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Chiral Acetals in Organic Synthesis[1]: Regioselective Synthesis of 2-and 3-Hydroxy Acetals from 2,3-Olefinic Acetals. Reinvestigation and Further Applications

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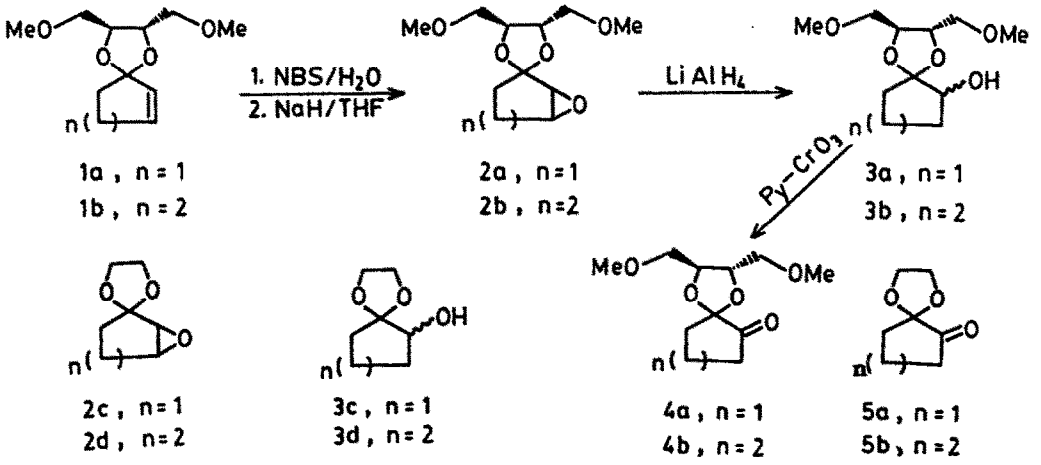
Abstract: Achiral as well as chiral 2,3-olefinic acetals are converted into 2- and 3- hydroxy acetals via LAH reduction of the corresponding epoxides and via bromohydrins followed by TBTH reductions respectively. Synthesis of 1,3-diones is described. Compounds from chiral systems are further utilized for asymmetric synthesis.

A few years ago we reported[2] transformation of 2,3-olefinic acetals into 1,2- and 1,3- diones via regioselective reductions of the corresponding epoxides with Zn-$ClSiMe_3$ and $LiAlH_4$ respectively. In a programme[3] directed towards exploring the potential of chiral acetals in organic synthesis we attempted our earlier procedure in converting the 2,3-olefinic acetal **1b** (Scheme 1) into 3-keto acetals via the reduction of epoxides with lithium aluminium hydride followed by oxidation. However, reduction with $LiAlH_4$ (obtained from E. Merck) consistently gave



Scheme 1

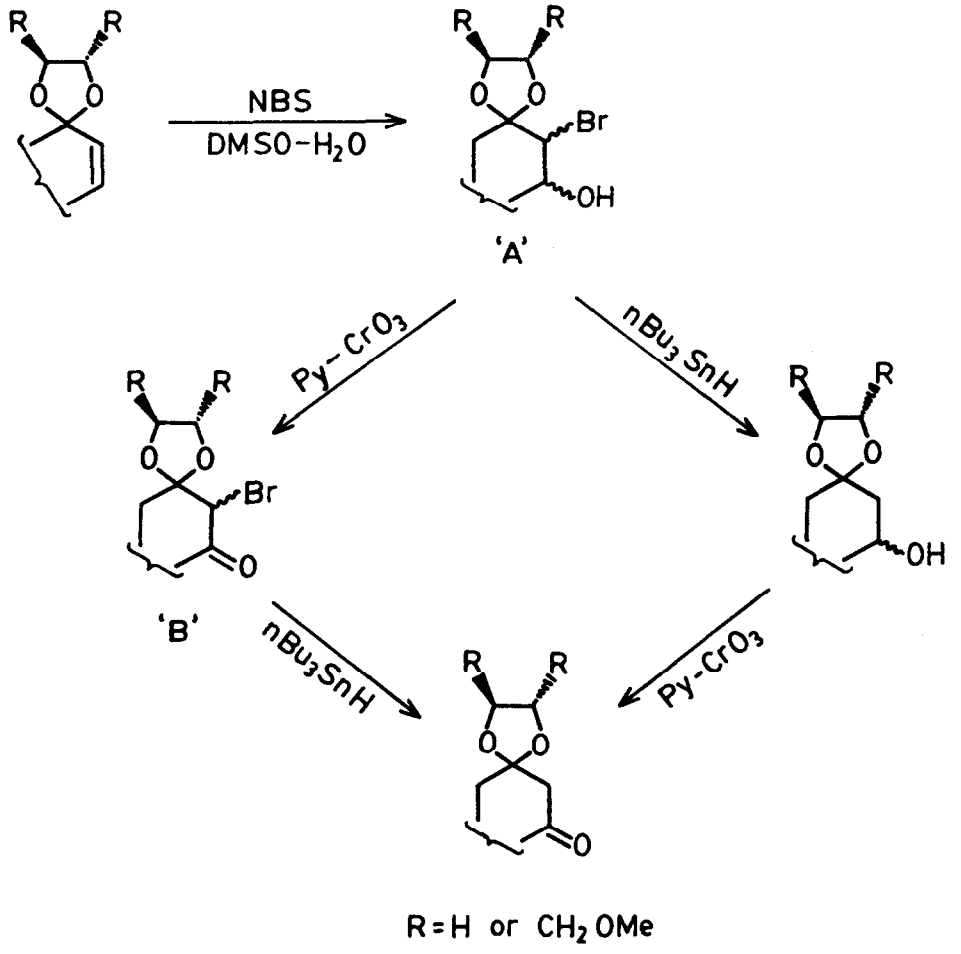
2-hydroxy acetal[4] 3b instead of 3-hydroxy acetal with both chiral as well as achiral epoxides. This reversal of the regioselectivity was surprising. The only difference in the reaction conditions had been in using $LiAlH_4$ obtained from two different sources[5]. The $LiAlH_4$ obtained from either of the sources was used as solid and no attempts were made to use ethereal solution. However it was noted that with $LiAlH_4$ (ex. SRL) a large excess of it was required for complete disappearance of the starting epoxide.

It is, therefore, suspected that impurities present in $LiAlH_4$ may have caused isomerisation[6] of epoxides to 3-keto acetals which, upon reduction, gave the corresponding 3-hydroxy acetals. One of the crucial ways in judging if the compound is 2-hydroxy or 3-hydroxy acetal was to examine the ^1H NMR spectra of the corresponding keto acetals. In 3-keto acetals, the characteristic singlet is observed at ~ δ 2.65 for the methylene protons sandwiched between the acetal and the carbonyl group. This singlet, as expected, is absent in 2-keto acetals. Thus, from cyclopentane as well as cyclohexane systems we were able to procure 2-keto acetals viz. **4a, 4b, 5a and 5b.** It may be noted that chiral 2-keto acetals have already been found[7] to give very high degree of diastereoselectivity during Grignard additions which result into chiral 2-alkyl, 2-hydroxy cycloalkanones. In view of this, the present route to 2-keto acetals is expected to be useful.

