

New C_2 Symmetric Bis-Aziridines

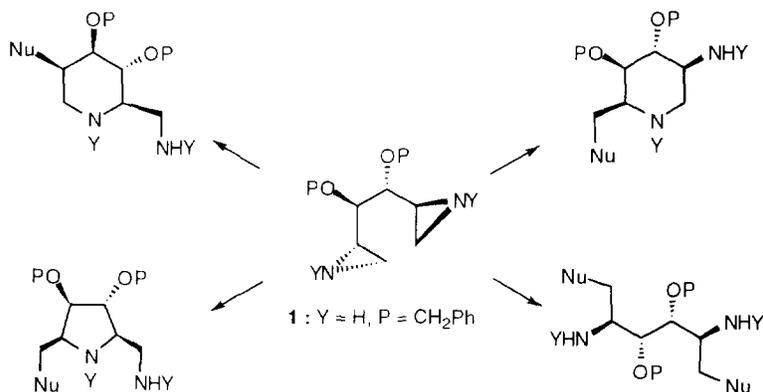
Efficient Synthesis of (2*S*,5*S*)-1,6-Di(*p*-toluenesulfonyloxy)-2,5-Hexanediol, and (2*S*,3*E*,5*S*)-1,6-Di(*p*-toluenesulfonyloxy)-2,5-Hexanediol

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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 diazidodisols 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 acids². Aziridine bis-opening offers a flexible and enantioselective synthesis of a range of symmetric inhibitors which is not limited to amino acid derived substituents³.

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 enzymes⁴.

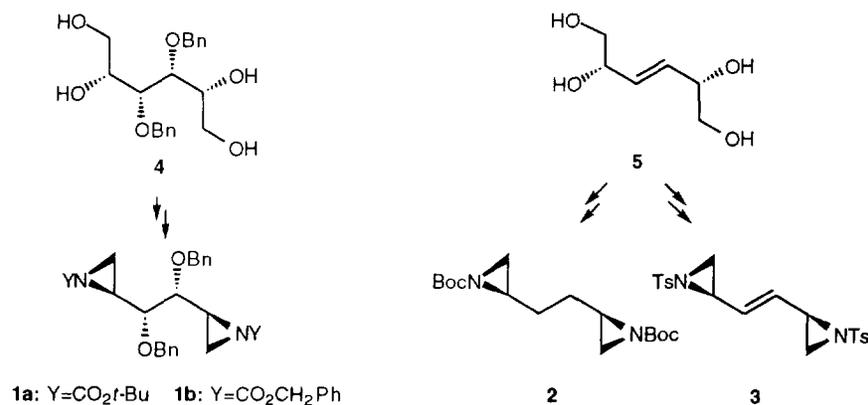
Our initial studies referred to the synthesis of 3,4-di-*O*-isopropylidene-D-mannitol-derived bis-aziridines⁵ and the study of their reactivity towards various nucleophiles⁶. Opening of both aziridine rings provided access to a variety of C_2 symmetric diamino diols, while nucleophilic opening followed 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*-heterocyclization⁷.

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 structure⁸. 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 antibiotic⁹.

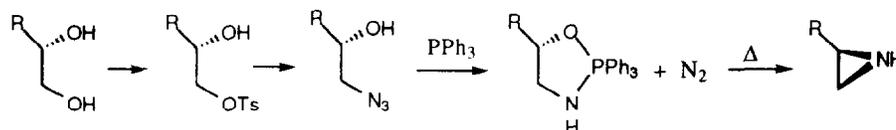
Considering the versatility of reactivity of C_2 symmetric bis-aziridines, and their potentiality as precursors, in a one step procedure, of a wide range of *cis*-2,5-disubstituted pyrrolidines, we have carried out the preparation of **1** as its *N*-Boc (**1a**) and *N*-Cbz (**1b**) derivatives, and 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 developed⁵.

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-mannitol¹¹ was the common precursor of **2** and **3** (scheme 2).



Scheme 2

The transformation of each terminal 1,2-diol into the *NH*-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.



