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# Complementarity of (4 + 2) cycloaddition reactions and [2,3] sigmatropic rearrangements in synthesis. New synthesis of functionalized hasubanan derivatives

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planarity; even in the trans isomer, F-1 is never in proximity to H-8'.

The fluorine signals of **1** did not coalesce even at 220°. This behavior contrasts sharply with the ease of the cis-trans isomerization of 1,1'-dialkoxycarbonyl derivatives of **2**.<sup>3e</sup> Undoubtedly, such bulky substituents, through their contribution to the ground-state strain, lower substantially the activation energy for the interconversion of the geometrical isomers. The energy barriers associated with the cis-trans isomerization of **1**, in which the ground-state strain is much diminished, are significantly higher.

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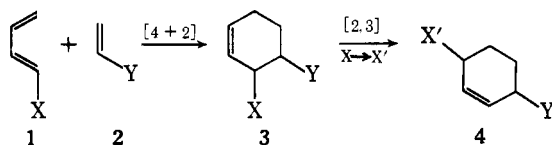
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### The Complementarity of (4 + 2) Cycloaddition<sup>1</sup> Reactions and [2,3] Sigmatropic Rearrangements in Synthesis. A New Synthesis of Functionalized Hasubanan Derivatives

Sir:

Although a number of elegant rearrangements generally classified as [2,3] sigmatropic processes have recently been reported,<sup>2</sup> the incorporation of this class of reactions into synthetic methodology has been quite limited.<sup>3</sup> The purpose of this communication is to define the complementary nature of certain (4 + 2) cycloaddition and [2,3] sigmatropic reactions. As illustrated in Scheme I, the merging of these two processes

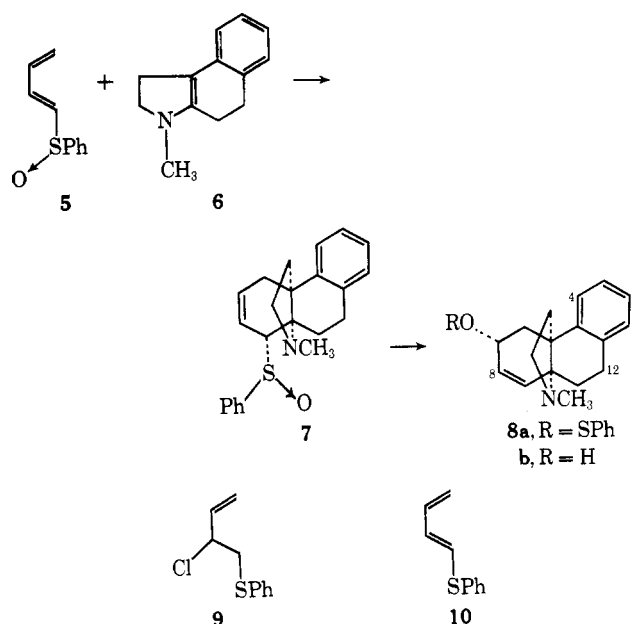
Scheme I



leads to substituted cyclohexene derivatives such as **4** which may be relatively inaccessible *via* the direct cycloaddition route.

In the course of our current work directed toward the synthesis of both the hasubanan and morphine bases,<sup>4</sup> an annelation sequence like that depicted in Scheme I appeared to offer an attractive solution to the construction of hasubanan derivatives (*cf.* **8b**) embodying a ring-C oxidation pattern common to both classes of alkaloids. The application of this merged cycloaddition-rearrangement process as applied to the synthesis of

Scheme II



the tetracyclic amino alcohol **8b** is illustrated in Scheme II.

The pivotal feature in the annelation scheme depicted above involves the conversion of sulfoxide **7** into allylic alcohol **8b**, a transformation which relies upon the interception of the corresponding sulfenyl ester **8a** with appropriate thiophilic reagents.<sup>3a,b</sup> In an effort to test the viability of this proposed sequence a synthesis of the previously unreported 1-butadienyl phenyl sulfoxide (**5**) was undertaken. The addition of phenyl sulfinyl chloride to butadiene cleanly afforded the chloro sulfide **9** in greater than 90% yield.<sup>5</sup> Subsequent dehydrohalogenation of **9** with potassium *tert*-butoxide in THF at 0° gave the *trans*-dienyl sulfide **10** as a colorless liquid (bp 50–53° (0.04 mm)) in 60% yield.<sup>6,7</sup> Although **10** has been synthesized by an alternate procedure,<sup>7</sup> the present route is decidedly more flexible in that a wide variety of chloro sulfides have recently been prepared from substituted dienes.<sup>5</sup> Oxidation of **10** with sodium periodate in methanol at 0° afforded the desired sulfoxide in 76% yield as a colorless oil (molecular distillation, 50° (0.01 mm)).<sup>6</sup>

