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Variable Strategy toward Carbasugars and Relatives As Illustrated by Diastereoselective Synthesis of 1-Deoxy-1-amino-pseudo-β-D-gulopyranose (Alias 1,2,4-Tri-*epi*-validamine)

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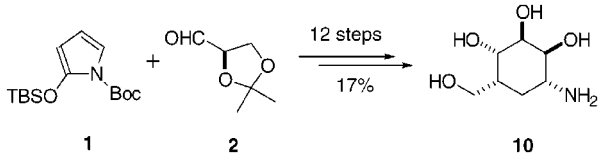
ABSTRACT



1 2 10

A quick arrival at chiral nonracemic cyclohexanoids is provided, which incorporates useful variability for large product diversity. Central to the construction is the exploitation of the dual nucleophilic character of an easily accessible triad of silyloxy diene synthons derived from the popular five-membered heterocycles furan, pyrrole, and thiophene. To assess the reliability of the procedure, the total synthesis of 1-deoxy-1-amino-pseudo-β-D-gulopyranose (10) (alias 1,2,4-tri-*epi*-validamine) is executed, in 12 steps and with a 17% overall yield, by starting with *N*-*tert*-butoxycarbonyl-2-[(*tert*-butyldimethylsilyl)oxy]pyrrole (1) and 2,3-*O*-isopropylidene-D-glyceraldehyde (2).

Carbasugars, also called pseudosugars, are a family of carbohydrate mimics which have attracted a great deal of interest among organic and medicinal chemists.[1] These small molecules were postulated—and then proven—to possess activity as glycosidase enzyme inhibitors, the carbasugar resembling the parent carbohydrate.

Since the first representative of this compound class was synthesized in 1966,[2] a variety of approaches have been developed, in both racemic and chiral domains, to assemble pseudofuranose and pseudopyranose entities, including either annulation of acyclic, functionality rich carbon fragments, cycloadditive procedures, or elaboration of proper carbohydrates and carbocycles.[3]

To arrive at these relevant constructs in a nonracemic format, we addressed the retrosynthetic pathway in Scheme 1, where the generic cyclohexanoid structure **A** was assembled by conjoining two complementary subunits, the intrinsically chiral malondialdehyde-related segment **F′** and the butyric acid α,γ-dianion **E′**. Our choice, here, was to exploit two easily accessible reaction components, the

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(1) Suami, T.; Ogawa, S. *Adv. Carbohydr. Chem. Biochem.* **1990**, *48*, 21−90.

(2) (a) McCasland, G. E.; Furuta, S.; Durham, L. J. *J. Org. Chem.* **1966**, *31*, 1516−1521. (b) McCasland, G. E.; Furuta, S.; Durham, L. J. *J. Org. Chem.* **1968**, *33*, 2835−2841. (c) McCasland, G. E.; Furuta, S.; Durham, L. J. *J. Org. Chem.* **1968**, *33*, 2841−2844.

(3) For general pseudosugar synthesis, see: (a) Ogawa, S. *J. Synth. Org. Chem. Jpn.* **1985**, *43*, 26−39. (b) Ogawa, S. In *Carbohydrate Mimics*; Chapleur, Y., Ed.; Wiley-VCH: Weinheim, 1998; pp 87−106. (c) Pingli, L.; Vandewalle, M. *Synlett* **1994**, 228−230. (d) Hudlicky, T.; Entwistle, D. A.; Pitzer, K. K.; Thorpe, A. J. *Chem. Rev.* **1996**, *96*, 1195−1220. (e) Dalko, P. I.; Sinay, P. *Angew. Chem. Int. Ed.* **1999**, *38*, 773−777.

