Total Synthesis of Ingenol

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Contents

1. Introduction

Ingenol **1**, a highly oxygenated tetracyclic diterpene classified as a member of the phorboid family, was isolated from the genus *Euphorbia* and characterized by Hecker's group in 1968 (Figure 1).[1] Various esters of ingenol have shown remarkable biological properties to mimic diacylglycerol and function as endogenous activators of protein kinase (PKC).[2] Further, they were found to exhibit antitumor or tumor-promoting,[3] antileukemic,[4] and anti-HIV properties.[5] Hence, a large supply of ingenol and its analogues through chemical synthesis as well as isolation from natural sources[6] has been expected to promote the development of new therapeutic agents.

In addition to its biological significance, the structural feature has attracted much attention and ingenol has been one of the most challenging targets in synthetic organic chemistry for the past 25 years. Different from the usual cis-fused bicarbocycles, it contains an unusual trans-fused bicyclo[4.4.1]undecane ring system, which brings about great strain to the molecule. Efficient construction of this highly strained inside−outside[7] intrabridgehead stereochemistry of the BC ring system is the most imposing obstacle to the synthesis of ingenol. In addition, the high degree of oxygenation, the *cis*-triol segment located on the upper face from C(3) to C(5),[8] represents a substantial synthetic challenge as well.

Circumventing the synthetic problem on construction of such highly strained carbocycles of ingenol, a number of studies have initially targeted isomeric isoingenol which is configurationally isomeric at C(8)[8] and considerably less strained as a consequence. Although these artificial isomers could be synthesized more readily, they are completely devoid of biological activities.[9]

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Thus, increased interest on ingenol itself both in synthetic chemistry as well as its biological aspects
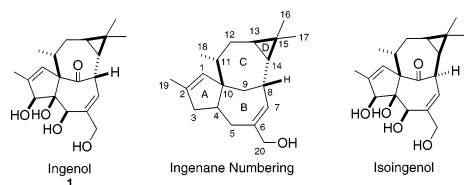
Figure 1. Ingenane.

has prompted development of methodologies for constructing the *trans*-bicyclo[4.4.1]undecane framework, aiming at total synthesis.

2. Synthetic Approaches toward Ingenol

Since the mid-1980s several approaches for constructing trans- as well as cis-fused ingenane skeletons have been developed,[10] but only a few have succeeded for the former.

Winkler[11] reported the first synthesis of an ingenane tricyclic ring system having the correct trans-bridgehead stereochemical relationship using an intramolecular version of the modified de Mayo reaction (eq 1). Namely, irradiation of dioxenone **2** afforded [2 + 2] photoadduct **3**, whose cyclobutane ring underwent fragmentation to the keto ester. Subsequent elimination of HCl, reduction, and protection afforded **4**.
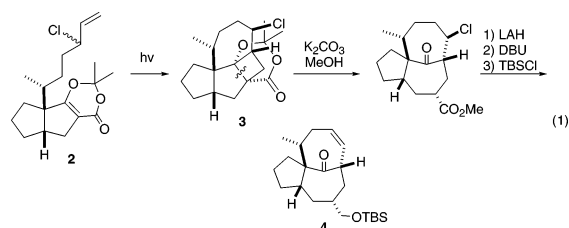

Funk[12] cleared the problem of the inside−outside stereochemistry using an intramolecular Ireland−Claisen rearrangement in which more readily accessible bicyclo[6.4.1]dodecane ring lactone **6** prepared from the keto ester **5a** was employed for the formation of the highly strained trans-fused bicyclo[4.4.1]-undecane **7** (eq 2). Subsequent attachment of A ring
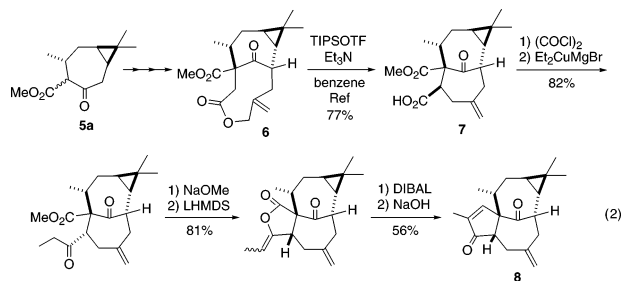

utilizing two carboxylic groups led to the first synthesis of the tetracyclic ring system **8** with inside−outside stereochemistry.[12b] They also explored a convenient synthetic route from carene to the cycloheptanone **5a**, which was later employed as a useful CD ring unit of the ingenol skeleton by other groups. Initial ozonolysis of carene followed by selective protection of the aldehyde function as an acetal produced methyl ketone. Alkoxycarbonylation of the methyl ketone afforded the β-keto ester, which un-

derwent aldol cyclization to form the cycloheptenonecarboxylic ester. Introduction of methyl group could be effected predominantly from the α-face to give the keto ester **5a** (eq 3).[12a]
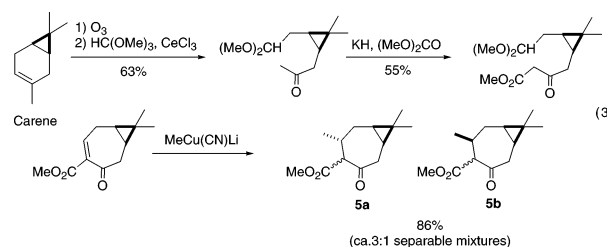
Rigby[13] converted the out−out bicyclo[4.4.1]undecadieneol **10**, accessible by Pd-mediated ring opening of the epoxide **9**, into the more strained in−out stereoisomer **11** using an alkoxide-mediated [1.5] sigmatropic H shift to establish the stereochemistry of the C-8β[8] bridgehead hydrogen (eq 4).
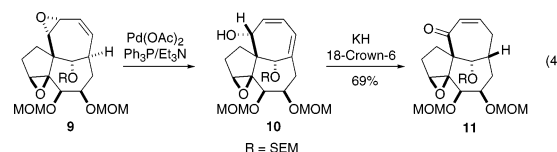

At present, in addition to our methodology including cationic cyclization[14] (see section 2.1), two groups[15] have succeeded in constructing the ring system using RCM methodology. However, due to the longer distance (3.8 Å for **12a**, 3.6 Å for **12b**)[15a] between the two terminal olefins, a first generation of Grubbs catalyst has proven less effective to induce cyclization, giving the cyclized products in only moderate yields. Use of a large amount of catalyst as well as appropriate choice of substituent seems to be required to effect the desired RCM.
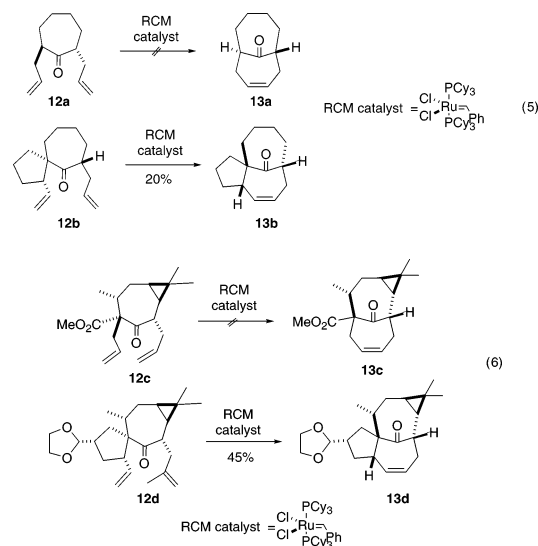
Thus, several methodologies are now available for construction of the trans-fused ring system, but the requirement for introduction of polyoxygenated functionalities is another problem to be solved for the total synthesis. Winkler's group overcame these difficulties and reported a first total synthesis[11c] of ingenol utilizing the methodology shown in eq 1. They

