Preparation of a Semisynthetic Analogue of Mevinolin and Compactin

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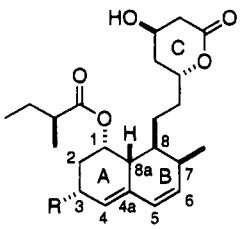
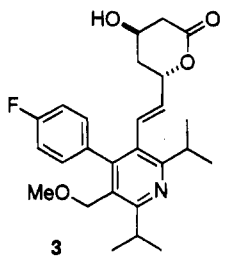
Enone **5**, derived by chemical degradation of compactin (**1**), was elaborated into the semisynthetic analogue **4**, which is an inhibitor of cholesterol biosynthesis in rat liver microsomes.

Introduction

Control of blood cholesterol levels is an important problem in medicinal chemistry, and a considerable effort has been devoted to the subject.[1] Much of the modern research has involved compactin (**1**) and mevinolin (**2**), fungal metabolites that are competitive inhibitors of HMG CoA reductase and that lower blood levels of cholesterol in humans by a sufficient amount to have become important in medical practice.[1]



1 R = H
2 R = Me



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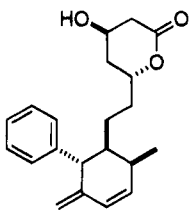

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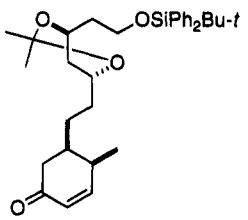

5

Many analogues of **1** and **2** have been prepared—usually by total synthesis[1,2] or by modification of the natural materials.[3] These studies have indicated that potent inhibitors of HMG CoA reductase can be made by taking the hydroxy lactone unit and attaching it by a two-carbon chain to a cyclic structure carrying an aromatic substituent in a position corresponding to C(8a) of the natural materials. For example, compound **3** (as its open hydroxy acid) is 110 times as potent an inhibitor of HMG CoA as is mevinolin.[4]

We report here the preparation of the semisynthetic analogue **4**. Our choice of this structure was based in part on the known biological activity of compounds such as **3** and in part on the fact that enone **5**, which is an advanced intermediate in our synthesis[5] of mevinolin and compactin, can also be obtained by partial degradation[6] of the natural products and should serve[7] as a starting material for the preparation of *semisynthetic* analogues. The phenyl substituent in **4** corresponds to the benzene ring in **3** (and in many other analogues), and the exocyclic olefin serves to imitate the diene chromophore of the natural products.

In elaborating **5** into **4**, we were faced with the task of introducing an aryl group α to the enone carbonyl. Several methods for α arylation of ketones have been reported,[8] but of those we tried,[8k–n] using 2-cyclohexenone as a model, only the epoxide-based approach of Marino[8n,9] was successful.

Synthetic Work

We initially converted enone **5** into epoxide **6** (Scheme 1) and then into the derived trimethylsilyl enol ether **7**. This unstable compound was treated with phenylmagnesium bromide and copper cyanide to afford the phenylated ketone **8**, with the phenyl group *syn* to the other substituents ($J_{5,6}$ = *ca.* 4 Hz). These experiments were done without full characterization of **7** or **8** because our attempts to epimerize the phenylated ketone at C(6) were unsuccessful—we could never drive the process beyond about a 1:1 mixture of the two epimers, and they were

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(1) Review: Endo, A.; Hasumi, K. *Nat. Prod. Rep.* **1993**, *10*, 541.

(2) See also: (a) Minami, T.; Hiyama, T. *Tetrahedron Lett.* **1992**, *33*, 7525. (b) Patel, D. V.; Schmidt, R. J.; Gordon, E. M. *J. Org. Chem.* **1992**, *57*, 7143. (c) Patel, D. V.; Gordon, E. M. *Bioorg. Med. Chem. Lett.* **1991**, *1*, 509. (d) Boquel, P.; Taillefumier, C.; Chapleur, Y.; Renaut, P.; Samreth, S.; Bellamy, F. D. *Tetrahedron* **1993**, *49*, 83. (e) Ermolenko, M. S.; Oleskar, A.; Lukacs, G. *Tetrahedron Lett.* **1994**, *35*, 715.

(3) E.g., (a) Karanewsky, D. S. *Tetrahedron Lett.* **1991**, *32*, 3911. (b) Askin, D.; Verhoeven, T. R.; Liu, T. M.-H.; Shinkai, I. *J. Org. Chem.* **1991**, *56*, 4929. (c) DeCamp, A. E.; Mills, S. G.; Kawaguchi, A. T.; Desmond, R.; Reamer, R. A.; DiMichele, L.; Volante, R. P. *J. Org. Chem.* **1991**, *56*, 3564.

(4) Quoted in ref 1.

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(6) Clive, D. L. J.; Zhang, C. *J. Org. Chem.* **1995**, *60*, 1413.

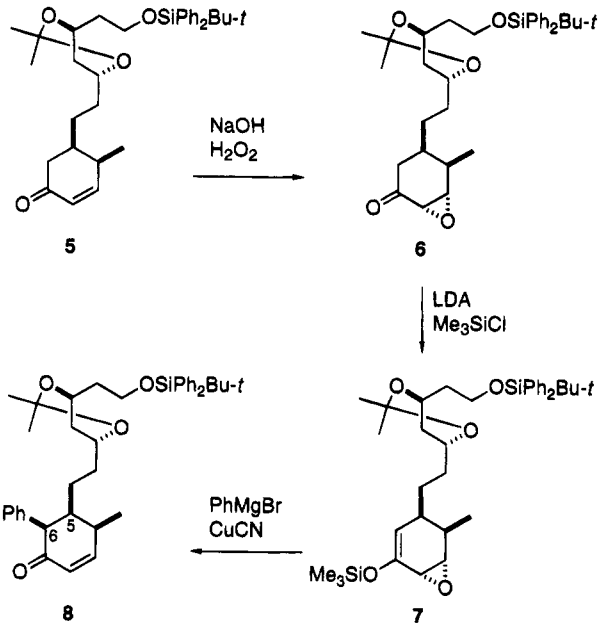
(7) *Cf.* Clive, D. L. J.; Keshava Murthy, K. S.; George, R.; Poznansky, M. J. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2099.

