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Electrophilic Amination of Amino Acids with N-Boc-oxaziridines: Efficient Preparation of N-Orthogonally Diprotected Hydrazino Acids and Piperazic Acid Derivatives

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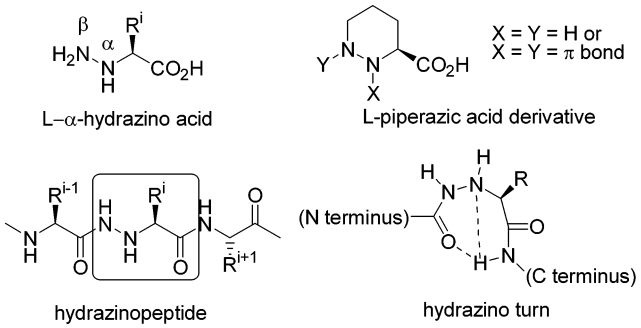
A general two-step preparation of enantiopure N_α,N_β-orthogonally diprotected α-hydrazino acids **1** is developed on a multigram scale. The key reaction is the efficient electrophilic amination of *N*-benzyl amino acids **6** with *N*-Boc-oxaziridine **7** and accommodates various functional groups encountered in side chains of amino acids. The cyclic 2,3,4,5-tetrahydro-3-pyridazine carboxylic acid (piperazic acid) derivatives **2** and **3** or the cyclic 3,4-dihydro-3-pyrazolecarboxylate **4** are conveniently prepared from glutamic acid or aspartic acid via orthogonally diprotected α-hydrazino acids **1m** and **1n**.

Introduction

Chemical modification of the peptide backbone is a fruitful and well-established tool in the search for bioactive compounds or elucidation of biological mechanisms.[1] Among pseudopeptides or peptidomimetics investigated in medicinal chemistry, those containing an N−N−C−C═O fragment have a real potential. This motif is found in several natural peptide compounds: the antibiotic negamycine[2] or the B6 vitamin antagonist linatine[3] are derivatives of α-hydrazino acids and more than 20 linear or macrocyclic peptides with remarkable biological properties contain the piperazic acid residue[4,5] (Scheme 1). The L-enantiomer of piperazic acid also resides within the bicyclic ring system of many bioactive synthetic products such as cilazapril,[6] a drug widely used in the treatment of hypertension or pranalcasan,[7] currently in phase II clinical trials as an antiinflammatory agent. Synthetic hydrazinopeptides in which an α-amino acid residue is replaced by an α-hydrazino acid (Scheme 1) behave as bioactive eledoisin analogues,[8,9] turn-mimetics,[10] or reversible inhibitors of human leukocyte elastase.[11] Hydrazinopeptides bearing an N-terminal

SCHEME 1. Structures Containing an N−N−C−C═O Fragment



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(1) (a) *Houben-Weyl: Methods of organic chemistry. Synthesis of Peptides and Peptidomimetics;* Goodman, M., Felix, A., Moroder, L., Toniolo, C., Eds.; Georg Thieme Verlag: Stuttgart, Germany, 2002; Vol. E22c. (b) Gante, J. *Angew. Chem., Int. Ed. Eng.* **1994**, *33*, 1699−1720. (c) Nakanishi, H.; Kahn, M. *Pract. Med. Chem.* **1996**, 571−590. (d) Goodman, M.; Shao, H. *Pure Appl. Chem.* **1996**, *68*, 1303−1306. (e) Hannessian, S.; McNaughton-Smith G.; Lombart, H.-G.; Lubell, W. D. *Tetrahedron* **1997**, *53*, 12789−12854. (f) Ahn, J.-M.; Boyle, N. A.; MacDonald, M. T.; Janda, K. D. *Mini-Rev. Med. Chem.* **2002**, *2*, 463−473.

(2) Hamada, M.; Takeuchi, T.; Kondo, S.; Ikeda, Y.; Naganawa, H.; Maeda, K.; Okami, Y.; Umezawa, H. *J. Antibiot.* **1970**, *23*, 170−171.

(3) Klosterman, H. J.; Lamoureux, G. L.; Parsons, J. L. *Biochemistry* **1967**, *6*, 170−177.

(4) For a review, see: (a) Ciufolini, M.; Xi, N. *Chem. Soc. Rev.* **1998**, *27*, 437−445. (b) Hale, K. J.; Cai, J.; Delisser, V.; Manaviazar, S.; Peak, S. A.; Bhatia, G. S.; Collins, T. C.; Jogiya, N. *Tetrahedron* **1996**, *52*, 1047−1068.

(5) Sanglifehrin (a powerful immunosupressant), chloptosin, and pipalamycin (an apoptosis-inducing agent) are recently discovered natural macrocyclic peptides containing the piperazic acid residue: (a) Fehr, T.; Kallen, J.; Oberer, L.; Sanglier, J.-J.; Schilling, W. *J. Antibiot.* **1999**, *52*, 474−479. (b) Umezawa, K.; Ikeda, Y.; Uchihata, Y.; Naganawa, H.; Kondo, S. *J. Org. Chem.* **2000**, *65*, 459−463. (c) Uchihata, Y.; Ando, N.; Ikeda, Y.; Kondo, S.; Hamada, M.; Umezawa, K. *J. Antibiot.* **2002**, *55*, 1−5.

(6) Attwood, M. R.; Hassall, C. H.; Kröhn, A.; Lawton, G.; Redshaw, S. *J. Chem. Soc., Perkin Trans. 1* **1986**, 1011−1019.

(7) (a) Batchelor, M. J.; Bebbington, D.; Bemis, G. W.; Fridman, W. H.; Gillespie, R. J.; Golec, J. M. C.; Gu, Y.; Lauffer, D. J.; Livingston, D. J.; Matharu, S. S.; Mullican, M. D.; Murcko, M. A.; Murdoch, R.; Nyce, P. L.; Robidoux, A. L. C.; Su, M.; Wannamaker, M.; Wilson, K. P.; Zelle, R. E. PCT Int. Appl. WO 9722619, 1997. (b) Siegmund, B.; Zeitz, M. *IDrugs* **2003**, *6*, 154−158.

(8) (a) Niedrich, H. *Chem. Ber.* **1967**, *100*, 3273−3282. (b) Grupe, R.; Niedrich, H. *Chem. Ber.* **1967**, *100*, 3283−3288. (c) Niedrich, H.; Köller, G. *J. Prakt. Chem.* **1974**, *316*, 729−740.

(9) (a) Oehme, P.; Bergmann, J.; Niedrich, H.; Jung, F.; Menzel, G.; Eichstädt, M.; Rudel, M. *Acta Biol. Med. Ger.* **1970**, *25*, 613−625. (b) Oehme, P.; Katzwinkel, S.; Vogt, W. E.; Niedrich, H. *Experientia* **1973**, *29*, 947−948.

(10) Review: Kahn M. *Synlett* **1993**, 821−826.

(11) Guy, L.; Vidal, J.; Collet, A.; Amour, A.; Reboud-Ravaux M. *J. Med. Chem.* **1998**, *41*, 4833−4843.

