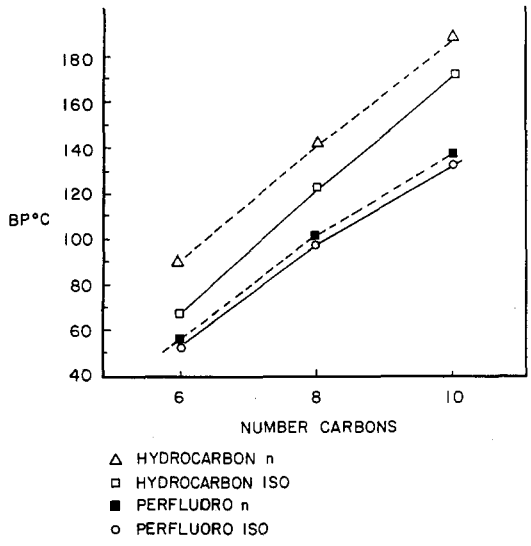

Figure 1.

It is probable that these ethers can not be produced by cobalt trifluoride, silver difluoride, or electrochemical fluorination. Perfluoro ethers are thought to be excellent candidates for emulsification with fluorocarbon surfactants and thus have properties conducive to long emulsion stability so necessary for many oxygen carrier applications.

^{19}F NMR analysis of the perfluoro ethers shows examples of the unusual coupling encountered when dealing with perfluoro systems. Coupling through two and three carbons, as well as through oxygen, is observed. This effect along with the noncoupling between fluorines on vicinal carbons makes characterization by ^{19}F NMR alone challenging, but not impossible.

The mass spectra of the ethers yielded a parent minus fluorine fragment as the highest m/e. This fragment was only seen when the ion source in the spectrometer was cooled to ambient. Characteristic of all the spectra were rearrangements yielding secondary fragments that were not possible by primary cleavage alone.

Highly branched hydrocarbons melt higher and boil at lower temperatures than their linear isomers. With even more highly branched fluorocarbons than the perfluorinated "iso" compounds plotted in Figure 1, this effect is even more pronounced[11] since there is little intermolecular attraction (only van der Waals forces) causing the heat of vaporization to be extremely low.

An interesting effect along these lines is illustrated in Figure 1. It is apparent that the effect is much greater in the hydrocarbon series than that found in the fluorocarbon series. In the hydrocarbons, the H,H, C,H, and C,C interactions are all important, owing to the small size of the hydrogen atom. In fluorocarbons, because the fluorine atom is larger than the hydrogen atom, only the F,F and perhaps the C,F interactions make a substantial contribution to the intermolecular potential within the molecules.[12]

It is obvious that almost any perfluorocarbon ether structure that one could draw could be synthesized by this method. In fact, within a 2-mo period after research is initiated, with any luck whatsoever, experimentalists skilled in these techniques can deliver a 10-g sample for further study.

Acknowledgment. We are grateful for support of this work by the Air Force Office of Scientific Research (AFOSR-82-0197).

Registry No. Isopropyl ether, 108-20-3; bis(perfluoroisopropyl) ether, 83935-39-1; isobutyl ether, 628-55-7; bis(perfluoroisobutyl) ether, 97187-06-9; isopentyl ether, 544-01-4; bis(perfluoroisopentyl) ether, 73309-73-6; neopentyl ether, 28509-24-2; bis(perfluoroneopentyl) ether, 97187-05-8.

(11) Lagow, R. J., Huang, H. N., to be published.
(12) Reed, T. M. "Physical Chemistry of Fluorocarbons"; Simons, J. H., Ed.; Academic Press: New York, 1965; Vol. 5, pp 133–236.

An Approach to the Synthesis of Mevinolin Based on Intramolecular Diels–Alder Cycloaddition

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Received March 1, 1985

An approach to the hypocholesterolemic agent mevinolin (**1b**) is presented which utilizes an intramolecular Diels–Alder strategy for construction of the hexahydronaphthalene moiety. Alkylation of diene alcohol 11 with 1-chloro-3-phosphoranylidene-2-propanone gives stabilized phosphorane **12**, which is condensed with acetaldehyde to afford trans enone **7b**. Thermal cyclization of **7b** affords endo (desired) and exo (undesired) adducts **8b** and **13b** in a ratio of 2:3. The influence of dienophile β-methyl group substitution on adduct endo/exo ratio is explored via compounds **7c** (*cis*-methyl), **7a** (unsubstituted), and **7d** (dimethyl), which give endo/exo ratios of 6:1, 6:1, and 1:1 upon thermal cyclization. An alternative highly stereoselective route to **8b** is reported. Alkylation of alcohol 11 with chloroacetic acid affords carboxylic acid **14**, which is converted via imidazolide **15** to *N*-methoxy, *N*-methyl amide **28**. Treatment of **28** with lithium acetylide–ethylenediamine complex gives acetylenic ketone **24**, which is converted to dienone **25** by cyclization in refluxing toluene. Stereoselective axial conjugate addition of a methyl group to **25** is accomplished with methylcopper–boron trifluoride complex, affording key intermediate **8b** in seven steps and 28% overall yield from dihydroorcinol ethyl enol ether.

The discoveries of the potent hypocholesterolemic agents compactin[1,2] (**1a**) and mevinolin[3,4] (**1b**) have led to a great deal of work on the synthesis of these and related compounds.[5–7] As part of our own research in this area, we

(1) (a) Endo, A.; Kuroda, M.; Tsujita, Y. *J. Antibiot.* **1976**, *29*, 1346. (b) Endo, A.; Kuroda, M.; Tanzawa, K. *FEBS Lett.* **1976**, *72*, 323. (c) Endo, A.; Tsujita, Y.; Kuroda, M.; Tanzawa, K. *Eur. J. Biochem.* **1977**, *77*, 31.

(2) Brown, A. G.; Smale, T. C.; King, T. J.; Hasenkamp, R.; Thompson, R. H. *J. Chem. Soc., Perkin Trans. 1* **1976**, 1165.
(3) Endo, A. *J. Antibiot.* **1979**, *32*, 852. Endo, A. *Ibid.* **1980**, *33*, 334.

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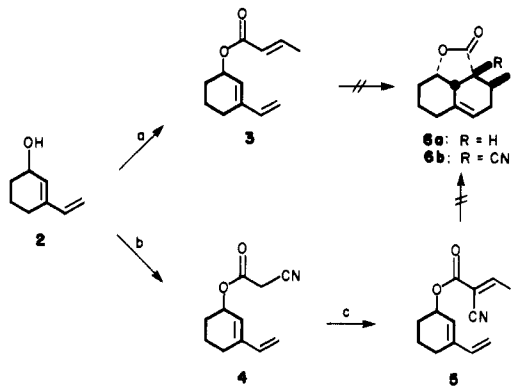
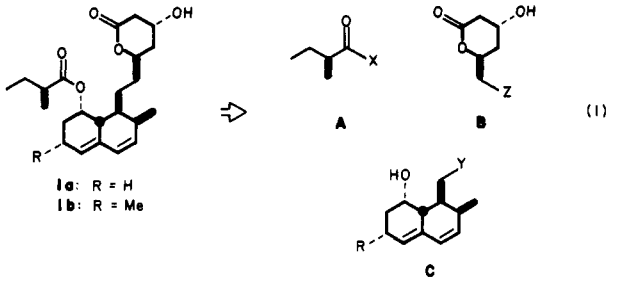
Scheme I[a]



[a] (a) *n*-BuLi, THF; $CH_3CH{=}CHCOCl$; (b) $NCCH_2COCl$, Et_3N, DMAP; (c) CH_3CHO, AcOH, piperidine.

report herein the results of an exploration of a route to mevinolin based on intramolecular Diels–Alder formation of ring B.

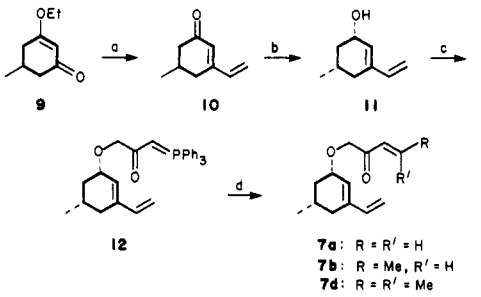
A common dissection of compounds 1 has involved separation into three subunits: an ester side chain (A), a lactone portion (B), and a hexahydronaphthalene moiety (C) (eq 1).[5g-j,6a,d-f,h,k-o] The foregoing strategy has, in fact, been successfully applied to the synthesis of several mevinic acids.[5h-j]



(1)

An early approach to compactin in this group centered around synthesis of the hexahydronaphthalene portion via intramolecular Diels–Alder reaction of crotonate ester 3, prepared conveniently by esterification of 3-vinylcyclohex-2-enol (2).[8] Intramolecular cycloaddition of 3 could provide lactone 6a, which would represent a synthon for subunit C. However, when a benzene solution of 3 was heated, the only products observed were crotonic acid and polymeric material (Scheme I). In retrospect, this result is not unduly surprising, given the relative stability of both the cation and anion generated by heterolytic fragmentation of 3. Furthermore, in accord with Boeckman's discussion of intramolecular Diels–Alder reactions in which the diene and dienophile are tethered by an ester functionality,[9] one might surmise that compound 3 would be resistant to cyclization.

