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Improved Stereoselective Synthesis of Both Methyl α- and β-Glycosides Corresponding to the Amino Sugar Component of the E Ring of Calicheamicin γ_1^I and Esperamicin A_1

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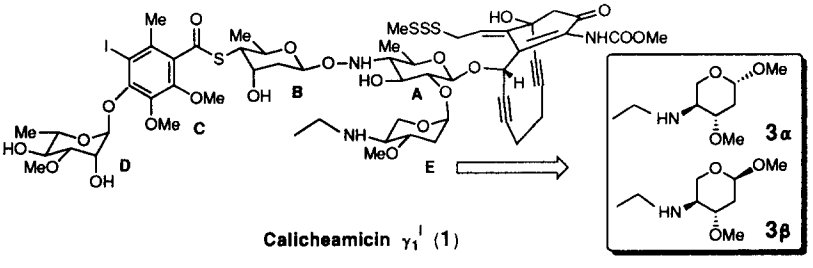
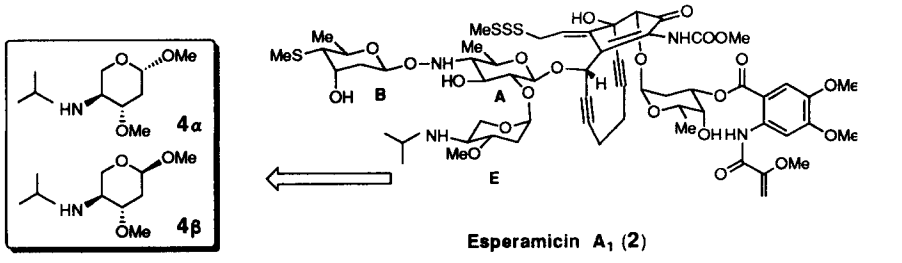
Abstract: The monosaccharide component (α and β-anomer) of the E Ring of calicheamicin γ_1^I and esperamicin A_1 has been synthetized by an efficient and improved stereoselective procedure starting from methyl 2-deoxy-α- and β-D-ribopyranoside. The synthetic procedure makes use, in each case, of a cyclic sulphate and of the regioselective ring opening of an intermediate activated aziridine.

Calicheamicin γ_1^I (**1**) and esperamicin A_1 (**2**), components of a class of compounds, the enediyne antibiotics, possessing a remarkable antitumor activity,[1] have attracted chemists in view of the achievement of their total or partial synthesis. At the moment, two total syntheses of **1** have been realized,[2,3] while other partial syntheses have commonly aimed to construct the important oligosaccharide system of **1** and **2**.[4]



Calicheamicin γ_1^I (1)



Esperamicin A_1 (2)

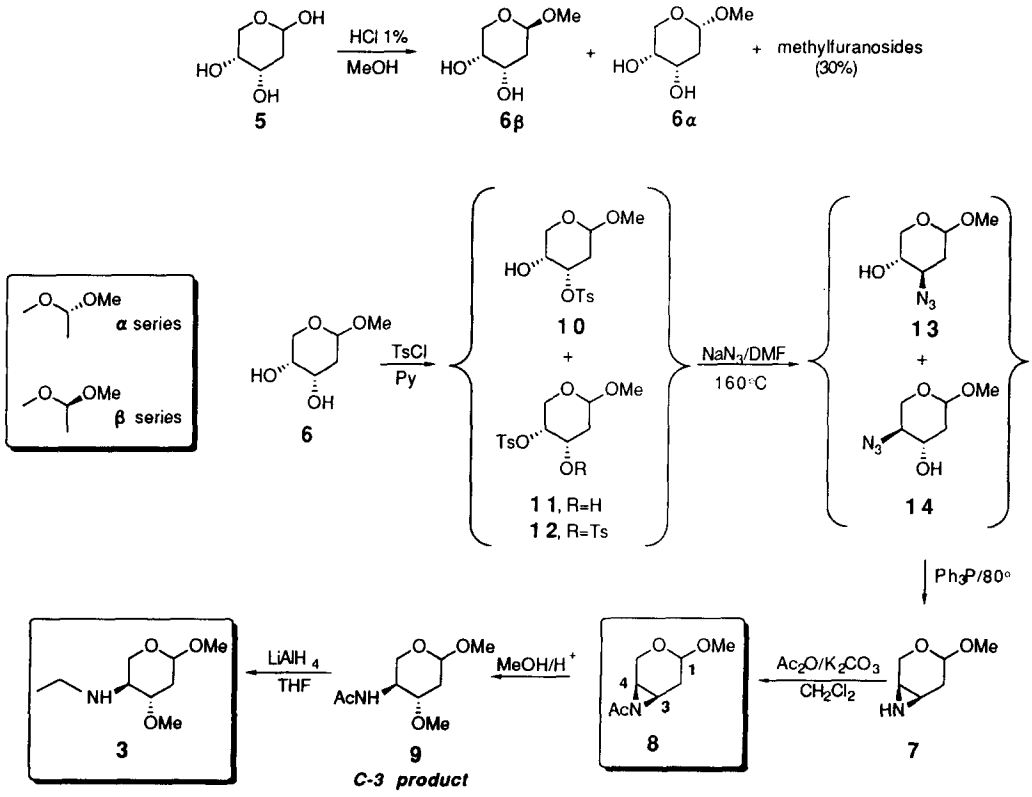
We found recently an effective enantioselective synthesis of the amino sugar **3β** (β anomer) corresponding to the E Ring of **1** starting from methyl 2-deoxy-β-D-ribopyranoside (**6β**):[5] the core of our approach to **3β** was

the use of an activated aziridine (aziridine **8β**) whose regioselective ring opening with methanol under acid conditions gave the exact stereo- and regiochemistry (compound **9β**) of the target compound **3β**, as shown in Scheme 1.[5]

In consideration of the fact that the monosaccharidic starting material (methyl β-ribopyranoside **6β**)[5,6] necessary for the above-described enantioselective synthesis of **3β** is separated from the corresponding α-anomer **6α** only with difficulty and in an unsatisfactory yield (Scheme 1),[5,6] and in view of the possible utilization of both **3α** and **3β** for the construction of the β-glycosidic linkage of the E Ring to the remaining oligosaccharide moiety of **1**,[3a] we thought it worthwhile to check whether the above-described synthetic procedure for **3β**, starting from **6β**, could be efficently utilized also for the synthesis of **3α**, starting from **6α**.

The synthesis of aziridine **7α** through the sequence **6α** — monotosylates **10-11α** — azido alcohols **13-14α** (Scheme 1), as previously achieved in the case of the diastereoisomeric aziridine **7β**,[5] turned out to be

