mono-EtOH solvate, mp 114–116 °C. Recrystallization from EtOH gave pure **15**·EtOH (mp 114–116 °C) which contained a trace of the 6β-ol **7** as indicated by TLC: NMR δ 4.70 (d, H5, J = 7 Hz). Anal. Calcd for $C_{27}H_{29}NO_7S \cdot C_2H_6O$: C, 62.24; H, 6.66; N, 2.50. Found: C, 62.07; H, 6.29; N, 2.40.

6α,7α:14,7β-Bis(oxymethylene)-4,5α-epoxy-3-methoxy-17-methylmorphinan (16). A solution of **15**·EtOH (3.36 g, 6.0 mmol) in dioxane (75 mL) containing 1 N NaOH (20 mL) was refluxed for 10 h. The mixture was evaporated to a small volume and the residue partitioned between H_2O and $CHCl_3$. Processing in the usual fashion gave 2.38 g of a foam which was chromatographed to give 1.88 g (92%) of **16** as a foam. Crystallization from EtOH gave 1.21 g of **16** as white crystals, mp 213–215 °C. One additional crystallization gave analytically pure **16**: mp 214–215.5 °C; NMR δ 6.70 (m, 2 H, aromatic), 5.06 (d, 1 H, J = 7 Hz), 3.3–3.0 (m, 2 H), 2.43 (CH_3N); mass spectrum, m/e (relative intensity) 341 (M^+, 100), 284 (66), 254 (25), 230 (56). Anal. Calcd for $C_{20}H_{23}NO_4$: C, 70.36; H, 6.79; N, 4.10. Found: C, 70.08; H, 6.76; N, 4.23.

7α-(Bromomethyl)-4,5α-epoxy-3-hydroxy-14,7β-(oxymethylene)morphinan-6-one (17). A suspension of **14**·0.5H_2O (8.00 g, 15.4 mmol) in 48% HBr (80 mL) was immersed in an oil bath preheated to 140 °C and the mixture refluxed for 15 min. The clear solution was cooled, diluted with ice and H_2O, and made basic with concentrated NH_4OH. Extraction with $CHCl_3$ followed by processing in the usual fashion gave a gum which was crystallized from EtOH to give 5.80 g (93%) of **17** as white needles [mp 239–241 °C (sinters)] which contained trace impurities as indicated by TLC. Chromatography of 1.00 g of this material gave 0.98 g of pure **17** as a foam. Crystallization from EtOH gave an analytical sample of **17**: mp, sinters above 248 °C; NMR δ 6.68 (m, 2 H, aromatic), 6.2 (br, 1 H, HO), 5.00 (s, 1 H, H5), 4.17 (s, 2 H, $BrCH_2$); mass spectrum, m/e (relative intensity) 407 (71), 405 (68), 326 (23), 296 (92), 241 (100). Anal. Calcd for $C_{19}H_{20}BrNO_4$: C, 56.17; H, 4.96; N, 3.45. Found: C, 56.31; H, 5.22; N, 3.40.

7α-(Bromomethyl)-4,5α-epoxy-14,7β-(oxymethylene)morphinan-3,6α-diol (18). A solution of **17** (4.64 g, 11.4 mmol) in MeOH (150 mL) and $CHCl_3$ (100 mL) was cooled in an ice bath and $NaBH_4$ (0.40 g, 10.6 mmol) added in one portion. The mixture was stirred for 20 min in the cold and then adjusted to ca. pH 6 with HOAc. After evaporation, the residue was dissolved in H_2O, excess NH_4OH added, and the mixture processed with $CHCl_3$ in the usual manner to give a foam which was chromatographed. Homogenous fractions were pooled and evaporated to give 4.68 g of **18** as a foam which was warmed with a small amount of dioxane. Crystals (3.84 g, 68%) of the dioxane solvate of **18** (mp 225–226 °C), were collected after cooling. Recrystallization of this material from dioxane gave solvated **18**: mp, crystal change at 130–140 °C, melts at 226–227 °C. Solvent-free material was prepared by drying at 120 °C under high vacuum: NMR δ 4.70 (d, 1 H, H5, J = 6 Hz); mass spectrum, m/e (relative intensity) 409 (74), 407 (81), 298 (100), 241 (52). Anal. Calcd for $C_{19}H_{22}BrNO_4$: C, 55.89; H, 5.43; N, 3.43. Found: C, 55.90; H, 5.45; N, 3.47.

6α,7α:14,7β-Bis(oxymethylene)-4,5α-epxoy-17-methylmorphinan-3-ol (19). A suspension of the dioxane solvate of **18** (3.00 g, 6.0 mmol) in dioxane (100 mL), under argon, was warmed to give a clear solution and 1 N NaOH (24 mL) added. The mixture was refluxed for 2 h, cooled, and concentrated to a small volume. The residue was diluted with H_2O, 1 N HCl (25 mL) was added, and then the solution was immediately made basic with excess NH_4OH. Extraction with $CHCl_3$ and processing in the usual fashion gave 1.84 g of a foam which was chromatographed. Appropriate fractions were combined and evaporated to give 1.45 g (73%) of **19** which contained trace impurities as shown by TLC. This material was rechromatographed to give homogeneous **19** which was twice crystallized from EtoAc to provide a sample of pure **19**: mp >265 °C; NMR δ 6.72 (m, 3 H, H 1, H 2, HO), 5.15 (d, 1 H, H5), 4.48 (q, 2 H, 7α CH_2, J = 20, 6 Hz), 4.65 (d, 1 H, H6), 3.73 (q, 2 H, 7β-CH_2O, J = 15, 8 Hz); mass spectrum, m/e (relative intensity) 327 (M^+, 100), 216 (29). Anal. Calcd for $C_{19}H_{21}NO_4$: C, 69.71; H, 6.47; N, 4.28. Found: C, 69.50; H, 6.65; N, 4.26.

Acknowledgment. I am indebted to D. L. Leland for the original preparation and characterization of **2**.

Registry No. 1, 76-42-6; **2**, 85454-72-4; **3**, 85454-73-5; **4**, 85454-75-7; **4** tartrate, 85454-76-8; **5**, 85454-77-9; **7**, 85454-78-0; **8**, 85454-79-1; **9**, 85454-80-4; **9** tartrate, 85454-81-5; **10**, 85454-82-6; **11**, 85454-83-7; **14**, 85454-84-8; **15**, 85479-35-2; **16**, 85454-85-9; **17**, 85454-86-0; **18**, 85454-87-1; **19**, 85454-88-2.

Sequential Ene Reactions. A New Annelation Procedure

Barry B. Snider*[1] and Ethan A. Deutsch

Departments of Chemistry, Brandeis University, Waltham, Massachusetts 02254, and Princeton University, Princeton, New Jersey 08544

Received September 14, 1982

Alkylidenecycloalkanes **1** undergo two sequential Me_2AlCl-catalyzed ene reactions with α,β-unsaturated carbonyl compounds to give bicyclic alcohols **3**. At low temperatures, the initial ene adducts **2** can be isolated when vinyl ketones are used. This reaction has been used for the synthesis of 24-oxocholesterol. Other classes of alkenes give more complex mixtures. The scope, limitations, and mechanism of this reaction are discussed.

The use of carbon–carbon double bonds as activating groups for the formation of new carbon–carbon bonds under mild conditions is a challenge to synthetic chemists. The ene reaction provides a potential solution to this problem.[2] We have found that Lewis acid catalyzed ene reactions with acrylate esters as the enophile occur at 25 °C and that the ene reactions of α-substituted acrylate esters are regioselective and stereoselective, with the carboalkoxy group adding endo.[2b,3] Lewis acid catalysis offers significant advantages over the corresponding thermal ene reactions which occur at 200–300 °C. We have also shown that alkylaluminum halides are preferred catalysts for these reactions since the alkyl group functions as a proton scavenger.[4]

α,β-Unsaturated ketones and aldehydes have seen little use as enophiles.[5] Acrolein reacts with β-pinene at 140

(1) Fellow of the Alfred P. Sloan Foundation, 1979–1983. Address correspondence to Department of Chemistry, Brandeis University, Waltham, MA 02254.

(2) (a) Hoffmann, H. M. R. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 556. (b) Snider, B. B. *Acc. Chem. Res.* **1980**, *13*, 426.

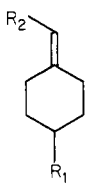
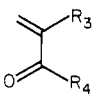
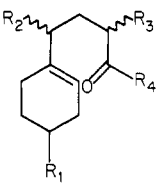
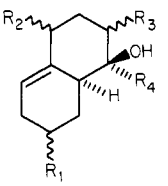
(3) Duncia, J. V.; Lansbury, Peter T., Jr.; Miller, T.; Snider, B. B. *J. Am. Chem. Soc.* **1982**, *104*, 1930.

(4) Snider, B. B.; Rodini, D. J.; Karras, M.; Kirk, T. C.; Deutsch, E. A.; Cordova, R.; Price, R. T. *Tetrahedron* **1981**, *37*, 3927.

(5) (a) Albisetti, C. J.; Fisher, N. G.; Hogsed, M. J.; Joyce, R. M. *J. Am. Chem. Soc.* **1956**, *78*, 2637. (b) Kruk, C.; Velzen, J. C. V.; de Boer, T. J. *Recl. Trav. Chim. Pays-Bas* **1969**, *88*, 139.

