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Total Synthesis of Ingenol

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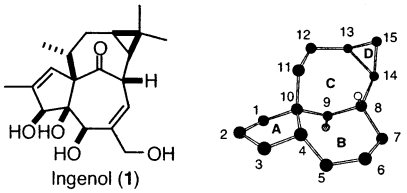
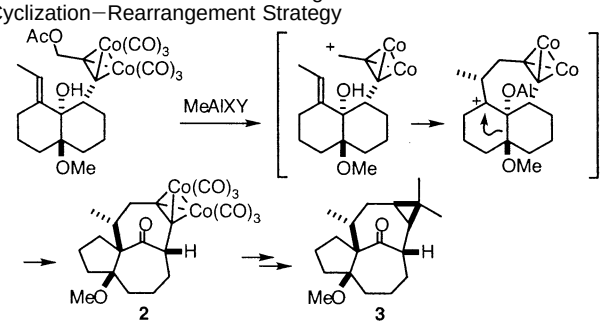
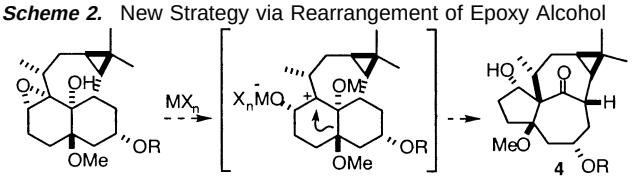
Ingenol (**1**),[1] isolated from the genus *Euphorbia*, has been of great interest as a synthetic target[2] because of its unusual structure involving an "inside−outside" bridged BC ring coupled with a broad spectrum of biological activities.[3] The difficulties in constructing the highly strained ingenane skeleton required special approaches, and five strategically distinct methods[2,4] have been disclosed to date. The first total synthesis of ingenol has recently been achieved by Winkler[5] on the basis of an intramolecular de Mayo reaction that had been originally reported by the same authors[6] as the first entry for constructing the trans-bicyclo[4.4.1]-undecane system.



Scheme 1. Construction of the Ingenane Skeleton via Tandem Cyclization−Rearrangement Strategy



Scheme 2. New Strategy via Rearrangement of Epoxy Alcohol



In 1997, we reported an efficient method for ingenane synthesis by employing a "tandem cyclization−rearrangement strategy"[7] as shown in Scheme 1. Although the product **2** was further converted into compound **3** having the complete CD ring system of ingenol,[8] the methoxy group at the C(4) position was not sufficient to serve as an anchor for installation of the hydroxyl groups and the olefin moieties of the AB ring.

The present work describes the total synthesis of ingenol on the basis of a new strategy, namely a rearrangement reaction of an epoxy alcohol giving rise to the key intermediate **4** which possesses two oxygen functional groups on both the A and B rings (Scheme 2).

The synthetic route for the key intermediate is depicted in Scheme 3. An allyl ether derived from commercially available alcohol **5** was subjected to a Claisen rearrangement reaction promoted by dichloroacetic acid. The resulting ketone **6** reacted with NBS in water−DMSO[9] to yield bromohydrin derivatives **7** and **8** as an almost 1:1 mixture, which was recrystallized from ethyl acetate to give pure **8** as crystals. It is noteworthy that ketone **6** can be easily recovered from the mother liquid containing **7** by treating with zinc dust. Silylation of **8** by using TESCl and imidazole effected selective protection of the secondary hydroxyl group via opening of the lactol ring. The aldol reaction of ketone **9** with acetaldehyde followed by dehydration afforded (*E*)-enone **10** stereoselectively. In the presence of LiBr, enone **10** reacted with lithium enolate of *tert*-butyl acetate to afford adduct **11** as a single isomer. In the stereoselective addition reaction, the conformation of the α-methoxyketone would be restricted by forming a five-membered chelate ring, and the nucleophile attacks the carbonyl group from the opposite side of the side chain (Figure 1, **A**).

