cooled reaction mixture was poured into ice and acidified with 3 N hydrochloric acid, and the products were extracted with ethyl acetate (3 × 20 mL). The crude product was purified by LC on Partisil by using 15% ethyl acetate in hexane as eluant to obtain the dimethoxy derivative **13** (22 mg, 51% yield): oil, ^{1}H NMR ($CDCl_3$) δ 0.88 (s, 3 H), 0.88 (d, 3 H, J = 7 Hz), 0.91 (s, 3 H), 1.19 (s, 3 H), 2.65 (m, 1 H), 3.83 (s, 3 H), 3.99 (s, 3 H), 6.13 (s, 1 H), 7.01 (s, 1 H), 10.29 (s, 1 H), 11.42 (s, 1 H).

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Supplementary Material Available: Tables of fractional coordinates, thermal parameters, interatomic distances, and interatomic angles for siphonodictyal D (**5**) (5 pages). Ordering information is given on any current masthead page.

Practical Routes to Two Functionalized Decalones for the Synthesis of Quassinoids

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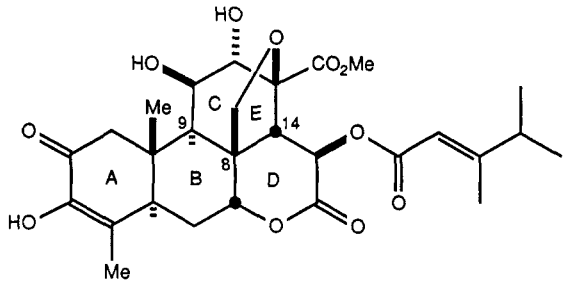
The chiral keto alcohol **6a** was prepared from (*S*)-(+)-carvone. Because two steps in this process gave only modest yields of isolated materials, an alternative route was developed. Racemic keto alcohol **6b** was prepared from enedione *rac*-**13a** by a more efficient process.

We have recently reported[1] a strategy for the synthesis of quassinoids,[2] in particular bruceantin (**1**), that employs



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a Claisen rearrangement to set the C_8, C_9, C_{14} stereochemistry and utilizes three successive ring closures (C → CE → CED) to realize the pentacyclic model *rac*-**5** (Scheme I).[3] While this model study provided important information regarding the elaboration of the CDE ring system, it did not provide latent functionality in ring A for eventual transformation into the substitution pattern present in ring A of bruceantin. Our goal was to prepare chiral, nonracemic keto alcohol **6a** that would ultimately lead to (−)-bruceantin and to be able to prepare **6a** with sufficient ease and in ample quantity to realize our synthetic goal. This paper details our efforts toward this end.

We have reported[4] that (+)-6-epi-α-cyperone (**7**) can be prepared in 67% yield by the Mueller lithium–bronze reduction of (+)-carvone, followed by annulation of the resultant enolate with ethyl vinyl ketone and subsequent KOH–MeOH dehydration. This 10-g scale reaction proved amenable to scale up (200–300 g), providing enone **7** (40% yield, 91% purity) along with 19% recovered dihydrocarvone, which could be recycled. The contaminant (GLC analysis) present in enone **7**, although not identified, was presumably *ent*-cyperone.[5] The presence of this substance did not adversely affect subsequent transformations and was eventually removed by crystallization. Successful double lithium–bronze reduction[6] of enone **7** to alcohol **8a** required the expected formation of the trans ring junction (*t*-BuOH proton source) and stereoselective α-axial protonation of the resultant enolate (EtOH proton source) prior to reduction of the intermediate saturated ketone. This procedure provided a complex mixture of products wherein alcohol **8a** was the major component. Alternatively, stepwise reduction proved successful. Lithium–bronze reduction (*t*-BuOH) of enone **7** afforded a mixture of three ketones from which **8b** (% ds = 85) could be isolated in 47% yield by crystallization. Unfortunately, the residual amount of ketone **8b**, while still the major component remaining in the mother liquors, could not be separated from the other isomers. Two of the minor components were presumed to be *cis*-decalones. The inordinately high percentage of cis isomer formed in the enone reduction is a result of the steric hindrance of the isopropenyl group associated with protonation of the intermediate anion radical of enone **7** from the α face.[7]

(1) Ziegler, F. E.; Klein, S. I.; Pati, U. K.; Wang, T.-F. *J. Am. Chem. Soc.* **1985**, *50*, 2730.

(2) For recent synthetic studies on the quassinoids, see: (a) Schlessinger, R. H.; Wong, J.-W.; Poss, M. A.; Springer, J. P. *J. Org. Chem.* **1985**, *50*, 3950. (b) Stevens, R. V.; Vinogradoff, A. P. *J. Org. Chem.* **1985**, *50*, 4056. (c) Ganem, B.; McKittrick, B. A. *J. Org. Chem.* **1985**, *50*, 5897. (d) Chandler, M.; Mincione, E.; Parson, P. J. *J. Chem. Soc., Chem. Commun.* **1985**, 1233. (e) Shishido, K.; Takahashi, K.; Oshio, Y.; Fukumoto, K.; Kametani, T.; Honda, T. *Tetrahedron Lett.* **1986**, 1339. For earlier studies, see ref 1.

(3) All structures are the enantiomers shown, unless specified otherwise (racemate = rac; enantiomer = ent). Quassinoid numbering is employed.

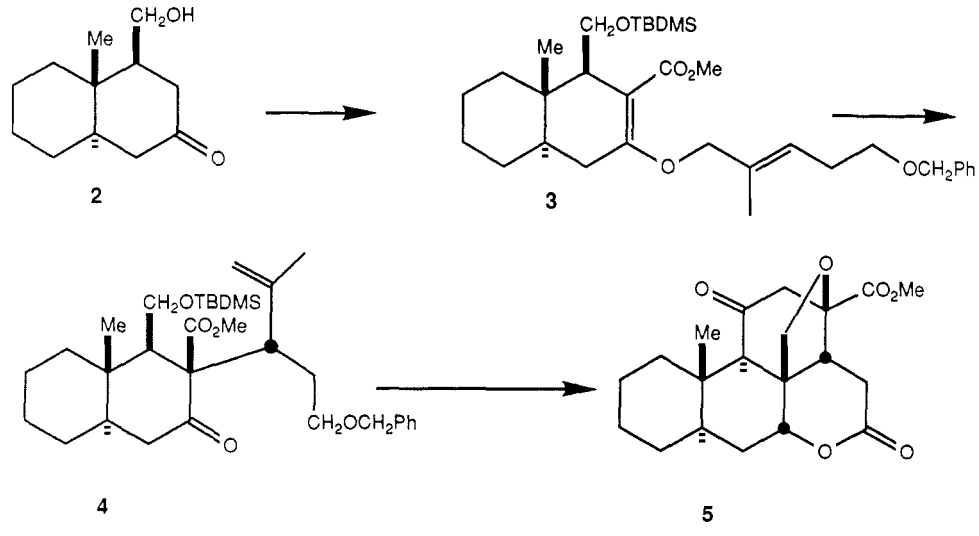
(4) Ziegler, F. E.; Hwang, K.-J. *J. Org. Chem.* **1983**, *48*, 3349.

(5) Marshall, J. A.; Fanta, W. I. *J. Org. Chem.* **1964**, *29*, 2501.

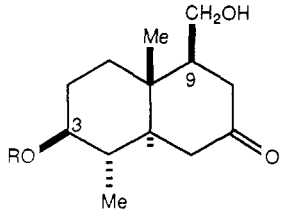
(6) Cf.: (a) Snitman, D. L.; Tsai, M-Y.; Watt, D. S. *Synth. Commun.* **1978**, *8*, 195. (b) Voyle, M.; Kyle, K. S.; Arseniyadis, S.; Dunlap, N. K.; Watt, D. S. *J. Org. Chem.* **1983**, *48*, 470.

0022-3263/86/1951-4573$01.50/0

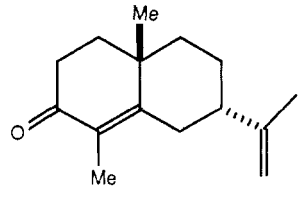
Scheme I



Reduction of ketone **8b** with lithium–bronze afforded the equatorial alcohol without complication and in near quantitative yield.