0022-3263/83/1948-1822$01.50/0

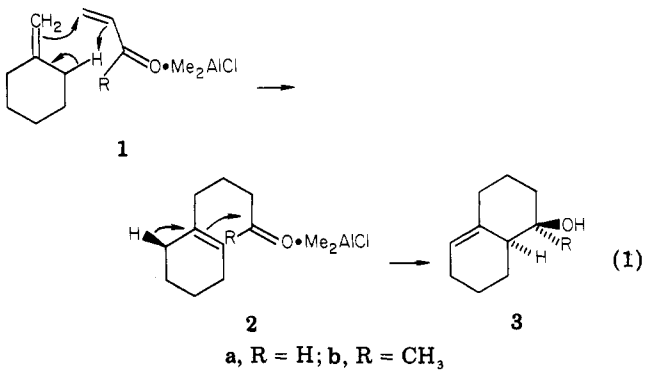
Table I. Sequential Ene Reactions of Alkylidenecyclohexanes

		ene	enophile	product; yield, %	
					
		1		2	3
run	temp, °C				
1	0	a, $R_1 = R_2 = H$	$R_3 = R_4 = H$		a; 63
2	−20		$R_3 = H$, $R_4 = CH_3$	b; 39	b; 4
3	25		$R_3 = H$, $R_4 = CH_3$	b; 9	b; 49
4	0		$R_3 = CH_3$, $R_4 = H$		c, R_3 = α-CH_3; 17 d, R_3 = β-CH_3; 49
5	0		$R_3 = Br$, $R_4 = H$		e, R_3 = α-Br; 55 f, R_3 = β-Br; 4
6	0	b, $R_1 = CH_3$, $R_2 = H$	$R_3 = R_4 = H$		g, R_1 = α-CH_3; 20 h, R_1 = β-CH_3; 30
7	0	c, R_1 = *t*-Bu, $R_2 = H$	$R_3 = R_4 = H$		i, R_1 = α-*t*-Bu; 33 j, R_1 = β-*t*-Bu; 38
8	0	d, $R_1 = H$, $R_2 = CH_3$	$R_3 = R_4 = H$		k, R_2 = β-CH_3; 40
9	25		$R_3 = H$, $R_4 = CH_3$		l, R_2 = β-CH_3; 61 m, R_2 = α-CH_3; 4
10	−30		$R_3 = CH_3$, $R_4 = H$		n, $R_2 = R_3$ = β-CH_3
11	−78		$R_3 = Br$, $R_4 = H$		o, R_2 = β-CH_3, R_3 = β-Br; 42 p, R_2 = β-CH_3, R_3 = α-Br; 3 q, R_2 = α-CH_3, R_3 = α-Br; 3

°C[5b] or with $ZnBr_2$ catalysis at 25 °C.[6] Methyl vinyl ketone (MVK) reacts with β-pinene at 25 °C with $ZnBr_2$ catalysis[6] and has been reported to react with limonene with $AlCl_3$ catalysis.[7] We report here a detailed study of the scope and limitations of this class of electron-deficient alkenes as enophiles.[8]

Results and Discussion

Alkylidenecycloalkanes. Alkylidenecycloalkanes react with β-unsubstituted α,β-unsaturated aldehydes or ketones in the presence of Me_2AlCl to give a bicyclic alcohol resulting from two sequential ene reactions. For instance, methylenecyclohexane (**1a**), acrolein, and Me_2AlCl in CH_2Cl_2 react at 0 °C to give a 63% yield of **3a** (see eq 1).



1 2 3

a, R = H; b, R = CH_3 (1)

The initially formed ene adduct **2a** undergoes a second, intramolecular ene reaction with the complexed aldehyde functioning as the enophile. Loss of methane from the resulting alcohol–Lewis acid complex to give the aluminum alkoxide prevents proton-catalyzed side reactions or solvolysis of the alcohol. Cyclization of **2a** to **3a** is much faster than the formation of **2a**, since no **2a** could be detected, even when the reaction is run to low conversion at −78 °C.

Reaction of **1a**, MVK, and Me_2AlCl at −20 °C for 2 h gives a 39% yield of **2b** and a 4% yield of **3b**. The same reaction at 25 °C for 1 h gives a 9% yield of **2b** and a 49% yield of **3b**. Thus, at different reaction times, either **2b** or **3b** can be isolated as the major product. The successful isolation of **2b**, as opposed to **2a**, results from the diminished reactivity of the ketone carbonyl as an enophile.[9] The isolation of a tertiary alcohol, **3b**, from a Lewis acid catalyzed reaction is due to its protection as an aluminum alkoxide.

The reactions of a variety of alkylidenecycloalkenes with acrolein, α-bromoacrolein, methacrolein, and vinyl and isopropenyl ketones are shown in Tables I and II. The stereochemistry of the hydroxyl and bromine substituents was established by the characteristic chemical shifts and coupling constants of the α-protons. The protons α to the hydroxyl groups absorb as broad singlets ($w_{1/2}$ = 7–11 Hz), typical of equatorial protons.

The stereochemistry of all substituents was established by comparison of the ^{13}C NMR spectra with spectra calculated from appropriate models. The reported ^{13}C NMR spectra[10] of octahydronaphthalene (**7**) and hexahydroindene (**8**) were assigned by using the spectra of the appropriate cycloalkene[11] and 2-methylmethylenecyclo-

(6) Snider, B. B. *J. Org. Chem.* **1974**, *39*, 255.
(7) Mehta, G.; Reddy, A. V. *Tetrahedron Lett.* **1979**, 2625. We have been unable to repeat this reaction. Professor Mehta has indicated that "the yields are somewhat erratic and decrease enormously on scale up above 10 mmol". In addition the reported yield of 75% is based on recovery of 80% of the limonene. From the spectral data reported, there is not doubt that the ene adduct was obtained. However, our results make it clear that the ene adduct will not be stable to $AlCl_3$ for 12 h in benzene. The most likely explanation is that a partially hydrated, and therefore much less active, sample of $AlCl_3$ was used.
(8) For a preliminary report of this work see: Snider, B. B.; Deutsch, E. A. *J. Org. Chem.* **1982**, *47*, 745.
(9) (a) Karras, M.; Snider, B. B. *J. Am. Chem. Soc.* **1980**, *102*, 7951. (b) Snider, B. B.; Karras, M.; Price, R. T.; Rodini, D. J. *J. Org. Chem.* **1982**, *47*, 4538.
(10) Becker, K. B. *Helv. Chim. Acta* **1977**, *60*, 68.
(11) "Sadtler Standard Carbon-13 NMR Spectra"; Sadtler Chemical Co.: 1982: (a) 1-methylcyclohexene, 2884; (b) 1-methylcyclohexanol, 1508; (c) cyclopentene, 12286; (d) *tert*-butylcyclohexane, 4069.

Table II. Sequential Ene Reactions of Alkylidenecyclopentanes

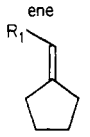
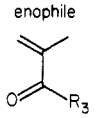
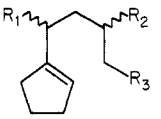
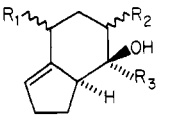
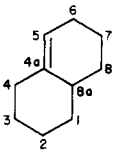
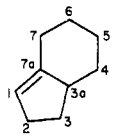
		ene	enophile	product; yield, %	
					
		4		5	6
run	temp, °C				
1	0	a, R_1 = H	R_2 = R_3 = H		a; 38
2	0	b, R_1 = CH_3	R_2 = R_3 = H		b, R_1 = β-CH_3; 51
3	−78		R_2 = H, R_3 = CH_3	c; 65	
4	25		R_2 = H, R_3 = CH_3		c, R_1 = β-CH_3; 72
5	−20		R_2 = CH_3, R_3 = C_2H_5	d, R_1 = R_2 = β-CH_3; 49 e, R_1 = α-CH_3, R_2 = β-CH_3; 5	

Table III. ^{13}C NMR Spectral Data of Bicyclic Ene Adducts



7



8

	chemical shift, ppm									
adduct	C(1)	C(2)	C(3)	C(4)	C(4a)	C(5)	C(6)	C(7)	C(8)	C(8a)	other
7[a]	35.6	26.9	27.9	35.3	140.9	119.1	25.5	21.6	31.2	37.4	
3a[b]	71.3	33.5	20.9	34.8	136.0	124.3	26.4	21.9	25.2	42.1	
3b[c]	72.2	40.4	22.5	35.2	137.0	124.6	26.8	23.1	25.2	46.3	22.0
3c[d]	76.4	33.5	26.2	29.3		123.9	26.6	22.1	25.2	36.6	15.9
3d[d]	75.6	37.4	28.7	34.6	135.5	124.3	26.4	21.9	25.2	42.7	18.5
3e[e]	74.5	53.8	28.9	29.3	134.2	125.1	25.7	21.7	25.0	35.5	
3f[e]	78.4	58.7	31.6	35.3	132.5	125.0	26.5	21.6	25.0	41.8	
3g[d]	73.0	33.8	21.4	34.8	135.1	122.2	32.7	26.2	32.7	40.7	21.0
3h[d]	69.8	33.1	20.6	34.1	136.1	123.5	34.6	28.7	33.4	43.2	22.4
3i[f]	74.1	34.0	21.5	35.0	135.3	123.3	28.6	41.6	25.1	40.7	26.7, 32.1
3j[g]	69.5	32.8	19.8	33.5	135.3	123.2	26.9	43.5	26.4	43.5	26.9, 31.7
3k[h]	71.3	33.5	30.2	37.0	139.6	121.6	26.9	21.7	25.4	42.4	18.0
3l[i]	72.6	40.3	31.7	37.0	140.7	121.9	26.6	23.5	25.3	46.6	21.6, 18.2
3m[i]	72.4	35.1	27.9	37.3	141.2	124.5	26.8	23.0	25.3	41.7	22.1, 19.9
3n[j]	76.3	37.2	38.2	36.5		121.9	26.6	21.7	25.3	43.0	18.1, 17.8
3o[k]	75.0	58.1	40.3	37.8	136.4	122.3	27.0	21.5	25.2	42.0	17.3

	chemical shift, ppm									
adduct	C(1)	C(2)	C(3)	C(3a)	C(4)	C(5)	C(6)	C(7)	C(7a)	other
8[l]	119.9	29.1	30.9	45.7	36.1	26.4	27.6	31.2	145.9	
6a[m]	123.6	28.3	24.2	50.9	69.6	32.8	20.4	31.2	141.3	
6b[n]	121.7	29.4	24.2	51.4	69.8	32.8	31.5	33.6	146.4	18.5
6c[o]	121.6	31.0	27.4	55.9	71.8	39.3	31.4	33.3	147.5	18.4, 22.4

