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C_2-Symmetric Val-Val Dipeptide Isosteres *via* Diethylaluminium Azide Ring Opening of Epoxyalcohols

Fabio Benedetti,[a,*] *Stanislav Miertus,*[b] *and Stefano Norbedo*[a]

[a]*Department of Chemical Sciences, University of Trieste, Via L. Giorgieri 1, I-34127 Trieste, Italy*

[b]*International Centre for Science and High Technology, UNIDO, Trieste, Italy*

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Diethylaluminium azide has been used as a highly regio- and stereo-selective reagent for the ring opening of valine-derived, sterically hindered epoxyalcohols. This reagent has enabled extending a previously described synthesis of diaminodiol dipeptide isosteres (P_1-Ψ[CH(OH)-CH(OH)]-P_1') also to isosteres with branched residues in position P_1'. The new methodology is compatible with Boc and Cbz protection of the starting aminoacid and has been applied to the synthesis of a C_2-symmetric diaminodiol Val-Val dipeptide isostere **11**, starting from the methyl ester of L-valine, in 25% overall yield over seven (for Boc protection) or six (for Cbz protection) passages. A C_2-symmetric di-MEM protected diaminodiol **17** and a mono-Boc protected, desymmetrized derivative **10** have also been obtained by the same approach. Compounds **10**, **11** and **17** can be used as core units of C_2-symmetric and non-symmetric peptidomimetic inhibitors of aspartic proteases and as intermediates for the synthesis of cyclic urea inhibitors of HIV-protease.

Key words: diethylaluminium azide, epoxyalcohol, diaminodiol dipeptide isostere, ring opening.

* Author to whom correspondence should be addressed. (E-mail: benedett@univ.trieste.it)

INTRODUCTION

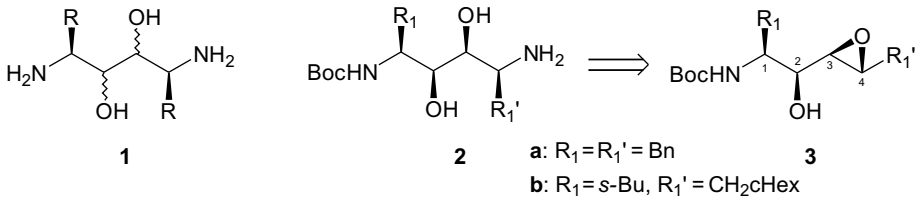
In the last two decades, the important biological role of aspartic proteases has come into clear focus. In particular, it is now established that enzymes of this class are involved in several pathologies such as, for example, AIDS, cancer, Alzheimer's disease, hypertension, malaria, *Candida* infections.[1] Aspartic proteases have thus become important therapeutic targets and inhibitors of these enzymes show great promise in the treatment of these diseases.[1,2a] Among these, inhibitors of the human immunodeficiency virus protease (HIV-1 PR) have proved to be efficient in anti-AIDS therapies and have rapidly become available as drugs.[3]

Peptidomimetic inhibitors of the general structure $P_n \cdots P_2\text{-}\Psi(P_1\text{-}P_1')\text{-}P_2' \cdots P_n'$, in which a non-cleavable isostere $\Psi(P_1\text{-}P_1')$ replaces the scissile central dipeptide $P_1\text{-}P_1'$ in a short peptide sequence that is recognized by the enzyme, are efficient inhibitors of most aspartic proteases.[1,2a,4] The structure of the dipeptide isostere $\Psi(P_1\text{-}P_1')$ is designed to provide optimal interactions with the protease active site, while the flanking residues $P_n \cdots P_2$ and $P_2' \cdots P_n'$ provide additional interactions with the corresponding enzyme subsites and can be adjusted so as to improve the bioavailability and other pharmacological properties of the inhibitor. Hydroxy-containing isosteres, such as the hydroxyethylamine group [-CH(OH)CH_2N-], the dihydroxyethylene group [-CH(OH)CH(OH)-] and the monohydroxyethylene group [-CH(OH)CH_2-] are among the most efficient replacements for the scissile amide bond.[2a,5] These groups simulate the tetrahedral transition state of amide bond hydrolysis and the incorporation of such analogs into a substrate sequence has resulted in very efficient inhibitors, with an up to 10^4-fold increment of affinity for the enzyme, with respect to the substrate.[5,6]

The spread of AIDS in the late 80's and early 90's has led to a rapid development of new approaches to designing specific inhibitors for the HIV-1 PR. One of the most elegant and original approaches exploits the C_2 symmetry of the native enzyme.[2a,5] Diaminodiols **1** have thus been developed as dipeptide isosteres and have been inserted between identical side chains. The resulting C_2-symmetric inhibitors display excellent affinity for HIV-PR, with K_i in the nM range, and lower.[7] However, until recently, the development of this class of inhibitors has been somewhat prevented by the lack of stereoselective synthetic methodologies which would give access to the different stereoisomers of **1**. All the synthetic work published until 1996 referred to C_2 symmetric (*S,R,R,S*) diaminodiols **1**, which were the only stereoisomers readily available at the time. Even if several HIV-PR inhibitors containing (*S,S,R,S*) and (*S,S,S,S*) diaminodiols as central cores had been synthesized and their biological activity had been evaluated,[8] these diastereoisomers were obtained either as by-products from homo-coupling

reactions or by inversion of the configuration of the main (*S,R,R,S*) product.[9] Difficult separations or further synthetic steps were thus required.

In 1997, we described a direct and stereoselective approach to homochiral (*S,S,S,S*) diaminodiols of the general structure of **2**.[10] Our synthesis of diaminodiols **2** was based on the epoxyalcohol **3**. Ring opening of this intermediate with ammonia or azide takes place regioselectively at C4, giving diaminodiols **2** either directly or by reduction of the azide. In our synthesis, the two amino terminals can be orthogonally protected and the synthesis is not restricted to identical R_1 and R_1' residues, as in **1**. These properties considerably expanded the scope of synthetic approaches to HIV-PR inhibitors in terms of stereocontrol and versatility. A number of peptidomimetic inhibitors based on diaminodiols **2a** and **2b** were thus synthesized and their biological activity was studied, in several cases showing IC_{50} values in the low nM range.[11]



