loses ~13% and (*E*)-[9-^{3}H]chorismate[6] loses ~35% of the radiolabel under similar conditions (see Figure 2).[16] These data require that the chorismate mutase reaction proceeds through a chairlike transition state[18] in which the *Z* proton of chorismate becomes the *pro-S* proton of prephenate.

Acknowledgment. We are grateful to Steven Benner, who first suggested phenylpyruvate tautomerase as a simpler route than phenylalanine ammonia lyase[17] for the analysis of the product tritium distribution, and to the National Institutes of Health and Merck Sharp & Dohme for support.

(15) It should be noted that the absolute value of the extrapolated burst is rather imprecise, since a compromise between a pH low enough for rapid decarboxylative dehydration of prephenate yet high enough for reasonable mutase and tautomerase activity is necessary. The *relative* rate of tritium washout from the *Z* and *E* isomers is, however, unambiguous.

(16) The synthetic chorismate[6] is racemic, so only half of the chorismate sample is taken to prephenate by chorismate mutase. The percentage bursts are therefore 26% and 70% of the natural enantiomer.

(17) Ife, R. J.; Ball, L. F.; Lowe, P.; Haslam, E. *J. Chem. Soc., Perkin Trans. 1* **1976**, 1776.

(18) Our results provide proof for the suggestion made earlier on the basis of studies of the inhibition of chorismate mutase by various dicarboxylates: Andrews, P. R.; Cain, E. N.; Rizzardo, E., Smith, G. D. *Biochemistry* **1977**, *16*, 4848.

Cyclomevalonic Acid

Paul Dowd* and Christopher Kaufman

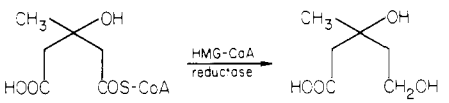
Department of Chemistry, University of Pittsburgh Pittsburgh, Pennsylvania 15260

Robert H. Abeles*

Graduate Department of Biochemistry Brandeis University Waltham, Massachusetts 02254

Received October 12, 1983

Reduction of 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) (I) to mevalonic acid (II) by HMG-CoA reductase (EC 1.1.1.34)

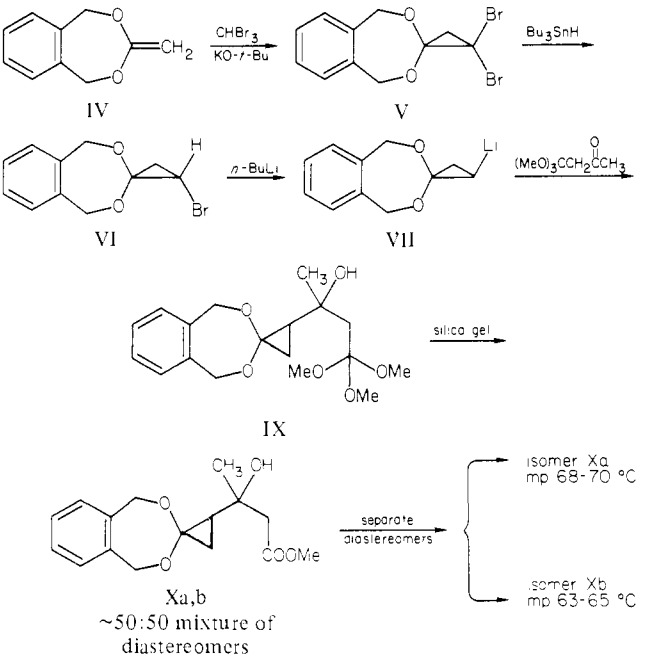


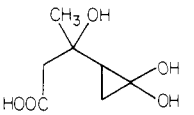
I II

is the rate-limiting step in the biosynthesis of cholesterol.[1,2] As a consequence, the discovery of substances capable of specifically inhibiting this enzymic transformation[3] is important.

Reduction by HMG-CoA reductase occurs at an active-site thiol whose role is analogous to the active-site thiol in aldehyde dehydrogenase. The latter has been shown to be inhibited by cyclopropanone hydrate, which is, in size, comparable to acetaldehyde.[4] Accordingly, incorporation of a cyclopropanone hydrate into mevalonic acid, to learn whether such a strategm might lead to an inhibitor of HMG-CoA reductase, became attractive. This communication describes the synthesis of cyclomevalonic acid (III), a novel derivative of mevalonic acid (II).

