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A new route to some enantiomerically pure substituted morpholines from D-ribono- and D-gulono-1,4-lactones

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Abstract

D-Ribono-1,4-lactone, after acetalation, tritylation, and reduction, leads to a cyclization compound which gave with tosyl chloride 1,4-anhydro-2,3-*O*-isopropylidene-5-*O*-trityl-D-ribitol. The latter was transformed (acid hydrolysis, periodate oxidation, reduction, tritylation, and tosylation) into a ditosylated derivative **16**, which was cyclized into morpholines by the action of primary amines. Acid hydrolysis, followed by acetylation, gives the (2*S*)-acetoxymethyl-4-isopropyltetrahydro-1,4-oxazine (**21**). A similar sequence has been applied to D-gulonolactone to give access to oxazines **33**, **34**, and **35**.

Keywords: Synthesis; D-Ribono-1,4-lactone; D-Gulono-1,4-lactone; Morpholine derivatives

1. Introduction

For many years morpholines have been known for their biological and/or pharmacological properties, and there are reports of various examples in the literature which can be classified into four categories: (*i*) simple association of the morpholine by admixture with an active compound [1], (*ii*) *N*-substitution of the morpholine by compounds with biological activity [2,3], (*iii*) *C*-substitution of the cycle with pharmacologically active substituents [4–7], and (*iv*) functionalized morpholines [8–10]. In all these examples, the morpholines were racemic. Some years ago we decided to prepare some morpholines with potential biological interest in the enantiomerically pure form starting from monosaccharides [11]. Very few examples are known of optically active derivatives in this family of substances [12–16]. Herein we present routes to two series of functionalized 1,4-oxazines starting from readily available lactones.

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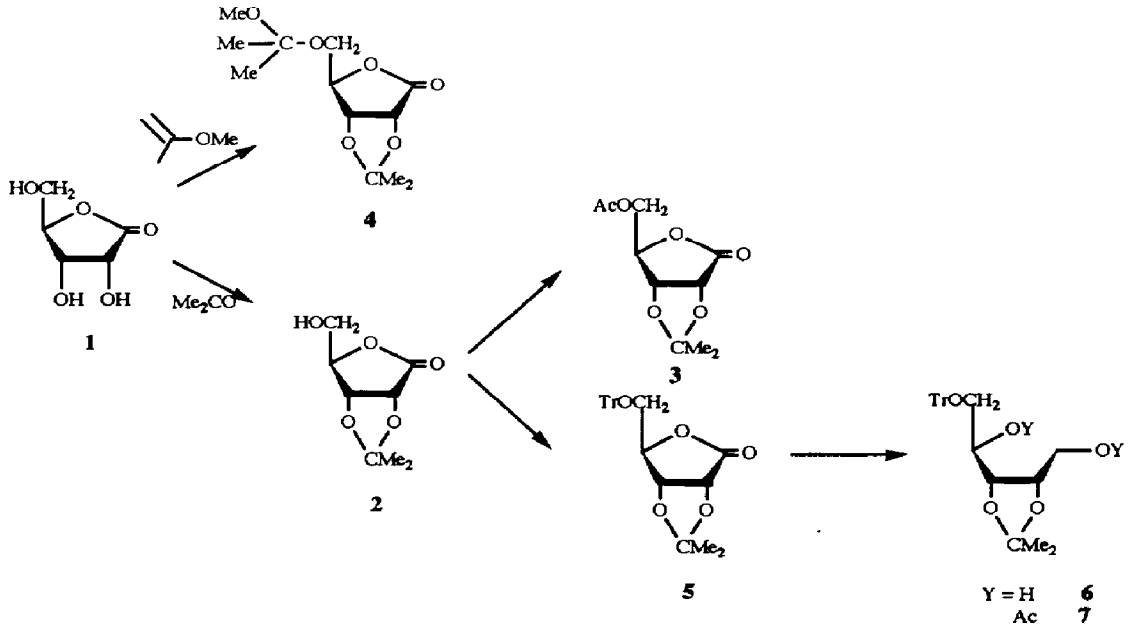
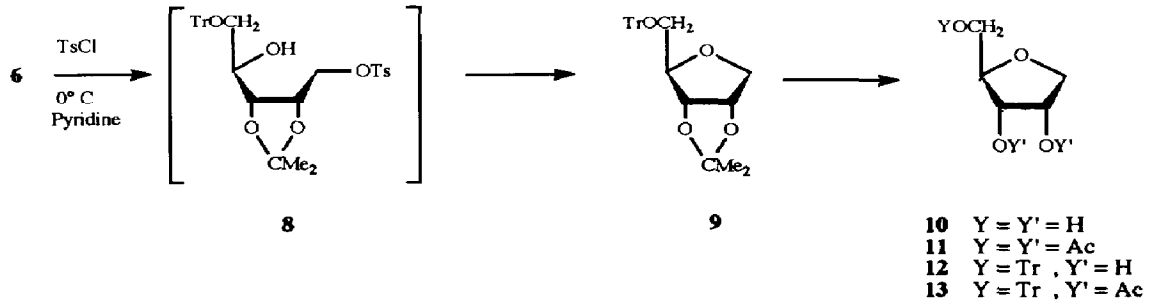
2. Results and discussion

Morpholine derivatives from D-*ribono-1,4-lactone* (**1**).—Protection of the 2- and 3-hydroxyl groups of lactone **1** was attempted by classical acetonation with acetone and sulfuric acid (thermodynamic control), or with 2-methoxypropene [17,18] (kinetic control) in *N,N*-dimethylformamide. Better results were obtained with the classical method, which afforded 2,3-*O*-isopropylidene-D-ribono-1,4-lactone (**2**). This was then converted into the acetate **3** (Scheme 1). At 0°C, acetonation under kinetically controlled conditions gave a major product which was identified as the bis-acetal **4**, and at 20°C, a mixture was obtained from which acetals **2** and **4** were isolated by column chromatography. Compound **2** probably resulted from partial hydrolysis of **4** on the silica gel column. The low yield observed for the formation of acetal **2** was indicative of the weak reactivity of the 2-hydroxyl group, probably due to the electronic deficiency of the oxygen atom vicinal to the carbonyl group. This hypothesis was confirmed by the observation of acetalation under kinetically controlled conditions of lactones containing a hydroxyl group at C-2 [19].

