Tetrahedron Letters No. 4, pp 351 - 354, 1977. Pergamon Press. Printed in Great Britain.

ISOSTERES OF NATURAL PHOSPHATES.7. THE PREPARATION OF 5-CARBOXY-4-HYDROXY-4-METHYLPENTYL-1-PHOSPHONIC ACID

Virander Sarin, Burton E. Tropp, and Robert Engel*

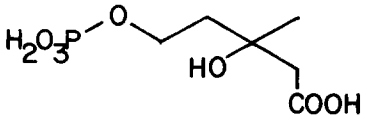
Doctoral Programs in Chemistry and Biochemistry

The City University of New York, Queens College, Flushing, New York 11367

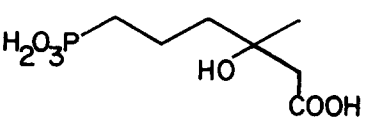
(Received in U.S.A. 25 October 1976; received in U.K. for publication 28 December 1976)

In continued efforts at the further elucidation of the mechanism of terpene biosynthesis, numerous analogues of the natural phosphorus-containing intermediates have been prepared and studied. A very interesting class of compounds for investigation are the phosphonic acids, isosteric with the natural materials, in which a methylene group is present in place of the normal esteric phosphate oxygen. Significant results have been obtained in this laboratory by the use of such isosteric analogues of several natural phosphates with bacterial systems. [1-7]

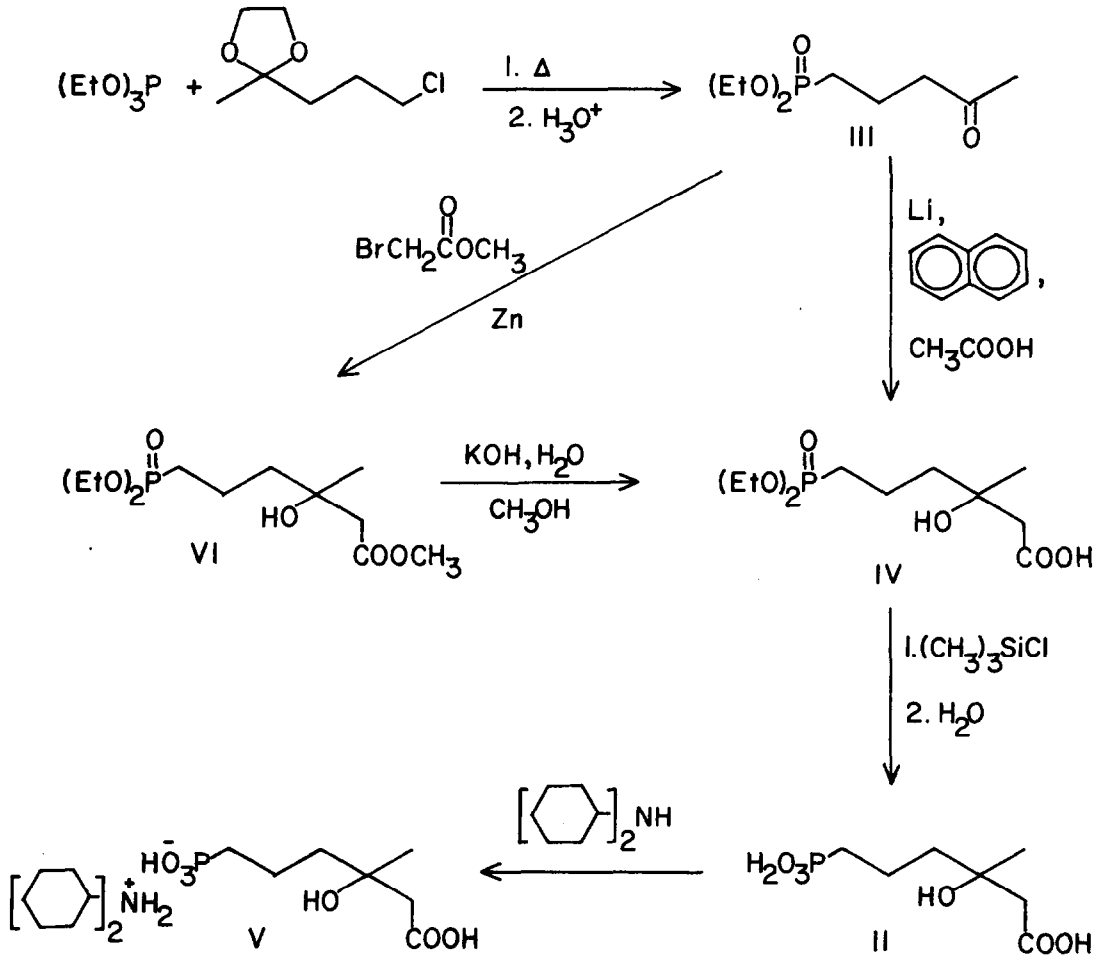
Corey and Volante recently reported [8] the synthesis and preliminary enzymatic evaluation of the isosteric phosphonic acid analogues (C-substituted methylphosphonophosphates) of several pyrophosphate intermediates in terpene biosynthesis. These include the analogues of isopentenyl pyrophosphate, γ,γ-dimethylallyl pyrophosphate, geranyl pyrophosphate, farnesyl pyrophosphate, and presqualene pyrophosphate. There remains for the completion of this series an analogue of the initial phosphorylated species in the biosynthetic pathway, 5-phosphomevalonic acid (I); such an analogue could not readily be prepared using the methods reported for the others. [8] We here report the preparation of this analogue, 5-carboxy-4-hydroxy-4-methylpentyl-1-phosphonic acid (II).



