# Regiochemistry in the Intramolecular Cycloadditions of Substituted 5-Alkenyl and 6-Alkenyl Nitrones

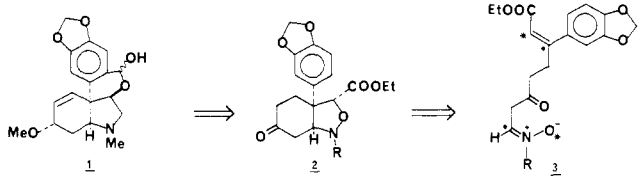
S. W. Baldwin,* J. D. Wilson, and J. Aubé

*Paul M. Gross Chemical Laboratory, Duke University, Durham, North Carolina 27706*

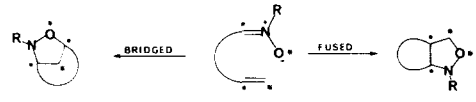
*Received December 18, 1984*

A series of 5-alkenyl and 6-alkenyl aldehydes bearing aryl and ester functionality on the alkene and with and without 1,3-dioxolane substitution at the 3 position has been prepared. The *N*-methyl and *N*-benzyl nitrones derived by the condensation of the aldehydes with the corresponding hydroxylamines undergo intramolecular 1,3-dipolar cycloaddition on heating (or at room temperature in two instances) to give either bridged or fused isoxazolidines depending on the regiochemistry of the cycloaddition reaction. The 6-alkenyl nitrones give fused products in all cases except those bearing an aryl group at C-6, which give bridged products. All of the 5-alkenyl nitrones prepared in this study cyclized to afford fused isoxazolidines.

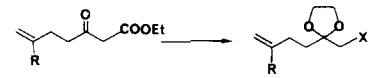
The 1,3-dipolar cycloaddition reaction between nitrones and alkenes has attracted considerable attention as a convenient tool for the rapid construction of widely varied classes of natural products.[2] In connection with our evaluation of general methods for alkaloid synthesis, and in particular alkaloids of the Amaryllidaceae family, we have prepared several substituted alkene-aldehydes in order to determine those factors which control regiochemical preferences in intramolecular cycloadditions of the derived nitrones. For illustrative purposes, the antitumor agent pretazettine (1) might be prepared from alkene nitrone **3**, through the intermediacy of isoxazolidine cycloadduct **2**, provided that the cycloaddition reaction were to occur between the starred (*) and dotted (●) atoms of the nitrone and alkene rather than in the opposite sense.



A significant body of information regarding the regiochemistry of nitrone cycloadditions has been collected since the pioneering work of Huisgen.[3] Most of this data has been interpreted by considering frontier molecular orbital properties of the nitrone and alkene reaction partners.[4] The regiochemistry of the intramolecular version of this reaction, however, is complicated by a complex interplay among such factors as alkene polarity, ring strain, and other nonbonded interactions. In general, the intramolecular situation can be assessed as a competition between the *bridged* and *fused* modes of cycloaddition. In the




Scheme I



16, R = H

17, R = H; X = $CO_2Et$
18, R = H; X = $CO_2OH$
19, R = H; X = CHO

20, R = $C_6H_5$

21, R = $C_6H_5$; X = $CO_2Et$
22, R = $C_6H_5$; X = $CH_2OH$
23, R = $C_6H_5$; X = CHO

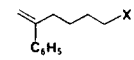
24, X = $CH_2CH_2OTHP$

25, R = H; X = $CH_2CH_2OTHP$
26, R = H; X = $CH_2CH_2OH$
27, R = H; X = $CH_2CHO$

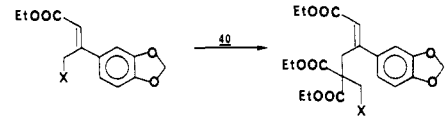
28, R = $C_6H_5$; X = $CH_2CH_2OTHP$
29, R = $C_6H_5$; X = $CH_2CH_2OH$
30, R = $C_6H_5$; X = $CH_2CHO$

31, X = $CH_2OTHP$

32, R = $C_6H_5$; X = $CH_2OTHP$
33, R = $C_6H_5$; X = $CH_2OH$
34, R = $C_6H_5$; X = CHO



35, X = $CO_2Et$
36, X = $CH_2OH$
37, X = CHO




38, X = H
39, X = Br

41, X = $CH(OCH_2CH_3)_2$
42, X = CHO

context of this work, the latter was desired due to the obvious similarities between the fused [4.3.0] isoxazolidines and the A/B ring system of pretazettine and other target alkaloids.

Le Bel's fundamental studies of the regiochemistry of intramolecular cycloadditions of acyclic alkene nitrones are instructive but not conclusive for our purposes.[5] For instance, a series of methylated nirones nitrones derived from 6-heptenal (**4**) gave predominantly fused products **5** (cis and trans ring fusion), although the effect of simultaneous substitution at the C-2 alkene carbon ($R_3$) and the nitrone carbon ($R_5$) was not examined. In a related study of 5-alkenyl nitrogens **7**, fused products (**8**, cis) were usually the exclusive product, although when both $R_3$ and

(1) (a) Taken in part from the PhD theses of J.D.W., Duke University, 1982 and J.A., Duke University, 1984. (b) Presented in part at the 188th National Meeting of the American Chemical Society, Philadelphia, PA., August 27–31, 1980, Abstr ORGN 171. (c) Partial support from the National Institutes of Health is gratefully acknowledged (GM 31634-01A1).

(2) (a) Black, D., St. C.; Crozier, R. F.; Davis, V. C. *Synthesis* **1975**, *7*, 205. (b) Tufariello, J. J.; *Acc. Chem. Res.* **1979**, *12*, 396. (c) Kametani, T.; Huang, S. D.; Nakayama, A.; Hondu, T. *J. Org. Chem.* **1982**, *47*, 2328. (d) Oppolzer, W.; Grayson, J. I.; Wegmann, H.; Urrea, M. *Tetrahedron.* **1983**, *39*, 3695. (e) Wovkulich, P. M.; Uskokovic, M. R. *J. Am. Chem. Soc.* **1981**, *103*, 3956. (f) Baggiolini, E. G.; Lee, H. L.; Pizzolato, G.; Uskokovic, M. R. *Ibid.* **1982**, *104*, 6460. (g) Deshong, P.; Leginus, J. M. *Ibid.* **1983**, *105*, 1686.

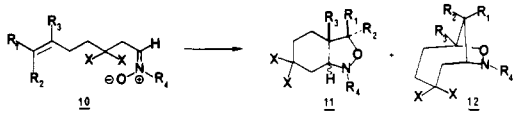
(3) Huisgen, R.; *Angew. Chem., Int. Ed. Engl.* **1963**, *2*, 565 and 6339.

(4) (a) Houk, K. N.; Sims, J.; Watts, C. R.; Luskus, L. J.; *J. Am. Chem. Soc.* **1973**, *95*, 7301. (b) Houk, K. N.; Sims, J.; Duke, R. E.; Strozier, R. W.; George, S. K. *Ibid.* **1973**, *95*, 7287. (c) For an alternative viewpoint see Firestone, R. A. *J. Org. Chem.* **1968**, *33*, 2285.

(5) (a) Le Bel, N. A.; Post, M. E.; Whang, J. J. *J. Am. Chem. Soc.* **1964**, *86*, 3759. (b) Le Bel, N. A.; Banucci, E. G. *J. Org. Chem.* **1971**, *36*, 2440. (c) Le Bel, N. A. *Trans. N. Y. Acad. Sci.* **1965**, *27*, 858.

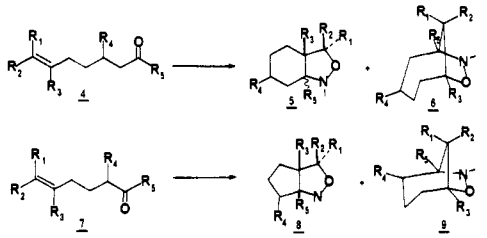
0022-3263/85/1950-4432$01.50/0 © 1985 American Chemical Society

**Table I. Intramolecular Cycloaddition of 6-Alkenyl Nitrones**



| compd | $R_1$ | $R_2$ | $R_3$ | $R_4$ | X | yield, %[a] | 11:12[b] |
|---|---|---|---|---|---|---|---|
| **10a** | H | H | H | $CH_3$ | $-OCH_2CH_2O-$ | 41 | >99:1 |
| **10b** | H | H | H | $CH_2C_6H_5$ | $-OCH_2CH_2O-$ | 62 | >99:1 |
| **10c** | $CO_2C_2H_5$ | H | H | $CH_3$ | H | 71 | >99:1 |
| **10d** | H | H | $C_6H_5$ | $CH_2C_6H_5$ | H | 59 | <1:99 |
| **10e** | H | H | $C_6H_5$ | $CH_2C_6H_5$ | $-OCH_2CH_2O-$ | 47 | <1:99 |
| **10f** | $CO_2C_2H_5$ | H | $C_6H_5$ | $CH_3$ | H | 51 | <1:99 |

[a] Yields are of purified products. [b] Ratios (isomeric purities) were determined by $^1H$ NMR and $^{13}C$ NMR.



$R_5$ were $CH_3$, essentially equal amounts of **8** and **9** were formed suggesting that steric effects at the reacting carbon termini may operate against fused-product regiochemistry. To better understand the factors controlling the balance between these two reaction pathways, Le Bel's work has been extended to include other substituents (ester and aryl) capable of providing greater alkene polarization, as well as groups which might subsequently be converted to the various functionalities contained in the target alkaloids. It should be mentioned that the alkene nitrones derived from each of the substrates reported in this study, (**19**, **23**, **27**, **30**, **34**, **37**, and **42**), would be expected to give bridged rather than fused products on the basis of the analogous intermolecular reactions.

