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Preparation of an Advanced Intermediate for the Synthesis of Epi-Thromboxanes

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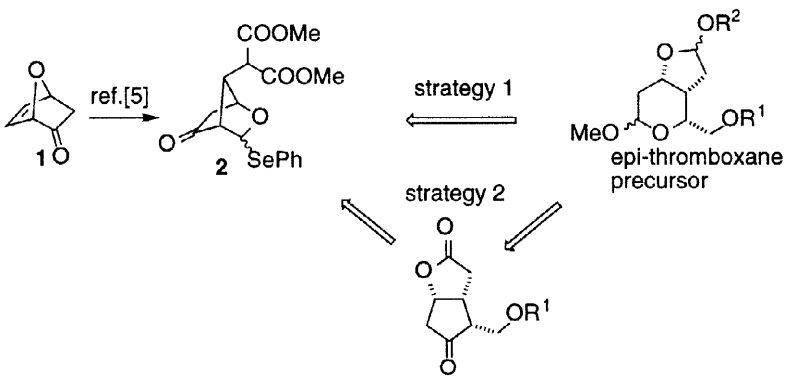
Abstract: Two different approaches for the synthesis of an advanced intermediate of epi thromboxanes (all-*cis* thromboxanes) have been evaluated. The key intermediate **2**, prepared by malonyl radical addition to the 7-oxabicyclo[2.2.1]hept-5-en-2-one **1**, has been transformed into the tetrahydropyran derivative **12** in 14 steps and 30% overall yield. © 1998 Elsevier Science Ltd. All rights reserved.

The discovery of epimeric prostanoids, known as isoprostanes, by Roberts et al[1] has stimulated research programs towards their biological activity[2] and their preparation.[3] We have recently reported a new access to 12-epi-prostaglandins based on a phenylseleno mediated radical addition to 7-oxabicyclo[2.2.1]hept-5-en-2-one[4] **1** leading to **2**.[5] The key intermediate of our synthesis was an all-*cis* Corey lactone aldehyde. We report here our effort to convert **2** to an advanced intermediate (Scheme 1) for the synthesis of all-*cis* thromboxanes. The synthesis has been performed in the racemic series, however, since both enantiomers of **1** are readily available,[6] our strategy is expected to be useful for the preparation of enantiopure epi-thromboxanes. Two major approaches have been investigated. In the most concise one (strategy 1), the bicyclic lactone **2** is directly converted to the tetrahydropyran target compound, the key step is a regioselective Baeyer-Villiger oxidation of the bicyclic ketone **2**. The second approach, more classical, is going through a Baeyer-Villiger oxidation of a cyclopentanone derivative.



