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Stereocontrol in radical Mannich equivalents for aminosugar synthesis: haloacetal and 2-(phenylthio)vinyl tethered radical additions to α-hydroxyhydrazones

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ABSTRACT

Studies of stereocontrol in two types of radical equivalents of Mannich addition reactions offer new insights for application to aminosugar synthesis. In the first method, haloacetal addition (Ueno–Stork reaction) is extended to dihydroxyhydrazones, leading to an adduct with the unexpected 3-*epi*-L-daunosamine configuration. A neighboring α-benzyloxy substituent causes a dramatic reversal of stereocontrol compared with hydrazones where this substituent is absent; vicinal dipole repulsion is proposed to account for the diastereoselectivity. In the second method, radical addition–cyclization with thiophenol and treatment with fluoride leads to diastereoselective group transfer from a silicon-tethered ethynyl group to the C=N bond of hydrazones, affording *anti*-hydrazino alcohols with a *trans*-2-(phenylthio)vinyl substituent. The one-pot process occurs under neutral, tin-free radical conditions, and offers stereocontrol which is complementary to the haloacetal method. Synthetic utility of the radical Mannich concept is demonstrated in a brief asymmetric synthesis of *N*-trifluoroacetyl-L-daunosamine from achiral precursors.

1. Introduction

A carbon–carbon bond construction approach to α-branched amines may create both a stereogenic center and a C–C bond in a single synthetic transformation.[1] Among the methods for stereocontrolled additions to C=N bonds are a wide range of methods involving carbon nucleophiles, including Mannich reactions, which have been extensively developed to the point of widespread application.[1a,2] Radical additions are complementary to existing methodology for additions to imino compounds;[3,4] the radical intermediates are non-basic, avoiding *aza*-enolization,[5] are chemoselective, and can be generated under mild conditions. Such features avoid some of the problems inherent to carbanion-type organometallic reagents. For example, reactions of carbon centered radicals permit the presence of –OH or –OR groups at the β-position of carbonyl or imine compounds without concern for base-induced elimination.

In the ideal scenario, the addition of functionalized radicals to imino compounds could be accomplished in an intermolecular fashion with some acyclic stereocontrol. Although a number of such intermolecular addition methods are now known,[6–9] the radicals employed in those studies have rarely accommodated additional functionality. Our alternative strategy employs temporary tethers[10] (silyl ether or acetal linkages) so that the C–C bond is constructed via cyclization, in which the internal conformational constraints can control diastereoselectivity. Several functionalized C1 and C2 units can be installed in this fashion; after removal of the tether this achieves 'formal acyclic stereocontrol'. The relevant methods we have developed include Si-tethered additions of hydroxymethyl[11] (Fig. 1, **A**), vinyl[12] (**B**), and 2-(thiophenyl)vinyl[13] (**C**) groups. The latter are radical equivalents of an acetaldehyde Mannich reaction.[14] The resulting hydroxyalkyl amine structures are found in a variety of common compound classes of interest for their biological activity, including sphingolipids,[15] hydroxylated pyrrolidines and piperidines ('azasugars'),[16] and aminosugars.[17]

To complement the Si-tethered ethynyl cyclizations (Fig. 1, **C**) we have also developed a variation on the theme of Mannich equivalents, which engages an acetal tether to connect a two-carbon alkyl halide radical precursor to the imino acceptor (Fig. 1, **D**).[18] This transformation adds an acetaldehyde equivalent to the C=N bond of α-hydroxyhydrazones, directly affording furanose or pyranose aminosugar structures.

The radical Mannich methodologies **C** and **D** appear to be well-suited to syntheses of 3-aminosugars containing the β-aminoaldehyde functional group array. However, the underlying methodology for additions to C=N bonds via the acetal tether has only been examined in simple α- and β-hydroxyhydrazones, and methodology for conversion of the 2-(phenylthio)vinyl adducts to aminosugars was not yet demonstrated. Here we describe stereocontrol studies directed toward application of radical Mannich

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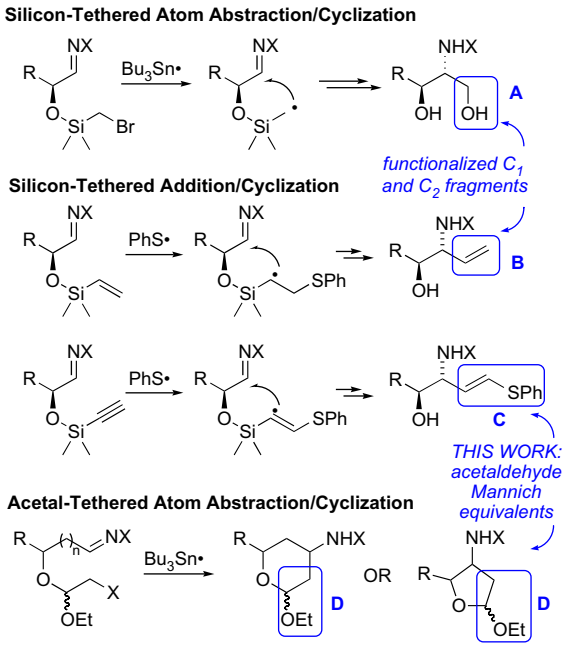
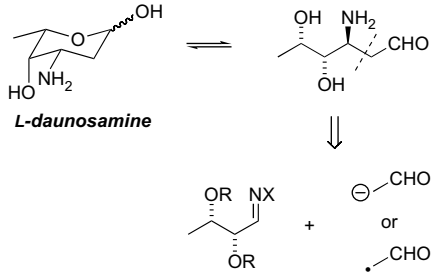


Figure 1. Summary of the temporary tether strategy for addition of functionalized radicals to imino compounds.

equivalents to aminosugar synthesis, including a surprising reversal of diastereoselectivity in a 6-*exo* Ueno–Stork haloacetal cyclization of an α,β-dihydroxyhydrazone, expansion of our preliminary study of 2-(phenylthio)vinyl addition,[13] and an application of the latter to synthesis of a biologically relevant target, the aminosugar L-daunosamine.

Daunosamine was specifically of interest for its ongoing biological relevance; for example, the daunosamine nitrogen serves as a linkage point to construct dimeric or chimeric structures related to DNA-binding antitumor agent daunomycin.[19] Furthermore, beneficial effects on DNA-binding thermodynamics in dimeric analogs of daunomycin have been attributed in part to electrostatic attractions between the DNA and the ammonium cation within the daunosamine segments.[20] Considering their biological importance, it is not surprising that numerous strategies to access aminosugars have been reported, the vast majority of which involve functional group interconversions from other carbohydrates.[17,21]

A potentially efficient approach to L-daunosamine involves addition of an acetaldehyde equivalent to a 2,3-dihydroxyimine acceptor (Scheme 1). Among several prior approaches to daunosamine are nitrone cycloadditions[22] and Mannich-type reactions,[23,42] which accomplish this same bond construction using negatively charged or polarized acetaldehyde *enolate* equivalents. We sought to develop a complementary alternative, which would involve a non-polar acetaldehyde *radical* Mannich equivalent according to Scheme 1 and Figure 1.

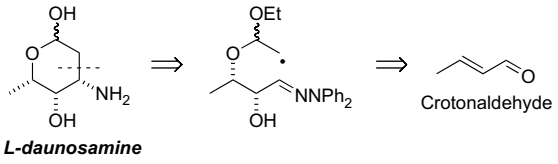


Scheme 1.

