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Synthetic Studies on the Ingenane Diterpenes. An Improved Entry into a *trans*-Intrabridgehead System

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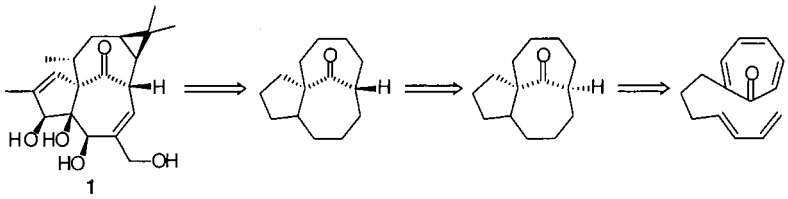
ABSTRACT

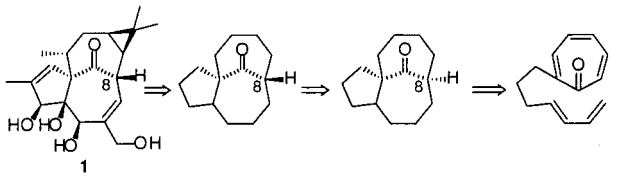


The efficient construction of an ingenol intermediate exhibiting "inside–outside" intrabridgehead stereochemistry is reported. The sequence features the net conversion of a *cis*-intrabridgehead compound into a highly strained *trans*-species via palladium-mediated isomerization of an allylic epoxide followed by a low-temperature alkoxide-accelerated 1,5-hydrogen migration.

The ingenane diterpenes continue to attract the attention of synthetic chemists worldwide as a result of their potent biological activity and novel structural features.[1] Ingenol (**1**), the parent compound in this series, has yet to succumb to total synthesis.[2] One of the principal challenges facing any synthetic entry into these compounds is the construction of the highly strained *trans*-intrabridgehead stereochemical relationship at the bicyclo[4.4.1]undecanone BC ring substructure.[3]

We have previously reported that this challenging stereochemical feature of ingenol can be established by what is, in essence, an isomerization from the relatively unstrained and readily accessible out,out-bicyclo[4.4.1] undecane system, displaying an α-H substituent at C-8, into a compound possessing the corresponding *β*-H (Scheme 1).

Scheme 1



This ostensibly contra-thermodynamic interconversion was achieved by employing a rarely used alkoxide-accelerated 1,5-H shift[4] to deliver the requisite proton intramolecularly

(1) (a) Hecker, E. *Pure Appl. Chem.* **1977**, *49*, 1423. (b) Sorg, B.; Schmidt, R.; Hecker, E. *Carcinogenesis* **1987**, *8*, 1. (c) Fujiwara, M.; Ijichi, K.; Tokuhisa, K.; Katsuura, K.; Shigeta, S.; Konno, K.; Wang, G.-Y.; Uemura, D.; Yokota, T.; Baba, M. *Antimicrob. Agents Chemother.* **1996**, *40*, 271. (d) Haslar, C. M.; Acs, G.; Blumberg, M. *Cancer Res.* **1992**, *52*, 202. (e) Yamaguchi, K.; Uemura, D.; Tsuji, T.; Kondo, K. *Biosci. Biotechnol. Biochem.* **1994**, *9*, 1749. (f) Blanco-Molina, M.; Tron, G. C.; Macho, A.; Lucena, C.; Calzado, M. A.; Muñoz, E.; Appendino, G. *Chem. Biol.* **2001**, *8*, 767.

(2) (a) For recent advances in the synthesis of these natural products, see: Kim, S.; Winkler, J. D. *Chem. Soc. Rev.* **1997**, *26*, 387. (b) Rigby, J. H. In *Studies in Natural Products Chemistry;* Rahman, A.-U., Ed.; Elsevier: Amsterdam, 1993; Vol. 12 (Part H), pp 233−274. (c) Tang, H.; Yusuff, N.; Wood, J. L. *Org. Lett.* **2001**, *10*, 1563.

