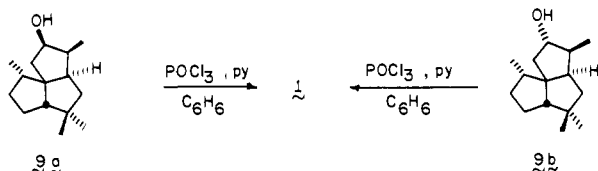


Figure 1. A computer-generated drawing of **9a** derived from the X-ray coordinates. Hydrogens have been omitted and no absolute stereochemistry is implied.

Scheme II



ment to **7** was supported by infrared absorptions at 1710 and 1660 cm^{-1} , a fully consistent ^1H NMR spectrum [(CDCl_3) δ 2.60 (d, $J = 18$ Hz, 1 H), 2.40 (d, $J = 18$ Hz, 1 H), 2.31–1.61 (m, 7 H), 1.72 (d, $J = 1.5$ Hz, 3 H), 1.19 (m, 1 H), 1.12 (s, 3 H), 0.80 (s, 3 H), 0.71 (d, $J = 7.0$ Hz, 3 H)], and combustion analysis.

With **7** in hand, our plan called for dissolving metal reduction as a means of saturating the conjugated double bond with a high guarantee that the β hydrogen would enter from the α face to generate the thermodynamically more stable ring juncture. In actuality, the action of lithium in liquid ammonium on **7** gave a single ketone (^{13}C NMR), which was directly reduced with sodium borohydride to obtain pure samples of **9a** (mp 50–52 $^\circ\text{C}$) and **9b** (mp 78–80 $^\circ\text{C}$) after silica gel chromatography (84% combined, Scheme II).

Although the relative configurations of the neighboring hydroxyl and methyl substituents were not yet known, both isomers could be uneventfully dehydrated to **1**. The C_{15} hydrocarbon so obtained was immediately recognized to differ by ^1H NMR from the natural product (Table I).⁹

So that the correctness of the assembly of atoms in the synthetic material could be established, the lower melting saturated alcohol was directly subjected to X-ray analysis.¹⁰ The clear-cut confirmatory definition of this substance as **9a** (Figure 1) suggests that **9b** is likely the α -hydroxy β -methyl derivative. More importantly, the amassed body of knowledge leaves no doubt that senoxydene has been incorrectly formulated. Currently, it is our

(9) The authors are indebted to Professor Bohlmann for making a copy of the senoxydene spectrum available to them. Although only the methyl shifts are summarized in Table I, other spectral differences between the two samples are also clearly apparent.

(10) Suitable crystals of **9a** formed as thick rods from ether at -10 $^\circ\text{C}$. Preliminary diffraction experiments indicated the cell constants to be $a = b = 18.082$ (3) \AA and $c = 8.559$ (1) \AA with space group symmetry $P4_2/n$ (origin at $\bar{1}$). Because crystals of **9a** sublimed at room temperature, the crystal used for data collection was sealed in a thin-walled glass capillary. A total of 2197 unique reflections were measured with a four circle diffractometer and Cu radiation ($\lambda = 1.5418$ \AA). Of these, 1239 were observed ($I \geq 3\sigma(I)$) and corrected for Lorentz and polarized effects. Application of a multiresolution tangent formula approach to phase solution gave an initial model, which was subsequently refined using Fourier methods and full-matrix least-squares analysis. Positions and anisotropic temperature parameters were refined for the non-hydrogen atoms while just the positions for the hydrogens were refined. The function $\sum w(|F_o| - |F_c|)^2$ with $w = 1/F_o^2$ was minimized to give an unweighted residual index of 0.062. Figure 1 is a perspective drawing of **9a** showing the relative stereochemistry, while Tables II–IV (supplementary material) contain the fractional coordinates, temperature parameters, bond distances, and bond angles. The only short contact is an intermolecular hydrogen bond between O16 and a symmetry related O16 of length 2.81 \AA .

