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Stereocontrol in the $EtAlCl_2$-Induced Cyclization of Chiral γ,δ-Unsaturated Methyl Ketones To Form Cyclopentanones

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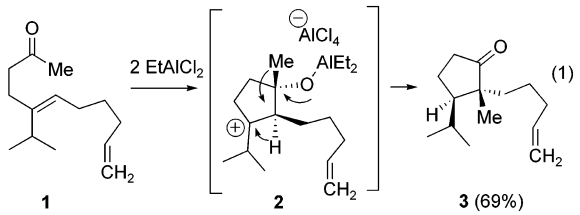
Abstract: $EtAlCl_2$-induced cyclization of chiral γ,δ-unsaturated ketones **11c** and **17b** takes place mainly from the expected face. The selectivity is modest for **11c** (60:40) in which the large substituent is a primary alkyl group and the medium substituent is a methyl group and excellent for **17b** (93:7) in which the large substituent is a cyclohexyl group and the medium substituent is a methyl group. The cyclization of **17a** is anomalous, suggesting that the phenyl group has more than a simple steric effect.

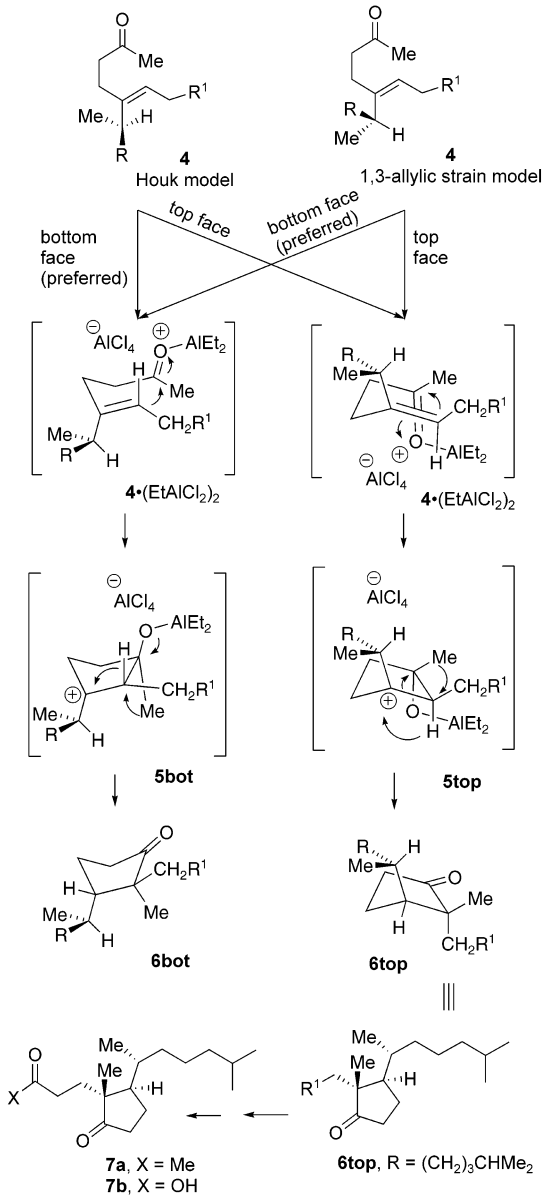
We recently reported the $EtAlCl_2$-induced cyclization of γ,δ-unsaturated methyl ketone **1** to give cyclopentanone **3**, which was used for the synthesis of (±)-guanacastepene A (see eq 1).[1,2] Ketone **1** reacts with 1.5 equiv of $EtAlCl_2$ to give a very electrophilic $R_2C{=}OAlEt_2$ cation that cyclizes to give tertiary cation **2** as the $AlCl_4$ salt. A 1,2-hydride shift followed by a 1,2-methyl shift gives cyclopentanone **3** stereospecifically as a single diastereomer. The relative stereochemistry may be controlled by the preferential addition to give the larger $OAlEt_2$ substituent on the less hindered side of the cyclopentane with the adjacent hydrogen. Alternatively, the cyclization may be reversible with the stereochemistry controlled by the preference for the two migrating substituents to be trans in the Wagner−Meerwein shifts.



