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IDENTIFICATION OF A CRUCIAL SUBSTRUCTURAL UNIT FOR THROMBOXANE A_2 RECEPTOR BINDING

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Summary: A stereospecific synthesis of the 9α,10α-epoxyprostanoic acid derivative **3**, a potent and stable mimic of thromboxane A_2, is described.

Thromboxane A_2 (TXA_2, **1**) is produced by the activation of blood platelets as a result of various physiological stimuli. Contact of platelets with damaged walls of blood vessels causes platelet activation, TXA_2 synthesis and thrombus formation in a process which initiates the repair of blood vessels. On the other hand, platelet activation and TXA_2 formation play an important role in disease states such as angina and myocardial infarction which are believed to be initiated by the rupture of atherosclerotic plaques as a platelet activating process. Because of the association of TXA_2 with serious conditions such as myocardial ischemia, coronary vasospasm, shock, and cell death, there has been much interest in TXA_2, TXA_2 receptors and TXA_2-antagonists.[1] In this paper we present significant new information regarding the mode of binding between TXA_2 and its receptor (the TP receptor[2]) which leads to the conclusion that there is a major binding interaction between $O_{9,11}$ and the TP receptor (quite possibly a hydrogen bond), but much less (if any) binding between $O_{11,12}$ and TP. This is consistent with earlier work in this laboratory which demonstrated that the synthetic TXA_2 analog **2** is essentially inactive.[3,4]

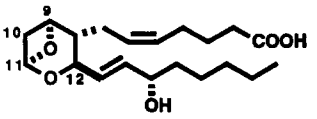
The structure of a potential new mimic of TXA_2 was derived simply from the proposition that if $O_{9,11}$ were involved in a key hydrogen bond to the TP receptor (rather than $O_{11,12}$), the 9,10-epoxyprostanoic acid **3** should be capable of similar binding. Structure **3** can be regarded as a modification of **1** in which $O_{11,12}$ has been replaced by CH_2 and the 10-CH_2 group has been extruded. Structure **3** maps very well onto TXA_2 in three dimensions with the exception that the 10-CH_2 group of **1** is missing and C(9) and C(10) are brought a little closer together. The *exo* electron pair of the oxirane oxygen of **3** is in a three-dimensional location corresponding to the *exo* long pair of $O_{9,11}$ of **1**. Epoxide **3** was synthesized from **4**, the methyl ester 15-*t*-butyldimethylsilyl ether of prostaglandin A_2 (PGA_2), which was prepared by reaction of PGA_2 with ethereal diazomethane and subsequent silylation by *t*-butyldimethylsilyl chloride (TBSCl) and imidazole in dimethylformamide (DMF) (at 23°C for 4 h, 95% yield). Reaction of **4** with neat triethylsilane in the

presence of 0.01 equiv of tristriphenylphosphine rhodium(I) chloride at 60°C for 5 h afforded, after chromatography on silica gel (SGC) using 1-5% ether in hexane as eluent, the triethylsilyl (TES) enol ether **5** (91%) as a colorless oil.[5] Bromination of **5** with 1.2 equiv of *N*-bromosuccinimide in acetonitrile at -40°C gave the bromo ketone **6** in 94% yield, R_f (SGTLC) 0.36 using 2 : 1 hexane-ether as eluent (red spot upon development with anisaldehyde as stain).[6] Reduction of **6** using sodium borohydride in methanol at 0°C for 20 min gave a single bromohydrin, **7**, (92% yield after SGC), which can be assigned configuration at C(9) and C(10) as shown on the basis of chemical data. Debromination of **7** by heating with tri-*n*-butyltinhydride in benzene at reflux provided the 9(*S*)-alcohol **8**, identified by comparison with an authentic sample of **8** and its 9(*R*)-epimer.[7,8] In addition **7** must be a *cis* bromohydrin since it affords no 9,10-epoxide upon treatment with sodium methoxide in methanol at 23°C for 12 h, but only the 9-ketone **9** (92% yield after SGC). Reduction of bromo ketone **6** with a variety of other reagents (e.g. $LiAlH(OtBu)_3$ in THF at -78°C, L-Selectride in THF at -78°C, or Et_3SiH-$ZnCl_2$ in CH_2Cl_2 at 0°C) also afforded the *cis* bromohydrin **7** instead of the isomeric *trans* bromohydrin. We were not able to find suitable conditions for the conversion of bromo ketone **6** to the 9α-hydroxy-10β-bromo (*trans*) isomer of **7**.