Scheme II[a]



[a] (a) $CH_2{=}CHLi$, ether; H^+, H_2O; (b) $LiAlH_4$, THF; (c) $Ph_3P{=}CHCOCH_2Cl$, NaH, THF; (d) aldehyde or ketone.

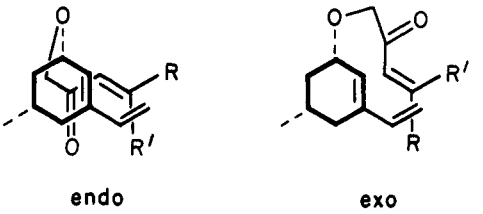


Figure 1. Interactions in the endo and exo[12] transition states for intramolecular cycloaddition of compounds 7a–d.

In an attempt to further activate this system toward cyclization, cyano enone 5 was synthesized by Knoevenagel condensation of cyano ester 4 with acetaldehyde. However, this compound suffered the same fate as compound 3: fragmentation was the only process observed.

It was clear from these results that a successful intramolecular Diels–Alder reaction would necessitate modification of the ester linkage in order to diminish the propensity of this system for heterolysis. An attractive possibility involved insertion of a methylene unit between the "acyl" and "alkoxy" halves of the ester, as in 7. This

change would disfavor fragmentation, as the anion formed would be alkoxide instead of carboxylate. Cyclization via a transition state having the carbonyl oxygen endo to the diene would provide pyranone 8, and the additional carbon atom could either be retained or excised during appropriate modification for coupling to a lactone synthon.

Treatment of the ethyl enol ether of dihydroorcinol (9) with vinyllithium, followed by acidic hydrolysis, affords dienone 10, which is reduced with lithium aluminum hydride to give, in 74% yield from 9, exclusively the *cis*-diene

(4) Alberts, A. W.; Chen, J.; Kuron, G.; Hunt, V.; Huff, J.; Hoffman, C.; Rothrock, J.; Lopez, M.; Joshua, H.; Harris, E.; Patchett, A.; Monaghan, R.; Currie, S.; Stapley, E.; Albers-Schonberg, G.; Hensens, O.; Hirshfield, J.; Hoogsteen, K.; Liesch, J. *Proc. Natl. Acad. Sci. U.S.A.* **1980**, *77*, 3957.

(5) Total syntheses: (a) Wang, N. Y.; Hsu, C. T.; Sih, C. J. *J. Am. Chem. Soc.* **1981**, *103*, 6538. (b) Hirama, M.; Uei, M. *Ibid.* **1982**, *104*, 4251. (c) Grieco, P. A.; Zelle, R. E.; Lis, R.; Finn, J. *Ibid.* **1983**, *105*, 1403. (d) Girotra, N. N.; Wendler, N. L. *Tetrahedron Lett.* **1982**, *23*, 5501. (e) Girotra, N. N.; Wendler, N. L. *Ibid.* **1983**, *24*, 3687. (f) Hirama, M.; Iwashita, M. *Tetrahedron Lett.* **1983**, *24*, 1811. (g) Yang, Y.-L.; Manna, S.; Falck, J. R. *J. Am. Chem. Soc.* **1984**, *106*, 3811. (h) Falck, J. R.; Yang, Y. L. *Tetrahedron Lett.* **1984**, *25*, 3563. (i) Rosen, T.; Heathcock, C. H. *J. Am. Chem. Soc.* **1985**, *107*, 3731.

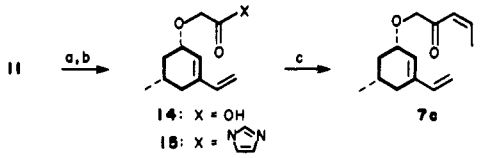
(6) Synthetic studies: (a) Danishefsky, S.; Kerwin, J. F., Jr.; Kobayashi, S. *J. Am. Chem. Soc.* **1982**, *104*, 358. (b) Funk, R. L.; Zeller, W. E. *J. Org. Chem.* **1982**, *47*, 180. (c) Deutsch, E. A.; Snider, B. B. *Ibid.* **1982**, *47*, 2682. (d) Prugh, J. D.; Deana, A. A. *Tetrahedron Lett.* **1982**, *23*, 281. (e) Yang, Y.-L.; Falck, J. R. *Ibid.* **1982**, *23*, 4305. (f) Heathcock, C. H.; Taschner, M. J.; Rosen, T.; Thomas, J. A.; Hadley, C. R.; Popjâk, G. *Ibid.* **1982**, *23*, 4747. (g) Lee, T.-J.; Holtz, W. J.; Smith, R. L. *J. Org. Chem.* **1982**, *47*, 4750. (h) Anderson, P. C.; Clive, D. L. J.; Evans, C. F. *Tetrahedron Lett.* **1983**, *24*, 1373. (i) Kuo, C. H.; Patchett, A. A.; Wendler, N. L. *J. Org. Chem.* **1983**, *48*, 1991. (j) Deutsch, E. A.; Snider, B. B. *Tetrahedron Lett.* **1983**, *24*, 3701. (k) Funk, R. L.; Mossman, C. J.; Zeller, W. E. *Ibid.* **1984**, *25*, 1655. (l) Majewski, M.; Clive, D. L. J.; Anderson, P. C. *Ibid.* **1984**, *25*, 2101. (m) Prasad, K.; Repic, O. *Ibid.* **1984**, *25*, 2435. (n) Rosen, T.; Taschner, M. J.; Heathcock, C. H. *J. Org. Chem.* **1984**, *49*, 3994. (o) Rosen, T.; Taschner, M. J.; Heathcock, C. H. *J. Org. Chem.* **1985**, *50*, 1190. (p) Burke, S. D.; Saunders, J. O.; Oplinger, J. A.; Murtiashaw, C. W. *Tetrahedron Lett.* **1985**, *26*, 1131. (q) Guindon, Y.; Yoakim, C.; Bernstein, M. A.; Morton, H. E. *Ibid.* **1985**, *26*, 1185. (r) Kozikowski, A. P.; Li, C.-S. *J. Org. Chem.* **1985**, *50*, 778.

(7) For a review, see: Rosen, T.; Heathcock, C. H. *Tetrahedron*, in press.

(8) Heathcock, C. H.; Thomas, J. A., unpublished results, 1978.

(9) Boeckman, R. K., Jr.; Demko, D. M. *J. Org. Chem.* **1982**, *47*, 1789.

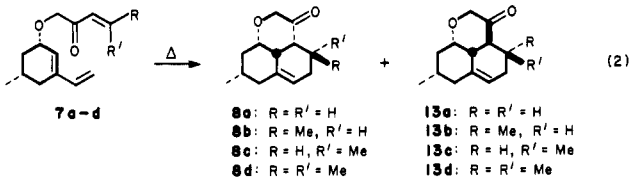
Scheme III[a]



[a] (a) $ClCH_2CO_2H$, NaH, THF; (b) 1,1'-carbonyldiimidazole, CH_2Cl_2; (c) $LiCH{=}CHCH_3$, Et_2O.

alcohol **11** (Scheme II). Alkylation of **11** with 1-chloro-3-phosphoranylidene-2-propanone[10] using sodium hydride in refluxing THF affords stabilized phosphorane **12** in 65% yield. This compound is converted to trans enone **7b** in 67% yield by treatment with acetaldehyde. As expected,[11] the trans isomer greatly predominated; in fact, none of the corresponding cis isomer could be detected.

Intramolecular Diels–Alder cyclization of **7b** was effected by heating a benzene solution in a sealed tube at 80 °C for several hours. Although cyclization takes place cleanly, it proceeds to give a mixture containing a 2:3 ratio of adducts **8b** and **13b** (eq 2).



(2)

Inspection of the transition state (exo)[12] for formation of the undesired isomer **13b** shows that there is an eclipsing interaction between the β-methyl of the enone and the vinyl terminus of the diene (Figure 1, R = Me, R' = H). Since this transition state leads to the major product, it seemed that elimination of this interaction (e.g., with cis enone **7c**) would provide even more of the exo product. Furthermore, with cis enone **7c** there should be a corresponding interaction in the endo transition state (Figure 1, R = H, R' = Me). The foregoing analysis leads one to expect that the exo/endo ratio in cyclization of cis enone **7c** should be good, resulting in an attractive synthesis of isomer **13c**. This would be a particularly useful result for application to a mevinolin synthesis, since the need for epimerization next to the carbonyl would be removed.

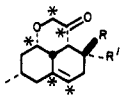
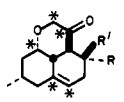
To this end, alcohol **11** was alkylated with chloroacetic acid to provide carboxylic acid **14** in 81% yield (Scheme III). Conversion to imidazolide **15** followed by reaction with a mixture of (*E*)- and (*Z*)-propenyllithium affords enones **7b** and **7c**, from which the *Z* isomer can be separated by column chromatography. With the desired substrate in hand, we set out to explore its thermal cyclization behavior.

Thermal cyclization of **7c** (90 °C, several hours) gives **8c** and **13c** in a ratio of 6:1, in complete disagreement with our expectation (eq 2). In an attempt to understand this unexpected result, we embarked upon a further exploration of the influence of dienophile substitution pattern on the stereochemistry of this intramolecular Diels–Alder reaction. Enones **7a** and **7d** were synthesized by treatment of phosphorane **12** with aqueous formaldehyde and acetone, respectively (Scheme II). Enone **7a** cyclizes at room temperature to afford adducts **8a** and **13a** in a ratio of 6:1, compound **7d** cyclizes at 130 °C (toluene) to give adducts **8d** and **13d** in a ratio of 1:1 (eq 2).

