The most striking feature of the data in Table I is the invariance of both the Brønsted α and ksie for acetals of widely different reactivity; only changes in the R_1 moiety of 1 cause a substantial lowering from the "average" ksie = 3.2, α = 0.9. The slightly lower values observed for Ar = p-OCH_3 and for $R_1 = CH_2CH_2OCH_3$ may be statistically significant for the ksie = 2.90 and 2.77, respectively, but are not for the α = 0.85 and 0.86, respectively. Thus, these two acetals are examples of substances designed to model behavior at the point of mechanism changeover. Table I, therefore, contains data for one acetal hydrolyzing by a concerted catalysis ($A_{SE}2$) mechanism, three acetals hydrolyzing by a mechanism consistent with ksie = 3.2 and α = 0.9, and two acetals at the changeover point.

The mechanism for the hydrolysis of 1 where R_1 does not contain strongly electron withdrawing groups cannot be $A_{SE}2$: ksie = 3.2 requires a preequilibrium proton transfer.[13,14] However, the transition state must contain the elements of general acid, since general acid catalysis is measurable for at least one of these acetals. Therefore, the observation of large, inverse ksie (>3), the observation of general acid catalysis (α = 0.9), and the large, negative Hammett ρ (–3), taken together, require a transition state closely resembling the aggregate 2. The constancy of the ksie requires that the nature of the isotopic bond in the transition state not change substantially as Ar is changed, despite a change in reactivity of 2×10^3 (ksie = 3.2 ± 0.2 for 1 when $R_1 = R_2 = CH_2CH_3$, Ar = Ar); this is inconsistent with a rate-limiting step 4, which changes an onium O–H bond to an alcohol O–H bond.

Thus, Table I provides good evidence for rate-limiting diffusional separation, and the changeover in mechanism is simply a change in rate-limiting step, brought about by a decreased lifetime of 2; that is, when 2 is longer lived because the oxocarbocation is exceptionally stabilized or becaused R_1OH is weakly nucleophilic, 2 is formed irreversibly by step 3. When 2 is shorter lived, because the oxocarbocation is less stable or because R_1OH is more nucleophilic, the fate of 2 is normally reversed to starting material. In this latter case, whether 2 is produced by step 3 or step 4 is impossible to say; however, we have shown that the rate-limiting step is subsequent to formation of 2. Also, in cases where the oxocarbocation does not have an aryl group to provide some stabilization, step 5 may occur faster than step 4, and 2 may no longer be a viable intermediate. This is an example of catalysis being enforced by an intermediate serving as a reaction intermediate and denied by its inviability as a reaction intermediate.[11]

Finally, although Scheme II nicely accommodates the data, there is an alternative interpretation that appears not to have been discussed previously. Namely, the hydronium ion catalyst is >6 pK units stronger an acid than the general acid catalysts employed in the buffer studies: The hydronium ion catalysis might be occurring via a classical A-1 mechanism (steps 1, 2, 5, 6, 8 in Scheme II) while the weaker carboxylic acids might catalyze hydrolysis via step 3 or 4 (step 3 being more likely in these cases, on the basis of an analysis of steps 2, 3, and 4 using contour energy diagrams).[2] That is, the assumption that all acid catalysts effect hydrolysis by the same mechanism is no more (or less) a truism than the assumption that structural changes in the substrate do not affect the nature of the reaction mechanism. (This latter assumption is one frequently employed in Hammett LFER studies.) Evidence for or against the validity of this assumption is of the most difficult type to generate definitively—a "break" in the LFER relationship. In the case of the Brønsted relationship this is particularly difficult, since the catalyst of greatest interest in this regard is usually 4–6 pK units away from a "cluster" of general acid catalysts whose pK_a span is often only 3 pK_a units or so. For the Brønsted α experiments cited in Table I, the hydronium ion lies "on" the Brønsted α line generated by the pK_{HA} vs. log k_{HA} data for the buffer acids, within a reasonable experimental error; in other words, the Brønsted α is the same, ±0.05, whether or not the k_{H^+} point is included in the computation. In addition, the "break" in the Brønsted relationship, were k_{H^+} to be for an A-1 mechanism (α = 1.0) and k_{HA} to be for any of the catalytic processes in Scheme II (α < 0.9), would place the k_{H^+} point *above* the line generated by the pK_{HA} vs. log k_{HA} data. In no case was this evident; k_{H^+} tends to fall below the Brønsted line generated in this manner, and thus the Brønsted α typically is 0.05 unit smaller when k_{H^+} is incorporated into the calculation.[2] These results argue against a change in mechanism with changing catalysts in this series of studies.

