A New Approach for Ingenol Synthesis

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Ingenol[1] (**1**), isolated from the genus *Euphorbia*, has been of great interest as a synthetic target[2] because of its unusual structure involving an "inside-outside" bridged BC ring coupled with a broad spectrum of biological activities (Figure 1).[3] Construction of the highly strained *trans*-bridged BC ring system of ingenol through a direct cyclization reaction has proved difficult, and therefore, multistep transformations have been required.[2f,h,p] In the present paper, we describe a new entry to ingenane skeleton synthesis via a tandem cyclization−rearrangement strategy.[4]

The *trans*-decalinol derivative, including the side chain with a dicobalt hexacarbonyl propargyl cation,[5] was designed as a precursor of tandem cyclization−rearrangement reactions (Scheme 1). The intramolecular electrophilic addition of the propargyl cation moiety to the ethylidene carbon would afford the tricyclic tertiary cation intermediate that, in turn, undergoes rearrangement to yield the desired ingenane skeleton.

This strategy has several advantages: (1) The conformational rigidity of the *trans*-decalin framework as well as the dicobalt hexacarbonyl propargyl cation moiety would facilitate the cyclization of the C ring. (2) The *trans*-diaxial relationship between Ha and the hydroxy group of the decalinol would be advantageous for inducing smooth transformation to the ingenane skeleton having the unique "inside" α-proton that is almost antiparallel to the carbonyl group. (3) Stereocontrol at the C(11) position (ingenane numbering) would be achieved by using the (*E*)-isomer of the ethylidenedecalin derivative. (4) The dicobalt hexacarbonyl acetylene moiety of the product would be useful as a flag for installation of the D ring.

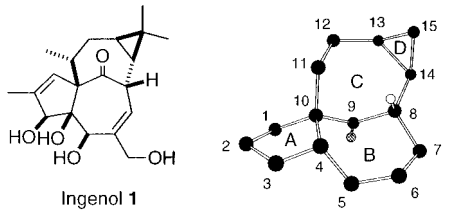
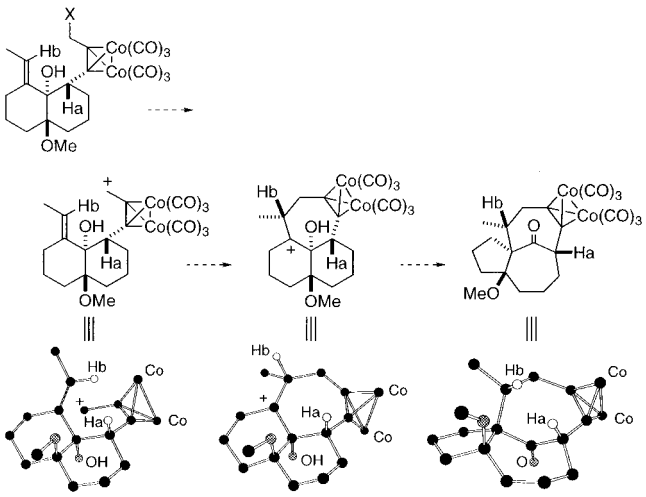
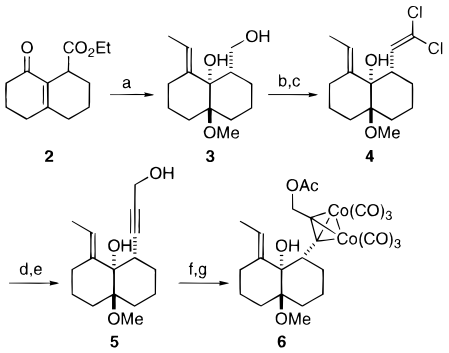


Figure 1.

Scheme 1



Scheme 2[a]



[a] Key: (a) Supporting Information; (b) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, 100%; (c) $Cl_3CPO(OEt)_2$, BuLi, THF−Et_2O, −100 °C to rt, 95%; (d) BuLi, THF, −78 °C then MeOCOCl, −45 °C; (e) DIBAL, toluene, −78 °C, two steps 67%; (f) Ac_2O, Et_3N, DMAP, CH_2Cl_2, 97%; (g) $Co_2(CO)_8$, CH_2Cl_2, rt, 98%.

The ingenane skeleton precursor was prepared as shown in Scheme 2. *trans*-Decalinol **3** with three continuous chiral centers was synthesized from keto ester **2**, which was easily prepared according to a previously described procedure,[6] through diastereoselective epoxidation followed by regioselective hydrolysis of the epoxide.[7] Diol **3** was converted into dichloroolefin **4** via Swern oxidation and Horner−Emmons reaction. Successive treatment of **4** with excess butyllithium and methyl chloroformate afforded an acetylenic ester that was reduced to propargyl alcohol **5**. Acetylation followed

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Scheme 3

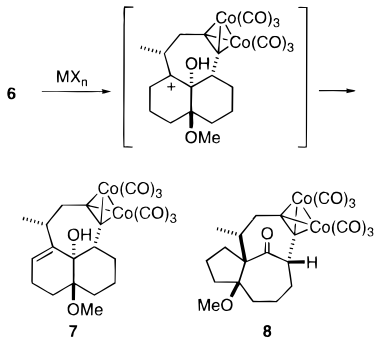


Table 1. Reactions of 6 with Aluminum Reagents

		products (%)[b]		
entry	AlX_3[a]	**7**	**8**	**6**
1	Me_2AlCl	50		
2	$Me_2Al(OTf)$	69	13	
3	$MeAl(OTf)_2$	66	13	
4	$MeAl(OCOCF_3)_2$	23	38	24
5	$MeAl(OCOCF_3)(OAr^1)$[c]	21	77	
6	$MeAl(OCOCF_3)(OAr^2)$[c]			80

