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Synthesis and nucleophilic opening of a new C_2 symmetric bis-aziridine. First synthesis of aziridines using polymer-supported triphenylphosphine

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Abstract—The synthesis of (2*S*,2′*S*)-2,3-bis(aziridin-2-yl)quinoxaline **4** from D-mannitol is reported. Reductive aminocyclization of diazidodiols has been achieved by polymer-supported PPh_3 in a suitable manner. The *N*-Boc and *N*-Tos aziridines **4b** and **4c** have been reacted with different nucleophiles either in protic or aprotic media.

1. Introduction

N-Protected bis-aziridines derived from D-mannitol are versatile building blocks for the synthesis of a wide range of compounds of biological interest.[1–4] We have already disclosed the synthesis of conformationally restricted[5] (**1**: X=*O*-isopropylidene) and flexible[6,7] (**2**: X=*O*-Bn, **3**: X=H) bis-aziridines as well as results concerning their reactivity towards various nucleophiles (Fig. 1).

Bis-opening of the aziridine rings at C-1 and C-6 leads to C_2 symmetric diaminodiols **A**.[7–11] When hydroxylated at carbons 3 and 4, diamines **A** can be the precursors of either the central core unit of a class of non hydrolysable HIV-1 protease inhibitors[2] or enantiopure α-aminoaldehydes[8] and acids.[9] Regioselective opening at C-1 or C-2 and subsequent regioselective intramolecular heterocyclization enables the preparation of pyrrolidines **B**[3,7,10,11] and piperidines **C**[8,9] or **D**.[3,7,11] 3,4-Deoxy cyclic derivatives have a structure close to that of many natural alkaloids,[12,13] whereas enantiopure polyhydroxylated nitrogen heterocycles constitute an important class of glycosidase inhibitors.[14] These cyclic templates can be functionalized independently at different sites: ring nitrogen, exocyclic amino group, newly introduced nucleophile and through derivatization of the substituents at C-3 and C-4. A bis-aziridine fused with an aromatic ring through the C_3–C_4 bond should lead to compounds with high potentiality as scaffolds, due to a semi-rigid conformation and a relative lipophilic character. Therefore, we have carried out the synthesis of bis-aziridine

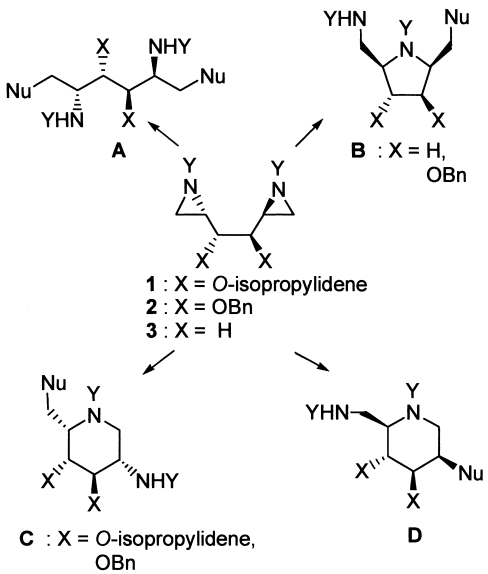
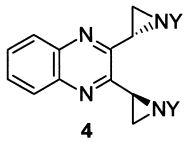


Figure 1.

4 attached with a quinoxaline ring through the C-3 and C-4 bond and studied its reactivity.



We have previously shown that the orientation of the nucleophilic attack of aziridines **1**–**3** was influenced notably by the substitution pattern at nitrogen, the nature of the nucleophile and by the presence of Lewis acids or protic

Keywords: heterocyclization; quinoxaline; aziridines.

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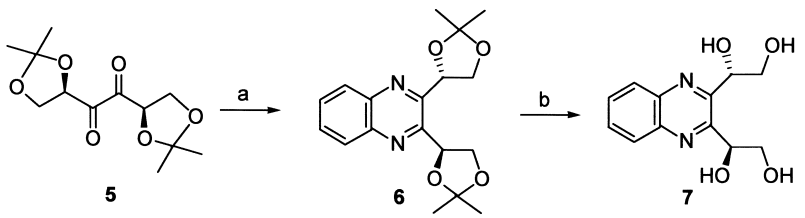
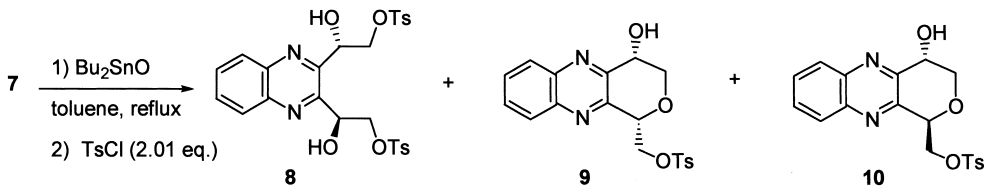


Scheme 1. *Reagents and conditions*: (a) 1,2-phenylenediamine, CH_2Cl_2, room temperature, 1 h, 98%; (b) AcOH/H_2O, reflux, 4 h, 90%.



Scheme 2.

reaction media. Thus, compounds of type **A** and **C** have always been obtained in aprotic solvent.[8] The regioselectivity of intramolecular heterocyclization is highly dependent on the substituents at C-3 and C-4 of the carbon chain. Indeed, when C-3 and C-4 are involved in a cyclic acetal, heterocyclization yielding piperidines **C** exclusively occurs for steric reasons. However, high regioselectivity towards any of these three heterocycles can be reached with conformationally flexible bis-aziridine **2**.

We report here the synthesis of (2*S*,2′*S*)-2,3-bis(aziridin-2-yl)quinoxaline **4**, a new bis-aziridine, by triphenylphosphine-mediated reductive aminocyclization of the α-azidoalcohol **12**. Moreover, we show for the first time that *N*H-aziridines **1**, **2** and **4** are cleanly obtained when the reaction is carried out with polymer-supported PPh_3. Our results using this new experimental procedure are compared to those previously obtained in solution. We also present results concerning the reactivity of **4** towards nucleophilic opening and heterocyclization in protic and aprotic solvents.

2. Results and discussion

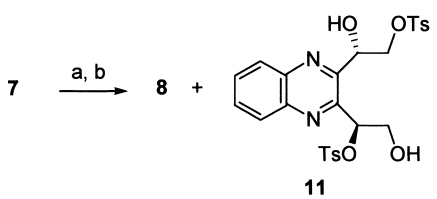
The D-mannitol derived diketone **5** previously described by Kuszmann[15] was prepared in two steps (selective acetalization and oxidation in Moffat conditions) and was the precursor in the synthesis of bis-aziridine **4**. The coupling of 1,2-phenylenediamine with **5** at room temperature furnished quinoxaline derivative **6** in 98% yield, which was subsequently hydrolyzed under acidic conditions to yield **7** (Scheme 1).

The transformation of each terminal 1,2-diol into a *N*H-aziridine ring involves selective tosylation at the primary hydroxyl groups, sodium azide substitution and reductive aminocyclization of the resulting azidoalcohol, with inversion of configuration at the secondary carbon. In order to obtain the bis-aziridine **4**, these different steps have to take place independently at both extremities of the symmetric tetraol **7**.

The tosylation selectivity of C_2 symmetric 1,2:5,6-D-mannitol-derived tetraols at the primary hydroxyl group is closely related to the steric hindrance at C-2 and C-5. The tosylation of **7** in standard conditions (TsCl, pyridine, 0°C)[5] led to a complex mixture of products whose separation was difficult. These products include pyrans whose formation is favoured by the conformation of the carbon backbone. Therefore, we turned towards the organotin-mediated tosylation previously employed.[6] Formation of dibutylstannylene acetals under stoichiometric conditions followed by in situ reaction with TsCl led to bis-tosylated compound **8** (56% yield) in addition to pyran **9** (9% yield) at room temperature, whereas at 60°C, cyclization predominated leading to pyran **9** in 58% yield along with **8** and **10** (Scheme 2).

Compounds **8** and **9** result from the regioselective bis-tosylation at the primary oxygens of the tin acetal. Intramolecular displacement of the 1-*O*-tosyl group by the oxygen at C-5 of the intermediate secondary tin alcoholate provides **9**. Pyran **10** derives from intramolecular displacement of a secondary tosylate competitively formed at 60°C.