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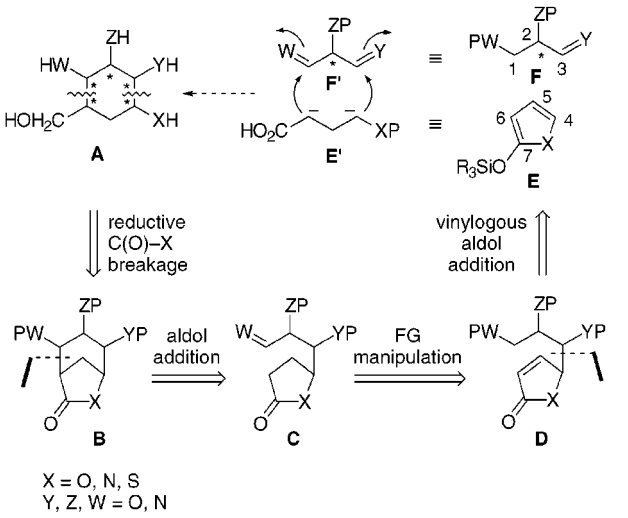
Scheme 1. Design of Carbasugar Synthesis

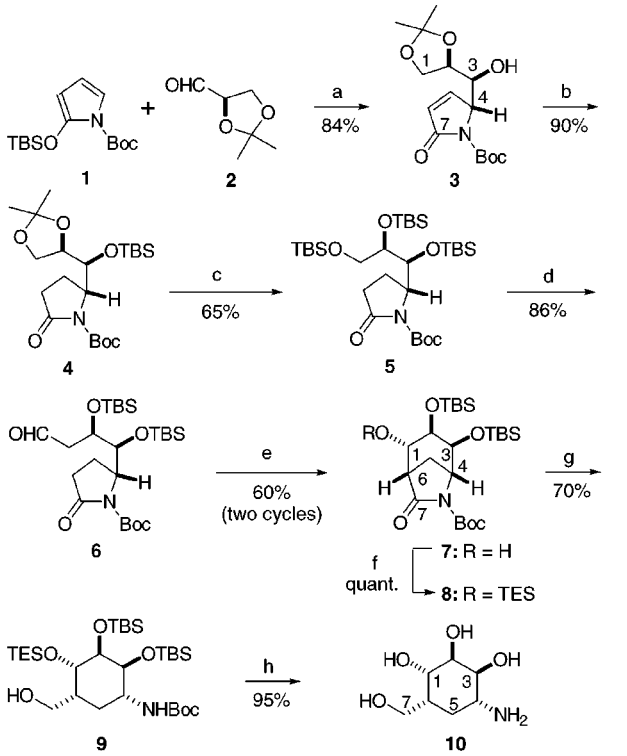


vinylogous enoxysilane **E**,[4] a synthetic equivalent of **E′**, and the glyceraldehyde-derived chiral synthon **F**, a chiral surrogate of **F′**. The guidelines to be followed were to implement the C3−C4 juncture, leading to **D** and **C**, in advance of the installation of the C1−C6 linkage that terminated the pseudopyranose ring closure and produced **B**, the immediate precursor of **A**. Central to this construction was a sort of [3 + 3] cycloadditive maneuver featuring sequential vinylogous cross aldolization−intramolecular aldolization. Remarkably, this plan incorporates useful malleability for large synthetic variability, allowing for one to play around one ternary heteroatom variable (X) and four binary variables (Y, Z, W, and the starter chirality).

Our inaugural synthesis, which forms the subject of this Letter, was targeted to 1-deoxy-1-amino-pseudo-β-D-gulopyranose (**10**)—a pseudo-aminohexose of the validamine family[5]—by adopting the variable combination X = N; Y, Z, W = O; starter chirality = *R*.

As shown in Scheme 2, the synthesis was initiated with the vinylogous cross-aldol addition of *N*-*tert*-butoxycarbonyl-2-[(*tert*-butyldimethylsilyl)oxy]pyrrole (**1**) to 2,3-*O*-isopropylidene-D-glyceraldehyde (**2**) under the influence of $SnCl_4$ in diethyl ether. As previously experienced,[6] crystalline 2,3-*anti*-3,4-*syn* configured adduct **3** formed in a high chemical yield (84%) with excellent regio- and diastereo-

Scheme 2. Synthesis of 1-Deoxy-1-amino-pseudo-β-D-gulopyranose[a]



