THE JOURNAL OF Organic Chemistry

VOLUME 47, NUMBER 26

DECEMBER 17, 1982

Cyclopentene and Cyclohexene Annulation via Copper-Catalyzed Conjugate Addition of Acetal-Containing Grignard Reagents

Swati A. Bal, Anthony Marfat, and Paul Helquist*

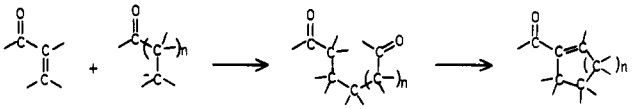
Department of Chemistry, State University of New York, Stony Brook, New York 11794

Received May 13, 1982

The Grignard reagents **2** derived from 2-(2-bromoethyl)- and 2-(3-chloropropyl)-1,3-dioxolane undergo conjugate addition to a number of α,β-unsaturated ketones in the presence of a catalytic amount of a cuprous salt. The resulting keto acetals, upon treatment with hydrochloric acid, undergo sequential hydrolysis, intramolecular aldol condensation, and dehydration to give cyclopentene and cyclohexene annulation products. The entire series of reactions, starting with the conjugate addition, may be performed as a one-flask experiment leading to direct formation of the cyclization products. The Grignard reagents may also be alkylated with epoxides or acylated with an acid chloride to give intermediates that may be converted into cyclic products by pathways related to those above.

The construction of carbocyclic compounds, and five- and six-membered rings in particular, is a central theme of much of synthetic organic chemistry because of the countless numbers of natural products and industrially important compounds that contain these ring systems. The numerous methods that have been developed for the synthesis of these compounds have been the subject of several reviews.[1]

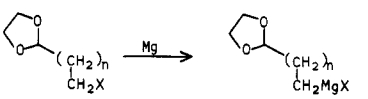
Our work in this area has been directed toward the direct annulation of rings of various sizes onto preexisting carbon skeletons, usually containing carbon–carbon double bonds as the sites of ring attachment.[2-6] One of the general concepts that we have been exploring is illustrated in eq 1 in which a synthetic equivalent of the carbanionic species



1 (1)

1 undergoes conjugate 1,4-addition to an α,β-unsaturated carbonyl compound, and the resulting dicarbonyl compound undergoes intramolecular condensation and subsequent dehydration to give the desired annulation product. The use of reagents equivalent to **1** having $n = 1$ or 2 would permit, overall, the annulation of cyclopentene and cyclohexene rings onto the original unsaturated carbonyl compounds, although the basic route may also be applicable to other, less commonly encountered ring sizes.

The specific reagents that we have chosen to study as equivalents of **1** are the acetal-containing Grignard reagents **2**. These and related organometallic derivatives have been known for several years.[7] Upon generation from the corresponding halides **3** (eq 2), these Grignard reagents



3a, n=1
b, n=2

2 (2)

(1) (a) "Advances in Alicyclic Chemistry"; Hart, H.; Karabatsos, G. J., Ed.; Academic Press: New York, 1971; Vol. 3, and the earlier volumes of this series. (b) Ellison, R. A. *Synthesis* **1973**, 397–412. (c) Ho, T.-L. *Synth. Commun.* **1974**, *4*, 265–287. (d) Martin, J. In "International Review of Science: Organic Chemistry, Series Two"; Ginsburg, D., Ed.; Butterworths: London, 1976; Vol. 5, Chapter 2. (e) Jung, M. E. *Tetrahedron* **1976**, *32*, 3–31. (f) "Alicyclic Chemistry"; McKervey, M. A., Senior Reporter; The Chemical Society: London, 1978; Vol. 6, and the earlier volumes of this series. (g) Kametani, T.; Nemoto, H. *Heterocycles* **1978**, *10*, 349–390. (h) Mundy, B. P. "Concepts of Organic Synthesis. Carbocyclic Chemistry"; Marcel Dekker: New York, 1979. (i) "Methodicum Chimicum. Basic Skeletons; Carbon–Hydrogen Compounds and Heteroaromatic"; Falbe, J. Ed.; Georg Thieme Verlag: Stuttgart, 1980; Vol. 4. (j) Becker, K. B. *Tetrahedron* **1980**, *36*, 1717–1745. (k) Smith, A. B.; Dieter, R. K. *Ibid.* *37*, 2407–2439. (l) "Recent Developments in Polycyclopentanoid Chemistry"; Paquette, L. A., Ed.; *Tetrahedron* **1981**, *37*, 4359–3559.

(2) For a preliminary account of the portion of this work concerned with cyclopentene annulation, see: Marfat, A.; Helquist, P. *Tetrahedron Lett.* **1978**, 4217–4220. See also: Marfat, A. Ph.D. Dissertation, The State University of New York, Stony Brook, NY, 1978. Bal, S. A. Ph.D. Dissertation, The State University of New York, Stony Brook, NY, 1981.

(3) Brandt, S.; Helquist, P. *J. Am. Chem. Soc.* **1979**, *101*, 6473–6475.

(4) Kremer, K. A. M.; Helquist, P.; Kerber, R. C. *J. Am. Chem. Soc.* **1981**, *103*, 1862–1864.

(5) Ponton, J.; Helquist, P.; Conrad, P. C.; Fuchs, P. L. *J. Org. Chem.* **1981**, *46*, 118–122.

(6) Helquist, P.; Bornack, W. K.; Bhagwat, S. S.; Ponton, J.; Marfat, A.; Bal, S. A. *Kemia-Kemi* **1982**, *9*, 93–97.

(7) (a) Feugeas, C.; Normant, H. *Bull. Chem. Soc. Fr.* **1963**, 1441–1443. (b) Feugeas, C. *Ibid.* **1963**, 2568–2579.

0022-3263/82/1947-5045$01.25/0

have been observed to undergo, most commonly, 1,2-addition reactions with carbonyl compounds,[8] although acylations[8i,9] and other reactions[10] have also been investigated. The value of these reactions has been demonstrated in a number of natural product syntheses.[8a,c-f,10] There were surprisingly few reports, though, of conjugate addition reactions[11] of these organomagnesium compounds before the start of our work in this area. In one of the earlier papers, a sequence of reactions related to our pathway was described as part of a proposed route to dendrobine, but because of difficulty with later steps, the approach was abandoned.[11a] We now describe the details of our investigation of annulation reactions employing the approach discussed above.

