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A Cope Rearrangement-Based Route to Hexahydroazulenes

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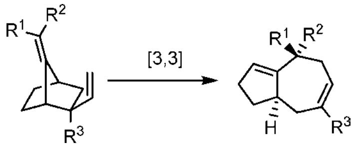
ABSTRACT



2-*exo*-Vinyl-7-alkylidenenorbornanes, readily prepared from fulvene Diels−Alder adducts, undergo smooth Cope rearrangement at elevated temperatures to produce hexahydroazulene derivatives.

The bicyclo[5.3.0]decane (hydroazulene) ring system lies at the heart of a wealth of natural products, including many that are of biological or medicinal interest. A variety of methods for its construction have been described over the years.[1] However, development of new synthetic approaches that would provide easy access to previously unavailable substitution patterns remains an important objective. In this context, we envisioned a structural variant of the Cope rearrangement[2] that remained unexplored in synthesis[3] as the key step in a potentially general strategy for access to the hydroazulene ring system (Figure 1). It was expected that the precursors for this rearrangement (**2a** or **b**) would be readily accessible from Diels−Alder adducts of fulvenes (**3**).[4] In this communication, we report the successful demonstration of this rearrangement in several examples and the preparation of 2-*exo*-vinyl-7-alkylidenenorbornanes (**2b**) by several different methods.

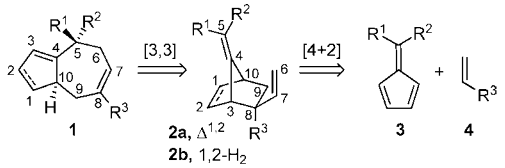


Figure 1. Cope rearrangement approach to hexahydroazulenes.

On undertaking this project, we were initially unsure about the facility of the proposed sigmatropic rearrangement. Inspection of 3D models revealed that overlap of the reacting vinyl termini would require considerable molecular distortion. Therefore, we set out to obtain proof of principle on the most readily available substrate. The thermal instability of Diels−Alder adducts of fulvenes (cf. **2a**)[5] was expected to interfere with the rearrangement step. Therefore, we decided to hydrogenate the endocyclic double bond, removing the possibility of the unwanted retro-Diels−Alder reaction. The

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[1] For a recent review, see: Foley, D. A.; Maguire, A. R. *Tetrahedron* **2010**, *66*, 1131.

[2] (a) Cope, A. C.; Hardy, E. M. *J. Am. Chem. Soc.* **1940**, *62*, 441. (b) For a recent review, see: Mullins, R. J.; McCracken, K. W. In *Name Reactions for Homologations*; Li, J. J., Ed.; Wiley: Hoboken, NJ, 2009; Part 2, pp 88−135.

[3] Structurally analogous Cope rearrangements were invoked in explaining the formation of the observed products in the dimerization and trimerization of dimethylfulvene: (a) Uebersax, M.; Neuenschwander, M.; Engel, P. *Helv. Chim. Acta* **1982**, *65*, 89. (b) Hong, B. C.; Yeong, J. S.; Liao, J. H. *Org. Lett.* **2002**, *4*, 663.

[4] Previously, transformation of fulvenes into hydroazulene derivatives was achieved via [6 + 4] cycloaddition: (a) Dunn, L. C.; Chang, Y.-M.; Houk, K. N. *J. Am. Chem. Soc.* **1976**, *98*, 7095. (b) Dunn, L. C.; Houk, K. N. *Tetrahedron Lett.* **1978**, 3411.

[5] For examples of retro-Diels−Alder reaction of 6,6-dimethylfulvene adducts, see: (a) Ichihara, A.; Kobayashi, M.; Oda, K.; Sakamura, S. *Tetrahedron Lett.* **1974**, 4231. (b) Ref 6.

