Chiral Acetals in Organic Synthesis: 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 LAK 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 transformation of 2,3-olefinic acetals into 1,2- and 1,3- diones via regioselective reductions of the corresponding epoxides with Zn-ClSiMe₃ and LiAlH₄ respectively. In a programme 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 LiAlH₄ (obtained from E. Merck) consistently gave

Scheme 1

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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. 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 \(^1\)H NMR spectra of the corresponding keto acetals. In 3-keto acetals, the characteristic singlet is observed at \(~\delta~2.65\) 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-Bu\(_3\)SnH 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-Bu\(_3\)SnH 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-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\textsuperscript{9}.

\textbf{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 $\delta$ 3.17 and $\delta$ 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

<table>
<thead>
<tr>
<th>Entry</th>
<th>2, 3 Olefinicetal</th>
<th>Bromohydrin 'A' (% yield)</th>
<th>Bromoketone 'B' (% yield)</th>
<th>3 Hydroxyacetal (% yield)</th>
<th>3 Ketoacetal (% yield)</th>
<th>1, 3 Dione (% yield)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>6 (n = 1)</td>
<td>6A (81)</td>
<td>12 (76)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.</td>
<td>7 (n = 2)</td>
<td>7A (89)</td>
<td>7B (65)</td>
<td></td>
<td>15 (81)</td>
<td>20 (70)</td>
</tr>
<tr>
<td>3.</td>
<td>8 (n = 3)</td>
<td>8A (93)</td>
<td>8B (78)</td>
<td></td>
<td>16 (80)</td>
<td>21 (71)</td>
</tr>
<tr>
<td>4.</td>
<td>9</td>
<td>9A (87)</td>
<td>9B (80)</td>
<td></td>
<td>17 (85)</td>
<td></td>
</tr>
<tr>
<td>5.</td>
<td>10</td>
<td>10A (83)</td>
<td>10B (80)</td>
<td></td>
<td>18 (89)</td>
<td></td>
</tr>
<tr>
<td>6.</td>
<td>11</td>
<td>11A (81)</td>
<td>11B (71)</td>
<td></td>
<td>14 (95)</td>
<td>12 (78)</td>
</tr>
</tbody>
</table>
inseparable. On the other hand, LiAlH₄ 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.

\[
\text{MeO} \quad \text{MeO} \quad \text{MeO} \\
\text{O} \quad \text{O} \quad \text{O}
\]

\[
2a \text{ I} \quad 2a \text{ II} \quad 3a \text{ I (Less polar)}
\]

\[
\text{MeO} \quad \text{MeO} \quad \text{MeO} \\
\text{O} \quad \text{O} \quad \text{O}
\]

\[
3a \text{ II (More polar)}
\]

Scheme 3

This observation is not surprising, as, recently Mash and Hemperly\textsuperscript{10}
have found similar polarity differences between these two diastereomers
prepared from \(\alpha\)-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 \(\alpha\)-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.
Similar rationalisation is evidently applicable in the present study also for 3a I and 3a II and to account for the chromatographic inseparability between 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 LiAlH₄ 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).

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 (\(\text{Me}^\text{Me} \text{CH}_3\)) 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 LiAlH₄ 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-CrO₃ gave the corresponding ketone 4b in 78% yield. Reduction of this ketone with LiAlH₄ 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)₂. On the basis of observations in the cyclopentane series, it is possible to extrapolate here that the major diastereomer is 26a (Scheme 5).

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)₂ 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 1H 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 1H NMR analysis indicated it to be a mixture of two
diastereomers in the ratio 65:35. The methyl group (\(\text{CH}_3\)) 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

