JOC Article

# Variable Strategy toward Carbasugars and Relatives. 5.[1] Focus on Preparation of Chiral Nonracemic Medium-Sized Carbocycles

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The feasibility of sequential vinylogous aldol (intermolecular)/silylative aldol (intramolecular) addition reactions involving furan- and pyrrole-based dienoxysilanes, **6** and 1**2**, in the synthesis of carbasugar frameworks is illustrated by the preparation of the scantily investigated carbaseptanose and carbaoctanose representatives of this class of compounds. The target compounds, **1**, **2**, **3**, *ent*-**2**, *ent*-**3**, and **4**, were obtained from readily available carbohydrate precursors (**5** and **19**) in yields of 21−30% over 8−12 steps. The irreversible silylative ring-closing aldolisation of $\gamma$-substituted dihydro-5*H*-furan-2-one and pyrrolidin-2-one aldehydes (**9**, **16**, *ent*-**16**, and **22**) driven by the TBSOTf/$Pr^{i}_{2}EtN$ Lewis acid−Lewis base couple was shown to be a practical, diastereoselective maneuver to forge the densely functionalized, medium-sized core carbocycles.

## Introduction

Just as Nature has elected, for its various functions, the five- and six-membered ring monosaccharides as favorite structural motifs[2] while neglecting the ring-expanded homologues,[3] organic synthesis practitioners, in their quest for novel sugar-product mimicking entities, have dedicated themselves to the construction of cyclopentane and cyclohexane polyols[4] while pushing the higher carbocycles into the sidelines of their interests.[5] The scanty occurrence of medium-sized-ring sugar analogues and the unforeseen biological properties these structures could display, in conjunction with our long-standing interest in the construction of differently shaped carbocycles,[1,6] prompted us to embark on a synthetic venture targeting a set of cycloheptanoid and cyclooctanoid carbasugars in a nonracemic format. From the synthetic perspective, the challenging feature of these carbocycles lies in the long carbon chain adorned by multiple, adjacent chiral centers and in its being blocked in a macrocyclic motif.

As a further addition to the works of this series,[1,6] herein we describe, in full, the total asymmetric synthesis of a small repertoire of medium-sized carbasugars, comprising septanoses **1**, **2**, **3**, *ent*-**2**, and *ent*-**3** (6a-

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(1) 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.

(2) (a) Dwek, R. A. *Chem. Rev.* **1996**, *96*, 683−720. (b) Varki, A. *Glycobiology* **1993**, *3*, 97−130. (c) *Glycoscience: Chemistry and Chemical Biology*; Fraser-Reid, B., Tatsuta, K., Thiem, J., Eds.; Springer-Verlag: Berlin, 2001; Vols. I−III.

(3) For selected references on the synthesis of septanose and octanose derivatives, see: (a) Defaye, J.; Gadelle, A.; Movilliat, F.; Nardin, R.; Baer, H. H. *Carbohydr. Res.* **1991**, *212*, 129−157. (b) Baschang, G. *Liebigs Ann. Chem.* **1963**, *663*, 167−173. Maier, M. E. *Angew. Chem., Int. Ed.* **2000**, *39*, 2073−2077. (c) Gurjar, M. K.; Chakrabarti, A.; Rao, B. V.; Kumar, P. *Tetrahedron Lett.* **1997**, *38*, 6885−6888. (d) Ng, C. J.; Stevens, J. D. *Methods Carbohydr. Chem.* **1968**, *7*, 7−14. (e) Butcher, M. E.; Ireson, J. C.; Lee, J. B.; Tyler, M. J. *Tetrahedron* **1977**, *33*, 1501−1507.

(4) (a) *Carbohydrate Mimics: Concepts and Methods*; Chapleur, Y., Ed.; Wiley-VCH: Weinheim, 1998. (b) Suami, T. *Top. Curr. Chem.* **1990**, *154*, 257−283. (c) Suami, T.; Ogawa, S. *Adv. Carbohydr. Chem. Biochem.* **1990**, *48*, 21−90. (d) Crimmins, M. T. *Tetrahedron* **1998**, *54*, 9229−9272.