## Preparation of Nitrones

The alkene aldehydes required for this study were prepared by standard reaction sequences as outlined in Scheme I. In an attempt to survey the efficacy of a number of different routes to these substrates, several general approaches were studied although yields were not optimized. First, in the 6-alkenyl series (Table I), the ethylenedioxy-containing aldehydes **19** and **23** were prepared from keto esters **16** and **20** by successive ketalization, ester reduction, and Swern oxidation ($Me_2SO$, $(COCl)_2$, $Et_3N$).[6] The starting keto esters were obtained by alkylation of the dianion of ethyl acetoacetate with either allyl bromide or $\alpha$-(bromomethyl)styrene[7] according to the procedure of Weiler.[8] Unsaturated esters **27** and **30** were obtained by oxidation of the corresponding primary alcohols **26** and **29**, which were in turn formed by the stereospecific low-temperature addition of the cuprate (Grignard) derived from 5-bromo-1-pentanol tetrahydropyranyl ether (**24**) to either ethyl propiolate or ethyl phenylpropiolate.[9] Finally, the $\alpha$-substituted styrene aldehyde **37** was generated from the known ester **35**[10] by reduction (LAH) followed by partial oxidation.

Of the 5-alkenyl aldehydes described in Table II, **34** was prepared, as for the higher homologue, **30**, by the stereospecific conjugate addition of the cuprate derived from 4-bromo-1-butanol tetrahydropyranyl ether (**31**) to ethyl phenylpropiolate,[9] followed by hydrolysis and oxidation. Malonate-substituted aldehyde **42** was formed by alkylation of **40**[11] with *Z*-bromide **39**, itself formed by NBS free radical bromination of the parent compound **38**[12] (*E* or *Z*).[13]

Once the alkene aldehydes were in hand, the target nitrones were readily prepared by standard methods. In general, a freshly prepared sample of alkene aldehyde was dissolved in benzene containing an alkyl hydroxylamine (methyl or benzyl) as the hydrochloride salt and suspended potassium carbonate. After the mixture was stirred several hours at room temperature, the presence of the crude nitrone was confirmed by the appearance of an absorption at $\sim \delta$ 6.60 in the $^1H$ NMR spectrum, whereupon the crude nitrone was dissolved in toluene and heated at reflux for 5–24 h to effect cycloaddition. When TLC analysis of the reaction mixture indicated that no more nitrone remained, the reaction was worked up and analyzed directly. Subsequent crystallization or flash chromatography[14] gave the pure isoxazolidine products. In two cases, nitrones **10c** and **13c**, the cycloaddition occurred at room temperature during formation of the nitrone, requiring no additional heating.

## Results and Discussion

In many respects the results of these studies parallel those of Le Bel. For instance, in the case of the 6-alkenyl nitrones (Table I), there was a marked tendency for the formation of fused products **11** in substrates bearing no $R_3$ substituent at C-6 ($R_3$) (**10a**, **10b**, and **10c**). In fact no bridged products, **12**, whatsoever were detected in the crude reaction mixture either chromatographically or spectroscopically. It is interesting that the ethylenedioxy ketal of **10a** and **10b** afforded only fused material in contrast to the unsubstituted example of Le Bel (**4**, $R_1 = R_2 = R_3 = R_4 = R_5 = H$) which gave significant amounts ($\sim$20%) of bridged product. Placement of the $R_1$ carboethoxy group on the alkene, **10c**, also led to the exclusive formation of fused product **11c** as indicated in the $^1H$ NMR spectrum by the presence of diagnostic doublet ($J$ = 4 Hz) at $\delta$ 4.15. Moreover, these fused products were homogeneous chromatographically and spectroscopically.

The nature of the ring fusion stereochemistry in isoxazolidines **11a**, **11b**, and **11c** (cis or trans) is of some interest. In a series of four related nitrones derived from simple methylated 6-alkenyl aldehydes, **4**, Le Bel noted a decided

(6) Mancuso, A. J. Huang, S. L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.
(7) Pines, H.; Alul, H.; Kolobielski, M. *J. Org. Chem.* **1957**, *22*, 1113.
(8) Weiler, L.; Huckin, S. N. *J. Am. Chem. Soc.* **1974**, *96*, 1082.
(9) (a) Marfat, A.; McGuirk, P. R.; Helquist, P. *J. Org. Chem.* **1979**, *44*, 3888. (b) Sundberg, R. J.; Pearce, B. C. *Ibid.* **1982**, *47*, 725.
(10) Baldwin, S. W.; Page, E. H., Jr. *J. Chem. Soc., Chem. Commun* **1972**, 1337.
(11) Kametani, T.; Ihara, M.; Suzuki, T.; Shima, K. *J. Heterocycl. Chem.* **1968**, *5*, 799.
(12) Klein, J.; Amanadev, N. *J. Chem. Soc., C*, **1970**, 1380.
(13) The same *Z*-bromide **39** was formed by NBS bromination of either **38** (*Z* isomer) or its geometrical (*E*) isomer. Control experiments indicate that *Z*-**38** is isomerized to the more stable *E*-**38** under the conditions of the reaction followed by bromination of the latter species.
(14) Still, W. C.; Kahan, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

kinetic preference for the trans-fused isoxazolidine isomer, trans/cis ratios ranging from 66/34 to 93/7 depending on methyl substitution.[5b] Analysis of the $^1$H NMR spectra of compounds **11a**, **11b**, and **11c** allows one to assign with some confidence the ring fusion stereochemistry of **11a** and **11b** as trans and the carboethoxyl containing isomer **11c** as cis. Particularly diagnostic are the absorptions for the protons adjacent to the isoxazolidine ring oxygen. In **11a** these two protons appear at $\delta$ 3.58 and 4.11 and exhibit vicinal coupling with the bridgehead proton of 7.7 Hz and 8.0 Hz respectively. The *N*-benzyl derivative **11b** shows a similar pattern for these two protons with absorptions at $\delta$ 3.64 and 4.16 exhibiting vicinal coupling constants of 7.5 Hz and 9.1 Hz. In compound **11c**, the single comparable proton appears at $\delta$ 4.15 with a vicinal coupling constant of 4.0 Hz. The relatively small value of this coupling constant as compared with those of **11a** and **11b** strongly suggests that the latter are stereochemically distinct from **11c**.

If **11c** were trans-fused, the dihedral angle between the C-5 H and bridgehead proton would be large (150–160°), resulting in a relatively large vicinal coupling ($\geq$7 Hz). On the other hand, a cis ring fusion (axial nitrogen) would afford a dihedral angle of ca 110°, and thus smaller vicinal coupling ($\leq$5 Hz), as is observed. Similarly, trans ring fusion in **11a** and **11b** would lead to dihedral angles for the corresponding vicinal protons of approximately 35° and 155°, angles consistent with larger and nearly equal coupling constants (7–10 Hz), which were observed. Conversely, if **11a** and **11b** were cis-fused (equatorial nitrogen), dihedral angles of 10° and 130° would result in one large and one medium vicinal coupling. That this was not observed is further support of the trans assignment for these compounds.

In contrast to the above results, the incorporation of a phenyl group at $R_3$ led to complete regiochemical reversal of the cycloaddition. Thus nitrone **10d** afforded bicyclic product **12d** in 59% isolated yield. The assignment of structure was readily made by noting the absence of the $^1$H NMR absorption expected for the isoxazolidine protons $R_1$ and $R_2$ adjacent to oxygen in fused product **11d**. An ethylenedioxy ketal at C-3 in nitrone **10e**, which had improved the fused/bridged product ratio in **10a** and **10b**, was without effect in changing the course of this reaction. The sole product of the cycloaddition in this case was bridged isoxazolidine **12e**. Finally, the incorporation of both an ester ($R_1$) and phenyl group ($R_3$) as in nitrone **10f** afforded only bridged bicyclic material as indicated by a singlet at $\delta$ 3.41 for the proton on the one carbon bridge ($R_2$ = H) in the $^1$H NMR spectrum as well as a quaternary carbon absorption at 89 ppm in the $^{13}$C NMR spectrum (INEPT pulse sequence)[15] for the bridgehead carbon bearing the phenyl and oxygen substituents.[16]

The above results strongly indicate that the desired fused [4.3.0] bicyclic isoxazolidine nucleus **2** bearing the angular aromatic substituent of the target alkaloids will not be directly available by cycloaddition of a substituted 6-alkenyl nitrone such as **10f**. In contrast, however, the corresponding 5-alkenyl nitrones **13** gave only the desired cis-fused [3.3.0] bicyclic isoxazolidines, none of the bridged isomers being detected on careful scrutiny of the crude reaction products. For instance, nitrone **13b** afforded a single isoxazolidine **14b** in 77% yield, the structure of which was indicated from the $^1$H NMR spectrum by a sharp singlet at $\delta$ 4.38 as well as a quaternary carbon absorption at 67 ppm in its $^{13}$C NMR spectrum (INEPT pulse sequence).[15] This result is not totally unexpected in that the bridged product **15** (as well as the transition state leading to it) is probably considerably more strained than in the higher homologue **12**. However, the complete reversal in regioselectivity observed in going from **10f** to **13** is remarkable, the effect of removing the single methylene group being to totally overcome the "normal" reactivity of the nitrone group as predicted from molecular orbital considerations.

(15) (a) Morris, G. A.; Freeman, R. *J. Am. Chem. Soc.* **1979**, *101*, 760. (b) Doddrell, D. M.; Pegs, D. T. *Ibid.* **1980**, *102*, 6388.

(16) The aryl-bearing quaternary carbon in the fused compound **11f** would be expected to occur in the 60–70 ppm range on the basis of chemical shift additivities.

## Summary

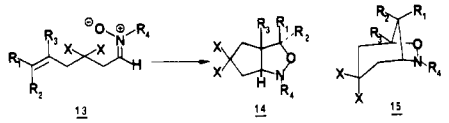
The regiochemical outcome of the intramolecular cycloaddition of the 6-alkenyl aldonitrones studied in this work depends on the substitution at the alkene carbons, particularly at C-6 ($R_3$). Thus fused products, e.g., **11**, result when C-6 is unsubstituted ($R_3$ = H) but bridged products such as **12** are formed when $R_3$ is an aryl group. This latter result indicates that Amryllidaceae alkaloids such as pretazettine (**1**) will not be available by this particular version of the nitrone/alkene cycloaddition reaction. However, 5-alkenyl aldonitrones substituted at C-5 ($R_3$ = $C_6H_5$) give exclusively the *fused* products **14** (cis). This result suggests that cycloaddition of a substrate **13** bearing the appropriate substitution at C-3 (X) would lead to a product **14** which could be induced to undergo ring expansion of the cyclopentane ring, affording indirect access to the desired cis-fused [4.3.0] ring system of the target alkaloids. Such work is currently in progress.

