ORGANIC LETTERS

2005
Vol. 7, No. 8
1489−1491

A Pauson–Khand Approach to the Synthesis of Ingenol

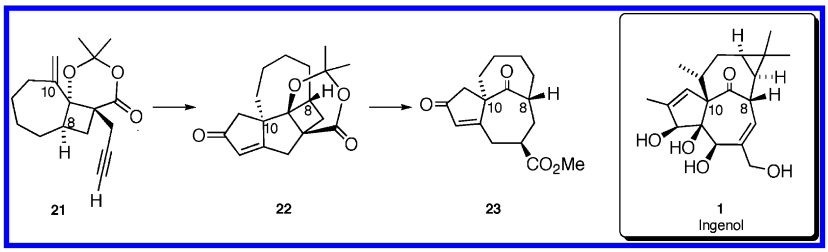
Jeffrey D. Winkler,* Esther C. Y. Lee, and LaToya I. Nevels

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

winkler@sas.upenn.edu

Received January 18, 2005

ABSTRACT

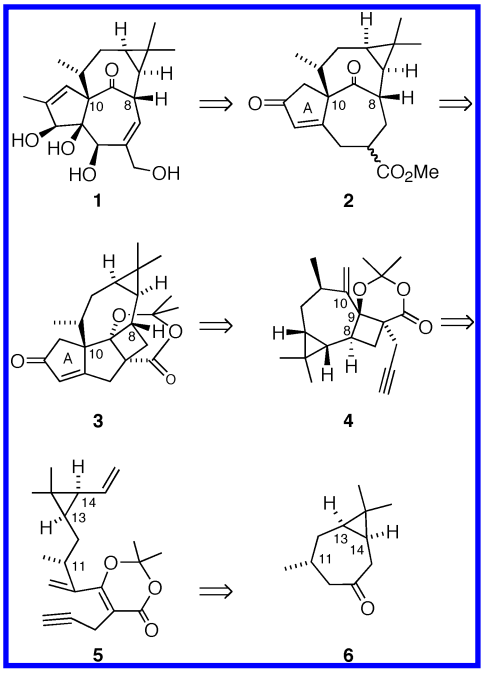


Pauson–Khand cyclization of dioxanone photoadduct 21 leads to the formation of a single product in good yield. However, retro-aldol fragmentation of the pentacyclic cyclopentenone 22 leads to the formation of 23, with cis C-8/C-10 intrabridgehead stereochemistry, unlike the target compound ingenol 1, which possesses C-8/C-10 trans intrabridgehead stereochemistry.

The therapeutic importance of C-3 esters of ingenol **1** and the dearth of exploration of structure−activity relationship data for this class of compounds make the development of efficient pathways for the synthesis of ingenol and analogues an important goal. Of particular note in the synthesis of ingenol is the establishment of the C-8/C-10 trans intrabridgehead stereochemistry, which is critical for the biological activity of **1**. In 2002, we reported the first total synthesis of racemic **1**, in which the trans intrabridgehead stereochemistry was established via intramolecular dioxenone photoaddition. The total synthesis proceeded in 42 steps from commercially available starting materials in an overall yield of 0.042%.[1] Since that time, two other total syntheses have appeared by: Tanino and Kuwajima (2003) and Wood (2004), which proceeded in ca. 45 and 38 steps, respectively.[2]

In an effort to develop a more efficient approach to the synthesis of ingenol, we have examined the strategy outlined in Scheme 1 for the synthesis of **1**, in which the C-8/C-10 intrabridgehead stereochemical relationship is established via

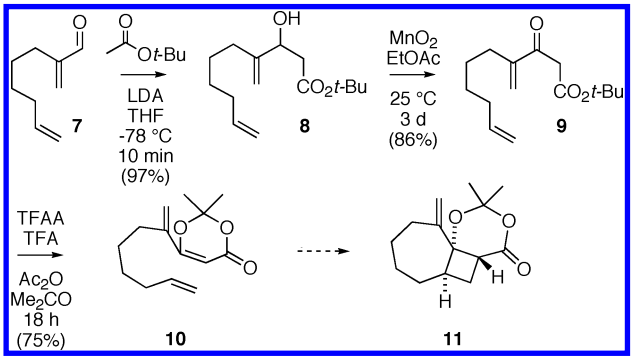
Scheme 1



(1) Winkler, J. D.; Rouse, M. B.; Greaney, M. F.; Harrison, S. J.; Jeon, Y. T. *J. Am. Chem. Soc.* **2002**, *124*, 9726−9728.