Scheme 1

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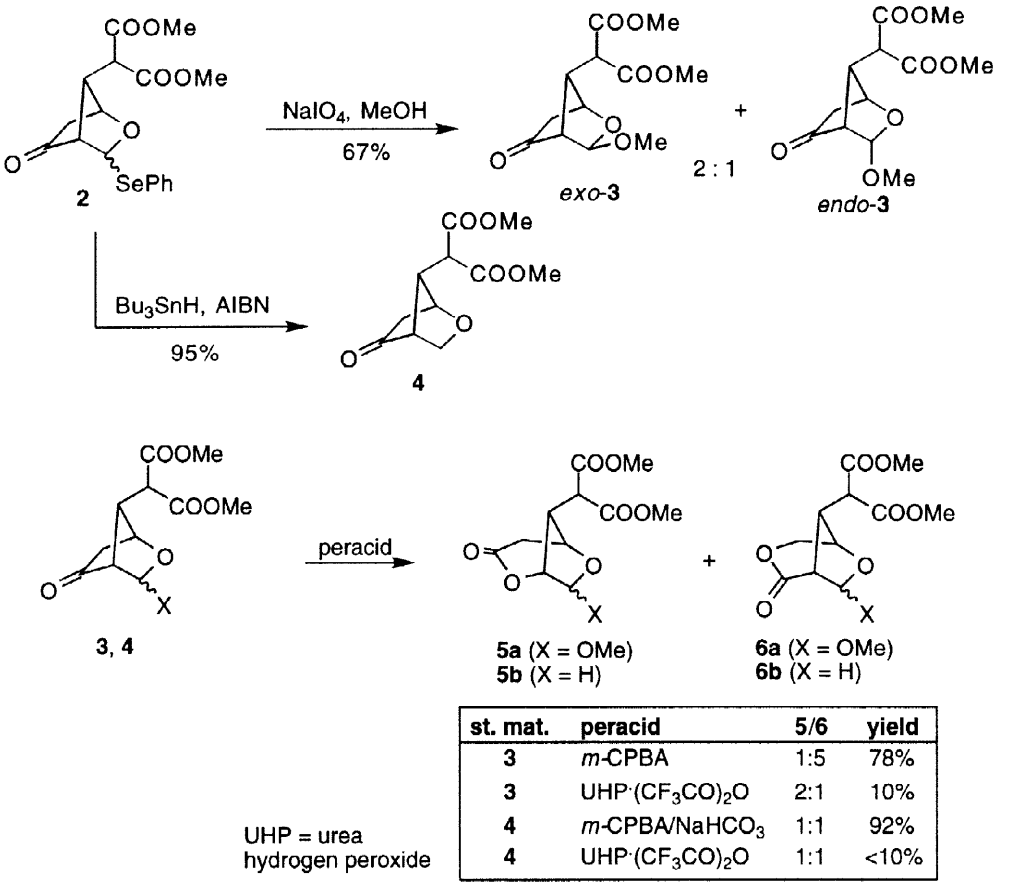
Approach 1: Baeyer-Villiger oxidation of the bicyclic lactone. The selenoacetal **2** was converted into the acetal **3** by treatment with $NaIO_4$ in MeOH (Scheme 2), this method proved to be much milder and high yielding than acidic MeOH. Baeyer-Villiger oxidation of **3** (*exo/endo* 2:1 mixture) with several reagents has been investigated. Typical examples are reported in Scheme 2, *m*-CPBA gave preferentially **6a**, the undesired product resulting from oxygen insertion at the less substituted position. Trifluoroperacetic acid, generated from urea hydrogen peroxide (UHP) and trifluoroacetic anhydride gave very low yield and selectivity, the preferential formation of **5a** is mainly due to decomposition of **6a**. Interestingly, when the purified *exo* isomer of **3** was treated with *m*-CPBA, only the lactone **6** was isolated. This observation indicates that the *exo*-methoxy group has to be removed for a better regiocontrol in favor of **5**. In order to test this hypothesis, the reduced compound **4** was prepared by treatment of **2** with tributyltinhydride. The Baeyer-Villiger oxidation was high yielding but a 1:1 ratio of regioisomer was formed.[7]



st. mat.	peracid	5/6	yield
3	*m*-CPBA	1:5	78%
3	UHP·$(CF_3CO)_2O$	2:1	10%
4	*m*-CPBA/$NaHCO_3$	1:1	92%
4	UHP·$(CF_3CO)_2O$	1:1	<10%

