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Rate Acceleration of Anionic Oxy-Cope Rearrangements Induced by an Additional Unsaturation

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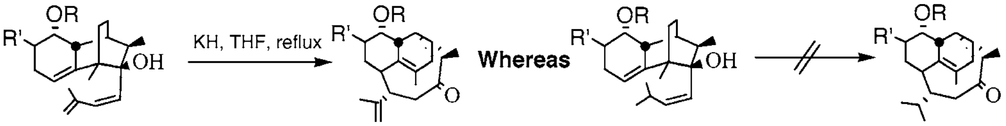
ABSTRACT

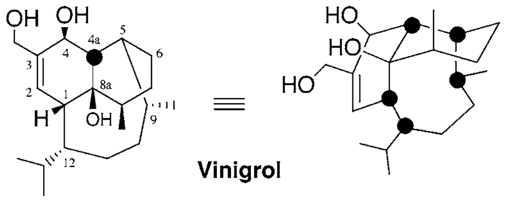


In sharp contrast to their isopropyl counterparts, a variety of (*Z*)-isopropenyl tertiary bicyclo[2.2.2]octenols undergo facile anionic oxy-Cope rearrangements allowing the stereoselective incorporation of an isopropenyl group into polycyclic skeletons such as the tricyclic system of vinigrol, bicyclo[5.3.1]undecane, and *cis*-decalin frameworks. This rate acceleration is probably due to the stabilization of the transition state by the additional unsaturation on the terminal position.

Since the discovery by Evans and co-workers that oxy-Cope rearrangements are greatly accelerated (by a factor of up to 10^{17}!) by conversion into the respective potassium alkoxides,[1,2] this reaction has emerged as a highly useful tool for the construction of complex organic molecules. Various 1,5-hexadien-3-ols readily undergo this electronic reorganization, and their usually easy preparation contributes to the popularity of this reaction. A particularly advantageous feature of this process is that it proceeds under mild conditions, so that many sensitive functional groups are tolerated.[3]

Very early on, substituent effects were observed. While sulfur-substituted diene alkoxides undergo the rearrangement under very mild conditions,[4] the presence of bulky alkyl groups on the termini positions may completely impede the transposition. For instance, crowded substituted dienes are unreactive under typical anionic oxy-Cope conditions. Under rather vigorous conditions, they lead to fragmentation products. This competing process is a consequence of the steric strain encoutered during the mutual approach of the two trigonal centers to reach the transition state.[2,5]

A recent report from our laboratory described an efficient entry into the fully elaborated skeleton of vinigrol. A particulary advantageous feature of this synthesis is the installation of the desired stereochemistry at C(12) and the construction of the eight-membered ring *in one operation* via an anionic oxy-Cope rearrangement.



Vinigrol

In the course of this study, we found that (*Z*)-isopropenyl isomer **1**, in sharp contrast to its isopropyl counterpart **3**, underwent a remarkably facile anionic oxy-Cope rearrange-

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(1) Evans, D. A.; Golob, A. M. *J. Am. Chem. Soc.* **1975**, *97*, 4765−4766.

(2) For a review on anion-assisted sigmatropic rearrangements, see: Wilson, S. *Org. React*. **1993**, *43*, 93−250.

(3) For reviews, see: Paquette, L. A. *Angew. Chem., Int. Ed. Engl*. **1990**, *29*, 609−626. Paquette, L. A. *Tetrahedron* **1997**, *53*, 13971−14020.

(4) (a) Evans, D. A.; Baillargeon, D. J.; Nelson, J. V. *J. Am. Chem. Soc.* **1978**, *100*, 2242−2243. (b) Paquette, L. A.; Wang, H.-L.; Zeng, Q.; Shih, T.-L. *J. Org. Chem.* **1998**, *63*, 6432−6433. (c) Paquette, L. A.; Reddy, Y. R.; Vayner, G.; Houk, K. N. *J. Am. Chem. Soc.* **2000**, *122*, 10788−10794.

(5) (a) Gregson, R. P.; Mirrington, R. N. *Aust. J. Chem.* **1976**, *29*, 2037−2048. (b) Koreeda, M.; Tanaka, Y.; Schwartz, A. *J. Org. Chem.* **1980**, *45*, 1172−1174.

