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USE OF MALIC ACID AS A CHIRAL SYNTHON: 24,25-DIHYDROXYCHOLECALCIFEROL

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Abstract: A new chiral synthon prepared from malic acid is introduced and utilized in a synthesis of 24,25-dihydroxycholecalciferol.

Despite the increasing sophistication and stereoselectivity of synthetic methods of generating new chiral centers[1], the high optical purity of naturally occurring chiral molecules often makes this the method of choice for the introduction of asymmetry. Malic acid has often been used as a chiral synthon[2], in part because of its availability in both enantiomeric forms[3]. Its use has been limited, however, by the difficulty in differentiating chemically between its two carboxylate groups. In general, selective chemistry at the C-1 or C-4 terminals of the molecule is possible only at later stages of the synthesis[2].

We report a facile means of introducing chemical asymmetry into this useful chiral building-block and its use in the preparation of the chiral side-chain fragment for 24,25-dihydroxy-cholesterol which is a precursor of natural 24,25-dihydroxycholecalciferol.

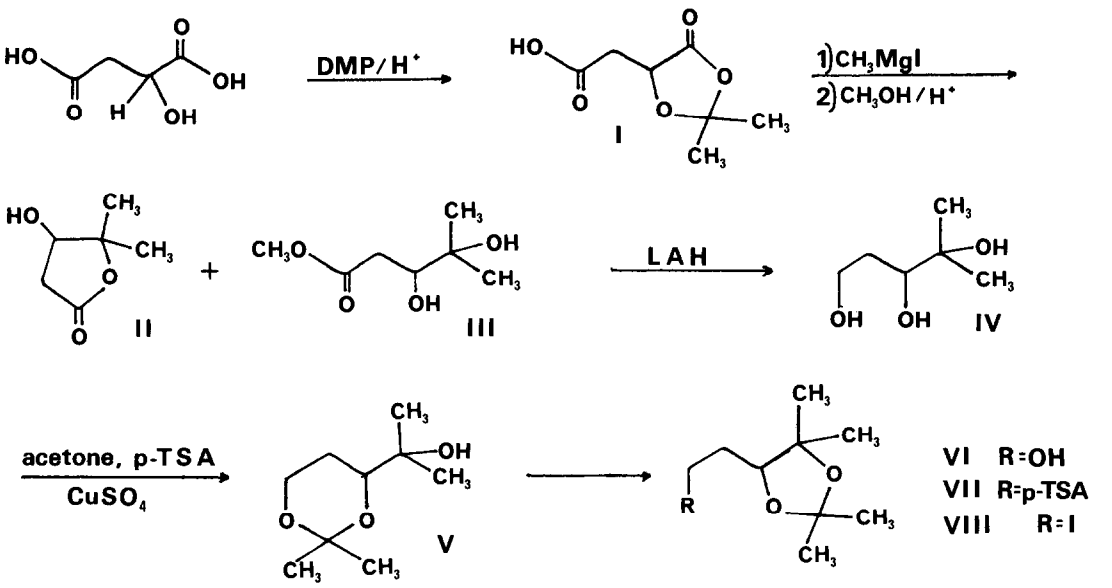
Malic acid reacts with dimethoxypropane in the presence of pyridinium toluenesulfonate to give the dioxolanone (I) in essentially quantitative yield. The mild acid catalysis avoids any racemization of the chiral center. The alternative 6-membered ring closure was not observed. This completely specific mono-esterification of malic acid enables ready differentiation between the 1-ester and 4-carboxylic acid for a variety of synthetic procedures.

Thus a suspension of 75g (559 mmole) of D-malic acid and 12g (48 mmole) of pyridinium-p-toluenesulfonate in 250ml (211g, 2.014 moles) of 2,2-dimethoxypropane was stirred at room temperature until a clear solution resulted (approximately 48 hours). The reaction mixture was evaporated under reduced pressure and the residue purified by suction chromatography on silica gel with ethyl acetate as eluent. Solvent removal gave (-)I in 96% yield, m.p. 106-9°C (recrystallized from methylene chloride/hexane).[4]

The above procedure was repeated using L-malic acid to give (+)I, m.p. 110-2°C.[5]

