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An Efficient Stereoselective Synthesis of the Amino Sugar Component (E Ring) of Calicheamicin γ_1^I

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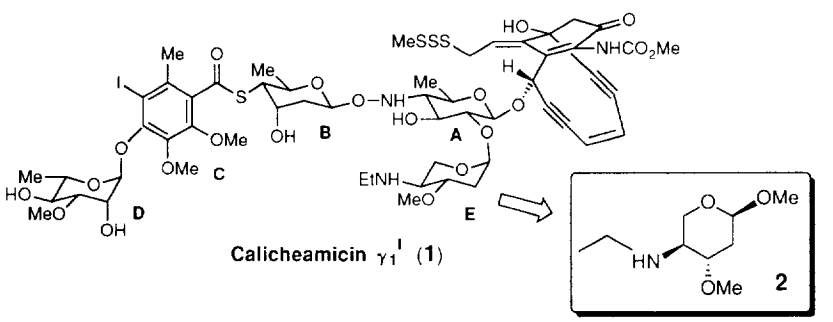
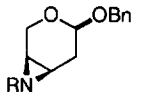
Abstract: A simple, efficient, stereoselective synthesis of the methyl 2,4-dideoxy-4-(ethylamino)-3-*O*-methyl-β-L-*threo*-pentopyranoside **2**, corresponding to the E monosaccharide unit (E ring) of calicheamicin **1**, is described. The synthetic procedure utilizes the methyl 2-deoxy-β-D-ribopyranoside **3** as the enantiopure starting material and the acid methanolysis of the intermediate activated aziridine **12** to give the desired amino sugar **2** in 6 steps and in satisfactorily high overall yield (60%). No separation stage is necessary at any point of the synthetic process. Copyright © 1996 Elsevier Science Ltd

Calicheamicin γ_1^I **1** is a member of a new class (the enedyines class) of antitumor antibiotics possessing a potent biological activity which has been attributed to the capability of **1** to destroy DNA in tumor cells.[1] In view of the remarkable activity of **1**, there has been much interest and considerable effort in recent years to achieve the total synthesis of **1**; two very effective procedures have so far been completed.[2,3] Other studies have been, more simply, directed to the development of effective procedures for the synthesis of fragments of **1**, and in particular of the oligosaccharide portion of **1**,[2a,4,5] to be utilized, if considered valuable, for the total synthesis of **1**, along with any of the procedures already discovered.[2,3]



Synthetic approaches to the amino sugar **2**, corresponding to the E monosaccharide unit of **1** have been described by different research groups starting from L-serine methyl ester (Nicolaou),[2a] methyl 2-deoxy-β-D-ribopyranoside **3** (Mash),[5a] and isopropylidene-*N*-Boc-L-serinal (Roush and Kahne).[5b,c] In spite of their

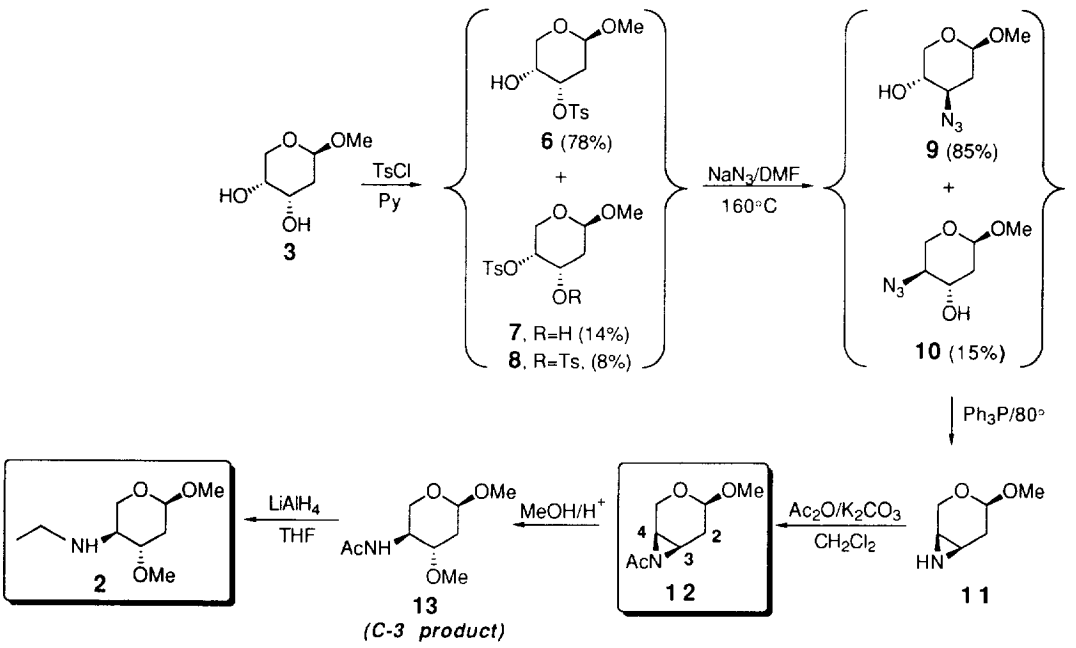
effectiveness, the above-mentioned approaches to **2** appear, in our opinion, to suffer from certain limitations, particularly due to their low overall yields, the excessive length, and the necessity of a separatory stage at a certain point of the synthetic scheme.



