Total synthesis of buergerinin F *via* effective construction of the asymmetric quaternary carbons using an enantioselective aldol reaction†

Isamu Shiina,* Yo-ichi Kawakita, Ryoutarou Ibuka, Kazutoshi Yokoyama and Yu-suke Yamai

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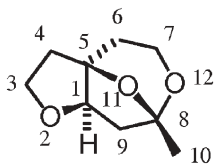
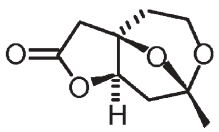
An efficient method for the synthesis of (+)-buergerinin F is established *via* the enantioselective aldol reaction of a tetra-substituted ketene silyl acetal with crotonaldehyde, followed by intramolecular Wacker-type ketalization.

Buergerinin F (**1**), a potentially antiphlogistic and febrifuge agent, was isolated in 2000 from the root of *Scrophularia buergeriana* together with buergerinin G (**2**) by Zhu *et al.*[1] Its structure consists of a peculiar trioxatricyclo[5.3.1.0^{1,5}]undecane skeleton, including a ketal moiety with asymmetric quaternary carbons. The relative stereochemistries of **1** and **2** were first shown by NOE correlations and X-ray crystallography, and the absolute configurations of **1** and **2** were recently determined through the total synthesis starting from thymidine by Lowary *et al.*[2] Independently, we planned to synthesize **1** *via* the asymmetric aldol reaction of a tetrasubstituted ketene silyl acetal with a simple achiral aldehyde, followed by the intramolecular ketalization of the precursory dihydroxy alkene using an abnormal intramolecular Wacker-type ketalization. In this communication,[3] determination of the stereochemistry of **1** and its asymmetric total synthesis using our chiral induction technology[4] for providing optically active compounds are described.



Buergerinin F (1)



Buergerinin G (2)

Recently, we reported an effective method for the construction of asymmetric quaternary carbons using the enantioselective aldol reaction;[5] namely, in the presence of Sn(II) triflate coordinated with a chiral diamine, tetrasubstituted ketene silyl acetals react with achiral aldehydes to produce the corresponding optically active aldols with a highly functionalized structure (Scheme 1). These successful results prompted us to develop an enantioselective method for the construction of the basic skeleton of **1**, which possesses an asymmetric quaternary carbon at C-5.

Department of Applied Chemistry, Faculty of Science, Tokyo University of Science, Kagurazaka, Shinjuku-ku, Tokyo 162-8601, Japan. E-mail: shiina@ch.kagu.tus.ac.jp; Fax: (+81)-3-3260-5609
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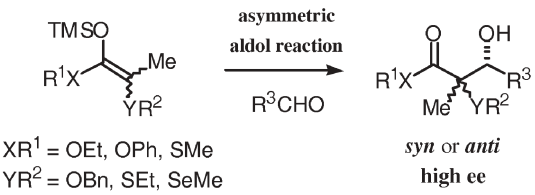
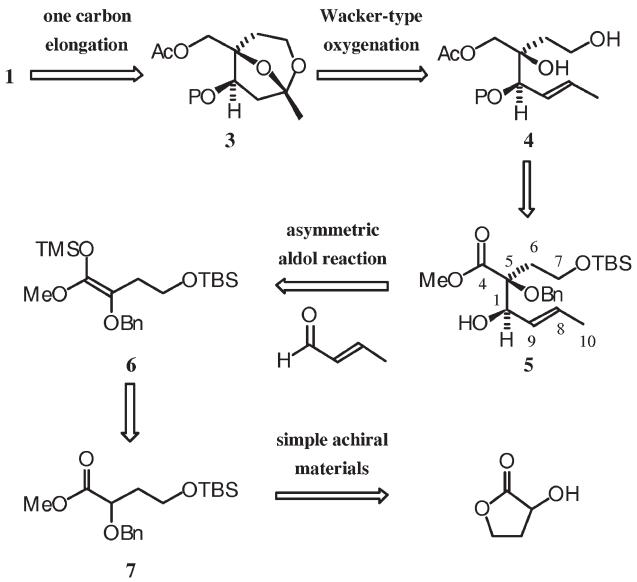