initially cleared an enolate generated by Birch reduction of bicyclo[3.3.0]octenone and underwent stereoselective conjugate addition toward crotonic ester to secure the stereochemical outcome of C18-methyl, giving the keto ester derivative, which was then converted to the chloro dioxenone **2**. An intramolecular [2 + 2] cycloaddition of **2** led to the formation of a unique cyclobutane photoadduct **3** in 60% yield as a mixture of C-13 chloro epimers. Treatment of **3** with methanolic K_2CO_3 induced fragmentation of the cyclobutane ring to form the corresponding keto ester, and subsequent reduction and elimination of HCl afforded **4** containing an ingenane ABC carbon framework. Dibromocarbene addition to the $\Delta^{13,14}$ double bond of **4** took place selectively from the sterically favored β-face, and bromine could be replaced with a methyl group using methylcopper reagents and MeI (Scheme 1).

Scheme 1. Winkler's Total Synthesis of Ingenol: 1
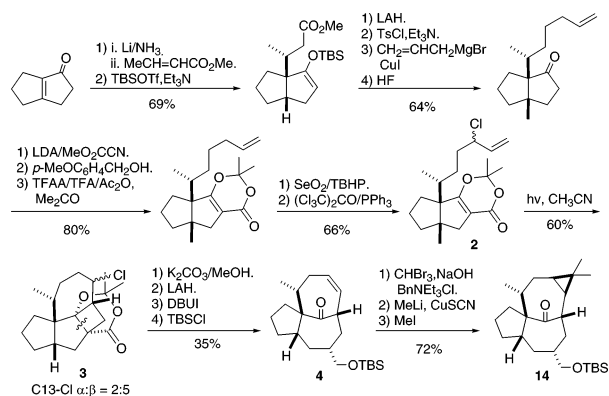
Then, they fully utilized a siloxymethyl substituent on a C(6) site[8] as the sole handle to introduce requisite functionalities to the A and B rings. After removal of the silyl protecting group, the resulting alcohol was oxidized to the aldehyde **16**, which was then converted to dienol **18** by way of the dienal **17** by repeating a successive bromination and dehydrobromination. Introduction of the C3, C4, C5 triad of oxygen functionalities was achieved via two successive dihydroxylation reactions, both of which occur from the sterically demanding β-face of the tetracyclic ring system. Initial dihydroxylation with OsO_4 occurred selectively on the $\Delta^{5,6}$ double bond, and after protection of each pri- and sec-OH with an appropriate silyl group, second dihydroxylation could be effected on $\Delta^{3,4}$ alkene, giving **20** after benzoylation of the resulting sec-OH. Although selective introduction of $\Delta^{6,7}$ unsaturation via removal of C6−OH appeared to be problematic, they deduced a nice procedure involving the cyclic sulfate.[11b] Thus, reaction of **20** with thionyl chloride followed by oxidation of the resulting sulfite gave the cyclic sulfate **21**. Exposure to DBU and then treatment with H_2SO_4 led to the formation of **22** in good yield. Finally, **22** was converted to **23** via exchange of the protecting group and oxidation. Introduction of C19-methyl and $\Delta^{1,2}$ unsaturation was performed in the usual manner. Luche reduction of C-3 carbonyl and removal of protecting groups completed the total synthesis of racemic ingenol (Scheme 2).

Scheme 2. Winkler's Total Synthesis of Ingenol: 2
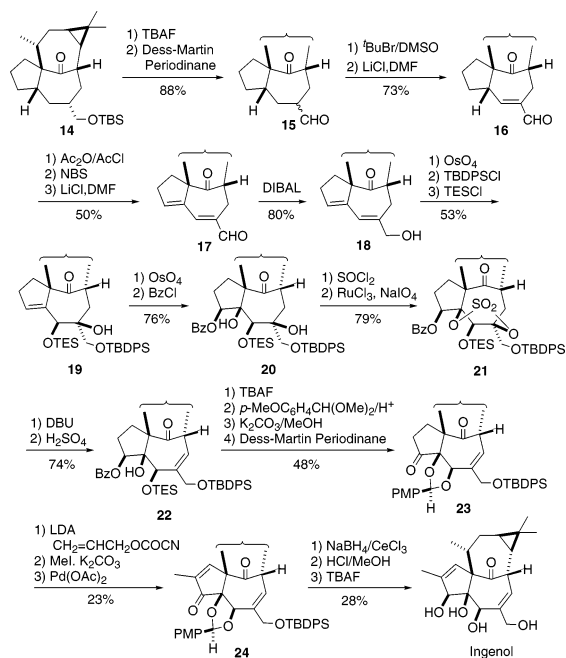
2.1. Exploration of a Tandem Cyclization/Rearrangement Methodologies

We started synthetic studies of ingenol in the mid-1990s. Our basic concept for access to the ingenane carbocycle involved a sequence of seven-membered ring cyclization and pinacol rearrangement shown in Scheme 3. On treating with **I**, a Lewis acid may coordinate to two oxygens to fix the conformation as **Ia**, where two reacting sites, a cationic site and ethylidene part, are located close enough to interact. Then, an allylcationic species generated via removal of the acetoxy group undergoes seven-membered ring cyclization (1) to form **II**, and a subsequent carbon skeleton rearrangement of the cationic species **II** would be accelerated by a neighboring alkoxide to lead to the formation of the trans-fused ingenane structure. Further, starting from an (E)-ethylidene substrate, the stereochemical outcome of C(18)-methyl[8] would also be situated on the desired α site through this transformation.

### Scheme 3. Hypothetical Pathway to Ingenane Carbocycle
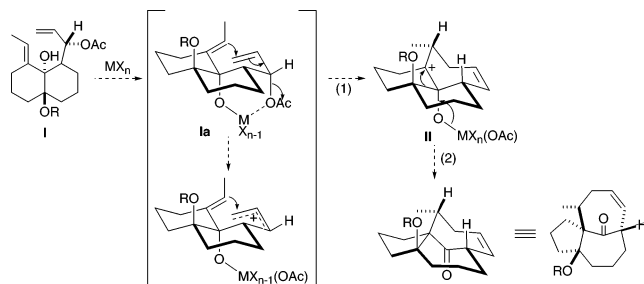
Through a tandem cyclization/rearrangement process leading to the ingenane skeleton directly, Lewis-acid-mediated reactions of allylic acetate or trichloroacetate **25** were attempted. However, treatment of **25** with several Lewis acids did not yield the expected product but produced the bicyclo[5.3.0]undecanone **26**