Treatment of hydroxyester **11** with trimethylaluminum followed by LDA effected an intramolecular alkylation reaction to give *trans*-decaline derivative **12** as a single isomer. Since a reaction in the absence of trimethylaluminum failed to give **12**, formation of a six-membered cyclic aluminum enolate intermediate would be essential for the stereoselective cyclization reaction (Figure 1, **B**). Silylation of the secondary hydroxyl group followed by elongation of the side chain led to a propargyl alcohol which was converted into dicobalt acetylene complex **15** in good yield. Under the influence of methylaluminum bis(2,6-dimethyl-4-nitrophenoxide), cobalt complex **15** underwent a cyclization reaction to afford allyl alcohol **16** containing the C(11) α-methyl group. The dicobalt acetylene complex moiety of **16** was used for stereoselective construction of the D ring through Birch reduction, dibromocyclopropanation, and methylation. Transformation of the tetracyclic carbon framework into an ingenane skeleton was achieved via stereoselective epoxidation of allyl alcohol **17** followed by treatment with trimethylaluminum.[10]

The key intermediate **19** having a complete ABCD ring system of ingenol in hand, the stage was set for stereoselective functionalization of the AB ring moiety (Scheme 4). The condensation reaction of ketone **20** with *tert*-butoxy-bis(dimethylamino)methane[11] followed by reduction with DIBAL[12] afforded enone **21** in an excellent yield. The C(1)−C(2) double bond was introduced by dehydration of a secondary alcohol which was obtained through

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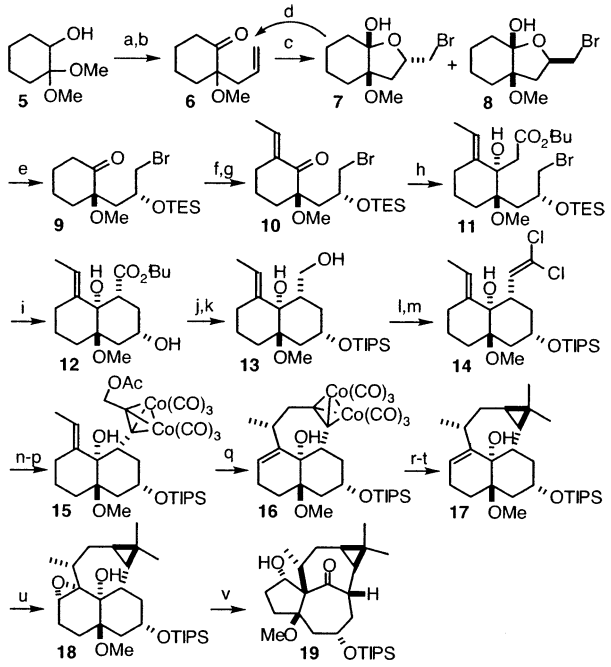
Scheme 3. Construction of the Ingenane Skeleton via Rearrangement Strategy[a]



[a] Reagents and conditions: (a) NaH, $BrCH_2CH{=}CH_2$, benzene; (b) $CHCl_2CO_2H$, DMF, reflux (79% in 2 steps); (c) NBS, H_2O, DMSO (**8**: 32% after recrystallization); (d) Zn dust, NH_4Cl, ether, H_2O (52% of **6** was recovered); (e) TESCl, imidazole, DMF, rt (99%); (f) LHMDS, $ZnBr_2$, CH_3CHO, THF (71%); (g) $(CF_3CO)_2O$, pyridine, DBU, benzene (95%); (h) ^{t}BuOAc, LDA, LiBr, ether (91%); (i) Me_3Al, LDA, THF, then HCl (66%); (j) TIPSCl, DMAP, DMF (quant); (k) $LiAlH_4$, THF (84%); (l) SO_3·pyridine, DMSO, Et_3N (97%); (m) $(EtO)_2P(=O)CCl_3$, BuLi, THF (85%); (n) BuLi, THF, then $(CH_2O)_n$ (91%); (o) Ac_2O, Et_3N, DMAP, CH_2Cl_2 (99%); (p) $Co_2(CO)_8$, CH_2Cl_2 (95%); (q) methylaluminum bis(2,6-dimethyl-4-nitrophenoxide CH_2Cl_2; (r) Li, liq. NH_3 (67% in 2 steps); (s) $CHBr_3$, NaOH, $BnEt_3NCl$, CH_2Cl_2, H_2O (71%); (t) Me_3CuLi_2, ether, then MeI (95%); (u) TBHP, $Ti(O^iPr)_4$, MS 4A, CH_2Cl_2; (v) Me_3Al, CH_2Cl_2 (76% in 2 steps).