Tritylation of lactone **2** using chlorotriphenylmethane afforded the derivative **5** (82% yield), which was reduced with sodium borohydride to give, quantitatively, 2,3-*O*-isopropylidene-5-*O*-(triphenylmethyl)-D-ribitol (**6**) identified by ^{1}H NMR spectroscopy, and by its conversion into the diacetate **7**. Heterocyclization of diol **6** with tosyl chloride was conducted at 0°C [11,20] and gave the corresponding anhydro-D-ribitol derivative **9** in 94% yield (Scheme 2). Various attempts to selectively hydrolyze the acetal in the presence of the trityl group were unsuccessful, and total hydrolysis gave the unsubstituted 1,4-anhydro-D-ribitol (**10**) identified by comparison with the literature [21–24], and by its conversion into the triacetate **11**. It should be noted that compound **10** was obtained here in six steps in a total yield greater than 65%, which represents an interesting alternative to the methods described in the literature [20–23,25], (Barker and Fletcher, Jr., [23], for example, obtained **10** in six steps, with a total yield of 15–20%). Compound **10** was selectively



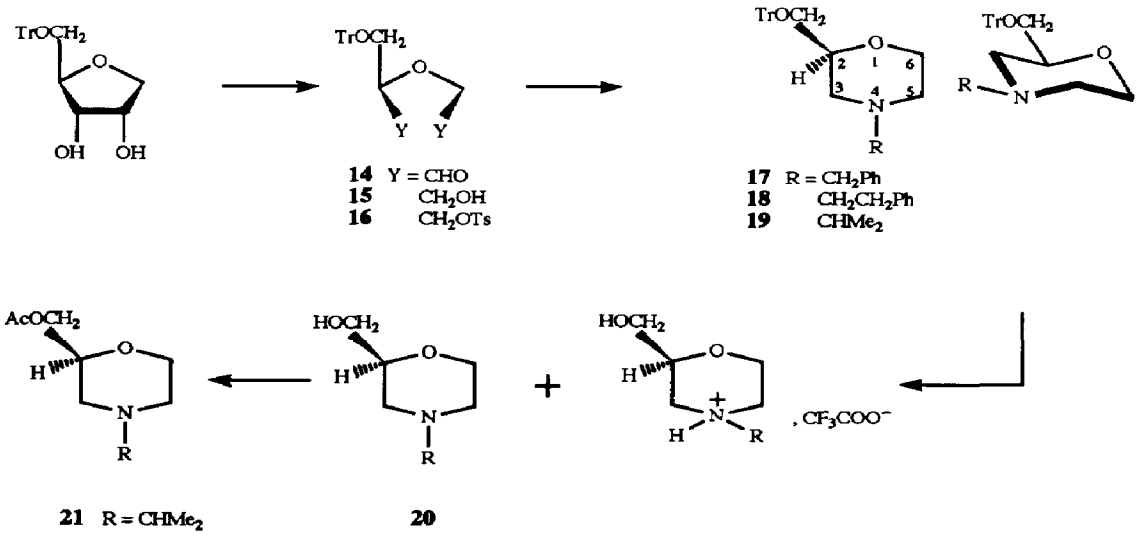


tritylated to give **12** (yield 60%), the structure of which was confirmed by its conversion into the corresponding diacetate **13**. The α-diol function of derivative **12** was cleaved with sodium metaperiodate according to Ireland et al. [26], and the resulting dialdehyde **14** was reduced in situ with sodium borohydride to give the diol **15** (yield 77% from **12**), which was identified by ^{1}H NMR spectroscopy and transformed [27] into the ditosylate **16** (Scheme 3).

Finally heterocyclization of the ditosylate with different primary amines, either pure or in *N,N* dimethylformamide (successively benzylamine, 2-phenylethylamine, and isopropylamine), gave the expected morpholines **17**, **18**, and **19** (67, 60, and 73% yields, respectively), which were identified by NMR spectroscopy. For example, the 300 MHz ^{1}H NMR spectral data (with 2D COSY) of compound **17** showed, in particular, a triplet at 2.01 ppm corresponding to H-3ax coupled with H-3eq (at 2.92 ppm) ($J_{3a,3e}$ 10.5 Hz) and with H-2 (at 3.87 ppm) ($J_{3a,2}$ 10.5 Hz). These coupling constants were consistent with an antiperiplanar conformation of these two protons in a chair form of the cyclic structure. Thus, H-2 was necessarily in the axial position, with the substituent in the equatorial position on the morpholine, which was essentially in one of the two possible *chair* conformations (Scheme 3). Comparable observations could be made from the ^{1}H NMR spectral data of compounds **18** and **19** that were similar to those of some morpholines previously synthesized in our laboratory [11]. They showed that compounds **17**, **18**, and **19** were only in one of the two possible diastereoisomeric forms (no splitting of signals, particulary those corresponding to protons of the *N*-substituent). These results were in agreement with studies [28] from Booth and Little concerning the *cis*-2,6-dimethylmorpholine where the *N*-Me group was shown to be exclusively in the equatorial position, and studies on *N*-alkylhexacyclic derivatives [29]. Determination of axial–axial and equatorial–axial coupling constants of some vicinal protons indicated an exclusive antiperiplanar conformation and eliminated the possibility of an equilibrium of interconverted chairs for which a lower coupling constant would be observed.

As an example of the final access to the free morpholines, compound **19** was submitted to acid hydrolysis with 17:83 trifluoracetic acid–water, which gave a mixture of the free amine **20** and the corresponding ammonium trifluoroacetate salt. Acetylation of the mixture gave the pure acetate **21**.

Substituted morpholines starting from D-*gulonolactone* (**22**).—Classical acetonation of lactone **22** gave the known [30,31] diacetal **23** (Scheme 4) that was subsequently reduced with sodium borohydride. The resulting diol **24** reacted with tosyl chloride to give the anhydro-D-gulitol **25**, probably through the primary monotosylate. 2D COSY ^{1}H NMR

