products, vide supra. Products **4a,b**[5] as well as **4c-f**[6] have been reported previously.

4g: oil; IR (neat) 1730 (C=O), 1610, 1575 cm^{-1} (C=N); ^1H NMR (270 MHz, $CDCl_3$) δ 2.23, 2.29 (s, 3 + 6 H, Me), 6.88 (s, 2 H, mesityl-H), 7.4-7.6 (m, 5 H, phenyl H), 9.71 (s, 1 H, CHO); mass spectrum m/e 311 (1, M^+). Anal. Calcd for $[C_{17}H_{16}NOS]^+$ (M - CHO) m/z 282.09444, found m/z 282.09450.

4h: mp 103-104 °C; IR (KBr): 1662 (C=O), 1600, 1585 cm^{-1} (C=N); ^1H NMR (80 MHz, $CDCl_3$): δ 2.15, 2.23 (s, 3 + 6 H, Me), 6.87 (s, 2 H, mesityl H), 7.0-8.2 (m, 10 H, phenyl H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 19.31, 21.04 (Me), 112.4 (C-5), 122.3-139.97 (aryl C), 155.66 (C-3), 193.42 (C=O). Anal. Calcd for $C_{24}H_{21}NO_2S$: C, 74.39; H, 5.46; N, 3.62; S, 8.27. Found: C, 74.04; H, 5.54; N, 3.67; S, 8.13.

Acknowledgment. We thank the Deutsche Forschungsgemeinschaft (Scha 231/5-2) and the Fonds der Chemischen Industrie, Frankfurt, for financial support.

Competitive Intramolecular Cyclizations of Epoxides to Aromatic and Double Bond Positions

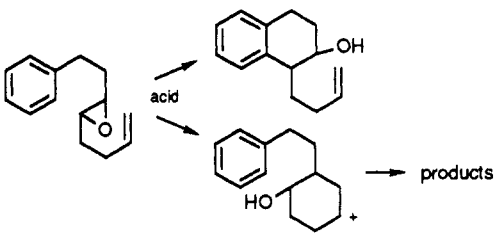
Stephen K. Taylor,* David S. Bischoff,†
Curtis L. Blankespoor, Paul A. Deck, Suzanne M. Harvey,†
Patricia L. Johnson, Ariane E. Marolewski, Steven W. Mork,
Douglas H. Motry, and Ronald Van Eenenaam

Department of Chemistry, Hope College, Holland, Michigan 49423

Received February 3, 1989 (Revised Manuscript Received March 13, 1990)

Epoxy-ene cyclizations have been extensively investigated,[1] and epoxy-arene cyclizations have received considerable attention recently.[2,3] In both the former[4] and latter[2,3,5] transformations, Baldwin's rules have been useful in predicting cyclization preferences and relative yields.[2-4]

We felt it would be instructive to investigate epoxides which can undergo intramolecular cyclization to either a double bond or aromatic position (eq 1). The determi-



(1)

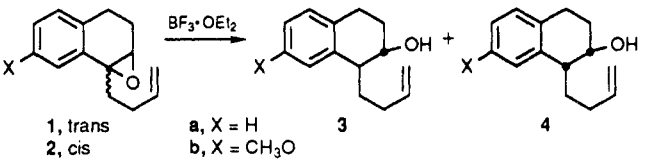
nation of the relative facility of these two processes, under conditions where stereoelectronic effects can play a major role, is the thrust of this report. We believe this is the first systematic report of this nature. In certain cases, it is shown that Baldwin's rules can be used to predict which ring formation process will occur (even though these rules heretofore have not been used to compare the relative propensity of epoxy-ene versus epoxy-arene cyclizations). In other cases, no predictions can be made based on Baldwin's rules, and our work is a first step in elucidating the cyclization preferences in these types of situations.

Results and Discussion

Since five-membered ring formation is less favorable than six-membered ring formation,[1-5] eq 1 represents the most probable transformations of **1a** and **2a,b** (Table I). When treated with $AlCl_3$, $SnCl_4$, or BF_3·OEt_2, all of these

† Student research participants from Olivet Nazarene University.

Table I. Products of the Reaction of BF_3·OEt_2 and 3,4-Epoxy-1-aryl-7-octenes



epoxide	trans:cis	ratio of 3:4[a]	yield,[b] % of 3 + 4
1a	>99:1	99:1	72
2a	8:92	7:93	62
2b	10:90	13:87	91

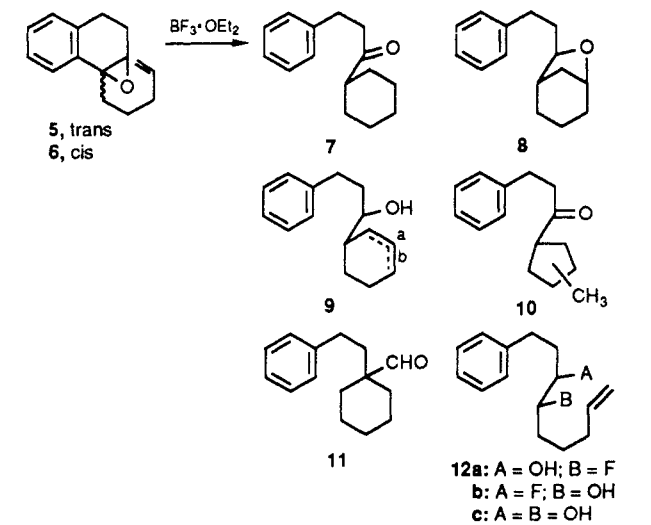
[a] Ratios were determined by capillary GC. [b] NMR yields.

Table II. Product Composition for the Reactions of 5 and 6

		percent composition[a]							
epoxide	trans:cis	7	8	9a[b]	9b	10	11	12a + b	12c
5	>99:1	8	41	12	11	10	<1	6	12
6	8:92	63	2	1	1	5	20	8	-

[a] Area percents by flame ionization detector GC. [b] A small quantity of an allylic alcohol, **6c** the 1-substituted cyclohexenyl isomer of **9c**, was detected at 5 min reaction time, but this compound disappeared rapidly after that.

Scheme I



epoxides cyclize predominantly to the aromatic group. However, BF_3·OEt_2 gave the highest yields and smallest amounts of halohydrin side products. A catalytic quantity of BF_3·OEt_2 in CH_2Cl_2 is sufficient to transform epoxides **1a**, **2a** and **2b** in good yields to the products shown in Table I. These compounds account for 95% or greater of the volatile products. It should also be noted that the reactions are highly stereospecific as cis epoxides lead to cis-disubstituted tetralols and trans epoxides give the

(1) (a) van Tamelen, E. E. *Acc. Chem. Res.* **1975**, *8*, 152 and references therein. (b) See Brown, E. D.; Sutherland, J. K.; Sam, T. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, *22*, 2332 for a representative medium ring epoxy-ene cyclization.