1 **2** **3** (69%)

We report here the stereochemical effect of a chiral center adjacent to the double bond as in **4** (see Scheme 1). The stereochemistry of additions to α-chiral alkenes has been much less studied and is more poorly understood than additions to α-chiral carbonyl compounds (Cram or Felkin−Anh rule).[3] Additions to alkenes are more complex than additions to carbonyl compounds because the addition may be either electrophilic or nucleophilic, and there are substituents on both ends of an alkene. In the Houk model, the large substituent is

SCHEME 1



oriented perpendicular to the π-bond, the small substituent is oriented toward the double bond, and the electrophile adds from the face opposite to the large substituent.[3] In the 1,3-allylic strain model, the hydrogen is eclipsed with the cis substituent on the alkene.[3] The electrophile adds preferentially from the face with the medium methyl substituent rather than the large R substituent. Both of these models predict that cyclization of **4**·$(EtAlCl_2)_2$ should occur preferentially from the bottom face to give **5bot**, which should rearrange to **6bot**.

Assigning the stereochemistry of **6bot** and **6top** is not trivial. We therefore decided to examine the cyclization of **4** with R = $(CH_2)_3CHMe_2$ and with R^1 as a substituent that can be converted to either the methyl ketone of **7a**

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(1) (a) Snider, B. B.; Hawryluk, N. A. *Org. Lett.* **2001**, *4*, 569−572. (b) Shi, B.; Hawryluk, N. A.; Snider, B. B. *J. Org. Chem.* **2003**, *68*, 1030−1042.

(2) For earlier studies on the synthesis of bicyclic systems, see: (a) Snider, B. B.; Kirk, T. C. *J. Am. Chem. Soc.* **1983**, *105*, 2364−2368. (b) Snider, B. B.; Cartaya-Marin, C. P. *J. Org. Chem.* **1984**, *49*, 153−157.

(3) (a) Mengel, A.; Reiser, O. *Chem. Rev.* **1999**, *99*, 1191−1223. (b) Fleming, I. *J. Chem. Soc., Perkin Trans. 1* **1992**, 3363−3369. (c) Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841−1860.

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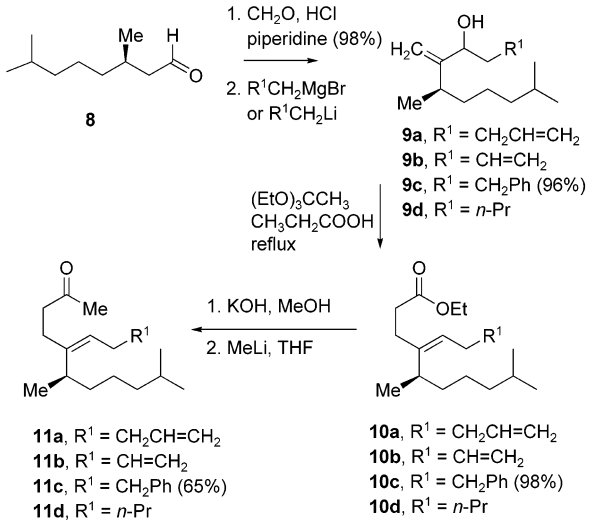
SCHEME 2

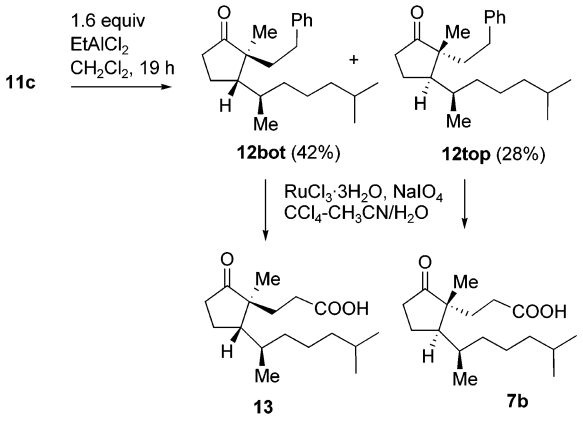


or the carboxylic acid of **7b**. Both **7a** and **7b** have been fully characterized because these compounds are intermediates in the syntheses of Grundmann's ketone and vitamin D_3.[4] The $(CH_2)_3CHMe_2$ side chain was also synthetically attractive because the requisite γ,δ-unsaturated ketone **11** can be easily prepared from (*R*)-citronellol.

Reaction of (*R*)-3,7-dimethyloctanal (**8**)[5] with formalin, piperidine, and hydrochloric acid[6] afforded 98% of (*R*)-3,7-dimethyl-2-methyleneoctanal,[7] which was treated with 3-butenyllithium, allylmagnesium bromide, phenethylmagnesium bromide, or *n*-BuLi to give **9a**−**d** as a mixture of diastereomers (see Scheme 2). Johnson ortho ester Claisen rearrangement of **9a**−**d** with triethyl orthoacetate and propionic acid at reflux afforded ethyl ester **10a**−**d** as an 87:13 *Z*/*E* mixture. Hydrolysis with KOH in aqueous MeOH and reaction of the resulting acid with 2 equiv of MeLi afforded ketone **11a**−**d**.

