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Synthesis of Thromboxane B_2 via Ketalization/Ring-Closing Metathesis

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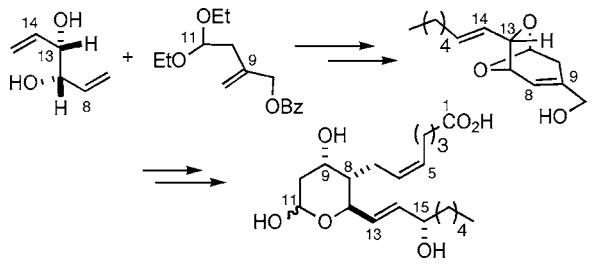
ABSTRACT



Total synthesis of thromboxane B_2 using intermolecular ketalization followed by ring-closing metathesis is reported. Other key steps include a Sharpless asymmetric epoxidation to form an oxirane on the endo face of the bicyclic acetal, epoxide opening using lithioacetonitrile, an allylic alcohol 1,3-transposition, and Mitsunobu lactonization.

A synthetic strategy that has been of recent interest to our group is that of ketalization/ring-closing metathesis (K/RCM).[1] An advantage of this strategy is the rapid assembly of rigid bicyclic acetal scaffolds, which can then be stereoselectively functionalized. In previous applications of the K/RCM strategy, use of C_2-symmetric diene diols (**1** in Figure 1) was predicated upon identification of an embedded 1,2- or 1,3-diol segment within the target, where both secondary carbinol centers had the same configuration. Conversion to ketal **3** renders the vinyl groups diastereotopic; one becomes involved in ring formation via RCM,[2] and the other remains available for alternative reaction as in bicyclic acetal **4**. The availability of reliable means for alkene extension via cross metathesis and methods for stereoselective 1,3-transposition of allylic alcohols suggested that application of the K/RCM strategy to targets where the carbinol centers have vinylogous 1,2- or 1,3-relationships would be possible. We became interested in the synthesis of thromboxane B_2 [TXB_2 (**5**), Figure 2] as an illustration of this concept.

TXB_2 is the stable hydrolysis product of thromboxane A_2 [TXA_2 (**6**), Figure 2], a prostanoid signaling molecule generated by blood platelets and involved in blood clotting

(1) (a) Burke, S. D.; Müller, N.; Beaudry, C. M. *Org. Lett.* **1999**, *1*, 1827. (b) Burke, S. D.; Voight, E. A. *Org. Lett.* **2001**, *3*, 237. (c) Voight, E. A.; Rein, C.; Burke, S. D. *Tetrahedron Lett.* **2001**, *42*, 8747. (d) Keller, V. A.; Martinelli, J. R.; Strieter, E. R.; Burke, S. D. *Org. Lett.* **2002**, *4*, 467. (e) Voight, E. A.; Rein, C.; Burke, S. D. *J. Org. Chem.* **2002**, *67*, 8489. (f) Voight, E. A.; Seradj, H.; Roethle, P. A.; Burke, S. D. *Org. Lett.* **2004**, *6*, 4045. (g) Marvin, C. C.; Voight, E. A.; Burke, S. D. *Org. Lett.* **2007**, *9*, 5357.

(2) For recent reviews, see: (a) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4490. (b) Grubbs, R. H. *Tetrahedron* **2004**, *60*, 7117. (c) Deiters, A.; Martin, S. F. *Chem. Rev.* **2004**, *104*, 2199. (d) Vernall, A. J.; Abell, A. D. *Alrichimica Acta* **2003**, *36*, 93. (e) Connon, S. J.; Blechert, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 1900. (f) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18. (g) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012.

(3) Hamberg, M.; Svensson, J.; Samuelsson, B. *Proc. Natl. Acad. Sci. U.S.A.* **1975**, *72*, 2994.

(4) Reviews: (a) Pelyvás, I. F.; Thiem, J.; Toth, Z. G. *J. Carbohydr. Chem.* **1998**, *17*, 1. (b) Newton, R. F.; Roberts, S. M. *Synthesis* **1984**, 449. (c) Nicolaou, K. C.; Gasic, G. P.; Barnette, W. E. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 293. Total synthesis: (d) Masaki, Y.; Yoshizawa, K.; Itoh, A. *Tetrahedron Lett.* **1996**, *37*, 9321. (e) Hanessian, S.; Lavallee, P. *Can. J. Chem.* **1981**, *59*, 870. (f) Hanessian, S.; Lavallee, P. *Can. J. Chem.* **1977**, *55*, 562. (g) Corey, E. J.; Shibasaki, M.; Knolle, J.; Sugahara, T. *Tetrahedron Lett.* **1977**, *18*, 785. (h) Corey, E. J.; Shibasaki, M.; Knolle, J. *Tetrahedron Lett.* **1977**, *18*, 1625. (i) Nelson, N. A.; Jackson, R. W. *Tetrahedron Lett.* **1976**, *17*, 3275. (j) Kelly, R. C.; Schletter, I.; Stein, S. J. *Tetrahedron Lett.* **1976**, *17*, 3279. (k) Schneider, W. P.; Morge, R. A. *Tetrahedron Lett.* **1976**, *17*, 3286.

