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SEQUENTIAL ENE REACTIONS—II

SYNTHESIS OF BICYCLIC ADDUCTS WITH ANGULAR METHYL GROUPS. *IN SITU* OPPENAUER OXIDATION[1]

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Abstract—The sequential ene reaction annelation sequence has been shown to be applicable to 2- and 3-substituted methylenecycloalkanes. Methyl groups in the 2-position are transformed into angular methyl groups in decalin or indane derivatives. The chloromethylaluminum alkoxides produced in these reactions, i.e. **3** and **7**, undergo an Oppenauer oxidation *in situ* in the presence of excess acrolein to give the corresponding ketone in good yield. Using these procedures, indenone **8a** has been prepared from **4a** in one pot in 60% yield.

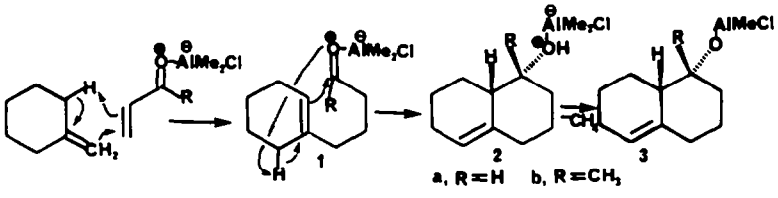
Procedures for the carbofunctionalization of C=C bonds are an important class of synthetic methods since alkenes are so readily available and are easily constructed both stereo- and regiospecifically. Unfortunately, the development of such methods has been difficult since alkenes do not react with nucleophiles and react only with strong electrophiles. We have found that Lewis acid catalyzed ene reactions provide a general solution to this problem.[2] Reaction of any of a wide variety of alkenes with acrylate esters,[3] propiolate esters,[4] α,β-unsaturated aldehydes or ketones,[1] or aldehydes[5] with the appropriate Lewis acid[6] leads to the ene adduct in good yield, often with surprisingly high regio- and stereoselectivity.

We recently reported a new annelation procedure based on two sequential ene reactions using an alkylidenecycloalkane as the ene component and acrolein or methyl vinyl ketone as the enophile.[1] Methylenecyclohexane undergoes an ene reaction with the dimethylaluminum chloride (Me_2AlCl) complex of acrolein at 0° to give the Me_2AlCl–aldehyde complex **1a** as a reactive intermediate. The initially formed aldehyde complex **1a** then undergoes a second, intramolecular, ene reaction, with the complexed aldehyde functioning as the enophile to give **2a**. Loss of methane from the resulting alcohol–Lewis acid complex **2a**, to give the aluminum alkoxide **3a**, prevents proton-catalyzed side reactions or solvolysis of the alcohol. Cyclization of **1a** to **2a** is much faster than the formation of **1a** since no **1a** could be detected, even when the reaction was run to low conversion at −78°. The methyl vinyl ketone–Me_2AlCl complex reacts similarly to give **1b**, which does not react further if the reaction is run at −20° since a ketone is not as enophilic as an aldehyde. The ketone complex **1b** does react at 25° to give **2b**, which can be isolated since the tertiary alcohol is protected from Lewis acid catalyzed reactions by loss of methane to form the aluminum alkoxide **3b**.

The sequential ene reaction sequence is a general annelation procedure applicable to a wide variety of alkylidenecycloalkanes.[1] We report here studies of several 2- and 3-substituted methylenecycloalkanes which establish the regioselectivity of the initial ene reaction and establish that this annelation procedure can be used to produce indane and decalin derivatives with angular methyl groups.

RESULTS AND DISCUSSION

Indenone **8a**, a potential steroid intermediate, has been prepared by Jung and Hatfield in seven steps from the optically active Wieland–Miescher ketone.[7] It appeared to us that **8a** could be more easily prepared in only two steps by the sequential ene reaction annelation sequence from 2,5-dimethylmethylenecyclopentane (**4a**) followed by oxidation. Two serious questions remained to be answered. Firstly, would the methyl groups of **4a** or **5a** interfere with the ene reaction? Secondly, would **5a** undergo a type II intramolecular ene reaction to give the desired product **6a** or would it undergo a type I intramolecular ene reaction to give the spiro[4.4]nonanol **9a**? Since ene reactions using aldehydes as enophiles are well known to give cyclopentanols and cyclohexanols in type I reactions and cyclohexanols and cycloheptanols in type II reactions, the formation of both **6a** and **9a** was well precedented.[8]



Treatment of **4a** with 1 equiv of acrolein and 1 equiv of Me_2AlCl in dichloromethane for 45 min at 0° gives **6a** (69%) and **8a** (12%). This result establishes that

