also possible (e.g., Scheme III, R = $CH_2CMe_2CO_2Me$, 72% yield, diastereoselectivities as per Table I, entry 13) and promise to provide exceptionally convenient access to protected, optically active aldol products.

Experiments designed to further probe the scope, mechanism, and synthetic utility of this new approach to diastereoselective enol functionalization are in progress.

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Supplementary Material Available: Spectroscopic and analytical data for all new compounds and crystallographic details for the aldol products of entries 5 and 12, including ORTEP diagrams, tables of atomic coordinates, thermal parameters, bond angles, and bond lengths (32 pages). Ordering information is given on any current masthead page.

Synthesis of 10,10-Difluorothromboxane A_2, a Potent and Chemically Stable Thromboxane Agonist†

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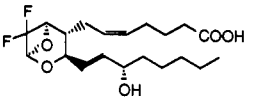
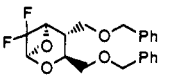
Thromboxane A_2,[1] a member of the eicosanoid family, exerts powerful contractile effects on vascular and bronchial tissues and causes aggregation of blood platelets. Its unique oxetane acetal structure suffers facile hydrolytic cleavage even at pH 7.4 ($t_{1/2}$ = 30 s) by a general acid catalyzed reaction.[2] As a result there has been much interest in synthesizing stable analogues of this important substance in order to mimic its biological properties, inhibit its biosynthesis, or serve as receptor antagonists.[3] A common feature of all these reports is that stabilization of the molecule is achieved by replacement of one or both of the acetalic oxygens by carbon or sulfur. It is the purpose of this paper to describe the first TXA_2 mimic, (+)-10,10-difluoro-TXA_2, in which the acetalic structure of TXA_2 is retained, and stabilization of the molecule is achieved solely by the electronic influence of two neighboring fluorine atoms.

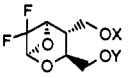
We recently described the synthesis of two model compounds possessing the 2,6-dioxa[3.1.1]bicycloheptane system present in TXA_2, in which the 7-hydrogens are replaced by fluorine.[4] The bimolecular rate constant of hydrolysis for one of these, compound **2**, was found to be 2.4×10^{-3} M^{-1} s^{-1} compared to 5.5×10^5 M^{-1} s^{-1} for TXA_2, an astonishing 10^8-fold decrease in rate. This finding permitted the prognosis that **2** and related compounds possessing this fluorinated ring system would be sufficiently stable to serve as intermediates for the synthesis of **1**. The use of **2** itself presented two major problems: (1) the two substituents on the ring are identical and (2) the compound is racemic. In spite of this we chose to proceed with **2** in the hope that the diacetate **4** derived from **2** could be converted in a regio- and enantioselective manner to the monoacetate **5** or **6** by selective enzymatic hydrolysis with either porcine liver esterase (PLE) or pancreatic lipase (PPL). These enzymes have been used extensively for the preparation of chiral synthons from prochiral substrates.[5] However, this approach has only rarely been employed with racemic substrates.[6]



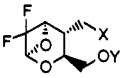
1



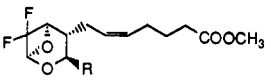
2



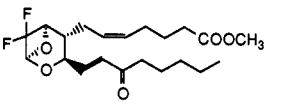
3 X=Y=H
4 X=Y=CH_3CO
5 X=H, Y=CH_3CO
6 X=CH_3CO, Y=H



7 X=CN, Y=CH_3CO
8 X=CHO, Y=H
9 X=CO_2CH_3, Y=H
10 X=CH_2OCOCH_3, Y=$COCH_3$



11 R=CH_2OH
12 R=CH_2OH, 5,6-trans
13 R=CHO
14 R=CHO, 5,6-trans



15
16 5,6-trans
17 15S-OH
18 15R-OH
19 15S-OH, 5,6-trans
20 15R-OH, 5,6-trans
21 15R-OH, CH_3=H
22 15S-OH, 5,6-trans, CH_3=H
23 t5 R-OH, 5,6-trans, CH_3=H

