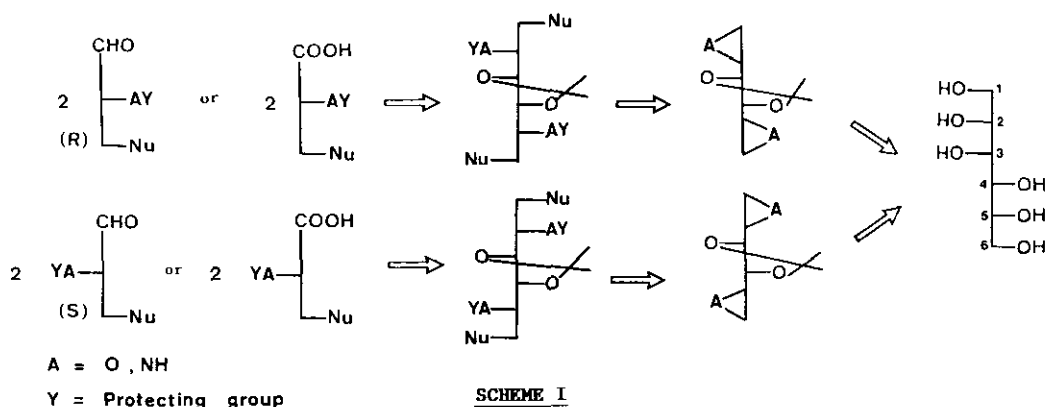


SYNTHESIS OF DIEPOXIDES AND DIAZIRIDINES, PRECURSORS
OF ENANTIOMERICALLY PURE α -HYDROXY AND α -AMINO
ALDEHYDES OR ACIDS, FROM D-MANNITOL

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Abstract—Specific activations or protections of the hydroxyl groups
of 3-4-O-isopropylidene-D-mannitol **2** followed by intramolecular SN2
reactions, lead to the chiral diepoxides **4** and **7** and to the chiral
diaziridines **9** and **13** precursors of enantiomerically pure α -hy-
droxy and α -amino aldehydes or acids.

Enantiomerically pure α -hydroxyaldehydes or acids and
 α -aminoaldehydes or acids are key intermediates for the synthesis of
biologically active compounds as arachidonic acid metabolites,
peptides analogues. These intermediates can be obtained^{1,2} from a
unique, inexpensive, chiral, naturally occurring comp-
ound, D-mannitol, according to the following scheme:



Each molecule of D-mannitol leads, via diepoxides or
diaziridines, without "wastage of carbons", to two molecules
of highly functionalised enantiomerically pure compound.
Indeed, the molecule of D-mannitol has a twofold axis of
symmetry. If this symmetry is preserved during chemical
transformations and consequently, if there is a control of the
configuration of asymmetric carbons, then C₂ and C₅ will have

—Respectueusement dédié au Professeur Gilbert STORK pour son 65^{ème} anniversaire.

identical absolute configurations and the cleavage of the C₃-C₄ bond will lead to two identical, chiral molecules.

We describe in this paper the syntheses of diepoxides and diaziridines.

Syntheses of diastereoisomeric diepoxides 4 and 7 (Scheme II).

Diepoxides, 1,2:5,6-dianhydro-3,4-O-isopropylidene-D-mannitol **4** and -L-iditol **7**, were known^{3a,b}. We have simplified and improved their syntheses^{3c}. Yields for **4** and **7**, with respect to D-mannitol, are respectively 40% and 38%.

D-mannitol is first transformed into 3,4-O-isopropylidene-D-mannitol **2**⁴ which is tosylated (**2**→**3**).

