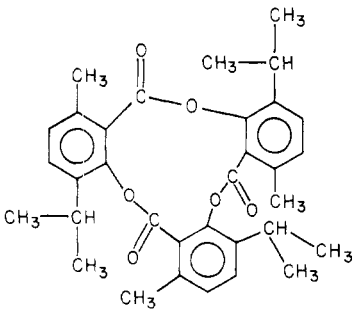

2

The rigidity of **1a** would seem to be responsible, at least in part, for its much more limited complexing ability, although this is countered by the hydrogen-bonding capability of **1b**. In any case, **1b** provides a potentially valuable addition to the collection of complexing agents, each of which has its own specific selectivity in the choice of guest molecules.

Acknowledgment. We thank the National Science Foundation for partial support of this work.

Registry No. **1a**·ethyl acetate, 75234-34-3; **1a**·methyl ethyl ketone, 75234-35-4; **1a**·ethanol, 75234-36-5; **1b**·*N*,*N*-dimethylformamide, 75247-87-9; **1b**·*N*-methylpyrrolidinone, 75247-88-0; **1b**·*N*,*N*-dimethylacetamide, 75247-89-1; **1b**·dimethyl sulfoxide, 75247-90-4; **1b**·water, 75247-91-5; **1b**·hexamethylphosphoric triamide, 75247-92-6; **1b**·acetone, 75247-93-7; **1b**·2-propanol, 75247-94-8.

Supplementary Material Available: Thermal parameters and intermolecular contacts for the **1b**–2-propanol complex (6 pages). Ordering information is given on any current masthead page.

Unique Bisannelation Strategy. Total Synthesis of Epizonarene, Clarification of Cadalane Stereochemistry, and Allylic Strain

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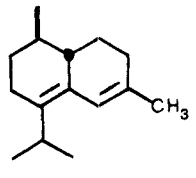
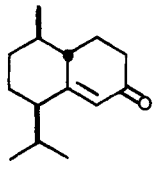
Received March 14, 1980

Bicyclic γ,δ-unsaturated ketones **3**, **5**, **15a**, and **15b** obtained via intramolecular Diels–Alder cyclizations were found to undergo acid-catalyzed isomerization to the corresponding α,β-unsaturated ketones in high yield. Ketone **15b** was isomerized to a 78:22 equilibrium mixture of enones **16b** and **16a**, respectively. The isopropyl stereochemistry was unequivocally established as pseudoequatorial in the minor isomer, **16a**, by X-ray diffraction. The mixture of **16a,b** has been converted to the natural product epizonarene (**1**).

The sesquiterpene epizonarene (**1**)[2] is a member of the cadalane class and has recently been synthesized[3] via ketone **2**. In this report, we use the synthesis of **2** to illustrate a new approach to enone synthesis based on the intramolecular Diels–Alder reaction.[4] The overall sequence in eq 1 presents this unique strategy for cyclohexenone annelation which is based on the fact that bicyclic γ,δ-unsaturated ketones can be isomerized into α,β-unsaturated ketones.



1



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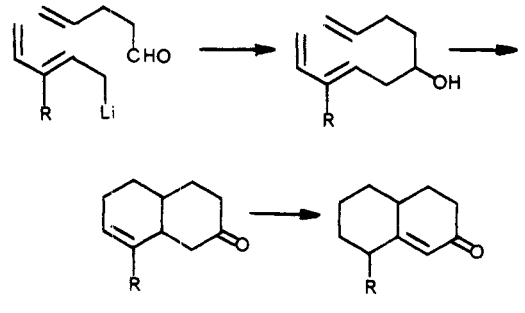
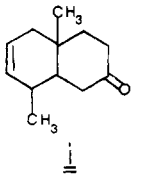


(1)

General Method

We recently reported the preparation of **3** which was used in a synthesis of (±)-selenadiene.[4b] When **3** was treated[5] with 5% H_2SO_4 in acetic acid[6,7] the double bond cleanly isomerized into conjugation with the ketone, yielding compound **4** (96%).[8] Compound **4** was exclusively the isomer with the quasi-equatorial methyl group and, surprisingly, can not readily be made by Robinson annelation.[9]



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(1) Address correspondence to this author at the Department of Chemistry, New York University, Washington Square, New York, NY 10003.