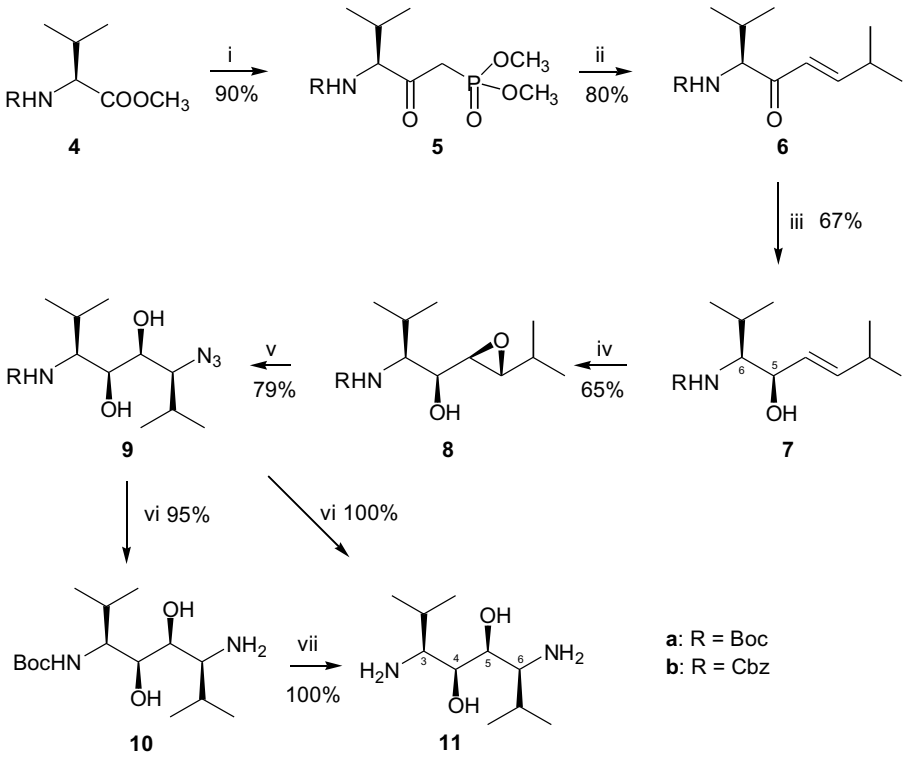
Scheme 1

The approach however has a limitation: the ring opening of the epoxide is efficient and regioselective only when the R_1' residue is not bulky. Thus dipeptide isosteres **2** with branched residues in R_1', corresponding for example to Val or Ile in P_1', were not available by this method. This drawback has now been overcome by the use of aluminium reagents for the ring opening step and the new methodology is illustrated here by the synthesis of a previously non accessible C_2-symmetric Val-Val dipeptide isostere.

RESULTS AND DISCUSSION

The synthesis of the Val-Val diaminodiols **10** and **11** (Scheme 2) starts from valine, which provides the first asymmetric centre from which chirality is then transferred by induction to the other three asymmetric carbons. Treatment of *N*-Boc valine methyl ester **4a** with an excess of lithiated methyldimethylphosphonate[12] gave the known phosphonoketone **5a** in 90% yield.[10] Horner-Emmons olefination of crude **5a** with isobutyraldehyde was carried out with potassium carbonate in dry ethanol[13] and gave the *trans*

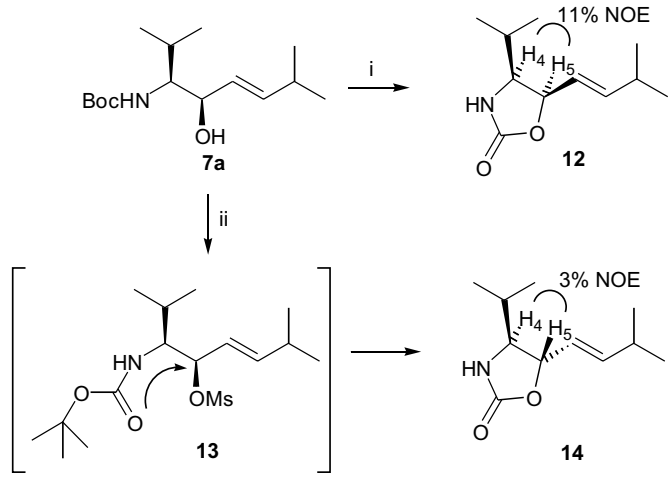
enone **6a**. The *trans* geometry of the enone was confirmed by the 16 Hz coupling constant between the vinylic protons in its ^{1}H NMR spectrum. The enone was then stereoselectively reduced with sodium borohydride in methanol to give the allylic alcohol **7a** in 95% d.e.



Scheme 2. i. *n*-BuLi, $CH_3P(O)(OCH_3)_2$, THF, –78 °C; ii. i-Pr-CHO, K_2CO_3, EtOH, 25 °C; iii. $NaBH_4$, MeOH, 0 °C; iv. *m*CPBA, CH_2Cl_2, 25 °C; v. Et_2AlN_3, toluene, 0-25 °C; vi. H_2, Pd/C, MeOH, 25 °C; vii. 6M HCl.

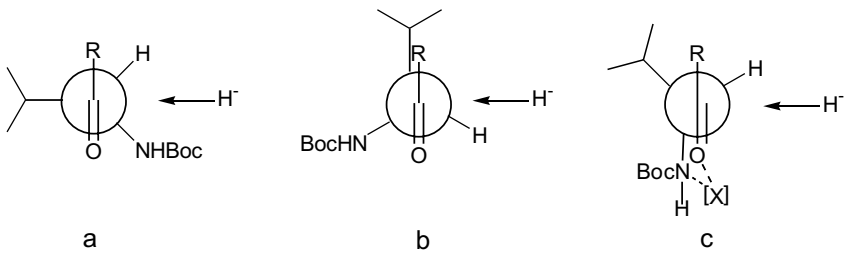
The (5*R*,6*S*) configuration of this alcohol was demonstrated by conversion into the corresponding oxazolidinone **12** (Scheme 3). NOE experiments showed a 11% enhancement between H4 and H5, indicating a *syn* configuration for **12**. In order to confirm the assignment, the corresponding *anti* diastereoisomer **14** was also obtained, as shown in Scheme 2. The *N*-Boc allylic aminoalcohol **7a** was treated with methanesulfonyl chloride and triethylamine, at 0 °C in dichloromethane, to give mesylate **13**, which immediately reacted *via* an intramolecular S_N2 displacement with the Boc carbonyl oxygen acting as the nucleophile, leading to the formation of oxazolidinone **14**

with an inversion of configuration.[14] In this compound only a 3% NOE was measured between H4 and H5, in agreement with the proposed stereochemistry for compounds **12** and **14**.



Scheme 3. i. NaH, THF, 25 °C; ii. MsCl, Et_3N, CH_2Cl_2, 0 °C.

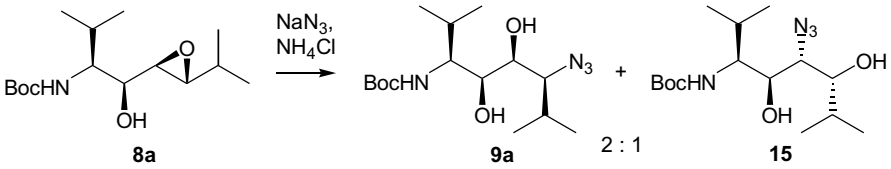
The stereochemical course of the reduction is in agreement with both the Cram and Felkin-Anh models (Scheme 4), since there is strong evidence that in α-amino ketones derived from aminoacids the side chain and the Boc-protected amino group are the *large* and *medium* residues, respectively.[10,15] A cyclic-Cram model, resulting from H-bonding or chelation between the carbonyl and the protected amino group (c, Scheme 4), would also lead to the same prediction, in agreement with the observation that the reduction of this and other α-amino ketones is generally insensitive to the nature of the solvent and reducing agent.[10]



Scheme 4. Stereochemical models for the reduction of α-aminoketones: a) Cram; b) Felkin-Anh; c) cyclic (chelated) Cram.

