SYNTHESIS OF METHYL 3(*R*)-METHYL-5-OXOPENTANOATE, A POTENTIAL CHIRAL SYNTHON FOR VERSATILE NATURAL PRODUCTS, FROM COMMON CHIRAL INTERMEDIATES

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Abstract-----Conversion of both 3(*R*)-methylcyclopentanone(4) and *l*-menthone(8) into methyl 3(*R*)-methyl-5-oxopentanoate(7) and its derivatives through a α-diketone monothioketal intermediate has been achieved. Using these chiral products as common synthons, an enantioselective route to rose oxide[(4*R*)-(21)] and its enantiomer[(4*S*)-(21)] has been developed.

Provided the enantiomeric discrimination of two carboxylic groups of 3-methylglutaric acid(1:R=OH) is possible, enantioselective synthesis of a large number of natural products possessed a secondary methyl group such as juvabione(2) and epijuvabione(3) would be undoubtedly facilitated[1](Scheme 1). With the intention of obtaining "enantiomerically discriminated 3-methylglutaric acid" in a formal sense, we have undertaken the synthesis of chiral 3-methyl-5-oxopentanoic acid(1:R=H) as the equivalent using two readily available chiral starting materials either 3(*R*)-methylcyclopentanone(4) or *l*-menthone(8). Since the oxo-acid(1:R=H) possesses two different carbonyl functions at the same relative position from the chiral center, it can be used as the dual chiral synthon regardless of its chirality by simply discriminating two carbonyl groups chemically(Scheme 1).

Sequential treatment of 3(*R*)-methylcyclopentanone(4)[2] with pyrrolidine and trimethylene dithiotosylate[3] allowed regioselective thioketalization to give the α-diketone monothioketal(5)[4], $[\alpha]_D$ -106.9°(c=0.92, $CHCl_3$)[5], bp 124∿129 °C(0.2 Torr), in 70.5 % yield. Alkaline cleavage of the α-diketone monothioketal bond[6] of (5) yielded 3(*R*)-methyl-4-(2-dithianyl)butyric acid(6:R=H), $[\alpha]_D$ +14.8°(c=0.96, $CHCl_3$), quantitatively, which was converted into the methyl ester(6:R=Me), $[\alpha]_D$ +15.7°(c=0.72, $CHCl_3$), bp 145∿155 °C(6 Torr), in 90 % yield, with ethereal diazomethane.

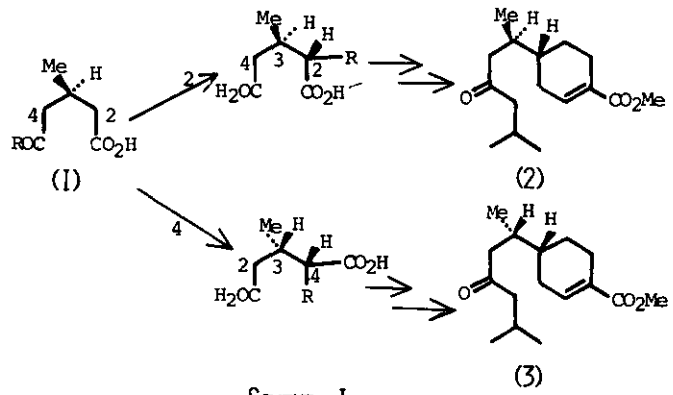
Upon treatment with methyl iodide in aqueous acetonitrile[7], the ester(6:R=Me) furnished the expected methyl 3(*R*)-methyl-5-oxopentanoate(7), $[\alpha]_D$ -3.1°(c=0.72, $CHCl_3$), in 74 % yield(Scheme 2).

Conversion of *l*-menthone(8)[8] into the same ester(7) with 3(*R*)-configuration could be also accomplished as follows. Treatment of (8) with acetic acid in carbon tetrachloride in the presence of perchloric acid[9] selectively afforded the tetrasubstituted enol acetate(9), bp 106∿107 °C(16 Torr), $[\alpha]_D$ +75.0°(c=2.31, $CHCl_3$), in 98 % yield, which was transformed into the keto-ester(10), bp 150∿155 °C(18 Torr), $[\alpha]_D$ +8.1°(c=2.92, $CHCl_3$), in 39 % overall yield through sequential ozonolysis, hydrolysis(aq. K_2CO_3), and esterification(CH_2N_2). Although conventional methodologies[3,10] did not allow α-thioketalization of the acyclic ketone(10), the desired conversion could be attained through the cyclic β-diketo intermediate(11). Namely cyclization of (10) with potassium tert. butoxide in tetrahydrofuran afforded 83% yield of the β-diketone(11) which, on treatment with trimethylene dithiotosylate in methanol in the presence of potassium acetate[11], gave the acyclic α-diketone monothioketal(13), $[\alpha]_D$ +6.4°(c=0.70, $CHCl_3$), in 47 % yield, selectively(path a). In the conversion a formation of the alternative one(5) through path b could not be observed. However, in contrast to the cyclic compound(5), the acyclic monothioketal(13) failed to give the cleaved product(6:R=H) under the alkaline conditions[6] and the starting material was recovered unchanged. Cleavage, therefore, was achieved sequentially. Reduction of (13) with sodium borohydride, followed by acetylation (Ac_2O, AcONa), afforded the acetates(14) which on treatment with mercuric salt ($HgCl_2$-$CdCO_3$) in aqueous media[12] gave the α-acetoxyketone(15) in 57 % overall yield. Reduction of (15) with sodium borohydride, followed by treating the reaction mixture with sodium metaperiodate in the same flask yielded methyl 3(*R*)-methyl-5-oxopentanoate(7).

