

PROSTAGLANDINS VII - UTILITY OF THE NEF REACTION IN THE SYNTHESIS OF PROSTANOIC ACIDS.
A TOTAL SYNTHESIS OF (\pm)-11-DEOXY-PGE₁, -PGE₂, AND THEIR C-15 EPIMERS.

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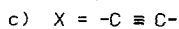
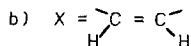
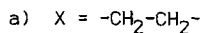
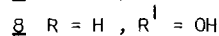
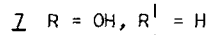
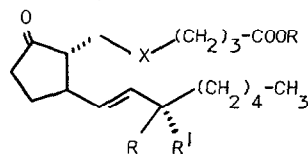
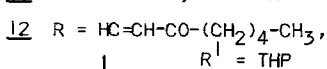
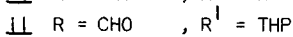
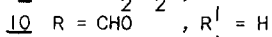
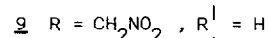
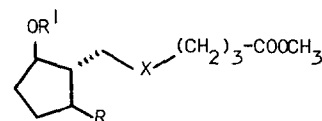
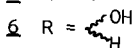
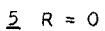
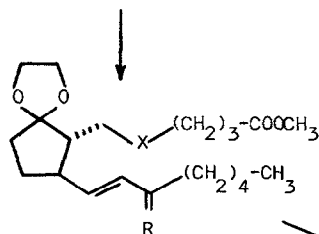
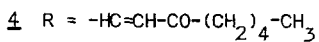
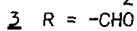
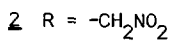
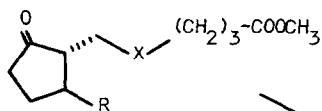
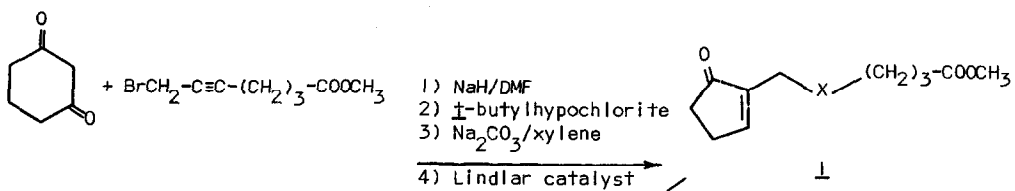
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The importance of cyclopentenone (1a) as a useful intermediate in the prostanoic acid synthesis has been well documented.¹ One of the most convenient approaches to the generation of the side chain containing the allylic alcohol in prostaglandin like compounds was described by the Harvard group.² We wish to report the utility of the Nef reaction in the generation of cyclopentane aldehydes leading to 11-deoxyprostaglandins.

Reaction of cyclopentenone (1a) with nitromethane in dry methanol containing one equivalent of sodium methoxide yielded the corresponding 1,4 adduct⁴ 2a (77% yield, ν max 1727, 1550 cm⁻¹, nmr, δ 4.5, 2H, CH₂NO₂). The above nitroketone was converted to the sodium salt of the corresponding nitronic acid, on treatment with an equimolar amount of sodium in methanol and hydrolysed by dropwise addition to ice cold dilute sulfuric acid³ (H₂SO₄ : H₂O, 1 : 6.4 by volume), to yield keto aldehyde^{4b} (3a) (71% yield, ν max 2700 cm⁻¹, nmr δ 9.6, 1H, H-C=O). Treatment of the aldehyde 3a with dimethoxy-2-ketoheptyl phosphonate led to the unsaturated ketone^{4b} 4a. Selective ketalization at C-9 followed by sodium borohydride reduction yielded the alcohol 6a as the mixture of C-15 epimers. Deketalization gave the 11-deoxy PGE methyl ester 8a⁴ and its C-15 epimer 7a⁴.

Alternatively, the reduction of the nitroketone 2a with sodium borohydride, followed by hydrolysis of the nitronic acid salt of 9a and transformation to its THP ether 11a, was achieved in an overall yield of 50% (from 2a). Treatment of 11a with dimethoxy-2-oxoheptyl phosphonate gave 12a⁴. This was transformed to dl-11-deoxy PGE₁ as described.⁵

The cis-7-(5-oxocyclopentenyl)-5-heptanoic acid methyl ester 1b was prepared from cyclohexane-1,3-dione and 7-bromo-5-heptynoic acid methyl ester, using a modification of a described⁶ sequence. Treatment of 1b with nitromethane followed by borohydride reduction yielded the nitrocyclopentanol 9b (87.4% yield, from 1b). On treatment of the corresponding sodium salt of 9b



with dilute sulfuric acid yielded the aldehyde 10b in 56% yield. This was transformed using the sequence described for the 11-deoxy PGE₁ series to the corresponding C-15 epimers 7b and 8b of the 11-deoxy PGE₂ methyl ester.^{4b}

Finally the 7-(5-oxocyclopentenyl)-5-heptynoic acid methyl ester 1c has been transformed to the aldehyde 10c (36% yield) via the nitro methane adduct 9c.

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