ilarly to those of isomeric 2-phenyl-4-ethylidene(or propylidene)-5(4*H*)-oxazolones, in which the Z-isomers showed more upfield shifts for β protons to carbonyl groups (7.02 ppm) than the *E*-isomers did (7.10 ppm). And the *E* assignments of the methyl and the rest of the molecule were made based upon the large coupling constants of two olefinic protons (14.2 Hz for **2ZE** and 15.0 Hz for **2EE**) which were determined by decoupling experiments.

8. (a) Cativiela, C.; Mayoral, J. A.; Melendez, E. *Synthesis* **1983**, 899-902. (b) Cativiela, C.; Melendez, E. *Synthesis* **1978**, 832-834.
9. Other possible Z,Z- and *E*,Z-isomers were not found in the photolysis of **2ZE**.
10. **3**: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.00 (d, 2H, *J*=7.0 Hz), 7.60-7.39 (m, 3H), 5.20 (septet, 1H, *J*=6.2 Hz), 2.24 (d, 2H, *J*=7.1 Hz), 1.38 (d, 6H, *J*=6.2 Hz), 0.92 (m, 1H), 0.40 (m, 2H), 0.08 (m, 2H). For comparison, the spectroscopic data of 2-phenyl-4-ethylidene(or propylidene)-5(4*H*)-oxazolone can be found in ref. 14.
11. **4**: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.51 (broad s, 1H), 7.83 (d, 2H, *J*=7.0 Hz), 7.62-7.45 (m, 3H), 2.93 (d, 2H, *J*=6.7 Hz), 1.01-0.83 (m, 3H), 0.64 (m, 1H), 0.25 (m, 1H).
12. **1E**: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.05 (d, 2H, *J*=6.0 Hz), 7.61-7.40 (m, 3H), 6.21 (d, 1H, *J*=16.0 Hz), 2.90 (m, 1H), 1.27 (m, 2H), 0.88 (m, 2H).
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15. For comparison, the absorption maxima in the ultraviolet absorption spectra are 236, 298 nm for Z-2-phenyl-4-ethylidene-5(4*H*)-oxazolone, 248, 324 nm for **1Z** and 256, 346 nm for **2ZE**.

Study toward the Total Synthesis of Forskolin(II) Synthesis of the Epoxy-trien as the Key Intermediates

Byungoo Kim, Kyunghae Lee, and Hongbum Kim*

Department of Chemistry, Dongguk University, Seoul 100-715, Korea
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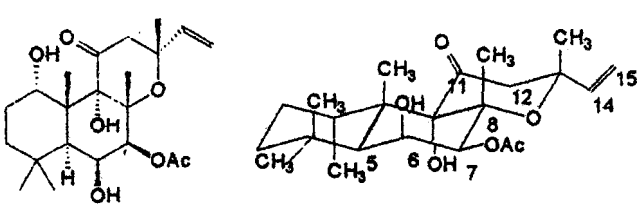
In connection with our continuing efforts[1] to utilize an polyene cyclization reaction to build up a carbon skeleton for forskolin **1**, we wish to report the synthesis of the epoxy triene **13** as a key intermediate. The forskolin **1** is a diterpene obtained from the roots of *Coleus forskohlii* (Willd.)[2] Brig. (*Lamiaceae*), which has been described in Ayurvedic materia medica and in ancient Hindu medicinal texts as a remedy for several complaints, including heart diseases and central nervous system (CNS) disorders such as insomnia and convulsions.

In clinical studies, forskolin **1** has shown a promising therapeutic potential as a novel drug for the treatment of diseases such as glaucoma, congestive heart failure,[3] and bronchial asthma.[4] The absolute structure of **1** was determined from the crude methanolic extract of *Coleus forsolii* in 1977 by the research group at Hoechest.[2,5] It has eight chiral centers and various oxygenated functional groups-hydroxyl, acetate, ketone, ether-with an ether linkage within its tricylic carbon skeleton. Forskolin **1** has attracted considerable interests from many synthetic organic chemists[6] because of its unique structures and biological activities. The first total synthesis of **1** was reported by Ziegler[7a] followed by Corey[7b] and Ikegami.[7c] The formal syntheses for the Ziegler intermediate **2** were reported by several others.[8] (Figure 2)

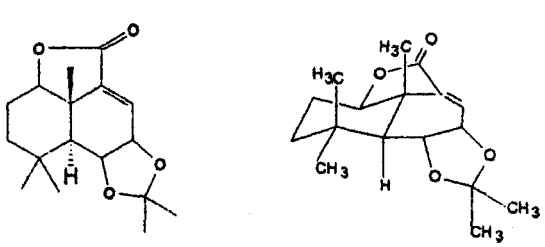
However, all of these synthetic routes required more than 20 steps in order to build the carbon skeleton with the necessary functional groups. We have investigated a conceptually different approach to synthesize Zieglar intermediate 2 utilizing polyene cyclization.[9] Our retrosynthetic analysis is depicted in Scheme 1. Forskolin **1** would be synthesized from the key intermediate **4**. The tetramethyl hexahydrobenzochromone of **4** would be constructed from the