1H NMR spectra were recorded on Jeol PMX 60, Bruker WP 80 and
Bruker WM 400 spectrometers with Me₄Si 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
procedure11 from the corresponding ketones. Tartaric acid was
transformed into (-) \((2S, 3S)\)-1,4-dimethoxy-2, 3-butanediol by following
a literature procedure12 which was subsequently utilised for the acetal
formation again according to a literature procedure11 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 NaHCO₃ 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 NaI (175 mg, 3.6 mmol) in 3 ml THF at 0°C 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%). \([\alpha]^{25}_{D} = -4.8^0 (c 2.7, CHCl₃) \). \(^1H\) NMR (60 MHz, CCl₄): δ 4.15-3.85 (2H, m, methines), 3.7-3.27 (11H, m (containing a 6H singlet at δ 3.4), 2 x CH₂-OCH₃ and C₂-H), 3.17, 3.07 (1H, two d, J = 3 Hz, C₂-H), 2.1-1.4 (4H, m, 2x-CH₂-). MS m/z: 230 (M⁺). Anal. Calcd. for C₁₁H₁₈O₅: C, 57.38; H, 7.88. Found: C, 57.38; H, 7.88%.

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. \([\alpha]^{25}_{D} = -1.8^0 (c 4.5, CHCl₃) \). \(^1H\) NMR (60 MHz, CDCl₃): δ 4.18-3.93 (2H, m, methines), 3.7-3.2 (11H, m (containing a 6H singlet at δ 3.4), 2x-CH₂-OCH₃ and C₃-H), 3.12, 3.02 (1H, 2d, J = 3Hz, C₂-H), 2.01-1.37 (6H, m, 3x-CH₂-). MS m/z: 244 (M⁺). Anal. Calcd. for C₁₂H₂₀O₅: C, 59.0; H, 8.25. Found: C, 59.12; H: 8.11%.

**LiAlH₄ reduction of epoxides 2a and 2b:**

A solution of the epoxide (2 mmol) in THF (4ml) was slowly added to a suspension of LiAlH₄ (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 NaOH solution (0.1 ml) and water (0.3 ml) followed by addition of 2g of anhydrous Na₂SO₄. 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-Hydroxycyclopentanone Cyclic (1S, 2S)-1,2-Bis (methoxymethyl) ethylene acetal 3aI:**

(Less polar) IR (neat): 3450 cm⁻¹; \(^1H\) NMR (60 MHz, CCl₄): δ 4.3-
3.73 (3H, m, methines), 3.7-3.2 (10H, m, with splitting of the -OCH₃ signal), 2x-CH₂-CH₃), 2.5 (1H, br. -OH) and 2.0-1.37 (6H, m, 3x-CH₂-).
MS m/z: 232 (M⁺). Anal. Calcd. for C₁₁H₂O₅: 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, CCl₄): δ 4.3-3.8 (3H, m, methines), 3.7-3.3 [10H, m (with a singlet at 3.4) 2x-CH₂CH₃], 2.5 (1H, br, -OH), 2.1-1.37 (6H, m, methylenes). MS m/z: 232 (M⁺). Anal. Calcd. for C₁₁H₂O₅: 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 CH₂Cl₂ (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 CH₂Cl₂ was added to it and stirring continued for further 40 min. Dilution of the reaction mixture with ether (25 ml), filtration through a pad of SiO₂ 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 (CCl₄): δ 4.05-3.8 (2H, H, H), 3.67-3.3 (10H, m, (containing a singlet at δ 3.5), 2x -CH₂-OCH₃) and 2.4-1.6 (6H, m, 3x-CH₂-); 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 (CCl₄): δ 4.1-3.83 (2H, m,
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 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, 850 cm⁻¹

$^1$H NMR (CDCl₃) δ 4.1-3.8 (4H, m, -OCN=CH₂), 3.5 (1H, m, $^3_J=3$ Hz) and 2.2-1.5 (4H, m, 2 x -CH₂-); MS m/z: 142; Anal. Calcd. for C₇H₁₀O₃: C, 59.14; H, 7.09. Found: C, 59.10; H, 7.10%.

To a solution of 2.07 g (9.6 mmol) of 80% m-CPBA in anhydrous CH₂Cl₂ (2 ml) was slowly added a solution of 7 in CH₂Cl₂ (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 Na₂SO₃ (20 ml), 10% NaOH solution (10 ml), water (2x10 ml) and brine (10 ml) and dried over anhydrous Na₂SO₄. 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, 870 cm⁻¹; $^1$H NMR (CCl₄): δ 3.9-3.7 (4H, m, -OCH₂-CH₂O-) 3.1-2.8 (1H, m, $^3_J=3.7$ Hz), 2.73 (1H, d, $^3_J=4$ Hz), 2.01-1.3 (6H, m, methylenes); MS m/z: 156, Anal. Calcd. for C₈H₁₂O₃: C, 61.52; H, 7.75. Found :C, 61.48; H, 7.78%.

