Total Synthesis of (+)-Galactostatin. An Illustration of the Utility of the Thiazole–Aldehyde Synthesis

Alessandro Dondoni* and Daniela Perrone

Dipartimento di Chimica, Laboratorio di Chimica Organica, Università, Ferrara, Italy

Received March 8, 1995[⊗]

The natural aza sugar (+)-galactostatin (+)-**1** has been prepared from D-serine by sequential installation of chiral 1C and 2C units employing thiazole-based reagents. Thus, the D-serine-derived methyl ester **3** was transformed by 2-thiazolyllithium (**4**) into the thiazolyl amino ketone **5** which, via *syn* stereoselective carbonyl reduction and thiazolyl-to-formyl conversion, gave the first key intermediate, the α-hydroxy β-amino aldehyde **10**. The olefination of this compound by [(2-thiazolyl)-methylene]triphenylphosphorane (**14**) followed by osmium tetroxide *cis* dihydroxylation of the resulting alkene ***E*-16** and cleavage of the thiazole ring produced the second key intermediate, the amino- and hydroxyl-protected 5-deoxy-5-amino- D-galactose **20**. The removal of all protecting groups of this compound afforded the target aza sugar (+)-**1** in 17.3% overall yield from **3**.

One of the attractive features of the thiazole–aldehyde synthesis is its wide synthetic potential arising from the availability of different types of thiazole-based reagents.[1] For instance, suitable reaction sequences with an organometallic, a ketone, and a phosphorane, all bearing the 2-thiazolyl ring, provided a stereocontrolled synthesis of the azahexoses (−)-nojirimycin and the C-2 epimer (−)-mannojirimycin, as well as their 3-deoxy derivatives, from L-serine.[2] We give here a further illustration of the utility of the thiazole–aldehyde route to aza sugars by describing an improved synthesis[3] of the relatively less popular azahexose (+)-galactostatin (+)-**1**. This natural product, recently isolated by Miyake et al.[4] from the culture broth of *Streptomyces lydicus* PA-5725, has been reported to be a potent and specific inhibitor of several α- and β-galactosidases.[4b,5] There is, in fact, considerable interest in either chemical or enzymatic synthetic routes to naturally occurring aza sugars and unnatural analogs[6] since these modified furanoses and pyranoses with the ring oxygen replaced by an amino group are potent inhibitors of enzymes associated with carbohydrate processing.[7] Glycosidase inhibitors[8] have been shown to have potential therapeutic utility against various deseases such as diabetes, cancer, and viral infections.[9] Particular attention has been focused on the anti-HIV activity of aza sugars arising from the inhibition of the glycoprotein processing necessary for virus replication, an essential step for infectivity.[10]

The synthesis of (+)-galactostatin (+)-**1**, also named *galacto*-nojirimycin, was reported earlier from carbohydrate precursors such as 1,6-anhydro-α-D-galactofuranose (2.4%)[11] and D-glucose (ca. 6%)[12] and more recently from a functionalized allylic alcohol (4.6%)[13] derived from L-tartaric acid and from a chiral cyclitol (9.3%)[14] available from the serum of the rubber tree. A retrosynthetic analysis outlined in Figure 1 indicates a route to (+)-**1** from D-serine **2** through the aldehydes **A**–**C**. This synthesis plan was carried out very efficiently by the use of two thiazole-based reagents as described below.

Results and Discussion

Execution of the first phase of the synthesis (Figure 1, **2** → **C**) required the reduction of the amino acid **2** and insertion of a chiral hydroxymethylene group. A recent

[⊗] Abstract published in *Advance ACS Abstracts,* June 15, 1995.

(1) For reviews on the thiazole–aldehyde synthesis, see: (a) Dondoni, A. In *Modern Synthetic Methods*; Scheffold, R., Ed.; Helvetica Chimica Acta: Basel, 1992; pp 377–437. (b) Dondoni, A. In *New Aspects of Organic Chemistry II*; Yoshida, Z., Ohshiro, Y., Eds.; Kodansha: Tokyo and VCH: Weinheim, 1992; pp 105–128.

(2) Dondoni, A.; Merino, P.; Perrone, D. *Tetrahedron* **1993**, *49*, 2939.

(3) For a preliminary communication describing the synthesis of the unnatural isomer, see: Dondoni, A.; Merino, P.; Perrone, D. *J. Chem. Soc., Chem. Commun.* **1991**, 1576.

(4) (a) Miyake, Y.; Ebata, M. *J. Antibiot.* **1987**, *40*, 122. (b) Miyake, Y.; Ebata, M. *Agric. Biol. Chem.* **1988**, *52*, 153.

(5) Miyake, Y.; Ebata, M. *Agric. Biol. Chem.* **1988**, *52*, 1649.

(6) For recent papers with leading references, see: (a) ref 2. (b) Look, G. C.; Fotsch, C. H.; Wong, C.-H. *Acc. Chem. Res.* **1993**, *26*, 182. (c) Ardron, H.; Butters, T. D.; Platt, F. M.; Wormald, M. R.; Dwek, R. A.; Fleet, G. W. J.; Jacob, G. S. *Tetrahedron: Asymmetry* **1993**, *4*, 2011. (d) Lay, L.; Nicotra, F.; Paganini, A.; Pangrazio, C.; Panza, L. *Tetrahedron Lett.* **1993**, *34*, 4555. (e) Arnone, A.; Bravo, P.; Donadelli, A.; Resnati, G. *J. Chem. Soc., Chem. Commun.* **1993**, 984. (f) Casiraghi, G.; Rassu, G.; Spanu, P.; Pinna, L.; Ulgheri, F. *J. Org. Chem.* **1993**, *58*, 3397. (g) Zhou, P.; Salleh, H. M.; Honek, J. F. *J. Org. Chem.* **1993**, *58*, 264. (h) Jirousek, M. R.; Cheung, A. W.-H.; Babine, R. E.; Sass, P. M.; Schow, S. R.; Wick, M. M. *Tetrahedron Lett.* **1993**, *34*, 3671. (i) Martin, S. F.; Chen, H.-J.; Yang, C.-P. *J. Org. Chem.* **1993**, *58*, 2867. (j) Furneaux, R. H.; Lynch, G. P.; Way, G.; Winchester, B. *Tetrahedron Lett.* **1993**, *34*, 3477. (k) Furneaux, R. H.; Tyler, P. C.; Whitehouse, L. A. *Tetrahedron Lett.* **1993**, *34*, 3613. (l) Ina, H.; Kibayashi, C. *J. Org. Chem.* **1993**, *58*, 52. (m) Hudlicky, T.; Rouden, J.; Luna, H. *J. Org. Chem.* **1993**, *58*, 985. (n) Holt, K. E.; Leeper, F. J.; Handa, S. *J. Chem. Soc., Perkin Trans. 1* **1994**, 231. (o) Chen, Y.; Vogel, P. *J. Org. Chem.* **1994**, *59*, 2487. (p) Baxter, E. W.; Reits, A. B. *J. Org. Chem.* **1994**, *59*, 3175. (q) Cook, G. R.; Beholz, L. G.; Stille, J. R. *J. Org. Chem.* **1994**, *59*, 3575.

(7) An extensive collection of references on this topic can be found in almost every paper cited in ref 6.

(8) For glycosidase inhibitors other than aza sugars, see: (a) Trost, B. M.; Van Vranken, D. L. *J. Am. Chem. Soc.* **1993**, *115*, 444. (b) Papandreou, G.; Tong, M. K.; Ganem, B. *J. Am. Chem. Soc.* **1993**, *115*, 11682.

(9) For references, see: (a) Reitz, A. B.; Baxter, E. W. *Tetrahedron Lett.* **1990**, *31*, 6777. (b) Kajimoto, T.; Liu, K. K.-C.; Pederson, R. L.; Zhong, Z.; Ichikawa, Y.; Porco, J. A., Jr.; Wong, C.-H. *J. Am. Chem. Soc.* **1991**, *113*, 6187.

