STRATEGIES FOR THE TOTAL SYNTHESIS OF (±)-INGENOL AND RELATED IN-OUT RING SYSTEMS

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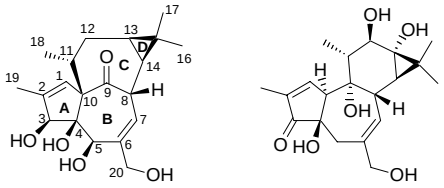
INTRODUCTION

Ingenol (**1**) (Figure 1), isolated from *Euphorbia ingens*, is a highly oxygenated tetracyclic diterpene that is structurally related to phorbol (**2**).[1] The naturally occurring 3-monoester derivatives of ingenol are widely regarded to be among the most potent tumor promoters, presumably by mimicking diacylglycerol, the activator of protein kinase C.[2] Protein kinase C itself is comprised of at least eight isozymes that are involved in reversible phosphorylation in the regulation of neuronal and hormonal enzyme activity.[3] Some ingenol esters also display anti-HIV and anti-leukemic properties.[4,5]



Ingenol (1) **Phorbol (2)**

Figure 1. Structures of Ingenol and Phorbol

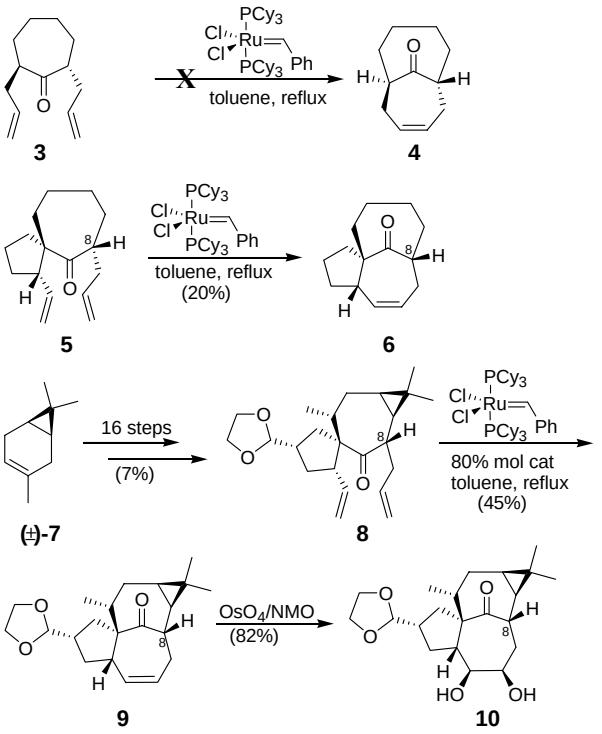
The absolute configuration of the natural product was determined by X-ray analysis of the 3,5,20-triacetate using the Bijvoet reflection method.[6] While the eight stereocenters and the all cis 3, 4, 5-triol represent a daunting synthetic challenge, the most imposing aspect of the molecule is the highly strained trans intra-bridgehead configuration of the B and C rings. Bridged bicyclic systems can exist in three stereoisomeric forms – cis "out-out", cis "in-in", and trans "in-out."[7] Due to the unavoidable steric interactions between the inside hydrogen atoms, the in-in isomer is the least stable for small and medium-sized bicyclic compounds. However, the energy difference between the out-out and in-out varies depending on the particular ring sizes. In the case of ingenol, the natural product was estimated to be 5.9 kcal mol^{-1} more strained than the C(8) epimer, isoingenol.[8] Only two other natural products, both in the secotrinervitane class of diterpenes, are known to exhibit this highly unusual in-out bridgehead configuration.[7] The complex structural features and potential for elucidating the mechanism of chemical and viral carcinogenesis have made ingenol an attractive target for total synthesis. This review will focus on the strategies that have successfully addressed the in-out trans intrabridgehead stereochemistry and on the two racemic total syntheses of the natural product.

