ABSTRACT: Platelet activation results in the generation of thromboxane A₂ (TxA₂), which promotes thrombus formation by further amplifying platelet function, as well as causing vasocostriction. Due to its role in thrombus formation and cardiovascular disease, its production is the target of antiplatelet drugs such as aspirin. However, the study of TxA₂-stimulated cellular function has been limited by its instability ($t_{1/2} = 32 \, s$ at pH = 7.4). Although more stable analogues such as U46619 and difluorinated 10,10-F₂-TxA₂ have been prepared, we targeted a closer mimic to TxA₂ itself, mono-fluorinated 10-F-TxA₂, since the number of fluorine atoms can affect function. Key steps in the synthesis of F-TxA₂ included α-fluorination of a lactone bearing a β-alkoxy group, and a novel synthesis of the strained acetal. F-TxA₂ was found to be 10⁵ more stable than TxA₂, and surprisingly was only slightly less stable than F₂-TxA₂. Preliminary biological studies showed that F-TxA₂ has similar potency as TxA₂ toward inducing platelet aggregation but was superior to F₂-TxA₂ in activating integrin αIIbβ₃.

1. INTRODUCTION
Thromboxane A₂ (TxA₂) is produced enzymatically from arachidonic acid through the action of several enzymes including cyclooxygenase (COX) and thromboxane synthase in response to tissue injury, promoting hemostasis, vasocostriction, and wound healing.¹⁻³ However, these necessary features for survival can also cause death to those susceptible to or suffering from cardiovascular disease (CVD).⁴⁻⁹ Current first-line therapy involves the use of nonsteroidal anti-inflammatory drugs (NSAIDs) which block >95% of COX1 activity and therefore TxA₂ production.¹⁰ However, the treatment suffers from side effects associated with shutting down the whole prostanoid cascade and with resistance in some patient groups.¹¹ The study of TxA₂ has been limited by its high instability ($t_{1/2} = 32 \, s$, pH = 7.4)¹ and so a number of more stable analogues have been prepared in which one or both oxygens of the strained acetal have been replaced by carbon,¹² sulfur,¹³ or a less strained bicyclic structure (e.g., U46619, Figure 1).¹⁴,¹⁵ A different strategy is to retain the strained acetal but reduce the rate of hydrolysis by incorporating either bromine¹⁶ or, more importantly, fluorine¹⁷⁻²⁰ atoms at the C-10 position (Figure 1). Although the synthesis²¹,²² of monofluorinated F-TxA₂ 1 has been attempted,²³ only the difluoro analogue 2 has succumbed to total synthesis,¹⁷ which showed similar potency in platelet aggregation to the parent compound.²⁰ The stability of 2 has only been investigated using a model compound (3), which, as expected, showed much higher stability than TxA₂ ($t_{1/2} > 30 \, d$, pH = 7.4).²⁰ We were interested in targeting F-TxA₂ 1 since the number of fluorine atoms can have a significant impact on function. For example, in a comparative study of the CHF-
and CF₂-phosphonate analogues of sn-glycerol-3-phosphate, O’Hagan found that the monofluorinated was better than the difluorinated substrate for the dehydrogenase enzyme.24−26 We now report the first synthesis of F-TxA₂ 1 and compare its stability and biological activity with that of F₂-TxA₂ 2.

2. RESULTS AND DISCUSSION

Our retrosynthetic analysis of F-TxA₂ is shown in Scheme 1. We envisioned forming the strained acetal by an intramolecular cyclization and introducing the upper side chain by a Wittig reaction on the corresponding fluorous lactol. Lactone 6 could be obtained by fluoration of the enolate of lactone 7, which itself could be synthesized by Baeyer–Villiger oxidation of ketone 8. Ketone 8 could then be obtained from conjugate addition of the lower side chain 9 to our key enal intermediate 10 followed by ozonolysis. At the outset, the main challenges presented in the synthesis were formation of the strained acetal and fluorination of the enolate bearing a potential leaving group at the β-position.

