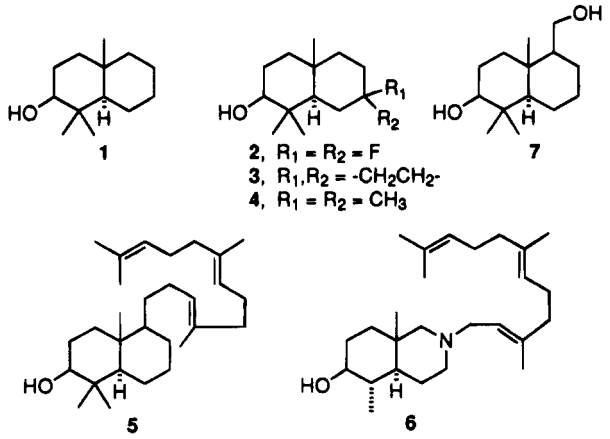
Syntheses of 9β-(Hydroxymethyl)-4,4,10β-trimethyl-*trans*-decal-3β-ol

Brian J. Lavey, John G. Westkaemper, and Thomas A. Spencer*

Department of Chemistry, Dartmouth College, Hanover, New Hampshire 03755

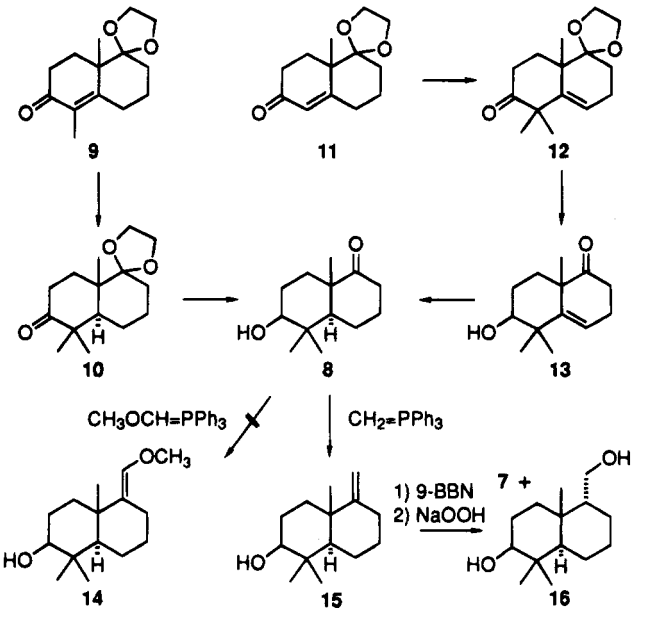
Received May 9, 1994

Since the discovery that 4,4,10β-trimethyl-*trans*-decal-3β-ol (TMD, **1**) is an effective specific inhibitor of the enzymatic cyclization of squalene 2,3(*S*)-oxide to lanosterol in rat liver homogenates[1] and in Chinese hamster ovary cells,[2] this compound has proved to be a valuable research tool in various biological media in a large number of laboratories.[3] TMD itself is ineffective in whole animals[4] or in primary rat hepatocytes,[5] due to rapid metabolism by hydroxylation at C7,[5,6] but this problem has been circumvented by preparation of the C7-disubstituted derivatives **2**, **3**, and **4**.[7,8] In order to try to enhance the potency of this type of oxidosqualene cyclase inhibitor, it was desired to prepare compounds such as **5**, containing what could be considered the remainder of the squalene 2,3(*S*)-oxide structure, if one assumes that **1** acts as an inhibitor because it resembles the first two rings of a partially formed steroid. Such an approach has proved fruitful in the case of **6**, which is a more effective inhibitor than analogues without the farnesyl side chain.[9] In order to prepare **5** or similar compounds, TMD derivatives with functionality at C9 were required. This paper describes two syntheses of one such intermediate, 9β-(hydroxymethyl)-TMD (**7**).



Two disparate approaches to decalins with appropriate substitution patterns for the synthesis of **5** have been described, and both of these were applied to the preparation of **7**.[10] The first approach, outlined in Scheme 1, proceeding via Robinson annulations of 2-methylcyclohexane-1,3-dione, has been used by three groups to prepare hydroxy ketone **8**. Watt and Stotter[11] employed reductive methylation of **9** to **10** as the key step in their preparation of **8**, whereas Ireland[12] and de Groot[13] used dimethylation of **11** to **12**, followed by direct or indirect reduction of the double bond to afford **8**. Watt and Stotter[11] encountered difficulties with Ireland's route,[12] and de Groot[13] reported problems with both the Ireland and Watt–Stotter pathways. We had similar frustrations with both routes but finally settled on Ireland's[12] as the most convenient preparation of **8**, although, as previously described,[11] the catalytic reduction of **13** yielded far less than the 80% of **8** reported by Ireland,[12] affording us a mixture from which 48% of **8** was isolable, along with 27% of the *cis*-decalin isomer and 12% of a diol.