SYNTHETIC STRATEGIES

Ring Closing Metathesis

Kigoshi et al[9] reported an attempt to synthesize a *trans*-bicyclo [4.4.1] undecanone by means of ring closing metathesis (RCM) with *trans*-2,7-diallylcycloheptanone (**3**). However, the failure of this reaction to provide the bicyclic enone **4** led to the hypothesis that the intramolecular distance between the terminal double bonds is a key feature. When this distance was decreased from 3.8 Å to 3.6 Å by modification of the substrate to **5**, the reaction proceeded in 20% yield, but required a relatively high temperature (Scheme 1). In 2001, Wood and coworkers[10] also investigated this strategy with a *trans*-2,7-diallylcycloheptanone substrate that had the fully functionalized C ring of the natural product. Unfortunately, all attempts to form the trans intrabridgehead were unsuccessful due to the 4.2 Å distance between the terminal olefins. Conformational analyses by Wood confirmed Kigoshi's hypothesis that the inclusion of the cyclopentyl ring would indeed decrease the distance between the olefins, in this case by 0.4 Å, presumably due to the resultant twisting of C(8), which in turn is predicted to lead to a smaller dihedral angle between the two side chains. After synthesis of the tricyclic diene **8** from (±)-3-carene (**7**), Wood observed that the RCM proceeded to provide the tetracyclic enone **9** with the trans bridgehead stereochemistry in 45% yield, albeit with high catalyst loading and elevated temperature. The apparent inconsistency in that **3** and **8** both have an intramolecular distance of 3.8 Å and yet only **8** gave the RCM product may be attributable to the almost stoichiometic catalyst loading that Wood's protocol employed. The synthesis was continued to provide the highly oxygenated ingenane diol **10**. The ring closing metathesis strategy represents a feasible method for the introduction of the highly strained trans intrabridgehead relationship, particularly since the starting monoterpene carene is commercially available in enantio-enriched form, thus possibly making this method easily amenable to an asymmetric synthesis.

Scheme 1. RCM of *trans*-dially Cycloheptanone Substrates

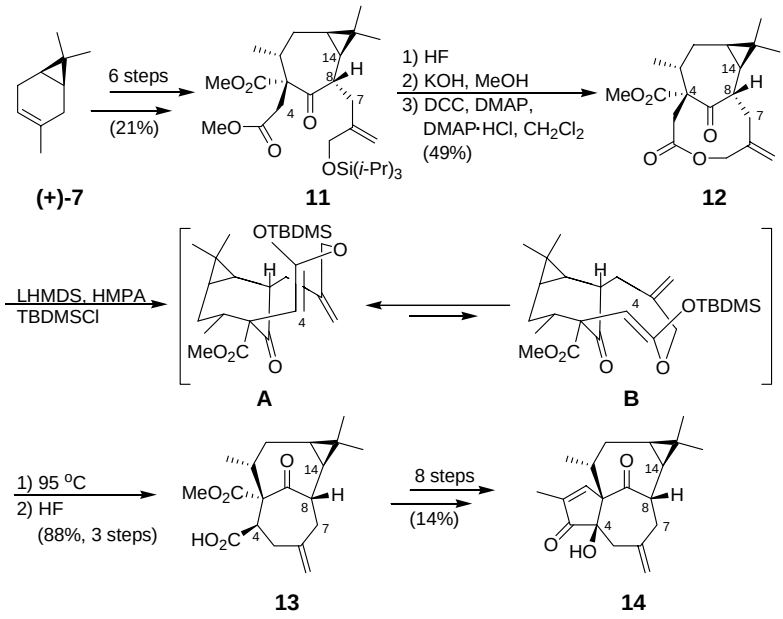


Ireland-Claisen Rearrangement

In the mid 90's, Funk and coworkers[11] devised an ingenious strategy to circumvent the strain associated with the trans intrabridgehead connectivity of the bicyclic BC rings. This method involved

synthesis of **11** by attachment of two functionalized side chains with a trans relationship to an enantiopure β-keto ester of cycloheptanone derived from (+)-3-carene.[8] This was followed by formation of the macrobicyclic lactone **12** with the required trans intrabridgehead, which X-ray analysis showed was significantly less strained than the ingenane system and had only a minor distortion of the C(7)- C(8)-C(14) bond angle (111.3º compared to 126.5º in ingenol). Conversion of the lactone to the silyl ketene acetal and an Ireland-Claisen rearrangement via a proposed chair-like transition state provided compound **13,** which possessed the incorrect stereochemistry at C(4) for installation of the cyclopentene A ring (Scheme 2). Verification of the stereochemical assignment supported the hypothesis that the rearrangement proceeded through a transition state resembling **A** rather than **B**, possibly due to through-space destabilization between the oxygen atoms of the ketone carbonyl and enol ether that would disfavor **B**. Nevertheless, base-catalyzed epimerization at C(4) and further elaboration led to dione **14**, containing the tetracyclic core with highly functionalized A, C and D rings. The utility of this strategy is limited by the unpredictable stereochemistry of the enolate Claisen rearrangement, which is highly dependent on the type and size of the substituents.