In view of the ready availability of the *cis* bromohydrin **7** and the difficulty of obtaining the 10-epimeric *trans* bromohydrin, the following process was developed for the conversion of **7** to the desired 9α,10α-epoxide **3**: (1) acetylation of the 9-hydroxyl group (5 equiv of Ac_2O and 2 equiv of 4-*N*,*N*-dimethylaminopyridine in CH_2Cl_2 at 23°C for 24 h; 99%); (2) S_N2 displacement at C(10) using 1.4 equiv of sodium methanethiolate in dry DMF at 23°C for 1 h (60%); (3) S-methylation using 1.5 equiv of methyl triflate in CH_2Cl_2 at 23°C for 2 h and desilylation by the addition of methanol and stirring for an additional 10 min before isolation of the product, sulfonium salt **10**; (4) treatment of crude **10** with 3 equiv of sodium methoxide in dry methanol at 23°C for 1 h to afford after isolation and SGC the methyl ester of **3** (79% yield overall from the 10β-methyl thioether); and (5) saponification of **3** methyl ester using 0.3 *M* lithium hydroxide in 5 : 1 : 1 THF-MeOH-H_2O at 23°C for 6 h to give **3** (99%).

The 9β,10β-epoxy diastereomer of **3**, epoxide **11**, was also synthesized from the *cis* bromohydrin **7**, using a novel procedure. Reaction of **7** with 3 equiv of methanesulfonic anhydride and 10 equiv of pyridine in CH_2Cl_2 at -20°C provided after SGC the corresponding 9-mesylate (88%) which upon treatment with potassium superoxide-18-crown-6 in DMSO-DMF (2 : 1) gave crude epoxide **11**, which was obtained in pure form by esterification (ethereal CH_2N_2), SGC and saponification (55%).[7]

Reaction of **5** with 2 equiv of *N*-bromosuccinimide in CH_2Cl_2 at -78°C provided, in addition to bromo ketone **6**, a dibromo ketone (ratio *ca.* 1 : 1) which was shown to be **12** on the basis of spectroscopic and chemical data. Reduction of **12** with sodium borohydride in methanol afforded a mixture of **13** and the 9α-hydroxy epimer in a ratio of 3 to 1. The configuration of **13** at C(9) was demonstrated by debromination with tri-*n*-butyltin hydride to give the 9β-alcohol **14**, identified by comparison with an authentic sample.[8,9] Treatment of the dibromo alcohol **13** with potassium carbonate in methanol at 0°C resulted in rapid conversion to the 9β,10β-epoxide **15**.[10]



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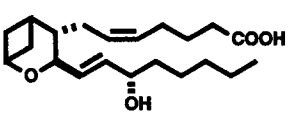

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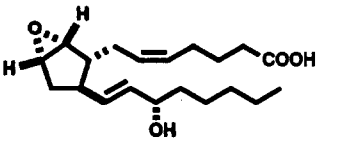

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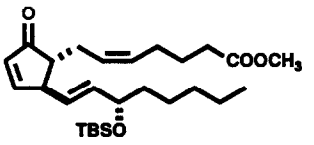

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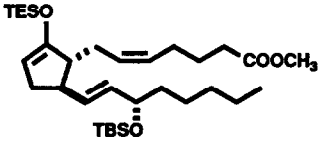

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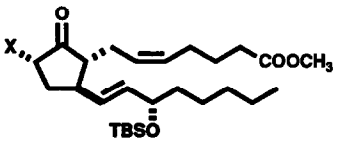

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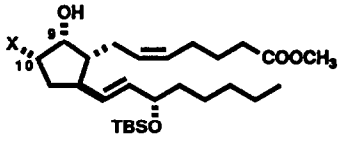
9 X = H



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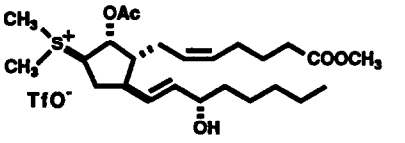
8 X = H



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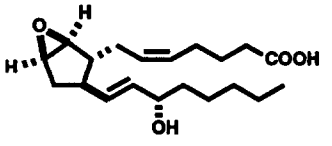

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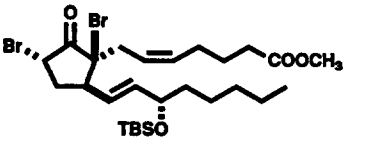

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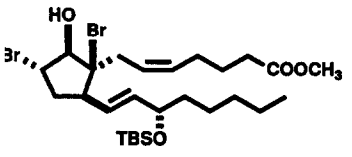

