Tetrahedron Letters, Vol. 22, No. 14, pp 1349 - 1352, 1981
Printed in Great Britain

0040-4039/81/141349-04$02.00/0

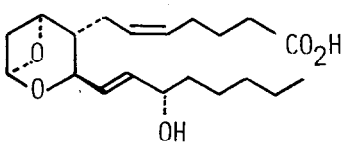
SYNTHESIS OF THROMBOXANE A_2 ANALOG DL-(9,11),(11,12)-DIDEOXA-(9,11)-EPITHIO-(11,12)-METHYLENE-THROMBOXANE A_2

Shuichi Ohuchida, Nobuyuki Hamanaka* and Masaki Hayashi
Research Institute, ONO Pharmaceutical Co.,Ltd.
Shimamoto-cho, Mishima-gun, Osaka 618, Japan

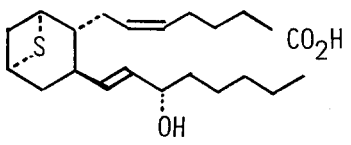
Summary: A synthesis of the thromboxane A_2 analog, dl-(9,11),(11,12)-dideoxa-(9,11)-epithio-(11,12)-methylene-thromboxane A_2 is described.

In the preceding paper, we have already reported the synthesis of the thromboxane A_2 (TXA_2) analog, (9,11)-methylene-(11,12)-epithio-TXA_2 methyl ester[1]. In this paper, we would like to describe the synthesis of the other methylene-sulfur analog of TXA_2, (9,11)-epithio-(11,12)-methylene-TXA_2 1.

Diels-Alder reaction of methyl trans-4-oxobutenoate[2] with butadiene in the presence of stannic chloride[3] in CH_2Cl_2 at 0° for 1h afforded the aldehyde 2 [70%, δ 9.72(1H,d,1Hz),5.72(2H,m),3.72(3H,s), m/e 168]. The aldehyde 2 was converted into the nitrile 3 by the following reactions ($NaBH_4$ in MeOH; NaCN in HMPA) [61%, ν 2270,1740, m/e 179]. After hydrolysis of the ester group in 3 with aqueous KOH, iodolactonization of the resulted carboxylic acid with $KI-I_2-KHCO_3$ followed by dehydroiodination using DBU in benzene gave the lactone 4 [60%, ν 2250,1780, δ 6.43(1H,dd,9,6Hz),5.81(1H,d,9Hz),4.83(1H,t,5Hz), m/e 163]. The lactone 4 was reduced with $NaBH_4$ to the corresponding diol, which was protected as THP ether, and then the cyano group was hydrolyzed to the carboxylic acid 5 [70%, ν 3220(br),1718, m/e 270].



TXA_2



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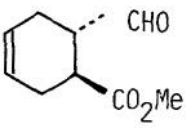
The compound 5 was transformed by iodolactonization under the above condition into the iodolactone, which was reduced with n-Bu_3SnH to provide 6 [80%, ν 1785, δ 4.70(2H,m),4.54(1H,m) m/e 354]. Reduction of the lactone 6 with i-Bu_2AlH followed by Wittig reaction with ylide derived from 5-triphenylphosphoniopentanoic acid[4], and then esterification with CH_2N_2 furnished 7 [94%, ν 3745,1745, δ 5.52-5.34(2H,m),3.67(3H,m), m/e 454]. Since inversion of

the hydroxyl group at C_9 in 7 with diethyl azodicarboxylate-triphenylphosphine —formic acid[5] was unsuccessful, the compound 7 was oxidized to the ketone by PCC[6] (88%), and then reduced with $NaBH_4$ to give the compound 8 as a main product (70%), accompanied with 7 (30%). The compound 8 was converted to the mesylate, and replacement of the mesylate by NaSAc in DMSO followed by removal of two THP groups afforded the diol 9 [30% from 8, ν 3360,1730,1688, δ 3.67 (3H,s),2.33(3H,s), m/e 344].

The most crucial problem in this synthesis was the constraction of thiabicyclo[3.1.1]heptane skeleton(tietane). We attempted the transformation of 10 to the thietane. The compound 10 was prepared from the diol 9 in two steps (selective benzoylation and then mesylation). Stirring of 10 with NaOMe (3 eq) in MeOH at 55° for 0.5h afforded the desired thietane compound 11.[7] But the compound 11 was very unstable and decomposed on silica gel during column chromatography. The instability of this compound is probably caused by the presence of C_{13}-hydroxy group. Therefore, the formation of the thietane should be done after the extention of ω- chain.

