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SYNTHESIS OF 9α,11α-THIATHROMBOXANE A_2 METHYL ESTER

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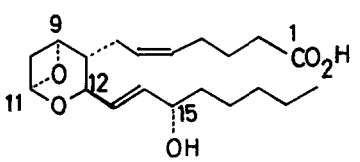
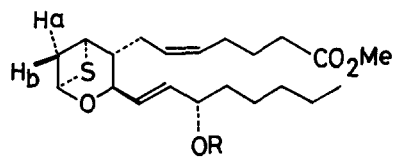
Abstract: The synthesis of thromboxane A_2 (TXA_2) analogue, 9α,11α-thia-TXA_2 methyl ester 2, in which the oxygen atom in the oxetane ring of TXA_2 was replaced by a sulfur atom, is described.

Among a number of the metabolites of arachidonic acid, thromboxane A_2 (TXA_2)[1] is a particularly conspicuous substance because of the powerful biological activities (e.g. platelet aggregation and vasoconstriction), the chemically rare structure, and the extreme instability ($t_{1/2}$ = 32 sec in pH 7.4 solution at 37 °C). To utilize practically its very important biological properties, some stable analogues possessing biological effects were synthesized.[2] We have recently reported the synthesis of (±)-dithia-TXA_2 1 which is one of the most potent agonists.[3] In this report we wish to disclose the first synthesis of 9α,11α-thia-TXA_2 methyl ester 2 in which the oxygen atom in the oxetane ring of TXA_2 was replaced by a sulfur atom. Since this analogue possesses the skeleton very similar to thromboxane A_2, it is of special interest as a TXA_2 analogue.

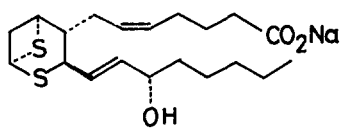


TXA_2



2 R = H

3 R = $SiPh_3$



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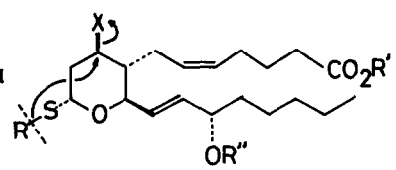
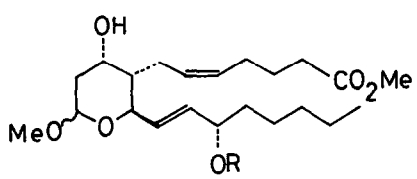


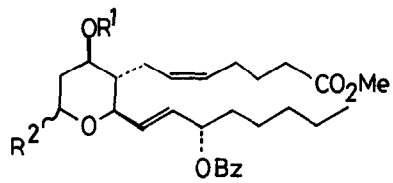
A

The synthesis was designed on the assumption that intermediate A would be an ideal precursor to the desired bicyclic system, 2-oxa-6-thia-bicyclo[3.1.1]heptane skeleton.[3] We furthermore expected that A should be stereoselectively derived from a corresponding lactol such as 7 because of an anomeric effect. These expectations will be demonstrated to have been realized.

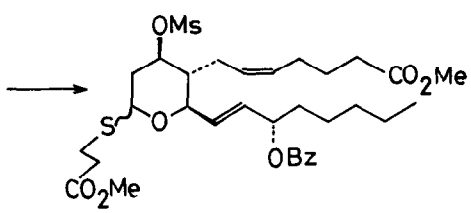
The thromboxane B_2 derivative 4 was chosen as a starting material.[4] Conversion of 4 into 7 was carried out as follows. After one of the two hydroxyl groups in 4 (C_{15}-OH) was selectively protected as its benzoate (5, benzoyl chloride, pyridine, -25 °C, 1h, 90%), inversion of the other hydroxyl group (C_9-OH) with triphenylphosphine, formic acid, and diethyl azodicarboxylate[5] [THF, 0 °C, 2h] followed by removal of the formyl group of the resulting product (potassium bicarbonate, methanol, 25 °C, 30 min) afforded a $C_9\beta$ equatorial alcohol 6 (45% from 5). The compound 6 was converted into 7 by mesylation (methanesulfonyl chloride, triethylamine, -25 °C, 10 min, 98%) and then treatment with acetic acid, THF, H_2O, and 85% phosphoric acid (40:20:10:1) (55 °C, 4 h, 67%).