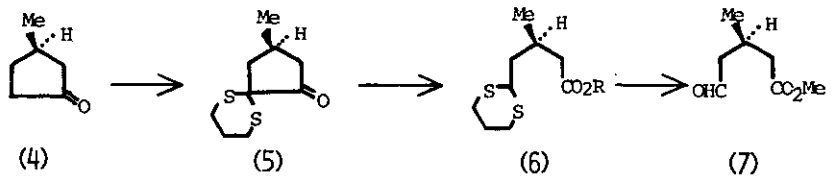
In order to test enantiomerical duality of 3(*R*)-methylglutaric acid derivatives obtained in this work, an enantioselective synthesis of both rose oxide[(4*R*)-(21)] and its enantiomer[(4*S*)-(21)][13] was attempted. Thus, the oxo-ester(7) was converted into the 4(*R*)-δ-lactone(17), $[\alpha]_D$ +23.1°(c=1.31, $CHCl_3$), in 83 % yield by reduction with sodium borohydride, followed by acid work-up. The lactone(17), upon reduction with diisobutylaluminum hydride, yielded the epimeric lactol[(4*R*)-(18)], $[\alpha]_D$ -32.1° (c=1.15, $CHCl_3$), near quantitatively, which upon treatment with ethyl sodiodiethylphosphonoacetate[14], underwent concurrent Wittig type condensation and Michael addition to give the tetrahydropyran[(4R)-(19)], $[\alpha]_D$ -5.9°(c=0.84, $CHCl_3$), bp 120∿125°C

(21 Torr), in 70 % yield as an inseparable mixture of epimers at C-2 center. Treatment of [(4*R*)-(19)] with excess methyllithium yielded the known tertiary alcohol[(4*R*)-(20)][14,15], $[\alpha]_D$ +3.3°(c=1.22, $CHCl_3$), bp 70∿75 °C(1 Torr)(lit.[15] bp 75∿80 °C(2 Torr)), which has been converted into rose oxide[(4*R*)-(21)] as a mixture of the epimers at C-2 center.

On the other hand, reduction of the dithiane ester(6:R=Me) with lithium aluminum hydride gave the primary alcohol(22:R=H), $[\alpha]_D$ +9.7°(c=0.97, $CHCl_3$), in 82 % yield, which on sequential acetylation(Ac_2O, C_5H_5N), hydrolysis of dithiane group (MeI, aq. CH_3CN)[7], and deacetylation furnished the enantiomeric lactol[(4*S*)-(18)], $[\alpha]_D$ +36.2°(c=1.80, $CHCl_3$), in 94 % overall yield. The same lactol[(4*S*)-(18)], $[\alpha]_D$ +16.3°(c=1.20, $CHCl_3$), was also obtained in 94 % overall yield from the *l*-menthone derived α-ketoacetate(15) by sequential reduction with lithium aluminum hydride and oxidative cleavage with sodium metaperiodate. On the similar treatment as the enantiomeric counterpart[(4*R*)-(18)], the lactol[(4*S*)-(18)] obtained furnished the penultimate intermediate[(4*S*)-(20)], $[\alpha]_D$ -6.5°(c=1.19, $CHCl_3$) in 59.5 % overall yield as a mixture of enantiomers at C-2 center via the ester[(4*S*)-(19)], $[\alpha]_D$ +9.1° (c=1.23, $CHCl_3$).



SCHEME 1



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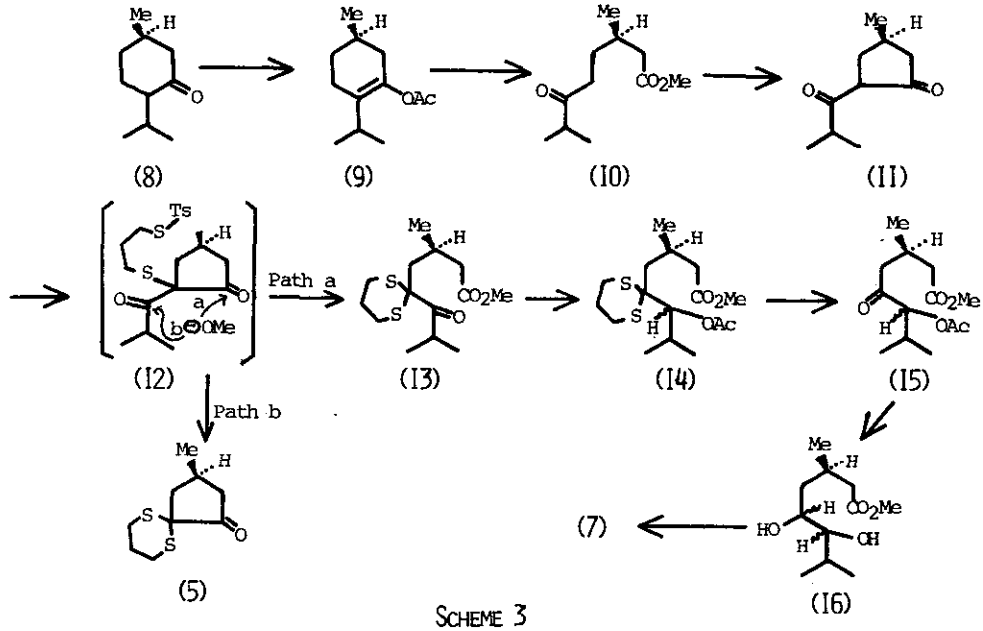

