Synthetic Methods

Rapid Access to the "in,out"-Tetracyclic Core of Ingenol**

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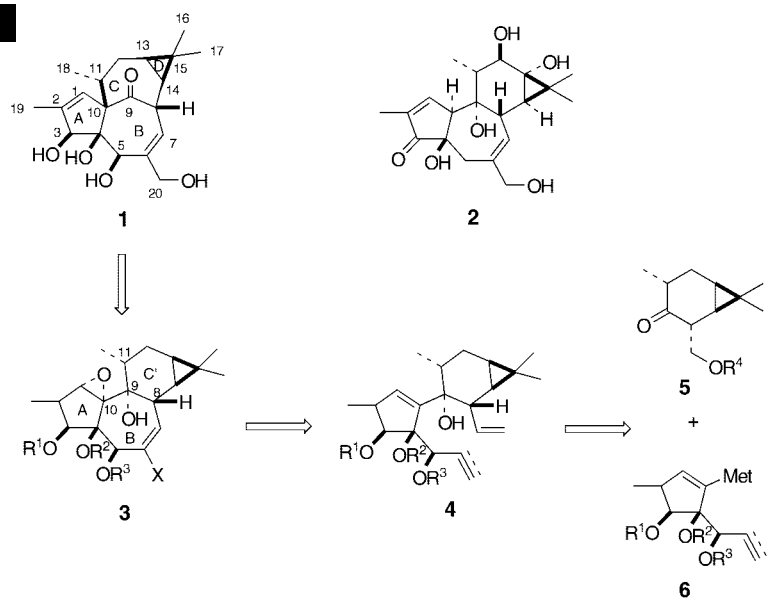
Ingenol (**1**), a prototypical diterpene of ingenanes, was first isolated from *Euphorbia ingens* by Hecker and co-workers.[1] Along with esters of the structurally related phorbol (**2**), the naturally occurring C3-monoesters of **1** are known to be among the most potent tumor promoters. The mode of action of these esters at the molecular level is believed to be associated with binding to protein kinase C, a key enzyme involved in cell signal transduction, and with mimicking the function of 1,2-diacylglycerol, the endogenous activator of the enzyme.[2] Surprisingly, certain ester derivatives of **1** were reported to possess anti-leukemic and anti-HIV activity.[3] Biological activity of this class of natural products is thus significantly altered by subtle, yet little-understood, structural modifications. For more than two decades these structurally complex molecules have attracted many studies directed toward total syntheses.[4,5] The highly strained "inside–outside" intrabridgehead stereochemistry of the BC ring system of **1** presents a particularly taxing synthetic challenge.[6] Several attractive solutions were developed by several groups,[7,8] culminating in an elegant total synthesis of (±)-**1** by Winkler et al.[9] followed by another by Kuwajima and co-workers.[10] Nonetheless, an efficient, convergent approach to **1** remains highly desirable. To this end, we report herein a rapid assembly of the carbocyclic core of **1** by a pinacol rearrangement.

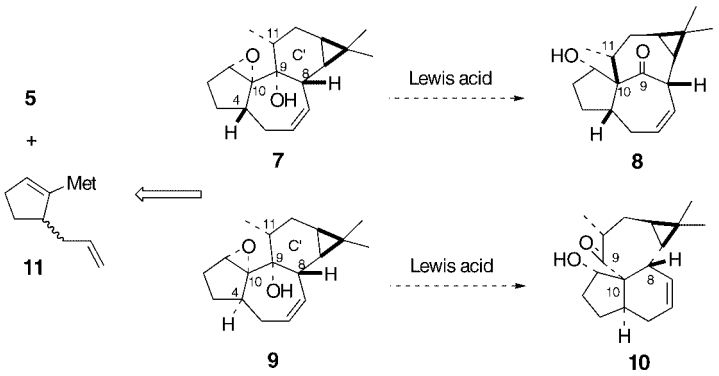
Our key strategy for addressing the requisite inside–outside *trans* stereochemistry of **1** with concomitant, diastereoselective construction of the quaternary C10 center was based on a 1,2-alkyl shift (**3**→**1**) at a late stage by adaptation of the Tsuchihashi–Suzuki rearrangement of 2,3-epoxy alcohols or silyl ethers (Scheme 1).[11–13] We speculated that a related 1,2-alkyl shift may well be involved in the biosynthesis of **1** for the conversion of its ABC′D ring system into the ABCD ring system.[14,15] Among several possible variations within this approach (A + C′D→ABC′D), a most expedient route to **3** seemed available by ring-closing olefin metathesis of **4** for the formation of the rigid, yet relatively strain-free, seven-membered ring B.[16] In turn, **4** could be prepared by straightforward coupling of two fragments of comparable complexity, **5** and **6**. Particularly attractive was the innate



Scheme 1. Retrosynthetic analysis of **1**. X = alkyl or alkenyl group, Met = metal.

convergence of the overall approach which could provide a most expeditious route to **1** and its analogues.

