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Chelation-Controlled Reduction: Stereoselective Formation of *syn*-1,3-Diols and Synthesis of Compactin and Mevinolin Lactone

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Chelation-controlled reduction of chiral β-alkoxy ketones containing a competing β′-oxygen functionality has been investigated. Various *syn*-1,3-diols were prepared conveniently by reduction of β-alkoxy ketones with LiI/$LiAlH_4$ (*syn*:*anti* selectivity up to >99:1). The corresponding β-alkoxy ketones were derived from nitro-aldol reactions of chiral alkoxy aldehydes with a series of nitro compounds. This methodology is utilized in a short and efficient synthesis of the δ-lactone moiety of the HMG-CoA reductase inhibitors compactin and mevinolin.

syn-1,3-Diol subunits are common structural features imbedded in numerous biologically important natural products.[1] Among known methodologies, stereoselective reductions directed by preexisting chiral β-alkoxy or hydroxy centers are particularly useful. In this context, asymmetric reductions of β-hydroxy ketones[2] and δ-hydroxy-β-keto esters[3] have been reported. Although directed reductions of acyclic β-hydroxy ketones are known to provide excellent *syn*-diastereoselectivities, the corresponding reduction of β-alkoxy ketones generally provides lower stereochemical control. Reductions of acyclic β-alkoxy ketones with $LiAlH_4$ in the presence of LiI, however, has been shown to proceed with high diastereoselectivities by Mori, Suzuki, and co-workers.[4] In connection with our synthetic studies toward madumycin and griseoviridin, we investigated the stereoselective reduction of acyclic chiral β-alkoxy ketones containing a competing β′-oxygen functionality.[5] Herein, we report a useful synthetic route to a variety of functionalized optically active *syn*-1,3-diols by chelation-controlled reduction of chiral β-alkoxy ketones using Mori and Suzuki's $LiAlH_4$−LiI protocol.[4] The syntheses of various chiral β-alkoxy ketones involve nitro-aldol reaction of chiral α-alkoxy aldehydes and conversion of the aldolates to the corresponding nitro alkene derivatives and then to chiral β-alkoxy ketones. This methodology has been utilized in a short and efficient synthesis of the (4*R*,6*S*)-tetrahydro-2-pyrone moiety of the HMG-CoA reductase inhibitors compactin and mevinolin, which is essential for their biological properties.[6]

Reaction steps leading to various β-alkoxy ketones from chiral α-alkoxy aldehydes are described in Scheme 1. Henry reaction of (+)-2,3-*O*-isopropylidene-D-glyceraldehyde **1a**[7] with 3-nitropropanol triisopropylsilyl ether **2c**[8] in the presence of a catalytic amount of DBU (0.1 equiv) in CH_3CN provided the nitro-aldol product (**3**) as a diastereomeric mixture in 83% yield. The nitro-aldol product was dehydrated using copper chloride and dicyclohexylcarbodiimide (DCC) as described by Seebach and co-workers.[9] Treatment of the above mixture of nitro-aldols with DCC (2.2 equiv) and CuCl (1.5 equiv) in CH_3CN followed by heating the resulting mixture at 60 °C for 15 h afforded nitro alkene **4d** as a mixture (3.6:1 by ^1H NMR analysis) of *Z*/*E* isomers in 87% yield. Reduction of the nitro alkene mixture with zinc (3 equiv) and 4 N aqueous HOAc in THF at 0 °C for 15 min provided the corresponding oxime.[10] Heating the oxime with $NaHSO_3$ (5 equiv) in a mixture of H_2O and EtOH (1:2) at reflux furnished ketone **5d**[11] in 90% yield for two steps. Following the above procedures, aldehyde **1a** and other nitro derivatives (**2a**, **2b**, and **2d)** afforded various β-alkoxy ketones **5a**−**c** and **5f**.[12] Other chiral alkoxy aldehydes **1b**−**e** were prepared from the corresponding known[13] alcohols by Swern oxidation. Reaction of the resulting aldehydes with nitro alkane **2c** provided the corresponding nitro aldols, which were converted to ketones **5e** and **5g**−**i** following the reaction sequence described above. Of particular note, various protecting group compatibility

(1) (a) Nicolaou, K. C.; Daines, R. A.; Ogawa, Y.; Chakraborty, T. K. *J. Am. Chem. Soc.* **1988**, *110*, 4696. (b) Rychnovsky, S. D.; Griesegraber, G.; Kim, J. *J. Am. Chem.. Soc.* **1994**, *116*, 2621 and references therein.

(2) Narasaka, K.; Pai, F. *Tetrahedron* **1984**, *40*, 2223.

(3) Chen, K.-M.; Hardtmann, G. E.; Prasad, K.; Repic, O.; Shapiro, M. *Tetrahedron Lett.* **1987**, *28*, 155.

(4) (a) Mori, Y.; Kuhara, M.; Takeuchi, A.; Suzuki, M. *Tetrahedron Lett.* **1988**, *29*, 5419. (b) Mori, Y.; Takeuchi, A.; Kageyama, H.; Suzuki, M. *Tetrahedron Lett.* **1988**, *29*, 5423. (c) Mori, Y.; Suzuki, M. *Tetrahedron Lett.* **1989**, *30*, 4383. (d) Mori, Y.; Suzuki, M. *Tetrahedron Lett.* **1989**, *30*, 4387. (e) Mori, Y.; Furukawa, H. *Chem. Pharm. Bull.* **1994**, *42*, 2161.

