Tetrahedron Letters,Vol.25,No.6,pp 671-674,1984 0040-4039/84 $3.00 + .00
Printed in Great Britain

A NEW AND UNUSUALLY FLEXIBLE ROUTE TO CYCLOPENTANOIDS
SYNTHESIS OF SARKOMYCIN AND PROSTAGLANDINS

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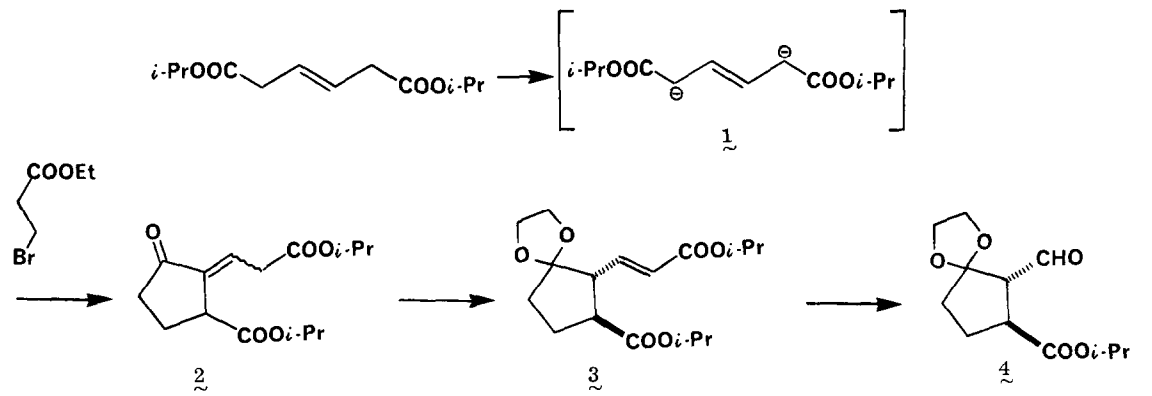
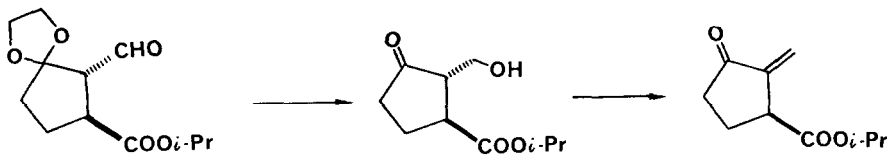
Summary: Combination of the dianion of dialky 3-hexenedioate and β-bromopropionate leads directly to a 2,3-disubstituted cyclopentanone, which can be transformed to a variety of primary prostaglandins and sarkomycin.

In the foregoing paper we described an efficient coupling of α-bromomethylacrylate and the doubly charged succinate ion.[1] Our approach characterized by the successful regiospecific cyclization after the initial alkylation step. In view of the inefficiency of condensation of β-halopropionate with reagents of succinate dianion,[1] the behavior of certain dianions having unsymmetrical intermediates after the initial alkylation was studied. Gratifyingly, the dianion 1[2] prepared by reaction of diisopropyl 3-hexenedioate with 2.2 equiv of LDA in THF-HMPA at -78°C for 30 min was found to be satisfactory. Thus, the reaction of 1 with ethyl 3-bromopropionate (0.67 equiv) at -78°C for 1 h and -20°C for 3 h produced cyclopentanone 2 as a mixture of olefinic isomers, from which the ketal 3 was isolated as a sole product in 52% over-all yield.[3] Of special significance is the regio- and stereoselective shift of the double bond of 2 to the β,γ-position during ketalization.[4] Furthermore, the E-double bond in 3 could be cleaved cleanly to the aldehyde 4[5] with $NaIO_4$-OsO_4 (87%).[6]



The potential of the present methodology for simplification of synthetic strategy appears exciting. For example, the ketal 4 has the necessary structural features for cyclopentanoid synthesis.[7] This is highlighted by the short syntheses of sarkomycin[8] and prostaglandins.[9]

