Val-Ala Dipeptide Isosteres by Hydrocyanation of α′-Amino α,β-Unsaturated Ketones − Control of Stereoselectivity by the *N*-Protecting Group

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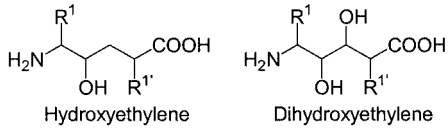
Three diastereoisomeric hydroxyethylene isosters of the Val-Ala dipeptide were synthesized from α,β-unsaturated ketones **1** derived from *N*-Boc- and *N*,*N*-dibenzyl-L-valine. The enones were hydrocyanated with diethylaluminum cyanide to give the corresponding β-cyano ketones with the stereoselectivity depending on the protecting group. *N*-Boc protected enone **1a** gave a 1:1 mixture of *anti* and *syn* adducts **4a**, **5a** while the corresponding *N*,*N*-dibenzyl compound **1c** gave a 6:1 mixture of *anti, syn* adducts **4c**, **5c**. Borohydride reduction of the resulting cyano ketones is also controlled by the protecting group, resulting in opposite stereoselectivities for *N*-Boc and *N*,*N*-dibenzyl compounds. The cyano alcohols thus obtained were converted, in several steps, into two series of enantiomerically pure hydroxyethylene isosters of the Val-Ala dipeptide. In the first series the hydroxy group and the *N*-terminal of the isoster are internally protected through the formation of an oxazolidine; in the second series the hydroxy group and the C-terminal are protected as lactone. Two oxazolidines (**28**, **29**), corresponding to *syn*,*syn* and *syn*,*anti* 4-hydroxy-5-amino acid isosters, and three lactones (**23**–**25**), corresponding to *syn*,*syn*, *syn*,*anti*, and *anti*,*anti* isosters were obtained by this approach.

Peptidomimetics of general structure Pn−P1−X−Y−P1′−Pn′, in which a non-hydrolizable isoster P1−X−Y−P1′ replaces the scissile dipeptide P1−P1′ in a short peptide chain Pn−P1−P1′−Pn′, are efficient inhibitors of aspartic proteases.[1] Enzymes of this class play an important role in many biological processes and are involved in a variety of pathologies. Thus, extensive investigations have been devoted to the discovery of peptidomimetic inhibitors potentially useful in therapy.[2] Renin inhibitors, for example, have long been recognized for their potential in the control of hypertension[3] and inhibitors of HIV-1 protease (HIV-PR) are currently in clinical use for the treatment of acquired immunodeficiency syndrome (AIDS).[4,5] More recently, other aspartic proteases, such as candidapepsins, involved in fungal invasiveness, plasmepsins from malaria parasites and human cathepsin D, involved in Alzheimer's disease, have emerged as new targets for peptidomimetic inhibitors.[2]

Peptidomimetic inhibitors of aspartyl proteases displace the substrate from the enzyme's active site, interacting with the protease through a network of hydrogen bonds, electrostatic and hydrophobic interactions. In particular, the P1−X−Y−P1′ isoster interacts with the aspartate catalytic residues and with S1, S1′ subsites in close proximity with the active site, while the flanking residues make contact with corresponding subsites on the enzyme.[1,2] Hydroxyethylene and dihydroxyethylene isosters have proved particularly useful as dipeptide replacements in the design of potent inhibitors of HIV-1 PR[6−10] and other aspartic proteases,[2] as the hydroxy groups can make favorable polar interactions with the catalytic aspartates, while R^1 and $R^{1'}$ groups interact with the hydrophobic S1, S1′ subsites.[11]



A number of studies have shown that the configuration of the isoster can affect both the in vitro and the in vivo activity of peptidomimetic inhibitors[9,12,13] and the importance of synthesizing and evaluating stereoisomers of a given inhibitor clearly emerges from these studies. Synthetic routes that give access to stereoisomeric dipeptide isosters in enantiomerically pure form are thus highly valuable in the search for new inhibitors. Recently, we have described a novel approach to enantiomerically pure 4-hydroxy-5-amino acids following the retrosynthetic analysis shown in Scheme 1.[14] Here we present a full account of that work and describe how the selectivity can be controlled by choice of the *N*-protecting group, resulting in the synthesis of different diastereoisomers of the same isoster.

The synthesis is based on the conjugate addition of a suitable precursor of the carboxylate group (X) to the α′-

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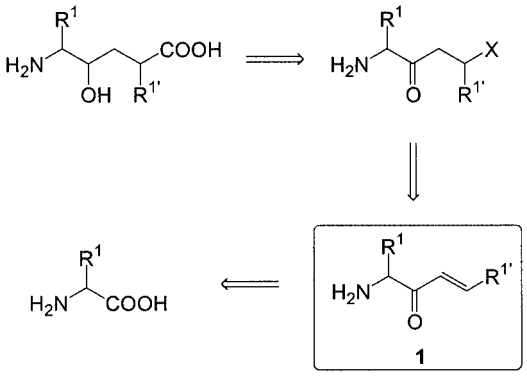
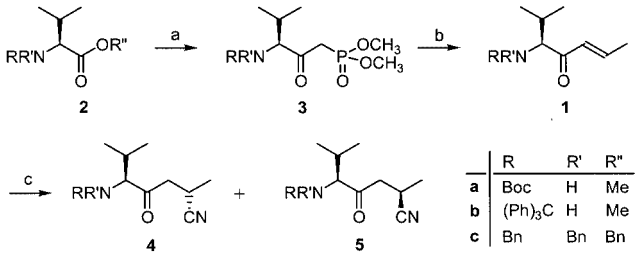


Scheme 1. Retrosynthetic analysis of hydroxyethylene dipeptide isosters

amino α,β-unsaturated ketone **1**. This intermediate is readily obtained from α-amino acids and has been recently used by us as precursor of epoxy alcohols, in the synthesis of dihydroxyethylene dipeptide isosters.[15,16] In view of the well-known preference of aspartic proteases for hydrophobic residues at the scissile bond,[1,2] aliphatic residues R^1 and $R^{1'}$ were chosen for this study and the approach described in Scheme 1 was demonstrated with the synthesis of three enantiomerically pure diastereoisomeric analogs of the Val-Ala dipeptide.

Results and Discussion

The *N*-Boc protected α,β-unsaturated ketone **1a** was obtained in two steps from the methyl ester of *N*-Boc L-valine **2a** (Scheme 2). This was initially converted into the phosphonate **3a**[17] following the procedure (dimethyl methylphosphonate, *n*BuLi, −78 to −30 °C) described by Chakravarty.[18] Horner−Emmons olefination of **3a** with acetaldehyde was carried out in ethanol, in the presence of potassium carbonate,[19] giving **1a**. The *trans* geometry of the enone was confirmed by the NMR spectrum showing a 15 Hz coupling constant between the vinyl protons.



Scheme 2. Synthesis of cyano ketones **4**, **5**: a) $(CH_3O)_2P(O)CH_3$, *n*BuLi, THF, −78 °C, 69−92%; b) CH_3CHO, K_2CO_3, EtOH, 25 °C, 81−97%; c) Et_2AlCN, toluene, 25 °C, 75−96%

Addition of the carboxylate precursor to **1a** is the crucial step in the synthesis and much effort was devoted to optimize this reaction. The initial reagent chosen for the conjugate addition was Et_2AlCN (Nagata's reagent), for it is known that this reagent adds to α,β-unsaturated ketones in a complete 1,4 fashion,[20] providing a nitrile ready for further manipulation. When **1a** was treated with excess diethylaluminum cyanide, in toluene at room temperature, a mixture of diastereoisomeric cyano ketones **4a** and **5a** was obtained, in a 1:1 ratio (Scheme 2). The same reaction was also carried out with bis(2,6-di-*tert*-butyl-4-methylphenoxy)-aluminum cyanide, obtained in situ from diethylaluminum cyanide and 2,6-di-*tert*-butyl-4-methylphenol,[21] but even this bulky reagent failed to display any appreciable diastereofacial selectivity. A moderate stereoselectivity, favoring **5a**, was observed at lower temperature and a 2:1 mixture of **5a** and **4a** was obtained at −70 °C. The results are consistent with the hypothesis that, under these conditions, the conjugate hydrocyanation of unsaturated ketone **1** is reversible resulting, at room temperature, in a fast equilibration of the adducts via the corresponding aluminium enolates, as suggested by Nagata.[20] The moderate stereoselectivity observed at −70 °C indicates that equilibration is slower at this temperature; unfortunately, the reaction was sluggish and these conditions were not further pursued.

If diethylaluminum cyanide is replaced by a trialkylaluminum and hydrogen cyanide, hydrocyanation of α,β-unsaturated ketones becomes irreversible because the enolate is rapidly protonated thus preventing equilibration.[22] We modified these conditions by carrying out the hydrocyanation of enone **1a** with diethylaluminum cyanide and acetone cyanohydrin as proton donor to decompose the aluminium enolate (Scheme 2, Table 1). This resulted in shorter reaction time (6 h vs. 48 h) and better yield (96% vs. 70%), if compared with Et_2AlCN alone (Table 1), but did not lead to any appreciable diastereomeric excess, indicating an insufficient facial discrimination by the nucleophile. Even if the lack of stereoselectivity was disappointing, pure *anti* **4a** could be obtained by crystallization and further steps (see Scheme 5) allowed us to assign the configuration of the newly formed chiral center which is *S* in **4a** and *R* in **5a**.