(5) (a) Ghosh, A. K.; Liu, W.-M. *J. Org. Chem.* **1997**, *62*, 7908. (b) Ghosh, A. K.; Lei, H. *Synthesis* **2002**, 371.

(6) Stokker, G. E.; Hoffman, W. F.; Alberts, A. W.; Cragoe, E. J.; Deana, A. A.; Gilfilan, J. L.; Huff, J. W.; Novello, F. C.; Prugh, J. D.; Smith, R. L.; Willard, A. K. *J. Med. Chem.* **1985**, *28*, 347.

(7) Jackson, D. *Synth. Commun.* **1988**, *18*, 337

(8) Prepared by protection of 3-nitro propanol with TIPSOTf and 2,6-lutidine. Please see: Öhrlein, R.; Schwab, W.; Ehrler, R.; Jäger, V. *Synthesis* **1986**, 535.

(9) Knochel, P.; Seebach, D. *Synthesis* **1982**, 1017.

(10) Baer, H. H.; Rank, W. *Can. J. Chem.* **1969**, *47*, 145.

(11) Araújo, H. C.; Mahajan, J. R. *Synthesis* **1981**, 49.

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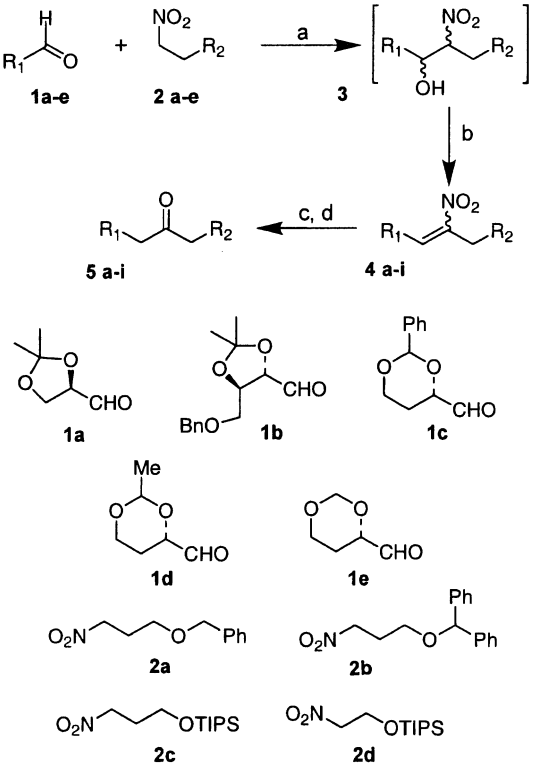
SCHEME 1[a]

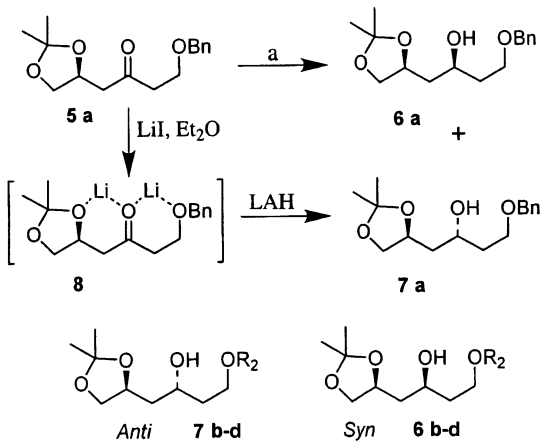


[a] Reagents and conditions: (a) DBU, CH_3CN, 15 h; (b) CuCl, DCC, CH_3CN, 60 °C, 15 h; (c) Zn, HOAc, THF, 0 °C, 15 min; (d) $NaHSO_3$, EtOH−H_2O, reflux.

in both aldehyde and nitroalkane substrates is evident in Scheme 1.

Various β-alkoxy ketones thus obtained from convenient transposition of α-alkoxy aldehydes were subjected to LAH reduction in the presence of LiI following the procedure of Mori and Suzuki.[4] As shown in Scheme 2, reduction of ketone **5a** with $LiAlH_4$ (10 equiv) and LiI (10 equiv) at −78 °C in ether resulted in the formation of a mixture (diastereomeric ratio 2.4:1) of *syn*- and *anti*-1,3-diol derivatives **6a** and **7a**, respectively, in 83% combined yield after silica gel chromatography.[14] Interestingly, the observed diastereoselectivity is modest compared to that of the reduction of a β-alkoxy ketone with β'-alkyl substituents reported by Mori and Suzuki.[4]

SCHEME 2[a]

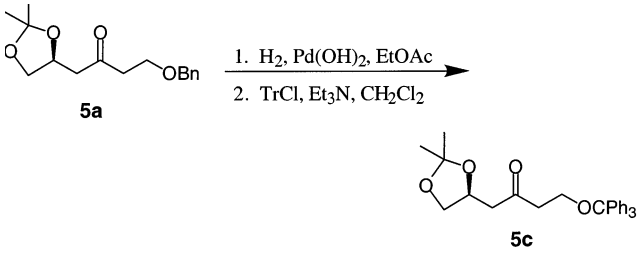


[a] Reagents and conditions: (a) LiI, $LiAlH_4$, Et_2O, −78 °C, 83%.

