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New C_2 Symmetric Bis-Aziridines Efficient Synthesis of (2*S*,5*S*)-1,6-Di(*p*-toluenesulfonyloxy)-2,5-Hexanediol, and (2*S*,3*E*,5*S*)-1,6-Di(*p*-toluenesulfonyloxy)-2,5-Hexenediol

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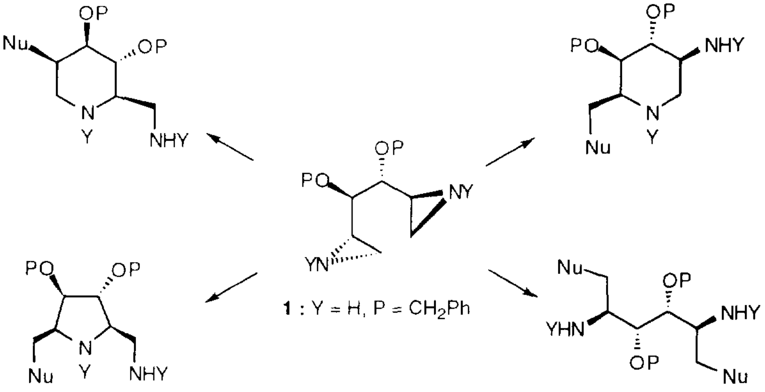
Abstract: The regioselective tosylation and functionalization of (*S*,*S*)-1,2,5,6-hexanetetrol is reported. The reductive aminocyclization of conformationally flexible diazidodiols by PPh_3 leads to C_2 symmetric bis-aziridines and to substituted furans.

D-mannitol-derived bis-aziridines are attractive building blocks, precursors of derivatives possessing a broad range of physiological properties, such as enantiopure diamino diols, highly functionalized polyhydroxylated piperidines or 2,5-disubstituted pyrrolidines (scheme1).



Scheme 1

The symmetric diaminodiols consist in the core unit of a class of HIV-1 proteinase inhibitors which have been designed, based on the symmetric disposition of the enzyme structure[1,2], and first synthesized starting from amino acids[2]. Aziridine bis-opening offers a flexible and enantioselective synthesis of a range of symmetric inhibitors which is not limited to amino acid derived substituents[3].

Natural and synthetic nitrogen analogues of carbohydrates have potential as chemotherapeutic agents. Both highly oxygenated piperidines (azapyranoses) and pyrrolidines (azafuranoses) belong to an important family of glycosidases and glycosyltransferases inhibitors, primarily for the N-linked oligosaccharide processing enzymes[4].

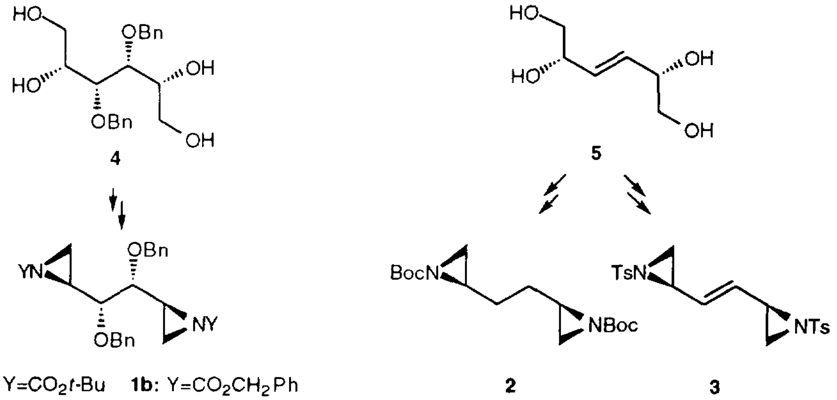
Our initial studies referred to the synthesis of 3,4-di-*O*-isopropylidene-D-mannitol-derived bis-aziridines[5] and the study of their reactivity towards various nucleophiles[6]. Opening of both aziridine rings provided access to a variety of C_2 symmetric diamino diols, while nucleophilic opening followed by intramolecular cyclization led to differently substituted polyhydroxylated piperidines.

Recently we have reported the nucleophilic ring-opening of *N*-substituted 3,4-di-*O*-benzyl bis-aziridines **1**, which show a conformationally flexible backbone. Nucleophilic opening followed by intramolecular cyclization enables the preparation of 3,4-dihydroxylated pyrrolidines of D-gluco configuration, substituted at C-2 and C-5 with two different functional groups, nucleophilic ring closure by nitrogen occurring preferentially onto the secondary carbon of the aziridine ring in a favorable 5-*exo*-heterocyclization[7].

Optically active *cis*-2,5-disubstituted pyrrolidine derivatives carrying two different functional groups have attracted interest since there are many natural products such as ant venom alkaloids, with this structure[8]. They are also useful as building block in the synthesis of biologically active compounds; a 5-substituted-2-formylpyrrolidine for example, is the key ring fragment required for the synthesis of unnatural Quinocarcin, a novel antitumor antibiotic[9].

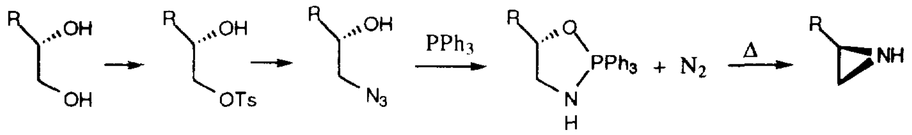
Considering the versatility of reactivity of C_2 symmetric bis-aziridines, and their potentiality as precursors, in a one step procedure, of a wide range of cis-2,5-disubstituted pyrrolidines, we have carried out the preparation of **1** as its *N*-Boc (**1a**) and *N*-Cbz (**1b**) derivatives, and of two new from D-mannitol-derived bis-aziridines: the (2*R*,2'*R*)-(1,2-ethan-diyl) bis-aziridine **2** and the (2*R*,2'*R*,*E*)-(1,2-ethen-diyl) bis-aziridine **3** via the three-step procedure we had previously developed[5].

1 was synthesized starting from 3,4-di-*O*-benzyl-D-mannitol **4**[10], while (2*S*,3*E*,5*S*)-1,2,5,6-tetrahydroxy-hex-3-ene **5**, prepared from D-mannitol[11] was the common precursor of **2** and **3** (scheme 2).



Scheme 2

The transformation of each terminal 1,2-diol into the *N*H-aziridine ring involves, selective sulfonylation at the primary hydroxy group, sodium azide substitution of the primary ditosylate, and triphenylphosphine promoted reductive aminocyclization of the resulting α–azido alcohol. In order to form a bis-aziridine these different reaction steps are bound to take place independantly at both extremities of the symmetric tetrol.