Experimental Section

Materials. The acetals were synthesized as reported earlier.[2] Deuterium chloride solutions were prepared by dilution of 20% DCl/D_2O with D_2O, both purchased from Aldrich Chemical Co. Concentrations of acid and chloride were checked by titration.[12]

Kinetic Method. The rate of production of aldehyde was monitored at λ_{max} for at least 3 half-lives of reaction time, using either a modified Beckman DU or a Durrum stopped-flow spectrophotometer. The traditional procedures used to obtain rate constants have been described previously.[2] Specific problems arising from the calculation of second-order rate constants from experimental measurements of acidity and k_{obsd} data have been defined recently,[12] and our exact method is defined in footnote b of Table I. The pH and pD measurements were obtained by using a Beckman Model 4500 pH meter and a Beckman 39030 combination glass electrode. pD values for the deuterated solutions were obtained by adding 0.41 to the observed meter reading.[14] In all solutions the "slope control" was used, using 0.100 N HCl, standard pH 4 buffer, and standard pH 7 buffer. All rate and pH (pD) measurements were made in solutions 0.1–0.005 N HCl (DCl), μ = 0.5 (KCl).

Acknowledgment. Support from the National Science Foundation (CHE 7907588 and PRM 7919451) is gratefully acknowledged. The kind hospitality of the Chemistry Department at University of California, Irvine, was much appreciated during a 1981–82 sabbatical leave (J.L.J.) from CSULB.

Registry No. $PhCH(OC_2H_3)_2$, 774-48-1; $PhCH(OCH_2CH_3)(OCH_2CH_2OCH_3)$, 71412-86-7; $PhCH(OCH_2CH_3)(OCH_2CF_3)$, 71412-85-6; p-$CH_3OC_6H_4CH(OCH_2CH_3)_2$, 2403-58-9; m-$ClC_6H_4CH(OCH_2CH_3)_2$, 68578-52-9; m-$O_2NC_6H_4CH(OCH_2CH_3)_2$, 2403-49-8; deuterium, 7782-39-0.

The Bicyclo[3.3.1]nonane Solution to the Problem of Vicinal Stereochemical Control at a Substituted Cyclohexane Ring. A Total Synthesis of *dl*-*erythro*-Juvabione

Arthur G. Schultz* and James P. Dittami†

Department of Chemistry, Rensselaer Polytechnic Institute, Troy, New York 12181

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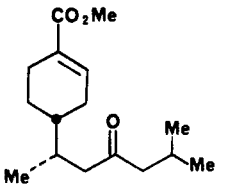
We have recently reported an efficient construction of bicyclo[3.3.1]non-3-en-2-ones by intramolecular enolate alkylation; the flexibility of the method was demonstrated by a formal total synthesis of *dl*-clovene.[1] In this paper,

† Texaco Fellow, 1982–1983.

0022-3263/84/1949-2615$01.50/0

we describe a total synthesis of the naturally occurring juvenile hormone, *dl-erythro*-juvabione (**1**)[2] by a cyclohexane ring transposition via the bicyclo[3.3.1]nonane ring system. Previous stereocontrolled syntheses of **1** include those of Ficini[3] and Evans.[4] Our synthesis converges with that of Ficini and co-workers via intermediate **8a**.[5]



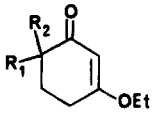
1

Vicinal stereochemical control is the key requirement of juvabione synthesis design. In our plan, catalytic olefin hydrogenation of a suitably constructed bicyclo[3.3.1]non-3-en-2-one was expected to occur with high diastereoface selection. The desired transformation (e.g., **4** →**5a**) does indeed occur with excellent stereochemical control (**5a**:**5b**, 25:1), thus insuring a highly stereoselective total synthesis of the natural product. From **5a**, oxidative cleavage of the original cyclohexane ring at C(1) and C(2) was expected to unveil a new cyclohexane ring with stereochemistry and functionality necessary to complete the synthesis.

Results and Discussion

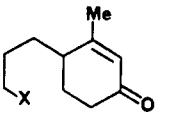
Alkylation of 3-ethoxy-2-cyclohexenone (**2a**) with lithium diisopropylamide (LDA) and 1-chloro-3-iodopropane gives **2b**, and this is converted to **3a** in ~50% overall yield by reaction with methylmagnesium bromide, followed by acid-catalyzed hydrolysis–dehydration. In contrast to the behavior of a related alkyl chloride in the clovene synthesis,[1] which efficiently provided a bicyclo[3.3.1]non-3-en-2-one, intramolecular enolate alkylation from **3a** does not occur in synthetically useful yield. However, conversion of **3a** to the more reactive iodide **3b** and reaction of **3b** with LDA in THF (–78 °C to room temperature) gives the required bicyclic enone **4** in 83% isolated yield. The key hydrogenation of **4** (quantitative yield with palladium on carbon in ethanol) occurs preferentially from the least hindered side of the carbon–carbon double bond to give a 25:1 mixture of **5a** and **5b**.[6a] The hydrogenation correctly establishes the relative stereochemistry at C(5) and C(4) in **5a** and, therefore, at these same stereocenters in *erythro*-juvabione (**1**).