[a] (a) $SnCl_4$, Et_2O, −80 °C, 1 h; (b) (i) H_2, Pd/C, THF, (ii) TBSOTf, 2,6-lutidine, CH_2Cl_2; (c) (i) 70% aqueous AcOH, 50 °C, (ii) TBSOTf, 2,6-lutidine, Et_3N, CH_2Cl_2, 50 °C, (iii) Boc_2O, MeCN, DMAP; (d) (i) 80% aqueous AcOH, 20 °C, (ii) $(COCl)_2$, DMSO, CH_2Cl_2, Et_3N, −78 °C; (e) LDA, THF, −80 °C, 15 min; (f) TESCl, pyridine, DMAP; (g) $NaBH_4$ (4 equiv), wet THF, 25 °C; (h) 6 N HCl, THF, MeOH (1:2:2); then SiO_2 chromatography, MeOH, EtOAc, 25% aqueous NH_4OH (2:2:1).

selectivity (≥95% de by ^1H NMR analysis). Exposure to catalytic hydrogenation and silylation cleanly furnished saturated lactam **4** in 90% yield (two steps), on which permutation of the terminal acetonide to robust *tert*-butyldimethylsilyl protecting groups was effected. Owing to the sluggish nature of this protection reaction, no conditions were found that obviated the concomitant unmasking of the nitrogen substituent. Therefore, reintroduction of the *N*-Boc protecting group was required. We thus arrived at persilylated lactam **5** with a good 65% yield for three steps. Following liberation of the primary carbinol within **5** and Swern oxidation to aldehyde **6** (86% yield for two steps), the stage was set to perform the crucial cycloaldolization.

In a series of preliminary experiments using a variety of bases and solvent systems, we recognized that attempts to obtain complete consumption of aldehyde **6** resulted in unwanted destruction of the aldol cycloadduct itself. An acceptable compromise was to allow aldolization to proceed to 50−60% aldehyde consumption and to recycle the unconverted **6**. Using LDA in THF at −80 °C (15 min), the cycloaldolization step revealed a spectacular level of diastereocontrol with the binuclear adduct **7** being formed in a

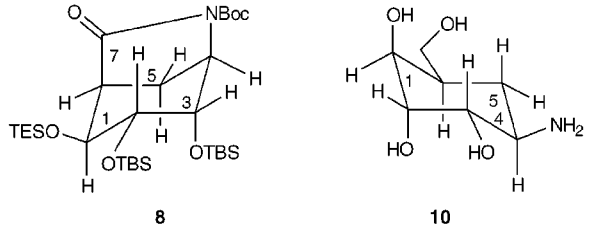
(4) For general reviews on the use of furan-, pyrrole-, and thiophene-based 2-silyloxy dienes, see: (a) Casiraghi, G.; Rassu, G. *Synthesis* **1995**, 607−629. (b) Casiraghi, G.; Rassu, G.; Zanardi, F.; Battistini, L. In *Advances in Asymmetric Synthesis*; Hassner, A., Ed.; JAI Press: Stamford; 1998; Vol. 3, pp 113−189.

(5) For recent syntheses of validamine and related stereoisomers, see: (a) Shing, T. K. M.; Tai, V. W.-F. *J. Org. Chem.* **1995**, *60*, 5332−5334. (b) Aceña, J. L.; Arjona, O.; Fernández de la Pradilla, R.; Plumet, J.; Viso, A. *J. Org. Chem.* **1994**, *59*, 6419−6424. (c) Yoshikawa, M.; Murakami, N.; Yokokawa, Y.; Inoue, Y.; Kuroda, Y.; Kitagawa, I. *Tetrahedron* **1994**, *50*, 9619−9628. (d) Takahashi, T.; Kotsubo, H.; Iyobe, A.; Namiki, T.; Koizumi, T. *J. Chem. Soc., Perkin Trans. 1* **1990**, 3065−3072. (e) Ogawa, S.; Suzuki, M.; Tonegawa, T. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 1824−1826. (f) Ogawa, S.; Ara, M.; Kondoh, T.; Saitoh, M.; Masuda, R.; Tokokuni, T.; Suami, T. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 1121−1126.