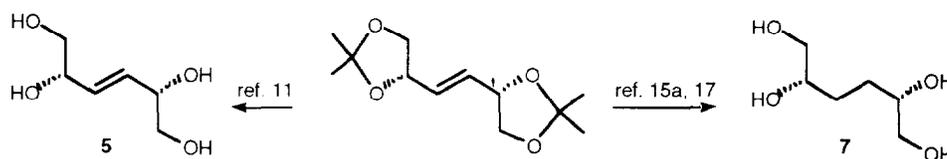
The selectivity of tosylation at the primary oxygens of C₂ symmetric 1,2,5,6-D-mannitol-derived tetrols is subordinate to the steric hindrance at C-2 and C-5. Whereas 3,4-di-*O*-isopropylidene-D-mannitol is 1,6-ditosylated in 80% yield by conventional manner⁵ (TsCl, pyridine, 0°C), 3,4-di-*O*-benzyl-D-mannitol **4** provides the corresponding 1,6-ditosylate **6** in only 48% yield after purification⁷. 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 been 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% yield¹³. Selective activation of the primary hydroxyl groups even using the more bulky 1-naphthalenesulfonyl chloride provided the 1,6-di-*O*-naphthalenesulfonyl derivative in only 42% yield^{13b}.

The regioselective manipulation of hydroxyl groups via organotin derivatives has found large applications in the field of carbohydrates¹⁴, and more recently in the one of acyclic polyols. Dibutylstannylene acetals deriving from acyclic primary-secondary diols have been shown to react with both alkylating¹⁵ and sulfonylating¹⁶ reagents to give as a general rule higher regioselectivity for reaction at the primary oxygen than does direct reaction.

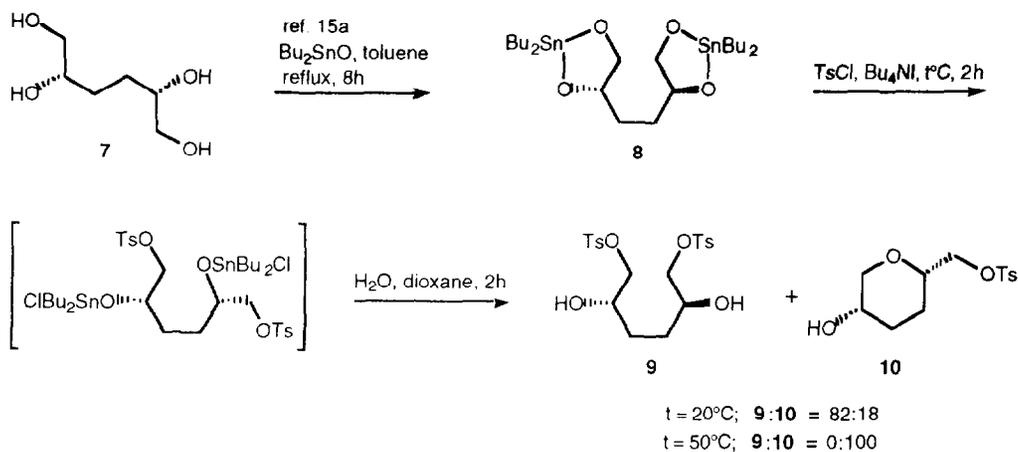
In an alternative procedure for regioselective tosylation of **7** we tested utilization of the organotin derivative **8**^{15a} easily available from **7** (scheme 3). The benzylation and the benzylation of organotin derivative **8** had been previously reported. Although the benzylation of **8** yielded the 1,6-dibenzyl ether in 60% yield^{15a}, unexpectedly its benzylation 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-Al₂O₃ 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 ¹³C NMR spectrum analysis of the crude C₂ 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**.

