Intramolecular and Intermolecular Lewis Acid Catalyzed Ene Reactions Using Ketones as Enophiles

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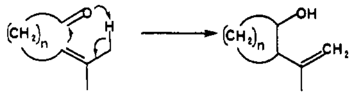
Alkylaluminum halide catalyzed intramolecular ene reactions of β-keto esters proceed in high yield to give cyclohexanols, via either a type I or type II process. Treatment of β-keto ester **3** with Me_2AlCl gives cis-fused ene adduct **5** in 67% yield. Similarly, **10** gives a 90% yield of **11** while treatment of **14** with Me_3Al gives a 63% yield of **15**. Treatment of **21** with Me_2AlCl gives a 52% yield of a mixture of isomeric ene adducts **22** and **23**. Treatment of **24** with $Me_{1.33}AlCl_{1.67}$ does not give the ene adduct but rather the hydrocarbon **26** which results from an unusual metathesis reaction—stepwise cycloaddition to give **25** followed by cycloreversion with loss of acetone. Intermolecular $EtAlCl_2$-catalyzed ene reactions of ketones with reactive ene components proceed in low to moderate yield.

Introduction

The ene reaction of carbonyl compounds is a versatile route to homoallylic alcohols.[2a,3] With reactive, i.e., electron deficient, aldehydes or ketones such as chloral, methyl glyoxylate, or diethyl oxomalonate, these reactions can be carried out thermally at 100–200 °C. Formaldehyde reacts with alkenes at 150 °C with optimal yields often being obtained in the presence of acid. These enophiles also react with a wide variety of alkenes to give ene adducts with Lewis acid catalysis at 25 °C.[2b]

We have recently reported that dimethylaluminum chloride (Me_2AlCl)[3,4] and ethylaluminum dichloride ($EtAlCl_2$)[5] in equivalent or greater amounts are useful catalysts for the ene reaction of aliphatic aldehydes and lead to significantly improved yields of ene adducts from formaldehyde. Me_2AlCl is a mild Lewis acid and a proton scavenger.[6] A problem with Lewis acid catalyzed ene reactions of aldehydes using standard Lewis acids is that the alcohol–Lewis acid complex produced in the reaction is susceptible to solvolysis and is a strong protic acid capable of protonating the double bond of the ene adduct or starting alkene. With Me_2AlCl, the alcohol–Me_2AlCl complex formed in the ene reaction decomposes rapidly to give methane and an aluminum alkoxide which is less susceptible to solvolysis.

The intramolecular ene reaction of unsaturated carbonyl compounds is an attractive approach to the synthesis of highly functionalized cyclic compounds.[2c,7] Type I intramolecular ene reactions proceed efficiently to give cyclohexanols and cyclopentanols (eq 1, n = 4, 3) at 150 °C or with Lewis acid catalysis at room temperature.[8] Type II intramolecular ene reactions proceed similarly to give cyclohexanols and cycloheptanols (eq 2, n = 3, 4).[8]



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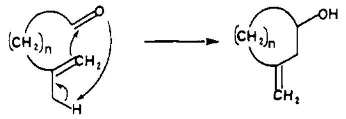

(2)

The use of ketones as enophiles is much less well developed. This is not surprising since ketones are less reactive than aldehydes due to both steric and electronic effects. To the best of our knowledge no intermolecular ene reactions of unactivated ketones have been reported. Intramolecular ene reactions where the ketone serves as the enophile are rare and generally occur only when the reaction results in relief of steric congestion.[9] Ketones have also been used as initiators in cation–olefin cyclizations.[10]

We have previously reported that Me_2AlCl is a useful catalyst for the type I or type II intramolecular ene reactions of methyl ketones to give cyclohexanols.[11,12] The isolation of a tertiary alcohol in the presence of a Lewis acid is remarkable and is presumably due to the rapid loss of CH_4 from the alcohol–Me_2AlCl complex to give the more stable aluminum alkoxide.[13] Me_2AlCl is especially useful for the intramolecular ene reactions of ketones since the adducts are often not stable at the temperatures required for uncatalyzed thermal reactions.[14]

We report here studies demonstrating the utility of cycloalkanones as enophiles in both intramolecular and intermolecular Lewis acid catalyzed ene reactions. The intramolecular version of this reaction constitutes a general new annelation procedure. The intermolecular version provides a simple route to 1-allylic cycloalkanols.

Results and Discussion

Intramolecular Reactions. Cyclohexanones **3** and **4** were examined to determine the suitability of cyclo-

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[1] Fellow of the Alfred P. Sloan Foundation 1979–1983. Camille and Henry Dreyfus Teacher-Scholar 1982–1987.

[2] For reviews see: (a) Hoffmann, H. M. R. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 556. (b) Snider, B. B. *Acc. Chem. Res.* **1980**, *13*, 426. (c) Oppolzer, W.; Snieckus, V. *Angew. Chem., Int. Ed. Engl.* **1978**, 17, 476.

[3] Snider, B. B.; Rodini, D. J.; Kirk, T. C.; Cordova, R. *J. Am. Chem. Soc.* **1982**, *104*, 555. See also ref 3-8 therein.

[4] Snider, B. B.; Rodini, D. J. *Tetrahedron Lett.* **1980**, *21*, 1815.

[5] Snider, B. B.; Phillips, G. B. *J. Org. Chem.* **1983**, *48*, 464.

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

[7] Many examples of intramolecular ene reactions are known in which the enol form of ketone is the ene component: Conia, J. M.; Le Perchec, P. *Synthesis* **1975**, 1.

[8] Andersen, N. H.; Ladner, D. W. *Synth. Commun.* **1978**, *8*, 449 and references cited therein.

[9] (a) Wender, P. A.; Hubbs, J. C. *J. Org. Chem.* **1980**, *45*, 367 and references cited therein. (b) Trost, B. M.; McDougal, P. G. *J. Am. Chem. Soc.* **1982**, *104*, 6110. (c) Amupitan, A. J.; Scovell, E. G.; Sutherland, J. K. *J. Chem. Soc., Perkin Trans. 1* **1983**, 755. (d) Thomas, A. F.; Ozainne, M.; *J. Chem. Soc., Chem. Commun.* **1977**, 120.

[10] van Tamelen, E. E.; Leiden, T. M. *J. Am. Chem. Soc.* **1982**, *104*, 1785.

[11] Snider, B. B., Deutsch, E. A. *J. Org. Chem.* **1983**, *48*, 1822.

[12] Snider, B. B.; Karras, M.; Price, R. T.; Rodini, D. J. *J. Org. Chem.* **1982**, *47*, 4538.

[13] $EtAlCl_2$ has also proven useful in Lewis acid catalyzed cyclizations of ketones to allylic silanes: (a) Trost, B. M.; Coppola, B. P. *J. Am. Chem. Soc.* **1982**, 104, 6879. (b) Trost, B. M.; Hiemstra, H. *J. Am. Chem. Soc.* **1982**, *104*, 886.

[14] Roussac, F.; Le Perchec, P.; Conia, J.-M. *Bull. Soc. Chim. Fr.* **1967**, 818.

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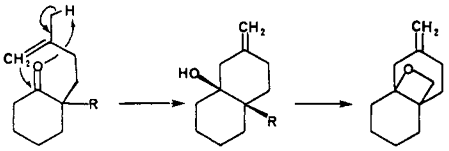
alkanones as enophiles in type II intramolecular ene reactions. Alkylation of the potassium salt of ethyl 2-oxocyclohexanecarboxylate (1) with 4-iodo-2-methyl-1-butene (2)[15] in *tert*-butyl alcohol gave a 73% yield of **3**. Hydrolysis and decarboxylation gave a 69% yield of **4**. Treatment of **3** with 1.0–1.2 equiv of Me$_2$AlCl in nitromethane for 60 h at 25 °C gave a 67% yield (74% based on recovered **3**) of the desired ene adduct **5**. Use of dichloromethane as solvent led to the formation of byproducts. Use of the stronger Lewis acid EtAlCl$_2$ for 1 h at 25 °C in dichloromethane gave a 44% yield of **5** along with double bond position isomers and chlorine-containing products.