## Experimental Section[17]

**Preparation of Alkene Aldehydes and Their Precursors. Ethyl 3,3-(Ethylenedioxy)-6-heptenoate (17).** In a 250-mL flask were placed 3.75 g (22.0 mmol) of keto ester **16**,[8] 4.1 g (66.0 mmol) of ethylene glycol, and a few crystals of *p*-toluenesulfonic acid in 175 mL of benzene. The solution was then heated at reflux overnight with mechanical removal of water (Dean–Stark water separator), cooled to room temperature, washed with 100 mL portions of saturated $NaHCO_3$ and brine, dried ($Na_2SO_4$), and concentrated to yielded 4.52 g (96%) of ketal **17**. Flash chromatography (ether/petroleum ether) provided the analytical

(17) Melting points were obtained on a Thomas-Hoover melting points apparatus and are uncorrected; boiling points are uncorrected. Infrared spectra (IR) were recorded on a Perkin-Elmer 297 infrared spectrophotometer either as thin films or as solutions in $CDCl_3$. Routine nuclear magnetic resonance ($^1$H NMR) spectra were recorded on a JEOL MH100 spectrometer (100 MHz) in $CCl_4$ or $CDCl_3$ or an IBM NR/80 (80 MHz) in $CDCl_3$. High-field $^1$H NMR spectra were recorded on a Bruker WH 250 spectrometer (250 MHz) in $CDCl_3$. Unless otherwise noted, all $^1$H NMR spectra were obtained at 80 MHz. $^{13}$C NMR spectra were recorded on a Jeol JNM-FX60 or JEOL FX90Q spectrometer in $CDCl_3$, with the latter being employed for all INEPT studies. All resonances are reported in ppm ($\delta$) downfield from a $Me_4Si$ internal standard. Analytical thin layer chromatography (TLC) was performed on 0.2-mm microscope slide size plates cut from 20 × 20 cm precoated with silica gel 60 $F_{254}$ on aluminum backings with components visualized by the $Ce(NH_4)_2(NO_3)_6$/char technique. Flash chromatography[14] was performed with silica gel (230–400 mesh) with house air as a source of medium pressure. Anhydrous solvents were dried immediately prior to use. Tetrahydrofuran (THF) and diethyl ether (ether) were distilled from sodium and benzophenone. Dimethoxyethane (DME), dimethylsulfoxide ($Me_2SO$), and diisopropylamine were distilled from calcium hydride and stored over 3-Å molecular sieves. Petroleum ether refers to that hydrocarbon fraction boiling between 30° and 60° C. Concentration refers to the evaporation of solvent on a Buchi rotary evaporator at aspirator pressure followed by additional evacuation at high vacuum until a constant weight was obtained. Kugelrohr distillation refers to the standard bulb to bulb process using a Buchi Kugelrohr apparatus with the listed temperature being the temperature of the air bath. All reactions were conducted under a positive pressure of nitrogen or argon unless otherwise specified. Elemental analyses were performed by M-H-W Laboratories, P.O. Box 15853, Phoenix, Arizona 85018. All Compounds reported in this work are racemic; the prefix "*dl*" has been omitted.

**Table II. Intramolecular Cycloaddition of 5-Alkenyl Nitrones**



13 14 15

| compd | $R_1$ | $R_2$ | $R_3$ | $R_4$ | X | yield, %[a] | 14:15[b] |
|---|---|---|---|---|---|---|---|
| **13a** | $CO_2C_2H_5$ | H | $C_6H_5$ | $CH_3$ | H | 41 | 99:1 |
| **13b** | $CO_2C_2H_5$ | H | $C_6H_5$ | $CH_2C_6H_5$ | H | 77 | 99:1 |
| **13c** | H | $CO_2C_2H_5$ | 3,4-$OCH_2OC_6H_3$ | $CH_2C_6H_5$ | $CO_2C_2H_5$ | 75 | 99:1 |

[a] Yields are of purified products. [b] Ratios (isomeric purities) were determined by $^1H$ NMR and $^{13}C$ NMR.

sample. $^1H$ NMR $\delta$ 1.24 (t, $J$ = 7 Hz, 2 H, $—CO_2CH_2CH_3$), 4.8–5.2 (m, 2 H, $=CH_2$), 5.6–6.1 (m, 1 H, —CH=).

Anal. Calcd for $C_{11}H_{18}O_4$: C, 61.68; H, 8.41. Found: C, 61.30; H, 8.18.

**3,3-(Ethylenedioxy)-6-hepten-1-ol (18).** To a stirred mixture of 840 mg (22 mmol) of LAH in 50 mL of dry ether was added 4.38 g (20.5 mmol) of ester **17** at 0°C. After stirring for 3 h at room temperature the reaction was quenched by the cautious sequential addition of 0.85 mL of $H_2O$, 1.2 mL of 10% NaOH, and 2.5 mL of $H_2O$. After filtration, the salts were washed thoroughly with ether and the combined ethereal solutions concentrated. The residue was then taken up in 30 mL of methylene chloride, dried ($Na_2SO_4$), and concentrated to yield 3.4 g (90%) of alcohol **18**, and analytical sample of which was prepared by flash chromatography. $^1H$ NMR $\delta$ 2.0–2.8 (m, 6 H, C-2, 4, and 5 $—CH_2—$'s), 4.15 (t, $J$ = 6.6 Hz, 2 H, $—CH_2OH$), 4.34 (s, 4 H, ketal), 5.2–5.6 (m, 2 H, $=CH_2$), 5.9–6.5 (m, 1 H, —CH=).

Anal. Calcd for $C_9H_{16}O_3$: C, 62.79; H, 9.30. Found: C, 62.53; H, 9.03.

**3,3-(Ethylenedioxy)-6-heptenal (19).** According to the procedure of Swern,[6] a solution of 732 mg (2.91 mmol) of oxalyl chloride in 15 mL of methylene chloride was placed in a flame-dried 50-mL round bottom flask equipped with an addition funnel, a magnetic stirrer, a rubber septum, and a nitrogen inlet. The solution was cooled to −60 °C ($CO_2/CHCl_3$) and 906 mg (2.91 mmol) of $Me_2SO$ in 1 mL of methylene chloride were added dropwise. After stirring for 2 min at −60 °C, 500 mg (2.91 mmol) of alcohol **18** in 3 mL of methylene chloride was added and stirring continued for 15 min at −60 °C and subsequent warming to room temperature, the reaction was quenched by the addition of 20 mL of $H_2O$ followed by separation of the layers. Extraction of the aqueous layer with methylene chloride (25 mL), washing the combined organic layers with 25 mL portions of 10% HCl, saturated $NaHCO_3$, and brine followed by drying ($Na_2SO_4$) and concentration yielded 430 mg (87%) of aldehyde **19** which was used directly in the next reaction. $^1H$ NMR $\delta$ 1.6–2.3 (m, 4 H, C-2 and C-4 $—CH_2—$), 2.7 (d, $J$ = 2 Hz, C-2 $—CH_2—$), 4.0 (s, 4 H, ketal), 4.7–5.2 (m, 2 H, $=CH_2$), 5.5–6.1 (m, 1 H, —CH=), 9.7 (t, $J$ = 2 Hz, 1 H, —CHO).

**Ethyl 3-Oxo-6-phenyl-6-heptenoate (20).** In an adaptation of the procedure of Weiler,[8] a flame-dried 100-mL flask equipped with an addition funnel, a magnetic stirrer, and a nitrogen inlet was charged with 3.23 g (32.0 mmol) of diisopropylamine and 50 mL of dry THF. The solution was then cooled to −78 °C and 12mL of 2.5 M $n$-BuLi (30.0 mmol) in hexane was slowly added via syringe. Stirring was continued for an additional 15 min whereupon 1.86 g (14.3 mmol) of ethyl acetoacetate in 3 mL of dry THF was added. After the mixture stirred for 20 min at 0 °C, 2.81 g (14.2 mmol) of $\alpha$-bromomethylstyrene in 3 mL of dry THF was added and stirring continued for an additional 20 min. The reaction was then quenched by the addition of 50 mL of saturated $NH_4Cl$, the layers were separated, and the aqueous layer was extracted with ether (2 × 75 mL). The combined organic extracts were then washed with saturated $NaHCO_3$ and brine and then dried ($Na_2SO_4$) and concentrated to give the alkylated keto ester **20** as a crude oil which was then purified by Kugelrohr distillation (165 °C, 0.2 mmHg) to afford 2.3 g (65%) of pure material. $^1H$ NMR $\delta$ 1.25 (t, $J$ = 6.5 Hz, 3 H, $—CO_2CH_2CH_3$), 2.6–2.9 (m, 4 H, C-4 and C-5 $—CH_2$-'s), 3.41 (s, 2 H, $—COCH_2CO—$), 4.18 (q, $J$ = 6.5 Hz, 2 H, $—CO_2CH_2—$), 5.07 (d, $J$ = 1, 1 H, $=CH_2$), 5.29 (s, 1 H, $=CH_2$), 7.2–7.4 (m, 5 H, ArH).

Anal. Calcd for $C_{15}H_{18}O_3$: C; 73.50; H, 7.37. Found: C, 73.43; H, 7.12.

**Ethyl 3,3-(Ethylenedioxy)-6-phenyl-6-heptenoate (21).** A solution of 600 mg (2.40 mmol) of ketone **20**, 1 mL of ethylene glycol, and a few crystals of $p$-toluenesulfonic acid in 50 mL of benzene was heated at reflux overnight with mechanical removal of water (Dean–Stark water separator). The solution was then cooled to room temperature, washed with saturated $NaHCO_3$ and brine, dried ($Na_2SO_4$), and concentrated. The NMR spectrum of the crude product showed the presence of approximately 10% of the isomerized trisubstituted styrene. Chromatography of the crude oil on alumina (Activity III) yielded 357 mg (51%) of pure ketal **21**. $^1H$ NMR $\delta$ 1.23 (t, $J$ = 6.5 Hz, 3 H, $—CO_2CH_2CH_3$), 1.8–2.1 (m, 2 H, C-4 $—CH_2—$), 2.4–2.8 (m, 2 H, C-5 $—CH_2—$), 2.68 (s, 2 H, $—CH_2CO_2—$), 4.05 ns, 4 H, ketal), 4.13 (q, $J$ = 6.5 Hz, 2 H $—CO_2CH_2—$), 5.08 (d, $J$ = 1.5 Hz, 1 H, $=CH_2$), 5.17 (s, 1 H, $=CH_2$), 7.2–7.5 (m, 5 H, ArH).