The next operation in the synthesis plan required a regioselective oxidative cleavage of the C(1)–C(2) bond in **5a**. Baeyer–Villiger oxidation of **5a** with *m*-chloroperbenzoic acid gives a mixture of two lactones **6** and **7** in a ratio of 5.7:1 (^{1}H NMR spectral analysis.[6b] Separation of the mixture by high-performance liquid chromatography (HPLC) gives lactone **6** in 58% yield. Preliminary experiments indicate that a more favorable regioisomer distribution is obtained by oxidation with peracetic acid (11.7:1 of **6** and **7**).[7]



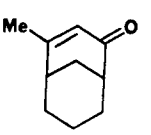
2a, $R_1 = R_2 = H$

b, $R_1 = H$; $R_2 = CH_2CH_2CH_2Cl$

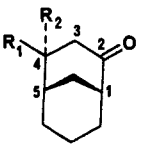


3a, X = Cl

b, X = I

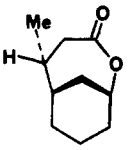


4

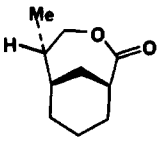


5a, $R_1 = H$; $R_2 = Me$

b, $R_1 = Me$; $R_2 = H$



6



7

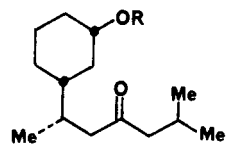
The direct addition of isobutylmagnesium chloride to lactone **6** in ether or THF solution produces an uncharacterized mixture of products. Monoaddition of Grignard reagents to esters in nonpolar solvents with triethylamine as cosolvent has been reported.[8] Under these conditions[8] employing benzene as solvent, ketone **8a** can be obtained, but these reactions always are complicated by formation of ether **8b**, which is presumably the result of alkoxide ion alkylation with residual isobutyl chloride. Attempts to prepare halide-free Grignard reagent by several techniques, which include distillation of volatile components from the organometallic preparation and the use of activated magnesium metal,[9] were ineffective.

A less direct method of Grignard addition proved to be considerably more efficient. Reaction of lactone **6** with methanol and *p*-toluenesulfonic acid gives alcoholic ester **9a**, which is protected as the *tert*-butyldimethylsilyl ether **9b**[10] and reacted with isobutylmagnesium chloride to give ketone **9c** in ~90% overall isolated yield. Deprotection of the hydroxyl group gives a material, **8a**, identical with that prepared by Grignard addition to lactone **6**.

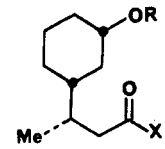
Keto alcohol **8a** is an intermediate in the Ficini synthesis of **1**; however, this alcohol is prepared by Ficini and coworkers as a mixture of diastereoisomers, which means that direct spectral comparison between our **8a** and the Ficini material is unreliable.[11] We, therefore, elected to convert **8a** to *dl-erythro*-juvabione by the literature procedure.[3]

Ketalization of the side-chain carbonyl group can be accomplished with either **8a** or **9c**, but cleaner product mixtures are obtained with **9c**. Deprotection of the silyl ether **10a** gives **10b**, which is converted to cyclohexanone **11** in ~60% overall yield from **9c** by oxidation with pyridinium chlorochromate. ^{1}H NMR, IR, and ^{13}C NMR