(2) Andersen, H. H.; Syrdal, D. D.; Lawrence, B. M.; Terhune, S. J.; Hogg, J. W., *Phytochemistry* **1973**, *12*, 827–833.

(3) Belavadi, V. K.; Kulkarni, S. N. *Indian J. Chem., Sect. B* **1976**, *14B*, 901–902.

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(5) See the paragraph at the end of this paper regarding supplemental data.

(6) Cf.: Marshall, J. A.; Hochstetler, A. R. *J. Am. Chem. Soc.* **1969**, *91*, 648–657.

(7) A transition-metal catalyst ($RhCl_3 \cdot 3H_2O$) isomerized **3** into i and mostly recovered starting material with no trace of **4**. Grieco, P. A.; Nishizawa, M.; Marinovic, N.; Ehman, W. J. *J. Am. Chem. Soc.* **1976**, *98*, 7102–7104.

(8) Compound **4** is a natural product. Maurer, B.; Fracheboud, M.; Grieder, A.; Ohloff, G. *Helv. Chim. Acta* **1972**, *55*, 2371–2382.

(9) (a) Marshall, J. A.; Schaeffer, D. J. *J. Org. Chem.* **1965**, *30*, 3642–3646. (b) Caine, D.; Tuller, F. N. *Ibid.* **1969**, *34*, 222–224. (c) Caine, D.; Boucugnani, A. A.; Pennington, W. R. *Ibid.* **1976**, *41*, 3632–3634. (d) Still, W. C.; Van Middlesworth, F. L. *Ibid.* **1977**, *42*, 1258–1259. (e) Caine, D.; Smith, T. L., Jr. *Ibid.* **1978**, *43*, 755–757.

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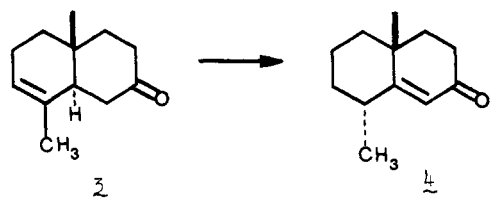
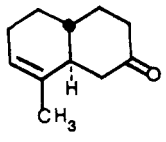


(2)

When ketone **5**, obtained by our reported method,[4b] was treated with acid, the two epimeric enones **6a** and **6b**[10]



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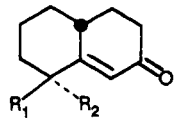
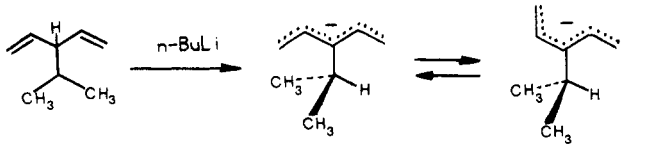


6a R_1 = H, R_2 = CH_3
6b R_1 = CH_3, R_2 = H
6c R_1 = H, R_2 = isopropyl
6d R_1 = isopropyl, R_2 = H

were produced in a 77:23 ratio (93%). The increased proportion of the isomer with a quasi-axial methyl group (relative to **4**) is due to a modest $A_{1,3}$ strain[11] in **6a**. This strain is relieved upon isomerization to axial isomer **6b**. In the case of the corresponding axial epimer of **4**, a severe 1,3-methyl–methyl interaction makes this isomer less favorable.[9c,d,12]

Approach to Cadalanes

For the application of this method to the synthesis of cadalanes, in particular **1**, 3-isopropylpentadienyllithium (**8**) was required. This reagent could be generated from 3-isopropyl-1,4-pentadiene **7** which was prepared by the reaction of pentadienyllithium and isopropyl tosylate.[5]



7 **8** (W-form) **8** (Sickle-form)

