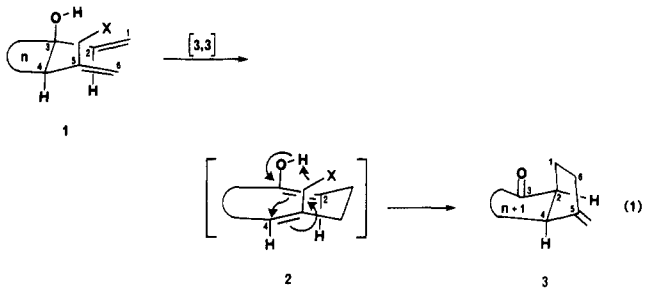
Cyclopentanoid Synthesis via the Intramolecular Trapping of Oxy-Cope Intermediates. Stereocontrolled Synthesis of the *cis*- and *trans*-Hydroazulene Skeleton

Summary: The [3,3]-sigmatropic rearrangement of C5-substituted oxy-Cope derivatives was examined. With halomethyl groups the reaction sequence is efficiently directed to cyclopentanoid ring formation.

Sir: The hydroazulene ring system constitutes the fundamental carbocyclic skeleton observed in the guaianolide and pseudoguaianolide group of sesquiterpene lactones.[1] Considerable interest in these lactones has developed since the discovery that many members of this group possess an impressive range of biological activity.[1,2] Synthetic activity has been intense and several basic strategies have been employed to construct the hydroazulene-based natural products.[3] Our interests are aimed at new methodologies to construct substituted cyclopentanoids. Thus, we envisioned the general stereocontrolled synthesis, readily applicable to the hydroazulene ring system, outlined in eq 1. In this paper we report our initial study

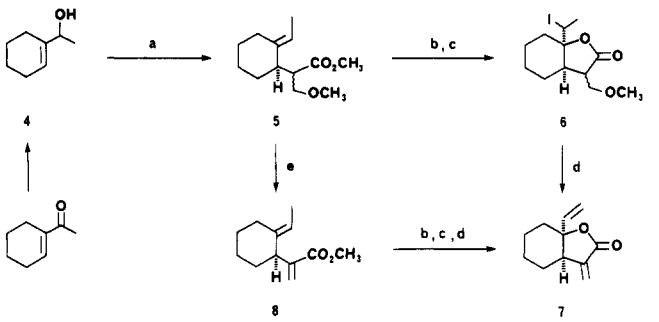


1 2 3

on the effectiveness of intramolecular Michael addition and alkylation reactions to direct oxy-Cope intermediate **2** → **3** and the successful use of this new methodology to stereoselectively prepare the thermodynamically less stable *cis*-hydroazulenone ring system.

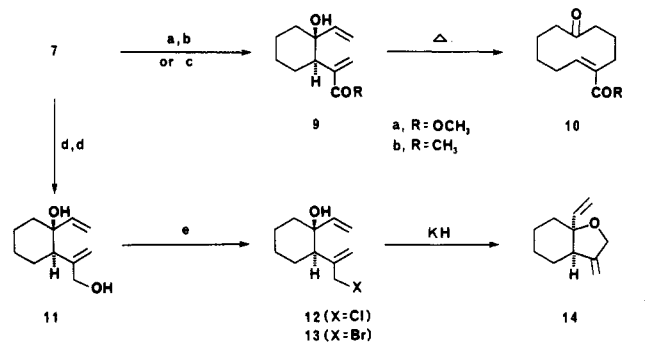
The Cope rearrangement and its variants are powerful reactions that transfer stereochemistry via well-defined transition states.[4,5] Our strategy was to convert this stereoselective generation of asymmetry by incorporating latent functionality into oxy-Cope precursors which upon rearrangement would irreversibly trap the mildly nucleophilic enol (eq 1). When the vinyl substitutents are oriented trans in oxy-Cope substrate **1** sigmatropic rearrangement through a chair-like transition state generates *trans,trans*-dienol **2** in which H2 and H4 have a cis relationship. If intramolecular ring closure is more rapid than ketonization, only the cis-fused cyclopentanoid **3** would result. Therefore, our selection of C5 substituents was aimed at inducing facile proton transfer.

Scheme I[a]



[a] Reagents: (a) $CH_3OCH_2CH_2CH(OCH_3)_3$, H^+(cat.), 140 °C, 91%; (b) KOH, H_2O, CH_3OH; (c) KI_3, $NaHCO_3$, H_2O, (d) DBU, toluene, 110 °C, 69% from **5**, 83% from **8**; (e) *t*-BuOK, THF, 0 °C, 98%.