Scheme 1

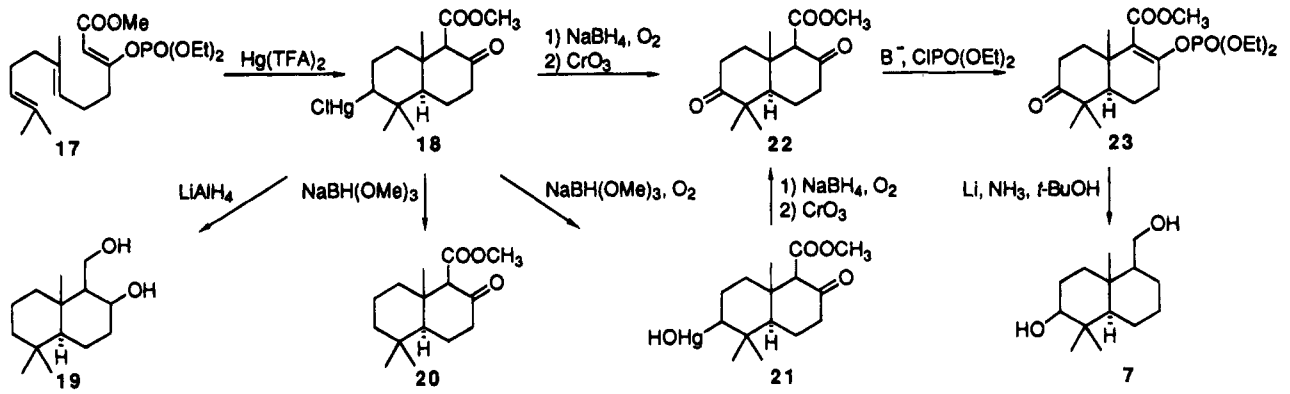


Incorporation of the C9 hydroxymethyl side chain of **7** was first attempted by reaction of **8** with excess (methoxymethylene)triphenylphosphorane, but none of the desired **14** could be obtained, even by use of a procedure reported to succeed with a comparably hindered ketone.[14] On the other hand, a procedure for Wittig methylenation

(1) Nelson, J. A.; Czarny, M. R.; Spencer, T. A.; Limanek, J. S.; McRae, K. R.; Chang, T. Y. *J. Am. Chem. Soc.* **1978**, *100*, 4900.
(2) Chang, T. Y.; Schiavoni, E. S., Jr.; McRae, K. R.; Nelson, J. A.; Spencer, T. A. *J. Biol. Chem.* **1979**, *254*, 11258.
(3) Relatively recent selected examples: (a) Popjak, G.; Meenan, A. *Proc. R. Soc. London* **1987**, *B231*, 391. (b) Burki, E.; Logel, J.; Sinensky, M. *J. Lipid Res.* **1987**, *28*, 1199. (c) Cadigan, K. M.; Heider, J. G.; Chang, T. Y. *J. Biol. Chem.* **1988**, *263*, 274. (d) Lange, Y.; Muraski, M. F. *J. Biol. Chem.* **1988**, *263*, 9366. (e) Panini, S. R.; Schnitzer-Polokoff, R.; Spencer, T. A.; Sinensky, M. *J. Biol. Chem.* **1989**, *264*, 11044. (f) Wyne, K. L.; Schreiber, J. R.; Larsen, A. L.; Getz, G. S. *J. Biol. Chem.* **1989**, *264*, 16530. (g) Panini, S. R.; Everson, G. T.; Spencer, T. A. *J. Lipid Res.* **1991**, *32*, 1657. (h) van den Koedijk, C. D. M. A.; vis van Heemst, C.; Elsendoorn, G. M.; Thijssen, J. H. H.; Blankenstein, M. A. *Biochem. Pharmacol.* **1992**, *43*, 2511.
(4) Feingold, K.; Erickson, S. K.; Siperstein, M. D.; Spencer, T. A. Unpublished results.
(5) Panini, S. R.; Miller, S.; Lutz, R.; Sinensky, M.; Spencer, T. A. Unpublished results.
(6) Nelson, J. A.; Czarny, M. R.; Spencer, T. A. *Bioorganic Chem.* **1982**, *11*, 371.
(7) Raveendranath, P. C.; Newcomb, L. F.; Ray, N. C.; Clark, D. S.; Spencer, T. A. *Synth. Comm.* **1990**, *20*, 2723.
(8) Sinensky, M.; Spencer, T. A. Squalene Oxide Cyclase Inhibitors and Therapeutic Use Thereof, U.S. Patent 4 863 932.
(9) Taton, M.; Benveniste, P.; Rahier, A.; Johnson, W. S.; Liu, H.; Sudhakar, A. R. *Biochemistry* **1992**, *31*, 7892.
(10) Falck et al. (Falck, J. R.; Chandrasekar, S.; Manna, S.; Chiu, C.-C. S.; Mioskowski, C.; Wetzel, I. *J. Am. Chem. Soc.* **1993**, *115*, 11606) have recently reported a novel route to analogues of **7** bearing a C8 methyl group via thermolysis of 18β-glycyrrhetinic acid.
(11) Snitman, D. L.; Tsai, M.-Y.; Watt, D. S.; Edwards, C. L.; Stotter, P. L. *J. Org. Chem.* **1979**, *44*, 2838.
(12) Ireland, R. E. *Organic Synthesis*; Prentice-Hall: Englewood Cliffs, NJ, 1969; pp 40–44, 50–52.
(13) Reuvers, J. T. A.; de Groot, A. *J. Org. Chem.* **1984**, *49*, 1110.
(14) Danishefsky, S.; Nagasawa, K.; Wang, N. *J. Org. Chem.* **1975**, *40*, 1989.

