JOC Article

Synthesis of Stereoisomeric Medium-Ring α,α′-Dihydroxy Cycloalkanones

Leo A. Paquette,* Ryan E. Hartung, John E. Hofferberth, Ivan Vilotijevic, and Jiong Yang

Evans Chemical Laboratories, The Ohio State University, Columbus, Ohio 43210

paquette.1@osu.edu

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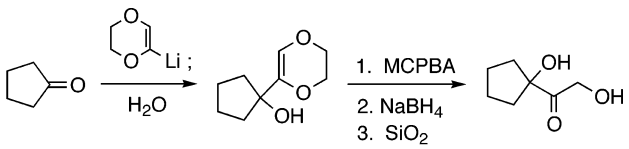
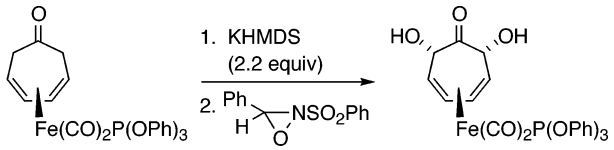
The stereochemical course of the epoxidation of the silyl enol ethers of 2-*tert*-butyldimethylsilyloxycycloheptanone and -cyclooctanone has been investigated and shown to proceed exclusively anti to the existing α-substituent. 2-(Benzyloxy)cyclooctanone behaves similarly, and the presence of a transannular double bond does not alter the outcome. α-Ketol rearrangements are seen to operate during ensuing fluoride ion-induced removal of the silyl protecting groups in select examples. The preferred means for generating the cis isomers of the α,α′-dihydroxy cycloalkanones involves methylenation of the monoprotected *trans*-dihydroxy ketones with the Nysted reagent, followed by oxidation and subsequent reduction with sodium borohydride. Ozonolysis and fluoride ion-induced desilylation complete the route.

The literature documents several options for acquiring *acyclic* α,α′-dihydroxy ketones. These approaches include the ruthenium-catalyzed oxidation of allenes,[1] the overoxidation of silyl enol ethers with *m*-chloroperbenzoic acid,[2] the use of 1-chloroalkyl *p*-tolyl sulfoxides as hydroxycarbonyl anion equivalents,[3] and most notably the addition of 2-lithio-1,4-dioxane to aldehydes and ketones followed by peracid oxidation, borohydride reduction, and acidic hydrolysis as reflected in the conversion of **1** to **2**.[4]



1 **2**

Curiously, the preparation of *cyclic* variants of this compound class has not been pursued despite the attractive density of functionality resident therein. To our knowledge,[5] the only example reported to this time is the conversion of **3** to **4**.[6] When rings are involved, the nuances associated with the cis or trans disposition of the pair of hydroxyl groups warrant consideration. In the case of **3**, pertinent stereochemical considerations are obviously overridden by the iron atom and its attached ligands. The latter overwhelmingly deny anti oxygenation at the enolizable positions.



3 **4**

A synthetic investigation being undertaken by us required the availability of the stereoisomers of α,α′-dihydroxy cycloheptanone and cyclooctanone.[7] The study described below underscores a number of factors that must be given consideration as these targets are approached.

Results and Discussion

***trans*-2,7-Dihydroxycycloheptanone.** The first phase of the program began with cycloheptene oxide (**5**), the ring opening of which with dimethyl sulfoxide and triflic acid,[8] with subsequent exposure to triethylamine, occurred uneventfully to give α-ketol **6a** in 76% yield (Scheme 1). The hydroxyl group was protected as defined by TBS ether **6b** in advance of regioselective enolate anion generation.[9] This reactive intermediate was trapped with TBS chloride in advance of oxidation with *m*-chloroperbenzoic acid. Spontaneous rearrangement of the epoxide followed, with generation of a lone doubly functionalized cycloheptanone. To define the stereochemistry of **7**, we turned to sodium borohydride reduction, whereupon a 2.7:1 mixture of **8** and **9** was generated. The silyl

(1) Laux, M.; Krause, N. *Synlett* **1997**, 765.
(2) Horiguchi, Y.; Nakamura, E.; Kuwajima, I. *Tetrahedron Lett.* **1989**, *30*, 3323.
(3) Satoh, T.; Onda, K.; Yamakawa, K. *J. Org. Chem.* **1991**, *56*, 4129.
(4) Fetizon, M.; Goulaouic, P.; Hanna, I. *Tetrahedron Lett.* **1985**, *26*, 4925.
(5) (a) For a timely review covering the generation of α-hydroxy carbonyl systems, see: Chen, B.-C.; Zhou, P.; Davis, F. A.; Ciganek, E. *Org. React.* **2003**, *62*, 1. (b) Following completion of the present investigation, a synthetic route to enantiomerically pure, orthogonally protected 2,4,6-trihydroxycyclohexanones was reported: Kirsch, S.; Bach, T. *Synthesis* **2003**, 1827. All of the compounds prepared by us are racemic.
(6) Pearson, A. J.; Chang, K. *J. Org. Chem.* **1993**, *58*, 1228.
(7) Paquette, L. A.; Hartung, R. E.; Hofferberth, J. E.; Gallucci, J. C. *Org. Lett.* **2004**, *6*, 969.
(8) Trost, B. M.; Fray, M. J. *Tetrahedron Lett.* **1988**, *29*, 2163.
(9) Paquette, L. A.; O'Neill, S. V.; Guillo, N.; Zeng, Q.; Young, D. G. *Synlett* **1999**, 1857.

