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A GENERAL SYNTHESIS OF 4-HYDROXY-2-ALKYLCYCLOPENTENONES

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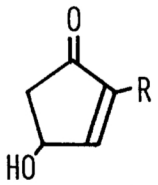
The electrooxidation of t-butyl 2-furylacetate (**2**) yielded dimethoxy dihydrofuran (**3**), which was transformed by hydrolysis to 4-hydroxy-5-carbo-t-butoxycyclopentenone (**4**). The reaction of the cyclopentenone with alkyl halides, followed by the decarboxylation and rearrangement afforded the 4-hydroxy-2-alkylcyclopentenone (**1**), one of which was the PGE_2 precursor.

Owing to their wide potentiality in the syntheses of some physiologically important compounds, the synthesis of 4-hydroxy-2-alkylcyclopentenones (**1**) has attracted much attention in recent years.[1)]



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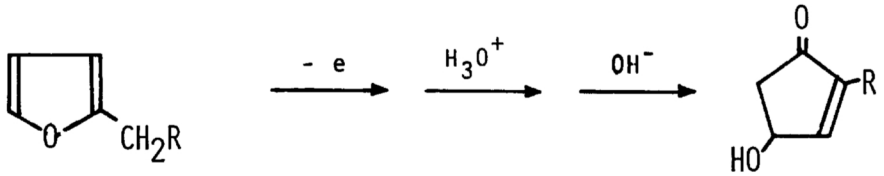
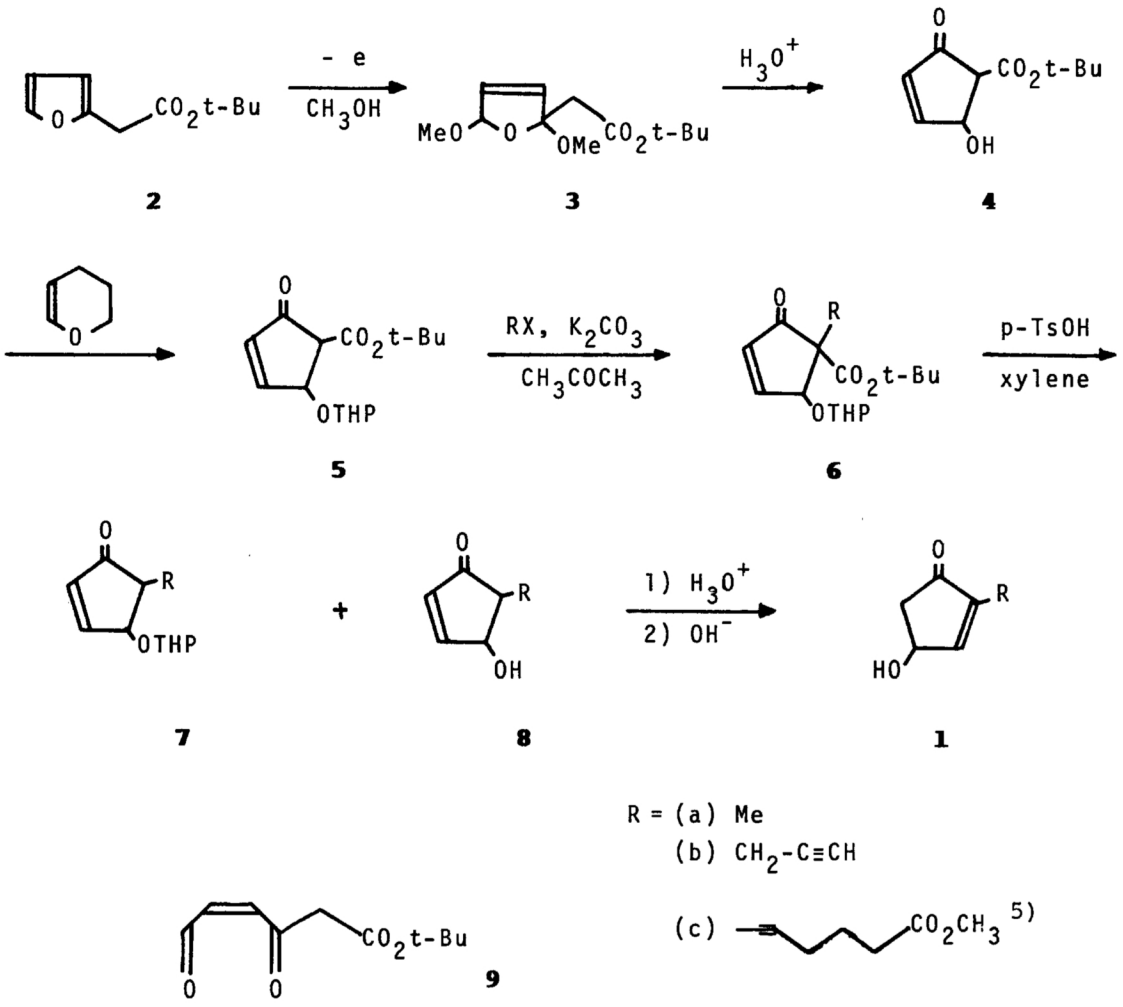
Previously, we have found a general synthetic method of rethrolones from 2,5-dialkylfurans using electrooxidation as one of the key steps.[2)] Although this novel method is also applicable to the synthesis of 4-hydroxy-2-alkyl-cyclopentenones from 2-alkylfurans,[2)] the presence of the substituent R in the