Table I. Cycloaddition of Compounds 7a–d (eq 2)

entry	compd	temp, °C	endo/exo ratio (8:13)
1	7a	25	6:1
2	7b	80	2:3
3	7c	90	6:1
4	7d	130	1:1

Table II. Carbon NMR Chemical Shifts of Diels–Alder Adducts

	8a	8b	8c	8d	avg
	208.7	208.4	208.0	207.4	208.1 ± 0.6
	132.7	131.5	133.0	131.6	132.2 ± 0.8
	124.7	122.4	125.2	124.4	124.2 ± 1.8
	76.2	76.2	75.9	76.2	76.1 ± 0.3
	74.5	74.3	74.9	72.6	74.1 ± 1.5
	13a	**13b**	**13c**	**13d**	avg
	213.3	213.2	212.7	212.7	213.0 ± 0.3
	133.4	132.5	132.7	132.2	132.7 ± 0.7
	122.8	122.4	121.5	122.1	122.2 ± 0.6
	74.1	74.3	74.4	75.1	74.5 ± 0.6
	71.4	72.0	72.0	72.6	72.0 ± 0.6

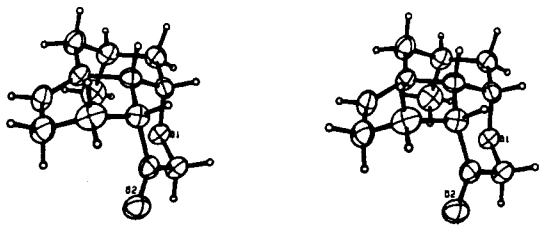


Figure 2. ORTEP stereoscopic projection of compound **8a**.

Table I summarizes the results of the four Diels–Alder cyclizations. The "intrinsic" stereochemical bias of this system is given by entry 1; that is, an unsubstituted dienophile (**7a**) shows a 6:1 preference for the endo product. Placement of a β-methyl group cis to the ketone (**7c**) results in no change, whereas placement of a β-methyl group in a trans position (**7b**) results in reversal of selectivity. β,β-dimethyl substrate **7d** is similarly unselective. Attempts to modify the observed ratios with Lewis acid catalysis were unsuccessful;[13] decomposition of Diels–Alder substrates was observed with a variety of Lewis acids, presumably due to a heterolysis reaction analogous to that observed for esters **3** and **5**.

The structures of the eight Diels–Alder adducts were assigned as follows. Single-crystal X-ray analysis of the major isomer from cyclization of **7a** established its structure as the endo isomer **8a** (Figure 2). The ^{13}C NMR spectra for all eight compounds were then compared, allowing assignment of endo and exo isomers by correlation of the five signals farthest downfield in each spectrum (one carbonyl, two olefinic, and two C–O). Chemical shifts values are given in Table II. The most useful resonances for diagnosis are those of the carbonyl, which differ by approximately 5 ppm. Smaller, but statistically significant, differences are also seen in the C–O resonances.

Further support for these assignments was provided by the demonstration that treatment of either **13b** or **8c** with a sodium methoxide/methanol solution results in conversion to a 3:1 mixture of **8c**:**13b**, indicating that this is a thermodynamic ratio. Under the same conditions, a 6:1 mixture of **8a** and **13a** changes to a 10:1 mixture.

A number of reported examples of intramolecular Diels–Alder reactions of systems analogous to ours are

(10) Hudson, R. F.; Chopard, P. A. *J. Org. Chem.* **1963**, *28*, 2446.
(11) House, H. O. "Modern Synthetic Reactions", 2nd ed.; W. A. Benjamin, Inc., Menlo Park, CA, 1972; pp 682–709.
(12) In the discussion to follow, "endo" and "exo" refer to the transition states in which the carbonyl group is endo or exo, respectively, to the diene.
(13) Roush, W. R.; Ko, A. J.; Gillis, H. R. *J. Org. Chem.* **1980**, *45*, 4264.

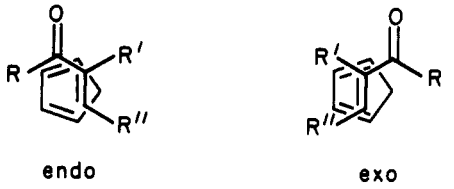
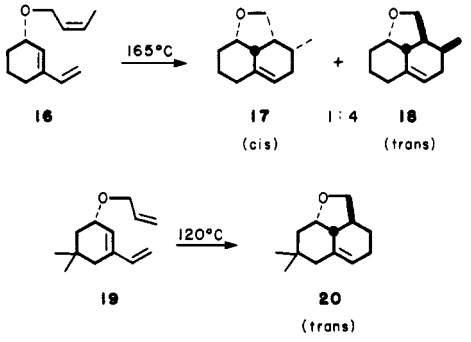


Figure 3. Transition states for Diels–Alder reactions of cyclopentadiene with dienophiles.

worthy of note. En route to a synthesis of the hexahydronaphthalene portion of compactin, Funk has reported that thermal cyclization of substrate **16** affords cis and trans adducts **17** and **18** in a ratio of 1:4.[6k] In a similar system reported by Burke, compound **19** cyclizes to give exclusively the trans adduct **20**.[14]

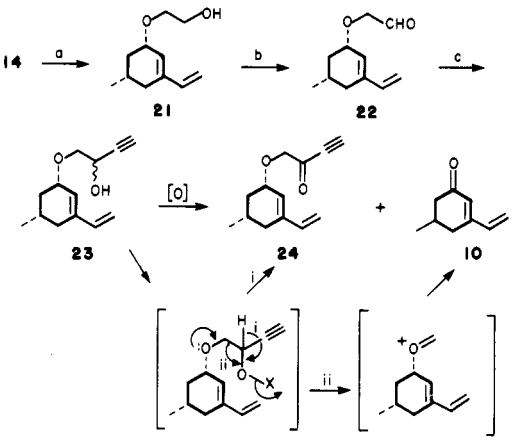


The tendency for formation of *trans*-hydrindenes is a general one, as shown in recent reviews of the intramolecular Diels–Alder reaction by Fallis[15] and Ciganek.[16] Although the analogous formation of octalin systems is somewhat less selective, a trend can be observed; examples in which the activating group of the dienophile is part of the tether between diene and dienophile (as in **7a–d**) generally favor formation of the *cis*-octalin.[15,16]

Although the examples of Funk and Burke appear to be quite similar to our own, it is obvious that intramolecular Diels–Alder reactions which form the hydrindene nucleus make poor models for predicting the stereochemical outcome of reactions which form the octalin nucleus. Indeed, the intrinsic preference of our system to form the *cis*-octalin (e.g., **7a** and **7c**) is opposite to that observed for very similar hydrindene-forming systems (**16** and **19**), yet is in good agreement with results of other octalin-forming systems.[15,16]

The reason for the observed reversal of stereochemical preference in the cyclization of trans enone **8** is unclear. It is obvious that the simple argument that was advanced regarding steric interactions in the transition state (Figure 1) is wholly inadequate. Particularly intriguing is the fact that methyl substitution on the dienophile has an effect precisely the opposite as that expected on the basis of that argument; that is, switching the methyl group from the cis position (6:1 favoring endo) to the trans position causes that transition state with what appears to be the *greater* steric interaction to be preferred (3:2 favoring exo). A similar effect of dienophilic methyl substitution has been observed by Furukawa in a study of the intermolecular Diels–Alder reactions of various dienophiles with cyclopentadiene.[17] In particular, a methyl group in the α or

Scheme IV[a]



[a] (a) $LiAlH_4$, THF; (b) $(ClCO)_2$, Me_2SO, Et_3N; (c) LiC≡CH, THF.

trans-β position on the dienophile appears to compete with the carbonyl for occupation of the endo position in the transition state (Figure 3). Furukawa has attributed this result to van der Waals attraction forces between the methyl group and the diene, although Houk has argued that steric repulsion between the methyl group and the methylene of cyclopentadiene adequately accounts for the observed trend.[18] In the transition state for cyclization of compound **7b** these steric interactions are not present since the termini of the diene are not linked together; however, we do observe a preference of the methyl group to occupy the endo position. Although this effect does not appear to be general for intermolecular reactions with acyclic dienes,[19] our results are in agreement with Furukawa's observations.

