A General Method for the Preparation of γ-Substituted Cyclohexenals and Cycloheptenals†

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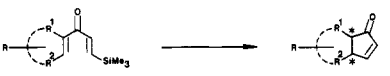
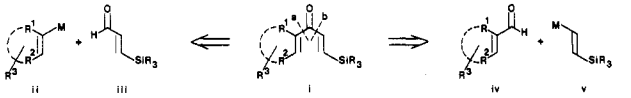
A general procedure for the preparation of γ-substituted or β′-unsaturated cycloalkenals is described. Starting from 2-cycloalkenones substituents may be introduced as nucleophiles by 1,4-addition followed by trapping of the regiospecifically generated enolate (86–92%). Peracid oxidation of the enol silane derivative produces an α-hydroxy ketone which, after protection (70–93%), is homologated to an enol ether by a Horner–Wittig reaction. Mild hydrolysis of the labile vinylogous acetal produces the aldehydes in good yields (62–75%). Advantages of this method in comparison to known procedures are discussed as are other unsuccessful approaches to this substitution pattern.

We have recently described the silicon-directed Nazarov reaction as a general method for the regio- and stereoselective annelation of 2-cyclopentenones[1a–c] (eq 1). The



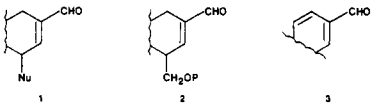
(1)

versatility of this process hinges on the accessibility of the precursors, β-silyl divinyl ketones. Two simple disconnections have been explored as indicated in eq 2.[2] For-



(2)

mation of bond a involves reaction of a cycloalkenyl lithium species (ii) with a 3-silylpropenal derivative. General access to ii via the Shapiro reaction and an improved synthesis of iii[1d,e] have been described.[1a] Creation of bond b entails addition of a β-silylethenyl organometallic derivative[2b,c] (v; M = Li, MgX) with α,β-unsaturated aldehyde iv. Compounds of the general type iv are available by a number of routes[3] and we have used these methods to prepare simple representatives. However, for certain specific synthetic objectives, we required access to substrates illustrated by the structures **1**, **2**, and **3** below. Of

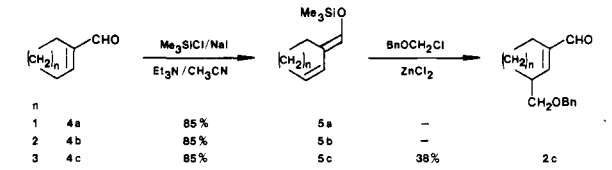


the reported methods for the synthesis of α,β-unsaturated aldehydes, only one, the introduction of a formyl group followed by protection, alkylation, reduction and hydrolysis[3a–c] seemed applicable. However, limitations on the type of alkylating agents compatible with this sequence rendered it inappropriate. The other methods suffer from either a difficult reduction,[3d–f] a lack of stereochemical control when introducing the olefin,[3g–j] or the inability to introduce a substituent in the γ-position.[3g–q] The purpose of this paper is to describe a new, general preparation of unsaturated aldehydes that overcomes these problems and provides for the structural types **1**–**3**.

Results

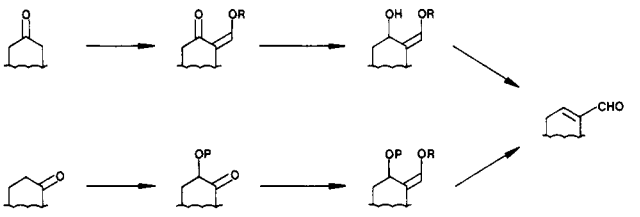
(A) γ Alkylation. We initially felt that problems with regioselectivity and alkylation could be overcome by introducing the desired substituent after the enal was in place. Lewis acid catalyzed electrophilic γ alkylation of a trimethylsilyl dienol ether[4] was attempted with cyclic dienol ethers as shown in Scheme I.

Scheme I



n					
1	4a	85%	5a	–	
2	4b	85%	5b	–	
3	4c	85%	5c	38%	2c

Scheme II



† This paper is based in part on the Ph.D. thesis of T.K.J., University of Illinois, Urbana, 1984.

‡ Fellow of the A. P. Sloan Foundation 1985–1987. NSF Presidential Young Investigator 1985–1990.

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(2) A third approach involving the three component coupling of a vinyl triflate carbon monoxide and a vinyl stannane has been reported recently.[2a] (a) Crisp, G. T.; Scott, W. J.; Stille, J. K. *J. Am. Chem. Soc.* **1984**, *106*, 7500. (b) Mironov, V. F.; Maksimova, N. G. *Bull. Acad. Sci. USSR, Div. Chem. Sci. (Engl. Transl.)* **1960**, 1911. (c) Cunico, R. F.; Clayton, F. J. *J. Org. Chem.* **1976**, *41*, 1480.

(3) Formylation, protection, reduction–hydrolysis: (a) Bernstein, P. R. *Tetrahedron Lett.* **1979**, 1015. (b) Church, R. F.; Ireland, R. E.; Marshall, J. A. *J. Org. Chem.* **1962**, *27*, 1118. (c) Ireland, R. E.; Marshall, J. A. *J. Org. Chem.* **1962**, *27*, 1615. Vilsmeier formylation, reduction: (d) Traas, P. C.; Takken, H. J.; Boelens, H. *Tetrahedron Lett.* **1977**, 2027. (e) Paquette, L. A.; Johnson, B. A.; Hinga, F. M. In "Organic Syntheses"; Baumgarten, H. E., Ed.; Wiley: New York, 1973, Collect. Vol. 5, p 215. (f) Heathcock, C. H.; Clark, R. D. *J. Org. Chem.* **1973**, *38*, 3658. Shapiro reaction: (g) Chamberlain, A. R.; Stemke, J. E.; Bond, F. T. *J. Org. Chem.* **1978**, *43*, 147. Vinylsilanes: (h) Yamamoto, K.; Yoshitake, J.; Qui, N. T.; Tsuji, J. *Chem. Lett.* **1978**, 859. (i) Yamamoto, K.; Nunokawa, O.; Tsuji, J. *Synthesis* **1977**, 721. Photooxygenation of methyl enol ethers: (j) Rousseau, G.; LePerchel, P.; Conia, J. M. *Synthesis* **1978**, 67. Benzothiazoles: (k) Corey, E. J.; Boger, D. L. *Tetrahedron Lett.* **1978**, 5. (l) Liso, G.; Trapani, G.; Reho, A.; Latrofa, A. *Tetrahedron Lett.* **1981**, *22*, 1641. Pyrolysis of epoxy sulfoxides: (m) Reutrakul, V.; Kanghae, W. *Tetrahedron Lett.* **1977**, 1377. (n) Taber, D. F.; Gunn, B. P. *J. Org. Chem.* **1979**, *44*, 450. (o) Durst, T.; Tin, K.-C. *Tetrahedron Lett.* **1970**, 2369. Nitromethyl alkenes: (p) Ho, T.-L.; Wong, C. M. *Synthesis* **1974**, 196. (q) Hogg, J. L.; Goodwin, T. E.; Nave, D. W. *Org. Prep. Proc. Intl.* **1978**, 9.

(4) (a) Ishida, A.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 2077. (b) Mukaiyama, T.; Ishida, A. *Chem. Lett.* **1975**, 1201. For a review of Lewis acid induced alkylation, see (c) Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 96.

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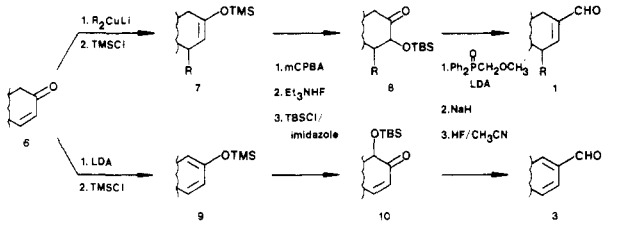
Scheme III

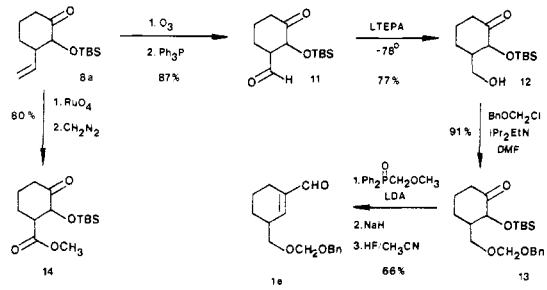


The enal was transformed into a trimethylsilyl dienol ether with in situ generated trimethylsilyl iodide.[5] Benzyl chloromethyl ether was chosen as the electrophile to provide a protected hydroxymethyl group. The alkylation worked smoothly only for **5c**; the other silyl ethers rapidly polymerized upon exposure to $ZnCl_2$. The alkylation reaction yielded two major products of alkylation (α and γ regioisomers[6]), in a ratio of 1:1.4, respectively (by GC). Experiments with other Lewis acids resulted in (1) little reaction ($ZnCl_4$, CuCl), (2) polymerization ($SnCl_4$), or (3) predominantly α alkylation (9:1/α:γ, $FeCl_3$). These failures led us to try to introduce the substituent at an earlier stage by alkylation of protected formyl ketones. The problems associated with this approach will be addressed in the Discussion section of this paper.

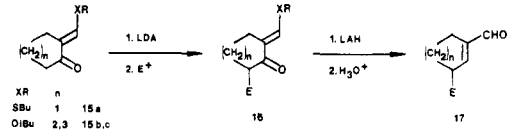
(B) Homologation of Enones. Careful consideration of the difficulties experienced with alkylation of formyl ketones prompted us to explore an alternate route to the intermediate hydroxy enol ether that arises from 1,2-hydride reduction of a protected formyl ketone (Scheme II). A Horner–Wittig reaction with (methoxymethyl)diphenylphosphine oxide[7] on a protected α-hydroxy ketone provides this intermediate. Rubottom and Gruber[8] have reported that *m*-chloroperoxybenzoic acid (mCPBA) oxidation of trimethylsilyl enol ethers produces α-trimethylsiloxy ketones. Our aldehyde synthesis couples these reactions with a 1,4-conjugate addition or enolization and trapping sequence with Me_3SiCl as shown in Scheme III.

In the forward direction, conjugate addition or enolization and trapping provide a silyl enol ether which is oxidized with mCPBA as described by Rubottom and Gruber (−15 °C to 25 °C, hexane). The trimethylsilyl group must be removed (Et_3NHF, CH_2Cl_2, 25 °C) and replaced with the less reactive *tert*-butyldimethylsilyl group (*t*-$BuMe_2SiCl$, imidazole, DMF, 25 °C) in order to perform the Horner–Wittig reaction. The trimethylsilyl group cannot be substituted by a *tert*-butyldimethylsilyl group in the oxidation step because the bulkier silyl group does not migrate cleanly. Using the method of Warren,[7] (methoxymethyl)diphenylphosphine oxide is deprotonated (LDA, 0 °C) and cooled (−78 °C), and the protected hydroxy ketone is added. The adduct is isolated and treated with NaH in THF to induce elimination. The crude enol ether is then subjected to HF/CH_3CN (5:95)[9] to remove the silyl protecting group. The enol ether is rapidly hydrolyzed under the reaction conditions to provide the desired aldehyde. Table I summarizes our results from a variety of ketones.