3 R=COOEt
4 R=H

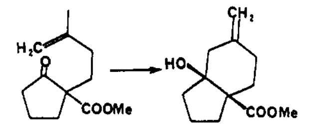
5 R=COOEt
6 R=CHO
7 R=CH$_2$OH
8 R=CH$_2$OTs

9

The cis stereochemistry of **5** was evident from the IR spectrum in CCl$_4$ which showed only an intramolecularly hydrogen bonded hydroxyl group at 3520 cm^{-1}.[16] This was confirmed by chemical transformations. Reduction of **5** with LAH in THF at 25 °C for 30 min gave a 75% yield of the diol **7** and an 11% yield of the hydroxy aldehyde **6**. The notable isolation of an aldehyde from an LAH reduction may be explained by stabilization of the initially formed hemiacetal as an aluminum chelate. Selective tosylation of the primary alcohol of **7** with tosyl chloride in pyridine at 0 °C gave **8** in 76% yield. Treatment of **8** with sodium hydride in THF for 1 h gave the oxetane **9** in 65% yield. A fragmentation reaction to give a cyclodecanone is precluded by the inabiity of the orbitals to line up properly.

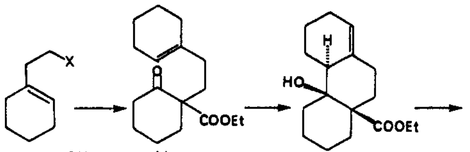
The Lewis acid catalyzed ene reaction of **4** was not successful. Treatment of **4** with 1 equiv of Me$_2$AlCl, or 1 equiv of Me$_3$Al, in nitromethane or 0.2 equiv of BF$_3$·OEt$_2$ in dichloromethane led to complex mixtures of products. The absence of the carbethoxy group has a profound effect on the reaction. Me$_2$AlCl coordinates with both the ketone and ester groups of **3**. This leads to only moderate activation of the ketone resulting in a slow concerted ene reaction. The ene adduct–Me$_2$AlCl complex loses methane to give a chloromethylaluminum alkoxide which is stabilized by chelation to the ester. The **4**–Me$_2$AlCl complex reacts more rapidly than that of **3**. The complex mixture of products results from either a stepwise reaction or the formation of a more reactive aluminum alkoxide. Although, tertiary alcohols at a ring fusion are not particularly susceptible to solvolysis,[17] the ene adduct from **4** has a low-energy conformation in which the double bond can accelerate solvolysis via homoallylic participation.

Cyclization of **10**, prepared in 60% yield from methyl 2-oxocyclopentanecarboxylate and **2**, with 2 equiv of Me$_2$AlCl in nitromethane for 17 h at 25 °C gave a 90% yield of **11** whose stereochemistry was established by IR spectroscopy as above. When only 1.2 equiv of Me$_2$AlCl was used, ~20% of starting ketone was present after 48 h.



10 11

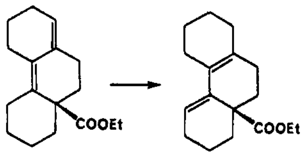
The cyclization of **14** illustrates the ability to control the cyclization by choice of alkylaluminum halide. Me$_2$AlCl-catalyzed ene reaction of methylenecyclohexane with paraformaldehyde gave **12** in 62% yield[3] which was converted to the iodide **13**, via the tosylate, in 75% yield. Alkylation of the potassium salt of **1** with **13** in *tert*-butyl alcohol gave a 79% yield of **14**. Treatment of **14** with Me$_2$AlCl in nitromethane led to a 2:1 mixture of the expected ene adduct **15** and dehydration products **16** and **17**. Use of the milder Lewis acid Me$_3$Al with more basic methyl groups afforded a 63% yield of ene adduct **15**, a 4% yield of **16**, and a 17% yield of **17**. Use of 2.0 equiv of the stronger Lewis acid methylaluminum sesquichloride (Me$_{1.5}$AlCl$_{1.5}$) for 22 h provided a 67% yield of **17**. The structures of **16** and **17** were assigned on the basis of the olefinic proton signal in the NMR spectrum. The olefinic proton of **17**, absorbs as a sharp triplet, while that of **16** is a triplet broadened by homallylic coupling. In addition, the exclusive formation of **17** with Me$_{1.5}$AlCl$_{1.5}$ and the formation of mixtures of **16** and **17** under milder conditions requires the proposed assignments since **16** is an intermediate in the formation of **17** from **15**. Fieser's modification of Woodwards rules predict a λ$_{max}$ of 254 nm for **16** and 244 nm for **17**. The data are ambiguous with λ$_{max}$ 246 nm for **16** and 245 nm for **17**.



12 X=OH
13 X=I

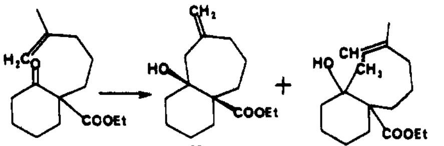
14

15



16 17

Attempted extension of these type II intramolecular ene reactions to the synthesis of five- and 7-membered rings was unsuccessful. Treatment of **18** with 3 equiv of Me$_2$AlCl in nitromethane for 3 days led to a low yield of **19** and a 40% yield of the product **20** resulting from addition of a methyl group to the ketone. Attempted cyclization of ethyl 1-methallyl-2-oxocyclohexanecarboxylate with Me$_2$AlCl gave only the product of methyl addition to the ketone. Similar results were obtained with Me$_{1.5}$AlCl$_{1.5}$ and MeAlCl$_2$ even though they are stronger Lewis acids with less nucleophilic methyl groups.



18 19 20

Alkylation of **1** with 6-iodo-2-methyl-2-hexene gave a 72% yield of **21**, a suitable substrate for examining type I intramolecular ene reactions. Treatment of **21** with 2 equiv of Me$_2$AlCl in nitromethane for 1 day gave a 33% yield of **22**, a 19% yield of **23**, and a 10% yield of recovered **21**. The cis ring fusion stereochemistry of both **22** and **23**

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[15] Trost, B. M.; Kunz, R. A. *J. Am. Chem. Soc.* **1975**, *97*, 7152.

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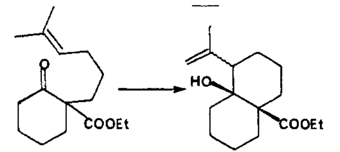
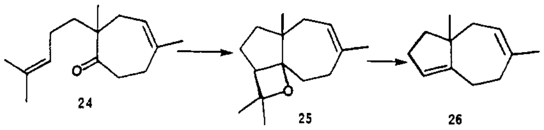
was assigned based on the IR spectra which showed only intramolecularly hydrogen bonded hydroxyl groups (3510 cm^{-1}) in dilute CCl_4 solution. The stereochemistry of the isoprenyl group follows from the chromatographic properties (**22** is much less polar than **23**) and the NMR spectrum of **22** which shows an unusual long range *W* coupling of 2 Hz between the rigidly hydrogen bonded OH proton and the allylic methine proton.



21

22 β-C_3H_5
23 α-C_3H_5

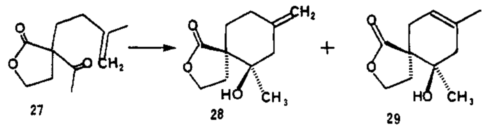
Demole et al. have reported that treatment of **24** with $SnCl_4$ gave the oxetane **25**.[18] We chose to reexamine this reaction with alkylaluminum halides since a type I intramolecular ene reaction would provide a simple route to carotol. Treatment of **24** with $^2/_3$ equiv of $MeAlCl_2$ and $^1/_3$ equiv of Me_2AlCl in CH_2Cl_2 for 10 h at 25 °C gave a ca. 30% yield of **26** and a ca. 7% yield of β-acoratriene.[18] The formation of the unusual metathesis product **26** presumably results from stepwise cycloaddition to give **25** which then opens in the other direction and loses acetone. The choice of Lewis acid, nominally 1 equiv of $Me_{1.33}AlCl_{1.67}$ resulted from trial reactions which established that no reaction occurred with $Me_{1.5}AlCl_{1.5}$ indicating that it was too weak and that a complex mixture of products were formed with $MeAlCl_2$ indicating that it was too strong.