0022-3263/94/1959-5492$04.50/0

Scheme 2



of hindered ketones[15] worked well, affording 72% of **15** from **8**. It was hoped that oxidative hydroboration of **15** with 9-BBN would proceed highly selectively from the apparently less hindered α face of **15**, but only a 2:1 ratio of **7** to **16** was realized. Assignment of the 9β stereochemistry to **7** was made by observation of NOE enhancement of the signal for the methylene protons of the C9 substituent upon irradiation of the C10 angular methyl group.

The second approach to synthesis of **7**, shown in Scheme 2, had as its key step the known mercuric ion catalyzed cyclization of enol phosphate **17** to form **18**,[16] which has already been used as an intermediate in natural product synthesis after reduction[16] or elimination[17,18] of mercury. Preparation of **17**[19] and its cyclization to **18**[16] proceeded as described, and the identity of **18** was confirmed by its $LiAlH_4$ reduction in 64% yield to known diol **19**.[20] Application of Whitesides procedure[21] for converting organomercuric halides to alcohols by treatment with $NaBH_4$ in oxygen-saturated DMF would serve to introduce the required C3 functionality into **18** but would also reduce the C8 carbonyl group. To try to maintain distinction among the three functional groups of **18**, efforts were made to develop a procedure for converting the C3 mercuric chloride group to a hydroxyl group by use of sodium trimethoxyborohydride, a reducing agent which had been shown to reduce organomercurials without affecting carbonyl groups,[22] in an oxygen atmosphere. Reduction of **18** with $NaBH(OMe)_3$ in an oxygen-free environment did indeed afford 77% of known[20,23,24] keto ester **20**, but the same procedure in the presence of oxygen gave what appears to be hydroxymercurio derivative **21** as the major product, probably as a consequence of trapping by oxygen of an organomercury radical intermediate.[25]

Application of the standard Whitesides procedure[21] to **18** gave, as expected, a complex mixture of stereoisomeric diols, which was treated with Jones reagent to afford 63% of **22** from **18**, plus 14% of **20**. Diketo ester **22** was also obtained by application of the same sequence to **21**. Completion of this second synthesis of **7** was then readily accomplished by conversion of **22** to its enol phosphate **23** in 77% yield, followed by Li/NH_3 reduction to an 8:1 mixture of **7** and **16** in 85% yield. The overall yield of **7** from methyl acetoacetate in six steps by this route is 19%, and intermediate diketo ester **22** should be a versatile intermediate for the preparation of other TMD analogues substituted at C7, C8, or C9.

Experimental Section

NMR spectra were run at 300 MHz. ^1H NMR chemical shifts are reported in δ units from TMS and ^{13}C chemical shifts are reported in δ units from the center $CDCl_3$ peak which is referenced at 77.0 ppm. All NMR spectra were run in $CDCl_3$ unless otherwise noted. When ^{13}C NMR spectra are reported, a "d" or "u" indicates that an attached proton test was done; d (down) indicates that the carbon is 1° or 3° while u (up) indicates that it is 2° or 4°. IR spectra are referenced to the 1601 cm^{-1} peak of polystyrene. Melting point determinations were made in open capillaries and are uncorrected. All chromatography was flash,[26] using hexane:ethyl acetate mixtures as eluent, on EM Reagent silica gel 60 (230–400 mesh). TLC plates were coated with 0.25 mm layers of silica gel 60 F254. THF and Et_2O were distilled from sodium/benzophenone ketyl, nitromethane from $CaCl_2/CaH_2$, and *tert*-butyl alcohol from CaH_2 under an atmosphere of nitrogen. DMF was distilled from BaO onto activated 4-Å molecular sieves at aspirator pressure. Unless otherwise noted, all reaction solvents were distilled immediately before use and all workup solvents were used as supplied. All reactions were magnetically stirred. Slow additions were carried out by using a syringe pump. All reagents were purchased from Aldrich except anhydrous ammonia from Matheson and $NaBH_4$ from Alfa. Brine refers to a saturated aqueous solution of sodium chloride. *n*-Butyllithium was titrated against diphenylacetic acid before use. Unless otherwise noted, all reagents were used as received. Elemental analyses were performed by Atlantic Microlab, Inc.

