

Synthetic studies on phloroglucins: a new approach to the bicyclo[3.3.1]nonane system via the regioselective ring-opening of the methoxycyclopropane

Masahito Abe and Masahisa Nakada*

Department of Chemistry and Biochemistry, Faculty of Advanced Science and Engineering, Waseda University, 3-4-1 Ohkubo, Shinjuku-ku, Tokyo 169-8555, Japan

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Abstract—A new synthetic approach to the bicyclo[3.3.1]nonane system, a common structure in a number of polyisoprenylated phloroglucinol derivatives (phloroglucins), has been developed. The key step in our approach is a ‘one-pot’ procedure of two successive reactions, the intramolecular cyclopropanation reaction which affords the tricyclo[4.4.0.0^{5,7}]dec-2-ene derivative and its methoxy group directed regioselective ring-opening reaction mediated by ZnCl₂, producing the desired bicyclo[3.3.1]nonane as the sole product.

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Phloroglucins, polyisoprenylated phloroglucinol derivatives, are a growing family of natural products, possessing a bicyclo[3.3.1]nonane framework as a common structure.¹ Numerous natural products belonging to this family have been reported. The various oxygenation and functionalization patterns on the bicyclo[3.3.1]nonane framework give rise to diverse and complex structural features. Besides their complex structure, phloroglucins exhibit wide-ranging biological activities, including cytotoxicity against several human cancer cell lines;² hence, synthetic studies on this class of natural products have been carried out.^{3,4}

Hyperforin (Fig. 1) is a representative compound of the phloroglucins, isolated as a metabolite from St. John’s

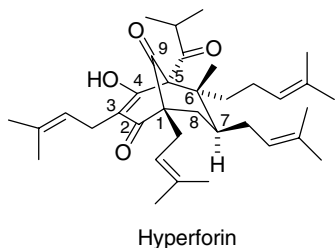
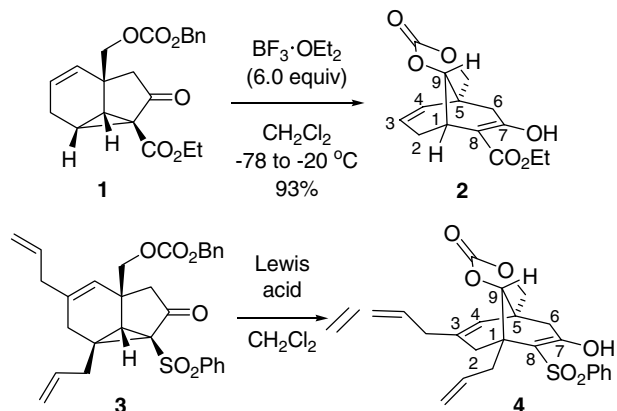


Figure 1.

* Corresponding author. Tel./fax: +81 3 5286 3240; e-mail: mnakada@waseda.jp

wort, a medicinal plant traditionally used to treat depression, superficial wounds, burns, and dermatitis.⁵ Hyperforin possesses a complex trioxygenated bicyclo[3.3.1]nonane system which incorporates a homoprenyl group and a methyl group at C6, three prenyl groups at C1, C3, and C7, and an isobutyryl functionality at the bridgehead C5. Hyperforin shows antibacterial,⁶ antitumor,⁷ apoptotic,⁸ and other interesting biological activities.^{9,10} The complex structure of hyperforin as well as its potent bioactivity have made it an attractive synthetic target.

Recently, we reported a synthetic approach to the bicyclo[3.3.1]nonane system (Scheme 1).¹¹ The key reaction in this approach is the Lewis acid promoted regioselective ring-opening reaction of the cyclopropane by the intramolecular attack of the benzyl carbonate of a tricyclo[4.4.0.0^{5,7}]dec-2-ene derivative **1** to provide the bicyclo[3.3.1]nonane derivative **2** as the sole product in high yield. Nevertheless, further transformations would be required to convert **2** to hyperforin. Particularly, oxygen atoms should be introduced into the bicyclo[3.3.1]nonane framework. This operation should be carried out at an early stage in the total synthesis because hyperforin is sensitive to oxidation.⁴ Furthermore, the reaction of **3** under the same conditions as those used for the conversion from **1** to **2** did not provide **4** (Scheme 1). This result suggested the limitation of the transformation via the Lewis acid promoted