Further, in the synthesis of (+)-Pedamide, Matsumoto et al[8] have observed high degree of diastereoselectivity in $LiAlH_4$ reduction of chiral 3-keto acetals which constituted the key step in this synthesis. Thus, alternate routes to 3-keto acetals would also be useful.

During our earlier studies it was noted that while epoxidation of 2,3-olefinic acetals generally took place with m-chloroperbenzoic acid, 2,3-cyclopentene acetals were unreactive towards it. However, we had synthesised these epoxides in two steps via their bromohydrins 'A' (Scheme 2) followed by base treatment. The study of regiochemistry of bromohydrins was unimportant in view of the epoxide formation. But we have now found that debromination of bromohydrins with $n\text{-}Bu_3SnH$ followed by Pyridine-Chromium trioxide oxidation gives only 3-keto acetals. This indicates that bromohydrin formation has been a highly regioselective reaction in the present study. Alternatively, oxidation of bromohydrins to bromoketones 'B' and then debromination with $n\text{-}Bu_3SnH$ also leads to 3-keto acetals. Hydrolysis of 3-keto acetals under standard conditions gave 1,3-diones (Table 1). Unfortunately, oxidation of hydroxy acetals, derived from cyclopentanone and 3-pentanone systems, with $py\text{-}cro_3$ as well as under Swern oxidation conditions was found to be

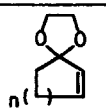
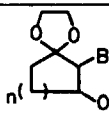
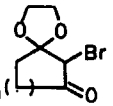
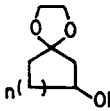
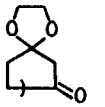
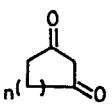
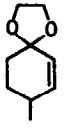
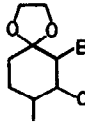
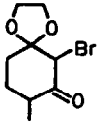
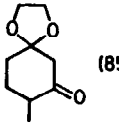
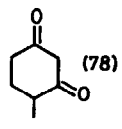
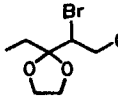
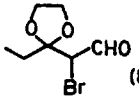
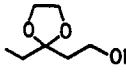
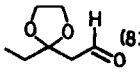
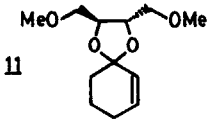
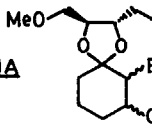
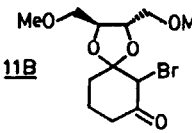
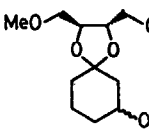
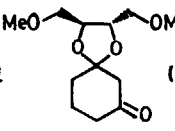
unclean and the corresponding carbonyl compounds could not be isolated in pure forms[9].



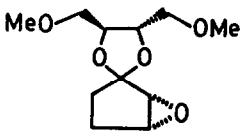
Scheme 2

Formation of 2,3-epoxy acetals either via bromohydrins or directly with m-CPBA oxidation did not show any stereochemical preference. Thus, epoxide 2a showed two doublets centering at δ 3.17 and δ 3.07 in its ^{1}H NMR spectrum which accounted for one proton. Further, the integration values of these two doublets indicated them to be of almost equal ratio. This, we attribute to the presence of two diastereomers viz. 2a I and 2a II (scheme 3) which were chromatographically

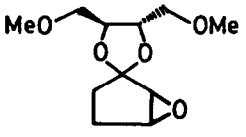
Table 1

Entry	2, 3 Olefinicacetal	Bromohydrin 'A' (% yield)	Bromoketone 'B' (% yield)	3 Hydroxyacetal (% yield)	3 Ketoacetal (% yield)	1,3 Dione (% yield)
						
1.	6 (n = 1)	6A (81)	—	12 (76)	—	—
2.	7 (n = 2)	7A (89)	7B (65)	—	15 (81)	20 (70)
3.	8 (n = 3)	8A (93)	8B (78)	—	16 (88)	21 (71)
4.	9 	9A  (87)	9B  (80)	—	17  (85)	22  (78)
5.	10 	10A  (83)	10B  (80)	 (89) 13: R=H 13A R=OAc	18  (83)	—
6.	11 	11A  (81)	11B  (71)	14  (95)	19  (78)	—

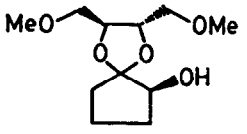
inseparable. On the other hand, $LiAlH_4$ reduction of this epoxide 2a gave two alcohols 3a I and 3a II which were easily separated by column chromatography. Separate oxidation of these alcohols resulted into the same keto acetal 4a, as was evident by their spectral data thus confirming that 2a I and 2a II are indeed two diastereomers. Interestingly, although the two alcohols 3a I and 3a II are chromatographically easily separable, the corresponding acetates were found to be inseparable in a variety of solvent systems.



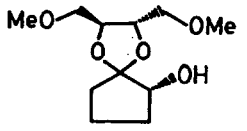
2a I



2a II



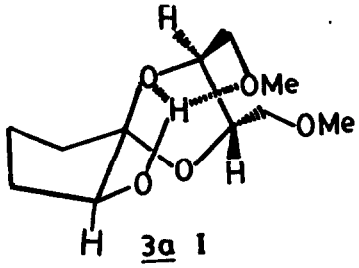
3a I (Less polar)



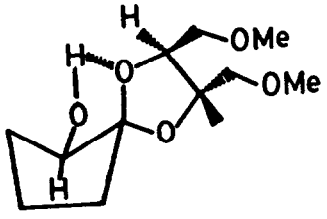
3a II (More polar)

Scheme 3

This observation is not surprising, as, recently Mash and Hemperly[10] have found similar polarity differences between these two diastereomers prepared from α-hydroxycyclopentanone, whereas the corresponding methyl ethers were found to be chromatographically inseparable. They rationalised their observations by invoking intramolecular hydrogen bonding arrays between the proximal dioxolane and appendage oxygen atoms with the α-hydroxyl group. In one of the diastereomers such a hydrogen bonding is possible (cf. 3a I) which renders it to be less polar than the other one in which hydrogen bonding is only possible with one of the acetal oxygens.

