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BORON FLUORIDE PROMOTED CLEAVAGE OF ACETALS BY ORGANOCOPPER REAGENTS APPLICATION TO ASYMMETRIC SYNTHESIS

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Summary - In the presence of $BF_3.Et_2O$, organocopper and cuprate reagents promote the substitution of one alkoxy group of an acetal. Under the same conditions, alkoxy tetrahydropyrans react selectively, by ring cleavage. Chiral cyclic acetals, having a C2 axis of symmetry are diastereoselectively cleaved. The method serves to synthesize chiral secondary alcohols, after the removal of the chiral auxiliary.

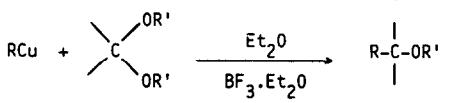
INTRODUCTION -

Aldehydes and ketones are usually protected from nucleophilic reagents, through formation of acetals and ketals[1]. This protective group is normally stable towards various organometallic reagents[2], such as organolithium[3], Grignard-[4] or organocopper reagents. On the other hand, organometallic reagents having a Lewis acid character, such as aluminum hydrides (DIBAH, $LiAlH_4/AlX_3$), are known to cleave them[2b,5] as well as some organoboron derivatives[2b,6]. Also, association of a Lewis acid (BF_3, $AlCl_3$, $TiCl_4$, $SnCl_4$, etc...) with a silicon derivative[7] or a Grignard reagent[8] effects the replacement of an alkoxy group of the acetal by an organic group. These last examples point to the synthetic potential of "classical" organometallic derivatives when associated with a strong Lewis acid. The limitation of this concept arises from the possible transmetallation (Ex : $RLi + TiCl_4 \longrightarrow RTiCl_3 + LiCl$).

Among such mixed reagents, organocopper and cuprate derivatives (RCu and R_2CuLi) associated with BF_3 (or other Lewis acids) have successfully been used in substitution and conjugate addition reactions[9]. Our contribution in this field concerns the reactivity of these reagents towards epoxides[10] and acetals[11].

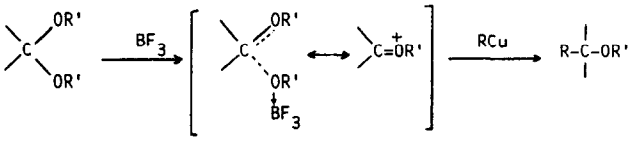
CLEAVAGE OF ACETALS -

The acetal functionality is normally stable towards organocopper and cuprate reagents[12]. However, upon addition of one eq. of $BF_3.Et_2O$, in Et_2O at -78°C, a fast reaction takes place, with substitution of one alkoxy group by the organocopper reagent :



The same reaction occurs when RCu and $BF_3.Et_2O$ are premixed at low temperature before the addition of the acetal, according to the first report on RCu,BF_3[13] . For practical purposes it is more convenient to add $BF_3.Et_2O$ to the mixture of the electrophile and the organometallic reagent and all the following results are obtained according to this procedure.

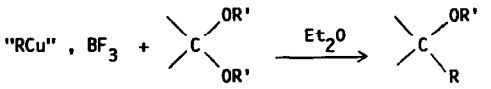
The cleavage of acetals by the RCu/BF_3 combination proceeds probably via an electrophilic activation, possibly through an oxonium intermediate :

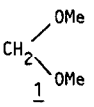
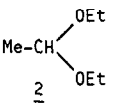
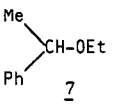
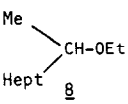
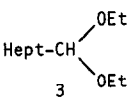
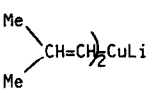
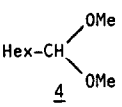
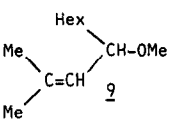
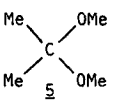
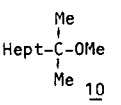


Although a possible modification of the reactivity of the organocopper reagent by BF_3 cannot be ruled out[16], the above equation is more in accordance with the results obtained with the combination $RLi/TiCl_4$[14,15] or $RMgX/TiCl_4$[8,15].

Our results with some simple acetals are shown in table I. As a general rule, the reaction proceeds well in Et_2O solvent. In THF solvent no reaction at all occurs. This solvent competes efficiently with the acetal for the complexation of the Lewis acid, and also, in this polar solvent, the destruction of the organocopper reagent by transmetallation ($RCu + BF_3 \longrightarrow R\text{-}BF_2 + CuF$, etc...) becomes a competitive process.