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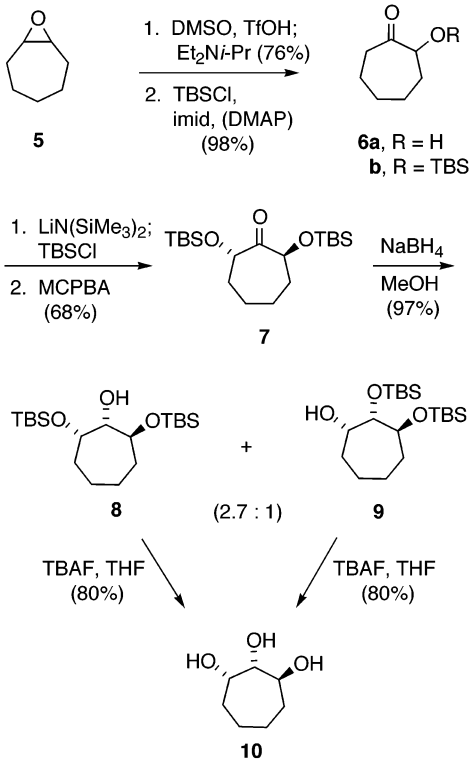
SCHEME 1



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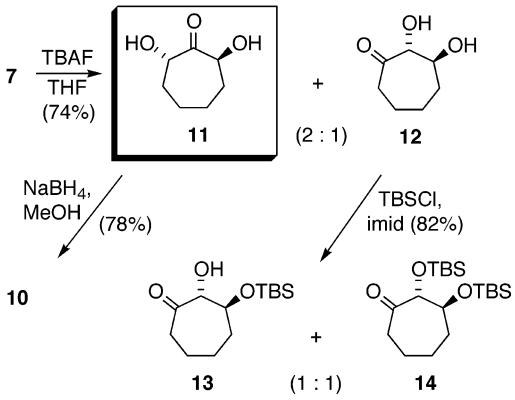
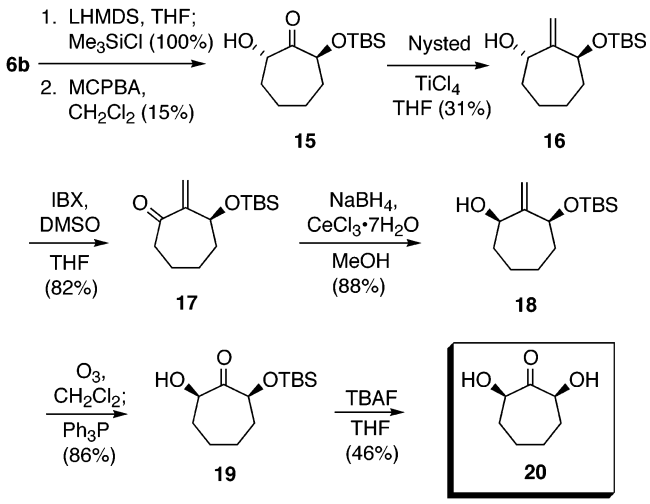


migration involved in the production of **9** was anticipated. Independent exposure of **8** and **9** to fluoride ion in THF resulted in smooth conversion to the identical triol **10**. Should the OTBS groups in **7** be cis-oriented, reduction of its ketone carbonyl followed by desilylation could lead to two symmetrical products, both of which would exhibit four ^{13}C NMR signals. In contrast, comparable processing of the trans isomer would generate a single unsymmetrical triol featuring seven carbon signals. The lower symmetry criterion was uniquely met by **10**, which must therefore be defined as the syn,anti isomer shown.

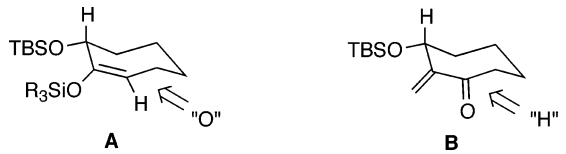
We next addressed the direct desilylation of **7** with TBAF in THF. In the event, the dihydroxy ketones **11** and **12** were formed in a ratio of 2:1 (Scheme 2). The nonidentity of **7** and **14** provided confirmatory evidence of a structural change. The isomerization embodied in the **11** → **12** conversion was not expected since MM3 calculations show *trans*-2,3-dihydroxycycloheptanone to be 6−7 kcal/mol more sterically strained than the *trans*-2,7-isomer. Since **11** and **12** are not interconverted under the reaction conditions, some level of kinetic control is clearly operative. In the present context, it is evident that operation of the α-ketol rearrangement[10] must be carefully monitored and curtailed if maximum overall efficiency with regard to the acquisition of **11** is to be achieved.

SCHEME 3



***cis*-2,7-Dihydroxycycloheptanone.** In light of the findings defined in Schemes 1 and 2, the stereochemical markers present in **20** were considered to require configurational inversion at either the α or α′ position. To facilitate this process while simultaneously minimizing possible operation of an α-ketol rearrangement, the trans monoprotected dihydroxy ketone **15** was prepared and homologated to the exomethylene cycloheptane **16** by reaction with the Nysted reagent[11] (Scheme 3). As indicated by the modest yields, both steps were plagued by competing side reactions. Nonetheless, the ease of execution and the significantly reduced polarity of **16** allowed for suitable scaling of this two-step process.

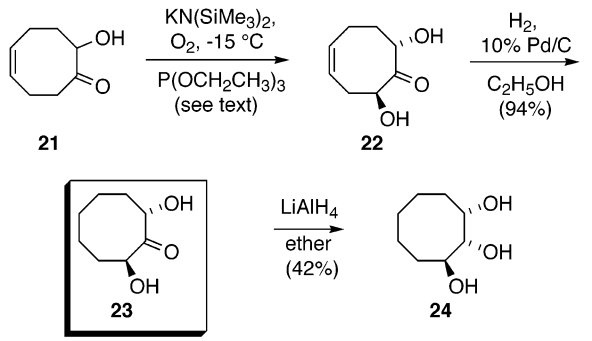
The allylic alcohol generated in this manner reacted with IBX[12] to give the α,*β*-unsaturated ketone **17** efficiently. The formation of this product served to allow for subsequent Luche reduction[13] and conversion exclusively to **18**. The elevated stereoselectivities associated with the epoxidation reaction that delivers **15** and the borohydride reduction that leads to **18** can be adequately explained by taking into account conformations such as **A** and **B** with reagent approach relegated to the exo-surface of the respective π bonds for obvious steric reasons.



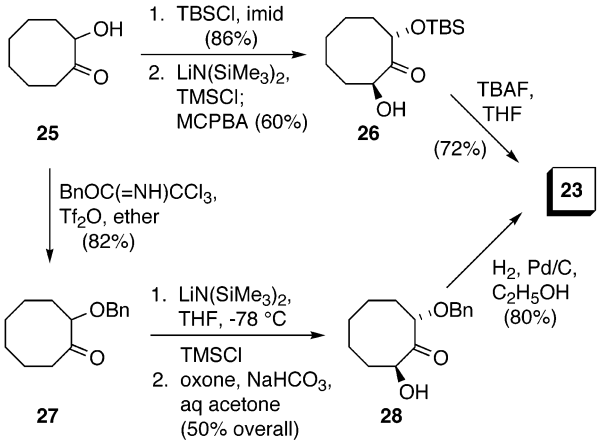
The route to **20** was completed by conventional ozonolysis to introduce the carbonyl group and subsequent

(10) Paquette, L. A.; Hofferberth, J. E. *Org. React.* **2003**, *62*, 477.
(11) Nysted, L. N. U.S. Patent 3,865,848, 1975. This reagent was purchased from the Aldrich Chemical Co.
(12) Nicolaou, K. C.; Baran, P. S.; Zhong, Y.-L.; Barluenga, S.; Hunt, K. W.; Kranich, R.; Vega, J. A. *J. Am. Chem. Soc.* **2002**, *124*, 2233.
(13) Luche, J. L. *J. Am. Chem. Soc.* **1978**, *100*, 2226.