while the allyl acetate moiety remained unattached (eq 7). These results suggested the failure to fix the conformation, and instead of the desired cyclization, protonation on the ethylidene group followed by pinacol rearrangement took place to afford **26**.
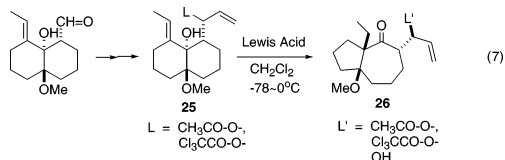
Use of an allyl chloride **27** in place of the esters **25** produced a six-membered cyclic ether **28** (eq 8).
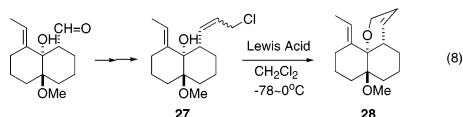
To overcome these problems, we decided to introduce a dicobalt hexacarbonyl group on a carbon chain of the starting material like **A** (Figure 2). Use of **A** was expected to bring about several advantages to induce the desired transformation. First, the steric bulk of the cobalt carbonyl group would help to keep the conformation like **A**, where two reaction sites are located closely, and, second, the presence of the metal on this position may allow a facile generation of the cationic species as **B** (Figure 2) due to its β-cation-stabilizing effect.[16] Further, introduction of a dicobalt group, $-\text{Co(CO)}_3-\text{Co(CO)}_3-$, results in broadening the bond angle of the carbon chains,[17] which may favor a larger ring cyclization, namely, a seven-membered ring over an oxygen-containing six-membered one. Finally, the cobalt moiety could be removed under reduction conditions to regenerate the C=C bond, which was nicely located for attachment of the D ring. Keeping these features in mind, reactions of **34** were examined using methylaluminum-based Lewis acids.
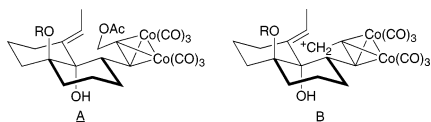

Figure 2.

The requisite **29** was prepared from the corresponding aldehyde via a propargylic acetate, and it has been disclosed that under the influence of Lewis acids, MeAlXY, **29** reacted in the expected manner to produce the desired **30** in good yield.[14] In addition to **30**, **31** resulting from a sequence of cyclization–deprotonation process was also formed, sometimes as the major product. Typical examples are summarized in Scheme 5.

In general, use of weaker Lewis acids led to a predominant formation of **30**, whereas **31** was the major product from reactions mediated by stronger Lewis acids. The reaction course leading to either **30** or **31** appears to be critically determined by the behavior of the hydroxyl. A weaker Lewis acid may initially react with alcohol to generate Al alkoxide,[18] whereas stronger Lewis acids just coordinate to the

alcoholic oxygen, not removing the proton. After seven-membered ring cyclization of **III**, a subsequent pinacol rearrangement of the resulting cationic species **IVa** may be facilitated by the electron-donating Al alkoxide on the vicinal position to form **30** preferentially.

When using a stronger Lewis acid, however, bonding of alcoholic oxygen to both the proton and a Lewis acid as **IVb** decreases the electron density on oxygen, which may disfavor inducing the carbon skeleton rearrangement, and instead, deprotonation takes place to lead to **31**.

Scheme 4. Reaction Pathways Leading to 30 and 31

	30	31
MeAl(O-4-NO$_2$-2,6-Me$_2$C$_6$H$_2$)(O$_2$CCF$_3$)	77%	21%
Me$_2$AlOTf	13	69
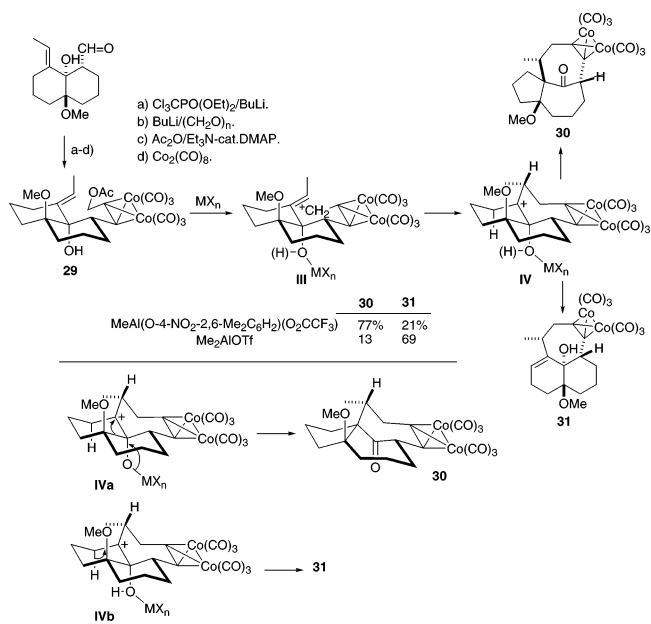
Birch reduction of **30** in the absence of a proton source afforded the corresponding $\Delta^{9,10}$-unsaturated substrate. Addition of dibromocarbene on this carbon–carbon double bond followed by replacement with methyl produced the ingenane tetracarbocycle **32** in good overall yield (Scheme 5). Thus, we could explore

**Scheme 5. Construction of Ingenane Tetracarbocycle 38**
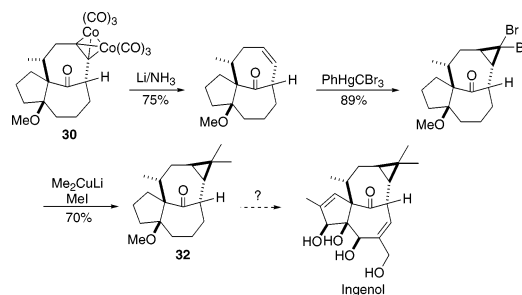
a new methodology for ingenane tetracarbocycle including the inside–outside intrabridgehead stereochemistry of the BC ring system containing α-C(18) methyl, but here we faced another problem on how to introduce the requisite functionalities to **32** to lead to natural ingenol. Hence, we had to reconsider a scheme for the total synthesis at this stage.

2.2. Tandem Cyclization/Deprotonation Methodology for the Total Synthesis of Ingenol

For the total synthesis of ingenol we adapted a second sequence including the cyclization−deprotonation process shown in Scheme 6. Starting from **29b** containing an additional oxygen functionality at the position corresponding to C(6),[8] application of a cyclization−deprotonation process would give us **31b**. Removal of the Co(CO)$_3$ group and cyclopropation may afford the allylic alcohol **33**. Epoxidation of the C=C bond of **33** could be achieved selectively from the α-face owing to assistance of the neighboring α-OH. Ring opening of the epoxide mediated by the appropriate Lewis acid should accompany a subsequent pinacol rearrangement[9] to form **34** containing two additional oxygen functionalities, which may help to introduce the requisite functional groups on the A and B rings.

Scheme 6. Second Approach toward Ingenol from 35b
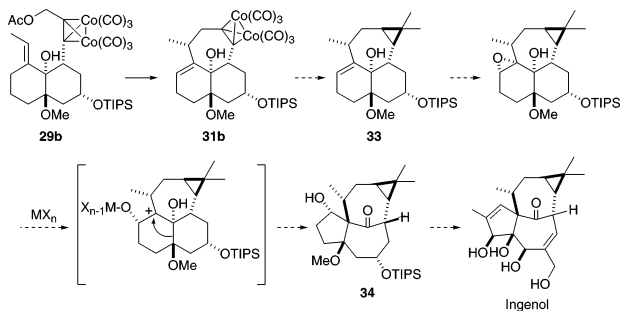
Starting materials were prepared as follows. Heating 2-allyloxycyclohexanone dimethylacetal with dichloroacetic acid induced Claisen rearrangement to give 2-allylcyclohexanone **S-2**, which was converted to the bromohydrin **S-3** by treating with NBS in aqueous DMSO. The resulting cyclized hemiacetal obtained as a mixture of two stereoisomers was separated, and the desired one **S-3a** having a β-bromomethyl substituent was silylated to give **S-4**. The undesired isomer **S-3b** was recovered as the starting allylcyclohexanone by treating with Zn and aqueous NH$_4$Cl and reused for **S-4**. Aldol addition of **S-4** to acetaldehyde followed by dehydration gave (E)-ethylidenecyclohexanone **S-5** (Scheme 7).