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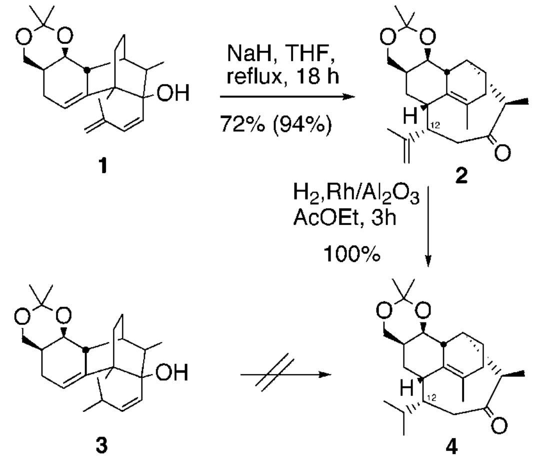
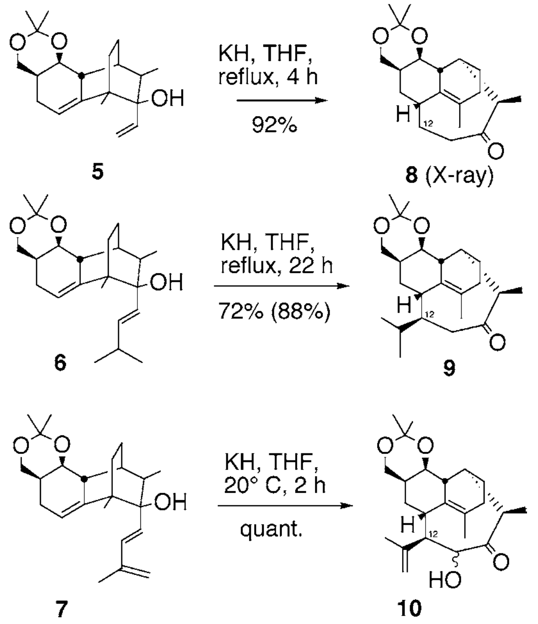
Scheme 1



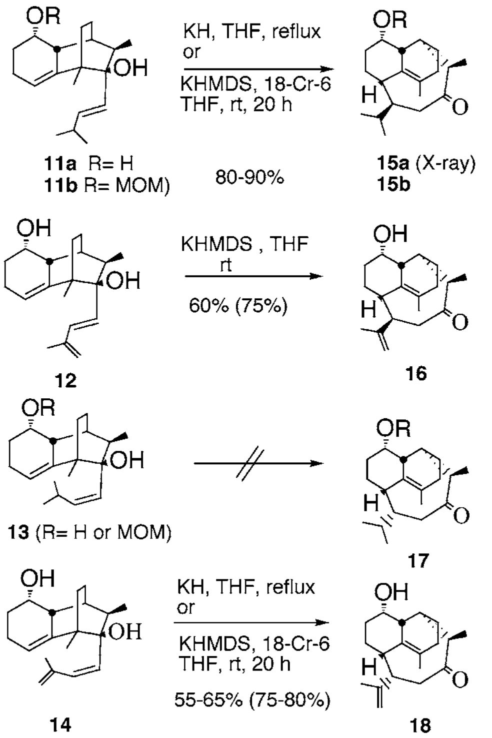
ment, affording **2** in high yield (Scheme 1). In this reaction the potassium salt is not even required: simply heating **1** and NaH in THF for 18 h[6] cleanly produced **2** with high reproducibility.[7]

To assess the effect of the additional unsaturation, allylic alcohols **5**−**7**[8] were submitted to the rearrangement conditions. While the potassium salts of **5** and **6** required refluxing temperature in order to rearrange into **8** and **9**, respectively, the isopropenyl derivative **7** completely isomerized *in 2 h at room temperatur*e to give **10**[9] in quantitative yield (Scheme 2).[10]

Scheme 2

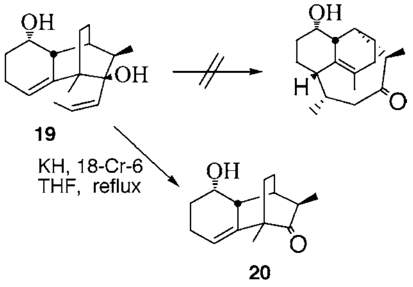


Scheme 3



Next, the anionic oxy-Cope rearrangement of compounds **11**−**14**[8] was examined. The results are shown in Scheme 3. As for the acetonide series, the presence of an additional double bond greatly facilitated the transposition. For intance, the potassium salt of **12** did not require the presence of 18-crown-6 in order to rearrange at room temperature, giving **16** in good yield.[11] As expected, (*Z*)-isopropenyl isomer **14** underwent the [3,3] sigmatropic rearrangement under much harder conditions, affording **18** in good yield. It is worthy of note that all attempts at oxy-Cope rearrangement on **13** failed.

