JOC The Journal of Organic Chemistry

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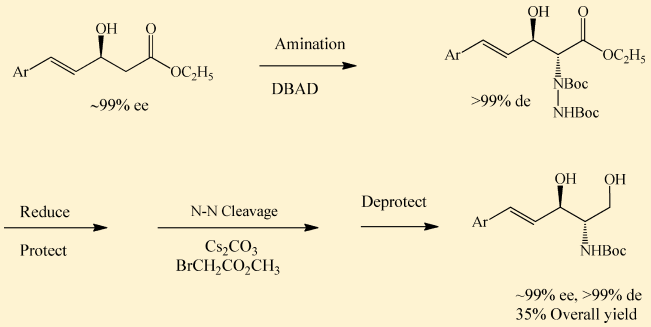
Synthesis of Aromatic Sphingosine Analogues by Diastereoselective Amination of Enantioenriched *trans*-γ,δ-Unsaturated β-Hydroxyesters

Zhipeng Dai and Thomas K. Green*

Department of Chemistry and Biochemistry, Institute of Arctic Biology, University of Alaska, Fairbanks, Alaska 99775, United States

Supporting Information

ABSTRACT: An effective route to *N*-Boc-protected aromatic sphingosine analogues is accomplished. The strategy is based on the diastereoselective amination of enantioenriched *trans*-γ,δ-unsaturated β-hydroxyesters to establish *anti*,*N*-Boc-α-hydrazino-β-hydroxyesters. Nonreductive E1cB elimination is essential for the successful N−N bond cleavage of hydrazine while preserving the *trans* double bond. Either the (3*R*,2*S*) and (3*S*,2*R*) enantiomer of *N*-Boc-protected sphingosine analogues has been synthesized in five steps with excellent optical purity with ∼99% ee and >99% de.



Sphingolipids serve as extra- and intracellular mediators in cell signaling,[1−5] including regulation of antiproliferative and apoptotic responses in various cancer cells,[6,7] serving as messengers for controlling cell growth, maturity, survival, and death. To date, over 70 syntheses of analogues of (−)-D-*erythro*-sphingosine, which serves as the backbone of the majority of sphingolipids, have been reported.[8−16] With the emergence of the aromatic sphingosine analogue FTY720 (Figure 1) for the treatment of multiple sclerosis,[17] the development of other aromatic analogues of sphingosine have received increased attention compared to natural sphingosines due to their enhanced aqueous solubility, cell permeability, and bioactivity.[18−28] Kim et al. produced sphingosine analogue SG-12, which possesses an aromatic ring in place of the unsaturated C_{14} and lacks the C4−C5 *trans* double bond.[22] SG-12 exhibited specific inhibitory effects against sphingosine kinase 2. A synthesis of BML-258 was the subject of a patent by Zipkin[24] utilizing Garner aldehyde-based strategies. BML-258 is a water-soluble sphingosine analogue, which is evaluated as an SK1 selective inhibitor and shown to be efficacious both in vitro and in vivo.[29,30] Van Overmeire et al. synthesized and evaluated the biological activities of several aromatic ceramide analogues, which were able to reverse fumonisin B1 (FB1) inhibited ceramide synthesis.[18,19] Murakami et al. made aromatic sphingosine derivatives, which have been suggested as EDG/S1P receptor (endothelial differentiation gene family of sphingosine 1 phosphate receptors) inhibitors that block S1P-mediated Ca^{2+} increase.[21] In 2011, several aromatic ceramide analogues were synthesized by Moreno et al.[25]

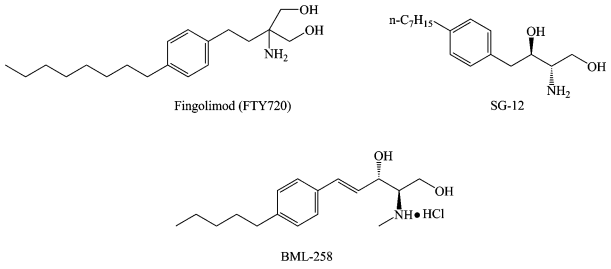


Figure 1. Structures of aromatic sphingosine analogues with biological activity.

Most syntheses of sphingosine analogues use the amino acid L-serine as starting material,[18,20,21,24,25,27,31,32] but there are limitations with this approach as discussed by Yang and Liebeskind.[9] Specifically, few methods based on L-serine are able to deliver sphingosine in >99% ee. Yang and Liebeskind report one of the few exceptions using peptidyl thiol ester−boronic acid cross-coupling. They were able to achieve high enantiopurity of (−)-D-*erythro*-sphingosine in 71% yield over six steps starting with *N*-Boc-L-serine. High diastereoselectivity was also achieved with de >94%, which was improved to 99% through recrystallization.

Given the potential high value of sphingosine analogues as described above,[17−28] alternative syntheses which are not L-serine-based may be of synthetic value if they are highly stereoselective, provide good yields in a reasonable number of steps, are scalable, and provide versatility in the potential number of sphingosine analogues that it can provide. Herein we report an alternative synthetic route to obtain a family of aromatic sphingosine analogues. The route employs *trans*-γ,δ-unsaturated β-hydroxyesters as starting materials, as shown in Figure 2. Enantioenriched (*R*)-**1A**, (*R*)-**1B**, and (*S*)-**1B** (≥99% ee) were recently prepared for the first time in our lab by reduction of the corresponding *trans*-γ,δ-unsaturated β-

Received: July 10, 2014
Published: July 21, 2014

   dx.doi.org/10.1021/jo501533g | J. Org. Chem. 2014, 79, 7778−7784

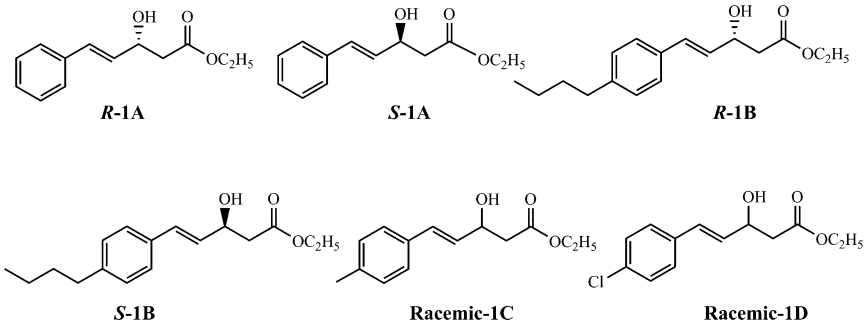
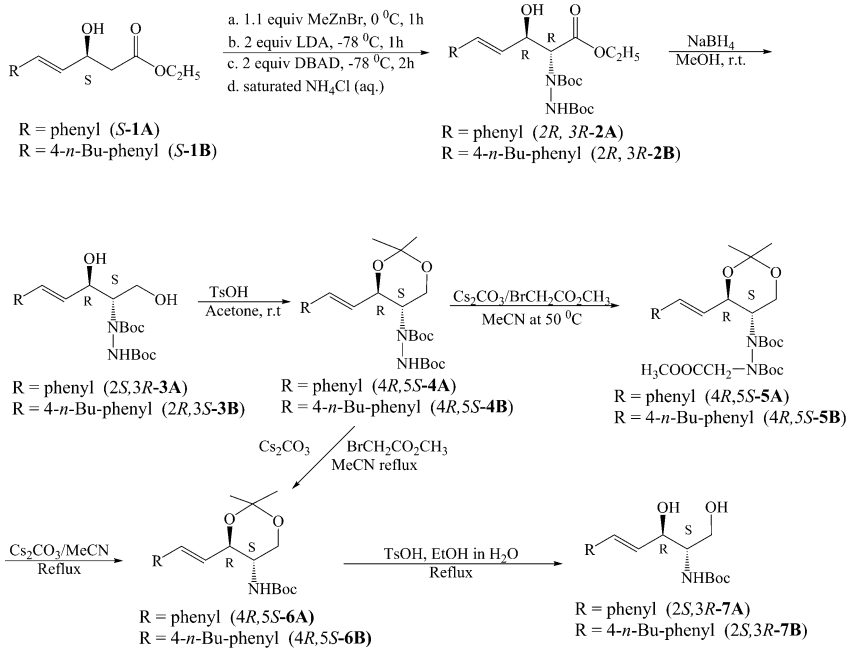