Synthesis of Fluorinated Thromboxane A₂. Our synthesis began from PMB-acetal 12, available in 3 steps in higher using our established proline-catalyzed aldol dimerization of succinaldehyde (Scheme 2).27,28 Initially, we elected to carry through the major β-isomer of the acetal to simplify analysis. Conjugate addition of the mixed vinyl cuprate 13 followed by trapping with TMSCl and ozonolysis27 gave ketone 14 which was converted into the key lactone intermediate 15 through a Baeyer–Villiger oxidation.29,30 (64% yield, over 3 steps).

With a scalable synthesis of lactone 15 in hand, we embarked on the fluorination reaction. Lactones bearing silyloxy and benzyloxy groups in the β-position are particularly prone to elimination upon deprotonation and have to be trapped by reactive electrophiles at low temperature.31−35 Initial investigation showed that NFSI was a sufficiently reactive electrophile, and after optimization we found that the reaction proceeded with good selectivity (10:1 dr) and yield (51%) using 1.2 equiv KHMDS and 2.5 equiv NFSI in Et₂O. Following PMB deprotection with DDQ, we explored the Wittig reaction with (4-carboxybutyl)triphenyl-phosphonium bromide (18), but this invariably led to intractable mixtures. We suspected that the lactone was interfering in this step and so converted lactone 16 into silyloxyacetal. This time, following PMB deprotection, Wittig reaction using phosphonium salt 18 with t-BuOK surprisingly gave the corresponding epoxide in 67% yield.36 To avoid epoxide formation, we screened alternative conditions and found that using LiHMDS with a ratio of hemiacetal (17):Wittig salt:LiHMDS of 1:4:8 at 0 °C gave the corresponding alkene in 82% yield as a separable 5:1 mixture of Z/E isomers after esterification with TMSCHN₂. Selective desilylation of the TIPS group with TBAF/AcOH gave the required lactol 19 in 98% yield.37−41

Scheme 1. Retrosynthesis of Fluorinated Thromboxanes from Bicyclic Enal

Scheme 2. Synthesis of Key Lactone Precursor and Completion of the Synthesis of the Monofluorinated Thromboxane A₂
To complete the synthesis of 10-F-TxA2, we required a method for the construction of the strained acetal. Owing to its known sensitivity and the low yields previously obtained for the construction of this motif, we decided to explore this key step on model substrate 23. This was prepared from d-arabinal-derived glycal 22 by fluorination with selectfluor (Scheme 3).\(^{42-44}\) Two methods for making the strained acetal had been reported previously, Still’s Mitsunobu reaction\(^{45,46}\) and Fried’s displacement of the mesylate, \(^{17}\) but neither was successful on hemiacetal 23 as shown in Scheme 3. These synthetic hurdles required us to find a new method to make the strained acetal. Shoda reported that treatment of unprotected glycopyranoses with 2-chloro-1,3-dimethylimidazolinium chloride (DMC) gave the corresponding 1,6-anhydro sugars directly.\(^{47,48}\) This reagent was tested on hemiacetal 23, but although we did not obtain the desired acetal 24 directly, we did isolate chloride 26 with complete chemoselectivity. The fortuitous formation of the (unstable) chloride presented another opportunity, since glycosyl chlorides can be activated by silver salts to promote their displacement.\(^{49}\) Indeed, treatment with Ag2O promoted cyclization giving the acetal 24 in 40% yield, providing a novel solution to the synthesis of strained acetals.

Moving onto the real target, brief optimization of the chlorination/cyclization steps was again required but optimum conditions were quickly established. Treatment of hemiacetal 19 with 6 equiv of each of the chlorination reagent, DIPEA, and Ag2O gave the desired acetal 21 in 52% yield (Scheme 2). Finally, hydrolysis of 21 with 1.0 N NaOH in 50% 1,4-dioxane/water followed by deprotection with TBAF furnished F-TxA2 1 in 78% yield.

