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PREPARATION OF THE FOUR ISOMERIC 2-TRIFLUOROMETHYL-4-DIMETHYLAMINOMETHYL-1,3-DIOXOLAN METHIODIDES

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SUMMARY

The four isomers of the title compound have been prepared almost entirely optical pure, along five sequences starting from D-mannitol. Some new preparative steps, preventing optical loss have been developed. Diox(ol)an formation can easily been achieved with polyhalogenated carbonyl derivatives when the corresponding diol is used as its mono tosylate. Formation of dioxolan is exclusively preferred over dioxan formation if both systems during this reaction can be formed. Glycidol is shown to react stereospecifically with trifluoroacetaldehyde. It was possible to avoid racemisation completely during the substitution reaction of hydroxyl by chlorine ($P\emptyset_3/CCl_4$) in the presence of a non-nucleophilic base.

The 2-CF_3-dioxolanic moiety on itself is incapable to complex with chiral LIS-reagents in order to induce diastereotopicity.

INTRODUCTION

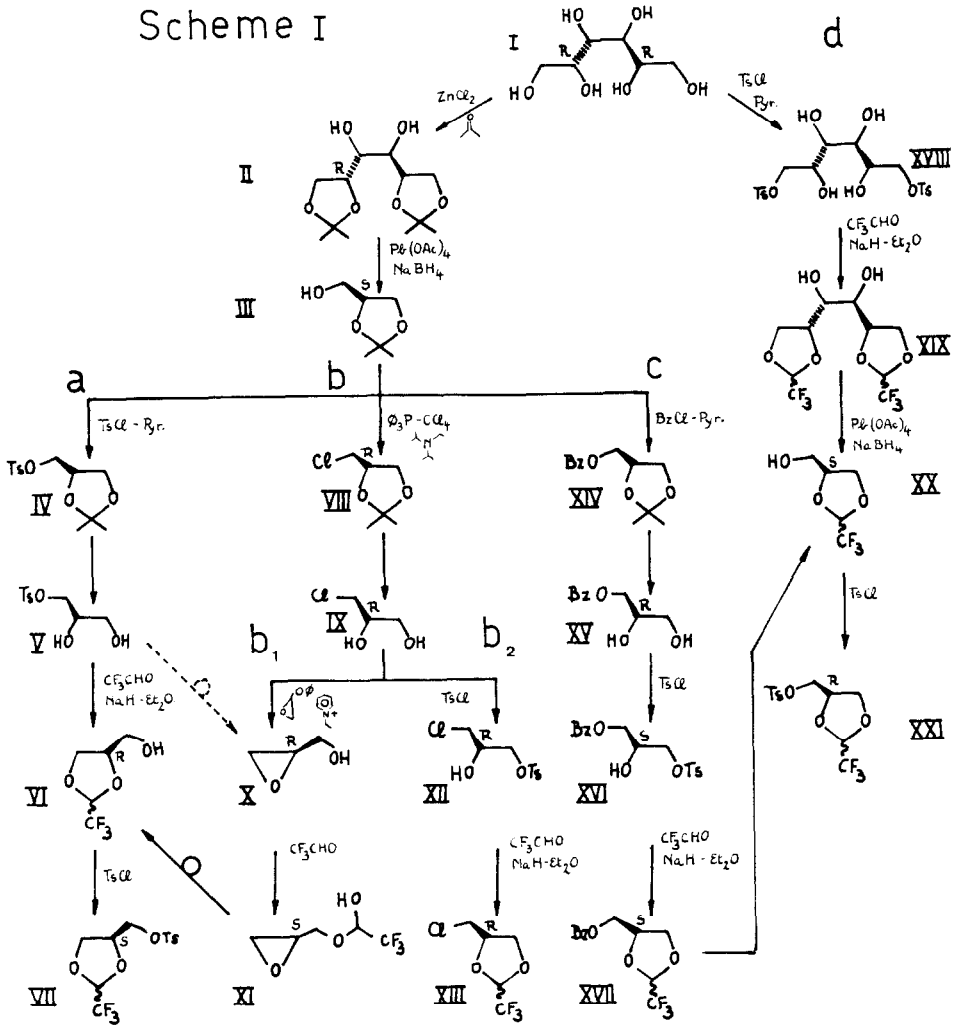
We have described recently the synthesis of side-chain fluorinated 1,3-dioxans and 1,3-dioxolans[1,2] but for 2-CF_3-4-$CH_2\overset{+}{N}Me_3$-1,3-dioxolan the method[2] afforded only a mixture of the (dl) cis-, and trans-derivatives. As the racemic mixture possesses an interesting cholinergic activity[3], it was of interest to develop a stereospecific synthetic route, leading to all of the four possible isomers. This paper describes their preparation in high enantiomeric purity, and the extracted parameters in their ^{1}H-NMR spectra are reported.