SCHEME 4



SCHEME 5

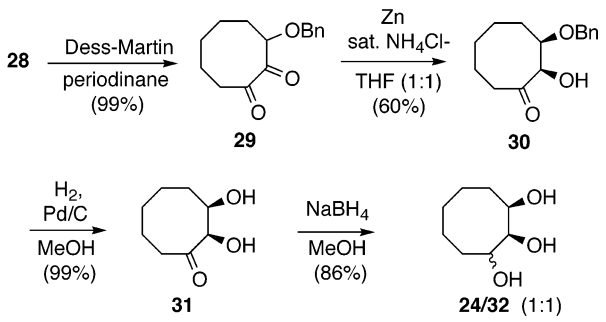


exposure of **19** to TBAF in THF. The spectral properties of **11** (C_{2v}-symmetric) and **20** (C_s-symmetric) are sufficiently distinctive to permit their independent recognition (see the Experimental Section).

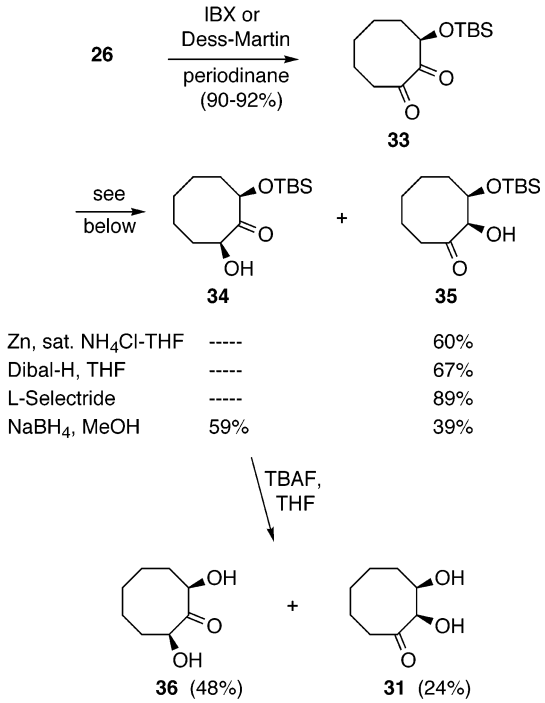
***trans*-2,8-Dihydroxycyclooctanone.** The ready availability of α-ketol **21** by oxidative acid-catalyzed ring opening of 1,5-cyclooctadiene monoxide in the presence of dimethyl sulfoxide followed by treatment with diisopropylethylamine[8] caused us to regard it as a serviceable starting material (Scheme 4). The α′-hydroxyl was introduced by exposure of the potassium enolate to oxygen, followed by the addition of triethyl phosphite. A single dihydroxy ketone was isolated from this reaction (26% yield at 74% conversion). The relative stereochemical disposition of the two OH groups was shown to be trans by a two-step sequence involving catalytic hydrogenation in tandem with lithium aluminum hydride reduction. Based on the eight ^{13}C NMR signals exhibited by **24**, its OH substituents must be related in a cis,anti fashion.

A route to **23** involving early reduction of the unsaturated bond in **21** was simultaneously explored as a potential means for improving overall efficiency. To this end, the hydroxyl group in **25** was transformed into the *tert*-butyldimethylsilyl ether as well as the benzyl ether[14] to gauge if differing protective measures would be influential. Both intermediates were *O*-silylated and epoxidized. The generation of **26** and **28** in this manner (Scheme 5) proceeded in entirely comparable fashion. Desilylation of **26** with TBAF and hydrogenolysis of **28**

SCHEME 6



SCHEME 7



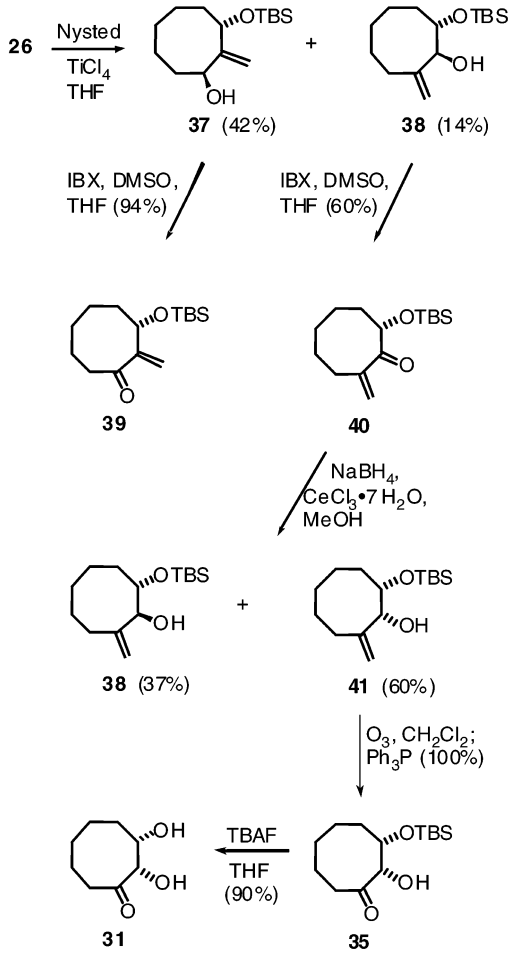
over 10% palladium on charcoal furnished **23** in 72−80% yield. Thus, both intermediates can be regarded as equivalently useful progenitors of **23**.