6a, R = CH_2OCH_3
b, R = CH_2Ph



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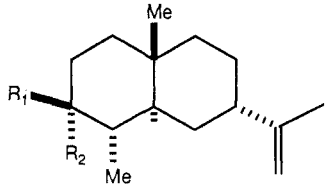
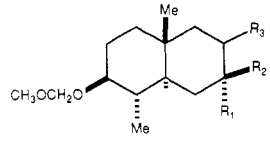


8a, R_1 = OH, R_2 = H
b, R_1, R_2 = O
c, R_1 = OCH_2OCH_3, R_2 = H

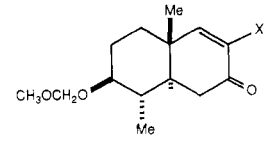
At this juncture of our overall synthetic strategy for bruceantin, we considered the methoxymethyl ether (MOM) as suitable for protection of the hydroxyl group of alcohol **8a**. Etherification, providing ether **8c**, was accomplished with facility with chloromethyl methyl ether in the presence of diisopropylethylamine.

With the isopropenyl group having served its purpose as a handle for diastereomeric control in the annulation process, it was now destined to function as the progenitor for the carbonyl group of ketone **9d**. The required degradation was readily accomplished by ozonolysis (CH_3OH/CH_2Cl_2, O_3; DMS; 89% yield) of olefin **8c** to provide ketone **9a**, which, in turn, was subjected to facile Baeyer–Villiger oxidation (*m*-CpBA) to give acetate **9b**. Saponification (aqueous LiOH) and oxidation (PDC–DMF) gave rise to the required ketone **9d**. The degradation sequence **8c** → **9d** proceeded in 69% yield.

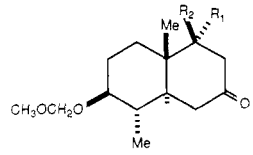
Formation of enone **10a** from ketone **9d** was necessary to permit introduction of the hydroxymethyl group present in decalone **6a**. Phenyl selenoxide elimination proved to be the method of choice. Thus, exposure of ketone **9d** to phenylselenyl chloride in ethyl acetate predictably effected substitution through enolization parallel to the ring junction. The success of the phenylselenylation required the use of sublimed reagent and careful control of temperature and addition rate to avoid formation of contaminating α-chloro ketone **10b**. Oxidation of phenylselenyl ketone **9e** with hydrogen peroxide occurred without incident, affording the desired enone **10a** in 75% yield from ketone **9d**.



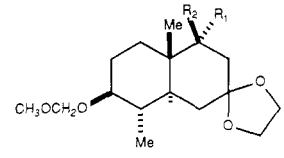
9a, R_1 = $COCH_3$, R_2,R_3 = H
b, R_1 = $OCOCH_3$, R_2,R_3 = H
c, R_1 = OH, R_2,R_3 = H
d, R_1,R_2 = O, R_3 = H
e, R_1,R_2 = O, R_3 = SePh



10a, X = H
b, X = Cl



11a, R_1 = $CH{=}CH_2$, R_2 = H
b, R_1 = CHO, R_2 = H
c, R_1 = H, R_2 = CHO
d, R_1 = CN, R_2 = H



12a, R_1 = CN, R_2 = H
b, R_1 = H, R_2 = CO_2H
c, R_1 = H, R_2 = CH_2OH
d, R_1 = H, R_2 = CO_2Me

The introduction of the hydroxymethyl group present in alcohol **6a** was initially explored through cuprous bromide catalyzed addition of vinylmagnesium bromide to enone **10a**. A single vinyl ketone **11a**, the product of axial addition,[8] could be isolated in 68% yield on decigram scale; however, attempts at scale up proved cumbersome and gave products of 1,2 addition. In addition, aldehyde **11b**, the product of ozonolysis of vinyl ketone **11a**, proved to be unstable, and its epimerization to equatorial aldehyde **11c** was capricious. Consequently, we turned our attention to a sequence employed by Wenkert in the drimenic acid series.[9] Conjugate addition of cyanide ($KCN–NH_4Cl$, aqueous DMF) gave rise to the crystalline cyano ketone **11d** in 70% yield. The ethylene glycol ketal **12a**, derived

(7) Caine, D. In *Organic Reactions*; Baldwin, J. E., et al., Eds.; Wiley: New York, 1976, Vol. 23, p 27.

(8) Piers, E.; de Waal, W.; Britton, R. W. *Can. J. Chem.* **1969**, *47*, 4299.
(9) Wenkert, E.; Strike, D. P. *J. Am. Chem. Soc.* **1964**, *86*, 2044.

from **11d**, revealed the axial nature of the cyano group by the appearance of the equatorial C_9-H at δ 2.62 with coupling constants J = 4.7 and 3.0 Hz. Vigorous saponification of the cyano ketal (KOH, DEG, 180 °C) produced ketal acid **12b**, which had undergone epimerization under the reaction conditions.

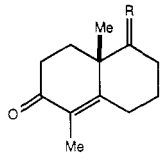
With the carbon framework and correct absolute stereochemistry established in ketal acid **12b**, straightforward functional group manipulation remained to be accomplished. Ketal acid **12b** was esterified and reduced with $LiAlH_4$ to alcohol **12c**. Deketalization was readily achieved in acetone (technical) in the presence of *p*-toluenesulfonic acid, affording the desired chiral keto alcohol **6a**.

Keto alcohol **6a** ultimately proved inadequate in subsequent operations involving ring construction that had proved eminently successful in our model system.[1] While several of these problems could be seemingly avoided through the simple expedient of exchanging the MOM ether protecting group for a benzyl ether unit, the serious problem of maintaining viable supply lines of material militated against the current synthetic plan. In particular, the initial annulation sequence and the ensuing metal–ammonia reduction proved, at least at their current state of development, unsuitable for the task at hand.

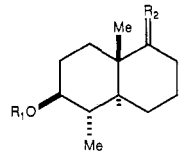
We sought a more efficient approach that would improve the yield of these early operations and would prove more amenable to direct crystallization for the purpose of purification, rather than resort to costly chromatography. Such a scheme materialized with the concession to synthetic design that keto alcohol **6b** be prepared as a racemate.

Dione *rac*-**13a** was prepared on a 0.4-mol scale (76%) by the annulation procedure of Liu[10] with the proviso that the aldolization–dehydration step was conducted in refluxing xylene (140 °C) rather than benzene (80 °C), at which temperature enone formation was slow. Dione *rac*-**13a** was converted into its monoketal *rac*-**13b** by the traditional benzene–ethylene glycol–*p*-TsOH procedure. Both Halsall[11] and Watt[6a] have reported the preparation of ketal *rac*-**13b** by this technique. Halsall employed a 12-fold excess of glycol over substrate while Watt used equimolar quantities. We have found the former procedure better, which requires monitoring the progress of the monoketalization by gas chromatography. Direct, double lithium–bronze reduction of the crude ketal afforded in two crops crystalline ketal alcohol *rac*-**14a** in 85% overall yield on a 0.6 M scale. Benzylation of the hydroxyl group was accomplished by the procedure of Provelenghiou[12] and hydrolysis, as described by Watt,[6a] provided crystalline decalone *rac*-**14c** in 94% yield for the two operations.

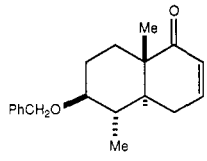
The transformation of ketone *rac*-**14c** to its corresponding α,β-unsaturated ketone was required to permit eventual enone transposition to enone *rac*-**17c**. Although we previously utilized acid-catalyzed phenylselenylation to convert ketone *rac*-**9d** to enone *rac*-**10a**, a variety of acid- and base-initiated phenylselenylation and phenylsulfenylation techniques proved inadequate in the present instance owing to variable yields and a need to perform chromatographies. Direct bromination of the ketone (pyridinium hydrobromide perbromide) afforded α-bromo ketones, but the product was contaminated with 10–15% of debenzylated material. The most efficient method for introduction of the olefin was conversion of the ketone into its trimethylsilyl enol ether followed by bromination and subsequent dehydrohalogenation of the crude α-bromo ketones with diazabicycloundecene (DBU) in refluxing toluene to give rise to enone *rac*-**15** in 83% overall yield. A Wharton rearrangement[13] sequence was employed to transpose enone functionality (*rac*-**15** → *rac*-**17c**). Alkaline hydrogen peroxide epoxidation afforded principally the α-epoxide *rac*-**16a**. The mixture (*rac*-**16a,b**) was exposed to Wharton conditions, and the resultant allylic alcohols *rac*-**17a,b** were oxidized with MnO_2[14] to provide enone *rac*-**17c** in 60% yield.[10,15]