The cyclization of **1** to give 2-(4-pentenyl)cyclopentanone **3** established that a terminal double bond is compatible with these very acidic conditions if three methylene groups separate it from the cyclopentanone. We therefore first investigated the cyclization of **11a** that would give a 2-(3-butenyl)cyclopentanone that could be converted to methyl ketone **7a** by a Wacker oxidation. However, treatment of **11a** with $EtAlCl_2$ did not afford any cyclopentanone, possibly because the cationic intermediate analogous to **2** can cyclize to the double bond to give a cyclohexyl cation. We then investigated the cyclization of **11b** that would give a 2-(2-propenyl)cyclopentanone that could be converted to acid **7b** by hydroboration and oxidation. As with **11a**, no cyclopentanone was formed on treatment of **11b** with $EtAlCl_2$. This indicates that at least three methylene groups must be between a terminal double bond and the trisubstituted

SCHEME 3



double bond for successful cyclization to give a cyclopentanone.

We then examined the cyclization of **11c** that would give 2-(phenethyl)cyclopentanone **12bot** and **12top** that can be converted to acids **13** and **7b**, respectively, by oxidative cleavage of the benzene ring (see Scheme 3). The benzene ring of **11c** is much less reactive toward electrophiles than the double bonds of **11a** and **11b** and should therefore not participate in the cyclization. We were delighted to find that treatment of **11c** with 1.6 equiv of $EtAlCl_2$ in CH_2Cl_2 for 19 h at 25 °C afforded a difficultly separable mixture of the expected major product **12bot** (42%) and minor product **12top** (28%). Oxidation of a mixture rich in the minor isomer **12top** with RuO_4[8] afforded mainly the known keto acid **7b**, with ^1H and ^{13}C NMR spectral data identical to those previously reported.[4b,c] A similar oxidation of a mixture rich in the major isomer **12bot** afforded mainly keto acid **13** with distinctly different spectral data.

These results indicate that cyclization of **11c** with $EtAlCl_2$ occurred with 60:40 selectivity in the expected direction. This selectivity is good considering that the large (primary alkyl) and medium (methyl) substituents are very similar in size. Cyclization of **11d** with a butyl side chain gave a 73% yield of a 66:33 mixture of cyclopentanones. Comparison of spectral data[9] indicated that the major isomer corresponded to **12bot**, indicating that in this case (vide infra) the phenyl substituent has at most a modest effect on the stereochemistry of the cyclization.

We next turned our attention to the cyclization of **17a** and **17b**, in which the large substituent is either a phenyl or a cyclohexyl group. Aldehydes **14a** and **14b**[10] were converted to **17a** and **17b** as shown in Scheme 4 analogously to the preparation of **11a**−**d**. To our surprise, cyclization of **17a** with 1.8 equiv of $EtAlCl_2$ in CH_2Cl_2 for 24 h at 25 °C afforded only 18% of the expected major

(4) For **7a**, see: (a) Duhamel, P.; Dujardin, G.; Hennequin, L.; Poirier, J.-M. *J. Chem. Soc., Perkin Trans. 1* **1992**, 387−396. For **7b**, see: (b) Nemoto, H.; Kurobe, H.; Fukumoto, K.; Kametani, T. *J. Org. Chem.* **1986**, *51*, 5311−5320. (c) Grzywacz, P.; Marczak, S.; Wicha, J. *J. Org. Chem.* **1997**, *62*, 5293−5298.

(5) Tietze, L. F.; Schiemann, K.; Wegner, C.; Wulff, C. *Chem. Eur. J.* **1996**, *2*, 1164−1172.

(6) Riehs, G.; Urban, E. *Tetrahedron* **1996**, *52*, 1221−1230.