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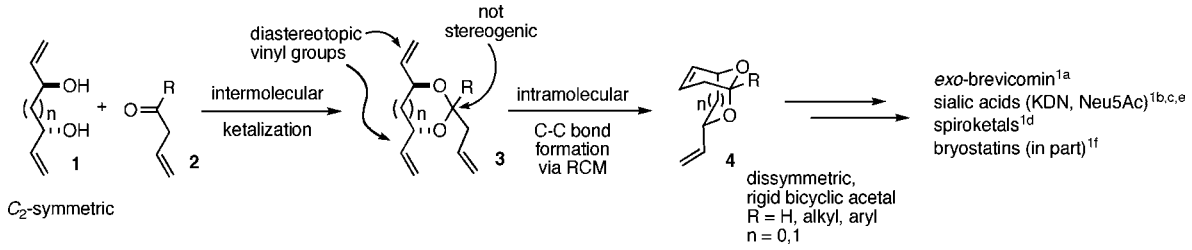


Figure 1. Generalized K/RCM strategy.

(thrombosis).[3] At the conclusion of its short half-life within the body (32 s), the strained oxetane ring is hydrolyzed to give the essentially biologically inactive TXB_2. As TXB_2 has seen significant interest from the synthetic community over the years,[4] it is an appealing target for our K/RCM strategy as there are benchmarks for comparison. Furthermore, it has been demonstrated that TXB_2 can be converted to the biologically active TXA_2.[5]

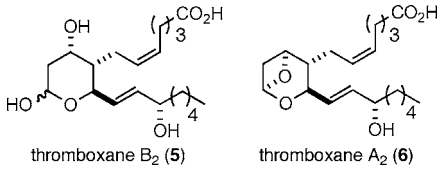


Figure 2. The thromboxanes.

Our retrosynthesis is shown in Figure 3. Carbons 1−5 would be installed via a well-precedented Wittig olefination,

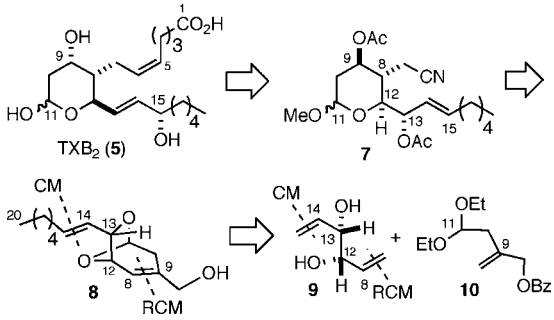


Figure 3. Thromboxane B_2 retrosynthetic analysis.

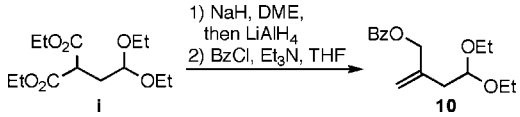
as in prior syntheses.[4] Retrosynthetic 1,3-transposition of the C15 allylic alcohol provides intermediate **7**, which was envisioned to be accessible from bicyclic acetal **8**. The superfluous allylic carbinol at C9 in **8** enabled Sharpless asymmetric epoxidation[6] for differentiating the olefins and provided a means for the installation of the C1−C7 side chain. The embedded C_2-symmetric diene diol **9** is discernible in **7** and **8**, encompassing C8 and C12−C14. Bicyclic acetal **8** would be readily available after a ketalization/ring-closing metathesis sequence involving diethyl acetal **10** and C_2-symmetric diene diol **9**, followed by cross metathesis with 1-heptene to install C15−C20 of the aliphatic side chain.

