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Synthesis of New Chiral Auxiliaries Derived From Isosorbide

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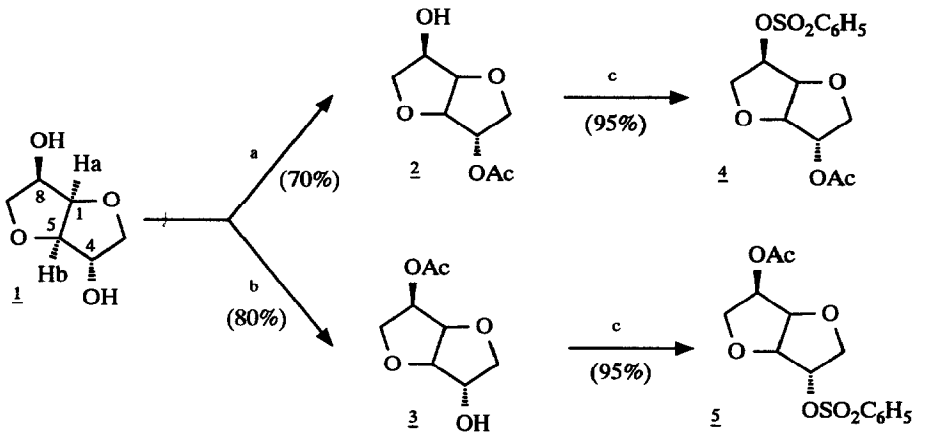
***Abstract** : Synthesis of both monobenzenesulfonates of isosorbide (1,4:3,6-dianhydrosorbitol) was regioselectively achieved in high yields via a three-step sequence. These monoesters were O-alkylated before being reacted with various primary amines to give the corresponding amino ethers. The full control of regioselectivity led either to the exo-exo or endo-endo isomers. In an independent pathway, isosorbide derived amino ethers and amino alcohols with both amino and hydroxy functions in the endo position, were synthesized from isosorbide in a four-step procedure including selective monobenzylation, tosylation, substitution by amines and debenzylation.*

INTRODUCTION: Chiral amino alcohols and amino ethers are often used as catalysts or auxiliaries in asymmetric synthesis.[1,2,3] They are employed for instance in enantioselective Reformatsky reactions,[4] cyclopropanation of olefins,[5] 1,4-addition on α,β-unsaturated ketones[6] and reduction of ketones.[7] In addition, their quaternary ammonium salts can be used in asymmetric phase transfer catalysis.[8] In this field, the need of an inexpensive source of chiral auxiliaries for asymmetric synthesis prompted chemists to work on natural chiral molecules such as carbohydrates.[9] For this purpose, our groups have been interested recently in the synthesis of new templates derived from isosorbide[10] 1 ([1R,4S,5R,8R]-2,6-dioxabicyclo[3.3.0]octan-4,8-diol also called 1,4:3,6-dianhydrosorbitol). Isosorbide is a very attractive chiral reagent which is cheap and commercially available. It is industrially obtained from starch by dehydration of sorbitol and can be thus considered as a biomass product. It is currently of commercial importance as the nitro and methylether derivatives.[10c] Surprisingly little work has been done on its use in asymmetric synthesis.[11] Diamino derivatives of isosorbide are well known [12] while amino alcohols have been scarcely described. [12d, 13] To our knowledge, no preparation of amino ethers of isosorbide has been published. We wish to report in the present paper the synthesis of chiral amino alcohols and amino ethers derived from isosorbide using two different selective routes.

RESULTS and DISCUSSION

I) Monoacetylation Route: Isosorbide can be selectively monoacetylated[14] into the exo or endo compound **2** or **3** (scheme 1).



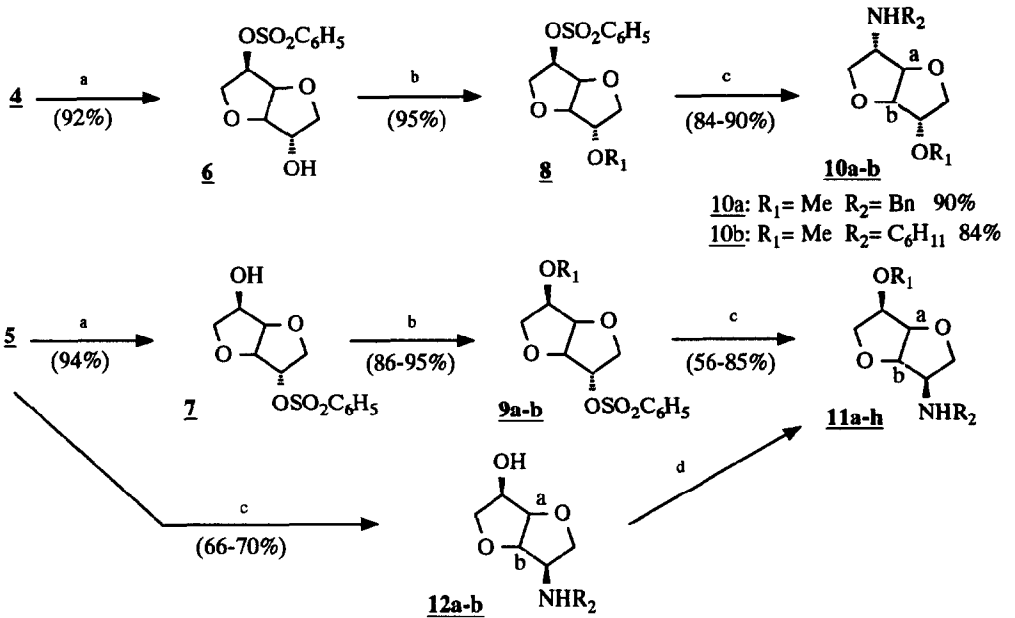
Scheme1: (a) Ac_2O, 120-140°C, 1h, then KOH, distillation; (b) Ac_2O, PbO, r.t., 20h. (c) $PhSO_2Cl$, pyridine, 0°C.

The free hydroxy group of **2** and **3** was activated as its sulfonate by treatment with benzenesulfonyl chloride in the presence of pyridine. Products **4** and **5** were purified by crystallization and showed only one epimer by GPC analysis. The chemoselective deacetylation of **4** and **5** was achieved by treament with a refluxing mixture of water-EtOH-Et_3N.[15] Compounds **6** and **7** were both obtained in a chemically pure form and in high overall yields (71 % and 65 % respectively from isosorbide) (Scheme 2).

This three-step route provides an alternative and more selective pathway to both isosorbide monosulfonates than the direct sulfonylation. [13] The latter reaction requires treatment of isosorbide with one equivalent of arylsulfonyl chloride and subsequent separation of the two resulting monosulfonates and the disulfonate.

