J|A|C|S
COMMUNICATIONS

Published on Web 11/24/2004

Total Synthesis of Ingenol

Andrew Nickel, Toru Maruyama, Haifeng Tang, Prescott D. Murphy, Blake Greene, Naeem Yusuff, and John L. Wood*

Sterling Chemistry Laboratory, Department of Chemistry, Yale University, New Haven, Connecticut 06520-8107

Received September 27, 2004; E-mail: john.wood@yale.edu

Isolated in 1968, ingenol (**1**) is the parent compound of several dozen naturally occurring ingenanes that possess the same carbon skeleton but varied peripheral functionalities.[1] In addition to their intriguing "inside−outside" bridged BC ring system,[2] the ingenanes display interesting biological profiles that range from tumor-promoting to anti-leukemic and anti-HIV activities.[3] Since the early 1980s, this combination of important biological function and complex architecture has inspired the efforts of numerous synthetic chemists.[4] Previously, we reported an approach toward **1** wherein known β-ketoester **2**[5] was advanced to diene **3**, which served as a ring-closing metathesis substrate in a first generation Grubbs reaction that delivers the ingenane tetracycle **4** (Scheme 1).[4e]

Although this work established the feasibility of ring closure via metathesis chemistry, further experiments indicated that competing ring-opening reactions were likely responsible for the observed poor conversion. This, coupled with the underfunctionalized nature of **4**, led us to explore a modified substrate (**5**), which, upon ring closure, would furnish a more stable trisubstituted olefinic product **6** possessing the requisite C-20 hydroxymethyl group. In the event, we were delighted to find that substrate **5**[6] undergoes ring-closing metathesis with improved yield and catalyst loading with respect to diene **3** (Scheme 2).[7]

Having prepared an intermediate possessing all of the requisite carbon atoms and fully functionalized C and D rings, attention was turned to completing rings A and B. Accordingly, dioxolane **6** was converted to diene **7** via a deprotection/reduction/elimination sequence (Scheme 3). Allylic oxidation of **7** (SeO_2/*t*-BuOOH)[8] proved highly selective and furnished only one of several possible allylic alcohol products (**8**). Further oxidation of **8** to the exo-enone was followed by rhodium(III) chloride catalyzed isomerization[9] to the corresponding endocyclic isomer **9**, which set the stage for introducing the C-4 hydroxyl. Treatment of **9** with potassium *tert*-butoxide in the presence of molecular oxygen and trimethyl phosphite efficiently delivered α-hydroxy ketone **10**.

At this point, all that remained to complete the ingenol A ring was stereoselective reduction of the C-3 ketone. Unfortunately, reduction of both free alcohol **10** and the derived silyl ether **11** resulted in predominant reduction from the convex β face, delivering the undesired anti products **12** and **13**, respectively.[10]

Encouraged by reports in the ingenol literature of structural alterations in the B ring translating into marked differences in reactivity of the A ring,[11] we opted to address the problem of stereoselective reduction at C-3 on more advanced substrates. Thus, attention turned to completing the B ring. Initial studies explored the feasibility of a singlet oxygen ene reaction[12] which was expected to stereoselectively furnish the requisite alcohol and $\Delta^{6,7}$ unsaturation (i.e., **10** → **15**) in a single step; unfortunately, **10** proved inert to singlet oxygen.[13]

Forced to explore alternatives, we turned to a stepwise, epoxidation ring-opening approach. Toward this end, it was found that epoxidation of alkene **10** with $VO(acac)_2$ and *tert*-butyl hydroperoxide proceeded smoothly; however, attempts to convert the derived epoxide (**14**) to the desired allylic alcohol **15** with a variety of either Lewis acids or strong bases were unfruitful (Scheme 4).[14]

Suspecting that the free tertiary alcohol in **14** was interfering with epoxide opening and aware of the possibility that the desired α,β-hydroxy ketone (**15**) might be prone to undergo a retro-aldol