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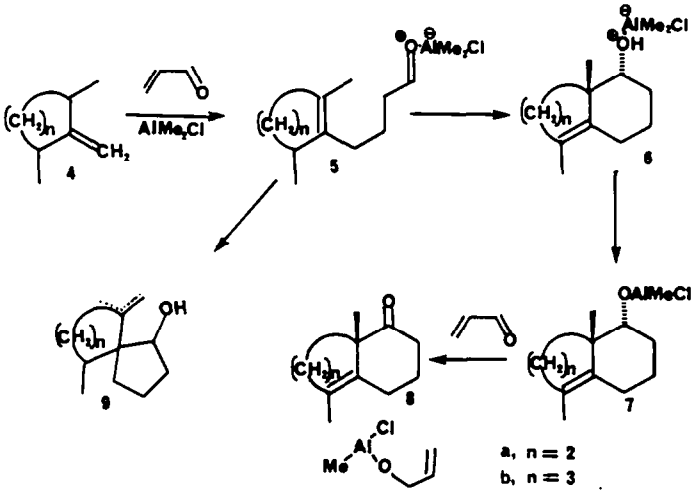
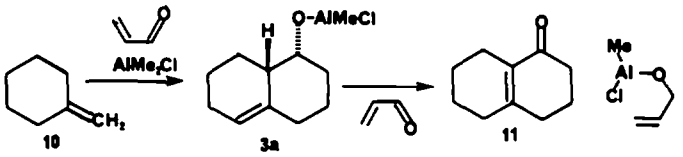


the methyl groups do not interfere with the ene reaction and that the type II ene reaction to give **6a** occurs exclusively. The formation of **8a** in 12% yield was surprising since there did not seem to be an oxidant! Further consideration suggested that the aluminum alkoxide **7a** could undergo an Oppenauer oxidation with acrolein as the oxidant to give **8a** and allyloxymethylchloroaluminum.

That an *in situ* Oppenauer was occurring was established by carrying out the reaction of **4a** with 2 equiv of acrolein. After reaction for 6 h at 0°, **8a** is obtained in 60% yield with only 1% of **6a** still present. This establishes that acrolein will oxidize **7a** stoichiometrically to **8a** in an Oppenauer oxidation, a result that is expected on thermodynamic grounds. Indenone **8a** is now readily available in 60% yield from **4a** in a one-pot reaction procedure involving a sequential ene reaction annelation followed by an *in situ* Oppenauer oxidation. The reaction is quite facile, being complete in 6 h at 0°. These reaction conditions are much milder than those usually used for Oppenauer oxidations.[9] Rathke and co-workers have shown that electron-withdrawing groups on the aluminum accelerate the Oppenauer oxidation.[10] Since both methyl and chloro groups are electron-withdrawing relative to the alkoxy groups usually present uniformly as substituents in the Oppenauer oxidation, this reaction should, and does, proceed under very mild conditions.



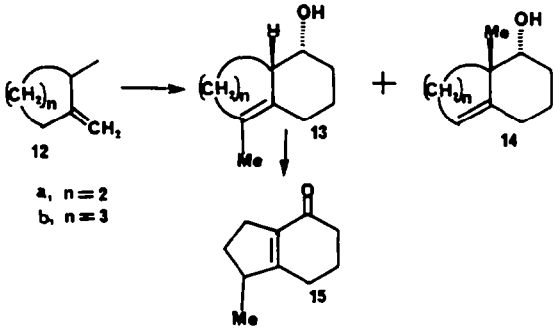
This annelation–oxidation sequence appears to be generally applicable. Reaction of 2,6-dimethylmethylenecyclohexane (**4b**) with 1 equiv of acrolein and 1 equiv of Me_2AlCl gives **6b** (51%) and **8b** (5%). Reaction of **4b** with 2 equiv of acrolein for 6 h at 0° gives **8b** (47%) and **6b** (3%). The formation of small amounts of **8b** when only 1 equiv of acrolein is used was distressing. Presumably acrolein is complexing to both Me_2AlCl and **7b**. If acrolein complexes to **7b** an Oppenauer oxidation ensues. Therefore addition of excess Me_2AlCl should inhibit the Oppenauer oxidation. As expected, reaction of **4b** with 1 equiv of acrolein and 1.5 equiv of Me_2AlCl gives **6b** (57%), uncontaminated with **8b**.

In the absence of the angular methyl group the initially formed β,γ-unsaturated ketone isomerizes to the more stable α,β-unsaturated ketone.[9] Reaction of methylenecyclohexane (**10**) with 2 equiv of acrolein and 1 equiv of Me_2AlCl for 8 h at 0° gives **11** in 44% yield. While the yield is only moderate, alternative routes to **11** are much longer and do not proceed in a better overall yield.