Reductions of 5a and 5b with LiAlH₄ 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\(^{-1}\); \(^1\)H NMR (CDCl\(_3\)): \(\delta\) 4.4-3.77 (4H, m, \(-\text{OCH}_2\text{CH}_2-\)), 2.47-1.47 (6H, m, methylenes); MS m/z: 142. Anal. Calcd. for C\(_7\)H\(_{20}\)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\(^{-1}\); \(^1\)H NMR (CDCl\(_3\)): \(\delta\) 4.13 (4H, s, \(-\text{OCH}_2\text{CH}_2-\)), 2.77-2.4 (2H, m, \(-\text{OCH}_2\text{CH}_2-\)), 2.17-1.57 (6H, m, remaining methylenes); MS m/z: 156. Anal. Calcd. for C\(_8\)H\(_{12}\)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\(^{-1}\)
\(^1\)H NMR (CCl\(_4\)): \(\delta\) 5.9-5.37 (2H, m, olefinic), 3.83 (4H, s, \(-\text{OCH}_2\text{CH}_2-\)), 2.32-1.42 (5H, m, \(-\text{OCH}_2\text{CH}_2-\)), 1.0 (3H, d, \(-\text{CH}_3\), \(J = 7\) Hz). MS m/z: 154.

1-Pentene-3-one ethylene acetal 10:

B.P. 100°C/30 mm; IR (neat): 1630 cm\(^{-1}\)
\(^1\)H NMR (CCl\(_4\)): \(\delta\) 5.83-4.8 (3H, m, olefinic), 3.77 (4H, s, \(-\text{OCH}_2\text{CH}_2-\)), 1.63 (4H, q, \(-\text{CH}_2\text{CH}_3\), \(J = 7\) Hz), 0.83 (3H, t, \(-\text{CH}_2\text{CH}_3\), \(J = 7\) 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\(_3\)OH 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 (Na₂SO₄) 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 NaHCO₃ (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 (CCl₄): 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-CH₂OCH₃), 2.15-1.87 (2H, m, allylic-CH₂-), 1.87-1.45 (4H, m, 2x CH₂); MS m/z: 228. Anal. Calcd. for C₁₂H₂₀O₄: 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 using NBS-DMSO-H₂O combination at 10°C.

Bromohydrin 6A

Yield: 81%; IR (neat) 3460 cm⁻¹; ¹H NMR (CCl₄): δ 4.5-3.67 (6H, m, -OCH₂CH₂O-, -CHBr, -CHOH), 3.0 (1H, br s, -OH), 2.47-1.33 (4H, m, 2x CH₂).

Bromohydrin 7A

Yield: 89% ; m.p. 95°C; IR (KBr). 3460 cm⁻¹; ¹H NMR (CDCl₃): δ
4.45-3.7 (6H, m, \(-\text{OCH}_2\text{CH}_2\text{O}^-, -\text{CHBr}, -\text{CHOH}\)), 2.67 (1H, br s, -\text{OH}) and 2.37-1.27 (6H, m, 3x CH\(_2\)).

**Bromohydrin 8A**

Yield: 93%; IR (neat): 3460 cm\(^{-1}\); \(^1\)H NMR (CCl\(_4\)): \(\delta\) 4.2-3.83 (6H, m, \(-\text{OCH}_2\text{CH}_2\text{O}^-, -\text{CHBr}, -\text{CHOH}\)), 2.53 (1H, br s, -\text{OH}), 2.53-1.4 (8H, m, 4x CH\(_2\)).

**Bromohydrin 9A**

Yield: 87% IR (neat): 3500 cm\(^{-1}\); \(^1\)H NMR (CCl\(_4\)): \(\delta\) 4.37-3.53 (6H, m, \(-\text{OCH}_2\text{CH}_2\text{O}^-, -\text{CHBr}, -\text{CHOH}\)), 2.57 (1H, br s, -\text{OH}), 2.4-1.17 (5H, m, 2x CH\(_2\), -\text{CHCH}_3), 0.97, 1.07 (3H, 2s, -CH\(_3\)).