(3) The ring strain for these systems has been estimated to be between 3.3 and 10 kcal/mol: (a) Funk, R. L.; Olmstead, T. A.; Parvez, M. *J. Am. Chem. Soc.* **1988**, *110*, 3298. (b) Winkler, J. D.; Henegar, K. E.; Hong, B.-C.; Williard, P. G. *J. Am. Chem. Soc.* **1994**, *116*, 4183.

(4) Paquette, L. A.; Crouse, G. D.; Sharma, A. K. *J. Am. Chem. Soc.* **1980**, *102*, 3972.

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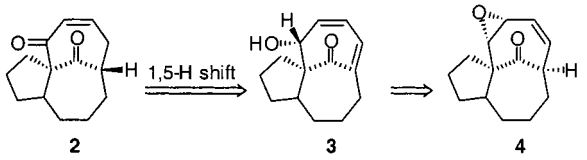
via what is presumably a suprafacial process with a substantial thermodynamic driving force (Scheme 2).[5]

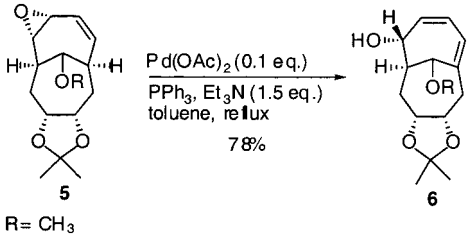
Scheme 2



We now wish to disclose a much improved method for achieving this overall transformation, which exploits an intriguing Pd-promoted isomerization of an allylic epoxide into the dienol function required for sigmatropic rearrangement.[5b]

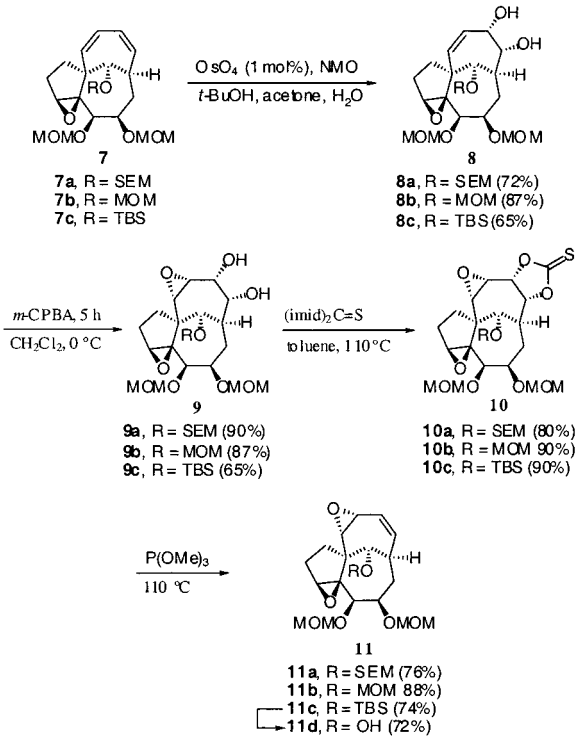
Initial studies, performed on a bicyclic model system, were predicated on the notion promulgated by Takacs, Andersson, and others that stereospecific *anti*-elimination of a LnPd(X)-H fragment from a π-allyl-Pd intermediate could be effected in the presence of base.[6] Early experiments from our laboratory revealed that catalytic $Pd(OAc)_2$ in the presence of a mild base (Et_3N) could indeed effect the desired isomerization to afford dienol **6**[7] with reasonable efficiency (Scheme 3).

