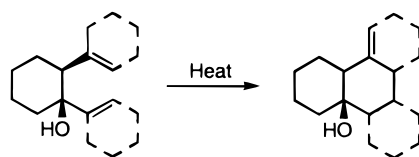


Tandem Oxy-Cope/Transannular Ene
Reaction of 1,2-DivinylcyclohexanolsJeffrey M. Warrington, Glenn P. A. Yap,[†] and Louis Barriault*Department of Chemistry, University of Ottawa, 10 Marie Curie,
Ottawa, Ontario, Canada, K1N 6N5

lbarriau@science.uottawa.ca

Received January 2, 2000

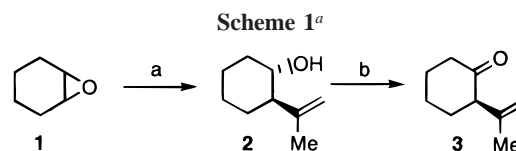
ABSTRACT



The syntheses via tandem oxy-Cope/transannular ene reaction of 1,2-divinylcyclohexanols to bi- and tricyclic skeletons are described. This strategy generates a rapid method for the preparation of advanced polycyclic intermediates with high diastereoselectivity.

Tandem reaction strategies have emerged as powerful methods for the formation of new carbon–carbon bonds.¹ The tandem combination oxy-Cope/transannular ene has been observed accidentally by Sutherland et al. as an undesired side reaction of the oxy-Cope rearrangement.² It was also reported by Paquette³ and Rajagopalan⁴ that the transannular ene reaction byproducts occurred in some cases during the anionic oxy-Cope rearrangement. Thus, the tandem oxy-Cope/ene reaction reveals a reliable method to rapidly obtain polycyclic structures with a tertiary alcohol at the ring junction. To demonstrate its feasibility, we have investigated this tandem combination using different 1,2-divinylcyclohexanols.

The synthesis started with the epoxide opening⁵ of cyclohexene oxide **1** with isopropenylmagnesium bromide and a catalytic amount of CuBr–DMS in THF to afford cyclohexanol **2** in 88% yield (Scheme 1). Oxidation of **2**



^a (a) CH₂=C(CH₃)MgBr, CuBr–DMS in THF, –30 °C to rt, 88%; (b) (COCl)₂, DMSO in CH₂Cl₂, –78 °C then Et₃N, 80%.

using the Swern method⁶ gave ketone **3** in 80% yield. 1,2-Divinylcyclohexanols **4** and **5** were obtained as single diastereoisomers in good yields by treatment of ketone **3** with vinylmagnesium bromide and isopropenylmagnesium bromide in THF at –78 °C (Scheme 2).

Alkylation of **3** with cyclohexenyllithiums **6**⁷ and **8**⁸ and lithiodihydropyran **10**⁹ in THF at –78 °C furnished the corresponding tertiary alcohols **7**, **9**, and **11** in 50–73% yields as single trans diastereoisomers. Tertiary alcohol **13** was prepared via [1,2]-migration of the chlorohydrin generated from commercially available 2-chlorocyclohexanone **12** in 50% yield.¹⁰ The 1,2-divinylcyclohexanols were heated

[†] To whom X-ray inquiries should be addressed.

