JOC Article

Variable Strategy toward Carbasugars and Relatives. 4.[1] Viable Access to (4a-Carbapentofuranosyl)amines, (5a-Carbahexopyranosyl)amines, and Amino Acids Thereof

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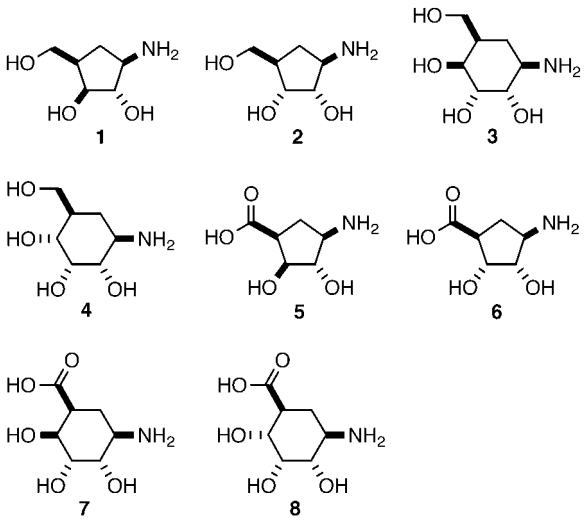
A chiral, divergent synthesis of two carbafuranosylamines, **1** and **2**, two carbapyranosylamines, **3** and **4**, two carbafuranosylamino acids, **5** and **6**, and two carbapyranosylamino acids, **7** and **8**, has been achieved. Highlights of the procedure include the following: a diastereoselective crossed vinylogous Mukaiyama aldol coupling between *N*-(*tert*-butoxycarbonyl)-2-[(*tert*-butyldimethylsilyl)-oxy]pyrrole (TBSOP, **9**) and 2,3-*O*-isopropylidene-D-glyceraldehyde (**10**) for the assembly of the target compound carbon backbone; a high-yielding silylative cycloaldolization that gives the cyclopentanoid and cyclohexanoid motifs; and a reductive or hydrolytic breakage of the lactam C(O)−N link to liberate the carbasugar and install the desired pseudo-anomeric amine and the hydroxymethyl or carboxyl functionalities. The sequences leading to trans-configured carbafuranosyl compounds **1** and **5** and carbapyranosyl compounds **3** and **7** were 12- and 13-step processes, with overall yields of 34%, 35%, 17%, and 16%. Cis-configured isomers **2**, **4**, **6**, and **8** were obtained only in minor yields.

Introduction

Varied repertoires of natural and natural product-like small molecules form the basis for the discovery of new bioactive lead candidates and for understanding the structural determinants involved in molecular recognition events of pharmacological importance. As part of an ongoing program targeted at the assemblage of collections of structurally diverse carbasugar entities, we have envisaged a variable, highly efficient synthetic pathway with which a number of 4a-carbapentofuranose and 5a-carbahexopyranose compounds have been accessed.[1,2] Capitalizing on the knowledge gained from these studies, we have now moved on to synthesize a further series of carbasugar constructs embodying amino functionalities.

Herein disclosed is the synthesis of (4a-carbapentofuranosyl)amines **1** and **2**, (5a-carbahexopyranosyl)-amines **3** and **4**, as well as the corresponding carbaglycuronylamines **5**, **6**, **7**, and **8**. These compounds, other than finding a possible application as anticancer and antiviral agents due to their ability to inhibit the glycosydase enzymes,[3] may also be envisioned as secondary structure-inducing platforms with which designed glycopeptidomimetics (from e.g. **5**−**8**) or functionality rich biomimetic structures may be engineered.[4]



Results and Discussion

Synthesis Plan. Synthesis of the nitrogen-containing, highly oxygenated structure of the targeted compounds

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# Centro Interfacoltà di Misure.

(1) 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.

(2) (a) Rassu, G.; Auzzas, L.; Pinna, L.; Zanardi, F.; Battistini, L.; Casiraghi, G. *Org. Lett.* **1999**, *1*, 1213−1215. (b) Rassu, G.; Auzzas, L.; Pinna, L.; Battistini, L.; Zanardi, F.; Marzocchi, L.; Acquotti, D.; Casiraghi, G. *J. Org. Chem*. **2000**, *65*, 6307−6318. (c) 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.