At this point attention was turned to the synthesis of acetylenic ketone **24** as a means of circumventing the problem of stereochemical control thus far encountered. Cycloaddition of this substance would yield an enone, and control of stereochemistry would be postponed to the stage of introduction of an axial methyl group by conjugate addition. Toward this end, carboxylic acid **14** was reduced with lithium aluminum hydride to obtain alcohol **21** in nearly quantitative yield (Scheme IV) Swern oxidation[20] of alcohol **21** provides aldehyde **22**, which, due to its sensitivity to aldol dimerization, is immediately treated with lithium acetylide in THF[21] to provide a 1:1 ratio of diastereomeric acetylenic carbinols **23** (70% from **21**). Oxidation of **23** to acetylenic ketone **24** proved to be surprisingly difficult. The Swern protocol[20] gave a complex mixture of products, while Collins reagent[22] and manganese dioxide gave ketone **10** as the predominant product, in low yield. Chromic acid in acetone[23] or ether[24] gives **24**, albeit in low yield (25%); dienone **10** is still a major product under these conditions. This ketone apparently arises from preferential cleavage of the C–C rather than the C–H bond to give an oxonium ion; hydrolysis and further oxidation yield the observed ketone. Related fragmentations in oxidation reactions have been described.[25]

(14) Burke, S. D.; Strickland, S. M. M.; Powner, T. H. *J. Org. Chem.* **1983**, *48*, 454.
(15) Fallis, A. G. *Can. J. Chem.* **1984**, *62*, 183.
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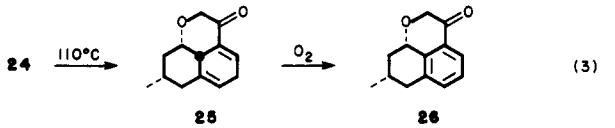
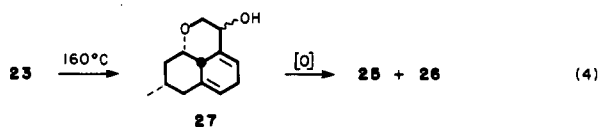
Although the foregoing route to **24** was far from satisfactory, the isolation of this compound allowed exploration of its cyclization behavior. Heating a toluene solution of **24** at reflux for 4 h causes clean conversion to dienone **25** (eq 3). It is interesting to compare this cyclization to that



(3)

of vinyl ketone **7a**, which undergoes Diels–Alder reaction at room temperature. Undoubtedly, the presence of an sp-hybridized carbon in **24** creates strain in the transition state for cyclization, and a higher reaction temperature is therefore required. Dienone **25** is sensitive to air oxidation to aryl ketone **26** while in solution; however, after purification by flash chromatography it crystallizes readily and can be stored at 0 °C indefinitely. Sensitivity to aromatization is a common problem in the adducts of intramolecular Diels–Alder reactions of acetylenic dienophiles.[26]

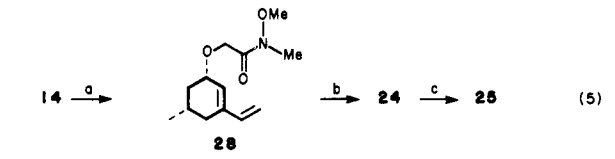
The poor yield obtained in the oxidation of **23** to **24** led us to seek an alternate route to dienone **25**. One possibility involved postponing the troublesome oxidation until after Diels–Alder cyclization. Thermal cyclization of epimeric acetylenic carbinols **23** is effected by heating a toluene solution of the substrate in a sealed tube at 160 °C for 30 h. A 1:1 mixture of dienols **27** is obtained in 69% yield, after chromatographic purification (eq 4). Unfortunately,



(4)

the oxidation of **27** to dienone **25** is no more straightforward than that of **23**; under a variety of conditions (Collins reagent,[22] Swern oxidation,[20] manganese dioxide, sulfur trioxide/pyridine complex[27]), overoxidation to aryl ketone **26** is an annoying side reaction. This is not surprising in light of the sensitivity of **25** to air oxidation (vide supra). In the best case, a 2:1 ratio of **25**:**26** was obtained (Swern oxidation).

Clearly, a route to **25** which avoids an oxidation reaction was necessary; this idea was successfully executed as shown in eq 5. Carboxylic acid **14** was converted quantitatively



(5)

(a) 1,1'-carbonyldiimidazole, CH_2Cl_2; MeNHOMe·HCl.
(b) LiC≡CH·$H_2NCH_2CH_2NH_2$, THF. (c) toluene, 110°C, 4 h.

via imidazolide **15** to *N*-methoxy, *N*-methyl amide **28**. Reaction of **28** with lithium acetylide/ethylene diamine complex[28] affords acetylenic ketone **24**, which is subjected immedately to conditions for thermal cyclization to **25**. After flash chromatography,[29] compound **25** is obtained in 60% yield, based on acid **14**.

With a viable synthesis of **25** in hand, the stage was set for exploration of the conjugate addition of a methyl group (Table III). A number of cuprate reagents were investigated. Lithium dimethylcuprate affords an 86:14 ratio of

Table III

24 + reagent → 8b + 8c

reagent	8b:8c ratio	yield, %
Me_2CuLi	86:14	77
$Me_2Cu(CN)Li_2$	80:20	78
$MeCu(CN)Li$	67:33	61
$MeCu{\cdot}BF_3$	>98:2	79

axial and equatorial addition products, **8b** and **8c**; kinetic protonation of the intermediate enolate occurs exclusively from the β face. Selectivity decreases with both the 2:1 adduct[30] and the 1:1 adduct[31] of methyllithium and copper(I) cyanide, which give **8b**:**8c** ratios of 80:20 and 67:33, respectively. The most selective reagent studied was the methylcopper–boron trifluoride complex,[32] which affords *only* the axial addition product; pyranone **8b** is obtained in 79% yield after flash chromatography.[29]

In summary, target intermediate **8b** is obtained in eight steps in overall 26% yield from dihydroorcinol. Conversion of **8b** into an appropriate intermediate for a mevinolin synthesis will be reported in a future publication from these laboratories.

Experimental Section[33]

3-Vinylcyclohex-2-en-1-yl Crotonate (3). To a stirring solution of 3-vinylcyclohex-2-en-1-ol (**2**)[6k] (746 mg, 6.02 mmol) in THF (16 mL) at −78 °C was added a solution of *n*-butyllithium in hexane (1.5 M, 3.91 mL, 5.86 mmol). Crotonyl chloride (0.61 mL, 6.40 mmol) was added, and the mixture was allowed to warm to room temperature. After 15 min, ether was added, and the mixture was poured into saturated aqueous $NaHCO_3$ (40 mL). The organic layer was dried ($MgSO_4$) and filtered, and the solvent was removed with a rotary evaporator. The residue was subjected to column chromatography on silica gel (3% ether/hexanes) to afford 816 mg (70%) of colorless oil **3**: IR (neat) 3100, 3050, 3010, 1715, 1655 cm^{-1}; ^1H NMR δ 1.4–2.4 (m, 9), 3.02 (d, 1, J = 10), 5.19 (d, 1, J = 17), 5.39 (m, 1), 5.70 (m, 1), 5.78 (dq, 1, J = 16.1), 6.28 (dd, 1, J = 10, 17), 6.87 (dq, 1, J = 16, 7). Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.95; H, 8.39. Found: C, 74.87; H, 8.22.

3-Vinylcyclohex-2-en-1-yl Cyanoacetate (4). To a stirring solution of 3-vinylcyclohex-2-en-1-ol (**2**)[6k] (0.536 g, 4.32 mmol), triethylamine (2.78 mL, 20 mmol), and 4-(dimethylamino)pyridine (56 mg, 0.459 mmol) in dry ether (6 mL) at 0 °C under nitrogen was added a solution of cyanoacetyl chloride[34] in ether (3.84 M, 4.99 mL, 9.5 mmol). After 0.5 h at 0 °C, the mixture was filtered through a sintered glass funnel, leaving behind much dark red material. The filtrate was washed successively with saturated aqueous $NaHCO_3$ (10 mL), 1 M aqueous HCl (10 mL), and saturated aqueous $NaHCO_3$ (10 mL), dried ($MgSO_4$), and filtered; the solvent was removed with a rotary evaporator affording 394 mg (48%) of crude **4**. Attempts to chromatograph this material on silica gel resulted in regeneration of **2**; therefore, the crude product was immediately subjected to further transformation: ^1H NMR ($CDCl_3$) δ 1.4–2.4 (m, 6), 3.45 (s, 2), 5.08 (d, 1, J = 11), 5.22 (d, 1, J = 19), 5.44 (m, 1), 5.70 (m, 1), 6.33 (dd, 1, J = 11, 19).

3-Vinylcyclohex-2-en-1-yl (*E*)-2-Cyano-2-butenoate (5). To a solution of 3-vinylcyclohex-2-en-1-yl cyanoacetate (**4**) (394 mg, 2.06 mmol) and acetaldehyde (0.2 mL, 3.59 mmol, distilled) in glacial acetic acid (0.5 mL) was added piperidine (20 μL, 0.20 mmol). The resulting red-brown solution was swirled; after 0.5

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(33) ^1H NMR spectra were determined at 200, 250, or 300 MHz. Unless otherwise specified, all NMR spectra were recorded in $CDCl_3$, and the chemical shifts are expressed in ppm downfield from tetramethylsilane. Data are presented in the order: multiplicity, number of hydrogens, coupling constant in hertz.
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h ether (10 mL) was added, and this mixture was washed successively with saturated aqueous $NaHCO_3$ (15 mL), 1 M aqueous HCl (15 mL), and saturated aqueous $NaHCO_3$ (15 mL) and dried ($MgSO_4$). The solvent was removed with a rotary evaporator, and the crude product was purified by flash chromatography on silica gel (3% ether/hexane), affording 140 mg (31%) of **5** as a colorless oil: IR ($CHCl_3$) 2940, 2225, 1717, 1628, 1600, 1260, 1135, 905 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.4–2.6 (m, 6), 2.22 (d, 3, J = 8), 5.10 (d, 1, J = 12), 5.27 (d, 1, J =18), 5.47 (m, 1), 5.75 (m, 1), 6.34 (dd, 1, J = 12, 18), 7.68 (q, 1, J = 8); mass spectrum (70 eV), m/z 217 (parent), 91 (base). Anal. Calcd for $C_{13}H_{15}O_2$: C, 71.87; H, 6.96; N, 6.45. Found: C, 72.04; H, 7.03; N, 6.41.