For our preliminary study, we chose to employ a simplified derivative of **6**, namely **11**, which is devoid of oxygen and remaining functionalities, to establish the feasibility of a convergent synthesis of the complete tetracyclic core of **1** (Scheme 2). According to molecular models, the stereochem-



Scheme 2. Met = metal.

istry about C4 was considered to be of principal importance to the key Lewis acid catalyzed rearrangement of **3** with respect to the antiperiplanar stereoelectronic requirements to ensure the desired migration of the C9–C11 (ingenol numbering) bond. With the natural configuration at C4 (e.g. **7**), the epoxide C10–O bond is antiperiplanar to the C9–C11 bond as required for the conversion of **7**→**8**, whereas the C8–C9 bond is nearly orthogonal. However, in the case of the opposite configuration at C4 (e.g. **9**), migration of only the undesired C8–C9 bond that occupies the antiperiplanar alignment could occur. These considerations prompted us to utilize racemic **11**

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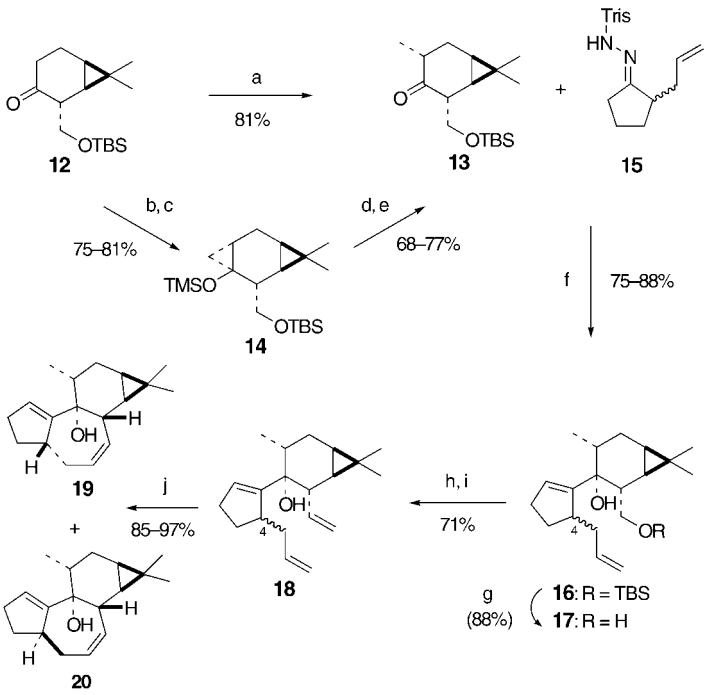
so that the stereochemical outcomes of both C4 epimers could be assessed simultaneously.

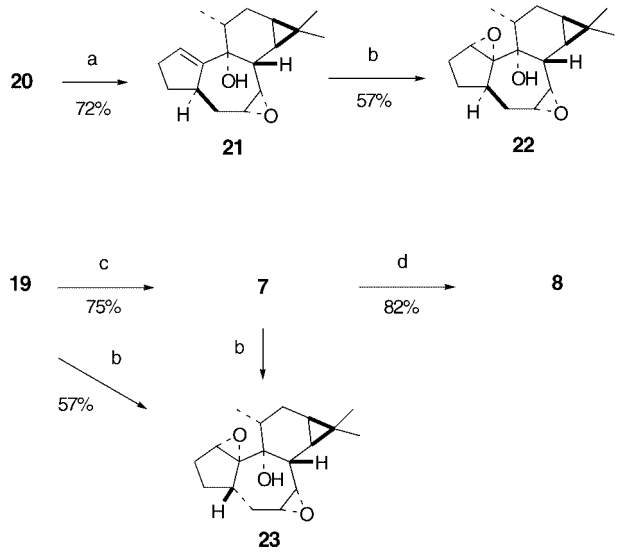
Our study began with the ketone **12**, which was readily prepared in large quantities from (+)-3-carene according to the method of Paquette et al. (Scheme 3).[17] Formation of the



