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Variable Strategy toward Carbasugars and Relatives. 6.[1] Diastereoselective Synthesis of 2-Deoxy-2-amino-5a-carba-β-L-mannopyranuronic Acid and 2-Deoxy-2-amino-5a-carba-β-L-mannopyranose

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Efficient, total syntheses of novel 2-deoxy-2-amino-5a-carba-β-L-mannopyranuronic acid (**1**) and 2-deoxy-2-amino-5a-carba-β-L-mannopyranose (**2**), a positional stereoisomer of validamine, have been achieved in 28% and 24% overall yields and in 12 steps and 13 steps, respectively, from 2-[(*tert*-butyldimethylsilyl)oxy]furan (**3**) and (2*S*)-2,3-*O*-isopropylideneglyceraldehyde *N*-benzyl imine (**4**) via two highly diastereoselective Mukaiyama aldol-related chemical maneuvers. The strategy, which furnishes the targeted carbasugars in enantiopure forms, allows for complete control of the configuration at all five contiguous stereocenters of the targets by utilizing the sole element of chirality present in the aldimine progenitor **4**.

Introduction

Diversity is a leading concern in medicinal organic chemistry, and synthetic methodologies oriented toward this end can provide a solid foundation for the discovery of novel pharmaceutical leads and biological probes.[2] Among the more versatile of small functional organic molecules, the carbasugar matrix emerges as an ideal architecture for diversity, being its robust carbocyclic structure generously adorned with various attributes including ring size, poly-functionality, and multiple chirality.[3] In the context of a program concerned with the exploitation of carbasugars and carbasugar amino acids as leads for new therapeutic agents and constrained scaffolds in peptidomimetic studies,[1,4] we formulated a general vision toward a malleable synthesis of these entities and demonstrated that the approach could be used to construct a vast repertoire of diverse, enantiopure carbocycles, encompassing carbafuranoid[4b,d] and carbapyranoid[4c,d] structures, as well as rare medium-sized ring congeners.[1]

As shown in Figure 1, the first component of the construction of a generic carbapyranose **F** (**A** + **B** → **C**) involves the use of a Lewis acid-promoted vinylogous crossed Mukaiyama-aldol reaction between heterosubstituted dienoxy silanes **A** and suitable chiral aldehyde progenitors **B** to build the stereocenters at the future carbons 1−3, while the second decisive maneuver (**D** → **E**) contemplates adoption of a novel, highly productive intramolecular silylative aldolization to create the stereocenters at carbons 4 and 5 and to complete the joining of the carbocycle framework. This approach was designed with diversity in mind, to enable chemical and stereochemical modification of both the core and substituents of the targets by varying chirality, substituents, and carbon chain length of the chiral predecessor **B** as well as the nature of the heteroatom embodied in the nucleophilic diene **A**.

To illustrate our progress, an efficient stereocontrolled synthetic sequence to β-L-configured 5a-carbapyranuronic δ-amino acid **1** and 5a-carbapyranosylamine **2**, a positional stereoisomer of validamine,[5] is described in this paper. The method we planned to use in this study (Figure 2) is based on a rational adaptation of our original project and involves the use of a suitable chiral nonra-

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(1) Rassu, G.; Auzzas, L.; Pinna, L.; Zambrano, V.; Zanardi, F.; Battistini, L.; Gaetani, E.; Curti, C.; Casiraghi, G. *J. Org. Chem.* **2003**, *68*, 5881−5885.

(2) For recent reviews on diversity-oriented synthesis, see: (a) Schreiber, S. L. *Science* **2000**, *287*, 1964−1969. (b) Burke, M. D.; Berger, E. M.; Schreiber, S. L. *Science* **2003**, *302*, 613−618.

(3) For recent reviews on carbasugars and relatives, see: (a) Rassu, G.; Auzzas, L.; Pinna, L.; Battistini, L.; Curti, C. In *Studies in Natural Products Chemistry*; Atta-ur-Rahman, Ed.; Elsevier Science B.V.: Amsterdam, The Netherlands, 2003; Vol. 29, pp 449−520. (b) Berecibar, A.; Grandjean, C.; Siriwardena, A. *Chem. Rev.* **1999**, *99*, 779−844. (c) Hudlicky, T.; Entwistle, D. A.; Pitzer, K. K.; Thorpe, A. J. *Chem. Rev.* **1996**, *96*, 1195−1220.