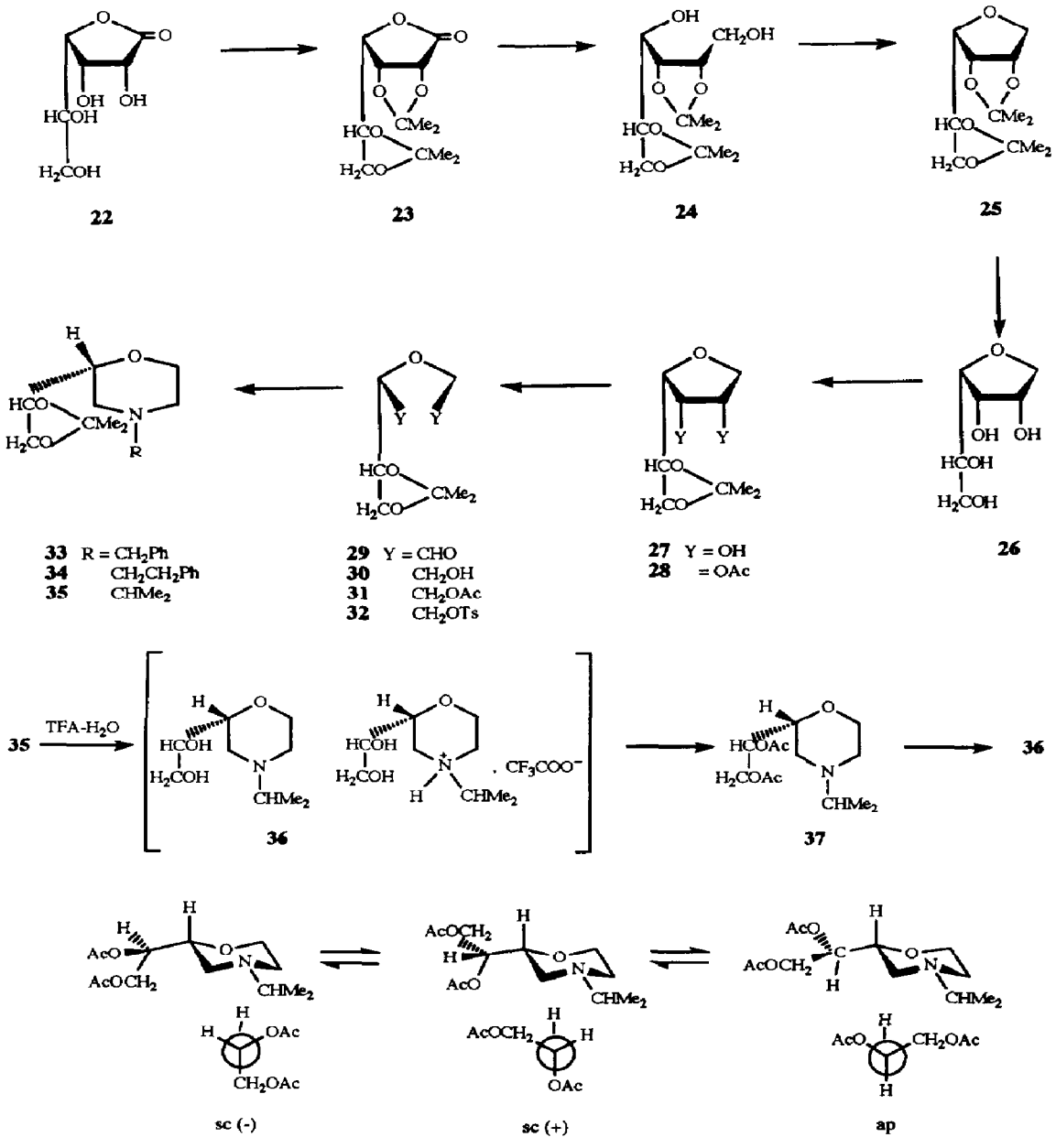


showed, inter alia, a doublet of doublets (1 proton, 3.46 ppm) attributed to H-4, while H-5 gave a complex signal due to coupling with H-4, H-6, and H-6′.

In order to reach the ditosylate **32**, we needed to selectively protect the 5,6-diol. As expected, we were unsuccessful in selectively deprotecting the 2,3-diol without any cleavage of the 5,6-acetal, which is clearly the most labile of the two protecting groups. So we decided to completely hydrolyze [32] the diacetal and to proceed with a selective acetonation under kinetically controlled conditions with 2-methoxypropene [17,18], which gave the monoacetal **27**, as identified by NMR spectroscopy and by its conversion to the diacetate **28**. Diol **27** was treated with sodium metaperiodate and then with sodium borohydride to give (2*R*)-2-*O*-(2-hydroxyethyl)-3,4-*O*-isopropylidene-D-threitol (**30**, 91% yield), identified by NMR spectroscopy and by its conversion into the diacetate **31**. Treatment of compound **30** with tosyl chloride gave the ditosylate **32**. Finally, the latter was successively treated with benzylamine, phenethylamine, and isopropylamine (these amines were used as solvent) to give the expected morpholines **33**, **34**, and **35** (72, 60, and 64% yields, respectively).

The spectral data of these derivatives (2D COSY ^{1}H NMR and ^{13}C NMR) were very similar to the spectral data of previously prepared morpholines. The remark given for the conformation of morpholines **17**, **18**, and **19** (vide supra) is still valid for compounds **33**, **34**, and **35**: the coupling constant between H-2ax and H-3ax of the 1,4-oxazines ($J_{2a,3a}$ 10.57 Hz) was in accordance with an exclusive chair conformation with equatorial substituents at position C-2 and N-4. Hydrolysis of compound **35** with 17:83 trifluoracetic acid–water gave a mixture of the ammonium trifluoroacetate salt of the morpholine and the free diol **36**, which could be acetylated to the diacetate **37** (Scheme 5). It is noteworthy that the ^{1}H NMR data of compound **37** showed a coupling constant $J_{2a,2'}$ of 3.9 Hz, which is indicative of a gauche position (sc) of the protons.

In conclusion, we have described convenient routes to chiral morpholines that are both *C*- and *N*-substituted, and are available for further structural modification and biological evaluation.



3. Experimental

General methods.—Melting points were determined on a Büchi apparatus. Evaporations were performed under diminished pressure. Optical rotations were measured on a Perkin–Elmer 241 polarimeter in 1-dm tubes at 20°C (*c* 1, $CHCl_3$). Column chromatography was performed with Silica Gel 60 (E. Merck 70–230 mesh) or 60A (E. Merck 35–70 mesh), and TLC was carried out on precoated plates (E. Merck 5724), with detection by charring with H_2SO_4 and heating. Solvents for chromatography were dried and distilled. Pyridine and *N*,*N*-dimethylformamide were dried and distilled under diminished pressure. ^1H NMR

spectra (60 or 300 MHz) were recorded on a Varian T60 spectrometer, or on a Bruker MSL 300 spectrometer. Chemical shift data are given in δ-units (ppm) measured downfield from internal Me_4Si, and spin–spin coupling constants are in Hz. ^{13}C NMR spectra (75.55 MHz) were recorded on a Bruker MSL 300 spectrometer.

Preparation of 2,3-O-isopropylidene-D-ribono-1,4-lactone (**2**).—Two methods were used. (*i*) To 5 g (33 mmol) of D-ribonolactone in 250 mL of acetone was added 3–4 mL of concd H_2SO_4, and the mixture was stirred for 5 h until monitoring by TLC (EtOAc) indicated that all starting material had disappeared. Sodium carbonate was added, and the filtered solution was dried and evaporated to give **2** (58 g, 91%); mp 137–139°C; $[\alpha]_D$ −66°C; lit. [33] mp 138–139°C; $[\alpha]_D^{24}$ −65.7° (*c* 2.13, pyridine); lit. [34] mp 137–138°C; $[\alpha]_D^{25}$ −80.6° (*c* 0.9, $CHCl_3$). (*ii*) To a solution of D-ribonolactone (5 g, 33 mmol) in 30 mL of *N*,*N*-dimethylformamide at 0°C, was added 2 equiv of 2-methoxypropene and 20 mg of *p*-toluenesulfonic acid. After stirring for 5 h, monitoring by TLC (EtOAc) indicated the presence of four compounds. The mixture was neutralized with sodium carbonate and stirred for 1 h. The solution was then filtered, evaporated, and chromatographed (1:1 EtOAc–hexane) to give two products. First eluted was compound **4** (yield <10%). NMR data ($CDCl_3$): ^1H, δ 1.33 (s, 6 H), 1.4 (s, 3 H), 1.48 (s, 3 H), 3.2 (s, 3 H), 3.4–3.9 (m, 2 H), 4.48–4.90 (m, 3 H). The second product eluted was **2**, which was identified by comparison with the sample prepared by classical acetonation (see *i*, above).

