

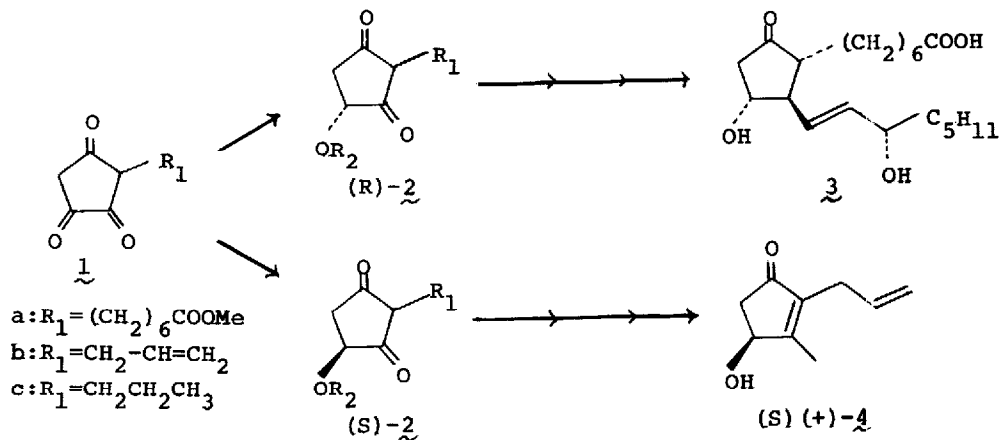
ASYMMETRIC SYNTHESIS OF OPTICALLY ACTIVE ALLETHROLONE AND
 PROSTAGLANDINS: REDUCTION OF 2-ALKYL-1,3,4-CYCLO-
 PENTANETRIONES WITH LITHIUM ALUMINUM HYDRIDE
 DECOMPOSED BY (-)-N-METHYLEPHEDRINE

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Asymmetric reduction of 2-alkyl-1,3,4-cyclopentanetriones (1) is considered one of the most efficient ways for synthesizing optically active functionalized cyclopentanes such as rethrolones^{1a)} and prostaglandins.¹⁾ When (R)-2-alkyl-4-hydroxy-1,3-cyclopentanedione ((R)-2a (R₂=H)) is successfully prepared from 1a by asymmetric reduction, it can be utilized as a starting material for synthesis of PGE₁ (3).²⁾ On the other hand, when preparation of (S)-2-alkyl-4-hydroxy-1,3-cyclopentanedione ((S)-2b (R₂=H)) is achieved by asymmetric reduction of 1b, it is expected that allethrolone ((S)(+)-4) can be readily synthesized from (S)-2b (R₂=H).

Considering the above-mentioned availability, an effective method was sought which would produce (R)- or (S)-2 from 1 without reducing other functional groups such as double bond and ester, being present in the side chain (R₁).



We have now found that $\underline{1}$ can be readily reduced to optically active (R)- $\underline{2}$ (regularly 55-58% e.e.) by employing lithium aluminum hydride (LAH) partially decomposed by 3.0 equivalents (eq.) of (-)-N-methylephedrine as reducing agent.^{3,4)}