(4) (a) Rassu, G.; Auzzas, L.; Pinna, L.; Battistini, L.; Zanardi, F.; Marzocchi, L.; Acquotti, D.; Casiraghi, G. *J. Org. Chem.* **2000**, *65*, 6307−6318. (b) Rassu, G.; Auzzas, L.; Pinna, L.; Zambrano, V.; Battistini, L.; Zanardi, F.; Marzocchi, L.; Acquotti, D.; Casiraghi, G. *J. Org. Chem.* **2001**, *66*, 8070−8075. (c) Zanardi, F.; Battistini, L.; Marzocchi, L.; Acquotti, D.; Rassu, G.; Pinna, L.; Auzzas, L.; Zambrano, V.; Casiraghi, G. *Eur. J. Org. Chem.* **2002**, 1956−1964. (d) Rassu, G.; Auzzas, L.; Pinna, L.; Zambrano, V.; Zanardi, F.; Battistini, L.; Marzocchi, L.; Acquotti, D.; Casiraghi, G. *J. Org. Chem.* **2002**, *67*, 5338−5342.

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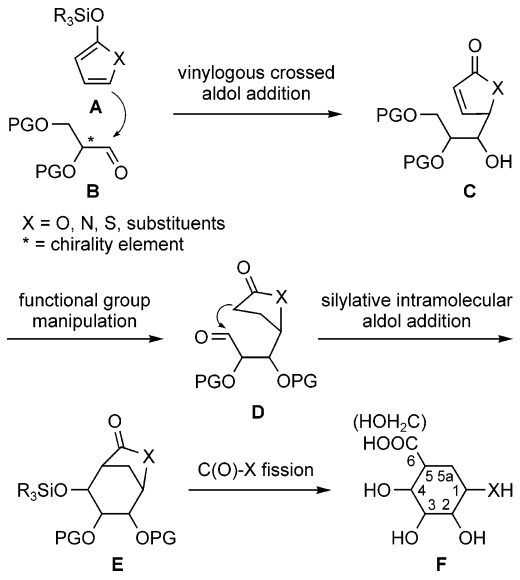


FIGURE 1. Vinylogous aldol/silylative aldol approach to carbasugars: access to carbapyranoses.

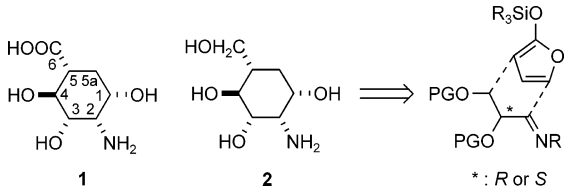


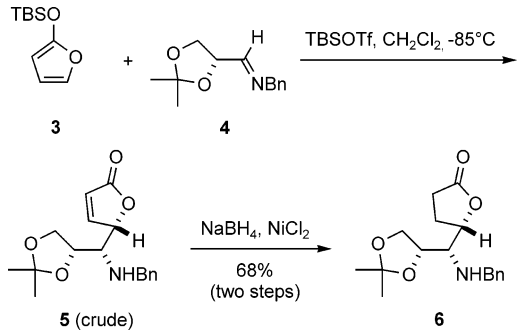
FIGURE 2. Structures of 5a-carbapyranuronic amino acid **1** and 5a-carbapyranosylamine **2**: synthetic strategy.

cemic aldimine predecessor, in lieu of the aldehyde component, to position the requisite amine function at carbon 2 of the targeted carbasugars **1** and **2**.