starting compound brings about such a restriction that each goal compound needs its own starting compound, and in some cases, the introduction of the group RCH_2

into furan is not necessarily facile. In order to overcome the restriction, we exploited a new general method in which the process was started from a common starting compound and the substituent R was introduced by a general method in a later step. The process is depicted in Scheme I.[3,4]

Scheme I.



2 3 4

5 6

7 8 1

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In the presence of ammonium bromide as a supporting electrolyte, the electrooxidation of t-butyl 2-furylacetate[6] with platimum electrodes in methanol at -30°C gave dimethoxydihydrofuran derivatives (**3**) [IR ν (cm^{-1}) 2820 (OCH_3), 1380 (t-bu), 1160, 1100, 1020, (O-C); nmr (CCl_4) δ 5.7-6.3 (m., 2H), 5.47 and 5.37 (broad s., 1H), 3.30 (d., 3H), 3.02 (d., 3H), 2.67 (m., 2H), 1.37 (s., 9H)] in an yield of 92%.[2] The treatment of the dimethoxy compound (**3**) with an acidic ion exchange resin in aqueous solution afforded a hydroxycyclopentenone derivative

(**4**) [IR ν (cm^{-1}) 3450 (-OH), 1725 (C(=O)-O), 1700 (C(=O)-C=C), 1640 (C=C), 1140 (C-O); nmr ($CDCl_3$) δ 7.57 (d.d., 1H), 6.10 (d.d., 1H), 5.13 (broad s., 1H), 3.93 (broad s., 1H), 3.10 (d., 1H), 1.47 (s., 9H)] in an yield of 92%. The transformation of the dihydrofuran (**3**) to the hydroxy ketoester (**4**) may be explained by the intermediary formation of the compound (**9**) followed by the acid - catalyzed intramolecular aldol condensation of the intermediate (**9**). In view of the remarkably simple procedure and high yield in the formation of the compound (**4**), the hydroxycyclopentenone (**4**) is undoubtedly one of the promising key compounds in the syntheses of the target compounds involving the hydroxycyclopentenone skeleton.

After the hydroxy group of the compound (**4**) was protected with dihydropyran, the reaction of the protected compound (**5**) with alkyl halide and potassium carbonate in refluxing acetone provided the alkylated compoud (**6**). **6**a [yield 70%; IR ν (cm^{-1}) 1740 (C(=O)-O), 1720 (C(=O)-C=C), 1590 (C=C), 1375 (t-bu), 1160, 1120, 1082, 1040, (C-O); nmr (CCl_4) δ 7.37 (d.d., 1H), 6.00 (d.d., 1H), 5.04 (t., 1H), 4.53 (broad s., 1H), 3.57 (broad s., 2H), 1.63 (m., 6H), 1.38 (s., 9H), 1.13 (s., 3H)]. **6**b [yield 72%; IR ν (cm^{-1}) 3280 (C≡CH), 1730 (C(=O)-O), 1705 (C(=O)-C=C), 1590 (C=C), 1150, 1120, 1072, 1030, (C-O); nmr (CCl_4) δ 7.47 (d.d., 1H), 6.18 (d.d., 1H), 5.01 (broad s., 1H), 4.72 (broad s., 1H), 3.83 (broad s., 2H), 2.78 (d., 2H), 1.77 (t., 1H), 1.62 (m., 6H), 1.33 (s., 9H)]. **6**c [yield 75.5%; IR ν (cm^{-1}) 1730 (C(=O)-O), 1710 (C(=O)-C=C), 1590 (C=C), 1150, 1120, 1075, 1032, (C-O); nmr (CCl_4) δ 7.55 (d.d., 1H), 6.07 (d.d., 1H), 5.10 (m., 1H), 4.70 (broad s., 1H), 3.60 (s., 3H), 3.60 (m., 2H), 2.70 (m., 2H), 2.0-2.5 (m., 4H), 1.5-2.0 (m., 8H), 1.4 (s., 9H)].