Scheme IV



Scheme V



Several comments are in order. Only those intermediates shown are purified and characterized; all others are used in crude form. Purification could be achieved in all cases by distillation; only the aldehydes required chromatography to remove phosphorus containing impurities. The deprotection–hydrolysis is very rapid. The intermediate hydroxy enol ethers are not detectable by TLC analysis as they are from hydride reductions of protected formyl ketones. This is probably due to the two-phase nature of the latter hydrolysis.

(C) Introduction of the γ-Hydroxymethyl Group. The sequences outlined above solved two of our objectives. The third, installation of a protected hydroxymethyl group, remained. All attempts to form a cuprate from [(benzyloxy)methyl]lithium[10,11] failed, so we explored the use of a vinyl substituent as a hydroxymethyl synthetic equivalent as shown in Scheme IV. Ozonolysis of **8a** followed by reduction with Ph_3P produces aldehyde **11**. Selective reduction of the aldehyde functionality is accomplished by the method of Krishnamurthy[12] with lithium tris[(3-ethyl-3-pentyl)oxy]aluminum hydride (LTEPA). No diol was detected by TLC analysis. All attempts to protect alcohol **12** with a benzyl group failed. The alkoxide was unreactive toward benzyl bromide with sodium or potassium as a counterion under a variety of conditions (THF or Me_2SO, crown ether, Bu_4NI) and decomposed upon warming. Attempts to introduce the benzyl group with thallous ethoxide[13] or with in situ generated benzyl triflate[14] also failed.[15] However, benzyl chloromethyl ether (*i*-Pr_2EtN, DMF) reacted smoothly to provide **13**. The homologation and hydrolysis proceeded readily to yield the desired aldehyde, **1e**, in 35% yield from 2-cyclohexenone. Olefin **8a** was also oxidized with ruthenium tetroxide by the method of Sharpless[16] to produce

(5) Cazeau, P.; Moulines, F.; Laporte, O.; Duboudin, F. *J. Organomet. Chem.* **1980**, *201*, C9-C13.

(6) The γ-alkylated product could easily be isolated in a pure form by chromatography. The α-alkylated isomer was contaminated with many other reaction products of the same R_f by TLC analysis.

(7) (a) Earnshaw, C.; Wallis, C. J.; Warren, S. *J. Chem. Soc., Chem. Commun.* **1977**, 314. (b) Earnshaw, C.; Wallis, C. J.; Warren, S. *J. Chem. Soc., Perkin Trans. 1* **1979**, 3099.

(8) Rubottom, G. M.; Gruber, J. M. *J. Org. Chem.* **1978**, *43*, 1599.

(9) Newton, R. F.; Reynolds, D. P.; Finch, M. A. W.; Kelly, D. R.; Roberts, S. M. *Tetrahedron Lett.* **1979**, 3981.

(10) Still, W. C. *J. Am. Chem. Soc.* **1978**, *100*, 1481.

(11) Corey, however, has reported forming a cuprate from (*tert*-butoxymethyl)lithium: Corey, E. J.; Eckrich, T. M. *Tetrahedron Lett.* **1983**, *24*, 3165.

(12) Krishnamurthy, S. *J. Org. Chem.* **1981**, *46*, 4628.

(13) Kalinowski, H.-O.; Crass, G.; Seebach, D. *Chem. Ber.* **1981**, *114*, 477.

(14) (a) Lemieux, R. U.; Kondo, T. *Carbohydr. Res.* **1974**, *35*, C4-C6. (b) Berry, J. M.; Hall, L. D. *Ibid.* **1976**, *47*, 307.

(15) The difficulty in introducing a benzyl group is not associated with the silyl protecting group. Protection of the hydroxy ketone with benzyl chloromethyl ether followed by ozonolysis and reduction produces alcohol vi which also will not yield to protection with a benzyl group.

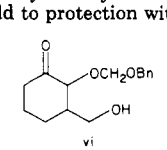
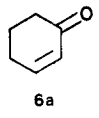
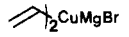
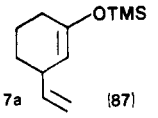
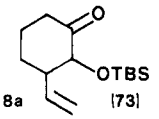
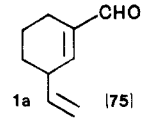
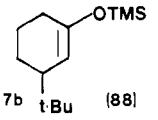
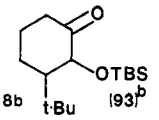
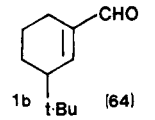
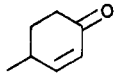
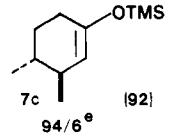
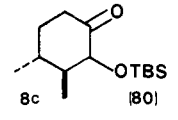
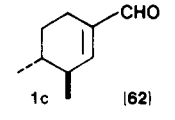
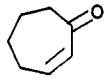
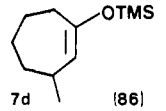
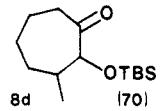
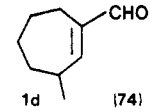
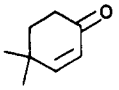
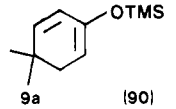
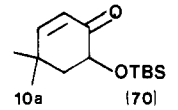
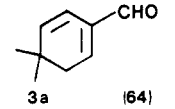
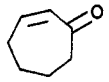
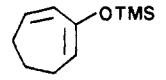
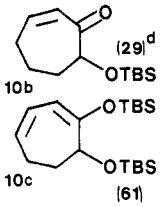
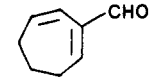


Table I. Unsaturated Aldehydes from Enones via Hydroxy Ketones[a]

entry	enone	cuprate or base	enol ether (yield, %)	α-oxy ketone (yield, %)	aldehyde (yield, %)	overall yield, %
1	 6a		 7a (87)	 8a (73) 60/40[e]	 1a (75)	48
2	 6a	t-BuPhSCuLi	 7b (88)	 8b (93)[b] 90/10[e]	 1b (64)	52
3	 6b	Me_2CuLi	 7c (92) 94/6[e]	 8c (80)	 1c (62)	46[c]
4	 6c	Me_2CuLi	 7d (86)	 8d (70) 88/12[e]	 1d (74)	45
5	 6d	LDA	 9a (90)	 10a (70)	 3a (64)	40
6	 6c	LDA	 9b (92)	 (29)[d] 10b 10c (61)	 3b (57)	15

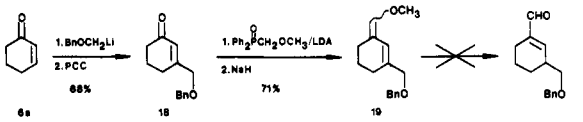
[a] All yields refer to distilled analytically pure materials and are not optimized. [b] Introduction of the *t*-$BuMe_3Si$ group required 60 °C/72 h. [c] Isomer ratio 91:4:3:2, see Experimental Section. [d] Introduction of the *t*-$BuMe_3Si$ group required *t*-$BuMe_2Si$/2,6-lutidine, see discussion. [e] Trans/cis.

a carboxylic acid. Interestingly, this ketone reacted selectively at the ketone with borane–dimethyl sulfide (CH_2Cl_2, 0 °C). Keto ester **14**, obtained by esterification with diazomethane, failed to react cleanly at the ketone carbonyl with the phosphine oxide anion. The stability of **14** toward elimination is noteworthy.

Discussion

(A) Alternate Methods. Alkylation of protected formyl ketones is an alternate method for introducing a substituent in the γ position[3a–c] of α,β-unsaturated aldehydes (Scheme V). However, alkylation of **15b** (LDA, −78 °C, with or without HMPA) with benzyl chloromethyl ether (−78 °C to 25 °C) failed. Alkylation does not occur until the reaction mixture is warmed to the point where many side reactions occur (ca. 0 °C). More surprising was the inability to successfully kinetically deprotonate **15a** and **15c**. Even at −100 °C, self-condensation was competitive with enolization. Alkylation prior to introducing the formyl group is a possible general solution to this problem. In this case, however, the benzyloxy substituent might eliminate under the reaction conditions used to introduce the formyl group.

Scheme VI

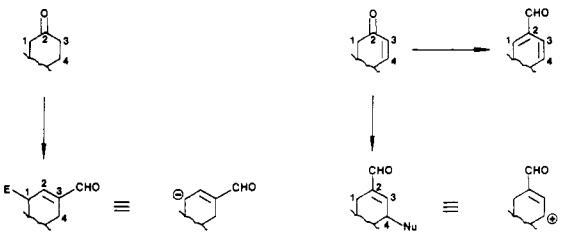


The trimethylsilyl enol ether of **15b** was prepared[5] (Me_3SiI) and electrophilic alkylation with benzyl chloromethyl ether was attempted. Once again, the silyl ether polymerized under the mild conditions ($ZnCl_2$, −15 °C, CH_2Cl_2). The silyl enol ethers of **15a** and **15c** could not be prepared by this method. Noyori's[17] alkylation of silyl enol ethers with bis(benzyloxy)methane catalyzed with Me_3SiOTf and 2,6-di-*tert*-butylpyridine was also unsuccessful.

(16) Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936.

(17) Murata, S.; Suzuki, M.; Noyori, R. *Tetrahedron Lett.* **1980**, *21*, 2527.

Scheme VII



A further alternative employed a methanol dianion equivalent. Addition of [(benzyloxy)methyl]lithium[10] to cyclohexenone followed by PCC oxidation[18] produced enone **18** as shown in Scheme VI. The Horner–Wittig reaction with this ketone produced methyl enol ether **19** as a mixture of isomers. All attempts to hydrolyze this compound (aqueous acid or via oxymercuration) without loss of the benzyloxy group met with little success.

(B) Homologation of Enones. Some of the examples found in Table I are noteworthy because they could in principle be obtained by alternate routes. For example, entry 4 could be prepared by reduction of a protected formyl ketone. Our overall yield from cycloheptanone to 1-cycloheptenecarbaldehyde (**17c**, E = H) was 34%.[19] This is considerably lower than the overall yield for **1d** when the yield for alkylation is taken into account. Entry 3 demonstrates the ability to introduce alkyl groups with stereocontrol.

Entry 6 presented special problems because of the acidity of the γ protons of 7-hydroxy-2-cycloheptenone. Imidazole in DMF caused polymerization of this enone, and 2,6-lutidine readily induced enolization at −15 °C as evidenced by trapping with t-BuMe$_2$SiOTf to form **10c**. We have encountered this behavior in our laboratories previously during many unsuccessful attempts to prepare a trisylhydrazone of 2-cycloheptenone. The enone readily deconjugates and polymerizes under a variety of acidic or neutral conditions without forming a hydrazone. This hydrazone could be used to generate 1,3-cycloheptadien-2-yllithium which could be trapped with DMF to provide **3b**. Optimization of the silyl protection in this sequence could provide a general solution to this problem.