The ene–ene oxidation sequence provides a versatile annelation route to unsaturated ketones of a type not available by the Robinson annelation. These reactions are related to the oxidative cyclization reactions reported by Corey using PCC as an acid catalyst for the intramolecular ene reaction and an oxidant to generate the ketone.[11] However, Corey's procedure requires the separate synthesis of the unsaturated aldehyde. Since alkylaluminum halides are much stronger Lewis acids than PCC, our procedure is potentially more versatile and should be applicable to intermolecular ene reaction–oxidation sequences using aldehydes as enophiles. Wolinsky and coworkers have reported a single example of an ene–ene annelation sequence using acrylol chloride which produces an adduct similar to **11** from β-pinene.[12]

The sequential ene reaction annelation sequence on 2-substituted alkylidenecycloalkanes will give a mixture of isomers depending on the regioselectivity of the initial ene reaction. Reaction of 2-methylmethylenecyclopentane (**12a**) with 1 equiv of acrolein and 1 equiv of Me_2AlCl gives a 43% yield of a 1.3:1 mixture of **13a** and **14a** and a 9% yield of **15**. Reaction of 2-methylmethylenecyclohexane (**12b**), as described above, gives a 41% yield of a 1.5:1 mixture of **13b**

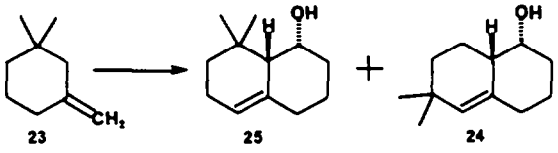
and **14b**. Alcohol **14b** has been prepared in five steps from the Wieland–Miescher ketone and used as an intermediate for the synthesis of a proposed structure of cycloeudesmol.[13] The initial ene reaction thus shows a *ca* 1.6:1 preference for transfer of one of the two methylene hydrogens rather than the methine hydrogen. After correction for the statistical factor, there is a 1.25:1 preference for the methine hydrogen.



Reaction of 3-methylmethylenecyclohexane (**16**) was examined to determine the regioselectivity of the initial ene reaction and the stereoselectivity of the second ene reaction. Reaction of **16** as described above gives **19–22** in 2, 16, 14 and 11% yield, respectively. Therefore, the initial ene reaction shows a 1.4:1 selectivity (**21**+**22**:**19**+**20**) for the abstraction of a hydrogen from C-6 to form **18** over the abstraction of a hydrogen from C-2 to form **17**. The intramolecular ene reaction of **17** proceeds with 8:1 selectivity for the face *anti* to the 3-methyl group due to severe steric interactions in leading to **19**. The intramolecular ene reaction of **18**, in which steric interactions are minimal, proceeds with a slight selectivity for the face *syn* to the 5-methyl group.

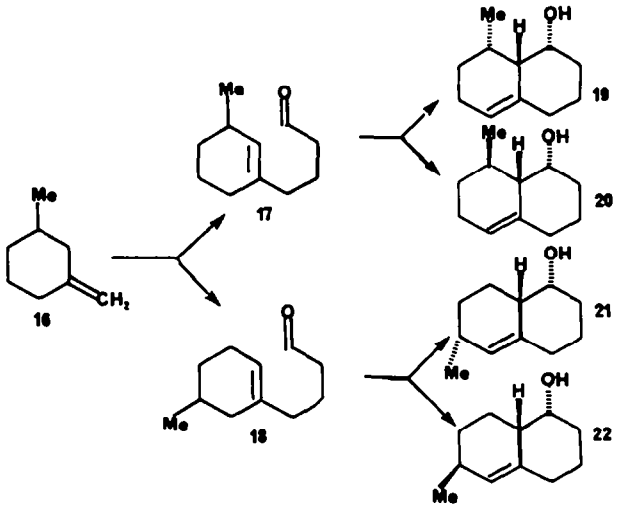
protons α to the hydroxyl groups of **19** and **20** are deshielded by 0.3 ppm by the methyl groups. The ^{13}C-NMR spectra of **19–22** show the expected shielding effects for the methyl groups as compared to **2a**.[1]

Reaction of 3,3-dimethylcyclohexane (**23**), as described above, gives **24** (35%) and **25** (18%). The presence of two methyl groups on C-3 increases the selectivity for the C-6 hydrogens in the initial ene reaction to 2:1 from the value of 1.4:1 obtained with **16**. As in the NMR spectra of **19–22**, the methyl groups of **24** shield the alkenyl hydrogen by 0.2 ppm while the methyl groups of **25** deshield the proton α to the hydroxyl group by 0.3 ppm.



We have shown that aldehydes **5a** and **5b** undergo type II ene reactions to give **6**, rather than type I intramolecular ene reactions to give **9**. To complete the series, we examined the Lewis acid catalyzed intramolecular ene reaction of the homologous aldehyde **29**. Addition of 5-tetrahydropyranyloxypentylmagnesium bromide (**27**) to 2,6-dimethylcyclohexanone followed by acid hydrolysis gives **28** in 50% yield. Oxidation with PCC gives **29** in 83% yield.

