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Effects of α -Alkoxy Substitution and Conformational Constraints on 6-exo Radical Cyclizations of Hydrazones via Reversible Thiyl and Stannyl Additions

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Abstract

Access to multifunctional hydrazones of relevance to dysiherbaine synthesis studies is described. Subsequent radical cyclizations of multifunctional hydrazones via a Si- and C-linked tethering strategy are shown to function effectively in 6-exo fashion. Conformational constraints are proposed to play a key role in suppressing unproductive premature reduction pathways. The stereochemical outcomes suggest that minimizing the dipole repulsion between neighboring C=N and C-O bonds favors a C_{α} -C(=N) dihedral angle placing the C=N bond axial within a chairlike transition state, in contrast to the usual Beckwith-Houk model.

Keywords

radical cyclization; stereoselectivity; aminosugars; dysiherbaine

1. Introduction

Amino alcohols and polyhydroxylated amines are important substructures of biologically active compounds, and include sphingolipids,¹ azasugars² and aminosugars.^{3,4} An interesting conjugate of amino acid and aminosugar functionality is found in the neuroexcitotoxin (-)-dysiherbaine (**1**; Scheme 1), which was isolated from the Micronesian marine sponge *Dysidea herbacea* in 1996.⁵ Neurotoxins are in high demand to study glutamate receptors and associated central nervous system function, and **1** is a non-NMDA glutamate agonist with 5-fold selectivity for KA vs. AMPA receptors.⁶ Synthetic studies toward **1** have led to total syntheses by Hatakeyama,⁷ Snider,⁸ Sasaki,⁹ and Chamberlin,¹⁰ as well as preparation of analogues.¹¹ Through our prior studies of Si-tethered¹² and acetal-tethered¹³ radical additions to imino compounds¹⁴ for synthesis of chiral hydroxyalkylamines, practical understanding of stereocontrol in these processes has been emerging. With predictions of relative configuration thus available, we became attracted to the prospect of testing the stereocontrol models on more complex substrates of relevance to synthesis of dysiherbaine and related compounds. The aminosugar **2** (Scheme 1) was judged to be an important subgoal to be pursued via allylic amine **3**, which in turn could arise through stereocontrolled vinyl addition to imino compound **4**.

The key C-C bond construction for synthesis of the aminosugar would entail stereocontrolled delivery of a tethered vinyl radical synthon via the 6-exo cyclization implied by structure **5**.

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We have previously shown that this strategy offers high diastereoselectivity for Si-tethered vinyl group transfer to hydrazone acceptors via the 5-*exo* cyclization mode.^{12b-12e} However, prior attempts in the 6-*exo* mode using vinylsilyl ethers linked to *acyclic* β -hydroxyhydrazones were previously found to suffer β -elimination during preparation of the substrates, premature reduction during thiyl-mediated vinyl addition, and poor diastereoselectivity.^{12e,12f} It was not altogether clear whether these challenges could be met in this more highly functionalized system, but it was envisioned that the additional conformational constraints imposed by the benzylidene acetal of the *cyclic* substrate **5** could be beneficial. Tests of this hypothesis are reported herein. In the course of these studies, a modification of the currently accepted Beckwith-Houk stereocontrol model¹⁵ for 6-*exo* radical cyclization was required in order to accommodate unexpected results with α -alkoxyhydrazones.

2. Results and Discussion

2.1. Si-Tethered Cyclizations

Formation of the radical cyclization precursor **5** began with transformation of D-arabitol (Scheme 2) to the corresponding benzylidene derivative¹⁶ (mixture of regioisomers¹⁷) and oxidative cleavage with sodium periodate to afford threose derivative **6**. Alternatively, reaction of D-galactose with benzaldehyde dimethyl acetal produced a single benzylidene derivative,¹⁸ then periodate cleavage furnished **6** in 67% yield for the two steps.¹⁹ Condensation of **6** with dibenzylhydrazine afforded hydroxyhydrazone **7**, and installation of the silicon tethered radical precursor was achieved in excellent yields, furnishing the vinylsilyl ether **5**.

With silyl ether **5** in hand, the radical addition-cyclization using tin-free thiyl-mediated reaction conditions was next examined (Scheme 3).^{12b,12d} Upon heating a mixture of **5**, PhSH and AIBN in benzene, followed by exposure to fluoride ion, vinyl transfer from silicon to the imino carbon occurred to afford **8** in moderate yield. This result was a dramatic departure from our prior attempts with *acyclic* precursors in which the premature reduction predominated under these conditions.^{12f} Even more surprisingly, only one diastereomer could be detected, whereas the only prior examples of 6-*exo* Si-tethered additions to C=N bonds were non-diastereoselective.^{12f}

Further optimization of the radical cyclization was attempted using different initiators (Scheme 3). Replacing AIBN with ABC (1,1-azodicyclohexanecarbonitrile) produced much lower yields (10%), as did photochemical activation of phenyl disulfide to directly generate thiyl radicals under non-reductive conditions. However, initiation with triethylborane/oxygen conditions afforded results similar to those obtained with AIBN.

The vinyl transfer process **5** $\rightarrow$ **8** is envisioned to involve the sequence of steps shown in Scheme 4, including (a) generation of PhS $\cdot$ upon heating PhSH in the presence of AIBN, (b) PhS $\cdot$ addition to the terminus of the vinyl group, (c) cyclization of the resulting carbon-centered radical **9**, (d) H-atom abstraction from thiophenol by aminyl radical **10**, (e) fluoride-induced cleavage of Si-O bond in **11**, and (f) desilylative β -elimination with loss of PhS $^-$ from an intermediate of the type illustrated in hypervalent silicate **12** to reform the alkene in the observed product.

For subsequent elaboration toward aminosugars, direct dihydroxylation of hydrazone **8** was desirable, but allylic amines are troublesome substrates without prior acylation.²⁰ Treatment of **8** with Boc₂O furnished an *O*-acylated derivative, presumably **13** (Scheme 5), as benzoic anhydride also preferentially acylated the hydroxyl function in **8** to afford **14**. Silica gel chromatography of the *O*-Boc derivative afforded 68% of cyclic carbamate **15**.²¹ More importantly, when nOe data were obtained for the cyclic carbamate **15**, the correlation was between H_a and H_c as depicted in Scheme 5, with no observed nOe between H_a and H_b. This

offered strong evidence for the indicated stereostructure bearing the undesired configuration at the newly-formed amine center. Preliminary examination of dihydroxylation of **15** showed some promise,²² but was postponed pending further examination of the unexpected stereoselectivity in the radical addition.

The foregoing results raised two fundamental questions of relevance to the understanding of radical cyclization to imino compounds. First, why are these thiyl-mediated 6-*exo* cyclizations with the Si-tethered vinyl group successful, where several other related 6-*exo* cyclizations have failed?^{12e,12f} Second, why does the diastereoselectivity defy the usual predictions of the Beckwith-Houk model?

2.4. Factors Enabling the Si-Tethered 6-*exo* Cyclization

Previously, irreversible generation of more reactive vinyl radicals from a vinyl bromide was required for the Si-tethered 6-*exo* cyclization to hydrazones.^{12f} In contrast, in this work compound **5** cyclizes smoothly in the 6-*exo* cyclization, even with the reversible thiyl addition method. Key structural differences are the presence of the alkoxy substituent adjacent to the imino acceptor carbon and conformational restrictions imparted by the benzylidene acetal ring (Figure 1). Are such conformational constraints sufficient to enable the 6-*exo* cyclization, or is some further effect of the α -oxygen required?