(10) (a) Gruters, R. A.; Neefjes, J. J.; Tersmette, M.; de Goede, R. E. Y.; Tulp, A.; Huisman, H. G.; Miedema, F.; Ploegh, H. L. *Nature* **1987**, *330*, 74. (b) Karpas, A.; Fleet, G. W. J.; Dwek, R. A.; Petursson, S.; Namgoong, S. K.; Ramsden, N. G.; Jacob, G. S.; Rademacher, T. W. *Proc. Natl. Acad. Sci. U.S.A.* **1988**, *85*, 9229. (c) Montefiori, D. C.; Robinson, W. E., Jr.; Mitchell, W. M. *Proc. Natl. Acad. Sci. U.S.A.* **1988**, *85*, 9248. (d) Liu, P. S.; Hoekstra, W. J.; King, C.-H. R. *Tetrahedron Lett.* **1990**, *31*, 2829.

(11) Paulsen, H.; Hayauchi, Y.; Sinnwell, V. *Chem. Ber.* **1980**, *113*, 2601. The anhydro sugar employed for the synthesis was obtained in 1.5% yield by pyrolysis of D-galactose.

(12) Legler, G.; Pohl, S. *Carbohydr. Res.* **1986**, *155*, 119.

(13) Aoyagi, S.; Fujimaki, S.; Yamazaki, N.; Kibayashi, C. *J. Org. Chem.* **1991**, *56*, 815. The allylic alcohol employed for the synthesis was obtained in 70% yield from L-tartaric acid.

(14) Chida, N.; Tanikawa, T.; Tobe, T.; Ogawa, S. *J. Chem. Soc., Chem. Commun.* **1994**, 1247.

0022-3263/95/1960-4749$09.00/0

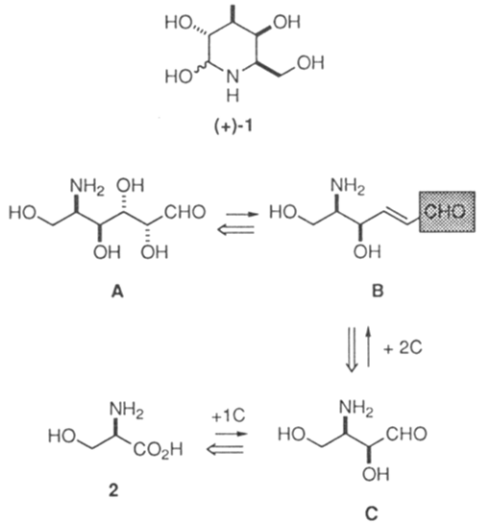
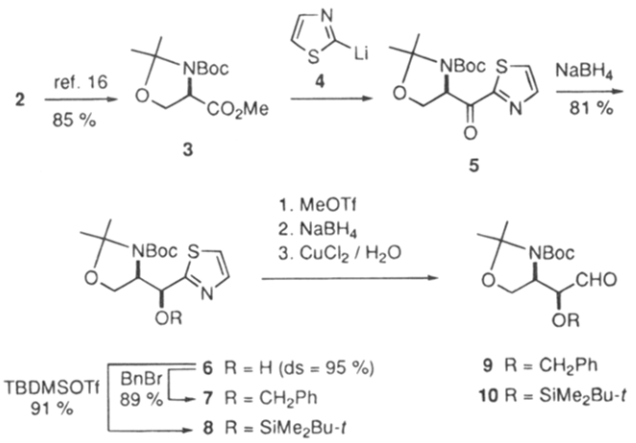


Figure 1. Synthesis plan.

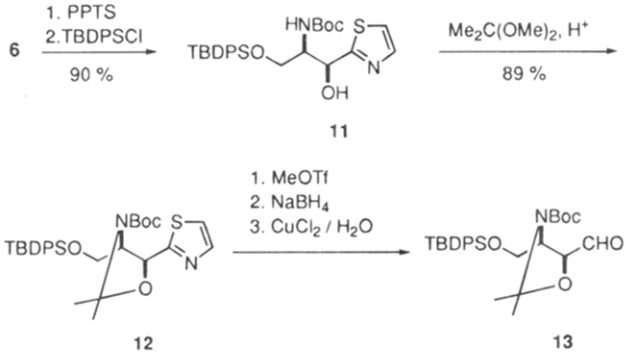
Scheme 1



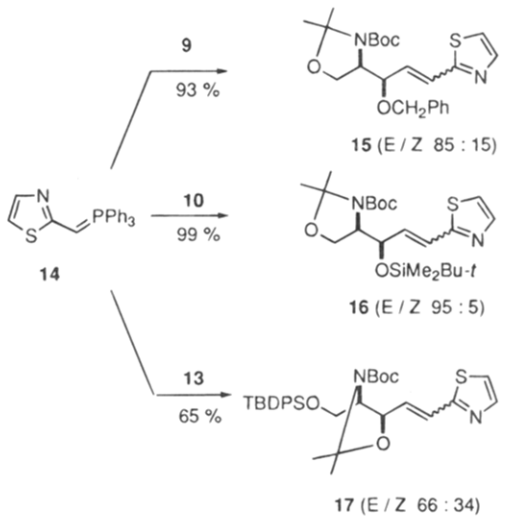
strategy for α-amino acid homologation via 2-thiazolyl α-amino ketones[15] provided a simple solution to this problem. Hence, D-serine **2** was transformed into the *N*-Boc methyl ester acetonide **3** in three steps (85% yield) as previously described,[16] and this compound was then treated with 2-thiazolyllithium (**4**) generated *in situ* at −78 °C from 2-bromothiazole and *n*-butyllithium (Scheme 1). The resulting crude amino ketone **5** was reduced by $NaBH_4$ to the *syn* amino alcohol[17] **6** with excellent stereoselectivity (ds = 95%) and good isolated chemical yield (81%). The spectral and physical properties (NMR and $[\alpha]_D$) of this compound were identical, except for the sign of the optical rotation, with those of the antipode ***ent*-6** obtained by the same route from L-serine.[15] Moreover, it was established through the ^1H NMR analysis of the Mosher esters of **6** and ***ent*-6** that the enantiomeric purity was >95%. This result supported the configurational stability of the ketone **5** as well.

We then turned to the aldehyde release from **6**. To this end, the compound was transformed into the benzyl and silyl ethers **7** and **8**, respectively, which in turn were subjected to the standard one-pot thiazolyl-to-formyl deblocking protocol to give the aldehydes **9** and **10** in fairly good yields. In addition, following the previous synthetic approach[3] to the antipode of (+)-**1**, the acetonide protective group of **6** was shifted to incorporate the secondary hydroxyl group (Scheme 2) and the resulting 2-thiazolyloxazolidine **12** was transformed into the aldehyde **13**. The synthesis of this compound proved to be less convenient than reported[3] due to inefficient N-methylation of the thiazole ring of **12**, particularly in large scale experiments. Fortunately enough, the readily available aldehydes **9** and **10** appeared to be more useful than **13** for the continuation of the synthesis plan (see below).

Scheme 2



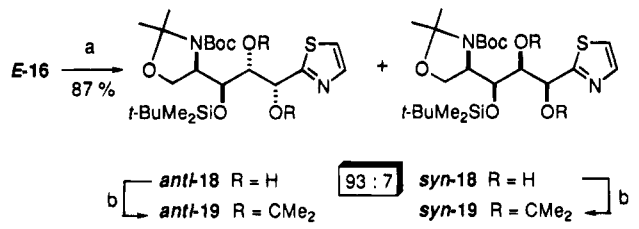
Scheme 3



As the second phase required the construction of a protected α,β-enal (Figure 1, **C** → **B**), a quite logical approach was to apply the Wittig-type olefination to aldehydes **9**, **10**, and **13** with the thiazolylphosphorane[1a] **14**. Work on the use of this formyl-protected semistabilized ylide for the installation of a 2C unit in various polyalkoxy aldehydes had been reported from this laboratory.[2,18] The reaction of **14** with aldehydes **9**, **10**, and **13** in toluene at room temperature (Scheme 3) afforded the corresponding alkenes **15**−**17** with different *E*/*Z* selectivities and yields. These were quite good for **15** and **16** but very low[19] for **17**. Unfortunately, the olefination of the aldehyde **9** produced ***E*-15** contaminated by 6−7%