13a, R = O
b, R = OCH_2CH_2O



14a, R_1 = H, R_2 = OCH_2CH_2O
b, R_1 = CH_2Ph, R_2 = OCH_2CH_2O
c, R_1 = CH_2Ph, R_2 = O



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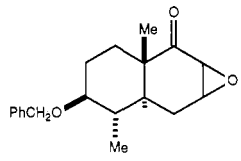
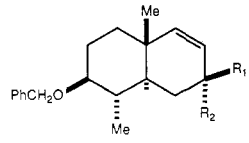
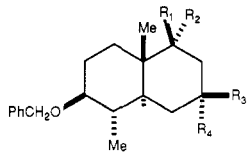


16a, α - epoxide
b, β - epoxide



17a, R_1 = OH, R_2 = H
b, R_1 = H, R_2 = OH
c, R_1,R_2 = O



18a, R_1 = H, R_2 = CN, R_3, R_4 =O
b, R_1 = H, R_2 = CN, R_3, R_4 = OMe
c, R = CO_2H, R_2 = H, R_3, R_4 = OMe
d, R_1 = CO_2Me, R_2 = H, R_3, R_4 = OMe

The addition of cyanide to enone *rac*-**17c** was accomplished as described earlier affording the crystalline, axial nitrile *rac*-**18a** in 74% yield. Ketalization [CH_3OH, $(CH_3O)_3CH$, *p*-TsOH], hydrolysis, and diazomethane esterification provided ketal ester *rac*-**18d** in 52% yield. Finally, $LiAlH_4$ reduction of *rac*-**18d** and subsequent hydrolysis afforded the desired keto alcohol *rac*-**6b**.

The correlation between the chiral, nonracemic and the racemic series was achieved by catalytic hydrogenation (Pd/C) of octalone *rac*-**17c** to provide a keto alcohol that upon etherification [CH_3OCH_2Cl, $(i\text{-}C_3H_5)_2NEt$] gave decalone *rac*-**9d**.

Decalone **6a** is currently being employed in the advanced stages of our bruceantin strategy.

Experimental Section

All reactions were performed in flame-dried glassware under a N_2 atmosphere, unless otherwise noted. Diethyl ether and tetrahydrofuran (THF) were distilled from benzophenone ketyl. Methylene chloride, hexanes, ethyl acetate (for phenylselenyl chloride reaction only), triethylamine, diisopropylamine, and diisopropylethylamine were distilled from calcium hydride. Diazomethane was prepared from Diazald (Aldrich). Chloromethyl methyl ether was distilled and phenylselenyl chloride was

(10) Liu, H. J.; Wynn, H. *Tetrahedron Lett.* **1964**, 1763.
(11) Arden-Jimenez, A.; Halsall, T. G. *J. Chem. Soc., Perkin Trans. 1* **1978**, 1461.
(12) Czernecki, S.; Georgoulis, C.; Provelenghiou, C. *Tetrahedron Lett.* **1976**, 3535.
(13) Wharton, P. S.; Bohlen, D. H. *J. Org. Chem.* **1961**, *26*, 3615.
(14) Attenburrow, J.; Cameron, A. F. B.; Chapman, J. H.; Evans, R. M.; Hems, B. A.; Jansen, A. B. A.; Walker, T. *J. Chem. Soc.* **1952**, 1094.
(15) A similar route has been employed by Kametani. Kametani, T.; Suzuki, K.; Nemoto, H. *J. Org. Chem.* **1980**, *45*, 2204.

sublimed prior to use. All other reagents and solvents were used as received.

Reactions were monitored by thin-layer chromatography using EM Reagents precoated silica gel 60 F-254 TLC plates. Flash chromatography was performed on Baker silica gel 60 (230–400 mesh).

Melting points were obtained on a Fisher-Johns apparatus and are uncorrected. Ozonolyses were performed with a Welsbach T-816 ozonator. Infrared spectra were obtained on a Nicolet 5-SX FT spectrometer in CCl_4 solution. Proton and carbon nuclear magnetic resonance spectra were obtained on a Bruker WM-250 (250 and 62.89 MHz, respectively) spectrometer, using $CDCl_3$ as internal standard. Gas chromatographic analyses were performed on Perkin-Elmer 3920 (flame) chromatograph using a 6 ft × $^1/_8$ in. 5% Carbowax/Anakrom AS 100/120 column. High-resolution mass spectra were obtained on a Kratos MS-80 RFA instrument in the EI mode. Elemental analyses were performed by Atlantic Microlab, Inc., Atlanta, GA.

(+)-6-*epi*-α-Cyperone (7). A flame-dried 5-L flask equipped with a mechanical stirrer, dry ice condenser, and argon inlet was charged with lithium wire (26.0 g, 3.76 mol) that had been prewashed with hexane and cut into 1-cm lengths. The flask was cooled to −78 °C, and 500 mL of ammonia (distilled from sodium) was condensed onto the lithium. After complete formation of the lithium–bronze at −78 °C, 300 mL of dry THF was added. A solution of (+)-carvone (280.0 g, 1.9 mol) and *tert*-butyl alcohol (138.0 g, 1.9 mol) in dry THF (400 mL) was added over 3.5 h, maintaining an internal temperature of −70 °C. The cooling bath was replaced with an acetone bath, and ammonia was allowed to evaporate under a steady flow of argon. After 1.5 h, the flask was recooled to −78 °C and a solution of ethyl vinyl ketone (200.0 g, 2.4 mol) in 350 mL of THF was added dropwise over 2.5 h. After the addition was complete, the cooling bath was removed and the reaction mixture was allowed to warm to room temperature. After stirring for 2 h, the reaction mixture was acidified with 15% aqueous HCl and then extracted with ether (4 × 1 L). The combined organic extracts were washed with 500 mL of saturated aqueous NaCl, dried over anhydrous $MgSO_4$, and concentrated in vacuo, to give 433 g of a brown oil. The residue was dissolved in 1200 mL of an 8% solution of KOH in ethanol, and the solution was brought to reflux for 4 h. Ethanol (≈800 mL) was removed in vacuo prior to acidification of the reaction mixture with 15% aqueous HCl at 5 °C. The mixture was extracted with 1 L of ether followed by 2 × 400 mL ether extractions. The combined organic extracts were washed with 400 mL of saturated aqueous $NaHCO_3$, 400 mL of saturated aqueous NaCl, and then dried over anhydrous $MgSO_4$. Concentration and distillation through a 6-in. Vigreaux column (0.02 torr) provided 33.4 g of dihydrocarvone (bp 60–95 °C) and 183.6 g (bp 95–120 °C) of the desired enone contaminated with dihydrocarvone. Redistillation provided 17.9 g of dihydrocarvone and 164.0 g of enone (40%) [bp 105–115 °C (0.015 torr)]. GC analysis showed a mixture of the desired enone **7** and *ent*-cyperone (9:1). The NMR spectrum of the major component was identical with that in the literature.[4]

Decalone 8b. Lithium wire (9.50 g, 1.37 mol) was washed with hexane, cut into 1-cm lengths, and placed in a flask under an atmosphere of argon. The flask was cooled to −78 °C, and 125 mL of ammonia (distilled from sodium) was condensed on the lithium with stirring. After the lithium had dissolved, the cooling bath was removed and excess ammonia was removed under a stream of argon. The lithium–bronze was recooled to −78 °C, and 400 mL of anhydrous ether was added. A solution of enone **7** (142.3 g, 0.65 mol) and *tert*-butyl alcohol (48.33 g, 0.65 mol) in 450 mL of ether was added dropwise over 2 h. The reaction mixture was stirred 15 min after addition was complete, and then the excess lithium was decomposed with a solution of acetone–ethanol–ether (1:1:1). The reaction mixture was allowed to warm to 0 °C, and 400 mL of water was added to dissolve the salts. The mixture was extracted with 3 × 400 mL of ether, and the combined organic extracts were dried over anhydrous $MgSO_4$. Filtration and concentration in vacuo gave 143.4 g (≈100%) of a yellow oil that contained two major isomers (3:1, GC) and small amounts of minor components. Several recrystallizations from pentane at low temperature (∼−10 °C) provided 66.5 g (47%) of a white crystalline product: mp 47.5–49 °C (pentane); IR (CCl_4) 1711.0 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.86 (s, 1 H), 4.74 (s, 1 H), 2.55–2.07 (m, 4 H), 1.95–1.51 (m, 3 H), 1.68 (s, 3 H), 1.48–1.21 (m, 6 H), 1.10 (s, 3 H), 0.98 (d, J = 6.5 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 212.6, 146.2, 110.9, 45.6, 45.1, 41.6, 38.3, 38.0, 36.3, 33.8, 27.5, 23.0, 22.5, 15.9, 11.0; $[\alpha]^{21}_D$ +11.9 (*c* 0.23, $CHCl_3$). Anal. Calcd for $C_{15}H_{24}O$: C, 81.76; H, 10.98. Found: C, 81.78; H, 10.98.