Scheme 1

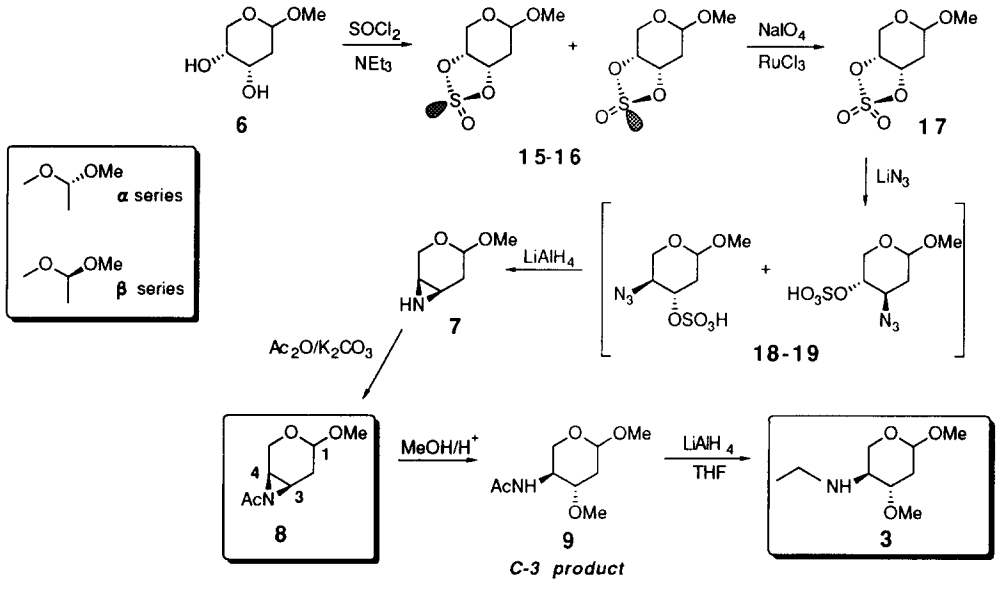


unsatisfactory in this case, due to the low yield of **7α** obtained (52% yield from **6α**). Particularly difficult and critical was the extraction with cold water (or other solvent) of **7α**, as performed in the case of **7β**, from the

crude reaction mixture obtained by treatment of azido alcohols **13-14α** with PPh_3 (Scheme 1).[5,7] As a consequence, it was necessary, in this case, to change the synthetic approach to **7α**, and the use of a cyclic sulfate appeared promising.

The reaction of **6α** with $SOCl_2$[8a] afforded an 80:20 mixture of cyclic sulfites **15α** and **16α** (or viceversa, Scheme 2) which were directly oxidized with $RuCl_3$ and $NaIO_4$ to cyclic sulfate **17α**.[8b] Nucleophilic aliphatic substitution of **17α** with LiN_3 afforded a mixture of azido sulphates **18α** and **19α** which were directly reduced with $LiAlH_4$[8c] to give pure aziridine **7α** (76% yield from **6α**). Acetylation of **7α** afforded the activated aziridine **8α** which was subjected to acid methanolysis to yield methoxy amide **9α** (a *C-3 product*, Scheme 2), as practically the only reaction product,[9] possessing the exact regio- and stereochemistry of the target compound. $LiAlH_4$ reduction of **9α** afforded the desired anomer **3α** (54% yield fom **6α**).[3a,10]

Scheme 2

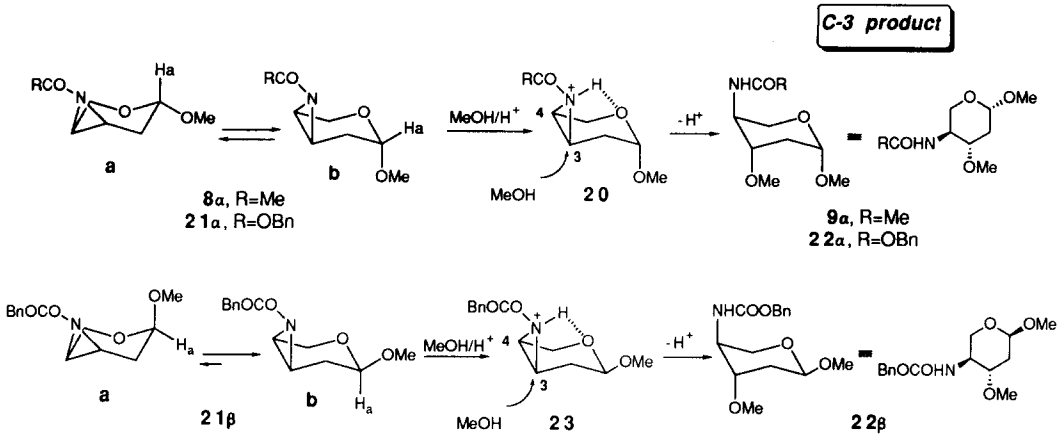


The complete C-3 selectivity observed in the acid methanolysis of aziridine **8α** can be rationalized, in accordance with previous results in other similar aziridine systems,[11] by admitting a reactivity of aziridine **8α** in its conformation **b**[12] which allows the protonation process of the aziridine nitrogen to be efficiently stabilized by an intramolecular hydrogen bond with the endocyclic oxygen, as shown in structure **20** (Scheme 3). The diaxial nucleophilic attack[13] of MeOH on **20** can occur only on the C(3) aziridine carbon to give exclusively the *C-3 product* (compound **9α**), as observed.[9]

The above-described procedure for the synthesis of aziridine **7α**, which makes use of an intermediate cyclic sulphate, was also repeated for the synthesis of aziridine **7β** on the synthetic route to **3β**,[5] as shown in Scheme 2. In this way, aziridine **7β** was obtained in a lower yield (80% yield from **6β**) than when synthesized

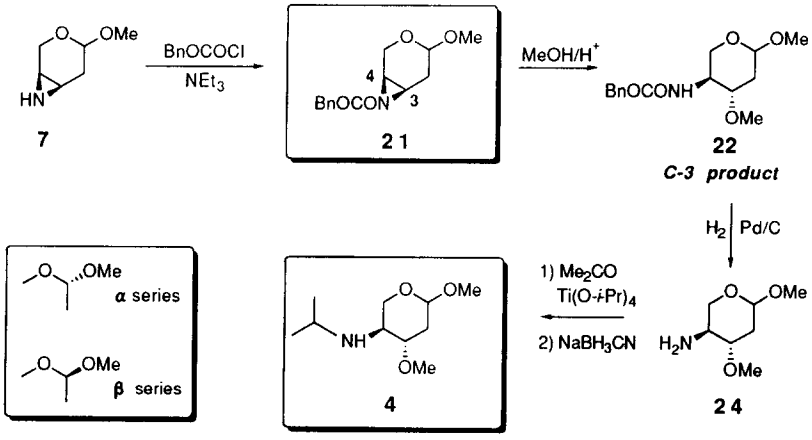
following the previously described procedure (84% yield, Scheme 1),[5] but in a more reproducible way, which is to be decidedly preferred.

Scheme 3



This simple and efficient synthetic procedure to both aziridines **7α** and **7β**, allowed us to utilize these intermediates also for the synthesis of both methyl α- and β-glycosides **4α** and **4β** (Scheme 4), respectively, corresponding to the *N*-isopropyl-substituted amino sugar constituent of the E Ring of esperamicin A_1 (**2**). For

Scheme 4



the synthesis of **4α** and **4β**, the synthetic procedure previously utilized for the preparation of the corresponding *N*-ethyl derivatives (compounds **3α** and **3β**, Scheme 2) had to be appropriately modified. The reaction of aziridine **7β** with benzylchloroformate yielded the new activated aziridine **21β**, which by acid methanolysis gave the methoxy urethane **22β**, as practically the only opening product.[9] Deprotection of **22β** by catalytic hydrogenation afforded the methoxy amine **24β** which was alkylated by reductive amination with acetone in the

presence of Ti(*O*-*i*-Pr)$_4$[14] to give the target compound **4β** (39% yield starting from **6β**) (Scheme 4). Analogous treatment of aziridine **7α** initially afforded the corresponding *N*-activated aziridine **21α** which was opened with methanol under acid conditions to give exclusively the methoxy urethane **22α**,[9] then deprotected to the amine **24α** which was alkylated to the anomeric target compound **4α** (40% yield from **6α**) (Scheme 4).

