Highly Stereocontrolled Synthesis of Carbacyclin from Acyclic Starting Materials via Ti(II)-Mediated Tandem Cyclization

Sentaro Okamoto, Kandasamy Subburaj, and Fumie Sato*

Department of Biomolecular Engineering
Tokyo Institute of Technology, 4259 Nagatsuta-cho
Midori-ku, Yokohama, Kanagawa 226-8501, Japan

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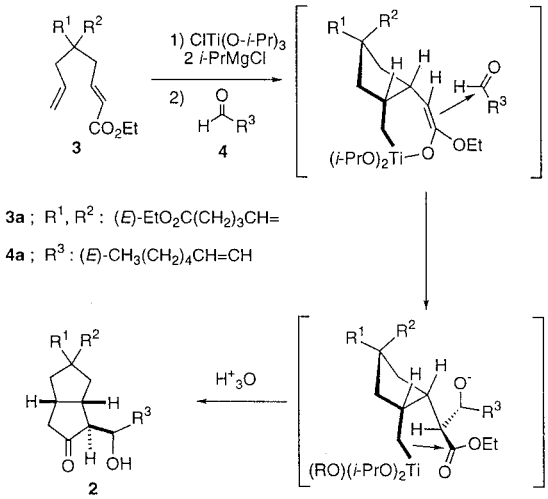
Since the discovery of prostaglandin I_2 (prostacyclin) which plays an important role in human physiology, a number of chemically and metabolically stable prostaglandin I_2 analogues have been developed as clinically effective agents such as antithrombotic drugs. Among these analogues, carbacyclin (**1**) is one of the most attractive agents, and its synthesis has attracted much interest.[1] Available synthetic approaches to **1** usually start from five-membered cyclic compounds such as the Corey lactone (or its derivatives) and bicyclo[3.3.0]octan-3-ones.[2] Herein we report a highly stereocontrolled construction of the carbacyclin framework starting from acyclic hydrocarbons where a titanium-(II)-mediated multistep sequential transformation in a single reaction vessel plays a key role.[3]

Recently, we have developed several synthetically useful reactions mediated by a divalent titanium reagent, $XTi(O\text{-}i\text{-}Pr)_3$ (X = O-*i*-Pr or Cl)/2 equiv of *i*-PrMgCl.[4] One of these reactions is a one-pot preparation of bicyclo[3.3.0]octanes **2** having a side chain by the Ti(II)-mediated tandem cyclization of 2,7-dienoates **3** and subsequent reaction with aldehydes **4**, which might proceed through the reaction mechanism shown in Scheme 1.[5] Although the stereochemistry of **2** thus produced has not been determined with the exception of the cis-ring junction of **2**, we anticipated that the reaction of the titanabicyclic intermediate with the aldehyde would proceed through the convex face and, thus, the relative configuration of three consecutive stereogenic centers on the ring of **2** would be controlled as depicted in Scheme 1.

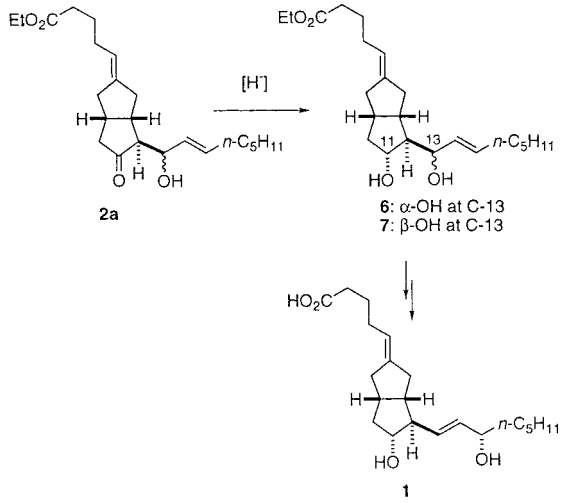
With this assumption, we planned one-pot preparation of carbacyclin intermediate **2a** using ethyl (*E*,*E*)-5-alkylidene-2,7-octadienoate (**3a**) as the starting 2,7-bis-unsaturated ester and (*E*)-2-octenal (**4a**) as an aldehyde. From **2a**, carbacyclin was expected to be prepared readily by stereoselective reduction of the ketone moiety and isomerization of the allylic alcohol moiety as summarized in Scheme 2.