Figure 2. Structure of *trans*-γ,δ-unsaturated β-hydroxyesters. Enantioenriched (≥99%) (*R*)-**1A**, (*R*)-**1B**, and (*S*)-**1B** were prepared from reduction of corresponding *trans*-γ,δ-unsaturated β-ketoesters by ketoreductases.[33] (*S*)-**1A** (ee 75%) was prepared according to the literature.[34] Racemic-**1C** and racemic-**1D** were prepared from reduction of corresponding *trans*-γ,δ-unsaturated β-ketoesters by $NaBH_4$.

Scheme 1. General Reaction Scheme for the Stereospecific Synthesis of Ceramide and Sphingosine Derivatives from *trans*-γ,δ-Unsaturated β-(*S*)-Hydroxyesters (*S*)-1A and (*S*)-1B



ketoesters with ketoreductases (KRED).[33] Our ability to produce highly stereochemically enriched sphingosine analogues by the described synthetic route is dependent on the use of these enantioenriched starting materials.

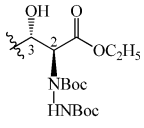
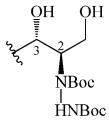
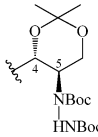
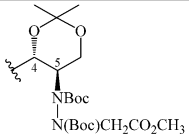
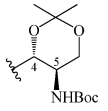
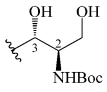
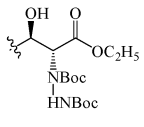
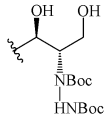
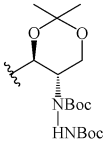
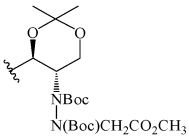
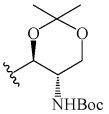
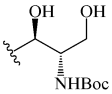
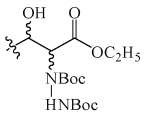
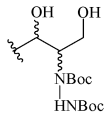
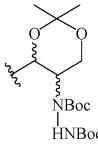
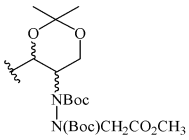
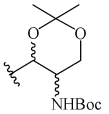
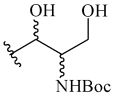
The synthetic pathway is displayed in Scheme 1, which shows the stereoselective synthesis of sphingosine analogues starting from *trans*-γ,δ-unsaturated β-hydroxyesters (*S*)-**1A** (75% ee) and (*S*)-**1B** (≥99% ee). Racemic-**1C**, racemic-**1D**, and highly enantioenriched (*R*)-**1A** and (*R*)-**1B** (≥99% ee) were also used as starting materials. The configurations, diastereoisomeric excesses, and isolated yields of all intermediates and final sphingosine analogues are listed in Table 1. The N-protected sphingosine analogues are obtained in 32–41% yield in five or six steps from the *trans*-γ,δ-unsaturated β-hydroxyesters **1**. The use of enantioenriched (*R*)-**1A**, (*R*)-**1B**, and (*S*)-**1B** results in products of (*R*)-**7A**, (*R*)-**7B**, and (*S*)-**7B** with 99.6, 99.2, and 98.8% ee, respectively, as determined by chiral capillary electrophoresis, and with >99% de as determined by quantitative NMR techniques.[35]

The diastereoselective formation of *anti*-*N*-Boc-α-hydrazino-β-hydroxyesters **2** was performed via electrophilic amination of β-hydroxyesters **1** with di-*tert*-butylazodicarboxylate (DBAD) according to the method of Genêt and co-workers.[36−39] In order to obtain high diastereoisomeric excesses, the zinc enolate form of β-hydroxyesters **1** was required by adding 1.1 equiv of MeZnBr followed by 2 equiv of LDA. Then, electrophilic amination was achieved through Michael addition after addition of DBAD with a yield of 50−60%. Unreacted β-hydroxyesters **1** could be recovered without racemization. Due to the rigid zinc enolate form of β-hydroxyesters **1**, the *anti*-configurational relationship of diastereoisomer between the hydroxyl and hydrazino functionalities was obtained with excellent diastereoisomeric excesses of >99%.

Although *syn*-diastereoisomers were not available for comparison, we observed no quantifiable minor resonances in the ^{1}H NMR spectra of intermediates **2** using quantitative techniques for diastereomer detection,[35] thus establishing a minimum of 99% de for intermediates **2**. Also, the ^{1}H NMR chemical shifts of both (2*S*,3*R*)-**7A** (*anti*) and (2*S*,3*S*)-**7A** (*syn*) have been reported,[40] which show significant differences in their 3.0−5.5 ppm spectral regions. Whereas our *anti*-**7A** spectrum agrees well with the literature, we observe no resonances for the *syn* product, although ^{13}C NMR satellite

dx.doi.org/10.1021/jo501533g | J. Org. Chem. 2014, 79, 7778−7784

Table 1. Configuration, Diastereoisomeric Excesses and Isolated Yields of All Intermediates Synthesized from Corresponding Racemic and Enantioenriched *trans*-γ,δ-Unsaturated β-Hydroxyesters

	Intermediates Configuration[a], isolated yield (%), de (%)[b]					SP analogues 7	Overall yield
	2	**3**	**4**	**5**	**6**		
Substance ee (%)[b]							
R-**1A** ≥99	(2*S*,3*S*), 58% >99 de	(2*R*, 3*S*), 85%	(4*S*,5*R*), 94%	(4*S*, 5*R*), 99%	(4*S*, 5*R*), 85%	(2*R*, 3*S*), 96% 99.6 ee, >99 de	37%
R-**1B** ≥99	(2*S*,3S), 50% >99 de	(2*R*, 3*S*), 80%	(4*S*, 5*R*), 94%	(4*S*, 5*R*), 94%	(4S, 5*R*), 95%	(2*R*, 3*S*), 95% 99.2 ee, >99 de	32%
							
S-**1A** 75	(2*R*,3*R*), 58% >99 de	(2*S*,3*R*), 88%	(4*R*,5*S*), 93%	Not isolated	(4*R*,5*S*), 94%	(2*S*,3*R*), 93% 75 ee, >99 de	41%
S-**1B** ≥99	(2*R*,3*R*), 60% >99 de	(2*S*,3*R*) 81%	(4*R*,5*S*), 94%	(4*R*,5*S*), 95%	(4*R*,5*S*), 86%	(2*S*,3*R*), 95% 98.8 ee, >99 de	35%
							