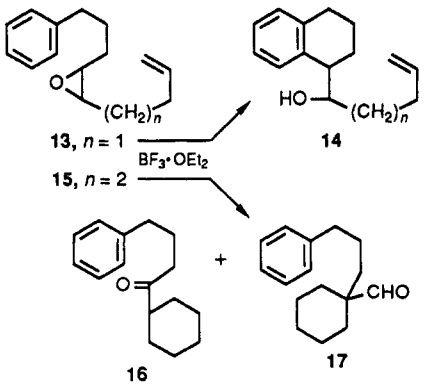
(2) (a) Taylor, S. K.; Hockerman, G. H.; Karrick, G. L.; Lyle, S. B.; Schramm, S. B. *J. Org. Chem.* **1983**, *48*, 2449. (b) Taylor, S. K.; Davisson, M. E.; Hissom, B. R., Jr.; Brown, S. L.; Pristach, H. A.; Schramm, S. B.; Harvey, S. M. *Ibid.* **1987**, *52*, 425. (c) Taylor, S. K.; Blankespoor, C. L.; Harvey, S. M.; Richardson, L. J. *J. Org. Chem.* **1988**, *53*, 3309.

(3) (a) Tanis, S. P.; Herrington, P. M. *J. Org. Chem.* **1983**, *48*, 4572. (b) Tanis, S. P.; Raggon, J. W. *Ibid.* **1987**, *52*, 819. (c) Burnell, R. H.; Dufour, J. M. *Can. J. Chem.* **1987**, *65*, 21.

(4) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734.

(5) Baldwin did not discuss aromatic compounds, but we did show that relative epoxyarene cyclization yields could be reliably predicted by using his ideas.[2a] Tanis has also shown this.[3]

Scheme II



corresponding trans tetralols (the stereochemistry of the products was established by ^1H NMR comparison with *cis*- and *trans*-1-methyl-1,2,3,4-tetrahydro-2-naphthol model compounds reported earlier[2b]).

Compared to compounds **1a** and **2a**, trans and cis isomers **5** and **6** (Scheme I) simply have an extra methylene unit between the epoxide group and the double bond. However, this minor structural change has major consequences. When treated with BF_3·OEt_2, these compounds cyclize almost exclusively to the double bond (Scheme I and Table II). The major product of the *trans*-epoxide is an ether (**8**) whereas the *cis*-epoxide yields mainly a ketone (**7**), which apparently results from hydride shifts (literature precedents exist for the formation of these types of products[1a,6]). It is noteworthy that **11**, a major product of the cyclization of **6**, is barely present in the products of the reaction of **5**.

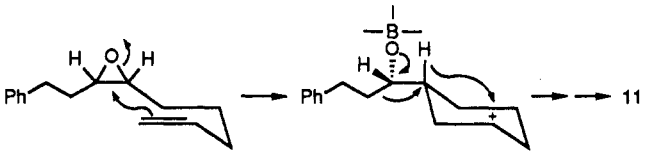
Compared to **1a** and **2a**, **13** (Scheme II) has the extra methylene group between the aryl and epoxide groups. This compound cyclizes to the aromatic group to give **14** in 75% NMR yield.[7]

For **15** (Scheme II), there are extra methylene units between both the epoxide and the aryl and double bond positions. This compound undergoes epoxy–ene ring closure when treated with BF_3·OEt_2 to give predominantly **16** and **17** in a 2:1 ratio. From GCMS data, we conclude that the minor products of this reaction are the analogs of those shown in Scheme I, but there are smaller amounts of them.

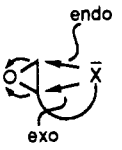
An examination of Table I and Scheme II reveals that very few products are formed when epoxy–arene cyclization predominates. However, the product composition is very complex when epoxy–ene closures occur. This can be explained by the fact that when the former pathway occurs, an arenium ion hydrogen will be eliminated to regenerate the aromatic ring. The driving force for the loss of this proton and the consequent rearomatization will ensure that this is the only hydrogen transaction. However, when the epoxy–ene cyclization occurs, a number of hydrogen migrations (and eliminations) of similar energy requirements can and do occur.

The transformation of the *cis*-epoxide **6** (Scheme I) produces significantly more of the skeletal rearrangement product **11** than does the corresponding trans isomer **5** (Table II). In a related cyclization, the cis isomer **15** (Scheme II) also produces significant amounts of an analogue of **11**, **17**, which most likely results from a similar reaction pathway.

This significant difference between the behavior of the cis and trans isomers can be accounted for by examining Dreiding models of the cyclization intermediates. For the *cis*-epoxide, the migrating $PhCH_2CH_2$ group is anti to the hydrogen[8] that migrates during the rearrangement: hence the alkyl group is well-positioned for a facile migration. For the trans isomer, the $PhCH_2CH_2$ group is essentially syn to the migrating hydrogen and hence the alkyl shift is less facile, and less **11** is produced.



Baldwin's Rules. Baldwin[4] has specified rules which are useful for predicting the relative facility of ring formation processes. These rules successfully accounted for the behavior of epoxy–ene cyclizations[4] and more recently have been used to predict the relative ease of epoxide ring formation at aromatic positions.[2c,3] According to Baldwin's rules, the exo ring formation process is generally preferred over the endo mode.



We wanted to determine if Baldwin's rules would be useful for predicting whether aromatic or double bond cyclization would occur in our compounds. Accordingly, we classified each of the potential 6-membered ring formation processes (5-membered ring formation is less favorable,[2c,3,4] and we have not observed it) as exo or endo. For **5** and **6** the epoxy–ene closure is exo whereas the epoxy–arene process is endo. From this, one might predict that the double bond process would predominate, and this is indeed observed. For **13**, the exo aromatic closure might be expected to predominate over the endo double bond cyclization. Again this expectation is borne out.

For the other epoxides, both double bond cyclization processes have the same classifications, and no predictions can be made from these conventions. In the compounds with short alkyl chains between both groups (**1a** or **2a**), aromatic cyclization predominated. But in the epoxide with longer chains between both groups (**15**), epoxy–ene cyclization was the major transformation.

Our best explanation of this difference is that in the reaction of **15** the transition states leading to double bond or aromatic ring closure can readily occur through the favored chair conformation.[1] This compound probably affords the fairest comparison of the reactivity of the two functional groups: here the double bond reacts preferentially. **1a** and **2a** and **2b** have more difficulty in attaining the required geometry and, at least in these cases, the aromatic ring participates. It thus appears that the aryl group has a higher propensity for ring formation with epoxides when the transition states do not highly favor cyclization.

We currently have no evidence to support a mechanistic explanation for this behavior, and more work would be

(6) van Tamelen, E. E.; Murphy, J. W. *J. Am. Chem. Soc.* **1970**, *92*, 7204.

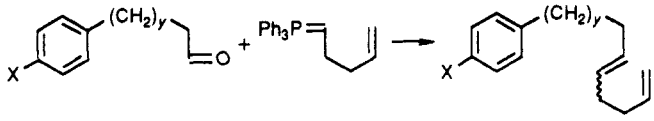
(7) This compound was at least 86% of the volatile product mixture. Eight other compounds were present at 1–2% levels and were not identified. (The epoxide starting material had 2–4% of the isomeric terminal epoxide in it as an impurity and the source of products at the 1–2% level would be uncertain.)

(8) For convenience, we have drawn the proton migration as a 1,3-hydride shift. From initial deuterium labeling studies, this appears to be the case.

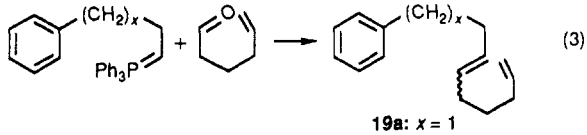
necessary to prove the generality of it. However, the aromatic ring is larger and capable of more participation pathways than is the double bond.[9] This may account for the preference for aromatic ring closure in **1a** and **2a,b**. Also, the possibility of Lewis acid interaction differences between the aromatic and double bond functionalities (or complex interactions between the unsaturated group, epoxide, and Lewis acid) may afford an explanation.