In order to gain some further insight, a substrate was prepared which lacked the α -alkoxy substituent, yet maintained the conformational constraints of **5**. Racemic β -hydroxyhydrazone **16** (Scheme 6) was obtained from the corresponding β -hydroxyester by reduction (DIBAL), condensation with Ph₂NNH₂ (β -hydroxy hydrazones prepared with Bn₂NNH₂ are more prone to β -elimination), and desilylation (TBAF). Silylation of **16** furnished cyclization precursor **17** in 88% yield. Upon exposure to the thiyl-mediated addition conditions there was no detectable cyclization. As in other unsuccessful 6-*exo* radical cyclizations,^{12f} TLC indicated conversion of **17** to a new compound, presumably via addition of PhSH across the vinyl group (the new compound was converted back to hydroxyhydrazone **16** upon treatment with TBAF). This observation suggests that in this case the hydrogen atom abstraction from PhSH supercedes cyclization of the carbon-centered radical of the type illustrated in Figure 1. Thus the conformational constraint alone is insufficient to accelerate the 6-*exo* cyclization, and it can be proposed that the α -alkoxy substituent plays a more active role than previously expected.

In prior work, the Beckwith-Houk model effectively predicted the configuration obtained in thiyl-mediated vinyl additions to hydrazones.^{12d,12e} In the case of **5**, the Beckwith-Houk model predicts transition state **A** (Figure 2) which minimizes strain by orienting substituents equatorially, including the C=N bond. However, the observed product configuration suggests a strong preference for transition state **B** with the C=N bond in an axial position. To explain these results, we suggest that the α -alkoxy substituent increases the energy of **A** through a vicinal dipole repulsion due to the gauche relationship of the C=N and C-O bonds. In transition state **B**, this dihedral angle is 180°, minimizing the dipole repulsion and thus favoring reaction through **B** to the observed configuration. To test this hypothesis, a diastereomeric hydrazone **19** (Scheme 7) was designed which would possess a gauche relationship with the neighboring C-O bond in *both* transition state models **A'** and **B'**. All substituents could occupy an equatorial position in structure **A'**, so the Beckwith-Houk model would predict excellent stereocontrol. In contrast, our hypothesis incorporating the dipole repulsion predicts a lower diastereomeric ratio for this substrate.

The requisite hydrazone **20** was prepared from commercially available 4,6-*O*-benzylidene-D-glucose (Scheme 7) by periodate cleavage and condensation with Bn₂NNH₂ to afford crystalline **19**, followed by silylation with chlorodimethylvinylsilane. Cyclization of **20** under the thiyl-mediated conditions resulted in a 53% yield of **21** with a diastereomeric ratio of

70:30.²³ The complete stereocontrol from **5** changed to very weak diastereoselectivity from **20**, consistent with the prediction in Figure 2. This provides experimental support for the hypothesized dipole repulsion modification to the Beckwith-Houk model.

2.2. Preliminary Study of C-Linked Cyclization

In light of the undesired configuration emanating from the Si-tethered cyclization above, a revised plan was formulated to explore the possibility of modified conditions to reverse the stereocontrol. Use of a Lewis acid for two-point binding between the C=N and C-O bonds could potentially restrict conformer populations to the gauche conformer in transition state **A'** (Figure 3). Unfortunately, identifying a Lewis acid compatible with both the thiyl conditions and the Si tether functionality was non-trivial. Instead, a propargyl ether was selected as a C-linked radical precursor, with recognition of some advantages over the temporary Si-tether. First, the more robust ether linkage would potentially accommodate a variety of Lewis acids in the radical addition. Second, the alkyne could serve as a precursor of more reactive vinyl radicals such as **C** in the presence of Lewis acid-compatible tin reagents. Third, the pyran ring found in dysiherbaine would be formed directly in the cyclization, which could avoid subsequent steps to elaborate that ring. After a 6-*exo* radical cyclization via **C** and removal of tin, the *exo*-methylene would provide a handle for stereocontrolled hydroxyl introduction.

Alkylation of **7** with propargyl bromide in the presence of sodium iodide gave high yields of propargyl ether **22** (Scheme 8), conveniently purified by recrystallization from a 3:1 mixture of hexane and ethyl acetate. Exposure to tributyltin hydride in the presence of AIBN led to smooth conversion to vinylstannane **23**. Although the cyclization could be accomplished in benzene, DMF was preferred, offering a 90% yield over 12-24 h. Alternatively, microwave irradiation in DMF (0.5M) produced **23** in 10-15 minutes. Protodestannylation was achieved readily upon transmetalation with *n*-BuLi and treatment with propionic acid, used stoichiometrically to preserve the benzylidene acetal. Directly applying the protodestannylation to the crude cyclization product (after filtration through silica gel to remove excess tin hydride) furnished **24** in 80% yield for the two steps. It is noteworthy that this differentially functionalized compound is obtained with complete diastereoselectivity in 48% yield from D-galactose.

Assignment of configuration of **24** by NMR was accomplished with COSY and NOESY experiments on the dibenzoyl derivative **26**, prepared by successive hydrolysis and benzoylation (Scheme 9). The NOESY spectrum suggested the chair conformation indicated below, based on a crosspeak for H₂-H_{6a}. The equatorial orientation of H₄ was then inferred from crosspeaks between H_{6e}-H_{5Z} and H_{5E}-H₄. No through-space interaction of H₄ with H₂ or H_{6a} was detected.

The results suggest that the dipole repulsion stereocontrol model operative in the Si-tethered cyclizations also confers excellent selectivity in the propargyl ether cyclization. The greater stability of the propargyl ether radical precursor offers greater opportunities for potential modification of reaction conditions, for example with Lewis acidic additives.

4. Conclusions

A four-carbon trihydroxylated hydrazone prepared from arabitrol or galactose undergoes highly stereoselective 6-*exo* radical cyclization onto the hydrazone unit; reversible thiyl radical addition to silicon-tethered vinyl group initiates the cyclization. Because the product configuration was opposite that predicted by the Beckwith-Houk model for application to the dysiherbaine aminosugar, interesting fundamental issues of stereocontrol emerged. In order to rationalize unexpected stereoselectivity, a dipole repulsion model is presented as a modification of the Beckwith-Houk model for α -alkoxyhydrazones. Cyclizations using stannyl

addition to a propargylic ether were examined, resulting in a very efficient preparation of aminosugar **24** in 48% yield from D-galactose. Although these more robust substrates should be amenable to Lewis acid chelation and potential reversal of stereocontrol, preliminary experiments toward this end have not identified conditions for such a reversal. The dipole repulsion stereocontrol model, and studies designed to modulate it, may offer new possibilities for synthetic application of stereocontrolled radical additions to polyhydroxylated chiral amine targets.

