Tetrahedron Letters No. 28, pp 2445 - 2448, 1977. Pergamon Press. Printed in Great Britain.

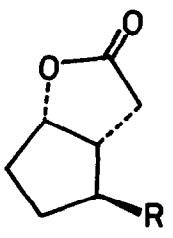
A PHOTOCHEMICAL APPROACH TO THE 11-DEOXYPROSTAGLANDIN INTERMEDIATE

Toshio Ogino*
Laboratory of Chemistry, Faculty of Education (Nagaoka), Niigata University, Nagaoka 940, Japan

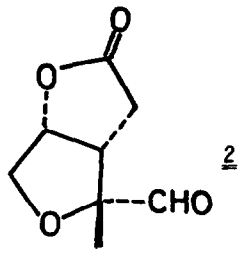
Kazuyoshi Yamada and Koji Isogai
Department of Applied Chemistry, Faculty of Engineering, Niigata University, Nagaoka 940, Japan

(Received in Japan 9 May 1977; received in UK for publication 31 May 1977)

Several recent papers have reported effective syntheses of 11-deoxyprostaglandins using the lactone aldehyde 1 as a key intermediate[1),2)] In connection with our previous report[3)] on the photoannelation reaction of 5-methyl-2,3-dihydro-3-furanone with olefins, we wish to describe in this letter a simple three-step synthesis of the lactone 1 and its 11-oxa-12-methyl analogue 2[4)] starting from photochemical cycloaddition of methyl β-acetoxyacrylate to 2-cyclopentenone and 5-methyl-2,3-dihydro-3-furanone. In spite of the synthetic or mechanistic interest in the regioselectivity of the photochemical cycloaddition reaction of β-alkoxy- or β-acyloxyacrylic acid esters with cyclic enone, there have been no reports as to the photochemical reaction of this type of olefin with cyclic enone.



1 R=CHO
13 R=CH_2OH



2

Irradiation of 5-methyl-2,3-dihydro-3-furanone 3[5)] and excess amount of methyl β-acetoxyacrylate 4[6)] in benzene for 24 hours with a 500 W high pressure mercury lamp through pyrex resulted in the formation of a mixture of 1:1 adducts in 82 % yield. From the VPC analysis (on a DEGS at 180 °C), the product was found to consist mainly of four components, 5, 6, 7 and 8, in the ratio of 12:4:1:3 and those were preparatively separated in this order.

The head-to-head structures proposed for two major adducts, 5 [ν (CCl_4) 1748, 1224 cm^{-1}; δ (CCl_4) 1.51(Me, s), 2.07(OAc, s), 2.72(H_1, dd, J=6, 2 Hz), 3.03(H_2, t, J=6 Hz), 3.72(CO_2Me, s), 4.12 and 4.13(Ha and Hb, Jab=17 Hz), 4.88(H_3, dd, J=6, 2 Hz)] and 8 [ν (CCl_4) 1754, 1222 cm^{-1}; δ (CCl_4) 1.43(Me, s), 2.07(OAc, s), 2.75(H_1, d, J=10 Hz), 2.95(H_2, dd, J=10, 5 Hz), 3.68 (OMe, s), 4.08 and 4.31(Ha and Hb, Jab=17 Hz), 5.30(H_3, d, J=5 Hz)], were evident on the basis

