Tetrahedron Letters No. 41, pp 3927 - 3930. 0040-4039/78/1008-3927$02.00/0

A NEW STEREOSELECTIVE SYNTHESIS OF dl-PROSTAGLANDIN $F_{2\alpha}$

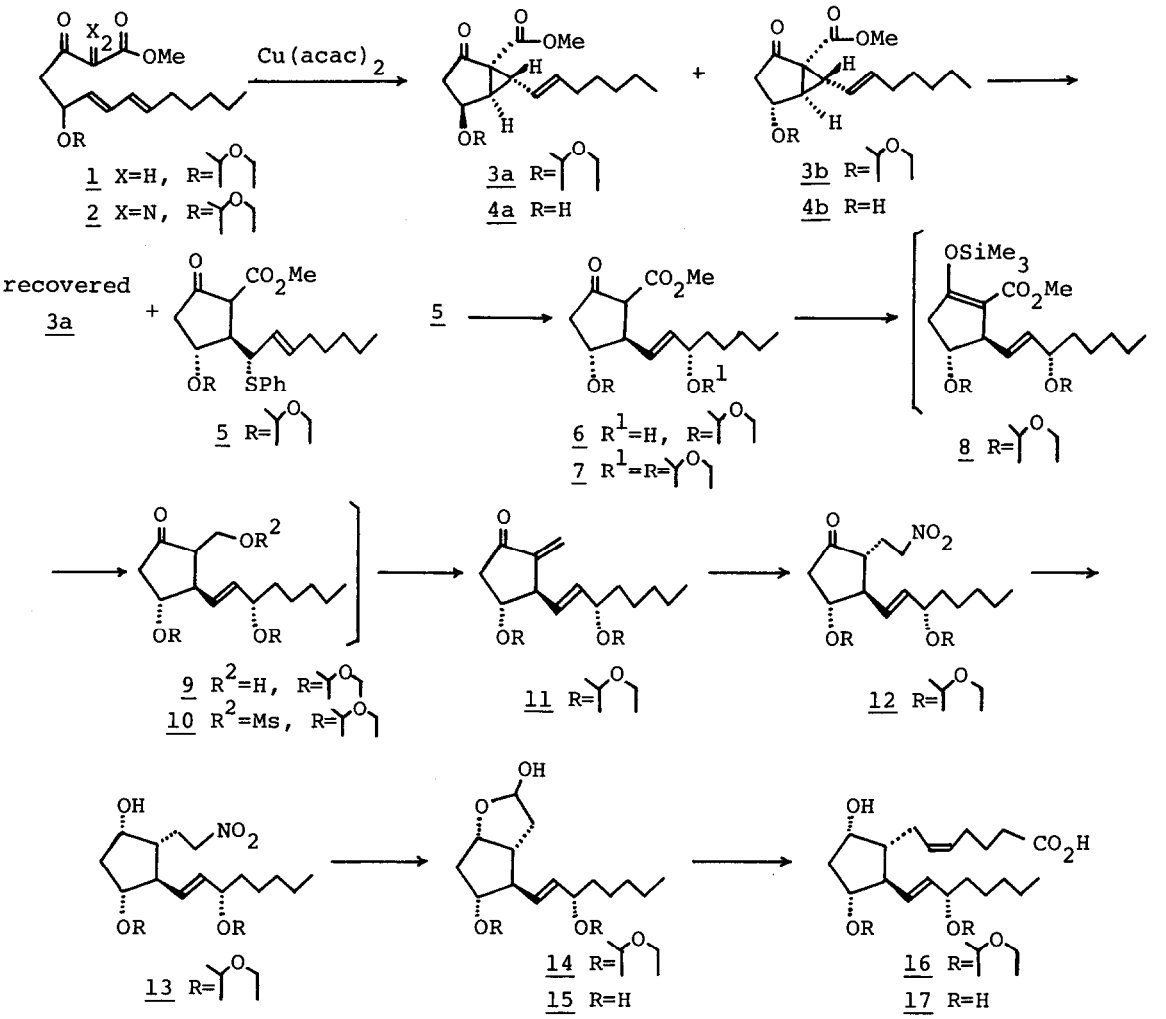
Kiyosi Kondo,* Teruo Umemoto, Kumiko Yako, and Daiei Tunemoto