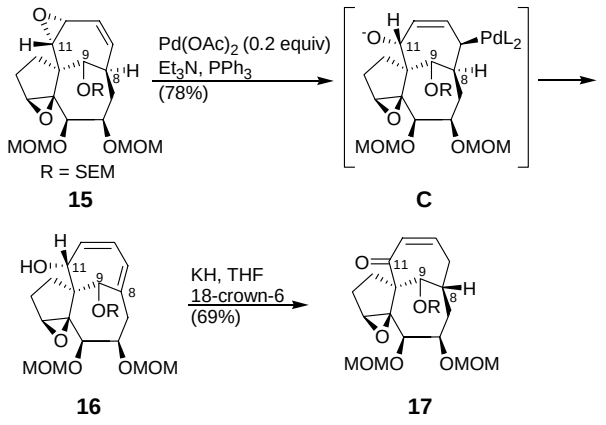
Scheme 2. Ireland-Claisen Ring Contraction



1,5-Hydrogen Sigmatropic Rearrangement

In the previous two methods, the formation of the more stable cis out-out intrabridgehead stereochemistry was seen as undesirable. However, in 2002 Rigby and coworkers[12] reported a strategy that involves the appropriately functionalized tricyclic allylic epoxide **15** containing the cis bridgehead configuration.[13] Stereoselective epoxidation to locked the C(11) hydrogen in the β position, and Pd-promoted isomerization provided the corresponding dienol **16** via intermediate **C** (Scheme 3). The presence of an external base is known to cause an anti β-hydride elimination from the allyl

Scheme 3. Epoxide Opening and 1,5-H Sigmatropic Rearrangement



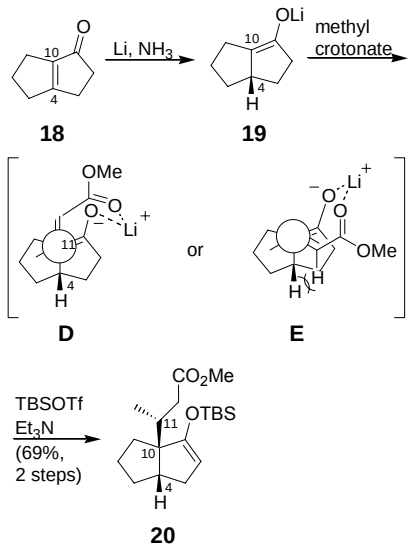
palladium complex, rather than the syn elimination commonly observed in these types of processes.[14,15] Dienol **16** then underwent an alkoxide-accelerated suprafacial 1,5 H-sigmatropic rearrangement[16] to transfer the C(11) β-hydrogen to the C(8) position, and thus creating the less stable trans intrabridgehead relationship in conjugated enone **17**. It should be noted that the ketone related to **15** (with a carbonyl in place of CHOSi at C(9)) underwent isomerization with syn elimination, and the resulting conjugated dienol isomerized to the more thermodynamically stable C(8) epimer of **17**. A possible reason for this change in stereochemistry is that the conformation of the ring is altered when the sp^3 C(9) carbon becomes sp^2 hybridized. One interesting feature of this method is that it has the potential to convert the easily formed out-out cis bridgehead stereochemistry[17] to the required in-out trans relationship. The disadvantages are that elaboration to the dienol substrate is rather lengthy and the resulting product is not particularly well suited for further manipulation of the C ring.