It is well known that peracid epoxidation of acyclic allylic alcohols leads preferentially to *threo* epoxyalcohols.[16] Accordingly, when we treated the allylic alcohol **7a** with *m*-chloroperoxybenzoic acid (Scheme 2), we obtained the *syn* epoxyalcohol **8a** as the only product, while no traces of the corresponding product of *anti*-epoxidation were detected. The very high level of stereocontrol of this reaction is remarkable, as the stereoselectivity is often poor in the epoxidation of *trans* allylic alcohols,[17] and confirms previous results on structurally similar substrates.[10]

Having obtained this intermediate, it was now necessary to introduce the second amino group *via* ring opening of the epoxide **8a** with a suitable nucleophile. The first attempt was carried out with sodium azide in the presence of ammonium chloride as a catalyst.[18] Attack of the nucleophile, however, was hindered by the large isopropyl group; as a result, the reaction was sluggish and yielded a 2:1 mixture of regioisomers **9a** and **15** (Scheme 5).



Scheme 5

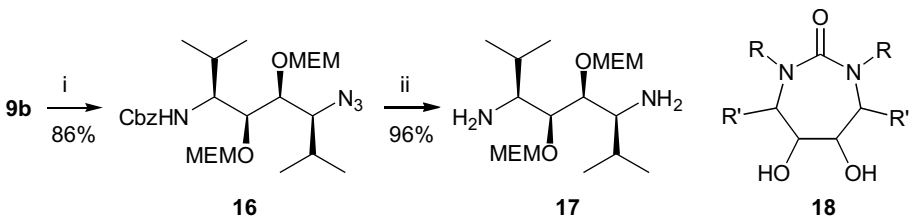
Trimethylsilyl azide, in the presence of catalytic titanium tetraisopropoxide or aluminium triisopropoxide,[19] also failed to afford the required product **9a**, leading instead to the loss of the Boc protecting group, with the formation of an oxazolidinone. It is likely that the basic alcoxide ligands promote the cyclization of the hydroxy group on the carbonyl of the Boc protecting group, with the loss of *tert*-butoxide, in a reaction similar to the cyclization of the allylic alcohol **7a** (Scheme 3). An attempt with trimethylsilyl azide and diethylaluminium chloride[20] was also unsuccessful, since this reagent gave a mixture of regioisomeric azido-diols **9a**, **15** and the corresponding chlorodiols.

Our choice fell eventually on diethylaluminium azide. This reagent was prepared and studied already in the 60's,[21] but only recently its use in the regioselective ring opening of 2,3-epoxyalcohols has been reported.[22] In agreement with the expectations, treatment of the epoxyalcohol **8a** (Scheme 2) with diethylaluminium azide, prepared *in situ* from diethylaluminium chloride and sodium azide in toluene,[20] gave azidodiol **9a** with complete regioselectivity and inversion of configuration. Finally, azide **9a** was catalyti-

cally hydrogenated to give the monoprotected diaminodiol **10**, in 24% overall yield from **4a**.

The stereochemistry of **10** was confirmed by deprotection to the free diamine **11**. ^{1}H and ^{13}C NMR spectra clearly showed that **11** is a symmetric structure. Since the configuration of C3, which corresponds to the α-carbon of the starting L-aminoester (Scheme 2), must necessarily be *S*, four configurations are possible for a symmetric species, namely (*S,S,R,R*), (*S,R,S,R*), (*S,R,R,S*) and (*S,S,S,S*). The first and second possibilities can be excluded because they correspond to *meso* structures, while **11** is chiral ($[\alpha]_D^{25}$ -3.0°). The third configuration (*S,R,R,S*) is not consistent with the preferred *anti* approach of the nucleophile to the *trans* epoxide **8a** in the ring opening step (Scheme 2). Therefore, the configuration of **11** must necessarily be (3*S*,4*S*,5*S*,6*S*).

An identical synthetic sequence was applied to the Cbz-protected amino ester **4b** (Scheme 2) through the same series of steps as described above, obtaining azide **9b** with comparable yields and stereocontrol. In this case, catalytic hydrogenation of the azide leads directly to the free diaminodiol **11**, avoiding one step with respect to the Boc-protected compound, if differentiation of the two amino terminals is not required. In addition (Scheme 6), the hydroxy groups of azide **9b** can be protected as di-MEM derivative (**16**), leading, after hydrogenation, to the symmetric, protected diaminodiol **17**. The C_2-symmetric structure of this compound is again confirmed by the NMR spectra and optical rotation ($[\alpha]_D^{25}$ –44°), which excludes a *meso* structure. OH-Protected diaminodiols such as **17** are useful intermediates in the synthesis of symmetric cyclic ureas **18**, which, in turn, have been shown to possess excellent activity as inhibitors of HIV-1 PR.[23]



16 **17** **18**

Scheme 6. i. MEMCl, DIPEA, CH_2Cl_2, 25 °C; ii. H_2, Pd/C, MeOH, 25 °C.

In summary, the introduction of Et_2AlN_3 as the reagent of choice for the ring opening of epoxyalcohols (Scheme 2) allows considerable expanding of the scope of our previously described stereoselective approach to all-*S* diaminodiol dipeptide isosteres. The use of the *in situ* generated reagent is par-

ticularly convenient as the procedure is fast and does not lead, in this case, to the formation of by-products. The utility and versatility of this route is demonstrated by the synthesis of three diaminodiol isosteres of the Val-Val dipeptide: the unprotected, C_2-symmetric diaminodiol **11**, the non-symmetric (desymmetrized) mono-Boc-protected compound **10** and the di-MEM-protected C_2-symmetric compound **17**. Compounds **10**, **11** and **17** can be subjected to further couplings and modifications in order to produce either symmetric or non–symmetric peptidomimetic aspartic protease inhibitors.

EXPERIMENTAL

Moisture sensitive reactions were carried out in oven-dried vessels under a positive argon pressure. THF was pre-dried over KOH, fractionated and redistilled from sodium benzophenone before use. Dichloromethane was dried over $CaCl_2$ and fractionated.

Flash column chromatography was performed on silica gel 60 (230–400 mesh); silica gel 60 F_{254} coated plastic sheets were used for TLC and developed with I_2 or with aqueous $KMnO_4/H_2SO_4$.

Melting points were determined in an open capillary apparatus and are uncorrected.

^{1}H NMR spectra (400 MHz) and ^{13}C NMR spectra (100.4 MHz) were recorded for $CDCl_3$ solutions containing Me_4Si as an internal standard. Mass spectra were obtained by electron impact (MS) and/or electrospray ionization (ES-MS). Optical rotations were determined with a Perkin-Elmer 241 polarimeter in a 1 dm cell; *c* in g/100 mL. Elemental analyses were obtained at the in-house facility of the Department of Chemical Sciences.