Sagami Chemical Research Center, Nishi-Ohnuma 4-4-1, Sagamihara

Kanagawa 229, Japan

Recently we have shown that the combination of a regioselective nucleophilic addition of thiophenoxide to activated bicyclo[3.1.0]hexanone and a [2,3]sigmatropic rearrangement of allylic sulfoxide can efficiently be utilized to the stereoselective synthesis of 11-deoxyprostaglandin(PG)E_1,[1] and 10-oxa-11-deoxy-PGE_1.[2] Since a route from 11-deoxy-PGE to PGA has already been developed by Stork,[3] the above synthesis means the completion of a new process to natural PGs. As an alternative and our own approach to natural PGs, the possibility of introducing an additional hydroxy function on C-11 (PG numbering) at the very beginning of the synthesis was now examined.[4]

Reaction of the dianion of methyl acetoacetate with trans,trans-2,4-decadienal at -78° for 30 min and then at -30° for 2 hr in THF-HMPA (1.1 equiv to the substrate) afforded an addition product in almost quantitative yield. As the crude product was relatively unstable, it was directly treated with ethyl vinyl ether/$POCl_3$ at 0° to afford the protected β-keto-ester 1 in 90% overall yield. After conversion of 1 to the diazo compound 2 by treatment with TsN_3/Et_3N,[5] 2 was heated in benzene under reflux for 12 hr in the presence of $Cu(acac)_2$ as catalyst to give a mixture of the bicyclic compounds 3 in 61% yield. As the NMR spectrum of 3 was too complex to be analyzed,[6] it was hydrolyzed in i-PrOH-H_2O (4:1) in the presence of p-TsOH to afford a mixture of 4a and 4b in 86% yield. The structure of 4a and 4b were determined by comparison of their NMR absorption peaks with those reported on analogous ring systems.[7] The relative intensity of respective peaks[8] assignable to 4a and 4b was 1:2 and thus the ratio of 3a and 3b should be 1:2.



Although it was unable to separate the desirable isomer 3b from its epimer 3a by column chromatography, they could be differenciated from each other by the following reaction. Thus the mixture was subjected to the base catalyzed ring-opening reaction with thiophenol. When the mixture was treated with thiophenol in t-BuOH in the presence of an equimolar amount of t-BuOK or Et_3N, both isomers afforded ring-opened products. Fortunately, when the mixture was treated with thiophenol (1.1 equiv) in the presence of a catalytic amount of Et_3N in t-BuOH-H_2O (4:1) for 20 min at 0°, the only one isomer 3b suffered ring-opening to afford 5 in 85% yield (based on 3b in the mixture). The product 5 could easily be separated from the unreacted 3a by column chromatography (silica gel, EtOAc

:n-hexane=4:1). Recovery of the isomer 3a was almost quantivative and thus 3a was completely intact under these conditions.[9] The β-keto-ester 5 was oxidized with m-CPBA in MeOH at -30° for 2 hr and successively treated with excess trimethyl phosphite at 0-5° to give the allylic alcohol 6 in 97% yield. The newly generated hydroxy function on C-15 was protected by treatment with ethyl vinyl ether/$POCl_3$ at 0-5° to afford the β-keto-ester 7 in 83% yield.

Based on literature information,[10] it seemed to be difficult to introduce directly the α-side chain of PG on the intermediate 7. Thus we decided to change the methoxycarbonyl in 7 to exo-methylene function by the following sequence of reactions. Firstly, the keto-function in 7 was protected by treatment with bis(trimethylsilyl)acetamide[11] in ether. After removal of the volatile materials in vacuo, the resulting silyloxy unsaturated ester 8 was reduced with diisobutylaluminum hydride in toluene at -78° to afford the alcohol 9, which was further treated with 1.5 equiv of MsCl in pyridine at 0° to give the mesylate 10. Finally, the resulting 10 was coverted to the α-methylenecyclopentanone 11 by treatment with Et_3N at 0° in 75% overall yield from 7.