The complete C-3 selectivity observed in the acid methanolysis of both aziridines **21α** and **21β** can be explained, in the case of **21α**, by means of the same rationalizations already used in the case of the corresponding activated aziridine **8α** (see above and Scheme 3),[12] and, in the case of **21β**, by admitting a practically complete reactivity of **21β** in its more stable conformation **b**:[15] diaxial attack[13] of MeOH on the corresponding protonated species **23** can occur only on the C(3) aziridine carbon to give the complete selectivity so far observed.

In conclusion, we have obtained the enantioselective synthesis of both methyl α- and β-glycosides corresponding to the amino sugars constituent of the E Ring of calicheamicin (**1**) and esperamicin A_1 (**2**), starting from methyl 2-deoxy-α- (**6α**) and β-D-ribopyranoside (**6β**), respectively, through a completely stereoselective and regioselective process. The complete stereoselectivity and regioselectivity so far observed in these transformations advantageously allows the direct use of the difficult-to separate mixture of **6α** and **6β** (Scheme 1) to obtain an almost corresponding mixture of the anomeric target compounds (**3α** and **3β** or **4α** and **4β**) by a simple and time-saving procedure which does not need any purification or separation process. The mixture of **3α** and **3β** or **4α** and **4β** can then be utilized for the construction of the oligosaccharide moiety (E Ring) of **1** and **2**, respectively.

Experimental

Melting points were determined on a Kofler apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were determined with a Bruker AC-200 spectrometer on $CDCl_3$ solutions using tetramethylsilane as the internal standard. Optical rotations were measured with a Perkin-Elmer 241 digital polarimeter with a 1 dm cell. All reactions were followed by TLC on Alugram SIL G/UV$_{254}$ silica gel sheets (Macherey-Nagel) with detection by UV or with 0.5% phosphomolybdic acid solution in 95% EtOH. Silica gel 60 (Macherey-Nagel 230-400 mesh) was used for flash chromatography. Pure methyl 2-deoxy-β- (**6β**) and α-D-ribopyranoside (**6α**) and their 75:25 mixture were prepared as previously described.[5,6]

Mixture of Azido Alcohols 13α and 14α. Following a previously described procedure,[5] a solution of methy β-glycoside **6α** (0.518 g, 3.5 mmol) in anhydrous pyridine (10 ml) was treated at 0°C with TsCl (0.67 g, 3.5 mmol) and the reaction mixture was stirred at r.t. for 48 h. Dilution with CH_2Cl_2 and evaporation of the washed (water) organic solution afforded a crude reaction product (1.08 g) consisting of a 67:22:11 mixture of monotosylates **10α** and **11α** (89%) and ditosylate **12α** (11%) (^{1}H NMR) which was dissolved in anhydrous DMF (4.0 ml) and then treated with NaN_3 (0.93 g, 14.3 mmol); the reaction mixture was stirred for 1 h at 120°C. Dilution with ether and evaporation of the washed (saturated aqueous NaCl solution) organic solution afforded a crude reaction product which was subjected to flash chromatography (a 1:1 mixture of hexane and AcOEt was used as the eluant) to give a 77:23 purified mixture of azido alcohols **13α** and **14α** (0.402 g, 66% yield, based on **6α**) (^{1}H NMR) which was directly utilized in the next step. An analytical sample (0.35 g) of the purified mixture of **13α** and **14α** was subjected to semipreparative TLC (a 6:4 mixture of ether

and hexane was used as the solvent). Extraction of two most intense bands (the faster moving band contained **13α**) afforded pure azido alcohols **13α** (0.230 g) and **14α** (0.050 g).

Methyl 2,3-Dideoxy-3-azido-α-L-*threo*-pentopyranoside (13α), a liquid, IR 2104 cm^{-1}, $[\alpha]_D^{22}$=+110.8 (*c* 1.3, $CHCl_3$); ^1H NMR δ 4.74 (dd, 1H, *J*=3.4 and 1.7), 3.42-3.82 (m, 4H), 3.35 (s, 3H), 2.14 (ddd, 1H, *J*=13.2, 4.7 and 1.8), 1.66 (ddd, 1H, *J*=13.2, 11.6, and 3.4). ^{13}C NMR δ 98.32, 70.51, 62.68, 61.15, 55.5, 34.9. Anal. Calcd for $C_6H_{11}N_3O_3$: C, 41.62; H, 6.40; N, 24.26. Found: C, 41.78; H, 6.38; N, 24.30.

Methyl 2,4-Dideoxy-4-azido-α-L-*threo*-pentopyranoside (14α), a solid m.p. 54°C (from hexane), IR 2104 cm^{-1} $[\alpha]_D^{22}$=+140.5 (*c* 0.7, $CHCl_3$); ^1H NMR δ 4.68 (t, 1H, *J*=3.1) 4.14 (dd, 1H, *J*=12.6 and 2.6), 3.69-3.85 (m, 1H), 3.41-3.65 (m, 2H), 3.39 (s, 3H), 2.15 (dd, 1H, *J*=14.3 and 3.5), 1.77 (ddd, 1H, *J*=14.3 and 3.9).^{13}C NMR δ 99.73, 67.14, 60.77, 58.43, 56.44, 33.16. Anal. Calcd for $C_6H_{11}N_3O_3$: C, 41.62; H, 6.40; N, 24.26. Found: C, 41.70; H, 6.37; N, 24.35.

While monotosylates **10α** and **11α** [**10α** (75%), ^1H NMR δ 4.33 (dd, 1H, *J*=7.0 and 2.9), 3.40 (s, 3H); **11α** (25%), ^1H NMR δ 4.53 (ddd, 1H, *J*=9.1, 4.5 and 3.1), 3.37 (s, 3H)] turned out to be completely unseparable by any chromatographic technique, ditosylate **12α** was easily separated from **10α** and **11α** by flash chromatography (an 1:1 mixture of hexane and AcOEt was used as the eluant) to give pure **12α** as a solid m.p. 113-114°C (dec.) (from hexane/acetone): ^1H NMR δ 7.75 (d, 2H, *J*=8.3), 7.72 (d, 2H, *J*=8.3), 7.32 (d, 4H, *J*=8.2), 4.50-4.66 (m, 2H), 4.37 (dd, 1H, *J*=6.2 and 3.0), 4.12 (dd, 1H, *J*=12.5 and 5.2), 3.43 (dd, 1H, *J*=10.2 and 2.4), 3.38 (s, 3H), 2.45 (s, 6H), 2.10 (ddd, 1H, *J*=13.5, 8.6 and 6.2), 1.88 (ddd, 1H, *J*=13.6 and 3.6). ^{13}C NMR δ 145.74, 133.95, 133.81, 130.52, 128.63, 128.55, 99.46, 74.41, 73.88, 61.77, 56.87, 34.04, 22.35. Anal. Calcd for $C_{20}H_{24}O_8S_2$: C, 52.62; H, 5.30. Found: C, 52.88; H, 5.07.

Cyclic Sulphites 15α and 16α. Following a previously described procedure,[8a] $SOCl_2$ (0.9 ml, 12.3 mmol) was added dropwise at 0°C to a solution of **6α** (0.500 g, 3.38 mmol) in anhydrous THF (10 ml) in the presence of NEt_3 (2.0 ml, 14.35 mmol). The reaction mixture was stirred for 1 h at the same temperature, then diluted with $CHCl_3$. Evaporation of the washed (water) organic solution afforded a crude product which was purified by flash chromatography (a 7:3 mixture of hexane and AcOEt was used as the eluant) to give an unseparable mixture (0.574 g, 87% yield) of sulphites **15α** and **16α** (80:20 or viceversa, ^1H NMR) [**15α** (or **16α**) ^1H NMR δ 5.17 (q, 1H, *J*=5.5 Hz), 4.61 (t, 1H, *J*=4.2), 4.22 (dd, 1H, *J*=12.9 and 7.1), 3.86 (dd, 1H, *J* = 12.9 and 4.8 Hz), 3.43 (s, 3H); **16α** (or **15α**) ^1H NMR δ 5.08 (q, 1H, *J*=5.4 Hz), 3.39 (s, 3H)].