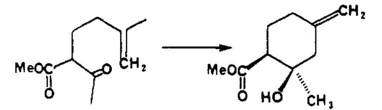
24 25 26

Intramolecular ene reactions of similar methyl ketones are more problematical. Treatment of **27** with 2 equiv of Me_2AlCl in nitromethane for 18 h gave an 85% yield of a 2:1 mixture of **28** and three isomers and a 7% yield of **29**. Cyclization of **30** gave a 27% yield (93% based on recovered **30**) of a 2:1 mixture of **31** and double bond position isomers. The low yield in this case appears to result from competing enolization of the Me_2AlCl–ketone complex with loss of methane to give the chelated aluminum enolate which gives recovered starting material on workup.

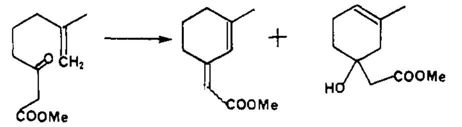
This problem became more severe with **32**[19] which gave primarily recovered **32** after treatment with Me_2AlCl or $MeAlCl_2$. Treatment of **32** with 0.2 equiv of $BF_3{\cdot}OEt_2$ did lead to cyclization. A complex mixture of products was obtained from which a 1:1 mixture of (*E*)- and (*Z*)-**33** (20%)[20] and **34** (18%) could be isolated. This result clearly indicates that the advantages of alkylaluminum halides as catalysts in these reactions lies primarily in their proton scavenging ability which stabilizes the product tertiary alcohol. Alkylaluminum halides may not be the optimal catalyst when the ketone–Lewis acid complex can readily form an enol which will be converted to the aluminum alkoxide. Since the alkylaluminum halide reacts with the ene adduct it must be used in equivalent or greater amounts, whereas standard Lewis acids can be used in catalytic amounts.



27 28 29



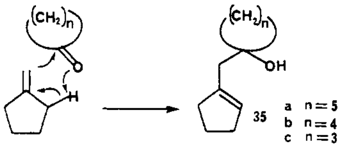
30 31



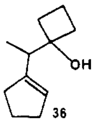
32 33 34

Intermolecular Reactions. Intermolecular ene reactions using unactivated ketones as enophiles presents a more serious challenge since the reaction lacks the entropic assistance of the intramolecular reactions but produces tertiary alcohols subject to solvolysis. We have found that ene adducts can be isolated from the $EtAlCl_2$-catalyzed ene reactions of cycloalkanones and reactive ene components—alkenes with one end of the double bond sterically accessible and the other end capable of stabilizing a positive charge in an intermediate or transition state.[1b] The yields are moderate at best, but the reaction does provide an extremely simple route to homoallylic tertiary alcohols.

Reaction of cyclohexanone, methylenecyclopentane and $EtAlCl_2$ in equimolar amounts at 0 °C in CH_2Cl_2 for 45 min gave a 47% yield of **35a**. A similar reaction with cyclobutanone gave a 32% yield of **35c**. However, cyclopentanone gave only a 6% yield of **35b**. Reaction of cyclobutanone with ethylidenecyclopentane, 2-ethyl-1-butene, and methylenecyclohexane gave **36** (13%), **37** (30%), and **39a** (55%), respectively. Reaction of 4-*tert*-butylcyclohexanone with methylenecyclopentane showed a slight preference for equatorial attack giving a 6% yield of **38a** and a 4.7% yield of **38b**. The low yield indicates that the reaction is very sensitive to slight changes in the ketone since cyclohexanone gave a 47% yield of **35a**. Reaction of methylenecyclohexane with acetone gave a 9% yield of **39b**.[21] No ene adducts could be obtained from acetophenone, benzophenone, 2-methylcyclohexanone, or methylcyclopropyl ketone.



35 a n = 5
b n = 4
c n = 3



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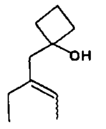

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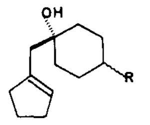
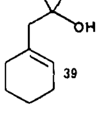


38 a R = α-*t*-Bu
b R = β-*t*-Bu



39 a R,R = $(CH_2)_3$
b R = CH_3

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Conclusion

We have shown that Lewis acid catalyzed intramolecular ene reactions using the ketone group of a β-keto ester as the enophile proceed efficiently to cyclohexanols by either a type I or a type II process. Since the starting materials are available in a single step by alkylation of a β-keto ester, this constitutes an attractive new annelation procedure. Formation of cyclopentanols by either type I or II processes cannot be accomplished. Formation of a cycloheptanol by a type II process occurs in low yield.

$EtAlCl_2$-catalyzed intermolecular ene reactions of ketones with reactive ene components proceed in low to moderate yield providing a simple route to homoallylic tertiary alcohols. The key to the success of both the intra and intermolecular reactions is the use of a proton scavenging alkylaluminum halide as the Lewis acid. The tertiary alcohol complex formed in the ene reaction is converted to an aluminum alkoxide which minimizes solvolysis. The optimal Lewis acid is the weakest (most alkyl groups) which will catalyze the desired reaction.

We are currently exploring the scope of intramolecular ene reactions of ketones using other functional groups to stabilize the aluminum alkoxide.

Experimental Section

NMR spectra were obtained on Varian EM-390, Perkin-Elmer R-32, or Bruker WH-90 spectrometers. IR spectra were obtained on a Perkin-Elmer 683 spectrometer. Mass spectra were recorded on a Hewlett-Packard 5992 spectrometer. Combustion analyses were performed by Galbraith Laboratories. GC Analyses were carried out on 10 ft × 0.25 in. 10% Carbowax 20M (A) or 10 ft × 0.25 in. 3% SE-30 (B) column at flow rates of 50 mL/min. MPLC refers to medium-pressure liquid chromatography on a Merck Lobar silica gel column.

Methylene chloride was dried by distillation from calcium hydride. Nitromethane was dried by fractional distillation. Me_2AlCl, $MeAlCl_2$, $EtAlCl_2$, and Me_3Al were obtained from Texas Alkyls Inc. as solutions in hexane or heptane as indicated below. $Me_{1.5}AlCl_{1.5}$ was prepared by mixing equimolar amounts of solutions of Me_2AlCl and $MeAlCl_2$.

All air-sensitive reactions were run in flame-dried glassware under N_2. Reagents were added via dry syringes through septa.

4-Iodo-2-methyl-1-butene (**2**) was prepared by the procedure of Trost and Kunz,[15] except that the iodide was purified by chromatography on silica gel (99:1 hexane–EtOAc). 5-Methyl-4-hexen-1-ol was prepared by the procedure of Corey et al.[22] except that HMPA was not used as a cosolvent in the alkylation step.

Preparation of 3. 2-Methyl-4-iodo-1-butene (1.96 g, 10 mmol) was added to a stirred solution of ethyl 2-oxocyclohexanecarboxylate (1.70 g, 10 mmol in 11 mL of 1 M potassium *tert*-butoxide in *tert*-butyl alcohol. The yellow solution was heated slowly to reflux and maintained there for 19 h. After cooling, the cream colored mixture was treated with water to dissolve the precipitate, and extracted with ether (3×). The combined extracts were washed with saturated brine, dried (Na_2SO_4), and evaporated in vacuo to give a faintly colored liquid (2.315 g). The crude product was purified by MPLC (9:1 pentane–ether) to afford **3** as a colorless liquid (1.615 g, 73%): NMR (CCl_4) δ 4.65 (br s, 2), 4.17 (q, 2, J = 7 Hz), 1.72 (s, 3), 1.3–2.8 (m, 12), 1.28 (t, 3, J = 7 Hz); IR (neat) 3075, 2940, 2875, 1653, 1454, 1250, 1221, 1193, 1141, 1101, 1032, 895 cm^{-1}; GC (A, 180 °C) t_R 29.4 min. Evaporative distillation (94 °C, 0.6 torr) provided an analytical sample. Anal. Calcd for $C_{14}H_{22}O_3$: C, 70.56; H, 9.30. Found: C, 70.50; H, 9.27.