When there is a clear-cut exo versus endo situation, it is noteworthy that conformational preferences are important enough to control which cyclization process occurs, even when these two electronically different (alkene and aromatic) groups are involved. It is also interesting that when the epoxy–arene cyclization occurs, very little epoxy–ene closure results and vice-versa.

The epoxides used in this study were synthesized by epoxidation of aryl diene precursors. The cis epoxides (**2a**, **2b**, **6**, **13**, and **15**) were made from *cis*-arylidienes prepared by Wittig procedures[10] as shown in eqs 2 and 3. There was generally 8–10% trans isomer present in aryldienes and epoxides prepared by these procedures.



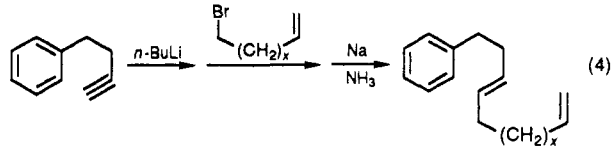
18a: X = H; y = 1
b: X = CH_3O; y = 1
c: X = H; y = 2 (2)



(3)

19a: x = 1
b: x = 2

The aryl diene precursors to the *trans*-epoxides (**1a** and **5**) were prepared by Na/NH_3 reduction of the coupling product of the lithium salt of 4-phenyl-1-butyne and the appropriate alkenyl bromide (eq 4).



(4)

20a: x = 1
b: x = 2

The products of these reactions could only be cleanly separated by capillary GC: only a few compounds could be isolated in pure form by, for example, semipreparative HPLC using a 12 000 theoretical plate silica gel column. To be conclusive about our product identifications and GC peak assignments, we made **7**, **9a**, **9b**, **11**, **16**, and **17** by independent methods (see the Experimental Section) and used these compounds for spectral and chromatographic comparison with our reaction products.

Experimental Section

Infrared spectra were obtained on Perkin-Elmer 727 and Pye-Unicam 3-300 spectrophotometers. GC analyses were performed on Hewlett-Packard 5890 and 5880A capillary gas chromatographs using 30-m SPB-5 and 15-m SP-2330 columns. Routine NMR spectra were recorded on Varian EM 360A and FT-80A spectrometers. Low-resolution GCMS data were obtained on Hewlett-Packard 5995A and 5970B instruments: HRMS measurements were done on a VG 70-70. Elemental analyses were determined by Galbraith Labs, Inc. Boiling points and melting points (obtained on a Mel-Temp apparatus) are uncorrected. The CH_2Cl_2 used in cyclization reactions was distilled under N_2 from CaH_2 immediately before use. All chemicals used were reagent purity unless otherwise noted. Reagent $BF_3{\cdot}OEt_2$ was used as obtained from a freshly opened bottle. Aldehydes were prepared by oxidation of the appropriate alcohol with pyridinium chlorochromate (PCC)[11] or pyridinium dichromate (PDC).[12] All reactions described below, except the epoxidations, were done under a dry N_2 atmosphere. Semipreparative HPLC separations were done using a 25 cm × 9.2 mm 10 μ silica gel column. Several of the compounds lack satisfactory combustion analyses: 300-MHz ^1H and ^{13}C NMR spectra of these compounds (**1a**, **4a**, **4b**, **5**, **8**, **14**, **18b**, and **22**) are provided as supplementary material to prove product purities (≥95%).

General Procedure for *cis*-Aryl Diene Preparation (18a–c and 19a–b, eqs 2 and 3). The *cis*-aryl dienes were prepared by combining the appropriate aldehydes with Wittig reagents (eqs 2 and 3). The phosphonium salts used to make the Wittig reagents were made by a general procedure[10] from $P(Ph)_3$ and 5-bromo-1-pentene, 6-bromo-1-hexene,[13] and 1-bromo-3-phenylpropane.

General Wittig Procedure. To 30 mL of dry DMSO was added dropwise 16.4 mL of 2.6 M *n*-butyllithium. After 0.5 h of stirring, a solution of 40.0 mmol of phosphonium salt in 50 mL of dry DMSO was added dropwise, and the mixture was stirred 1 h. Then 50.0 mmol of the appropriate aldehyde in 5 mL of dry DMSO was added dropwise, and the mixture was stirred for 5 h, added to 200 mL of ice water, and extracted with a mixture of 180 mL of hexane and 20 mL of ether. The organic layer was dried ($MgSO_4$) and concentrated to about 50 mL and run through 40 g of neutral alumina. The alumina was rinsed with 400 mL of a 9:1 hexane–ether mixture to elute the product. After concentration of the combined organic layers, the organic products were purified by short-path distillation to give arylidenes in yields of 45–65% (cis:trans ratios were typically 9:1).

8-Phenyl-*cis*-1,5-octadiene (18a) was obtained by the above procedure from hydrocinnamaldehyde and the phosphonium salt made from 5-bromo-1-pentene and triphenylphosphine[10] (8% of the trans product was present): bp 93–94 °C (2 mm); ^1H NMR (CCl_4) δ 1.8–3.1 (m, 6 H), 2.5 (t, 2 H, J = 7 Hz), 4.7–6.0 (m, 5 H), 7.1 (s, 5 H); IR (NaCl disks) 1640 (m), 1610 (w), 990 (m), 905 (s), 740 (m), and 690 (s, cis) cm^{-1}; mass spectrum, m/e (relative intensity) 186 (2), 104 (21), 95 (10), 92 (12), 91 (100), 67 (12), 65 (25), and 41 (22). Anal. Calcd for $C_{14}H_{18}$: C, 90.25; H, 9.75. Found: C, 89.91; H, 9.51.

8-(*p*-Methoxyphenyl)-*cis*-1,5-octadiene (18b) was prepared from 3-(*p*-methoxyphenyl)propanal and the above phosphonium salt (10% of the trans isomer was present): bp 86–87 °C (0.09 mm); NMR (CCl_4) δ 1.9–2.7 (m, 6 H), 2.5 (t, 2 H, J = 7 Hz), 3.7 (s, CH_3O), 4.7–5.95 (m, 5 H), and 6.6–7.05 (A_2B_2, 4 H); IR (NaCl disks) 1245 (s, ether), 995 (m), 910 (m), and 690 (m, cis) cm^{-1}; mass spectrum, m/e (relative intensity) 216 (12), 121 (100); exact mass m/e calcd for $C_{15}H_{20}O$ 216.1514, found 216.1530. ^1H and ^{13}C NMR spectra are provided as supplementary material.

9-Phenyl-*cis*-1,5-nonadiene (18c) was obtained from 4-phenylbutanal and the phosphonium salt (10% of the product mixture was the trans isomer): bp 70–71 °C (0.1 mm); NMR (CCl_4) δ 1.5–2.5 (m, 8 H), 2.6 (t, 2 H, J = 7 Hz), 4.8–6.0 (m, 5 H), 7.1 (s, 5 H); IR (AgCl disks) 990 (s), 905 (s), 740 (s), and 690 (s, cis) cm^{-1}; mass spectrum, m/e (relative intensity), 200 (3), 117 (27), 104 (54), 92 (22), 91 (100), 41 (22). Anal. Calcd for $C_{15}H_{20}$: C, 89.94; H, 10.06. Found: C, 89.88; H, 10.06.