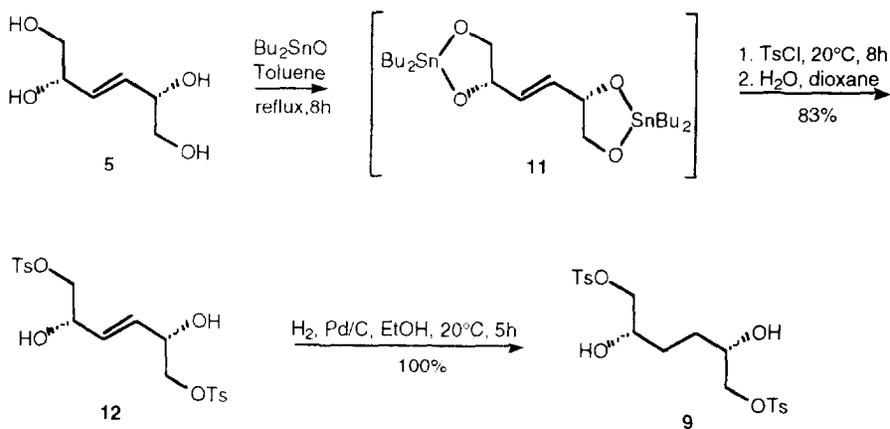
Starting from the tetrol **7**, compound **9** results from the regioselective bis-tosylation at the primary oxygens of the tin acetal, and the pyran **10** from the intramolecular displacement of the 1-O-tosyl group by the oxygen at C-5, of the intermediate secondary tin alcoholate.



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 sulfonation, through stannylidene activation of the ethylenic tetrol **5**, and reduction of the resulting ethylenic ditosylate yielded the ditosylate **9** (scheme 4).



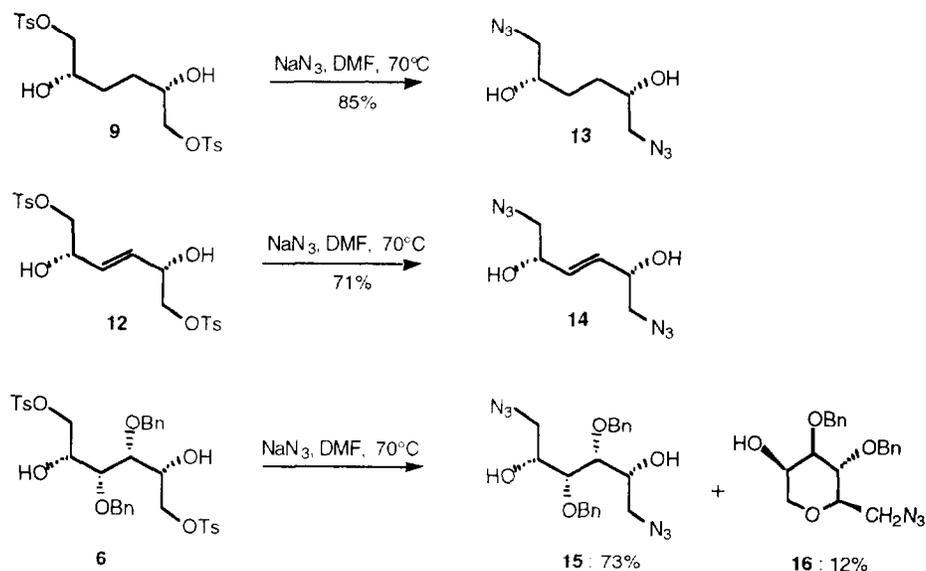
Scheme 4

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 (*2S,3E,5S*)-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 dibutyltin oxide, 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).

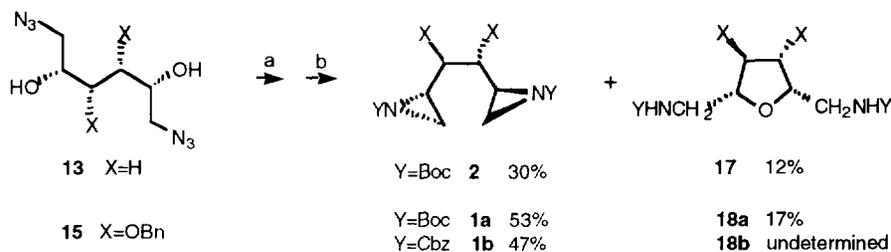
Starting from **6** we could not prevent the formation of 12% of the pyran **16** besides **15**, which results from the competitive attack of a secondary hydroxyl group onto a primary *O*-sulfonylated carbon; however such cyclization was not observed starting from the conformationally flexible ditosylate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



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.



