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SYNTHESIS OF THROMBOXANE A_2 ANALOG, DL-(9,11)-METHANO-(11,12)-AMINO THROMBOXANE A_2

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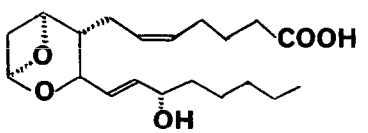
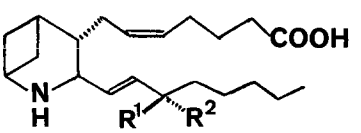
Abstract: A synthesis of nitrogen containing thromboxane A_2 analog, dl-(9,11)-methano-(11,12)-amino thromboxane A_2 (1) is described.

Thromboxane A_2 (TXA_2) is an extremely unstable substance possessing very important biological activities (platelet aggregation and vasoconstriction).[1] In conection with our studies directed toward the synthesis of stable and biologically active TXA_2 analogs,[2a,b] we wish to report the synthesis of new analogs 1a,b in which two oxygen atoms in the bicyclic system of TXA_2 were replaced by methylene and amino groups. These compounds are the first analogs which have a nitrogen atom in the bicyclic system.



TXA_2



1a: R^1= H, R^2= OH
1b: R^1= OH, R^2= H

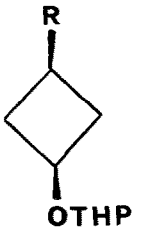
The compound 2[2a] was chosen as a starting material. This compound was converted to the aldehyde 3 with OsO_4-$NaIO_4$, which, without purification, was treated with $Ph_3P{=}CHCO_2Et$ to afford the α,β-unsaturated ester 4 [80% from 2, δ 6.86 (1H, dd, J=16, 5.5 Hz) and 5.66 (1H, d, J=16 Hz)]. Reduction of the ester group in 4 with DIBAH at -70°C in toluene (73%) followed by heating of the resulting allylic alcohol 5 with triethylorthoacetate (7eq) in the presence of a catalytic amount of pivalic acid at 160°C for 1 hr gave the Claisen rearrangement product 6 [92%, δ 5.53 (1H,m), 4.93 (2H,m) and 3.52 (3H, m)]. After epoxidation of the double bond in 6 with m-CPBA, the epoxide was ring-opened with PhSH and Et_3N in MeOH and then lactonization with acid provided the γ-lactone 7 [63% from 6, ν 1780, δ 7.20 (5H, m), 4.50 (1H, m) and 3.12 (2H, m), m/e 362]. The cis-cyclobutanol moiety in 7 was converted to trans-configuration into 8 by the following reactions: 1) hydrolysis of THP ether; 2) inversion of the corresponding alcohol with $(=N\text{-}CO_2Et)_2$-Ph_3P-HCO_2H;[3] 3) hydrolysis of the

resulting formate; 4) protection as a THP ether. The lactone 8 was reduced to the corresponding hemiacetal with DIBAH, of which Wittig reaction with the ylide prepared from 5-triphenylphosphoniopentanoic acid followed by treatment with diazomethane provided the compound 9 [63%, ν 3500, 1740, δ 7.18 (5H, m), 5.28 (2H, m), 4.48 (1H, m) and 3.61 (3H, s), m/e 462].

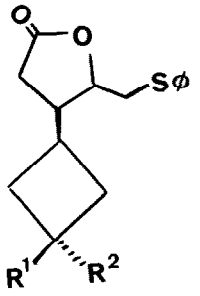
Introduction of an amino group into the system and construction of 2-azabicyclo[3,1,1]heptane skeleton were achieved as follows. The compound 9 was transformed into the compound 10 in four steps: 1) MsCl-Et_3N; 2) NaN_3, HMPA, 40°C for 50 hr; 3) hydrolysis of THP ether; 4) MsCl-Et_3N [27%, ν 2100, 1730, δ 7.23 (5H, m), 5.26 (2H, m), 4.85 (1H, m), 3.56 (3H, s) and 2.90 (3H, s), m/e 481]. The azide group in 10 was smoothly converted to the corresponding amine 11 (90%) using $CrCl_2$.[4] After some attempts to form the desired bicyclic system, treatment of 11 with NaH in DMF (40°C for 34 hr) gave the bicyclic compound which was treated with $(CF_3CO)_2O$[5] to provide the desired amide 12 after purification by SiO_2 chromatography [30%, ν 1730, 1680, δ 7.35 (5H, m), 5.35 (2H, m), 4.52 (1H, m), 4.01 (1H, m) and 3.65 (3H, s), m/e 455]. The sulfur group in 12 was oxidized with $NaIO_4$ to the sulfoxide 13 (88%: ν 1730, 1680, 1040, m/e 471), which was transformed into the compound 14 by Pummerer reaction with $(CF_3CO)_2O$[6] followed by treatment with aqueous $NaHCO_3$ [14: δ 9.26 (1H, d), 5.35 (2H, m) and 3.60 (3H, s), m/e 361].