Scheme 4



To rule out the possibility that the difference of reactivity between these compounds and their isopropyl analogues is primarily steric in nature, we prepared allylic alcohol **19** (Scheme 4). We assumed that this substrate, in which the isopropenyl group was replaced by a methyl group, has a

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(6) It was shown by Evans and co-workers[1] that the magnitude of the rate acceleration was directly related to the degree of alkoxide-metal dissociation, with maximum acceleration obtained with a more "naked anion". Thus, under identical conditions, the potassium alkoxide rearranged at a much greater rate than sodium alkoxide.

less sterically hindered allylic group. Treatment of **19** under the same conditions used for the rearrangement of **14** failed to give the rearranged product, and the starting alcohol remained unchanged. Under more vigorous conditions (KH, 18-crown-6, THF, reflux, 15 h) this compound underwent fragmentation leading to ketone **20**.[12] This result lends support for an electronic effect underlying the rate acceleration of the rearrangement.

The heightened tendency for oxy-Cope rearrangement shown by isopropenyl derivatives, in comparison to their isopropyl counterparts, is probably the result of stabilization of the transition state by the additional unsaturation on the terminal position (Figure 1).[13]

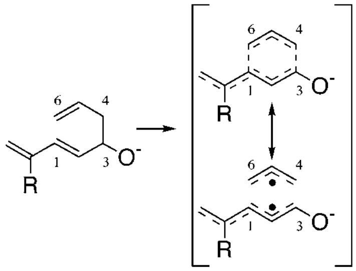
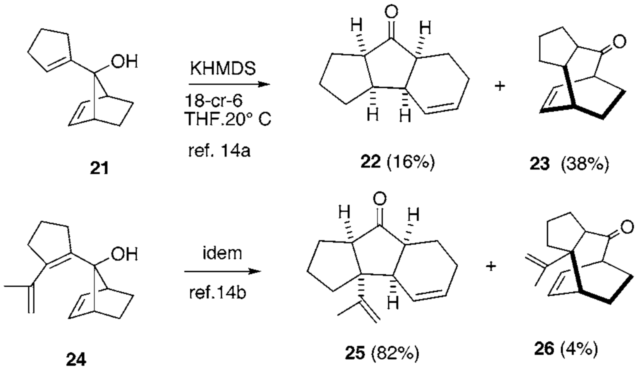


Figure 1.

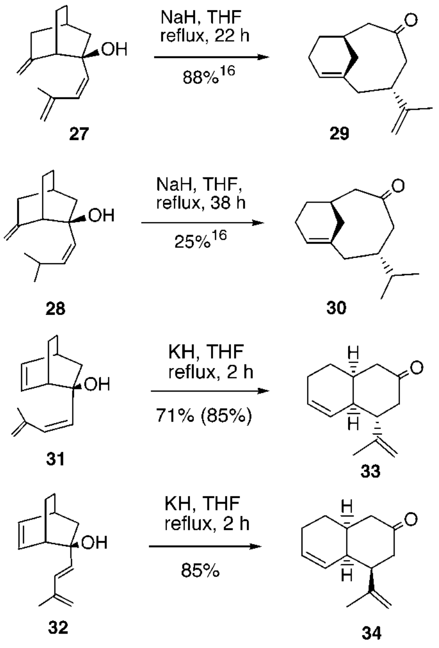
To our knowledge, only one example of such an effect has hitherto been reported, by Paquette and co-workers, in the rearrangement of allylic alcohols prepared from bicyclo[2.2.1]heptenones (Scheme 5).[14] Whereas **21** isomerized to give the [1.3] sigmatropic rearrangement product **23** as the major component, under the same conditions, **24** underwent almost exclusively the anionic oxy-Cope rearrangement producing **25** in 82%.

Scheme 5



To gain further insight into this effect, we have designed substrates allowing the stereoselective incorporation of isopropenyl substituent into bicyclo[5.3.1]undecane and *cis*-decalin frameworks. To this end, anionic oxy-Cope rearrangement of **27** and **28** was examined (Scheme 6).[15] Heating a solution of (*Z*)-isopropenyl isomer **27** in THF at reflux in the presence of sodium hydride for 22 h resulted in a smooth rearrangement to give bicyclo[5.3.1]undecenone **29** in 88% yield.[16] Under the same conditions, the (*Z*)-isopropyl analogue **28** underwent only 25% conversion even after 38 h, affording the isopropyl derivative **30**.

