CHEMISTRY LETTERS, pp. 1121-1124, 1977. Published by the Chemical Society of Japan

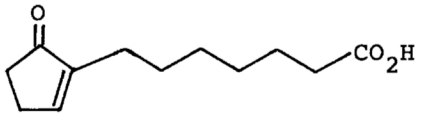
A NEW SYNTHESIS OF 2-(6-CARBOXYHEXYL)CYCLOPENT-2-EN-1-ONE, A PROSTANOID SYNTHON

Eiji WADA, Takeshi NAKAI*, and Makoto OKAWARA

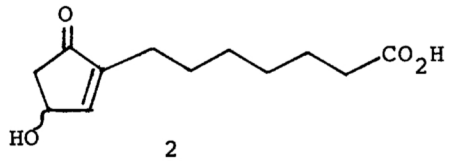
Research Laboratory of Resources Utilization and* Department of Chemical Engineering, Tokyo Institute of Technology, Ookayama, Meguro, Tokyo 152

A new synthesis of the title compound (1), an useful intermediate in the synthesis of various prostanoids, is described which involves the acid-catalyzed cyclopropane rearrangement of 9-cyclopropyl-9-oxononanoic acid (7) as a key step. The cyclopropyl ketone 7 was prepared via the three steps from cyclopropyl methyl ketone.

2-(6-Carboxyhexyl)cyclopent-2-en-1-one (1) has served as a valuable intermediate in the synthesis of a variety of 11-deoxy prostanoids, for example, PGB_1,[1] 11-deoxy-PGE_2[2] and 11,15-bis-deoxy-13-dihydro-PGE_1.[3] The intermediate 1 has also been converted into the hydroxy cyclopentenone (2)[4] which has been successfully elaborated into (+)-[5] and (-)-PGE_1.[6] Thus the utility of the cyclopentenone 1 as a versatile prostanoid synthon is well secured.



1

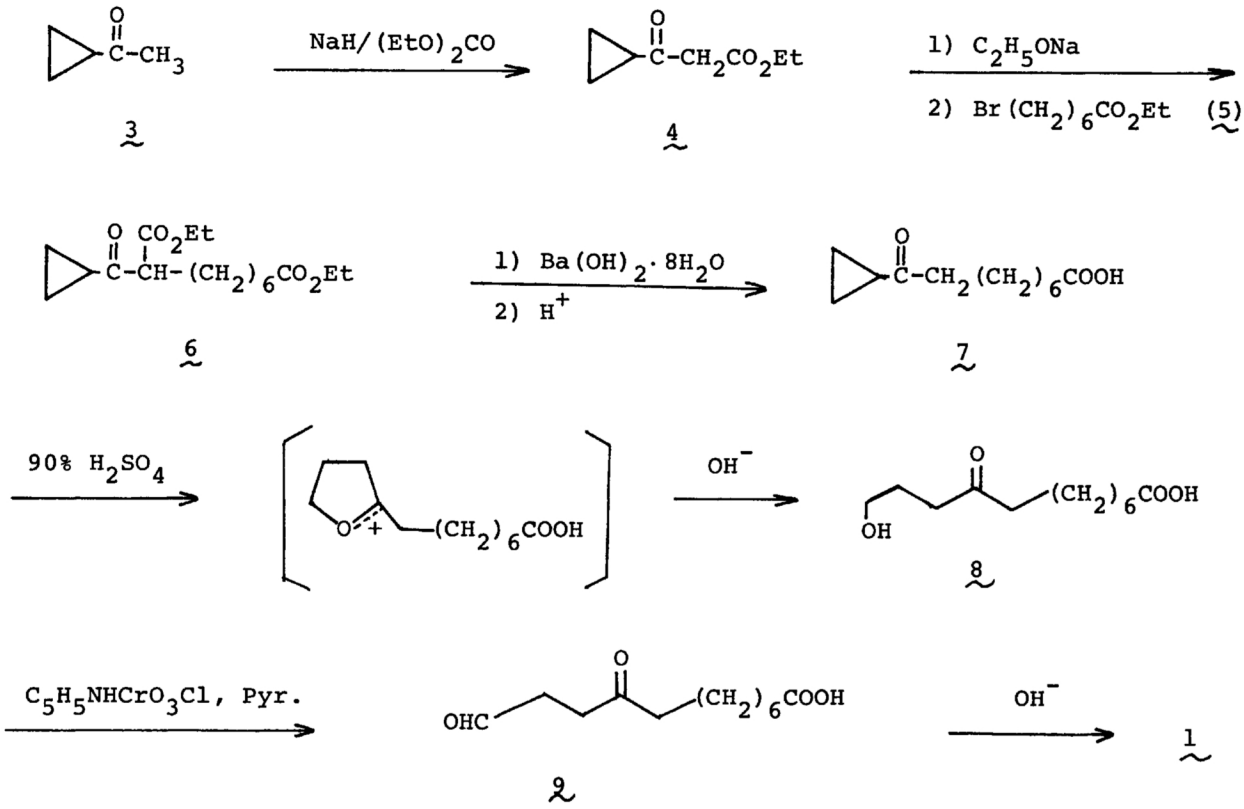


2

Since Bagli first reported the synthesis of 1,[7] several synthetic routes to 1 and 2 have appeared in the literature.[8] In our continuing investigation of the synthetic utilization of cyclopropane rearrangements, we have recently demonstrated the synthetic potentiality of the rearrangement of protonated cyclopropyl ketones which provided new routes to 1,4-dicarbonyl compounds and cyclopentenones [9] and a new procedure for cyclopentenone annelation.[10]

Herein we wish to report a new, simple synthetic route to the important prostanoid synthon 1 which involves the acid-catalyzed cyclopropane rearrangement as a key step. Scheme I outlines the sequence of reactions utilized.