Scheme 7. Preparation of Starting Material S-5
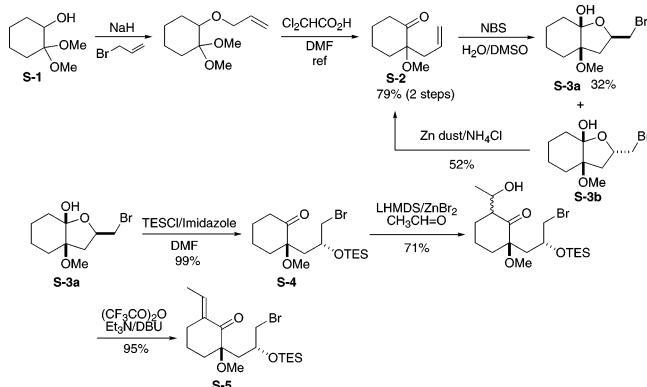
Addition of ester enolate to **S-5** under chelation-controlled conditions took place preferentially from

an upper face to produce **S-6** as a single isomer. Although six-membered ring cyclization via an intramolecular alkylation could not be effected in the presence of LDA, treatment of the hydroxy ester **S-6** initially with Me$_3$Al and then with LDA cleanly induced cyclization to give the bicyclic intermediate **S-7** as a single stereoisomer. Since use of Me$_3$Al was essential for the intramolecular alkylation, formation of six-membered Al enolate shown as **C** (Scheme 9) might be responsible for this stereoselective cyclization. Protection of the sec-OH with TIPS, reduction of the ester, and oxidation gave the aldehyde **S-8**.

Scheme 8. Preparation of Bicyclic Substrate S-8
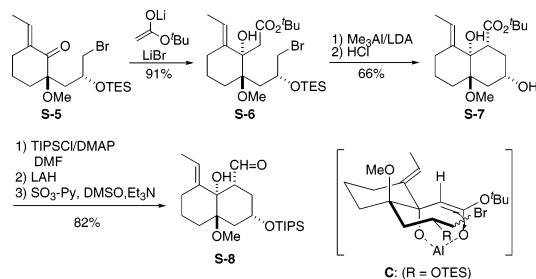
The aldehyde **S-8** was converted to the propargyl alcohol **S-10** via 1,1-dichloroethylene **S-9**.[20] Acetylation and reaction with Co$_2$(CO)$_8$ afforded **29b** in excellent yield.

**Scheme 9. Preparation of Seven-Membered Ring Cyclization Precursor 29b**
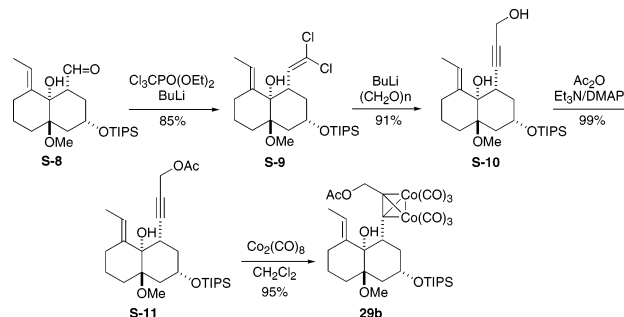
Under the influence of methylaluminum bis(2,6-dimethyl-4-nitrophenoxide), the cobalt complex **29b** underwent a cyclization and deprotonation sequence cleanly, and subsequent Birch reduction afforded the tricarbocycle **31b** in good overall yield. Then, a cyclopropane ring corresponding to the D ring was attached through a phase-transfer-catalyzed addition of dibromocarbene to the C=C bond followed by replacement of Br with methyl, giving **33**. Thus, the stage was set to examine the most critical rearrangement process. Successive treatment with TBHP/Ti-(O^{i}Pr)$_3$ and then Me$_3$Al induced the expected rearrangement to afford the ingenane tetracarbocycle **34** in good overall yield, which was converted to the diketone **35** by Swern oxidation (Scheme 10).

Although several attempts to introduce C(19)-methyl using Li enolate of **35** failed, the following three-step transformation served nicely for this end: Treatment of **35** with tert-butoxy-bis(dimethylamino)-methane[21] gave the enamino ketone, which was converted to the methylenecyclopentanone **36** through

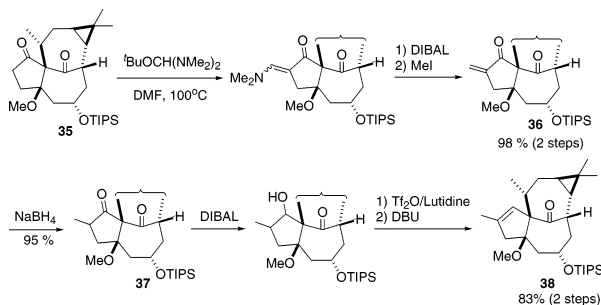**Scheme 10. Construction of Ingenane Tetracarbocycle 41**
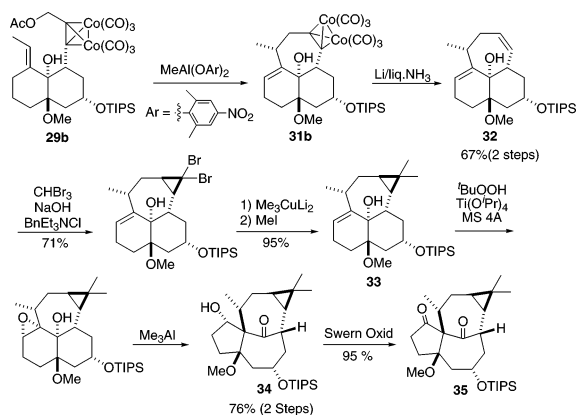
a sequence of DIBAL reduction and heating with MeI. Finally, borohydride reduction of **36** afforded
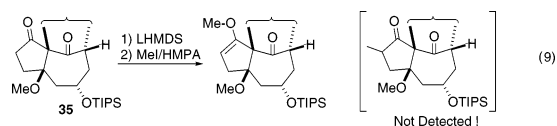
methyl ketone **37**.[22] Dehydration afforded the $\Delta^{1,2}$-unsaturated substrate **38** (Scheme 11).