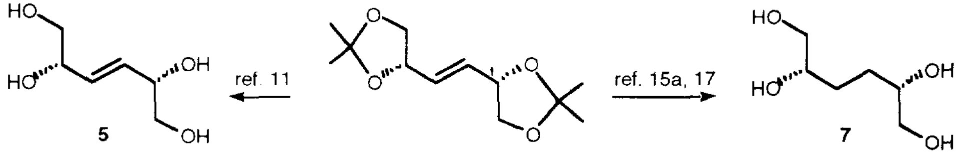
The selectivity of tosylation at the primary oxygens of C_2 symmetric 1,2,5,6-D-mannitol-derived tetrols is subordinate to the steric hindrance at C-2 and C-5. Whereas 3,4-di-*O*-isopropylidene-D-mannitol is 1,6-ditosylated in 80% yield by conventionnal manner[5] (TsCl, pyridine, 0°C), 3,4-di-*O*-benzyl-D-mannitol **4** provides the corresponding 1,6-ditosylate **6** in only 48% yield after purification[7]. This lowering of the yield is probably partly due to the flexibility of the carbon backbone which allows the formation of secondary cyclization products.

The tosylation of (*S,S*)-1,2,5,6-hexanetetrol **7** into the 1,6-ditosylate **9** had not be carried through till now, although the reaction of **7** with tosylchloride had been reported[12,13]. When the reaction was followed by alkaline treatment, the crude ditosylate provided the corresponding bis-epoxide in 58% yield[13]. Selective activation of the primary hydroxyl groups even using the more bulky 1-naphtalenesulfonyl chloride provided the 1,6-di-*O*-naphtalenesulfonyl derivative in only 42% yield[13b].

The regioselective manipulation of hydroxyl groups via organotin derivatives has found large applications in the field of carbohydrates[14], and more recently in the one of acyclic polyols. Dibutylstannylene acetals deriving from acyclic primary-secondary diols have been shown to react with both alkylating[15] and sulfonylating[16] reagents to give as a general rule higher regioselectivity for reaction at the primary oxygen than does direct reaction.

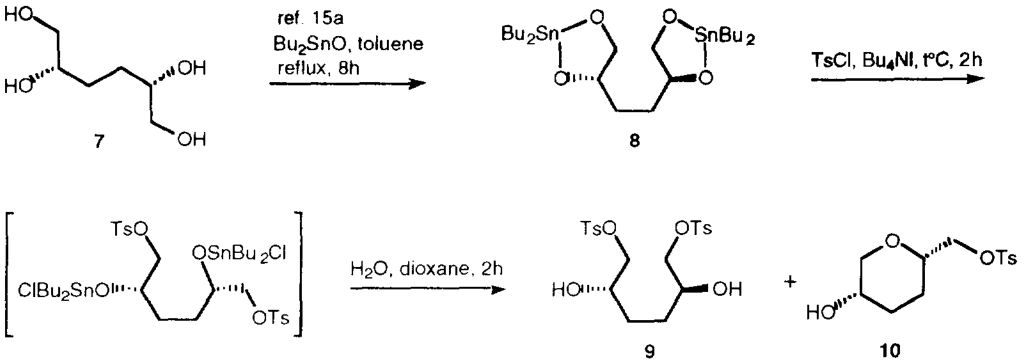
In an alternative procedure for regioselective tosylation of **7** we tested utilization of the organotin derivative **8**[15a] easily available from **7** (scheme 3). The benzylation and the benzoylation of organotin derivative **8** had been previously reported. Although the benzylation of **8** yielded the 1,6-dibenzyl ether in 60% yield[15a], unexpectedly its benzoylation led to a mixture of 1,6-dibenzoyl, 1,5-dibenzoyl and 1,2,6-tribenzoyl derivatives[13b].

In our hands the obtention of the tetrol **7** in enantiopure form proved delicate even following the improved procedure[15a,17], in the absence of intermediate purifications. Sequential Rh-Al_2O_3 catalyzed hydrogenation and hydrolysis of pure (2*S*,3*E*,5*S*)-1,2:5,6-di-*O*-isopropylidene-3-hexenetetrol led to **7** together with about 30% of the meso diastereoisomer. The epimerization occurs during the hydrogenation step. The rate of epimerization was determined by ^{13}C NMR spectrum analysis of the crude C_2 symmetric tetrol **7** which shows three distinct undoubled signals.



Nethertheless we have carried out the tosylation of **8** and found it to occur regioselectively at the primary oxygens, however the 1,6-ditosylate **9** was obtained in only moderate yield since its formation was accompanied by some cyclization into the tosylated pyran **10**.

Starting from the tetrol **7**, compound **9** results from the regioselective bis-tosylation at the primary oxygens of the tin acetal, and the pyran **10** from the intramolecular displacement of the 1-*O*-tosyl group by the oxygen at C-5, of the intermediate secondary tin alcoholate.

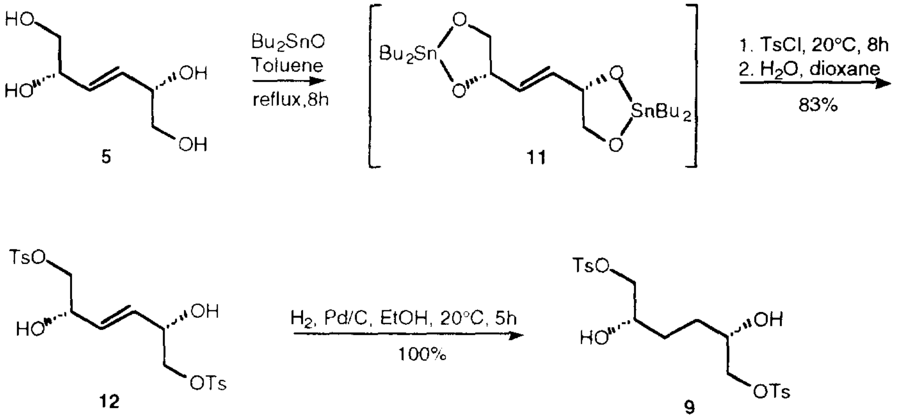


t = 20°C; **9**:**10** = 82:18
t = 50°C; **9**:**10** = 0:100

Scheme 3

The reaction of **8** with tosylchloride and tetrabutylammonium iodide, in conditions where cyclization products are minimized (concentration up to 0.2 mol dm^{-3}, 20°C), affords a 82:18 mixture of the 1,6-ditosylate **9** and of the tosylated pyran **10** with a rate of conversion of 80%. When the tosylation of **8** is carried out at 50°C, the pyran **10** is the only product of the reaction.

Both problems of epimerization and of competitive cyclization were overcome by the use of the ethylenic tetrol **5** for the preparation of **9**. Sequential sulfonylation, through stannylidene activation of the ethylenic tetrol **5**, and reduction of the resulting ethylenic ditosylate yielded the ditosylate **9** (scheme 4).