9-Phenyl-*cis*-1,6-nonadiene (19a) was prepared from 5-hexenal and (3-phenylpropyl)triphenylphosphonium bromide by the above technique: bp 62–64 °C (0.2 mm); NMR (CCl_4) δ 1.0–2.8

(9) A phenonium ion could form. This possibility is discussed in ref 2b.

(10) Rapport, H.; Bhalerao, U. T. *J. Am. Chem. Soc.* **1971**, *93*, 4835.

(11) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, 2647.

(12) Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1979**, 399.

(13) Some rearrangement occurred during the formation of the phosphonium salt. The procedure[10] must be altered to minimize this rearrangement product. Rather than refluxing a benzene/6-bromo-1-hexene/triphenylphosphine mixture, we stirred the mixture 8 h and then purified the product by trituration of the salt with CH_2Cl_2/benzene.

(14) (a) Campbell, K. N.; Eby, L. T. *J. Am. Chem. Soc.* **1941**, *63*, 2683. (b) Campbell, K. N.; Eby, L. T. *Ibid.* **1941**, *63*, 216.

(15) This compound was tentatively identified as 1-phenyl-7-octen-3-one by GCMS data. A fluorohydrin was also detected in trace quantities.

(m, 10 H), 4.7–6.0 (m, 5 H), 7.1 (s, 5 H); IR (NaCl disks) 1640 (m), 1610 (w), 990 (m), 910 (s), and 695 (s) cm^{-1}. Anal. Calcd for $C_{15}H_{20}$: C, 89.94; H, 10.06. Found: C, 89.34; H, 10.20.

10-Phenyl-*cis*-1,6-decadiene (19b) was made from the phosphonium salt of Ph_3P and 6-bromo-1-hexene[13] and 4-phenylbutanal: bp 75–78 °C (0.1 mm); NMR (CCl_4) δ 1.1–2.3 (m, 10 H), 2.6 (t, 2 H, J = 7 Hz), 4.8–6.1 (m, 5 H), 7.1 (s, 5 H); IR (NaCl disks) 1640 (w), 1605 (w), 995 (m), 910 (s), 740 (s), 700 (s) cm^{-1}; mass spectrum, m/e (relative intensity) 214 (5), 105 (25), 104 (97), 91 (100), 81 (25), 67 (27). Anal. Calcd for $C_{16}H_{22}$: C, 89.65; H, 10.35. Found: C, 89.20; H, 10.20.

General Method for Making *trans*-Epoxides. The *trans*-epoxides (**1a** and **5**) were prepared by the representative method below (eq 4).

Under N_2, 33.5 mmol of 4-phenyl-1-butyne was dissolved in 30 mL of dry THF. After cooling to −40 °C, 11.6 mL of 2.6 M *n*-butyllithium was added dropwise to this solution. After the solution was stirred for 1.5 h and warmed to 0 °C, 54 mmol of 4-bromo-1-butene in 42.3 mL of dry THF was added dropwise to the flask, and the solution was stirred 2 h and refluxed for 12 h. The reaction mixture was quenched with ice/H_2O and acidified with 3 M HCl. The organic layer was extracted with ether, washed with 50 mL of 5% $NaHCO_3$ twice, and dried ($MgSO_4$). The organic layer was concentrated, and the resulting oil was distilled, yielding 2.98 g (45%) of **8-phenyl-1-octen-5-yne (21)**: bp 82–84 °C (0.5 mm); ^1H NMR (CCl_4) δ 2.0–2.9 (m, 8 H), 4.8–6.1 (m, 3 H), 7.2 (s, 5 H); IR (NaCl disks) 1640 (m, vinyl), 995 and 915 (terminal vinyl), 760 and 695 (monosubstituted benzene) cm^{-1}; mass spectrum, m/e (relative intensity) 184 (2), 143 (12), 142 (16), 141 (20), 128 (14), 91 (100), 65 (24), 39 (17). Anal. Calcd for $C_{14}H_{16}$: C, 91.25; H, 8.75. Found: C, 91.19; H, 9.14.

9-Phenyl-1-nonen-6-yne (22) was prepared as described above from 12.55 g of 4-phenyl-1-butyne (97 mmol in 100 mL of THF), 40 mL of 2.5 M *n*-butyllithium, and 15.97 g (107 mmol) of 5-bromo-1-pentene. The product was distilled to give 9.56 g of the desired enyne (49%): bp 97–99 °C (0.4 mm); ^1H NMR ($CDCl_3$) δ 1.0–3.0 (m, 10 H), 4.7–6.1 (m, 3 H), 7.2 (s, 5 H); IR (NaCl disks) 2210 (w, C≡C), 920 (m), 920 (s), 760 (s), and 700 (s) cm^{-1}; mass spectrum, m/e (relative intensity) 198 (1), 129 (21), 91 (100), 65 (23); mass spectrum, m/e calcd for $C_{15}H_{18}$ 198.1408, found 198.1390. 300-MHz ^1H and ^{13}C NMR spectra of **22** are provided as supplementary material.

8-Phenyl-*trans*-1,5-octadiene (20a) was made in 55% yield by the procedure described below for the preparation of **20b** (less than 1% of the cis isomer was present): bp 88–89 °C (1.3 mm); ^1H NMR (CCl_4) δ 1.8–2.9 (m, 8 H), 5.4 (m, 2 H, *trans*-CH=CH), 6.0–6.4 (m, 3 H), 7.1 (s, 5 H); IR (NaCl disks), 995 (m), 970 (s, trans). 750 (m), and 700 (s) cm^{-1}. Anal. Calcd for $C_{14}H_{18}$: C, 90.25; H, 9.75. Found: C, 90.17; H, 9.66.

9-Phenyl-*trans*-1,6-nonadiene (20b) was obtained by Na/NH_3 reduction of **22**. To a mixture of 2.44 g of freshly cut sodium metal and 140 mL of liquid ammonia cooled to −78 °C was added 7.5 g of **22** (adding by slowly syringing it in underneath the Na/NH_3). The dark blue solution turned green in about 3.5 h and then proceeded to turn yellow, orange, and red. After letting the mixture stir overnight, 250 mL of 3 M NH_4OH was slowly added, and the mixture was extracted twice with ether. The combined ether extracts were washed with 5% HCl, 6 M HCl, H_2O, and 5% $NaHCO_3$ and dried ($MgSO_4$). After evaporation of the solvent distillation of the product gave 5.0 g of **20b** (67%): bp 58–60 °C (0.05 mm); ^1H NMR (CCl_4) δ 1.2–2.9 (m, 10 H), 4.7–6.1 (m, 5 H), 7.1 (m, 5 H); IR (NaCl disks) 990 (m), 960 (s, trans), 905 (s), 740 (m), and 690 (s) cm^{-1}; mass spectrum, m/e (relative intensity), 200 (8), 104 (35), 91 (100), and 67 (47). Anal. Calcd for $C_{15}H_{20}$: C, 89.94; H, 10.06. Found: C, 89.53; H, 9.75.

Epoxidation Procedure. The epoxides were made by the following general procedure.

A mixture of 2.81 g (85% pure, 13 mmol) of MCPBA in 70 mL of CH_2Cl_2 was added dropwise at room temperature over 1.25 h to a solution of 13 mmol of aryl diene in 40 mL of CH_2Cl_2. The mixture was stirred for 1.5 h, refluxed for 1.5 h, and stirred again for 4 h at ambient temperature. Petroleum ether (25 mL) was added, and the mixture was cooled with ice water. The resulting precipitate was filtered off, and the filtrate was washed twice with 20% $NaHSO_3$, twice with 5% $NaHCO_3$, and once with 16% NaCl. After drying ($MgSO_4$) and rotary evaporation, the product was distilled using a 10-cm column packed with stainless steel sponge. This method minimized epoxidation at the terminal double bond. Products described below, after distillation, had ≤2% of the terminal epoxidation products.