(8) E.g. (a) Dell'Erba, C.; Novi, M.; Petrillo, G.; Tavani, C. *Tetrahedron* **1992**, *48*, 325. (b) Rathke, M. W.; Vogiazoglou, D. *J. Org. Chem.* **1987**, *52*, 3697. (c) Heck, R. F. *J. Am. Chem. Soc.* **1968**, *90*, 5535. (d) Dell'Erba, C.; Novi, M.; Petrillo, G.; Tavani, C. *Tetrahedron* **1993**, *49*, 235. (e) Alonso, F.; Miguel, Y. *Tetrahedron* **1991**, *47*, 9119 and references therein. (f) Chen, K.; Koser, G. F. *J. Org. Chem.* **1991**, *56*, 5764. (g) Negishi, E.; Akiyoshi, K. *Chem. Lett.* **1987**, 1007. (h) RajanBabu, T. V.; Chenard, B. L.; Petti, M. A. *J. Org. Chem.* **1986**, *51*, 1704. (i) Sakakura, T.; Hara, M.; Tanaka, M. *J. Chem. Soc., Chem. Commun.* **1985**, 1545. (j) Vaillancourt, V.; Albizati, K. F. *J. Org. Chem.* **1992**, *57*, 3627. (k) Kosugi, M.; Hagiwara, I.; Sumiya, T.; Migita, T. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 242. (l) Semmelhack, M. F.; Stauffer, R. D.; Rogerson, T. D. *Tetrahedron Lett.* **1973**, 4519. (m) Barton, D. H. R.; Blazejewski, J.-C.; Charpiot, B.; Finet, J.-P.; Motherwell, W. B.; Teresa Barros Papoula, M.; Stanforth, S. P. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2667. (We applied this method after ethoxycarbonylation of 2-cyclohexenone at C-6.) (n) Marino, J. P.; Jaén, J. C. *J. Am. Chem. Soc.* **1982**, *104*, 3165.

(9) *Cf.* (a) Wender, P. A.; Erhardt, J. M.; Letendre, L. J. *J. Am. Chem. Soc.* **1981**, *103*, 2114. (b) Marshall, J. A.; Crute, T. D., III; Hsi, J. D. *J. Org. Chem.* **1992**, *57*, 115. (c) Marshall, J. A. *Chem. Rev.* **1989**, *89*, 1503.

0022-3263/95/1960-5532$09.00/0

Scheme 1

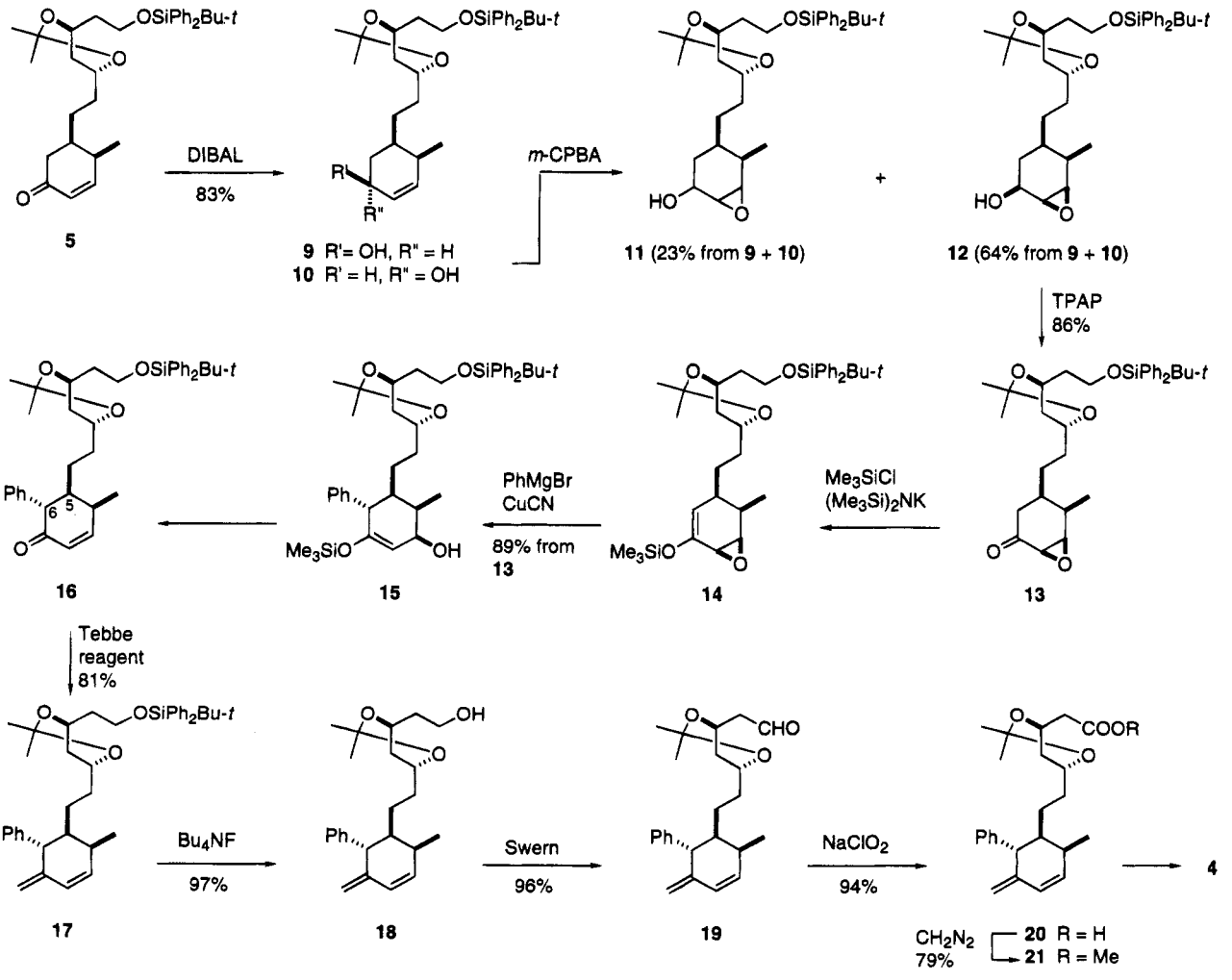


difficult to separate. However, as the cuprate addition follows a strict *anti* pathway[8n,9] with respect to the epoxide oxygen (*cf.* **7** → **8**), we were able to avoid the need for epimerization by starting with epoxide **12** (Scheme 2). This was made, as shown in Scheme 2, by a route involving DIBAL reduction (**5** → **9** + **10**) followed by epoxidation with *m*-CPBA and oxidation (**12** → **13**). The DIBAL reduction gives two epimeric alcohols, with the desired one being the major product (≥64% yield). These alcohols are easily separated after the epoxidation, which largely, if not completely, takes the normal stereochemical course, being directed by the hydroxyl group. In this particular case, the more common method—use of VO(acac)$_2$ and *t*-BuOOH—did not work; however, *m*-CPBA[10] gave satisfactory results, and the desired epoxide **12** was obtained in 64% yield from a mixture of **9** and **10**. A minor hydroxy epoxide (**11**) of undetermined stereochemistry was also isolated (23% from **9** and **10**).