In basic medium, ditosylate **3** undergoes intramolecular S_N2 reaction, leading to diepoxide **4**, with retention of configuration at C₂ and C₅. Attack of **3** at C₁ and C₆ by various nucleophiles (N₃⁻, CN⁻, ...) is an easy way to prepare interesting compounds as the diazide **8** precursor of the diaziridines **9** and **13**. Access to the diepoxide **7** is achieved by transformations of **2**: dibenzoylation⁵ (**2**→**5**), ditosylation⁵ (**5**→**6**), transesterification-cyclisation (**6**→**7**). Experimental conditions, which were used for the preparation of **5** and **6**, minimise polybenzoylation and benzoyl group migrations.

During the last step, transesterification of the benzoate of **6** liberates primary alkoxides and the concomitant intramolecular S_N2 reaction occurs with inversion of configuration at C₂ and C₅.

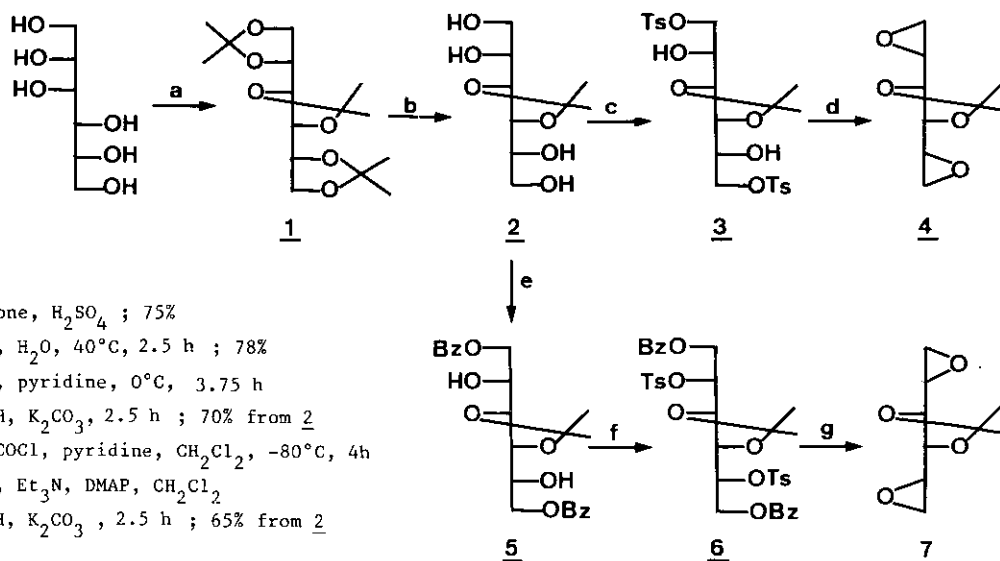
Nucleophilic opening of the diastereoisomeric diepoxides **4** and **7** and cleavage of the C₃-C₄ bond, leads to enantiomerically pure α-hydroxyaldehydes¹. We used this strategy to prepare starting materials for a synthesis of leukotriene (+)-LTB₄⁶.

Syntheses of diastereoisomeric diaziridines 9 and 13 (Scheme III)