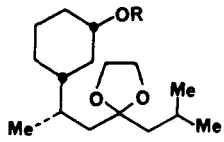
(1) Schultz, A. G.; Dittami, J. P. *J. Org. Chem.* **1983**, *48*, 2318.
(2) Rogers, I. H.; Manville, J. F.; Sahota, T. *Can. J. Chem.* **1974**, *52*, 1192. Manville, J. F. *Ibid.* **1975**, *53*, 1579; **1976**, *54*, 2365.
(3) Ficini, J.; D'Angelo, J.; Noirē, J. *J. Am. Chem. Soc.* **1974**, *96*, 1213.
(4) Evans, D. A.; Nelson, J. V. *J. Am. Chem. Soc.* **1980**, *102*, 774.
(5) For a recent total synthesis of *dl-threo*-juvabione, see: Morgans, D. J., Jr.; Feigelson, G. B. *J. Am. Chem. Soc.* **1983**, *105*, 5477.
(6) (a) For an analogous hydrogenation in the bicyclo[4.3.1]decene series, see: Marshall, J. A.; Partridge, J. J. *Tetrahedron* **1969**, *25*, 2159. (b) For an analogous Baeyer–Villiger oxidation, see: Atarashi, S.; Momose, T.; Muraoka, O. *Tetrahedron Lett.* **1974**, 3697. Atarashi, S.; Horita, T.; Momose, T.; Muraoka, O. *Chem. Pharm. Bull.* **1979**, *27*, 222.
(7) See: (Krow, G. *Tetrahedron* **1981**, *37*, 2697) for a review of the Baeyer–Villiger reaction and Krow, et al. (Krow, G. R.; Johnson, C. A.; Guare, J. P.; Kubrak, D.; Henz, K. J.; Shaw, D. A.; Szczepanski, S. W.; Carey, J. T. *J. Org. Chem.* **1982**, *47*, 5239) for a report on the regioselectivity of Baeyer–Villiger oxidations.
(8) Kikkawa, I.; Yorifuji, T. *Synthesis* **1980**, 877.
(9) Rieke, R. D.; Bales, S. E. *J. Am. Chem. Soc.* **1974**, *96*, 1775. Buske, G. R.; Ford, W. T. *J. Org. Chem.* **1976**, *41*, 1995, 1998.
(10) Corey, E. J.; Venkateswarlu, A. K. *J. Am. Chem. Soc.* **1972**, *94*, 6190.
(11) We thank Professor Ficini for providing IR and 60-MHz spectral data related to her synthesis of juvabione.



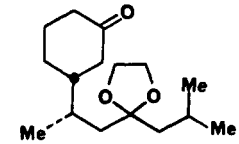
8a, R = H
b, R = CH_2CHMe_2



9a, R = H; X = OMe
b, R = t-$BuMe_2Si$; X = OMe
c, R = t-$BuMe_2Si$; X = CH_2CHMe_2



10a, R = t-$BuMe_2Si$
b, R = H



11

spectra for synthetic 1 are in excellent agreement with literature data.[3,4,12,13]

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. IR spectra were determined on a Perkin-Elmer Model 137 spectrophotometer, and ^1H NMR spectra were recorded on a Hitachi Perkin-Elmer Model R600 nuclear magnetic resonance spectrometer at 60 MHz and on a Varian Model XL200 nuclear magnetic resonance spectrometer at 200 MHz. ^1H NMR spectra were taken in $CDCl_3$ solvent with tetramethylsilane as internal standard. Mass spectra were obtained on a Hitachi Perkin-Elmer RMU-6E mass spectrometer as well as on a Finnigan OWA-1020 GC/MS system. UV spectra were recorded on a Perkin-Elmer Model 552 spectrophotometer. Elemental analyses were carried out by Spang Microanalytical Laboratories, Eagle Harbor, MI, and by Galbraith Laboratories, Inc., Knoxville, TN. Preparative chromatography was performed on a Waters Preparative 500 HPLC system by using Prep Pak 500 silica gel cartridges.

Preparation of 6-(3-Chloropropyl)-3-ethoxy-2-cyclohexen-1-one (2b). Lithium diisopropylamide (0.157 mol) was generated in dry THF (36 mL) at −12 °C. The mixture was cooled to −78 °C and a solution of 3-ethoxy-2-cyclohexenone (**2a**;[14] 20 g, 0.143 mol) in THF (36 mL) was added over 15 min. The resulting solution was stirred for 45 min. A solution of HMPA (28.1 g, 0.157 mol) and 1-chloro-3-iodopropane (32.1 g, 0.157 mol) in THF (17 mL) was added rapidly. The reaction mixture was stirred for 1 h at −78 °C and then was allowed to warm slowly to room temperature. The solution was stirred for 24 h at room temperature and water (20 mL) was added. The solvent was removed on a rotary evaporator and the residue extracted with ether (3 × 100 mL). The combined organic extracts were washed with water (3 × 100 mL), sodium thiosulfate solution (10%, 1 × 100 mL), and brine (2 × 100 mL) and dried over anhydrous magnesium sulfate. Removal of solvent under reduced pressure gave an oil (34.3 g), which was chromatographed by HPLC (hexane:ethyl acetate, 2.1:1) to afford **2b** (16.4 g, 53%): ^1H NMR ($CDCl_3$) δ 1.37 (t, 3 H, J = 7 Hz), 1.49–2.3 (m, 7 H), 2.4–2.53 (m, 2 H), 3.58 (t, 2 H, J = 6 Hz), 3.91 (q, 2 H, J = 7 Hz), 5.34 (s, 1 H); IR (film) 1650, 1610 cm^{-1}.