1C racemic	racemic, *anti* 55%, >99 de	racemic, *anti* 83%	racemic, *anti* 94%	Not isolated	racemic, *anti* 93%	racemic, *anti* 94%, >99 de	34%
1D racemic	racemic, *anti* 58%, >99 de	racemic, *anti* 83%	racemic, *anti* 94%	racemic, *anti* 99%	racemic, *anti* 83%	racemic, *anti* 92%, >99 de	34%

[a]Numbering system corresponds to compound names in the Experimental Section. [b]The percent ee was measured by chiral capillary electrophoresis and HPLC, and the percent de was measured by quantitative ^{1}H NMR techniques.[35]

resonances could be quantified, consistent with a minimum of 99% de in the final products.[35]

A number of methods are available for cleaving N−N bonds of hydrazines to obtain the corresponding amino products, but most of these methods involve exposure to either reductive or oxidative conditions.[41] Recently, nonreductive cleavage of the N−N bond of several diethoxycarbonyl hydrazine derivatives was reported by Magnus et al.,[41] and several of their reactions illustrated the advantage of using nonreductive conditions to preserve a carbon−carbon double bond in the substrate. However, efforts using similar conditions to cleave the N−N bond of intermediates **2** were unsuccessful, with a complex mixture of products forming. Therefore, hydroxyester **2** was effectively reduced to the diol **3** with excess $NaBH_4$ in methanol,[42,43] followed by protection of diol **3** in the form of ketal **4** in 94% yield. We then found that the N−N bond of the di-*tert*-butylcarbonyl hydrazine derivatives **4** could be conveniently cleaved using the same E1cB reaction conditions employed by Magnus et al.[41] This reaction can be performed in either one or two steps. In two steps, ketal **4** was N-alkylated with methyl bromoacetate in the presence of Cs_2CO_3 at 50 °C to obtain alkylated ketal **5** which was isolated and purified in 98% yield. Alkylated ketal **5** was then reacted further at reflux with Cs_2CO_3 to undergo N−N bond cleavage to *N*-Boc-protected ketal **6** in 87% yield. Alternatively, in the specific cases of (*S*)-**4A** and racemic-**4C**, the ketal was refluxed with methyl bromoacetate and Cs_2CO_3 in acetonitrile to directly yield **6** in 94 and 93% yield, respectively. The one-step reaction significantly improves the yield and is preferred. Compound **6** was conveniently deprotected to obtain the *N*-Boc-protected **7** in 92−96% yield. Chiral HPLC was employed to all intermediates, which demonstrate that high stereochemical purity was preserved throughout the pathway of **2** to **7**. Chiral capillary electrophoresis, using sulfoalkylated cyclodextrins as chiral selectors,[44,45] was also applied to (*R*)-**7A**, (*R*)-**7B**, and (*S*)-**7B** to quantitatively establish 99.6, 99.2, and 98.8% ee, respectively, for these final products.

The Garner aldehyde (serine-derived oxazolidine) route to aromatic ceramide analogues[18,24,40] is a well-established synthetic route to the aromatic substrates described here. For example, Van Overmeire et al. synthesized a series of related compounds including (2*S*,3*R*)-**7A** in 35% yield in three steps from the serine-derived aldehyde.[18] Murakami and Furusawa also synthesized this molecule with a modified Garner aldehyde route in 43% yield in two steps by alkenylation in place of alkynylation.[40] Diastereoselectivity in the alkenylation step was modest with *anti*/*syn* ratio of 15:1, which required further purification, reducing the overall yield to 11%. Zipkin et al.

dx.doi.org/10.1021/jo501533g | J. Org. Chem. 2014, 79, 7778−7784

synthesized a precursor to BML-258[24] which differs only slightly from (2*R*,3*S*)-**7B** (*para*-pentyl versus *para*-butyl group) in three steps from the Garner aldehyde in 34% overall yield. Diastereoselectivity was modest with *anti*/*syn* ratio of 7.5:1. Our synthesis compares well with the synthetic scheme of Moreno et al.,[25] who used a chiral epoxide as starting material to produce (2*S*,3*R*)-**7A** in five steps with an overall yield of 16% yield. Our synthesis also compares well to that of Yang and Liebeskind, whose synthesis of (−)-D-*erythro*-sphingosine in six steps was 71% from *N*-Boc-L-serine. Our lower overall yield is primarily attributed to inefficiency of the electrophilic amination of *β*-hydroxyesters **1** to *anti*-*N*-Boc-*α*-hydrazino-*β*-hydroxyesters **2**, with yields of 50−60%, which are similar to yields reported by Greck et al.[22]

We have developed an effective route for synthesis of sphingosine analogues starting from racemic and enantiomerically enriched *trans*-*γ*,*δ*-unsaturated *β*-hydroxyesters. The synthetic pathway can be accomplished in five or six steps in 32−41% overall yield. Strategies of diastereoselective formation of hydrazino and nonreductively eliminated cleavage of the hydrazino N−N bonds are essential to the stereoselective formation of an amino group. Either (2*S*,3*R*) or (2*R*,3*S*) enantiomer of aromatic sphingosine analogues is synthesized with ∼99% ee and ∼99% de. No loss of stereochemistry is detected over the entire synthesis.

EXPERIMENTAL SECTION

General Experimental Methods. All chemicals were of the highest purity unless otherwise noted. Zinc bromide was dried in an oven at 110 °C for a minimum of 24 h before using. Methylzinc bromide was prepared via the reaction of zinc bromide and methylmagnesium bromide.[46] THF was freshly distilled from sodium metal with a benzophenone ketal indicator. Acetone was dried by simple distillation and stored over molecular sieves (4 Å, 8−12 mesh). Acetonitrile was distilled from CaH_2 and stored over 4 Å molecular sieves. Aluminum-coated silica gel WF_{254s} plates were used to monitor reaction products and flash chromatography eluents. Column chromatography was performed with silica gel (40−60 *μ*m, 230−400 mesh).

NMR spectra were obtained on an FT-NMR spectrometer operating at 300 MHz for ^{1}H NMR and 75 MHz for ^{13}C NMR unless otherwise noted. Assignments were made by ^{1}H, ^{13}C, and gCOSY techniques. Chemical shifts were reported in parts per million (ppm, *δ*) relative to tetramethylsilane (TMS, *δ* 0.00 ppm). ^{1}H NMR splitting patterns are designated as singlet (s), doublet (d), triplet (t), doublet of doublets (dd), multiplet (m), broad (br). Coupling constants (*J* values) are reported in hertz (Hz). For quantitative diastereomer analysis, ^{1}H NMR spectroscopy was employed at 600 MHz with 25 s relaxation delay, no spinning, and no line broadening.[35] HPLC was performed with an isocratic pump and UV−visible detector. A cellulose column (50 × 4.60 mm) was used for the chiral separation at 23 °C. The mobile phase consisted of hexanes and isopropyl alcohol in the ratio of 90:10 and flow rate of 0.5 mL/min. Detection was at 254 nm. Accurate mass spectra were obtained on all compounds by electrospray ionization (positive ion mode) with a TOF analyzer. Capillary electrophoresis was used for estimation of % ee of the final products. Chiral selectors were single isomer sulfoalkylated cyclodextrins synthesized and characterized in our lab.[44,45] Capillary; 50 *μ*m i.d., 48.5 cm total length, 40.0 cm length to detector. Background electrolyte (BGE); 20 mM phosphate buffer, pH 2.5, 7.5, or 10 mM cyclodextrin. Voltage; −15 or −22 kV (reverse polarity). Detection at 254 nm. Pressure injection; 50−150 mbar·s. Detection at 254 nm. Sample; ∼1 mg/mL dissolved in 2:1 methanol/water.