We also tried to prepare the other diastereoisomer 10α-F-TxA2 from the minor diastereomer formed in the fluorination of lactone 15. While we were able to carry this diastereoisomer through to the corresponding dial (hydroxy hemiacetal, diastereomer of 19), attempts to prepare the chloride and the subsequent cyclization were thwarted by competing elimination and hydrolysis.

By adapting this strategy, we were able to prepare F₂-TxA2 (see Supporting Information), so that its stability and biological activity could also be assessed. With both fluorinated TxA2 analogues in hand, we were then able to compare their stabilities with the parent TxA2 and study their biological activity.

**Stability Studies of Fluorinated Thromboxane A₂ and Model Compounds.** The hydrolytic stability of TxA2 at pH 7.4 (37 °C) was measured and found to have a \( t_{1/2} \) of 32 s.\(^{24}\) Fried measured the stability of his F₁-TxA2 model compound 3, which is similar in structure to F₁-TxA2, at pH 1.27 (22 °C) to have a \( t_{1/2} \) of 86 min. While this 10⁸ difference in rate constant is interesting to note, the difference in pH and temperature of these measurements renders a direct comparison of stability, and an assessment of the effect of fluoride, very difficult. Hence, we sought to compare the stability of TxA2 with its fluorinated analogues by measuring the kinetics of hydrolysis under the same conditions. Using \(^{19}F\) NMR to monitor the decay of the acetal moiety, we determined pseudo first-order rate constants for the hydrolysis of 1 and 2 (Table 1) under buffered conditions. At pH 7.4, we found that F-TxA2 (1) has a half-life of 20 days, which is 10⁷ more stable than TxA2. Interestingly, F₂-TxA2 (2) was only 1 order of magnitude more stable at pH 7.4 with a half-life of over 40 weeks. We then measured hydrolysis rates of 1 and 2 at lower pHs (Table 1), where, as expected, decreasing the pH decreased the stability. The rate of hydrolysis we measured for F₂-TxA2 (2) at pH 1.25 (\( t_{1/2} = 64 \text{ min} \)) was in good agreement with that of Fried’s model compound 3 at pH 1.27 (\( t_{1/2} = 86 \text{ min} \)).\(^{25,26}\)

The marginal increase in stability of 2 compared to 1 at pH 7.4 was unexpected, as the increase in stability caused by inductive effects of the electronegative fluoride atoms is usually additive.\(^{51,52}\) Thus, we speculated that there might be a strong stereoelectronic effect governing the stability of the strained acetal. Unfortunately, we were not able to prepare 10α-F-TxA2 to test this, so we compared the stability of the two diastereoisomers of model compound 24 (3αr-24 with 3βr-24, Scheme 4). Indeed, we measured a very substantial difference in hydrolysis rate between the isomers: 3βr-24 was ca. 200× more stable than 3αr-24. The greater lability of 3αr vs 3βr presumably originates from having a better σ-donor (C–H vs C–F bond) aligned to the incipient oxocarbenium ion, as supported by DFT calculations on a model substrate (Scheme 4; see Supporting Information for further discussion). Our inability to make 10α-F-TxA2 could therefore be due to its greater instability. Furthermore, as 3αr-24 exhibited a half-life of just 15 h at pH 7.4, it is likely that 10αr-F-TxA2 would not have been suitable for biological studies (see Supporting Information for full details). These studies therefore reveal that the stability derived from the

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**Scheme 3. Formation of Strained Acetal on Model Hemiacetal 23**

![Scheme 3](image)

**Table 1. Kinetics of Hydrolysis.**\(^{42}\)

| compound | pH  | \( k_{1/2} (s^{-1}) \) | \( t_{1/2} \) |
|----------|-----|----------------------|-------------|
| F-TxA2 (1) | 7.40 | 3.93 \times 10^{-7} | 20 days |
| F₂-TxA2 (2) | 7.40 | 2.5 \times 10^{-8} | 46 weeks |
| F₂-TxA2 (2) | 1.25 | 1.80 \times 10^{-4} | 64 min |

\(^{42}\)Hydrolys of 1 and 2 were measured under buffered conditions (50 mM), using \(^{19}F\) NMR to monitor the decay of the ketal. \( k_{1/2} \) = pseudo first-order rate constants. \( t_{1/2} \) = half-life. \(^{42}\) Average of two runs.