Cyclic Sulphites 15β and 16β. Proceeding as described above for the preparation of **15α** and **16α**, the reaction of methyl β-glycoside **6β** (1.014 g, 6.85 mmol) in anhydrous THF (20 ml) with $SOCl_2$ (1.8 ml, 24.6 mmol) in the presence of NEt_3 (4.0 ml, 28.7 mmol) afforded a crude product which was filtered by flash cromatography (a 7:3 mixture of hexane and AcOEt was used as the eluant), to give an unseparable mixture (1.13 g, 85% yield) of sulphites **15β** and **16β** (73:27 or viceversa). [**15β** (or **16β**): ^1H NMR δ 5.17 (q, 1H, *J*=5.9), 4.76 (t, 1H, *J*=4.3), 4.04 (dd, 1H, *J*=13.5 and 2.6), 3.95 (dd, 1H, *J*=13.7 and 1.9), 3.38 (s, 3H), 2.08 (ddd, 1H, *J*=14.4, 5.7 and 4.3), 2.00 (ddd, 1H, *J*=14.4, 6.8 and 4.3); **16β** (or **15β**) ^1H NMR δ 4.83 (t, 1H, *J*=3.6), 4.51 (quintet, 1H, *J*=2.8), 4.18 (dd, 1H, *J*=13.4 and 2.4), 3.39 (s, 3H), 2.53 (ddd, 1H, *J*=14.0, 8.8 and 3.5), 2.22 (ddd, 1H, *J*=14.0, 6.1 and 3.5)].

Cyclic Sulphate 17α. Following a previously described procedure,[8b] $NaIO_4$ (0.641 g, 3.0 mmol) and $RuCl_3$ (6 mg) were added to a solution of the mixture of sulphites **15α** and **16α** (0.582 g, 3.0 mmol) in 1:1:1.5 CH_2Cl_2:MeCN:H_2O (17 ml) and the reaction mixture was stirred for 1 h at room temperature. Dilution with

CH_2Cl_2 and evaporation of the washed (water) and filtered (celite) organic solvent afforded a crude solid product, consisting of practically pure **17α** (0.624 g, 99% yield) which was directly utilized in the next step. An analytical sample of crude **17α** was recrystallized from hexane to give pure **17α**, as a solid m.p. 64-67°C, $[\alpha]_D^{22}$=+110.6 (*c* 1.1, $CHCl_3$); ^1H NMR δ 5.09 (q, 1H, *J*=5.4 Hz), 4.87 (ddd, *J*=7.3 and 5.1 Hz), 4.55 (t, 1H, *J*=4.2 Hz), 4.15 (dd, 1H, *J*=12.8 and 7.3 Hz), 3.79 (dd, 1H, *J*=12.8 and 5.1 Hz), 3.36 (s, 3H), 2.25 (dd, 2H, *J*=5.0 and 4.2 Hz). ^{13}C NMR δ 97.15, 78.61, 76.65, 57.78, 56.60, 31.81. Anal. Calcd for $C_6H_{10}O_6S$: C, 34.28; H, 4.80. Found: C, 34.65; H, 4.45.

Cyclic Sulphate 17β. Proceeding as described above for the preparation of **17α**, the reaction of the mixture of sulphites **15β** and **16β** (1.052 g, 5.4 mmol) in 1:1:1.5 CH_2Cl_2: MeCN: H_2O (35 ml), with $NaIO_4$ (1.158 g, 5.4 mmol) and $RuCl_3$ (11 mg) afforded a crude solid product consisting of pratically pure **17β** (1.136 g, 99% yield) which was directly utilized in the next step. An analytical sample was recrystallized from hexane to give pure **17β**, as a solid m.p. 75-77°C (dec.), $[\alpha]_D^{22}$=-155.6 (*c* 1.1, $CHCl_3$): ^1H NMR δ 5.20 (ddd, 1H, *J*=8.4 and 5.7 Hz), 4.95-5.02 (m, 1H), 4.88 (t, 1H, *J*=3.5 Hz), 4.11 (dd, 1H, *J*=14.4 and 1.5 Hz), 3.99 (dd, 1H, *J*=14.4 and 2,3 Hz), 3.38 (s, 3H), 2.38 (ddd, 1H, *J*=14.1, 8.6 and 3.9 Hz), 2.22 (ddd, 1H, *J*=14.1, 5.9 and 3.5 Hz). ^{13}C NMR δ 97.60, 78.60, 78.12, 58.28, 56.18, 31.37. Anal. Calcd for $C_6H_{10}O_6S$: C, 34.28; H, 4.80. Found: C, 34.61; H, 4.37.

(1*R*,4*S*,6*R*)-4-Methoxy-3-oxa-7-azabicyclo[4.1.0]heptane (7α).[16] (a) Following a previously described procedure,[8c] LiN_3 (0.255 g, 5.2 mmol) was added to a solution of cyclic sulfate **17α** (0.555 g, 2.6 mmol) in anhydrous THF (26 ml) and the reaction mixture was refluxed for 12 h. After cooling to 0°C, $LiAlH_4$ (0.131 g, 3.57 mmol) was added and the reaction mixture was refluxed for 8 h. The usual workup afforded a crude liquid product consisting of practically pure aziridine **7α** (0.304 g, 89% yield), as a liquid, $[\alpha]_D^{22}$=+166.6 (*c* 0.93, $CHCl_3$): ^1H NMR δ 4.49 (dd, 1H, *J*=5.0 and 2.3 Hz), 4.06 (dd, 1H, *J*=12.2 and 2.3 Hz), 3.80 (d, 1H, *J*=12.2 Hz), 3.36 (s, 3H), 2.30 (t, 1H, *J*=6.0 Hz), 2.20 (dd, 1H, *J*=6.2 and 2.2 Hz), 2.08 (dd, 1H, *J*=15.0 and 5.0 Hz), 1.89 (ddd, 1H, *J*=15.1, 5.8 and 2.4). ^{13}C NMR δ 96.1, 57.85, 55.90, 29.07, 28.89, 26.57. Anal. Calcd for $C_6H_{11}NO_2$: C, 55.79; H, 8.58; N, 10.84. Found: C, 55.90; H, 8.21; N, 10.63.

(b) A solution of the mixture of azido alcohols **13α** and **14α** (0.774 g, 4.47 mmol) in MeCN (5.0 ml) was treated with PPh_3 (1.17 g, 4.47 mmol) and the reaction mixture was stirred at room temperature until evolving of gas (N_2) was no longer observed (30 min), and then for 18 h at 80°C. Evaporation of the solvent afforded a crude product which was dissolved in cold (4°C) water (20 ml) and the suspension was filtered. The aqueous solution was concentrated, filtered again if necessary, and then evaporated to give practically pure aziridine **7α** (^1H NMR) (0.537 g, 80% yield, 1% Ph_3PO was still present), as a liquid, which was directly utilized in the next step. An analytical sample was purified by flash chromatography (a 5:4:1 mixture of CH_2Cl_2, hexane and NEt_3 was used as the eluant) to give pure **7α**.