Results and Discussion

Cyclopentene Annulation. As a starting material for the construction of five-membered rings by our general strategy, the bromo acetal **3a** (X = Br) is readily available by the reaction of acrolein with ethylene glycol and hydrogen bromide.[8a] The use of this acetal required optimization of conditions for its conversion into the corresponding Grignard reagent **2a** (X = Br). A difficulty that was encountered early in our studies is that generation of the desired intermediate under many of the commonly used conditions for forming Grignard reagents led to production of significant amounts (15–30%) of the Wurtz coupling product. On the other hand, the use of magnesium powder prepared from *anhydrous* magnesium dichloride and potassium metal according to the procedure of Rieke[12] was quite successful. The reaction of this form of magnesium with the bromo acetal permits rapid formation of the Grignard reagent with very little (<5%) of the undesired coupling product being produced. An alternative procedure that we have adopted more recently is to grind magnesium turnings in a mortar and pestle followed by immediate reaction of a three-fold excess of these turnings with a very concentrated solution of the bromo acetal under conditions analogous to those reported by Forbes.[8k] The overall results obtained by the two procedures are quite comparable, but the latter procedure is certainly more convenient to employ.

The next step in the reaction sequence is copper-catalyzed conjugate addition of the Grignard reagent to α,β-unsaturated ketones.[13] The dimethyl sulfide complex of cuprous bromide[14] is a convenient form of copper to use for this purpose because of the high state of purity in which it can be obtained[15] and because of its favorable solubility characteristics. Once the conjugate addition is accomplished, the resulting keto acetals **4** may be isolated after quenching of the reaction mixture with aqueous ammonium chloride. In turn, treatment of these intermediates with hydrochloric acid induces sequential acetal hydrolysis, intramolecular aldol condensation, and dehydration, thus giving the bicyclic annulation products **5**. Alternatively, the entire multistep process from the bromo acetal to the cyclopentenes may be accomplished in a one-flask experiment by quenching the conjugate addition reaction mixture with hydrochloric acid (Scheme I). Our results are summarized in Table I. In each of these cases, nearly equivalent stoichiometric amounts of the bromo acetal and the unsaturated ketone were employed except that for cyclopenten-3-one, a notoriously difficult case for conjugate additions, 2 equiv of the acetal was employed. We also note that in this case, the aldol product did not undergo dehydration under our usual conditions,[16] and **5d** (Table

Scheme I

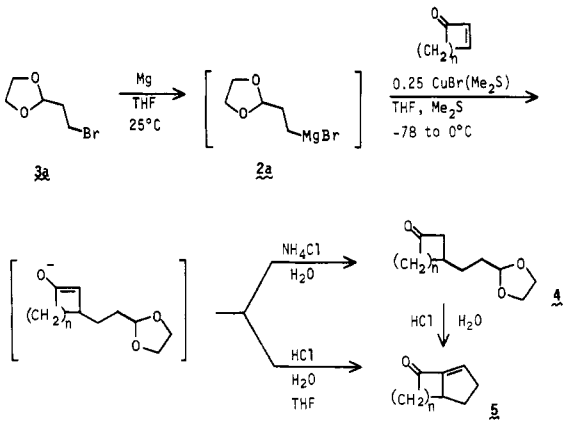
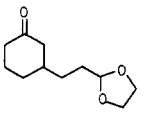
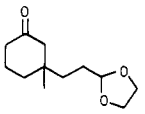
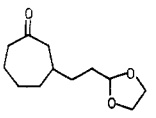
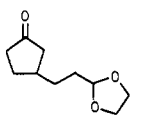
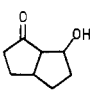


Table I. Cyclopentene Annulation

substrate	keto acetal (4)		% yield[a]	annulation product (5)	% yield[b]
		(a)	85		89 (62)[c]
		(b)	74		77 (48)[c]
		(c)	87		80
		(d)	77		54

[a] Yield determined by GLC, using an internal standard. [b] Isolated yield. [c] Yield from the one-flask procedure without isolation of 4.

(8) (a) Büchi, G.; Wüest, H. *J. Org. Chem.* **1969**, *34*, 1122–1123. (b) Loozen, H. J. J.; Godefroi, E. F. *Ibid.* **1973**, *38*, 1056–1057; 3495–3497. (c) Johnson, W. S.; Wiedhaup, K.; Brady, S. F.; Olson, G. L. *J. Am. Chem. Soc.* **1974**, *96*, 3979–3984. (d) Corey, E. J.; Balanson, R. D. *Ibid.* **1974**, *96*, 6516–6517. (e) Weyerstahl, P.; Zummack, W. *Chem. Ber.* **1975**, *108*, 377–378. (f) Gottschalk, F.-J.; Weyerstahl, P. *Ibid.* **1975**, *108*, 2799–2802. (g) Loozen, H. J. J. *J. Org. Chem.* **1975**, *40*, 520–521. (h) Loozen, H. J. J.; Godefroi, E. F.; Besters, J. S. S. M. *Ibid.* **1975**, *40*, 892–894. (i) Ponaras, A. A. *Tetrahedron Lett.* **1976**, 3105–3108. (j) Götschi, E.; Schneider, F.; Wagner, H.; Bernauer, K. *Helv. Chim. Acta* **1977**, *60*, 1416–1418. (k) Forbes, C. P.; Wenteler, G. L.; Wiechers, A. *J. Chem. Soc., Perkin Trans. 1*, **1977**, 2353–2355. (l) Kozikowski, A. P.; Ishida, H.; Chen, Y.-Y. *J. Org. Chem.* **1980**, *45*, 3350–3352.

(9) (a) van der Gen, A.; Wiedhaup, K.; Swoboda, J. J.; Dunathan, H. C.; Johnson, W. S. *J. Am. Chem. Soc.* **1973**, *95*, 2656–2663. (b) Bucort, R.; Pietrasanta, Y.; Pucci, B.; Rousselou, J. C.; Vignau, M. *Tetrahedron* **1975**, *31*, 3041–3047. (c) Stowell, J. C. *J. Org. Chem.* **1976**, *41*, 560–561.

(10) (a) Wiesner, C. J.; Tan, S.-H. *Chem. Ind. (London)* **1980**, 627–628. (b) Gössinger, E. *Tetrahedron Lett.* **1980**, *21*, 2229–2232.

(11) (a) Brattesani, D. N.; Heathcock, C. H. *J. Org. Chem.* **1975**, *40*, 2165–2170. (b) Overman, L. *Tetrahedron Lett.* **1975**, 1149–1152.