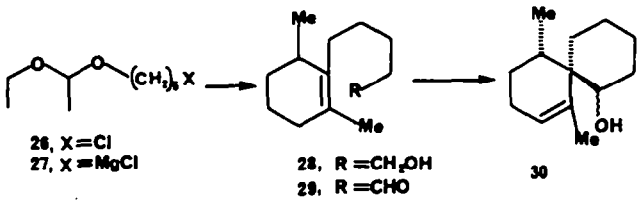
Treatment of **29** with 1.2 equiv of Me_2AlCl in dichloromethane for 1 h at 0° gives **30** (65%) and a complex mixture of minor isomeric adducts (27%) which contains, among other isomers, the exocyclic methylene isomer corresponding to **30**. Alcohol **30** is a single diastereomer. The relative stereochemistry of the methyl group can be assigned assuming approach



The structures of **19–22** were assigned by analysis of their NMR spectra and chromatographic properties. Alcohol **19**, in which the hydroxyl and methyl groups are in a 1,3-diaxial relationship, elutes most rapidly, followed by **21**, in which the alcohol and methyl groups are in a 1,5-diaxial relationship. In the NMR spectra, the alkenyl hydrogens of **21** and **22** are shielded by 0.2 ppm by the methyl groups while the

of the aldehyde from the *anti*-face. The stereochemistry of the hydroxyl group cannot be assigned since both isomers are mechanistically possible and the conformational flexibility of the spiro[5.5]nonane system limits the utility of the NMR data. Thus **29** reacts, in a manner opposite to **5**, to give mainly the type I adduct rather than the type II adduct. Similar preferential formation of six- rather than five-membered

rings has been observed in related cation–olefin cyclizations to tetrasubstituted double bonds.[14]



CONCLUSION

These results establish that the sequential ene reaction annelation sequence can be used to construct ring systems containing angular methyl groups. They also delineate the selectivity with 2- and 3-substituted methylenecycloalkanes. The observation that the intermediate chloromethylaluminum alkoxide undergoes an Oppenauer oxidation in high yield in the presence of 1 equiv excess of acrolein at 0° makes this an even more powerful synthetic method. When the alcohol is desired, the Oppenauer oxidation can be prevented by the use of excess Me_2AlCl. We are currently exploring the scope of this modified Oppenauer oxidation as a synthetic method.

EXPERIMENTAL

NMR spectra were recorded on Varian-EM390 and XL-300 NMR spectrometers in $CDCl_3$. Chemical shifts are reported in δ. IR spectra were obtained on a Perkin–Elmer 683 spectrometer. M.ps are uncorrected. GC analyses were performed on a Perkin–Elmer 3920 gas chromatograph with a 10 ft × 0.25 in column packed with 10% Carbowax 20M on Chromosorb WNAW, at a flow rate of 60 ml min^{-1} at 180°. MPLC refers to medium-pressure chromatography on Merck Lobar silica columns. Elemental analyses were performed by Galbraith Laboratories.

Preparation of starting materials. Compounds **4a**, **12a**, **16** and **23** were prepared by Wittig reactions from the commerically available ketones.[15] Methylenetriphenylphosphorane was prepared from the bromide salt in DMSO using dimsyl sodium. The ketone was added at 25° and allowed to react for 30 min. The desired alkene was isolated by distillation from the reaction mixture (45–70°, 65 Torr). The alkene, isolated in 50–70% yield, was contaminated with 20–40% C_6H_6, which did not affect the ene reaction. 2-Methylmethylenecyclohexane and 2,6-dimethylmethylenecyclohexane were obtained from Wiley Organics. Dimethylaluminum chloride (Me_2AlCl) was obtained from Texas Alkyls as a 25% sol in hexane (1.9 M). Acrolein was predried with $MgSO_4$ in the presence of 1% hydroquinone and then distilled twice from $CuSO_4$. The purified acrolein (with 1% added hydroquinone) was stored at −20° under N_2. Dichloromethane was dried by distillation from calcium hydride.