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stereoelectronic effect of an antiperiplanar fluorine is very significant compared to a syn-periplanar fluorine and provides a rationale for the nonadditive inductive effect of fluorine atoms on acetal hydrolysis.

**Biological Studies.** To evaluate the biological activity of the fluorinated thromboxanes 1 and 2, concentration–response experiments were performed on human platelets, and platelet aggregation was recorded by light transmission aggregometer. The stable PGH2 analogue U46619 has been used widely as a standard of comparison for evaluating TxA2-like activity and so was included in this study. Concentration–response curves were fitted (Figure 2) and EC50 values were calculated (Table 2). The data show that F-TxA2 has similar activity as U46619 in inducing platelet aggregation but is almost 3-fold less potent than F2-TxA2. While F2-TxA2 was more potent, the EMax was significantly lower than U46619 and F-TxA2, suggesting partial agonism at TxA2 receptors. As platelet amplification pathways such as ADP release and integrin αIIbβ3 outside-in signaling can potentially mask a weaker agonist response in aggregation experiments, we were also interested to study a more direct functional readout of platelet activation: integrin αIIbβ3 activation (Figure 3). Since both F-TxA2 and U46619 have similar activity in both aggregation and integrin αIIbβ3 activation experiments and U46619 has comparative activity to TxA2,23 our data strongly indicates that F-TxA2 is a closer mimic to TxA2 than F2-TxA2. Further biological and pharmacological studies are ongoing.

3. **CONCLUSIONS**

In summary, we have developed novel syntheses of chemically stable fluorinated thromboxanes, utilizing our key enal intermediate, which is readily available in high ee. The total synthesis of the F-TxA2 and F2-TxA2 were completed in 17 and 18 steps, respectively, from 2,5-dimethoxytetrahydrofuran. The scalable route enabled >100 mg of advanced material (e.g., 21) to be prepared for chemical and biological screening. In addition to overcoming some unexpected challenges associated with incorporating and carrying fluorine through a synthesis, we have also developed a new method for constructing the highly strained acetal.

![Scheme 4. Investigations into Hydrolysis of Model Compound 24](image)

![Figure 2. TxA2-like properties of mono- and difluorinated TxA2 analogues on platelet aggregation. Aggregation of human platelet-rich plasma induced by U46619, F-TxA2, and F2-TxA2 (average ± SEM, n = 3).](image)

![Figure 3. TxA2-like properties of mono and difluorinated TxA2 analogues on platelet integrin αIIbβ3 activation. Washed platelets were stimulated with U46619, F-TxA2, and F2-TxA2 in the presence of 1 µM ADP for 15 min and integrin αIIbβ3 activation was determined using FITC-PAC1 by FACS analysis. Data is expressed as a percentage of the maximal α-thrombin (0.5 U/mL) response (average ± SEM, n = 5).](image)

![Table 2. Concentration of TxA2 Analogues Which Produces 50% Of Maximal Aggregation](table)
**ASSOCIATED CONTENT**

**Supporting Information**

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscentsci.0c00310.

Experimental procedures and characterization data for new compounds (PDF)

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**Notes**

The authors declare no competing financial interest.

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**REFERENCES**

1. Hamberg, M.; Svensson, J.; Samuelsson, B. Thromboxanes: A new group of biologically active compounds derived from prostaglandin endoperoxides. *Proc. Natl. Acad. Sci. U. S. A.* 1975, 72, 2994−2998.

2. Narumiya, S.; Sugimoto, Y.; Ushikubi, F. Prostanoid Receptors: Structures, Properties, and Functions. *Physiol. Rev.* 1999, 79, 1193−1226.