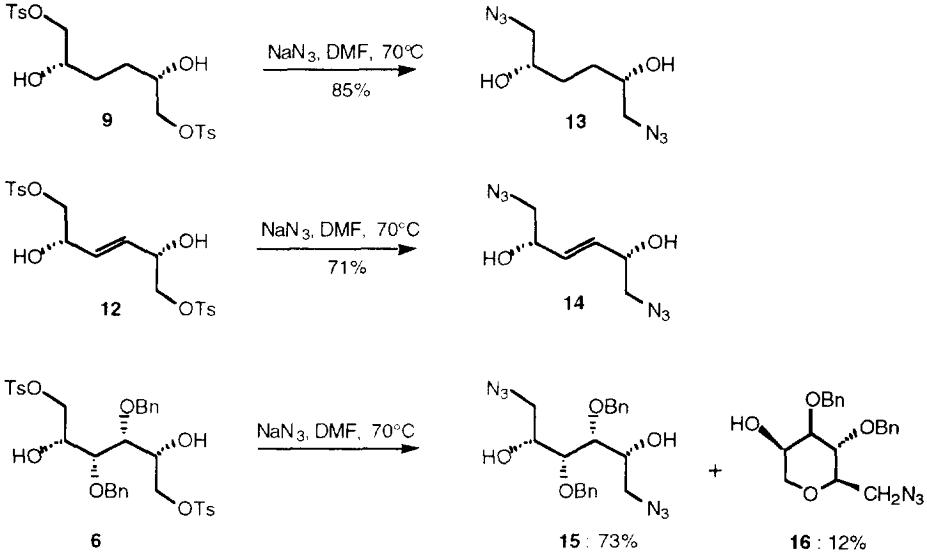
Scheme 4

We show here that tosylation of the partially rigid hexitol **5** is regioselective at the primary hydroxy groups and leads to enantiopure (*S,S*)-1,6-bis-paratoluenesulfonyloxy-2,5-hexanediol **9** in 83% yield after hydrogenation of the intermediate (2*S*,3*E*,5*S*)-1,6-di-paratoluenesulfonyloxy-2,5-dihydroxy-hex-3-ene **12**. This way proved all the more convenient for the obtention of the ditosylate **9** as there was no epimerization in the hydrogenation step.

Selective tosylation of the two primary hydroxy groups of the ethylenic tetrol **5** was achieved through the preparation of the organotin derivative **11**. **5** was refluxed for 8h in toluene with dibutyltinoxide, with azeotropic removal of water, then tosylchloride was added, and the solution stirred at 20°C for 8h. Hydrolysis of the mixture afforded the 1,6-ditosylate **12** in 83% yield; **12** could be quantitatively and without epimerization hydrogenated into the ditosylate **9** using Pd on charcoal as catalyst.

Sodium azide substitution of the 1,6-ditosylates **9**, **12**, and **6**, effected at 70°C during 5 hours resulted in formation of the corresponding diazidodiols **13**, **14**, and **15**, in respectively 85, 71 and 73% yields (scheme 5).

Starting from **6** we could not prevent the formation of 12% of the pyran **16** besides **15**, which results from the competitive attack of a secondary hydroxyl group onto a primary *O*-sulfonylated carbon; however such cyclization was not observed starting from the conformationnally flexible ditosylate **9**.

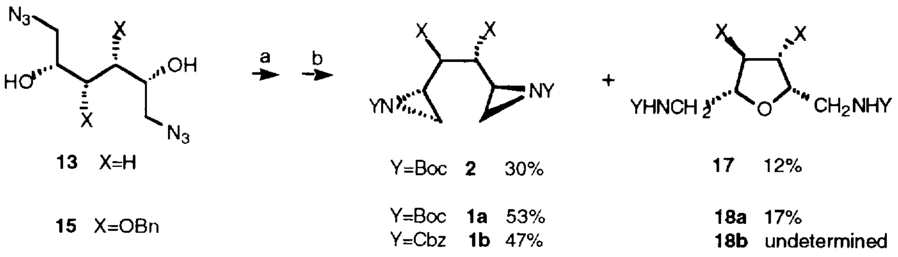


Scheme 5

When reacted with triphenylphosphine, the conformationally flexible diazidodiols **13** and **15** led to a mixture of the corresponding *N*-H bis-aziridines and tetrasubstituted furans (scheme 6). Both derivatives were isolated as their *N*-protected form.

13 led to the highly reactive *N*-Boc bis-aziridine **2** in 30% yield and to the furan **17** in 12% yield. The modest yield in purified bis-aziridine **2** is due to decomposition occurring in the course of the chromatographic purification.

Reductive aminocyclization of the diazidodiol **15** by triphenylphosphine led, after nitrogen protection to the *N*-Boc bis-aziridine **1a** and *N*-Cbz bis-aziridine **1b** in respectively 53% and 47% yields. The *N*-Boc-2,5-diaminomethyl-3,4-dihydroxyfuran **18a** was obtained in 17% yield.



13 X=H

15 X=OBn

Y=Boc **2** 30%

Y=Boc **1a** 53%
Y=Cbz **1b** 47%

17 12%

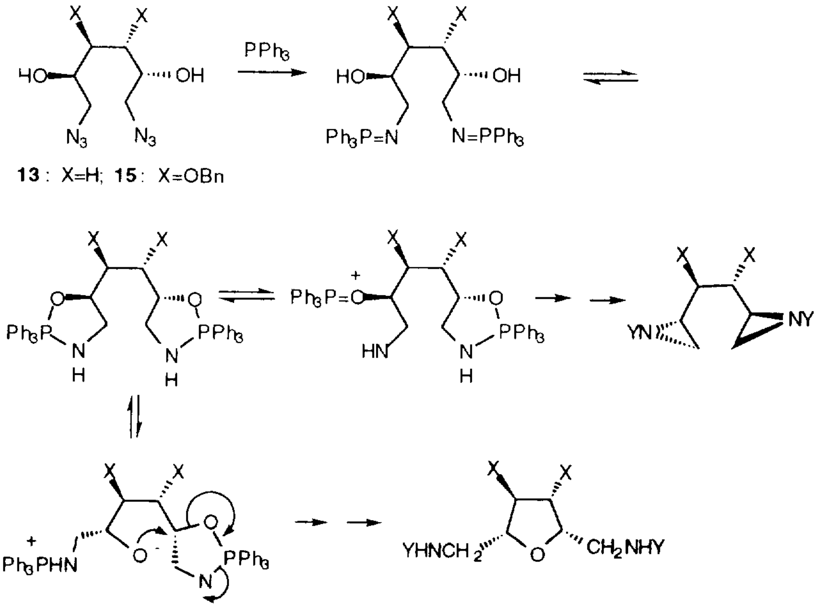
18a 17%
18b undetermined

a) Ph_3P, $PhCH_3$, 35°C, 2h, then 90°C, 8h.
b) $(CO_2tBu)_2O$, Et_3N, THF, 0°C to rt, 3h; or $ClCO_2CH_2Ph$, Et_3N, CH_2Cl_2, 0°C to rt, 3h

Scheme 6

The structure of the furan **18a** has been established by ^1H and ^{13}C NMR analysis. It presents the configuration of D-glucose, resulting of an inversion of configuration at C-2.

The formation of the furans **17** and **18** could result from a competitive thermal decomposition, allowed by the flexibility of the carbon chain, of the intermediate oxazaphospholidine as depicted in the scheme 7.



13: X=H; **15**: X=OBn

Scheme 7

PPh_3 reductive aminocyclization of the diazidodiol **14** led to the corresponding ethylenic bis-aziridine as single product, which was isolated as its *N*-tosylated derivative **3** in 13% yield. The low yield is due to degradations which go with the formation of the unstable *N*H ethylenic bis-aziridine in the course of the thermal decomposition of the oxazaphospholidine at 70°C.