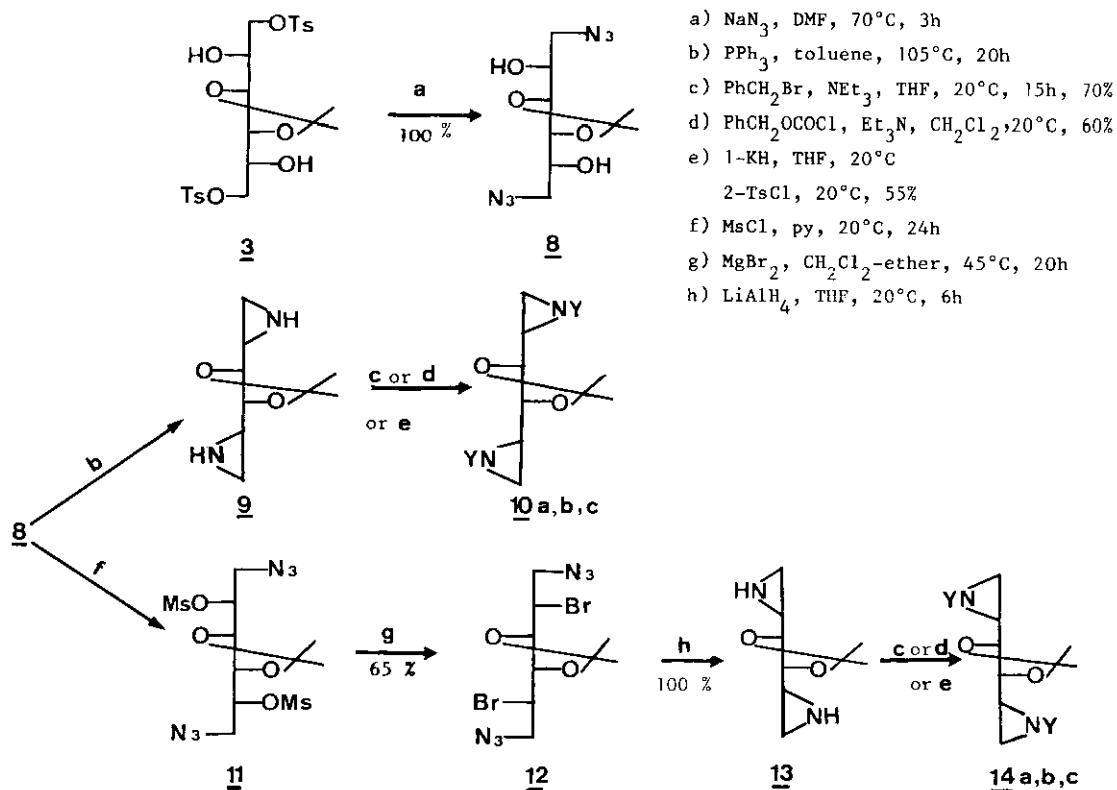
Diaziridines, (2S,3R,4R,5S)-1,2:5,6-diimino-3,4-O-isopropylidene-3,4-hexanediol **9** and (2R,3R,4R,5R) diastereoisomer **13** are obtained with 100% and 60% yields respectively, from diazidodiol **8**, prepared with 50% yield from D-mannitol.

Ring closure of **8** by triphenylphosphine⁷ occurs with inversion of configuration at C₂ and C₅ and leads to diaziridine **9** quantitatively after heating for 20h at 105°C in toluene. Diaziridine **13** is formed by the following transformations of **8**: dimesylation(**8**→**11**), dibromination(**11**→**12**), reduction-cyclisation (**12**→**13**). S_N2 reactions by bromide ions (MgBr₂)⁸ on the dimesylate **11** involve the inversions of configuration at C₂ and C₅. A second inversion at the same centers occurs during the reduction of **12** by lithium aluminium hydride and concomitant cyclisation⁹ into diaziridine **13**. The N-unsubstituted crude diaziridines **9** and **13** are transformed into the N-protected diaziridines **10** a,b,c and **14** a,b,c respectively (a:Y=CH₂Ph; b:Y=COOCH₂Ph; c:Y=Ts).

SCHEME II



SCHEME III



Nucleophilic opening of these diaziridines depends on the nature of the N-protecting group. N-Tosyldiaziridines are easily symmetrically opened at low temperature, without catalyst, by organocuprates, and are good educts for the synthesis of α -amino acids 2.

EXPERIMENTAL

Reactions were carried out under N_2 atmosphere. IR spectra were measured with a Perkin-Elmer 783 spectrophotometer. 1H -NMR spectra were recorded in $CDCl_3$ on 250 MHz Bruker spectrometer (except otherwise mentioned) and on EM 390 Varian spectrometer. ^{13}C -NMR spectra were recorded in $CDCl_3$ on Bruker spectrometer. Specific rotation were measured for $\lambda=589$ nm at 20°C with a Perkin-Elmer 241 polarimeter.

1,2:3,4:5,6-Tri-O-isopropylidene-D-mannitol (1).

