THE FIRST, THE GOOD, AND THE BEST? 25 YEARS OF INGENOL SYNTHESIS

Reported by Carolyn Levinn December 01, 2015

INTRODUCTION

Ingenol **1** (Figure 1), a polyoxygenated diterpene, was first isolated from the *Euphorbia ingens* plant by Hecker and co-workers in 1968.[1] The full structure of ingenol was unambiguously established by single crystal X-ray analysis in 1970, from which its complex architecture was revealed.[2] The structure of **1** contains a number of interesting features, including four rings, eight stereocenters (five contiguous, one quaternary), a congested alcohol tetrad, and a dimethylcyclopropane. Arguably, however, the most unique feature in **1** is the *trans*-bicyclo[4.4.1]undecane core; this "in/out" bridged BC ring system creates a significant angular strain in the molecule.[3] In addition to its intriguing structure, ingenol and its derivatives display a diverse biological profile, ranging from tumor-promoting, to anti-cancer and anti-HIV activities. In fact, the recently FDA-approved treatment for actinic keratosis, Picato®, is ingenol mebutate, an ester derivative of **1**.[4] This structural complexity and notable bioactivity, coupled with low isolation yields, have driven the efforts of synthetic organic chemists for the past thirty years.

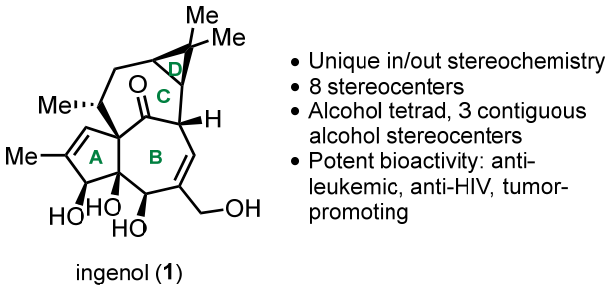


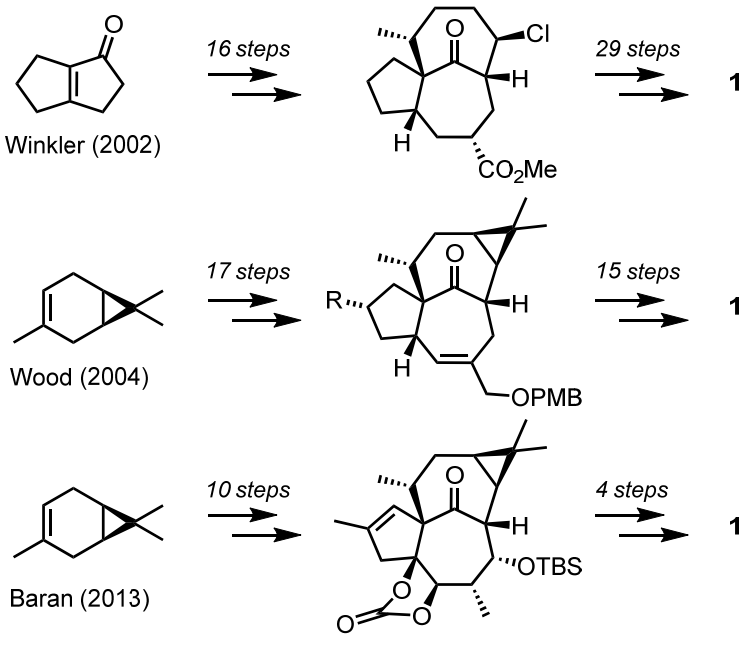
Figure 1. The structure of ingenol,

SUCCESSFUL SYNTHESES OF INGENOL

Out of the many synthetic attempts, four groups thus far have successfully completed the total synthesis of ingenol (Scheme 1). Interestingly, each group approached the two major synthetic hurdles, the in/out bridged core and the alcohol tetrad, using very different strategies. Winkler and co-workers completed the first total synthesis of **1** in 2002, employing an elegant de Mayo fragmentation to install the requisite bicycloundecane configuration. Subsequent oxidations and functional group manipulations afforded the target molecule in 45 steps and 0.0066% overall yield.[5] The first asymmetric route to ingenol was published in 2004 by Wood and coworkers, who took the novel approach of installing the stereochemistry of the bridged bicycle BC ring system in an open-chain form, then using a biased ring-closing metathesis to furnish the cyclized product.[7]

The most recent synthesis of ingenol, accomplished in only 14 steps from the chiral-pool starting material (+)-carene, was reported by Baran and coworkers in 2013. With much inspiration from the

previous syntheses, a similar bioinspired, two-phase synthetic strategy was taken: first establishing the polycyclic core in the "cyclase phase" by an allene-yne Pauson-Khand reaction and a vinylogous pinacol rearrangement, then furnishing the final functional groups in the "oxidase phase," to afford **1** in 1.2% overall yield. Importantly, this route is modular, allowing for late-stage diversification, and the development of analogs for biological testing.[8]



Scheme 1. Starting materials, key intermediates, and step count for the four successful syntheses of 1.

CONCLUSIONS AND UNMET CHALLENGES

Although the 2013 synthesis of ingenol by the Baran group is noted as the most practical route to access **1**, its scalability and applicability to industrial synthesis are limited by the necessity of super-stoichiometric amounts of osmium and selenium reagents, which are both extremely toxic and very expensive. Nevertheless, the efforts of this group, as well as those of Winkler, Wood, and others, have led to the development of numerous new synthetic disconnections and techniques, and stand as impressive achievements in the field of organic synthesis.

REFERENCES

1. Hecker, E. *Cancer Res.,* **1968**, *28*, 2338 – 2349.
2. Zechmeister, K.; Brandl, F.; Hoppe, W.; Hecker, E.; Opferkuch, H. J.; Adolf, W. *Tetrahedron Lett.,* **1970**, *11*, 4075 – 4078.
3. Alder, R. W.; East, S. P. *Chem. Rev.,* **1996**, *96*, 2097 – 2111.
4. McKerrall, S. J.; Jorgensen, L.; Kuttruff, C. A.; Ungeheuer, F.; Baran, P. S. *J. Am. Chem. Soc.,* **2014**, *136*, 5799 – 5810.
5. Winkler, J. D.; Rouse, M. B.; Greaney, M. F.; Harrison, S. J.; Jeon, Y. T. *J. Am. Chem. Soc.,* **2002**, *124*, 9726 – 9728.
6. Nickel, A.; Maruyama, T.; Tang, H.; Murphy, P. D.;Greene, B.; Yusuff, N.; Wood, J. L. *J. Am. Chem. Soc.* **2004**, *126*, 16300 – 16301.
7. Jorgensen, L.; McKerrall, S. J.; Kuttruff, C. A.; Ungeheuer, F.; Felding, J.; Baran, P. S. *Science*, **2013**, *341*, 878 – 882.