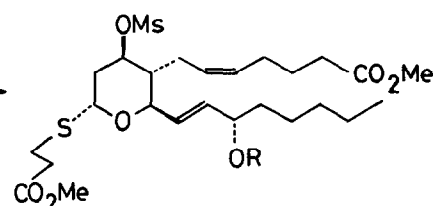
4 R = H
5 R = Bz



6 R^1 = H , R^2 = OMe
7 R^1 = Ms , R^2 = OH



8



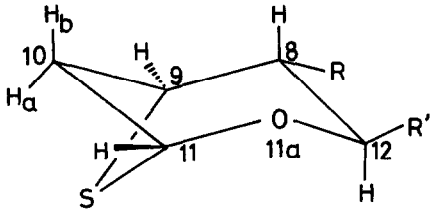
9 R = H
10 R = $SiPh_3$

The next problem was the introduction of a functionalized thiol into the system with proper stereochemistry. This was realized by reaction of 7 with methyl 3-mercaptopropionate[3] (4 equiv) in the presence of boron trifluoride etherate (1.3 equiv) (dichloromethane, 0 °C, 15 min) to provide 8 as an epimeric mixture at C_{11} in 88% yield. Although these isomers were inseparable in this step, removal of the benzoyl group (sodium methoxide, methanol, 25 °C, 6 h) gave two products which were separable by column

chromatography on silica gel (9[6] :62%, C_{11}-isomer[7] :20%). The compound 9 was transformed into the corresponding triphenylsilyl ether 10[6] (triphenylsilyl chloride, pyridine, 0 °C, 30 min, 80%).

The stage was now set for the construction of the desired bicyclic system. After numerous attempts to form the thietane ring by intramolecular attack of sulfur anion liberated with base,[8] we found that the use of sodium bis(trimethylsilyl)amide [$NaN(TMS)_2$] was the most effective. Reaction of 10 with 2 equiv of $NaN(TMS)_2$ in benzene at 60 °C for 1 h followed by addition of hexamethylphosphoric triamide (1.5 equiv) and then stirring at 70 °C for 20 min afforded the desired bicyclic compound 3[6,9] in 36% yield (51% conversion yield).[10] Finally the compound 3 was treated with tetra-n-butylammonium fluoride (2 equiv) (THF, 0 °C, 1 h) to provide cleanly the final product 2.[6,11]

Some valuable information on the bicyclic system was obtained from NMR studies on 2 and 3. Examination of their molecular models shows that dihedral angles between C_9-H and C_{10}-H_b and between C_{10}-H_b and C_{11}-H are approximate 90°, respectively. As expected, the NMR spectrums of 2 and 3 (200 MHz, $CDCl_3$) exhibit C_{10}-H_b as a doublet coupled to C_{10}-H_a (J = 9.5 Hz). In addition, a long-range coupling between C_9-H and C_{11}-H was observed (J = 5 Hz).[12]



J Value (Hz)

$J_{8,9} = 1$, $J_{8,12} = 8$, $J_{9,10a} = 5$

$J_{9,10b} = 0$, $J_{9,11} = 5$, $J_{10a,10b} = 9.5$

$J_{10a,11} = 3$, $J_{10b,11} = 0$

Preliminary experiments on biological activities show that the analogue 2 possesses potent biological activities (e.g. contracting dose on rat aorta strip, CD_{50}: 10^{-7} M).

References and Notes

1. M. Hamberg, J. Svensson, and B. Samuelsson, Proc. Natl. Acad. Sci. U.S.A 72, 2994 (1975).
2. For some carbon analogues, see T. K. Schaaf, D. L. Bussolotti, M. J. Parry, and E. J. Corey, J. Am. Chem. Soc. 103, 6502 (1981) and references cited therein. For some sulfur analogues, see S. Kosuge, N. Hamanaka, and M. Hayashi, Tetrahedron Lett. 22, 1345 (1981). S. Ohuchida, N. Hamanaka, and M. Hayashi, Ibid. 22, 1349 (1981). Idem, Ibid. 22, 5301