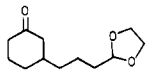
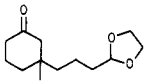
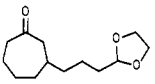
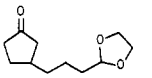
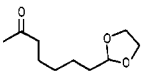
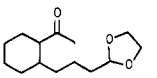
(12) Rieke, R. D.; Bales, S. E. *J. Am. Chem. Soc.* **1974**, *96*, 1775–1781.

(13) (a) Normant, J. F. *Synthesis* **1972**, 63–80. (b) Posner, G. H. *Org. React.* **1972**, *19*, 1–113. (c) *Ibid.* **1975**, *22*, 253–400. (d) Jukes, A. E. *Adv. Organomet. Chem.* **1974**, *12*, 215–322.

(14) House, H. O.; Chu, C.-Y.; Wilkins, J. M.; Umen, M. J. *J. Org. Chem.* **1975**, *40*, 1460–1469.

(15) (a) Wuts, P. G. M. *Synth. Commun.* **1981**, *11*, 139–140. (b) Theis, A. B.; Townsend, C. A. *Ibid.* **1981**, *11*, 157–166.

Table II. Cyclohexene Annulation

substrate	keto acetal (6)		% yield[a]	annulation product (7)	% yield[a]
		(a)	75		70 (60)[b]
		(b)	70[d]		45
		(c)	76		58
		(d)	38		85
		(e)	33 (66)[c]		52 (40)[b]
		(f)	69[d]		

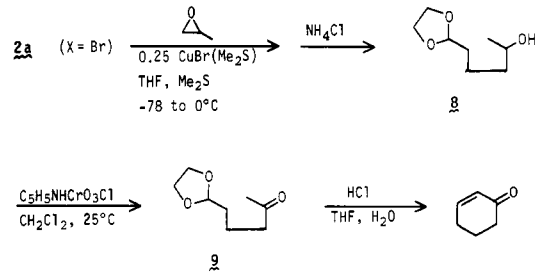
[a] Isolated yield after column chromatography. [b] Yield from one-flask procedure without isolation of **6**. [c] Yield from use of 2 equiv of **3b** instead of the usual 1.25 equiv. [d] Yield from the use of 0.50 equiv of $CuBr(Me_2S)$ instead of the usual 0.25 equiv.

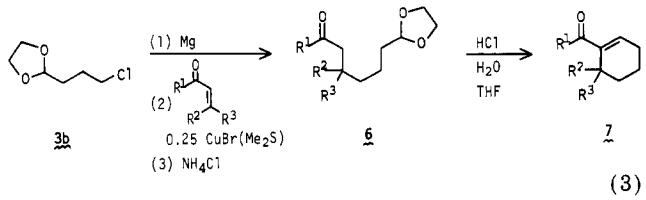
I) was isolated as the final product. This very direct preparation of **5d** is noteworthy, however, in that a very similar compound, the corresponding diketone, has been obtained previously by a five-step route also employing cyclopenten-3-one as the starting material.[17]

Since the time that we completed the development of the above route,[2] this methodology has also been employed in other laboratories for the preparation of possible precursors of pseudoguaianolides[18] and in total syntheses of isocomene,[19] modhephene,[20] and silphinene.[34] In addition, a related reaction sequence has been reported by Posner.[21]

Cyclohexene Annulation. The simple extension of the above work to the formation of cyclohexene derivatives employs the chloro acetal **3b** (X = Cl) as the starting material. This compound is obtained from commercially available 4-chlorobutyryl chloride by a two-step procedure described by Pleshakov.[22] The corresponding Grignard reagent **2b** (X = Cl) may be generated as described for **2a** above and then employed in a sequence of reactions exactly analogous to that developed for the cyclopentenes. The only signficant changes in conditions are that in comparison to the earlier route higher concentrations of hydrochloric acid and higher temperatures (see Experimental Section) are required to effect conversion of the initially obtained keto acetals **6** into the cyclohexenes **7**. Again, the overall sequence may be performed in two distinct steps (eq 3) or by a one-flask experiment in which the conjugate addition intermediates are not isolated but are treated with hydrochloric acid to give the cyclohexenes directly. Our results are summarized in Table II. Not surprisingly, cyclopenten-3-one and methyl vinyl ketone give lower than usual yields of the desired adducts, but the yield from the latter substrate may be improved through use of a 100% excess of the Grignard reagent. Conditions for significant improvement of the former were not found. In two other instances, 1-methylcyclohexen-3-one and 1-acetylcyclohexene, the use of larger amounts (0.50 equiv) of the copper catalyst gives improved yields of the adducts; when the usual 0.25 equiv is employed, 1,2-addition to the carbonyl groups of these ketones occurs to a significant extent. With respect to the further reactions of the keto acetals, the adduct **6f** is the only case that presents serious difficulties in obtaining the desired annulation product. Not expectedly, treatment of **6f** under various hydrolysis conditions gives complex mixtures of products, none of which has been characterized.

Scheme II





(3)

While this study was in its final stages, other workers also accomplished cyclohexene annulation by modifying the route described in our preliminary communication.[2] However, the only example reported by these later investigators was the preparation of **7a** derived from cyclohexen-3-one but through the use of 3 equiv of Grignard reagent.[23]

Other Uses of the Grignard Reagents. We have briefly investigated two other applications of the Grignard reagents **2** leading to ring formation. In the first of these, epoxides are used to alkylate the organomagnesium intermediates in the presence of copper catalyst.[24] A sequence of reactions starting with propylene oxide is shown in Scheme II. The hydroxy acetal **8** is obtained in 54% yield from the alkylation step. Oxidation with pyridinium chlorochromate[25] produces the keto acetal **9**, which when

(16) Dehydration of a derivative of **5d** has been accomplished straightforwardly using MsCl and DBN. See ref 20a.

(17) (a) Stetter, H.; Krüger-Hansen, I.; Rizk, M. *Chem. Ber.* **1961**, *94*, 2702–2707. (b) Eaton, P. E.; Muller, R. H. *J. Am. Chem. Soc.* **1972**, *94*, 1014–1016.

(18) Germroth, T. C. Ph.D. Dissertation, University of California, Berkeley, CA, 1979; *Dissertation Abstr. Int. B* **1980**, *41*, 196.