Table 1. Addition of Et_2AlCN to enones **1**

Enone	R	R′	Acetone cyanohydrin	*anti* (**4**)/*syn* (**5**)[a]	Yield%
1a	Boc	H	No	1:1	70
1a	Boc	H	Yes	1:1	96
1b	Tr	H	Yes	n. d.[b]	94
1c	Bn	Bn	Yes	6:1	75

[a] By NMR spectroscopy. [b] A 2:1 mixture of diastereoisomers was detected by NMR spectroscopy.

Hoping for a better stereoselectivity, the addition to **1a** of other precursors of the carboxylate group was investigated under non-equilibrating conditions. The addition of vinylmagnesium bromide to enone **1a** was carried out in THF, in the presence of DMAP and of several Cu^{I}, Cu^{II}, Ti^{IV} and Al^{III} catalysts to favor 1,4-addition, but only 2:1 diastereomeric mixtures of *anti* and *syn* adducts were obtained

in the best cases. Diethyl-2-phenylethinylalane, obtained in situ from diethylaluminum chloride and lithiated phenylacetylene, was also tested as a nucleophile, carrying out the reaction at room temperature in toluene/diethyl ether in the presence of catalytic CuBr. When applied to enone **1a**, this reagent gave again a 2:1 mixture of adducts prompting us to consider other factors to control the selectivity of the reaction.

To this end we reverted to using diethylaluminum cyanide and investigated whether a change in the *N*-protecting group on the remote asymmetric center of the enone **1** had any effect on the stereoselectivity of the addition. The enones **1b** and **1c** (Table 1) were thus prepared by the same route followed for the synthesis of **1a**, starting from *N*-trityl and *N*,*N*-dibenzyl-L-Val (Scheme 2). Replacement of the Boc protecting group of **1a** with the more hindered trityl group (**1b**) resulted in a modest 2:1 selectivity. However, by switching to the dibenzyl derivative **1c** the selectivity increased to 6:1 in favor of the *anti* adduct **4c**; the configuration of the latter was established by the X-ray crystal structure of lactone **22** (Figure 1), derived from **4c** (Scheme 5).

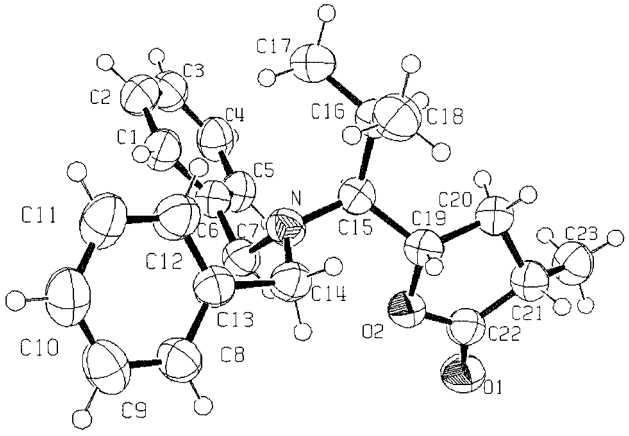
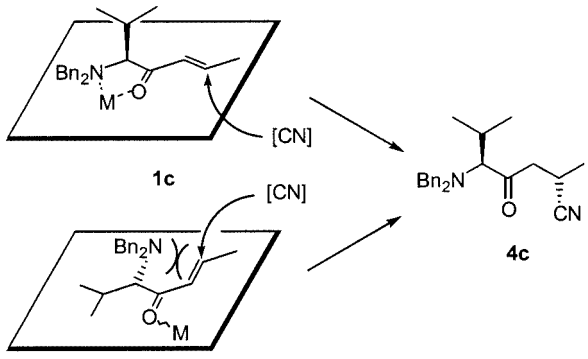


Figure 1. X-ray crystal structure of lactone **22** showing crystallographic numbering scheme

The high 1,4-asymmetric induction displayed by **1c** is remarkable, and can be explained with a model (Scheme 3) in which the unsaturated system adopts a s-*cis* conformation with the metal chelated between the carbonyl and the amino group. In this conformation the *re* face of the double bond is shielded by the isopropyl group and the nucleophile attacks preferentially the *si* face (backside attack). Alternatively, the stereoselectivity would be also consistent with a nonchelated model (Scheme) and topside attack of the nucleophile on the *s-trans* enone. The latter conformation, however, involves an unfavorable interaction between the vinyl and dibenzylamino groups: we thus favor the chelated model. This hypothesis is also consistent with the results obtained with the *N*-Boc enone **1a**, as replacement of the dibenzylaminogroup of **1c** with the less basic carbamate of **1a** may prevent chelation resulting thus in the loss of stereoselectivity.

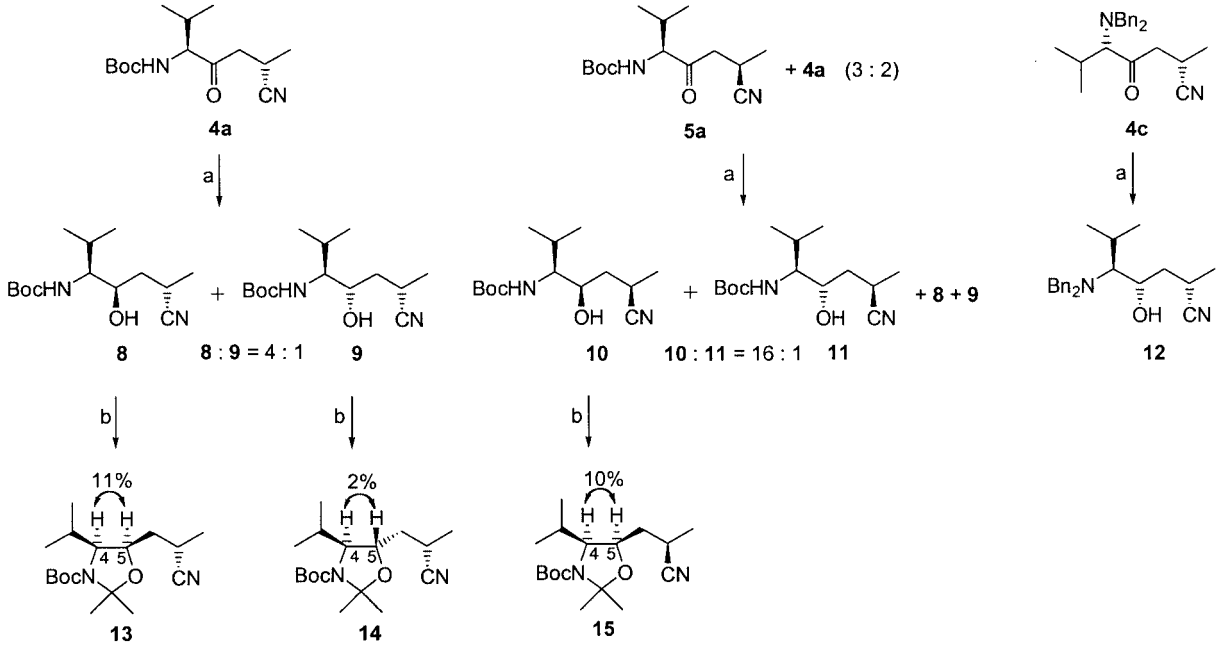


Scheme 3. Chelated and nonchelated models for 1,4-addition to α′-*N*,*N*-dibenzylamino α,β-unsaturated ketones

It was now possible to proceed to the next step in the synthesis of the isosters, namely the reduction of the carbonyl with sodium borohydride in methanol, at 0 °C (Scheme 4). Again, as in the hydrocyanation of the enones **1**, the stereochemical course of the reaction is determined by the nature of the protecting groups on nitrogen. Thus, the reduction of *N*-Boc α-amino ketone **4a** gives a 4:1 mixture of 4*R* and 4*S* alcohols **8** and **9**; similarly, **5a** (an inseparable 3:2 mixture with **4a**) gave the 4*R* and 4*S* alcohols **10** and **11** in 16:1 ratio (together with the corresponding amounts of **8** and **9**). However, the reduction of the *N*,*N*-dibenzyl protected enone **4c** proceeds with the opposite stereoselectivity, giving the 4*S* amino alcohol **12** with 90% diastereoselectivity.

The stereochemistry of the newly formed asymmetric center was confirmed by converting the *N*-Boc amino alcohols **8**−**10** into the corresponding 2,2-dimethyl oxazolidines **13**−**15** (Scheme 4). In $CDCl_3$ solution these compounds are present as 1:1 mixtures of rotamers around the amide bond with a coalescence temperature above 70 °C; NOE experiments, in which transfer of saturation between rotamers was observed upon irradiating the oxazolidine ring protons, reveal 11% and 10% enhancements between H-4 and H-5 in oxazolidines **13** and **15**, consistent with a *cis* relationship between these protons. The H-4, H-5 coupling constant (4.9, 5.1 Hz for **13** and **15** respectively) is also consistent with a *cis* structure for these oxazolidines.[15] Since in both compounds the configuration of C-4 is *S*, as in the starting amino ester, it follows that the configuration of C-5 must be *R*. In the oxazolidine **14**, derived from the minor reduction product **9**, only 2% NOE enhancement is observed between H-4 and H-5, consistent with a *trans* relationship between these protons, thus confirming the *S* configuration for C-5. In the case of the *N*,*N*-diprotected amino alcohol **12**, the *S* configuration of the newly established stereocenter was assigned from the X-ray crystal structure of its derivative **22** (Figure 1).