Aziridine 7β. The treatment of the cylic sulfate **17β** (1.136 g, 5.4 mmol), as described above for **17α**, afforded a crude liquid product consisting of aziridine **7β** (0.662 g, 95% yield), practically pure.[5]

(1*R*,4*S*,6*R*)-4-Methoxy-7-acetyl-3-oxa-7-azabicyclo[4.1.0]heptane (8α).[16] Following a previously described procedure,[5] a solution of aziridine **7α** (0.425 g, 3.29 mmol) in anhydrous CH_2Cl_2 (10 ml) was treated with K_2CO_3 (3.62 g, 20.0 mmol) and Ac_2O (0.36 ml, 3.81 mmol) and the reaction mixture was stirred for 3 h at room temperature. Evaporation of the filtered organic solution afforded a crude solid product consisting of practically pure **8α** (0.41 g, 96% yield) which was directly utilized in the next step. An

analytical sample of crude **8α** was purified by flash chromatography (a 5:4:1 mixture of CH_2Cl_2, hexane and NEt_3 was used as the eluant) to give pure **8α**, as a liquid, $[\alpha]_D^{22}$=+155.3 (*c* 0.9, $CHCl_3$):^{1}H NMR δ 4.53 (dd, 1H, *J*=4.7 and 2.4), 4.05 (dd, 1H, *J*=12.6 and 2.3 Hz), 3.92 (d, 1H, *J*=12.6 Hz), 3.38 (s, 3H), 2.81 (t, 1H, *J*=6.1 Hz), 2.71 (dd, 1H, *J*=6.4 and 2.2 Hz), 2.22 (ddd, 1H, *J*=15.1, 4.9 and 0.7 Hz), 2.16 (s, 3H), 1.92 (ddd, 1H, *J*=15.1, 5.7 and 2.5 Hz). ^{13}C NMR δ 183.11, 95.92, 57.99, 55.95, 34.13, 32.33, 28.46, 24.13. Anal. Calcd for $C_8H_{13}NO_3$: C, 56.13; H, 7.65; N, 8.17. Found: C, 56.44; H, 7.49; N, 8.31.

Methyl 2,4-Dideoxy-4-acetamido-3-*O*-methyl-α-L-*threo*-pentopyranoside (9α). A solution of aziridine **8α** (0.254 g, 1.5 mmol) in 0.2 N H_2SO_4 in anhydrous MeOH (4.0 ml) was stirred at 0°C for 20 min. K_2CO_3 was added in order to neutralize the acidity, and the solvent was evaporated. The solid residue was extracted with CH_2Cl_2: evaporation of the filtered (celite) organic solution afforded a crude reaction product (0.305 g) mostly consisting of compound **9α** (93%), together with a complex mixture of products (7%) (^{1}H NMR).[9] The crude reaction product was directly utilized in the next step without any further purification. Another sample of the crude reaction product (0.20 g) was subjected to flash chromatography (a 9.5:0.5 mixture of AcOEt and MeOH was used as the eluant) to give pure **9α** (0.166 g) and the complex mixture (0.08 g): **9α**, a solid, m.p. 159-162°C (from AcOEt), $[\alpha]_D^{22}$=+133.0 (*c* 0.28, $CHCl_3$) [lit.[3a] m.p.155-157°C, $[\alpha]_D^{23}$=+99.1 (*c* 0.23, $CHCl_3$)]; ^{1}H NMR δ 4.56 (t, 1H, *J*=3.6 Hz), 4.28 (dd, 1H, *J*=11.8 and 2.7 Hz), 3.88-3.98 (m, 1H), 3.35-3.51 (m, 1H), 3.42 (s, 3H), 3.40 (s, 3H), 3.28 (dd, 1H, *J*=11.8 and 4.1 Hz), 2.03 (ddd, 1H, *J*=14.6 and 4.1 Hz), 2.02 (s, 3H), 1.80 (ddd, 1H, *J*=14.6 and 3.9 Hz). ^{13}C NMR δ 170.64, 99.27, 75.08, 60.26, 57.26, 56.53, 47.87, 32.02, 23.95. Anal.Calcd for $C_9H_{17}NO_4$: C, 53.19; H, 8.43; N, 6.88. Found: C, 53.34; H, 8.66; N, 6.58.

Methyl 2,4-Dideoxy-4-(ethylamino)-3-*O*-methyl-α-L-*threo*-pentopyranoside (3α). The above-described crude reaction mixture containing amide **9α** (0.270 g) in anhydrous THF (8 ml) was treated with $LiAlH_4$ (0.12 g) and the resulting reaction mixture was gently refluxed for 2 h. After cooling, aqueous 4N NaOH was added in order to destroy the excess of hydride. Evaporation of the filtered organic solution afforded a crude product (0.244 g), consisting of the amino sugar **3α**, practically pure, which was subjected to flash chromatography (a 6:4:0.3 mixture of hexane, CH_2Cl_2, and NEt_3 was used as the eluant) to give pure amino sugar **3α** (0.210 g, 80% yield), as a liquid, $[\alpha]_D^{22}$=+145.8 (*c* 1.1, $CHCl_3$) [lit.[3a,10] solid, m.p. 123°C, $[\alpha]_D^{23}$=+99.7 (*c* 1.0, $CHCl_3$)]; ^{1}H NMR (C_6D_6) δ 4.14-4.00 (m, 2H), 3.33 (s, 3H), 3.10-2.88 (m, 2H), 3.02 (s, 3H), 2.61 (ddd, 1H, *J*=9.0 and 4.5 Hz), 2.50-2.27 (m, 2H), 2.11 (ddd, 1H, *J*=12.4, 4.5 and 2.4 Hz), 1.66-1.43 (m, 1H), 0.88 (t, 3H, *J*=7.1 Hz). ^{13}C NMR δ 102.01, 79.61, 65.70, 59.24, 57.05, 56.67, 42.91, 35.05, 16.25. Anal. Calcd for $C_9H_{19}NO_3$: C, 57.12; H, 10.11; N, 7.39. Found: C, 57.34; H, 10.20; N, 7.18.

(1*R*,4*R*,6*R*)-4-Methoxy-7-(benzyloxycarbonyl)-3-oxa-7-azabicyclo[4.1.0]heptane (21β). A solution of aziridine **7β** (0.95 g, 7.4 mmol) in anhydrous Et_2O (25 ml) containing Et_3N (1.26 ml, 8.9 mmol) was treated at 0°C with a solution of benzylchloroformate (1.26 ml, 8.9 mmol), in anhydrous Et_2O (5 ml), and the reaction mixture was stirred at the same temperature for 1 h. Evaporation of the washed (saturated aqueous $NaHCO_3$ and water) organic solution afforded a crude product which was subjected to flash chromatography (a 6:4 mixture of hexane and AcOEt was used as the eluant) to give the pure aziridine **21β** (1.4 g, 72% yield) as a solid, m.p. 71-72°C (from hexane), $[\alpha]_D^{22}$=-33.5 (*c* 1.7, $CHCl_3$); ^{1}H NMR δ 7.28-7.42 (m, 5H), 5.12 (s, 2H), 4.29 (t, 1H, *J*=6.0 Hz), 4.26 (d, 1H, *J*=12.3 Hz), 3.87 (dd, 1H, *J*=12.3 and 2.4 Hz), 3.38 (s, 3H), 2.76 (ddd, 1H, *J*=6.2 and 3.6 Hz), 2.63 (ddd, 1H, *J*=6.0, 2.4 and 0.8 Hz), 2.10 (d, 1H, *J*=3.7 Hz), 2.07 (d, 1H, *J*=3.7 Hz). ^{13}C NMR δ 162.77, 136.38, 129.16, 128.96, 99.67, 68.77, 62.23, 56.64,

34.76, 33.74, 28.37. Anal. Calcd for $C_{14}H_{17}NO_4$: C, 63.87; H, 6.51; N, 5.32. Found: C, 63.54; H, 6.22; N, 5.11.