5. Experimental Section

5.1. Materials and Methods

Reactions employed oven- or flame-dried glassware under nitrogen unless otherwise noted. THF, diethyl ether, benzene and toluene were distilled from sodium/benzophenone ketyl under argon. CH₂Cl₂ was distilled from CaH₂ under argon or nitrogen. Alternatively, these solvents were purchased inhibitor-free and were sparged with argon and passed through columns of activated alumina prior to use (dropwise addition of blue benzophenone ketyl solution revealed the THF purified in this manner sustained the blue color more readily than the control sample purified by distillation). Nitrogen was passed successively through columns of anhydrous CaSO₄ and R3-11 catalyst for removal of water and oxygen, respectively. All other materials were used as received from commercial sources unless otherwise noted. Thin layer chromatography (TLC) employed glass 0.25 mm silica gel plates with UV indicator. Flash chromatography columns were packed with 230-400 mesh silica gel as a slurry in the initial elution solvent. Gradient flash chromatography was conducted by adsorption of product mixtures on silica gel, packing over a short pad of clean silica gel as a slurry in hexane, and eluting with a continuous gradient from hexane to the indicated solvent. Radial chromatography refers to centrifugally accelerated thin-layer chromatography performed with a Chromatotron using commercially supplied rotors. Melting points are uncorrected. Nuclear magnetic resonance (NMR) data were obtained at operating frequencies of 500 or 300 MHz for ¹H and 125 or 75 MHz for ¹³C and chemical shifts are reported in parts per million (ppm). Infrared spectra were recorded using a single beam FT-IR spectrophotometer by standard transmission methods or by use of an attenuated total reflectance (ATR) probe. Optical rotations were determined using a digital polarimeter operating at ambient temperature. Low resolution mass spectra were obtained using sample introduction by dip, liquid chromatography or gas chromatography. High resolution mass spectra and combustion analyses were obtained from external commercial and institutional services. Chromatographic diastereomer ratio analyses employed GCMS with 15 mL × 0.25 mm I.D X 0.25 μ F.T 5%-phenyl-95%-dimethylsiloxane column and helium as mobile phase or HPLC with Microsorb-MV Si 8um 100A or Chiralcel OD columns (2-propanol/hexane as mobile phase) or Chirex 3014 column (chloroform/hexane as mobile phase).

1,1-Dibenzyl-2-(((2S,4R,5R)-5-hydroxy-2-phenyl-1,3-dioxan-4-yl)methylene)hydrazine (7)—To a solution of aldehyde **6**²⁴ (1.16 g, 5.58 mmol) in toluene (12 mL) was added dibenzylhydrazine (1.42 g, 6.70 mmol) and magnesium sulfate (30 mg). After 24 h, concentration and flash chromatography (5:1 to 1:1 hexanes/ethyl acetate) afforded **7** (2.20 g, 98%) as a colorless oil: [α]_D²⁴ = -41.3 (c 0.725, CHCl₃); IR (film) 3452 (br), 3060, 2923, 2848, 1601, 1493, 1452, 1078, 1027 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.51-7.49 (m, 2H), 7.36-7.21 (m, 13H), 6.63 (d, *J* = 4.8 Hz, 1H), 5.61 (s, 1H), 4.50 (d, *J* = 4.8 Hz, 1H), 4.40 (s, 4H), 4.28 (dd, *J* = 12.0, 1.5 Hz, 1H), 4.07 (d, *J* = 12.0 Hz, 1H), 3.77 (d, *J* = 7.3 Hz, 1H), 3.28 (d, *J* = 7.3 Hz, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 137.7, 136.9, 130.5, 128.9, 128.5, 128.1, 127.6, 127.2, 126.1, 101.4, 79.3, 72.1, 65.4, 57.4; MS (CI) *m/z* (relative intensity) 403 ([M + 1]⁺, 100%), 385 (7%), 297 (24%), 279 (18%), 198 (15%); Anal. Calcd for C₂₅H₂₆N₂O₃: C, 74.60; H, 6.51; N, 6.96. Found: C, 74.36; H, 6.67; N, 6.62.

1,1-Dibenzyl-2-(((2S,4R,5R)-5-(dimethyl(vinyl)silyloxy)-2-phenyl-1,3-dioxan-4-yl) methylene)hydrazine (5)—To a solution of hydrazone **7** (77 mg, 0.19 mmol) triethylamine (0.08 mL, 0.57 mmol), and DMAP (3 mg) in THF (2 mL) was added dimethylvinylchlorosilane (0.08 mL, 0.57 mmol). After 4 h, concentration and flash chromatography (10:1 hexanes/ethyl acetate) afforded **5** (93 mg, 100%) as a colorless oil: $[\alpha]_D^{24} = -22.5$ ($c = 0.855$, CHCl_3); IR (film) 3060, 2862, 1844, 1594, 1494, 1474, 1096, 1068, 840 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 7.55–7.52 (m, 2H), 7.38–7.22 (m, 13H), 6.69 (d, $J = 6.2$ Hz, 1H), 6.08–5.69 (m, 3H), 5.60 (s, 1H), 4.49 (dd, $J = 6.2, 1.7$ Hz, 1H), 4.36 (s, 4H), 4.10 (ABX, $J_{AB} = 12.2$ Hz, $J_{AX} = 1.6$ Hz, $J_{BX} = 1.5$ Hz, $\Delta\nu = 30.5$ Hz, 2H), 3.71–3.68 (m, 1H), 0.09 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 138.2, 137.7, 137.4, 133.3, 131.5, 128.7, 128.5, 128.1, 127.7, 127.2, 126.3, 101.2, 81.2, 72.3, 67.0, 57.4, -1.4, -1.8; MS (EI) m/z 487 ($[\text{M}+1]^+$, 90%), 403 (50%), 381 (75%), 351 (75%), 297 (80%), 279 (100%); Anal. Calcd for $\text{C}_{29}\text{H}_{34}\text{N}_2\text{O}_3\text{Si}$: C, 71.57; H, 7.04; N, 5.76. Found: C, 71.43; H, 7.18; N, 5.82.

1,1-Dibenzyl-2-((S)-1-((2S,4R,5R)-5-hydroxy-2-phenyl-1,3-dioxan-4-yl)allyl) hydrazine (8)—To a solution of hydrazone **5** (846 mg, 1.74 mmol) in refluxing deoxygenated cyclohexane (17.4 mL) was added a solution of AIBN (371 mg, 2.26 mmol) and thiophenol (0.55 mL, 5.2 mmol) in deoxygenated benzene (9.4 mL) over 12 h via syringe pump and heating was continued at reflux for 10 h. The solvent was replaced with THF (17.4 mL), and a solution of TBAF (1 M in THF, 3.83 mL, 3.83 mmol) was added. After 16 h, concentration and flash chromatography (20:1 to 1:1 hexane/ethyl acetate) afforded **8** (391 mg, 55%) as a colorless oil: $[\alpha]_D^{23} = +28.0$ ($c = 0.575$, CHCl_3); IR (film) 2973, 2361, 1655, 1531, 1453, 1339, 1148, 1114 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 7.48–7.22 (m, 15H), 5.66–5.49 (m, 1H), 5.47 (s, 1H), 5.35 (dd, $J = 17.3, 2.0$ Hz, 1H), 5.23 (dd, $J = 10.0, 2.1$ Hz, 1H), 4.02 (ABX, $J_{AB} = 11.9$ Hz, $J_{AX} = 1.9$ Hz, $J_{BX} = 1.2$ Hz, $\Delta\nu = 70.8$ Hz, 2H), 3.71 (s, 4H), 3.67–3.65 (m, 2H), 3.50 (s, 1H), 1.60 (br s, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 137.8, 137.7, 136.8, 129.6, 129.0, 128.2, 128.1, 127.1, 126.1, 118.7, 101.5, 80.5, 72.8, 64.3, 62.5, 60.5; MS (EI) m/z (relative intensity) 431 ($[\text{M}+1]^+$, 100%), 325 (60%), 301 (90%), 211 (60%).