Preparation of **6a**. Me_2AlCl (1.6 ml of 1.9 M, 3 mmol in hexane was added via syringe to a soln of **4a** (0.38 g, 3.45 mmol) and acrolein (0.17 g, 3.15 mmol) in 10 ml of CH_2Cl_2 at 0° under N_2. The mixture was stirred for 45 min at 0°. The reaction was quenched by cautious addition of an equal vol of H_2O followed by enough Et_2O to place the organic layer on top. The layers were separated, and the aq layer was washed with three portions of Et_2O, each equal in vol to one-third of the aq layer. The combined organic layers were washed with brine, dried ($MgSO_4$) and evaporated *in vacuo* to give 0.757 g of crude adduct. MPLC (10:1 hexane–EtOAc) gave 0.363 g (69%) of **6a** and 0.063 g (12%) of **8a**. The data for **6a** follow: ^{1}H-NMR 3.58 (br, 1, $w_{1/2}$ = 7 Hz), 1.25–2.50 (m, 11), 1.58 (s, 3), 1.09 (s, 3); ^{13}C-NMR 135.4, 131.0, 74.2, 52.6, 35.6, 31.7, 28.7, 23.7, 22.3, 20.2, 13.8; IR (neat) 3100–3500 cm^{-1}; GC t_r = 15.9 min.

The tetrasubstituted double bond of **6a** is very susceptible to autoxidation. This phenomenon has been documented in related compounds such as bulnesol.[16] Autoxidation precluded obtaining accurate elemental analyses for many of these compounds.

Preparation of **8a**. Reaction of Me_2AlCl (1.6 ml of 1.9 M, 3 mmol), **4a** (0.38 g, 3.45 mmol) and acrolein (0.42 g, 7.5 mmol) in 10 ml of CH_2Cl_2 for 6 h at 0° followed by normal workup gave 0.750 g of crude product. Purification as described above gave 0.339 g (60%) of **8a** and 0.004 g (1%) of **6a**. The data for **8a** follow: ^{1}H-NMR 1.80–2.80 (m, 10), 1.60 (s, 3), 1.20 (s, 3); ^{13}C-NMR 137.5, 130.5, 61.9, 38.2, 34.4, 30.8, 25.6, 23.8, 22.2, 14.1; IR (neat) 1710 cm^{-1}; GC t_r = 14.8 min. (Found: C, 79.46; H, 10.00. Calc for $C_{11}H_{16}O$: C, 80.44; H, 9.82%.)

Preparation of **6b**. Reaction of Me_2AlCl (2.5 ml of 1.9 M, 4.75 mmol), **4b** (0.670 g, 5.5 mmol) and acrolein (0.28 g, 5 mmol) in 15 ml of CH_2Cl_2 at 0° for 45 min, as described above, gave 0.933 g of crude product which contained roughly 5% of **8b**. MPLC (10:1 hexane–EtOAc) gave 0.456 g (51%) of pure **6b**: m.p. 51–52°; ^{1}H-NMR 3.48 (br, 1, $w_{1/2}$ = 6 Hz), 1.50–2.66 (m, 11), 1.68 (s, 3), 1.09 (s, 3); ^{13}C-NMR 130.9 (C_5•), 129.7 (C_{4a}•), 75.9 (C_1), 40.4 (C_{8a}), 33.6 (C_6•), 32.9 (C_8•), 28.6 (C_2), 24.4 (Me), 24.3 (C_4), 20.7 (C_3), 19.7 (Me), 19.2 (C_7); IR (neat) 3300 cm^{-1}; GC t_r = 16.4 min. (Found: C, 80.13; H, 10.90. Calc for $C_{12}H_{20}O$: C, 79.95; H, 10.62%.)

A similar reaction carried out with 3.75 ml of Me_2AlCl (7.1 mmol) gave, after purification, 0.510 g (57%) of pure **6b**. No **8b** was present in the crude product.

Preparation of **8b**. Reaction of Me_2AlCl (1.6 ml of 1.9 M, 3 mmol), **4b** (0.42 g, 3.45 mmol) and acrolein (0.42 g, 7.5 mmol) in 10 ml of CH_2Cl_2 for 6.5 h at 0° as described above gave 0.842 g of crude product. Purification as above gave 0.290 g (47%) of **8b** and 0.021 g (3%) of **6b**. The data for **8b** follow: ^{1}H-NMR 1.39–1.82 (m, 12), 1.62 (s, 3), 1.28 (s, 3); ^{13}C-NMR 132.1, 128.4, 50.6, 38.0, 32.3, 31.6, 25.5, 24.4, 24.3, 19.8, 18.9; IR (neat) 1710 cm^{-1}; GC t_r = 19.2 min.

Preparation of **11**. Reaction of Me_2AlCl (1.6 ml of 1.9 M, 3 mmol), **10** (0.33 g, 3.45 mmol) and acrolein (0.42 g, 7.5 mmol) in 10 ml of CH_2Cl_2 for 8 h at 0°, as described above, gave 0.749 g of crude product. MPLC (1:1 hexane–EtOAc) gave 0.226 g (44%) of pure **11**: ^{1}H-NMR 2.35 (t, 2, J = 6 Hz), 2.09–2.24 (m, 6), 1.89–1.96 (m, 2), 1.54–1.61 (m, 4); ^{13}C-NMR 199.1, 156.9, 132.2, 37.9, 31.7, 31.4, 22.5, 22.1, 22.05, 22.0; IR (neat) 1660, 1640 cm^{-1}; UV max (MeOH) 247 nm (ε 11,500).