Conversion of α,β-epoxy ketone **13** into the silyl enol ether **14**, followed by addition of freshly-prepared phenylmagnesium bromide and copper cyanide, led to the hydrolytically sensitive hydroxy silyl enol ether **15**. This was treated with mesyl chloride and pyridine, affording directly the required phenylated enone **16**, with the C-5 and C-6 substituents *trans* ($J_{5,6}$ = 11 Hz). From this point, olefination was most easily achieved with the Tebbe reagent (**16** → **17**), and deprotection of the primary hydroxyl in the usual way (Bu$_4$NF) then gave alcohol **18**.

Oxidation to the acid, deketalization, and closure to lactone **4** proved a little troublesome, but the following satisfactory route was eventually developed: Swern oxidation gave aldehyde **19**, and further oxidation (NaClO$_2$) led to acid **20**, which was immediately esterified with diazomethane. When the resulting ester **21** was allowed to stand in benzene containing 1 equiv of

Scheme 2



toluenesulfonic acid monohydrate the ketal was removed and the intermediate diol cyclized to the required lactone **4**.

Biological Evaluation

Compound **4** bears an obvious structural relationship to the natural products **1** and **2** and was found to inhibit cholesterol biosynthesis in rat liver microsomes. In this test[11] compound **4** has an IC_{50} of 0.54 μg/mL while compactin has an IC_{50} of 10 ng/mL.

Experimental Section

General Procedures. Unless stated to the contrary, the following conditions apply: Reactions were carried out under a slight static pressure of Ar that had been purified by passage through a column (3.5 × 42 cm) of R-311 catalyst[12] and then through a similar column of Drierite. All solvents for reactions were dried, as described below. Glassware was dried in an oven for at least 3 h before use (120 °C) and either cooled in a desiccator over Drierite or assembled quickly, sealed with rubber septa, and allowed to cool under a slight static pressure of Ar. Reaction mixtures were stirred by Teflon-coated magnetic stirring bars.

Hexane used for chromatography was distilled before use. Products were isolated from solution by evaporation under water aspirator vacuum at, or below, room temperature, using a rotary evaporator.

Microliter syringes were washed with water and acetone, using a suction device to draw the solvents through. Then air was sucked through for 1 min. The solution to be dispensed was drawn up and expelled, and this operation was repeated several times before drawing up the sample to be used. Cannula transfers were always done under slight pressure (Ar), not by suction.

Commercial thin layer chromatography (TLC) plates (silica gel, Merck 60F−254) were used. Spots were detected by spraying the plate with a solution of phosphomolybdic acid[13] or *p*-anisaldehyde,[14] followed by charring with a heat gun or by examination under UV light. Silica gel for flash chromatography was Merck type 60 (230−400 mesh).

Dry solvents were prepared under an inert atmosphere and transferred by syringe or cannula. Dry tetrahydrofuran (THF) and Et_2O were distilled from sodium and benzophenone ketyl. Dry PhH was distilled from sodium. Dry Et_3N, CH_2Cl_2, and pyridine were distilled from CaH_2.

FT-IR measurements were made as casts from the specified solvent using potassium bromide plates.

The symbols s′, d′, t′, and q′ used for ^{13}C NMR signals indicate 0, 1, 2, or 3 attached hydrogens, respectively.

Mass spectra were recorded with AEI Models MS-12, MS-50, MS9 (modified), or Kratos MS50 (modified) mass spectrometers.

Microanalyses were performed by the microanalytical laboratory of this department.

[1*S*-[1α,4α,5α(4*S,6*R**)]]-5-[2-[6-[2-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]ethyl]-2,2-dimethyl-1,3-dioxan-4-yl]-ethyl]-4-methyl-2-cyclohexen-1-ol (9).** DIBAL (1.9 mL, 1 M in CH_2Cl_2, 1.88 mmol) was added dropwise to a stirred and cooled (0 °C) solution of enone **5** (689 mg, 1.25 mmol) in dry CH_2Cl_2 (135 mL). The mixture was then transferred dropwise, using a cannula, into stirred and cooled (−78 °C) 1:2 MeOH: CH_2Cl_2 (250 mL). The cooling bath was removed, and water (100 mL) was added while the mixture was still cold (*ca.* 0 °C). The mixture was stirred vigorously for 1 h to allow a precipitate to form. The precipitate was filtered off, and the layers were separated. The organic phase was dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (4 × 25 cm), using first 1:4 EtOAc−hexane and then 3:7 EtOAc−hexane, gave a mixture of **9** and **10** (571 mg, 82%) as a colorless oil: FTIR (CH_2Cl_2 cast) 3600−3100, 1111 cm^{-1}; ^1H NMR (acetone-d_6, 400 MHz) (signals indicated by an asterisk are due to the C(1) epimer, which could not be separated) δ 0.80* (d, J = 7.2 Hz, 0.24 H), 0.84 (d, J = 7.1 Hz, 3 H), 0.98−1.32 [m, including singlets at δ 1.05 (9 H) and δ 1.30 (3 H), 15 H in all], 1.32−1.57 [m, including a singlet at δ 1.42 (3 H), 7 H in all], 1.57−1.77 (m, 4 H), 1.9* (broad s, 0.08 H), 2.10−2.20 (m, 1 H), 3.30−3.50* (m, 0.39 H), 3.65 (d, J = 6.1 Hz, 0.6 H), 3.68−3.78 (m, 1 H), 3.78−3.90 (m, 2 H), 4.05* (broad s, 0.15 H), 4.10−4.22 (m, 2 H), 5.50−5.80 (m, 2 H), 7.40−7.50 (m, 6 H), 7.68−7.78 (m, 4 H); ^{13}C NMR (acetone-d_6, 100.6 MHz) δ 13.58* (d′), 14.37 (d′), 19.56 (s′), 20.13 (d′), 27.15 (q′), 27.90* (t′), 29.24 (t′), 30.65 (q′), 32.51* (q′), 32.62 (q′), 32.93* (q′), 34.17* (t′), 34.48 (t′), 34.51 (t′), 34.84* (t′), 36.29 (q′), 38.00 (t′), 40.06 (t′), 60.30 (t′), 64.17* (d′), 66.05 (d′), 68.25 (d′), 69.58 (d′), 98.63 (s′), 128.38 (d′), 128.87* (d′), 130.36 (d′), 132.14 (d′), 134.37 (s′), 134.37* (d′), 136.06 (d′), 136.24 (d′); exact mass m/z calcd for $C_{32}H_{45}O_4Si$ (M − CH_3) 521.3087, found 521.3077.