1,1-Dibenzyl-2-((S)-1-((2S,4R,5R)-5-benzyloxy-2-phenyl-1,3-dioxan-4-yl)allyl) hydrazine (14)—To a solution of hydrazine **8** (219 mg, 0.509 mmol) in CH_2Cl_2 (25 mL) was added *N,N*-dimethylaminopyridine (93 mg, 0.76 mmol) followed by benzoic anhydride (173 mg, 0.764 mmol). After 3 h, additional benzoic anhydride was added (151 mg, 0.667 mmol). After another 4 h, concentration and flash chromatography (10:1 hexane/EtOAc) afforded **14** (326 mg, 100%) as a yellow oil. This material contained an unidentified benzoyl-derived compound in a ratio of ca. 1.5:1. IR (film) 3031, 1718, 1694, 1452, 1271, 1092 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 8.08–8.04 (m, 2H), 7.63–7.22 (m, 18H), 5.55 (s, 1H), 5.48–5.38 (m, 1H), 5.12 (d, $J = 10.3$ Hz, 1H), 5.03 (d, $J = 17.1$ Hz, 1H), 4.81 (s, 1H), 4.38 (d, $J = 13.0$ Hz, 1H), 4.04 (d, $J = 12.7$ Hz, 1H), 3.89 (d, $J = 9.1$ Hz, 1H), 3.76 (d, $J = 8.6$ Hz, 1H), 3.76 (d, $J = 13.5$ Hz, 2H), 3.69 (d, $J = 13.4$ Hz, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 171.1, 165.8, 137.9, 137.8, 135.9, 133.7, 133.2, 130.2, 129.9, 129.8, 129.6, 129.3, 129.2, 128.5, 128.4, 128.3, 128.0, 127.0, 126.4, 119.4, 101.5, 78.7, 69.6, 65.9, 62.0, 60.5 (includes ^{13}C peaks for inseparable byproduct); MS (CI) m/z (relative intensity) 535 ($[\text{M}+1]^+$, 100%), 444 (16%), 429 (50%), 338 (35%), 211 (70%).

(2S,4aR,8S,8aR)-7-(dibenzylamino)-2-phenyl-8-vinyl-tetrahydro-[1,3]dioxino [4,5-e] [1,3]oxazin-6(7H)-one (15)—To a solution of hydrazine **8** (60 mg, 0.140 mmol) in CH_2Cl_2 (2 mL) was added pyridine (0.01 mL, 0.14 mmol) followed by Boc_2O (31 mg, 0.14 mmol) at 0 °C. After 4 h, concentration and flash chromatography (5:1 hexanes/ethyl acetate) afforded **15** (43 mg, 68%) as a colorless solid; mp 166–167 °C; $[\alpha]_D^{27} +104$ ($c = 1.36$, CHCl_3); IR (film) 2864, 1701, 1385, 1260, 1102 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.45–7.21 (m, 15H), 5.80 (ddd, $J = 16.9$ Hz, 9.7 Hz, 9.7 Hz, 1H), 5.40 (s, 1H), 5.25 (d, $J = 10.0$ Hz, 1H), 5.07

(d, $J = 17.2$ Hz, 1H), 4.57 (d, $J = 13.4$ Hz, 1H), 4.35 (d, $J = 12.1$ Hz, 1H), 4.31 (d, $J = 12.1$ Hz, 1H), 4.25 (d, $J = 13.6$ Hz, 1H), 3.88 (dd, $J = 12.7, 1.4$ Hz, 1H), 3.79 (dd, $J = 3.7, 1.2$ Hz, 1H), 3.74 (d, $J = 12.0$ Hz, 1H), 3.69 (d, $J = 1.3$ Hz, 1H), 3.09 (dd, $J = 9.3, 3.7$ Hz, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 151.3, 138.2, 137.5, 137.2, 134.0, 130.3, 129.1, 189.9, 128.2, 128.1, 128.0, 127.7, 127.2, 126.1, 119.0, 100.7, 73.2, 69.2, 68.2, 67.1, 60.8, 54.1; MS (CI) m/z (relative intensity) 457 ($[\text{M}+1]^+$, 100%), 397 (62%); Anal. Calcd for $\text{C}_{28}\text{H}_{28}\text{N}_2\text{O}_4$: C, 73.66; H, 6.18; N, 6.14; Found: C, 73.41; H, 6.26; N, 6.10.

rac-2-((cis-2-Hydroxycyclohexyl)methylene)-1,1-diphenylhydrazine (16)—To a solution of ethyl *cis*-2-(*tert*-butyldimethylsilyloxy)cyclohexane carboxylate²⁵ (1.52 g, 5.30 mmol) in CH_2Cl_2 (7 mL) was added diisobutylaluminum hydride (1.2 M in hexane, 5.3 mL, 6.4 mmol) over 30 min at -78°C . After 2 h, the reaction was quenched with saturated aqueous sodium potassium tartrate (300 mL), extracted with CH_2Cl_2 (3×100 mL), dried over MgSO_4 and concentrated. The residue (crude aldehyde) was dissolved in pyridine (5 mL). Diphenylhydrazine hydrochloride (1.29 g, 5.83 mmol) was added. After 16 h, the mixture was concentrated and purified by flash chromatography (10:1 petroleum ether/EtOAc) to afford the corresponding hydrazone (1.72 g, 80%) as a colorless oil: IR (film) 3060, 3027, 2931, 2856, 1591, 1494, 836 cm^{-1} ; ^1H NMR (300 MHz, CHCl_3) δ 7.39–7.34 (m, 4H), 7.14–7.09 (m, 6H), 6.58 (d, $J = 5.98$ Hz, 1H), 3.99–3.94 (m, 1H), 2.48–2.40 (m, 1H), 1.88–1.26 (m, 8H), 0.75 (s, 9H), -0.03 (s, 3H), -0.18 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 144.3, 142.8, 129.5, 123.7, 122.4, 69.7, 46.0, 33.3, 25.7, 25.3, 24.7, 20.4, 17.9, -4.3 , -5.1 ; MS (CI) m/z (relative intensity) 409 ($[\text{M}+1]^+$, 84%), 277 (22%), 168 (100%); Anal. Calcd for $\text{C}_{25}\text{H}_{36}\text{N}_2\text{OSi}$: C, 73.48; H, 8.88; N, 6.86. Found: C, 73.43; H, 8.99; N, 6.70. To a solution of the hydrazone obtained as described above (490 mg, 1.20 mmol) in THF (12 mL) was added tetrabutylammonium fluoride (1 M in THF, 1.4 mL, 1.4 mmol). After 30 min, the reaction was concentrated and filtered through silica gel, eluting with ethyl acetate. Concentration afforded **16** (280 mg, 79%) as a colorless oil: IR (film) 3432 (br), 2930, 2847, 1590, 1495, 1296, 1211 cm^{-1} ; ^1H NMR (300 MHz, CHCl_3) δ 7.49–7.28 (m, 4H), 7.18–7.02 (m, 6H), 6.58 (d, $J = 3.9$ Hz, 1H), 4.26–4.21 (m, 1H), 2.45–2.28 (m, 1H), 1.94–1.22 (m, 9H); ^{13}C NMR (75 MHz, CDCl_3) δ 143.7, 142.2, 129.8, 124.2, 122.3, 68.0, 44.0, 32.1, 25.8, 25.0, 20.9; MS (CI) m/z (relative intensity) 317 ($[\text{M}+\text{Na}]^+$, 15%), 295 ($[\text{M}+1]^+$, 100%), 277 (12%), 168 (27%); HRMS (EI) calcd for $\text{C}_{19}\text{H}_{22}\text{N}_2\text{O}$ 294.1734, found 294.1732.