I



II



The route used for the preparation of (II) is illustrated above. Formation of the carbon-phosphorus bond is accomplished in the initial step by an Arbuzov reaction [9] of triethylphosphite on the ethylene ketal of 5-chloro-2-pentamone. The yield of purified product, diethyl 4-oxopentyl-1-phosphonate (III), while relatively low (37.5%), was not atypical for such reactions; no improvement could be obtained either by use of a Michaelis-Becker reaction [10] using diethyl phosphite, or by an Arbuzov reaction on the free ketone. The ketone (III) is then converted to the tertiary β-hydroxy-acid in a single step by the addition of acetic acid, reacting as the dianion generated by reaction with lithium naphthalenide. [11,12] The

yield (35%) of the purified diethyl 5-carboxy-4-hydroxy-4-methylpentyl-1-phosphonate (IV) was comparable to those for other systems previously reported. [11,12] This route proved to be far superior to the Reformatsky reaction, [13] from which product could be obtained but only with minimal yield.

For the cleavage of the remaining phosphonate diester linkages the method of Rabinowitz [14] with trimethylchlorosilane was used. The didealkylation technique, heating the diester with sodium iodide in DMF, described by Moffatt and Jones [15] was attempted here, but again only poor yields were obtained. Conversion of the free acid (II) to the dicyclohexylammonium salt (V) was effected for final purification; this was accomplished by twice dissolving the salt in methanol and precipitation by the addition of acetone. This material is currently undergoing testing for enzyme inhibitory activity in the terpene biosynthetic pathway.

Spectral data were obtained (Tabulation of Physical and Spectral Data) for species (III)-(VI) and were in complete accord with the assigned structures; satisfactory elemental analyses (Galbraith Laboratories, Knoxville, Tennessee) were also obtained for these compounds. The free acid (II) could be purified sufficiently for quality spectral and elemental analysis only by salt formation.

This work was supported by a grant from the C.U.N.Y. Faculty Research Assistance Program.

Tabulation of Physical and Spectral Data

III, Diethyl 4-oxopentyl-1-phosphonate:bp 56°/0.01 Torr; NMR (CCl_4) 1.3δ (t) 6H (CH_2CH_3), 1.7δ (m) 2H (PCH_2), 2.1δ (s)3H ($COCH_3$), 2.4δ (m)2H($CH_2CH_2CH_2$), 3.5δ (m)2H (CH_2CO), 4.0δ (m)4H(CH_2CH_3); IR (CCl_4), 3050-2900 cm.$^{-1}$, 1725 cm.$^{-1}$, 1370 cm.$^{-1}$, 1255 cm.$^{-1}$, 1165 cm.$^{-1}$, 1050 cm.$^{-1}$.