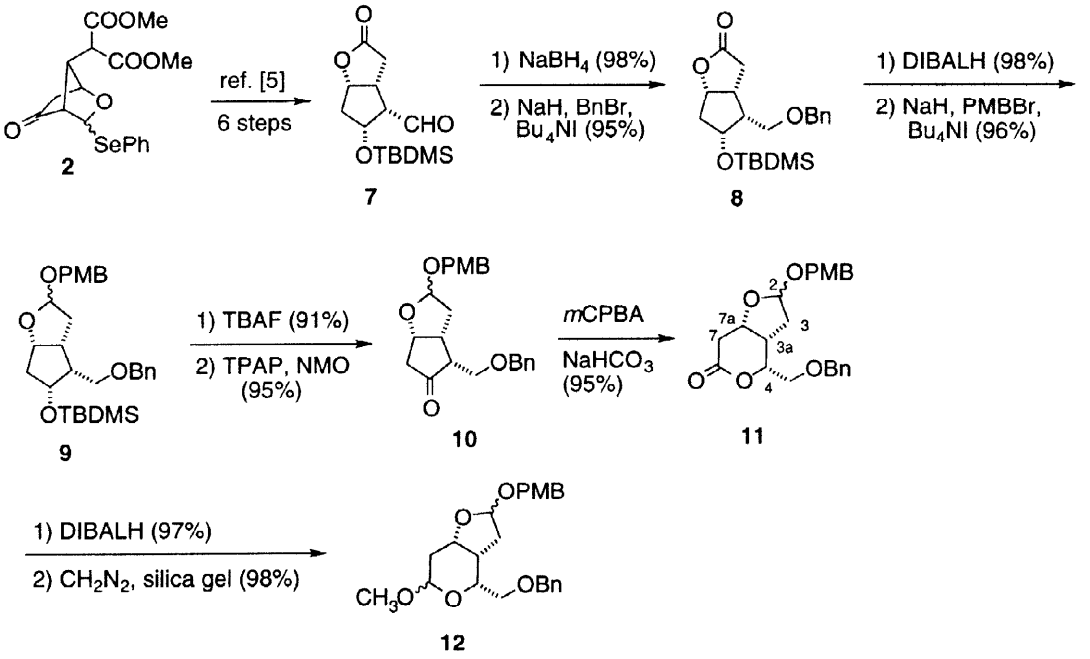
UHP = urea hydrogen peroxide

Scheme 2

The deceiving regioselectivity of the Baeyer-Villiger oxidation of the bicyclic ketone incite us to look at the strategy 2 which is well documented in the series possessing the natural relative configuration.

Approach 2. Baeyer-Villiger oxidation of a all-*cis* Corey lactone. The all-*cis* Corey lactone aldehyde **7** was prepared in 6 steps starting from the selenoacetal **2** (Scheme 3) according to the published procedure.[5] The aldehyde **7** was then reduced with sodium borohydride and the alcohol was protected as benzyl ether. The reduction of lactone **8** was carried out with DIBALH and the lactol protected as a *para*-methoxybenzyl (PMB) acetal **9** in 96% yield by treatment with NaH, Bu_4NI and *para*-methoxybenzyl bromide.

The introduction of two different benzyl protective groups should facilitate the introduction of the α and ω chains of the thromboxane by either a selective deprotection of the PMB group (oxidative deprotection) or a common deprotection of both benzyl groups (hydrogenation). The deprotection of the silyl group was done with TBAF. The alcohol was oxidized using TPAP/NMO to afford the ketone **10** in 95 % yield. Under these conditions, no epimerization at of the α-center was observed. The two acetal epimers of **10** were isolated and fully characterized by NOESY, COESY and HETCOR experiments to confirm the structure and the relative stereochemistry.



Scheme 3

The Baeyer-Villiger oxidation of **10** with *m*CPBA/$NaHCO_3$ in CH_2Cl_2 at r.t. afforded the lacone **11** in 95% yield with a complete regioselectivity.[8] Reduction of **11** with DIBALH at -60 °C gave the lactol (97%) which was directly acetalized to give the target epi-thromboxane intermediate **12** in 98% yield by treatment with diazomethane/silica gel.[9]

Conclusions. We have presented here the first stereoselective synthesis of an advanced intermediate for the synthesis of all-*cis* thromboxanes. The 9 steps necessary for the the preparation of **12** from the all-*cis* Corey lactone **7** were achieved with a yield of 68%. This approach is satisfactory from a preparative standpoint, indeed, the global yield starting from 7-oxabicyclo[2.2.1]hept-5-en-2-one **1** reaches 30% over 14 steps. The building block **12** is expected to be a versatile synthon for the synthesis of both enantiomeric forms of all-*cis* thromboxanes, a class of compounds whose biological activity has not been tested so far.

Acknowledgments. We are very grateful to the Swiss National Science Foundation (project 20-44'234.95) for financial support.