Preparation of 4-(3-Chloropropyl)-3-methyl-2-cyclohexen-1-one (3a). A solution of **2b** (4.7 g, 21.7 mmol) in THF (25 mL) was cooled to 0 °C in an ice bath. Methylmagnesium bromide (3.0 M, 8.7 mL, 26 mmol) was added, after which the ice bath was removed and the solution was stirred at room temperature overnight. The reaction mixture was then poured over ice-cold saturated ammonium chloride solution. The solvent was removed on a rotary evaporator and the residue extracted with ether (3 × 50 mL). The combined ether extracts were washed with brine (2 × 50 mL), dried over anhydrous magnesium sulfate, and concentrated on a rotary evaporator. To the resulting oil was added ethanol (95%, 25 mL) and hydrochloric acid solution (10%, 5 mL). The mixture was stirred at room temperature for 45 min and neutralized with solid sodium bicarbonate. The ethanol was removed under reduced pressure and the residue was partitioned between ether (50 mL) and water (50 mL). The aqueous layer was extracted with ether (3 × 50 mL). The combined ether extracts were dried over anhydrous magnesium sulfate and evaporated to afford **3a** (oil, 3.4 g, 84%). The product was chromatographed by HPLC (hexane:ethyl acetate, 3:1) to give **3a** (oil, 2.7 g, 67%): ^1H NMR ($CDCl_3$) δ 1.5–2.18 (m with overlapping br s at 1.98 9 H), 2.2–2.55 (m, 3 H), 3.6 (t, 2 H, J = 6 Hz), 5.88 (br s, 1 H); IR (film) 1660 cm^{-1}.

Anal. Calcd for $C_{10}H_{15}ClO$: C, 64.33; H, 8.10. Found: C, 64.13; H, 8.24.

Preparation of 4-(3-Iodopropyl)-3-methyl-2-cyclohexen-1-one (3b). A mixture of **3a** (11.96 g, 0.064 mol), sodium iodide (19.23 g, 0.128 mol), and acetone (300 mL) was heated to reflux temperature for 10 h. The resulting precipitate was filtered, the solvent was evaporated, and the residue was partitioned between chloroform (100 mL) and water (100 mL). The aqueous layer was extracted with chloroform (2 × 100 mL), and the combined organic extracts were washed with sodium thiosulfate solution (10%, 2 × 50 mL) and water (2 × 50 mL) and dried over anhydrous magnesium sulfate. Evaporation of the solvent gave **3b** (oil, 17.09 g, 96%): ^1H NMR ($CDCl_3$) δ 1.5–2.5 (m overlapping d at 2.0, 12 H, J = 1.5 Hz), 3.27 (t, 2 H, J = 6 Hz), 5.87 (br s, 1 H); IR (film) 1660 cm^{-1}.

Preparation of 4-Methylbicyclo[3.3.1]non-3-en-2-one (4). Lithium diisopropylamide (0.073 mol) was generated at −20 °C in THF (60 mL). The mixture was cooled to −78 °C and a solution of **3b** (17.09 g, 0.061 mol) in THF (60 mL) was added. The temperature of the reaction mixture was maintained at −78 °C for 1 h. The cooling bath was removed and the reaction was stirred for 24 h at room temperature. Water (20 mL) was added and the solvent was removed on a rotary evaporator. The residue was extracted with ether (3 × 100 mL), and the combined ether extracts were washed with water (3 × 100 mL) and brine (2 × 100 mL) and dried over anhydrous magnesium sulfate. Evaporation of solvent gave an oil, which was chromatographed by HPLC (hexane:ethyl acetate, 6:1) to give **4** (oil, 7.56 g, 83%): ^1H NMR ($CDCl_3$) δ 1.36–1.88 (m, 7 H), 1.96 (d, 3 H, J = 1.5 Hz), 2.1–2.26 (m, 1 H), 2.44 (br s, 2 H), 6.08 (br s, 1 H); IR (film) 1660, 1625 cm^{-1}.

Anal. Calcd for $C_{10}H_{14}O$: C, 80.01; H, 9.33. Found: C, 79.88; H, 9.30.