Preparation of 4. A suspension of **3** (1.634 g, 6.86 mmol) in a solution of potassium hydroxide (1.2 g) in ethanol–water (1:1, 24 mL) was heated at reflux, under nitrogen, for 15 h. The solution was allowed to cool, and extracted with ether (3 × 25 mL). The combined ether extracts were washed with saturated brine, dried ($MgSO_4$), and evaporated in vacuo to give 0.832 g of almost pure **4**. Evaporative distillation (65 °C, 0.6 torr) of this material (0.811 g) gave analytically pure **4** (0.763 g, 69%) as a colorless liquid: NMR ($CDCl_3$) δ 4.67 (br s, 2), 1.1–2.5 (m, 13), 1.69 (br s, 3); IR (neat) 3080, 2940, 2865, 1717, 1653, 1452, 1130, 885 cm^{-1}; GC (A, 150 °C) t_R 22.3 min. Anal. Calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.91. Found: C, 79.63; H, 10.88.

Preparation of 10. 2-Methyl-4-iodo-1-butene (**2**)(0.98 g, 5 mmol) was added to a stirred solution of methyl 2-oxocyclopentanecarboxylate (0.71 g, 5 mmol) in 5.5 mL of 1 M potassium *tert*-butoxide in *tert*-butyl alcohol. After 18 h at reflux, the cooled cream-colored mixture was worked up as usual to give a yellow liquid (0.900 g). The crude product was purified by MPLC (9:1 pentane–ether) to afford **10** as a colorless liquid (0.635 g, 60%). This material (0.477 g) was further purified by evaporative distillation (75 °C, 0.1 torr) to afford an analytical sample (0.444 g, 56%): NMR (CCl_4) δ 4.66 (br s, 2), 3.67 (s, 3), 1.71 (br s, 3), 1.3–2.8 (m, 10); IR (neat) 3080, 2960, 1755, 1728, 1653, 1453, 1409, 1378, 1321, 1259, 1232, 1181, 1166, 1150, 1116, 891 cm^{-1}; GC (A, 180 °C) t_R 22.8 min. Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.55; H, 8.63. Found: C, 68.60; H, 8.73.

Preparation of 1-Cyclohexene-1-ethanol (12). Me_2AlCl (18 mL of a 1.9 M solution in hexane, 1.35 equiv) was added dropwise to a cooled (0 °C), stirred suspension of paraformaldehyde (0.68 g, 0.9 equiv) in a solution of methylenecyclohexane (2.40 g, 25 mmol) in CH_2Cl_2 (60 mL). The pale yellow solution was allowed to warm to 25 °C. The reaction was stirred for 2.5 h and quenched by cautious addition of water (foaming !!). The precipitated aluminum salts were dissolved by addition of 10% hydrochloric acid. The aqueous layer was separated and extracted with ether (2×). The combined extracts were washed with saturated $NaHCO_3$ solution, water, and saturated brine, dried (Na_2SO_4), and evaporated in vacuo (0 °C) to give a faintly colored liquid (2.271 g). Evaporative distillation (82 °C, 7 torr) afforded **12** as a colorless liquid (1.770 g, 62%): NMR (CCl_4) δ 5.44 (br s, 1), 3.55 (t, 2, J = 6.5 Hz), 3.03 (br s, 1, OH), 1.4–2.3 (m, 10).

Preparation of 1-(2-Iodoethyl)cyclohexene (13). Alcohol **12** (1.728 g, 13.7 mmol) was converted to the iodide **13** via the tosylate as described below for the preparation of 6-iodo-2-methyl-2-hexene. The crude iodide was passed through a column of silica gel (pentane) to afford **13** as a colorless liquid (2.436 g, 75%): NMR ($CDCl_3$) δ 5.49 (br s, 1), 3.23 (t, 2, J = 8 Hz), 2.48 (br t, 2, J = 9 Hz), 1.4–2.2 (m, 8).

Preparation of 14. The alkylation of **1** was repeated using **13** (1.18 g, 5 mmol). After 18 h, the cooled yellow mixture was worked up to give a pale yellow liquid (1.395 g). The crude product was purified by MPLC (19:1 pentane–ether) to afford **14** as a colorless oil (0.987 g, 79%). This material (0.927 g) was further purified by evaporative distillation (118 °C, 0.02 torr) to afford an analytical sample (0.875 g, 75%): NMR ($CDCl_3$) δ 5.41 (br s, 1), 4.20 (q, 2, J = 7 Hz), 1.4–2.8 (m, 20), 1.25 (t, 3, J = 7 Hz); IR (neat) 2930, 1716, 1450, 1190 cm^{-1}; GC (B, 200 °C) t_R 28.0 min. Anal. Calcd for $C_{17}H_{26}O_3$: C, 73.35; H, 9.41. Found: C, 73.45; H, 9.57.

Preparation of 18. 5-Iodo-2-methyl-1-pentene (1.05 g, 5 mmol) was added to a stirred solution of **1** (0.85 g, 5 mmol) in 5.5 mL of 1 M potassium *tert*-butoxide in *tert*-butyl alcohol. The solution was heated slowly to reflux and maintained there for 18 h. After cooling, the cream-colored mixture was worked up as before to give a pale yellow oil (1.192 g). The crude product (1.166 g) was purified by MPLC (19:1 pentane–ether) to afford **18** as a colorless liquid (0.856 g, 69%): NMR (CCl_4) δ 4.65 (br s, 2), 4.17 (q, 2, J = 7 Hz), 1.68 (br s, 3), 1.27 (t, 3, J = 7 Hz), 1.1–2.7 (m, 14); IR (neat) 3080, 2945, 2875, 1717, 1651, 1451, 1208, 1180, 1144, 1096, 1280, 1021, 884 cm^{-1}; GC (A, 180 °C) t_R 50.5 min.

Preparation of 6-Iodo-2-methyl-2-hexene. A solution of *p*-toluenesulfonyl chloride (7.0 g, 37 mmol) in pyridine (30 mL) was stirred at 0 °C while 5-methyl-4-hexen-1-ol (2.00 g, 17.5 mmol) was added in 3 portions over a 2-min period. The mixture was stirred for 4 h at 0 °C, poured into ice–water (150 mL), and extracted with ether (3 × 50 mL). The combined extracts were washed with saturated copper sulfate solution, water, and saturated brine, dried (Na_2SO_4), and evaporated in vacuo to give the tosylate as a faintly colored liquid (4.99 g). The crude tosylate (4.930 g) and sodium iodide (10.0 g) were stirred together in refluxing acetone (50 mL) for 2 h. The cooled mixture was treated

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[22] Corey, E. J.; Hashimoto, S.; Barton, A. F. *J. Am. Chem. Soc.* **1981**, *103*, 721.

with water to dissolve the precipitate and extracted with ether (3×). The combined extracts were washed with saturated brine, dried ($MgSO_4$), and evaporated in vacuo (0 °C) to give an orange liquid (3.307 g). The crude iodide (3.265 g) was passed through a column of silica gel (pentane) to afford the pure iodide as a colorless liquid (2.969 g, 78%): NMR ($CDCl_3$) δ 5.08 (br t, 1, J = 7 Hz), 3.20 (t, 2, J = 6.5 Hz), 1.6–2.3 (m, 4), 1.70 (br s, 3), 1.64 (br s, 3).

