β-Hydroxy Esters: (E)- versus (Z)-Enolate Geometry in Dianionic Claisen Rearrangements

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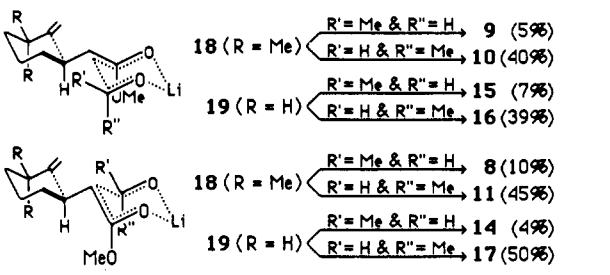
Control elements operative in the β-hydroxy ester dianionic Claisen rearrangements are probed. Stereochemistry at C_β dictates face selectivity at C_α and $C_{\beta'}$ in **1** → **2–5**, but only to the extent that it controls ester enolate geometry since a second important control element, chair/boat selectivity, is also operative. Evidence for excellent (*E*)-enolate selectivity in the enolization of β-hydroxy esters (cf. **7** and **13**) and substrate-dependent chair/boat selectivity in the ensuing Claisen rearrangement are described.

In conjunction with our synthetic efforts in the area of acyclic stereocontrol, we developed a β-hydroxy ester dianionic Claisen rearrangement which delivers highly functionalized adducts with three contiguous stereocenters.[2] In this transformation, stereochemistry at C_β dictates diastereotopic face selectivity at C_α and $C_{\beta'}$ in the Claisen rearrangement, but only to the extent that it controls ester enolate geometry since a second important control element, chair/boat selectivity, is also operative. Inspection of Scheme I brings the interplay between these two control elements into focus since each Claisen adduct can be rationalized from two distinctly different reactive conformations: for example, **2** could be derived from either an *E*–chair conformation or a *Z*–boat conformation. Similar stereochemical ambiguity exists in the alkylation of β-hydroxy ester enolates[3] since either (*E*)- or (*Z*)-enolates may be formed and the π-facial selectivity of each may be chelation dependent.[4] In light of the importance and potential of β-hydroxy ester dianions in synthesis, particularly enantioselective transformations based on bakers' yeast β-keto ester reductions,[5] we undertook a study to dichotomize these *E*/*Z* versus chair/boat issues and report here (i) evidence for excellent (*E*)-enolate selectivity in the enolization of β-hydroxy esters and (ii) substrate-dependent chair/boat selectivity in the ensuing Claisen rearrangement.

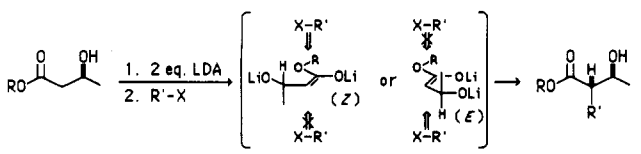
The 6,6-dimethylcyclohexenyl moiety was chosen to probe this (*E*/*Z*)-enolate versus chair/boat question since in our aza-Claisen work it was shown to provide ≥97% chair selectivity.[6] Thus, the first substrate selected for our investigation was β-hydroxy ester **7**, which was prepared from 2,2-dimethylcyclohexanone (*p*-tolylsulfonyl)-hydrazone by Shapiro reaction, subsequent quench with dimethylformamide, and immediate reduction of the aldehyde with diisobutylaluminum hydride. The resulting allylic alcohol **6** was acetylated with acetyl chloride, deprotonated with lithium hexamethyldisilylamide, and condensed with acetaldehyde, giving β-hydroxy ester **7** in 55% overall yield. Upon treatment with 2 equiv of lithium diisopropylamide in THF at −78 °C, warming to 50 °C for 12 h, hydrolysis, and esterification with diazomethane, **7** gave Claisen adducts **8** and **9** in a 98:2 ratio, respectively (Scheme II). It is unlikely that the improved diastereoselectivity with **7** relative to **1** is due to increased (*E*)-enolate selectivity in the rearrangement of **7** in that both dianionic Claisen rearrangements were performed under identical conditions. Rather, these results are consistent with improved chair selectivity for **7** and, assuming **8** is exclusively the result of a chair-like transition state,[7] indicate that (*E*/*Z*)-enolate selectivity under these conditions is on the order of 98:2.[8]