***trans*-3,4-Epoxy-1-phenyl-7-octene (1a)** was prepared by epoxidation of **20a**: bp 72–74 °C (0.07 mm); ^1H NMR (CCl_4) δ 1.3–3.0 (10 H), 4.8–6.1 (m, 3 H), 7.25 (s, 5 H); IR (NaCl disks) 1640 (w), 995 (s), 910 (s), 890 (trans epoxide), 745 (s), and 695 (s) cm^{-1}; mass spectrum, m/e (relative intensity) 202 (1), 117 (44), 104 (49), 91 (100), 67 (35), 65 (30), exact mass m/e calcd for $C_{14}H_{18}O$ 202.1358, found 202.1331. ^1H and ^{13}C NMR are provided as supplementary material.

***cis*-3,4-Epoxy-1-phenyl-7-octene (2a)** was made from **18a** and MCPBA (**1a**:**2a** = 8:92): bp 82–85 °C (0.8 mm); ^1H NMR (CCl_4) δ 1.3–3.1 (m, 10 H), 4.9–6.2 (m, 3 H), 7.25 (s, 5 H); IR (NaCl disks) 1660 (m), 995 and 915 (terminal C=C), and 750 and 700 (s, monosubstituted benzene); mass spectrum, m/e (relative abundance) 202 (0.6), 117 (52), 104 (37), 91 (100), 67 (35), and 65 (30). Anal. Calcd for $C_{14}H_{18}O$: C, 83.12; H, 8.97. Found: C, 83.03; H, 8.89.

***cis*-3,4-Epoxy-1-(*p*-methoxyphenyl)-7-octene (2b)** was prepared from **18b** (10% of the trans isomer was present): bp 116–117 °C (0.15 mm); ^1H NMR (CCl_4) δ 1.3–3.1 (m, 10 H), 3.78 (s, 3 H), 4.8–6.2 (m, 3 H), 6.7–7.25 (A_2B_2, J_{AB} = 8 Hz); IR (CCl_4) 1640 (m), 1510 (s), 1250 (s, ether), 1040 (s), 830 (s), 815 (m, *cis*-epoxide) cm^{-1}; mass spectrum, m/e (relative intensity) 232 (14), 148 (17), 147 (20), 134 (51), 121 (100), 91 (15), 77 (15). Anal. Calcd for $C_{15}H_{20}O_2$: C, 77.56; H, 8.68. Found: C, 77.62; H, 8.55.

***trans*-3,4-Epoxy-1-phenyl-8-nonene (5)** was made by epoxidation of **20b**: bp 85–87 °C (0.7 mm); ^1H NMR ($CDCl_3$) δ 1.2–3.0 (12 H), 4.8–6.1 (m, 3 H), 7.2 (s, 5 H); IR (NaCl disks) 1640 (w), 1610 (w), 990 (m), 910 (s), 740 (m), and 700 cm^{-1}; mass spectrum, m/e (relative intensity) 216 (4), 104 (44), 91 (100), 67 (48), 55 (39), 41 (46); exact mass m/e calcd for $C_{15}H_{20}O$ 216.1514, found 216.1529. ^1H and ^{13}C NMR spectra are provided as supplementary material.

***cis*-3,4-Epoxy-1-phenyl-8-nonene (6)** was made from **19a** (**5**:**6** = 8:92): bp 86–88 °C (0.5 mm): ^1H NMR ($CDCl_3$) δ 1.1–3.1 (12 H), 4.8–6.0 (3 H), 7.2 (s, H); IR (NaCl disks) 1650 (m), 995 (m), 920 (s), 745 (s), and 695 (s); mass spectrum, m/e (relative intensity) 216 (2), 104 (29), 91 (100), 67 (51), 65 (33), 55 (39). Anal. Calcd for $C_{15}H_{20}O$: C, 83.28; H, 9.32. Found: C, 83.21; H, 9.19.

***cis*-4,5-Epoxy-1-phenyl-8-nonene (13)** was prepared from **18c** and MCPBA as described above (10% trans isomer was present): bp 79–80 °C (0.03 mm); ^1H NMR ($CDCl_3$) δ 1.2–2.5 (m, 7 H), 2.5–2.8 (m, 3 H), 2.98 (t, 2 H, J = 6 Hz), 4.8–6.1 (m, 3 H), 7.2 (s, 5 H); IR (NaCl disks) 1640 (m), 910 (s), 750 (s), 700 (s) cm^{-1}; mass spectrum, m/e (relative intensity) 216 (0.3), 105 (15), 104 (100), 91 (55), 65 (15). Anal. Calcd for $C_{15}H_{20}O$: C, 83.28; H, 9.32. Found: C, 83.68; H, 9.52.

***cis*-4,5-Epoxy-1-phenyl-9-decene (15)** was prepared from **19b** and MCPBA (8% trans isomer): bp 85–88 °C (0.05 mm); ^1H NMR (CCl_4) δ 1.0–2.9 (m 14 H), 4.7–6.1 (m, 3 H), 7.2 (s, 5 H); IR (NaCl disks) 995 (m), 915 (s), 740 (s), 700 (s); mass spectrum, m/e (relative intensity), 230 (3), 104 (100), 91 (61). Anal. Calcd for $C_{16}H_{22}O$: C, 83.43; H, 9.63. Found: C, 83.22; H, 9.52.

General Cyclization Procedure. Into a mixture of 70 mL of dried CH_2Cl_2 and 23 μL of $BF_3{\cdot}OEt_2$ was added dropwise 1.6 mmol of epoxide in 2 mL of CH_2Cl_2 at room temperature. The solution was stirred for 20 min to 4 h (in some cases, aliquots were extracted at 1-, 5-, and 15-min intervals and worked up and analyzed to follow the reaction's progress). The reaction solution was washed with 5% $NaHCO_3$ and 16% NaCl and dried ($MgSO_4$). After evaporation of the solvent, the sample was dissolved in $CDCl_3$, and 1,4-dinitrobenzene was added as an NMR internal standard. Alternatively, 2-indanol was added as a GC internal standard.

Cyclization of 1a was performed as described above only the reaction time was 4 h. The product distribution was determined by capillary VPC (SPB-5 column), which showed a **3a**:**4a** ratio of 99:1 [retention times of 18.05 and 18.39 min, respectively, using our standard temperature program of 90 °C (1 min) to 260 °C at 10°/min]. The only other compound detected (<2%) was identified by GCMS as a noncyclization product. Reactions run at shorter reaction times showed no evidence of rearrangement. The yield was determined by NMR using *p*-dinitrobenzene as an

internal standard. The predominant product, 3a, was isolated by HPLC using a 8 cm × 30 cm 10μ silica gel column (solvent 80:20:trace hexane–CH_2Cl_2–CH_3CH_2OH): ^1H NMR (CCl_4) δ 1.2–3.1 (m, 10 H), 3.7–4.1 (m, CHO), 4.65–6.2 (m, 3 H), 7.0 (s, 4 ArH); IR (NaCl disks) 3600–3100 (s, OH), 755 (s, ortho) cm^{-1}; mass spectrum, *m/e* (relative intensity) 202 (5), 160 (46), 143 (42), 142 (68), 130 (46), 129 (100), 128 (53), 117 (74), 115 (72), 91 (57). Anal. Calcd for $C_{14}H_{18}O$: C, 83.12; H, 8.97. Found: C, 83.05; H, 8.91.