Results and Discussion

Our synthesis commenced with 2-[(*tert*-butyldimethylsilyl)oxy]furan (**3**), which was coupled to enantiopure (2*S*)-2,3-*O*-isopropylideneglyceraldehyde *N*-benzyl imine (**4**) via a Mukaiyama-type vinylogous imino-aldol (Mannich-type) crossed addition (Scheme 1).[6] Literature precedents in this field[7] indicated that silicon triflates were suitable triggers to initiate similar transformations; thus we employed a triflate Lewis acid, namely *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf), to govern the present addition.[8]

SCHEME 1



Extreme care was needed for this maneuver, since the expected unsaturated adduct (i.e. **5**) is exceedingly prone to epimerization and retrograde addition. In fact, attempts to isolate **5** in a pure state by the usual crystallization or chromatographic procedures failed, and variable epimeric adduct mixtures formed, which proved very difficult to separate. Upon further study, we surmounted the obstacle by adopting a two-stage protocol where the crude unsaturated product **5** was immediately subjected to double bond saturation with nickel boride. In the event, stable butanolide **6** was obtained *as a single isomer* in a gratifying 68% isolated yield for the two steps. The 4*S*,5*S*,6*S*-stereochemistry in **6** (and in its unsaturated precursor **5**) could not be established with certainty at this point and was inferred from the structure of a more advanced intermediate, i.e., compound **12**, and the final products (vide infra).[9]

With ready access to **6**, we now had to deal with the delicate question of forming the carbocyclic ring. We opted to tackle this problem by using a sequence featuring the mild silylative cycloaldolization protocol we had already experienced during our syntheses of carbasugars. As depicted in Figure 3, there were two plausible options: (1) elaboration of **6** into γ-lactone aldehyde **A** followed by cyclization to oxabicyclo[3.2.1]octanone **B** and (2) ring enlargement to δ-lactam aldehyde **C** followed by annulation to azabicyclo[2.2.2]octanone **D**. With selectivity in mind, we reasoned that, during carbon−carbon bond formation, the more compact structure of lactam **C**, as compared to the flexible lactone **A**, would have guaranteed a more precise positioning of the C(4) aldehyde carbonyl vis-à-vis the incoming nucleophilic C(5), thus ensuring superior facial diastereocontrol.[10]

On these bases, we moved ahead with the transformation of lactone **6** into aldehyde **11** (Scheme 2). Thus,

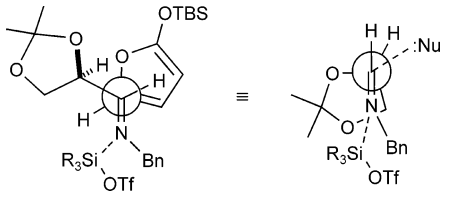
(5) For related examples, see: (a) Ogawa, S.; Tsunoda, H. *Liebigs Ann. Chem.* **1992**, 637−641. (b) Mehta, G.; Lakshminath, S.; Talukdar, P. *Tetrahedron Lett.* **2002**, *43*, 335−338. (c) Miyamoto, M.; Baker, M. L.; Lewis, M. D. *Tetrahedron Lett.* **1992**, *33*, 3725−3728. (d) Augy-Dorey, S.; Dalko, P.; Géro, S. D.; Quiclet-Sire, B.; Eustache, J.; Stütz, P. *Tetrahedron* **1993**, *49*, 7997−8006. (e) Ogawa, S.; Nishi, K.; Shibata, Y. *Carbohydr. Res.* **1990**, *206*, 352−360. (f) Barton, D. H.; Géro, S. D.; Augy, S.; Quiclet-Sire, B. *Chem. Commun.* **1986**, *18*, 1399−1401.

(6) Reviews: (a) Casiraghi, G.; Zanardi, F.; Appendino, G.; Rassu, G. *Chem. Rev.* **2000**, *100*, 1929−1972. (b) Bur, S. K.; Martin, S. F. *Tetrahedron* **2001**, *57*, 3221−3242. (c) Martin, S. F. *Acc. Chem. Res.* **2002**, *35*, 895−904.

(7) (a) Barnes, D. M.; McLaughlin, M. A.; Oie, T.; Rasmussen, M. W.; Stewart, K. D.; Wittenberger, S. J. *Org. Lett.* **2002**, *4*, 1427−1430. (b) DeGoey, D. A.; Chen, H.-J.; Flosi, W. J.; Grampovnik, D. J.; Yeung, C. M.; Klein, L. L.; Kempf, D. J. *J. Org. Chem.* **2002**, *67*, 5445−5453. (c) Martin, S. F.; Barr, K. J.; Smith, D. W.; Bur, S. K. *J. Am. Chem. Soc.* **1999**, *121*, 6990−6997. (d) Martin, S. F.; Barr, K. J. *J. Am. Chem. Soc.* **1996**, *118*, 3299−3300. (e) Lombardo, M.; Trombini, C. *Tetrahedron* **2000**, *56*, 323−326. See also: Dilman, A. D.; Ioffe, S. L. *Chem. Rev.* **2003**, *103*, 733−772.

