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A FACILE SYNTHESIS OF 2-(6-ETHOXYCARBONYL-2-CIS-HEXENYL)-4-HYDROXY-2-CYCLOPENTENONE[1]

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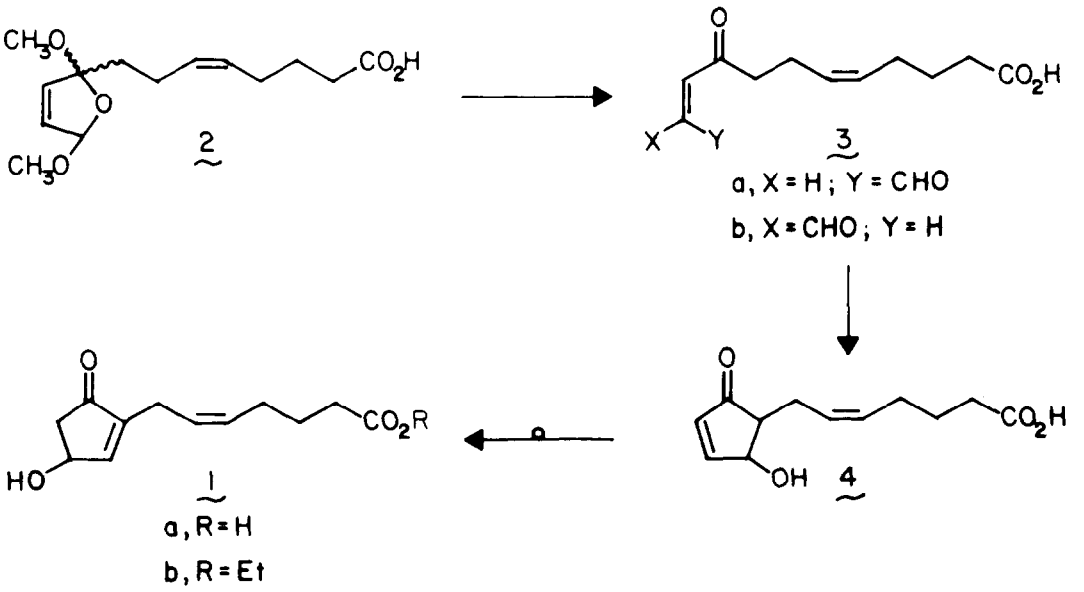
SUMMARY

The title compound 1b, a key intermediate for PGE_2 elaboration, is readily available in nine steps from furfuryl alcohol. The crucial steps include the exclusive formation of 6a from 5 and the subsequent intramolecular Aldol condensation to 1b.

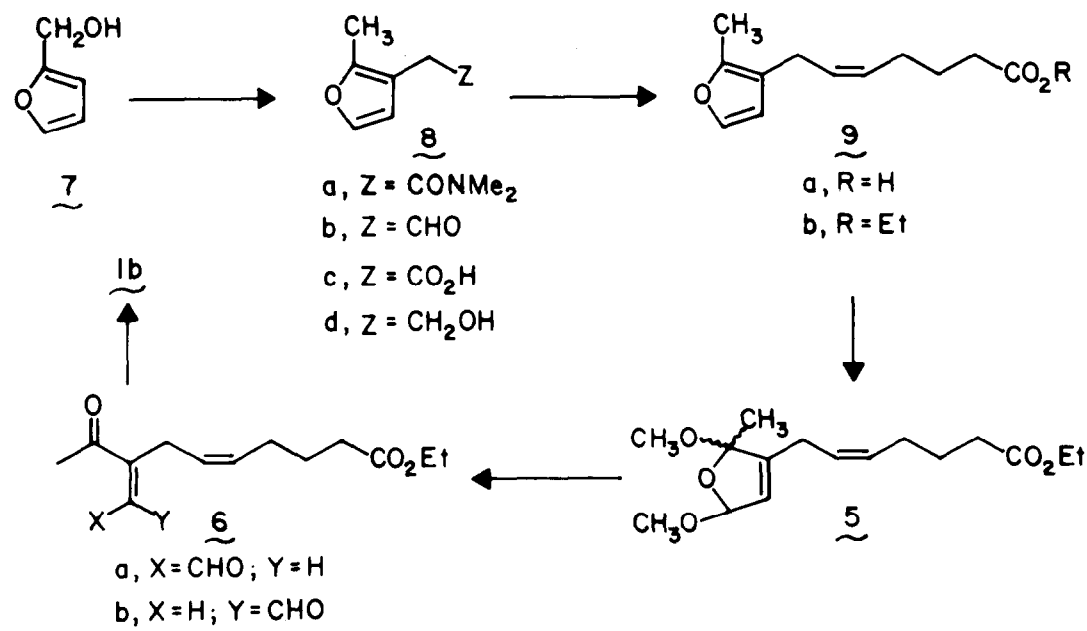
The ready accessibility of prostanoid structures via the conjugate addition of functionalized organocuprates to enones[2,3] has stimulated considerable interest in the development of an efficient synthetic route to 4-hydroxy-2-cyclopentenone 1,[3,4] an intermediate useful for the elaboration of prostaglandin E_2.[3] Floyd[4a] recently described an interesting synthesis of acid 1a beginning with dihydrofuran 2 (Scheme 1). Unfortunately, the attractiveness of this synthetic route is somewhat diminished due to (a) the concomitant formation of unwanted trans-enedione 3b during the hydrolysis of 2 and (b) the necessity of rearranging the initial cyclization product 4 to obtain the desired target 1a. In view of the reported[5] stability of 3-cis-hexen-2,5-dione to Amberlite 120 in aqueous solution (i.e., acid-catalyzed isomerization to the corresponding trans-enedione was not detected), we reasoned that substituted cis-enedione 6a might be generated cleanly from dihydrofuran 5 under carefully controlled hydrolytic conditions and, subsequently, converted directly to target ester 1b via an intramolecular Aldol condensation. Herein we wish to report an efficient synthesis of intermediate 5 and its facile conversion to ester 1b (Scheme 2).