Phosphonate **5a** was obtained as described in Ref. 10.

*Dimethyl {(3*S*)-[*N*-(benzyloxycarbonyl)amino]-4-methyl-2-oxopentyl}phosphonate (**5b**)*

70 mL of a 2.5 M BuLi solution in hexane (175 mmol) was added portionwise, at –78 °C, to a stirred solution of 21.7 g (175 mmol) of dimethylmethylphosphonate in dry THF under argon. After 10 min, a solution of 8.49 g of **4b** (31.8 mmol) in THF was added dropwise. The mixture was stirred at –78 °C for 2 h and at –30 °C for 1 h and then neutralized with a 20% aqueous citric acid solution. The aqueous phase was extracted twice with ethyl acetate and the combined organic phases were washed with saturated $NaHCO_3$ solution and brine and dried over sodium sulfate. The solvent was rotary evaporated to furnish crude **5b** as a colorless oil (10.2 g, 90%) which was used without further purification. $[\alpha]_D^{25}$ –16° (*c* 0.2, MeOH); IR (film) ν_{max}/cm^{-1}: 3270 (NH), 1700 (C=O), 1210 (P=O); ^{1}H NMR δ/ppm: 0.80 (d, 3H, CH_3; J = 6.8 Hz), 1.01 (d, 3H, CH_3; J = 6.8 Hz), 2.32 (m, 1H, CH), 3.09 (dd, 1H, CH_2P; J = 14.4, 22.0 Hz), 3.29 (dd, 1H, CH_2P; J = 14.4, 22.7 Hz), 3.74 (d, 3H, OCH_3; J = 8.4 Hz), 3.77 (d, 3H, OCH_3; J = 8.4 Hz), 4.42 (dd, 1H, C<u>H</u>NH; J = 4.2, 9.2 Hz), 5.12 (s, 2H, CH_2Ph), 5.78 (d, NH; J = 9.2 Hz), 7.33 (m, 5H, Ph); ^{13}C NMR δ/ppm: 16.5 (CH_3), 19.7

(CH_3), 29.1 (CH), 38.6 (d, CH_2P; J = 131.4 Hz), 53.0 (CHNH), 65.4 (OCH_3), 66.9 (CH_2Ph), 127.9 (Ar), 128.0 (Ar), 128.4 (Ar), 136.2 (C1 Ar), 156.4 (C=O), 200.7 (d, C=O; J = 6.4 Hz); ES-MS m/z: 358 $[MH]^+$.

*(6*S*)-2,7-Dimethyl-6-[*N*-(*tert*-butoxycarbonyl)amino]-3-octen-5-one (**6a**)*

Oven–dried K_2CO_3 (3.66 g, 26.5 mmol) was added in small portions, over 15 min, to a stirred solution of phosphonoketone **5a** (8.57 g, 26.5 mmol) and isobutyraldehyde (2.10 g, 29 mmol) in absolute ethanol (50 mL), at 25 °C. After 3 h, the reaction mixture was filtered and the solution was neutralized with glacial acetic acid. The solvent was rotary evaporated and the residue was partitioned betweeen ethyl acetate and saturated aqueous $NaHCO_3$. The aqueous phase was extracted with ethyl acetate, and the combined organic phases were washed with brine and dried over sodium sulfate. The solvent was rotary evaporated, and the crude, oily product was purified by flash chromatography with diethyl ether/petroleum ether 1:1 as eluent (5.71 g, 80%). $[\alpha]_D^{25}$ +3.6° (*c* 0.4, MeOH); IR (neat) ν_{max}/cm^{-1}: 3427, 3335 (NH), 1716, 1693 (C=O), 1626 (C=C); ^1H NMR δ/ppm: 0.71 (d, 3H, CH_3, J = 7.0 Hz), 0.93 (d, 3H, CH_3, J = 6.6 Hz), 1.01 (d, 6H, CH_3, J = 6.6 Hz), 1.37 (s, 9H, *t*-Bu), 2.04 (m, 1H, CH), 2.42 (m, 1H, CH), 4.46 (dd, 1H, C<u>H</u>NH, J = 4.0, 8.8 Hz), 5.22 (d, NH, J = 8.8 Hz), 6.08 (d, 1H, CH=C<u>H</u>-CO, J = 15.7 Hz), 6.88 (dd, 1H, C=C<u>H</u>-CH(CH_3)$_2$, J = 6.6, 15.7 Hz); ^{13}C NMR δ/ppm: 16.6 (CH_3), 19.8 (CH_3), 21.1 (2 × CH_3), 28.2 (*t*-Bu), 30.9 (CH), 31.2 (CH), 61.9 (CHNH), 79.4 (*t*-Bu), 124.7 (CH=<u>C</u>HCO), 155.3 (CH=<u>C</u>H-CH(CH_3)$_2$), 155.9 (Boc), 198.7 (C=O); ES-MS m/z: 270 $[MH]^+$, 214 $[MH\text{-}C_4H_8]^+$, 170 $[MH\text{-Boc}]^+$.

*(6*S*)-2,7-Dimethyl-6-[*N*-(benzyloxycarbonyl)amino]-3-octen-5-one (**6b**)*

Phosphonate **5b** (5 g, 14.0 mmol) and isobutyraldehyde (1.5 g, 21 mmol), using the same procedure as described for **6a**, gave **6b** as a colorless oil (3.48 g, 82%). $[\alpha]_D^{25}$ +13.5° (*c* 0.5, MeOH); IR (film) ν_{max}/cm^{-1}: 3340 (NH), 1690 (C=O), 1610 (C=C); ^1H NMR δ/ppm: 0.78 (d, 3H, CH_3; J = 7.0 Hz), 1.02 (d, 3H, CH_3; J = 6.8 Hz), 1.08 (d, 6H, 2 × CH_3; J = 6.8 Hz), 2.14 (m, 1H, CH), 2.48 (m, 1H, CH), 4.60 (dd, 1H, C<u>H</u>NH; J = 4.0, 8.6 Hz), 5.10 (s, 2H, CH_2Ph), 5.58 (d, NH; J = 8.6 Hz), 6.15 (dd, 1H, =CHCO; J = 1.0, 15.8 Hz), 6.96 (dd, 1H, =CH; J = 6.7, 15.8 Hz), 7.33 (m, 5H, Ph); ^{13}C NMR δ/ppm: 16.6 (CH_3), 19.8 (CH_3), 21.1 (2 × CH_3), 30.9 (CH), 31.2 (CH), 62.4 (CHNH), 66.8 (CH_2Ph), 124.6 (=CHCO), 127.9 (Ar), 128.0 (Ar), 128.4 (Ar), 136.3 (C1 Ar), 155.6 (=CH), 156.4 (C=O), 198.1 (C=O); ES-MS m/z: 304 $[MH]^+$.

