(AB)_2$ system, 2H, $J_{AB} = 6.5$ Hz, $\Delta\nu = 39$ Hz), 4.99 (s, 0.3H, enol), 4.00 (A part of an AB system, 0.7H, ketone, $J_{AB} = 13.5$ Hz, $\Delta\nu = 17.8$ Hz), 3.91 (B part of an AB system, 0.7H, ketone, $J_{AB} = 13.5$ Hz, $\Delta\nu = 17.8$ Hz), 3.54 (A part of an AB system, 0.3H, enol, $J_{AB} = 9$ Hz, $\Delta\nu = 36.3$ Hz), 3.36 (B part of an AB system, 0.3H, enol, $J_{AB} = 9$ Hz, $\Delta\nu = 36.3$ Hz), 3.46 (A part of an AB system, 0.7H, ketone, $J_{AB} = 13$ Hz, $\Delta\nu = 12.3$ Hz), 3.40 (B part of an AB system, 0.7H, ketone, $J_{AB} = 13$ Hz, $\Delta\nu = 12.3$ Hz), 2.39 (s, 3H), 1.45 (s, 6.3H, ketone), 1.42 (s, 2.7H, enol); ^{13}C NMR ($CDCl_3$) $\delta = 195.3$, 172.1, 166.0, 165.9, 142.7, 142.5, 140.6, 139.9, 130.6, 130.4, 124.5, 96.3, 82.9, 82.1, 68.0, 64.1, 52.4, 28.6, 28.4, 21.9. Anal. Calcd for $C_{15}H_{20}O_4S$ (296.38): C, 60.79; H, 6.80. Found: C, 60.89; H, 6.65.

***tert*-Butyl (−)-(3*R*,S_S)-3-Hydroxy-4-p-tolylsulfinyl-butanoate (9).** Dibal-H, 1 M in toluene (12.6 mL; 1.43 equiv), was added dropwise at −75 °C to a solution of **8** (2.61 g; 8.8 mmol) in THF (65 mL). After 45 min, the solution was quenched at −70 °C with MeOH (3 mL) and stirred for 1 h and then treated with a saturated solution of disodium L-tartrate dihydrate (10 mL). The mixture was left overnight at room temperature. The aqueous layer was acidified to pH = 5 with HCl concentrated, then extracted with AcOEt (3 × 60 mL). The combined organic layers were washed with brine (40 mL), dried over $MgSO_4$, and concentrated to an orange oil. This crude product was purified by rapid chromatography on silica gel, and the resulting pale yellow crystals were recrystallized (ether/hexane) to obtain **9** as white crystals (1.71 g; 66.6%): mp = 94 °C; $[\alpha]^{20}_D = -207$ ($c = 1.04$, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) $\delta = 7.53$ (A fragment of an $(AB)_2$ system, 2H, $J_{AB} = 8$ Hz, $\Delta\nu = 39$ Hz), 7.34 (B fragment of an $(AB)_2$ system, 2H, $J_{AB} = 8$ Hz, $\Delta\nu = 39$ Hz), 4.56 (m, 1H, Hx of an ABX system), 4.07 (d, 1H, OH, $J = 3.5$ Hz), 2.88 (AB part of ABX system, 2H, $J_{AB} = 13.5$ Hz, $J_{AX} = 10$ Hz, $J_{BX} = 2.5$ Hz, $\Delta\nu = 61$ Hz), 2.45 (d, 2H, $J = 6$ Hz), 2.42 (s, 3H), 1.41 (s, 9H); ^{13}C NMR ($CDCl_3$) $\delta = 170.7$, 141.7, 139.9, 130.2, 124.0, 81.7, 63.8, 61.8, 42.1, 28.1, 21.5. Anal. Calcd for $C_{15}H_{22}O_4S$ (298.40): C, 60.38; H, 7.43. Found: C, 60.53; H, 7.35.