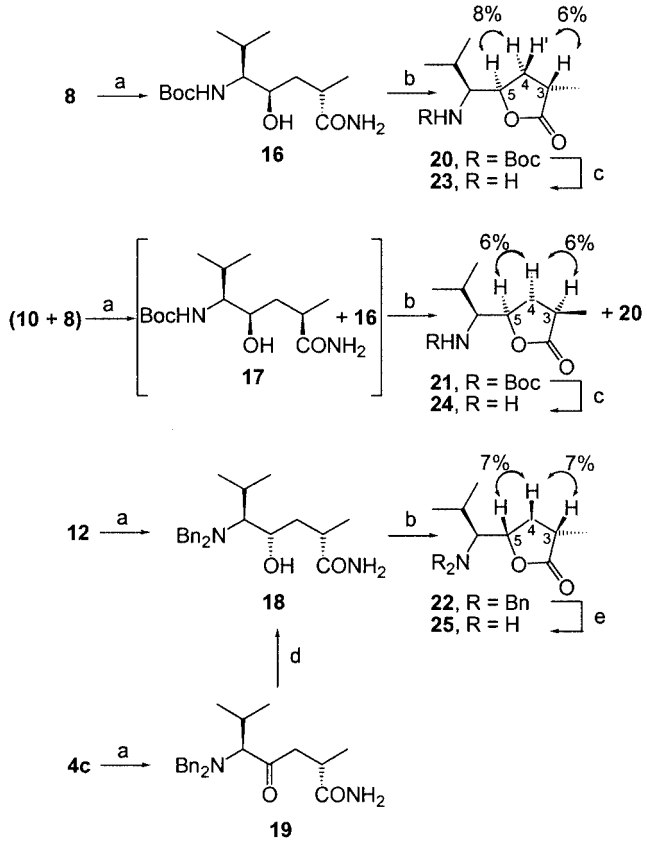
The selectivity of the reduction of *N*-Boc amino ketones **4a**, **5a** is in agreement with previous results,[15,24,25] and is consistent with the Cram model assuming that NHBoc is the medium-size group.[15] The inversion of stereoselectivity observed in the reduction of **4c** is consistent with the non-



Scheme 4. Reduction of cyano ketones **4**,**5**: a) $NaBH_4$, MeOH, 0 °C, 82−90%; b) 2,2-dimethoxypropane, cat. *p*TsOH, 60−62%

chelated Cram model proposed for *N*,*N*-dibenzylamino ketones (Bn_2N = Large).[23,26] The different selectivities observed in the reduction of ketones **4a** and **5a** indicate that the remote asymmetric center also has some influence on the stereochemistry of the reaction. In the cyano ketone **4a** the approach of the nucleophile to the preferred *si* face of the carbonyl is hindered by the *syn* cyano group when the chain adopts the extended conformation represented in Scheme 4. In the reduction of **5a** the approach is unhindered by the substituent on C-2 and the selectivity is the same (16:1) as that observed in the reduction of enone **1a**.[27]

Having established the configuration of the stereocenter resulting from the reduction of the carbonyl, it was now possible to proceed with the synthesis of the Val-Ala isosters; en route to these, it was also possible to demonstrate the configuration of the third stereocenter, resulting from the hydrocyanation of enones **1a** and **1c**. To this end, nitriles **8**,**10** (as a 7:3 mixture with **8**) and **12** were hydrated with hydrogen peroxide in dimethyl sulfoxide[28] to give the corresponding amides **16**−**18** (Scheme 5). In the hydration of nitrile **12** partial (20%) epimerization at the carbon atom vicinal to the amide was observed, probably due to longer reaction times required by this substrate. This problem was overcome by inverting the order of carbonyl reduction and nitrile hydration, and the amide **18** could be obtained, without any detectable epimerization, from **4c** via ketone **19** and stereoselective reduction of the latter (Scheme 5). Amides **16**−**18** readily cyclize to lactones **20**−**22** in aqueous dioxane at pH = 2. An analysis of the NOE spectra of the lactones (Scheme 5) allowed to assign the configuration of the chiral center adjacent to the carbonyl. In lactone **20** enhancements are observed between H-3 and H′-4 (8%) and between H-5 and H-4 (6%), indicating that H-3 and H-



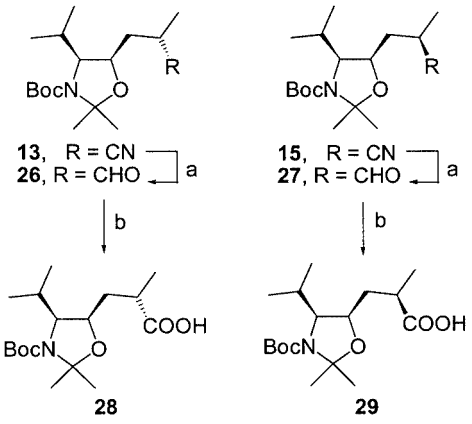
Scheme 5. Synthesis of lactones **20**−**25**: a) H_2O_2, K_2CO_3, DMSO, 80−96%; b) 1 N HCl, H_2O/dioxane, 25 °C, 83%; c) TFA, CH_2Cl_2, 95%; d) $NaBH_4$, MeOH, 0 °C, 94%; e) 1 Atm H_2, $Pd(OH)_2$/C, 93%

5 are on opposite sides with respect to the plane of the ring. In lactones **21** (obtained as a 7:3 mixture with **20** from which it was separated by chromatography) and **22**, on the

contrary, protons H-3 and H-5 correlate with the same proton H-4 (6% and 7% enhancements, respectively) indicating that these protons are on the same side with respect to the mid-plane of the lactone ring. Since the configuration of C-5 is *R* in lactones **20** and **21** and *S* in lactone **22** it follows that the configuration of C-3 is *S* in **20**, *R* in **21** and *S* in **22**, as shown in Scheme 5. The stereochemical assignment was unanmbiguously confirmed, for lactone **22**, by the X-ray crystal structure (Figure 1) showing that all three stereocenters possess the same *S* configuration, as predicted by NMR spectroscopy.

Finally, removal of the *tert*-butoxycarbonyl protection (Scheme 5) gave enantiomerically pure amino lactones **23** and **24** in 77% and 80% yield from the corresponding cyano alcohols **8** and **10**, respectively. Similarly, reductive debenzylation of **22** gave amino lactone **25** in 58% overall yield from the cyano ketone **4c**. Aminolactones **23**−**25** are masked hydroxyethylene dipeptide isosters in which the hydroxy group and *C*-terminal are internally protected; as such they are potentially useful for the synthesis of more complex peptidomimetics by direct amide coupling, while also the lactone can be directly converted into hydroxy amide under Weinreb's conditions.[29−31]

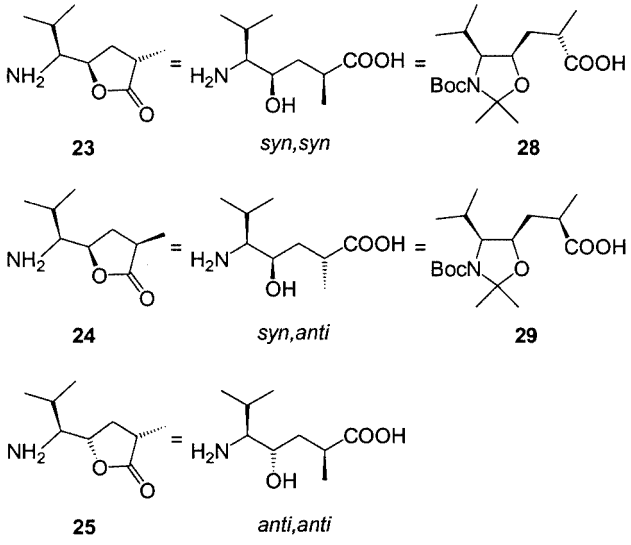
A second series of *N,O*-protected hydroxyethylene isosters was readily available by simple elaboration of oxazolidines **13** and **15**, as shown in Scheme 6. Direct conversion of the oxazolidine-protected nitriles **13** and **15** into acids by basic hydrolysis (30% KOH in refluxing methanol) resulted in epimerization at the chiral center adjacent to the nitrile group. The conversion was thus performed stepwise (Scheme 6): diisobutylaluminum hydride reduction was carried out first and gave the aldehydes **26** and **27**. In order to prevent epimerization on the side chain, it is essential to avoid an excess of DIBALH in this step. If one equivalent of reducing agent is used, no epimerization is detected and the products are formed as single diastereoisomers. Aldehydes **26**, **27** were then oxidized with potassium permanganate in buffered aqueous *tert*-butyl alcohol.[32] By this procedure, the acids **28**, **29** were obtained in 45% and 39% yields from the corresponding cyanoalcohols **8**, **10**. 1,3-Oxazolidines can be hydrolyzed to amino alcohols under mild conditions; thus acids **28** and **29** correspond to masked hydroxyethylene isosters. Similar compounds have been used for the synthesis of pseudopeptide inhibitors by coupling the free carboxylate group with an amino acid or a peptide.[33]



Scheme 6. Synthesis of acids **28**, **29**: a) DIBALH, toluene, 25 °C, then H_3O^+, 77−80%; b) $KMnO_4$, *t*BuOH, phosphate buffer, pH = 7, 95%

Conclusion

We have described a novel approach to the synthesis of masked hydroxyethylene dipeptide isosters based on the hydrocyanation of α′-amino α,β-unsaturated ketones derived from valine. The stereochemistry of both cyanide addition to the enone and the reduction of the resulting α-amino ketone can be controlled by the choice of the protecting group on nitrogen. In particular, *N,N*-dibenzyl protected substrates give excellent selectivities in both the hydrocyanation and the reduction. Replacing the *N*,*N*-dibenzyl protection with *N*-Boc results in a complete loss of selectivity in the addition step, while in the following reduction of the α-amino ketone the selectivity is reversed as a consequence of the smaller size of the protecting group. By applying the concept of protecting group controlled stereoselectivity to the synthesis of isosters of the Val-Ala dipeptide we have synthesized enantiomerically pure *syn*,*syn* isosters **28**, **23** and *syn*,*anti* isosters **29**, **24** from the *N*-Boc enone **1a** and the *anti*,*anti* isoster **25** from the *N*,*N*-dibenzyl enone **1c**.