General Procedure for Diastereoselective Formation of *anti*-*N*-Boc-*α*-hydrazino-*β*-hydroxyesters (2). Under N_2, to a solution of *trans*-*γ*,*δ*-unsaturated *β*-hydroxyesters (**1**) (1.0 mmol) in 2.0 mL of anhydrous THF at 0 °C was added 1.1 equiv of zinc methyl bromide (1.1 mmol, 0.4 M in THF). The reaction mixture was stirred for 1 h. After the reaction mixture was cooled to −78 °C, 2.0 equiv of LDA (2.0 mmol, 2 M in heptane/THF/ethylbenzene) was added dropwise. After 1 h at −78 °C, 2.0 equiv of DBAD (2.0 mmol) in 1.0 mL of anhydrous THF was added slowly, and the reaction mixture was stirred for another 2 h. Addition of 4.0 mL of saturated NH_4Cl solution (aq) was used to quench the reaction at −78 °C followed by warming to room temperature. The mixture was concentrated in vacuo at 60−70 °C, and the resulting mixture was extracted with EtOAc (2 × 10 mL). The combined extracts were dried over anhydrous Na_2SO_4 and concentrated in vacuo to afford crude product. Purification was by column chromatography on silica gel using 100% CH_2Cl_2 to elute unreacted DBAD, then gradient elution using 10:1 CH_2Cl_2/EtOAc eluent to afford *anti*-*N*-Boc-*α*-hydrazino-*β*-hydroxyesters **2**.

*(E)-Di-tert-butyl 1-(1-Ethoxy-3-hydroxy-1-oxo-5-phenylpent-4-en-2-yl)hydrazine-1,2-dicarboxylate (**2A**):* (2*S*,3*S*)-**2A** (287 mg, 58%); white solid, mp 153−155 °C; $[\alpha]_{590}^{23}$ +105 (*c* = 1.71, $CHCl_3$); (2*R*,3*R*)-**2A** (184 mg, 58%); white solid, mp 154−155 °C. Diastereomeric excess (de) >99% (*anti*): ^{1}H NMR (300 MHz, $CDCl_3$) *δ* 7.15−7.28 (5H), 6.77 (s, 1H), 6.65 (dd, *J* = 3.0, 15.0 Hz, 1H), 6.15 (dd, *J* = 3.0 Hz, 15.0 Hz, 1H), 5.09−5.37 (br, 1H), 4.90 (m, 1H), 4.53−4.72 (br, 1H), 4.23 (m, *J* = 6.0 Hz, 2H), 1.45 (s, 9H), 1.28 (t, *J* = 6.0 Hz, 3H), 1.26 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) *δ* 169.5, 169.3, 156.6, 155.0, 137.0, 129.8, 128.4, 127.9, 127.4, 126.5, 83.1, 82.4, 82.1, 69.8, 65.6, 63.4, 61.6, 28.0, 14.3; HRMS (ESI-TOF) calcd for $C_{23}H_{34}N_2O_7Na$ $(M + Na)^+$ 473.2264, found 473.2271.

*(E)-Di-tert-butyl 1-(5-(4-Butylphenyl)-1-ethoxy-3-hydroxy-1-oxopent-4-en-2-yl)hydrazine-1,2-dicarboxylate (**2B**):* (2*S*,3*S*)-**2B** (164 mg, 50%); white solid, mp 125−127 °C; $[\alpha]_{590}^{23}$ +130 (*c* = 0.23, $CHCl_3$); (2*R*,3*R*)-**2B** (228 mg, 60%); slightly yellow solid, mp 124−126 °C; $[\alpha]_{590}^{23}$ −89 (*c* = 0.56, $CHCl_3$). Diastereomeric excess (de) >99% (*anti*): ^{1}H NMR (300 MHz, $CDCl_3$) *δ* 7.21 (d, *J* = 9.0 Hz, 2H), 7.08 (d, *J* = 9.0 Hz, 2H), 6.85 (dd, *J* = 3.0, 15.0 Hz, 1H), 6.11 (dd, *J* = 3.0, 15.0 Hz, 1H), 5.11−5.38 (br, 1H), 4.91 (m, 1H), 4.50−4.70 (br, 1H), 4.21 (m, *J* = 6.0 Hz, 2H), 2.58 (t, *J* = 6.0 Hz, 2H), 1.57 (m, 2H), 1.47 (s, 9H), 1.36 (m, 2H), 1.33 (t, *J* = 6.0 Hz, 3H), 1.30 (s, 9H), 0.91 (t, *J* = 6.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) *δ* 169.6, 169.3, 157.2, 156.5, 155.2, 155.1, 142.3, 134.4, 129.8, 128.4, 126.8, 126.4, 83.1, 82.4, 82.1, 70.0, 65.6, 63.4, 61.6, 35.3, 33.4, 28.0, 22.2, 14.3, 14.0; HRMS (ESI-TOF) calcd for $C_{27}H_{42}N_2O_7Na$ $(M + Na)^+$ 529.2884, found 529.2886.

*Racemic anti-(E)-Di-tert-butyl 1-(1-Ethoxy-3-hydroxy-1-oxo-5-(p-tolyl)pent-4-en-2-yl)hydrazine-1,2-dicarboxylate (**2C**):* 302 mg, 55%; white solid, mp 163−164 °C. Diastereomeric excess (de) >99% (*anti*): ^{1}H NMR (300 MHz, $CDCl_3$) *δ* 7.19 (d, *J* = 9.0 Hz, 2H), 7.08 (d, *J* = 9.0 Hz, 2H), 6.75 (s, 1H), 6.63 (d, *J* = 15.0 Hz, 1H), 6.10 (dd, *J* = 3.0 Hz, 15.0 Hz, 1H), 5.11−5.38 (br, 1H), 4.90 (m, 1H), 4.53−4.73 (br, 1H), 4.23 (m, *J* = 6.0 Hz, 2H), 2.32 (s, 3H), 1.47 (s, 9H), 1.31 (s, 9H), 1.30 (t, *J* = 6.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) *δ* 169.5, 169.3, 157.2, 156.6, 155.0, 137.2, 134.2, 129.8, 129.1, 126.8, 126.4, 83.1, 82.4, 82.1, 70.0, 65.6, 63.4, 61.6, 28.0, 21.2, 14.3; HRMS (ESI-TOF) calcd for $C_{24}H_{36}N_2O_7Na$ $(M + Na)^+$ 487.2415, found 487.2419.

*Racemic anti-(E)-Di-tert-butyl 1-(5-(4-Chlorophenyl)-1-ethoxy-3-hydroxy-1-oxopent-4-en-2-yl)hydrazine-1,2-dicarboxylate (**2D**):* 382 mg, 58%; white solid, mp 169−170 °C. Diastereomeric excess (de) >99% (*anti*): ^{1}H NMR (300 MHz, $CDCl_3$) *δ* 7.20−7.28 (m, 5H), 6.72 (s, 1H), 6.85 (d, *J* = 15.0 Hz, 1H), 6.15 (dd, *J* = 3.0, 15.0 Hz, 1H), 5.10−5.38 (br, 1H), 4.91 (m, 1H), 4.54−4.70 (br, 1H), 4.21−4.29 (m, 2H), 1.47 (s, 9H), 1.31 (t, *J* = 6.0 Hz, 3H) 1.29 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) *δ* 169.5, 169.3, 157.3, 156.6, 155.1, 155.0, 135.5, 133.0, 128.7, 128.6, 128.4, 127.7, 83.3, 82.5, 82.2, 69.6, 65.5, 63.3, 61.7, 28.0, 14.3; HRMS (ESI-TOF) calcd for $C_{23}H_{33}N_2O_7ClNa$ $(M + Na)^+$ 507.1869, found 507.1877.