Preparation of 4-Methylbicyclo[3.3.1]nonan-2-one (5a + 5b). A solution of **4** (7.52 g, 0.05 mol) in absolute ethanol (500 mL) was stirred in the presence of palladium on carbon (5% 2.3 g) under an atmosphere of hydrogen. The uptake of hydrogen was monitored and after about 1 h the reaction appeared complete. Nitrogen gas was passed into the solution for 10 min, after which the reaction mixture was filtered through Celite. The solid residue was washed with ethyl acetate (6 × 100 mL), and the combined filtrate and washes were evaporated under reduced pressure to afford **5** (oil, 7.52 g, 99%) as a mixture of isomers (25:1 by ^1H NMR). An analytical sample was prepared by Kugelrohr distillation: pb 100 °C (1.3 mmHg); ^1H NMR ($CDCl_3$) δ 0.92 (minor isomer) and 1.08 (major isomer) (d, 3 H, J = 7 Hz), 1.42–2.3 (m, 11 H), 2.48–2.68 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 19.66, 20.68, 25.30, 28.39, 32.13, 34.33, 35.20, 45.07, 48.61, 215.17; IR (film) 1700 cm^{-1}; mass spectrum, m/e (relative intensity) 152 (M^+, 43), 137 (38), 108 (100).

Anal. Calcd for $C_{10}H_{16}O$: C, 78.89; H, 10.59. Found: C, 78.98; H, 10.65.

Preparation of 5-Methyl-2-oxabicyclo[4.3.1]decan-3-one (6 and 7). Method A. A solution of **5** (0.271 g, 1.78 mmol), *m*-chloroperbenzoic acid (85%, 0.54 g, 2.67 mmol), and methylene chloride (7 mL) was stirred for 3 h in the dark. The reaction mixture was washed with sodium bicarbonate–sodium thiosulfate solution (5%–5%, 3 × 50 mL). The organic layer was washed

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(13) For full details of the conversion of **8a** to **1**, see: Dittami, J. P. Ph.D. Thesis, Rensselaer Polytechnic Institute, Troy, NY, 1983.
(14) Gannon, W.; House, H. O. "Organic Syntheses"; Wiley: New York, 1973; Collect Vol. V, p 539.

with water (2 × 20 mL) and brine (2 × 20 mL) and dried over anhydrous magnesium sulfate. Evaporation of the solvent yielded an oil (0.284 g, 95%) which was shown to be a mixture of lactones **6** and **7** (5.7:1) by ^{1}H NMR analysis. Chromatography by HPLC (hexane:ethyl acetate, 10:1) provided **6** (oil, 0.174 g, 58%) and **7** (oil, 0.036 g, 12%), which showed the following spectral and analytical data. **Lactone 6**: ^{1}H NMR ($CDCl_3$) δ 1.04 (d, 3 H, J = 6.7 Hz), 1.46–2.18 (m, 10 H), 2.62–3.06 (m, 2 H), 4.61 (br s, 1 H); IR (film) 1710 cm^{-1}; mass spectrum m/e (relative intensity) 168 (M^+, 1), 150 (47), 124 (14), 109 (18), 96 (36), 82 (100).

Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.24; H, 9.56.

Lactone 7: ^{1}H NMR ($CDCl_3$) δ 0.95 (d, 3 H, J = 6.6 Hz), 1.2–2.53 (m, 10 H), 3.13 (br s, 1 H), 3.76–4.58 (m, 2 H); IR (film) 1720 cm^{-1}; mass spectrum m/e (relative intensity) 168 (M^+, 20, 150 (17), 138 (38), 109 (21), 95 (37), 81 (100).

Anal. Calcd for $C_{14}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.30; H, 9.68.

Preparation of Lactone 6. Method B. To a solution of **5** (0.121 g, 0.79 mmol) and anhydrous sodium acetate (0.1 g) in glacial acetic acid (1 mL) was added peracetic acid (40% in acetic acid, 0.54 mL). The resulting mixture was stirred for 24 h at room temperature in the dark, after which methylene chloride (10 mL) was added. The reaction mixture was washed with saturated sodium sulfite solution (4 × 5 mL), sodium bicarbonate solution (1 N, 3 × 5 mL), and brine (2 × 5 mL) and dried over anhydrous magnesium sulfate. Removal of solvent on a rotary evaporator gave a mixture of **6** and **7** in a ratio of 11.7:1 by ^{1}H NMR analysis (oil, 0.067 g, 50%).