[a] Assigned by using 2-methylmethylenecyclohexane[12] and 1-methylcyclohexene[11a] as models. [b] Assigned by using 7 and shift values for an axial OH group.[13] [c] Assigned by using 3a and shift values for an equatorial 3-methyl group on methylenecyclohexane[12] and 1-methylcyclohexanol.[11b] [d] Assigned by using 3a and shift values for axial and equatorial methyl groups.[13] [e] Assigned by using 3a and shift values for equatorial and axial bromide groups.[13] [f] Due to the presence of the α-*tert*-butyl group the cyclohexene ring adopts a nonchair conformation, resulting in a poor fit with predicted values. [g] Assigned by using 3a and data from *tert*-butylcyclohexane.[11d] [h] Assigned by using 3a and shift values for an equatorial 2-methyl group on methylenecyclohexane.[12] [i] Assigned from 3b and shift values for equatorial and axial 2-methyl groups on methylenecyclohexane.[12] [j] Assigned by using 3d and shift values for an equatorial 2-methyl group on methylenecyclohexane.[12] [k] Assigned by using 3f and shift values for an equatorial 2-methyl group on methylenecyclohexane.[12] [l] Assigned by using 2-methylmethylenecyclohexane and cyclopentene[11c] as models. [m] Assigned by using 8 analogously to 3a. [n] Assigned by using 6a analogously to 3b. [o] Assigned by using 6b analogously to 3l.

hexane[12] as models. From this base, the ^{13}C NMR spectra of 3 and 6 could be predicted by using shift values for axial or equatorial substituents on cyclohexanes[13] and methyl substituents on methylenecyclohexanes.[12] In all cases this allowed an unambiguous assignment of stereochemistry (see Table III).

For instance, carbons 1–4 of 7[10] were assigned by analogy to 2-methylmethylenecyclohexane.[12] Carbons 6–8a were assigned by analogy to 1-methylcyclohexene,[11a] adding substituent affects for the additional alkyl group. The stereochemistry of 3a follows from the large upfield shift for carbons 3, 5, and 8 which are typical of those expected for an axial γ substituent.[13] The NMR spectrum of 3c, with an axial methyl group, shows similar upfield shifts, relative to 3a, for carbons 4 and 8a. The NMR spectrum of 3d, with an equatorial methyl group, shows no upfield shift for carbons 4 and 8a and the expected larger down-

(12) Grover, S. H.; Stothers, J. B. *Can. J. Chem.* **1975**, *53*, 589.
(13) (a) Abraham, R. J.; Loftus, P. "Proton and Carbon-13 NMR Spectroscopy"; Heyden: London, 1978; p 30. (b) Sergeev, N. M.; Subbotin, O. A. *Russ Chem. Rev. (Engl. Transl.)* **1978**, *47*, 265.

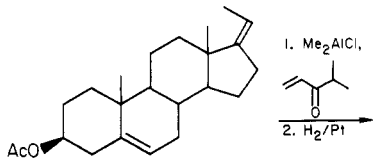
field shifts for carbons 1–3. Similar analysis allowed the assignment of stereochemistry to other adducts (see Table III for details).

Methylenecyclohexane (**1a**) reacts with methacrolein to give mainly (3:1) the isomer, **3d**, with an equatorial methyl group. On the other hand, **1a** reacts with α-bromoacrolein to give mainly (14:1) the isomer, **3e**, with an axial bromine group. The large preference for axial bromine may result from increased reactivity of the conformer of **2** with the antiperiplanar orientation of the bromine and carbonyl group. This has been previously proposed to rationalize the stereoselectivity of the Cornforth olefin synthesis.[14] Reaction of ethylidenecyclohexane (**1d**) or ethylidenecyclopentane (**4b**) with acrolein or MVK gives almost exclusively the adduct with an equatorial methyl group.

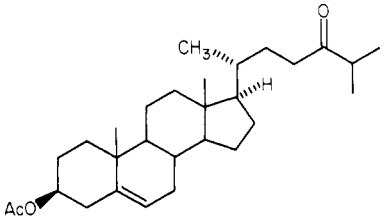
Reaction of ethylidenecycloalkanes with disubstituted enophiles can give two stereoisomers. Reaction of ethylidenecyclopentane with ethyl isopropenyl ketone gives a 10:1 mixture of **5d** and **5e**. We have previously observed similar selectivities in the ene reactions of α-substituted acrylate esters.[3] In these reactions it was established that the major isomer resulted from an ene reaction in which the carbonyl group was endo. The stereochemistry of **5d** and **5e** was assigned by analogy. Reaction of ethylidenecyclohexane (**1d**) with α-substituted acroleins gives mainly the adducts **3n** and **3o** with two equatorial substituents. This implies that **2n** and **2o**, which result from an ene reaction with the carbonyl group endo, are the major products of the initial ene reactions. Aldehydes **2n** and **2o** cyclize to give the adducts in which both substituents are equatorial since the transition state leading to the adducts in which both substituents are axial is very hindered.

Reaction of acrolein with 4-substituted methylenecyclohexanes **1b** and **1c** leads to ca. 3:2 mixtures of adducts. There is thus little facial selectivity in the second ene reaction, even with a *tert*-butyl group present to anchor the cyclohexene.

24-Oxocholesteryl acetate (**10**) was synthesized from (*Z*)-5,17(20)-pregnadien-3β-yl acetate (**9**)[15] by reaction with isopropyl vinyl ketone[16] and Me_2AlCl (eq 2) at 25 °C to



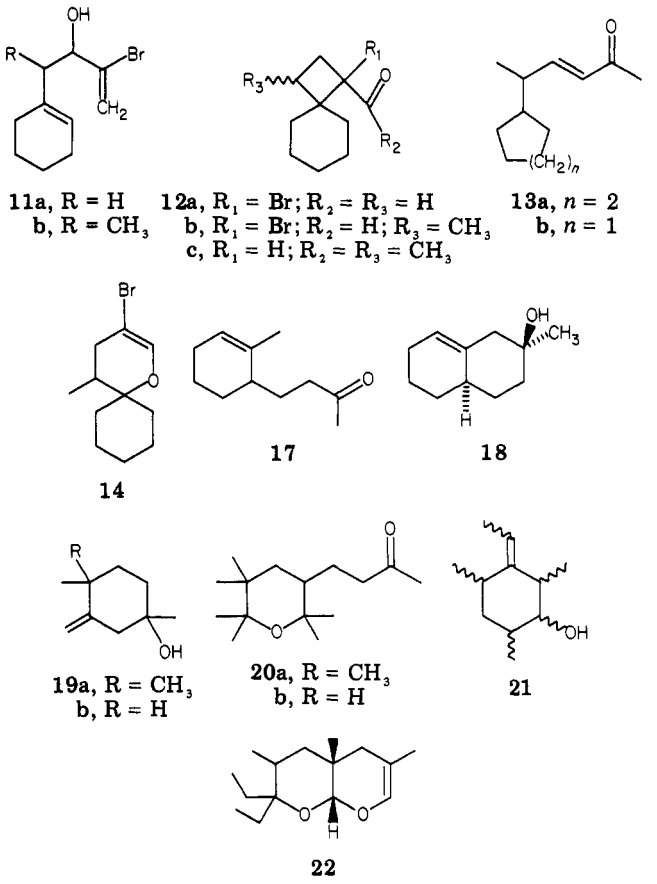
9



10 (2)

give 46% of the ene adduct with 20-*S* stereochemistry,[17]

Chart I



followed by hydrogenation of the C(16)–C(17) double bond of the ene adduct over Pt/C (80%).[17] The use of the ene reaction for establishing 20-*R* stereochemistry has been developed by Uskoković.[17a,b]

The yields of bicyclic alcohols in these reactions are typically 40–65%. In most cases, the residue is unreacted starting material or uncharacterizable mixtures. In some cases, minor products were identified. Run 5 gives 21% of **11a**, (Chart I), in which the aldehyde functions as the enophile, and 2% of **12a**. Run 9 gives 6% of **12c** as a 2:1 mixture of isomers and 6% of **13a**. Run 11 gives 1% of **11b**, 13% of **12b**, and 1% of **14**. Run 15 gives 1% of **13b**. The cyclobutanes **12** are probably formed from the collapse of a zwitterionic intermediate. The α,β-unsaturated ketones **13** are formed from a zwitterionic intermediate via two 1,2 hydride shifts.[18]

Other Alkenes. Reaction of MVK with other classes of alkenes gives more complex mixtures. 1-Methylcyclohexene, MVK, and Me_2AlCl give ca. 12% of the cyclobutane 6-methyl-7-acetylbicyclo[4.2.0]octane (**15**), 11% of 4-(2-methylcyclohexyl)-(*E*)-3-buten-2-one (**16**) which is formed analogously to **11**,[18] 11% of the ene adduct **17**, and 16% of bicyclic alcohol **18** which results from two sequential ene reactions. Alkenes such as 1-methylcyclohexene which can give two initial ene adducts are not attractive substrates for this annelation reaction.

