pyrrolidone (25 mL) under nitrogen at 25 °C was added bromobutenolide **20** (1.57 g, 8.9 mmol). After 24 h the mixture was poured into 1 N HCl (100 mL) and extracted with ethyl acetate (3 × 50 mL). The combined organic extract was washed with water (50 mL) and saturated aqueous NaCl, dried over $MgSO_4$, and filtered, and the solvent was evaporated at reduced pressure to give 2.18 g of crude product. Chromatography (silica gel, gradient elution with dichloromethane to 30% ethyl acetate in dichloromethane gave first 0.66 g (39%) of (±)-4'-epistrigol (**21**) as a white solid and then 0.60 g (35%) of (±)-strigol (**1**) as a white solid.

(±)-Strigol (**1**): mp 202-205 °C (ethyl acetate-hexane); ^{1}H NMR (470 MHz) δ 1.09 (s, 3), 1.16 (s, 3), 1.44 (dt, J = 12.4, 2.5 Hz, 1), 1.56 (ddd, J = 12.4, 6.7, 2.8 Hz, 1), 1.68 (m, 1), 1.78 (br, 1, OH), 1.98 (m, 1), 2.01 (br s, 3), 2.70 (m, 2), 3.64 (m, 1), 4.11 (br t, J = 6.49 Hz, 1), 5.50 (br d, J = 7.84 Hz, 1), 6.16 (br s, 1), 6.93 (br s, 1), 7.45 (d, J = 2.29 Hz, 1); ^{13}C NMR (50 MHz) δ 10.73 (CH_3), 27.53 (CH_3), 27.65 (CH_3), 29.69 (CH_2), 32.37 (C), 36.63 (CH), 36.96 (CH_2), 37.86 (CH_2), 67.28 (CH), 88.00 (CH), 100.65 (CH), 113.65 (C=), 135.73 (C=), 141.15 (CH=), 142.41 (C=), 142.66 (C=), 150.72 (CH=), 170.38 (C=O), 171.54 (C=O).

(±)-4'-Epistrigol (**21**): mp 178-180 °C (ethyl acetate-hexane); ^{1}H NMR (470 MHz) δ 1.08 (s, 3), 1.15 (s, 3), 1.44 (dt, J = 12.5, 2.6 Hz, 1), 1.55 (ddd, J = 12.5, 6.7, 2.9 Hz, 1), 1.67 (m, 1), 1.77 (br, 1, OH), 1.98 (m, 1), 2.01 (t, J = 1.2 Hz, 3), 2.69 (m, 2), 3.63 (m, 1), 4.08 (br t, J = 6.59 Hz, 1), 5.50 (br d, J = 7.94 Hz, 1), 6.16 (t, J = 1.2 Hz, 1), 6.93 (t, J = 1.2 Hz, 1), 7.44 (d, J = 2.5 Hz, 1); ^{13}C NMR δ 10.73 (CH_3), 27.56 (CH_3), 27.65 (CH_3), 29.63 (CH_2), 32.35 (C), 36.57 (CH), 37.04 (CH_2), 37.96 (CH_2), 69.24 (CH), 88.04 (CH), 100.47 (CH), 113.75 (C=), 135.82 (C=), 141.18 (CH=), 142.17 (C=), 142.92 (C=), 150.40 (CH=), 170.32 (C=O), 171.57 (C=O).

Acknowledgment. We express appreciation to the United States Department of Agriculture and Purdue University for financial support and to Drs. A. Pepperman and S. Vail for helpful discussions during the course of this work.

Registry No. **1**, 51820-11-2; **2**, 127-41-3; **3** (isomer I), 84107-27-7; **3** (isomer II), 84107-28-8; **4** (isomer I), 94425-37-3; **4** (isomer II), 94425-38-4; **5** (isomer I), 84057-28-3; **5** (isomer II), 84107-29-9; **6**, 60078-92-4; **7**, 18378-66-0; **8**, 51823-74-6; **9**, 94348-18-2; **10**, 51799-97-4; **11a**, 60078-95-7; **12**, 94348-19-3; **13**, 59488-99-2; **14**, 61343-45-1; **15**, 51800-01-2; **16**, 51820-15-6; **17** (isomer I), 94348-20-6; **17** (isomer II), 94348-21-7; **18**, 59518-85-3; **19**, 94480-17-8; **20**, 59488-94-7; **21**, 52389-58-9; dimethyl malonate, 108-59-8; methyl bromoacetate, 96-32-2; ethyl formate, 109-94-4.

Synthetic Approach to the Amphilectane Diterpenes: The Use of Nitriles as Terminators of Carbocation-Olefin Cyclizations

Robert V. Stevens† and Kim F. Albizati*[1]

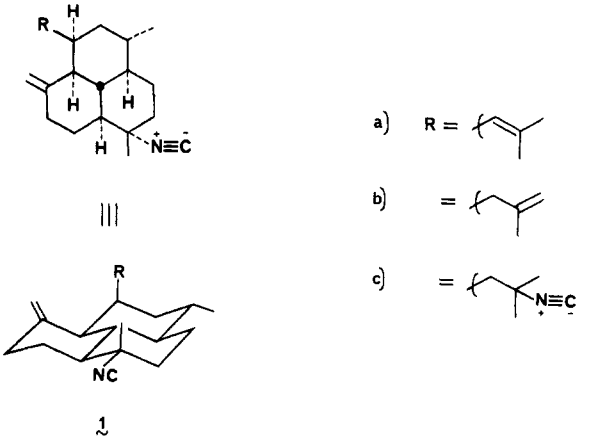
Department of Chemistry and Biochemistry, University of California, Los Angeles, California 90024

Received August 3, 1984

A biomimetic approach to the synthesis of tricyclic terpenoid isonitriles from marine sponges is described which involves carbocation-olefin cyclization of polyolefinic precursors terminated by the stereoselective formation of a carbon-nitrogen bond. The key intermediate **8** was produced in racemic and optically pure form and was subjected to a cuprate addition-aldol trapping sequence to produce the olefinic substrates **15-17**. Cyclization of **16** and **17** was successful utilizing mercury(II) nitrate in nitrile solvents to produce bicyclic amides **28-33** after reductive cleavage of the carbon-mercury bond. Transformation of the mercuri halide group in the intermediate organomercurial amides **37** and **40** to several types of functionality provided potential intermediates for the synthesis of amphilectane diterpenes.

Carbocation-olefin cyclization provides the means to introduce or transform functionality while simultaneously forming carbon-carbon and carbon-heteroatom bonds in a stereocontrolled fashion.[2,3] A major thrust in this area has been the formulation of new initiators and terminators of the cyclization process, thus expanding the functionalization aspect of the transformation. While oxygen nucleophiles have been used very successfully in this regard, nitrogen nucleophiles as terminators are rare,[4] despite their obvious potential for the synthesis of nitrogenous heterocycles. We wish to describe our findings in this area within the context of our work in the field of marine natural products synthesis.

The amphilectane diterpenes are a group of nine tri- and tetracyclic isonitrile-containing metabolites isolated from the tropical marine sponges *Hymeniacidon amphilecta* and an unidentified *Adocia* species.[5] Three of the compounds possess the common structure **1** differing only in the four-carbon side chain at C-1. In general, the metabolites display in vitro antimicrobial activity and "in vivo...marked toxicity".[5a] Our desire was to synthesize **1a-c** in optically pure form by combining the concepts of the



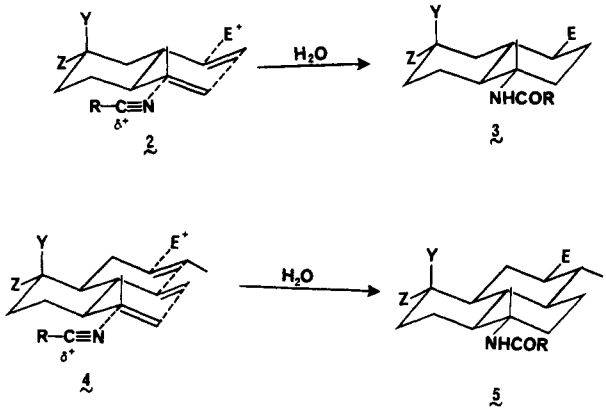
1

†Deceased March 9, 1984.

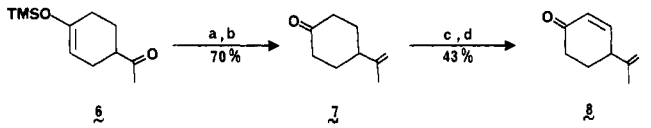
(1) Current address The Scripps Institution of Oceanography, La Jolla, CA.

0022-3263/85/1950-0632$01.50/0

Scheme I



Scheme II[a]



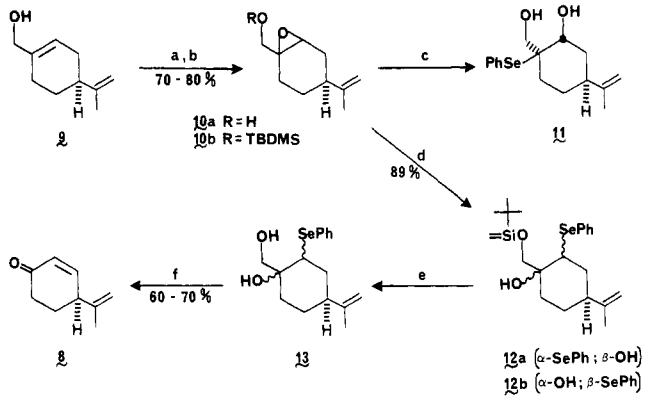
[a] (a) $Ph_3P{=}CH_2$/THF; (b) CH_3OH/25 °C; (c) LDA/THF −78 °C followed by 1.0 equiv of PhSeBr; (d) H_2O_2/H_2O.

classical Ritter reaction and carbocation–olefin cyclization in a single process.

Results and Discussion

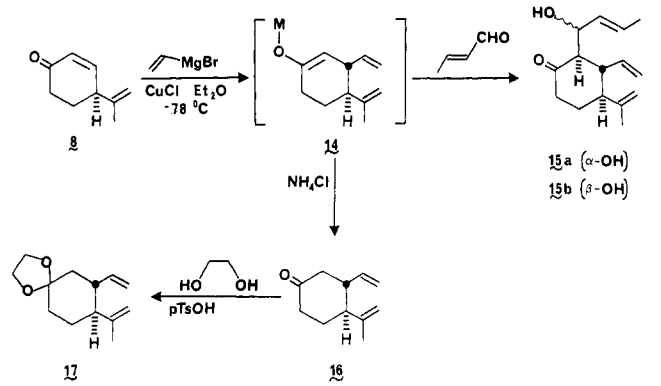
Our basic strategy was geared toward generating the tricarbocyclic ring system of the natural products in a single step via an "appendage-based"[6] carbocation–olefin cyclization where a nitrile acts as a terminator[7] to generate the solitary quaternary carbon in the targeted metabolites.

Scheme III[a]



[a] (a) *t*-BuOOH/VO(AcAc)$_2$/$PhCH_3$; (b) $TBMe_2Cl$/imidazole/CH_2Cl_2; (c) PhSeSePh/$NaBH_4$/EtOH/25 °C 0.5 h; (d) same as (c) except reflux 24 h; (e) *n*-$Bu_4N^+F^-$/THF; (f) excess $NaIO_4$/aqueous THF/25 °C.

