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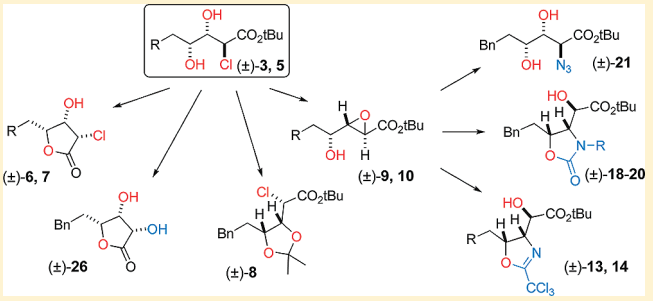
Highly Stereocontrolled and Regiocontrolled Syntheses of 2,3,4-Trisubstituted Alkanoates and Lactones

Christopher P. Hencken, Douglas T. Genna, Maxime A. Siegler, and Gary H. Posner*

Department of Chemistry, The Johns Hopkins University, 3400 North Charles Street, Baltimore, Maryland 21218, United States

Supporting Information

ABSTRACT: New chlorodiols (±)-**3** and (±)-**5** are densely functionalized and versatile synthons. They are converted in one step on a gram scale into 2-chlorolactones (±)-**6** and (±)-**7** and into 4-hydroxy glycidate esters (±)-**9** and (±)-**10**. The 4-hydroxy glycidate esters (±)-**9** and (±)-**10** are converted stereospecifically and regiospecifically into oxazolines (±)-**13** and (±)-**14** and into cyclic carbamates (±)-**18**−(±)-**20**. The 4-hydroxy glycidate ester (±)-**10** undergoes stereocontrolled and regiocontrolled epoxide opening by sodium azide to form the 2-azido-3,4-dihydroxy alkanoate (±)-**21**. Finally, chlorodiol (±)-**5** reacts stereospecifically with silver triflate to form the 2,3-dihydroxyfuranone (±)-**26**.



Chemoselective synthesis of new, versatile, densely functionalized synthons is a growing field in organic chemistry. Among these valuable intermediates are optically active vicinal amino alcohols,[1] diols,[2] amino diols,[3] polyols[4] such as carbohydrates, and dihydroxyfuranones.[5] These structurally significant motifs are found in many natural products.[6,7] The value of these building blocks is enhanced even more when stereocontrolled transformations of only one or two of the several resident functionalities can be achieved selectively in good yields. We recently developed[8] an asymmetric synthesis of densely functionalized and highly enantiomerically enriched 2,3,4-trisubstituted alkanoate esters illustrated by ester (−)-**3** (Scheme 1). Faithful transfer of chirality from the allylic selenide (−)-**1** to the corresponding allylic chloride (−)-**2**, followed by syn-dihydroxylation,[9,10] produced the new chemical entity 2-chloro-3,4-dihydroxy alkanoate ester (−)-**3**, as the major diastereomer in 63% yield and in 95% ee. X-ray crystallography confirmed the absolute stereochemistry of chiron (−)-**3** to be 2(*S*),3(*S*),4(*R*).

From the previously unknown chloro diol (±)-**3** and its less crowded homologue (±)-**5**, we chemoselectively synthesized seven versatile, densely functionalized synthons with high stereochemical control of three contiguous carbon stereocenters. Clearly, starting with enantiomerically pure chloro diols **3** and **5** will provide the corresponding enantiomerically pure products.

In natural products synthesis, α-chloro esters and α-chlorolactones are often highly desirable intermediates.[11] The new chloro diols (±)-**3** and (±)-**5** were treated with hydrochloric acid in dioxane to form the all-cis 2-chloro-3-hydroxy γ-lactone (±)-**6** in 85% yield on a $^1/_2$ g scale and the homologous all-cis lactone (±)-**7** in 70% yield (Scheme 2). The proton NMR spectra of lactones (±)-**6** and (±)-**7** have the coupling constant $J_{2,3}$ = 4.4 and 4.0 Hz, respectively, consistent with the cis stereochemistry of the hydrogen atoms at positions 2 and 3;[12] this result was confirmed via X-ray crystallography. The racemic chloro diol (±)-**5** was treated with 2,2-dimethoxypropane and catalytic *p*-toluenesulfonic acid in THF to form acetonide α-chloro ester (±)-**8** in 95% yield (Scheme 2).

Glycidate esters are important intermediates in the synthesis of many functionally rich building blocks.[13,14] Treatment of chloro diols (±)-**3** and (±)-**5** with cesium carbonate in acetone converted the vicinal chlorohydrin unit into the corresponding epoxide in the form of the trans 2,3-epoxy-4-hydroxy alkanoate (±)-**9** in 92% yield on a $^1/_2$ g scale and in the form of homologous alkanoate (±)-**10** in 90% yield on a 1 g scale (Scheme 2). The proton NMR spectra of both glycidate esters (±)-**9** and (±)-**10** showed the coupling constant $J_{2,3}$ = 2.0 Hz, characteristic of the trans stereochemistry (cis glycidate esters typically have $J_{2,3}$ = 4.5 Hz) of the hydrogen atoms at positions 2 and 3;[15,16] this result was confirmed via X-ray crystallography. No evidence of the regioisomeric 2-hydroxy-3,4-epoxide Payne rearrangement[17,18] product was detected in the proton NMR spectra of the crude products (±)-**9** and (±)-**10**.