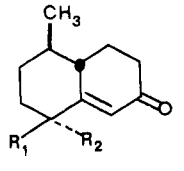
The synthesis of ketone **15** proceeds as shown in Scheme I. Several points should be noted. First, the addition of 3-isopropylpentadienyllithium (**8**) to **9** proceeds to give mixtures of *E* and *Z* double bond isomers. This is probably a reflection of increased nonbonded interactions in the W-shaped ion **8** (W-form) relative to 3-methylpentadienyl anions.[14] The relative ratios of **10**/**11** could be adjusted over wide limits (Table I). The optimum conditions (Li^+ salt, HMPA/THF, −78 °C)[5] gave an 84:16 ratio of **10a**/**11a**. Second, the *Z* isomer does *not* undergo an intramolecular Diels–Alder cyclization, but rather a 1,5 hydrogen shift to yield **13a,b**. Compounds **12** and **13** can be easily separated by short-column chromatography. Raney nickel desulfurization of compounds **12a**/**12b** afforded alcohols **14a**/**14b** which upon Jones oxidation gave ketones **15a**/**16b**. The ketone mixture appeared to be exclusively trans.[15] Treatment of **15a** with *p*-TsOH in refluxing benzene gave a 78:22 mixture of **6d**/**6c** (65%), respectively. Alternatively, TFA/CH_2Cl_2 (1:1, v/v) at room temperature affords a 50:50 mixture, a reflection of kinetic axial protonation. Treatment of this mixture with sodium methoxide (MeOH, 65 °C, 6 h) results in the identical 78:22 equilibrium ratio. Attempts to isomerize **15a**/**15b** with H_2SO_4 in acetic acid required sufficiently long reaction times to cause extensive decomposition. The stereochemical assignments were based in part on the relative retention time of isomer pairs **6a**/**6b** and **6c**/**6d** on an OV-101 GLC column (the quasiaxial isomers **6b** and **6d** emerge first).

Table I. Solvent and Cation Effects on the Ratio of 10a/11a (*E*/*Z*) from 3-Isopropylpentadienyl Anion[a-c]

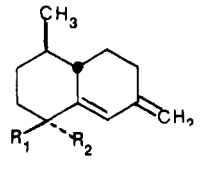
M^+	solvent	temp, °C	*E*/*Z* ratio
Li^+	Et_2O	−78	0:100
Li^+	THF	−78	64:36
Li^+	THF	−20	46:54
Li^+	DME	−20	48:52
Li^+	10% HMPA/THF	−78	84:16
Li^+	10% HMPA/THF	−20	82:18
K^+	THF	−78	14:86
K^+	10% HMPA/THF	−20	33:67
Mg^{2+}	20% Et_2O/THF	0	72:28

[a] Potassium anion was prepared in KO-*t*-Bu/*n*-BuLi/hexane.[21,22] [b] Lithium anion was prepared by addition of excess lithium bromide solution (1.2 M in THF) to the potassium anion. [c] Magnesium anion was prepared by washing the potassium anion with hexane and then adding excess $MgBr_2 \cdot 2OEt_2$.

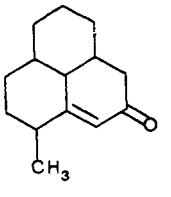
When compound **15b** was treated with acid, again a 78:22 mixture of unsaturated ketones was produced (**16b**/**16a**). Although this enone mixture has been the subject of a number of reports,[3,17,18] the isopropyl stereo-