Scheme IV



We had synthesized cyclization substrates of general structures **2** and **4** with the intention of inducing cyclization in the manner shown (Scheme I) to produce advanced intermediates with the critical stereochemistry established in bi- and tricyclic ring systems.

The previously unreported 4-isopropenyl-2-cyclohexen-1-one (**8**) was a key intermediate in this study. Early work utilized racemic **8** prepared as shown in Scheme II. The known Diels–Alder adduct **6**[8] was converted to 4-isopropenylcyclohexanone (**7**) by Wittig methylenation followed by methanolic cleavage of the trimethylsilyl group of the crude product. Distillation provided **7** in a three-step process (including diene preparation) proceeding in 13% overall yield. Although this yield is relatively low, **7** could be produced in 30–50-g quantities in greater than 95% purity from inexpensive materials. Unfortunately, the ensuing phenylselenenylation–selenoxide fragmentation protocol proceeded in only moderate yield (43%) to a product mixture which required laborious chromatographic separation of enone **8** from selenium containing byproducts. A requirement for larger amounts of **8** in optically pure form was satisfied by the route shown in Scheme III. (*S*)-(−)-Perillyl alcohol (**9**) was converted to **8** in a five-step process in 40% overall yield. Chromatographic purification was required only of the final product. Epoxidation of **9** by the Sharpless reagent[9] gave rise to an essentially 1:1 mixture of inseparable diastereomeric epoxides **10a**. Direct opening of the epoxy alcohols by the reagent generated from diphenyl diselenide and $NaBH_4$

(2) (a) Johnson, W. S. *Bioorg. Chem.* **1976**, *5*, 51. (b) Sutherland, J. K. *Chem. Soc. Rev.* **1980**, *3*, 265. (c) Schoemaker, H. E.; Dijkink, J.; Speckamp, W. N. *Tetrahedron* **1978**, *34*, 163.

(3) The advantages conferred by these types of reactions have been discussed by Bertz and Hendrickson, inter alia. See: Bertz, S. H. *J. Am. Chem. Soc.* **1982**, *104*, 5801. Hendrickson, J. B. *Tetrahedron* **1981**, *37*, 359.

(4) (a) Harding, K. E.; Burks, S. R. *J. Org. Chem.* **1981**, *46*, 3920. (b) Danishefsky, S.; Taniyama, E.; Webb, R. R., II. *Tetrahedron Lett.* **1983**, *24*, 11, and the following paper in that issue. (c) Aida, T.; Legault, R.; Dugat, D.; Durst, T. *Tetrahedron Lett.* **1979**, 4933. (d) Biloski, A. J.; Wood, R. D.; Ganem, B. *J. Am. Chem. Soc.* **1982**, *104*, 3233.

(5) (a) Kazlauskas, R.; Murphy, P. T.; Wells, R. J.; Blount, J. F. *Tetrahedron Lett.* **1980**, *21*, 315. (b) Baker, J. T.; Wells, R. J.; Oberhänsli, W. E.; Hawes, G. B. *J. Am. Chem. Soc.* **1976**, *98*, 4010. (c) Wratten, S. J.; Faulkner, D. J.; Hirotsu, K.; Clardy, J. *Tetrahedron Lett.* **1978**, 4345.

(6) The great majority of polyolefin cyclizations utilize a linear arrangement of olefins i as opposed to a branched arrangement ii. For an

example of a nonlinear or branched carbocation–olefin cyclization, see: Ziegler, F. E.; Wang, T.-F. *Tetrahedron Lett.* **1981**, *22*, 1179.

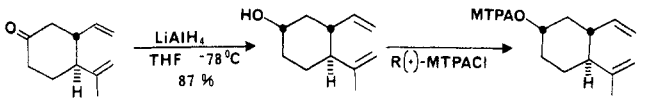
(7) Subsequent to the completion of this work, this general strategy was utilized in these laboratories for the construction of *Aristotelia* alkaloids. See: Kenney, P. M.; Stevens, R. V. *J. Chem. Soc., Chem. Commun.* **1983**, 384. Also see: Mirand, L.; Massiot, G.; Levy, J. *J. Org. Chem.* **1982**, *47*, 4169. Delpech, B.; Khuong-Huu, Q. *Ibid.* **1978**, *43*, 4898. In a pertinent related development, the Lewis acid promoted opening of epoxides by trimethylsilyl cyanide has been shown to produce β-hydroxy isonitriles. This reaction holds considerable promise for the synthesis of naturally occurring isonitriles such as kalihinol A (Chang, C. W. J.; Patra, A.; Roll, D. M.; Scheuer, P. J.; Matsumoto, G. K.; Clardy, J. *J. Am. Chem. Soc.* **1984**, *106*, 4644). See: Gassman, P. G.; Guggenheim, T. L. *Ibid.* **1982**, *104*, 5849. Spessard, G. O.; Ritter, A. R.; Johnson, D. M.; Montgomery, A. M. *Tetrahedron Lett.* **1983**, *24*, 655. Gassman, P. G.; Gremban, R. S. *Ibid.* **1984**, *25*, 3259.

(8) Jung, M. E.; McCombs, C. A. *Tetrahedron Lett.* **1976**, 2935.

(9) Sharpless, K. B.; Verhoeven, T. R. *Aldrichchimica Acta* **1979**, *12*, 63.

in ethanol[10] resulted in a product mixture consisting of 34% of the inseparable desired diols **13** and 40% of the useless diol **11**. Conversion of **10** to the *tert*-butyldimethylsilyl derivative **10b** caused epoxide opening to occur predominantly at the tertiary carbon[11] to give the desired selenides **12a** and **12b**. Both acetoxy- and trimethylsilyl-protected **10** did not serve as useful substrates for the ring-cleavage reaction. Instead, these substrates underwent initial desilylation (or deacetylation) and subsequent ring opening in addition to providing unwanted side products. Desilylation of **12** followed by oxidation–selenoxide fragmentation provided (*S*)-(−)-enone **8**.

Conjugate addition of the organocopper reagent generated from 2 equiv of vinylmagnesium bromide and 1 equiv of copper(I) chloride[12] to **8** at −78 °C provided the desired trans-substituted cyclohexanone **16** in good yield (Scheme IV). Neither the cis isomer nor 1,2-addition products were detected in the crude product. At this point the optical purity of the synthetic line was appraised. Reduction of **16** by lithium aluminum hydride in THF at −78 °C[13] to the equatorial alcohol **18** followed by esterification with (*R*)-(+)-(methoxytrifluoromethyl)phenylacetyl chloride[14] yielded a crude MTPA ester **19**. This substance exhibited



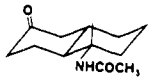
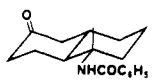
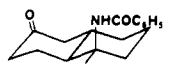
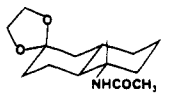
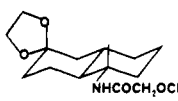
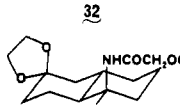
16 18 19

a single ^{19}F NMR resonance for the trifluoromethyl group and a single set of ^{13}C NMR signals. From these data we conclude that enone **8** is optically stable when refrigerated at −5 °C and its optical purity is greater than 95%.

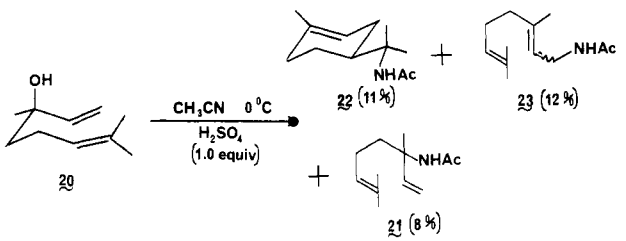
To synthesize the more highly branched cyclization substrate **15** the intermediate enolate **14** was quenched with crotonaldehyde to provide a diastereomeric mixture of only two aldol adducts.[15] The structural assignments of **15a** and **15b** rest on ^1H NMR decoupling experiments at 500 MHz. The large values (11–11.5 Hz) of the ring methine coupling constants are decisive in assigning the all-equatorial configuration to the appendages on the cyclohexanone ring. The isomer with the larger value of J was assigned the threo structure **15a**.[16] However, this seemingly general trend in aldol coupling constants has recently come under close scrutiny and has been repudiated in at least one case.[17,18] With the desired polyolefinic substrates in hand and with their optical purity confirmed, the cyclization studies were initiated.

In an early experiment, linalool **18** was treated with 1 equiv of sulfuric acid in acetonitrile at 0 °C, which provided

Table I. Nitrile-Terminated Cyclizations of Dienes 16 and 17

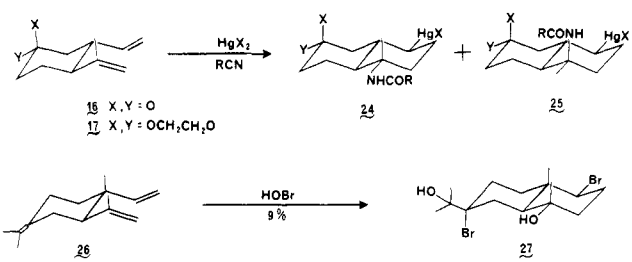
substrate	terminator	prod(s) (% yield)	^{13}C NMR shift of 4° methyl, δ
16	CH_3CN	 (81)	20.0
		28	
16	C_6H_5CN	 (55)	20.0
		29	
		 (11)	25.3
		30	
17	CH_3CN	 (89)	19.7
		31	
17	CH_3OCH_2CN	 (53)	19.4
		32	
17		 (12)	25.1
		33	

the cyclized product **22** in 11% yield along with the acyclic Ritter products **23** and **21**. The structure of **22** was as-



signed on the basis of the similarity of its spectral data and melting point to the compound reported by Khuong-Huu.[19] This result confirmed our belief that, at least in certain

Scheme V



(10) This reagent has classically been assumed as being "sodium phenylselenide". From the results of this work and especially that of Liotta, this picture must clearly be revised. See: Liotta, D.; Markiewicz, W.; Santiesteban, H. *Tetrahedron Lett.* **1977**, 4365.

(11) While steric hindrance of the approach of the selenide anion to the quaternary epoxide carbon of **10b** is a tidy rationalization of these results, this is probably not the whole story. Epoxide **10b** and similar trisubstituted epoxides require prolonged reflux periods for ring opening to occur (see: Clive, D. L. J. *Tetrahedron* **1978**, *34*, 1049) whereas epoxy alcohol **10a** was opened at room temperature in less than $^1/_2$ h. We speculate that the rate enhancement observed for **10a** is due to intramolecular delivery of the selenium reagent by the OH group, a cheletropically assisted opening, or both.

(12) Rivierê, H.; Tostain, J. *Bull. Soc. Chim. Fr.* **1975**, 375.

(13) The stereospecific formation of the equatorial alcohol was expected as this is a relatively unhindered cyclohexanone. See: Boone, J. R.; Ashby, E. C. *Topics Stereochem.* **1979**, *11*, 97.

(14) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512.

(15) (a) Heng, K. K.; Smith, R. A. J. *Tetrahedron* **1979**, *35*, 425. (b) Reetz, M. T.; Peter, R. *Tetrahedron Lett.* **1981**, *22*, 4691. (c) House, H. O.; Crumrine, D. S.; Teranishi, A. Y.; Olmstead, H. D. *J. Am. Chem. Soc.* **1973**, *95*, 3310.