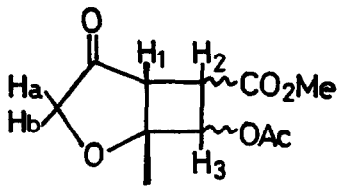
of the NMR spin-spin splitting of the methine protons (H_1, H_2 and H_3) on the cyclobutane ring. The stereochemistry of 5 and 8 were established in the following manner. Reduction of 5 with sodium borohydride at 0 °C gave an alcohol 9 [$\nu(CCl_4)$ 3580, 1725 cm^{-1}; δ (CCl_4) 1.36(Me, s), 2.01(OAc, s), 2.62(H_1, br.t, J=6 Hz), 3.23(H_2, t, J=6 Hz), 3.56(Ha, d, J=9 Hz), 3.73(OMe, s), 4.09(Hb, dd, J=9, 7 Hz), 4.45(H_4, t, J=7 Hz), 4.88(H_3, dd, J=6, 2 Hz)] while sodium borohydride reduction of 8 at -40 °C[7] yielded a γ-lactone 10 [ν (CCl_4) 1788, 1757, 1220 cm^{-1}; δ (CCl_4) 1.24(Me, s), 2.12(OAc, s), 2.94(H_2, dd, J=8.5, 2 Hz), 3.26(H_1, dd, J=8.5, 7 Hz), 3.82(Ha, dd, J=11, 3 Hz), 4.15(Hb, d, J=11Hz), 4.80(H_3, d, J=2 Hz), 5.12(H_4, dd, J=7, 3 Hz)].

Since the endo configuration of the hydroxyl group in the sodium borohydride reduction products of similar photoadducts was well established[3], these results firmly establish exo configuration for the methoxycarbonyl group in 5 and endo configuration for that in 8. The proposed configuration of acetoxy group, i.e., endo in 5 and exo in 8, might be deduced from the fact that the long range spin-spin coupling between H_1 and H_3 was only observed with 5.

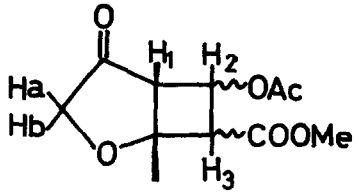
The head-to-tail structures of two minor adducts, 6 [ν (CCl_4) 1752, 1216 cm^{-1}; δ (CCl_4) 1.43(Me, s), 2.02(OAc, s), 3.03(H_1, dd, J=9, 1 Hz), 3.40(H_3, dd, J=8, 1 Hz), 3.77(OMe, s), 4.17(Ha and Hb, s), 5.08(H_2, dd, J=8, 9 Hz)] and 7 [ν (CCl_4) 1747, 1212 cm^{-1}; δ (CCl_4) 1.60(Me, s), 2.07(OAc, s), 2.80(H_1, dd, J=4.5, 1.5 Hz), 3.23(H_3, dd, J=6, 1.5 Hz), 3.77(OMe, s), 4.10 and 4.17(Ha and Hb, Jab=17 Hz), 5.23(H_2, dd, J=6, 4.5 Hz)], were evident on the basis of the NMR spectral data, but the stereochemistry of those compounds remained unsolved.

The alcohol 9, obtained from the major adduct 5 (vide supra), was treated at 0 °C with methanolic potassium hydroxide for 30 minutes under nitrogen atmosphere. The reaction mixture was acidified with 6N-sulfuric acid, neutralized with ammonium carbonate and the solvent evaporated. Extraction of resulting residue with methylene chloride gave a lactone aldehyde 2 with quantitative recovery. The spectral data for 2 [ν (CCl_4) 2820, 2700, 1790, 1740, 1160 cm^{-1}; δ ($CDCl_3$) 1.33(Me, s), 2.6-3.1(3H, m), 4.23(2H, d, J=3 Hz), 5.20(1H, dt, J=3, 5.5 Hz), 9.75(1H, s)] were consistent with the structure proposed[8].

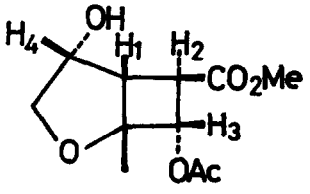
Similar procedure was applied to the preparation of 11-deoxyprostaglandin intermediate 1 in the following manner. Irradiation of 2-cyclopentenone with excess amount of methyl β-acetoxyacrylate 4 in benzene afforded a mixture of 1:1 adducts in 65 % yield which was found to consist of more than five isomers by VPC analysis. Without any separation the mixture was reduced with sodium borohydride at -40 °C, and resulting products [$\nu(CCl_4)$ 3520, 1780, 1745 cm^{-1}][9] were subsequently treated with sodium methoxide in methanol at 0 °C for 40 minutes under nitrogen atmosphere. Usual work-up and fractionation by chromatography yielded three