CONCLUSION

In summary we have developed an efficient method for the selective 1,6 activation and functionalization of 1,2,5,6-hexane and-hexenetetrols, in particular the synthesis of (2*S*,5*S*)-1,6-di-(*p*-toluenesulfonyloxy)-2,5-hexanediol, useful precursor of C_2 symmetric compounds has been achieved in high yield. We have carried out the syntheses of new bis-aziridines with a flexible carbon backbone and our efforts are now aimed, at the one-step preparation of *cis*-2,5-disubstituted pyrrolidine derivatives.

EXPERIMENTAL SECTION

General methods

Prior to use, tetrahydrofuran (THF) and diethylether (Et_2O) were distilled from sodium-benzophenone and dichloromethane (CH_2Cl_2) from P_2O_5. CH_2Cl_2 and ethyl acetate (AcOEt) were filtered on K_2CO_3 prior to use. ^1H NMR (250MHz) and ^{13}C NMR (62.9MHz) spectra were recorded in $CDCl_3$ (unless otherwise indicated) on a Bruker AM 250. Chemical shifts are reported in δ (ppm) and coupling constants are given in Hertz. IR spectra were recorded on a Perkin Elmer 783 Infrared Spectrophotometer. Specific rotations were measured on a Perkin Elmer 241C polarimeter with sodium (589 nm) or mercury (365 nm) lamps. Mass spectra were recorded in Service de Spectrométrie de Masse, Université Pierre et Marie Curie, Paris. All reactions were carried out under argon atmosphere, and were monitored by thin-layer chromatography with Merck 60F-254 precoated silica (0.2 mm) on glass. Chromatography was performed with Merck Kieselgel 60 (200-500 μm) or 60H (5-40 μm). Spectroscopic (^1H and ^{13}C NMR, MS) and/or analytical data were obtained using chromatographically homogeneous samples.

1,2,5,6-Tetrahydroxy-hexane (**7**)

A solution of (2*S*,3*E*,5*S*)-1,2,5,6-tetrahydroxy-1,2:5,6-di-*O*-isopropylidene-hex-3-ene (2g, 8.8 mmol) in ethanol (60ml) was hydrogenated over 10% Rh-Al_2O_3 (200mg) at 1 atm. for 14h, as previously described[15a,17]. After filtration and concentration, the residue (2g) was diluted in 80% aqueous trifluoracetic acid (20ml), stirred at 0°C for 3h, then concentrated *in vacuo*. The residual oil was diluted in methanol (200ml), applied to an Amberlite CG 400 column for neutralization and eluted with methanol. Concentration yielded crude tetrol **7** as an oil which slowly cristallized (1.3g, 97%) : mp 81°C; $[\alpha]_D$ -16 (*c* 2.11, CH_3OH) (litt[14a] : mp 84°C, $[\alpha]_D$ -24; litt[17] : mp 93-94°C, $[\alpha]_D$ -24; ^{13}C NMR (D_2O) δ: 31.2, 31.4 (2/1, C-3); 68.2, 68.3 (2/1, C-1); 74.4, 74.8 (2/1, C-2).

Tosylation of crude tetrol 7 through organotin derivative 8

To a suspension of the crude tetrol **7** (0.10 g, 0.67 mmol) in toluene (20ml) was added Bu_2SnO (0.41 g, 1.65 mmol) and the mixture was refluxed for 8h with azeotropic removal of water. The mixture containing the in situ generated tinacetal **8** was concentrated *in vacuo* to 4 ml, then $Bu_4N^+I^-$ (0.259g, 0.70 mmol) and TsCl (0.268 g, 1.40 mmol) were added. The resulting suspension was stirred for 3h at 20°C, then hydrolyzed by adding water (10ml) and dioxane (60ml) and stirring for 3h. After concentration and extraction with CH_2Cl_2 (3x50ml), the organic layer was washed with a 1N $Na_2S_2O_3$ aqueous solution in order to reduce the iodine formed in the course of the reaction. After removal of the solvent, the residue was purified by flash chromatography, eluting with 3:2 AcOEt / cyclohexane. The ditosylates (0.205g, 67%) and the pyrans (27mg, 15%) were separately collected as mixtures of diastereoisomers.

1,6-Di-p-toluenesulfonyloxy-2,5-dihydroxy-hexane : mp 120-126°C; 2:1 mixture of diastereoisomers as expressed by relative intensity of the undoubled ^{13}C NMR signals δ : 20.7 (CH_3); 28.8, 29.0 (2/1, C-3); 68.3, 68.6 (2/1, C-2); 74.0 (C-1); 127.9, 130.0, 133.4, 145.0 (C_{arom}); CIMS, m/z : 476 ($M+NH_4^+$, 55%); 459 ($M+H^+$, 10%).

1-O-p-Toluenesulfonyl-2,6-anhydro-1,2,5,6-hexanetetrols.

The crude previous organotin derivative (0.9 mmol), in toluene (10ml), was tosylated for 3h at 50°C as previously described. Flash chromatography offered 144.8 mg of the pyran **10** (cis isomer) and 55.8 mg of the trans isomer (78% total yield).

Cis isomer **10** : $[\alpha]_D$ -10; $[\alpha]_{365}$ -30 (*c* 1.10, CH_2Cl_2); ^1H NMR (500 MHz) δ: 1.44-1.53 (m, 1H, H-3eq); 1.62-1.75 (m, 2H, H-3ax, H-4ax); 1.90-2.00 (m, 1H, H-4eq); 2.03 (d, 1H, $J_{OH,5}$ = 7.5 Hz, OH); 2.47 (s, 3H, CH_3); 3.56 (dd, 1H, $J_{5,6ax}$ = 1 Hz, $J_{6ax,6eq}$ = 12 Hz, H-6ax); 3.62 (m, 1H, $J_{1,2}$ = 5 Hz, H-2); 3.78 (m, 1H, H-5); 3.88 (ddd, 1H, $J_{5,6eq} \approx J_{4eq,6eq} \approx$ 2 Hz, H-6eq); 4.02 (d, 2H, H-1, H-1'); ^{13}C NMR (126 MHz; $CDCl_3$) δ: 21.6 (CH_3); 21.7 (C-3); 28.8 (C-4); 64.1 (C-5); 72.0 (C-1); 72.4 (C-6); 74.9 (C-2); 127.9, 129.7, 132.9, 144.8 (C_{arom}); CIMS, m/z : 304 ($M+NH_4^+$, 100%); 287 ($M+H^+$, 20%).