5-O-Acetyl-2,3-O-isopropylidene-D-ribonolactone (**3**).—Acetylation of **2** (4 g, 17 mmol) was performed by a classical method (2 equiv of acetic anhydride in pyridine at 0°C). After disappearance of all starting material (TLC 1:1 EtOAc–hexane), the mixture was stirred overnight at room temperature, poured onto an ice–sodium carbonate mixture, extracted with CH_2Cl_2, dried, and coevaporated with anhyd toluene (to remove residual pyridine) to give **3** (4.3 g, 87%); mp 50–51°C (EtOAc); $[\alpha]_D$ −59°. NMR data ($CDCl_3$): ^1H, δ 1.39 and 1.48 (2 s, 6 H, CMe_2), 2.1 (s, 3 H, Ac), 4.28 (m, 2 H), 4.8 (m, 3 H). Anal. Calcd for $C_{10}H_{14}O_6$: C, 52.17; H, 6.08; O, 41.74. Found: C, 52.66; H, 6.10; O, 40.84.

2,3-O-Isopropylidene-5-O-(triphenylmethyl)-D-ribonolactone (**5**).—A mixture of **2** (6 g, 32 mmol) and 10.6 g (1.2 equiv) of chlorotriphenylmethane in pyridine (70 mL) was heated for 16 h at 70°C. After disappearance of all the starting material (TLC 1:1 EtOAc–hexane), the mixture was cooled, diluted with 400 mL of $CHCl_3$, washed twice with 300 mL of 5% H_2SO_4, washed twice with 100 mL of satd $NaHCO_3$, dried, and concentrated to give, after column chromatography (1:4 EtOAc–hexane), compound **5** (11.2 g, 82%); mp 125–126°C; $[\alpha]_D$ +2.1°. NMR data ($CDCl_3$): ^1H, δ 1.33 and 1.46 (2 s, 6 H, CMe_2), 3.06 (dd, 1 H, $J_{5,5'}$ 10.8, $J_{5,4}$ 1.8 Hz, H-5), 3.73 (dd, 1 H, $J_{5',4}$ 2.4 Hz, H-5'), 4.40 (d, 1 H, H-3), 4.53 (dd, 1 H, H-4), 4.93 (d, 1 H, $J_{2,3}$ 5.8 Hz, H-2), 7.2-7.6 (m, 15 H, Ar). Anal. Calcd for $C_{27}H_{26}O_5$: C, 75.35; H, 6.04; O, 18.60. Found: C, 75.12; H, 5.91; O, 18.19.

2,3-O-Isopropylidene-5-O-(triphenylmethyl)-D-ribitol (**6**).—To a solution of 8 g (18 mmol) of compound **5** in 80 mL of MeOH, 1.4 g (2 equiv) of sodium borohydride was added in portions. The reaction was monitored by TLC (1:2 EtOAc–hexane) and stirred for 2 h at room temperature. The mixture was evaporated, then dissolved in water and extracted continuously with EtOAc (24–48 h). After evaporation of the solvent, the diol was chromatographed (1:2 EtOAc–hexane) to give pure **6** as a syrup (7.5 g, 93%); $[\alpha]_D$ −21.1°. NMR data (Me_2SO-d_6): ^1H, δ 1.23 (s, 6 H, CMe_2), 3.00–3.23 (m, 2 H), 3.50–4.30 (m, 5 H), 4.82 (t, 1 H, $J_{H,OH}$ 5.2 Hz, CH_2OH), 5.18 (d, 1 H, $J_{H,OH}$ 5 Hz, OH), 7.2–

7.65 (m, 15 H, Ar). Anal. Calcd for $C_{27}H_{30}O_5$: C, 74.65; H, 6.91; O, 18.43. Found: C, 74.37; H, 6.81; O, 18.78.

1,4-Di-O-acetyl-2,3-O-isopropylidene-5-O-(triphenylmethyl)-D-ribitol (**7**).—Acetylation of 0.8 g of **6** gave (after recrystallization in EtOH) 0.8 g (84%) of pure **7**; mp 101–102°C; $[\alpha]_D$ −27.5°. NMR data ($CDCl_3$): ^1H, δ 1.36 (s, 6 H), 1.96 (s, 3 H), 2.03 (s, 3 H), 3.3–3.5 (m, 2 H), 3.8–4.7 (m, 4 H), 4.9–5.3 (m, 1 H), 7.1–7.6 (m, 15 H, Ar). Anal. Calcd for $C_{31}H_{34}O_7$: C, 71.81; H, 6.56; O, 21.62. Found: C, 71.60; H, 6.50; O, 21.50.

1,4-Anhydro-2,3-O-isopropylidene-5-O-(triphenylmethyl)-D-ribitol (**9**).—Following the procedure described by Sinclair [20], a solution of 9 g (20 mmol) of compound **6** in 70 mL of pyridine cooled in an ice bath was treated with 11.4 g (3 equiv) of tosyl chloride, and the solution was allowed to stand overnight at room temperature with magnetic stirring. When TLC (1:2 EtOAc–hexane) showed disappearance of the starting material, water was added to decompose the excess tosyl chloride (1 mL/g of tosyl chloride). The mixture was extracted with CH_2Cl_2, and the solution was dried and concentrated to give compound **9**, which was used directly in the next step without purification. Recrystallization in EtOAc gave pure **9** (8.1 g, 94%); mp 131–133°C; $[\alpha]_D$ +28°. NMR data ($CDCl_3$): ^1H, δ 1.36 and 1.52 (s, 6 H, CMe_2), 3.15 (dd, 1 H, $J_{5,5'}$ 10 Hz, H-5), 3.29 (dd, 1 H, $J_{5',4}$ 4 Hz, H-5'), 4.07 (d, 1 H, $J_{1,1'}$ 10 Hz, H-1), 4.15 (dd, 1 H, $J_{1',2}$ 4.5 Hz, H-1'), 4.22 (dd, 1 H, $J_{2,3}$ 6 Hz, H-2), 4.67 (dd, 1 H, $J_{3,4}$ <1 Hz, H-3), 4.9 (ddd, 1 H, $J_{4,5}$ 4.5 Hz, H-4), 7.1–7.6 (m, 15 H, Ar); ^{13}C, δ 25.2 and 26.7 (2 Me), 64.9 (C-1), 74.1 (CH_2OTr), 81.7 (C-3), 83.2 (C-2), 84.1 (C-4), 87.2 (CPh_3), 112.5 (CMe_2), 127.2, 127.9, 128.7, 143.8 (Ar). Anal. Calcd for $C_{27}H_{28}O_4$: C, 77.88 ; H, 6.73; O, 15.38. Found: C, 77.65; H, 6.72; O, 15.88.

Preparation of 1,4-anhydro-D-ribitol (**10**).—A solution of 8 g of compound **9** (19 mmol) in 120 mL of 5:1 water–CF_3CO_2H was heated (70°C) for 2 h and then concentrated to give **10**, which was used without purification for the next steps. Crystallization with acetone–EtOAc, followed by recrystallization in EtOH gave pure **10** (2.5 g, 98%); mp 102–103°C; lit. [21,23] 98–99°C; $[\alpha]_D$ +66.5° (*c* 0.1, H_2O). Acetylation gave, after column chromatography (EtOAc), pure triacetate **11**; $[\alpha]_D$ +69°; NMR data ($CDCl_3$): ^1H, δ 2.0 (m, 9 H), 3.6–4.4 (m, 5 H), 5.0–5.5 (m, 2 H). Anal. Calcd for $C_{11}H_{16}O_7$: C, 50.77 ; H, 6.15; O, 43.07. Found: C, 50.72; H, 6.20; O, 43.33.