Scheme 3. Reagents and conditions: a) LiHMDS, MeI, −78 to 0 °C; b) LiHMDS, TMSCl; c) Et_2Zn, CH_2I_2; d) K_2CO_3, MeOH; e) $[Pt_2Cl_4(C_2H_4)_2]$; f) *t*BuLi (2 equiv); g) TBAF; h) SO_3Py, DMSO, *i*Pr_2NEt; i) Ph_3PCH_3Br, NaHMDS; j) RCM. HMDS = hexamethyldisilazide, TBS = *tert*-butyldimethylsilyl, Tris = 2,4,6-triisopropylbenzenesulfonyl, TMSCl = trimethylsilyl chloride, TBAF = tetra-*n*-butylammonium fluoride, Py = pyridine, DMSO = dimethylsulfoxide, RCM = ring-closing metathesis.

kinetic enolate of **12** with LiHMDS (lithium hexamethyldisilazide) followed by alkylation with methyl iodide yielded **13** as a single diastereomer in 81% yield. Alternatively, **13** was obtained through subsequent ring opening of **14** with $[Pt_2Cl_4(C_2H_4)_2]$. This served to corroborate the α stereochemistry of the C11 methyl group in **13** from NOE measurements (interaction between the hydrogen atom at C13 and the hydrogen atoms of the methyl group at C18 in **13**). Addition of the 5-allylcyclopentenyl subunit to **13** was best achieved by means of the lithium reagent of **15**, which was prepared in situ by the Shapiro reaction,[18] to yield **16** in 75–88% yield. To set the stage for the construction of the seven-membered ring B, **16** was then converted into **18** by standard methods to give an inseparable 1:1 mixture of the two C4 epimers in 62% overall yield. Ring-closing olefin metathesis of **18** (5 mM in CH_2Cl_2) with Grubbs' second-generation catalyst (10 mol%) and heating at reflux proceeded smoothly to give **19** and **20** in excellent yield.

Following chromatographic separation of **19** and **20**, treatment of the less-polar isomer **20** with MCPBA (*m*-chloroperbenzoic acid) or *t*BuOOH–$VO(acac)_2$ resulted in regioselective epoxidation at the C6–C7 double bond to furnish **21** (Scheme 4). Upon prolonged exposure to MCPBA, the latter was converted into bisepoxide **22**. In sharp contrast, epoxidation of the more-polar isomer **19** with *t*BuOOH–$VO(acac)_2$ afforded the desired C1–C10 epoxide **7** in 75% yield. The bisepoxide **23** was obtained by treating **7** with MCPBA. On the basis of these conspicuous differences in the epoxidation of **19** and **20**, their C4 configuration was assigned as shown in Scheme 3. Inspection of molecular models clearly reveals that the hydroxy group at C9 in **20** is located in closer proximity to the C6–C7 double bond. Finally, upon exposure of epoxide **7** to $AlMe_3$ (3 equiv), the key Lewis acid mediated semipinacol rearragement proceeded cleanly to afford the desired ingenane **8** as the sole isomer (82% yield) which contains the complete skeleton of ingenol (**1**). The "inside–outside" stereochemistry of **8** was in accord with mechanistic considerations and difference-NOE measurements. Irradiation of the hydrogen atom at C8 ($\delta = 3.85$ ppm) showed diagnostic nuclear Overhauser enhancements at C(4)–H, C(11)–H, C(12)–H_β, and C(16)–Me.[7b] The indicated stereochemistry was subsequently confirmed by single crystal X-ray analysis of **8**.[19] Note that under identical conditions, bisepoxide **22** produced a complex mixture of polar products presumably owing to ring opening of epoxide(s), whereas bisepoxide **23** was found to be relatively inert to rearrangement conditions.



Scheme 4. Reagents and conditions: a) MCPBA or *t*BuOOH/$VO(acac)_2$; b) MCPBA; c) *t*BuOOH/$VO(acac)_2$; d) $AlMe_3$, CH_2Cl_2, −78 to 0 °C.

In conclusion, the demanding "inside–outside" stereochemistry of ingenol (**1**) and the stereoselective construction of the quaternary center at C10 have been successfully addressed by the pinacol-type rearrangement of an epoxy alcohol to develop a convergent synthesis of the fully assembled tetracyclic core of **1**. Thus, **8** was prepared in 8 steps from the known, readily available ketone **12**. We believe our approach holds promise in completing a concise, convergent synthesis of ingenol itself and its analogues by preinstallation of all the necessary functionalities in fragment

6 prior to its coupling to **5**. A unified approach to the syntheses of the ingenane, tigliane, and daphnane diterpenes is also anticipated to be forthcoming and will be reported in due course.

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[19] a) The crystal structure of **8** can be found in the Supporting Information; b) We thank Dr. Fook Tham at the University of California, Riverside for X-ray crystallographic analysis.