The two isosorbide sulfonates **6** and **7** were O-alkylated under phase transfer catalysis[16] in almost quantative yields. The resulting ethers **8** and **9** were reacted with excess of primary amines at reflux temperature or in a sealed tube at 160°C to give the corresponding amino ethers **10a-b** and **11a-h**. As expected, amination of sulfonates **8** and **9** occurs via a Sn^2-type substitution. In both cases complete inversion of configuration is observed with a favored exo-attack on **8** and a more hindered endo-attack on **9**. [12b,12c]

Thus, amino ethers **10** and **11** respectively possess exo-exo and endo-endo configurations. This was easily established from ^1H NMR analysis based on the observation of the H_1-H_8 or H_4-H_5 coupling (cis $J_{1H\text{-}1H}$ = 5 Hz and trans $J_{1H\text{-}1H}$ = 0 Hz). The doublet of doublet of H_a in **8** became a doublet in **10** whereas the doublet of H_b in **9** became a doublet of doublet in **11**.



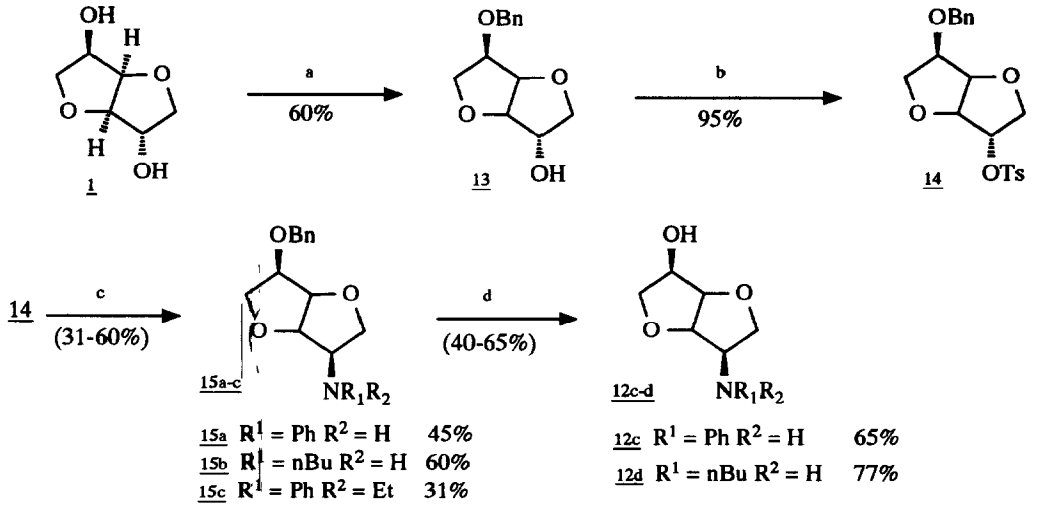
Product	R_1	R_2	yield (%)[a]
11a	CH_3	benzyl	68
11b	CH_3	cyclohexyl	63
11c	CH_3	cyclohexylmethyl	85
11d	CH_3	isopropyl	76
11e	CH_3	terbutyl	56
11f	CH_3	$(iPr)_2CH$	48
11g	benzyl	cyclohexyl	83
12a	H	cyclohexyl	66
12b	H	benzyl	70
11h	neopentyl	benzyl	79

(a) yield of amination reaction (step c) excepted for 11h (alkylation reaction, step d).

Scheme 2: (a) H_2O/EtOH/Et_3N, reflux, 6h; (b) Me_2SO_4, 50% NaOH, TBAI, CH_2Cl_2, rt, 3h or $PhCH_2Cl$, 50% NaOH, TBAHS, 60°C, 3h. (c) R_2NH_2, reflux or pressure; (d) NaH, DMF, then $tBuCH_2Br$, 100°C.

Amino ether **11h** was obtained in a different way starting from the O-acetylarylsulfonate **5**. This sulfonate was reacted with a primary amine as previously described. The selective substitution of the arylsulfonate moiety occurs with simultaneous cleavage of the acetate group to give the amino alcohols **12a-b**. O-Alkylation of compound **12b** according to the Williamson's procedure[17] gave amino ether **11h** which proved to have an endo-endo configuration (both H_a and H_b appear as doublets of doublet in ^1H NMR).

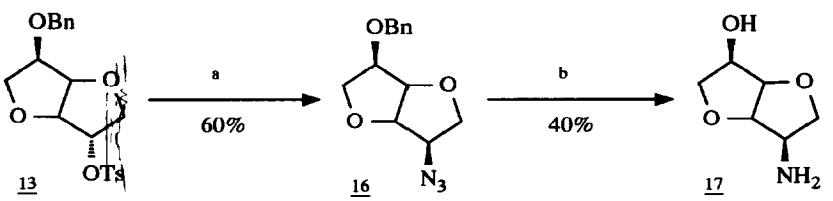
II) Monobenzylation Route: Taking advantage of the regioselective monobenzylation of isosorbide (endo position),[18] amino ethers **15a-c** and amino alcohols **12c** and **12d** were conveniently prepared according to Scheme 3.



Scheme 3: (a) LiH, $PhCH_2Cl$, DMF,))); (b) TsCl, pyridine; (c) R_1R_2NH; (d) H_2, Pd 10%/C, EtOH

Tosylation of the endo monobenzylether **13** with an excess of tosyl chloride in pyridine led to compound **14** in high yield. Sn^2-type amination of tosylate **14** has been already studied [12d, 19] but in our case only poor yields were obtained even at high temperatures in a sealed tube. This reaction was best performed without solvent in excess of amine at reflux temperature or under microwave irradiation in a mono mode reactor.[20] Thus, the crude amino ethers **15a** and **15b** were obtained in good yields (up to 70 % by GC analysis) but purification by flash chromatography on silica gel led to lower yields of isolated products. It should be noted than amination of **14** with N-ethylaniline led to two epimers with the endo-endo amino ether **15c** as the major product.

The endo-endo configuration of amino ethers **15** was established as previously described from the ^1H NMR spectra. Catalytic hydrogenation of amino ethers **15a** and **15b** in ethanol with 10% Palladium on charcoal (1 bar) respectively led to amino alcohols **12c** (65%) and **12d** (77%). Amino alcohol **17** was isolated after catalytic hydrogenation (azide reduction and debenzylation) of azido ether **16** . The latter compound was also obtained from tosylate **13** by reaction of sodium azide (Scheme 4).



Scheme 4: (a) NaN_3, DMSO, 120°C. (b) H_2, Pd 10%/C, EtOH, r.t.

CONCLUSION: In conclusion, various chiral amino alcohols and amino ethers derived from isosorbide were synthesized with useful overall yields (35-60%) and full chemo and stereoselectivities. Two different and complementary routes were studied either by selective monoacetylation or monobenzylation of isosorbide. Asymmetric synthesis (alkylation, aldolization,...) using these chiral amines is currently being investigated.

Experimental: IR spectra were recorded on a Beckman IR 4250. ^1H and ^{13}C N.M.R. spectra were recorded on a Brucker AC 200F (200 MHz) in deuteriochloroform using tetramethylsilane as internal standard, chemical shifts are expressed in ppm. Mass spectra were performed on a Jeol JMS-AX500 instrument. Optical rotations were measured on a Perkin Elmer type 241.

General Procedure for the synthesis of sulfonates (4-5): To a solution of 2 or 3 (0,1 mol, 18.9 g) in 80 ml of freshly distilled pyridine was slowly added benzenesulfonyl chloride or tosyl chloride (0.125 mol) at 0°C. After being stirred overnight, the mixture was poured into 200 ml of cold water. The resulting precipitate was filtered off and purified by crystallization from water-EtOH (1/1).