Scheme 11. Functional Groups Manipulation on a Ring

For introduction of *cis*-1,2,3-trihydroxyls on the A and B rings, transformation of **38** to dienone **39** was next examined. Removal of the silicon protecting group followed by PDC oxidation afforded diketone, which, under the influence of a guanidine base, underwent removal of methanol followed by isomerization of $\Delta^{1,2}$-unsaturation to form the conjugated dienone **39**. Since direct OsO$_4$ oxidation of **39** was

**Scheme 12. Introduction of Hydroxyls for Tetraol 47**
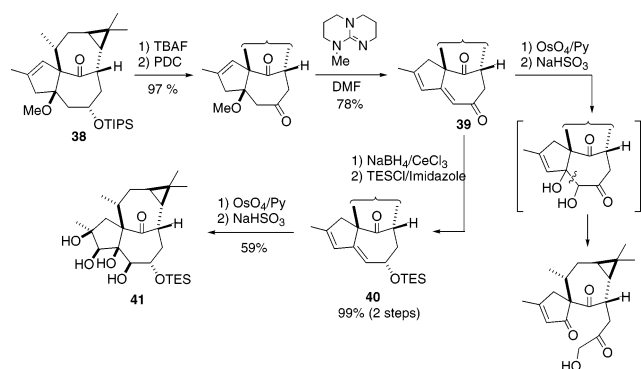
found to accompany the B ring cleavage, it was converted to the siloxy ketone **40** by Luche reduction and silylation. Osmium tetraoxide oxidation of the siloxydiene **40** took place preferentially from the sterically demanding β-face to yield the tetraol **41** (Scheme 12).

Among the successive four cis hydroxyls of **41**, protecting the inner diol selectively was required . The reaction with carbonyldiimidazole gave desired **42a** as a minor product together with a predominant formation of **42b**, which was separable from **42a** by silica gel column chromatography. For conversion of isomeric **42b** to **42a**, it was fortunately disclosed that on heating **42b** with DMAP in toluene equilibration took place to produce a mixture of **42a** and **42b** in a ratio of 1:3. Repeating this equilibration and separation procedure nine times the tetraol **41** could finally be converted to the suitably protected **42a** in 86% yield along with the undesired isomer **42b** (8%).

After protection of the remaining diol as an acetal, treatment with SOCl$_2$/Py allowed introducing a $\Delta^{1,2}$ double bond, which was converted to **44** by removing the acetal protecting group. Then, several attempts for selective oxidation of C(6)−OH were performed using a variety of reagents, among which only a Corey−Kim reagent[23] gave a satisfactory result to produce 5-hydroxy 6-keto substance **45** in 75% yield (Scheme 13).

Scheme 13. Selective Protection of Polyol 47 and Introduction of $\Delta^{1,2}$ Double Bond
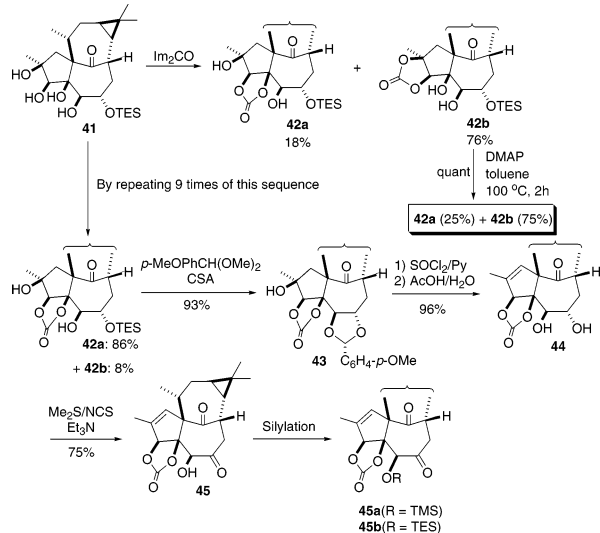
The remaining task to complete the total synthesis was to introduce a hydroxymethyl group on C(6) and $\Delta^{6,7}$ carbon−carbon double bond. To accomplish this transformation the epoxide **46** seemed to be an appropriate precursor: Methylenation of C(6) carbonyl took place nicely by treating **45** with CH$_2$I$_2$ and methyllithium[24] at lower temperature, and the epoxide **46** was isolated in good yield after acetylation of the remaining C(5) hydroxy group. However, various efforts to isomerize **46** to the 3,4-diol-protected ingenol by conventional methods using aluminum amide,[25] aluminum isopropoxide,[26] or TM-SOTf-DBU[27] were fruitless (eq 10).

(10)
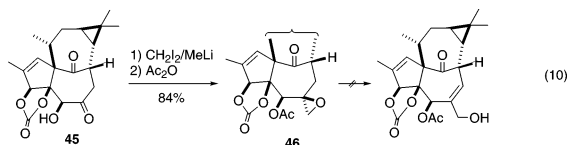
2.3. Toward Ingenol

On using **45** for several transformations it was disclosed that protection of C(5)−OH has made it very labile! For example, attempts at purification of TES-protected substrate **45b** with silica gel column chromatography induced rapid decomposition to a complex mixture. Reactions of crude **45b** with several nucleophilic reagents also gave a complex mixture: Attempts at methylenation of C(6) carbonyl using $(^iPrO)Me_2SiCH_2MgCl$[28] or Tebbe reagent[29] led to complicated results, whereas a low-valent Ti-mediated reaction[30] produced the pinacol coupling product. Among the several nucleophiles examined, only a Horner−Emmons reagent reacted to give the unsaturated nitrile in good yield (eq 11).

(11)
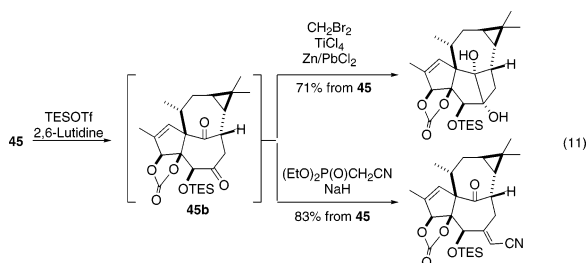
A semiempirical calculation using the Spartan program indicated **45** contains a chairlike seven-membered B ring including hydrogen bonding of C(5)−OH with C(6) carbonyl, whereas silylation introduces severe steric hindrance to change the favored conformation of **45a** where the B ring has a boat form with two carbonyls closely located (ca. 2.6 Å between two carbonyl carbons, Figure 3).
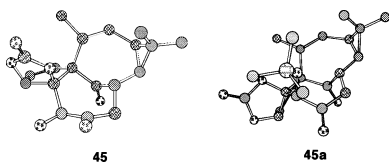
**Figure 3.** Most preferable conformations of **45** and **45a**.

A synthetic route by way of unsaturated nitrile **49** prepared from α-seleno ketone **48** was also examined (Scheme 15). A sigmatropic rearrangement of the allyl selenoxide derived from **49** may produce the cyanohydrin **50**, which could be converted to the parent unsaturated aldehyde **51**. Finally, reduction and deprotection would lead to the formation of ingenol.

With a focus of introducing a phenylselenenyl group at the C(7) position, conversion of **45b** to its enol silyl ether was attempted, but treatment with LDA even at −78 °C resulted in decomposition of **45b**. Considering the unusual lability of **45b** under basic conditions, it was then attempted to generate the lithium enolate in the presence of TMSCl: addition of LDA to a mixture of silylated **45b**, an excess

amount of TMSCl, and Et_3N yielded the enol silyl ether **47** of sufficient purity, which was treated with PhSeCl yielding α-seleno ketone **48**. Successive reaction with H_2O_2 and then Et_3N afforded the unsaturated aldehyde **51**, which was converted into ingenol by treating with DIBAL and then TBAF.

