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SYNTHESIS OF THROMBOXANE A_2 ANALOG DL-(9,11),(11,12)-DIDEOXA-(9,11)-METHYLENE-(11,12)-EPITHIO-THROMBOXANE A_2 METHYL ESTER

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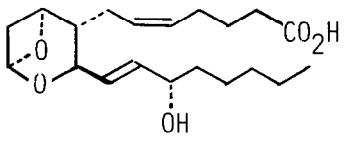
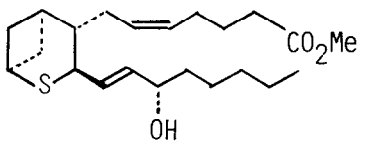
Summary: A synthesis of the thromboxane A_2 analog, dl-(9,11),(11,12)-dideoxa-(9,11)-methylene-(11,12)-epithio-thromboxane A_2 methyl ester 2, is described.

Thromboxane A_2 (TXA_2) 1[1], which was discovered in the metabolites of arachidonic acid in human platelets, is a potent inducer of platelet aggregation and contraction of vascular and bronchial smooth muscle. However, this substance is very unstable in spite of its important biological actions. That has urged a number of chemists to synthesize the stable analogs possessing biological activities.

In the previous paper, we have reported the synthesis of the dimethylene analog of TXA_2[2] . Furthermore, some analogs have been also reported[3] . In the particularly unstable prostaglandins, e.g. PGH_2 or PGI_2, the analogs, in which the oxygen atoms in the chemically unstable moieties were replaced by methylene groups, nitrogen atoms and/so sulfur atoms, possessed the chemical stabilities and the interesting biological activities[4]. We would like to report here the synthesis of TXA_2 analog 2, in which the two oxygen atoms in the bicyclic rings were replaced by a methylene group and a sulfur atom[5].



TXA_2 1



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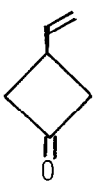
The vinylcyclobutanone 3[6] was reduced with $NaBH_4$ in MeOH to afford cis-alcohol 4(90%), which was converted to the trans-vinyl ester 5 by using diethyl azodicarboxylate-triphenylphosphine-benzoic acid[7] in THF at 0° [87%, ν 1730,1640,900,m/e 202]. After oxidative cleavage of the olefinic double bond with $NaIO_4$-OsO_4, Jones oxidation of the resulted aldehyde followed by esterification with diazomethane gave the diester 6 [70%, ν 1740, δ 5.36(1H,

quintet, J=7Hz),3.68(3H,s),m/e 234]. The diester 6 was transformed into the mesylate 7 in two steps; 1) K_2CO_3-MeOH, 2) MsCl-Et_3N [86%, ν 1735, δ 3.73(3H,s)]. The mesylate 7 was treated with sodium 2-mercaptoacetoaldehyde diethylacetal (2eq) in DMSO at 50° to afford the compound 8 [68%, ν 1730, δ 4.56(1H,t,J=5.5Hz), 2.69(2H,d,J=5.5Hz), m/e 262]. The ester group in 8 was reduced with i-Bu_2AlH to the corresponding aldehyde, which was condensed with dimethyl malonate in the presence of AcOH-pyrrolidine to provide the compound 9 [87%, ν 1730, 1640, δ 7.1(1H,dd,J=12,9Hz),m/e 346].

After deprotection of the diethylacetal in 9, the intramolecular Michael reaction of the resulted aldehyde 10 was attempted. This cyclization was unsuccessful under several conditions. However, stirring of 10 with a catalytic amount of pyrrolidin-AcOH(2:3) in benzene at rt was effected to give the bicyclic compound 11 [36%, ν 1730, δ 9.49(1H,d,1Hz),3.73(6H ,s),m/e 272], accompanied with the compound 12[8] [14%, δ 9.30(1H,s),7.30(1H,d,J=6Hz), m/e 140].

The compound 11 was condensed with tri-butyl-2-oxoheptylphosphorane[9] to form the enone 13 [74%, δ 6.63(1H,dd,J=15,9Hz),6.19(1H,d,J=15Hz)],of which reduction with $NaBH_4$ gave two allylic alcohols as a diastereomeric mixture. The hydroxy group was protected with THP without separation of the mixture to give the compound 14. The compound 14 was converted to the corresponding half ester with aqueous NaOH, and then heated in quinoline at 160° for 0.5 h to furnish the compound 15 [72% from 14, ν 1735, δ 5.55(2H,m),4.62(1H,m),3.65 (3H,s),m/e 294 (M-HOTHP)]. The compound 15 was reduced by i-Bu_2AlH to the aldehyde, of which Wittig reaction with the ylide prepared from 5-triphenylphosphoniopentanoic acid[10], and then treatment with diazomethane gave the compound 16 [77%, ν 1735, δ 5.45(4H,m),4.55(1H,m),3.70(3H,s),m/e 464]. Finally, after removal of THP group, separation of the diastereomers by column chromatography on silica gel provided the compound 2 and 17 [40% and 20%, respectively; 2 ν 3450, 1735, 965, δ 5.63(2H,m),4.12(1H,m),3.68(3H,s), 3.14(1H,m), m/e 380 ;17 ν 3500,1730,960, δ 5.61(2H,m),5.40(2H,m),4.11(1H,m), 3.67(3H,s),3.13(1H,m),m/e 380].