(5) For selected references on the synthesis of carbaseptanose and carbaoctanose derivatives, see: (a) Wang, W.; Zhang, Y.; Sollogoub, M.; Sinaÿ, P. *Angew. Chem., Int. Ed.* **2000**, *39*, 2466−2467. (b) Wang, W.; Zhang, Y.; Zhou, H.; Blériot, Y.; Sinaÿ, P. *Eur. J. Org. Chem.* **2001**, 1053−1059. (c) Marco-Contelles, J.; de Opazo, E. *J. Org. Chem.* **2002**, *67*, 3705−3717. (d) Marco-Contelles, J.; de Opazo, E. *J. Org. Chem.* **2000**, *65*, 5416−5419. (e) Hanna, I.; Ricard, L. *Org. Lett.* **2000**, *2*, 2651−2654. (f) Boyer, F.-D.; Hanna, I.; Nolan, S. P. *J. Org. Chem.* **2001**, *66*, 4094−4096. (g) van Hooft, P. A. V.; Litjens, R. E. J. N.; van der Marel, G. A.; van Boeckel, C. A. A.; van Boom, J. H. *Org. Lett.* **2001**, *3*, 731−733. (h) McNulty, J.; Grunner, V.; Mao, J. *Tetrahedron Lett.* **2001**, *42*, 5609−5612. (i) Pearson, A. J.; Katiyar, S. *Tetrahedron* **2000**, *56*, 2297−2304. (j) Roy, A.; Chakrabarty, K.; Dutta, P. K.; Bar, N. C.; Basu, N.; Achari, B.; Mandal, S. B. *J. Org. Chem.* **1999**, *64*, 2304−2309. (k) Patra, R.; Bar, N. C.; Roy, A.; Achari, B.; Ghoshal, N.; Mandal, S. B. *Tetrahedron* **1996**, *52*, 11265−11272. (l) Le Merrer, Y.; Gravier-Pelletier, C.; Maton, W.; Numa, M.; Depezay, J.-C. *Synlett* **1999**, 1322−1324. (m) Gravier-Pelletier, C.; Maton, W.; Lecourt, T.; Le Merrer, Y. *Tetrahedron Lett.* **2001**, *42*, 4475−4478. (n) Blériot, Y.; Giroult, A.; Mallet, J.-M.; Rodriguez, E.; Vogel, P.; Sinay, P. *Tetrahedron: Asymmetry* **2002**, *13*, 2553−2565.

(6) (a) 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. (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) Rassu, G.; Auzzas, L.; Pinna, L.; Battistini, L.; Zanardi, F.; Marzocchi, L.; Acquotti, D.; Casiraghi, G. *J. Org. Chem.* **2000**, *65*, 6307−6318.

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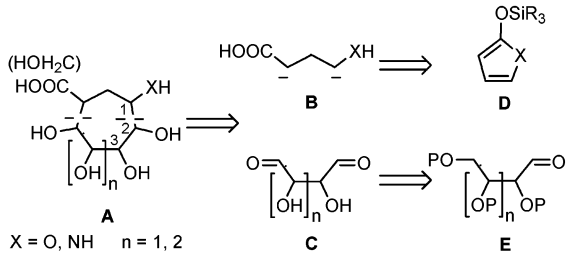
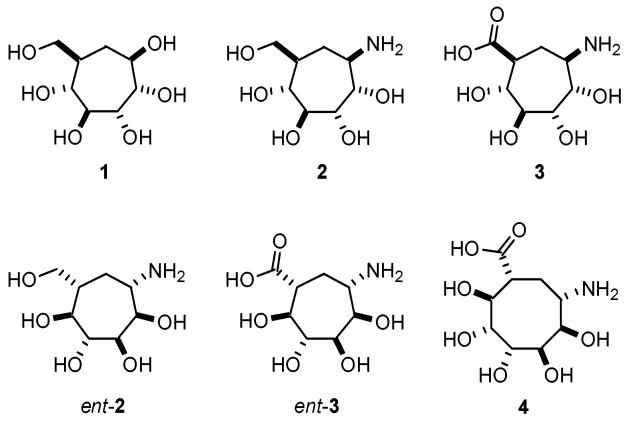
**SCHEME 1**




carbaheptoseptanoses), as well as octanose **4** (7a-carbaoctooctanose).[7]