Anal. Calcd for $C_{17}H_{24}O_4$: C, 70.34; H, 7.58. Found: C, 70.54; H, 7.46.

**3,3-(Ethylenedioxy)-6-phenyl-6-hepten-1-ol (22).** A solution of 357 mg (1.23 mmol) of ester **21** in 5 mL of dry ether was added dropwise to a solution of of 50 mg (1.30 mmol) of LAH in 20 mL of dry ether. After stirring overnight under nitrogen, the reaction was quenched by the cautious addition of 10% NaOH. The reaction mixture was then filtered, the salts washed well with ether, and the combined organic layers dried ($Na_2SO_4$) and concentrated to give 242 mg (76%) of alcohol **22** suitable for the next reaction. $^1H$ NMR $\delta$ 1.6–2.1 (m, 4 H, C-2 C-4 $—CH_2—$), 2.59 (t, $J$ = 7 Hz, 2 H, C-5 $—CH_2—$), 2.85 (br, 1 H, —OH), 3.75 (t, $J$ = 4.8 Hz, 2 H, $—CH_2O—$), 3.92 (s, 4 H, ketal), 5.06 (d, $J$ = 1.5 Hz, 1 H, $=CH_2$), 5.28 (s, 1 H, $=CH_2$), 7.2–7.5 (m, 1 H, ArH).

**3,3-(Ethylenedioxy)-6-phenyl-6-heptenal (23).** According to the procedure of Swern,[6] a solution of 238 mg (1.88 mmol) of oxalyl chloride in 15 mL of methylene chloride was placed in a flame-dried 50-mL flask equipped with an additional funnel, a magnetic stirrer, a rubber septum, and a nitrogen inlet. The solution was cooled to −60 °C ($CO_2/CHCl_3$) and 293 mg (3.76 mmol) of $Me_2SO$ in 3mL of methylene chloride was added dropwise followed in 2 min by 242 mg (0.94 mmol) of alcohol **22** in 3 mL of methylene chloride. The solution was then stirred 15 min at −60 °C whereupon 1 mL of dry triethylamine was added. Stirring was continued an additional 5 min at −60 °C folowed by warming to room temperature, the addition of 25 mL of water, and separation of the organic and aqueous layers. After extraction of the aqueous layer with 25 mL of methylene chloride, the combined organic layers were washed successively with 1N HCl, saturated $NaHCO_3$, and brine and then dried ($Na_2SO_4$) and concentrated to yield 218 mg (90%) of aldehyde **23**, homogeneous by TLC, which was directly used in the next reaction. $^1H$ NMR $\delta$ 1.7–2.0 (m, 2 H, C-4 $—CH_2—$), 2.4–2.6 (m, 2 H, C-5 $—CH_2—$), 2.67 (d, $J$ = 3 Hz, 2 H, C-2 $—CH_2—$), 3.95 (s, 4 H, ketal), 5.08 (d, $J$ = 1 Hz, 1 H, $=CH_2$), 5.21 (s, 1 H, $=CH_2$), 7.2–7.5 (m, 5 H, ArH), 9.71 (t, $J$ = 3 Hz, 1 H, —CHO).

**1-Bromo-5-[(tetrahydro-2*H*-pyran-2-yl)oxy]pentane (24).** According to the procedure of Grieco,[18] 3.9 g (23.2 mmol) of 5-bromo-1-pentanol,[19] 2.92 g (34.8 mmol) of dihydropyran, and 580 mg (23.0 mmol) of pyridine $p$-toluenesulfonate (PPTS) were stirred 5 h at room temperature in 100 mL of methylene chloride. The solution was then washed with brine, dried ($MgSO_4$), and concentrated to give a crude oil which was purified by flash chromatography (20% ether/petroleum ether) to yield 4.8 g (82%)

(18) Miyashita, M.; Yoshikoshi, A.; Grieco, P. A. *J. Org. Chem.* **1977**, *42*, 3772.

(19) Goldfard, Y. L.; Ispiryan, R. M.; Belenkii, L. I. *Dokl. Akad. Nauk. SSSR* **1967**, *173*, 97; *Chem. Abstr.* **1967**, *67*, 43639r. This procedure was used to secure 1-acetoxy-5-bromopentane, which was then hydrolyzed to 5-bromo-1-pentanol with methanolic potassium carbonate.

of THP ether **24**. $^1$H NMR $\delta$ 1.3–2.0 (m, 12 H, C-2, C-3, C-4, THP —$CH_2$—'s), 3.41 (t, $J$ = 6 Hz, 2 H, —$CH_2O$—), 3.5–4.0 (m, 2 H, —$CH_2O$— of THF), 4.56 (br s, 1 H, —OCHO—).

Anal. Calcd for $C_{10}H_{19}O_2Br$: C, 47.81; H, 7.57. Found: C, 47.62; H, 7.31.

**(*Z*)-Ethyl 3-Phenyl-8-[(tetrahydro-2*H*-pyran-2-yl)oxy]-2-octenoate (28).** In a flame-dried 250-mL flask, equipped with a magnetic stirrer, a nitrogen inlet, and a reflux condenser, were placed 19.78 g (0.078 mol) of bromide **24** and 2.16 g (0.090 mol) of freshly dried magnesium turnings in 100 mL of dry THF. Stirring was continued 5 h at room temperature to allow complete formation of the Grignard reagent, which was then cooled to 0 °C. An additional flame-dried 250-mL flask containing 8.09 g (39.4 mmol) of CuBr·$Me_2S$ complex in 40 mL of dry THF was equipped with a magnetic stirrer, a nitrogen inlet, a rubber septum, and an addition funnel containing 4.57 g (26.3 mmol) of ethyl phenylpropiolate in 5 mL of dry THF. All solutions were then deoxygenated by bubbling nitrogen through a double-ended neeedle. At this point the cooled Grignard reagent was slowly cannulated into the CuBr·$Me_2S$ solution at −78 °C. Stirring was continued at −78 °C for 20 min followed by the addition of the ethyl phenylpropiolate solution and further stirring at −78 °C for 2.5 h. The reaction was quenched by the addition of 10 mL of methanol with stirring over 10 min followed by the addition of 200 mL of $H_2O$, whereupon the reaction mixture was extracted with two 100-mL portions of ether. The combined ethereal extracts were washed with brine, dried ($MgSO_4$), and concentrated to yield an oil containing with desired product and the tetrahydropyranyl ether of 1-pentanol. Flash chromatography (10% ether/petroleum ether) yielded 6.46 g (71%) of alkene **28**. $^1$H NMR $\delta$ 1.05 (t, $J$ = 7 Hz, 3H, $-CO_2CH_2CH_3$), 1.2–1.8 (m, 12 H, C-5, C-6, C-7, and THP —$CH_2$—'s), 2.46 (br t, $J$ = 6 Hz, 2 H, allylic —$CH_2$—), 3.2–3.7 (m, 4 H, —$CH_2O$—, 4.52 (bs, 1 H, —OCHO—), 5.88 (t, $J$ = 1.5 Hz, =CH), 7.1–7.5 (m, 5 H, ArH). IR ($CDCl_3$) 2950, 2860, 1710, 1160, 1025, and 705 cm$^{-1}$.

Anal. Calcd for $C_{21}H_{28}O_3$: C, 72.83; H, 8.67. Found: C, 72.69; H, 8.73.

**(*Z*)-Ethyl 8-Hydroxy-3-phenyl-2-octenoate (29).** To a solution of 0.92 g (2.6 mmol) of tetrahydropyranyl ether **28** in 20 mL of absolute ethanol were added 5 drops of concentrated HCl. After stirring overnight at room temperature, the reaction mixture was concentrated and the residual oil dissolved in 50 mL of methylene chloride. The resulting solution was then washed with saturated $NaHCO_3$, dried ($Na_2SO_4$), and concentrated to afford 0.66 g (96%) of alcohol **29**. $^1$H NMR $\delta$ 1.12 (t, $J$ = 7 Hz, 3 H, $-CO_2CH_2CH_3$), 1.2–1.6 (m, 6 H, C-5, C-6, and C-7 —$CH_2$—'s), 2.04 (br s, 1 H, —OH), 2.44 (t, $J$ = 6 Hz, allylic —$CH_2$—), 3.46 (t, $J$ = 6 Hz, 2 H, —$CH_2OH$), 3.95 (q, $J$ = 7 Hz, 2 H, —$CO_2CH_2CH_3$), 5.86 (t, $J$ = 1.3 Hz, 1 H, =CH), 7.1–7.4 (m, 5 H, ArH).

Anal. Calcd for $C_{16}H_{23}O_3$: C, 73.28; H, 8.37. Found: C, 73.39; H, 8.58.

**(*Z*)-Ethyl 3-Phenyl-8-oxo-2-octenoate (30).** According to the procedure of Corey,[20] in a flask equipped with an addition funnel, a magnetic stirrer, and a nitrogen inlet was placed 1.41 g (10.4 mmol) of *N*-chlorosuccinimide dissolved in 40 mL of toluene. The solution was cooled to 0 °C and 1.3 g (21.0 mmol) of dimethyl sulfide in 3 mL of toluene was added dropwise. After stirring 10 min the solution was cooled to −25 °C and 1.37 g (5.23 mmol) of alcohol **29** in 2 mL of toluene was added. Stirring was continued 90 min at −25 °C whereupon 2.2 g (22.0 mmol) of triethylamine was added. After 5 min the reaction mixture was warmed to room temperature, poured into 50 mL of water, and extracted with ether (2 × 50 mL). The combined ethereal extracts were washed with 10% HCl, saturated $NaHCO_3$, and brine, dried ($MgSO_4$), and concentrated to give the desired aldehyde as a crude oil. Purification was accomplished by chromatography on Activity III alumina (20% ether/petroleum ether) to afford 639 mg (47%) of pure aldehyde **30** suitable for the next reaction. $^1$H NMR $\delta$ 0.98 (t, $J$ = 7 Hz, 3 H, $-CO_2CH_2CH_3$), 1.2–1.7 (m, 4 H, C-5 anbd 6 —$CH_2$—'s), 2.2–2.5 (m, 4 H, C-4 and 7 —$CH_2$—'s), 3.90 (q, $J$ = 7 Hz, 2 H, $-CO_2CH_2CH_3$), 5.80 (t, $J$ = 1.1 Hz, 1 H, =CH—), 7.0–7.4 (m, 5 H, ArH).