STEREOSPECIFIC SYNTHETIC ROUTES

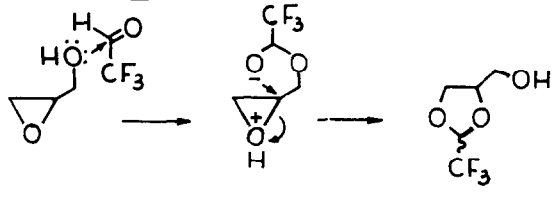
We have selected five reaction routes (a, b_1, b_2, c, d; SCHEME I) which afforded us in excellent enantiomeric purity the desired compounds, and enabled us to cross-check the stereochemical outcome of these paths. The starting material is D-mannitol, as it was for the preparation[4] of the analogous 2-Me-derivatives (Fourneau's dioxolan F 2268) and for which the absolute configuration of the L-(+)-cis isomer was assessed[4] by X-ray analysis. Our present reaction scheme differs from that of the Fourneau case, by the fact that we had to develop a different strategy for the acetalisation of 1,2 (also for 1,3)-diols, because direct closure between polyols and highly halogenated carbonyl compounds fails, leading only to the hemiacetal stage. We have previously deve-

loped a method[2] using oxirans (resp. oxetans) as the reaction partners, but were at that time unsuccessfull[2] in using directly the diol as such. We have now found that polyhalogenated carbonyl compounds may be brought into reaction, provided we can transform the diol previously in a mono-tosylated derivative. After the hemiacetal is formed with the remaining free hydroxyl function, ring closure with excellent yields to the desired acetal with inversion of configuration at the tosyloxy center is possible under the action of sodium hydride (e.g. V → VI; XII → XIII; XVI → XVII and XVIII → XIX; Scheme I). This reaction, characterised by a ring opening of the epoxide, is probably catalysed by the strong acidic character of the previously formed hemiacetal (Scheme II). As follows from a confrontation of the derivative so obtained with those obtained along the other itineraries, this reaction occurs with inversion of configuration at the epoxide center that is attached by the hemi-acetal function, the L-epoxide resulting in the L-dioxolan. These reactions are obviously kinetically controlled, because in the two kinds of the present dioxolan formations, also six-ring (1,3-dioxan) formation (the more stable derivatives[6]) had each time been possible. It turns out (GC) that no dioxan formation has occurred and the nature of reaction products were ascertained by the facts that : (i) the final reaction products show the expected specific rotations, mutually in accordance for enantiomers and/or identical optical isomers, irrespective the followed routes for their preparation;

Scheme I



Scheme II



(ii) the nmr spectra reveal (data in Table 1) the typical patterns and parameters which are not in agreement with 1,3-dioxanic derivatives, but are typical for dioxolans (a previous study has shown the possibility, especially at 300 MHz, for discrimination between these two possibilities[7]); and (iii) in the case of the 1,6-ditosylate of D-mannitol (XVIII) the same reaction sequence has resulted in a vicinal diol (XIX), that was subsequently intersected by lead tetra-acetate (XIX ⟶ XX), a reaction that would have been impossible if the bis-dioxan had been formed.