2. Results and discussion

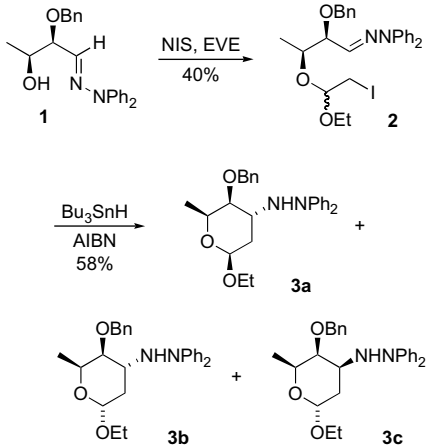
2.1. Haloacetal method

The haloacetal radical cyclization was first introduced by Ueno[24] for the functionalization of butyrolactones and by Stork[25] for the construction of bicyclic acetals and lactones in the early 1980s, and numerous synthetic applications have followed.[26] Despite the broad utility of the Ueno–Stork haloacetal cyclization for addition to alkenes, imine acceptors have rarely been used.[14b,27] We envisioned application of 6-*exo* haloacetal cyclization for direct access to aminosugars from achiral precursors (Scheme 2). In an attempt to access L-daunosamine and expand on the prior findings regarding stereocontrol in Ueno–Stork reactions,[28,18] we initiated a study of the stereochemical outcome of haloacetal cyclizations using an α,β-dioxygenated imino compound as the radical acceptor.



Scheme 2.

Monobenzyl-protected dihydroxyhydrazone **1** (Scheme 3) was prepared from commercially available *trans*-crotonaldehyde by a three-step method[12] involving condensation with diphenylhydrazine, Sharpless asymmetric dihydroxylation[29] (89% ee), and stannylene-mediated hydroxyl differentiation.[30] Reaction of **1** with *N*-iodosuccinimide (NIS) in ethyl vinyl ether afforded iodoacetal **2** in modest yield as a mixture of diastereomers (Scheme 3). Cyclization using typical tin-mediated conditions (1.2 equiv Bu_3SnH, 0.02 M in refluxing benzene) initiated by 2,2′-azobisisobutyronitrile (AIBN) resulted in the formation of a mixture of three cyclized products **3a**–**c** in a ratio of 5.0:3.8:1 (58% yield).



Scheme 3.

The relative configurations of isolated **3a** were determined through straightforward analysis of the coupling constants among hydrogens at C1–C3, and were found to correspond to an equatorial anomer with the configuration of L-3-*epi*-daunosamine (Fig. 2).[31] Unfortunately, efforts to isolate the two minor components **3b** and **3c** in pure form were unsuccessful, although the ^1H NMR coupling constants obtained in a spectrum of the mixture clearly indicated

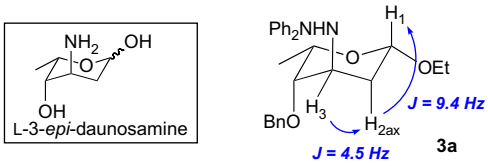
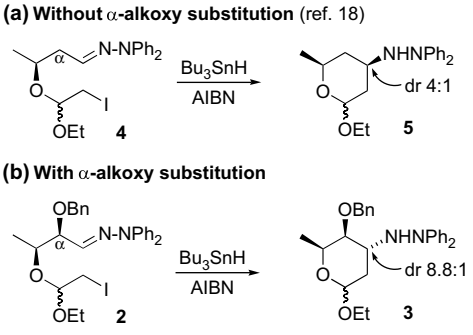


Figure 2. Diagnostic coupling constants for assignment of relative configurations of the major diastereomer **3a**.

both were axial anomers.[32] The second component **3b** had the same configuration as **3a** at C3 (i.e., the stereocenter generated during the radical cyclization). Minor component **3c** exhibited a large axial–axial coupling between $H2_{ax}$ and H3, consistent with the equatorial *N*-substituent at C3, as required for L-daunosamine. Therefore, combining the anomers **3a** and **3b**, the C3 diastereomer ratio of the radical cyclization at C3 was 8.8:1, favoring the relative configuration found in L-3-*epi*-daunosamine.

These results and the prior findings[18] with less-substituted analog **4** lacking the 2-OBn group exhibit a dramatic reversal of the diastereoselectivity at the nitrogen-bearing stereocenter (Scheme 4). The stereocontrol in Ueno–Stork cyclizations emanates from the Beckwith–Houk chairlike transition state model,[33] with perturbations originating in the anomeric effect.[34,28] Haloacetal cyclizations of hydrazones such as **4** may be explained analogously, and due to the replacement of the typical Ueno–Stork C=C acceptor with a polarized C=N bond, a 1,3-diaxial dipole repulsion effect is superimposed upon the usual stereocontrol model.[18] The surprising diastereoselectivity in formation of **3** called for further analysis of these models to accommodate the interesting reversal of stereocontrol affected by the additional alkoxy substituent.



Scheme 4.

In analogy with the earlier study,[18] a series of twist and chair transition states leading to **3** may be proposed (Fig. 3), all having ethoxy substituents in the pseudoaxial orientation due to the anomeric effect. Previously, diastereomer **5** (Scheme 4) was attributed to a transition state analogous to **E**, and no diastereomer was found with a configuration corresponding to the transition state **F**, an observation suggesting the importance of a 1,3-diaxial dipole repulsion between C=N and OEt groups.[18] In contrast, with an additional alkoxy substituent present for cyclization of the more substituted analog **2**, the minor amount of **3c** (6% vs 22% of **3b**) suggests **E** is less favorable than **F**. It may be inferred that the vicinal dipole repulsion in **E** is more unfavorable than the 1,3-dipole repulsion in **F**. Thus, the major C3 configuration arising from α-**2** is reversed by the presence of the α-benzyloxy substituent as a consequence of vicinal dipole repulsion.[35] A transannular dipole repulsion between pseudoaxial OBn and OEt substituents would be expected to further destabilize **G** (β,cis). Finally, transition state **H** relieves both vicinal and 1,3-diaxial dipole repulsions, suggesting it should be the most favorable, consistent with the observed product

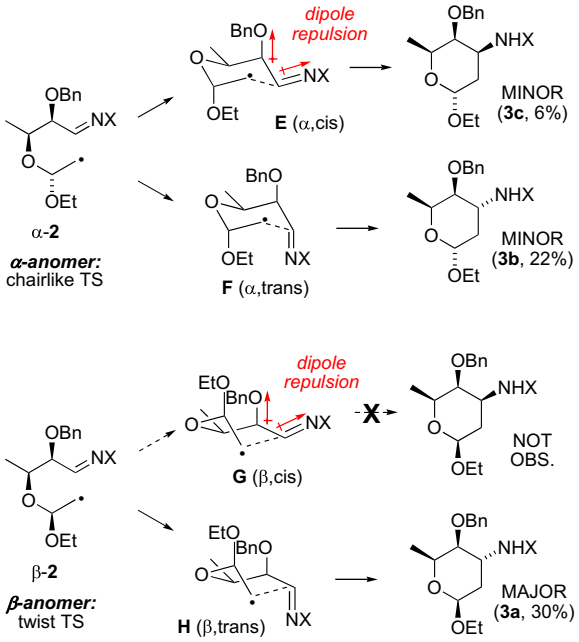


Figure 3. Proposed stereocontrol models for formation of **3a**–**3c** (X=NPh_2). Vicinal dipole repulsion with the α-OBn substituent restricts conformation of the hydrazone.

distribution. Thus, in addition to the anomeric effect examined previously by Renaud and Schiesser and coworkers,[28] effecting stereocontrol in these cyclizations requires careful consideration of a dominant vicinal dipole repulsion and less important 1,3-diaxial dipole repulsions.