Table I -



Entry	"RCu"	Acetal	Temp.	Time	Product[a]	Yield
1	HeptCu,LiX	 1	-60°	30 min	Hept-CH_2-OMe 6	81%
2	PhCu,LiX	 2	-30°	30 min	 7	89%
3	HeptCu,LiX	2	-40°	20 min	 8	84%
4	MeCu,LiX	 3	-30°	30 min	8	58%[b]
5	Me_2CuLi	3	-30°	30 min	8	93%
6		 4	-30°	30 min	 9	93%
7	HeptCu,LiX	 5	-30°	30 min	 10	70%
8	$Hept_2CuLi$	5	-30°	30 min	10	94%

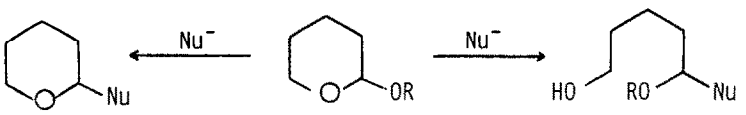
a. These products are fully characterized by GLPC, I.R. , ^1H and ^{13}C NMR

b. A gummy precipitate prevents the reaction to proceed further.

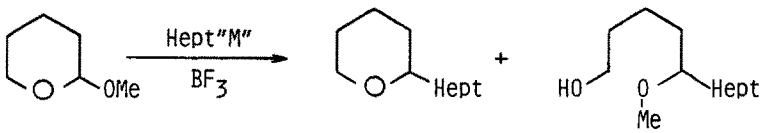
The substitution reaction is quite fast (10-60 min), even at low temperatures, despite the increasing steric congestion of the acetalic carbon (compare entries 1, 3 and 7). It should be recalled that these reactions are performed with stoichiometric amounts of reagents and that the yields are those of isolated products.

As expected in organo-copper chemistry, organocuprates (R_2CuLi) are more reactive than the corresponding organocopper reagents (RCu)[17] (compare entries 4 and 5, and 7 and 8). With these latter reagents we have also noted that a gummy precipitate prevents the reaction to proceed further, especially with the very insoluble MeCu reagent. Finally it should be pointed out that various organic groups in RCu or R_2CuLi may be used in this reaction : Methyl, n-alkyl, aryl or alkenyl.

Alcohols protected as tetrahydropyranyl ethers are a particular case of acetals. They can react with ring cleavage or with substitution of the alkoxy group :



Both products have been obtained with RMgX in refluxing toluene[2a], whereas ArOTHP react with the combination $RMgX/TiCl_4$ in THF with exclusive substitution of the aryloxy group[18]. In our case, MeOTHP was reacted with $HeptCu/BF_3$ to give a mixture of both products. However the more reactive cuprate reagent R_2CuLi/BF_3 gave exclusively the ring opened product :



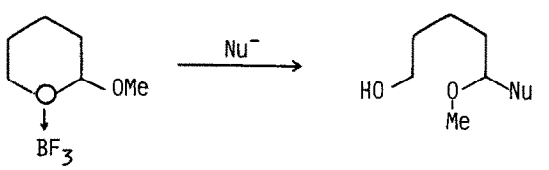
11 12 13

HeptCu,LiX (0°C, 1h)	40 : 60	90% (crude)
$Hept_2CuLi$ (-50°C,15mn)	0 :100	83% (isolated)

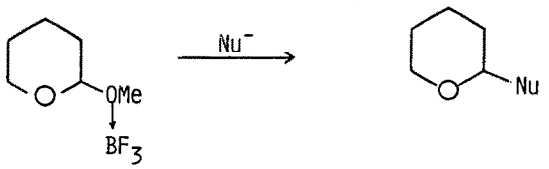
EtOTHP and iPrOTHP reacted exactly in the same manner (exclusive ring opening) with $Hept_2CuLi$ (79% and 82% yield respectively).

This difference in the final result may reflect a kinetic preference for the ring opened product with R_2CuLi. A similar conclusion was also drawn by Guindon et al. in very closely related systems[19]. (R_2CuLi/Me_2BBr and glycopyranosides).

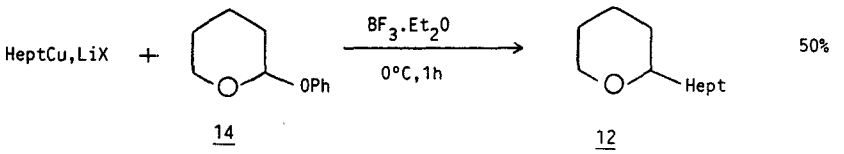
"kinetic" :



"thermodynamic" :



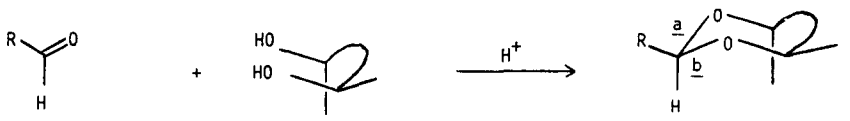
Such an hypothesis may be sustained by the fact that PhOTHP is poorly reactive in our system. With R_2CuLi/BF_3 , almost no reaction takes place, the transmetallation (see above) being the main path. With RCu/BF_3 which transmetallates more slowly, a 50% crude yield of only one substitution product is obtained :