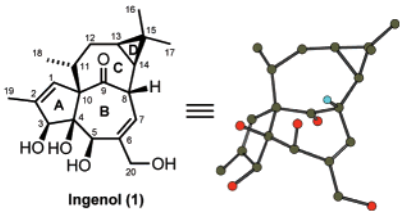
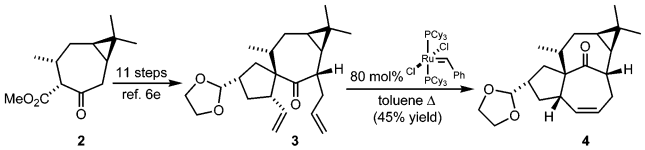
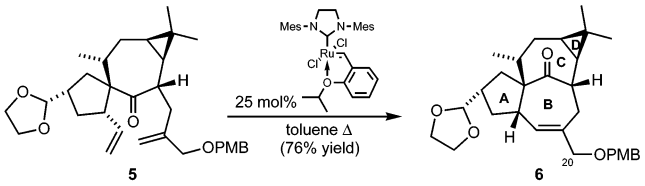


Figure 1. Structure of ingenol and Chem3D representation of the "inside−outside" bridged BC ring system.

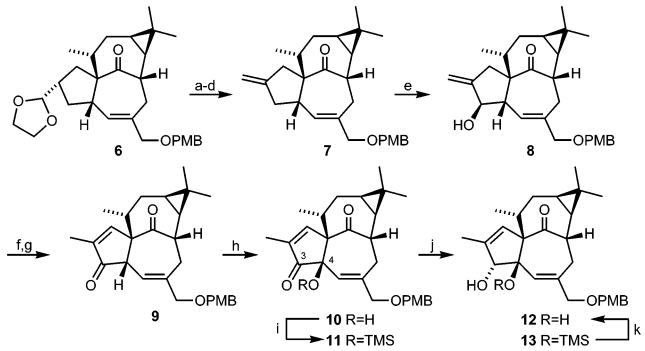
Scheme 1



Scheme 2



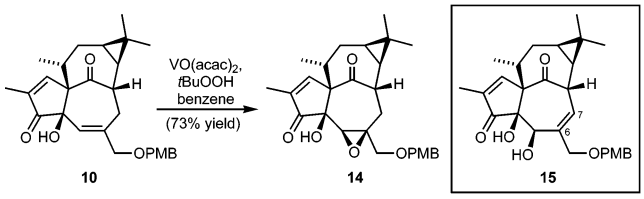
Scheme 3 [a]



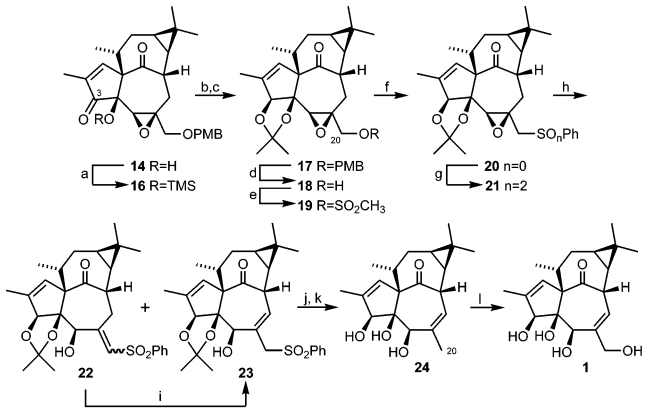
[a] Reagents and conditions: (a) HCl, THF−H_2O; (b) $NaBH_4$, EtOH−THF (77% over two steps); (c) I_2, PPh_3, imidazole, THF; (d) KO*t*Bu, THF−DMSO (94% over two steps); (e) SeO_2, *t*BuOOH, CH_2Cl_2−H_2O−HOAc (49%, 68% brsm); (f) Dess−Martin periodinane, CH_2Cl_2 (74%); (g) $RhCl_3$, EtOH−H_2O (74%); (h) KO*t*Bu, O_2, $P(OMe)_3$, THF−*t*BuOH (94%); (i) TMSOTf, NEt_3, CH_2Cl_2 (60%); (j) $NaBH_4$, MeOH (99% for **10** → **12**, 90% for **11** → **13**); (k) HCl, THF−H_2O (76%).