(20) Corey, E. J.; Kim, C. V. *J. Am. Chem. Soc.* **1972**, *94*, 7586.

**6-Phenyl-6-hepten-1-ol (36).** To 505 mg (13.3 mmol) of stirred LAH in 20 mL of dry ether was added 1.45 g (6.65 mmol) of ester **35** in 3 mL of ether. The reaction was stirred 5 h at room temperature and then quenched by the successive addition of 0.5 mL of water, 0.5 mL of 15% NaOH, and 1.5 mL of water. The solution was then filtered, the salts were washed with ether, and the combined ethereal filtrates concentrated at reduced pressure to yield 1.2 g (95%) of alcohol **36**. $^1$H NMR (60 MHz) $\delta$ 1.2–1.8 (m, 6 H, C-2, C-3 and C-4 —$CH_2$—s), 2.3 (br s, 1 H, —OH), 2.5 (t, $J$ = 6 Hz, =$CPhCH_2$—), 3.5 (t, $J$ = 6 Hz, 2 H, —$CH_2OH$), 5.0 (d, $J$ = 2 Hz, 1 H, =CH), 5.2 (d, $J$ = 2 Hz, 1 H, =CH), and 7.1–7.5 (m, 5 H, ArH).

Anal. Calcd for $C_{13}H_{18}O$: C, 82.10; H, 9.57. Found: C, 81.76; H, 9.47.

**6-Phenyl-6-heptenal (37).** According to the general procedure of Swern,[6] a solution of 258 mg (2.05 mmol) of oxalyl chloride in 10 mL of methylene chloride was placed in a flame-dried 50-mL flask equipped with an addition funnel, a magnetic stirrer, a rubber septum, and a nitrogen inlet. The solution was cooled to −60 °C ($CO_2$/$CHCl_3$) and 320 mg (4.1 mmol) of $Me_2SO$ was added dropwise. Stirring was continued 2 min at −60 °C followed by the addition of 195 mg (1.02 mmol) of alcohol **36** in 1 mL of methylene chloride. After 15 min, 1 mL of triethylamine was added, stirring was continued an additional 5 min at −60 °C, and the solution was then allowed to warm to room temperature, whereupon 20 mL of water was added and the aqueous layer extracted with methylene chloride. The combined organic extracts were washed with 10% HCl, saturated $NaHCO_3$, and brine, dried ($Na_2SO_4$), and the solvent was concentrated at reduced pressure to yield 180 mg (92%) of aldehyde **37**. $^1$H NMR (60 MHz) $\delta$ 1.2–1.8 (m, 4 H, C-3 and C-4 H), 2.38 (t, $J$ = 6Hz, 2 H, =$CCH_2$—), 2.55 (t, $J$ = 6 Hz, 2H, =$CPhCH_2$—), 5.0 (bs, 1 H, =CH—, 5.25 (br s, 1 H, =CH—), 7.1–7.5 (m, 5 H, ArH) and 9.52 (t, $J$ = 2Hz, 1 H, —CHO). IR ($CDCl_3$) 2940, 1720, 880, and 700 cm$^{-1}$.

**1-Bromo-4-[(tetrahydro-2*H*-pyran-2-yl)oxy]butane (31).** In an adaptation of the procedure of Grieco,[18] 2.2 g (14.4 mmol) of 4-bromo-1-butanol[21], 181 mg (21.6 mmol) of dihydropyran, and 350 mg (1.4 mmol) of PPTS were stirred 4 h in 40 mL of methylene chloride. The solution was then washed with saturated NaCl, dried ($Na_2SO_4$), and concentrated. The resulting oil was purified by flash chromatography (10% ether/petroleum ether) to afford 2.52 g (74%) of tetrahydropyranyl ether **31**, suitable for the next reaction. $^1$H NMR $\delta$ 1.3–2.1 (m, 8 H, C-28 C-3, and THP —$CH_2$—'s), 3.47 (t, $J$ = 7 Hz, 2H, —$CH_2Br$), 3.6–4.0 (m, 4 H, —$CH_2O$—), 3.58 (br s, 1 H, —OCHO—).

**Ethyl (*Z*)-7-[(Tetrahydro-2*H*-pyran-2-yl)oxy]-3-phenylhept-2-enoate (32).** In a flame-dried 100-mL flask equipped with a magnetic stirrer, a nitrogen inlet, a reflux condenser, and a magnetic stirrer were placed 5.51 g (23.2 mmol) of bromide **31** and 600 mg (25.01 mmol) of freshly dried Mg metal in 50 mL of dry THF. Stirring was continued 4 h at room temperature to allow complete formation of the Grignard reaction. An additional flame-dried 250-mL flask containing 2.38 g (11.6 mmol) of CuBr·$Me_2S$ in 20 mL of dry THF and 2 mL of dimethyl sulfide was equipped with a magnetic stirrer, a nitrogen inlet, a rubber septum, and an addition funnel containing 1.55 g (8.92 mmol) of ethyl phenylpropiolate in 2 mL of dry THF. All solutions were deoxygenated by bubbling nitrogen through the solutions with a double-ended needle. The Grignard reagent was then cooled to 0 °C and slowly cannulated into the CuBr·$Me_2S$ solution at −78 °C. Stirring was continued 20 min at −78 °C folowed by the addition of the ethyl phenylproprolate solution. Stirring was continued 3 h at −78 °C, 2 mL of methanol added, stirring continued an additional 5 min followed by the addition of 75 mL of $H_2O$. The mixture was then extracted with ether (3 × 50 mL) and the combined ether extracts washed with brine, dried ($Na_2SO_4$), and concentrated to yield an oil along with residual copper salts. The mixture was then dissolved in 50 mL of petroleum ether, filtered, and concentrated. The product was separated from the butanol tetrahydropyranyl ether by flash chromatography (15% ether/petroleum ether) to afford 2.02 g (69%) of alkene **32b**. $^1$H NMR $\delta$ 1.05 t, $J$ = 7 Hz, 3 H, —

(21) Cloke, J. B.; Pilgrim, F. J. *J. Am. Chem. Soc.* **1939**, *61*, 2667. This procedure afforded 1-acetoxy-4-bromobutane, which was then hydrolyzed to 4-bromo-1-butanol with methanolic potassium carbonate.

$CO_2CH_2CH_3$), 1.3–1.9 (m, 10 H, C-5, C-6, and THF —$CH_2$—'s), 2.48 (t, $J$ = 6 Hz, 2 H, =$CPhH_2$—), 3.1–3.7 (m, 4 H, —$CH_2O$—), 3.98 (q, $J$ = 7 Hz, 2 H, —$CO_2CH_2CH_3$), 45.2 (br s, 1 H, —OCHO—), 5.88 (s, 1 H, =CH—) and 7.0–7.4 (m, 5 H, ArH).

Anal. Calcd for $C_2H_{28}O_4$: C, 72.29; H, 8.43. Found: C, 72.24; H, 8.50.

**(*Z*)-Ethyl 7-Hydroxy-3-phenyl-2-heptenoate (33).** A sample of 0.8 g (2.41 mmol) of tetrahydropyranyl ether **32** was dissolved in 20 mL of absolute ethanol containing 5 drops of concentrated HCl, and the solution was stirred overnight at room temperature. The solvent was then removed and the remaining oil dissolved in 50 mL of methylene chloride. The solution was then washed with saturated $NaHCO_3$ and saturated NaCl, dried ($Na_2SO_4$), and concentrated to yield 480 mg (80%) of alcohol **33**. $^1$H NMR $\delta$ 1.03 (t, $J$ = 7 Hz, 3 H, —$CO_2CH_2CH_3$), 1.4–1.7 (m, 4 H, C-5 and C-6 —$CH_2$'s), 2.45 (t, $J$ = 6 Hz, 2 H, =$CPhCH_2$—), 3.56 (t, $J$ = 6 Hz, 2 H, —$CH_2OH$), 3.95 (q, $J$ = 7 Hz, 2 H, —$Co_2CH_2CH_3$), 5.86 (t, $J$ = 1 Hz, 2 H, =CH—) and 7.0–7.4 (m, 5 H, ArH). IR ($CDCl_3$) 3600–3400 (br, 2950, 1690, 1630, 1440, 1380, 1230, 1160, and 1040 $cm^{-1}$.

Anal. Calcd for $C_{15}H_{20}O_3$: C, 72.29; H, 9.43. Found: C, 72.09; H, 9.25.

**Ethyl (*Z*)-7-Oxo-3-phenyl-2-heptenoate (34).** According to the general procedure of Swern,[6] a solution of 1.54 g (12.1 mmol) of oxalyl chloride in 40 mL of methylene chloride was placed in a flame-dried 100-mL flask equipped with an addition funnel, a magnetic stirrer, a rubber septum and a nitrogen inlet. The solution was cooled to –60 °C ($CO_2$/$CHCl_3$) and 1.87 g (24.0 mmol) of $Me_2SO$ in 2 mL of methylene chloride was added slowly. Stirring was continued 2 min at –60 °C and 1.5 g (6.05 mmol) of alcohol **33** in methylene chloride was then added. After 15 min, 6.6 mL of triethylamine was added and stirring continued an additional 5 minutes at –60 °C whereupon the solution was warmed to room temperature and then quenched by the addition of 50 mL of water. The aqueous layer was extracted with methylene chloride (2 × 50 mL), and the combined organic extracts were washed with 10% HCl, saturated $NaHCO_3$, and brine, dried ($Na_2SO_4$), and concentrated. The resulting aldehyde was then purified by flash chromatography (20% ether/petroleum ether) to yield 930 mg (62%) of pure aldehyde **34**. $^1$H NMR $\delta$ 1.05 (t, $J$ = 7 Hz, 3 H, —$CO_2CH_2CH_3$), 1.71 (m, 3 H, C-5 Hz), 2.45 (m, 4 H, =$CPhCH_2$— and —$CH_2CHO$), 3.97 (q, $J$ = 7 Hz, 2 H, —$CO_2CH_2CH_3$), 5.88 (s, 1 H, =CH"bd), 7.1–7.4 (m, 5 H, Ar*H*) and 9.72 (t, $J$ = 1.5 Hz, 1 H, —*CH*O).