IV, Diethyl 5-carboxy-4-hydroxy-4-methylpentyl-1-phosphonate:decomposed upon all attempts at distillation; NMR (CCl_4), 1.1δ (t)6H(CH_2CH_3), 1.3-2.6δ (m)9H ($CH_2CH_2CH_2CCH_3$), 3.3δ (m) 2H (CH_2COOH), 3.9δ (m)4H (CH_2CH_3), 9.1δ (s)2H (H on oxygen); IR (CCl_4), 3400 cm.$^{-1}$ (broad), 3050-2900 cm.$^{-1}$, 1705 cm.$^{-1}$, 1410 cm.$^{-1}$, 1300 cm.$^{-1}$, 1210 cm.$^{-1}$, 1045 cm.$^{-1}$, 970 cm.$^{-1}$.

V, 5-Carboxy-4-hydroxy-4-methylpentyl-1-phosphonic acid, dicyclohexylammonium salt:NMR (D_2O), 0.9-2.0δ (broad) 29H, 2.1δ (s)2H(CH_2COOH), 3.2δ (m)2H(CH-N); IR (Fluorolube) 3300 cm.$^{-1}$ (broad), 2900-2750 cm.$^{-1}$, 1630 cm.$^{-1}$ (broad), 1440 cm.$^{-1}$, 1190 cm.$^{-1}$.

VI. Diethyl 5-carbomethoxy-4-hydroxy-4-methylpentyl-1-phosphonate:bp 61°/0.005 Torr; NMR (CCl_4), 1.1δ (t) 6H (CH_2CH_3), 1.3δ (s)3H(CCH_3), 1.3-2.5δ (broad)6H($CH_2CH_2CH_2$), 2.0δ (s)

1H (OH), 3.2-3.4 δ (broad) 5H (CH_2COOCH_3), 3.9 δ (m) 4H (CH_2CH_3); IR (CCl_4), 3400 $cm.^{-1}$, 3000-2850 $cm.^{-1}$, 1710 $cm.^{-1}$, 1430 $cm.^{-1}$, 1270 $cm.^{-1}$, 1180 $cm.^{-1}$, 1025 $cm.^{-1}$, 950 $cm.^{-1}$.

+ The non-equivalence of the protons alpha to the carboxylic acid function indicated by the NMR signal at 3.3 δ may be understood in view of the presence of only hydrogen-bonded hydroxyl in relatively dilute solution of CCl_4; binding of the hydroxy proton to the carboxyl group (intramolecularly) is quite favorable on steric grounds. This results in locking the two alpha-protons into decidedly non-equivalent positions within a ring system.

References

1. J. Kabak, L. DeFilippe, R. Engel, and B.E. Tropp, J. Med. Chem., 15, 1074 (1972).
2. C. Shopsis, R. Engel, and B. Tropp, J. Bacteriology, 112, 408 (1972).
3. C.S. Shopsis, W.D. Nunn, R. Engel, and B.E. Tropp, Antimicrobial Agents and Chemotherapy, 4, 467 (1973).
4. S.L. Goldstein, D. Braksmayer, B. Tropp, and R. Engel, J. Med. Chem., 17, 363 (1974).
5. P.-J. Cheng, R. Hickey, R. Engel, and B.E. Tropp, Biochim. Biophys. Acta, 341, 85 (1974).
6. C.S. Shopsis, R. Engel, and B.E. Tropp, J. Biol. Chem., 249, 2473 (1974).
7. P.-J. Cheng, W.D. Nunn, R.J. Tyhach, S.L. Goldstein, R. Engel, and B.E.Tropp, J. Biol. Chem., 250, 1633 (1975).
8. E.J. Corey and R.P. Volante, J. Amer. Chem. Soc., 98, 1291 (1976).
9. R.G. Harvey and E.R. De Sombre, in Topics in Phosphorus Chemistry, Vol. 1, editors, M. Grayson and E.J. Griffith, Interscience, New York, N.Y., 1974, pp. 57-112.
10. "Methoden der Organischen Chemie," Vol. 12, Part 1, Georg Thieme Verlag, Stuttgart, 1963, p. 446.
11. S. Watanabe, K. Suga, T. Fujita, and K. Fujiyoshi, Chem. and Ind. (London), 1181 (1969).
12. B. Angelo, Bull. Soc. Chim. France, 1848 (1970).
13. C.A. Grob and P. Brenneisen, Helv. Chim. Acta, 41, 1184 (1958).
14. R. Rabinowitz, J. Org. Chem., 28, 2975 (1963).
15. J.G. Moffatt and G.H. Jones, U.S. 3,524,846, 18 Aug. 1970; Chem. Abstr., 74, 31940 p (1971).