The yields for the overall transformation from enone to enal are respectable (15–52%) and except for one case vary over a narrow range (40–52%). The silyl enol ether oxidation is not applicable to cyclopentyl enol ethers. Butyl and vinyl homocuprates were added to cyclopentenone and trapped with Me$_3$SiCl (77% and 68%, respectively). Oxidation produced a myriad of products from which only 10–25% of impure hydroxy ketones could be isolated. The Horner–Wittig reaction, however, has been successfully used on cyclopentenones in our laboratories.[20] Intramolecular aldol reactions may well be the best route to 1-cyclopentenecarbaldehydes because of the availability of cyclohexenes.[21]

Conclusions

In summary we have developed a viable access to cyclic α,β-unsaturated aldehydes with γ-substitution (**1** and **2**) or β'-unsaturation (**3**), starting with 2-cycloalkenones. This method complements existing methods insofar as it allows incorporation of substituents as nucleophiles and results in a different substitution pattern (Scheme VII).

Experimental Section

(1) General Methods. Bulb-to-bulb distillations were done on a Buchi GKR-50 Kugelrohr apparatus; boiling points (bp) refer to air bath temperatures and are uncorrected. Analytical TLC was performed on Merck silica gel plates with QF-254 indicator. Visualization was accomplished with UV light, phosphomolybdic acid, and or I_2. R_f data are given in the following solvent systems: hexane/EtOAc or pentane/Et$_2$O. Column chromatography was performed by the method of Still[22] (32–36 μm silica gel, Woelm). Analytical GC was performed on a Varian 3700 chromatograph fitted with a flame ionization detector. (N_2 carrier gas for packed columns (30 mL/min), H_2 for capillary column (1 mL/min, split ratio 30:1)). Columns: (A) 50-m OV-17 WCOT, split ratio 30:1, (B) 11% QF-1 on 60–80 Chromosorb G (6 ft × $^1/_8$ in.), (C) 5% OV-17 on 60–80 Chromosorb G (6 ft × $^1/_8$ in.). Retention times (t_R) and integrals were obtained from a Hewlett Packard 3390 recorder. THF and Et$_2$O were distilled from sodium benzophenone. CH$_2$Cl$_2$, hexane, acetonitrile, hexamethylphosphoramide (HMPA), trimethylchlorosilane, triethylamine, diisopropylamine, dimethylformamide (DMF), dimethyl sulfide (DMS), and vinyl bromide were distilled from CaH$_2$ prior to use. MeLi, n-BuLi and t-BuLi were titrated by the method of Gilman. Chloroperoxybenzoic acid was washed with pH 7.5 phosphate buffer and vacuum dried prior to use. CuI was recrystallized according to Kauffman and Teter.[23] All other chemicals were used as obtained or purified by distillation as needed. Brine refers to saturated aqueous sodium chloride solution. All reactions were performed in oven- (140 °C) or flame-dried glassware under an atmosphere of dry N_2. IR spectra were obtained on a Perkin-Elmer 1320 IR spectrophotometer as films on NaCl disks unless otherwise stated. Peaks are reported in cm^{-1} with the following relative intensities: s (strong, 67–100%), m (medium, 34–66%), w (weak, 0–33%). ^{1}H NMR spectra were recorded on either Varian EM-390 (90 MHz), Varian XL 200 (200 MHz), or Nicolet NTC-360 (360 MHz) spectrometers in CDCl$_3$ with CHCl$_3$ as an internal standard (δ 7.26) unless otherwise stated. Chemical shifts are given in ppm (δ); multiplicities indicated by s (singlet), d (doublet), t (triplet), q (quadruplet), m (multiplet), or br (broadened). Mass spectra were obtained on a Finnigan MAT CH-5 spectrometer with ionization voltages of 10 and 70 eV. Data are reported in the form m/z (intensity relative to base = 100). Elemental analyses were performed by the University of Illinois Microanalytical Service Laboratory.

(2) Starting Materials. 1-Cycloheptenecarbaldehyde,[24] 1-cyclohexenecarbaldehyde,[24] 1-cyclopentenecarbaldehyde,[25] 4-methyl-2-cyclohexenone,[26] 4,4-dimethyl-2-cyclohexenone,[27] 2-cycloheptenone,[28] formylcyclohexanone,[24a] formylcycloheptanone,[24a] chloromethyl benzyl ether,[30] (methoxymethyl)diphenylphosphine oxide,[31] LTEPA,[12] PhSCu,[32a] CuBr·DMS,[32b] and Et$_3$NHF[33] were prepared by literature procedures.

(3) γ Alkylation. 1-[(Trimethylsiloxy)methylidene]-2-cycloheptene (5c). This silyl enol ether was prepared by the

(18) Dauben, W. G.; Michno, D. M. *J. Org. Chem.* **1977**, *42*, 682.
(19) Reduction of **13c** to produce **4c** proceeds in only 60–65% yield with a substantial amount (ca. 15–20%) of 1,4 reduction producing 2-methylidenecycloheptanol.
(20) Denmark, S. E.; Carreira, E. M., unpublished results from these laboratories.
(21) See for example ref 25 and (a) Elliott, J. D.; Kelson, A. B.; Purcell, N.; Stoodley, R. J.; Palfreyman, M. N. *J. Chem. Soc., Perkin Trans. 1* **1983**, 2441. (b) Corey, E. J.; Danheiser, R. L.; Chandrasekaran, S.; Siret, P.; Keck, G. E.; Gras, J-L. *J. Am. Chem. Soc.* **1978**, *100*, 8031.
(22) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.
(23) Kauffman, G. B.; Teter, L. A. In "Inorganic Syntheses"; Kleinberg, J., Ed., 1963; Vol. 7, p 9.
(24) (a) Ainsworth, C. In "Organic Syntheses"; Rabjohn, N., Ed.; 1963; Collect. Vol. IV, p 536. (b) Analogous procedure. Ruzicka, L.; Seidel, C. F.; Schinz, H.; Pfeiffer, M. *Helv. Chim. Acta* **1948**, *31*, 422.
(25) (a) Brown, J. B.; Henbest, H. B.; Jones, E. R. H. *J. Chem. Soc.* **1950**, 3634. (b) Roebuck, A.; Adkins, H. In "Organic Syntheses"; Horning, E. C., Ed.; 1955; Collect. Vol. III, p 217.
(26) Stork, G.; Danheiser, R. L. *J. Org. Chem.* **1973**, *38*, 1775.
(27) Chan, Y.; Epstein, W. W. In "Organic Syntheses"; Brossi, A., Ed.; 1973; Vol. 53, p 48.
(28) (a) House, H. O.; Lee, T. V. *J. Org. Chem.* **1979**, *44*, 2819. See also: (b) Pinder, A. R. *J. Org. Chem.* **1982**, *47*, 3607.
(29) Eaton, P. E.; Jobe, P. G. *Synthesis* **1983**, 796.
(30) Taylor, G. N.; Connor, D. S. In "Organic Syntheses"; House, H. O., Ed.; 1972; Vol. 52, p 16. An improved, more easily reproducible procedure will appear in "Organic Syntheses" Coll. Vol. VI.
(31) Trippett, S. *J. Chem. Soc.* **1961**, 2813.
(32) (a) Posner, G. H.; Brunelle, D. J.; Sinoway, L. *Synthesis* **1974**, 662. (b) Wuts, P. G. M. *Synth. Commun.* **1981**, *11*, 139.
(33) Hunig, S.; Wehner, G. *Synthesis* **1975**, 180.

method of Duboudin et al.[5] Aldehyde **4c** (2.50 g, 20 mmol) was dissolved in 20 mL of acetonitrile. Triethylamine (5.60 mL, 40 mmol), NaI (6.07 g, 40 mmol), and Me_3SiCl (5.10 mL, 40 mmol) were added sequentially. After 15 min at 25 °C, the reaction mixture was heated to 70 °C for 1 h. The progress of the reaction was monitored by GC analysis: column C (100 °C (2 min), 25 °C/min, 270 °C (5 min)) t_R (**4c**) 4.2 min, t_R (**5c**) 5.20 min. Upon consumption of **4c**, 30 mL of saturated aqueous $NaHCO_3$ and 30 mL of pentane were added. The aqueous phase was separated and extracted with pentane (2 × 30 mL). The individual organic extracts were washed with water (30 mL) and brine (30 mL). The combined organic layers were dried (K_2CO_3), evaporated, and distilled: bp 90 °C (10 torr); yield 3.46 g (87%); IR 3000 m, 2945 s, 2920 s, 2845 m, 1640 s, 1602 s, 1448 m, 1325 m, 1250 s, 1200 s, 1150 s, 1095 m, 1040 w, 905 s, 855 s, 755 s, 695 m; ^1H NMR (90 MHz, $CDCl_3$) δ 6.32 (s, 1 H, H-c(8)), 5.90 (dm, J = 12.0, 1 H, H-C(2)), 5.47 (dt, J = 12, 4, 1 H, H-C(3)), 2.63–2.43 (m, 2 H, 2 H-C(4)), 2.43–2.17 (m, 2 H, 2 H-C(7)), 1.87–1.63 (m, 4 H, 2 H-C(5), 2 H-C(6)), 0.33 (s, 9 H, $(CH_3)_3Si$). Anal. Calcd for $C_{11}H_{20}OSi$ (196.37): C, 67.28; H, 10.27. Found: C, 67.68; H, 10.35.

3-[(Benzyloxy)methyl]-2-cycloheptenecarbaldehyde (2c). Enol ether **5c** (2.30 g, 11.7 mmol) was dissolved in CH_2Cl_2 (25 mL) in a 100-mL three-necked flask fitted with a thermometer, septum, N_2 inlet, and a magnetic stirring bar. The flask was cooled to 0 °C. Benzyl chloromethyl ether (1.63 mL, 11.7 mmol) was added followed by $ZnCl_2$[34] (0.160 g, 1.17 mmol) in one portion. The reaction was monitored by GC analysis: column C (100 °C (2 min), 25 °C/min, 270 °C (5 min)) t_R (α alkyl) 8.15 min, t_R (**6c**) 8.68 min. After 20 min at 0 °C, the mixture was poured into a mixture of water (50 mL) and Et_2O (75 mL). The aqueous phase was separated and extracted with ether (2 × 75 mL). The individual organic extracts were washed with water (50 mL) and brine (50 mL). The combined organic layers were dried ($MgSO_4$) and evaporated. The resulting clear yellow oil was immediately chromatographed (4:1 hexane/EtOAc, R_f 0.30) and distilled: bp 200 °C (0.05 torr); yield 1.43 g (38%); IR 3085 w, 3060 w, 3030 w, 2920 s, 2850 s, 2720 w, 1680 s (C=O), 1640 m (C=C), 1500 w, 1450 m, 1370 m, 1180 m, 1110 s, 1030 m, 868 w, 740 m, 705 m; ^1H NMR (90 MHz) δ 9.33 (s, 1 H, CHO), 7.37 (s, 5 H, Ar H), 6.73–6.63 (m, 1 H, H-C(2)), 4.55 (s, 2 H, CH_2Ph), 3.52 (d, J = 7.0, 2 H, $CH_2C(3)$), 2.97–2.67 (m, 3 H, 1 H-C(3), 2 H-C(7)), 2.20–1.03 (m, 6 H, 2 H-C(4), 2 H-C(5), 2 H-C(6)); MS (70 eV), m/z (relative intensity) 104 (13), 92 (12), 91 (100), 79 (12), 77 (18), 65 (11), 51 (11), 41 (12), 39 (11). Anal. Calcd for $C_{16}H_{20}O_2$ (244.34): C, 78.65; H, 8.25. Found: C, 78.40; H, 8.15.