The availability, by the same route, of stereoisomeric isosters protected either at the amino group (**28, 29**) or at the carboxy group (**23**−**25**) is another feature of this approach and should be particularly useful for the flexible synthesis of pseudopeptide inhibitors of aspartic proteases containing a 5-amino-4-hydroxypentanoate core as non-hydrolizable dipeptide replacement.

Experimental Section

General Remarks: Moisture-sensitive reactions were carried out in oven-dried vessels under a positive argon pressure. Tetrahydrofuran and toluene were distilled from sodium-benzophenone prior to use. Flash column chromatography was performed on Merck silica gel 60 (230−400 mesh); Merck silica gel 60_{F254} coated plastic sheets (0.25 mm) were used for TLC and developed with iodine and/or permanganate. Melting points were determined with a Büchi 510 open capillary apparatus and are uncorrected. Optical rotations were measured at 589 nm in methanol with a Perkin−Elmer 261 polarimeter fitted with a 10 cm cell. IR spectra were recorded as Nujol mulls, unless otherwise noted, on a JASCO 200 FT/IR spectrophotometer. ^{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, unless otherwise noted, on a Jeol EX 400 spectrometer. Electrospray ionization mass spectra (ESI-MS) were obtained on a SCIEX Perkin−Elmer API1 spectrometer at the interdepartmental center for mass spectrometry of the University of Trieste. CHN analyses were obtained on a Carlo Erba 1106 elemental analyzer. Diastereomeric ratios were measured by NMR spectroscopy. Compounds **2a**, **2c** and **3a** were obtained as described.[15,34] Full characterization for known compound **1a**[35] is given.

L-*N*-Trityl-valine Methyl Ester (2b): Finely powdered potassium carbonate (2.00 g, 20 mmol) was added to a suspension of L-valine methyl ester hydrochloride (1.50 g, 8.85 mmol) in 15 mL dichloromethane with stirring at room temperature. After 15 min the mixture was filtered and the solvent was evaporated to obtain the free amine as an oil (1.1 g, 8.4 mmol, 92%). To a solution of this oil (1.0 g, 7.6 mmol) in anhydrous dichloromethane (15 mL) were added, under argon and with stirring, triethylamine (1.0 mL, 7.6 mmol) and trityl chloride (2.1 g, 7.6 mmol). After 15 h at room temperature, 20 mL of water were added and stirring was continued for 15 min. The organic layer was dried over anhydrous Na_2SO_4 and the solvents evaporated to give a residue that was crystallized from *n*-pentane to give 2.1 g (5.6 mmol, 75%) of a white solid. m. p. 88 °C − $[\alpha]_D^{25}$ = +2.9 (*c* = 0.3). IR (KBr): $\tilde{\nu}$ = 3472, 3302, 1733, 1595 cm^{-1}. ^{1}H NMR: δ = 0.94 (d, *J* = 7.0 Hz, 3 H), 1.00 (d, *J* = 7.0 Hz, 3 H), 2.18 (m, 1 H), 2.66 (d, NH, *J* = 11.0 Hz), 3.10 (s, 3 H), 3.25 (dd, *J* = 4.9, 11.0 Hz, 1 H), 7.29 (m, 10 H), 7.51 (m, 5 H). ^{13}C NMR: δ = 17.9, 19.6, 33.7, 50.9, 60.7, 70.9, 126.3, 127.7, 128.9, 146.1, 173.9. ESI-MS: *m*/*z* = 374 $[MH]^+$, 243. $C_{25}H_{27}NO_2$ (373.50): calcd. C 80.4, H 7.24, N 3.75; found C 80.2, H 7.40, N 3.69.

Dimethyl (3*S*)-[4-Methyl-2-oxo-3-(tritylamino)pentyl]phosphonate (3b): A 2.5 M BuLi solution in hexanes (12.9 mL, 32.2 mmol) was added portionwise to a stirred solution of dimethyl methylphosphonate (3.4 mL, 32.2 mmol) in anhydrous tetrahydrofuran (50 mL) under Argon and cooling at −78 °C. After additional stirring for 15 min , a solution of **2b** (2.00 g, 5.36 mmol) in 10 mL anhydrous THF was added portionwise and the mixture was stirred at −78 °C for 2 h and then at −30 °C for 1 h. The mixture was poured into 200 mL of 10% citric acid solution and the aqueous layer extracted twice with ethyl acetate. The combined organic layers were washed with saturated $NaHCO_3$ solution and with brine, then dried over Na_2SO_4 and the solvents evaporated to give crude **3b** (2.04 g, 4.55 mmol, 85%) which was used without further purification. $[\alpha]_D^{25}$ = +49 (*c* = 0.2). IR (neat): 3400, 3317, 1708, 1255 cm^{-1}. ^{1}H NMR: δ = 0.94 (d, *J* = 7.0 Hz, 3 H), 1.10 (d, *J* = 7.0 Hz, 3 H), 2.05 (dd, *J* = 16.7, 22.4 Hz, 1 H), 2.12 (m, 1 H), 2.57 (dd, *J* = 16.7, 16.7 Hz, 1 H), 3.06 (d, NH, *J* = 9.5 Hz), 3.40 (dd, *J* = 3.0, 9.5 Hz, 1 H), 3.63 (d, *J* = 11.1 Hz, 3 H), 3.65 (d, *J* = 11.1 Hz, 3 H), 7.29 (m, 10 H), 7.51 (m, 5 H). ^{13}C NMR: δ = 18.2, 19.3, 31.3, 38.6 (d, *J* = 138 Hz), 52.5 (d, *J* = 6.8 Hz), 67.1, 70.7, 126.5, 127.8, 129.1, 146.3, 204.6 (d, *J* = 8.4 Hz). ESI-MS: *m*/*z* = 466 $[MH]^+$, 243, 224.

Dimethyl (3*S*)-[3-(Dibenzylamino)-4-methyl-2-oxopentyl]phosphonate (3c): Following the same procedure, **2c** (3.0 g, 7.75 mmol), 2.5 M BuLi (9.3 mL, 23.2 mmol) and dimethyl methylphosphonate (2.52 mL, 23.2 mmol), gave an oil, which was purified by flash chromatography (10% MeOH in diethyl ether) to give 2.13 g of **3c** (5.28 mmol, 69%). $[\alpha]_D^{25}$ = −181 (*c* = 0.3). IR (neat): $\tilde{\nu}$ = 1706, 1257 cm^{-1}. ^{1}H NMR (CD_3CN): δ = 0.81 (d, *J* = 6.0 Hz, 3 H), 1.15 (d, *J* = 6.0 Hz, 3 H), 2.32 (m, 1 H), 2.90 (dd, *J* = 14.5, 21.5 Hz, 1 H), 3.07 (dd, *J* = 14.5, 21.8 Hz, 1 H), 3.17 (d, *J* = 10.4 Hz, 1 H), 3.62 (d, *J* = 11.3 Hz, 3 H), 3.69 (d, *J* = 11.3 Hz, 3 H), 3.70 (d, *J* = 13.7 Hz, 2 H), 3.87 (d, *J* = 13.7 Hz, 2 H), 7.28 (m, 10 H). ^{13}C NMR (CD_3CN): δ = 20.2, 20.6, 27.0, 41.2 (d, *J* = 129 Hz), 52.5, 54.4, 72.0, 128.1, 129.3, 130.1, 140.6, 201.8 (d, *J* = 5.4 Hz). ESI-MS: *m*/*z* = 404 $[MH]^+$.

***tert*-Butyl (1*S*,3*E*)-1-Isopropyl-2-oxopent-3-enylcarbamate (1a):** Oven dried K_2CO_3 (5.78 g, 41.8 mmol) was added portionwise over 15 min, with vigorous stirring, to a solution of phosphonate **3a** (13.5 g, 41.8 mmol) and acetaldehyde (10 mL, 179 mmol) in 150 mL absolute ethanol. After 2 h at 25 °C the solid was filtered off and the solution neutralized with glacial acetic acid. The solvent was removed under reduced pressure and the residue was partitioned between 250 mL ethyl acetate and 100 mL saturated aqueous $NaHCO_3$. The aqueous layer was extracted with 100 mL ethyl acetate; the combined organic phases were washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the crude product **1a** was purified by flash chromatography on silica gel (diethyl ether/petroleum ether, 1:1) to give 9.80 g (40.7 mmol, 97%) of a colorless oil. $[\alpha]_D^{25}$ = +14.3 (*c* = 0.23). IR (film): $\tilde{\nu}$ = 3430, 3340, 1714, 1694, 1630 cm^{-1}. ^{1}H NMR: δ = 0.78 (d, *J* = 6.8 Hz, 3 H), 1.00 (d, *J* = 6.8 Hz, 3 H), 1.44 (s, 9 H), 1.93 (dd, 3 H, *J* = 1.6, 6.8 Hz), 2.13 (m, 1 H), 4.50 (dd, *J* = 4.2, 8.8 Hz, 1 H), 5.29 (d, NH, *J* = 8.8 Hz), 6.24 (d, *J* = 15.6 Hz, 1 H), 7.00 (dq, *J* = 6.8, 15.6 Hz, 1 H). ^{13}C NMR: δ = 16.6, 18.4, 19.8, 28.2, 30.7, 61.8, 79.3, 129.2, 144.4, 155.8, 198.1. ESI-MS: *m*/*z* = 242 $[MH]^+$, 186, 142.