10.1021/ja044123l CCC: $27.50

Scheme 4



Scheme 5 [a]



[a] Reagents and conditions: (a) TMSOTf, NEt_3, CH_2Cl_2 (72%); (b) $NaBH_4$, MeOH; (c) 2,2-dimethoxypropane, PPTS, CH_2Cl_2 (86% over two steps); (d) DDQ, $CH_2Cl_2-H_2O$ (90%); (e) MsCl, NEt_3, CH_2Cl_2 (96%); (f) PhSH, Li_2CO_3, DMF (76%); (g) $(NH_4)_6Mo_7O_{24}$, H_2O_2, EtOH$-H_2O$ (97%); (h) DBU, benzene (47%, 88% based on recovered **22**); (i) DBU, benzene (47%, 94% based on recovered **22**); (j) Na(Hg), Na_2HPO_4, MeOH (76%); (k) HCl, THF$-H_2O$ (92%); (l) SeO_2/SiO_2, THF (40%, 85% brsm).

reaction under strongly acidic or basic conditions, we considered numerous protection scenarios, eventually recognizing reduction of the C-3 ketone and protection of the derived diol as an efficient possibility. In stark contrast to previous reductions (i.e., **11** → **13**, Scheme 3), we were delighted to find that conversion of the tertiary alcohol in **14** to its TMS ether, followed by reduction and protection, stereoselectively delivered acetonide **17**. Although this result clearly demonstrates how subtle changes in the ingenane skeleton can influence reactivity, the underlying forces controlling the stereochemical outcome of the C-3 reduction remain undelineated.

Despite a fully protected A ring, the epoxide in **17** again proved unreactive toward ring-opening conditions. In an attempt to bias the system, the protected C-20 alcohol in **17** was unmasked and converted to phenyl sulfone **21** via nucleophilic displacement of the corresponding mesylate (**19**) with lithium phenylthiolate followed by oxidation. Gratifyingly, treatment of epoxy sulfone **21** under mildly basic conditions initially gave vinyl sulfone **22**, which smoothly isomerized under the reaction conditions to desired allylic sulfone **23** (Scheme 5).[15]

With allylic sulfone **23** in hand, the major remaining challenge in the synthesis of ingenol was the conversion of the C-20 sulfonyl to the corresponding primary alcohol. While attempts to effect this transformation via displacement or oxidation were unsuccessful, sodium amalgam reduction of **23** followed by hydrolytic removal of the acetonide furnished 20-deoxyingenol (**24**).[16] Upon treatment with silica supported selenium dioxide, **24** was found to undergo selective oxidation at the least hindered allylic site to furnish **1**,[17] completing the most concise total synthesis of ingenol reported to date.

In conclusion, a ring-closing metathesis approach has been effectively employed in an efficient total synthesis that delivers the biologically important diterpene ingenol in 32 overall steps from **2**.[5]

Acknowledgment. This report is dedicated to Prof. Amos B. Smith, III on the occasion of his 60th birthday. Financial support was provided by Bristol-Myers Squibb, Yamanouchi, Merck, Amgen, and Pfizer. A.N. thanks Bristol-Myers Squibb for a graduate student fellowship. T.M. thanks Ono Pharmaceutical Co. Ltd. In addition, we acknowledge V. B. Birman for helpful suggestions and C. D. Incarvito for X-ray crystallographic analysis.