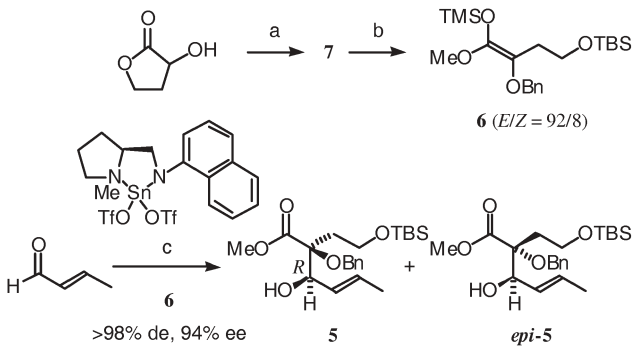
Scheme 1 Enantioselective construction of asymmetric quaternary carbons.

Retrosynthetic analysis of **1** is shown in Scheme 2. An optically active linear compound **4** might be used as an intermediate for the construction of the framework **3** by the intramolecular Wacker-type cyclization. A highly oxygenated aldol **5**, a precursor of **4** including the asymmetric quaternary carbon at C-5, could be synthesized by an enantioselective aldol reaction between the tetrasubstituted ketene silyl acetal **6** and crotonaldehyde. According to the above hypothesis, the α,γ-dioxy ester **7** derived from a simple α-hydroxy-γ-butyrolactone was chosen as the starting material.

First, the benzylation of the racemic α-hydroxy-γ-butyrolactone was carried out and successive cleavage of the lactone ring followed by silylation of the resulting primary alcohol, produced the α,γ-dioxy ester **7** in a good yield (Scheme 3). The desired ketene



Scheme 2 Retrosynthetic analysis of buergerinin F.

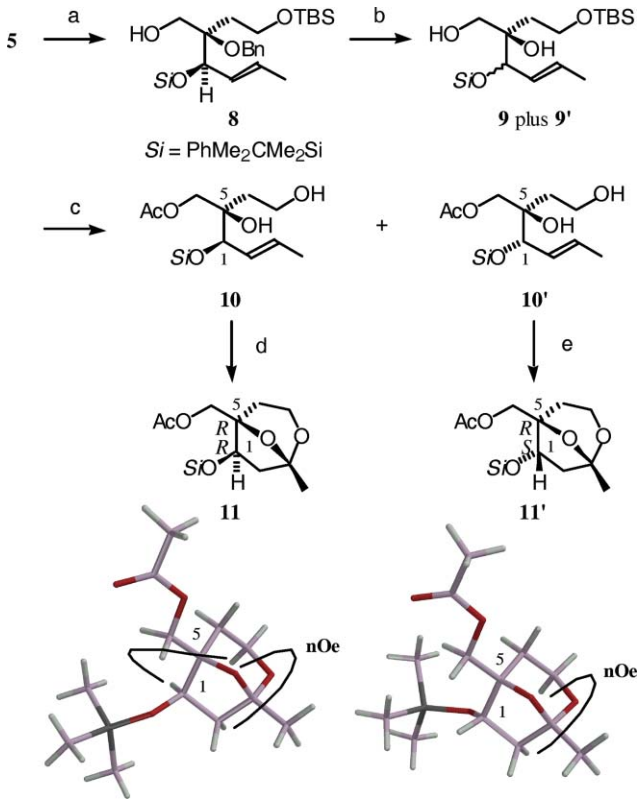


Scheme 3 *Reagents and conditions:* (a) NaH, BnBr, THF, DMF, 0 °C to rt (83%); NaOMe, MeOH, rt; TBSCl, imidazole, DMF, 0 °C to rt (80%, two steps); (b) LDA, TMSCl, THF, −78 °C to rt (97%, *E*/*Z* = 92:8); (c) $Sn(OTf)_2$, $^nBu_2Sn(OAc)_2$, (*S*)-1-methyl-2-(1-naphthylaminomethyl)pyrrolidine, EtCN, −78 °C (74%, **5**/***epi*-5** = >99:1, 94% ee for **5**).