Alcohol 8a. A flame-dried flask was charged with 1-cm lengths of Li wire (3.45 g, 0.50 mol) under an atmosphere of argon and then cooled to −78 °C. Excess NH_3 (≈200 mL, from sodium) was condensed onto the lithium with stirring. After complete consumption of the solid lithium, the flask was allowed to warm to room temperature and the excess NH_3 was removed under a stream of argon. The lithium–bronze was recooled to −78 °C, and 200 mL of dry ether was added. A solution of ketone **8b** (43.6 g, 0.20 mol) and *tert*-butyl alcohol (31.3 mL, 0.33 mol) in 200 mL of dry ether was added dropwise over 80 min.

The reaction mixture was stirred for 15 min and then allowed to warm to 10 °C over 1.5 h. The flask was recooled to −78 °C, and the excess lithium was decomposed with methanol. The reaction mixture was warmed to 0 °C, and 400 mL of water was added to dissolve the salts. The mixture was extracted with 3 × 500 mL portions of ether, and the combined organic extracts were dried over anhydrous $MgSO_4$. Filtration, concentration in vacuo, and crystallization from pentane gave 43.2 g (98%) of white solid: mp 72–72.5 °C (EtOAc–hexane); IR (CCl_4) 3627, 3352, 2929, 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.86 (s, 1 H), 4.77 (s, 1 H), 3.04 (dt, J = 5.4, 10.8 Hz, 1 H, C_3-H) 2.31 (br s, 1 H), 2.14 (br s, 1 H), 1.72 (s, 3 H, vinylmethyl), 1.92–1.08 (m, 12 H), 0.94 (d, J = 6.3 Hz, 3 H, C_4-CH_3), 0.87 (s, 3 H, angular CH_3); ^{13}C NMR ($CDCl_3$) δ 146.9, 110.5, 76.6, 43.1, 39.9, 39.1, 38.8, 37.0, 33.6, 30.8, 26.0, 23.0, 22.6, 16.5, 14.8; $[\alpha]^{21}_D$ +22.0 (*c* = 0.21, $CHCl_3$). Anal. Calcd for $C_{15}H_{26}O$: C, 81.02; H, 11.74. Found: C, 81.14, H, 11.76.

Methoxymethyl Ether 8c. To a solution of diisopropylethylamine (91.9 g, 0.71 mol) and alcohol **8a** (55.0 g, 0.25 mol) in 150 mL of CH_2Cl_2 maintained at 0 °C under N_2 was added chloromethyl methyl ether (42.68 g, 0.53 mol) [*CAUTION: CARCINOGEN*] over a period of 20 min. The reaction mixture was allowed to warm to room temperature, was stirred for 12 h, and then was poured into 500 mL of ether and 250 mL of saturated aqueous $NaHCO_3$. The layers were separated, and the aqueous layer was extracted with 3 × 250 mL ether. The combined organic extracts were washed with saturated aqueous NaCl and dried over anhydrous $MgSO_4$. Filtration, concentration in vacuo, and flash chromatography (4% ether–hexane) provided 62.5 g (95%) of a colorless oil: IR (CCl_4) 2934, 1639, 1455 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.86 (s, 1 H), 4.77 (s, 1 H), 4.70 (d, J = 6.8 Hz, 1 H), 4.56 (d, J = 6.8 Hz, 1 H), 3.35 (s, 3 H), 2.98 (dt, J = 10.9, 4.9 Hz, 1 H, C_3-H), 2.31 (br s, 1 H, allylic H), 1.93–1.01 (m, 12 H), 1.69 (s, 3 H), 0.93 (d, J = 6.5 Hz, 3 H), 0.87 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 146.9, 110.6, 95.5, 82.7, 55.3, 43.5, 39.9, 38.9, 37.4, 37.1, 33.6, 27.7, 26.2, 23.1, 22.6, 16.6, 14.9; $[\alpha]^{21}_D$ +44.0 (*c* 0.26, $CHCl_3$). Anal. Calcd for $C_{17}H_{30}O_2$: C, 76.64; H, 11.35. Found: C, 76.59; H, 11.38.

Methyl Ketone 9a. Ozone was bubbled through a solution of olefin **8c** (42.8 g, 0.16 mol), in methanol (125 mL) and dichloromethane (250 mL) containing $NaHCO_3$ (6.8 g, 0.08 mol) at −78 °C until the solution remained blue. The excess ozone was removed under a stream of N_2, and then dimethyl sulfide (60 mL, 0.82 mol) was added over 10 min at −78 °C. The reaction mixture was allowed to warm to room temperature and stirred for 12 h. Concentration in vacuo and flash chromatography (12:1 hexane–EtOAc) provided 38.4 g (89%) of ketone **9a** as an oil that was homogeneous by proton NMR and TLC, but the carbon NMR spectrum revealed the presence of an unidentified impurity (less than 10%). This material proved suitable for subsequent transformations: IR (CCl_4) 2940, 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.60 (d, J = 6.8 Hz, 1 H), 4.44 (d, J = 6.8 Hz, 1 H), 3.22 (s, 3 H), 2.86 (dt, J = 4.9, 10.6 Hz, 1 H, C_3-H) 2.48 (br s, 1 H), 2.04–0.88 (m, 12 H), 2.00 (s, 3 H), 0.84 (d, J = 6.3 Hz, 3 H), 0.74 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 210.4, 95.3, 82.1, 55.1, 47.1, 44.8, 39.2, 37.6, 37.2, 32.8, 27.4, 27.3, 24.7, 21.2, 15.9, 14.6.

Decalone 9d. *m*-Chloroperbenzoic acid (80–85%, 44.4 g, 205 mmol) was added over 10 min to a stirred solution of ketone **9a** (39.01 g, 146 mmol) in 350 mL of CH_2Cl_2 at 0 °C. The ice bath was removed after 10 min, and the reaction mixture was stirred for 32 h at room temperature. The reaction mixture was cooled to 0 °C, and 200 mL of 10% aqueous $NaHSO_3$ solution was added cautiously with stirring. The mixture was extracted with 500 mL

of CH_2Cl_2. The organic extract was washed with 100 mL of 10% aqueous $NaHSO_3$ and 100 mL of saturated aqueous $NaHCO_3$. The solvent was removed in vacuo to give the crude acetate **9b** (49.3 g) as an amorphous solid. The solid was dissolved in 150 mL of methanol and 360 mL of 1 N aqueous LiOH. The solution was brought to reflux for 9 h, cooled, acidified to pH 7 using 10% aqueous HCl, concentrated to remove the majority of methanol, and extracted with 3 × 500 mL portions of ether. The combined extracts were dried over anhydrous $MgSO_4$ prior to concentration in vacuo to give 42.8 g of crude alcohol **9c**. Flash chromatography using hexane–EtOAc (6:1) provided 29.95 g (85%) of a viscous gum: IR (CCl_4) 3625, 3485, 1457 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.68 (d, J = 6.8 Hz, 1 H), 4.52 (d, J = 6.8 Hz, 1 H), 4.01 (br s, 1 H), 3.30 (s, 3 H), 2.99 (dt, J = 4.3, 9.5 Hz, 1 H, C_3-H), 2.50 (br s, 1 H), 1.90–1.00 (m, 12 H), 0.84 (d, J = 5.6 Hz, 3 H), 0.77 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 95.4, 82.6, 66.0, 55.2, 41.6, 39.3, 37.2, 35.0, 33.1, 31.7, 28.2, 27.7, 15.6, 14.8.

