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CONCISE ASSEMBLY OF THE BCD RING PART OF GINGKOLIDE C VIA A NOVEL CYCLIZATION REACTION

Ayaka Hibi, Kazutaka Takeda, and Masahiro Toyota*

Department of Chemistry, Graduate School of Science, Osaka Prefecture University, Sakai, Osaka 599-8531, Japan. E-mail: toyota@c.s.osakafu-u.ac.jp

Abstract – Efforts to synthesize a 6-oxatricyclo[6.3.0.0^{1,5}]undecane ring system are described. A novel Pd(II)-promoted oxidative cyclization of the lactone ester constructs the tricyclic core of ginkgolide C.

Ginkgo biloba is the only surviving member of a family of trees that appeared in the Jurassic period 170 million years ago and for this reason is called a “living fossil”. For approximately 5000 years, extracts of *G. biloba* have been used as herbal medicines to treat a variety of ailments, including coughs, asthma, and circulatory disorders. Recent clinical studies have attested to the potential benefits of ginkgolides in the delay of the onset of dementia.¹

Ginkgolides vary only in the number and positions of their hydroxy groups (**Figure 1**). Ginkgolide A, B, C, and M were initially isolated from the root bark of *G. biloba* in 1932 by Furukawa.² However, their structures were not elucidated until 1967.^{3,4} In 1987, ginkgolide J was isolated from the leaves of *G. biloba*.⁵

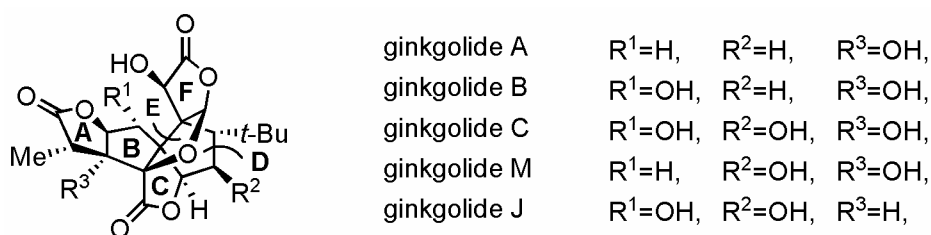
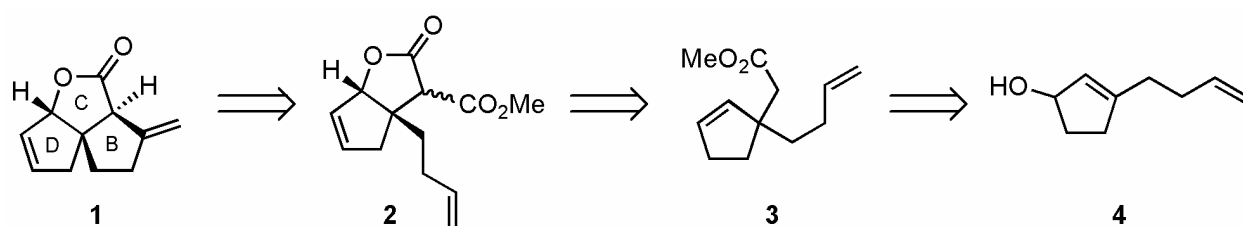


Figure 1. Structures of native ginkgolides

This paper is dedicated to Professor Emeritus Keiichiro Fukumoto in recognition of his many important contributions to the field of heterocyclic chemistry.

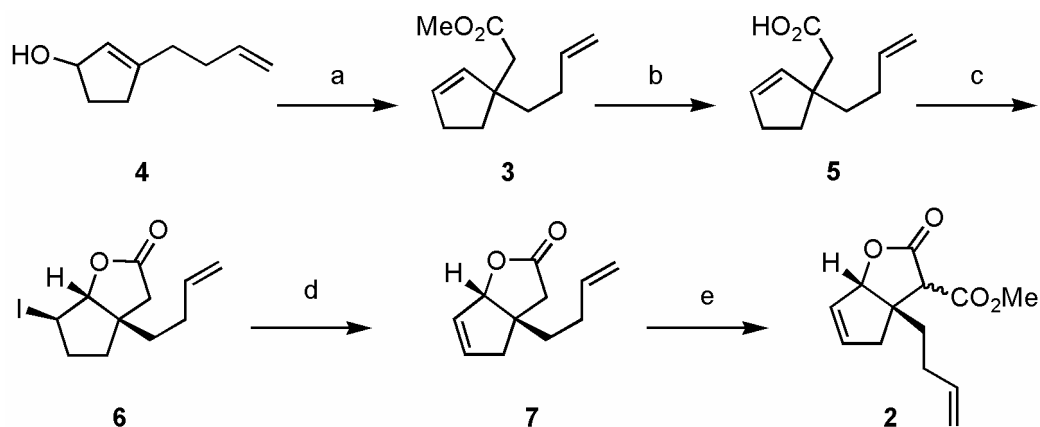
Ginkgolides are diterpenes with a cage skeleton consisting of six five-membered rings, i.e., a spiro[4.4]nonane carbocyclic ring, three lactones, and a tetrahydrofuran moiety. Furthermore, they contain an unprecedented *tert*-butyl group.