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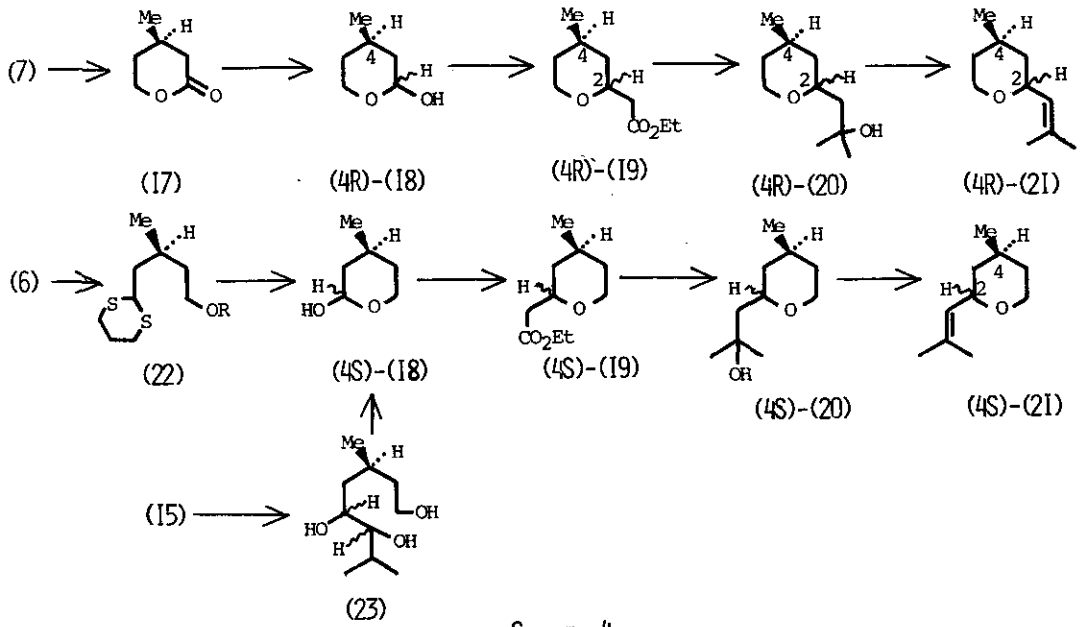

SCHEME 4

REFERENCES AND NOTES

1. Enantioselective synthesis of (+)-juvabione(2) and (+)-epijuvabione(3) along this strategy is under investigation.
2. 3(R)-Methylcyclopentanone(4) ($[\alpha]_D$ +148°(c=4.5, CH_3OH)) was purchased from Aldrich Chemical Co. and was used without further purification.
3. Cf. R.B. Woodward, I.J. Pachter, and M.L. Sheinbaum, Org. Synth., 54, 39 (1974).
4. All compounds isolated were oil. All new compounds obtained on this work gave satisfactory spectral(IR, NMR, MS) and analytical(combustion and/or high resolution MS) data.
5. Optical rotations were measured with a JASCO-DIP-4 automatic polarimeter.
6. Cf. J.A. Marshall and D.E. Seitz, J. Org. Chem., 39, 1814 (1974).
7. M. Fetizon and M. Jurion, J. Chem. Soc., Chem. Commun., 382 (1972).
8. *l*-Menthone(8) was prepared in 85 % yield from commercial *l*-menthol($[\alpha]_D$ -50° (c=10, C_2H_5OH)) by Jones oxidation.
9. Cf. H.O. House and C.J. Blankley, J. Org. Chem., 32, 1741 (1967).
10. R.B. Woodward, I.J. Pachter, and M.L. Scheinbaum, Org. Synth., 54, 37 (1974).
11. Cf. R.J.Bryant and E. McDomald, Tetrahedron Lett., 3841 (1975).
12. J.A. Marshall and H. Roebke, J. Org. Chem., 34, 4188 (1969).
13. Only 4(*R*)/2(*R*)- and 4(*R*)/2(*S*)-enantiomers are occuring naturally.
14. Y.R. Naves and P. Ochsner, Helv. Chim. Acta, 45, 397 (1962).
15. E.H. Eschinasi, J. Org. Chem., 35, 1097 (1970).

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