Scheme 3



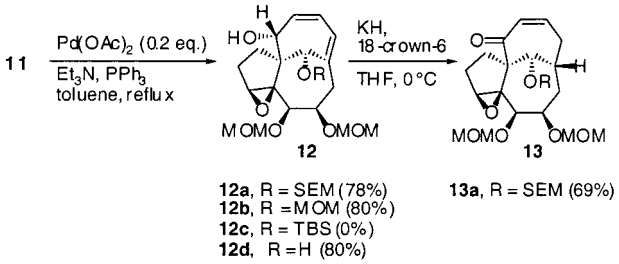
When this set of conditions was applied to structurally more elaborate tricyclic substrates, a number of interesting and relevant observations were made. It should be noted at this juncture that these investigations were prompted by the need to achieve an epoxide opening reaction chemoselectively at an allylic epoxide in the presence of an isolated oxirane located elsewhere in the tricycle. Epoxide **11**, required for this study, was prepared, starting from diene **7**,[5] following a simple sequence of steps: dihydroxylation, epoxidation, followed by a Corey-Winter olefination (Scheme 4).[8]

Scheme 4



When compounds **11a,b,d**[7,8] were exposed to the palladium-mediated isomerization conditions, the desired dienols **12a,b,d**[7] were obtained in quite good yields (Scheme 5).[9]

Scheme 5



No products derived from reaction at the other epoxide were observed. Quite surprisingly, compound **11c** failed to react even in the presence of stoichiometric $Pd(OAc)_2$ under more forcing conditions. This lack of reactivity is attributed to C-ring conformational changes induced by the bulky and quite congested TBS group located at C-9. In contrast, the reaction has been successfully performed with **11a** on scales

(5) (a) Rigby, J. H.; De Sainte Claire, V.; Cuisiat, S. V.; Heeg, M. J. *J. Org. Chem.* **1996**, *61*, 7992. (b) Rigby, J. H.; Hu, J.; Heeg, M. J. *Tetrahedron Lett.* **1998**, *39*, 2265.

(6) (a) Takacs, J. M.; Lawson, E. C.; Clement, F. *J. Am. Chem. Soc.* **1997**, *119*, 5956. (b) Schwarz, I.; Braun, M. *Chem. Eur. J.* **1999**, *5*, 2300. (c) Andersson, P. G.; Schab, S. *Organometallics* **1995**, *14*, 1. (d) Takahashi, T.; Nakagawa, N.; Minoshima, T.; Yamada, H.; Tsuji, J. *Tetrahedron Lett.* **1990**, *30*, 4333.

(7) These compounds exhibited structural (IR, ^{1}H NMR, ^{13}C NMR) and analytical (combustion analyses and/or HRMS) data fully consistent with the assigned structures.

(8) Corey, E. J.; Winter, R. A. E. *J. Am. Chem. Soc.* **1963**, *85*, 2677.

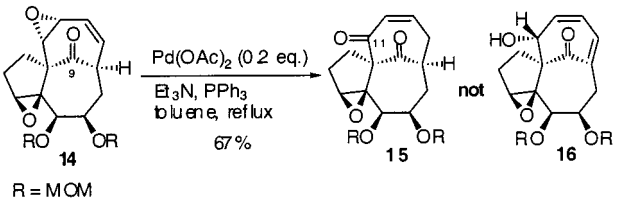
(9) The reaction of **7b** was conducted in THF rather than toluene with no deleterious effects.

up to 1.4 g, and the product **12a**[7] has been smoothly converted into the requisite *trans*-intrabridgehead system **13a**[7] using our previously reported conditions.[5]

In a noteworthy observation, compound **14**, which possesses a carbonyl group at C-9, gave a product that appears to stem from an entirely different reaction channel than the one followed by the other compounds in this study. Indeed, compound **15**[7] was produced to the complete exclusion of the expected product **16**. In this case, it appears that the H-elimination has occurred at the alkoxide center (C-11) to initially provide the corresponding enolate, which gave the ketone after protonation. Alkene conjugation completed the process. Products of this nature have been observed previously by Noyori[10a] and Radinov,[10b] but not normally in the presence of a base. We did not observe this type of product in any other situation during our study and attribute it to conformational and ring strain changes in going from sp^3 hybridization at C-9 in **11a,b,d** to the corresponding sp^2 hybridized carbon in compound **14**.