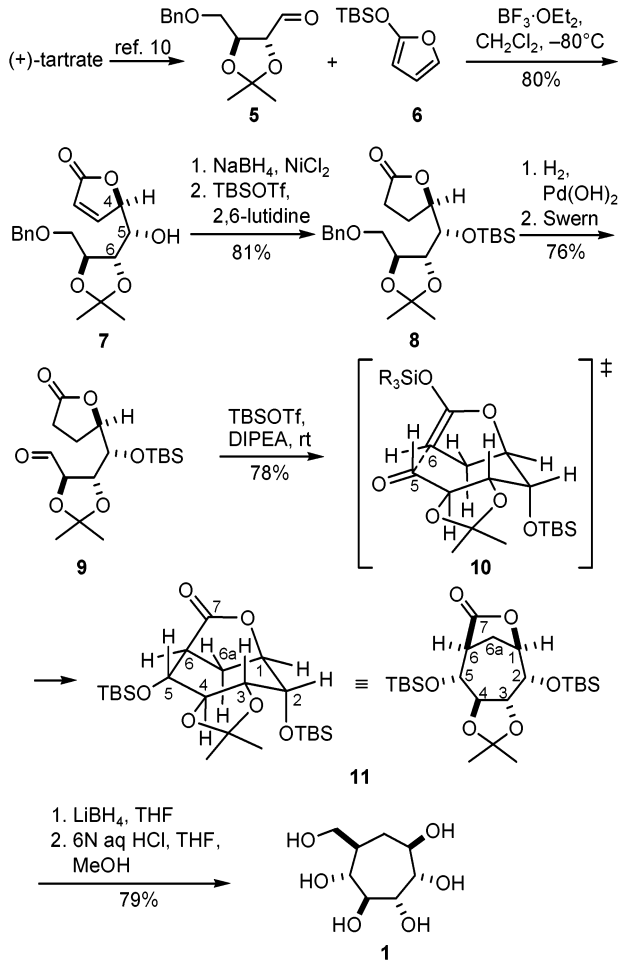



**Synthetic Strategy.** Our analysis of the generic target **A** (Scheme 1) emphasized two strategic disconnections of the macrocycle, along the two carbon−carbon bonds C(1)−C(2) and C(5)−C(6) ($n = 1$) or C(6)−C(7) ($n = 2$). This unveiled two subunits that trace the top half back to the butanoic acid dianion **B** and the bottom half to the hydroxylated dicarbonyl frame **C**. Our experience in these constructs enticed us to correlate fragment **B** to the heterocyclic dienoxysilanes **D** (X = O, NR)[8] and fragment **C** to the four-membered and five-membered aldoses **E**. In the synthetic direction, we envisioned the C(1)−C(2) junction first to be installed via a vinylogous crossed aldolization of dienoxysilanes **D** with aldoses **E**,[9] followed by completion of the macrocycle via a cycloaldolization maneuver. In substance, this design is flexible, and one can easily imagine various heterocyclic dienoxysilanes as precursors to the top half of the ring and a wide range of readily available, ex chiral-pool synthons for the bottom half, the nature of which ultimately dictates ring size and chirality.

## Results and Discussion

**Synthesis of Carbaseptanose 1.** Our point of departure for construction of carbasugar **1** was the known L-threose **5**, prepared in four steps from (*R*,*R*)-tartaric acid dimethyl ester (Scheme 2).[10] Boron trifluoride assisted vinylogous aldol reaction between aldehyde **5** and 2-[(*tert*-butyldimethylsilyl)oxy]furan (**6**) proceeded smoothly to provide the butenolide adduct **7** both in a high yield (80%) and excellent diastereomeric excess (>95%). The 4,5-*threo*-5,6-*erythro* configuration of **7**[11] was only hypothesized at this point, principally on the basis of our previous experiences where intermolecular vinylogous aldol addition reactions between heterocyclic silyloxydienes (e.g., **6** and **12**) and chiral nonracemic α-alkoxyaldehydes (e.g., 2,3-*O*-isopropylidene-D-glyceraldehye) inexorably gave rise to a highly diastereoselective behavior in favor of aldol adducts with a 4,5-*threo*-5,6-*erythro* relative configuration.[8] In such instances, a Felkin−Ahn-type induction was called upon to justify the facial (5,6-*erythro*) diastereoselectivity, whereas a sterically and an electronically favorable Diels−Alder-like transition state was contemplated to account for the simple (4,5-*threo*) diastereoselectivity observed.[8] The relative and absolute configurations of the stereocenters within **7** were eventually confirmed at a later stage of

**SCHEME 2**




(7) For a comprehensive, updated treatise on sugar and carbasugar nomenclature, see: McNaught, A. D. *Carbohydr. Res.* **1997**, *297*, 1−92.