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

References

(1) Initial isolation and characterization: (a) Hecker, E. *Cancer Res.* **1968**, *28*, 2338−2349. (b) Zechmeister, K.; Brandl, F.; Hoppe, W.; Hecker, E.; Opferkuch, H. J.; Adolf, W. *Tetrahedron Lett.* **1970**, *11*, 4075−4078.
(2) For a review on in/out isomerism, see: Alder, R. W.; East, S. P. *Chem. Rev.* **1996**, *96*, 2097−2111.
(3) See Blanco-Molina, M.; Tron, G. C.; Macho, A.; Lucena, C.; Calzado, M. A.; Muñoz, E.; Appendino, G. *Chem. Biol.* **2001**, *8*, 767−778 and references therein.
(4) There have been two previous total syntheses: (a) Winkler, J. D.; Rouse, M. B.; Greaney, M. F.; Harrison, S. J.; Jeon, Y. T. *J. Am. Chem. Soc.* **2002**, *124*, 9726−9728. (b) Tanino, K.; Onuki, K.; Asano, K.; Miyashita, M.; Nakamura, T.; Takahashi, Y.; Kuwajima, I. *J. Am. Chem. Soc.* **2003**, *125*, 1498−1500. For a formal total synthesis, see: (c) Watanabe, K.; Suzuki, Y.; Aoki, K.; Sakakura, A.; Suenaga, K.; Kigoshi, H. *J. Org. Chem.* **2004**, *69*, 7802−7808. For successful construction of the ingenane "inside−outside" skeleton, see: (d) Funk, R. L.; Olmstead, T. A.; Parvez, M.; Stallman, J. B. *J. Am. Chem. Soc.* **1993**, *58*, 5873−5875. (e) Tang, H.; Yusuff, N.; Wood, J. L. *Org. Lett.* **2001**, *3*, 1563−1566. (f) Rigby, J. H.; Bazin, B.; Meyer, J. H.; Mohammadi, F. *Org. Lett.* **2002**, *4*, 799−801.
(5) Prepared as a single enantiomer in five steps from commercially available 3-carene: Funk, R. L.; Olmstead, T. A.; Parvez, M. *J. Am. Chem. Soc.* **1988**, *110*, 3298−3300.
(6) Prepared in an analagous manner to **3**. See Supporting Information.
(7) The conversion of **5** to **6** required the Hoveyda modified second generation Grubbs catalyst for acceptable yields. See: Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168−8179.
(8) Umbreit, M. A.; Sharpless, K. B. *J. Am. Chem. Soc.* **1977**, *99*, 5526−5528.
(9) Disanayaka, B. W.; Weedon, A. C. *Synthesis* **1983**, 952.
(10) In reductions of **10**, **11**, or C-20 variants with $NaBH_4$ ± $CeCl_3 \cdot 7H_2O$, DIBAL, or L-selectride, none of the desired syn diol was detected.
(11) Kim, S.; Winkler, J. D. *Chem. Soc. Rev.* **1997**, *26*, 387−399.
(12) For recent reviews, see: (a) Stratakis, M.; Orfanopoulos, M. *Tetrahedron* **2000**, *56*, 1595−1615. (b) Clennan, E. L. *Tetrahedron* **2000**, *56*, 9151−9179.
(13) Enone **10** and C-20 variants were recovered unreacted from reactions under typical conditions for the generation of singlet oxygen: O_2, *hν*, and either rose bengal, TPP, or methylene blue in suitable solvents.
(14) A similar epoxide-opening approach also proved unsuccessful for the Kuwajima group. See ref 4b.
(15) Sulfones **22** and **23** were isolated as a 1:1 mixture. For a leading reference of the isomerizion of α,*β*-unsaturated sulfones to *β*,*γ*-unsaturated sulfones, see: (a) O'Connor, D. E.; Lyness, W. I. *J. Am. Chem. Soc.* **1964**, *86*, 3840−3846. For recent examples of one-pot epoxide-opening/isomerization of *β*,*γ*-epoxysulfones, see: (b) Trost, B. M.; Acemoglu, M. *Tetrahedron Lett.* **1989**, *30*, 1495−1498. (c) Lee, S. W.; Fuchs, P. L. *Tetrahedron Lett.* **1991**, *32*, 2861−2864. (d) Ohtani, Y.; Shinada, T.; Ohfune, Y. *Synlett* **2003**, 619−622.
(16) 20-Deoxyingenol (**24**) is a natural product: (a) Uemura, D.; Ohwaki, H.; Hirata, Y.; Chen, Y.-P.; Hsu, H.-Y. *Tetrahedron Lett.* **1974**, *15*, 2527−2528. The intermediate 3,4-*O*-isopropylidene of **24** is a previously reported natural product derivative: (b) Gotta, H.; Adolf, W.; Opferkuch, H. J.; Hecker, E. *Z. Naturforsch.* **1984**, *39b*, 683−694. This is the first total synthesis of **24**, and its first structural confirmation by X-ray crystallographic analysis.
(17) Chromatographically and spectroscopically identical to an authentic sample (Sigma).

JA044123L