General Procedure for Synthesis of *anti*-2-Di-*tert*-butoxycarbonyl Hydrazino 1,3-Diol (3). Into a solution of *anti*-*N*-Boc-*α*-hydrazino-*β*-hydroxyesters (**2**) (1 mmol) in 25 mL of methanol, was added 3 equiv of $NaBH_4$ every 15 min until the starting material was consumed as indicated by TLC. A total of 36−51 equiv was added. Afterward, the reaction was quenched with saturated NH_4Cl (aq) (10

dx.doi.org/10.1021/jo501533g | J. Org. Chem. 2014, 79, 7778−7784

mL), and the reaction mixture was concentrated in vacuo and extracted twice with EtOAc. The combined extracts were washed with brine, dried over anhydrous Na_2SO_4, and the organic solvent was removed by rotovaporization at 60−70 °C. Purification by column chromatography on silica gel using 5:3 CH_2Cl_2/EtOAc as eluent afforded the product.

*anti-(E)-Di-tert-butyl 1-(1,3-Dihydroxy-5-phenylpent-4-en-2-yl)-hydrazine-1,2-dicarboxylate (**3A**):* (2*R*,3*S*)-**3A** (142 mg, 85%); colorless oil; $[\alpha]_{590}^{23}$ −18 (*c* = 1.13, $CHCl_3$); (2*S*,3*R*)-**3A** (52 mg, 88%); colorless oil; $[\alpha]_{590}^{23}$ +10 (*c* = 0.49, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24 (m, 5H), 6.60 (d, *J* = 15.0 Hz, 1H), 6.35 (br, 1H), 6.21 (br, *J* = 6.0, 15.0 Hz, 1H), 2.85−4.98 (br, 6H), 1.47 (s, 9H), 1.42 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.5, 157.8, 155.4, 136.3, 132.3, 129.1, 128.5, 127.9, 126.6, 82.6, 82.4, 81.9, 72.0, 64.7, 62.4, 59.2, 28.1; HRMS (ESI-TOF) calcd for $C_{21}H_{32}N_2O_6Na$ (M + Na)$^+$ 431.2153, found 431.2147.

*anti-(E)-Di-tert-butyl 1-(5-(4-Butylphenyl)-1,3-dihydroxypent-4-en-2-yl)hydrazine-1,2-dicarboxylate (**3B**):* (2*R*,3*S*)-**3B** (290 mg, 80%); colorless oil; $[\alpha]_{590}^{23}$ −35 (*c* = 0.29, $CHCl_3$); (2*S*,3*R*)-**3B** (53 mg, 81%); colorless oil; $[\alpha]_{590}^{23}$ +83 (*c* = 0.24, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (d, *J* = 9.0 Hz, 2H), 7.12 (d, *J* = 9.0 Hz, 2H), 6.58 (d, *J* = 15.0 Hz, 1H), 6.34 (br, 1H), 6.17 (dd, *J* = 6.0, 15.0 Hz, 1H), 3.35−5.00 (br, 5H), 2.59 (t, *J* = 6.0 Hz, 2H), 2.0 (s, 1H), 1.58 (m, 2H), 1.48 (s, 9H), 1.45 (s, 9H), 1.34 (m, 2H), 0.92 (t, *J* = 6.0 Hz, 3H); ^{13}CNMR (75 MHz, $CDCl_3$) δ 158.5, 157.7, 155.4, 143.0, 133.6, 132.3, 128.6, 127.9, 126.5, 82.7, 82.5, 81.9, 72.4, 64.6, 62.6, 59.3, 35.4, 33.6, 28.1, 22.3, 13.9; HRMS (ESI-TOF) calcd for $C_{25}H_{40}N_2O_6Na$ (M + Na)$^+$ 487.2779, found 487.2792.

*Racemic anti-(E)-Di-tert-butyl 1-(1,3-Dihydroxy-5-(p-tolyl)pent-4-en-2-yl)hydrazine-1,2-dicarboxylate (**3C**):* 350 mg, 83%; white solid, mp 165−167 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24 (d, *J* = 6.0 Hz, 2H), 7.10 (d, *J* = 6.0 Hz, 2H), 6.58 (d, *J* = 15.0 Hz, 1H), 6.36 (br, 1H), 6.18 (dd, *J* = 6.0, 15.0 Hz, 1H), 3.50−4.70 (br, 5H), 2.50−3.10 (br, 1H), 2.32 (s, 3H), 1.48 (s, 9H), 1.42 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.5, 157.7, 155.4, 137.8, 133.4, 132.2, 129.3, 127.9, 126.5, 82.7, 82.5, 81.9, 72.3, 64.6, 62.5, 59.3, 28.1, 21.2; HRMS (ESI-TOF) calcd for $C_{22}H_{34}N_2O_6Na$ (M + Na)$^+$ 445.2309, found 445.2305.

*Racemic anti-(E)-Di-tert-butyl 1-(5-(4-Chlorophenyl)-1,3-dihydroxypent-4-en-2-yl)hydrazine-1,2-dicarboxylate (**3D**):* 162 mg, 83%; white solid, mp 159−160 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 (s, 4H), 6.55 (d, *J* = 15.0 Hz, 1H), 6.35 (br, 1H), 6.20 (dd, *J* = 6.0, 15.0 Hz, 1H), 2.85−4.90 (br, 6H), 1.47 (s, 9H), 1.41 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.4, 157.8, 155.4, 135.1, 133.3, 130.6, 129.9, 128.9, 127.7, 82.5, 82.0, 71.8, 64.5, 62.5, 59.3, 28.1; HRMS (ESI-TOF) calcd for $C_{21}H_{31}N_2O_6ClNa$ (M + Na)$^+$ 465.1763, found 465.1764.

General Procedure for Synthesis of *anti*-2-Di-*tert*-butoxycarbonyl Hydrazino 1,3-Diol Ketal (4). Under N_2, the mixture of *anti*-2-di-*tert*-butoxycarbonyl hydrazino 1,3-diol (**3**) (0.15 mmol) and 10% molar equiv of *p*-toluene sulfonic acid monohydrate (0.015 mmol) in 5.0 mL of anhydrous acetone was stirred at room temperature until the reaction was completed as monitored by TLC plate (eluent, CH_2Cl_2/EtOAc = 5:3) (24 h). The reaction mixture was quenched with 5% $NaHCO_3$ and extracted by CH_2Cl_2. The combined organic layers were dried over anhydrous Na_2SO_4 and removed in vacuo. The product was purified by flash chromatography on silica gel using 10:1 CH_2Cl_2/EtOAc as eluent.