Scheme 6



Finally, the stereoselective incorporation of an isopropenyl group into the *cis*-decalin system was considered. The synthesis of such a framework having stereochemically

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(7) Gentric, L.; Hanna, I.; Ricard, L. *Org. Lett.* **2003**, *5*, 1139−1142.

(8) Details concerning the preparation of the starting allylic alcohols used in this Letter will be given in due course.

(9) Formation of hydroxyketone **10** resulted from in situ over-oxidation of the enolate formed as a result of the oxy-Cope process. See for example: Paquette, L. A.; De Russy, N. T.; Pegg, N. A.; Taylor, R. T.; Zydowsky, T. M. *J. Org. Chem.* **1989**, *54*, 4576−4581 and references therein.

(10) Satisfactory spectral and analytical data were obtained for all new compounds.

(11) Stereochemistry of the isopropenyl group in **16** was ascertained by comparison with **15**: catalytic hydrogenation of **16** provided **15** in which the relative configuration of the isopropyl group was determined by X-ray crystallographic analysis.

(12) For a similar fragmentation, see ref 5b.

(13) For theoretical studies of the effects of vinyl substitution on the Cope rearrangements of 1,5-hexadienes, see: Hrovat, D. A.; Beno, B. R.; Lange, H.; Yoo, H.-Y.; Houk, K. N.; Borden W.; T. *J. Am. Chem. Soc.* **1999**, *121*, 10529−10537.

(14) (a) Paquette, L. A.; Pierre, F. Cottrel, C. E. *J. Am. Chem. Soc.* **1987**, *109*, 5731−5740. (b) Paquette, L. A.; DeRussy, D. T.; Rogers, R. D. *Tetrahedron* **1988**, *44*, 3139−3148.

(15) For related rearrangements of substituted bicyclo[2.2.2]octadienols to the AB-ring system of taxoids, see: (a) Martin, S. F.; Assercq, J.-M.; Austin, R. E.; Dantanarayama, A. P.; Fishpaugh, J. R.; Gluchowski, C.; Guinn, D. E.; Hartmann, M.; Tanaka, T.; Wagner, R.; White, J. B. *Tetrahedron* **1995**, *51*, 3455−3482. (b) Banwell, M. G.; Darmos, P.; McLeod, M. D.; Hockless, D. C. R. *Synlett* **1998**, 897−899.

(16) Yields were determined by ^{1}H NMR.

defined substituents is of great interest due to its presence as a substructure in many natural products.[17] Both (*E*)- and (*Z*)-isopropenyl-substituted isomers **31** and **32** were prepared and subjected to the rearrangement. Treatment of **31** with KH in refluxing THF for 2 h, led to *cis*-decalone **33** in 71% yield along with recoverd starting alcohol (14%). Under the same conditions, (*E*)-isomer **32** was completely converted into the epimeric isopropenyl derivative **34**.[18] Worthy of note is that treatment of either **31** or **32** with NaH in refluxing THF, even for a prolonged period of time, left them intact (Scheme 6).

In conclusion, we have established that, in contrast to their isopropyl counterparts, a variety of (*Z*)-isopropenyl tertiary bicyclo[2.2.2]octenols undergo facile anionic oxy-Cope rearrangements and can be used for the stereoselective incorporation of an isopropyl group. We clearly demonstrated that extension of the allylic chain into a conjugated dienyl unit greatly facilitates anionic oxy-Cope rearrangements. This effect may be explained in terms of stabilization of the transition state by the additional vinyl group.

Acknowledgment. We gratefully thank Professor Thierry Prangé (Université de Paris Nord) and Dr. Louis Ricard (Ecole Polytechnique) for the X-ray structure determination of compounds **8** and **15a**.

Supporting Information Available: Characterization data for compounds **8−10**, **15−18**, and **29−34**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) To our knowledge, only one example of thermal oxy-Cope rearrangement on isopropyl-substituted bicyclo[2.2.2]octenols has hitherto been reported. See ref 5a. Whereas the (*E*)-isomer underwent the transposition leading to a β-isopropyl *cis*-decalone, attempts to synthesize its α-epimer from the (*Z*)-isomer failed. Under the same conditions, this substrate only afforded aromatic compounds.

(18) High volatility of both epimers **33** and **34** contributed to material losses when care was not taken during their isolation. Examination of the spectal data of these epimers revealed appreciable changes. In particular, in ^{1}H and ^{13}C NMR spectra, signals of the methylene group located between the carbonyl and isopropenyl groups are shifted downfield for **33** with respect to its epimer. On the other hand, the infrared spectra showed carbonyl absorptions at 1705 and 1718 cm^{-1} for **33** and **34**, respectively (see Supporting Information).