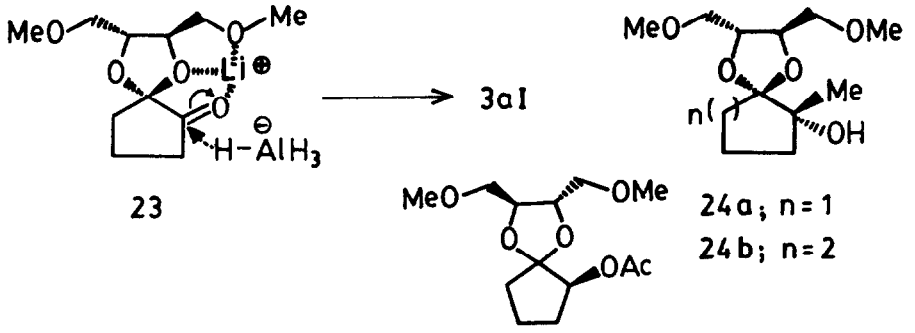


3a I



3a II

Similar rationalisation is evidently applicable in the present study also for 3a I and 3a II and to account for the chromatographic inseparability betweeen the corresponding acetates. Due to these differences in the extent of hydrogen bonding, the methoxy protons in 3a I are found as two separate singlets,whereas in 3a II they appear as a single peak. Reduction of the keto-acetal 4a with $LiAlH_4$ at 0°C gave only one compound viz. 3a I. The ^1H NMR spectrum of 3a I, thus obtained, was exactly identical with one of the alcohols (cf. less polar one) obtained from the epoxide reduction. It is possible to explain the preferential formation of 3a I through the transition state 23 (Scheme 4).



23 25

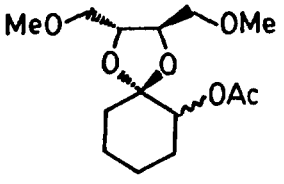
Scheme 4

Further confirmation of the presence of only one of the diastereomers was obtained on the basis of ^1H NMR spectral analysis (400 MHz) of the corresponding acetate 25 in the presence of $Eu(hfc)_3$.

Reaction of 4a with MeMgBr at 0°C was also carried out and, as expected, it gave a high degree of diastereoselectivity (95:5). The two methoxy groups in this case appeared as a single peak; however, the methyl group ($\{>C<^{Me}_{OH}$) separated out in the presence of $Eu(hfc)_3$. The two diastereomers were found to be inseparable on tlc but since the two methoxy groups appeared as a single peak the configuration of the major diastereomer could be written as shown in 24a (see scheme 4).

The epoxide 2b also showed two doublets of almost equal intensities at δ 3.02 and 3.12 indicating that it is a mixture of two diastereomers. However, unlike in the case of 2a, reduction of 2b with $LiAlH_4$ gave a compound which was found to be homogeneous by thin layer chromatography in different solvent systems. In its ^1H NMR spectrum the methoxy groups appeared as two singlets at δ 3.37 and 3.4. If, in this case also, the two diastereomers exhibit different extent of hydrogen bonding one would expect them to have different polarities. However, the two

diastereomers were inseparable on tlc in a variety of solvent systems. Mash and Hemperly have also observed a somewhat similar behaviour of diastereomeric α -hydroxy cyclohexanone 1,4-di-O-benzyl-L-threitol acetals. The inseparability of the diastereomers has been attributed to the averaging of the various possible hydrogen-bonded forms due to cyclohexane ring inversion. This results in an extremely small difference in polarity to be of any significance for chromatographic separation. Oxidation of this alcohol with pyridine-CrO_3 gave the corresponding ketone 4b in 78% yield. Reduction of this ketone with $LiAlH_4$ at 0 °C followed by acetylation gave the acetate **26** as a mixture of two diastereomers in a ratio of 75:25 as revealed by its ^1H NMR spectrum in the presence of $Eu(hfc)_3$. On the basis of observations in the cyclopentane series, it is possible to extrapolate here that the major diastereomer is 26a (Scheme 5).



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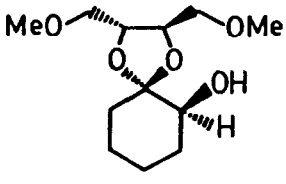
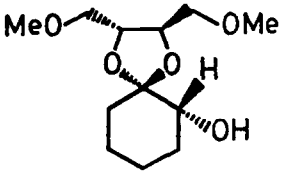
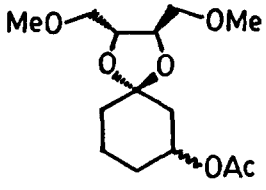


26a



26b



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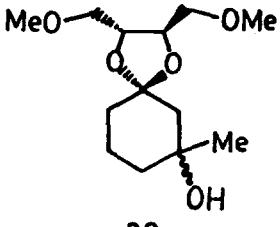

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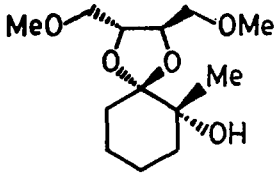
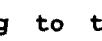


24b

Scheme 5

Addition of MeMgBr to the ketone 4b gave the corresponding tertiary alcohol which showed a singlet for each, the methoxy as well as methyl groups in the 90 MHz ^1H NMR spectrum. On the other hand, in the presence of $Eu(hfc)_3$ it showed some separation in both the peaks in its 400 MHz ^1H NMR spectrum accounting for a 96:4 ratio of the two diastereomers. The major diastereomer could thus be assigned the configuration as 24b once again on the basis of earlier arguments (vide supra) as here also the two methoxy protons appear mainly as a single peak. This is in agreement with the literature report. On the other

hand, 3-keto acetal **19** (Table 1) upon reaction with lithium aluminium hydride (-78°C) gave an alcohol **14** whose acetate **27** showed in its ^{1}H NMR spectrum (400 MHz), in the presence of Eu(hfc)$_3$, two peaks of the acetate in the ratio 67:33. Likewise, addition of MeMgBr at 0°C gave the tertiary alcohol **28** whose ^{1}H NMR analysis indicated it to be a mixture of two diastereomers in the ratio 65:35. The methyl group () appeared as two singlets corresponding to two diastereomers. Clearly, the reduction as well as Grignard reaction is not highly diastereoselective with 3-keto acetal **19**. It is likely that the carbonyl group being one more carbon away from the acetal moiety compared to 2-keto acetal, offers much less coordination of the metal simultaneously both with it as well as with the acetal oxygens. This appears to be particularly the case with cyclic systems where conformational rigidity prevents such proximity. In acyclic systems such as that studied by Matsumoto et al[8], high diastereoselectivity as a result of simultaneous metal ion coordination is possible.

Further study to explore the scope and limitations of chiral acetals is in progress.

Experimental:

General

^{1}H NMR spectra were recorded on Jeol PMX 60, Bruker WP 80 and Bruker WM 400 spectrometers with Me_4Si as internal standard. IR spectra were recorded on Perkin-Elmer 1320 spectrophotometer. Mass spectra were recorded at 70 eV on a Jeol MS-300 D mass spectrometer. Elemental analyses were carried out in Coleman automatic analyser. Optical rotations were recorded using JASCO DIP-370 polarimeter.

Achiral 2,3-olefinic acetals were prepared according to literature procedure[11] from the corresponding ketones. Tartaric acid was transformed into (-) (2S, 3S)-1,4-dimethoxy-2, 3-butanediol by following a literature procedure[12] which was subsequently utilised for the acetal formation again according to a literature procedure[11] in which instead of ethylene glycol this chiral diol was utilised.

