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Total Synthesis of Thromboxane B_2 via a Key Bicyclic Enal Intermediate

Changcheng Jing and Varinder K. Aggarwal*

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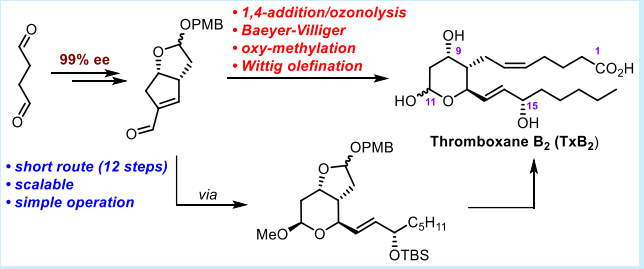
ABSTRACT: A 12-step asymmetric synthesis of thromboxane B_2 (TxB_2) from 2,5-dimethoxytetrahydrofuran is described. The synthesis employs our organocatalytic aldol reaction of succinaldehyde to give a key bicyclic enal intermediate. From here, the synthetic strategy involves a conjugate addition of an alkenyl side chain to the bicyclic enal, Baeyer–Villiger oxidation, and a highly *Z*-selective Wittig olefination of a hemiacetal. Key to success was minimizing redox operations and the manipulation of functional groups in the correct order.



Thromboxane B_2 (TxB_2) is a metabolite of thromboxane A_2 (TxA_2, $t_{1/2}$ (37 °C) = 32 s at pH 7.40), a prostanoid which causes contraction of coronary vessels and platelet aggregation (thrombosis) (Figure 1).[1] Although TxB_2 is generally regarded as biologically inert, there are reports that it inhibits the pulmonary inactivation of PGE_2[2] and that it may play a role in the immune[3] and vascular systems too.[4] It's main use is as a marker for TxA_2, and it is recognized as a valuable molecule for the studies of prostanoid-related biochemical processes.[5] For example, Still employed TxB_2 as a synthetic precursor to the biologically active TxA_2.[5a,6] The interesting molecular architecture of the natural product TxB_2 has made it an appealing target for chemists over the years.[7] In this context, several asymmetric syntheses of TxB_2 have been reported.[8] However, the previous synthetic strategies are rather lengthy and lack atom economy, costing time and energy, and so improved syntheses are still in demand.

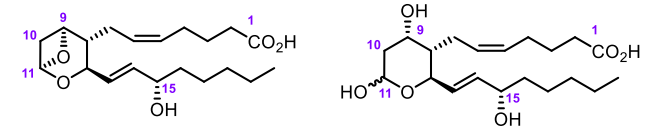
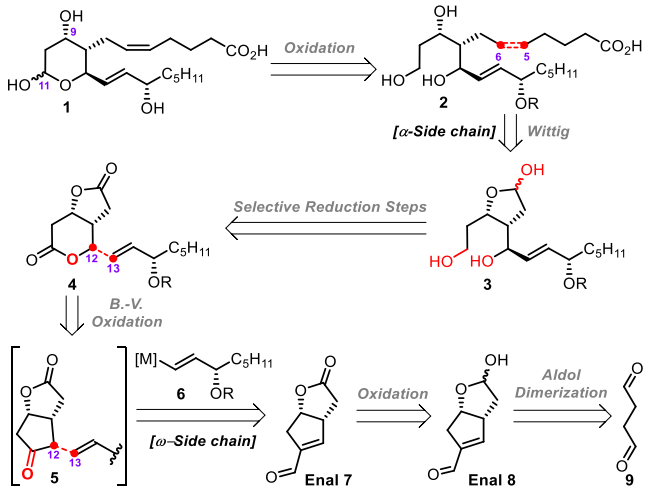


Figure 1. Structures of thromboxane A_2 and thromboxane B_2.