***tert*-Butyl (−)-(3*R*,S_S)-3-*tert*-Butyldimethylsilyloxy-4-p-tolylsulfinyl-butanoate (10).** The alcohol **9** (4.98 g; 16.6 mmol) was dissolved at 0 °C under argon in dry DMF (80 mL). Imidazole (3 g; 2.65 equiv) and *tert*-butyldimethylsilyl chloride (3.8 g; 1.51 equiv) were added successively. After 15 h at room temperature, the reaction was hydrolyzed with water (100 mL) and diluted with ether (100 mL). The aqueous layer was extracted with ether (5 × 15 mL). The combined organic layers were washed with brine (20 mL), dried ($MgSO_4$), and concentrated. The crude orange oil was purified by rapid chromatography on silica gel to afford the clear yellow oil **10** (6.05 g; 88.3%): $[\alpha]^{20}_D = -138$ ($c = 0.94$, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) $\delta = 7.48$ (A fragment of an $(AB)_2$ system, 2H, $J_{AB} = 8$ Hz, $\Delta\nu = 41$ Hz), 7.28 (B fragment of an $(AB)_2$ system, 2H, $J_{AB} = 8$ Hz, $\Delta\nu = 41$ Hz), 4.58 (m, 1H, Hx of the two ABX system), 2.94 (AB of an ABX system, 2H, $J_{AB} = 13$ Hz, $J_{AX} = 8.5$ Hz, $J_{BX} = 4$ Hz, $\Delta\nu = 21$ Hz), 2.46 (AB of an ABX system, 2H, $J_{AB} = 15$ Hz, $J_{AX} = 6$ Hz, $J_{BX} = 4$ Hz, $\Delta\nu = 19$ Hz), 2.37 (s, 3H), 1.39 (s, 9H), 0.90 (s, 9H), 0.20 (s, 3H), 0.12 (s, 3H); ^{13}C NMR ($CDCl_3$) $\delta = 170.0$, 142.0, 141.8, 130.5, 124.3, 81.5, 67.0, 64.7, 44.1, 28.7, 26.4, 21.5, 18.7, −3.9, −4.2. Anal. Calcd for $C_{21}H_{36}O_4SSi$ (412.66): C, 61.12; H, 8.79. Found: C, 61.33; H, 8.63.

***tert*-Butyl (3*R*)-3-*tert*-Butyldimethylsilyloxy-4-acetoxy-4-p-tolylsulfenyl-butanoate (11).** Anhydrous sodium acetate (8.7 g; 14 equiv) was added to the sulfoxide **10** (3.88 g; 9.4 mmol). Acetic anhydride (230 mL) was then added and the mixture was refluxed for 14 h at 135 °C. After the solution was cooled, the brown heterogeneous solution was filtered, and the solvent was removed by azeotropic distillation with toluene (6 × 50 mL). The resulting deep brown residue was diluted with CH_2Cl_2 (20 mL) and filtered on Celite. The crude product was purified by column chromatography on silica gel (CH_2Cl_2/hexane 1:3) to afford **11** as a colorless oil (3.32 g; 78%). We obtained two stereoisomers at the C4 position in a ratio of 56:44 which were not separated: ^{1}H NMR (200 MHz, $CDCl_3$) 2 diastereomers (56/44) $\delta = 7.38$ (A fragment of an $(AB)_2$ system, 2H, $J_{AB} = 8$ Hz, $\Delta\nu = 55$ Hz), 7.10 (B fragment of an $(AB)_2$ system, 2H, $J_{AB} = 8$ Hz, $\Delta\nu = 55$ Hz), 6.15 (d, 0.56H, $J = 6$ Hz, one dia), 6.10 (d, 0.44H, $J = 2$ Hz, other dia), 4.40 (m, 0.44H, Hx of an ABX system, one dia), 4.32 (q, 0.56H, Hx of an ABX system, $J = 6$ Hz, other dia), 2.64 (2 superposed ABX