The free hydroxyl group in 2,3-epoxy-4-hydroxy alkanoates (±)-**9** and (±)-**10** served as a reliable handle for derivatization and then intramolecular opening of the epoxide. Thus, following the Overman protocol,[19] epoxy alcohols (±)-**9** and (±)-**10** reacted with trichloroacetonitrile under Cramer's conditions[20] to give the crude acyclic trichloroacetimidates (±)-**11** and (±)-**12** (Scheme 3). Promoted by diethylaluminum chloride, epoxy imidates (±)-**11** and (±)-**12** underwent regiospecific cyclization to give oxazolines (±)-**13** and (±)-**14** in greater than 70% yield

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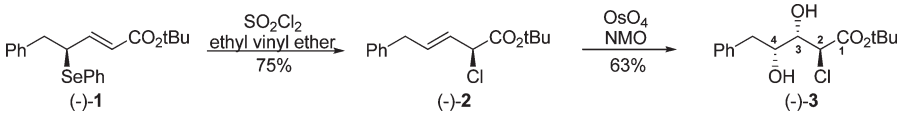
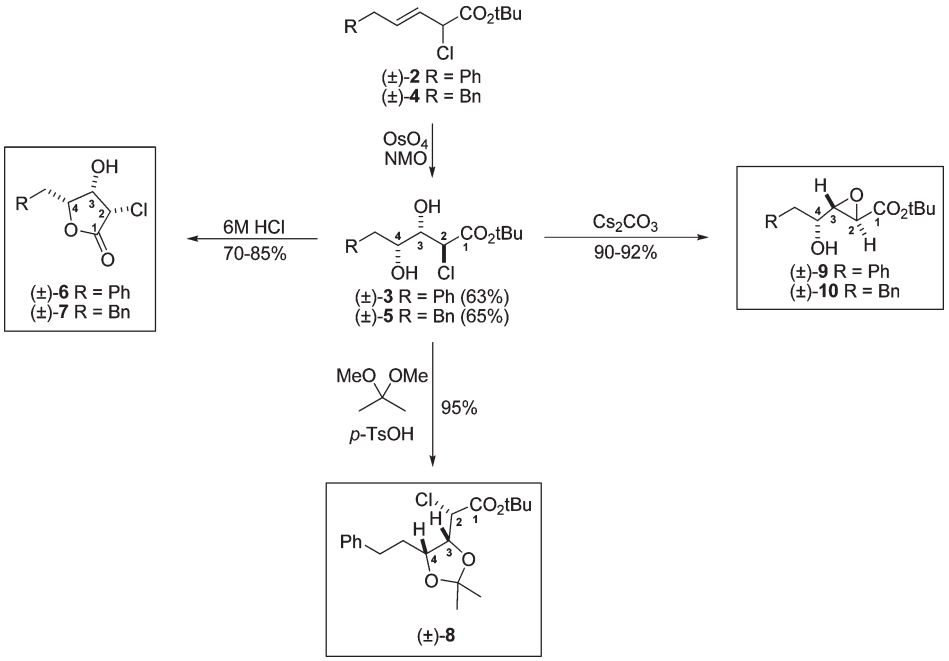
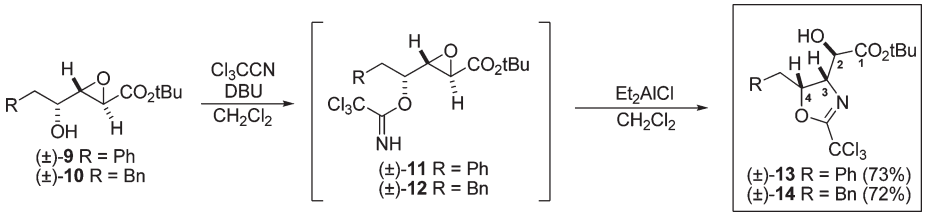
Scheme 1



Scheme 2



Scheme 3



over two steps. The proton NMR spectra of both oxazolines (±)-**13** and (±)-**14** showed the coupling constant $J_{3,4}$ = 9.0 and 9.2 Hz, respectively, characteristic of the cis stereochemistry (trans oxazolines typically have $J_{3,4}$ = 6.0 Hz) of the hydrogen atoms at positions 3 and 4.[21] X-ray crystallography confirmed the structure of oxazoline (±)-**13** to be as shown. Oxazolines (±)-**13** and (±)-**14** are single-diastereomer derivatives of 3-amino-2,4-dihydroxy alkanoate esters.

Epoxy alcohol (±)-**10** reacted separately with three different isocyanates (Scheme 4) to give acyclic carbamates (±)-**15**−(±)-**17**. It is noteworthy that more electrophilic isocyanates produced acyclic carbamates (±)-**15** and (±)-**16** in good yields, whereas a less electrophilic isocyanate slowly produced acyclic carbamate (±)-**17** in much lower yield. Lewis acid mediated intramolecular epoxide opening would have generated a cyclic carbonate[22] and not the desired cyclic carbamate; therefore, base-catalyzed opening of the epoxide was investigated. DBU[23,24] and cesium carbonate were both investigated, and cesium carbonate had a cleaner reaction profile, converting (±)-**15**−(±)-**17** to (±)-**18**−(±)-**20** as a spot-to-spot transformation by TLC. Promoted by cesium carbonate,[25,26] epoxy carbamates (±)-**15**−(±)-**17** underwent regiospecific 5-*exo*-tet cyclization with inversion of stereochemistry at C-3 to give cyclic carbamates (±)-**18**−(±)-**20**. Cyclic carbamates (±)-**18**−(±)-**20** are valuable and versatile single-diastereomer derivatives of 3-amino-2,4-dihydroxy alkanoate esters.

Direct S_N2 opening of the epoxide in the glycidate ester (±)-**10** with sodium azide and ammonium chloride in dimethylformamide afforded the 2-azido-3,4-diol ester (±)-**21** (Scheme 5).[27] The nucleophilic attack by azide regiospecifically at the carbonyl-activated C-2 position of epoxy alcohol (±)-**10** proceeded with inversion of stereochemistry at C-2.[28] The sequence of