Preparation of 21. The alkylation of 1 was repeated using 6-iodo-2-methyl-2-hexene (1.120 g, 5 mmol). After 18 h at reflux, the cooled yellow mixture was worked up to give a faintly colored liquid (1.277 g). The crude product was purified by MPLC (9:1 pentane–ether) to afford **21** as a colorless liquid (1.035 g, 78%). This material was further purified by evaporative distillation (105 °C, 0.05 torr) to afford an analytical sample (0.925 g, 72%): NMR ($CDCl_3$) δ 5.09 (br t, 1, J = 7 Hz), 4.20 (q, 2, J = 7 Hz), 1.1–2.7 (m, 14), 1.66 (br s, 3), 1.58 (br s, 3,), 1.25 (t, 3, J = 7 Hz); IR (neat) 2940, 2870, 1716, 1453, 1378, 1309, 1201, 1175, 1132, 1092, 1024 cm^{-1}; GC (A, 180 °C) t_R 73.7 min. Anal. Calcd for $C_{16}H_{26}O_3$: C, 72.14; H, 9.84. Found: C, 72.34; H, 10.00.

Preparation of 27. A solution of 2-acetylbutyrolactone (0.64 g, 5 mmol) in benzene (0.4 mL) was added dropwise over ca. 20 min (frothing!!) to a stirred suspension of NaH (0.22 g of a 60% dispersion, washed free of mineral oil with hexane, 5.5 mmol) in refluxing benzene (1.4 mL). A solution of 4-iodo-2-methyl-1-butene (**2**) (0.98 g, 5 mmol) in DMF (0.4 mL) was added, and the resulting solution stirred at reflux for 5 h. Normal workup gave 0.680 g of crude **27**. MPLC of 0.632 g (2:1 hexane–ether) gave **27** (0.279 g, 31%) as a faintly colored liquid.

The data for **27** follow: NMR ($CDCl_3$) δ 4.75 (m, 2), 4.00–4.47 (m, 2), 2.81–3.13 (m, 1), 2.33 (s, 3), 1.7–2.5 (m, 8), 1.73 (br s, 3); IR (neat) 3080, 2970, 2925, 1770, 1715, 1653, 1450, 1374, 1361, 1219, 1170, 1022, 890 cm^{-1}. Evaporative distillation (83 °C, 0.025 torr) provided an analytically pure sample as a colorless liquid. Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.27; H, 8.40.

Preparation of 30. 2-Methyl-4-iodo-1-butene (**2**) (0.98 g, 5 mmol) was added to a stirred solution of methyl acetoacetate (0.58 g, 5 mmol) and sodium (0.13 g) in dry ethanol (2 mL). The solution was heated slowly to reflux and maintained there for 1.5 h. Normal workup gave 0.823 g of crude product. MPLC of 0.753 g (9:1 hexane–ether) gave 39 mg (3%) of dialkylated material, 0.486 g (54%) of **30**, and 45 mg (5%) of the corresponding ethyl ester.

The data for **30** follow: NMR ($CDCl_3$) δ 4.78 (m, 1), 4.72 (br s, 1), 4.22 (q, 2, J = 7 Hz), 3.45 (m, 1), 2.23 (s, 3), 2.0 (m, 4), 1.72 (br s, 3), 1.23 (t, 3, J = 7 Hz); IR (neat) 3080, 2980, 2945, 1747, 1718, 1652, 1450, 1361, 1244, 1149, 890 cm^{-1}; GC (B, 150 °C) t_R 7.6 min. Evaporative distillation (61 °C, 0.03 torr) provided an analytical sample of **30** as a colorless liquid. Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15. Found: C, 66.31; H, 9.01.

Cyclization of 3. Me_2AlCl (1.33 mL of a 1.9 M solution in hexane, 1.2 equiv) was added to a stirred solution of **3** (0.50 g, 2.10 mmol) in $MeNO_2$ (10 mL) 25 °C. After 60 h the solution was diluted with CH_2Cl_2 and quenched with water. The aqueous layer was separated and extracted with CH_2Cl_2 (2×). The combined organic extracts were washed with saturated brine, dried (Na_2SO_4), and evaporated in vacuo to give a faintly colored liquid (0.502 g). The product was purified by MPLC (9:1 pentane–ether) to afford first recovered **3** (46 mg) and then **5** as a colorless liquid (0.323 g, 67%, 74% based on recovered **3**). Evaporative distillation (80 °C, 0.05 torr) of this material (0.263 g) afforded an analytically pure sample of **5** (0.244 g): NMR ($CDCl_3$) δ 4.69 (br s, 2), 4.21 (q, 2, J = 7 Hz), 2.33 (br s, 2), 1.28 (t, 3, J = 7 Hz), 1.1–2.5 (m, 13); ^{13}C NMR ($CDCl_3$) δ 177.8, 145.2, 108.9, 72.1, 60.2, 50.3, 46.0, 33.5, 31.1, 30.6, 30.3, 21.1, 20.9, 13.7; IR (CCl_4) 3520, 3080, 2940, 1705, 1654, 1453, 1395, 1298, 1284, 1226, 1182, 1156, 1100, 1075, 1036, 897, 792 cm^{-1}; GC (A, 180 °C) t_R 33.7 min. Anal. Calcd for $C_{14}H_{22}O_3$: C, 70.56; H, 9.30. Found: C, 70.67; H, 9.41.

Reduction of 5. LAH (0.63 mL of a 1 M solution in THF) was added dropwise to a stirred solution of **5** (101 mg, 0.42 mmol) in THF (2 mL) at 25 °C. After a further 0.5 h, the solution was quenched by addition to ice–water, treated with 10% sulfuric acid (1 mL), and extracted with CH_2Cl_2 (6×). The combined extracts were washed successively with 10% $NaHCO_3$ solution and saturated brine, dried (Na_2SO_4), and evaporated in vacuo to give a colorless oil (82 mg). The crude product was purified by chromatography on silica gel (1:1 pentane–ether) to afford first **7** (9 mg, 11%) and then **6** (65 mg, 78%).

The data for **7** follow: NMR ($CDCl_3$) δ 9.70 (s, 1), 4.80 (br s, 1), 4.73 (br s, 1), 3.13 (br s, 1, OH), 2.0–2.6 (m, 4), 1.3–2.0 (m, 10); IR (CCl_4) 3620, 3550, 3080, 1713, 1654, 898 cm^{-1}.

The data for **6** follow: NMR ($CDCl_3$) δ 4.79 (br s, 1), 4.70 (br s, 1), 3.84 (br s, 2), 3.2 (br, 2, OH), 2.49 (d, 1, J = 13.5 Hz), 2.21 (d, 1, J = 13.5 Hz), 2.2 (m, 2), 1.2–2.0 (m, 10); IR (CCl_4) 3640, 3615, 3520, 3380, 3080, 2940, 2930, 2870, 1652, 1458, 1032, 897 cm^{-1}.

Preparation of 8. *p*-Toluenesulfonyl chloride (125 mg) was added to a stirred solution of **6** (65 mg, 0.33 mmol) in pyridine (5 mL) at 0 °C. The yellow solution was kept at 0 °C for 27 h, by which time the color had turned to pink-violet. The solution was poured into water and extracted with ether (3×). The combined extracts were washed successively with water, saturated $CuSO_4$ solution, water, and saturated brine, dried (Na_2SO_4), and evaporated in vacuo to give **8** as a colorless oil (88 mg, 76%), which was used directly in the next step: NMR ($CDCl_3$) δ 7.80 (d, 2, J = 8 Hz), 7.35 (d, 2, J = 8 Hz), 4.78 (br s, 1), 4.67 (br s, 1), 4.32 (d, 1, J = 9 Hz), 4.18 (d, 1, J = 9 Hz), 2.43 (s, 3), 1.9–2.7 (m, 5), 1.2–1.8 (m, 10).

Preparation of 9. The tosylate **8** (61 mg, 0.17 mmol) was stirred with a suspension of 60% NaH (36 mg, 0.9 mmol, washed free of mineral oil with hexane) in THF (2 mL) at room temperature for 1 h. The solution was diluted with ether and quenched by addition of water. The aqueous layer was separated and extracted once with ether. The combined extracts were washed with saturated brine, dried (Na_2SO_4), and evaporated in vacuo to give a faintly colored oil (34 mg). The crude product (29 mg) was chromatographed on silica gel (9:1 hexane–ether) to afford **9** as a colorless oil (17 mg, 65%). On increasing the eluent polarity with ether, unreacted **8** (8 mg, 13%) was recovered.