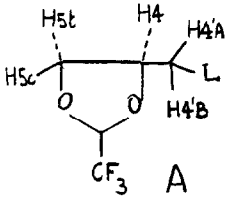
ENANTIOMERIC PURITY

We have gathered in Table 2 the enantiomeric purities of the several compounds and some of the relevant intermediates. For most of the key-intermediates it has been possible to check their optical purity by a direct ^{1}H-NMR spectroscopic method using tris-[3-(heptafluoropropyl)hydroxymethylene-d-camphorato] Europium ($Eu(HFC)_3$) as the LIS-reagent[8]. The ability to provoke diastereotopicity (at 300 MHz for ^{1}H) was each time checked on artificial mixtures of the enantiomers. Induction of diastereotopicity was only possible by the presence of a(n) (functionalized) hydroxyl function and a (dimethyl) aminogroup (both classes belonging to the most important stages of the reaction routes), but this was not possible when these groupings were absent, even in the presence of the dioxolan ringsystems*.

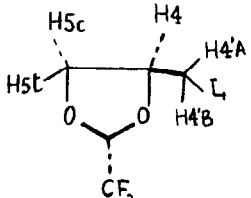
* We also tried in these cases the use of the chiral solvent α-naphtylethylamine[13] but without success (neither with ^{1}H nor ^{19}F spectroscopy).

TABLE 1

^{1}H-NMR Parameters for 2-CF_3-4-CH_2L-1,3-dioxolans [a] (SCHEME I), obtained at 300 MHz; shifts in ppm [b]; coupling values in Hz



A



B

S H I F T S

Compound (L)	H2	H4c	H4t	H4'A
A(OH)	5.19	-	4.31	3.81
B(OH)	5.23	4.43	-	3.73
A(Cl)	5.18	-	4.41	3.45
B(Cl)	5.25	4.56	-	3.47
A(NMe_2)	5.11	-	4.23	2.52
B(NMe_2)	5.16	4.36	-	2.44
A($NMe_3^+;I^-$)	5.56	-		3.71
B($NMe_3^+;I^-$)	5.66	5.05	-	3.71

C O U P L I N G S

Compound (L)	$^2J_{4'}$	$^2J_5$	^3J(H2,F)	^3J(4'A,4
A(OH)	-12.3	-8.0	3.54	4.0
B(OH)	-12.0	-7.0	4.14	3.8
A(Cl)	-10.8	-8.4	3.97	9.5
B(Cl)	-10.9	-8.2	4.40	8.5
A(NMe_2)	-12.8	-7.6	4.10	5.6
B(NMe_2)	-12.6	-7.0	4.46	5.4
A($NMe_3^+;I^-$)	-14.4	-8.7	4.04	3.2
B($NMe_3^+;I^-$)	-14.0	-8.6	4.3	9.8

(a) For a discussion of ^{1}H-NMR spectra in this class, see ref. 7.

(b) In $CDCl_3$ except in D_2O when L = $\overset{+}{N}Me_3;I^-$, TMS respectively DDS as the internal standard. Concentration : 2-5 %, temperature : 18°C.

H4'B	H5c	H5t	NMe
3.69	4.13	3.91	-
3.58	4.16	3.90	-
3.70	4.00	4.24	-
3.62	4.26	4.01	-
2.47	4.15	3.69	2.22
2.40	4.17	3.74	2.23
3.67	4.46	3.88	3.28
3.64	4.46	3.90	3.28

$^{3}J(4'B,4)$	$^{3}J(4,5C)$	$^{3}J(4,5t)$	$^{5}J(5c,F)$	$^{5}J(5t,F)$	$^{5}J(4,F)$
5.0	6.2	8.0	1.0	0.8	0.5
4.5	7.0	6.5	0.5	1.2	0.4
4.4	6.4	6.4$_5$	0.8	0.5	0.5
4.5	6.4	4.5	0.5	1.3	∿0
6.2	6.1	8.4	1.3	0.8	0.6
6.6	7.8	7.0	∿0	0.8	∿0
8.4	6.4	7.6	1.2	1.0	1.0
1.4	7.0	6.2	0.5	1.0	1.0

TABLE 2

Enantiomeric purities and optical activities of cis- and trans-2-CF_3-4-XCH_2-1,3-dioxolans (X = OH, Cl, NMe_2, $^+NMe_3$ I^-)