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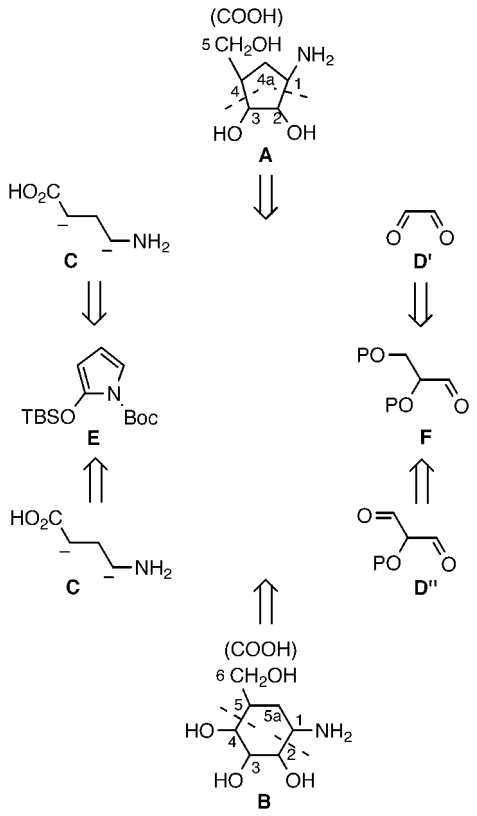
SCHEME 1. Retrosynthetic Analysis of (Carbaglycosyl)amines A and B

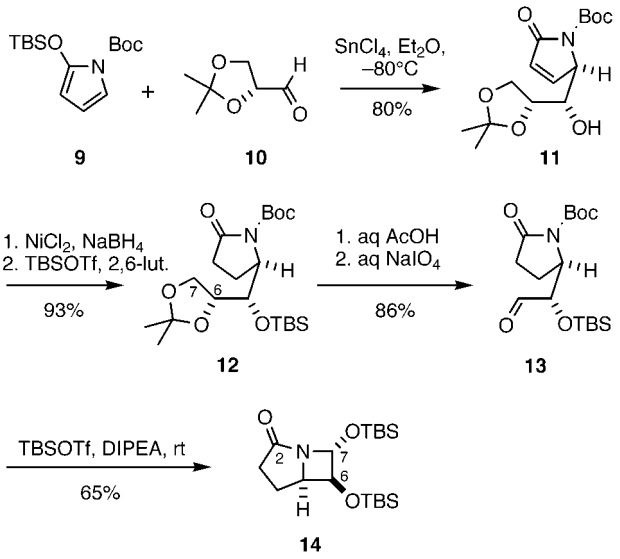


is a main challenge in itself. Specifically, this involves the stereocontrolled installation of an amino function at the pseudo-anomeric site of the cycloalkane moiety, the implementation of hydroxymethyl or carboxyl fragments in γ to the amino group, and the incorporation of hydroxyls at two or three carbon atoms of the ring.

Basically, our resulting retrosynthesis of carbafuranoses **A** and carbapyranoses **B** (Scheme 1) is based on two key aldol-type disconnections across C1/C2 and C3/C4 (or C4/C5) leading back to two complementary fragments, namely the aminated four-carbon dianion **C** and the appropriately oxygenated acceptors **D′** or **D″**. We envisioned substrate **C** arising from pyrrole-based dienoxy silane **E**, and frames **D′** or **D″** originating from glyceraldehyde **F**.

Synthesis of (4a-Carba-*β*-D-xylofuranosyl)amine (1), (4a-Carba-*β*-D-ribofuranosyl)amine (2), (4a-Carba-*β*-D-xylofuranuronyl)amine (5), and (4a-Carba-*β*-D-ribofuranuronyl)amine (6). The project was initiated with a 10-g-scale preparation of *N*-Boc-protected unsaturated lactam **11** by joining *N*-(*tert*-butoxycarbonyl)-2-[(*tert*-butyldimethylsilyl)oxy]pyrrole (TBSOP, **9**) to 2,3-*O*-isopropylidene-D-glyceraldehyde (**10**), as previously

SCHEME 2



described (Scheme 2).[2a,b] After saturation of the carbon−carbon double bond ($NiCl_2$, $NaBH_4$) and protection of the free secondary hydroxyl as a TBS ether (TBSOTf, 2,6-lutidine), the fully protected lactam **12** was isolated in 93% yield (two steps).