(8) (a) 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. (b) Rassu, G.; Zanardi, F.; Battistini, L.; Casiraghi, G. *Chem. Soc. Rev.* **2000**, 109−118. (c) Rassu, G.; Zanardi, F.; Battistini, L.; Casiraghi, G. *Synlett* **1999**, 1333−1350.

(9) Casiraghi, G.; Zanardi, F.; Appendino, G.; Rassu, G. *Chem. Rev.* **2000**, *100*, 1929−1972.

(10) (a) Mukaiyama, T.; Suzuki, K.; Yamada, T.; Tabusa, F. *Tetrahedron* **1990**, *46*, 265−276. (b) Hungerbühler, E.; Seebach, D. *Helv. Chim. Acta* **1981**, *64*, 687−702.

(11) A handy form of numeration was adopted throughout this text both for the intermediate and target compounds which does not correspond to IUPAC nomenclature. IUPAC nomenclature was, however, adopted in the Supporting Information chapter of the Experimental Section.

the synthesis (vide infra) and were found to agree with the hypothetical assignments.

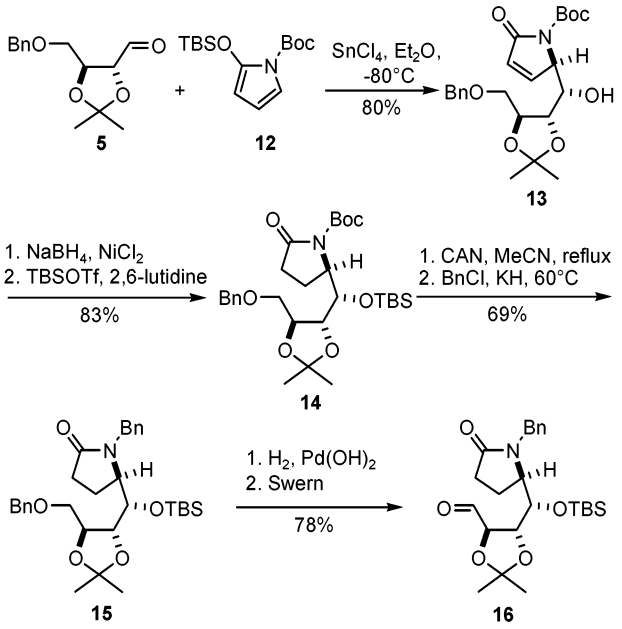
Chemoselective saturation of the butenolide double bond ($NiCl_2$, $NaBH_4$),[12] followed by silylation (TBSOTf, 2,6-lutidine) delivered orthogonally protected lactone **8** in a 81% yield (two steps). Installation of the terminal formyl function to give aldehyde **9** was performed via two clean maneuvers, namely, debenzylation of the primary carbinol group ($H_2$, $Pd(OH)_2$) followed by Swern oxidation; the overall yield from **8** was 76% (two steps). The crucial cycloaldolization reaction that installs the heptanoid ring was carried out on aldehyde **9** using a highly efficient, direct silylative protocol driven by the TBSOTf/DIPEA reagent mixture at room temperature.[1] To our pleasure, this operation furnished silylated 4,5-*trans*-configured tricyclic compound **11** in a 78% yield, with little, if any, diastereomeric contamination (<2%). Presumably, this transformation proceeds via transition state **10**, where the aldehyde acceptor site exposes its *re* face to the incoming C(6)-enolate donor (*re* face). Indeed, the conformational restraint impressed onto the aldehyde side chain by the acetonide group at C(3)−C(4) together with the possibility of allocating the C(5)-siloxyl group of product **11** in a thermodynamically favorable pseudoequatorial position emerge as crucial factors in driving the reaction toward the stereochemical outcome disclosed in this study. The structure of **11** was secured via extensive spectroscopic analysis. As a result of the conformationally locked nature of **11**, $^1$H NMR diagnosis was straightforward, allowing complete assignment of the relative and absolute stereochemistry as 1*R*,2*S*,3*S*,4*S*,5*R*,6*S*.[13] It should be emphasized at this point that the stereochemistry in **7**, **8**, and **9** was thus established, as shown.