3. Bhagwat, S. S.; Hamann, P. R.; Still, W. C.; Bunting, S.; Fitzpatrick, F. A. Synthesis and structure of the platelet aggregating factor thromboxane A2. *Nature* 1985, 315, 511−513.

4. Szczeklik, A.; Gryglewski, R. J.; Musial, J.; Grodzinska, L.; Serwowska, M.; Wójcik-Switek, L.; Marcinkiewicz, E. Arachidonic acid-induced platelet aggregation and thromboxane A2 generation in patients with coronary heart disease. *Acta Biol. Med. Ger.* 1978, 37, 741−742.

5. Lewy, R. I.; Smith, J. B.; Silver, M. J.; Saia, J.; Walinsky, P.; Wiener, L. Detection of thromboxane B2 in peripheral blood of patients with Prinzmetal’s angina. *Prostaglandins Med.* 1979, 2, 243−248.

6. Zipser, R. D.; Radvan, G. H.; Kronborg, I. J.; Duke, R.; Little, T. E. Urinary thromboxane B2 and prostaglandin E2 in the hepatorenal syndrome: evidence for increased vasoconstrictor and decreased vasodilator factors. *Gastroenterology* 1983, 84, 697−703.

7. Parelon, G.; Mirouze, D.; Michel, F.; Crastes de Paulet, P.; Chaintreuil, J.; Crastes de Paulet, A.; Michel, F. Urinary prostaglandins in the hepatorenal syndrome of cirrhotic patients: role of thromboxane A2 and an imbalance of precursor polynsaturated fatty acids. *Gastroenterol. Clin. Biol.* 1985, 9, 290−297.

8. Nagai, H.; Shimazawa, T.; Yaku, I.; Aoki, M.; Koda, A.; Kasahara, M. The role of thromboxane A2 [TxA2] in liver injury in mice. *Prostaglandins 1989*, 38, 439−446.

9. Ma, H. B.; Young, M.; Yang, Y. Thromboxane (TX), Prostaglandins (PG) and Atorvastatin (Liptor) Literatures. *N. Y. Sci. J.* 2015, 8, 93−100.

10. Catella-Lawson, F.; Reilly, M. P.; Kapoor, S. C.; Cucchiara, A. J.; DeMarco, S.; Tournier, B.; Vyas, S. N.; Fitzgerald, G. A. Cytochrome P450 Inhibitors and the Antiplatelet Effects of Aspirin. *N. Engl. J. Med.* 2001, 345, 1809−1817.

11. Eikeland, J. W.; Hirsh, J.; Weitz, J. I.; Johnston, M.; Yi, Q. L.; Yusuf, S. Aspirin-resistant thromboxane biosynthesis and the risk of myocardial infarction, stroke, or cardiovascular death in patients at high risk for cardiovascular events. *Circulation 2002*, 105, 1650−1655.

12. Nicolau, K. C.; Magolda, R. L.; Smith, J. B.; Aharony, D.; Smith, E. F.; Lefer, A. M. Synthesis and biological properties of pinanethromboxane A2, a selective inhibitor of coronary artery constriction, platelet aggregation, and thromboxane formation. *Proc. Natl. Acad. Sci. U. S. A.* 1979, 76, 2566−2570.

13. Hamanaka, N.; Ohuchida, S.; Hayashi, M. Syntheses of thromboxane A2 analogs: Thia- and dithiathromboxane A2. *Adv. Prostaglandin Thromboxane Leukot Res.* 1983, 11, 319−322.

14. Bundy, G. L. The synthesis of prostaglandin endoperoxide analogs. *Tetrahedron Lett.* 1975, 16, 1957−1960.

15. Coleman, R. A.; Humphrey, P. P. A.; Kennedy, I.; Levy, G. P.; Lumley, P. U-46619, a selective thromboxane A2-like agonist? *Br. J. Pharmacol.* 1980, 68, 127−128.