Intramolecular Dioxolenone Photocycloaddition and Fragmentation

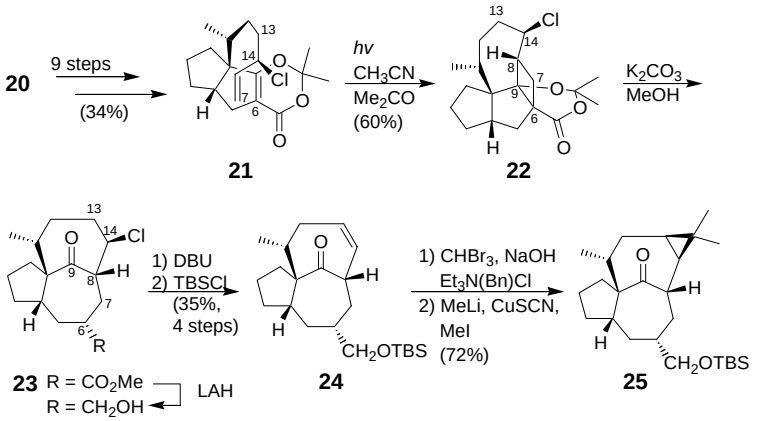
Winkler *et al* employed a modified de Mayo photocycloaddition-fragmentation to form the trans intrabridgehead configuration. The de Mayo reaction is the cycloaddition between an enol of a β-diketone and an olefin to form a cyclobutanol intermediate that undergoes retro aldol fragmentation to provide a 1,5-dicarbonyl product.[18] Because the regioselectivity of the enolization of unsymmetrical β-diketones has been a significant problem, attention turned to the use of β-keto esters. To avoid Paterno-Büchi reactions to form oxetanes, Baldwin[19] introduced the use of dioxolenones as a covalently locked enol form of a β-keto ester. The intramolecular version of this modified de Mayo reaction is very effective, as demonstrated by the synthesis of the trans bridged [4.3.1] undecane, the smallest known bicyclic compound to have the trans bridgehead hydrogens.[20] This reaction was utilized as the key step in the first total synthesis of (±)-ingenol by Winkler.[21]

The synthesis began with a diastereoselective Michael addition[22] of the enolate derived from the dissolving metal reduction of enone **18** to methyl crotonate, as shown in Scheme 4. The observed stereochemistry was rationalized by lithium coordination in transition state **D**. This reaction sets three contiguous stereocenters at C(4), C(10), and C(11). The product was then elaborated to a 1:1 mixture of photosubstrate **21** and its chloro epimer, which upon irradiation formed the photoadduct **22** and its C(13) β chloro isomer (5:2) in 60% yield (Scheme 5). It has been proposed[23] that **22** was derived exclusively from **21** while the other photoadduct was produced from the C(13) β chloro isomer.[24] Base-induced fragmentation of **22** via a retro aldol to keto ester **23** was followed by hydride reduction, elimination of the chloride, and protection of the primary hydroxyl to give enone **24**, which possesses the ingenane ABC ring system with the required trans intrabridgehead relationship and the $\Delta^{13,14}$ double bond. This intermediate was cyclopropanated by dibromocarbene generated with bromoform and

Scheme 4. Diastereoselective Michael Addition



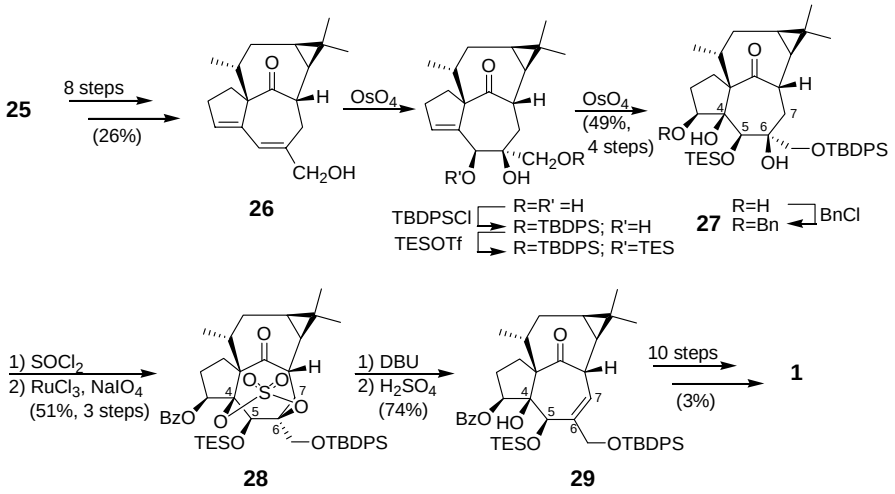
Scheme 5. Photocycloaddition, Fragmentation, and Cyclopropanation



sodium hydroxide. Methylation of the resulting dibromocyclopropyl product provided the tetracyclic core **25** of the natural product.