Cyclization of 2a (which contained 8% **1a**) was accomplished in the same manner as described for **1a** to give **3a** and **4a** in a ratio of 7:93, 62% NMR yield: distillation, bp 120–126 °C (0.7–0.1 mm) gave predominantly **4a**; ^1H NMR (CCl_4) δ 1.3–3.0 (m, 10 H), 3.8–4.2 (d of t, 1 H, *J* = 6, 6, and 5 Hz), 4.7–6.1 (m, 3 H), 7.0 (s, 4 ArH); IR (NaCl disks) 3600–3100 (s, OH), 760 (s, ortho) cm^{-1}; mass spectrum, *m/e* (relative intensity) 202 (10), 160 (42), 143 (58), 142 (61), 130 (53), 129 (100), 128 (56), 117 (76), 115 (76), 91 (50); exact mass *m/e* calcd for TMS derivative $C_{17}H_{26}OSi$ 274.1753, found 274.1764. ^1H and ^{13}C NMR spectra are provided as supplementary material.

Cyclization of 2b (containing 10% **1b**), reaction time 4 h, yielded a 13:87 ratio of **3b**:**4b** in 91% NMR yield. Flash distillation at 95–100 °C (0.05 mm) gave predominantly **4b** (contaminated with 13% of the isomeric **3b**): ^1H NMR (CCl_4) δ 1.2–3.0 (m, 10 H), 3.7 (s, CH_3O), 3.7–4.2 (m, 1 H), 4.7–6.1 (m, 3 H), 6.4–7.1 (m, 3 H, 1,2,4-trisubstituted benzene); IR 3700–3100 (s, OH), 1245 (s, CH_3OAr), 843 and 801 (1,2,4-trisubstituted benzene) cm^{-1}; mass spectrum, *m/e* (relative intensity) 232 (80), 175 (50), 173 (70), 172 (55), 160 (92), 159 (92), 147 (100), 115 (54), 91 (63); exact mass *m/e* calcd for TMS derivative $C_{18}H_{28}O_2Si$ 304.1859, found 304.1864. NMR spectra are provided as supplementary material.

Cyclization of 5, reaction time 30 min, gave a complex mixture of products in approximately 70% combined yield (Scheme I and Table II). The product distribution was determined by capillary GC, and the compounds were isolated by semipreparative HPLC using the above column and a 60:39:1 mixture of hexane–CH_2Cl_2–CH_3CH_2OH as the eluting solvent. Most of the major products isolated were identified by spectral and chromatographic comparison with independently synthesized compounds.

1-Cyclohexyl-3-phenyl-1-propanone[16] **(7)** was prepared by combining the Grignard of (2-bromoethyl)benzene with freshly distilled cyclohexanecarbaldehyde and oxidizing the alcoholic product by standard Jones procedures: The Grignard reagent was prepared from 18.5 g (0.1 mol) of (2-bromoethyl)benzene, 100 mL of dry ether, and 2.43 g (0.1 mol) of Mg turnings. A mixture of cyclohexanecarboxaldehyde (11.2 g, 0.1 mol) in 40 mL of ether was added dropwise, and the resulting mixture was refluxed overnight and then worked up in a typical manner. After evaporation of the solvent, 19.72 g (90% yield) of **1-cyclohexyl-3-phenyl-1-propanol (23)** was isolated as white crystals, mp 74–75 °C (hexane): ^1H NMR (CCl_4) δ 0.9–2.1 (m, 14 H), 2.5–3.0 (m, 2 H), 3.0–3.5 (m, 1 H), 7.2 (s, 5 H); IR (NaCl disk melt) 3600–3200 (OH), 750, and 690 cm^{-1}; mass spectrum, *m/e* (relative intensity) 200 (18), 117 (22), 104 (91), 55 (34), 41 (26). Anal. Calcd for $C_{15}H_{22}O$: C, 82.52; H, 10.16. Found: C, 82.82; H, 9.96.

A mixture of 1.401 g of CrO_3, 4.0 mL of H_2O, and 1.4 mL of concentrated H_2SO_4 was titrimetrically added dropwise to an ice bath cooled solution of 3.09 g of **23** in 35 mL of acetone. The mixture was neutralized with Na_2CO_3 and then extracted three times with ether. The combined ether extracts were washed with water, dried ($MgSO_4$), and concentrated. The resulting oil (2.75 g) was distilled to give pure **7**: bp 82–83 °C (0.03 mm); ^1H NMR (CCl_4) δ 0.9–2.5 (m, 11 H), 2.7 (m, 4 H), 7.15 (s, 5 ArH); IR (NaCl disks) 1710 (s, C=O), 755 and 705 (monosubstituted benzene) cm^{-1}; mass spectrum, *m/e* (relative intensity) 216 (67), 133 (55), 105 (72), 91 (78), 83 (100), 55 (82), 41 (44). Anal. Calcd for $C_{15}H_{20}O$: C, 83.28; H, 9.32. Found: C, 83.30; H, 9.28.

7-(2-Phenylethyl)-6-oxabicyclo[3.2.1]octane (8)[17] was isolated by HPLC: NMR (CCl_4) δ 0.8–3.1 (m, 13 H), 3.6–4.0 (t of d, 1 H, *J*'s of 7 and 3 Hz), 4.0–4.4 (m, 1 H), 7.1 (s, 5 ArH); IR (NaCl disks) 1105 (s), 1045 (s), 755 and 705 (monosubstituted benzene) cm^{-1}; mass spectrum, *m/e* (relative intensity), 216 (27), 138 (44), 104 (52), 92 (66), 91 (100), 67 (64), exact mass *m/e* calcd for $C_{15}H_{20}O$ 216.1514, found 216.1509. ^1H and ^{13}C NMR spectra are provided to establish product purity (>90%).

α-Phenethyl-2-cyclohexene-1-methanol (9a). A mixture of 50 mL of ether and 8.05 g of 3-bromocyclohexene (50 mmol) was added dropwise over 3.5 h to a mixture of 2.1 g of Mg and 20 mL of ether while the mixture was cooled with an ice/H_2O bath. After 1 h of stirring at room temperature, 2.62 g (20 mmol) of hydrocinnamaldehyde in 15 mL of ether was added dropwise to the Grignard solution. The resulting mixture was stirred overnight. After typical workup the product (approximately 5% yield) was isolated by semipreparative HPLC (80:19:1 hexane–CH_2Cl_2–ethanol) and then spectrally compared with the product of the cyclization of **5**: mp 42–45 °C; ^1H NMR ($CDCl_3$) δ 1.0–2.5 (m, 11 H), 2.5 (t, 2 H, *J* = 8 Hz), 3.6 (m, 1 H), 5.25–6.0 (m, 2 H), and 7.25 (s, 5 H); IR (NaCl disk, melt) 3600–3200 (s, OH), 710 (m, cis double bond), 750 and 695 (s, monosubstituted benzene); mass spectrum, *m/e* (relative intensity) 216 (0.6), 214 (2), 134 (56), 117 (20), 105 (18), 92 (46), 91 (100), 79 (22), 77 (19), 67 (16), 65 (17). Anal. Calcd for $C_{15}H_{20}O$: C, 83.28; H, 9.32. Found: C, 83.22; H, 9.52.