**Bromohydrin 10A**

Yield: 83% IR (neat): 3450 cm\(^{-1}\); \(^1\)H NMR (CCl\(_4\)): \(\delta\) 4.27-3.67 (7H, m, \(-\text{OCH}_2-\text{CH}_2\text{O}^-, -\text{CH}_2\text{OH}, -\text{CHBr}\)), 2.9 (1H, s, -\text{OH}), 2.33-1.37 (2H, m, \(-\text{CH}_2\text{CH}_3\)), 0.9 (3H, t, J = 7 Hz, -CH\(_2\text{CH}_3\)).

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

Yield: 81%; IR (CCl\(_4\)): 3450 cm\(^{-1}\); \(^1\)H NMR (CCl\(_4\)): \(\delta\) 4.2-3.6 (3H, m, -\text{CHOH}), 3.6-3.07 (11H, m, 2x-\text{CH}_2\text{OMe}, -\text{CHBr}), 2.27-1.4 (7H, m, 3x CH\(_2\), -\text{CHOH}).

**General procedure for oxidation of bromohydrins to \(\alpha\)-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\(^\circ\)C; IR (KBr): 1720 cm\(^{-1}\); \(^1\)H NMR (CCl\(_4\)): \(\delta\) 4.17-3.77 (5H, m, -\text{CHBr}, -\text{OCH}_2\text{CH}_2\text{O}^-), 3.33-1.4 (6H, m, methylenes).
Chiral acetals in organic synthesis

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

Yield: 78%, IR (neat): 1695 cm\(^{-1}\); \(^1\)H NMR (CCl\(_4\)): \(\delta 4.5-3.73 (5\ H, m, -OCH\(_2\)CH\(_2\)O-, -CHBr)\), 3.17-1.53 (8\ H, m, 4\ x CH\(_2\)).

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

Yield: 80%; IR (neat): 1715 cm\(^{-1}\); \(^1\)H NMR (CCl\(_4\)): \(\delta 4.0-3.7 (5\ H, m, -CHBr, -OCH\(_2\)CH\(_2\)O-)\), 3.4-1.07 (5\ H, m, 2\ CH\(_2\)and >CH\(_2\)CH\(_3\)), 0.97 (3\ H, d, J = 7 Hz, -CH\(_2\)CH\(_3\)).

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

Yield: 80%; IR (neat): 1720 cm\(^{-1}\); \(^1\)H NMR (CCl\(_4\)): \(\delta 9.23 (1\ H, d, J = 5\ Hz, -CHO)\), 4.33-3.8 (5\ H, m, -OCI\(_2\)Cl\(_2\)O-), 1.93-1.47 (2\ H, m, -CH\(_2\)CH\(_3\)), 0.9 (3\ H, t, J = 7 Hz, -CH\(_2\)CH\(_3\)).

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

Yield: 71%; IR (neat): 1710 cm\(^{-1}\); \(^1\)H NMR (CCl\(_4\)): \(\delta 4.4-3.93 (3\ H, m, methines)\), 3.47 (4\ H, d, J = 3 Hz, MeOCH\(_2\) x 2), 3.37 (6\ H, s, -OMe x 2), 2.5-1.53 (6\ H, m, methylenes).

General procedure for n-Bu\(_3\)SnH 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\(^{-1}\); \(^1\)H NMR (CCl\(_4\)): \(\delta 3.83 (4\ H, s, -OCH\(_2\)CH\(_2\)O-)\), 2.37 (2\ H, s, -CH\(_2\)O-), 2.3-1.93 (2\ H, m, \(-CH\(_2\)CH\(_2\)-)), 1.93-1.6 (4\ H, m, 2 x CH\(_2\)). MS m/z: 156.
3-oxo-cycloheptanone ethylene acetal 16

Yield: 88%, IR (neat): 1710 cm⁻¹; \(^1\)H NMR (CCl₄): \(\delta\) 3.83 (4H, s, \(-OCH₂CH₂O\)), 2.67 (2H, s, \(-CH₂\)), 2.53-2.13 (2H, m, \(-CH₂\)), 2.0-1.53 (6H, m, 3 x CH₂). MS m/z: 170.