14 12

CLEAVAGE OF CHIRAL ACETALS -

The cleavage of chiral acetals having a C_2 axis of symmetry has recently attracted much attention[20]. These chiral acetals are easily prepared from an aldehyde or its dialkyl acetal and a chiral diol :



Thus, in the ground state, the two sides si and re of the aldehyde are, now, differentiated having an equatorial (si face) or an axial (re face) Me group on the acetal ring. The diastereo selectivity of the reaction with RCu/BF_3 (as well as with $R\text{-}SiMe_3/TiCl_4$ according to W.S. Johnson[20b] or R_3Al according to H. Yamamoto[20c])will depend, now, on which C-O bond, a or b, will be broken and what type of substitution will occur, a syn or an anti one.

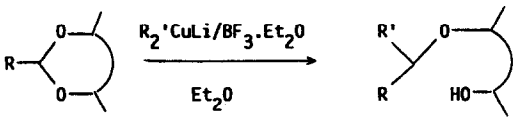
Benzaldehyde acetal derived from R,R,-2,3-butanediol was reacted with a threefold excess of Me_2CuLi in Et_2O, and $BF_3.Et_2O$ was added at -78°C (see table II, entry 9).

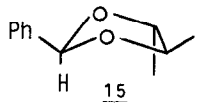
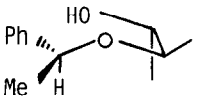
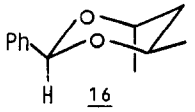
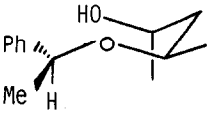
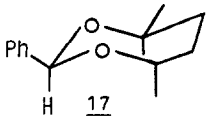
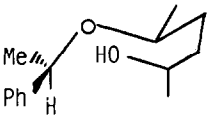
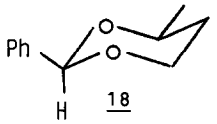
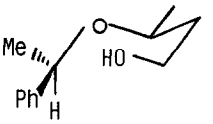
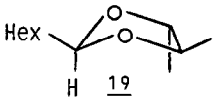
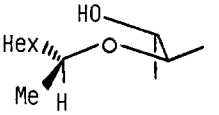
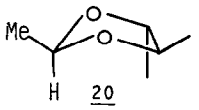
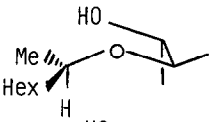
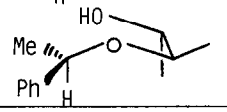
After 10 min at -78°C and then 20 min at -50°C all of the starting material was consumed and two diastereoisomers were obtained in a 83.5/16.5 ratio (d.e. 67%) after G.L.C. analysis. Changing the experimental procedure, by preformation of the mixture Me_2CuLi/BF_3[13], did not modify the above result. In order to check if there was any kinetic preference for one of the two diastereoisomers, the same experiment was performed, and aliquots were taken every 5 min. G.L.C. analysis showed that the two diastereoisomers were present in the same ratio from the begining up to the end of the reaction, indicating no kinetic diastereoselection. On the other hand, changing the nature of the organometallic reagent has some influence on the degree of diastereo-selection ; the same isomer was always the predominant one. $MeCu,LiX/BF_3$ was slightly more selective (d.e. : 72% ; yield : 50%) whereas $Me_2CuLi/TiCl_4$[21] was clearly more selective (d.e. 88%, yield : 48%). Although in both cases, the yield was low, these results suggest that the observed selectivity depends more on the nature of the Lewis acid than on the type of the organocopper or organocuprate reagents. From a practical point of view, the use of $TiCl_4$ in ethereal solvent is quite cumbersome because of the formation of an insoluble etherate ($TiCl_4.Et_2O$). This problem is not encountered with $BF_3.Et_2O$.