Table I



The next substrate investigated was β-hydroxy ester **13**, the normethyl analogue of **7**. It was prepared in 62% overall yield from alcohol **12**[6] by acetylation and aldol condensation. As anticipated on the basis of steric bulk in the allyl moiety, the dianionic Claisen rearrangement of **13** (→ **14**/**15**/**16** in a 94:2:4 ratio) was less selective than that of **7** but more selective than that of **1**. Indeed, the relative diastereoselectivities with **1**, **7**, and **13** corroborate our conclusion that (*E*)-enolate selectivity is nearly complete in each rearrangement while chair/boat selectivity is variable (ranging from 83:17 for **1** to ≈98:2 for **7** and **13**). Moreover, it can be concluded that the (*E*)-enolate of **7** is ≈100% face selective at C_α in the Claisen rearrangement, while C_α-face selectivities for the (*E*)-enolates of **1** and **13** are 90 and 96%, respectively: hence **1** → **4** (10%) and **13** → **16** (4%) are a consequence of incomplete face, not enolate, selectivity. Finally, it is noteworthy that the C_α-face selectivities of **1** and **13** closely parallel the C_α-face

(1) Recipient of an Alfred P. Sloan Research Fellowship, 1987–1989.
(2) Kurth, M. J.; Yu, C.-M. *J. Org. Chem.* **1985**, *50*, 1840.
(3) (a) Frater, G.; Muller, U.; Gunther, W. *Tetrahedron* **1984**, *40*, 1269. (b) Frater, G. *Helv. Chim. Acta* **1980**, *63*, 1383. (c) Frater, G. *Helv. Chim. Acta* **1979**, *62*, 2825. (d) Frater, G. *Helv. Chim. Acta* **1979**, *62*, 2829.
(4) That is, alkylation of either the (*E*)- or (*Z*)-enolate of i from the least hindered face would give ii. For discussion of this and other control elements operative in the alkylation of chiral enolates, see: Evans, D. A. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic: New York, 1984; Vol. 3, Part B, p 80.



(5) Review: Sih, C. J.; Chen, C.-S. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 570. (b) Wipf, B.; Kupfer, E.; Bertazzi, R.; Leuenberger, H. G. W. *Helv. Chim. Acta* **1983**, 485. (c) Hungerbuhler, E.; Seebach, S.; Wasmuth, D. *Helv. Chim. Acta* **1981**, *64*, 1467. (d) Seuring, B.; Seebach, D. *Helv. Chim. Acta* **1977**, *60*, 1175.
(6) Kurth, M. J.; Decker, O. H. W. *J. Org. Chem.* **1985**, *50*, 5769.
(7) Ireland, R. E.; Muller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868 and references therein.
(8) Since the dianionic Claisen rearrangement requires elevated temperatures relative to the deprotonation step (50 °C vs −78 °C), this may represent thermodynamic enolate selectivity.

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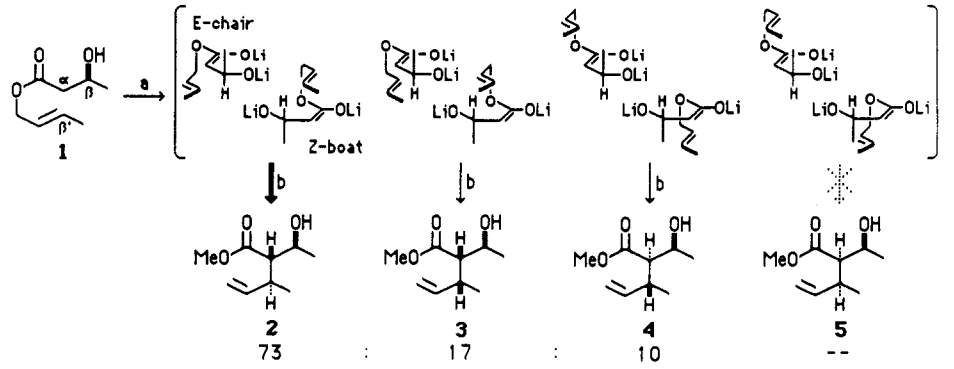
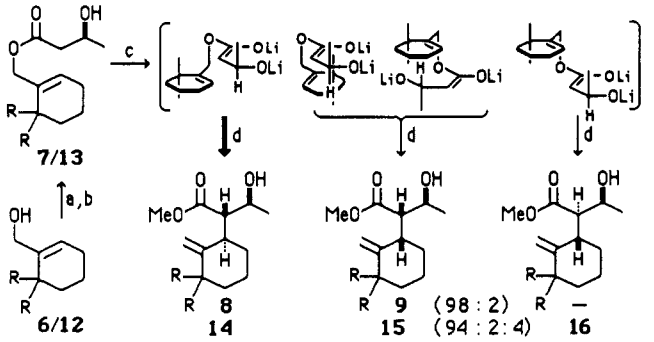
Scheme I[a]



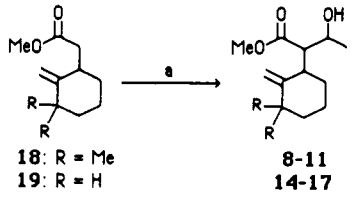
[a] (a) LDA, THF, −78 °C. (b) (i) −78 °C → 55 °C, [3,3]; (ii) H_3O^+; (iii) CH_2N_2.