Pyridinium dichromate[16] (31.0 g, 82.5 mmol) was added to a stirred solution of alcohol **9c** (10.0 g, 41.3 mmol) in 100 mL of DMF at 0 °C under N_2. The black reaction mixture was stirred 10 min at 0 °C followed by 3 h at room temperature. The reaction mixture was poured into 1 L of water and extracted with 3 × 500 mL of ether. The organic extracts were dried over $MgSO_4$, concentrated in vacuo, and purified by flash chromatography (hexane–EtOAc, 10:1) to give 8.95 g (90%) of decalone **9d** as a white, crystalline solid: mp 26–28 °C (neat); IR (CCl_4) 1705 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.69 (d, J = 6.8 Hz, 1 H), 4.52 (d, J = 6.8 Hz, 1 H), 3.39 (s, 3 H), 2.96 (dt, J = 4.8, 9.6 Hz, 1 H), 2.48–1.19 (m, 12 H), 1.09 (s, 3 H), 0.92 (d, J = 6.3 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 210.5, 95.2, 81.1, 55.0, 48.3, 40.9, 39.8, 37.9, 37.8, 37.1, 32.4, 27.2, 15.5, 14.3; $[\alpha]^{25}_D$ +12.9 (c 0.33, $CHCl_3$). Anal. Calcd for $C_{14}H_{24}O_3$: C, 69.96; H, 10.06. Found: C, 69.98; H, 10.06.

Octalone 10a. A solution of sublimed phenylselenyl chloride (6.9 g, 36.0 mmol) in 105 mL of ethyl acetate (distilled from CaH_2) was added dropwise to a stirred solution of decalone **9d** (7.2 g, 30.0 mmol) in 105 mL of ethyl acetate maintained under N_2 at an internal temperature of 5 °C. After addition was complete, the solution was allowed to warm to 10 °C over 5 min and was then stirred an additional 35 min at 10 °C. The reaction mixture was washed with 100 mL of saturated aqueous $NaHCO_3$ solution and 100 mL of water. The organic layer was cooled to 0 °C, and 13 mL (0.11 mol) of 30% H_2O_2 was added over 10 min. The reaction mixture was allowed to warm to room temperature and was stirred an additional 70 min. The organic layer was washed with 50 mL of 5% aqueous Na_2CO_3 and then 100 mL of water. The aqueous layers were extracted with 150 mL of EtOAc. The combined organic extracts were washed with 100 mL of water and then dried over anhydrous $MgSO_4$. Flash chromatography (hexane–ethyl acetate, 6:1) gave 5.36 g (75%) of white solid: mp 67–68.5 °C (hexane–EtOAc); IR (CCl_4) 2941, 1684 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.67 (d, J = 9.8 Hz, 1 H), 5.77 (d, J = 9.8 Hz, 1 H), 4.68 (d, J = 6.9 Hz, 1 H), 4.53 (d, J = 6.9 Hz, 1 H), 3.31 (s, 3 H), 2.99 (dt, J = 9.7, 5.60 Hz, 1 H), 2.45 (dd, J = 2.8, 17.5 Hz, 1 H), 2.14–1.92 (m, 3 H), 1.64–1.31 (m, 4 H), 1.02 (s, 3 H), 0.90 (d, J = 5.7 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 199.3, 160.6, 126.6, 95.6, 81.2, 55.3, 46.2, 37.4, 37.0, 35.65, 35.6, 27.3, 17.1, 14.3; $[\alpha]^{25}_D$ +16.9 (c 0.06, MeOH). Anal. Calcd for $C_{14}H_{22}O_3$: C, 70.55; H, 9.30. Found: C, 70.39; H, 9.31.

Cyano Ketone 11d. A solution of ammonium chloride (5.07 g, 0.095 mol) and potassium cyanide (7.79 g, 0.12 mol) in water (50 mL) was added to a solution of enone **10a** (19.0 g, 0.080 mol) in DMF (100 mL). The reaction mixture was heated at 90 °C for 40 min and then allowed to cool to room temperature. The mixture was extracted with 6 × 250 mL portions of 1:1 ether–CH_2Cl_2, and the combined organic extracts were washed with water and saturated aqueous NaCl and dried over anhydrous $MgSO_4$. Concentration in vacuo and removal of DMF by heating at 45 °C for 5 h under vacuum provided a brown gum. Crystallization from chloroform–hexane provided 15.2 g (72%) of cyano ketone **11d** as a white crystalline solid: mp 125.5–127 °C (EtOAc–hexane); IR ($CHCl_3$) 2948, 2250, 1716, 1040 cm^{-1}; ^1H NMR δ 4.68 (d, J = 6.8 Hz, 1 H), 4.54 (d, J = 6.8 Hz, 1 H), 3.31 (s, 3 H), 3.04 (dt, J = 10.1, 4.7 Hz, 1 H, C_3-H), 2.84–2.67 (m, 2 H), 2.54 (br s, 1 H), 2.48 (br s, 1 H), 2.04–1.92 (m, 2 H), 1.77–1.38 (m, 5 H), 1.12 (s, 3 H), 0.90 (d, J = 6.3 Hz, 3 H); ^{13}C NMR δ 205.2, 119.2, 95.6, 80.2, 55.4, 43.6, 40.8, 40.2, 39.9, 38.2, 35.1, 34.9, 27.1, 16.3, 14.3; $[\alpha]^{25}_D$ −8.12 (c 0.016, MeOH); HRMS, calcd 265.1979, found 265.1683.

Cyano Ketal 12a. A solution of cyano ketone **11d** (2.00 g, 7.53 mmol), triethyl orthoacetate (4.14 mL, 22.6 mmol), and ethylene glycol (distilled, 12.6 mL, 225.9 mmol) was heated to 60 °C to dissolve the ketone and then cooled to room temperature. p-Toluenesulfonic acid monohydrate (100 mg, 0.53 mmol) was added, and the reaction mixture was stirred 3 h at room temperature. The reaction mixture was diluted with ether and washed with aqueous $NaHCO_3$ and saturated aqueous NaCl. The organic layer was dried over anhydrous $MgSO_4$, concentrated in vacuo, and subjected to flash chromatography (30% EtOAc–hexane) to give 0.30 g (15%) of starting material and 1.40 g (60%) of cyano ketal **12a** as a white solid: mp 102–103 °C (hexane–EtOAc); IR ($CHCl_3$) 2250, 1040 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.68 (d, J = 6.7 Hz, 1 H), 4.55 (d, J = 6.7 Hz, 1 H), 3.93 (m, 4 H), 3.31 (s, 3 H), 3.03 (dt, J = 10.1, 4.9 Hz, 1 H, C_3-H), 2.57 (dd, J = 6.1, 4.0 Hz, 1 H, C_9-H), 2.01–1.74 (m, 5 H), 1.56–1.23 (m, 5 H), 0.96 (s, 3 H), 0.91 (d, J = 6.1 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 120.0, 107.0, 95.6, 81.0, 64.3, 64.2, 55.3, 42.1, 38.5, 37.5, 35.4, 34.9, 34.1, 31.9, 27.3, 16.7, 14.6; $[\alpha]^{25}_D$ +16.1 (c 0.01, $CHCl_3$); HRMS, calcd 309.1941, found 309.1956.

Ketal Acid 12b. Cyano ketal **12a** (14.5 g, 46.8 mmol) and KOH pellets (52.0 g, 0.93 mol) in 250 mL of diethylene glycol was heated in an oil bath (190–210 °C) for 36 h under N_2. The solution was allowed to cool and was acidified to pH 5.5 at 0 °C with 10% aqueous HCl. The mixture was extracted with 3 × 1 L portions of ethyl acetate; the combined organic extracts were washed with water (2 × 200 mL) and saturated aqueous NaCl (100 mL), and then dried over anhydrous $MgSO_4$. Concentration in vacuo and flash chromatography (3% MeOH–$CHCl_3$) gave 9.84 g (64%) of ketal acid **12b** as a white solid: mp (EtOAc–hexane) 171–172 °C; IR ($CHCl_3$) 3400, 1715, 1105, 1040 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.76 (d, J = 6.8 Hz, 1 H), 4.61 (d, J = 6.8 Hz, 1 H), 3.95 (br s, 4 H), 3.38 (s, 3 H), 3.04 (dt, J = 10.2, 4.7 Hz, 1 H, C_3-H), 2.39 (dd, J = 13.2, 2.6 Hz, 1 H), 2.04–1.17 (m, 10 H), 1.00 (s, 3 H), 0.94 (d, J = 6.1 Hz, 3 H); $[\alpha]^{25}_D$ +32.7 (c 0.01, $CHCl_3$).