1

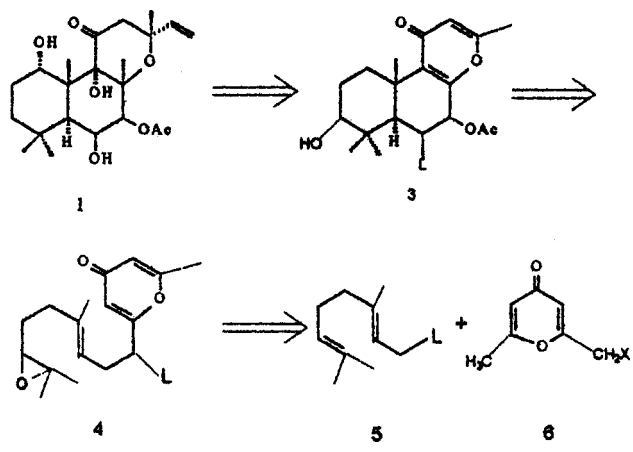
Forskolin

Figure 1.



2

Figure 2.

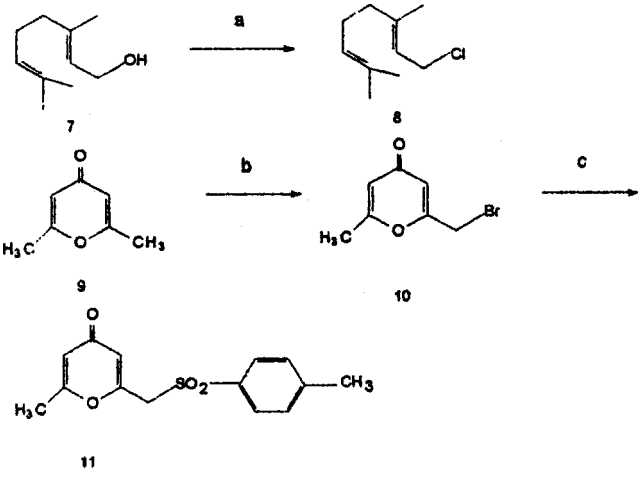


Scheme 1.

diene **5** utilizing adequate polyene cyclization reaction (Scheme 1).

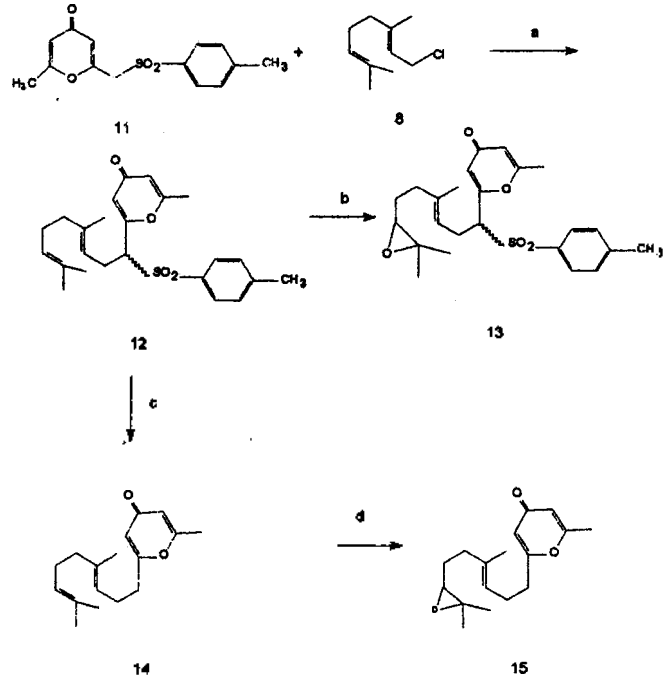
Our retrosynthetic analysis led us to prepare (E)-4,8-dimethyl-3,7-nonadiene chloride **8** and sulfone pyrone **11** (Scheme 2). Geranyl chloride **8**[10] was obtained by treatment of geraniol **7** with 1.50 equivalent of LiCl , 1.20 equivalent of mesyl chloride and 1.20 equivalent of 2,4,6-collidine in DMF at room temperature for 2 hr. The reaction was completed under the mild conditions in 93.0% yield without isolation of the mesylate. Isolation of the mesylate was not recommended since it was very labile for work-up and column chromatography conditions.

The 2-(bromomethyl-6-methyl)-4H-pyran-4-one **10**, has been synthesized by the modified literature procedure.[1] The yield of selective monobromination of 2,6-dimethyl-γ-pyrone **9** could be increased from 19.6% (literature value)[11] up to 45.6% based on the recovered starting material (about 20%) by the careful control of the addition mode and the amount of reagents (0.36 equivalent of benzoyl peroxide as an initiator and 2.12 equivalent of N-bromosuccinimide as a



Reagents and Conditions; (a) 1.50 eq. LiCl, 1.20 eq. MsCl, 1.20 eq. Collidine, DMF, RT, 2h, 93.0%. (b) 0.36 eq. BPO, 2.12 eq. NBS, Benzene, Reflux, 8h, 45.6%. (c) Sodium p-toluenesulfinate, EtOH, Reflux, 2h, 93.0%

Scheme 2.