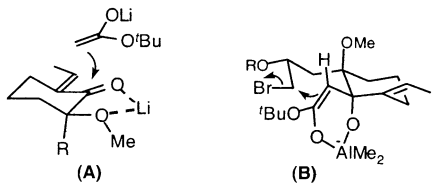
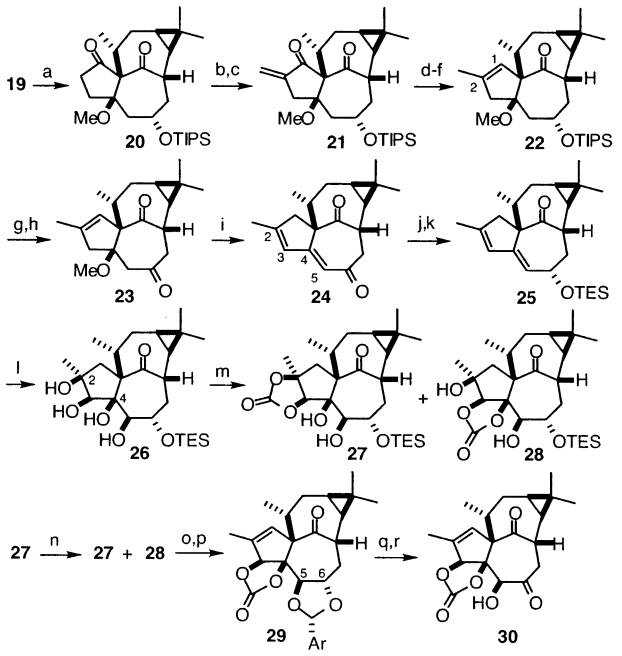


Figure 1. Suggested intermediates of the stereoselective C−C bond-forming reactions.

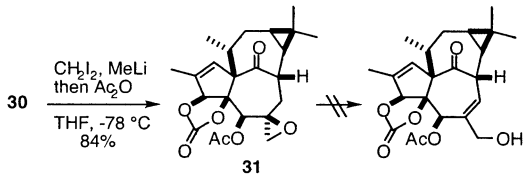
successive treatment of enone **21** with sodium borohydride and DIBAL. Next, silyl ether **22** was converted into the corresponding ketone with a view to introducing the C(4)−C(5) double bond by a β-elimination reaction. Under the influence of a guanidine base, however, ketone **23** yielded conjugated diene **24** via isomerization of the C(1)−C(2) double bond. The result led us to examine construction of the polyol moiety by osmium tetroxide oxidation of both C(2)−C(3) and C(4)−C(5) double bonds in one stage. Since the oxidation reaction of enone **24** resulted in cleavage of the B ring via a retro aldol reaction, the C(6) carbonyl group was masked by stereoselective reduction and silylation. Treatment of diene **25** with an excess amount of osmium tetroxide followed by sodium hydrogen sulfite gave polyol **26**, containing all of the stereogenic centers of ingenol, as a single isomer. To accomplish functionalization of the A ring, it was then required to protect the C(3), C(4), and C(5) hydroxyl groups selectively. The reaction of **26** with 1,1′-carbonyldiimidazole yielded a ca. 4:1 mixture of cyclic carbonates **27** and **28**, which can be easily separated by silica gel column

Scheme 4. Stereoselective Introduction of the Oxygen Functionalities[a]



[a] Reagents and conditions: (a) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2 (93%);. (b) ^{t}BuO$(Me_2N)_2$CH, DMF, 100 °C; (c) DIBAL, CH_2Cl_2, MeI, THF (98% in 2 steps); (d) $NaBH_4$, EtOH (95%); (e) DIBAL, CH_2Cl_2; (f) $(CF_3SO_2)_2O$, 2,6-lutidine, DBU, CH_2Cl_2 (83% in 2 steps); (g) TBAF, THF (100%); (h) PDC, CH_2Cl_2 (97%); (i) 1,3,4,6,7,8-hexahydro-1-methyl-2H-pyrimido[1,2-a]pyrimidine, DMF, 120 °C (86%); (j) $NaBH_4$, $CeCl_3$, MeOH−H_2O; (k) TESCl, imidazole, DMF (99% in 2 steps); (l) OsO_4, pyridine, ether, then $NaHSO_3$, H_2O (59%); (m) 1,1′-carbonyldiimidazole, toluene (**27**: 76%, **28**: 18%); (n) 4-(dimethyl-amino)pyridine, toluene, 100 °C; (**27**: 72%, **28**: 27%) (o) *p*-$MeOC_6H_4CH(OMe)_2$, CSA, DMF (93%); (p) $SOCl_2$, pyridine; (q) AcOH−H_2O (96% in 2 steps); (r) Me_2S, NCS, toluene (75%).