Our synthesis commenced with transacetalization of **10**[7] with diene diol **9**,[8] driven to completion by the azeotropic removal of ethanol to give pseudo-C_2-symmetric acetal **11** as the major product (Scheme 1). RCM was achieved at room temperature using Grubbs' second generation metathesis

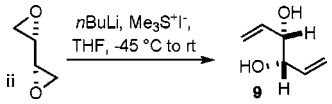
(5) (a) Bhagwat, S. S.; Hamann, P. R.; Still, W. C. *J. Am. Chem. Soc.* **1985**, *107*, 6372. (b) Bhagwat, S. S.; Hamann, P. R.; Still, W. C.; Bunting, S.; Fitzpatrick, F. A. *Nature* **1985**, *315*, 511.

(6) Review: (a) Katsuki, T.; Martin, V. S. *Org. React.* **1996**, *48*, 1. Also see: (b) Hanson, R. M.; Sharpless, K. B. *J. Org. Chem.* **1986**, *51*, 1922. (c) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974.

(7) Diethyl acetal **10** was made in two steps as shown below from substituted malonate **i**. Synthesis of malonate **i**: Bailey, S.; Harnden, M. R. *J. Chem. Soc., Perkin Trans. 1* **1988**, 2767. Reduction with $LiAlH_4$: Marshall, J. A.; Andersen, N. H.; Hochstetler, A. R. *J. Org. Chem.* **1967**, *32*, 113. For more details, see the Supporting Information.



(8) Diene diol **9** was synthesized in one step as shown below from known bisepoxide **ii**: Robbins, M. A.; Devine, P. N.; Oh, T. *Org. Synth.* **1999**, *76*, 101. For more details, see the Supporting Information.



(9) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953.

(10) While we initially pursued a TBS ether protection in **10**, conversion to the RCM product was a disappointing 9%. After some experimentation, we discovered that an ester was the optimal protecting group for the allylic alcohol in **10**−**13**. Whereas an acetate provided satisfactory conversion to the ring-closed product (60%), the benzoate ester was preferred due to its physical properties. For a similar system, see: Hyldtoft, L.; Madsen, R. *J. Am. Chem. Soc.* **2000**, *122*, 8444.

(11) Fürst, A.; Plattner, P. A. *Helv. Chim. Acta* **1949**, *32*, 275.

(12) (a) Smith, D. M.; Tran, M. B.; Woerpel, K. A. *J. Am. Chem. Soc.* **2003**, *125*, 14149. (b) Bartlett, P. A.; Ting, P. C. *J. Org. Chem.* **1986**, *51*, 2230.

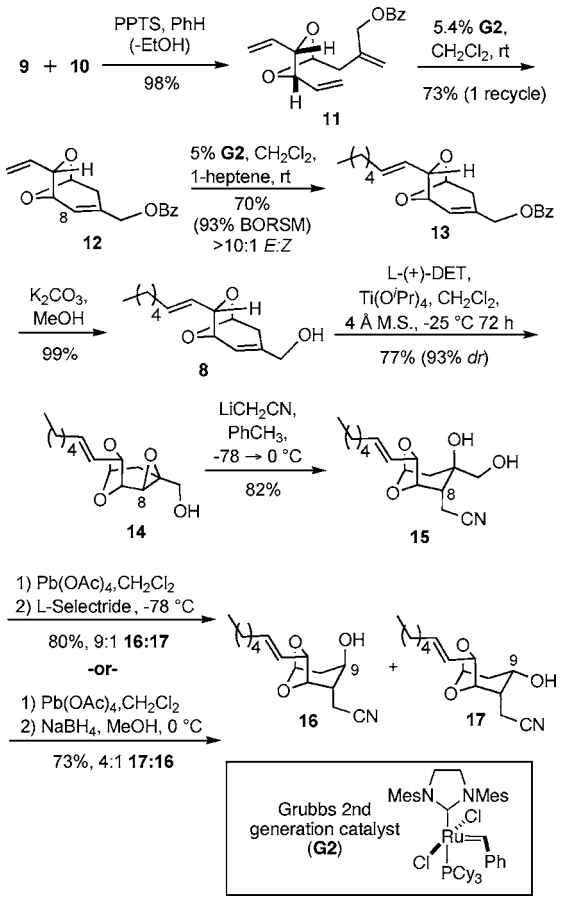
(13) (a) Criegee, R. *Ber. Dtsch. Chem. Ges.* **1931**, *64*, 260. Review: (b) Mihailovic, M. L.; Cekovic, Z. *Synthesis* **1970**, 209.

(14) Hydroxyl has an *A* value of only 0.87 kcal/mol in protic solvents: Hirsch, J. A. *Top. Stereochem.* **1967**, *1*, 199.