We recently developed a short synthetic strategy to prostaglandins, completing the total synthesis of $PGF_{2\alpha}$ in just 7 steps[9a] and applied this methodology to several prostaglandin-based drugs[9b,c] and to Δ^{12}-PGJ_3.[9d] The key step in the synthesis employed a (*L*)-proline catalyzed double aldol dimerization of succinaldehyde to prepare the key bicyclic enal intermediate (**8**).[9a,d] We were keen to broaden the reach of this chemistry and in particular to demonstrate its application to other prostanoids. Just as the Corey lactone[10] has been used for the preparation of a wide range of prostanoids, we see our enal intermediate, **8**, as being perfectly set up for further transformations to access the whole family of prostanoids in an efficient manner. As part of this effort, we now report the application of this strategy to a 12-step synthesis of the natural prostanoid TxB_2.[11]

Our retrosynthetic analysis for the stereoselective synthesis of TxB_2 **1** is shown in Scheme 1. We envisaged that the α-side chain

Scheme 1. Retrosynthetic Analysis of Thromboxane B_2 from the Key Bicyclic Enal Intermediate



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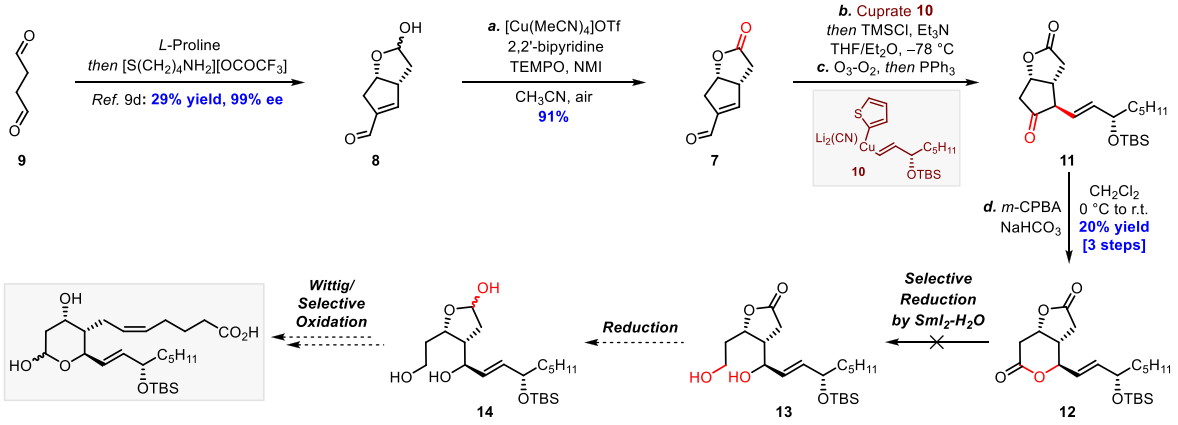
Scheme 2. Initial Attempts to Thromboxane B_2 via the Formation of Dilactone 12[a]



[a]Reagents and conditions: (a) $[Cu(MeCN)_4]OTf$ (5 mol %), 2′-bpyridine (5 mol %), TEMPO (5 mol %), NMI (10 mol %), CH_3CN, air, r.t., overnight, 91% yield. (b) Cuprate **10** (1.2 equiv), THF/Et_2O, −78 °C; then TMSCl (5 equiv), Et_3N (6 equiv), −78 °C to −20 °C. (c) O_3−O_2, CH_2Cl_2/MeOH (v/v, 3:1), −78 °C; then PPh_3 (1.5 equiv). (d) *m*-CPBA (2.5 equiv), $NaHCO_3$ (2.7 equiv), CH_2Cl_2, 0 °C to r.t., 36 h, 20% yield, 3 steps. TEMPO, 2,2,6,6-tetramethyl-1-piperidinyloxy; NMI, *N*-methylimidazole; TBS, *tert*-butyldimethylsilyl; TMS, trimethylsilyl; *m*-CPBA, *m*-chloroperoxybenzoic acid; DDQ, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone.

could be introduced by a Wittig reaction on the corresponding hemiacetal **3**. This could be obtained by selective reduction of lactone **4**, which itself could be synthesized by Baeyer−Villiger oxidation of ketone **5**. Ketone **5** could be generated from a stereoselective conjugate addition of the chiral ω-side chain **6** to the key enal intermediate **7** followed by ozonolysis. Although selective redox steps are required (**4** → **3**), this analysis was deemed preferable over using the acetal since (i) the lactone is a crystalline compound, (ii) it is a single diastereoisomer whereas the acetal is a mixture, and (iii) it minimizes the use of protecting groups.