(±) **4**, R=COOEt
(±) **5**, R=Ts

A study on the regiochemical behaviour of the ring opening reactions, under different operating conditions, of the racemic *N*-COOEt and *N*-Ts substituted cis aziridines **4** and **5**[6] had shown us the possibility of carrying out a completely stereoselective synthesis of the enantiopure amino sugar **2**, starting from the methyl β-glycoside **3**, as in the interesting stereoconvergent procedure described by Mash.[5a] However, whereas the synthetic strategy of Mash was substantially based on appropriate sequences of selective functionalizations carried out on both the separated monobenzyl derivatives of **3**,[5a] the core of our new approach utilizes the intermediate incursion of the enantiopure activated aziridine **12**,[9] structurally related to **4** and **5**,[6] followed by its almost completely regioselective opening with MeOH under acid conditions to give the desired stereo- and regiochemistry present in the target amino sugar **2**, as hereafter described and shown in Scheme 1.

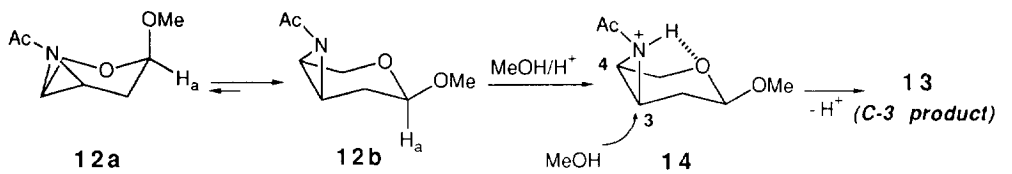
SCHEME 1



Monotosylation of the readily available methyl β-glycoside **3**[10] with TsCl (1.1 equiv/mol) in anhydrous pyridine at 25°C afforded a 78:14 mixture (92% yield) of the two corresponding monotosylates **6** and **7**, together with a small amount (8%) of the undesired ditosylate **8**. The crude reaction mixture was directly subjected, without any further purification, to azidolysis with NaN_3 in DMF at 160°C to give a corresponding unseparable mixture of the azido alcohols **9** and **10** (85:15) which was easily purified by flash chromatography (85.3% yield, based on **3**). By treatment with $(Ph)_3P$ at r.t. for 30 min and then at 80°C for 18 h,[11] the mixture of the azido alcohols **9** and **10**, both having the appropriate trans relationship between the

azido and the hydroxy functionality and the cis relationship between the azido and the glycosidic β-methoxy group, was converted into a crude reaction product containing only the *N*-unsubstituted cis aziridine **11**, contaminated with considerable amounts of $(Ph)_3P$ and $(Ph)_3PO$. Extraction with cold water of the crude mixture and accurate evaporation of the water extracts afforded aziridine **11**, practically pure, in a high yield (99%). Other attempts to purify **11** from the contaminants by flash chromatography or by extraction with a solvent different from water, or by carrying out the reaction with polymer-supported $(Ph)_3P$ (Aldrich) turned out to be completely unsuccessful or to lead to pure **11** in very unsatisfactory yields. Aziridine **11** was converted into the *N*-acetyl derivative **12** (the activated aziridine)[9] (96% yield), then treated with MeOH under acid conditions: the methoxy derivative **13** (a *C-3 product*),[7] with the appropriate stereo- and regiochemistry of target compound **2**, was largely the main reaction product (91% yield), with only a small amount (9%) of a complex mixture of non-separable compounds.[12]