References and notes

1. Morrow, J. D.; Hill, K. E.; Burk, R. F.; Roberts II, L. J. *Proc. Natl. Acad. Sci. USA* **1990**, *87*, 9383-9387.
2. Morrow, J. D.; Roberts, L. J. *Biochem. Pharmacol.* **1996**, *51*, 1-9.
3. Larock, R. C.; Lee, N. H. *J. Am. Chem. Soc.* **1991**, *113*, 7815-7816. Rondot, B; Durand, T.; Girard, J. P.; Rossi, J. C.; Schio, L.; Khanapure, S. P.; Rokach, J. *Tetrahedron Lett.* **1993**, *34*, 8245. Roland, A.; Durand, T.; Rondot, B.; Vidal, J. P.; Rossi, J. C. *Bull. Soc. Chim. Fr.* **1996**, *133*, 1149-1154. Guy, A.; Durand, T.; Vidal, J. P.; Rossi, J. C. *Tetrahedron Lett.* **1997**, *38*, 1543-1546. Hwang, S. W.; Adiyaman, M.; Khanapure, S.; Schio, L.; Rokach, J. *J. Am. Chem. Soc.* **1994**, *116*, 10829-10830. Adiyanman, M.; Lawson, J. A.; Hwang, S. W.; Khanapure, S. P.; FitzGerald, G. A.; Rokach, J. *Tetrahedron Lett.* **1996**, *37*, 4849-4852. Mulzer, J.; Kermanchahi, A. K.; Bruschmann, J.; Luger, P. *Liebigs Ann. Chem.* **1994**, 531-539. Taber, D. F.; Herr, R. J.; Gleave, D. M. *J. Org. Chem.* **1997**, *62*, 194-198.
4. Vogel, P.; Fattori, D.; Gasparini, F.; Le Drian, C. *Synlett* **1990**, 173-185.
5. Renaud, P.; Vionnet, J. P. *J. Org. Chem.* **1993**, *58*, 5895-5896. Renaud, P.; Vionnet, J. P. *Helv. Chim. Acta* **1994**, *77*, 1781-1790.
6. Vogel, P.; Vieira, E. *Helv. Chim. Acta* **1983**, *66*, 1865-1871. Vogel, P.; Black, K. A. *Helv. Chim. Acta* **1984**, *67*, 1612-1615. Vogel, P.; Reymond, J.-L. *Tetrahedron Asymmetry* **1990**, 1, 729-736. Kagan, H. B.; Ronan, B. *Tetrahedron Asymmetry* **1991**, *2*, 75-90. Corey, E. J.; Loh, T. P. *Tetrahedron Lett.* **1993**, *34*, 3979-3982.
7. For a review on the Baeyer-Villiger oxidation of bicyclic ketones, see: Krow, G. R. *Tetrahedron* **1981**, *37*, 2697-2724.
8. *endo*-**11:** ^{1}H-NMR (500 MHz, $CDCl_3$): 7.40-7.19 (*m*, 7 arom. H); 6.90-6.82 (*m*, 2 arom. H); 5.18 (*d*, *J* = 5.0, H-C(2)); 4.68 (*ddd*, *J* = 9.4, 4.7, 1.6, H-C(7a)); 4.51 (AB, J_{AB}=11.4, CH_2Ph); 4.49 (AB, J_{AB} = 11.4, CH_2PhOMe); 3.72 (*s*, OMe), 3.69 (*m*, 2 H, AB of ABX, J_{AB} = 10.1, J_{AX} = 6.4, J_{BX} = 5.7, CH_2OBn); 3.00 (*ddd*, *J* = 18.3, 9.2, 2.7, H-C(3a)), 2.86-2.80 (2 *dd*, 2 H, *J* = 0.7, 15.8 (4.8, 15.8) CH_2-C(7)); 1.99-1.87 (*m*, CH_2-C(3)). ^{13}C-NMR (125.76 MHz, $CDCl_3$): 170.30 (*s*), 159.26 (*s*), 137.36 (*s*), 129.81 (*s*), 128.72 (*d*), 128.18 (*d*), 113.85 (*d*), 101.99 (*d*), 76.25 (*d*), 73.73 (*t*), 73.12 (*d*), 69.28 (*t*), 68.42 (*t*), 55.28 (*q*), 36.61 (*d*),35.12 (*t*), 31.38 (*t*). IR (KBr): 2928, 2856, 1753, 1614, 1514, 1465, 1357, 1246, 1097, 1031. CI-MS: 398(M), 377(1), 261(2), 211(17), 121(100), 91(40).
exo-**11**: ^{1}H-NMR (500 MHz, $CDCl_3$, selected signals): 5.27 (*d*, *J* = 4.57, H-C(2)), 4.23-4.16 (*m*, H-C(7a)); 3.71-3.64 (*m*, CH_2OBn); 3.00 (*dd*, *J* = 6.6, 15.3, H-C(3a)). Anal. calc. for $C_{23}H_{26}O_6Si$ (426.55): C 69.33, H 6.58; found: C 69.45, H 6.51.
9. **12**: Anal. calc. for $C_{24}H_{30}O_6$ (414.50): C 69.55, H 7.30; found: C 69.53, H 7.36.