Trans isomer : mp 50°C; ^1H NMR (500 MHz) δ: 1.30-1.40 (m, 2H, H-3ax, H-4ax); 1.47 (d, 1H, $J_{OH,5}$ = 4.7 Hz, OH); 1.63-1.72 (m, 1H, H-3eq); 2.11 (m, 1H, H-4eq); 2.42 (s, 3H, CH_3); 3.03 (dd, 1H, $J_{6ax,6eq}$ = 10 Hz, H-6ax); 3.46 (m, 1H, H-2); 3.63 (m, 1H, $J_{5,6ax} = J_{5,4ax}$ = 10 Hz; $J_{5,6eq} = J_{5,4eq}$ = 5 Hz; H-5); 3.93 (ddd, 1H, $J_{6ax,4eq}$ = 2 Hz, H-6eq); 3.95 (d, 2H, H-1, H-1'); 7.32, 7.76 (2d, 4H , J = 8 Hz, H_{arom}); ^{13}C NMR (126 MHz; $CDCl_3$) δ: 21.6 (CH_3); 26.4 (C-3); 32.0 (C-4); 65.7 (C-5); 71.6 (C-1); 72.4 (C-6); 74.2 (C-2); 127.9, 129.7, 132.9, 144.8 (C_{arom}); CIMS, m/z : 304 ($M+NH_4^+$, 100%); 287 ($M+H^+$, 20%).

(2R,3E,5R)-1,6-Di-(p-toluenesulfonyloxy)-2,5-dihydroxy-hex-3-ene (12)

To a suspension of **5**[11] (0.72g, 4.86mmol) in toluene (140ml) was added Bu_2SnO (3.03 g, 12.2 mmol) and the mixture was refluxed for 8h with azeotropic removal of water. The mixture containing the in situ generated tinacetal **11** was concentrated *in vacuo* to 20 ml and TsCl (1.85g, 9.8mmol) was added. The resulting suspension was stirred for 8h at 20°C, then hydrolyzed by adding water (20ml) and stirring for 15h. The mixture was extracted with CH_2Cl_2 (3x50ml), the organic layer was dried with $MgSO_4$ and then evaporated under reduced pressure. The crude product was purified by flash chromatography, eluting with 3:2 AcOEt / cyclohexane to afford **12** as a white solid (1.84g, 83%) : mp 99°C; $[\alpha]_D$ -7.5; $[\alpha]_{365}$ -33 (*c* 0.815, CH_2Cl_2); ^1H NMR δ: 2.24 (d, 2H, $J_{OH,2}$ = 4.5 Hz, OH), 2.44 (s, 6H, CH_3), 3.86 (dd, 2H, $J_{1,1'}$ = 10 Hz, $J_{1,2}$ = 7.5 Hz, H-1), 4.01 (dd, 2H, $J_{1',2}$ = 3 Hz, H-1'); 4.38 (m, 2H, H-2); 5.74 (m, 2H, H-3); 7.34, 7.77 (2d, 8H, J = 8 Hz, H_{arom}); ^{13}C NMR δ: 21.5 (CH_3), 69.2 (C-2); 72.7 (C-1), 130.2 (C-3), 127.9, 129.9; 132.3, 145.1 (C_{arom}). Anal. calcd for $C_{20}H_{24}O_8S_2$: C, 52.62; H, 5.30. Found: C, 52.39; H, 5.21.

(2S,5S)-1,6-Di-(p-toluenesulfonyloxy)-2,5-dihydroxy-hexane (**9**)

A solution of **12** (2.80g, 6.13mmol) in ethanol (140ml) was hydrogenated in the presence of Pd black (0.77g) at atmospheric pressure for 5h. After addition of DMF (10ml) to the mixture and removal of the catalyst by filtration through celite, the filtrate was evaporated to give **9** in quantitative yield (2.80g), which was reacted without further purification. Flash chromatography of a sample, eluting with 3:2 AcOEt / cyclohexane gave **9** as white cristals: m p 124°C; $[\alpha]_D$ -2; $[\alpha]_{365}$ -6 (*c* 0.895, DMF); ^1H NMR δ: 1.40-1.65 (m, 4H, H-3, H-3'); 2.44 (s, 6H, CH_3); 2.58 (d, 2H, $J_{OH,2}$ = 3.5 Hz, HO); 3.83 (m, 2H, H-2); 3.87 (dd, 2H, $J_{1,2}$ = 6.5 Hz, H-1); 3.97 (dd, 2H, $J_{1,1'}$ = 9.5 Hz, $J_{1',2}$ = 3 Hz, H-1'); 7.34, 7.77 (2d, 8H, J = 8 Hz, H_{arom}); ^{13}C NMR δ: 21.7 (CH_3); 28.7 (C-3); 69.1 (C-2); 73.6 (C-1); 128.0, 130.0, 132.5, 145.2 (C_{arom}). Anal. calcd for $C_{20}H_{26}O_8S_2$: C, 52.39; H, 5.72. Found. C, 51.90; H, 5.67.

(2R,5R)-1,6-Diazido-2,5-dihydroxy-hexane (**13**)

Crude ditosylate **9** (2.80g, 6.13mmol) dissolved in DMF (35ml) was treated with sodium azide (3g, 46mmol). The reaction mixture was stirred at 70°C for 4 h , then evaporated to dryness. CH_2Cl_2 (50ml) and brine (10ml) were added to the residue, the aqueous phase was extracted with CH_2Cl_2 (3x50ml). The organic layer was dried over $MgSO_4$, filtered and evaporated. The residue was purified by flash chromatography eluting with AcOEt/cyclohexane 3:2 to give **13** as a colorless oil (1.04g, 85% from **12**) : $[\alpha]_D$ +1.5; $[\alpha]_{365}$ +4.0 (*c* 0.87, CH_2Cl_2); ^1H NMR δ: 1.45-1.75 (m, 4H, H-3, H-3'); 3.25 (m, 4H, $J_{1,2}$ = 7 Hz, H-1, OH) 3.35 (dd, 2H, $J_{1,1'}$ = 12.5 Hz, $J_{1',2}$ = 4 Hz, H-1'); 3.76 (m, 2H, H-2); ^{13}C NMR δ: 30.6 (C-3); 57.0 (C-1); 70.7 (C-2). Anal. calcd for $C_6H_{12}N_6O_2$: C, 36.00; H, 6.04; N, 41.98. Found: C, 36.10; H, 6.05; N, 41.98.

(2R,3E,5R)-1,6-Diazido-2,5-dihydroxy-hex-3-ene (**14**)

Ditosylate **12** (1.51g, 3.31mmol) dissolved in DMF (20ml) was treated with sodium azide (1.76g, 27mmol) as described for **9**. Flash chromatography eluting with AcOEt/cyclohexane 1:1 gave diazide **14** as an oil (0.46g, 71%) : ^1H NMR δ: 2.28 (s, 2H, OH): 3.29 (dd, 2H, $J_{1,1'}$ = 12.5 Hz, $J_{1,2}$ = 7 Hz, H-1), 3.38 (dd, 2H, $J_{1',2}$ = 4 Hz, H-1'): 4.33 (m, 2H, H-2); 5.77-5.91 (m, 2H, H-3). **14** is unstable and slowly decomposes even when stored at -20°C.

Reaction of diazidodiol 13 with triphenylphosphine

A solution of diazidodiol **13** (270mg, 1.35mmol) and triphenylphosphine (708mg, 2.70mmol) in dry toluene (10ml) was stirred at 40°C until nitrogen evolution had ceased (3h). The mixture was then carried at 90°C and stirred for 8 h under argon. After evaporation to dryness the crude residue was protected without further purification.