Tritylation performed as for **3** (but without heating) gave, after column chomatography (1:1 EtOAc–hexane), 6.7 g (60%) of pure 1,4-anhydro-5-*O*-(triphenylmethyl)-D-ribitol (**12**); mp 139°C; $[\alpha]_D$ +21.8°; NMR data (Me_2SO-d_6): ^1H, δ 3.0–3.6 (m, 3 H), 3.9–4.3 (m, 2 H), 4.1–4.8 (m, 2 H), 5.4 (d, disappearing after addition of D_2O, OH, $J_{HO,CH}$ 4 Hz), 5.9 (d, disappearing after addition of D_2O, $J_{HO,CH}$ 7.5 Hz), 7.1–7.6 (m, 15 H, Ar). Anal. Calcd for $C_{24}H_{24}O_4$: C, 76.59 ; H, 6.38; O, 17.02. Found: C, 76.78; H, 6.48; O, 17.06.

Acetylation of **12** gave 1,4-anhydro-2,3-di-*O*-acetyl-5-*O*-(triphenylmethyl)-D-ribitol (**13**); mp 149–150°C; $[\alpha]_D$ +40.2°. NMR data ($CDCl_3$): ^1H, δ 2.02 (s, 3 H), 2.05 (s, 3 H), 3.25 (m, 2 H, H-5 and H-5'), 4.0 (m, 3 H), 5.4 (m, 2 H, H-2, H-3), 7.37 (m, 15 H, Ar). Anal. Calcd for $C_{28}H_{28}O_6$: C, 73.04 ; H, 6.09; O, 20.87. Found: C, 72.5; H, 6.05; O, 20.4.

(2S)-2-O-(2-Hydroxyethyl)-1-O-triphenylmethylglycerol (**15**).—To a solution of 4 g (10 mmol) of **12** in 40 mL of MeOH was added dropwise a solution of sodium metaperiodate [35] (3.2 g, 1.5 equiv) in water. The mixture was stirred magnetically for 3 h. After TLC (1:1 EtOAc–hexane) indicated that all starting material had disappeared, dialdehyde **14**

was totally reduced in situ by the addition of 0.8 g (2.2 equiv) of sodium borohydride within 1 h. The solution was extracted with CH_2Cl_2, dried, and concentrated to give, after column chromatography (1:1 EtOAc–hexane), 3.1 g (77%) of pure diol **15**; $[\alpha]_D$ +16.5°. NMR data (Me_2SO-d_6): ^1H, δ 3.1 (m, 2 H), 3.5 (m, 7 H), 4.6 (m, 2 OH), 7.3 (m, 15 H, Ar); ^{13}C, δ 62.24 and 63.02 (CH_2OH), 65.30 (CH_2O), 73.16 (CH_2OTr), 81.34 (C-2), 87.77 (CPh_3), 128.84, 129.62, 130.01, 145.60 (Ar).

*(2S)-3-*O-p-*Tolylsulfonyl-2-*O-*(2-*p-*tolylsulfonyloxyethyl)-1-*O-*(triphenylmethyl)glycerol* (**16**).—To a solution of 3 g (7 mmol) of **15** in 10 mL of $CHCl_3$ cooled in an ice bath was added 3 equiv of tosyl chloride dissolved in 2:1 $CHCl_3$-pyridine [27]. After stirring overnight, TLC (1:1 EtOAc-hexane) indicated the end of the reaction and the solution was poured onto a mixture of ice and sodium carbonate, and extracted with CH_2Cl_2, dried, and concentrated. Column chromatography (1:2 EtOAc-hexane) gave 2.8 g (52%) of pure **16**; $[\alpha]_D$ −9.2°. NMR data ($CDCl_3$): ^1H, δ 2.4 (s, 6 H, 2 Me), 3.1 (m, 2 H), 3.85 (m, 3 H), 4 (m, 4 H), 7.0–8.0 (m, 23 H); ^{13}C, δ 21.57 (Me), 69.10 and 69.78 (CH_2OTs),74.98 (CH_2OTr), 79.20 (CH), 87.06 (CPh_3),127.20, 127.93, 128.60, 129.88, and 143.59 (Ar). Anal. Calcd for $C_{38}H_{38}O_8S_2$: C, 66.45; H, 5.58; O, 18.64; S, 9.34. Found: C, 66.04; H, 5.32; O, 17.85; S, 8.89.

(2S)-4-Benzyl-2-(triphenylmethyloxymethyl)tetrahydro-1,4-oxazine (**17**).—To a solution of 3 g (4 mmol) of ditosylate **16** in 30 mL of *N,N*-dimethylformamide was added 1.5 g (3.2 equiv) benzylamine, and the mixture was heated at 120°C overnight. After cooling, the mixture was diluted with 200 mL of $CHCl_3$, washed with 50 mL of 0.1 N aq NaOH, dried, concentrated, and chromatographed (1:4 EtOAc–hexane) to give 1.31 g (67%) of pure oxazine **17**; mp 106–107°C; $[\alpha]_D$ −2.2°. NMR data ($CDCl_3$): ^1H, δ 2.01 (t, 1 H, $J_{3a,3e}$ 10.5, $J_{3a,2a}$ 10.5 Hz, H-3a), 2.18 (dt, 1 H, $J_{5a,6a}$ 11, $J_{5a,5e}$ 11, $J_{5a,6e}$ 3 Hz, H-5a), 2.68 (d, 1 H, $J_{5e,6a}$ 2 Hz, H-5e), 2.92 (d, 1 H, H-3e), 3.03 (dd, 1 H, $J_{2^1,2'}$ 1 9, $J_{2^1,2a}$ 6 Hz, H-2^1), 3.24 (dd, 1 H, $J_{2'^1,2a}$ 5 Hz, H-$2'^1$), 3.55 (2 d, 2 H, $J_{H,H}$ 13 Hz, NCH_2Ph), 3.72 (dt, 1 H, $J_{6a,6e}$ 11 Hz, H-6a), 3.85–3.9 (m, 2 H, H-6e and H-2a), 7.3 (m, 20 H, Ar); ^{13}C, δ 53.0 (C-5), 56.3 (C-3), 63.4 (NCH_2Ph), 65.2 (C-6), 66.7 (C-2^1), 75.1 (C-2), 86.5 (CPh_3), 127.0, 127.3, 127.8, 128.3, 128.7, 129.3, 144.0 (Ar). Anal. Calcd for $C_{31}H_{31}NO_2$: C, 82.82; H, 6.95; N, 3.12; O, 7.12. Found: C, 82.73; H, 6.82; N, 3.15; O, 7.56.