Scheme II[a]



[a] **6–9**, R = Me; **12–15**, R = H. (a) CH_3COCl, Et_3N, CH_2Cl_2, DMAP. (b) (i) LiHMDS, THF, −78 °C; (ii) CH_3CHO; (iii) H_3O^+. (c) LDA, THF, −78 °C. (d) (i) −78 °C → 50 °C, [3,3]; (ii) H_3O^+; (iii) CH_2N_2.

Scheme III[a]



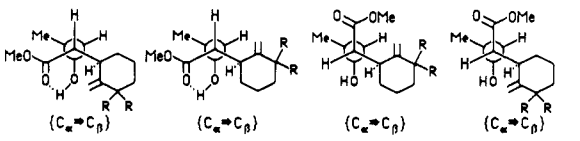
[a] (a) (i) LDA, THF, −78 °C; (ii) CH_3CHO; (iii) H_3O^+.

selectivity observed in Fräter dianion alkylations (90–95% de).

In order to verify the l-C_α/C_β stereochemical assignments of the β-hydroxy ester dianion Claisen products from **7** and **13**, the corresponding u-C_α/C_β β-hydroxy esters were prepared by aldol condensation. Thus, alcohol **6** was acetylated and the resulting acetate was employed in an Ireland enolate-Claisen rearrangement. Subsequent diazomethane esterification provided methyl ester **18**, the lithium enolate of which was condensed with acetaldehyde, giving the diastereomeric β-hydroxy esters **8–11** (see Table I) in a 10:5:40:45 ratio, respectively (Scheme III). By an analogous procedure, allylic alcohol **12** was converted to methyl ester **19**, which, upon aldol condensation with acetaldehyde, gave β-hydroxy esters **14–17** (see Table I) in a 4:7:39:50 ratio, respectively.

Both of these aldol condensations are C_α/C_β-l selective: 15:85 u/l selectivity for **18** → **8–11** and 11:89 u/l selectivity for **19** → **14–17**. Thus, while enolate face selectivity is only marginal (50:50 re/si for **18** and 43:57 re/si for **19**; see Table I), this C_α/C_β-u/l selectivity, which is presumably the consequence of dissimilar nonbonding interactions between the cyclohexyl moiety of the (*Z*)-enolate and the CH_3 versus H groups of acetaldehyde, is quite high. Indeed, the C_α/C_β-u/l selectivities of **18** and **19** are particularly remarkable when contrasted with that observed in the condensation of lithium enolates of alkyl esters formed under analogous conditions (LDA, THF, −78 °C), which show essentially no C_α/C_β-u/l selectivity.[9]

Table II



R = Me	8	9	10	11
$J_{\alpha,\beta}$	2.1 Hz	1.8 Hz	4.9 Hz	6.6 Hz
$J_{\alpha,\beta'}$	10.1 Hz	10.0 Hz	10.6 Hz	8.9 Hz
R = H	**14**	**15**	**16**	**17**
$J_{\alpha,\beta}$	2.5 Hz	2.5 Hz	5.1 Hz	6.2 Hz
$J_{\alpha,\beta'}$	11.4 Hz	--	11.1 Hz	11.0 Hz

Vicinal coupling constant $J_{\alpha,\beta}$ proved invaluable in making stereochemical assignments for the dianionic Claisen rearrangement products of **7** and **13** since anti β-hydroxy esters **8**, **9**, **14**, and **15** give $J_{\alpha,\beta}$ values ranging from 1.8 to 2.5 Hz, while syn β-hydroxy esters **10**, **11**, **16**, and **17** give $J_{\alpha,\beta}$ values ranging from 4.9 to 6.6 Hz (see Table II). As reviewed by Heathcock,[10] $J_{\alpha,\beta}$-anti coupling constants are smaller than $J_{\alpha,\beta}$-syn coupling constants when C_α-alkyl/C_β-alkyl gauche interaction, not hydrogen bonding, is the dominant conformational determinant. The most important conformations for **8–11** and **14–17** put the C_α-cyclohexyl and C_β-methyl substituents antiperiplanar as verified by the magnitude of $J_{\alpha,\beta}$, a weighted average of conformer populations. It is interesting to note that $J_{\alpha,\beta'}$ values for all of these compounds fall within a narrow range, 8.9–11.4 Hz, suggesting that the C_α-H and $C_{\beta'}$-H are antiperiplanar in the major conformer regardless of the $C_\alpha/C_{\beta'}$ relative stereochemistry (cf. **8** versus **9**/**10**/**11** or **14** versus **15**/**16**/**17**).[11]

Experimental Section

Melting points are uncorrected. MPLC refers to column chromatography done at 10–50 psi through EM Lobar columns packed with LiChroprep Si60 (40–63 μm) with hexane/EtOAc

(9) (a) Meyers, A. I.; and Reider, P. *J. Am. Chem. Soc.* **1979**, *101*, 2501. (b) Heathcock, C. H.; Buse, C. T.; Kleschick, W. A.; Pirrung, W. C.; Sohn, J. E.; Lampe, J. *J. Org. Chem.* **1980**, *45*, 1066.