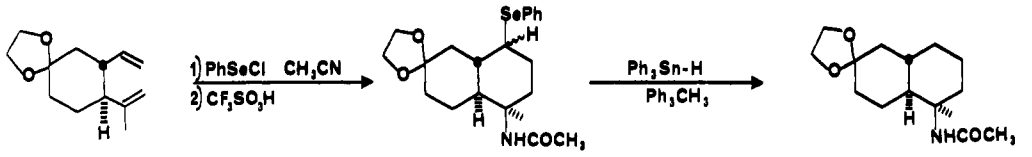
(16) The use of vicinal coupling constant magnitudes appears to be the most frequently cited method of this kind of stereochemical assignment in aldol adducts. See ref 15 and: Stiles, M.; Winkler, R.; Chang, Y.; Traynor, L. *J. Am. Chem. Soc.* **1964**, *86*, 3337.

(17) Heng, K. K.; Simpson, J.; Smith, R. A. J.; Robinson, W. T. *J. Org. Chem.* **1981**, *46*, 2932.

(18) A ^{13}C NMR based method for making the threo–erythro assignment in aldol adducts has been described by: Heathcock, C. H.; Pirrung, M. C.; Sohn, J. E. *J. Org. Chem.* **1979**, *44*, 4294.

(19) Pancrazi, A.; Kaborê, I.; Khuong-Huu, Q. *Bull. Soc. Chim. Fr.* **1977**, 162.

Scheme VI

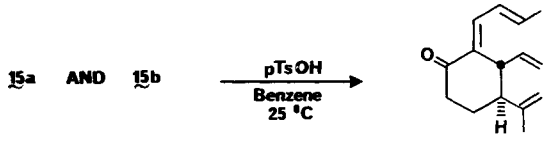


17 34 35

cases, cyclization could compete with carbocation trapping by nitriles. We therefore anticipated that cyclization would occur with **16** to give **24** (Scheme V) analogous to the known elemene-to-selinane conversions induced by bromonium and mercurinium ions (e.g., **26–27**).[20,21] The most successful initiator of this cyclization proved to be mercury(II) nitrate although mercury(II) trifluoroacetate also worked well but much more slowly.[22] For characterization purposes, the intermediate organomercurials were demercurated with aqueous basic sodium borohydride. The results are shown in Table I. When acetonitrile was utilized as the solvent (and terminator) only the equatorial amide products were produced. The use of benzonitrile or methoxyacetonitrile as terminators resulted in diastereomeric mixtures. The isomeric pairs were characterized by the relative ^{13}C NMR chemical shifts of the quaternary methyl groups, with the axial methyl carbons resonating 5–6 ppm upfield from their equatorial methyl counterparts.[23]

Interestingly enough, when a similar cyclization of **17** was performed with phenylselenium ion as the initiator[24] ($PhSeCl/CH_3CN/25$ °C) the only cyclization products isolated possessed the opposite stereochemistry at the quaternary carbon (Scheme VI). The resulting amido selenide **34** (a single isomer) was reduced by triphenyltin hydride[25] to give the axial amide isomer **35** characterized by a quaternary ^{13}C methyl resonance at δ 25.0. At this time we cannot put forth a plausible reason for this discrepancy, although this would seem to indicate that there is a major structural difference between the complexes of diene **17** and either $PhSe^+$ or Hg^{2+}.

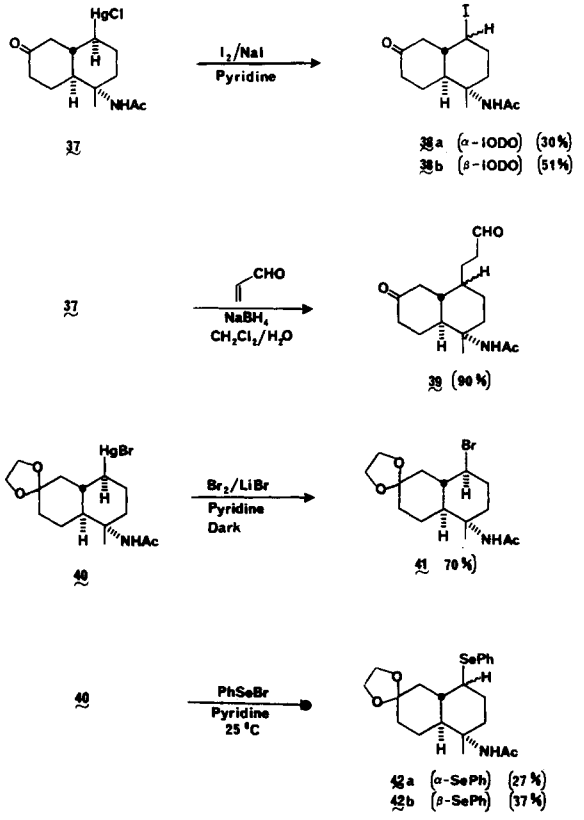
While the initial results of the cyclization study were quite gratifying, cyclization of more highly branched substrates such as **15a** or **15b** and related derivatives has so far provided either simple solvolysis products or unidentifiably complex mixtures. Especially disappointing



36

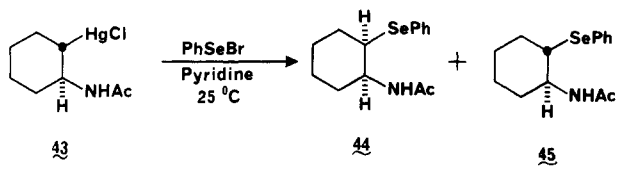
was the failure of tetraenone **36** to react with Hg^{2+} at all. We therefore began to investigate the chemistry of the organomercurial intermediates of the successful cyclizations.

Scheme VII



The organomercuric halides were isolated from the cyclization mixtures by quenching with aqueous solutions of alkali-metal halide salts.[26] Various electrophilic and free-radical transformations of **37** and **40** are shown in Scheme VII. Electrophilic substitution of the mercuri halide group by bromine, expected to occur with retention of configuration via an SE_2 process,[27] produced the equatorial bromide **41**. This confirmed the equatorial configuration of the mercuri halide in **40** and (presumably) **37**. In contrast, iodination produces epimers **38a** and **38b** in either a "dark" or "light" reaction. These preliminary data suggest a free-radical mechanism for this transformation.[28] In an interesting and potentially very useful reaction, treatment of **40** with phenylselenyl bromide in pyridine produces the phenylselenide epimers **42a** and **42b**. A similar lack of stereospecificity was observed with the mercurial **43**,[29] which produced selenide epimers **44** and **45** in a 1.5:1 ratio. To our knowledge, this is the first

(20) Brown, E. P.; Sutherland, J. K.; Sam, T. W. *J. Chem. Soc. Perkin Trans. 1*, **1975**, 2332.
(21) Renold, W.; Ohloff, G.; Norin, T. *Helv. Chim. Acta* **1979**, *62*, 985.
(22) (a) Beger, J.; Vogel, D. *J. Prakt. Chem.* **1969**, *311*, 737. (b) Brown, H. C.; Kurek, J. *J. Am. Chem. Soc.* **1969**, *91*, 5647.
(23) (a) Crews, P.; Kho-Wiseman, E. *Tetrahedron Lett.* **1978**, 2483 and references cited therein. (b) Jones, A.; Eliel, E.; Grant, D.; Knoeber, M.; Bailey, W. *J. Am. Chem. Soc.* **1971**, *93*, 4772. (c) Kellie, G.; Riddell, F. *J. Chem. Soc. B* **1971**, 1030. (d) Cazaux, L.; Gorrichow, J.-P.; Maroni, P. *Can. J. Chem.* **1978**, *56*, 3016.
(24) Toshimitsu, A.; Aoai, T.; Owada, H.; Uemara, S.; Okano, M. *J. Org. Chem.* **1981**, *46*, 4727.
(25) Clive, D. L.; Chittattu, G. J.; Farina, V.; Kiel, W. A.; Menchen, S. M.; Russell, C. G.; Singh, A.; Wong, C. K.; Curtis, N. J. *J. Am. Chem. Soc.* **1980**, *102*, 4438.
(26) (a) Larock, R. C. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 27. (b) A series of annual reviews of the chemistry of organomercurials has been written by: Seyferth, D. *J. Organomet. Chem.* **1973**, *62*, 33; **1974**, *75*, 13; **1975**, *98*, 133; **1977**, *143*, 153; **1978**, *176*, 132; **1979**, *183*, 141; **1980**, *203*, 183.
(27) Jensen, F. R.; Gale, L. H. *J. Am. Chem. Soc.* **1959**, *81*, 1261. Also see ref 28.
(28) Jensen, F. R.; Rickborn, B. "Electrophilic Substitution of Organomercurials"; McGraw-Hill: New York, 1968.
(29) Kretchmer, R. A.; Daly, P. J. *J. Org. Chem.* **1976**, *41*, 192.



43 44 45

reported example of the displacement of a mercuri halide group by phenyl selenide. Finally, cleavage of the organomercurial **37** to free-radicals by borohydride in the presence of activated olefins leads to epimeric mixtures of 1,4-addition products.[30] With acrolein as the acceptor,[31] a mixture of epimeric keto aldehydes **39** was produced in high yield. Significantly, little or no reduction of the aldehyde or ketone groups was observed.

Summary. Mercuric ion initiated cation–olefin cyclization of the optically active dienes **16** and **17** proceeded with termination by acetonitrile to stereospecifically generate carbon–nitrogen bonds. The intermediate organomercurials proved to be amenable to substitution processes, leading to a variety of optically active bicyclic intermediates possessing suitable functionality for conversion to amphilectane diterpenes.

Experimental Section

General Information. Thin-layer chromatography was carried out on precoated 0.25-mm layer thickness silica gel, alumina, and reverse-phase plates. Optical rotations were measured in a 1-dm cell at 22 °C at the sodium D line. Melting points were determined on a Thomas–Hoover apparatus and are uncorrected.

Chemical reactions were run in an atmosphere of dry argon. Bulb to bulb distillation refers to the use of a Kugelrohr apparatus operating at the specified oven temperature. All solvents, without exception, were distilled prior to use. Tetrahydrofuran, diethyl ether, and dioxane were distilled from sodium benzophenone ketyl. Benzene, pyridine, triethylamine, toluene, dichloromethane, acetonitrile, and diisopropylamine were distilled from calcium hydride. Methanol was distilled from magnesium methoxide. Dimethylformamide was dried over 3Å molecular sieves and distilled under reduced pressure.

