J|A|C|S
COMMUNICATIONS

Published on Web 07/31/2002

The First Total Synthesis of (±)-Ingenol

Jeffrey D. Winkler,* Meagan B. Rouse, Michael F. Greaney,† Sean J. Harrison,‡ and Yoon T. Jeon§

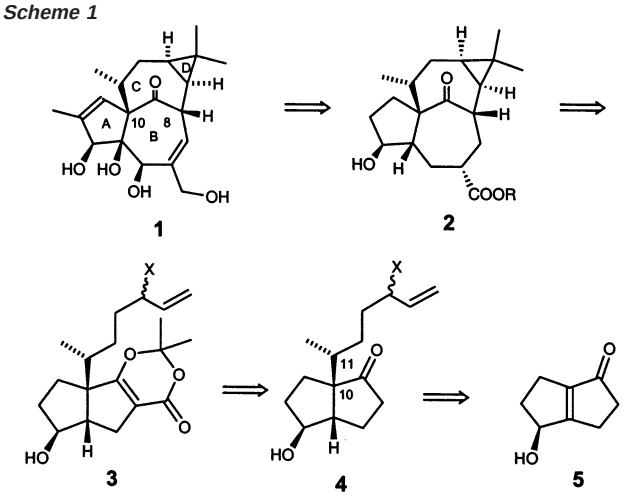
Department of Chemistry, The University of Pennsylvania, Philadelphia, Pennsylvania 19104

Received April 19, 2002

The diverse biological activities and the structural complexity of ingenol have generated intense activity directed toward the total synthesis of this highly oxygenated diterpene for almost 20 years.[1] The establishment of the highly unusual C-8/C-10 "inside−outside" or trans intrabridgehead stereochemistry of the BC ring system presents a particularly daunting challenge.[2] We report herein the first total synthesis of (±)-ingenol. Outlined below is the preparation of a key tetracyclic intermediate **16** (Scheme 2), containing both the C-11 methyl group and the D-ring cyclopropane, and its elaboration into (±)-ingenol, **1** (Scheme 3).

The retrosynthetic strategy that we employed for the total synthesis of ingenol is outlined in Scheme 1. We anticipated that ingenol **1** should be available from dioxenone photoaddition-fragmentation product **2** via the methodology developed in our laboratory. The requisite photosubstrate **3** would be prepared by dioxenone formation from bicyclooctane **4**, the product of angular substitution of **5**.

Scheme 1



The first goal in our total synthesis of ingenol was the establishment of the requisite C-10/C-11 relative stereochemistry as shown in **4** (Scheme 1). We anticipated that the C-11α methyl stereochemistry could be established via Michael addition of the enolate derived from dissolving metal reduction of **5** to methyl crotonate, based on the models advanced by Heathcock and Seebach.[3] We first examined this reaction sequence with C-3-deoxyenone **6** (Scheme 2).[4] In the event, the conjugate reduction/Michael reaction led, after silylation (TBSOTf, DIEA) of the intermediate ketone, to the formation of **7** in a 14:1 ratio of α:β C-11 methyl epimers. Three contiguous stereocenters are established in this reductive alkylation reaction. The cis AB ring fusion results from addition of the crotonate to the sterically less hindered β face of the enolate derived from **6**.[5] The establishment of the requisite C-10/C-11 relative stereochemistry can be rationalized by examination of the diastereomeric chelated transition state structures A and B in Figure 1. While both A and B experience gauche interactions between the crotonate and the enolate, conformer B also suffers from an unfavorable steric interaction between the crotonate α-proton and the C-4 methine of the enolate leading to the preferential formation of **7** from conformer A.

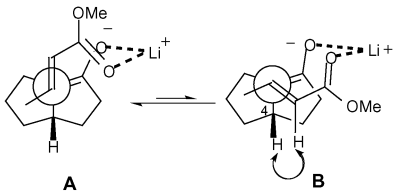


Figure 1. Rationale for the highly diastereoselective Michael reaction.