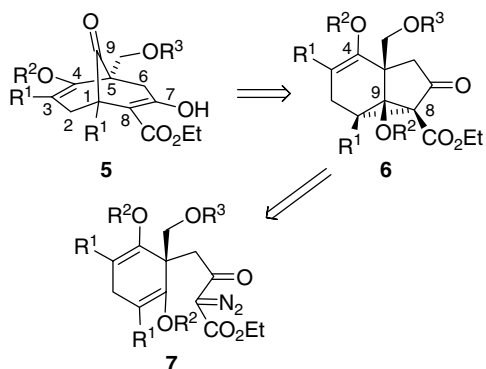
Scheme 1.

ring-opening reaction of the benzyl carbonate of tricyclo[4.4.0.0^{5,7}]dec-2-ene derivatives.

Consequently, we tried another approach to construct the bicyclo[3.3.1]nonane framework in hyperforin from a tricyclo[4.4.0.0^{5,7}]dec-2-ene derivative, and we herein report a new approach to the bicyclo[3.3.1]nonane system via the methoxy group directed regioselective ring-opening reaction of the tricyclo[4.4.0.0^{5,7}]dec-2-ene derivative.

We devised a new intermediate **6** (Scheme 2) as a precursor for **5** because use of **6** was expected to bring the following advantages: (1) Oxygen atoms introduced at C4 and C9 positions in **6** would correspond to the oxygen-containing functional groups at C4 and C9 positions in **5**. (2) A ring-opening reaction of **6** between C8 and C9 under acidic conditions was expected to be facile because the cationic center which could be generated at C9 would be stabilized by the oxygen atom at C9. (3) Chiral tricyclo[4.4.0.0^{5,7}]dec-2-ene derivative **6** would be prepared by the asymmetric intramolecular cyclopropanation of α -diazo- β -keto ester **7**. (4) The methoxyalkene moiety in **6** would be sensitive to the acidic conditions for the ring-opening reaction; however, the methoxycyclopropane was expected to be cleaved faster under acidic conditions because of its strain.

We have been studying the intramolecular cyclopropanation reaction (IMCP);^{11,12} however, we have never

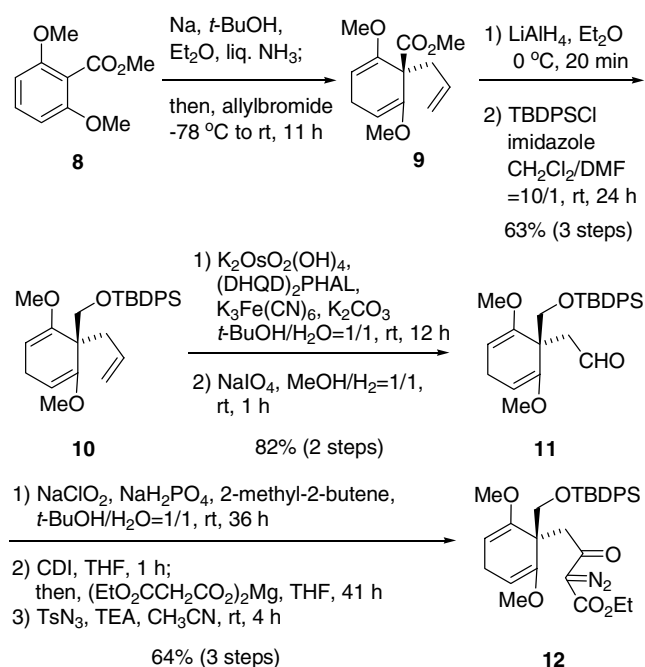


Scheme 2.