(2) a) Tanino, K.; Onuki, K.; Miyashita, M.; Nakamura, T.; Takahashi, Y.; Kuwajima, I. *J. Am. Chem. Soc.* **2003**, *125*, 1498−1500. (b) Nickel, A.; Maruyama, T.; Tang, H.; Murphy, P.; Greene, B.; Yusuff, N.; Wood, J. L. *J. Am. Chem. Soc.* **2004**, *126*, 16300−16301.

Scheme 2

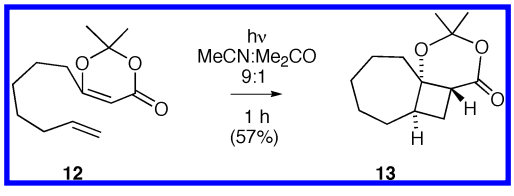


Pauson−Khand cyclization of **4** to give **3**. The A-ring cyclopentenone moiety in retroaldol product **2** would then be used to complete the synthesis of **1**. The Pauson−Khand substrate **4** should be available by the intramolecular dioxenone photocycloaddition of **5**. We envisioned that the C-11 methyl group (ingenol numbering) and the *gem*-dimethylcyclopropane in **5** would be derived from **6**, the preparation of which has been described from (+)-carene.[3] We report herein the results of our model study for this new reaction sequence.

To determine the viability of the route outlined in Scheme 1, we examined the irradiation of **10** (Scheme 2) as a model system for the photocycloaddition of methylene dioxenone **5** (Scheme 1). The synthesis of **10** is outlined in Scheme 2. Unsaturated aldehyde **7** was prepared in a one-pot procedure by Swern oxidation of 7-octen-1-ol followed by reaction of the intermediate aldehyde with Eschenmoser's salt.[4] Reaction of **7** with the conjugate base of *tert*-butyl acetate then gave **8**, which on MnO_2 oxidation afforded ketoester **9**. Exposure of **9** to dioxenone-forming conditions (TFAA, TFA, Ac_2O, Me_2CO) led to the formation of the dioxenone photosubstrate **10** in 75% yield. However, irradiation of **10** (3.0 mM in 10% Me_2CO/MeCN, 450 W Hanovia mercury lamp, 3 h) resulted only in the recovery of unreacted **10** without formation of the desired photoadduct **11**.

While we have shown that irradiation of **12** leads to the formation of **13** in good yield (Scheme 3),[5] irradiation of a

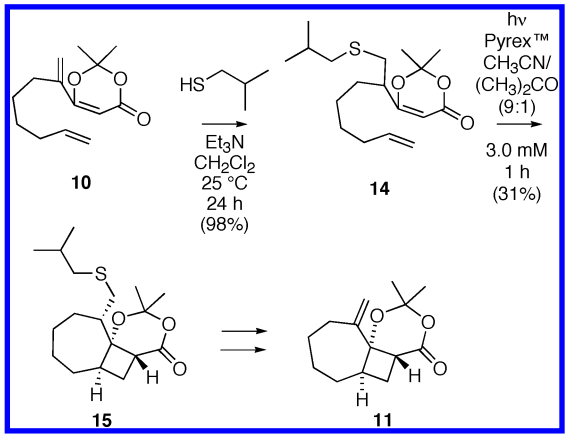
Scheme 3



1:1 mixture of **10** and **12** led to the formation of none of the desired photoadduct **13**, a result that is consistent with quenching of the dioxenone triplet (of both **10** and **12**) by the diene moiety present in **10**.