Upon heating equimolar quantities of **5** with the tetrahydrobenzindole (**6**)<sup>4</sup> in acetonitrile at 70° for 24 hr, a diastereomeric mixture of sulfoxides **7** as well as some rearranged amino alcohol **8b** was obtained indicating that cycloaddition and rearrangement were occurring consecutively.<sup>8</sup> As we have recently demonstrated, the formal transposition of sulfoxide and alcohol functions with allylic rearrangement (*i.e.*, **7** → **8b**) can be conveniently accomplished in good yields.<sup>3a,b</sup> Thus, on treatment of the unpurified reaction mixture from **5** and **6** with Na<sub>2</sub>S·9H<sub>2</sub>O in methanol for 8 hr at 65° followed by chromatography on Florisil, the desired amino alcohol **8b** was obtained as an oil which

(1) The term cycloaddition is used here in accordance with the liberalized definition recently suggested by J. E. Baldwin, *J. Org. Chem.*, **32**, 2438 (1967).

(2) J. E. Baldwin and J. E. Patrick, *J. Amer. Chem. Soc.*, **93**, 3556 (1971), and references cited therein; P. Bickart, F. W. Carson, J. Jacobus, E. G. Miller, and K. Mislav, *ibid.*, **90**, 4869 (1968), and references cited therein.

(3) (a) D. A. Evans, G. C. Andrews, and C. L. Sims, *ibid.*, **93**, 4956 (1971); (b) D. A. Evans and G. C. Andrews, *ibid.*, in press; (c) J. F. Biellmann and J. B. Ducep, *Tetrahedron Lett.*, **33** (1971); (d) J. E. Baldwin, R. E. Hackler, and D. P. Kelly, *J. Amer. Chem. Soc.*, **90**, 4758 (1968); (e) J. E. Baldwin, J. DeBernardis, and J. E. Patrick, *Tetrahedron Lett.*, **353** (1970).

(4) D. A. Evans, C. A. Bryan, and G. M. Wahl, *J. Org. Chem.*, **35**, 4122 (1970), and references cited therein.

(5) W. H. Mueller and P. G. Butler, *J. Org. Chem.*, **33**, 2642 (1968).

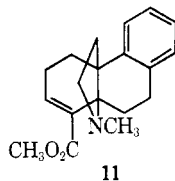
(6) All new compounds reported gave consistent ir, nmr, and mass spectra and combustion analyses.

(7) E. N. Prileshaeva, G. S. Vasilev, and V. H. Petrov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 2217 (1967).

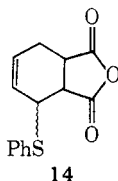
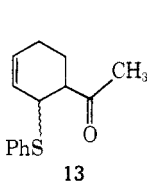
(8) Apparently during the reaction between **5** and **6** some **7** rearranges to **8a** and is intercepted by a nitrogen nucleophile; *cf.* D. J. Abbott and C. J. M. Stirling, *J. Chem. Soc. C*, 818 (1969).

formed the  $\beta$ -resorcylic acid salt, mp 180–181°. The evidence that **8b** is a single isomer rather than an epimeric alcohol mixture was derived from its behavior on tlc, its cleanly resolved nmr spectrum, and the sharp melting range of the amine salt. The structure of **8b** followed unambiguously from the nmr (60 MHz,  $\text{CDCl}_3$ ) which clearly revealed all ring-C protons. The  $\text{C}_8$ – $\text{C}_9$  vinyl hydrogens appeared as an AB quartet (5.74 ppm,  $J = 9$  Hz) coupled allylically ( $J = 2.5$  Hz) to the  $\text{C}_7$  H. The  $\text{C}_7$  H appeared as a broadened triplet (3.75 ppm,  $J = 7$  Hz) coupled with the magnetically equivalent protons at  $\text{C}_6$  (doublet, 2.2 ppm,  $J = 7$  Hz).<sup>9</sup>

The syn relationship between hydroxyl and nitrogen functions follows from the observance of intramolecular hydrogen bonding in the ir spectrum ( $\text{CCl}_4$  at 0.006  $M$ ), 3611 (free OH) and 3323  $\text{cm}^{-1}$  (bonded OH). Other examples of intramolecular hydrogen bonding from a similar configuration have also been reported.<sup>10</sup> Thus, from the known stereochemical relationships in **8b**, the syn relation between sulfoxide and amine functions in **7** may be inferred. This is the geometry that would be predicted from the preferred endo orientation of **5** and **6** during the cycloaddition step.<sup>11</sup>