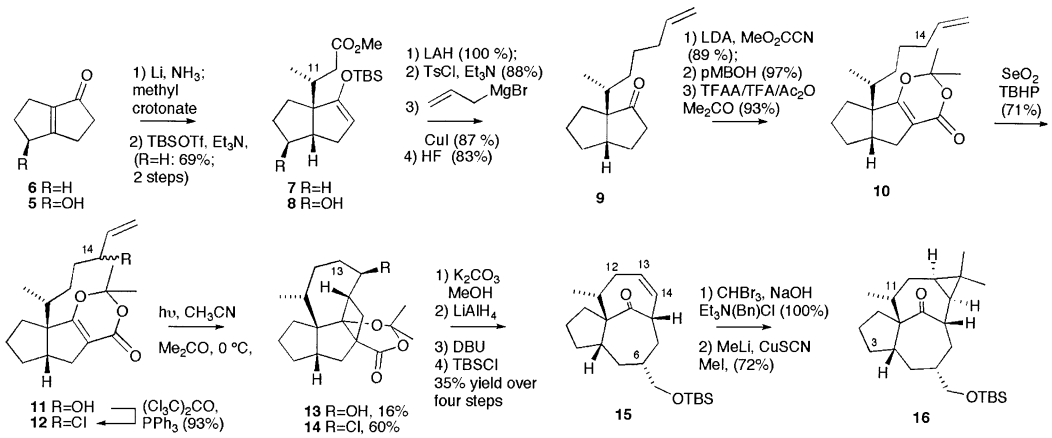
We were disappointed to find that the extension of this reaction to the C-3 hydroxyenone **5**[6] led to attenuated yields and diminished stereoselectivity. We therefore elected to transform **7**, albeit devoid of A ring functionality, into the key tetracyclic intermediate **16**. The absence of oxygen functionality at C-3 in **16** does not significantly increase the number of steps required for the completion of the total synthesis of ingenol. Reduction of the ester **7** with LAH, followed by tosylate formation (TsCl, Et_3N) and reaction of the derived tosylate with allyl cuprate (CH_2═$CHCH_2MgBr$, CuI), gave on desilylation (HF) the homologated ketone **9**. Elaboration of **9** to the dioxenone chromophore **10** proceeded by carboxylation with Mander's reagent,[7] ester exchange (*p*-methoxybenzyl alcohol), and dioxenone formation (TFAA, TFA, Ac_2O, Me_2-CO).

We reasoned that the incorporation of heteroatom functionality at C-14 (ingenol numbering) in **10** would facilitate the introduction of the ingenol D-ring cyclopropane via $\Delta^{13,14}$ olefin formation and cyclopropanation. Toward that end, we found that allylic oxidation of **10** (SeO_2, TBHP) led to the formation of a 1:1 mixture of alcohols **11**, epimeric at C-14. While irradiation of **11** led to the formation of a unique cyclobutane photoadduct **13** in low (16%) yield, we were delighted to find that photocycloaddition of the derived allylic chloride **12** [$(Cl_3C)_2CO$, Ph_3P] proceeded in 60% yield to give the desired photoadduct **14**, accompanied by the C-13 chloro-isomer (5:2 ratio)![8] Fragmentation of **14** with methanolic potassium carbonate, followed by LAH reduction of the derived ester, elimination of the chloride with DBU, and silylation of the

* To whom correspondence should be addressed. E-mail: winkler@sas.upenn.edu.
† Current address: Department of Chemistry, University of Edinburgh.
‡ Current address: Millenium Pharmaceuticals, Cambridge, MA.
§ Current address: Bristol-Myers Squibb, Hopewell, NJ.

10.1021/ja026600a CCC: $22.00

Scheme 2



primary alcohol (TBSCl), gave **15** as a 7:1 ratio of C-6 α:*β* epimers in 35% yield over four steps, accompanied by the chromatographically separable $\Delta^{12,13}$ double bond isomer of **15**.

We anticipated that carbene addition to the $\Delta^{13,14}$ alkene in **15** would occur from the sterically less hindered *β*-face since the trans intrabridgehead stereochemistry of the tricyclic ring system projects the carbonyl group to the α face of **15**. In the event, reaction of **15** with dibromocarbene and benzyl-triethylammonium chloride gave a quantitative yield of a dibromocyclopropane as a single diastereomer, which on reductive methylation (MeLi, CuSCN, MeI) gave **16**.[9]