Herein, we describe the synthesis of the BCD tricyclic core of ginkgolide C. **Scheme 1** shows our retrosynthetic analysis for **1**. Namely, target molecule **1** would be synthesized by a cyclization reaction of lactone ester **2** followed by decarboxylation. Lactone **2** would be obtained from unsaturated ester **3** via halolactonization. Finally, unsaturated ester **3** would be provided from allyl alcohol **4** via a Claisen rearrangement.



Scheme 1. Retrosynthetic analysis of BCD tricyclic core **1** of ginkgolide C

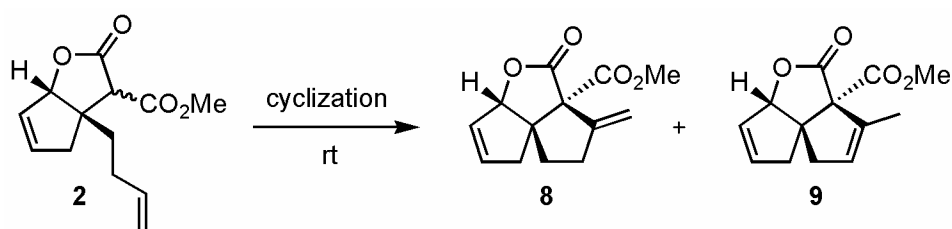
We initially pursued the synthesis of cyclization precursor **2** as depicted in **Scheme 2**. The synthesis began with a Johnson-Claisen rearrangement⁶ of allyl alcohol **4**⁷ and trimethyl orthoacetate in the presence of *p*-anisic acid to afford methyl ester **3** in 70% yield. Hydrolysis of ester **3** with lithium hydroxide monohydrate, and subsequent iodolactonization furnished γ -butyrolactone **6** in 85% yield in two steps. Unsaturated lactone **7** was obtained in 95% yield by treating iodolactone **6** with DBU. Subsequent methoxycarbonylation of lactone **7** afforded desired lactone ester **2** in 98% yield.



Scheme 2. Reagent and conditions: (a) MeC(OMe)₃, *p*-anisic acid, toluene, 180 °C, 70%; (b) LiOH·H₂O, THF/H₂O (1:1), 100 °C; (c) I₂, KI, NaHCO₃, MeCN/H₂O (1:1), 0 °C, 85% (2 steps); (d) DBU, THF, 90 °C, 95%; (e) LHMDS, THF, ClCO₂Me, -78 °C, 98% (α : β = 2:1)

The crucial cyclization was attempted under various conditions, some of which are listed in **Table 1**. Manganese(III)-promoted oxidative cyclization of **2** was adopted,⁸ and desired *exo*-olefin **8**⁹ was isolated

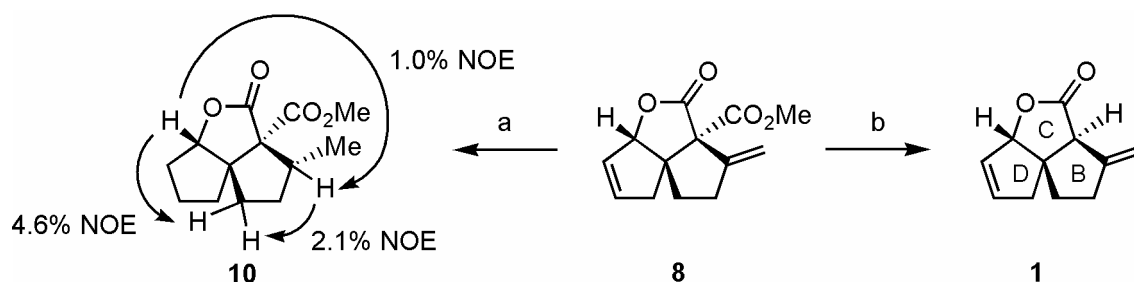
in 64% yield (Entry 1). Next, palladium-promoted oxidative cyclizations of **2** were investigated. Treatment of **2** with a stoichiometric amount of Pd(OAc)₂ in THF afforded 26% yield of *exo*-olefin **8** and 12% yield of *endo*-olefin **9** (Entry 2). Among the reaction conditions examined, employing DMSO as solvent was found to be the best condition as **8** was exclusively produced in 78% yield (Entry 3). To our best knowledge, there is not a report concerning palladium(II)-promoted oxidative cyclization of a lactone ester.