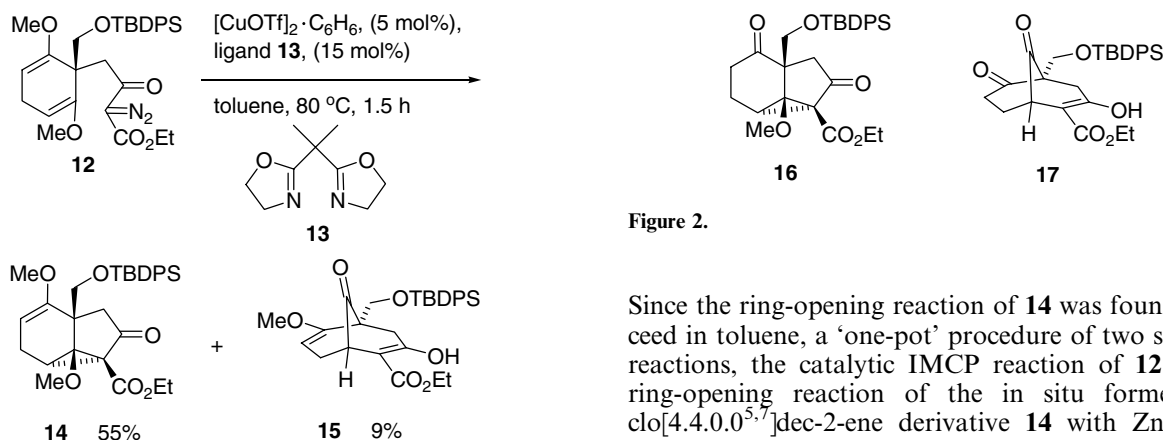
examined the IMCP reaction of an alkene substituted by an oxygen atom. Therefore, we prepared the most accessible substrate **12** (Scheme 3) from readily available 2, 6-dimethoxybenzoic acid methyl ester **8** to explore the possibility of the IMCP reaction.

Birch reduction of **8** and a subsequent ‘one-pot’ reaction with allylbromide provided **9**, and subsequent LiAlH₄ reduction and protection of the resulting alcohol as a TBDPS ether afforded **10** (63%, 3 steps). Regioselective dihydroxylation of **10** using Sharpless’s ligand¹³ and following oxidative cleavage of the resulting diol by NaIO₄ provided aldehyde **11** in 82% yield (2 steps). Attempts to convert **11** to β -keto ester corresponding to **12** via a two-step sequence that encompassed the aldol reaction of **11** with a lithium enolate of ethyl acetate followed by oxidation of the resulting alcohol was low-yielding. Furthermore, reaction of **11** with ethyl diazoacetate and SnCl₂¹⁴ afforded the product in moderate yield. However, Masamune’s protocol¹⁵ successfully converted **11** to the required β -keto ester in good yield. Thus, aldehyde **11** was oxidized to the carboxylic acid, which was converted to the acyl imidazolide to react with monoethyl malonate magnesium salt, providing the desired β -keto ester, which was successfully converted to the α -diazo- β -keto ester **12** (64%, 3 steps).

The reaction of α -diazo- β -keto ester **12** with CuOTf (10 mol %) in toluene at 80 °C proceeded very slowly; however, use of ligand **13** (15 mol %) accelerated the reaction to afford **14** in 55% isolated yield (Scheme 4). The ring-opened product **15** (9%) also formed probably because the initially formed **14** was further transformed to **15** under the acidic reaction conditions.¹⁶ This result indicated that the ring-opening reaction of **14** would afford **15** under appropriate acidic conditions; hence, the



Scheme 3.



Scheme 4.

ring-opening reaction of **14** with Lewis acid was next examined.

Reaction of **14** with TiCl_4 (Table 1, entry 1) at -78°C was completed within 1 h to cause cleavage of the alkenyl ether to generate diketone **16** in 84% (Fig. 2), but no ring-opened products **15** or **17** were obtained. The reaction of **14** with $\text{BF}_3\cdot\text{OEt}_2$ (entry 2) afforded the desired **15** in a rather low yield (19%), and use of Me_2BBr (entry 3)¹⁷ provided compound **16** (67%) as the sole product again. After screening several Lewis acids,¹⁸ we found that use of ZnCl_2 was favorable for this ring-opening reaction, providing **15** in 47% yield (entry 4). The reaction must be carried out at room temperature to be completed and the optimized reaction time was 3.5 h because the prolonged reaction at room temperature caused cleavage of the alkenyl ether to afford **17** only instead (55%, entry 5). Among the solvents examined for this reaction, toluene was found to improve the yield slightly (51%, entry 6).