As shown in table II, various acetals and organocuprates were tested, in order to check the generality of this reaction. Acetals of aliphatic aldehydes and R,R-2,3-butanediol (entries 13, 14, 15) afford only one detectable diastereoisomer, whereas the same acetal derived from benzaldehyde, where an potential oxonium carbocation could be better stabilized, gives a d.e. of 67% (entry 9). As reported by W.S. Johnson and al[22] and by H. Yamamoto et al[23], a much better stereocontrol is achieved with the less flexible dioxane system : d.e. 91% (entry 10). Even the seven membered cyclic acetal, obtained from benzaldehyde and S,S,-2,5-hexanediol[24], is very diastereoselective : d.e. 86% (entry 11). Interestingly, the dioxane acetal with S-1,3-butanediol and benzaldehyde (entry 12) is cleaved only on the non substituted side of the molecule[25] ; however, the d.e. is lower than the one obtained with the disubstituted dioxane

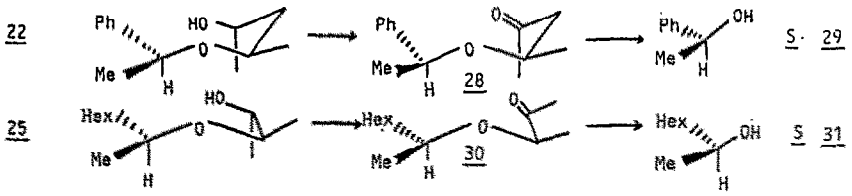
(entry 10). Nevertheless the stereochemistry of the obtained product clearly shows that an anti substitution takes place.

Table II



Entry	Acetal	Cuprate	Yield	Major product	d.e.
9	 15	Me_2CuLi	95%	21 	67%
10	 16	"	93%	22 	91%
11	 17	"	92%	23 	86%
12	 18	"	96%	24 	72%
13	 19	"	96%	25 	100%
14	 20	Hex_2CuLi	89%	26 	100%
15	20	Ph_2CuLi	94%	27 	100%)

The absolute configuration of the newly created asymmetric center was determined by correlation with known compounds after an oxidation-elimination sequence. Thus the product obtained in entry 10 was flash chromatographied to afford the pure major diastereoisomer, which was oxidized[26] (oxalyl chloride/DMSO in CH_2Cl_2) and subjected to β-elimination[22] (THF/MeOH/7.5M KOH, +20°C, overnight). Pure 1-phenyl-1-ethanol of S configuration was obtained. In an analogous manner, the product from entry 13 was oxidized[27] (PCC) and then treated with excess Na in Et_2O, at +20°C, for 4 days[22] to afford pure S-2-octanol :

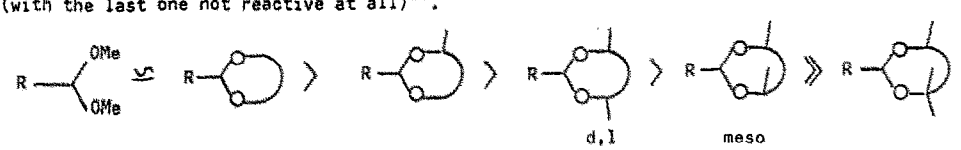


Such a high diastereocontrol is better accounted by a concerted mechanism rather than by a cationic one[25], even though a strong Lewis acid is present in the reaction medium. The anti nucleophilic attack of the cuprate reagent should be very fast once the electrophilic assistance of BF_3 has weakened one of the two C-O bonds, a or b, of the acetal

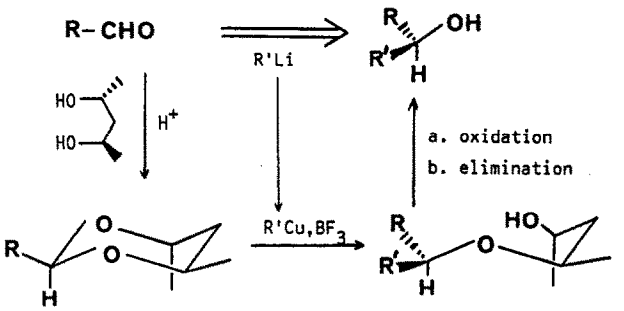
Our stereochemical results which are the same as those of W.S. Johnson[20b] and H. Yamamoto[20c], suggest an anti nucleophilic attack from the si face with concomitant cleavage of the a C-O bond, the one which is on the side of the axial Me group on the ring. The preferential cleavage of the a C-O bond may be attributed to the 2-4 diaxial interaction (H ↔Me) which is released when the bond is cleaved as shown in the transition state A. This is not the case when the b C-O bond is broken, thus disfavoring the transition state B[25].

The site of complexation of the Lewis acid is also noteworthy[23]. The complexation with the oxygen next to the axial Me group is prefered for steric as well as for electronic reasons : in this case the b C-O bond will be shortened due to the anomeric effect while in transition state B the shortening of the a C-O bond increases the steric 2-4 (H ↔Me) diaxial interaction.
This preferential complexation of the Lewis acid on an oxygen next to an axial Me group can also be substantiated by the fact that the meso acetal C is much less reactive than the d,l one D with RCu,BF_3[28] :

In all the above studies we have, thus, roughly established the following order of reactivity (with the last one not reactive at all)[29].



