A Study toward the Total Synthesis of Forskolin(IV)

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In connection with our continuing interest in forskolin **1**,[1] we wish to report our efforts on the polyene cyclization reactions[2] of 2-[4,8-dimethyl-1-(toluene-4-sulfonyl)-nona-3,7-dienyl]-6-methyl-pyran-4-one **2**.[3] Forskolin **1** has attracted considerable interest from many synthetic organic chemists[3-4] due to its unique structure and biological activities.[5-6] The total syntheses of **1** involving the Ziegler intermediate **3**[7a] were reported by Ziegler,[7b] Ikegami,[8] and Corey,[9] respectively. Others have elegantly synthesized **3**.[10] However, all of these synthetic routes required more than 20 steps for building the desired carbon skeleton. We have investigated a conceptually different approach to synthesize **1** utilizing a polyene cyclization.[2] Our approach commences with the synthesis of the polyene substrate **2** from geraniol and 2,6-dimethyl-γ-pyrone in a preparative scale (about ten grams scale). With the availability of **2**, we focused our efforts on transformation of the acylic polyene system into the tricylic carbon skeleton.

In a previous paper,[3] we reported the preliminary result of a cyclization reaction of **2**. Treatment of **2** with mercury(II) triflate and N,N-dimethylaniline[11] followed by $NaBH_4$ reduction gave rise to the exo olefin **4** in 46.2% and the endo olefin **5** in 2.4%, respectively (Scheme 1).

The structures of **4** and **5** were proposed by interpretation of spectroscopic data and chemical reactivity but not fully confirmed. It was necessary to elucidate an unambiguous structure of **4** and **5** for further progress of our research. For X-ray crystallography analysis, the single crystal of **4** was carefully prepared by very slow recrystalization for several days using the mixed solvent of methylene chloride and *n*-hexane (2 : 5). Now we confirm our assigned structure of **4** by the X-ray crystallographic data (Figure 2).

It is noteworthy that the bulky toluenesulfonyl pyranone group at C-1 in **4** is located at the axial position. It was assumed that the structure **4** was favoured over **10** due to allylic interaction[12] caused by methylene group at C-6 and the bulky side chain at C-1 in **10** (Figure 3).

In addition, the favored structure **4** gave a clue to the nature of the cyclization reaction. The calculation based upon MM2 force field utilizing HyperChem 4.0 shows that **4**, which is the major product under our reaction condition, is the least stable compound among the possible configurations (Figure 4).

It means that our cyclization is strongly governed by kinetic control. Since the bulky side chain at the axial posi-

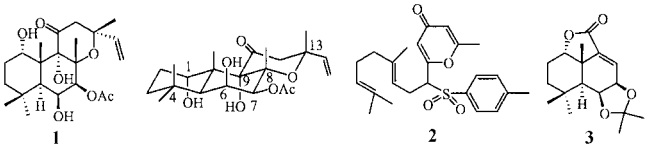
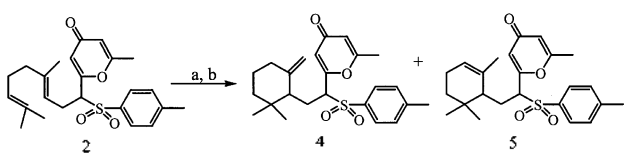


Figure 1. The structure of Forskolin and key intermediates.



(a) $Hg(OTf)_2$ - N,N-dimethylaniline 2.00 eq. CH_3NO_2, -20 ℃, 1 hr; then sat'd NaCl(aq.) RT, 3 hrs. (b) $NaBH_4$-NaOH/H_2O, EtOH:CH_2Cl_2 (1:1), RT, 1 hr. 2 steps: 4(46.2%), 5(2.4%).

Scheme 1

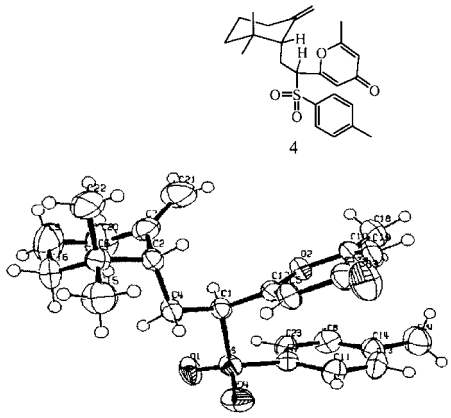


Figure 2. X-ray structure of **4**.