Epoxidation of 1a and 1b

To a stirred solution of **1a** (428 mg, 2 mmol) in DMSO (3 ml) containing 0.13 ml of water was added N-bromosuccinimide (445 mg, 2.5 mmol) in small portions at 10°C. Resulting yellow coloured solution was

stirred for 1/2 hr. It was neutralised with a saturated solution of $NaHCO_3$ and worked up with ether. The crude product was purified by column chromatography using silica gel (eluents: 30:70 - ethyl acetate, pet. ether) to obtain the corresponding bromohydrin 558 mg (90%). The bromohydrin so obtained was dissolved in 2 ml anhydrous THF and added dropwise to a stirred suspension of NaH (175 mg, 3.6 mmol) in 3 ml THF at 0^oC during 4 hr. Removal of THF, addition of ice cold water (5 ml) followed by extraction of the product into ether (4 x 20 ml) gave a crude product which was purified by column chromatography [eluent, pet. ether: ether (60:40)] to obtain **2a** colourless liquid. Yield : 400 mg (87%). $[\alpha]_D^{25} = -4.8^o$ (C 2.7, $CHCl_3$). ^1H (NMR)(60 MHz, CCl_4) δ 4.15-3.85 (2H, m, methines), 3.7-3.27 [11H, m (containing a 6H singlet at δ 3.4), 2 x CH_2-OCH_3 and C_3-H], 3.17, 3.07 (1H, two d, J = 3 Hz , C_2-H), 2.1-1.4 (4H, m, 2x-CH_2-). MS m/z: 230 (M^+). Anal. Calcd. for $C_{11}H_{18}O_5$: C, 57.38; H, 7.88. Found: C, 57.61; H, 7.85%.

Likewise the epoxide **2b** was prepared from **1b** (456 mg, 2 mmol) and NBS (460 mg, 2.6 mmol) in an analogous manner as above in 81% yield. $[\alpha]_D^{25} = -1.8^o$(C 4.5, $CHCl_3$) ^1H NMR (60 MHz, $CDCl_3$) δ 4.18- 3.93 (2H, m, methines), 3.7-3.2[11H,m(containing a 6H singlet at δ 3.4), 2x-CH_2-OCH_3 and C_3-H), 3.12, 3.02 (1H, 2d, J = 3Hz, C_2-H), 2.01-1.37(6H, m, 3x-CH_2-). MS m/z: 244 (M^+). Anal Calcd. for $C_{12}H_{20}O_5$: C, 59.0; H, 8.25. Found: C, 59.12; H: 8.11%..

$LiAlH_4$ reduction of epoxides 2a and 2b:

A solution of the epoxide (2 mmol) in THF (4ml) was slowly added to a suspension of $LiAlH_4$ (100 mg, 2.6 mmol) in THF (1 ml) and the reaction mixture was refluxed for 8 hrs. The reaction mixture was quenched by successive addition of water (0.1 ml), 15% aqueous NaOHsolution (0.1 ml) and water (0.3 ml) followed by addition of 2g of anhydrous Na_2SO_4. It was filtered through a sintered funnel and the solid residue was washed with ethyl acetate (25 ml). The filtrate was concentrated to get a crude product whose purification by column chromatography (eluent: benzene- chloroform) gave the reduced products.

2-Hydroxy Cyclopentanone Cyclic (1S, 2S)-1,2-Bis (methoxymethyl) ethylene acetal 3aI:

(Less polar) IR (neat): 3450 cm^{-1}; ^1H NMR (60 MHz, CCl_4): δ 4.3-

3.73(3H, m, methines), 3.7-3.2[(10H, m, (with splitting of the $-OCH_3$ signal), 2x-CH_2-CH_3)], 2.5 (1H, br.-OH) and 2.03-1.37 (6H, m, 3x-CH_2-). MS m/z: 232 (M^+). Anal. Calcd. for $C_{11}H_{20}O_5$: C, 56.88; H, 8.68. Found: C, 56.7; H, 8.66%.

2-Hydroxy Cyclohexanone Cyclic (1S, 2S)-1,2-Bis (methoxymethyl) ethylene acetal 3aII:

(More polar) IR (neat): 3450 cm^{-1}; ^1H NMR (60 MHz, CCl_4): δ 4.3-3.8(3H, m, methines), 3.7-3.3 [10H, m (with a singlet at 3.4) 2x-CH_2CH_3], 2.5(1H, br, -OH), 2.1-1.37(6H, m, methylenes). MS m/z: 232 (M^+). Anal. Calcd. for $C_{11}H_{20}O_5$: C, 56.88; H, 8.68. Found C, 57.0; H, 8.8%.

Oxidation of hydroxy acetals 3a and 3b

To a mixture of dry pyridine (1.58 g, 20 mmol) in dry CH_2Cl_2 (15 ml) was added chromium trioxide (1.0 g, 10 mmol) and dry celite (1.0 g). After stirring for 30 min. at 20-25°C, hydroxy acetal (1 mmol) in 2 ml of CH_2Cl_2 was added to it and stirring continued for further 40min. Dilution of the reaction mixture with ether (25 ml), filtration through a pad of SiO_2 gel and concentration of the filtrate gave a crude product whose purification by preparative TLC [eluent, benzene: acetone (85:15)] gave pure keto acetals 4a and 4b.

2-Oxo-Cyclopentanone Cyclic (1S, 2S)-1,2-Bis (methoxymethyl) ethylene acetal 4a:

Yield: 74% IR (neat): 1750 cm^{-1}; ^1H NMR (CCl_4): δ 4.05-3.8 (2H, m, ), 3.67-3.3 [10H, m, (containing a singlet at δ 3.5), 2x -CH_2-OCH_3] and 2.4-1.6 (6H, m, 3x-CH_2-); MS m/z 230.

2-Oxo-Cyclohexanone Cyclic (1S, 2S)-1,2-Bis (methoxymethyl) ethylene acetal 4b:

Yield: 78%; IR (neat): 1710 cm^{-1}; ^1H NMR (CCl_4): δ 4.1-3.83(2H, m,


), 3.65-3.3 (10H, m, 2x-CH_2OCH_3), 2.63-1.5 (8H, m, 4x-CH_2-); MS m/z: 244.

Preparation of 2-keto Cycloalkanone acetals 5a and 5b:

Compounds **5a** and **5b** were prepared from the olefinic acetals **6** and **7** (see table), which in turn were obtained as per literature[11] procedure, via an analogous route as followed for **4a** and **4b**. Spectroscopic details of the bromohydrins **6a** and **7a** are given later in this paper.

Compound **2c** was prepared in a similar manner as **2a** in 80% yield.