We began our synthesis with the preparation of enal-lactone **7**, available in just 3 steps on multigram scale with high ee using our *L*-proline-catalyzed double aldol reaction of succinaldehyde (**9**), generated by hydrolysis of commercially obtainable 2,5-dimethoxytetrahydrofuran (Scheme 2).[9] Subsequent conjugate addition of the mixed vinyl cuprate **10** to **7** followed by trapping with TMSCl and selective ozonolysis[9a,b] gave ketone **11**, which was then converted to the dilactone intermediate **12** via Baeyer−Villiger oxidation[12] [20% yield (unoptimized), over 3 steps]. Unfortunately, all attempts to selectively reduce dilactone **12** to the corresponding Wittig reaction precursor **14** via the formation of **13** using Proctor's SmI_2−H_2O method[13] led to complex reaction mixtures (see the Supporting Information for detailed information). Although this method had been reported to reduce 6-membered lactones to the diol in the presence of 5-membered ring lactones, we observed the formation of multiple reaction products when applied to dilactone **12**.

Due to the difficulty in selectively reducing one of the two lactones, we decided to begin with the acetal in place, since the hemiacetal is formed directly from the proline catalyzed aldol reaction. Furthermore, this would avoid additional oxidation and reduction steps. We selected the *para*-methoxybenzyl acetal **15** to aid deprotection under neutral conditions (Scheme 3). Although this route has the acetal at the required oxidation state, it is complicated by having to manipulate and carry through two diastereoisomers. In fact, we found it better to separate the acetal diastereomers and manipulate them separately, as this allowed us to monitor reactions more easily and purify and characterize compounds more fully. Initially, the major β-isomer of the acetals was selected, and we carried through the established 1,4-addition/ozonolysis/Baeyer−Villiger oxidation, delivering the key lactone intermediate β-**17** (64% yield, over 3 steps). Following PMB deprotection with DDQ, we explored the Wittig reaction with (4-carboxybutyl)triphenyl-phosphonium bromide or [4-(4-methyl-2,6,7-trioxabicyclo[2.2.2]oct-1-yl)butyl]-triphenylphosphonium iodide,[14] but these invariably led to intractable mixtures (Scheme 3b). We suspected that under basic conditions, the lactone moiety in intermediate **18** was interfering in this step causing side reactions, and so we decided to remove it. Initially, we considered reduction to the diol since, as shown in Scheme 3b, this could lead to a short synthesis of TxB_2, simply requiring reduction, Wittig reaction, selective oxidation, and deprotection. Unfortunately, while $LiAlH_4$ reduction to diol **20** was successful, we were unable to deprotect the PMB group cleanly.

We therefore considered an alternative strategy in which we conducted a controlled reduction of the lactone to the required oxidation state and employed a protecting group instead, i.e., conversion of lactone β-**17** into the methoxy acetal. Starting with β-**17**, reduction (DIBAL-H, THF, −78 °C) and oxy-methylation of the "naked" anion generated by deprotonation with KHMDS in the presence of 18-crown-6 afforded acetal β-**22** as a single diastereoisomer.[15] The established 1,4-addition/ozonolysis/Baeyer−Villiger oxidation protocol was also applied to the minor α-isomer of PMB-acetals **15**, affording lactone α-**17** in 63% yield over 3 steps. Reduction with DIBAL-H, followed by oxy-methylation again furnished a single diastereomer α-**22**. Interestingly, the α- and β-isomers of hemiacetal **21** (isomers at the PMBO acetal) showed quite different reactivity: the α-isomer was far more labile under oxy-methylation conditions than the β-isomer giving several unidentified side products (36% yield for α vs 73% yield for β). Following PMB deprotection of acetals **22** with DDQ, Wittig olefination using phosphonium salt **24** with *t*-BuOK now successfully gave the corresponding alkene **25** in 97% yield with Z/E > 95:5. Desilylation of the TBS group with TBAF gave the required thromboxane B_2 methyl glycoside **26** in 89% yield. Finally, subjecting methyl glycoside **26** to hydrolysis with excess Dowex-50 resin in water furnished thromboxane B_2 (TxB_2, **1**) in 90% yield.[16]