(1981).
3. S. Ohuchida, N. Hamanaka, and M. Hayashi, J. Am. Chem. Soc. 103, 4592 (1981).
4. W. P. Schneider and R. A. Morge, Tetrahedron Lett. 3283 (1976).
5. A. K. Bose, B. Lal, W. A. Hoffman, and M. S. Manhas, Tetrahedron Lett. 1619 (1973).
6. Partial spectral data. 9: NMR(200 MHz, $CDCl_3$) δ 5.87 (dd, J = 15 and 6 Hz, 1 H), 5.68 (dd, J = 15 and 6 Hz, 1 H), 5.45 (m, 3 H), 4.91 (dt, J = 5 and 10 Hz, 1 H), 4.43 (dd, J = 10 and 6 Hz, 1 H), 4.15 (m, 1 H), 3.71 (s, 3 H), 3.68 (s, 3H), 3.01 (s, 3 H); IR (neat) 3500, 1730, 1430, 1350, 1240, 1170, 970, 930, 850 cm^{-1}; mass (m/e) 468 (M^+-MsOH), 450, 445, 349, 331. 10: NMR (200 MHz, $CDCl_3$) δ 7.62 (m, 6 H), 7.39 (m, 9 H), 5.82 (dd, J = 15 and 6 Hz, 1H), 5.54 (dd, J = 15 and 7 Hz, 1H), 5.39 (m, 3 H), 4.89 (dt, J = 5 and 10 Hz, 1 H), 4.38 (m, 2 H), 3.67 (s, 3 H), 3.66 (s, 3 H), 3.01 (s, 3 H); IR (neat) 1730, 1585, 1420, 1350, 1240, 1170, 1100, 1040, 970, 930, 850, 740, 700 cm^{-1}; mass (m/e) 726 (M^+-MsOH), 702, 606. 3: NMR (200 MHz, $CDCl_3$) δ 7.66 (m, 6 H), 7.41 (m, 9 H), 5.85 (dd, J = 15 and 6 Hz, 1 H, C_{13}-H), 5.63 (dd, J = 15 and 6 Hz, 1 H, C_{14}-H), 5.43, 5.27 (each m, 2 H, $C_{5,6}$-H), 5.36 (dd, J = 5 and 3.5 Hz, 1 H, C_{11}-H), 4.59 (dd, J = 8 and 6 Hz, 1 H, C_{12}-H), 4.36 (br q, J = 6 Hz, 1 H, C_{15}-H), 3.68 (s, 3 H, OMe), 3.49 (ddd, J = 9.5, 5, and 1 Hz, 1 H, C_{10}-H_a), 3.31 (dt, J = 1 and 5 Hz, 1 H, C_9-H), 2.29 (t, J = 6.5 Hz, 2 H, C_2-H), 1.99 (d, J = 9.5 Hz, 1 H, C_{10}-H_b), 0.81 (t, J = 6.5 Hz, 3 H, C_{20}-H); IR (neat) 1730, 1580, 1420, 1240, 1110, 1010, 970, 850, 730, 700 cm^{-1}. 2: NMR (200 MHz, $CDCl_3$) δ 5.89 (dd, J = 15 and 6 Hz, 1 H, C_{13}-H), 5.78 (dd, J = 15 and 6 Hz, 1 H, C_{14}-H), 5.44, 5.33 (each m, 2 H, $C_{5,6}$-H), 5.37 (dd, J = 5 and 3 Hz, 1 H, C_{11}-H), 4.70 (dd, J = 8 and 6 Hz, 1 H, C_{12}-H), 4.18 (br q, J =6 Hz, 1 H, C_{15}-H), 3.69 (s, 3 H, OMe), 3.55 (ddd, J = 9.5, 5, and 1 Hz, C_{10}-H_a), 3.40 (dt, J = 1 and 5 Hz, 1 H, C_9-H), 2.31 (t, J = 7 Hz, 2 H, C_2-H), 2.10 (d, J = 9.5 Hz, 1 H, C_{10}-H_b), 0.89 (t, J = 6 Hz, 3 H, C_{20}-H); mass (m/e) 382 (M^+), 364, 349.
7. The anomeric proton (C_{11}-H) was observed as a double doublet (J = 12 and 2 Hz) at δ 4.59.
8. Potassium tert-butoxide[3] in hexamethylphosphoric triamide which was used in the construction of 2,6-dithiabicyclo[3.1.1]heptane skeleton gave only a trace of the desired product.
9. This compound was very sensitive to acid. Therefore silica gel for TLC was treated with 5% triethylamine-ether solution prior to use.
10. The starting material (30%) was recovered.
11. Many trials to hydrolyze the methyl ester in 2 with base resulted in failure because the thietane ring opened. That will be reported in detail.
12. In the case of 1 (200 MHz, $CDCl_3$), the value of $J_{9,11}$ was 4 Hz.[3]

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