The compound 9 was converted to 12 by the sequent procedures (Ph_3SiCl-Et_3N ; DHP-pTsOH; KF in HMPA)[68%, ν 3450, δ 3.67(3H,s),2.33(3H,s), m/e 428]. The compound 12 was oxidized with Collins reagent to the aldehyde, which was treated with the sodium salt of dimethyl 2-oxoheptylphosphonate[4] to yield the enone 13 [71%, ν 1740,1695,1675,1630, δ 6.61(1H,dd,J=16 and 9 Hz), 6.08(1H,d, J=16Hz), m/e 522]. Reduction of the enone with $NaBH_4$ in MeOH gave a mixture of two diastereomeric allylic alcohols 14 and 15 [46% and 49%, respectively, 14; ν 3450, δ 5.33—5.12 (4H,m),3.67(3H,s),2.99(3H,s), m/e 524]. The compound 16 was produced from 14 in three steps:(1) acetylation, (2) removal of THP group and (3) mesylation of the resulted alcohol [65%, δ 3.67(3H,s),2.04(3H,s), 2.35(3H,s),2.04(3H,s), m/e 560]. Treatment of 16 with NaOMe at 55° for 0.5h formed cleanly the thietane compound 17 [94%, ν 3450,975, δ 3.68(3H,s),3.38 (3H,m),2.86(1H,m), m/e 380]. This compound was stable under ordinary conditions. Finally, the compound 17 was hydrolyzed with 5% aqueous KOH to produce the title compound 1 quantitatively [ν 3400(br),1707,980, δ 5.64(2H,m), 5.40(2H,m),4.16(1H,m),3.40(2H,m), m/e 366]. Similarly, the C-15 epimer 18 was obtained from 15 [ν 3370(br),1705,980, δ 5.60(2H,m),4.15(1H,m),3.38(2H,m), m/e 366].

Both compounds 1 and 18 showed the potent contractile activities on the isolated rat aorta. The values of their CD_{50} were $5X10^{-9}$g/ml and 10^{-7}g/ml, respectively. Additionally, the compound 1 induced the aggregation in human platelets-rich plasma at 10^{-6} Mol, however, the compound 18 did not show aggregation activities.



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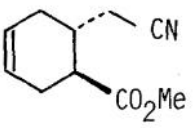

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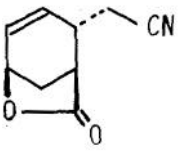

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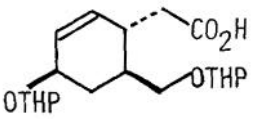

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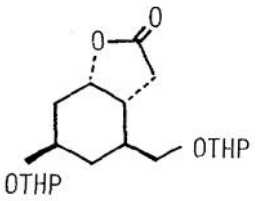

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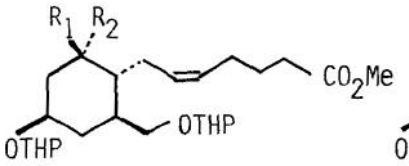
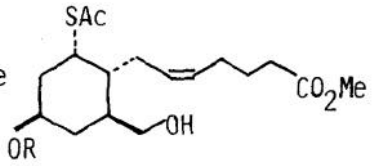


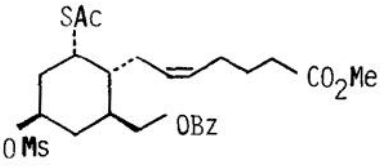
7 R_1= H, R_2= OH

8 R_1= OH, R_2= H



9 R= H

12 R= THP



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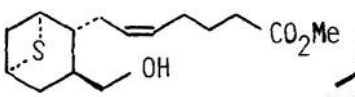

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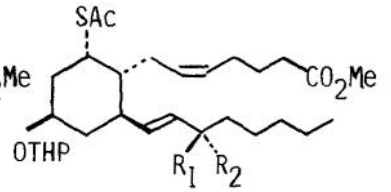
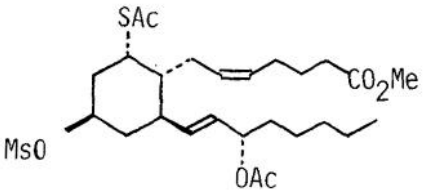


13 R_1, R_2= O

14 R_1=H , R_2=OH

15 R_1=OH, R_2=H



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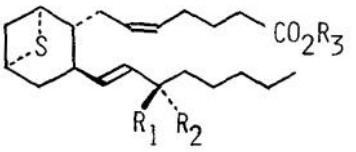

17 R_1=H, R_2=OH, R_3=Me

18 R_1=OH, R_2=H, R_3=H

REFERENCES AND NOTES

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(Received in Japan 11 December 1980)