(10) Heathcock, C. H. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic: New York, 1984; Vol. 3, Part B, p 115.

(11) Consequently, $C_\alpha/C_{\beta'}$ stereochemical assignments were made by analogy to **2–4**.[2]

eluent and monitored by refractive index detection. Capillary gas chromatography (GC) was performed on a Hewlett-Packard 5890A gas chromatograph using a DB-1701 column (30 m × 0.259 mm; film thickness = 0.25 mm): initial temperature = 90 °C; initial time = 2 min; rate = 1 °C/min; gas pressures (psi: He, 56; N_2, 40; air, 34; H_2, 18); retention times are in minutes. The purity of all products (title compounds) was established to be >95% by ^1H NMR and GC analyses.

2,2-Dimethylcyclohexanone (*p*-Tolylsulfonyl)hydrazone. (*p*-Tolylsulfonyl)hydrazine (4.43 g, 23.8 mmol) and ethanol (9.5 mL) containing 1 drop of concentrated HCl were heated until the solid completely dissolved. The solution was removed from the hot bath and allowed to cool for 5 min before 2,2-dimethylcyclohexanone (3.0 g, 23.8 mmol) was added in one portion. The solution was then heated for 1 min, allowed to cool to room temperature, and finally put in the freezer for an hour. The colorless crystals so obtained were collected by suction filtration, recrystallized from ethanol, filtered, and dried under low pressure to yield 5.6 g (80%) of the (*p*-tolylsulfonyl)hydrazone (mp 124.5 °C dec: IR (KBr) 3416, 3202, 2978, 2849, 1406, 1333, 1163, 1093, 1017 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.03 (s, 6 H), 1.44 (m, 2 H), 1.57 (m, 4 H), 2.21 (m, 2 H), 2.42 (s, 3 H), 7.31 (d, 2 H, J = 8.5 Hz), 7.85 (d, 2 H, J = 8.5 Hz). Anal. Calcd for $C_{15}H_{22}N_2O_2S$: C, 61.19; H, 7.53; N, 9.52; S, 10.89. Found: C, 61.07; H, 7.66; N, 9.49; S, 10.87.

(6,6-Dimethyl-1-cyclohexen-1-yl)methanol (6).[6] An oven-dried, two-necked 100-mL round-bottom flask equipped with a magnetic stir bar, a rubber septum, and an Erlenmeyer flask containing 2,2-dimethylcyclohexanone (*p*-tolylsulfonyl)hydrazone (5.6 g, 19.0 mmol) connected by a short piece of bent glass tubing was allowed to cool under a static pressure of dry nitrogen. The flask was charged with dry TMEDA (27 mL) and a 1.66 M solution of *n*-butyllithium in hexanes (41 mL, 68.0 mmol) and cooled to −78 °C. The solid hydrazone was added over a period of 20 min, and the resulting mixture was stirred at about −78 °C for an additional 60 min. The red solution was warmed to room temperature, during which time nitrogen gas evolved. After 1.5 h, the solution was cooled to 0 °C and dry dimethylformamide (5.8 mL, 74.8 mmol) was added over about 5 min. The solution was stirred for 3 h at room temperature and then poured into water (200 mL) and ether (100 mL). The organic layer was washed with water (2 × 200 mL), aqueous saturated copper sulfate (200 mL), and brine (200 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure to yield 2.85 g of a light yellow oil. To a solution of the crude aldehyde (2.63 g) and dry methylene chloride (210 mL) at −78 °C was added dropwise a 1 M solution of diisobutylaluminum hydride in hexane (21.7 mL, 21.7 mmol). The solution was stirred at this temperature for an additional 3 h. Methanol (9 mL) was then added, and the solution was allowed to warm to room temperature. Aqueous sodium tartrate (20%; 100 mL) was added, and the mixture was stirred for an additional 30 min before being diluted with water (100 mL) and extracted with ether (3 × 100 mL). The combined ether layers were washed with water (100 mL) and brine (300 mL) and dried (Na_2SO_4), and the solvents were removed under reduced pressure to give 1.73 g (65% from the tosylhydrazone) of **6** after Kugelrohr distillation: bp 118–121 °C (5 Torr); IR (neat) 3350, 2960, 2890, 1460, 1380, 1360, 1165, 1010, 870, 705 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.05 (s, 1 H), 1.45 (m, 2 H), 1.61 (m, 2 H), 2.02 (m, 1 H), 4.10 (m, 2 H), 5.65 (br s, 1 H).