Table I. Comparison of the ^1H NMR Spectra of Natural Senoxydene and **1a**

natural senoxydene ^b	synthetic 1c
0.84 (d)	0.85 (d)
1.08 (s)	0.93 (s)
1.17 (s)	0.99 (s)
1.60 (ddd)	1.65 (ddd)

^a CDCl_3 solution, methyl signals only. ^b Recorded at 270 MHz. ^c Recorded at 200 MHz.

intention to establish the proper structure of the sesquiterpene by independent synthesis.

Acknowledgment. It is a pleasure to acknowledge the support of this investigation by the National Institutes of Health through Grant GM-28468.

Supplementary Material Available: Tables containing the fractional coordinates, temperature parameters, bond distances, and bond angles for **9a** (2 pages). Ordering information is given on any current masthead page.

Asymmetric Induction in the Intramolecular 1,3-Diyl Trapping Reaction. Chirality on the Linking Chain

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The intramolecular 1,3-diyl trapping reaction has proven to be a very useful process for the construction of the linearly fused tricyclopentanoid ring system, one which is common to a number of natural products.³ A variety of experiments have served to demonstrate that the stereo- and regiochemical outcome of the reaction is influenced by conformational, stereoelectronic, and steric factors.⁴

One intriguing aspect of the reaction which has received comparatively little attention is that of asymmetric induction. Two reasonable approaches that might be explored in an effort to achieve asymmetric induction include (a) the use of a chiral ester attached to the diylophile π bond and (b) the placement of an asymmetric center on the carbon chain that links the diylophile to the diyl. In both instances, the objective, of course, is to bias the direction associated with the coiling of the linking chain. While the first approach leads to insignificant amounts of asymmetric induction,⁵ we are pleased to report that the second provides exceptionally useful results (vide infra).

The plan is illustrated below. Focus attention upon the two *cis,anti* ring-junction-producing transition-state representations **A*** and **B***. In **A***, the OR group is oriented in a pseudo-equatorial



fashion, while in **B***, it is pseudoaxial; in both, the configuration at the carbon bearing the OR units is *S*. On the basis of the results of previous experiments,⁶ it can reasonably be argued that the nonbonded interaction between the pseudoaxial OR group and

(1) Alfred P. Sloan Foundation Fellow, 1980–1984.

(2) UCSB Graduate Student Fellowship awardee.

(3) See, for example, the references in: Greene, A. E.; Luche, M.-J.; Depres, J.-P. *J. Am. Chem. Soc.* **1983**, *105*, 2435.

(4) (a) Little, R. D.; Muller, G. W.; Venegas, M. G.; Carroll, G. L.; Bukhari, A.; Patton, L.; Stone, K. *Tetrahedron* **1981**, *37*, 4371. (b) Little, R. D.; Carroll, G. L. *Tetrahedron Lett.* **1981**, *22*, 4389.

(5) Little, R. D.; Moeller, K. D. *J. Org. Chem.*, in press.

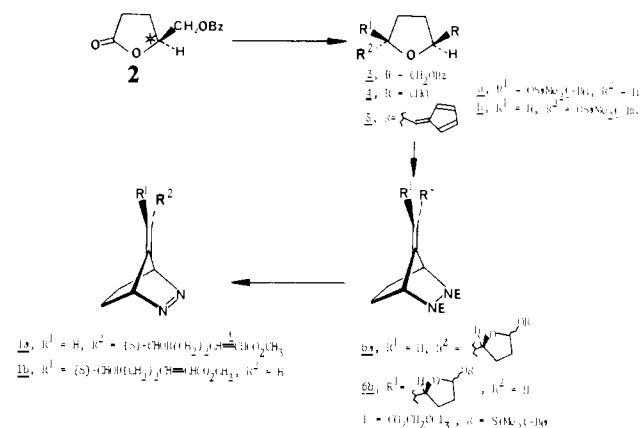
(6) Little, R. D.; Carroll, G. L.; Petersen, J. L. *J. Am. Chem. Soc.* **1983**, *105*, 928.

the diyl ring hydrogen labeled H_A in **B*** should be energy raising relative to that of transition state **A*** wherein these interactions are absent, thereby leading to preferential reaction by way of the lower energy transition-state representation **A*** and asymmetric induction.