Despite the rather complicated stereocontrol models outlined above, the resulting stereocontrol (**3a**,**b**/**3c**=8.8:1) is sufficient for practical application, with the assumption that a mixture of anomers **3a**,**b** can be further processed in a stereoconvergent manner (for example, via oxidation or oxocarbenium-mediated processes at the anomeric center). The net result in this case is a very rapid access, from crotonaldehyde via asymmetric catalysis, to an aminosugar analog of the 3-*epi*-L-daunosamine configuration.

2.2. Si-tethered ethynyl method

To generate the alternative L-daunosamine configuration, we regarded our Si-tethered strategy to be quite reliable, and indeed we had shown that vinyl adduct **6** (Fig. 4, R=$COCF_3$) could be efficiently transformed to methyl *N*-trifluoroacetyl-L-daunosaminide.[21a] A limiting factor to the net efficiency of that sequence was the requirement for an aldehyde-selective Wacker oxidation, for which the optimal selectivity was 82:18. We envisioned avoiding this late-stage oxidation step, and consequently we explored the replacement of the silicon-tethered vinyl group with an ethynyl group as the radical precursor.

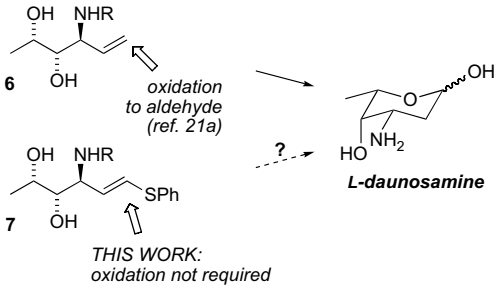
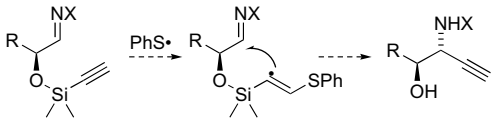


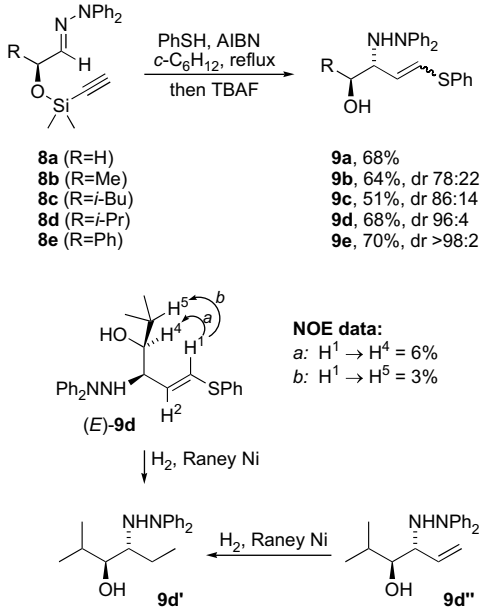
Figure 4. Comparison of oxidative and non-oxidative routes from radical adducts to L-daunosamine.

Intermolecular addition of heteroatom radicals, such as thiyl (e.g., PhS$^{\bullet}$) or stannyl (e.g., $Bu_3Sn^{\bullet}$), to an alkene or alkyne can initiate a cyclization event when a second radical acceptor moiety is appropriately situated (Fig. 1, **B** and **C**).[36] In using the silicon-tethered vinyl addition to access **6**, fluoride-induced thiolate elimination had occurred during removal of the silicon tether. This returned the vinyl functionality present in the original radical precursor, resulting in a net vinyl addition process with excellent stereocontrol. We hypothesized that an analogous sequence (Eq. 1) might take place using an ethynyl group as a silicon-tethered radical precursor, a reaction type, which, to our knowledge, was without direct precedent.[37] Because of the additional options available for functionalization of alkynes, an ethynyl group addition would be a potentially useful complement to our vinyl addition methodology.



(1)

Ultimately, our examination of this ethynyl group transfer hypothesis of Eq. 1 revealed that the alkyne was not regenerated.[38] A series of α-hydroxyhydrazones[11,12] were silylated with chlorodimethylethynylsilane[39] to afford hydrazones **8a**–**8e** (Scheme 5) in 83–93% yields. Sequential treatment with thiophenol/AIBN and TBAF (or refluxing methanolic KF) led to allylic *anti*-hydrazino alcohols **9a**–**9e**, predominantly as the (*E*)-isomers.[38] Thus, rather than regenerating the alkyne by thiolate elimination, simple protodesilylation occurred upon fluoride treatment, affording the 2-(phenylthio)vinyl adducts. Assignment of configurations in **9** rests on chemical correlation of **9d**; both **9d** and known compound **9d″**[40] afforded the same reduction product **9d′** (Scheme 5). Difference NOE data supported the *E* configuration of **9d**, and the assignment of *anti* relative configuration in the amino alcohol was also consistent with the chemical correlation of a related compound to L-daunosamine (vide infra). The preference for the *anti* diastereomer is in close agreement with the corresponding reactions of vinylsilanes, which proceed via 5-*exo* cyclization of an alkyl radical,[11,12] though the ethynylsilane cyclizations are slightly less selective.



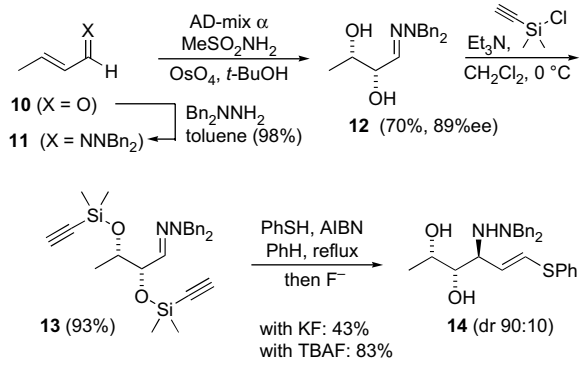
Scheme 5.

Considering the abundant methods for conversion of vinyl sulfides to carbonyl compounds,[41] vinyl sulfides **9a**–**9e** are masked β-aminoaldehydes, and thus these reactions are a radical equivalent of an acetaldehyde Mannich reaction. Furthermore, vinyl sulfides have been observed to undergo direct acid-catalyzed cyclization with a remote hydroxyl group to afford cyclic hemithioacetals[42] (i.e., thioglycosides), an attractive entry to precursors for glycoside and oligosaccharide synthesis.

2.3. Synthesis of *N*-trifluoroacetyl-L-daunosamine

An application to a brief asymmetric synthesis of an aminosugar was exploited in order to demonstrate the utility of the ethynylsilanes as radical Mannich equivalents. Previously, 2,3-dihydroxyaldehyde hydrazones derived from glyceraldehyde or crotonaldehyde were successfully employed for vinyl group addition,[12] furnishing allylic hydrazines such as **6** through vinyl group transfer from the proximal hydroxyl group via 5-*exo* cyclization.[21a] Simply applying the silicon-tethered radical precursor to both hydroxyl groups obviates the protection and hydroxyl differentiation sequences common in carbohydrate manipulations.