(1R,4S,5R,8R)-4-Acetoxy-8-benzenesulfonyloxy-2,6-dioxabicyclo[3.3.0]octane 4.
Yield 96 % from 2 ; white crystals; mp 72-74°C; $[\alpha]_D^{20}$ +82.0(*c* 0.600, $CHCl_3$). ^1H NMR($CDCl_3$) δ 2.04 (s,3H,OCH_3), 3.71-4.00 (m,4H,H_{3a},H_{3b}, H_{7a},H_{7b}), 4.45 (d,1H,H_5), 4.66 (dd,1H,H_1), 4.93 (ddd,1H,H_8), 5.13 (m,1H,H_4), 7.52-7.72 (m,3H,phenyl), 7.92-7.98 (m,2H,phenyl); $J_{1,5}$ = 4.5 Hz, $J_{1,8}$ = 4.8 Hz, $J_{7b,8}$ = 6.1 Hz; ^{13}C NMR ($CDCl_3$) δ 20.7, 69.6, 73.6, 77.8, 78.6, 80.3, 85.6, 127.7, 129.1, 133.9, 136.0, 169.8 ; IR (KBR) 1734, 1448, 1381, 1236, 1189, 1114, 1086, 973, 914, 796, 591 ; Anal. Calcd for $C_{14}H_{16}O_7S$: C,51.21 ; H, 4.91. Found : C, 50.96 ; H, 4.87.

(1R,4R,5R,8S)-4-Acetoxy-8-benzenesulfonyloxy-2,6-dioxabicyclo[3.3.0]octane 5.
Yield 95 % from 3 ; white crystals ; mp 74-76°C; $[\alpha]_D^{20}$ +90.0(*c* 0.738, $CHCl_3$).^1H NMR($CDCl_3$) δ 2.08 (s,3H,OCH_3), 3.70 (dd,1H,H_{3b}), 3.83-4.03 (m,3H,H_{3a},H_{7a},H_{7b}), 4.49 (d,1H,H_1), 4.80 (dd,1H,H_5), 4.94 (d,1H,H_8), 5.10 (ddd,1H,H_4), 7.53-7.73 (m,3H,phenyl), 7.92-7.97 (m,2H,phenyl); $J_{1,5}$ = 4.6 Hz; $J_{4,5}$ = 5.0 Hz; $J_{3b,4}$ = 5.6 Hz; $J_{3a,3b}$ = 9.8 Hz; $J_{7a,8}$ = 3.2 Hz; ^{13}C NMR($CDCl_3$) δ 20.4, 70.1, 72.8, 73.5, 80.5, 83.4, 85.5, 127.6, 129.3, 134.1, 136.1, 170.0 ; IR(KBr) 1740, 1451, 1364, 1235, 1191, 1115, 980, 760, 589. Anal. Calcd for $C_{14}H_{16}O_7S$: C,51.21 ; H,4.91. Found : C,51.14 ; H,4.84.

(1R,4S,5R,8R)-8-Benzenesulfonyloxy-2,6-dioxabicyclo[3.3.0]octan-4-ol 6.
Compound 4 (0.03 mol, 10g) was dissolved in 150 ml of a water-EtOH-Et_3N (1/1/1) mixture and refluxed for 6h. Removal of the solvent in vacuo and purification by flash chromatography with 50 % ethyl acetate - hexane on silica gel gave sulfonate 6. Yield 92 % ; colorless oil; $[\alpha]_D^{20}$ +55.4(*c* 0.838, $CHCl_3$). ^1H NMR($CDCl_3$) δ 3.17 (s,1H,OH), 3.68 (dd,1H,H_{7b}), 3.78-3.88 (m,3H,H_{3a},H_{3b},H_{7a}), 4.24 (s,1H,H_4), 4.34 (d,1H,H_5), 4.64 (dd,1H,H_1), 4.85 (ddd,1H,H_8), 7.49-7.70 (m,3H,phenyl), 7.89-7.95(m,2H,phenyl) ; $J_{1,5}$ = 4.3 Hz ; $J_{1,8}$ = 4.6Hz ; $J_{7a,8}$ = 6.2 Hz, $J_{7b,8}$ = 6.4 Hz, $J_{7a,7b}$ = 9.7 Hz; ^{13}C NMR($CDCl_3$) δ 69.3, 75.7, 75.8, 79.0, 79.9, 87.8, 127.7, 129.2, 134.0, 135.9 ; IR(neat) 3427, 1585, 1448, 1363, 1188, 1095, 973, 916, 570 ; Anal. Calcd for $C_{12}H_{14}O_6S$: C,50.34 ; H,4.93. Found : C,50.46 ; H, 5.20.

(1R,4R,5R,8S)-8-Benzenesulfonyloxy-2,6-dioxabicyclo[3.3.0]octan-4-ol 7.

Sulfonate 7 was synthesized by the same procedure than 6 and purified by crystallization from water. Yield 94 % from 5 ; white crystals; mp 83-85°C; $[\alpha]_D^{20}$ +45.4(*c* 0.835, $CHCl_3$). ^1H NMR($CDCl_3$) δ 2.58 (d,1H,OH), 3.49 (dd,1H,H_{3b}), 3.78-3.92 (m,2H,H_{3a},H_{7a}), 4.08 (d,1H,H_{7b}), 4.28 (ddd,1H,H_4), 4.48 (d,1H,H_1), 4.62 (dd,1H,H_5), 4.95 (d,1H,H_8), 7.54-7.73 (m,3H,phenyl), 7.90-7.95 (m,2H,phenyl); $J_{3b,4}$ = 6.0 Hz, $J_{3a,3b}$ = 9.5 Hz, $J_{1,5}$ = 4.4 Hz, $J_{4,5}$ = 4.8 Hz, $J_{7a,7b}$ = 11.1 Hz, $J_{7a,8}$ = 3.4 Hz; ^{13}C NMR($CDCl_3$) δ 72.0(C4), 72.9(C7), 73.3(C3), 81.8(C5), 83.7(C8), 85.3(C1), 127.7, 129.4, 134.1, 136.1; IR(KBr) 3430, 1585, 1450, 1370, 1180, 1080, 1010, 970, 950, 910, 870, 835, 740, 685, 580, 570; Anal. Calcd for $C_{12}H_{14}O_6S$: C,50.34 ; H,4.93. Found : C,50.28 ; H,4.84. M.S.: 287(M^++ 1, 4); 227(5); 128(100); 85(62); 69(87); 43(23).

General procedure for the synthesis of methylethers 8 and 9a: To a solution of 6 or 7 (0.5 mol, 144 g) and tetrabutylammonium iodide (2.7 mmol, 1 g) in 500 ml of CH_2Cl_2 was added 50 % NaOH (1.3 mol, 110 ml) with vigorous stirring for 0.5 h. Dimethylsulfate (0.6 mol, 60 ml) was then added dropwise. The mixture was stirred for 2 h at room temperature. The organic layer was washed with water (2x150 ml), dried over anhydrous Na_2SO_4 and the solvent was evaporated in vacuo.