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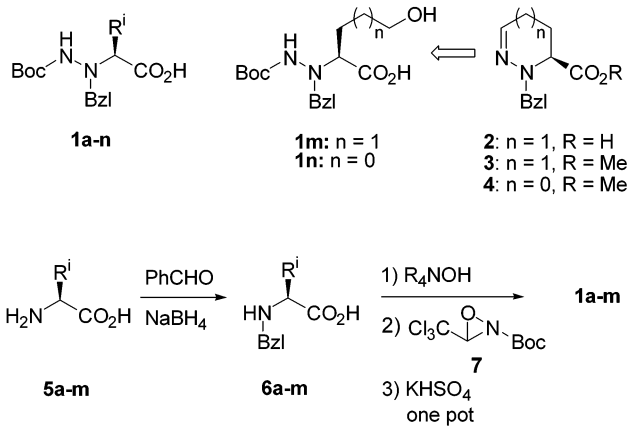
SCHEME 2



achiral hydrazinoacetic acid residue prove to display anticancer properties[12] or to be very useful intermediates in the preparation of lipopeptides,[13] clustered glycoside−antigen conjugates,[14] or synthetic mannose receptor ligands grafted on vesicles.[15]

From a structural point of view, we have shown that the introduction of an N−N−C−C=O fragment in a peptide chain induces a conformational bias, called a hydrazino turn,[16] which folds the peptide backbone locally by way of a well-defined intramolecular bifurcated H-bonding (Scheme 1). Such a folding is also found in oligomers of N_α-substituted hydrazino acetic acid.[17] In addition, recent quantum and molecular mechanics calculations reveal that oligomers of α-hydrazino acids[18] may adopt a wide variety of secondary structures and thus may behave as foldamers.[19]

Recently, we reported that incorporation of L-α-hydrazino acids in peptides is generally best accomplished by means of N_α,N_β-orthogonally bis-protected derivatives **1** using conventional peptide synthesis methods[11] (Scheme 2). As yet, diversity of α-hydrazino acids introduced in synthetic hydrazinopeptides has been limited to aliphatic or aromatic side chains (R^i = H, Me, CH_2Ph, ^{i}Pr, ^{s}Bu).[8−15] To carry on further structural or biological studies about pseudopeptides containing an N−N−C−C=O fragment, we needed a general and short access to synthons **1**[20] bearing diversely functionalized side chains. We wish to report here an efficient two-step procedure leading to a library of enantiopure N_α-benzyl-N_β-Boc-α-hydrazino acids **1a**−**n** from L-amino acids **5a**−**m** (Scheme 2). The key step rests on our methodology of electrophilic amination by oxaziridines[21] and allows a smooth reaction on a multigram scale between benzyl amino acids **6a**−**m** and the highly reactive *N*-Boc-oxaziridine **7**.[22] A convenient transformation of synthons **1m** and **1n** into piperazic acid derivatives **2**−**4** is also presented.

TABLE 1. Preparation of N_α,N_β-Diprotected L-Hydrazino Acid 1a−m

entry	R^i	*N*-benzylamino acid (yield from **5**)	L-hydrazino acid derivative (yield from **6**)
1	$CH(CH_3)_2$	**6a**[a] (74%)	**1a** (48%)
2	CH_3	**6b**[a] (77%)	**1b** (81%)
3	(*S*)-$CH(CH_3)CH_2CH_3$	**6c**[b]	**1c** (52%)
4	3-methyleneindole	**6d**[a] (72%)	**1d**[c] (63%)
5	$(CH_2)_4NHCO_2Bzl$	**6e**[a] (65%)	**1e**[d] (40%)
6	$CH_2C_6H_4$-*p*OBzl	**6f**[a] (52%)	**1f**[e] (71%)
7	$(CH_2)_3S(O)CH_3$	**6g**[a] (75%)	**1g**[f,g] (91%)
8	CH_2CONH_2	**6h**[a] (53%)	**1h**[g] (41%)
9	$(CH_2)_2CO_2H$	**6i**[a] (73%)	**1i** (46%)
10	$(CH_2)_2CO_2CH_3$	**6j** (57%)	**1j**[e,h] (71%)
11	CH_2CO_2Bzl	**6k** (86%)	**1k**[e] (56%)
12	CH_2OH	**6l**[b]	**1l** (57%)
13	$(CH_2)_3OH$	**6m** (71%)	**1m**[e] (60%)

[a] Prepared according to ref 23. [b] Commercially available. [c] The product was isolated as its hexylamine salt. [d] The product was isolated as its dibenzylamine salt. [e] The product was isolated as its dicyclohexylamine salt. [f] Mixture of the two diastereomeric sulfoxides. [g] The product was not recrystallized. [h] See ref 22.

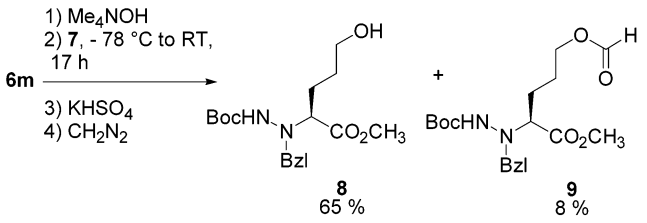
Results and Discussion

Synthesis of N-Orthogonally Diprotected Hydrazino Acids 1a−m. Orthogonal protection of both α- and *β*-nitrogens was necessary in order to make synthons **1** compatible with conventional peptide synthesis.[11] Our synthetic strategy relied on delivering the N_βH-Boc group by electrophilic amination with oxaziridine **7**[22] to an easily available enantiopure amino acid derivative. At this stage, the alternative was to introduce the N_α-protecting group before or after the electrophilic amination step. As we showed[21a] that electrophilic amination was cleaner with secondary amines over primary amines and proceeded faster when amines were more basic, we chose *N*-benzyl rather than Z-protected α-amino acids as nucleophilic precursor to **1** (Scheme 2).

L-Benzyl amino acids **6a**−**m** were prepared by reductive alkylation of enantiopure amino acids **5a**−**m**. Quitt's method[23] using benzaldehyde, $NaBH_4$, and NaOH in water generally gave good yields (Table 1, entries 1−9)

(12) Bouget, K.; Aubin, S.; Delcros, J.-G.; Arlot-Bonnemains Y.; Baudy-Floc'h, M. *Biorg. Med. Chem.* **2003**, *11*, 4881−4889.
(13) Bonnet, D.; Ollivier, N.; Gras-Masse, H.; Melnyk, O. *J. Org. Chem.* **2001**, *66*, 443−449.
(14) Grandjean, C.; Gras-Masse, H.; Melnyk, O. *Chem. Eur. J.* **2001**, *7*, 203−239.
(15) Chenevier, P.; Grandjean, C.; Loing, E.; Malingue, F.; Angyalosi, G.; Gras-Masse, H.; Roux, D.; Melnyck, O. Bourel-Bonnet, L. *J. Chem. Soc., Chem. Commun.* **2002**, 2446−2447.
(16) (a) Aubry, A.; Bayeul, D.; Mangeot, J.-P.; Vidal, J.; Stérin, S.; Collet, A.; Lecoq, A.; Marraud, M. *Biopolymers* **1991**, *31*, 793−801. (b) Zerkout, S.; Dupont, V.; Aubry, A.; Vidal, J.; Collet, A.; Vicherat, A.; Marraud M. *Int. J. Pept. Prot. Res.* **1994**, *44*, 378. (c) Aubry, A.; Mangeot, J. P.; Vidal, J.; Collet, A.; Zerkout, S.; Lecoq, A.; Marraud M. *Int. J. Pept. Prot. Res.* **1994**, *43*, 305. (d) Marraud, M.; Boussard, G.; Vanderesse, R.; Collet, A.; Vidal, J.; Aubry, A. *Actualités Chim. Thér.* 22nd Ser., **1995**−**96**, 67−82.
(17) Cheguillaume A.; Salaün, A.; Sinbandhit, S.; Potel, M.; Gall, P.; Baudy-Floc'h, M.; Le Grel, P. *J. Org. Chem.* **2001**, *66*, 4923−4929.
(18) Günther, R.; Hofmann, H.-J. *J. Am. Chem. Soc.* **2001**, *123*, 247−255.
(19) (a) Gellman, S. H. *Acc. Chem. Res.* **1998**, *31*, 173−180. (b) Hill, D. J.; Mio, M. J.; Prince, R. B.; Hughes, T. S.; Moore, J. S. *Chem. Rev.* **2001**, *101*, 3893−4011.
(20) For recent preparations of α-hydrazino acid derivatives, see: (a) Oguz, U.; Guilbeau, G. G.; McLaughlin, M. L. *Tetrahedron Lett.* **2002**, *43*, 2873−2875. (b) Portlock, D. E.; Naskar, D.; West, L.; Li, M. *Tetrahedron Lett.* **2002**, *43*, 6845−6847. (c) Brosse, N.; Pinto, M. F.; Bodiguel, J.; Jamart-Grégoire, B. *J. Org. Chem.* **2001**, *66*, 2869−2873.
(21) (a) For electrophilic amination with oxaziridines, see: Vidal, J.; Damestoy, S.; Guy, L.; Hannachi, J.-C.; Aubry, A.; Collet, A. *Chem. Eur. J.* **1997**, *3*, 1691−1709. (b) For recent reviews on electrophilic amination, see: Dembech, P.; Seconi, G.; Ricci, A. *Chem. Eur. J.* **2000**, *6*, 1281−1286. (c) Genet, J. P.; Greck, C.; Lavergne, D. In *Modern amination methods;* Ricci, A., Ed.; Wiley-VCH: Weinheim, Germany, 2000; p 65−102.
(22) Vidal, J.; Hannachi, J.-C.; Hourdin, G.; Mulatier, J.-C.; Collet, A. *Tetrahedron Lett.* **1998**, *39*, 8845−8848.
(23) Quitt, P.; Hellerbach, J.; Vogler, K. *Helv. Chim. Acta* **1963**, *46*, 327−333.