**(*E*)-Ethyl 8-[(Tetrahydro-2*H*-pyran-2-yl)oxy]-2-octenoate (25).** To a flame-dried 50-mL flask equipped with a magnetic stirrer, a nitrogen inlet, and a magnetic stirrer were placed 4.0 g (15.9 mmol) of bromide **24** and 408 mg (17.0 mmol) of Mg turnings in 25 mL of dry THF. Stirring was continued 4 h at room temperature to allow complete formation of the Grignard reagent. An additional flame-dried 100-mL flask containing 1.64 g (8.0 mmol) of CuBr·$Me_2S$ in 20 mL of dry THF was equipped with a magnetic stirrer, a nitrogen inlet, a rubber septum, and an addition funnel containing 784 mg (8 mmol) of ethyl propiolate in 2 mL in THF. All solutions were then deoxygenated by bubbling nitrogen through the solution with a double-ended needle. The Grignard reagent was then cooled to 0 °C and then directly cannulated slowly into the CuBr·$Me_2S$ solution at –78 °C. Stirring was continued 15 min at –78 °C followed by the addition of the ethyl propiolate solution. After stirring for 1.5 h at –78 °C, 2 mL of methanol was added, stirring continued an additional 5 min, followed by the addition of 5 mL of $H_2O$. The mixture was then extracted with ether (3 × 50 mL), and the combined ether extracts were washed with brine, dried ($Na_2SO_4$), and concentrated. The resulting mixture was then purified by flash chromatography (30% ether/petroleum ether) to afford 919 mg (43%) of alkene **25**. $^1$H NMR $\delta$ 1.1–2.4 (br, 17 H, C-4, C-5, C-6, C-7, THP —$CH_2$—'s and —$CO_2CH_2CH_3$), 3.3–3.9 (m, 4 H, —$CH_2O$—'s), 4.18 (q, $J$ = 7 Hz, 2 H, —$CO_2CH_2CH_3$) 4.55 (bs, 1 H, —OCHO—) 5.80 (dt, $J$ = 15.7 and 1.5 Hz,1 H, $\alpha$=CH—) and 5.96 (d to t, 1 H, $J$ = 15.7 and 7 Hz, $\beta$=*CH*—).

Anal. Calcd for $C_{15}H_{26}O_4$: C, 66.67; H, 9.63. Found: C, 66.64; H, 9.83.

**(*E*)-Ethyl 8-Hydroxy-2-octenoate (26).** A sample of 0.5 g (1.85 mmol) of THF ether **25** was dissolved in 30 mL of absolute ethanol containing 3 drops of concentrated HCl and the solution stirred overnight at room temperature. The solvent was then concentrated and the remaining oil dissolved in 50 mL of methylene chloride whereupon the solution was washed with saturated $NaHCO_3$, dried ($Na_2SO_4$), and concentrated to afford 298 mg (87%) of alcohol **26** suitable for the next reaction. $^1$H NMR $\delta$ 1.28 (t, $J$ = 7 Hz, 3 H, —$CO_2CH_2CH_3$), 1.4–1.8 (m, 6 H, C-5, C-6, C-7 —$CH_2$—'s), 2.19 distorted t, 2 H, =$CHCH_2$—), 3.63 (t, $J$ = 6 Hz, 2 H, —$CH_2OH$), 4.18 (q, $J$ = 7 Hz, 2 H, —$CO_2CH_2CH_3$), 5.80 (dt, $J$ = 15 and 1.4 Hz, $\alpha$=CH—), 6.97 (dt, $J$ = 15 H and 6 Hz, $\beta$=CH—).

**(*E*)-Ethyl 8-Oxooct-2-enoate (27).** According to the general procedure of Swern,[6] a solution of 396 mg of oxalyl chloride (3.12 mmol) in 15 mL of methylene chloride was placed in a flame-dried 50-mL flask equipped with an addition funnel, a magnetic stirrer, a rubber septum, and a nitrogen inlet. The solution was cooled to –60 °C ($CO_2$/$CHCl_3$) and 487 mg (6.24 mmol) of $Me_2SO$ in 2 mL of methylene chloride was added slowly. Stirring was continued 2 min at –60 °C followed by the addition of 290 mg (1.56 mmol) of alcohol **26** in 1 mL of methylene chloride. After 15 min, 1.7 mL of triethylamine was added and stirring continued an additional 5 min at –60 °C. The solution was then warmed to room temperature and 50 mL of water added. The aqueous layer was extracted with methylene chloride (2 × 30 mL), and the combined organic extracts washed with 10% HCl, saturated $NaHCO_3$, and brine, dried ($Na_2SO_4$), and concentrated. The resulting aldehyde was then purified by flash chromatography (20% ether/petroleum ether) to afford 180 mg (62%) of aldehyde **27** which was used directly in the next reaction. $^1$H NMR $\delta$ 1.28 (t, $J$ = 7 Hz, 3 H, —$CO_2CH_2CH_3$), 1.4–1.9 (m, 2 H, C-5 —$CH_2$—), 2.2–2.6 (m, 4 H, C-7 C-7 —$CH_2$—'s), 4.18 (q, $J$ = 7 Hz, 2 H, —$CO_2CH_2CH_3$), 5.85 (dt, 1 H, $J$ = 15 and 1.5 Hz, $\alpha$-CH=), 6.93 (dt, $J$ = 15 and 6 Hz, 1 H, $\beta$—*CH*=), and 9.76 (t, $J$ = 1.5 Hz, 1 H, —*CH*O).

**Ethyl (*Z*)-3-(1,3-Benzodioxol-5-yl)-4-bromo-2-butenoate (39).** A mixture of 329 mg (1.40 mmol) of (*E*)-ester **38**[22], 250 mg (1.40 mmol) of *N*-bromosuccinimide, and ca. 20 mg of dibenzoyl peroxide in 10 mL of $CCl_4$ was heated at reflux for 4 h. The reaction mixture was then cooled and filtered through Celite, and solids were washed thoroughly with additional $CCl_4$. The combined filtrates were concentrated to yield an oil which was flash chromatographed (5% $Et_2O$/petroleum ether) to afford 206 mg (47%) bromide **39** which was used without further purification. $^1$H NMR $\delta$ 6.76–7.28 (m, 3 H, ArH), 6.13 (s, 1 H, =CH), 6.01 (s, 2 H, —$OCH_2O$—). IR ($CDCl_3$) 2900, 1700, 1230, 1160, 1030 $cm^{-1}$.

**Ethyl 3-(1,3-Benzodioxol-5-yl)-5,5-dicarbethoxy-7,7-diethoxy-2-heptenoate (41).** To a 50-mL flask equipped with an addition funnel and reflux condenser was added 0.259 g of 50% NaH/mineral oil (5.40 mmol), which was washed with petroleum ether (2 × 2 mL), and suspended in 10 mL of THF. A solution of malonate **40**[11] (4.90 mmol) in 5 mL of THF was added dropwise at room temperature followed by a solution of 1.52 g (4.90 mmol) of bromide **39** in 5 mL of THF. The mixture was then heated at reflux for 2 h whereupon it was cooled, worked up with water and ether, dried ($Na_2SO_4$), and concentrated to give crude product as a yellow oil. Flash chromatography (15% EtOAc/petroleum ether) afforded 1.48 g (59%) of acetal **41** as an oily solid, mp 82–7 °C. $^1$H NMR $\delta$ 1.00–1.40 (m, 15 H, —$CH_3$'s), 2.09 (d, $J$ = 6 Hz, 2 H, C-6 —$CH_2$—), 3.50 (m, 4 H, —$OCH_2CH_3$), 3.92 (q, $J$ = 7 Hz, 4 H, —$CO_2CH_2CH_3$), 3.95 (d, $J$ = 1 Hz, 2 H, =$CCH_2$—), 4.21 (q, $J$ = 7, 2 H, —$CO_2CH_2CH_3$), 4.68 (t, $J$ = 6 Hz, 1 H, —$CH(OEt)_2$), 5.97 (br s, 3 H, —$CH_2O$— and =CH—), 6.77 (br s, 2 H, ArH), 7.37 (d, $J$ = 10 Hz, 1 H, ArH). IR ($CDCl_3$) 2900, 1720, 1730 (sh), 1605, 1430, 1230, 1170 $cm^{-1}$.

Anal. Calcd for $C_{26}H_{36}O_{10}$: C, 61.40; H, 7.14. Found: C, 61.70; H, 6.91.

**Formation and Cyclization of Alkene Nitrones. From Aldehyde 19. Octahydro-1-methyl-6-oxa-2,1-benzisoxazole, Cyclic Ethylene Ketal (11a).** A solution of 1.27 g (7.47 mmol) of aldehyde **19**, 686 mg (8.21 mmol) of *N*-methylhydroxylamine hydrochloride and 1 g of $K_2CO_3$ in 200 mL of benzene was stirred at room temperature for 5 h. The solution was then filtered, the salts were washed with benzene, and the solvent was removed at reduced pressure to yield an oil which showed no starting aldehyde

(22) Klein, J.; Aminadav, N. *J. Chem. Soc. C* **1970**, 1380.

by $^1$H NMR. The crude oil was then dissolved in 100 mL of toluene and heated at reflux for 8 h. After cooling to room temperature and concentration, the crude product was chromatographed on Activity III alumina (ether/hexane) to yield 720 mg (41%) of isoxazolidine **10a**. Elemental analysis was performed on the oxalate salt, mp 140–2 °C. $^1$H NMR $\delta$ 1.5–2.0 (m, 7 H, —$CH_2$'s— and —CH—), 2.64 (s, 3 H, —$NCH_3$), 2.9 (m, 1 H, —CHN—), 3.58 (t, $J$ = 7.7 Hz, 1 H, —C$H_2$—), 3.93 (s, 4 H, ketal), 4.11 (distorted t, $J$ = 8 Hz, 1 H, —$CH_2$—).