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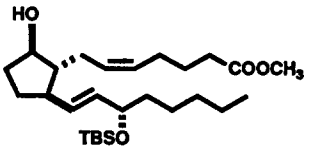

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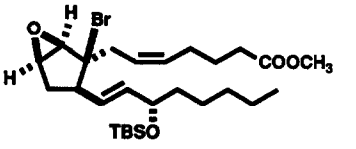

15

As we had surmised, the 9α,10α-epoxide **3** is a potent TXA_2 agonist. It binds to the TX-specific TP receptor of guinea pig aorta with a binding constant of *ca.* 10^8, comparable to that for TXA_2 itself.[11] In contrast, the hydroxy acids corresponding to the 9β,10β-epoxides **11** and **15** possess little if any TXA_2 agonist activity.

Either no binding or relatively weak binding was observed with **3** to the EP_1, EP_2 or EP_3 (PGE) receptors and likewise with the rat colon FP (PGF) receptor.[11]

Three conclusions may be drawn from the above studies. First, the binding of TXA_2 to its receptor likely involves a hydrogen bond to $O_{9,11}$, an especially basic oxygen as an acetal function in a strained ring. Second, the 9β,10β-epoxide **3** is a useful and quite stable (> 1 month at pH 7 and 25°C) TXA_2 mimic. Third, it is quite likely that the 9α,10α-epoxy cyclopentyl subunit of **3** will be a useful structural element for the design of synthetic TXA_2 antagonists.[12,13]

References and Notes

1. P. E. Cross and R. P. Dickson, *Ann. Reports. Med. Chem.*, **22**, 95 (1987).
2. See R. M. Eglen and R. L. Whiting, *CRC Handbook of Eicosanoids, Prostaglandins and Related Lipids* (CRC Press, 1989), Vol. II, P. 273 for an excellent overview of eicosanoid receptors.
3. E. J. Corey, J. W. Ponder, and P. Ulrich, *Tetrahedron Letters*, **21**, 137 (1980).
4. For interesting TXA_2 analogs with varying degrees of activity (generally significantly lower than TXA_2), see (a) S. Ohuchida, N. Hamanaka, and M. Hayashi, *Tetrahedron Letters*, **20**, 3661 (1979); (b) S. Kosuge, N. Hamanaka, and M. Hayashi, *Tetrahedron Letters*, **22**, 1345 (1981); (c) S. Ohuchida, N. Hamanaka, and M. Hayashi, *Tetrahedron Letters*, **22**, 1349 (1981); (d) S. Ohuchida, N. Hamanaka, and M. Hayashi, *J. Am. Chem. Soc.*, **103**, 4597 (1981); (e) T. K. Schaaf, D. L. Bussolotti, M. J. Parry, and E. J. Corey, *J. Am. Chem. Soc.*, **103**, 6502 (1981).
5. (a) I. Ojima, M. Nihonyanagi, T. Kogure, M. Kumaga, S. Horiuchi, and K. Nakatsugawa, *J. Orgmet. Chem.*, **94**, 449 (1975); (b) Satisfactory infrared, ^1H NMR and mass spectral data were obtained for reaction products using chromatographically purified samples which were homogeneous by SG TLC or HPLC.
6. The ^1H NMR spectrum of **6** in $CDCl_3$ showed a mutiplet due to C*H*Br at 4.31 δ. Since **6** is rather unstable it is best stored in frozen benzene below -40°C.
7. E. J. Corey, K. C. Nicolaou, and M. Shibasaki, *J. Chem. Soc. Chem. Comm.*, 658 (1975).
8. F. H. Lincoln, W. P. Schneider, and J. E. Pike, *J. Org. Chem.*, **38**, 951 (1973).
9. We have also demonstrated that the reaction of **8** (but not its C(9)-epimer) with I_2-$KHCO_3$ in CH_2Cl_2-H_2O affords an iodo ether by internal addition to the 5,6-double bond.
10. The configuration at C(8) in **13** and **15** has not been proven rigorously.
11. We thank Dr. Richard M. Eglen of the Syntex Corporation, Palo Alto, California, for these binding studies (Aug., 1989) which will be published in full elsewhere.
12. We are grateful to Dr. Richard M. Eglen and Ms. Georgina C. Harris (Syntex Corporation) for their expert quantitative study of the binding of **3** with various TP, EP and FP receptors and to Dr. Robert A. Lewis (Syntex Corporation) for helpful suggestions and advice.
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