To arrive at the key aldehyde intermediate **13**, we had to excise the terminal C6−C7 bond oxidatively, and this was effected by acetonide deprotection (aq AcOH, 50 °C) followed by periodate oxidation. Aldehyde **13** was thus obtained as a white solid in 86% yield for the two steps. The stage was set now for the crucial cyclization maneuver of connecting the carbon atom α to the lactam carbonyl to the formyl group. The installation of the new carbon−carbon bond to generate the requisite cyclitol frame was attempted by direct treatment of aldehyde **13** with a 1:1 mixture of DIPEA/TBSOTf (3.0 mol equiv) at room temperature. Rather unexpectedly, this treatment, which had already proved successful with a number of lactone and thiolactone aldehydes,[1,2c] failed with *N*-Boc lactam **13**, and provided the silylated bicyclic azetidine **14** as the sole reaction product (65% yield).[5] Treatment of **13** with silyl triflate likely promoted an unwanted, competitive fission of the *N*-Boc linkage, ultimately resulting in a diastereoselective silylative amination of the aldehyde terminus.

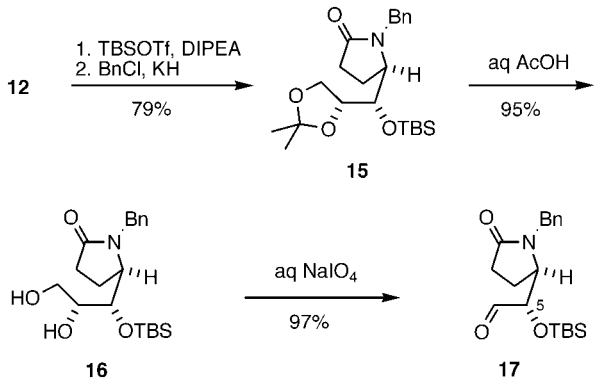
To overcome this obstacle, an alternative route had to be pursued, whereby the nitrogen of the lactam precursor **13** was protected with a group that could withstand silyl triflate exposure. Our choice fell on the benzyl protecting group as it is resistant to silyl triflate treatment. First of all, we decided to reprogram the synthesis by employing *N*-benzyl-2-[(*tert*-butyldimethylsilyl)oxy]pyrrole as the initial building block. Disappointingly, the Lewis acid-mediated vinylogous aldol addition to glyceraldehyde **10** under varied conditions resulted in, at best, a low yield of the expected aldol product. We thus abandoned this approach and opted to change the *N*-Boc protective group to *N*-Bn in a later phase of the synthesis. Hence, the advanced intermediate **12** was subjected to selective

(3) (a) Suami, T.; Ogawa, S. *Adv. Carbohydr. Chem. Biochem.* **1990**, *48*, 21−90. (b) *Carbohydrate Mimics: Concepts and Methods*; Chapleur, Y., Ed.; Wiley-VCH: Weinheim, Germany, 1998.

