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Diastereoselective Total Synthesis of Isocarbacyclin from L-Ascorbic Acid

Teruhiko Ishikawa,† Hirokazu Ishii,‡ Kazuo Shimizu,‡ Hiroe Nakao,‡ Jin Urano,‡ Takayuki Kudo,‡ and Seiki Saito*,‡

School of Education, and Department of Bioscience and Biotechnology, School of Engineering, Okayama University, Tsushima, Okayama, Japan 700-8530

seisaito@biotech.okayama-u.ac.jp

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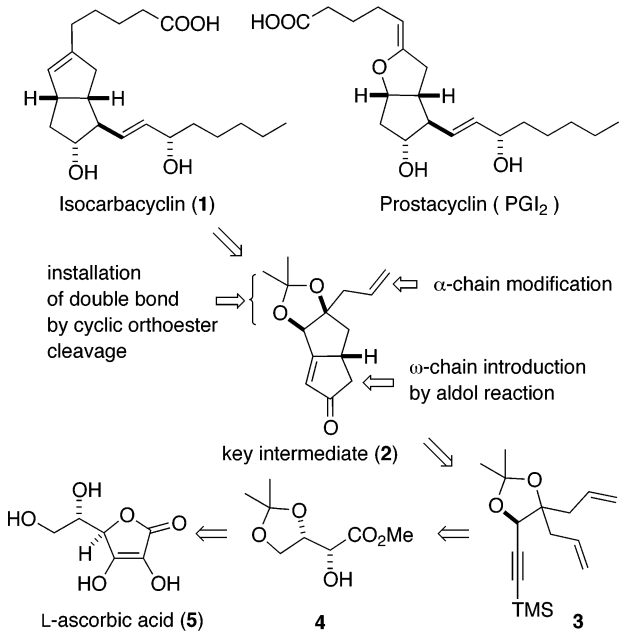
Abstract: Diastereoselective total synthesis of isocarbacyclin, which features a fused bicyclic key intermediate available from L-ascorbic acid, is described. The key intermediate was prepared in multigram quantities by the Pauson−Khand reaction of L-ascorbic acid-based (*R*)-4,4-diallyl-2,2-dimethyl-5-(trimethylsilyl)ethynyl-1,3-dioxolane (**3**), discriminating diastereotopic groups and faces of the geminal allyl substituents.

Prostacyclin (PGI_2)[1] is a potent vasodilator and inhibitor of blood platelet aggregation and plays an important role in the central nervous system.[2] Clinical applications of PGI_2 in its natural form suffer from severe limitations because of its lability (its half-life is ∼10 min at pH 7.6, 25 °C). Therefore, extensive efforts have been made to develop or synthesize metabolically stable analogues bearing physiological activities similar to those of PGI_2. Isocarbacyclin (**1**),[4] one of these analogues, is a therapeutically useful agent[3] for the treatment of various vascular diseases. In addition, some derivatives of **1**, carrying modified side chains, have been utilized as agents for studying the role of PGI_2 in the brain.[5] In any event, due to its chemical stability and potent physiological activities, including an antiaggregatory profile, a number of methods for the synthesis of **1** have been reported.[6] In our continuing interest in the synthesis of **1**,[6i] we had a promising clue to a novel method for the synthesis of **1**. This features a key intermediate, such as **2**, prepared by the diastereoselective Pauson−Khand reaction of **3**, available from L-ascorbic acid (**5**), via (2*R*,3*S*)-3,4-*O*-isopropylidene-2,3,4-trihydroxybutanoic acid ester (**4**), as shown in Scheme 1. It can readily be recognized that enone **2** has a functional group assembly suitable for introducing the α- and ω-side chains and the endocyclic olefinic moiety of **1**.

SCHEME 1. Retro Synthetic Analysis of Isocarbacyclin 1 from L-Ascorbic Acid 5



Scheme 2 outlines the previous synthesis of the Pauson−Khand substrate **3**[7] starting from an expensive three-carbon chiral source, such as **I**, which required eight steps with an acceptable overall yield (∼40%). However, to prepare for a large-scale production of **3**, we felt that we should replace **I** with a less-expensive alternative. Thus, we examined chiral carbon sources other than **I** and found that **4**, available from L-ascorbic acid **5**,[8] provided a solution to this problem. In light of both the availability and the inexpensive cost of **5**, **2** would be obtained in multigram quantities if so desired,

* To whom correspondence should be addressed. Tel.(Fax) +81 86-251-8209.
† School of Education.
‡ School of Engineering.