Preparation of **13a**, **14a** *and* **15**. Reaction of Me_2AlCl (1.6 ml of 1.9 M, 3 mmol), **12a** (0.33 g, 3.45 mmol) and acrolein (0.18 g, 3.15 mmol) in 10 ml of CH_2Cl_2 at 0° for 45 min, as described above, gave 0.690 g of crude product. MPLC (10:1 hexane–EtOAc) gave 0.208 g (43%) of a 1.3:1 mixture of **13a** and **14a** followed by 0.045 g (9%) of **15**. Alcohols **13a** and **14a** were separated by preparative GC.

The data for **13a** follow: ^{1}H-NMR 3.89 (br, 1, $w_{1/2}$ = 12 Hz), 1.25–2.90 (m, 12), 1.60 (s, 3); ^{13}C-NMR 131.9, 131.6, 69.8, 52.1, 37.3, 32.6, 25.4, 22.8, 19.8, 13.5; IR 3300 cm^{-1}; GC t_r = 16 min.

The data for **14a** follow: ^{1}H-NMR 5.32 (br s, 1), 3.62 (br, 1, $w_{1/2}$ = 12 Hz), 1.20–2.60 (m, 11), 1.10 (s, 3); ^{13}C-NMR 145.1, 123.1, 74.3, 51.4, 32.0, 29.6, 28.8, 25.2, 23.8, 20.8; IR 3300 cm^{-1}; GC t_r = 13.9 min.

The data for **15** follow: ^{1}H-NMR 1.89–2.95 (m, 9), 1.46–1.78 (m, 2), 1.10 (d, 3, J = 7 Hz); IR (neat) 1670, 1643 cm^{-1}; UV max (MeOH) 250 nm (ε = 11,900); GC t_r = 24.9 min.

Preparation of **13b** *and* **14b**. Reaction of Me_2AlCl (2.5 ml of 1.9 M, 4.75 mmol), **12b** (0.61 g, 5 mmol) and acrolein (0.28 g, 5 mmol) in 15 ml of CH_2Cl_2 at 0° for 45 min, as described above, gave 0.743 g of crude product. MPLC (10:1 hexane–EtOAc) gave 0.338 g (41%) of a 3:2 mixture of **13b** and **14b** as an inseparable mixture. The spectral data were determined from the mixture: **13b** ^{1}H-NMR 3.80 (br, 1, $w_{1/2}$ = 12 Hz), 2.50–2.80 (m, 2), 1.25–2.50 (m, 10), 1.60 (s, 3); ^{13}C-NMR 129.6 (C_5), 127.4 (C_{4a}), 71.9 (C_1), 42.6 (C_{8a}), 33.5 (C_2), 32.0 (C_6), 28.8 (C_4), 27.0 (C_8), 24.1 (Me), 21.9 (C_7), 20.7 (C_3); IR (neat) 3300 cm^{-1}; GC t_r = 11.4 min: **14b** ^{1}H-NMR 5.56 (br s, 1), 3.47 (br, 1, $w_{1/2}$ = 12 Hz), 2.50–2.85 (m, 2), 1.25–2.50 (m, 10), 1.10 (s, 3); ^{13}C-NMR 139.3 (C_{4a}), 124.5 (C_5), 75.4 (C_1), 40.0 (C_{8a}), 32.7 (C_8*), 31.2 (C_4*), 28.5 (C_2), 25.6 (C_6), 20.9 (C_3), 19.3 (Me), 19.2 (C_7); IR (neat) 3300 cm^{-1}; GC t_r = 11.4 min. The data for **14b** correspond to those previously reported.[13]

Preparation of **19–22**. Reaction of Me_2AlCl (2.5 ml of 1.9 M, 4.75 mmol), **16** (0.61 g, 5.5 mmol) and acrolein (0.28 g, 5 mmol) in 15 ml of CH_2Cl_2 at 0°, as described above, gave 804 mg of crude product. MPLC (10:1 hexane–EtOAc) gave 0.018 g (2%) of **19**, followed by 0.116 g (14%) of **21** and 0.233 g (27%) of a 1.5:1 mixture of **20** and **22**.

The data for **19** follow: ^{1}H-NMR 5.70 (br s, 1), 4.15 (br, 1, $w_{1/2}$ = 15 Hz), 1.12–2.30 (m, 13), 1.09 (d, 3, J = 6 Hz); IR (neat) 3300 cm^{-1}; GC t_r = 22.5 min.