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

Yield: 85%, IR (neat): 1710 cm⁻¹; \(^1\)H NMR (CCl₄): \(\delta\) 3.87 (4H, m, \(-OCH₂CH₂O\)), 2.47 (2H, s, \(-CH₂\)), 2.4-1.13 (5H, m, \(-CHCH₃, 2 x CH₂\)), 0.97 (3H, d, \(J = 6\) Hz, \(-CH₃\)). MS m/z: 170.

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

Yield: 78%, IR (neat): 1720 cm⁻¹; \(^1\)H NMR (CCl₄): \(\delta\) 4.16-3.97 (2H, m, 2 methines), 3.5 (4H, d, \(J = 3.75\) Hz, 2 x \(-CH₂OMe\)), 3.44 (6H, s, 2 x \(-OCH₃\)), 2.65 (2H, s, \(-OCH₂\)), 2.43-1.63 (6H, m, 3 x CH₂). MS m/z: 244. Anal. Calcd. for C₁₂H₂₀O₅: 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-Bu₃SnH (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 [(SiO₂), pet-ether: ethyl acetate: 92:8] to obtain pure 12 (110 mg).

Yield 76%, IR (neat): 3400 cm⁻¹; \(^1\)H NMR (CCl₄): \(\delta\) 4.57-3.9 (2H, m, \(-CHOH\)), 3.77 (4H, s, \(-OCH₂CH₂O\)), 2.3-1.4 (6H, m, 3 x CH₂).

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
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$_2$Cl$_2$ (3 x 10 ml). Drying (Na$_2$SO$_4$) 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$^{-1}$; $^1$H NMR (CCl$_4$): $\delta$ 3.97 (2H, t, J = 7 Hz, -CH$_2$OAc), 3.8 (4H, s, -OCCH$_2$), 1.87-1.07 (4H, m, 2 x CH$_2$), 0.87 (3H, t, J = 7 Hz,-CH$_2$CH$_3$). MS m/z: 188. Anal. Calcd. for C$_9$H$_{16}$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$_2$SO$_4$) 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$_2$Cl$_2$ (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$^{-1}$; $^1$H NMR (CCl$_4$): $\delta$ 3.93-3.53 (3H, m, methines), 3.4 (4H, d, J = 3 Hz, -CH$_2$OME 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$^{-1}$; $^1$H NMR (CCl$_4$): $\delta$ 4.67 (1H, m, -CHOAc), 3.83 (2H, m, methines), 3.4 (10H, br s, -CH$_2$OCH$_3$ x 2), 1.93 (3H, s, OOCOCH$_3$), 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 CH₂Cl₂ (5 ml) was added oxalyl chloride (140 mg, 1.1 mmol). After 10 min, the hydroxy compound 13 (146 mg, 1 mmol) in CH₂Cl₂ (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 CH₂Cl₂ (3×10 ml). The combined organic layer was dried over anhydrous Na₂SO₄ and solvent removed under vacuum to obtain a crude product. Purification by column chromatography [(SiO₂), eluent pet. ether- ethyl acetate: 98:2] gave compound 18 (120 mg).

Yield: 83%, IR (neat): 1720 cm⁻¹; ¹H NMR (CDCl₃): δ 9.43 (1H, t, J = 3 Hz, -CHO), 3.9 (4H, s, -OCH₂CH₂O⁻), 2.47 (2H, d, J = 3 Hz, -CH₂CHO), 1.63 (2H, q, J = 7 Hz, -CH₂CH₃), 0.83 (3X, t, J = 7 Hz, -CH₂CH₃).

LiAlH₄ 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.

2-0x0-cyclopentanone cyclic (1S, 2S)-1, 2-Bis (methoxymethyl) ethylene acetal 4a

Yield: 74%; IR (neat): 1750 cm⁻¹; ¹H NMR (CDCl₃): δ 4.05-3.8 (2H, m, ), 3.67-3.3 [10 H, m, ( containing a singlet at δ 3.5)], 2 x -CH₂-OCH₃] and 2.4-1.6 (6H, m, 3 x -CH₂-); MS m/z: 230.