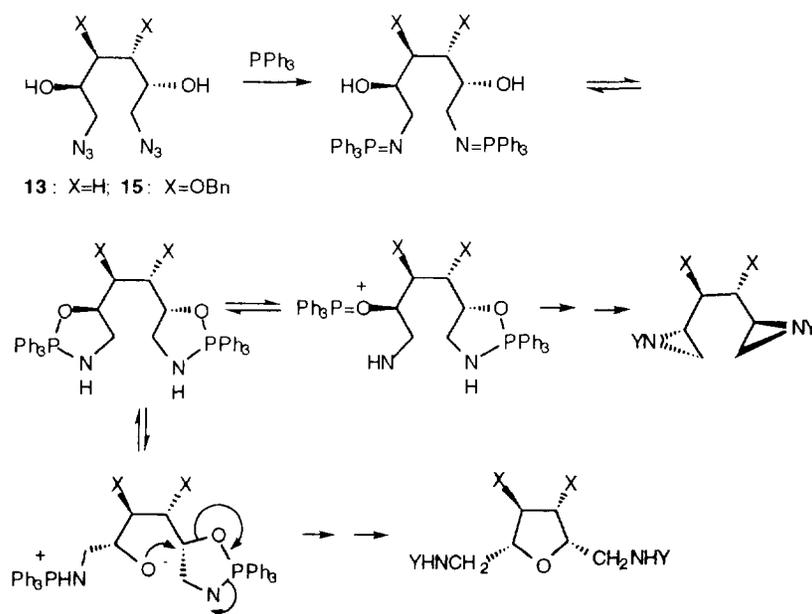
a) Ph_3P , PhCH_3 , 35°C , 2h, then 90°C , 8h.

b) $(\text{CO}_2\text{tBu})_2\text{O}$, Et_3N , THF, 0°C to rt, 3h, or: $\text{ClCO}_2\text{CH}_2\text{Ph}$, 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.



Scheme 7

PPh₃ 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 *NH* 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*-tolucenesulfonyloxy)-2,5-hexanediol, useful precursor of C₂ 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 (Et₂O) were distilled from sodium-benzophenone and dichloromethane (CH₂Cl₂) from P₂O₅. CH₂Cl₂ and ethyl acetate (AcOEt) were filtered on K₂CO₃ prior to use. ¹H NMR (250MHz) and ¹³C NMR (62.9MHz) spectra were recorded in CDCl₃ (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 ¹³C 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-Al₂O₃ (200mg) at 1 atm. for 14h, as previously described^{15a,17}. After filtration and concentration, the residue (2g) was diluted in 80% aqueous trifluoroacetic 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 crystallized (1.3g, 97%) : mp 81°C; [α]_D -16 (*c* 2.11, CH₃OH) (lit^{14a} : mp 84°C, [α]_D -24; lit¹⁷ : mp 93-94°C, [α]_D -24; ¹³C NMR (D₂O) 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 Bu₂SnO (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 Bu₄N⁺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 CH₂Cl₂ (3x50ml), the organic layer was washed with a 1N Na₂S₂O₃ 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 ¹³C NMR signals δ : 20.7 (CH₃); 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+NH₄⁺, 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 : [α]_D -10; [α]₃₆₅ -30 (c 1.10, CH₂Cl₂); 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, CH₃); 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} = J_{4eq,6eq} ≈ 2 Hz, H-6eq); 4.02 (d, 2H, H-1, H-1'); ¹³C NMR (126 MHz; CDCl₃) δ: 21.6 (CH₃); 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+NH₄⁺, 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, CH₃); 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}); ¹³C NMR (126 MHz; CDCl₃) δ: 21.6 (CH₃); 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+NH₄⁺, 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 Bu₂SnO (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 tinactal **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 CH₂Cl₂ (3x50ml), the organic layer was dried with MgSO₄ 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; [α]_D -7.5; [α]₃₆₅ -33 (c 0.815, CH₂Cl₂); ¹H NMR δ : 2.24 (d, 2H, J_{OH,2} = 4.5 Hz, OH), 2.44 (s, 6H, CH₃), 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}); ¹³C NMR δ : 21.5 (CH₃), 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 C₂₀H₂₄O₈S₂: 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 crystals: m p 124°C; [α]_D -2; [α]₃₆₅ -6 (c 0.895, DMF); ¹H NMR δ : 1.40-1.65 (m, 4H, H-3, H-3'); 2.44 (s, 6H, CH₃); 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}); ¹³C NMR δ : 21.7 (CH₃); 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 C₂₀H₂₆O₈S₂: 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. CH₂Cl₂ (50ml) and brine (10ml) were added to the residue, the aqueous phase was extracted with CH₂Cl₂ (3x50ml). The organic layer was dried over MgSO₄, 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**) : [α]_D +1.5; [α]₃₆₅ +4.0 (c 0.87, CH₂Cl₂); 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); ¹³C NMR δ : 30.6 (C-3); 57.0 (C-1); 70.7 (C-2). Anal. calcd for C₆H₁₂N₆O₂: 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/Et₃N 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.