(*E*,1′*SR*,5′*SR*)-1-[(3′-Vinyl-5′-methylcyclohex-2′-enyl)oxy]-3-penten-2-one (7b). Acetaldehyde (1 mL) was distilled into a flask containing compound **12** (241 mg, 0.531 mmol). The flask was stoppered, swirled to effect solution, and allowed to stand at room temperature for 7 h. The excess acetaldehyde was removed with a rotary evaporator and the residue was subjected to column chromatography on silica gel (5% ether/hexane) to afford 78.7 mg (67%) of **7b** as a colorless oil: IR (neat) 2950, 2925, 1685, 1620, 1435, 1100; ^1H NMR ($CDCl_3$) δ 1.06 (d, 3, J = 6), 1.25 (m, 1), 1.73 (m, 2), 1.92 (dd, 3, J = 7, 1.6), 2.08 (m, 1), 2.28 (m, 1), 4.19 (m, 1), 4.26 (s, 2), 5.04 (d, 1, J = 11), 5.19 (d, 1, J = 17), 5.75 (s, 1), 6.37 (dq, 1, J = 16, 1.6), 6.37 (dd, 1, J = 11, 17), 7.02 (dq, 1, J = 16, 7). Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15. Found: 76.08; H, 9.30.

(*Z*,1′*SR*,5′*SR*)-1-[(3′-Vinyl-5′-methylcyclohex-2′-enyl)oxy]-3-penten-2-one (7c). To a stirring solution of 1-bromo-1-propene (*E*,*Z* mixture, Columbia Organics; 0.5 mL, 6 mmol) in ether (5 mL) at −78 °C was added a solution of *tert*-butyllithium in pentane (2.3 M, 0.72 mL, 1.65 mmol). After 25 min at −78 °C, this solution was transferred by cannula into a flask containing a solution of compound **15** (203 mg, 0.83 mmol) in ether (5 mL) at −78 °C. After being stirred for 3 h at −78 °C, the reaction was quenched by addition of saturated aqueous NH_4Cl (20 mL). The organic layer was separated, dried ($MgSO_4$), and filtered; the solvent was removed with a rotary evaporator. The residue was subjected to column chromatography on silica gel (10% ether/hexane) to afford, in order of elution, 4.9 mg (2%) of tertiary alcohol, 27.7 mg (15%) of **7c** as a colorless oil, and 47.7 mg (25%) of trans enone **7b**. Compound **7c** exhibited the following properties: IR (neat) 2952, 2925, 1709, 1692, 1614, 1440, 1365, 1102; ^1H NMR ($CDCl_3$) δ 1.07 (d, 3, J = 6), 1.21 (m, 1), 1.71 (m, 2), 2.10 (m, 1), 2.17 (d, 3, J = 6), 2.26 (m, 1), 4.16 (s, 2), 4.19 (m, 1), 5.05 (d, 1, J = 11), 5.19 (d, 1, J = 17), 5.76 (s, 1), 6.35 (m, 3); ^{13}C NMR ($CDCl_3$) δ 16.13, 21.97, 27.53, 32.45, 37.13, 73.73, 76.32, 112.66, 123.59, 128.93, 138.23, 138.70, 145.04, 199.10. Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15. Found: C, 76.22; H, 9.09.

(1′*SR*,5′*SR*)-1-[(3′-Vinyl-5′-methylcyclohex-2′-enyl)oxy]-4-methyl-3-penten-2-one (7d). Compound **12** (180 mg, 0.396 mmol), acetone (2 mL), and benzoic acid (20 mg) were combined and heated at 60 °C for 60 h. The excess acetone was removed with a rotary evaporator, and the residue was chromatographed on silica gel (10% ether/hexane) to afford 20.6 mg (22%) of **7d** as a colorless oil: IR ($CHCl_3$) 2953, 2925, 1695, 1680, 1615, 1440, 1100; ^1H NMR ($CDCl_3$) δ 1.06 (d, 3, J = 6), 1.22 (m, 1), 1.74 (m, 2), 1.94 (d, 3, J = 1.1), 2.11 (m, 1), 2.20 (d, 3, J = 0.9), 2.28 (m, 1), 4.12 (s, 2), 4.15 (m, 1), 5.04 (d, 1, J = 11), 5.19 (d, 1, J = 17), 5.77 (s, 1), 6.28 (m, 1), 6.38 (dd, 1, J = 11, 17). Anal. Calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 77.03; H, 9.53.

(3a*RS*,8*SR*,9a*SR*,9b*RS*)-2,3,3a,4,5,7,8,9,9a,9b-Decahydro-3-oxo-8-methylnaphtho[1,8-*bc*]pyran (8a) and (3a*SR*,8*SR*,9a*SR*,9b*RS*)-2,3,3a,4,5,7,8,9,9a,9b-Decahydro-3-oxo-8-methylnaphtho[1,8-*bc*]pyran (13a). Compound **12** (324 mg, 0.714 mmol), ether (4 mL), and formaldehyde (37% aqueous, 3 mL) were combined and stirred at room temperature for 4 h. Ether (10 mL) was added, and the organic layer was separated, dried ($MgSO_4$), and filtered. Solvent was removed with a rotary evaporator and the crude mixture was subjected to silica gel chromatography to afford 105 mg (71%) of a 6:1 mixture of **8a** and **13a**: IR ($CHCl_3$) 2955, 2930, 1720, 1605, 1185, 1115. Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80. Found: C, 75.38; H, 8.67.

Compound **8a**. A pure sample, mp 70–72 °C, was obtained by fractional crystallization from hexane: ^1H NMR δ 1.02 (d, 3, J = 7), 1.38 (m, 1), 1.7–2.2 (m, 6), 2.2–2.5 (m, 2), 2.67 (m, 1), 2.80 (m, 1), 3.88 (d, 1, J = 16), 4.06 (m, 1), 4.09 (d, 1, J = 16), 5.58 (m, 1); ^{13}C NMR δ 20.9, 21.4, 21.9, 27.5, 36.2, 40.1, 41.0, 45.0, 74.5, 76.2, 124.7, 132.7, 208.7.

Compound **13a**: ^{13}C NMR δ 19.7, 22.4, 24.1, 25.6, 35.1, 37.1, 38.8, 42.3, 71.4, 74.1, 122.8, 133.4, 213.3.

(3a*RS*,4*SR*,8*SR*,9a*SR*,9b*RS*)-2,3,3a,4,5,7,8,9,9a,9b-Decahydro-3-oxo-4,8-dimethylnaphtho[1,8-*bc*]pyran (8b) and (3a*SR*,4*RS*,8*SR*,9a*SR*,9b*RS*)-2,3,3a,4,5,7,8,9,9a,9b-Decahydro-3-oxo-4,8-dimethylnaphtho[1,8-*bc*]pyran (13b). A solution of 37.3 mg of compound **7b** in 3 mL of degassed benzene (3 mL) was heated in a sealed tube at 80 °C for 12 h. ^1H NMR analysis of the crude mixture showed that the reaction was approximately 50% complete, and that the product consisted of a 3:2 mixture of **13b** and **8b**. Column chromatography on silica gel afforded 12.0 mg (32%) of a 2:1 mixture of **13b** and **8b** and 17.0 mg (46%) of a mixture of **7b**, **8b**, and **13b**. Since **13b** and **8b** are not readily separable, data for characterization were obtained on a mixture: IR (neat) 2955, 2930, 2878, 1736, 1458, 1377, 1105. ^1H NMR (**13b**) δ 0.96 (d, 3, J = 6), 1.17 (d, 3, J = 6), 1.6–2.5 (m, 9), 2.62 (dd, 1, J = 15, 12), 3.92 (d, 1, J = 15), 4.00 (m, 1), 4.09 (d, 1, J = 15), 5.40 (m, 1); ^{13}C NMR (**13b**) 72.0, 74.3, 122.4, 132.5, 213.5; ^{13}C NMR (**8b**) 74.3, 76.2, 122.4, 131.5, 208.4. Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15. Found: C, 76.11; H, 9.14.

