Pergamon

Tetrahedron Letters, Vol. 37, No. 52, pp. 9321-9324, 1996

0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)02212-5

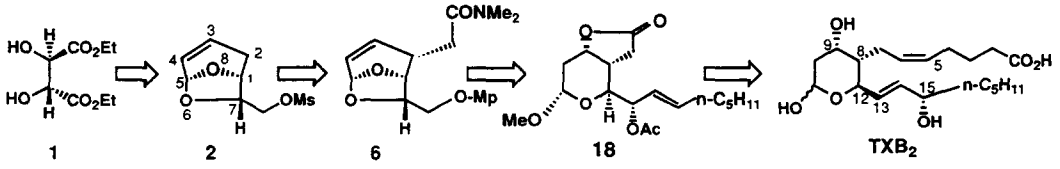
Total Synthesis of Thromboxane B_2 Starting from (*R,R*)-Tartaric Acid as a Chiral Pool

Yukio Masaki,* Kazuhiro Yoshizawa, and Akichika Itoh

Gifu Pharmaceutical University, 5-6-1 Mitahora-Higashi, Gifu 502, Japan

Abstract: Optically active natural thromboxane B_2 (**TXB$_2$**) was synthesized from (*R,R*)-tartaric acid as only chiral source. The synthesis was achieved through regio- and stereoselective introduction of acetate moiety at the C2-position of the 6,8-dioxabicyclo[3.2.1]octene derivative (**2**) to provide an acetamide derivative (**6**), partial ring opening of **6** to give a pyranoid (**10**), and construction of the C15-hydroxyl group of **TXB$_2$** by stereospecific allylic transposition of the inherent chirality of tartaric acid in the *trans*-allylic acetate (**18**). Copyright © 1996 Elsevier Science Ltd

Thromboxane B_2 (**TXB$_2$**) is a metabolite of thromboxane A_2 (**TXA$_2$**) which causes platelets to clump and aggregate and is known to be remarkably unstable under the physiological conditions ($t_{1/2}$ (37 °C) = 32 s at pH 7.4).[1] In spite of biological inertness as a platelet aggregating agent, **TXB$_2$** is recognized as a valuable substance for study of a variety of biochemical processes as well as an important synthetic precursor to **TXA$_2$**.[2] In this context, there have been reported several syntheses of optically active **TXB$_2$**, which divided into two groups of synthetic strategies: (1) utilization of the Corey's lactone including Baeyer-Villiger oxidation to lead to the pyranoid skeleton;[3] (2) manipulation of *D*-glucose providing the pyranoid intermediate.[4] Among the syntheses reported, no one construct highly stereoselectively the C15-chiral center which is important for bioactivity. Now we disclose a highly stereoselective total synthesis of **TXB$_2$** featuring effective use of (*R,R*)-diethyl tartrate (**1**) as only chiral source. The synthesis involves regio- and stereoselective functionalization of 6,8-dioxabicyclo[3.2.1]octene derivative (**2**) to provide an acetamide derivative (**6**) and stereospecific construction of the secondary C15-hydroxyl group via allylic transposition of the inherent chirality of tartaric acid in the *trans*-allylic acetate (**18**).