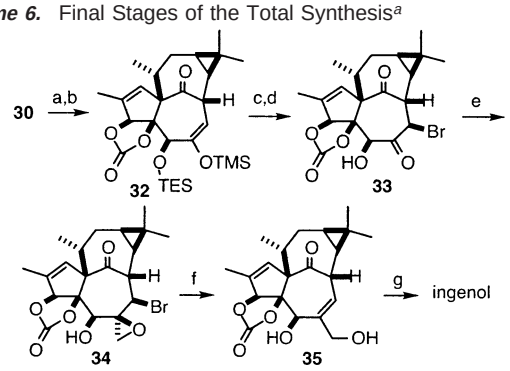
Scheme 5



chromatography. Although the desired compound **28** was the minor product, **27** was found to undergo isomerization to give a ca. 3:1 mixture of **27** and **28** simply by heating with 4-(dimethylamino)-pyridine. Removal of the triethylsilyl group and protection of the C(5) and C(6) hydroxyl groups as a cyclic acetal was achieved in one pot, and the resulting *tert*-alcohol was subjected to a dehydration reaction to afford olefin **29** as a single regioisomer. Since attempts for distinction between the C(5) and C(6) hydroxyl groups via regioselective cleavage of the cyclic acetal moiety were fruitless, **29** was hydrolyzed to the corresponding C(5)−C(6) diol. Fortunately, the diol was selectively converted into α-ketol **30** by adopting the Corey−Kim protocol[13] through oxidation of the less hindered C(6) hydroxyl group.

Construction of the allylic alcohol moiety by using the C(6) keto group remained as the final step in the total synthesis. We initially chose epoxide **31**, which was prepared from ketol **30** by successive treatment with diiodomethane, methyllithium,[14] and acetic anhydride, as a precursor of an allylic alcohol (Scheme 5). However, the conventional methods using an aluminum amide,[15] aluminum isopropoxide,[16] or TMSOTf-DBU[17] failed to effect the desired

Scheme 6. Final Stages of the Total Synthesis[a]



[a] Reagents and conditions: (a) TESOTf, 2,6-lutidine, CH_2Cl_2; (b) TMSCl, Et_3N, LDA, THF; (c) NBS, CH_2Cl_2; (d) HF, CH_3CN; (e) CH_2I_2, MeLi, THF (39% in 5 steps); (f) Zn, NH_4Cl, THF−H_2O (91%); (g) KOH, MeOH (89%).

isomerization reaction. These results led us to examine an alternative method for ring-opening, namely, reductive cleavage of a halo epoxide.[18]

With a view to introducing a bromine at the C(7) position, ketol **30** was converted into enol silyl ether **32**. In these reactions, the α-siloxyketone intermediate showed unusual lability and gave a complex mixture even by silica gel column chromatography. Although the α-siloxyketone also underwent complete decomposition in the presence of LDA, it was found that addition of LDA to a mixture of the crude α-siloxyketone and TMSCl effects the desired transformation.

The reaction of **32** with NBS[19] followed by desilylation afforded α-bromoketone **33** that was converted into epoxide **34** by adopting a method similar to that described above. Treatment of **34** with zinc dust and an aqueous NH_4Cl solution induced reductive cleavage of the bromo epoxide moiety, and the resulting allylic alcohol **35** was subjected to hydrolysis to afford ingenol, which gave spectral data in full agreement with those of the natural product.

In conclusion, total synthesis of ingenol was accomplished on the basis of novel key reactions, namely an intramolecular cyclization reaction of acetylene dicobalt complex **15**, a rearrangement reaction of epoxy alcohol **18** for constructing the ingenane skeleton, and a stereoselective double dihydroxylation reaction of diene **25**. The 45-step transformation from commercially available compound **5** afforded ingenol in ca. 0.1% overall yield. Further studies on asymmetric total synthesis of ingenol are currently under way in our laboratory.

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Supporting Information Available: Experimental details and spectroscopic data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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