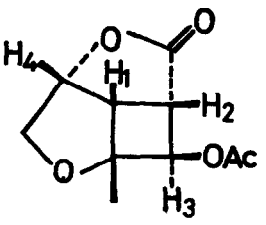
5 CO_2Me=exo
OAc=endo
8 CO_2Me=endo
OAc=exo



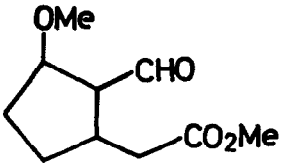
6 and 7



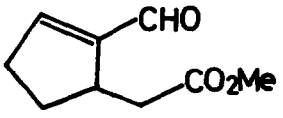
9



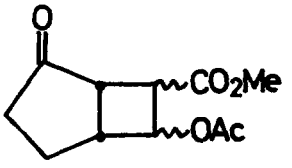
10



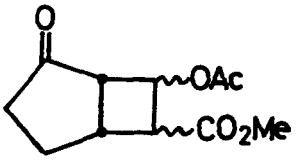
11



12



14



15

products 1, 11 and 12 in 31%, 16% and 4% yield respectively.

The spectral data of 1 [ν (neat) 2720, 1760, 1720, 1165 cm^{-1}; δ ($CDCl_3$) 9.73(1H, s), 5.06(1H, m), 1.4-3.6(8H, m)] were consistent with those reported for 11-deoxyprostaglandin intermediate by Corey et al.[1] Additional support for the structure of 1 was provided when 1 was treated with sodium borohydride to give an alcohol 13 which was found to be identical with the alcohol having proposed structure reported by Sakai et al[10] by direct comparisons of NMR and IR spectra.

The structures of minor products, 11 [ν (CCl_4) 2825, 2720, 1743, 1735 cm^{-1}; δ (CCl_4) 3.27 (OMe, s), 3.62(CO_2Me, s), 3.98(1H, m), 9.77 (1H, s)] and 12 [ν (CCl_4) 2825, 2730, 1745, 1694 cm^{-1}; δ (CCl_4) 3.60(CO_2Me, s), 6.82(1H, m), 9.77(1H, s); λ_{max} (EtOH) 234 nm], were deduced on the basis of the spectral data. In support of these structure assignments, 11 was rapidly converted to 12 on heating with p-toluenesulfonic acid in benzene. The formation of these methyl esters could be attributed to head-to-tail adducts 15, while the formation of 1 attributed to head-to-head adducts 14.

Acknowledgment: The authors wish to express their gratiude to Dr. K. Sakai, Sankyo Co., Ltd., for the gift of the NMR and IR spectra of the alcohol 13.

References and Notes

1) E. J. Corey and T. Ravindranathan, Tetrahedron Letters, 4753 (1971); E. J. Corey and B. B. Snider, J. Org. Chem., 39, 256 (1974).

2) P. Crabbé and A. Guzmán, Tetrahedron Letters, 115 (1972).
3) T. Ogino, T. Kubota and K. Manaka, Chemistry Letters, 323 (1976).
4) Numbering follows that of prostaglandins.
5) G. Casnati and A. Ricca, Tetrahedron Letters, 327 (1967).
6) Prepared by the procedure similar to Pechmann's synthesis of ethyl β-acetoxyacrylate; H. v. Pechmann, Ber., 25, 1050 (1892).
7) When the reduction was conducted at 0 °C, a γ-lactol was obtained instead of the lactone 10.
8) Although 2 appeared as a single spot on TLC, the NMR spectrum showed an extra signal at 1.27 ppm (br, s) due to impurity. Attempts of further purification by means of chromatography and distillation failed.
9) The absorption band at 1780 cm^{-1} indicating presence of γ-lactone was not observed when the reduction was carried out at 0 °C.
10) K. Inoue and K. Sakai, Tetrahedron Letters, 4107 (1976).