4-Isopropenylcyclohexanone (7). Methyltriphenylphosphonium bromide[32] (92.8 g, 0.260 mol) was suspended in 1.2 L of THF. While stirring at 25 °C 165 mL of a 1.6 M solution of commercial *n*-BuLi in hexane was added dropwise over 1 h. The ylide was stirred for 3 h at 25 °C and a solution in THF of 4-acetyl-1-[(trimethylsilyl)oxy]cyclohexene (47.85 g, 0.225 mol, prepared according to Jung and McCombs[8]) was added dropwise over 30 min. The reaction was heated to 60 °C for 10 h and cooled with an ice bath while 100 mL of CH_3OH was added and allowed to warm to room temperature overnight. The reaction mixture was concentrated in vacuo and filtered. The solvents were evaporated and the residue was filtered through a short column of silica using ethyl acetate/hexanes (1:1) as eluant to give a yellow liquid. This was distilled at 80 °C at 0.1 mmHg to yield 21.8 g (70%) of pure **7** as a colorless liquid: ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.77 (br s, H_2C=C), 2.5–2.0 (m, CH_2's), 1.79 (s, CH_3), 1.8–1.5 (m, CH_2s); IR (film) 3030, 2900, 1703, 1636, 1430, 1370, 1320, 1240, 1155, 880 cm^{-1}; ^{13}C NMR (50 MHz, $CDCl_3$) δ 210.0, 147.7, 109.3, 43.2, 40.6, 31.1, 20.7; mass spectrum, *m/e* calcd for $C_9H_{14}O$ (M^+) 138.1044, found 138.1042.

(±)-**4-Isopropenyl-2-cyclohexen-1-one (8).** A solution of lithium diisopropylamide was generated in 100 mL of THF by adding 16.95 mL of 2.3 M *n*-BuLi/hexanes to diisopropylamine (3.94 g, 39 mmol) at −78 °C (acetone/dry ice bath). After 20 min a solution of 4-isopropenylcyclohexanone (**7**) (4.92 g, 35.6 mmol) in 30 mL of THF was added dropwise over 10 min. The solution of the enolate was stirred for 0.5 h at −78 °C, and a solution of phenylselenenyl bromide[33] (9.43 g, 40 mmol) in 30 mL of THF was added rapidly. The reaction was brought to ~0 °C with an ice bath, and 4 mL of HOAc and 20 mL of H_2O were added followed by 14 mL of 30% aqueous hydrogen peroxide (~0.123 mol). The reaction mixture was allowed to rise to room temperature and stirred for 1 h. The reaction mixture was poured into 200 mL of aqueous saturated $NaHCO_3$ solution and extracted 3 times with 100 mL of ether. The combined extracts were washed successively with 50-mL portions of H_2O, 0.1 N HCl, and brine. The ether solution was dried (Na_2SO_4) and evaporated to leave 4.8 g of a brown liquid. This residue was chromatographed on silica (MPLC) with hexane/ethyl acetate (10:1) as eluant to give (after two passes) 2.10 g (43%) of >95% pure racemic enone **8**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.85 (dq, J = 14, 5, 1 Hz, enone β-H), 6.03 (q, J = 14, 4 Hz, enone α-H), 4.89 (t, J = 1 Hz, CH_2=C), 4.76 (br s, CH=C), 3.03 (m, γ-H), 2.60–1.90 (m, CH_2CH_2), 1.79 (br s, CH_3C=C); IR (film) 3070, 3020, 2940, 1685, 1610, 1450, 1385, 1245, 1205, 900, 850, 735 cm^{-1}; ^{13}C NMR (50 MHz, $CDCl_3$) δ 198.9, 152.4, 145.2, 129.6, 112.3, 43.2, 36.3, 27.7, 21.2; mass spectrum, *m/e* calcd for $C_9H_{12}O$ (M^+) 136.0888, found 136.0883.

Epoxy Alcohol 10a. (*S*)-(−)-Perillyl alcohol[32] (10 g, 65.6 mmol) was dissolved in 100 mL of dry toluene along with 300 mg of $VO(AcAc)_2$. While stirring (with ice cooling) a 70% solution of *tert*-butyl hydroperoxide in *tert*-butyl alcohol[32] (~85 mmol) was added dropwise over 0.5 h. The reaction was allowed to warm to room temperature and stir for 10 h. The reaction mixture was diluted with 250 mL of ether and washed successively with 10% aqueous Na_2SO_3 (twice) and brine. The ether layer was dried (Na_2SO_4) and evaporated to leave an orange liquid. The crude product is sufficiently pure for the ensuing reactions. The product can be distilled at 100–110 °C at 0.2 mmHg to produce a colorless liquid (70–80% yield): ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.77 (br s, CH_2=C), 4.65 (br s, H_2C=C), 3.75–3.25 (overlapping resonances, CH_2OH and CHO), 2.3–2.11 (m, overlapping CH_2's and CH), 1.70 (br s, CH_3); IR (film) 3400, 3070, 2920, 1640, 1450, 1370, 1040, 960, 890, 845 cm^{-1}; ^{13}C NMR (50 MHz, $CDCl_3$) δ 148.6, 109.0, 64.5, 64.3, 60.3, 60.0, 56.8, 55.7, 40.7, 36.6, 30.1, 29.2, 25.7, 24.5, 23.7, 20.7, 20.0; mass spectrum, *m/e* calcd for $C_{10}H_{16}O_2$ (M^+) 168.1150, found 168.1154.

Silyloxy Epoxide 10b. Forty grams (0.23 mol) of epoxide **10a** was dissolved in 200 mL of dry DMF. Imidazole (34 g, 0.5 mol) was added followed by *tert*-butyldimethylsilyl chloride[32] (37.7 g, 0.25 mol). The reaction mixture was stirred for 12 h at room temperature and diluted with 1 L of ether. The ethereal solution was washed successively with 200-mL portions of H_2O (twice) and brine. The ether was dried (Na_2SO_4) and evaporated to leave a light yellow liquid. This was passed through a short column of silica using ethyl acetate/hexanes (1:15) as eluant to leave 65.9 g (100%) of a colorless liquid: ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.72 and 4.68 (br s, CH_2=C), 3.64 and 3.59 (s, CH_2O) 3.20–3.10 (m, CHO), 2.2–1.2 (overlapping resonances, CH_2's and CH), 1.70 and 1.68 (s, CH_3), 0.89 (s, *t*-Bu), 0.08 and 0.07 (s, CH_3Si's); IR (film) 3060, 2940, 2840, 1635, 1445, 1439, 1370, 1310, 1240, 1100, 1070, 870, 835, 740, 675 cm^{-1}; ^{13}C NMR (50 MHz, $CDCl_3$) δ 148.4, 108.9, 108.8, 66.3, 57.1, 40.6, 36.5, 30.3, 29.4, 29.3, 26.0, 25.5, 24.0, 23.7, 20.5, 19.8, −0.80; mass spectrum, no parent, *m/e* calcd for $C_{12}H_{21}O_2Si$ (-*t*-Bu) 225.1310, found 225.1307.

General Procedure for Epoxide Openings with Phenylselenide Anion. Diphenyl diselenide[32] (1.10 equiv) was dissolved in absolute ethanol (5 mL/mmol) and while stirring at room temperature solid $NaBH_4$ (2.25 equiv) was added in portions so as to keep the reaction below reflux temperature. Vigorous frothing usually accompanies the addition. The epoxide (2.0 equiv) was added and the reaction was stirred at the designated temperature for the designated time. The reaction mixture was diluted with aqueous saturated $NaHCO_3$ and extracted 3–4 times

(30) Giese has reported a large body of work on this reaction since 1977. Among the more relevant to our interests are: (a) Giese, B.; Meister, J. *Chem. Ber.* **1977**, *110*, 2588. (b) Giese, B.; Heuck, K. *Ibid.* **1979**, *112*, 3759. Giese, B.; Heuck, K. *Ibid.* **1981**, *114*, 1572. (d) Giese, B. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 753.

(31) A number of acceptors were utilized. Methyl acrylate was successful in this reaction but also nonstereospecific. Methyl 2-butynoate, α-bromoacrolein, 2,5-dihydrothiophen-2-one, and a myriad of functionalized 2-butenes did not act as acceptors. Instead simple demercuration was observed. This was not entirely unexpected. See: Giese, B.; Lachlein, S. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 967. Danishefsky, S.; Chackalamannil, S.; Uang, B.-J. *J. Org. Chem.* **1982**, *47*, 2231.

(32) This substance was obtained from the Aldrich Chemical Co., Milwaukee, WI.

(33) Petrzilka, M.; Pitteloud, R. *Helv. Chim. Acta* **1979**, *62*, 1319.

with ether. The combined extracts were washed with brine, dried (Na_2SO_4), and evaporated. The products were separated by chromatography as described.

Diol Selenides 11 and 13. The epoxide **10a** was opened by the selenium reagent at 25 °C in 0.5 h. The crude reaction product was chromatographed on silica (MPLC) using ethyl acetate/hexanes (1:5) as eluant to provide the pure undesired diol **11** in 40% yield: mp 62–64 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.60–7.20 (m, Ar H), 4.77 (br s, H_2C=C), 4.06 (br s, W_H = 9 Hz, C*H*OH), 3.53 (dd, J = 11.9 Hz, CH_2OSi), 3.0 (br, OH), 2.4–1.6 (overlapping resonances, CH_2's and CH), 1.78 (s, CH_3); IR (melt) 3400, 3080, 2920, 2860, 1640, 1575, 1475, 1440, 1000, 880, 740, 695 cm^{-1}; ^{13}C NMR (50 MHz, $CDCl_3$) δ 149.4, 138.1, 129.1, 125.0, 108.8, 70.3, 67.2, 58.6, 38.1, 35.0, 26.7, 20.8; mass spectrum, m/e calcd for $C_{16}H_{22}O_2{}^{80}Se$ (M^+) 326.0784, found 326.0781.

The mixture of the inseparable desired regioisomers **13** was produced in 34% yield: ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.62 (m, Ar H), 7.30 (m, Ar H), 4.72 (m, CH_2=C), 3.91 (d, J = 12 Hz, CH_2OH), 3.75 (s, CH_2OH), 3.6–3.5 (br, overlapping resonances, CH_2O*H*), 3.35 (q, J = 13, 4 Hz, C*H*OH), 2.35–1.20 (overlapping resonances, CH_2's and CH), 1.78 and 1.70 (s, CH_3); IR (film) 3400, 3060, 2930, 2860, 1640, 1575, 1470, 1435, 1105, 1050, 880, 735, 685 cm^{-1}; ^{13}C NMR (50 MHz, $CDCl_3$) δ 148.0, 134.2, 129.2, 129.1, 127.6, 109.3, 108.9, 74.0, 69.6, 64.5, 56.7, 49.8, 46.1, 40.3, 37.7, 37.1, 34.0, 33.1, 29.9, 29.5, 28.0, 25.6, 20.9, 20.7; mass spectrum, m/e calcd for $C_{16}H_{22}O_2{}^{78}Se$ (M^+) 324.0792, found 324.0794.

Silyloxy Selenides 12a and 12b. The silyl-protected epoxide **10b** was opened by the selenium reagent at the reflux temperature of ethanol in 24 h. The major products **12a** and **12b** were obtained in a combined yield of 89%. A small sample was separated by chromatography on silica (MPLC) using ethyl acetate/hexanes (1:15) as eluant to give the high R_f **12a** as a colorless glass: ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.55 (m, Ar H), 7.23 (m, Ar H), 4.72 (br s, H_2C=C), 3.85 (d, J = 10.0 Hz, CHOSi), 3.53 (d, overlapped on m, J = 10.0 Hz, CHOSi and CHSePh), 2.77 (s, OH), 2.45–2.15 (m, overlapping resonances), 1.9–1.55 (m, overlapping resonances), 1.72 (br s, CH_3C=C), 0.89 (s, *t*-Bu), 0.05 (s, CH_3Si), 0.01 (s, CH_3Si); IR (film) 3540, 3065, 2920, 2830, 1635, 1570, 1480, 1455, 1435, 1075, 1050, 830, 770, 730, 685 cm^{-1}; ^{13}C NMR (50 MHz, $CDCl_3$) δ 149.6, 133.9, 130.6, 128.9, 127.2, 108.7, 72.9, 70.1, 50.2, 40.4, 33.2, 30.6, 25.8, 20.9, 18.2, –5.5, –5.6; mass spectrum, m/e calcd for $C_{22}H_{36}O_2{}^{78}SeSi$ (M^+) 438.1657, found 438.1649.