(15) Dondoni, A.; Perrone, D. *Synthesis* **1993**, 1162.
(16) Garner, P.; Park, J. M. *J. Org. Chem.* **1987**, *52*, 2361.
(17) Various examples have been reported (ref 15) wherein the hydride reduction of N,N-diprotected 2-thiazolyl α-amino ketones is *syn*-selective, whereas the same reaction with N-monoprotected derivatives is *anti*-selective. Tunable diastereoselectivity has also been observed in addition reactions of 2-metalated thiazoles to differentially protected α-amino aldehydes (Dondoni, A.; Fantin, G.; Fogagnolo, M.; Pedrini, P. *J. Org. Chem.* **1990**, *55*, 1439) and their nitrones (Dondoni, A.; Merchan, F. L.; Merino, P.; Tejero, T.; Bertolasi, V. *J. Chem. Soc., Chem. Commun.* **1994**, 1731).
(18) (a) Dondoni, A.; Fantin, G.; Fogagnolo, M.; Pedrini, P. *Tetrahedron* **1989**, *45*, 5141. (b) Dondoni, A.; Fantin, G.; Fogagnolo, M.; Merino, P. *J. Carbohydr. Chem.* **1990**, *9*, 735. (c) Dondoni, A.; Merino, P.; Orduna, J.; Perrone, D. *Synthesis* **1993**, 277.

Scheme 4[a]

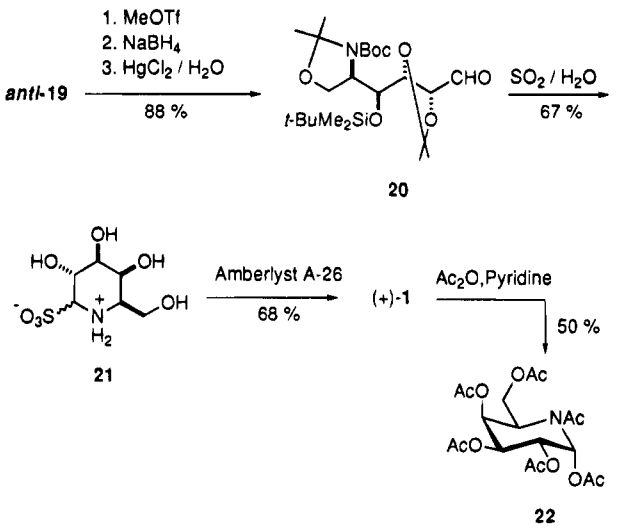


[a] Key: (a) OsO_4, 4-methylmorpholine *N*-oxide; (b) MeC(OMe)=CH_2, PPTS.

of a hardly removable byproduct.[20] Consequently, this ***E*-15** olefin was isolated in rather poor yield (45%) by flash chromatography and crystallization. On the other hand, the isolation of pure ***E*-16** in 92% yield was carried out without any problem by flash chromatography. The configuration of alkenes ***E*-15** and ***E*-16** was substantiated by their vinyl proton coupling constant values which were higher (J = ca. 16 Hz) than those of the corresponding *Z*-isomers (J = ca. 12 Hz).

Because of the convenient access to the masked α,β-enal ***E*-16**, the synthesis was continued with this compound (Figure 1, **B** → **A**). The osmium tetroxide *cis* dihydroxylation of the double bond[21] was considered. The reaction of ***E*-16** with a catalytic amount of osmium tetroxide and 2 equiv of *N*-methylmorpholine *N*-oxide as reoxidant (Scheme 4) occurred with good stereoselectivity to give a 93:7 mixture of *cis* 1,2-diols ***anti*-18** and ***syn*-18** in a 87% combined yield. The configuration of the major isomer ***anti*-18** was assigned on the basis of previous asymmetric *cis* dihydroxylation reactions with osmium tetroxide.[2,22] Convenient separation of diastereomers ***anti*-18** and ***syn*-18** was carried out by flash chromatography of their acetonide derivatives **19**. In this way, the main isomer ***anti*-19** was isolated in 85% yield. Having completed the assemblage of the chiral moiety, we released the protected 5-deoxy-5-amino-D-galactose **20** in good yield from ***anti*-19** by the conventional thiazolyl-to-formyl deblocking protocol (Scheme 5). Treatment of the aldehyde **20** with an aqueous solution of sulfur dioxide at 40 °C removed all protecting groups and afforded the crystalline and easily isolable galactostatin bisulfite adduct **21** (67% yield), whose optical rotation $[\alpha]_D$ +19.0 was in good agreement with that of the natural product (lit.[4b] $[\alpha]_D$ +17.2 (*c* 0.5, H_2O)). This compound, upon treatment with Amberlyst A-26 ion exchange resin, gave (+)-galactostatin (+)-**1** as a colorless amorphous powder in 68% yield (17.3% from the ester **3**). The physical properties of synthetic (+)-**1**, mp 94–96 °C and $[\alpha]_D$ +81.2 (*c* 0.5, H_2O), were in excellent agreement with those of the natural product (lit.[4b] mp 94–98 °C, $[\alpha]_D$ +84.6 (*c* 0.3, H_2O)). Verification of the structure and stereochemistry of (+)-**1** was obtained by conversion into

Scheme 5



the peracetylated derivative **22** and ^1H NMR analysis of this compound.

Thus, an improved synthesis of the natural aza sugar (+)-galactostatin (+)-**1** from D-serine exploiting two thiazole-based reagents has been accomplished. The overall chemical yield is higher than those registered by other approaches reported in the literature. The D-serine-derived ester **3** employed as starting material in the present synthesis is readily accessible from the free amino acid by three very simple and high-yield chemical transformations. Finally, since the stereochemistry of the amino acid is employed to initiate the construction of the new stereocenters, the synthetic route appears equally amenable for the preparation of the unnatural antipode (−)-galactostatin starting from L-serine.

Experimental Section

All moisture-sensitive reactions were performed under an argon atmosphere using oven-dried glassware. Solvents were dried over standard drying agents[23] and freshly distilled prior to use. Flash column chromatography[24] was performed on silica gel 60 (230–400 mesh). Reactions were monitored by TLC on silica gel 60 F_{254} with detection by charring with ninhydrin or sulfuric acid alcoholic solutions. Melting points were determined with a capillary apparatus and are uncorrected. Optical rotations were measured at 20 ± 2 °C in the stated solvent. ^1H (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded at room temperature for $CDCl_3$ solutions, unless otherwise specified. ^1H NMR peak assignments for compound **22** were derived from homonuclear two-dimensional experiments.

N-(*tert*-Butoxycarbonyl)-*N*,*O*-isopropylideneserinate methyl ester (**3**) was prepared as reported[16] starting from D-serine.[25] [(2-Thiazolyl)methylene]triphenylphosphorane (**14**) was prepared as previously described[26] from 2-formylthiazole (**23**) and 2-(hydroxymethyl)thiazole (**24**) whose improved syntheses are described below.

2-Formylthiazole (23). To a cold (−78 °C) stirred solution of *n*-BuLi (23 mL, 36.5 mmol of a 1.6 M solution in hexane) in Et_2O (40 mL) was added dropwise a solution of freshly distilled 2-bromothiazole (5 g, 30.4 mmol) in the same solvent (15 mL). The rate of addition of 2-bromothiazole was adjusted so as to

(19) From these results, it appears that the *E*-selectivity reported in our preliminary communication (ref 3) for the olefination of the antipode of **13** with **14** has to be revised. The wrong conclusion was due to the inaccurate NMR analysis of the crude reaction mixture. Fortunately enough, after hydroxylation of the resulting mixture of olefins, the correct 1,2-diol stereoisomer was isolated and employed for the continuation of the synthesis.

(20) The ^1H NMR signals of this impurity corresponded to those of the olefin obtained from **14** and the C-2 epimer of **9**. For the synthesis of the antipode, see: Dondoni, A.; Marra, A.; Perrone, D. *J. Org. Chem.* **1993**, *58*, 275.

(21) Schröder, M. *Chem. Rev.* **1980**, *80*, 187.