As shown in Scheme 3, the starting **3a** was readily synthesized from readily available **5**[6] in 22% overall yield by using the Ti-(II)-mediated coupling reaction developed by us recently[7] and the Suzuki-Miyaura coupling reaction[8] as the key steps. The

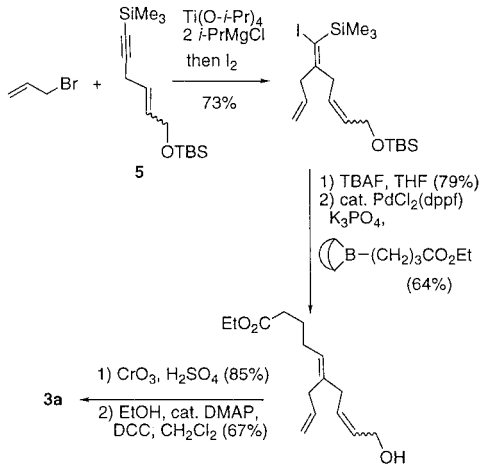
Scheme 1



Scheme 2



Scheme 3



(1) Reviews: (a) Schinzer, D. Carbacyclines: Stable Analogs of Prostacyclines. In *Organic Synthesis Highlights II*; Waldmann, H., Ed.; VCH: New York, 1995; pp 301−307. (b) Collins, P. W.; Djuric, S. W. *Chem. Rev.* **1993**, *93*, 1533.

(2) For syntheses of **1**, see: (a) Kojima, K.; Sakai, K. *Tetrahedron Lett.* **1978**, 3743. (b) Nicolaou, K. C.; Sipio, W. J.; Magolda, R. L.; Seitz, S.; Barnette, W. E. *J. Chem. Soc., Chem. Commun.* **1978**, 1067. (c) Shibasaki, M.; Ueda, J.; Ikegami, S. *Tetrahedron Lett.* **1979**, 433. (d) Morton, D. R., Jr.; Brokaw, F. C. *J. Org. Chem.* **1979**, *44*, 2880. (e) Aristoff, P. A. *J. Org. Chem.* **1981**, *46*, 1954. (f) Shibasaki, M.; Sodeoka, M.; Ogawa, Y. *J. Org. Chem.* **1984**, *49*, 4096. (g) Hutchinson, D. K.; Fuchs, P. L. *J. Am. Chem. Soc.* **1987**, *109*, 4755. (h) Nagao, Y.; Nakamura, T.; Ochiai, M.; Fuji, K.; Fujita, E. *J. Chem. Soc., Chem. Commun.* **1987**, 267. (i) Sodeoka, M.; Ogawa, Y.; Kirio, Y.; Shibasaki, M. *Chem. Pharm. Bull.* **1991**, *39*, 309.

(3) An effort to synthesize carbacyclin from acyclic starting materials has been made by Negishi et al. where the zirconium-mediated enyne cyclization is a key reaction: Negishi, E.; Pour, M.; Cederbaum, F. E.; Kotora, M. *Tetrahedron* **1998**, *54*, 7057.

(4) Reviews for synthetic reactions mediated by the titanium(II) reagent: Sato, F.; Urabe, H.; Okamoto, S. *Pure Appl. Chem.* **1999**, *71*, 1511. Sato, F.; Urabe, H.; Okamoto, S. *J. Synth. Org. Chem. Jpn.* **1998**, *56*, 424. Sato, F.; Urabe, H.; Okamoto, S. *Synlett* **2000**, 753. Sato, F.; Urabe, H.; Okamoto, S. *Chem. Rev.* **2000**, *100*, 2835.

(5) Suzuki, K.; Urabe, H.; Sato, F. *J. Am. Chem. Soc.* **1996**, *118*, 8729. Urabe, H.; Suzuki, K.; Sato, F. *J. Am. Chem. Soc.* **1997**, *119*, 10014.

(6) Compound **5** was prepared from 2-buten-1,4-diol through a three-step reaction in 72−85% yield. See Supporting Information.

(7) Takayama, Y.; Gao, Y.; Sato, F. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 851. Okamoto, S.; Takayama, Y.; Gao, Y.; Sato, F. *Synthesis* **2000**, 975.

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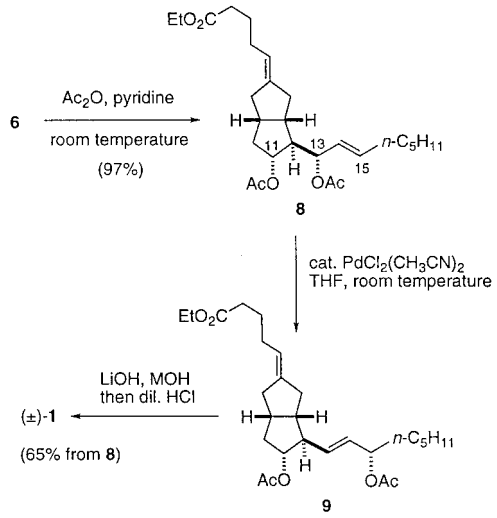
Scheme 4