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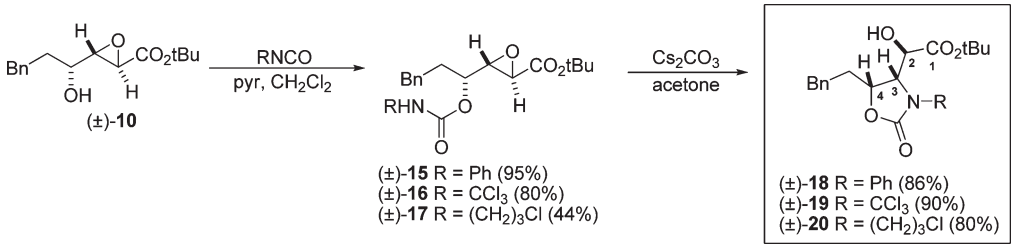
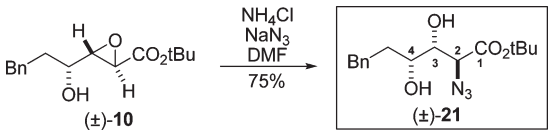
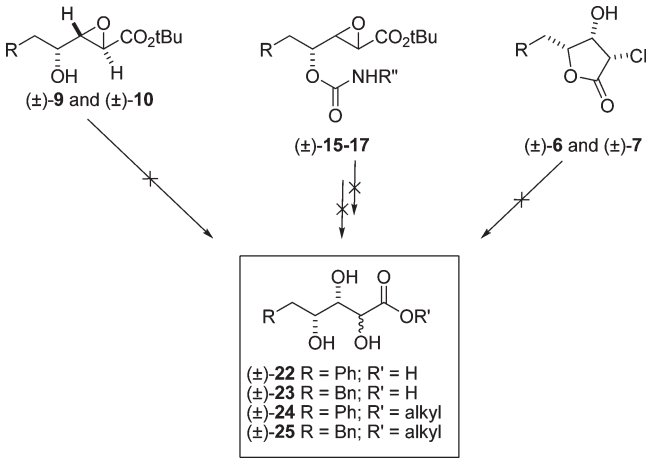
Scheme 4



Scheme 5



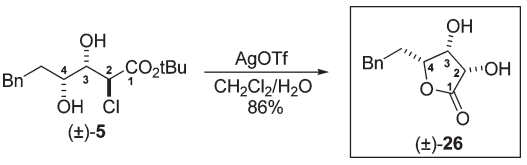
Scheme 6



transformations **5** → **10** → **21** achieved the stereospecific replacement of the chloride in α-chloro ester **5** by azide with overall retention (double inversion) of configuration at C-2. This transformation produced a single-diastereomer precursor of a β,γ-dihydroxy α-amino acid or ester.

Triols,[29] triol acids,[30] triol esters,[31] and diol furanones[32] are found in many natural products and are useful synthons.[33] Synthesis of triols (±)-**22**−(±)-**25** proved elusive from the chlorolactones (±)-**6** and (±)-**7**, from the epoxy alcohols (±)-**9** and (±)-**10**, and from the acyclic carbamates (±)-**15**−(±)-**17** (Scheme 6). Several attempts toward a 2,3,4-trihydroxyalkanoate motif were made using a variety of nucleophiles and Lewis acids. When chlorolactones (±)-**6** and (±)-**7** were treated with various nucleophilic oxygen species such as peroxide, superoxide, hydroxide, nitrite, and water, the α-chlorolactones either did not react or reacted to generate epimeric lactone products. Epimeric products have been noted previously, where it was found that a retro-aldol reaction can occur in (±)-**6** and (±)-**7** with the resultant planar enolate adding back into the aldehyde and forming this mixture of two epimers.[14,34] In situ generated hemiacetal intramolecular nucleophiles were investigated; cesium carbonate was mixed with epoxy alcohols (±)-**9** and (±)-**10** in the presence of several aldehydes, including chloral, paraformaldehyde, benzaldehyde, and *p*-nitrobenzaldehyde, in an effort to prepare an α-hydroxy-1,3-dioxolane. These attempts to produce a hemiacetal or dioxolane were unsuccessful. Additionally, when Lewis acid mediated epoxide openings were attempted on acyclic carbamates (±)-**15**−(±)-**17** in order to prepare cyclic carbonates, a mixture of three regioisomers and constitutional isomers resulted in varying percentages rather than providing (±)-**22**−(±)-**25** cleanly.[22,35,36] When hydroxy glycidate ester (±)-**10** was treated with silver triflate, the ^{1}H and ^{13}C NMR spectra for the crude product did not correspond to any 2,3,4-trihydroxylated product.

Scheme 7



However, when chloro diol (±)-**5** was treated with excess silver triflate in 10/1 dichloromethane/water, a lactone was formed in 86% yield (Scheme 7). The isolated product was the single-diastereomer 2,3-dihydroxyfuranone (±)-**26**. The proton NMR spectrum of (±)-**26** had a coupling constant of $J_{2,3}$ = 4.0 Hz, consistent with the cis stereochemistry of the hydrogen atoms at positions 2 and 3.[37] This transformation provides a stereocontrolled synthesis of γ-alkyl-γ-butyrolactones containing α,β-dihydroxy substitution that is relatively rare.[32,38−41] Many γ-butyrolactones are present in natural products themselves[38] and are also synthons used in the preparation of biologically active natural products.[42,43] While the exact pathway of the reaction in Scheme 7 was not determined conclusively, the conversion of α-chloro carboxylic acid derivatives to α-hydroxy carboxylic acid derivatives with retention of stereochemistry at the α-carbon using silver salts is well precedented as a double-inversion process via an α-lactone intermediate.[44]

In conclusion, many natural product syntheses rely on stereochemically pure vicinal amino alcohols, diols, amino diols, polyols, and furanones as densely functionalized compounds. We report herein highly stereocontrolled and regiocontrolled syntheses of one γ-alkyl-α,β-dihydroxy-γ-butyrolactone and of six structurally diverse and valuable 2,3,4-trisubstituted alkanoates. The one-step transformation **5** → **26** represents a direct, facile, and highly stereoselective synthesis of a γ-alkyl-α,β-dihydroxy-γ-butyrolactone in 86% overall yield; the **5** → **26** sequence represents a reliable and useful replacement of the chloride in

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diol α-chloro ester **5** by hydroxyl with retention of configuration followed by γ-lactonization.