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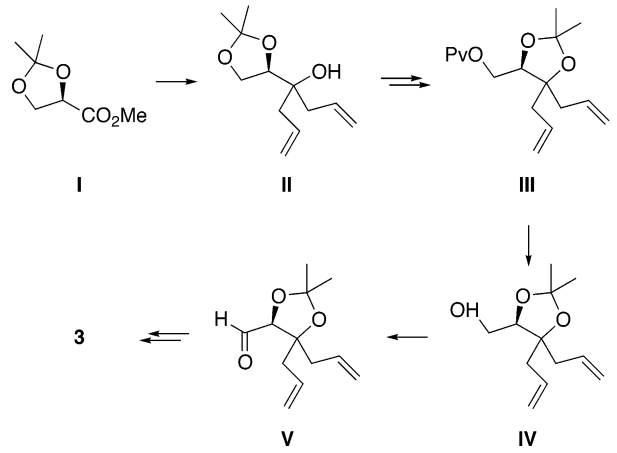
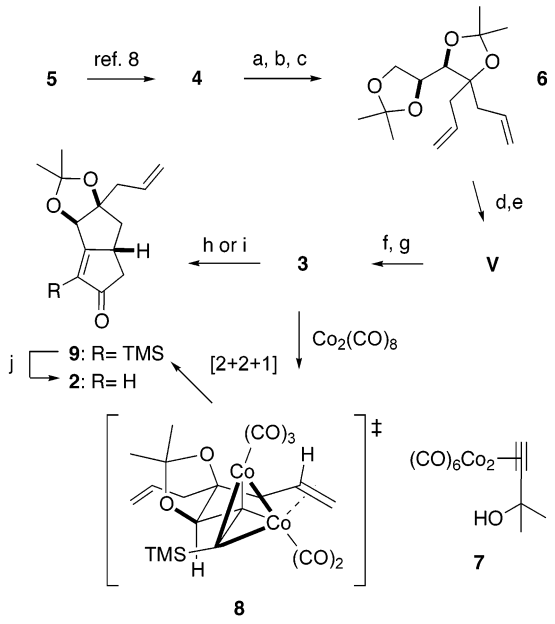
SCHEME 2. Previous Synthesis of the Pauson–Khand Substrate 3



SCHEME 3. Synthesis of the Key Intermediate 2 from L-Ascorbic Acid Featuring the Diastereoselective Pauson–Khand Reaction[a]