2c: B.P. 90°C/7 mm; IR (neat): 1240, 1170, 1130, 1100, 1060, 850cm^{-1} ^1H NMR ($CDCl_3$) δ 4.1-3.8 (4H, m, -OCH_2CH_2-O), 3.5 (1H, m, ) 3.25(1H, d,  , J = 3 Hz) and 2.2-1.5 (4H, m, 2 x -CH-); MS m/z: 142; Anal. Calcd. for $C_7H_{10}O_3$. C, 59.14; H, 7.09. Found: C, 59.10; H, 7.10%.

2d: To a solution of 2.07 g (9.6 mmol) of 80% m-CPBA in anhydrous CH_2Cl_2 (2 ml) was slowly added a solution of **7** in CH_2Cl_2 (2 ml) at 0°C. The resulting mixture was stirred for 15 h at 0-15°C. The reaction mixture was filtered and the filtrate washed with saturated solution of Na_2SO_3 (20 ml), 10% NaOH solution (10 ml), water (2x10 ml) and brine (10 ml) and dried over anhydrous Na_2SO_4. Removal of solvent gave crude **2d** which was purified by distillation, b.p. 105-110°C/7 mm. IR (neat): 1260, 1180, 1150, 1120, 1070, 870cm^{-1}; ^1H NMR (CCl_4): δ 3.9-3.7 (4H, m,-OCH_2-CH_2O-) 3.1-2.8 (1H, m, ), 2.73 (1H, d,  , J = 4 Hz),2.01-1.3 (6H, m, methylenes; MS m/z: 156, Anal. Calcd. for $C_8H_{12}O_3$: C, 61.52; H, 7.75. Found :C, 61.48; H, 7.78%.

Reductions of **5a** and **5b** with $LiAlH_4$ followed by oxidation were done in an analogous manner as that for **2a** and **2b** (vide supra).

3c: Yield, 81%; thick oil.

5a: Yield, 85%. IR (neat): 1750 cm^{-1}; ^1H NMR ($CDCl_3$): δ 4.4-3.77 (4H, m, $-OCH_2CH_2-O-$), 2.47-1.47 (6H, m, methylenes); MS m/z: 142, Anal. Calcd. for $C_7H_{20}O_3$: C, 59.14; H, 7.09. Found: C, 59.08, H, 7.00%.

3d Yield, 87%, Thick oil.

5b: Yield, 90%, IR (neat): 1710 cm^{-1}; ^1H NMR ($CDCl_3$): δ 4.13 (4H, s, $-OCH_2CH_2-$), 2.77-2.4 (2H, m, $-\overset{O}{\overset{\|}{C}}-CH_2-$), 2.17-1.57 (6H, m, remaining methylenes); MS m/z: 156. Anal. Calcd. for $C_8H_{12}O_3$: C, 61.52; H, 7.75. Found: C, 61.60, H, 7.76%.

4-Methyl-2-Cyclohexenone ethylene acetal 9:

B.P. 90°C/10 mm; IR (neat): 1650, 1180, 1120, 1060, 1040 cm^{-1}
^1H NMR (CCl_4): δ 5.9-5.37 (2H, m, olefinic), 3.83 (4H, s, $-OCH_2-CH_2-O-$), 2.32-1.42 (5H, m, $>C=\overset{H}{\underset{CH_3}{}}$ and 2x CH_2), 1.0 (3H, d, $>C=\overset{H}{\underset{CH_3}{}}$, J = 7 Hz). MS m/z: 154.

1-Pentene-3-one ethylene acetal 10:

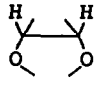
B.P. 100°C/30 mm; IR (neat): 1630 cm^{-1}
^1H NMR (CCl_4): δ 5.83-4.8 (3H, m, olefinic), 3.77 (4H, s, $-OCH_2CH_2O-$), 1.63 (4H, q, $-CH_2CH_3$, J = 7 Hz), 0.83 (3H, t, $-CH_2CH_3$, J = 7 Hz); MS m/z: 128.

2-Cyclohexene-1-one Cyclic (1S, 2S)-1, 2-Bis (methoxy methyl) ethylene acetal 11

A solution of 1.96 g (20 mmol) of cyclohexanone in 25 ml dry CH_3OH was added a small portion of bromine at room temperature. The solution was warmed slightly so that the uptake of bromine was complete. The remainder of bromine 3.2 g (20 mmol) was then added at 35-40°C at such a rate that a faint colouration of bromine was maintained at all times.

After additional 10 min. of stirring, the reaction mixture was poured into a suspension of 2.0 g of NaOMe and 20 ml of petroleum ether (40-60°C) cooled in an ice-water bath. After stirring for 5 min, 25 ml of cold water was added to it. Separation of the organic layer followed by extraction of the aqueous layer with petroleum ether (3x15 ml) and drying (Na_2SO_4) and evaporation of the solvent under reduced pressure gave the unstable 2-bromocyclohexanone dimethyl acetal. To this compound was added 3.2 g (21.4 mmol) and anhydrous p-toluenesulfonic acid (52 mg) in dry benzene (20 ml) was refluxed for 2.5 hr. Neutralisation of the reaction mixture with satd. solution of $NaHCO_3$ (10 ml), extraction with ether (3x30 ml) followed by usual work up gave the corresponding crude 2-bromo acetal. Sodium methoxide (650 mg, 12 mmol) was taken in dry DMSO (10 ml) and stirred at 40°C until a homogeneous mixture was obtained. The bromo acetal (5 mmol) was then added slowly to it at 20°C and then the whole mixture stirred at 50°C for 10 hr. Usual work up i.e., washing with ice cold water extraction with ether and evaporation gave a crude 11 which was purified by Kugelrhor distillation.

Yield: 66% (based on 2-bromocyclohexanone dimethyl acetal); B.P.: 100-105°C/0.1 mm; IR (neat): 3030, 1640 cm^{-1}; ^1H NMR (CCl_4): δ 5.93-5.67 (1H, m, olefinic), 5.55-5.4 (1H, m, olefinic), 4.03-3.77 (2H, m,



), 3.6-3.25 (10H, m, 2x-CH_2OCH_3), 2.15-1.87 (2H, m, allylic-CH_2-), 1.87-1.45 (4H, m, 2x CH_2); MS m/z: 228. Anal. Calcd. for $C_{12}H_{20}O_4$: C, 63.13; H, 8.88. Found: C, 63.0; H, 8.68%.

General procedure for bromohydrin 'A' synthesis:

Bromohydrins were synthesised by following a literature procedure[18] using NBS-DMSO-H_2O combination at 10°C.

Bromohydrin 6A

Yield: 81%; IR (neat) 3460 cm^{-1} ; ^1H NMR (CCl_4): δ 4.5-3.67 (6H, m, -OCH_2CH_2O-, -$\dot{C}HBr$, -$\dot{C}HOH$), 3.0 (1H, br s,-OH), 2.47-1.33 (4H, m, 2x CH_2).