Our next objective toward the completion of the synthesis was to employ the C-6α hydroxymethyl substituent in **16** to introduce the A ring functionality present in ingenol. Toward that end, deprotection of silyl ether **16** with TBAF and oxidation of the resulting C-20 alcohol **17** with the Dess−Martin periodinane led to the formation of the aldehyde **18** as a mixture of C-6 epimers in 88% yield from **16** (Scheme 3). Oxidation of **18** to the $\Delta^{5,6}$ unsaturated aldehyde **20** was effected by bromination of **18** using *t*-BuBr/DMSO,[10] followed by regioselective elimination of the resulting mixture of epimeric α-bromoaldehydes **19** with LiCl/DMF to give **20** in 73% overall yield from **18**.[11] Functionalization of the A ring was then achieved from **20** by a three-step sequence: (1) formation of the dienol acetate (Ac_2O, AcCl) of **20**; (2) NBS-mediated bromination of the derived enol acetate to give the C-4 brominated product **21**; and (3) elimination of the C-4 bromo substituent in **21** with LiCl/DMF to introduce the requisite $\Delta^{3,4}$ alkene, affording diene aldehyde **22** in three steps from **20** in 50% overall yield.

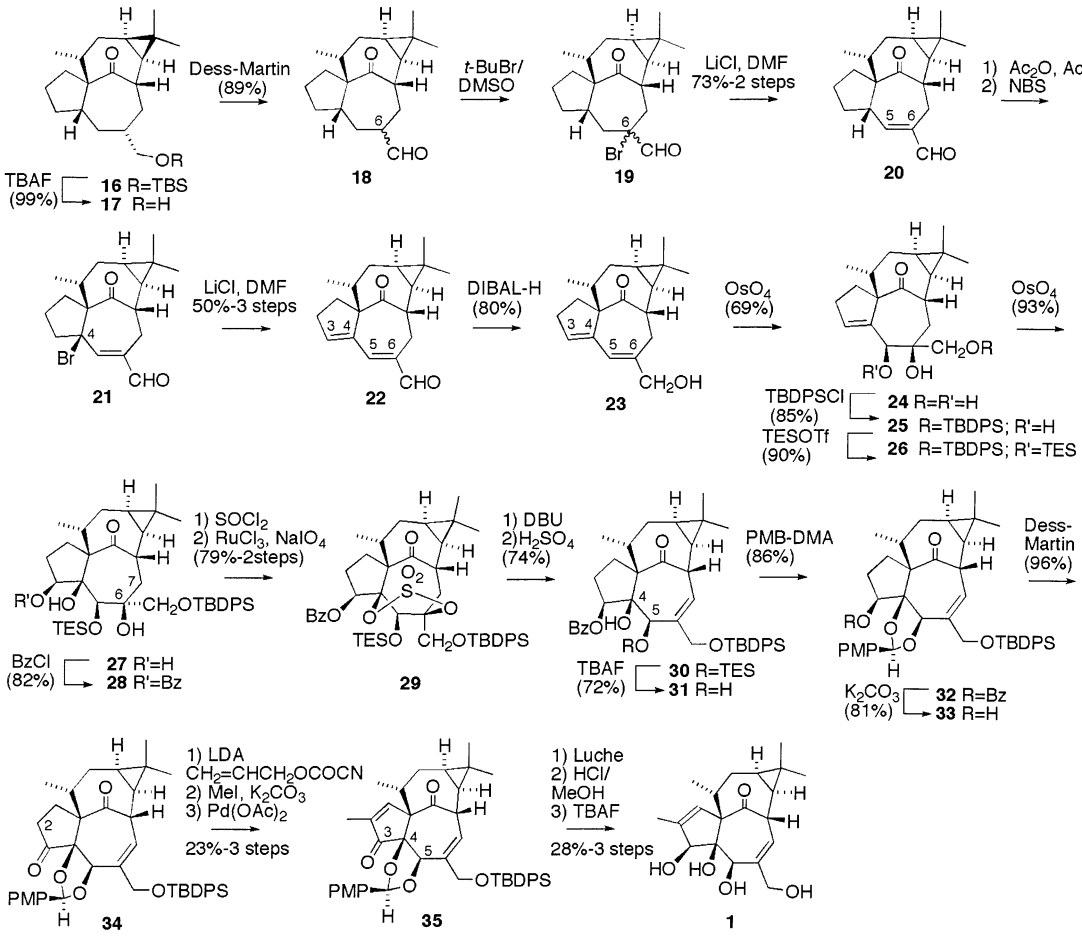
The introduction of the C-3, C-4, C-5 triad of oxygen functionalities into **22** that are present in ingenol was achieved via two successive dihydroxylation reactions, both of which occur from the sterically more accessible *β* face of the tetracyclic ring system. We were delighted to find that dihydroxylation of **23**, the diene carbinol obtained by reaction of **22** with DIBAL-H, led to the selective formation of the C-5*β*, C-6*β* diol **24**, which on regioselective silylation (TBDPSCl) of the sole primary hydroxyl in the derived triol gave **25**. The regioselectivity of the osmylation reaction is consistent with the selective reaction at the more sterically accessible $\Delta^{5,6}$ alkene in **23**.