Scheme I



An initial synthetic problem was how to prepare 9-cyclopropyl-9-oxononanoic acid 7 required for our scheme from readily available cyclopropane derivatives. This problem was solved by applying the procedures of Johnson[11], starting with cyclopropyl methyl ketone 3.

First, the ketone 3 was converted, by condensation with diethyl carbonate, to the keto ester 4. The enolate anion of 4 was treated with ethyl 7-bromoheptanoate[12] 5 in ethanol under refluxing for 24 hr giving 6 [96% ; IR(neat) 1735(COOEt), 1695cm^{-1}(C=O); NMR(CCl_4)δ=4.40-3.80(m, 4H), 3.40(t, 1H), and 2.70-0.60(m, 23H)]. The keto diester 6 was further converted, on treatment with barium hydroxide followed by acidification, to the cyclopropyl ketone 7 [96% ; mp. 76-8°C, IR(KBr) 1690cm^{-1}(C=O); NMR($CDCl_3$)δ=11.3(s, 1H), 2.60-2.00(m, 4H), and 2.00-0.50(m, 15H)].

The cyclopropyl ketone 7 was then subjected to the acid catalyzed rearrangement (cyclopropyl ketone ⟶ oxolan-2-ylium ion) under the standard conditions[9]. Thus the rearrangement of 7 was carried out in 90% sulfuric acid at 80°C for 1 hr. Though the structure of the oxolan-2-ylium ion derived from 7 was not confirmed, further treatments of the resulting solutions with an aqueous solution of sodium

hydrogencarbonate followed by extractive work-up afforded the γ-hydroxyketone 8 [87% ; mp. 60°C; IR(KBr) 3400-3000(COOH, OH), 1700cm^{-1}(C=O); NMR($CDCl_3$)δ=3.70(t, 2H) 2,80-2.20(m, 6H), and 2.10-1.10(m, 12H)].

Oxidation of 8 with pyridinium chlorochromate[13] in methylene chloride in the presence of pyridine[14] gave the γ-keto aldehyde 9 [70% ; mp. 56-9°C; IR(KBr) 3500-3000(COOH), 1690cm^{-1} (C=O); NMR($CDCl_3$)δ=9.26(s, 1H), 2.15(s, 4H), 2.10-1.90(m, 4H), and 1.70-0.90(m, 10H)].

The γ-keto aldehyde 9 was further cyclized with an aqueous solution of potassium hydroxide (0.1-0.5%) to the cyclopentenone 1 [70% ; mp. 38-40°C(lit. 39°C)[4]; IR(KBr) 3400-3000(COOH), 1700(C=O), 1620cm^{-1}(C=C); NMR(CCl_4)δ=7.20(br.s, 1H), and 2.80-1.20(m, 16H); mass(m/e) 210(M^+), 198, 175, 164, 123, 109, 96]. The spectral properties of 1 thus obtained were in agreement with the literature values.

In summary, this work demonstrates that the potential utility of the rearrangement of protonated cyclopropyl ketone provides a simple and efficient synthetic route to the prostanoid synthon 1.

We thank Dr. Seizi Kurozumi (Teijin Ltd.) for providing the IR, NMR, and mass spectra of an authentic sample of 1. This work was supported in part by the Grant-in-Aid (to T.N.) from the Ministry of Education.

References and Notes

1) E. Hardegger, H. P. Schenk, and E. Borger, Helv. Chim. Acta., 50, 2501(1967); R. Klok, H. J. J. Pabon, and D. A. Van Dorp, Rec. Trav. Chim., 87, 813(1968); 89, 1043(1970).

2) J. F. Bagli and T. Bogri, J. Org. Chem., 37, 2132(1972); Tetrahedron Lett., 1972, 3815; C. J. Sih, R. G. Salomon, P. Price, R. Stood, and G. Peruzotti, Tetrahedron Lett., 1972, 2435.

3) K. F. Bernady and M. J. Weiss, Tetrahedron Lett., 1972, 4083; R. F. Schaub and M. J. Weiss, Tetrahedron Lett., 1973, 129.

4) S. Kurozumi, T. Toru, and S. Ishimoto, Tetrahedron Lett., 1973, 4959.

5) F. S. Alvarez, D. Wren, and A. Price, J. Am. Chem. Soc., 94, 7823(1972); A. F. Kluge, K. G. Untch, and J. H. Fried, ibid., 94, 7827, 9256(1972).

6) C. J. Sih, et al., J. Am. Chem. Soc., 94, 3643(1972); C. J. Sih, et al., J. Am. Chem. Soc., 95, 1676(1973).

7) J. F. Bagli, T. Bogri, R. Deghenghi, and K. Wiesner, Tetrahedron Lett., 1966, 465.

8) B. M. Trost and S. Kurozumi, Tetrahedron Lett., 1974, 1929; P. D. Gokhale, et al., Synthesis, 718 (1974); M. Kobayashi, S. Kurozumi, T. Toru, and S. Ishimoto, Chem. Lett., 1976, 1341; see ref. 2), 6).

9) T. Nakai, E. Wada, and M. Okawara, Tetrahedron Lett., 1975, 1531.

10) E. Wada, T. Nakai, and M. Okawara, Chem. Lett., 1976, 1025.

11) S. F. Brandy, M. A. Ilton, and W. S. Johnson, J. Am. Chem. Soc., 90, 2882(1968).

12) The bromide 5 was prepared via the three steps from tetrahydropyran according to the method of Ames; D. E. Ames, R. E. Bowman, and R. G. Mason, J. Chem. Soc., 1950, 174.

13) E. J. Corey and J. W. Suggs, Tetrahedron Lett., 1975, 2674.

14) The absence of pyridine resulted in the low yield (50%) of 9.

(Received July 4, 1977)