(3a*RS*,4*SR*,8*SR*,9a*SR*,9b*RS*)-2,3,3a,4,5,7,8,9,9a,9b-Decahydro-4,8-dimethyl-3-oxonaphtho[1,8-*bc*]pyran (8b). To a stirring suspension of CuBr:Me_2S (698 mg, 3.40 mmol) in ether (3 mL) at 0 °C was added methyllithium (1.4 M in ether, 2.2 mL, 3.09 mmol). The resulting suspension was stirred at 0 °C for 30 min and was then cooled to −55 °C. Boron trifluoride etherate (0.38 mL, 3.09 mmol) was added dropwise, and the mixture was stirred for 10 min. To this mixture was added dropwise a solution of dienone **25** (210 mg, 1.03 mmol) in ether (2 mL), and the resulting suspension was allowed to warm to −35 °C and stir for 1.5 h. Aqueous ammonia buffer (9:1 saturated aqueous NH_4Cl/NH_4OH, 15 mL) and ether (15 mL) were added, and the mixture was allowed to warm to room temperature. The organic layer was separated, dried ($MgSO_4$), and filtered. The solvent was removed with a rotary evaporator, and the crude product was purified by flash chromatography[29] to afford 179 mg (79%) of white crystalline solid **8b**: mp 59–61 °C; IR ($CHCl_3$) 2925, 1716, 1425, 1105; ^1H NMR δ 0.92, (d, 3, J = 7), 1.02 (d, 3, J = 7), 1.65 (m, 1), 1.75 (m, 1), 2.0 (m, 3), 2.3 (m, 3), 2.65 (m, 2), 3.86 (d, 1, J = 16), 4.02 (m, 1), 4.09 (d, 1, J = 16), 5.48 (m, 1); ^{13}C NMR δ 17.8, 21.0, 25.0, 27.5, 28.5, 36.5, 37.4, 39.9, 50.8, 74.5, 76.4, 122.7, 131.7, 208.8. Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15. Found: C, 76.07; H, 9.18.

(3a*RS*,4*RS*,8*SR*,9a*SR*,9b*RS*)-2,3,3a,4,5,7,8,9,9a,9b-Decahydro-3-oxo-4,8-dimethylnaphtho[1,8-*bc*]pyran (8c) and (3a*SR*,4*SR*,8*SR*,9a*SR*,9b*RS*)-2,3,3a,4,5,7,8,9,9a,9b-Decahydro-3-oxo-4,8-dimethylnaphtho[1,8-*bc*]pyran (13c). A solution of **7c** (20.4 mg, 0.093 mmol) in degassed toluene (3 mL) was heated in a sealed tube at 90 °C for 19.5 h. ^1H NMR analysis of the crude mixture showed that the reaction was approximately 75% complete and that the product consisted of a 6:1 ratio of **8c** to **13c**. Column chromatography on silica gel afforded 4.1 mg (20%) of **8c** and 1.4 mg (7%) of **13c**, as well as a mixture of the two products and starting material.

Compound **8c**: IR (neat) 2950, 2900, 2860, 1715, 1450, 1375, 1095; ^1H NMR δ 1.00 (d, 3, J = 7), 1.30 (d, 3, J = 7), 1.6–2.4 (m, 8), 2.55 (m, 1), 2.80 (m, 1), 3.79 (d, 1, J = 15), 3.92 (d, 1, J = 15), 4.06 (m, 1), 5.55 (m, 1); ^{13}C NMR δ 19.7, 21.2, 27.2, 29.8, 32.5, 36.3, 39.2, 44.2, 50.1, 74.9, 75.9, 125.2, 133.0, 208.0. Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15. Found: C, 76.61; H, 9.39.

Compound **13c**: ^1H NMR δ 0.87 (d, 3, J = 7), 0.98 (d, 3, J = 7), 1.6–2.6 (m, 9), 2.72 (dd, 1, J = 2.7, 13), 3.87 (d, 1, J = 18), 4.05 (d, 1, J = 18), 4.09 (m, 1), 5.38 (m, 1); ^{13}C NMR δ 14.0, 22.5, 23.0, 25.7, 27.6, 32.4, 33.0, 35.5, 44.5, 72.0, 74.4, 121.5, 132.7, 212.7.

(3a*SR*,8*SR*,9a*SR*,9b*RS*)-2,3,3a,4,5,7,8,9,9a,9b-Decahydro-3-oxo-4,4,8-trimethylnaphtho[1,8-*bc*]pyran (8d) and (3a*RS*,8*SR*,9a*SR*,9b*RS*)-2,3,3a,4,5,7,8,9,9a,9b-Decahydro-3-oxo-4,4,8-trimethylnaphtho[1,8-*bc*]pyran (13d). Compound **7d** (18.5 mg, 0.079 mmol) was heated in degassed toluene (3 mL) in a sealed tube at 131 °C for 37 h. The solvent was removed with a rotary evaporator; ^1H NMR analysis indicated that reaction was approximately 50% complete and that the ratio of **8d** to **13d** was 1:1. The crude mixture was chromatographed on silica gel (5% ether/hexane) to afford 3.1 mg (17%) of **8d** as a colorless

oil, 2.8 mg (15%) of a mixture of **8d** and **13d**, and 1.5 mg (8%) of **13d** as a colorless oil.

Compound **8d**: IR ($CHCl_3$) 2952, 2925, 1718, 1600, 1455, 1433, 1198, 1108; ^1H NMR ($CDCl_3$) δ 0.86 (s, 3), 1.00 (d, 3, J = 7), 1.28 (s, 3), 1.68 (m, 2), 1.8–2.2 (m, 3), 2.2–2.5 (m, 3), 2.85 (m, 1), 3.78 (d, 1, J = 14), 3.90 (d, 1, J = 14), 4.08 (m, 1), 5.47 (m, 1); ^{13}C NMR δ 72.6, 76.2, 124.4, 131.6, 207.4.

Compound **13d**: IR ($CHCl_3$) 3022, 2960, 2880, 1733, 1613, 1520, 1422, 1207; ^1H NMR ($CDCl_3$) δ 0.96 (s, 3), 0.97 (d, 3, J = 6), 1.23 (s, 3), 1.6–2.5 (m, 8), 2.65 (d, 1, J = 15), 3.84 (d, 1, J = 18), 4.02 (d, 1, J = 18), 4.06 (m, 1), 5.38 (m, 1); ^{13}C NMR δ 72.6, 75.1, 122.1, 132.2, 212.7.

Combustion analysis was carried out on the mixed fraction. Anal. Calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 77.04; H, 9.54.

3-Ethoxy-5-methylcyclohex-2-en-1-one[35] **(9)** was prepared according to the method of Gannon and House.[36]

3-Vinyl-5-methylcyclohex-2-en-1-one (10). Vinyl bromide (2 mL, 28 mmol) was condensed into a 50-mL three-necked flask at −78 °C. Ether (20 mL) was added, and magnetic stirring was commenced. A solution of *tert*-butyllithium in pentane (2.3 M, 3.11 mL, 7.15 mmol) was added with a syringe. After 30 min at −78 °C, a solution of 3-ethoxy-5-methylcyclohex-2-en-1-one (**9**) (0.495 g, 3.21 mmol) in ether (3 mL) was added with a syringe, taking care that the tip of the needle was underneath the surface for cooling as the solution was added. After 2 h at −78 °C, water (10 mL) was added, and the mixture was allowed to warm to room temperature. The layers were separated, and the organic layer was washed with 1 M HCl (10 mL) and saturated aqueous $NaHCO_3$ (10 mL), dried ($MgSO_4$), and filtered. The solvent was removed with a rotary evaporator to afford 396 mg (91%) of a light yellow oil. Column chromatography on silica gel (25% ether/hexane) gave 306 mg (70%) of light yellow oil **10**: IR (neat) 2950, 1659, 1579, 1377, 1294, 1238; ^1H NMR ($CDCl_3$) δ 1.12 (d, 3, J = 6), 2.0–2.7 (m, 5), 5.47 (d, 1, J = 11), 5.70 (d, 1, J = 17), 5.95 (s, 1), 6.51 (dd, 1, J = 11, 17). Anal. Calcd for $C_9H_{12}O$: C, 79.37; H, 8.88. Found: C, 79.13; H, 8.93.

(1*SR*,5*SR*)-3-Vinyl-5-methylcyclohex-2-en-1-ol (11). To a stirring suspension of $LiAlH_4$ (72.4 mg, 1.91 mmol) in THF (5 mL) at −78 °C was added dropwise a solution of 3-vinyl-5-methylcyclohex-2-en-1-one (**10**) (111 mg, 0.816 mmol) in THF (5 mL). The mixture was warmed to 0 °C and stirred for 3 h, at which time the reaction was quenched by successive slow addition of water (72 μL), 15% aqueous NaOH (72 μL), and water (216 μL). After addition of $MgSO_4$, the mixture was filtered and the insoluble portion was washed thoroughly with ether. The solvent was removed with a rotary evaporator to afford 94.3 mg (83%) of a colorless oil. Column chromatography on silica gel (25% ether/hexane) provided 79.9 mg (71%) **11** as a colorless oil: IR (neat) 3320, 2949, 1603, 1447, 1027; ^1H NMR ($CDCl_3$) δ 1.05 (d, 3, J = 6), 1.5–2.4 (m, 6), 4.40 (m, 1), 5.04 (d, 1, J = 11), 5.18 (d, 1, J = 18), 5.68 (s, 1), 6.36 (dd, 1, J = 11, 18); ^{13}C NMR ($CDCl_3$) δ 21.96, 27.74, 32.40, 41.32, 68.33, 112.63, 132.04, 137.33, 138.86. Anal. Calcd for $C_9H_{14}O$: C, 78.21; H, 10.21. Found: C, 78.32; H, 10.30. When this two-step procedure (from **9**) was performed on a larger scale (0.435 mol), compound **11** was obtained by distillation (bp 51–55 °C (0.2 mm)) in 74% overall yield, without purification of intermediate **10**.