Entry	Reagent	Solvent	Time (h)	Yield (%)	
				8	9
1	Mn(OAc) ₃ ·2H ₂ O Cu(OAc) ₂ ·H ₂ O	AcOH	11	64	0
2	Pd(OAc) ₂	THF	24	26	12
3	Pd(OAc) ₂	DMSO	24	78	0

Table 1. Oxidative cyclization of lactone ester **2**

The relative stereochemistry was established using NOE experiments employing **10**⁹, the reduction product of **8**, as described in **Scheme 3**. Finally, **8** was subjected to a Krapcho reaction¹⁰ to give rise to tricyclic lactone **1**⁹, the BCD tricyclic core of ginkgolide C, in 77% yield.



Scheme 3. Reagent and conditions: (a) H₂, Rh-Al₂O₃, EtOH, rt. (b) LiCl, H₂O, DMSO, 150 °C, 77%

In conclusion, we developed a concise seven-step sequence to synthesize BCD tricyclic core **1** of ginkgolide C. A key feature of the synthesis is a new cyclization reaction. Further studies on the utility of this strategy for complex molecule synthesis as well as progress toward ginkgolide C will be reported in due course.

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9. Data for selected new compounds: Compound **8**: IR (KBr) 1781, 1732, 1264, 1056 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 2.00-2.13 (m, 2H), 2.43 (ddd, $J = 18.4, 2.1, 2.1$ Hz, 1H), 2.58 (dddd, $J = 16.4, 10.8, 8.0, 2.8, 2.8$ Hz, 1H), 2.66-2.74 (m, 2H), 3.76 (s, 3H), 4.95 (dd, $J = 2.2, 2.2$ Hz, 1H), 5.26 (dd, $J = 2.2, 2.2$ Hz, 1H), 5.40 (dd, $J = 3.0, 1.8$ Hz, 1H), 5.83 (ddd, $J = 8.0, 2.4, 2.4$ Hz, 1H), 6.12 (ddd, $J = 5.6, 2.4, 2.4$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 31.9, 36.5, 41.6, 52.8, 61.3, 67.0, 91.1, 113.0, 127.2, 138.7, 148.4, 169.4, 172.7; LRMS (FAB) m/z 235 [(M+H) $^+$], 154, 136; HRMS (FAB) calcd for $\text{C}_{13}\text{H}_{15}\text{O}_4$ [(M+H) $^+$] 235.0970, found 235.0981. Compound **9**: IR (KBr) 1760, 1731, 1257, 1075 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 1.83 (ddd, $J = 3.8, 2.2, 2.2$ Hz, 3H), 2.48 (ddd, $J = 18.4, 2.4, 2.4$ Hz, 1H), 2.58-2.69 (m, 2H), 2.77 (dddd, $J = 18.2, 2.4, 2.4, 2.4$ Hz, 1H), 3.79 (s, 3H), 4.96 (dd, $J = 2.0, 2.0$ Hz, 1H), 5.72-5.74 (m, 1H), 5.84 (ddd, $J = 5.6, 4.8, 2.4$ Hz, 1H), 6.14 (ddd, $J = 6.0, 2.4, 2.4$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 13.7, 41.3, 45.4, 52.8, 59.1, 72.8, 95.1, 127.1, 130.0, 137.2, 139.0, 169.0, 171.9; LRMS m/z 234 (M^+), 131, 129, 91; HRMS calcd for $\text{C}_{13}\text{H}_{14}\text{O}_4$ (M^+) 234.0892, found 234.0872. Compound **10**: IR (KBr) 1778, 1732, 1052 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 1.20 (d, $J = 6.8$ Hz, 3H), 1.57-1.70 (m, 3H), 1.78-2.09 (m, 7H), 2.40-2.49 (m, 1H), 3.78 (s, 3H), 4.54 (dd, $J = 5.2, 2.0$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 14.8, 24.4, 32.8, 33.9, 36.9, 38.6, 46.3,

51.9, 64.27, 67.7, 90.5, 168.9, 174.6; LRMS m/z 239 [(M+H)⁺], 178, 135, 134, 107; HRMS calcd for C₁₃H₁₉O₄ [(M+H)⁺] 239.1283, found 239.1271. Compound **1**: IR (KBr) 1764, 1157, 1001 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 1.88-1.95 (m, 1H), 2.77 (ddd, $J = 13.2, 6.0, 6.0$ Hz, 2H), 2.45-2.50 (m, 2H), 2.56 (ddd, $J = 1.6, 2.0, 17.8$ Hz, 1H), 2.75 (ddd, $J = 2.4, 4.8, 17.6$ Hz, 1H), 3.20 (s, 1H), 5.11-5.13 (m, 2H), 5.27 (ddd, $J = 2.0, 2.0, 2.0$ Hz, 1H) 5.84 (dddd, $J = 6.0, 4.0, 2.0, 2.0$ Hz, 1H) 6.09 (dddd, $J = 5.6, 5.6, 2.4, 0.8$ Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 33.5, 37.6, 45.2, 55.5, 57.6, 94.0, 110.3, 128.9, 137.4, 147.5, 177.2; LRMS m/z 176 (M⁺), 132, 117, 91; HRMS calcd for C₁₁H₁₂O₂ (M⁺) 176.0837, found 176.0820.

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