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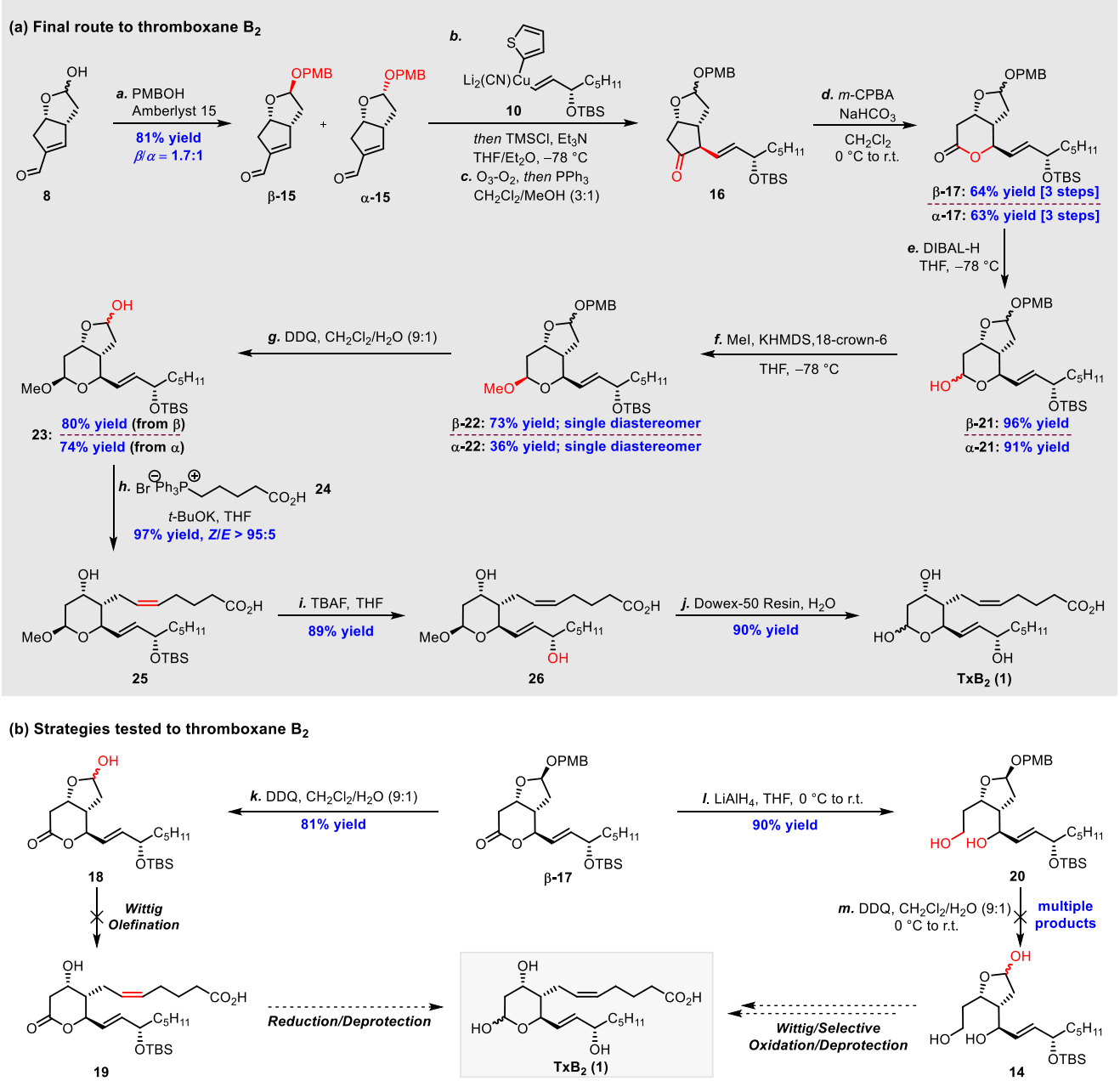
Scheme 3. Completion of the Synthesis of Thromboxane B_2[a]