rac-2-((cis-2-(Dimethylvinylsilyloxy)cyclohexyl)methylene)-1,1-diphenylhydrazine (17)—To a solution of hydrazone **16** (90 mg, 0.306 mmol), triethylamine (0.05 mL, 0.34 mmol), *N,N*-dimethylaminopyridine (4 mg) in THF (3 mL) was added dimethylvinyl chlorosilane (0.05 mL, 0.34 mmol). After 4 h, the reaction mixture was concentrated and filtered through silica gel, eluting with ethyl acetate. Concentration afforded **17** (102 mg, 88%) as a colorless oil: IR (film) 2930, 2848, 1590, 1495, 1252, 1019 cm^{-1} ; ^1H NMR (300 MHz, CHCl_3) δ 7.41–7.29 (m, 4H), 7.16–7.04 (m, 6H), 6.54 (d, $J = 5.8$ Hz, 1H), 6.07–5.80 (m, 2H), 5.63 (dd, $J = 18.5, 5.8$ Hz, 1H), 4.04–3.79 (m, 1H), 2.56–2.23 (m, 1H), 1.91–1.15 (m, 8H), 0.01 (s, 6H); ^{13}C NMR (75 MHz, CDCl_3) δ 144.4, 143.0, 138.1, 132.5, 129.6, 123.7, 122.4, 70.2, 45.6, 33.2, 25.2, 24.6, 20.5, -1.4 , -1.5 ; MS (EI) (relative intensity) m/z 378 (M^+ , 55%), 276 (8%), 195 (12%), 167 (100%); HRMS (EI) calcd for $\text{C}_{23}\text{H}_{30}\text{N}_2\text{OSi}$ 378.2129, found 378.2127.

1,1-Dibenzyl-2-(((2*R*,4*S*,5*R*)-5-hydroxy-2-phenyl-1,3-dioxan-4-yl)methylene)hydrazine (19)—To a mixture of 4,6-*O*-benzylidene-D-glucose (2.73 g, 13.1 mmol) and NaHCO_3 (3.3 g, 39 mmol) was added a solution of NaIO_4 (6.44 g, 30.1 mmol) in water (60 mL) over 30 min. After 2 h, the mixture was concentrated to a white solid which was triturated four times with hot EtOAc. The soluble portion was concentrated to afford the crude aldehyde, which was taken up in toluene (40 mL). To this solution was added dibenzylhydrazine (3.0 g,

14 mmol). After 36 h, concentration and flash chromatography (10:1 to 1:1 hexanes/ethyl acetate) afforded a solid which was recrystallized from diethyl ether/petroleum ether to afford **19** (3.83 g, 73%) as a colorless solid; mp 44.0–44.5 °C; $[\alpha]_D^{24}$ -6.47 (c 0.665, CHCl₃); IR (film) 3444 (br), 3030, 2852, 1955, 1601, 1392, 1075 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.48–7.25 (m, 15H), 6.64 (d, *J* = 2.35 Hz, 1H), 5.50 (s, 1H), 4.38 (s, 4H), 4.36 (dd, *J* = 10.8, 5.2 Hz, 1H), 4.19 (dd, *J* = 8.8, 2.7 Hz, 1H), 3.97 (ddd, *J* = 9.5, 9.0, 5.1 Hz, 1H), 3.70 (dd, 10.5 Hz, 10.5 Hz, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 37.4, 136.7, 129.0, 128.7, 128.3, 127.8, 127.5, 127.4, 126.1, 101.3, 80.4, 70.1, 65.2, 57.8; MS (CI) *m/z* (relative intensity) 403 ([*M*+1]⁺, 100%), 301 (100%); Anal. Calcd for C₂₅H₂₆N₂O₃: C, 74.60; H, 6.51; N, 6.96; Found: C, 74.87; H, 6.64; N, 6.89.

1,1-Dibenzyl-2-(((2*R*,4*S*,5*R*)-5-(dimethyl(vinyl)silyloxy)-2-phenyl-1,3-dioxan-4-yl)methylene)hydrazine (20)—To a solution of **19** (835 mg, 2.07 mmol), triethylamine (0.87 mL, 6.2 mmol) and *N,N*-dimethylaminopyridine (25 mg, 0.207 mmol) in THF (21 mL) was added dimethylvinylchlorosilane (0.86 mL, 6.2 mmol). After 4 h, the reaction mixture was filtered through silica gel, eluting with ethyl acetate. Concentration afforded **20** (96%) as a colorless oil: $[\alpha]_D^{23}$ +3.77 (c 0.610, CHCl₃); IR (film) 2922, 1596, 1493, 1452, 1098, 1012 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.47–7.44 (m, 2H), 7.36–7.19 (m, 13H), 6.43 (d, *J* = 6.44 Hz, 1H), 6.00–5.65 (m, 3H), 5.52 (s, 1H), 4.38 (ABq, *J* = 15.4 Hz, Δ*v* = 16.1 Hz, 4H), 4.21–4.11 (m, 2H), 3.75 (ddd, *J* = 10.9, 10.0, 5.0 Hz, 1H), 3.61 (t, *J* = 10.3 Hz, 1H), 0.11 (s, 3H), 0.07 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 137.7, 137.5, 137.2, 133.7, 129.7, 128.8, 128.5, 128.2, 127.7, 127.2, 126.2, 100.8, 82.9, 71.6, 64.9, 57.6, -1.5, -1.7; MS (CI) *m/z* (relative intensity) 487 ([*M*+1]⁺, 100%), 403 (10%), 381 (14%); Anal. Calcd for C₂₉H₃₄N₂O₃Si: C, 71.57; H, 7.04; N, 5.76; Found: C, 71.52; H, 7.26; N, 5.75.