The reason for this lower selectivity is presumably the presence of a competing chelating substitutent at the β'-position as shown in stereochemical model **8**. On the basis of this model, it appeared that the competing β'-chelation could be minimized by incorporating sterically demanding protecting groups for the β'-hydroxy position. Indeed, as shown in Table 1, protection of the β'-hydroxyl group with sterically more hindered diphenylmethyl and triphenylmethyl groups resulted in significant improvement in *syn*-diastereoselectivities with increasing bulkiness of the protective group (entries 2 and 3). Furthermore, reduction of the β-alkoxy ketone with a bulky TIPS group at the β'-alkoxy position (ketone **5d**, entry 4) provided a single *syn*-1,3-diol derivative (**6d**) by ^1H and ^{13}C NMR analysis.[14] Similarly, reduction of the corresponding β-alkoxy ketone with γ- and δ-alkoxy substituents (ketone **5e**, entry 5) also provided *syn*-1,3-diol derivative **6e** exclusively. We have also examined reduction of a β-alkoxy ketone with OTIPS in the α'-position. However, the selectivity is reduced significantly (4:1) as a result of the stronger chelation of the α'-oxygen compared to that of the β'-oxygen (entries 4 and 6). Initial stereochemical assignment of the major *syn*-isomer **6a** was based upon its conversion to *syn*-1,3-diol derivative **6d**.[15] The stereochemistry of **6d** was conclusively established after its conversion to the δ-lactone of HMG-CoA reductase inhibitors mevinolin and comparison of spectroscopic properties.[16]

We subsequently examined the stereochemical influence of various substituents at the β-oxygen. As shown, with decreasing size from benzylidene to ethylidene to methylene (**5g**−**i**), the *syn*-selectivities improved from 3.7:1 to 7:1 (entries 7−9). These results are consistent with the fact that a smaller substituent on the 1,3-dioxane ring leads to better metal chelation between the β-oxygen and ketone carbonyl oxygen, which translates into better reduction stereoselectivities. Stereochemical assignment of **6g** was established after its conversion to isopropylidene derivative **10** and analysis of its ^{13}C NMR chemical shifts based upon the report of Rychnovsky and

(12) Compound **5c** was prepared as follows:



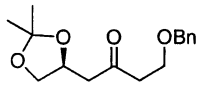
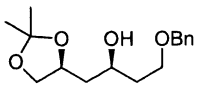
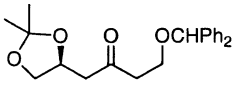
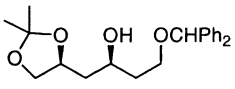
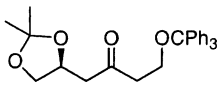
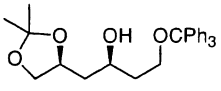
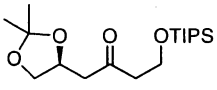
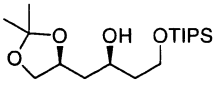
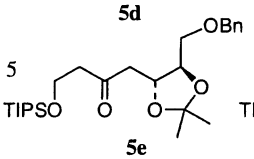
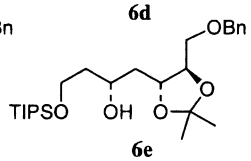
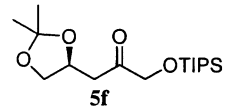
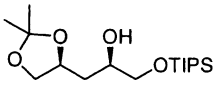
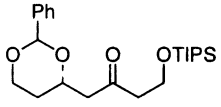
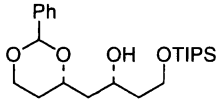
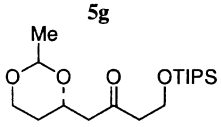
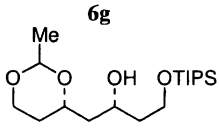
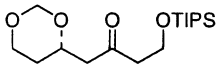
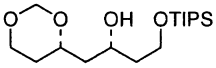
(13) (a) Pawlak, J. Nakanishi, K. *J. Org. Chem.* **1987**, *52*, 2896. (b) Rychnovshy, S. D.; Plzak, K.; Pickering, D. *Tetrahedron Lett.* **1994**, *35*, 6799. (c) Gras, J.; Nouguier, R.; Mchich, M. *Tetrahedron Lett.* **1987**, *28*, 6601. (d) Hungerbühler, E.; Seebach, D. *Helv. Chim. Acta.* **1981**, *64*, 687.

(14) Diastereomeric ratios (*syn*/*anti*) were calculated based upon the relative intensity of the stereogenic proton or carbon (by ^1H or ^{13}C NMR in C_6D_6 or $CDCl_3$) on the dioxane or dioxolane ring.

(15) Catalytic hydrogenation of **6a** in ethyl acetate over Pearlman's catalyst followed by TIPS protection with TIPSCl and imidazole in DMF provided **6d**.

(16) Ghosh, A. K.; Lei, H. *J. Org. Chem.*, **2000**, *65*, 4779.

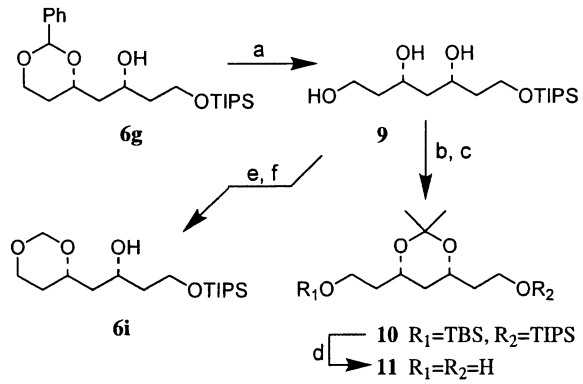
TABLE 1. Stereoselective Reduction of β-Alkoxy Ketones

Entry	β-alkoxy ketone	Major Product	*Syn:Anti*[a] (%Yield[b])
1	 **5a**	 **6a**	2.4 : 1 (83)
2	 **5b**	 **6b**	7.5 : 1 (82)
3	 **5c**	 **6c**	11.5 : 1 (86)
4	 **5d**	 **6d**	>99 : 1 (93)
5	 **5e**	 **6e**	>99 : 1 (87)
6	 **5f**	 **6f**	4 : 1 (95)
7	 **5g**	 **6g**	3.7 : 1 (94)
8	 **5h**	 **6h**	5 : 1 (94)
9	 **5i**	 **6i**	7 : 1 (90)

[a] Ratios determined by ^1H and ^{13}C NMR after chromatography. [b] Mixture yield after chromatography.