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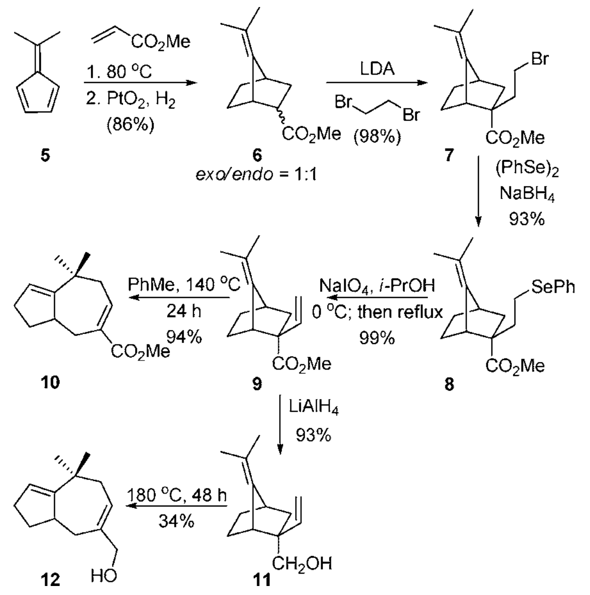
required *exo*-stereochemistry of the vinyl group would be difficult to achieve during the cycloaddition step, due to its expected poor *exo*/*endo*-selectivity. Fortunately, an encouraging report found in the literature indicated that the problem could be solved by subsequent *exo*-selective enolate alkylation.[6]

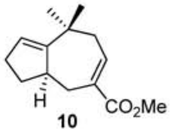
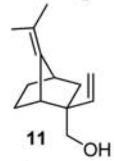
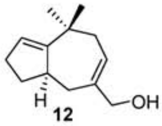
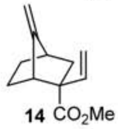
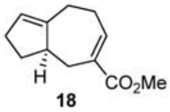
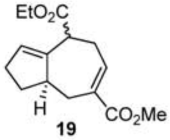
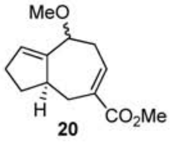
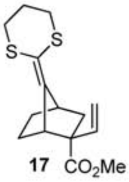
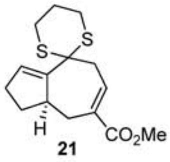
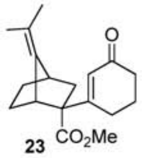
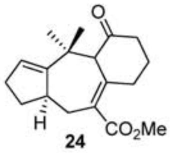
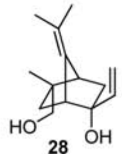
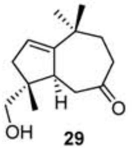
Refluxing 6,6-dimethylfulvene **5** in methyl acrylate followed by careful hydrogenation over PtO_2 produced ester **6** as an inconsequential mixture of diastereomers (Scheme 1). Its alkylation with 1,2-dibromoethane proceeded in excellent yield and with complete diastereoselectivity, in accord with the close literature precedent.[5] Replacement of bromide with phenylselenide followed by oxidation and elimination provided the diene **9**. Happily, we found that heating of this compound to 140 °C for 24 h cleanly provided hexahydroazulene **10**.

Scheme 1. Proof of Principle Experiments



Having thus confirmed the feasibility of the key step, we set out to investigate the scope and limitations of the new methodology. Seeking to determine the importance of the ester group, we reduced **9** to the corresponding primary alcohol **11**. This compound was much more reluctant to undergo rearrangement than the ester (Table 1, entries 1 and 2). Therefore, in further exploration of this chemistry we decided to keep the ester in place. Vinyl ketone **13**, which could be converted, in a divergent fashion, to a number of Cope rearrangement precursors, was expected to be easily obtainable from phenylselenide **8** via one-pot ozonolysis/selenide oxidation followed by selenoxide elimination. In practice, however, the normal course of ozonolysis was accompanied by Baeyer–Villiger oxidation to provide a mixture of isomeric lactones in addition to the desired product **13**. Yields of **13** were highly variable and dependent on the reaction conditions. While the exact mechanism of this side reaction is unknown, we were intrigued by a report of the in situ fragmentation of carbonyl oxides by tertiary amine oxides.[7] Addition of 5 equiv of *N*-methylmorpholine oxide to the ozonolysis reaction mixture significantly decreased the formation of side products and aided reproducibility. To obtain maximum yields, however, it was still necessary to shorten the substrate's exposure to ozone to a minimum, requiring the addition of $NaIO_4$ to oxidize the remaining selenide.