(2S)-4-(2-Phenylethyl)-2-(triphenylmethyloxymethyl)tetrahydro-1,4-oxazine (**18**).—Treatment of compound **16** (conducted as for the synthesis of oxazine **17**) gave, after column chromatography (1:2 EtOAc–hexane), 1.2 g (60%) of pure oxazine **18**; $[\alpha]_D$ −8.5°. NMR data ($CDCl_3$): ^1H, δ 2.01 (t, 1 H, $J_{3a,3e}$ 10.6, $J_{3a,2a}$ 10.6 Hz, H-3a), 2.22 (dt, 1 H, $J_{5a,5e}$ 11.25, $J_{5a,6e}$ 3 Hz, H-5a), 2.64 (m, 2 H, H-5e and $(CH_2)_2Ph$), 2.82 (m, 3 H, $(CH_2)_2Ph$), 3.02 (d, 1 H, H-3e), 3.07 (dd, 1 H, $J_{2^1,2'^1}$ 9.3, $J_{2^1,2a}$ 5.6 Hz, H-2^1), 3.27 (dd, 1 H, $J_{2'^1,2a}$ 5 Hz, H-$2'^1$), 3.76 (dt, 1 H, $J_{6a,6e}$ 11.25, $J_{6a,5e}$ 1.8 Hz, H-6a), 3.82–3.98 (m, 2 H, H-2a and H-6e), 7.3 (m, 20 H, Ar); ^{13}C, δ 53.28 (C-5), 56.46 (C-3), 33.39 (N-Ca), 60.75 (N-Cb), 65.3 (C-6), 66.8 (C-2^1), 74.98 (C-2), 86.67 (CPh_3), 126.11, 127.02, 127.28, 127.87, 128.06, 128.45, 128.78, 144.04 (Ar). Anal. Calcd for $C_{32}H_{33}NO_2$: C, 82.90; H, 7.17; N, 3.02. Found: C, 82.67; H, 7.18; N, 2.56.

(2S4-Isopropyl-(2S)-2-(triphenylmethyloxymethyl)tetrahydro-1,4-oxazine (**19**).—A solution of ditosylate **16**, (4 g, 5.8 mmol) in 10 mL of isopropylamine was heated at 120°C overnight. After cooling, the mixture was washed with saline, extracted with CH_2Cl_2, dried, concentrated, and chromatographed (2:1 EtOAc–hexane) to give 1.7 g (73%) of pure

oxazine **19**; mp 92–93°C; $[\alpha]_D$ −14.3°. NMR data ($CDCl_3$): ^1H, δ, 1.02 (d, 3 H, Me), 1.04 (d, 3 H, Me), 2.04 (t, 1 H, $J_{3a,3e}$ 10.5, $J_{3a,2a}$ 10.5 Hz, H-3a), 2.25 (dt, 1 H, $J_{5a,5e}$ 11.3, $J_{5a,6a}$ 11.3, $J_{5a,6e}$ 3.2 Hz, H-5a), 2.65 (m, 2 H, H-5e and H-CMe_2), 2.90 (d, 1 H, H-3e), 3.04 (dd, 1 H, $J_{2^1,2'^1}$ 9.1, $J_{2^1,2a}$ 5.9 Hz, H-2^1), 3.26 (dd, 1 H, $J_{2'^1,2a}$ 5.2 Hz, H-$2'^1$), 3.70 (dt, 1 H, $J_{6a,6e}$ 11.3, $J_{6a,5e}$ 1.8 Hz, H-6a), 3.80–3.96 (m, 2 H, H-6e and H-2a), 7.3 (m, 15 H, Ar); ^{13}C: δ 18.54 and 19.07 (2 Me), 49.03 (C-5), 52.67 (C-3), 55.11 (C-H), 65.78 (C-6), 67.50 (CH_2OTr), 75.76 (C-2), 86.92 (CPh_3), 127.30, 128.13, 129.10 and 144.37 (Ar). Anal. Calcd for $C_{27}H_{31}NO_2$: C, 80.76; H, 7.78; N, 3.49. Found: C, 79.62; H, 7.70; N, 3.44.

(2S)-Acetoxymethyl-4-isopropyltetrahydro-1,4-oxazine (**21**).—Acetylation of compound **20** (1.4 g, 5 mmol) gave, after chromatographic purification (EtOAc), 0.8 g (78%) of pure acetate **21**; $[\alpha]_D$ +8.5°; NMR data ($CDCl_3$): ^1H, δ 1.0 and 1.1 (2 d, 6 H, 2 Me), 2.05 (s, 3 H, Ac), 2.25 (m, 1 H), 2.4–2.8 (m, 4 H), 3.0–3.9 (m, 3 H); 4.1 (m, 2 H). Anal. Calcd for $C_{10}H_{19}NO_3$: C, 59.68; H, 9.52; N, 6.96; O, 23.85. Found: C, 59.6; H, 9.56; N, 6.85; O, 23.88.

*Preparation of 1,4-Anhydro-*D*-gulitol* (**26**).—Reaction of commercial D-gulonolactone (**22**; 8 g, 45 mmol) according to Refs [30] and [31] gave after recrystallization (EtOH) 8.7 g (75%) of pure **23**; mp 151–152°C; lit. [30]150–151°C; lit. [31] 153–153.5°C; $[\alpha]_D$ −67.9°; lit. [30] $[\alpha]_D$ −67.8° (*c* 4.16, $CHCl_3$; NMR data ($CDCl_3$): ^1H, δ 1.38, 1.40, 1.47, and 1.48 (4 s, 12 H, 2 CMe_2), 3.83 (m, 1 H, $J_{6,6'}$ 9 Hz, H-6), 4.22 (m, 1 H, H-6'), 4.44 (m, 2 H, H-5, H-4), 4.75 (dd, 1 H, $J_{3,4}$ 3.5 Hz, H-3), 4.85 (d, 1 H, $J_{2,3}$ 5.6 Hz, H-2); ^{13}C, δ 25.28, 25.90, 26.74 and 26.81 (4 Me), 65.30 (C-6), 75.34 (C-5), 75.83 (C-3), 76.12 (C-2), 80.99 (C-4), 110.60 and 114.79 (2 CMe_2), 172.97 (C=O). Anal. Calcd for $C_{12}H_{18}O_6$: C, 55.81; H, 7.02; O, 37.17. Found: C, 55.08; H, 6.86; O, 37.39.

Reduction of **23**, performed as for **6**, gave 83% of 2,3:5,6-di-*O*-isopropylidene-D-gulitol (**24**); mp 73–74°C; $[\alpha]_D$ +11.6°; Anal. Calcd for $C_{12}H_{22}O_6$: C, 54.96 ; H, 8.45; O, 36.60. Found: C, 54.05; H, 8.16; O, 37.36.

