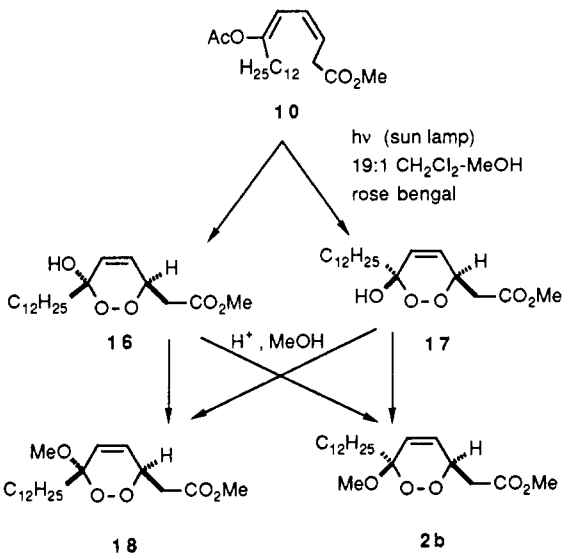
Scheme III



flood lamp for 2 h at 20 °C provides 40% of oxygenated enone **14** and 40% of unsaturated aldehyde **15**. Apparently, singlet oxygen adds to alkoxy diene **12** to give mainly the dioxetane **13**, as reported in related systems.[7]

Fortunately, photooxygenation of the acetoxy diene **10** did lead to products that could be converted to peroxy ketals **1** and **2**. Irradiation with a sun lamp of a 3×10^{-3} M solution of acetoxy diene **10** in 19:1 CH_2Cl_2:MeOH for 8 h at 10 °C in the presence of rose bengal (10^{-4} M) and oxygen affords 45% of a 3:2 mixture of peroxy hemiketals **16** and **17**. The sensitizer is fully photobleached during the first hour of irradiation. Yet, disappearance of the starting material requires irradiation for 8 h. The bleached products from rose bengal are necessary for reaction, since **10** is stable to irradiation with a sun lamp in the absence of rose bengal. Irradiation of **10**, rose bengal, and oxygen with a visible wavelength flood lamp, the usual conditions for singlet oxygen generation, results in isomerization of the diene to the *E,E* and *Z,E* isomer, followed by slow reaction to give other products. Irradiation of these isomeric dienes, rose bengal, and oxygen with a sun lamp also gives **16** and **17**. The preparation of hemiketals **16** and **17**, which involves addition of oxygen and cleavage of the ester, may not be a singlet oxygen reaction. We are exploring the mechanism of this photooxygenation and its potential for the preparation of cyclic peroxides that cannot be prepared by classical singlet oxygen reactions. Formation of a cyclic peroxide does not occur on irradiation of methoxy diene **3** and oxygen with a sun lamp using rose bengal as a sensitizer.

Peroxy hemiketals **16** and **17** are converted quantitatively to a 1.1:1 mixture of the desired peroxy ketals **18** and **2b** by reaction with a catalytic amount of *p*-toluenesulfonic acid in MeOH for 40 h at 25 °C. Either pure hemiketal isomer gives the same 1.1:1 mixture of peroxy ketals **18** and **2b**. The success of this reaction was expected, since Wells has reported that chondrillin (**1a**) is very sensitive to base, but relatively stable to acid.[1] The peroxy ketals can be separated by flash chromatography on silica gel. The spectral data of the minor isomer **2b** are identical with those reported for the natural product.[3] The spectral data of the major isomer **18** are virtually identical with those reported for chondrillin (**1a**),[1,3] which has four additional methylene groups in the side chain.

This synthesis produces peroxy ketals **2b** and **18** in seven steps from phenol in 15% overall yield by a route which will permit us to prepare analogues. The key step in the sequence is the rose bengal sensitized photooxygenation of acetoxy diene **10** to give peroxy hemiketals **16** and **17**, which proceeds with a sun lamp, but not with a visible wavelength flood lamp. We are currently exploring the mechanism of this photooxygenation and its scope for preparing other endo peroxides not available by standard singlet oxygen reactions.