Although the first total synthesis of ingenol could be achieved at this time,[31] serious problems remained in the latest transformations (Scheme 14). Each

Scheme 14. Total Synthesis of Ingenol: 1
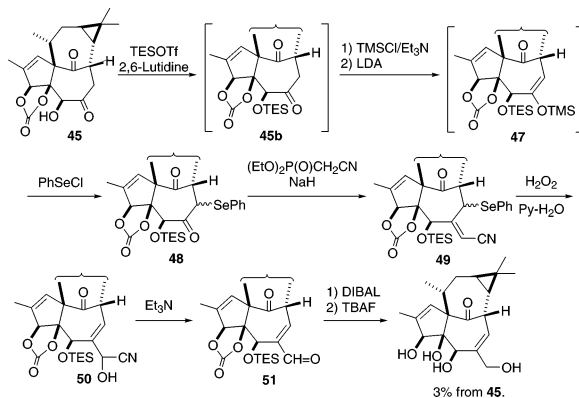
intermediate derived from **45b** was too labile to be purified or characterized by ^1H NMR, and the overall yield from the hydroxy ketone **45** was only 3%. Hence, it was decided to develop a more efficient route to ingenol by improving the following two aspects. First was the protection of C(5)−OH: since this made it quite difficult to manipulate a later synthetic intermediate, it should be removed as soon as possible after its role is completed. The second was to reexamine an attractive pathway from the epoxide to the allylic alcohol. Taking the results shown in eq 10 into account, reductive cleavage[32] of halo epoxide in place of a simple deprotonative isomerization was also examined for completion of the last step. The bromo ketone **52** was prepared from enol silyl ether **47**: After treating with NBS,[33] the crude mixture was quickly treated with HF in CH_3CN to remove the C(5)−OH protecting group, and the resulting bromo ketone **52** was converted into the bromo epoxide **53**. Thus, **53** could be prepared from hydroxy ketone **45** through five steps in 39% overall yield (83% average for each step). Reductive cleavage of the bromo epoxide could be effected cleanly under the influence of Zn dust and aqueous NH_4Cl solution. The resulting allylic alcohol **54** was subjected to hydrolysis to afford ingenol.[34]

Scheme 15. Total Synthesis of Ingenol: 2
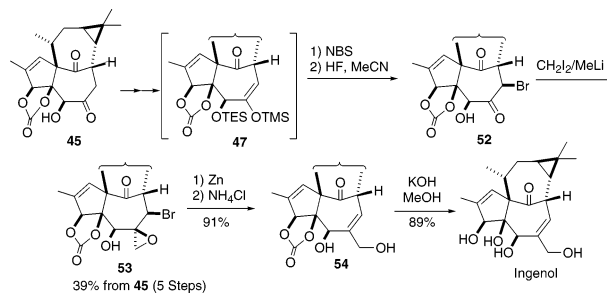
Finally, aiming for enantioselective total synthesis, an optically pure starting material (+)-**S-4** was prepared. Reduction of racemic **S-4** with LAH gave an alcohol as a single isomer, which was converted to the chloroacetate. In the presence of lipase PS in phosphate buffer, enantioselective hydrolysis of the desired enantiomer took place completely to give the alcohol (+)-**S-13a** (>99% ee) in 46% yield, whereas the other enantiomer remained as the parent ester (−)-**S-13b** (94% ee) in 50% yield. Oxidation of (+)-**S-13a** afforded optically pure (+)-ketone **S-4**.

Starting from (+)-**S-4**, the optically active (−)-ingenol could be synthesized through the synthetic operations described above. The value for the optical rotation of this substance thus prepared was almost the same as that of natural one (Scheme 16).[35,36]

Scheme 16. Preparation of Optically Pure Material (+)-S-4, and Total Synthesis of (−)-Ingenol

$[\alpha]_D^{28} = -20°(C = 0.15, MeOH)$
Natural: $[\alpha]_D^{28} = -19°(C = 0.12, MeOH)$
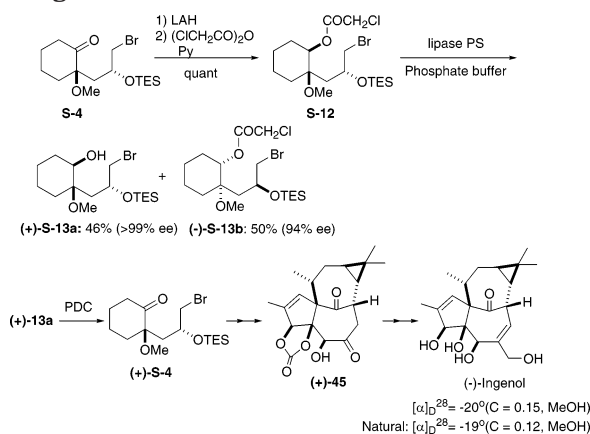
3. Kigoshi's Approach

After completion of our second total synthesis, two papers appeared introducing the RCM methodology for construction of the B ring. Kigoshi deduced a synthetic route from Funk's keto ester **5** to Winkler's aldehyde **14** using the RCM methodology[14a] to claim a formal total synthesis of optically active ingenol (Scheme 17).[37] Alkylation of Funk's keto ester **5a**

**Scheme 17. Preparation of Optically Pure Winkler's Aldehyde 14 by Kigoshi**
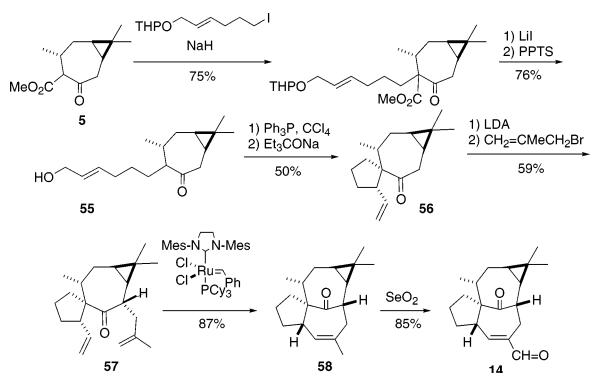
followed by removal of protecting groups produced **55**. Halogenation and intramolecular alkylation allowed a selective construction of the A ring to give **56**. Allylation of **56** was effected selectively from the

opposite side of the cyclopropane ring to form the RCM precursor. Different from their previous work, use of a methallyl substituent as well as application of a second generation of Grubbs catalyst greatly improved the efficiency of RCM for construction of the ingenane skeleton. The effect of the methallyl substituent in this RCM may be due to the stability of the trisubstituted double bond in the product under the reaction conditions and a high-frequency factor in encountering the two olefins. Allylic oxidation of the resulting **58** led to formation of **14**.