(8) A screen of various silyl triflates (TMSOTf, TESOTf, TBSOTf, TIPSOTf) indicated commercial TBSOTf to be the optimal promoter in this reaction.

(9) A plausible transition state to anti,anti-configured adduct **5** involves a synclinal-type approach of the silyloxy diene C(5) *re*-face to the C(1) *si*-face of the imine acceptor according to a relatively uncongested open-chain (Felkin-Ahn) model described here.



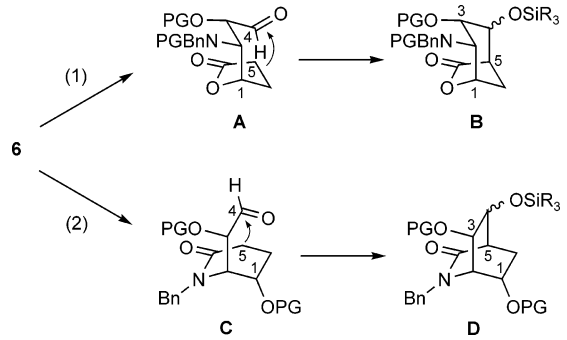
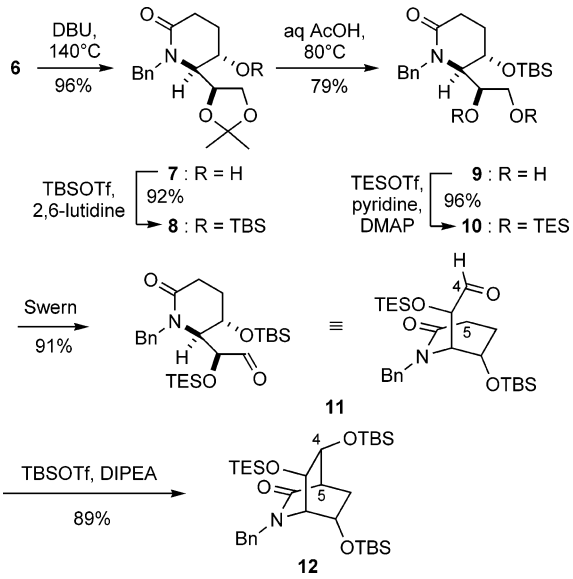


FIGURE 3. Strategic options toward six-membered carbocycles. Target numbering is adopted.

SCHEME 2



exposure of **6** to neat DBU at 140 °C cleanly furnished piperidinone **7** (96% yield), which was protected as the TBS ether **8** in 92% yield. To arrive at aldehyde **11**, we chose to employ direct Swern oxidation of triethylsilyl-protected terminal diols,[11] which required preparation of the predecessor **10**. Thus, the lactam **8** was exposed to 80% aqueous acetic acid at 80 °C to deliver diol **9**, which was protected as the bis-triethylsilyl ether **10** (76%, two steps). Treatment of **10** with a mixture of oxalyl chloride (10 mol equiv) and DMSO (20 mol equiv) in CH_2Cl_2 at −10 °C, followed by Et_3N (36 mol equiv) finally gave rise to the fully protected aldehyde **11** in a respectable yield of 91%.

With the key aldehyde **11** successfully prepared, the next step in the synthesis entailed the intramolecular union of the enolizable carbon 5 to the C(4) carbonyl terminal, and this was accomplished under the guidance of a freshly prepared mixture of TBSOTf and DIPEA (3 mol equiv each) in CH_2Cl_2 at room temperature.[12] Our line of reasoning was indeed confirmed: *the silylative cycloaldolization of **11**, employing the prescribed conditions, yielded trans-configured trihydroxy-azabicyclooctanone **12** as a single isomer in an exquisite 89% isolated yield*. It is useful to note that the cis stereoisomer (not shown), which should have arisen from the attack of C(5) on the opposite face of the aldehyde C(4) carbonyl, was not detected at all.