(1R,4R,5R,8S)-4-Benzenesulfonyloxy-8-methoxy-2,6-dioxabicyclo[3.3.0]octane 8.

Ether 8 was purified by crystallization from water-ethanol (8/2). Yield 95 % from 6 ; white crystals ; mp 52-54°C; $[\alpha]_D^{20}$ +56.6(*c* 0.812, $CHCl_3$). ^1H NMR($CDCl_3$) δ 3.29 (s,3H,OCH_3), 3.70 (dd,1H,H_{3b}), 3.77-3.94 (m,4H,H_{3a},H_{7a},H_{7b},H_8), 4.40 (d,1H,H_1), 4.54 (dd,1H,H_5), 4.86 (ddd,1H,H_4), 7.48-7.68 (m,3H,phenyl), 7.89-7.95 (m,2H,phenyl); $J_{1,5}$ = 4.6 Hz, $J_{4,5}$ = 4.7Hz, $J_{3a,4}$ = 6.2 Hz, $J_{3b,4}$ = 6.4 Hz, $J_{3a,3b}$ = 9.6 Hz; ^{13}C NMR($CDCl_3$) δ 56.9, 69.3, 72.9, 78.9, 79.9, 85.0, 85.3, 127.7, 129.1, 133.9, 136.0; IR(KBr) 1450, 1346, 1195, 1100, 1056, 921, 886, 561; Anal. Calcd for $C_{13}H_{16}O_6S$: C,51,99 ; H,5.37. Found : C,52.28 ; H,5.34.

(1R,4S,5R,8R)-4-Benzenesulfonyloxy-8-methoxy-2,6-dioxabicyclo[3.3.0]octane 9a.

Compound 9a was purified by flash chromatography on silica gel with 50 % ethyl acetate - hexane. Yield 95% from 7; yellow oil; $[\alpha]_D^{20}$ + 84.8(*c* 0.838, $CHCl_3$). ^1H NMR($CDCl_3$) δ 3.40 (s,3H,OCH_3), 3.50 (dd,1H,H_{7b}), 3.80-4.00 (m,4H,H_{3a},H_{3b},H_{7a},H_8), 4.53 (d,1H,H_5), 4.68 (dd,1H,H_1), 4.88 (m,1H,H_4), 7.45-7.65 (m,3H,phenyl), 7.81-7.93 (m,2H,phenyl) ; $J_{1,5}$ = 4.5 Hz, $J_{1,8}$ = 4.8 Hz, $J_{7b,8}$ = $J_{7a,7b}$ = 9.7 Hz; ^{13}C NMR($CDCl_3$) δ 58.1, 70.0, 73.0, 80.1, 81.2, 83.9, 85.6, 127.6, 129.3, 134.0, 136.1 ; IR(neat) 1590, 1450, 1370, 1290, 1100, 980, 950, 910, 820, 750, 690, 590. Anal. Calcd for $C_{13}H_{16}O_6S$: C,51.99 ; H,5.37. Found : C,51.70, H,5.27. M.S.: 300(M^++ 1, 6); 227(5); 142(81); 69(71); 58(100).

(1R,4S,5R,8R)-4-Benzenesulfonyloxy-8-benzyloxy-2,6-dioxabicyclo[3.3.0]octane 9b.

To a solution of 7 (0.02 mol,5.73 g) and n-tetrabutylammonium hydrogenosulfate in 50 ml of freshly distilled benzyl chloride was added 50 % sodium hydroxyde (0.1 mol,8 ml). The mixture was vigorously stirred for 3 h at 60°C. The organic layer was washed with water and dried over anhydrous Na_2SO_4. The solvent was removed in vacuo and the crude product was purified by flash chromatography on silica gel with ethyl acetate-hexane (8/2). Yield 86 %; white crystals; mp 93-95°C; $[\alpha]_D^{20}$ +94.3(*c* 0.800, $CHCl_3$). ^1H NMR($CDCl_3$) δ 3.58 (dd,1H,H_{7b}), 3.83 (dd,1H,H_{7a}), 3.95-4.10 (m,3H,H_{3a},H_{3b},H_8), 4.51-4.57

(m,2H,H_5,CH_2), 4.67-4.77 (m,2H,H_1,CH_2), 4.92 (m,1H,H_4), 7.34 (s,5H,Bz), 7.54-7.74 (m,3H,phenyl), 7.93-7.98 (m,2H,phenyl) ; $J_{1,5}$ = 4.4 Hz, $J_{1,8}$ = 4.5 Hz, $J_{7a,8}$ = 6.6 Hz, $J_{7b,8}$ = 7.7 Hz, $J_{7a,7b}$ = 8.9 Hz, J_{CH2} = 11.7Hz ; ^{13}C NMR($CDCl_3$) δ 70.4, 72.4, 73.1, 78.7, 80.4, 84.0, 85.7, 127.7, 127.8, 128.4, 129.3, 133.9, 136.2, 137.3 ; IR(KBr) 2840, 1490, 1450, 1350, 1180, 1170, 1100, 1080, 1020, 950, 885, 750, 590. Anal. Calcd for $C_{19}H_{20}O_6S$: C,60.62 ; H,5.36. Found : C,60.63 ; H,5,42.

General procedure for the synthesis of aminoethers (**10a-b, 11a-h, 12a-b**):

8, **9a-b** or **5** (0.02 mol) was refluxed in an excess of the required freshly distilled amine (25 ml) or heated in a sealed tube under pressure at 160°C for 24 h (if the boiling point of the amine is lower than 130°C). The excess of amine was removed in vacuo and the residue was dissolved in 100 ml of water, rendered alkaline with sodium hydroxyde and extracted with CH_2Cl_2 (5x50 ml). The organic extracts were dried over anhydrous sodium sulfate and the solvent was removed in vacuo. The products were purified by bulb-to-bulb distillation.

(1R,4S,5R,8S)-4-Benzylamino-8-methoxy-2,6-dioxabicyclo[3.3.0]octane 10a.

Benzylamine and **8**. Reflux 3 h. Yield 90 %; pale yellow liquid; bp 105°C (0.22 mmHg); $[\alpha]_D^{20}$ + 14.7 (*c* 0.823, $CHCl_3$). ^1H NMR($CDCl_3$) δ 1.51 (s,1H,NH), 3.34-3.36 (m,4H,OCH_3,H_3), 3.68 (dd,1H,H_3), 3.72-3.89 (m,6H,CH_2,H_7,H_7,H_4,H_8), 4.53 (d,1H,H_1), 4.60 (d,1H,H_5), 7.18-7.39 (m,5H,phenyl); $J_{1,5}$= 4.3 Hz; ^{13}C NMR($CDCl_3$) δ 51.9, 56.9, 63.9, 71.6, 72.8, 85.0, 85.1, 86.9, 127.0, 128.1, 128.4, 139.6; IR(neat) 3310, 1453, 1342, 1195, 1113, 1082, 913, 738, 700. Anal. Calcd for $C_{14}H_{19}NO_3$: C,67.45 ; H,7.68 ; N,5.62. Found : C,67.23 ; H,7,74 ; N,5.82.