(2*R*,2'*R*)-(1,2-Ethan-diyl) bis (1-tert-butoxycarbonyl)-aziridine (**2**) : mp 71-73°C; ν_{\max} (film): 1720, 1320, 1230; ¹H NMR δ : 1.3-1.5 (m, 18H, CH₃); 1.5-1.8 (m, 4H, CH₂); 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); ¹³C NMR δ : 27.9 (CH₃); 29.5, 31.8 (CH₂, C-3); 37.2 (C-2); 80.9 (C(CH₃)₃); 162.5 (CO). HRMS calcd for C₁₆H₂₈N₂O₄ (M⁺): 312.2049, found: 312.2050.

(2*R*,5*S*)-2,5-Di-*N*-tert-butoxycarbonylaminomethyl-3,4-dihydro-furan (**17**) : ν_{\max} (film): 3450, 3350, 1710, 1170, 1090; ¹H NMR δ : 1.3-1.7 (m, 20H, CH₃, H-3); 1.8-2.0 (m, 2H, H-3'); 3.04 (m, 2H, CH₂N); 3.32 (m, 2H, CH₂N); 3.85-4.1 (m, 2H, H-2); 4.7-5.0 (m, 2H, NH); ¹³C NMR δ : 28.2 (C-3); 28.3 (CH₃); 44.8 (CH₂N); 78.7 (C-2); 79.2 (C(CH₃)₃); 156.2 (CO); CIMS *m/z*: 331 (M+H⁺, 20%); Anal. calcd for C₁₆H₃₀N₂O₅: C, 58.16; H, 9.15; N, 8.48. Found: C, 58.93; H, 9.23; N, 8.34.

(2*R*,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, tars were 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 H₂O (1ml). After concentration, the residue was extracted with ether and the etheral layer dried over MgSO₄. Solvent evaporation and flash chromatography eluting with AcOEt/cyclohexane/Et₃N 3:7:0.01, gave **3** (30mg, 13%); ¹H NMR (90MHz) δ : 2.1 (d, 2H, J_{1,2} = 5 Hz, H-3); 2.4 (s, 6H, CH₃); 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 C₂₀H₂₂N₂O₄S₂ (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 NaHCO₃ (3%, 150ml), dried (MgSO₄) 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; [α]_D +32 (c 1.06; CH₂Cl₂); ¹H NMR δ : 2.41 (s, 6H, CH₃); 2.79 (d, 2H, J_{H1O,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, OCH₂Ph); 7.13-7.74 (m, 18H_{arom}); ¹³C NMR δ : 21.6 (CH₃); 69.5 (C-2), 76.5 (C-3); 71.3, 73.9 (C-1, C_{CH2}Ph); 128.0, 128.1, 128.3, 128.5, 129.9, 132.5, 136.9, 145.0 (C_{arom}). Anal. calcd for C₃₄H₃₈O₁₀S₂: 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 CH₂Cl₂. The extract was dried (MgSO₄), 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; [α]_D +78 (c 1.36; CH₂Cl₂); ¹H NMR δ : 3.26 (d, 2H, J_{H1O,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, CH₂Ph) 7.27-7.40 (m, 10H, H_{arom}); ¹³C NMR δ : 53.6 (C-1); 71.1 (C-2), 76.8 (C-3); 73.9 (C_{CH2}Ph); 128.5, 128.7, 136.6 (C_{arom}). Anal. calcd for C₂₀H₂₄N₆O₄: 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; [α]_D +16.5 (c 1.04; CH₂Cl₂); 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, OCH₂Ph); 4.66, 4.74 (AB, 2H, J_{AB} = 12 Hz, OCH₂Ph); 7.15-7.55 (m, 10H_{arom}); ¹³C NMR δ : 51.7 (C-1); 66.7 (C-2); 69.2 (C-6); 71.7, 75.3 (C_{CH2}Ph); 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+NH₄⁺, 100%); 342 (62%). Anal. calcd for C₂₀H₂₃N₃O₄: 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 / Et₃N provided NH-bis-aziridine **1** as an oil.