[1*S*-[1α,2β,4β(4*S,6*R**),5β,6α]]-4-[2-[6-[2-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]ethyl]-2,2-dimethyl-1,3-dioxan-4-yl]ethyl]-5-methyl-7-oxabicyclo[4.1.0]heptan-2-ol (12) and [1*R*-[1α,2α,4α(4*R**,6*S**),5α,6α]]-4-[2-[6-[2-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]ethyl]-2,2-dimethyl-1,3-dioxan-4-yl]ethyl]-5-methyl-7-oxabicyclo[4.1.0]heptan-2-ol (11).** *m*-CPBA (346 mg, 2.00 mmol) was diluted with dry CH_2Cl_2 (68 mL) and added dropwise to a stirred and cooled (−78 °C) mixture of **9** and **10** (539 mg, 1.00 mmol) and $NaHCO_3$ (422 mg, 3.98 mmol) in dry CH_2Cl_2 (68 mL). The mixture was stirred at −78 °C for 2 h, the cold bath was removed, and stirring was continued for 14 h. The mixture was filtered, and EtOAc (100 mL) was added. The organic phase was washed with aqueous Na_2SO_3 (10%, 1 × 50 mL), saturated aqueous $NaHCO_3$ (1 × 50 mL), water (1 × 50 mL), and brine (1 × 50 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (4 × 25 cm), using first 3:7 EtOAc−hexane and then 2:3 EtOAc−hexane, gave **12** (358 mg, 64%) as a pure (^1H NMR, 200 MHz), colorless oil, and an isomer (**11**) (131 mg, 23%) as a colorless oil containing a small impurity (^1H NMR, 300 MHz). Compound **12** had: FTIR (CH_2Cl_2 cast) 3600−3200, 1111 cm^{-1}; ^1H NMR (acetone-d_6, 200 MHz) δ 0.90 (d, J = 8 Hz, 3 H), 0.95−1.60 [m, including singlets at δ 1.05 (9 H), δ 1.30 (3 H) and δ 1.41 (3 H), 25 H in all], 1.60−1.78 (m, 2 H), 2.00−2.10 (m, including acetone, 1.31 H), 3.10−3.25 (m, 2 H), 3.70−4.00 (m, 4 H), 4.05−4.30 (m, 1 H), 7.38−7.55 (m, 6 H), 7.62−7.78 (m, 4 H); ^{13}C NMR (acetone-d_6, 50.3 MHz) δ 9.55 (d′), 19.62 (s′), 20.17 (d′), 27.21 (q′), 28.21 (t′), 29.32 (q′), 30.68 (q′), 30.83 (t′), 34.91 (t′), 37.48 (q′), 38.03 (t′), 40.13 (t′), 57.63 (d′), 59.15 (d′), 60.42 (t′), 66.18 (d′), 69.60 (d′), 70.14 (d′), 98.70 (s′), 128.44 (d′), 130.42 (d′), 134.47 (s′), 136.12 (d′); exact mass m/z calcd for $C_{32}H_{45}O_5Si$ (M − CH_3) 537.3037, found 537.3032.

Compound **11** had: FTIR (CH_2Cl_2 cast) 3600−3200, 1111 cm^{-1}; ^1H NMR (acetone-d_6, 300 MHz) δ 0.80−1.45 [m, including singlets at δ 1.05 (9 H), δ 1.28 (3 H), δ 1.42 (3 H), 24 H in all], 1.45−1.55 (m, 2 H), 1.55−1.80 (m, 2 H), 2.06−2.20 (m, 1 H), 2.90−3.25 (m, 2 H), 3.25−3.45 (m, 1 H), 3.65−3.95 (m, 4 H), 3.95−4.25 (m, 2 H), 7.30−7.50 (m, 6 H), 7.65−7.80 (m, 4 H); ^{13}C NMR (acetone-d_6, 50.3 MHz) (signals indicated by an asterisk are due to a minor impurity, which could not be separated) δ 10.24* (d′), 11.37 (d′), 20.03 (s′), 20.57 (d′), 27.60 (q′), 27.94 (t′), 29.10* (t′), 30.09 (q′), 31.08 (q′), 31.85* (q′), 32.27 (q′), 32.78 (t′), 32.87* (t′), 35.10 (t′), 38.44 (t′), 40.57 (t′), 55.02 (d′), 57.72* (d′), 59.73* (d′), 60.05 (d′), 60.85 (t′), 64.65 (d′), 66.61 (d′), 66.89* (d′), 70.04 (d′), 99.12 (s′), 128.87 (d′), 130.84 (d′), 134.91 (s′), 136.56 (d′); exact mass m/z calcd for $C_{32}H_{45}O_5Si$ (M − CH_3) 537.3037, found 537.3033.

[1*R*-[1α,4β(4*R,6*S**),5β,6α]]-4-[2-[6-[2-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]ethyl]-2,2-dimethyl-1,3-dioxan-4-yl]ethyl]-5-methyl-7-oxabicyclo[4.1.0]heptan-2-one (13).** TPAP (21 mg, 0.059 mmol) was added to a stirred and cooled

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(11) Endo, A.; Kuroda, M.; Tanzawa, K. *FEBS Lett.* **1976**, *72*, 323.
(12) Supplied by Chemical Dynamics Corp., South Plainfield, NJ.
(13) Phosphomolybdic acid (15 g) and ceric ammonium sulfate (2.5 g) dissolved in a mixture of water (485 mL) and concentrated sulfuric acid (15 mL).
(14) *p*-Anisaldehyde (15 drops) were added to concentrated sulfuric acid (6 mL) and ethanol (94 mL).