16a R_1 = H, R_2 = isopropyl
16b R_1 = isopropyl, R_2 = H

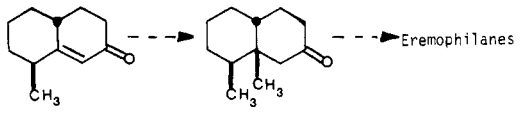


17a R_1 = H, R_2 = isopropyl
17b R_1 = isopropyl, R_2 = H



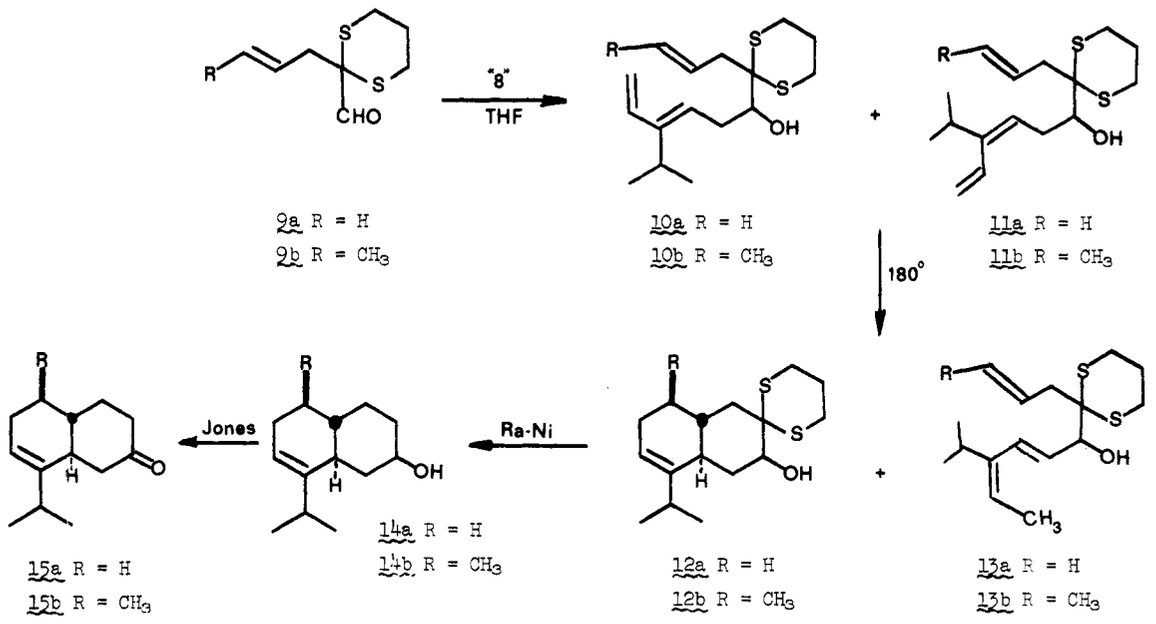
18

(10) Stork, G.; Brizzolara, A.; Landesman, H.; Szmuszkovicz, J.; Terrel, R. *J. Am. Chem. Soc.* **1963**, *85*, 207–222.
(11) Johnson, F. *Chem. Rev.* **1968**, *68*, 375–413.
(12) Our plan at the outset was to use compound **6b** as a precursor to eremophilanes;[13] however, the allylic strain present in **6a** was not sufficiently destablizing to make isomer **6b** predominate. Moreover, **6b** reacts with Me_2CuLi only by *1,2-addition*, a result not unknown for hindered enones such as **6b**.[13] Enone **6a** undergoes 1,4-addition to provide the undesired *trans*-8,9-dimethyl-*cis*-octalone. We thank Professor J. A. Marshall, Northwestern University, for providing spectra of the *cis*-8,9-dimethyl-*cis*-octalone for comparison.



(13) Devon, T. K.; Scott, A. I. "Handbook for Naturally Occurring Compounds: Terpenes"; Academic Press: New York; 1972; Vol. II.
(14) Wilson, S. R.; Jernberg, K. M.; Mao, D. T. *J. Org. Chem.* **1976**, *41*, 3209–3210.
(15) The Diels–Alder cyclization must experience nonbonded interactions in the transition state due to the isopropyl which are more severe than those described by us previously.[15,16]
(16) Wilson, S. R.; Huffman, J. C. *J. Org. Chem.* **1980**, *45*, 560–566.