Scheme II[a]



[a] Reagents: (a) NaOH, H_2O; (b) CH_2N_2, Et_2O, 0 °C, 99% from **7**; (c) CH_3Li, Et_2O, THF, −78 °C, 96%; (d) DIBAL, CH_2Cl_2, −78 °C, 89% overall; (e) CCl_4 or CBr_4, PPh_3, CH_3CN, 95% for **12**, 90% for **13**.

In addition, one of our primary objectives was to correlate the effects of the potentially facile charge-acceleration catalysis of the Cope sequence[5] versus the purely thermal series. Since the catalysis reactions offer the secondary benefit of an enhanced intramolecular ring closure step, we required a synthesis of a highly functionalized synthon that would allow us to screen a variety of electrophilic groups. With this in mind, we prepared *cis*-α-methylene lactone **7** as outlined in Scheme I.

A convenient one-step assembly of the carbon framework was accomplished via the Claisen rearrangement of allylic alcohol **4**,[6] using the functionalized ortho ester described by Raucher,[7] to give masked acrylate **5**.[8] The olefinic functionality was readily transformed into α-methylene lactone **7**[8] by iodolactonization to **6**[8] followed by DBU-initiated elimination. This sequence provides access to key intermediate **7** on a multigram scale in four steps and 62% overall yield from **4**.[9]

To examine the potential of an intramolecular Michael reaction[10] to effect ring closure, we converted lactone **7** to

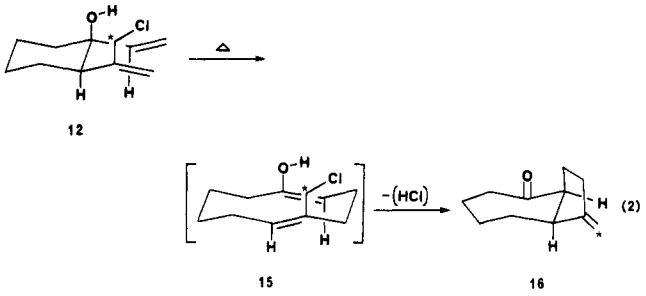
(1) Fischer, N. H.; Olivier, E. J.; Fischer, H. D. *Fortschr. Chem. Org. Naturst.* **1979**, *38*, 47.
(2) Rodriguez, E.; Towers, G. H. N.; Mitchell, J. C. *Phytochemistry* **1976**, *15*, 1573.
(3) For an excellent review through 1980, see: Heathcock, C. H.; Graham, S. L.; Pirrung, M. C.; Plavac, F.; White, C. T. In *The Total Synthesis of Natural Products*; ApSimon, J. W., Ed.; Wiley-Interscience: New York, 1982; Vol. 5, pp 333–384. For some recent developments, see: Rigby, J. H.; Wilson, J. Z. *J. Am. Chem. Soc.* **1984**, *106*, 8217 and references therein. Bohlmann, F.; Paul, A. H. K. *Tetrahedron Lett.* **1984**, *25*, 1697. Lansbury, P. T.; Mazur, D. J.; Springer, J. P. *J. Org. Chem.* **1985**, *50*, 1632. Hudlicky, T.; Govindan, S. V.; Frazier, J. O. *J. Org. Chem.* **1985**, *50*, 4166. Schultz, A. G.; Motyka, L. A.; Plummer, M. *J. Am. Chem. Soc.* **1986**, *108*, 1056.
(4) For reviews, see: Hill, R. K. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: Orlando, 1984; Vol. 3, Chapter 8. Rhoads, S. J.; Raulins, N. R. *Org. React.* **1975**, *22*, 1.
(5) For an excellent review through mid-1983, see: Lutz, R. P. *Chem. Rev.* **1984**, *84*, 205 and references therein.
(6) Available on large scale from Ce(III)-catalyzed $NaBH_4$ reduction of acetylcyclohexene. Cf.: Gemal, A. L.; Luche, J.-L. *J. Am. Chem. Soc.* **1981**, *103*, 5454.
(7) Raucher, S.; Macdonald, J. E.; Lawrence, R. F. *Tetrahedron Lett.* **1980**, *21*, 4335.
(8) All compounds reported were homogeneous by TLC analysis and provided 300-MHz ^1H NMR, 75-MHz ^{13}C NMR, and IR spectra consistent with the assigned structures. The molecular composition of key compounds was determined by high-resolution mass spectrometry or elemental analysis.
(9) Lactone **7** was also prepared from acrylate **8**. This five-step sequence was somewhat more efficient (74% overall yield).
(10) For a recent example of an intermolecular thermal Michael reaction variant, see: Coates, R. M.; Hobbs, S. J. *J. Org. Chem.* **1984**, *49*, 140.

