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New Enantioselective Entry to Cycloheptane Amino Acid Polyols

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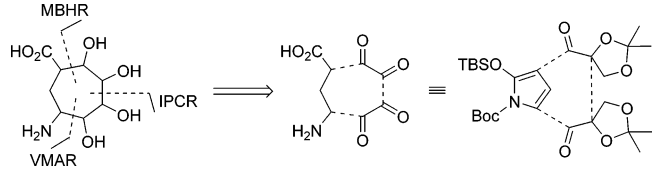

A diversity-oriented protocol has been developed for the assembly of densely hydroxylated cycloheptane amino acids via succession of a vinylogous Mukaiyama aldol reaction (VMAR), a Morita−Baylis−Hillman reaction (MBHR), and an intramolecular pinacol coupling reaction (IPCR). The plan utilizes D- or L-configured glyceraldehyde derivatives as "chiral" surrogates of glyoxal and *N*-[(*tert*-butoxycarbonyl)-2-(*tert*-butyldimethylsilyl)oxy]pyrrole as the synthetic equivalent of the α,γ-dianion of γ-aminobutanoic acid. The parallel, asymmetric syntheses of four cycloheptane representatives proceed with high diastereocontrol and virtually complete enantioselectivity in ten steps and overall yields of 15−37%.

Introduction

As difficult as they are to craft and as rare as they appear to be in nature, densely hydroxylated, medium-sized carbocyclic amino acids are intriguing molecular entities as they bring together in a robust, all-carbon ring the amine and carboxylic functionalities as well as the unique features of carbohydrates.[1,2] Our perception is that the merging of amino acid traits with a polyol carbohydrate frame into a structurally defined carbocycle would allow for unprecedented nature-like, and yet unnatural, hybrid structures to be used as ring-expanded sugar mimetics and conformationally restrained amino acid scaffolds as well.[3−5] Given the structural complexity of such frameworks arising from extensive and contiguous substitutions and the lack of general avenues to access them,[6] we deemed the development of an enantioselective entry into this area, enabling vast constitutional and stereochemical variations, our prime goal.

A few years ago, the synthetic potential of dienoxy pyrrole scaffolds of type **IV** (Scheme 1) was exploited to access densely functionalized, medium-sized carbocycles **I** by a first generation plan based on two key disconnections along the C5−C6 and C1−C2 linkages.[7] There, a vinylogous Mukaiyama aldol reaction (VMAR) and an intramolecular silylative aldol reaction (ISAR) were combined to install the requisite carbon−carbon

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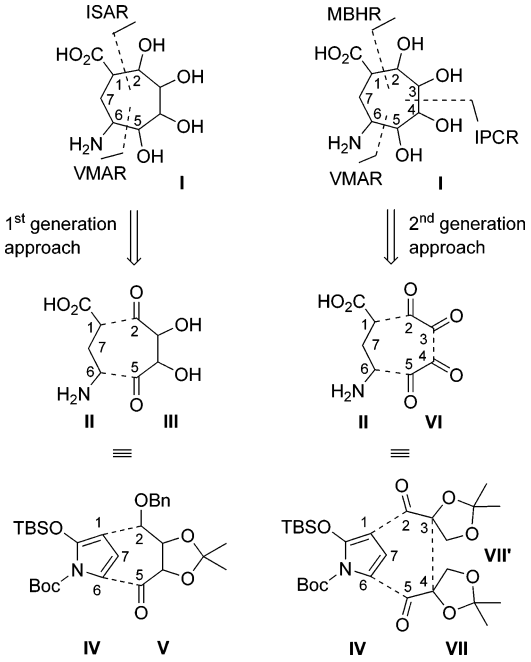
SCHEME 1. First and Second Generation Retrosyntheses of Cycloheptane Amino Acid Polyols Highlighting the Key Carbon−Carbon Bond Connections and Precursors[a]



[a] Only the option to seven-membered rings is depicted, for clarity. VMAR = vinylogous Mukaiyama aldol reaction. ISAR = intramolecular silylative aldol reaction. MBHR = Morita−Baylis−Hillman reaction. IPCR = intramolecular pinacol coupling reaction.

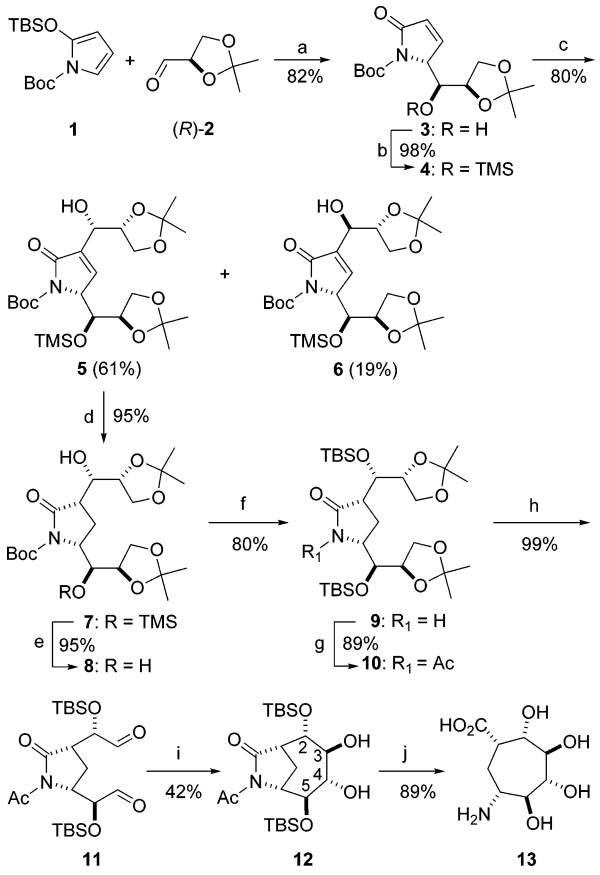
bonds, with aldehyde **V** involved as the reaction component. In this paper, a second generation approach is presented, highlighted by three disconnections of **I** along the C5−C6, C3−C4, and C1−C2 bonds. Here, pyrrole **IV** serves as the synthetic equivalent of an α,γ-dianion of γ-aminobutanoic acid **II**, and aldehydes **VII**−**VII′** serve as "chiral" surrogates of glyoxal **VI**.