(22) (a) Aoyagi, S.; Fujimaki, S.; Kibayashi, C. *J. Chem. Soc., Chem. Commun.* **1990**, 1457. (b) Saito, S.; Morikawa, Y.; Moriwake, T. *J. Org. Chem.* **1990**, *55*, 5424.

(23) Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals*, 3rd ed.; Pergamon Press: Oxford, 1988.

(24) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

(25) The ester **3** has been obtained in 73% yield over two steps (ref 16). However, we currently prepare **3** by the same procedure but in much higher yield (85–90%) simply by using PPTS instead of TsOH in the acetonization step.

keep the temperature of the reaction mixture below −70 °C. After the pale yellow solution of 2-thiazolyllithium (**4**) had been stirred at this temperature for 20 min,[26] a solution of freshly distilled DMF (4 mL, 48.6 mmol) in Et_2O (20 mL) was slowly added while the temperature of the mixture was maintained between −70 and −65 °C. The mixture was allowed to warm to −40 °C in 1 h, was stirred at this temperature for an additional 1 h, and then was treated with ice-cold 4 M HCl (25 mL). The reaction mixture was heated to 0 °C, and the layers were separated. The organic layer was washed with ice-cold 4 M HCl (2 × 25 mL). The combined aqueous layers were neutralized with solid K_2CO_3 and extracted with Et_2O (3 × 25 mL). The organic layers were dried (Na_2SO_4) and concentrated to give the aldehyde **23** as a clear pale yellow oil (3.0 g, 88%; 95% pure by NMR analysis): ^{1}H NMR δ 7.79 (d, 1 H, J = 3.2 Hz), 8.15 (d, 1 H, J = 3.2 Hz), 10.03 (s, 1 H); ^{13}C NMR δ 126.3, 145.5, 165.8, 183.7.

2-(Hydroxymethyl)thiazole (24). To a cold (−60 °C) and stirred solution of crude 2-formylthiazole (**23**) (3.0 g, 26.6 mmol) in MeOH (30 mL) was added portionwise $NaBH_4$ (1.0 g, 26.6 mmol). The mixture was stirred at −60 °C for 1.5 h, then treated with acetone (2 mL), and concentrated. Flash chromatography of the residue on silica gel (9.5:0.5 EtOAc−MeOH) gave the alcohol **24** (2.5 g, 72% from 2-bromothiazole) as a white solid: mp 66−67 °C; ^{1}H NMR δ 4.89 (s, 2 H), 5.30 (s, 1 H, ex D_2O), 7.25 (d, 1 H, J = 3.2 Hz), 7.64 (d, 1 H, J = 3.2 Hz); ^{13}C NMR δ 61.3, 119.1, 142.0, 172.4. Anal. Calcd for C_4H_5NOS: C, 41.72; H, 4.34; N, 12.16. Found: C, 41.74; H, 4.30; N, 12.12.

(*R*)-2-[(*tert*-Butoxycarbonyl)amino]-3-hydroxy-2-*N*,3-*O*-isopropylidene-1-(1,3-thiazol-2-yl)-1-propanone (5). To a cold (−78 °C) stirred solution of *n*-BuLi (9 mL, 14.46 mmol of a 1.6 M solution in hexane) in Et_2O (50 mL) was added dropwise a solution of freshly distilled 2-bromothiazole (2.28 g, 13.88 mmol) in the same solvent (45 mL). The rate of addition was adjusted so as to keep the temperature of the reaction mixture below −70 °C. After the pale yellow solution of 2-butyllithium (**4**) had been stirred at this temperature for 20 min,[27] a solution of the D-serine-derived ester[16] **3** (3 g, 11.57 mmol) in Et_2O (40 mL) was added slowly while the temperature of the mixture was maintained below −65 °C. The reaction mixture was stirred at −65 °C for 3 h, then aqueous phosphate buffer (pH 7, 50 mL) was added, and the mixture was allowed to warm to rt. The layers were separated, and the aqueous layer was extracted with Et_2O (2 × 25 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated. The crude ketone **5** (3.3 g) was utilized for the reduction without purification. Chromatography on silica gel with 8:2 hexane−Et_2O afforded an analytically pure sample of ketone **5** as a white solid: mp 118−120 °C; [α]$_D$ +111.3 (*c* 0.9, $CHCl_3$); ^{1}H NMR (DMSO-d_6, 120 °C) δ 1.32 (s, 9 H), 1.53 (s, 3 H), 1.62 (s, 3 H), 4.02 (dd, 1 H, J = 3.2, 9.1 Hz), 4.38 (dd, 1 H, J = 7.7, 9.1 Hz), 5.57 (dd, 1 H, J = 3.2, 7.7 Hz), 8.15 (d, 1 H, J = 3.1 Hz), 8.21 (d, 1 H, J = 3.1 Hz). Anal. Calcd for $C_{14}H_{20}N_2O_4S$: C, 53.84; H, 6.45; N, 8.97. Found: C, 53.69; H, 6.20; N, 9.12.

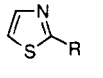
(1*S*,2*R*)-2-[(*tert*-Butoxycarbonyl)amino]-3-hydroxy-2-*N*,3-*O*-isopropylidene-1-(1,3-thiazol-2-yl)-1-propanol (6). To a cold (−55 °C) solution of crude **5** (3.3 g) in MeOH (40 mL) was added $NaBH_4$ (0.8 g, 21.08 mmol) with stirring. The mixture was stirred at this temperature for 2 h, allowed to warm to 0 °C, treated with acetone (2 mL), and concentrated. The residue appeared by ^{1}H NMR analysis, a 95:5 mixture of the alcohol **6** and its C-1 epimer. Separation of the mixture by chromatography on silica gel (9:1 CH_2Cl_2−acetone) afforded pure **6** (2.95 g, 81% from **3**) as a white solid (mp 82−83 °C, [α]$_D$ −4.3 (*c* 0.9, $CHCl_3$)) and 0.17 g (4.7%) of the C-1 epimer contaminated with **6**. Compound **6**: ^{1}H NMR δ 1.51 (s, 9 H), 1.53 (s, 3 H), 1.61 (s, 3 H), 3.87 (dd, 1 H, J = 6.0, 8.8 Hz), 4.23 (ddd, 1 H, J = 1.5, 6.0, 9.1 Hz), 4.38 (dd, 1 H, J = 1.4, 8.8 Hz), 5.06 (dd, 1 H, J = 4.5, 9.1 Hz), 5.89 (d, 1 H, J = 4.5 Hz, ex D_2O), 7.32 (d, 1 H, J = 3.2 Hz), 7.74 (d, 1 H, J = 3.2 Hz); ^{13}C NMR δ 23.7, 26.8, 28.1, 62.5, 64.5, 75.1, 82.1, 94.8, 119.6, 143.0, 156.0, 174.1. Anal. Calcd for $C_{14}H_{22}N_2O_4S$: C, 53.48; H, 7.05; N, 8.91. Found: C, 53.39; H, 7.16; N, 9.01.

(1*S*,2*R*)-1-(Benzyloxy)-2-[(*tert*-butoxycarbonyl)amino]-3-hydroxy-2-*N*,3-*O*-isopropylidene-1-(1,3-thiazol-2-yl)propane (7). To a stirred and cooled (0 °C) solution of **6** (0.5 g, 1.59 mmol) in dry DMF (8 mL) was added NaH as a 60% dispersion in oil (0.13 g, 3.18 mmol). Stirring was continued for 15 min at rt, and then the mixture was recooled to 0° C and treated with benzyl bromide (0.28 mL, 3.18 mmol). The suspension was stirred for 1 h at rt and treated with MeOH until a clear solution was obtained. After 15 min at rt, the solution was concentrated to give a syrup which was treated with cold H_2O (20 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were concentrated. Chromatography of the residue on silica gel (6:4 cyclohexane−Et_2O) gave **7** (0.84 g, 89%) as a syrup: [α]$_D$ −6.1 (*c* 0.6, $CHCl_3$); ^{1}H NMR (DMSO-d_6, 120 °C) δ 1.08 (s, 3 H), 1.38 (s, 3 H), 1.42 (s, 9 H), 3.97 (dd, 1 H, J = 6.5, 9.5 Hz), 4.19 (dd, 1 H, J = 1.9, 9.5 Hz), 4.31 (ddd, 1 H, J = 1.9, 5.8, 6.5 Hz), 4.50 (d, 1 H, J = 11.9 Hz), 4.63 (d, 1 H, J = 11.9 Hz), 5.14 (d, 1 H, J = 5.8 Hz), 7.26−7.38 (m, 5 H), 7.67 (d, 1 H, J = 3.2 Hz), 7.80 (d, 1 H, J = 3.2 Hz). Anal. Calcd for $C_{21}H_{28}N_2O_4S$: C, 62.35; H, 6.98; N, 6.92. Found: C, 62.36; H, 6.96; N, 6.46.