Scheme 2



The reason for the almost exclusive formation of the methoxy amide **13** in the acid methanolysis reaction of aziridine **12** can easily be found in a preferential reactivity of **12** in its more stable conformation **12b** with the equatorial glycosidic methoxy group.[13] In accordance with the Fürst-Plattner rule and with previous results obtained in our laboratory for the regiochemical behaviour of 1,2-epoxides derived from the tetrahydropyrane system,[8] the attack of the nucleophile (MeOH) on the protonated aziridine **14**[14] occurs at the C-3 aziridine carbon to give the regioisomer **13**, as observed (Scheme 2).[15] The crude **13** was then reduced with $LiAlH_4$ under standard operating conditions to give the desired amino sugar **2** (Scheme 1),[16] which was purified by flash chromatography (81% yield), $[\alpha]_D^{22}$= -56.7 (*c* 0.6, $CHCl_3$) [lit.[2a] $[\alpha]_D^{23}$= -56.7 (*c* 1.0, $CHCl_3$), lit.[5a] $[\alpha]_D^{26}$= -56.8 (*c* 1.4, $CHCl_3$), lit.[5b] $[\alpha]_D^{23}$= -56.7 (*c* 0.90, $CHCl_3$)].

In conclusion, the above described procedure for the synthesis of **2** appears decidedly simple and the desired amino sugar **2** is obtained in a straightforward manner with a satisfactorily high overall yield (60%, based on the starting methyl β-glycoside **3**), in only 6 simple steps. Moreover, no separating procedure between stereoisomers or regioisomers is necessary at any point of the synthetic procedure, and only a simple purification by flash chromatography of the mixture of azido alcohols **9** and **10** and, obviously, of the final product **2** was considered necessary. All these advantageous aspects combine to make our synthetic approach to **2** decidedly effective and competitive with the other methods previously described.[2a,5]

Experimental

Melting points were determined on a Kofler apparatus and are uncorrected. ^1H 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.

Methyl 2-deoxy-β-D-ribopyranoside 3. The treatment of 2-deoxy-D-ribose (Aldrich) (6.75 g) with 1% methanolic hydrogen chloride solution (124 ml), as previously described,[10a] afforded a crude solid product (7.50 g) which was recrystallized from ether to give a solid product (5.30 g) consisting of a 75:25 mixture of **3** and its α anomer **15** (^{1}H NMR). Unlike the previously reported method,[10a] this mixture was subjected to flash chromatography (a 9.5:0.5 mixture of CH_2Cl_2 and MeOH was used as the eluant) to give pure **3** (3.66 g), and **methyl 2-deoxy-α-D-ribopyranoside 15** (0.82 g).

3, a solid, m.p. 83-83.5°C, $[\alpha]_D^{22}$= -205.7 (*c* 1.1, $CHCl_3$) [lit.[10b] m.p. 83-84°C, $[\alpha]_D^{16}$= -200 (*c* 1.01, $CHCl_3$)]; ^{1}H NMR[10b] δ 4.78 (t, 1H, *J*= 2.7 Hz), 3.95-4.11 (m, 1H), 3.65-3.90 (m, 3H), 3.35 (s, 3H), 3.10 (d, 1H, *J*= 5.1 Hz), 2.93 (d, 1H, *J*= 7.0 Hz), 1.90-2.02 (m, 2H). ^{13}C NMR δ 99.50, 68.79, 65.55, 63.22, 55.82, 34.32. Anal.Calcd for $C_6H_{12}O_4$: C, 48.64; H, 8.16. Found: 48.51; H, 8.29.

15, a solid, m.p. 101.5-102.5°C, $[\alpha]_D^{22}$= +177.4 (*c* 0.19, $CHCl_3$) [compare physical data for *methyl-2-deoxy-α-L-ribopyranoside*,[10a] m.p. 99-100°C, $[\alpha]_D^{20}$= -176 (*c* 0.81, $CHCl_3$)]; ^{1}H NMR δ 4.68 (t, 1H, *J*=2.7 Hz), 3.91-4.00 (m, 1H), 3.58-3.78 (m, 3H), 3.39 (s, 3H), 2.10 (ddd, 1H, *J*= 14.4, 4.4 and 2.4 Hz), 1.90 (ddd, 1H, *J*= 14.4 and 3.4 Hz). ^{13}C NMR δ 98.81, 67.87, 67.04, 60.17, 56.07, 35.36. Anal.Calcd for $C_6H_{12}O_4$: C, 48.64; H, 8.16. Found: 48.41; H, 8.35.