In the synthetic direction, three sequential carbon−carbon bond-forming maneuvers are planned: a VMAR operation installing the C5−C6 connection, a Morita−Baylis−Hillman reaction (MBHR) forming the C1−C2 bond, and an intramolecular pinacol coupling reaction (IPCR) closing the cycle at C3−C4. From the perspective of diversity-oriented syntheses, this new scheme seems to possess an added asset in that it not only provides access to stereochemically diverse congeners by varying the stereochemistry of the starting chiral components but also permits a unified approach to differently sized cycloalkane structures simply by varying the size of the aldehyde synthons. This concept is demonstrated here by the asymmetric synthesis of two pairs of enantiomeric cycloheptane amino acids, namely, novel β-D-*glycero*-L-*ido*-configured polyol **13** and β-L-*glycero*-D-*ido*-configured polyol **31**, as well as known β-D-*glycero*-D-*gulo*-configured polyol **21** and β-L-*glycero*-L-*gulo*-configured polyol **32**.[7]

Results and Discussion

We began construction of **13** by using pyrrole-based dienoxy silane **1** and exploiting *R*-configured glyceraldehyde (*R*)-**2** twice in both the VMAR[8] and MBHR[9] reactions (Scheme 2). Thus, pyrrole **1** was coupled to (*R*)-**2** under the guidance of $SnCl_4$ in diethyl ether at −90 °C leading to known crystalline pyrrolinone **3** in a remarkable 82% yield with no trace of diastereomeric

SCHEME 2. Synthesis of Amino Acid 13 Using the Option 1 + (*R*)-2 + (*R*)-2[a]



[a] Reagents and conditions: (a) $SnCl_4$, Et_2O, −90 °C; (b) TMSCl, pyridine, 20 °C; (c) (*R*)-**2**, PhSeLi, THF, −90 °C; (d) H_2, Pd/C, EtOAc; (e) citric acid, MeOH, 20 °C; (f) TBSOTf, 2,6-lutidine, CH_2Cl_2, 20 °C and then CAN, MeCN, 80 °C; (g) Ac_2O, Et_3N, DMAP, MeCN, 70 °C; (h) H_5IO_6, EtOAc, 20 °C; (i) SmI_2, MeOH, THF, −90 to −50 °C; (j) 6 N aq HCl, 100 °C and then DOWEX.

contamination.[10] After standard protection of the alcohol as trimethylsilyl ether **4**, installation of a second polyol appendage at the α-position of the lactam moiety was carried out as planned, via a variant of the Morita−Baylis−Hillman reaction. Accordingly, a 1:2 mixture of lactam **4** and aldehyde (*R*)-**2** was treated with a solution of PhSeLi (1.6 molar equiv) in THF at −90 °C for 2 h, circumstances that led directly to the formation of adducts **5** (61%) and **6** (19%). We came across these somewhat scantily exploited experimental conditions[11] after a systematic investigation in which several standard MBHR conditions were unsuccessfully employed. At this point, the absolute configuration at the newly created stereocenter of both **5** and **6** was only tentative, assuming that the major isomer would result from a Felkin-type attack of **4** onto aldehyde (*R*)-**2**. This point was proven beyond doubt later in the synthesis.

Targeting cycloheptane **13**, we processed the major isomer **5**, but **6** was not abandoned (vide infra). Taking into account

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(11) Jauch, J. *J. Org. Chem.* **2001**, *66*, 609−611.

the forthcoming problem of seven-membered ring formation via an intramolecular pinacol coupling reaction (IPCR), which demands a relative cis orientation of the two precursor moieties involved in the annulation, saturation of the carbon−carbon double bond within **5** was affected via diastereoselective hydrogenation under catalytic heterogeneous conditions (H_2, Pd/C, EtOAc, room temperature) providing 3,5-cis-disposed pyrrolidinone **7** exclusively.

Having positioned both the polyol appendages on the pyrrolidinone nucleus, we now had to proceed with the bilateral manipulation of the side chains to arrive at dialdehyde **11**. Removal of the TMS group was thus carried out under mild acidic conditions producing lactam **8**, which was conveniently transformed to **10** via standard operations, namely, bis silylation and an *N*-Boc to *N*-Ac protection switch (68% yield, three steps). To arrive at **11**, we capitalized on a remarkable hydrolytic−oxidative protocol which could guarantee bilateral acetonide deprotection and oxidative one-carbon shortening in a single operation, using solid metaperiodic acid in ethyl acetate.[12] Thus, **10** was quantitatively converted to aldehyde **11** which proved to be both stable and storable.

The structure of the IPCR precursor **11** was designed in such a way that the local conformational restriction imposed by the pyrrolidinone ring would favor the pinacol annulation. Our assumption was confirmed by the successful IPCR using a SmI_2-assisted protocol.[13] Thus, exposure of **11** to freshly prepared SmI_2 (3.0 molar equiv, 0.06 M in THF) at −90 to −50 °C did produce bicycle **12** in a moderate 42% yield, alongside unreacted aldehyde **11** (12%) and some uncyclized byproducts.[14] Noticeably, bicycle **12** was obtained as a single, all-trans isomer indicating perfect chirality transmittal during ring formation (vide infra). Inspection of the recorded nuclear Overhauser effect (NOE) data for this bicycle allowed us to assign the absolute stereochemistry of the newly formed stereocenters and confirm the overall structure unambiguously, as indicated (Figure 1). Hydrolysis and deprotection of **12** was all that remained for the synthesis of **13**; treatment of this material with 6 N aq HCl at 100 °C followed by DOWEX (H^+ form)[15] cleanly afforded amino acid **13** in an 89% isolated yield. Overall, cycloheptane **13** was obtained in ten steps and a 12% global yield with the use of seven chromatographic separations.