EXPERIMENTAL SECTION

General Considerations. Microwave experiments were run using a Biotage Initiator system with an external contact temperature probe. ^{1}H NMR and ^{13}C NMR spectra were recorded at 400 and 100 MHz or at 300 and 75 MHz, respectively, using the residual solvent peak as the internal standard. High-resolution mass spectrum fast atom bombardment (HRMS-FAB) and electron impact (HRMS-EI) mass spectra were obtained using a VG70SE double-focusing magnetic sector mass spectrometer equipped with a Cs^+ ion gun (28 kV @ 2 μA), an off-axis multiplier, and an MSS data system. The resolution of the instrument was set at 10 000 (100 ppm peak width). Samples were mixed with *m*-nitrobenzyl alcohol matrix deposited on the target of a direct-insertion probe for introduction into the source. For accurate mass measurements, a mass scan range was employed with the matrix containing 10% polyethylene glycol (PEG) or polyethylene glycol monomethyl ether (PEGMME) mass calibrant. Fourier transform infrared (FT-IR) experiments were obtained from 4000 to 600 cm^{-1}. Thin-layer chromatography was performed with glass-backed 20 cm ×20 cm extra-hard layer 250 μm thickness 60 Å plates with F_{254} indicator cut down to 20 mm × 67 mm for analytical purposes.

Homologated Chlorodiol (±)-5. In a dried 500 mL single-neck flask, fitted with a magnetic stirrer and argon inlet/outlet, were added (±)-**4** (2.0 g, 7.1 mmol), THF (270 mL), *N*-methylmorpholine *N*-oxide (1.0 g, 8.6 mmol), and osmium tetroxide (8.9 mL, 2.5 w/w in *t*-BuOH) at room temperature. The reaction mixture was stirred at room temperature for 16 h. After 16 h, the reaction was quenched by the addition of 20% (w/w) sodium bisulfite solution (70 mL). The resulting bilayer was separated, and the aqueous layer was extracted with ethyl ether (3 × 50 mL). The organic layers were combined to afford a dark solution that was dried over magnesium sulfate for 60 min. The dried organics were concentrated, in vacuo, without external heating to afford 10 g of yellow oil. The oil was purified by flash silica gel chromatography (1 kg of silica gel, prepared with hexanes, 0−20% ethyl acetate in hexanes) to afford (±)-**5** as an amorphous off-white solid (1.4 g, 4.6 mmol, 65.1%). Crystals were grown by dissolving 11 mg of solid in approximately 0.5 mL of toluene in a 0.5 dram vial. Parafilm was placed over the opening and perforated. The vial was placed on an approximately 45° bias and allowed to evaporate over a period of approximately 5 days at room temperature, resulting in several needles, from which the crystallographic sample was taken. TLC: one spot, R_f = 0.50 (40% ethyl acetate in hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31−7.27 (m, 2H), 7.22−7.14 (m, 3H), 4.26−4.24 (d, 1H, *J* = 8.4 Hz), 3.96−3.92 (ddd, 1H, *J* = 8.8, 4.8, 1.6 Hz), 3.85−3.83 (d, 1H, *J* = 8.4 Hz), 3.11−2.88 (br s, 1H), 2.88−2.64 (AX of ABX, 2H), 2.05−1.82 (BX of ABX including br s, 3H), 1.49 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.4, 141.4, 128.5, 128.4, 126.0, 83.4, 74.5, 69.2, 56.4, 35.7, 32.0, 27.8. FT-IR (NaCl, thin film; cm^{-1}): 3427, 3029, 2980, 2935, 1723, 1455, 1370, 1304, 1257, 1151, 700. HRMS-FAB (*m*/*z*): [M − *t*-Bu]$^+$ calcd for $C_{12}H_{15}ClO_4$ 258.0659, found 258.0664 (^{35}Cl) and 260.0640 (^{37}Cl); [M + H − *t*-Bu]$^+$ calcd for $C_{12}H_{16}ClO_4$ 259.0737, found 259.0718 (^{35}Cl) and 261.0692 (^{37}Cl).

Chlorolactone (±)-6. In a dried 1 dram vial, fitted with a magnetic stirrer and argon inlet/outlet, were added (±)-**3** (32 mg, 0.11 mmol), *p*-dioxane (600 μL), DI water (400 μL), and concentrated hydrochloric acid (4.26 mmol, 355 μL) under argon. The resulting solution was stirred at room temperature for 21 h. After 21 h at room temperature the reaction mixture was diluted with DI water (1 mL) and then extracted with ethyl acetate (4 × 1 mL). The ethyl acetate extracts were pooled and washed with saturated aqueous sodium chloride solution (2 mL) and concentrated, in vacuo, without external heating to afford 28 mg of white glassy solid. The glassy solid was purified by flash silica gel chromatography (3 g of silica gel, prepared with hexanes, 0−10% ethyl acetate in hexanes) to afford (±)-**6** (20 mg, 0.09 mmol, 85.0%) as a crystalline white solid. TLC: one spot, R_f = 0.29 (40% ethyl acetate in hexanes). ^{1}H NMR (300 MHz, CD_3CN): δ 7.36−7.24 (m, 5H), 4.84−4.82 (d, 1H, *J* = 4.3 Hz), 4.68−4.62 (dt, 1H, *J* = 7.1, 2.7 Hz), 4.37−4.33 (dt, 1H, *J* = 4.7, 2.8 Hz), 3.99−3.97 (d, 1H, *J* = 4.8 Hz), 3.09−3.07 (d, 2H, *J* = 6.0 Hz). ^{13}C NMR (75 MHz, CD_3CN): δ 172.1, 137.7, 130.2, 129.4, 127.6, 83.2, 71.2, 59.4, 35.4. FT-IR (NaCl, thin film; cm^{-1}): 3447, 3062, 3029, 2934, 1777, 1496, 1455, 1174, 1116, 998, 947, 745, 705. HRMS-FAB (*m*/*z*): [M + H]$^+$ calcd for $C_{11}H_{11}ClO_3^+$ 227.0469, found 227.0468; [M + Na]$^+$ calcd for $C_{11}H_{11}ClNaO_3$ 249.0283, found 249.0293. Mp: 171−172 °C.