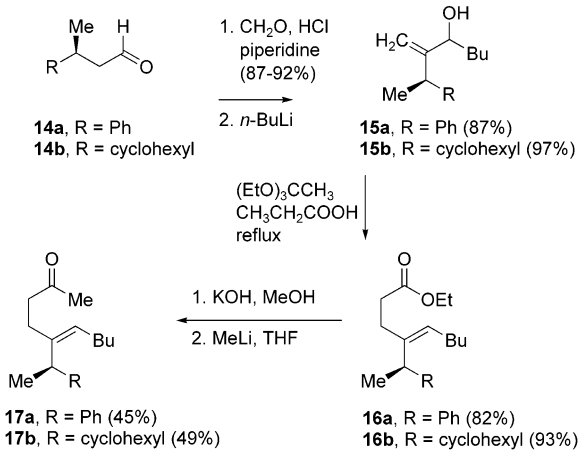
(7) Blumenthal, J. H. Fr. Patent 1,508,854, 1968; *Chem. Abstr.* **1969**, *70*, 37191*j*.

(8) Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936−3938.

(9) The methyl doublet of the major diastereomer from **11d** absorbs at δ 0.85−0.90. The methyl doublet of the minor diastereomer absorbs downfield at δ 0.98. The analogous methyl doublet of the minor diastereomer **12top** (δ 1.05) is also downfield from that of the major isomer **12bot** (δ 0.92). The differences between the carbon spectra of the diastereomers in the two series are similarly analogous.

(10) Aldehyde **14b** was prepared by reduction of **14a** with $NaBH_4$ (93%), hydrogenation (60 psi) of the alcohol over Rh/Al_2O_3 (86%), and PCC oxidation (83%). Hydrogenation of **14a** over Rh/Al_2O_3 was unsuccessful, suggesting that the catalyst was poisoned by decarbonylation.

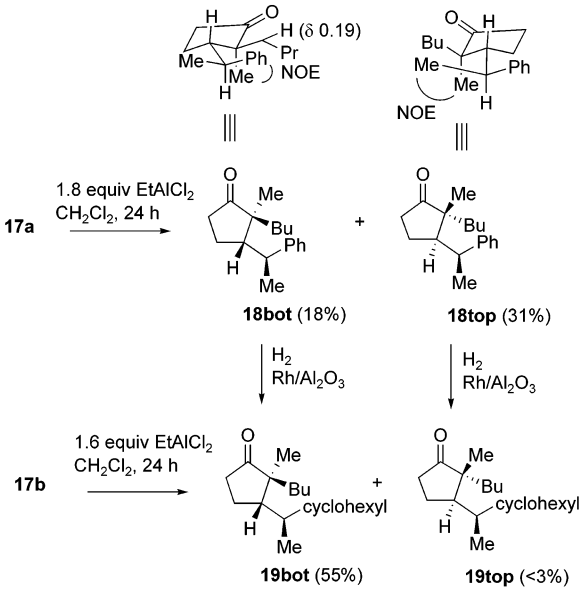
SCHEME 4



product **18bot** and 31% of the expected minor product **18top** (see Scheme 5). The remaining material was recovered **17a** and 5-(1-phenylethylidene)nonan-2-one formed by protonation of the double bond and loss of a proton to form the styrene.

The structure of **18** was established by NOE experiments. The vicinal coupling constant between the benzylic methine and the cyclopentane methine hydrogens is 11.0 Hz in both isomers. This established that these molecules exist largely in the conformations shown with these hydrogens anti-periplanar. The configuration was established by an NOE between the methyl singlet and the phenyl protons in **18bot** and the methyl singlet and the methyl doublet in **18top**. In addition, one of the butyl methylene hydrogens in **18bot** is shielded by the adjacent phenyl ring and absorbs upfield at δ 0.19.

SCHEME 5



On the other hand, cyclization of **17b** with 1.6 equiv of $EtAlCl_2$ in CH_2Cl_2 for 24 h at 25 °C was very selective, providing 55% of the expected major product **19bot** and <3% of the expected minor product **19top**. The structures were established by hydrogenation (60 psi) of **18bot** and **18top** over 5% Rh/Al_2O_3 to afford **19bot** and **19top**, respectively. Thus, there is a very high degree of stereocontrol in this cyclization when the large substituent is a secondary alkyl group and the medium substituent is a methyl group.

The formation of **18top** as the major isomer in the cyclization of **17a** may indicate that interactions with the phenyl group are more complex. The intermediate cation is a stabilized phenethyl cation. The phenyl group can also act as a Lewis base and bind to either the Lewis acid or the ketone−Lewis acid complex. Alternatively, the planar phenyl substituent might be smaller than the methyl group in this particular addition reaction. Although Ph is larger than cyclohexyl in the reduction of PhMeCHCOR and (C_6H_{11})MeCHCOR,[11] a flat phenyl group is smaller than a cyclohexyl group in some aldol reactions.[12]

In conclusion, we have shown that in favorable cases such as **17b**, the chiral center in the unsaturated ketone controls almost completely the newly formed chiral centers on the cyclopentanone with the expected orientation. Modest stereocontrol is obtained with **11c** in which the large primary alkyl substituent is similar in size to the medium methyl substituent. We have also established that the phenyl groups of **11c** and **17a** are compatible with these cyclizations.