The parallel route to cycloheptane **21** is summarized in Scheme 3, where the precursor chosen was **1** combined with (*R*)-**2** (VMAR) and (*S*)-**2** (MBHR). Thus, as expected, lactams **14** and **15** were obtained without trouble, by paralleling the protocols in Scheme 2 exactly (50 and 13% yields, respectively, three steps). Next, the major isomer **14** was processed further, and the minor isomer **15** was conserved (vide infra). A sequel of five simple reactions then secured the preparation of dialdehyde **19** (65% yield, five steps), ready for the crucial IPCR operation.

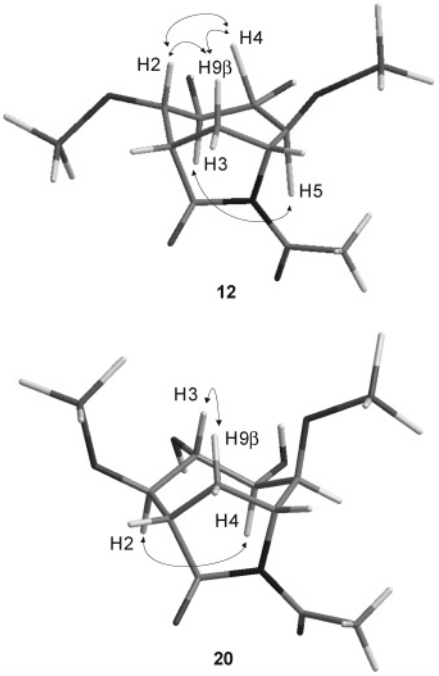
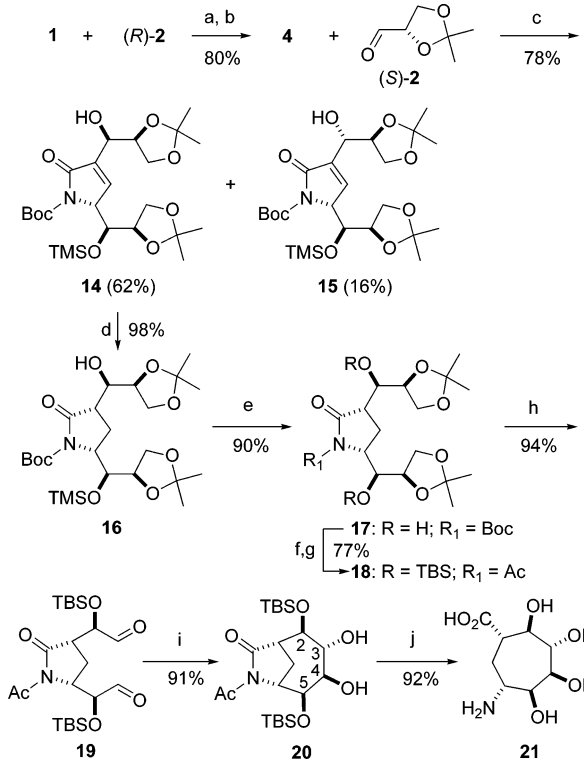


FIGURE 1. NOE effects (indicated with arrows) recorded in two-dimensional NOESY experiments relevant for the assignment of the stereochemistry of bicycles **12** and **20**. Silicon substituents omitted for clarity.

SCHEME 3. Synthesis of Amino Acid 21 Using the Option 1 + (*R*)-2 + (*S*)-2[a]



[a] Reagents and conditions: see Scheme 2.

(12) (a) Xie, M. D.; Berges, A.; Robins, M. J. *J. Org. Chem.* **1996**, *61*, 5178−5179. (b) Wu, W.-L.; Wu, Y.-L. *J. Org. Chem.* **1993**, *58*, 3586−3588.

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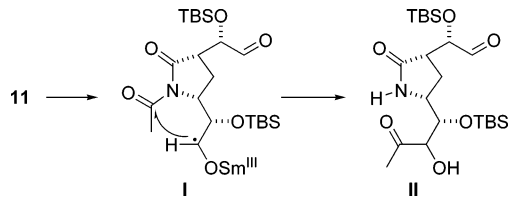
(14) A 21% yield of a second product was also isolated, to which structure **II** was assigned. Methyl ketone **II** probably arises from a trans acetylation process involving samarium ketyl **I**.



(15) This treatment cleanly eliminates lactone forms and metal contaminants, providing high-purity amino acid samples.

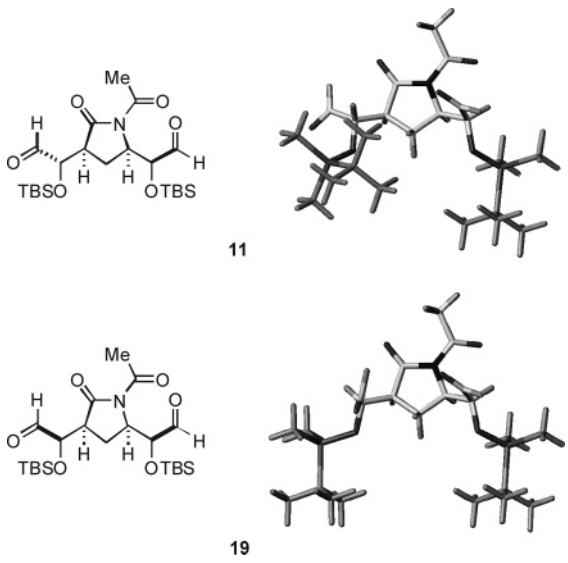


FIGURE 2. Minimum energy conformations of dialdehydes **11** and **19**, obtained with a MMFF94s force field, as implemented in Sybyl 7.0 (Tripos Inc.: St. Louis, MO).[17,18]