systems, 2H), 2.32 (s, 3H), 2.05 (s, 1.32H,one dia), 2.04 (s, 1.68H, other dia), 1.44 (s, 9H), 0.88 (s, 3.96H, one dia), 0.87 (s, 5.04H,other dia), 0.09 (s, 1.32H), 0.08 (s, 1.32H), 0.07 (s, 1.68H), 0.06 (s, 1.68H); ^{13}C NMR ($CDCl_3$) δ = 170.5, 169.9, 138.9, 138.6, 134.4, 133.9, 130.3, 129.9, 128.9, 86.5, 84.3, 81.3, 71.9, 70.6, 41.0, 40.6, 28.6, 26.3, 23.2, 21.7, 21.5, 18.6, 18.5, −4.1, −4.2, −4.3. Anal. Calcd for $C_{23}H_{38}O_5SSi$ (454.70): C, 60.76; H, 8.42. Found: C, 61.02; H, 8.31.

***tert*-Butyl (+)-(3*R*)-3-*tert*-Butyldimethylsilyloxy-4-acetoxy-butanoate (12).** Freshly actived Raney nickel was added by portions to a solution of compound **11** (0.573 g; 1.26 mmol) in MeOH (30 mL). The reaction at room temperature was monitored by TLC (AcOEt/hexane 1:9). The mixture was carefully filtered on Celite, and the cake was washed abundantly with MeOH. After the solvent was evaporated, the product was purified by rapid chromatography on silica gel (AcOEt/hexane 1:9) to afford a colorless liquid **12** (339 mg; 81%): $[\alpha]^{20}_D$ = +8 (c = 1.84, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ = 4.26 (m, 1H), 4.01 (d, 2H, J = 5.5 Hz), 2.40 (d, 2H, J = 6 Hz), 2.05 (s, 3H), 1.43 (s, 9H), 0.85 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H); ^{13}C NMR ($CDCl_3$) δ = 171.4, 170.8, 81.4, 68.4, 68.0, 41.8, 28.8, 26.4, 21.5, 18.7, −4.0, −4.2. Anal. Calcd for $C_{16}H_{32}O_5Si$ (332.51): C, 57.80; H, 9.70. Found: C, 57.89; H, 9.50.

***tert*-Butyl (+)-(3*R*)-3-*tert*-Butyldimethylsilyloxy-4-hydroxy-butanoate (13).** The ester **12** (1.38 g; 4.15 mmol) was dissolved in THF (100 mL) at −75 °C and Dibal-H, 1 M in toluene (9.2 mL; 2.2 equiv), was added dropwise. The colorless solution was stirred for 4 h, and the temperature was allowed to rise 5 °C. The reaction was then quenched with aqueous saturated NH_4Cl (30 mL), and the cold bath was removed. The solution was diluted with AcOEt (25 mL) and water (25 mL) and acidified to pH = 1 with HCl 1 N (6 mL). The aqueous layer was extracted with AcOEt (2 × 30 mL). The combined organic layers were washed with brine (50 mL), filtered, and concentrated. The crude colorless oily product was purified by rapid chromatography on silica gel (AcOEt/hexane 1:9) to afford a colorless liquid of **13** (1.05 g; 87%): $[\alpha]^{20}_D$ = +3 (c = 1.3, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ = 4.15 (m, 1H, Hx of an ABX system), 3.55 (m, 2H), 2.45 (AB of an ABX system, 2H, J_{AB} = 15.5 Hz, J_{AX} = 6.5 Hz, J_{BX} = 6 Hz, $\Delta\nu$ = 17 Hz), 2.07 (broad t, J = 6.5 Hz, 1H, OH), 1.43 (s, 9H), 0.87 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H); ^{13}C NMR ($CDCl_3$) 171.4, 81.3, 70.3, 66.8, 41.2, 28.7, 26.4, 18.6, −4.1, −4.2. Anal. Calcd for $C_{14}H_{30}O_4Si$ (290.48): C, 57.89; H, 10.41. Found: C, 57.63; H, 10.32.