Scheme I





III

It was recognized that cyclomevalonic acid (III) would be a sensitive substance and that the unmasking of the cyclopropanone hydrate[5] should be carried out under mild conditions and be the final step in the synthesis.

The synthetic scheme is outlined in Scheme I: The ketene acetal IV[6] was treated with bromoform and potassium *tert*-butoxide[7] in pentane yielding (75%) the dibromocyclopropane V, mp 136–137 °C.[8] Treatment of the dibromide V with tri-*n*-butyltin hydride[9,10] in benzene yielded (60%) the monobromide VI,[8] mp 75–76 °C. The monobromide VI in ether was treated with *n*-BuLi for 2.5 h at −78 °C generating the lithiated cyclopropane VII. Reaction of VII with 1,1,1-trimethoxybutan-3-one (VIII) followed by quenching at −78 °C with water yielded the adduct IX. Purification of IX by column chromatography on silica gel resulted

(1) Reviews: Rodwell, V. W.; Nordstrom, J. L.; Mitschelen, J. J. *Adv. Lipid Res.* **1976**, *14*, 1. Rodwell, V. W.; McNamara, D. J.; Shapiro, D. J. *Adv. Enzymol.* **1973**, *38*, 373.

(2) Lehninger, A. L. "Biochemistry", 2nd ed.; Worth: New York, 1975; p 681.

(3) Endo, A.; Kuroda, M.; Tanzawa, K. *FEBS Lett.* **1976**, *72*, 323. Endo, A.; Kuroda, M.; Tsujita, Y. *J. Antibiot.* **1976**, *29*, 1346. Brown, A. G.; Smale, T. C.; King, T. J.; Hasenkampe, R.; Thompson, R. H. *J. Chem. Soc., Perkin Trans. 1* 1165 (1976). M. S. Brown, J. R. Faust, J. L. Goldstein, L. Kaneko, and A. Endo, A. *J. Biol. Chem.* **1978**, *253*, 1121. Brown, M. S.; Goldstein, J. L. *Ibid.* **1974**, *249*, 7306. Kandutsch, A. A.; Chen, H. W. *Ibid.* **1974**, *249*, 6075. Nelson, J. A.; Czarny, M. R.; Spencer, T. A.; Limanek, J. S.; K. R. MacCrae, K. R.; Chang, T. Y. *J. Am. Chem. Soc.* **1978**, *100*, 4900 and references cited therein. Schroepfer, G. J., Jr.; Parish, E. J.; Gilliland, G. L.; Newcomer, M. E.; Somerville, L. L.; Quiacho, F. A.; Kandutsch, A. A. *Ibid.* **1978**, **84**, 823. Kuroda, M.; Ando, A. *Biochim. Biophys. Acta* **1977**, *486*, 70. George, R. J.; Menon, A. S.; Ramasarma, T. *Biochem. Biophys. Res. Commun.* **1978**, *84*, 544 and references cited therein.

(4) Wiseman, J. S.; Abeles, R. H. *Biochemistry* **1979**, *18*, 427. Wiseman, J. S.; Tayrien, G.; Abeles, R. H. *Ibid.* **1980**, 19, 4222. Lindberg, P.; Bergman, R.; Wickberg, B. *J. Chem. Soc., Perkin Trans. 1* **1977**, 684. Tottmar, O.; Lindberg, P. *Acta Pharmacol. Toxicol.* **1977**, *40*, 476.

(5) Cyclopropanone reviews: Wasserman, H. H.; Clark, G. M.; Turley, P. C. *Fortschr. Chem. Forsch.* **1974**, *47*, 73. Turro, N. J. *Acc. Chem. Res.* **1969**, *2*, 25. See also: Turro, N. J.; Hammond, W. B. *Tetrhedron* **1968**, *24*, 6017; 6029. Schaafsma, S. E.; Steinberg, H.; de Boer, Th. J. *Recl. Trav. Chim. Pays-Bas* **1966**, *85*, 1171. Tilborg, W. J. M.; Schaafsma, S. E.; Steinberg, H.; de Boer, Th. J. *Ibid.* **1967**, *86*, 417.

(6) Grewe, R.; Struve, A. *Chem. Ber.* **1963**, *96*, 2819.

(7) Doering, W. von E.; Hoffmann, A. K. *J. Am. Chem. Soc.* **1954**, *76*, 6162.

(8) All new substances showed satisfactory NMR, IR, and mass spectra, including exact mass determination.