4. Wood's Approach

Wood adapted the essentially same methdology[14b] for construction of the carbon skeleton **64**, starting from **5a**. A subsequent 5-step operation converted **5a** to the methylenecyclopentanone **59,** which underwent α-face-selective [4 + 2]cycloaddition with cyclopentadiene to form the A ring. For the subsequent functional group manipulations an olefin metathesis ring opening was performed with ethylene: In the presence of Grubbs catalyst, **60** reacted with ethylene almost quantitatively to afford the product **61** having two vinyl groups, one of which was selectively transformed into the acetal **62** via a sequence of oxidation and acetalization. Introduction of a methallyl moiety gave the RCM precursor **63**. Similar to Kigoshi's case (Scheme 17), use of a second generation of Grubbs catalyst cleanly effected RCM to give the ingenane tetracarbocycle **64** (Scheme 18). Then, **64** was trans-

Scheme 18. Wood's Total Synthesis of Ingenol: 1
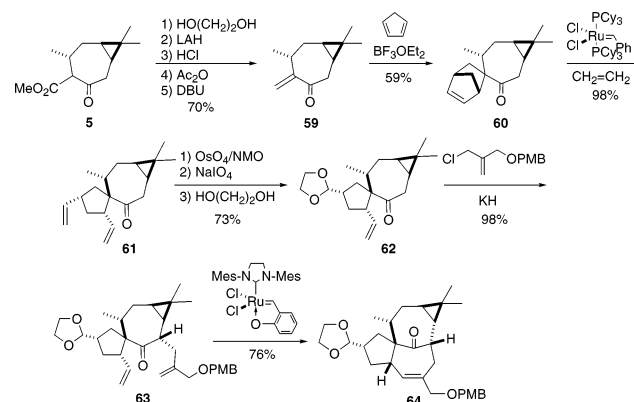
formed into methylenecyclopentane **65** by applying conventional four-step procedures. Introduction of oxygen functionalities into the C-3 and C-4 sites was accomplished as follows: SeO₂ and then Dess−Martin oxidation followed by isomerization gave the cyclopentenone **66**, and subsequent O₂ oxidation in the presence of KO^{t}Bu afforded **67**. At this stage they attempted $^1O_2$ oxidation of the allylic methylene group for B ring manipulation, but unfortunately **67** proved inert to this oxidation to recover the starting material.

They also examined several approaches toward similar intermediates via ring opening of the epoxide: Epoxidation of **67** with VO(acac)₂ and TBHP proceeded smoothly, but their efforts to convert the resulting epoxide **68** to the desired allylic alcohol **69** with a variety of either Lewis acids or strong bases

were fruitless. Further, the epoxide **70** prepared by reduction of C-3 carbonyl and protection was also found to be unreactive toward ring-opening conditions (Scheme 19).

Scheme 19. Attempts for A/B Rings Elaboration
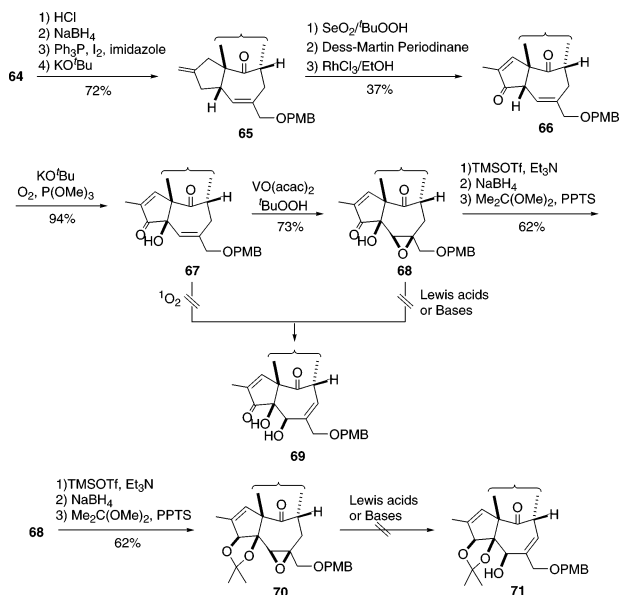
The unique structural features of the B ring appear to prevent the ring opening of 5,6- as well as 6,20-epoxides (see eq 10) via abstraction of hydrogen on C(7) to the corresponding allylic alcohols, although the precise reasons are not clear. Hence, they introduced a sulfone group on the C(20) site to facilitate the desired transformation. Thus, the epoxy ether **70** was converted to the epoxy sulfone **72** through a sequence of 4-step transformation, and exposure of the resulting **72** to DBU induced the desired ring opening to give a mixture of vinyl and allyl sulfone **73**. Using **73**, removal of the sulfone as well as an acetonide protecting group followed by allylic oxidation with SeO$_2$ completed the third total synthesis of ingenol (Scheme 20).[38]

Scheme 20. Wood's Total Synthesis of Ingenol: 2
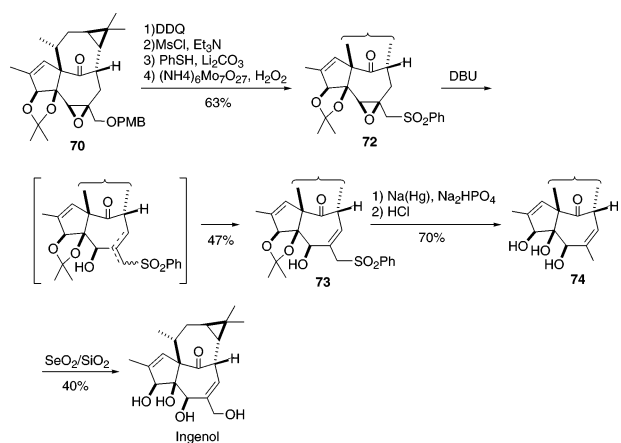
Total synthesis of ingenol, one of the most challenging synthetic targets in the past decade, has been achieved by three research groups in the past 3 years. Although major concerns initially focused on how to construct the highly distorted carbon framework, it

has also been disclosed that modification or introduction of functional groups on the distorted B ring sometimes results in a conformational change, which brings about a higher degree of strain to the ring system to prevent the usual synthetic transformations.

5. References

(1) (a) Hecker, E. *Cancer Res*. **1968**, *28*, 2338. (b) Zechmeister, K.; Brandl, F.; Hoppe, W.; Hecker, E.; Opferkuch, H. J.; Adolf, W. *Tetrahedron Lett*. **1970**, 4075. (c) Uemura, D.; Hirata, Y. *Tetrahedron Lett*. **1971**, 3673.

(2) Hasler, C. M.; Acs, G.; Blumberg, P. *Cancer Res*. **1992**, *52*, 202.

(3) (a) Hecker, E. *Pure Appl. Chem*. **1977**, *49*, 1423. (b) Hecker, E. *Exp. Cell Biol*. **1982**, *50*, 121.

(4) (a) Kupchan, S. M.; Uchida, I.; Branfman, A. R.; Daily, R. G.; Fei, B. Y. *Science* **1976**, *191*, 571. (b) Fatope, M. O.; Zeng, L.; Ohyama, J. E.; Shi, G.; McLaughlin, J. L. *J. Med. Chem*. **1996**, *39*, 1005.

(5) (a) Gustafson, K. R.; Cardellina, J. H., III; McMahon, J. B.; Gulakowski, R. J.; Ishitoya, J.; Szallasi, Z.; Lewin, N. E.; Blumberg, P. M.; Weislow, O. S.; Beutler, J. A.; Buckheit, R. W., Jr.; Cragg, G. M.; Cox, P. A.; Bader, J. P.; Boyd, M. R. *J. Med. Chem*. **1992**, *35*, 1978. (b) Fujiwara, M.; Ijichi, K.; Tokuhisa, K.; Katuura, K.; Shigeta, S.; Konno, K. Wang, G.-Y.-S.; Uemura, D.; Yokota, T.; Baba, M. *Antimicrob. Agents Chemother*. **1996**, *40*, 271.

(6) Studies for isolation of ingenol, see, for example: Appendino, G.; Tron, G. C.; Cravotto, G.; Palmisano, G.; Jakupovic, J. *J. Nat. Prod*. **1999**, *62*, 76.

(7) For a review on inside−outside chemistry, see: Alder, R. W.; East, S. P. *Chem. Rev*. **1996**, *96*, 2097.

(8) The ingenane numbering system, as illustrated in Figure 1, is used throughout.