*(5*R*,6*S*)-2,7-Dimethyl-5-hydroxy-6-[*N*-(tert-butoxycarbonyl)amino]-3-octene (**7a**)*

$NaBH_4$ (563 mg, 14.8 mmol) was added in small portions over 10 min, at 0 °C, to a stirred solution of enone **6a** (4.00 g, 14.8 mmol) in methanol (50 mL). After 1 h at 0 °C, the solution was neutralized with glacial acetic acid, the solvent was rotary evaporated and the residue was partitioned betweeen ethyl acetate and saturated aqueous $NaHCO_3$. The aqueous phase was extracted with ethyl acetate, and the combined organic phases were washed with brine and dried over sodium sulfate. The solvent was rotary evaporated to give the crude product, which was recrystallized from isopropyl ether (2.69 g, 67%); m.p. 105–106 °C; $[\alpha]_D^{25}$ –31.5° (*c* 0.5, MeOH); IR (nujol) ν_{max}/cm^{-1}: 3365 (OH, NH), 1684 (C=O, C=C); ^1H NMR δ/ppm: 0.89 (d, 3H, CH_3, J = 6.9 Hz), 0.92 (d, 3H, CH_3, J = 6.8 Hz), 0.94 (d, 6H, CH_3, J = 6.8 Hz), 1.37 (s, 9H, *t*-Bu), 1.71 (m, 1H, CH), 2.24 (m, 1H, CH), 2.61 (bs, OH), 3.46 (m, 1H, C<u>H</u>NH),

4.07 (m, 1H, CHOH), 4.38 (d, NH, J = 9.5 Hz), [5.34 (ddd, J = 15.4, 7.0, 1.1 Hz), 5.64 (dd, J = 15.4, 5.5 Hz), 2H, CH=CH]; ^{13}C NMR δ/ppm: 18.2 (CH_3), 20.1 (CH_3), 22.2 (2 × CH_3), 28.3 (*t*-Bu), 28.9 (CH), 30.8 (CH), 60.4 (CHNH), 73.6 (CHOH), 79.4 (*t*-Bu), 125.4 (CH=CHCHOH), 141.1 [CH=C-CH(CH_3)$_2$], 157.0 (C=O); ES-MS m/z: 272 $[MH]^+$, 216 $[MH\text{-}C_4H_8]^+$, 172 $[MH\text{-Boc}]^+$.

Anal. Calcd. for $C_{15}H_{29}NO_3$: C 66.4, H 10.8, N 5.18%; found: C 66.9, H 11.1, N 5.27%.

*(5*R*,6*S*)-2,7-Dimethyl-5-hydroxy-6-[*N*-(benzyloxycarbonyl)amino]-3-octene (**7b**)*

Reduction of **6b** (2.5 g, 8.24 mmol), as above, gave alcohol **7b** (2.09 g, 83%); m.p. 53–55 °C, from diisopropyl ether; $[\alpha]_D^{25}$ –26° (*c* 0.3, MeOH); IR (CCl_4) ν_{max}/cm^{-1}: 3450 (NH, OH), 1695 (C=O); ^{1}H NMR δ/ppm: 0.90 (d, 3H, CH_3; J = 6.8 Hz), 0.96 (m, 9H, 3 × CH_3), 1.83 (m, 1H, CH), 2.27 (m, 1H, CH), 2.57 (bs, OH), 3.59 (m, 1H, CHNH), 4.14 (dd, 1H, CHOH; J = 6.6 Hz), 4.75 (d, NH; J = 10.1 Hz), 5.08 (s, 2H, CH_2Ph), 5.39 (dd, 1H, =CH; J = 7.0, 15.4 Hz), 5.68 (dd, 1H, =CH; J = 6.6, 15.4 Hz), 7.33 (m, 5H, Ph); ^{13}C NMR δ/ppm: 17.9 (CH_3), 20.1 (CH_3), 22.2 (2 × CH_3), 28.6 (CH), 30.7 (CH), 60.7 (CHNH), 66.8 (CH_2Ph), 73.4 (CHOH), 125.3 (=CH), 127.8 (Ar), 127.98 (Ar), 128.02 (Ar), 128.3 (Ar), 128.4 (Ar), 136.3 (C1 Ar), 141.3 (=CH), 157.2 (C=O); MS m/z: 305 (0), 244 (1), 206 (8), 162 (16), 108 (31), 99 (53), 91 (100).

Anal. Calcd. for $C_{17}H_{27}NO_3$: C 70.8, H 8.91, N 4.60%; found: C 70.8, H 9.07, N 4.62%.

*(3*R*,4*R*,5*S*,6*S*)-2,7-Dimethyl-3,4-epoxy-5-hydroxy-6-[*N*-(*tert*-butoxycarbonyl)amino]octane (**8a**)*

60% *m*-Chloroperoxybenzoic acid (3.17 g, 11.1 mmol) was added to a stirred solution of alkene **7a** (2.5 g, 9.21 mmol) in dichloromethane. After 24 h at room temperature, the solution was washed with 10% aqueous sodium metabisulfite, saturated aqueous $NaHCO_3$ and brine and dried over sodium sulfate. The solvent was rotary evaporated and the crude product was purified by flash chromatography eluting with ethyl acetate/dichloromethane mixtures (1.72 g, 65%). Analytical samples were obtained by recrystallization from isopropyl ether/hexane; m.p. 80–81 °C; $[\alpha]_D^{25}$ +11.5° (*c* 0.7, MeOH); IR (nujol) ν_{max}/cm^{-1}: 3371 (NH, OH), 1686 (C=O); ^{1}H NMR δ/ppm: 0.84 (d, 3H, CH_3, J = 7.0 Hz), 0.89–0.93 (m, 9H, 3 × CH_3), 1.37 (s, 9H, *t*-Bu), 1.49 (m, 1H, CH), 2.02 (m, 1H, CH), 2.49 (bs, OH), [2.70 (m, 1H), 2.85 (m, 1H), epoxide], 3.43 (m, 1H, CHOH), 3.61 (m, 1H, CHNH), 4.54 (d, NH, J = 10.3 Hz); ^{13}C NMR δ/ppm: 16.0 (CH_3), 17.3 (CH_3), 17.9 (CH_3), 19.1 (CH_3), 27.3 (*t*-Bu), 27.6 (CH), 29.0 (CH), 57.2 (CHNH), 57.6, 61.0 (epoxide), 70.0 (CHOH), 78.4 (*t*-Bu), 155.2 (C=O); ESI-MS m/z: 288 $[MH]^+$, 232 $[MH\text{-}C_4H_8]^+$, 188 $[MH\text{-Boc}]^+$.

Anal. Calcd. for $C_{15}H_{29}NO_4$: C 62.7, H 10.2, N 4.87%; found: C 62.5, H 10.3, N 4.90%.

