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

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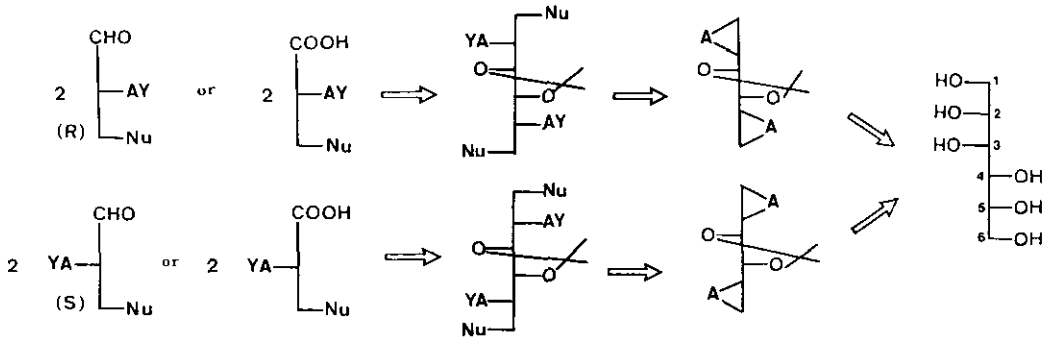
Abstract-Specific activations or protections of the hydroxyl groups of 3-4-O-isopropylidene-D-mannitol 2 followed by intramolecular SN2 reactions, lead to the chiral diepoxides 4 and 7 and to the chiral diaziridines 9 and 13 precursors of enantiomerically pure α-hydroxy and α-amino aldehydes or acids.

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 compound, D-mannitol, according to the following scheme:



SCHEME I

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 C_2 and C_5 will have

-Respectueusement dédié au Professeur Gilbert STORK pour son 65ème anniversaire.

identical absolute configurations and the cleavage of the C_3—C_4 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 SN2 reaction, leading to diepoxide 4, with retention of configuration at C_2 and C_5. Attack of 3 at C_1 and C_6 by various nucleophiles (N_3^-, 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: dibenzoylation[5] (2 ⟶ 5), ditosylation[5] (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 SN2 reaction occurs with inversion of configuration at C_2 and C_5.

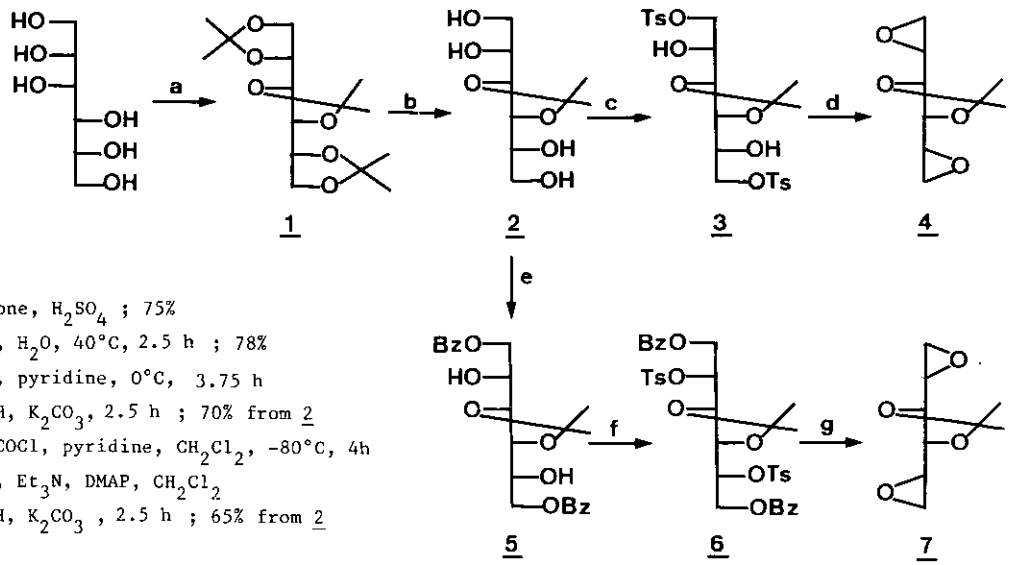
Nucleophilic opening of the diastereoisomeric diepoxides 4 and 7 and cleavage of the C_3——C_4 bond, leads to enantiomerically pure α-hydroxyaldehydes[1]. We used this strategy to prepare starting materials for a synthesis of leukotriene (+)-LTB_4[6].

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.