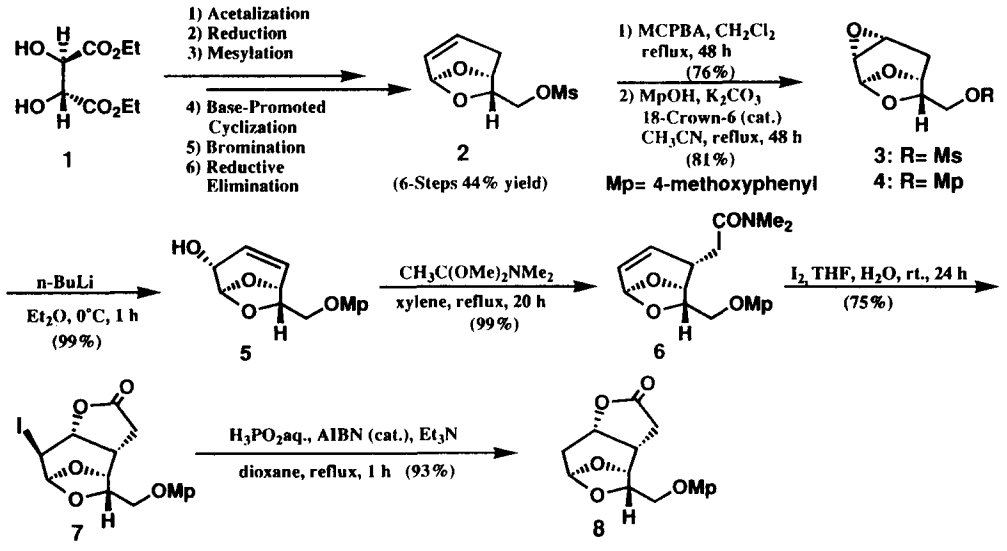
1 **2** **6** **18** **TXB$_2$**

(**Mp**: 4-methoxyphenyl)

(*R,R*)-(+)-Diethyl tartrate (**1**) was transformed to a (*1S,5S,7S*)-(+)-7-mesyloxymethyl-6,8-dioxabicyclo[3.2.1]oct-3-ene (**2**) ($[\alpha]_D$+61.9° (c=0.8, $CHCl_3$) through six step reactions in 44% overall yield according to the reported method.[5] Highly regio- and stereoselective functionalization of the bicyclic skeleton was realized as illustrated in Scheme 1. Oxidation of the olefin with MCPBA afforded stereoselectively the α-

epoxide (**3**) in the same mode reported by Brown.[6] After substitution of the mesyloxy group on the side chain at the C7-position with p-methoxyphenyloxy (Mp-O-) group,[7] the Mp-ether (**4**) was led to an allylic alcohol (**5**) by base-promoted isomerization with BuLi.[6] Regio- and stereoselective introduction of acetate moiety on the C2-position was attained by Claisen rearrangement of the alcohol using $CH_3C(OMe)_2NMe_2$ [8] in refluxing xylene to give an almost quantitative yield of an amide derivative (**6**). Iodolactonization followed by reductive deiodiation of the iodide (**7**) by means of hypophosphorus acid[9] proceeded smoothly to provide a lactone (**8**).