The data for **21** follow: m.p. 41–42°; ^{1}H-NMR 5.50 (br s, 1), 3.85 (br, $w_{1/2}$ = 12.5 Hz), 1.32–2.35 (m, 13), 0.98 (d, 3, J = 6 Hz); ^{13}C-NMR 134.7 (C_{4a}), 130.6 (C_5), 72.3 (C_1), 41.2 (C_{8a}), 34.8 (C_4), 33.5 (C_2), 29.3 (C_6), 24.2 (C_7), 21.5 (C_3*), 21.1 (C_8*), 15.2 (Me); IR (neat) 3300 cm^{-1}; GC t_r = 22.0 min.

The data for **22** and **20** determined from the mixture follow: **20**: ^{1}H-NMR 5.65 (br s, 1), 4.10 (br, 1, $w_{1/2}$ = 13 Hz), 1.20–2.50 (m, 13), 1.02 (d, 3, J = 5.5 Hz); ^{13}C-NMR 135.1 (C_{4a}), 124.2 (C_5), 67.8 (C_1), 50.0 (C_{8a}), 34.6 (C_4), 33.2 (C_2), 30.7 (C_7*), 29.9 (C_8*), 24.6 (C_6), 21.8 (Me), 20.5 (C_3); **22**: ^{1}H-NMR 5.40 (br s, 1), 3.85 (br, 1, $w_{1/2}$ = 7.5 Hz), 1.20–2.50 (m, 13), 1.02 (d, 3, J = 5.5 Hz); ^{13}C-NMR 135.5 (C_{4a}), 130.8 (C_5), 70.4 (C_1), 42.1 (C_{8a}), 34.4 (C_4), 33.1 (C_2), 31.1 (C_6*), 30.4 (C_7*), 25.3 (C_8), 20.6 (Me), 20.1 (C_3); IR (neat) 3300 cm^{-1}; GC t_r = 23.4 min.

Preparation of **24** *and* **25**. Reaction of Me_2AlCl (1.6 ml of 1.9 M, 3.0 mmol), **23** (0.43 g, 3.45 mmol) and acrolein (0.18 g, 3.15 mmol) in 10 ml of CH_2Cl_2 at 0° for 45 min, as described above, gave 0.628 g of crude product. MPLC (10:1 hexane–EtOAc) gave 0.102 g (18%) of **25** followed by 0.199 g (35%) of **24**.

The data for **24** follow: m.p. 47–48°; ^{1}H-NMR 5.35 (s, 1), 3.84 (br, 1, $w_{1/2}$ = 14 Hz), 1.20–2.30 (m, 12), 0.98 (s, 3), 0.90 (s, 3); ^{13}C-NMR 135.1 (C_5), 133.1 (C_{4a}), 71.0 (C_1), 41.8 (C_{8a}), 36.2 (C_7), 34.6 (C_4), 33.3 (C_2), 31.3 (Me*), 30.6 (C_6*), 29.1 (Me*), 22.7 (C_8), 20.8 (C_3); IR (neat) 3300 cm^{-1}; GC t_r = 22.1 min.

The data for **25** follow: m.p. 59.5–60.0°; ^{1}H-NMR 5.68 (br s, 1), 4.19 (br d, 1, J = 6 Hz), 1.30–2.10 (m, 12), 1.02 (s, 3), 0.89 (s, 3); ^{13}C-NMR 135.3 (C_{4a}), 122.4 (C_5), 69.5 (C_1), 51.9 (C_{8a}), 36.6 (C_7.), 34.6 (C_4*), 32.7 (C_2*), 28.4 (Me), 27.2 (Me), 23.1 (C_6*), 22.2 (C_3*), C_8 was not observed; IR (neat) 3300 cm^{-1}; GC t_r = 22.3 min.

Preparation of **28**. A soln of **26**[17] (4.7 g, 24 mmol) in 40 ml of anhyd THF was added to 0.69 g (28 mmol) of Mg turnings in a three-necked flask equipped with magnetic stirring bar, condenser and addition funnel. A crystal of I_2 was added and the soln was heated at reflux until all of the Mg had dissolved. The flask was immersed periodically in an ultrasound bath in an attempt to facilitate formation of the Grignard reagent. The soln was cooled to 25° and 2,6-dimethylcyclohexanone (1.77 g, 14 mmol) in 10 ml of THF was added dropwise. The mixture was stirred for 15 min and quenched by cautious addition of 2 ml of 6 N HCl. Normal workup gave 3.3 g of crude product which was taken up in 40 ml of Et_2O. Conc H_2SO_4 (2 ml) was added and the mixture was heated at reflux for 22 h. Normal workup gave 2.151 g of crude **28**. MPLC (1:1 hexane–EtOAc) gave 1.365 g (50%) of pure **28**: ^{1}H-NMR 3.62 (t, 2, J = 6 Hz), 1.59 (s, 3), 1.1–2.3 (m, 16), 0.98 (d, 3, J = 6 Hz); IR (neat) 3300 cm^{-1}.