Amide 8a, prepared in 70% yield from furfuryl alcohol via Eschenmoser's method,[6] was reduced with DIBAH to afford aldehyde 8b in 40% yield: bp 61-63°C (3.5 mm); ir (neat) ν 1730 cm^{-1}; nmr ($CDCl_3$) δ 2.23 (3H, s), 3.40 (2H, d, J=2 Hz), 6.20 (1H, d, J=2 Hz), 7.25 (1H, d, J=2 Hz) and 9.68 (1H, t, J=2 Hz).

Scheme I



Scheme II



An alternate conversion of 8a to 8b via the 3-step sequence, 8a ——> acid 8c ——> alcohol 8d ——> 8b, subsequently proved superior to the DIBAH conversion. Alkaline saponification of amide 8a gave crude acid 8c which, without purification, was reduced with LAH to yield alcohol 8d: bp 75°C (2.3 mm); ir (neat) ν 3350, 1020, 890, 730 cm^{-1}; nmr ($CDCl_3$) δ 1.97 (1H, s), 2.23 (3H, s), 2.57 (2H, t, J=6 Hz), 3.50 (2H, t, J=6 Hz), 6.20 (1H, d, J=2 Hz) and 7.21 (1H, d, J=2 Hz). Oxidation of the latter with Collin's reagent[7] provided aldehyde 8b in 65% overall yield. Condensation of 8b with the ylide derived from (4-carboxybutyl)triphenylphosphonium bromide[8] and LDA (2 eq) in HMPA-THF (1:1) afforded acid 9a in 60% yield: nmr ($CDCl_3$) δ 2.20 (3H, s), 3.04 (2H, d, J=5 Hz), 5.40 (2H, m), 6.10 (1H, d, J=2 Hz), 7.15 (1H, d, J=2 Hz) and 12.83 (1H, bs). Treatment of 9a with EtI-K_2CO_3 in DMF followed by Kugelrohr distillation (oven temp 160°C, 0.025 mm) gave ester 9b (50% overall yield from 8b): ir (neat) ν 1740 cm^{-1}; nmr ($CDCl_3$) δ 1.26 (3H, t, J=7 Hz), 2.20 (3H, s), 3.06 (2H, d, J=5 Hz), 4.10 (2H, q, J=7 Hz), 5.23 (2H, m), 6.14 (1H, d, J=2 Hz) and 7.19 (1H, d, J=7 Hz); ms calcd for $C_{14}H_{20}O_3$ 236.1412, found 236.1406. Oxidation of ester 9b with bromine in methanol-ether (4:1) at -65°C followed by treatment with triethylamine resulted in a mixture (ca. 1:1) of cis- and trans-2,5-dimethoxy-2,5-dihydrofuran 5: ir (neat) ν 1740, 1670 (w) cm^{-1}; nmr ($CDCl_3$) δ 1.46, 1.50 (3H, 2s), 2.72 (2H, d, J=6 Hz), 3.05, 3.13 (3H, 2s), 3.38, 3.47 (3H, 2s) and 5.2-5.8 (4H, m). Hydrolysis of 5 in the presence of Amberlite 120 (acid form) in 70% aqueous THF at 20°C yielded enedione 6a:[9] ir (neat) ν 1740, 1690, 1615 cm^{-1}; nmr ($CDCl_3$) δ 2.40 (3H, s), 5.2-5.8 (2H, m), 5.90 (1H, d of t, J=1.5, 6 Hz) and 9.67 (1H, d, J=6 Hz). Finally, the conversion of 6a to target ester 1b was effected with sodium carbonate (catalyst) in THF-water (5:2); chromatographic purification of the resulting crude product on silica gel (E. Merck, 0.063-0.20 mm mesh) afforded 1b as a viscous oil (31% overall yield from 9b): ir (neat) ν 3415, 1705, 1640 cm^{-1}; nmr ($CDCl_3$) δ 4.88 (1H, m), 5.47 (2H, t, J=4.5 Hz) and 7.12 (1H, m).

In conclusion, the above synthetic route circumvents the drawbacks of Floyd's method[4] and renders 4-hydroxy-2-cyclopentenone 1b, an important intermediate in the synthesis of prostaglandin E_2, readily accessible from commercially available furfuryl alcohol. Furthermore, by virtue of its inherent versatility, this route should be amenable to the preparation of a wide array of 2-substituted-4-hydroxy-2-cyclopentenones. Investigations directed toward determining the scope of possible applications of this methodology are currently in progress and will constitute the subject of future reports from these laboratories.

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References and Notes

(1) For other synthetic approaches to substituted 4-hydroxy-2-cyclopentenones, see: (a) G. Buchi, D. Minster and J. C. F. Young, J. Am. Chem. Soc., 93, 4319 (1971); (b) G. K. Cooper and L. J. Dolby, Tet. Letters, 4675 (1976); (c) G. R. Kieczykowski; C. S. Pogonowski, J. E. Richman and R. H. Schlessinger, J. Org. Chem., 42, 175 (1977).

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(9) The nmr spectrum of cis-enedione 6a displays a single doublet at δ 9.67 for the -CHO; possible contamination by trans-isomer 6b cannot be detected.

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