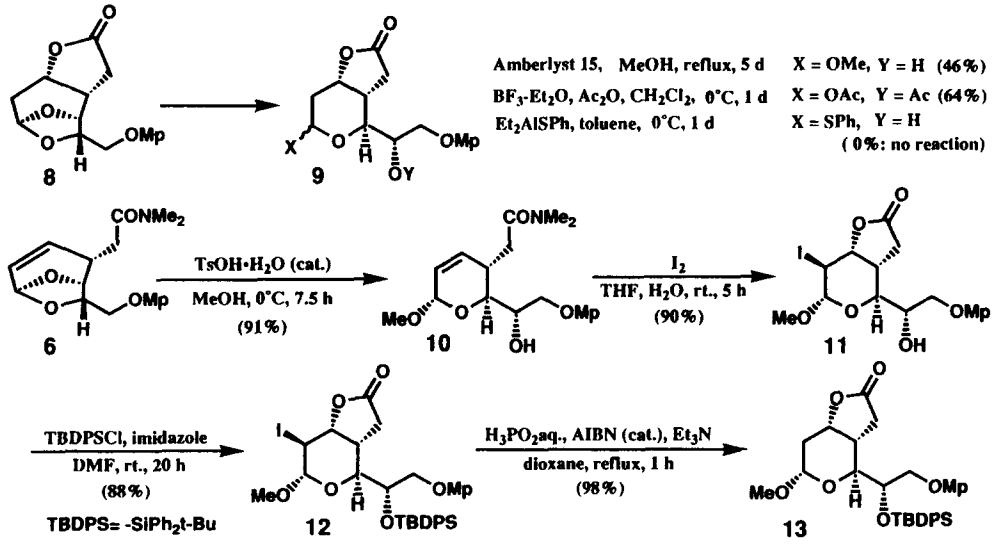
Scheme 1



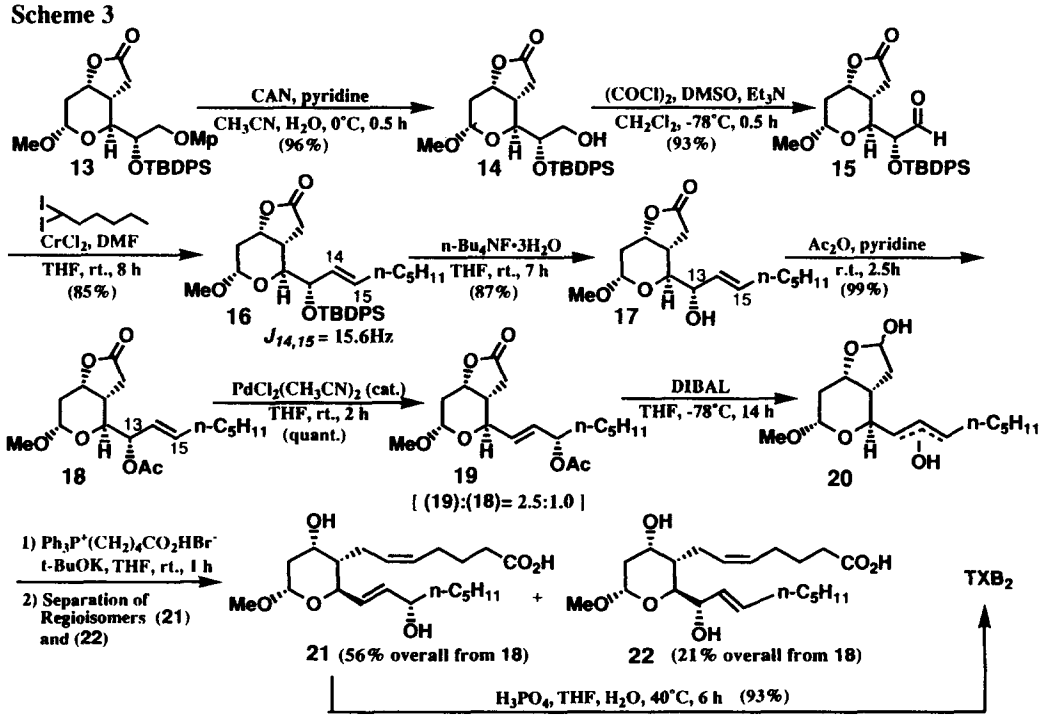
Several attempts at partial ring opening of the 6,8-dioxabicyclo[3.2.1]octane skeleton of **8** giving the pyranoid lactone structure (**9**) have been done by (1) methanolysis using Amberlyst-15 as a catalyst;[4b] (2) acetolysis using BF_3-Et_2O as a catalyst in Ac_2O;[5b] (3) thiolysis using Et_2AlSPh,[10] but none of these methods afforded satisfactory results providing pyranoids (**9**) in good yields. In turn, the amide (**6**) in which the C5-acetal carbon is located at the allylic position was chosen for partial ring opening to lead to pyranoid as shown in Scheme 2. Thus, treatment of the amide (**6**) with catalytic amounts of p-TsOH in MeOH at 0 °C gave the desired pyranoid (**10**) in an excellent yield. Three-step transformation of **10** involving iodolactonization, OH-protection with *t*-butyldiphenylsilyl (TBDPS) group,[7] and reductive deiodination through iodolactone (**11**) and *t*-butyldiphenylsilyl ether (**12**) provided a lactone-acetal (**13**) in a high overall yield (78%).

Construction of the ω-chain and the α−chain starting with **13** was realized according to Scheme 3. An aldehyde (**15**) was obtained from the pyranoid-lactone (**13**) through Swern oxidation of the alcohol (**14**), obtained by deprotection of Mp-group with $Ce(NH_4)_2(NO_3)_6$ (CAN). After considerable attempts, we achieved to make *trans*-olefinic bond of the side chain by Uchimoto's method[11] using 1,1-diiodohexane and $CrCl_2$ in DMF to yield a *trans*-olefin (**16**), from which a *trans*-allylic alcohol (**17**) was obtained by deprotection of the hydroxyl group. A crucial step involving stereospecific allylic tranposition[12] of the acetate (**18**) proceeded with a catalytic amount of $PdCl_2(CH_3CN)_2$ in THF at room temperature for 2 h to give an equibrium mixture of the allylic acetates (**19**) and (**18**) of a 2.5:1.0 ratio. Separation of the isomers by column

Scheme 2



Scheme 3



chromatography was difficult and the mixture was used for the next steps without separation. Reduction of the lactone portion of the acetate mixture with DIBAL, followed by Wittig reaction of the crude mixture of hemiacetals (**20**) with $Ph_3P=CH(CH_2)_3CO_2^-$ and column chromatographic separation of the products afforded the desired mono-methyl ether (**21**) of $\mathbf{TXB_2}$ in 56% overall yield from the allylic acetate (**18**) along with the isomer (**22**) as a minor product (21%). Hydrolysis of the methyl ether (**21**) with phosphoric acid gave crystalline $\mathbf{TXB_2}$ [mp. 92.0-94.0 °C, $[\alpha]_D$+56.8° (c=0.4, EtOH)] which was identified with the authentic sample [mp. 92.0-92.5 °C, $[\alpha]_D$+56.5° (c=1.0, EtOH)][3] in all respects.