Having secured the construction of the seven-membered carbon ring, synthesis of **1** was completed by reductive opening of the lactone moiety ($LiBH_4$), followed by global deprotection (6 N aqueous HCl, THF, MeOH; 79%, two steps). Chiral nonracemic *β*-D-*glycero*-D-*gulo*-configured carbasugar **1** was thus successfully synthesized via a highly diastereoselective, eight-step sequence with a good 30% global yield from **6**.

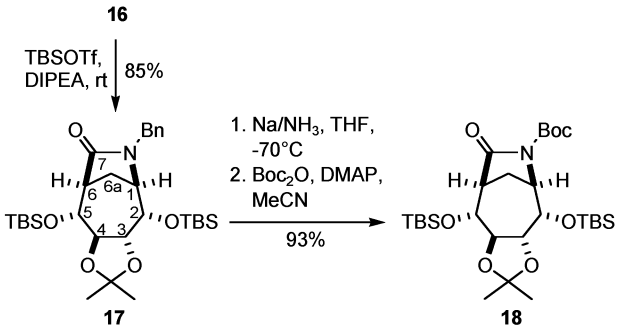
**Synthesis of Aminocycloheptane Derivatives 2 and 3.** The aminated nature of the title compounds called for the use of pyrrole-based building block **12**, which yields the upper four carbon atoms of the targeted constructs. At first, aldol coupling between *N*-(*tert*-butoxycarbonyl)-2-[(*tert*-butyldimethylsilyl)oxy]pyrrole (**12**) and aldehyde **5** under $SnCl_4$ guidance furnished the desired unsaturated lactam **13** in a 80% yield with little or no recovery of other diastereomeric isomers (Scheme 3). Even in this case, the considerations made for compound **7** led to the preliminary 4,5-*threo*-5,6-*erythro* stereoassignment of compound **13** (vide supra).

Paralleling the previously disclosed protocol of **1**, compound **13** was then converted into fully protected intermediary compound **14** (83% yield, two steps). With the crucial cycloaldolization step in mind and having

**SCHEME 3**




**SCHEME 4**




learnt from previous experience that the *N*-Boc protection does not tolerate our reaction promoter (TBSOTf-DIPEA),[1] we were obliged to change the protecting group to a *N*-Bn group. Thus, *N*-Boc-protected lactam **14** was transformed into the corresponding *N*-benzyl derivative **15** via chemoselective removal of the carbamoyl protection (CAN, MeCN)[14] followed by benzylation (BnCl, KH, 60 °C) (69%, two steps). Subsequent elaboration of **15** into aldehyde **16** occurred smoothly, by selective oxygen debenzylation ($H_2$, $Pd(OH)_2$) and Swern oxidation (78%, two steps).

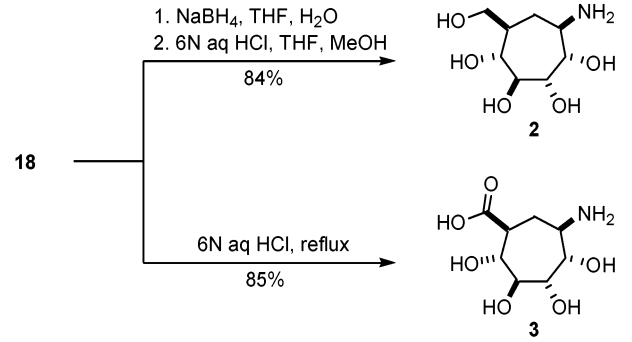
We were now ready to install the requisite seven-membered cycle via the proposed silylative intramolecular aldol reaction (Scheme 4). Once again, the TBSOTf/DIPEA couple proved an ideal candidate to drive this pivotal maneuver to success. Indeed, when aldehyde **16** was exposed to 3.0 mole equiv of the amine/triflate mixture, tricyclic adduct **17** was formed, in a good 85% isolated yield. Remarkably, 4,5-*trans*-configured compound **17** was obtained as the single diastereoisomer, with complete consumption of the starting aldehyde **16**. As for oxygenated compound **11**, the stereostructure of **17** was unambiguously ascertained via $^1$H NMR spectroscopy and NOE studies.[13]

(12) Caggiano, T. J. In *Handbook of Reagents for Organic Synthesis. Oxidizing and Reducing Agents*; Burke, S. D., Danheiser, R. L., Eds.; Wiley: Chichester; 1999; pp 246−250.