(15) Reviews: (a) Hofle, G.; Steglich, W.; Vorbruggen, H. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 569. (b) Scriven, E. F. V. *Chem. Soc. Rev.* **1983**, *12*, 129.

(16) (a) Overman, L. E.; Knoll, F. M. *Tetrahedron Lett.* **1979**, *20*, 321. (b) Grieco, P. A.; Takigawa, T.; Bongers, S. L.; Tanaka, H. *J. Am. Chem. Soc.* **1980**, *102*, 7587.

Scheme 1



catalyst[9] **G2** (73% yield of **12** after one recycle).[10] Cross metathesis of **12** with 1-heptene yielded **13** in 70% yield (93% BORSM) with >10:1 selectivity for the *E* olefin.

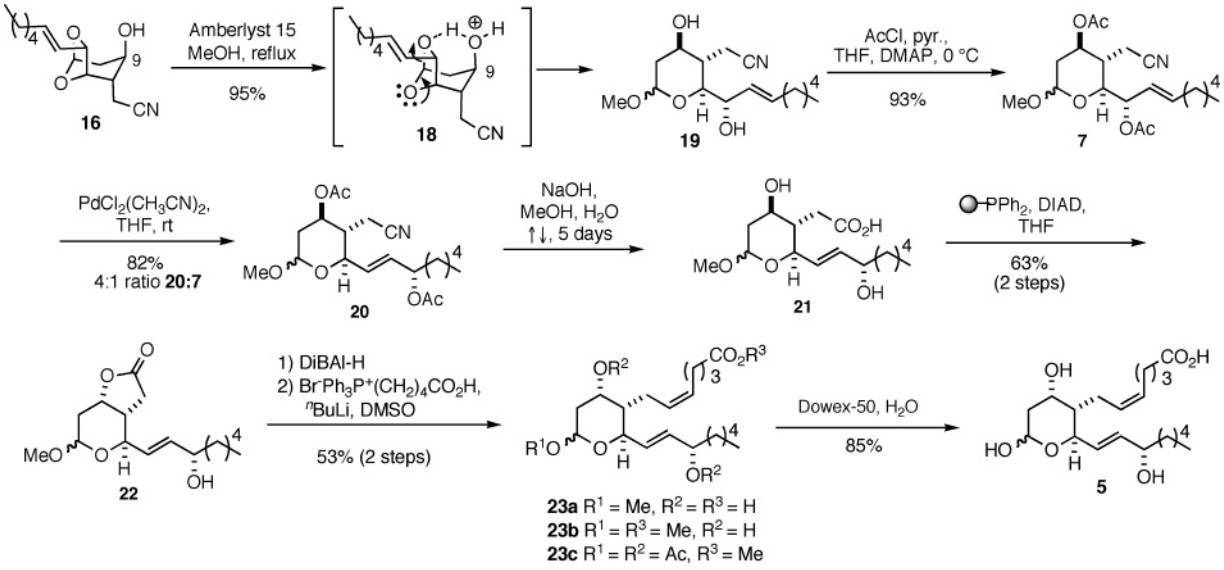
With two-thirds of the carbons for TXB_2 in place, the benzoate protecting group was removed upon treatment with K_2CO_3 in MeOH to give **8** in near quantitative yield. Reagent-controlled Sharpless asymmetric epoxidation[6] provided *endo*-epoxide **14** in preference to its *exo* diastereomer (77% combined yield, 93% dr). After optimization, it was found that this epoxide could be opened according to the Fürst−Plattner rule[11] with lithioacetonitrile[12] to provide diol **15** in 82% isolated yield as the only observed product.

Having served its purpose, the exocyclic hydroxymethyl was removed via oxidative cleavage to the ketone with $Pb(OAc)_4$,[13] followed by immediate treatment with L-Selectride at −78 °C to yield axial alcohol **16** as the major product (9:1 dr). Alternatively, the equatorial C9 alcohol **17** could be selectively formed from the ketone with $NaBH_4$ (4:1 dr).

Both C9 epimeric alcohols were evaluated in the hydrolysis of the bicyclic acetal. Although equatorial alcohol **17** bears the correct stereochemistry at C9 for TXB_2, it proved resistant to hydrolysis after an extensive screening of conditions. In contrast, the axial epimer **16** opened cleanly in refluxing methanol with Amberlyst-15 acidic resin (Scheme 2). This difference in reactivity was initially surprising. Although ease of bicyclic acetal cleavage can be attributed to the steric relief afforded when axial substituents become equatorial upon methanolysis, we believe a different rationale is operative here.[14] The axial alcohol likely facilitates bicycle opening via protonation of the bridging oxygen of the acetal via intramolecular hydrogen bonding between the acetal and axial alcohol (see **18**). This simultaneously makes the C9 oxygen the most basic site in the molecule, which upon protonation is poised to deliver a proton to the acetal oxygen, triggering acetal cleavage.