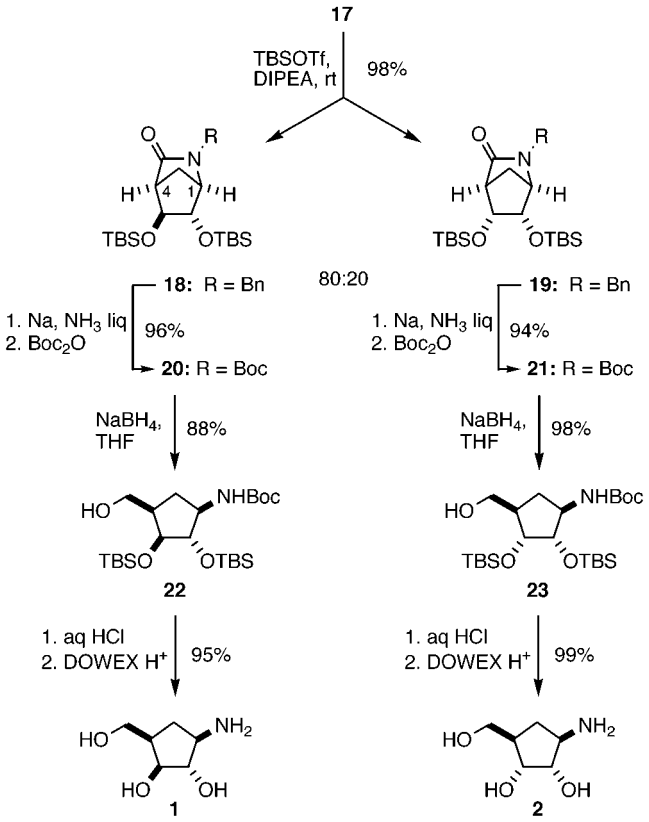
(4) (a) *Advances in Amino Acid Mimetics and Peptidomimetics*; Abell, A., Ed.; Jai Press: Greenwich, CT, 1997; Vol 1. (b) *Advances in Amino Acid Mimetics and Peptidomimetics*; Abell, A., Ed.; Jai Press: Stamford, CT, 1999; Vol 2. (c) Gruner, S. A. W.; Locardi, E.; Lohof, E.; Kessler, H. *Chem. Rev.* **2002**, *102*, 491−514. (d) *Recent Advances in Peptidomimetics*; Tetrahedron Symposia-in-Print, No. 83; Aubé, J., Guest Ed.; Pergamon Press: Oxford, UK, 2000; *Tetrahedron* **2000**, *56* (50).

(5) The 6,7-trans configuration of [3.2.0]-azabicycloheptanone **14** was ascertained by the absence of any NOE contact between trans-located H−C5 and H−C7.

SCHEME 3



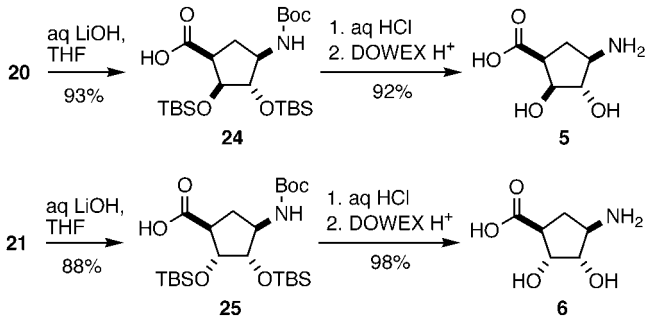
SCHEME 4



removal of the *N*-Boc function (TBSOTf, DIPEA, −15 °C) followed by *N*-Bn protection (BnCl, KH), as illustrated in Scheme 3, to give compound **15** in a 79% yield for the two steps. Acetonide deblocking (aq AcOH) and subsequent oxidative fragmentation of the diol moiety (aq $NaIO_4$) then furnished *N*-Bn-protected aldehyde **17** (92%, two steps) ready for the intramolecular aldolization step.

We were pleased to observe that addition of lactam aldehyde **17** to a 3-fold molar excess of a preformed 1:1 mixture of TBSOTf and DIPEA at room temperature resulted in complete conversion of **17** producing a 80:20 mixture of silylated bicycloheptanoids **18** and **19** in a 98% combined yield (Scheme 4). Interestingly, this annulative aldo-silylation proved to be completely chemoselective, as the DIPEA-promoted enolization exclusively involves the carbon adjacent to the lactam carbonyl group, leaving the although-acid H−C5 of the carbon atom adjacent to the formyl group unscathed. As a consequence, the

SCHEME 5



configuration of the stereocenter C5 was completely preserved. Individual bicycloheptanoids **18** and **19** were isolated in a pure state by chromatography on silica gel and readily analyzed by a combination of ^1H and ^{13}C NMR experiments. The rigid nature of the bicyclic core of these compounds facilitated the analysis, allowing us to assign their full stereostructures. In particular, the presence in both isomers of a *W* long-range coupling between the protons involved in the juncture (H−C1 and H−C4) suggested that the bicycle is cis-fused. Furthermore, the ^1H NMR coupling values between H−C2 and H−C3 ($^3J_{2,3}$ = 1.2 Hz for **18**; $^3J_{2,3}$ = 5.7 Hz for **19**) and strong NOE contacts involving H−C3−H−C4aα in **18** and H−C2−H−C3 in **19** accounted for a pseudoequatorial (2,3-trans) or pseudoaxial (2,3-cis) location of the oxygen substituent at C3 for **18** and **19**.