*(3*R*,4*R*,5*S*,6*S*)-2,7-Dimethyl-3,4-epoxy-5-hydroxy-6-[*N*-(benzyloxycarbonyl)amino]octane (**8b**)*

Epoxidation of **7b** (1.78 g, 5.82 mmol), as described above, gave **8b** (1.12 g, 60%); m.p. 109–111 °C, from isopropyl ether/hexane; $[\alpha]_D^{25}$ +2.4° (*c* 0.3, MeOH); IR (CCl_4)

ν_{max}/cm^{-1}: 3500, 3320 (NH, OH), 1700 (C=O); ^{1}H NMR δ/ppm: 0.89 (m, 6H, 2 × CH_3), 0.98 (m, 6H, 2 × CH_3), 1.50 (m, 1H, CH), 2.13 (m, 1H, CH), 2.64 (d, OH; J = 6.2 Hz), 2.72 (dd, 1H, CHO; J = 2.2, 6.8 Hz), 2.92 (dd, 1H, CHO; J = 2.2, 4.8 Hz), 3.48 (m, 1H, CHNH), 3.75 (m, 1H, CHOH), 4.90 (d, NH; J = 10.3 Hz), 5.05 (d, 1H, CH_2Ph; J = 12.2 Hz), 5.11 (d, 1H, CH_2Ph; J = 12.2 Hz), 7.34 (m, 5H, Ph); ^{13}C NMR δ/ppm: 16.8 (CH_3), 18.1 (CH_3), 18.8 (CH_3), 20.0 (CH_3), 28.2 (CH), 29.9 (CH), 58.6 (CHNH), 58.7 (CHO), 62.1 (CHO), 66.9 (CH_2Ph), 71.1 (CHOH), 128.0 (Ar), 128.2 (Ar), 128.5 (Ar), 136.2 (C1 Ar), 156.7 (C=O); MS m/z: 321 (0.05), 278 (0.1), 206 (6), 162 (14), 107 (19), 91 (100).

Anal. Calcd. for $C_{18}H_{27}NO_3$: C 62.7, H 10.2, N 4.89%; found: C 62.3, H 10.2, N 4.83%.

*(3*S*,4*S*,5*S*,6*S*)-2,7-Dimethyl-3-[*N*-(tert-butoxycarbonyl)amino]-4,5-dihydroxy-6-azidooctane (**9a**)*

1.9 mL of a 1.8 M solution (3.48 mmol) of Et_2AlCl in toluene was added, under argon, to a suspension of NaN_3 (250 mg, 3.83 mmol) in the same solvent (5 mL). The resulting suspension was stirred at room temperature for 4 hours and then cooled to 0 °C. A solution of epoxyalcohol **8a** (500 mg, 1.74 mmol) in toluene was added dropwise. After stirring at 0 °C for 1 h, the mixture was allowed to warm up to room temperature and was stirred overnight. Then the mixture was cooled to 0 °C and diluted with ethyl acetate (15 mL). NaF (1.02 g, 24.4 mmol) and water (0.44 ml, 24.4 mmol) were added portionwise and the resulting mixture was stirred for 30 min and filtered through a short pad of anhydrous Na_2SO_4, which was washed with ethyl acetate. The combined organic phases were rotary evaporated to furnish the crude product, which was purified by flash chromatography with ethyl acetate/petroleum ether as eluent. The white solid (455 mg, 79%) had m.p. 146–150 °C; $[\alpha]_D^{25}$ –11° (c 0.2, MeOH); IR (nujol) ν_{max}/cm^{-1}: 3350 (OH, NH), 2104 (N_3), 1695 (C=O); ^{1}H NMR δ/ppm: 0.78 (d, 3H, CH_3; J = 6.8 Hz), 0.84 (d, 3H, CH_3; J = 7.0 Hz), 0.93 (d, 3H, CH_3; J = 7.0 Hz), 1.01 (d, 3H, CH_3; J = 7.0 Hz), 1.37 (s, 9H, t-Bu), 2.20 (m, 1H, CH), 2,31 (m, 1H, CH), 3.34 (m, 2H, CHOHCHN$_3$ + CHNH), 3.40 (m, 1H, CHOHCHNH), 3.48 (dd, 1H, CHN$_3$; J = 2.6, 9.9 Hz), 4.51 (d, NH; J = 8.9 Hz); ^{13}C NMR δ/ppm: 15.0 (CH_3), 15.2 (CH_3), 20.4 (CH_3), 20.6 (CH_3), 26.2 (CH), 28.2 (t-Bu), 29.0 (CH), 56.6 (CHNH), 68.0 (CHN$_3$), 69.1 (CHOH), 70.8 (CHOH), 80.6 (t-Bu), 158.1 (C=O); ES-MS m/z: 331 [MH]$^+$, 288 [MH-NH_3]$^+$, 275 [MH-C_4H_8]$^+$, 231 [MH-Boc]$^+$.

Anal. Calcd. for $C_{15}H_{30}N_4O_4$: C 54.5, H 9.14, N 17.0%; found: C 55.0, H 9.28, N 16.7%.

*(3*S*,4*S*,5*S*,6*S*)-2,7-Dimethyl-3-[*N*-(benzyloxycarbonyl)amino]-4,5-dihydroxy-6-azidooctane (**9b**)*

The oily product (371 mg, 82%) was obtained from epoxide **8b** (400 mg, 1.24 mmol) and diethylaluminium azide (2.48 mmol), as described for the synthesis of **9a**. $[\alpha]_D^{25}$ +11° (c 0.3, MeOH); IR (film) ν_{max}/cm^{-1}: 3400 (NH, OH), 2100 (N_3), 1685 (C=O); ^{1}H NMR δ/ppm: 0.79 (d, 3H, CH_3; J = 6.8 Hz), 0.90 (d, 3H, CH_3; J = 6.8 Hz), 0.99 (d, 3H, CH_3; J = 6.8 Hz), 1.05 (d, 3H, CH_3; J = 6.8 Hz), 2.21 (m, 1H, CH), 2.35 (m, 1H, CH), 2.54 (bs, OH), 3.37 (dd, 1H, CHOH; J = 5.4, 9.8 Hz), 3.51 (m, 3H, CHOH + CHN$_3$ + CHNH), 4.00 (d, OH; J = 5.4 Hz), 4.87 (m, NH), 5.01 (d, 1H, CH_2Ph; J = 12.2 Hz), 5.20 (d, 1H, CH_2Ph; J = 12.2 Hz), 7.33 (m, 5H, Ph); ^{13}C NMR δ/ppm: 15.3 (2 × CH_3),

20.3 (CH_3), 20.5 (CH_3), 26.5 (CH), 28.9 (CH), 57.3 (CHNH), 67.3 (CH_2Ph), 68.2 (CHN_3), 69.1 (CHOH), 70.5 (CHOH), 127.9 (Ar), 128.3 (Ar), 128.6 (Ar), 136.0 (C1 Ar), 158.3 (C=O).