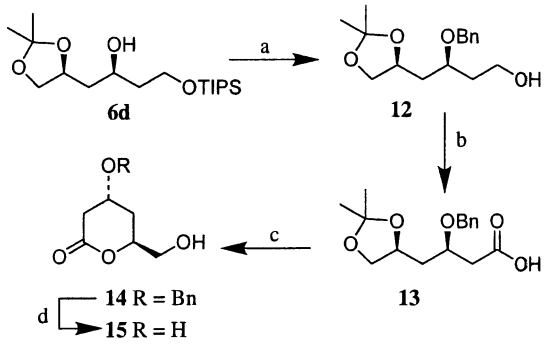
co-workers.[17] As depicted in Scheme 3, removal of the benzylidene protecting group in **6g** by catalytic hydrogenation provided triol **9**. Selective protection of the primary hydroxyl group as a TBS ether with TBSCl and triethylamine in the presence of a catalytic amount of DMAP followed by protection of the 1,3-diol as an acetonide with 2,2-dimethoxy propane and a catalytic amount of *p*-TsOH in CH_2Cl_2 furnished isopropylidene derivative **10**. The 18−31 ppm region of the ^{13}C NMR of **10** revealed the presence of two peaks corresponding to the two methyl groups of the acetonide: one being at 19.8 ppm and the other being at 30.2 ppm. Based upon the report of Rychnovsky, these chemical shift values are

SCHEME 3[a]



[a] Reagents and conditions: (a) H_2, 10% Pd-C, EtOAC; (b) TBSCl, Et_3N, DMAP, CH_2Cl_2 (c) $Me_2C(OMe)_2$, *p*-TsOH, CH_2Cl_2; (d) TBAF, THF; (e) MOMCl, iPr_2NEt, DMAP, CH_2Cl_2; (f) $BF_3{\cdot}OEt_2$, CH_2Cl_2.

SCHEME 4[a]



[a] Reagents and conditions: (a) (i) NaH, BnBr, TBAI, THF, reflux; (ii) TBAF, THF, 76% two steps; (b) $NaIO_4$, $RuCl_3{\cdot}3H_2O$, $CCl_4-CH_3CN-H_2O$; (c) *p*-TsOH, CH_2Cl_2, 65% two steps; (d) H_2, $Pd(OH)_2$, EtOAc, 85%.

diagnostic of a *syn*-1,3-diol derivative. Interestingly, isopropylidene derivative **10** provides access to an optically active *syn*-1,3-diol derivative containing differential protecting groups at the left and right sides. As expected, removal of the silyl group in **10** by treatment with tetrabutylammonium fluoride in THF provided known *meso*-diol **11**.[18] The stereochemistry of diol derivative **6i** derived from **5i** was confirmed by correlation with **6g**. The primary hydroxy group in triol **9** was protected as a MOM ether with MOMCl and iPr_2NEt in the presence of a catalytic amount of DMAP in CH_2Cl_2. The MOM group was converted to formal derivative **6i** by treatment with $BF_3{\cdot}OEt_2$ in CH_2Cl_2. The resulting compound was identical (by ^1H and ^{13}C NMR) to the major product obtained from reduction of ketone **5i**.

The synthetic application of this methodology was demonstrated in a short and efficient synthesis of lactone **15,** which is the key structural feature of compactin and mevinolin for their potent HMG-CoA reductase inhibitory properties.[6] As shown in Scheme 4, protection of alcohol **6d** as a benzyl ether by treatment with NaH and benzyl bromide in the presence of tetrabutylammonium iodide (catalytic) in THF for 5 h followed by removal of TIPS by treatment with tetrabutylammonium fluoride afforded

(17) Rychnovsky, S. D.; Skalitzky, D. J. *Tetrahedron Lett.* **1990**, *31*, 945.

(18) Bonini, A.; Racioppi, R.; Viggiani, L.; Righi, G.; Rossi, L. *Tetrahedron: Asymmetry* **1993**, *4*, 793.

alcohol **12** (76% yield for 2 steps). Oxidation of alcohol **12** according to Sharpless's procedure[19] using $NaIO_4$ and $RuCl_3 \cdot H_2O$ (catalytic) in a mixture of CCl_4, CH_3CN, and water at 23 °C for 30 min provided carboxylic acid **13**. Treatment of acid **13** with a catalytic amount of *p*-TsOH resulted in concomitant deprotection of the acetonide and lactonization (65% yield for two steps) to provide lactone **14**. Removal of the benzyl protection in **14** by catalytic hydrogenation using Pearlman's catalyst furnished compactin lactone **15** ($[\alpha]^{23}_D$ +2.2, *c* 2.5, MeOH; lit.[20] $[\alpha]^{23}_D$ +1.81, *c* 0.992, MeOH) in 85% yield after silica gel chromatography. The synthesis of lactone **15** thus provided evidence of the absolute configuration of alcohol **6d**.