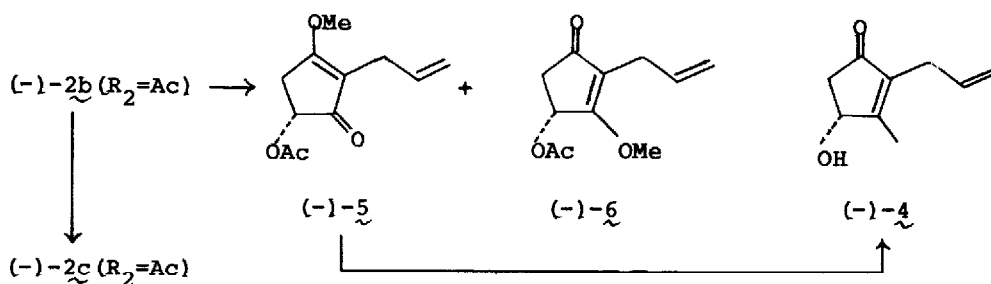
To an anhyd. tetrahydrofuran (THF) solution of LAH (3.3 eq.) was added a solution of (-)-N-methylephedrine (9.9 eq.), mp 87-88°, $[\alpha]_D^{20} -29.7^\circ$ (methanol),⁵⁾ in anhyd. THF at room temperature, and the whole mixture was stirred at the same temperature for 1 hr, giving a solution which contained partially decomposed LAH. After cooling to -70°, an anhyd. THF solution of $\underline{1}$ ⁶⁾ (1.0 eq.) was gradually added to the stirred solution obtained above. Stirring was continued for 3 hr at -70°, then the complex formed was decomposed with 10% hydrochloric acid at the same temperature. Usual extractive isolation with ethyl acetate, followed by purification with a silica gel column (solvent first ethyl acetate, then chloroform), gave the starting $\underline{1}$ in 19% recovery, and crude (R)- $\underline{2}$ ($R_2=H$)⁷⁾ as a pale yellow solid in 55% yield. The crude reduction product was treated with acetic anhydride-pyridine,⁸⁾ yielding (R)-(-)- $\underline{2}$ ($R_2=Ac$)⁷⁾ as a colorless solid, mp 111-121°, $[\alpha]_D^{20} -29.9^\circ$ (c=2.60, methanol), 58% e.e. (vide infra), in 42% yield based on $\underline{1}$.

When the same asymmetric reduction was examined using $\underline{1b}$ ⁹⁾ and the crude reduction product ((R)- $\underline{2b}$ ($R_2=H$))⁷⁾ was similarly acetylated, (R)-(-)- $\underline{2b}$ ($R_2=Ac$)⁷⁾ showing $[\alpha]_D^{20} -24.8^\circ$ (c=1.76, methanol), 55% e.e. (vide infra), was obtained as a colorless solid in 48% yield overall from $\underline{1b}$.

The steric course and the percent enantiomeric excess (% e.e.) for the asymmetric reduction were established by the chemical correlation of (-)- $\underline{2b}$ ($R_2=Ac$) and (-)- $\underline{2c}$ ($R_2=Ac$) with (R)-(-)- $\underline{4}$.

Treatment of (-)- $\underline{2b}$ ($R_2=Ac$), $[\alpha]_D^{20} -14.9^\circ$ (c=1.78, methanol),¹⁰⁾ with excess diazomethane in a mixture of ether and THF, afforded two sorts of enol ether, (-)- $\underline{5}$ ⁷⁾ $[\alpha]_D^{20} -17.2^\circ$ (c=2.18, chloroform), and (-)- $\underline{6}$ ^{7,11)} $[\alpha]_D^{20} -9.3^\circ$ (c=1.88, chloroform), in 42% and 40% yields, respectively. Addition of methyl lithium (3.0 eq.) to (-)- $\underline{5}$ and the work-up under acidic condition, gave (-)- $\underline{4}$ ¹²⁾ as a colorless oil, bp 105-107° (0.1 mmHg), $[\alpha]_D^{25} -2.4^\circ$ (c=9.94, ethanol), in 47% yield. On the other hand, catalytic reduction of (-)- $\underline{2b}$ ($R_2=Ac$), $[\alpha]_D^{20} -15.3^\circ$ (c=2.37, methanol),¹⁰⁾ over 10% Pd/C in ethyl acetate, yielded (-)- $\underline{2c}$ ($R_2=Ac$) as a colorless solid, $[\alpha]_D^{20} -17.6^\circ$ (c=2.62, methanol), in 87% yield. Since optically pure (S)-(+)- $\underline{4}$ was reported to have $[\alpha]_D^{25} +7.3^\circ$ (c=13.5, ethanol),¹³⁾ it was clearly determined that (-)- $\underline{2b}$ ($R_2=Ac$) and (-)- $\underline{2c}$ ($R_2=Ac$) had (R)-configuration and their optical rotations of optically pure samples could be calculated as $[\alpha]_D^{20} -45^\circ$ (methanol) and $[\alpha]_D^{20} -52^\circ$ (methanol), respectively.