Implementation of this plan called for construction of diazene **1** having a fixed configuration at the carbon bearing the OR group. To avoid a potentially time consuming and tedious optical resolution of intermediates, the synthesis began with the known benzyl lactone **2** derived from (*S*)-glutamic acid.⁷ Reduction of **2** using Dibal-H (-78 °C, 30 min, hexane-ether, 95%) followed by a routine silylation⁸ afforded a 1.9:1 mixture of the two readily separable diastereomers **3a** and **3b** (75–90%). It is worthwhile to note that the formation of a separable mixture of diastereomers provides a means of preserving the chirality should racemization occur at a later stage of the sequence. In practice, both **3a** and **3b** were separated from one another, and each was converted to **1** by following the synthetic scheme illustrated below.

Conversion of these compounds to the unstable aldehydes **4a,b** was achieved without epimerization by debenzoylation (H_2 , 10% Pd/C, 85–99%) and Swern oxidation (80–85%).⁹ In contrast with many other rapid, high-yield fulvene-forming reactions that have been conducted in these laboratories,¹⁰ aldehydes **4a** and **4b** were each slowly and inefficiently converted into fulvenes **5a** and **5b**, respectively (2.5 equiv of cyclopentadiene, 5.0 equiv of pyrrolidine, methanol, room temperature, 48 h, each in 45%). Fortunately, epimerization at C-4 did not prove to be a serious problem (i.e., the diastereomers were separable).

Application of a standard Diels–Alder–diimide reduction sequence⁴ converted fulvene **5a** and in a separate event **5b**, into carbamates **6a** and **6b** in 80–84% yield. Desilylation using 1:1 HF-*n*-Bu₄NF (THF, room temperature, 3.5 h, 73%) followed by a Wittig reaction ($Ph_3P=CHCO_2CH_3$ in refluxing acetonitrile, 15 h, 97%) provided a separable mixture of four products consisting of a diastereomeric pair (at C-8) of *Z* and a pair of *E* isomers (1:6 *Z/E* ratio). The *E* pair was silylated⁸ in 77–87% yields and then converted in 55–69% yield into the desired pair of diastereomeric diazenes **1a** and **1b** by using a standard reduction–oxidation sequence (Zn–Cu; $K_3Fe(CN)_6$).

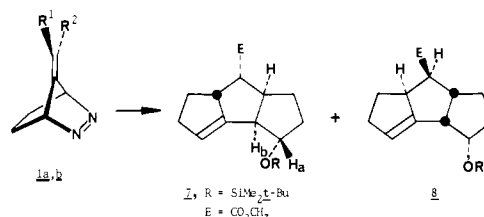


Availability of the pure diastereomers **1a** and **1b** provides the opportunity to test two items, namely, (1) whether the plan for asymmetric induction outlined above is a viable one and (2) whether diastereomers **1a** and **1b** both lead to a common, nitrogen-free and time-average planar 1,3-diyl intermediate.¹¹ If a

common intermediate is involved, then the configurational difference that is present at C-8 of diazenes **1a** and **1b** is lost and both diastereomers should lead to the same products and in the same ratios. However, if a common intermediate is not formed and bonding to the diylophile occurs during nitrogen departure, then different product ratios might be obtained.

In the critical experimental test, each diastereomer provided the same result. That is, after reflux (0.01 M in acetonitrile, 2.5 h), removal of the solvent, and chromatography, each afforded a synthetically useful $84.2 \pm 0.3\%$ de (cis,anti products) and a cis,anti:cis,syn product ratio of 16:1.¹² This value is significantly better than that of previous examples of the reaction wherein the ratio varied from 1.6:1 to 9:1.⁴

A series of nuclear Overhauser effect difference spectroscopy experiments (NOEDS)¹³ rigorously established that both the proper relative as well as absolute stereochemical outcome had been achieved. In particular, irradiation of proton H_a (δ 4.32) in the minor cis,anti ring fused product **8** resulted in a 20% enhancement of the signal for the bridgehead proton H_b (δ 3.01) whereas $\leq 2\%$ enhancement was observed when the same experiment was carried out using the major product **7**.¹⁴ These results establish the trans relationship between H_a and H_b in **7**. Since the absolute configuration at the OR-bearing carbon has remained fixed as *S* throughout, it follows that the absolute stereochemistry illustrated in structures **7** and **8** is indeed correct. Overall, the



