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(S)-CITRAMALIC ACID, A USEFUL CHIRAL SYNTHON FOR THE SYNTHESIS OF 15-DEOXY-16(S)-HYDROXY-16-METHYLPROSTAGLANDINS

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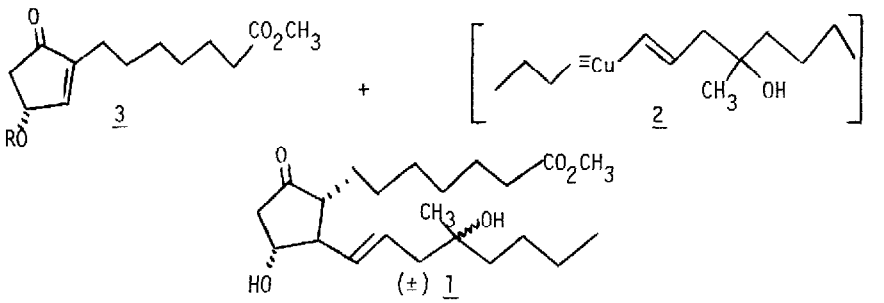
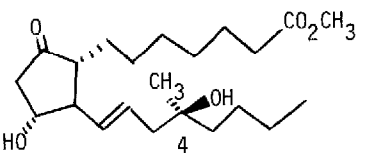
Abstract: (S)-Citramalic acid, a readily available microbial metabolite has been efficiently transformed into (2S)-2-methyl-2-hydroxy-1-hexanol (7), an important chiral synthon for the synthesis of 15-deoxy-16(S)-hydroxy-16-methylprostaglandins.

Pappo[1] and his coworkers at Searle first described the synthesis of racemic 15-deoxy-16-methyl-16-α,β-hydroxyprostaglandin E_1 methyl ester (1) via the stereospecific conjugate addition of the mixed cuprate, 2 to the hydroxycyclopentenone, 3.

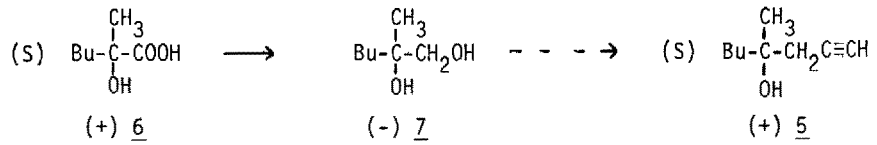


This transposition of the C-15 hydroxy group to the C-16 position greatly enhanced the gastric antisecretory and antiulcer actions of PGE_1. Also, this molecular alteration conferred oral activity, reduced the side effects and prolonged the biological actions of PGE_1.[2,3]

Because of the potential utility of 1 as an antiulcer agent in man, all four diastereomers have been prepared.[4] However, the gastric antisecretory activity was shown to be associated solely with the 16(S) isomer 4.



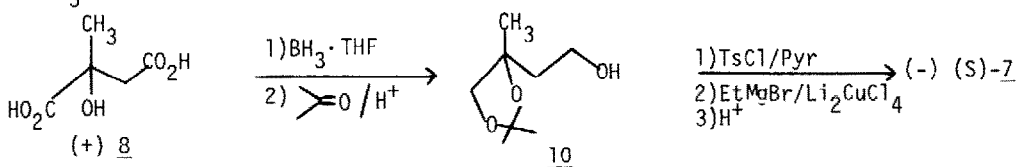
Although an asymmetric synthesis of (+)3 has already been accomplished,[5] 4(S)-4-methyl-1-octyn-4-ol (5), the precursor of 2 was prepared from (2S)-2-methyl-2-hydroxy-hexanoic acid (6), which in turn was obtained by chemical resolution in low yields.[4]



(+) 6 (-) 7 (+) 5

Our continuing interest in the utilization of microbial metabolites as synthons for organic synthesis led us to envisage that (-) 7 may be prepared from the readily available (S)-(+)-citramalic acid. We now report this facile conversion, which formally constitutes an asymmetric synthesis of (+) 5 and 4.

(S)-Citramalate (8), prepared by the exposure of mesaconate to mesaconase from Clostridium tetanomorphum,[6] was reduced with an excess of diborane-tetrahydrofuran complex in THF to yield the triol (9). Treatment of 9 with acetone and a catalytic quantity of perchloric acid gave 10 (73% from 8) which was converted into the tosylate 11 by reaction with tosyl chloride in pyridine. Alkylation was effected by reacting 11 with an excess of ethyl magnesium bromide with Li_2CuCl_4 as catalyst.[7] Upon acidification, (-) 7 (69% from 10) $[\alpha]_{589}^{25}$-3.0; $[\alpha]_{365}^{25}$-11.2; (c, 0.7 $CHCl_3$); (reported data[4] -4 and -12.1) was obtained.



(+) 8 10 (-) (S)-7

The efficient transformation of (+) 8 into (-) 7 (overall yield 50.4%) obviates the tedious chemical resolution of (±) 6 and illustrates one of the many potential synthetic applications of this readily available microbial metabolite. As this type of tertiary chiral center is widespread among natural products and that (R)-(+)-citramalate may be readily prepared from citraconate,[8] this bifunctional chiral synthon will probably prove to be of general synthetic utility.

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References and Notes

1) P.W. Collins, E.Z. Dajani, M.S. Bruhn, C.H. Brown, J.R. Palmer, and R. Pappo, Tetrahedron Lett., 4217 (1975).
2) E.Z. Dajani, D.R. Driskill, R.G. Bianchi, P.W. Collins and R. Pappo, Am. J. Dig. Dis., 21, 1049 (1976).
3) P.W. Collins, E.Z. Dajani, D.R. Driskill, M.S. Bruhn, C.J. Jung and R. Pappo, J. Med. Chem., 20, 1152 (1977).
4) R. Pappo, P.W. Collins, M.S. Bruhn, A.F. Gasiecki, C.J. Jung, H.W. Sause and J.A. Schulz in "Chemistry, Biochemistry and Pharmacological Activity of Prostanoids", Edited by S.M. Roberts and F. Scheinmann, Pergamon Press, N.Y., 1978, p. 17.
5) C.J. Sih, J.B. Heather, R. Sood, P. Price, G. Peruzzotti, L.F. Hsu Lee, and S.S. Lee, J. Amer. Chem. Soc., 97, 865 (1975).
6) H.A. Barker and A.H. Blair, Biochem prep 9, 21 (1962).
7) G. Fouquet and M. Schlosser, Angew Chem. Int. Edn. 13, 82 (1974).
8) R. Bentley, "Molecular Asymmetry in Biology", Vol. II, 1970, Academic Press, N.Y., p. 144.

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