(13) Selected $^1$H NMR resonances, coupling constants, and $^1$H−$^1$H NOE contacts for **11**, **17**, and **23** are reported in Supporting Information (Tables S1−S3).

(14) Hwu, J. R.; Jain, M. L.; Tsay, S.-C.; Hakimelahi, G. H. *Tetrahedron Lett.* **1996**, *37*, 2035−2038.

**SCHEME 5**




Because of the reluctance of *N*-benzyl lactams to undergo both hydrolytic and reductive amide fission, it was necessary at this point to remove the benzyl group in **17** and substitute it with a carbamate moiety. This was cleanly effected by a standard treatment with sodium in liquid ammonia followed by exposure to $Boc_2O$ (93%, two steps).

Lactam **18** thus formed represents a branching point in the synthesis where one can imagine this key precursor giving rise to either aminated polyols (via reductive opening) or carbocylic $\gamma$-amino acids (via hydrolytic opening) (Scheme 5).

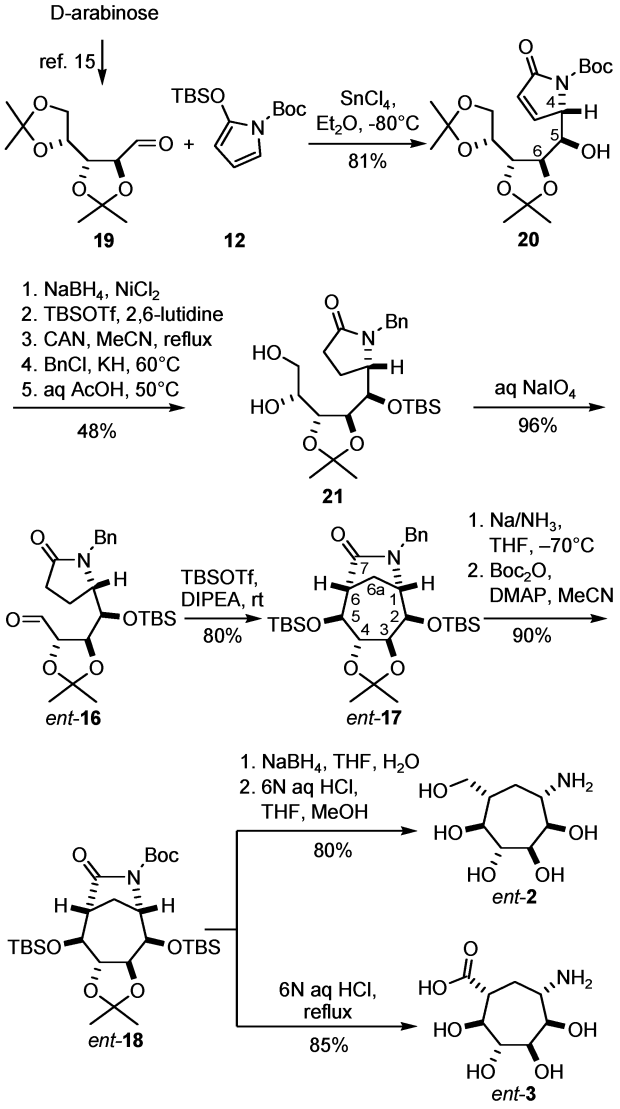
This did indeed turn out to be the case, and lactam reduction ($NaBH_4$, THF, $H_2O$) followed by complete deprotection (6 N aqueous HCl, THF, MeOH) led smoothly to the amino carbasugar **2** (84% yield, two steps), whereas its direct hydrolysis (6 N aqueous HCl) yielded the expected amino acid **3** (85% yield). On the whole, starting from **5**, synthesis of carbasugar **2** encompassed 12 individual steps and gave a global yield of 24%, whereas preparation of amino acid **3** necessitated 11 steps for a total yield of 24%.