(1R,4S,5R,8S)-4-Cyclohexylamino-8-methoxy-2,6-dioxabicyclo[3.3.0]octane 10b.

Cyclohexylamine and **8**. Reflux 24 h. Yield 84 %; pale yellow liquid ; bp 110°C (0.11 mmHg); $[\alpha]_D^{20}$ +9.8(*c* 0.884, $CHCl_3$). ^1H NMR($CDCl_3$) δ 0.89-1.93 (m,10H,cyclohexyl), 2.48 (m,1H,cyclohexyl), 3.34 (s,3H,OCH_3), 3.39 (m,1H,NH), 3.58 (dd,1H,H_3), 3.82-3.94 (m,5H,H_3,H_4,H_7,H_7,H_8), 4.43 (d,1H,H_1), 4.51 (d,1H,H_5); $J_{1,5}$= 4.4 Hz; ^{13}C NMR($CDCl_3$) δ 24.8, 24.9, 25.9, 33.6, 33.9, 54.8, 57.0, 61.5, 71.5, 73.4, 84.8, 85.0, 87.4; IR(neat) 3311, 1450, 1114, 1083, 913, 847, 784. Anal. Calcd for $C_{13}H_{23}NO_3$: C,64.70 ; H,9.61 ; N,5.81. Found : C,64,94 ; H,9.82 ; N : 6,03.

(1R,4R,5R,8R)-4-Benzylamino-8-methoxy-2,6-dioxabicyclo[3.3.0]octane 11a.

Benzylamine and **9a**. Reflux 2 h. Yield 68 % ; pale yellow liquid ; bp 130°C (0,15 mmHg) ; $[\alpha]_D^{20}$ + 130.3 (*c* 0.742, $CHCl_3$). ^1H NMR($CDCl_3$) δ 1,90 (s,1H,NH), 3.31-3.44 (m,2H,H_{7b},H_8), 3.45 (s,3H,OCH_3), 3.60 (dd,1H,H_{7b}), 3.73-4.20 (m,5H,H_{3a},H_{7a},H_8,CH_2), 4.50 (dd,1H,H_5), 4.62 (dd,1H,H_1), 7.19-7.39 (m,5H,phenyl); $J_{4,5}$ = $J_{1,5}$ = $J_{1,8}$ = 4.2Hz, J_{CH2}= 12.9 Hz; ^{13}C NMR($CDCl_3$) δ 52.2, 58.1, 62.1, 70.8, 72.6, 80.3, 80.6, 82.3, 126.9, 128.0, 128.2, 139.9; IR(neat) 3300, 1450, 1220, 1140, 1090, 740, 700. Anal. Calcd for $C_{14}H_{18}NO_3$: C,67.45, H,7.68 ; N,5.62. Found : C,67.70 ; H,7.82; N,5.76.

(1R,4R,5R,8R)-4-Cyclohexylamino-8-methoxy-2,6-dioxabicyclo[3.3.0]octane 11b.
Cyclohexylamine and **9a**. Reflux 10 h. Yield 63 %; colorless liquid; bp 105°C (0.15 mmHg); $[\alpha]_D^{20}$ +144.1(*c* 0.879, $CHCl_3$). ^1H NMR($CDCl_3$) δ 0.93-1.11 (m,5H,cyclohex), 1.51-1.76 (m,6H,cyclohex,NH) 2.38-2.49 (m,1H,cyclohex), 3.25 (dd,1H,H_{3b}), 3.37-3.47 (m,4H,H_4,OCH_3), 3.54 (dd,1H,H_{7b}), 3.82-3.98 (m,2H,H_{7a},H_8), 4.01 (dd,1H,H_{3a}), 4.37 (dd,1H,H_5), 4.54 (dd,1H,H_1); $J_{3a,3b}$ = 10.4 Hz, $J_{3b,4}$ = 8.2 Hz, $J_{3a,4}$ = 7.7 Hz, $J_{4,5}$ = $J_{1,5}$ = $J_{1,8}$= 4.3 Hz, $J_{7a,8}$ = $J_{7a,7b}$ = 7.7 Hz; ^{13}C NMR($CDCl_3$) δ 24.7, 24.8, 25.8, 33.4, 33.9, 55.0, 58.0 (OCH_3), 59.6(C4), 70.7(C7), 72.9(C3), 80.4(C1), 80.9(C5), 82.5(C8); IR(neat) 3300, 1450, 1220, 1140, 1100, 1080, 1030, 830. Anal. Calcd for $C_{13}H_{23}NO_3$: C,64.70 ; H,9.61 ; N,5.80. Found : C,64.49 ; H,9.78 ; N,6.06. M.S.: 242($M^{+\cdot}$+ 1, 93); 210(46); 198(65); 141(90); 69(100); 55(71).

(1R,4R,5R,8R)-4-Cyclohexylmethylamino-8-methoxy-2,6-dioxabicyclo[3.3.0]octane 11c.
(Cyclohexylmethyl)amine and **9a**. Reflux 3 h. Yield 85 %; colorless liquid; bp 115°C (0.13 mmHg); $[\alpha]_D^{20}$ +116.8(*c* 0.816, $CHCl_3$). ^1H NMR($CDCl_3$) δ 0.77-1.8 (m,12H,cyclohex,NH), 2.38 (dd,1H,CH_2N), 2.49 (dd,1H,CH_2N), 3.28-3.36 (m,2H,H_{3b},H_4), 3.43 (s,3H,OCH_3), 3.57 (dd,1H,H_{7b}), 3.85-4.13 (m,3H,H_{3a},H_{7a},H_8), 4.46 (dd,1H,H_5), 4.61 (dd,1H,H_1); $J_{4,5}$ = $J_{1,5}$ = $J_{1,8}$ = 4.3 Hz; ^{13}C NMR($CDCl_3$) δ 25.8, 26.5, 31.1, 31.3, 38.4, 55.0, 58.0, 63.3, 70.7, 72.6, 80.4, 80.6, 82.3 ; IR(neat) 3260, 1470, 1450, 1140, 1090, 1075, 1030. Anal. Calcd for $C_{14}H_{24}NO_3$: C,65.85 ; H,9.87 ; N,5.49. Found : C,65.63 ; H,9.68 ; N,5.43.

(1R,4R,5R,8R)-4-isopropylamino-8-methoxy-2,6-dioxabicyclo[3.3.0]octane 11d.
Isopropylamine and **9a**. Autoclave. Yield 76 %; yellow liquid; bp 70°C (0,1 mmHg); $[\alpha]_D^{20}$ +143.2(*c* 0.915, $CHCl_3$). ^1H NMR($CDCl_3$) δ 1.04 (dd,6H,CH_{3iPr}), 1.72 (s,1H,NH), 2.86 (ddd,1H,CH_{iPr}), 3.27-3.47 (m,5H,H_{3b},H_4,OCH_3), 3.57 (dd,1H,H_{7b}), 3.87-4.09 (m,3H,H_{3a},H_{7a},H_8), 4.44 (dd,1H,H_5), 4.61 (dd,1H,H_1); $J_{4,5}$ = $J_{1,5}$ = $J_{1,8}$ = 4.2 Hz, $J_{3a,3b}$= 6.5 Hz; ^{13}C NMR($CDCl_3$) δ 22.7, 23.4, 46.7, 58.1, 60.1, 70.8, 72.8, 80.5, 80.8, 82.3; IR(neat) 3300, 1470, 1380, 1220, 1180, 1140, 1080, 1030. Anal. Calcd for $C_{10}H_{19}NO_3$: C,59.68 ; H,9.51 ; N,6.96. Found : C,59.46 ; H ,9.72; N,7.15. M.S.: 201($M^{+\cdot}$, 24); 101(51); 86(85); 69(100); 58(54); 41(89).