16. Nakura, Y.; Nakazaki, A.; Nishikawa, T. Synthesis of Diprme Compounds Containing 2,6-Dioxabicyclo[3.1.1]heptane Similar to Core Moiety of Thromboxane A2. *Heterocycles* 2018, 96, 127−136.

17. Fried, J.; John, V.; Szvedo, M. J., Jr.; Chen, Ch.; K.; O’Yang, C. Synthesis of 10,10-Difluorothromboxane A2, a Potent and Chemically Stable Thromboxane Agonist. *J. Am. Chem. Soc.* 1989, 111, 4510−4511.

18. Morinelli, T. A.; Okwu, A. K.; Mais, D. E.; Halushka, P. V.; John, V.; Chen, Ch.-K.; Fried, J. Difluorothromboxane A2 and stereoisomers: Stable derivatives of thromboxane A2 with differential effects on platelets and blood vessels. *Proc. Natl. Acad. Sci. U. S. A.* 1989, 86, 5600−5604.

19. Witkowski, S.; Rao, Y. K.; Premchandran, R. H.; Halushka, P. V.; Fried, J. Total Synthesis of (+)-10,10-Difluorothromboxane A2 and Its 9,11 and 15 Stereoisomers. *J. Am. Chem. Soc.* 1992, 114, 8464−8472.

20. Fried, J.; Hallinan, E. A.; Szvedo, M. J., Jr. Synthesis and Properties of 7,7-Difluoro Derivatives of the 2,6-Dioxo[3.1.1]-bicycloheptane Ring System Present in Thromboxane A2. *J. Am. Chem. Soc.* 1984, 106, 3871−3872.

21. For a review on the synthesis of thromboxane compounds, see: Pelyvás, I. F.; Thiém, J.; Toth, Z. G. Access to Thromboxane Compounds: Syntheses from Carbohydrates, as Natural Chiral Pools. *J. Carbohydr. Chem.* 1998, 17, 1−26.

22. For a review on the synthesis of thromboxane compounds, see: Newton, R. F.; Roberts, S. M.; Taylor, R. J. K. Strategies Employed in the Synthesis of Prostacyclins and Thromboxanes. *Synthesis* 1984, 1984, 449−478.

23. Tamara, L. Studies Directed Towards the Synthesis of 10α-Fluoro-Thromboxane A2. Ph.D. Dissertation. University of Pennsylvania, 1986.
(24) Nieschalk, J.; O’Hagan, D. Monofluorophosphonates as Phosphate Mimics in Bioorganic Chemistry: A Comparative Study of CH2P(=O)(OPh)2 and CF2P(=O)(OPh)2 Phosphate Analouges of sn-Glycerol-3-phosphate as Substrates for sn-Glycerol-3-phosphate Dehydrogenase. J. Chem. Soc., Chem. Commun. 1995, 719−720.

(25) For an example where the mono fluorinated compound is superior to the dfluorinated compound, see: van Niel, M. B.; et al. Fluorination of 3-(3-(Piperidin-1-yl)propyl)indoles and 3-(3-(Piperazin-1-yl)propyl)indoles Gives Selective Human 5-HT1D Receptor Ligands with Improved Pharmacokinetic Profiles. J. Med. Chem. 1999, 42, 2087−2104.

(26) For another example where the mono fluorinated compound is superior to the dfluorinated compound, see: Zhu, Y. P.; et al. Phenylcyclobutyl triazoles as selective inhibitors of 11β-hydroxysteroid dehydrogenase type 1. Biorg. Med. Chem. Lett. 2008, 18, 3412−3416.

(27) Coulthard, G.; Erb, W.; Aggarwal, V. K. Stereocatalyzed organocatalytic synthesis of prostaglandin PGF2α in seven steps. Nature 2012, 489, 278−281.