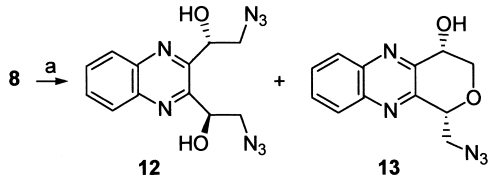
We have carried out the tosylation of **7** under the catalytic organotin conditions first described by Maki et al.[16] for selective monobenzoylation of diols and recently used by Martinelli et al.[17] for tosylation (Scheme 3). Interestingly, these conditions led quantitatively to an optimal 8/2 mixture of ditosylates **8** and **11**. These derivatives were separated for characterization purposes and the following azidation step



Scheme 3. *Reagents and conditions*: (a) Me_2SnCl_2 (1 mol%), K_2CO_3; (b) TsCl, 0°C, 4 h then room temperature, 12 h.

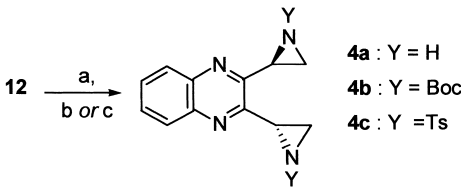
was performed on **8**; such purification is not necessary since both **8** and **11** are the precursors of the same bis-aziridine **4**.

Sodium azide substitution of the 1,6-ditosylate **8** carried out at 70°C for 3 h resulted in the formation of diazidodiol **12** (68%) besides pyran **13** (12%) (Scheme 4).



Scheme 4. *Reagents and conditions*: (a) NaN_3, DMF, 70°C, 4 h.

Reductive aminocyclization of the diazidodiol **12** by triphenylphosphine led to **4a** and after nitrogen protection, to the *N*-Boc bis-aziridine **4b** and *N*-Tos bis-aziridine **4c** in 60 and 50% yields, respectively (Scheme 5). In the course of the carbamoylation reaction, some epimerization took place since formation of 3% of the bis-aziridine *meso* **4b′** has been observed.



Scheme 5. *Reagents and conditions*: (a) PPh_3, THF, reflux 15 h; **4a** (b) Boc_2O, Et_3N, THF, 0°C to room temperature, 2 h, 60%; or (c) TsCl, Et_3N, DMF, −5°C, 2 h, 50% (two steps).

We describe, to our knowledge, the first example of reductive aminocyclization of an α-azidoalcohol using polymer-supported PPh_3 although a solid-supported iminophosphorane has previously been reported[18] in the Staudinger reaction.

Indeed, in the course of the reductive aminocyclization step, 1 equiv. of triphenylphosphine oxide is formed which in liquid phase cannot be completely removed from the reaction medium and prevents correct characterization of the *N*H-bis-aziridine **4a** and in a general manner complicates the *N*-protected aziridine purification. To circumvent these problems, we used polymer-supported PPh_3 for the Staudinger reaction of the diazidodiol **12** and then extended the procedure to other substrates, precursors of **1a** and **2a**.

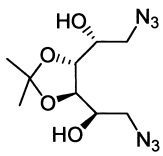
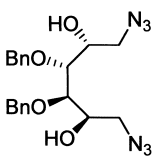
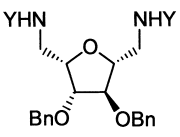
Three equivalents of polymer-supported PPh_3 (2% DVB, ~3 mmol/g resin, Aldrich) were used under conditions (solvent, temperature, time) identical to those used in the liquid phase, as depicted in Table 1. In each case, the crude aziridine was obtained quantitatively and ^1H and ^{13}C NMR spectra have shown a purity >90%.

This procedure is quite efficient for the synthesis of aziridines since it provides the bis-aziridines **4a** and **1a** in good yields (entries 1 and 2). It is noteworthy that, when reacted with polymer-supported PPh_3, the di-*O*-benzyl-diazidodiol (entry 3) led to a 1/1 mixture of the expected *N*H bis-aziridine **2a** and of the furan **14**. Under these conditions, formation of the furan allowed by the flexibility of the carbon chain is favoured up to >45% while it is limited to 15% in liquid phase.[6]

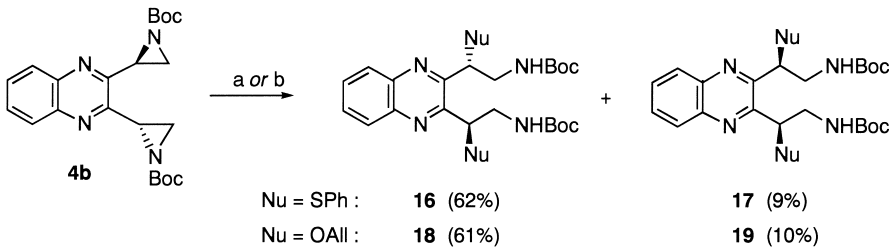
This difference could result from the fact that with PS-PPh_3 both oxazaphospholidines are not formed simultaneously. Thermal decomposition of the oxazaphospholidines leads to **2a**, while furan **14** results from a competitive intramolecular substitution by the hydroxyl group at the secondary site of the intermediate oxazaphospholidine. Compound **14** presents the D-*gluco* configuration, resulting from an inversion of configuration at C-2, since after *N*-carbamoylation (Y=Boc), the analytical data of the amino protected derivative were found identical to those previously reported for **15**.[6]

We have carried out the nucleophilic opening of the activated bis-aziridine **4b** or **4c** by sodium thiophenate, allylic alcohol, acetic acid and benzylamine. Unsurprisingly, ring-opening of **4b** and **4c** proceeds with high selectivity at the benzylic carbons and the reaction is oriented mostly towards bis-opening rather than heterocyclization.

Table 1. Prepared bis-aziridines using polymer-supported PPh_3

Entry	Diazidodiol	Conditions	Products[a]
1	**12**	PS-PPh_3 (3 equiv.) THF, 40°C, 1.5 h then reflux, 15 h	**4a**
2		PS-PPh_3 (3 equiv.) toluene, 40°C, 1.5 h then 105°C, 15 h	**1a**
3		PS-PPh_3 (3 equiv.) toluene, 40°C, 1.5 h then 90°C, 9 h	**2a** + **14** (Y = H) (1:1) ↓ **15** (Y = Boc) 

[a] The crude aziridines were obtained quantitatively and spectroscopic data have shown a purity >90%.

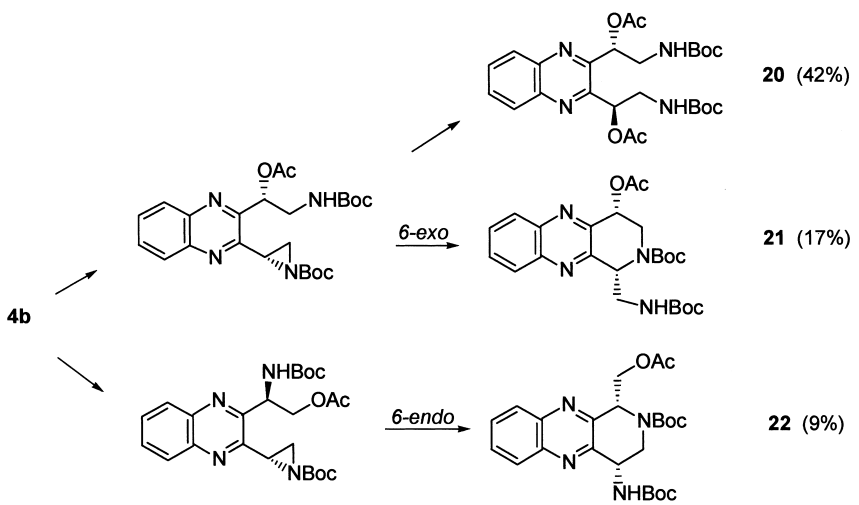


Scheme 6. *Reagents and conditions*: (a) PhSNa (2 equiv.), 0°C, 2 h; (b) AllOH, $Yb(OTf)_3$ (10 mol%), −10°C, 1 h then room temperature, 2 h.