(1*R*,4*S*,6*R*)-4-Methoxy-7-(benzyloxycarbonyl)-3-oxa-7-azabicyclo[4.1.0]heptane (21α). Following the procedure described above for the preparation of **21β**, the treatment of aziridine **7α** (0.302 g, 2.32 mmol) with benzylchloroformate (0.4 ml, 2.82 mmol) afforded a crude reaction product which was subjected to flash chromatography (a 7:3 mixture of hexane and AcOEt was used as the eluant) to give the pure aziridine **21α** (0.476 g, 78% yield) as a liquid, $[\alpha]_D^{22}$=+96.3 (*c* 0.95, $CHCl_3$); ^1H NMR δ 7.30-7.42 (m, 1H), 5.10 and 5.12 (ABdd, 2H, *J*=12.2 Hz), 4.48 (dd, 1H, *J*=5 and 2.5 Hz), 4.03 (dd, 1H, *J*=12.6 and 2.3 Hz), 3.94 (dd, 1H, *J*=12.6 and 0.7 Hz), 3.35 (s, 3H), 2.82 (t, 1H, *J*=6.1 Hz), 2.70 (ddd, 1H, *J*=6.2, 2.2 and 0.9 Hz), 2.29 (ddd, 1H, *J*=15.2, 4.9 and 0.6 Hz), 1.87 (ddd, 1H, *J*=15.2, 6.0 and 2.6 Hz). ^{13}C NMR δ 163.00, 136.35, 129.19, 128.96, 95.97, 68.79, 57.66, 56.01, 35.12, 33.48, 27.94. Anal. Calcd for $C_{14}H_{17}NO_4$: C, 63.87; H, 6.51; N, 5.32. Found: C, 63.59; H, 6.37; N, 5.09.

Methyl 2,4-Dideoxy-4-(benzyloxycarbonylamino)-3-*O*-methyl-β-L-*threo*-pentopyranoside (22β). Following the procedure described above for the preparation of **9α**, the reaction of aziridine **21β** (1.20 g, 4.55 mmol), with 0.2N H_2SO_4-MeOH afforded a crude reaction product (1.24 g), which was subjected to flash chromatography (a 6:4 mixture of hexane and AcOEt was used as the eluant) to give the pure urethane **22β**, as a semisolid (1.148 g, 85% yield), $[\alpha]_D^{22}$=-56.8 (*c* 0.78, $CHCl_3$); ^1H NMR δ 7.28-7.43 (m, 5H), 5.10 (s, 2H), 4.69 (dd, 1H, *J*=4.8 and 3.1 Hz), 3.85-4.04 (m, 1H), 3.60-3.76 (m, 1H), 3.44-3.60 (m, 2H), 3.38 (s, 3H), 3.36 (s, 3H), 1.73-2.10 (m, 1H), 1.63-1.82 (m, 1H). ^{13}C NMR δ 156.55, 136.93, 127.06, 128.66, 99.67, 76.24, 67.35, 62.91, 56.87, 55.92, 50.79, 33.90. Anal. Calcd for $C_{15}H_{21}NO_5$: C, 61.00; H, 7.17; N, 4.74. Found: C, 59.86; H, 7.01; N, 4.49.

Methyl 2,4-Dideoxy-4-(benzyloxycarbonylamino)-3-*O*-methyl-α-L-*threo*-pentopyranoside (22α). Proceeding as described above for the preparation of **22β**, the reaction of aziridine **21α** (0.33 g, 1.25 mmol) with 0.2 N H_2SO_4-MeOH afforded a crude reaction product (0.384 g) mostly consisting of **22α** which was recrystallized from hexane/AcOEt to give the pure urethane **22α**, as a solid, m.p. 136-137 °C (0.318 g, 86% yield), $[\alpha]_D^{22}$=+99.0 (*c* 1.2, $CHCl_3$); ^1H NMR δ 7.46-7.30 (m, 5H), 5.12 (s, 2H), 4.51 (t, 1H, *J*=3.8 Hz), 4.27 (unresolved dd, 1H, *J*=11.9 Hz), 3.78-3.60 (m, 1H), 3.40 (s, 7H), 3.38-3.20 (dd, 1H, *J*=11.8 and 4.6 Hz), 2.09 (ddd, 1H, *J*= 14.3 and 4.1 Hz), 1.76 (ddd, 1H, *J*= 14.4 and 4.4 Hz). ^{13}C NMR δ 156.54, 136.90, 129.25, 128.93, 128.87, 99.41, 75.68, 67.59, 60.58, 57.48, 56.67, 49.29, 32.09. Anal. Calcd for $C_{15}H_{21}NO_5$: C, 61.00; H, 7.17; N, 4.74. Found: C, 61.21; H, 6.94; N, 4.52.

Methyl 2,4-Dideoxy-4-(amino)-3-*O*-methyl-β-L-*threo*-pentopyranoside (24β). A solution of urethane **22β** (1.078 g, 3.6 mmol) in MeOH (50 ml) was stirred at r.t. under hydrogen in the presence of Pd/C (0.30 g). When the theoretical amount of hydrogen was adsorbed and the starting compound consumed (TLC), evaporation of the filtered (celite) organic solution afforded a crude liquid product consisting of amine **24β** (0.588 g, 99% yield), practically pure, $[\alpha]_D^{22}$=-88.5 (*c* 1.6, $CHCl_3$); ^1H NMR δ 4.80 (dd, 1H, *J*=3.2 and 2.1 Hz), 3.80 (dd, 1H, *J*=11.1 and 5.0 Hz), 3.59 (t, 1H, *J*=10.7 Hz), 3.42-3.60 (m, 1H), 3.39 (s, 3H), 3.34 (s, 3H), 2.97 (ddd, 1H, *J*=9.6, 4.8 Hz), 2.25 (ddd, 1H, *J*=13.2, 10.2 and 3.0 Hz). ^{13}C NMR δ 99.70, 77.78, 62.41, 56.97, 55.50, 52.78, 34.47. Anal. Calcd for $C_7H_{15}NO_3$: C, 52.16; H, 9.38; N, 8.69. Found: C, 52.45; H, 9.59; N, 8.32.

Methyl 2,4-Dideoxy-4-(amino)-3-*O*-methyl-α-L-*threo*-pentopyranoside (24α). Following the procedure described above for the preparation of **24β**, hydrogenation of urethane **22α** (0.213 g, 0.72

mmol), afforded a crude liquid reaction product consisting of amine **24α** (0.116 g, 99% yield), practically pure, $[\alpha]_D^{22}$=+131.0 (*c* 1.2, $CHCl_3$); ^1H NMR δ 4.28 (dd, 1H, *J*=8.8 and 2.5 Hz), 3.89 (dd, 1H, *J*=11.5 and 4.6 Hz), 3.40 (s, 3H), 3.31 (s, 3H), 3.04 (dd, 1H, *J*=11.5 and 9.6 Hz), 2.96 (ddd, 1H, *J*=10.0 and 4.2 Hz), 2.75 (ddd, 1H, *J*=9.0 and 4.6 Hz), 2.23 (ddd, 1H, *J*=12.6, 4.5 and 2.3 Hz), 1.34 (ddd, 1H, *J*=12.5, 10.3 and 8.9 Hz). ^{13}C NMR δ 102.00, 81.63, 67.36, 56.88, 56.69, 52.34, 34.87. Anal. Calcd for $C_7H_{15}NO_3$: C, 52.16; H, 9.38; N, 8.69. Found: C, 52.28; H, 9.70; N, 8.41.