SCHEME 3



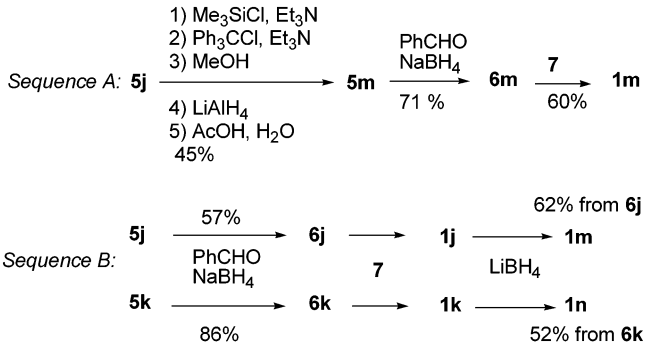
except for the hydroxide-sensitive esters **6j** and **6k** or the water-soluble **6m**. To overcome these difficulties, the intermediate benzylidene imines were prepared in situ from **5j**, **5k**, or **5m**; benzaldehyde; and triethylamine in anhydrous methanol and then reduced by $NaBH_4$ to give benzyl amino acids **6j**, **6k**, and **6m** in good yields (Table 1, entries 10, 11, and 13).

Electrophilic amination of benzyl amino acids **6** used *N*-Boc-3-(trichloromethyl)oxaziridine **7**, which was easily prepared on a large scale (75 g) in two steps from chloral.[22] The reaction was run in CH_2Cl_2 and in order to obtain dissolution, benzyl amino acids **6** were converted into their tetramethyl or tetraethylammonium salt using the corresponding hydroxide. Exothermic reaction of oxaziridine **7** with **6a** salt was very rapid at 4 °C and gave **1a** with 38% yield. The yield was improved to 48% when the reaction was carried out from −78 °C to room temperature (Table 1, entry 1). Workup allowed the easy removal of chloral released during the reaction, so that crude diprotected hydrazino acids **1a**−**m** were generally pure enough for most purposes. N-Orthogonally diprotected hydrazino acids **1a**−**m** were either crystalline or amorphous solids that were stable at 4 °C. After recrystallization or derivatization as the appropriate amine salt, good yields of crystalline **1a**−**m** were obtained on a multigram scale, allowing their commercial diffusion by fine chemical suppliers (Table 1).

The indole side chain of tryptophane **6d** did not require protection, only the secondary amino group being sufficiently reactive to be aminated by oxaziridine **7** (entry 4). We used conventional Z or Bzl protection on the basic side chain of lysine **6e** (primary amine, entry 5) or tyrosine **6f** (phenate,[24] entry 6) derivatives. The thioether[25] function of *N*-benzylmethionine needed to be protected by oxidation to diastereomeric sulfoxides **6g** (entry 7). No protection of the hydroxyl group of serine **6l** or δ-hydroxynorvaline **6m** derivatives was required when the reaction conditions were controlled (entries 12, 13). In fact, a small amount of formiate **9** (8%) resulting from acylation of the hydroxyl function of the side chain with chloral[26] released by oxaziridine **7** during the amination step (step 2, Scheme 3) was isolated after column chromatography along with expected compound **8** (65%). This side reaction could easily be avoided when the temperature was set from −78 to 0 °C for 5 h.

Racemization is not normally a critical problem here, because the asymmetric center is involved in neither the reductive alkylation step nor the electrophilic amination reaction. So the enantiopurity of compounds **1** was checked in one case. Only one enantiomer was detected by chiral column HPLC analysis (Chiralpack OT+) after CH_2N_2 derivatization of either crude L-Boc-aminobenzylalanine **1b** or D-Boc-aminobenzylalanine **1b**.

SCHEME 4. Comparative Preparations of N-Diprotected Amino-(5)-hydroxynorvaline 1m and Access to N-Diprotected Aminohomoserine 1n



Access to Piperazic Acid Derivatives 2−4. We next examined the building of the dehydropiperazic acid six-membered ring from enantiopure diprotected hydrazino acid **1m**. In the literature, the asymmetric synthesis of the dehydropiperazic acid subunit, which is found in several bioactive peptides,[4] has been achieved in more than six steps using stereoselective synthesis (trapping of enolates bearing Evans' chiral auxiliary with azodicarboxylate,[27] stereoselective cycloaddition of azodicarboxylate to a chiral diene,[28] or asymmetric reduction of a dehydroamino acid followed by nitrosation[29]). Here, we present a short access to enantiopure piperazic acid derivatives **2**−**4** from commercial L-amino acids **5j** or **5k,** via orthogonally diprotected hydrazino acids **1m** or **1n**.

Two sequences were investigated in order to prepare **1m** (Scheme 4). The first one used the nonproteogenic δ-hydroxynorvaline **5m**, which was prepared from glutamic acid methyl ester **5j** according to the method of Barlos[30] (Scheme 4, sequence A). This approach required seven steps from **5j** (19% overall yield). Then, a shorter route to **1m** also starting from **5j** and using the smooth $LiBH_4$ reduction of methyl ester in N-diprotected aminoglutamic acid compound **1j** was explored (Scheme 4, sequence B). Synthon **1m** was thus obtained on a several-gram scale with 35% overall yield from **5j**. Sequence B was also successfully applied to aspartic acid benzyl ester **5k** and led to diprotected aminohomoserine **1n** in 45% overall yield.

Next, we carried out oxidation of the hydroxy compound **1m** with the mild and selective 1-hydroxy-1,2-benziodoxol-3(1*H*)-one 1-oxide (IBX)[31] in DMSO solution, since lactals obtained after PCC or perruthenate (TPAP) oxidation of N-protected 1,4-amino alcohols are prone to

(24) Alkoxides are efficiently aminated by oxaziridine **7**, see: Foot, O. F.; Knight, D. W. *J. Chem. Soc., Chem. Commun.* **2000**, 975−976.

(25) Thioethers are aminated to sulfilimines by oxaziridines. See ref 21a and: Armstrong, A.; Cooke, R. S. *J. Chem. Soc., Chem. Commun.* **2002**, 904−905.

(26) For formylation of alcohols with chloral, see: Ram, R.; Meher, N. K. *Tetrahedron* **2002**, *58*, 2997−3001.