**Synthesis of Aminocycloheptanes *ent*-2 and *ent*-3 and Aminocyclooctane 4.** In pursuing synthetic divergency, the scaffolding of the lower part of the target compounds necessitated a common aldose embodied with the possibility of either yielding a polyol frame four carbon atoms long (to enter *ent*-**2** and *ent*-**3**) or giving rise to a five carbon atom length (for compound **4**). Our choice fell on 2,3:4,5-di-*O*-isopropylidene-D-arabinose (**19**) (Scheme 6), easily obtainable from inexpensive D-arabinose,[15] as its carbon skeleton could be shortened by one carbon atom or left as such.

Initially we proceeded as already planned, with the first step being the $SnCl_4$-promoted vinylogous aldol reaction between arabinose **19** and pyrrole **12**. As we expected, the reaction worked efficiently to form nine-carbon lactam **20** in a 81% yield and with a gratifying 98% diastereoselectivity. At this point, the 4,5-*threo*-5,6-*erythro* configuration of **20** was only a hypothesis based on the considerations made for the previous analogues **7** and **13** and was confirmed at a later stage in the synthesis.

The divergent lactam intermediate **21** was then accessed by a five-step sequence encompassing reduction of the carbon−carbon double bond, silylation, changing

**SCHEME 6**

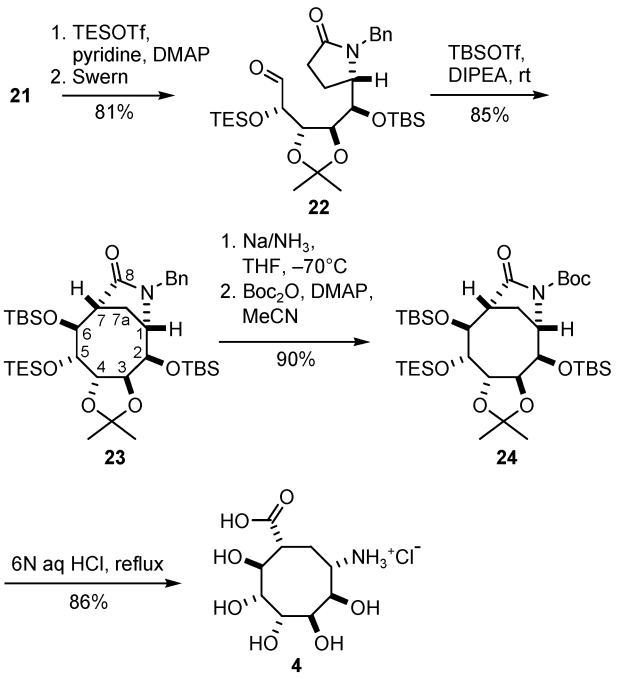



*N*-Boc protection for *N*-Bn, and selective removal of the terminal acetonide blockage (48% overall yield). Focusing on seven-membered structures *ent*-**2** and *ent*-**3** and to achieve a chemical correlation with their respective enantiomers **2** and **3** already mentioned, the polyol chain in **21** was oxidatively shortened by one carbon atom (aqueous $NaIO_4$) to furnish aldehyde *ent*-**16**, whose spectral characteristics proved identical in all respects to the spectral data derived from **16**, apart from chiroptical data, which proved to be opposite in sign {e.g., *ent*-**16**, $[\alpha]^{20}_D = +21.4$ (*c* 0.7, $CHCl_3$); **16**, $[\alpha]^{20}_D = -21.0$ (*c* 1.2, $CHCl_3$)}.

From here onward, we paralleled the chemistry previously disclosed for the enantiomeric series (vide supra). In short, *ent*-**16** was elaborated to *ent*-**18** (via *ent*-**17**, 72% yield, three steps), the useful precursor for both the amino carbasugar *ent*-**2** (80% yield, two steps) and the amino acid *ent*-**3** (85% yield). This arabinose-based synthesis provided *ent*-**2** within 12 steps (22% global yield) and *ent*-**3** within 11 steps (23% global yield), with a synthetic efficiency comparable to that of the above-discussed synthesis of enantiomers **2** and **3** from L-threose.

(15) (a) Zinner, H.; Brandner, H.; Rembarz, G. *Chem. Ber.* **1956**, *89*, 800−813. (b) Zinner, H.; Wittenburg, E.; Rembarz, G. *Chem. Ber.* **1959**, *92*, 1614−1617.