(2*E*,3*S*)-6-Methyl-5-(tritylamino)hept-2-en-4-one (1b): Following the procedure described above and starting from **3b** (2.15 g, 4.62 mmol), acetaldehyde (2 mL, 35.6 mmol) and dry K_2CO_3 (640 mg, 4.6 mmol), an oil was obtained. Purification by flash chromatography (diethyl ether/petroleum ether, 1:1) gave 1.51 g (3.93 mmol, 85%) of **1b**. $[\alpha]_D^{25}$ = +90 (*c* = 0.24). IR (film): $\tilde{\nu}$ = 3308, 1689, 1627 cm^{-1}. ^{1}H NMR: δ = 0.94 (d, *J* = 6.9 Hz, 3 H), 1.00 (d, *J* = 6.9 Hz, 3 H), 1.64 (dd, 3 H, *J* = 1.5, 7.0 Hz), 2.10 (m, 1 H), 3.17 (d, NH, *J* = 11.0 Hz), 3.55 (dd, *J* = 4.0, 11.0 Hz, 1 H), 5.62 (dq, *J* = 1.5, 15.4 Hz, 1 H), 6.23 (dq, *J* = 7.0, 15.4 Hz, 1 H), 7.25−7.51 (m, 15 H). ^{13}C NMR: δ = 17.8, 18.7, 19.6, 33.2, 63.8, 71.1, 126.3, 127.8, 129.0, 130.4, 140.4, 146.7, 201.6. ESI-MS: *m*/*z* = 384 $[MH]^+$, 243.

(2*E*,5*S*)-5-(Dibenzylamino)-6-methylhept-2-en-4-one (1c): Following the procedure described above and starting from **3c** (2.00 g, 4.96 mmol), acetaldehyde (2 mL, 35.6 mmol) and dry K_2CO_3 (690 mg, 4.96 mmol), an oil was obtained. Purification by flash chromatography (diethyl ether/petroleum ether, 1:1) gave 1.30 g (4.05 mmol, 81%) of **1c**. $[\alpha]_D^{25}$ = −170 (*c* = 0.3). IR (film): $\tilde{\nu}$ = 1687, 1660, 1621 cm^{-1}. ^{1}H NMR: δ = 0.73 (d, *J* = 6.6 Hz, 3 H), 1.14 (d, *J* = 6.6 Hz, 3 H), 1.86 (dd, 3 H, *J* = 1.5, 6.6 Hz), 2.26 (m,

1 H), 3.29 (d, J = 10.6 Hz, 1 H), 3.39 (d, J = 14.3 Hz, 2 H), 4.00 (d, J = 14.3 Hz, 2 H), 6.10 (dq, J = 1.5, 15.6 Hz, 1 H), 6.56 (dq, J = 6.6, 15.6 Hz, 1 H), 7.21−7.38 (m, 10 H). ^{13}C NMR: δ = 18.3, 20.13, 20.16, 27.1, 54.3, 67.9, 126.8, 128.2, 128.6, 134.0, 139.9, 143.1, 201.8. ESI-MS: m/z = 322 $[MH]^+$, 232.

tert*-Butyl (1*S*,4*S*)- and (1*S*,4*R*)-4-Cyano-1-isopropyl-2-oxopentylcarbamate (4a, 5a):** Diethylaluminium cyanide (49.8 mL of 1 M solution in toluene) and acetone cyanohydrin (2.2 mL, 24.9 mmol) were added, under an argon atmosphere, to enone **1a** (6.00 g, 24.9 mmol) in 100 mL dry toluene. After 6 h at 25 °C, the reaction mixture was cooled to 0 °C and NaF (14.6 g, 342 mmol) and water (6.30 mL, 342 mmol) were carefully added (CAUTION:*** HCN can be formed!) (Workup with aqueous $NaHCO_3$ resulted in poor recovery). The mixture was stirred for 30 min at 25 °C, then filtered through a short pad of anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the crude product was purified by flash chromatography on silica gel (diethyl ether/petroleum ether, 1:1) to give 6.40 g (23.9 mmol, 96%) of a 1:1 mixture of cyano ketones **4a** and **5a**. Crystallization from diisopropyl ether/petroleum ether gave 1.59 g (5.94 mmol, 23%) of pure **4a**: m. p. 73 °C. $[\alpha]_D^{25}$ = +33.6 (c = 0.22). IR: $\tilde{\nu}$ = 3360, 2240, 1714, 1694 cm^{-1}. ^{1}H NMR: δ = 0.84 (d, J = 6.8 Hz, 3 H), 1.01 (d, J = 6.8 Hz, 3 H), 1.33 (d, J = 7.2 Hz, 3 H), 1.45 (s, 9 H), 2.15 (m, 1 H), 2.78 (dd, J = 7.2, 18.3 Hz, 1 H), 2.94 (dd, J = 6.1, 18.3 Hz, 1 H), 3.16 (m, 1 H), 4.17 (dd, J = 5.0, 7.9 Hz, 1 H), 5.06 (d, NH, J = 7.9 Hz). ^{13}C NMR: δ = 17.0, 17.6, 19.6, 20.0, 28.2, 29.9, 44.0, 64.0, 80.1, 122.1, 155.8, 205.6. ESI-MS: m/z = 269 $[MH]^+$, 213, 169. $C_{14}H_{24}N_2O_3$ (268.36): calcd. C 62.7, H 8.95, N 10.4; found C 62.3, H 9.05, N 10.2.

5a: ^{1}H NMR: δ = 0.85 (d, J = 6.9 Hz, 3 H), 1.02 (d, J = 6.9 Hz, 3 H), 1.34 (d, J = 7.1 Hz, 3 H), 1.44 (s, 9 H), 2.15 (m, 1 H), 2.74 (dd, J = 6.3, 18.2 Hz, 1 H), 2.96 (dd, J = 7.4, 18.2 Hz, 1 H), 3.16 (m, 1 H), 4.20 (dd, J = 5.0, 8.2 Hz, 1 H), 5.08 (d, NH, J = 8.2 Hz). ^{13}C NMR: δ = 16.9, 17.6, 19.7, 20.0, 28.2, 29.9, 44.5, 63.9, 80.0, 122.1, 155.9, 205.6.

(5*S*)-5-(Dibenzylamino)-2,6-dimethyl-4-oxoheptanenitrile (4c): With the same procedure, **1c** (100 mg, 0.31 mmol), 1 M Et_2AlCN (0.47 mL) and acetone cyanohydrin (0.057 mL, 0.62 mmol) gave a 6:1 mixture of diastereoisomers (**4c** was the major diastereoisomer), which was purified by flash chromatography (diethyl ether/petroleum ether, 1:1) to give 80 mg (0.23 mmol, 75%) of oil, still consisting of a diastereomeric mixture in the same ratio. IR (neat): $\tilde{\nu}$ = 3360, 2242, 1712, 1662 cm^{-1}. ^{1}H NMR: δ = 0.75 (d, J = 6.2 Hz, 3 H), 1.13 (d, J = 6.2 Hz, 3 H), 1.28 (d, J = 7.0 Hz, 3 H), 2.26 (m, 1 H), 2.34 (dd, J = 6.6, 18.7 Hz, 1 H), 2.74 (dd, J = 6.6, 18.7 Hz, 1 H), 3.01 (d, J = 10.6 Hz, 1 H), 3.14 (m, 1 H), 3.55 (d, J = 14.3 Hz, 2 H), 3.98 (d, J = 14.3 Hz, 2 H), 7.25−7.35 (m, 10 H). ^{13}C NMR: δ = 17.7, 19.6, 20.1, 20.3, 27.3, 48.9, 54.4, 70.4, 122.5, 127.1, 128.4, 128.6, 139.2, 207.5. ESI-MS: m/z = 349 $[MH]^+$.

***tert*-Butyl (1*S*,2*R*,4*S*)- and (1*S*,2*S*,4*S*)-4-Cyano-2-hydroxy-1-isopropylpentylcarbamate (8, 9):** $NaBH_4$ (99 mg, 2.6 mmol) was added portionwise to cyano ketone **4a** (700 mg, 2.61 mmol) in 20 mL methanol at 0 °C and stirring was continued for 1 h. The mixture was neutralized with glacial acetic acid, the solvent was removed under reduced pressure and the residue was partitioned between 30 mL ethyl acetate and saturated aqueous $NaHCO_3$. The aqueous layer was extracted with 30 mL ethyl acetate and the combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and flash chromatography of the residue on silica gel (diethyl ether/petroleum ether, 7:3) gave pure alcohols **8** (505 mg, 72%) and **9** (127 mg, 18%).

8: Oil. $[\alpha]_D^{25}$ = +18 (c = 0.22). IR (film): $\tilde{\nu}$ = 3455, 2250, 1690 cm^{-1}. ^{1}H NMR: δ = 0.94 (d, J = 6.7 Hz, 3 H), 0.98 (d, J = 6.7 Hz, 3 H), 1.35 (d, J = 7.2 Hz, 3 H), 1.45 (s, 9 H), 1.53 (m, 1 H), 1.73 (m, 1 H), 1.90 (m, 1 H), 3.03 (m, 1 H), 3.23 (br. s, OH), 3.50 (m, 1 H), 3.83 (m, 1 H), 4.49 (d, NH, J = 8.9 Hz). ^{13}C NMR: δ = 17.8, 18.5, 19.9, 22.5, 28.3, 28.5, 37.5, 60.5, 70.2, 79.9, 122.9, 157.1. ESI-MS: m/z = 271 $[MH]^+$, 215, 171.