(0 °C) solution of **12** (334 mg, 0.588 mmol), NMO (172 mg, 1.47 mmol), and powdered 4 Å molecular sieves (201 mg) in CH_2Cl_2 (18 mL). The cold bath was removed after 1 h, and stirring was continued for 4 h. Evaporation of the solvent and flash chromatography of the residue over silica gel (3 × 20 cm), using 1:4 EtOAc–hexane, gave **13** (289 mg, 86%) as a pure (^{1}H NMR, 200 MHz), colorless oil: FTIR (CH_2Cl_2 cast) 1718 cm^{-1}; ^{1}H NMR (acetone-d_6, 200 MHz) δ 0.78–1.25 [m, including a singlet at δ 1.05 (9 H), 14 H in all], 1.25–1.57 [m, including singlets at δ 1.30 (3 H) and δ 1.45 (3 H), 10 H in all], 1.57–1.90 (m, 3 H), 1.90–2.10 (m, 1 H), 2.30–2.42 (m, 1 H), 2.42–2.60 (dd, J = 14, 14 Hz, 1 H), 3.10–3.20 (m, 1 H), 3.55–3.65 (m, 1 H), 3.65–3.95 (m, 3 H), 4.10–4.30 (m, 1 H), 7.40–7.55 (m, 6 H), 7.60–7.80 (m, 4 H); ^{13}C NMR (acetone-d_6, 50.3 MHz) δ 9.69 (d′), 19.53 (s′), 20.06 (d′), 27.10 (q′), 28.26 (t′), 29.75 (q′), 30.56 (q′), 34.42 (t′), 37.87 (t′), 38.61 (t′), 40.01 (t′), 41.76 (q′), 55.93 (d′), 60.28 (t′), 63.23 (d′), 65.99 (d′), 69.30 (d′), 98.63 (s′), 128.34 (d′), 130.30 (d′), 134.37 (s′), 136.01 (d′), 206.65 (s′); exact mass m/z calcd for $C_{32}H_{43}O_5Si$ (M − CH_3) 535.2880, found 535.2876.

[4*S*-[4α(1α*S,4β,5β,6α),6α]]-4-[2-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]ethyl]-2,2-dimethyl-6-[2-[5-methyl-2-[(trimethylsilyl)oxy]-7-oxabicyclo[4.1.0]hept-2-en-4-yl]ethyl]-1,3-dioxolane (14).** A 1:1 mixture of Me_3SiCl and Et_3N (0.28 mmol of Me_3SiCl) was added to a stirred and cooled (−78 °C) solution of **13** (268 mg, 0.487 mmol) in THF (23 mL). $(Me_3Si)_2NLi$ (0.5 M in PhMe, 1.95 mL, 0.974 mmol) was added dropwise. The solution was stirred at −78 °C for 4 h after the addition, the cold bath was then removed, and stirring was continued for 13 h. Et_2O (50 mL) was added, and the resulting precipitate was removed by filtration through Celite (3 × 6 cm). Evaporation of the filtrate gave **14** as a colorless oil, sufficiently pure for the next step: ^{1}H NMR (acetone-d_6, 300 MHz) (significant signals only) δ 0.15–0.30, (TMS signal, 9 H), 5.1 (m, olefin signal, 1 H).

[1*R*-[1α,4β,5α(4*R,6*S**),6α]]-5-[2-[6-[2-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]ethyl]-2,2-dimethyl-1,3-dioxan-4-yl]ethyl]-6-methyl-3-[(trimethylsilyl)oxy]-4-phenyl-2-cyclohexen-1-ol (15). (a) Formation of PhMgBr.** PhBr (1.18 mL) was added dropwise to a stirred and refluxing mixture of freshly ground (mortar and pestle) Mg (233 mg, 11.22 mmol) in dry Et_2O (18 mL). After addition of PhBr the solution was refluxed for 45 min, by which time all the Mg had dissolved.

(b) Purification of CuCN. CuCN (15 g) was stirred with water (60 mL) for 19 h. The mixture was filtered, and the solid was washed with water (3 × 50 mL) and absolute EtOH (2 × 20 mL). The resulting CuCN was transferred to a round-bottomed flask with PhMe, and water was removed by evaporation with PhMe (3 × 50 mL). The solid was kept under diffusion pump vacuum for 15 h.

(c) Formation of the Cuprate. The phenylmagnesium bromide solution was added to a stirred and cooled (−42 °C) mixture of CuCN (1.01 g, 11.2 mmol) (weighed out in glovebag) in Et_2O (18 mL). The mixture was stirred for 45 min, by which stage a yellow color had appeared. (If the mixture is white it should be warmed slightly until the yellow color develops.)

(d) Conjugate Addition. PhCuCNMgBr (*ca.* 36 mL, *ca.* 11 mmol in Et_2O) (at −42 °C) was added by cannula to a stirred and cooled (−78 °C) solution of **14** (268 mg, 0.431 mmol) in dry Et_2O (18 mL). The mixture was stirred at −78 °C for 2 h, the cold bath was then removed, and stirring was continued for 18 h. Et_2O (100 mL) was added, and the organic phase was washed with saturated aqueous NH_4Cl (1 × 50 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (3 × 20 cm), using first 1:9 EtOAc–hexane and then 1:4 EtOAc–hexane, gave **15** (304 mg, 89% over two steps) as a pure (^{1}H NMR, 400 MHz), colorless oil: FTIR (CH_2Cl_2 cast) 3600–3200, 3100–3000, 1659 cm^{-1}; ^{1}H NMR (acetone-d_6, 400 MHz) δ 0.0 (s, 9 H), 0.80–1.50 [m, including a doublet at δ 0.90 (J = 7 Hz, 3 H) and singlets at δ 1.05 (9 H), δ 1.17 (3 H), δ 1.32 (3 H), 24 H in all], 1.55–1.70 (m, 2 H), 1.75–1.85 (m, 1 H), 2.07–2.20 (m, 1 H), 2.90–3.05 (m, 1 H), 3.60–3.75 (m, 3 H), 3.75–3.90 (m, 1 H), 4.00–4.15 (m, 1 H), 4.50–4.60 (m, 1 H), 4.85–4.95 (m, 1 H), 7.10–7.22 (m, 3 H), 7.22–7.30 (m, 2 H), 7.30–7.50 (m, 6 H), 7.60–7.75 (m, 4 H); ^{13}C NMR (acetone-d_6, 100.6 MHz) δ 0.20 (q′), 19.55 (s′), 19.99 (d′), 25.37 (t′), 27.16 (q′), 30.53 (two overlapping signals, d′, q′), 34.70 (t′), 35.09 (d′), 37.99 (t′), 40.01 (t′), 50.94 (q′), 60.23 (t′), 65.92 (d′), 68.87 (d′), 69.80 (two overlapping signals, d′, q′), 98.56 (s′), 109.45 (d′), 126.70 (d′), 128.35 (d′), 128.39 (d′), 129.70 (d′), 130.34 (d′), 134.37 (s′), 136.05 (d′), 143.62 (s′), 151.98 (s′); exact mass m/z calcd for $C_{41}H_{57}O_5Si_2$ (M − CH_3) 685.3745, found 685.3749.