A suspension of D-mannitol (125g, 687 mmol) in dry acetone (1,56 l) containing sulphuric acid (96%, 12.5ml) was stirred at room temperature for 24 h. Neutralisation with an aqueous solution of NH_4OH (33%, 44ml) and sodium carbonate (78g) and evaporation gave a solid which was solubilised in ethanol and recrystallized from acetone (75% yield); mp 69°C (Lit. 68-70°C¹⁰, 70°C^{5b}); $[\alpha] +13.6^\circ$ (c 1.0, CH_2Cl_2). (Lit. $+12.5^\circ$ (C_2H_5OH)¹⁰, $+13.8^\circ$ (c 1.7, $CHCl_3$)^{5b}).

3,4-O-Isopropylidene-D-mannitol (2).

The monoacetone 2 was prepared from triacetone 1 (90g, 300mmol) by using procedures described previously^{3,5b} (78% yield after recrystallization from acetone); mp 90°C (Lit. 86-87°C³, 87°C^{5b}); $[\alpha] +19^\circ$ (c 0.97, pyridine) (Lit. ^{5b} $+18.7^\circ$ (c 1.52, pyridine)).

1,6-Di-O-tosyl-3,4-O-isopropylidene-D-mannitol (3).

The monoacetone 2 (22.2g, 100mmol) in pyridine (320ml) was stirred at -5°C and the tosyl chloride (2.05 eq.) was slowly added. The mixture was kept at 0°C for 3.75 h, then poured into a cold mixture of hydrochloric acid (6N, 640ml) and diethyl ether (300ml). The ether extract was washed with an aqueous solution of sodium bicarbonate (3%, 400ml), dried ($MgSO_4$) and evaporated to a syrup which was used without further purification. An analytical sample can be obtained after column chromatography (silica gel; 4:1 dichloromethane:ether), mp 86°C ;

$[\alpha] +24^\circ$ (c 2.58, CH_2Cl_2); 1H -NMR (90MHz): 8-7.1 (m, 8H); 4.5-3.6 (m, 10H); 2.4 (s, 6H); 1.25 (s, 6H).

1,2:5,6-Dianhydro-3,4-O-isopropylidene-D-mannitol (4).

The crude ditosylate 3 (33.9g, 63mmol) in methanol (400ml) was stirred with anhydrous potassium carbonate (5eq.) for 2.50 h at 25°C. The mixture was diluted with water and extracted with dichloromethane. Washing of the extract with an aqueous solution of ammonium chloride, drying ($MgSO_4$) and evaporation gave a syrup after distillation (70% overall yield from 2); eb₀ 569-71°C; $[\alpha] -2.3^\circ$ (c 2.8, $CHCl_3$) (Lit.^{4a} 0°, $CHCl_3$); 1H -NMR: 3.77 (m, 2H, H_3); 3.06 (m, 2H, H_2); 2.78 (ABX, 1H, J = 5 Hz, J = 4.25 Hz, H_1); 2.66 (ABX, 1H, J = 5 Hz, J = 2.7 Hz, H_1); 1.38 (s, 6H, $C(CH_3)_2$).

^{13}C -NMR: 109.8(s, C(CH₃)₂); 77.9(d, C₃); 51.1(d, C₂); 44.7(t, C₁); 26.5 (q, C(CH₃)₂).

SM(70eV): 171 (M-15 100%); 85(33); 81(29); 69(25); 59(80). Anal. Calcd. for C₉H₁₄O₄: C, 58.05; H, 7.58. Found: C, 57.95; H, 7.78.

1,6-Di-O-benzoyl-3,4-O-isopropylidene-D-mannitol (5).