(1*R*,2*S*)-2-[(*tert*-Butoxycarbonyl)amino]-1-[(*tert*-butyldimethylsilyl)oxy]-3-hydroxy-2-*N*,3-*O*-isopropylidene-1-(1,3-thiazol-2-yl)propane (8). To a stirred solution of **6** (0.7 g, 2.23 mmol) in dry DMF (5 mL) were added Et_3N (0.46 mL, 3.34 mmol), DMAP (catalytic), and *tert*-butyldimethylsilyl trifluoromethanesulfonate (0.88 g, 3.34 mmol). After stirring for 1 h at rt, the solution was concentrated, and the residue was treated with H_2O (20 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were dried (Na_2SO_4) and concentrated to give a crude syrup. Chromatography on silica gel (8:2 cyclohexane−Et_2O) gave pure **8** (0.87 g, 91%) as a syrup: [α]$_D$ +46.8 (*c* 1.5, $CHCl_3$); ^{1}H NMR (DMSO-d_6, 120 °C) δ 0.01 (s, 3 H), 0.12 (s, 3 H), 0.91 (s, 9 H), 1.02 (s, 3 H), 1.34 (s, 3 H), 1.52 (s, 9 H), 3.97 (dd, 1 H, J = 6.7, 9.2 Hz), 4.16 (ddd, 1 H, J = 2.0, 4.9, 6.7 Hz), 4.21 (dd, 1 H, J = 2.0, 9.2 Hz), 5.50 (d, 1 H, J = 4.9 Hz), 7.59 (d, 1 H, J = 3.2 Hz), 7.72 (d, 1 H, J = 3.2 Hz). Anal. Calcd for $C_{20}H_{36}N_2O_4SSi$: C, 56.04; H, 8.46; N, 6.53. Found: C, 56.08; H, 8.31; N, 6.33.

2-*O*-Benzyl-3-[(*tert*-butoxycarbonyl)amino]-3-deoxy-3-*N*,4-*O*-isopropylidene-D-threose (9). A mixture of the *O*-benzyl ether **7** (0.5 g, 1.24 mmol), activated 4 Å powdered molecular sieves (2.48 g), and anhydrous CH_3CN (12.5 mL) was stirred at rt for 10 min, and then methyl triflate (0.21 mL, 1.86 mmol) was added. The suspension was stirred for 15 min and then concentrated to dryness. The residue was suspended in MeOH (12.5 mL), cooled to 0 °C, and treated with $NaBH_4$ (0.1 g, 2.73 mmol). The mixture was stirred at rt for 10 min, diluted with acetone (0.5 mL), filtered through Celite, and concentrated. To a solution of the residue in 10:1 CH_3CN−H_2O (12.5 mL) were added CuO (0.79 g, 9.92 mmol) and then $CuCl_2 \cdot H_2O$ (0.21 g, 1.24 mmol) portionwise and under vigorous stirring. The mixture was stirred for 15 min and filtered through Celite, and the solvent was evaporated under reduced pressure (bath temperature not exceeding 40 °C). The brown syrup was taken up in Et_2O (5 × 12 mL), and the liquid phase was filtered through a pad of Florisil (100−200 mesh). The clear solution was concentrated to give crude **9** (0.35 g, 80%; 95% pure by H NMR analysis) which was utilized for the Wittig olefination without purification. An analytical sample of **9** was obtained by column chromatography on silica

(26) After the first report (Dondoni, A.; Fantin, G.; Fogagnolo, M.; Medici, A.; Pedrini, P. *Tetrahedron* **1988**, *44*, 2021), several improvements have been made for the preparation of the phosphorane **14** (ref 1a). However, the difficult purification of the aldehyde **23** and alcohol **24** prevented the large scale synthesis of **14**. This problem has been solved by the improved synthesis of these intermediates as reported here.



23, R = CHO
24, R = CH_2OH

(27) For a general note on the *in situ* preparation of 2-thiazolyllithium (**4**) from 2-bromothiazole, see: Dondoni, A.; Scherrmann, M.-C. *J. Org. Chem.* **1994**, *59*, 6404.

gel (7:3 hexane–Et_2O): $[\alpha]_D$ +8.0 (*c* 1.0, $CHCl_3$); ^1H NMR (DMSO-d_6, 100 °C) δ 1.41 (s, 9 H), 1.42 (s, 3 H), 1.43 (s, 3 H), 4.00 (dd, 1 H, J = 3.3, 10.5 Hz), 4.03 (dd, 1 H, J = 3.8, 10.5 Hz), 4.08 (dd, 1 H, J = 2.1, 4.3 Hz), 4.20 (ddd, 1 H, J = 3.3, 3.8, 4.3 Hz), 4.57 (d, 1 H, J = 11.7 Hz), 4.69 (d, 1 H, J = 11.7 Hz), 7.26–7.38 (m, 5 H), 9.65 (d, 1 H, J = 2.1 Hz). Anal. Calcd for $C_{19}H_{27}NO_5$: C, 65.31; H, 7.79; N, 4.01. Found: C, 65.57; H, 7.93; N, 3.92.

3-[(*tert*-Butoxycarbonyl)amino]-2-*O*-(*tert*-butyldimethylsilyl)-3-deoxy-3-*N*,4-*O*-isopropylidene-D-threose (10). A mixture of the *O*-silyl ether **8** (0.7 g, 1.63 mmol), activated 4 Å powdered molecular sieves (3.26 g), and anhydrous CH_3CN (16 mL) was stirred at rt for 10 min, and then methyl triflate (0.28 mL, 2.44 mmol) was added. The suspension was stirred for 15 min and then concentrated to dryness. The residue was suspended in MeOH (16 mL), cooled to 0 °C, and treated with $NaBH_4$ (0.14 g, 3.59 mmol). The mixture was stirred at rt for 10 min, diluted with acetone (0.5 mL), filtered through Celite, and concentrated. The residue was dissolved in 10:1 CH_3CN–H_2O (16 mL) and the solution treated with $HgCl_2$ (0.44 g, 1.63 mmol) in 1 mL of the same solvent mixture. The mixture was stirred for 15 min, then filtered through Celite, and concentrated (bath temperature not exceeding 40 °C). The residue was dissolved in CH_2Cl_2 (16 mL) and washed with 20% aqueous KI (20 mL), and the two phases were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 16 mL), and the combined organic layers were dried (Na_2SO_4) and concentrated. The residue was dissolved in Et_2O and quickly filtered through a pad of Florisil to give crude **10** as a clear yellow syrup (0.52 g, 86%; 95% pure by ^1H NMR analysis) which was utilized for the Wittig olefination without purification. Chromatography of a sample of crude **10** on silica gel (7:3 hexane–Et_2O) afforded the analytically pure product as a white solid: mp 48–50 °C; $[\alpha]_D$ +49.6 (*c* 0.5, $CHCl_3$); ^1H NMR (DMSO-d_6, 120 °C) δ 0.10 (s, 6 H), 0.92 (s, 9 H), 1.44 (s, 3 H), 1.49 (s, 12 H), 3.97–4.11 (m, 3 H), 4.31 (dd, 1 H, J = 1.9, 3.8 Hz), 9.59 (d, 1 H, J = 1.9 Hz). Anal. Calcd for $C_{18}H_{35}NO_5Si$: C, 57.87; H, 9.44; N, 3.75. Found: C, 57.36; H, 9.31; N, 3.55.