α-Phenethyl-3-cyclohexene-1-methanol (9b). Approximately 50 mmol of Grignard reagent in 44 mL of dry ether was prepared from 1.20 g of Mg and 9.14 g of (2-bromoethyl)benzene. Then 5.0 g (45 mmol) of 3-cyclohexene-1-carbaldehyde in 32 mL of ether was added dropwise to the Grignard, and the mixture was refluxed for 6.5 h. After typical workup, 9.04 g (93%) of white needles were isolated, mp 57–59 °C (recrystallized from CH_3CH_2OH): ^1H NMR (CCl_4) δ 1.1–3.0 (m, 12 H), 3.3–3.6 (m, 1 H), 5.6 (s, 2 H), 7.1 (s, 5 H); IR (NaCl disk, melt) 3600–3200 (s, OH), 1660 (w, C=C), 750 and 699 (s, monosubstituted benzene), 656 (s, cis) cm^{-1}; mass spectrum, *m/e* (relative intensity) 216 (0.4), 198 (14), 105 (29), 104 (27), 94 (24), 91 (100), 79 (54), 77 (22), 65 (22), 39 (19). Anal. Calcd for $C_{15}H_{20}O$: C, 83.28; H, 9.32. Found: C, 83.68; H, 9.52.

Compound **10** was a minor component in the reaction products of **5** and **6**, and it could not be isolated pure, even by HPLC with a 12 000 theoretical plate column. It was tentatively identified as **10** based on the fact that its MS was very similar to that of the cyclohexyl analogue **7** except for the loss of a methyl group: mass spectrum, *m/e* (relative intensity) 216 (100), 201 (3), 133 (35), 111 (37), 105 (43), 91 (46), 83 (76), 55 (42).

1-Phenethylcyclohexanecarbaldehyde (11) was difficult to isolate because small quantities of it oxidized extremely fast to the corresponding acid. It was made independently by condensation of the enolate of cyclohexanecarbonitrile[18] with (2-bromoethyl)benzene and subsequent reduction of the product with diisobutylaluminum hydride by the method described below for the preparation of **17**.[19] **1-(2-Phenethyl)cyclohexanecarbonitrile (24)**: bp 98–99 °C (0.01–0.02 mm); ^1H NMR ($CDCl_3$) δ 0.9–2.3 (m, 12 H), 2.6–3.0 (m, 2 H), 7.2 (s, 5 H); IR (NaCl disks) 2200 (m, CN), 750 and 690 (s, monosubstituted benzene) cm^{-1}; mass spectrum, *m/e* (relative intensity) 213 (48), 109 (99), 105 (90), and 91 (100). Anal. Calcd for $C_{15}H_{19}N$: C, 84.46; H, 8.98. Found: C, 84.54; H, 9.18.

The diisobutylaluminum hydride reduction (see below) gave a 30% yield of **11**: ^1H NMR (CCl_4) δ 0.9–2.7 (m, 14 H), 7.1 (s, 5 H), 9.4 (s, CHO); IR (NaCl disks) 1695 (s, C=O), 700 and 740 (monosubstituted benzene) cm^{-1}; mass spectrum, *m/e* (relative intensity) 216 (4), 112 (100), 91 (71). A satisfactory C, H analysis could not be obtained, so 2 mg of the aldehyde was allowed to sit open to the air for 2 weeks to oxidize to the acid, exact mass *m/e* calcd for $C_{15}H_{20}O_2$ 232.1463, found 232.1476.

Compounds 12a–c were isolated as a mixture by HPLC. NMR multiplets centered at 4.1 and 3.4, as well as a strong OH IR, band, were highly suggestive of halohydrin and diol products like those observed in earlier work.[2a–c] **12a,b** could not be separated from one another but were easily separated from **12c** by capillary GCMS. **12a,b**: mass spectrum, *m/e* (relative intensity) 236 (4), 218 (18), 216 (17), 138 (20), 117 (23), 105 (28), 104 (91), 92 (54), 91 (100). **12c**: 234 (4), 218 (38), 117 (36), 104 (69), 92 (48), 91 (100); exact mass *m/e* calcd for $C_{15}H_{20}O_2$ 232.1458, found 232.1463.

(16) Fujisawa, T.; Mori, T.; Higuchi, K.; Sato, T. *Chem. Lett.* **1983**, 1781.

(17) We thank Fulton Kitson (Du Pont) and Dr. Kevin Lilley (of Dr. David Lynn's group at The University of Chicago) for verifying the structure of this compound from MS and NMR spectra.

(18) Murata, S.; Matsada, I. *Synthesis* **1978**, 221.

(19) Szántay, C.; Töke, L.; Kolonits, P. *J. Org. Chem.* **1966**, *31*, 1447.

Cyclization of 6 (6:5 = 92:8) was accomplished in the same manner as that as described for **5**. The major products, **7** (61% GC yield) and **11**, were conclusively identified by independent synthesis and spectral comparison, and the product distribution was determined by GC using the SPB-5 column. The reactions of **5** and **6** were followed by quenching aliquots of the reaction solution at 1-, 5-, 15-, and 30-min intervals and then analyzing the aliquots by GC. Characterization of the products is described above.

Cyclization of 13 (contained 10% of the trans isomer) was performed in the same manner as that described for **1a**. There was predominantly one product,[7] 75% yield, which was isolated by silica gel HPLC (solvent 80:19:1 hexane–CH_2Cl_2–CH_3CH_2OH) to give pure **α-3-buten-1-yl-1,2,3,4-tetrahydro-1-naphthalenemethanol (14)**: ^1H NMR (CCl_4) δ 1.2–3.0 (m, 12 H), 3.5–4.0 (q, 1 H, J = 6 Hz), 4.7–6.1 (m, 3 H), 7.0 (s, 4 H); IR (NaCl disks) 3600–3200 (OH), 745 (s, ortho-disubstituted benzene) cm^{-1}: mass spectrum, m/e (relative intensity) 198 (1), 132 (100), 131 (37), 115 (19), 104 (69), 91 (41); exact mass, m/e calcd for TMS derivative ($M^+ - CH_3$) 273.1675, found 273.1705. ^1H and ^{13}C NMR spectra are provided to prove product purity.

Cyclization of 15, reaction time 30 min, gave predominantly **16** and **17** (Scheme II) in a 2:1 ratio (61% combined yield). The compounds were independently synthesized as described below.

1-Cyclohexyl-4-phenyl-1-butanone (16) was prepared by combining the Grignard reagent of 1-bromo-3-phenylpropane with freshly distilled cyclohexanecarbaldehyde and oxidation of the product by standard Jones procedures as described above for the preparation of **7**. The alcohol, **4-phenyl-1-cyclohexyl-1-butanol (25)** was isolated as white crystals in 91% yield: mp 60–61 °C (recrystallized from hexane); ^1H NMR (CCl_4) δ 0.9–2.2 (m, 16 H), 2.4–2.8 (t, 2 H, J = 7 Hz), 3.0–3.5 (m, 1 H), 7.2 (s, 5 H); IR (Nujol mull) 3500–3100 (OH) and 750 and 690 (monosubstituted benzene) cm^{-1}; mass spectrum, m/e (relative intensity) 214 (13), 131 (24), 104 (100), 91 (32), and 55 (20). Anal. Calcd for $C_{16}H_{24}O$: C, 82.70; H, 10.41. Found: C, 82.66; H, 10.62. Oxidation of **25** on the same scale and by the same procedure as that used to prepare **7** yielded **16** (73% yield): bp 86–86.5 °C (0.02 mm); ^1H NMR (CCl_4) δ 0.9–2.1 (m, 13 H), 2.1–2.8 (m, 5 H), 7.15 (s, 5 H); IR (NaCl disks) 1710 (s, C=O), 755 and 705 (s, monosubstituted benzene) cm^{-1}; mass spectrum, m/e (relative intensity), 230 (50), 147 (28), 126 (44), 111 (28), 104 (78), 91 (100), 83 (55), 71 (33), 55 (88), 41 (59). Anal. Calcd for $C_{16}H_{22}O$: C, 83.43; H, 9.63. Found: 83.42; H, 9.74.