Since (+)-N-methylephedrine is readily obtainable from commercially available d-ephedrine, the use of (+)-N-methylephedrine as chiral source might similarly afford (S)-(+)- $\underline{2b}$ ($R_2=Ac$) and (S)-(+)- $\underline{2c}$ ($R_2=Ac$) whose absolute configurations are opposite to those of the samples obtained above.



Recrystallization from ether seemed unpromising for improving the optical purity of (R) $(-)-2c$ ($R_2=Ac$), but when (R) $(-)-2b$ ($R_2=Ac$) was recrystallized once from the same solvent, (R) $(-)-2b$ ($R_2=Ac$)⁷⁾ mp 126-130°, $[\alpha]_D^{20} -43.6^\circ$ ($c=1.20$, methanol), 97% optically pure, could be obtained as colorless needles.

When $1a$ ²⁾ was submitted to the same asymmetric reduction and the reaction product was separated by column chromatography (silica gel, solvent ethyl acetate), (R) $(+)-2a$ ($R_2=H$)⁷⁾ $[\alpha]_D^{23} +8.8 \pm 1^\circ$ ($c=1.00$, chloroform), 54±6% optically pure,¹⁴⁾ was obtained in 58% yield without reduction of the ester group, and 27% of $1a$ was recovered. One recrystallization of (R) $(+)-2a$ ($R_2=H$) from ethyl acetate afforded colorless crystals⁷⁾ which showed mp 80-84° and $[\alpha]_D^{23} +11.4 \pm 1.5^\circ$ ($c=0.63$, chloroform), 70±10% optically pure.¹⁴⁾ (R) $(+)-2a$ ($R_2=H$) so obtained has been already transformed into 3 by Sih, *et al.*²⁾

Although elucidation of the reduction mechanism seems to be quite difficult because LAH partially decomposed by $(-)-N$ -methylephedrine is present as a complex oligomer in THF, the asymmetric reduction developed here might have some practical values due to its operational simplicity and wide applicability.

References

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3. For examples of asymmetric reductions of simple open chain ketones which

- utilized LAH partially decomposed by optically active compounds, see J.P. Vigneron and I. Jacquet, Tetrahedron, 32, 939(1976), and references therein.
4. While the asymmetric reduction of 1a to (R)- or (S)-2a has been examined in the field of prostaglandin synthesis by using enzymic reduction or catalytic hydrogenation over optically active phosphine-rhodium catalyst(see ref 2), the preparation of 2 by reducing 1 with partially decomposed LAH has never been attempted.
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 7. The structure of this compound was confirmed by comparing its spectral(ir and/or nmr) and chromatographic(tlc) behavior with that of the authentic dl-compound independently prepared by us.
 8. The acetylation was performed to convert (R) (-)-2c(R₂=H) into the compound which could be purified by column chromatography(silica gel, solvent benzene: THF:acetic acid 80:20:1) more easily than (R) (-)-2c(R₂=H).
 9. K. Yoshioka, T. Asako, G. Goto, K. Hiraga, and T. Miki, Chem. Pharm. Bull. (Tokyo), 21, 2195(1973).
 10. This sample was obtained during a study for improving the optical yield.
 11. This can be converted into (-)-2b(R₂=Ac) in 83% yield by successive treatment with 2N hydrochloric acid at room temperature and acetic anhydride-pyridine at 0°.
 12. This compound showed identical spectral(ir and nmr) and chromatographic (tlc) properties with those of dl-4 generously provided by Sumitomo Chemical Industry Co. Ltd.
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 14. (R) (+)-2a(R₂=H) showing $[\alpha]_D^{23} +16.2^{\circ}$ (c=1.02, chloroform) was assumed to be optically pure(see ref 2).