Keto Alcohol 6a. To a THF solution (200 mL) of ketal acid **12b** (14.04 g, 42.7 mmol) in an Erlenmeyer flask [*Caution!* the flask must be free of chips and scratches to avoid a diazomethane explosion.] was added an ethereal solution of (3.0 g 71.0 mmol) diazomethane (from Diazald, Aldrich). After N_2 evolution had ceased, glacial acetic acid was added dropwise to destroy excess diazomethane followed by removal of solvents in vacuo to afford 14.8 g of crude ketal ester **12d**: ^1H NMR ($CDCl_3$) δ 3.62 (s, 3 H).

The ketal ester was dissolved in 70 mL of ether, and the solution was added dropwise to a stirred, ethereal suspension of $LiAlH_4$ (3.8 g, 0.11 mmol) in 140 mL of ether under N_2 at ambient temperature. After the addition was complete, stirring was continued for 2 h. The reaction mixture was decomposed by the sequential, dropwise addition of 4 mL of H_2O, 4 mL of 15% aqueous NaOH, and 12 mL of H_2O. Filtration through Celite and concentration in vacuo gave 12.6 g of crude, viscous oil that was dissolved in 150 mL of technical grade acetone containing 0.50 g (2.62 mmol) of p-toluenesulfonic acid. The mixture was stirred for 4 h at ambient temperature, and then 10 mL of saturated aqueous $NaHCO_3$ solution was added. Stirring was continued for 10 min, and the solvent was removed in vacuo. The residue was diluted with ether, washed with water, dried over anhydrous $MgSO_4$, and concentrated in vacuo to give the crude product as a yellow oil. Flash chromatography (hexane–EtOAc, 1:1) followed by hexane–EtOAc (2:3) gave 9.46 g (82%) of keto alcohol **6a** as a colorless, viscous oil: IR ($CHCl_3$) 3627, 3451, 2937, 1706 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.76 (d, J = 6.9 Hz, 1 H), 4.60 (d, J = 6.9 Hz, 1 H), 3.85 (dd, J = 7.2, 3.0 Hz, 1 H), 3.49 (m, 1 H), 3.38 (s, 3 H), 3.04 (dt, J = 10.5, 4.8 Hz, 1 H, C_3-H), 2.62–2.45 (m, 2 H), 2.32–2.20 (m, 1 H), 2.10–1.46 (m, 6 H), 1.30–1.18 (m, 3 H), 1.00 (s, 3 H), 0.94 (d, J = 6.4 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 210.7, 95.6, 81.3, 62.6, 55.5, 50.3, 50.2, 41.4, 40.8, 37.7, 35.8, 35.1, 27.3, 14.9, 12.4; $[\alpha]^{25}_D$ +22.0 (c 0.014 $CHCl_3$). Anal. Calcd for $C_{15}H_{26}O_4$: C, 66.64; H, 9.69. Found: C, 66.51; H, 9.73.

Enedione *rac*-13a (Modification of Liu's[10] Procedure). To a suspension of 2-methyl-1,3-cyclohexanedione (50.0 g, 0.4 mol)

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in 200 mL of DME was added 1,4-diazabicyclooctane (DABCO; 49.3 g, 0.44 mol) in one portion at room temperature. Ethyl vinyl ketone (43.8 mL, 0.44 mol) was added in one portion at room temperature, and the solution was allowed to stir 12 h. After the mixture was cooled to 0 °C, 300 mL of 20% aqueous HCl was added slowly. After addition was complete, stirring was continued 10 min at 0 °C. The mixture was extracted with ether (4 × 300 mL); the organic layers were combined and dried over $MgSO_4$, filtered, and concentrated, to give 77.0 g (100%) of crude Michael adduct: ^1H NMR δ 2.78–2.54 (m, 4 H), 2.40–2.26 (m, 4 H), 2.06–1.84 (m, 4 H), 1.21 (s, 3 H), 0.99 (t, 3 H, J = 7.3 Hz).

The crude Michael adduct was dissolved in xylenes (400 mL), and triethylamine (44.8 mL, 0.32 mol) and benzoic acid (54.0 g, 0.44 mol) were added. The solution was heated at reflux until water was no longer collected in a Dean–Stark trap (~24 h). After cooling, 200 mL of saturated aqueous $NaHCO_3$ was added and stirring was continued 30 min. The layers were separated; the organic layer was washed with water, dried over $MgSO_4$, filtered, and concentrated. Distillation [140 °C (1.2 torr)] gave 58.0 g (75.6%) of the enone *rac*-**13a**: IR (CCl_4) 1713, 1672 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.94 (t, J = 4.7 Hz, 1 H), 2.85 (t, J = 4.2 Hz, 1 H), 2.74 dd, J = 7.2, 4.7 Hz, 1 H), 2.68 (dd, J = 7.5, 4.2 Hz, 1 H), 2.59–2.05 (m, 6 H), 1.67 (d, J = 1.2 Hz, 3 H, C_4-CH_3), 1.30 (s, 3 H, angular CH_3).

Ketal Alcohol *rac*-14a. A 5-L three-neck flask equipped with a mechanical stirrer and dry ice condenser was charged with 500 mL of THF and lithium metal (4.2 g, 0.6 mol). The suspension was cooled to −78 °C, and ammonia, which had previously been dried over sodium metal, was condensed into the flask until all of the lithium metal had dissolved and a pool of lithium–bronze had formed on the surface of the THF. The dry ice condenser was replaced with an additional funnel, and the ketal enone *rac*-**13b** (140.0 g, 0.6 mol) and *tert*-butyl alcohol (170 mL, 1.8 mol) were added as a solution in 300 mL of THF at a rate such that the internal temperature of the reaction mixture remained below −68 °C. After addition was complete, stirring was continued 45 min at −70 °C. Ethanol (141 mL, 2.4 mol) was then added via an addition funnel over ~10 min at −70 °C. Fresh acetone was added to the dry ice bath to bring the internal temperature to −45 °C, and stirring was continued for 2 h at −45 °C. An additional 500 mL of ethanol was added dropwise, and stirring was continued until all of the excess lithium–bronze had decomposed. Solid NH_4Cl (250 g) was added, and stirring was continued overnight at room temperature to evaporate ammonia. The reaction mixture was diluted with ether and washed sequentially with water, with brine, and again with water. The aqueous layers were combined and back-washed twice with ether. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The crude solid was recrystallized from ethyl acetate–hexane to give 122.3 g (85%) of keto alcohol *rac*-**14a** as a white solid in two crops. The spectral data were in accord with that reported by Watt:[6a] mp 87–88 °C; IR (CCl_4) 3627 cm^1; ^1H NMR (CCl_3) δ 3.99–3.82 (m, 4 H), 3.16–3.08 (m, 1 H), 1.89–1.01 (m, 13 H), 1.01 (s, 3 H), 0.97 (d, J = 5.8 Hz, 3 H); ^{13}C NMR δ 112.8, 75.8, 64.9, 64.7, 45.5, 42.1, 39.0, 30.4, 29.9, 28.1, 23.4, 22.7, 15.1, 14.6.

Keto Ether *rac*-14c. To a suspension of sodium hydride (60% dispersion in mineral oil, 17.0 g, 0.43 mol) in 100 mL of THF was added a solution of ketal alcohol *rac*-**14a** (51.16 g, 0.21 mol) in 200 mL of THF via addition funnel at room temperature. After addition was complete, the mixture was heated at reflux for 2 h. Benzyl bromide (52.16 mL, 0.43 mol) was added in one portion, followed by tetra-*n*-butylammonium iodide (3.7 g, 0.01 mol) in one portion. The mixture was brought to reflux for 1 h and cooled to room temperature, and excess sodium hydride was decomposed by the slow addition of ethanol. The reaction mixture was diluted with ether and washed twice with water. The combined aqueous layers were back-washed once with ether. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated to give a yellow oil. The oil was dissolved in 300 mL of THF, 100 mL of 1 N aqueous HCl, and 200 mL of glacial acetic acid. The resulting solution was stirred at room temperature for 17 h. Concentrated (>6 N) aqueous NaOH solution was added until the solution reached neutrality. The layers were separated, the aqueous layer was extracted with ether (2×), and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated to give a yellow solid. Recrystallization from ethyl acetate–hexane gave 57.3 g (94%) of ketone *rac*-**14c** as a white solid, in three crops. The spectral data were comparable to those reported by Watt:[6a] mp 81–83 °C (EtOAc–hexane); ^1H NMR ($CDCl_3$) δ 7.28–7.23 (m, 5 H), 4.58 (d, J = 11.4 Hz, 1 H, CH_2Ph), 4.34 (d, J = 11.4 Hz, 1 H, CH_2Ph), 2.77 (dt, J = 3.8, 8.0 Hz, 1 H, C_3-H), 2.65–2.50 (m, 1 H), 2.18–1.97 (m, 2 H), 1.80–1.30 (m, 9 H), 1.07 (s, 3 H, angular CH_3), 0.96 (d, J = 6.3 Hz, 3 H, C_4-CH_3).

