Synthetic Studies on the Ingenane Diterpenes. Direct Conversion of the *out,out*-Bicyclo[4.4.1]undecane System into a Highly Strained In,out Stereoisomer

James H. Rigby,* Valérie de Sainte Claire, Stephane V. Cuisiat, and Mary Jane Heeg[1]

Department of Chemistry, Wayne State University, Detroit, Michigan 48202-3489

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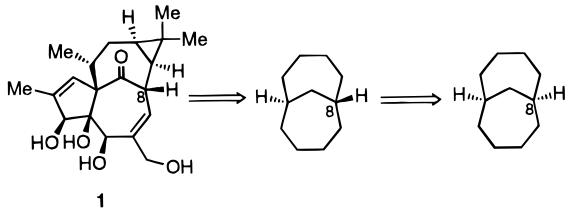
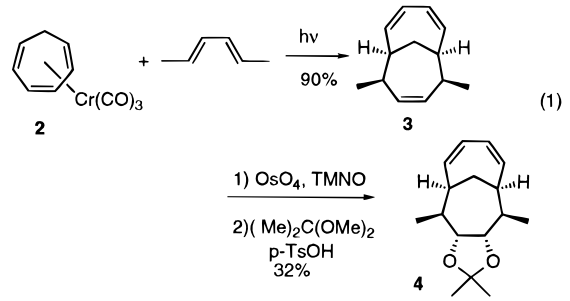
The ingenane diterpenes are a group of highly oxygenated esters isolated from the genus *Euphorbia*, many of which have been found to exhibit potent tumor-promoting properties.[2] As a consequence of this activity, these compounds have recently come under intense scrutiny in connection with studies on the molecular basis of carcinogenesis.[3] The structural complexity of the parent diterpene, ingenol (**1**), from which these compounds are derived, has prompted extensive synthetic investigations as well.[4] While introduction of the various substituents situated along the southern perimeter of **1** clearly represents a synthetic challenge, a more significant obstacle to total synthesis is the construction of the bicyclo[4.4.1]undecane BC ring substructure possessing a highly strained inside, outside intrabridgehead stereochemical relationship. To date, only two approaches have emerged for addressing this crucial synthetic issue.[5] Winkler was the first to construct an *in,out*-ingenane tricyclic system by employing an intramolecular dioxenone photocycloaddition sequence.[6] Subsequently, Funk and co-workers reported the synthesis of the most advanced ingenol intermediate yet prepared by exploiting a novel macrocyclic Claisen rearrangement protocol for setting the *trans*-intrabridgehead stereochemistry.[7] In this paper, we report a fundamentally different solution to the in,out-stereochemical problem by, in essence, *isomerizing* a readily available *out,out*-bicyclo[4.4.1]-undecane species (*cis*-intrabridgehead stereochemistry)[8]

Scheme 1



into one displaying the considerably more strained in,-out-bridging relationship (Scheme 1).[9]

From the outset of this investigation it was recognized that the ring strain present in the *trans*-bridged bicycle would demand an intramolecular delivery strategy for incorporating the β-hydrogen required at the C-8 (ingenol numbering) bridgehead position of the target system. It was anticipated that rapid entry into the requisite *out,out*-bicyclo[4.4.1]undecane isomer could be realized by employing a metal-promoted [$6\pi + 4\pi$] cycloaddition,[10] and the well-established facial bias characteristic of these ring systems[4] would then be exploited for affixing the necessary substitution for internal delivery of the C-8 hydrogen with the proper spatial orientation. [1,5]-Hydrogen sigmatropy was selected for this task.



Chromium(0)-mediated higher-order cycloaddition between complex **2** and 2,4-hexadiene afforded bicyclo[4.4.1]-undecane **3**,[11] which was produced as a single (endo) diastereomer in excellent yield and possessed the necessary *cis*-intrabridgehead stereochemistry. To minimize subsequent complications, routine *cis*-dihydroxylation was performed on the more accessible exo-surface of the isolated alkene in **3** to provide compound **4**[11] after protection of the resultant diol as the corresponding acetonide.

Next, exo-face selective epoxidation of **4** afforded **5**[11] in nearly quantitative yield, and regioselective lithium amide-mediated epoxide opening followed to provide

(1) Author to whom all inquiries regarding the X-ray determinations should be addressed.

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(7) (a) Funk, R. L.; Olmstead, T. A.; Parvez, M. *J. Am. Chem. Soc.* **1988**, *110*, 3298. (b) Funk, R. L.; Olmstead, T. A.; Parvez, M.; Stallman, J. B. *J. Org. Chem.* **1993**, *58*, 5873.

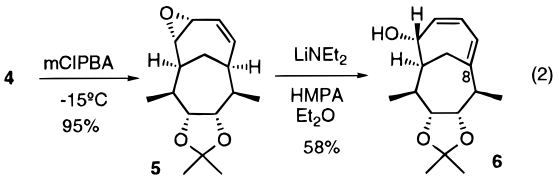
(8) For recent approaches to 8-isoingenol, possessing the out,out intrabridgehead stereochemistry, see: (a) Paquette, L. A.; Nitz, T. J.; Ross, R. J.; Springer, J. P. *J. Am. Chem. Soc.* **1984**, *106*, 1446. (b) Rigby, J. H.; Moore, T. L.; Rege, S. *J. Org. Chem.* **1986**, *51*, 2398. (c) Funk, R. L.; Bolton, G. L. *J. Am. Chem. Soc.* **1986**, *108*, 4655. (d) Ross, R. J.; Paquette, L. A. *J. Org. Chem.* **1987**, *52*, 5497. (e) Mehta, G.; Pathak, V. P. *J. Chem. Soc., Chem. Commun.* **1987**, 876. (f) Paquette, L. A.; Ross, R. J.; Springer, J. P. *J. Am. Chem. Soc.* **1988**, *110*, 6192. (g) Rigby, J. H.; Cuisiat, S. V. *J. Org. Chem.* **1993**, *58*, 6286. (h) Harmata, M.; Elahmad, S.; Barnes, C. L. *Tetrahedron Lett.* **1995**, *36*, 1397.