The Michael addition of functionalized vinyl cuprate to an α-methylenecyclopentanone analogous to 11 has already been reported by Stork.[12] We examined a different approach leading to the target compound 17. Thus the reaction of 11 with $MeNO_2$ in THF in the presence of an equimolar amount of NaH at room temp for 1 hr gave the adduct 12 in 97% yield. The keto-function in 12 was reduced by treatment with potassium tri-sec-butylborohydride in THF at -78% for 20 min to afford the nitroalcohol 13.[13] Then the nitromethyl group in 13 was transformed into formyl by treatment with aq. $TiCl_3$ buffered with NH_4OAc[14] to produce the protected lactol 14 in 64% overall yield from 12. Further hydrolysis of 14 in aq. AcOH at room temp afforded the trihydroxy compound 15 in 49% yield from 12.

Although the trihydroxy compound 15,[15] and also a compound[16] similar to 14 having a different protecting group are known as precursors to PGs, the final conversion of either 14 or 15 to the target compound was examined in order to confirm the stereochemistry and structural assignment of these intermediates in our hands. Condensation of 14 with 4-carboxy-n-butylidenetriphenylphosphorane, followed by hydrolysis of the resulting 16 in AcOH-H_2O (1:1) at room temp gave

the dl-$PGF_{2\alpha}$ 17 in 50% yield. Alternatively, condensation of 15 with the same Wittig reagent afforded 17 in 51% yield. The synthetic 17 and the corresponding methyl ester (CN_2N_2) exhibited the exactly identical IR and NMR spectra,[17] and TLC behaviors under several different condition,[18,12] with those of commercially available authentic $PGF_{2\alpha}$.

PEFERENCES AND NOTES

1. (a) K. Kondo, T. Umemoto, Y. Takahatake, and D. Tunemoto, Tetra. Letters, 113 (1977): (b) A similar approach has also been published by D. F. Taber; J. Amer. Chem. Soc., 99, 3513 (1977).
2. D. Tunemoto, Y. Takahatake, and K. Kondo, Chem. Letters, 189 (1978).
3. G. Stork and S. Raucher, J. Amer. Chem. Soc., 98, 1583 (1976).
4. This work was partly presented at the 26th Int. Cong. Pure Appl. Chem., Tokyo, Sept., 1977.
5. M. Regitz, Angew. Chem. Int. Ed., 6, 733 (1967).
6. Each of 3a and 3b would probably consist of two stereoisomers due to the presence of chiral center in the hydroxy protecting group.
7. (a) G. Just, C. Simonovitch, F. H. Lincoln, W. P. Schneider, U. Axen, G. B. Spero, and J. E. Pike, J. Amer. Chem. Soc., 91, 5364 (1969): (b) G. Cueille and R. Fraisse-Jullien, Tetrahedron, 28, 1331 (1972).
8. The chemical shifts for the protected carhinolie protons were δ (CCl_4) 4.69 (3a) and 4.31 (3b).
9. The recovered 3a could be transformed into the desirable isomer 4b via a bicyclohexenone and epoxide, by the following sequence of reactions: hydrolysis-mesylation-elimination-epoxidation-reduction. Cf. ref. 18.
10. T. Toru, S. Kurozumi, T. Tanaka, S. Miura, M. Kobayashi, and S. Ishimoto, Tetra. Letters, 4087 (1976).
11. J. F. Klebe, J. Finkbeiner, and D. M. White, J. Amer. Chem. Soc., 88, 3390 (1966).
12 (a) G. Stork and M. Isobe, J. Amer. Chem. Soc., 97, 4745, 6260 (1975); (b) G. Stork and G. Kraus, ihid., 98, 6747 (1976).
13. The nitroalcohol 13 was chromatographically homogeneous.
14. J. E. McMurry and J. Melton, J. Org. Chem., 38, 4367 (1973).
15. For example, J. Fried, C. H. Lin, J. C. Sih, P. Dalven, and G. F. Cooper, J. Amer. Chem. Soc., 94, 4342 (1972).
16. For example, E. J. Corey, N. M. Weinshenker, T. K. Schaaf, and W. Huber, J. Amer. Chem. Soc., 91, 5675 (1969).
17. We thank FUJI YAKUHIN KOGYO LTD for IR and NMR spectra of $PGF_{2\alpha}$.
18. W. P. Schneider, G. L. Bundy, F. H. Lincoln, E. G. Daniels, and J. E. Pike, J. Amer. Chem. Soc., 99, 1222 (1977).

(Received in Japan 7 July 1978; received in UK for publication 17 August 1978)