1-Cyclohexen-1-ylmethanol (12).[6] An oven-dried, two-necked 100-mL round-bottom flask equipped with a magnetic stir bar, a rubber septum, and an Erlenmeyer flask containing cyclohexanone (*p*-tolylsulfonyl)hydrazone[12] (5.0 g, 18.8 mmol) connected by a short piece of bent glass tubing was allowed to cool under a static pressure of dry nitrogen. The flask was charged with dry TMEDA (30 mL) and a 1.55 M solution of *n*-butyllithium in hexanes (53.4 mL, 82.7 mmol) and cooled to −45 °C. The solid hydrazone was added over a period of 20 min, and the resulting mixture was stirred at −45 °C for an additional 60 min. The red solution was warmed to room temperature, during which time nitrogen gas evolved. After 1.5 h, the solution was cooled to 0 °C and gaseous formaldehyde was introduced by heating paraformaldehyde (3.40 g, 113 mmol), during which time the solution turned gradually more yellow in color. The solution was stirred overnight at room temperature and then poured into 1% aqueous HCl (200 mL) and pentane (100 mL). The organic layer was washed with water (2 × 200 mL), aqueous saturated copper sulfate (200 mL), and brine (200 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure to yield 1.65 g of a light yellow oil, which was purified by Kugelrohr distillation, bp 83–85 °C (9 Torr), to yield 1.25 g (59%) of alcohol **12**: IR (neat) 3345–3327, 3122, 2948, 2873, 1650, 1464, 1443, 1101, 1068, 1025, 825 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz) δ 1.5–2.0 (m, 4 H), 2.0–2.4 (m, 4 H), 4.1 (br s, 2 H), 5.75 (br t, 1 H, 1.5 Hz).

(6,6-Dimethyl-1-cyclohexen-1-yl)methyl Acetate. General Procedure A. To an ice-cooled solution of allylic alcohol **6** (1.50 g, 10.7 mmol) in methylene chloride (32 mL) were added triethylamine (3.00 mL, 21.4 mmol) and a solution of DMAP (6.5 mg) in 3.2 mL of methylene chloride. After 5 min, acetyl chloride (0.913 mL, 12.8 mmol) was added dropwise and the solution was stirred at 0 °C for 30 min. The ice bath was removed, and the solution, which had turned noticeably cloudy, was stirred for an additional hour at room temperature. The solution was washed with cold 5% aqueous HCl (30 mL), water (30 mL), saturated aqueous $NaHCO_3$ (30 mL), and brine (30 mL). The organic layer was dried (Na_2SO_4) and filtered and the solvent removed under reduced pressure to give the acetate (1.45 g, 75%) as a clear colorless oil after MPLC (SiO_2, 9:1 hexane/ethyl acetate): IR (neat) 2931, 1741, 1653, 1229, 1024 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.03 (s, 6 H), 1.45 (m, 2 H), 1.60 (m, 2 H), 2.02 (m, 2 H), 2.04 (s, 3 H), 4.52 (br s, 2 H), 5.66 (br t, 1 H, J = 2 Hz); exact mass calcd for $C_{11}H_{18}O_2$ 182.1307, found 182.1310.

1-Cyclohexen-1-ylmethyl Acetate. This acetate was prepared according to general procedure A. In this way, allylic alchol **12** (860 mg, 7.67 mmol) and acetyl chloride were converted to 1.02 g (86%) of the acetate as a clear colorless oil after distillation [bp 94 °C (14 mm)]: IR (neat) 2931, 1741, 1653, 1229, 1024 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.5–1.8 (m, 4 H), 1.8–2.2 (m, 4 H), 2.1 (s, 3 H), 4.45 (br s, 2 H), 5.77 (br t, 1 H, J = 2 Hz); exact mass calcd for $C_9H_{14}O_2$ 154.0994, found 154.0986].

(±)-(6,6-Dimethyl-1-cyclohexen-1-yl)methyl 3-Hydroxybutanoate (7). General Procedure B. *n*-BuLi (1.66 M in hexanes, 7.0 mL, 11.6 mmol) was added dropwise over 5 min to a solution of freshly distilled 1,1,1,3,3,3-hexamethyldisilazane (2.60 mL, 12.4 mmol) and diethyl ether (15 mL) at room temperature under dry nitrogen. The resulting solution was heated to reflux for 30 min and then the solvent was removed under reduced pressure. The resulting white solid was redissolved in dry THF (10 mL) and cooled to −78 °C. (6,6-Dimethy-1-cyclohexen-1-yl)methyl acetate (1.5 g, 8.24 mmol) in 1.5 mL of THF was added dropwise over approximately 5 min, and the resulting solution was stirred at −78 °C for 15 min. Acetaldehyde (0.650 mL, 11.6 mmol) was added quickly, and after 10 min, the reaction was quenched with a solution of 3 mL of acetic acid and 3 mL of THF. The solution was poured into 10% HCl (25 mL) and washed with ethyl acetate (3 × 25 mL). The combined organic layers were washed with water (25 mL) and brine (75 mL) and dried (Na_2SO_4), and the solvent was removed under reduced pressure to give 1.65 g of a light yellow oil, which was purified by MPLC (SiO_2, 3:1 hexane/ethyl acetate) to yield 1.36 g (73%) of β-hydroxy ester **7** as a colorless oil: IR (neat) 3500–3200, 2970, 2861, 1734, 1650, 1292, 1175 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 0.90 (s, 6 H), 1.15 (d, 3 H, J = 6 Hz), 1.45–1.75 (m, 4 H), 1.78–2.00 (m, 2 H), 2.43 (2 d, 2 H, J = 5, 7 Hz), 3.0 (br s, H) 4.00–4.35 (m, 1 H), 4.40 (br s, 2 H), 5.40 (br t, 1 H, J = 2.5 Hz); exact mass calcd for $C_{13}H_{22}O_3$ 226.1569, found 226.1560.