Note Added in Proof. Photolysis of enone **11** under the conditions used to convert **10** to peroxy hemiketals **16** and **17** gives 67% of peroxy hemiketals **16** and **17** and 5% of **18** and **2b**. It therefore seems likely that the first step in the conversion of acetoxy diene **10** to **16** and **17** is hydrolysis to enone **11**. Photoenolization of *o*-methylaryl ketones and aldehydes in the presence of oxygen gives peroxy hemiketals.[14] Copper sulfate sensitized photooxygenation of mesityl oxide gives 6% of the peroxy hemiketal.[15]

Supplementary Material Available: Procedures for the preparation of **9**, **10**, **16**, **17**, **18**, and **2b** with spectral data (3 pages). Ordering information is given on any current masthead page.

(14) Sammes, P. G. *Tetrahedron* **1976**, *32*, 405.
(15) Sato, T.; Tamura, K.; Maruyama, K.; Ogawa, O.; Imamura, T. *J. Chem. Soc., Perkin Trans. 1* **1976**, 779.

A New, Highly Efficient Method for Isocarbacyclin Synthesis Based on Tandem Claisen Rearrangement and Ene Reactions

Tadakatsu Mandai,* Shin-ichi Matsumoto, Makoto Kohama, Mikio Kawada, and Jiro Tsuji

Department of Applied Chemistry, Okayama University of Science, Okayama, 700 Japan

Seiki Saito* and Toshio Moriwake

Department of Applied Chemistry, Faculty of Engineering, Okayama University, Tsushima, Okayama, 700 Japan

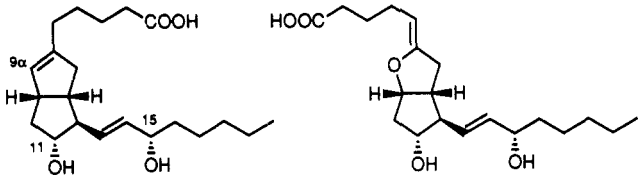
Received July 9, 1990

Summary: A new short-step synthesis of isocarbacyclin is described which features a crucial single-pot, three-step transformation, i.e., tandem tertiary allylic vinyl ether formation, Claisen rearrangement, and ene cyclization, to lead to a bicyclo[3.3.0] framework, overcoming previous endocyclic double bond and one-carbon elongation problems.

The remarkable biological activity of prostacyclin (PGI_2) (**2**) and its very low natural abundance have promoted

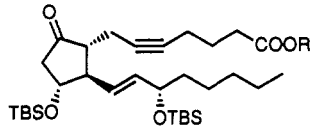
0022-3263/90/1955-5671$02.50/0

research on its efficient total synthesis.[1] However, prostacyclin is a very unstable compound owing to the presence of a labile enol ether group, and hence it cannot be used for therapeutic purpose in its natural form. The design of stable PGI_2 analogues which retain the biological activity has therefore been an important topic for active research.[2]