In conclusion, a nitro aldol reaction combined with chelation-controlled $LiAlH_4$ reduction provided stereocontrolled access to functionalized *syn*-1,3-diol derivatives. The overall protocol is practical and quite efficient. Further studies of these reactions are currently under investigation.

Experimental Section

Anhydrous solvents and reagents were obtained as follows: tetrahydrofuran and diethyl ether, distillation from sodium and benzophenone; methylene chloride, distillation from CaH_2; diisopropylethylamine and triethylamine, distillation from CaH_2. All other solvents were HPLC grade. Analytical HPLC analysis was performed on a reverse phase column (4.6 mm × 25 cm) with 60%CH_3CN/H_2O as the solvent, flow rate 1.0 mL/min, λ 185 nm). Column chromatography was performed with 240−400 mesh silica gel under low pressure of 5−10 psi. Thin-layer chromatography (TLC) was carried out with silica gel plates.

Synthesis of nitro Compounds 2a−d. 3-Nitro-*O*-benzyl-1-propanol 2a.[21] To a stirred solution of 3-nitropropanol (1.57 g, 14.9 mmol) and trichlorobenzyloxyacetimide (4.2 mL, 22.4 mmol) in CH_2Cl_2 (80 mL) at 0 °C was added TFA (0.2 mL, 2.2 mmol) dropwise, and the resulting mixture turned cloudy. The resulting mixture was stirred for 1.5 h, and the solvent was removed under reduced pressure. The residue was dissolved in hexane and ether (6:1), washed with $NaHCO_3$ and brine, dried over Na_2SO_4, and evaporated under reduced pressure. The residue was purified by silica gel chromatography (3% EtOAc in hexanes) to give the title compound (2.55 g, 88%) as a yellow oil: IR (film) 2932, 2865, 1552, 1453, 1098 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.26−2.34 (m, 2H), 3.57 (t, 2H, J = 5.7 Hz), 4.51−4.57 (m, 4H), 7.31−7.37 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.3, 65.8, 72.5, 72.9, 127.4, 127.5, 128.2, 137.5.

3-Nitro-*O*-diphenlymethyl-1-propanol 2b. To a stirred solution of 3-nitropropanol (119.9 mg, 1.1 mmol) and benzhydrol (251.2 mg, 1.3 mmol) in CH_2Cl_2 (10 mL) was added TsOH (216.9 mg, 1.1 mmol). The resulting mixture was stirred for 15 h and was quenched by saturated aqueous $NaHCO_3$. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure. The residue was purified by silica gel chromatography (5% EtOAc in hexanes) to give the title compound (209.8 mg, 81%) as a yellow oil: IR (film) 3028, 2869, 1551, 1452, 1382, 1095 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.31−2.35 (m, 2H), 3.56 (t, 2H, J = 5.7 Hz), 4.55 (t, 2H, J = 6.9 Hz), 5.38 (s, 1H), 7.30−7.39 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.4, 64.7, 72.6, 83.8, 126.5, 127.4, 128.2, 141.5.

3-Nitro-*O*-triisopropylsilyl-1-propanol 2c. To a stirred solution of 3-nitropropanol (1.55 g, 14.7 mmol) in CH_2Cl_2 (40 mL) was added TIPSOTf (5.9 mL, 22.1 mmol) and 2,6-lutidine (3.4 mL, 29.4 mmol). The resulting mixture was stirred for 1.5 h and quenched with saturated aqueous $NaHCO_3$. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure. The residue was purified by silica gel chromatography (2% EtOAc in hexanes) to give the title compound (3.51 g, 91%) as an yellow oil: IR (film) 2944, 2867, 1554, 1463, 1381, 1115 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.0−1.07 (m, 21H), 2.18−2.26 (m, 2H), 3.81 (t, 2H, J = 5.7 Hz), 4.54 (t, 2H, J = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.7, 17.9, 30.2, 59.5, 72.4.

2-Nitro-*O*-triisopropylsily-1-ethanol 2d. To a stirred solution of 2-nitroethanol (355.7 mg, 3.91 mmol) in CH_2Cl_2 (10 mL) was added TIPSOTf (1.5 mL, 5.8 mmol) and 2,6-lutidine (0.91 mL, 7.8 mmol). The resulting mixture was stirred for 1.5 h and quenched with saturated aqueous $NaHCO_3$. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure. The residue was purified by silica gel chromatography (5% EtOAc in hexanes) to give the title compound (941.2 mg, 97%) as a yellow oil: IR (film) 2945, 2868, 1561, 1463, 1367, 1127 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.96−1.05 (m, 21H), 4.21 (t, 2H, J = 5.2 Hz), 4.45 (t, 2H, J = 5.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.7, 17.7, 59.9, 77.7.