1,1-Dibenzyl-2-(1-((2*R*,4*S*,5*R*)-5-hydroxy-2-phenyl-1,3-dioxan-4-yl)allyl)hydrazine (21)—To a solution of hydrazone **20** (964 mg, 1.98 mmol) in refluxing deoxygenated benzene (20 mL) was added a solution of AIBN (325 mg, 1.98 mmol) and thiophenol (0.63 mL, 5.94 mmol) in deoxygenated benzene (8 mL) over 16 h. After an additional 10 h under reflux, tetrabutylammonium fluoride (1 M in THF, 4.4 mL, 4.4 mmol) was added and the mixture was allowed to cool to ambient temperature. After 24 h, concentration and flash chromatography (10:1 to 1:1 Hex/EtOAc) afforded **21** (452 mg, 53%, dr 70:30) as a colorless oil. Diastereomer 1: $[\alpha]_D^{25}$ +7.0 (c 0.90, CHCl₃); IR (film) 3580, 3384 (br), 3030, 2925, 2853, 1453, 1392, 1075 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.48–7.30 (m, 15H), 5.90 (ddd, *J* = 17.8, 10.1, 7.7 Hz, 1H), 5.44 (s, 1H), 5.30 (d, *J* = 10.3 Hz, 1H), 5.29 (d, *J* = 17.1 Hz, 1H), 4.18 (dd, *J* = 10.5, 5.0 Hz, 1H), 3.81–3.65 (m, 7H), 3.47 (dd, *J* = 10.5 Hz, 10.5 Hz, 1H), 3.38 (br s, 1H), 2.94 (br s, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 137.8, 137.1, 135.4, 129.6, 128.9, 128.4, 128.2, 127.5, 126.2, 118.2, 101.4, 80.8, 70.8, 63.2, 63.0, 59.9; MS (EI) *m/z* (relative intensity) 430 (M⁺, 27%), 429 (100%), 339 (10%), 282 (45%), 251 (15%); Anal. Calcd for C₂₇H₃₀N₂O₃: C, 75.32; H, 7.02; N, 6.51; Found: C, 75.08; H, 7.28; N, 6.33. Diastereomer 2: $[\alpha]_D^{25}$ = -4.6 (c 0.85, CHCl₃); IR (film) 3399 (br), 3031, 2854, 1495, 1452, 1391, 1075 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.41–7.27 (m, 15H), 5.73 (ddd, *J* = 17.3, 10.2, 8.5 Hz, 1H), 5.29 (s, 1H), 5.24 (dd, *J* = 17.3, 1.0 Hz, 1H), 5.21 (dd, *J* = 10.2, 1.6 Hz, 1H), 4.23 (dd, *J* = 8.6, 3.1 Hz, 1H), 3.86 (d, *J* = 13.0 Hz, 2H), 3.70 (d, *J* = 13.1 Hz, 2H), 3.62–3.43 (m, 4H), 3.36 (dd, *J* = 8.4, 7.1 Hz, 1H), 2.94 (br, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 137.8, 136.7, 136.5, 129.7, 128.7, 128.6, 128.4, 128.1, 127.6, 125.9, 118.4, 100.4, 82.1, 65.7, 65.3, 60.9; MS (CI) *m/z* (relative intensity) 431 ([*M*+1]⁺, 100%), 301 (100%); Anal. Calcd for C₂₇H₃₀N₂O₃: C, 75.32; H, 7.02; N, 6.51; Found: C, 75.31; H, 7.20; N, 6.45.

1,1-Dibenzyl-2-(((2*S*,4*R*,5*R*)-2-phenyl-5-(prop-2-ynyl)oxy)-1,3-dioxan-4-yl)methylene)hydrazine (22)—To a mixture of potassium hydride (30% in mineral oil, 71 mg, 0.53 mmol) in THF (1 mL) was added a solution of **7** (192 mg, 0.48 mmol) in THF (1 mL)

over 20 min. Sodium iodide (72 mg, 0.48 mmol) was added, followed by propargyl bromide (0.08 mL, 0.72 mmol). After 16 h, concentration and recrystallization from 3:1 hexanes/ethyl acetate afforded **22** (195 mg, 92%) as a light yellow solid: mp 49–50 °C; $[\alpha]_D^{25} = -23.0$ (c 0.95, CHCl₃); IR (film) 3288, 3030, 2850, 2105, 1599, 1452, 1075 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.56–7.46 (m, 2H), 7.37–7.20 (m, 13H), 6.67 (d, $J = 6.1$ Hz, 1H), 5.63 (s, 1H), 4.58 (dd, $J = 6.1, 1.8$ Hz, 1H), 4.43 (dd, $J = 12.5, 1.5$ Hz, 1H), 4.42 (ABq, $J = 15.4$ Hz, $\Delta\nu = 23.0$ Hz, 4H), 4.04 (dd, $J = 16.4, 2.4$ Hz, 1H), 4.02 (dd, $J = 12.5, 1.5$ Hz, 1H), 3.89 (dd, $J = 16.4, 2.3$ Hz, 1H), 3.59 (d, $J = 1.7$ Hz, 1H), 2.30 (t, $J = 2.4$ Hz, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 137.9, 137.5, 131.1, 128.8, 128.5, 128.1, 127.7, 127.2, 126.2, 101.2, 80.4, 79.7, 74.5, 72.1, 68.8, 57.6, 57.0; MS (CI) m/z (relative intensity) 441 (M⁺, 100%), 335 (30%); Anal. Calcd for C₂₈H₂₈N₂O₃: C, 76.34; H, 6.41; N, 6.36; Found: C, 76.51; H, 6.37; N, 6.44.

1,1-Dibenzyl-2-((2S,4aR,8S,8aR)-2-phenyl-7-((tributylstannyl)methylene)-hexahydropyrano[3,2-d][1,3]dioxin-8-yl)hydrazine (23)—To a solution of **22** (54 mg, 0.123 mmol) in deoxygenated DMF (6.2 mL) at 80 °C was added a solution of AIBN (10 mg, 0.062 mmol), and tributyltin hydride (0.04 mL, 0.15 mmol) in deoxygenated DMF (0.5 mL) over 12 h via a syringe pump. After an additional 10 h at 80 °C, the mixture was partitioned between brine (20 mL) and diethyl ether (2 × 20 mL). The organic phase was washed with brine (2 × 40 mL), dried and concentrated. Flash chromatography (10:1 to 3:1 hexanes/ethyl acetate) afforded **23** (81 mg, 90%) as a light yellow oil: $[\alpha]_D^{26} = -77.6$ (c 0.650, CHCl₃); IR (film) 2925, 2851, 1603, 1453, 1396, 1370, 1112, 1091, 1018 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.51–7.24 (m, 15H), 5.82 (s, 1H; satellite peaks indicated $J_{Sn-H} = 60.4$ Hz), 5.35 (s, 1H), 4.1 (d, $J = 12.4$ Hz, 1H), 3.95–3.82 (m, 4H), 3.75 (d, $J = 1.3$ Hz, 1H), 3.50–3.45 (m, 3H), 3.38 (dd, $J = 12.4, 1.6$ Hz, 1H), 2.47 (s, 1H), 2.15 (s, 1H), 1.60–1.38 (m, 6H), 1.36–1.18 (m, 6H), 0.87–0.80 (m, 15H); ¹³C NMR (75 MHz, CDCl₃) δ 149.5, 138.5, 137.8, 130.1, 129.9, 128.8, 128.2, 128.1, 127.2, 126.5, 101.5, 75.4, 70.0, 69.8, 65.7, 63.9, 60.7, 29.1, 27.2, 13.7, 10.3; MS (CI) m/z (relative intensity) 733 ([M+1]⁺, 70%), 732 (90%), 442 (42%), 212 (100%); Anal. Calcd for C₄₀H₅₆N₂O₃Sn: C, 65.67; H, 7.72; N, 3.83. Found: C, 65.94; H, 7.98; N, 3.55.