*(3*S*,4*S*,5*S*,6*S*)-2,7-Dimethyl-3-[*N*-(tert-butoxycarbonyl)amino]-4,5-dihydroxy-6-aminooctane (**10**)*

9a (200 mg, 0.60 mmol) in 5 mL MeOH were stirred overnight under H_2 (1 atm), in the presence of 10% Pd/C. The mixture was filtered through a pad of celite to afford, after removal of the solvent, 176 mg (95%) of a white solid, m.p. 100–101 °C; $[\alpha]_D^{25}$ –8.7° (*c* 0.2, MeOH); IR (CCl_4) ν_{max}/cm^{-1}: 3450, 3367 (OH, NH), 1693 (C=O); ^{1}H NMR δ/ppm: 0.78 (d, 3H, CH_3; J = 7.0 Hz), 0.86 (m, 6H, 2 × CH_3), 0.92 (d, 3H, CH_3; J = 6.6 Hz), 1.36 (s, 9H, *t*-Bu), 1.90 (m, 1H, CH), 2.24 (m, 1H, CH), 2.94 (m, 1H, C<u>H</u>NH_2), 3.55 (m, 3H, 2 × C<u>H</u>OH + C<u>H</u>NH), 4.52 (bs, 4H, 2 × OH + NH_2), 4.59 (d, NH; J = 8.8 Hz); ^{13}C NMR δ/ppm: 15.1 (CH_3), 18.6 (CH_3), 19.6 (CH_3), 20.2 (CH_3), 26.0 (CH), 28.2 (*t*-Bu), 28.6 (CH), 56.0 ($CHNH_2$), 60.3 (CHNH), 68.1 (CHOH), 70.5 (CHOH), 80.1 (*t*-Bu), 157.7 (C=O); ES-MS m/z: 305 $[MH]^+$, 249 $[MH\text{-}C_4H_8]^+$, 205 $[MH\text{-Boc}]^+$, 188 $[MH\text{-Boc-}NH_3]^+$, 170 $[MH\text{-Boc-}NH_3\text{-}H_2O]^+$, 152 $[MH\text{-Boc-}NH_3\text{-}H_2O\text{-}H_2O]^+$; MS m/z: 304 (0.01), 286 (0.3), 243 (0.3), 231 (0.6), 187 (1), 172 (0.5), 132 (7), 116 (12), 72 (100), 57 (22).

Anal. Calcd. for $C_{15}H_{32}N_2O_4$: C 59.2, H 10.6, N 9.24%; found: C 58.7, H 10.7, N 9.04%.

*(3*S*,4*S*,5*S*,6*S*)-2,7-Dimethyl-3,6-diamino-4,5-dihydroxyoctane (**11**)*

Method A: 100 mg (0.33 mmol) of **10** was suspended in a 6 M HCl solution and heated at 90 °C until dissolution (about 10 min). After 10 min, the solution was neutralized with saturated $NaHCO_3$ solution; then an equal volume of brine was added and the mixture was extracted three times with dichloromethane. The solution was dried over Na_2SO_4 and rotary evaporated to obtain white crystals (68 mg, 100%).

Method B: 220 mg (0.60 mmol) of **9b** in 5 mL MeOH were stirred overnight under 1 atm H_2 and in the presence of 10% Pd/C, to afford 123 mg (100%) of a white solid, m.p. 72–73 °C; $[\alpha]_D^{25}$ –3.0° (*c* 0.4, MeOH); IR (nujol) ν_{max}/cm^{-1}: 3300 (OH, NH_2); ^{1}H NMR δ/ppm: 0.87 (d, 6H, 2 × CH_3; J = 6.4 Hz), 0.93 (d, 6H, 2 × CH_3; J = 6.4 Hz), 1.80 (m, 2H, 2 × CH), 2.79 (dd, 2H, 2 × C<u>H</u>NH_2; J = 3.7, 8.6 Hz), 3.45 (bs, 4H, 2 × NH_2), 3.86 (m, 2H, 2 × C<u>H</u>OH); ^{13}C NMR δ/ppm: 19.69 (2 × CH_3), 19.72 (2 × CH_3), 29.0 (2 × CH), 61.3 (2 × $CHNH_2$), 70.3 (2 × CHOH); ES-MS m/z: 205 $[MH]^+$, 188 $[MH\text{-}NH_3]^+$, 170 $[MH\text{-}NH_3\text{-}H_2O]^+$, 152 $[MH\text{-}NH_3\text{-}H_2O\text{-}H_2O]^+$; MS m/z: 204 (0), 184 (3), 132 (26), 102 (20), 72 (100), 55 (70).

Anal. Calcd. for $C_{10}H_{24}N_2O_2$: C 58.7, H 11.8, N 13.8%; found: C 58.3, H 11.5, N 13.7%.

*(4*S*,5*R*)-4-Isopropyl-5-(1′-isopropyl-vin-2′-yl)-1,3-oxazolidin-2-one (**12**)*

147 mg of 60% NaH (3.68 mmol) in mineral oil was added portionwise to a solution of **7a** (500 mg, 1.84 mmol) in dry THF (10 mL) at room temperature under an argon atmosphere. The mixture was stirred overnight, then it was quenched with 2 volumes of a saturated NH_4Cl solution, under stirring for 30 min. The aqueous layer was extracted twice with ethyl acetate and the combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. The solvent was rotary evaporated

and the oily product (290 mg, 80%) was purified by flash chromatography: $[\alpha]_D^{25}$ +40° (*c* 0.2, MeOH); IR (film) ν_{max}/cm^{-1}: 3250 (NH), 1748 (C=O); ^{1}H NMR δ/ppm: 0.86 (d, 3H, CH_3, *J* = 6.6 Hz), 0.98 (d, 3H, CH_3, *J* = 6.6 Hz), 1.01 (m, 6H, CH_3), 1.79 (m, 1H, CH), 2.36 (m, 1H, CH), 3.56 (m, 1H, CH-N), 4.95 (m, 1H, CH-O), 5.56 (dd, 1H, =CH, *J* = 8.5, 15.6 Hz), 5.83 (dd, 1H =CH, *J* = 6.6, 15.6 Hz), 6.31 (bs, NH); ^{13}C NMR δ/ppm: 19.0 (CH_3), 19.2 (CH_3), 21.9 (CH_3), 28.3 (CH), 30.9 (CH), 62.4 (CH-N), 81.3 (CH-O), 119.6 (=CH), 144.9 (=CH), 160.0 (C=O); ES-MS *m*/*z*: 198 $[MH]^+$.