(1R,4R,5R,8R)-4-terbutylamino-8-methoxy-2,6-dioxabicyclo[3.3.0]octane 11e.
terButylamine and **9a**. Autoclave. Yield 56 %; yellow liquid; bp 95°C (0.23 mmHg); $[\alpha]_D^{20}$ +151.9(*c* 0.758, $CHCl_3$). ^1H NMR($CDCl_3$) δ 1.09 (s,9H,tBu), 1.64 (s,1H,NH), 3.45-3.23 (m,5H,H_{3b},H_4,OCH_3), 3.55 (dd,1H,H_{7b}), 3.87-4.05 (m,3H,H_{3a},H_{7a},H_8), 4.33 (dd,1H,H_5), 4.60 (dd,1H,H_1); $J_{4,5}$ = $J_{1,5}$ = $J_{1,8}$ = 4.4 Hz; ^{13}C NMR($CDCl_3$) δ 29.9, 50.0, 57.0, 58.0, 70.8, 73.9, 80.2, 82.4, 82.5: IR(neat) 3320, 2980, 1450, 1380, 1360, 1230, 1140, 1070, 1030. Anal. Calcd for $C_{11}H_{24}NO_3$: C,61.37 ; H,9.83 ; N,6.51. Found : C,61.62 ; H,9.77 ; N,6.41.

(1R,4R,5R,8R)-4-[1-(1-Methylethyl)-2-methylpropylamino]-8-methoxy-2,6-dioxabicyclo[3.3.0]octane 11f.
2,4-Dimethyl-3-propylamine and **9a**. Reflux 6h. Yield 48 %; yellow liquid; bp 75(0.10 mmHg); $[\alpha]_D^{20}$ +125.0(*c* 0.752, $CHCl_3$). ^1H NMR($CDCl_3$) δ 0.78-0.89 (m,12H,CH_3), 1,31 (s,1H,NH), 1,67 (m,2H,CH), 1.92 (dd,1H,CHN), 3.18-3.30 (m,2H,H_{3b},H_4), 3.40 (s,3H,OCH_3), 3.52 (dd,1H,H_{7b}), 3.84-4.02 (m,3H,H_{3a}, H_{7a},H_8), 4.35 (dd,1H,H_5), 4.53 (dd,1H,H_1); $J_{4,5}$ = $J_{1,5}$ = $J_{1,8}$ = 4.2 Hz; ^{13}C NMR($CDCl_3$) δ 17.9, 18.0, 20.7,

30.3, 30.7, 58.0, 64.6, 68.9, 70.6, 72.6, 80.1, 80.9, 82.5; IR(neat) 3300, 2980, 2880, 1470, 1385, 1220, 1140, 1100, 1075, 1030. Anal. Calcd for $C_{14}H_{27}NO_3$: C,65.33; H,10.57; N,5.44. Found : C,65.42; H,10.52; N,5.67.

(1R,4R,5R,8R)-8-Benzyloxy-4-cyclohexylamino-2,6-dioxabicyclo[3.3.0]octane 11g.

Cyclohexylamine and **9b**. Reflux 10 h. Yield 83 %; yellow liquid; bp 160°C (0.23 mmHg); $[\alpha]_D^{20}$ + 135.1 (*c* 0.916, $CHCl_3$). ^1H NMR($CDCl_3$) δ 1.00-1.17 (m,5H,cyclohex), 1.61-1.82 (m,6H,cyclohex,NH), 2.46 (m,1H,CHN), 3.32-3.50 (m,2H,H_{3b},H_4), 3.61 (dd,1H,H_{7b}), 3.87 (dd,1H,H_{7a}), 4.00-4.13 (m,2H,H_{3a},H_8), 4.38 (dd,1H,H_5), 4.48-4.59 (m,2H,H_1,CH_2), 4.72 (d,1H,CH_2), 7.26-7.34 (m,5H,Bz); J_{CH2} = 11.8 Hz, $J_{4,5}$ = $J_{1,5}$ = $J_{1,8}$ = 4.0 Hz; ^{13}C NMR($CDCl_3$) δ 24.7, 24.8, 25.9, 33.5, 33.9, 55.1, 59.5, 71.1, 72.3, 72.9, 79.8, 80.8, 80.9, 127.7, 127.8, 128.3, 137.7; IR(neat) 3320, 2930, 2850, 1450, 1370, 1150, 1080, 1070, 1030, 745, 700. Anal. Calcd for $C_{19}H_{27}NO_3$: C,71.89 ; H,8.57 ; N,4.41. Found : C,71.72 ; H,8,78 ; N,4.61. M.S.: 317($M^{+\cdot}$, 18); 210(21); 141(39); 91(100); 69(67); 55(43).

(1R,4R,5R,8R)-8-Cyclohexylamino-2,6-dioxabicyclo[3.3.0]octan-4-ol 12a.

Cyclohexylamine and **5**. Reflux 10 h. Yield 66 %; white crystals; bp 95°C (0.07 mmHg); mp 72-74°C; $[\alpha]_D^{20}$ +79.2(*c* 0.852, $CHCl_3$). ^1H NMR($CDCl_3$) δ 0.94-1.29 (m,5H,cyclohex), 1.54-1.85 (m,5H,cyclohex), 2.45 (m,1H,CHN), 2.78 (s,2H,OH,NH), 3.36-3.48 (m,2H,H_{7a},H_8), 3.62 (dd,1H,H_{3b}), 3.86 (dd,1H,H_{3a}), 4.00 (dd,1H,H_{7b}), 4.17 (ddd,1H,H_4), 4.43 (dd,1H,H_1), 4.50 (dd,1H,H_5) ; $J_{4,5}$ = $J_{1,5}$ = $J_{1,8}$ = 5.1 Hz; ^{13}C NMR($CDCl_3$) δ 24.8, 25.8, 33.6, 54.5, 58.3(C8), 72.1(C4), 72.8(C7), 75.1(C3), 80.9(C1), 82.2(C5); IR(KBR) 3280, 2850, 1450, 1410, 1130, 1090, 1060, 1015, 825, 805. Anal. Calcd for $C_{12}H_{21}NO_3$: C,63.41 ; H,9.31 ; N,6.16. Found : C,63.56 ; H,9.52 ; N,6.38. M.S.: 227($M^{+\cdot}$, 23); 142(58); 69(73); 55(100); 41(93).

(1R,4R,5R,8R)-8-Benzylamino-2,6-dioxabicyclo[3.3.0]octan-4-ol 12b.