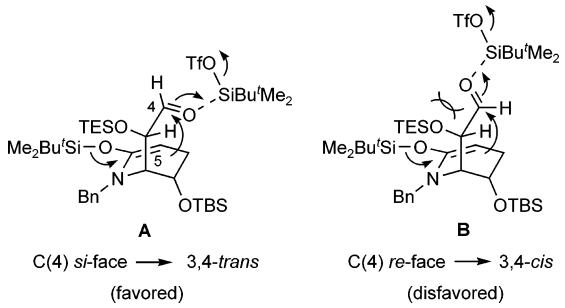


FIGURE 4. Reactive "near attack" conformers for the silylative intramolecular aldol reaction leading to carbocycle **12**.

A plausible mechanism to explain the exclusive formation of **12** under the reaction conditions used is shown in Figure 4. The initially formed enolsilane (from **11**) is envisaged to participate in a straightforward intramolecular nucleophilic attack of C(5) (convex *si*-face) onto the proximate C(4) carbonyl (*si*-face), which should result in the formation of 3,4-*trans*-configured bicycle **12** (see model **A**). The control element in **A** (as compared to **B**) is the antiperiplanar disposition of the C(3) heteroatom substituent and C(4) carbonyl oxygen, which minimizes the dipolar interaction between these electronegative groups. Definitive confirmation for the relative (and absolute) configuration in the bicycle **12** (and hence in its predecessors) was obtained by a detailed analysis of its solution structure with various NMR techniques. The assignments were carried out with the help of two-dimensional TOCSY and COSY experiments and were further confirmed by $^1H-^1H$ NOESY measurements which, in addition, provided diagnostic information on the proximity of the protons in the rigid bicycle backbone of **12**.[13]

To complete the synthesis of both carbapyranuronic amino acid **1** and carbapyranosylamine **2**, conversion of **12** into the protected amino acid **15** (a common predecessor) was planned (Scheme 3). Thus, benzyl-substituted bicycle **12** was transformed into the *N*-Boc derivative **14** in a 84% global yield via debenzylation with Na in liquid ammonia (i.e. **12** → **13**) followed by *N*-Boc reprotection (Boc_2O, MeCN, DMAP). Hydrolysis of **14** with LiOH in THF/water then provided protected amino acid **15** (93% yield), which was fully deprotected to **1** by exposure to 6 N HCl in THF/MeOH (1:2:1 ratio) followed by DOWEX (98% yield).

In a divergent way (Scheme 4), acid **15**, when treated with an excess of a 2 M solution of BH_3·DMS in THF (8 mol equiv), delivered the protected amino alcohol **16** (86%

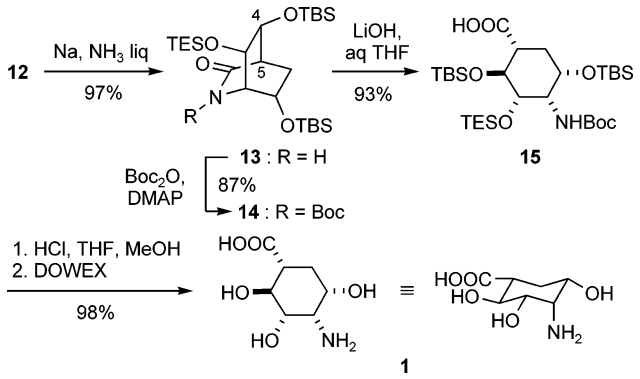
(10) In truth, the alternative cyclization protocol **A** to **B** was actually attempted. However, the extremely low yields obtained in elaborating adduct **6** into a suitably protected aldehyde lactone of type **A** (i.e., NPG = Cbz; OPG = TES) forced us to back down from this strategic option and follow the second and more fruitful route reported in this study.

(11) Rodríguez, A.; Nomen, M.; Spur, B. W.; Godfroid, J. J. *Tetrahedron Lett.* **1999**, *40*, 5161−5164.