Mixture of Azido Alcohols 9 and 10. A solution of methyl β-glycoside **3** (1.52 g, 10.3 mmol) in anhydrous pyridine (25 ml) was treated at 0°C with TsCl (2.15 g, 11.3 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 (3.20 g) consisting of a 78:14:8 mixture of monotosylates **6** and **7** (92%) and ditosylate **8** (8%) (^{1}H NMR) which was dissolved in anhydrous DMF (9.0 ml) and then treated with NaN_3 (2.76 g, 42.5 mmol); the reaction mixture was stirred for 40 min at 160°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 purified 85:15 mixture of azido alcohols **9** and **10** (1.52 g, 85.3% yield, based on **3**) (^{1}H NMR) which was directly utilized in the next step.

While monotosylates **6** and **7** [**6**, ^{1}H NMR δ 4.87 (ddd, 1H, *J*= 11.5, 4.9 and 3.0 Hz), 3.88-3.99 (m, 1H), 3.29 (s, 3H), 2.19 (ddd, 1H, *J*= 12.6, 11.7 and 3.4 Hz), 1.73 (dd, 1H, *J*= 12.6 and 4.9 Hz); **7**, ^{1}H NMR δ 4.70-4.80 (m, 1H), 4.64-4.70 (m, 1H), 4.04-4.18 (m, 1H), 3.31 (s, 3H), 1.86-1.96 (m, 2H)] and azido alcohols **9** and **10** [**9**, ^{1}H NMR δ 4.43 (dd, 1H, *J*= 8.2 and 2.4 Hz), 4.02 (dd, 1H, *J*= 11.6 and 4.3 Hz), 3.46 (s, 3H), 3.37 (dd, 1H, *J*= 11.8 and 8.6 Hz), 2.19 (ddd, 1H, *J*= 13.2, 4.6 and 2.4 Hz), 1.57 (ddd, 1H, *J*= 13.2, 10.5 and 8.1 Hz); **10**, ^{1}H NMR δ 4.75 (dd, 1H, *J*= 3.4 and 1.7 Hz), 3.31 (s, 3H)] turned out to be completely unseparable by any chromatographic technique, the ditosylate **8** was easily separated from **6** and **7** by flash chromatography (an 1:1 mixture of hexane and AcOEt was used as the eluant) to give pure **8** as a solid m.p 102-103°C (dec.); ^{1}H NMR δ 7.23 (d, 2H, *J*= 8.2 Hz), 7.59 (d, 2H, *J*=8.2 Hz), 7.14-7.33 (m, 4H), 4.62-4.77 (m, 2H), 3.80 (dd, 1H, *J*= 13.0 and 2.9 Hz), 3.64 (unresolved dd, 1H, *J*= 13.0 Hz), 3.20 (s, 3H), 2.38 (s, 3H), 2.07 (ddd, 1H, *J*= 12.5 and 3.2 Hz), 1.70 (dd, 1H, *J*= 12.5 and 4.5 Hz). ^{13}C NMR δ

145.77, 145.70, 133.98, 130.55, 128.69, 128.46, 98.83, 75.87, 72.85, 61.56, 55.89, 32.42, 22.37. Anal.Calcd for $C_{20}H_{24}O_8S_2$: C, 52.61; H, 5.29. Found: 52.24; H, 5.47.

(1*R*,4*R*,6*R*)-4-Methoxy-3-oxa-7-azabicyclo[4.1.0]heptane 11.[17] A solution of the above obtained mixture of azido alcohols **9** and **10** (0.52 g, 3.0 mmol) in MeCN (3.0 ml) was treated with triphenylphosphine (0.787 g, 3.0 mmol) and the reaction mixture was stirred at r.t. 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 **11** (^{1}H NMR) (0.391 g, 99% yield, 1% triphenylphosphonium oxide 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 **11**, as a liquid: $[\alpha]_D^{22}$= -66.8 (*c* 0.8, $CHCl_3$)]; ^{1}H NMR δ 4.30-4.38 (m, 1H, $W_{1/2}$= 15.4 Hz), 4.11 (unresolved dd, 1H, *J*= 12.6 Hz), 3.98 (dd, 1H, *J*= 12.5 and 2.5 Hz), 3.40 (s, 3H), 2.03-2.22 (m, 3H), 1.76-1.93 (m, 1H). ^{13}C NMR δ 100.05, 62.79, 56.39, 29.76, 28.87, 27.35. Anal.Calcd for $C_6H_{11}NO_2$: C, 55.79; H, 8.58; N, 10.84. Found: 55.45; H, 8.55; N, 10.61.