Preparation of **29**. Treatment of **28** (0.180 g, 0.95 mmol) with pyridinium chlorochromate (0.31 g, 1.42 mmol) in 7 ml of CH_2Cl_2 at 25° for 2.5 h, followed by normal workup, gave 148 mg (83%) of **29** which was used without purification: ^{1}H-NMR 9.75 (t, 1, J = 1.5 Hz), 2.3–2.7 (m, 2), 1.2–2.3 (m, 13), 1.56 (s, 3), 0.98 (d, 3, J = 6 Hz).

Cyclization of **29**. Me_2AlCl (0.29 ml of 1.9 M, 0.5 mmol) was added to a soln of **29** (0.08 g, 0.4 mmol) in 5 ml of CH_2Cl_2. The mixture was stirred for 1 h at 0° and worked up as described above to give 0.082 g of crude product. MPLC (5:1 hexane–EtOAc) gave 0.052 g (65%) of **30** followed by 0.022 g of a complex mixture of isomeric ene adducts. The data for **30** follow: ^{1}H-NMR 5.73 (br s, 1), 3.63 (dd, 1, J = 4, 11 Hz), 1.80–2.45 (m, 6), 1.72 (br s, 1, OH), 1.65 (dt, 3, J = 2.4, 1.7 Hz), 1.53–1.60 (m, 1), 1.21–1.45 (m, 6), 0.88 (d, 3, J = 7.3 Hz); ^{13}C-NMR 133.9, 127.0, 74.1, 45.1, 31.2, 27.8, 26.5, 26.2, 25.1, 20.9, 20.2, 19.1, 16.2; IR (neat) 3300 cm^{-1}.

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REFERENCES

[1] For previous papers in this series see: B. B. Snider and E. A. Deutsch, *J. Org. Chem.* **48**, 1822 (1983); B. B. Snider and E. A. Deutsch, *Ibid.* **47**, 745 (1982).
[2] B. B. Snider, *Accts Chem. Res.* **13**, 426 (1980).
[3] J. V. Duncia, P. T. Lansbury, Jr., T. C. Miller and B. B. Snider, *J. Am. Chem. Soc.* **104**, 1930 (1982).
[4] B. B. Snider, D. M. Roush, D. J. Rodini, D. Gonzalez and D. Spindell, *J. Org. Chem.* **45**, 2773 (1980) and refs cited therein.
[5] B. B. Snider and G. B. Phillips, *Ibid.* **48**, 464 (1983); B. B. Snider, D. J. Rodini, T. C. Kirk and R. Cordova, *J. Am. Chem. Soc.* **104**, 555 (1982).
[6] B. B. Snider, D. J. Rodini, M. Karras, T. C. Kirk, E. A. Deutsch, R. Cordova and R. T. Price, *Tetrahedron* **37**, 3927 (1981).
[7] M. E. Jung and G. L. Hatfield, *Tetrahedron Lett.* **24**, 3175 (1983).
[8] N. H. Andersen and D. W. Ladner, *Synth. Commun.* **8**, 449 (1978); W. Oppolzer and V. Snieckus, *Angew. Chem. Int. Ed. Engl.* **17**, 476 (1978).
[9] H. Lehmann, *Houben–Weyl Methoden Der Organischen Chemie*, Vol. IV/lb, pp. 901–933. Georg Thieme, Stuttgart (1975).
[10] R. Kow, R. Nygren and M. W. Rathke, *J. Org. Chem.* **42**, 826 (1977).
[11] E. J. Corey and D. L. Boger, *Tetrahedron Lett.* 2461 (1978).
[12] L. Moore, D. Gooding and J. Wolinsky, *J. Org. Chem.* **48**, 3750 (1983).
[13] M. Ando, S. Sayama and K. Takase, *Chem. Lett.* 377 (1981).
[14] P. Naegli and M. Wetli, *Tetrahedron* **37** (Supp. 1), 247 (1981) and refs cited therein; S. Kanno, T. Kato and Y.

Kitahara, *J. Chem. Soc. Chem. Commun.* 1257 (1967); L. E. Wolinsky and D. J. Faulkner, *J. Org. Chem.* **41**, 597 (1976); I. Ichinose and T. Kato, *Chem. Lett.* 61 (1979).
[15] R. Greenwald, M. Chaykovsky and E. J. Corey *J. Org. Chem.* **28**, 1128 (1963).
[16] J. A. Marshall and J. J. Partridge, *Tetrahedron* **25**, 2159 (1969).
[17] Prepared from 5-chloropentan-1-ol by the procedure of P. E. Eaton, G. F. Cooper, R. C. Johnson and R. C. Mueller, *J. Org. Chem.* **37**, 1947 (1972).