CONDITIONS	cis,anti:cis,syn	DIASTEREOMER RATIO (7:8)	de (%)
CH ₃ CN, reflux	16 : 1	11.8 : 1	84.2 ± 0.3
hc, CH ₃ CN, 7°C	18 : 1	26 : 1	92.6 ± 0.2

reaction served to generate two new carbon–carbon bonds and two new rings and set the proper relative as well as absolute stereochemistry for elaboration to natural products at four asymmetric centers, and it proceeded in 80–91% isolated yield.¹⁵

A still more dramatic result was obtained from the irradiation of **1** at 7 °C (450-W Hanovia, Pyrex filter, acetonitrile). In this very efficient reaction ($\geq 85\%$), the cis,anti to cis,syn ratio changed to 18:1 while the ratio of the cis,anti diastereomers increased from 11.8:1 ($84.2 \pm 0.3\%$ de) to 26:1 ($92.6 \pm 0.2\%$ de).¹⁶

The results of these experiments significantly expand the scope of the intramolecular 1,3-diyl trapping reaction and dramatically highlight its potential utility in organic synthesis. Additional studies are in progress.

(12) It is very interesting to note that asymmetric induction can be achieved by simply injecting the purified diazenes into a capillary GC unit (Hewlett-Packard 5830A with electronic integrator, J & W 60 meter DB-5 capillary column, isothermal run at 200 °C, injection port temperature 200 °C and detector temperature 240 °C). The amount of induction is considerably lower (ca. 68% de) and differs substantially from the values discussed in the text, while the cis,anti/cis,syn ratio of 15.3:1 is remarkably similar to those discussed therein.

(13) (a) Noggle, J. H.; Schirmer, R. E. "The Nuclear Overhauser Effect, Chemical Applications"; Academic Press: New York, 1971. (b) Williams, M. P.; Williams, D. H. *J. Am. Chem. Soc.* **1981**, *103*, 6580. (c) Kotovych, G.; Aarts, G. H. M. *Org. Magn. Reson.* **1982**, *18*, 77. (d) Mersh, J. D.; Sanders, J. K. M. *Ibid.* **1982**, *18*, 122. (e) DeShong, P.; Dicken, M.; Staib, R. R.; Freyer, A. J.; Weinreb, S. M. *J. Org. Chem.* **1982**, *47*, 4397.

(14) A set of decoupling experiments (at 300 MHz) were used to allow a firm assignment to the resonances corresponding to H_a and H_b . Details will be reported in our full manuscript.

(15) All new compounds have been fully characterized spectroscopically (¹H NMR, IR) and provided satisfactory high-resolution mass spectra and/or combustion analyses.

(16) Only one of the two possible cis,syn-tricyclopentanoids was formed in an amount that permitted isolation and characterization. As a result, the de for the formation of the cis,syn products was not determined. Capillary column GC analysis suggests that there may be a very small amount of another cis,syn isomer.

(7) (a) Tomioka, K.; Ishiguro, T.; Koga, K. *J. Chem. Soc., Chem. Commun.* **1979**, 652. (b) Taniguchi, M.; Koga, K.; Yamada, S. *Tetrahedron* **1974**, *30*, 3547. (c) Doolittle, R. E.; Tumlinson, J. H.; Proveaux, A. T.; Heath, R. R. *J. Chem. Ecol.* **1980**, 473.

(8) Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.

(9) (a) Mancuso, A. J.; Brownfain, D. S.; Swern, D. *J. Org. Chem.* **1979**, *44*, 4148. (b) Huang, S. L.; Swern, D. *Ibid.* **1978**, *43*, 4537. (c) Huang, S. L.; Omura, K.; Swern, D. *Synthesis* **1978**, 297.

(10) Note ref 4 and manuscript dealing with the preparation of fulvenes: Stone, K. S.; Little, R. D. *J. Org. Chem.*, submitted for publication.

(11) See also: Berson, J. A.; McDaniel, D. M.; Corwin, L. R. *J. Am. Chem. Soc.* **1972**, *94*, 5509.