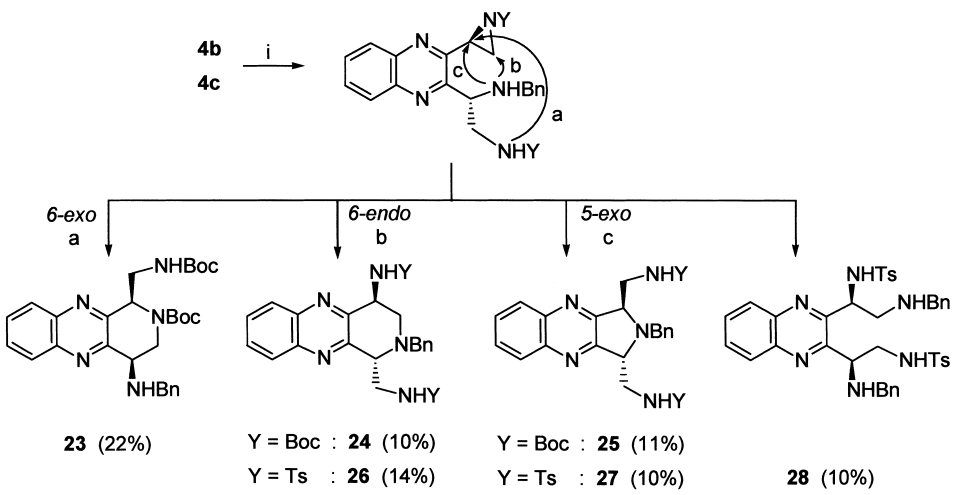
Compound **4b** underwent only symmetrical bis-substitution by sodium thiophenate, irrespective of the temperature (0 or −20°C), yielding **16** (62%) together with *meso* diastereomer **17** (9%). Reaction of **4b** with AllOH under ytterbium triflate catalysis under the conditions previously reported for **2b**[3] furnished the symmetrical diamino compounds **18** and **19** in 61 and 10% yields, respectively (Scheme 6). In aprotic medium or in the presence of $Yb(OTf)_3$, some epimerization occurred showing that the substitution presents a partial S_N1 character.

Since C–N bond cleavages of both aziridines are not simultaneous, the resulting intermediate of the first aziridine ring-opening can either undergo the attack of a second external nucleophile (bis-opening) or itself carry out the intramolecular opening of the second aziridine ring (heterocyclization). From bis-aziridines **1**–**3**, formation of the heterocyclic compound was favoured, whereas in the case of **4b**, bis-opening is faster than heterocyclization probably because of the smaller steric hindrance at the benzylic site.

Reaction of AcOH with **4b** was slow and nucleophilic attack took place mainly at C-2. Although symmetrical



Scheme 7. *Reagents and conditions*: (a) AcOH/THF (1:1), room temperature, 24 h.



Scheme 8. *Reagents and conditions*: (i) from **4b**: $BnNH_2$ (1 equiv.), $Yb(OTf)_3$ (10 mol%), CH_3CN, reflux, 24 h; from **4c**: $BnNH_2$ (1 equiv.), THF, room temperature, 12 h.

bis-opening was the major pathway, giving **20**, each mono-substituted intermediate furnished a cyclic compound, that is, piperidines **21** and **22** (Scheme 7).

Aminolysis of *N*-Boc aziridine[19] **4b** was achieved under ytterbium triflate catalysis but such activation was not necessary for the more reactive *N*-Tos aziridine **4c**. Nucleophilic opening by benzylamine took place with a complete regioselectivity at the secondary carbon leading to an α-diamino intermediate apt to cyclize from both nitrogen atoms (Scheme 8).

From *N*-Boc **4b**, the reaction was slow and required high temperature. Only heterocyclization occurred to give piperidine and pyrrolidine compounds **23**–**25**. Cyclization was not observed from *N*HTos of **4c** but from *N*HBn to yield compounds **26** and **27** along with unsymmetrically substituted product **28**.

3. Conclusion

In conclusion, we have accomplished the synthesis of a new enantiopure bis-aziridinyl-quinoxaline **4** starting from D-mannitol. Nucleophilic opening of **4** with various reagents shows that bis-opening is always favoured compared to heterocyclization.

Moreover, we show that the synthesis of aziridines by reductive aminocyclization of the α-azidoalcohol using polymer-supported PPh_3 is a very efficient method since the aziridines are isolated in quantitative yields without by-products. In the special case of a bis-aziridine, a competitive intramolecular evolution is possible depending on the flexibility of the backbone.

This procedure is quite adaptable to any α-azidoalcohol, allowing studies of the reactivity of *N*H-aziridine towards nucleophiles and considerably facilitating the purification of *N*-protected aziridines, such as *N*-benzyl.

4. Experimental

General directions. Prior to use, tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from sodium–benzophenone and dichloromethane (CH_2Cl_2) from CaH_2. CH_2Cl_2 and ethyl acetate (EtOAc) were filtered on K_2CO_3 prior to use. ^1H NMR (250 MHz) and ^{13}C NMR (63 MHz) spectra were recorded on a Brucker AM 250. Chemical shifts (δ) are reported in ppm. Specific rotations were measured on a Perkin–Elmer 241C polarimeter with sodium (589 nm) lamp. Mass spectra were recorded by the Service de Spectrométrie de Masse, Ecole Normale Supérieure, 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. Flash chromatography was performed with Merck Kieselgel 60 (200–500 μm); the solvent systems were given v/v. Spectroscopic (^1H and ^{13}C NMR, MS) and/or analytical data were obtained using chromatographically homogeneous samples.

4.1. (1*S*,1′*S*)-2,3-Bis(3,3-dimethyl-[2,4]dioxolanyl)-quinoxaline (6)

To a solution of 1,2:5,6-di-*O*-isopropylidene-D-*threo*-3,4-hexodiulose **5** (5.68 g, 22 mmol) in anhydrous CH_2Cl_2 (40 mL) was added 1,2 phenylenediamine (2.4 g, 22.2 mmol) dissolved in CH_2Cl_2 (30 mL). After 1 h stirring at room temperature, the mixture was washed with HCl 1N (2×50 mL), with brine (50 mL) and dried (Na_2SO_4). After evaporation to dryness, compound **6** (7.21 g, 98%) was obtained as a pale tan solid. A sample was purified by column chromatography (cyclohexane/EtOAc, from 9:1 to 7:3), R_f 0.66 (cyclohexane/EtOAc, 7:3), mp 105°C; $[\alpha]_D^{20}=+4$ (*c* 1.0, CH_2Cl_2). ^1H NMR ($CDCl_3$) δ 1.46, 1.52 (2s, 12H, CH_3), 4.44 (dd, $^2J=8.4$ Hz, $^3J=6.4$ Hz, 2H, CH_2), 4.70 (dd, $^2J=8.4$ Hz, $^3J=6.4$ Hz, 2H, CH_2), 5.69 (dd, $^3J=6.4$ Hz, 2H, CH), 7.6–7.8 (m, 2H, H_{arom}), 8.0–8.2 (m, 2H, H_{arom}); ^{13}C NMR ($CDCl_3$) δ 26.0, 26.4 (CH_3), 67.9 (CH_2), 75.0 (CH), 110.5 ($C(CH_3)_2$), 129.2, 129.9 (CH_{arom}), 141.0, 152.2 (Cq_{arom}); CIMS (NH_3) *m*/*z*: 331 (MH^+, 100%), 273 ($MH^+-[C_3H_6O]$, 90%), 215 ($MH^+-2[C_3H_6O]$, 80%); HRMS calcd for $C_{18}H_{23}N_2O_4$ (MH^+) 331.1658, found 331.1657.

4.2. (1*S*,1′*S*)-2,3-Bis(1,2-dihydroxyethyl)quinoxaline (7)

Diacetonide **6** (7.21 g, 21.8 mmol) was dissolved in 70% aqueous acetic acid (120 mL) and the solution was refluxed for 3 h. The solvent was removed under reduced pressure and then by co-evaporation four times with toluene. Tetraol **7** was recrystallised from ethanol and obtained after filtration quantitatively as a pale tan solid (5.46 g), mp 143°C; $[\alpha]_D^{20}=+6$ (*c* 0.73, MeOH). ^1H NMR (MeOD) δ 4.03 (*AB*X, $J_{AB}=11.2$ Hz, $J_{AX}=6.5$ Hz, $J_{BX}=5.2$ Hz, $\Delta\delta=0.07$ 4H, CH_2), 5.34 (dd, 2H, CH), 7.7–7.8 (m, 2H, H_{arom}), 8.0–8.1 (m, 2H, H_{arom}); ^{13}C NMR (MeOD) δ 66.7 (CH_2), 72.1 (CH), 129.7, 131.3 (CH_{arom}), 142.2, 155.8 (Cq_{arom}); FAB^+ *m*/*z*: 251 (MH^+, 100%).