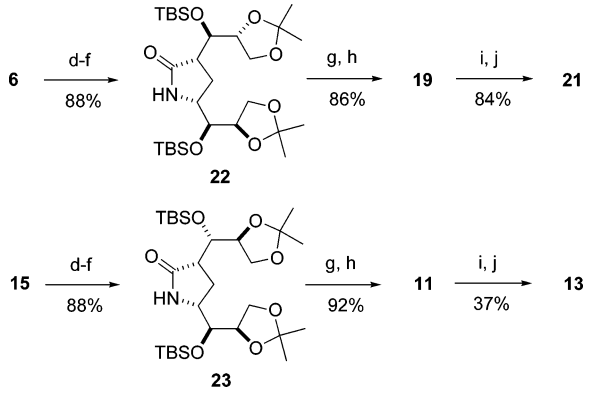
To our delight, using the protocol previously experienced for the **11** to **12** transformation, the ring formation occurred almost quantitatively (91%), producing **20** as the sole detectable stereoisomer.[16] As for **12**, the stereochemistry of **20** was ascertained by extensive NMR analyses, including two-dimensional nuclear Overhauser enhancement spectroscopy (NOESY) experiments (Figure 1).

The remarkable discrepancy between the behavior of SmI_2-induced pinacol cyclization of **11** and **19** deserves comment. Preliminary molecular modeling studies[17,18] performed on **11** and **19** showed that the lowest-energy conformers differ from each other markedly, with the formyl groups being in closer proximity to each other in **19** than in compound **11** (Figure 2). This suggests that not only the constraint imposed by the pyrrolidine nucleus but also the local constraint dictated by the protected hydroxyl substituents in α-position to the carbonyl groups play a substantial role to direct the pinacol ring closure, rendering **19** more prone to cyclization than the stereoisomeric counterpart **11**.

Hydrolysis and unmasking of the hydroxyl and amino functionalities within bicycle **20** led to amino acid **21**, which was isolated in 92% yield after DOWEX (H^+ form) treatment, corresponding to a 27% overall yield over ten steps.

As mentioned above, of the three key carbon−carbon bond-forming reactions employed in both the syntheses of **13** and **21** (Schemes 2 and 3), complete diastereocontrol was obtained for two (VMAR and IPCR) and diastereocontrol was only partial for one (MBHR), resulting in major (**5** and **14**) and minor isomers (**6** and **15**) being formed and separated. As shown in Scheme 4, **6** and **15** were not "dead ends", as convergence was easily accomplished to **21** and **13**, respectively, exploiting the chemistry already disclosed. With this contribution, the overall yields of **13** and **21** were increased to 16 and 37%, respectively, without material waste.

SCHEME 4. Convergence of Minor Isomers 6 and 15 into 21 and 13, Respectively[a]



[a] Reagents and conditions: see Scheme 2.

Replication of the protocols in Schemes 2−4 was finally executed independently, to craft the enantiomeric couple **31** and **32** by the sole reversal of the two aldehyde components in the VMAR and MBHR steps [(*S*)-**2**/(*S*)-**2** for **31** and (*S*)-**2**/(*R*)-**2** for **32**]. Scheme 5 shows a summary of this endeavor with only important products and intermediates displayed. Through the intermediacy of lactam **24**, pyrrolidinones **25**−**28**, and dialdehydes **29** and **30**, access to cycloheptane amino acids **31** and **32** was secured uneventfully in 15 and 36% overall yields, respectively, including the contribution from the convergent routes involving minor isomers **26** and **27**.

Scheme 5 also visualizes some notable aspects of our chemistry that include the high potential of the unified protocol to generate both molecular complexity and diversity by utilizing simple molecular sources, the reliability of the chemistry as proven by the faithful reproducibility of all synthetic operations, and the efficiency of the entire synthetic scheme featuring high-yielding steps, convenient byproduct recycling, and highly productive chirality transmittal.

In conclusion, the crafting of four cycloheptane amino acid tetraols, **13**, **21**, **31**, and **32**, from simple and readily available precursors has been accomplished through a unified, divergent−convergent ten-step pathway with good 15−37% overall yields and limited use of chromatographic separations. The results underscore the potential of this strategy to assemble a rich repertoire of medium-sized cycloalkanes with a large variability of size, substitution, and chirality.

Experimental Section

For general experimental procedures, see the Supporting Information.

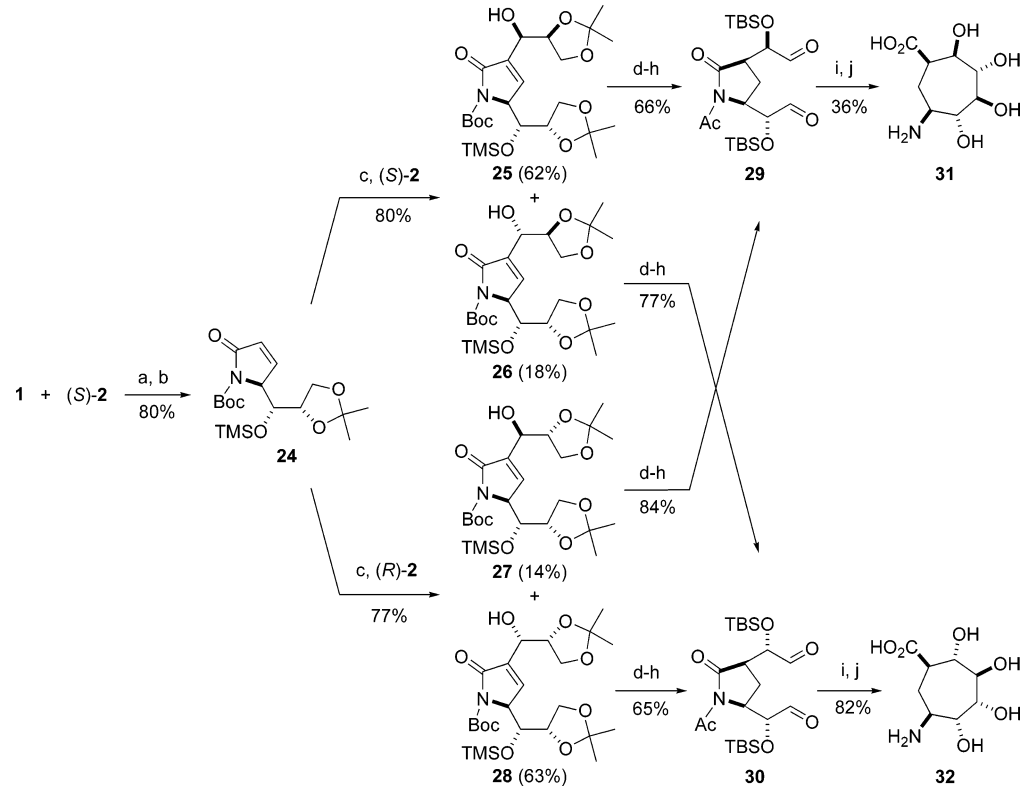
(1^{I}*S*,1^{III}*S*,4^{II}*R*,4^{IV}*R*,5*R*)-3-[(2,2-Dimethyl-[1,3]dioxolan-4-yl)-hydroxymethyl]-5-[(2,2-dimethyl-[1,3]dioxolan-4-yl)(trimethylsilanyloxy)methyl]-2-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxylic Acid *tert*-Butyl Ester (5) and (1^{I}*R*,1^{III}*S*,4^{II}*R*,4^{IV}*R*,5*R*)-3-[(2,2-Dimethyl-[1,3]dioxolan-4-yl)hydroxymethyl]-5-[(2,2-dimethyl-[1,3]dioxolan-4-yl)(trimethylsilanyloxy)methyl]-2-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxylic Acid *tert*-Butyl Ester (6). Typical Procedure. To a stirring solution of diphenyl diselenide (469 mg, 1.50 mmol) in anhydrous THF (10 mL) cooled to −15 °C, 0.94 mL of a 1.6 M solution of *n*-butyllithium in hexanes (1.50 mmol) was added dropwise under argon. After 30 min, the resulting colorless solution of lithium phenylselenide was cooled to −90 °C