***cis*-2,8-Dihydroxycyclooctanone.** The first reaction sequence targeting **36** involved the initial oxidation of **28** to α-diketone **29** (Scheme 6). The preparation of this material was projected to be of interest in connection with its possible regio- and stereocontrolled monoreduction. We were cognizant of a report by Hekmatshoar and coworkers[15] describing the ready conversion of α-diketones to α-ketols upon treatment with zinc dust and saturated ammonium chloride solution in THF. However, the examples provided by the Iranian group were exclusively acyclic and offered no insight into the two key considerations of interest here. Under the conditions defined earlier, **29** was smoothly transformed into a single product recognized convincingly by ^1H NMR analysis to be an isomer with the "external" carbonyl intact. The cis stereochemistry resident in **30** was established by conversion via **31** to a mixture of the triols **24** and **32**. Although the regioselectivity associated with the forma-

(14) Paquette, L., A.; Vilotijevich, I.; Hilmey, D.; Yang, J. *Org. Lett.* **2003**, *5*, 463.

(15) Hekmatshoar, R.; Heravi, M. M.; Beheshtiha, Y. S.; Faridbod, F. *Monathsh. Chem.* **2002**, *133*, 195.

SCHEME 8

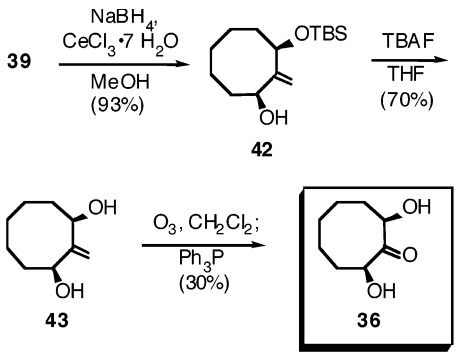


tion of **30** is of interest, care must be exercised in attributing chemical inertness to the "external" carbonyl group. It is possible that reduction of this functionality is actually favored kinetically and that α-ketol rearrangement ensues to deliver **30**. Whatever the precise mechanistic pathway, this transformation was not compatible with our goals.

The brief interlude outlined in Scheme 7 was taken to explore the possible role of a neighboring group effect, if operative. Accordingly, α-diketone **33** was reduced by several reagent combinations. The results recorded for the zinc/ammonium chloride system gave only **35** in a yield comparable to that realized in the case of **30**. Recourse to both Dibal-H and L-Selectride in THF did not lead to a crossover in product composition. However, sodium borohydride proved unique in giving rise to **34**, and predominantly so (59%). In light of the ease in separating **34** from **35** by chromatographic means, this routing came quickly to be regarded as the likely route of choice for preparing **36**. However, exposure of **34** to TBAF for desilylation purposes was met with competing α-ketol rearrangement. The need for repetitive chromatography ultimately caused this scheme to be disfavored and prompted the development of a pathway involving utilization of the Nysted reagent as in the cycloheptane series.

The methylenation of **26** led to a mixture of two isomeric products rich in **37** as desired (Scheme 8). Both

SCHEME 9



allylic alcohols proved to be amenable to further useful transformations. The structural assignment to minor constituent **38** was corroborated by IBX oxidation to enone **40**, the subsequent Luche reduction of which resulted in production of both **41** and **42**. Ozonolysis of **42** provided the previously synthesized α-ketol **35**, an immediate precursor of the well characterized dihydroxy ketone **31**.

Turning subsequently to **37**, we observed its smooth oxidation to **39** (94%, Scheme 8), fully stereocontrolled Luche reduction to **42** (93%, Scheme 9), desilylation without rearrangement, and ultimate ozonolytic cleavage to generate **36** in a preparatively useful manner.

Summary

Synthetic routes to the cis and trans isomers of α,α′-dihydroxy cycloheptanone and cyclooctanone have been developed. The trans isomers are readily accessed by Rubottom oxidation of α-alkoxy or α-silyloxy cyclic ketones, a likely result of the involvement of transition-state conformations such as that depicted in **A**. The competitive operation of α-ketol rearrangements needs to be curtailed in order to realize maximum efficiency. The preferred route to the cis isomers involves early application of the Nysted reagent. Once the exomethylene group is introduced, inversion of stereochemistry at the unprotected carbinol center is possible by sequential oxidation/reduction. It is anticipated that the lessons learned in this series of experiments can be fruitfully applied to other goals associated with the chemistry of medium-sized rings.

Experimental Section

2-Hydroxycycloheptanone (6a). Trifluoromethanesulfonic acid (6.7 mL, 75.9 mmol) was added to cold dimethyl sulfoxide (18.8 mL) and transferred to a solution of cycloheptene oxide (8.5 g, 75.9 mmol) in DMSO (55 mL). The reaction mixture was stirred for 45 min, diluted with CH_2Cl_2 (119 mL), cooled to −78 °C, and treated with diisopropylethylamine (66 mL, 378 mmol). After arrival at rt, the mixture was poured into 10% sodium bisulfate solution (200 mL) and transferred to a separatory funnel where 500 mL of water was added. Extraction with CH_2Cl_2 (4 × 100 mL) was followed by drying and concentration of the combined organic phases. The residue was chromatographed on silica gel (elution with 2:1 hexane/ethyl acetate) to give 7.4 g (76%) of **6a** as a colorless oil having the reported spectral features.[16]

***trans*-2,7-Bis(*tert*-butyldimethylsilyloxy)cycloheptanone (7).** A cold (−78 °C), stirred solution of **6b** (11.46 g, 47.4 mmol) in anhydrous THF (320 mL) was treated with

lithium hexamethyldisilazide (57 mL of 1 M in THF, 57 mmol). After 1 h, *tert*-butyldimethylchlorosilane (9.97 g, 66.4 mmol) was introduced, and the reaction mixture was allowed to warm to rt, quenched with saturated $NaHCO_3$ solution, and extracted with ether (3 × 200 mL). The combined organic layers were dried and concentrated to leave an oily residue that was dissolved in CH_2Cl_2 (575 mL) and cooled to 0 °C in advance of the addition of *m*-chloroperbenzoic acid (12.78 g, 56.9 mmol). The reaction mixture was stirred for 2 h, allowed to warm to rt, quenched with 1 M sodium hydroxide solution (700 mL), and extracted with CH_2Cl_2 (2 × 400 mL). The combined organic phases were washed with brine and saturated $NaHCO_3$ solution, dried, and concentrated. Chromatography of the residue on silica gel (elution with 10:1 hexane/ethyl acetate) afforded **7** as a pale yellow oil (11.65 g, 66%): IR (neat, cm^{-1}) 1728, 1472, 1255; ^1H NMR (300 MHz, $CDCl_3$) δ 4.53 (t, J = 4.4 Hz, 2 H), 1.98−1.43 (m, 8 H), 0.90−0.83 (m, 18 H), 0.11−0.00 (m, 12 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.9, 76.8 (2C), 33.6 (2C), 25.7 (6C), 21.4 (2C), 18.2 (2C), 18.2 (2C), −5.0 (2C), −5.3 (2C); ES HRMS m/z $(M + Na)^+$ calcd 395.2408, obsd 395.2402.