Protection with di-tert-butyl-dicarbonate

To a solution of the above residue (1.35mmol) and triethylamine (0.370ml, 2.70mmol) in THF (10ml), a solution of di-*tert*-butyl-dicarbonate (570mg, 2.70mmol) in THF (15ml) was added under argon at 0°C. After 3h stirring at 20°C, the solvent was evaporated and the residue diluted with ether and brine. The aqueous phase was extracted with ether. Solvent evaporation and flash chromatography, eluting with AcOEt/cyclohexane/Et$_3$N 3:7:0.01, yielded the bis-aziridine **2** as a solid (123mg, 30%) and the furan **17** as an oil (52mg, 12%). Significant decomposition took place in the course of the column chromatography.

(2R,2'R)-(1,2-Ethan-diyl) bis (1-tert-butoxycarbonyl)-aziridine (**2**) : mp 71-73°C; ν_{max} (film): 1720 , 1320, 1230; ^{1}H NMR δ: 1.3-1.5 (m, 18H, CH$_3$); 1.5-1.8 (m, 4H, CH$_2$); 1.93 (d, 2H, $J_{3,2}$ = 4 Hz, H-3); 2.26 (d, 2H, $J_{3',2}$ = 6 Hz, H-3'); 2.48 (m, 2H, H-2); ^{13}C NMR δ: 27.9 (CH$_3$); 29.5, 31.8 (CH$_2$, C-3); 37.2 (C-2); 80.9 ($\underline{C}$(CH$_3$)$_3$); 162.5 (CO). HRMS calcd for $C_{16}H_{28}N_2O_4$ (M^{+}): 312.2049, found: 312.2050.

(2R,5S)-2,5-Di-N-tert-butoxycarbonylaminomethyl-3,4-dihydro-furan (**17**) : ν_{max} (film): 3450, 3350, 1710, 1170, 1090; ^{1}H NMR δ: 1.3-1.7 (m, 20H, CH$_3$, H-3); 1.8-2.0 (m, 2H, H-3'); 3.04 (m, 2H, CH$_2$N); 3.32 (m, 2H, CH$_2$N); 3.85-4.1 (m, 2H, H-2); 4.7-5.0 (m, 2H, NH); ^{13}C NMR δ: 28.2 (C-3); 28.3 (CH$_3$); 44.8 (CH$_2$N); 78.7 (C-2); 79.2 ($\underline{C}$(CH$_3$)$_3$); 156.2 (CO); CIMS m/z: 331 (M+H$^+$, 20%); Anal. calcd for $C_{16}H_{30}N_2O_5$: C, 58.16; H, 9.15; N.8.48. Found: C, 58.93; H, 9.23; N, 8.34.

(2R,2'R,E)-(1,2-Ethen-diyl) bis (1-p-toluenesulfonyl)-aziridine (3)

A solution of the diazidodiol **14** (98mg, 0.5mmol) and triphenylphosphine (260mg, 1mmol) in dry toluene (4ml) was stirred at 40°C for 2h, then at 70°C for 7h. During the course of the reaction, tarrs where formed. The solvent was evaporated and the crude mixture was tosylated.

A solution of the above crude aziridine in dry THF (3ml), is added to KH (41mg, 1mmol) at 0°C under argon; after 1h stirring at 0°C, a solution of TsCl (236mg, 138mmol) in THF (1ml) is added and the resulting mixture is stirred for 4h at 20°C, before quenching with H$_2$O (1ml). After concentration, the residue was extracted with ether and the etheral layer dried over MgSO$_4$. Solvent evaporation and flash chromatography eluting with AcOEt/cyclohexane/Et$_3$N 3:7:0.01, gave **3** (30mg, 13%); ^{1}H NMR (90MHz) δ: 2.1 (d, 2H, $J_{1,2}$ = 5 Hz, H-3); 2.4 (s, 6H, CH$_3$); 2.7 (d, 2H, $J_{1',2}$ = 7 Hz, H-3'); 3.25 (m, 2H, H-2); 5.4-5.7 (m, 2H, HC=); 7.25, 7.75 (2d, 8H, J = 8 Hz, H$_{arom}$); HRMS calcd for $C_{20}H_{22}N_2O_4S_2$ (M$^+$): 418.1021, found: 418.1022.

1,6-Di-O-p-toluenesulfonyl-3,4-di-O-benzyl-D-mannitol (**6**)

To a solution of 3,4-di-*O*-benzyl-D-mannitol **4**[10] (8.83g, 24.5 mmol) in pyridine (40 ml), a solution of tosyl chloride (8.77 g, 45 mmol) in pyridine (40 ml) was slowly added at 0°C. The mixture was stirred for 10 h at 5°C, then poured into a cold mixture of hydrochloric acid (6N, 200 ml) and diethylether (100 ml). The ether extract was washed with an aqueous solution of $NaHCO_3$ (3%, 150ml), dried ($MgSO_4$) and evaporated to a syrup. The crude product was purified by flash chromatography, eluting with 2:3 AcOEt / cyclohexane to afford **6** as a white solid (7.88g, 48%) : mp 102°C; $[\alpha]_D$ +32 (c 1.06; CH_2Cl_2); ^1H NMR δ: 2.41 (s, 6H, CH_3); 2.79 (d, 2H, $J_{HO,2}$ = 5 Hz , HO); 3.75 (d, 2H, $J_{3,2}$ = 7 Hz, H-3); 4.00 (m, 2H, H-2); 4.09 (dd, 2H, $J_{1,1'}$ = 16 Hz, $J_{1,2}$ = 10 Hz, H-1); 4.18 (dd, 2H, $J_{1',2}$ = 3 Hz, H-1'); 4.44, 4.53 (AB, 4H, J_{AB} = 12 Hz, OCH_2Ph); 7.13-7.74 (m, 18H_{arom}); ^{13}C NMR δ: 21.6 (CH_3); 69.5 (C-2), 76.5 (C-3); 71.3, 73.9 (C-1, $\underline{C}H_2Ph$); 128.0, 128.1, 128.3, 128.5, 129.9 132.5, 136.9, 145.0 (C_{arom}). Anal. calcd for $C_{34}H_{38}O_{10}S_2$: C, 60.88; H, 5.71. Found: C, 60.78; H, 5.72.

Reaction of ditosylate 6 with sodium azide

A suspension of ditosylate **6** (7.66 g, 11.4 mmol) and sodium azide (3g, 2x2eq.) in DMF (46ml) was stirred at 70°C for 5 h. DMF was removed *in vacuo* , water was added (40ml), and the residue extracted with CH_2Cl_2. The extract was dried ($MgSO_4$), evaporated to a syrup and purified by flash chromatography, eluting with 3:7 AcOEt / cyclohexane to afford **15** (3.43g, 73%) and **16** (0.54 g, 12%) as white solids.