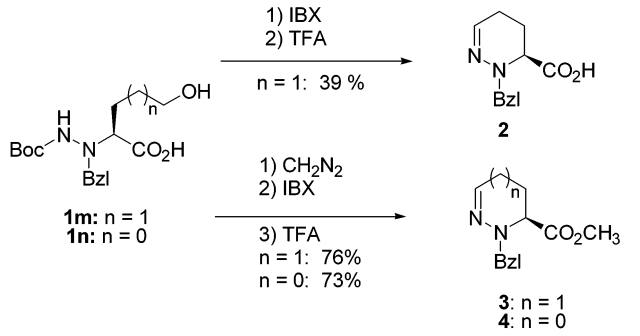
(27) (a) Nakamura, Y.; Shin, C. G. *Chem. Lett.* **1992**, 49−52. (b) Nakamura, Y.; Shin, C. G. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 2151−2161. (c) Schmidt, U.; Riedl, B. *J. Chem. Soc., Chem. Commun.* **1992**, 1186−1187. (d) Xi, N.; Alemany, L. B.; Ciufolini, M. *J. Am. Chem. Soc.* **1998**, *120*, 80−86.

(28) Aspinall, I. H.; Cowley, P. M.; Mitchell, G.; Stoodley, R. J. *J. Chem. Soc., Chem. Commun.* **1993**, 1179−1180. (b) Aspinall, I. H.; Cowley, P. M.; Mitchell, G.; Raynor, C. M.; Stoodley, R. J. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2591−2599.

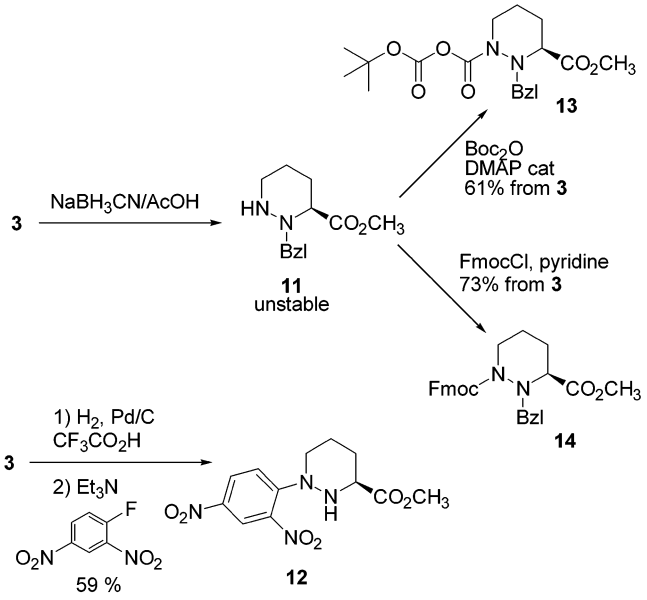
(29) Schmidt, U.; Braun, C.; Sutoris, H. *Synthesis* **1996**, 223−229.

(30) Barlos, K.; Mamos, P.; Papaioannou, D.; Patrianakou, S. *J. Chem. Soc., Chem. Commun.* **1987**, 1583−1584.

SCHEME 5. Preparation of Piperazic Derivatives 2−4 from 1m and 1n



SCHEME 6. Reduction of Piperazic Derivative 3



overoxidation to butyrolactams[32] (Scheme 5). Subsequent treatment with TFA allowed hydrazone formation and so delivered dehydropiperazic acid **2** in 39% overall yield. Diazomethane esterification of **1m** followed by oxidation with IBX and TFA treatment resulted in a cleaner reaction and led to dehydropiperazic acid derivatives **3** in good yield (76%; Scheme 5). Protection of the N_α in compound **8** proved to be essential, since cleavage of the benzyl group prior to oxidation and then acidic treatment did not lead to N_α-unprotected **3**. This sequence was also successfully applied to analogue **1n** and yielded (73%) derivative **4**, which is a useful precursor to a novel class of proline surrogates[33] (Scheme 5).

Reduction of the hydrazone function in **3** was also investigated (Scheme 6). The use of $NaBH_3CN$ yielded quantitatively **11**, which was unstable and spontaneously reoxidized to **3** (30% of **3** formed within 5 days at 4 °C[34]). To improve stability, N_β protection in **11** was examined. Reacting Boc_2O with **11** in the presence of catalytic DMAP resulted in the unexpected formation of carbamic carbonic anhydride **13**, which proved to be unusually stable. No evolution to the expected N-Boc carbazate[35] was observed after prolonged treatment of **13** with DMAP and thermal decomposition of **13** (studied by differential scanning calorimetry) occurred at 150 °C. The Fmoc protecting group was introduced using FmocCl to give the stable and entirely protected compound **14**. Hydrogenation over Pd on charcoal resulted in both reduction of the C=N double bond and cleavage of the benzyl N_α protecting group. The resulting unstable product was derivatized with Sanger's reagent to yield enantiopure, crystalline, and stable derivative **12** in 59% overall yield. All physical data of **12** were in agreement with literature,[36] except melting point, which was significantly higher.

Conclusion

In conclusion, a library of enantiopure N_α-benzyl-N_β-Boc-α-hydrazino acids **1a**−**n** was prepared on a multigram scale according to a two-step sequence, using reductive alkylation of L-amino acids **5** and subsequent efficient electrophilic amination with oxaziridine **7**. Hydroxy-substituted synthons **1m** and **1n** were also conveniently transformed into piperazic acid derivatives **2**−**4**. The highly functionalized synthons **1a**−**n** or **2** may find applications in the combinatorial discovery of new bioactive compounds or the design of stable peptide secondary structures containing one or several N−N−C−C=O fragments. Further introduction of **1a**−**n** or **2** in new hydrazinopeptides or oligomers of α-hydrazino acids using conventional peptide synthesis is currently under investigation in our laboratory.

Experimental Section

General Procedure for the Amination of *N*-Benzylamino Acids 6 by Oxaziridine 7. A suspension of the *N*-benzylamino acid (10 mmol) in MeOH (20 mL) was treated at 0 °C with a solution of Me_4NOH (or Et_4NOH) in MeOH (4.55 mL, 10 mmol). After stirring for 5 min, the solution was concentrated in vacuo. To the residue dissolved in CH_2Cl_2 (50 mL) was added dropwise at −78 °C a solution of oxaziridine **7**[22] (2.75 g, 10.5 mmol) in CH_2Cl_2 (50 mL). The cooling bath was allowed to warm slowly overnight. In the case of Bzl-Lys(ϵ-Z) **6e**, Bzl-Tyr(OBzl) **6f**, or Bzl-Met(O) **6g**, the reaction mixture was concentrated in vacuo and the residue was dissolved in water (120 mL). The basic aqueous phase was washed with isopropyl ether (25 mL), acidified with $KHSO_4$ (1.36 g) until pH = 3−4, and then extracted with CH_2Cl_2 (3 × 150 mL). In the other cases, the basic aqueous phase (3 × 200 mL) obtained after extraction of the reaction mixture was washed with CH_2Cl_2 (25 mL), acidified with $KHSO_4$ (1.36 g) until pH = 3−4, and then extracted with CH_2Cl_2 (3 × 150 mL). In all cases, the final CH_2Cl_2 phase was dried over Na_2SO_4

(31) For a convenient preparation of IBX (**CAUTION:** explosive under impact or heating), see: Frigerio, M.; Santagostino M., Sputore, S. *J. Org. Chem.* **1999**, *64*, 4537−4538.

(32) Olsen, R. K.; Ramasamy, K.; Emery, T. *J. Org. Chem.* **1984**, *49*, 3527−3534. (b) Altmann, K.-H. *Tetrahedron Lett.* **1993**, *34*, 7721−7724.

(33) Mish, M. R.; Guerra, F. M.; Carreira, E. M. *J. Am. Chem. Soc.* **1997**, *119*, 8379−8380.