Compound [a]		d_4^{20}	α	medium (conc. mg/ml)
L-cis	(X=OH)	1.406_9	- 8.31	pure
D-cis	(X=OH)	(1.407)	+ 1.36	$CHCl_3$ (191.6)
L-trans	(X=OH)	1.420	+ 9.81	pure
D-trans	(X=OH)	1.420	-11.28	pure
			- 7.26	$CHCl_3$ (914.4)
D-cis	(X=Cl)		+14.25	$CHCl_3$ (500)
D-trans	(X=Cl)		+ 4.81	$CHCl_3$ (500)
L-cis	($X=NMe_2$)		+ 1.32	Et_2O (55)
D-cis	($X=NMe_2$)	1.197_0	+15.51	
			+ 1.36	Et_2O (60.5)
L-trans	($X=NMe_2$)		+ 0.124	MeOH (50.77)
D-trans	($X=NMe_2$) [e]	1.186_8	+21.09	pure
L-cis	($X=^+NMe_3$)		+ 2.05	H_2O (182.4)
D-cis	($X=^+NMe_3$)		- 0.51_6	H_2O (86.77)
L-trans	($X=^+NMe_3$)		+ 1.19_5	H_2O (103.9)
D-trans	($X=^+NMe_3$)		- 1.08	H_2O (95.6)

(a) For assignment of L and D see also SCHEME I.

(b) Recalculated for P = 1.0 where necessary.

(c) Assumed from purity of following step.

(d) Assumed from purity of foregoing step.

$[\alpha]_D^{20}$	M.W.	$[M]_D$ (b)	Enant. purity p (method)
- 5.91	172	-12.2	0.83 (NMR)
+ 1.36	172	+12.2	1.00 (NMR)
+ 6.91	172	+13.6	0.87 (NMR)
- 7.95	172	-13.6	1.00 (NMR)
- 7.94	172	-13.6	1.00 (NMR)
+28.5	190.5	+41.3	0.76 (c)
+ 9.62	190.5	+13.9	0.76 (c)
-23.9_6	199	-47.7	1.00 (NMR)
+12.86			0.532 (NMR)
+17.9	19[illegible]	+47.7	0.75 (NMR)
+ 2.45	19[illegible]	+ 4.9 (e)	1 (d)
+17.77	199	+35.4	1.00 (NMR)
+11.24	341	+38.3	1.00 (d)
- 5.94	341	-38.3	0.529 (c)
			0.532 (d)
+11.5	341	+39.2	1.00 (d)
-11.6	341	-39.6	1.00 (d)

(e) As suggested from the date of the corresponding enantiomer, $[\alpha]_D$ greatly depends on the medium. Data obtained for the D-trans derivative are : (solvent; $[\alpha]_D^{20}$) : H_2O (24 mg/ml) : -12.7; MeOH(58.4 mg/ml) : -2.59; $CHCL_3$ (26.4 mg/ml) : +6.6; CH_2Cl_2 (13.8 mg/ml) : +11.48; Et_2O (58.6 mg/ml) : +22.5; Pentane (48.8 mg/ml) : +26.2.

The fact however that in the final ammonium derivatives the desired enantiomers were obtained with mutually identical rotational power*, as is also the case for the above mentioned intermediates is a further guarantee that no optical loss has occurred.
It must further been emphasized that once the 2-CF_3-1,3-dioxolanic system is build up, it is extremely resistent towards ring-opening.

OPTICAL YIELDS

All routes (a to d) could be optimalized as to obtain a nearly 100 % optical yield except for route c with respect to the D-cis-derivative. Some difficulties were encountered.

The preparation of S-glycerol-acetonate (III) from D-mannitol, as reported by Baer e.a.[10] afforded variable and unreproducable optical yields. The best optical yield reported by Baer seems to be 96.7 % (as deduced from $[\alpha]_D^{20}$ (pure liq.) = +13.98° in comparison with our final preparation of 100 % optical pure compound (NMR) with $[\alpha]_D^{20}$ = +14.48). The presence of HOAc as the sta-

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* The recently proposed tetraphenyloborate[9] as a shift reagent for 'onium compounds was found to be active for the present quaternary ammonium iodides. Therefore, the development of optical active borates could be an interesting outcome for the establishment of enantiomeric purities for such 'oniums.

bilizer in the commercial $Pb(OAc)_4$ reagent is the cause of possible optical loss, the acid causing opening-reclosing with the remaining OH-function of the dioxolan, resulting in racemisation. It is important to work quickly and at low temperature (< 0°) in order to guarantee a good optical yield.