***trans*-2-(*tert*-Butyldimethylsilyloxy)-7-hydroxymethylenecycloheptane (16).** To a flame-dried flask equipped with a stirring bar and a N_2-filled balloon was added a 20% suspension of the Nysted reagent (4.23 g in THF, 1.9 mmol) together with 3.5 mL of THF. The suspension was cooled to 0 °C, and neat titanium tetrachloride (0.21 mL, 1.9 mmol) was introduced dropwise followed by a solution of **15** (0.32 g, 1.24 mmol) in THF (2.4 mL). The mixture was stirred at rt for 24 h, quenched with 10% HCl (100 mL), and transferred to a separatory funnel. The product was extracted into ether (3 × 100 mL), and the combined organic phases were dried and concentrated to leave a residue that was chromatographed on silica gel (elution with 10:1 hexane/ethyl acetate) to give 74 mg (31%) of **16** as a colorless oil: IR (neat, cm^{-1}) 3400, 1472, 1255; ^1H NMR (300 MHz, $CDCl_3$) δ 5.16 (d, J = 5.9 Hz, 2 H), 4.49−4.44 (m, 2 H), 2.18−2.15 (m, 1 H), 1.91−1.86 (m, 1 H), 1.73−1.30 (series of m, 6 H), 0.92 (s, 9 H), 0.09 (s, 3 H), 0.07 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.9, 111.8, 73.2, 72.4, 39.5, 36.7, 26.2 (3C), 25.3, 24.1, 18.5, −4.3, −4.5; ES HRMS m/z $(M + Na)^+$ calcd 279.1750, obsd 279.1757.

3-(*tert*-Butyldimethylsilyloxy)-2-(methylene)cycloheptanone (17). A solution of **16** (74 mg, 0.29 mmol) and IBX (97 mg, 0.35 mmol) in an 8:1 mixture of THF and DMSO (1.6 mL) was stirred at rt for 12 h, quenched with saturated $NaHCO_3$ solution, and extracted with ether (3 × 30 mL). The combined organic phases were dried and concentrated to leave a residue that was chromatographed on silica gel (elution with 20:1 hexane/ethyl acetate) to provide 61 mg (82%) of **17** as a colorless oil: IR (neat, cm^{-1}) 1693, 1472, 1253; ^1H NMR (300 MHz, $CDCl_3$) δ 5.95 (d, J = 1.9 Hz, 1 H), 5.38 (s, 1 H), 4.62 (d, J = 7.0 Hz, 1 H), 2.81−2.75 (m, 1 H), 2.58−2.53 (m, 1 H), 2.09−1.29 (series of m, 6 H), 0.92 (s, 9 H), 0.09 (s, 3 H), 0.04 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.8, 152.2, 121.7, 73.8, 43.8, 38.9, 26.1 (3C), 25.4, 24.7, 18.5, −4.5, −4.7; ES HRMS m/z $(M + Na)^+$ calcd 277.1594, obsd 277.1594.

***cis*-2-(*tert*-Butyldimethylsilyloxy)-7-hydroxymethylenecycloheptane (18).** A solution of **17** (61 mg, 0.24 mmol) and cerium trichloride heptahydrate (89 mg, 0.24 mmol) in methanol (1.1 mL) was cooled to 0 °C and treated with sodium borohydride (9.0 mg, 0.24 mmol) in one portion. The reaction mixture was stirred for 10 min, allowed to warm to rt, quenched with saturated $NaHCO_3$ solution, and extracted with ether (3 × 20 mL). The combined organic phases were dried and concentrated. The product was purified by chromatography on silica gel (elution with 20:1 hexane/ethyl acetate) to furnish 54 mg (88%) of **18** as a colorless oil: IR (neat, cm^{-1}) 3437, 1472, 1254; ^1H NMR (300 MHz, $CDCl_3$) δ 5.08 (d, J = 7.7 Hz, 2 H), 4.47 (t, J = 5.4 Hz, 1 H), 4.35 (dd, J = 7.3, 5.6 Hz, 1 H), 2.00−1.94 (m, 1 H), 1.90−1.77 (m, 3 H), 1.74−1.59 (m, 2 H), 1.53−1.46 (m, 1 H), 1.43−1.36 (m, 1 H), 0.94 (s, 9 H), 0.12 (s, 3 H), 0.11 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.2, 112.9, 76.4, 75.3, 38.4, 37.5, 26.2 (3C), 24.8, 24.5, 18.4, −4.4, −4.5; ES HRMS m/z $(M + Na)^+$ calcd 279.1750, obsd 279.1757.

***cis*-2-(*tert*-Butyldimethylsilyloxy)-7-hydroxycycloheptanone (19).** Ozone was bubbled through a cold (−78 °C) solution of **18** (43 mg, 0.17 mmol) in CH_2Cl_2 (14 mL) until a faint blue color persisted. Oxygen bubbling followed until the reaction mixture became clear, at which point triphenylphosphine (53 mg, 0.20 mmol) was introduced and warming to rt ensued. The solvent was evaporated, and the residue was chromatographed on silica gel (elution with 10:1 hexane/ethyl acetate) to deliver **19** as a colorless oil (37 mg, 86%): IR (neat, cm^{-1}) 3482, 1722, 1472; ^1H NMR (300 MHz, $CDCl_3$) δ 4.43 (dd, J = 7.9, 4.1 Hz, 1 H), 4.29 (m,1 H), 1.99−1.30 (series of m, 8 H), 0.93 (s, 9 H), 0.14 (s, 3 H), 0.09 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 212.8, 75.4, 75.2, 34.7, 33.6, 26.1 (3C), 24.9, 24.8, 18.7, −4.2, −4.7; ES HRMS m/z $(M + Na)^+$ calcd 281.1543, obsd 281.1548.