The overall results of the above process may be viewed as the enantioselective addition of any kind of organolithium reagent with any kind of aldehyde :



Although in this reaction the chiral diol is immolated, the utility of this method stems from its generality since a great variety of organolithium reagents are available. It should also be pointed out that 2,4-pentanediol is easily available in both enantiomeric forms by asymmetric hydrogenation of acetonyl acetone[30] and that removal of the chiral auxiliary is easily effected without racemisation.

Acknowledgements -

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EXPERIMENTAL

^1H NMR spectra were recorded on a Jeol MH100 apparatus ($CDCl_3$; δ ppm from TMS).
^{13}C NMR on a Jeol FX90Q ($CDCl_3$; δ ppm from TMS).
IR spectra were obtained on a Perkin Elmer model 457 spectrometer (neat, cm^{-1}).
GLPC analyses were performed on a Carlo Erba chromatograph model G1 and 2150 using a 3m glass column (10% SE30 on silanized chromosorb G 80/100 mesh or Carbowax 20M) and 25m capillary glass column (OV 101).
The gas chromatograph was coupled to an integrator Hitachi D2000.
Organocopper and cuprate reagents are prepared in the usual way with RLi(hexane) or RLi,LiBr(Et_2O) and CuBr,Me_2S. Dimethoxy methane 1, 1,1-diethoxy ethane 2 and 2,2-dimethoxy propane 5 are commercially available, and are used without purification. 1,1-diethoxy octane 3 and 1,1-dimethoxy heptane 4 are prepared by reaction of RCu/BF_3 with triethyl or trimethyl orthoformate, in THF[11]. Alkoxy tetrahydropyrans 11 and 14 are prepared by reaction of methanol or phenol with dihydropyran in the presence of amberlite H-15 as acid catalyst[31]

CLEAVAGE OF NON CHIRAL ACETALS. General procedure

To a suspension of CuBr,Me_2S[32] (10.5 g ; 51 mmol) in Et_2O (100 ml) is added RLi (50 mmol for organocopper or 100 mmol for diorganocuprate) at -50°C. After stirring for 10 min at -35°C a clear solution (for R_2CuLi) or yellow brownish precipitate (for RCu) is obtained. The acetal (50 mmol) in solution in Et_2O (50 ml) is added at -50°C and the mixture is cooled to -78°C, whereupon a solution of $BF_3.Et_2O$ (6.3 ml ; 50 mmol) in Et_2O (20 ml) is slowly added. The reaction is exothermic. The temperature is allowed to rise to the value indicated in table I and the mixture is stirred for 20-60 min. The reaction is quenched at -40°C with a mixture of aqueous NH_4Cl (75 ml) and concentrated aqueous ammonia (25 ml) and worked up as usual. The products are purified by distillation through a 10 cm Vigreux column.

1-Methoxy octane 6
B.p. : 66-68°C/15 mmHg ; Litt.[33] 172°C/760 mmHg. ; n^{20} : 1.4154 ; I.R. : 1120 ; ^1H NMR : 3.44 (t,2H), 3.32(s,3H), 1.25 (m,12H), 0.90(t,3H).

1-Ethoxy-1-phenyl ethane 7
B.p. : 32-34°C/0.1 mmHg ; Litt.[34] 67°C/11 mmHg. ; n^{20} : 1.4842 ; I.R. : 3080, 3060, 3030, 1120, 765, 705 ; ^1H NMR : 7.43 (s,5H), 4.42(q,1H), 3.39(q,2H), 1.42(d,3H), 1.18(t,3H) ; ^{13}C NMR : 149.30, 128.39, 127.31, 126.09(C arom.), 77.82(-CHO-), 63.88(-CH_2O-), 24.31(CH_3), 15.43(CH_3).

2-Ethoxy nonane 8
B.p. : 43-44°C/15 mmHg ; n_D^{20} : 1.4165 ; I.R. : 1460, 1120 ; ^{1}H NMR : 3.60(m,1H), 3.45(q,2H), 1.3-1.2(m,12H), 1.12(t,3H), 1.06(d,3H), 0.92(t,3H).
Anal. $C_{11}H_{24}O$: 172.31. Calc. C : 76.68 , H : 14.04. Found C : 76.58 ; H : 14.12.

4-Methoxy-2-methyl-2-decene 9
B.p. : 43-45°C/0.1 mmHg ; n_D^{20} : 1.4356 ; I.R.. : 1675, 1090, 1125, 840 ; ^{1}H NMR : 5.08(d,1H), 3.92(m,1H) ; 3.26(s,3H), 1.82(s,3H), 1.76(s,3H), 1.35-1.20(m,10H), 0.90(t,3H) ; ^{13}C NMR : 135.63(C=), 126.45(-CH=), 77.53(-CHO-), 55.51(CH_3O-), 35.74, 31.94, 29.47, 25.86, 25.41, 22.67, 18.32, 14.09.
Ana. $C_{12}H_{24}O$: 184.32. Calc. C : 78.20 ; H : 13.12. Found C : 78.15 ; H : 13.02.