silyl acetal **6** was easily generated from **7** by a conventional method, and a nearly quantitative conversion yield was observed by ^{1}H NMR analysis of the crude mixture. Although the *E*- and *Z*-isomers were formed in a 92:8 ratio,[6] we used this mixture for the next reaction without further purification because similar stereoselectivities were attained regardless of the geometric difference between the two enolates during the course of our continuous studies on the asymmetric aldol reactions.[4,5] Actually, excellent diastereo- and enantioselectivities were attained in the asymmetric aldol reaction of the mixture of **6** with crotonaldehyde using the chiral Lewis acid that consisted of $Sn(OTf)_2$, (*S*)-1-methyl-2-(1-naphthylaminomethyl)pyrrolidine and $^nBu_2Sn(OAc)_2$ to give the coupling product **5** in satisfactory yield. The HPLC analysis of **5** referenced to the corresponding racemic sample showed the enantiomeric excess of **5** to be 94%. The relative stereochemistry of **5** had not yet been clarified at this stage, however, the absolute configuration at C-5 in **5** was determined as *R* using Mosher's method modified by Kusumi.[7] This stereoselectivity gave good agreement with the empirical rule of our asymmetric synthesis using the chiral Sn(II) complex.

As shown in Scheme 4, the major aldol **5** was converted to a primary alcohol **8** in good yield by protection with cumyldimethylsilyl triflate in pyridine and subsequent reduction with DIBAL. The debenzylation of **8** using lithium di-*tert*-butylbiphenylide (LDBB) took place smoothly but a mixture of the desired diol **9** and its epimer **9′** were produced. The successive treatment of the mixture with acetic anhydride and DMAP in pyridine and with 0.1 M HCl in THF gave the separate diols **10** and **10′**. The intramolecular Wacker-type ketalization of **10** and **10′** using an excess amount of palladium dichloride produced the corresponding bicyclic ketals **11** and **11′** in good and moderate yields, respectively. The NOE experiment of **11** and **11′** showed that each configuration is (1*R*,5*R*) and (1*S*,5*R*) as depicted in Scheme 4. Because **11**, derived from **5** *via* **10**, has the same relative stereochemistry as **1**, it was proved that **10**, in which the C-1 configuration is *R*, should be used as the precursor of **1**.

Next, we tried to exclusively synthesize the desired stereoisomer **10** from **5** as described in Scheme 5. The optically active **5** was directly treated with Red-Al® to form the corresponding 1,3-diol **12**, and then the debenzylation of **12** was carried out using LDBB. In this case, the unwanted epimerization at C-1 did not take place

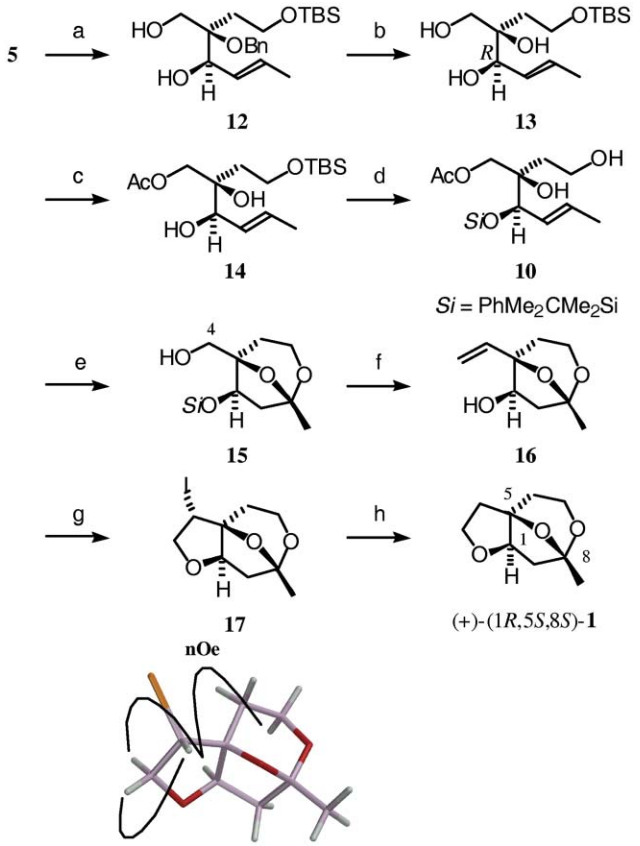


Scheme 4 *Reagents and conditions:* (a) $PhMe_2CMe_2SiOTf$, pyridine, 0 °C (83%); DIBAL, CH_2Cl_2, −18 °C (92%); (b) LDBB, THF, −78 °C (45%, **9**/**9′** = 45:55); (c) Ac_2O, DMAP, pyridine, rt (98%); 0.1 M HCl, THF, rt (43% for **10** and 45% for **10′** from a mixture of **9** and **9′**); (d) $PdCl_2$, DMF, 0 °C (91%); (e) $PdCl_2$, DMF, 0 °C to rt (60% of **11′** plus 38% of recovered **10′**).