Further elaboration utilized the primary hydroxyl as the lone functionality to introduce the conjugated double bonds in diene **26**. Two osmium tetroxide-mediated dihydroxylations on the less hindered β face of the ring system followed by selective protection installed the correct relative configurations at C(4) and C(5), giving compound **27** (Scheme 6). Initial attempts to install the $\Delta^{6,7}$ double bond were unsuccessful, presumably because neither hydrogen on C(7) is antiperiplanar to the hydroxyl-derived leaving group. However, formation of the 1,3-cyclic sulfite and subsequent oxidation to sulfate **28** is proposed to cause a conformational change that aligns the hydrogen and oxygen of the sulfate in the proper anti orientation. Use of the nonnucleophilic base DBU opened the cyclic sulfate to form the C(4) sulfate ester. Hydrolysis with dilute sulfuric acid produced the desired olefin **29**.[25] This product was carried on to complete the first total synthesis of ingenol in 43 steps in an overall yield of 0.007%.

Scheme 6. Formation and Elimination of Cyclic Sulfate



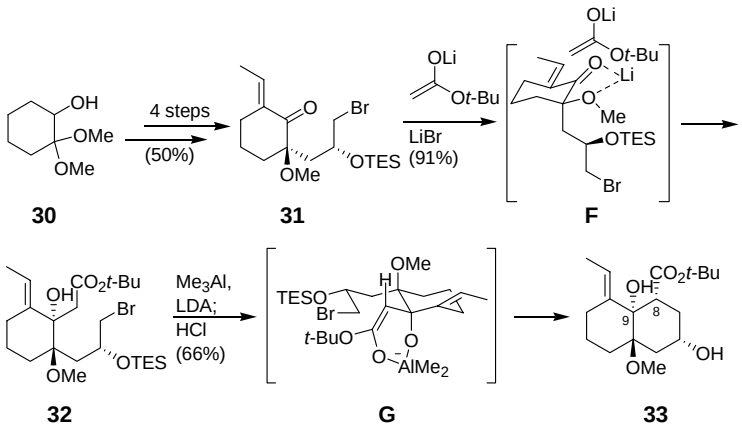
Although this method was successful in accessing the natural product, its main drawback is the inefficiency in functionalization of the A and B rings. This problem is derived in part from the lack of functionality tolerated in the Michael addition, resulting in a single primary hydroxyl group being the sole anchor to fully elaborate the A and B rings.

Pinacol Rearrangement

Tanino and coworkers[26] achieved the second total synthesis of (±)-ingenol by cyclization of an acetylene dicobalt complex and pinacol rearrangement of an epoxy alcohol. The key to this strategy is the use of a trans-decalin framework that provides a rigid conformation as well as the trans diaxial relationship between the hydrogen on C(8) and the C(9) hydroxyl, which is the same relationship they have in the natural product. In a previous report,[27] the authors generated the ABC ring system of ingenol containing the requisite trans intrabridgehead stereochemistry with an almost fully functionalized C ring by a similar strategy employing a tandem intramolecular cyclization of an acetylene dicobalt complex and rearrangement. However, the lone methoxy group in the rearranged product was insufficient to introduce the remaining functional groups. Thus, they modified their starting material in order to incorporate more functionality in the intermediate, which allowed them to complete the total synthesis.

Dimethoxycyclohexanol (**30**) was converted in four steps and 50% yield to enone **31**, which then underwent a stereoselective addition reaction with the lithium enolate of *t*-butyl acetate to form β-hydroxy ester **32** (Scheme 7). The selectivity was rationalized by the five-membered chelated ring **F**, which forces the cyclohexanone to adopt the sterically less favored conformation with the axial alkyl chain, thus effectively blocking the bottom face from the nucleophilic enolate. Treatment of **32** with LDA in the presence of trimethylaluminum effected the intramolecular alkylation to provide the trans-decalol ester **33** stereoselectively after deprotection. The lack of selectivity in the absence of trimethylaluminum suggests that the reaction proceeded through the six-membered chelated ring **G.**

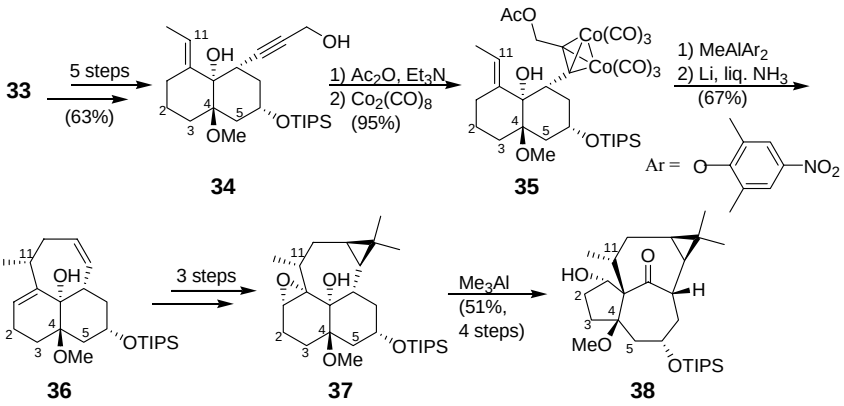
Scheme 7. Stereoselective Enolate Addition and Alkylation