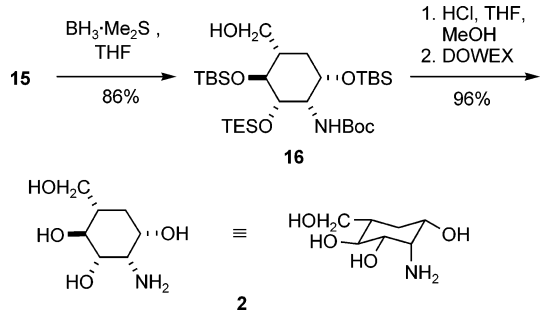
(12) For a recent example of a silylative Mukaiyama intermolecular aldol reaction with TBSOTf and Hünig's base, see: Jung, M. E.; van den Heuvel, A. *Org. Lett.* **2003**, *5*, 4705−4707. See also: Evans, D. A.; Tedrow, J. S.; Shaw, J. T.; Downey, C. W. *J. Am. Chem. Soc.* **2002**, *124*, 392−393.

(13) Stereochemical proofs for **12**, as well as **1** and **2**·HCl, are compiled in the Supporting Information (Tables S1−S3).

SCHEME 3



SCHEME 4



yield), which was liberated by acidic treatment to furnish amine **2** in 96% yield. Free amino acid **1** and its hydrochloride salt, as well as amino alcohol **2** (HCl salt), were shown (^{1}H NMR, D_2O, 25 °C) to adopt the expected $^1C_4$ (L-manno) solution conformation, as judged by the measurement of the vicinal and long-range coupling constants and inspection of the critical NOE correlations.[13]

To conclude, enantiopure 2-deoxy-2-amino-5a-carba-β-L-mannopyranuronic acid (**1**) and validamine isomer 2-deoxy-2-amino-5a-carba-β-L-mannopyranose (**2**) were synthesized from furan-based dienoxy silane **3** by utilizing the sole element of chirality present in the precursor glyceraldehyde imine **4** (28% and 24% overall yields; 12 steps and 13 steps, respectively). Success was achieved, as planned, by interfacing the silyloxy diene chemistry, developed in our laboratories in the 1990s,[14] with the potent silylative aldol-cyclization protocol we validated during this carbasugar synthesis program. These syntheses could easily be adapted for the preparation of β-D-manno-configured enantiomers of **1** and **2** by using (2*R*)-2,3-*O*-isopropylideneglyceraldehyde *N*-benzyl imine, which is available from the corresponding L-glyceraldehyde acetonide (ex L-ascorbic acid).[15] Highly functionalized δ-amino acid **1**, reported in this study, and its β-D-manno-configured enantiomer *ent*-**1** offer interesting topologies that could be useful in the study of constrained dipeptide surrogates[16] and as platforms for novel peptidomimetic constructions.[17]

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Supporting Information Available: Experimental details and characterization data for all synthesized compounds as well as ^{1}H NMR resonances, coupling constants, and ^{1}H−^{1}H NOE correlations for **12**, **1**, and **2**·HCl (Tables S1−S3). This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) Representative reviews: (a) Casiraghi, G.; Rassu, G.; Zanardi, F.; Battistini, L. In *Advances in Asymmetric Synthesis*; Hassner, A., Ed.; JAI Press: Stamford, CT, 1998; Vol. 3, pp 113−189. (b) Rassu, G.; Zanardi, F.; Battistini, L.; Casiraghi, G. *Synlett* **1999**, 1333−1350. (c) Rassu, G.; Zanardi, F.; Battistini, L.; Casiraghi, G. *Chem. Soc. Rev.* **2000**, 109−118.

(15) Hubschwerlen, C. *Synthesis* **1986**, 962−964.

(16) Interestingly, **1** and *ent*-**1** can be viewed as new, locked hydroxyethylene isosteres of D-Ser-D-Ser and L-Ser-L-Ser dipeptides, respectively.

(17) Lohof, E.; Burkhart, F.; Born, M. A.; Planker, E.; Kessler, H. In *Advances in Amino Acid Mimetics and Peptidomimetics*; Abell, A., Ed.; JAI Press: Stamford, CT, 1999; Vol. 2, pp 263−292.