4.3. Tosylation of the tetraol 7

4.3.1. Through organotin derivative under stoichiometric conditions. To a suspension of tetraol **7** (4.0 g, 16 mmol) in toluene (350 mL) was added Bu_2SnO (9.96 g, 40 mmol) and the mixture was refluxed for 16 h with azeotropic removal of water. The mixture containing the in situ generated tinacetal was concentrated in vacuo to 2/3 volume. Bu_4NI (6.2 g, 16.8 mmol) and tosyl chloride (6.4 g, 33.6 mmol) were added at 0°C.

Tosylation at room temperature. The resulting suspension was stirred at room temperature for 8 h then hydrolyzed by adding water (55 mL) and stirred overnight. After filtration of the salts, the aqueous layer was extracted with CH_2Cl_2 (3×130 mL). The organic layer was dried over Na_2SO_4, evaporated then purified by column chromatography (cyclohexane/EtOAc, 2:1 then 1:1), providing **8** (5.0 g, 56%) as a foam and **9** (0.55 g, 9%) as a solid.

Tosylation at 70°C. The resulting suspension was stirred at 70°C for 6 h, cooled down to 60°C, hydrolyzed by adding 120 mL of a solution H_2O/dioxane (15:85) and stirred vigorously for 5 h. After evaporation to dryness, the residue

was taken up in water (55 mL) and extracted with CH_2Cl_2 (3×130 mL). The organic layer was dried over Na_2SO_4, evaporated then purified by column chromatography (cyclohexane/EtOAc, 2:1 then 1:1), providing **8** (0.625 g, 7%) as a foam, and **9** (3.58 g, 58%) and **10** (0.49 g, 8%) as solids.

4.3.1.1. (1*S*,1′*S*)-2,3-Bis(1-hydroxy-2-*p*-toluenesulfonyloxy-ethyl)quinoxaline (8). R_f 0.49 (cyclohexane/EtOAc, 1:1); $[\alpha]_D^{20}=-8.5$ (*c* 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 2.35 (s, 6H, CH_3), 3.91 (d, $^3J=7.5$ Hz, 2H, D_2O exchangeable, OH), 4.43 (*AB*X, $J_{AB}=10.5$ Hz, $J_{AX}=6.1$ Hz, $J_{BX}=5.2$ Hz, $\Delta\delta=0.05$, 4H, CH_2), 5.31 (AB*X*, $J_{AX}=J_{BX}=5.8$ Hz, $^3J=7.3$ Hz, 2H, CH), 7.17 (d, $^3J=8.2$ Hz, 4H, H_{aromTs}), 7.64 (d, $^3J=8.2$ Hz, 4H, H_{aromTs}), 7.7–7.9 (m, 2H, H_{arom}), 7.9–8.1 (m, 2H, H_{arom}); ^{13}C NMR ($CDCl_3$) δ 21.6 (CH_3), 68.0 (CH), 72.6 (CH_2), 127.8, 128.8, 129.8, 130.8 (CH_{arom}), 132.3, 140.7, 145.0, 150.9 (Cq_{arom}); FAB^+ *m/z*: 559 (MH^+, 100%).

4.3.1.2. (1*S*,4*S*)-4-Hydroxy-1-(*p*-toluenesulfonyloxymethyl)-3,4-dihydro-1*H*-pyrano[3,4-*b*]quinoxaline (9). R_f 0.23 (cyclohexane/EtOAc, 1:1), mp 131°C; $[\alpha]_D^{20}=+81$ (*c* 1.0, CH_2Cl_2). ^1H NMR ($CDCl_3$) δ 2.37 (s, 3H, CH_3), 3.26 (d, $^3J=5.0$ Hz, 1H, D_2O exchangeable, OH), 4.12 (dd, $^2J=12.3$ Hz, $^3J=3.9$ Hz, 1H, CH_{ax}), 4.26 (dd, $^2J=12.3$ Hz, $^3J=3.9$ Hz, 1H, CH_{eq}), 4.66 (dd, $^2J=10.8$ Hz, $^3J=5.6$ Hz, 1H, CH_2OTs), 4.86 (m, 1H, C*H*OH), 4.91 (dd, $^2J=10.9$ Hz, $^3J=2.3$ Hz, 1H, CH_2OTs), 5.11 (dd, $^3J=5.5$, 2.3 Hz, 1H, OCH), 7.20 (d, $^3J=8.0$ Hz, 2H, H_{aromTs}), 7.68 (d, $^3J=8.0$ Hz, 2H, H_{aromTs}), 7.7–8.0 (m, 3H, H_{arom}), 8.0–8.2 (m, 1H, H_{arom}); ^{13}C NMR ($CDCl_3$) δ 21.4 (CH_3), 66.9 (CHOH), 68.9, 70.6 (CH_2), 76.2 (OCH), 127.6, 128.6, 128.9, 129.5, 130.2 (CH_{arom}), 132.5, 141.2, 141.5, 144.6, 148.5, 150.6 (Cq_{arom}); FAB^+ *m/z*: 387 (MH^+, 100%).

4.3.1.3. (1*R*,4*S*)-4-Hydroxy-1-(*p*-toluenesulfonyloxymethyl)-3,4-dihydro-1*H*-pyrano[3,4-*b*]quinoxaline (10). R_f 0.34 (cyclohexane/EtOAc, 1:1), mp 113°C; $[\alpha]_D^{20}=+15$ (*c* 1.0, CH_2Cl_2). ^1H NMR ($CDCl_3$) δ 2.34 (s, 3H, CH_3), 3.70 (dd, $^2J=11.2$ Hz, $^3J=9.8$ Hz, 1H, CH_{ax}), 4.22 (brs, 1H, D_2O exchangeable, OH), 4.45 (dd, $^2J=11.3$ Hz, $^3J=6.0$ Hz, 1H, CH_{eq}), 4.61 (dd, $^2J=10.7$ Hz, $^3J=5.1$ Hz, 1H, CH_2OTs), 4.79 (dd, $^2J=10.7$ Hz, $^3J=2.4$ Hz, 1H, CH_2OTs), 5.0 (dd, $^2J=9.7$ Hz, $^3J=6.0$ Hz, 1H, C*H*OH), 5.07 (dd, $^3J=5.1$, 2.3 Hz, 1H, OCH), 7.15 (d, $^3J=8.0$ Hz, 2H, H_{aromTs}), 7.62 (d, $^3J=8.0$ Hz, 2H, H_{aromTs}), 7.7–7.9 (m, 3H, H_{arom}), 8.0–8.2 (m, 1H, H_{arom}); ^{13}C NMR ($CDCl_3$) δ 21.6 (CH_3), 65.9 (CHOH), 68.6, 71.0 (CH_2), 77.2 (OCH), 127.9, 128.6, 129.0, 129.7, 130.2 (CH_{arom}), 132.8, 141.0, 141.5, 144.7, 148.5, 152.7 (Cq_{arom}); FAB^+ *m/z*: 387 (MH^+, 100%).

4.3.2. Through organotin derivative in catalytic conditions. To a suspension of tetraol **7** (2.08 g, 8.31 mmol) in dry THF (40 mL) was added $(CH_3)_2SnCl_2$ (36.5 mg, 0.166 mmol) and K_2CO_3 (4.6 g, 33.24 mmol). A solution of tosyl chloride (3.25 g, 17.03 mmol) in THF (10 mL) was added under argon at 0°C. After stirring the mixture 4 h at this temperature then overnight at room temperature, water was added (30 mL) and the residue extracted with CH_2Cl_2 (50 mL). The combined organic layers were washed with a saturated aqueous NH_4Cl solution, dried (Na_2SO_4) and concentrated in vacuo. Purification by column chromatography (cyclohexane/EtOAc, 1:1) afforded **8** (3.48 g, 75%) and **11** (0.87 g, 19%) as foams.