[a] Aluminum reagents except for Me_2AlCl were prepared from a 1 M hexane solution of Me_3Al and the corresponding acids or phenols at room temperature. Acetate **6** was treated with 2.2 equiv of an aluminum reagent in CH_2Cl_2 at −23 °C to rt. [b] Determined by ^1H NMR of the crude product using $CHBr_3$ as an internal standard. [c] Ar^1 = 2,6-$(CH_3)_2$-4-$(NO_2)C_6H_2$, Ar^2 = 4-$NO_2C_6H_4$.

by complexation using $Co_2(CO)_8$[5] gave dicobalt hexacarbonyl propargyl cation precursor **6**.[8]

Initial attempts to induce a tandem cyclization−rearrangement reaction of propargyl acetate **6** under the influence of an equimolar amount of Lewis acid were unsuccessful. Thus, the reactions with $TiCl_4$ and $SnCl_4$ gave complex mixtures, and only a small amount of allyl alcohol **7** was obtained in the presence of $BF_3{\cdot}OEt_2$, $EtAlCl_2$, or Me_2AlCl (Scheme 3).

The formation of **7** indicates that the dicobalt hexacarbonyl propargyl cation attacks the ethylidene carbon to generate the tricyclic tertiary cation intermediate, which prefers β-elimination rather than rearrangement of the carbon framework. We envisioned that *in situ* activation of the hydroxy group by forming a metal alkoxide would significantly accelerate the rearrangement pathway. Use of 2 equiv of an aluminum reagent was expected to be suitable for this purpose because a variety of aluminum reagents can be easily prepared from trimethylaluminum.[9] The reactions of **6** with several aluminum reagents are summarized in Table 1.

Although the use of Me_2AlCl was not effective (entry 1), a small amount of the desired product **8** (Figure 2)[8] was obtained by the use of Me_2AlOTf or $MeAl(OTf)_2$ (entries 2 and 3), and $MeAl(OCOCF_3)_2$[10] afforded **8** as the major product (entry 4). These results suggest that low Lewis-acidity of an aluminum reagent is essential for the pinacol-type rearrangement promoted by the aluminum alkoxide of the decalinol. After further investigation, aluminum 2,6-dimethyl-4-nitrophenoxide was found to give the most satisfactory results (entry 5), which contrast with the reaction of aluminum 4-nitrophenoxide, which resulted in recovery of the starting material (entry 6). The methyl groups at the *o*-position of 4-nitrophenol seem to play an important role perhaps by activating the aluminum reagent by reducing aggregation.[11]

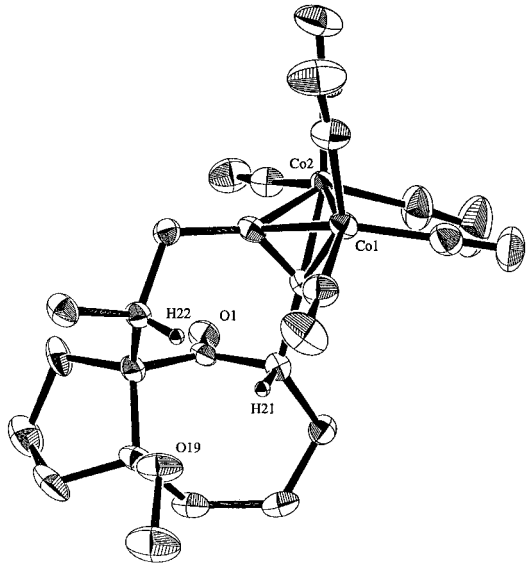
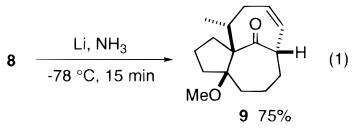


Figure 2. ORTEP drawing of cobalt complex **8**.

Finally, reductive deprotection of the dicobalt hexacarbonyl acetylene moiety of **8** was examined. The hydrogenation catalyzed by Wilkinson complex[12] as well as Birch reduction using lithium metal afforded the desired product **9** having the C(13)−C(14) double bond, which would be useful for installation of the D ring via cyclopropanation reaction (eq 1).



In conclusion, we developed a new method for constructing the highly strained ingenane skeleton by a tandem cyclization−rearrangement strategy. Product **9**, which contains the C(11) α-methyl group as well as the C(13)−C(14) double bond, shows promise for the total synthesis of ingenol. We are currently investigating the synthesis and tandem cyclization−rearrangement reactions of functionalized decalinol derivatives.

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Supporting Information Available: Experimental procedures and characterization data for all new compounds and the ORTEP drawings of **6** and **8** (10 pages).

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(7) *trans*-Decalinol **3** was derived in 12 steps from **2** and described fully in the Supporting Information.

(8) The stereochemistries of both **6** and **8** were eventually established by X-ray crystallographic structure determination.

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