**SCHEME 7**




On the other hand, **21** in maintaining all of its carbon length lent itself to forge cyclooctane amino acid **4** (Scheme 7). After persilylation (TESOTf, pyridine, DMAP), an adaptation of the Swern oxidation was chosen to arrive at aldehyde **22**.[16] This direct variation uses a strong excess of reagents and calls for higher temperatures to attain oxidation. The resulting compound **22** was obtained in a 81% yield over the two steps.

At this point, the formation of the eight-membered ring awaited the decisive step of ring closure. We embarked on this step with some trepidation, well aware of the problems aldol-based macrocyclization inherently presents.[17] However, exposure of **22** to the aforementioned TBSOTf/DIPEA reagent mixture (0.1 M $CH_2Cl_2$) pleasingly afforded tricycle **23** as the only product detectable in an 85% yield. Whereas the configurations of the C(1)−C(5) stereocenters of **23** had already been established (vide supra), the stereochemistry of C(6) and C(7) had yet to be ascertained and this was evinced through extensive $^1$H NMR and NOE evaluation.[13]

Swapping the *N*-benzyl protection within **23** for the Boc group proceeded smoothly to deliver lactam **24**, which was readily transformed into novel $\beta$-L-*erythro*-D-*manno*-configured cyclooctane amino acid **4** via exposure to refluxing 6 N aqueous HCl.[18] Thus, completion of **4** was achieved in a 86% yield, corresponding to a remarkable 21% overall yield for the 12-step sequence from arabinose aldehyde **19**. Unlike cycloheptane lactams **18** and *ent*-**18**, the amide bond within cyclooctanoid **24** proved extremely reluctant to reductive fragmentation, thus precluding direct access to the corresponding cyclooctanose amino carbasugar. For example, exposure of **24** to 10-fold molar excess $NaBH_4$ in wet THF left its structure unmarred, while a prolonged $LiAlH_4$ treatment only resulted in partial cleavage of NBoc and OTES protections. Equally unproductive was the use of $LiBH_4$ where the reduction of the amide functionality drew to a close with hemiaminal formation.[19]

## Summary

An adaptable, ex chiral-pool synthesis of scarcely represented medium-sized carbasugar compounds has been established. Key features of the unified synthetic scheme include the stereocontrolled construction of the multifunctional carbon framework of the targeted molecules via a vinylogous Mukaiyama-aldol reaction and the assembly of the medium-sized cyclic domain via diastereoselective intramolecular silylative aldolization. Installation of the exocyclic hydroxymethyl or carboxylic groups was eventually achieved by simple reductive or hydrolytic fragmentations. As demonstrated by the preparation of chiral nonracemic carbaseptanoses **1**, **2**, **3**, *ent*-**2**, and *ent*-**3** and carbaoctanose **4**, our methodology proved feasible, stereocontrolled, and synthetically efficient, with overall yields ranging from 21% to 30% for 8- to 12-step sequences. The successful exploitation of the silylative aldol annulation in the implementation of seven- and eight-membered ring systems presents itself as a viable solution to the challenging task of assembling these expanded carbocyclic motifs and establishes the basis for future applications.

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**Supporting Information Available:** Experimental details and characterization data for all synthesized compounds and $^1$H NMR resonances, coupling constants, and $^1$H−$^1$H NOE correlations for **11**, **17**, and **23** (Tables S1−S3). This material is available free of charge via the Internet at http://pubs.acs.org.

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

(17) (a) Molander, G. *Acc. Chem. Res.* **1998**, *31*, 603−609. (b) Illuminati, G.; Mandolini, L. *Acc. Chem. Res.* **1981**, *14*, 95−102. (c) Yet, L. *Chem. Rev.* **2000**, *100*, 2963−3008. (d) Yet, L. *Tetrahedron* **1999**, *55*, 9349−9403. (e) Petasis, N. A.; Patane, M. A. *Tetrahedron* **1992**, *48*, 5757−5821. (f) Mehta, G.; Singh, V. *Chem. Rev.* **1999**, *99*, 881−930.

(18) Contrary to the observations made for its seven-membered analogues **3** and *ent*-**3**, cyclooctane **4** showed a strong propensity towards reannulation into the bicyclic lactam. For this reason, compound characterizations were carried out on the hydrochloride salt.

(19) A less straightforward attempt to convert intermediate **24** to the corresponding amino-carbasugar via sequential hydrolytic opening (LiOH, aqueous THF) and reduction was frustrated owing to the unpredictable robustness of the C(O)-NH linkage.