An Easy Synthesis of (*RS*)-[3′-^{13}C]Mevalonic Acid Lactone

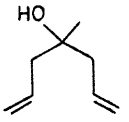
By A IAN SCOTT* and KOZO SHISHIDO
(*Department of Chemistry, Texas A&M University, College Station, Texas* 77843)

Summary A high-yielding synthesis of mevalonic acid lactone is described which is of particular value in the preparation of 3′ labelled compounds

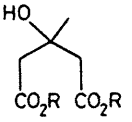
ALTHOUGH several elegant synthetic approaches [1–5] to mevalonic acid lactone have been described in recent years, short and efficient routes applicable to preparation of the 3′ and 3 labelled compounds are lacking We report herein an

improved synthesis of (*RS*)-mevalonic acid lactone by which 3′ and 3 labelled derivatives can be conveniently prepared in good yield.

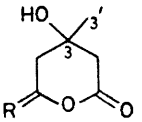
Reaction of ethyl acetate with 2·5 equiv. of allylmagnesium bromide in Et_2O–tetrahydrofuran (THF) (1 : 1) afforded the alcohol (**1**, 94%, b.p. 50–51 °)[3] which was subjected to ozonolysis in CH_2Cl_2–acetic acid (10 : 1) at −78 °C. Treatment of the crude product with H_2O_2–acetic acid gave the diacid (**2a**, 84%), m.p. 110–111 °C (lit.[3] 110–111 °C), characterised as the dimethyl ester (**2b**, $C_8H_{14}O_5$) (CH_2N_2 in Et_2O, THF) which showed singlets at δ 1·39 (3H, Me), 2·73 (4H, CH_2), and 3·75 (6H, OMe) in the ^1H n.m.r. spectrum.



(1)



(2) a; R = H
b; R = Me



(3) R = O
(4) R = H_2

Treatment of (**2a**) with an excess of acetic anhydride at room temperature for 14 h afforded the anhydride (**3**) in quantitative yield [m.p. 102—103 °C (lit.[6] 102—102·5 °C), M^+ at *m/e* 144; i.r. (Nujol) 3530 (OH), 1813 and 1765 (anhydride CO) cm^{-1}; ^1H n.m.r. 1·43 (3H, Me), 2·67 (1H, exchanged with D_2O, OH), 2·90 and 2·93 (each 2H, *J* 2·0 Hz, methylene H_{ax} and H_{eq})]. Treatment of the anhydride (**3**) with 2·5 equiv. of $NaBH_4$ in propan-2-ol,[7] acidification to pH 2, and extraction with Et_2O gave almost pure (*RS*)-mevalonic acid lactone (**4**, 75·6%), which, after purification by column chromatography on SilicAR CC-7 using hexane–Et_2O as eluant, was identical (t.l.c., m.s., i.r., and n.m.r.) with an authentic sample.

This procedure offers significant advantage over routes involving hydride reduction of (**2b**)[1,3] and is complementary to the method employed by Fetizon, *et al.*, *via* 3-methylpentane-1,3,6-triol.[5]

Utilizing the above procedure without purification of intermediates, (±)-[3′-^{13}C]mevalonic acid lactone was prepared in 58% overall yield from [2-^{13}C]ethyl acetate (90 atom%). The position of the ^{13}C enrichment in the purified product was apparent from the ^{13}C n.m.r. (single peak at 29·9 p.p.m.) and ^1H n.m.r. [3H doublet centred at δ1·40, $J(^{13}C–H)$ 63·0 Hz] spectra. The isotopic enrichment of the product was >86% as determined from its ^1H n.m.r. spectrum.

We thank The Robert A. Welch Foundation for support of this work.

(*Received*, 31*st December* 1979; *Com.* 1354.)

[1] C. H. Hoffman, A. F. Wagner, A. N. Wilson, E. Walton, C. H. Shunk, D. E. Wolf, F. W. Holly, and K. Folkers, *J. Am. Chem. Soc.*, 1957, **79**, 1486, 2316.
[2] J. W. Cornforth, R. H. Cornforth, A. Pelter, M. G. Horning, and G. Popják, *Tetrahedron*, 1959, **5**, 311.
[3] R. Tschesche and H Machleidt, *Justus Liebig's Ann. Chem.*, 1960, **631**, 61.
[4] R. A Ellison and P. K Bhatnagar, *Synthesis*, 1974, 719; J. A. Lawson, W. T. Colwell, J. I DeGraw, R. H. Peters, R. L. Dehn, and M. Tanabe, *ibid*, 1975, 729; F.-C. Huang, L F. Hsu Lee, R. S D Mittal, P R Ravikumar, J A. Chan, C. J. Sih, E. Caspi, and C. R. Eck, *J. Am. Chem. Soc.*, 1975, **97**, 4144, H. Daido, H. Machida, T. Miyakoshi, and S. Saito, *Bull. Chem. Soc. Jpn.*, 1977, 1021; E. Abushanab, D. Reed, F Suzuki, and C. J. Sih, *Tetrahedron Lett.*, 1978, 3415
[5] M. Fetizon, M. Golfier, and J.-M. Louis, *Tetrahedron*, 1975, **31**, 171.
[6] S. Goldfarb and H. C. Pitot, *J. Lipid Res*, 1971, **12**, 512.
[7] (a) K. Ishizumi, K. Koga, and S. Yamada, *Chem. Pharm. Bull.*, 1968, **16**, 492; (b) D. M. Bailey and K. E. Johnson, *J. Org. Chem.*, 1970, **35**, 3574.