The data for **9** follow: NMR ($CDCl_3$) δ 4.82 (br s, 2), 4.32 (s, 2), 2.1–2.9 (m, 4, including br s at 2.40) 1.8–2.1 (m, 10); IR (CCl_4) 3080, 2935, 2870, 1647, 1454, 976, 888 cm^{-1}.

Cyclization of 10. Me_2AlCl (1.8 mL of a 1.9 M solution in hexane, 2.0 equiv) was added to a stirred solution of **10** (0.361 g, 1.72 mmol) in $MeNO_2$ (15 mL) at 25 °C. Normal workup after 17 h gave 0.389 g of crude **11**. Evaporative distillation (72 °C, 0.05 torr) of the crude product afforded 0.323 g (90%) of analytically pure **11** as a colorless liquid: NMR ($CDCl_3$) δ 4.70 (br s, 2), 3.74 (s, 3), 3.61 (br s, 1, OH), 2.50 (br s, 2), 1.2–2.4 (m, 10); ^{13}C NMR ($CDCl_3$) δ 177.0, 145.5, 109.5, 82.3, 55.8, 51.5, 43.6, 34.5 (2 carbons ?) 33.1, 31.5, 19.1; IR (CCl_4) 3545, 3080, 2955, 1716, 1655, 1435, 1382, 1338, 1287, 1198, 1163, 1116, 1102, 1068, 1050, 1033, 894 cm^{-1}; GC (A, 180 °C) t_R 20.9 min. Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.55; H, 8.63. Found: C, 68.34; H, 8.53.

Cyclization of 14. Me_3Al (1.3 mL of a 1.5 M solution in heptane, 2 equiv) was added to a stirred solution of **14** (0.274 g, 0.98 mmol) in $MeNO_2$ (10 mL) at 25 °C. Normal workup after 15 h gave 0.272 g of crude product. Chromatography on silica gel (19:1 hexane–ether) gave three fractions. The first afforded **16** as a colorless liquid (10 mg, 4%). The second afforded **17** as a colorless liquid (25 mg, 10%). The third afforded pure **15** as a colorless liquid (0.150 g, 63%).

The data for **16** follow: NMR ($CDCl_3$) δ 5.43 (m, 1), 4.16 (q, 2, J = 7 Hz), 1.1–2.9 (m, 18), 1.24 (t, 3, J = 7 Hz); UV (ETOH) λ_{max} 246 nm (ϵ 17 700); GC (B, 200 °C) t_R 18.6 min.

The data for **17** follow: NMR ($CDCl_3$) δ 5.76 (br t, 1, J = 4.5 Hz), 4.12 (AB m of ABX_3, 2), 1.0–2.4 (m, 18), 1.19 (t, 3, J = 7 Hz); UV (EtOH) λ_{max} 245 nm (ϵ 19 000); IR (CCl_4) 2930, 1725, 1449, 1295, 1267, 1236, 1197, 1157, 1134, 1096, 1029 cm^{-1}; GC (B, 200 °C) t_R 18.2 min.

The data for **15** follow: NMR ($CDCl_3$) δ 5.63 (m, 1), 4.62 (d, 1, J = 2 Hz, OH), 4.19 (q, 2, J = 7 Hz), 1.0–2.8 (m, 19), 1.26 (t, 3, J = 7 Hz); ^{13}C NMR ($CDCl_3$) δ 178.7, 136.1, 122.9, 74.7, 60.5, 52.3, 37.8, 33.4, 32.1, 30.1, 29.3, 25.0, 23.4 (2 carbons?), 22.6, 21.9, 14.0; IR (CCl_4) 3515, 2935, 2870, 1705, 1450, 1391, 1310, 1299, 1230, 1217, 1190, 1146, 1126, 1095, 1047, 1025, 894 cm^{-1}; GC (B, 200 °C) t_R 31.3 min. Evaporative distillation (110 °C, 0.2 torr) provided an analytical sample. Anal. Calcd for $C_{17}H_{26}O_3$: C, 73.35; H, 9.41. Found: C, 73.45; H, 9.23.

Cyclization of 14 with $Me_{1.5}AlCl_{1.5}$. $Me_{1.5}AlCl_{1.5}$ (0.30 mL of a 1.6 M solution in hexane, 2 equiv) was added to a stirred solution of **14** (67 mg, 0.24 mmol) in $MeNO_2$ (2 mL) at 25 °C. Normal workup after 22 h gave 62 mg of crude product. Chromatography as above gave 42 mg (67%) of **17**.

Cyclization of 18. Me_2AlCl (0.33 mL of a 1.9 M solution in hexane, 3.0 equiv) was added to a stirred solution of **18** (54 mg, 0.21 mmol) in $MeNO_2$ (2 mL) at 25 °C. Normal workup after 39 h gave 58 mg of crude product. Chromatography on silica gel (19:1 pentane–ether) gave 13 mg of a colorless liquid that was a 69:31 mixture of **19** and recovered **18** (by GC). On increasing the solvent polarity to 10% ether in pentane the methyl addition product **20** (24 mg) was isolated. A pure sample of **19** was obtained by preparative GC (B, 200 °C) **18** t_R 19.0 min, **19** t_R 25.8 min.

The data for **19** follow: NMR ($CDCl_3$) δ 4.79 (br s, 1), 4.69 (br s, 1), 4.17 (q, 2, J = 7 Hz), 2.87 (d, 1, J = 14 Hz), 2.16 (d, 1, J = 14 Hz), 1.26 (t, J = 7 Hz), 2.5–1.1 (m, 15); GC (A, 180 °C) t_R 67.6 min.

Cyclization of 21. Me_2AlCl (2.0 mL of a 1.9 M solution in hexane, 2 equiv) was added to a stirred solution of **21** (0.50 g, 1.88 mmol) in $MeNO_2$ (15 mL) at 25 °C. Normal workup after 23 h gave 0.566 g of a dark yellow oil. Purification by MPLC (19:1 pentane–ether) afforded **22** (0.167 g, 33%), **23** (0.095 g, 19%), and recovered **21** (0.048 g, 10%) as colorless oils.

The data for **22** follow: NMR ($CDCl_3$) δ 4.79 (br s, 2), 4.57 (d, 1, J = 2 Hz, OH), 4.17 (q, 2, J = 7 Hz), 2.61 (ddd, 1, J = 2, 3, 12 Hz), 1.0–2.4 (m, 14), 1.81 (br s, 3), 1.25 (t, 3, J = 7 Hz). Irradiation at δ 2.61 caused the OH d to collapse to a singlet at δ 4.57. Irradiation at δ 4.57 caused the ddd at δ 2.61 to collapse to a dd with J = 3, 12 Hz; ^{13}C NMR ($CDCl_3$) δ 179.0, 147.5 112.9, 73.6, 60.4, 51.8, 45.9, 34.8, 31.1, 30.0, 26.7, 23.4 (2 carbons ?), 21.5, 21.1, 14.0; IR (CCl_4) 3510, 3080, 2940, 2870, 1705, 1638, 1457, 1236, 1228, 1204, 1184, 1167, 1141, 1102, 1028, 894 cm^{-1}; GC (A, 180 °C) t_R 51.9 min; R_f 0.30 (19:1 pentane–ether). An analytical sample was prepared by preparative GC (B, 200 °C) t_R 12.8 min. Anal. Calcd for $C_{16}H_{28}O_3$: C, 72.14; H, 9.84. Found: C, 72.40; H, 10.01.