4.3.2.1. (1*S*,1′*S*)-2-(1-Hydroxy-2-*p*-toluenesulfonyloxyethyl)-3-(2-hydroxy-1-*p*-toluenesulfonyloxyethyl)-quinoxaline (11). R_f 0.38 (cyclohexane/EtOAc, 1:1); ^1H NMR ($CDCl_3$) δ 2.38, 2.44 (2s, 6H, CH_3), 2.86 (m, 1H, CH_2OH), 3.61 (d, $^3J=5.5$ Hz, 1H, CHO*H*), 4.0–4.4 (m, 2H, CH_2OH), 4.60 (dd, $^2J=10.8$ Hz, $^3J=7.4$ Hz, 1H, CH_2OTs), 4.80 (dd, $^2J=10.8$ Hz, $^3J=3.3$ Hz, 1H, CH_2OTs), 5.49 (m, 1H, C*H*OH), 6.18 (dd, $^3J=5.8$, 4.7 Hz, 1H, C*H*OTs), 7.13, 7.33, 7.68, 7.84 (4d, $^3J=8.1$ Hz, 8H, H_{aromTs}), 7.7–8.1 (m, 4H, H_{arom}); ^{13}C NMR dept ($CDCl_3$) δ 21.7 (CH_3), 63.9 (CH_2OH), 68.7 (CHOH), 72.2 (CH_2OTs), 78.7 (CHOTs), 127.8, 128.0, 128.8, 129.1, 129.6, 129.9, 130.7, 131.0 (CH_{arom}); FAB^+ *m/z*: 559 (MH^+, 100%).

4.4. Reaction of ditosylate 8 with sodium azide

Ditosylate **8** (1.27 g, 2.27 mmol) in DMF (40 mL) was treated with sodium azide (1.18 g, 18.16 mmol). After stirring at 70°C for 4 h, the solvent was removed in vacuo. CH_2Cl_2 (60 mL) and water (12 mL) were added and the mixture extracted with CH_2Cl_2 (3×60 mL). The extracts were dried over Na_2SO_4, evaporated then purified by column chromatography (cyclohexane/EtOAc, 2:8 to 1:1), affording **12** (464 mg, 68%) and **13** (70 mg, 12%) as solids.

4.4.1. (1*R*,1′*R*)-2,3-Bis(1-hydroxy-2-azido-ethyl)quinoxaline (12). R_f 0.6 (cyclohexane/EtOAc, 1:1), mp 98°C; $[\alpha]_D^{20}=+195.5$ (*c* 1.0, CH_2Cl_2). ^1H NMR ($CDCl_3$) δ 3.75 (d, $^3J=5.5$ Hz, 4H, CH_2), 4.15 (d, $^3J=7.8$ Hz, 2H, D_2O exchangeable, OH), 5.26 (dt, $^3J=7.8$, 5.5 Hz, 2H, CH), 7.7–7.9 (m, 2H, H_{arom}), 8.0–8.2 (m, 2H, H_{arom}); ^{13}C NMR ($CDCl_3$) δ 56.5 (CH_2), 69.8 (CH), 128.8, 131.0 (CH_{arom}), 140.8, 151.6 (Cq_{arom}); HRMS calcd for $C_{12}H_{13}N_8O_2$ (MH^+) 301.1161, found 301.1155.

4.4.2. (1*R*,4*S*)-1-Azidomethyl-4-hydroxy-3,4-dihydro-1*H*-pyrano[3,4-*b*]quinoxaline (13). R_f 0.4 (cyclohexane/EtOAc, 1:1), mp 89°C; $[\alpha]_D^{20}=+115$ (*c* 1.0, CH_2Cl_2).^1H NMR ($CDCl_3$) δ 3.27 (brs, 1H, D_2O exchangeable, OH), 4.02 (*AB*X, $J_{AB}=13.0$ Hz, $J_{AX}=6.2$ Hz, $J_{BX}=3.1$ Hz, $\Delta\delta=0.08$, 2H, CH_2N_3), 4.19 (dd, $^2J=12.4$ Hz, $^3J=3.0$ Hz, 1H, CH_2O), 4.38 (dd, $^2J=12.4$ Hz, $^3J=3.5$ Hz, 1H, CH_2O), 4.91 (m, 1H, C*H*OH), 5.09 (AB*X*, $J_{AX}=6.2$ Hz, $J_{BX}=3.1$ Hz, 1H, CHO), 7.7–7.9 (m, 2H, H_{arom}), 8.0–8.2 (m, 2H, H_{arom}); ^{13}C NMR ($CDCl_3$) δ 53.6 (CH_2N_3), 67.5 (CH), 69.0 (CH_2O), 78.0 (CHOH), 129.0, 129.1, 130.4 130.7 (CH_{arom}), 141.7, 142.1, 149.9, 150.5 (Cq_{arom}); CIMS (NH_3) *m/z*: 258 (MH^+, 100%).

4.5. Reaction of diazidodiol 12 with triphenylphosphine

A solution of diazidodiol **12** (0.233 g, 0.776 mmol) and triphenylphosphine (0.407 g, 1.552 mmol) in dry THF (12 mL) was stirred and refluxed under argon until complete transformation of the bis-iminophosphorane into the *N*H-bis-aziridine (monitored by TLC using EtOH/CH_2Cl_2, 7:3 as eluent with R_f 0.0 and R_f 0.25, respectively). After evaporation to dryness, the crude residue containing **4a** was protected without further purification.

4.6. Protection with di-*tert*-butyldicarbonate

To a solution of the above residue **4a** (0.776 mmol) in THF

(7 mL) and triethylamine (216 μL, 1.552 mmol) at 0°C, was added di-*tert*-butyl-dicarbonate (0.34 g, 1.552 mmol) and stirred 2 h at room temperature. The solvent was then evaporated and the residue purified by flash chromatography (cyclohexane/EtOAc/Et_3N, 8:2:0.1) to yield the bis-aziridines **4b** (0.192 g, 60%) and **4b′** (9.6 mg, 3%) as oils.

4.6.1. (2*S*,2′*S*)-2,3-Bis[(*tert*-butyloxycarbonyl)aziridin-2-yl]quinoxaline (4b). R_f 0.47 (cyclohexane/EtOAc, 1:1); $[\alpha]_D^{20}=-235$ (*c* 1.0, CH_2Cl_2).^{1}H NMR ($CDCl_3$) δ 1.33 (s, 18H, CH_3), 2.75 (dd, ^2J=0.6 Hz, $^3J_{cis}$=5.7 Hz, 2H, CH_2), 3.30 (dd, ^2J=0.6 Hz, $^3J_{trans}$=3.5 Hz, 2H, CH_2), 4.38 (dd, ^3J=5.7, 3.5 Hz, 2H, CH), 7.6–7.8 (m, 2H, H_{arom}) 7.9–8.1 (m, 2H, H_{arom}); ^{13}C NMR ($CDCl_3$) δ 27.7 (CH_3), 30.1 (CH_2), 36.9 (CH), 81.8 (Cq_{Boc}), 129.0, 130.0 (CH_{arom}), 141.2, 150.7 (Cq_{arom}), 161.1 (CO); HRMS calcd for $C_{22}H_{29}N_4O_4$ (MH^+) 413.2189, found 413.2194.

4.6.2. (2*S*,2′*R*)-2,3-Bis[(*tert*-butyloxycarbonyl)aziridin-2-yl]quinoxaline (4b′). R_f 0.2 (cyclohexane/EtOAc, 1:1); ^{1}H NMR ($CDCl_3$) δ 1.37 (s, 18H, CH_3), 2.77 (dd, ^2J=0.9 Hz, $^3J_{cis}$=6.0 Hz, 2H, CH_2), 3.0 (dd, ^2J=0.9 Hz, $^3J_{trans}$=3.5 Hz, 2H, CH_2), 4.22 (dd, ^3J=6.0, 3.5 Hz, 2H, CH), 7.6–7.8 (m, 2H, H_{arom}) 7.9–8.1 (m, 2H, H_{arom}); ^{13}C NMR ($CDCl_3$) δ 27.9 (CH_3), 33.0 (CH_2), 37.0 (CH), 81.8 (Cq_{Boc}), 129.0, 130.1 (CH_{arom}), 141.1, 150.3 (Cq_{arom}), 161.2 (CO); CIMS (CH_4) *m*/*z*: 413 (MH^+, 20%), 357 ($MH^+-[C_4H_8]$, 25%), 313 ($MH^+-[C_4H_8-CO_2]$, 70%), 257 ($MH^+-2[C_4H_8]-CO_2$), 100%).