2,3-Dimethyl-2-butene, MVK, and Me_2AlCl react to give a 42% yield of the expected adduct **19a** and 7% of a

(14) Morrison, J. D.; Mosher, H. S. "Asymmetric Organic Reactions"; American Chemical Society: Washington, DC, 1976; pp 98–100. Felkin's model for the Cornforth reaction predicts formation of **3f** as the major isomer. See: Anh, N. T.; Eisenstein, O. *Nouv. J. Chim.* **1977**, *1*, 61. The failure of the Felkin model, in this case, may result from either the intramolecular nature of the reaction or the unusual nucleophile.

(15) Drefahl, G.; Ponsold, K.; Schick, H. *Chem. Ber.* **1965**, *98*, 604.

(16) Seguchi, K.; Sera, A.; Otsuki, Y.; Maruyama, K. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 3641.

(17) (a) Batcho, A. D.; Berger, D. E.; Davoust, S. G.; Wovkulich, P. M.; Uskoković, M. R. *Helv. Chim. Acta* **1981**, *64*, 1682. (b) Batcho, A. D.; Berger, D. E.; Uskoković, M. R.; Snider, B. B. *J. Am. Chem. Soc.* **1981**, *103*, 1293. (c) Dauben, W. G.; Brookhart, T. *Ibid.* **1981**, *103*, 237.

(18) Snider, B. B.; Rodini, D. J.; van Straten, J. *J. Am. Chem. Soc.* **1980**, *102*, 5872.

product tentatively identified as **20a**. 2-Methyl-2-butene reacts analogously to give 15% of **19b** and 18% of **20b**. 2-Ethyl-2-pentene reacts with methacrolein to give a 54% yield of **21** as 31:16:3:3 mixture of stereoisomers and a 33% yield of **22**. 1-Hexene, MVK, and Me_2AlCl give a 13% yield of 6-decen-2-one (**23**).

Mechanism. Lewis acid catalyzed ene reactions can proceed through a two-step mechanism with a zwitterionic intermediate or via a concerted mechanism.[2b] In these reactions, enones **13** and **16** are formed from a zwitterionic intermediate by two sequential hydride shifts.[18] Cyclobutanes **12** and **15** are probably also formed via a two-step mechanism. Although this suggets that a zwitterionic intermediate is formed, it does not rule out a concerted mechanism for the ene reaction.

Another side reaction is the Lewis acid catalyzed inverse-electron-demand Diels–Alder reaction which gives a dihydropyran, e.g., **14**.[19] The dihydropyran is more nucleophilic than the initial alkene, so it reacts with a second equivalent of unsaturated carbonyl compound.[20] With methacrolein a second inverse-electron-demand Diels–Alder reaction gives 2:1 adducts such as **22**. With MVK a zwitterion is formed which transfers a methyl group from the aluminum to the cationic center to give 2:1 adducts such as **20**.[21] The formation of the stable zwitterion leading to **20** may result from ring opening of a dioxabicyclodecene analogous to **22**. Ring opening of **22** does not occur since it would form a less stable zwitterion.

The suitability of an alkene as a substrate for sequential ene reactions depends on competition between the desired initial ene reaction and the competing reactions described above. Alkylidenecycloalkanes which give ene adducts with stable double bonds are more suitable than 2-methyl-2-butene which gives a relatively unstable 1,1-disubstituted double bond. Steric and strain effects of substituents may also influence the percentages of dihydropyran and cyclobutane formed.

β-Substituted enones and enals such as 3-penten-2-one and crotonaldehyde do not undergo Lewis acid catalyzed ene reactions with alkenes.[18] No reaction occurs when ≤1 equiv of Me_2AlCl or $EtAlCl_2$ is used. When more than 1 equiv of $EtAlCl_2$ is used, a more electrophilic complex is formed which is stoichiometrically equivalent to a 1:2 carbonyl–$EtAlCl_2$ complex. This complex adds reversibly to the alkene to give a zwitterion which collapses reversibly to a cyclobutane and undergoes two 1,2 hydride or methyl shifts to give new α,β-unsaturated carbonyl compounds analogous to **13** and **16**.[18] No ene adduct is obtained in this reaction. The addition of a β-methyl group to an α,β-unsaturated carbonyl compound increases its basicity which leads to a less electrophilic Lewis acid complex.[22] Steric interaction of the β-methyl group with the approaching alkene also contributes to the decreased reactivity of these enones and enals.

The second ene reaction to give **3** and **6** is an example of the well-known type II intramolecular ene reaction.[23] The reaction is probably concerted. It cannot be a simple two-step reaction since the rigidity of the intermediate which would be formed precludes a 1,5 proton shift to the oxygen to give the ene adduct. We cannot rule out a stepwise reaction with intermolecular proton transfer or direct protonation of the methyl group of complexed Me_2AlCl in an eight-membered-ring transition state. The moderate yields of bicyclic alcohols obtained in these reactions is probably a result of low yields in the first ene reaction since type II intramolecular ene reactions of aldehydes[23] and ketones[24] proceed in high yield.

Conclusion

Sequential ene reactions provide a very simple route, with predictable stereocontrol, to highly functionalized bicyclic alcohols not available by alternative routes.

Experimental Section

NMR spectra were obtained on Varian A-60, Perkin-Elmer R-32, or JEOL FX90Q spectrometers. IR spectra were obtained on a Perkin-Elmer 283 spectrophotometer. Melting points were uncorrected. Elemental analyses were carried out by Galbraith Laboratories.

Methylene chloride was dried by distillation from calcium hydride. Dimethylaluminum chloride (Me_2AlCl) was obtained from Texas Alkyls as a 14.6% (1.14 M) solution in heptane. Acrolein (Aldrich) was predried with $MgSO_4$ in the presence of 1% hydroquinone and then distilled twice from $CuSO_4$. The purified acrolein (with 1% hydroquinone) was stored at −20 °C under nitrogen. Methyl vinyl ketone (MVK) was predried over K_2CO_3 and $CaCl_2$ and then distilled twice from $CuSO_4$. Hydroquinone (1%) was added to the purified MVK which was stored at −20 °C under nitrogen. α-Bromoacrolein,[25] isopropyl vinyl ketone,[16] 2-methyl-1-penten-3-one[26] 4-methyl-methylenecyclohexane,[27] 4-*tert*-butylmethylenecyclohexane,[27] and 5,17(20)-pregnadien-3β-yl acetate[15,28] were prepared by literature procedures.

General Procedure. Enal or enone was added to a solution of Me_2AlCl in heptane/methylene chloride in a flame-dried flask under nitrogen at the specified temperature to produce a yellow solution. Alkene was added, and the reaction was monotored by TLC. The solution usually became colorless on completion. The reaction was quenched by cautious addition of an equal volume of water followed by enough ether to place the organic layer on top. The layers were separated, and the aqueous layer was washed with three portions of ether, each equal in volume to one-third of the aqueous layer. The combined organic layers were washed with brine, dried (Na_2SO_4), and evaporated in vacuo.

MPLC refers to medium-pressure liquid chromatography on a Merck Lobar silica gel column.

Reaction of Methylenecyclohexane (0.53 g, 5.5 mmol), **acrolein** (0.28 g, 5.0 mmol), **and Me_2AlCl** (4.16 mL of a 1.14 M solution in heptane, 4.75 mmol) in 15 mL of CH_2Cl_2 for 20 min at 0 °C gave 0.808 g of crude product. Evaporative distillation of 0.696 g of the product (100 °C, 0.25 torr) gave 0.411 g (63%) of pure **3a**: mp 54.5–55.5 °C; ^1H NMR (CCl_4) δ 5.6 (br s, 1), 3.8 (br, $w_{1/2}$ = 11 Hz, 1). Anal. Calcd for $C_{10}H_{16}O$: C, 78.90; H, 10.59. Found: C, 78.79; H, 10.36.

Reaction of methylenecyclohexane (0.53 g, 5.5 mmol), **MVK** (0.35 g, 5.0 mmol), **and Me_2AlCl** (4.16 mL of 1.14 M, 4.75 mmol) in 15 mL of CH_2Cl_2 at −20 °C for 2 h gave 0.646 g of crude product. MPLC of 0.423 g (7:1 pentane–ether) gave 0.212 g (39%) of **2b** and 0.022 g (4%) of **3b**.

An identical reaction for 4 h at 25 °C gave a 1.2:1 mixture of **3b** and **2b**.

(19) (a) Snider, B. B.; Duncia, J. V. *J. Org. Chem.* **1980**, *45*, 3461 and references cited therein. (b) Desimoni, G.; Tacconi, G. *Chem. Rev.* **1975**, *75*, 651.

(20) Guseinov, M. M.; Mamedov, M. B.; Akhmedov, I. M.; Kyazimova, T. G.; Veliev, M. G. *Azerb. Khim. Zh.* **1971**, *3*, 67; *Chem. Abstr.* **1972**, *76*, 86179.

(21) Snider, B. B.; Cordova, R.; Price, R. T. *J. Org. Chem.* **1982**, *47*, 3643.

(22) Jensen, J. L.; Thibeault, A. T. *J. Org. Chem.* **1977**, *42*, 2168 and references cited therein.

(23) Oppolzer, W.; Snieckus, V.; Angew. *Chem., Int. Ed. Engl.* **1978**, *17*, 476.

(24) Takazawa, O.; Tamura, H.; Kogami, K.; Hayashi, K. *Chem. Lett.* **1980**, 1257.

(25) Baker, R. H.; Tinsley, S. W.; Butler, D.; Riegel, B. *J. Am. Chem. Soc.* **1950**, *72*, 393.