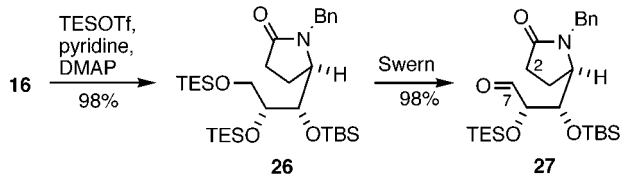
At this point we had to face the issue of disconnecting the C(O)−N lactam bond to liberate the amino and hydroxyl (or carboxyl) functions at C1 and C4. To help us in this task, we had to weaken the amide linkage by positioning a carbamate en lieu of the *N*-benzyl protection. Working in parallel, bicycles **18** and **19** were first exposed to sodium in liquid ammonia to cleave the *N*-benzyl group and then to Boc_2O in MeCN to reinstate the *tert*-butoxycarbonyl moiety. Compounds **20** and **21** were thus prepared in 96% and 94% yields, respectively (two steps). As expected, treatment of **20** and **21** with $NaBH_4$ in wet THF cleanly led to the corresponding protected cyclopentanoids **22** and **23** (88% and 98% yields), which were finally fully liberated by acidic treatment (aq HCl, THF, MeOH) followed by DOWEX (H^+ form). 4a-Carba-β-D-xylofuranose (**1**)[2b] and 4a-carba-β-D-ribofuranose (**2**)[6] were isolated in 95% and 99% yields, which correspond to 34% and 10% overall yields from the starting pyrrole **9** (12 steps each).

To access carbocyclic amino acids **5** and **6**, the lactam junction within bicycles **20** and **21** had to be opened hydrolytically, and this was favorably effected by treatment with aqueous LiOH in THF at room temperature (93% and 88% yields) (Scheme 5). Global deprotection (aq HCl, then DOWEX H^+ form) finally provided (4a-carba-β-D-xylofuranuronyl)amine (**5**) and (4a-carba-β-D-ribofuranuronyl)amine (**6**) in 92% and 98% yields, respectively (35% and 9% overall yields covering 12 steps).

Structural analysis of the target carbasugars **1** and **2**, as well as the amino acids **5** and **6**, carried out via extensive ^1H and ^{13}C NMR studies confirmed the stereochemical asset of the constructs, just as was the case for the corresponding bicyclic precursors (vide supra).[7]

(6) Boyer, S. J.; Leahy, J. W. *J. Org. Chem.* **1997**, *62*, 3976−3980.

SCHEME 6

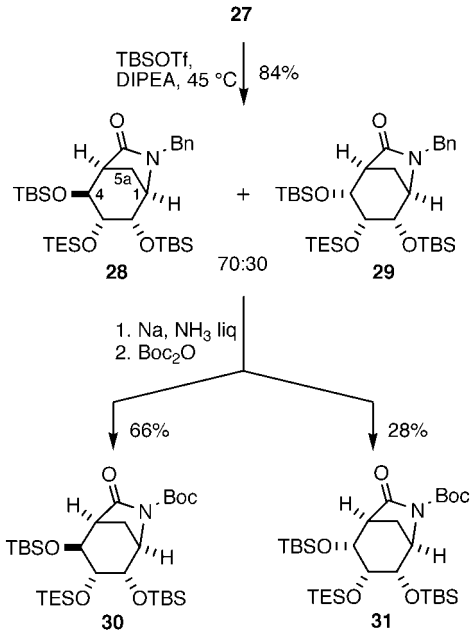


Synthesis of (5a-Carba-β-D-gulopyranosyl)amine (3), (5a-Carba-β-D-allopyranosyl)amine (4), (5a-Carba-β-D-gulopyranuronyl)amine (7), and (5a-Carba-β-D-allopyranuronyl)amine (8). To overcome the problems associated with our previous route to **3**, encountered during the LDA-assisted annulative aldolization,[2a,b] we decided to apply a revised synthetic sequence, in which the crucial carbon−carbon bond-forming reaction, which ultimately gives rise to the cyclohexane ring, was performed with use of the DIPEA/TBSOTf promoted silylative aldo-cyclization protocol exploited above. The special objective was to have a practical and scaleable procedure with the potential of delivering gram quantities of pyranosylamines **3** and **4**, as well as their amino acid counterparts **7** and **8**. The point of departure was the advanced intermediate diol **16**, which was accessed in 6 steps (56% overall yield) by the same sequence outlined in the previous section (see Schemes 2 and 3). The next stage of the synthesis (Scheme 6) required selective oxidation of the hydroxymethyl terminus of **16** to arrive at aldehyde **27**, onto which the requested C2−C7 bond connection could then be made.