(1*S*,2*R*)-2-[(*tert*-Butoxycarbonyl)amino]-3-[(*tert*-butyldiphenylsilyl)oxy]-1-(1,3-thiazol-2-yl)-1-propanol (11). A solution of the alcohol **6** (1 g, 3.18 mmol) and PPTS (15%) in MeOH (30 mL) was stirred at 60 °C for 18 h. The solution was concentrated, and the white solid (0.85 g, mp 156–158 °C) was dissolved in dry DMF (10 mL). The solution was treated with Et_3N (0.66 mL, 4.77 mmol), DMAP (catalytic), and *tert*-butyldiphenylsilyl chloride (1.3 g, 4.77 mmol) and stirred at rt for 5 h. The mixture was neutralized with aqueous NH_4Cl and extracted with Et_2O (2 × 25 mL). The combined organic layers were dried (Na_2SO_4) and concentrated to give crude **11** as a syrup. Chromatography on silica gel (1:1 cyclohexane–Et_2O) gave pure **11** (1.47 g, 90% from **6**) as a white solid: mp 78–79 °C; $[\alpha]_D$ –5.3 (*c* 0.7, $CHCl_3$); ^1H NMR (DMSO-d_6, 120 °C) δ 1.05 (s, 9 H), 1.32 (s, 9 H), 3.70 (dd, 1 H, J = 6.2, 10.1 Hz), 3.87 (dd, 1 H, J = 6.9, 10.1 Hz), 4.11 (dddd, 1 H, J = 3.5, 6.2, 6.9, 12.8 Hz), 5.17 (dd, 1 H, J = 3.5, 5.5 Hz), 5.72 (d, 1 H, J = 12.8 Hz), 5.93 (d, 1 H, J = 5.5 Hz, ex D_2O), 7.38–7.50 (m, 6 H), 7.52 (d, 1 H, J = 3.1 Hz), 7.60–7.70 (m, 4 H), 7.72 (d, 1 H, J = 3.1 Hz); ^{13}C NMR δ 18.8, 26.6, 28.0, 55.3, 64.7, 72.9, 79.8, 119.3, 128.2, 130.3, 132.8, 135.9, 142.8, 156.0, 173.2. Anal. Calcd for $C_{27}H_{36}N_2O_4SSi$: C, 63.23; H, 7.07; N, 5.46. Found: C, 63.25; H, 7.12; N, 5.19.

(1*S*,2*R*)-2-[(*tert*-Butoxycarbonyl)amino]-3-[(*tert*-butyldiphenylsilyl)oxy]-1-hydroxy-2-*N*,1-*O*-isopropylidene-1-(1,3-thiazol-2-yl)propane (12). To a solution of **11** (1.2 g, 2.34 mmol) in dry toluene (20 mL) were added 2,2-dimethoxypropane (DMP) (2.48 g, 23.40 mmol) and camphorsulfonic acid (CSA) (catalytic). The mixture was refluxed for 2 h, neutralized with Et_3N (1–2 drops), and concentrated to give a brown syrup. Flash chromatography of this material on silica gel (8:2 cyclohexane–Et_2O) afforded pure **12** as a colorless syrup (1.15 g, 89%): $[\alpha]_D$ +16.9 (*c* 1.1, $CHCl_3$); ^1H NMR (DMSO-d_6, 120 °C) δ 1.04 (s, 9 H), 1.38 (s, 9 H), 1.55 (s, 3 H), 1.59 (s, 3 H), 3.97 (dd, 1 H, J = 3.0, 10.1 Hz), 4.09 (dd, 1 H, J = 6.1, 10.1 Hz), 4.35 (ddd, 1 H, J = 3.0, 5.2, 6.1 Hz), 5.55 (d, 1 H, J = 5.2 Hz), 7.38–7.48 (m, 6 H), 7.62–7.68 (m, 4 H), 7.70 (d, 1 H, J = 3.2 Hz), 7.80 (d, 1 H, J = 3.2 Hz). Anal. Calcd for $C_{30}H_{40}N_2O_4SSi$: C, 65.19; H, 7.29; N, 5.07. Found: C, 65.08; H, 7.35; N, 5.22.

3-[(*tert*-Butoxycarbonyl)amino]-4-*O*-(*tert*-butyldiphenylsilyl)-3-deoxy-3-*N*,2-*O*-isopropylidene-D-threose (13). A mixture of the 2-thiazolyl derivative **12** (0.6 g, 1.08 mmol), activated 4 Å powdered molecular sieves (2.17 g), and anhydrous CH_3CN (10 mL) was stirred at rt for 10 min, and then 3 equiv of methyl triflate (0.37 mL, 3.24 mmol) was slowly added. The suspension was stirred at rt for 30 min and concentrated. The reduction and hydrolysis of the resulting *N*-methylthiazolium salt were carried out as described above to reveal the aldehyde **9**. The crude aldehyde **13** syrup (0.42 g; 90% pure by ^1H NMR analysis) was utilized for the Wittig olefination without purification. An analytical sample of **9** was obtained by column chromatography on silica gel (7:3 cyclohexane–Et_2O): $[\alpha]_D$ –7.5 (*c* 1.2, $CHCl_3$); ^1H NMR (DMSO-d_6, 140 °C) δ 1.09 (s, 9 H), 1.39 (s, 9 H), 1.53 (s, 3 H), 1.55 (s, 3 H), 3.88 (dd, 1 H, J = 6.2, 9.6 Hz), 3.92 (dd, 1 H, J = 4.8, 9.6 Hz), 4.24 (ddd, 1 H, J = 4.1, 4.8, 6.2 Hz), 4.62 (dd, 1 H, J = 0.9, 4.1 Hz), 7.35–7.51 (m, 5 H), 7.61–7.75 (m, 5 H), 9.75 (d, 1 H, J = 0.9 Hz). Anal. Calcd for $C_{28}H_{39}NO_5Si$: C, 67.56; H, 7.90; N, 2.81. Found: C, 67.43; H, 7.95; N, 2.99.

(*R*,*R*)-3-(Benzyloxy)-4-[(*tert*-butoxycarbonyl)amino]-5-hydroxy-4-*N*,5-*O*-isopropylidene-1-(1,3-thiazol-2-yl)-1(*E*)-pentene (*E*-15) and -1(*Z*)-pentene (*Z*-15). To a stirred solution of the crude aldehyde **9** (0.3 g) in dry toluene (8 mL) was added the thiazolylphosphorane **14**[26] (0.37 g, 1.03 mmol). The solution was stirred for 24 h at rt and then concentrated. Flash chromatography of the residue on silica gel (6:4 cyclohexane–EtOAc) gave a complex mixture (0.34 g, 93%) containing the olefins ***E*-15** and ***Z*-15** (85:15 ratio) and their *3S,4R*-diastereomers (7%) (H NMR analysis). Flash chromatography on silica gel (8:2 cyclohexane–Et_2O) gave first a mixture (48 mg, 13%) of ***Z*-15** and its epimer as a syrup and then a mixture (0.28 g, 75%) of ***E*-15** and its epimer as a solid. Recrystallization of the latter mixture from cyclohexane afforded pure ***E*-15** (0.17 g, 45%) as a white solid: mp 68–70 °C; $[\alpha]_D$ +138.7 (*c* 1.1, $CHCl_3$); ^1H NMR ($CDCl_3$, 55 °C) δ 1.40–1.55 (m, 15 H), 3.95 (dd, 1 H, J = 6.3, 9.8 Hz), 4.05–4.51 (m, 4 H), 4.68 (d, 1 H, J = 11.9 Hz), 6.54 (dd, 1 H, J = 7.9, 15.9 Hz), 6.87 (d, 1 H, J = 15.9 Hz), 7.19 (d, 1 H, J = 3.2 Hz), 7.20–7.40 (m, 5 H), 7.77 (d, 1 H, J = 3.2 Hz). Anal. Calcd for $C_{23}H_{30}N_2O_4S$: C, 64.16; H, 7.02; N, 6.51. Found: C, 64.43; H, 6.97; N, 6.43.