Anal. Calcd for $C_{12}H_{19}NO_7$: C, 49.82; H, 6.57; N, 4.84. Found: C, 49.56; H, 6.50; N, 4.75.

**Octahydro-1-(phenylmethyl)-6-oxa-2,1-benzisoxazole, Cyclic Ethylene Ketal (11b).** In the same manner as in the above procedure, a solution of 747 mg (4.39 mmol) of aldehyde **19**, 590 mg (4.80 mmol) of *N*-benzylhydroxylamine, and 1.0 g of $K_2CO_3$ in 20 mL benzene was stirred for 4 h at room temperature. The solution was then filtered, the salts were washed thoroughly with benzene, and the combined benzene layers were concentrated to give crude nitrone. This oil was dissolved in 60 mL of toluene and then heated at reflux for 10 h, cooled to room temperature, and concentrated to give crude product which still contained a small amount (~5%) of unreacted aldehyde. This oil was purified by chromatography on Activity III alumina (ether/hexane) to yield 430 mg (62%) of isoxazolidine **10b**, homogeneous by TLC. $^1$H NMR (250 MHz) $\delta$ 1.5–1.9 (m, 6 H, —$CH_2$—'s), 2.92 (m, 1 H, C-4a H), 3.28 (m, 1 H, —CHN—), 3.64 (dd, $J$ = 7.5 and 9.1 Hz, 1 H, —$CH_2$—), 3.82 (d, $J$ = 13.4 Hz, 1 H, —$NCH_2Ar$), 3.84–3.97 (m, 4 H, ketal), 4.02 (d, $J$ = 13.4 Hz, 1 H, —$NCH_2Ar$), 4.16 (distorted t, $J$ = 9.1 Hz, 1 H, —CHO—), 7.2–7.4 (m, 5 H, ArH).

**From Aldehyde 27. Ethyl (3$\beta$,3a$\beta$)-Octahydro-1-methyl-2,1-benzisoxazole-3-carboxylate (11c).** A mixture of 150 mg (0.87 mmol) of freshly chromatographed aldehyde **27**, (73 mg (0.87 mmol) of *N*-methylhydroxylamine hydrochloride, and 120 mg of $K_2CO_3$ in 5 mL of benzene was stirred overnight at room temperature. The solution was then filtered, the salts were washed thoroughly with additional benzene, and the benzene layer was concentrated to yield the crude isoxazolidine. The resulting oil was then purified by chromatography on Activity III alumina (20% ether/petroleum ether) to afford 155 mg (71%) of pure isoxazolidine (**11c**). $^1$H NMR $\delta$ 1.28 (t, $J$ = 7 Hz, 3 H, —$CO_2CH_2CH_3$), 1.4–1.9 (m, 8 H, cyclohexyl —$CH_2$'s), 2.79 (s, 3 H, —$NCH_3$), 2.6–2.9 (m, 2 H, —CH—'s), 4.15 (d, $J$ = 4 Hz, 1H, —OC$H$C$O_2CH_2CH_3$), 4.20 (q, $J$ = 7 Hz, 2 H, —$CO_2CH_2CH_3$).

Anal. Calcd for $C_{11}H_{19}NO_3$: C, 61.97; H, 8.92; N, 6.57. Found: C, 62.19; H, 8.79; N, 6.45.

**From Aldehyde 37. 8-Benzyl-6-phenyl-7-oxa-8-azabicyclo[4.2.1]nonane (12d).** A solution of 180 mg (0.96 mmol) of aldehyde **37** and 153 mg (1.22 mmol) of *N*-benzylhydroxylamine hydrochloride in 5 mL benzene containing 400 mg of suspended $K_2CO_3$ was stirred at room temperature for 5 h. The solution was filtered, the salts were washed thoroughly with additional benzene, and the reaction mixture was concentrated to yield crude nitrone **10d** as verified by the presence of a signal at 6.5 (t, $J$ = 7 Hz) in the $^1$H NMR spectrum. The nitrone was then dissolved in 20 mL of toluene and heated at reflux for 15 h, whereupon the solution was cooled to room temperature and concentrated. The crude oil was purified by flash chromatography (ether/petroleum ether) to yield 166 mg (59%) of bridged isoxazolidine **12d**. $^1$H NMR $\delta$ 1.6–1.9 (m 8 H, —C$H_2$—'s), 2.61 (s, 1 H, bridge *H*) 2.68 (d, $J$ = 4 Hz, bridge *H*), 3.45 (m, 1 H, —C$H$N—), 3.60 (d, $J$ = 13 Hz, 1 H, —NC$H_2$Ar), 4.12 (d, $J$ = 13 Hz, 1 H, —NC$H_2$Ar), 7.1–7.7 (m, 5 H, Ar$H$).

Anal. Calcd for $C_{20}H_{25}NO$: C, 81.91; H, 7.85, N, 4.78. Found: C, 81.86; H, 8.06; N, 4.54.

**From Aldehyde 23. 8-Benzyl-6-phenyl-7-oxa-8-azabicyclo[4.2.1]nonan-4-one, Cyclic Ethylene Ketal (12e).** A solution of 218 mg (0.85 mmol) of aldehyde **23**, 115 mg (0.94 mmol) of benzylhydroxylamine, and 200 mg of $K_2CO_3$ in 5 mL of benzene was stirred 5 h at room temperature whereupon the reaction mixture was filtered, the salts were washed with additional benzene, and then concentrated. The crude nitrone was then dissolved in 10 mL of toluene and heated overnight at reflux to yield crude isoxazolidine **12e** which was then purified by chromatography on Activity III alumina (ether/petroleum ether) to afford 144 mg (47%) of isoxazolidine **12e** as a white crystalline solid, mp 125–7 °C. $^1$H NMR (250 MHz) $\delta$ 1.7–2.2 (m, 6 H, —$CH_2$—'s), 2.46 (dd, $J$ = 12.7 and 8.5 Hz, 1 H, bridge H), 2.97 (d, $J$ = 12.5 Hz, 1 H, bridge H), 3.41 (t, $J$ = 6.7 Hz, 1 H, —CHN—), 3.71 (d, $J$ = 12.5 Hz, 1 H, —$NCH_2Ar$), 3.8–3.96 (m, 4 H, ketal), 4.23 (d, $J$ = 12.5 Hz, 1 H, —$NCH_2Ar$), 7.1–7.4 (m, 10 H, ArH).

Anal. Calcd for $C_{22}H_{25}NO_3$: C, 75.21; H, 7.12; N, 3.99. Found: C, 74.99; H, 6.94; N, 3.93.

**From Aldehyde 30. Ethyl *anti*-6-Phenyl-8-methyl-7-oxa-8-azabicyclo[4.2.1]nonane-9-carboxylate (12f).** A solution of 481 mg (1.85 mmol) of freshly chromatographed aldehyde **30**, 155 mg (1.85 mmol) of *N*-methylhydroxylamine hydrochloride, and 25 mg of $K_2CO_3$ in 5 mL of benzene was stirred overnight at room temperature. The reaction mixture was filtered, the salts were washed with additional benzene, and then the mixture was concentrated to afford the expected nitrone **10f**, 6.61 (t, $J$ = 5 Hz). The crude nitrone was then dissolved in 20 mL of toluene and heated at reflux for 22 h whereupon it was cooled to room temperature and concentrated. Chromatography on Activity III alumina (20% ether/petroleum ether) afforded 272 mg (51%) of pure isoxazolidine **12f**. $^1$H NMR $\delta$ 0.81 (t, $J$ = 7 Hz, 3 H, —$CO_2CH_3$), 1.2–2.2 (m, 8 H, ring —C$H_2$—'s), 3.07 (s, 3 H, —NC$H_3$), 3.3–3.8 (m, 3 H, —$CO_2CH_2CH_3$ and —C$H$N—), 7.0–7.5 (m, 5 H, Ar$H$). $^{13}$C NMR, substitution determined by INEPT[15], $\delta$ 13.4 (1°), 23.3 (2°), 23.8 (2°), 31.5 (2°), 44.3 (2°), 45.8 (1°), 59.0 (2°), 60.2 (2°), 69.3 (3°), 88.9 (4°), 125.4 (3°), 127.4 (3°), 142 (4°), 170 (4°).

Anal. Calcd for $C_{17}H_{23}NO_3$: C, 70.59; H, 7.96; N, 4.84 Found: C, 70.85; H, 7.94; N, 4.73.

**From Aldehyde 34. Ethyl (3$\beta$,3a$\beta$,6a$\beta$)-Hexahydro-1-methyl-3a-phenyl-1*H*-cyclopent[*c*]isoxazole-3-carboxylate (14a).** A solution of 225 mg (0.94 mmol) of freshly chromatographed aldehyde **34**, 80 mg (0.95 mmol) of *N*-methylhydroxylamine hydrochloride and 125 mg of $K_2CO_3$ in 5 mL of benzene was stirred overnight at room temperature and then filtered, the salts were washed with additional benzene, and the combined benzene solutions were concentrated to give the expected nitrone **13a**, $\delta$ 6.60 (t, $J$ = 5 Hz). The crude nitrone was then dissolved in 20 mL of toluene and heated at reflux for 12 h and then concentrated. Chromatography on Activity III alumina (ether/petroleum ether) afforded 116 mg (41%) of isoxazolidine **14a**. $^1$H NMR $\delta$ 0.88 (t, $J$ = 7 Hz, 3 H, —$CO_2CH_2CH_3$), 1.1–2.5 (m, 6 H, —$CH_2$—'s), 2.98 (s, 3 H, —$NCH_3$), 3.3–3.9 (m, 3 H, —$CO_2CH_2CH_3$ and —CHN—), 4.40 (s, 1 H, —OCHC)$_2$Et), 7.1–7.4 (m, 5 H, ArH). $^{13}$C NMR, substitution determined by INEPT[15], $\delta$ 13.7 (1°), 23.0 (2°), 35.6 (2°), 44.0 (1°), 60.5 (2°), 67.2 (4°), 82.4 (3°), 85.1 (3°), 126.8 (3°), 127.9 (3°), 167.7 (4°).