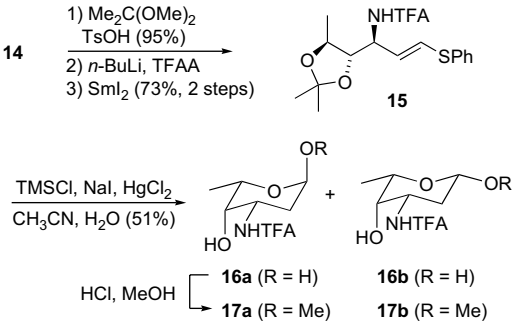
To access the aminosugar L-daunosamine, crotonaldehyde (**10**, Scheme 6) was converted to known dibenzylhydrazone **12** via Sharpless asymmetric dihydroxylation of hydrazone **11** (89% ee).[21a] Silylation of **12** with chlorodimethylethynylsilane[39] afforded **13** in 93% yield (Scheme 6), which in turn was submitted to thiyl addition–cyclization according to the standard method as described above;[43] hydrazinodiol **14** was obtained in 43% yield upon treatment with methanolic KF. Among the four possible diastereomers, which could be formed, the major isomer was assigned the *E* olefin configuration according to the large ^{1}H NMR olefinic vicinal coupling constant (15 Hz), and the 3,4-*anti* relative configuration (dr 9:1) by analogy to **9d**. After our preliminary communication of this reaction, TBAF in THF was found to be superior to the original KF/MeOH conditions, and the whole sequence **12**→**14** could be deployed with the only intermediate purification being a brief filtration of **13** through silica gel. Together these changes improved the yield of **14** to 83%. The adduct in this case is an open-chain form of L-daunosamine, prepared in 53% overall yield from crotonaldehyde. Conversion to the aminosugar via simple functional group transformations would confirm the absolute and relative stereochemical assignments.



Scheme 6.

Spontaneous cyclization to a thiopyranoside was envisaged upon exposure of **14** to anhydrous HCl, based on a close precedent.[42] Unfortunately, this cyclization was not achieved with **14**, perhaps due to the proximity of the basic nitrogen, a protonated form of which might inhibit acid-catalyzed cyclization[44] (an amide had been used in the precedent). Direct treatment of diol hydrazine

14 with $HgCl_2$ also gave none of the expected product. On the other hand, a different order of events proved successful. Protection of **14** as an acetonide (Scheme 7) followed by TFA-assisted N–N bond cleavage[45] furnished the corresponding amide **15** in 73% yield. The aldehyde was then unveiled from the vinyl sulfide by treatment under Grieco's conditions entailing in situ generation of hydrogen iodide in moist acetonitrile in the presence of mercuric chloride.[46,47] This furnished 51% of anomeric mixture **16a** and **16b**, from which **16a** was separated by recrystallization. This material showed good agreement with the literature ^{1}H NMR data for *N*-trifluoroacetyl-L-daunosamine, as well as the expected physical (mp 146–148 °C, lit. 146–147 °C) and chiroptical properties ($[\alpha]_D^{30}$ −120, lit. $[\alpha]_D^{20}$ −127).[48] Further confirmation was obtained upon exposure of **16a** (or the mixture **16a**/**16b**) to anhydrous HCl in MeOH, after which the methyl pyranosides **17a**/**17b** could be identified by spectroscopic comparison with data from the literature.[49] This mixture of methyl glycosides was identical to material produced through a different route.[21a] Thus, the chemical correlation of **14** to L-daunosamine ultimately confirmed the stereochemical course of the tandem thiyl radical addition–cyclizations using the tethered ethynylsilane as a radical precursor.



Scheme 7.

One final note is offered regarding the synthetic potential of vinyl sulfides such as **15**; OsO_4-catalyzed dihydroxylation has recently been exploited to convert related vinyl sulfides to pyranoses bearing hydroxyl groups at the 2-position (pyranose numbering).[50] Although we have not completed such experiments, this published method for transformation of vinyl sulfides to carbohydrates may confer broader applicability upon the methodology outlined herein.

3. Conclusion

Two alternative methods have been developed for introduction of the 2-acetyl fragment in radical equivalents of an acetaldehyde Mannich addition reaction. Haloacetal 6-*exo* radical cyclization is altered by the presence of a 2-benzyloxy substituent to invert the previously established stereochemical course, leading to the 3-*epi*-L-daunosamine configuration. The 2-(phenylthio)vinyl group can be installed via diastereoselective tin-free radical addition to α-hydroxyhydrazones via 5-*exo* cyclization of a silicon-tethered ethynyl group. Since stereocontrolled intermolecular radical addition methods to install the 2-acetyl unit are currently unavailable, these tethered approaches offer potentially useful alternatives.

The utility of the 2-(phenylthio)vinyl addition method is highlighted in a synthesis of *N*-trifluoroacetyl-L-daunosamine from achiral precursors using a combination of asymmetric catalysis and diastereoselective radical addition. The radical Mannich strategy avoids a late-stage oxidation and affords *N*-trifluoroacetyl-L-daunosamine in 17% overall yield from crotonaldehyde.[51]

4. Experimental section

4.1. 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. CH_2Cl_2 was distilled from CaH_2 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 that 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 $CaSO_4$ 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 ^{1}H and 125 or 75 MHz for ^{13}C. 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 GC–MS with 15 mL×0.25 mm I.D.×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).

4.2. Haloacetal cyclizations

*4.2.1. Iodoacetal **2***

A mixture of *N*-iodosuccinimide (0.19 g, 0.82 mmol) and freshly distilled ethyl vinyl ether (EVE, 5 mL) was stirred at 0 °C for 2 h. A solution of alcohol **1**[21a] (117 mg, 0.33 mmol) in EVE (3 mL) was added. After 10 h at 0 °C, the mixture was partitioned between saturated aqueous sodium thiosulfate and ether, washed with brine, dried over Na_2SO_4, and concentrated. Radial chromatography eluting with 10:1 hexane/ethyl acetate afforded, as an inseparable diastereomeric mixture, iodoacetal **2** (72.5 mg, 0.13 mmol, 40%) as a pale yellow oil; IR (film) 1592, 1495, 1299, 1213, 1050 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43–7.25 (m, 9H), 7.18–7.15 (m, 2H), 7.09–7.06 (m, 4H), 6.41 (d, *J*=7.3 Hz, 0.5H), 6.35 (d, *J*=7.4 Hz, 0.5H), 4.74 (dd, apparent triplet, *J*=5.4 Hz, 0.5H), 4.68 (dd, apparent triplet, *J*=5.9 Hz, 0.5H), 4.64 (d, *J*=12.4 Hz, 0.5H), 4.61 (d, *J*=12.5 Hz, 0.5H), 4.52 (d, *J*=12.0 Hz, 0.5H), 4.51 (d, *J*=12.2 Hz, 0.5H), 4.08 (dd, apparent triplet, *J*=7.1 Hz, 0.5H), 4.06 (dd, apparent triplet, *J*=7.4 Hz, 0.5H), 3.84 (dddd, apparent quintet, *J*=6.4 Hz, 0.5H), 3.80 (dddd, apparent quintet, *J*=6.4 Hz, 0.5H), 3.66–3.59 (m, 1H), 3.53–3.45 (m, 1H), 3.19–3.11 (m, 2H), 1.19 (dd, apparent triplet, *J*=6.9 Hz, 1.5H), 1.16–1.10 (m, 4.5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.6, 143.5, 138.4, 138.3, 135.5, 135.4, 129.8, 129.7, 128.3, 128.2, 127.9, 127.8, 127.5,

124.5, 124.4, 122.3, 102.6, 100.5, 83.1, 82.2, 75.4, 73.4, 70.8, 61.5, 61.4, 17.8, 16.8, 15.0, 14.9, 6.3, 6.0; MS (CI) *m*/*z* (relative intensity) 559 ([M+H], 10%), 315 (100%); Anal. Calcd for $C_{27}H_{31}N_2O_3I$: C, 58.07; H, 5.60; N, 5.02. Found: C, 58.11; H, 5.53; N, 4.99.