(4) Conjugate Addition/Trapping. 3-Ethenyl-1-(trimethylsiloxy)cyclohexene (7a). Mg (2.58 g, 106 mmol) was suspended in THF (20 mL) in a 500-mL, three-necked, round-bottomed flask fitted with an addition funnel, thermometer, and reflux condenser under N_2. Vinyl bromide (7.5 mL, ca. 106 mmol) was dissolved in THF (100 mL) and added dropwise over 90 min to the Mg maintaining the temperature at or below 40 °C. The resulting gray-brown solution was stirred 1 h at room temperature after complete addition. The reflux condenser was exchanged for a septum and the reaction mixture was cooled to −10 °C with an ice/salt bath. CuI (10.11 g, 53.1 mmol) was added to the slurry in one portion. After 1.5 min at −10 °C, the black mixture was cooled to −78 °C. Cyclohexenone (5.00 g, 52.0 mmol) was dissolved in THF (50 mL) and added dropwise over 30 min to the reaction mixture. GC analysis: column B (80 °C (2 min), 20°C/min, 200 °C (5 min)); t_R (enone) 5.6 min, t_R (ketone) 6.2 min; t_R (enol ether) 4.6 min. Cyclohexenone was immediately consumed. HMPA (18.1 mL, 104 mmol), Et_3N (21.8 mL, 156 mmol), and Me_3SiCl (19.8 mL, 156 mmol) were sequentially added to the reaction mixture. The cooling bath was removed and the reaction was warmed to room temperature. GC analysis showed a single product. The reaction mixture was added to 100 mL of a 9:1 mixture of saturated NH_4Cl:concentrated NH_4OH and 200 mL of pentane. The aqueous layer was separated and extracted with pentane (2 × 200 mL). The organic layers were individually washed with 9:1 NH_4Cl/NH_4OH (150 mL) until the aqueous phase was no longer blue (ca. 4–5 times). The organic layers were then washed with water (100 mL) and brine (100 mL), combined, dried (K_2CO_3), evaporated, and distilled: bp 86–9 °C (23 torr); yield 8.88 g (87%); IR 3080 m, 3050 w, 3000 m, 2960 s, 2935 m, 2865 m, 1665 s, 1640 m, 1445 m, 1435 m, 1410 m, 1368 s, 1345 m, 1265 s, 1250 s, 1190 s, 1122 m, 1110 m, 1070 m, 1055 m, 1040 m, 985 s, 910 s, 850 s, 755 s, 640 m; ^1H NMR (90 MHz) δ 5.80 (ddd, J = 17.0, 10.0, 7.0, 1 H, H-C(1′)), 5.00 (d, J = 17.0, 1 H, H-C(2′)), 4.97 (d, J = 10.0, 1 H, H-C(2′)), 4.87–4.73 (m, 1 H, H-C(2)), 3.03–2.87 (m, 1 H, H-C(3)), 2.20–1.23 (br m, 6 H, 2 H-C(4), 2 H-C(5), 2 H-C(6)), 0.23 (s, 9 H, $(CH_3)_3Si$); MS (70 eV), m/z (relative intensity) 198 (M^+ + 2, 16), 197 (M^+ + 1, 100), 141 (15), 129 (15), 115 (12), 105 (11), 75 (84), 73 (44), 67 (21), 59 (27), 41 (25), 31 (12). Anal. Calcd for $C_{11}H_{20}OSi$ (196.36): C, 67.28; H, 10.27. Found: C, 67.34;, H, 10.32.

3-*tert*-Butyl-1-(trimethylsiloxy)cyclohexene (7b). (Phenylthio)copper[32a] (4.49 g, 26.0 mmol) was suspended in 90 mL of dry THF in a 300-mL, three-necked, round-bottomed flask fitted with a septum, thermometer, magnetic sitrring bar, and N_2 inlet. The slurry was cooled to −20 °C with an ice/salt bath. t-BuLi (13.8 mL, 1.89 M, 26.0 mmol) was added via syringe over 5 min. The resulting gray-green solution was stirred 15 min at −20 °C and then cooled to −78 °C. Cyclohexenone (1.00 g 10.4 mmol) was dissolved in THF (10 mL) and added dropwise over 5 min to the reaction mixture. A yellow green precipitate immediately formed and the reaction was warmed to 0 °C and analyzed by GC: column C (80 °C (2 min), 20 °C/min, 250 °C (5 min)); t_R (enone) 4.3 min; t_R (ketone) 6.7 min; t_R (enol ether) 6.4 min. Cyclohexenone was consumed when the temperature reached −10 °C. HMPA (4.52 mL, 26.0 mmol), Et_3N (3.62 mL, 26.0 mmol), and Me_3SiCl (3.30 mL, 26.0 mmol) were added sequentially at 0 °C. The reaction was judged to be complete after 20 min at 0 °C by GC analysis. Water (100 mL) and pentane (100 mL) were cautiously added. The aqueous slurry was separated and extracted with pentane (2 × 100 mL). The individual organic layers were washed with water (5 × 100 mL), combined, dried (K_2CO_3), filtered through a Celite pad, and concentrated. The resulting clear oil was distilled: bp 65 °C (0.15 torr); yield 2.09 g (89%); IR 3050 w, 3020 w, 2985 s, 2860 s, 2840 m, 2820 m, 1660 s, 1470 m, 1450 m, 1430 w, 1390 m, 1368 m, 1362 m, 1348 m, 1250 s, 1190 s, 1170 s, 1145 w, 1060 w, 1008 m, 985 m, 950 w, 918 m, 845 s, 750 m, 685 w; ^1H NMR (90 MHz) δ 4.92 (s, 1 H, H-C(2)), 2.10–1.00 (br m, 7 H, 1 H-C(3), 2 H-C(4), 2 H-C(5), 2 H-C(6)), 0.88 (s, 9 H, $(CH_3)_3C$-C(3)), 0.20 (s, 9 H, $(CH_3)_3Si$); MS (70 eV), m/z (relative intensity) 226 (M^+, 1), 170 (15), 169 (M^+ − 57, 98), 75 (18), 73 (100), 45 (11), 41 (10). Anal. Calcd for $C_{13}H_{26}OSi$ (226.44): C, 68.96; H, 11.57. Found: C, 69.33; H, 11.73.

(4.1) Conjugate Addition/Trapping with Lithium Dimethylcuprate. General Procedure. CuBr·DMS (1.01 equiv) was dissolved in DMS (10 mL/g) in a three-necked, 200-mL round-bottomed flask fitted with a thermometer, N_2 inlet, septum, and magnetic stirring bar. The resulting clear solution was cooled to −20 °C and MeLi (2.02 equiv, 1.20 M in Et_2O) was added via syringe. The resulting clear solution was stirred for 15 min at −10 °C and then cooled to −78 °C. The enone (1.00 equiv) was dissolved in Et_2O (5 mL/g enone) and added dropwise over 5 min. The resulting yellow solution was stirred for 10 min at −78 °C at which time the enone had been consumed by GC analysis. HMPA (2 equiv), Et_3N (2 equiv), and Me_3SiCl (2 equiv) were added and the mixture was warmed to room temperature. After 20 min at 20 °C, pentane (25 mL/g enone) and 9:1 saturated NH_4Cl/NH_4OH (25 mL/g enone) were added. The aqueous phase was separated and extracted with pentane (2 × 25 mL/g enone). The individual organic layers were washed with 9:1 NH_4Cl/NH_4OH (4 × 25 mL/g enone) and brine (2 × 25 mL/g enone). The organic layers were combined, dried (K_2CO_3), filtered, concentrated, and distilled.

***trans*-3,4-Dimethyl-1-(trimethylsiloxy)cyclohexene (7c):** yield 2.30 g (94%); bp 80 °C (16 torr); GC analysis, column A (80 °C (5 min), 10°/min, 250 °C (5 min)) t_R (enone) 11.1 min, t_R (ketone) 12.0 min, t_R (enol ether, trans) 14.5 min, t_R (enol ether, cis) 15.0 min (GC analysis showed the product to be a 94:6 mixture of isomers.) IR 3010 w, 2955 s, 2925 s, 2870 s, 2838 m, 1665 s, 1500 m, 1430 w, 1368 s, 1348 m, 1250 s, 1235 s, 1185 s, 1110 w, 1080 w, 1028 m, 980 m, 970 m, 922 m, 888 s, 868 s, 845 s, 755 m, 690 w, 638 m; ^1H NMR (90 MHz) 4.70–4.63 (m, 1 H, H-C(2)), 2.13–0.80 (br m, 6 H, 1 H-C(3), 1 H-C(4), 2 H-C(5), 2 H-C(6)), 1.00 (d, J = 6.0, 6 H, CH_3-C(3), CH_3-C(4)), 0.27 (s, 9 H, $(CH_3)_3Si$).

(34) Danishefsky, S.; Kithara, T.; Schuda, P. F. In "Organic Synthesis"; Stevens, R. V., Ed.; 1983; Vol. 61, p 147.

Anal. Calcd for $C_{11}H_{22}OSi$ (198.38): C, 66.60; H, 11.18. Found: C, 66.52; H, 11.06.

3-Methyl-1-(trimethylsiloxy)cycloheptene (7d): yield 3.09 g (86%); bp 74–8 °C (12 torr); GC analysis, column A (100 °C (5 min), 10°/min, 250 °C (5 min)) t_R (enone) 9.5 min, t_R (ketone) 9.9 min, t_R (enol ether) 12.1 min; IR 2960 s, 2920 s, 2870 m, 2850 m, 1660 s, 1620 w, 1450 m, 1440 m, 1365 m, 1340 w, 1285 w, 1260 s, 1250 s, 1218 s, 1182 s, 1150 m, 1130 s, 1085 m, 1058 w, 1032 m, 988 w, 950 m, 898 s, 880 s, 835 s, 755 m, 723 w, 690 w; ^{1}H NMR (90 MHz) δ 4.75 (d, J = 4.0, 1 H, H-C(2)), 2.56–1.27 (br m, 9 H, 1 H-C(3), 2 H-C(4), 2 H-C(5), 2 H-C(6), 2 H-C(7)), 1.07 (d, J = 6.0, 3 H, CH_3-C(3)), 0.30 (s, 9 H, $(CH_3)_3Si$); MS (70 eV), m/z (relative intensity) 198 (M^+, 10), 183 (42), 169 (19), 75 (47), 73 (100), 45 (17), 41 (14). Anal. Calcd for $C_{11}H_{22}OSi$ (198.38): C, 6660, H, 11.18. Found: C, 66.49; H, 10.94.

(4.2) Enolization/Trapping. General Procedure. Diisopropylamine (1.10 equiv) was dissolved in THF (15 mL/g enone) in a three-necked, 100 mL, round-bottomed flask fitted with a thermometer, septum, N_2 inlet, and a magnetic stirring bar. The solution was cooled to −20 °C and n-BuLi (1.05 equiv, 1.18 M in hexane) was added dropwise. The resulting pale yellow solution was cooled to −78 °C. The enone (1.00 eq) was dissolved in THF (2.5 mL/g enone) and added dropwise to the LDA over 5 min. After stirring for 5 min, Me_3SiCl (1.9 equiv) was added and the reaction was warmed to room temperature. GC analysis showed the reaction to be over at 0 °C. Pentane (15 mL/g enone) and water (20 mL/g enone) were added. The aqueous layer was separated and extracted with pentane (2 × 15 mL/g enone). The individual organic extracts were washed with water (3 × 25 mL/g enone), combined, dried (K_2CO_3), filtered, evaporated, and distilled.