***Z*-15**: ^1H NMR ($CDCl_3$, 55 °C) δ 1.32–1.56 (m, 15 H), 3.95 (dd, 1 H, J = 5.8, 9.2 Hz), 4.15–4.40 (m, 2 H), 4.50 (d, 1 H, J = 11.1 Hz), 4.58–4.72 (m, 1 H), 5.55 (dd, 1 H, J = 3.9, 10.6 Hz), 5.98 (dd, 1 H, J = 10.6, 11.9 Hz), 6.89 (d, 1 H, J = 11.9 Hz), 7.15–7.45 (m, 6 H), 7.76 (d, 1 H, J = 3.2 Hz).

(*R*,*R*)-4-[(*tert*-Butoxycarbonyl)amino]-3-[(*tert*-butyldimethylsilyl)oxy]-5-hydroxy-4-*N*,5-*O*-isopropylidene-1-(1,3-thiazol-2-yl)-1(*E*)-pentene (*E*-16) and -1(*Z*)-pentene (*Z*-16). The reaction was carried out as described above starting from crude **10** (0.45 g). Flash chromatography of the crude product on silica gel (6:4 cyclohexane–Et_2O) gave a mixture (0.54 g, 99%) of the two olefins ***E*-16** and ***Z*-16** in 95:5 ratio (by H NMR analysis). Flash chromatography of this mixture on silica gel (8:2 cyclohexane–Et_2O) afforded first pure ***Z*-16** (22 mg, 4%) and then pure ***E*-16** (0.50 g, 92%) as syrups.

***E*-16**: $[\alpha]_D$ +105.6 (*c* 1.6, $CHCl_3$); ^1H NMR (DMSO-d_6, 120 °C) δ 0.12 (s, 3 H), 0.14 (s, 3 H), 0.92 (s, 9 H), 1.43 (s, 3 H), 1.45 (s, 3 H), 1.50 (s, 9 H), 3.92–4.07 (m, 3 H), 4.84 (dd, 1 H, J = 5.3, 6.4 Hz), 6.53 (dd, 1 H, J = 6.4, 16.1 Hz), 6.76 (dd, 1 H, J = 1.1, 16.1 Hz), 7.52 (d, 1 H, J = 3.2 Hz), 7.76 (d, 1 H, J = 3.2 Hz). Anal. Calcd for $C_{22}H_{38}N_2O_4SSi$: C, 58.11; H, 8.42; N, 6.16. Found: C, 58.36; H, 8.44; N, 6.05.

***Z*-16**: $[\alpha]_D$ +30.0 (*c* 0.5, $CHCl_3$); ^1H NMR (DMSO-d_6, 120 °C) δ 0.01 (s, 3 H), 0.08 (s, 3 H), 0.88 (s, 9 H), 1.38–1.46 (m, 15 H), 3.95 (dd, 1 H, J = 6.2, 9.3 Hz), 4.01–4.06 (m, 1 H), 4.12–4.18 (m, 1 H), 5.74 (dd, 1 H, J = 4.1, 10.1 Hz), 5.88 (dd, 1 H, J = 10.1, 12.0 Hz), 6.71 (d, 1 H, J = 12.0 Hz), 7.63 (d, 1 H, J = 3.2 Hz), 7.81 (d, 1 H, J = 3.2 Hz). Anal. Calcd for $C_{22}H_{38}N_2O_4SSi$: C, 58.11; H, 8.42; N, 6.16. Found: C, 58.23; H, 8.51; N, 6.24.

(*R*,*R*)-4-[(*tert*-Butoxycarbonyl)amino]-5-[(*tert*-butyldiphenylsilyl)oxy]-3-hydroxy-4-*N*,3-*O*-isopropylidene-1-

(1,3-thiazol-2-yl)-1(*E*)-pentene (*E*-17) and -1(*Z*)-pentene (*Z*-17). The reaction was carried out as described above starting from crude **13** (0.35 g). Flash chromatography of the crude product on silica gel (6:4 cyclohexane–Et_2O) afforded a mixture (0.26 g, 65%) of the *E*- and *Z*-olefins **17** in a 66:34 ratio (by H NMR analysis). Attempted separation of these compounds by flash chromatography failed: ^{1}H NMR ($CDCl_3$, 60 °C, selected data) δ 4.90 (dd, 0.66 H, J = 4.9, 6.1 Hz), 5.91 (dd, 0.34 H, J = 3.6, 8.5 Hz), 6.05 (dd, 0.34 H, J = 8.5, 11.0 Hz), 6.65 (dd, 0.66 H, J = 6.1, 15.9 Hz), 6.79 (d, 0.34 H, J = 11.0 Hz), 6.86 (d, 0.66 H, J = 15.9 Hz).

(1*R*,2*S*,3*S*,4*R*)- and (1*S*,2*R*,3*S*,4*R*)-4-[(*tert*-Butoxycarbonyl)amino]-3-[(*tert*-butyldimethylsilyl)oxy]-1,2-(isopropylidenedioxy)-5-hydroxy-4-*N*,5-*O*-isopropylidene-1-(1,3-thiazol-2-yl)pentane (*anti*-19 and *syn*-19). To a cold (−20 °C) solution of the olefin ***E*-16** (0.45 g, 0.99 mmol) in a 1:8 mixture of H_2O–acetone (10.3 mL) were added *N*-methylmorpholine *N*-oxide (NMMO) (0.23 g, 1.98 mmol) and then 2 mL of a 2.5 wt % *t*-BuOH solution of OsO_4 (0.19 mmol) stabilized with *tert*-butyl hydroperoxide (Janssen). After 20 h at −20 °C, the mixture was warmed to rt and then treated sequentially with Florisil (2.16 g), CH_2Cl_2 (3 mL), H_2O (0.3 mL), and $Na_2S_2O_5$ (0.5 g). The mixture was stirred at rt for 15 min, filtered through Celite, and concentrated. The crude residue (0.42 g, 87%) appeared by NMR as a mixture of *cis* 1,2-diols ***anti*-18** and ***syn*-18** in a 93:7 ratio (95% pure). These compounds were inseparable by flash chromatography. Hence, a solution of the mixture of 1,2-diols **18** (0.40 g, 0.82 mmol), 2-methoxypropene (0.8 mL, 8.20 mmol), and PPTS (catalytic) in toluene (10 mL) was heated at 90 °C for 1 h and then concentrated. Flash chromatography of the residue on silica gel (96:4 toluene–Et_2O) gave first pure ***syn*-19** (22 mg, 5%) and then pure ***anti*-19** (0.37 g, 85%) as syrups.

***anti*-19**: $[\alpha]_D$ +6.3 (*c* 1.5, $CHCl_3$); ^{1}H NMR (DMSO-d_6, 120 °C) δ 0.11 (s, 3 H), 0.13 (s, 3 H), 0.79 (s, 9 H), 1.39 (s, 3 H), 1.41 (s, 3 H), 1.44 (s, 3 H), 1.48 (s, 9 H), 1.57 (s, 3 H), 3.93 (dd, 1 H, J = 2.9, 8.1 Hz), 3.95–4.04 (m, 2 H), 4.39–4.47 (m, 1 H), 4.66 (t, 1 H, J = 6.5 Hz), 5.25 (d, 1 H, J = 6.9 Hz), 7.64 (d, 1 H, J = 3.2 Hz), 7.76 (d, 1 H, J = 3.2 Hz). Anal. Calcd for $C_{25}H_{44}N_2O_6SSi$: C, 56.78; H, 8.39; N, 5.30. Found: C, 57.08; H, 8.12; N, 5.24.

***syn*-19**: $[\alpha]_D$ +31.7 (*c* 0.6, $CHCl_3$); ^{1}H NMR (DMSO-d_6, 120 °C) δ 0.17 (s, 3 H), 0.22 (s, 3 H), 0.96 (s, 9 H), 1.32 (s, 9 H), 1.42 (s, 3 H), 1.44 (s, 3 H), 1.46 (s, 3 H), 1.50 (s, 3 H), 3.95–4.04 (m, 2 H), 4.12–4.17 (m, 1 H), 4.38 (dd, 1 H, J = 3.2, 8.5 Hz), 4.40–4.46 (m, 1 H), 5.11 (d, 1 H, J = 8.5 Hz), 7.65 (d, 1 H, J = 3.1 Hz), 7.77 (d, 1 H, J = 3.1 Hz). Anal. Calcd for $C_{25}H_{44}N_2O_6SSi$: C, 56.78; H, 8.39; N, 5.30. Found: C, 57.13; H, 8.32; N, 4.93.