***tert*-Butyl (+)-(3R)-3-*tert*-Butyldimethylsilyloxy-3-formyl-propanoate (14).** DMSO (165 mL) was added dropwise at −78 °C to a solution of oxalyl chloride (0.52 mL; 2.6 equiv) in CH_2Cl_2 (20 mL). After 15 min, the alcohol **13** (663 mg; 2.28 mmol) diluted in CH_2Cl_2 (7 mL) was slowly added. The reaction was stirred for 40 min and cooled at −70 °C. Then, NEt_3 (2 mL; 6.5 equiv) was added, and the mixture was stirred for 1 h in the cold bath and 40 min at room temperature. After completion, (TLC) the reaction was first quenched with CH_2Cl_2 (10 mL) and water (20 mL) and then neutralized with 1 N HCl (1 mL). The organic layer was washed with water (4 × 80 mL) and brine (60 mL) and then dried ($MgSO_4$). Evaporation of the solvent afforded **14** as a light yellow oil (292 mg; 93%), which was used in the next step without further purification: $[\alpha]^{20}_D$ = +30 (c = 1.04, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) 9.64 (s, 1H), 4.24 (t, 1H, J = 5.5 Hz), 2.63 (AB part of ABX system, 2H, J_{AB} = 16.5 Hz, J_{AX} = 5.4 Hz, J_{BX} = 5.5 Hz, $\Delta\nu$ = 0.4 Hz), 1.38 (s, 9H), 0.85 (s, 9H), 0.06 (s, 3H), 0.04 (s, 3H); ^{13}C NMR ($CDCl_3$) 203.7, 169.7, 81.9, 74.9, 40.6, 28.6, 26.2, 18.6, −4.2, −4.4. Anal. Calcd for $C_{14}H_{28}O_4Si$ (288.46): C, 58.29; H, 9.78. Found: C, 58.35; H, 9.72.

***tert*-Butyl (+)-(3*R*,4*S*)-3-*tert*-Butyldimethylsilyloxy-4-hydroxy-4-(2-thiazolyl)-butanoate (15).** 2-Trimethylsilylthiazole (0.57 mL; 1 equiv) was added to a solution of aldehyde **13** (1.03 g; 3.57 mmol) in dry CH_2Cl_2 (40 mL), and the solution was stirred overnight at room temperature. It was then evaporated to dryness under reduced pressure, and the resulting yellow oil was added to a 5% citric acid in methanol (60 mL). After the mixture was stirred for 4 h at room temperature, water was added (40 mL) as well as saturated $NaHCO_3$ (20 mL). The solution was then diluted with ether (80 mL), and the aqueous layer was extracted with ether (3 × 30 mL). The organic layers were combined, washed with brine (50 mL), dried over $MgSO_4$, and concentrated. The crude product was purified by column chromatography on silica gel (AcOEt/hexane 2:8) to afford **15** as a colorless oil (954 mg; 72%): $[\alpha]^{20}_D$ = +6 (c = 0.87, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) 7.75 (d, 1H, J = 3 Hz), 7.26 (d, 1H, J = 3 Hz), 4.94 (dd, 1H, J = 7.5 Hz, J = 2.5 Hz), 4.65 (m, 1H, Hx of an ABX system), 3.85 (d, 1H, OH, J = 7.5 Hz), 2.55 (AB of an ABX system, 2H, J_{AB} = 16 Hz, J_{AX} = 7 Hz, J_{BX} = 5.5 Hz, $\Delta\nu$ = 74 Hz), 1.43 (s, 9H), 0.80 (s, 9H), 0.02 (s, 3H), −0.25 (s, 3H); ^{13}C NMR ($CDCl_3$) 173.8, 171.0, 143.0, 119.8, 81.9, 74.7, 72.2, 40.5, 28.8, 26.3, 18.6, −4.3, −4.7. Anal. Calcd for $C_{17}H_{31}NO_4SSi$ (373.58): C, 54.66; N 3.75, H, 8.36. Found: C, 54.87; N, 3.12, H, 8.34.