Experimental Section

General Procedures. NMR spectra were recorded at 400 MHz in $CDCl_3$ unless otherwise indicated; chemical shifts are reported in δ, coupling constants in Hz, and IR spectra in cm^{-1}.

(2*S*,3*S*)- and (2*R*,3*R*)-3-(1*R*,5-Dimethylhexyl)-2-methyl-2-phenethylcyclopentanone (12bot and 12top). $EtAlCl_2$ (0.53 mL of a 1.0 M solution in hexanes, 0.53 mmol) was added dropwise to a solution of ketone **11c** as a 93:7 *Z*/*E* mixture (105 mg, 0.33 mmol) in CH_2Cl_2 (7 mL) at 0 °C. The reaction was stirred at 25 °C for 19 h and poured into an ice−water mixture, which was extracted with CH_2Cl_2. The combined extracts were washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure to yield 102 mg (97%) of a 3:2 mixture of diastereomers **12bot** and **12top** and the recovered minor *E*-isomer of **11c**. Careful chromatography on Bakerbond Octadecyl 40 μm Prep LC packing (15% H_2O−MeOH) yielded a trace of pure **12bot**, 33 mg of a 3:1 mixture of **12bot** and **12top**, 30 mg of a 1:1 mixture of **12bot** and **12top**, 7 mg of a 1:2.2 mixture of **12bot** and **12top**, and a trace of pure **12top**. ^{13}C NMR data were determined from the mixtures. The optical rotations for both diastereomers were calculated from the measurements of the 3:1 mixture ($[\alpha]^{20}_D$ +10.7 (*c* 0.205, $CHCl_3$)) and the 1:2.2 mixture ($[\alpha]^{20}_D$ −7.3 (*c* 0.250, $CHCl_3$)); HRMS(DEI) calcd for $C_{22}H_{34}O$ (M^+) 314.2610, found 314.2598.

Data for **12bot**: ^1H NMR ($CDCl_3$) 7.29−7.25 (m, 2), 7.19−7.15 (m, 3), 2.60 (dt, 1, *J* = 4.9, 12.8), 2.40−2.22 (m, 2), 2.16−1.94 (m, 4), 1.73 (dt, 1, *J* = 4.9, 13.5), 1.65−1.37 (m, 5), 1.32−1.14 (m, 4), 0.95 (s, 3), 0.92 (d, 3, *J* = 6.7), 0.88 (d, 6, *J* = 6.7); ^{13}C NMR 223.88, 142.26, 128.4 (2 C), 128.3 (2 C), 125.81, 52.2, 46.9, 40.1, 39.2, 37.57, 36.1, 33.5, 31.2, 28.0, 24.8, 22.7, 22.59, 22.45, 18.22, 17.3; IR (CH_2Cl_2) 1737 cm^{-1}; $[\alpha]^{20}_D$ +20.9 (calculated from the rotations of the mixtures).

Data for **12top**: ^1H NMR ($CDCl_3$) 7.29−7.25 (m, 2), 7.19−7.15 (m, 3), 2.62 (dt, 1, *J* = 4.9, 12.8), 2.40−2.23 (m, 2), 2.16−1.94 (m, 4), 1.77 (dt, 1, *J* = 4.9, 14.0), 1.65−1.37 (m, 5), 1.32−1.14 (m, 4), 1.05 (d, 3, *J* = 6.7), 0.94 (s, 3), 0.894 (d, 3, *J* = 6.7), 0.889 (d, 3, *J* = 6.7); ^{13}C NMR 223.90, 142.28, 128.4 (2 C), 128.3 (2 C), 125.79, 52.3, 47.0, 40.0, 39.4, 37.62, 34.5, 34.1, 31.4, 28.0, 24.0, 23.5, 22.8, 22.5, 18.4, 18.18; IR (CH_2Cl_2) 1737 cm^{-1}; $[\alpha]^{20}_D$ −19.9 (calculated from the rotations of the mixtures).

(11) Cherest, M.; Prudent, N. *Tetrahedron* **1980**, *36*, 1599−1606.
(12) (a) Gennari, C.; Vieth, S.; Comotti, A.; Vulpetti, A.; Goodman, J.; Paterson, I. *Tetrahedron* **1992**, *48*, 4439−4458. (b) Hoffmann, R. W.; Stürmer, R.; Harms, K. *Tetrahedron Lett.* **1994**, *35*, 6263−6266.