(16) At this point, we could not define the actual mechanism of this pinacol coupling reaction, but it was presumed that the pseudoequatorial location of the emerging C3 and C4 hydroxyls in compound **20**, as well as in isomer **12**, dictates the stereochemical outcome of the ring-closing process, regardless of the spatial orientation of the flanking C2 and C5 stereocenters (see Figure 1).

(17) Halgren, T. A. *J. Comput. Chem.* **1999**, *20*, 720−729.

(18) *Sybyl 7.0*, Tripos Inc.: St. Louis, MO.

SCHEME 5. Synthesis of Amino Acids 31 and 32 Using the Options 1 + (*S*)-2 + (*S*)-2 and 1 + (*S*)-2 + (*R*)-2, Respectively[a]



[a] Reagents and conditions: see Scheme 2.

and a mixture of lactam **4** (364 mg, 0.94 mmol) and aldehyde (*R*)-**2** (245 mg, 1.88 mmol) in 10 mL of anhydrous THF was slowly added dropwise. After 2 h, the reaction mixture was quenched by addition of distilled water and saturated NH_4Cl solution and extracted with hexanes (3 × 15 mL). The extracts were dried over $MgSO_4$, filtered, and concentrated under vacuum. Flash chromatographic purification (EtOAc/hexanes 35:65) of the residue afforded unsaturated lactams **5** (296 mg, 61%) and **6** (92 mg, 19%).

Compound 5: a glassy solid; $[\alpha]_D^{20}$ +99.2 (*c* 1.7, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.10 (dd, J = 1.8, 1.2 Hz, 1H, H4), 4.51 (ddd, J = 4.8, 2.4, 1.2 Hz, 1H, H5), 4.46 (dd, J = 6.0, 4.8 Hz, 1H, H1^{III}), 4.43 (tt, J = 5.4, 1.2 Hz, 1H, H1^{I}), 4.36 (q, J = 6.6 Hz, 1H, H4^{II}), 3.93 (dd, J = 8.4, 6.6 Hz, 1H, H5^{II}a), 3.88 (dd, J = 8.4, 6.0 Hz, 1H, H5^{II}b), 3.80 (dd, J = 7.8, 6.0 Hz, 1H, H5^{IV}a), 3.71 (q, J = 6.0 Hz, 1H, H4^{IV}), 3.61 (dd, J = 8.4, 7.2 Hz, 1H, H5^{IV}b), 3.21 (bd, J = 4.8 Hz, 1H, OH), 1.51 (s, 9H, Boc), 1.38 (s, 3H, Me), 1.27 (s, 3H, Me), 1.26 (s, 3H, Me), 1.18 (s, 3H, Me), 0.15 (s, 9H, TMS); ^{13}C NMR (150 MHz, $CDCl_3$) δ 168.7 (C2), 149.2 (Boc), 142.5 (C4), 137.8 (C3), 109.7 (*C*Me$_2$), 109.1 (*C*Me$_2$), 83.4 (Boc), 76.1 (C4^{II}), 74.8 (C4^{IV}), 71.2 (C1^{III}), 68.6 (C1^{I}), 66.4 (C5^{IV}), 65.6 (C5^{II}), 63.9 (C5), 28.2 (3C, Boc), 26.6 (Me), 26.4 (Me), 25.1 (Me), 24.9 (Me), 0.2 (3C, TMS). Anal. Calcd for $C_{24}H_{41}NO_9Si$: C, 55.90; H, 8.01; N, 2.72. Found: C, 55.78; H, 8.12; N, 2.79.