(6) Casiraghi, G.; Rassu, G.; Spanu, P.; Pinna, L. *J. Org. Chem.* **1992**, *57*, 3760−3763.

60% yield for two cycles, with no stereoisomer contamination, as judged by 300 MHz ^{1}H NMR analysis. In this intramolecular aldol reaction, advantage can be taken of the location of the aldehyde segment that orientates the incoming C1 carbonyl on the α-surface of the transient lithium enolate. The anti-Felkin facial selectivity favoring the C1−C2 *syn* (*threo*) orientation can be, instead, assumed to be dictated by the favorable *trans*-diequatorial arrangement of the C1 and C2 hydroxyl functions as in compound **7**.

Protection of the free hydroxyl at C1 as a triethylsilyl ether by a conventional protocol quantitatively gave rise to the crystalline bicyclic lactam **8**, whose ^{1}H NMR spectrum proved to be richly detailed and guided us in the definitive structural assignment of this product.[7] The relative configuration of **8** and the $^4C_1$ conformation of its cyclohexane ring ($^1C_4$ conformation using sugar numbering) (Figure 1)



8 **10**

Figure 1. Proposed structures for compounds **8** and **10**.

were ascertained by the large coupling constants of the axially disposed H1 and H2 protons ($J_{1,2}$ = 8.7 Hz) and by two long-range W couplings between equatorial H4 and H6 and H3 and H5$_{eq}$ ($^4J_{4,6}$ = 1.2 Hz; $^4J_{3,5eq}$ = 0.9 Hz). Furthermore, the equatorial disposition of the H3 and H4 protons was corroborated by their small coupling constant values ($J_{2,3}$ = 3.9 Hz; $J_{3,4}$ = 4.8 Hz; $J_{4,5eq}$ = 4.8 Hz), whereas the $J_{4,5ax}$ and $J_{6,5ax}$ couplings near to zero were diagnostic of a dihedral angle involving these protons approaching to 90°.

At this stage, what remained was the breakage of the five-membered lactam ring and the reduction of the carbonyl function to a hydroxymethyl.[8] Indeed, reductive cleavage of the amide linkage proceeded uneventfully under mild conditions, using $NaBH_4$ in wet THF, furnishing amino pseudosugar **9** in 70% yield. Exposure of **9** to 6 N HCl in THF/methanol finally completed the synthesis, giving 1-deoxy-1-amino-pseudo-β-D-gulopyranose (**10**) (1,2,4-tri-*epi*-validamine), which was isolated as the free base in 95% yield after chromatography over silica gel with MeOH/EtOAc/25% aqueous NH_4OH as eluant.[9]

Configurational and conformational assignment of the target pseudosugar **10** (Figure 1) was determined upon inspection of its ^{1}H NMR spectrum in D_2O. The $^4C_1$-D-*gulo* configuration ($^1C_4$ using target numbering) was attributed mainly based on the measurement of large coupling constants involving axially disposed H3, H4, H5ax, and H6 protons, with $J_{3,4} = J_{4,5ax}$ = 12.3 Hz and $J_{5ax,6}$ = 12.6 Hz. In addition, the equatorial disposition of the H1 and H2 protons was supported by the expected small vicinal coupling constants ($J_{1,6}$ = 4.8 Hz; $J_{2,3} = J_{1,2}$ = 3.0 Hz).