Representative Procedure for Nitro Aldol Reaction and Subsequent Dehydration. Nitroalkene 4d. To a stirred solution of nitro compound **2c** (2.82 g, 10.8 mmol) in dry CH_3CN (40 mL) was added DBU (0.15 mL, 1.0 mmol) dropwise. The reaction mixture was stirred for 5 min, aldehyde **1a** (1.40 g, 10.7 mmol) was added, and the resulting solution was stirred for 15 h. The reaction was quenched with saturated aqueous NH_4Cl. The layers were separated, and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (10% EtOAc in hexanes) to give nitro alcohol **3d** (3.77 g**,** 83%) as a mixture of isomers. To a stirred solution of the above nitro alcohols in CH_3CN were added DCC (4.85 g, 23.5 mmol) and CuCl (1.59 g. 16.1 mmol), and the resulting solution was heated at 60 °C for 15 h. After this period, the reaction was cooled to room temperature, diluted with ethyl acetate, and quenched with oxalic acid (6 g) in methanol. The suspension was filtered through a Celite pad, and the filtrate was washed with saturated aqueous $NaHCO_3$ and brine and dried over Na_2SO_4. After evaporation of the solvent under reduced pressure, the residue was purified by column chromatography (5% EtOAc in hexanes) to afford the nitro alkene (**4d**, 2.88 g 87%) as a yellow oil in a mixture of *E*/*Z* isomers. Major isomer: ^1H NMR (300 MHz, $CDCl_3$) δ 0.99−1.01 (m, 21H), 1.38 (s, 3H), 1.45 (s, 3H), 2.85−2.91 (m, 2H), 3.75 (dd, 1H, J = 6.6, 8.1 Hz), 3.80−3.85 (m, 2H), 4.18 (dd, 1H, J = 6.6, 9.0 Hz), 4.85 (q, 1H, J = 8.7 Hz), 7.10 (d, 1H, J = 8.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.8, 17.9, 25.6, 26.6, 30.6, 60.7, 68.8, 71.8, 110.6, 134.6, 151.0.

Representative Procedure for Ketones 5a−i. Ketone 5d. To a stirred solution of nitro alkene **4d** (1.96 g, 5.26 mmol) in THF (80 mL) at 0 °C was added freshly activated zinc dust (1.02 g, 15.8 mmol) and 4 N acetic acid (7.9 mL, 31.6 mmol). After 15 min, the suspension was filtered, and the filter cake was washed with ethyl acetate. Saturated $NaHCO_3$ was added to the filtrate, and this was extracted with ethyl acetate. The combined organic layers were washed with brine and dried over Na_2SO_4. After evaporation of the solvent under reduced pressure, the oxime was used directly for the next step without further purification. To a stirred solution of the above oxime in ethanol (20 mL) and H_2O (10 mL) was added $NaHSO_3$ (2.74 g, 26.3 mmol). The resulting solution was heated to reflux for

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5 h. After this period, the reaction was cooled to room temperature and concentrated under reduced pressure. The residue was diluted with H_2O and extracted with ethyl acetate (2 × 20 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. After evaporation of the solvent under reduced pressure, the residue was purified by column chromatography (10% EtOAc in hexanes) on silica gel to provide ketone **5d** (1.56 g, 86% 2 steps) as an oil: $[\alpha]^{23}_D$ +7.65 (*c* 4.72, $CHCl_3$); IR (film) 2942, 2866, 1713, 1463, 1379, 1100, 1066 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.02−1.07 (m, 21H), 1.34 (s, 3H), 1.39 (s, 3H), 2.62−2.70 (m, 3H), 2.98 (dd, 1H, J = 5.8, 17.4 Hz), 3.52 (dd, 1H, J = 6.9, 8.5 Hz), 3.97 (t, 2H, J = 6.4 Hz), 4.19 (dd, 1H, J = 5.8, 8.5 Hz), 4.44−4.48 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.8, 17.9, 25.4, 26.8, 46.3, 48.0, 59.1, 69.4, 71.5, 108.6, 207.7; HRMS (EI) *m*/*z* calcd for $C_{18}H_{36}O_4NaSi$ (M^+ + Na) 367.2281, found 367.2295.

Representative Procedure for LiI/$LiAlH_4$ Reduction. *syn*-1,3-Diol 6d. To a stirred solution of ketone **5d** (287 mg, 0.8 mmol) in ether (20 mL) was added LiI (1.11 g, 8.3 mmol), and the resulting mixture was stirred at −40 °C for 5 min. After this period, the mixture was cooled to −78 °C, and $LiAlH_4$ (315.0 mg, 8.3 mmol) was added. The reaction was stirred for 30 min and quenched with aqueous 10% potassium sodium tartrate solution. The layers were separated, and the aqueous layer was extracted with ether. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (20% EtOAc in hexanes) on silica gel to provide alcohol **6d** (273.3 mg, 95%) as a colorless oil: $[\alpha]^{23}_D$ +8.89 (*c* 0.98, $CHCl_3$); IR (film) 3500, 2941, 2866, 1463, 1098 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.03−1.07 (m, 21H), 1.36 (s, 3H), 1.41 (s, 3H), 1.63−1.85 (m, 4H), 3.57 (t, 1H, J = 7.7 Hz), 3.77 (d, 1H, H = 1.6 Hz), 3.87−4.01 (m, 3H), 4.11 (dd, 1H, J = 5.87, 8.07 Hz), 4.27−4.51 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.7, 17.9, 25.7, 26.9, 38.8, 40.6, 62.4, 69.6, 69.7, 74.3, 108.8; HRMS (EI) *m*/*z* calcd for $C_{18}H_{38}O_4NaSi$ (M^+ + Na) 369.2437, found 369.2425.