9-Oxo-4,4,10β-trimethyl-*trans*-decal-3β-ol (8). To 5 mL of acetic acid were added 0.371 g of 5% palladium on carbon and 2.27 g (10.8 mmol) of 4,4,10β-trimethyl-8-oxo-$\Delta^{5,6}$-decal-3β-ol (**13**), which had been prepared from 2-methylcyclohexane-1,3-dione by the route described by Ireland.[12] This mixture was

(15) Sharma, A. S.; Gayen, A. K. *Tetrahedron* **1985**, *41*, 4581.
(16) Corey, E. J.; Tius, M. A.; Das, J. *J. Am. Chem. Soc.* **1980**, *102*, 7612.
(17) McMurry, J. E.; Erion, M. D. *J. Am. Chem. Soc.* **1985**, *107*, 2712.
(18) Nicolaou, K. C.; Kubota, S.; Li, W. S. *J. Chem. Soc., Chem. Commun.* **1989**, 512.
(19) Huckin, S. N.; Weiler, L. *J. Am. Chem. Soc.* **1974**, *96*, 1082. Sum, F.; Weiler, L. *Can. J. Chem.* **1979**, *57*, 1431.
(20) Stadler, P. A.; Nechvatal, A.; Frey, A. J.; Eschenmoser, A. *Helv. Chim. Acta* **1957**, *151*, 1373.
(21) Hill, C. L.; Whitesides, G. M. *J. Am. Chem. Soc.* **1974**, *96*, 870.
(22) Danishefsky, S.; Chackalamannil, S.; Uang, B.-J. *J. Org. Chem.* **1982**, *47*, 2231.
(23) Skeean, R. W.; Trammell, G. L.; White, J. D. *Tetrahedron Lett.* **1976**, 525. White, J. D.; Skeean, R. W.; Trammell, G. L. *J. Org. Chem.* **1985**, *50*, 1939.
(24) Liapis, M.; Ragoussis, V.; Ragoussis, N. *J. Chem. Soc., Perkin Trans. 1* **1985**, 815.
(25) The mechanism of hydride reduction of organomercurials has been reviewed by Barluenga, J.; Yus, M. *Chem. Rev.* **1988**, *88*, 487. The intermediacy of organomercury radicals in a chain mechanism was proposed by Whitesides, G. M.; San Filippo, J., Jr. *J. Am. Chem. Soc.* **1970**, *92*, 6611. The formation of **21** suggests that there may be an increased concentration of $RHg^{\bullet}$ when the weaker reducing agent $NaBH(OMe)_3$ is used rather than $NaBH_4$.
(26) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

hydrogenated at atmospheric pressure for 28 h, when gas absorption had ceased. The solution was filtered through Celite, which was then washed several times with MeOH. The MeOH and acetic acid were removed by vacuum distillation. The residue was chromatographed to afford first 0.610 g (27%) of 4,4,10β-trimethyl-9-oxo-*cis*-decal-3β-ol, mp 119–130 °C (lit.[27] mp 138–139 °C; lit.[28] mp 134–135 °C; ^{1}H NMR 3.3 (m, 1H), 2.4 (m, 2H), 2.2–1.7 (m, 6H), 1.6–1.2 (m, 4H), 1.25 (s, 3H), 1.0 (s, 3H), 0.8 (s, 3H); ^{13}C NMR 216.9, 77.5, 48.2, 47.9, 38.6, 36.4, 29.4, 27.3, 27.1, 25.8, 24.9, 24.3, 20.0. Next eluted was 0.419 g of a mixture of this *cis* isomer and **8**, followed by 0.831 g (36%) of **8**: mp 71.5–72.5 °C (lit.[11] mp 72–73 °C) after recrystallization from hexane; IR 3540, 1695 cm^{-1} (lit.[11] 3600, 1695 cm^{-1}); ^{1}H NMR 3.18 (m, 1H), 2.55 (td, 1H), 2.2 (m, 1H), 2.05 (m, 1H), 1.8–1.5 (m, 8H), 1.13 (s, 3H), 1.01 (s, 3H), and 0.88 (s, 3H) (lit.[11] 3.22 (m, 1H), 1.16 (s, 3H), 1.04 (s, 3H), 0.91 (s, 3H)); ^{13}C NMR 215.3, 78.1, 52.6, 48.6, 39.7, 37.4, 31.2, 27.9, 26.9, 26.2, 20.7, 18.6, 15.8. The 0.419 g of isomeric mixture was rechromatographed to give another 0.276 g of **8**, bringing the total yield to 1.11 g (48%; 8.4% overall from 2-methylcyclohexane-1,3-dione).