(±)-1-Cyclohexen-1-ylmethyl 3-Hydroxybutanoate (13). β-Hydroxy ester **13** was prepared according to general procedure B. In this way, 1-cyclohexen-1-ylmethyl acetate (0.900 g, 5.84 mmol) and acetaldehyde were converted to 0.830 g (72%) of β-hydroxy ester **13** as a colorless oil after MPLC (SiO_2, 3:1 hexane/ethyl acetate): IR (neat) 3500–3200, 2970, 2861, 1734, 1650, 1292, 1175 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.35 (d, 3 H, J = 6 Hz), 1.45–1.95 (m, 4 H), 1.95–2.20 (m, 4 H), 2.52 (2 d, 2 H, J = 5, 7 Hz), 3.0 (br s, 1 H), 4.00–4.45 (m, 1 H), 4.50 (br s, 2 H), 5.78 (br t, 1 H, J = 2.5 Hz); exact mass calcd for $C_{11}H_{18}O_3$ 198.1256, found, 198.1272].

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Methyl (1*R,α*S**,1′*S**)-(±)- and (1*R**,α*R**,1′*R**)-(±)-3,3-Dimethyl-α-(1′-hydroxyethyl)-2-methylene-1-cyclohexaneacetate (8 and 9). General Procedure C.** Ester **7** (200 mg, 0.89 mmol) in 0.5 mL of dry THF was added dropwise over 5 min to a solution of lithium diisopropylamide (3.38 mmol) in THF/hexane (5.0 mL/2.1 mL) cooled to −78 °C. The resulting mixture was stirred at −78 °C for 10 min, then allowed to warm to room temperature, stirred for 6 h, and then heated to 50 °C for 12 h. The reaction mixture was poured into 5% aqueous NaOH (5 mL) and the ice-cooled aqueous layer acidified with ice-cold concentrated HCl and extracted with methylene chloride (5 × 10 mL). The combined organics were washed with water (15 mL) and brine (25 mL) and dried (Na_2SO_4), and the solvent was removed under reduced pressure to give a light yellow powder (113 mg, 57%). The crude acid was dissolved in ice-cold ether (2 mL) and added to a solution of excess diazomethane in ether (10 mL) at 0 °C. After 30 min, the excess diazomethane was destroyed by treating the solution with acetic acid until its yellow color was quenched. The remaining solution was washed with saturated aqueous $NaHCO_3$, water, and brine and dried (Na_2SO_4) and the solvent removed under reduced pressure to give 105 mg (88%, 49% based on starting ester **7**) of inseparable diastereomers **8** and **9** after MPLC (SiO_2, 1:1 hexane/EtOAc) in a ratio of 98:2 as judged by integration of the methoxycarbonyl singlets in the 300-MHz ^1H NMR spectrum. For **8**: IR (neat) 3472, 2966, 1715, 1381, 1363, 1267, 1196, 1122, 1032 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$), δ 1.08 (s, 6 H), 1.23 (d, 3 H, J = 6.4 Hz), 1.40–1.80 (m, 6 H), 2.02–2.11 (br s, 1 H), 2.62 (dd, 1 H, J = 2.1, 10.1 Hz), 2.89 (dt, 1 H, J = 10.1, 3.89 Hz), 3.67 (s, 3 H), 4.12 (dq, 1 H, J = 2.1, 6.4 Hz), 4.74 (s, 1 H), 4.76 (s, 1 H); ^{13}C NMR decoupled spectrfum (75 MHz, $CDCl_3$) δ 21.9, 22.6, 26.5, 29.7, 31.4, 37.5, 39.2, 42.1, 51.3, 53.6, 65.3, 101.9, 156.1, 170.1; exact mass calcd for $C_{14}H_{24}O_3$ 240.1725, found 240.1738.