The above-described procedure was repeated under the same operating conditions by using polymer-supported triphenylphosphine (Aldrich, 3 mmol P/g, 1.0 g): in this case, the crude reaction product from the evaporation of MeCN was taken up in CH_2Cl_2. Evaporation of the filtered CH_2Cl_2 solution afforded a crude liquid product which was filtered through a short silica gel column. Elution with a 5:4:1 mixture of hexane, CH_2Cl_2, and NEt_3 afforded pure aziridine **11** (0.18 g, 48% yield).

(1*R*,4*R*,6*R*)-4-Methoxy-7-acetyl-3-oxa-7-azabicyclo[4.1.0]heptane 12. Following a previously described procedure,[18] a solution of aziridine **11** (0.322 g, 2.50 mmol) in anhydrous CH_2Cl_2 (7.5 ml) was treated with K_2CO_3 (2.76 g, 20.0 mmol) and Ac_2O (0.26 ml, 2.75 mmol) and the reaction mixture was stirred for 3 h at r.t. Evaporation of the filtered organic solution afforded a crude solid product consisting of practically pure **12** (0.41 g, 96% yield) , which was directly utilized in the next step. An analytical sample was recrystallized from hexane/acetone to give pure **12**, as a solid, m.p. 80.5-82-5°C, $[\alpha]_D^{22}$= -45.7 (*c* 0.6, $CHCl_3$); ^{1}H NMR δ 4.31 (dd, 1H, *J*= 7.5 and 4.6 Hz, $W_{1/2}$= 14.0 Hz), 4.24 (unresolved dd, 1H, *J*= 12.9 Hz), 3.90 (dd, 1H, *J*= 12.8 and 2.3 Hz), 3.41 (s, 3H), 2.76 (ddd, 1H, *J*= 6.6 and 0.9 Hz), 2.64 (ddd, 1H, *J*= 6.2, 2.4 and 0.9 Hz), 2.16 (s, 3H), 2.07-2.22 (m, 1H), 1.98 (ddd, *J*= 14.8, 7.5 and 1.3 Hz). ^{13}C NMR δ 182.29, 99.39, 62.32, 56.01, 33.43, 32.28, 28.52, 23.64. Anal.Calcd for $C_8H_{13}NO_3$: C, 56.13; H, 7.65; N, 8.17. Found: 56.21; H, 7.98; N, 7.87.

Methyl 2,4-Dideoxy-4-acetamido-3-*O*-methyl-β-L-*threo*-pentopyranoside 13. A solution of aziridine **12** (0.342 g, 2.0 mmol) in 0.2 N H_2SO_4 in anhydrous MeOH (5.0 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 (0.405 g) mostly consisting of compound **13** (91%) together with a complex mixture of products (9%) (^{1}H NMR).[12] The crude reaction product was directly utilized in the next step, without any further purification. An analytical sample of the crude reaction product (0.200 g) was subjected to flash chromatography (a 5:4:1 mixture of hexane, CH_2Cl_2, and NEt_3 was used as the eluant) to give pure **13** (0.13

g) and the complex mixture (0.012 g):[12] **13**, a solid, m.p. 104-107°C, $[\alpha]_D^{22}$= -73.4 (*c* 0.58, $CHCl_3$) [lit.[5a] m.p. 105-106°C, lit.[5b] m.p.100-103°C, $[\alpha]_D^{23}$= -73.8 (*c* 0.42, $CHCl_3$)]; ^1H NMR[5b] δ 5.96-6.14 (m, 1H), 4.67 (dd, 1H, *J*= 5.8 and 3.0 Hz), 3.86-4.01 (m, 2H), 3.47-3.62 (m, 2H), 3.41 (s, 3H), 3.38 (s, 3H), 2.00 (s, 3H), 1.85-2.04 (m, 1H), 1.78 (ddd, 1H, *J*= 13.6, 6.6 and 3.0 Hz). ^{13}C NMR[5b] δ 170.64, 99.91, 75.95, 63.27, 56.91, 56.32, 48.66, 33.72, 23.96. Anal.Calcd for $C_9H_{17}NO_4$: C, 53.19; H, 8.43; N, 6.88. Found: 53.01; H, 8.11; N, 7.06.

