Tetrahedron Letters,Vol.25,No.9,pp 919-922,1984
Printed in Great Britain

0040-4039/84 $3.00 + .00

THE SYNTHESIS OF A 3-DIAZOBICYCLO[2.2.1]HEPTAN-2-ONE INHIBITOR OF THROMBOXANE A_2 SYNTHETASE

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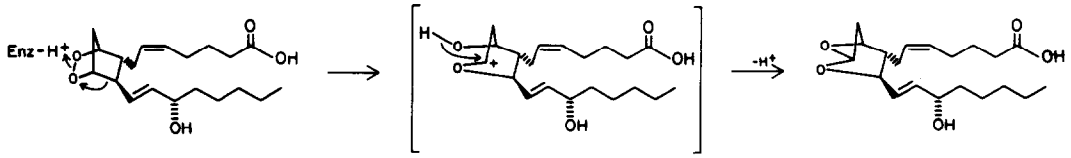
Abstract: The synthesis of a PGH_2 analog, 5-endo(2Z), 6-exo(1E)-3-diazo-5-(7-hydroxy-2-heptenyl)-6-(3-hydroxy-1-octenyl)bicyclo[2.2.1]heptan-2-one 2 is described.

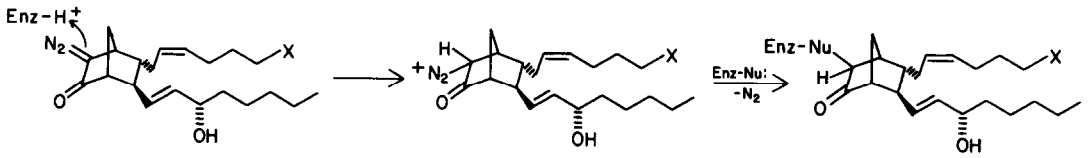
Thromboxane A_2 (TXA_2) is a physiologically important metabolite of arachidonic acid and may play a significant role in the development of several diseases.[1] If so, compounds which inhibit the synthesis of TXA_2 may be important therapeutic agents. This paper describes the synthesis of the diazoketone 2 which was designed to be an enzyme-activated, irreversible inhibitor of TXA_2 synthetase.

Although the mechanism for the isomerization of PGH_2 to TXA_2 is not known, the reaction is assumed to be initiated by a regiospecific protonation of the peroxy bridge which induces a Wagner-Meerwein type rearrangement (Scheme I). Subsequent loss of the initiating electrophile affords TXA_2. Consideration of this mechanism led us to propose the diazoketone 1 as a potential suicide inhibitor of TXA_2 synthetase. Protonation of 1 by the enzyme in a manner analogous to that of the normal substrate would create a reactive alkylating reagent which could trap an enzyme-bound nucleophile and thereby inactivate the enzyme (Scheme II). The utility of diazocarbonyl compounds as suicide inhibitors has been demonstrated for the natural product azaserine[2a] and for a diazosteroid.[2b,c] In both cases these compounds are believed to function in a manner similar to that proposed for 1.



Scheme I

As a matter of synthetic and practical expediency we chose the alcohol 2 as our target to test this proposal. Since several procedures exist for the introduction of a diazo moiety alpha to a ketone, we expected that a suitably protected form of the ketone 15 would serve as a precursor to 2.



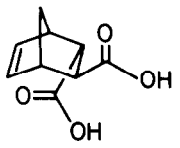
1 X=CO_2H
2 X=CH_2OH

Scheme II

Oxidative cyclization of the diacid 3[3] employing peroxyformic acid followed by esterification affords lactone 4[4] (85%, m.p. 141°-142°). The RuO_4-$NaIO_4$ oxidation of 4[5] proceeds cleanly in aqueous acetone to a mixture of ketone 5[4] and its hydrate (90%). Reduction (zinc, acetic acid) of keto-lactone 5 to yield 6[4] serves to differentiate the carboxyl moieties and thereby facilitate elaboration of the two side chains. The ketone was then protected as the dithiolane 7[4] ($BF_3 \cdot Et_2O$, ethanedithiol, acetic acid, 65% from 5, m.p. 157-159°). Homologation of the acid 7 to the nitrile 8,[4] is best accomplished using a three step sequence of reduction ($BH_3 \cdot SMe_2$, THF), tosylation (TsCl, pyridine), and nucleophilic displacement (KCN, DMSO, 70°, 24 hr., 61% yield from 7 following HPLC, m.p. 69-72°). The aldehyde 9[4] derived from 8 [1) NaOH-MeOH, 2) $BH_3 \cdot SMe_2$-THF, 3) Swern oxidation, 78%[6], m.p. 96-97°] undergoes the Emmons-Wadsworth reaction with dimethyl 2-oxoheptylphosphonate (NaH, glyme, 0°, 15 min.) to afford the pure trans enone 10[4] as an oil in 89% yield following HPLC purification to remove a few percent of the cis isomer. Reduction of the enone employing $NaBH_4$-$CeCl_3$ in methanol[7] provides a mixture of diastereomeric alcohols which were separated by HPLC (44% yield of each diasteromer).[8] The higher Rf diastereomer was assigned the natural "15-S" configuration.[9] The allylic alcohol was protected as its t-butyldimethylsilyl ether (TBDMSCl, DMAP, Et_3N, DMF, 25°) and reduced with diisobutylaluminum hydride to afford the aldehyde 11[4] (70%[6]).