9: Oil. $[\alpha]_D^{25}$ = −33 (c = 0.25). IR (neat): 3455, 3350, 2250, 1690 cm^{-1}. ^{1}H NMR: δ = 0.89 (d, J = 6.8 Hz, 3 H), 0.93 (d, J = 6.8 Hz, 3 H), 1.26 (d, J = 7.0 Hz, 3 H), 1.37 (s, 9 H), 1.57 (m, 1 H), 1.78 (m, 2 H), 2.71 (m, 1 H), 3.07 (m, 1 H), 3.15 (br. s, OH), 3.89 (m, 1 H), 4.78 (d, NH, J = 9.9 Hz). ^{13}C NMR: δ = 17.9, 19.3, 19.7, 21.9, 28.2, 29.6, 38.6, 59.4, 68.1, 79.3, 123.1, 156.7. ESI-MS: m/z = 271 $[MH]^+$, 215, 171.

***tert*-Butyl (1*S*,2*R*,4*R*)- and (1*S*,2*S*,4*R*)-4-Cyano-2-hydroxy-1-isopropylpentylcarbamate (10, 11):** $NaBH_4$ (282 mg, 7.5 mmol) reduction of a 3:2 mixture of ketones **5a** and **4a** (2.0 g, 7.5 mmol) gave, after chromatography, alcohols **9** (170 mg, 8%), **11** (50 mg, 2%) and an inseparable 7:3 mixture of alcohols **10** and **8** (1.49 g, 74%). **10**: ^{1}H NMR: δ = 0.95 (m, 6 H), 1.34 (d, J = 7.1 Hz, 3 H), 1.45 (s, 9 H), 1.45 (m, 1 H), 1.63 (m, 1 H), 1.83 (m, 1 H), 2.94 (m, 1 H), 3.32 (m, OH), 3.50 (m, 1 H), 3.73 (m, 1 H), 4.54 (d, NH, J = 8.8 Hz). ^{13}C NMR: δ = 16.9, 18.4, 20.0, 21.6, 28.3, 28.7, 36.1, 60.8, 69.0, 80.1, 123.7, 157.3.

11: $[\alpha]_D^{25}$ = +19 (c = 0.25). IR (film): $\tilde{\nu}$ = 3450, 2250, 1690 cm^{-1}. ^{1}H NMR: δ = 0.95 (d, J = 6.8 Hz, 3 H), 1.00 (d, J = 6.6 Hz, 3 H), 1.35 (d, J = 7.1 Hz, 3 H), 1.44 (s, 9 H), 1.65 (m, 1 H), 1.85 (m, 2 H), 2.94 (m, 2 H), 3.12 (m, 1 H), 3.98 (m, 1 H), 4.83 (d, NH, J = 9.2 Hz). ^{13}C NMR: δ = 14.0, 18.2, 18.9, 21.4, 28.0, 28.2, 39.1, 60.4, 68.2, 79.3, 122.9, 156.7. ESI-MS: m/z = 271 $[MH]^+$, 215, 171.

(5*S*)-5-(Dibenzylamino)-4-hydroxy-2,6-dimethylheptanenitrile (12): $NaBH_4$ (426 mg, 11.4 mmol) reduction of **4c** (800 mg, 2.28 mmol) gave, after flash chromatography (diethyl ether/petroleum ether, 1:1), 636 mg (1.82 mmol, 86%) of oily **12** as a single diastereoisomer. $[\alpha]_D^{25}$ = −31 (c = 0.2). IR (neat): $\tilde{\nu}$ = 2244, 1602, 1586 cm^{-1}. ^{1}H NMR: δ = 1.05 (m, 6 H), 1.32 (d, J = 6.8 Hz, 3 H), 1.51 (m, 1 H), 1.67 (m, 1 H), 2.30 (m, 2 H), 2.83 (m, 1 H), 3.45 (d, J = 14.2 Hz, 2 H), 3.74 (m, 1 H), 3.90 (d, J = 14.2 Hz, 2 H), 4.51 (br. s, OH), 7.30 (m, 10 H). ^{13}C NMR: δ = 16.7, 19.2, 21.6, 23.8, 25.0, 39.2, 53.9, 63.6, 123.6, 127.3, 128.4, 129.1, 138.5. ESI-MS: m/z = 352 $[MH]^+$.

***tert*-Butyl (4*S*,5*R*,2′*S*)-5-(2-Cyanopropyl)-4-isopropyl-2,2-dimethyl-1,3-oxazolidine-3-carboxylate (13):** Amino alcohol **8** (400 mg, 1.48 mmol) was heated at reflux for 15 h in 5 mL 2,2-dimethoxypropane containing a catalytic amount of p-toluensulfonic acid (8 mg, 0.04 mmol). The solvent was removed under reduced pressure and the residue partitioned between diethyl ether and saturated aqueous $NaHCO_3$. The organic phase was separated, washed with brine and dried over anhydrous Na_2SO_4. The solvent was rotary evaporated and the crude product was purified by flash chromatography on silica gel (diethyl ether/petroleum ether, 7:3) giving **13** (275 mg, 60%) as a white solid. m. p. 63 °C. $[\alpha]_D^{25}$ = +14.5 (c = 0.2). IR: $\tilde{\nu}$ = 2240, 1685 cm^{-1}. ^{1}H NMR (45 °C): δ = 0.97 (m, 6 H), 1.38 (d, J = 7.1 Hz, 3 H), 1.47 (s, 9 H), 1.47 (m, 1 H), 1.56 (s, 6 H), 1.83 (m, 1 H), 1.85 (m, 1 H), 2.91 (m, 1 H), 3.78 (m, 1 H), 4.26 (ddd, J = 2.8, 5.1, 10.8 Hz, 1 H). ^{13}C NMR (25 °C, two rotamers): δ = 18.5, 19.0, 19.4, 21.6, 22.0, 23.4, 24.9, 23.5, 26.3, 26.9, 28.3, 28.5, 28.8, 34.1, 34.2, 63.6, 63.7, 74.1, 74.3, 79.7, 79.9, 92.5, 93.1, 122.1, 122.2, 152.6, 153.2. ESI-MS: m/z = 311 $[MH]^+$, 255, 211. $C_{17}H_{30}N_2O_3$ (310.44): calcd. C 65.8, H 9.68, N 9.03; found C 66.1, H 9.64, N 9.06.

***tert*-Butyl (4*S*,5*S*,2′*S*)-5-(2-Cyanopropyl)-4-isopropyl-2,2-dimethyl-1,3-oxazolidine-3-carboxylate (14):** From amino alcohol **9** (300 mg, 1.11 mmol), with the same procedure, were obtained 206 mg of oxazolidine **14** as a white solid (60%), m. p. 80−83 °C. $[\alpha]_D^{25} = -6.0$ ($c = 0.28$). IR: $\tilde{\nu} = 2240, 1685\ cm^{-1}$. ^1H NMR (45 °C): δ = 0.92 (d, $J = 7.0$ Hz, 6 H), 1.37 (d, $J = 7.0$ Hz, 3 H), 1.48 (s, 9 H), 1.51 (s, 3 H), 1.60 (s, 3 H), 1.69 (ddd, 1 H, $J = 4.9, 8.3, 14$ Hz), 2.06 (ddd, $J = 6.0, 9.1, 14.0$ Hz, 1 H), 2.18 (m, 1 H), 2.80 (m, 1 H), 3.55 (m, 1 H), 4.01 (ddd, $J = 3.1, 4.9, 9.1$ Hz, 1 H). ^{13}C NMR (45 °C): δ = 17.3, 17.8, 19.1, 22.0, 23.5, 27.8, 28.4, 30.3, 40.4, 67.6, 74.1, 80.1, 94.6, 122.7, 152.5. ESI-MS: $m/z = 311\ [MH]^+$, 255, 211. $C_{17}H_{30}N_2O_3$ (310.44): calcd. C 65.8, H 9.68, N 9.03; found C 65.4, H 9.70, N 8.95.

***tert*-Butyl (4*S*,5*R*,2′*R*)-5-(2-Cyanopropyl)-4-isopropyl-2,2-dimethyl-1,3-oxazolidine-3-carboxylate (15):** With the same procedure, from a 7:3 mixture of amino alcohols **10** and **8** (1.50 g, 5.55 mmol) a 7:3 mixture of oxazolidines **15** and **13** was obtained (1.07 g, 62%). Flash chromatography of this mixture gave 629 mg (2.03 mmol, 53% from **10**) of pure **15** as a white solid, m. p. 98−100 °C. $[\alpha]_D^{25} = -29$ ($c = 0.43$). IR: $\tilde{\nu} = 2240, 1685\ cm^{-1}$. ^1H NMR (two rotamers): δ = 0.97 (m, 6 H), 1.37 (d, $J = 7$ Hz, 3 H), 1.46−1.57 (m, 15 H), 1.85 (m, 1 H), 1.85 (m, 1 H), 2.08 (ddd, $J = 5.2, 10.5, 15.7$ Hz, 1 H), 2.86 (m, 1 H), 3.62 (m, 0.5 H), 3.77 (m, 0.5 H), 4.10 (m, 1 H). ^{13}C NMR (two rotamers): δ = 16.8, 16.9, 19.0, 19.4, 21.7, 22.0, 22.5, 23.4, 25.0, 26.2, 26.8, 28.3, 28.6, 32.9, 33.0, 63.0, 63.6, 73.1, 73.3, 79.7, 79.9, 92.5, 93.0, 122.8, 152.6, 153.2. ESI-MS: $m/z = 311\ [MH]^+$, 255, 211. $C_{17}H_{30}N_2O_3$ (310.44): calcd. C 65.8, H 9.68, N 9.03; found C 65.6, H 9.91, N 9.09.

