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TOTAL SYNTHESIS OF PROSTAGLANDINS. III. 11-DESOXYPROSTAGLANDINS[1].

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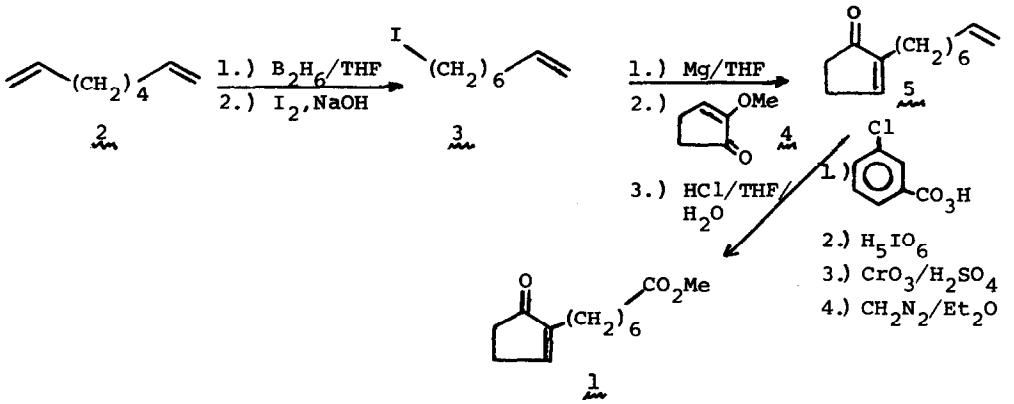
In addition to their interesting pharmacological properties,[2,3,4] the desoxyprostaglandins are also potentially important intermediates for conversion into the naturally occurring prostaglandins via microbiological hydroxylation. The recent report[5] of an improved synthesis of an important intermediate to the 11-desoxyprostaglandins prompts us to record our efficient preparation of this class of compounds.

The first total synthesis of a pharmacologically-active prostenoate was reported by Bagli and coworkers at Ayerst.[6] The prostenoate skeleton was elaborated in several steps beginning with a Michael-type 1,4-addition of HCN to the eneone (1). We report a new practical synthesis (Scheme 1) of the important prostaglandin synthon[7] (1)[2,6,8,9,10] and the one-step elaboration of the prostenoate skeleton by conjugate addition of C_8 nucleophiles to (1).

Scheme 1

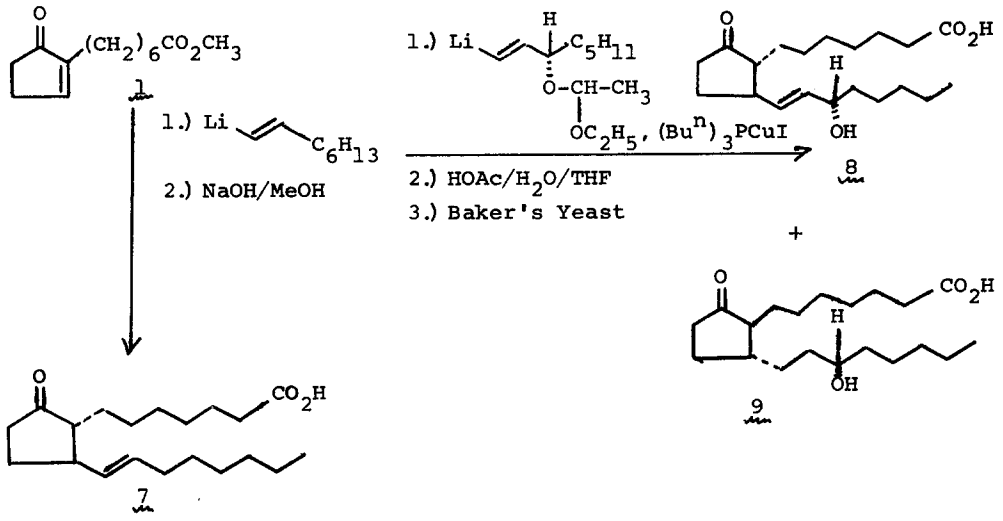


The synthon (1) was prepared from the inexpensive starting material, octa-1,7-diene (2)[11] starting with conversion into 8-iodooctene (3) (75%) by the hydroboration procedure of Brown, et al.[12] The Grignard reagent from (3) was condensed

with 2-methoxy-cyclopent-2-en-1-one (4)[13] to yield 2-(oct-7'-enyl)-cyclopent-2-en-1-one (5) by the general method of Ansell and Ducker.[14] The olefin (5) was converted to (1) in good yield (42% overall, not optimized). This was accomplished as follows. Treatment of (5) with m-chloroperbenzoic acid gave the epoxide; cleavage of the latter with periodic acid to the aldehyde,[15] followed by oxidation with Jones reagent and esterification with diazomethane yielded (1).

(dl)-11-15-Didesoxyprostaglandin E_1[16] (7) was constructed (Scheme 2) (75% from 1, not optimized) by the condensation of (1) with two molar equivalents of 1-lithio-trans-oct-1-ene, in the presence of a molar equivalent of tri-n-butylphosphinecopper(I) iodide complex[17] in ether at 0°, followed by the hydrolysis of the methyl ester with methanolic sodium hydroxide.

Scheme 2



When (1) was similarly treated with 3(S)-(α-ethoxy)-ethoxy-1-lithio-trans-oct-1-ene,[1] two diastereomeric products (60% from 1, not optimized) in approximately equal amounts were obtained after removal of the protecting groups[18] and ester hydrolysis.[1] These were characterized as 11-desoxyprostaglandin E_1[16] (8) and

11-desoxy-15-epi-ent-prostaglandin E_1[16] (9). The circular dichroism spectrum of (8) afforded a negative cotton effect ($\theta \times 10^{-3} = -8.9^{\circ}$ at 296 nm), whereas the CD spectrum of (9) exhibited a positive cotton effect ($\theta \times 10^{-3} = +7.5^{\circ}$ at 296 nm).

Acknowledgment

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Footnotes and References

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