4,4-Dimethyl-1-(trimethylsiloxy)-2,5-cyclohexadiene (9a): yield 2.84 g (90%); bp 130 °C (19 torr); GC analysis, column C (100 °C (2 min), 20°/min, 240 °C (5 min)), t_R (enone) 3.8 min, t_R (enol ether), 3.4 min; IR 3040 w, 3015 w, 2955 s, 2920 m, 2860 m, 2810 m, 1650 s, 1595 m, 1468 m, 1400 s, 1375 s, 1355 m, 1320 m, 1298 w, 1248 s, 1200 s, 1178 m, 1150 m, 1118 w, 1038 m, 980 s, 942 s, 900 s, 840 s, 780 s, 750 m, 688 w, 650 m, 635 m; ^{1}H NMR (90 MHz) δ 5.60–5.53 (m, 2 H, H-C(5), H-C(6)), 4.90–4.73 (br m, 1 H, H-C(2)), 2.18 (d, J = 4.0, 2 H, 2 H-C(3)), 1.13 (s, 6 H, 2 CH_3-C(4)), 0.17 (s, 9 H, $(CH_3)_3Si$); MS (70 eV), m/z (relative intensity) 196 (M^+, 28), 182 (14), 181 (93), 165 (36), 91 (16), 82 (19), 75 (63), 73 (100), 45 (18), 28 (30). Anal. Calcd for $C_{11}H_{20}OSi$ (196.37): C, 67.28; H, 10.27. Found: C, 67.55; H, 10.59.

2-(Trimethylsiloxy)-1,3-cycloheptadiene (9b): yield 2.44 g (92%); bp 120 °C (16 torr); GC analysis, column A (100 °C (5 min), 10°/min, 250 °C (5 min)), t_R (enone) 9.5, t_R (enol ether) 11.9; IR 3030 w, 2960 s, 2930 s, 2840 m, 1650 m, 1440 w, 1420 w, 1250 s, 1230 s, 1160 s, 1150 s, 1100 w, 1060 w, 960 w, 900 s, 885 s, 845 s, 795 m, 755 m, 690 w; ^{1}H NMR (90 MHz) δ 5.92 (dt, J = 13.0, 4.0, 1 H, H-C(4)), 5.68 (d, J = 13.0, 1 H, H-C(3)), 5.28 (tm, J = 5.0, 1 H, H-C(1)), 2.47–2.05 (m, 4 H, 2 H-C(5), 2 H-C(7)), 2.00–1.67 (m, 2 H, 2 H-C(6)), 0.30 (s, 9 H $(CH_3)_3Si$); MS (70 eV), m/z (relative intensity) 182 (M^+, 31), 167 (36), 154 (11), 151 (13), 91 (11), 76 (11), 75 (47), 73 (100), 45 (20), 39 (10). Anal. Calcd for $C_{10}H_{18}OSi$ (182.34): C, 65.87; H, 9.95. Found: C, 65.66; H, 9.77.

(5) Oxidation/Protection. General Procedure. The trimethylsilyl enol ethers were oxidized according to the procedure of Rubottom and Gruber.[8] mCPBA (1.10 equiv) was placed in hexane (0.10 M) and magnetically stirred for 20 min at 20 °C. The slurry was then cooled to −15 °C with an ice/salt bath. The enol ether was then added dropwise in hexane (1 mL/g enol ether) over 5 min. After being stirred for 15 min at −15 °C and 1 h at 20 °C, the reaction mixture was filtered and concentrated. The remaining chlorobenzoic acid was precipitated by the addition of pentane and removed by filtration. The crude product was dissolved in CH_2Cl_2 (0.2 M) and triethylammonium fluoride (4 equiv) was added. The trimethylsilyl ether was not stable to silica gel but the course of the reaction could be monitored by TLC (2:1 hexane/EtOAC) by watching the disappearance of the characteristic decomposition pattern of the silyl ether. After completion of the reaction (ca. 3–5 h) the reaction mixture was washed successively with saturated sodium bicarbonate (20 mL/g enol ether), 2 N HCl (20 mL/g enol ether), and saturated sodium bicarbonate (20 mL/g enol ether). The aqueous phases were extracted with CH_2Cl_2 (2 × 20 mL/g enol ether). The organic layers were combined, dried ($MgSO_4$), filtered, and evaporated. The crude alcohol was protected by the method of Corey and co-workers.[35] The alcohol was dissolved in dry DMF (10 mL/g alcohol), and imidazole (1.5 equiv) and *tert*-butyldimethylsilyl chloride (1.1 equiv) were added. The reaction was stirred at room temperature and monitored by TLC (2:1 hexane/EtOAC). After the alcohol was consumed (ca. 12–24 h), Et_2O (15 mL/g alcohol) and water (15 mL/g alcohol) were added. The aqueous phase was separated and extracted with Et_2O (2 × 15 mL/g alcohol). The organic layers were individually washed with water (5 × 15 mL/g alcohol) and brine (2 × 15 mL/g alcohol). The organic layers were then combined, dried ($MgSO_4$), filtered, concentrated, and distilled.

***cis,trans*-2-(*tert*-Butyldimethylsiloxy)-3-ethenylcyclohexanone (8a)**: yield 8.40 g (73%); bp 114–118 °C (0.7 torr); R_f 0.33, 0.41 (5:1 hexane/EtOAc), 1.5:1 trans/cis by NMR integration of the H_3CSi signals; IR 3080 w, 2960 s, 2940 s, 2890 s, 1733 s (C=O), 1640 w, 1475 m, 1465 m, 1420 w, 1390 w, 1363 m, 1318 w, 1255 s, 1190 m, 1150 s, 1130 s, 1110 m, 1090 s, 1040 s, 1005 m, 925 s, 900 m, 840 s, 782 s, 670 m; ^{1}H NMR (90 MHz) δ 6.07–5.64 (m, 1 H, H-C(1')), 5.34–4.97 (m, 2 H, 2 H-C(2')), 4.04–3.87 (m, 1 H, H-C(2)), 3.00–1.50 (br m, 7 H, 1 H-C(3), 2 H-C(4), 2 H-C(5), 2 H-C(6)), 0.97 (s, 9 H, $(CH_3)_3CSi$), 0.17 (s, 1.8 H, CH_3Si, trans), 0.10 (s, 1.2 H, CH_3Si, cis), 0.07 (s, 1.8 H, CH_3Si, trans), 0.03 (s, 1.2 H, CH_3Si, cis). Anal. Calcd for $C_{14}H_{26}O_2Si$ (254.45): C, 66.09; H, 10.30. Found: C, 66.00; H, 10.25.

***cis,trans*-3-*tert*-Butyl-2-(*tert*-butyldimethylsiloxy)-cyclohexanone (8b).** The protection step for this hydroxy ketone required 60 °C for 72 h: yield 2.37 g (93%); bp 80 °C (0.05 torr); R_f 0.35, 0.46 (10:1 hexane/EtOAC), 9:1 trans/cis by NMR integration of the H-C(2) signal; IR 2958 s, 2930 s, 2860 s, 1723 s (C=O), 1470 s, 1435, 1392 m, 1365 s, 1335 w, 1315 w, 1252 s, 1165 m, 1105 s, 1090 s, 1080 s, 1040 s, 1005 m, 995 m, 945 m, 890 m, 840 s, 818 m, 780 s, 745 w, 670 m; ^{1}H NMR (200 MHz) δ 4.06 (d, J = 6.4, 0.1 H, H-C(2), cis), 3.98–3.88 (m, 0.9 H, H-C(2), trans), 2.80 (dd, J = 12.0, 5.0, 0.9 H, H-C(6), trans), 2.25–1.20 (br m, 6.1 H, H-C(3), 2 H-C(4), 2 H-C(5), H-C(6), trans, 2 H-C(6), cis), 0.98 (s, 9 H, $(CH_3)_3CSi$, cis and trans), 0.90 (s, 9 H, $(CH_3)_3C$-C(3), both isomers), 0.05 (s, 3 H, CH_3Si, both isomers), 0.01 (s, 3 H, CH_3Si, both isomers); MS (70 eV), m/z (relative intensity) 227 (M^+ − 57, 10), 189 (25), 171 (46), 148 (16), 147 (100), 75 (29), 73 (35), 67 (31), 41 (10). Anal. Calcd for $C_{16}H_{32}O_2Si$ (284.52): C, 67.55; H, 11.34. Found: C, 67.38; H, 11.28.

2-(*tert*-Butyldimethylsiloxy)-3β,4α-dimethylcyclohexanone (8c): yield 2.38 g (80%); bp 100 °C (0.02 torr); R_f 0.50, 0.60 (4:1 hexane/EtOAc); IR 2960 s, 2930 s, 2890 s, 2860 s, 1730 s (C=O), 1460 m, 1425 m, 1380 m, 1360 m, 1320 w, 1290 w, 1253 s, 1212 w, 1150 s, 1130 s, 1110 s, 1090 m, 1060 s, 1040 s, 1025 s, 1003 m, 958 w, 940 w, 905 m, 875 m, 838 s, 778 s, 670 m; ^{1}H NMR (90 MHz) δ 3.88–3.75 (m, 1 H, H-C(2)), 3.10–1.27 (br m, 6 H, 1 H-C(3), 1 H-C(4), 2 H-C(5), 2 H-C(6)), 1.16–1.00 (m, 15 H, $(C-H_3)_3CSi$, CH_3-C(3)-CH_3-C(4)), 0.23 (s, 3 H, CH_3Si), 0.16 (s, 3 H, CH_3Si); MS (70 eV), m/z (relative intensity) 199 (M^+ − 57, 38), 189 (18), 148 (16), 147 (100), 129 (15), 107 (21), 75 (55), 73 (49), 59 (19), 41 (16). Anal. Calcd for $C_{14}H_{28}O_2Si$ (256.46): C, 65.67; H, 11.00. Found: C, 65.90; H, 11.18.

***cis,trans*-2-(*tert*-Butyldimethylsiloxy)-3-methylcycloheptanone (8d)**: yield 2.72 g (70%); bp 100–5 °C (0.50 torr); R_f 0.63, 0.70 (2:1 hexane/EtOAc), 7:1 trans/cis by NMR; IR 2960 s, 2938 s, 2860 s, 1712 (C=O), 1463 m, 1410 w, 1388 w, 1360 w, 1255 s, 1218 w, 1090 s, 1050 m, 1005 m, 945 w, 905 m, 860 s, 840 s, 780 s, 670 m; ^{1}H NMR (90 MHz) δ 3.98 (m, 0.12 H, H-C(2), cis), 3.91 (d, J = 7.0, 0.88 H, H-C(2), trans), 2.87–1.80 (br m, 9 H, 1 H-C(3), 2 H-C(4), 2 H-C(5), 2 H-C(6), 2 H-C(7)), 1.03 (d, J = 5.0 3 H, CH_3-C(3)), 1.00 (s, 9 H, $(CH_3)_3CSi$), 0.16 (s, 3 H, CH_3Si), 0.13 (s, 3 H, CH_3Si); MS (70 eV), m/z (relative intensity) 199 (M^+ − 57, 56), 189 (20), 155 (51), 148 (14), 147 (91), 75 (100), 73 (45), 59 (19), 41 (13). Anal. Calcd for $C_{14}H_{28}O_2Si$ (256.46): C, 65.57; H, 11.00. Found: C, 65.45; H, 11.05.