The substitution of OH by Cl (e.g. III → VIII) with $P\emptyset_3/CCl_4$ gives under the original described conditions[11,12] an appreciable loss of the optical purity (depending on the scale) even under rigorous dry conditions. We found now that the presence of a (stericaly hindered) baze, such as diisopropylethylamine, and seemingly serving as a captant for traces of acids, totally prevents this loss*.

Racemisation could not be avoided during the cata- no configurational equilibration was noted during race- misation. We were however able to obtain much better lytic hydrogenolysis of the benzyloxy-D-cis-XVII (affording D-cis-XX) on preparative scale. Small scale runs however were sucessfull. Peculiarly enough, this statement was not found on the corresponding trans-derivative. Moreover optical yields for the D-cis-derivative along route d.

EXPERIMENTAL

All spectra were taken at 300 MHz (VARIAN HR 300) at 18°C in $CDCl_3$, except for the ammoniumderivatives

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* From these findings it becomes possible that the previous found ring contraction of hydroxy dioxanes[12] might be catalyzed by minute amounts of acids.

which were taken in D_2O, and the data extracted (TABLE 2) have been refined by VARIAN 620-i computer aided simulation (SIMEQ 16/III) until full identity was obtained between experimental and simulated patterns. An ample discussion of the ^{1}H-NMR spectra of 2-CF_3-4-CH_2L-1,3-dioxolans can be found elsewhere[7]. The separation in the cis-trans isomers was preparatively carried out at (a) either the stage of the 2-CF_3-4-$ClCH_2$-1,3-dioxolans (0.5 ml shots on 20 m carbowax, t° = 150°C) or, (b) the 2-CF_3-4-$HOCH_2$-1,3-dioxolans (0.5 ml shots on carbowax 20 m, t° = 190°C). For the establishment of optical purities, artificial mixtures of both enantiomers were made and their composition determined[8] with the aid of $Eu(HFC)_3$. It is believed that under the conditions of higher concentrations used to this end, values of optical purity p = (% enantiomer) : total amount) are precise up to < 3 %.

Optical rotations were measured with the aid of a PERKIN-ELMER 141 polarimeter.

New compounds, either not previously reported at all, or described as only the racemic mixture are marked N.C. The nomenclature R or S denotes the chirality of the 4-position when dealing with 1,3-dioxolane derivatives, following the Cahn-Ingold-Prelog terminology[19]. The nomenclature D or L denotes the position of the (functionalised) hydroxyl at the secund carbon of the glycerol moiety in the Fischer projection.

D-glycerol acetonate (III).

The procedure of Baer[10] was followed. It is important to add under vigorous stirring fine powdered $Pb(OAc)_4$ (stabilized with 15 % HOAc) to the ice-cold solution of 1:2, R:6-D-mannitol-diacetonate in ethyl acetate. The reaction must be followed by checking the excess of $Pb(OAc)_4$ (KI-starch paper), and as soon as the reagent remains in excess, the precipitated diacetate is filtered off in the cold, and the cold solution is directly treated with $NaBH_4$ in $NaOH/H_2O$ (cooled at -10°C). The ethyl acetate layer is then treated in the usual way and after evaporation of the solvent, a distillation affords in 75 % yield (calc. on mannitol diacetonate) S-(+)-glycerol acetonate, b.p. 80°C/12 mm; $[\alpha]_D^{20}$(pure) = +14.48°; $d_4^{20} = 1.070_4$; ($[M]_D$ = +19.1°). (lit.[10] + 14.20; b.p. 79/12 mn).

D-glycerol-O_1-tosylate (V; route a).

Was obtained according to literature data[14].