Homologated Chlorolactone (±)-7. As above, (±)-**5** (28 mg, 0.09 mmol) gave (±)-7 (15 mg, 0.07 mmol, 70.0%) as an amorphous white solid. TLC: one spot, R_f = 0.30 (40% ethyl acetate in hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33−7.29 (m, 2H), 7.24−7.21 (m, 3H), 4.66−4.65 (d, 1H, *J* = 4.0 Hz), 4.38−4.35 (m, 2H), 2.91−2.74 (AX and BX of ABX, 2H), 2.37−2.29 (m incl br s and AX of ABX, 2H), 2.15−2.04 (BX of ABX, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.1, 140.3, 128.6, 128.5, 126.4, 80.4, 70.2, 58.7, 31.1, 30.0. FT-IR (NaCl, thin film; cm^{-1}): 3406, 3026, 2938, 1759, 1496, 1455, 1174, 1118, 947, 745, 698. HRMS-FAB (*m*/*z*): [M + H]$^+$ calcd for $C_{12}H_{14}ClO_3^+$ 241.0626, found 241.0628; [M + Na]$^+$ calcd for $C_{12}H_{13}ClNaO_3^+$ 263.0445, found 263.0447.

Acetonide Chloro Ester (±)-8. In a dried 5 dram vial, fitted with a magnetic stirrer and argon inlet/outlet, were added (±)-**5** (126 mg, 0.40 mmol), dichloromethane (6 mL), 2,2-dimethoxypropane (26 mg, 2.0 mmol, 0.25 mL), and freshly toluene-azeotroped *p*-toluenesulfonic acid (10 mg, catalytic) under argon. The resulting mixture was stirred at room temperature for 48 h. After 48 h at room temperature the reaction mixture was quenched with saturated ammonium chloride solution (6 mL). The layers were separated, and the aqueous layer was extracted with ethyl ether (2 × 5 mL). The organics were pooled and dried over magnesium sulfate for 10 min. The dried organics were filtered through a fritted-glass funnel, and the filtrate was concentrated, in vacuo, without external heating to afford 156 mg of a yellow oil. The oil was purified by flash silica gel chromatography (17 g of silica gel, prepared with hexanes, 0−10% ethyl acetate in hexanes) to afford (±)-**8** (133 mg, 0.37 mmol, 93.7%) as a colorless oil. TLC: one spot, R_f = 0.76 (40% ethyl acetate in hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31−7.27 (m, 2H), 7.22−7.18 (m, 3H), 4.14−4.08 (m, 3H), 2.89−2.82 (AX of ABX, 1H), 2.76−2.69 (BX of ABX, 1H), 2.10−2.01 (A′X of A′B′X, 1H), 1.99−1.90 (B′X of A′B′X, 1H), 1.49 (s, 9H), 1.45 (s, 3H), 1.41 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.7, 141.4, 128.4 (3C), 125.9 (2C), 110.2, 83.1, 81.0, 79.1, 57.9, 36.4, 32.0, 27.9, 27.8, 27.5. FT-IR (NaCl, thin film; cm^{-1}): 3027, 2984, 2936, 1746, 1497, 1455, 1370, 1150, 1069, 849, 699. HRMS-FAB (*m*/*z*): [M + H]$^+$ calcd for $C_{19}H_{28}ClO_4^+$ 355.1671, found 355.1672 (^{35}Cl) and 357.1657 (^{37}Cl).

Glycidate Ester (±)-9. In a dried 2 dram vial, fitted with a magnetic stirrer and argon inlet/outlet, were added (±)-**3** (50 mg, 0.17 mmol), acetone (3.6 mL), and cesium carbonate (81 mg, 0.25 mmol) under argon. The resulting mixture was stirred at room temperature for 15 h. After 15 h at room temperature the reaction mixture was filtered through Celite-545 to afford a clear filtrate. The filtrate was concentrated, in vacuo, without external heating to afford 43 mg of orange solid. The solid was purified by flash silica gel chromatography (5 g of silica gel, prepared with hexanes, 0−10% ethyl acetate in hexanes) to afford (±)-**6** (40 mg, 0.15 mmol, 90.0%) as an amorphous white solid. TLC: one spot, R_f = 0.39 (40% ethyl acetate in hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35−7.32 (m, 2H), 7.28−7.23 (m, 3H), 3.91−3.85 (dt, 1H, 6.8, 1.0 Hz), 3.26 (s, 1H), 3.23−3.22 (m, 1H), 3.02−2.90 (AX and BX of ABX, 2H), 1.85−1.83 (br d, 1H, 6.4 Hz), 1.47 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.5, 136.6, 129.3, 128.7, 126.8, 82.6, 70.8, 59.8,

51.6, 27.9. FT-IR (NaCl, thin film; cm^{-1}): 3445, 3062, 3029, 2980, 2934, 1743, 1496, 1456, 1158, 1078, 966, 906, 751, 700. HRMS-FAB (m/z): $[M + Na]^+$ calcd for $C_{15}H_{20}NaO_4$ 287.1259, found 287.1258.

Homologated Glycidate Ester (±)-10. As above, (±)-**5** (900 mg, 2.86 mmol) gave (±)-**10** (715 mg, 2.57 mmol, 90.8%) as an amorphous white solid. TLC: one spot, R_f = 0.45 (40% ethyl acetate in hexanes). ^1H NMR (400 MHz, CD_3CN): δ 7.30−7.16 (m, 5H), 3.48−3.42 (m, 1H), 3.25−3.24 (d, 1H, J = 4.0 Hz), 3.06−3.04 (m, 2H), 2.81−2.61 (AX and BX of ABX, 2H), 1.84−1.74 (A′X and B′X of A′B′X, 2H), 1.44 (s, 9H). ^{13}C NMR (100 MHz, CD_3CN): δ 168.8, 143.0, 129.3, 129.2, 127.6, 82.7, 70.1, 61.4, 52.1, 36.5, 32.1, 28.0. FT-IR (NaCl, thin film; cm^{-1}): 3468, 3062, 3027, 2980, 2934, 1743, 1496, 1455, 1369, 1157, 902, 749, 700. HRMS-FAB (m/z): $[M - t\text{-Bu}]^+$ calcd for $C_{12}H_{14}O_4$ 222.0892, found 222.0895.