Reaction of compound **24** (8 g, 30.5 mmol), performed with tosyl chloride as described above for **6**, yielded after chromatographic purification (1:1 EtOAc–hexane) 5.6 g (75%) of 1,4-anhydro-2,3:5,6-di-*O*-isopropylidene-D-gulitol (**25**); mp 79–81°C; lit. [35] 83–83.5°C; $[\alpha]_D$ +55°, [(+29.3° (*c* 1, toluene)], lit. [35] +30.4 (*c* 3.34, toluene). NMR data ($CDCl_3$): ^1H, δ 1.28, 1.38, 1.44, and 1.46 (4 s, 12 H, 2 CMe_2), 3.46 (dd, 1 H, $J_{4,5}$ 8 Hz, H-4), 3.54 (dd, 1 H, $J_{1,1'}$ 10.87 Hz, H-1), 3.70 (dd, 1 H, $J_{6,5}$ 6.75 Hz, H-6), 4.10 (d, 1 H, H-1'), 4.22 (dd, 1 H, $J_{6,6'}$ 8.3 Hz, H-6'), 4.39 (ddd, 1 H, $J_{5,6'}$ 6.75 Hz, H-5), 4.59 (dd, 1 H, $J_{3,4}$ 3.75 Hz, H-3), 4.76 (dd, 1 H, $J_{2,3}$ 6 Hz, H-2); ^{13}C: δ 24.88, 25.43, 26.06 and 26.62 (4 Me), 66.10 (C-6), 73.20 (C-1), 75.60 (C-5), 80.70 (C-3), 81.30 (C-2), 84.40 (C-4), 109.77 and 112.75 (2 CMe_2). Anal. Calcd for $C_{12}H_{20}O_5$: C, 59.01; H, 8.19; O, 32.78. Found: C, 59.25; H, 8.18, O, 32.57.

Deacetalation of **25** (10 g, 41 mmol) by stirring for 2 h at 60°C with 90 mL of 1:5 CF_3CO_2H–water, and treatment as for compound **10**, gave 6 g (89%) of pure (EtOH) compound **26**; mp 110–111°C; $[\alpha]_D$ −8° (*c* 1, MeOH); 7.6° (*c* 1, H_2O); lit. [35] mp 109–110°C; $[\alpha]_D$ +9° (*c* 8.6, H_2O). Anal. Calcd for $C_6H_{12}O_5$: C, 43.90; H, 7.37; O, 48.73. Found: C, 43.84; H, 7.14; O, 48.91.

*1,4-Anhydro-5,6-*O*-isopropylidene-*D*-gulitol* (**27**).—Treatment of lactone **26** (5 g, 30 mmol), performed as for lactone **4**, gave after column chromatography (4:1 EtOAc–

hexane) 3 g (49%) of pure **27**; mp 65–66°C; $[\alpha]_D$ −38.3°; Anal. Calcd for $C_9H_{16}O_5$: C, 52.93; H, 7.90; O, 39.17. Found: C, 52.50; H, 7.78; O, 39.36.

Acetylation gave 2,3-di-*O*-acetyl-1,4-anhydro-5,6-*O*-isopropylidene-D-gulitol (**28**) (86%); $[\alpha]_D$ +21.7°. NMR data ($CDCl_3$): ^{1}H, δ 1.33 and 1.38 (2 s, 6 H, CMe_2), 2.0 and 2.05 (2 s, 6 H, 2 Ac), 3.55 (dd, 1 H, $J_{6,6'}$ 8.5, $J_{6,5}$ 7.11 Hz, H-6), 3.9 (dd, 1 H, $J_{1,1'}$ 9.9, $J_{1,2}$ 5.14 Hz, H-1), 3.96 (t, 1 H, $J_{4,5}$ 8.45 Hz, H-4), 3.97 (dd 1 H, $J_{6',5}$ 6.8 Hz, H-6'), 4.05 (dd, 1 H, $J_{1',2}$ 6.11, Hz, H-1'), 4.3 (dt, 1 H, H-5), 5.33 (dd, 1 H, $J_{2,3}$ 5.14 Hz, H-2), 5.4 (t, 1 H, $J_{3,4}$ 5.14 Hz, H-3); ^{13}C, δ 20.43 and 20.51 (2 Ac), 25.14 and 26.52 (2 Me), 65.4 (C-6), 69.1 (C-1), 71.4 (C-5), 71.6 (C-3), 75.0 (C-2), 80.7 (C-4), 109.5 (*C*Me_2), 169.49 and 169.84 (2C=O). Anal. Calcd for $C_{13}H_{20}O_7$: C, 54.16; H, 6.99; O, 38.85. Found: C, 54.28; H, 6.78; O, 39.13.

(2R)-2-O-(2-Hydroxyethyl)-3,4-O-isopropylidene-D-threitol (**30**).—A solution of 8 g (39 mmol) of compound **27** in 50 mL of anhyd MeOH was treated with 12.5 g (1.5 equiv) of sodium metaperiodate in water, and stirred for 2 h until TLC (EtOAc) indicated that all starting material had disappeared. Sodium borohydride (3.2 g, 2.2 equiv) was then added. We obtained 7.3 g (91%) of pure **30** ($[\alpha]_D$ +4.5°), and acetylation gave (2*R*)-1-*O*-acetyl-2-*O*-(2-acetoxyethyl)-3,4-*O*-isopropylidene-D-threitol (**31**); $[\alpha]_D$ +16°. NMR data ($CDCl_3$): ^{1}H, δ 1.35 and 1.40 (2 s, 6 H, CMe_2), 2.08 (2 s, 6 H, 2 Ac), 3.40–4.33 (m, 10 H). Tosylation of 5 g (24 mmol) of **30**, performed as for **16**, gave quantitatively (2*R*)-3,4-*O*-isopropylidene-1-*O*-*p*-tolylsulfonyl-2-*O*-(2-*p*-tolylsulfonyloxyethyl)-D-threitol (**32**); $[\alpha]_D$ +5.3°. NMR data ($CDCl_3$): ^{1}H, δ 1.31 (2 s, 6 H, CMe_2), 2.46 (2 s, 6 H, 2 *Me*Ar), 3.39–4.22 (m, 10 H), 7.33, 7.81 (2 d, 8 H, *J* 8 Hz, Ar).

(2R)-4-Benzyl-2-(1,2-O-isopropylidene-D-glycero-1,2-dihydroxyethyl)tetrahydro-1,4-oxazine (**33**).—A solution of 4 g (7.7 mmol) of compound **32** in 10 mL of benzylamine was heated at 120°C for 15 h. After column chromatography (1:1 EtOAc–hexane) 1.55 g (72%) of pure morpholine **33** was obtained; mp 55–56°C; $[\alpha]_D$ −1.5°. NMR data ($CDCl_3$): ^{1}H, δ 1.38 and 1.43 (2 s, 6 H, CMe_2), 2.03 (t, 1 H, $J_{3a,3e}$ 10.57, $J_{3a,2a}$ 10.57 Hz, H-3a), 2.23 (dt, 1 H, $J_{5a,5e}$ 11.3, $J_{5a,6a}$ 11.3 Hz, H-5a), 2.67 (m, 2 H, H-3e, H-5e), 3.55 (2 d, 2 H, $J_{H,H}$ 13 Hz, NCH_2Ph), 3.7 (m, 2 H, H-2a, H-6a), 3.75 (m, 1 H, H-2^2), 3.98 (m, 2 H, H-2$^{2'}$, H-6e), 4.13 (m, 1 H, H-2^1), 7.2–7.4 (m, 5 H, Ar); ^{13}C, δ 25.86 (Me), 26.78 (Me), 53.33 (C-5), 54.61 (C-3), 63.90 (NCH_2Ph), 65.88 (C-2^2), 67.19 (C-6), 76.90 (C-2^1), 77.02 (C-2), 109.94 (*C*Me_2), 127.82, 128.79, 129.48 and 140.28 (Ar). Anal. Calcd for $C_{16}H_{23}NO_3$: C, 69.29; H, 8.36; N, 5.05. Found: C, 69.56; H, 8.36; N, 5.01.