Octalone *rac*-15. To a solution of diisopropylamine (31.9 mL, 0.23 mol) in 150 mL of THF was added *n*-BuLi (131.1 mL, 0.21 mol, 1.6 M solution in hexanes) dropwise via an additional funnel at 0 °C. After the addition was complete, stirring was continued 30 min at 0 °C. A solution of the ketone *rac*-**14c** (50.0 g, 0.17 mol) in 230 mL of THF was added via addition funnel at 0 °C. After the addition was complete, stirring was continued 30 min at 0 °C. A solution of triethylamine (58.4 mL, 0.42 mol) and trimethylsilyl chloride (53.0 mL, 0.42 mol) in 50 mL of THF was added dropwise to the solution of enolate at 0 °C. After addition was complete, stirring was continued 20 min at 0 °C. The solution was poured into 2 L of hexanes and 400 mL of a saturated $NaHCO_3$ solution. The aqueous layer was separated, and the organic layer was washed with brine. The organic layer was dried over anhydrous $NaSO_4$, filtered, and concentrated to give 63.0 g (100%) of a yellow oil: ^1H NMR δ 7.40–7.29 (m, 5 H), 4.66 (d, 1 H, J = 11.4 Hz, CH_2Ph), 4.59 (t, J = 3.6 Hz, 1 H, C_8-H), 4.44 (d, J = 11.4 Hz, 1 H, CH_2Ph), 2.91 (dt, J = 5.0, 10.0 Hz, 1 H, C_3-H), 2.10–0.96 (m, 10 H), 1.02 (s, 3 H, angular CH_3), 1.02 (d, J = 6.2 Hz, 3 H, C_4-CH_3), 0.18 [s, 9 H, $Si(CH_3)_3$].

The crude enol ether was dissolved in 500 mL of CH_2Cl_2 and the resulting solution cooled to −78 °C. Bromine (9.0 mL, 0.17 mol) was added slowly via an additional funnel at −78 °C over 45 min. After the addition was complete, 200 mL of saturated aqueous $NaHCO_3$ solution was added and stirring was continued 15 min at room temperature. The layers were separated; the organic layer was dried over $MgSO_4$, filtered, and concentrated to give the crude bromo ketones as a light yellow solid, 62.5 g (98%).

Equatorial Bromide: R_f (20% EtOAc–hexane) 0.46; ^1H NMR δ 5.04 (dd, J = 6.6, 13.3 Hz, C_8-H).

Axial Bromide: R_f (20% EtOAc–hexane) 0.56; ^1H NMR δ 4.47 (t, J = 3.5 Hz, C_8-H).

The mixture of crude bromides was dissolved in 200 mL of toluene, and diazabicycloundecene (DBU) (33.1 mL, 0.22 mol) was added in one portion. The solution was heated to reflux for 45 min, during which time a white precipitate formed. Upon cooling, the mixture was washed with water, and the organic layer was dried over $MgSO_4$, filtered, and concentrated. Filtration through silica gel (pad 80 × 150 mm, 20% EtOAc–hexane) provided 41.3 g (83%) of octalone *rac*-**15**: IR (CCl_4) 1681 cm^{-1}; ^1H NMR δ 7.37–7.28 (m, 5 H), 6.87 (ddd, J = 2.1, 5.8, 12.9 Hz, 1 H, C_7-H), 5.94 (dd, J = 0.8, 6.0 Hz, 1 H, C_8-H), 4.68 (d, J = 11.4 Hz, 1 H, CH_2Ph), 4.43 (d, J = 11.4 Hz, 1 H, CH_2Ph), 2.90 (dt, J = 4.5, 10.1 Hz, 1 H, C_3-H), 2.47 (dt, J = 4.7, 4.9 Hz, 1 H), 2.19–1.97 (m, 3 H), 1.72–1.38 (m, 4 H), 1.07 (s, 3 H, angular CH_3), 1.05 (d, J = 6.0 Hz, 3 H, C_4-CH_3); ^{13}C NMR δ 204.9, 147.6, 138.7, 128.3 (×2), 127.7 (×2), 127.6, 127.4, 82.5, 71.0, 45.5, 44.4, 37.6, 30.4, 27.6, 26.0, 15.4, 14.8. Anal. Calcd for $C_{19}H_{24}O_2$: C, 80.24; H, 8.51. Found: C, 80.16; H, 8.54.

Octalone *rac*-17c. To a solution of octalone *rac*-**15** (44.77 g, 0.16 mol) in 180 mL of methanol was added 30% hydrogen peroxide (48.24 mL, 0.47 mol) in one portion at room temperature. A solution of 6 N aqueous sodium hydroxide (13.1 mL, 0.079 mol) was slowly added via an additional funnel, maintaining the internal temperature between 15 and 20 °C with the aid of an ice–water bath. After addition was complete, a semisolid began to form. Stirring was continued for 3 h at room temperature. The solid material was filtered and washed with methanol. The filtrate was poured into a separatory funnel containing 200 mL water and was extracted with CH_2Cl_2 (3×). The organic extracts were dried over $MgSO_4$, filtered, concentrated, and combined with the solid material to give 47.57 g (100%) of crude epoxides: ^1H NMR δ 3.55–3.52 (m, 1 H, C_7-H), 3.19 (d, J = 3.5, 1 H, C_8-H).

The crude epoxides were dissolved in 400 mL of methanol; hydrazine (95%, 31.5 mL, 0.98 mol) was added in one portion, followed by glacial acetic acid (1.89 mL, 0.03 mol) in one portion. The solution was heated to reflux for 2 h. After cooling, the reaction mixture was poured into 500 mL of water and was ex-

tracted with ether. The organic layers were dried over $MgSO_4$, filtered, and concentrated to give 43.0 g (96%) of a yellow oil: ^1H NMR δ 5.72–5.64 (m, 2 H, vinyl), 4.19–4.17 (m, 1 H, C_7-H).

The crude allylic alcohols were dissolved in 1.5 L of CH_2Cl_2, and MnO_2[14] (70.64 g, 0.81 mol) was added in one portion. The mixture was stirred 18 h at room temperature (mechanical stirrer) and then filtered through Celite. The filtrate was concentrated and subjected to flash chromatography (20% ethyl acetate–hexane) to provide 26.92 g (60%) of the octalone *rac*-**17c**: IR (CCl_4) 1682 cm^{-1}; ^1H NMR δ 7.36–7.28 (m, 5 H), 6.75 (d, J = 9.9 Hz, 1 H, vinyl), 5.86 (d, J = 9.9 Hz, 1 H, vinyl), 4.67 (d, J = 11.3 Hz, 1 H, CH_2Ph), 4.45 (d, J = 11.3 Hz, 1 H, CH_2Ph), 2.95 (dt, J = 4.7, 9.6 Hz, 1 H, C_3-H), 2.55 (dd, J = 3.6, 17.6 Hz, 1 H, C_6-H ax.), 2.23–2.08 (m, 2 H), 1.74–1.44 (m, 5 H), 1.10 (s, 3 H, angular CH_3), 1.02 (d, J = 5.8 Hz, 3 H, C_4-CH_3); ^{13}C NMR δ 199.6, 160.8, 138.6, 128.2 (×2), 127.6 (×2), 127.4, 126.7, 82.6, 71.0, 46.1, 37.4, 37.0, 35.7, 35.5, 26.2, 17.0, 14.3. Anal. Calcd for $C_{19}H_{24}O_2$: C, 80.24, H, 8.51. Found: C, 80.30; H, 8.53.