The low R_f isomer **12b** was also obtained as a colorless glass: ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.61 (m, Ar H), 7.24 (m, Ar H), 4.68 (br s, CH_2=C), 3.91 (d, J = 10.2 Hz, CHOSi), 3.61 (d, J = 10.2 Hz, CHOSi), 3.30 (dd, J = 12.5, 4.6 Hz, CHSePh), 3.31 (s, OH), 2.2–1.2 (overlapping resonances), 1.65 (br s, CH_3C=C), 0.94 (s, *t*-Bu), 0.14 (s, CH_3Si), 0.12 (s, CH_3Si); IR (film) 3430, 3065, 2930, 2860, 1640, 1575, 1470, 1435, 1250, 1090, 835, 775, 735, 685, 660 cm^{-1}; ^{13}C NMR (50 MHz, $CDCl_3$) δ 148.3, 134.3, 131.3, 128.9, 127.2, 109.1, 73.0, 65.8, 55.3, 46.2, 38.0, 35.8, 28.3, 25.9, 20.8, 18.2, –5.3, –5.5; mass spectrum, m/e calcd for $C_{22}H_{36}O_2{}^{80}Se^{28}Si$ (M^+) 440.1649, found 440.1676.

Diol Selenides 13. The crude silylated epoxy alcohol mixture **12** (439 mg, 1 mmol) was dissolved in 10 mL of THF, and while the mixture was stirred at room temperature a 1.0 M solution of tetra-*n*-butylammonium fluoride (2 mL, 2 mmol) in THF[32] was added via syringe. The reaction was stirred for 6 h and diluted with 50 mL of ether. The organic solution was washed successively with 50-mL portions of water (4×) and brine. The ether was dried (Na_2SO_4) and evaporated. This material was usually contaminated with ~5–10% of a silicon-derived material, but removal of ths impurity made only a negligible improvement in the yield of the ensuing oxidation step. The crude product, therefore, was used directly. The mixture could be separated as previously described (vide supra).

***(S)*-(–)-4-Isopropenyl-2-cyclohexen-1-one (8).** The crude product of the desilylation procedure (1.0 g, 3.1 mmol, containing a small amount of silicon-derived material) was dissolved in 20 mL of 85% aqueous THF and cooled to 0–5 °C. Solid sodium metaperiodate (2.65 g, 12.4 mmol) was added in one portion with vigorous stirring. A heavy white precipitate formed. The reaction was allowed to warm slowly to room temperature over 1.5 h. At this time the mixture was diluted with 75-mL portions of ether and saturated aqueous $NaHCO_3$. The layers were separated and the aqueous layer was extracted twice with 50-mL portions of ether. The ether extracts were combined and washed successively with saturated aqueous $NaHCO_3$ and brine. The ether layer was dried (Na_2SO_4) and evaporated to leave a dark yellow liquid. This was chromatographed on silica (MPLC) using ethyl acetate/hexanes (1:4) as eluant to give 144 mg of optically active **8** as a colorless liquid. Its spectral data were identical with those of the racemic compound prepared via the alternate route: $[\alpha]^{22}_D$ –153.8° (10.3 mg/mL, CH_3OH). When the reaction was carried out on a larger scale (30–40 g) the yield after chromatography was 60–70% from **12**.

***trans*-3-Vinyl-4-isopropenylcyclohexanone (16).** A dry 3-neck 100-mL round-bottom flask was fitted with an addition funnel and two septum inlets. The flask was purged with argon and charged with purified CuCl[34] (237 mg, 2.42 mmol) and 10 mL of ether. The solution was cooled to –65 °C ($CHCl_3$/dry ice) and a commercial solution of 1.0 M vinylmagnesium bromide in THF[32] (4.84 mmol) was added dropwise via syringe over 4 min. The solution of the cuprate was allowed to rise slowly to –40 °C and held at that temperature for 10 min before cooling to –65 °C. The enone **8** (300 mg, 2.20 mmol) was added from the addition funnel as a solution in 5 mL of ether. The reaction was stirred for 0.5 h at –65 °C and quenched by addition to a mixture of 50 mL of ether and 75 mL of aqueous ammonium chlloride (pH 10). The layers were separated and the aqueous layer was extracted twice with 40-mL portions of fresh ether. The combined ether layers were washed successively with 20-mL portions of aqueous ammonium chloride (pH 10), H_2O, and brine. The ether was dried ($CaSO_4$) and evaporated to leave a light brown liquid. In most runs on this or a larger scale, the crude product could be distilled bulb to bulb at 100 °C and 0.1 mmHg pressure to give a colorless product in 70–80% yield: $[\alpha]^{22}_D$ +16.6° (10.2 mg/mL, CH_3OH); ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.67 (m, *H*C=CH_2), 5.02 (br s, HC=C*H*$_2$), 4.95 (d, J = 4 Hz, HC=C*H*$_2$), 4.80 (br s, CH_3C=C*H*$_2$), 2.60–1.70 (m, CH_2's and CH's), 1.68 (s, CH_3); IR (film) 3070, 2940, 2880, 1710, 1640, 1420, 1375, 1200, 995, 915, 890 cm^{-1}; ^{13}C NMR (50 MHz, $CDCl_3$) δ 210.1, 146.2, 139.9, 114.1, 112.1, 50.0, 46.5, 45.0, 40.8, 31.0, 18.9; mass spectrum, m/e calcd for $C_{11}H_{16}O$ (M^+) 164.1201, found 164.1195.

Aldol Adducts 15a and 15b. The copper reagent generated from 2 equiv of vinylmagnesium bromide and 1 equiv of cuprous chloride in ether was treated with 1 equiv of the enone **8** as previously described for **16**. This solution was stirred at –65 to –75 °C for 15–20 min and a saturated solution of zinc chloride in ether (1–2 equiv) was added followed by a 3–5-fold excess of crotonaldehyde. The reaction mixture was stirred for 0.5 h and quenched by pouring the mixture into an excess of 15% aqueous NH_4Cl (pH 9). The ether layer was separated and the aqueous layer was extracted 3 times with fresh ether. The combined ether extracts were washed successively with 15% aqueous NH_4Cl (pH 9), H_2O, and brine. The ether was dried ($CaSO_4$) and evaporated to leave a nearly colorless product consisting of >95% pure epimeric β-hydroxy ketones. The epimers were obtained in a combined yield of 88%. They were separated by MPLC on silica using ethyl acetate/hexanes (1:5) as eluant to give the pure epimers as colorless oils. The adduct **15b** had an R_f value of 0.25 in this system and was isolated as a colorless oil in 29% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.75 (dd, J = 7 and 15 Hz, C*H*=CHCH$_3$), 5.60 (m, CH=C*H*CH$_3$), 5.49 (m, C*H*=CH$_2$), 5.12 (s, C=CH$_2$), 5.12 (d, J = 10 Hz, C=CH$_2$), 4.17 (br, C*H*OH), 3.10 (br d, OH), 2.70 (q, J = 11 and 11 Hz, C*H*CH=CH$_2$), 2.52–2.40 (overlapping resonances, CH_2CH_2), 2.34 (d, J = 11 Hz, C*H*CHOH), 2.0 (m, CH_2CH_2), 1.67 (d, J = 6 Hz, C*H*$_3$CH=C), 1.63 (s, CH_3C=C); IR (film) 3520, 3070, 2920, 2860, 1700, 1640, 960, 915, 880 cm^{-1}; ^{13}C NMR (50 MHz, $CDCl_3$) δ 213.3, 138.6, 133.2, 126.6, 117.3, 112.3, 71.0, 58.6, 50.8, 49.6, 42.6, 32.1, 18.7, 17.6; mass spectrum, m/e calcd for $C_{15}H_{22}O_2$ (M^+) 234.1619, found 234.1602.

The low R_f isomer **15a** was also obtained as a colorless oil in 59% yield (R_f 0.15): ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.69 (m, C*H*=C*H*CH$_3$), 5.45 (m, C*H*=CH$_2$), 5.05 (dd, J = 2 and 10 Hz, C=CH$_2$), 4.87 (dd, J = 2 and 7 Hz, C=CH$_2$), 4.75 (br s, CH_3C=C*H*$_2$), 4.10 (br, C*H*OH), 3.53 (d, J = 11 Hz, OH), 2.55 (dd, J = 11.4 and 11.0 Hz, C*H*CH=CH$_2$), 2.49–2.10 (overlapping

(34) Perrin, D. D.; Armarego, W. L. F.; Perrin, D. R. "Purification of Laboratory Chemicals"; Pergamon Press: Oxford, 1980.

resonances CH_2CH_2), 1.71 (d, J = 5 Hz, CH=CHCH_3), 1.61 (t, J = 1 Hz, CH_3C=CH_2); IR (film) 3525, 3080, 2940, 2860, 1700, 1645, 970, 920, 890 cm^{-1}; ^{13}C NMR (50 MHz, $CDCl_3$) δ 213.0, 146.1, 138.1, 129.9, 129.5, 116.5, 112.2, 72.5, 56.9, 49.9, 48.0, 41.7, 30.1, 18.9, 17.7; mass spectrum, m/e calcd for $C_{15}H_{22}O_2$ (M^+) 234.1619, found 234.1610.

Tetraenone 36. A solution of the aldol mixture **15a** and **15b** (1.0 mmol) in 5 mL of benzene containing 20 mg of camphorsulfonic acid was stirred at room temperature for 24 h. The reaction mixture was partitioned between ether and aqueous saturated $NaHCO_3$. The organic layer was washed successively with water and brine. The ether was dried ($CaSO_4$) and evaporated. The crude product containing a small amount of starting material was chromatographed on silica (MPLC) using ethyl acetate/hexanes (1:15) as eluant to provide **36** as a slightly yellow oil. The spectral data indicated it as being a single isomer, and the all-*E* configuration was assigned based on the highly deshielded nature (δ 7.20) of the dienone β-proton: $[\alpha]^{22}_D$ -55.2° (13.5 mg/mL, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.20 (d, J = 10 Hz, C=CH), 6.21 (m, CH_3CH=CH), 5.85 (m, CH=CH_2), 5.1–4.7 (overlapping m, C=CH_2 and CH=CH_2), 3.74 (br, COC-CH, W_H ~17 Hz), 2.45–2.29 (overlapping resonances), 2.10–1.85 (overlapping resonances), 1.87 (d, J = 6 Hz, CH=CHCH_3), 1.78 (s, CH_3C=CH_2); IR (film) 3080, 3020, 2935, 1675, 1625, 1575, 1445, 1405, 1370, 1285, 1235, 1145, 1115, 965, 915, 890 cm^{-1}; ^{13}C NMR (50 MHz, $CDCl_3$) δ 201.1, 146.1, 141.2, 140.5, 138.3, 132.0, 126.7, 115.7, 112.2, 45.1, 43.0, 35.9, 22.0, 21.7, 19.2; mass spectrum, m/e calcd for $C_{15}H_{20}O$ 216.1514, found 216.1517.