[4*S*-[4α,5α(4*S,6*R**),6β]]-5-[2-[6-[2-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]ethyl]-2,2-dimethyl-1,3-dioxan-4-yl]ethyl]-4-methyl-6-phenyl-2-cyclohexen-1-one (16).** Pyridine (29 μL, 0.22 mmol) was added to a stirred and cooled (−78 °C) solution of **15** (*ca.* 18 mg, 0.026 mmol) in dry CH_2Cl_2 (1 mL). $MeSO_2Cl$ (15.1 μL, 0.196 mmol) was added, the mixture was stirred at −78 °C for 30 min, the cold bath was then removed, and stirring was continued for 12 h. Et_2O (25 mL) was added, and the organic phase was washed with water (25 mL), 10% aqueous $CuSO_4$ (25 mL), and saturated aqueous $NaHCO_3$ (25 mL). The organic extract was dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1 × 20 cm), using first 1:9 EtOAc–hexane and then 1:4 EtOAc–hexane and finally 3:7 EtOAc–hexane, gave **16** (14 mg, 87%) as a pure (^{1}H NMR, 360 MHz), colorless oil: FTIR (CH_2Cl_2 cast) 1678 cm^{-1}; ^{1}H NMR (acetone-d_6, 360 MHz) δ 0.90–1.50 [m, including singlets at δ 1.02 (9 H), δ 1.20 (3 H), δ 1.35 (3 H), and a doublet at δ 1.12 (J = 7.2 Hz, 3 H), 23 H in all], 1.55–1.70 (m, 2 H), 2.35–2.55 (m, 1 H), 2.70–2.82 (m, 2 H), 3.50–3.55 (d, J = 11.4 Hz, 1 H), 3.65–3.78 (m, 2 H), 3.78–3.90 (m, 1 H), 4.00–4.20 (m, 1 H), 5.90–6.00 (dd, J = 10.0, 1.5 Hz, 1 H) 7.05–7.35 (m, 6 H), 7.35–7.50 (m, 6 H), 7.65–7.75 (m, 4 H); ^{13}C NMR (acetone-d_6, 50.3 MHz) δ 12.95 (d′), 19.62 (s′), 20.14 (d′), 25.60 (t′), 27.20 (q′), 30.62 (q′), 32.06 (d′), 33.73 (t′), 38.06 (t′), 40.10 (t′), 43.29 (q′), 56.03 (q′), 60.37 (t′), 66.04 (d′), 68.88 (d′), 98.69 (s′), 127.11 (d′), 128.45 (d′), 128.59 (d′), 128.81 (d′), 130.02 (d′), 130.43 (d′), 134.51 (s′), 136.13 (d′), 140.23 (s′), 155.50 (d′), 199.05 (s′); exact mass m/z calcd for $C_{38}H_{47}O_4Si$ (M − CH_3) 595.3243, found 595.3235.

[4*R*-[4α(1α*S,2α,6β),6α]]-4-[2-(2-Methyl-5-methylene-6-phenyl-3-cyclohexen-1-yl)ethyl]-6-[2-[[(1,1-dimethylethyl)diphenylsilyl]oxy]ethyl]-2,2-dimethyl-1,3-dioxolane (17).** Commercial Tebbe reagent (0.5 M in PhMe, 0.70 mL, 0.35 mmol) was added dropwise to a stirred and cooled (−78 °C) solution of **16** (213 mg, 0.349 mmol) in dry THF (61 mL). After the addition the cold bath was removed and the mixture was stirred for 30 min. Et_2O (100 mL) was added, and then NaOH (0.1 N) was added dropwise until no more gas evolution was seen. Water (20 mL) was added, and the organic phase was dried ($MgSO_4$). Evaporation of the solvent and flash chromatography of the residue over silica gel (2.5 × 20 cm), using 5:95 EtOAc–hexane, gave **17** (178 mg, 81%) as a pure (^{1}H NMR, 200 MHz), colorless oil: FTIR (CH_2Cl_2 cast) unexceptional; ^{1}H NMR (acetone-d_6, 200 MHz) δ 0.80–1.20 [m, including a doublet at δ 0.95 (J = 7 Hz, 3 H) and a singlet at δ 1.05 (9 H), 14 H in all], 1.20–1.55 (m, including singlets at δ 1.28 (3 H) and δ 1.42 (3 H), 10 H in all], 1.55–1.75 (m, 2 H), 1.85–2.02 (m, 1 H), 2.20–2.40 (m, 1 H), 3.50–3.60 (m, 1 H), 3.62–3.95 (m, 3 H), 4.02–4.25 (m, 1 H), 4.50–4.60 (broad s, 1 H), 4.95–5.05 (broad s, 1 H), 5.65–5.80 (m, 1 H), 6.20–6.35 (m, 1 H), 7.10–7.35 (m, 5 H), 7.35–7.50 (m, 6 H), 7.65–7.78 (m, 4 H); ^{13}C NMR (acetone-d_6, 100.6 MHz) δ 16.13 (d′), 19.68 (s′), 20.23 (d′), 24.31 (t′), 27.26 (q′), 30.74 (two overlapping signals, d′, q′), 34.76 (t′), 38.22 (t′), 40.21 (t′), 43.84 (q′), 48.95 (q′), 60.48 (t′), 66.19 (d′), 69.61 (d′), 98.74 (s′), 115.10 (t′), 126.70 (d′), 128.48 (d′), 128.79 (d′), 129.19 (d′), 129.52 (d′), 130.45 (d′), 134.58 (s′), 135.47 (d′), 136.20 (d′), 144.72 (s′), 145.91 (s′); exact mass m/z calcd for $C_{39}H_{49}O_3Si$ (M − CH_3) 593.3451, found 593.3451.