Scheme I



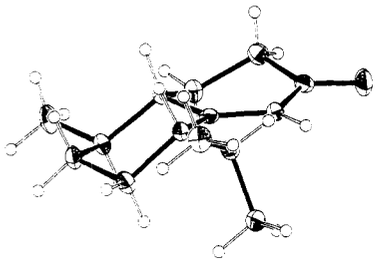


Figure 1. ORTEP drawing of molecule **16a**.

chemistry has not been clearly established. Presumably this is due to the erroneous assumption that the more stable isomer at C-7 would have an equatorial isopropyl group. The two epimers **16a** and **16b** could be distinguished by their ^{1}H NMR spectra which showed a characteristic doublet methyl signal at δ 0.78 in **16b** and δ 0.89 in **16a**. This doublet has been erroneously assigned to the C-10 methyl group.[3,17d-f] Our assignments attribute this δ 0.78 signal to one of the methyls of the quasi-axial isopropyl group, deshielded by the enone double bond. This assignment is clearly correct, since compound **6d** (lacking the C-10 methyl) also shows a doublet at δ 0.78. The isomers **16a/16b** can be separated, and each was epimerized (NaOMe, MeOH, 65 °C) to the same 78:22 equilibrium mixture. The *minor isomer* **16a** was crystallized (mp 68–69 °C), and the stereochemistry of this isomer (**16a**) was unequivocally established by a single-crystal X-ray diffraction experiment (Figure 1). The allylic interaction of the isopropyl and vinylic hydrogen can clearly be seen in Figure 1.

Compounds **16a/16b** as a mixture have been converted to (±)-epizonarene[3] (**1**) and also converted to (±)-epibicyclosesquiphellandrene (**17a**),[18] although the natural product **17a** was probably the minor component of a mixture of **17a/17b**.

Conclusion

We have thus established the efficacy of an enone bisannelation strategy involving the intramolecular Diels–Alder reaction. Although the enones prepared in this study could be made as well by classical methods, we have applied the approach to enone **18** and other systems where this procedure appears uniquely applicable. These will be the subject of future reports.

Acknowledgment. The authors thank the National Institutes of Health (Grant No. GM-26039) and the donors of the Petroleum Research Fund (11243-ACl), administered by the American Chemical Society, for support of this work. We also thank the NIH-MSU Regional Mass Spectrometry Facility, Ann Arbor, MI, for providing mass spectra, Mr. Kenneth J. Natalie, Jr., for performing some of the experiments described, and Dr. John C. Huffman for determining the X-ray structure of **16a**.

Registry No. 3, 75266-64-7; **4**, 17990-00-0; **5**, 75266-65-8; **6a**, 21060-36-6; **6b**, 21060-37-7; **6c**, 75266-66-9; **6d**, 75266-67-0; **7**, 41848-27-5; **9a**, 75266-68-1; **9b**, 75266-69-2; **10a**, 75266-70-5; **10b**, 75266-71-6; **11a**, 75266-72-7; **11b**, 75266-73-8; α-**12a**, 75266-74-9; β-**12a**, 75330-86-8; α-**12b**, 75266-75-0; β-**12b**, 75330-87-9; α-**14a**, 75266-76-1; β-**14a**, 75266-77-2; α-**14b**, 75266-78-3; β-**14b**, 75266-79-4; **15a**, 75266-80-7; **15b**, 75266-81-8; **16a**, 43209-91-2; **16b**, 61217-90-1; 1,3-dithiane, 505-23-7; allyl bromide, 107-05-1; 2-allyl-1,3-dithiane, 63382-29-6; crotyl bromide, 4784-77-4; 2-*trans*-butenyl-1,3-dithiane, 62947-41-5; 1,4-pentadiene, 591-93-5; isopropyl tosylate, 2307-69-9.

Supplementary Material Available: Complete experimental details of the preparation of all compounds discussed in this paper (13 pages). Ordering information is given on any current masthead page.

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(22) This mixture has also been reported to metalate 1,3-dienes. See: Bahl, J. J.; Bates, R. B.; Gordon, B., III *J. Org. Chem.* **1979**, *44*, 2290–2291.

(23) Posner, G. H., *Org. React.* **1972**, *19*, 1–114.