Bromohydrin 7A

Yield: 89% ; m.p. 95°C; IR (KBr). 3460 cm^{-1}; ^1H NMR ($CDCl_3$): δ

4.45-3.7 (6H, m, $-OCH_2CH_2O-$, $-\overset{|}{C}HBr$, $-\overset{|}{C}HOH$), 2.67 (1H, br s, -OH) and 2.37-1.27 (6H, m, 3x CH_2).

Bromohydrin 8A

Yield: 93%; IR (neat): 3460 cm^{-1}; ^1H NMR (CCl_4): δ 4.2-3.83 (6H, m, $-OCH_2CH_2O-$, $-\overset{|}{C}HBr$, $-\overset{|}{C}HOH$), 2.53 (1H, br s, -OH), 2.53-1.4 (8H, m, 4x CH_2).

Bromohydrin 9A

Yield: 87% IR (neat): 3500 cm^{-1}; ^1H NMR (CCl_4): δ 4.37-3.53 (6H, m, $-OCH_2CH_2O-$, $-\overset{|}{C}HBr$, $-\overset{|}{C}HOH$), 2.57 (1H, br s, -OH), 2.4-1.17 (5H, m, 2x CH_2, $-\overset{|}{C}HCH_3$), 0.97, 1.07 (3H, 2s, $-CH_3$).

Bromohydrin 10A

Yield: 83% IR (neat): 3450 cm^{-1}; ^1H NMR (CCl_4): δ 4.27-3.67 (7H, m, $-OCH_2-CH_2O-$, $-CH_2OH$, $-\overset{|}{C}HBr$), 2.9 (1H, s, -OH), 2.33-1.37 (2H, m, $-CH_2CH_3$), 0.9 (3H, t, J = 7 Hz, $-CH_2CH_3$).

2-Bromo-3-hydroxy-cyclohexanone Cyclic (1S, 2S)-1,2-Bis (methoxymethyl) ethylene acetal 11A:

Yield: 81%; IR (CCl_4): 3450 cm^{-1}; ^1H NMR (CCl_4): δ 4.2-3.6 (3H, m,  , $-\overset{|}{C}HOH$), 3.6-3.07 (11H, m, 2x$-CH_2OMe$, $-\overset{|}{C}HBr$), 2.27-1.4 (7H, m, 3x CH_2, $-\overset{|}{C}HOH$).

General procedure for oxidation of bromohydrins to α- bromo ketones 'B'

This oxidation was carried out in an analogous manner as that adopted for the oxidation of hydroxy acetals 3a and 3b.

2-Bromo, 3-oxo-cyclohexanone ethylene acetal 7B

Yield: 65%, m.p. 65°C; IR (KBr): 1720 cm^{-1}; ^1H NMR (CCl_4): δ 4.17-3.77 (5H, m, $-\overset{|}{C}HBr$, $-OCH_2CH_2O-$), 3.33-1.4 (6H, m, methylenes).

2-Bromo, 3-oxo cycloheptanone ethylene acetal 8B

Yield: 78%, IR (neat): 1695 cm^{-1}; ^1H NMR (CCl_4): δ 4.5-3.73 (5H, m, $-OCH_2CH_2O-$, $-\overset{|}{C}HBr$), 3.17-1.53 (8H, m, 4x CH_2).

2-Bromo,-4-methyl,-3-oxo cyclohexanone ethylene acetal 9B

Yield: 80%; IR (neat): 1715 cm^{-1}; ^1H NMR (CCl_4): δ 4.0-3.7 (5H, m, $-\overset{|}{C}HBr$, $-OCH_2CH_2O-$), 3.4-1.07 (5H, m, 2xCH_2 and $>CHCH_3$), 0.97 (3H, d, J = 7Hz, $HCCH_3$).

1-Bromo-1-formyl-butan-2-one ethylene acetal 10B

Yield: 80%, IR (neat): 1720 cm^{-1}; ^1H NMR (CCl_4): δ 9.23 (1H, d, J = 5 Hz, -CHO), 4.33-3.8 (5H, m, $-\overset{|}{C}HBr$, $-OCH_2CH_2O-$), 1.93-1.47 (2H, m, $-CH_2CH_3$), 0.9 (3H, t, J = 7Hz, $-CH_2CH_3$).

2-Bromo-3-oxo-cyclohexanone cyclic (1S, 2S)-1, 2-Bis (methoxy methyl) ethylene acetal 11B

Yield: 71%; IR (neat): 1710 cm^{-1}; ^1H NMR (CCl_4): δ 4.4-3.93 (3H, m, methines), 3.47 (4H, d, J = 3 Hz, $MeOCH_2-$ x 2), 3.37 (6H, s, -OMe x 2), 2.5-1.53 (6H, m, methylenes).

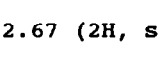
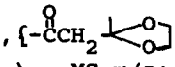
General procedure for n-Bu_3SnH reduction of bromoketones 7B, 8B, 9B and 11B

To a solution of a bromoketone (1 mmol) in benzene (10 ml) was added tributyltinhydride (2 mmol) and 50-80 mg of AIBN and the reaction mixture refluxed for 4 hr. Solvent was removed under vacuum and the crude product purified by column chromatography using pet. ether: ethyl acetate (80:20). Compounds 15, 16, 17 and 19 were obtained in pure form.

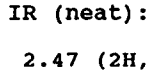
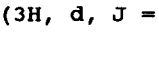
3-oxo-cyclohexanone ethylene acetal 15

Yield: 81%, IR (neat): 1720 cm^{-1}; ^1H NMR (CCl_4): δ 3.83 (4H, s, $-OCH_2CH_2O-$), 2.37 (2H, s, $-\overset{O}{\overset{\|}{C}}CH_2$ ), 2.3-1.93 (2H, m, $-\overset{O}{\overset{\|}{C}}-CH_2-CH_2-$), 1.93-1.6 (4H, m, 2 x CH_2). MS m/z: 156.

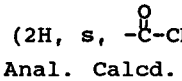
3-oxo-cycloheptanone ethylene acetal 16

Yield: 88%, IR (neat): 1710 cm^{-1}; ^1H NMR (CCl_4): δ 3.83 (4H, s, $-OCH_2CH_2O$), 2.67 (2H, s, ), 2.53-2.13 (2H, m, ), 2.0-1.53 (6H, m, 3 x CH_2). MS m/z: 170.

3-oxo-4-methyl-cyclohexanone ethylene acetal 17

Yield: 85%, IR (neat): 1710 cm^{-1}; ^1H NMR (CCl_4): δ 3.87 (4H, m, $-OCH_2CH_2O-$), 2.47 (2H, s, ), 2.4-1.13 (5H, m, $-CHCH_3$, 2 x CH_2), 0.97 (3H, d, J = 6 Hz, ). MS m/z: 170.