2-0xo-cyclohexanone cyclic (1S, 2S)-1, 2-Bis (methoxymethyl) ethylene acetal 4b

Yield: 78%, IR (neat): 1710 cm⁻¹; ¹H NMR (CDCl₃): δ 4.1-3.83 (2H, m, ), 3.65-3.3 (10H, m, 2 x -CH₂OCH₃), 2.63-1.5 (H, m, 4 x -CH₂-); MS m/z: 244.
Chiral acetals in organic synthesis

LiAlH₄ 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 (CCl₄): 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, -CH₂OCH₃ x 2), 2.0 (3H, s, -OCOCH₃), 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 (CCl₄): 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, -CH₂OCH₃ x 2), 1.93 (3H, s, -O-COCH₃), 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 N₂ 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°C 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. NH₄Cl 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 Na₂SO₄ 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 (CCl₄): δ 4.0-3.8 (2H, m,
methines), 3.7-3.1 (10 H, m, contains a singlet at δ 3.27 (2 x -\text{CH}_2\text{OCH}_3), 1.97 (1H, br s, OH), 1.83-1.4 (6H, m, methylenes), 1.1 (3H, s, -\text{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}; \textsuperscript{1}H NMR (CCl\textsubscript{4}): δ 4.0-3.73 (2H, m, methines), 3.6-3.17 (10H, m, containing a singlet at δ 3.27, 2 x -\text{CH}_2\text{OCH}_3), 1.8 (1H, br s, OH), 1.67-1.23 (8H, m, methylenes), 1.07 (3H, s, -\text{CH}_3). 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,2R)-1,2-Bis (methoxymethyl) ethylene acetal 28

Yield: 72%, IR (neat): 3450 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (CCl\textsubscript{4}): δ 3.93 (2H, m, methines), 3.6-3.27 (10H, m, containing a singlet at δ 3.4, -\text{CH}_2\text{OCH}_3 x 2), 2.3 (1H, br s, OH), 2.07-1.6 (8H, m, methylenes), 1.27 and 1.13 (3H, 2 s, -\text{CH}_3). MS m/z: 260.

General procedure for the hydrolysis\textsuperscript{17} of 3-keto acetals 15, 16 and 17

To a suspension of silica gel (100-200 mesh, 500 mg) in CH\textsubscript{2}Cl\textsubscript{2} (3 ml) was added 15% H\textsubscript{2}SO\textsubscript{4} (0.15 ml). The mixture was stirred at room temperature until the turbidity in the CH\textsubscript{2}Cl\textsubscript{2} layer had disappeared. A solution of a keto acetal (1 mmol) in 1 ml of CH\textsubscript{2}Cl\textsubscript{2} was added to it and the reaction mixture stirred at room temperature for 20 hr (50 hr in the case of 1,3-cycloheptanediol monoethylene acetal). It was neutralised with NaHCO\textsubscript{3}, filtered and the solid residue washed with CH\textsubcript{2}Cl\textsubscript{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\textsuperscript{13,16} Yield: 70%, m.p. 102 (Lit\textsuperscript{13}, mp 105-106°C); 1,3-cyclohexanedione\textsuperscript{21,14,16} Yield: 71% ; 4-Methyl-1,3-cyclohexanedione\textsuperscript{15} 22 Yield: 78%.
ACKNOWLEDGEMENT:

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REFERENCES AND NOTES

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.
5. The LiAlH4 utilised in earlier studies was obtained from Sisco Research Laboratories, (SRL) Pvt. Ltd., Bombay. On the other hand present studies have been conducted using LiAlH4 of E. Merck make.
6. Isomerisation to 3 keto acetal followed by reduction to the observed 3-hydroxy acetal may have taken place as shown below:

\[ \text{\textsuperscript{13}C} \quad \rightarrow \quad \text{\textsuperscript{13}C} \quad \text{LiAlH}_4 \quad \text{OH} \]

'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.

9. The crude reaction mixture led to extensive decomposition during purification by column chromatography.

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