***trans*-2,8-Dihydroxy-4-cycloocten-1-one (22).** Dry oxygen was bubbled through a solution of **21** (15 mg, 0.14 mmol) in THF (3 mL) for 5 min at −15 °C, at which point potassium hexamethyldisilazide (640 μL of 0.5 M in THF) was introduced. Stirring was maintained in the cold for 3 min prior to treatment with triethyl phosphite (1 mL), quenching with brine, and extraction with ethyl acetate. The combined organic layers were dried, filtered, and evaporated. The above protocol was repeated five times and the combined residues were chromatographed on silica gel (elution with 14−16% ethyl acetate in hexane) to give 20 mg (26%) of recovered **21** and 22 mg (26%) of **22** as white needles: mp 81−83 °C; IR (neat, cm^{-1}) 3406, 1715, 1458; ^1H NMR (300 MHz, $CDCl_3$) δ 5.83−5.68 (m, 2 H), 4.89 (dd, J = 8.9, 8.9 Hz, 1 H), 4.56−4.50 (m, 1 H), 3.40−3.29 (m, 1 H), 2.81−2.64 (m, 1 H), 2.40−2.31 (m, 2 H), 2.01−1.80 (m, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 215.0, 132.1, 128.9, 77.8, 76.0, 33.1, 29.4, 20.0; ES HRMS m/z $(M + Na)^+$ calcd 179.0679, obsd 179.0688.

***trans*-2-(*tert*-Butyldimethylsilyloxy)-8-hydroxycyclooctanone (26).** A solution of **25** (1.0 g, 7.0 mmol), imidazole (720 mg, 10.6 mmol), and DMAP (86 mg, 0.70 mmol) in CH_2Cl_2 (38 mL) was treated with *tert*-butyldimethylchlorosilane (1.59 g, 10.6 mmol) in one portion, heated at reflux, and stirred for 24 h. After cooling, saturated $NaHCO_3$ solution was introduced and the product was extracted into CH_2Cl_2 (3×). The combined organic phases were dried and concentrated to leave a residue that was chromatographed on silica gel. Elution with 10:1 hexane/ethyl acetate furnished the siloxy ketone as a colorless oil (1.63 g, 86%): IR (neat, cm^{-1}) 1706, 1464, 1254; ^1H NMR (300 MHz, $CDCl_3$) δ 4.19−4.18 (m, 1 H), 2.76−2.67 (m, 1 H), 2.24−1.51 (series of m, 11 H), 0.90 (s, 9 H), 0.05 (s, 3 H), 0.04 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 218.2, 78.1, 45.1, 39.2, 35.4, 27.2, 25.7 (3C), 25.2, 25.1, 20.8, 18.1, −5.0, −5.1; ES HRMS m/z $(M + Na)^+$ calcd 279.1750, obsd 279.1753.

A 0.91 g (3.6 mmol) sample of the above material was dissolved in THF (25 mL), cooled to −78 °C, treated with a solution of lithium hexamethyldisilazide in THF (4.26 mL of 1 M, 4.26 mmol), and stirred for 1 h in the cold. Chlorotrimethylsilane (0.75 g, 5.0 mmol) was introduced, and the reaction mixture was stirred at −78 °C for 1 h prior to warming to rt, quenching with saturated $NaHCO_3$ solution, and extraction with ether (3 × 50 mL). The combined organic phases were dried and concentrated in advance of chromatographic purification of the residue on silica gel. Elution with 10:1 hexane/ethyl acetate gave **26** as a colorless oil (56 mg, 60%): IR (neat, cm^{-1}) 3489, 1702, 1471; ^1H NMR (300 MHz, $CDCl_3$) δ 4.51 (dd,

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J = 5.2, 2.3 Hz, 1 H), 4.48 (dd, J = 5.8, 2.2 Hz, 1 H), 3.59 (s, 1 H), 2.96−2.90 (m, 1 H), 2.01−1.34 (series of m, 9 H), 0.95 (s, 9 H), 0.10 (s, 3 H), 0.07 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 219.6, 77.7, 74.6, 39.4, 27.6, 26.0 (3C), 24.8, 21.9, 19.1, 18.3, −4.4, −4.9; ES HRMS m/z $(M + Na)^+$ calcd 295.1699, obsd 295.1682.

3-Benzyloxy-1,2-cyclooctanedione (29). A solution of **28** (500 mg, 2.0 mmol) in dry CH_2Cl_2 (10 mL) was added to a stirred suspension of the Dess−Martin periodinane (1.27 g, 3.0 mmol) in 30 mL of the same solvent. The reaction mixture was stirred at rt for 2 h and quenched with water. The separated aqueous phase was extracted with CH_2Cl_2 (3×), and the combined organic solutions were washed with brine, dried, and evaporated. The residue was chromatographed on silica gel (elution with 10% ethyl acetate in hexane) to yield 490 mg (99%) of **29** as a yellow solid: mp 46−48 °C; IR (neat, cm^{-1}) 1704, 1464, 1454; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39−7.27 (m, 5 H), 4.77 (d, J = 11.6 Hz, 1 H), 4.43 (d, J = 11.6 Hz, 1 H), 4.39−4.35 (m, 1 H), 2.88 (ddd, J = 19.5, 11.7, 3.8 Hz, 1 H), 2.37 (ddd, J = 19.1, 13.5, 3.3 Hz, 1 H), 2.12−2.03 (m, 1 H), 2.02−1.71 (m, 4 H), 1.66−1.57 (m, 2 H), 1.49−1.35 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.5, 207.7, 137.4, 128.5 (2C), 128.0, 127.9 (2C), 81.2, 72.3, 39.0, 29.0, 27.4, 20.6, 19.9; ES HRMS m/z $(M + Na)^+$ calcd 269.1148, obsd 269.1138.

***cis*-3-Benzyloxy-2-hydroxycyclooctanone (30).** A solution of **29** (50 mg, 0.20 mmol) in 1 mL of a 1:1 mixture of saturated NH_4Cl and THF was treated with zinc dust (26 mg, 0.4 mmol), stirred vigorously at rt for 2 h, and diluted with CH_2Cl_2 and water. The separated aqueous layer was extracted with CH_2Cl_2, and the combined organic phases were dried and concentrated. Purification of the residue by chromatography on silica gel (elution with 10% ethyl acetate in hexane) furnished 30 mg (60%) of **30** as a colorless oil: IR (neat, cm^{-1}) 3466, 1703, 1465; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39−7.27 (m, 5 H), 4.65 (s, 2 H), 4.45 (d, J = 2.5 Hz, 1 H), 4.09 (ddd, J = 13.2, 6.6, 2.8 Hz,1 H), 3.55 (br s, 1 H), 2.50−2.45 (m, 2 H), 2.00−1.83 (m, 3 H), 1.80−1.49 (m, 3 H), 1.43−1.30 (m, 1 H), 1.16−1.02 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.0, 138.2, 128.4 (2C), 127.73, 127.68 (2C), 77.7, 77.6, 71.0, 38.6, 27.9, 26.9, 26.6, 21.6; ES HRMS m/z $(M + Na)^+$ calcd 271.1305, obsd 271.1303.