Methyl 2,4-Dideoxy-4-(ethylamino)-3-*O*-methyl-β-L-*threo*-pentopyranoside 2. The crude reaction mixture containing **13** (0.20 g) in anhydrous THF (6 ml) was treated with $LiAlH_4$ (0.10 g) and the resulting reaction mixture was gently refluxed for 2 h. After cooling, MeOH and 2N aqueous NaOH were added in order to destroy the excess of hydride.[5b] Evaporation of the filtered organic solution afforded a crude product, consisting of the amino sugar **2**, practically pure, which was subjected to flash chromatography (a 5:4:1 mixture of hexane, CH_2Cl_2, and NEt_3 was used as the eluant) to give pure amino sugar **2**, as a liquid (0.137 g, 81% yield): $[\alpha]_D^{22}$= -56.7 (*c* 0.6, $CHCl_3$) [lit.[2a] $[\alpha]_D^{23}$= -56.7 (*c* 1.0, $CHCl_3$), lit.[5a] $[\alpha]_D^{26}$= -56.8 (*c* 1.4, $CHCl_3$), lit.[5b] $[\alpha]_D^{23}$= -56.7 (*c* 0.90, $CHCl_3$). ^1H NMR[2a,5b] δ 4.79 (dd, 1H, *J*= 3.3 and 2.2 Hz), 3.75 (dd, 1H, *J*= 11.1 and 4.7 Hz), 3.35-3.53 (m, 2H), 3.35 (s, 3H), 3.33 (s, 3H), 2.53-2.75 (m, 2H), 2.21 (ddd, 1H, *J*= 13.1, 4.5 and 2.1 Hz), 1.52 (ddd, 1H, *J*= 13.1, 9.9 and 3.0 Hz), 1.12 (t, 3H, *J*=7.1 Hz). ^{13}C NMR[2a,5b] δ 99.61, 77.49, 62.60, 59.71, 56.73, 55.24, 42.67, 34.37, 16.25. Anal.Calcd for $C_9H_{19}NO_3$: C, 57.12; H, 10.11; N, 7.39. Found: 57.25; H, 10.37; N, 7.64.

***N*-Ethyl Aziridine 16.**[16] Following a previously described procedure,[19] a solution of aziridine **11** (0.065 g, 0.50 mmol) in anhydrous ether was treated at 0°C with 1.6 M BuLi in hexane (0.34 ml, 0.54 mmol) and the resulting reaction mixture was stirred for 1 h at r.t. After cooling at 0°C, ethyl iodide (0.10 g, 0.64 mmol) was added and the reaction mixture was stirred at r.t. for 2 h, then quenched with saturated aqueous NaCl solution. Extraction with ether and evaporation of the ether extracts afforded a crude reaction product (0.070 g) which was filtered through a short silica gel column. Elution with a 5:4:1 mixture of hexane, CH_2Cl_2, and NEt_3 afforded aziridine **16** (0.040 g), as a liquid: ^1H NMR δ 4.20 (dd, 1H, *J*= 7.6 and 4.4 Hz), 4.12 (unresolved dd, 1H, *J*= 12.3 Hz), 3.82 (dd, 1H, *J*= 12.2 and 2.7 Hz), 3.36 (s, 3H), 2.16-2.38 (m, 2H), 2.05 (ddd, 1H, *J*= 14.5, 6.7 and 4.4 Hz), 1.81 (ddd, 1H, *J*= 14.5, 7.7 and 0.8 Hz), 1.60 (unresolved ddd, 1H, *J*= 6.5 Hz), 1.46 (ddd, 1H, *J*= 6.5 and 2.2 Hz), 1.13 (t, 3H, *J*= 7.1 Hz).

Acid Methanolysis of Aziridine 16. A solution of aziridine **16** (0.040 g, 0.25 mmol) in 0.2 N $MeOH/H_2SO_4$ (3.0 ml) was stirred at 60°C for 30 min. After cooling, the usual workup afforded a crude reaction product consisting of amino sugar **2** (55%) and another compound (45%) which was not furtherly investigated (^1H NMR).[16]

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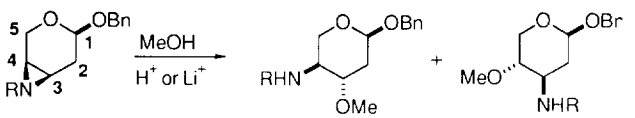
6. This study showed that, in the acid methanolysis, the cis aziridines **4** and **5** regioselectively open at the aziridine C-3 carbon to give exclusively the corresponding *C-3 product*.[7] In the case of **5**, when the



(±) **4**, R=COOEt
(±) **5**, R=Ts

C-3 product ***C-4 product***

same reaction was repeated in the presence of a metal salt ($LiClO_4$), the regioisomeric *C-4 product*[7] was the main reaction product. The manuscript relative to this study is presently under preparation.