To a stirred solution of monoacetone 2 (15g, 67.6 mmol) and pyridine (275 ml) in dichloromethane (275 ml) was dropwise added a solution of benzoyl chloride (2eq.) in dichloromethane (15 ml) at -80°C. The reaction mixture was stirred at -80°C for 4 h and slowly warmed to 0°C. The mixture was poured into a cold hydrochloric acid solution (6N, 550 ml) and extracted with dichloromethane. Washing of the extract with an aqueous solution of sodium bicarbonate (3%, 100 ml), drying (MgSO₄) and evaporation gave a syrup which was used without further purification. An analytical sample can be obtained by recrystallization from ether-hexane (1/1), mp 94°C; $[\alpha] +25.3^\circ$ (c 1.48, pyridine) (Lit.^{5b} mp 94°C; $\alpha +24.1^\circ$ (c 1.46, pyridine)); ^1H -NMR(90MHz): 8.1-7.1(m, 10H); 4.85-4.0(m, 8H); 1.4(s, 6H).

1,6-Di-O-benzoyl-2,5-di-O-tosyl-3,4-O-isopropylidene-D-mannitol (6)

To a stirred solution containing the crude compound 5 (16.5 g, 38 mmol), triethylamine (2eq.) and dimethylaminopyridine¹¹ (0.2eq.) in dichloromethane (152 ml) was slowly added tosyl chloride (2eq.) at 0°C. The reaction mixture was then stirred at 0°C for 1 h and at 25°C for 24 h. The mixture was poured into a cold hydrochloric acid solution (3N, 30 ml) and extracted with dichloromethane. Washing of the extract with brine, drying (MgSO₄) and evaporation gave a syrup (25g) which was used without further purification. An analytical sample can be obtained after column chromatography (silica gel; 98:2 dichloromethane:ether); mp 95°C (Lit. 96-97°C^{5a}; 99°C^{5b}); $[\alpha] +24.3^\circ$ (c 3.0, CHCl₃) (Lit. +27.0° (c 0.25, CHCl₃)^{5a}; +27° (CHCl₃)^{5b}); ^1H -NMR(90MHz): 8.05-7.15(m, 18H, arom); 5.05(m, 2H, H₂); 4.75-4.25 (m, 6H, H₁, H₃); 2.3(s, 6H, CH₃-arom); 1.4(s, 6H, C(CH₃)₂).

1,2:5,6-Dianhydro-3,4-O-isopropylidene-L-iditol (7).

Crude compound 6 (59.8 g, 81 mmol) in dichloromethane (250 ml) and methanol (300 ml) was stirred with anhydrous potassium carbonate (5eq.) for 2.50 h at 25°C. The reaction mixture was then worked-up using the procedure previously described (3 → 4). A white solid was obtained with 65% yield from 2, after column chromatography (silica gel; 1:4 ethyl acetate : dichloromethane) and recrystallization from hexane; mp 71°C; $[\alpha] -17.5^\circ$ (c 1.0, CH₂Cl₂) (Lit.^{4b} mp 71-72°C; $[\alpha] -17.0^\circ$ (c 2.0, CHCl₃)); ^1H -NMR(90MHz): 3.75(m, 2H, H₃); 3.05(m, 2H, H₂); 2.8(ABX, 1H, J=5Hz, J=4.5Hz, H₁); 2.65(ABX, 1H, J=5 Hz, J=2.7Hz, H₁); 1.4(s, 6H, C(CH₃)₂); ^{13}C -NMR: 110.4(s, C(CH₃)₂); 77.9(d, C₃); 51.0(d, C₂); 43.7(t, C₁); 26.4 (q, C(CH₃)₂); SM(70eV): 171(M-15, 60%); 85(25); 83(22); 69(22); 59(92); 55(100); Anal. Calcd. for C₉H₁₄O₄: C, 58.05; H, 7.58. Found: C, 57.91; H, 7.71.

1,6-Dideoxy-1,6-diazido-3,4-O-isopropylidene-D-mannitol (8).