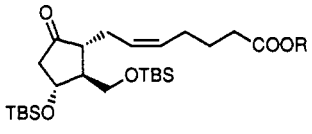


1

2



3

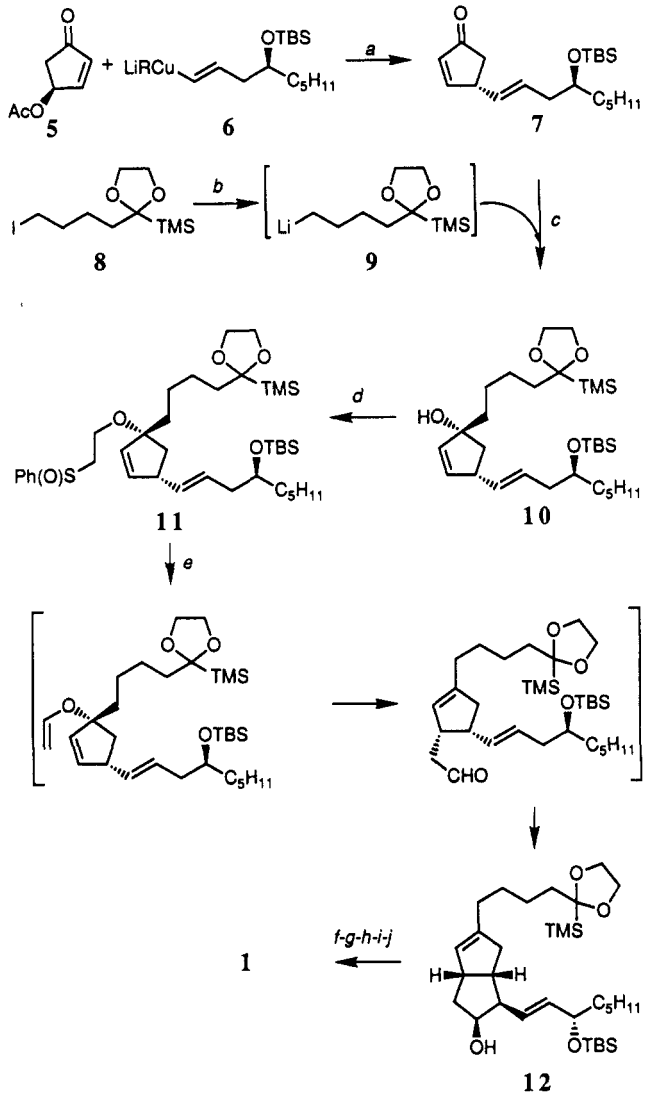


4

As one elegant solution, the stable analogue called isocarbacyclin (1) has recently been introduced as the "carba" version of prostacyclin[3] and shown to be a hopeful therapeutic agent for treatment of various vascular diseases.[4] A number of synthetic methods for 1 have been reported by several groups utilizing different intermediates.[3,5] In most cases, optically active intermediates involved in the well-established synthetic methods for primary PG's, for instance 3[5h] or 4,[5c] have been used as reasonable approaches. However, there emerge two main problems of adopting these aproaches to 1: one is how to elongate one carbon at the 9α-position efficiently and another is how to introduce the endocyclic double bond selectively. In this sense, a still more efficient synthetic approach to 1 is required.

In this paper, we report a new efficient synthetic approach to 1, which is outlined in Scheme I. A key feature of our approach is to build the so-called upper and lower five-membered rings in that order, which reverses the order

Scheme I[a]



[a] (a) i. Et_2O/−82 °C, 1 h; ii. SiO_2/hexane, room temperature, 36 h; (b) t-BuLi/Et_2O/−82 °C, 1 h; (c) Et_2O/−82 °C, 1 h; (d) phenyl vinyl sulfoxide/NaH (1 equiv)/KH (cat.)/THF, room temperature, 4 h; (e) $NaHCO_3$ (excess)/2:1 decalin-α-pinene, 200 °C, 24 h; (f) PCC (3 equiv)/CH_2Cl_2, room temperature; (g) $NaBH_4$/EtOH, room temperature; (h) n-Bu_4NF/THF, room temperature; (i) 0.5 N HCl–acetone, room temperature, 7.5 h; (j) t-BuOOH (excess), room temperature, 12 h.

taken in the hitherto reported methods. In the previous methods, the upper five-membered ring is assembled onto the preexisting lower five-membered rings, which is common in the primary PG's, by several means involving one-carbon elongations corresponding to C-9α. Our synthetic strategy starts from the upper five-membered ring. The lower one is constructed efficiently by tandem Claisen rearrangement leading to a formyl functionality, followed by ene cyclization of the 5-en-1-al framework to form the lower cyclopentanol framework.

As shown in the Scheme I, (4*S*)-4-acetoxy-2-cyclopenten-1-one (5)[6] was used as the starting compound. It should be noted that the corresponding 4*R* isomer bearing a (*tert*-butyldimethylsilyl)oxy group at C-4 is requisite for Noyori's elegant three-component coupling strategy for PG synthesis[7] including isocarbacyclin[5h] and, accordingly, the

(1) Reviews: (a) Nicolaou, K. C.; Gasic, G. P.; Barnette, W. E. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 293–378. (b) Vane, J. R. *Ibid.* **1983**, *22*, 741–804. (c) Sodeoka, M.; Ogawa, Y.; Mase, T.; Shibasaki, M. *Chem. Pharm. Bull.* **1989**, *37*, 586–598.