(2*S*,3*S*)- and (2*R*,3*R*)-3-[2-(1*R*,5-Dimethylhexyl)-1-methyl-5-oxocyclopentyl]propanoic Acid (13 and 7b). A solution of the 3:1 mixture of cyclopentanones **12bot** and **12top** (5 mg, 0.016 mmol) and $RuCl_3 \cdot 3H_2O$ (0.2 mg, 0.001 mmol) in CCl_4 (0.064 mL) and CH_3CN (0.064 mL) was treated with a solution of $NaIO_4$ (70 mg, 0.32 mmol) in H_2O (0.32 mL) and stirred at 25 °C for 19 h. The reaction mixture was then diluted with H_2O and extracted with CH_2Cl_2. The combined extracts were concentrated under reduced pressure to yield a green residue that was dissolved in Et_2O. The ether solution was extracted with 2% aqueous KOH. The combined aqueous extracts were acidified with 6 N HCl and extracted with EtOAc. The combined EtOAc extracts were washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure to yield 3 mg (70%) of a 3:1 mixture of acids **13** and **7b**.

A similar experiment sequence was carried out with 5 mg of the 1:2.2 mixture of **12bot** and **12top**, yielding 3 mg (70%) of a 1:2.2 mixture of acids **13** and **7b**.

^{1}H NMR and ^{13}C NMR data were determined from the mixtures. The optical rotations for both diastereomers were calculated from the measurements of the 3:1 mixture ($[\alpha]^{20}_D$ +20.4 (*c* 0.200, $CHCl_3$)) and the 1:2.2 mixture ($[\alpha]^{20}_D$ −19.6 (*c* 0.100, $CHCl_3$)); HRMS(DEI) calcd for $C_{17}H_{31}O_3$ (MH^+) 283.2273, found 283.2261.

Data for **13**: ^{1}H NMR ($CDCl_3$) 2.46−2.30 (m, 2), 2.24−1.96 (m, 4), 1.86−1.70 (m, 2), 1.60−1.09 (m, 9), 0.99 (d, 3, J = 6.7), 0.94 (s, 3), 0.88 (d, 3, J = 6.7), 0.87 (d, 3, J = 6.7); ^{13}C NMR 223.25, 177.5, 51.1, 47.7, 39.1, 37.1, 36.2, 33.3, 32.0, 29.0, 28.0, 24.7, 22.65, 22.58, 22.1, 17.6, 17.1; IR (CH_2Cl_2) 1732, 1712 cm^{-1}; $[\alpha]^{20}_D$ +43.0.

Data for **7b**: ^{1}H NMR ($CDCl_3$) 2.46−2.30 (m, 2), 2.24−1.96 (m, 4), 1.86−1.70 (m, 2), 1.60−1.09 (m, 9), 0.99 (d, 3, J = 6.7), 0.94 (s, 3), 0.88 (d, 3, J = 6.7), 0.87 (d, 3, J = 6.7); ^{13}C NMR 223.25, 177.53, 51.1, 47.8, 39.3, 37.1, 34.3, 33.9, 31.9, 29.6, 27.9, 24.0, 23.2, 22.7, 22.5, 18.5, 17.5; IR (CH_2Cl_2) 1732, 1712 cm^{-1}; $[\alpha]^{20}_D$ −47.5 (lit.[4c] −42.3; *c* 0.85). The ^{1}H and ^{13}C NMR spectral data are identical to those previously reported.[4b,c]

(2*S*,3*S*)- and (2*R*,3*R*)-3-(1*R*,5-Dimethylhexyl)-2-methyl-2-butylcyclopentanone. $EtAlCl_2$ (0.23 mL of a 1.0 M solution in hexanes, 0.23 mmol) was added dropwise to a solution of **11d** (40 mg, 0.15 mmol) in CH_2Cl_2 (3 mL) at 0 °C. The reaction mixture was stirred for 24 h at 25 °C and worked up as described above for the cyclization of **11c** to yield 39 mg (98%) of crude cyclopentanones. Flash chromatography (9/1 hexanes/EtOAc) gave 29 mg (73%) of a 2:1 mixture of (2*S*,3*S*)- and (2*R*,3*R*)-diastereomers: ^{1}H NMR (600 MHz, $CDCl_3$) 2.47−2.27 (m, 1), 2.10−1.99 (m, 2), 1.96−1.87 (m, 1), 1.72−1.39 (m, 5), 1.38−1.08 (m, 10), 0.98 (d, 3 × 0.33, J = 6.4), 0.90−0.85 (m, 12 + 3 × 0.67); ^{13}C NMR (major) 52.1, 46.5, 39.2, 37.70, 37.65, 35.9, 33.4, 28.1, 27.0, 24.6, 23.2, 22.64, 22.62, 22.4, 18.3, 17.3, 14.0; (minor) 52.0, 46.8, 39.4, 37.7, 37.6, 34.5, 34.1, 28.0, 27.2, 24.1, 23.23, 23.20, 22.8, 22.5, 18.2 (2 C), 14.0 (the ketone carbonyls were not observed).