Catalytic hydrogenation of (±)-**2** with 10% Pd on carbon in isopropyl alcohol gave the racemic diol **3**, mp 112-112.5 °C, in 86% yield after recrystallization from ethyl acetate/hexane. The diacetate (±)-**4**, mp 41 °C, prepared with acetic anhydride and pyridine, was reacted with PLE at 25-26 °C for 10 min. Workup with ethyl acetate and chromatographic separation gave pure monoacetate (+)-**5**, 24.5% (49% of theory), $[\alpha]_D^{25}$ = +49.7° (*c* 2.15 in $CHCl_3$), partially resolved monoacetate **6**, 9%, $[\alpha]_D^{25}$ = +13°, and partially resolved diol **3**, 64%, $[\alpha]_D^{25}$ = -12.6° (70% ee). Enantiomerically pure diol (+)-**3**, $[\alpha]_D^{25}$ = +18.1° (*c* 0.36, $CH_3OH/CHCl_3$, 1:4), and diacetate (+)-**4**, $[\alpha]_D^{25}$ = +37.5° (*c* 0.33, $CHCl_3$), were prepared from (+)-**5**. This result indicates that of the eight possible rates of sequential deacetylation available to the racemic substrate the rate of hydrolysis of (+)-**5** is sufficiently slow to permit complete kinetic resolution of that regioisomer. Reexposure of (+)-**5** to PLE for 10 min yielded material of unchanged specific rotation indicating that this process indeed yields (+)-**5** in 100% ee. Comparison of the ^1H and ^{19}F NMR spectra of the (-)-MTPA esters of (+)-**5** and partially resolved **5** showed no evidence for the presence of (-)-**5** in the former. The absolute configuration of the dextrorotatory series of products **3** to **6** was shown to be that of TXA_2 by comparison of the diacetate (+)-**10** derived from (+)-**5** with that prepared from (2*R*,3*S*)-2,3-oxido-5-(*tert*-butyldimethylsilyloxy)pentan-1-ol.[7,8] With (+)-**5** in hand the completion of the synthesis of the

† Dedicated to the memory of Tom Kaiser.

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natural enantiomer of 10,10-difluoro-TXA_2 followed known methodology.

Conversion of (+)-**5** to the mesylate, mp 73°, $[\alpha]_D^{25}$ = +31.3° (*c* 0.55 in $CHCl_3$), 94%, with MsCl and pyridine followed by reaction with NaCN in DMF at 42 °C for 18 h yielded the nitrile (+)-**7**, $[\alpha]_D^{25}$ = +25.9° (*c* 0.96 in $CHCl_3$), which was reduced with DIBAL-H at −25 °C → +22 °C to the aldehyde **8**. Alternatively, the nitrile was hydrolyzed with 1 N NaOH at 42 °C for 1 h and methylated to the methyl ester (+)-**9**, $[\alpha]_D^{25}$ +16.8° (*c* 0.81 in $CHCl_3$), 81%, and the latter was reduced to the aldehyde **8** with Red-Al at −78 °C. Reduction of (+)-**9** with DIBAL-H at −20 °C gave the diol, which was converted to the diacetate (+)-**10** $[\alpha]_D^{25}$ = +29.1° (*c* 0.4).[8] Wittig reaction of **8** with the dianion of 4-carboxybutyltriphenylphosphonium bromide prepared with lithium hexamethyldisilazide in THF followed by methylation gave the cis and trans methyl esters **11** and **12** in 69% yield from **7**, in a 7:3 ratio. Separation was achieved by HPLC on silica gel using hexane/CH_2Cl_2/EtOAc in a 10:10:3 ratio. Swern oxidation of **11** [*m/z* 306 (M^+) 3.3%, 275 (M − CH_3O) 9%] gave the aldehyde **13**, which was converted with the anion of dimethyl 2-oxoheptylphosphonate to 10,10-difluoro-15-keto-TXA_2, **15**, $[\alpha]_D^{25}$ = +35° (*c* 0.2, $CHCl_3$). Similarly, the trans ester **12** afforded **16** via the aldehyde **14**. Diastereoselective reduction of **15** with the $LiAlH_4$ complex of (*S*)-(−)-1,1′-bi-2-naphthol[9] in THF yielded the methyl ester of 10,10-difluoro-TXA_2 **17**, $[\alpha]_D^{25}$ = +43.6° (*c* 0.05), *m/z* (TMS ether) 474.2617 (M^+) 8%, 443.2398 (M − OCH_3) 5%, 403.1713 (M − C_5H_{11}) 65%, 366.2656 ($C_{21}H_{38}O_3Si$) 19%, 225.1686 ($C_{13}H_{25}OSi$) 100%, 199.1501 ($C_{11}H_{23}OSi$) 35%, and its (*R*) isomer in a 9:1 ratio in 80% overall yield. Separation was achieved by HPLC on silica gel by using 1% *n*-propanol in hexane as the eluent.[10] A 1:1 mixture of **17** and **18** was obtained by reduction with $NaBH_4$ and $CeCl_3$. The corresponding trans isomers **19** and **20** were prepared from **16**. Hydrolysis of **17** with 0.5 N NaOH in 50% methanol/water afforded **1**: ^1H NMR ($CDCl_3$, 500 MHz) δ 5.87 (dd, 1 H, $J_{13,14}$ = 15.5 Hz, $J_{14,15}$ = 5.0 Hz, H-14), 5.77 (dd, 1 H, $J_{13,14}$ = 15.5 Hz, $J_{12,13}$ = 7.2 Hz, H-13), 5.64 (d, 1 H, $J_{9,11}$ = 4.5 Hz, H-11), 5.49 (dt, 1 H, $J_{5,6}$ = 10.3 Hz, $J_{6,7}$ = 6.5 Hz, H-6), 5.43 (dt, 1 H, $J_{5,6}$ = 10.3 Hz, $J_{4,5}$ = 6.5 Hz, H-5), 4.84 (dd, 1 H, $J_{H,F}$ = 8.6 Hz, $J_{9,11}$ = 4.5 Hz, H-9), 4.23 (q, 1 H, $J_{14,15}$ = $J_{15,16}$ = 5.0 Hz, H-15), 4.16 (t, 1 H, $J_{8,12}$ = $J_{12,13}$ = 7.2 Hz, H-12), 2.35 (m, 2 H, H-2), 2.23 (m, 3 H, H-4 and H-8), 2.05 (m, 2 H, H-7), 1.78 (m, 2 H, H-3), 1.60 (m, 2 H, H-16), 1.33 (m, 6 H, H-17, H-18, and H-19), 0.91 (t, 3 H, *J* = 6.5 Hz, H-20); ^{19}F NMR ($CDCl_3$, 376.2) Φ 110.07 (d, $J_{F,F}$ = 183.6 Hz), 138.30 (dd, $J_{F,F}$ = 183.6 Hz, $J_{H,F}$ = 8.5 Hz); *m/z* 370 (M^+ − H_2O); 299 (M^+ − H_2O − C_5H_{11}); 281 (M^+ − C_5H_{11} − $2H_2O$). Similarly, hydrolysis of **18**, **19**, and **20** yielded the corresponding free acids **21**, **22**, and **23**, respectively.