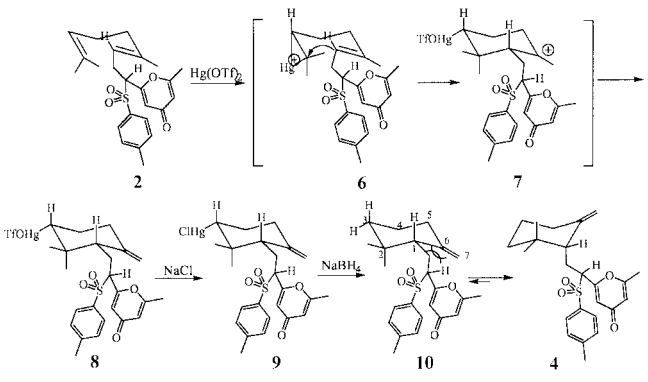


Figure 3. Proposed reaction path.

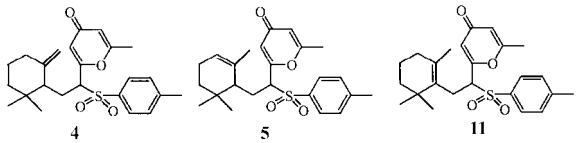
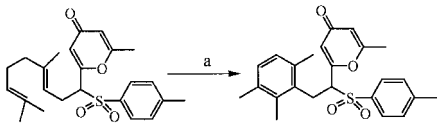


Figure 4. MM2 calculated energy of **4**, **5** and **11**.



(a) $ClSO_3H$ 1.80 eq.,$CH_3CH_2NO_2$-CH_2Cl_2(10:1), -78℃ to RT, 2hrs, 71.9 %.

Scheme 2

tion at C-1 in **7** was caused to distortion of cyclohexane conformation. the axial proton at C-5 is less liable for elimination than protons of the methyl group at C-6.

After thorough literature search, we found very few precedents for the exo methylene cyclic compound.[13]

In order to overcome a monocyclization caused by a Lewis acid promoted[14] cyclization, we turned our attention to utilizing a protonic acid promoted cyclization. Treatment of **2** with 1.80 equivalent of chlorosulfonic acid[15] in mixed solvents (nitroethane and methylene chloride) gave rise to a colorless solid in 71.9%. Without nitroethane, the starting material was decomposed completely. The structure of unknown solid was investigated by the careful interpretation of elementary analysis and spectroscopic data.[16] Too much surprise to us, the aromatized compound **12** was assigned to the unknown product (Scheme 2).

The unexpected product **12** can be rationalized by the formation of carbocation intermediate which was produced by the initial protonation at the terminal olefin of **2** followed by sequential shifts of the hydride and methine and then cyclization. respectively. For the time being. several triene precursors were subjected to the same reaction conditions but gave rise to inconsistent results. Studies to probe the generality of this reaction and to transform **12** and into the useful natural products are currently in progress.

In this communication we detail the various effort on cyclization attempt for triene precursor **2**. The structure of the key intermediate **4** was firmly confirmed by X-ray crystallography and showed an unique conformation. Treatment of **2** utilizing protonic acid promoted cyclization gave rise to the unexpected **12**. The study for further elaboration to build a carbon skeleton of forskolin **1** is actively under investigation in our laboratory and will be reported in detail.

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16. All compounds were isolated and fully characterized by spectroscopic methods. For example compound **15**. Rf = 0.43 (ethyl acetate : hexane = 1 : 1). Melting point: 130-132 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.76 (d, 2H, 7.2 Hz), 7.34 (d, 2H, 7.2 Hz), 6.93 (ABQ, 1H, 8.0 Hz), 6.85 (ABQ, 1H, 8.0 Hz), 6.01(s, 1H), 5.80 (s, 1H), 3.87 (dd, 1H, 14.0, 3.34 Hz), 3.65 (m, 2H), 2.40 (s, 3H), 2.18 (s, 9H), 2.16 (s, 3H). Anal. Calcd for $C_{24}H_{26}SO_4$: C, 70.21; H, 6.38; S, 7.81, Found C, 70.06; H, 6.34: S, 7.73.