***tert*-Butyl (+)-(3R,4S)-3,4-Dihydroxy-4-(2-thiazolyl)-butanoate (16).** Tetrabutylammonium fluoride, 1 M in THF (0.165 mL; 1.1 equiv), was added to a solution of protected alcohol **15** (56 mg; 0.15 mmol) in dry THF (5 mL) at 0 °C. After the TLC had shown that the reaction was complete, the reaction was quenched by adding a spatula of silica. The solution was stirred on for 30 min before evaporating the solvent under reduced pressure. The crude compound kept on the silica was purified by chromatography on silica gel (AcOEt/hexane 1:3) to afford a light yellow oil **16** (36 mg; 93%): $[\alpha]^{20}_D$ = +7 (c = 0.96, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) 7.68 (d, 1H, J = 3 Hz), 7.29 (d, 1H, J = 3 Hz), 4.90 (d, 1H, J = 4 Hz), 4.39 (dt, 1H, Hx of an ABX system, J = 8 Hz, J = 4 Hz), 3.96 (m, 2H, 2 × OH), 2.59 (AB of an ABX system, 2H, J_{AB} = 16.5 Hz, J_{AX} = 5 Hz, J_{BX} = 7 Hz, $\Delta\nu$ = 22 Hz), 1.45 (s, 9H); ^{13}C NMR ($CDCl_3$) 172.9, 172.3, 142.9, 120.1, 82.1, 74.1, 71.5, 39.2, 28.7. Anal. Calcd for $C_{11}H_{17}NO_4S$ (259.32): C, 50.95; H, 6.61; N, 5.40. Found: C, 50.78; H, 6.62; N, 5.12.

***tert*-Butyl (+)-(3*R*,4*S*)-3,4-Isopropylidenedioxy-4-(2-thiazolyl)-butanoate (17).** 2,2-Dimethoxypropane (0.15 mL; 4 equiv) and *p*-toluenesulfonic acid (30 mg; 0.5 equiv) were added successively to a solution of diol **16** (81 mg; 0.31 mmol) in acetone (5 mL). The solution was stirred overnight at room temperature and then evaporated to dryness under reduced pressure. The resulting yellow oil was dissolved in CH_2Cl_2 (4 mL), and saturated $NaHCO_3$ (4 mL) was added. The solution was stirred for 2 h, and then the aqueous layer was extracted with CH_2Cl_2 (3 × 7 mL). The organic layers were washed with brine (20 mL), dried over $MgSO_4$, and concentrated. The crude compound was purified on silica gel (AcOEt/hexane 1:3) to afford **17** as a yellow oil (86 mg; 92%): $[\alpha]^{20}_D$ = +13 (c = 0.92, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) 7.74 (d, 1H, J = 3 Hz), 7.32 (d, 1H, J = 3 Hz), 5.00 (d, 1H, J = 8 Hz), 4.37 (dt, 1H, Hx of an ABX system, J = 8 Hz, J = 3.5 Hz), 2.74 (AB of an ABX system, 2H, J_{AB} = 16 Hz, J_{AX} = 4 Hz, J_{BX} = 8 Hz, $\Delta\nu$ = 42 Hz), 1.53 (s, 3H), 1.51 (s, 3H), 1.42 (s, 9H); ^{13}C NMR ($CDCl_3$) 170.1, 169.7, 143.6, 119.9, 111.2, 81.7, 80.1, 79.0, 38.5, 28.7, 27.9, 27.3. Anal. Calcd for $C_{14}H_{21}NO_4S$ (299.38): C, 56.17; H, 7.07; N, 4.68. Found: C, 56.37; H, 6.97; N, 4.47.