(19) Paquette, L. A.; Han, Y.-K. *J. Am. Chem. Soc.* **1981**, *103*, 1835–1838.

(20) (a) Oppolzer, W.; Marazza, F. *Helv. Chim. Acta* **1981**, *64*, 1575–1578. (b) Oppolzer, W.; Bättig, K. *Ibid.* **1981**, *64*, 2489–2491.

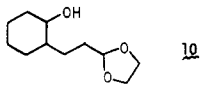
(21) Alexakis, A.; Chapdelaine, M. J.; Posner, G. H.; Runquist, A. W. *Tetrahedron Lett.* **1978**, 4205–4208.

(22) Pleshakov, M. G.; Vasil'ev, A. E.; Sarycheva, I. K.; Preobrazhenskii, N. A. *J. Gen. Chem. USSR (Engl. Transl.)* **1961**, *31*, 1433–1435.

(23) Abbott, R. E.; Spencer, T. A. *J. Org. Chem.* **1980**, *45*, 5398–5399.

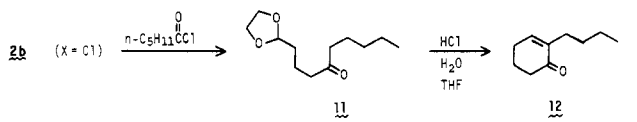
(24) For other examples of the reactions of organocopper compounds with epoxides, see: (a) Herr, R. W.; Wieland, D. M.; Johnson, C. R. *J. Am. Chem. Soc.* **1970**, *92*, 3813–3814. (b) Acker, R.-D. *Tetrahedron Lett.* **1977**, 3407–3410. (c) Marfat, A.; McGuirk, P. R.; Helquist, P. *J. Org. Chem.* **1979**, *44*, 3888–3901. (d) Huynh, C.; Derguini-Boumechal, F.; Linstrumelle, G. *Tetrahedron Lett.* **1979**, 1503–1506.

treated with hydrochloric acid gives cyclohexen-3-one (80% overall yield from 8). Although this route is a potentially general means of employing epoxides in annulation reactions, we have not explored it further except to use cyclohexene oxide in the alkylation step, in which case the hydroxy acetal **10** is obtained in a low yield of 26%. In each of these two cases, significant amounts of Wurtz coupling products are obtained.



10

The final reaction of **2b** that we have studied is acylation by hexanoyl chloride, which produces the keto acetal **11** in 66% yield (eq 4). A few examples of this type of acylation have been reported previously, although in one of these cases, the reaction was plagued by poor yields.[9a,c] In the present case when the product **11** is treated with hydrochloric acid, 2-butylcyclohexen-3-one (**12**) is obtained in 94% yield. This pathway is potentially applicable to a wide variety of substituted cycloalkenones.



(4)

Conclusion

We have shown that the acetal-containing Grignard reagents **2** are quite versatile for the construction of several types of carbocyclic systems by very direct and practical routes. As mentioned above, these and related reagents have already been demonstrated to be of considerable value in natural products synthesis.[18-20] Furthermore, the annulation products of types **5** and **7** bear a very close resemblance to not only the key intermediates in several other syntheses[26] but also to various natural products themselves.[27] In addition, the α,β-unsaturated ketone functionality of **5** and **7** is ripe for further transformations (e.g., conjugate additions, annulations, conversion into Diels–Alder dienes, etc.). Therefore, we are confident that the methodology reported in this paper will be subjected to continued applications in the future.

Experimental Section

General Procedures. All reactions of organometallic reagents and other air-sensitive materials were performed in flame-dried glassware under nitrogen by using double-manifold techniques.[28] Solutions of these materials were transferred with hypodermic needles. Tetrahydrofuran (THF) was distilled from dark-blue or dark-purple solutions of sodium benzophenone radical anion or dianion under nitrogen. The 2-(2-bromoethyl)-1,3-dioxolan,[8a] 2-(3-chloropropyl)-1,3-dioxolane,[22] and $CuBr(Me_2S)$[14] were prepared and purified according to the previously reported procedures. The commercially available reagents, including α,β-unsaturated carbonyl compounds, were distilled prior to use. Commercial anhydrous magnesium dichloride (Alfa) was used directly. Low temperatures were maintained through use of our previously described apparatus.[24c]

The ^1H NMR spectra were recorded at 60 MHz with a Varian EM-360 spectrometer or at 80 MHz with a Varian HFT-80 spectrometer. The NMR spectra were obtained from $CDCl_3$ solutions containing tetramethylsilane (Me_4Si) as the internal standard. The chemical shifts are expressed in parts per million (δ) downfield from Me_4Si, and the ^1H NMR peak areas are expressed as the number of hydrogen atoms (H). Mass spectra were recorded with Hewlett-Packard Model 2982A and AEI Model MS-30 mass spectrometers by using electron-impact ionization at 70 eV. The IR spectra were obtained with a Pye-Unicam Model SP-1000 on a Perkin-Elmer Model 727 spectrophotometer as neat liquid films and were calibrated with a polystyrene standard. Elemental analyses were performed by Galbraith Laboratories, Inc. The analytical results are given only when they agree with the calculated values within ±0.3%. In all other cases, the homogeneity of the compounds was demonstrated by careful GLC and TLC, and molecular formulas were determined by high-resolution mass spectroscopy. Preparative GLC was performed with a Varian Aerograph Model 900 gas chromatograph and analytical GLC was performed with a Hewlett-Packard Model 5711 gas chromatograph equipped with a flame-ionization detector, a linear temperature programmer, and a Hewlett-Packard Model 3380A electronic integrator. The following GLC columns were used: A, 6 ft × $^1/_8$ in. 5% OV-1; B, 6 ft × $^1/_8$ in. 5% OV-17; C, 6 ft × $^1/_2$ in. 5% SE-30; D, 6 ft × $^1/_2$ in. 5% OV-17.