*anti-(E)-Di-tert-butyl 1-(2,2-Dimethyl-4-styryl-1,3-dioxan-5-yl)-hydrazine-1,2-dicarboxylate (**4A**):* (4*S*, 5*R*)-**4A** (147 mg, 94%); colorless oil; $[\alpha]_{590}^{23}$ −40 (*c* = 0.75, $CHCl_3$); (4*R*,5*S*)-**4A** (51 mg, 93%); colorless oil; $[\alpha]_{590}^{23}$ +44 (*c* = 0.45, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 (d, *J* = 6.0 Hz, 2H), 7.20−7.32 (m, 3H), 6.66 (d, *J* = 15.0 Hz, 1H), 6.00−6.35 (br, 2H), 4.56 (m, 1H), 3.70−4.28 (br, 1H), 4.02 (br, 2H), 1.55 (s, 3H), 1.48 (s, 9H), 1.45 (s, 3H), 1.37 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.6, 155.8, 154.6, 154.3, 136.4, 136.2, 133.3, 128.4, 127.9, 127.3, 126.7, 126.6, 98.6, 82.2, 81.8, 81.6, 72.0, 71.4, 60.9, 60.5, 56.2, 53.4, 29.0, 28.1, 28.0, 19.6, 19.4; HRMS (ESI-TOF) calcd for $C_{24}H_{36}N_2O_6Na$ (M + Na)$^+$ 471.2466, found 471.2470.

*anti-(E)-Di-tert-butyl 1-(4-(4-Butylstyryl)-2,2-dimethyl-1,3-dioxan-5-yl)hydrazine-1,2-dicarboxylate (**4B**):* (4*S*, 5*R*)-**4B** (55 mg, 94%); colorless oil; $[\alpha]_{590}^{23}$ −56 (*c* = 0.61, $CHCl_3$); (4*R*, 5*S*)-**4B** (42 mg, 94%); colorless oil; $[\alpha]_{590}^{23}$ +67 (*c* = 0.30, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28 (d, *J* = 6.0 Hz, 2H), 7.10 (d, *J* = 6.0 Hz, 2H), 6.63 (d, *J* = 15.0 Hz, 3H), 5.85−6.11 (br, 2H), 4.55 (m, 1H), 3.75−4.26 (br, 1H), 4.01 (br, 2H), 2.58 (t, *J* = 6.0 Hz, 2H), 1.58 (m, 2H), 1.55 (s, 3H), 1.48 (s, 9H), 1.46 (s, 3H), 1.39 (s, 9H), 1.32 (m, 2H), 0.92 (t, *J* = 6.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.6, 155.8, 154.6, 154.3, 142.9, 134.4, 133.6, 128.2, 126.7, 126.5, 126.2, 125.6, 98.6, 82.3, 81.9, 81.6, 71.6, 61.0, 60.5, 56.3, 53.6, 35.6, 33.5, 29.0, 28.1, 28.0, 22.3, 19.4, 13.9; HRMS (ESI-TOF) calcd for $C_{28}H_{44}N_2O_6Na$ (M + Na)$^+$ 527.3092, found 527.3088.

*Racemic anti-(E)-Di-tert-butyl 1-(2,2-Dimethyl-4-(4-methylstyryl)-1,3-dioxan-5-yl)hydrazine-1,2-dicarboxylate (**4C**):* 61 mg, 94%; white solid, mp 138−139 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 (d, *J* = 6.0 Hz, 2H), 7.08 (d, *J* = 6.0 Hz, 3H), 6.62 (d, *J* = 15.0 Hz, 1H), 5.86−6.30 (br, 2H), 4.53 (br, 1H), 3.75−4.26 (br, 1H), 4.00 (br, 2H), 2.31 (s, 3H), 1.54 (s, 3H), 1.47 (s, 9H), 1.43 (s, 3H), 1.37 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.6, 155.8, 154.6, 154.3, 137.8, 133.6, 133.4, 129.2, 126.7, 126.5, 126.1, 125.5, 98.6, 82.2, 81.8, 81.6, 72.2, 71.6, 60.9, 60.5, 56.3, 53.4, 29.0, 28.1, 28.0, 21.2, 19.6, 19.4; HRMS (ESI-TOF) calcd for $C_{25}H_{38}N_2O_6Na$ (M + Na)$^+$ 485.2622, found 485.2632.

*Racemic anti-(E)-Di-tert-butyl 1-(4-(4-Chlorostyryl)-2,2-dimethyl-1,3-dioxan-5-yl)hydrazine-1,2-dicarboxylate (**4D**):* 157 mg, 93%; white solid, mp 165−166 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (d, *J* = 9.0 Hz, 2H), 7.26 (d, *J* = 9.0 Hz, 2H), 6.63 (d, *J* = 15.0 Hz, 1H), 6.00−6.55(br, 2H), 4.56 (br, 1H), 4.00−4.39 (br, 1H), 4.01 (br, 2H), 1.54 (s, 3H), 1.48 (s, 9H), 1.44 (s, 3H), 1.36 (s, 9H); ^{13}CNMR (75 MHz, $CDCl_3$) δ 156.6, 155.8, 154.6, 154.3, 134.9, 133.4, 132.3, 131.7, 128.6, 128.6, 127.9, 127.8, 98.6, 82.2, 81.8, 81.6, 71.8, 71.1, 80.8, 60.4, 56.4, 53.3, 28.9, 28.1, 28.0, 19.4; HRMS (ESI-TOF) calcd for $C_{24}H_{35}N_2O_6ClNa$ (M + Na)$^+$ 505.2076, found 505.2068.

General Procedure for Synthesis *anti*-2-Alkylhydrazino Acetonide of 1,3-diol (5). Into a suspension solution of *anti*-2-di-*tert*-butoxycarbonyl hydrazine acetonide of 1,3-diol (**4**) (0.242 mmol) and Cs_2CO_3 (0.61 mmol) in 2.5 mL of CH_3CN under N_2 was added methyl bromoacetate (0.484 mmol) in 0.5 mL of CH_3CN. The reaction mixture was stirred at 50 °C for 3−8 h as indicated by TLC plate (eluent, 10:1 CH_2Cl_2/EtOAc). After the reaction was completed, 2.0 mL of saturated NH_4Cl (aq) was added to quench the reaction. The solution was then extracted with EtOAc (2 × 5 mL). The combined extracts were washed with brine, dried over anhydrous Na_2SO_4, and the solvent was removed in vacuo. The *anti*-2-alkylhydrazino acetonide of 1,3-diol (**5**) was purified by flash chromatography on silica gel using 10:1 CH_2Cl_2/EtOAc as eluent. All intermediates **5** revealed complicated NMR spectra due to the presence of a number of rotamers (see Supporting Information). A temperature study was carried on **5C** to provide evidence for rotamerism of these compounds.

*anti-(E)-Di-tert-butyl 1-(2,2-Dimethyl-4-styryl-1,3-dioxan-5-yl)-2-(2-methoxy-2-oxoethyl)hydrazine-1,2-dicarboxylate (**5A**):* (4*S*,5*R*)-**5A** (96 mg, >99%); colorless oil; $[\alpha]_{590}^{23}$ −63 (*c* = 1.76, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23−7.26 (m, 5H), 6.50−6.62 (m, 1H), 6.05−6.26 (m, 1H), 3.31−5.36 (m, 9H), 1.34−1.68 (m, 24H); ^{13}C NMR (75 MHz, $CDCl_3$) a large number of ^{13}C resonances were observed due to the presence of several rotamers at 25 °C; see Supporting Information for detailed peak listing; HRMS (ESI-TOF) calcd for $C_{27}H_{40}N_2O_8Na$ (M + Na)$^+$ 543.2677, found 543.2689.