(26) Gore, W. E.; Pearce, G. T.; Silverstein, R. M. *J. Org. Chem.* **1975**, *40*, 1705.

(27) Senda, Y.; Kamiyama, S.; Imaizumi, S. *J. Chem. Soc., Perkin Trans. 1* **1978**, 530.

(28) Trost, B. M.; Verhoeven, T. R. *J. Am. Chem. Soc.* **1978**, *100*, 3435.

A similar reaction with 8.77 mL (10 mmol) of Me_2AlCl at 25 °C for 1 h gave 0.936 g of crude product. Purification as above gave 0.067 g (9%) of **2b** and 0.365 g (49%) of **3b**.

The data for **2b** follow: ^1H NMR (CCl_4) δ 5.38 (br s, 1), 2.31 (t, J = 5 Hz, 2), 2.06 (s, 3); ^{13}C NMR (C_6D_6) 206.1, 137.3, 121.7, 42.9, 37.8, 29.4, 28.4, 25.6, 23.4, 23.0, 22.1. Anal. Calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.91. Found: C, 79.53; H, 10.97. The data for **3b** follow: ^1H NMR ($CDCl_3$) δ 5.7 (br s, 1), 1.20 (s, 3). Anal. Calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.91. Found: C, 79.15; H, 10.69.

Reaction of methylenecyclohexane (0.33 g, 5.5 mmol), **methacrolein** (0.35 g, 5.0 mmol), **and Me_2AlCl** (4.16 mL of a 1.14 M solution, 4.75 mmol) in 15 mL of CH_2Cl_2 for 30 min at 0–25 °C gave 0.779 g of crude product. MPLC (5:1 hexane–ethyl acetate) of 0.4925 g of the crude product gave 0.257 g (49%) of **3d**, which was further purified by sublimation to give white crystals (mp 69–71 °C) followed by 0.084 g (17%) of **3c**, which was further purified by sublimation to give white cyrstals, mp 51.5–53.5 °C.

The data for **3d** follow: ^1H NMR ($CDCl_3$) δ 5.68 (br s, 1), 3.68 (br, $w_{1/2}$ = 8 Hz, 1), 1.00 (d, J = 7 Hz, 3).

The data for **3c** follow: ^1H NMR ($CDCl_3$) δ 5.67 (br s, 1), 3.57 (br, $w_{1/2}$ = 8 Hz, 1), 1.06 (d, J = 7 Hz, 3). Anal. Calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.91. Found: C, 79.34; H, 11.06.

Reaction of methylenecyclohexane (0.53 g, 5.5 mmol), **α-bromoacrolein** (0.67 g, 5.0 mmol), **and Me_2AlCl** (4.16 mL of a 1.14 M solution, 4.75 mmol) at −78 °C for 30 min gave 1.069 g of crude product. MPLC (pentane, then 5:1 pentane–ether) of 0.874 g of the crude product gave 0.022 g (2%) of **12a** followed by 0.034 g (4%) of **3f**, 0.197 g (21%) of **11a**, and 0.516 g (55%) of **3e**, mp 79–82 °C.

Alcohol **3e** was recrystallized from methanol: mp 85.5–86.5 °C; ^1H NMR ($CDCl_3$) δ 5.75 (br s, 1), 4.4 (br, $w_{1/2}$ = 8 Hz, 1), 3.88 (br, $w_{1/2}$ = 8 Hz, 1).

The data for **11a** follow: ^1H NMR ($CDCl_3$) δ 5.9 (d, J = 1.5 Hz, 1), 5.54 (d, J = 1.5 Hz, 1), 5.54 (br s, 1), 4.2 (dd, J = 9, 7 Hz, 1); ^{13}C NMR ($CDCl_3$) δ 136.8 (s), 133.3 (s), 125.6 (d), 116.3 (t), 73.4 (d), 44.4 (t), 28.2 (t), 25.2 (t), 22.7 (t), 22.1 (t); IR (neat) 1628, 894 cm^{-1}. Anal. Calcd for $C_{10}H_{15}BrO$: C, 51.96; H, 6.54; Br, 34.57. Found: C, 51.93; H, 6.54; Br, 34.34.

The data for **3f** follow: ^1H NMR ($CDCl_3$) δ 5.67 (br s, 1), 4.32 (ddd, J = 12, 4, 2.5 Hz, 1), 3.95 (br, $w_{1/2}$ = 7 Hz).

The data for **12a** follow: ^1H NMR ($CDCl_3$) δ 9.57 (s, 1), 3.0 (m, 1), 2.5 (m, 1); ^{13}C NMR ($CDCl_3$) δ 193.5 (d), 73.5 (d), 49.0 (s), 36.2 (t), 33.4 (t), 28.5 (t), 27.3 (t), 25.7 (t), 22.5 (t), 22.4 (t).

Reaction of 4-methylmethylenecyclohexane (0.55 g, 5.0 mmol), **acrolein** (0.28 g, 5.0 mmol), **and Me_2AlCl** (6.58 mL of a 1.14 M solution, 7.5 mmol) in 15 mL of CH_2Cl_2 at −40 °C for 4 h gave 1.196 g of crude product. MPLC (6:1 hexane–ethyl acetate) of 0.839 g of the crude product gave 0.303 g (49%) of a 60:40 mixture of **3h** and **3g**: GC (Carbowax 20 M, 170 °C, 40 mL/min) t_R = 18.6 (**3h**), 19.7 min (**3g**). Recrystallization twice from acetone gave a white solid (mp 62–64 °C) which was shown by ^{13}C NMR to be ~90% **3g**: ^1H NMR ($CDCl_3$) δ 5.59 (br s, 1), 3.86 (br, $w_{1/2}$ = 11 Hz, 1), 0.90 (d, J = 7 Hz, 3). Anal. Calcd for $C_{11}H_{18}O$: C, 79.47; H, 10.91. Found: C, 79.24; H, 10.83.

The data for **3h** were determined from the mixture: ^1H NMR ($CDCl_3$) δ 5.59 (br s, 1), 3.86 (br, $w_{1/2}$ = 11 Hz), 0.93 (d, J = 7 Hz, 3).

Reaction of 4-*tert*-butylmethylenecyclohexane (0.76 g, 5 mmol), **acrolein** (0.28 g, 5.0 mmol), **and Me_2AlCl** (6.58 mL of a 1.14 M solution, 7.5 mmol) in 15 mL of CH_2Cl_2 for 4 h at −40 °C gave 1.248 g of crude product. MPLC (6:1 hexane–ethyl acetate) of 0.969 g of the crude product gave 0.281 g (33%) of **3i** and 0.323 g (38%) of **3j**.

The data for **3i** follow: mp 84–86 °C, 90–91 °C after recrystalization from EtOH: ^1H NMR ($CDCl_3$) δ 5.66 (d, J = 7 Hz, 1), 3.88 (br s, $w_{1/2}$ = 8 Hz, 1), 0.83 (s, 9). Anal. Calcd for $C_{14}H_{24}O$: C, 80.71; H, 11.61. Found: C, 80.96; H, 11.66.

The α-*tert*-butyl group of **3i** distorts the geometry of the cyclohexene ring to a boat like conformation. This results in the vinylic proton absorbing as a doublet (J = 7 Hz) in the ^1H NMR spectrum and leads to a poor fit between calculated and observed ^{13}C NMR spectra.

The data for **3j** follow: mp 85–89 °C, 88–90 °C after recrystallization from EtOH: ^1H NMR ($CDCl_3$) δ 5.55 (br s, 1), 3.83 (br, $w_{1/2}$ = 9 Hz, 1), 0.83 (s, 9). Anal. Calcd for $C_{14}H_{24}O$: C, 80.71; H, 11.61. Found: C, 80.90; H, 11.83.

Reaction of ethylidenecyclohexane (0.61 g, 5.5 mmol), **acrolein** (0.28 g, 5.0 mmol), **and Me_2AlCl** (4.16 mL of a 1.14 M solution, 4.75 mmol) in 15 mL of CH_2Cl_2 for 1.5 h at 0 °C gave 1.030 g of crude product. MPLC (5:1 pentane–ether) of 0.923 g of the crude product gave 0.287 g (39%) of pure **3k**: mp 53.0–55.0 °C; ^1H NMR (CCl_4) δ 5.60 (br s, 1), 3.70 (br, $w_{1/2}$ = 8 Hz, 1), 1.04 (d, J = 6 Hz, 3). Anal. Calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.91. Found: C, 79.39; H, 11.01.

Reaction of ethylidenecyclohexane (0.61 g, 5.5 mmol), **MVK** (0.35 g, 5.0 mmol), **and Me_2AlCl** (8.77 mL of a 1.14 M solution, 10 mmol) in 15 mL of CH_2Cl_2 for 45 min at 25 °C gave 1.38 g of crude product. MPLC (7:1 hexane–ethyl acetate) of 0.830 g of the crude product gave 0.032 g (6%) of **12c** as a 2:1 mixture of diastereomers, followed by 0.050 g (9%) of **13a**, 0.344 g (63%) of a 97:3 mixture of **3l** and **3m**, and 0.024 g (4%) of a 65:35 mixture of **3m** and **3l**.

The data for **3l** follow: ^1H NMR ($CDCl_3$) δ 5.70 (br s, 1), 1.22 (s, 3), 1.08 (d, J = 7 Hz, 3). Anal. Calcd for $C_{12}H_{20}O$: C, 79.94; H, 11.18. Found: C, 75.86; H, 10.99.

The data for **3m** follow: ^1H NMR ($CDCl_3$) δ 5.68 (br s, 1), 1.19 (s, 3), 1.13 (d, J = 8 Hz, 3).