Oxazoline (±)-13. In a 2 dram vial equipped with a magnetic stirrer under argon was added epoxide (±)-**9** (0.03 g, 0.11 mmol, 1.0 equiv) in CH_2Cl_2 (0.9 mL). The vial was cooled to −78 °C, and DBU (0.021 μL, 0.14 mmol, 1.2 equiv) followed by Cl_3CN (0.020 g, 0.14 mmol, 1.2 equiv) was added. The reaction mixture was stirred overnight at −78 °C. TLC analysis indicated consumption of the starting epoxide (±)-**9**. The reaction was then quenched with H_2O and extracted with Et_2O (3×). The combined organics were dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. In a 1 dram vial equipped with a magnetic stirrer under argon was added crude trichloroacetimidate (±)-**11** (0.011 g, 0.28 mmol, 1.0 equiv) in CH_2Cl_2 (0.3 mL). The vial was cooled to 0 °C, a 1 M solution of Et_2AlCl in hexanes (0.028 mL, 1.0 equiv) was added, and the reaction mixture was stirred for 30 min, after which the cooling bath was removed and the reaction was stirred for an additional 1 h. At this time, a 1 M solution of Et_2AlCl (0.014 mL, 0.5 equiv) was added and the reaction mixture stirred at room temperature for 1 h, after which an additional 1 M solution of Et_2AlCl (0.014 mL, 0.5 equiv) was added and the reaction stirred for an additional 1 h. At this time, TLC analysis indicated complete consumption of the starting trichloroacetimidate (±)-**11**. The reaction mixture was quenched with H_2O and extracted with EtOAc (4×). The combined organics were dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The crude solid was triturated with hexanes, the mother liquor was removed, and the desired oxazoline (±)-**13** was isolated as an amorphous white solid (0.008 g, 0.020 mmol) in 73% yield from the epoxy alcohol (±)-**9**. A small amount of white solid was transferred to a 0.5 dram vial and dissolved in toluene and 1 drop of EtOAc. The vial was placed on a 45° bias and the solution was allowed to evaporate. After 24 h a single crystal was produced for X-ray analysis. ^1H NMR (400 MHz, CD_3CN): δ 7.34−7.23 (m, 5H), 5.26−5.21 (m, 1H), 4.65−4.61 (dd, 1H, J = 6, 9.6 Hz), 4.37−4.35 (t, 1H, J = 5.2 Hz), 3.80−3.79 (d, 1H, J = 5.2 Hz), 3.20−3.14 (dd, 1H, J = 11.6, 14.4 Hz), 3.063−3.022 (dd, 1H, J = 2, 14.4 Hz), 1.51 (s, 9H). ^{13}C NMR (100 MHz, CD_3CN): δ 172.3, 163.0, 139.2, 130.2, 129.5, 127.6, 88.7, 83.2, 71.7, 36.5, 28.2, 9.7, 7.5. IR (cm^{-1}): 3435 (b), 2979, 1728, 1662, 1393, 1248, 1157, 820. HRMS (m/z): calcd for $C_{17}H_{21}Cl_3NO_4$ (M + H) 410.0503, found 410.0508.

Homologated Oxazoline (±)-14. As above, (±)-**10** (30 mg, 0.11 mmol) gave (±)-**14** (30 mg, 0.07 mmol, 72%) as an amorphous white solid. ^1H NMR (400 MHz, $CDCl_3$): δ 7.31−715 (m, 5H); 4.95−4.90 (t, 1H, J = 9.2 Hz), 4.51−4.47 (dd, 1H, J = 4.8, 9.6 Hz), 4.37−4.36 (d, 1H, J = 5.2 Hz), 2.98−2.92 (m, 1H), 2.77−2.69 (m, 1H), 2.39−2.29 (m, 1H), 1.99−1.91 (m, 1H), 1.48 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.7, 140.6, 128.6, 128.5, 128.4, 126.2, 86.8, 85.7, 83.6, 70.9, 70.3, 32.5, 31.0, 27.9. IR (cm^{-1}): 3405 (b), 3027, 2932, 1725, 1661, 1394, 1250, 1158. HRMS (m/z): calcd for $C_{18}H_{23}Cl_3NO_4$ (M + H) 422.0699, found 422.0702.

Acyclic Phenyl Carbamate (±)-15. In a dried 1 dram vial, fitted with a magnetic stirrer and argon inlet/outlet, were added (±)-**10** (20 mg, 0.07 mmol), dichloromethane (0.9 mL), pyridine (28 mg, 0.36 mmol, 29 μL), and phenyl isocyanate (17 mg, 0.14 mmol, 16 μL) under argon. The resulting mixture was stirred at room temperature for 60 h. After 60 h at room temperature the reaction mixture was filtered through a cotton plug and concentrated, in vacuo, without external heating to afford 47 mg of yellow oil. The oil was purified by flash silica gel chromatography (5 g of silica gel, prepared with hexanes, 0−5% ethyl acetate in hexanes) to afford (±)-**15** (27.3 mg, 0.07 mmol, 95.4%) as a colorless oil. TLC: one spot, R_f = 0.57 (40% ethyl acetate in hexanes). ^1H NMR (400 MHz, $CDCl_3$): δ 7.38−7.36 (m, 2H), 7.33−7.24 (m, 4H), 7.20−7.17 (m, 3H), 7.09−7.06 (t, 1H, J = 7.2 Hz), 6.68 (br s, 1H), 5.00−4.96 (dt, 1H, J = 7.6, 4.8 Hz), 3.33−3.32 (dd, 1H, J = 4.0, 1.6 Hz), 3.30−3.29 (d, 1H, J = 1.6 Hz), 2.81−2.70 (m, 2H), 2.17−1.99 (m, 2H), 1.47 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.3, 152.5, 144.6, 140.7, 137.4, 129.1, 128.5, 128.3, 126.2, 123.7, 82.9, 71.5, 58.3, 51.3, 33.2, 31.3, 27.9. FT-IR (NaCl, thin film; cm^{-1}): 3344, 3062, 3028, 2980, 2935, 2866, 1735, 1601, 1540, 1500, 1445, 1370, 1251, 1216, 1156, 1083, 1063, 1028, 753, 694. HRMS-FAB (m/z): $[M + H]^+$ calcd for $C_{23}H_{28}NO_5^+$ 398.1962, found 398.1955.