2,2-diMe-R-4-$ClCH_2$-1,3-dioxolan n.c. (VIII; route b)

13.2 g (0.10 mol) of III is dissolved in 50 ml C_6H_6, together with 27.5 g $P\emptyset_3$ (0.10_5 mol) and 0.2 ml $Et(\underline{i}.Pr)_2N$, and the mixture is dropwise added in 30 minutes to refluxing CCl_4 containing an additional amount of the base (0.1 ml). After 0.5 hour the reaction mixture is imme-

diately fractionated, affording 13.5 g of VIII (yield 89 %); b.p. 51°C/12 mm; $[\alpha]_D^{20}$(pure liq.) = +40.75°; d_4^{20} = 1.105_4; ($[M]_D^{20}$ = 62°).

The glycidol (X) prepared subsequently out from VIII was found to be optical pure (vide infra).

Note : Without adding the amine, a product $[\alpha]_D^{20}$ = +5.0/ +16.0° was obtained.

R-1-Cl-2,3-propanediol n.c. (IX; route b)

15.05 g (0.1 mol) of VIII are refluxed for 2 hours in 100 ml aquous 0.5 N HCl water where 100 ml of p.dioxan has been added. After the heterogenous mixture has become homogenous, the whole is evaporated (at 12 mm, rotavap) and the residue extracted with 3 times 100 ml $CHCl_3$. The organic layer is evaporated and IX remains almost pure (NMR) as a residue. Yield 11 g, $[\alpha]_D$ ($CHCl_3$; 500 mg/ml) = +3.76°.

R-glycidol (X; route b_1)

This compound has previously been prepared[15] from V. However, in our hands the reaction route V ⟶ X gave very bad yields, the main crop being a polymerized sirupy fraction. We therefore adapted the oxiranic exchange - procedure of Bradley e.a., as reported[16] for the preparation of racemic glycidol, using phenyl glycidyl ether[17] as the metathetic reagent. Yield : 90 %; b.p. 57°/10 mm; $[\alpha]_D^{20}$(pure liq.) = +14.77°; d_4^{20} = 1.117; ($[M]_D$ = 10.9°). Lit. : yield[16] : 96 %; $[\alpha]_D^{20}$(pure liq.)[15] = 15.04°.

Although from the $[\alpha]_D^{20}$ values it follows that the optical purity should only be 98.5 %, NMR data shows the presence of only one single enantiomer.

L-cis-, and trans-2-CF_3-4-$HOCH_2$-1,3-dioxolan n.c.

(VI & XI; routes a and b_1)

(a) From R-glycidol (X) (route b_1).

7.4 g (0.1 mol) R-glycidol is dissolved in 100 ml ether and to this 9.8 g (0.1 mol) trifluoroacetaldehyde* is condensed at -70°C. The mixture is allowed to warm up to room temperature and ether is removed by distillation. Fractionation affords 9 g VI (yield 52 %); b.p. 79°C/12 mm. Separation by GC affords 50 % of the cis-derivative [$[\alpha]_D^{20}$(pure liq.) = -5.91°; d_4^{20} = 1.406 g; optical purity : 0.83 b.p. 139°C (micromethod ref. 21)] and 50 % of the trans-derivative [$[\alpha]_D^{20}$(pure liquid) = +6.91°; d_4^{20} = 1.4199) optical purity : 0.87, b.p. 148° (micromethod ref. 21)]. (b) From V (route a). General procedure for acetalisation. 0.1 mol of V (or alternatively XII, XVI and XVIII) in 100 ml dry ether is cooled to -70°C wherein 9.8 g trifluoroacetaldehyde is condensed (obtained from 14.5 g of the hydrate dropped into 100 ml PPA*). The so obtained hemiacetals are allowed to warm up to room

* Trifluoroacetaldehyde may be prepared[18] by LAH reduction in ether of trifluoroacetic acid at -70°C in 85 % yield. However the hydrate is much better dehydrated with polyphosphoric acid than with sulfuric acid, as original described[18]. With the latter procedure much lower yields of SO_2-containing fractions are obtained.

temperature and 3.6 g (0.15 mol) NaH are slowly added. After 30 min. reflux H_2 formation has ceased and the excess of NaH is destroyed with 10 ml EtOH. The mixture is poured into 200 ml water. After the usual work up the desired 1,3-dioxolans are isolated by fractionation (Table 3).