The data for **23** follow: NMR ($CDCl_3$) δ 4.96 (br s, 1, OH), 4.69 (br s, 1) 4.20 (q, 2, J = 7 Hz), 2.62 (dd, 1, J = 7, 10.5 Hz), 1.0–2.2 (m, 14), 1.88 (br s, 3), 1.26 (t, 3, J = 7 Hz); ^{13}C NMR ($CDCl_3$) δ 179.6, 146.8, 112.5, 74.7, 60.6, 52.1, 51.8, 32.3, 29.9, 29.3, 26.8, 26.4, 23.8, 20.5 (2 carbons?), 14.4; IR (CCl_4) 3510, 2950, 1704, 1243, 1224, 1153, 1033, 891 cm^{-1}; GC (A, 180 °C) t_R 63.5 min; R_f 0.19 (19:1 pentane–ether); preparative GC (B, 200 °C) t_R 13.3 min. Anal. Calcd for $C_{16}H_{28}O_3$: C, 72.14; H, 9.84. Found: C, 72.33; H, 9.77.

Metathesis of 24. Me_2AlCl (0.41 mL of a 1.9 M solution in hexane, 0.78 mmol) and then $MeAlCl_2$ (1.1 mL of a 1.4 M solution in hexane, 1.56 mmol) were added to a stirred solution of **24** (0.515 g, 2.34 mmol) in CH_2Cl_2 (12 mL) at 0 °C. The bright yellow solution was allowed to warm to 25 °C. Normal workup after 10 h gave a bright yellow oil (0.428 g). Evaporative distillation (85 °C, 0.15 torr) afforded 0.213 g of a colorless liquid. Nonvolatile residue amounted to 0.205 g. GC (A, 150 °C) of the distillate indicated that several components were present: t_R 4.6 min (**26**, 64%), 5.6 min (2%), 13.0 min (β-acoratriene, 15%), 16.7 min (1%), 29.3 min (14%), and 33.3 min (3%). Pure **26** was isolated by preparative GC: NMR (CCl_4) δ 5.43 (br t, 1, J = 7 Hz), 5.15 (br s, 1), 1.5–2.5 (m, 10), 1.75 (br s, 3), 0.92 (s, 3); MS, m/e (relative intensity) 162 (M^+, 99), 147 (100), 134 (25), 133 (29), 120 (39), 119 (38), 105 (47), 94 (28), 93 (30), 91 (59), 79 (80), 77 (34). Anal. Calcd for $C_{12}H_{18}$: C, 88.82; H, 11.18. Found: C, 88.63; H, 11.29.

Cyclization of 27. Me_2AlCl (0.85 mL of a 1.9 M solution in hexane, 2.0 equiv) was added to a stirred solution of **27** (159 mg, 0.81 mmol) in $MeNO_2$ (12 mL) at 25 °C. Normal workup after 18 h gave 172 mg of a solid. Chromatography on silica gel (4:1 ether–hexane) gave 11 mg (7%) of **29**, followed by 136 mg (85%) of a 64:16:16:4 mixture of **28**, and three stereoposition or double bond position isomers as determined by analysis of the NMR spectrum.

The data for **29** follow: NMR ($CDCl_3$) δ 5.37 (br s, 1), 4.43–4.17 (m, 2), 2.67–1.40 (m, 7), 1.67 (br s, 3), 1.25 (s, 3); IR (CCl_4) 3530, 1760 cm^{-1}.

The data for **28** and isomers follow: NMR ($CDCl_3$) δ 4.77 (m, 2), 4.40–4.07 (m, 2), 2.83–1.53 (m), 1.53 (s, 3, 4%), 1.48 (s, 3, 16%), 1.27 (s, 3, 16%), 1.20 (s, 3, 28, 64%); IR (CCl_4) 3620, 3520, 1760 cm^{-1}.

Cyclization of 30. $Me_{1.5}AlCl_{1.5}$ (1.3 mL of a 1.6 M solution in hexane, 2 equiv) was added to a stirred solution of **30** (0.201 g, 1.01 mmol) in $MeNO_2$ (12 mL) at 25 °C. Normal workup after 18 h gave 0.184 g of crude product. MPLC (3:1 hexane–ether) gave 72 mg (32%) of recovered **30**, followed by 55 mg (27%, 43% based on recovered **30**) of a 64:36 mixture of **31** and isomers as determined by NMR analysis: NMR ($CDCl_3$) δ 5.4 (m, 0.34×1), 4.79 (m, 0.64×2), 4.19 (q, 2, J = 7 Hz), 3.46 (d, 0.64×1, J = 2 Hz, OH), 3.40 (br, 0.34×1, OH), 1.8–2.6 (m), 1.66 (br s, 0.34×3), 1.27 (s, 3), 1.24 (t, 3, J = 7 Hz); IR (CCl_4) 3540, 3085, 2975, 2960, 1716, 1662, 1447, 1375, 1177, 1160, 1034, 975, 894 cm^{-1}.

Cyclization of 32. $BF_3{\cdot}OEt_2$ (17 mg, 0.2 equiv) in $MeNO_2$ (1 mL) was added to a stirred solution of **32** (113 mg, 0.61 mmol) in $MeNO_2$ (1 mL) at 25 °C. Normal workup after 20 h gave 92 mg of crude product. Chromatography on silica gel (4:1 hexane–Et_2O) gave 22 mg (20%) of a 1:1 mixture of (*E*)- and (*Z*)-**33**,[20] 17 mg (15%) of a complex mixture, and 20 mg (18%) of **34**.

The data for **33** follow: NMR ($CDCl_3$) δ 7.33 (br, s, 1 (*Z*)-**33**), 5.93 (br s, 1, (*E*)-**33**), 5.45 (br s, 1, (*E*)-**33**), 5.40 (br s, 1, (*Z*)-**33**), 3.63 (s, 3), 2.90 (t, 2, J = 6 Hz, (*E*)-**33**), 2.33 (t, 2, J = 6 Hz, (*Z*)-**33**), 2.27–1.60 (m, 7); IR (neat) 2940, 2870, 1715, 1635, 1610 cm^{-1}.

The data for **34** follow: NMR ($CDCl_3$) δ 5.43 (br s, 1), 3.73 (s, 3), 3.45 (br s, 1, OH), 2.53 (s, 2), 2.13 (m, 4), 1.67 (m, 5); IR (neat) 3520, 1730 cm^{-1}.

Synthesis of 35a. $EtAlCl_2$ (2.8 mL of 1.48 M solution in hexane, 4 mmol) was added to a solution of cyclohexanone (0.4 g, 4 mmol) and methylenecyclopentane (0.33 g, 4 mmol) in 6 mL of CH_2Cl_2 at 0 °C under nitrogen. The reaction was stirred for 1 h at 0 °C and worked up to 697 mg of crude product. MPLC (10:1 hexane–EtOAc) gave 340 mg (47%) of pure **35a**: NMR ($CDCl_3$) δ 5.45 (br, 1), 2.3 (m, 6), 1.8–2.0 (m, 2), 1.25–1.5 (m, 11); IR (neat) 3300 cm^{-1}. Anal. Calcd for $C_{12}H_{20}O$: C, 79.94; H, 11.18. Found: C, 79.44; H, 11.00.

Synthesis of 35c. $EtAlCl_2$ (2.8 mL of 1.48 M solution in hexane, 4 mmol) was added to a solution of cyclobutanone (0.28 g, 4 mmol) and methylenecyclopentane (0.33 g, 4 mmol) in 6 mL of CH_2Cl_2 at 0 °C under nitrogen. The reaction was stirred for 1 h at 0 °C and worked up to give 383 mg of crude product. Chromatography on silica gel (10:1 hexane–EtOAc) gave 191 mg (32%) of pure **35c**: NMR ($CDCl_3$) δ 5.5 (br, 1), 1.5–2.6 (m, 14); IR (neat) 3300 cm^{-1}. Anal. Calcd for $C_{10}H_{16}O$: C, 78.90; H, 10.59. Found: C, 78.66; H, 10.44.