General Procedure for Cyclopentene Annulation. Bicyclo[4.3.0]non-9-en-2-one (5a). Magnesium powder was generated under nitrogen from anhydrous magnesium dichloride (0.68 g, 7.1 mmol) and potassium (0.50 g, 13 mmol) in THF (10 mL) according to the procedure of Rieke.[12] To the heterogeneous mixture at 25 °C was added neat 2-(2-bromoethyl)-1,3-dioxolane[8a] (1.14 g, 6.3 mmol) with a syringe over a period of 2.5 min. After 20 min, the mixture was cooled to −78 °C, a solution of $CuBr(Me_2S)$[14] (0.33 g, 1.6 mmol) and dimethyl sulfide (3.0 mL) was added over a period of 3 min, the mixture was stirred at −78 °C for 1 h, and a solution of cyclohexen-3-one (0.48 g, 5.0 mmol) and ether (6 mL) was added with an addition funnel over a period of 4 h. The mixture was stirred at −78 °C for 10 h, allowed to warm up to 0 °C over a period of 6 h, and stirred at 0 °C for 2 h. After the mixture was quenched by the addition of a saturated aqueous solution (10 mL) of ammonium chloride (adjusted to pH 8 with aqueous ammonia), it was stirred at 25 °C in the air for 1.5 h. The dark-blue aqueous layer was removed, and the ether layer was washed with two additional 10-mL portions of water and a saturated aqueous solution (15 mL) of sodium chloride, dried over anhydrous magnesium sulfate, filtered, and concentrated by rotary evaporation to give 1.0 g of the crude 3-[2-(1,3-dioxolan-2-yl)ethyl]cyclohexanone (**4a**) as a yellow oil. Although this material was sufficiently pure for further transformation into **5a**, a small sample was purified by preparative GLC (column C, 150–200 °C): IR (neat) 2900, 1710, 1140, 1030 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.78 (t, J = 4 Hz, 1 H), 3.7–4.0 (m, 4 H), 1.1–2.6 (m, 13 H). Through use of this sample for calibration and of biphenyl as an internal standard, the yield of **4a** was found to be 85% by GLC (column C, 110–204 °C at 16 °C/min). The crude product was dissolved in a mixture of THF (18 mL) and a 0.1 N solution (2 mL) of hydrochloric acid at 25 °C. After being stirred at 25 °C for 72 h, the mixture was neutralized with a 5% aqueous sodium bicarbonate solution, diluted with ether, washed with three portions of water and one portion of saturated aqueous sodium chloride solution, dried over anhydrous magnesium sulfate, filtered, and concentrated by rotary evaporation. The residue was purified by column chromatography (silica gel, 2% acetone in methylene chloride) to give 0.51 g (89%) of **5a** as a colorless oil, which was homogeneous by TLC and GLC: IR (neat) 2900, 1682, 1615 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.70 (dd, J = 5.5, 2.5 Hz, 1 H), 0.7–3.3 (m, 11 H); mass spectrum (70 eV), m/e 136.0880 (M^+; 136.0885 calcd for $C_9H_{12}O$). Alternatively, the mixture resulting from the copper-catalyzed reaction of the Grignard reagent was quenched at 0 °C with the mixture of THF and 0.1 N hydrochloric acid instead of the aqueous ammonium chloride. The mixture

(25) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, 2647–2650.
(26) (a) Wender, P. A.; Lechleiter, J. C. *J. Am. Chem. Soc.* **1978**, *100*, 4321–4322. (b) Kok, P.; DeClerq, P.; Vandewall, M.; Declerq, J. P.; Germain, G.; Van Meerssche, M. *Tetrahedron Lett.* **1979**, 2063–2066. (c) Hiyama, T.; Shinoda, M.; Nozaki, H. *Ibid.* **1979**, 3529–3532. (d) Whitesell, J. K.; Matthews, R. S.; Minton, M. A.; Helbling, A. M. *J. Am. Chem. Soc.* **1981**, *103*, 3468–3472.
(27) (a) Rodriquez-Hahn, L.; Guzmán, A.; Romo, J. *Tetrahedron* **1968**, *24*, 477–483. (b) Harmatha, J.; Samek, Z.; Novotný, L.; Herout, V.; Sorm, F. *Tetrahedron Lett.* **1968**, 1409–1412. (c) Sakai, T.; Nakajima, K.; Yoshihara, K., Sakan, T.; Isoe, S. *Tetrahedron* **1980**, *36*, 3115–3119.
(28) (a) Shriver, D. F. "The Manipulation of Air-Sensitive Compounds"; McGraw-Hill: New York, NY, 1969. (b) Burlitch, J. M. "How to Use Ace No-Air Glassware"; Ace Glass: Vineland, NJ, 1971.

was stirred at 25 °C for 72 h, and the product was isolated as above to give a 62% yield of **5a** directly.

Analogous procedures were used for the following compounds.

6-Methylbicyclo[4.3.0]non-9-en-2-one (5b): prepared from 1-methylcyclohexen-3-one (0.56 mL, 5.0 mmol). Obtained as the intermediate was 3-methyl-3-[2-(1,3-dioxolan-2-yl)ethyl]cyclohexanone (**4b**) in 74% yield (GLC, column B, 110–210 °C at 16 °C/min, *n*-tetradecane internal standard). A pure sample was obtained by preparative GLC (column C, 160–240 °C): IR (neat) 2900, 1710, 1140, 1030 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.78 (t, J = 4 Hz, 1 H), 3.6–4.0 (m, 4 H), 1.0–2.5 (m, 12 H), 0.92 (s, 3 H). Hydrolysis as in the general procedure and purification of the product by column chromatography (silica gel, 2% acetone in methylene chloride) afforded 0.43 g (77%) of **5b** as a colorless oil that was homogeneous by TLC and GLC: IR (neat) 3070, 2940, 1685, 1160 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.45 (t, J = 2.5 Hz, 1 H), 1.5–2.7 (m, 10 H), 1.10 (s, 3 H); mass spectrum (70 eV), m/e 150.1078 (M^+, 150.11044 calcd for $C_{10}H_{14}O$). The direct, one-step procedure gave a 57% yield of **5b**.

Bicyclo[5.3.0]dec-10-en-2-one (5c): prepared from cyclohepten-3-one (0.55 g, 5.0 mmol). Intermediate 3-[2-(1,3-dioxolan-2-yl)ethyl]cycloheptanone (**4c**) was obtained in 87% yield (GLC, column A, 110–240 °C at 16 °C/min, *n*-tetradecane internal standard). A pure sample was obtained by preparative GLC (column C, 160–240 °C): IR (neat) 2900, 1702, 1140 cm^{-1}; ^1H NMR ($CDCl_3$) 4.85 (t, J = 4 Hz, 1 H), 3.6–4.1 (m, 4 H), 0.9–2.9 (m, 15 H). Hydrolysis followed by purification by column chromatography (silica gel, methylene chloride) afforded 0.52 g (80%) of **5c** as a colorless oil that was homogeneous by TLC and GLC: IR (neat) 3060, 2910, 2850, 1678, 1607, 830 cm^{-1}; ^1H NMR ($CDCl_3$) 6.72 (br d, J = 2 Hz, 1 H), 1.0–3.3 (m, 13 H).