*4.2.2. Aminosugars **3a**–**3c***

To a solution of iodoacetal **2** (67.8 mg, 0.12 mmol) in benzene (6 mL) were added 2,2′-azobisisobutyronitrile (AIBN, 10 mol %) and Bu_3SnH (0.06 mL, 0.15 mmol). The reaction mixture was deoxygenated via nitrogen bubbling through a syringe needle for 20 min, then heated at reflux for 10 h. The solvent was removed and the residue was partitioned between CH_3CN and hexane. Concentration of the CH_3CN fraction and flash chromatography (hexane/ethyl acetate) afforded a mixture of aminoglycosides **3a**, **3b**, and **3c** (dr 5.0:3.8:1.0) as a pale yellow oil (30.5 mg, 58%). Major diastereomer **3a**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31–7.24 (m, 9H), 7.07–7.03 (m, 6H), 4.86 (dd, *J*=9.4, 2.2 Hz, 1H), 4.48 (d, *J*=12.1 Hz, 1H), 4.43 (d, *J*=12.1 Hz, 1H), 4.18 (qd, *J*=6.6, 1.9 Hz, 1H), 3.95 (dq, *J*=9.4, 7.1 Hz, 1H), 3.77 (s, 1H), 3.50 (dq, *J*=9.6, 7.1 Hz, 1H), 3.53–3.46 (m, 1H), 3.22 (dd, apparent t, *J*=2.2 Hz, 1H), 2.00 (ddd, *J*=13.9, 9.4, 4.5 Hz, 1H), 1.59 (ddd, apparent dt, *J*=13.9, 2.2 Hz, 1H), 1.24 (d, *J*=6.5 Hz, 3H), 1.20 (dd, apparent triplet, *J*=7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.3, 138.4, 129.3, 128.2, 127.9, 127.6, 122.8, 120.5, 97.8, 74.6, 72.5, 69.5, 63.8, 53.5, 31.7, 16.9, 15.1; MS (CI) *m*/*z* (relative intensity) 433 ([M+H]$^+$, 60%), 387 (30%), 361 (17%). Anal. Calcd for $C_{27}H_{32}N_2O_3$: C, 75.15; H, 7.24; N, 6.49. Found: C, 74.89; H, 7.48; N, 6.39 (diastereomeric mixture). Minor diastereomer **3b**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32–6.98 (m, 15H), 4.80 (dd, *J*=3.2, 2.9 Hz, 1H), 4.58–4.45 (m, 3H), 4.30 (qd, *J*=6.7, 1.5 Hz, 1H), 3.76 (dq, *J*=9.75, 7.1 Hz, 1H), 3.55–3.35 (m, 3H), 2.17 (ddd, *J*=14.4, 3.8, 3.8 Hz, 1H), 1.51 (br d, *J*=14.3 Hz, 1H), 1.21 (dd, apparent t, *J*=7.1 Hz, 3H), 1.16 (d, *J*=6.7 Hz, 3H). Minor diastereomer **3c**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.92 (br d, *J*=3.1 Hz, 1H), 3.84 (q, *J*=6.6 Hz, 1H), 3.67–3.60 (m, 1H), 2.01 (ddd, *J*=12.5, 12.4, 3.2 Hz, 1H), 1.75 (dd, *J*=12.5, 3.0 Hz, 1H); several **3c** resonances were unresolved from those of **3b**.

4.3. General procedure A: preparation of dimethylethynylsilyl ethers 8a–8e

A solution of α-hydroxy hydrazone in dry methylene chloride (1 M) under nitrogen was treated sequentially with triethylamine (1.2 equiv) and chlorodimethylethynylsilane[39] (1.15–1.2 equiv) at 0 °C. After 2 h, the mixture was warmed to room temperature, concentrated, and diluted with ether. The precipitated salts were filtered off and washed three times with ether. Concentration of the combined filtrates and flash chromatography (10:1 hexane/ethyl acetate) furnished the silyl ethers **8a**–**8e** as pale yellow oils. A closely related procedure of similar effectiveness involves replacing dichloromethane with toluene or benzene and incorporating a catalytic amount of DMAP (ca. 10 mol %) in the procedure above; simple filtration of the reaction mixture through a short plug of silica gel furnished material of sufficient purity for the thiyl addition–cyclization process.

*4.3.1. Ethynylsilyl ether **8a** (R=H)*

Pale yellow oil; IR (film, $CHCl_3$) 3275, 2035, 1596, 1496, 1055 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40–7.35 (m, 6H), 7.17–7.10 (m, 4H), 6.55 (t, *J*=5.2 Hz, 1H), 4.44 (d, *J*=5.2 Hz, 2H), 2.43 (s, 1H), 0.30 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.6, 135.7, 129.7, 124.3, 122.4, 93.7, 87.3, 64.1, −0.1; MS (EI) *m*/*z* (relative intensity) 308 (M$^+$, 25%), 168 (100%). Anal. Calcd for $C_{18}H_{20}N_2OSi$: C, 70.09; H, 6.54; N, 9.08. Found: C, 70.16; H, 6.65; N, 8.96.

*4.3.2. Ethynylsilyl ether **8b** (R=Me)*

Pale yellow oil; $[\alpha]_D^{26}$ −24.1 (*c* 0.90, $CHCl_3$); IR (film, $CHCl_3$) 3275, 2973, 2035, 1591, 1496, 1060 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40–7.35 (m, 6H), 7.17–7.10 (m, 4H), 6.45 (d, *J*=5.7 Hz, 1H), 4.71 (m, apparent quintet, *J*=6.3 Hz, 1H), 2.44 (s, 1H), 1.37 (d, *J*=6.4 Hz, 3H), 0.30 (s, 3H), 0.28 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.7, 140.1, 129.7, 124.2, 122.3, 93.4, 87.9, 70.3, 22.1, 0.6, 0.5; MS (EI) *m*/*z* (relative intensity) 322 (M$^+$, 15%), 168 (100%). Anal. Calcd for $C_{19}H_{22}N_2OSi$: C, 70.77; H, 6.88; N, 8.69. Found: C, 71.25; H, 6.85; N, 8.79.

*4.3.3. Ethynylsilyl ether **8c** (R=i-Bu)*

Colorless oil; $[\alpha]_D^{26}$ −29.9 (*c* 1.6, $CHCl_3$); IR (film, $CHCl_3$) 3275, 2957, 2035, 1592, 1496, 1054 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40–7.35 (m, 4H), 7.17–7.10 (m, 6H), 6.39 (d, *J*=6.4 Hz, 1H), 4.61 (ddd, *J*=8.2, 6.0, 6.0 Hz, 1H), 2.42 (s, 1H), 1.73 (m, apparent nonet, *J*=6.7 Hz, 1H), 1.57 (ddd, *J*=13.7, 8.2, 6.1 Hz, 1H), 1.39 (ddd, *J*=13.5, 7.7, 5.8 Hz, 1H), 0.96 (d, *J*=6.6 Hz, 3H), 0.95 (d, *J*=6.6 Hz, 3H), 0.30 (s, 3H), 0.28 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.8, 139.9, 129.7, 124.2, 122.4, 93.3, 88.1, 72.6, 45.0, 24.1, 23.0, 22.4, 0.9, 0.4; MS (CI) *m*/*z* (relative intensity) 365.1 ([M+H]$^+$, 60%), 162.3 (100%). Anal. Calcd for $C_{22}H_{28}N_2OSi$: C, 72.48; H, 7.74; N, 7.68. Found: C, 72.21; H, 7.71; N, 7.60.