*(4*S*,5*S*)-4-Isopropyl-5-(1′-isopropyl-vin-2′-yl)-1,3-oxazolidin-2-one (**14**)*

To a solution of 500 mg (1.84 mmol) of **7a** in dichloromethane (10 mL), 712 mg (5.52 mmol) of DIPEA and 316 mg (2.76 mmol) of methanesulfonyl chloride were added at 0 °C. After 2 h, the solution was diluted with one volume of dichloromethane, washed with ice-cold water, ice-cold 10% HCl solution, saturated $NaHCO_3$ solution and brine. After drying over anhydrous Na_2SO_4, the solvent was rotary evaporated to afford a crude product which was purified by flash chromatography (ethyl acetate/petroleum ether mixtures) (236 mg, 65%); $[\alpha]_D^{25}$ –91° (*c* 0.2, MeOH); IR (film) ν_{max}/cm^{-1}: 3261 (NH), 1751 (C=O); ^{1}H NMR δ/ppm: 0.92 (d, 3H, CH_3, *J* = 6.8 Hz), 0.96 (d, 3H, CH_3, *J* = 6.6 Hz), 1.01 (m, 6H, CH_3), 1.76 (m, 1H, CH), 2.32 (m, 1H, CH), 3.29 (m, 1H, CH-N), 4.63 (m, 1H, CH-O), 5.47 (ddd, 1H, =CH, *J* = 1.3, 7.7, 15.4 Hz), 5.80 (dd, 1H, =CH, *J* = 6.6, 15.4 Hz), 6.78 (bs, NH); ^{13}C NMR δ/ppm: 17.9 (CH_3), 18.1 (CH_3), 21.8 (CH_3), 30.6 (CH), 32.2 (CH), 64.2 (CH-N), 81.3 (CH-O), 124.3 (=CH), 143.0 (=CH), 159.6 (C=O); ES-MS *m*/*z*: 198 $[MH]^+$.

*(3*S*,4*S*,5*S*,6*S*)-2,7-Dimethyl-3-[*N*-(benzyloxycarbonyl)amino]-4,5-di-[2′-(methoxy)ethoxymethoxy]-6-azidooctane (**16**)*

MEMCl (0.94 mL, 8.2 mmol) and DIPEA (1.43 mL, 8.2 mmol) were added to a solution of **8b** (300 mg, 0.82 mmol) in 3 mL dry dichloromethane. After 6 days, the solvent was rotary evaporated and the residue partitioned between ethyl acetate and 5% aqueous $NaHCO_3$. The organic phase was washed with brine and dried over sodium sulfate. The solvent was rotary evaporated and the oily product was purified by flash chromatography with ethyl acetate/petroleum ether as eluant (381 mg, 86%). $[\alpha]_D^{25}$ –10.4° (*c* 0.8, MeOH); IR (film) ν_{max}/ cm^{-1}: 3330 (NH), 2100 (N_3), 1700 (C=O); ^{1}H NMR δ/ppm: 0.96 (m, 9H, CH_3), 1.07 (d, 3H, CH_3; *J* = 6.8 Hz), 1.90 (m, 1H, CH), 2.04 (m, 1H, CH), 3.30 (s, 3H, OCH_3), 3.35 (s, 3H, OCH_3), 3.36–3.60 (m, 5H), 3.68–3.78 (m, 6H), 3.95 (dd, 1H, C<u>H</u>O; *J* = 2.1, 5.6 Hz), 4.82 (m, 2H, OCH_2O), 4.89 (m, 2H, OCH_2O), 5.03 (d, 1H, CH_2Ph; *J* = 12.2 Hz), 5.12 (d, 1H, CH_2Ph; *J* = 12.2 Hz), 5.95 (d, NH; *J* = 10.4 Hz), 7.33 (m, 5H, Ph); ^{13}C NMR δ/ppm: 16.7 (CH_3), 18.8 (CH_3), 20.2 (CH_3), 21.2 (CH_3), 29.0 (CH), 29.3 (CH), 57.0 (CHNH), 58.8 (2 × OCH_3), 66.3 (CH_2Ph), 68.1 (CH_2), 68.2 (CH_2), 68.7 (CHN_3), 71.5 (CH_2), 71.6 (CH_2), 76.3 (CHO), 78.1 (CHO), 96.0 (OCH_2O), 97.8 (OCH_2O), 127.8 (Ar), 127.9 (Ar), 128.2 (Ar), 136.9 (C1 Ar), 156.8 (C=O).

*(3*S*,4*S*,5*S*,6*S*)-2,7-Dimethyl-3,6-diamino-4,5-di-[2′-(methoxyethoxy)-methoxy]-octane (**17**)*

A suspension of **12** (0.37 g, 0.68 mmol) in 5 mL MeOH was stirred overnight at room temperature under 1 atm H_2 and in the presence of 10% Pd/C, to afford, after

filtration over celite and removal of the solvent, 243 mg (96%) of oily diamine **17**. $[\alpha]_D^{25}$ – 44° (*c* 1.0, MeOH); IR (film) ν_{max}/cm^{-1}: 3350 (NH); ^{1}H NMR δ/ppm: 0.78 (d, 6H, 2 × CH_3; *J* = 6.8 Hz), 0.89 (d, 6H, 2 × CH_3; *J* = 6.8 Hz), 1.42 (bs, 4H, 2 × NH_2), 1.90 (m, 2H, 2 × CH), 2.71 (dd, 2H, 2 × C<u>H</u>NH_2; *J* = 2.6, 8.2 Hz), 3.28 (s, 6H, 2 × OCH_3), 3.44 (m, 4H), 3.59–3.74 (m, 6H), 4.71 (d, 1H, CH_2Ph; *J* = 7.2 Hz), 4.79 (d, 1H, CH_2Ph; *J* = 7.2 Hz); ^{13}C NMR δ/ppm: 15.0 (CH_3), 20.8 (CH_3), 27.3 (CH), 56.2 ($CHNH_2$), 58.8 (OCH_3), 67.9 (CHO), 71.4 (CH_2O), 80.0 (CH_2O), 96.7 (OCH_2O); ES-MS *m*/*z*: 558 $[M+NH_4]^+$, 541 $[MH]^+$, 437 $[MH\text{-}MEM]^+$.

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SAŽETAK

Priprava C_2-simetričnih Val-Val dipeptidnih izostera otvaranjem prstena u epoksialkoholima djelovanjem dietilaluminijeva azida

Fabio Benedetti, Stanislav Miertus i Stefano Norbedo

Opisana je primjena visoko regio- i stereo-selektivnog reagensa dietilaluminijeva azida za otvaranje prstena u sterički ometanim epoksialkoholima izvedenima iz valina. Taj je reagens omogućio proširenje ranije opisane sinteze diamindioldipeptid-izosteraze (P_1-Ψ[CH(OH)-CH(OH)]-P_1') na izosteraze s razgranatim ostatcima u položaju P_1'. Nova metodologija sukladna je Boc i Cbz zaštiti početne aminokiseline, a primijenjena je za pripravu C_2-simetričnog diamindiola dipeptidne izostere Val-Val **11** iz metilestera L-valina uz 25% iskorištenje u 7 (za Boc zaštitu), odnosno u 6 stupnjeva za Cbz zaštitu.

Istim su pristupom pripravljeni i C_2-simetrični di-MEM-zaštićeni diamindiol **17** i mono-Boc-zaštićeni, disimetrični derivat **10**. Spojevi **10**, **11** i **17** osnovne su jedinice simetričnih i nesimetrični peptidomimetičkih inhibitora aspartatnih proteaza i međuprodukti u sintezi cikličkih urea-inhibitora HIV-proteaza.