(2*S*,2'*S*)-[(1*R*,2*R*)-1,2-Dibenzoyloxy-ethan-diyl] bis-aziridine (**1**): ¹H 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, CHOBn); 4.66, 4.77 (AB, 4H, J = 12 Hz; CH₂Ph); 7.2-7.4 (m, 10H_{arom}); ¹³C NMR δ: 20.99 (C-3); 30.62 (C-2); 72.64 (CH₂Ph); 81.92 (CHOBn); 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 crystallized (0.826g, 53%) and furan **18a** as an oil (0.274g, 17%).

(2*S*,2'*S*)-[(1*R*,2*R*)-1,2-Dibenzoyloxy-ethan-diyl] bis (1-tert-butoxycarbonyl)-aziridine (**1a**): mp 65°C; [α]_D -100 (c 1.59, CH₂Cl₂); ν_{max} (film): 1720, 1320, 1220 cm⁻¹; ¹H NMR δ 1.45 (s, 18H, C(CH₃)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, CHOBn); 4.73, 4.89 (AB, 4H, J = 16.5 Hz, CH₂Ph); 7.25-7.40 (m, 10H, H_{arom}); ¹³C NMR δ: 26.8 (C-3); 27.7 (CH₃); 38.2 (C-2); 71.6 (OCH₂Ph); 79.4 (CHOBn); 81.3 (C(CH₃)₃); 127.8, 128.1, 128.3, 137.9 (C_{arom}); 162.0 (CO). Anal. calcd for C₃₀H₄₀N₂O₆: 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**): [α]_D +21.6 (c 1.12, CH₂Cl₂); ν_{max} (film): 3450, 3360, 1710, 1090 cm⁻¹; ¹H 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, OCH₂Ph); 4.50 (m, 2H, OCH₂Ph); 4.80 (m, 1H, NH); 5.00 (m, 1H, NH); 7.20-7.45 (m, 10H, H_{arom}); ¹³C NMR δ: 28.4 (CH₃); 40.1, 42.9 (C-1, C-6); 71.5, 71.9 (OCH₂Ph); 79.2 (C(CH₃)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+NH₄⁺, 10%); 543 (M+H⁺, 100%). Anal. calcd for C₃₀H₄₂N₂O₇: 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 NH-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/Et₃N afforded **1b** as a white solid, (0.35 g, 47%).

(2*S*,2'*S*)-[*(1R,2R)*-1,2-Dibenzoyloxy-ethan-diyl] bis (1-benzoyloxycarbonyl)-aziridine (**1b**): mp 69°C; [α]_D -80.5 (c 1.01, CH₂Cl₂); 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, CHOBn); 4.66, 4.85 (AB, 4H, J_{AB} = 12 Hz, OCH₂Ph); 5.10, 5.16 (AB, 4H, J_{AB} = 8 Hz; CO₂CH₂Ph); 7.15-7.45 (m, 20H_{arom}); ¹³C NMR δ 27.5 (C-1); 38.3 (C-2); 68.40 (OCH₂Ph); 72.1 (CO₂CH₂Ph); 79.4 (CHOBn); 127.7, 128.2, 128.6, 135.6, 137.8 (C_{arom}); 162.9 (CO). Anal. calcd for C₃₆H₃₆N₂O₆: C, 72.95; H, 6.12; N, 4.73. Found: C, 71.85; H, 6.16; N, 4.61.

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