Compound 6: a glassy solid; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.26 (bt, J = 1.8 Hz, 1H, H4), 4.59 (dd, J = 4.2, 1.8 Hz, 1H, H5), 4.57 (dd, J = 6.0, 4.2 Hz, 1H, H1^{III}), 4.49 (m, 1H, H1^{I}), 4.44 (m, 1H, H4^{II}), 4.09 (dd, J = 8.4, 6.6 Hz, 1H, H5^{II}a), 4.02 (dd, J = 8.4, 6.6 Hz, 1H, H5^{II}b), 3.90 (dd, J = 7.8, 6.0 Hz, 1H, H5^{IV}a), 3.74 (q, J = 6.0 Hz, 1H, H4^{IV}), 3.70 (dd, J = 7.2, 5.4 Hz, 1H, H5^{IV}b), 2.79 (d, J = 7.2 Hz, 1H, OH), 1.59 (s, 9H, Boc), 1.49 (s, 3H, Me), 1.47 (s, 3H, Me), 1.36 (s, 3H, Me), 1.26 (s, 3H, Me), 0.24 (s, 9H, TMS); ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.9 (C2), 149.3 (Boc), 142.1 (C4), 139.7 (C3), 109.7 (*C*Me$_2$), 109.1 (*C*Me$_2$), 83.3 (Boc), 76.1 (C4^{II}), 74.9 (C4^{IV}), 71.1 (C1^{III}), 67.7 (C1^{I}), 66.4 (C5^{IV}), 65.9 (C5^{II}), 63.7 (C5), 28.2 (3C, Boc), 28.1 (Me), 26.4 (Me), 25.1 (Me), 24.9 (Me), 0.3 (3C, TMS). Anal. Calcd for $C_{24}H_{41}NO_9Si$: C, 55.90; H, 8.01; N, 2.72. Found: C, 55.94; H, 8.17; N, 2.59.

(1^{I}*S*,1^{III}*S*,3*S*,4^{II}*R*,4^{IV}*R*,5*R*)-3-[(2,2-Dimethyl-[1,3]dioxolan-4-yl)hydroxymethyl]-5-[(2,2-dimethyl-[1,3]dioxolan-4-yl)(trimethylsilanyloxy)methyl]-2-oxopyrrolidine-1-carboxylic Acid *tert*-Butyl Ester (7). Typical Procedure. Palladium on carbon (10%, 30 mg) was added to a stirring solution of unsaturated lactam **5** (296 mg, 0.57 mmol) in anhydrous EtOAc (25 mL) in the presence of a small amount of NaOAc (8 mg) at room temperature. The reaction vessel was evacuated by an aspirator and thoroughly purged with hydrogen (three times), and the resulting heterogeneous mixture was stirred under a hydrogen balloon. After 16 h, the hydrogen was evacuated and the catalyst was filtered off. The filtrate was concentrated under vacuum to give a crude residue which was purified by silica gel flash chromatography (EtOAc/hexanes 6:4) to give pure saturated lactam **7** (280 mg, 95%) as a glassy solid: $[\alpha]_D^{20}$ +25.4 (*c* 5.6, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.36 (dd, J = 7.8, 4.2 Hz, 1H, H1^{III}), 4.2−4.3 (m, 3H, H1^{I}, H4^{IV}, H5), 4.15 (m, 1H, H5^{II}a), 4.10 (dd, J = 7.8, 6.0 Hz, 1H, H5^{IV}a), 4.04 (m, 1H, H4^{II}), 4.02 (t, J = 4.8 Hz, 1H, H5^{II}b), 3.79 (dd, J = 8.4, 6.6 Hz, 1H, H5^{IV}b), 3.01 (ddd, J = 11.4, 9.0, 2.4 Hz, 1H, H3), 2.73 (d, J = 3.0 Hz, 1H, OH), 2.21 (ddd, J = 13.8, 9.0, 6.6 Hz, 1H, H4a), 2.16 (ddd, J = 13.8, 11.4, 9.0 Hz, 1H, H4b), 1.57 (s, 9H, Boc), 1.43 (s, 3H, Me), 1.37 (s, 3H, Me), 1.36 (s, 3H, Me), 1.30 (s, 3H, Me), 0.19 (s, 9H, TMS); ^{13}C NMR (150 MHz, $CDCl_3$) δ 174.8 (C2), 150.0 (Boc), 109.7 (*C*Me$_2$), 109.5 (*C*Me$_2$), 83.0 (Boc), 75.8 (C4^{II}), 74.4 (C4^{IV}), 71.7 (C1^{III}), 70.8 (C1^{I}), 67.8 (C5^{IV}), 67.3 (C5^{II}), 57.9 (C5), 45.2 (C3), 28.1 (3C, Boc), 26.8 (Me), 26.3 (Me), 25.3 (2C, Me), 16.2 (C4), 0.3 (3C, TMS). Anal. Calcd for $C_{24}H_{43}NO_9Si$: C, 55.68; H, 8.37; N, 2.71. Found: C, 55.57; H, 8.44; N, 2.63.

(2*S*,2^{I}*S*,2^{II}*R*,4^{II}*S*)-2,2^{I}-(1-Acetyl-5-oxopyrrolidine-2,4-diyl)-bis-(*tert*-butyldimethylsilanyloxyacetaldehyde) (11). Typical Procedure. To a suspension of H_5IO_6 (492 mg, 2.16 mmol) in freshly distilled EtOAc (10 mL) was added dropwise a solution of lactam

10 (225 mg, 0.36 mmol) in EtOAc (10 mL), and the resulting heterogeneous mixture was vigorously stirred at ambient temperature for 3 h. Filtration of the mixture through a short pad of Celite and silica gel and evaporation of the filtrate afforded bisaldehyde **11** (170 mg, 99%) as a colorless oil: $[\alpha]^{20}_D$ −53.7 (*c* 1.0, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.73 (s, 1H, H1$^{\mathbf{I}}$), 9.56 (s, 1H, H1), 4.67 (d, *J* = 2.4 Hz, 1H, H2$^{\mathbf{I}}$), 4.31 (d, *J* = 3.0 Hz, 1H, H2), 4.25 (ddd, *J* = 10.2, 7.2, 3.0 Hz, 1H, H2$^{\mathbf{II}}$), 3.06 (ddd, *J* = 12.0, 9.0, 2.4 Hz, 1H, H4$^{\mathbf{II}}$), 2.54 (s, 3H, Ac), 2.14 (ddd, *J* = 14.4, 9.0, 7.2 Hz, 1H, H3$^{\mathbf{II}}$a), 2.06 (m, 1H, H3$^{\mathbf{II}}$b), 0.95 (s, 9H, TBS), 0.93 (s, 9H, TBS), 0.14 (s, 3H, TBS), 0.13 (s, 6H, TBS), 0.12 (s, 3H, TBS); ^{13}C NMR (150 MHz, $CDCl_3$) δ 202.5, 202.0, 174.2, 172.5, 75.3, 75.2, 57.5, 45.3, 25.8 (3C), 25.7 (3C), 25.4, 21.2, 18.3, 18.0, −4.6 (2C), −4.7 (2C). Anal. Calcd for $C_{22}H_{41}NO_6Si_2$: C, 56.01; H, 8.76; N, 2.97. Found: C, 55.42; H, 8.96; N, 2.60.