7. The *C-3* and the *C-4 product* nomenclature refers to the attacking site of the nucleophile (i.e. at the C-3 or C-4 aziridine carbon of **4**, **5** and **12**) in accordance with the arbitrary numbering scheme shown in Schemes 1-2 and note 6, as previously in the case of the corresponding oxirane systems.[8]
8. a) Chini, M.; Crotti, P.; Gardelli, C.; Macchia, F. *J.Org.Chem.* **1994**, *59*, 4131-4137. b) Calvani, F.; Crotti, P.; Gardelli, C.; Pineschi, M. *Tetrahedron* **1994**, *50*, 12999-13022.
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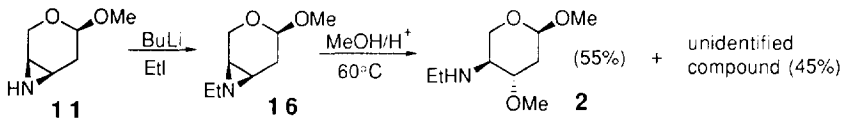
10. a) Methyl β-glycoside **3** and its α anomer **15** (not shown) were prepared from commercially available 2-deoxy-D-ribose by a slight modification (see Experimental) of a previously described procedure: Deriaz, R.E.; Overend, W.G.; Stacey, M.; Wiggins, L.F. *J.Chem.Soc.* **1949**, 2836-2841. b) For the physical data for compound **3**, see: Inokawa, S.; Mitsuyoshi, T.; Kawamoto, H.; Yamamoto, H.; Yamashita, M. *Carbohydr.Res.* **1985**, *142*, 321-323.
11. Pochlauer, P.; Muller, E.P.; Peringer, P. *Helv.Chim.Acta* **1984**, *67*, 1238-1247.b) Legters, J.; Thijs, L.; Zwanenburg, B. *Tetrahedron Lett.* **1989**, *30*, 4881-4884.
12. The accurate examination and comparison (^1H NMR) of the crude methanolysis opening reaction product from cis aziridine **12** and the ones obtained from the structurally related racemic aziridine **5**,[6] cannot reasonably allow us to rule out completely the presence of the regioisomeric *C-4 product*.[6,7]

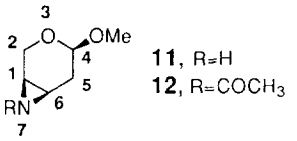
of **13** in the complex mixture fraction from **12**. However, if present, the regiosomeric *C-4 product* of **13** is present to an extent not superior to 5%.

13. The proton α to the methoxy group (the anomeric H_a proton, Scheme 2) in the cis aziridine **12** shows a signal (doublet of doublets) with a large (J= 7.5 Hz) and a small (J= 4.6 Hz) coupling constant suggesting for this compound, as in the case of the corresponding oxirane systems,[8] a preference for conformation **12b** in which the methoxy group is equatorial (H_a axial).
14. Crotti, P.; Favero, L.; Gardelli, C.; Macchia, F.; Pineschi, M. *J.Org.Chem.* **1995**, *60*, 2514-2525.
15. It cannot be completely ruled out that in the present case, under acid opening conditions, the preferential reactivity of **12** in conformation **12b** may be further favored by the intervention of a hydrogen bond between the protonated aziridine and the endocyclic oxygen, as tentatively shown in structure **14** (Scheme 2).[8,14]
16. A preliminary attempt to prepare the amino sugar **2** directly by acid methanolysis (at 60°C) of the *N*-ethyl derivative of aziridine **11** (aziridine **16**), was unsuccessful: the desired amino sugar **2** was



obtained only in an unsatisfactory yield (55%) and in a mixture with another glycosidic product (45%) which, at that moment, was not further investigated (see Experimental).

17. For the bicyclo-type nomenclature used in the case of aziridines **11** and **12**, the numbering scheme is the following:



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