(2*R*,3*R*)- and (2*S*,3*S*)-2-Butyl-2-methyl-3-(1*R-phenylethyl)cyclopentanone (18bot and 18top).** $EtAlCl_2$ (0.22 mL of a 1.0 M solution in hexanes, 0.22 mmol) was added dropwise to a solution of ketone **17a** (30 mg, 0.12 mmol) in CH_2Cl_2 (5 mL) at 0 °C. The reaction was stirred for 24 h and worked up as described above for the cyclization of **11c** to give 43 mg of crude **18**. Flash chromatography (99.5:0.5 hexanes/EtOAc) gave 6 mg of pure **18top**, followed by 6 mg of a 4:2.2:1 mixture of **18top**, 5-(1-phenylethylidene)nonan-2-one, and **18bot**, and 8 mg of a 1.4:1 mixture of **18bot** and recovered **17a**. The calculated yields of **18top** and **18bot** are 9.3 mg (31%) and 5.5 mg (18%), respectively. This ratio is consistent with the NMR spectrum of the crude mixture.

Data for **18top**: ^{1}H NMR 7.34−7.30 (m, 2), 7.23−7.20 (m, 3), 2.70 (dq, 1, J = 11.0, 6.7), 2.34−2.20 (m, 2), 1.95−1.81 (m, 2), 1.64−1.56 (m, 1), 1.50−1.24 (m, 5), 1.35 (d, 3, J = 6.7), 1.00 (s, 3), 1.00−0.87 (m, 1), 0.92 (t, 3, J = 7.3); ^{13}C NMR 224.1, 146.8, 128.5 (2 C), 127.3 (2 C), 126.2, 52.0, 47.4, 42.5, 37.9, 37.5, 27.4, 25.5, 23.3, 21.0, 18.5, 14.0; IR (neat) 1731 cm^{-1}; HRMS(DEI) calcd for $C_{18}H_{26}O$ (M^+) 258.1984, found 258.1980. Irradiation of the methyl singlet at δ 1.00 in a 1D NOESY experiment showed NOEs to the benzylic methine at δ 2.7 and the methyl doublet at δ 1.35. Irradiation of the benzylic methine at δ 2.7 showed NOEs to the aromatic protons at δ 7.23−7.20, the methyl singlet at δ 1.00, and the methyl doublet at δ 1.35.

Partial data for 5-(1-phenylethylidene)nonan-2-one was determined from the mixture: ^{1}H NMR 7.07 (d, 2, J = 7.9), 2.58 (t, 2, J = 7.3), 2.43 (t, 2, J = 7.3), 2.20 (s, 3), 1.93 (s, 3), 1.83 (t, 2, J = 7.3), 0.79 (t, 3, J = 7.3).