Reagents and Conditions; (a) NaH, THF, rt, 2h, 65.0%. (b) MCPBA, CH_2Cl_2, 0 °C, 30 min, 92.3%. (c) SmI_2, HMPA, THF, 20 °C, 2h, 43.0%. (d) MCPBA, $CHCl_3$, 0 °C, 30 min, 85%

Scheme 3.

bromine source). In addition, dilution of the reaction mixture also led to a significant increase in yield due to the low solubility of 2,6-dimethy-γ-pyrone **9** in organic solvent. The bromopyrone **10** was readily converted to the sufone-pyrone **11** by refluxing with sodium *p*-toluenesulfinate in ethyl alcohol in 93.0% yield.

Treatment with (E)-4,8-dimethyl-3,7-nonadiene chloride **8** with sodium hydride followed by the addition of the sulfone-pyrone **11** gave the triene **12** in 65.0% yield (Scheme 3). The various reaction conditions such as the different bases, solvents and additives were tried but did not give the significant improvement.

The key intermediate **13** was obtained from **12** by the modified epoxidation reaction[12] using *m*-chloroperbenzoic acid in methylene chloride at 0 °C in 92.3% yield. In addition, the compound **14** was prepared from **12** utilizing samarium(II) Iodide[13] and converted to the epoxide **15** in order to compare the reactivity of triens with different functional groups under various polyene cyclization conditions.

In summary, the key intermediate the epoxy-triene **13** was synthesized from geraniol by a convergent manner. The study for the optimized reaction conditions for its polyene cyclization is currently under investigation in our laboratory and the preliminary results will be reported soon.

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14. All compounds were isolated and fully characterized by spectroscopic methods. For example: Compound **13** ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.67 (d, 2H, *J*=8.06), 7.35 (d, 2H, *J*=8.06), 6.05 (s, 2H), 5.05 (t, 1H), 3.90 (dd, 1H, *J*=11.6, 4.2), 2.98 (ABq, 1H, *J*=15.5, 11.6), 2.75 (ABq, 1H, *J*=15.5, 4.2), 2.66 (m, 1H), 2.45 (s, 3H), 2.10 (s, 3H), 1.62 (s, 3H), 1.55 (m, 4H), 1.28 (s, 3H), 1.18 (s, 3H); exact mass calcd for $C_{24}H_{30}SO_5$ (M+1) 430.562, Obsd 430.560.

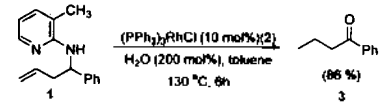
Chelation-Assisted Olefin-Isomerization and C-N Bond Cleavage by Rh(I)

So-Hee Jang and Chul-Ho Jun*

Department of Chemistry, Yonsei University, Seoul 120-749, Korea
Received August 8, 1997

Double bond migration is one of the most extensively studied transition metal catalytic reactions. While many examples are focused on the conversion of 1-alkene into the more stable *trans*-2-alkene by a transition metal catalyst with a single movement of the double bond,[1] multiple double bond migration has been less explored in spite of its usefulness. Facile olefin-isomerization has been achieved with functionalized olefins including allylamine,[2] allyl alcohol[3] and allyl ether[4] by transition metal catalysts. Transition-metal can activate the allylic C-H bonds through coordination of an adjacent heteroatom, and a subsequent hydride transfer to the olefin completes the double bond migration. Therefore, studies of the useful double bond migrations have centered on the allylic olefin, not on the homoallylic olefin. The introduction of a pertinent auxiliary may provide an effective method for the multiple double-bond migration. The silyl group was used for this purpose, but not successful.[5] The pyridyl group should be a promising candidate since it is used as a good directing group in many C-H bond activation reactions.[6] In the present study, we explain the development of a model system that would undergo multiple double bond migrations into imine, which could be hydrolyzed to produce ketones.

(3-Methyl-2-pyridyl)-N-(1-phenyl-3-butenyl)amine (**1**)[7] reacted with H_2O at 130 °C for 6 h under a catalytic amount (10 mol%) of tris(triphenylphosphine)rhodium(I) chloride (**2**) to give butanophenone (**3**) in 86% isolated



(1)

yield after chromatographic isolation.

The reaction mechanism is believed to be that **1** is isomerized to imine **4**, which is hydrolyzed by adding H_2O to produce **3**. In this double bond migration, the pyridyl group in **1** was the important auxiliary, since **3** was not isolated when **5**[8] with no coordination site was used in place of **1**. The first step of this double bond migration must be precoordination of the rhodium catalyst to the nitrogen atom in the pyridyl group. Then, multiple double-bond migration continues until imine is formed. The generated imine might form metal complex **6**.