(5*S*)-5-(Dibenzylamino)-4-hydroxy-2,6-dimethylheptaneamide (18): Reduction of ketone **19** (1.00 g, 2.73 mmol) with $NaBH_4$ as described for the synthesis of **12** gave the crude product which was crystallized from diisopropyl ether and petroleum ether yielding 945 mg (2.57 mmol, 94%) of alcohol **18** as a single diastereoisomer. White solid, m. p. 93 °C. $[\alpha]_D^{25} = -29$ ($c = 0.4$). IR: $\tilde{\nu} = 3359, 1668, 1602\ cm^{-1}$. ^1H NMR: δ = 1.06 (m, 6 H), 1.16 (d, $J = 7.0$ Hz, 3 H), 1.41 (m, 1 H), 1.55 (m, 1 H), 2.28 (m, 2 H), 2.58 (m, 1 H), 3.45 (d, $J = 13$ Hz, 2 H), 3.80 (m, 1 H), 3.92 (d, $J = 13$ Hz, 2 H), 4.72 (br. s, OH), 5.32 (br. s, 1 H, NH_2), 5.82 (br. s, 1 H, NH_2), 7.22÷7.32 (m, 10 H). ^{13}C NMR: δ = 16.6, 19.2, 24.0, 24.9, 37.0, 39.7, 53.8, 65.1, 66.3, 127.3, 128.3, 128.5, 138.8, 179.5. ESI-MS: $m/z = 369\ [MH]^+$. $C_{23}H_{32}N_2O_2$ (368.52): calcd. C 74.96, H 8.75, N 7.60; found C 75.0, H 8.81, N 7.47.

(5*S*)-5-(Dibenzylamino)-2,6-dimethyl-4-oxoheptaneamide (19): K_2CO_3 (1.54 g, 11.2 mmol) and 30% H_2O_2 (0.65 mL) were added to **4c** (1.30 g, 3.73 mmol) in 5 mL DMSO. The mixture was stirred overnight at room temperature, poured into 20 mL of water and extracted with 3 × 30 mL ethyl acetate. The combined organic layers were washed with water and brine, dried over Na_2SO_4 and the solvents evaporated to give a crude oil which was purified by flash chromatography (diethyl ether), giving 1.10 g (2.98 mmol, 80%) of oily amide **19** as a single diastereoisomer. $[\alpha]_D^{25} = -154$ ($c = 0.6$). IR (neat): $\tilde{\nu} = 3436, 1738, 1674\ cm^{-1}$. ^1H NMR: δ = 0.74 (d, $J = 6.2$ Hz, 3 H), 1.10 (d, $J = 6.2$ Hz, 3 H), 1.16 (d, $J = 7.0$ Hz, 3 H), 2.19 (m, 1 H), 2.26 (dd, $J = 3.7, 18.7$ Hz, 1 H), 2.89 (m, 1 H), 3.00 (dd, $J = 9.2, 18.7$ Hz, 1 H), 3.04 (d, $J = 10.3$ Hz, 1 H), 3.52 (d, $J = 14.3$ Hz, 2 H), 4.00 (d, $J = 14.3$ Hz, 2 H), 6.17 (br. s, 1 H, NH_2), 6.24 (br. s, 1 H, NH_2), 7.22−7.43 (m, 10 H). ^{13}C NMR: δ = 17.8, 20.0, 20.2, 27.4, 34.4, 50.8, 54.6, 70.4, 127.0, 127.5, 128.6, 139.6, 178.1, 212.2. ESI-MS: $m/z = 367\ [MH]^+$.

***tert*-Butyl (1*S*,2′*R*,4′*S*)-2-Methyl-1-(4-methyl-5-oxotetrahydrofuran-2-yl)propylcarbamate (20):** 30% hydrogen peroxide (0.30 mL, 2.6 mmol) was added dropwise to a vigorously stirred mixture of $K_2CO_3 \cdot 1.5H_2O$ (38 mg, 0.23 mmol) and nitrile **8** (200 mg, 0.74 mmol) in 1 mL dimethyl sulfoxide. The reaction mixture was stirred at 25 °C for 3 h, poured into 10 mL water and extracted with ethyl acetate (2 × 30 mL). The combined organic phases were washed with water and brine, dried over anhydrous Na_2SO_4 and rotary evaporated to give the oily amide **16** (200 mg). IR (neat): $\tilde{\nu} = 3420, 3370, 1670\ cm^{-1}$. ^1H NMR: δ = 0.89 (d, $J = 6.8$ Hz, 3 H), 0.92 (d, $J = 6.8$ Hz, 3 H), 1.20 (d, $J = 7$ Hz, 3 H), 1.44 (s, 9 H), 1.45 (m, 1 H), 1.78 (m, 1 H), 1.86 (m, 1 H), 2.71 (m, 1 H), 3.45 (m, 1 H), 3.66 (m, 1 H), 3.93 (br. s, OH), 4.62 (d, NH, $J = 9.5$ Hz), 5.89 (s, 1 H, NH_2), 6.43 (s, 1 H, NH_2). ^{13}C NMR: δ = 18.0, 18.6, 19.9, 28.3, 28.7, 36.3, 36.4, 60.6, 69.9, 79.7, 157.2, 179.7. ESI-MS: $m/z = 289\ [MH]^+$, 233, 216, 189. The crude amide **16** (200 mg) was hydrolyzed in 5 mL dioxane and 0.57 mL 1 N HCl for 4 days at 25 °C. The reaction mixture was poured into 20 mL water and extracted twice with 20 mL ethyl acetate. The combined extracts were washed with saturated aqueous $NaHCO_3$ and brine and dried over anhydrous Na_2SO_4. The solvent was removed in vacuo to give lactone **20** as a white solid (163 mg, 81% for the two steps), m. p. 60 °C. $[\alpha]_D^{25} = -27.5$ ($c = 0.24$). IR (nujol): $\tilde{\nu} = 3375, 1760, 1715\ cm^{-1}$. ^1H NMR: δ = 0.89 (d, $J = 6.8$ Hz, 3 H), 0.95 (d, $J = 6.8$ Hz, 3 H), 1.28 (d, $J = 7.1$ Hz, 3 H), 1.45 (s, 9 H), 1.95 (m, 1 H), 2.38 (m, 1 H), 2.13 (m, 1 H), 2.77 (m, 1 H), 3.61 (m, 1 H), 4.29 (m, 1 H), 4.41 (d, NH, $J = 10.1$ Hz). ^{13}C NMR: δ = 15.3, 15.7, 19.8, 27.7, 28.3, 32.7, 33.2, 56.9, 77.2, 79.9, 156.1, 179.8. ESI-MS: $m/z = 272\ [MH]^+$, 216, 172. $C_{14}H_{25}NO_4$ (271.36): calcd. C 62.0, H 9.22, N 5.17; found C 62.2, H 9.15, N 5.12.

***tert*-Butyl (1*S*,2′*R*,4′*R*)-2-Methyl-1-(4-methyl-5-oxotetrahydrofuran-2-yl)propylcarbamate (21):** A 7:3 mixture of nitriles **10** (350 mg, 1.30 mmol) and **8** (150 mg) in 1 mL DMSO containing $K_2CO_3 \cdot 1.5H_2O$ (70 mg, 0.42 mmol) was hydrated with 0.26 mL 30% hydrogen peroxide. Workup as described gave a 7:3 mixture of amides **17** and **16**. IR (neat): $\tilde{\nu} = 3430, 3370, 1670\ cm^{-1}$. ^1H NMR: δ = 0.84 (m, 6 H), 1.09 (d, $J = 6.6$ Hz, 3 H), 1.36 (s, 9 H), 1.45 (m, 1 H), 1.85 (m, 1 H), 1.68 (m, 1 H), 2.50 (m, 1 H), 3.36 (m, 1 H), 3.59 (m, 1H + OH), 4.8 (d, NH, $J = 9.9$ Hz), 6.17 and 6.51 (2 br. s, 2 H, NH_2). ^{13}C NMR: δ = 17.3, 17.8, 20.1, 28.3, 28.5, 36.7, 37.2, 60.4, 69.7, 79.4, 157.0, 180.6. ESI-MS: $m/z = 289\ [MH]^+$, 233, 216, 189. Hydrolysis of the 7:3 mixture of crude amides **17** and **16** was carried out as described for **16** and gave the corresponding lactones **21** and **20**, from which **21** was isolated by flash chromatography (ethyl ether/petroleum ether, 1:1) as a white solid (296 mg, 84% from **10**), m. p. 94 °C. $[\alpha]_D^{25} = -11.5$ ($c = 0.22$). IR: $\tilde{\nu} = 3370, 1750, 1710\ cm^{-1}$. ^1H NMR: δ = 0.89 (d, $J = 7$ Hz, 3 H); 0.96 (d, $J = 7$ Hz, 3 H), 1.29 (d, $J = 7$ Hz, 3 H), 1.45 (s, 9 H), 1.78 (m, 1 H), 2.48 (m, 1 H), 2.16 (m, 1 H), 2.64 (m, 1 H), 3.67 (m, 1 H), 4.20 (m, 1 H), 4.39 (d, NH, $J = 9.5$ Hz). ^{13}C NMR: δ = 15.1, 15.6, 19.7, 28.1, 28.3, 34.8, 35.5, 54.8, 77.6, 79.7, 155.9, 179.1. ESI-MS: $m/z = 272\ [MH]^+$, 216, 172. $C_{14}H_{25}NO_4$ (271.36): calcd. C 62.0, H 9.22, N 5.17; found C 61.7, H 9.18, N 5.17.