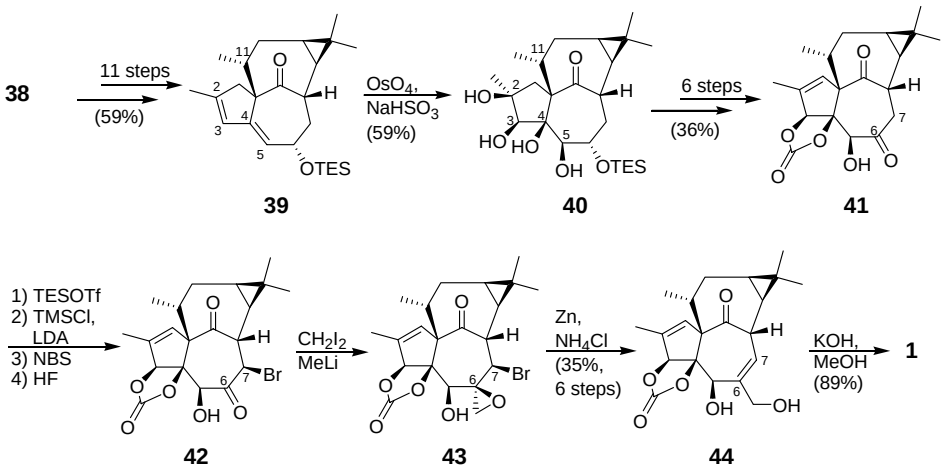
Chain elongation of **33** eventually resulted in propargyl alcohol **34**, which was then acetylated before formation of the dicobalt acetylene complex **35** (Scheme 8).[28] The electrophilic cyclization of the propargyl cation complex, achieved with methylaluminum bis(2,6-dimethyl-4-nitrophenoxide), was

followed by β elimination to provide the tri-substituted olefin **36**. After removal of the dicobalt hexacarbonyl complex via dissolving metal reduction, the dimethylcyclopropane D ring was installed using the previously described method. Hydroxyl-directed epoxidation furnished α-hydroxy epoxide **37**, which underwent trimethylaluminum-mediated pinacol rearrangement to **38**, which contained the ingenane skeleton and stereochemistry. Further manipulation gave access to diene **39**, which was then dihydroxylated at both double bonds to provide tetrol **40** (Scheme 9). The high stereoselectivity was rationalized by steric control. The bulky silyl protecting group prevents approach from the α face of the $\Delta^{4,5}$ double bond, and the resulting β diol forces enforces even greater rigidity, so as to make the silyl group block the α face even more effectively. Thus, during the second osmylation, the triethylsiloxy group exerts more steric influence than the C(11) methyl substituent.

Scheme 8. Cyclization Pinacol Rearrangement



Scheme 9. Double Dihydroxylation and Reductive Elimination



In striking similarity to Winkler's observation, the $\Delta^{6,7}$ double bond proved difficult to install under a variety of conditions. However, after stereoselective bromination of ketone **41** and methylene transfer, reductive cleavage of the bromo epoxide **43** provided the allylic alcohol **44**. Hydrolysis of the cyclic carbonate gave the natural product. This total synthesis employs 45 steps and has an overall yield of 0.1%. Unfortunately, it suffers from the same problem as Winkler's method in that after formation of the tetracyclic ingenane core, many linear steps are required to introduce the A and B ring functionality.

CONCLUSION

The complex architecture and interesting biological properties have made ingenol the target of total synthesis for the past two decades. Despite the failure of early attempts at entry into the ingenane system, five strategies have recently emerged to solve the problem of the trans intrabridgehead. Of these, only Winkler's method of dioxolenone photocycloaddition and fragmentation and Tanino's method of cyclization and pinacol rearrangement have resulted in total syntheses, although the other three represent promising alternatives that require further development.

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