(9) Estimates of the difference in strain energy between the out,-out and in,out isomers of the parent bicyclo[4.4.1]undecane vary between 6.3 kcal/mol[7a] and 10 kcal/mol.[6c] Ingenol was calculated to be 5.9 kcal/mol more strained than 8-isoingenol.[7a]

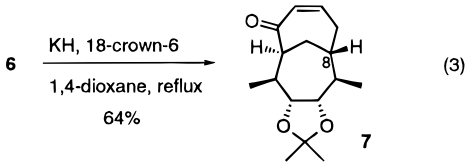
(10) (a) Rigby, J. H. *Acc. Chem. Res.* **1993**, *26*, 579. (b) Rigby, J. H.; Sugathapala, P.; Heeg, M. J. *J. Am. Chem. Soc.* **1995**, *117*, 8851. (c) Rigby, J. H.; Niyaz, N. M.; Short, K.; Heeg, M. J. *J. Org. Chem.* **1995**, *60*, 7720.

(11) This compound exhibited (^{1}H NMR, ^{13}C NMR, IR) and analytical (combustion analysis and/or HRMS) data fully consistent with the assigned structure.

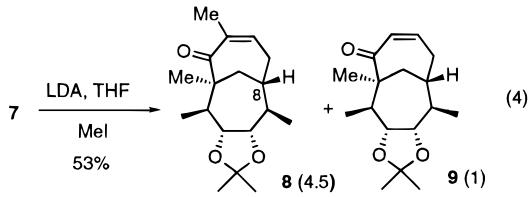
S0022-3263(96)01714-8 CCC: $12.00



exclusively the dienol **6**.[11,12] This series of steps efficiently installs the key bridgehead double bond required for introduction of the β-hydrogen in the target system. The origin of the unusual regioselectivity in this elimination process appears to derive from a conformational effect in the bicyclo[4.4.1]undecane system that forces the proximate bridgehead proton out of proper stereoelectronic alignment for participation in the ring-opening event.



Sigmatropic rearrangement was viewed as an ideal method for delivering the β-H to the bridgehead position with control of stereochemistry, and an alkoxide-accelerated version of this reaction was employed for this purpose.[13] In the event, heating **6** in the presence of KH and 18-crown-6 resulted in the formation of an enone, **7**[11,14] in which the β-proton on the alkoxide carbon was transferred with complete retention of stereochemistry to the opposite bridgehead position as revealed by single-crystal X-ray analysis of the product. Not only does this protocol rapidly and efficiently provide bicyclo[4.4.1]-undecane systems possessing the inside, outside ring topology, it also represents the first example that we are aware of in which the stereochemical course of *alkoxide-accelerated* [1,5]-hydrogen sigmatropy has been shown to be suprafacial in nature.[15]



To extend this methodology to the synthesis of the ingenane ring system itself would require modification of the substitution pattern on the bicyclic moiety as well as the introduction of a carbon substituent at the bridgehead position exhibiting "outside" stereochemistry. The presence of the carbonyl function in **7** suggested enolate alkylation as a possible tactic for this carbon–carbon bond installation, and inspection of models indicated that the bridgehead proton was appropriately aligned with the carbonyl π system for deprotonation to occur. Previously, we have demonstrated that bridgehead enolates in the less strained bicyclo[4.4.1]undecane system are well-behaved,[16] and it would be instructive to see if this trend extended to the in,out isomeric series as well. Thus, treatment of **7** with excess LDA followed by quenching with excess methyl iodide afforded the bismethylated bicyclic product **8**[11,14,17] along with lesser amounts of the monoalkylated product **9**[11] *without loss of the in,out intrabridgehead stereochemical relationship in either compound!* This result was expected, however, since epimerization at the bridgehead position adjacent to the carbonyl group in compound **7** (the "out" center) would lead to the even more strained in,in-bicyclic stereochemistry. It is also noteworthy that no material methylated only on the enone was generated in this reaction. Formation of bridgehead alkylated products will be optimized on intermediates more relevant to the ingenol target.

In summary, we have developed a strategy for the direct transformation of a readily available *out,out*-bicyclo[4.4.1]undecane system into the much more strained in,out isomer by exploiting the facial biases inherent in the former series to deliver the requisite "inside" bridgehead hydrogen through the stereocontrol afforded by [1,5]-hydrogen sigmatropy.

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Supporting Information Available: Typical experimental procedures and complete spectroscopic data for all new compounds (9 pages).

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(14) The structure of this compound was determined by single-crystal X-ray analysis.

(15) The neutral version of this rearrangement has been shown to proceed in a suprafacial fashion: Eggert, U.; Stohrer, I.; Hoffmann, H. M. R. *Tetrahedron Lett.* **1992**, *33*, 3465.

(16) Rigby, J. H.; Moore, T. L. *J. Org. Chem.* **1990**, *55*, 2959.

(17) The author has deposited atomic coordinates for **7** and **8** with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.