In conclusion, optically active $\mathbf{TXB_2}$ was synthesized from tartaric acid as only chiral source, which solves the longstanding problem of establishing the stereospecific construction of the C15-hydroxyl group.

Acknowledgements: This research was supported in part by Suzuken memorial foundation for research on medical sciences. Ono Pharmaceutical Co. Ltd., is gratefully acknowledged for providing an authentic sample of $\mathbf{TXB_2}$.

References

1 Hamberg, M., Svensson, J., Samuelson, B., *Proc. Natl. Acad. Sci., U.S.A.*, **1975**, 72, 2994-2998; Fried, J., Zhou, Z., Chen, C.-K., *Tetrahedron Lett.*, **1984**, 25, 3271-3272.

2 Bhagwat, S.S., Hamann, P.R., Still, W.C., *J. Am. Chem. Soc.*, **1985**, 107, 6372-6376.

3 Kelly, R.C., Schletter, I., Stein, S.J., *Tetrahedron Lett.*, **1976**, 3279-3282; Nelson, N.A., Jackson, R.W., *Ibid*, **1976**, 3275-3278.

4 a) Basson, M.M., Holzapfel, C.W., Verdoorn, G.H., *Heterocycles*, **1989**, 29, 2261-2265; Hernandez, O., *Tetrahedron Lett.*, **1978**, 219-222; Hanessian, S., Lavallee, P., *Can. J. Chem.*, **1977**, 55, 562-565; **1981**, 59, 870-877; Corey, E.J., Shibasaki, M., Knolle, J., *Tetrahedron Lett.*, **1977**, 1625-1626; b) Kelly, A.G., Roberts, J.S., *J. Chem. Soc., Chem. Commun.*, **1980**, 228-229.

5 a) Masaki, Y., Iwata, I., Imaeda, T., Oda, H., Nagashima, H., *Chem. Pharm. Bull.*, **1988**, 36, 1241-1244; b) Masaki, Y., Nagata, K., Serizawa, Y., Kaji, K., *Tetrahedron Lett.*, **1984**, 25, 95-96.

6 Sweet, F., Brown, R.K., *Can. J. Chem.*, **1968**, 46, 2289-2298; Singh,U.P., Brown, R.K., *Ibid.*, **1970**, 48, 1791-1792.

7 Green, T.W., Wuts, P.G.M., "Protective Groups in Organic Synthesis" 2nd ed, JohnWily & Sons, Inc., New York (1991), pp 46-47; 83-84, and references cited therein.

8 Wick, A.W., Felix, D., Steen, K., Eschenmoser, A., *Helv. Chim. Acta*, **1964**, 47, 2425-2429.

9 Barton, D.H.R., Jang, D.O., Jaszberenyi, J.C., *Tetrahedron Lett.*, **1992**, 33, 5709-5712.

10 Masaki, Y., Serizawa, Y., Nagata, K., Oda, H., Nagashima, H., Kaji, K., *Tetrahedron Lett.*, **1986**, 27, 231-234.

11 Okazoe, T., Takai, K., Uchimoto, K., *J. Am. Chem. Soc.*, **1987**, 109, 951-953.

12 Grieco, P.A., Takigawa, T., Bongers, S.L., Tanaka, H., *J. Am. Chem. Soc.*, **1980**, 102, 7587-7588; Danishefsky, S.J., Cabal, M.P., Chow, K., *Ibid.*, **1989**, 111, 3456-3457; Nakazawa, M., Sakamato, Y., Takahashi, T., Tomooka, K., Ishikawa, K., Nakai, T., *Tetrahedron Lett.*, **1993**, 34, 5923-5926.

(*Received in Japan* 30 *September* 1996; *revised* 5 *November* 1996; *accepted* 11 *November* 1996)