Finally, there was eluted 0.276 g (12%) of (presumably) 4,4,-10β-trimethyl-*trans*-decalin-3β,9β-diol, mp 175–177 °C. After one recrystallization from hexane:EtOAc, this diol had mp 178.5–179.0 °C (lit.[29] mp 180–182 °C); IR 3380 cm^{-1}; ^{1}H NMR 3.24–3.16 (dd, 1H), 3.14–3.06 (dd, 1H), 1.9–1.0 (m, 11H), 0.96 (s, 3H), 0.85 (s, 3H), 0.78 (s, 3H); ^{13}C NMR ($CDCl_3$) 80.8, 78.9, 51.6, 39.2, 38.7, 35.8, 30.2, 28.0, 27.1, 24,7, 20.7, 15.5, 12.2.

8-Methylidene-4,4,10β-trimethyl-*trans*-decal-3β-ol (15). To 0.788 g of 60% NaH (19.7 mmol), which had been washed 3 times with hexane and blown dry with N_2, were added 80 mL of dry THF and 8.13 g (20.1 mmol) of methyltriphenylphosphonium iodide. The mixture was stirred overnight and then the yellow solution was heated at 50 °C for 90 min. The solution was transferred under N_2 via cannula into another dry flask, with care being taken not to transfer the precipitate. The THF was removed first by distillation at rt first at atmospheric pressure and then in vacuo. The residue was dried for 90 min at 0.5 Torr and dissolved in 60 mL of benzene with warming. To a solution of 0.206 g (0.98 mmol) of **8** in 8 mL of benzene was added a 15-mL portion of the ylide solution dropwise over 1 h. TLC indicated that a little **8** remained so an additional 15 mL of the ylide solution was added over 15 min. The solution was stirred for another 15 min and cooled to rt, and excess ylide was decomposed by the addition of 5 mL of acetone. The solvents were evaporated and the residue was chromatographed to afford 0.146 g (72%) of **15**, mp 96–98 °C. Two recrystallizations from hexane and sublimation at 0.35 Torr and 57 °C yielded **15**: mp 99.8–100.0 °C; IR 3350, 1635, 890 cm^{-1}; ^{1}H NMR 4.5 (bs, 2H), 3.25–3.15 (dd, 1H), 2.35–2.20 (td, 1H), 2.15–2.05 (m, 1H), 2.0–1.1 (m, 10H), 1.05 (s, 3H), 0.95 (s, 3H), and 0.80 (s, 3H); ^{13}C NMR 159.7, 102.8, 78.9, 53.1, 39.7, 39.4, 35.3, 32.9, 28.6, 28.1, 27.7, 21.9, 20.7, and 15.4. Anal. Calcd for $C_{14}H_{24}O$: C, 80.71; H, 11.61. Found: C, 80.41; H, 11.71.

9β-(Hydroxymethyl)-4,4,10β-trimethyl-*trans*-decal-3β-ol (7). To 0.765 g (3.67 mmol) of **15** were added 2 mL of THF and then 22 mL (11 mmol) of a 0.5 M solution of 9-BBN in THF dropwise over 1 h under N_2. Evolution of gas was observed during the addition of the first 10 mL of solution. The mixture was stirred for 3 h, after which time 3 mL of 3 M NaOH solution was added slowly with evolution of gas. The mixture was cooled to 0 °C, 3 mL of 30% hydrogen peroxide was added dropwise, and the solution was stirred for 30 min, after which time solid K_2CO_3 was added to saturate the aqueous phase. The aqueous layer was extracted with 3 × 10 mL of Et_2O. The organic layers were combined, washed with 25 mL of brine, dried over $MgSO_4$, and evaporated to give an oily residue which was chromatographed to afford 0.699 g (84%) of a *ca.* 2:1 mixture of **7** and **16** (based on integration of ^{1}H NMR methyl peaks, *e.g.* δ 1.01 for **16** vs δ 0.97 for **7**): mp 141–148 °C; IR 3320 cm^{-1}; MS *m/z* 226; inseparable by TLC. Five recrystallizations from hexane: ethyl acetate gave essentially pure **7**: mp 161–163 °C. An analytical sample of **7** prepared by recrystallization from hexane: EtOAc had mp 162–163.5 °C: ^{1}H NMR 3.81 (dd, *J* = 10.2, 3.9 Hz, 1H), 3.25 (m, 2H), 2.0–1.7 (m, 2H), 1.7–1.5 (m, 4H), 1.4–1.0 (m, 6H), 0.97 (s, 3H), 0.82 (s, 3H), 0.79 (s, 3H); ^{13}C NMR δ 78.8, 63.5, 54.2, 53.6, 38.9, 37.4, 36.6, 28.2, 27.4, 26.8, 25.3, 21.6, 15.5, 14.5. Irradiation of the peak at 0.97 gave NOE difference peaks at 3.2, 1.6, and 0.84; irradiation at 0.84 gave NOE signals at 3.2 and 1.4; irradiation at 0.72 gave no NOE signal. Anal. Calcd for $C_{14}H_{26}O_2$: C, 74.29; H, 11.58. Found: C, 74.14; H, 11.63.