The data for **12c** follow: ^1H NMR ($CDCl_3$) δ 2.10 (s, 0.33 × 3), 2.08 (s, 0.67 × 3), 1.08 (d, J = 7 Hz, 0.67 × 3), 0.98 (d, J = 7 Hz, 0.33 × 3); IR (neat) 1709, 1705 cm^{-1}.

The data for **13a** follow: ^1H NMR ($CDCl_3$) δ 6.69 (dd, J = 16.2, 8.2 Hz, 1), 5.98 (dd, J = 16.2, 0.9 Hz, 1), 2.21 (s, 3), 1.00 (d, J = 6.8 Hz, 3); IR (neat) 1680, 1630 cm^{-1}. Anal. Calcd for $C_{12}H_{20}O$: C, 79.94; H, 11.18. Found: C, 79.27; H, 11.19.

Reaction of ethylidenecyclohexane (0.61 g, 5.5 mmol), **methacrolein** (0.35 g, 5.0 mmol), **and Me_2AlCl** (4.16 mL of a 1.14 M solution, 4.75 mmol) in 15 mL of CH_2Cl_2 for 4.5 h at −30 °C gave 0.606 g of crude product. MPLC (7:1 hexane–ethyl acetate) of 0.485 g of the crude product gave three unidentified fractions (3%, 4%, and 6%, respectively), none of which was a stereoisomer of **3n**, and 0.252 g (35%) of **3n**: mp 45–47 °C (MeOH); ^1H NMR ($CDCl_3$) δ 5.70 (br s, 1), 1.04 (d, J = 7 Hz, 3), 0.97 (d, J = 7 Hz, 3).

Reaction of ethylidenecyclohexane (0.61 g, 5.5 mmol), **α-bromoacrolein** (0.67 g, 5.0 mmol), **and Me_2AlCl** (4.16 mL of a 1.14 M solution, 4.75 mmol) in 15 mL of CH_2Cl_2 for 30 min at −78 °C gave 1.332 g of crude product. MPLC (7:1 hexane–ethyl acetate) of 1.060 g of the crude product gave 0.038 g (4%) of a 3:1 mixture of **12b** and **14** which was followed by 0.094 g (10%) of **12b**, as predominantly one diastereomer, 0.411 g (42%) of **3o**, 0.019 g (2%) of a mixture of **11b** and an unidentified bicyclic isomer, and 0.047 g (5%) of a 1:1 mixture of **3p** and **3q**.

The data for **12b** follow: ^1H NMR ($CDCl_3$) δ 9.61 (s, 1), 2.8–2.1 (m, 3), 1.16 (d, J = 7 Hz, ~0.20 × 3, minor diastereomer), 1.02 (d, J = 7 Hz, 0.8 × 3, major diastereomer); IR (neat) 2860, 2720, 1720 cm^{-1}.

The data for **14** follow: ^1H NMR ($CDCl_3$) δ 6.52 (s, 1); IR (neat) 1650 cm^{-1}.

The data for **3o** follow: ^1H NMR ($CDCl_3$) δ 5.65 (s, 1), 4.38 (ddd, J = 11, 4, 2 Hz, 1), 3.93 (br, $w_{1/2}$ = 7 Hz, 1), 1.07 (d, J = 7 Hz, 3). The sample decomposed on storage at 0 °C.

The data for **11b** follow: ^1H NMR ($CDCl_3$) δ 5.88 (br s, 1), 5.63 (m, 2), 4.10 (br s, 1).

The data for **3p** and **3q** follow: ^1H NMR ($CDCl_3$) δ 5.75 (m, 1), 4.3 (m, 1), 3.95 (br, 1), 1.32 (d, J = 7 Hz, 0.5 × 3), 1.06 (d, J = 7 Hz, 0.5 × 3); mol wt calcd for $C_{11}H_{17}BrO$ 244.0463, found 244.0453.

Reaction of methylenecyclopentane (0.45 g, 5.5 mmol), **acrolein** (0.28 g, 5.0 mmol), **and Me_2AlCl** (4.16 mL of a 1.14 M solution, 4.75 mmol) in 15 mL of CH_2Cl_2 for 15 min at 0 °C gave 0.793 g of crude product. MPLC (5:1 hexane–ethyl acetate) of 0.725 g of the crude product gave 0.239 g (38%) of **6a** (mp 36–37 °C) which was recrystallized from acetone: mp 41.5–42.5 °C; ^1H NMR ($CDCl_3$) δ 5.41 (d, J = 2 Hz, 1), 3.93 (br, $w_{1/2}$ = 10 Hz, 1).

Reaction of ethylidenecyclopentane (0.53 g, 5.5 mmol), **acrolein** (0.28 g, 5.0 mmol), **and Me_2AlCl** (6.56 mL of a 1.14 M solution, 7.5 mmol) in 15 mL of CH_2Cl_2 for 2 h at 0 °C gave 0.953 g of crude product. MPLC (3:1 hexane–ethyl acetate) of 0.715 g of the crude product gave 0.409 g (72%) of **6b**: mp 47.0–48.0 °C (after recrystallization from acetone); ^1H NMR (CCl_4) δ 5.38 (s, 1), 3.87 (br, $w_{1/2}$ = 9 Hz, 1), 1.13 (d, J = 8 Hz, 3). Anal. Calcd for $C_{10}H_{16}O$: C, 78.90; H, 10.59. Found: C, 78.89; H, 10.42.

Reaction of ethylidenecyclopentane (0.53 g, 5.5 mmol), **MVK** (0.35 g, 5.0 mmol), **and Me_2AlCl** (4.16 mL of a 1.14 M solution, 4.75 mmol) in 15 mL of CH_2Cl_2 for 30 min at −78 °C gave 0.754 g of crude product. MPLC (5:1 hexane–ethyl acetate) of 0.532 g of the crude product gave 0.379 g (65%) of **5c**: bp 73–74 °C (1 torr); ^1H NMR ($CDCl_3$) δ 5.36 (br s, 1), 2.5–2.2 (m, 6), 2.13 (s, 3), 2.0–1.2 (m, 5), 1.02 (d, J = 7 Hz, 3); IR (neat) 1720 cm^{-1}.

Reaction of ethylidenecyclopentane (0.53 g, 5.5 mmol), **MVK** (0.35 g, 5.0 mmol), **and Me_2AlCl** (8.77 mL of a 1.14 M solution, 10 mmol) in 15 mL of CH_2Cl_2 for 30 min at 0–25 °C gave 0.764 g of crude product. MPLC (5:1 hexane–ethyl acetate) of 0.574 g of the crude product gave 0.32 g (51%) of **6c** followed by 0.007 g (1%) of **13b**.

The data for **6c** follow: ^1H NMR ($CDCl_3$) δ 5.4 (br s, 1), 1.20 (s, 3), 1.12 (d, J = 7 Hz, 3).

The data for **13b** follow: ^1H NMR ($CDCl_3$) δ 6.70 (dd, J = 16, 8 Hz, 1), 6.00 (d, J = 16 Hz, 1), 2.2 (s, 3), 1.04 (d, J = 8 Hz, 3); IR (neat) 1675, 1625 cm^{-1}.

Reaction of ethylidenecyclopentane (0.48 g, 5.0 mmol), **2-methyl-1-penten-3-one** (0.74 g, 7.5 mmol), **and Me_2AlCl** (4.16 mL of a 1.14 M solution, 4.75 mmol) in 15 mL of CH_2Cl_2 at −20 °C for 75 min gave 1.014 g of crude product. MPLC (6:1 hexane–ethyl acetate) of 0.648 g of the crude product gave 0.374 g (54%) of a 10:1 mixture of **5d** and **5e** as determined by examination of the ^{13}C NMR spectrum: ^1H NMR ($CDCl_3$) δ 5.31 (br s, 1), 2.52 (q, J = 7 Hz, 1), 2.38 (d, J = 7 Hz, 2), 2.3–2.0 (m, 4), 2.0–1.4 (m, 5), 1.1–0.9 (m, 9); ^{13}C NMR ($CDCl_3$) of **5d** δ 213.7, 147.7, 123.1, 43.7, 38.0, 33.5, 33.1, 31.5, 30.6, 22.8, 19.4, 16.1, 7.2; ^{13}C NMR ($CDCl_3$) of **5e** δ 148.3, 122.6, 43.1, 35.6, 34.0, 32.5, 31.0, 23.7; IR (neat) 1715 cm^{-1}. Anal. Calcd for $C_{13}H_{22}O$: C, 80.35; H, 11.41. Found: C, 79.31; H, 11.33.

Reaction of (*Z*)-pregna-5,17(20)-dien-3β-yl acetate (9) (0.045 g, 0.13 mmol), **isopropyl vinyl ketone** (0.029 g, 0.3 mmol), **and Me_2AlCl** (0.23 mL of a 1.14 M solution, 0.26 mmol) in 2.25 mL of CH_2Cl_2 for 3 h at 25 °C gave 0.052 g of a yellow oil. Chromatography on silica gel (8 g; hexane then 7:1 hexane–ethyl acetate as the eluant) gave 0.002 g of recovered **9** and 0.025 g (46%) of 3β-acetoxy-5,16-cholestadien-24-one: mp 100–101 °C; ^1H NMR ($CDCl_3$) δ 5.37 (m, 2), 4.6 (m, 1), 2.04 (s, 3), 1.09 (d, J = 7 Hz, 6), 1.06 (s, 3), 1.02 (d, J = 7 Hz, 3), 0.79 (s, 3). Anal. Calcd for $C_{29}H_{44}O_3$: C, 79.04; H, 10.06. Found: C, 78.85; H, 10.07.