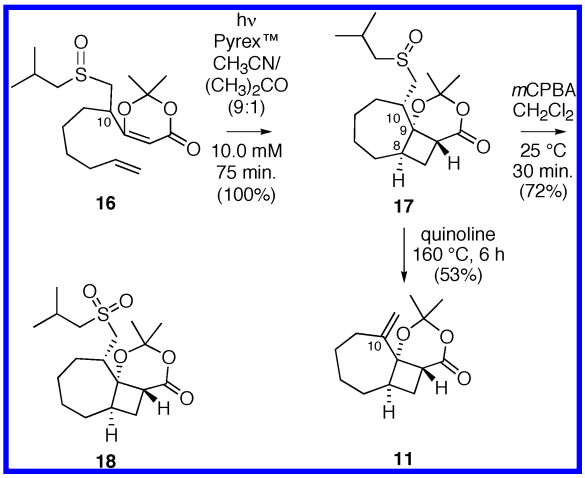
We therefore turned our attention to sulfide **14** as a protecting group for the offending diene functionality in **10** (Scheme 4). Oxidative elimination of **15**, the photoadduct obtained from **14**, would then lead to the formation of **11**. Conjugate addition of isobutylthiol to **10** gave **14**). While

Scheme 4



irradiation of **14** does lead to the formation of the desired photoadduct **15**, the irradiation of the corresponding sulfoxide **16** (Scheme 5), obtained by reaction of **14** with *m*-CPBA

Scheme 5



(−78 °C, 97% yield, as a ca. 1:1 ratio of sulfoxide diastereomers), gave a cleaner reaction and higher yields.

Irradiation of **16** led to the formation of a ca. 1:1 mixture of diastereomeric photoadducts **17**. Oxidation of the mixture of diastereomeric products to a single sulfone (*m*-CPBA, 72% yield) confirmed that the photocycloaddition of **16** proceeded with a unique sense of induction from the C-10 stereocenter.

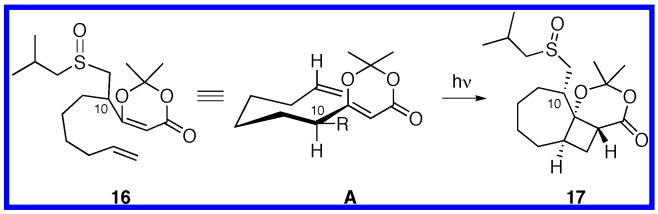
(3) Satoh, T.; Kaneko, Y.; Okuda, T.; Uwaya, S.; Yamakawa, K. *Chem. Pharm. Bull.* **1984**, *32*, 3453−3460.

(4) Takano, S.; Inomata, K.; Samizu, K.; Tomita, S.; Yanase, M.; Suzuki, M.; Iwaubuchi, Y.; Sugihara, T.; Ogasawara, K. *Chem. Lett.* **1989**, 1283−1284.

(5) Winkler, J. D.; Hey, J. P.; Hannon, F. J. *Heterocycles* **1987**, *25*, 55−60.

The stereochemical outcome of the photocycloaddition of **16** can be attributed to allylic strain effects. Selective formation of **17** is consistent with reaction via the conformation shown in **A** [Scheme 6; R = $CH_2S(O)i$-Bu], in which