**Ethyl (3$\beta$,3a$\beta$,6a$\beta$)-Hexahydro-1-benzyl-3a-phenyl-1*H*-cyclopent[*c*]isoxazole-3-carboxylate (14b).** A solution of 915 mg (3.72 mmol) of aldehyde **34**, 475 mg (3.89 mmol) of benzylhydroxylamine hydrooxalate, and 300 mg of $K_2CO_3$ in 30 mL of benzene was stirred overnight at room temperature. Filtration and washing of the salts with additional benzene followed by concentration led to crude nitrone **13b**, which was then dissolved in 125 mL of toluene and heated at reflux for 9 h. Concentration afforded a crude oil which was purified by flash chromatography (15% water/hexane) to yield 685 mg (77%) of isoxazolidine **14b**. $^1$H NMR $\delta$ 0.86 (t, 3 H, —$CO_2CH_2CH_3$), 1.1–2.5 (m, 6 H, —$CH_2$—'s), 3.4 3–9 (m, 3 H, —CHN— and —$CO_2CH_2CH_3$), 4.14 (d, $J$ = 13 Hz, 1 H, —$NCH_2Ar$), 4.46 (d, $J$ = 13 Hz, 1 H, —$NCH_2Ar$), 4.28 (s, 1 H, —OCHC$O_2$Et), 7.0–7.5 (m, 10 H, ArH). IR ($CDCl_3$) 2950, 1740, 1145, 1375, 1200, 1120, 1030, and 690 cm$^{-1}$.

Anal. Calcd for $C_{22}H_{25}NO_3$: C, 75.21; H, 7.12; N, 3.99. Found: C, 75.35; H, 7.09; N, 3.97.

**From Aldehyde 42. Triethyl (3$\alpha$,3a$\beta$,6a$\beta$)-Hexahydro-3a-(1,3-benzodioxol-5-yl)-1-(phenylmethyl)-1*H*-cyclopent-[*c*]isoxazole-3,5,5-tricarboxylate (14c).** To a solution of 100 mg (0.20 mmol) of **41** in 1 mL of THF was added 1 mL of 10% HCl and the mixture was stirred 2 h at room temperature. An aqueous workup (ether/saturated $NaHCO_3$/brine) followed by drying ($Na_2SO_4$) and concentration yielded aldehyde **42**, $\delta$ 9.54, as a yellow oil which was used without further purification. Aldehyde **42** was dissolved in 5 mL of benzene, 45 mg (0.21 mmol) of benzylhydroxylamine hydrooxalate and ca. 50 mg of potassium carbonate were added, and the reaction mixture was stirred 24 h at room temperature. The solution was passed through a pad of Celite, the salts were washed thoroughly with benzene, and the combined filtrates concentrated. Flash chromatography (10%

EtOAc/petroleum ether) of the crude product afforded 81 mg of isoxazolidine **14c** (75%) as an oil. $^1$H NMR δ 0.95–1.60 (m, 9 H, —COOCH$_2$C*H*$_3$'s), 2.04–3.10 (m, 4 H, C-4 and C-6 —CH$_2$'s), 3.70–4.50 (m, 8 H, —COOC*H*$_2$CH$_3$'s and —NCH$_2$Ph), 4.58 (s, 2 H, C-3 and C-6a —CH—'s), 5.94 (s, 2 H, —OCH$_2$O—), 6.66–7.10 (m, 3 H, ArH), 7.17–7.50 (m, 5 H, —C$_6$*H*$_5$). IR 3000, 2800, 1720, 1500, 1440, 1240, 1200, 1040, 800 cm$^{-1}$.

Anal. Calcd for $C_{29}H_{33}NO_9$: C, 64.55; H, 6.16; N, 2.60. Found: C, 64.66; H, 5.93; N, 2.48.

**Registry No.** **11a**, 98525-96-3; **11b**, 98525-88-3; **11c**, 98525-89-4; **11d**, 98526-00-2; **11e**, 98526-01-3; **11f**, 98526-02-4; **12a**, 98525-97-4; **12b**, 98525-98-5; **12c**, 98525-99-6; **12d**, 98525-90-7; **12e**, 98539-82-3; **12f**, 98525-91-8; **14a**, 98525-92-9; **14b**, 98526-05-7; **14c**, 98525-94-1; **15a**, 98526-03-5; **15b**, 98539-83-4; **15c**, 98526-04-6; **16**, 17605-06-0; **17**, 98525-68-9; **18**, 98525-69-0; **19**, 98525-70-3; **20**, 98525-71-4; **21**, 98525-72-5; **22**, 98525-73-6; **23**, 98525-74-7; **24**, 37935-47-0; **24** (X = CH$_2$CH$_2$OH), 34626-51-2; **25**, 98525-84-9; **26**, 75958-95-1; **27**, 98525-85-0; **28**, 98525-75-8; **29**, 98525-76-9; **30**, 98525-77-0; **31**, 31608-22-7; **32**, 98525-81-6; **33**, 98525-82-7; **34**, 98525-83-8; **35**, 98525-78-1; **36**, 98525-79-2; **37**, 98525-80-5; **38**, 98525-86-1; **39**, 98525-87-2; **40**, 21339-47-9; **41**, 98539-81-2; **42**, 98525-95-2; CH$_3$COCH$_2$COOEt, 141-97-9; C$_6$H$_5$C(CH$_2$Br)=CH$_2$, 3360-54-1; C$_6$H$_5$C≡CCOOEt, 2216-94-6; Br(CH$_2$)$_4$OH, 33036-62-3; HC≡CCOOEt, 623-47-2; CH$_3$NHOH·HCl, 4229-44-1; C$_6$H$_5$CH$_2$NHOH, 495-18-1; C$_6$H$_5$CH$_2$NHOH·oxalate, 98525-93-0.

# Structural Studies of 2-(*p*-Chlorophenyl)-2-methyl-5-phenyl-1,3-dioxane

K. J. Shea* and T. K. Dougherty

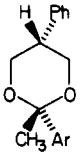
*Department of Chemistry, University of California, Irvine, California 92717*

*Received February 15, 1985*

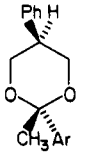
The structure and conformation of *cis*- and *trans*-2-(*p*-chlorophenyl)-2-methyl-5-phenyl-1,3-dioxane have been established by a combination of NMR and X-ray analysis.

We recently required precise information regarding stereochemical preferences and interatomic distances for a number of 2,2,5-trisubstituted 1,3-dioxanes. The unusually large conformational strain that results from axial 2-alkyl groups and the diminished 1,3-diaxial nonbonded interactions from 5-axial substituents make this substitution pattern particularly interesting.[1] The absence of detailed stereochemical or structural studies for compounds of this type prompts a report of our results.

We have synthesized the isomeric 2-(*p*-chlorophenyl)-2-methyl-5-phenyl-1,3-dioxanes **1** and **2** and elucidated




*cis*-**1**




*trans*-**2**

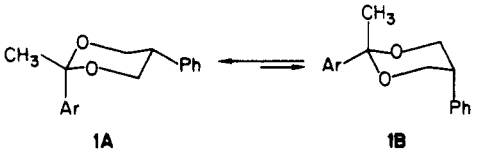
their structure by a combination of NMR spectroscopy and X-ray crystallography. These results have provided us with the needed structural parameters and have also contributed to our understanding of the structural and conformational preferences of this intriguing ring system.[2]

## Results and Discussion

Condensation of *p*-chloroacetophenone with 2-phenyl-1,3-propandiol (TSA, CHCl$_3$, Dean–Stark trap) results in formation of an isomeric mixture of 1,3-dioxanes (**1**, **2**). The reaction conditions used for their preparation often results in an equilibrium mixture; this was confirmed by equlibration studies on the isomeric mixture and pure major and minor components **1** and **2**. Dilute solutions of pure isomers in dry ether were equilibrated in the presence of Amberlyst ion exchange resin. After 48 h at 23.8 °C each isomer gave an identical 84:16 ratio of cis–trans isomers corresponding to a free energy difference of $\Delta G^\circ_{297}$ = 1.05 kcal/mol.

Fractional crystalization in 10% ether–hexane afforded pure samples of the isomeric 1,3-dioxanes.

The proton NMR of the major isomer (**1**) contains a nine-line triplet of triplets ($J$ = 11.3, 4.8 Hz) at 3.3 ppm which is assigned to the methine proton at C-5. The methylene protons at C-4(6) are resolved in this isomer and are found at 3.8 and 3.96 ppm. The high-field proton of the methylene group (3.8 ppm, dd) can be assigned the axial position with vicinal and geminal couplings of 11.3 and 11.4 Hz, respectively. The low-field proton (3.96 ppm) consists of a doublet of doublets ($J$ = 11.4, 4.8 Hz). With the reasonable assumption that this substitution pattern will not produce any unusual distortions resulting in nonchair conformations,[3] the NMR results for the major isomer are consistent with a 1,3-dioxane in which the 5-phenyl group occupies an equatorial position. Furthermore, on the basis of conformational equilibrium studies,[4] an axial 2-methyl group is expected to have greater steric strain than an axial 2-phenyl group. The NMR spectrum of the major isomer is entirely consistent with the *cis*-1,3-dioxane (**1**) that exists predominately in conformation *A*.




**1A** **1B**

The proton NMR spectra of the minor isomer **2** is characterized by an apparent pentuplet (overlapping

(1) (a) Eliel, E. L.; Knoeber, M. C. *J. Am. Chem. Soc.* **1968**, *90*, 3444. (b) Riddell, F. G.; Robinson, M. J. T. *Tetrahedron* **1967**, *23*, 3417.

(2) (a) Eliel, E. L. *Acc. Chem. Res.* **1970**, *3*, 1. (b) Riddell, F. G. "The Conformational Analysis of Heterocyclic Compounds"; Academic Press: New York, 1980.

(3) Kellie, G. M.; Murry-Rust, P.; Riddell, F. G. *J. Chem. Soc., Perkin 2*, **1972**, 2384.

(4) (a) Nader, F. W.; Eliel, E. L. *J. Am. Chem. Soc.* **1970**, *92*, 3050. (b) Robinson, M. J. T. *Tetrahedron* **1974**, *30*, 1971. The preferences (in kcal/mol) of the alkyl substituents for the equatorial (over the axial) position used in the calculation are 2-Me, 3.98; 2-Ph, 3.12; 5-Ph, 1.03.

0022-3263/85/1950-4439$01.50/0 © 1985 American Chemical Society