1,1-Dibenzyl-2-((2S,4aR,8S,8aR)-7-methylene-2-phenyl-hexahydropyrano[3,2-d][1,3]dioxin-8-yl)hydrazine (24)—A solution of **22** (344 mg, 0.781 mmol), AIBN (64 mg, 0.39 mmol), and tributyltin hydride (0.26 mL, 0.94 mmol) in deoxygenated DMF (35 mL) was heated at 80 °C for 16 h. The mixture was partitioned between brine (50 mL) and diethyl ether (2 × 50 mL). The organic phase was washed with brine (2 × 75 mL), dried and concentrated. The residue was dissolved in THF (16 mL) and *n*-butyllithium (1.6 M in THF, 1.22 mL, 1.95 mmol) was added at -78 °C. After 1 h propionic acid (0.12 mL, 1.64 mL) was added. Concentration and flash chromatography (10:1 to 1:1 hexanes/ethyl acetate) afforded **24** (265 mg, 80%) as a colorless solid: $[\alpha]_D^{24} = -25.2$ (c 1.10, CHCl₃); IR (film) 3411, 3064, 3027, 2923, 2848, 1452, 1090, 1023 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.52–7.25 (m, 15H), 5.41 (s, 1H), 5.06 (s, 1H), 5.04 (s, 1H), 4.03 (s, 1H), 3.97 (d, $J = 12.7$ Hz, 2H), 3.90 (dd, $J = 12.3, 1.3$ Hz, 1H), 3.81 (dd, $J = 2.2, 1.1$ Hz, 1H), 3.54 (d, $J = 2.4$ Hz, 1H), 3.50 (d, $J = 12.7$ Hz, 2H), 3.44 (dd, $J = 12.4, 1.8$ Hz, 1H), 2.51 (d, $J = 1.2$ Hz, 1H), 2.41 (br s, 1H); ¹H NMR (600 MHz, C₆D₆) δ 7.73–7.66 (m, 2H), 7.32–6.92 (m, 13H), 5.53 (s, 1H), 4.77 (s, 1H), 4.76 (s, 1H), 4.14 (dd, $J = 12.2, 1.3$ Hz, 1H), 4.00 (s, 2H), 3.90–3.88 (m, 1H), 3.67 (d, $J = 12.6$ Hz, 2H), 3.53 (d, $J = 2.3$ Hz, 1H), 3.43 (dd, $J = 12.2, 1.8$ Hz, 1H), 3.18 (d, $J = 12.6$ Hz, 2H), 2.62 (d, $J = 1.3$ Hz, 1H), 1.88 (s, 1H); ¹³C NMR (75 MHz, CDCl₃) δ ppm 140.8, 138.2, 137.7, 130.0, 128.7, 128.2, 128.0, 127.3, 126.3, 115.2, 101.2, 75.2, 70.2, 68.1, 66.0, 60.9, 60.0; MS (EI) m/z (relative intensity) 442 (M⁺, 3%), 351 (5%), 211 (50%), 91 (50%); Anal. Calcd for C₂₈H₃₀N₂O₃: C, 75.99; H, 6.83; N, 6.33. Found: C, 75.63; H, 6.81; N, 6.13.

(2R,3R)-4-(2,2-Dibenzylhydrazinyl)-2-(hydroxymethyl)-5-methylene-tetrahydro-2H-pyran-3-ol (25)—To a solution of **24** (65 mg, 0.15 mmol) in methanol (0.7

mL) was added *p*-toluenesulfonic acid (7 mg). After 1 h, concentration and flash chromatography (1:1 to 1:3 hexanes/ethyl acetate) afforded **25** (40 mg, 75%) as a yellow oil: $[\alpha]_D^{23} = -49.5$ (c 0.810, CHCl₃); IR (film) 3583, 3415 (br), 2924, 1493, 1452, 1067, 920 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.39–7.25 (m, 10H), 5.11 (s, 1H), 5.05 (s, 1H), 4.02–3.86 (m, 4H), 3.68 (dd, *J* = 9.3, 2.7 Hz, 1H), 3.48–3.25 (m, 5H), 2.95–2.90 (m, 1H), 2.33 (s, br, 1H), 2.29 (d, *J* = 9.2 Hz, 1H), 1.64 (t, *J* = 6.3 Hz, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 141.2, 137.9, 129.9, 128.2, 127.2, 116.9, 73.8, 69.7, 68.9, 64.0, 62.4, 61.0; MS (CI) *m/z* (relative intensity) 377 ([M+Na]⁺, 60%), 355 ([M+1]⁺, 100%), 355 (10%), 301 (15%); Anal. Calcd for C₂₁H₂₆N₂O₃: C, 71.16; H, 7.39; N, 7.90; Found: C, 71.66; H, 7.69; N, 7.85.

1,1-Dibenzyl-2-((2*R*,3*R*)-3-benzoyloxy-2-(benzoyloxymethyl)-5-methylene tetrahydro-2H-pyran-4-yl)hydrazine (26**)**—To a solution of **25** (72 mg, 0.203 mmol), triethylamine (0.07 mL, 0.81 mmol), *N,N*-dimethylaminopyridine (10 mg) and 4 Å MS in CH₂Cl₂ (2 mL) was added benzoyl chloride (0.09 mL, 0.81 mmol). After 12 h, the reaction was poured into brine (10 mL), extracted with CH₂Cl₂ (10 mL × 2), dried, concentrated and flash chromatography (1:1 petroleum ether: EtOAc) to afford **26** (111 mg, 97%) as a light yellow solid; mp 144–147 °C; IR (film) 3583, 3064, 3031, 2847, 1722, 1712, 1451, 1268, 1111 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 8.42–6.88 (m, 20H), 5.39 (d, *J* = 2.2 Hz, 1H), 5.08 (s, 1H), 4.96 (s, 1H), 4.19 (dd, *J* = 11.6, 8.2 Hz, 1H), 4.15 (d, *J* = 11.7 Hz, 1H), 4.05 (d, *J* = 11.9 Hz, 1H), 4.02 (d, *J* = 11.9 Hz, 2H), 3.87 (dd, *J* = 11.6, 3.5 Hz, 1H), 3.69 (d, *J* = 2.5 Hz, 1H), 3.49 (d, *J* = 12.5 Hz, 2H), 3.32 (dd, *J* = 8.0, 3.3 Hz, 1H), 2.45 (br s, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 166.2, 165.7, 140.8, 137.9, 133.0, 132.8, 130.1, 130.0, 129.9, 129.8, 129.7, 128.4, 128.3, 128.2, 127.3, 115.8, 70.7, 70.6, 68.3, 64.9, 60.9, 59.2; MS (EI) *m/z* (relative intensity) 563 (M⁺, 1%), 429 (25%), 325 (100%), 254 (25%), 221 (20%); HRMS (EI) calcd for C₃₅H₃₄N₂O₅ 562.2469, found 562.2473.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Kolter T, Sandhoff K. *Angew. Chem. Int Ed* 1999;38:1532–1568.
2. Reviews: Heightman TD, Vasella AT. *Angew. Chem. Int. Ed* 1999;38:750–770. (b) Bols M. *Acc. Chem. Res* 1998;31:1–8. Chapleur, Y., editor. *Carbohydrate Mimics*. Weinheim; Wiley-VCH: 1998. Nash, RJ.; Watson, AA.; Asano, N. *Alkaloids: Chemical and Biological Perspectives*. Pelletier, SW., editor. Pergamon; Tarrytown, New York: 1996. p. 345–376.
3. Arcamone, F.; Penco, S. *Anthracycline and Anthracenedione-Based Anticancer Agents*. Lown, JW., editor. Elsevier; New York: 1988.
4. Review Hauser FM, Ellenberger SR. *Chem. Rev* 1986;86:35–67.
5. Sakai R, Kamiya H, Murata M, Shimamoto K. *J. Am. Chem. Soc* 1997;119:4112–4116.
6. For studies of activity of (-)-dysiherbaine see: Sanders J, Ito K, Settimo L, Pentikainen O, Shoji M, Sasaki M, Johnson M, Sakai R, Swanson GJ. *Pharmacol. Exp. Ther* 2005;314:1068–1078. Sanders J, Pentikainen O, Settimo L, Pentikainen U, Shoji M, Sasaki M, Sakai R, Johnson M, Swanson G. *Mol. Pharmacol* 2006;69:1849–1860. [PubMed: 16537793]
7. Masaki H, Maeyama J, Kamada K, Esumi T, Iwabuchi Y, Hatakeyama S. *J. Am. Chem. Soc* 2000;122:5216–5217.
8. Snider BB, Hawryluk NA. *Org. Lett* 2000;2:635–638. [PubMed: 10814397]
9. Sasaki M, Koike T, Sakai R, Tachibana K. *Tetrahedron Lett* 2000;41:3923–3926.
10. Phillips D, Chamberlin AR. *J. Org. Chem* 2002;67:3194–3201. [PubMed: 12003525]