*4.3.4. Ethynylsilyl ether **8d** (R=i-Pr)*

Pale yellow oil; $[\alpha]_D^{26}$ +2.7 (*c* 0.6, $CHCl_3$); IR (film, $CHCl_3$) 3274.0, 2961.0, 2036.0, 1592.0, 1496.0, 1047.0 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41–7.37 (m, 4H), 7.17–7.10 (m, 6H), 6.40 (d, *J*=6.4 Hz, 1H), 4.22 (dd, *J*=6.9, 6.9 Hz, 1H), 2.44 (s, 1H), 1.79 (m, apparent octet, *J*=6.8 Hz, 1H), 0.95 (d, *J*=6.7 Hz, 3H), 0.85 (d, *J*=6.8 Hz, 3H), 0.30 (s, 3H), 0.28 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.8, 139.4, 129.7, 124.2, 122.4, 93.3, 88.1, 79.1, 33.5, 18.3, 18.3, 0.8, 0.3; MS (EI) *m*/*z* (relative intensity) 350 (M$^+$, 10%), 167 (100%). Anal. Calcd for $C_{21}H_{26}N_2OSi$: C, 71.93; H, 7.47; N, 8.02. Found: C, 71.89; H, 7.51; N, 7.95.

*4.3.5. Ethynylsilyl ether **8e** (R=Ph)*

Pale yellow oil; $[\alpha]_D^{26}$ −86.5 (*c* 0.95, $CHCl_3$); IR (film, $CHCl_3$) 3271, 3029, 2036, 1592, 1496, 1215, 1054 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40–7.32 (m, 8H), 7.27–7.23 (m, 1H), 7.16–7.10 (m, 6H), 6.51 (d, *J*=6.6 Hz, 1H), 5.65 (d, *J*=6.6 Hz, 1H), 2.45 (s, 1H), 0.35 (s, 3H), 0.32 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.7, 141.4, 138.8, 129.7, 128.2, 127.3, 126.1, 124.3, 122.4, 93.7, 87.7, 75.8, 0.8, 0.3; MS (CI) *m*/*z* (relative intensity) 385.1 ([M+H]$^+$, 35%), 384 (M$^+$, 100%), 285 (75%), 162 (75%). Anal. Calcd for $C_{24}H_{24}N_2OSi$: C, 74.96; H, 6.29; N, 7.29. Found: C, 74.80; H, 6.37; N, 7.40.

4.4. General procedure B: tandem thiyl addition–cyclization and desilylation

A solution of ethynylsilyl ether in cyclohexane (0.1 M) was deoxygenated (N_2, via syringe needle) for ca. 10 min, then heated to reflux. A solution of 2,2′-azobis(isobutyronitrile) (AIBN, 10 mol %) and thiophenol (1.4 equiv) in benzene (1 M in PhSH) was added via syringe pump (0.34 mL/h). Additional portions of AIBN (3×10 mol %) were added in 3 h intervals until the reaction was complete (as judged by TLC), then the cooled reaction mixture was concentrated. The residue was dissolved in THF (1 M) and treated with tetrabutylammonium fluoride (1 M in THF, 3 equiv) at room temperature for ca. 1 h. When complete (as judged by TLC), the reaction mixture was diluted with hexane, washed with water, dried over Na_2SO_4, and concentrated. Flash chromatography (hexane/ethyl acetate) furnished the vinyl sulfides **9a**–**9e** and **14** as mixtures of diastereomers in the ratios previously described,[13] from which pure diastereomers were isolated by radial chromatography (hexane/ethyl acetate).

*4.4.1. Vinyl sulfide (Z)-anti-**9a** (R=H)*

Pale yellow oil; IR (film, $CHCl_3$) 3396, 2925, 1588, 1496, 1272, 1025 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35–7.20 (m, 13H), 7.05–7.00 (m, 2H), 6.45 (d, *J*=9.5 Hz, 1H), 5.85 (dd, *J*=9.5, 8.7 Hz,

1H), 4.24 (br s, 1H), 4.20–4.16 (m, 1H), 3.85–3.80 (ddd, J=11.1, 4.2, 3.9 Hz, 1H), 3.72–3.66 (ddd, J=11.0, 7.8, 5.9 Hz, 1H), 1.87 (dd, J=7.9, 4.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.1 135.4, 129.4, 129.2, 129.0, 128.6, 128.4, 126.75, 122.6, 120.5, 63.4, 58.3; MS (CI) m/z (relative intensity) 363.3 ([M+H]$^+$, 25%), 117.1 (100%). Anal. Calcd for $C_{22}H_{22}N_2OS$: C, 72.90; H, 6.12; N, 7.73. Found: C, 72.57; H, 6.41; N, 7.51. For the major diastereomer (*E*)-*anti*-**9a**, which was not obtained in pure form, ^{1}H NMR spectroscopy showed vinylic signals at 6.40 (dd, J=15.0, 0.4 Hz) and 5.78 (dd, J=15.1, 7.9 Hz, 1H).

4.4.2. *Vinyl sulfide (E)-anti-**9b** (R=Me)*

Pale yellow oil; $[\alpha]_D^{26}$ −3.5 (*c* 1.7, $CHCl_3$); IR (film, $CHCl_3$) 3434, 2974, 1588, 1495, 1271, 1077 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35–7.30 (m, 9H), 7.15–7.10 (m, 4H), 7.05–7.00 (m, 2H), 6.36 (d, J=15.2 Hz, 1H), 5.85 (dd, J=15.3, 9.0 Hz, 1H), 4.11 (s, 1H), 4.07 (br q, J=6.4 Hz, 1H), 3.53 (dd, J=8.9, 2.7 Hz, 1H), 2.39 (s, 1H), 1.16 (d, J=6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.9, 134.5, 130.1, 129.3 (2C), 129.1, 127.3, 127.0, 122.7, 120.4, 66.9, 65.8, 18.3; MS (CI) m/z (relative intensity) 377.6 ([M+H]$^+$, 80%), 193.1 (100%). Anal. Calcd for $C_{23}H_{24}N_2OS$: C, 73.37; H, 6.42; N, 7.44. Found: C, 73.14; H, 6.47; N, 7.31.

4.4.3. *Vinyl sulfide (E)-anti-**9c** (R=i-Bu)*

Pale yellow oil; $[\alpha]_D^{28}$ −12.0 (*c* 1.25, $CHCl_3$); IR (film, $CHCl_3$) 3447, 3060, 2955, 1588, 1495, 1272, 1071, 1025 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31–7.22 (m, 9H), 7.14–7.11 (m, 4H), 7.05–7.00 (m, 2H), 6.35 (d, J=15.1 Hz, 1H), 5.90 (dd, J=15.2, 8.9 Hz, 1H), 4.09 (s, 1H), 4.00–3.95 (m, 1H), 3.52 (dd, J=8.9, 2.4 Hz, 1H), 2.35 (s, 1H), 1.80–1.72 (m, 1H), 1.45 (ddd, J=14.0, 9.3, 5.6 Hz, 1H), 1.12 (ddd, J=13.1, 8.1, 3.6 Hz, 1H), 0.92 (d, J=6.7 Hz, 3H), 0.89 (d, J=6.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.96, 134.65, 129.96, 129.28, 129.08, 128.79, 127.70, 126.93, 122.72, 120.36, 68.70, 65.28, 41.85, 24.65, 23.34, 22.08; MS (CI) m/z (relative intensity) 419 ([M+H]$^+$, 80%), 164 (100%). Anal. Calcd for $C_{26}H_{30}N_2OS$: C, 74.60; H, 7.22; N, 6.69. Found: C, 74.32; H, 7.28; N, 6.43.