Anal. Calcd for $C_{10}H_{14}O$: C, 79.95; H, 9.31. Found: C, 79.71; H, 9.34.

2-Oxobicyclo[3.3.0]nonan-8-ol (5d): prepared from cyclopenten-3-one (0.88 mL, 10 mmol). Intermediate 3-[2-(1,3-dioxolan-2-yl)ethyl]cyclopentanone (**4d**) was obtained in 77% yield (GLC, column B, 110–220 °C at 16 °C/min, *n*-hexadecane internal standard). A pure sample was obtained by preparative GLC (column D): IR (neat) 2920, 1740, 1150, 1040 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.86 (br t, J = 4 Hz, 1 H), 3.7–4.1 (m, 4 H), 1.1–2.7 (m, 11 H). Hydrolysis followed by purification by column chromatography (silica gel, methylene chloride) afforded 0.58 g (54%) of **5d** as a colorless oil that was homogeneous by TLC and GLC: IR (neat) 3420, 2940, 1730, 1370, and 1010 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.1–4.5 (m, 1 H), 2.9–3.3 (m, 1 H), 1.2–2.8 (m, 10 H); mass spectrum (70 eV), m/e 140.0856 (M^+; 140.0837 calcd for $C_8H_{12}O_2$).

General Procedure for Cyclohexene Annulation. Bicyclo[4.4.0]dec-10-en-2-one (7a). Magnesium turnings (0.60 g, 25 mmol) were ground for a few minutes with a mortar and pestle and were immediately placed into a nitrogen-filled flask. A solution of 2-(3-chloropropyl)-1,3-dioxolane[22] (1.2 mL, 8.3 mmol), 1,2-dibromoethane (0.05 mL), and THF (1.6 mL) was added at 25 °C, and the mixture was warmed and stirred in a 70 °C bath at which temperature the reaction began with no need for further measures to initiate Grignard reagent formation. The reaction flask was then placed in a 25 °C bath, and the mixture was stirred for 30 min, diluted with additional THF (5 mL), stirred for 1.25 h, and cooled to −78 °C. A solution of $CuBr(Me_2S)$[14] (0.41 g, 2.0 mmol) and dimethyl sulfide (4 mL) was added dropwise, the mixture was stirred at −78 °C for 1 h, a solution of cyclohexen-3-one (0.65 mL, 6.8 mmol) and diethyl ether (7 mL) was added dropwise over a 7-min period, and the mixture was stirred at −78 °C for 2.5 h and transferred to an ice–water bath. After being stirred at 0 °C for 5 min, the mixture was quenched by the addition of a saturated aqueous solution (5 mL) of ammonium chloride (adjusted to pH 8 with aqueous ammonia), and the product was isolated as in the general procedure for cyclopentene annulation. The crude product (1.28 g) was purified by flash column chromatography[29] (silica gel, 1:1 hexanes/ethyl acetate) to give 1.05 g (75%) of 3-[3-(1,3-dioxolan-2-yl)propyl]cyclohexanone (**6a**) as a colorless oil. The analytical sample was obtained by bulb-to-bulb distillation [oven temperature 80 °C (0.2 torr)]: IR (neat) 2950, 1712 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.83 (t, J = 4.8 Hz, 1 H), 3.90 (m, 4 H), 1.15–2.55 (m, 15 H).

Anal. Calcd for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50. Found: C, 67.76; H, 9.53.

The intermediate **6a** (0.150 g, 0.71 mmol) was dissolved in a solution of THF (3 mL) and 1 N hydrochloric acid (2.5 mL) and heated for 2 h in a bath at 75–80 °C. The reaction mixture was cooled to 25 °C and treated as in the cyclopentene annulation procedure to give 0.101 g of crude product. Flash column chromatography (silica gel, 3.1:1 hexanes/ethyl acetate) provided 0.075 g (69%) of **7a** as a colorless oil having spectroscopic properties in agreement with earlier data:[23,30] IR (neat) 2915, 2860, 1685, 1617 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.65 (m, 1 H), 1.1–2.6 (m, 13 H). Alternatively, the mixture resulting from the copper-catalyzed reaction was hydrolyzed with a solution of THF and hydrochloric acid as described above to give a 60% yield of **7a** directly.

Analogous procedures were used for the following compounds.

6-Methylbicyclo[4.4.0]dec-10-en-2-one (7b): prepared from 1-methylcyclohexen-3-one and 0.5 mol equiv of $CuBr(Me_2S)$. The reaction mixture was stirred at −78 °C for 17.5 h and was allowed to warm up to 0 °C over a period of 4 h before being quenched. The crude product was purified by flash column chromatography (silica gel, 0.6:1 hexanes/ethyl acetate) to give a 70% yield of 3-methyl-3-[3-(1,3-dioxolan-2-yl)propyl]cyclohexanone (**6b**). The analytical sample was obtained by bulb-to-bulb distillation [oven temperature 95 °C (0.3 torr)]: IR (neat) 2960, 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.82 (t, J = 4.8 Hz, 1 H), 3.90 (m, 4 H), 1.05–2.40 (m, 14 H), 0.93 (s, 3 H).

Anal. Calcd for $C_{13}H_{22}O_3$: C, 68.99; H, 9.80. Found: C, 68.80; H, 9.84.

Hydrolysis of this intermediate in a 10:1 mixture of THF and 1 N hydrochloric acid at reflux for 13 h followed by purification of the product by flash column chromatography (silica gel, 5:1 hexanes/ethyl acetate) afforded a 45% yield of **7b** as a colorless oil having spectroscopic properties in accord with earlier data:[31] IR (neat) 2940, 1688, 1620 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.43 (t, J = 4 Hz, 1 H), 1.25–2.50 (m, 12 H), 1.04 (s, 3 H).