(1*S*,2*S*,3*S*,4*S*,5*S*,6*R*)-7-Acetyl-3,4-dihydroxy-2,5-bis(*tert*-butyldimethylsilanyloxy)-7-azabicyclo[4.2.1]nonan-8-one (12). Typical Procedure. To a 0.06 M solution of SmI_2 in THF (18 mL, 1.08 mmol), prepared as described in the general experimental procedures (Supporting Information) and cooled to −90 °C under argon, was slowly added dropwise a solution of aldehyde **11** (170 mg, 0.36 mmol) and methanol (32 μL, 0.79 mmol) in anhydrous THF (40 mL), and the resulting mixture was stirred at the same temperature for 2 h. After this time, the reaction was allowed to reach −50 °C over a period of 3 h, then quenched with 10% aqueous $Na_2S_2O_3$ solution and saturated aqueous $NaHCO_3$ solution. The mixture was extracted with EtOAc (6 × 20 mL), and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Flash chromatography purification (EtOAc/hexanes 3:7) of the crude residue afforded pure bicycle **12** (72 mg, 42%) as a glassy solid: $[\alpha]^{20}_D$ +39.0 (*c* 0.8, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.33 (dd, *J* = 9.0, 1.8 Hz, 1H, H6), 3.93 (dt, *J* = 6.6, 1.2 Hz, 1H, H5), 3.73 (dd, *J* = 8.4, 4.2 Hz, 1H, H2), 3.64 (ddd, *J* = 10.2, 6.6, 1.2 Hz, 1H, H4), 3.45 (ddd, *J* = 10.2, 9.0, 1.2 Hz, 1H, H3), 2.98 (d, *J* = 0.6 Hz, 1H, OH), 2.91 (d, *J* = 1.8 Hz, 1H, OH), 2.81 (dd, *J* = 8.4, 4.2 Hz, 1H, H1), 2.55 (s, 3H, Ac), 2.17 (dtd, *J* = 13.8, 8.4, 1.2 Hz, 1H, H9α), 2.00 (d, *J* = 13.8 Hz, 1H, H9β), 1.01 (s, 9H, TBS), 0.96 (s, 9H, TBS), 0.25 (s, 3H, TBS), 0.24 (s, 3H, TBS), 0.21 (s, 3H, TBS), 0.20 (s, 3H, TBS); ^{13}C NMR (150 MHz, $CDCl_3$) δ 173.1, 170.5 (C8, Ac), 76.3 (C2), 75.6 (C4), 74.5 (C5), 72.0 (C3), 59.5 (C6), 47.6 (C1), 25.8 (3C, TBS), 25.7 (3C, TBS), 25.5 (Ac), 22.2 (C9), 18.1 (TBS), 18.0 (TBS), −4.6 (TBS), −4.7 (TBS), −4.8 (TBS), −4.9 (TBS). Anal. Calcd for $C_{22}H_{43}NO_6Si_2$: C, 55.78; H, 9.15; N, 2.96. Found: C, 55.71; H, 9.05; N, 2.88.

(1*S*,2*R*,3*R*,4*R*,5*S*,6*R*)-7-Acetyl-3,4-dihydroxy-2,5-bis(*tert*-butyldimethylsilanyloxy)-7-azabicyclo[4.2.1]nonan-8-one (20). Bicyclic compound **20** was prepared from aldehyde **19** (170 mg, 0.36 mmol) by adopting the typical procedure described for **12**. After flash chromatographic purification (EtOAc/hexanes 3:7), compound **20** was obtained (155 mg, 91%) as a glassy solid: $[\alpha]^{20}_{578}$ +39.6 (*c* 0.8, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.51 (dd, *J* = 7.2, 4.8 Hz, 1H, H6), 4.40 (dd, *J* = 4.2, 2.4 Hz, 1H, H5), 3.90 (d, *J* = 7.2 Hz, 1H, H2), 3.86 (dd, *J* = 9.0, 7.8 Hz, 1H, H3), 3.30 (ddd, *J* = 10.2, 5.4, 2.4 Hz, 1H, H4), 2.76 (d, *J* = 9.0 Hz, 1H, H1), 2.64 (bs, 1H, OH), 2.62 (d, *J* = 5.4 Hz, 1H, OH), 2.50 (s, 3H, Ac), 2.42 (d, *J* = 13.8 Hz, 1H, H9β), 1.95 (dt, *J* = 13.8, 8.4 Hz, 1H, H9α), 0.97 (s, 9H, TBS), 0.96 (s, 9H, TBS), 0.22 (s, 3H, TBS), 0.21 (s, 3H, TBS), 0.20 (s, 3H, TBS), 0.19 (s, 3H, TBS); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.5, 170.2, 76.4, 72.4, 69.6, 68.6, 58.0, 50.3, 25.8 (6C), 24.9, 19.7, 18.1, 18.0, −4.5, −4.6, −4.8, −4.9. Anal. Calcd for $C_{22}H_{43}NO_6Si_2$: C, 55.78; H, 9.15; N, 2.96. Found: C, 55.83; H, 9.21; N, 2.82.