Methyl 2,4-Dideoxy-4-(isopropylamino)-3-*O*-methyl-β-L-*threo*-pentopyranoside (4β). Following a previously described procedure,[14] a mixture of the amine **24β** (0.488 g, 3.03 mmol), acetone (0.33 ml, 4.52 mmol) and Ti(O-*i*-Pr)$_4$ (1.12 ml, 3.79 mmol) was stirred at room temperature for 1 h. Absolute ethanol (3 ml) and $NaBH_3CN$ (0.15 g, 2.39 mmol) were added and the resulting reaction mixture was stirred at the same temperature for 20 h. The reaction mixture was diluted with CH_2Cl_2 and water (0.8 ml) and KF hydrate was added under stirring until the solvent was clear; evaporation of the filtered (celite) organic solvent afforded a crude liquid product (0.60 g), which was subjected to flash chromatography (an 8:1.5:0.5 mixture of hexane, AcOEt and NEt_3 was used as the eluant) to give the pure amine **4β** (0.50 g, 81% yield), as a liquid, $[\alpha]_D^{22}$=-59.9 (*c* 2.1, $CHCl_3$); ^1H NMR δ 4.77 (t, 1H, *J*=2.9 Hz), 3.71 (dd, 1H, *J*=11.2 and 4.6 Hz), 3.43 (dd, 1H, *J*=11.0 and 9.4 Hz), 3.33-3.48 (m, 1H), 3.35 (s, 3H), 3.33 (s, 3H), 2.85 (quintet, 1H, *J*=6.3 Hz), 2.72 (ddd, 1H, *J*=9.1 and 4.5 Hz), 2.18 (ddd, 1H, *J*=12.9, 4.4 and 2.6 Hz), 1.55 (ddd, 1H, *J*=12.9, 9.7 and 3.1 Hz), 1.07 (d, 6H, *J*=6.2). ^{13}C NMR δ 99.68, 77.87, 63.40, 56.79, 55.35, 47.26, 34.42, 25.15, 23.48. Anal. Calcd for $C_{10}H_{21}NO_3$: C, 59.09; H, 10.41; N, 6.89. Found: C, 58.87; H, 10.11; N, 7.07.

Methyl 2,4-Dideoxy-4-(isopropylamino)-3-*O*-methyl-α-L-*threo*-pentopyranoside (4α). Proceeding as described above for the preparation of **4β**, the reaction of amine **24β** (0.084 g 0.52 mmol), with acetone in the presence of Ti(O-*i*-Pr)$_4$ and $NaBH_3CN$ afforded a crude reaction product (0.105 g) which was subjected to flash chromatography (an 8:1:1 mixture of hexane, AcOEt, and NEt_3 was used as the eluant) to give the pure amine **4β** (0.85 g, 80% yield), as a liquid, $[\alpha]_D^{22}$=+135.3 (*c* 1.0, $CHCl_3$); ^1H NMR δ 4.36 (dd, 1H, *J*=8.3 and 2.5 Hz), 4.06 (dd, 1H, *J*=4.3 and 11.7 Hz), 3.47 (s, 3H), 3.36 (s, 3H), 3.09-3.23 (m, 1H), 3.11 (dd, 1H, *J*=114 and 9.1 Hz), 2.84 (septet, 1H, *J*=6.2 Hz), 2.71 (ddd, 1H, *J*=8.7 and 4.3 Hz), 2.29 (ddd, 1H, *J*=12.7, 4.5 and 2.6 Hz), 1.48 (ddd, 1H, *J*=12.7, 9.9 and 8.4 Hz), 1.07 (d, 6H, *J*=6.2 Hz). ^{13}C NMR δ 101.73, 79.52, 65.79, 56.94, 56.59, 56.18, 47.29, 34.83, 25.09, 23.31. Anal. Calcd for $C_{10}H_{21}NO_3$: C, 59.09; H, 10.41; N, 6.89. Found: C, 59.21; H, 10.09; N, 6.99.

Reaction Sequence for the Mixture of 6α and 6β. a) Following the above-described procedures, the 75:25 mixture of methyl glycosides **6β** and **6α** (0.49 g, 3.31 mmol)[5,6] was treated with TsCl (0.63 g, 3.3 mmol) to give a crude product (1.0 g) which was treated with NaN_3 (0.86 g, 13.2 mmol) in DMF (3.7 ml) at 90°C to give a mixture of azido alcohols **13α**, **13β**, **14α**, and **14β** (0.45 g, 79% yield, based on the starting mixture of **6α** and **6β**). The reaction of this mixture of azido alcohols **13-14α,β** with PPh_3 (0.71 g, 2.7 mmol) at 80°C yielded a 73:27 mixture of aziridines **7β** and **7α** (0.32 g, 93% yield) which was reacted with Ac_2O to give a crude product (0.42 g) which was filtered through a silica gel column (flash chromatography conditions). Elution with a 5:4:1 mixture of hexane, CH_2Cl_2 and NEt_3 afforded a 73:27 mixture of the *N*-acetyl aziridines **8β** and **8α** (0.39 g, 94% yield). Acid methanolysis of this mixture with 0.2N H_2SO_4-MeOH afforded a crude reaction product (0.457 g) largely consisting of a 75:25 mixture of amides **9β** and **9α** (^1H NMR) which was dissolved in anhydrous THF (13 ml) and treated with $LiAlH_4$ (0.22 g). The usual workup afforded a crude reaction product (0.33 g) consisting of a 75:25 mixture of amino sugars **3β** and **3α** (80% yield).

b) Following the above-described procedures, $SOCl_2$ (0.9 ml, 12.3 mmol) was added dropwise at 0°C to a solution of the 75:25 mixture of methyl glycosides **6β and 6α** (0.50 g, 3.38 mmol) in anhydrous THF (10 ml) in the presence of Et_3N (2 ml, 14.35 mmol). The reaction mixture was stirred for 1h at the same temperature, then diluted with $CHCl_3$. Evaporation of the washed (water) organic solution afforded a crude product which was purified by flash chromatography (a 7:3 mixture of hexane and AcOEt was used as the eluant) to give an unseparable mixture (0.55 g, 84% yield) of sulphites **15-16α,β**. The mixture of sulphites **15-16 α,β** was dissolved in 1:1:1.5 CH_2Cl_2: MeCN: H_2O (18 ml) and $NaIO_4$ (0.607 g, 2.84 mmol) and $RuCl_3$ (6 mg) were added to the solution; the reaction mixture was stirred for 1h at room temperature. Dilution with CH_2Cl_2 and evaporation of the washed (water) and filtred (celite) organic solvent afforded a crude product consisting of a 73:27 (^1H NMR) mixture of cyclic sulphates **17β and 17α** (0.59 g, 99% yield). The mixture of cyclic sulphates **17β** and **17α** was dissolved in anhydrous THF (28 ml) and LiN_3 (0.275, 5.6 mmol) was added to the solution; the reaction mixture was refluxed for 12 h. After cooling to 0°C, $LiAlH_4$ (0.139 g, 3.66 mmol) was added and the reaction mixture was refluxed for 8h. The usual workup afforded a crude liquid product consisting of a 73:27 mixture of aziridines **7β** and **7α** (0.34 g, 92% yield) which were directly utilized in the next step of acetylation as described in point a).