0022-3263/87/1952-5640$01.50/0

methyl ester **9a**[8] (Scheme II). Thermal rearrangement provided only the functionized medium ring **10a**[8] in 80–91% yield. Similar results were obtained with the methyl ketone (**9b** → **10b**);[11] consequently, we examined catalysis reactions[5,12] as a means to enhance the intramolecular ring closure. Unfortunately, all attempts to employ either anionic or cationic acceleration has led to polymerization of ketone **9b** and facile relactonization of ester **9a** to **7**.

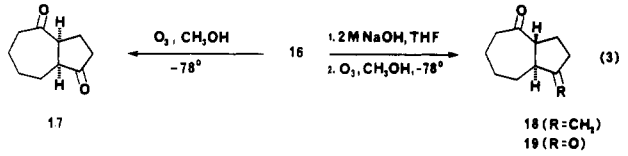
Having been unable to induce intramolecular ring closure under Michael-type conditions, we turned to the alkylation-based sequence. Along with an irreversible alkylation step, this approach offered the potential of kinetically controlled reaction conditions that would avoid equilibration of the labile *cis*-hydroazulenones. Thus, we prepared the required halides **12**[8] and **13**[8] from lactone **7** by stepwise reduction with DIBAL to diol **11**[8] followed by exchange with Ph_3P–CX_4 (Scheme II).

When allylic chloride **12** was heated at 210 °C in cyclohexane for 2 h (Fischer–Porter pressure bottle) with excess propylene oxide as HCl scavenger,[13,14] *cis*-hydroazulenone **16**[8] was obtained as the only product[15] in 81% yield after chromatographic purification (eq 2). This



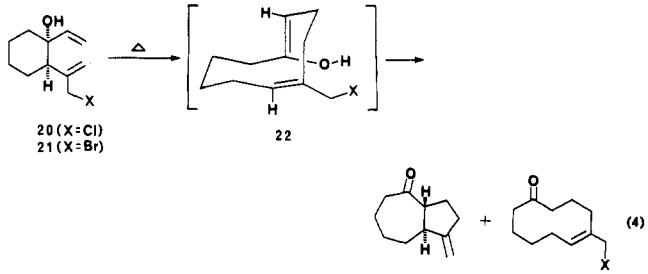
efficient sigmatropic rearrangement–alkylation sequence occurred over a wide temperature range (155–210 °C) with >95% total mass balance.[15] Interestingly, substitution of bromide **13** for chloride **12** provided only a modest rate increase (~2) in the formation of *cis*-**16**. To examine the stereochemical integrity of the rearrangement process, we prepared dideuteriochloride **12** by stepwise reduction of lactone **7** with DIBAL-D[16] followed by halide exchange. When D_2-chloride **12** (* indicates carbon atom containing deuterium label)[17] was subjected to the previously described rearrangement conditions at temperatures ranging from 165 to 205 °C and stopped at 50–65% conversion, the D_2 label was cleanly located on the terminal methylene carbon of *cis*-hydroazulenone **16** (eq 2).[17] Minor amounts of scrambling (up to 10%) only appeared in reactions that underwent prolonged heating to achieve ~100% conversion or at significantly elevated rearrangement temperatures (T ~255 °C). Coupled with the absence of any medium ring ketone (vide infra), these results support an initial rate-determining oxy-Cope rearrangement of **12** to transient *trans,trans*-cyclodecadienol **15** followed by rapid intramolecular ring closure with concurrent loss of HCl. Additional mechanistic studies to further elucidate this stereoselective sequence are under way and will be reported in due course.[18]

The stereochemistry of *cis*-hydroazulenone **16** was unambiguously demonstrated by ozonolysis to the known *cis*-bicyclo[5.3.0]decane-2,8-dione (**17**).[19] The thermodynamic preference for the trans fusion was confirmed by base catalyzed equilibration to *trans*-hydroazulenone **18**[8,20] followed by ozonolysis to *trans*-dione **19**[19] (eq 3).