Ketal 17. *trans*-3-Vinyl-4-isopropenylcyclohexanone (**16**) (465 mg, 2.83 mmol) was dissolved in 25 mL of benzene along with ethylene glycol (310 mg, 5.0 mmol) and 10 mg of *p*-toluenesulfonic acid. The mixture was refluxed under a Dean–Stark trap filled with 4-Å molecular sieves for 2.5 h. The reaction mixture was diluted with 70 mL of ether and washed successively with 25 mL-portions of aqueous saturated $NaHCO_3$ and brine. The organic layer was dried (Na_2SO_4) and evaporated to leave a yellow liquid. The crude product was distilled (bulb to bulb) at 100 °C (0.1 mmHg) to give 580 mg (98%) of **17** as a colorless liquid: $[\alpha]^{22}_D$ +3.3° (7.3 mg/mL, CH_3OH); ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.61 (m, CH=CH_2), 4.98 (m, CH=CH_2), 4.73 (br s, C=CH_2), 3.99 (br s, OCH_2CH_2O), 2.30 (m, CHC=C), 1.9–1.4 (overlapping resonances, CH_2), 1.68 (br s, CH_3): IR (film) 3070, 2940, 2880, 1640, 1445, 1360, 1120, 1065, 910, 890, 670 cm^{-1}; ^{13}C NMR (50 MHz, $CDCl_3$) δ 147.7, 141.4, 113.1, 111.1, 108.4, 64.2, 64.0, 50.5, 42.0, 40.5, 34.5, 29.0, 18.9; mass spectrum, m/e calcd for $C_{13}H_{20}O_2$ 208.1463, found 208.1468.

Cyclohexanol 18. To a slurry of $LiAlH_4$ (30 mg, 0.79 mmol) in 10 mL of THF at -78 °C was added a solution of dienone **16** (164 mg, 1.0 mmol) in 4 mL of THF. The reaction was quenched after 10 min by the sequential addition of 0.5 mL of 15% aqueous NaOH and 1.5 mL of H_2O. This mixture was diluted with $CHCl_3$ and H_2O, and the H_2O layer was extracted 3 times with fresh $CHCl_3$. The combined $CHCl_3$ layers were washed with water and brine, dried ($CaSO_4$), and evaporated. The crude product was chromatographed on silica (MPLC) using ethyl acetate/hexanes (1:4) as eluant to give 145 mg (87%) of **18** as a colorless oil: $[\alpha]^{22}_D$ +28.3° (9.8 mg/mL, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.65 (m, CH=CH_2), 4.97 (m, CH=CH_2), 4.70 (m, C=CH_2), 3.67 (m, CHOH), 2.15–1.10 (overlapping resonances), 1.61 (br, CH_3); IR (film) 3320, 3060, 2920, 2850, 1635, 1440, 1365, 1040, 980, 955, 905, 880 cm^{-1}; ^{13}C NMR (50 MHz, $CDCl_3$) δ 147.8, 141.6, 113.2, 111.2, 70.2, 50.6, 42.9, 41.1, 35.3, 30.0, 19.0; mass spectrum (no parent), m/e calcd for $C_{11}H_{16}$ (M^+ - H_2O) 148.1252, found 148.1253.

(*R*)-(+)-MTPA Ester 19. The general procedure of Mosher and Dale[14] was used to synthesize **19** from cyclohexanol **18** and (*R*)-(+)-methoxy(trifluoromethyl)phenylacetic acid[32] via its acid chloride. The crude product was analyzed spectroscopically: $[\alpha]^{22}_D$ +63.4° (18.2 mg/mL, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.70–7.40 (m, Ar H), 5.61 (m, CH=CH_2), 5.00 (m, CH=CH_2), 4.73 (m, C=CH_2), 3.56 (s, OCH_3), 2.30–1.25 (overlapping resonances), 1.64 (br s, CH_3C=CH_2); IR (film) 3060, 2930, 2850, 1740, 1635, 1445, 1370, 1260, 1175, 1115, 1020, 715, 690 cm^{-1}; ^{19}F NMR (84.25 MHz, $CFCl_3$) δ -71.64; ^{13}C NMR (50 MHz, $CDCl_3$) δ 165.8, 147.1, 140.7, 132.4, 131.8, 128.2, 127.2, 126.1, 120.4, 114.6, 113.9, 111.6, 75.0, 55.3, 50.4, 42.8, 37.0, 31.2, 29.6, 19.0 (J_{C-F} ~288 Hz); mass spectrum (no parent), m/e calcd for $C_{11}H_{16}$ (- MTP-acetic acid) 148.1252, found 148.1257.

Ketal Selenide 34. Diene **17** (65 mg, 0.31 mmol) was dissolved in 2 mL of CH_3CN and while stirring at room temperature phenylselenenyl chloride[32] (60 mg, 0.31 mmol) was added in one portion as a solid. The dark orange color of the PhSeCl quenched immediately upon dissolution. After 10 min a solution of trifluoromethanesulfonic acid[32] (46 mg, 0.31 mmol) in water (5 equiv) was added and the reaction was refluxed for 0.5 h. The reaction mixture was cooled and added to 10 mL of saturated aqueous $NaHCO_3$. This mixture was extracted 3 times with 10-mL portions of $CHCl_3$. The combined $CHCl_3$ extracts were washed with brine, dried (Na_2SO_4), and evaporated. The crude product was chromatographed on silica (MPLC) using ethyl acetate/hexanes (20:1) as eluant to give 26 mg (20%) of the ketal **34** as a slightly yellow solid: mp 175–178 °C dec; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.60–7.20 (m, Ar H), 5.00 (br, NH), 4.00 (m, OCH_2CH_2O), 2.81–2.58 (overlapping m, CHSePh and axial C-6 H), 2.00–1.00 (overlapping resonances), 1.83 (s, CH_3CO), 1.41 (s, CH_3CN); IR ($CHCl_3$) 3350, 2910, 2820, 1650, 1510, 1430, 1360, 1110, 730, 680 cm^{-1}; ^{13}C NMR (50 MHz, $CDCl_3$) δ 169.6, 136.3, 128.7, 128.3, 127.7, 108.2, 64.3, 54.6, 51.4, 48.9, 41.1, 39.2, 35.9, 34.8, 30.4, 29.6, 24.3, 23.0; mass spectrum, m/e calcd for $C_{21}H_{29}NO_3Se$ 423.1312, found 423.1295.

The ketone corresponding to ketal **34** was also isolated as a slightly lower R_f material in 21% yield: ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.65–7.20 (m, Ar H), 5.01 (br, NH), 3.23 (dq, J = 2.1, 14.6, 3.7 Hz), 2.90–2.65 (overlapping m, CHSe and axial C-6 H), 2.50–1.90 (overlapping resonances), 1.83 (s, CH_3CO), 1.75–1.10 (overlapping resonances), 1.48 (s, CH_3CN); ^{13}C NMR (50 MHz, $CDCl_3$) δ 209.3, 169.8, 136.3, 129.0, 128.2, 127.2, 54.8, 51.2, 48.9, 47.3, 42.4, 36.3, 30.2, 29.6, 25.6, 25.0, 24.3.

Amide 22. 3,7-Dimethyl-1,6-octadien-3-ol **20**[32] (308 mg, 2.0 mmol) was dissolved in 7 mL of CH_3CN. While stirring at 0–5 °C 2.20 mL of a 0.9 M solution of H_2SO_4 in CH_3CN was added dropwise over a 3-min period. When the addition was complete the reaction was allowed to rise to room temperature and stir for 3 h. The reaction mixture was then poured into a mixture of 30 mL of $CHCl_3$ and 30 mL of aqueous saturated $NaHCO_3$ solution. The layers were separated and the aqueous layer was extracted 2 times with fresh chloroform (30 mL). The combined extracts were washed with brine, dried (Na_2SO_4), and evaporated to leave a red oil. This was chromatographed on silica (MPLC) using ethyl acetate/hexanes (3:1) as eluant to give the three Ritter products **21**, **22**, and **23**. The cyclized Ritter product **22** was obtained as white crystals (43 mg): mp 113–115 °C (lit.[19] 111 °C); ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.35 (br s, HC=C), 5.20 (br, NH), 2.2–1.7 (overlapping m, CH_2's), 1.93 (s, CH_3CO), 1.63 (s, CH_3C=C), 1.27 (s, CH_3), 1.24 (s, CH_3 overlapping m, CH_2); IR ($CHCl_3$) 3430, 2905, 1665, 1480, 1360, 1300, 1270 cm^{-1}; ^{13}C NMR (50 MHz, $CDCl_3$) δ 169.2, 157.0, 120.3, 66.4, 56.2, 40.9, 31.0, 26.4, 24.5, 24.0, 23.8, 23.1; mass spectrum, m/e calcd for $C_{12}H_{21}NO$ (M^+) 195.1625, found 195.1635.

General Procedure for Mercury(II)-Initiated Cyclizations. The olefinic substrate (1.0 mmol) was dissolved in 10 mL of the nitrile. While stirring at the designated temperature, the mercuric salt (1.1 mmol) was added as a solid and the reaction was allowed to stir until TLC analysis showed consumption of the starting olefin. To isolate the intermediate organomercurial, the reaction mixture is poured into an excess of a metal halide (e.g., NaCl, KBr, etc.) in water and filtered; to isolate the amide containing no mercury, a solution of 1.0 equiv of $NaBH_4$ in 2 mL of water were added dropwise. In either case, workup consisted of extracting the reaction mixture 3–4 times with chloroform, washing of the chloroform layer with water, drying (Na_2SO_4 or $CaSO_4$), and solvent evaporation. The crude products were purified by chromatography on silica (MPLC), if necessary.

Octalone 28. This compound was made in 81% yield by cyclization of ketone **16** at 0 °C with $Hg(NO_3)_2$[35] in acetonitrile followed by demercuration with $NaBH_4$. Final purification could be achieved by chromatography on silica using ethyl acetate as eluant to give **28** as a colorless glass: ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.31 (br, NH), 2.72–1.95 (overlapping resonances), 1.92 (s, $COCH_3$), 1.70–1.20 (overlapping resonances), 1.14 (s, CH_3CN);

(35) This substance was obtained from Alfa/Ventron, Danvers, MA.

IR (film) 3300, 3070, 2920, 2860, 1700, 1650, 1535, 1440, 1370 cm^{-1}; ^{13}C NMR (50 MHz, $CDCl_3$) δ 211.0, 169.4, 57.1, 48.5, 44.3, 41.3, 38.9, 36.6, 33.8, 26.4, 24.7, 22.1, 20.0; mass spectrum, m/e calcd for $C_{13}H_{21}NO_2$ 223.1572, found 223.1585.