1-(3-Phenylpropyl)cyclohexanecarbaldehyde (17). To a solution of 100 mL of dry THF and 20.6 mL (46 mmol) of 2.22 M n-butyllithium was added dropwise 4.63 g (45.8 mmol) of diisopropylamine. After stirring at −70 °C for 30 min, 4.97 g (45.8 mmol) of cyclohexanecarbonitrile was added and the resulting rust-colored solution was stirred at −70 °C for 45 min. After adding 9.12 g (45.8 mmole) of 1-bromo-3-phenylpropane to the mixture, the temperature was allowed to rise to 0 °C, where it was kept for 1.25 h. After 2.5 h at room temperature, the mixture was refluxed 2 h and then stirred overnight at room temperature. The mixture was poured into 250 mL of ether and extracted twice with 5% HCl and once with saturated aqueous NaCl. After drying ($MgSO_4$) the organic layer was concentrated, giving 9.48 g of oil, which was estimated to be >85% pure by ^1H NMR (77% yield). Five grams of the oil was distilled, yielding 3.8 g of **1-(3-phenylpropyl)cyclohexanecarbonitrile (26)**: bp 118–121 °C (0.07 mm); ^1H NMR ($CDCl_3$) δ 0.9–2.1 (m, 14 H), 2.6 (t, 2 H, J = 7 Hz), 7.2 (s, 5 H); IR (NaCl disks) 2210 (m, CN), 750 and 700 (monosubstituted benzene) cm^{-1}; mass spectrum, m/e (relative intensity) 227 (45), 172 (100), and 91 (73). Anal. Calcd for $C_{16}H_{21}N$: C, 84.53; H, 9.31. Found: C, 84.59; H, 9.73.

To 30 mL of dry benzene was added 3.48 g (15 mmol) of 1-(3-phenylpropyl)cyclohexanecarbonitrile. Diisobutylaluminum hydride[19] (20 mL of 1 M hexane solution) was added dropwise over 22 min, and the mixture was stirred at room temperature for 2 h. The solution was carefully poured into 400 mL of 5% H_2SO_4 and then stirred for 1 h. After extracting the mixture twice with 175-mL portions of ether, the combined organic layers were washed twice with 200 mL of 5% $NaHCO_3$ and once with saturated aqueous NaCl and dried ($MgSO_4$). The concentrated organic layer was distilled, giving 1.03 g (31% yield of **17**, bp 96–102 °C. Further purification of the product was accomplished by semipreparative HPLC (75:24 hexane–CH_2H_2–ethanol): ^1H NMR (CCl_4) δ 0.8–3.0 (m, 16 H), 7.2 (s, 5 H), 9.4 (s, 1 H); IR (NaCl disks) 2700 (w, CHO), 1720 (s, C=O), 715 and 760 (s, monosubstituted benzene); mass spectrum, m/e (relative intensity) 230 (39), 105 (26), 104 (35), 91 (100), 55 (22), 41 (21). As did **11**, **17** air oxidized very fast and hence was isolated for C, H analysis as a DNP derivative, mp 137–138 °C. Anal. Calcd for $C_{22}H_{26}N_4O_4$: C, 64.37; H, 6.38. Found: C, 64.43; H, 6.26.

Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this work and to the National Science Foundation (CHE-8807450 and 8405642) for support for the purchase of NMR and mass spectrometers. We also thank John Grutzner (Purdue University) for NMR help and Fulton Kitson (Du Pont) for MS help. Eric S. Stansby did some experimental work required for the revision of this manuscript.

Supplementary Material Available: ^1H and ^{13}C 300-MHz NMR spectra of **1a**, **4a,b**, **5**, **8**, **14**, **18b**, and **23** (16 pages). Ordering information is given on any current masthead page.

A Novel Route to the 4-Anilido-4-(methoxycarbonyl)piperidine Class of Analgetics

Paul L. Feldman* and Marcus F. Brackeen

Glaxo Research Laboratories, Five Moore Drive, Research Triangle Park, North Carolina 27709

Received January 8, 1990

The 4-anilidopiperidine class of opioid analgetics is widely used during surgical procedures as adjuncts to anesthesia. The prototype, fentanyl (**1a**), was introduced in the early 1960s, and since that time research devoted to structurally modifying the piperidine ring has yielded analgetics which are much more potent and longer acting than fentanyl.[1] One such analogue, carfentanil (**1b**), is 27 times more potent than fentanyl and nearly 8000 times as potent as morphine in the rat tail withdrawal assay.[1e]

The synthesis of carfentanil has been described and is depicted in Scheme I.[1e] Upon repeating this procedure we were able to improve the yields on several steps, but all attempts at modifying the procedure in such a way that the α-amino nitrile **3** would be converted to the acid **5** directly were unsuccessful. Heating the α-amino nitrile **3** in either acid or base causes a retro-Strecker reaction. In order to avoid the stepwise hydrolysis sequence, which is complicated by the tedious isolation of the intermediate amide **4**, an operationally convenient route to the methyl ester **6** was developed and is shown in Scheme II.

The reaction of *N*-benzyl-4-piperidinone (**2**) with aniline and potassium cyanide in aqueous acetic acid yielded 71% of **3**. An anhydrous modification of the Strecker reaction

(1) Structure–activity relations along with references to other papers describing modifications of the 4-anilidopiperidine nucleus are given in: (a) Colapret, J. A.; Diamantidis, G.; Spencer, H. K.; Spaulding, T. C.; Rudo, F. G. *J. Med. Chem.* **1989**, *32*, 968. (b) Bagley, J. R.; Wynn, R. L.; Rudo, F. G.; Doorley, B. M.; Spencer, H. K.; Spaulding, T. *J. Med. Chem.* **1989**, *32*, 663. (c) Casey, A. F.; Huckstep, M. R. *J. Pharm. Pharmacol.* **1988**, *40*, 605. (d) Janssens, F.; Torremans, J.; Janssen, P. A. J. *J. Med. Chem.* **1986**, *29*, 2290. (e) Van Daele, P. G. H.; DeBruyn, M. F. L.; Boey, J. M.; Sanczuk, S.; Agten, J. T. M.; Janssen, P. A. J. *Arzeneim.-Forsch. Drug Res.* **1976**, *26*, 1521. (f) Van Beaver, W. F. M.; Niemegeers, C. J. E.; Janssen, P. A. J. *J. Med. Chem.* **1974**, *17*, 1047. (g) Kudzma, L. V.; Severnak, S. A.; Benvenga, M. J.; Ezell, E. F.; Ossipov, M. H.; Knight, V. V.; Rudo, F. G.; Spencer, H. K.; Spaulding, T. C. *J. Med. Chem.* **1989**, *32*, 2534.