24-Oxocholesteryl Acetate (10). A solution of 3-β-acetoxy-5,16-cholestadien-24-one (10 mg) in 2 mL of ethanol containing 2 mg of 5% Pt/C was stirred under 1 atm of hydrogen for 22 min. Filtration and evaporation of the solvent gave 9.5 mg of a 1:1 mixture of starting material and **10**. Two repetitions of the above procedure for 25 and 40 min give 7.8 mg of crude **10**, mp 118–119 °C. Recrystallization from methanol gave pure **10**: mp 124–125 °C (lit.[29] mp 127–128 °C); ^1H NMR ($CDCl_3$) δ 5.4 (br, 1), 4.6 (m, 1), 2.03 (s, 3), 1.09 (d, J = 7 Hz, 9), 1.03 (s, 3), 0.68 (s, 3); IR (neat) 1730, 1705 cm^{-1}.

Reaction of 1-methylcyclohexene (0.53 g, 5.5 mmol), **MVK** (0.35 g, 5.0 mmol), **and Me_2AlCl** (8.77 mL of a 1.14 M solution, 10 mmol) in 15 mL of CH_2Cl_2 for 45 min at 0–25 °C gave 0.874 g of crude product. MPLC (3:1 hexane–ethyl acetate) of 0.649 g of the crude product gave 0.072 g (12%) of product which appeared to contain **15**, followed by 0.135 g (23%) of a 1:1 mixture of **16** and **17**, 0.025 g (4%) of an unidentified compound, and 0.099 g (16%) of **18**.

The data for **16** follow: ^1H NMR ($CDCl_3$) δ 6.95 (dd, J = 17, 9 Hz, 0.7 × 1, trans isomer), 6.70 (dd, J = 17, 9 Hz, 0.3 × 1, cis isomer), 6.10 (d, J = 17 Hz, 1), 2.3 (s, 3), 0.93 (d, J = 7 Hz, 0.3 × 3, cis isomer), 0.85 (d, J = 7 Hz, 0.7 × 3, trans isomer); IR (neat) 1680, 1625 cm^{-1}.

The data for **17** follow: ^1H NMR ($CDCl_3$) δ 5.45 (br s, 1), 2.49 (t, J = 8 Hz, 2), 2.20 (s, 3), 1.67 (br s, 3); IR (neat) 1720 cm^{-1}.

The data for **18** follow: ^1H NMR ($CDCl_3$) δ 5.57 (br s, 1), 1.28 (s, 3); IR (neat) 3470, 3060, 1110 cm^{-1}.

Reaction of 2,3-dimethyl-2-butene (0.46 g, 5.5 mmol), **MVK** (0.35 g, 5.0 mmol), **and Me_2AlCl** (8.77 mL fo a 1.14 M solution, 10 mmol) in 15 mL of CH_2Cl_2 for 1 h at 0–25 °C gave 0.823 g of crude product. MPLC (5:1 hexane–ethyl acetate) of 0.622 g of the crude product gave 0.032 g (7%) of **20a** followed by 0.244 g (42%) of **19a**.

The data for **19a** follow: ^1H NMR ($CDCl_3$) δ 4.78 (d, J = 7 Hz, 2), 2.31 (AB q, J = 13 Hz, $\Delta\nu$ = 18 Hz, 2), 2.2–1.3 (m, 5), 1.23 (s, 3), 1.12 (s, 3), 1.07 (s, 3); ^{13}C NMR ($CDCl_3$) δ 153.0, 108.8, 71.2, 46.6, 37.2, 35.6, 35.5, 28.6, 27.9, 26.1; IR (neat) 3400, 1640, 890 cm^{-1}. Anal. Calcd for $C_{10}H_{18}O$: C, 77.87; H, 11.76. Found: C, 77.10; H, 11.79.

The data for **20a** follow: ^1H NMR ($CDCl_3$) δ 2.6–2.3 (m, 2), 2.2 (s, 3), 2.0–1.3 (m, 5), 1.21 (s, 6), 1.12 (s, 3), 1.02 (s, 3), 0.97 (s, 3), 0.83 (s, 3); IR (neat), 1720 cm^{-1}; MS, m/e (relative intensity) 225 (M − 15, 9), 184 (7), 183 (6), 182 (8), 149 (14), 139 (6), 137 (14), 133 (5), 127 (10), 126 (100), 123 (8), 121 (12), 111 (24), 109 (19), 108 (93), 107 (11), 98 (21), 95 (14), 93 (27), 84 (55), 71 (32), 59 (37).

Reaction of 2-methyl-2-butene (0.39 g, 5.5 mmol), **MVK** (0.35 g, 5.0 mmol), **and Me_2AlCl** (8.77 mL of a 1.14 M solution, 10 mmol) in 15 mL of CH_2Cl_2 for 16 min at 0–25 °C gave 0.554 g of crude product. MPLC (2:1 pentane–ether) of 0.323 g of the crude product gave 0.060 g (18%) of **20b** followed by 0.060 (15%) of **19b**.

The data for **20b** follow: ^1H NMR ($CDCl_3$) δ 2.7–2.2 (m, 2), 2.17 (s, 3), 2.0–1.3 (m, 6), 1.25 (s, 3), 1.19 (s, 3), 1.15 (s, 3), 1.10 (s, 3), 0.84 (d, J = 7 Hz, 3); IR (neat) 1720 cm^{-1}; MS, m/e (relative intensity) 227 (0.4), 226 (M^+, 0.2), 225 (0.2), 213 (0.3), 212 (3), 211 (5), 193 (2), 184 (1), 183 (5), 176 (1), 175 (6), 169 (5), 168 (3), 158 (3), 157 (8), 153 (9), 139 (4), 135 (6), 133 (6), 126 (31), 121 (11), 111 (26), 110 (18), 99 (32), 98 (10), 70 (100), 69 (48).

The data for **19b** follow: ^1H NMR ($CDCl_3$) δ 4.81 (s, 2), 2.24 (br s, $w_{1/2}$ = 5 Hz, 2), 2.0–1.4 (m, 5), 1.28 (s, 3), 1.09 (d, J = 7 Hz, 3); ^{13}C NMR ($CDCl_3$) δ 150.4, 108.3, 70.9, 49.6, 38.5, 36.8, 32.3, 29.4, 17.9; IR (neat) 3450, 1650, 890 cm^{-1}.

Reaction of 3-ethyl-2-pentene (~75% pure, 0.74 g, ~5.5 mmol), **methacrolein** (0.35 g, 5.0 mmol), **and Me_2AlCl** (4.16 mL of a 1.14 M solution, 4.75 mmol) in 15 mL of CH_2Cl_2 for 30 min at 0–25 °C gave 0.940 g of crude product. MPLC (7:1 hexane–ethyl acetate) of 0.673 g of the crude product gave 0.153 g (33%) of **22** followed by 0.033 g (5%) of a 3:1 mixture of **21a** and an unknown compound as determined by ^{13}C NMR. The last three fractions consisted of 0.019 g (3%) of **21b**, 0.187 g (31%) of **21c**, and 0.099 g (16%) of **21d**.

The data for **22** follow: ^1H NMR ($CDCl_3$) δ 6.07 (s, 1), 4.55 (s, 1), 2.5–1.6 (m, 2), 1.57 (s, 3), 0.95 (d, J = 7 Hz, 3), 0.93 (s, 3), 0.9–0.5 (m, 13); ^{13}C NMR ($CDCl_3$) δ 133.0, 95.5, 80.7, 40.9, 31.6, 31.5, 28.9, 28.2, 24.3, 21.5, 18.4, 15.9, 6.9, 6.1; IR (neat) 1690 cm^{-1}.

The data for **21b** follow: ^1H NMR ($CDCl_3$) δ 5.22 (q, J = 7 Hz, 1), 3.45 (s, 1), 3.0 (m, 1), 2.55 (m, 1), 1.66 (dd, J = 7, 2 Hz, 3), 1.08 (d, J = 7 Hz, 6), 0.94 (d, J = 7 Hz, 3); ^{13}C NMR ($CDCl_3$) δ 142.0, 117.6, 43.4, 37.9, 35.0, 32.0, 29.7, 18.6, 18.3, 14.9, 12.8.

The data for **21c** follow: mp 40–45 °C; ^1H NMR ($CDCl_3$) δ 5.40 (qd, J = 7, 2 Hz, 1), 3.55 (br s, 1), 3.05 (qd, J = 7, 3 Hz, 1), 2.5–1.8 (m, 4), 1.68 (dd, J = 7, 2 Hz, 3), 1.07 (d, J = 7 Hz, 3), 1.01 (d, J = 5 Hz, 3), 0.94 (d, J = 7 Hz, 3); ^{13}C NMR ($CDCl_3$) δ 142.9, 117.4, 76.9, 39.1, 38.6, 31.7, 31.1, 18.4, 18.0, 16.7, 12.7.

The data for **21d** follow: ^1H NMR ($CDCl_3$) δ 5.2 (q, J = 7 Hz, 1), 3.70 (dd, J = 7, 2 Hz, 1), 2.73 (qd, J = 7, 2 Hz, 1), 2.5 (m, 1), 1.65 (dd, J = 7, 2 Hz, 3), 1.10 (d, J = 7 Hz, 3), 1.05 (d, J = 7 Hz, 3), 1.02 (d, J = 6 Hz, 3); ^{13}C NMR ($CDCl_3$) δ 142.5, 117.2, 78.7, 38.4, 36.2, 35.8, 31.6, 20.4, 20.2, 12.9, 12.8.