2-(*tert*-Butyldimethylsiloxy)-4,4-dimethyl-5-cyclohexenone (10a): yield 2.60 g (70%); bp 105 °C (0.30 torr); R_f 0.54 (2:1 hexane/EtOAc); IR 3020 w, 2960 s, 2930 s, 2890 s, 2860

(35) Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.

s, 1700 s (C=O), 1620 w, 1468 m, 1388 w, 1362 m, 1250 s, 1178 s, 1153 s, 1120 s, 1110 sh, 1075 w, 1052 m, 1005 w, 985 w, 942 m, 890 s, 835 s, 830 s, 805 m, 780 s, 745 w, 670 m; ^{1}H NMR (200 MHz) δ 6.53 (dm, J = 9.70, 1 H, H-C(5)), 5.78 (d, J = 9.70, 1 H, H-C(6)), 4.31 (dd, J = 10.2, 8.1, 1 H, H-C(2)), 1.98–1.93 (m, 2 H, 2 H-C(3)), 1.21 (s, 3 H, CH_3-C(4)), 1.16 (s, 3 H, CH_3-C(4)), 0.90 (s, 9 H, $(CH_3)_3CSi$), 0.15 (s, 3 H, CH_3Si), 0.07 (s, 3 H, CH_3Si). Anal. Calcd for $C_{14}H_{26}O_2Si$ (254.45): C, 66.09; H, 10.30. Found: C, 65.87; H, 10.59.

2-(*tert*-Butyldimethylsiloxy)-6-cycloheptenone (10b). Crude 2-hydroxy-6-cycloheptenone was protected according to the method of Corey and co-workers.[36] The alcohol (1.14 g, 9.0 mmol, 84% from enol ether) was dissolved in CH_2Cl_2 (10 mL) and cooled to −15 °C. Freshly distilled 2,6-lutidine (2.35 mL, 20.2 mmol) was added followed by *tert*-butyldimethylsilyl triflate (3.50 mL, 15.2 mmol). The reaction was complete within seconds (TLC analysis, 9:1 hexane/EtOAc) producing two products: R_f 0.35, 0.73. Saturated aqueous sodium bicarbonate (15 mL) was added and the reaction mixture was extracted with CH_2Cl_2 (3 × 20 mL). The organic layers were washed with water (3 × 30 mL) and brine (30 mL). The organic layers were combined, dried (K_2CO_3), concentrated, and chromatographed (12:1 hexane/EtOAc). The higher R_f product was shown to be 1,2-bis(*tert*-butyldimethylsiloxy)-2,4-cycloheptadiene (**10c**): yield 1.95 g (61%); IR 3030 w, 2960 m, 2935 m, 2900 m, 2860 m, 1645 w, 1615 m, 1475 m, 1465 m, 1440 w, 1390 m, 1372 m, 1255 s, 1195 s, 1170 s, 1110 s, 1070 s, 1005 m, 995 m, 945 w, 890 m, 870 m, 840 s, 815 m, 780 s, 738 w, 715 w, 690 m, 675 m; ^{1}H NMR (90 MHz) δ 5.90–5.40 (m, 2 H, H-C(4), H-C(5)), 5.18 (d, J = 8.0 H-C(3)), 4.30 (d, J = 5.0, 1 H, H-C(1)), 2.93–1.20 (br m, 4 H, 2 H-C(6), 2 H-C(7)), 1.07 (s, 9 H, $(CH_3)_3CSi$), 1.02 (s, 9 H, (CH_3CSi), 0.28 (s, 6 H, 2 $(CH_3)Si$), 0.22 (s, 6 H, 2 $(CH_3)Si$). The lower R_f product was shown to be **10b**: yield 0.64 g (29%); bp 130 °C (0.30 torr); IR 3035 w, 2958 s, 2935 s, 2895 s, 2860 s, 1690 s (C=O), 1472 m, 1462 m, 1390 m, 1360 m, 1252 s, 1215 m, 1188 w, 1155 sh, 1125 s, 1080 s, 1040 m, 1005 m, 940 w, 925 w, 890 m, 868 m, 840 s, 780 s; ^{1}H NMR (90 MHz) δ 6.63 (dt, J = 12.0, 5.0, 1 H, H-C(3)), 5.98 (d, J = 12.0, 1 H, H-C(2)), 4.47–4.30 (m, 1 H, H-C(7)), 2.60–2.33 (br m, 2 H, 2 H-C(4)), 2.13–1.67 (br m, 4 H, 2 H-C(5), 2 H-C(6)), 1.00 (s, 9 H, $(CH_3)_3Si$), 0.23 (s, 3 H, CH_3Si), 0.18 (s, 3 H, CH_3Si); MS (70 eV), m/z (relative intensity) 225 (M^+ − 15, 4), 184 (16), 183 (100), 139 (10), 129 (13), 79 (12), 75 (85), 73 (36), 67 (14), 59 (20), 41 (13). Anal. Calcd for $C_{13}H_{24}O_2Si$ (240.42): C, 64.95; H, 10.06. Found: C, 64.90; H, 10.35.

(6) Horner–Wittig Hydrolysis. General Procedure. The Horner–Wittig procedure is essentially that of Warren and co-workers.[7] Diisopropylamine (1.10 eq) was dissolved in THF (2 mL/g ketone) in a three-necked round-bottomed flask fitted with a septum, thermometer, magnetic stirring bar, and an addition funnel under N_2. After cooling to −10 °C, *n*-Butyllithium (1.03 equiv), 1.18 M in hexane) was added at such a rate as to maintain the temperature at 0 °C or less. (Methoxymethyl)diphenylphosphine oxide (1.03 equiv) was dissolved in THF (10 mL/g phosphine oxide) and added dropwise to the LDA solution (ca. 10 min). The resulting orange-red solution was cooled to −78 °C. The ketone was dissolved in THF (10 mL/g ketone) and added dropwise over 20 min to the reaction mixture. The reaction was monitored by TLC (1:1 hexane/EtOAc) and warmed to room temperature. Water (25 mL/g ketone) was added and the reaction mixture was extracted with Et_2O (3 × 30 mL/g ketone). The individual organic extracts were washed with water (3 × 25 mL/g ketone) and brine (2 × 25 mL/g ketone). The organic layers were combined, dried (K_2CO_3), filtered, and concentrated. Sodium hydride (1.0 equiv, 50% oil dispersion) was placed in a three-necked round-bottomed flask fitted with a septum and N_2 inlet. The sodium hydride was washed with hexane (3 × 1 mL/0.1 g dispersion) and suspended in THF (2 mL/0.1 g dispersion). The crude addition product was dissolved in THF (5 mL/g ketone) and added to the suspension over 5 min. An immediate yellow-orange precipitate resulted. The elimination was followed by TLC (ca. 0.5–2 h, 1:1 hexane/EtOAc). Upon completion of the reaction, water (15 mL/g ketone) was cautiously added. The reaction was extracted exactly as described above. The crude enol ether was dissolved in a minimum of acetonitrile and added to 95% acetonitrile/5% aqueous HF (10 mL/g ketone). The hydrolysis was monitored by TLC (ca. 10 min–2 h, 4:1 hexane/EtOAc). After the hydrolysis was judged complete, saturated aqueous sodium bicarbonate (10 mL/g ketone) was cautiously added. The reaction mixture was extracted with Et_2O (3 × 30 mL/g ketone). The individual extracts were washed with water (2 × 30 mL/g ketone) and brine (30 mL/g ketone). The organic layers were combined, dried ($MgSO_4$), filtered, and concentrated. The crude aldehyde was immediately chromatographed and then distilled.

3-Ethenyl-1-cyclohexenecarbaldehyde (1a): yield 401 mg (75%); R_f 0.25 (13:1 pentane/Et_2O); bp 100–110 °C (16 torr); IR 3080 m, 3000 sh, 2980 m, 2935 s, 2860 m, 2810 m, 2750 w, 2710 w, 1683 (C=O), 1633 m, 1448 w, 1432 w, 1392 w, 1375 w, 1340 w, 1295 w, 1245 w, 1203 w, 1175 m, 1165 sh, 1118 w, 1070 w, 1028 w, 990 m, 912 m, 862 w, 835 w, 785 w, 698 m, 680 m; ^{1}H NMR (200 MHz) δ 9.44 (s, 1 H, CHO), 6.67–6.64 (m, 1 H, H-C(2)), 5.83 (ddd, J = 17.0, 10.4, 6.7, 1 H, H-C(1′)), 5.14–5.02 (m, 2 H, 2 H-C(2′)), 3.38–3.06 (br m, 1 H, H-C(3)), 2.35–2.05 (br m, 2 H, 2 H-C(6)), 1.95–1.41 (br m, 4 H, 2 H-C(4), 2 H-C(5)); MS (70 eV), m/z (relative intensity) 136 (M^+, 18), 107 (86), 105 (11), 91 (38), 79 (100), 77 (33), 67 (13), 53 (16), 51 (16), 41 (30), 39 (34). Anal. Calcd for $C_9H_{12}O$ (136.19): C, 79.37; H, 8.88. Found: C, 79.62; H, 8.98.

3-*tert*-Butyl-1-cyclohexenecarbaldehyde (1b): yield 863 mg (64%); R_f 0.30 (9:1 hexane/EtOAc); bp 100 °C (3 torr); IR 2950 s, 2900 s, 2885 s, 2820 s, 2715 m, 1690 s (C=O), 1635 s (C=C), 1470 m, 1420 m, 1395 m, 1365 s, 1300 w, 1260 w, 1225 m, 1200 w, 1180 m, 1155 s, 1095 w, 1050 w, 1020 w, 960 w, 940 w, 908 w, 868 w, 788 w, 762 w, 685 m; ^{1}H NMR (90 MHz) δ 9.40 (s, 1 H, CHO), 6.83 (t, J = 4.0, 1 H, H-C(2)), 2.87–2.57 (m, 1 H, H-C(3)), 2.40–2.17 (m, 2 H, 2 H-C(6)), 2.16–1.20 (br m, 4 H, 2 H-C(4), 2 H-C(5)), 0.90 (s, 9 H, $(CH_3)_3C$); MS (70 eV), m/z (relative intensity) 166 (M^+, 1), 110 (65), 97 (14), 95 (19), 81 (24), 79 (24), 77 (11), 67 (16), 57 (100), 56 (11), 53 (12), 43 (17), 41 (64), 39 (21). Anal. Calcd for $C_{11}H_{18}O$ (166.26): C, 79.46; H, 10.91. Found: C, 79.62; H, 11.01.