Bicyclo[5.4.0]undec-11-en-2-one (7c): prepared from cyclohepten-3-one. The intermediate was purified by flash column chromatography (silica gel, 1:1 hexanes/ethyl acetate) to give a 76% yield of 3-[3-(1,3-dioxolan-2-yl)propyl]cycloheptanone (**6c**). The analytical sample was obtained by bulb-to-bulb distillation [oven temperature 105 °C (0.3 torr)]: IR (neat) 2930, 1700 cm^{-1}; ^1H NMR ($CDCl_3$) 4.82 (t, J = 4.8 Hz, 1 H), 3.90 (m, 4 H), 1.15–2.55 (m, 17 H).

Anal. Calcd for $C_{13}H_{22}O_3$: C, 68.99; H, 9.80. Found: C, 68.90; H, 9.94.

This intermediate was heated in 7 N hydrochloric acid at 80 °C for 2 h. Purification of the product by flash column chromatography (silica gel, 5:1 hexanes/ethyl acetate) gave a 58% yield of **7c** which was >95% pure (GLC, column A, 150–260 °C at 8 °C/min): IR (neat) 2930, 2860, 1685, 1615 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.80 (br t, 1 H), 1.15–2.70 (m, 15 H); mass spectrum (70 eV), m/e 164.1204 (M^+; 164.1202 calcd for $C_{11}H_{16}O$). When the hydrolysis was performed in a mixture of dioxane and 1 N hydrochloric acid, the yield of **7c** was 45%.

Bicyclo[4.3.0]non-1-en-9-one (7d): prepared from cyclopenten-3-one. The intermediate was purified by flash column chromatography (silica gel, 2:1 ethyl acetate/hexanes) to afford a 38% yield of 3-[3-(1,3-dioxolan-2-yl)propyl]cyclopentanone (**6d**). The analytical sample was obtained by bulb-to-bulb distillation [oven temperature 60 °C (0.2 torr)]: IR (neat) 2960, 2900, 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.83 (t, J = 4.8 Hz, 1 H), 3.90 (m, 4 H), 1.25–2.40 (m, 13 H).

Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15. Found: C, 66.40; H, 9.30.

Hydrolysis in a 1:1 mixture of THF and 1 N hydrochloric acid at 25 °C for 48 h and purification by flash column chromatography (silica gel, 3.5:1 hexanes/ethyl acetate) gave an 85% yield of **7d** as a colorless oil having spectroscopic properties in agreement with earlier data:[32] IR (neat) 2940, 1720, 1650 cm^{-1}; ^1H NMR

(29) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923–2925.

(30) House, H. O.; Thompson, H. W. *J. Org. Chem.* **1961**, *26*, 3729–3734.

(31) Boeckman, R. K.; Silver, S. M. *J. Org. Chem.* **1975**, *40*, 1755–1759.

(32) Paquette, L. A.; Henzel, R. P.; Eizember, R. F. *J. Org. Chem.* **1973**, *38*, 3257–3268.

($CDCl_3$) δ 6.50 (m, 1 H), 1.70–2.85 (m, 11 H).

1-Acetylcyclohexene (7e): prepared from methyl vinyl ketone. The intermediate was purified by flash column chromatography (silica gel, 2:1 ethyl acetate/hexanes) to give a 33% yield of 2-(6-oxoheptyl)-1,3-dioxolane (**6e**). Further purification by bulb-to-bulb distillation [oven temperature 40 °C (0.1 torr)]gave a sample that was homogeneous by TLC: IR (neat) 2950, 1712 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.81 (t, J = 4.8 Hz, 1 H), 3.89 (m, 4 H), 2.43 (m, 2 H), 2.22 (s, 3 H), 1.20–2.05 (m, 8 H); mass spectrum (70 eV), m/e 186.1222 (M^+; 186.1256 calcd for $C_{10}H_{18}O_3$). Hydrolysis at 75–80 °C for 2 h with a 1:1 mixture of THF and 1 N hydrochloric acid followed by flash column chromatography (silica gel, 5:1 hexanes/ethyl acetate) afforded a 52% yield of **7e** as a colorless oil that was identical with a commercial sample (Aldrich) by direct spectroscopic comparison: IR (neat) 3040, 2940, 1665, 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.86 (m, 1 H), 2.08–2.43 (m, overlapping a singlet at 2.27, 7 H), 1.50–1.75 (m, 4 H). Alternatively, the direct one-step procedure produced **7e** in an overall yield of 40%.

2-[3-(1,3-Dioxolan-2-yl)propyl]-1-acetylcyclohexane (6f): prepared from 1-acetylcyclohexene according to the procedure employed for the preparation of intermediate **6b**. The product was purified by flash column chromatography (silica gel, 1.3:1 hexanes/ethyl acetate) to give a 69% yield of **6f** as a colorless oil. The analytical sample was obtained by bulb-to-bulb distillation [oven temperature 95 °C (0.2 torr)]: IR (neat) 2940, 1704 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.82 (t, J = 4.8 Hz, 1 H), 3.88 (m, 4 H), 2.50 (m, 1 H), 1.0–2.2 (m, overlapping a singlet at 2.10, 18 H).

Anal. Calcd for $C_{14}H_{24}O_3$: C, 69.96; H, 10.06. Found: C, 69.69; H, 10.10.

Copper-Promoted Reaction of the Grignard Reagent with Epoxides. 2-(4-Hydroxypentyl)-1,3-dioxolane (8) and Conversion to Cyclohexen-3-one. The Grignard reagent was formed from 2-(2-bromoethyl)-1,3-dioxolane (0.18 mL, 1.5 mmol), 1,2-dibromoethane (9 μL), and magnesium turnings (0.11 g, 4.5 mmol) in THF (2 mL) at 30–35 °C. The mixture was cooled to −78 °C, a solution of $CuBr(Me_2S)$ (0.075 g, 0.37 mmol) and dimethyl sulfide (0.7 mL) was added dropwise, and the mixture was stirred at −78 °C for 1 h. After propylene oxide (0.10 mL, 1.5 mmol) was added with a chilled syringe, the mixture was allowed to warm up to −30 °C over a 3.5-h period, stirred at that temperature for 17 h, allowed to warm to 0 °C over a 1.5-h period, and then quenched with the usual ammonium chloride/ammonia solution. The standard workup procedure gave 0.172 g of crude product that was purified by flash column chromatography (silica gel, 2:1 ethyl acetate/hexanes) to afford 0.130 g (54%) of **8** as a colorless oil. The analytical sample was obtained by bulb-to-bulb distillation [oven temperature 50 °C (0.25 torr)]: IR (neat) 3440, 2980, 2905, 1410, 1145 cm^{-1}; ^1H NMR δ 4.83 (t, J = 4 Hz, 1 H), 3.90 (m, 5 H), 2.90 (s, 1 H), 1.54 (m, 6 H), 1.18 (d, J = 6 Hz, 3 H).