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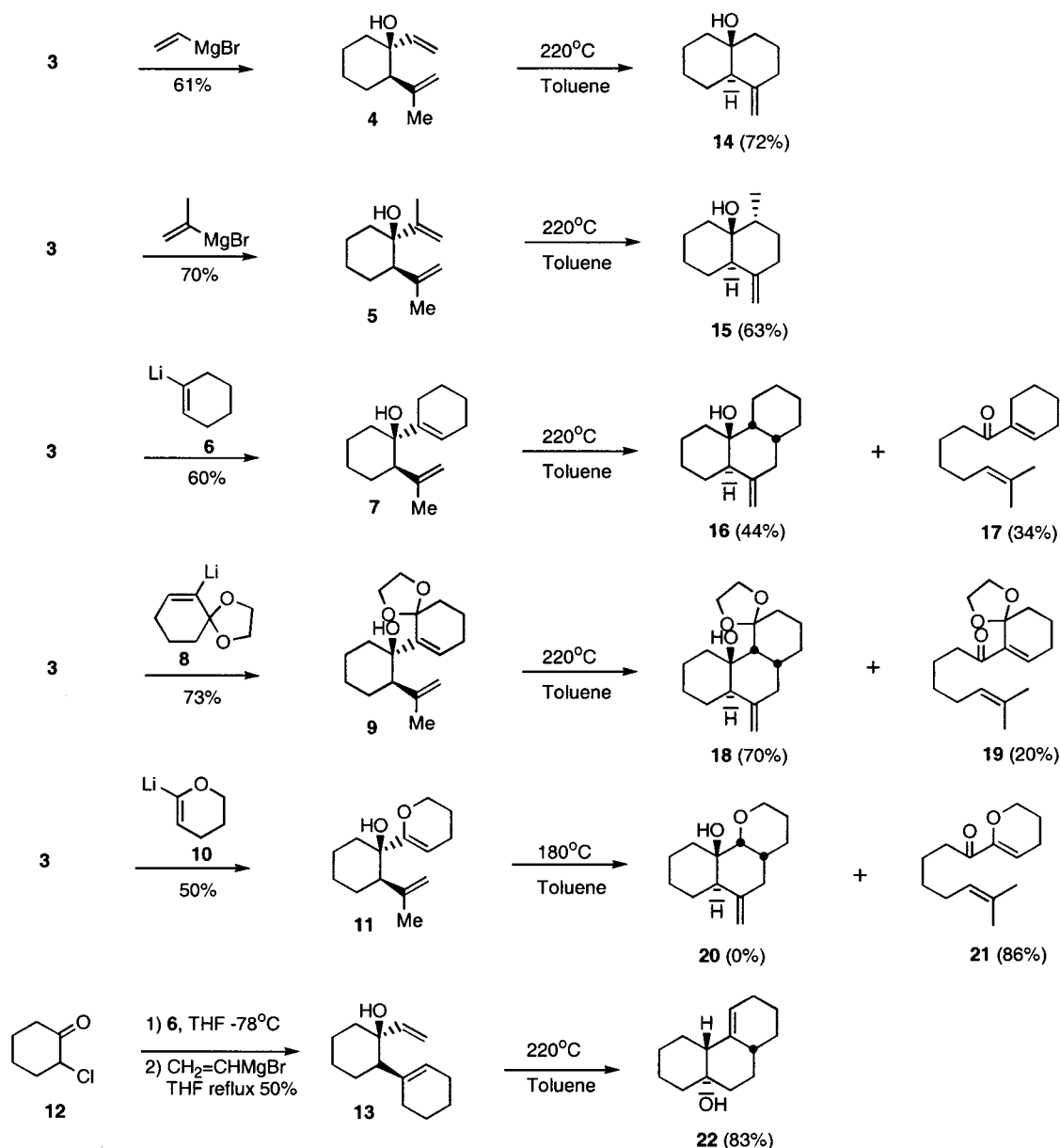
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Scheme 2



in toluene 5 h in a sealed tube, yielding the corresponding cyclic products in 44–86% yields.¹¹ NMR spectroscopy and X-ray analysis established the stereochemistry of the bi- and tricyclic compounds.

The high diastereoselectivity observed in the tandem oxy-Cope/ene reaction can be explained by the proposed mechanism shown in Figure 1. At first glance, the thermal oxy-Cope rearrangement of divinylcyclohexanol **7** affords enol intermediate **23**.

Highly diastereoselective tautomerisation produces, in situ, ketone intermediate **24**, which reacts via transannular ene

reaction to furnish tricycle **16** as a single diastereoisomer. The *E* olefin geometry of ketone **24** secures the exclusive formation of the trans ring junction. Moreover, Terada and Yamamura have demonstrated by computational modeling¹² that the transannular ene reaction adopts a chair-like conformation at the transition state. An examination of the transition states **B** and **C** reveals pseudo-1,3-diaxial methyl–methylene interactions in **B** and a boat-like conformation in transition state **C**. Therefore, transition states **B** and **C** are less favored than **A** and the preferential formation of **16** over **25** is thus readily explained.