[a]Reagents and conditions: (a) PMBOH (2 equiv), Amberlyst 15 (cat.), $MgSO_4$ (2.5 equiv), CH_2Cl_2, 0 °C to r.t., 24 h; then MnO_2 (6 equiv), r.t., 12 h, 81% yield, 1.7:1 β/α. (b) Cuprate **10** (1.2 equiv), THF/Et_2O, −78 °C; then TMSCl (5 equiv), Et_3N (6 equiv), −78 °C to −20 °C. (c) O_3−O_2, CH_2Cl_2/MeOH (v/v, 3:1), −78 °C; then PPh_3 (1.5 equiv). (d) *m*-CPBA (2.5 equiv), $NaHCO_3$ (2.7 equiv), CH_2Cl_2, 0 °C to r.t., 36 h, 64% yield for β, 63% yield for α, 3 steps. (e) DIBAL-H (3.0 equiv), THF, −78 °C, 3 h, 96% yield for β, 91% yield for α. (f) MeI (3 equiv), KHMDS (1.1 equiv), 18-crown-6 (1.1 equiv), THF, −78 °C, 18 h, single diastereomer, 73% yield for β, 36% yield for α. (g) DDQ (1.5 equiv), CH_2Cl_2/H_2O (v/v, 9:1), 0 °C to r.t., 6 h, 80% yield for β, 74% yield for α. (h) (4-Carboxybutyl)triphenyl-phosphonium bromide (4 equiv), *t*-BuOK (8 equiv), THF, 0 °C to r.t., 2 h, 97% yield with Z/E > 95:5. (i) TBAF (2 equiv), THF, 0 °C to r.t., 12 h, 89% yield. (j) Dowex-50 Resin, H_2O, r.t., 16 h, 90% yield. (k) DDQ (1.5 equiv), CH_2Cl_2/H_2O (v/v, 9:1), 0 °C to r.t., 6 h, 81% yield. (l) $LiAlH_4$ (1.2 equiv), THF, 0 °C to r.t., 6 h, 90% yield. (m) DDQ (1.5 equiv), CH_2Cl_2/H_2O (*v*/*v*, 9:1), 0 °C to r.t., 6 h, multiple products. PMBOH, *p*-methoxybenzyl; TBS, *tert*-butyldimethylsilyl. TMS, trimethylsilyl; *m*-CPBA, *m*-chloroperoxybenzoic acid; DIBAL-H, diisobutylaluminum hydride; HMDS, bis(trimethylsilyl)amide; DDQ, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; TBAF, tetrabutylammonium fluoride.

In conclusion, we have developed a highly stereoselective synthesis of thromboxane B_2 in 12 steps with an overall yield of 5%, utilizing our key enal intermediate, which is readily available in two steps by a *L*-proline-catalyzed aldol dimerization of succinaldehyde in high ee. The key features include an efficient 1,4-addition/ozonolysis/Baeyer−Villiger oxidation protocol and a Wittig olefination of hemiacetals with excellent levels of *Z* selectivity. Although carrying through the diastereomeric acetals complicates analysis, it avoids additional redox steps enabling the synthesis to be completed in short order. The synthesis adds to the growing list of prostanoids that can now be

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accessed from our key enal intermediate, available on scale in high enantioselectivity in just two steps.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c02299.

General procedures, characterization data, and copies of NMR spectra for all novel compounds (PDF)

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Notes

The authors declare no competing financial interest.

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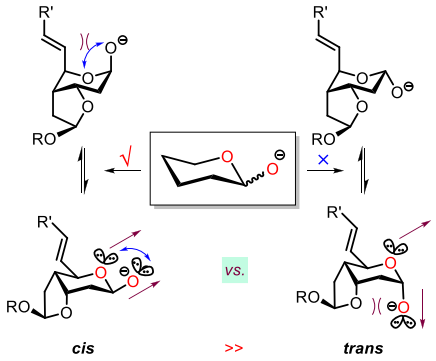
(15) Although the diastereoselectivity of the alkylation is inconsequential, it is noteworthy nonetheless and can be accounted for as follows. The repulsion between the oxygen lone pairs as well as overlapping of a p-type orbital of the ring oxygen and sp-type orbital of the exocyclic oxygen increases the nucleophilicity of the *cis*-O-"naked" anion generated from alkoxide *β*-**21** upon deprotonation. However, a similar enhancement in reactivity is not expected for *trans*-O-"naked" anion (see graphic below). For selected articles, see (a) Adderley, N. J.;



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(16) We obtained full spectroscopic data (^{1}H NMR, ^{13}C NMR, HRMS, and $[\alpha]_D^{24}$) of the methyl glycoside, but obtaining high-quality data for TxB_2 itself was more challenging. We were able to obtain HRMS (see the Supporting Information); mp, 91−94 °C; and $[\alpha]_D^{24}$ = +57.10 (*c* 1.0, EtOH) which matched the literature [lit.[8b] mp, 92.0−92.5 °C; $[\alpha]_D$ = +56.50 (*c* 1.0, EtOH)]. However, ^{1}H NMR spectrum of our sample was somewhat broad with multiple peaks, reflecting perhaps different aggregation states of the molecule in $CDCl_3$. This has been documented in previous syntheses of TxB_2.[8k] For comparison, we have included the ^{1}H NMR of our sample with that of a commercial sample from Cayman in the Supporting Information.

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