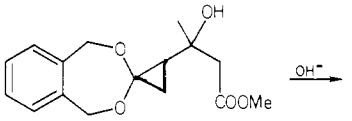
(9) Kuivila, H. G. *J. Org. Chem.* **1961**, *25*, 284. Kuivila, H. G.; Walsh, E. J., Jr. *J. Am. Chem. Soc.* **1966**, **88**, 571. Kuivila, H. G.; Menapace, L. W.; Warner, C. R. *Ibid.* **1962**, *84*, 3584.

(10) Seyferth, D.; Yamazaki, H.; Alleston, D. L. *J. Org. Chem.* **1963**, *28*, 703.

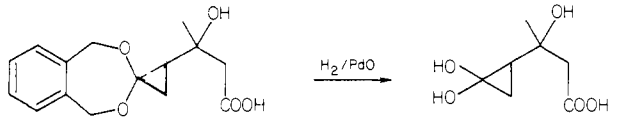
0002-7863/84/1506-2703$01.50/0

in hydrolysis of the ortho ester IX to the corresponding methyl ester X, an approximately 50:50 mixture of diastereomers Xa[8] and Xb.[8] The latter were separated by chromatography on silica gel and were readily distinguished by their NMR spectra.

The methyl esters Xa and Xb were hydrolyzed to the corresponding acids XIa,[8] mp 90-91.5 °C, and XIb,[8] mp 105-107 °C, respectively. Each acid was then hydrogenated to remove the

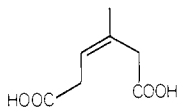


Xa,b



XIa,b IIIa,b

protecting *o*-xylylene group. This reaction required careful control because the cyclopropanone hydrate tends to undergo ring opening to the dicarboxylic acid XIII.[11] In the most successful and



XIII

reproducible regimen, the reduction was carried out at −5 °C (ice–salt bath) with dry PdO, prepared according to Schopf.[12] The catalyst was prereduced in EtOAc for 3 h; then the substrate was added. The disappearance of starting material was monitored at R_f 0.7 on silica gel plates in 60:40 ethyl acetate–hexane. When the reaction was complete, it was worked up by filtration and solvent removal at 0 °C. The diastereomeric cyclomevalonic acids IIIa[8] and IIIb[8] appear to be stable at −15 °C. Complete decomposition to XIII occurred after 24 h at room temperature.

Cyclomevalonate IIIa is an active inhibitor of HMG-CoA reductase[13] with $K_i = 10^{-4}$ M. Cyclomevalonate IIIb showed no inhibitory activity.

The lithium derivative VII of the protected cyclopropanone provides a useful link, not available before, in the synthesis of functionalized cyclopropanone hydrates. A second feature of the synthesis is the use of the ortho ester VIII[14] to direct the condensation reaction to the ketone carbonyl group of acetoacetate.[15,16] The ortho acetoacetate VIII is readily available and the ortho ester protecting group is cleanly removed under the mild conditions of silica gel chromatography.

Acknowledgment. This research was generously supported by the National Institute for General Medical Sciences under Grant GM 27667.

Supplementary Material Available: Experimental data for compounds V, VI, Xa,b, and IIIa,b (3 pages). Ordering information is given on any current masthead page.

(11) The diester corresponding to XIII has been prepared by: Tsuji, J.; Hosaka, S. *J. Am. Chem. Soc.* **1965**, *87*, 4075.

(12) Schopf, C.; Brass, E.; Jacobi, E.; Jorde, W.; Mochik, W.; Neuroth, L.; Salzer, W. *Leibigs Ann. Chem.* **1940**, *544*, 53. In our preparation we omitted the final washings with methanol to remove unreacted $PdCl_2$.

(13) Purified according to: Oureshi, N.; Dugan, R. E.; Nimmannit, S.; Wu, W.-H.; Porter, J. W. *Biochemistry* **1976**, *15*, 4185.

(14) Prepared according to: Banville, J.; Brassard, P. *J. Chem. Soc., Perkin Tran. 1* **1976**, 1852.

(15) Cf.: Rousseau, B.; Beaucourt, J.-P.; Pichat, L. *Tetrahedron Lett.* **1982**, 2183. These authors have, while our work was in progress, developed several mevalonate syntheses making use of a *cis,cis*-1,3,5-cyclohexanetriol protected ortho acetoacetate.[12,13]

(16) Stetter, H.; Steinwacker, K. H. *Chem. Ber.* **1964**, *97*, 1839. Pichat, L.; Beaucort, J. P. Herbert, M. *Radioisotopy* **1971**, *12*, 519.