2-Methoxy-2-methyl nonane 10
B.p. : 42-44°C/0.1 mmHg ; n_D^{20} : 1.4224 ; I.R. : 1470, 1380, 1365, 1085 ; ^{1}H NMR : 3.20(s,3H), 1.3-1.2(m,12H), 1.16(s,6H), 0.92(t,3H).
Anal. $C_{11}H_{24}O$: 172.31. Calc. C : 76.68 ; H : 14.04. Found C : 76.54 ; H : 14.06

2-Heptyl tetrahydropyran 12
B.p. : 44-45°C/0.1 mmHg ; Litt.[35] : 112°C/12 mmHg. I.R. : 1090 ; ^{1}H NMR / 3.96(m,1H), 3.30 (m,2H), 1.50-1.20(m,18H), 0.92(t,3H) ; ^{13}C NMR : 78.06(-CHO), 77.23(-CH_2O-), 36.86, 32.03, 29.88, 29.47, 26.46, 25.71, 23.84, 22.82, 14.12.

5-Methoxy-1-dodecanol 13
B.p. : 110-112°C/0.1 mmHg ; n_D^{20} : 1.4452 ; I.R. : 3350, 1460, 1100 ; ^{1}H NMR : 3.64(t,2H), 3.36 s,3H), 3.20(m,1H), 1.40-1.25(m,18H), 0.94(t,3H) ; ^{13}C NMR : 81.16(-CHO-), 62.36(-CH_2O-), 56.34 CH_3O-), 33.49, 33.34, 32.92, 31.94, 29.91, 29.41, 25.35, 22.73, 21.66, 14.12.
Anal. $C_{13}H_{28}O_2$: 216.36. Calc. C : 72.17 ; H : 13.04. Found C : 72.15 ; H : 12.89.

PREPARATION OF CHIRAL ACETALS -

R,R-2,3-Butanediol, R,R-2,4-Pentanediol and S-1,3-Butanediol are commercially available. S,S-2,5-Hexanediol is prepared by reduction of 2,5 hexanedione with baker's yeast[24]. Racemic 2,3-Butanediol and 2,4-Pentanediol are commercially available as a 60:40 d,l : meso mixture.
All chiral acetals, except 20, are prepared by mixing an aldehyde (10 mmol), a chiral diol (10 mmol) and paratoluene sulfonic acid (20 mg) in 100 ml of cyclohexane. This mixture is refluxed and the water is removed by a Dean Stark trap. When no starting material is left (10-15 hr) the homogeneous solution is poured into 50 ml aqueous $NaHCO_3$ and worked up as usual. The crude acetals are purified either by distillation or by flash chromatography on SiO_2 (eluent : Hexane/EtOAc : 95/5).
For acetaldehyde acetal 20 a different procedure was used, due to the low boiling point of the aldehyde and the obtained acetal. 1,1-Diethoxy ethane (2.36 g, 20 mmol) and R,R-2,3-Butanediol (1.9 g, 21 mmol) are stirred in Et_2O (50 ml) in the presence of paratoluenesulfonic acid (40 mg) at room temperature. When no starting material is left by G.L.C. control (12 h), the acid is neutralized by addition of 5 ml aqueous Na_2CO_3 and the organic phase is dried over K_2CO_3. The solvent is removed by distillation on a 30 cm Vigreux column and the residue is distilled through a smaller Vigreux column (10 cm).

R,R-2,4,5 Trimethyl dioxolane 20
B.p. : 107°C/760 mmHg ; ^{1}H NMR : 5.24(q,1H), 3.60(m,2H), 1.36(d,3H), 1.30(d,3H), 1.20(d,3H) ; ^{13}C NMR : 100.17(-CH<O>O), 80.04(-CHO-), 78.81(-CHO-), 20.62(CH_3), 17.33(CH_3), 17.13(CH_3)

2-Hexyl-R,R-4,5-dimethyl-dioxolane 19
^{1}H NMR : 5.08(t,1H), 3.60(m,2H), 1.55-1.20(m,16H), 0.92(t,3H).
^{13}C NMR : 103.45(-CH<O>O), 79.79(-CHO-), 78.12(-CHO-), 34.98, 32.03, 29.49, 24.04, 22.73, 17.40(CH_3), 17.07(CH_3),14.12(CH_3).

2-Phenyl-R,R-4,5-dimethyl dioxolane 15
B.p. : 75°C/1 mmHg ; n^{20} : 1.4992 ; ^{1}H NMR : 7.30-7.62(m,5H), 5.97(s,1H), 3.60(m,2H) ; ^{13}C NMR : 138.93, 128.83, 128.12, 126.42(C arom.), 102.49(-CH<O>O), 80.15, 78.42(-CHO-), 17.10, 16.83(CH_3).