*anti-(E)-Di-tert-butyl 1-(4-(4-Butylstyryl)-2,2-dimethyl-1,3-dioxan-5-yl)-2-(2-methoxy-2-oxoethyl)hydrazine-1,2-dicarboxylate (**5B**):* (4*S*,5*R*)-**5B** (46 mg, 94%); colorless oil; $[\alpha]_{590}^{23}$ −65 (*c* = 0.77, $CHCl_3$); (4*R*, 5*S*)-**5B** (28 mg, 95%); colorless oil; $[\alpha]_{590}^{23}$ +83 (*c* = 0.24, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22 (m, 2H), 7.11 (m, 2H), 6.47−6.59 (m, 1H), 5.99−6.20 (m, 1H), 3.32−5.30 (m, 9H), 2.58 (t, *J* = 6.0 Hz, 2H), 1.26−1.68 (m, 28H), 0.92 (dt, *J* = 3.0, 6.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) a large number of ^{13}C resonances were observed due to the presence of several rotamers at 25 °C; see Supporting Information for detailed peak listing; HRMS (ESI-TOF) calcd for $C_{31}H_{48}N_2O_8Na$ (M + Na)$^+$ 599.3303, found 599.3309.

dx.doi.org/10.1021/jo501533g | *J. Org. Chem.* 2014, 79, 7778−7784

*Racemic anti-(E)-Di-tert-butyl 1-(2,2-Dimethyl-4-(4-methylstyryl)-1,3-dioxan-5-yl)-2-(2-methoxy-2-oxoethyl)hydrazine-1,2-dicarboxylate (**5C**):* 26 mg, 98%; colorless oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.23−7.26 (m, J = 3.0, 6.0 Hz, 1H), 7.18−7.21 (m, J = 6.0 Hz, 1H), 7.10 (dd, J = 3.0, 6.0 Hz, 2H), 6.49−6.58 (m, 1H), 6.01−6.19 (m, 1H), 3.33−5.31 (m, 9H), 2.33 (s, 3H), 1.35−1.68 (m, 24H); ^{13}C NMR (150 MHz, $CDCl_3$) a large number of ^{13}C resonances were observed due to the presence of several rotamers at 25 °C; see Supporting Information for detailed peak listing; HRMS (ESI-TOF) calcd for $C_{28}H_{42}N_2O_8Na$ $(M + Na)^+$ 557.2833, found 557.2852.

*Racemic anti-(E)-Di-tert-butyl 1-(4-(4-Chlorostyryl)-2,2-dimethyl-1,3-dioxan-5-yl)-2-(2-methoxy-2-oxoethyl)hydrazine-1,2-dicarboxylate (**5D**):* 134 mg, 99%; colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (m, 4H), 6.46−6.59 (m, 1H), 6.05−6.25 (m, 1H), 3.28−5.32 (m, 9H), 1.35−1.67 (m, 24); ^{13}C NMR (75 MHz, $CDCl_3$) a large number of ^{13}C resonances were observed due to the presence of several rotamers at 25 °C; see Supporting Information for detailed peak listing; HRMS (ESI-TOF) calcd for $C_{27}H_{39}N_2O_8ClNa$ $(M + Na)^+$ 577.2287, found 577.2299.

General Procedure for Synthesis of *anti*-2-Boc-amino Acetonide of 1,3-Diol (6). Into a suspension solution of **5** (0.22 mmol) in 5.0 mL of CH_3CN under argon was added 3 equiv of Cs_2CO_3 (0.66 mmol), and the reaction mixture was refluxed for over 20 h until the starting material was consumed as indicated by TLC plate (eluent, 10:1 CH_2Cl_2/EtOAc). The reaction was quenched with saturated NH_4Cl (aq) and then extracted twice with EtOAc. The combined extracts were washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed in vacuo. The product **6** was purified by flash chromatography on silica gel using 10:1 CH_2Cl_2/EtOAc as eluent.

*anti-(E)-tert-Butyl (2,2-Dimethyl-4-styryl-1,3-dioxan-5-yl)-carbamate (**6A**):* (4*S*,5*R*)-**6A** (46 mg, 85%); colorless oil; $[\alpha]_{590}^{23}$ −25 (c = 0.79, $CHCl_3$); (4*R*,5*S*)-**6A** (18 mg from (4*R*,5*S*)-**4A**, 94%); colorless oil; $[\alpha]_{590}^{23}$ +21 (c = 0.24, $CHCl_3$), lit.[23] +17.2; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 (m, 2H), 7.20−7.32 (m, 3H), 6.65 (d, J = 15.0 Hz, 1H), 6.18 (dd, J = 6.0, 15.0 Hz, 1H), 4.43 (d, J = 9.0 Hz, 1H), 4.27 (br, 1H), 4.00 (dd, J = 6.0 Hz, 1H), 3.72 (m, 1H), 3.61 (m, 1H), 1.53 (s, 3H), 1.46 (s, 3H), 1.35 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.1, 136.3, 133.6, 128.4, 127.9, 126.7, 126.6, 98.8, 79.8, 74.6, 63.0, 49.1, 28.7, 28.2, 19.6; HRMS (ESI-TOF) calcd for $C_{19}H_{27}NO_4Na$ $(M + Na)^+$ 356.1832, found 356.1841.

*anti-(E)-tert-Butyl (4-(4-Butylstyryl)-2,2-dimethyl-1,3-dioxan-5-yl)carbamate (**6B**):* (4*S*,5*R*)-**6B** (25 mg, 95%), white solid, mp 118−120 °C; $[\alpha]_{590}^{23}$ −61 (c = 0.49, $CHCl_3$); (4*R*,5*S*)-**6B** (13 mg, 86%); white solid, mp 119−121 °C; $[\alpha]_{590}^{23}$ +59 (c = 0.17, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (d, J = 6.0 Hz, 2H), 7.11(d, J = 6.0 Hz, 2H), 6.63 (d, J = 15.0 Hz, 1H), 6.12 (dd, J = 6.0, 15.0 Hz, 1H), 4.37 (br, 1H), 4.25 (br, 1H), 4.02 (dd, J = 6.0 Hz, 1H), 3.71 (m, 1H), 3.59 (m, 1H), 2.58 (t, J = 6.0 Hz, 2H), 1.58 (m, 2H), 1.53 (s, 3H), 1.46 (s, 3H), 1.35 (s, 9H), 1.32 (m, 2H), 0.92 (t, J = 6.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.1, 142.9, 133.7, 128.5, 126.6, 125.5, 98.8, 79.9, 74.7, 63.0, 49.2, 35.4, 33.5, 28.7, 28.2, 22.3, 19.6, 13.9; HRMS (ESI-TOF) calcd for $C_{23}H_{35}NO_4Na$ $(M + Na)^+$ 412.2458, found 412.2468.

*Racemic anti-(E)-tert-Butyl (2,2-Dimethyl-4-(4-methylstyryl)-1,3-dioxan-5-yl)carbamate (**6C**):* 14 mg, 87%; white solid, mp 144−145 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28 (d, J = 6.0 Hz, 2H), 7.10 (d, J = 6.0 Hz, 2H), 6.62 (d, J = 15.0 Hz, 1H), 6.11 (dd, J = 6.0, 15.0 Hz, 1H), 4.41 (d, J = 9.0 Hz, 1H), 4.25 (br, 1H), 4.00 (dd, J = 6.0 Hz, 1H), 3.71 (m, 1H), 3.63 (m, 1H), 2.32 (s, 3H), 1.53 (s, 3H), 1.46 (s, 3H), 1.35 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.1, 137.8, 133.7, 133.5, 129.2, 126.6, 125.5, 98.8, 97.8, 74.7, 63.0, 49.1, 28.8, 28.2, 21.2, 19.6; HRMS (ESI-TOF) calcd for $C_{20}H_{29}NO_4Na$ $(M + Na)^+$ 370.1989, found 370.1993.