The intriguing result depicted in Scheme 6 prompted a

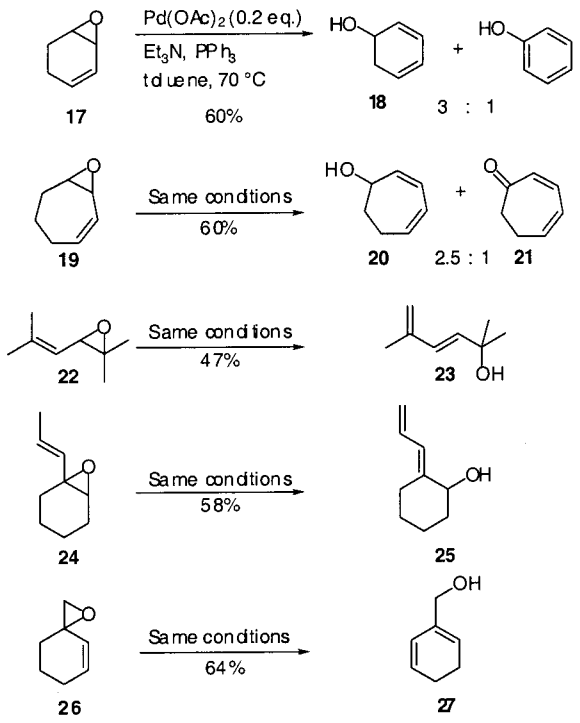
Scheme 6



further investigation into the course of these reactions in simpler systems that lack the geometrical constraints present in the bicyclic and tricyclic systems. The results are presented in Scheme 7.[11] It is noteworthy that in each case the standard isomerization conditions afforded the expected dienol products rather than the alternative ketone products, so it would appear that the observations made with compound **14** represent an exceptional pathway in the presence of base.

The results with substrates **17** and **19**, in particular, contrast sharply with observations made by Noyori in his earlier work

Scheme 7



in the same area.[10a] Once again, these differences can be traced to the presence of base, a reagent absent from the Noyori reactions. The production of phenol and cycloheptadienone in these reactions as minor side products is presumably due to a small amount of air oxidation of the corresponding dienols, a reaction known to be facilitated by the presence of $Pd(OAc)_2$.[12]

In summary, Pd-mediated isomerization of allylic epoxides to dienols can be effected in the presence of mild bases such as Et_3N and can provide for an efficient and chemoselective method for accessing the highly strained *trans*-intrabridgehead stereochemical relationship in the ingenane diterpenes.

Acknowledgment. The authors thank the National Institutes of Health (grant CA-36543) for financial support of these investigations.

Supporting Information Available: Experimental procedures, full characterization and spectra for compounds **7a**−**13a** and experimental procedure and full characterization for compound **15**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL017280N

(10) (a) Suzuki, M.; Oda, Y.; Noyori, R. *J. Am. Chem. Soc.* **1979**, *101*, 1623. (b) More recently: Kabat, M. M.; Garofalo, L. M.; Daniewski, A. R.; Hutchings, S. D.; Liu, W.; Okabe, M.; Radinov, R.; Zhou, Y. *J. Org. Chem.* **2001**, *66*, 6141.

(11) **General Procedure for Pd-Mediated Isomerization of Allylic Epoxide.** A solution of freshly distilled and degassed toluene (15 mL) and starting material (100 mg) was introduced at room temperature to a two-neck round-bottom flask, equipped with a condenser, that contained $Pd(OAc)_2$ (0.2 equiv) and PPh_3 (0.4 equiv). Triethylamine (1.5 equiv) was added at room temperature, and the solution was heated at reflux for 15 min. After completion of the reaction, as judged by TLC analysis, the solution was cooled, filtered, and concentrated under reduced pressure and the crude product was purified by flash chromatography (hexanes/ethyl acetate, 4:1).

(12) Kakiuchi, N.; Maeda, Y.; Nishimura, T.; Uemura, S. *J. Org. Chem.* **2001**, *66*, 6620.