Regioselective silylation of the C-5*β* secondary hydroxyl group in diol **25** led to the formation of the corresponding C-5*β* TES ether **26**. Dihydroxylation of **26** from the *β*-face of the $\Delta^{3,4}$ alkene gave the C-3*β*, C-4*β* diol **27**, which could be selectively benzoylated at the sterically more accessible C-3*β* secondary hydroxyl to give **28**. Having achieved the stereoselective incorporation of the C-3, C-4, and C-5 oxygen functionalities, it remained only to effect elimination of the C-6 hydroxyl to generate the $\Delta^{6,7}$ alkene, thereby completing the functionalization of the B ring of ingenol. Previous work from our laboratories revealed that the C-6 hydroxyl was resistant to elimination under standard reaction conditions. We have described an efficient procedure for the formation of the $\Delta^{6,7}$ alkene via elimination of the cyclic sulfate derived from the C-4, C-6 diol in a closely related system.[1e,12] The application of that methodology to **28** proved straightforward. Reaction of **28** with thionyl chloride, followed by oxidation of the derived sulfite (RuO_4), led to the formation of cyclic sulfate **29** in good yield. Exposure of **29** to DBU, followed by treatment of the eliminated sulfate product with H_2SO_4, gave the desired $\Delta^{6,7}$ alkene, as a mixture of TES ether **30** and diol **31**. Treatment of **30** with TBAF cleanly afforded the requisite diol **31** without the removal of the TBDPS group. Having completed the functionalization of the B and C rings, it remained only to introduce the requisite A ring functionality (C-2 methyl and $\Delta^{1,2}$ alkene) to complete the synthesis of ingenol.

Reaction of the C-4*β*, C-5*β* diol functionality in **31** with *p*-methoxybenzaldehyde dimethyl acetal led to the formation of a single acetal product **32**, the stereochemistry of which was established by NOESY. Hydrolysis of **32** (K_2CO_3, MeOH) and reaction of the resulting carbinol **33** with the Dess−Martin reagent afforded the C-3 ketone **34**. Introduction of the C-2 methyl group and the $\Delta^{1,2}$-alkene was achieved via carboxyallylation of **34** (LDA, $CH_2{=}CH{-}CH_2OCOCN$), followed by methylation of the derived *β*-ketoester (K_2CO_3, MeI) and $Pd(OAc)_2$ oxidation[13] of the methylated ketoester to generate the C-2 methylated enone **35**. Luche reduction ($NaBH_4$, $CeCl_3$)[14] of **35** provided the C-3*β* allylic alcohol, via addition of hydride anti to the C-4*β*, C-5*β* acetal ring. Deprotection of the acetal with methanolic HCl, followed by desilylation of the C-20 TBDPS ether with nBu$_4$NF, led to the formation of (±)-ingenol **1**, which was, in all respects, identical to an authentic sample with the exception of optical rotation.

The total synthesis of ingenol outlined above proceeds in 43 steps from enone **6** with an 80% average yield per step. It is notable for the use of a highly diastereoselective Michael reaction to fix the C-11 methyl stereochemistry and the incorporation of the dimethylcyclopropane via diastereoselective carbene addition to the $\Delta^{13,14}$ olefin. The establishment of the C-8/C-10 trans intrabridgehead stereochemistry serves as a testament to the utility of the intramolecular dioxenone photoaddition-fragmentation approach to the synthesis of structurally and stereochemically complex natural products.[15] The elaboration of **16** into **1**, using the C-6 hydroxy-

Scheme 3



methyl group as the sole handle for oxidation of seven contiguous carbon centers, leads to the completion of the total synthesis of ingenol.