1-*O*-(Triisopropylsilyl)-3,5,7-heptatriol 9. To a stirred solution of **6g** (102 mg, 0.25 mmol) in ethyl acetate (10 mL) and methanol (3 mL) was added $Pd(OH)_2$ (25 mg), and the resulting solution was placed under a H_2 balloon and stirred for 15 h at room temperature. The mixture was filtered, and the filtrate was evaporated under reduced pressure to provide compound **9** (79.6 mg, 99%) as a colorless oil. The purity of **9** was determined to be >98% by HPLC (retention time 9.12 min): $[\alpha]^{23}_D$ −11.4 (*c* 0.92, $CHCl_3$); IR (film) 3356, 2942, 2866, 1462, 1099 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.04−1.10 (m, 21H), 1.50 (td, 1H, J = 14.1, 2.2 Hz), 1.60−1.65 (m, 1H), 1.68−1.79 (m, 4H), 3.79−3.86 (m, 2H), 3.93 (dt, 1H, J = 9.6, 3.3 Hz), 4.00 (td, 1H, J = 10.1, 4.5 Hz), 4.14−4.20 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 12.0, 18.3, 38.9, 39.0, 43.6, 61.9, 63.8, 73.2, 74.4.

1,3-*O*-Methylene-7-*O*-(triisopropylsilyl)-5-heptanol 6i (from 9). To a stirred solution of **9** (7.8 mg, 0.024 mmol) and DMAP (1 mg) in CH_2Cl_2 (5 mL) was added iPr_2NEt (42 μL, 0.24 mmol). The resulting solution was cooled to 0 °C, and MOMCl (3 μL, 0.04 mmol) was added. The reaction was stirred for 12 h and quenched with NH_4Cl. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure. The residue was dissolved in CH_2Cl_2 (3 mL), and the mixture was cooled to 0 °C. $BF_3{\cdot}OEt_2$ (3 μL, 0.02 mmol) in CH_2Cl_2 (1 mL) was added. After 5 min, the reaction was quenched with $NaHCO_3$. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure. The residue was purified by column chromatography (20% EtOAc in hexanes) on silica gel to provide **6i** (3 mg): IR (film) 3503, 2944, 2924, 2866, 1099 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.05−1.10 (m, 21H), 1.53−1.88 (m, 6H), 3.73 (dt, 2H, J = 2.5, 11.9 Hz), 3.84−3.98 (m, 3H), 4.00−4.06 (m, 1H), 4.10 (dd, 1H, J = 4.9, 11.4 Hz), 4.72 (d,1H, J = 6.2 Hz), 5.05 (d, 1H, J = 6.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.7, 17.9, 31.9, 38.9, 43.1, 62.5, 66.6, 69.1, 75.4, 93.7; MS (EI) *m*/*z* 153.3, 333.2.

(3*S*,5*R*)-1-*O*-(*tert*-Butyldimethylsilyl)-7-*O*-(triisopropylsilyl)-3,5-*O*-isopropylidene-heptane 10. To a stirred solution of compound **9** (48.6 mg, 0.15 mmol) in CH_2Cl_2 (5 mL) were added DMAP (1.8 mg, 0.01 mmol), TBSCl (22.6 mg, 0.15 mmol), and Et_3N (23 μL, 0.17 mmol). The resulting solution was stirred at room temperature for 15 h and quenched with aqueous NH_4Cl. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure. The residue was dissolved in CH_2Cl_2 (10 mL), and *p*-TsOH (3 mg, 0.015 mmol) was added. The resulting solution was stirred for 30 min and quenched with aqueous $NaHCO_3$. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine and dried over Na_2SO_4. After evaporation of the solvent under reduced pressure, the residue oil was purified by column chromatography (5% EtOAc in hexanes) on silica gel to provide compound **10** (58.5 mg, 82% 2 steps) as a colorless oil: ^1H NMR (400 MHz, $CDCl_3$) δ 0.04 (s, 6H), 0.88 (s, 9H), 1.04−1.07 (m, 21H), 1.18 (m 1H), 1.36 (s, 3H), 1.42 (s, 3H), 1.52 (td, 1H, J = 2.5, 13 Hz), 1.58−1.71 (m, 4H), 3.62−3.75 (m, 3H), 3.80 (m, 1H), 4.0−4.10 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.3, 11.9, 18.0, 19.8, 25.9, 29.7, 30.2, 37.4, 39.5, 39.7, 58.9, 59.1, 65.6 (2C), 98.4; HRMS (EI) *m*/*z* calcd for $C_{25}H_{54}O_4NaSi_2$ (M^+ + Na) 497.3458, found 497.3460.

***meso*-3,5-*O*-Isopropylidene-1,7-heptadiol 11.** To a stirred solution of **10** (13.0 mg, 0.03 mmol) in THF (5 mL) was added 1 M tetrabutylammonium flouride in THF (0.12 mL, 0.12 mmol), and the reaction mixture was stirred for 2 h. The reaction was quenched with aqueous NH_4Cl. The layers were separated, and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine and dried over Na_2SO_4. After evaporation of solvent under reduced pressure, the residue was purified by column chromatography (80% EtOAc in hexanes) on silica gel to provide alcohol **11** (5.3 mg, 87%) as a colorless oil: ^1H NMR (400 MHz, $CDCl_3$) δ 1.36−1.40 (m, 1H), 1.39 (s, 3H), 1.44−1.46 (m, 1H), 1.49 (s, 3H), 1.67−1.77 (m, 4H), 2.41 (br, 2H), 3.63−3.82 (m, 4H), 4.08−4.17 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.8, 30.2, 36.4 38.0, 60.7, 69.2, 98.7.