Preparation of 2-(3-Hydroxycyclohexyl)-6-methyl-4-heptanone (8a). A solution of isobutylmagnesium chloride (2 M, 1 mL, 2 mmol) was dissolved in benzene (5 mL) and the mixture was distilled to a volume of approximately 2 mL. The resulting mixture was added to a solution of **6** in benzene (2 mL). The reaction mixture was stirred for 4 h at room temperature, after which saturated ammonium chloride solution (2 mL) was added. The resulting mixture was extracted with ether (3 × 20 mL). The combined organic extracts were washed with water (2 × 20 mL) and brine (2 × 20 mL) and dried over anhydrous magnesium sulfate. Evaporation of solvent gave an oil, which was purified by flash chromatography (SiO_2, hexane:ethyl acetate, 3:1) to give **8a** (oil, 0.087 g, 55%). An analytical sample was prepared by Kugelrohr distillation: bp 90 °C (0.15 mmHg); ^{1}H NMR ($CDCl_3$) δ 0.78–1.02 (complex array of overlapping peaks, 9 H), 1.06–1.44 (m, 4 H), 1.48–1.66 (m, 3 H), 1.72–2.52 (m, 9 H), 3.58 (m, 1 H); IR (film) 3400 (br), 1710 cm^{-1}.

Anal. Calcd for $C_{14}H_{26}O_2$: C, 74.28; H, 11.58. Found: C, 74.40; H, 11.59.

Preparation of Methyl 3-(3-Hydroxycyclohexyl)-3-methylpropionate (9a). A solution of lactone **6** (0.108 g, 0.64 mmol) and *p*-toluenesulfonic acid (0.010 g, 0.05 mmol) in methanol (7 mL) was heated at reflux temperature for 4 h. The solvent was removed on a rotary evaporator and the residue was partitioned between ether (5 mL) and water (5 mL). The aqueous layer was extracted with ether (3 × 10 mL), washed with sodium carbonate solution (1 N, 2 × 10 mL), water (1 × 10 mL), and brine (1 × 10 mL), and dried over anhydrous magnesium sulfate. Removal of solvent gave **9a** (oil, 0.125 g, 98%), which appeared to be of good purity by ^{1}H NMR analysis. An analytical sample was prepared by Kugelrohr distillation: bp 105 °C (1 mmHg); ^{1}H NMR ($CDCl_3$) δ 0.62–1.4 (m overlapping d at 0.92, 8 H, J = 6.5 Hz), 1.5–2.2 (m, 7 H), 2.32–2.48 (m, 1 H), 3.58 (m, 1 H), 3.68 (s, 3 H); IR (film) 3400, 1735 cm^{-1}.

Anal. Calcd for $C_{11}H_{20}O_3$: C, 65.96; H, 10.07. Found: C, 65.81; H, 9.98.

Preparation of Methyl 3-[3-(*tert*-Butyldimethylsiloxy)-cyclohexyl]-3-methylpropionate (9b). To a solution of **9a** (0.273 g, 1.36 mmol) in DMF (5 mL) at room temperature were added *tert*-butyldimethylsilyl chloride (0.246 g, 1.63 mmol) and imidazole (0.24 g, 3.5 mmol). The resulting solution was stirred for 17 h at 40 °C, after which hexane (5 mL) and water (5 mL) were added. The aqueous layer was extracted with hexane (2 × 5 mL), and the combined organic extracts were washed with water (4 × 10 mL) and brine (2 × 20 mL) and dried over anhydrous magnesium sulfate. Evaporation of solvent under reduced pressure gave **9b** (oil, 0.42 g, 98%). An analytical sample was prepared by Kugelrohr distillation: bp 82 °C (0.05 mmHg); ^{1}H NMR ($CDCl_3$) δ 0.06 (s, 6 H), 0.88 (s overlapping d at 0.90, 12 H, J = 6 Hz), 0.94–1.36 (m, 4 H), 1.46–2.22 (m, 7 H), 2.32–2.46 (m, 1 H), 3.54 (m, 1 H), 3.7 (m, 3 H); IR (film) 1740 cm^{-1}.

Anal. Calcd for $C_{17}H_{34}O_3Si$: C, 64.91; H, 10.89. Found: C, 64.83; H, 10.81.

Preparation of 2-[3-(*tert*-Butyldimethylsiloxy)cyclohexyl]-6-methyl-4-heptanone (9c). To a solution of isobutylmagnesium chloride (2 M, 2.54 mL, 5.08 mmol) in dry benzene (4 mL) was added triethylamine (1.54 g, 15.2 mmol). The resulting mixture was cooled to 10 °C and a solution of **9b** (0.399 g, 1.27 mmol) in benzene (4 mL) was added. The solution was stirred at 10 °C for 20 min and at room temperature for 7.5 h. Saturated ammonium chloride solution (2 mL) was added and the resulting mixture was extracted with ether (3 × 5 mL). The combined organic layers were washed with water (2 × 10 mL) and brine (2 × 10 mL) and dried over anhydrous magnesium sulfate. Evaporation of solvent gave an oil, which was purified by Kugelrohr distillation [bp 110 °C (0.25 mmHg)] to give **9c** (oil, 0.401 g, 93%): ^{1}H NMR ($CDCl_3$) δ 0.05 (s, 6 H), 0.78–1.02 (complex array of overlapping peaks, 18 H), 1.06–1.34 (m, 4 H), 1.34–1.58 (m, 2 H), 1.66–1.88 (m, 4 H), 1.88–2.5 (m, 5 H), 3.54 (m, 1 H); IR (film) 1710 cm^{-1}.