Acknowledgment. This work is dedicated to the memory of Professor Josef Fried, in gratitude for his enthusiasm and encouragement during the early stages of this work. This work is presented in part by J.D.W. at the Pfizer Lecture in Organic Synthesis at the University of Waterloo (April 8, 2002) and by M.B.R. as Paper 427 at the 223rd ACS National Meeting (Orlando, April 7−11, 2002). The invaluable assistance of Dr. George Furst (University of Pennsylvania), Dr. Sharon Callahan, Dr. Sarah Traeger, and Dr. Xiaohua Huang (Bristol-Myers Squibb) in obtaining NMR spectral characterization is gratefully acknowledged. We would like to thank the National Institutes of Health (CA40250 and 45686), Boehringer-Ingelheim, Bristol-Myers Squibb, Dupont Pharmaceuticals, Glaxo SmithKline, GPC Biotech, Merck, Pfizer, and Wyeth-Ayerst for generous financial support of this project. M.F.G. is the recipient of the GlaxoWellcome Fellowship for Postdoctoral Research.

Supporting Information Available: Experimental procedures and spectral data for **1**−**35** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) For recent reviews on approaches to the synthesis of ingenol, see: Kim, S.; Winkler, J. *Chem. Soc. Rev.* **1997**, *26*, 387 and Rigby, J. *Stud. Nat. Prod. Chem.* **1993**, *12*, 233. For more recent contributions, see: (a) Rigby, J. *Org. Lett.* **2002**, *4*, 799. (b) Tang, H.; Yusuff, N.; Wood, J. *Org. Lett.* **2001**, *3*, 1563. (c) Kigoshi, H.; Suzuki, Y.; Aoki, K.; Uemura, D. *Tetrahedron Lett.* **2000**, *41*, 3927. (d) Tanino, K.; Nakamura, T.; Matsui, T.; Kuwajima, I. *Tennen Yuki Kagobutsu Toronkai Koen Yoshishu* **1997**, *39*, 1. (e) Winkler, J.; Kim, S.; Harrison, S.; Lewin, N.; Blumberg, P. *J. Am. Chem. Soc.* **1999**, *121*, 296. (f) Nakamura, T.; Matsui, T.; Tanino, K.; Kuwajima, I. *J. Org. Chem.* **1997**, *62*, 3032.

(2) For the first synthesis of the tricyclic core of the ingenane ring system with *trans*-intrabridgehead stereochemistry, see: Winkler, J.; Henegar, K.; Willard, P. *J. Am. Chem. Soc.* **1987**, *109*, 2850.

(3) (a) Oare, D.; Heathcock, C. *Top. Stereochem.* **1989**, *19*, 227. (b) Seebach, D.; Golinski, J. *Helv. Acta* **1981**, *64*, 1413.

(4) (a) Kotsuki, H.; Arimura, K.; Ohishi, T.; Maruzasa, R. *J. Org. Chem.* **1999**, *64*, 3770. (b) Cook, A.; Linstead, R. *J. Chem. Soc.* **1934**, 946. (c) Kulkarni, S.; Dev, S. *Tetrahedron* **1968**, *24*, 553.

(5) All new compounds were characterized by full spectroscopic (NMR, IR, high resolution MS) data. Yields refer to spectroscopically and chromatographically homogeneous (>95%) materials.

(6) We thank Professor Philip E. Eaton (University of Chicago) for providing an unpublished procedure for the conversion of **6** to **5**.

(7) Crabtree, S.; Chu, W.; Mander, L. *Synlett* **1990**, *3*, 169.

(8) The details of the pathways of the photocycloaddition of the allylic alcohol and allylic chloride photosubstrates **11** and **12** will be reported separately: Winkler, J.; Harrison, S.; Greaney, M., manuscript in preparation.

(9) The introduction of the dimethylcyclopropane ring by dibromocarbene addition and reductive methylation in a closely related system has also been reported by Kuwajima and co-workers (ref 1f).

(10) Armani, E.; Dossena, A.; Marchelli, R.; Casnati, G. *Tetrahedron* **1984**, *40*, 2035.

(11) For similar selectivity in a closely related system, see ref 1e.

(12) (a) Kolb, C. H.; Vannievwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483. (b) Schaub, C.; Mueller, B.; Schmidt, R. R. *Eur. J. Org. Chem.* **2000**, *9*, 1745.

(13) Shimizu, I.; Tsuji, J. *J. Am. Chem. Soc.* **1982**, *104*, 5844. Tsuji, J.; Khiro, M.; Shimizu, I.; Kataoka, H. *Chem. Lett.* **1984**, 1133.

(14) Luche, J. *J. Am. Chem. Soc.* **1978**, *100*, 2226.

(15) Winkler, J.; Mazur, C.; Liotta, F. *Chem. Rev.* **1995**, *95*, 2003.

JA026600A