4.7. Protection with *p*-toluenesulfonyl chloride

To a solution of the above residue **4a** (0.776 mmol) in DMF (3 mL) and triethylamine (1.5 mL) at −5°C, was added a solution of *p*-toluenesulfonyl chloride (0.296 g, 1.552 mmol) in DMF (1.5 mL). After stirring 2 h at this temperature, the solvent was evaporated and the residue diluted with water, extracted with ether and the combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated in vacuo. Flash chromatography (cyclohexane/EtOAc/Et_3N, 1:1:0.1) yielded the bis-aziridine **4c** (0.202 g, 50%) as a white solid.

4.7.1. (2*S*,2′*S*)-2,3-Bis[(*p*-toluenesulfonyl)aziridin-2-yl]quinoxaline (4c). R_f 0.54 (cyclohexane/EtOAc, 1:1), mp 57°C; $[\alpha]_D^{20}=-186.5$ (*c* 1.0; CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 2.43 (s, 6H, CH_3), 2.99 (d, $^3J_{cis}$=6.9 Hz, 2H, CH_2), 3.36 (d, $^3J_{trans}$=4.2 Hz, 2H, CH_2), 4.35 (dd, ^3J=6.8, 4.2 Hz, 2H, CH), 7.35 (d, ^3J=8.1 Hz, 4H, H_{aromTs}), 7.6–7.8 (m, 2H, H_{arom}), 7.9–8.1 (m, 6H, $H_{arom}+H_{aromTs}$); ^{13}C NMR ($CDCl_3$) δ 21.4 (CH_3), 31.8 (CH_2), 37.4 (CH), 128.4, 129.0, 129.8, 130.9 (CH_{arom}), 133.8, 141.4, 145.0, 148.3 (Cq_{arom}); HRMS calcd for $C_{26}H_{25}N_4O_4S_2$ (MH^+) 521.1317, found 521.1312.

4.8. Reaction of diazidodiols with polymer-supported triphenylphosphine

A solution of diazidodiol (0.5 mmol) in the appropriate dry solvent (5 mL) was added to a suspension of polymer-supported PPh_3, 2% DVB (0.5 g, 3.0 mmol) in the same solvent (3 mL). The resulting mixture was gently stirred until nitrogen evolution ceased at room temperature (1.5 h) then at 40°C (1.5 h). The reaction mixture was then heated for several hours under argon. The resin, was filtered, rinsed with dry THF, and the filtrate was evaporated to dryness to give the corresponding *N*H-bis-aziridine as an oil.

4.8.1. (2*S*,2*S*′)-2,3-Bis(aziridin-2-yl)quinoxaline (4a). (1*R*,1′*R*)-2,3-Bis(1-hydroxy-2-azido-ethyl)quinoxaline **12** was refluxed as above in THF for 15 h to give the *N*H-bis-aziridine **4a**. ^{1}H NMR ($CDCl_3$) δ 2.0 (brs, 2H, CH_2), 2.2 (d, $^3J_{cis}$=5.0 Hz, 2H, CH_2), 3.45 (dd, ^3J=5.0, 3.0 Hz, 2H, CH), 7.6–7.8 (m, 2H, H_{arom}), 7.85–8.1 (m, 2H, H_{arom}).

4.8.2. (2*S*,2′*S*)-[(1*R*,2*R*)-1,2-Isopropylidene-ethan-diyl]-bis-aziridine (1a). 1,6-Diazido-1,6-dideoxy-3,4-*O*-isopropylidene-D-mannitol was treated as above in toluene at 105°C for 15 h to give the *N*H-bis-aziridine **1a**. ^{1}H NMR ($CDCl_3$) δ 1.47 (s, 6H, CH_3), 1.64 (d, $^3J_{trans}$=2.5 Hz, 2H, CH_2), 1.88 (d, $^3J_{cis}$=5.4 Hz, 2H, CH_2), 2.16 (m, 2H, CHN), 3.59 (m, 2H, OCH); ^{13}C NMR ($CDCl_3$) δ 21.4 (CH_2), 26.8 (CH_3), 30.3 (CN), 81.3 (OC), 109.2 (Cq).

4.8.3. (2*S*,2′*S*)-[(1*R*,2*R*)-1,2-Dibenzyloxy-ethan-diyl]bis-aziridine (2a) and 1,6-diamino-1,6-dideoxy-2,5-anhydro-3,4-di-*O*-benzyl-D-glucitol (14). 1,6-Diazido-1,6-dideoxy-3,4-di-*O*-benzyl-D-mannitol was treated as above in toluene at 90°C for 9 h to give a 1/1 mixture of the *N*H bis-aziridine **2a** and the furan **14**.

Compound **2a**. ^{1}H NMR ($CDCl_3$) δ 1.42 (d, $^3J_{trans}$=3.5 Hz, 2H, CH_2), 1.68 (d, $^3J_{cis}$=6.0 Hz, 2H, CH_2), 2.32 (m, 2H, CHN), 3.19 (d, ^3J=5.5 Hz, 2H, OCH), 4.70 (AB, $^2J_{AB}$= 11.9 Hz, $\Delta\delta$=0.04, 4H, OCH_2), 7.2–7.4 m, 10H, H_{arom}).

Compound **14**. ^{1}H NMR ($CDCl_3$) δ 2.7–3.05 (m, 4H, CH_2), 3.75–4.0 (m, 4H, CH), 7.2–7.4 (m, 10H, H_{arom}).

4.9. Opening of the bis-aziridine 4b by thiophenate

At 0°C, to a suspension of sodium hydride (6 mg, 0.247 mmol) in DMF (2 mL) was added thiophenol (25 μL, 0.247 mmol). After being stirred for 30 min from 0 to 20°C, the *N*,*N*′-diBoc bis-aziridine **4b** (51 mg, 0.123 mmol) in DMF (1.6 mL) was added at 0°C. The reaction mixture was stirred for 2 h, quenched by the addition of water (1 mL) and extracted with ether (3×2 mL). The combined organic extracts were dried over Na_2SO_4 and the solvent was removed under reduced pressure. Flash chromatography (cyclohexane/EtOAc, 1:1) provided **16** (48.6 mg, 62%) as a solid and **17** (7.3 mg, 9%) as an oil.

4.9.1. (1*R*,1′*R*)-2,3-Bis(2-*tert*-butyloxycarbonylamino-1-phenylthio-ethyl)quinoxaline (16). R_f 0.37 (cyclohexane/EtOAc, 1:1), mp 132°C; $[\alpha]_D^{20}=+65$ (*c* 1.0, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 1.34 (s, 18H, CH_3), 4.04 (m, 4H, CH_2), 4.8–5.3 (m, 4H, NH+CH), 7.1–7.5 (m, 10H, $H_{aromSPh}$), 7.6–7.8 (m, 2H, H_{arom}) 7.8–8.0 (m, 2H, H_{arom}); ^{13}C NMR ($CDCl_3$) δ 28.4 (CH_3), 42.2 (CH_2), 48.3 (CH), 79.2 (Cq_{Boc}), 128.2, 128.8, 129.0, 129.8, 133.4 (CH_{arom}), 135.5, 140.1, 152.9 (Cq_{arom}), 155.7 (CO_{Boc}); CIMS (NH_3) *m*/*z*: 633 (MH^+, 15%), 525 (10%), 417 (100%).

4.9.2. (1*S*,1′*R*)-2,3-Bis(2-*tert*-butyloxycarbonylamino-1-phenylthio-ethyl)quinoxaline (17). R_f 0.26 (cyclohexane/

EtOAc, 1:1); ^{1}H NMR ($CDCl_3$) δ 1.27 (s, 18H, CH_3), 3.85 (m, 4H, CH_2), 4.9–5.3 (m, 4H, NH+CH), 7.0–7.5 (m, 10H, $H_{aromSPh}$), 7.6–7.8 (m, 2H, H_{arom}), 7.9–8.1 (m, 2H, H_{arom}); CIMS (NH_3) *m/z*: 633 (MH^+, 15%), 525 (10%), 417 (100%).

4.10. Opening of the bis-aziridine 4b by allyl alcohol

To **4b** (40 mg, 0.097 mmol) in allyl alcohol (1 mL) was added ytterbium triflate (6 mg, 0.1 equiv.) at −10°C and the mixture was stirred for 1 h and at room temperature for 2 h. After concentration, the products were further separated by column chromatography (cyclohexane/EtOAc/Et_3N, 9:1:0.1), affording **18** (31.5 mg, 61%) and **19** (5.2 mg, 10%) as colourless oils.