*Racemic anti-(E)-tert-Butyl (4-(4-Chlorostyryl)-2,2-dimethyl-1,3-dioxan-5-yl)carbamate (**6D**):* 67 mg, 83%; white solid, yield 83%, mp 147−148 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28 (ddd, J = 3.0, 6.0 Hz, 4H), 6.66 (d, J = 15.0 Hz, 1H), 6.16 (dd, J = 6.0, 15.0 Hz, 1H), 4.51 (br, 1H), 4.24 (br, 1H), 3.97 (dd, J = 6.0 Hz, 1H), 3.66 (m, 2H), 1.52 (s, 3H), 1.46 (s, 3H), 1.35 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.1, 134.9, 133.5, 132.0, 128.6, 127.9, 127.4, 98.8, 79.8, 74.6, 62.9, 48.9, 28.7, 28.2, 19.5; HRMS (ESI-TOF) calcd for $C_{19}H_{26}NO_4ClNa$ $(M + Na)^+$ 390.1443, found 390.1448.

General Procedure for Synthesis of *trans*-4,5-Unsaturated *anti* 2-Boc-amino 1,3-Diol (7). A mixture of *anti* 2-Boc-amino acetonide of 1,3-diol (**6**) (0.1 mmol) and 10 mol % of TsOH (0.05 mmol) in 10.0 mL of 80% EtOH in H_2O (v/v) was stirred at reflux until the starting material was consumed as indicated by TLC plate (eluent, CH_2Cl_2/EtOAc = 5:3). After the reaction was completed (usually 1 h), the reaction was quenched by 4 mL of 5% $NaHCO_3$. The mixture was concentrated in vacuo at 60−70 °C, extracted by EtOAc, and dried over anhydrous Na_2SO_4. The product was isolated by column chromatography on silica gel using 5:3 CH_2Cl_2/EtOAc as eluent.

*anti-(E)-tert-Butyl (1,3-Dihydroxy-5-phenylpent-4-en-2-yl)-carbamate (**7A**):* (2*R*,3*S*)-**7A** (28 mg, 96%); colorless oil; $[\alpha]_{590}^{23}$ +13 (c = 2.40, $CHCl_3$); (2*S*,3*R*)-**7A** (10 mg, 93%); colorless oil; $[\alpha]_{590}^{23}$ −9 (c = 0.57, $CHCl_3$), lit.[25] −19.4; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.21−7.39 (m, 5H), 6.68 (d, J = 15.0 Hz, 1H), 6.26 (dd, J = 6.0, 15.0 Hz, 1H), 5.42 (d, J = 6.0 Hz, 1H), 4.53 (t, J = 6.0 Hz, 1H), 3.97 (dd, J = 3.0, 12.0 Hz, 1H), 3.76 (dd, J = 3.0, 12.0 Hz, 1H), 3.72 (br, 1H), 3.05 (br, 2H), 1.42 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.3, 136.3, 131.8, 128.6, 128.5, 127.9, 126.6, 80.0, 74.6, 62.5, 55.4, 28.3; HRMS (ESI-TOF) calcd for $C_{16}H_{23}NO_4Na$ $(M + Na)^+$ 316.1519, found 316.1524.

*anti-(E)-tert-Butyl (5-(4-Butylphenyl)-1,3-dihydroxypent-4-en-2-yl)carbamate (**7B**):* (2*R*,3*S*)-**7B** (16 mg, 94%); white solid, mp 94−96 °C; $[\alpha]_{590}^{23}$ +10 (c = 0.97, $CHCl_3$); (2*S*,3*R*)-**7B** (10 mg, 95%); white solid, mp 96−98 °C; $[\alpha]_{590}^{23}$ −15 (c = 0.67, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 (d, J = 9.0 Hz, 2H), 7.13 (d, J = 9.0 Hz, 2H), 6.67 (d, J = 15.0 Hz, 1H), 6.21 (dd, J = 6.0, 15.0 Hz, 1H), 5.36 (d, J = 9.0 Hz, 1H), 4.54 (t, J = 3.0 Hz, 1H), 3.99 (dd, J = 3.0, 12.0 Hz, 1H), 3.76 (dt, J = 3.0, 12.0 Hz, 1H), 3.71 (m, 1H), 2.84 (br, 2H), 2.59 (t, J = 6.0 Hz, 2H), 1.54−1.65 (m, 2H), 1.44 (s, 9H), 1.29−1.41 (m, 2H), 0.92 (t, J = 6.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.2, 142.9, 133.7, 131.8, 128.7, 127.4, 126.5, 79.9, 74.9, 62.6, 55.4, 35.4, 33.6, 28.3, 22.3, 13.9; HRMS (ESI-TOF) calcd for $C_{20}H_{31}NO_4Na$ $(M + Na)^+$ 372.2145, found 372.2156.

*Racemic anti-(E)-tert-Butyl (1,3-Dihydroxy-5-(p-tolyl)pent-4-en-2-yl)carbamate (**7C**):* 29 mg, 95%; white solid, mp 57−59 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (d, J = 6.0 Hz, 2H), 7.11 (d, J = 6.0 Hz, 2H), 6.63 (d, J = 15.0 Hz, 1H), 6.20 (dd, J = 6.0, 15.0 Hz, 1H), 5.41 (d, J = 6.0 Hz, 1H), 4.51 (dd, J = 3.0, 6.0 Hz, 1H), 3.97 (dt, J = 3.0, 12.0 Hz, 1H), 3.75 (dt, J = 3.0, 12.0 Hz, 1H), 3.72 (m, 1H), 3.31 (d, J = 3.0 Hz, 1H), 3.00 (s, 1H), 2.33 (s, 3H), 1.43 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.3, 137.8, 133.5, 131.8, 129.3, 127.4, 126.5, 80.0, 74.7, 62.6, 55.5, 28.4, 21.2; HRMS (ESI-TOF) calcd for $C_{17}H_{25}NO_4Na$ $(M + Na)^+$ 330.1676, found 330.1671.

*Racemic anti-(E)-tert-Butyl (5-(4-Chlorophenyl)-1,3-dihydroxypent-4-en-2-yl)carbamate (**7D**):* 15 mg, 92%; white solid, mp 66−68 °C ; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27 (m, 4H), 6.65 (d, J = 15.0 Hz, 1H), 6.25 (dd, J = 6.0, 15.0 Hz, 1H), 5.38 (d, J = 9.0 Hz, 1H), 4.53 (dd, J = 3.0, 6.0 Hz, 1H), 3.98 (dt, J = 3.0, 12.0 Hz, 1H), 3.78 (dt, J = 3.0, 12.0 Hz, 1H), 3.72 (m, 1H), 3.24 (d, J = 3.0 Hz, 1H), 2.77 (s, 1H), 1.43 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.2, 134.8, 133.5, 130.5, 129.3, 128.8, 127.8, 80.1, 74.6, 62.5, 55.4, 28.4; HRMS (ESI-TOF) calcd for $C_{16}H_{22}NO_4ClNa$ $(M + Na)^+$ 350.1130, found 350.1124.

■ ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C NMR spectra are available for compounds **2**−**7**. Chiral HPLC chromatograms are also available for compounds **6** and **7**. Chiral capillary electropherograms are available for compounds **7A**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: tkgreen@alaska.edu.

Notes

The authors declare no competing financial interest.

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