To summarize, we have discovered a strategic methodology for the construction of chiral nonracemic carbasugars and related cyclohexanoids and applied it successfully to the total synthesis of 1-deoxy-1-amino-pseudo-β-D-gulopyranose (**10**) (17% yield over 12 steps). Expansion of the scope of this synthesis plan to include wide permutation of the heteroatom and chirality variables is underway. Once completed, this study will allow us to determine whether and to what extent the vast theoretical structural variability of such a plan is able to be implemented in practice.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra (300 and 75.4 MHz, respectively) of compounds **8** and **10**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) All new compounds shown in Scheme 2, as well as the numerous intermediates not indicated, were fully characterized by ^{1}H and ^{13}C NMR analyses. Satisfactory elemental analyses were provided for compounds **6**, **8**, **9**, and **10**. Compound **8**: colorless needles; $[\alpha]^{20}_D$ = +27.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.26 (td, *J* = 3.6, 0.9 Hz, 1H, H3), 4.11 (td, *J* = 4.8, 1.2 Hz, 1H, H4), 3.87 (dd, *J* = 8.7, 2.7 Hz, 1H, H1), 3.57 (dd, *J* = 8.7, 3.9 Hz, 1H, H2), 2.52 (ddd, *J* = 5.4, 2.7, 1.2 Hz, 1H, H6), 2.24 (d, *J* = 13.5 Hz, 1H, H5ax), 1.87 (dddd, *J* = 13.5, 5.4, 5.4, 0.9 Hz, 1H, H5eq), 1.52 (s, 9H, Bu^t), 0.99 (t, *J* = 8.1 Hz, 9H, CH_3), 0.91 (s, 18H, Bu^t), 0.65 (q, *J* = 8.1 Hz, 6H, CH_2), 0.12 (s, 3H, CH_3), 0.09 (s, 3H, CH_3), 0.06 (s, 3H, CH_3), 0.04 (s, 3H, CH_3); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 176.2, 145.1, 82.6, 74.2, 72.2, 70.2, 59.4, 48.9, 28.1 (3C), 27.1, 26.3 (3C), 25.8 (3C), 18.0 (2C), 6.8 (3C), 5.1 (3C), −4.0, −4.2 (2C), −4.7.

(8) Methanolysis of lactam **8** cleanly afforded the corresponding amino acid ester, a nice example of functional, conformationally restricted GABA analogue.

(9) Compound **10**: glassy solid; $[\alpha]^{20}_D$ −82.0 (*c* 0.5, D_2O); ^{1}H NMR (300 MHz, D_2O) δ 3.99 (dd, *J* = 4.8, 3.0 Hz, 1H, H1), 3.97 (t, *J* = 3.0 Hz, 1H, H2), 3.82 (dd, *J* = 10.8, 3.0 Hz, 1H, H3), 3.63 (dd, *J* = 11.1, 7.5 Hz, 1H, H7a), 3.52 (dd, *J* = 11.1, 6.6 Hz, 1H, H7b), 3.32 (td, *J* = 12.3, 4.2 Hz, 1H, H4), 2.05 (m, 1H, H6), 1.87 (dt, *J* = 12.6, 4.2 Hz, 1H, H5eq), 1.44 (q, *J* = 12.6 Hz, 1H, H5ax); ^{13}C NMR (75.4 MHz, D_2O) δ 72.2, 69.6, 69.4, 62.3, 50.5, 36.5, 25.7. Penta-*N*,*O*,*O*,*O*,*O*-acetyl derivative: white crystals; mp 194−195 °C; $[\alpha]^{20}_D$ +5.0 (*c* 0.6, $CDCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.63 (d, *J* = 8.1 Hz, 1H, NH), 5.31 (t, *J* = 3.6 Hz, 1H, H2), 5.10 (bt, *J* = 3.6 Hz, 1H, H1), 5.03 (dd, *J* = 11.1, 3.3 Hz, 1H, H3), 4.36 (tdd, *J* = 11.7, 8.5, 4.5 Hz, 1H, H4), 4.02 (dd, *J* = 11.1, 8.1 Hz, 1H, H7a), 3.84 (dd, *J* = 11.1, 6.6 Hz, 1H, H7b), 2.43 (m, 1H, H6), 2.14 (s, 3H, Me), 2.11 (s, 3H, Me), 2.04 (s, 3H, Me), 2.03 (s, 3H, Me), 1.94 (s, 3H, Me), 1.64 (m, 1H, H5eq), 1.37 (q, *J* = 12.9 Hz, 1H, H5ax); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 171.7, 170.8, 169.9, 169.1 (2C), 70.7, 68.4, 68.3, 63.2, 47.4, 33.9, 29.1, 23.4, 20.9 (2C), 20.7 (2C).