[4*S*-[4α,6α(1α*R,2α,6β)]]-2-[6-[2-(2-Methyl-5-methylene-6-phenyl-3-cyclohexen-1-yl)ethyl]-2,2-dimethyl-1,3-dioxan-4-yl]ethanol (18).** TBAF (1 M in THF, 0.77 mL, 0.77 mmol) was added to a stirred and cooled (−78 °C) solution of **17** (171 mg, 0.273 mmol) in dry THF (36 mL). The cold bath was removed after 30 min, and the mixture was stirred for 16 h and then partitioned between Et_2O (100 mL) and water (100 mL). The organic phase was dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 × 25

cm), using 3:7 EtOAc–hexane, gave **18** (99 mg, 97%) as a pure (^{1}H NMR, 200 MHz), colorless oil: FTIR (CH_2Cl_2 cast) 3600–3200 cm^{-1}; ^{1}H NMR (acetone-d_6, 200 MHz) δ 0.80–1.70 [m, including a doublet at δ 0.95 (J = 7 Hz, 3 H) and singlets at δ 1.25 (3 H) and δ 1.40 (3 H), 17 H in all], 1.85–2.00 (m, 1 H), 2.20–2.38 (m, 1 H), 3.30–3.40 (dd, J = 4.8, 4.8 Hz, 1 H), 3.50–3.70 (m, 3 H), 3.70–3.90 (m, 1 H), 3.95–4.12 (m, 1 H), 4.50–4.58 (broad s, 1 H), 4.95–5.05 (broad s, 1 H), 5.65–5.75 (m, 1 H), 6.20–6.35 (dd, J = 10.0, 2.5 Hz, 1 H), 7.10–7.35 (m, 5 H); ^{13}C NMR (acetone-d_6, 50.3 MHz) δ 16.06 (d′), 20.20 (d′), 24.32 (t′), 30.75 (two overlapping signals, d′, q′), 34.76 (t′), 38.15 (t′), 40.32 (t′), 43.82 (q′), 48.98 (q′), 59.05 (t′), 67.51 (d′), 69.62 (d′), 98.77 (s′), 115.05 (t′), 126.72 (d′), 128.82 (d′), 129.22 (d′), 129.53 (d′), 135.52 (d′), 144.76 (s′), 146.02 (s′); exact mass m/z calcd for $C_{23}H_{31}O_3$ (M − CH_3) 355.2273, found 355.2279.

[4*R*-[4α,6α(1α*S,2α,6β)]]-[6-[2-(2-Methyl-5-methylene-6-phenyl-3-cyclohexen-1-yl)ethyl]-2,2-dimethyl-1,3-dioxan-4-yl]ethanal (19).** DMSO (37 μL, 0.52 mmol) was added to a stirred and cooled (−78 °C) solution of $(COCl)_2$ (30 μL, 0.34 mmol) in CH_2Cl_2 (3.7 mL). After 10 min, alcohol **18** (*ca.* 28.7 mg, 0.077 mmol) in dry CH_2Cl_2 (3.7 mL, plus 1.7 mL as a rinse) was added. The mixture was stirred for 20 min, and Et_3N (0.19 mL) was added. After 10 min the cold bath was removed and then the mixture was stirred for an additional 20 min. Water (eight drops) and Et_2O (50 mL) were added. The organic phase was dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1 × 15 cm), using 3:7 EtOAc–hexane, gave **19** (*ca.* 27.4 mg, 96%) as a pure (^{1}H NMR, 400 MHz), colorless oil: FTIR (CH_2Cl_2 cast) 2871, 2726, 1726 cm^{-1}; ^{1}H NMR (acetone-d_6, 400 MHz) δ 0.80–1.65 [m, including a doublet at δ 0.96 (J = 7.3 Hz, 3 H) and singlets at δ 1.28 (3 H) and δ 1.43 (3 H), 15 H in all], 1.85–2.0 (m, 1 H), 2.25–2.38 (m, 1 H), 2.38–2.50 (m, 2 H), 3.50–3.60 (d, J = 7 Hz, 1 H), 3.80–3.90 (m, 1 H), 4.40–4.60 (m and broad s at δ 4.55, 2 H), 4.95–5.05 (broad s, 1 H), 5.65–5.75 (m, 1 H), 6.20–6.30 (dd, J = 9.8, 2.1 Hz, 1 H), 7.15–7.23 (m, 3 H), 7.23–7.35 (m, 2 H), 9.65–9.73 (broad s, 1 H); ^{13}C NMR (acetone-d_6, 100.6 MHz) δ 16.03 (d′), 20.08 (d′), 24.25 (t′), 30.48 (d′), 30.76 (q′), 34.59 (t′), 37.57 (t′), 43.75 (q′), 48.92 (q′), 50.48 (t′), 65.49 (d′), 69.46 (d′), 99.10 (s′), 115.09 (t′), 126.78 (d′), 128.87 (d′), 129.26 (d′), 129.54 (d′), 135.52 (d′), 144.76 (s′), 146.04 (s′), 201.42 (d′); exact mass m/z calcd for $C_{24}H_{32}O_3$ 368.2351, found 368.2344.