In a parallel experiment designed to compare the relative reactivity of sulfoxide **5** with more commonly used electron-deficient dienes, enamine **6** was also found to add to methyl pentadienoate<sup>12</sup> (**12**) ( $\text{CH}_3\text{CN}$ , 24 hr, 40°) affording the nicely crystalline tetracyclic ester **11**, mp 96–98°, in 50% yield.<sup>6</sup> Qualitatively, it appears that the sulfoxide-substituted diene **5** is slightly less reactive than **12**, an observation in agreement with the expected activating abilities of ester and sulfoxide functions in nucleophilic addition reactions with substituted ethylene derivatives.<sup>13</sup>



In order to extend this annelation sequence to include both electron-deficient as well as electron-rich dienophiles one may simply change the oxidation state of the sulfur-substituted diene. We have found that dienyl sulfide **10** reacts quite cleanly with both methyl vinyl ketone (neat, 125°, 11.5 hr) and maleic anhydride (re-

flux, benzene, 25 hr) affording adducts **13** and **14** in 67 and 84% yields, respectively.<sup>6,14</sup>

These results indicate that both dienyl sulfoxide **5** and sulfide **10** appear to be effective dienes in Diels–Alder reactions with electron-rich and electron-deficient dienophiles, respectively. As a result of the fact that such sulfoxides can be efficiently transformed into alcohols with allylic rearrangement, this synthetic sequence should extend the utility of the Diels–Alder reaction.

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(14) Compound **14** was characterized as the crystalline diacid, mp 154–155°.

(15) Camille and Henry Dreyfus Teacher–Scholar recipient, 1971–1976.

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Received December 8, 1971

### Nucleophilic Participation by Remote Cyclopropane in an Intramolecular Analog to the $\text{SN}2'$ Reaction

Sir:

Previous work in this laboratory<sup>1</sup> has provided non-enzymic precedent for the previously suggested<sup>2</sup> possibility that the squalene oxide cyclization involves a transition state incorporating concerted, multiple, remote double bond  $\pi$ – $\sigma$  participation. Our interest in nucleophilic participation by remote cyclopropane,<sup>3</sup> the increasing awareness that cyclopropane compounds with widely diverse structures are to be found across the spectrum of natural products,<sup>4</sup> and the emergence of an apparent cyclopropylcarbinyl biosynthetic intermediate<sup>5</sup> prompted us to explore the possibility that a cyclopropane ring might be capable of mimicking the role of one of the internal double bonds in the squalene oxide polycyclization.

The question to be posed, then, is: can a cyclopropane ring function as a remote, nucleophilic neighboring group by attacking a carbon–carbon double bond which is itself a source of electronic stabilization for a developing cationic center? We chose to examine this question by probing for participation by a structurally remote cyclopropane ring functioning as an internal analog to the nucleophile in an  $\text{SN}2'$  reaction. We are now pleased to report not only that a cyclopropane ring can prove to be *more* efficient in a reaction of this type than an identically situated carbon–carbon double bond, but also to describe a striking example of sterically hindered, stereospecific, leaving group return to a

(1) G. D. Sargent, J. A. Hall, M. J. Harrison, W. H. Demisch, and M. A. Schwartz, *J. Amer. Chem. Soc.*, **91**, 2379 (1969).

(2) A. Eschenmoser, L. Ruzicka, O. Jeger, and D. Arigoni, *Helv. Chim. Acta*, **38**, 1890 (1955); G. Stork and A. W. Burgstahler, *J. Amer. Chem. Soc.*, **77**, 5068 (1955).

(3) G. D. Sargent, R. L. Taylor, and W. F. Demisch, *Tetrahedron Lett.*, 2275 (1968); G. D. Sargent, M. J. Harrison, and G. Khoury, *J. Amer. Chem. Soc.*, **91**, 4937 (1969).

(4) See, for example: J. H. Law, *Accounts Chem. Res.*, **4**, 199 (1971).

(5) E. E. van Tamelen and M. A. Schwartz, *J. Amer. Chem. Soc.*, **93**, 1780 (1971); L. J. Altman, R. C. Kowerski, and H. C. Rilling, *ibid.*, **93**, 1782 (1971); H. C. Rilling, C. D. Poulter, W. W. Epstein, and B. Larsen, *ibid.*, **93**, 1783 (1971); R. M. Coates and W. H. Robinson, *ibid.*, **93**, 1785 (1971); and references therein cited.

(9) The appropriate double resonance experiments were carried out to assign proton couplings.

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(11) (a) S. Hunig and H. Kahane, *Chem. Ber.*, **90**, 238 (1957); (b) G. A. Berchtold, J. Ciabattini, and A. A. Tunick, *J. Org. Chem.*, **30**, 3677 (1965).

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(13) H. Shenhav, Z. Rappoport, and S. Patai, *J. Chem. Soc. B*, 469 (1970).