***tert*-Butyl (+)-(3*R*,4*S*)-4-Formyl 3,4-isopropylidenedioxy-butanoate (18).** To a solution of compound **17** (35 mg; 0.12 mmol) in dry acetonitrile (2 mL) were added powdered activated molecular sieves (200 mg) and methyltriflate (17 μL; 1.3 equiv). The solution was stirred at rt, and the reaction was followed by TLC. When there was no more starting material left (~2 h), the solution was evaporated to dryness under reduced pressure. The residue was dissolved in dry methanol (2 mL) and cooled at 0 °C before adding sodium borohydride (10 mg; 2.2 equiv). After 30 min at 0 °C, the cold bath was removed and the solution stirred for 30 min at room temperature before quenching with acetone (3 mL). Filtration through Celite and solvent evaporation led to a light yellow oil, which was dissolved again in acetonitrile (2 mL), and a solution of mercury(II) chloride (38 mg; 1.2 equiv) in CH_3CN/H_2O (5 mL, 4:1) was added dropwise. After the solution was stirred for 15 min, the reaction mixture was filtered through Celite, which was carefully washed with CH_2Cl_2 (15 mL). After solvent evaporation, the residue was dissolved in CH_2Cl_2 (4 mL) and brine (4 mL) was added. The biphasic solution was stirred vigorously for 2 h, and then the two layers were separated.

The aqueous layer was extracted with CH_2Cl_2 (3 × 4 mL), and the organic layers were combined and dried on $MgSO_4$. After filtration and evaporation of the solvent, an orange oil was obtained (37 mg) and used without any purification in the next step: ^{1}H NMR (200 MHz, $CDCl_3$) 9.74 (d, 1H, J = 2 Hz), 4.46−4.39 (m, 1H), 4.10 (dd, 1H, J = 7.5 Hz, J = 2 Hz), 2.65 (dd, 2H, J = 6.5 Hz, J = 2.5 Hz), 1.47 (s, 3H), 1.45 (s, 9H), 1.42 (s, 3H); ^{13}C NMR ($CDCl_3$) 200.7, 169.8, 112.0, 84.7, 82.2, 73.8, 39.9, 28.7, 27.7, 26.9.

***tert*-Butyl (−)-(3*S*,5*S*,*R*,10*R*,11*R*)-1-*tert*-Butyldimethylsilyloxy-di-3,5−10,11-isopropylidene-dioxy-7-oxo-tridec-8-en-13-oate (20).** To a solution of phosphonate **2** (70 mg; 0.16 mmol) in dry DME (1.5 mL) at 0 °C was added sodium hydride (4 mg; 1.1 equiv). The solution was then heated for 45 min at 55 °C and became bright orange. After the solution was cooled to −78 °C, a solution of the crude aldehyde **18** (∼35 mg; 1.1 equiv) in dry DME (0.6 mL) was added. The temperature of the cold bath was allowed to rise slowly to room temperature, and the reaction was followed on TLC. The reaction was quenched after 4 h by adding saturated NH_4Cl (3 mL). Water (3 mL) was also added, the two layers were separated, and the organic layer was washed with saturated $NaHCO_3$ (3 mL) and brine (3 mL). The aqueous layers were combined, saturated with NaCl, and extracted with ether (3 × 3 mL). The combined organic layers were dried on $MgSO_4$ and concentrated to 82 mg of a yellow oil. Purification on TLC (CH_2Cl_2/hexane 1:1) gave a colorless oil (60 mg; 68%) of **20**: $[\alpha]^{20}_D$ = −7 (c = 1.02, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) 6.75 (dd, 1H, J = 16 Hz, ^3J = 6 Hz), 6.37 (dd, 1H, J = 16 Hz, ^4J = 1 Hz), 4.44−4.33 (m, 2H), 4.31−4.01 (m, 2H), 3.78−3.58 (m, 2H), 2.71 (AB of an ABX system, 2H, J_{AB} = 16 Hz, J_{AX} = 6.5 Hz, J_{BX} = 5 Hz, $\Delta\nu$ = 67 Hz), 2.66−2.45 (m, 2H), 1.68−1.62 (m, 3H), 1.58 (s, 6H), 1.45 (s, 12H), 1.34 (s, 3H), 1.25−1.14 (m, 1H), 0.89 (s, 9H), 0.04 (s, 6H); ^{13}C NMR ($CDCl_3$) 198.4, 169.8, 142.6, 132.1, 110.6, 99.4, 82.1, 80.5, 77.5, 66.5, 66.1, 59.4, 47.8, 40.1, 38.9, 37.8, 30.8, 28.8, 27.8, 27.4, 26.6, 20.5, 18.9, −4.7. Anal. Calcd for $C_{29}H_{52}O_8Si$ (556.81): C, 62.56; H, 9.41. Found: C, 62.31; H, 9.47.