3-Oxo-cyclohexanone cyclic (1S, 2S)-1, 2-Bis (methoxymethyl) ethylene acetal 19

Yield: 78%, IR (neat): 1720 cm^{-1}; ^1H NMR (CCl_4): δ 4.16-3.97 (2H, m, 2 methines), 3.5 (4H, d, J = 3.75 Hz, 2 x $-CH_2OMe$), 3.44 (6H, s, 2 x -OMe), 2.65 (2H, s, ), 2.43-1.63 (6H, m, 3 x CH_2). MS m/z: 244. Anal. Calcd. for $C_{12}H_{20}O_5$: C, 59.01, H, 8.20. Found: C, 59.2; H, 8.25%.

3-Hydroxy-cyclopentanone ethylene acetal 12

To a solution of 6A in benzene (5 ml) was added n-Bu_3SnH (580 mg, 2 mmol) and AIBN (50 mg). The reaction mixture was then heated under reflux for 2 hr. Solvent was removed under vacuum and the residue chromatographed [(SiO_2), pet-ether: ethyl acetate: 92:8] to obtain pure 12 (110 mg).

Yield 76%, IR (neat): 3400 cm^{-1}; ^1H NMR (CCl_4): δ 4.57-3.9 (2H, m, -CHOH), 3.77 (4H, s, $-OCH_2CH_2O-$), 2.3-1.4 (6H, m, 3 x CH_2).

1-Acetyl-3-pentanone ethylene acetal 13A

Bromohydrin 10A (1 g, 4.44 mmol), tributyltin hydride (2 g, 6.87 mmol) and AIBN (100 mg) were mixed in benzene (10 ml) and refluxed for 4

hr. Solvent was removed under vacuum and the crude product purified by column chromatography using pet. ether: ethyl acetate (80:20) as eluent to obtain 13 in 89% yield. For characterisation purpose, 0.1 g (0.44 mmol) of the pure bromohydrin was acetylated by treating it with acetic anhydride (170 mg, 1.7 mmol), pyridine (0.5 ml) and a catalytic amount of N, N-dimethylamino pyridine (10 mg) and stirred for 10 hr. After the reaction was complete it was washed with water and extracted with CH_2Cl_2 (3 x 10 ml). Drying (Na_2SO_4) and evaporation of the solvent gave the crude product whose purification by column chromatography using ethyl acetate: pet.ether (5:95) as eluent gave the acetate 13A (90 mg). Yield: 77%, IR (neat): 1720 cm^{-1}; ^1H NMR (CCl_4): δ 3.97 (2H, t, J = 7 Hz, $-CH_2OAc$), 3.8 (4H, s, $-OCH_2CH_2O-$), 1.93 (3H, s, $-O\overset{O}{\overset{\|}{C}}CH_3$), 1.87-1.07 (4H, m, 2 x CH_2), 0.87 (3H, t, J = 7 Hz, $-CH_2CH_3$). MS m/z: 188. Anal. Calcd. for $C_9H_{16}O_4$: C, 57.45; H, 8.51; Found: C, 57.13; H, 8.73%.

3-Hydroxy-cyclohexanone cyclic (1S, 2S)-1,2-Bis (methoxymethyl) ethylene acetal 14

To an ethereal solution of $LiAlH_4$ (18 mg, 0.5 mmol) at - 78°C was added a solution of compound 19 (234 mg, 1 mmol) in ether (6 ml). After stirring the reaction mixture for 4 hr, it was quenched with water and extracted with ether. Drying (Na_2SO_4) and removal of the solvent gave almost pure 14 (234 mg, 95%). A portion of this alcohol (82 mg, 0.33 mmol) was dissolved in dry CH_2Cl_2 (2 ml) and treated with acetic anhydride (100 mg, 1 mmol) pyridine (79 mg, 1 mmol) and DMAP (5 mg). The reaction mixture was then stirred at room temperature for 15 hr. Usual work up gave a crude product which was purified by column chromatography (pet ether-ethyl acetate: 90:10) to obtain pure 27 (90 mg, 82%).
IR (neat): 3450 cm^{-1}; ^1H NMR (CCl_4): δ 3.93-3.53 (3H, m, methines), 3.4 (4H, d, J = 3 Hz, $-CH_2OMe$ x 2), 3.27 (6H, s, -OMe x 2), 2.93 (1H, br s,-OH), 1.94-1.1 (5H, m, methylenes).

3-Acetoxy-cyclohexanone cyclic (1S, 2S)-1,2-Bis (methoxymethyl) ethylene acetal 27

Yield: 82%, IR (CCl_4): 1720 cm^{-1}; ^1H NMR (CCl_4): δ 4.67 (1H, m, -CHOAc), 3.83 (2H, m, methines), 3.4 (10H, br s, $-CH_2OCH_3$ x 2), 1.93 (3H, s, $OCOCH_3$), 2.06-1.26 (8H, m, methylenes). MS m/z: 208.

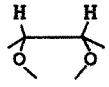
1-Formyl-butan-2-one ethylene acetal 18

To a solution of DMSO (187 mg, 2.4 mmol) at -60°C in dry CH_2Cl_2 (5 ml) was added oxalyl chloride (140 mg, 1.1 mmol). After 10 min, the hydroxy compound 13 (146 mg, 1 mmol) in CH_2Cl_2 (2 ml) was added to the reaction mixture dropwise over 5 min., and stirred for 15 min. Triethylamine (505 mg, 5 mmol) was then added to it and the cooling bath removed. After 15 min. the reaction mixture was quenched with water followed by separation of the organic layer and reextraction of the aqueous layer with CH_2Cl_2 (3x10 ml). The combined organic layer was dried over anhydrous Na_2SO_4 and solvent removed under vacuum to obtain a crude product. Purification by column chromatography [(SiO_2), eluent pet. ether- ethyl acetate: 98:2] gave compound 18 (120 mg).
Yield: 83%, IR (neat): 1720 cm^{-1}; ^1H NMR (CCl_4): δ 9.43 (1H, t, J = 3 Hz, -CHO), 3.9 (4H, s, $-OCH_2CH_2O-$), 2.47 (2H, d, J = 3 Hz, $-CH_2CHO$), 1.63 (2H, q, J = 7 Hz,$-CH_2CH_3$), 0.83 (3H, t, J = 7 Hz, $-CH_2CH_3$).

$LiAlH_4$ reduction of 2-ketoacetals 4a and 4b followed by acetylation

An analogous procedure as described for the reduction of compound 19 was followed in these cases too.

2-Oxo-cyclopentanone cyclic (1S, 2S)-1, 2-Bis (methoxymethyl) ethylene acetal 4a

Yield: 74%; IR (neat): 1750 cm^{-1}; ^1H NMR (CCl_4): δ 4.05-3.8 (2H, m, ), 3.67-3.3 [10 H, m, (containing a singlet at δ 3.5), 2 x $-CH_2-OCH_3$] and 2.4-1.6 (6H, m, 3 x $-CH_2-$); MS m/z: 230.

2-Oxo-cyclohexanone cyclic (1S, 2S)-1, 2-Bis (methoxymethyl) ethylene acetal 4b

Yield: 78%, IR (neat): 1710 cm^{-1}; ^1H NMR (CCl_4): δ 4.1-3.83 (2H, m, ), 3.65-3.3 (10H, m, 2 x $-CH_2OCH_3$), 2.63-1.5 (H, m, 4 x $-CH_2-$); MS m/z: 244.