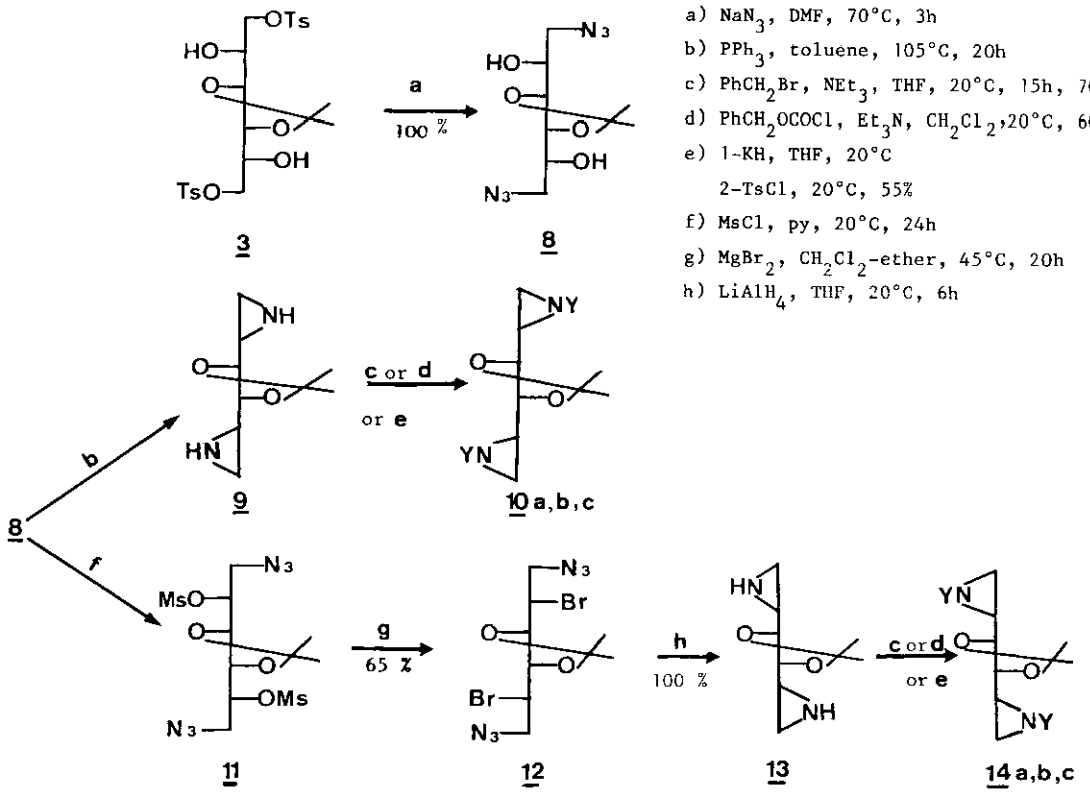
Ring closure of 8 by triphenylphosphine[7] occurs with inversion of configuration at C_2 and C_5 and leads to diaziridine 9 quantitatively after heating for 20h at 105°C in toluene. Diaziridine 13 is formed by the following transformations of 8: dimesylation(8 ⟶ 11), dibromation(11 ⟶ 12), reduction-cyclisation (12 ⟶ 13). SN2 reactions by bromide ions ($MgBr_2$)[8] on the dimesylate 11 involve the inversions of configuration at C_2 and C_5. A second inversion at the same centers occurs during the reduction of 12 by lithium aluminium hydride and concomitant cyclisation[9] 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=CH_2Ph; b:Y=$COOCH_2Ph$; c:Y=Ts).

SCHEME II



a) Acetone, H_2SO_4 ; 75%
b) AcOH, H_2O, 40°C, 2.5 h ; 78%
c) TsCl, pyridine, 0°C, 3.75 h
d) CH_3OH, K_2CO_3, 2.5 h ; 70% from 2
e) C_6H_5COCl, pyridine, CH_2Cl_2, -80°C, 4h
f) TsCl, Et_3N, DMAP, CH_2Cl_2
g) CH_3OH, K_2CO_3 , 2.5 h ; 65% from 2

SCHEME III



a) NaN_3, DMF, 70°C, 3h
b) PPh_3, toluene, 105°C, 20h
c) $PhCH_2Br$, NEt_3, THF, 20°C, 15h, 70%
d) $PhCH_2OCOCl$, Et_3N, CH_2Cl_2,20°C, 60%
e) 1-KH, THF, 20°C
2-TsCl, 20°C, 55%
f) MsCl, py, 20°C, 24h
g) $MgBr_2$, CH_2Cl_2-ether, 45°C, 20h
h) $LiAlH_4$, THF, 20°C, 6h

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. ^{1}H-NMR spectra were recorded in $CDCl_3$ on 250 MHz Bruker spectrometer (except otherwise mentionned) and on EM 390 Varian spectrometer. ^{13}C-NMR spectra were recorded in $CDCl_3$ on Bruker spectrometer. *Specific rotation were measured for* λ=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°C[10], 70°C [5b]); $[\alpha]$+13.6°(c 1.0,CH_2Cl_2). (Lit. +12.5°(C_2H_5OH)[10], +13.8(c 1.7, $CHCl_3$)[5b]).