Anal. Calcd for $C_8H_{16}O_3$: C, 59.98; H, 10.07. Found: C, 59.82; H, 10.18.

To a suspension of pyridinium chlorochromate[25] (0.51 g, 2.4 mmol) in anhydrous methylene chloride (3 mL) at 25 °C was added a solution of **8** (0.20 g, 1.2 mmol) in methylene chloride (1 mL). The black mixture was stirred for 1.5 h, diluted with diethyl ether (5 mL), filtered through a pad of Florisil, dried over anhydrous magnesium sulfate, and concentrated by rotary evaporation to give 0.16 g (84%) of 2-(4-oxopentyl)-1,3-dioxolane (**9**) as a yellow oil that showed one spot by TLC and that was >95% pure by GLC (column A, 110–240 °C at 16 °C/min): IR (neat) 2940, 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.83 (m, 1 H), 3.88 (m, 4 H), 2.50 (m, 2 H), 2.10 (s, 3 H), 1.65 (m, 4 H). Without purification, this compound was treated with a mixture of THF (2.5 mL) and 1 N hydrochloric acid (2 mL) in an 80 °C bath for 2 h. The usual workup procedure provided 0.093 g (80%) of cyclohexen-3-one, which was identical with a commercial sample (Aldrich) by direct spectroscopic comparison: IR (neat) 3040, 2940, 1670, 1610 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.90 (m, 1 H), 5.88 (m, 1 H), 1.70–2.60 (m, 6 H).

2-[2-(1,3-Dioxolan-2-yl)ethyl]cyclohexanol (10). This compound was prepared according to the preceding procedure through copper-promoted reaction of the Grignard reagent with cyclohexene oxide (2-mmol scale) at −30 °C for 24 h followed by warming to 0 °C. The principle side product was the Wurtz coupling product derived from the Grignard reagent. Flash column chromatography (silica gel, 1.8:1 ethyl acetate/hexanes) of the crude product mixture afforded a 26% yield of **10** as a colorless oil. A homogeneous (TLC, GLC) sample was obtained by bulb-to-bulb distillation [oven temperature 85 °C (0.25 torr)]: IR (neat) 3440, 2940, 2875, 1408, 1140 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.83 (m, 1 H), 3.89 (m, 4 H), 3.70 (m, 1 H), 2.57 (s, 1 H), 0.95–2.55 (m, 13 H); mass spectrum (70 eV), m/e 200.1403 (M^+; 200.1412 calcd for $C_{11}H_{20}O_3$).

Reaction of the Grignard Reagent with an Acyl Chloride and Conversion of the Product to 2-Butylcyclohexen-3-one (12). The Grignard reagent was generated under the usual conditions from 2-(3-chloropropyl)-1,3-dioxolane (0.23 mL, 1.6 mmol), 1,2-dibromoethane (10 μL), and magnesium turnings (0.12 g, 5.0 mmol) in THF (1.6 mL). The solution was added over a 10-min period with a syringe to hexanoyl chloride (0.22 mL, 1.6 mmol) in THF (1.3 mL) at −78 °C under nitrogen. The mixture was stirred at −78 °C for 30 min and then allowed to warm up to 25 °C over a period of 1.75 h. After the reaction mixture was concentrated by rotary evaporation, water was added to the residual oil, and the mixture was extracted with hexanes. The extract was washed with 5% aqueous sodium carbonate and saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate, filtered, and concentrated by rotary evaporation to give 0.247 g of yellow oil. Purification by flash column chromatography (silica gel, 3:1 hexanes/ethyl acetate) afforded 0.226 g (66%) of 2-(4-oxononyl)-1,3-dioxolane (**11**) as a colorless oil that was >95% pure according to GLC (column A, 150–280 °C at 8 °C/min): IR (neat) 2950, 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.84 (m, 1 H), 3.89 (m, 4 H), 2.46 (m, 4 H), 1.05–1.95 (m, 10 H), 0.88 (m, 3 H). A portion (0.148 g, 0.69 mmol) of this product was treated in THF (3 mL) and 1 N hydrochloric acid (2.4 mL) in an 80 °C bath for 2 h. The usual workup procedure afforded 0.102 g (94%) of **12** as a colorless oil having spectroscopic properties in agreement with earlier data:[33] IR (neat) 2950, 2890, 1675, 1630, 1378 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.70 (br t, J ≃ 4 Hz, 1 H), 1.65–2.70 (m, 8 H), 1.07–1.65 (m, 4 H), 0.89 (br t, J ≃ 5 Hz, 3 H).

Acknowledgment. We are grateful to the National Institutes of Health (Grant No. CA 22741) for the financial support of this work.

Registry No. **3a**, 18742-02-4; **3b**, 16686-11-6; **4a**, 70147-63-6; **4b**, 70147-64-7; **4c**, 70147-62-5; **4d**, 70147-65-8; **5a**, 50785-10-9; **5b**, 40730-44-7; **5c**, 70147-66-9; **5d**, 70147-61-4; **6a**, 75506-74-0; **6b**, 83333-58-8; **6c**, 83333-59-9; **6d**, 83333-60-2; **6e**, 83333-61-3; **6f**, 83333-62-4; **7a**, 24037-79-4; **7b**, 54339-54-7; **7c**, 83333-63-5; **7d**, 40954-63-0; **7e**, 932-66-1; **8**, 78647-35-5; **9**, 4421-14-1; **10**, 83333-64-6; **11**, 83333-65-7; **12**, 34737-39-8; CuBr, 7787-70-4; cyclohexen-3-one, 930-68-7; 1-methylcyclohexen-3-one, 1193-18-6; cyclohepten-3-one, 1121-66-0; cyclopenten-3-one, 930-30-3; methyl vinyl ketone, 78-94-4; propylene oxide, 75-56-9; cyclohexene oxide, 286-20-4; hexanoyl chloride, 142-61-0.

(33) Taylor, K. G.; Hobbs, W. E.; Clark, M. S.; Chaney, J. *J. Org. Chem.* **1972**, *37*, 2436–2443.

(34) Paquette, L. A.; Leone-Bay, A. *J. Org. Chem.* **1982**, *47*, 4173–4174.