A solution of the 1.4:1 mixture of **18bot** and **17a** (8 mg), and $NaBH_4$ (0.29 mg, 7.74 × 10^{-3} mmol), in EtOH (3 mL) was stirred for 30 min.[13] The reaction mixture was concentrated, diluted with water, and extracted with Et_2O. The combined extracts were washed with brine, dried ($MgSO_4$), and concentrated to yield 6.2 mg (77%) of **18bot** and 5-(1-phenylethyl)-5*E*-decen-2-ol. Flash chromatography (95:5 hexanes/EtOAc) gave 3 mg of pure **18bot**: ^{1}H NMR 7.30−7.26 (m, 2), 7.23−7.18 (m, 3), 2.75 (dq, 1, J = 11.0, 6.7), 2.43−2.37 (m, 2), 2.25 (ddd, 1, J = 12.2, 9.8, 6.1), 2.04 (ddd, 1, J = 18, 12.2, 9.2), 1.56 (dddd, 1, J = 12.2, 12.2, 12.2, 8.5), 1.4−1.26 (m, 2), 1.26−1.17 (m, 1), 1.29 (d, 3, J = 6.7), 1.05−0.70 (m, 2), 0.89 (s, 3), 0.68 (t, 3, J = 6.7), 0.19 (ddd, 1, J = 12.8, 12.8, 3.7); ^{13}C NMR 224.3, 146.4, 128.3 (2 C), 127.2 (2 C), 126.3, 52.4, 46.9, 41.3, 37.8, 35.5, 26.5, 24.4, 22.9, 21.6, 19.3, 13.8. Irradiation of the aromatic hydrogens at δ 7.2 in a 1D NOESY experiment showed NOEs to the methyl doublet at δ 1.29 and the methyl singlet at δ 0.89. Irradiation of the benzylic methine at δ 2.75 showed NOEs to the methyl singlet at δ 0.89, and the methyl doublet at δ 1.29 and the aromatic protons at δ 7.2. Irradiation of H_{4a} at δ 2.25 showed NOEs to the methyl doublet at δ 1.29, H_{4b} at δ 1.56, and H_{5a} at δ 2.43.

(2*R*,3*R*)-2-Butyl-3-(1*R-cyclohexylethyl)-2-methylcyclopentanone (19bot).** $EtAlCl_2$ (0.69 mL of a 1.0 M solution in hexanes, 0.69 mmol) was added dropwise to a solution of ketone **17b** (121 mg, 0.457 mmol) in CH_2Cl_2 (16.9 mL) at 0 °C. The reaction was stirred at 25 °C for 24 h and worked up as described for the cyclization of **11c** yielding 112 mg (93%) of a 93:7 mixture of **19bot** and **19top** as determined by integration of the δ 2.3−2.4 region. Flash chromatography (99.7:0.3 hexanes/EtOAc) yielded 66.5 mg (55%) of **19bot** containing a trace of **19top**: ^{1}H NMR 2.32 (dd, 1, J = 8.6, 17.1), 2.14−1.92 (m, 3), 1.80−1.73 (m, 2), 1.70−1.56 (m, 3), 1.56−1.37 (m, 5), 1.34−0.98 (m, 9), 0.88 (s, 3), 0.87 (t, 3, J = 7.3), 0.83 (d, 3, J = 6.7); ^{13}C NMR 224.5, 52.0, 43.6, 41.6, 38.6, 38.1, 37.5, 31.8, 27.8, 27.1, 26.8, 26.72, 26.68, 23.5, 23.2, 18.5, 13.9, 13.4; HRMS(DEI) calcd for $C_{18}H_{32}O$ 264.2453, found 264.2448.

Hydrogenation of 18bot. Cyclopentanone **18bot** (2.0 mg, 7.56 × 10^{-3} mmol), 5% Rh/Al_2O_3 (12 mg), acetic acid (66 μL), and EtOH (1.1 mL) were combined and shaken under H_2 (60 psi) for 24 h. The reaction mixture was filtered through Celite and concentrated to give 2.0 mg (98%) of **19bot**, whose ^{1}H NMR spectrum is identical to that obtained from the cyclization of **17b**.

(2*S*,3*S*)-2-Butyl-3-(1*R-cyclohexylethyl)-2-methylcyclopentanone (19top).** Cyclopentanone **18top** (4.0 mg, 1.54 × 10^{-2} mmol), 5% Rh/Al_2O_3 (2.3 mg), and acetic acid (60 μL) in EtOH (1.0 mL) were combined and shaken under H_2 (60 psi) for 24 h. The reaction mixture was filtered through Celite and concentrated under reduced pressure to yield 4 mg of **19top**: ^{1}H NMR 2.36 (dd, 1, J = 8.5, 18.3), 2.10−1.95 (m, 3), 1.78−1.56 (m, 6), 1.56−1.19 (m, 12) 1.06−0.98 (m, 1), 0.88 (d, 3, J = 5.5), 0.87 (s, 3), 0.86 (t, 3, J = 7.3); ^{13}C NMR 224.7, 52.0, 43.7, 39.4, 38.0, 37.7, 32.2, 29.7, 27.3, 27.2, 26.9, 26.8, 25.7, 24.2, 23.2, 18.5, 13.9, 13.0.

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Supporting Information Available: Experimental procedures for the preparation of **11c** and **17a**,**b**. Copies of ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) The cyclopentanone is very hindered, so that treatment of the inseparable mixture with $NaBH_4$ reduces **17a** to the more polar alcohol without reducing **18bot**.