9β-Carbomethoxy-3β-(chloromercurio)-4,4,10β-trimethyl-*trans*-decal-8-one (18). To a solution of 1.36 g (3.11 mmol, 1.1 equiv) of $Hg(TFA)_2$ in 15 mL of nitromethane under N_2 at 0 °C was added a solution of 1.09 g (2.78 mol, 1.0 equiv) of **17**, prepared essentially quantitatively by the method of Sum and Weiler[17] and used without purification, in 15 mL of nitromethane via syringe over 1.5 h. The reaction temperature was maintained at 0 °C with stirring for an additional 1 h. Brine (10 mL) was added, causing a precipatate to form, the ice bath was removed, and the mixture was stirred for another 20 min. THF (15 mL) was added and the solids were gravity filtered. The aqueous layer was extracted with 2 × 10 mL of THF and the solvent was evaporated to give 2.04 g of amber oil, containing some solid, which was dissolved in a minimum amount of THF and chromatographed to afford 0.699 g (52%) of off-white **18**: mp 178 °C (lit.[16] mp 179–181 °C); IR 1745, 1705 cm^{-1} (lit.[16] ($CHCl_3$) 1760, 1725 cm^{-1}); ^{1}H NMR (CD_3NO_2) 3.59 (s, 3H), 3.32 (s, 1H), 2.82 (dd, *J* = 13.5, 3.6 Hz, 1H), 2.55–2.33 (m, 2H), 2.30–1.95 (m, 2H), 1.95–1.65 (m, 4H), 1.47–1.32 (td, *J* = 12.9, 3.9 Hz, 1H), 1.17 (s, 3H), 1.16 (s, 3H), 1.11 (s, 3H); COSY 3.59 slightly coupled to (ct) 3.32, 2.82 ct (2.30–1.95), 2.55–2.33 ct (2.30–1.95), 1.95–1.65 ct (1.47–1.32), 1.17, 1.16, 1.11 no coupling (lit.[16] 2.90 (dd, *J* = 10, 5 Hz, 1H)); ^{13}C NMR 205.1, 169.1, 71.0, 69.8, 55.0, 51.3, 42.2, 41.8, 41.5, 39.5, 36.5, 26.4, 26.1, 25.1, 16.3.

Conversion of 18 to 9β-(Hydroxymethyl)-4,4,10β-trimethyl-*trans*-decal-8β-ol (19). To a solution of 287 mg (0.5 mmol) of **18** in a mixture of 25 mL of Et_2O and 8 mL of THF at 0 °C was added 298 mg (7.8 mmol) of $LiAlH_4$ with stirring. The ice bath was removed, the reaction mixture was stirred for 5 h at rt, and 10 mL of H_2O and 5 mL of saturated aqueous NH_4Cl were added. The mixture was filtered through Celite, which was then rinsed with Et_2O. After the aqueous layer had been extracted with 3 × 10 mL of THF, the organic layer was dried over $MgSO_4$ and evaporated to yield 115 mg (87%) of crude **19**, which was recrystallized from hexane:acetone to afford 85 mg (64%) of **19**: mp 152–155 °C (lit.[18] mp 153 °C): ^{1}H NMR 4.28–4.22 (m, 1H), 4.0–3.8 (m, 2H), 3.47 (s, 2H), 1.98–1.88 (m, 1H), 1.8–1.4 (m, 6H), 1.44–1.34 (m, 2H), 1.23–1.13 (m, 2H), 1.12 (s, 3H), 1.02–0.90 (m, 1H), 0.86 (s, 3H), 0.84 (s, 3H); ^{13}C NMR (acetone-d_6) 67.2 (d), 59.7 (u), 57.1 (d), 56.7 (d), 42.7 (u), 40.4 (u), 37.9 (u), 36.1 (u), 34.7 (u), 34.0 (d), 22.0 (d), 18.9 (u), 17.9 (u), 17.2 (d).