Table 1. Lewis acid mediated ring-opening reaction of **14**

Entry	Lewis acid ^a	Temp (°C)	Time (h)	Product	Yield ^b (%)
1	TiCl_4	-78	1	16 ^d	84
2	$\text{BF}_3\cdot\text{OEt}_2$	$-78, -30$	1, 12 ^c	15	19 ^d
3	Me_2BBr	$-78, -50, -20$	1, 1, 0.5 ^c	16	67
4	ZnCl_2	$-78, 0, \text{rt}$	1, 1, 3.5 ^c	15	47
5	ZnCl_2	$-78, 0, \text{rt}$	1, 1, 60 ^c	17	55
6 ^c	ZnCl_2	$-78, 0, \text{rt}$	1, 1, 3.5 ^c	15	51

^a 1.5 equiv of Lewis acid was used.

^b Isolated yields except entry 2.

^c Time at the corresponding reaction temperature.

^d Yield determined by 400 MHz ^1H NMR due to the remaining inseparable TBDPSF.

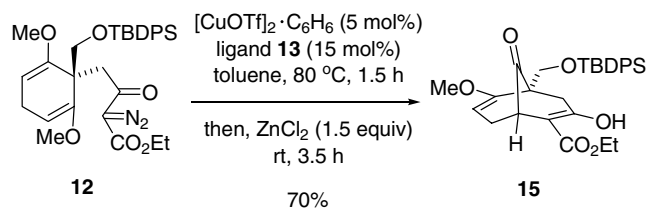
^e Toluene was used as the solvent.

Figure 2.

Since the ring-opening reaction of **14** was found to proceed in toluene, a ‘one-pot’ procedure of two successive reactions, the catalytic IMCP reaction of **12** and the ring-opening reaction of the in situ formed tricyclo[4.4.0.0.5.7]dec-2-ene derivative **14** with ZnCl_2 , was examined. After checking the completion of the IMCP reaction of **12**, the diethyl ether solution of ZnCl_2 was carefully added to the reaction mixture at -78°C . The reaction mixture was warmed up to room temperature to bring about the ring-opening reaction to provide the desired bicyclo[3.3.1]nonane derivative **15** in 70% yield.

Since the IMCP reaction of **12** afforded **14** and **15** in 64% combined yield and the ring-opening reaction of **14** provided **15** in 51% yield, this ‘one-pot’ procedure greatly improved the yield of **15**, which was practical enough for the synthetic purpose. We examined the ring-opening reaction of **14** under the same conditions as those employed in Scheme 5, too, but this attempt did not improve the yield. Therefore, the improved yield in the ‘one-pot’ procedure did not depend on the reagent system in Scheme 5. The yield of **15** in the ZnCl_2 -mediated ring-opening reaction of **14** (entry 6) was reproducible, and the formation of some structurally unidentified side-products reduced the yield. Hence, the moderate yield of **15** in entry 6 of Table 1 could be affected by something remaining (possibly moisture) in **14**.

In summary, a new effective approach to the bicyclo[3.3.1]nonane system, a common structure in a number of polyisoprenylated phloroglucinol derivatives (phloroglucins), has been developed. A ‘one-pot’ two successive reactions, the intramolecular cyclopropanation affording the tricyclo[4.4.0.0.5.7]dec-2-ene derivative **12** and its ZnCl_2 mediated regioselective ring-opening reaction directed by the methoxy group, produced the desired **15** as the sole product. We expect this procedure to be applicable to tricyclo[4.4.0.0.5.7]dec-2-ene derivative **6** possessing suitable substituent at its C1 and C3, which would be prepared from the corresponding α -diazo- β -keto ester **7**. Hence, further studies on the



Scheme 5.

asymmetric synthesis of hyperforin are now underway in this laboratory.

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