reaction of **3a** with a ClTi(O-*i*-Pr)$_3$/2 *i*-PrMgCl reagent in ether (6 h at −78 to −20 °C) and the following addition of **4a** to the reaction mixture at −50 °C proceeded as expected to furnish **2a** having the structure shown in Scheme 1. Since **2a** was easily dehydrated during column chromatography, the crude **2a** thus obtained was directly subjected to reduction to the corresponding alcohol. Thus, the reduction of **2a** with $NaBH_4$ in MeOH (0 °C) proceeded through the convex face exclusively to provide the 11α-hydroxy products (prostaglandin-numbering) as a mixture of **6** and **7** in a ratio of 84:16 in 55% combined yield (Scheme 2). From the mixture, **6** was isolated in 43% yield (based on **3a**) by column chromatography. The structure of **6** was confirmed by ^{1}H NMR analysis after converting to the corresponding acetonide.[9]

From **6**, carbacyclin **1** was synthesized in 62% yield according to the reaction sequence shown in Scheme 4. After acetylation of **6** (97%), the resulting 11,13-bis acetate **8** was rearranged to 11,15-bis acetate **9** by treatment with a catalytic amount of $PdCl_2(CH_3CN)_2$ (4 mol %) in THF at room temperature.[10,11] The saponification of the product followed by column chromatography furnished (±)-**1** in 65% isolated yield.[12] Thus, carbacyclin can be prepared from simple and readily available acyclic starting materials **3a** and **4a** via five steps in 27% overall yield. We have found that the enantiomers of racemic **1** thus prepared can be readily separated by HPLC using a chiral column.[13] The ^{1}H and ^{13}C NMR and HPLC mobility of **1** thus prepared were identical with those recorded for authentic carbacyclin purchased from Cayman.

In conclusion, the synthesis of carbacyclin starting from acyclic compounds has been accomplished in which a Ti(II)-mediated tandem cyclization is a key reaction. In this synthesis, all but one of the five sp^3-hybridized stereocenters were introduced with almost complete stereoselectivity, three by a one-pot procedure. Another characteristic feature of the present method is its flexibility, thus allowing preparation of carbacyclin analogues[1b] having a variety of α- and ω-side chains by using **3** having a different kind of alkylidene group (R^1, R^2) and/or α,β-unsaturated aldehydes other than **4a**, and further investigation in this direction is underway in our laboratory. As mentioned above, optically active **1** has been synthesized starting from the Corey lactone or its derivatives[2e,f,i] or bicyclo[3.3.0]octan-3-ones.[2a−d,h] Although it is difficult to compare the present synthesis of carbacyclin with previously established methods because the starting compounds are quite different, we believe that this adds another efficient access to optically active carbacyclin even considering the fact that resolution of the compound is required at the final stage.

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Supporting Information Available: Experimental procedures, spectral data for **1**, **3a**, **6**, **8**, and the acetonide derived from **6**, and chiral HPLC data for **1** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) Miyaura, N.; Ishiyama, T.; Sasaki, H.; Ishikawa, M.; Satoh, M.; Suzuki, A. *J. Am. Chem. Soc.* **1989**, *111*, 314.

(9) Cosy and noesy experiments. See Supporting Information.

(10) Review for the Pd-catalyzed 1,3-transposition of allylic acetates, see: Overman, L. E. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 579. Application of this transposition reaction to the preparation of prostaglandin intermediates was reported: Grieco, P. A.; Takigawa, T.; Bongers, S. L.; Tanaka, H. *J. Am. Chem. Soc.* **1980**, *102*, 7588. Danishefsky, S. J.; Cabal, M. P.; Chow, K. *J. Am. Chem. Soc.* **1989**, *111*, 3456.

(11) The reaction product consisted of **9** and unreacted **8** in a ratio of 80:20. These could not be separated at this stage and were separated after the saponification.

(12) Unreacted **8** was recovered as the corresponding dihydroxy acid after saponification in 14% isolated yield: the yield of **1** based on the consumed **8**, therefore, was calculated to be 75%. The dihydroxy acid thus obtained could be converted quantitatively to **6** by treatment with EtI and K_2CO_3 in DMF.

(13) Separation by HPLC was performed using a chiral column (CHIRALCEL OD-H, Daicel) eluting with hexanes/EtOH = 30/1 and compounds were detected by UV absorption (210 nm): retention time was 40.6 min for (−)-**1** and 56.7 min for (+)-**1**; α = 1.42. The optical rotation value of (+)-carbacyclin thus separated was $[\alpha]^{27}_D$ +90 (*c* 0.24, MeOH) (lit.[2h] $[\alpha]^{21}_D$ +90.9 (*c* 0.19, MeOH)).