Conversion of 18 to 9β-Carbomethoxy-4,4,10β-trimethyl-*trans*-decal-8-one (20). To 35 mg (0.27 mmol) of $NaBH(OMe)_3$ in 6 mL of THF under N_2 at 0 °C was added a solution of 121 mg (0.246 mmol) of **18** in 11 mL of THF via syringe. The ice bath was removed and Hg precipitated shortly thereafter. The mixture was stirred at rt for 3 h, diluted with 5 mL of water, and extracted with 3 × 10 mL of Et_2O. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated to give 82 mg of an off-white solid, which was chromatographed to afford 48 mg (77%) of **20** and 6 mg (5%) of **18**. Recrystallization from pentane:Et_2O gave **20**: mp 83.5–85.0 °C (lit. mp 83–84.5 °C,[18] 83.5–84 °C,[22] 85–86 °C[23]); IR (CCl_4) 1760, 1721 cm^{-1} (lit. 1745, 1707 cm^{-1},[18] 1754, 1715 cm^{-1},[22] 1760, 1720 cm^{-1} [23]); ^{1}H NMR 3.64 (s, 3H), 3.21 (s, 1H), 2.51 (dd, *J* = 14.7, 3.6 Hz, 1H), 2.35 (m, 1H), 2.05 (m, 1H), 1.82–1.40 (m, 6H), 1.32–1.20 (m, 2H), 1.16 (s, 3H), 0.96 (s, 3H), 0.90 (s, 3H); ^{13}C NMR 205.5, 168.6, 70.0, 53.2, 51.5, 42.0, 41.9, 41.3, 39.2, 33.6, 33.5, 23.0, 21.7, 18.6, 14.8.

Conversion of 18 to 3β-(Hydroxymercurio)-9β-carbomethoxy-4,4,10β-trimethyl-*trans*-decal-8-one (21). To a flame-dried flask under N_2 were added 0.330 g (2.57 mmol) of $NaBH(OMe)_3$ and 35 mL of DMF. The N_2 was replaced by O_2 that had been passed through Drierite and which was bubbled rapidly through the DMF via syringe for 10 min. A solution of 0.519 g (1.06 mmol) of **18** in 25 mL of DMF was then added via syringe over 5 min, causing the reaction mixture to turn dark gray. The mixture was stirred at rt for 2 h with continuous O_2

(27) Kalvoda, J.; Loeffel, H. *Helv. Chim. Acta* **1957**, *40*, 2340.
(28) Haynes, N. B.; Timmons, C. J. *Proc. Chem. Soc.* **1958**, 345.
(29) Danieli, N.; Mazur, Y.; Sondheimer, F. *Tetrahedron* **1967**, *23*, 509.

bubbling. After the O_2 bubbling was stopped, excess (0.464 g) solid $NaHSO_3$ was added, and the mixture was stirred for an additional 30 min, diluted with 375 mL of Et_2O, and filtered through Florisil. The filtrate was washed with 5 × 10 mL of H_2O and 10 mL of brine and evaporated to afford 246 mg of colorless solid, which was recrystallized from Et_2O to afford 109 mg of **21** in two crops. Further recrystallization from THF gave 85 mg of **21**: mp 177.2–178.4 °C; IR ($CDCl_3$) 3164, 1746, 1703 cm^{-1}; ^1H NMR 3.66 (s, 3H), 3.17 (s, 1H), 2.75 (dd, J = 13.8, 4.0 Hz, 1H), 2.51 (dd, 1H), 2.40–2.26 (m, 1H), 2.19–1.90 (m, 4H), 1.86–1.50 (m, 2H), 1.57 (s, 1H, H–O peak, disappears upon addition of D_2O), 1.32 (td, J = 13.0, 3.7 Hz, 1H), 1.16 (s, 3H), 1.14 (s, 3H), 1.07 (s, 3H); ^{13}C NMR 204.6, 168.3, 72.2 (d), 69.4 (d), 55.2 (d), 51.6 (d), 41.7 (u), 41.2 (u), 41.1 (u), 39.2 (u), 36.5 (d), 26.2 (u), 26.1 (d), 24.5 (u), 14.8 (d). Anal. Calcd for $C_{15}H_{24}HgO_4$: C, 38.38; H, 5.15. Found C, 38.87; H, 5.24.

