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A CONVENIENT ROUTE TO (+)-(9,11)-EPITHIA-(11,12)-METHANO-THROMBOXANE A_2 FROM PROSTAGLANDIN E_2 METHYL ESTER

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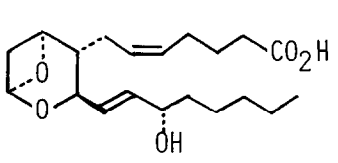
Abstract: (+)-(9,11)-Epithia-(11,12)-methano-thromboxane A_2, which is of great importance in thromboxane research, has been synthesized from prostaglandin E_2 methyl ester.

Thromboxane A_2 (TXA_2) is a very unstable substance with the important biological activities.[1] However, the syntheses of the stable TXA_2 analogs have not been reported very much because of the chemically rare structure.[2] We have recently reported the total synthesis of the stable analog, d,l-(9,11)-epithia-(11,12)-methano-TXA_2 1, which has the biological activities very similar to natural TXA_2 and is one of the most remarkable agonists in thromboxane research.[2b] That had been prompting us to synthesize the optically active form of this analog in short route. We report herein the synthesis of (+)-(9,11)-epithia-(11,12)-methano-TXA_2 from prostaglandin E_2(PGE_2) methyl ester.

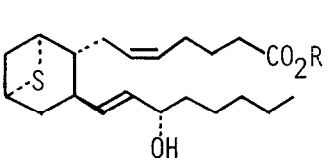
The compound 3, obtained by reaction of PGE_2 methyl ester with acetic anhydride in pyridine (87%), was converted into the compound 4 by reduction with $NaBH_4$ followed by oxidation using PCC [73%, ν 1730, m/e 392(M^+)]. Ring-expansion reaction of cyclopentanone in 4 with ethyl diazoacetate in the presence of $BF_3{\cdot}Et_2O$[3] gave the compound 5[4] [ν 1730, 1640, δ 12.40 (s,3/4H), 4.21 (quartet, J = 7Hz, 2H), m/e 418 (M^+-EtOH)]. The compound 5 was transformed into the compound 6 in 34% overall yield by a four-step sequence: (1) introduction of phenylseleno group at α-position of β-keto ester (NaH, PhSeCl, THF, 0°C)[5]; (2) oxidative elimination of phenylseleno functionality with 35% H_2O_2 ; (3) addition of n-PrSH to the resulting α,β-unsaturated system [$(i\text{-Pr})_2$NEt, DMF, rt]; (4) decarboxylation[6] (NaCl, DMSO-H_2O, 150°C) [6 ν 1730, 1670, δ 6.86 (m,1H), 6.01 (d, J = 10Hz, 1H), m/e 404(M^+)].

Conjugate addition of thiolacetic acid to the enone in 6 with t-BuOK as a base at -78°C provided the compound 7 (56%) accompanied by the C_{11}-epimer (28%) [7 ν 1730, 1710, 1690, δ 2.30 (s,3H), 2.03 (s,3H), m/e 420(M^+-AcOH)].[7] After reduction of the ketone in 7 with $Zn(BH_4)_2$ in DME at 0°C (24%),[8] the resulting alcohol was treated with MsCl-Et_3N to yield the mesylate 8 (68%) [ν 1730, 1690, δ 3.00 (s,3H), 2.33 (s,3H), 2.03 (s,3H)]. The compound 8 was stirred with NaOMe in MeOH at 55°C to lead the desired bicyclic compound 2 in 75% yield.[2b] Finally, the compound 2 was hydrolyzed with 5% aqueous KOH

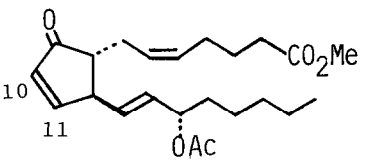
to afford the title compound 1 which was identical with an authentic sample[2b] by NMR, IR, Mass, and TLC (91%, $[\alpha]_D^{20}$ +79.6 EtOH).



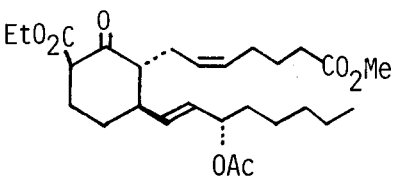
TXA_2



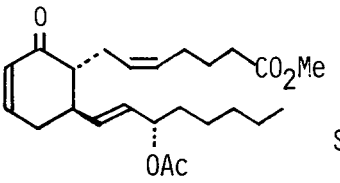
1 R=H
2 R=Me



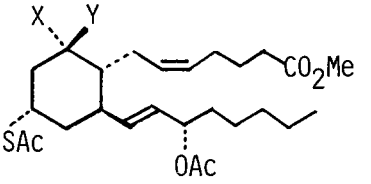
3
4 $\Delta^{10,11}$saturated



5



6



7 X,Y=O
8 X=H, Y=OMs

References and Notes

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2. (a) S. Ohuchida, N. Hamanaka, and M. Hayashi, J. Am. Chem. Soc., in press and references cited therein, (b) Idem, Tetrahedron Lett., 22, 1349 (1981).
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4. In order to obtain the pure compound 5, the crude product was once reduced with $NaBH_4$ (54% from 4) and then the resulting alcohol was oxidized with Collins reagent back again to 5 (70%), of which a large amount (75%) changed into the enol form during column chromatography on silica gel.
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8. The C_9-epimer was obtained in 46% yield. This isomer was oxidized with PDC to the former ketone 7 (88%).

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