(1′*SR*,5′*SR*)-1-[(3′-Vinyl-5′-methylcyclohex-2′-enyl)oxy]-3-(triphenylphosphoranylidene)-2-propanone (12). To a suspension of NaH (0.24 g, 10 mmol) in THF (3 mL) at room temperature under nitrogen was added a solution of alcohol **11** (350 mg, 2.54 mmol) in THF (4 mL), followed by 1-chloro-3-(triphenylphosphoranylidene)-2-propanone[9] (797 mg, 2.26 mmol). After 22 h of stirring, the mixture was poured into water (20 mL), and the layers were shaken and separated. The organic layer was dried ($MgSO_4$) and filtered, and the solvent was removed with a rotary evaporator. Column chromatography on silica gel (1% MeOH/$CHCl_3$) afforded 671 mg (65%) of **12** as a tan-colored foamy solid: IR (neat) 2952, 2930, 1530, 1439, 1402, 1110; ^1H NMR δ 1.05 (d, 3, J = 6), 1.24 (m, 1), 1.75 (m, 2), 2.21 (m, 2), 4.01 (d, 1, J = 15), 4.08 (d, 1, J = 15), 4.23 (d, 1, J = 26), 4.27 (m, 1), 5.00 (d, 1, J = 11), 5.15 (d, 1, J = 17), 5.84 (br s, 1), 6.36 (dd, 1, J = 11, 17), 7.55 (m, 15); HRMS calcd for $C_{30}H_{31}O_2P$ 454.2062, found 454.2051.

(1*SR*,5*SR*)-[(5-Methyl-3-vinylcyclohex-2-enyl)oxy]acetic Acid (14). To a slurry of NaH (5.76 g, 240 mmol, washed with hexane to remove oil) in THF (70 mL) at room temperature under nitrogen was added a solution of alcohol **11** (10.18 g, 73.8 mmol) in THF (10 mL). To this mixture was added dropwise a solution of chloroacetic acid (8.37 g, 88.5 mmol) in THF (20 mL). The mixture was heated at reflux for 1.5 h and was allowed to cool to room temperature. Ether (50 mL) was added, and the excess NaH was quenched by dropwise addition of ethanol. Water (100 mL) was added, and the organic layer was removed. The aqueous layer was acidified with aqueous H_3PO_4 (1 M, 350 mL) and was extracted with ether (2 × 100 mL). The organic layer was dried and filtered, and the solvent was removed with a rotary evaporator to afford 11.80 g (81%) of yellow oil **14**: IR (neat) 3800–2300, 2950, 1725, 1603, 1117; ^1H NMR δ 1.07 (d, 3, J = 6), 1.22 (m, 1), 1.71 (m, 2), 2.08 (m, 1), 2.18 (m, 1), 4.20 (s, 2), 4.23 (m, 1), 5.05 (d, 1, J = 11), 5.19 (d, 1, J = 17), 5.72 (s, 1), 6.36 (dd, 1, J = 11, 17). An analytical sample, mp 61–63 °C, was obtained by crystallization from petroleum ether. Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 66.98; H, 8.11.

(1*SR*,5*SR*)-*N*-[[(3-Vinyl-5-methylcyclohex-2-enyl)oxy]acetoyl]imidazole (15). To a stirring solution of carbonyldiimidazole (1.00 g, 6.17 mmol) in CH_2Cl_2 (15 mL) at 0 °C was added a solution of compound **14** (1.00 g, 5.10 mmol) in CH_2Cl_2 (15 mL). The mixture was allowed to warm to room temperature and stir for 1 h and was then washed with water (3 × 25 mL), dried ($MgSO_4$), and filtered. Removal of solvent with a rotary evaporator afforded 1.30 g (104%) of **15** as a tan solid. Further purification proved to be difficult and was unnecessary for subsequent reaction: IR ($CHCl_3$) 2958, 2932, 1756, 1734, 1467, 1378, 1305; ^1H NMR ($CDCl_3$) δ 1.07 (d, 3, J = 6), 1.24 (m, 1), 1.75 (m, 2), 2.12 (m, 1), 2.30 (m, 1), 4.30 (m, 1), 4.63 (s, 2), 5.09 (d, 1, J = 11), 5.23 (d, 1, J = 17), 5.73 (s, 1), 6.36 (dd, 1, J = 11, 17), 7.12 (s, 1), 7.58 (s, 1), 8.35 (s, 1); HRMS, calcd for $C_{14}H_{18}N_2O_2$ 246.1368, found 246.1370.

(1*SR*,5*SR*)-1-(2′-Hydroxyethoxy)-5-methyl-3-vinylcyclohex-2-ene (21). To a stirring suspension of $LiAlH_4$ (24 mg, 0.638 mmol) in ether (2 mL) at 0 °C under nitrogen was added dropwise a solution of carboxylic acid **14** (100 mg, 0.15 mmol) in ether (2 mL). The mixture was allowed to warm to room temperature and stir for 1.5 h. The reaction was quenched by addition of 24 μL of H_2O, 24 μL of 15% NaOH, and 72 μL of H_2O. After addition of $MgSO_4$, the mixture was filtered, and the solvent was removed with a rotary evaporator to afford 90.5 mg (98%) of crude **21**. Column chromatography on silica gel (50% ether/hexanes) provided 77.4 mg (83%) of **50** as a colorless oil: IR (neat) 3430, 2950, 1610, 1355, 1095; ^1H NMR δ 1.06 (d, 3, J = 6), 1.18 (m, 1), 1.75 (m, 2), 2.10 (m, 1), 2.28 (m, 1), 2.40 (s br, 1), 3.68 (m, 4), 4.13 (m, 1), 5.03 (d, 1, J = 11), 5.18 (d, 1, J = 17), 5.73 (s br, 1), 6.36 (dd, 1, J = 11, 17). Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95. Found: C, 72.45; H, 9.98.

(1*SR*,5*SR*)-[(5-Methyl-3-vinylcyclohex-2-enyl)oxy]acetaldehyde (22). According to the Swern procedure,[20] to a stirring solution of oxalyl chloride (133 mg, 1.05 mmol) in CH_2Cl_2 (2.4 mL) at −60 °C under nitrogen was added a solution of Me_2SO (164 mg, 2.10 mmol) in CH_2Cl_2 (0.5 mL). After 2 min, a solution of compound **21** (174 mg, 0.956 mmol) in CH_2Cl_2 (1 mL) was added. After 5 min, triethylamine (483 mg, 4.78 mmol) was added and the mixture was stirred for 5 min at −60 °C. After warming to room temperature, water (15 mL) and CH_2Cl_2 (15 mL) were added; the layers were separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic phases were washed successively with 1 M aqueous H_3PO_4, saturated aqueous $NaHCO_3$ and brine. Drying ($MgSO_4$) and filtration followed by removal of solvent with a rotary evaporator afforded 171.3 mg (99%) of **22** as a colorless oil: ^1H NMR δ 1.07 (d, 3, J = 6), 1.21 (m, 1), 1.74 (m, 2), 2.09 (m, 1), 2.28 (m, 1), 4.15 (s, 2), 4.22 (m, 1) 5.05 (d, 1, J = 11), 5.20 (d, 1, J = 17), 5.72 (s br, 1), 6.37 (dd, 1, J = 11, 17), 9.75 (s, 1). A sample of **22** that had been subjected to column chromatography and which therefore contained about 15% of aldol dimer gave the following data: IR (neat) 2950, 2925, 1740, 1607, 1450, 1100. Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.04; H, 8.69.

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(1′*SR*,5′*SR*,2*SR*)-1-[(5′-Methyl-3′-vinylcyclohex-2′-enyl)-oxy]-3-butyn-2-ol (23a) and (1′*SR*,5′*SR*,2*RS*)-1-[(5′-Methyl-3′-vinylcyclohex-2′-enyl)oxy]-3-butyn-2-ol (23b). A solution of lithium acetylide[21] in THF was prepared as follows: acetylene gas was allowed to pass rapidly into 25 mL of THF at −78 °C for 5 min. To this solution was added a solution of *n*-butyllithium in hexane (11.86 mmol, 1.5 M), and the acetylene flow was stopped. After 10 min, a solution of crude aldehyde **22** (1.07 g, 5.93 mmol) in THF (10 mL) was added. The mixture was stirred at −78 °C for 2.5 h, was allowed to warm to room temperature, and was poured into saturated aqueous NH_4Cl (30 mL). The aqueous layer was extracted with ether (25 mL), and the combined organic phases were dried ($MgSO_4$) and filtered. Removal of solvent with a rotary evaporator followed by column chromatography on silica gel (15% ether/hexane) afforded 858 mg (70%) of a 1:1 mixture of epimers **23** as a colorless oil: IR (neat) 3420, 3300, 2950, 2920, 2865, 2100, 1605, 1095; ^1H NMR δ 1.05 (d, 3, *J* = 6), 1.21 (m, 1), 1.70 (m, 2), 2.09 (m, 1), 2.28 (m, 1), 2.46 (d, 1, *J* = 2), 2.59 (s br, 1), 3.65 (m, 2), 4.21 (m, 1), 4.54 (m, 1), 5.04 (d, 1, *J* = 11), 5.19 (d, 1, *J* = 17), 5.72 (m, 1), 6.36 (dd, 1, *J* = 11, 17). Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80. Found: C, 75.45; H, 8.59.