Ketal Amide 31. This compound was made in 89% yield by cyclization of ketal **17** using $Hg(NO_3)_2$ in acetonitrile at 0 °C followed by demercuration with $NaBH_4$. Final purification was achieved by chromatography on silica (MPLC) using ethyl acetate as eluant to give **31** as white crystals: mp 155–157 °C dec; ^1H NMR (200 MHz, $CDCl_3$) δ 5.15 (br, NH), 3.94 (br s, OCH_2CH_2O), 2.30–2.05 (m, CH_2), 1.91 (s, $COCH_3$), 1.85–1.25 (overlapping resonances), 1.21 (s, CH_3CN); IR (melt) 3300, 3070, 2920, 2860, 1650, 1540, 1440, 1356 cm^{-1}; ^{13}C NMR (50 MHz, $CDCl_3$) δ 169.2, 108.8, 64.2, 57.0, 45.9, 42.5, 37.1, 35.3, 34.9, 33.3, 24.8, 23.3, 22.2, 19.7; mass spectrum, m/e calcd for $C_{15}H_{25}NO_3$ 267.1828, found 267.1837.

Octalones 29 and 30. These compounds were prepared from ketone **16** by cyclization using $Hg(NO_3)_2$ in benzonitrile at 0 °C followed by demercuration with $NaBH_4$. The crude reaction product was freed of benzonitrile by passage through a small column of silica with ethyl acetate/hexanes (1:20) to first elute the benzonitrile and then ethyl acetate to recover the crude amides. The two isomers were separated by chromatography on silica (MPLC) using ethyl acetate/hexanes (1:2) as eluant to provide an 11% yield of the high R_f minor product **30** as a colorless glass: $[\alpha]^{22}_D$ +5.7° (2.3 mg/mL, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ 7.70–7.30 (m, Ar H), 5.78 (br, NH), 2.80 (br d, axial C-6 H), 2.50–2.2 (overlapping resonances), 1.60 (s, CH_3): IR ($CHCl_3$) 3430, 2900, 2850, 1705, 1660, 1595, 1570, 1470, 1430, 1300 cm^{-1}; ^{13}C NMR (50 MHz, $CDCl_3$) δ 210.0, 166.8, 135.8, 131.2, 128.6, 126.4, 55.5, 50.8, 48.4, 41.1, 38.3, 35.9, 34.4, 26.3, 25.3, 21.2; mass spectrum, m/e calcd for $C_{18}H_{23}NO_2$ 285.1729, found 285.1733.

The low R_f major isomer **29** was obtained in 55% yield as a colorless glass: $[\alpha]^{22}_D$ +53.6° (10.6 mg/mL, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ 7.70–7.30 (m, Ar H), 5.88 (br, NH), 2.80–1.35 (overlapping resonances), 1.22 (s, CH_3); IR ($CHCl_3$) 3440, 2930, 2860, 1710, 1660, 1575, 1480, 1315, 700 cm^{-1}; ^{13}C NMR (50 MHz, $CDCl_3$) δ 210.9, 166.7, 135.7, 131.1, 128.5, 126.5, 57.4, 48.4, 44.3, 41.2, 38.9, 36.6, 33.8, 26.4, 22.1, 20.0; mass spectrum, m/e calcd for $C_{18}H_{23}NO_3$ 285.1729, found 285.1732.

Ketal Amides 32 and 33. These were prepared by cyclization of ketal **17** with $Hg(NO_3)_2$ at 0 °C in methoxyacetonitrile[32] followed by demercuration with $NaBH_4$. The crude amides were separated by chromatography on silica (MPLC) using ethyl acetate/hexanes (2:1) as eluant to give the high R_f minor isomer **33** as a colorless oil in 12% yield: ^1H NMR (200 MHz, $CDCl_3$) δ 6.42 (br, NH), 3.98 (s, OCH_2CH_2O), 3.81 (s, CH_2OCH_3), 3.45 (s, OCH_3), 2.70 (br d, axial C-6 H), 2.00–0.90 (overlapping resonances), 1.48 (s, CH_3CN); IR (film) 3405, 2920, 1685, 1520, 1445, 1110 cm^{-1}; ^{13}C NMR (50 MHz, $CDCl_3$) δ 167.2, 72.6, 64.2, 64.1, 50.9, 42.5, 36.1, 34.7, 34.4, 33.7, 29.6, 25.1, 22.8, 21.2; mass spectrum, m/e calcd for $C_{16}H_{27}NO_4$ 297.1940, found 297.1944.

The low R_f major isomer **32** was obtained in 53% yield as a colorless glass: ^1H NMR (200 MHz, $CDCl_3$) δ 6.23 (br, NH), 3.94 (s, OCH_2CH_2O), 3.78 (s, CH_2OCH_3), 3.40 (s, OCH_3), 2.13 (td), 1.95–1.30 (overlapping resonances), 1.2 (s, CH_3); IR (film) 3400, 2930, 1680, 1525, 1450, 1360, 1295, 1115, 925 cm^{-1}; ^{13}C NMR (50 MHz, $CDCl_3$) δ 168.2, 108.7, 72.4, 64.2, 64.1, 58.9, 56.6, 46.3, 42.4, 37.3, 35.3, 34.7, 33.3, 23.3, 22.1, 19.4; mass spectrum, m/e calcd for $C_{16}H_{27}NO_4$ 297.1940, found 297.2955.

Keto Mercurial 37. This compound was made from dienone **16** via the standard cyclization–aqueous NaCl quenching sequence. The mercurial was obtained in 91% yield as a white amorphous solid, which slowly decomposed on melting over a wide temperature range (65–80 °C): ^1H NMR (200 MHz, $CDCl_3$) δ 5.13 (br, NH), 2.85–2.00 (overlapping resonances), 1.95 (s, CH_3CO), 1.80–1.35 (overlapping resonances), 1.18 (s, CH_3CH); IR (Nujol) 3320, 1705, 1650, 1540 cm^{-1}; ^{13}C NMR (50 MHz, $CDCl_3$) δ 208.6, 169.4, 60.5, 56.5, 51.0, 46.9, 43.8, 41.3, 38.5, 29.5, 26.0, 24.7, 20.3; mass spectrum, m/e 296, 272, 202, 163, 121, 105, 60 (base).

Keto Aldehydes 39. The mercurial **37** (1.0 mmol) was suspended in CH_2Cl_2 containing a large (~100-fold) excess of acrolein. A 1 M solution of $NaBH_4$ (~3 equiv) in H_2O was added cautiously (vigorous gas evolution ensues). The reaction was stirred at room temperature for 1–2 h and poured into a mixture of $CHCl_3$ and aqueous saturated $NaHCO_3$. The aqueous layer was extracted 3 times with $CHCl_3$ and the combined extracts were washed with brine, dried (Na_2SO_4), and evaporated. The keto aldehydes were produced in 100% crude yield but chromatography on silica led to a very low (40–50%) recovery of the isomers. A small amount (5–10%) of the reduced product **16** can be isolated from the reactions. Partial spectral data of **39** mixture: ^1H NMR (200 MHz, $CDCl_3$) δ 9.78 (overlapping triplets, J = 1 Hz, CHO), 5.22 (br, NH), 2.80–2.00 (overlapping resonances), 1.90 (s, CH_3CO), 1.21 and 1.09 (s, CH_3CN); IR (film) 3300, 3070, 2920, 2860, 1705, 1650, 1535, 1440, 1370 cm^{-1}; ^{13}C NMR (50 MHz, $CDCl_3$) δ 210.1, 208.8, 202.0, 169.8, 21.0, 20.0; mass spectrum, m/e (no parent) calcd for $C_{14}H_{22}NO_2$ ($M^+ - CH_2CHO$) 236.1650, found 236.1627. Anal. Calcd for $C_{13}H_{20}NO_2$: 222.1494. Found: 222.1498.

General Procedure for S_E2 Displacements by Halogens. The organomercurial was dissolved in pyridine (10 mL/mmol). While the mixture was stirred at room temperature a solution of the halogen (1.1 equiv) and metal halide (2 equiv) in pyridine was added dropwise. When the reaction was judged complete the reaction mixture was diluted with $CHCl_3$ and washed successively with 10% aqueous $CuSO_4$ (2×), water, and brine. The $CHCl_3$ solution was dried (Na_2SO_4) and evaporated. The crude products were purified by chromatography.

Ketal Bromide 41. This compound was made from the corresponding mercuric bromide with Br_2 and LiBr in the dark for 4 h. The crude product was chromatographed on silica (MPLC) to give a 75% yield of the bromide **41** as the only observable isomer as a white solid: mp 139–141 °C; ^1H NMR (200 MHz, $CDCl_3$) δ 5.17 (br, NH), 4.95 (m, OCH_2CH_2O), 3.78 (td, J = 11.7, 12.0, and 4.6 Hz, CHBr), 2.60–1.95 (overlapping m), 1.93 (s, CH_3CO), 1.90–1.10 (overlapping resonances), 1.22 (s, CH_3CN); IR (melt) 3300, 3060, 2920, 1650, 1540, 1440, 1365, 1155, 1110, 930 cm^{-1}; ^{13}C NMR (50 MHz, $CDCl_3$) δ 169.3, 108.4, 64.2, 58.0, 56.3, 45.2, 43.6, 40.7, 36.9, 34.7, 29.6, 24.6, 23.6, 20.1; mass spectrum, m/e calcd for $C_{15}H_{24}BrNO_3$ 347.0919, found 347.0930.

Keto Iodides 38a and 38b. These compounds were made by treating the corresponding mercuric chloride **37** with iodine and NaI in the dark for 16 h. The workup differed from the general procedure in that two 5% aqueous HCl washes were substituted from the aqueous $CuSO_4$ washes. The crude product was chromatographed on silica (MPLC) using ethyl acetate as the eluant to give the high R_f axial iodide **38a** in 30% yield as a white gum: ^1H NMR (200 MHz, $CDCl_3$) δ 5.39 (br, NH), 4.54 (br s, W_H ~ 9 Hz), 2.95–1.45 (overlapping resonances), 1.97, (s, CH_3CO), 1.22 (s, CH_3CN), 0.9–0.8 (m); IR (film) 3280, 3060, 2920, 1700, 1650, 1535, 1425, 1360, 1250 cm^{-1}; ^{13}C NMR (50 MHz, $CDCl_3$) δ 209.8, 169.5, 56.5, 50.9, 44.8, 43.1, 40.6, 33.5, 33.0, 29.6, 25.0, 24.6, 20.9; mass spectrum, m/e (no parent) calcd for $C_{13}H_{20}NO_2$ (M^+ - I) 222.1494, found 222.1498. Anal. Calcd for I: 126.9045. Found: 126.9046.

The lower R_f equatorial iodide **38b** was isolated in 51% yield, also as a white gum: ^1H NMR (200 MHz, $CDCl_3$) δ 5.39 (br, NH), 3.93 (m, CHI), 3.00–1.95 (overlapping multiplets), 1.92 (s, CH_3CO), 1.51–1.30 (overlapping multiplets), 1.18 (s, CH_3CN): IR (film) 3300, 3060, 2915, 2850, 1700, 1650, 1535, 1430, 1360, 1260, 1120 cm^{-1}; ^{13}C NMR (50 MHz, $CDCl_3$) δ 209.5, 169.5, 56.5, 49.7, 46.8, 44.6, 41.3, 38.2, 37.2, 36.4, 25.7, 24.6, 20.1; mass spectrum, m/e calcd for $C_{13}H_{20}INO_2$ 349.0539, found 349.0578.