The decarboxylation of **6** by the usual method[9] afforded **7** and/or **8**.[10] **8**a [yield 30%; nmr ($CDCl_3$) δ 7.40 (d.d., 1H), 6.1 (d.d., 1H), 4.42 (broad s., 1H), 3.85 (broad s., 1H), 2.2 (m., 1H), 1.17 (d., 3H)]. **7**b [yield 50.2%; IR ν (cm^{-1}) 3280 (C≡CH), 1705 (C(=O)-C=C), 1130, 1110, 1070, 1030, (C-O); nmr (CCl_4) δ 7.56 (m., 1H), 6.18 (m., 1H), 4.80 (m., 2H), 3.66 (broad s., 2H), 2.5 (m., 3H), 1.83 (t., 1H), 1.62 (m., 6H)]. **7**c [yield 63.6% IR ν (cm^{-1}) 1720 (C(=O)-O), 1705 (C(=O)-C=C), 1150, 1110, 1070, 1035, (C-O); nmr (CCl_4) δ 7.5 (m., 1H), 6.15 (m., 1H), 4.8 (m., 2H), 3.60

(s., 3H), 3.60 (broad s., 2H), 2.00-2.80 (m., 5H), 1.4-2.0 (m., 8H)].

After the mixture of **7** and **8** was hydrolyzed, the rearrangement of 5-alkyl-4-hydroxycyclopentenone (**8**b) or (**8**c) to 2-alkyl-4-hydroxycyclopentenone (**1**) was carried out by the Stork's method.[11,12] **1**b [yield 70%; IR ν (cm^{-1}) 3400 (-OH), 3290 (C≡CH), 1700 (C=O); nmr ($CDCl_3$) δ 7.5 (m., 1H), 5.0 (m., 1H), 3.1 (broad s., 2H), 2.7 (m., 2H), 2.1 (m., 1H)]. **1**c [yield 36%; IR ν (cm^{-1}) 3400 (-OH), 1700 (C=O), 1420, 1360, 1220, 1150, 1040; nmr (CCl_4) δ 7.3 (d., 1H), 4.8 (m., 1H), 3.62 (s., 3H), 3.35 (broad s., 1H), 3.00 (broad s., 2H), 2.0-2.8 (m., 6H), 1.8 (m., 2H)].

References and Notes

1) R. A. Ellison, Synthesis, 1973, 397. G. Piancatelli and A. Scettri, Synthesis, 1977, 116.
2) T. Shono, Y. Matsumura, H. Hamaguchi, and K. Nakamura, Chem. Lett., 1976, 1249.
3) The stereoconfigurations of compounds (**3**), (**4**), (**5**), (**6**), (**7**), and (**8**) were not determined.
4) All new compounds gave correct elemental analyses and or parent ion peaks in their mass spectra.
5) E. S. Ferdnandi and G. Just, Can. J. Chem., 49, 1070 (1971).
6) 2-Furylacetyl chloride was prepared by the reported method.[7] The t-butyl ester (**2**) was prepared from 2-furylacetyl chloride by the general method.[8]
7) K. Yu. Noritskii, Kh. Gresl, and Yu. K. Y'usen, Zh. Org. Khim., 1 (3), 539 (1965).
8) C. R. Hauser, B. E. Hudson, B. Abramovitch, and J. C. Shirrers, Org. Syn. Coll. Vol. III, 142.
9) D. S. Breslow, E. Baumgarten, and C. R. Hauser, J. Am. Chem. Soc., 66, 1286 (1944).
10) The compound (**8**a) was the only detectable product from **6**a, while a mixture of **7** and **8** was formed from **6**b or **6**c. The yield was calculated after the mixture of **7** and **8** was transformed to **7** by the usual method, since the separation of **7** and **8** was handly achievable.
11) The rearrangement of the cyclopentenone (**8**a) to **1**a was reported by G. Piancatelli and A. Scettri.[1]
12) G. Stork, C. Kowalski, and G. Garcia, J. Am. Chem. Soc., 97, 3258 (1975).

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