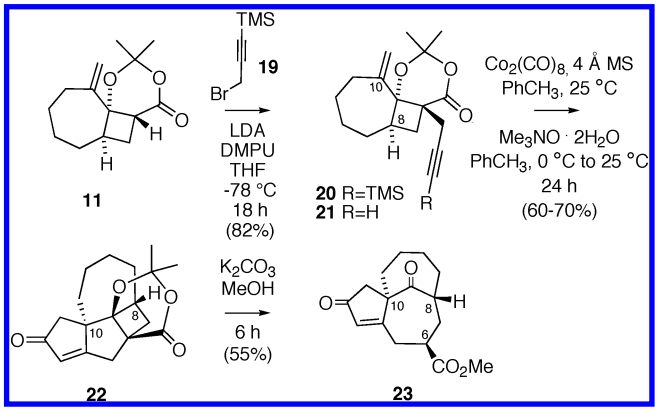
Scheme 6



the C-10 hydrogen eclipses the dioxenone ring. The structure of **18**, the sulfone derived from **17**, was confirmed by X-ray crystallographic analysis. Heating sulfoxide photoadduct **17** to 160 °C in quinoline led to the formation of the desired methylene photoadduct **11**, the formal product of [2 + 2] cycloaddition of **10** (Scheme 4) in good yield.

The Pauson−Khand substrate **21** was then prepared via alkylation of the conjugate base of **11** (LDA, THF, DMPU, −78 °C) with 3-trimethylsilylpropargyl bromide **19** to give **20**, followed by desilylation with TBAF (THF, 100%) to give **21** (Scheme 7). Reaction of **21** with $Co_2(CO)_8$ and 4 Å

Scheme 7



molecular sieves in toluene at room temperature for 2 h followed by slow addition of a suspension of trimethylamine *N*-oxide dihydrate in toluene at 0 °C led to the formation of **22** as a single diastereomer in 60−70% yield.[6] It is noteworthy that the Pauson−Khand reaction of **21** in the presence of the trimethylamine *N*-oxide *dihydrate* was considerably more efficient than the reaction using anhydrous trimethylamine *N*-oxide. This pronounced difference could be attributed to the attenuation of the nucleophilicity of the hydrated amine oxide ligand, which could retard decomplexation of the initially formed cobalt−alkyne complex.[7]

The structure and stereochemistry of **22** was confirmed by X-ray crystallographic analysis, which revealed that it did not contain the requisite C-8/C-10 relative stereochemistry for the synthesis of ingenol. Retro-aldol fragmentation of **22** led to the formation of **23**, with cis intrabridghead stereochemistry, which was verified by X-ray crystallographic analysis. While the fragmentation product was initially formed as a single C-6 epimer (C-6β ester as shown in **23**), prolonged exposure of **23** to the basic reaction conditions (K_2CO_3, MeOH) led to the formation of a mixture of C-6 epimeric products.

While the C-8/C-10 intrabridghead stereochemical relationship in **22** is established in the Pauson−Khand reaction of **21**, that relationship is indirectly established in **21**, since the propargyl moiety in **21** can only approach the C-10 exocyclic methylene from the β-face as shown to give **22**.

In the retrosynthetic plan outlined in Scheme 1, the C-8/C-9 ring fusion stereochemistry in **4** is trans, which forces the approach of the propargyl moiety in **4** to the α-face of the C-10 methylene, thereby generating the requisite C-8/C-10 trans intrabridgehead stereochemistry shown in **3**. However, irradiation of **16** led to the exclusive formation of the cis-fused bicyclo[5.2.0]nonane moiety as shown in **17** (Scheme 5). The successful implementation of the retrosynthetic plan in Scheme 1 therefore depends on the preparation of a trans-fused photoadduct or its equivalent from **16**. Studies directed toward the construction of the requisite trans-fused photoadduct are currently in progress, and our results will be reported in due course.

Acknowledgment. We would like to thank the National Institutes of Health (CA40250), GlaxoSmithKline, Amgen, and Merck for their generous support of this program.

Supporting Information Available: Spectral data and experimental procedures for **8**−**11**, **14**−**18**, and **20**−**23** and X-ray data for **18**, **22**, and **23**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL050103S

(6) Perez-Serrano, L.; Casarrubios, L.; Dominguez, G.; Perez-Castells, J. *Org. Lett.* **1999**, *1*, 1187−1188.

(7) (a) Shen, J.; Shi, Y.; Gao, Y.; Shi, Q.; Basolo, F. *J. Am. Chem. Soc.* **1988**, *110*, 2414−2418. (b) Shojaie, A.; Atwood, J. D. *Organometallics* **1985**, *4*, 187−190.