***trans*-3,4-Dimethyl-1-cyclohexenecarbaldehyde (1c)**: yield 831 mg (69%); R_f 0.25 (13:1 pentane/Et_2O); bp 100 °C (5 torr). This aldehyde isomerizes upon distillation. Prior to distillation, 91% one isomer by GC analysis: column A (80 °C (5 min), 10°/min, 200 °C (5 min)); t_R 9.6 min. IR 3040 w, 2960 s, 2925 s, 2875 s, 2800 m, 2710 w, 1688 s (C=O), 1645 m, 1455 m, 1435 w, 1398 w, 1370 m, 1275 w, 1240 w, 1175 s, 1110 w, 1095 w, 1070 m, 1040 w, 1020 w, 980 w, 960 w, 870 w, 840 w, 805 w, 755 w, 710 m; ^{1}H NMR (360 MHz) δ 9.43 (s, 1 H, CHO), 6.55 (s, 1 H, H-C(2)), 2.40–2.30 (m, 1 H, H-C(3)), 2.10–2.00 (m, 2 H, 2 H-C(6)), 1.79–1.74 (m, 1 H, H-C(4)), 1.38–1.22 (m, 2 H, 2 H-C(5)), 1.14 (d, J = 7.1, 3 H, CH_3-C(3)), 1.02 (d, J = 6.3, 3 H, CH_3-C(4)); MS (70 eV), m/z (relative intensity) 138 (M^+, 25), 123 (19), 109 (33), 95 (23), 93 (11), 81 (20), 79 (13), 77 (14), 69 (25), 67 (56), 65 (12), 55 (32), 53 (28), 51 (14), 43 (24), 41 (100), 40 (12), 39 (58). Anal. Calcd for $C_9H_{14}O$ (138.21): C, 78.21; H, 10.21. Found: C, 78.45; H, 10.47.

3-Methyl-1-cycloheptenecarbaldehyde (1d): yield 1.05 g (74%); R_f 0.30 (7:1 hexane/EtOAc); bp 140 °C (18 torr); IR 2980 sh, 2922 s, 2850 m, 2810 sh, 2710 w, 1685 s (C=O), 1640 m (C=C), 1445 m, 1405 w, 1375 m, 1360 w, 1350 w, 1342 w, 1325 w, 1288 w, 1275 w, 1225 m, 1188 m, 1145 w, 1113 m, 1088 w, 1000 w, 990 w, 938 w, 882 w, 862 w, 828 w, 798 w, 760 w, 680 m; ^{1}H NMR (90 MHz) δ 9.30 (s, 1 H, CHO), 6.60–6.48 (m, 1 H, H-C(2)), 2.96–2.53 (m, 2 H, 1 H-C(3), 1 H-C(7)), 2.27–1.06 (br m, 7 H, 2 H-C(4), 2 H-C(5), 2 H-C(6), 1 H-C(7)), 1.25 (d, J = 7.0, 3 H, CH_3-C(3)); MS (70 eV), m/z (relative intensity) 138 (M^+, 67), 123 (35), 109 (71), 107 (12), 95 (24), 91 (15), 81 (36), 79 (34), 77 (15), 69 (11), 68 (12), 67 (100), 65 (12), 55 (45), 53 (23), 43 (37), 41 (70), 39 (48), 32 (19). Anal. Calcd for $C_9H_{14}O$ (138.21): C, 78.21; H, 10.21. Found: C, 78.22; H, 9.94.

4,4-Dimethyl-1,5-cyclohexadienecarbaldehyde (3a): yield 676 mg (64%); R_f 0.28 (7:1 hexane/EtOAc); bp 90 °C (25 torr); IR 3040 w, 3005 w, 2958 w, 2922 s, 2870 m, 2810 m, 2720, 2685 w, 1685 s (C=O), 1640 m, 1593 m, 1460 m, 1420 m, 1380 w, 1360 m, 1333 s, 1265 w, 1230 m, 1200 m, 1168 s, 1155 m, 1118 m, 1038 m, 1000 w, 933 w, 878 w, 808 m, 760 s, 703 m; ^{1}H NMR (200 MHz) δ 9.41 (s, 1 H, CHO), 6.69 (t, J = 4.7, 1 H, 1 H-C(2)), 6.28 (dd, J = 9.5, 1.3, 1 H, H-C(5)), 5.70 (d, J = 9.5, 1 H, H-C(6)), 2.40 (d, J = 4.7, 2 H, 2 H-C(3)), 1.03 (s, 6 H, 2 CH_3-C(4)); MS (70 eV),

(36) Corey, E. J.; Cho, H.; Rucker, C.; Hua, D. H. *Tetrahedron Lett.* **1981**, *22*, 3455.

m/z (relative intensity) 136 (M^+, 31), 121 (53), 107 (26), 93 (100), 92 (10), 91 (85), 79 (15), 78 (12), 77 (82), 65 (29), 53 (11), 51 (21), 41 (25), 39 (46). Anal. Calcd for $C_9H_{12}O$ (136.19): C, 79.39; H, 8.88. Found: C, 79.10; H, 9.04.

1,6-Cycloheptadienecarbaldehyde (3b): yield 250 mg (57%); R_f 0.28 (9:1 hexane/EtOAc); bp 100 °C (18 torr); IR 3035 w, 2935 s, 2885 m, 2865 m, 2835 m, 2770 w, 2740 w, 2710 w, 1692 s (C=O), 1645 w, 1625 m, 1450 m, 1432 m, 1362 w, 1332 w, 1255 w, 1238 m, 1160 s, 1088 w, 1043 w, 1000 w, 955 w, 918 w, 895 w, 860 w, 812 w, 782 m, 750 m, 732 m; ^{1}H NMR (90 MHz) δ 9.63 (s, 2 H, CHO), 6.68 (t, J = 4.5, 1 H, H-C(2)), 6.30 (dm, J = 12.0, 1 H, H-C(7)), 5.98 (dt, J = 12.0, 4.5, 1 H, H-C(6)), 2.90–2.27 (m, 4 H, 2 H-C(3), 2 H-C(5)), 2.03–1.67 (m, 2 H, 2 H-C(4)); MS (70 eV), m/z (relative intensity) 122 (M^+, 71), 107 (28), 104 (12), 94 (15), 93 (57), 92 (16), 91 (70), 80 (10), 79 (2), 78 (79), 77 (100), 66 (25), 65 (35), 63 (14), 53 (18), 51 (19), 43 (23), 41 (25), 40 (11), 39 (63). Anal. Calcd for $C_8H_{10}O$ (122.17): C, 78.65; H, 8.25. Found: C, 78.55; H, 8.33.

(7) Conversion of Vinyl Substituent to a Protected Hydroxymethyl Group. (7.1) *cis,trans*-2-(*tert*-Butyldimethylsiloxy)-3-oxocyclohexanecarbaldehyde (11). Compound **8a** (1.57 g, 6.16 mmol) was dissolved in CH_2Cl_2 (50 mL) in a three-necked, 50-mL, round-bottomed flask fitted with a gas inlet tube, stopper, magnetic stirring bar, and gas exit to an aqueous KI bubbling tower. The solution was cooled to −78 °C and ozone (1.3 mmol/min) was passed through the solution until the reaction mixture was blue (ca. 10 min). The generation of ozone was ceased and oxygen was passed through the solution until the solution was colorless. Triphenylphosphine (1.90 g, 7.24 mmol) was added and the reaction mixture was warmed to room temperature. After 4 h at room temperature, the mixture was extracted with CH_2Cl_2 (3 × 40 mL). The individual organic extracts were washed with water (2 × 40 mL) and brine (40 mL). The organic layers were combined, dried ($MgSO_4$), filtered, concentrated, chromatographed (R_f 0.30 (5:1 hexane/EtOAc)), and distilled: bp 100 °C (0.30 torr); yield 1.38 g (87%); IR 2900 s, 2830 s, 1725 s (C=O), 1460 m, 1420 m, 1390 w, 1358 w, 1250 s, 1190 m, 1140 s, 1100 sh, 1040 m, 920 m, 840 s, 815 w, 780 s; ^{1}H NMR (90 MHz) δ 9.83 (d, J = 2.0, 0.6 H, CHO, trans), 9.67 (s, 0.4 H, CHO, cis), 4.45 (d, J = 3.0, 0.4 H, H-C(2), cis), 4.43 (d, J = 10.5, 0.6 H, H-C(2), trans), 3.00–1.67 (br m, 7 H, 2 H-C(4), 2 H-C(5), 2 H-C(6), 1 H-C(2)), 0.98 (s, 9 H, $(CH_3)_3CSi$, both isomers), 0.28 (s, 1.8 H, CH_3Si, trans), 0.17 (s, 1.2 H, CH_3Si, cis), 0.13 (s, 3 H, CH_3Si, both isomers). Anal. Calcd for $C_{13}H_{24}O_3Si$ (256.42): C, 60.89; H, 9.43. Found: C, 60.85; H, 9.33.

(7.2) *cis,trans*-2-(*tert*-Butyldimethylsiloxy)-3-(hydroxymethyl)cyclohexanone (12). Aldehyde **11** (1.35 g, 5.26 mmol) was dissolved in THF (13 mL) in a three-necked, 50-mL, round-bottomed flask fitted with a magnetic stirring bar, N_2 inlet, septum, and stopper. The solution was cooled to −78 °C and LTEPA (7.63 mL, 0.69 M in THF) was added dropwise over 30 min. The reaction was judged complete by TLC analysis (2:1 hexane/EtOAc) after 10 min at −78 °C and methanol (1 mL) was injected. The reaction mixture was warmed to room temperature and poured into water (120 mL). The aqueous phase was extracted with Et_2O (3 × 50 mL). The individual organic extracts were washed with water (2 × 50 mL) and brine (50 mL). The organic layers were combined, dried ($MgSO_4$), filtered, concentrated, chromatographed (R_f 0.25, 0.28 (2:1 hexane/EtOAc)), and distilled, bp 100 °C (0.05 torr), to yield 1.045 (77%): IR 3440 m (OH), 2955 s, 2930 s, 2885 s, 2860 s, 1725 s (C=O), 1470 m, 1460 m, 1450 m, 1425 m, 1390 m, 1335 m, 1310 m, 1255 m, 1215 m, 1180 m, 1125 s, 1080 s, 1050 s, 1030 s, 1010 s, 920 s, 840 s, 780 s, 670 s; ^{1}H NMR (90 MHz) δ 4.30–4.10 (m, 0.4 H, H-C(2), cis), 4.22 (d, J = 10.5, 0.6 H, H-C(2), trans), 3.83–3.50 (m, 0.8 H, 2 H-C(1′), cis), 3.77 (d, J = 4.0, 1.2 H, 2 H-C(1′), trans), 2.50–1.50 (br m, 8 H, 1 H-C(3), 2 H-C(4), 2 H-C(5), 2 H-C(6), OH), 1.03 (s, 9 H, $(CH_3)_3CSi$, both isomers), 0.25 (s, 3 H, CH_3Si, both isomers), 0.10 (s, 3 H, CH_2Si, both isomers). Anal. Calcd for $C_{13}H_{26}O_3Si$ (258.44): C, 60.42; H, 10.14. Found: C, 60.32; H, 10.25.