The remaining carbon skeleton was attached by reaction of 11 with the ylide derived from (5-hydroxypentyl)triphenylphosphonium bromide and 2 equivalents of n-BuLi in THF/HMPA (2/1) to provide the cis olefin 12[4] (80%[6]). If HMPA is not employed a 6/4 ratio of cis/trans olefins is obtained (determined by ^{13}C NMR and capillary GC). The standard conditions of DMSO-potassium t-butoxide gave 12 stereochemically pure, but in low yield. Removal of the dithiolane (MeI, $CaCO_3$, CH_3CN, H_2O, 75°, 4 hr.) affords the ketone 13[10] in 70% yield[6].

Following conversion of 13 to its bis-t-butyldimethylsilyl ether 14, we were ready to examine methods for the introduction of the diazo function. We initially planned to introduce the diazo group employing a diazo transfer reaction.[11] However reaction of the formyl ketone derived from 14 and p-toluenesulfonylazide-Et_3N in CH_2Cl_2 failed to yield isolable amounts of the desired diazoketone. Likewise the direct diazo transfer using 14 or 15 and 2,4,6-triisopropylsulfonyl azide was not successful.[12] Fortunately oxidation of the mixture of *syn* and *anti* keto-oximes 16 (prepared from 14, 10 eq. potassium t-butoxide, 4 eq. amyl nitrite, t-butanol followed by pyridinium tosylate, ethanol, 60%[6] from 13) employing chloramine (NaOCl, NH_4OH, NaOH, THF, 0°, 30 min.) affords the target diazoketone 2 [IR (film) ν 2080, 1675, 1360;



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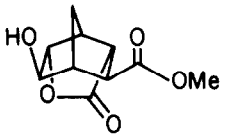

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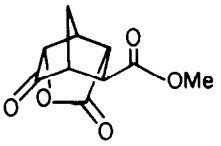

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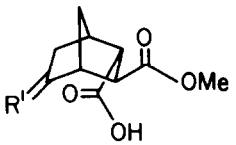
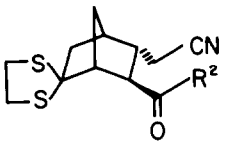
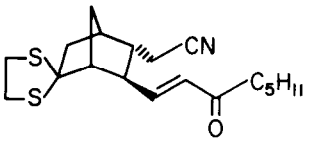


6 R' = O
7 R' = SCH_2CH_2S



8 R^2 = OMe
9 R^2 = H



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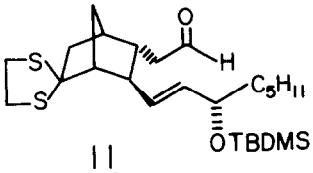

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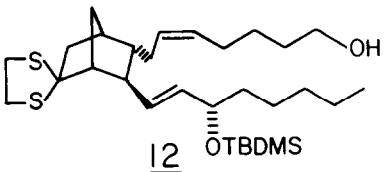

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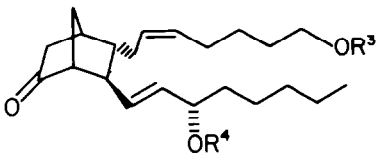
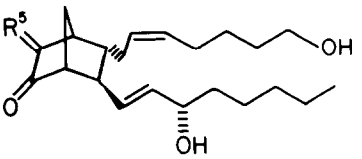


13 R^3=H, R^4=TBDMS
14 R^3=R^4=TBDMS
15 R^3=R^4=H



16 R^5=NOH
2 R^5=N_2

NMR ($CDCl_3$) δ 0.8-2.4 (m, 25H), 2.47 (br s, 1H, H_1), 3.35 (br s, 1H, H_4), 3.60 (t, 2H, J=6Hz, CH_2OH), 4.00 (m, 1H, CHOH), 5.2-5.7 (m, 4H, olefinic H)][13] in 30% yield[6].

Both compound 2 and 16 are moderately good non-time-dependent inhibitors of thromboxane synthetase(IC_{50} 20μM).[14]

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4. Structural assignment supported by NMR, IR, and correct elemental analysis.
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6. Isolated yields after purification by flash chromatography on silica gel.
7. J.-L. Luche, L. Rodriguez-Hahn and P. Crabbé, J.C.S. Chem. Comm., pp. 601 (1978).
8. The lower Rf diastereomer was converted to higher Rf diastereomer by esterification with inversion (diethyl diazodicarboxylate, triphenylphosphine, benzoic acid, THF) followed by saponification (NaOH, MeOH) in 60% yield.
9. Upon conversion to 13 the relative Rf of the diastereomers is reversed; the final product 2 is the lower Rf diastereomer. For a similar example see E.J. Corey et al., Tetrahedron Lett., pp. 737 (1976).
10. Compound 13[4] was further characterized as the diol 15.[4] The ^{13}C NMR of 15, which exhibited no significant impurities, is: ($CDCl_3$) δ 13.6, 22.2, 24.7, 25.4, 26.6, 28.6, 31.3, 31.8, 35.8, 36.9, 38.6 (two carbons), 46.2, 46.5, 56.2, 62.0, 72.0, 127.2, 130.3, 131.3, 132.8, 216.9.
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13. See P. Yates and G.F. Hambly, Can. J. Chem., 57, pp. 1656 (1979) for the characterization of related 3-diazobicyclo[2.2.1]heptan-2-ones.

14. We wish to thank Dr. T.R. Blohm and Mr. G. Schatzman for the enzyme test results.

(Received in USA 7 November 1983)