***tert*-Butyl (+)-(3*S*,5*S*,7*S*,10*R*,11*R*)-1-*tert*-Butyldimethylsilyloxy-7-hydroxy-di-3,5−10,11-isoproylidenedioxy-tridec-8-en-13-oate (21).** To a solution of ketone **20** (9 mg; 16 μmol) in dry methanol (1 mL) at 0 °C was added sodium borohydride (3 mg; 4 equiv). The solution was stirred for 30 min in a cold bath, and the reaction was then quenched by adding saturated NH_4Cl (1 mL). The cold bath was removed, and the aqueous layer was acidified to pH = 3 and then extracted with CH_2Cl_2 (3 × 1 mL). The organic layers were combined and dried on $MgSO_4$. After filtration and evaporation of the solvent, a colorless oil (10 mg) was obtained. ^{1}H NMR showed a mixture of two diastereomers (72/28), which could be separated by TLC (AcOEt/hexane 1:3). For the main isomer (6 mg, 64% isolated yield): $[\alpha]^{20}_D$ = +6 (c = 1.06, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) 5.84 (dd, 1H, J = 15.5 Hz, ^3J = 4.5 Hz), 5.70 (dd, 1H, J = 15.5 Hz, ^3J = 6 Hz), 4.36 (m, 1H), 4.17−3.99 (m, 4H), 3.78−3.58 (m, 2H), 3.46 (s, 1H, OH), 2.47 (d, 2H, J = 5.5 Hz), 1.73−1.62 (m, 5H), 1.58 (s, 3H), 1.46 (s, 9H), 1.45 (s, 3H), 1.41 (s, 3H), 1.33−1.21 (m, 1H), 0.89 (s, 9H), 0.04 (s, 6H); ^{13}C NMR ($CDCl_3$) 170.4, 138.0, 126.5, 109.7, 99.4, 81.7, 80.5, 77.7, 71.8, 66.1, 59.3, 43.7, 39.9, 38.7, 30.9, 28.8, 27.8, 27.6, 26.6, 20.6, 18.9, −4.7. Anal. Calcd for $C_{29}H_{54}O_8Si$ (558.83): C, 62.33; H, 9.74. Found: C, 62.15; H, 9.52.