(7.3) *cis,trans*-3-[(Benzyloxy)methoxymethyl]-2-(*tert*-butyldimethylsiloxy)cyclohexanone (13). Alcohol **12** (1.00 g, 3.87 mmol) was dissolved in DMF (10 mL) in a 30-mL, round-bottomed flask. Diisopropylethylamine (1.01 mL, 5.80 mmol) and chloromethyl benzyl ether (0.81 mL, 5.80 mmol) were added and the mixture was stirred for 20 h at room temperature. The reaction mixture was poured into water (30 mL) and extracted with Et_2O (3 × 30 mL). The individual organic extracts were washed with water (5 × 30 mL) and brine (30 mL). The organic layers were combined, dried ($MgSO_4$), filtered, concentrated, chromatographed (R_f 0.26, 0.32 (6:1 hexane/EtOAc), and distilled: 190 °C (0.05 torr); yield 1.33 g (91%); IR 3085 w, 3060 w, 3030 w, 2940 s, 2880 s, 2860 s, 1725 s (C=O), 1495 w, 1455 s, 1380 m, 1360 m, 1310 m, 1250 s, 1190 s, 1125 s, 1045 s, 940 s, 920 s, 840 s, 780 s, 738 s, 695 s, 670 m; ^{1}H NMR (90 MHz) δ 7.35 (s, 5 H, Ar H), 5.92–5.60 (m, 4 H, OCH_2O, OCH_2Ph), 4.23–4.07 (m 1 H, H-C(2)), 3.83–3.53 (m, OCH_2-C(3)), 2.50–1.26 (br m, 7 H, H-C(3), 2 H-C(4), 2 H-C(5), 2 H-C(6)), 0.98 (s, 9 H, $(CH_3)_3CSi$), 0.23 (s, 3 H, CH_3Si), 0.10 (s, 3 H, CH_3Si). Anal. Calcd for $C_{21}H_{34}O_4Si$ (378.59): C, 66.62; H, 9.05. Found: C, 66.40; H, 9.03.

(7.4) 3-[(Benzyloxy)methoxymethyl]-1-cyclohexenecarbaldehyde (1e) was prepared according to the general procedure outlined above: yield 773 mg (66%); R_f 0.30 (4:1 hexane/EtOAc); bp 160 °C (0.20 torr); IR 3100 w, 3090 w, 3060 w, 3030 m, 2930 s, 2865 s, 2910 m, 2705 w, 1685 s (C=O), 1640 m (C=C), 1495 m, 1452 m, 1432 m, 1375 m, 1300 w, 1205 m, 1175 s, 1110 s, 1045 s, 950 s, 900 m, 885 m, 770 m, 740 s, 700 s; ^{1}H NMR (90 MHz) δ 9.38 (s, 1 H, CHO), 7.33 (s, 5 H, Ar H), 6.67 (br s, 1 H, H-C(2)), 4.75 (s, 2 H, OCH_2O), 4.62 (s, 2 H, OCH_2Ph), 3.73–3.40 (highly structured multiplet, 2 H, 2 H-C(3′)), 2.86–1.20 (br m, 7 H, 1 H-C(3), 2 H-C(4), 2 H-C(5), 2 H-C(6)); MS (70 eV), m/z (relative intensity) 200 (19), 154 (12), 108 (11), 92 (10), 91 (100). Anal. Calcd for $C_{16}H_{20}O_3$ (260.34): C, 73.82; H, 7.74. Found: C, 73.88; H, 7.34.

(7.5) *cis,trans*-Methyl-2-(*tert*-butyldimethylsiloxy)-3-oxocyclohexanecarboxylate (14). Keto olefin **8a** was oxidized by the method of Sharpless et al.[16] The olefin (1.50 g, 5.90 mmol) was dissolved in a mixture of acetonitrile (50 mL), carbon tetrachloride (50 mL), and water (75 mL). Sodium periodate (5.67 g, 26.5 mmol) was added to the magnetically stirred solution. Ruthenium(III) chloride trihydrate (34 mg, 0.13 mmol) was added and the mixture was vigorously stirred for 3 h. The reaction was monitored by TLC, watching for the disappearance of olefin and aldehyde. The reaction mixture turned from brown to gray green when the oxidation was complete. The reaction mixture was extracted with CH_2Cl_2 (3 × 50 mL). The organic layers were individually washed with water (3 × 50 mL), combined, dried ($MgSO_4$), filtered, and concentrated. An excess of diazomethane in Et_2O was added to the crude acid. Acetic acid (1 mL) was added and the Et_2O was washed with saturated aqueous sodium bicarbonate (3 × 30 mL). The aqueous layers were extracted with Et_2O (2 × 30 mL). The organic layers were combined, dried ($MgSO_4$), filtered, and evaporated. The ester was then chromatographed to remove a brown impurity (R_f 0.23, 0.25 (6:1 hexane/EtOAc)): yield 1.36 g (80%); bp 135 °C (0.30 torr); IR 3000 w, 2960 s, 2930 s, 2890 m, 2860 m, 1730 s, (C=O), 1460 m, 1450 m, 1428 m, 1370 m, 1360 m, 1340 m, 1300 m, 1250 s, 1170 s, 1140 s, 1115 m, 1100 m, 982 m, 925 m, 890 m, 840 s; ^{1}H NMR (200 MHz) δ 4.45 (d, J = 10.4, 0.6 H, H-C(2), trans), 4.30 (d, J = 2.8, 0.4 H, H-C(2), cis), 3.71 (s, 1.8 H, CH_3O, trans), 3.69 (s, 1.2 H, CH_3O, cis), 2.85–1.80 (br m, 7 H, 1 H-C(1), 2 H-C(4), 2 H-C(5), 2 H-C(6), both isomers), 0.86 (s, 9 H, $(CH_3)_3CSi$, both isomers), 0.15 (s, 1.8 H, CH_3Si, trans), 0.02 (s, 1.2 H, CH_3Si, cis), 0.01 (s, 1.2 H, CH_3Si, cis), 0.00 (s, 1.8 H, CH_3Si, trans); MS (70 eV), m/z (relative intensity) 271 (M^+ − 15, 1), 229 (M^+ − 57, 51), 170 (15), 169 (100), 151 (15), 89 (21), 75 (34), 73 (29), 59 (19). Anal. Calcd for $C_{14}H_{26}O_4Si$ (286.45): C, 58.70; H, 9.15. Found: C, 58.43; H, 9.45.

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Registry No. **1a**, 97997-02-9; **1b**, 97997-03-0; **1c**, 97997-04-1; **1d**, 97997-05-2; **2b**, 97997-06-3; **2c**, 97997-07-4; **3a**, 97997-08-5; **3b**, 65093-90-5; **4a**, 6140-65-4; **4b**, 1192-88-7; **4c**, 6140-67-6; **5a**, 97997-09-6; **5b**, 61967-80-4; **5c**, 97997-10-9; **6a**, 930-68-7; **6b**, 5515-76-4; **6c**, 1121-66-0; **6d**, 1073-13-8; **7a**, 78828-42-9; **7b**,

71837-46-2; **7c**, 89088-84-6; **7d**, 97997-11-0; *cis*-**8a**, 97997-12-1; *trans*-**8a**, 97997-13-2; *cis*-**8b**, 97997-14-3; *trans*-**8b**, 97997-15-4; **8c**, 97997-16-5; *cis*-**8d**, 97997-17-6; *trans*-**8d**, 97997-18-7; **9a**, 54781-30-5; **9b**, 71964-38-0; **10a**, 97997-19-8; **10b**, 97997-20-1; **10c**, 97997-21-2; *cis*-**11**, 97997-22-3; *trans*-**11**, 97997-23-4; *cis*-**12**, 97997-24-5; *trans*-**12**, 97997-25-6; *cis*-**13**, 97997-26-7; *trans*-**13**, 97997-27-8; *cis*-**14**, 97997-28-9; *trans*-**14**, 97997-29-0; *cis*-**14** (free acid), 97997-30-3; *trans*-**14** (free acid), 97997-31-4; **18**, 97997-32-5; **19**, 97997-33-6; vinyl bromide, 593-60-2; 2-hydroxy-6-cycloheptenone, 97997-34-7.

Asymmetric Synthesis Using Chiral Lithium Alkoxytrialkylaluminates: Obtention of (2*S*)-2-Hydroxy-2-phenyl-4-methylpentanoic Acid with 85% Optical Purity

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The chiral reagent prepared by mixing equimolecular amounts of triisobutylaluminium and lithium alcoholate of (+)-Darvon alcohol reacts readily in hexane solvent with methyl phenylglyoxylate to give the expected α-isobutyl α-hydroxy ester in 95% chemical yield with no significant reduction byproduct, and best optical yields are achieved at 0 °C and high dilution (0.04 M) in hexane. Upon saponification of the ester, (2*S*)-2-hydroxy-2-phenyl-4-methylpropanoic acid is obtained in 85% enantiomeric excess. Reacting the lithium alkoxytriethylaluminate and lithium alkoxytri-*n*-butylaluminate with the same α-keto ester provided confirmatory evidence for the influence of dilution on the extent of asymmetric induction.

Stereoselective synthesis of chiral α-alkyl α-hydroxy acids is the subject of extended studies and many recent papers deal with it.[1-10]

In previous reports we have shown that alkoxytrialkylaluminates react with α-keto esters to give α-alkyl α-hydroxy esters (or acids).[11-14] We have also described a convenient synthesis of this type of reagent by mixing equimolecular amounts of trialkylaluminum and alkaline alcoholates obtained from an alcohol or an amino alcohol. If a chiral alkoxy radical is chosen, optically active α-alkyl α-hydroxy esters (or acids) may be obtained from nonchiral α-keto esters as, for example, in the reaction of methyl phenylglyoxylate with the alkoxytributylaluminates derived from (+)-(2*S*,3*R*)-4-(dimethylamino)-1,2-diphenyl-3-methyl-2-butanol, (+)-Darvon alcohol,[14,15] and from (−)-*N*-methylephedrin.[11]

Results and Discussion

In the present work, we report in Table I the results obtained by the reaction of the lithium alkoxytriisobutylaluminate derived from (+)-Darvon alcohol with methyl phenylglyoxylate.

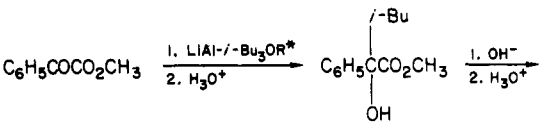
Scheme I[a]

$$R^*OH + n\text{-BuLi} \longrightarrow R^*OLi + C_4H_{10}$$

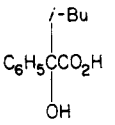
$$R^*OLi + Al\text{-}i\text{-}Bu_3 \longrightarrow LiAl\text{-}i\text{-}Bu_3OR^*$$

[a] R*OH = (+)-Darvon alcohol.

Scheme II



1a



2a

Examination of the results summarized in Table I highlight the following facts:

(1) The nature of the solvent is highly influential in determining the enantiomeric purity. For example, best enantiomeric excess is obtained in hexane, while adding diethyl ether results in an inversion of induction and a large decrease of enantiomeric excess (entry 2).

(2) In all experiments, appreciable amounts of reduction byproducts are not formed. According to GC analysis, the yields remain less than 10% and, in addition, the smallest values (<5%) are obtained in experiments for which the highest optical yields are obtained (temperature of 0 °C and low concentration). This is undoubtly the most striking fact with reference to the nature of the organometallic reagent. Indeed, it is well-known that Grignard reagents from isobutyl chloride and bromide, on reacting with carbonyl compounds, lead to mixtures with significant amounts of the corresponding reducted alcohols. As for

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