(34) The N_α-unprotected analogue of **11** underwent decomposition to the achiral conjugated hydrazone derivative at room temperature; see: Paquette, L. A.; Duan, M.; Konetzki, I.; Kempmann, C. *J. Am. Chem. Soc.* **2002**, *124*, 4257−4270.

(35) It was recently shown that carbamic carbonic anhydrides are unstable intermediates in the formation of N-Boc-carbamates; see: Basel, Y.; Hassner, A. *J. Org. Chem.* **2000**, *65*, 6368−6380.

(36) Bevan, K.; Davies, J. S.; Hassall, C. H.; Morton, R. B.; Phillips, D. A. S. *J. Chem. Soc. C* **1971**, 514−522. (b) Aspinall, I. H.; Cowley, P. M.; Mitchell, G.; Stoodley, R. J. *J. Chem. Soc., Chem. Commun.* **1993**, 1179−1180. (c) References 4b and 27b.

(37) De Boer, T. J.; Backer, H. J. *Organic Syntheses*; John Wiley & Sons: New York, 1963; Collect. Vol. IV, p 250−253.

and concentrated in vacuo. The crude product was generally pure enough for most purpose. It could be either recrystallized or reacted with an amine to afford a crystalline salt derivative.

L-***N*-Benzyl-*N*-(*tert*-butoxycarbonylamino)valine 1a.** As described above, L-*N*-benzylvaline (3.78 g, 18.2 mmol) and Me_4-NOH afforded crude **1a** (3.51 g, 59%). Recrystallization from boiling hexane (70 mL) yielded pure **1a** as a colorless solid (2.85 g, 48%): mp 108 °C; $[\alpha]^{25}_D$ +26.6 (*c* 1, MeOH) (lit.[21a] $[\alpha]^{25}_D$ +25.6 (*c* 1, MeOH)). Analytical data were in full agreement with those reported.[21a]

L-***N*-Benzyl-*N*-(*tert*-butoxycarbonylamino)alanine 1b.** As described above, L-*N*-benzylalanine (2.69 g, 15 mmol) and Et_4NOH afforded crude **1b** (3.71 g, 84%). Recrystallization from boiling cyclohexane (74 mL) yielded pure **1b** as a colorless solid (3.60 g, 81%): mp 118 °C; $[\alpha]^{25}_D$ +22.6 (*c* 1.2, MeOH); ^{1}H NMR ($CDCl_3$) δ 1.32 (s, 9H), 1.38 (d, J = 7 Hz, 3H), 3.64 (q, J = 7 Hz, 1H), 3.95 (s, 2H), 6.08 (br s, 1H), 7.24−7.37 (m, 5H), 10.21 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 12.6, 28.0, 60.9, 81.3, 127.9, 128.5, 129.4, 135.6, 156.6, 175.7. Anal. Calcd for $C_{15}H_{22}N_2O_4$ (294.3): C, 61.21; H, 7.53; N, 9.52. Found: C, 60.95; H, 7.56; N, 9.57.

L-***N*-Benzyl-*N*-(*tert*-butoxycarbonylamino)isoleucine 1c.** As described above, l-*N*-benzylisoleucine (4.44 g, 20 mmol) and Et_4NOH afforded crude **1c** (4.40 g, 65%). Recrystallization from boiling hexane (40 mL) yielded pure **1c** (3.51 g, 52%). Analytical data were in full agreement with those reported.[11]

L-***N*-Benzyl-*N*-(*tert*-butoxycarbonylamino)tryptophane 1d, Hexylamine Salt.** As described above, L-*N*-benzyltryptophane (3.52 g, 12 mmol) and Me_4NOH afforded crude **1d** (4.60 g, 93%) as a glassy solid. A portion of this solid (0.331 g) was dissolved in ether (10 mL) and treated by hexylamine (0.132 mL, 1 mmol) to yield pure **1d**·hexylamine salt as a colorless solid (0.322 g, 63%): mp 142 °C; $[\alpha]^{25}_D$ +28.6 (*c* 1.8, MeOH); ^{1}H NMR ($CDCl_3$,) δ 0.77 (t, J = 7 Hz, 3H), 1.02−1.16 (m, 8H), 1.33 (s, 9H), 2.25 (t, J = 8 Hz, 2H), 3.15 (m, 2H), 3.61 (m, 1H), 3.98 and 3.88 (AB system, J = 13 Hz, 2H), 6.93−7.49 (m, 10H), 7.77 (br s, 3H), 9.04 and 9.37 (two rotamers, br s, 0.27H and 0.73H); ^{13}C NMR ($CDCl_3$) δ (major rotamer) 13.9, 22.4, 26.5, 26.2, 28.0, 28.2, 31.2, 39.4, 61.0, 70.3, 79.8, 111.5, 112.0, 118.4, 118.9, 121.5, 123.5, 127.3, 127.6, 128.1, 129.7, 136.0, 136.4, 156.3, 182.5. Anal. Calcd for $C_{29}H_{42}N_4O_4$ (510.7): C, 68.21; H, 8.29; N, 10.97. Found: C, 68.54; H, 8.17; N, 10.86.

L-*N*-α-**Benzyl-*N*-ϵ-benzyloxycarbonyl-*N*-α-(*tert*-butoxycarbonylamino)lysine 1e, Dibenzylamine Salt.** As described above, l-*N*-α-benzyl-*N*-(ϵ-benzyloxycarbonyl)lysine **6e** (0.200 g, 0.55 mmol) and Et_4NOH afforded crude **1e** (0.200 g, 75%), which was dissolved in ether (10 mL). Treatment of the solution by dibenzylamine (0.088 mL, 0.45 mmol) yielded pure **1e**·dibenzylamine salt as a colorless solid (0.150 g, 40%): mp 54 °C; $[\alpha]^{25}_D$ +24.7 (*c* 1.5, MeOH); ^{1}H NMR ($CDCl_3$) δ 1.20−1.49 (m, 15H), 3.09 (m, 3H), 3.83 (br s, 6H), 5.02 (s, 2H), 5.23 (br s, 1H), 6.99−7.37 (m, 20H); ^{13}C NMR ($CDCl_3$) δ 23.0, 28.0, 28.9, 29.3, 40.0, 50.3, 61.1, 62.2, 66.1, 79.2, 127.0, 127.7, 127.8, 128.2, 128.3, 128.5, 129.0, 129.2, 129.3, 133.6, 136.7, 137.9, 155.6, 156.3, 178.4. Anal. Calcd for $C_{40}H_{50}N_4O_6$·$0.5H_2O$ (691.9): C, 69.44; H, 7.43; N, 8.10. Found: C, 69.68; H, 7.42; N, 7.98.

L-***N*,*O*-Dibenzyl-*N*-(*tert*-butoxycarbonylamino)tyrosine 1f, Dicyclohexylamine Salt.** As described above, L-*N*,*O*-dibenzyltyrosine (2.9 g, 8 mmol) and Me_4NOH afforded crude **1f** (3.59 g, 94%) as a glassy solid, which was dissolved in a mixture of ether (15 mL) and hexane (30 mL). Treatment of the solution by dicyclohexylamine (1.8 mL, 9 mmol) yielded pure **1f**·dicyclohexylamine salt as a colorless solid (3.73 g, 71%): mp 105 °C; $[\alpha]^{25}_D$ +37.3 (*c* 1.4, MeOH); ^{1}H NMR ($CDCl_3$) δ 1.16−1.67 (m, 21H), 1.80 (m, 4H), 2.00 (m, 4H), 2.95 (m, 4H), 3.39 (m, 1H), 3.96 (s, 2H), 5.03 (s, 2H), 6.84 (d, J = 8,5 Hz, 2H), 7.17−7.40 (m, 12H), 7.83 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 24.7, 25.2, 28.2, 29.1, 29.3, 35.8 and 36.3 (two rotamers), 52.5, 61.8, 69.2, 70.0, 78.7 and 79.0 (two rotamers), 114.1, 126.8, 127.4, 127.8, 128.3, 128.5, 129.3, 130.4, 132.9, 137.4, 137.8, 138.3, 155.4, 157.0, 177.9. Anal. Calcd for $C_{40}H_{55}N_3O_5$ (657.9): C, 73.03; H, 8.43; N, 6.39. Found: C, 73.07; H, 8.47; N, 6.33.