2-Phenyl-R,R-4,6-dimethyl dioxane 16
n^{20} : 1.5002 ; ^{1}H NMR ; 7.28-7.60(m,5H), 5.80(s,1H), 4.36(m,1H), 4.08(m,1H), 1.82(m,2H), 1.36(d,3H), 1.15(d,3H) ; ^{13}C NMR : 139.79, 128.33, 127.94, 126.24(C arom.), 93.73(-CH<O>O), 68.35, 67.78(-CHO-), 36.65(CH_2), 21.90, 17.07(CH_3).

2-Phenyl-S,S-4,7-dimethyl-1,3-dioxacycloheptane 17
n^{20} : 1.5006 ; ^{1}H NMR : 7.28-7.68(m,5H), 5.85(s,1H), 4.04(m,2H), 1.64(m,4H), 1.24(d,3H), 1.08(d,3H) ; ^{13}C NMR : 140.57, 127.85, 127.76, 126.39(C arom.), 98.38(-CH<O>O), 73.50, 67.50(-CHO-), 36.32, 35.99(CH_2), 22.67, 22.58(CH_3)

R-2-Phenyl-S-4-methyl dioxane 18
B.p. : 65-66°C/0.5 mmHg ; ^{1}H NMR : 7.6-7.35(m,5H), 5.52(s,1H), 4.22(dd,1H), 3.86(m,2H), 1.68(m,1H), 1.36(m,1H), 1.24(d,3H) ; ^{13}C NMR : 138.91, 128.57, 128.10, 126.09(C arom.), 101.18(-CH<O>O), 73.24(-CHO-), 66.92(-CH_2O-), 32.92(-CH_2-), 21.75(CH_3).

CLEAVAGE OF CHIRAL ACETALS. General procedure

To a cooled (-78°C) solution of R_2CuLi (15 mmol) in Et_2O (100 ml) is added a solution of the chiral acetal (5 mmol) in Et_2O (5 ml). After 5 min $BF_3.Et_2O$ (1.9 ml, 15 mmol) is added and the stirred mixture is warmed up to -55°C. After 15 min no starting material is left (G.L.C. control) and the mixture is hydrolyzed by addition of 30 ml aqueous NH_4Cl and 20 ml aqueous ammonia. The salts are filtered off and the aqueous layer extracted twice (2 x 50 ml Et_2O). The combined organic phases are dried over Na_2SO_4 and the solvents are removed in vacuo. The residue is flash chromatographied on SiO_2 (eluent : cyclohexane/EtOAc : 80/20).
A sample of the crude residue is silylated[36] (with Me_3SiCl) for a better accuracy in the determination of the diastereomeric excess by capillary gas chromatography.
The data given bellow refer to the major diastereoisomer.

21 : I.R. : 3300, 3080, 3060, 3025, 1100, 765, 705 ; ^1H NMR : 4.54(q,1H), 3.62(m,1H), 3.30 (m,1H), 1.40(d,3H), 1.14(d,3H), 0.92(d,3H) ; ^{13}C NMR : 143.34, 128.54, 127.64, 126.42(C arom.), 76.33(Ar-C-O), 74.84(-CHO-), 70.94(-CHOH), 24.46, 18.56, 15.16(CH_3).

22 : I.R. : 3300, 3080, 3065, 3030, 1090, 765, 710 ; ^1H NMR : 7.45-7.20(m,5H), 4.58(q,1H), 4.06(m,1H), 3.62(m,1H), 1.42(d,3H), 1.18(d,3H), 1.06(d,3H) ; ^{13}C NMR : 143.49, 128.48, 127.64, 126.36(C arom.), 74.67(Ar-C-O), 69.48(-CHO-), 64.18(-CHOH), 45.38(CH_2), 24.40, 23.36, 18.86(CH_3).
Anal. $C_{13}H_{20}O_2$: 208.30. Calc. C : 74.96 ; H : 9.68. Found C : 74.89 ; H : 9.72.

23 : I.R. : 3300, 3085, 3060, 3030, 1100, 765, 710 ; ^1H NMR : 7.45-7.25(m,5H), 4.60(q,1H), 3.66(m,1H), 3.38(m,1H), 1.48(m,4H), 1.44(d,3H), 1.18(d,3H), 1.08(d,3H) ; ^{13}C NMR : 143.76, 128.30, 127.43, 126.51(C arom.), 74.52(Ar-C-O), 71.54(-CHO-), 67.57(-CHOH), 35.01, 33.55(CH_2), 24.49, 23.44, 19.07(CH_3).