(28) Pels, A.; Gandhamsettty, N.; Smith, J. R.; Mailhol, D.; Silvi, M.; Watson, A. J. A.; Perez-Powell, I.; Prévost, S.; Schützenmeister, N.; Moore, P. R.; Aggarwal, V. K. Re-optimization of the Organocatalyzed Double Aldol Domino Process to a Key Enal Intermediate and its Application to the Total Synthesis of A2-Prostaglandin J3. Chem. - Eur. J. 2018, 24, 9542−9545.

(29) Forster, A.; Fittremann, J.; Renaud, P. Preparation of an advanced intermediate for the synthesis of epi-thromboxanes. Tetrahedron Lett. 1998, 39, 3483−3488.

(30) Leonard, J.; Ouali, D.; Rahman, S. K. A short enantioselective route to cortanthyte alkaloid precursors. Tetrahedron Lett. 1990, 31, 739−742.

(31) Scott, R. W.; Mazzetti, C.; Simpson, T. J.; Willis, C. L. γ-lactones from δ-lactones: total synthesis of the biosynthetic derailment product mupirocin H. J. Chem. Soc., Perkin Trans. 1 1998, 2161−2167.

(32) Mckay, C.; Simpson, T. J.; Willis, C. L.; Forrest, A. K.; O’Hanlon, P. J. A versatile approach to the total synthesis of the pseudomonic acids. Chem. Commun. 2000, 1109−1110.

(33) Yoshimura, T.; Yanagisawa, S.; Nagawa, H. Asymmetric Synthesis of the Core Structure of (−)-CP-263,114. Org. Lett. 2000, 2, 3751−3754.

(34) Mcaette, J. J.; Schinazi, R. F.; Liotta, D. C. A Completely Diastereoselective Electrophilic Fluorination of a Chiral, Noncarbohydrate Sugar Ring Precursor: Application to the Synthesis of Several Novel 2′-Fluorouronucleosides. J. Org. Chem. 1998, 63, 2161−2167.

(35) Dupradeau, F.-Y.; Hakomori, S.-I.; Toyokuni, T. Electrophilic azidation of 2-deoxy-α-L-lyxo-hexopyranosyl-1,5-lactones: an alternative route to 2-azido-2-deoxy-α-L-lyxo-hexopyranosyl-1,5-lactones. J. Chem. Soc., Chem. Commun. 1995, 221−222.

(36) The formation of the corresponding epoxide was unexpected since it involves displacement of fluoride but being a strained cyclic ether with the same stereochemistry it bore some similarity to TxA2. It was therefore deprotected and tested for biological activity, but it (9,10-epoxy TxA2) was essentially inactive.

(37) Trost, B. M.; Wroblewski, S. T.; Chisholm, J. D.; Harrington, P. E.; Jung, M. Total Synthesis of (-)-Amphiphilinolide A. Assembly of the Fragments. J. Am. Chem. Soc. 2005, 127, 13589−13597.

(38) Trost, B. M.; Harrington, P. E.; Chisholm, J. D.; Wroblewski, S. T. Total Synthesis of (-)-Amphiphilinolide A. Structure Elucidation and Completion of the Synthesis. J. Am. Chem. Soc. 2005, 127, 13598−13610.

(39) Swarts, B. M.; Guo, Z. W. Chemical Synthesis of Glycosylphosphatidylinositol Anchors. Adv. Carbohydr. Chem. Biochem. 2012, 67, 137−219.

(40) Soliman, S. E.; Bennett, C. S. Reagent-Controlled Synthesis of the Branched Trisaccharide Fragment of the Antibiotic Saccharomycin B. Org. Lett. 2018, 20, 3413−3417.

(41) Brumsted, C. J.; Carpenter, E. L.; Indra, A. K.; Mahmud, T. Asymmetric Synthesis and Biological Activities of Pectactin-Inspired Aminocyclolipids. Org. Lett. 2018, 20, 397−400.

(42) Matsumori, N.; Umegawa, Y.; Oishi, T.; Murata, M. Bioactive fluorinated derivative of amphoterin B. Biorg. Med. Chem. Lett. 2005, 15, 3565−3567.