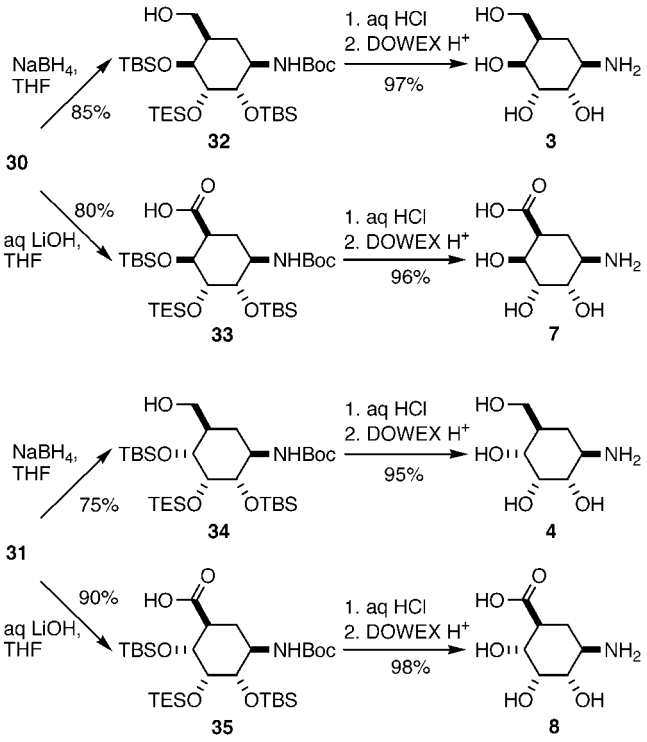
Avoiding an elaborate protection/deprotection scheme, an interesting protocol was identified, consisting of direct oxidative conversion of TES-protected carbinols to aldehydes.[8] Thus, diol **16** was first persilylated (TESOTf, pyridine, DMAP) to give TES ether **26**, which was directly subjected to Swern oxidation ($(COCl)_2$, DMSO; then Et_3N). We were pleased to find that the secondary TES-protected hydroxyl survived the oxidation conditions, allowing formation of lactam aldehyde **27** in 96% yield for the two steps. With the desired aldehyde **27** in hand, the silylative aldol cyclization with the TBSOTf-DIPEA mixture (3.3 mol equiv, rt) was investigated. As we had hoped, the cycloaddition proceeded nicely, to provide a 70:30 mixture of two bicyclooctanoid compounds, namely, the 3,4-trans-configured product **28** and the 3,4-cis-disposed isomer **29** in 84% combined yield (Scheme 7). The problems connected with the chromatographic purification and isolation of individual **28** and **29** enticed us to proceed along the synthetic path, leaving this task to be sorted out at a later stage of the synthesis. Only a small fraction of the **28**/**29** mixture was subjected to chromatographic separation enabling us to isolate **28** and **29** as pure products and completely characterize their structure.

The configuration of the reaction products was assigned as that of **28** and **29** mainly by inspection of their

SCHEME 7



SCHEME 8



1D and 2D ^{1}H NMR spectra. Because of the bicyclic structure of **28** and **29**, the six-membered ring is expected to adopt a stable $^1C_4$ conformation; therefore, the analysis was straightforward. For **28**, the $^3J_{3,4}$ was calculated to be 8.7 Hz, which suggested that both C3 and C4 hydroxy substituents are in equatorial positions. On the other hand, the $^3J_{3,4}$ value of 4.1 Hz for **29** revealed a cis-stereodisposition (equatorial-axial) for the C3 and C4 hydroxy substituents. In both compounds, the signal of H−C2 showed small couplings to the protons H−C1 and H−C3 (**28**, $^3J_{1,2}$ = 4.2 Hz and $^3J_{2,3}$ = 4.3 Hz; **29**, $^3J_{1,2}$ = 4.3 Hz and $^3J_{2,3}$ = 4.3 Hz), and this confirmed an axial