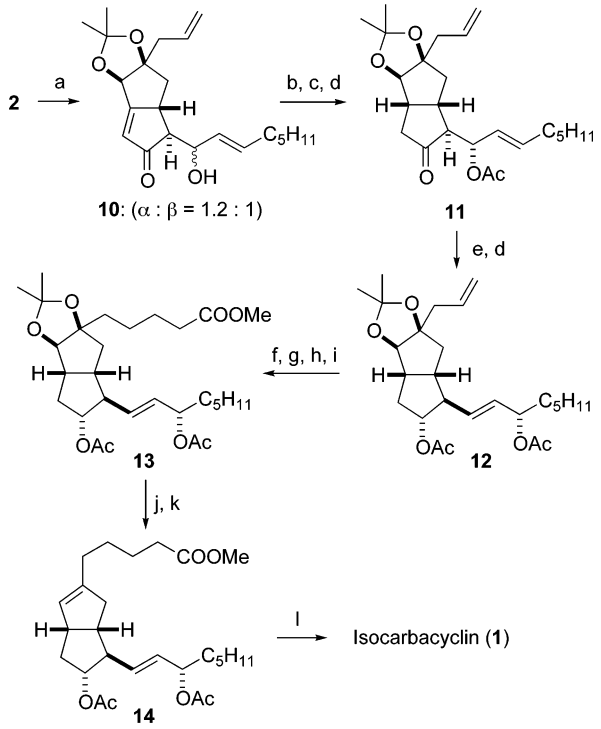


[a] Reagents and conditions: (a) TMSCl, imidazole, CH_2Cl_2, 0 °C, 30 min; (b) CH_2=$CHCH_2MgBr$, THF, −78 °C, 1 h; (c) *p*-TsOH·H_2O, THF, and then 2-methoxypropene, 60 °C, 6 h, 87% from **4**; (d) 2 N HCl, THF, rt, 12 h, 82%; (e) HIO_4·$2H_2O$, THF, 0 °C, 45 min, 92%; (f) PPh_3, CBr_4, CH_2Cl_2, rt, 16 h; (g) *n*-BuLi, −30 °C, 30 min, and then TMSCl, THF, −78 °C, 1 h, 73% from **7**; (h) $Co_2(CO)_8$, CH_2Cl_2, 0 °C to rt, 3 h, and then MeCN, 65 °C, 3 h, 78%; (i) CO, 5 mol % **7**, 10 mol % Et_3SiH, 10 mol % $CyNH_2$, DME, 70 °C, 76% (67% conversion); (j) K_2CO_3, MeOH, rt, 3.5 h, 80%.

which would make the present synthesis highly practical and attractive.

Scheme 3 outlines the L-ascorbic acid route to **3** and the key intermediate **2**, as well. Chiral hydroxyester **4** was converted to **6** via a four-step sequence involving silylation (TMSCl, imidazole) of the hydroxy group, conversion of the ester group to an α,α-diallyl alcohol unit with allylmagnesium bromide, deprotection of the TMS group, and acetonide protection of the generated internal 1,2-diol functionality. Treatment of **6** with 2 N HCl in THF, and followed with periodic acid treatment, effected

SCHEME 4. Transformation of 2 to 1[a]



[a] Reagents and conditions: (a) 1. LDA, THF, 1 h; 2. (2*E*)-octenal, THF, −78 °C, 50 min, 88%; (b) separation of diastereomers; (c) NaTeH, EtOH, rt, 3.5 h, 91%; (d) Ac_2O, pyridine, DMAP, THF, rt, 2 h, 87%; (e) $Pd(MeCN)_2Cl_2$, THF, rt, 4 h, and then $NaBH_4$, 0 °C, 30 min, 50%; (d **11** to **12**) rt, 4 h, 93%; (f) 9-BBN, THF, rt, 4 h, and then H_2O_2, $NaHCO_3$, rt, 1 h, 93%; (g) SO_3·Py, Et_3N, DMSO, rt, 30 min, 86%; (h) (*i*-PrO)$_2$P(O)CH(Na)COOMe, THF, −78 °C, 1 h, 99%; (i) NaTeH, EtOH, rt, 12 h, 88%; (j) 80% AcOH/H_2O, 70 °C, 15 h, 69%; (k) $HC(OEt)_3$, 130 °C, 15 h, and then Ac_2O, 150 °C, 4 h, 66%; (l) NaOH, EtOH/H_2O, rt, 24 h, 95%.

the deprotection of the terminal acetonide group of **6** and the subsequent oxidative diol cleavage to give the desired aldehyde **V**. Application of Corey's protocol[9] to **V** afforded dienyne **3** in high yield (48% overall yield from **4**), and the Pauson–Khand reaction of **3** (3.64 g) with 100 mol % cobalt complex nicely proceeded to afford **9** (3.30 g, 78% yield) as a single diastereomer.[10] Furthermore, we found that desilylation of **9** readily took place by using potassium carbonate in methanol at room temperature to give the desired enone **2** in good yield (80%), which is ready for elaborating the whole carbon framework of **1**.

Careful NOE experiments for **9** led to the relative configurations, as indicated in Scheme 3.[11] This finding clearly indicated that the reaction proceeded with the simultaneous discrimination of both diastereotopic allyl groups, and the π-faces of the allyl group reacted. Thus, the protected diol unit can play an important role as a stereocontrol element in this diastereo differentiation reaction. We presumed that the expected transition state

(9) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett*. **1972**, *36*, 3769–3772.