$LiAlH_4$ reduction of 2-keto acetals 4a and 4b followed by acetylation

An analogous procedure as described for the reduction of compound 19 was followed in these cases too.

2-Acetoxy-cyclopentanone cyclic (1S,2S)-1,2-Bis (methoxymethyl) ethylene acetal 25

Yield 79%, IR (neat): 1730 cm^{-1}; ^1H NMR (CCl_4): δ 4.89-4.57 (1H, m, -CHOAc), 3.9-3.67 (2H, m, methines), 3.5-3.23 (10H, m, containing a singlet at δ 3.27, $-CH_2OCH_3$ x 2), 2.0 (3H, s, $-OCOCH_3$), 1.9-1.4 (6H, m, methylenes). MS m/z: 274.

2-Acetoxy-cyclohexanone cyclic (1S,2S)-1,2-Bis (methoxymethyl) ethylene acetal 26

Yield: 82%, IR (neat): 1725 cm^{-1}; ^1H NMR (CCl_4): δ 4.83-4.47 (1H, m, -CHOAc), 4.0-3.6 (2H, m, methines), 3.47-3.23 (10H, m, containing a singlet at δ 3.27, $-CH_2OCH_3$ x 2), 1.93 (3H, s, $-O-COCH_3$), 1.87-1.13 (8H, m, methylenes). MS m/z: 288.

General Procedure for MeMgI addition to keto acetals 4a, 4b and 19

To a suspension of clean and dry magnesium turnings (29 mg) in anhydrous ether (0.5 ml) under N_2 atmosphere (containing a small crystal of iodine) was added methyl iodide (175 mg, 1.23 mmol) in 0.5 ml of ether at room temperature. After all the magnesium had reacted, the reaction mixture was cooled to 0^oC and a solution of keto acetal (1 mmol) in 1 ml of ether was added. It was brought to room temperature during 1 hr,and stirred for further 2 hr. Satd. aq. NH_4Cl solution (5 ml) was slowly added to it and the stirring continued for another 10 min. Extraction with ether (3 x 15 ml), washing with brine (5 ml), drying with Na_2SO_4 followed by removal of the solvent gave a crude product whose purification by column chromatography gave pure hydroxy compound 24a, 24b or 28.

2-Hydroxy, 2-methyl-cyclopentanone cyclic (1S,2S)-1,2-Bis (methoxymethyl) ethylene acetal 24a

Yield: 60%, IR (neat) 3450 cm^{-1}; ^1H NMR (CCl_4): δ 4.0-3.8 (2H, m,

methines), 3.7-3.1 (10 H, m, contains a singlet at δ 3.27 (2 x $-CH_2OCH_3$), 1.97 (1H, br s, OH), 1.83-1.4 (6H, m, methylenes), 1.1 (3H, s, $-CH_3$). MS m/z: 246. Anal. Calcd. for $C_{12}H_{22}O_5$: C, 58.51; H, 9.01. Found: C, 58.42; H, 9.1%.

2-Hydroxy, 2-methyl-cyclohexanone cyclic (1S,2S)-1,2-Bis (methoxymethyl) ethylene acetal 24b

Yield: 80%, IR (neat) 3425 cm^{-1}; ^1H NMR (CCl_4): δ 4.0-3.73 (2H, m, methines), 3.6-3.17 (10H, m, containing a singlet at δ 3.27, 2 x $-CH_2OCH_3$), 1.8 (1H, br s, OH), 1.67-1.23 (H, m, methylenes), 1.07 (3H, s, $-\overset{|}{\underset{|}{C}}\!\!<^{CH_3}_{OH}$). MS m/z: 260. Anal. Calcd. for $C_{13}H_{24}O_5$: C, 59.98; H, 9.29. Found: C, 60.2; H, 9.41%.

3-Hydroxy, 3-methyl-cyclohexanone cyclic (1S,2S)-1,2-Bis (methoxymethyl) ethylene acetal 28

Yield: 72%, IR (neat): 3450 cm^{-1}; ^1H NMR (CCl_4): δ 3.93 (2H, m, methines), 3.6-3.27 (10H, m, containing a singlet at δ 3.4,$-CH_2OCH_3$ x 2), 2.3 (1H, br s, OH), 2.07-1.6 (8H, m, methylenes), 1.27 and 1.13 (3H, 2 s, $-\overset{|}{\underset{|}{C}}-CH_3$). MS m/z: 260.

General procedure for the hydrolysis[17] of 3-keto acetals 15, 16 and 17

To a suspension of silica gel (100-200 mesh, 500 mg) in CH_2Cl_2 (3 ml) was added 15% H_2SO_4 (0.15 ml). The mixture was stirred at room temperature until the turbidity in the CH_2Cl_2 layer had disappeared. A solution of a keto acetal (1 mmol) in 1 ml of CH_2Cl_2 was added to it and the reaction mixture stirred at room temperature for 20 hr (50 hr in the case of 1,3-cycloheptanedione monoethylene acetal). It was neutralised with $NaHCO_3$, filtered and the solid residue washed with CH_2Cl_2. The filtrate was concentrated and the crude dione purified by preparative TLC [eluent, benzene; acetone (75:25)] or by vacuum distillation.

1,3-cyclohexanedione 20[13,16] Yield: 70%, m.p. 102 (Lit[13], mp 105-106°C);
1,3-cycloheptanedione 21[14,16] Yield: 71% ;
4-Methyl-1,3-cyclohexanedione[15] 22 Yield: 78%.

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3. Please see part 1 (cf. ref. 1 above).
4. This was also the case with 2a as well as with other epoxides studied earlier (cf. ref. 2). A similar observation has recently been made by Ferraz et al. Please see H.M.C. Ferraz, M. Sasahara and P. Losco. Tetrahedron Lett., 1992, 33, 8131.
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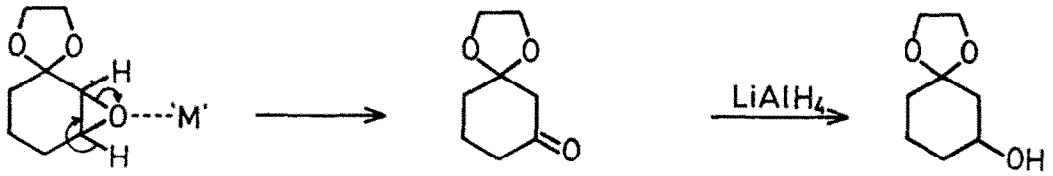
6. Isomerisation to 3 keto acetal followed by reduction to the observed 3-hydroxy acetal may have taken place as shown below:



'M' : METAL IMPURITY

This is merely a hypothetical proposition based on the fact that we did observe the formation of 3-keto acetal in our earlier studies.

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