After opening the bicyclic acetal in near quantitative yield to **19**, the free alcohols were converted to acetates using acetyl chloride with pyridine and catalytic DMAP (93% yield).[15] The resulting diacetate **7** was then treated with palladium(II) to promote allylic transposition[4d,16] via cy-

Scheme 2. Completion of Thromboxane B_2



clization-induced rearrangement to regioisomer **20** in 82% combined yield favoring **20** by a 4:1 ratio.[17]

Treatment of **20** with NaOH in refluxing methanol/water hydrolyzed both the acetates and the nitrile to yield carboxylic acid **21**. The crude acid was subjected to Mitsunobu lactonization[18] to differentiate the alcohols and correct the stereochemistry at C9. Use of triphenyl phosphine for this inversion lead to difficulties in purification, as we were unable to completely separate triphenylphosphine oxide from lactone **22**. Switching to polymer-bound triphenylphosphine[19] enabled clean isolation of **22** in 63% yield for this two-step global hydrolysis/Mitsunobu sequence.

Although **22** is a known intermediate,[4i] it had not been fully characterized in the literature. We therefore subjected lactone **22** to the reported[4i] three-step sequence to thromboxane B_2. Reduction of the lactone with *i*-Bu_2AlH followed by Wittig olefination (53% yield, two steps) provided thromboxane B_2 methyl glycoside (**23a**). For comparative characterization, methyl glycoside **23a** was derivatized to its methyl ester **23b**. Esterification of the carboxylic acid with trimethylsilyldiazomethane (**23b**) intersected the methyl ester of TXB_2 methyl glycoside previously synthesized by Hanessian[4e,f] to provide an intermediate for direct spectroscopic comparison. We also subjected methyl glycoside **23a** to hydrolysis with DOWEX-50 resin in water to provide thromboxane B_2 (**5**). In our hands, the natural product was difficult to characterize by NMR because it has a tendency to aggregate in deuterated chloroform. However, high-resolution mass spectrometry did confirm methyl glycoside hydrolysis. As further confirmation of the synthesis of TXB_2, we derivatized the natural product to the triacetate of the methyl ester (**23c**).[5] This derivative matched published data in terms of both HRMS and ^1H NMR.

In summary, the synthesis of thromboxane B_2 has been completed in 16 steps from C_2-symmetric diene diol **9**. Central to our strategy was use of K/RCM in establishment of bicyclic acetal **12** as a scaffold for installation of the C8 stereochemistry and as an expedient solution, intrinsic to **9**, for the C13−C15 *trans*-allylic alcohol installation via 1,3-transposition.[4d] Extension of this K/RCM strategy to other targets is ongoing in these labs and will be reported in due course.

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Supporting Information Available: Experimental procedures and NMR spectra for compounds **5**, **7**−**17**, **19**, **20**, **22**, and **23a**−**c** and the comparison of derivatives **23b** and **23c** with literature data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) Resubjection of clean **20** to the palladium(II) conditions provided a 5:1 ratio of **20**/**7**, suggesting this reaction is under thermodynamic control.

(18) Reviews: (a) Mitsunobu, O. *Synthesis* **1981**, 1. (b) Hughes, D. L. *Org. React.* **1992**, *42*, 335. Intramolecular examples: (c) Lucas, B. S.; Luther, L. M.; Burke, S. D. *Org. Lett.* **2004**, *6*, 2965. (d) Boto, A.; Betancor, C.; Prangé, T.; Suárez, E. *J. Org. Chem.* **1994**, *59*, 4393. (e) Smith, A. B., III; Sulikowski, G. A.; Sulikowski, M. M.; Fujimoto, K. *J. Am. Chem. Soc.* **1992**, *114*, 2567.

(19) (a) Relles, H. M.; Schluenz, R. W. *J. Am. Chem. Soc.* **1974**, *96*, 6469. Use of polymer-supported phosphine in the Mitsunobu reaction: (b) Amos, R. A.; Emblidge, R. W.; Havens, N. *J. Org. Chem.* **1983**, *48*, 3598. (c) Tunoori, A. R.; Dutta, D.; Georg, G. I. *Tetrahedron Lett.* **1998**, *39*, 8751.