4.10.1. (1*R*,1′*R*)-2,3-Bis(1-allyloxy-2-*tert*-butyloxycarbonylamino-ethyl)quinoxaline (18). R_f 0.33 (cyclohexane/EtOAc, 1:1); $[\alpha]_D^{20}$=+36 (*c* 1.0, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 1.36 (s, 18H, CH_3), 3.79 (*AB*X*Y*, $^2J_{AB}$=13.9 Hz, J_{AX}=J_{AY}=5.6 Hz, J_{BX}=J_{BY}=6.6 Hz, 4H, CH_2N), 4.12 (d, ^2J=5.7 Hz, 4H, OCH_2), 5.06 (AB*X*Y, J_{XA}=J_{YA}=5.6 Hz, 2H, OCH), 5.1–5.4 (m, 6H, CH=CH_2+NH), 5.8–6.1 (m, 2H, C*H*=CH_2), 7.7–7.9 (m, 2H, H_{arom}), 8.0–8.2 (m, 2H, H_{arom}); ^{13}C NMR ($CDCl_3$) δ 28.3 (CH_3), 42.1 (CH_2N), 70.8 (CHO), 79.2 (Cq_{Boc}), 118.1 (CH=*C*H_2), 129.2, 130.2 (CH_{arom}), 134.3 (*C*H=CH_2), 141.1, 153.1 (Cq_{arom}), 155.9 (CO_{Boc}); CIMS (NH_3) *m/z*: 529 (MH^+, 100%).

4.10.2. (1*S*,1′*R*)-2,3-Bis(1-allyloxy-2-*tert*-butyloxycarbonylamino-ethyl)quinoxaline (19). R_f 0.29 (cyclohexane/EtOAc, 1:1); ^{1}H NMR ($CDCl_3$) δ 1.35 (s, 18H, CH_3), 3.5–4.0 (m, 4H, CH_2N), 4.0–4.3 (m, 4H, OCH_2), 4.9–5.5 (m, 8H, CH=CH_2+NH+OCH), 5.7–6.1 (m, 2H, C*H*=CH_2), 7.7–7.9 (m, 2H, H_{arom}), 7.9–8.2 (m, 2H, H_{arom}); CIMS (NH_3) *m/z*: 529 (MH^+, 100%).

4.11. Opening of the bis-aziridine 4b by acetic acid

To a solution of **4b** (88 mg, 0.21 mmol) in THF (1 mL) at 0°C was added acetic acid (1 mL) and the resulting mixture was stirred for 24 h at room temperature. After concentration in vacuo, the products were further separated by column chromatography (cyclohexane/EtOAc, 1:1), affording **20** (47.4 mg, 42%), **21** (17 mg, 17%) and **22** (9 mg, 9%) as colourless oils.

4.11.1. (1*R*,1′*R*)-2,3-Bis(1-acetoxy-2-*tert*-butyloxycarbonylamino-ethyl)quinoxaline (20). R_f 0.25 (cyclohexane/EtOAc, 1:1); $[\alpha]_D^{20}$=+66.5 (*c* 1.0, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 1.40 (s, 18H, CH_3), 2.10 (s, 6H, OCH_3), 3.73 (dt, ^2J=14.4 Hz, ^3J=5.6 Hz, 2H, CH_2), 4.03 (ddd, ^2J=14.4 Hz, ^3J=7.6, 4.4 Hz, 2H, CH_2), 5.25 (brs, 2H, NH), 6.17 (brs, 2H, CH), 7.7–7.9 (m, 2H, H_{arom}), 8.0–8.2 (m, 2H, H_{arom}); ^{13}C NMR ($CDCl_3$) δ 20.8 (CH_3O), 28.3 (CH_{3Boc}), 41.9 (CH_2), 71.5 (CH), 79.4 (Cq_{Boc}), 129.1, 130.5 (CH_{arom}), 141.0, 151.1 (Cq_{arom}), 155.7 (CO_{Boc}), 170.4 (CO_{Ac}); CIMS (NH_3) *m/z*: 533 (MH^+, 100%).

4.11.2. (1*R*,4*R*)-4-Acetoxy-1-(*tert*-butyloxycarbonylamino-methyl)-2-*tert*-butyloxycarbonyl-3,4-dihydro-1*H*-pyrido[3,4-*b*]quinoxaline (21). R_f 0.41 (cyclohexane/EtOAc, 1:1); ^{1}H NMR ($CDCl_3$) δ 1.41, 1.50 (2s, 18H, CH_3), 2.23 (s, 3H, OCH_3), 3.3–4.0 (m, 3H, CH_{ax}NBoc+CH_2NHBoc), 4.4–5.7 (m, 3H, CH_{eq}NBoc+NH+CHN), 6.10 (dd, ^2J=10.3 Hz, ^3J=6.5 Hz, 1H, OCH), 7.6–7.8 (m, 2H, H_{arom}), 7.9–8.1 (m, 2H, H_{arom}); ^{13}C NMR ($CDCl_3$) δ 21.0 (CH_3O), 28.3 (CH_{3Boc}), 40.3, 41.5 (CH_2), 56.4 (CHN), 67.4 (OCH), 79.5, 81.4 (Cq_{Boc}), 128.7, 129.4, 130.1, 130.5 (CH_{arom}), 141.3, 141.5, 149.4, 150.0 (Cq_{arom}), 155.9 (CO_{Boc}), 170.2 (CO_{Ac}); HRMS calcd for $C_{24}H_{33}N_4O_6$ (MH^+) 473.2400, found 473.2396.

4.11.3. (1*R*,4*S*)-1-Acetoxymethyl-2-*tert*-butyloxycarbonyl-4-*tert*-butyloxycarbonylamino-3,4-dihydro-1*H*-pyrido[3,4-*b*]quinoxaline (22). R_f 0.54 (cyclohexane/EtOAc, 1:1); ^{1}H NMR ($CDCl_3$) δ 1.50 (s, 18H, CH_3), 1.96 (s, 6H, OCH_3), 3.1–3.3 (m, 1H, CH_{ax}NBoc), 4.6–5.2 (m, 3H, CH_2O+CH_{eq}NBoc+NH), 5.5–5.8 (m, 1H, CHN), 7.6–7.8 (m, 2H, H_{arom}), 7.9–8.1 (m, 2H, H_{arom}); ^{13}C NMR ($CDCl_3$) δ 20.8 (CH_3O), 28.4 (CH_{3Boc}), 44.6 (CH_2N), 51.3 (CHN), 64.6 (CH_2O), 81.2 (Cq_{Boc}), 128.8, 130.3 (CH_{arom}), 141.3, 141.4, 149.2 (Cq_{arom}), 155.8 (CO_{Boc}), 170.6 (CO_{Ac}); HRMS calcd for $C_{24}H_{33}N_4O_6$ (MH^+) 473.2400, found 473.2402.

4.12. Opening of the bis-aziridine 4b by benzylamine

To a solution of **4b** (101 mg, 0.245 mmol) in CH_3CN (3 mL) at room temperature was added benzylamine (27 μL, 0.247 mmol) and ytterbium triflate (15.2 mg, 0.1 equiv.) and the reaction mixture was refluxed for 24 h. After concentration in vacuo, the products were further separated by column chromatography (cyclohexane/EtOAc, 3:1), affording **23** (28 mg, 22%), **24** (13.2 mg, 10%) and **25** (14 mg, 11%) as oils.

4.12.1. (1*R*,4*R*)-2-Benzylamino-2-*tert*-butyloxycarbonyl-1-(*tert*-butyloxycarbonylaminomethyl)-3,4-dihydro-1*H*-pyrido[3,4-*b*]quinoxaline (23). R_f 0.41 (cyclohexane/EtOAc, 1:1); ^{1}H NMR ($CDCl_3$) δ 1.40, 1.51 (2s, 18H, CH_3), 2.3–3.0 (brs, 1H, NHBn), 3.0–3.3 (m, 1H, CH_{ax}-NBoc), 3.5–4.2 (m, 5H, containing at 4.07 (AB, J_{AB}=13.3 Hz, $\Delta\delta$=0.08, 2H)), 4.7–4.9 (m, 1H), 5.0–5.7 (m, 2H), 7.1–7.5 (m, 5H, H_{arom}), 7.6–7.8 (m, 2H, H_{arom}), 7.9–8.1 (m, 2H, H_{arom}); ^{13}C NMR ($CDCl_3$) δ 28.4 (CH_3), 41.9, 43.5 (CH_2NBoc), 51.9 (CH_2Ph), 56.9 (CHN), 80.8, 81.3 (Cq_{Boc}), 127.1, 128.2, 128.5, 129.9, 130.5 (CH_{arom}), 140.1, 141.1, 152.3 (Cq_{arom}), 154.5, 155.7 (CO); HRMS calcd for $C_{29}H_{38}N_5O_4$ (MH^+) 520.2924, found 520.2904.