A suspension of ditosylate 3 (23.0 g, 43.5 mmol) and sodium azide (2 x 2 eq.) in dry dimethylformamide (175 ml) was stirred at 70°C for 3 h. After dimethylformamide evaporation, 100 ml of water were added to the residue which was then extracted with methylene chloride; the extract was dried (MgSO₄) and evaporated to a syrup (100% yield). An analytical sample can be obtained after flash

chromatography (silica gel; 90:10 dichloro methane:diethyl ether) ; $[\alpha]_D^{25} +46^\circ$ (c 2, CH_2Cl_2); $^1\text{H-NMR}$: 3.90-3.70 (m, 6H, $\text{H}_2\text{H}_3\text{OH}$); 3.64, 3.45 (ABX, $J_{AB} = 12.5\text{Hz}$, 4H, CH_2N_3); 1.36 (s, 6H, $\text{C}(\text{CH}_3)_2$); IR: $\nu_{\text{OH}} 3350\text{cm}^{-1}$; $\nu_{\text{N}_3} 2100\text{cm}^{-1}$. Anal. calcd. for $\text{C}_9\text{H}_{16}\text{N}_6\text{O}_4$: C, 39.70; H, 5.92; N, 30.87. Found: C, 39.72; H, 6.23; N, 29.93.

(2S,3R,4R,5S) 1,2:5,6-Diimino-3,4-O-isopropylidenehexanediol (2).

A solution of diazidodiol **8** (2.72 g, 10 mmol) and triphenyl phosphine (5.2 g, 20 mmol) in dry toluene (60 ml) was stirred at 40°C until nitrogen evolution had ceased. The mixture was then carried at 105°C and stirred 20 h under nitrogen. After evaporation to dryness, triphenyl phosphine oxide precipitated as a white powder upon addition of diethyl ether (10 ml). Filtration of $\text{PO}(\text{Ph})_3$ and evaporation of ether afforded quantitatively a syrup of crude N-unsubstituted aziridine **9** (containing about 25% w/w of $\text{PO}(\text{Ph})_3$) which was protected without further purification.

(2S,3R,4R,5S) 1,2:5,6-N-Benzylidimino-3,4-O-isopropylidenehexanediol (10a).

To a mixture of benzyl bromide (2.1 ml, 17.2 mmol) and triethylamine (10 ml, 72 mmol) was added at 0°C crude diaziridine **9** (1.75 g, 7 mmol) in anhydrous tetrahydrofuran (25 ml). After stirring 15 h at room temperature, tetrahydrofuran was evaporated, anhydrous ether (50 ml) was added and the precipitated solids filtered. The supernatant was concentrated in vacuo to afford, after column chromatography (silica gel; 50:50 hexane:ethyl acetate) a syrup (yield: 70%); $[\alpha]_D^{25} -45^\circ$ (c 1.0, CH_2Cl_2); $^1\text{H-NMR}$: 7.30-7.20 (m, 10H, arom.); 3.55 (m, 2H, H_3); 3.41, 3.30 (AB, $J = 12.5\text{Hz}$, 4H, NCH_2); 1.90 (d, $J_{1,2} = 3.5\text{Hz}$, 2H, H_1trans); 1.57 (m, 2H, H_2); 1.40 (d, $J_{1,2} = 6.3\text{Hz}$, 2H, H_1cis); 1.34 (s, 6H, $\text{C}(\text{CH}_3)_2$); Anal. Calcd. for $\text{C}_{23}\text{H}_{28}\text{N}_2\text{O}_2$: C, 75.79; H, 7.74. Found: C, 75.51; H, 7.86.

(2S,3R,4R,5S) 1,2:5,6-N-Benzylloxycarbonyldimino-3,4-O-isopropylidenehexanediol (10b).