Benzylamine and **5**. Reflux 2 h. Yield 70 %; white crystals; bp 135°C (0.2 mmHg); mp: 71-73°C; $[\alpha]_D^{20}$ +71.3(*c* 0.868, $CHCl_3$). ^1H NMR($CDCl_3$) δ 2.83 (s,2H,OH,NH), 3.31 (m,1H,H_8), 3.57 (dd,1H,H_{7a}), 3.69 (dd,1H,H_{3b}), 3.78-3.82 (m,2H,CH_2), 3.90 (dd,1H,H_{3a}), 4.02 (dd,1H,H_{7b}), 4.19 (ddd,1H,H_4), 4.50 (dd,1H,H_1), 4.54 (dd,1H,H_5), 7.21 (m,5H,phenyl); $J_{4,5}$ = $J_{1,5}$ = $J_{1,8}$ = 5.3 Hz; ^{13}C NMR($CDCl_3$) δ 51.9(CH_2), 60.8(C8), 72.1(C4), 72.6(C7), 75.4(C3), 80.5(C1), 82.4(C5), 127.1, 128.0, 128.4; IR(KBr) 3300, 3120, 2860, 1470, 1450, 1130, 1080, 1060, 865, 752, 700. Anal. Calcd for $C_{13}H_{17}NO_3$: C,66.36; H,7.28 ; N,5.95. Found : C,66.52 ; H,7.39 ; N,6.05.

(1R,4R,5R,8R)-4-Cyclohexylamino-8-(2,2-dimethylpropoxy)-2,6-dioxabicyclo[3.3.0]octane 11h.

A mixture of **12b** (0.025, 5.68 g), sodium hydride (0.0375 mol,1.13 g) and DMF (50 ml) was stirred for 2 h at 50°C. Neopentyle bromide (0.375 mol, 4.8 ml) was added and the mixture was stirred for additional 2h à 100°C. After a second addition of neopentyle bromide (0.375 mol, 4.8 ml) the mixture was stirred for 8h at 100°C before being hydrolyzed with 20 ml of 10 % NH_4Cl solution and extracted with ethyl acetate (2x50 ml). The organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuo. The crude product was purified by bulb-to-bulb distillation. Yield 79 %; yellow liquid; bp 125°C (0.15 mmHg); $[\alpha]_D^{20}$ +130.9 (*c* 0.618, $CHCl_3$). ^1H NMR($CDCl_3$) δ 0.90 (s,9H,tBu), 1.00-1.18 (m,5H,cyclohex), 1.63-1.85 (m,6H,cyclohex,NH), 2.43-2.55 (m,1H,CHN), 3.03 (d,1H,CH_2tBu), 3.29-3.48 (m,3H,H_{3b},H_4,CH_2tBu), 3.58-3.63 (m,1H,H_{7b}), 3.86-3.99 (m,2H,H_{7a},H_8), 4.02 (dd,1H,H_{3a}), 4.40 (dd,1H,H_5), 4.59 (dd,1H,H_1); $J_{4,5}$ =

$J_{1,5} = J_{1,8} = 4.3$ Hz, $J_{CH2tBu} = 8,6$ Hz; ^{13}C NMR($CDCl_3$) δ 24.7, 24.8, 25.9, 26.4, 32.0, 33.4, 34.0, 55.1, 59.4, 71.4, 72.7, 80.7, 80.8, 81.1, 81.4; IR(neat) 3430, 2930, 2850, 1477, 1450, 1360, 1148, 1083, 1022; Anal. Calcd for $C_{17}H_{31}NO_3$: C,68.65 ; H,10.50 ; N,4.71. Found : C,68.79 ; H,10.32 ; N,4.98.

(1R,4S,5R,8R)-8-benzyloxy-2,6-dioxabicyclo[3.3.0]octan-4-ol 13.

Isosorbide 1 (0.125 mol) and lithium hydride (0.125 mol) were mixed in 60 mL of dimethylformamide. Benzyl chloride (0.125 mol) was added dropwise and the solution was sonicated at 50°C for 24h. The solvent was evaporated in vacuo and the residual oil was chromatographied on silica gel with 50% pentane - ethyl acetate. Yield 60 % from 1; white solid; bp 150°C (1.5 mmHg); mp 60-62°C; $[\alpha]^{27}_D$ +121.2(c 0.536, $CHCl_3$). ^1H NMR($CDCl_3$) δ 2.62 (s,1H,OH), 3.85 (dd,1H,H_{7b}), 3.95-4.11 (m,4H,H_{3a},H_{3b},H_{7a},H_8), 4.30 (m,1H,H_4), 4.40 (d,1H,H_5), 4.55 (d,1H,CH_2), 4.70 (dd,1H,H_1), 4.76 (d,1H,CH_2), 7.29-7.40 (m,5H,phenyl); $J_{1,5}$= 4.2 Hz; $J_{1,8}$= 4.4 Hz; $J_{7b,8} = J_{7a,7b}$= 8.8 Hz; ^{13}C NMR($CDCl_3$) δ 70.0, 72.3, 75.7, 78.3, 79.0, 80.0, 88.2, 127.6, 128.3, 137.5; IR(neat) 3386, 1070, 1014, 836, 756, 703, 630; Anal. Calcd for $C_{13}H_{16}O_4$: C,66.09; H,6.83. Found: C, 65,87; H, 6,99.

(1R,4S,5R,8R)-8-benzyloxy-4-toluenesulfonyloxy-2,6-dioxabicyclo[3.3.0] octane 14.

Compound 14 was prepared following the same procedure as for compounds 4 and 5. Yield 95 % from 13; mp 85°C; $[\alpha]^{27}_D$ +95.1(c 0.515, $CHCl_3$). ^{1}HNMR ($CDCl_3$) δ 2.45 ppm (s,3H,CH_3), 3.60 (dd,1H,H_3), 3.80 (dd,1H,H_7), 4.00 (m,3H,H_3,H_5,H_7), 4.50 (d,1H,CH_2), 4.70 (dd,1H,H_1), 4.75 (d,1H,CH_2), 4.90 (m,1H,H_4), 7.35 (m,7H,phenyl,Tos), 7.8 (d,2H,Tos); $J_{1,5} = J_{1,8} = 5$ Hz; $J_{7,8} = 7$ Hz; $J_{CH2} = 13$ Hz; $J_{Tos} = 7$ Hz; ^{13}C NMR ($CDCl_3$) δ 18.1, 21.4, 57.8, 70.2, 72.2, 72.9, 78.6, 80.3, 83.8, 85.5, 127.5, 127.6, 128.2, 129.8, 132.9, 137.3, 145.4; Anal. Calcd for $C_{20}H_{22}O_6S$: C,61.52; H,5.67. Found: C,61.95; H,5.86.

(1R,4R,5R,8R)-8-benzyloxy-4-phenylamino-2,6-dioxabicyclo[3.3.0]octane 15a.