at all and only the 1,2,3-triol **13** was obtained in high yield. Though the protection of **13** with acetic anhydride and triethylamine gave the mono-acetylated diol **14** in 71% yield along with the formation of a mixture of undesired acetates in 14% yield, the by-products were easily converted to the starting material **13** in quantitative yields. The successive silylation and desilylation of **14** afforded synthetic intermediate **10** without producing its C-1 epimer **10′**. The dihydroxy alkene **10** was transformed into the corresponding ketal **11** by the Wacker-type cyclization using a catalytic amount of palladium dichloride, which was in turn selectively deprotected to form a primary alcohol **15** in good yield.

The one carbon elongation at the C-4 position in **15** and cyclization to construct the 5-membered ether ring were then examined. The successive oxidation[8] of **15** and Wittig olefination of the resulting aldehyde, followed by deprotection of the silyl group, afforded the corresponding secondary alcohol **16**. After screening several cyclization reactions involving oxymercuration and oxypalladation to produce a tricyclic compound from **16**, it was found that the iodine-promoted ether ring formation rapidly proceeded to afford the desired **17** in high yield. The NOE relationships and conformational analysis showed the relative stereochemistry of **17** to be as illustrated in Scheme 5.

Finally, treatment of the iodide **17** with potassium *tert*-butoxide and consecutive hydrogenation catalyzed by palladium on charcoal, gave the target molecule in good yield. The ^{1}H and



Scheme 5 *Reagents and conditions:* (a) Red-Al®, toluene, −45 to 0 °C (99%); (b) LDBB, THF, −78 °C (quant.); (c) Ac_2O, Et_3N, CH_2Cl_2, 0 °C (71%); (d) $PhMe_2CMe_2SiOTf$, toluene, pyridine, 0 °C (93%); 1 M HCl, THF, 0 °C (98%); (e) $PdCl_2$, CuCl, O_2, DME, rt (88%); K_2CO_3, MeOH, rt (quant.); (f) $PhSNH^tBu$, NCS, K_2CO_3, MS 4Å, CH_2Cl_2, rt (quant.); $Ph_3PCH_3{}^+I^-$, KHMDS, toluene, THF, −78 °C to rt (quant.); TBAF, THF, 0 °C (quant.); (g) I_2, $NaHCO_3$, CH_3CN, 0 °C to rt (80%); (h) ^{t}BuOK, DMSO, rt (quant.); H_2, Pd/C, AcOEt, rt (quant.).

^{13}C NMR spectra of the obtained **1** showed that the synthetic sample has the same relative stereochemistry as the naturally occurring buergerinin F. Other properties of **1**, including its optical rotation, were identical with those of buergerinin F isolated by Zhu *et al.*;[9] therefore, it was shown that the naturally occurring **1** has the (1*R*,5*S*,8*S*) configuration as Lowary *et al.* reported.[2]

Thus, an efficient method for the synthesis of (+)-buergerinin F (**1**) was established *via* the enantioselective aldol reaction of a tetrasubstituted ketene silyl acetal with a simple achiral aldehyde, followed by Wacker-type ketalization and then iodocyclization. The synthesis of **1** proceeds in 14 steps and 33% overall yield from crotonaldehyde with an achiral nucleophile. The absolute stereochemistry of **1**, including the asymmetric quaternary carbons, was additionally confirmed by the enantioselective synthesis. Since it is already known that **1** can be converted to **2** by oxygenation using $RuCl_3/NaIO_4$,[2] the present report is related to the formal synthesis of buergerinin G (**2**). An advanced investigation of an alternative synthesis of **2** is now in progress in this laboratory.

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9 $[\alpha]_D^{23}$ +38° (*c* 0.41, $CHCl_3$) [ref. $[\alpha]_D^{18}$ +41° (*c* 0.43, $CHCl_3$)[1] $[\alpha]_D$ +39° (*c* 0.9, $CHCl_3$)[2]].