4.4.4. *Vinyl sulfide (E)-anti-**9d** (R=i-Pr)*

Pale yellow oil; $[\alpha]_D^{26}$ −6.8 (*c* 1.15, $CHCl_3$); IR (film, $CHCl_3$) 3485, 2960, 1588, 1495, 1272, 1060 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35–7.25 (m, 9H), 7.15–7.10 (m, 4H), 7.05–7.00 (m, 2H), 6.37 (d, J=15.5 Hz, 1H), 5.93 (dd, J=15.3, 9.1 Hz, 1H), 4.00 (s, 1H), 3.72 (dd, J=9.1, 2.5 Hz, 1H), 3.49 (ddd, J=9.0, 2.0, 2.0 Hz, 1H), 2.60 (s, 1H), 1.72–1.62 (m, 1H), 1.03 (d, J=6.6 Hz, 3H), 0.82 (d, J=6.7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.0, 134.5, 130.0, 129.4, 129.2, 129.0, 127.0, 126.9, 122.8, 120.5, 75.5, 62.8, 30.4, 19.8, 18.4; MS (CI) m/z (relative intensity) 405.3 ([M+H]$^+$, 10%), 221 (35%), 117.2 (100%). Anal. Calcd for $C_{25}H_{28}N_2OS$: C, 74.19; H, 6.97; N, 6.96. Found: C, 74.05; H, 7.00; N, 7.04.

4.4.5. *Vinyl sulfide (E)-anti-**9e** (R=Ph)*

This compound was obtained as a pale yellow oil, ca. 90% purity by ^{1}H NMR; inseparable impurities were not identified; IR (film, $CHCl_3$) 3462, 3059, 1588, 1494, 1272, 1027 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40–7.18 (m, 12H), 7.12–7.00 (m, 8H), 6.12 (dd, J=15.1, 0.5 Hz, 1H), 5.80 (dd, J=15.2, 8.8 Hz, 1H), 4.97 (d, J=4.2 Hz, 1H), 4.12 (br s, 1H), 3.75 (dd, J=8.7, 4.6 Hz, 1H), 2.65 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.7, 140.2, 134.4, 130.0, 129.3, 129.1, 129.0, 128.3, 127.8, 126.8, 126.4, 122.7, 120.4, 73.1, 66.7; MS (CI) m/z (relative intensity) 439.8 ([M+H]$^+$, 10%), 330.7 (100%), 255.6 (40%).

4.5. Stereochemical proof of 4d by chemical correlation: reduction of 9d

Raney Ni (100 mg, in aqueous suspension) was washed with ethanol (2×10 mL) and THF (2×10 mL), then suspended in THF (10 mL). A solution of vinyl sulfide **9d** (25 mg) in THF (1 mL) was added, and the mixture was stirred under H_2 (1 atm, balloon). The reaction was complete within 10 min, as judged by TLC (>95% conversion by NMR). Flash chromatography (10:1 hexane/ethyl acetate) afforded **9d′**, which was identified by comparison with a sample of **9d′** obtained by reduction of **9d″**[12] using the same procedure (reaction time 5 h); $[\alpha]_D^{26}$ +43.9 (*c* 0.80, $CHCl_3$); IR (film, $CHCl_3$) 3487, 2961, 1589, 1497, 1271, 1029 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33–7.29 (m, 4H), 7.15–7.10 (m, 4H), 7.05–7.00 (m, 2H), 3.95 (br s, 1H), 3.49 (br d, J=9.2 Hz, 1H), 2.92 (ddd, J=9.0, 2.7, 2.7 Hz, 1H), 2.50 (br s, 1H), 1.76–1.67 (m, 1H), 1.64–1.55 (m, 1H), 1.42–1.32 (m, 1H), 1.05 (d, J=6.5 Hz, 3H), 0.90 (t, J=7.6 Hz, 3H), 0.75 (d, J=6.7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.5, 129.2, 122.8, 120.8, 75.6, 60.3, 29.7, 20.3, 18.7, 18.4, 11.1; MS (CI) m/z (relative intensity) 299.3 ([M+H]$^+$, 30%), 168 (100%). Anal. Calcd for $C_{19}H_{26}N_2O$: C, 76.47; H, 8.78; N, 9.39. Found: C, 76.83; H, 8.79; N, 9.10.

4.6. Synthesis of N-TFA-L-daunosamine

4.6.1. *Bis(dimethylethynylsilyl) ether **13***

To a mixture of **12**[21a] (173 mg, 0.581 mmol) and DMAP (ca. 5 mg) in toluene (10 mL) and triethylamine (0.22 mL, 1.45 mmol) at 0 °C was added chlorodimethylethynylsilane[39] (d 0.88 g/mL, 0.22 mL, 1.45 mmol). After 2 h at room temperature, the mixture was filtered, and the filtrate was concentrated and partitioned between water and ethyl acetate. The organic phase was washed with brine, dried (Na_2SO_4), and concentrated. Flash chromatography (10:1 hexane/ethyl acetate → 5:1 hexane/ethyl acetate) furnished silyl ether **13** (249 mg, 93%) as a pale yellow oil; IR (film, $CHCl_3$) 3275, 2970, 2035, 1601, 1495, 1454, 1255, 1071 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35–7.22 (m, 10H), 6.40 (d, J=6.6 Hz, 1H), 4.40 (s, 4H), 4.25 (dd, J=6.4, 5.7 Hz, 1H), 3.95 (dddd, J=6.4, 6.4, 6.4, 5.7 Hz, 1H), 2.40 (s, 1H), 2.39 (s, 1H), 1.10 (d, J=6.3 Hz, 3H), 0.28 (s, 3H), 0.27 (s, 3H), 0.25 (s, 3H), 0.24 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.8, 133.5, 128.4, 127.7, 127.0, 93.1, 92.9, 88.5, 88.5, 78.5, 72.2, 57.6, 19.0, 0.9, 0.8, 0.5, 0.5; MS (EI) m/z (relative intensity) 462 (M$^+$, 2%), 335 (100%), 127 (70%). Anal. Calcd for $C_{26}H_{34}N_2O_2Si_2$: C, 67.49; H, 7.41; N, 6.05. Found: C, 67.40; H, 7.46; N, 6.02.

4.6.2. *(E,2S,3S,4S)-4-(N,N-Dibenzylhydrazino)-6-(phenylthio)hex-5-ene-2,3-diol ((E)-**14**)*

From bis(silyl) ether **13** (167 mg, 0.36 mmol) by general procedure B was obtained **14** (125 mg, 83%, dr 9:1) as a light yellow oil, which was carried forward as a diastereomeric mixture. Radial chromatography afforded an analytical sample of the major diastereomer; $[\alpha]_D^{26}$ −32.0 (*c* 1.2, $CHCl_3$); IR (film, $CHCl_3$) 3400, 3028, 1583, 1453, 1027 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40–7.28 (m, 15H), 6.21 (d, J=15.1 Hz, 1H), 5.65 (dd, J=15.3, 8.8 Hz, 1H), 3.73 (ABq, J_{AB}=12.9 Hz, $\Delta\nu$=67.4 Hz, 4H), 3.59 (m, apparent quintet, J=6.4 Hz, 1H), 3.42–3.37 (m, 2H), 2.55 (br s, 2H), 1.06 (d, J=6.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.3, 134.6, 130.0, 129.6, 129.1, 128.4, 128.2, 127.8, 127.6, 127.0, 75.6, 67.7, 62.0, 61.3, 18.1; MS (CI) m/z (relative intensity) 435.9 ([M+H]$^+$,100%), 195.2 (80%). Anal. Calcd for $C_{26}H_{30}N_2O_2S$: C, 71.86; H, 6.96; N, 6.45. Found: C, 72.06; H, 7.02; N, 6.56.