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

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

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

The monoacetonide 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° (c 2.58,CH_2Cl_2);^{1}H-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); $eb_{0.5}$69-71°C;$[\alpha]$-2.3°(c 2.8, $CHCl_3$)(Lit[4a] 0°,$CHCl_3$);^{1}H-NMR:3.77(m,2H,H_3);3.06(m,2H,H_2);2.78(ABX,1H,J=5Hz,J=4.25Hz,H_1);2.66(ABX,1H,J=5Hz,J=2.7Hz,H_1);1.38(s,6H,C(CH_3)$_2$).

^{13}C-NMR:109.8(s,$\underline{C}(CH_3)_2$);77.9(d,C_3);51.1(d,C_2);44.7(t,C_1),26.5 (q,$C(\underline{C}H_3)_2$). SM(70ev):171 (M-15 100%);85(33);81(29);69(25);59(80). Anal.Calcd.for $C_9H_{14}O_4$: 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 monoacetonide 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 ($MgSO_4$) 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° (c 1.48,pyridine) (Lit.[5b] mp 94°C; α +24.1° (c 1.46,pyridine)); ^{1}H-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 dimethylaminopyridine[11] (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 ($MgSO_4$) 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°(c 3.0,$CHCl_3$) (Lit.+27.0°(c 0.25, $CHCl_3$)[5a] ;+27°($CHCl_3$)[5b]); ^{1}H-NMR(90MHz):8.05-7.15(m,18H,arom); 5.05(m, 2H,H_2; 4.75-4.25 (m,6H,H_1,H_3); 2.3(s,6H,CH_3-arom); 1.4(s,6H, $C(CH_3)_2$).

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°(c 1.0,CH_2Cl_2) (Lit.[4b]:mp 71-72°C; $[\alpha]$ -17.0°(c 2.0,$CHCl_3$)); ^{1}H-NMR(90MHz):3.75(m,2H,H_3); 3.05(m,2H,H_2); 2.8(ABX,1H,J=5Hz,J=4.5Hz,H_1) 2.65(ABX,1H,J=5 Hz, J=2.7Hz, H_1,); 1.4(s,6H, $C(CH_3)_2$); ^{13}C-NMR:110.4(s,$\underline{C}(CH_3)_2$);77.9(d,C_3); 51.0(d,C_2);43.7(t,C_1);26.4 (q,$C(\underline{C}H_3)_2$; SM(70eV):171(M-15, 60%); 85(25); 83(22); 69(22); 59(92); 55(100); Anal.Calcd. for $C_9H_{14}O_4$: 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 ($MgSO_4$) and evaporated to a syrup (100% yield). An analytical sample can be obtained after flash

chromatography (silica gel; 90:10 dichloro methane:diethyl ether) ; $[\alpha]$+46°(c 2, CH_2Cl_2);^{1}H-NMR:3.90-3.70 (m,6H,H_2H_3OH); 3.64, 3.45 (ABX,J_{AB}= 12.5Hz, 4H, CH_2N_3); 1.36(s,6H, $C(CH_3)_2$); IR: ν_{OH}3350cm^{-1}; ν_{N3}2100cm^{-1}. Anal.calcd.for $C_9H_{16}N_6O_4$: 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(9).
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 $PO(Ph)_3$ and evaporation of ether afforded quantitatively a syrup of crude N-unsubstituted aziridine 9 (containing about 25% w/w of $PO(Ph)_3$) which was protected without further purification.

(2S,3R,4R,5S) 1,2:5,6-N-Benzyldiimino-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:ethylacetate) a syrup (yield:70%); $[\alpha]$-45°(c 1.0,CH_2Cl_2); ^{1}H-NMR: 7.30-7.20(m,10H,arom.); 3.55(m,2H,H_3); 3.41,3.30(AB,J=12.5Hz,4H, NCH_2); 1.90(d,$J_{1,2}$=3.5Hz, 2H,H_1trans) ; 1.57(m,2H,H_2); 1.40(d,$J_{1,2}$=6.3Hz,2H,H_1cis); 1.34 (s,6H,$C(CH_3)_2$); Anal. Calcd.for $C_{23}H_{28}N_2O_2$: C, 75.79; H, 7.74. Found: C, 75.51; H, 7.86.