(43) Suzuki, K.; Ohtake, A.; Ito, Y.; Kanie, O. Synthesis of a fluorocently tagged sialic acid analogue useful for live-cell imaging. Chem. Commun. 2012, 48, 9744−9746.

(44) Suzuki, K.; Daikoku, S.; Son, S.-H.; Ito, Y.; Kanie, O. Synthetic study of 3-fluorinated sialic acid derivatives. Carbohydr. Res. 2015, 405, 1−9.

(45) Bhagwat, S. S.; Hamann, P. R.; Still, W. C. Synthesis of Thromboxane A2: J. Am. Chem. Soc. 1985, 107, 6372−6376.

(46) Mitsuobu, O. The Use of Diethyl Azodicarboxylate and Triphenylphosphine in Synthesis and Transformation of Natural Products. Synthesis 1981, 1981, 1−28.

(47) Isobe, T. 2-Chloro-1,3-dimethylimidazolinium Chloride. 3. Utility for Chlorination, Oxidation, Reduction, and Rearrangement Reactions. J. Org. Chem. 1999, 64, 5832−5835.

(48) Tanaka, T.; Huang, W. C.; Noguchi, M.; Kobayashi, A.; Shoda, S.-I. Direct synthesis of 1,6-anhydro sugars from unproctected glycopyranoses by using 2-chloro-1,3-dimethylimidazolinium chloride. Tetrahedron Lett. 2009, 50, 2154−2157.

(49) Koenigs, W.; Knorr, E. Ueber einige Derivate des Traubenzuckers und der Galactose. Ber. Dtsch. Chem. Ges. 1901, 34, 957−981.

(50) Fried reported a 102 difference of second-order rate constants for the hydrolysis of 10,10-F2-TxA2 model compound 3 at pH 1.27 (22 °C) with that of TxA2 at pH 7.4 (37 °C). This translates to a 102 decrease in pseudo first-order rate constants (1.4 × 104 vs 2.2 × 102) and half-lives of 86 min and 32 seconds for the fluorinated model compound 3 (at pH 1.27) and TxA2 (at pH 7.4), respectively.

(51) Szytlowicz, H.; Jezuita, A.; Siodla, T.; Varaksin, K. S.; Domanski, M. A.; Ejsmont, K.; Krygowski, T. M. Toward the Physical Interpretation of Inductive and Resonance Substituent Effects and Reexamination Based on Quantum Chemical Modeling. ACS Omega 2017, 2, 7163−7171.

(52) Withers, S. G.; Percival, M. D.; Street, I. P. The synthesis and hydrolysis of a series of deoxy- and deoxyfluoro-o-d-“glycopyranosyl” phosphates. Carbohydr. Res. 1989, 187, 43−66.

(53) Coleman, R. A.; Humphrey, P. P. A.; Kennedy, I.; Levy, G. P.; Lumley, P. Comparison of the actions of U-46619, a prostaglandin H2-analogue, with those of prostaglandin H2 and thromboxane A2 on some isolated smooth muscle preparations. Br. J. Pharmacol. 1981, 73, 773−778.

(54) di Minno, G.; Bertelé, V.; Bianchi, L.; Barbieri, B.; Cerletti, C.; Dejana, E.; de Gaetano, G.; Silver, M. J. Effects of an Epoxymethano Stable Analogue of Prostaglandin Endoperoxides (U-46619) on Human Platelets. Thromb. Haemostasis 1981, 45, 103−106.

(55) Liel, N.; Mais, D. E.; Halushka, P. V. Binding of a thromboxane A2/prostaglandin H2 agonist [3H]U46619 to washed human platelets. Prostaglandins 1987, 33, 789−797.

(56) Morinelli, T. A.; Niewiarowski, S.; Daniel, J. L.; Smith, J. B. Receptor-mediated effects of a PGH2 analogue (U46619) on human platelets. Am. J. Physiol. 1987, 253, H1035−H1043.