11. (a) Cohen J, Limon A, Miledi R, Chamberlin AR. *Bioorg. Med. Chem* 2006;16:2189–2194. (b) Shoji M, Akiyama N, Tsubone K, Lash L, Sanders J, Swanson G, Sakai R, Shimamoto K, Oikawa M, Sasaki M. *J. Org. Chem* 2006;71:5208–5220. [PubMed: 16808508] (c) Shoji M, Shiohara K, Oikawa M, Sakai R, Sasaki M. *Tetrahedron Lett* 2005;46:5559–5562. (d) Tamura O, Shiro T, Ogasawara M, Toyao A, Ishibashi H. *J. Org. Chem* 2005;70:4569–4577. [PubMed: 15932291] (e) Kang S, Lee Y. *Synlett* 2003;993:994. (f) Miyata O, Iba R, Hashimoto J, Naito T. *Org. Biomol. Chem* 2003;1:772–774. [PubMed: 12929358] (g) Huang J, Xu K, Loh T. *Synthesi* 2003;755:764. (h) Sakai R, Koike T, Sasaki M, Shimamoto K, Oiwa C, Yano A, Suzuki K, Tachibana K, Kamiya H. *Org. Lett* 2001;3:1479–1482. [PubMed: 11388846] (i) Naito T, Nair J, Nishiki A, Yamashita K, Kiguchi T. *Heterocycle* 2000;53:2611–2615. (j) Sasaki M, Maruyama T, Sakai R, Tachibana K. *Tetrahedron Lett* 1999;40:3195–3198.
12. (a) Friestad GK. *Org. Lett* 1999;1:1499–1501. (b) Friestad GK, Massari SE. *Org. Lett* 2000;2:4237–4240. [PubMed: 11150208] (c) Friestad GK, Jiang T, Fioroni GM. *Tetrahedron: Asymmetry* 2003;14:2853–2856. (d) Friestad GK, Massari SE. *J. Org. Chem* 2004;69:863–875. [PubMed: 14750816] (e) Friestad GK, Jiang T, Mathies AK. *Org. Lett* 2007;9:777–780. [PubMed: 17284042] (f) Friestad GK, Jiang T, Mathies AK. *Tetrahedron* 2007;63:3964–3972.
13. Friestad GK, Fioroni GM. *Org. Lett* 2005;7:2393–2396. [PubMed: 15932206]
14. Reviews of radical addition to C=N bonds: Friestad GK. *Tetrahedron* 2001;57:5461–5496. (b) Bertrand M, Feray L, Gastaldi S. *Comptes Rend. Acad. Sci. Paris, Chimie* 2002;5:623–638. (c) Miyabe H, Ueda M, Naito T. *Synlett* 2004:1140–1157.
15. Beckwith ALJ, Schiesser CH. *Tetrahedron* 1985;41:3925–3941. Spellmeyer DC, Houk KN. *J. Org. Chem* 1987;52:959–974.
16. Haskins W, Hann R, Hudson C. *J. Am. Chem. Soc* 1943;65:1663–1667.
17. A mixture of 5- and 6-membered acetals was present, from which the desired regioisomer was obtained in 27% yield after recrystallization.
18. Patroni J, Stick R, Skelton B, White A. *Aust. J. Chem* 1988;41:91–102.
19. On larger scale, the arabitol route was preferred due to the cumbersome purification of the 4,6-*O*-benzylidene-D-galactopyranose
20. Xu Z, Johannes C, La D, Hofilena G, Hoveyda A. *Tetrahedron* 1997;53:16377–16390.
21. TLC showed complete conversion, and the ¹H NMR spectrum of the crude reaction mixture was consistent with *O*-acylation. However, 30% recovery of 8 was observed after chromatography
22. Treatment of 15 with OsO₄/NMO under standard conditions afforded a substance with ¹H NMR spectrum consistent with 4:1 mixture of diastereomeric diols
23. Attempts to form the cyclic carbamate from 21 for nOe analysis were unsuccessful
24. Schmid R, Maier T. *Carbohydr. Res* 1988;174:169–179.
25. Panunzio M, Camerini R, Pachera R, Donati D, Marchioro C, Perboni A. *Tetrahedron: Asymmetry* 1996;7:2929–2938.

Key Structural Differences

- conformationally constrained C2–C3 bond
- α -alkoxy substituent adjacent to C=N

Figure 1.
Comparison of structural features in unsuccessful and successful 6-*exo* cyclizations.

equatorial C=N is *gauche* to α -C-O bond
(inconsistent with product configuration)

axial C=N is *anti* to α -C-O bond
(predicts observed product configuration)

Control experiment: Both **A'** and **B'** place the C=N *gauche* to α -C-O bond
Prediction: If dipole repulsion effect is operative, selectivity should be lower

Figure 2.
Transition state models for 6-exo cyclizations of diastereomeric hydrazones.

Figure 3.
Potential for use of Lewis acid chelation to override dipole repulsion.

Scheme 1

Scheme 2

initiator	PhS $\cdot$ source	temperature	yield
AIBN	PhSH	80 °C	55%
ABC	PhSH	80 °C	10%
light	PhSSPh	r.t.	10%
Et ₃ B/O ₂	PhSH	r.t.	52%

Scheme 3

Scheme 4

Scheme 5

Scheme 6

Scheme 7

Scheme 8

Scheme 9