Photoreactivity of α,β-Unsaturated Carbonyl Compounds. 2. Fast Transients from Irradiation of 2-Cyclohexenones and Amines

Norbert J. Pienta

Department of Chemistry, University of Arkansas Fayetteville, Akansas 72701

Received August 8, 1983

We recently reported results of steady irradiation experiments of 2-cyclohexenone (**1**) in the presence of triethylamine (**2**) that suggested enone dimerization was competitive with adduct formation to the amine.[1] We proposed that an enone excimer or some other dimeric metastable species was the precursor to the cyclobutane dimers (via unimolecular decay) and to the amine adducts via a mechanism first order in each amine and excimer. Evidence that the latter involves electron transfer or at least substantial charge transfer is consistent with CIDNP results.[2] Further support for this mechanism comes from transient decay measured on absorption changes using a Q-switched Nd:YAG laser line at 355 nm as the excitation beam.

A transient absorption change in the region 270–290 nm was reported for various enones in the absence of amines.[3,4] The transient is observed between 260 and 330 nm, a window in the ground-state absorption, as a maximum centered at 280 nm. Table I presents lifetimes at 280 nm for **1** irradiated in the presence of **2**.[5] The observation of *increasing lifetime* with added amine cannot be accounted for by any mechanism where amine simply reacts with or quenches the transient. In the presence of amine, we are likely to be observing a second transient of longer lifetime in fast equlibrium with the original species. The plateau in lifetime reached with added 1,4-diazabicyclo[2.2.2]octane (DABCO) (**4**) and the change in behavior with a given concentration of **2** at higher enone concentration support this.[5] Equation 1 is suggested

$$\mathrm{EN} \rightarrow \rightarrow \mathrm{EN}^3 \rightarrow \text{twisted } \pi,\pi^* \text{ (I)} \underset{}{\overset{K[\mathrm{AM}]}{\rightleftharpoons}} (\mathrm{EN}\cdot\mathrm{AM})^* \text{ (II)} \quad (1)$$

to account for both transients (EN = enone; AM = amine).[6] Equation 2 represents the observed lifetime expressed in terms

$$1/\tau = k_{obsd} = \alpha k_1 + (1-\alpha)k_2 \quad (2)$$

of the decay of I (rate = k_1; α = mole fraction of I) and II (rate = k_2; $(1-\alpha)$ = mole fraction of II). Since the equilibrium can be represented by $K = [\mathrm{II}]/([\mathrm{I}][\mathrm{AM}])$ and $\alpha = [\mathrm{I}]/([\mathrm{I}]+[\mathrm{II}])$:

$$1/\tau = k_{obsd} = \left(\frac{1}{1+K[\mathrm{AM}]}\right)k_1 + \left(\frac{K[\mathrm{AM}]}{1+K[\mathrm{AM}]}\right)k_2 \quad (3)$$

This can be simplified to the form of eq 4. At low amine con-

$$k_{obsd} = \frac{k_1 + k_2K[\mathrm{AM}]}{1+K[\mathrm{AM}]} \quad (4)$$

centration $k_1 >> k_2K[\mathrm{AM}]$ and the lifetime becomes linearly dependent on amine concentration (eq 5) with a slope/intercept

$$\tau_{obsd} = (1+K[\mathrm{AM}])/k_1 \quad (5)$$

(1) Pienta, N. J.; McKimmey, J. E. *J. Am. Chem. Soc.* **1982**, *104*, 5501–5502.

(2) Back electron transfer from the radical anion of **1** and **7** to the radical cation of DABCO explains observed polarizations: Smith, DW.; Pienta, N.J. *Tetrahedron Lett.* **1984**, 915.

(3) Goldfarb, T. D. *J. Photochem.* **1978**, *8*, 29–38.

(4) Bonneau, R. *J. Am. Chem. Soc.* **1980**, *102*, 3816–3822.

(5) Enone **1** (46.5 mM in acetonitrile) was also irradiated in the presence of triethylamine (**2**), *n*-butylamine (**3**), and DABCO (**4**) and gave the following data ([amine] (mM), lifetime at 280 nm (ns)): For **2** 120, 38.8; 310, 48.5; 550, 67.5. For **3** 67, 33.2; 202, 33; 405, 34.1; 742, 36.8. For **4** 10, 63; 20, 286; 30, 342; 40, 338; 70, 346.

(6) The assignment of I as a twisted π,π^* state of the enone was made by Bonneau[4] and still best explains all data in the absence of amine: Structure II represents some exciplex of this state with amine.

0002-7863/84/1506-2704$01.50/0