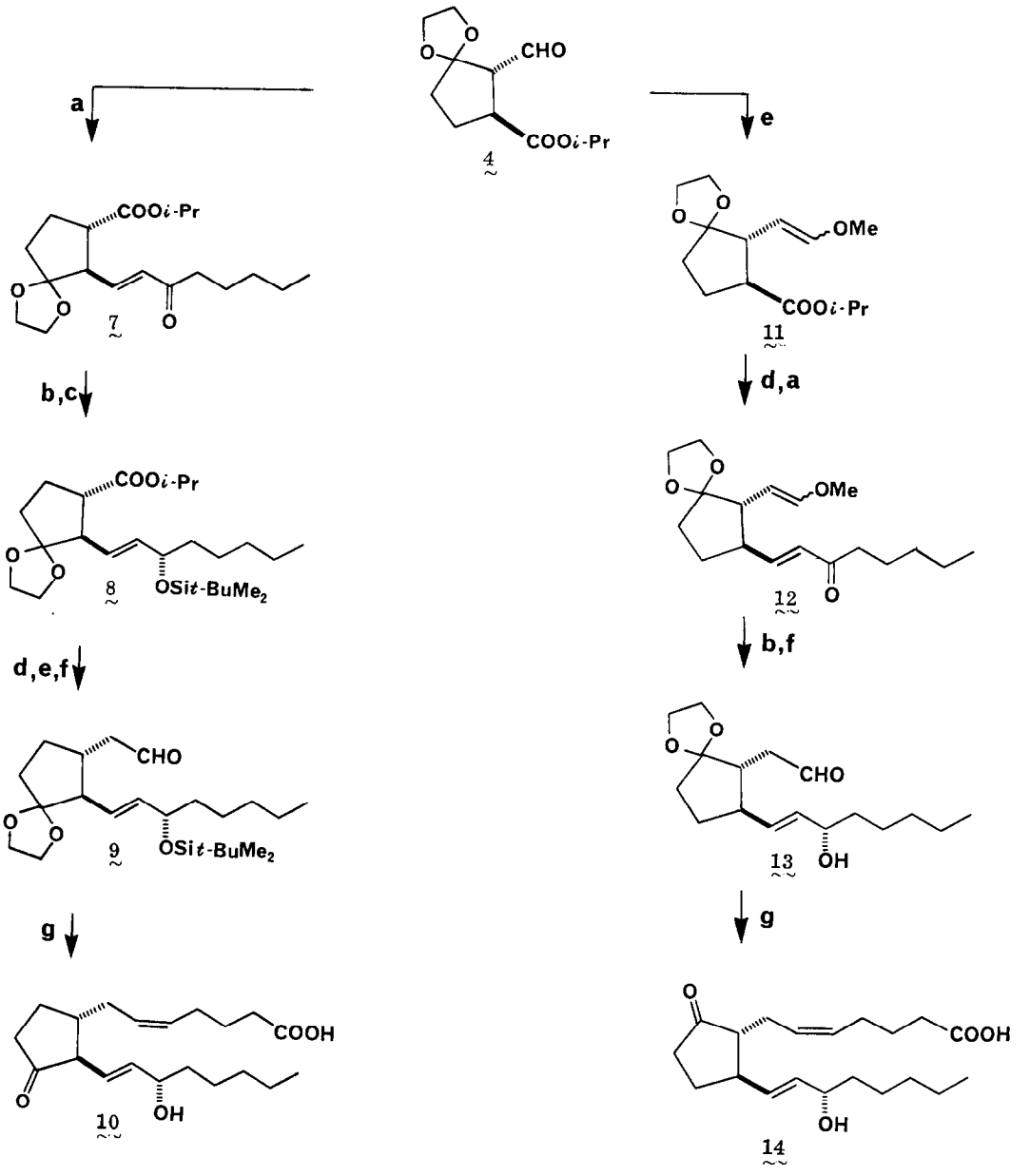
Reduction of the aldehyde 4 with sodium borohydride in methanol (0°C, 1 h) followed by mild acid treatment gave the hydroxyketone 5 in 70% yield. Exposure of 5 with mesyl chloride and triethylamine in methylene chloride (0°C, 2 h) produced isopropyl ester of sarkomycin (6) in 96% yield.[10,11]