24 : I.R. : 3350, 1100 ; ^1H NMR : 4.54(q,1H), 3.56(m,3H), 1.62(m,2H), 1.39(d,3H), 1.12(d,3H) ; ^{13}C NMR : 143.67, 128.42, 127.49, 126.30(C arom.), 74.46(Ph-CH-O-), 70.52(-CHO-), 59.82(-CH_2OH), 39.60(CH_2), 24.55(CH_3), 19.13(CH_3).

25 : I.R. : 3300, 1100 ; ^1H NMR : 3.58(m,1H), 3.50(m,1H), 3.28(m,1H), 1.40-1.30(m,10H), 1.14(d,3H), 1.12(d,3H), 1.08(d,3H), 0.90(t,3H) ; ^{13}C NMR : 78.18(-CHO-), 74.55(-CHO-), 70.97(-CHOH), 36.92, 31.97, 29.61, 25.71, 22.73(CH_2), 21.27, 18.62, 16.86, 14.12(CH_3).
Anal. $C_{12}H_{26}O_2$: 202.33. Calc. C : 71.23 ; H : 12.95. Found C : 71.12 ; H : 12.98.

26 : I.R. 3300, 1100 ; ^1H NMR : 3.52(m,2H), 3.14(m,1H), 1.45-1.30(m,10H), 1.16(d,6H), 1.10(d,3H), 0.90(t,3H) ; ^{13}C NMR : 77.50(-CHO-), 73.06(-CHO-), 71.06(-CHOH), 37.66, 31.94, 29.44, 25.77, 22.67(CH_2), 20.00, 18.53, 16.15, 14.09(CH_3).

27 : I.R. : 3300, 3085, 3065, 3020, 1100, 760, 710 ; ^1H NMR : 4.52(q,1H), 3.64(m,1H), 3.30(m,1H), 1.42(d,3H), 1.12(d,3H), 0.90(d,3H) ; ^{13}C NMR : 144.50, 128.65, 128.21, 126.98(C arom.), 78.96(Ar-C-O-), 77.14(-CHO-), 70.76(-CHOH), 23.51, 18.47, 16.57(CH_3).

Removal of the chiral auxiliary -

Compound 22 was oxidized to the ketone 28 (Swern oxidation) according to ref. 37.

28 : I.R. : 3080, 3060, 3025, 1705, 1200, 760, 710 ; ^1H NMR : 7.40(s,5H), 4.58(q,1H), 3.86(m,1H), 2.36(m,2H), 2.04(s,3H), 1.36(d,3H), 1.18(d,3H).

Compound 25 was oxidized, with PCC[27], to afford the ketone 30 :

30 : I.R. : 1710, 1160 ; ^1H NMR : 3.90(q,1H), 3.46(m,1H), 2.14(s,3H), 1.3-1.2(m,10H), 1.18(d,3H), 1.12(d,3H), 0.90(t,3H) ; ^{13}C NMR : 210.92(C=O), 79.13(-CHO-), 75.08(-CHO-), 37.36, 32.6, 29.65, 25.77(CH_2), 24.70(CH_3), 22.79(CH_2), 19.81, 18.26, 14.15(CH_3).

Ketone 28 was stirred for 15 hr in a mixture of THF/MeOH/7.5N KOH, at room temperature. The alcohol 29 was purified by flash chromatography on SiO_2 (eluent : CH_2Cl_2/MeOH : 95/5).

S-1-Phenyl-1-ethanol 29

$[\alpha]_D^{20}$: -59,45°(c : 6.17, pentane) ; Litt.[38] $[\alpha]_D^{25}$:-55.36°C(c 0.98 cyclopentane) ; ^1H NMR : 7.45-7.35 (m,5H), 4.92(q,1H), 1.48(d,3H) ;
^{13}C NMR: 146.03, 128.36, 127.24, 125.45(C arom.), 70.08(CHOH), 25.09(CH_3).

Ketone 30 was stirred, for 4 days, in Et_2O, at room temperature with excess Na cut in small pieces.
2-Octanol 31 was purified by chromatography (eluent : Pentane/EtOAc : 90/10).

S-2-Octanol 31

$[\alpha]_D^{20}$: +9.06 (C : 15, pentane) ; Litt.[39] $[\alpha]_D^{17}$: +9.9°C (neat) ; ^1H NMR : 3.84(m,1H), 1.5-1.3 (m,10H), 1.18(d,3H), 0.90(t,3H) ; ^{13}C NMR : 67.84(CHOH), 39.57, 32.09, 29.61, 26.01, 23.42, 22.79, 14.12.

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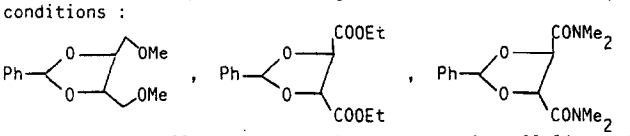

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