Methyl (1*R,α*S**,1′*S**)-(±)-, (1*R**,α*R**,1′*R**)-(±)-, and (1*R**,α*S**,1′*R**)-(±)-α-(1′-Hydroxyethyl)-2-methylene-1-cyclohexaneacetate (14, 15, and 16).** β-Hydroxy ester **14** was prepared according to general procedure C. In this way, β-hydroxy ester **13** (750 mg, 3.78 mmol) was rearranged and esterified with diazomethane to give 396 mg (50%) of inseparable diastereomers **14**, **15**, and **16** after MPLC (SiO_2, 1:1 hexane/EtOAc) in a ratio of 94:1.5:4.5 as judged by capillary GC (retention times: **14**, 25.73; **15**, 27.15; **16**, 35.34). It was later determined that esters **14** and **15** could be separated from **16** by MPLC (SiO_2, 9:1 hexane/EtOAc), but this was not done at this time. For **14**: IR (neat) 3500–3400, 2985, 2861, 1736, 1646, 1247, 1047, 734 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$), δ 1.22 (d, 3 H, J = 6.44 Hz), 1.24–1.78 (m, 7 H), 2.96–2.28 (m, 2 H), 2.74 (dd, 1 H, J = 2.55, 11.43 Hz), 2.84 (dt, 1 H, J = 4.09, 11.43 Hz), 3.64 (s, 3 H), 4.01 (dq, 1 H, J = 2.55, 6.44 Hz), 4.63 (br d, 2 H, J = 5.23 Hz); exact mass calcd for $C_{12}H_{20}O_3$ 212.1412, found 212.1422.

(±)-Methyl 3,3-Dimethyl-2-methylene-1-cyclohexaneacetate (18). General Procedure D. A 1.6 M solution of *n*-BuLi in hexane (1.90 mL, 3.04 mmol) was added dropwise to an ice-cooled solution of diisopropylamine (0.470 mL, 3.35 mmol) in THF (2 mL) under an atmosphere of dry nitrogen. After 10 min, the solution was cooled to −78 °C and (6,6-dimethyl-1-cyclohexen-1-yl)methyl acetate (277 mg, 1.52 mmol) in THF (0.5 mL) was added over 5 min. After 10 min, trimethylsilyl chloride (0.425 mL, 3.35 mmol) was added in one portion. Two minutes later, the dry ice bath was removed and the solution was allowed to warm to room temperature. The solution was then heated to reflux for 2 h and then allowed to cool to room temperature. Methanol (1 mL) was added, and the solution was stirred for an additional 15 min at room temperature to cleave the silyl ester. The solution was poured into 5% aqueous NaOH (5 mL) and washed once with ether. The base layer was cooled to 0 °C, acidified with concentrated HCl, and extracted several times with methylene chloride. The organic layers were collected, washed with brine, and dried (Na_2SO_4) and the solvents removed under reduced pressure to give 135 mg (48.7%) of the acid as a light yellow oil. The crude acid was dissolved in 1 mL of ether and was added to a solution of excess diazomethane in ether at 0 °C. After 30 min, the excess diazomethane was destroyed by the addition of acetic acid until the evolution of nitrogen ceased. The solution was washed with saturated $NaHCO_3$ and brine and dried (Na_2SO_4) and the solvent removed under reduced pressure to yield a light yellow oil. MPLC (SiO_2, 3:1 hexane/ethyl acetate) provided 125 mg (41.9%) of the rearranged ester **18**: IR (neat) 3098, 2928, 2880, 2856, 1740, 1633, 1435, 125, 1167, 895, 864 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.08 (s, 6 H), 1.43–1.90 (m, 6 H), 2.25 (dd, 1 H, J = 6.91, 15.1 Hz), 2.57 (dd, 1 H, J = 6.16, 15.1 Hz), 2.75 (m, 1 H), 3.66 (s, 3 H), 4.50 (2 d, 2 H, J = 6.06 Hz); exact mass calcd for $C_{12}H_{20}O_2$ 196.1463, found 196.1468.

(±)-Methyl 2-Methylene-1-cyclohexaneacetate (19). Ester **19** was prepared according to general procedure D. In this way, 1-cyclohexen-1-ylmethyl acetate (324 mg, 2.10 mmol) was rearranged and esterified with diazomethane to give 181 mg (54%) of ester **19** after MPLC (SiO_2, 3:1 hexane/EtOAc): IR (neat) 3082, 2933, 2856, 1741, 1646, 1281, 1263, 1236, 1170, 1120 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.0–2.0 (m, 6 H), 2.0–2.8 (m, 5 H), 3.7 (s, 3 H), 4.5 (br s, 1 H), 4.65 (br s, 1 H); exact mass calcd for $C_{10}H_{16}O_2$ 168.1150, found 168.1143.