Acknowledgment. We are pleased to acknowledge the National Institutes of Health (National Cancer Institute Grant CA 21144) and the Alfred P. Sloan Foundation for their support of our research. K.S. thanks the UCSB Committee on Research for the receipt of Patent Funds, Sigma Xi for research funds, and UCSB for a research fellowship. We express our gratitude to Professor F. Rouessac (Universite du Maine, Le Mans, France) for a preprint of an *Organic Syntheses* preparation of the lactone acid precursor [(*S*)-oxo-5-tetrahydro-2-furancarboxylic acid] of compound **2** and to Dr. R. E. Doolittle for a useful discussion regarding the physical properties of this compound. We express our gratitude to Dr. Hugh Webb for obtaining high-resolution mass spectra and to Curt Breneman for assistance in obtaining the NOEDS results.

Control of Stereochemistry in Potassium Alkoxide Accelerated [1,3] Sigmatropic Rearrangements by the Use of a Crown Ether for the Apparent Destruction of Ion Pairs. Evidence for a Fragmentation Mechanism in a Vinylcyclobutane Rearrangement

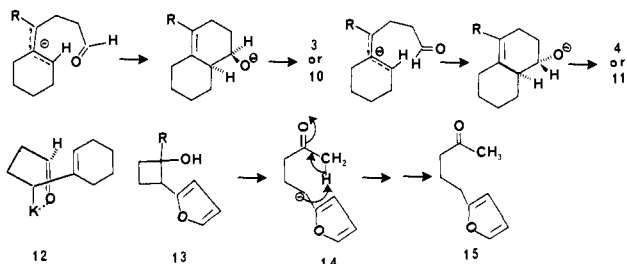
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We wish to report that a striking reversal of the stereochemical course of a potassium alkoxide accelerated vinylcyclobutane rearrangement²⁻⁵ can be induced by the use of complexing agents for potassium ion. This novel use of complexing agents has important mechanistic as well as synthetic implications.

When *trans*-2-(1-cyclohexenyl)cyclobutanol (**2**)⁶ is treated with potassium hydride in refluxing THF for 2 h, it undergoes a ring expansion in 88% yield to a mixture of *cis*- and *trans*-octalinols^{6b} (**3** and **4**, respectively) in a ratio of 70:30. This reaction thus favors Scheme I



formation of the presumably less stable axial alcohol. When the same alcohol is treated with KH at 25 °C for 15 min in THF containing catalytic or equivalent quantities of 18-crown-6, it is converted in 98% yield to the same octalinols but this time the more stable *trans* (equatorial) alcohol is by far the major product: ratio of **3** to **4**, 10:90; the products are stable to the reaction conditions. Thus, the addition of a complexing agent for potassium ion not only greatly accelerates the rearrangement but reverses its stereochemical course, causing the ratio of epimeric products to change by a factor of 21. The *cis*-cyclobutanol **1** behaves in a similar fashion, but we have found that at lower temperatures (25 °C in the absence of crown ether and -23 °C in its presence) **1** epimerizes to **2**; we³ and Gadwood⁴ had noted similar epimerizations previously.

(1) Andrew Mellon Predoctoral Fellow.

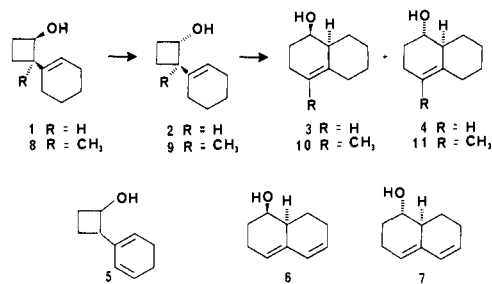
(2) Wilson, S. R.; Mao, D. T. *J. Chem. Soc., Chem. Commun.* **1978**, 479.

(3) Danheiser, R. L.; Martinez-Davila, C.; Sard, H. *Tetrahedron* **1981**, *37*, 3943.

(4) Gadwood, R. C.; Lett, R. M. *J. Org. Chem.* **1982**, *47*, 2268.

(5) Cohen, T.; Bhupathy, M.; Matz, J. R. *J. Am. Chem. Soc.* **1983**, *105*, 520.