4 5 6

The aldehyde 4 is a possible starting point for the synthesis of prostaglandins by a number of reasonable pathways. Specifically, upon treatment of 4 with the sodio salt of dimethyl 2-oxoheptylphosphate,[12] the enone 7 was formed in 87% yield. Reduction with sodium borohydride (1 mol equiv) in methanol at 0°C for 1 h gave an easily separable mixture of the diastereomeric alcohols, from which the α-isomer was isolated (33%)[13] and transformed to its tert-butyldimethylsilyl derivative 8 (100%). One carbon homologation of 8 to 9 was successfully achieved by the following sequence: (1) selective reduction of 8 with diisobutylaluminum hydride (1.5 equiv) in hexane at -78°C (93%); (2) reaction with methoxymethylenetriphenylphosphorane (3 equiv) in toluene-THF at 0°C for 1 h (96%); and finally (3) treatment with $Hg(OAc)_2$ (3 equiv) in THF-water (10:1) at 25°C for 15 min (86%).[14] Treatment of 9 with the ylide derived from 5-triphenylphosphoniovalerate ion (2.0 equiv) in DMSO,[12] followed by exposure to acetic acid-water (4:1) at 25°C overnight, afforded 56% of the desired (±)-9-deoxyprostaglandin D_2 (10).[15,16]

The flexibility inherent in this approach to the construction of prostaglandin D_2 system suggests the application of the method to the synthesis of other prostanoids. Studies in this area will be reported in future publications. One obvious objective, the synthesis of the position isomer of 10, 11-deoxyprostaglandin E_2, has already been attained in the following way using the procedure which parallel those described above. Thus, the aldehyde 4 was converted to the vinyl ether 11 with methoxymethylenetriphenylphosphorane at 0°C (84%). Exposure of 11 to DIBAH at -78°C in toluene, followed by condensation with dimethyl 2-oxoheptylphosphonate,[12] led to the highly selective formation of the enone 12 (70% from 11). The enone 12 was reduced with sodium borohydride and the aldehyde 13 was generated by the reaction with $Hg(OAc)_2$ (53% from 12).[14] Treatment of 13 with the ylide drived from 5-triphenylphosphinovalerate ion in DMSO (97%),[12] followed by exposure to acetic acid-water, afforded 88% of the desired (±)-11-deoxyprostaglandin E_2 (14).[17,18]



a: $(MeO)_2P(O)\bar{C}HC(O)C_5H_{11}$, THF; b: $NaBH_4$, MeOH; c: t-$BuMe_2SiCl$, imidazole, DMF; d: DIBAH at -78°C for 1 h; e: $Ph_3P{=}CHOMe$, toluene-THF; f: $Hg(OAc)_2$, THF-H_2O; g: $Ph_3P{=}CH(CH_2)_3CO_2^-$; AcOH-H_2O (4:1)

References and Notes

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2. P. J. Garratt and R. Zahler, J. Am. Chem. Soc., 100, 7753 (1978).
3. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.2 (m, 12H), 1.8-2.15 (m, 4H), 2.8 (m, 1H), 3.01 (dd, J = 8, 8 Hz, 1H), 3.88 (s, 4H), 4.98, 5.04 (sept, sept, J = 6.4 Hz, 1H each), 5.86 (d, J = 16 Hz, 1H), 6.87 (dd, J = 8, 16 Hz, 1H); IR (CCl_4) 2980, 1720, 1650, 1110 cm^{-1}.
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5. ^{1}H NMR ($CDCl_3$) δ 9.67 (s, 1H); IR (CCl_4) 2740 (sh), 1725 cm^{-1}.
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13. By analogy to the tlc behavior of natural prostaglandins and their 15-epimers, the more polar isomer has tentatively been assigned the natural α-configuration in 8.
14. E. J. Corey, K. Narasaka, M. Shibasaki, J. Am. Chem. Soc., 98, 6417 (1976).
15. Identical in all respects with the authentic sample, which was generously supplied by Dr. Y. Arai of Ono Pharmaceutical Company.
16. 9-Deoxy-PGD_2 was shown to be more potent than PGD_2 with regard to their ability to inhibit ADP-induced human platelet aggregation: G. L. Bundy, D. R. Morton, D. C. Peterson, E. E. Nishizawa, W. L. Miller, J. Medicinal Chem., 26, 790 (1983).
17. The transformation from 15-ethoxyethyl ether of 14 to PGA_2 has been accomplished previously, see G. Stork and S. Rauche, J. Am. Chem. Soc., 98, 1583 (1976).

18. This work was supported in part by a grant from Foundation for the Promotion of Research on Medicinal Resources.

(Received in Japan 10 November 1983)