L-***N*-Benzyl-*N*-(*tert*-butoxycarbonylamino)methionine (*RS*)-*S*-oxide 1g.** As described above, l-*N*-benzylmethionine (*RS*)-*S*-oxide (3.83 g, 15 mmol) and Et_4NOH afforded **1g** (5.05 g, 91%) as a colorless and solid mixture of two diastereomers: $[\alpha]^{25}_D$ +7.5 (*c* 1.3, MeOH); ^{1}H NMR ($CDCl_3$) δ 1.34 (s, 9H), 2.04−2.28 (m, 2H), 2.60 and 2.63 (2 s, 3H), 3.12 (m, 1H), 3.37−3.48 (m, 2H), 3.99 and 4.06 (AB system, J = 13 Hz, 2H), 6.86 (br s, 1H), 7.24−7.34 (m, 5H), 11.45 (br s, 1H); ^{13}C NMR (CD_3OD) δ 23.4 and 25.0 (two diastereomers), 28.5, 37.7 and 38.3 (two diastereomers), 51.2 and 52.1 (two diastereomers), 62.0, 64.4 and 65.6 (two diastereomers), 81.0, 128.6, 129.3, 130.9, 138.2, 157.7, 174.8 and 174.9 (two diastereomers). Anal. Calcd for $C_{17}H_{26}N_2O_5S$ (370.5): C, 55.12; H, 7.07; N, 7.56; S, 8.65. Found: C, 54.87; H, 7.00; N, 7.84; S, 8.22.

L-***N*-Benzyl-*N*-(*tert*-butoxycarbonylamino)asparagine 1h.** As described above, l-*N*-benzylasparagine (0.223 g, 1 mmol) and Me_4NOH afforded **1h** as a colorless glassy solid (0.158 g, 41%): mp 169 °C; $[\alpha]^{25}_D$ −13.6 (*c* 1, MeOH); ^{1}H NMR ($CDCl_3$) δ 1.28 (s, 9H), 2.70 (d, J = 6.5 Hz, 2H), 3.82 (t, J = 6.5 Hz, 1H), 4.06 and 4.14 (AB system, J = 12.5 Hz, 2H), 6.40 (br s, 1H), 6.67 (br s, 1H), 7.24−7.32 (m, 5H), 8.55 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 28.0, 35.9, 61.5, 62.8, 80.9, 127.8, 128.3, 129.7, 135.8, 156.9, 173.9, 176.1. Anal. Calcd for $C_{16}H_{23}N_3O_5$ (337.4): C, 56.96; H, 6.87; N, 12.46. Found: C, 56.75; H, 7.09; N, 12.28.

L-***N*-Benzyl-*N*-(*tert*-butoxycarbonylamino)glutamic Acid 1i.** As described above, l-*N*-benzylglutamic acid (0.238 g, 1 mmol) and Et_4NOH (2 mmol) afforded crude **1i** (0.278 g, 79%). Recrystallization from boiling isopropyl ether yielded pure **1i** as a colorless solid (0.162 g, 46%): mp 130 °C; $[\alpha]^{25}_D$ +12.2 (*c* 1.3, MeOH); ^{1}H NMR ($CDCl_3$) δ 1.33 (s, 9H), 1.97−2.14 (m, 2H), 2.55−2.78 (m, 2H), 3.51 (br s, 1H), 4.06 (br s, 2H), 6.45 (1H), 7.24−7.44 (m, 5H), 9.62 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 24.6, 28.0, 30.7, 61.2, 63.8, 80.7, 81.7, 127.7, 128.3, 129.7, 136.8, 155.9, 158.2, 175.8, 179.2. Anal. Calcd for $C_{17}H_{24}N_2O_6$ (352.4): C, 57.94; H, 6.86; N, 7.95. Found: C, 58.14; H, 6.77; N, 7.92.

L-***N*-Benzyl-*N*-(*tert*-butoxycarbonylamino)aspartic Acid 4-(Benzyl Ester) 1k, Dicyclohexylamine Salt.** L-*N*-benzylaspartic acid 4-benzyl ester **6k** (3.13 g, 10 mmol) was dissolved in ice-cold water and reacted with ice-cold aqueous Me_4NOH. After lyophilization and as described above, crude **1k** (3.93 g, 92%) was obtained. A portion of the crude **1k** (0.275 g) in ether (5 mL) was reacted with dicyclohexylamine (0.130 mL, 0.66 mmol) to yield pure **1k**·dicyclohexylamine salt as a colorless solid (0.231 g, 56%): mp 136 °C; $[\alpha]^{25}_D$ +16.7 (*c* 0.9, MeOH); ^{1}H NMR ($CDCl_3$) δ 1.15−1.65 (m, 21H), 1.76 (m, 4H), 1.96−2.02 (m, 4H), 2.76−2.92 (m, 4H), 3.83 (t, J = 8 Hz, 1H), 4.05 (br s, 2H), 5.11 (s, 2H), 7.21−7.30 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 24.7, 25.2, 28.2, 29.0 and 29.1 (two rotamers), 37.1, 52.5, 61.6, 64.0 and 66.0 (two rotamers), 77.6 and 78.7 (two rotamers), 127.0, 127.9, 128.0, 128.4, 129.3, 136.3, 138.3, 155.2 and 156.5 (two rotamers), 171.6, 176.3. Anal. Calcd for $C_{35}H_{51}N_3O_6$ (609.8): C, 68.94; H, 8.43; N, 6.89. Found: C, 69.04; H, 8.25; N, 6.86.

L-***N*-Benzyl-*N*-(*tert*-butoxycarbonylamino)serine 1l.** As described above, L-*N*-benzylserine (4.68 g, 24 mmol) and Et_4-NOH afforded crude **1l** (5.45 g, 73%). Recrystallization from a mixture of boiling AcOEt (40 mL) and heptane (100 mL) yielded pure **1l** as a colorless solid (4.25 g, 57%): mp 145 °C (dec); $[\alpha]^{25}_D$ +9.6 (*c* 1.1, MeOH); ^{1}H NMR ($CDCl_3$) δ 1.30 (s, 9H), 3.68−4.36 (m, 5H), 6.38 (br s, 1H), 7.23−7.36 (m, 5H); ^{13}C NMR ($CDCl_3$) (two rotamers) δ major and (minor): 28.0 and (27.8), 59.7 and (59.3), 61.5 and (62.3), 66.4 and (67.5), 81.2 and (82.8), 127.8, 128.4, 129.2, 130.0, 136.1 and (136.4), 157.2 and (158.0), 174.2 and (172.8). Anal. Calcd for $C_{15}H_{22}N_2O_5$ (310.3): C, 58.05; H, 7.14; N, 9.03. Found: C, 57.63; H, 7.02; N, 8.95.