General Procedure for Displacements by Phenylselenenyl Bromide. The organomercurial (0.2 mmol) was dissolved in 2 mL of pyridine, and while the mixture was stirred at room temperature a solution of 1.0 equiv of phenylselenenyl bromide[33] in 1 mL of pyridine was added dropwise. The reaction was stirred at room temperature for 6–8 h and diluted with $CHCl_3$. This solution was washed successively with 7% aqueous HCl (2×) and brine. The $CHCl_3$ was dried ($CaSO_4$) and evaporated. The crude products were isolated by chromatography on silica.

Ketal Selenides 42a and 42b. These compounds were synthesized from the mercurial **40** according to the general procedure and isolated by MPLC using hexanes/ethyl acetate (4:1) as eluant. The low R_f isomer **42b** was isolated as a white gum: ^1H NMR (200 MHz, $CDCl_3$) δ 7.60–7.20 (m, Ar H), 5.11 (br, NH), 3.96 (m, OCH_2CH_2O), 2.90 (td, J = 12.5, 12.3, and 4.0 Hz, CHSePh), 2.60–1.95 (overlapping m), 1.91 (s, CH_3CO), 1.80–1.20 (overlapping m), 1.09 (s, CH_3CN); IR (film) 3300, 3050, 2925, 2860, 1650, 1530, 1430, 1360, 1290, 730, 680 cm^{-1}; ^{13}C NMR (50 MHz, $CDCl_3$) δ 169.2, 135.4, 128.8, 128.4, 127.5, 108.7, 64.2, 56.5, 48.9, 45.7, 41.2, 40.4,

37.2, 36.5, 34.9, 31.7, 24.7, 23.6, 19.9; mass spectrum, m/e calcd for $C_{21}H_{29}NO_3Se$ 423.1312, found 423.1328.

The high R_f isomer **42a** was isolated as white crystals: mp 203–206 °C dec; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.60–7.20 (m, Ar H), 5.20 (br, NH), 3.93 (m, OCH_2CH_2O), 3.41 (br, $W_H \sim 8$ Hz, CHSe), 2.50 (td, J = 14.4, 12.5, and 5.5 Hz) 2.10–1.20 (overlapping resonances), 1.96 (s, CH_3CO), 1.31 (s, CH_3CN); IR (Nujol) 3350, 1650, 1530, 1150, 1115, 1085, 915, 735, 685 cm^{-1}; ^{13}C NMR (50 MHz, $CDCl_3$) δ 169.4, 134.2, 130.9, 128.9, 127.0, 108.7, 64.3, 64.1, 56.6, 52.6, 42.3, 41.5, 39.6, 34.3, 33.3, 29.7, 24.6, 23.1, 19.6; mass spectrum, m/e calcd for $C_{21}H_{29}NO_3Se$ 423.1312, found 423.1290.

Amido Selenides 44 and 45. These isomers were synthesized from the *trans*-mercurial **43**[29] using the general procedure. The high R_f cis isomer **44** was isolated as a slightly yellow oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.60–7.20 (m, Ar H), 5.78 (br, NH), 4.03 (m, CHN), 3.78 (m, $W_H \sim 9$ Hz, CHSe), 2.30–1.90 (overlapping resonances), 1.81 (s, CH_3CO), 1.80–1.35 (overlapping resonances); IR ($CHCl_3$) 3405, 2910, 2850, 1660, 1570, 1370, 1120, 970 cm^{-1}; ^{13}C NMR (50 MHz, $CDCl_3$) δ 169.0, 133.5, 129.0, 126.9, 52.3, 50.2, 33.0, 29.9, 25.0, 23.0, 22.0; mass spectrum, m/e calcd for $C_{14}H_{19}NOSe$ 297.0632, found 297.0641.

The low R_f *trans*-**45** was isolated as off-white crystals: mp 147–149 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.60–7.20 (m, Ar H), 5.55 (br, NH), 3.78 (br q, CHN), 2.99 (td, J = 11.0, 11.3, and 4.0 Hz, CHSe), 2.20–2.05 (br, overlapping resonances), 1.87 (s, CH_3CO), 1.70–1.10 (overlapping resonances); IR (Nujol) 3300, 3060, 1640, 1535, 1310, 1175, 980, 730, 690 cm^{-1}; ^{13}C NMR (50 MHz, $CDCl_3$) δ 169.1, 135.2, 128.9, 127.6, 53.2, 47.8, 33.9, 33.7, 26.5, 24.4, 23.3; mass spectrum, m/e calcd for $C_{14}H_{19}NOSe$ 297.0632, found 297.0639.

Acknowledgment. This work was supported by a grant from the National Institutes of Health. K.F.A. thanks The Upjohn Co. and the Regents of the University of California for graduate fellowships. Special thanks is due to Loretta Jackson and Susan Oliva for assistance in preparing this manuscript.

Synthesis of Steroidal 16,17-Fused Unsaturated δ-Lactones[1]

Brian Green,* Richard I. Crane, Ibomacha S. Khaidem, R. Scott Leighton, S. S. Newaz, and Thomas E. Smyser

Department of Chemistry, University of Maine, Orono, Maine 04469

Received June 1, 1984

The synthesis of the [16,17-*e*] fused ring α-pyrones **2b** and **10** has been achieved in a one-step process from the corresponding hydroxymethylene compounds **3a** and **9** by using a titanium tetrachloride mediated Knoevenagel condensation with dimethyl malonate. The corresponding unsubstituted α-pyrone **2a** was prepared by a stepwise method utilizing a Wittig reaction of **3a** as the key step. Other approaches to these pyrones are also described.

In recent years many naturally occurring unsaturated lactones have been shown to possess cytotoxicity and/or antitumor activity.[2] By far the majority of these compounds are of the α-methylene γ-lactone type,[3] but certain endocyclic five- and six-membered α,β-unsaturated lactones such as the cardenolides,[4] bufadienolides,[5] withanolides,[6] and others[7] have also shown this kind of biological activity. Consequently a great deal of effort has been expended in the synthesis of naturally occurring unsaturated lactones and their analogues.[8,9]

Prompted by this situation and an early report of Pike[10] that certain steroidal [17,16-*d*] unsaturated γ-lactones exhibited an unusual order of cytotoxicity together with low whole animal toxicity, we embarked on a program of synthesis of 16,17-fused ring unsaturated steroidal δ-lactones. Up to that time the only synthesis of related systems had been reported by Kurath[11] and Valcavi[12] who prepared saturated [16,17-*e*]-lactones, by Igarashi[13] who transformed a kryptogenin derivative into a [16,17-d]-lactone, and by Gandolfi[14] who produced [16,17-*d*] enol lactones by means of a Reformatsky-type reaction on 16-

(1) Presented in part at the 176th National Meeting of the American Chemical Society, Miami Beach, FL, Sept 1978.

(2) For general reviews, see: Ferguson, L. N. *Chem. Soc. Rev.* **1975**, *4*, 289. Fujita, E.; Nagao, Y. *Bioorg. Chem.* **1977**, *6*, 187.

(3) Kupchan, S. M. *Pure Appl. Chem.* **1970**, *21*, 227. Doskotch, R. W.; El-Feraly, F. S.; Huang, C.-T. *J. Chem. Soc., Chem. Commun.* **1976**, 402. Lee, K. H.; Kimura, T.; Okamoto, M.; Cowherd, C. M. *Tetrahedron Lett.* **1976**, 1051. Samek, Z.; Holub, M.; Drozdz, B.; Grabarczyk, H.; Hladon, B. *Collect. Czech. Chem. Commun.* **1977**, *42*, 2441. Ogura, M.; Cordell, G. A.; Farnsworth, N. R. *Phytochem.* **1978**, *17*, 957.

(4) Kupchan, S. M.; Knox, J. R.; Kelsey, J. E.; Saenz Renauld, J. A. *Science (Washington, D.C.)* **1965**, *146*, 1685. Kupchan, S. M.; Hemingway, R. J.; Doskotch, R. W. *J. Med. Chem.* **1964**, *7*, 803.

(5) Kupchan, S. M.; Hemingway, R. J.; Hemingway, J. C. *J. Org. Chem.* **1969**, *34*, 3894. Kupchan, S. M. *Bioorg. Chem.* **1971**, *1*, 13.

(6) Shohat, B.; Gitter, S.; Lavie, D. *Int. J. Cancer* **1970**, *5*, 244. Kupchan, S. M.; Anderson, W. K.; Bollinger, P.; Doskotch, R. W.; Smith, R. M.; Saenz Renauld, J. A.; Schnoes, H. K.; Burlingame, A. L.; Smith, D. H. *J. Org. Chem.* **1969**, *34*, 3858. For biological activity of withaferin A, see: Nicholas, A. W.; Rosazza, J. P. *Bioorg. Chem.* **1976**, *5*, 367.

(7) Kupchan, S. M.; Dessertine, A. L.; Blaylock, B. T.; Bryan, R. F. *J. Org. Chem.* **1974**, *39*, 2477. Jolad, S. *Tetrahedron Lett.* **1976**, 4119. Hayashi, Y.; Yuki, Y.; Matsumoto, T.; Sakan, T. *Tetrahedron Lett.* **1977**, 3637.

(8) Grieco, P. A. *Synthesis* **1975**, 67. Newaz, S. S. *Aldrichimica Acta* **1977**, *10*, 64. Kamano, Y.; Pettit, G. R.; Tozawa, M.; Komeichi, Y.; Inoue, M. *J. Org. Chem.* **1975**, *40*, 2136, and preceding papers. Yoshii, E.; Oribe, T.; Koizumi, T.; Hayashi, I.; Tumura, K. *Chem. Pharm. Bull.* **1977**, *25*, 2249. Stache, U.; Radscheit, K.; Fritsch, W.; Haede, W.; Kohl, H.; Ruschig, H. *Justus Liebigs Ann. Chem.* **1971**, *750*, 149. Sondheimer, F.; McCrae, W.; Salmond, W. G. *J. Am. Chem. Soc.* **1969**, *91*, 1228. Engel, Ch. R.; Dionne, G. *Can. J. Chem.* **1978**, *56*, 424. Bauer, P. E.; Kyler, K. S.; Watt, D. S. *J. Org. Chem.* **1983**, *48*, 34. Sen, A.; Jaggi, F. J.; Tsai, T. Y. R.; Wiesner, K. *J. Chem. Soc., Chem. Commun.* **1982**, 1213. Kabat, M. M.; Kurek, A.; Wicha, J. *J. Org. Chem.* **1983**, *48*, 4248.

(9) Engel, Ch. R.; Bouchard, R.; deKrassny, A. F.; Ruest, L.; Lessard, J. *Steroids* **1969**, *14*, 637.

(10) Pike, J. E.; Grady, J. E.; Evans, J. S.; Smith, C. J. *J. Med. Chem.* **1964**, *7*, 348.

(11) Bielefeld, M. A.; Kurath, P. *J. Org. Chem.* **1969**, *34*, 237.

(12) Valcavi, U.; Sianesi, I. L. *Gazz. Chim. Ital.* **1963**, *98*, 803.

(13) Igarashi, K. Fr. Pat. M1677, 1963; *Chem. Abstr.* **1963**, *59*, 12878.

(14) Gandolfi, C.; Doria, G.; Amendola, M.; Dradi, E. *Tetrahedron Lett.* **1970**, 3923.

0022-3263/85/1950-0640$01.50/0