However, we isolated unsaturated ketones **17** and **19** as side products in 34% and 20% yields, respectively. Interestingly, 1,2-divinylcyclohexanol **11** heated at 180 °C gave exclusively unsaturated ketone **21** in 86% yield. According

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(11) **Typical procedure:** A solution of **13** (24 mg, 0.12 mmol) in dry toluene (5 mL) was heated in a pressure tube (previously washed with aqueous 2-propanol/NaOH solution, water, and acetone) for 5 h at 220 °C. The tube was cooled to room temperature, and the solution was transferred and concentrated. The residue was purified by flash chromatography (10% ether in hexanes) to give **22** as a colorless oil (20 mg, 83%).

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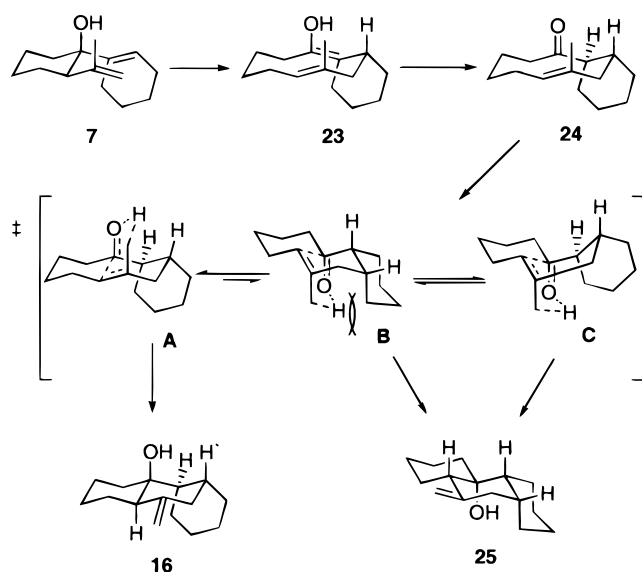


Figure 1. Mechanism and transition state of tandem oxy-Cope/ene reaction.

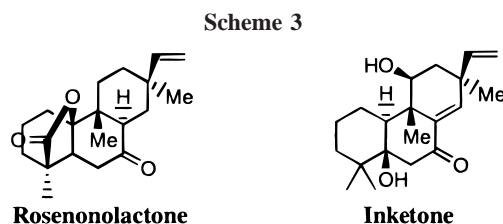
to preliminary results obtained in our laboratory, the electronic density on the olefin influences the ratio of oxy-Cope/ene versus the retroene products. In fact, the retroene pathway is favored when the olefin is electron rich.^{13,14} On the basis of the ratio of tandem versus retroene products depicted in Scheme 2, the cyclic acetal has an effect on the rate formation

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(14) Recently, Paquette et al. reported that alkoxy substituents on the olefin have a deceleration rate effect on the anionic oxy-Cope rearrangement. See: Haeffner, F.; Houk, K. N.; Reddy, R. Y.; Paquette, L. A. *J. Am. Chem. Soc.*, in press.

of tricyclic product. This indicates that the acetal moiety may behave like an electron-withdrawing group and, therefore, increases the yield of tandem oxy-Cope/ene product.

This strategy offers a simple highly diastereoselective method for the synthesis polycyclic structures with a tertiary alcohol at ring junction. Indeed, the synthesis of polycyclic cores **18** and **22** of rosenonolactone¹⁵ and inketone¹⁶ has been achieved in a few steps (Scheme 3). Total synthesis of these molecules is currently in progress.



Acknowledgment. Financial support from the University of Ottawa, Natural Sciences and Engineering Research Council of Canada (undergraduate fellowship to J.M.W.), and La Cité Collégiale d'Ottawa is gratefully acknowledged.

Supporting Information Available: ORTEP view of **15** and X-ray crystallographic data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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