(2*S*,4*S*)-1,2-*O*-Isopropylidene-4-*O*-benzyl-6-hexanol 12. To a stirred solution of NaH (81.6 mg, 2.0 mmol) and alcohol **6d** (190 mg, 0.5 mmol) in THF (20 mL) were added tetrabutylammonium iodide (19 mg, 0.05 mmol) and benzyl bromide (0.12 mL, 2 mmol). The resulting mixture was heated to reflux for 5 h. After this period, the solution was cooled to room temperature and quenched by aqueous NH_4Cl. The layers were separated, and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine and dried over Na_2SO_4. Evaporation of the solvent under reduced pressure provided a residue, which was used for next step without further purification. To a stirred solution of the above residue in THF (10 mL) was added tetrabutylammonium flouride (1.0 M solution in THF) (1.53 mL, 1.5 mmol), and the reaction mixture was stirred for an additional 5 h. The reaction was quenched with aqueous NH_4Cl. The layers were separated, and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine and dried over Na_2SO_4. After evaporation of the solvent under reduced pressure, the residue was purified by column chromatography (50% EtOAc in hexanes) on silica gel to provide alcohol **12** (119.3 mg, 76% 2 steps) as a colorless oil: $[\alpha]^{23}_D$ −18.6 (*c* 2.20, $CHCl_3$); IR 3422, 2984, 2936, 2874, 1370, 1214, 1055 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.34 (s, 3H), 1.41 (s, 3H), 1.72−1.90 (m, 3H), 1.99−2.07 (m, 1H), 2.31 (br, 1H), 3.52 (t, 1H, J = 7.8 Hz), 3.72−3.83 (m, 3H), 4.01 (dd, 1H, J = 6.0, 8.1 Hz), 4.15−4.24 (m, 1H), 4.54 (ABq, 2H, J = 11.7, $\Delta\nu$ = 22.8 Hz),

7.32−7.36 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.7, 27.0, 36.1, 37.3, 60.1, 69.6, 70.9, 72.8, 75.2, 108.7, 127.8, 127.9, 128.4, 138.0.

(4*R*,6*S*)-4-Benzyloxy-6-hydroxymethyltetrahydro-2-pyrone 14. To a stirred solution of alcohol **12** (87 mg, 0.28 mmol) and $NaIO_4$ (181.8 mg, 0.84 mmol) in CCl_4 (1 mL), CH_3CN (1 mL), and H_2O (0.6 mL) was added ruthemium trichloride hydrate (5.8 mg, 0.03 mmol), and the mixture was stirred for 30 min at room temperature. After this period, CH_2Cl_2 (5 mL) was added, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and filtered. To the solution was added *p*-TsOH (5.3 mg, 0.03 mmol). The resulting mixture was stirred for 1 h at room temperature and quenched with aqueous $NaHCO_3$. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (80% EtOAc in hexanes) on silica gel to provide alcohol **14** (43 mg, 65% 2 steps) as a colorless oil: $[\alpha]^{23}_D$ +0.9 (*c* 1.71, $CHCl_3$); IR (film) 3409, 2924, 1727, 1254, 1072 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.93 (ddd, 1H, J = 3.0, 11.5, 14.3 Hz), 2.07−2.07 (m, 1H), 2.57 (br, 1H), 2.64 (dd, 1H, J = 4.7, 17.6 Hz), 2.80 (ddd, 1H, J = 2.0, 3.0, 17.6 Hz), 3.63 (dd, 1H, J = 4.4, 12.4 Hz), 3.88 (dd, 1H, J = 3.0, 12.4 Hz), 4.03−4.07 (m, 1H), 4.54 (ABq, 2H, J = 12.0 Hz, $\Delta\nu$ = 13.7 Hz), 4.71−4.77 (m, 1H), 7.29−7.36 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.7, 35.8, 64.4, 69.2, 70.5, 77.3, 127.5, 127.9, 128.5, 137.5, 170.0; HRMS (EI) *m*/*z* calcd for $C_{13}H_{17}O_4$ (M^+ + H) 237.1127, found 237.1137.

(4*R*,6*S*)-4-Hydroxy-6-hydroxymethyltetrahydro-2-pyrone 15. To a stirred solution of **7** (28 mg, 0.1 mmol) in ethyl acetate (3 mL) was added $Pd(OH)_2$ (3.5 mg), and the resulting solution was placed under a H_2 balloon and stirred for 5 h at room temperature. The mixture was filtered, and the filtrate was evaporated under reduced pressure. The residue oil was purified by column chromatography (EtOAc) on silica gel to provide title compound **15** (15 mg, 85%) as a colorless oil: $[\alpha]^{23}_D$ +2.2 (*c* 2.5, MeOH); lit.[20] $[\alpha]^{23}_D$ +1.81 (*c* 0.992, MeOH); IR (film) 3377, 2930, 1712 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.90−2.04 (m, 4H), 2.68−2.76 (m, 2H), 3.68 (dd, 1H, J = 12.4, 4.6 Hz), 3.93 (dd, 1H, J = 12.4, 2.8 Hz), 4.48 (m, 1H), 4.83 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.3, 38.5, 62.7, 64.5, 76.2, 169.6; MS (CI) *m*/*z* 147 (M^++H); HRMS (EI) *m*/*z* calcd for $C_6H_9O_3$ (M^+ − OH) 129.0552, found 129.0545.

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Supporting Information Available: Reaction yields and spectral and analytical data for compounds **4a,b,e**−**i**, **5a**−**c,e**−**i**; spectral data for **6a**−**c,e**−**i**; and copies of ^{1}H and ^{13}C NMR spectra for compounds **2**, **5**, **6**, **9**−**12**, **14**. This material is available free of charge via the Internet at http://pubs.acs.org.

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