Cyano Ketone *rac*-18a. To a solution of enone *rac*-**17c** (29.0 g, 102.1 mmol) in 450 mL of DMF was added 175 mL of water. The mixture was heated at 70 °C to dissolve the enone, and then solid KCN (10.0 g, 153.2 mmol) and NH_4Cl (7.6 g, 142.9 mmol) were added as heating was continued at 70–80 °C for 3 h. The reaction mixture was poured into 500 mL of water and was extracted with 3:1 ether–CH_2Cl_2 (4 × 500 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated. Flash chromatography using 20% and then 30% EtOAc–hexane gave 23.5 g (74%) of pure nitrile *rac*-**18a**: mp 134–135 °C (20% EtOAc–hexane); IR (CCl_4) 2238, 1719 cm^{-1}; ^1H NMR δ 7.40–7.29 (m, 5 H), 4.66 (d, J = 11.3 Hz, 1 H, CH_2Ph), 4.47 (d, J = 11.3 Hz, 1 H, CH_2Ph), 2.99 (dt, J = 5.4, 10.3 Hz, 1 H C_3-H), 2.88 (dd, J = 2.0, 6.5 Hz, 1 H, C_9-H), 2.81–2.59 (m, 2 H), 2.22–2.14 (m, 1 H), 2.10–1.98 (m, 1 H), 1.86–1.20 (m, 6 H), 1.20 (s, 3 H, angular CH_3), 1.01 (d, J = 6.3 Hz, 3 H, C_4-CH_3); ^{13}C NMR δ 205.4, 138.4, 128.3 (×2), 127.7 (×2), 127.5, 119.3, 81.8, 71.3, 43.8, 40.9, 40.3, 39.5, 38.4, 35.3, 35.1, 26.2, 16.4, 14.5. Anal. Calcd for $C_{20}H_{25}NO_2$: C, 77.13; H, 8.09. Found: C, 72.22; H, 8.12.

Cyano Ketal *rac*-18b. A methanol solution (1 L) of cyano ketone *rac*-**18a** (33.17 g, 106.7 mmol), triethyl orthoacetate (39 mL, 213 mmol), and *p*-TsOH (1.2 g, 6.4 mmol) was stirred at room temperature for 24 h. A saturated aqueous $NaHCO_3$ solution (100 mL) was added, and stirring was continued for 10 min. Methanol was removed in vacuo, and the residue was taken up in ethyl acetate and washed twice with water. The organic layer was dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (20% ethyl acetate–hexane) gave 31.61 g (83%) of dimethoxy ketal *rac*-**18b** along with 2.32 g (7%) of recovered ketone. Cyano ketal *rac*-**18b**: IR (CCl_4) 2238 cm^{-1}; ^1H NMR δ 7.36–7.30 (m, 5 H), 4.65 (d, J = 11.3 Hz, 1 H, benzyl), 4.44 (d, J = 11.3 Hz, 1 H, benzyl), 3.22 (s, 6 H), 2.99 (dt, J = 5.3, 10.2 Hz, 1 H, C_3-H), 2.55 (dd, J = 1.5, 5.5 Hz, 1 H, C_9-H), 2.46–2.05 (m, 3 H), 1.86–1.76 (m, 2 H), 1.57–1.12 (m, 5 H), 1.04 (d, J = 5.4 Hz, 3 H, C_4-CH_3), 1.00 (s, 3 H, angular CH_3); ^{13}C NMR δ 138.7, 128.3 (×2), 127.8 (×2), 127.5, 120.2, 98.9, 98.8, 82.5, 71.1, 47.4, 41.1, 38.0, 37.4, 35.5, 35.3, 31.5, 29.5, 26.2, 16.9, 14.8.

Ketal Ester *rac*-18d. To a solution of cyano ketal *rac*-**18b** (16.85 g, 47.2 mmol) in 800 mL of diethylene glycol was added KOH (66.08 g, 0.94 mol) in one portion. The resulting solution was heated at 200 °C for 36 h. The solution was cooled to 0 °C and neutralized with 1 N aqueous HCl. The pH was adjusted to 6–7, at which point the acid precipitated. The solid was filtered, the filtrate was extracted with ethyl acetate (3×), and the organic extracts were back-washed with water. The organic layers were dried over $MgSO_4$, filtered, and concentrated. The filter cake was recrystallized (ethyl acetate–hexane). The mother liquors from the recrystallization were combined with the material obtained from extraction and placed in a new Erlenmeyer flask and dissolved in 75 mL of THF [see *Caution* above]. The crystalline material was placed in a separate, new Erlenmeyer flask as a solution in 200 mL of THF. Each flask was treated separately with an excess of ethereal diazomethane (vide supra) until no further evolution of N_2 was observed. Excess diazomethane was decomposed by the dropwise addition of glacial acetic acid. Solvents were removed in vacuo, and the residues were chromatographed with 20% ethyl acetate–hexane as eluent to provide 0.9 g of ester from the combined mother liquor extracts and 10.6 g of ester from the recrystallized material: total yield of yellow oil 11.6 g (63%); IR (CCl_4) 2950, 1735, 1107 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.35–7.28 (m, 5 H), 4.65 (d, J = 11.4 Hz, 1 H), 4.43 (d, J = 11.4 Hz, 1 H), 3.65 (s, 3 H), 3.21 (s, 3 H), 3.13 (s, 3 H), 2.91 (dt, J = 10.4, 4.81 Hz, 1 H, C_3-H), 2.32 (dd, J = 13.0, 3.7 Hz, 1 H, C_9-H), 2.05–1.08 (m, 10 H), 1.02 (d, J = 6.35 Hz, 3 H), 0.96 (s, 3 H); ^{13}C NMR ($CDCl_3$, 22 of 23 carbons) δ 173.9, 138.9, 128.2 (2×), 127.6 (2×), 127.3, 99.4, 82.9, 70.7, 50.9, 47.4, 47.0, 46.1, 36.7, 36.4, 35.9, 31.4, 30.6, 26.1, 15.0, 12.2; HRMS, calcd 390.2407, found 390.2421.

Keto Alcohol *rac*-6b: To a stirred suspension of 0.49 g (12.8 mmol) of $LiAlH_4$ in 15 mL of dry ether was added dropwise a solution of 2.50 g (6.4 mmol) of ketal ester *rac*-**18d** dissolved in 8 mL of ether. After the addition was complete, stirring was continued for an additional 2.5 h. The reaction mixture was successively and cautiously decomposed with 0.5 mL of water, 0.5 mL of 25% aqueous NaOH, and 2.0 mL of water. The mixture was filtered through Celite, and the filtrate was concentrated in vacuo to give a yellow oil that was dissolved in 15 mL of technical grade acetone containing 61.0 mg (0.30 mmol) of *p*-toluenesulfonic acid. The solution was stirred at 25 °C for 3.5 h, 5 mL of saturated aqueous $NaHCO_3$ was added, and stirring was continued for 30 min. The solvent was removed in vacuo, and the residue was taken up in ether, washed with water, and dried over anhydrous Na_2SO_4. Concentration in vacuo followed by flash chromatography (50% hexane–EtOAc) provided 1.85 g (91%) of keto alcohol *rac*-**6a** as a white solid: mp 117–119 °C (ether–EtOAc); IR (CCl_4) 3640, 3458, 2935, 1713 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.36–7.28 (m, 5 H), 4.66 (d, J = 11.4 Hz, 1 H), 4.44 (d, J = 11.4 Hz, 1 H), 3.86 (dd, J = 11.0, 3.3 Hz, 1 H), 3.48 (br t, J = 8.8 Hz, 1 H, HC*H*-OH), 2.92 (dt, J = 10.5, 4.7 Hz, 1 H, C_3-H), 2.63–2.46 (m, 1 H), 2.27 (dd, J = 15.6, 13.0 Hz, 1 H), 2.13–2.05 (m, 3 H), 1.95 (dt, J = 13.2, 3.5 Hz, 1 H), 1.68–1.45 (m, 4 H), 1.29–1.17 (m, 2 H), 1.01 (s, 3 H), 0.99 (d, J = 6.4 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 192.6, 138.6, 128.3 (2×), 127.7 (2×), 127.4, 82.7, 71.1, 62.6, 50.3, 50.2, 41.4, 40.8, 37.7, 35.7, 35.2, 26.2, 15.0, 12.4. Anal. Calcd for $C_{20}H_{28}O_3$: C, 75.91; H, 8.92. Found: C, 75.84; H, 8.97.

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