We deduced the stereochemical relationship expressed by 12 with the two vicinal carbon appendages trans to one another from inspections of molecular model. In addition, the compound 14 produced from the above reactions obviously possesses the trans configuration since treatment of 14 with potassium carbonate under conditions sufficient to cause epimerization of aldehydes dose not effect epimerization. These observations are the same as a case of (11,12)-oxa TXA_2 analogs.[7]

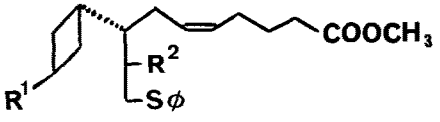
The compound 14, which was moderately unstable, was immediately condenced with tri-butyl-2-oxoheptylphosphorane to provide the enone [15: 48% from 12, ν 1730, 1680, 1625, δ 6.76 (1H, dd, J=6, 17 Hz), 6.18 (1H, d, J=17 Hz), 4.56 (1H, m, C_{12}-H) and 4.26 (1H, m, C_{11}-H), m/e 457]. Reduction of the ketone group in 15 with $NaBH_4$ gave two allylic alcohols as a diastereomeric mixture, which were separated by reverse-phase chromatography.[8] The less polar compound was tentatively assigned to α-isomer 16 and more polar to 17 by comparison between the biological activities coupled with mobility on reverse-phase TLC plate allowing for the observation in the fields of prostaglandins [16; 38% and 17 41%, both compounds showed very similar spectra: ν 3500, 1730, 1680, 980, δ 5.61 (2H, m), 5.43 (2H, m), 4.49 (2H, m), 4.09 (1H, m) and 3.66 (3H, s), m/e 459]. Finally, the compounds 16 and 17 were hydrolyzed with 0.1N aqueous LiOH in MeOH (40°C for 2 hr) to produce cleanly the desired compounds 1a and 1b, respectively [1a: ν 3600-2400, 1705, 980, δ 6.22 (1H, m), 5.90 (2H, m), 5.40 (2H, m), 4.20 (1H, m) and 3.85 (2H, m), m/e 349].



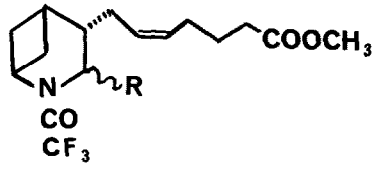
2: R= $CH=CH_2$
3: R= CHO
4: R= $CH=CHCO_2Et$
5: R= $CH=CHCH_2OH$
6: R= $CHCH_2CO_2CH_3$ (CH=CH_2)



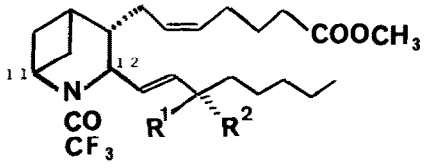
7: R^1= OTHP, R^2= H
8: R^1= H, R^2= OTHP



9. R^1= OTHP, R^2= OH
10: R^1= OMs, R^2= N_3
11: R^1= OMs, R^2= NH_2



12. R= $CH_2SC_6H_5$
13: R= $CH_2S(O)C_6H_5$
14 R= CHO



15: R^1= R^2= O
16: R^1= H, R^2= OH
17: R^1= OH, R^2= H

The compound 1a showed the contractile activity on an isolated rat aorta [CD_{50} 3×10^{-8} g/ml]. However, the compound 1b did not show any contractile activities. In addition, both compounds showed no aggregation effect on human platelets.

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5. When acetyl group or other protecting group was used, the deprotection of the amino group in the compounds 16 and 17 were unsuccessful.
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8. TLC: R_f values of these diastereomers are 0.43 and 0.50, respectively (silica gel $60F_{254}$ silanised TLC plate, Merk, developed three times with 1% EtOH in benzene).

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