(7) Notable NOE contacts: compound **1**, H−C2−H−C4a*β*, H−C1−H−C4a*α*, H−C3−H−C4; compound **2**, H−C1−H−C4a*α*, H−C1−H−C4, H−C5a,*β*−H−C4a*β*, H−C2−H−C4a*β*; compound **5**, H−C2−H−C4a*β*, H−C1−H−C4a*α*, H−C4a*α*−H−C4, H−C3−H−C4, H−C1−H−C4; compound **6**, H−C1−H−C4a*α*, H−C1−H−C4, H−C2−H−C4a*β*, H−C3−H−C4a*β*.

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

positioning for the C2 silyloxy group. The presence of strong NOE contacts between axially located H−C4 and H−C5aα for **28** and equatorially located H−C4 and H−C5 for **29** further corroborated the assignment.

The **28**/**29** isomeric mixture was then manipulated further to arrive at either carbasugars **3** and **4** or carba-amino acids **7** and **8**. Thus, the *N*-Bn protection within **28**/**29** was first switched to *N*-Boc (Na, NH_3 liquid; then Boc_2O) delivering, after meticulous chromatographic purification on silica gel (1,2-dichloroethane/Et_2O/CH_2Cl_2 90:5:5), a 66% yield of 3,4-trans isomer **30** along with a minor amount (28%) of its C4-epimer **31**. Individual lactams **30** and **31** were then fragmented, reductively or hydrolytically, as previously disclosed for their cyclopentanoid analogues (Scheme 8). Both operations proceeded smoothly, with the reductive opening of **30** and **31** providing amino alcohols **3**[2b] and **4** (83% and 72% yield, respectively, two steps) and hydrolytic cleavage affording amino acids **7** and **8** in 77% and 88% yield, respectively.

Once the C(O)−N bond holding the five-membered ring together had been broken, the cyclohexanoid ring in compounds **3**, **4**, **7**, and **8** preferentially assumed a $^4C_1$ conformation where the majority of substituents were able to lie in the equatorial position. With the ^{1}H NMR spectra of these four compounds easy to interpret, it was not at all difficult to decipher the stereostructures on the basis of H−H coupling constants and NOE contacts of ^{1}H−^{1}H NOESY spectra.[9]

Conclusions

A highly efficient, "chiral-pool" synthetic grid delivering preparatively useful yields of amino alcohols **1**−**4** and amino acids **5**−**8** has been established. As foreseen in the retrosynthetic analysis of Scheme 1, the carbasugar products were assembled by conjoining two readily accessible substructures, TBSOP **9** (ex pyrrole) and glyceraldehyde **10** (ex D-mannitol). The pathways are highlighted by three key transformations: (1) a crossed vinylogous Mukaiyama-type aldolization to install the first carbon−carbon juncture between **9** and **10**; (2) a novel silylative cycloaldolization[10] to implement the second carbon−carbon linkage and complete the construction of the desired cyclopentanoid and cyclohexanoid structures; and (3) a reductive or hydrolytic cleavage of the lactam tether, which liberates both the amino and the hydroxymethyl or carboxyl functionalities within the cyclitol frames. This approach, whose scope could be enlarged to include aldehyde acceptors other than D-glyceraldehyde, enabled us to provide preparatively useful quantities of enantiopure amino alcohol or amino acid entities with which many diverse, oxygen-decorated oligomeric architectures may be assembled.

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Supporting Information Available: Experimental details and characterization data for all synthesized compounds and ^{1}H and ^{13}C NMR spectra of compounds **1**−**8**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) Notable NOE contacts: compound **3**, H−C1−H−C5, H−C2−H−C5a*β*; compound **4**, H−C2−H−C5a*β*, H−C1−H−C5, H−C4−H−C5a*β*, H−C5−H−C5aα; compound **7**, H−C1−H−C5, H−C2−H−C5a*β*; compound **8**, H−C2−H−C4, H−C4−H−C5a*β*, H−C2−H−C5a*β*, H−C1−H−C5.

(10) For a related silylative Michael−aldol annulation, see: Takasu, K.; Ueno, M.; Ihara, M. *J. Org. Chem.* **2001**, *66*, 4667−4672.