10,10-Difluoro-TXA_2 caused aggregation of washed human platelets at EC_{50} = 36 ± 3.6 nM indicating a potency 4.5 times greater than that reported for TXA_2.[11,12] Compound **1** stimulated contraction of canine saphenous veins with a potency (EC_{50} = 3.7 ± 0.8 nM) very similar to that reported for the TXA_2 mimic U46619.[13,14] In contrast, the isomeric compounds **21**, **22**, and **23** were antagonists of platelet aggregation stimulated by compound **1**. Compounds **21** and **22** were equipotent and approximately ten times more potent than **23**. On the other hand, compounds **21**, **22**, and **23** caused contraction of canine saphenous veins. All four compounds were capable of displacing the TXA_2 antagonist [^{125}I-PTA-OH[15] from its platelet binding site. Details of the bioassays will be reported elsewhere.[16]

The above results raise the possibility that platelet and vascular TXA_2 receptors are different. This class of compounds should prove to be useful tools to further explore these and other TXA_2 receptors. Moreover, the 7,7-difluoro-2,6-dioxo[1.1.3]bicycloheptane ring system, because of its close structural similarity to the TXA_2 nucleus and its stability during chemical reactions, presents unique opportunities for the construction of new molecules capable of binding to and interacting with TXA_2 receptors.

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Supplementary Material Available: Complete experimental data including spectroscopic data (^1H NMR and ^{19}F NMR) for all compounds (29 pages). Ordering information is given on any current masthead page.

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A Manganese(V)-Oxo Complex

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In metal-based oxidizing agents the metal center can have one of two roles: (i) in a *prima facie metallo-oxidant*, electron transfer from and/or atom transfer to or from the substrate is accompanied by a formal oxidation state change at the metal center;[2] (ii) in a *metallotemplate-oxidant* the metal center does not undergo a formal oxidation state change but activates the primary oxidant and/or substrate and/or arranges the primary oxidant and substrate in a favorable geometry for oxidation to proceed. For a number of years we have been working on perfecting ligand complements for prima facie metallo-oxidants.[3] We believe that the principal feature limiting the range of higher oxidation state middle and later transition-metal complexes is the rarity of strongly binding, oxidation resistant ligands. An important feature has

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