The compounds 2 and 17 showed the moderate contractile activities on the isolated rat aorta [2; CD_{50} $5X10^{-7}$ g/ml, 17; CD_{25} 10^{-5} g/ml]. However, both compounds did not show any aggregation activities of human platelets.



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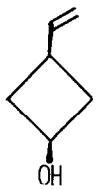

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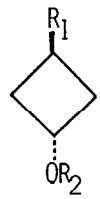
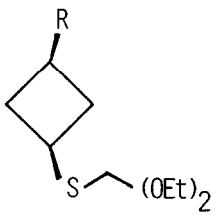


5 R_1=CH=CH_2, R_2=Bz

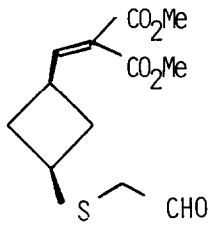
6 R_1=CO_2Me, R_2=Bz

7 R_1=CO_2Me, R_2=OMs



8 R=CO_2Me

9 R=CH(CO_2Me)(CO_2Me)



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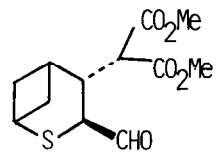

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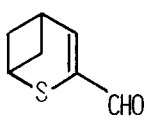

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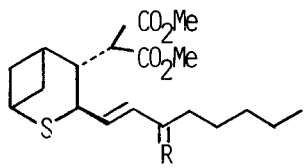
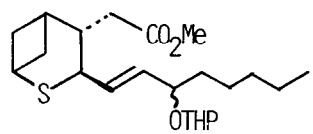


13 R=O

14 R=H,OTHP



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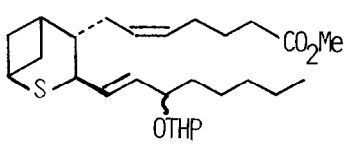

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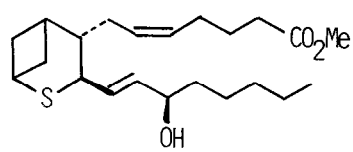

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REFERENCES AND NOTES

1. B.Samuelsson, M.Goldyne, F.Gromström, S.Hammarström and C.Malmsten, Am. Rev. Biochem., 47, 997 (1978) and refereces cited.
2. S.Ohuchida, N.Hamanaka and M.Hayashi, Tetrahedron Lett., 3661 (1979).
3. M.F.Ansell, M.P.L.Caton, M.N.Palfreyman and K.A.J.Stuttle, Tetrahedron Lett., 4497 (1979); K.C.Nicolaou, R.L.Magolda and D.A.Claremon, J. Am. Chem. Soc., 102, 1404 (1980); E.J.Corey, J.W.Pouder and P.Ulrich, Tetrahedron Lett., 137 (1980); K.M.Maxey, and G.L.Bundy, ibid, 445 (1980).
4. See (PGH_2 analogs) K.C.Nicolaou, G.P.Gasic and W.E.Barnette, Angew. Chem. Intern. Ed., 17, 293 (1978) and references cited; B.M.Trost, J.M.Timko and J.L.Stanten, J. Chem. Soc. Chem. Commun., 436 (1978); E.J.Corey, H.Niwa, M.Bloom and P.W.Ramwell, Tetrahedron Lett., 671 (1979); (PGI_2 analogs) K.Shimoji, Y.Arai and M.Hayashi, Chemistry Lett., 1375 (1978) and references cited.; D.R.Morton,Jr. and F.C.Brokaw, J. Org. Chem., 44, 2880 (1979); Y.Konishi, M.Kawamura, Y.Arai and M.Hayashi, Chemistry Lett., 1437 (1979) and references cited; G.L.Bundy and J.M.Baldwin, Tetrahedron Lett., 1371 (1978).
5. In the accompanying paper, we report the synthesis of the other methylene-sulfur analog of TXA_2.
6. L.Ghosez, R.Montaigue, A.Roussel, H.Vanlierde and P.Mollet, Tetrahedron, 27, 615 (1971).
7. A.K.Bose, B.Lal, W.A.Hoffman and M.S.Manhas, Tetrahedron Lett., 1619 (1973).
8. When NaOMe was used as a base, the product was the compound 12.
9. N.Finch, L.D.Vecchia, J.J.Fitt, R.Sephani and I.Vlattas, J. Org. Chem., 38, 4412 (1973).
10. E.J.Corey, N.M.Weinshenker, T.K.Schaaf and W.Huber, J. Am. Chem. Soc., 91, 5675 (1969).

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