TABLE 3

Experimental data of dioxolan formation from polyol-monotosylates (cf.SCHEME I)

Starting material (route)	Reaction product	B.p. °C	Yield	% cis[a] (% trans)	Optical yield[b]
V (a)	VI	85/25 mm	75	25	0.98
				(75)	1.00
XIII(b2)	XII	50/25 mm	85	25	0.89_5[d]
				(75)	0.89_5[d]
XVI (c)	XVII	80/0.05 mm	87	25	0.53[e]
				(75)	1.00[e]
XVIII (d)	XX	85/25 mm	25	20	1.00
				(80)	1.00

(a) From GC analyses.

(b) After preparative GC separation.

(c) After $Pb(OAc)_4$ treatment, see further text.

(d) From measurements of the subsequent diMe amino derivatives.

(e) After hydrogenolysis.

D-cis-, and trans-2-CF_3-4-$HOCH_2$-1,3-dioxolan n.c.

(XX; route d)

a) 1,6-ditosyl-D-mannitol (XVIII)

9.1 g (0.05 mol) D-mannitol is dissolved in 100 ml dry pyridine and at 0°, 19.2 g (0.1 mol) tosyl chloride is added under stirring. After being left for 10 hours at room temperature, 300 ml water is added and the mixture extracted with ether, washed with dilute sulfuric acid, dried and evaporated. The sirupy residue is directly used for the next step.

b) The crude reaction product is dissolved in 200 ml ethyl acetate and powdered $Pb(OAc)_4$ at 0°C is added until positive reaction on KI-starch paper. After filtration the filtrate is dropwise added (15 min) to a cooled solution (-15°C) of 10 g $NaBH_4$ in 20 g NaOH in 100 ml water. The organic layer is separated, washed, filtrated, dried and evaporated. Fractionation affords 4.4 g XX (yield : 25 % calculated on D-mannitol); b.p. 85°/25 mm. GC separation affords 20 % of the cis-D-isomer [$[\alpha]_D^{20}$(95.2 mg/ml $CHCl_3$) = -0.99°; $[M]_D$ = -3.23°; optical yield : 1.00] and 80 % of the trans-D-isomer [$[\alpha]_D^{20}$(pure liq.) = -7.94°; d_4^{20} = 1.412; $[M]_D$ = -13.6°; optical yield 1.00)] (see TABLE 3).

S-O_1-benzyl-3-tosyl-2-hydroxypropane (XVI; route c)

R-O_1-benzyl glycerol acetonate (XIV) was prepared according to a known procedure[20]. The conversion to XV is done as for IX in 90 % yield, and the diol was tosylated

as for the preparation of XII. The crude XVI was obtained in excellent yield as a residue after evaporation, and directly used in the following step.

Catalytic debenzylation. Preparation of XX from XVII.

On a 1 g scale of XVII treated with 0.2 g 5 % Pd/C for 3 hours in 50 ml MeOH (MERCK uvasol) at normal pressure, the optical yield of XX was excellent (cis- and trans (PGC) : 100 % optical yield (NMR)).
On a larger scale however the reduction was often slow, and needed some pressure (3 atm). Although the yield was good (80 %) the optical purity of the cis-derivative was only 53 % (NMR) while the trans-derivative showed an optical purity of 100 %.

Preparation of the 2-CF_3-4-Me_2NCH_2-1,3-dioxolans-methiodides n.c.

a) The chloride or tosylate (separated previously in cis- and trans-isomers) are heated in a pressure tube with an excess of dimethylamine in benzene. After stirring the benzene layer with 40 % NaOH, the evaporated residue is purified by GC. Rotatory power data are to be found in TABLE 2.
   B.p. cis : 105°C, trans : 132.5°C (micromethod[21]).
b) Quaternization is done with MeI in benzene. The quaternized methiodides may be purified through crystallization from ethyl acetate.
   M.p. (corrected, Köfler-bank) cis : 144°O C, trans : 185°O C.

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