(1*S*,2*S*,3*R*,4*R*,5*S*,6*R*)-6-Amino-2,3,4,5-tetrahydroxycycloheptanecarboxylic Acid (13). Typical Procedure. The bicyclic compound **12** (72 mg, 0.15 mmol) was dissolved in 6 N aq HCl (15 mL), and the resulting mixture was allowed to react at reflux (100 °C) for 8 h. After ambient temperature was reached, the mixture was diluted with distilled water and washed with hexanes (3 × 10 mL). The aqueous phase was concentrated under vacuum, and the crude residue was passed through DOWEX 50 W × 8 ion-exchange resin (H^+ form). Elution of the resin with 1.5% aq NH_4-OH furnished free amino acid **13** (30 mg, 89%) as a white solid: $[\alpha]^{20}_D$ −3.2 (*c* 0.5, H_2O); ^{1}H NMR (600 MHz, D_2O) δ 3.98 (dd, *J* = 6.0, 3.6 Hz, 1H, H2), 3.47 (dd, *J* = 8.4, 6.0 Hz, 1H, H3), 3.46 (t, *J* = 9.6 Hz, 1H, H5), 3.38 (t, *J* = 9.0 Hz, 1H, H4), 3.11 (td, *J* = 9.6, 3.6 Hz, 1H, H6), 2.51 (dd, *J* = 10.8, 3.6 Hz, 1H, H1), 2.04 (dd, *J* = 13.2, 3.6 Hz, 1H, H7β), 1.85 (dt, *J* = 13.8, 10.8 Hz, 1H, H7α); ^{13}C NMR (150 MHz, D_2O) δ 177.4 (CO_2H), 75.9, 74.1, 73.4, 72.1 (C5, C4, C3, C2), 55.0 (C6), 45.1 (C1), 25.0 (C7); HRMS (ES) found [M + H^+] 222.0974, $C_8H_{16}NO_6$ requires 222.0978. Anal. Calcd for $C_8H_{15}NO_6$: C, 43.44; H, 6.83; N, 6.33. Found: C, 43.25; H, 6.88; N, 6.66.

(1*S*,2*R*,3*S*,4*S*,5*S*,6*R*)-6-Amino-2,3,4,5-tetrahydroxycycloheptanecarboxylic Acid (21). Amino acid **21** was obtained from compound **20** (155 mg, 0.33 mmol) according to the typical procedure described for compound **13**. After ion-exchange purification with DOWEX 50 W × 8 (H^+ form) and elution with 1.5% aq NH_4OH, free amino acid **21** (67 mg, 92%) was recovered as a white solid: $[\alpha]^{20}_D$ −2.7 (*c* 0.3, H_2O); ^{1}H NMR (600 MHz, D_2O) δ 3.97 (dd, *J* = 5.4, 1.8 Hz, 1H, H4), 3.82 (dd, *J* = 9.6, 1.8 Hz, 1H, H5), 3.73 (dd, *J* = 6.0, 5.4 Hz, 1H, H3), 3.66 (dd, *J* = 9.6, 6.0 Hz, 1H, H2), 3.47 (ddd, *J* = 12.0, 9.6, 4.2 Hz, 1H, H6), 2.84 (td, *J* = 10.8, 1.8 Hz, 1H, H1), 2.12 (ddd, *J* = 14.4, 4.2, 1.8 Hz, 1H, H7β), 1.81 (dt, *J* = 13.8, 12.0 Hz, 1H, H7α); ^{13}C NMR (150 MHz, D_2O) δ 177.2 (CO_2H), 75.9, 75.7, 74.9, 69.8 (C5, C4, C3, C2), 51.6 (C6), 45.9 (C1), 29.1 (C7); HRMS (ES) found [M + H^+] 222.0975, $C_8H_{16}NO_6$ requires 222.0978. Anal. Calcd for $C_8H_{15}NO_6$: C, 43.44; H, 6.83; N, 6.33. Found: C, 43.19; H, 6.90; N, 6.70.

(1*R*,2*R*,3*S*,4*S*,5*R*,6*S*)-6-Amino-2,3,4,5-tetrahydroxycycloheptanecarboxylic Acid (31). Amino acid **31** was obtained from aldehyde **29** (180 mg, 0.38 mmol) in two steps, according to the typical procedures described for compound **13**. After ion-exchange purification with DOWEX 50 W × 8 (H^+ form) and elution with 1.5% aq NH_4OH, free amino acid **31** (30 mg, 36%) was recovered as a white solid: $[\alpha]^{20}_D$ +4.0 (*c* 0.7, H_2O); ^{1}H and ^{13}C NMR, see enantiomer **13**; HRMS (ES) found [M + H^+] 222.0981, $C_8H_{16}NO_6$ requires 222.0978. Anal. Calcd for $C_8H_{15}NO_6$: C, 43.44; H, 6.83; N, 6.33. Found: C, 43.31; H, 6.84; N, 6.59.

(1*R*,2*S*,3*R*,4*R*,5*R*,6*S*)-6-Amino-2,3,4,5-tetrahydroxycycloheptanecarboxylic Acid (32). Amino acid **32** was obtained from aldehyde **30** (180 mg, 0.38 mmol) in two steps, according to the typical procedures described for compound **13**. After ion-exchange purification with DOWEX 50 W × 8 (H^+ form) and elution with 1.5% aq NH_4OH, free amino acid **32** (69 mg, 82%) was recovered as a white solid: $[\alpha]^{20}_D$ +3.9 (*c* 1.0, H_2O); ^{1}H and ^{13}C NMR, see enantiomer **21**; HRMS (ES) found [M + H^+] 222.0980, $C_8H_{16}NO_6$ requires 222.0978. Anal. Calcd for $C_8H_{15}NO_6$: C, 43.44; H, 6.83; N, 6.33. Found: C, 43.21; H, 6.89; N, 6.68.

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Supporting Information Available: Detailed procedures and spectroscopic data for compounds **3**−**4**, **8**−**10**, **14**−**19**, and **22**−**30** and copies of ^{1}H NMR spectra (600 MHz, $CDCl_3$ or D_2O) for compounds **5**, **12**−**14**, **20**, and **21**. This material is available free of charge via the Internet at http://pubs.acs.org.

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