***tert*-Butyl (+)-(3*S*,5*R*,7*R*,10*R*,11*R*)-1-*tert*-Butyldimethylsilyoxy-7-hydroxy-di-3,5−10,11-isopropylidenedioxy-tridecanoate (1).** To a solution of alkene **21** (16 mg; 29 μmol) in AcOEt (0.5 mL) was added Pd/C, and the heterogeneous solution was stirred for 3 h at room temperature under hydrogen atmosphere. The palladium was then filtered through Celite, and the solution was concentrated to a colorless oil. Purification by TLC (AcOEt/hexane 1:3) gave a colorless oil (8 mg; 50%) of **1**: $[\alpha]^{20}_D$ = +9 (c = 0.57, $CHCl_3$); ^{1}H NMR (200 MHz, C_6D_6) 4.30−4.20 (m, 1H), 4.01−3.58 (m, 6H), 3.39 (s, 1H), 2.46 (AB of an ABX system, 2H, J_{AB} = 15 Hz, J_{AX} = 7 Hz, J_{BX} = 5 Hz, $\Delta\nu$ = 26.9 Hz), 1.84−1.51 (m, 9H), 1.41 (s, 6H), 1.39 (s, 12H), 1.35−1.20 (m, 1H), 1.31 (s, 3H), 1.00 (s, 9H), 0.07 (s, 6H); ^{13}C NMR ($CDCl_3$) 170.6, 109.2, 99.4, 81.7, 81.1, 77.7, 71.6, 70.9, 66.3, 59.6, 43.8, 40.0, 39.98, 39.90, 38.1, 34.4, 30.9, 28.8, 28.0, 27.9, 26.6, 20.7, 18.9, −4.7. Anal. Calcd for $C_{29}H_{56}O_8Si$ (560.84): C, 62.11; H, 10.06. Found: C, 61.95; H, 9.97.

***tert*-Butyl (+)-(3*R*,4*S*)-3,4-Di-*tert*-butyldimethylsilyloxy-4-formyl-butanoate (19).** Methyl iodide (0.8 mL; 45 equiv) was added to a solution of thiazole **15** (132 mg; 0.28 mmol) in dry acetonitrile (5 mL), and the solution was stirred under reflux ($T_{\text{oil bath}}$ = 95 °C). When the reaction was completed (TLC, 17 h), the solution was evaporated to dryness under reduced pressure. The resulting orange oil was dissolved in dry methanol (5 mL) and sodium borohydride (16 mg; 1.5 equiv) was added at 0 °C. After the reaction was warmed to at room temperauture, the reaction was followed on TLC. When all the starting permethylated thiazole had reacted, acetone was added (0.5 mL). The solution was evaporated again to dryness, the resulting yellow oil was dissolved in CH_2Cl_2 (5 mL), and water (5 mL) was added. The solution was stirred for 10 min, and then the aqueous layer was extracted with CH_2Cl_2. The organic layers were combined and dried on $MgSO_4$. The residue was dissolved in acetonitrile (4 mL), and a solution of mercuric chloride (93 mg; 1.2 equiv) in CH_3CN/H_2O (15 mL; 4:1) was added. After the solution was stirred for 30 min at room temperature, the mixture was filtered over Celite. The Celite was washed with ether (20 mL). The solution was concentrated, and the residue was dissolved in CH_2Cl_2 (6 mL) and brine (8 mL). This solution was stirred overnight at room temperature, and then the aqueous layer was extracted with CH_2Cl_2 (3 × 4 mL). The organic layers were combined and dried over $MgSO_4$. After evaporation of the solvent under reduced pressure, an orange oil was obtained (113 mg; 93%), which was pure enough to be used in the next step: $[\alpha]^{20}_D$ = +45 (c = 1.04, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) 9.72 (d, 1H, J = 1 Hz), 4.39 (m, 1H, Hx part of an ABX system), 4.09 (dd, 1H, J = 4.5 Hz, J = 1 Hz), 2.48 (AB part of an ABX system, 2H, J_{AB} = 16 Hz, J_{AX} = 4.5 Hz, J_{BX} = 8 Hz, $\Delta\nu$ = 94 Hz), 1.43 (s, 9H), 0.91 (s, 9H), 0.85 (s, 9H), 0.09 (s, 3H), 0.07 (s, 3H), 0.06 (s, 3H), 0.04 (s, 3H);^{13}C NMR ($CDCl_3$) 203.4, 171.8, 81.4, 79.8, 39.4, 28.8, 26.4, 18.6, −3.9, −4.0, −4.1, −4.5.

JO990245Y