(2R)-2-(1,2-O-Isopropylidene-D-glycero-1,2-dihydroxyethyl)-4-(2-phenylethyl)tetrahydro-1,4-oxazine (**34**).—Prepared as described for **33**, 4 g (7.7 mmol) of **32** gave, after column chromatography (2:1 EtOAc–hexane), 1.35 g (60%) of morpholine **34**; $[\alpha]_D$ +12.1°. NMR data ($CDCl_3$): ^{1}H, δ 1.40 and 1.48 (2 s, 6 H, CMe_2), 2.04 (t, 1 H, $J_{3a,3e}$ 10.7, $J_{3a,2a}$ 10.7 Hz, H-3a), 2.26 (dt, 1 H, $J_{5a,5e}$ 11.2, $J_{5a,6a}$ 11.2, $J_{5a,6e}$ 3.2 Hz, H-5a), 2.56–2.68 (m, 2 H, H-3e, H-5e), 2.70–2.90 (m, 4 H, $(CH_2)_2$Ph), 3.60–3.82 (m, 3 H, H-2a, H-2^2 and H-6a), 3.94–4.05 (m, 2 H, H-2$^{2'}$, H-6e), 4.13 (m, 1 H, H-2^1), 7.12–7.45 (m, 5 H, Ar); ^{13}C, δ 25.68 (Me), 26.62 (Me), 33.57 (N-Ca), 53.27 (C-5), 54.51 (C-3), 60.67 (N-Cb, 65.71 (C-2^2), 67.05 (C-6), 76.37 (C-2^1), 76.49 (C-2), 109.8 (*C*Me_2), 126.11, 128.4, 128.88, 140.28 (Ar). Anal. Calcd for $C_{17}H_{25}NO_3$: C, 70.07; H, 8.65; N, 4.81. Found: C, 70.35; H, 8.81; N, 5.03.

*(2R)-4-Isopropyl-2-(1,2-O-isopropylidene-*D-glycero-*1,2-dihydroxyethyl)tetrahydro-1,4-oxazine* (**35**).—As described above for morpholines **33** and **34**, reaction of ditosylate **32** (5 g, 9.7 mmol) with isopropylamine gave, after purification (5:2 EtOAc–MeOH), 1.4 g (64%) of pure morpholine **35**; $[\alpha]_D$ +9.8°; NMR data, ($CDCl_3$): ^{1}H, δ 1,00 and 1,02 (2 d, 6 H, $J_{H,H}$ 3 Hz, CH*Me*$_2$), 1.32 and 1.38 (2 s, 6 H, CMe_2), 2.06 (t, 1 H, $J_{3a,3e}$ 10.7, $J_{3a,2a}$ 10.7 Hz, H-3a), 2.27 (dt, 1 H, $J_{5a,5e}$ 11.35, $J_{5a,6a}$ 11.35, $J_{5a,6e}$ 3.2 Hz, H-5a), 2.54 (m, 1 H, H-3e), 2.65 (m, 2 H, NCH, H-5e), 3.50–3.73 (m, 3 H, H-2a and H-6a, H-2^2), 3.87–3.98 (m, 2 H, H-2$^{2'}$, H-6e), 4.05 (m, 1 H, H-2^1,); ^{13}C, δ 18.44 (Me), 18.84 (Me), 25.80 and 26.70 (2 Me), 48.78 (C-5), 50.37 (C-3), 55.17 (*C*HMe$_2$), 65.39 (C-6), 65.83 (C-2^2), 76.95 (C-2^1), 77.02 (C-2), 109.85 (*C*Me$_2$). Anal. Calcd for $C_{12}H_{23}NO_3$: C, 62.85; H, 10.11; N, 6.11. Found: C, 61.93; H, 10.12; N, 5.95.

*(2R)-2-(1,2-O-Diacetyl-*D-glycero-*1,2-dihydroxyethyl)-4-isopropyltetrahydro-1,4-oxazine* (**37**).—Stirring of compound **35** (4 g, 17 mmol) for 2 h at room temperature with a solution of 17% CF_3CO_2H in water gave, after evaporation and purification of the residue by flash chromatography (1:1 EtOAc–hexane), 5.2 g (98%) of a mixture of morpholine **36** and its trifluoroacetate derivative. Acetylation of this product (1.5 g, 5 mmol) gave after chromatographic purification (EtOAc) 1 g (74%) of pure acetate **37**: $[\alpha]_D$ +22.9°; NMR data ($CDCl_3$): ^{1}H, δ 1.00 and 1.02 (2 d, 6 H, $J_{H,H}$ 3 Hz, CH*Me*$_2$), 2.02 and 2.10 (2 s, 6 H, 2 Ac), 2.07 (t, 1 H, $J_{3a,3e}$ and $J_{3a,2a}$ 10.57 Hz, H-3a), 2.27 (dt, 1 H, $J_{5a,5e}$ and $J_{5a,6a}$ 11.33, $J_{5a,6e}$ 3.2 Hz, H-5a), 2.64 (m, 3 H, H-3e,C*H*Me$_2$, and H-5e), 3.59 (dt, 1 H, $J_{6a,6e}$ 11.33 Hz, $J_{6a,5e}$ 2.49 Hz, H-6a); 3.70 (2 dd, 1 H, $J_{2a,3e}$ 1.57 Hz, $J_{2a,2^1}$ 3.9 Hz, H-2a), 3.91 (dd, 1 H, $J_{6e,5e}$ 1.5 Hz, H-6e), 4.15 (dd, 1 H, $J_{2^2,2'^2}$ 11.8 Hz, $J_{2^2,2^1}$ 7.4 Hz, H-2^2), 4.3 (dd, 1 H, $J_{2'^2,2^1}$ 3.9 Hz, H-2'^{2}), 5.15 (m, 1 H, H-2^1). Anal. Calcd for $C_{13}H_{23}NO_5$: C, 57.14; H, 8.42; N, 5.12; O, 29.31. Found: C, 57.00; H, 8.41; N, 5.24; O, 29.30.

*(2R)-2-(*D-glycero-*1,2-Dihydroxyethyl)-4-isopropyltetrahydro-1,4-oxazine* (**36**).—Deacetylation of **37** (1 g, 3 mmol) in 10 mL of MeOH with 1 mL of 0.01 N sodium methanolate at room temperature with stirring gave, after evaporation of the solvent, 0.66 g (95%) of pure morpholine **36**; $[\alpha]_D$ −21.1°. NMR data (Me_2SO-d_6): ^{1}H, d 0.96 and 1.03 (2 d, 6 H, CH*Me*$_2$), 1.99–2.80 (m, 5 H), 3.2–4 (m, 6 H), 4.30 (m, 2 H, 2 OH). Anal. Calcd for $C_9H_{19}NO_3$: C, 57,14; H, 10.05; N, 7.40; O, 25.39. Found: C, 55.33; H, 9.99; N, 6.99; O, 26.74.

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