L-***N*-Benzyl-*N*-(*tert*-butoxycarbonylamino)-δ-hydroxynorvaline 1m, Dicyclohexylamine Salt.** As described above, L-*N*-benzyl-δ-hydroxynorvaline (0.222 g, 1 mmol) and Et_4NOH

were reacted with oxaziridine **7** for 5.5 h from −78 to 0 °C. Crude **1m** (0.338 g, 100%) was then dissolved in AcOEt and reacted with dicyclohexylamine (0.200 mL, 1 mmol) to yield pure **1m**·dicyclohexylamine salt as a colorless solid (0.314 g, 60%): mp 159 °C; $[\alpha]^{25}_D$ +39.8 (*c* 1, MeOH); ^{1}H NMR ($CDCl_3$) δ 1.18−1.46 (m, 25H), 1.80 (m, 4H), 2.00−2.05 (m, 4H), 2.89−3.01 (m, 2H), 3.23 (m, 1H), 3.56−3.65 (m, 2H), 3.94−4.10 (m, 2H), 7.24−7.37 (m, 5H), 7.87 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 24.7, 25.2, 27.3, 28.1 and 28.3 (two rotamers), 29.2 and 29.4 (two rotamers), 31.3, 52.6, 61.6, 62.1, 67.5, 79.0, 127.1, 128.0, 129.6, 137.6, 156.1, 179.1. Anal. Calcd for $C_{29}H_{49}N_3O_5$ (519.7): C, 67.02; H, 9.50; N, 8.09. Found: C, 67.10; H, 9.33; N, 8.05.

L-*N*-Benzyl-*N*-(*tert*-butoxycarbonylamino)-*δ*-hydroxynorvaline 1m, Dicyclohexylamine Salt (by Reduction of 1j). $LiBH_4$ (0.590 g, 25.6 mmol) was slowly added at 0 °C and under Ar to a solution in dry THF (30 mL) and dry MeOH (1.05 mL, 25.6 mmol) of crude L-*N*-benzyl-*N*-(*tert*-butoxycarbonylamino)-5-(methyl ester)glutamic acid (4.71 g, 12.8 mmol) prepared[22] from L-*N*-benzyl-5-(methyl ester)glutamic acid (3.77 g, 15 mmol). The resulting mixture was refluxed for 2.5 h, cooled to 0 °C, and then slowly poured into a cold mixture of 0.1 M aqueous citric acid (200 mL) and CH_2Cl_2 (200 mL). The aqueous phase was extracted by CH_2Cl_2. The combined organic phases were dried over Na_2SO_4 and then concentrated in vacuo. The residue (4.21 g) was dissolved in diisopropyl ether (80 mL) and reacted with diclyclohexylamine (2.5 mL, 12.5 mmol) to yield 4.87 g of l-*N*-benzyl-*N*-(*tert*-butoxycarbonylamino)-*δ*-hydroxynorvaline **1m**, dicyclohexylamine salt (62% from **6j**).

L-*N*-Benzyl-*N*-(*tert*-butoxycarbonylamino)homoserine 1n, Dibenzylamine Salt (by Reduction of 1k). In the same way, reduction of crude L-*N*-benzyl-*N*-(*tert*-butoxycarbonylamino)aspartic acid 4-(benzyl ester) (3.93 g) prepared from L-*N*-benzylaspartic acid 4-(benzyl ester) (3.13 g, 10 mmol) with $LiBH_4$ afforded crude **1n** (3.5 g). It was dissolved in ether (40 mL) and reacted with dibenzylamine (2 mL, 10. mmol) to yield 2.69 g of **1n**·dibenzylamine salt (52% from **6k**) as a colorless solid: mp 124 °C; $[\alpha]^{25}_D$ +25.5 (*c* 1, MeOH); ^{1}H NMR ($CDCl_3$) δ 1.36 (s, 9H), 1.80 (m, 2H), 3.35 (m, 1H), 3.59 (m, 1H), 3.74 (m, 1H), 3.86 (s, 4H), 3.94 (s, 2H), 7.24−7.52 (m, 15H); ^{13}C NMR ($CDCl_3$) δ 28.1 and 28.3 (two rotamers), 50.5, 60.9, 61.7, 62.7, 65.8 and 66.1 (two rotamers), 80.0 and 80.5 (two rotamers), 127.4, 128.3, 128.6, 128.8, 129.5, 130.8, 133.5, 137.0 and 137.4 (two rotamers), 155.8 and 156.2 (two rotamers), 177.8. Anal. Calcd for $C_{30}H_{39}N_3O_5$ (521.6): C, 69.07; H, 7.54; N, 8.06. Found: C, 68.89; H, 7.67; N, 8.08.

(*S*)-2-Benzyl-2,3,4,5-tetrahydro-3-pyridazinecarboxylic Acid 2. L-*N*-Benzyl-*N*-(*tert*-butoxycarbonylamino)-*δ*-hydroxynorvaline (0.185 g) [obtained after extraction by ether of a mixture of the dicyclohexylamine salt **1m** (0.260 g, 0.5 mmol) and $KHSO_4$ (0.070 g, 0.5 mmol) in water] was dissolved in DMSO (2 mL) and reacted at room temperature with IBX[31] (0.182 g, 0.65 mmol) for 15 h. The resulting mixture was diluted with water (20 mL) and CH_2Cl_2 (20 mL). After filtration of the solid, the aqueous phase was extracted with CH_2Cl_2. The combined organic phases were washed with water, dried over Na_2SO_4, and concentrated in vacuo. The resulting oily residue (185 mg) was dissolved in CH_2Cl_2 (3 mL) and reacted with TFA (0.1 mL, 1.3 mmol) for 3 h at room temperature. The resulting mixture was diluted with CH_2Cl_2 and saturated $NaHCO_3$. The aqueous phase was washed with CH_2Cl_2, acidified to pH 2 by aqueous citric acid, and then extracted by CH_2Cl_2. The combined organic phases were dried over Na_2SO_4 and then concentrated in vacuo. The resulting solid (65 mg) was recrystallized in a THF/ether mixture to yield **2** (43 mg, 39%) as white needles: mp 140 °C; $[\alpha]^{25}_D$ −18.0 (*c* 0.55, THF); ^{1}H NMR ($CDCl_3$) δ 1.80−1.85 (m, 1H), 2.09−2.12 (m, 2H), 2.22−2.26 (m, 1H), 3.79 (t, *J* = 4.5 Hz, 1H), 4.34 and 4.63 (AB system, *J* = 14.5 Hz, 2H), 6.84 (t, *J* = 1 Hz, 1H), 7.28−7.36 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 19.9, 20.2, 56.4, 60.5, 127.6, 128.5, 128.8, 137.0, 138.0, 175.0. Anal. Calcd. for $C_{12}H_{14}N_2O_2$ (218.2): C, 66.04; H, 6.47; N, 12.84. Found: C, 65.53; H, 6.38; N, 12.84.

Methyl (*S*)-2-Benzyl-2,3,4,5-tetrahydro-3-pyridazinecarboxylate 3. L-*N*-Benzyl-*N*-(*tert*-butoxycarbonylamino)-*δ*-hydroxynorvaline [obtained after extraction by ether of a mixture of the dicyclohexylamine salt **1m** (4.42 g, 8.5 mmol) and $KHSO_4$ (1.19 g, 0.5 mmol) in water] was reacted with a slight excess of CH_2N_2[37] in ether. The mixture was concentrated in vacuo to give the crude methyl ester **8** as a colorless solid, which was dissolved in DMSO (25 mL) and reacted with IBX[31] (2.81 g, 10 mmol) for 15 h. The resulting mixture was diluted with water (50 mL) and CH_2Cl_2 (200 mL). After filtration of the solid, the aqueous phase was extracted by CH_2Cl_2. The combined organic phases were washed with water, dried over Na_2SO_4, and concentrated in vacuo. The resulting oily residue was dissolved in CH_2Cl_2 (80 mL) and reacted with TFA (4.2 mL, 1.3 mmol) for 4 h at room temperature. The mixture was washed with water and aqueous saturated $NaHCO_3$, dried over Na_2SO_4, and concentrated in vacuo. Purification by column chromatography (silica gel; ether/hexane, 1:2) afforded methyl (*S*)-2-benzyl-2,3,4,5-tetrahydro-3-pyridazinecarboxylate **3** (1.50 g, 76% from **1m**) as a light brown solid: mp 30 °C; $[\alpha]^{25}_{436}$ +13.7 (*c* 1, MeOH); ^{1}H NMR ($CDCl_3$) δ 1.94−2.18 (m, 4H), 3.68 (t, *J* = 4.5 Hz, 1H), 3.71 (s, 3H), 4.25 and 4.56 (AB system, *J* = 14.5 Hz, 2H), 6.65 (t, *J* = 3 Hz, 1H), 7.24−7.31 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 20.1, 21.7, 51.9, 56.4, 60.3, 127.3, 128.3, 128.62, 135.9, 137.7, 172.0. Anal. Calcd for $C_{13}H_{16}N_2O_2$ (232.3): C, 67.22; H, 6.94; N, 12.06. Found: C, 67.41; H, 6.97; N, 11.99.