Methyl (1*R,α*S**,1′*R**)-(±)- and (1*R**,α*R**,1′*S**)-(±)-3,3-Dimethyl-α-(1′-hydroxyethyl)-2-methylene-1-cyclohexaneacetate (10 and 11). General Procedure E.** To a solution of LDA (0.572 mmol) in dry THF/hexane (2.0 mL/0.356 mL) at −78 °C under dry nitrogen was added dropwise over 2 min a solution of ester **18** (93.5 mg, 0.447 mmol) in 0.5 mL of THF. After 15 min, acetaldehyde (0.572 mmol) was added in one portion and the solution was stirred for an additional 10 min at −78 °C. The reaction was quenched at −78 °C by the addition of a solution of acetic acid (0.5 mL) in THF (0.5 mL) and then warmed to room temperature. The solution was carefully poured into saturated aqueous $NaHCO_3$ and extracted with ethyl acetate (3 × 5 mL). The collected organic layers were washed with water (1×) and brine (1×) and dried (Na_2SO_4) and the solvents removed under reduced pressure. MPLC (SiO_2, 9:1 hexane/EtOAc) provided esters **8** and **9** as an inseparable mixture of diastereomers (10 mg, 8.8%), ester **10** (26.1 mg, 22.9%), and ester **11** (29.7 mg, 26%). For **10**: IR (neat) 3447, 3100, 2932, 2864, 1736, 1636, 1435, 1242, 1167, 901 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 0.95–1.93 (m, 6 H), 1.07 (2 s, 6 H), 1.20 (d, 3 H, J = 6.44 Hz), 2.11 (br s, 1 H), 2.64 (br dt, 1 H), 2.92 (dd, 1 H, J = 4.90, 10.55 Hz), 3.65 (s, 3 H), 4.16 (m, 1 H, J = 6.44, 4.90 Hz), 4.64 (s, 1 H), 4.72 (s, 1 H); exact mass calcd for $C_{14}H_{24}O_3$ 240.1725, found 240.1724. For **11**: IR (neat) 3443, 3098, 2939, 2869, 1725, 1636, 1437, 1170, 910 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.95–1.80 (m, 6 H), 1.07 (2 s, 6 H), 1.16 (d, 3 H, J = 6.30 Hz), 2.26 (br s, 1 H), 2.69 (br dt, 1 H), 2.93 (dd, 1 H, J = 6.58, 8.85 Hz), 3.66 (s, 3 H), 4.12 (m, 1 H, J = 6.30, 6.58 Hz), 4.81 (s, 1 H), 4.84 (s, 1 H); exact mass calcd for $C_{14}H_{24}O_3$ 240.1725, found 240.1727.

Methyl (1*R,α*S**,1′*R**)-(±)- and (1*R**,α*R**,1′*S**)-(±)-α-(1′-Hydroxyethyl)-2-methylene-1-cyclohexaneacetate (16 and 17).** β-Hydroxy esters **16** and **17** were prepared according to general procedure E. In this way, methyl ester **19** (150 mg, 0.893 mmol) and acetaldehyde were converted to β-hydroxy esters **14–17** in a ratio determined by capillary GC to be 3.7:6.9:38.7:50.7 **14**/**15**/**16**/**17** (retention times: **14**, 25.73; **15**, 27.15; **16**, 35.34; **17**, 32.40) before separation. MPLC (SiO_2, 9:1 hexane/EtOAc) provided esters **14** and **15** as an inseparable mixture of diastereomers (15.1 mg, 8.0%), ester **16** (55.3 mg, 29.2%), and ester **17** (72.1 mg, 38.3%). For **16**: IR (neat) 3455, 3072, 2934, 2881, 1738, 1646, 1437, 1233, 1165, 895 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.79–0.86 (m, 2 H), 1.26 (d, 3 H, J = 6.4o Hz), 1.5–1.65 (m, 4 H), 2.03–2.34 (m, 3 H), 2.55 (m, 1 H), 3.03 (dd, 1 H, J = 5.89, 11.10 Hz)8 3.62 (s, 3 H), 4.13 (m, 1 H), 4.60 (s, 1 H), 4.64 (br s, 1 H); exact mass calcd for $C_{12}H_{20}O_3$ 212.1412, found 212.1420. For **17**: IR (neat) 3463, 3071, 2934, 2859, 1734, 1646, 1439, 1169, 926 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.16 (d, 3 H, J = 6.29 Hz), 1.33–1.63 (m, 4 H), 1.75–1.79 (m, 2 H), 2.17 (dd, 2 H, J = 3.24, 8.71 Hz), 2.55 (br s, 1 H), 2.67 (br dt, 1 H, J = 11.03 Hz), 3.00 (dd, 1 H, J = 6.24, 11.03 Hz), 3.69 (s, 3 H), 3.93 (m, 1 H, J = 6.26 Hz), 4.78 (br s, 1 H), 4.83 (br s, 1 H); exact mass calcd for $C_{12}H_{14}O_3$ 212.1412, found 212.1420.

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