In another experiment, the 75:25 mixture of amides **9β and 9α** [0.20 g, point a)] was subjected to flash chromatography (a 95:5 mixture of AcOEt was used as the eluant) to give pure **9β** (0.11 g) and **9α** (0.040 g) (75% yield) which were then independently reduced ($LiAlH_4$) to the amino sugars **3β** (0.092 g, 90% yield) and **3α** (0.034 g, 91% yield), respectively.

References and Notes

1. a) Lee, M.D.; Dunne, T.S.; Siegel, M.M.; Chang, C.C.; Morton, G.O.; Borders, D.B. *J.Am.Chem.Soc.* **1987**, *109*, 3464-3466. b) Lee, M.D.; Dunne, T.S.; Chang, C.C.; Ellestad, G.A.; Siegel, M.M.; Morton, G.O.; McGahren, W.J.; Borders, D.B. *J.Am.Chem.Soc.***1987**, *109*, 3466-3468. c) Lee, M.D.; Dunne, T.S.; Chang, C.C.; Siegel, M.M.; Morton, G.O.; Ellestad, G.A; McGahren, W.J.; Borders, D.B. *J.Am.Chem.Soc.* **1992**, *114*, 985-997. d) Zein N.; Sinha, A.M.; McGahren, W.J.; Ellestad, G.A. *Science* **1988**, *240*, 1198-1201. e) Zein, N.; Poncin, M.; Nilakantan, R.; Ellestad, G.A. *Science* **1989**, *244*, 697-699. f) Zein, N.; McGahren, W.J.; Morton, G.O.; Ashcroft, J.; Ellestad, G.A. *J.Am.Chem.Soc.* **1989**, *111*, 6888-6890.
2. a) Hitchcock, S.A.; Boyer, S.H.; Chu-Moyer, M.Y.; Olson, S.H.; Danishefsky, S.J. *Angew.Chem.Int.Ed.Engl.* **1994**, *33*, 858-862. b) Haseltine, J.N.; Cabal, M.P.; Mantlo, N.P.; Iwasawa, N.; Yamashita, D.S.; Coleman, R.S.; Schulte, G.K.; Danishefsky, S.J. *J.Am.Chem.Soc.* **1991**, *113*, 3850-3866. c) Cabal, M.P.; Coleman, R.S.;, Danishefsky, S.J. *J.Am.Chem.Soc.* **1990**, *112*, 3253-3255.
3. a) Groneberg, R.D.; Miyazaki, T.; Stylianides, N.A.; Schulze, T.J.; Stahl, W.; Schreiner, E.P.; Suzuki, T.; Iwabuchi, Y.; Smith, A.L.; Nicolaou, K.C. *J.Am.Chem.Soc.* **1993**, *115*, 7593-7611. b) Smith, A.L.; Pitsinos, E.N.; Hwang, C.-K.; Mizuno, Y.; Saimoto, H.; Scarlato, G.R.; Suzuki, T.; Nicolaou, K.C. *J.Am.Chem.Soc.* **1993**, *115*, 7612-7624. c) Nicolaou, K.C.; Hummel, C.W.; Nakada, M.; Shibayama, K.; Pitsinos, E.N.; Saimoto, H.; Mizuno, Y; Baldenius, K.-U.; Smith, A.L. *J.Am.Chem.Soc.* **1993**, *115*, 7625-7635.

4. a) Halcomb, R.L.; Boyer, S.H.; Wittman, M.D.; Olson, S.H.; Denhart, D. J.; Liu, K.K.; Danishefsky, S.J. *J.Am.Chem.Soc.* **1995**, *117*, 5720-5749. b) Roush, W.R.; Hunt, J.A. *J.Org.Chem.* **1995**, *60*, 798-806. c) Dupradeau, F.-Y.; Prandi, J.; Beau, J.-M. *Tetrahedron* **1995**, *51*, 3205-3220. d) Mash, E.A.; Nimkar, S.K. *Tetrahedron Lett.* **1993**, *34*, 385-388. e) Kahne, D.; Yang, D.; Lee, M.D. *Tetrahedron Lett.* **1990**, *31*, 21-22. f) Golik, J.; Wong, H.; Vyas, D.M.; Doyle, T.W. *Tetrahedron Lett.* **1989**, *30* , 2497-2500.
5. Crotti, P.; Di Bussolo, V.; Favero, L.; Macchia, F.; Pineschi, M. *Tetrahedron Asym.* **1996**, *7*, 779-786.
6. a) Deriaz, R.E.; Overend, W.G.; Stacey, M.; Wiggins, L.F. *J.Chem.Soc.* **1949**, 2836-2841.
7. a) Pöchlauer, P.; Müller, E. P.; Peringer, P. *Helv. Chim. Acta* **1984**, *67*, 12381247. b) Legters, J.; Thijs, L.; Zwanenburg, B. *Tetrahedron Lett.* **1989**,*30*, 4881-4884.
8. a) Dubois, L.; Dodd, R.N. *Tetrahedron* **1993**, *49*, 901-910. b) Van der Klein, P. A. M.; Filemon, W.; Veeneman, G. H.; Van der Marel, G.A.; Van Boom J. H. *J. Carbohydrate Chemistry*, **1992**, *11*, 837-848. c) Lohray, B.B.; Gao, Y.; Sharpless, K.B. *Tetrahedron Lett.* **1989**,*30*, 2623-2626.
9. The presence of the corresponding regioisomeric *C-4 product* cannot be completely ruled out. However, accurate examination of the crude reaction product in each case indicated that the regioisomeric *C-4 product* is not present or is present to an extent not more than 3%.
10. The ^{1}H NMR (C_6D_6) data of compound **3α** obtained by us are perfectly consistent with the corresponding data of the same compound obtained by Nicolaou.[3a] However, Nicolaou describes compound **3α** as a solid (m.p. 123°C),[3a] whereas it turned out to be a liquid in our hands. In analogy with other similar compounds (such as **3β**)[3a,5] we tend to think that **3α** should reasonably be a liquid.
11. a) Crotti, P.; Favero, L.; Gardelli, C.; Macchia, F.; Pineschi, M. *J.Org.Chem.* **1995**, *60*, 2514-2525. b) Crotti, P.; Di Bussolo V.; Favero, L.; Pineschi, M. *Tetrahedron* **1997**,*53*, 1417-1438.
12. The proton α to the methoxy group (the anomeric Ha proton, Scheme 3) in both the aziridines **8α** and **21α** shows a signal (dd) with intermediate values of the coupling constants (J= 4.7 and 2.4 Hz in **8α** and J=5.0 and 2.5 Hz in **21α**) indicating an almost 1:1 equilibrium between the two conformers **a** and **b**.
13. a) Eliel, E.L.; Wilen, S.H. *Stereochemistry of Organic Compounds*, Wiley Interscience, New York, 1994, p 758-762. b) Furst, A.; Plattner, P.A. *Proc. 12th International Congress of Pure and Applied Chemistry*, New York, 1951, p 409.
14. Mattson, R. J.; Pham, K. M.; Leuck, D. J. ; Cowen, K. A.; *J.Org.Chem.* **1990**, *55*, 2552-2554.
15. The value of the coupling constant of the signal of the anomeric proton (Ha, J= 6.0 Hz, Scheme 3) in aziridine **21β** indicates a slight preference for conformer **b** with the methoxy group equatorial. Under acidic opening conditions, conformer **b** appears to be further favored by the incursion of an effective hydrogen bong between the protonated aziridine nitrogen and the endocyclic oxygen.[5]
16. In the case of aziridines **7,8α,β**, the numbering is the one commonly used in the nomenclature of the bicyclo compounds.[5]

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