Compared to the thermal series, charge-acceleration catalysis reactions were primarily discouraging. Evans' anionic conditions[5] resulted in only rapid intramolecular ether formation to give **14** (Scheme II), while silver(I)-promoted cation formation[5,12] provides a mixture of ether **14** and *cis*-**16**.[15] A more definitive study on this latter sequence is planned.

To fully explore the stereochemical consequences and general merit of this new hydroazulenone synthesis requires access to the isomeric rearrangement series. Recently, we prepared the *cis*-divinyl-substituted chloride **20**[8] and bromide **21**[8,21] and examined their thermal properties under the previously described rearrangement conditions. In contrast to our earlier study, chloride **20** was ineffective at inducing intramolecular ring closure, yielding *cis*-cyclodecenone **23**[8] as the major product (eq 4). However,



simple substitution of bromide **21** for chloride **20** dramatically shifted the product distribution in this series. When bromide **21** was heated at 155 °C in benzene for 7

(11) These results suggest that proton transfer to generate the allyl oxonium cation–enolate anion intermediate[10] is unfavorable. Since the enol is directly formed in the oxy-Cope rearrangement, activation of the thermal Michael reaction[10] must be largely determined by enolic acidity.

(12) Numerous applications of an endocyclic Mannich reaction to efficiently trap an enol in the aza-Cope series have been reported by Overman; see: Overman, L. E.; Kakimoto, M.; Okazaki, M. E.; Meier, G. P. *J. Am. Chem. Soc.* **1983**, *105*, 6622. Overman, L. E.; Mendelson, L. T.; Jacobson, E. J. *J. Am. Chem. Soc.* **1983**, *105*, 6629 and references therein.

(13) Corey, E. J.; Danheiser, R. L.; Chandrasekaran, S.; Keck, G. E.; Gopalan, B.; Larsen, S. D.; Siret, P.; Gras, J.-L. *J. Am. Chem. Soc.* **1978**, *100*, 8034.

(14) Propylene oxide was crucial to the stereochemical integrity of the rearrangement–alkylation sequence; amine bases were generally ineffectual, the two exceptions being 2,6-di-*tert*-butylpyridine and 1,8-bis(dimethylamino)naphthalene.

(15) Isomer ratios and product purities were determined by capillary GC analysis (15 m × 0.53 mm i.d., 1.5 μm DB-1 film).

(16) Kalvin, D. M.; Woodard, R. W. *Tetrahedron* **1984**, *40*, 3387. Eisch, J. J.; Rhee, S. G. *J. Am. Chem. Soc.* **1974**, *96*, 7276.

(17) On the basis of ^1H NMR integration of the residual proton resonance, deuterium incorporation for chloride **12** was 95–96%. Product isomer ratios and percent conversion to **16** was readily determined by ^1H NMR integration of the reaction mixtures.

(18) Although we have chosen to discuss this sequence as a [3,3]-sigmatropic rearrangement followed by a thermal alkylation, alternate mechanisms with similar topographical constraints are possible. Experiments that address these mechanistic issues are also under investigation.

(19) Weller, T.; Seebach, D.; Davis, R. E.; Laird, B. B. *Helv. Chim. Acta* **1981**, *64*, 736.

(20) The observed ratio at equilibrium (mass balance > 98%) was approximately 84:16 (*trans*-**18**/*cis*-**16**).[15] The isomers were separated by flash chromatography.

(21) The halides were prepared from the *cis*-divinyl-substituted diol via PPh_3–CX_4 exchange. The diol was prepared in four steps from masked acrylate **5** via the following sequence: (a) *m*-CPBA epoxidation, (b) KO-*t*-Bu-catalyzed elimination, (c) DIBAL reduction, (d) PhSeNa, H_2O_2 epoxide ring opening followed by selenoxide elimination. Unpublished results of M. Sworin and K.-C. Lin.

h, *trans*-hydroazulenone **18**[8] and medium ring bromide **24**[8] were obtained in approximately a 5:1 ratio (**18**/**24**).[22] None of the *cis*-hydroazulenone **16** could be detected in the reaction mixture.[22] The exclusive formation of **18** and **24** requires preferential rearrangement of bromide **21** via a single chair-like transition-state to form *trans,cis*-cyclodecadienol **22** which can undergo either intramolecular ring closure or ketonization (eq 4). Experiments aimed at enhancing the ring-closure step in this series are under way and will be reported in a full account of this work.