(2S,3R,4R,5S) 1,2:5,6-N-Benzyloxycarbonyldiimino-3,4-O-isopropylidene hexanediol(10b).
To a mixture of crude diaziridine 9 (500 mg, 2 mmol) and triethylamine (0.7ml, 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 fitered. 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; $[\alpha]$-64.6°(c 1.0, CH_2Cl_2); ^{1}H-NMR: 7.25 (m,10H,arom.); 5.06,5.01 (AB, J=12Hz,4H,CH_2Ph); 3.90(m,2H,H_3); 2.51 (m,2H,H_2); 2.28 (d,$J_{1,2}$=6.5Hz,2H,H_1cis); 2.25(d,$J_{1,2}$=3.5Hz,2H,H_1 trans); 1.26(s,6H,$C(CH_3)_2$); Anal.Calcd.for $C_{25}H_{28}N_2O_6$: 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-Tosyldiimino-3,4-O-isopropylidene hexanediol (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; $[\alpha]$-24°(c 1.0, CH_2Cl_2); ^{1}H-NMR: 7.82 (d,J=8Hz,4H,arom.); 7.35 (d,4H,arom); 3.81 (m,2H,H_3); 2.76 (m,2H,H_2); 2.60 (d,$J_{1,2}$=7Hz,2H,H_1cis); 2.45 (s,6H,CH_3-Ph); 2.38 (d,$J_{1,2}$=5Hz,2H,H_1trans); 1.23 (s,6H, C(CH_3)$_2$). Anal.Calcd. for $C_{23}H_{28}N_2S_2O_6$: 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 ($MgSO_4$) 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; $[\alpha]$+3.5° (c 1.0,CH_2Cl_2);^{1}H-NMR(90Mz): 4.8 (m,2H,H_2); 4.3 (m,2H,H_3); 3.8,3.6 (AB, J=14Hz,4H,H_1); 3.1 (s,6H,CH_3-S); 1.3 (s,6H,C(CH_3)$_2$); Anal.Calcd. for $C_{11}H_{20}N_6S_2O_8$: 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; $[\alpha]$+41°(c 1.9,CH_2Cl_2);^{1}H-NMR: 4.2 (s,2H,H_3); 4.08 (t,2H,H_2); 3.78 (d,$J_{1,2}$=14Hz,4H,H_1); 1.48 (s,6H C(CH_3)$_2$); Anal.Calcd. for $C_9H_{14}O_2N_6$: 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-Diimino-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 9.

(2R,3R,4R,5R) 1,2:5,6-N-Benzyldiimino-3,4-O-isopropylidenehexanediol (14a)
Syrup; $[\alpha]$+54° (c 1.0,CH_2Cl_2);^{1}H-NMR: 7.33-7.25 (m,10H,arom.); 3.50 (m,2H,H_3); 3.67,3.20 (AB,J=13.5Hz, 4H,NCH_2); 1.66 (d,$J_{1,2}$=3.5Hz,2H, H_1trans); 1.60 (m,2H,H_2); 1.39 (s,6H,C(CH_3)$_2$); 1.34(d,$J_{1,2}$=6.5Hz, 2H,H_1cis).

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

^{1}H-NMR: 7.25 (m,10H,arom.); 5.01 (s,4H,CH_2Ph); 3.81 (m,2H,H_3); 2.63 (m,2H,H_2); 2.31 (d,$J_{1,2}$=6.5Hz,2H,H_1cis); 2.20 (d,$J_{1,2}$=3.5Hz,2H, H_1trans); 1.3 (s,6H, $C(CH_3)_2$).

(2R,3R,4R,5R) 1,2:5,6-N-Tosyldiimino-3,4-O-isopropylidenehexanediol (14c) m.p.121°C. $[\alpha]$ +42°(c 2.1,CH_2Cl_2);^{1}H-NMR: 7.81 (d,J=8.5Hz,4H,arom.); 7.35 (d,4H,arom.); 3.62 (m,2H,H_3); 2.90(m,2H,H_2);2.61 (d,$J_{1,2}$=7Hz,2H, H_1cis); 2.43 (s,6H,CH_3-Ph); 2.25 (d,$J_{1,2}$=4.5Hz,2H,H_1trans); 1.21 (s,6H,$C(CH_3)_2$).

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Received, 20th June, 1986