5-[(*tert*-Butoxycarbonyl)amino]-4-*O*-(*tert*-butyldimethylsilyl)-5-deoxy-2-*O*,3-*O*-isopropylidene-5-*N*,6-*O*-isopropylidene-D-galactose (20). The same procedure as described above for **10** was applied to ***anti*-19** (0.35 g, 0.66 mmol). Flash chromatography of the crude product on silica gel (85:15 Et_2O–cyclohexane) gave the aldehyde **20** (0.27 g, 88%) as a syrup: $[\alpha]_D$ +20.4 (*c* 1.8, $CHCl_3$); ^{1}H NMR (DMSO-d_6, 120 °C) δ 0.17 (s, 6 H), 0.91 (s, 9 H), 1.34 (s, 3 H), 1.40 (s, 3 H), 1.41 (s, 3 H), 1.48 (s, 9 H), 1.58 (s, 3 H), 3.91–4.03 (m, 4 H), 4.32–4.39 (m, 2 H), 9.66 (d, 1 H, J = 1.6 Hz). Anal. Calcd for $C_{23}H_{43}NO_7Si$: C, 58.32; H, 9.15; N, 2.96. Found: C, 58.25; H, 8.99; N, 3.05.

(+)-Galactostatin-1-sulfonic Acid (21). An ice-cold suspension of the aldehyde **20** (0.23 g, 0.48 mmol) in water (2.4 mL) was saturated with sulfur dioxide (SO_2) and stirred at 40 °C for 2 days. The reaction mixture was diluted with MeOH (1 mL), cooled to 0 °C, saturated again with SO_2, and allowed to stand at 0 °C for 12 h. The white precipitate was collected by filtration and washed with MeOH to give **21** (80 mg, 67%) as a colorless powder: mp 146–150 °C dec; $[\alpha]_D$ +19.0 (*c* 0.8, H_2O) (lit.[4b] mp 133–135 °C, $[\alpha]_D$ +17.2 (*c* 0.5, H_2O); lit.[13] mp 146–150 °C, $[\alpha]_D$ +19.6 (*c* 0.9, H_2O)); lit.[14] mp 133–135 °C, $[\alpha]_D$ +16 (*c* 0.25, H_2O)); ^{1}H NMR (D_2O) δ DOH (4.63), 3.35 (bt, 1 H, J = 6.7 Hz), 3.56 (dd, 1 H, J = 3.2, 9.4 Hz), 3.73 (d, 2 H, J = 6.7 Hz), 3.95 (d, 1 H, J = 10.6 Hz), 3.99–4.20 (m, 2 H); ^{13}C NMR (D_2O with acetone as internal standard) δ 59.5, 60.7, 67.2, 68.0, 71.7, 73.7. Anal. Calcd for $C_6H_{13}NO_7S$: C, 29.63; H, 5.39; N, 5.76. Found: C, 29.75; H, 5.55; N, 6.02.

(+)-Galactostatin (+)-1. A solution of **21** (20 mg, 0.08 mmol) in H_2O was treated with 0.25 g of Amberlyst A-26 (OH^-) resin. After 30 min at rt, the solution was filtered and lyophilized to give (+)-**1** (10 mg, 68%) as a white powder: mp 94–96 °C dec; $[\alpha]_D$ +81.2 (*c* 0.5, H_2O) (lit.[4b] mp 94–98 °C, $[\alpha]_D$ +84.6 (*c* 0.3, H_2O); lit.[13] mp 93–95 °C, $[\alpha]_D$ +84.6 (*c* 0.3, H_2O)). Anal. Calcd for $C_6H_{13}NO_5$: C, 40.22; H, 7.31; N, 7.82. Found: C, 40.38; H, 7.59; N, 7.98.

5-*N*-Acetyl-1,2,4,6-tetra-*O*-acetylgalactostatin (22). To a solution of (+)-**1** (5 mg, 0.03 mmol) in dry pyridine (a drop) was added acetic anhydride (Ac_2O) (a drop). After 6 h at rt, the solution was concentrated, and the residue was purified by flash chromatography on silica gel (1:1 cyclohexane–EtOAc) to give the peracetylated galactostatin **22** (6 mg, 50%) as a syrup: ^{1}H NMR δ 2.03 (s, 3 H), 2.04 (s, 3 H), 2.09 (s, 3 H), 2.12 (s, 3 H), 2.19 (s, 3 H), 2.23 (s, 3 H), 4.11 (ddd, H_5, J = 3.2, 4.3, 7.6 Hz), 4.51 (dd, H_{6a}, J = 7.6, 11.9 Hz), 4.65 (dd, H_{6b}, J = 4.3, 11.9 Hz), 5.29 (dd, H_2, J = 4.1, 9.3 Hz), 5.39 (dd, H_3, J = 4.5, 9.3 Hz), 5.59 (dd, H_4, J = 3.2, 4.5 Hz), 6.75 (d, H_1, J = 4.1 Hz); ^{13}C NMR δ 20.5, 20.7, 20.9, 22.5, 52.1, 60.8, 65.9, 68.1, 69.1, 89.4, 69.7, 169.8, 170.2, 170.4, 170.5, 170.9.

Determination of the Configurational Stability of the Ketone 5. Preparation of (+)-MTPA Esters of 6 and *ent*-6. To a solution of the alcohol **6** (20 mg, 0.06 mmol), DCC (13.6 mg, 0.07 mmol), and DMAP (a crystal) in dry CH_2Cl_2 (0.5 mL) was added (+)-MTPA (16 mg, 0.07 mmol). The mixture was stirred at rt for 12 h, filtered to remove the *N*,*N*′-dicyclohexylurea, and partitioned with EtOAc (2 × 5 mL) and H_2O (5 mL). The combined organic layers were washed with 5 mL each of 1 M HCl, H_2O, saturated aqueous $NaHCO_3$, and brine, then dried (Na_2SO_4), and concentrated. The residue was purified by flash chromatography on silica gel (6:4 cyclohexane–Et_2O) to give the (+)-MTPA ester of **6** (29 mg, 91%): ^{1}H NMR (DMSO-d_6, 120 °C) δ 1.10 (s, 3 H), 1.38 (s, 3 H), 1.48 (s, 9 H), 3.48 (s, 3 H), 4.03 (dd, 1 H, J = 6.6, 9.4 Hz), 4.14 (d, 1 H, J = 1.9, 9.4 Hz), 4.45 (ddd, 1 H, J = 1.9, 5.6, 6.6 Hz), 6.60 (d, 1 H, J = 5.6 Hz), 7.44 (s, 5 H), 7.70 (d, 1 H, J = 3.2 Hz), 7.81 (d, 1 H, J = 3.2 Hz).

The same procedure was followed with ***ent*-6** prepared as previously described[15] to give its (+)-MTPA ester: ^{1}H NMR (DMSO-d_6, 120 °C) δ 1.04 (s, 3 H), 1.35 (s, 3 H), 1.50 (s, 9 H), 3.52 (s, 3 H), 3.94 (dd, 1 H, J = 6.5, 10.0 Hz), 4.13 (dd, 1 H, J = 2.1, 10.0 Hz), 4.37 (ddd, 1 H, J = 2.1, 5.2, 6.5 Hz), 6.63 (d, 1 H, J = 5.2 Hz), 7.48 (s, 5 H), 7.75 (d, 1 H, J = 3.2 Hz), 7.86 (d, 1 H, J = 3.2 Hz).

Acknowledgment. Financial support was provided by the Ministero della Università e della Ricerca Scientifica (MURST, Rome). We are grateful to the Istituto Superiore della Sanità (Rome) for a Grant to D.P. finalized to research against AIDS. We also thank Mr. Paolo Formaglio (University of Ferrara) for technical assistance in NMR spectroscopy and Dr. Pedro Merino (University of Zaragoza) for exploratory work.

JO9504575