In summary, we have established a new method to direct sigmatropic rearrangements in which the ubiquitous cyclopentanoid ring system is readily derived from an acyclic precursor. The scope, stereochemical criteria, and applications in the natural products area are currently under investigation and will be the subject of future publications.

(22) Product ratios were determined by ^{1}H NMR integration of the olefinic resonances. The absence of *cis*-**16** was readily discerned by the lack of resonances at δ 4.89, 4.80, and 3.13.

Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, and to the National Science Foundation (Instrumentation Grant CHE-8506671) for support of this research. High-resolution mass spectral determinations were performed by the Midwest Center for Mass Spectrometry, a National Science Foundation Regional Instrumentation Facility (Grant CHE-8211164).

Supplementary Material Available: Complete experimental details and spectral data for compounds **5**, **6**, **7**, **11**, **12**, **13**, **16**, and **18** and the ^{1}H, ^{13}C, DEPT, and IR spectra of **21** and **24** along with the ^{1}H NMR spectrum of the rearrangement mixture of **18** + **24** (19 pages). Ordering information is given on any current masthead page.

Michael Sworin,* Ko-Chung Lin
Department of Chemistry
University of Missouri—St. Louis
St. Louis, Missouri 63121
Received November 12, 1986

Additions and Corrections

Vol. 51, 1986

J. E. Toth and P. L. Fuchs*. Formation of the Neopinone/Codeinone Ring System via Intramolecular 1,6-Addition of an Amino Moiety to a Dienyl Ketone.

Page 2596, column 1, line 16, 7.28 (d, 1 H, J = 8.0 Hz), 7.57 (d, 1 H, J = 8.0 Hz) should read 7.28 (d, 2 H, J = 8.0 Hz), 7.57 (d, 2 H, J = 8.0 Hz).

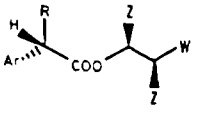
Line 34, 3.38 (dd, 1 H, J = 6.1, 20.0 Hz), ... 6.41 (d, 1 H, J = 6.1 Hz) should read 3.38 (dd, 1 H, J = 6.8, 20.0 Hz), ... 6.41 (d, 1 H, J = 5.5 Hz); in addition, the resonance 7.24 (d, 1 H, J = 10.2 Hz) should be added.

Vol. 52, 1987

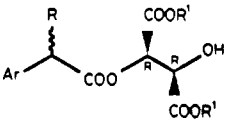
Graziano Castaldi,* Silvia Cavicchioli, Claudio Giordano,* and Fulvio Uggeri. Tartaric Acid, an Efficient Chiral Auxiliary: New Asymmetric Synthesis of 2-Alkyl-2-arylacetic Acids.

Page 3018. There are some unfortunate errors in the drawings of some tartaric acid derivatives in Schemes I–III and Table III. Specifically, one of the centers of tartaric acid derivatives has been drawn as the *S* configuration when it should be *R* (and, indeed, is labeled *R* in the printed version). These errors in drawings do not affect the discussion and conclusions which, to the best of our knowledge, are correct as stated in the text. The specific corrections are itemized below.

Page 3019. In Scheme I, the ester should be as follows:

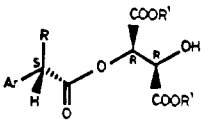


Pages 3021 and 3022. In Scheme II and in Table III, the structure of **10,11** should be as follows:

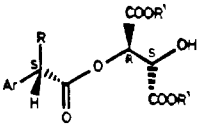


10,**11**

Page 3021. In Scheme III the structures of **10** and **16** should be as follows:



10



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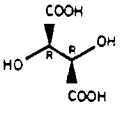
Page 3022. In Table III the structure **10,11** should be as shown in the correction for Scheme II and the structure of tartaric acid should be as follows:



James A. Marshall,* Todd M. Jenson, and Bradley S. DeHoff. Synthesis of Cembrane Natural Products via [2,3] Wittig Ring Contraction of Propargylic Ethers.

Page 3863, Table III. The "yield, %" and "**43**/**44**" entries for lines 3 and 6 are misplaced, generating an unwanted additional column. The values should be as follows (entry no.; yield, %; **43**/**44**): entry 3, 50, 67:33[b]; entry 6, 35, 67:33[b].