To a mixture of crude diaziridine **9** (500 mg, 2 mmol) and triethylamine (0.7 ml, 5 mmol) in dichloromethane (4 ml), benzylchlorocarbonate (0.7 ml, 5 mmol) was added under nitrogen at 0°C . The mixture was stirred 4 h at 20°C , anhydrous ether was added (15 ml) and the precipitated solids filtered. The supernatant was concentrated in vacuo to afford the crude aziridine carbamate which crystallized after flash chromatography (silica gel; 2:1 hexane:ethyl acetate) in 60% yield; mp 104°C ; $[\alpha]_D^{25} -64.6^\circ$ (c 1.0, CH_2Cl_2); $^1\text{H-NMR}$: 7.25 (m, 10H, arom.); 5.06, 5.01 (AB, $J = 12\text{Hz}$, 4H, CH_2Ph); 3.90 (m, 2H, H_3); 2.51 (m, 2H, H_2); 2.28 (d, $J_{1,2} = 6.5\text{Hz}$, 2H, H_1cis); 2.25 (d, $J_{1,2} = 3.5\text{Hz}$, 2H, H_1trans); 1.26 (s, 6H, $\text{C}(\text{CH}_3)_2$); Anal. Calcd. for $\text{C}_{25}\text{H}_{28}\text{N}_2\text{O}_6$: C, 66.34; H, 6.24; N, 6.19. Found: C, 66.25; H, 6.11; N, 6.18.

(2S,3R,4R,5S) 1,2:5,6-N-Tosyldimino-3,4-O-isopropylidenehexanediol (10c).

To a suspension of potassium hydride (200 mg, 5 mmol) in tetrahydrofuran (2 ml) a solution of **9** (500 mg, 2 mmol) in tetrahydrofuran (3 ml) was added under nitrogen at 20°C . After 30 min, the weak gas evolution had ceased and a solution of tosyl chloride (950 mg, 5 mmol) in tetrahydrofuran (4 ml) was slowly added at 0°C to the mixture, gas evolution occurred. After 3 h stirring at 20°C , water

hydrolysis (3 ml), dichloromethane extraction, evaporation of the solvent and flash chromatography (silica gel; 2:1 hexane:ethyl acetate) **10c** was obtained as white crystals in 55% yield; mp 60°C; $[\alpha]_D^{25} -24^\circ$ (c 1.0, CH₂Cl₂); ¹H-NMR: 7.82 (d, J=8Hz, 4H, arom.); 7.35 (d, 4H, arom.); 3.81 (m, 2H, H₃); 2.76 (m, 2H, H₂); 2.60 (d, J_{1,2}=7Hz, 2H, H₁ cis); 2.45 (s, 6H, CH₃-Ph); 2.38 (d, J_{1,2}=5Hz, 2H, H₁ trans); 1.23 (s, 6H, C(CH₃)₂). Anal. Calcd. for C₂₃H₂₈N₂S₂O₆: C, 56.06; H, 5.73; N, 5.69. Found: C, 55.88; H, 5.85; N, 5.76.

(2R,3S,4S,5R) 1,6-Diazido-2,5-di-O-mesyl-3,4-O-isopropylidenehexanetetrol (11).

To a solution of diazidodiol **8** (5.4 g, 20 mmol) in pyridine (64 ml), mesyl chloride (2.1 eq.) was slowly added at 0°C. The mixture was stirred 24 h at 20°C, then poured into a cold mixture of hydrochloric acid (6N, 128 ml) and extracted with dichloromethane. The extract was washed with a solution of sodium bicarbonate (3%, 100 ml), dried (MgSO₄) and evaporated to afford after flash chromatography (silica gel; 95:5 dichloromethane:diethyl ether) compound **11** as a white solid in 95% yield; mp 91.5°C; $[\alpha]_D^{25} +3.5^\circ$ (c 1.0, CH₂Cl₂); ¹H-NMR (90Mz): 4.8 (m, 2H, H₂); 4.3 (m, 2H, H₃); 3.8, 3.6 (AB, J=14Hz, 4H, H₁); 3.1 (s, 6H, CH₃-S); 1.3 (s, 6H, C(CH₃)₂); Anal. Calcd. for C₁₁H₂₀N₆S₂O₈: C, 30.82; H, 4.65; N, 19.63. Found: C, 30.71; H, 4.67; N, 19.26.