Anal. Calcd for $C_{20}H_{40}O_2Si$: C, 70.52; H, 11.84. Found: C, 70.40; H, 11.69.

Preparation of 3-[1-Methyl-2-[2-(2-methylpropyl)-1,3-dioxolan-2-yl]ethyl]cyclohexanol (10b). To a solution of **9c** (0.073 g, 0.21 mmol) in dry benzene (2 mL) was added ethylene glycol (0.68 g, 1.1 mmol) followed by a small crystal of *p*-toluenesulfonic acid. The mixture was heated to reflux temperature in a Dean–Stark apparatus for 48 h. The resulting solution was dissolved in ether (20 mL), washed with potassium carbonate solution (1 M, 2 × 10 mL), water (2 × 10 mL), and brine (2 × 10 mL), and dried over anhydrous magnesium sulfate. Removal of solvent under reduced pressure gave an oil, which was dissolved in dry THF (2 mL). The mixture was cooled to 0 °C, after which a solution of tetra-*n*-butylammonium fluoride in THF (1 M, 0.62 mL, 0.62 mmol) was added. The resulting solution was stirred for 18 h at room temperature, after which hexane (20 mL) was added. The reaction mixture was washed with water (2 × 10 mL) and brine (2 × 10 mL) and dried over anhydrous magnesium sulfate. Removal of solvent gave an oil (0.52 g, 91%), which was chromatographed on Florisil (hexane:ethyl acetate, 1:1) to yield **10b** (oil, 0.037 g, 65%): ^{1}H NMR ($CDCl_3$) δ 0.82–1.02 (complex array of overlapping peaks, 9 H), 1.02–2.02 (m, 16 H), 3.58 (m, 1 H), 3.92 (s, 4 H); IR (film) 3360 cm^{-1} (br).

Anal. Calcd for $C_{16}H_{30}O_3$: C, 71.06; H, 11.18. Found: C, 71.17; H, 11.23.

Preparation of 3-[1-Methyl-2-[2-(2-methylpropyl)-1,3-dioxolan-2-yl]ethyl]cyclohexane (11). A solution of **10b** (0.0218 g, 0.08 mmol) in methylene chloride (1 mL) was rapidly added to a suspension of pyridinium chlorochromate (98%, 0.031 g, 0.14 mmol) in methylene chloride (1 mL). The reaction mixture was stirred for 2 h at room temperature, after which ether (15 mL) was added. The liquid phase was decanted and the residue washed with ether (3 × 10 mL). The combined organic extracts were filtered through a short column of Florisil and evaporated to give **11** (oil, 0.020 g, 97%). An analytical sample was prepared by Kugelrohr distillation: bp 85 °C (0.05 mmHg); ^{1}H NMR ($CDCl_3$) δ 0.8–1.04 (complex array of overlapping peaks, 9 H), 1.3–1.86 (m, 5 H), 1.98–2.46 (m, 5 H), 3.93 (s, 4 H); IR (film) 1710 cm^{-1}.

Anal. Calcd for $C_{16}H_{28}O_3$: C, 71.60; H, 10.51. Found: C, 71.79; H, 10.60.

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Registry No. (±)-**1**, 16981-74-1; **2a**, 5323-87-5; (±)-**2b**, 90083-64-0; (±)-**3a**, 90083-65-1; (±)-**3b**, 90106-89-1; (±)-**4**, 90083-66-2; (±)-**5a**, 90083-67-3; (±)-**5b**, 90083-68-4; (±)-**6**, 90083-69-5; (±)-**7**, 90083-70-8; (±)-**8a**, 90130-46-4; (±)-**8b**, 90083-71-9; (±)-**9a**, 90083-72-0; (±)-**9b**, 90083-73-1; (±)-**9c**, 90083-74-2; (±)-**10a**, 90083-75-3; (±)-**10b**, 90083-76-4; (±)-**11**, 52216-63-4; $Cl(CH_2)_3I$, 6940-76-7; *i*-BuCl, 513-36-0.