***cis*-2,3-Dihydroxycyclooctanone (31).** A solution of **30** (10 mg, 0.04 mmol) in ethanol (1.5 mL) was admixed with 10% palladium on carbon (5 mg), and the mixture was stirred for 2 h under 1 atm of hydrogen. The predescribed workup afforded 6 mg (99%) of **31** as a colorless oil: IR (neat, cm^{-1}) 3398, 1702, 1059; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.49−4.39 (m, 1 H), 4.44 (d, J = 3.5 Hz, 1 H), 2.67 (ddd, J = 14.3, 10.7, 3.6 Hz, 1 H), 2.50−2.46 (m, 1 H), 2.00−1.68 (series of m, 6 H), 1.50−1.41 (m, 1 H), 1.03−0.96 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.1, 79.6, 70.9, 38.6, 31.6, 28.1, 26.5, 22.6; ES HRMS m/z $(M + Na)^+$ calcd 181.0835, obsd 181.0839.

Borohydride Reduction of 31. A solution of **31** (2.6 mg, 0.015 mmol) in methanol (0.5 mL) was cooled to 0 °C, treated with sodium borohydride (0.2 mg, 0.015 mmol), and stirred for 10 min prior to being quenched with saturated $NaHCO_3$ solution. The separated aqueous layer was extracted with ether (3 × 15 mL), and the combined organic phases were dried and concentrated. Chromatographic purification of the residue on silica gel (elution with 50% hexane/ethyl acetate) gave an inseparable 1:1 mixture of **24** and **32** as recognized by high-field ^{1}H NMR analysis.

Pure triol **32** was independently prepared by comparable reduction of **34** followed by desilylation: white solid; mp 84−85 °C; IR (neat, cm^{-1}) 3614, 1477, 1236; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.03−3.99 (m, 2 H), 3.96 (d, J = 2.5 Hz, 1 H), 2.37 (s, OH), 2.10−2.04 (m, 2 H), 1.92−1.80 (m, 4 H), 1.71−1.34 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 77.6, 76.1 (2C), 32.6 (2C), 29.1, 22.9 (2C); ES HRMS m/z $(M + Na)^+$ calcd 183.0991, obsd 183.0993.

Oxidation of 26. A. With IBX. A solution of **26** (50.0 mg, 1.82 mmol) and IBX (608 mg, 2.18 mmol) in 8:1 THF/DMSO (2.25 mL) was stirred at rt for 12 h and quenched with saturated $NaHCO_3$ solution. The aqueous layer was extracted with ether (3 × 50 mL), and the combined organic phases were dried and purified.

Chromatography of the residue on silica gel (elution with 10:1 hexane/ethyl acetate) gave **33** as a colorless oil (46 mg, 92%): IR (neat, cm^{-1}) 1707, 1464, 1253; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.66 (dd, J = 8.8, 4.9 Hz, 1 H), 2.94−2.80 (m, 1 H), 2.40−2.34 (m, 1 H), 2.09−1.41 (series of m, 8 H), 0.94 (s, 9 H), 0.15 (s, 3 H), 0.08 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.6, 208.5, 75.9, 40.0, 31.9, 27.3, 26.1 (3C), 21.2, 20.3, 18.7, −4.4, −5.0; ES HRMS m/z $(M + Na)^+$ calcd 293.1543, obsd 293.1532.

B. With the Dess−Martin Periodinane. A solution of **26** (50 mg, 1.82 mmol) and the Dess−Martin periodinane (924 mg, 2.18 mmol) in 8:1 THF/DMSO (2.25 mL) was stirred at rt for 4 h, quenched with saturated $NaHCO_3$ solution, and extracted with ether (3 × 50 mL). The combined organic phases were dried and concentrated, and the residue was chromatographed on silica gel (elution with 10:1 hexane/ethyl acetate) to give **33** as a colorless oil (47 mg, 90%), identical in all respects with the material prepared above.

Reduction of 33. A. With Zinc and Saturated Ammonium Chloride. A solution of **33** (70 mg, 0.29 mmol) in THF (0.7 mL) containing ammonium chloride (0.7 mg) was treated with zinc dust (36 mg, 0.57 mmol) in one portion. The reaction mixture was stirred for 2 h, quenched with saturated $NaHCO_3$ solution, and extracted with ether (3 × 50 mL). The combined organic phases were dried, concentrated, and subjected to chromatograpy on silica gel. Elution with 20:1 hexanes/ethyl acetate furnished 42 mg (60%) of **35** as a yellowish oil: IR (neat, cm^{-1}) 3487, 1702, 1472; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.35 (d, J = 2.9 Hz, 1 H), 4.30 (dt, J = 9.2, 3.1 Hz, 1 H), 2.59−2.51 (m, 2 H), 2.01−1.89 (series of m, 5 H), 0.94 (s, 9 H), 0.15 (s, 3 H), 0.12 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.0, 79.5, 73.9, 40.1, 31.2, 27.9 (3C), 24.4, 20.5, 18.5, −4.3, −4.4; ES HRMS m/z $(M + Na)^+$ calcd 295.1699, obsd 295.1713.

Desilylation of 34. To a solution of **34** (10 mg, 0.037 mmol) in THF (1 mL) was added 30 μL (0.039 mmol) of 1 M TBAF in the same solvent. After 15 min at rt, the reaction mixture was concentrated in vacuo, and the residue was chromatographed on silica gel. Elution with 50% hexane in ethyl acetate afforded 2.8 mg (48%) of **36** and 1.4 mg (24%) of **31**, both as colorless oils.

For **36**: white solid; mp 120−121 °C; IR (neat, cm^{-1}) 3693, 1705, 1246; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.41 (dd, J = 7.7, 3.7 Hz, 2 H), 3.26 (s, 2 H), 2.33−2.27 (m, 2 H), 1.97−1.90 (m, 2 H), 1.84−1.66 (m, 4 H), 1.48−1.40 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 218.2, 74.1 (2C), 33.4 (2C), 24.6, 21.9 (2C); ES HRMS m/z $(M + Na)^+$ calcd 181.0835, obsd 181.0829.