1,6-Diazido-1,6-dideoxy-3,4-di-O-benzyl-D-mannitol (**15**) : mp 44°C; $[\alpha]_D$ +78 (c 1.36; CH_2Cl_2); ^1H NMR δ: 3.26 (d, 2H, $J_{HO,2}$ = 3 Hz, HO); 3.33 (dd, 2H, $J_{1,1'}$ = 13 Hz, $J_{1,2}$ = 5 Hz, H-1); 3.54 (dd, 2H, $J_{1',2}$ = 3 Hz, H-1'); 3.75 (d, 2H, $J_{3,2}$ = 7 Hz, H-3); 4.05 (m, 2H, H-2); 4.52, 4.59 (AB, 4H, J_{AB} = 14 Hz, CH_2Ph) 7.27-7.40 (m, 10H, H_{arom}); ^{13}C NMR δ: 53.6 (C-1); 71.1 (C-2), 76.8 (C-3); 73.9 ($\underline{C}H_2Ph$); 128.5, 128.7 136.6 (Carom). Anal. calcd for $C_{20}H_{24}N_6O_4$: C, 58.24; H, 5.86; N, 20.38. Found: C, 58;34; H, 5.91; N, 20.49.

1-Azido-1-deoxy-2,6-anhydro-3,4-di-O-benzyl-D-mannitol (**16**) : mp 90°C; $[\alpha]_D$ +16.5 (*c* 1.04; CH_2Cl_2); ν max (film): 3570, 3470, 2110, 1210, 1110 cm^{-1}; ^1H NMR δ: 2.56 (s, 1H, OH); 3.25-3.55 (m, 4H, $J_{2,3}$ = 9 Hz, H-1, H-1', H-2, H-6_{ax}); 3.60 (dd, 1H, $J_{3,4}$ = 9 Hz; $J_{4,5}$ = 3 Hz, H-4); 3.68 (dd, 1H, H-3); 4.01 (bs, 1H, $J_{5,6eq}$ = 2 Hz, H-5); 4.07 (dd, 1H, $J_{6ax,6eq}$ = 12.5 Hz, H-6_{eq}); 4.60, 4.91 (2d, 2H, J = 12 Hz, OCH_2Ph); 4.66, 4.74 (AB, 2H, J_{AB} = 12 Hz, OCH_2Ph); 7.15-7.55 (m, 10H_{arom}); ^{13}C NMR δ: 51.7 (C-1); 66.7 (C-2); 69.2 (C-6); 71.7, 75.3 ($\underline{C}H_2Ph$); 75.2, 78.9, 82.4 (C-3, C-4, C-5); 127.8, 128.0, 128.1, 128.5, 128.6 137.5, 137.9 (C_{arom}). CIMS, m/z : 387 ($M+NH_4^+$, 100%); 342 (62%). Anal. calcd for $C_{20}H_{23}N_3O_4$: C, 65.03; H, 6.28; N, 11.37. Found: C, 64.92; H, 6.24; N, 11.46.

Reaction of diazidodiol 15 with triphenylphosphine

A solution of diazidodiol **15** (520mg, 1.26mmol) and triphenylphosphine (662mg, 2.52mmol) in dry toluene (8ml) was stirred at 40°C until nitrogen evolution had ceased. The mixture was then carried at 90°C and stirred 8 h under argon. After evaporation to dryness the crude residue was protected without further purification. Flash chromatography of a sample, eluting with 67:17:18:1 AcOEt / cyclohexane / MeOH / Et_3N provided *N*H-bis-aziridine **1** as an oil.

(2S,2'S)-[(1R,2R)-1,2-Dibenzyloxy-ethan-diyl] bis-aziridine (**1**) : ^{1}H NMR δ: 1.42 (d, 2H, $J_{3,2}$ = 3 Hz, H-3); 1.52 (m, 2H, NH); 1.68 (d, 2H, $J_{3',2}$ = 6.5 Hz, H-3'); 2.32 (m, 2H, H-2); 3.19 (d, 2H, $J_{3,2}$ = 5.5 Hz, C$\underline{H}$OBn); 4.66, 4.77 (AB, 4H, J = 12 Hz; C$\underline{H}_2$Ph); 7.2-7.4 (m, 10H$_{arom}$); ^{13}C NMR δ: 20.99 (C-3); 30.62 (C-2); 72.64 ($\underline{C}H_2$Ph); 81.92 ($\underline{C}$HOBn); 127.61, 127.79, 128.32, 138.37 (C$_{arom}$).

Protection with di-tert-butyl-dicarbonate

To a solution of the crude residue (2.97mmol) and triethylamine (0.83ml, 6.0mmol) in THF (45ml), a solution of di-*tert*-butyl-dicarbonate (1.30g, 6mmol) in THF (10ml) was added under argon at 0°C. After 3h stirring at 20°C, the solvent was evaporated and the residue diluted with ether and brine. Evaporation of the ether and flash chromatography, yielded bis-aziridine **1a** as an oil which slowly cristallized (0.826g, 53%) and furan **18a** as an oil (0.274g, 17%).

(2S,2'S)-[(1R,2R)-1,2-Dibenzyloxy-ethan-diyl] bis (1-tert-butoxycarbonyl)-aziridine (**1a**) : mp 65°C; $[\alpha]_D$ -100 (*c* 1.59, CH_2Cl_2); ν_{max} (film): 1720, 1320, 1220 cm^{-1}; ^{1}H NMR δ 1.45 (s, 18H, $C(CH_3)_3$); 1.81 (d, 2H, $J_{3,2}$ = 4 Hz, H-3); 2.15 (d, 2H, $J_{3',2}$ = 6.5 Hz, H-3'); 2.85 (m, 2H, H-2); 3.12 (d, 2H, J = 6 Hz, C$\underline{H}$OBn); 4.73, 4.89 (AB, 4H, J = 16.5 Hz, C$\underline{H}_2$Ph); 7.25-7.40 (m, 10H, H$_{arom}$); ^{13}C NMR δ: 26.8 (C-3); 27.7 (CH_3); 38.2 (C-2); 71.6 (O$\underline{C}H_2$Ph); 79.4 ($\underline{C}$HOBn); 81.3 ($\underline{C}(CH_3)_3$); 127.8, 128.1, 128.3, 137.9 (C$_{arom}$.); 162.0 (CO). Anal. calcd for $C_{30}H_{40}N_2O_6$: C, 68.68; H, 7.68; N, 5.34. Found: C, 68.03; H, 7.79; N, 5.19.

1,6-Dideoxy-1,6-di-(tert-butoxycarbonylamino)-2,5-anhydro-3,4-di-O-benzyl-D-glucitol (**18a**) : $[\alpha]_D$ +21.6 (*c* 1.12, CH_2Cl_2); ν_{max} (film): 3450, 3360, 1710, 1090 cm^{-1}; ^{1}H NMR δ: 3.22-3.63 (m, 4H, H-1, H-1', H-6, H-6'); 3.83 (d, 1H, $J_{2,3}$ = 2.5 Hz, H-3); 3.90 (d, 1H, $J_{4,5}$ = 4 Hz, H-4); 3.96 (m, 1H, H-2); 4.03 (ddd, 1H, $J_{5,6}$ = 7.5 Hz, $J_{5,6'}$ = 4 Hz, H-5); 4.35, 4.56 (2d, 2H, J = 12 Hz, OCH_2Ph); 4.50 (m, 2H, OCH_2Ph); 4.80 (m, 1H, NH); 5.00 (m, 1H, NH); 7.20-7.45 (m, 10H, H$_{arom}$); ^{13}C NMR δ: 28.4 (CH_3); 40.1, 42.9 (C-1, C-6); 71.5, 71.9 (OCH_2Ph); 79.2 ($C(CH_3)_3$); 79.8, 82.8, 83.9 (C-2, C-3, C-4, C-5); 127.7, 128.0, 128.5, 128.6, 137.4 (C$_{arom}$). CIMS, m/z : 560 ($M+NH_4^+$, 10%); 543 ($M+H^+$, 100%). Anal. calcd for $C_{30}H_{42}N_2O_7$: C, 66.40; H, 7.80; N, 5.16. Found: C, 66.29; H, 7.74; N, 5.03.