(9) Paquette, L.; Ross, R.; Springer, J. *J. Am. Chem. Soc*. **1988**, *110*, 6192 and references therein.

(10) For reviews on synthetic studies of ingenol and related compounds, see: (a) Rigby, J. H. *Stud. Nat. Prod. Chem*. **1993**, *12*, 233. (b) Kim, S.; Winkler, J. D. *Chem. Soc. Rev*. **1997**, *26*, 387.

(11) (a) Winkler, J. D.; Henegar, K. E. *J. Am. Chem. Soc*. **1987**, *109*, 2850. (b) Winkler, J. D.; Kim, S.; Harrison, S.; Lewin, N. E.; Blumberg, P. M. *J. Am. Chem. Soc*. **1999**, *121*, 296. (c) Winkler, J. D.; Rouse, M. B.; Greaney, M. F.; Harrison, S. J.; Jeon, Y. T. *J. Am. Chem. Soc*. **2002**, *124*, 9726.

(12) (a) Funk, R. L.; Olmstead, J. A.; Parvez, M. *J. Am. Chem. Soc*. **1988**, *110*, 3298. (b) Funk, R. L.; Olmstead, J. A.; Parvez, M.; Stallman, B. J. *J. Org. Chem*. **1993**, *58*, 5873.

(13) (a) Rigby, J. H.; Claire, V. S.; Cusiat, S. V.; Heeg, M. J. *J. Org. Chem*. **1996**, *61*, 1446. (b) Rigby, J. H.; Hu, J.; Heeg, M. J. *Tetrahedron Lett*. **1998**, *39*, 2265. (c) Rigby, J. H.; Bazin, B.; Meyer, J. H.; Mohammadi, F. *Org. Lett*. **2002**, *4*, 799.

(14) Nakamura, T.; Matsui, T.; Tanino, K.; Kuwajima, I. *J. Org. Chem*. **1997**, *62*, 3032.

(15) (a) Kigoshi, H.; Suzuki, Y.; Aoki, K.; Uemura, D. *Tetrahedron Lett*. **2000**, *41*, 3927. (b) Tang, H.; Yusuff, N.; Wood, J. *Org. Lett*. **2001**, *3*, 1563.

(16) Ittel, S. D.; Ibers, J. A. *Adv. Organomet. Chem*. **1976**, *14*, 33.

(17) Cotton, F. A.; Jamerson, J. D.; Stults, B. R. *J. Am. Chem. Soc*. **1976**, *98*, 1774.

(18) Suzuki, K.; Tomooka, K.; Shimazaki, M.; Tsuchihashi, G. *Tetrahedron Lett*. **1985**, *26*, 4781.

(19) Ring enlargement reactions via pinacol rearrangement of an epoxy alcohol, see: (a) Maruoka, K.; Hasegawa, M.; Yamamoto, H.; Suzuki, K.; Shimazaki, M.; Tsuchihashi, G. *J. Am. Chem. Soc*. **1986**, *108*, 3827. (b) Tu, Y. Q.; Sun, L. D.; Wang, P. Z. *J. Org. Chem*. **1999**, *64*, 629. Application to taxane synthesis, see: (c) Holton, R. A.; Juo, R. R.; Kim, H. B.; Williams, A. D.; Harusawa, S.; Lowenthal, R. S.; Yogai, S. *J. Am. Chem. Soc*. **1988**, *110*, 6558. (d) Holton, R. A.; Somoza, C.; Kim, H. B.; Liang, F.; Biediger, R. J.; Boatman, P. D.; Shindo, M.; Smith, C. C.; Kim, S.; Nadizadeh, H.; Suzuki, Y.; Tao, C.; Vu, P.; Tang, S.; Zhang, P.; Murthi, K. K.; Gentile, L. N.; Liu, J. H. *J. Am. Chem. Soc*. **1994**, *116*, 1597.

(20) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett*. **1972**, 3769−3772.

(21) Bredereck, H.; Simchen, G.; Rebsdat, S.; Kantlehner, W.; Hom, P.; Wahl, R.; Hoffman, H.; Grieshaber, P. *Ber*. **1968**, *101*, 41. Trost, B. M.; Preckel, M. *J. Am. Chem. Soc*. **1973**, *95*, 7862.

(22) Murai, A.; Tanimoto, N.; Sakamoto, N.; Masamune, T. *J. Am. Chem. Soc*. **1988**, *110*, 1985.

(23) Corey, E. J.; Kim, S. U. *J. Am. Chem. Soc*. **1972**, *94*, 7586.

(24) Mukaiyama, T.; Sato, T.; Hanna, J. *Chem. Lett*. **1973**, 1041.

(25) (a) Tarhouni, R.; Kirschleger, B.; Rambaud, M.; Villieras, J. *Tetrahedron Lett.* **1984**, *25*, 835. (b) Sadhu, K. M.; Matteson, D. S. *Tetrahedron Lett.* **1986**, *27*, 795.
(26) (a) Yasuda, A.; Tanaka, S.; Oshima, K.; Yamamoto, H.; Nozaki, H. *J. Am. Chem. Soc.* **1974**, *96*, 6513. (b) Eschinasi, E. H. *J. Org. Chem.* **1970**, *35*, 1598. (c) Murata, S.; Suzuki, M.; Noyori, R. *J. Am. Chem. Soc.* **1979**, *101*, 2738.
(27) Eschinasi, E. H. *J. Org. Chem.* **1970**, *35*, 1598.
(28) Tamao, K.; Ishida, N. *Tetrahedron Lett.* **1984**, *25*, 4249.
(29) Tebbe, F. N.; Parshall, G. W.; Reddy, G. S. *J. Am. Chem. Soc.* **1978**, *100*, 3611.
(30) Takai, K.; Hotta, Y.; Oshima, K.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 1698. Takai, K.; Kakiuchi, T.; Kataoka, Y.; Utimoto, K. *J. Org. Chem.* **1994**, *59*, 2668.
(31) Tanino, K.; Onuki, K.; Asano, K.; Miyashoita, M.; Kuwajima, I. *43th Tennen Yuki Kagobutsu Toronkai Koen Yoshishu* **2001**, *45*, 85.
(32) For a similar transformation, see: Concellon, J. M.; Llavona, L.; Bernad, P. L. *Tetrahedron* **1995**, *51*, 5573.
(33) Reuss, R. H.; Hassner, A. *J. Org. Chem.* **1974**, *39*, 1785.
(34) Tanino, K.; Onuki, K.; Asano, K.; Miyashita, M.; Nakamura, T.; Takahashi, Y.; Kuwajima, I. *J. Am. Chem. Soc.* **2003**, *125*, 1498.
(35) Tanino, K.; Onuki, K.; Asano, K.; Miyashita, M.; Kuwajima, I. Manuscript in preparation.
(36) We are indebted to Professor G. Appendino (Dipartimento di Scienze e Tecnologia del Farmaco) for providing natural ingenol.
(37) Watanabe, K.; Suzuki, Y.; Aoki, K.; Sakakura, A.; Suenaga, K.; Kigoshi, H. *J. Org. Chem.* **2004**, *69*, 7802.
(38) Nickel, A.; Maruyama, T.; Tang, H.; Murphy, P. D.; Greene, B.; Yusuff, N.; Wood, J. L. *J. Am. Chem. Soc.* **2004**, *126*, 16300.