Nysted Homologation of 26. Into a flame-dried flask equipped with a stirring bar and a N_2-filled balloon was placed a 20% suspension of the Nysted reagent in THF (14.7 g, 6.45 mmol) and additional THF (12 mL). The suspension was cooled to 0 °C, and neat titanium tetrachloride (0.71 mL, 6.45 mmol) was introduced dropwise followed by the addition of **26** (1.17 g, 4.3 mmol) dissolved in THF (8 mL). The reaction mixture was stirred at rt for 24 h, quenched with 10% HCl (100 mL), transferred to an addition funnel, and extracted with ether (3 × 100 mL). The combined organic layers were dried and evaporated to leave a residue that was purified by chromatography on silica gel. Elution with 20:1 hexane/ethyl acetate gave 48 mg (42%) of **37** and 157 mg (14%) of **38**, both as colorless oils.

For **37**: IR (neat, cm^{-1}) 3581, 1462, 1253; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.18 (s, 1 H), 5.18 (d, J = 0.6 Hz, 1 H), 4.48 (dd, J = 9.2, 4.7 Hz, 1 H), 4.27 (dd, J = 8.4, 4. Hz, 1 H), 2.04−1.99 (m,1 H), 1.83−1.38 (m, 9 H), 0.91 (s, 9 H), 0.08 (s, 3 H), 0.05 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.0, 113.5, 73.6, 71.7, 36.8, 35.3, 26.2 (3C), 26.1, 22.4, 21.7, 18.4, −4.2, −4.4; ES HRMS m/z $(M + Na)^+$ calcd 293.1907, obsd 293.1901.

For **38**: IR (neat, cm^{-1}) 3581, 1462, 1253; ^1H NMR (300 MHz, $CDCl_3$) δ 5.24 (s, 1 H), 5.09 (s, 1 H), 3.98 (d, $J = 8.4$ Hz, 1 H), 3.61 (dt, $J = 9.0$, 3.3 Hz, 1 H), 2.41−2.29 (m, 2 H), 1.84−1.50 (m, 8 H), 0.96 (s, 9 H), 0.18 (s, 3 H), 0.16 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.4, 114.8, 79.1, 78.2, 34.3, 32.8, 27.3, 26.1 (3C), 26.1, 22.8, 18.4, −3.6, −4.2; ES HRMS *m*/*z* $(M + Na)^+$ calcd 293.1907, obsd 293.1902.

Luche Reduction of 40. A solution of **40** (30 mg, 0.11 mmol) in methanol (0.5 mL) containing cerium trichloride heptahydrate (42 mg, 0.11 mmol) was cooled to 0 °C, treated with sodium borohydride (4.3 mg, 0.11 mmol), and after 5 min quenched with water (30 mL). The products were extracted into ether (3 × 30 mL), and the combined organic phases were dried and concentrated. Chromatography of the residue on silica gel (elution with 10:1 hexane/ethyl acetate) furnished 11 mg (37%) of **38** and 18 mg (60%) of **41**, both as colorless oils.

For **41**: IR (neat, cm^{-1}) 3581, 1462, 1253; ^1H NMR (300 MHz, $CDCl_3$) δ 5.24 (s, 1 H), 5.09 (s, 1 H), 3.98 (d, $J = 8.4$ Hz, 1 H), 3.61 (dt, $J = 9.0$, 3.3 Hz, 1 H), 2.41−2.29 (m, 2 H), 1.84−1.50 (m, 8 H), 0.96 (s, 9 H), 0.18 (s, 3 H), 0.16 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.4, 114.8, 79.1, 78.2, 34.3, 32.8, 27.3, 26.1 (3C), 26.1, 22.8, 18.4, −3.6, −4.2; ES HRMS *m*/*z* $(M + Na)^+$ calcd 293.1907, obsd 293.1902.

***cis*-(3-*tert*-Butyldimethylsilyloxy)-2-hydroxycyclooctanone (35).** A solution of **42** (9.5 mg, 0.035 mmol) in CH_2Cl_2 (3 mL) was cooled to −78 °C and ozonolyzed until a faint blue color persisted. Oxygen was bubbled through the system until the solution became clear, at which point triphenylphosphine (11 mg, 0.042 mmol) was introduced. After being warmed to rt, the reaction mixture was concentrated and the residue was purified by chromatography on silica gel (elution with 10:1 hexane/ethyl acetate) to provide 9.5 mg (100%) of **35**.

Desilylation of 35. A solution of **35** (70.7 mg, 0.26 mmol) in dry THF (3 mL) was treated with a 1 M solution of TBAF in THF (312 μL, 0.312 mmol), stirred for 30 min, and worked up in the usual manner to give 38 mg (93%) of **31** as a white solid, identical to the substance isolated earlier.

***cis*-2-(*tert*-Butyldimethylsilyloxy)-8-hydroxymethylenecyclooctane (42).** A solution of **39** (85 mg, 0.32 mmol) and cerium trichloride heptahydrate (119 mg, 0.32 mmol) in methanol (1.4 mL) was cooled to 0 °C, at which point sodium borohydride (12 mg, 0.32 mmol) was introduced in one portion. The reaction mixture was stirred for 10 min, allowed to warm to rt, and worked up in the predescribed manner. Chromatography on silica gel (elution with 10:1 hexane/ethyl acetate) gave 79 mg (93%) of **42** as a colorless oil: IR (neat, cm^{-1}) 3395, 1461, 1253; ^1H NMR (300 MHz, $CDCl_3$) δ 5.15 (s, 2 H), 4.36 (dd, $J = 8.5$, 5.7 Hz, 1 H), 4.28 (dd, $J = 9.2$, 4.5 Hz, 1 H), 2.07−1.27 (series of m, 10 H), 0.93 (s, 9 H), 0.11 (s, 3 H), 0.10 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.7, 114.5, 77.0, 75.6, 36.9, 35.5, 27.4, 26.2 (3C), 22.4, 22.3, 18.4, −4.4, −4.5; ES HRMS *m*/*z* $(M + Na)^+$ calcd 293.1907, obsd 293.1901.

Supporting Information Available: Select experimental details and copies of the high-field ^1H and ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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