(2S,3S,4S,5S) 1,6-Diazido-2,5-dibromo-3,4-O-isopropylidenehexanediol (12).

Dimesylate **11** (1.25 g, 3 mmol) in dichloromethane (7 ml) is added on magnesium bromide (24 mmol) prepared in diethyl ether (7 ml). The mixture is stirred 20 h at 45°C, hydrolysed with water and extracted with dichloromethane to afford after solvent evaporation and flash chromatography (silica gel; 3:2 dichloromethane:hexane) compound **12** as an oil in 65% yield; $[\alpha]_D^{25} +41^\circ$ (c 1.9, CH₂Cl₂); ¹H-NMR: 4.2 (s, 2H, H₃); 4.08 (t, 2H, H₂); 3.78 (d, J_{1,2}=14Hz, 4H, H₁); 1.48 (s, 6H, C(CH₃)₂); Anal. Calcd. for C₉H₁₄O₂N₆: C, 27.16; H, 3.54; N, 21.11; Found: C, 27.55; H, 3.55; N, 20.03.

(2R,3R,4R,5R) 1,2:5,6-Dilimino-3,4-O-isopropylidenehexanediol (13).

A solution of compound **12** (1.79 g, 4.5 mmol) in tetrahydrofuran (9 ml) is added, under nitrogen, at 0°C to a stirred suspension of lithium aluminium hydride (10 mmol) in tetrahydrofuran (9 ml). Gas evolution occurs at 5°C, the mixture is stirred 6 h at 20°C before hydrolysis with, water (0.4 ml), 15% sodium hydroxide (0.4 ml) and water (1.2 ml) at 0°C. The organic layer was filtered through a celite pad and the salts were washed with diethyl ether. The solvents were removed in vacuo, the crude N-unsubstituted diaziridine was obtained quantitatively as an oil and was protected without purification. Transformation of crude **13** into **14a**, **14b** and **14c** was performed following the same procedures as described for **2**.

(2R,3R,4R,5R) 1,2:5,6-N-Benzylidilimino-3,4-O-isopropylidenehexanediol (14a)

Syrup; $[\alpha]_D^{25} +54^\circ$ (c 1.0, CH₂Cl₂); ¹H-NMR: 7.33-7.25 (m, 10H, arom.); 3.50 (m, 2H, H₃); 3.67, 3.20 (AB, J=13.5Hz, 4H, NCH₂); 1.66 (d, J_{1,2}=3.5Hz, 2H, H₁ trans); 1.60 (m, 2H, H₂); 1.39 (s, 6H, C(CH₃)₂); 1.34 (d, J_{1,2}=6.5Hz, 2H, H₁ cis).

(2R,3R,4R,5R)1,2:5,6-N-Benzoyloxycarbonyldiimino-3,4-O-isopropylidenehexanediol (14b).

¹H-NMR: 7.25 (m, 10H, arom.); 5.01 (s, 4H, CH₂Ph); 3.81 (m, 2H, H₃); 2.63 (m, 2H, H₂); 2.31 (d, J_{1,2}=6.5Hz, 2H, H₁cis); 2.20 (d, J_{1,2}=3.5Hz, 2H, H₁trans); 1.3 (s, 6H, C(CH₃)₂).

(2R,3R,4R,5R)1,2:5,6-N-Tosyldiimino-3,4-O-isopropylidenehexanediol (14c)

m.p. 121°C. [α]_D+42° (c 2.1, CH₂Cl₂); ¹H-NMR: 7.81 (d, J=8.5Hz, 4H, arom.); 7.35 (d, 4H, arom.); 3.62 (m, 2H, H₃); 2.90 (m, 2H, H₂); 2.61 (d, J_{1,2}=7Hz, 2H, H₁cis); 2.43 (s, 6H, CH₃-Ph); 2.25 (d, J_{1,2}=4.5Hz, 2H, H₁trans); 1.21 (s, 6H, C(CH₃)₂).

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