(2) (a) Pace-Asciak, C. R.; Rosenthal, A.; Domazet, A. *Biochem. Biophys. Acta* **1974**, *574*, 182–186. (b) Nicolaou, K. C.; Barnette, W. E.; Magolda, R. L. *J. Am. Chem. Soc.* **1978**, *100*, 2567. (c) Bundy, G. L.; Baldwin, J. M. *Tetrahedron Lett.* **1978**, 1371. (d) Sun, F. F.; Taylor, B. M. *Biochemistry* **1978**, *19*, 4096–4101. (e) Kojima, K.; Sakai, K. *Tetrahedron Lett.* **1978**, 3743. (f) Bartmann, W.; Beck, G.; Knolle, J.; Ruppe, R. H. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 819. (g) Konishi, Y.; Kawamura, M.; Arai, Y.; Hayashi, M. *Tetrahedron* **1981**, *37*, 4391. (h) Bartmann, W.; Beck, G. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 751. (i) Adaikan, P. G.; Lau, L. C.; Tai, M. Y.; Karim, S. M. *Prostaglandins Leukotrienes Med.* **1983**, *10*, 53–65. (j) Whittle, B. J. R.; Moncada, S. *Prog. Med. Chem.* **1984**, *21*, 238–279. (k) Skuballa, W.; Schillinger, E.; Sturzebecher, C.-St.; Vorbruggen, H. *J. Med. Chem.* **1986**, *29*, 315–317. (l) Tomiyama, T.; Wakabayashi, S.; Yokota, M. *J. Med. Chem.* **1989**, *32*, 1988–1996.

(3) Shibasaki, M.; Torisawa, Y.; Ikegami, S. *Tetrahedron Lett.* **1983**, *24*, 3493–3496.

(4) *Prostacyclin; Clinical Trials*; Gryglewski, R. J., Szczeklik, A., McGiff, J. C., Eds.; Rarven Press: New York, 1985.

(5) (a) Shibasaki, M.; Fukasawa, H.; Ikegami, S. *Tetrahedron Lett.* **1983**, *24*, 3497–3500. (b) Sodeoka, M.; Shibasaki, M. *Chem. Lett.* **1984**, 579–582. (c) Torisawa, Y.; Okabe, H.; Shibasaki, M.; Ikegami, S. *Chem. Lett.* **1984**, 1069–1072. (d) Mase, T.; Sodeoka, M.; Shibasaki, M. *Tetrahedron Lett.* **1984**, *25*, 5087–5090. (e) Torisawa, Y.; Okabe, H.; Ikegami, S. *J. Chem. Soc., Chem. Commun.* **1984**, 1602–1603. (f) Ogawa, Y.; Shibasaki, M. *Tetrahedron Lett.* **1984**, *25*, 1067–1070. (g) Bannai, K.; Tanaka, T.; Okamura, N.; Hazato, A.; Sugiura, S.; Manabe, K.; Tomimori, T.; Kurozumi, S. *Tetrahedron Lett.* **1986**, *27*, 6353–6356. (h) Suzuki, M.; Koyano, H.; Noyori, R. *J. Org. Chem.* **1987**, *52*, 5583–5588.

(6) Prepared from 4-(*tert*-butyldimethylsiloxy)-2-cyclopenten-1-one isomer supplyed from Teijin Co. through TBDS deprotection (HF-pyridine) and acetylation (Ac_2O/pyridine): $[\alpha]^{20}_D$ −111° (c, 0.51, $CHCl_3$).

4*S* antipode has been a valueless compound in the previous synthetic methods. The one exception in this context is a novel approach reported quite recently by Danishefsky which features the 4*S* antipode as a starting material.[8] The present method revives **5** as the upper ring synthon in isocarbacyclin synthesis, which ensures the construction of the bicyclo[3.3.0] backbone with desired absolute stereochemistry and the endocyclic double bond with proper location, in simple operations, without suffering from the two main problems mentioned above.