(1′*SR*,5′*SR*)-1-[(5′-Methyl-3′-vinylcyclohex-2′-enyl)-oxy]-3-butyn-2-one (24). To a stirring suspension of lithium acetylide–ethylenediamine complex (533 mg, 5.79 mmol) in THF (10 mL) at 0 °C was added a solution of amide **55** (847 mg, 3.54 mmol) in THF (5 mL). After 45 min, the mixture was added with a syringe to a vigorously stirring mixture of acetic acid (3 mL), water (30 mL), and ether (30 mL). The layers were separated, and the organic phase was washed with water (30 mL) and saturated aqueous $NaHCO_3$ (2 × 30 mL), dried ($MgSO_4$), and filtered. The solvent was removed with a rotary evaporator, and the crude product was normally subjected immediately to Diels–Alder cyclization. A sample purified by column chromatography (10% ether/hexane) gave the following spectral and analytical data: IR (CH_2Cl_2) 3300, 2951, 2080, 1705, 1685, 1060 cm^{-1}; ^1H NMR δ 1.06 (d, 3, *J* = 6), 1.24 (m, 1), 1.75 (m, 2), 2.08 (m, 1), 2.29 (m, 1), 3.33 (s, 1), 4.25 (m, 1), 4.30 (s, 2), 5.05 (d, 1, *J* = 11), 5.19 (d, 1, *J* = 17), 5.74 (s, 1), 6.36 (dd, 1, *J* = 11, 17). Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.19; H, 8.00.

(8*SR*,9a*SR*,9b*SR*)-2,3,5,7,8,9,9a,9b-Octahydro-8-methyl-3-oxonaphtho[1,8-*bc*]pyran (25) and (8*SR*,9a*SR*)-2,3,7,8,9,9a-Hexahydro-8-methyl-3-oxonaphtho[1,8-*bc*]pyran (26). According to the Swern procedure,[20] to a solution of oxalyl chloride (35.4 mg, 0.279 mmol) in CH_2Cl_2 (0.7 mL) at −60 °C under nitrogen was added a solution of Me_2SO (43.6 mg, 0.559 mmol) in CH_2Cl_2 (0.15 mL). After 2 min, a solution of compound **27** (52.3 mg, 0.254 mmol) in CH_2Cl_2 (0.25 mL)) was added. The mixture was stirred at −60 °C for 15 min; triethylamine (128 mg, 1.27 mmol) was added, and the mixture was stirred at −60 °C for 5 min and then warmed to room temperature. Water (10 mL) and CH_2Cl_2 (10 mL) were added, and the organic layer was washed with 1 M aqueous H_3PO_4 (10 mL), saturated aqueous $NaHCO_3$ (10 mL), and brine (10 mL). The resulting organic layer was dried ($MgSO_4$) and filtered, and the solvent was removed with a rotary evaporator. The residue was chromatographed on silica gel with 10% ether/hexanes as eluant to obtain 15.2 mg (30%) of **26** as a white amorphous solid, mp 75.5–76.5 °C, and 19.5 mg (38%) of **25** as a colorless oil.

Compound **26**: IR ($CHCl_3$) 2955, 1695, 1590, 1295, 1125; ^1H NMR δ 1.16 (d, 3, *J* = 7), 1.49 (q, 1, *J* = 12), 2.05 (m, 1), 2.25 (m, 1), 2.46 (dd, 1, *J* = 12, 17), 2.94 (dd, 1, *J* = 5, 17), 4.31 (dd, 1, *J* = 1, 17), 4.53 (d, 1, *J* = 17), 4.73 (dd, 1, *J* = 5, 11), 7.35 (m, 2), 7.86 (m, 1). Anal. Calcd for $C_{13}H_{14}O_2$: C, 77.20; H, 6.98. Found: C, 76.96; H 6.87.

Compound **25**: IR ($CHCl_3$) 2955, 2870, 1707, 1687, 1635, 1100; ^1H NMR δ 0.99 (3, d, *J* = 6), 1.35 (m, 1), 1.90 (m, 3), 2.45 (m, 1), 2.7–3.3 (m, 3), 4.00 (d, 1, *J* = 17), 4.09 (m, 1), 4.16 (d, 1, *J* = 17), 5.54 (m, 1), 6.89 (m, 1). Anal. Calcd. for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.47, H, 7.78.

(8*SR*,9a*SR*,9b*SR*)-2,3,5,7,8,9,9a,9b-Octahydro-8-methyl-3-oxonaphtho[1,8-*bc*]pyran (25). A solution of crude acetylenic ketone **24** (3.54 mmol) in toluene was degassed with a stream of dry nitrogen and was heated at reflux under a nitrogen atmosphere for 4 h. After cooling to room temperature, the solvent was removed with a rotary evaporator and the crude product was subjected to flash chromatography[29] on silica gel (10% ether/hexane), affording 436 mg (60%) of **25** as an off-white solid, mp 62–64 °C; IR ($CHCl_3$) 2955, 2870, 1707, 1687, 1635, 1100; ^1H NMR δ 0.99 (d, 3, *J* = 6), 1.35 (m, 1), 1.90 (m, 3), 2.45 (m, 1), 2.7–3.3 (m, 3), 4.00 (d, 1, *J* = 17), 4.09 (m, 1), 4.16 (d, 1, *J* = 17), 5.54 (m, 1), 6.89 (m, 1). Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.47; H, 7.78.

(3*RS*,8*SR*,9a*SR*,9b*SR*)-2,3,5,7,8,9,9a,9b-Octahydro-3-hydroxy-8-methylnaphtho[1,8-*bc*]pyran (27a) and (3*SR*,8*SR*,9a*SR*,9b*SR*)-2,3,5,7,8,9,9a,9b-Octahydro-3-hydroxy-8-methylnaphtho[1,8-*bc*]pyran (27b). A solution of **23** (1:1 mixture, 215 mg, 1.04 mmol) in toluene (2 mL) was sealed in a Pyrex tube and heated at 160 °C for 29.5 h. After cooling to room temperature, the tube was opened, and the solvent was removed from the contents with a rotary evaporator. Column chromatography on silica gel (25% ether/hexane) afforded 15.5 mg (8%) of unreacted **23**, followed by 148 mg (69%) of a 1:1 mixture of epimers of **27** as a colorless oil: IR (neat) 3600, 3400, 2925, 2860, 1603, 1450, 1097; ^1H NMR (less polar isomer) δ 0.92 (d, 3, *J* = 7), 1.13 (m, 1), 1.70 (m, 3), 1.92 (m, 1), 2.36 (m, 1), 2.79 (m, 2), 3.02 (m, 1), 3.47 (dd, 1, *J* = 11, 6.5) 3.85 (dd, 1, *J* = 11, 5.5), 3.97 (m, 1), 4.35 (m, 1), 5.55 (m, 1), 6.03 (m, 1); ^1H NMR (more polar isomer) δ 0.93 (d, 3, *J* = 7), 1.27 (m, 1), 1.5–2.1 (m, 4), 2.40 (m, 1), 2.75 (m, 2), 3.27 (m, 1), 3.67 (dd, 1, *J* = 2.5, 12), 3.94 (dd, 1, *J* = 12, 4.5), 4.13 (m, 1), 4.25 (m, 1), 5.50 (m, 1), 5.90 (m, 1). Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80. Found: C, 75.43; H, 8.65.

(1*SR*,5*SR*)-*N*-Methoxy-*N*-methyl-α-[(5-methyl-3-vinylcyclohex-2-enyl)oxy]acetamide (28). To a stirring solution of acid **14** (1.36 g, 6.94 mmol) in CH_2Cl_2 (15 mL) at 0 °C was added a solution of carbonyldiimidazole (1.24 g, 7.63 mmol) in CH_2Cl_2 (15 mL). The mixture was allowed to warm to room temperature and stir for 25 min. To this solution was added (neat) *O*,*N*-dimethylhydroxylamine hydrochloride (0.812 g, 8.33 mmol). The mixture was stirred overnight at room temperature and was then poured into 1 M aqueous H_3PO_4 (30 mL). The organic phase was washed with saturated aqueous $NaHCO_3$ and brine, dried ($MgSO_4$), and filtered. The solvent was removed with a rotary evaporator to afford 1.66 g (100%) of **28** as a yellow oil: IR (neat) 2953, 2930, 1685, 1135, 1080, 985; ^1H NMR δ 1.05 (d, 3, *J* = 6), 1.22 (m, 1), 1.70 (m, 2), 2.15 (m, 1), 2.27 (m, 1), 3.20 (s, 3), 3.70 (s, 3), 4.25 (m, 1), 4.34 (s, 2), 5.02 (d, 1, *J* = 11), 5.17 (d, 1, *J* = 17), 5.80 (s, 1), 6.36 (dd, 1, *J* = 11, 17). A sample was purified by column chromatography on silica gel (50% ether/hexane) for elemental analysis. Anal. Calcd for $C_{13}H_{21}O_3N$: C, 65.25; H, 8.84; N, 5.85. Found: C, 65.11; H, 8.86; N, 5.79.

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Supplementary Material Available: X-ray crystallographic data for compound **8a**, including experimental details, general temperature factor expressions, thermal and positional parameters of non-hydrogen atoms, bond lengths, bond angles, and torsional angles (11 pages). Ordering information is given on any current masthead page.