(10) Tricyclic enone **9** was previously synthesized in a small-scale experiment in which **3** (0.100 g) led to **9** (0.075 g, 74%) in the presence of $Co_2(CO)_8$ (0.367 g) in CH_3CN (65 °C, 11 h). The present larger-scale case resulted in a better yield (78%) during a shortened reaction time (3 h). Elucidation for the exact nature of this significant scale effect must await future systematic studies.

(11) For the determination of relative configurations, see ref 7.

(**8**, Scheme 3)[7] could explain such a remarkable stereochemical consequence in this case.

Besides the L-ascorbic acid route to **3** (Scheme 3), the Pauson−Khand reaction of **3** should be switched from the present stoichiometric system to the desired catalytic system in order to prepare for a large-scale production of **9**. According to Livinghouse's protocol,[12] we employed the cobalt complex **7**, shown in Scheme 3, for this purpose and found that a catalytic amount of **7** (5 mol %), indeed, led to the formation of **9**. However, at the present stage, the catalytic process was so slow that it was difficult to quantitatively convert **3** to **9** under the given catalytic conditions; **9** was obtained in 76% yield based on 67% conversion of **3**.

The synthetic route to **1** from **2** is summarized in Scheme 4. The introduction of the ω-chain was the first task in this synthesis. Aldol reaction of **2** with (2*E*)-octenal led to **10** in good yield (88%). However, the level of enantioface differentiation for the formyl group was unacceptable (1.2:1 in preference to the desired **10**α)[13] under the given conditions (LDA, THF, 1 h; (2*E*)-octenal, THF, −78 °C, 50 min), whereas diastereoface differentiation of an enolate generated from **2** was almost perfect. Fortunately, separation of the resulting mixture of diastereomers (**10**α and **10**β) by column chromatography on silica gel was successful. Thus, a series of routine reactions from **10**α involving 1,4-reduction of the enone unit, using NaTeH,[14] and acetylation afforded **11**. Pd(II)-catalyzed stereospecific allylic rearrangement[15] followed by reduction of the cyclopentanone moiety ($NaBH_4$) and acetylation of the generated hydroxy group gave **12** as an exclusive stereoisomer.

A requisite two-carbon unit for the complete α-chain was incorporated into **12** as follows. Hydroboration−oxidation of the allyl group in **12**, using **9**-BBN-H, and oxidation of the produced primary alcohol followed by H-W-E olefination and selective reduction of the conjugated double bond (NaTeH)[14] gave **13** in good yield. After deprotection of the acetonide group of **13**, the formed *syn*-1,2-diol unit was converted into the desired double bond via thermal cleavage of the intermediary *ortho*-ester[16] upon treatment with triethylorthoformate in the presence of acetic anhydride. Final saponification of **14** afforded isocarbacyclin **1**, of which spectral data and optical rotation were identical in all respects with those reported previously.[6]

In conclusion, we have demonstrated the enantioselective total synthesis of isocarbacyclin from the key intermediate **2**, available from L-ascorbic acid in multigram quantities in optically pure form (26% overall yield from **4**). Not only the functional group assembly in **2** but also the conventional synthetic reactions required for converting **2** to **1** might make the present approach attractive and deserving of consideration for flexible access to the side-chain analogues of **1**.

Acknowledgment. We thank the NMR Laboratory of Okayama University for 500 MHz NMR experiments.

Supporting Information Available: Complete experimental procedures and copies of the ^1H and ^{13}C NMR spectra for compounds **1**−**3**, **6**, **V**, and **9**−**14**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) Belanger, D. B.; Livinghouse, T. *Tetrahedron Lett*. **1998**, *39*, 7641−7644.

(13) No effort has been made to improve this ratio. Aldol reaction between **9** and (2*E*)-octenal led to a diastereomeric ratio of 1:2 in preference of the undesired β-isomer (**10**β) (LDA, THF, −78 °C, 1 h, and then the aldehyde, −78 °C, 50 min).

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(16) For a review regarding the cleavage of cyclic *ortho*-esters, see: Block, E. *Org. React*. **1984**, *30*, 457−566.