At first, a precursor of the ω-side chain was stereoselectively introduced, relying on the widely accepted Michael addition of the optically pure mixed homocuprate **6**, prepared from the corresponding vinylic iodide[9] and 1-pentyne, to **5**[6] from the opposite side of the (4*S*)-acetoxyl group. The treatment of the crude product with silica gel suspended in hexane-promoted acid-catalyzed elimination of the (4*S*)-acetoxyl group to afford the substituted cyclopentenone **7** in 73% yield in optically pure form after chromatographic purification.

The upper side chain **8**, containing the terminal acylsilane acetal functionality as a masked carboxylic acid, was prepared by our previous method.[10] Halogen–metal exchange reaction between **8** and *tert*-butyllithium was nicely effected to afford the lithium reagent **9**, which underwent clean 1,2-addition to **7**, giving rise to the tertiary allylic alcohol **10** as a separable epimeric mixture in a ratio of 5:1.

The next problem was the preparation of the tertiary allylic vinyl ether for Claisen rearrangement. Although this can be achieved by the traditional mercury salt catalyzed reaction of **10**, with a large excess of ethyl vinyl ether,[11] we were anxious to replace this reaction with a more practical methodology without using toxic mercury salts. No satisfactory mercury-free method for allyl vinyl ether formation, applicable particularly to tertiary allylic alcohols, has been available so far.[12] After much effort toward this goal, resorting to the vinyl sulfoxide technique[13] provided us with a fruitful result. We expected that Michael type additions of alcohols to vinyl sulfoxide, followed by thermal syn elimination of the ArSOH unit, should generate allyl vinyl ethers. Eventually, the tertiary hydroxyl group in **10** added smoothly to vinyl phenyl sulfoxide by the action of NaH and a catalytic amount of KH to afford **11** in 89% yield.

Thus, a novel system was in hand with appropriate functionalities for the tandem vinyl ether formation, the Claisen rearrangement, and the ene reaction in a single operation. A solution of **11** in decalin was heated at 200 °C for 24 h under argon in the presence of both sodium bicarbonate and α-pinene (for scavenging released sulfinic acid and minimizing unwanted side reactions), to give the bicyclic compound **12** in 45% yield. While only one disappointing outcome in this transformation was that the 11-hydroxyl group had the stereochemistry opposite to that required for **1**, its chirality conversion was accomplished by a conventional means, i.e., an oxidation–reduction sequence as shown in the Scheme I.

A series of functional group transformations from **12** leading to **1** was executed in a straightforward manner. Oxidation of the hydroxyl group and ensuing reduction with $NaBH_4$ regenerated the C-11 OH with the desired configuration in 90% overall yield. Sequential deprotections of both the silyl (C-15–*O*) and acetal groups upon exposure to fluoride anion and acid, respectively, proceeded smoothly to afford the silyl ketone, which was demasked to generate **1** under oxidative conditions in 52% overall yield from **12**. The NMR spectra as well as the melting point (78–79.5 °C) and optical rotation ($[\alpha]^{26}_D$ +9.7° (*c* 2.32, MeOH)) of synthetic **1** were completely consistent with those of an authentic sample.[14]

The synthetic method reported in this communication has provided the shortest access to **1** starting from the easily available,[15] but the hitherto unused and valueless epimer in this field, which provided a solution to the one-carbon elongation problem. Introduction of the new mercury-free preparative method for tertiary allyl vinyl ethers is particularly significant from a practical standpoint. The importance of using the tandem Claisen-ene process[16] can be appreciated because of simple and certain introduction of the bicyclo[3.3.0] backbone and endocyclic double bond. The whole synthesis has been carried out on a preparative scale without any problem. The underlying synthetic strategy may obviously provide versatile routes to more complex polycyclopentanoid structures containing bicyclo[3.3.0]octane frameworks.

Acknowledgment. We deeply appreciate Teijin Co. for the generous supply of optically pure (4*S*)-4-[(*tert*-butyldimethylsilyl)oxy]-2-cyclopenten-1-one and authentic isocarbacyclin. We thank "The SC-NMR Laboratory of Okayama University" for 500-MHz NMR measurements. This work was aided by the Synth. Org. Chem., Jpn. Award (Sankyo Award).