5-[(1*S*,2*S*,3*S*)-1-(Dibenzylamino)-2-methylpropyl]-3-methyldihydrofuran-2(3*H*)-one (22): 2.73 mL of a 1 N HCl solution (2.73 mmol) were added to a solution of **18** (500 mg, 1.59 mmol) in 10 mL dioxane. After stirring at room temperature for 4 days, the mixture was neutralized with saturated $NaHCO_3$ solution. The aqueous layer was extracted with 2 × 30 mL ethyl acetate; the combined organic layers were washed with brine, dried over Na_2SO_4 and the solvents evaporated. The residue was crystallized from dichloromethane/petroleum ether to give 440 mg (1.32 mmol, 83%) of **22** as colorless crystals. m. p. 112 °C. $[\alpha]_D^{25} = +90$ ($c = 0.1$). IR (KBr): $\tilde{\nu} = 1773\ cm^{-1}$. ^1H NMR: δ = 0.85 (d, $J = 7.0$ Hz, 3 H), 1.02 (d,

J = 7.0 Hz, 3 H), 1.24 (d, J = 7.0 Hz, 1 H), 1.81 (m, 1 H), 1.97 (m, 1 H), 2.15 (m, 1 H), 2.49 (m, 1 H), 2.66 (m, 1 H), 3.83 (d, J = 13.2 Hz, 2 H), 3.87 (d, J = 13.2 Hz, 2 H), 4.69 (m, 1 H), 7.22÷7.35 (m, 10 H). ^{13}C NMR: δ = 15.0, 20.4, 21.2, 28.38, 28.42, 35.4, 56.3, 64.2, 79.4, 126.9, 128.1, 129.4, 140.1, 179.4. ESI-MS: m/z = 352 $[MH]^+$ − $C_{23}H_{29}NO_2$ (351.49): calcd. C 78.63, H 8.26, N 3.99; found C 79.0, H 8.38, N 4.23.

(3*S*,5*R*,1′*S*)-5-(1-Amino-2-methylpropyl)-3-methyldihydrofuran-2(3*H*)-one (23) and (3*R*,5*R*,1′*S*)-5-(1-amino-2-methylpropyl)-3-methyldihydrofuran-2(3*H*)-one (24): Trifluoroacetic acid (0.5 mL) was added to the lactone **20** or **21**, respectively, (50 mg, 0.18 mmol) in 1 mL dichloromethane and the solution was kept at 25 °C for 10 min. The solvent was evaporated in vacuo and the residue was partitioned between 15 mL dichloromethane and 15 mL of saturated $NaHCO_3$ solution. The aqueous layer was extracted twice with 5 mL dichloromethane and the combined organic phases were washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to give the oily free amines **23**, **24** [14] (30 mg, 95%). **23:** IR (neat): $\tilde{\nu}$ = 1768 cm^{-1}. **24:** IR (neat): $\tilde{\nu}$ = 1770 cm^{-1}.

(3*S*,5*S*,1′*S*)-5-(1-Amino-2-methylpropyl)-3-methyldihydrofuran-2(3*H*)-one (25): 50 mg of **22** (0.14 mmol) in 5 mL methanol were stirred, in the presence of 10 mg of $Pd(OH)_2$/C and under 1 Atm of hydrogen, for 24 h. The suspension was filtered through celite and the solvents evaporated in vacuo to give 23 mg (0.13 mmol, 93%) of an oil. IR (neat): $\tilde{\nu}$ = 1772 cm^{-1}. ^{1}H NMR: δ = 0.93 (d, J = 6.8 Hz, 3 H), 1.01 (d, J = 6.8 Hz, 3 H), 1.29 (d, J = 7.0 Hz, 3 H), 1.59 (br. s, 2 H, NH_2), 1.79 (m, 2 H), 2.39 (m, 1 H), 2.56 (dd, 1 H, J = 5.1 Hz), 2.70 (m, 1 H), 4.34 (m, 1 H). ^{13}C NMR: δ = 15.0, 16.6, 20.2, 30.2, 34.1, 35.8, 59.8, 80.8, 179.4.

***tert*-Butyl (4*S*,5*R*,2′*S*)-4-Isopropyl-5-(2-methyl-3-oxopropyl)-2,2-dimethyl-1,3-oxazolidine-3-carboxylate (26):** 0.90 mL of a 1 M solution of diisobutylaluminium hydride in toluene were added dropwise to the cyano-oxazolidine **13** (280 mg, 0.90 mmol) in 10 mL dry toluene, under an argon atmosphere. The solution was kept for 15 h at 25 °C, then 10 mL aqueous 5% tartaric acid were added and the mixture was stirred for further 4 h and filtered through celite. The filtrate was washed with brine, dried over anhydrous Na_2SO_4, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography on silica gel (diethyl ether/petroleum ether, 1:1) to give the aldehyde **26** (225 mg, 80%) as a colorless oil. $[\alpha]_D^{25}$ = −20.5 (c = 0.20). IR (neat): $\tilde{\nu}$ = 1720, 1685 cm^{-1}. ^{1}H NMR (two rotamers): δ = 0.96 (m, 6 H), 1.19 (m, 3 H), 1.47 (s, 9 H), 1.56 (m, 6 H), 1.75 (m, 1 H), 1.90 (m, 1 H), 2.04 (m, 1 H), 2.62 (m, 1 H), 3.63 (m, 0.5 H), 3.78 (m, 0.5 H), 4.06 (ddd, J = 2.9, 4.9, 10.6 Hz, 1 H), 9.66 (s, 1 H). ^{13}C NMR (two rotamers): δ = 13.7, 14.0, 19.1, 19.5, 21.8, 22.2, 23.3, 24.9, 26.2, 26.8, 28.3, 28.5, 30.1, 43.7, 63.8, 63.9, 74.2, 74.7, 79.5, 79.7, 92.3, 92.8, 153.3, 204.1, 204.3. ESI-MS: m/z = 314 $[MH]^+$, 258, 214.

***tert*-Butyl (4*S*,5*R*,2′*R*)-4-Isopropyl-5-(2-methyl-3-oxopropyl)-2,2-dimethyl-1,3-oxazolidine-3-carboxylate (27):** Reduction of nitrile **15** (350 mg, 1.13 mmol) with diethylaluminium hydride, as described, gave aldehyde **27** as a white solid (272 mg, 77% after chromatography), m. p. 68−70 °C − $[\alpha]_D^{25}$ = −11 (c = 0.19). IR : $\tilde{\nu}$ = 1725, 1685 cm^{-1}. ^{1}H NMR (two rotamers): δ = 0.97 (m, 6 H), 1.14 (m, 3 H), 1.48 (s, 9 H), 1.53 (m, 7 H), 1.91 (m, 1 H), 2.09 (m, 1 H), 2.59 (m, 1 H), 3.64 (m, 0.5 H), 3.80 (m, 0.5 H), 4.08 (m, 1 H), 9.67 (s, 1 H). ^{13}C NMR (two rotamers): δ = 13.3, 13.4, 19.1, 19.5, 21.8, 22.2, 23.4, 25.0, 26.2, 26.9, 28.4, 28.7, 30.0, 30.3, 44.1, 44.3, 63.9, 64.1, 74.4, 74.6, 79.5, 79.8, 92.3, 92.8, 152.7, 153.4, 204.2, 204.4. ESI-MS: m/z = 314 $[MH]^+$, 258, 214.

(2*S*,4′*S*,5′*R*)-3-[3-(*tert*-Butoxycarbonyl)-4-isopropyl-2,2-dimethyl-1,3-oxazolidin-5-yl]-2-methylpropanoic Acid (28): 3 mL of 1 M $KMnO_4$ were added dropwise, with stirring, to a solution of aldehyde **26** (100 mg, 0.32 mmol) in 3 mL of *tert*-butyl alcohol and 2 mL of 5% aqueous KH_2PO_4. After 10 min saturated Na_2SO_3 was added and the resulting solution was acidified to pH = 3 with dilute HCl and extracted with ethyl acetate (3 × 20 mL). The organic phases were washed with brine and dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure to give the acid **28**[14] as an oil (99 mg, 0.30 mmol, 94%). IR: $\tilde{\nu}$ = 3500−3000, 1690 cm^{-1}. ESI-MS: m/z = 330 $[MH]^+$, 274, 230.

(2*S*,4′*S*,5′*R*)-3-[3-(*tert*-Butoxycarbonyl)-4-isopropyl-2,2-dimethyl-1,3-oxazolidin-5-yl]-2-methylpropanoic Acid (29): Permanganate oxidation of aldehyde **27** (100 mg, 0.32 mmol), as described, gave the corresponding acid **29**[14] as an oil (100 mg, 0.30 mmol, 95%), IR (neat): 3500−3000, 1690 cm^{-1}. ESI-MS: m/z = 330 $[MH]^+$, 274, 230.

Crystal Data for 22: $C_{23}H_{54}NO_2$, M = 376.67 g mol^{-1}, crystal dimensions 0.30 × 0.20 × 0.05 mm, orthorhombic, space group $P2_12_12_1$, a = 7.690(3), b = 9.542(9), c = 26.882(5) Å, V = 1973(2) Å^3, Z = 4, $\rho_{calcd.}$ = 1.268 g cm^{-3}, μ = 0.08 mm^{-1}, R = 0.0746, R_w = 0.1721 for 2690 reflections with $I > 3\sigma(I)$ and 238 parameters. Data were collected at 293 K with a Nonius-DIP1030 diffractometer equipped with a Nonius R590 X-ray generator using a graphite-monochromated Mo-K_α radiation (λ = 0.7107 Å). The structure was solved by direct methods and refined by full-matrix methods (SHELX-97).

CCDC-197056 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc. cam. ac. uk/conts/retrieving. html [or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; Fax: (internat.) + 44-1223/336-033; E-mail: deposit@ccdc. cam. ac. uk].

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