Table 1. Rearrangements of 2-Vinyl-7-alkylidenenorbornanes

entry	substrate	product	conditions/yield
1	 **9** CO_2Me	 **10** CO_2Me	PhMe, 140 °C 24 h 94% yield
2	 **11** OH	 **12** OH	Xylenes, 180 °C 48 h 62% conversion 34% yield
3	 **14** CO_2Me	 **18** CO_2Me	PhMe, 140 °C 12 h quant. yield
4	 CO_2Et **15** CO_2Me	 EtO_2C **19** CO_2Me	PhMe, 140 °C 5.5 h quant. yield
5	 OMe **16** CO_2Me	 MeO **20** CO_2Me	PhMe, 140 °C 18.5 h 95% yield
6	 **17** CO_2Me	 **21** CO_2Me	PhMe, 140 °C 24 h 90% yield
7	 **23** CO_2Me	 **24** CO_2Me	Xylenes, 165 °C 48 h 26% conversion 23% yield
8	 HO **28** OH	 OH **29**	THF, 18-crown-6 KH, 23 °C, 5.5 h 71% yield

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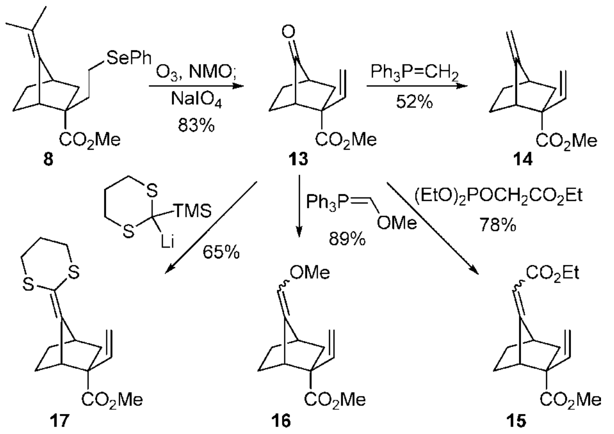
(6) Ichihara, A.; Nio, N.; Sakamura, S. *Tetrahedron Lett.* **1980**, *21*, 4467.

(7) Schwartz, C.; Raible, J.; Mott, K.; Dussault, P. H. *Org. Lett.* **2006**, *8*, 3199.

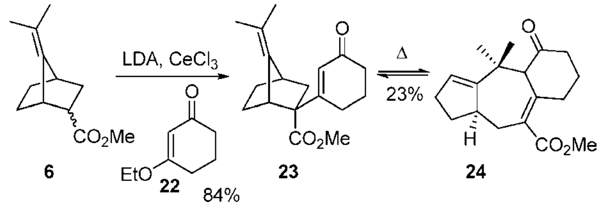
With a reliable protocol for producing ketone **13** in hand, we were able to produce several representative rearrangement precursors **14**−**17** using known olefination protocols (Scheme 2). All these substrates underwent the rearrangement cleanly producing hexahydroazulenes **18**−**21**, respectively (Table 1, entries 3−6). Interestingly, the rate difference for the methylene vs isopropylidene cases was insignificant (entry 1 vs entry 3). Addition of attached electron-donating substituents did not seem to make a large difference in the rate either (entries 5 and 6), although the presence of an ester group did facilitate the rearrangement slightly (entry 4).

Scheme 2. Substituting the “Left-Hand” Olefin



Now confident in our ability to introduce various substituents on one side, we set out to create structural analogues replacing the vinyl terminus with other alkenyl groups. Initial endeavors to effect direct alkenylation of the lithium enolate of **6** via transition metal catalyzed coupling with vinyl halides and triflates proved disappointing. Thus, we decided to develop a Stork−Danheiser[8]-like approach to the desired rearrangement precursors. The aldol reaction between the lithium enolate of **6** and (3-ethoxy)-2-cyclohexenone **22** (Scheme 3) at −40 °C produced incomplete conversions even with prolonged (48 h) reaction times. Hoping to exploit the well-documented ability of cerium trichloride to suppress abnormal side reactions in the addition of nucleophiles to carbonyl compounds,[9] we repeated the reaction using this reagent as a stoichiometric additive. Gratifyingly, when a solution of the lithium enolate was stirred with a suspension of anhydrous $CeCl_3$ in THF prior to addition of the vinylogous ester, the reaction took place quickly at −78 °C to furnish the desired product (**23**) in 84% yield.