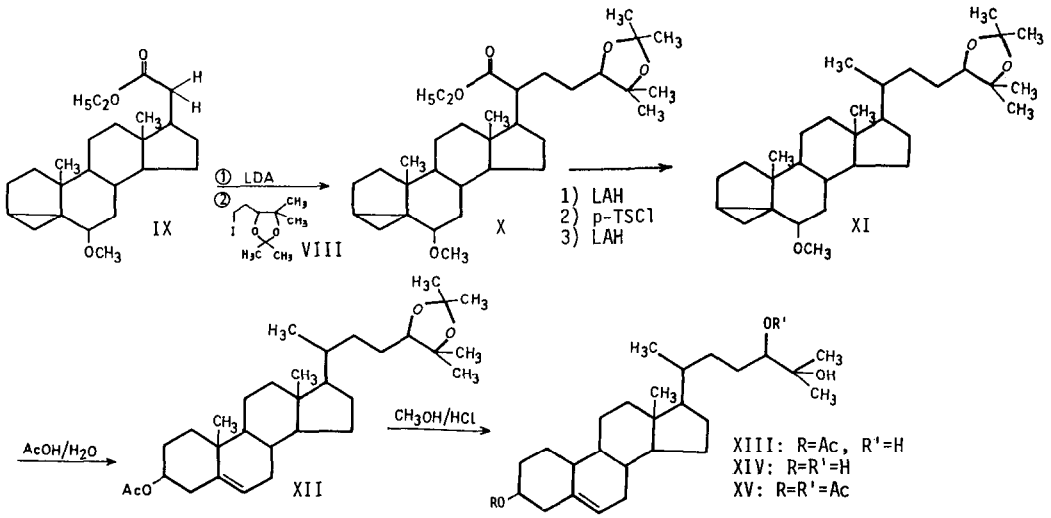
We used compound I prepared from D(+) malic acid in our synthesis of 24(R),25-dihydroxy-cholecalciferol by reacting it with an excess of methyl magnesium iodide in ether[6] to di-methylate the dioxolanyl carboxyl group with complete regioselectivity. A non-aqueous work-up with acidic methanol gave the lactone (II)[7] (36%) as the major isolated product and only a

small amount of the methyl ester (III). This mixture of products was reduced with LAH in refluxing THF (69%) and the resulting triol (IV) protected as the acetonide (VI) with copper sulfate in acetone, catalyzed by toluenesulfonic acid[8] (68%). The synthesis of the steroidal side-chain fragment was completed by treatment of VI with toluenesulfonyl chloride in pyridine (64%) and conversion of the resulting tosylate (VII) to the iodide (VIII) with sodium iodide in acetone (96%).



Steroid (IX) was prepared in analogy with the procedure of Wicha and Bal[11] and the desired C-20 carbanion, generated with lithium diisopropylamide in THF according to the procedure described therein, was alkylated with the iodide (VIII) to give the compound (X) after aqueous work-up and flash column chromatography (ether/methylene chloride, 3:97; 50%). In continued analogy with the procedure of Wicha and Bal[11a] the C-21 ethyl ester was reduced with LAH in refluxing THF (85%, isolated by flash column chromatography in ethyl acetate/hexane, 1:3)[12], the resulting primary alcohol converted to the tosylate with toluenesulfonyl chloride in pyridine (97%) and reduced to compound (XI) (98%) with LAH in refluxing THF.

The i-ether was opened directly to the 3β -acetate (XII) by heating at 90° for 1 hour in acetic acid solution containing about 1% water (97%) and the C-24,25 acetonide hydrolyzed by refluxing in a 9:1 methanol:water solution containing about 1% concentrated HCl. The solvent and HCl were removed in vacuo leaving a mixture of 3β-acetate (XIII) and triol (XIV)[13] which was directly acetylated with acetic anhydride in pyridine to give the diacetate (XV) (89%) which was isolated by flash chromatography (ethyl acetate/hexane, 25/75).



This cholesterol derivative was dehydrogenated and irradiated by the usual procedure to give 24(R),25-dihydroxycholecalciferol with analytic properties in complete accordance with the literature[14].