Supplementary Material Available: Experimental procedures for the main steps and physical data including NMR spectra for the important compounds (13 pages). Ordering information is given on any current masthead page.

(7) Noyori, R.; Suzuki, M. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 847–876.

(8) Danishefsky, S. J.; Cabal, M. P. Chow, K. *J. Am. Chem. Soc.* **1989**, *111*, 3456–3457.

(9) The ω-chain bearing hydroxyl functionality corresponding to C-15 in optically pure form was prepared by hydrozirconation (Hart, D. W.; Blackburn, T. F.; Schwartz, J. *J. Am. Chem. Soc.* **1975**, *97*, 679) and ensuing halogen–metal exchange processes of 4-*O*-(*tert*-butyldimethylsilyl)-protected derivative ($[\alpha]^{24}_D$ −22.3° (*c* 5.53, $CHCl_3$)) of (4*S*)-4-hydroxy-1-nonyne ($[\alpha]^{24}_D$ −26.4° (*c* 2.82, $CHCl_3$)) derived from optically pure (2*S*)-1,2-epoxyheptane (Schmidt, U.; Talbiersky, J.; Barkowiak, F.; Wild, J. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 198–199) through the oxirane cleavage with lithium acetylide–TMEDA complex. For previous elegant one-pot synthesis of this acetylenic alcohol by asymmetric synthesis, see: (a) Haruta, R.; Ishiguro, M.; Ikeda, N.; Yamamoto, H. *J. Am. Chem. Soc.* **1982**, *104*, 7667–7669. (b) Ikeda, N.; Arai, I.; Yamamoto, H. *Ibid.* **1986**, *108*, 483–486. (c) Corey, E. J.; Yu, C.-M.; Lee, D.-H. *Ibid.* **1990**, *112*, 878–879.

(10) The coupling of 1,4-dichlorobutane with (phenylthio)(methoxy)(trimethylsilyl)methyllithium (Mandai, T.; Yamaguchi,; Nakayama, Y.; Otera, J.; Kawada, M. *Tetrahedron Lett.* **1985**, *26*, 2675–2676), followed by oxidative rearrangement and ensuing hydrolysis ($NaIO_4$/dioxane–H_2O/room temperature, 1 h), afforded 4-chlorobutyl trimethylsilyl ketone (acylsilane), which, on treatment with bis-*O*,*O*′-(trimethylsilyl)-ethylene glycol in the presence of catalytic trimethylsilyl triflate (Tsunoda, T.; Suzuki, M.; Noyori, Y. *Tetrahedron Lett.* **1980**, *21*, 1357–1358) at 0 °C for 1 h led to the corresponding protected acylsilane. Displacement of the chlorine with iodine (NaI/acetone/overnight under reflux) gave **7** in 77% overall yield from (phenylthio)methoxy(trimethylsilyl)-methane.

(11) In fact, treatment of **9** with 250-fold excess of ethyl vinyl ether in the presence of $Hg(OAc)_2$ (2 mol equiv) for 1 day under reflux afforded the corresponding vinyl ether in good yield.

(12) A representative procedure developed by Büchi, G.; Vogel, D. E. *J. Org. Chem.* **1983**, *48*, 5406. Vogel, D. E.; Büchi, G. *Org. Synth.* **1987**, *66*, 29) is free of mercury but is not applicable to tertiary allylic alcohols.

(13) Mandai, T.; Ueda, M.; Hasegawa, S.; Kawada, M.; Tsuji, J.; Saito, S. *Tetrahedron Lett.* **1990**, *31*, 4041.

(14) An optically pure authentic sample was supplyed through the courtesy of Teijin Co. A full assignment of NMR signals observed for synthetic **1** is shown in the supplementary material.

(15) Availability of (4*S*)-4-acetoxy-2-cyclopenten-1-one has been discussed; see references cited in ref 8.

(16) For a recent elegant entry of asymmetric tandem Claisen-ene process, see: Mikami, K.; Takahashi, K.; Nakai, T. *J. Am. Chem. Soc.* **1990**, *112*, 4035.