[4*R*-[4α,6α(1α*S,2α,6β)]]-[6-[2-(2-Methyl-5-methylene-6-phenyl-3-cyclohexen-1-yl)ethyl]-2,2-dimethyl-1,3-dioxan-4-yl]ethanoic acid (20).** $NaClO_2$·$2H_2O$ (1 g) and NaH_2PO_4 (1 g) were dissolved in water (10 mL) just prior to use. An aliquot (0.41 mL) of this oxidizing solution was added to a stirred and cooled (0 °C) solution of aldehyde **19** (19 mg, 0.052 mmol) in *t*-BuOH (2.1 mL) containing 2-methyl-2-butene (0.52 mL). The cold bath was removed after 10 min, and the mixture was stirred for 1 h. Saturated aqueous NH_4Cl (20 drops) and Et_2O (25 mL) were added. The organic phase was dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1 × 20 cm), using first EtOAc and then 2:3 MeOH-EtOAc, gave **20** (*ca.* 18.7 mg, 94%) as a pure (^{1}H NMR, 400 MHz), colorless oil: FTIR (CH_2Cl_2 cast) 3600–2400, 1710 cm^{-1}; ^{1}H NMR (acetone-d_6, 400 MHz) δ 0.90–1.55 [m, including a doublet at δ 0.95 (J = 7.3 Hz, 3 H) and singlets at δ 1.25 (3 H) and δ 1.40 (3 H), 15 H in all], 1.55–1.65 (m, 1 H), 1.85–2.0 (m, 1 H), 2.25–2.45 (m, 3 H), 3.50–3.60 (broad d, J = 6.9 Hz, 1 H), 3.75–3.90 (m, 1 H), 4.20–4.35 (m, 1 H), 4.45–4.60 (broad s, 1 H), 4.95–5.05 (broad s, 1 H), 5.65–5.75 (m, 1 H), 6.20–6.30 (dd, J = 9.8, 2.0 Hz, 1 H), 7.10–7.20 (m, 3 H), 7.20–7.35 (m, 2 H); ^{13}C NMR (acetone-d_6, 100.6 MHz) δ 16.09 (d′), 20.21 (d′), 24.32 (t′), 30.61 (q′), 30.76 (d′), 34.70 (t′), 37.69 (t′), 42.40 (t′), 43.75 (q′), 48.94 (q′), 67.04 (d′), 69.47 (d′), 99.00 (s′), 115.11 (t′), 126.76 (d′), 128.86 (d′), 129.26 (d′), 129.54 (d′), 135.56 (d′), 144.78 (s′), 146.05 (s′), 172–174 (broad s′); exact mass m/z calcd for $C_{23}H_{29}O_4$ (M − CH_3) 369.2066, found 369.2046.

Methyl [4*R*-[4α,6α[1α*S,2α,6β]]]-[6-[2-(2-Methyl-5-methylene-6-phenyl-3-cyclohexen-1-yl)ethyl]-2,2-dimethyl-1,3-dioxan-4-yl]ethanoate (21).** Ethereal CH_2N_2 (0.15 M, 1 mL) was added to a stirred solution of **20** (*ca.* 2.3 mg, 0.006 mmol) in Et_2O (1 mL). More ethereal CH_2N_2 (*ca.* 0.15 M) was added until all the starting material had reacted (TLC control, silica, 5:95 MeOH–EtOAc). Evaporation of the solvent and flash chromatography of the residue over silica gel (0.5 × 6 cm), using 1:9 EtOAc–hexane, gave **21** (*ca.* 1.9 mg, 79%) as a pure (^{1}H NMR, 300 MHz), colorless oil: FTIR (CH_2Cl_2 cast) 1741 cm^{-1}; ^{1}H NMR (acetone-d_6, 400 MHz) δ 0.90–1.60 [m, including a doublet at δ 0.95 (J = 7.3 Hz, 3 H) and singlets at δ 1.25 (3 H) and δ 1.40 (3 H), 15 H in all], 1.85–2.00 (m, 1 H), 2.25–2.35 (m, 1 H), 2.35–2.45 (d, J = 6.4 Hz, 2 H), 3.50–3.65 [m, including a singlet at δ 3.60 (3 H), 4 H in all], 3.75–3.90 (m, 1 H), 4.20–4.35 (m, 1 H), 4.50–4.60 (broad s, 1 H), 4.95–5.05 (broad s, 1 H), 5.65–5.75 (m, 1 H), 6.20–6.30 (dd, J = 9.9, 2.2 Hz, (1 H)), 7.10–7.23 (m, 3 H), 7.23–7.35 (m, 2 H); ^{13}C NMR (acetone-d_6, 100.6 MHz) δ 16.03 (d′), 20.04 (d′), 24.26 (t′), 30.52 (q′), 30.77 (d′), 34.64 (t′), 37.45 (t′), 41.82 (t′), 43.77 (q′), 48.94 (q′), 51.53 (q′), 66.79 (d′), 69.44 (d′), 99.05 (s′), 115.08 (t′), 126.78 (d′), 128.87 (d′), 129.27 (d′), 129.55 (d′), 135.55 (d′), 144.80 (s′), 146.00 (s′), 171.54 (s′); exact mass m/z calcd for $C_{25}H_{34}O_4$ 398.2457, found 398.2451.

[4*R*-*trans*-[1α*S,2α,6β]]-6-[2-(2-Methyl-5-methylene-6-phenyl-3-cyclohexen-1-yl)ethyl]tetrahydro-4-hydroxy-2*H*-pyran-2-one (4).** PhH (4.05 mL) was added to **21** (*ca.* 7.7 mg, 0.020 mmol) and TsOH·H_2O (*ca.* 3.7 mg, 0.020 mmol). The mixture was stirred at room temperature for 6 h. $NaHCO_3$ (5 mg) was added, followed by EtOAc (25 mL) and water (10 mL). The mixture was stirred briefly, and the organic phase was dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1 × 15 cm), using 1:1 EtOAc–hexane, gave **4** (*ca.* 3.8 mg, 60%) as a pure (^{1}H NMR, 300 MHz), colorless oil: FTIR (CH_2Cl_2 cast) 3600–3200, 1709 cm^{-1}; ^{1}H NMR (acetone-d_6, 400 MHz) δ 0.80–1.80 [m, including a doublet at δ 1.0 (J = 7.3 Hz, 3 H), 9 H in all], 1.80–2.02 (m, 2 H), 2.25–2.40 (m, 1 H), 2.40–2.70 (m, 2 H), 3.55–3.65 (d, J = 6.6 Hz, 1 H), 4.20–4.35 (broad s, 1 H), 4.50–4.60 (m, 2 H), 4.95–5.05 (broad s, 1 H), 5.65–5.80 (m, 1 H), 6.20–6.35 (dd, J = 9.8, 2.1 Hz, 1 H), 7.10–7.40 (m, 5 H); ^{13}C NMR (acetone-d_6, 100.6 MHz) δ 16.11 (d′), 24.89 (t′), 30.92 (q′), 34.22 (t′), 36.81 (t′), 39.38 (t′), 44.17 (d′), 49.01 (d′), 63.12 (d′), 76.64 (d′), 115.18 (t′), 126.87 (d′), 128.95 (d′), 129.30 (d′), 129.60 (d′), 135.46 (d′), 144.67 (s′), 145.90 (s′), 170.23 (s′); exact mass m/z calcd for $C_{21}H_{26}O_3$ 326.1882, found 326.1880.

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Supporting Information Available: NMR spectra for compounds that were not analyzed (13 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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