Acyclic Trichloromethyl Carbamate (±)-16. As above, (±)-**10** (28 mg, 0.10 mmol) gave (±)-**16** (35.3 mg, 0.09 mmol, 90.7%) as a colorless oil. TLC: one spot, R_f = 0.74 (40% ethyl acetate in hexanes). ^1H NMR (400 MHz, $CDCl_3$): δ 7.33−7.29 (m, 2H), 7.24−7.18 (m, 3H), 4.93−4.89 (dt, 1H, J = 8.0, 5.6 Hz), 3.36−3.34 (dd, 1H, J = 5.2, 2.0 Hz), 3.31−3.30 (d, 1H, J = 2.0 Hz), 2.83−2.68 (AX and BX of ABX, 2H), 2.20−2.01 (A′X and B′X of A′B′X, 2H), 1.48 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.8, 154.4, 140.0, 135.7, 128.7, 128.3, 126.5, 107.6, 83.1, 75.8, 57.4, 51.4, 32.6, 31.0, 27.9. FT-IR (NaCl, thin film; cm^{-1}): 3064, 3028, 2981, 2935, 1750, 1657, 1497, 1456, 1370, 1228, 1157, 932, 699. HRMS-FAB (m/z): $[M - t\text{-Bu} - CCl_3]^+$ calcd for $C_{13}H_{16}NO_5^+$ 266.1023, found 266.1031.

Acyclic Chloropropyl Carbamate (±)-17. As above, (±)-**10** (28 mg, 0.10 mmol) gave, in 5 days, (±)-**17** (19.5 mg, 0.04 mmol, 44.3%) as a colorless oil. TLC: one spot, R_f = 0.56 (40% ethyl acetate in hexanes). ^1H NMR (400 MHz, $CDCl_3$): δ 7.31−7.27 (m, 2H), 7.22−7.18 (m, 3H), 4.89−4.85 (m, 1H), 3.61−3.58 (t, 2H, J = 6.4 Hz), 3.40−3.33 (q, 2H, J = 6.8 Hz), 3.27−3.26 (dd, 1H, J = 4.4, 1.6 Hz), 3.24−3.23 (d, 1H, J = 1.6 Hz), 2.74−2.70 (t, 2H, J = 7.6 Hz), 2.10−1.97 (m, 4H), 1.48 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.3, 155.6, 140.8, 128.5, 128.3, 126.2, 82.8, 71.3, 58.4, 51.3, 42.2, 38.4, 33.2, 32.2, 31.3, 27.9. FT-IR (NaCl, thin film; cm^{-1}): 3367, 2979, 1726, 1653, 1521, 1456, 1369, 1249, 1157. HRMS-FAB (m/z): $[M + H]^+$ calcd for $C^{20}H_{29}ClNO_5^+$ 398.1729, found 398.1725 (^{35}Cl) and 400.1704 (^{37}Cl).

Cyclic Phenyl Carbamate (±)-18. In a dried 2 dram vial, fitted with a magnetic stirrer and argon inlet/outlet, were added (±)-**15** (26 mg, 0.07 mmol), acetone (2 mL), and cesium carbonate (33 mg, 0.10 mmol) under argon. The resulting mixture was stirred at room temperature for 16 h. After 16 h at room temperature the reaction mixture was filtered through a cotton plug and concentrated, in vacuo, without external heating to afford 32 mg of yellow oil. The oil was purified by flash silica gel chromatography (4 g of silica gel, prepared with hexanes, 0−15% ethyl acetate in hexanes) to afford (±)-**18** (22 mg, 0.06 mmol, 86.0%) as a colorless oil. TLC: one spot, R_f = 0.40 (40% ethyl acetate in hexanes). ^1H NMR (400 MHz, $CDCl_3$): δ 7.53−7.50 (m, 2H), 7.44−7.37 (m, 2H), 7.30−7.29 (m, 2H), 7.24−7.20 (m, 4H), 4.72−4.61 (m, 2H), 4.24−4.23 (d, 1H, J = 2.0 Hz), 3.04−2.98 (AX of ABX, 1H), 2.87 (br s, 1H), 2.81−2.73 (BX of ABX, 1H), 2.50−2.40 (A′X of A′B′X, 1H), 1.88−1.79 (B′X of A′B′X, 1H), 1.44 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.9, 155.7, 140.4, 136.4, 129.3, 128.6, 128.6, 126.2, 126.0, 123.4, 84.5, 75.4, 69.0, 62.1, 32.2, 30.9, 27.8. FT-IR (NaCl, thin film; cm^{-1}): 3435, 3063, 3028, 2978, 2934, 1742, 1600, 1456, 1370, 1256, 1148, 1086, 912, 759. HRMS-FAB (m/z): $[M + H]^+$ calcd for $C_{23}H_{28}NO_5^+$ 398.1962, found 398.1960.

Cyclic Trichloromethyl Carbamate (±)-19. As above, (±)-**16** (10 mg, 0.02 mmol) gave (±)-**19** as a golden yellow oil (9 mg, 0.02 mmol, 90.0%). The oil was sufficiently pure for analysis. TLC: one

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spot, R_f = 0.22 (40% ethyl acetate in hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32−7.26 (m, 2H), 7.32−7.26 (m, 2H), 7.20−7.18 (m, 3H), 4.88−4.85 (m, 1H), 4.70 (br s, 1H), 3.28−3.27 (m, 2H), 2.76−2.69 (m, 2H), 2.09−1.97 (m, 2H), 1.48 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.3, 155.8, 140.8, 128.5, 128.3, 126.2, 100.0, 82.8, 71.4, 58.3, 51.3, 33.2, 31.3, 27.9. FT-IR (NaCl, thin film; cm^{-1}): 3371, 3064, 3028, 2979, 2935, 1730, 1602, 1455, 1370, 1330, 1251, 1157, 1079, 905, 701. HRMS-FAB (m/z): $[M + H - t\text{-Bu} - CCl_3]^+$ calcd for $C_{13}H_{16}NO_5$ 266.1028, found 266.1029.