4.12.2. (1*R*,4*S*)-2-Benzyl-4-*tert*-butyloxycarbonylamino-1-(*tert*-butyloxycarbonylaminomethyl)-3,4-dihydro-1*H*-pyrido[3,4-*b*]quinoxaline (24). R_f 0.61 (cyclohexane/EtOAc, 1:1); ^{1}H NMR ($CDCl_3$) δ 1.30, 1.42 (2s, 18H, CH_3), 2.4–2.7 (m, 1H, CH_{ax}NBn), 3.4–4.3 (m, 6H), 4.8–5.2 (m, 2H, NH), 5.5–5.7 (m, 1H), 7.1–7.4, (m, 5H, H_{arom}), 7.6–7.8 (m, 2H, H_{arom}), 7.9–8.1 (m, 2H, H_{arom}).

4.12.3. (1*R*,3*R*)-2-Benzyl-1,3-di-(*tert*-butyloxycarbonylamino-methyl)-1,3-dihydro-pyrrolo[3,4-*b*]quinoxaline (25). R_f 0.56 (cyclohexane/EtOAc, 1:1); ^{1}H NMR ($CDCl_3$) δ 1.38 (s, 18H, CH_3), 3.5–4.0 (m, 4H, CH_2NHBoc), 4.28 (AB, J_{AB}=14.2 Hz, $\Delta\delta$=0.17, 2H, NCH_2Ph), 4.4 (m, 1H, CH), 4.9 (m, 2H, NH), 7.2–7.5, (m, 5H, H_{arom}), 7.6–7.8 (m, 2H, H_{arom}), 8.0–8.2 (m, 2H, H_{arom}); ^{13}C NMR ($CDCl_3$) δ

28.4 (CH_3), 40.7 (CH_2NHBoc), 50.3 (CH_2Ph), 62.6 (CHN), 79.5 (Cq_{Boc}), 127.4, 128.4, 128.6, 129.3, 129.6 (CH_{arom}), 138.0, 142.2, 155.6 (Cq_{arom}), 157.3 (CO); HRMS calcd for $C_{29}H_{38}N_5O_4$ (MH^+) 520.2924, found 520.2925.

4.13. Opening of the bis-aziridine 4c by benzylamine

A solution of the *N*,*N*′-ditosyl bis-aziridine **4c** (86 mg, 0.165 mmol) in THF (0.5 mL) was stirred with benzylamine (18 μL, 0.165 mmol) at room temperature for 12 h. After evaporation of the solvent, the residue was purified by column chromatography (cyclohexane/EtOAc, from 1:9 to 1:4), affording **26** (15 mg, 14%), **27** (10 mg, 10%) and **28** (12 mg, 10%) as oils.

4.13.1. (1*R*,4*S*)-2-Benzyl-4-*p*-toluenesulfonylamino-1-(*p*-toluenesulfonylaminomethyl)-3,4-dihydro-1*H*-pyrido-[3,4-*b*]quinoxaline (26). R_f 0.60 (cyclohexane/EtOAc, 1:1); ^{1}H NMR ($CDCl_3$) δ 2.13, 2.42 (2s, 6H, CH_3), 2.56 (dd, ^2J=^3J=10.9 Hz, 1H, CH_{ax}), 3.45–3.65 (m, 2H, containing at 3.57 (d, ^3J=13.9 Hz, 1H), NCH_2Ph+CH_2NHTs), 3.70 (dd, ^2J=11.5 Hz, ^3J=5.0 Hz, 1H, CH_{eq}), 3.9–4.05 (m, 2H, NCH_2Ph+CH_2NHTs), 4.35 (ddd, ^3J=10.9, 5.2 Hz, 1H, CHNBn), 5.27 (d, ^2J=9.0 Hz, 1H, CH_2N*H*Ts), 6.24 (d, ^2J=1.6 Hz, 1H, CHN*H*Ts), 6.73 (d, ^3J=8.0 Hz, 1H, H_{aromTs}), 7.1–7.4 (m, 9H, H_{arom}), 7.7–8.0 (m, 6H, H_{arom}); ^{13}C NMR ($CDCl_3$) δ 21.4, 21.6 (CH_3), 44.0 (CH_2NHTs), 52.9 (CHNBn), 53.6 (NCH_2Ph), 57.5 (CH_2NBn), 63.1 (CHNHTs), 126.5, 127.5, 127.9, 128.4, 128.7, 129.0, 129.2, 129.7, 129.9, 130.2, 130.4 (CH_{arom}), 135.7, 135.7, 136.2, 141.5, 142.9, 143.9, 148.7, 151.0 (Cq_{arom}); HRMS calcd for $C_{33}H_{34}N_5O_4S_2$ (MH^+) 628.2052, found 628.2050.

4.13.2. (1*R*,3*R*)-2-Benzyl-1,3-di-(*p*-toluenesulfonylamino-methyl)-1,3-dihydro-pyrrolo[3,4-*b*]quinoxaline (27). R_f 0.57 (cyclohexane/EtOAc, 1:1); ^{1}H NMR ($CDCl_3$) δ 2.32 (s, 6H, CH_3), 3.23 (ddd, ^2J=12.7 Hz, ^3J=6.7, 3.9 Hz, 2H, CH_2), 3.61 (ddd, ^2J=12.6 Hz, ^3J=8.4, 2.9 Hz, 2H, CH_2), 4.08 (AB, J_{AB}=14.8 Hz, $\Delta\delta$=0.03, 2H, NCH_2Ph), 4.33 (dd, ^3J=6.4, 2.7 Hz, 2H, CH), 5.12 (dd, ^3J=8.3, 3.8 Hz, 2H, NHTs), 7.10 (d, ^3J=8.1 Hz, 2H, H_{arom}), 7.2–7.4 (m, 6H, H_{arom}), 7.53 (d, ^3J=8.3 Hz, 2H, H_{arom}), 7.7–7.9 (m, 2H, H_{arom}), 7.9–8.1 (m, 2H, H_{arom}); ^{13}C NMR ($CDCl_3$) δ 21.5 (CH_3), 43.4 (CH_2-NHTs), 50.5 (NCH_2Ph), 61.6 (CH), 126.9, 128.0, 128.6, 128.9, 129.3, 129.6, 130.0 (CH_{arom}), 136.5, 142.1, 143.5, 155.9 (Cq_{arom}).

4.13.3. (1*S*,1′*R*)-2-(2-Benzylamino-1-*p*-toluenesulfonyl-amino-ethyl)-3-(1-benzylamino-2-*p*-toluenesulfonyl-amino-ethyl)-quinoxaline (28). R_f 0.5 (cyclohexane/EtOAc, 1:1); ^{1}H NMR ($CDCl_3$) δ 2.0, 2.32 (2s, 6H, CH_3), 2.86 (d, ^3J=6.0 Hz, 2H, CH_2NBn), 3.07 (dd, ^2J=12.8 Hz, ^3J=6.0 Hz, 1H, CH_2NTs), 3.47 (dd, ^2J=12.9 Hz, ^3J=5.3 Hz, 1H, CH_2NTs), 3.49 (AB, J_{AB}=12.9 Hz, $\Delta\delta$=0.18, 2H, NCH_2Ph), 3.65 (AB, J_{AB}=13.5 Hz, $\Delta\delta$=0.07, 2H, NCH_2Ph), 4.19 (dd, ^3J=5.7 Hz, 1H, CH), 5.07 (dd, ^3J=6.0 Hz, 1H, CH), 6.82 (d, ^3J=8.2 Hz, 2H, H_{aromTs}), 7.0–7.4 (m, 11H, H_{arom}), 7.54 (d, ^3J=8.3 Hz, 2H, H_{arom}), 7.6–8.0 (m, 7H, H_{arom}).

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