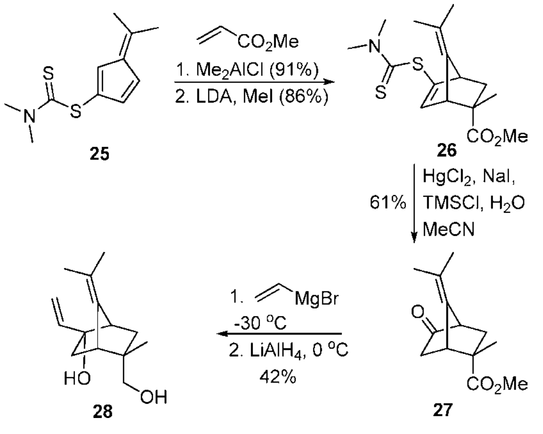
Scheme 3. Stork−Danheiser Approach



Because of an increase in steric congestion compared to our previous substrates, we expected that higher temperatures would be required to effect rearrangement of cyclohexenone **23**. This did prove to be the case, but conversions uniformly reached only about 25%, not increasing with higher temperature (160−200 °C) or longer reaction times (24−48 h). The reaction appeared to reach this conversion and stop without decomposition of either the starting material or the product, suggesting the formation of an equilibrium mixture. We were initially skeptical of the existence of such an equilibrium considering that the ring strain inherent in the bicyclo[2.2.1]heptane system would be relieved in the product. Nonetheless, when keto-ester **24** was heated under the same conditions as those used for its formation, essentially the same 3:1 composition was reached, thus indicating that Cope rearrangement was indeed reversible in this case and that the bridged isomer **23** was actually favored.

Finally, we decided to explore the analogous anionic oxy-Cope rearrangement,[10] which would further expand the range of accessible substitution patterns. The alternative strategy we had envisioned required access to a stereochemically biased bicyclic ketone (cf. **27**, Scheme 4). With this in mind, we investigated the Diels−Alder reaction of easily available dithiocarbamoyl fulvene **25**[11] with methyl acrylate. Although the desired adduct could be obtained under thermal conditions, we found that the addition of stoichiometric Me_2AlCl and low temperatures (−10 °C to rt) was advantageous in

Scheme 4. Preparation of Anionic Oxy-Cope Precursor **24**



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(8) Stork, G.; Danheiser, R. L. *J. Org. Chem.* **1973**, *38*, 1775.

(9) (a) Johnson, C. R.; Tait, B. D. *J. Org. Chem.* **1987**, *52*, 281. (b) Imamoto, T.; Takiyama, N.; Nakamura, K.; Hatajima, T.; Kamiya, Y. *J. Am. Chem. Soc.* **1989**, *111*, 4392.

(10) Paquette, L. A. *Tetrahedron* **1997**, *53*, 13971.

(11) Hartke, K.; Timpe, C. *Liebigs* **1994**, *2*, 183.

terms of yield, purity of the product, and reaction scalability. The intermediate was isolated as a single regioisomer (and an inconsequential mixture of diastereomers) and converted exclusively into *exo*-methyl derivative **26** by alkylation with MeI. Use of conditions developed by Grieco et al. for the hydrolysis of enol phenyl thioethers[12] gave rise to ketone **27** in a 61% yield. Addition of vinylmagnesium bromide at −30 °C followed by reduction of the ester function with $LiAlH_4$ gave the desired oxy-Cope precursor **28**. When this was treated with 2 equiv of 18-crown-6 and excess KH in THF at room temperature, smooth rearrangement occurred giving ketone **29** in 71% isolated yield.

The synthesis of the hydroazulene ring system thus described is complementary to the many known approaches. Precursors are readily available by short, high-yield sequences, which makes this variant of the Cope rearrangement particularly attractive as the basis for divergent synthesis of libraries of bicyclo[5.3.0]decane-containing products. Further work into potential applications of this methodology is underway and will be reported in due course.

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Supporting Information Available: ^1H and ^{13}C spectra of new compounds and procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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[12] Grieco, P. A.; Dai, Y. *Tetrahedron Lett.* **1998**, *39*, 6997.