Cyclic Chloropropyl Carbamate (±)-20. As above (±)-**17** (14 mg, 0.04 mmol) gave (±)-**20** as a yellow oil (11 mg, 0.03 mmol, 80%). The oil was sufficiently pure for analysis. TLC: one spot, R_f = 0.50 (40% ethyl acetate in hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28−7.25 (m, 2H), 7.19−7.15 (m, 3H), 4.86−4.82 (m, 1H), 3.58−3.55 (t, 2H, J = 12.4 Hz), 3.36−3.31 (q, 2H, J = 6.4 Hz), 3.25−3.23 (dd, 1H, J = 4.4, 2.0 Hz), 3.21−3.20 (d, 1H, J = 2.0 Hz), 2.71−2.67 (m, 2H), 2.06−1.94 (m, 4H), 1.46 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.3, 155.6, 140.8, 128.5, 128.3, 126.2, 82.8, 71.3, 58.4, 51.4, 42.2, 38.4, 33.3, 32.2, 31.3, 27.9. FT-IR (NaCl, thin film; cm^{-1}): 3364, 3063, 3028, 2979, 2935, 2869, 1726, 1603, 1455, 1369, 1318, 1248, 1156, 1081, 904, 700. HRMS-FAB (m/z): $[M + H]^+$ calcd for $C_{20}H_{29}ClNO_5^+$ 398.1729, found 398.1735 (^{35}Cl) and 400.1712 (^{37}Cl).

Azido Diol (±)-21. In a dried 0.5−2.0 mL conical microwave vial, fitted with a magnetic stirrer, were added (±)-**10** (10 mg, 0.04 mmol), dimethylformamide (0.5 mL), ammonium chloride (6 mg, 0.12 mmol), and sodium azide (7 mg, 0.12 mmol). The vial was crimped shut with a Teflon-lined silicone septum and was placed in a microwave reactor. The resulting mixture was heated to a temperature of 90 °C for 2 h. After 2 h the reaction mixture was cooled to room temperature and diluted with water (5 mL). The aqueous layer was extracted with dichloromethane (3 × 3 mL). The organic extracts were pooled and dried over magnesium sulfate for 10 min. The dried organics were concentrated, in vacuo, without external heating to afford 14 mg of reddish brown oil. The oil was purified by flash silica gel chromatography (2 g silica gel, prepared with hexanes, 0−15% ethyl acetate in hexanes) to afford (±)-**21** (9.0 mg, 0.03 mmol, 75.0%) as a colorless oil. TLC: one spot, R_f = 0.44 (40% ethyl acetate in hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31−7.27 (m, 2H), 7.22−7.17 (m, 3H), 4.06−4.04 (d, 1H, J = 6.4 Hz), 3.75−3.72 (m, 2H), 3.17−3.15 (d, 1H, J = 6.4 Hz), 2.84−2.77 (AX of ABX, 1H), 2.74−2.66 (BX of ABX, 1H), 2.17−2.15 (br d, 1H, J = 5.6 Hz), 2.02−1.93 (A′X of A′B′X, 1H), 1.85−1.76 (B′X of A′B′X, 1H), 1.49 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.8, 141.5, 128.5, 128.4 (3C), 126.0, 84.2, 72.7, 69.7, 64.3, 35.6, 31.8, 28.0. FT-IR (NaCl, thin film; cm^{-1}): 3442, 3063, 3028, 2980, 2934, 2111, 1731, 1496, 1455, 1370, 1152, 1066, 839, 699. HRMS-FAB (m/z): $[M + H]^+$ calcd for $C_{16}H_{24}N_3O_4^+$ 322.1761, found 322.1763.

Dihydroxy Lactone (±)-26. In a 0.5−2.0 mL conical microwave vial, fitted with a magnetic stirrer and argon inlet/outlet, were added (±)-**8** (31 mg, 0.10 mmol), dichloromethane (1.0 mL), DI water (0.1 mL), and silver triflate (128 mg, 0.50 mmol) at room temperature. The vial was crimped shut with a Teflon-lined silicone septum and was placed in a microwave reactor. The reaction mixture was heated to 60 °C for 12 h. After 12 h at 60 °C the reaction mixture was diluted with dichloromethane (3 mL) and then dried over magnesium sulfate for 10 min. The dried organics were concentrated, in vacuo, without external heating to afford 25 mg of white solid. The solid was purified by flash silica gel chromatography (5 g of silica gel, prepared with pentane, 0, 20, 40, 60% ethyl ether in pentane) to afford (±)-**26** (19 mg, 0.09 mmol, 86.3%) as an amorphous white solid. TLC: one spot, R_f = 0.28 (40% ethyl acetate in hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33−7.29 (m, 2H), 7.24−7.21 (m, 3H), 4.66−4.65 (d, 1H, J = 4.0 Hz), 4.38−4.34 (m, 2H), 2.91−2.84 (AX of ABX, 1H), 2.82−2.75 (BX of ABX, 1H), 2.38−2.29 (A′X of A′B′X including br s at 2.32, 2H), 2.16−2.07 (B′X of A′B′X, 1H), 1.56 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.1, 140.3, 128.6, 128.5, 126.4, 80.5, 70.2, 58.7, 31.1, 30.0. FT-IR (NaCl, thin film; cm^{-1}): 3404, 3026, 2937, 1759, 1496, 1455, 1175, 1118, 981, 949, 746, 700. HRMS-FAB (m/z): $[M + H]^+$ calcd for $C_{12}H_{15}O_4^+$ 223.0965, found 223.0972; $[M + Na]^+$ calcd for $C_{12}H_{14}NaO_4^+$ 245.0784, found 245.0786.

■ ASSOCIATED CONTENT

Supporting Information. Text, figures, and CIF files giving NMR spectra, X-ray ORTEP images, details of the X-ray structure determination, and crystallographic data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author
*E-mail: gposner1@jhu.edu. Tel: (410) 516-4670.

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