Reaction of 1-hexene (0.46 g, 5.5 mmol), **MVK** (0.35 g, 5.0 mmol), **and Me_2AlCl** (8.77 mL of a 1.14 M solution, 10.0 mmol) in 15 mL of CH_2Cl_2 for 1 h at 0–25 °C gave 0.476 g of crude product. MPLC (5:1 hexane–ethyl acetate) of 0.285 g of the crude product gave 0.062 g (13%) of **23**: ^1H NMR ($CDCl_3$) δ 5.4 (m, 2), 2.44 (t, J = 8 Hz, 2), 2.13 (s, 3), 2.1–1.8 (m, 2), 1.7 (dt, J = 8, 8 Hz, 2), 1.54–1.11 (m, 4), 0.9 (t, J = 7 Hz, 3); IR (neat) 1715, 965 cm^{-1}. Anal. Calcd for $C_{10}H_{18}O$: C, 77.87; H, 11.76. Found: C, 77.53; H, 11.55.

Acknowledgment. We thank the National Institutes of Health for financial support of this work. Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for the partial support of this research.

Registry No. **1a**, 1192-37-6; **1b**, 2808-80-2; **1c**, 13294-73-0; **1d**, 1003-64-1; **2b**, 80376-43-8; **3a**, 80376-44-9; **3b**, 80376-45-0; **3c**,

(29) Motzfeldt, A.-M. *Acta Chem. Scand.* **1970**, *24*, 1846.

80376-46-1; **3d**, 80376-47-2; **3e**, 80376-48-3; **3f**, 80387-11-7; **3g**, 85406-27-5; **3h**, 85406-28-6; **3i**, 85406-29-7; **3j**, 85406-30-0; **3k**, 80376-52-9; **3l**, 80376-53-0; **3m**, 80376-57-4; **3n**, 80376-54-1; **3o**, 80376-56-3; **3p**, 80376-55-2; **3q**, 85406-31-1; **4a**, 1528-30-9; **4b**, 2146-37-4; **5c**, 80376-58-5; **5d**, 85406-32-2; **5e**, 85406-33-3; **6a**, 80376-59-6; **6b**, 80376-60-9; **6c**, 80376-61-0; **9**, 1167-33-5; **10**, 20981-59-3; **10** (16-ene), 80376-63-2; **11a**, 80376-64-3; **11b**, 85406-34-4; **12a**, 85406-35-5; **12b** (isomer 1), 85406-36-6; **12b** (isomer 2), 85406-37-7; **12c** (isomer 1), 85406-38-8; **12c** (isomer 2), 85406-39-9; **13a**, 80376-62-1; **13b**, 85406-40-2; **14**, 85406-41-3; **15**, 85406-42-4; **16**, 13155-62-9; **17**, 85406-43-5; **18**, 85406-44-6; **19a**, 85406-45-7; **19b**, 85406-46-8; **20a**, 85406-47-9; **20b**, 85406-48-0; **21**, 85406-49-1; **22**, 85406-50-4; **23**, 85406-51-5; Me_2AlCl, 1184-58-3; acrolein, 107-02-8; MVK, 78-94-4; methacrolein, 78-85-3; α-bromoacrolein, 14925-39-4; 2-methyl-1-penten-3-one, 25044-01-3; isopropyl vinyl ketone, 1606-47-9; 1-methylcyclohexene, 591-49-1; 2,3-dimethyl-2-butene, 563-79-1; 2-methyl-2-butene, 513-35-9; 3-ethyl-2-pentene, 816-79-5; 1-hexene, 592-41-6.

Stereochemistry of the Claisen Rearrangement of Derivatives of 5-*tert*-Butyl-1-(hydroxymethyl)-1-cyclohexene: Preferred Axial Attachment of the Side Chain[1]

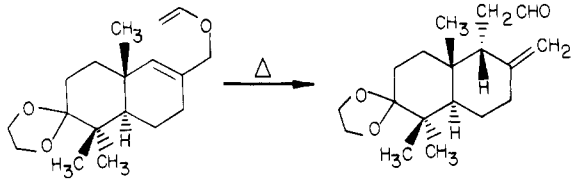
Robert E. Ireland* and Michael D. Varney

The Chemical Laboratories, California Institute of Technology, Pasadena, California 91125

Received August 31, 1982

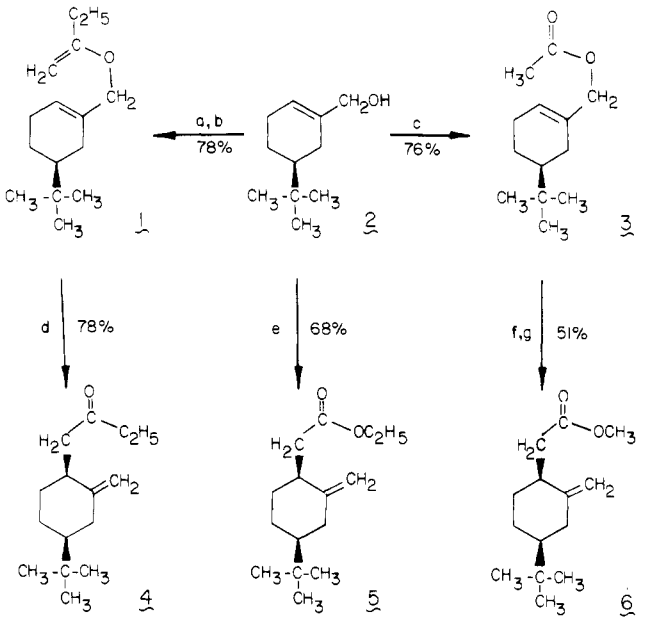
The Claisen rearrangement of vinyl ethyl derivatives of 5-*tert*-butyl-1-(hydroxymethyl)-1-cyclohexene is reported. The standard allyl vinyl ether conditions as well as the triethyl orthoacetate and ester enolate variants of the Claisen rearrangement all resulted in the formation of *cis*(axial)-4-*tert*-butylcyclohexyl-substituted systems. Thus, in sterically unbiased cases, this [3,3] sigmatropic process results in the axial attachment of the side chain in a cyclohexyl system.

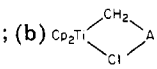
The Claisen rearrangement is a synthetically useful transformation,[2] and most of its stereochemical aspects are now well understood.[3] One stereochemical point that has not been addressed directly in the public literature[4,5] is whether there is a preference for axial or equatorial attachment of the side chain that results from such a rearrangement in certain cyclohexene series. In an earlier sterically biased case reported from these laboratories,[6] only the axially oriented product was observed (see below).



Since it was not clear if this result was the consequence of the steric congestion on the top face of this dicyclic molecule or a preferred stereoelectronically controlled quasi-axial approach of the vinyl ether to the cyclohexene ring system, it was decided to investigate the rearrangement in a stereochemically defined but sterically unbiased situation. The substrate chosen for this work was 5-*tert*-butyl-1-(hydroxymethyl)-1-cyclohexene (**2**),[7] and several variations of the Claisen rearrangement were explored (Scheme I).

Scheme I. Claisen Rearrangements with 5-*tert*-Butyl-1-(hydroxymethyl)-1-cyclohexene (**2**)[a]



[a] (a) C_2H_5COCl, pyr; (b)  $C_6H_5CH_3$; (c) CH_3COCl, pyr; (d) 142 °C (sealed tube), 6 h; (e) $CH_3C(OC_2H_5)_3$, $C_5H_{11}CO_2H$, 166 °C, 44 h; (f) LDA, THF, HMPA; *t*-$BuMe_2SiCl$; 60 °C; H_3O^+; (g) CH_2N_2, Et_2O.

In one instance, the ketone **4** was prepared through the standard[6,13] allyl vinyl ether type rearrangement of the vinyl ether **1**. Alternately, direct formation of the ethyl ester **5** was accomplished through application of the Johnson[8] triethyl orthoacetate variant of the rearrange-

(1) Contribution No. 6697. Grateful acknowledgement is made for the support of this investigation through National Science Foundation Grant CHE-78-21066.

(2) (a) Rhoads, S. J.; Raulins, N. R. *Org. React.* **1975**, *22*, 1. (b) Bennett, G. B. *Synthesis* **1977**, 589. (c) Ziegler, F. E. *Acc. Chem. Res.* **1977**, *10*, 227. (d) Bartlett, P. A. *Tetrahedron* **1980**, *36*, 1–72.

(3) (a) Gill, G. B. *Q. Rev., Chem. Soc.* **1968**, *22*, 338. (b) Hansen, H. J. Schmidt, H. *Tetrahedron* **1974**, *30*, 1959. (c) Takahashi, H.; Oshima, K.; Yamamoto, H.; Nazaki, H. *J. Am. Chem. Soc.* **1973**, *95*, 5803. (d) Doering, W. von E.; Roth, W. R. *Tetrahedron* **1962**, *18*, 67. (e) Vittovelli, P.; Winkler, T.; Hansen, H. J.; Schmidt, H. *Helv. Chim. Acta* **1968**, *51*, 1457. (f) Sucrow, W.; Richter, W. *Chem. Ber.* **1971**, *104*, 3679. (g) Faulkner, D. J.; Peterson, M. R. *Tetrahedron Lett.* **1969**, 3243. (h) Bartlett, P. A.; Hahne, W. F. *J. Org. Chem.* **1979**, *44*, 882.

(4) Dr. A. A. Panaras has informed us that his research group is investigating similar systems. See also ref 2c and 5.

(5) House, H. O.; Lubinkowski, J.; Good, J. J. *J. Org. Chem.* **1975**, *40*, 86.

(6) Ireland, R. E.; Marshall, J. A.; Church, R. F. *J. Org. Chem.* **1962**, *27*, 1118.

(7) Gream, G. E.; Serelis, A. K. *Aust. J. Chem.* **1978**, *31*, 863–91.

0022-3263/83/1948-1829$01.50/0