Compound 15a was prepared following the general procedure previously described for synthesis of amino ethers. Aniline and 14. Reflux 2h. Yield 45 % from 14; colorless liquid; $[\alpha]^{27}_D$ + 100° (c 0.590, $CHCl_3$). ^1H NMR($CDCl_3$) δ 3.5 (dd,1H,H_3), 3.70 (dd,1H,H_3), 3.95 (dd,1H,H_7), 4.10 (m,2H,H_4,H_8), 4.35 (dd,1H,H_7), 4.55 (d,1H,CH_2), 4.65 (dd,1H,H_1), 4.80 (d,1H,CH_2), 6.70 (m,3H,phenyl), 7.2 (m,2H,phenyl), 7.4 (m,5H,phenyl); $J_{1,5} = J_{1,8} = 5$ Hz; $J_{CH2} = 13$ Hz; ^{13}C NMR($CDCl_3$) δ 57.0, 71.2, 72.4, 79.5, 80.5, 81.4, 113.1, 117.6, 127.6, 128.3, 129.2, 137.5, 147.1.

(1R,4R,5R,8R)-8-benzyloxy-4-butylamino-2,6-dioxabicyclo[3.3.0] octane 15b.

Compound 14 (0.0025, 0.975 g) was dissolved in 5 mL of butylamine in a sealed tube. The solution was irradiated for 15 minutes at 90 W in a mono-mode microwave oven (Prolabo). The tube was cooled and the same operation was repeated 14 times (overall irradiation time of 3h). The solution was then chromatographied on silica gel with 50% pentane - ether. Yield 60 % from 14; colorless liquid; $[\alpha]^{27}_D$ +137.8(c 0.450, $CHCl_3$). ^{1}HNMR ($CDCl_3$) δ 0.90 (t,3H,CH_3), 1.20-1.50 (m,4H,CH_2), 2.25 (s,1H,NH), 2.73 (m,2H,CH_2N), 3.40 (m,2H,H_3,H_4), 3.65 (dd,1H,H_3), 3.90 (dd,1H,H_7), 4.11 (m,2H,H_7,H_8), 4.45 (dd,1H,H_5), 4.55 (d,1H,CH_2O), 4.60 (dd,1H,H_1), 4.75 (d,1H,CH_2O), 7.35 (m,5H,phenyl); $J_{1,5}$ = 5 Hz; J_{CH2O} = 13 Hz; ^{13}C NMR($CDCl_3$) δ 13.0, 20.9, 32.3, 48.3, 62.6, 71.6, 72.6, 79.6, 80.4, 81.4, 128.0, 128.5.

(1R,4R,5R,8R)-8-benzyloxy-4-(N-ethylphenylamino)-2,6-dioxabicyclo[3.3.0] octane 15c.

This compound was prepared by the same procedure than **15a**. N-ethylaniline and **14**. Reflux 2h. Yield 31 % from **14**; $[\alpha]^{27}_D$ +206.5(c 0.397, $CHCl_3$); ^1H NMR($CDCl_3$) δ 1.00 (t,3H,CH_3), 1.40 (d,2H,CH_2), 3.20-3.50 (m,2H,H_3,H_4), 3.75 (dd,1H,H_3), 3.70 (dd,1H,H_7), 3.95 (dd,1H,H_7), 4.10 (m,2H,H_7,H_8), 4.30 (dd,1H,H_5), 4.55 (d,1H,CH_2), 4.60 (dd,1H,H_1), 4.75 (d,1H,CH_2), 6.90 (m,3H,phenyl), 7.25 (m,2H,phenyl), 7.40 (m,5H,phenyl); $J_{1,5} = J_{1,8} = 5$ Hz; $J_{CH2} = 13$ Hz; ^{13}C NMR($CDCl_3$) δ 13.2, 44.1, 62.6, 70.0, 71.4, 72.6, 79.6, 81.2, 116.2, 118.0, 118.8, 127.9, 128.5, 129.1; Anal. Calcd for $C_{21}H_{25}NO_3$: C,74.31; H,7.42; N,4.13. Found: C,74.19; H,7.48; N,4.22.

General procedure for hydrogenation of compounds (**15a-c**):

Amino ethers (1 mmol) and the same weight of Palladium 10% on charcoal in 2 mL of ethanol were stirred under a 1 bar Hydrogen pressure for 24h. Removal of the catalyst by filtration and evaporation of the solvent afforded a crude oil which was purified by flash chromatography on silica gel with CH_2Cl_2/MeOH/NH_3 (85/15/1%).

(1R,4R,5R,8R)-8-phenylamino-2,6-dioxabicyclo[3.3.0]octan-4-ol 12c.

Yield 65 % from **15a**; $[\alpha]_D^{20}$ +33.8(c 0.551, $CHCl_3$); ^1H NMR($CDCl_3$) δ 3.45 (dd,1H,H_7), 3.65 (dd,1H,H_7), 3.95 (dd,1H,H_3), 4.10 (m,1H,H_8), 4.30 (m,3H,H_3,H_4,OH), 4.60 (m,2H,H_5,H_1), 6.65 (d,2H,phenyl), 6.75 (dd,1H,phenyl), 7.2 (m,2H,phenyl); $J_{1,5} = J_{1,8} = 5$ Hz; ^{13}C NMR ($CDCl_3$) δ 57.2, 72.4, 72.6, 74.5, 81.4, 81.8, 113.3, 118.0, 146.7, 129.4.

(1R,4R,5R,8R)-8-butylamino-2,6-dioxabicyclo[3.3.0]octan-4-ol 12d.

Yield 77 % from **15b**; $[\alpha]_D^{20}$ +62.0(c 0.437, $CHCl_3$); ^1H NMR($CDCl_3$) δ 0.90 (t,3H,CH_3), 1.30-1.60 (m,4H,CH_2), 2.70 (m,2H,CH_2), 3.30 (m,2H,H_7,H_8), 3.4 (s,1H,NH), 3.75 (m,1H,H_7), 3.80 (d,1H,OH), 3.95 (dd,1H,H_3), 4.05 (dd,1H,H_3), 4.20 (dd,1H, H_4), 4.60 (m,2H,H_1,H_5); ^{13}C NMR ($CDCl_3$) δ 13.7, 20.2, 32.1, 47.5, 61.1, 71.7, 72.7, 75.9, 80.7, 82.4.

(1R,4R,5R,8R)-4-azido-8-benzyloxy-2,6-dioxa bicyclo[3.3.0] octane 16.

13 (0.007 mol, 2.73 g) and sodium azide (0.010 mol, 0.65 g) were dissolved in 15 ml of dimethylsulfoxyde. The solution was stirred at 120°C for 8h. Water was then added and products were extracted with ether. The organic layers were dried over anhydrous sodium sulfate and the solvent was evaporated in vacuo to give a crude oil which was used without purification. Yield 75 % from **13**.

(1R,4R,5R,8R)-8-amino-2,6-dioxabicyclo[3.3.3]octan-4-ol 17.

Compound **16** was reduced following the general procedure described for compounds **12**. Yield 40 % from **16**; $[\alpha]^{20}_D$ +110.1(c 0.208, $CHCl_3$); ^1H NMR($CDCl_3$) δ 1.50 (d,1H,OH), 2.65 (s,2H,NH_2), 3.45 (m,1H,H_8), 3.55 (dd,1H,H_7), 3.70 (dd,1H,H_7), 4.25 (dd,1H,H_3), 4.40 (dd,1H,H_1), 4.55 (dd,1H,H_5).

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