Protection with benzylchloroformate

To a mixture of the crude *N*H-bis-aziridine **1** (1.26mmol) and triethylamine (0.45ml, 3.2mmol) in dichloromethane (10ml), benzylchloroformate (0.45ml, 3.2mmol) was added under argon at 0°C. The mixture was stirred 3 h at 20°C, anhydrous ether was added (15 ml) and the precipitated solids filtered. The supernatant was concentrated *in vacuo*, flash chromatography eluting with 19:80:1 AcOEt/cyclohexane/Et_3N afforded **1b** as a white solid, (0.35 g, 47%).

(2S,2'S)-[(1R,2R)-1,2-Dibenzyloxy-ethan-diyl] bis (1-benzyloxycarbonyl)-aziridine (**1b**) : mp 69°C; $[\alpha]_D$ -80.5 (*c* 1.01, CH_2Cl_2); ν_{max} (film): 1730, 1300, 1210 cm^{-1}; ^1H NMR δ 1.93 (d, 2H, $J_{3,2}$ = 3.5 Hz, H-3); 2.20 (d, 2H, $J_{3',2}$ = 6 Hz, H-3'); 2.93 (m, 2H, H-2); 3.18 (d, 2H, J = 5 Hz, $C\underline{H}OBn$); 4.66, 4.85 (AB, 4H, J_{AB} = 12 Hz, $OC\underline{H}_2Ph$); 5.10, 5.16 (AB, 4H, J_{AB} = 8 Hz; $CO_2C\underline{H}_2Ph$); 7.15-7.45 (m, $20H_{arom}$); ^{13}C NMR δ 27.5 (C-1); 38.3 (C-2); 68.40 ($O\underline{C}H_2Ph$); 72.1 ($CO_2\underline{C}H_2Ph$); 79.4 ($\underline{C}HOBn$); 127.7, 128.2, 128.6, 135.6, 137.8 (C_{arom}); 162.9 (CO). Anal. calcd for $C_{36}H_{36}N_2O_6$: C, 72.95; H, 6.12; N, 4.73. Found: C, 71.85; H, 6.16; N, 4.61.

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REFERENCES

1. Erickson,.J.; Neidhart, D.J.; VanDrie, J.; Kempf, D.J.; Wang, X.C.; Norbeck, D.W.; Plattner, J.J.; Rittenhouse, J.W.; Turon, M.; Wideburg, N.E.; Kohlbrenner, W.E.; Simmer, R.; Helfrich, R.; Paul, D.A.; Knigge, M. *Science*, **1990**, *249, 527-533;*
2. Kempf, D.J.; Norbeck, D.W.; Codacovi, L.; Wang, X.C.; Kohlbrenner, W.E.; Wideburg, N.E.; Paul, D.A.; Knigge, M.F.; Vasavanonda, S.; Craig-Kennard, A.; Saldivar, A.; Rosenbrook, Jr.,W.; Clement, J.J.; Plattner, J.J.; Erickson,.J. *J. Med. Chem.*, **1990**, *33*, 2687-2689.
3. (a) Chenera, B.; Boehm, J.C.; Dreyer, G.B. *Bioorganic & Medicinal Chemistry Letters*, **1991**, *1*, 219-222.
   (b) Jadhav, P.K.; Woerner, F.J. *Bioorganic & Medicinal Chemistry Letters*, **1992**, *2*, 353-356.
4. (a) Winchester, B.; Fleet, G.W. *Glycobiology*, **1992**, *2*, 199-210.
   (b) Look, G.C.; Fotsch, C.H.; Wong, C.-H. *Acc. Chem. Res.*, **1993**, *26*, 182-190.
5. (a) Duréault, A.; Greck,.C.; Depezay, J.C. *Tetrahedron Lett.* **1986**, *27*, 4157-4160.
   (b) Le Merrer, Y.; Duréault, A.; Greck,.C.; Micas-Languin, D.; Gravier, C.; Depezay, J.C. *Heterocycles*, **1987**, *25*, 541-548.
6. Duréault, A.; Tranchepain, I.; Depezay, J.C. *J. Org. Chem.*, **1989**, *54*, 5324-5330.
7. (a) Fitremann, J.; Duréault , A.; Depezay, J.C. *Tetrahedron Lett.*, **1994**, *35*, 1201-1204.
   (b) Fitremann, J.; Duréault , A.; Depezay, J.C. *Synlett*, **1995**, *3*, 235-237.
8. Bäckvall, J-E.; Schink, H.E.; Renko, Z.D. *J. Org. Chem.*, **1990**, *55*, 826-831.

9. Katoh, T.; Nagata, Y.; Kobayashi, Y.; Arai, K.; Minami, J.; Terashima, S. *Tetrahedron Lett.* **1993**, *36*, 5743-5746.
10. Jurczak, J., Bauer, T., Chmielewski, M. *Carbohydr. Res.*, **1987**, *164*, 493-498.
11. (a) Haines, A.H. *Carbohydr. Res.*, **1965**, *1*, 214-228; (b) Tipson, R.S.; Cohen, A. *Carbohydr. Res.*, **1965**, *1*, 338-340.
12. Kuszmann, J.; Sohar, P. *Carbohydr. Res.*, **1980**, *83*, 63-72.
13. (a) Machinaga, N.; Kibayashi, C. *J. Org. Chem.*, **1991**, *56*, 1386-1393
    (b) Machinaga, N.; Kibayashi, C. *Synthesis*, **1992**, 989-994.
14. David, S.; Hanessian, S. *Tetrahedron* , **1985**, *41*, 643-663.
15. (a) Marzi, M.; Misiti, D. *Tetrahedron Lett.* **1989**, *30*, 6075-6076.
    (b) Duréault, A.; Portal, M.; Depezay,.J.C. *Synlett*, **1991**, *4*, 225-226.
16. (a) Takano,S.; Moriya, N.; Suzuki, M.; Iwabuchi, Y.; Sugimura, T.; Ogasawara, K. *Heterocycles*, **1990**, *31*, 1555
    (b) Carreaux, F.; Duréault, A.; Depezay, J.C. *Synlett*, **1992**, *6*, 527-529.
17. Machinaga, N.; Kibayashi, C. *J. Org. Chem.*, **1992**, *57*, 5178-5189.

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