9β-Carbomethoxy-4,4,10β-trimethyl-*trans*-decal-3,8-dione (22). Oxygen that had been passed over Drierite was bubbled rapidly through 26 mL of DMF for 10 min with stirring, after which 0.796 g (1.63 mmol) of **18** was added in one portion. Stirring was continued until the **18** had dissolved, and 0.180 g (4.76 mmol) of $NaBH_4$ dissolved in 6 mL of DMF was added dropwise via syringe over 5 min with continuous O_2 bubbling, causing the mixture to turn black and become opaque. The mixture was stirred for 25 min with O_2 bubbling and for an additional 15 min without O_2, then diluted with 10 mL of H_2O and 1 mL of 1 M aqueous HCl (gas evolution), and filtered. The filtrate was extracted with 3 × 30 mL of 1:1 EtOAc:Et_2O, and the organic layer was washed with 10 mL of H_2O and 10 mL of brine and evaporated to give 396 mg of yellow oil, which was dissolved in 25 mL of acetone and treated with Jones reagent with stirring until the solution turned orange. The resulting mixture was diluted with 50 mL of Et_2O and 10 mL of saturated aqueous $NaHCO_3$. The aqueous layer was diluted with 5 mL of H_2O and extracted with 3 × 25 mL of Et_2O. The combined organic layers were washed with 3 × 10 mL of saturated aqueous $NaHCO_3$ and 10 mL of brine and evaporated to give 284 mg of off-white solid, which was chromatographed to give 274 mg (63%) of **22** and 6 mg (14%) of **20**. Recrystallization from Et_2O gave, in two crops, 206 mg of **22**: mp 129.5–131.0 °C; IR (TCE) 1755, 1713, 1694 cm^{-1}; ^1H NMR 3.71 (s, 3H), 3.26 (s, 1H), 2.72 (td, J = 14.7, 5.7 Hz, 1H), 2.54 (m, 1H), 2.43–2.24 (m, 2H), 2.05–1.82 (m, 4H), 1.70 (td, J = 14.7, 4.2 Hz, 1H), 1.39 (s, 3H), 1.18 (s, 3H), 1.12 (s, 3H); ^{13}C NMR 214.3, 204.3, 168.2, 68.6, 53.3, 51.7, 47.8, 41.1, 40.3, 36.9, 33.9, 25.7, 23.1, 22.0, 14.3. Anal. Calcd for $C_{15}H_{22}O_4$: C, 67.64; H, 8.32. Found: C, 67.42; H, 8.31.

Enol Diethyl Phosphate 23 from 22. To a solution of 206 mg (0.774 mmol) of **22** in 8 mL of dry THF under N_2 at 0 °C was added 156 mg (0.782 mmol) of potassium hexamethyldisilazide with stirring, and the mixture was allowed to warm to rt for 30 min, during which time it turned light yellow. Diethyl chlorophosphate (119 μL, 0.823 mmol) was added via syringe, the mixture was stirred for 17 h and diluted with 10 mL of Et_2O, and the reaction was quenched with 10 mL of pH 7 phosphate buffer. The aqueous layer was extracted with 3 × 15 mL of Et_2O. The combined organic layers were washed with 10 mL of brine, dried over $MgSO_4$, and evaporated to give 265 mg of yellow oil, which was chromatographed to give 18 mg (9%) of **22** and 241 mg (77%) of clear oily **23**: IR (film) 1723, 1703, 1369, 1284 cm^{-1}; ^1H NMR 4.12 (quintet of mult, 4H), 3.75 (s, 3H), 2.64–2.42 (m, 4H), 1.89–1.71 (m, 2H), 1.80–1.72 (m, 3H), 1.35 (s, 3H), 1.35 (tt, J = 6.9, 1.2 Hz, 6H), 1.12 (s, 3H), 1.08 (s, 3H); ^{13}C NMR 215.7, 167.0, 147.1, 126.4, 64.3, 51.5, 49.3, 46.9, 36.4, 34.2, 33.7, 27.9, 26.5, 21.0, 19.9, 19.1, 16.0; HRMS (EI) calcd for $C_{19}H_{31}O_7P$ 403.1885, found 403.1880.

Conversion of 23 to 7. Anhydrous NH_3 (*ca.* 60 mL) was condensed into a flame-dried Schlenk flask under Ar, and pieces of Li ribbon (160 mg, 23.1 mmol), which had been dipped in MeOH and then pentane, were added to the NH_3, causing a deep blue color. The mixture was stirred for 15 min under Ar pressure at −70 °C, and a solution of 194 mg (0.478 mmol) of **23** in 7 mL of dry THF and 0.8 mL (8.4 mmol) of *tert*-butyl alcohol was added dropwise over 15 min. The reaction was stirred for 70 min at −65 to −70 °C, 13 mL of 95% EtOH was added (until the blue color disappeared), the mixture was poured into 50 mL of saturated aqueous NH_4Cl (gas evolution), and the resulting solution was extracted with 3 × 30 mL of Et_2O. The combined organic layers were washed with 15 mL of brine and evaporated to give 131 mg of white solid, which was chromatographed to give 97 mg (85%) of an 8:1 mixture of **7** and **16**: mp 157–159 °C. Recrystallization from EtOAc/hexanes afforded 56 mg of **7**: mp 160–161 °C, which had a ^1H NMR spectrum identical with that of **7** prepared from **15**.

Acknowledgment. Partial financial support was provided by NIH grant HL23083.