Notes and References

1. J.P. Morrison; "Asymmetric Synthesis", Academic Press: New York. Vols. 2 and 3 (1983/4).

2. a) H.M. Shieh and G.D. Prestwich, J. Org. Chem., 46, 4319 (1981).
   b) V.K. Tandon, A.M. van Leusen and H. Wynberg, ibid. 48, 2767 (1983).
   c) J.S. Bajwa and M.J. Miller, ibid. 48, 1114 (1983).
   d) E.J. Corey, H. Niwa and J. Knolle, J. Amer. Chem. Soc., 100, 1942 (1978).
   e) E.J. Corey, H. Shirahama, H. Yamanoto, S. Terashima, A. Venkareswara and T.K. Schaaf, ibid. 93, 1490 (1971).
   f) K. Mori, T. Takigawa and T. Matsuo, Tetrahedron, 35, 933 (1979).

3. H. Wynberg and E.G.J. Staring, J. Amer. Chem. Soc., 104, 166 (1982).

4. Anal. calculated for $C_7H_{10}O_5$: C, 48.29; H,5.79; found C,48.44; H,6.00.
   NMR (δ,$CDCl_3$) 4.70-4.74 (1H); 2.83-3.04 (2H); 2.58 (3H); 1.63 (3H); $(\alpha)_D = -18.10^\circ$.

5. Anal. calculated for $C_7H_{10}O_5$: C,48.29; H,5.79; found: C,48.13; H,5.57.
   NMR (δ,$CDCl_3$) 4.71-4.74 (1H); 2.82-304 (2H); 2.57 (3H); 1.64 (3H); $(\alpha)_D = +20.19^\circ$.

6. Freudenber, Todd and Seidler, Ann. 501, 210 (1933).

7. This useful intermediate has heretofore been available only from the exhaustive oxidative degradation of natural products, for example:
   a) T. Matsumoto, K. Fukui and M. Nanbu, Chem. Letters, 603 (1974)
   b) J. Lemmich and B.E. Nielsen, Tetrahedron Letters, 3 (1969).
   c) J.F. Collins and M.F. Grundon. J. Chem. Soc., Perkin I, 161 (1973).

8. In analogy with the previously reported 1,2,4-butanetriol acetonide system[9], the six-membered acetonide (V) is initially formed as the kinetic product, which isomerizes to the desired five-membered acetonide (VI) under the reaction conditions. In contrast to the butanetriol system, however, the equilibrium mixture of (V) and (VI) contains only a trace of the six-membered acetonide which is readily resolvable by TLC (6:4, hexane/ethyl acetate) and easily distinguished by NMR spectroscopy.[10]

9. A.I. Meyers and J.P. Lawson, Tetrahedron Letters, 23, 4883 (1982).

10. These compounds have been previously prepared from different starting materials. M.A. Abdallah and J.N. Shah, J. Chem. Soc., Perkin I, 888 (1975).

11. a) J.Wicha and K. Bal., J. Chem. Soc., Perkin I, 1282 (1978).
b) J. Wicha, K. Bal and S. Piekut, Syn. Comm., 7, 215 (1977).

12. This column resolved a small amount (2-3%) of the C-20 unnatural isomer which arises from the lack of total stereospecificity in the condensation reaction (the mechanistic basis for this stereoselectivity is discussed in ref. 11a). The major product (Rf=0.4) had the following ^{1}H-NMR absorption: δ 3.75 and 3.66 (2m, 2 H, 21-H) superimposed on 3.68 (m, 1 H, 24-H); 3.33 (s, 3 H, OCH_3); 2.78 (m, 1 H, 6-H); and methyl proton singlets at 1.42, 1.34, 1.26, 1.11, 1.03 and 0.75. The minor product (Rf=0.3) had all of the above absorptions except that the C-21 multiplets were at 3.68 and 3.50. Note that the R and S isomers at C-24 (prepared from racemic I) were not resolvable at this stage of the synthesis.

13. This 2-step procedure avoids the need for an extractive work-up with the triol (XIV) which is only partially soluble in the appropriate solvents.

14. a) H.Y. Lam, et al., Biochemistry, 12, 4851 (1973).
b) H. Takayama, et al., Tetrahedron Letters, 21, 5027 (1980).
c) U.S. Patent 4,021,423.

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