Methyl (*S*)-2-Benzyl-3,4-dihydro-3-pyrazolecarboxylate 4. In the same way, L-*N*-benzyl-*N*-(*tert*-butoxycarbonylamino)homoserine **1n**, dibenzylamine salt (0.261 g, 0.5 mmol) afforded **4** (0.080 g, 73% from **1n**) as a light yellow oil: $[\alpha]^{25}_D$ −193.8 (*c* 1.1, MeOH); ^{1}H NMR ($CDCl_3$) δ 2.82−3.07 (2H), 3.64 (s, 3H), 3.64 (t, *J* = 12 Hz, 1H), 4.30 and 4.39 (AB system, *J* = 14 Hz, 2H), 6.67 (s, 1H), 7.14−7.41 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 38.7, 52.3, 58.8, 64.4, 127.5, 128.3, 129.7, 136.0, 140.9, 171.9. Anal. Calcd. for $C_{12}H_{14}N_2O_2$ (218.2): C, 66.04; H, 6.47; N, 12.84. Found: C, 65.87; H, 6.55; N, 12.64.

Carbamic Carbonic Anhydride 13. To methyl (*S*)-2-benzyl-2,3,4,5-tetrahydro-3-pyridazinecarboxylate **3** (0.116 g, 0.50 mmol) in acetic acid (1 mL) was added in small portions sodium cyanoborohydride (0.085 g, 1.4 mmol). The resulting mixture was stirred for 30 min at room temperature and then diluted with water (20 mL) and CH_2Cl_2 (20 mL). Saturated aqueous $NaHCO_3$ was added until pH = 8. After usual workup, the crude product, which was unstable, was dissolved in THF (1 mL) and immediately reacted with Boc_2O (0.218 g, 1 mmol) in the presence of (dimethylamino)pyridine (7 mg, 0.06 mmol) and triethylamine (140 mL, 1 mmol) at room temperature. The mixture was stirred overnight and then diluted with ether and washed with aqueous citric acid. The organic phase was dried over Na_2SO_4 and concentrated in vacuo. The resulting solid was recrystallized in boiling hexane to give carbamic carbonic anhydride **13** (0.116 g, 61% from **3**): mp 62 °C; IR (KBr): 1728, 1742, 1764 cm^{-1}. $[\alpha]^{25}_D$ −90.2 (*c* 1, MeOH); ^{1}H NMR ($CDCl_3$) δ 1.46−2.15 (m, 13H), 3.17−4.24 (m, 8H), 7.24−7.51 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 18.4, 20.1, 27.6, 37.5, 52.2, 57.6 and 57.7 (two rotamers), 84.0, 127.9, 128.6, 129.0, 129.2, 129.6, 136.0, 148.1, 150.1, 171.5. HRMS (FAB) calcd for $C_{19}H_{27}N_2O_6$ (MH^+) 379.1869, found 379.1878. Anal. Calcd for $C_{19}H_{26}N_2O_6$ (378.4): C, 60.31; H, 6.92; N, 7.40. Found: C, 60.48; H, 6.96; N, 7.40.

Methyl (*S*)-1-(9-Fluorenylmethoxycarbonyl)-2-benzylhexahydro-3-pyridazinecarboxylate 14. To methyl (*S*)-2-benzyl-2,3,4,5-tetrahydro-3-pyridazinecarboxylate **3** (0.141 g, 0.61 mmol) in acetic acid (1.3 mL) was added in small portions sodium cyanoborohydride (0.104 g, 1.74 mmol). The resulting mixture was stirred for 30 min at room temperature and then diluted with water (20 mL) and CH_2Cl_2 (20 mL). Saturated aqueous $NaHCO_3$ was added until pH = 8. After usual workup,

the crude product, which was unstable, was dissolved in CH_2Cl_2 (2 mL) and immediately reacted with FmocCl (0.174 g, 0.67 mmol) in the presence of pyridine (150 μL, 1.85 mmol) for 5 h. The mixture was diluted with CH_2Cl_2 and the organic phase was washed with water and aqueous citric acid, dried over Na_2SO_4, and concentrated in vacuo. Purification by column chromatography (silica gel; ether/hexane, 2:3) afforded methyl (*S*)-1-(9-fluorenylmethoxycarbonyl)-2-benzylhexahydro-3-pyridazinecarboxylate **14** (0.203 g, 73% from **3**) as a colorless oil: $[\alpha]^{25}_D$ −48.8 (*c* 1, MeOH); ^{1}H NMR ($CDCl_3$) δ 1.58−2.06 (m, 4H), 3.25 (t, J = 11.5 Hz, 1H), 3.53 (sl, 3H), 3.53−4.33 (m, 7H), 7.24−7.45 and 7.73−7.83 (m, 13H); ^{13}C NMR ($CDCl_3$) δ 18.7, 20.2, 36.6, 47.4, 51.8, 57.1 and 57.8 (two conformers), 67.7, 119.8, 125.4−129.4, 136.4, 141.3, 144.2 and 144.3 (two conformers), 156.6, 171.7. Anal. Calcd for $C_{28}H_{28}N_2O_4$ (456.5): C, 73.66; H, 6.18; N, 6.14. Found: C, 73.43; H, 6.06; N, 6.16.

Methyl (*S*)-1-(2,4-Dinitrophenyl)hexahydro-3-pyridazinecarboxylate 12. A mixture of methyl (*S*)-2-benzyl-2,3,4,5-tetrahydro-3-pyridazinecarboxylate **3** (77 mg, 0.33 mmol) and TFA (0.026 mL, 0.33 mmol) in MeOH (2 mL) was hydrogenated (1 bar, room temperature) for 17 h in the presence of wet 5% Pd on charcoal (13 mg, Degussa type E101). After filtration over Celite and concentration in vacuo, the residue was dissolved in EtOH (0.5 mL) and reacted for 6 h with triethylamine (0.046 mL, 0.33 mmol) and 2,4-dinitro-1-fluorobenzene (0.042 mL, 0.33 mmol). Purification by column chromatography (silica gel; AcOEt/hexane, 1:3) afforded methyl (*S*)-1-(2,4-dinitrophenyl)hexahydro-3-pyridazinecarboxylate **12** (60 mg, 59%) as a yellow solid: mp 115 °C (lit. mp 37−39 °C,[36a] 96−97 °C,[4b] 95−96 °C,[27b] 94−95 °C[36b]); $[\alpha]^{25}_D$ −365 (*c* 0.7, MeOH) (lit.[4b] $[\alpha]_D$ +358 (*c* 0.64, MeOH) for the (*R*) isomer). ^{1}H and ^{13}C NMR spectra were in full agreement with those reported.[36]

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Supporting Information Available: General methods, experimental procedures, and characterization data for compounds **5m**, **6d**, **6f**, **6g**, **6h**, **6i**, **6j**, **6k**, **6m**, **8**, and **9**; HPLC analysis of **1b**; and NMR spectra for **9**. This material is available free of charge via the Internet at http://pubs.acs.org.

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