Synthesis of 36. $EtAlCl_2$ (1.7 mL of 1.48 M solution in hexane, 2.5 mmol) was added to a solution of cyclobutanone (0.24 g, 2.5 mmol) and ethylidenecyclopentane (0.19 g, 2.5 mmol) in 6 mL of CH_2Cl_2 at 0 °C under nitrogen. The reaction was stirred for 45 min at 0 °C and worked up to give 262 mg of crude product. Chromatography on silica gel (10:1 hexane–EtOAc) gave 52 mg (13%) of pure **36**: NMR ($CDCl_3$) δ 5.5 (br s, 1), 1.4–2.7 (m, 20) 1.1 (d, 3, J = 6 Hz); IR (neat) 3300 cm^{-1}. Anal. Calcd for $C_{11}H_{18}O$: C, 79.47; H, 10.31. Found: C, 79.44: H, 11.00.

Synthesis of 37. $EtAlCl_2$ (2.8 mL of 1.48 M solution in hexane, 4 mmol) was added to a solution of cyclobutanone (0.28 g, 4 mmol) and 2-ethyl-1-butene (0.33 g, 4 mmol) in 6 mL of CH_2Cl_2 at 0 °C under nitrogen. The reaction was stirred for 45 min at 0 °C and worked up to give 451 mg of crude product. Chromatography on silica gel (10:1 hexane–EtOAc) gave 183 mg (30%) of pure **37**: NMR ($CDCl_3$) δ 5.5 (q, 0.33×1, J = 6.6 Hz), 5.33 (q, 0.67×1, J = 6.6 Hz), 1.2–2.5 (m, 14), 1.0 (t, 3, J = 6 Hz); IR (neat) 3300 cm^{-1}. Anal. Calcd for $C_{10}H_{18}O$: C, 77.89; H, 11.76. Found: C, 77.58; H, 11.59.

Synthesis of 38. $EtAlCl_2$ (2.8 mL of 1.48 M solution in hexane, 4 mmol) was added to a solution of 4-*tert*-butylcyclohexanone (0.62 g, 4 mmol) and methylenecyclopentane (0.33 g, 4 mmol) in 6 mL of CH_2Cl_2 at 0 °C under nitrogen. The reaction was stirred for 45 min at 0 °C and worked up to give 793 mg of crude product. MPLC (20:1 hexane–EtOAc) gave 56 mg (6%) of the less polar isomer **38a** with an axial hydroxyl group[23] and 47 mg (4.7%) of the more polar isomer **38b** (mp 47–53 °C) with an equatorial hydroxyl group.[23]

The data for **38a** follow: NMR ($CDCl_3$) δ 5.49 (br s, 1), 1.1–2.5 (m, 18 with s (2) at 2.24), 0.89 (s, 9); IR (neat 3300 cm^{-1}; GC (A, 185 °C) t_R 7.2 min.

The data for **38b** follow: NMR ($CDCl_3$) δ 5.49 (br s, 1), 1.1–2.5 (m, 18 with s (2) at 2.36), 0.89 (s, 9); IR (neat) 3300 cm^{-1}; GC (A, 185 °C) t_R 8.2 min.

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Registry No. **1**, 1655-07-8; **2**, 53750-52-0; **3**, 81763-01-1; **4**, 84433-95-4; **5**, 91781-66-7; **6**, 91781-67-8; **7**, 91781-68-9; **8**, 91781-69-0; **9**, 91781-70-3; **10**, 91781-71-4; **11**, 91781-72-5; **12**, 3197-68-0; **12** (tosylate), 3399-72-2; **13**, 82201-80-7; **14**, 91781-73-6; **15**, 91781-74-7; **16**, 91781-75-8; **17**, 91781-76-9; **18**, 91781-77-0; **19**, 91781-78-1; **20**, 91781-79-2; **21**, 91781-80-5; **22**, 91781-81-6; **23**, 91781-82-7; **24**, 35944-13-9; **25**, 75685-75-5; **26**, 91781-83-8; **27**, 91781-84-9; **28**, 91781-85-0; **29**, 91781-86-1; **30**, 87887-29-4; **31**, 91781-87-2; **32**, 71203-75-3; (*E*)-**33**, 71203-75-3; (*Z*)-**33**, 91781-98-5; **34**, 91781-89-4; **35a**, 91781-90-7; **35b**, 91781-91-8; **35c**, 91781-92-9; **36**, 91781-93-0; **37**, 91781-94-1; **38a**, 91781-95-2; **38b**, 91781-96-3; **39a**, 91781-97-4; **39b**, 76519-80-7; Me_2AlCl, 1184-58-3; $Me_{1.5}AlCl_{1.5}$, 12542-85-7; $MeAlCl_2$, 917-65-7; HCHO, 50-00-0; $EtAlCl_2$, 563-43-9; cyclohexanone, 108-94-1; cyclopentanone, 120-92-3; cyclobutanone, 1191-95-3; 4-*tert*-butylcyclohexanone, 98-53-3; acetophenone, 98-86-2; benzophenone, 119-61-9; 2-methylcyclohexanone, 583-60-8; methyl cyclopropyl ketone, 10472-24-9; methyl 2-oxocyclopentanecarboxylate, 10472-24-9; 2-acetylbutyrolactone, 517-23-7; methyl acetoacetate, 105-45-3; methylenecyclopentane, 1528-30-9; ethylidenecyclopentane, 2146-37-4; 2-ethyl-1-butene, 760-21-4; methylenecyclohexane, 1192-37-6; 5-iodo-2-methyl-1-pentene, 73541-16-9; 6-iodo-2-methyl-2-hexene, 63588-94-3; 5-methyl-4-hexen-1-ol, 42272-94-6; 5-methyl-4-hexen-1-ol tosylate, 61755-53-1.

Synthetic and Biological Studies of Compactin and Related Compounds. 2. Synthesis of the Lactone Moiety of Compactin[1]

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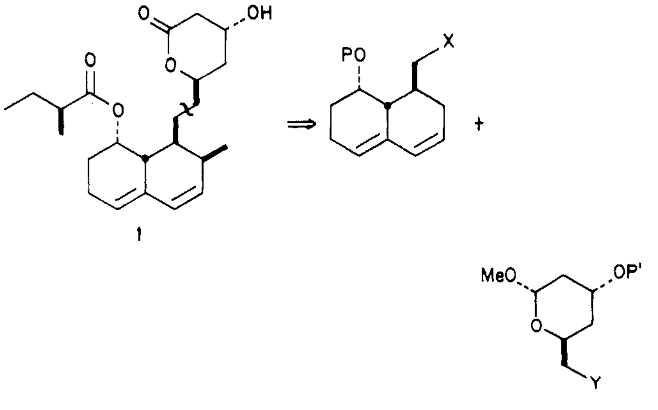
Several optically active synthons for the lactone portion of compactin have been prepared. Lithium aluminum hydride opening of epoxide **23** affords a 92:8 mixture of axial alcohol **27** and regioisomer **28** in 96% yield. Silylation of this material followed by removal of the trityl group with sodium in ammonia gives primary alcohol **31**. Tosylation of **31** (90%) followed by iodide displacement furnishes iodide **36** (96%). Sulfone **49** is obtained (31%) accompanied by **36** (55%) upon treatment of tosylate **35** with sodium benzenesulfinate and tetra-*n*-butylammonium iodide. Oxidation of **31** by the Swern method affords aldehyde **37** (93%) which reacts with ylide **43** to give coupled product **44** (54%). Hydrogenation of **44** (100%) followed by acidic hydrolysis gives hydroxy hemiacetals **47** (69%). The hemiacetal functionality is selectively oxidized with Fetizon's reagent to obtain β-hydroxy-δ-lactone **48** (70%).

Introduction

In 1976, Endo and co-workers isolated a potent inhibitor of HMG CoA reductase, named ML236B, from the metabolites of *Penicillium citrinium*.[3] This compound proved to be identical with a compound isolated from *P. breviocompactum* and named compactin (**1**) by Brown and co-workers at Beecham Pharmaceuticals.[4] Since that time, several other naturally occurring mevinic acids, compounds possessing a highly functionalized hexalin or octalin unit and a β-hydroxy-δ-lactone portion which are linked by an ethylene bridge, have been isolated.[5] The potential utility of this class of compounds as hypocholesterolemic agents[6] and their interesting structural features have prompted extensive synthetic investigations.[1,7,8]



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