(6) (a) The cyclobutanols were prepared and characterized as in the previous report.⁵ (b) All new compounds have been characterized by IR and NMR spectroscopy and by mass spectrometry, including the determination of their exact masses.



Earlier,⁵ we had noted that the *cis* and *trans* isomers of 2-(1,3-cyclohexadien-2-yl)cyclobutanol (**5**) rearrange in KH-THF to yield the *cis* (axial) alcohol **6** and the *trans* (equatorial) alcohol **7** in ratios of 72:28 and 92:8, respectively, and we were puzzled by the nearly opposite results reported by Danheiser³ that both **8** and **9** rearrange to a mixture consisting of a high ratio of **11** to **10**. It now appears very likely that the greatly different steric results of the rearrangement of **5** on the one hand and **8** and **9** on the other are due to the presence in the latter case of the complexing agent for potassium ion hexamethylphosphoric triamide (HMPT). We have now repeated the rearrangement of **8** and **9**^{3,6,7} but in the absence of HMPT and we find that both isomers rearrange far more slowly, that the product mixture is richer in the less stable *cis* alcohol **10**, and that the (*Z*)-cyclobutanol **8**, like **1**, isomerizes to its epimer (**9**). After 4 days at 25 °C, **8** provides 63% of **9** and small amounts of **10** and **11**. **9**, which is stable under these conditions, gives 43% of **10** and 29% of **11** after being heated at reflux for 5.5 h in THF-KH. As expected, 18-crown-6 greatly accelerates both the epimerization and ring expansion, and it reverses the stereochemical outcome of the latter, leading to a 3:97 ratio of **10** to **11** from the (*E*)-cyclobutanol **9**, a 47-fold change in product ratio (the *Z* alcohol **8** also gives mainly **11**, presumably via **9**); the products do not epimerize under these conditions. The stereochemical outcome is similar with HMPT and crown ether but the latter has a greater accelerating effect.

It is extremely difficult to explain our stereochemical results by a concerted [1,3] rearrangement. On the other hand both the ring expansion and epimerizations are completely consistent with a fragmentation to an aldehyde allylic anion that can recombine to a 4- or a 6-member ring.^{8,9} The sharply different results in the presence and absence of complexing agents for potassium ion strongly suggest that this ion plays a key role in determining the stereochemistry of the ring expansion reaction in the absence of a complexing agent. This role is readily rationalized when it is realized that the formation of the axial alcohols requires that the oxygen atom be pointing toward the allylic anion as the carbonyl group and anion approach each other (Scheme I). The attractive interaction between the two groups, to which we alluded earlier,⁵ thus appears to be chelation with a potassium ion; **12** represents a reasonable structure for the intermediate in the absence of complexing agents, but the exact juxtaposition of the potassium and allylic ions is, of course, uncertain.¹⁰ When the potassium ion is complexed instead with external agents, the two groups must approach each other with the oxygen atom pointing away from the allylic anion, a consequence of steric and charge repulsions;

(7) Danheiser's assignment of stereochemistry to **8** and **9** was confirmed by the use of Eu(tfc)₃ chemical shift reagent. The changes in δ per mol of Eu were 7.23 and 2.79 respectively for the vinyl protons of the *Z* (**8**) and *E* (**9**) isomers.

(8) Gadwood and Lett⁴ have also invoked such a fragmentation mechanism and have referenced literature precedents for ionic fragmentation of metal salts of homoallylic alcohols. A diradical cleavage is calculated to be far less favorable: Evans, D. A.; Baillargeon, D. *J. Tetrahedron Lett.* **1978**, 3315, 3319.

(9) The formation of a ketone and an allylic anion has recently been suggested as the mechanism of fragmentation of the potassium salt of a doubly homoallylic anion: Snowden, R. L.; Muller, B. L.; Schulte-Elte, K. H. *Tetrahedron Lett.* **1982**, 23, 335.

(10) The structure of an allyl anion with a potassium counterion is believed to be a contact ion pair: Schlosser, M.; Hartmann, J. *J. Am. Chem. Soc.* **1976**, *98*, 4674.