4.6.3. *N-Trifluoroacetamide **15***

A solution of adduct **14** (180 mg, 0.42 mmol, dr 9:1), obtained as described above, and TsOH·H_2O (79 mg, 0.42 mmol) in 2,2-dimethoxypropane (15 mL) was stirred at room temperature for 1 h. The mixture was diluted with ether, washed with aqueous $NaHCO_3$, dried over Na_2SO_4, and concentrated. Flash chromatography (SiO_2 column packed with 1% Et_3N in 20:1 petroleum ether/ethyl acetate and eluted with 20:1 petroleum ether/ethyl acetate) afforded the acetonide derivative (190 mg, 0.40 mmol, 95%) as a light yellow oil, still containing the minor diastereomer; IR (film) 2983, 1455, 1378, 1243, 1173, 1089 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37–7.34 (m,

6H), 7.33–7.30 (m, 6H), 7.28–7.23 (m, 3H), 6.15 (d, J=15.2 Hz, 1H), 5.55 (dd, J=15.2, 8.8 Hz, 1H), 3.81–3.73 (m, 1H), 3.79 (d, J=13.2 Hz, 2H), 3.67 (d, J=13.0 Hz, 2H), 3.62 (dd, J=8.5, 2.2 Hz, 1H), 3.27 (dd, J=8.7, 2.4 Hz, 1H), 3.00–2.80 (br s, 1H), 1.35 (s, 3H), 1.29 (s, 3H), 1.11 (d, J=5.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.2, 130.6, 130.1, 129.5, 129.1, 128.2, 127.2, 126.9, 126.4, 108.1, 83.1, 72.9, 61.7, 61.5, 27.3, 26.8, 18.2; MS (CI) m/z (relative intensity) 476 ([M+H]$^+$, 100%), 366 (20%), 263 (24%), 211 (35%). Anal. Calcd for $C_{29}H_{34}N_2O_2S$: C, 73.38; H, 7.22; N, 5.90. Found: C, 73.32; H, 7.05; N, 5.79.

To a solution of the acetonide obtained as described above (150 mg, 0.317 mmol) in THF (6 mL) at −78 °C was added n-BuLi (2.5 M, 0.38 mL, 0.95 mmol). After 1 h, trifluoroacetic anhydride (freshly distilled from P_2O_5, 0.26 mL, 1.9 mmol) was added dropwise over 2 min, whereupon the red color turned to yellow. The reaction mixture was allowed to warm to room temperature over 2 h, partitioned between saturated aqueous NH_4Cl and ethyl acetate, and dried over Na_2SO_4. Concentration and flash chromatography (SiO_2 column packed with 1% Et_3N in 20:1 petroleum ether/ethyl acetate and eluted with 20:1 petroleum ether/ethyl acetate) afforded the N-trifluoroacetamide (135.6 mg, 75%). A solution of the N-trifluoroacetamide (246 mg) in 10:1 THF/MeOH (10 mL) was treated with freshly prepared SmI_2 (0.2 M in THF, 17.3 mL, 3.45 mmol) until the blue color of SmI_2 persisted for 15 min. After concentration, the residue was triturated with Et_2O and the soluble portion was purified by flash chromatography (SiO_2 column packed with 1% Et_3N in 20:1 petroleum ether/ethyl acetate and eluted with 5:1 petroleum ether/ethyl acetate) to afford **15** (133 mg, 82%) as a diastereomerically pure colorless oil. In another run, without purification of the intermediate trifluoroacetamide, **15** was obtained in 73% yield for the two steps; $[\alpha]_D^{18}$ +46.8 (c 0.795, $CHCl_3$); IR (film) 3291, 1701, 1540, 1210, 1171 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40–7.25 (m, 5H), 6.66 (d, J=7.5 Hz, 1H), 6.58 (d, J=15.2 Hz, 1H), 5.63 (dd, J=15.1, 8.7 Hz, 1H), 4.59 (ddd, apparent dt, J=8.7, 2.7 Hz, 1H), 3.85 (dddd, apparent dq, J=8.4, 6.1 Hz, 1H), 3.66 (dd, J=8.5, 2.8 Hz, 1H), 1.40 (s, 3H), 1.30 (s, 3H), 1.29 (d, J=6.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.3 (quartet, $^2J_{CF}$=37.5 Hz), 131.8, 130.3 (quartet, $^1J_{CF}$=196 Hz), 122.1, 109.2, 82.8, 73.4, 52.3, 27.3, 26.6, 17.3; MS (CI) m/z (relative intensity) 376 ([M+H]$^+$, 15%), 360 (15%). Anal. Calcd for $C_{17}H_{20}NO_3F_3S$: C, 54.39; H, 5.37; N, 3.73. Found: C, 54.61; H, 5.39; N, 3.75.

4.6.4. *N-Trifluoroacetyl-L-daunosamine*[48] (**16**)

To a mixture of NaI (190 mg, 1.27 mmol) and $HgCl_2$ (265 mg, 0.98 mmol) in CH_3CN (2 mL) was added TMSCl (0.16 mL, 1.27 mmol). After 5 min, water (10% v/v in CH_3CN, 0.45 mL, 2.5 mmol) was added and stirring was continued for another 5 min. A solution of compound **15** (79 mg, 0.21 mmol) in CH_3CN (2 mL) was added. After 7 h, the reaction mixture was partitioned between ethyl acetate and saturated aqueous $NaHCO_3$. The organic phase was dried over Na_2SO_4 and concentrated in vacuo. The yellow solid, which remained was triturated with ethyl acetate (3×0.5 mL), and the soluble portion was subjected to flash chromatography (1:1 petroleum ether/ethyl acetate, then ethyl acetate) to afford an anomeric mixture of α- and β-pyranoses **16a** and **16b** (26.4 mg, 51%) as a pale yellow solid.[47] Recrystallization from petroleum ether/ethyl acetate afforded the α-anomer **16a**: mp 146–148 °C; $[\alpha]_D^{30}$ −120 (c 0.070, MeOH) [lit. mp 146–147 °C; $[\alpha]_D^{20}$ −127 (*c* 0.10, MeOH)];[48] ^{1}H NMR (300 MHz, CD_3CN) δ 7.30 (br s, 1H), 5.21–5.18 (m, 1H), 4.33–4.28 (m, 1H), 4.10 (qd, J=6.5, 2.2 Hz, 1H), 4.00 (dd, J=3.6, 1.8 Hz, 1H), 3.51 (dd, J=6.8, 2.2 Hz, 1H), 3.04 (d, J=7.0 Hz, 1H), 1.87 (dddd, J=12.8, 12.8, 3.5, 1.8 Hz, 1H), 1.62 (dddd, J=12.8, 4.8, 1.1, 1.1 Hz, 1H), 1.10 (d, J=6.6 Hz, 3H). The ^{1}H NMR spectrum in DMSO was in agreement with the literature data.[48]

4.6.5. *Methyl N-trifluoroacetyl-L-daunosaminides* (**17a** *and* **17b**)

The α-anomer **16a** (8.2 mg, 0.034 mmol) was taken up in 0.1 M methanolic HCl (2 mL). After 16 h, the mixture was diluted with ether, washed with saturated aqueous $NaHCO_3$, dried over Na_2SO_4, and concentrated. Filtration through a short pad of silica gel, eluting with 1:1 petroleum ether/ethyl acetate, afforded the anomeric mixture (8.8 mg, 100% yield) of known methyl pyranosides **17a** and **17b**.[21a,49] The same mixture of isomers was obtained employing anomeric mixture **16a**/**16b** in this procedure. Varying amounts of known methyl furanoside isomers[52] were observed in different runs of this experiment, as described by Harding.[49]

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