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New synthesis of 5-amino-4-hydroxy-2,6-dimethylheptanoic acid, a hydroxyethylene isostere of the Val-Ala dipeptide

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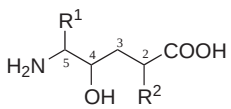
Abstract

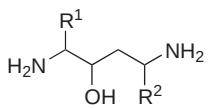
Two stereoisomers of the title compound have been synthesized from the methyl ester of *N*-Boc L-valine. The aminoester was initially converted into an α′-amino α,β-unsaturated ketone via a phosphonoketone and a Horner–Emmons olefination with acetaldehyde. Hydrocyanation of the enone with diethylaluminium cyanide and functional group conversions gave the hydroxyaminoacids protected as oxazolidines or as lactones.

Peptidomimetics of general structure P_n--P_1-X-Y-P'_1--P'_n, in which a non-hydrolizable isostere (P_1-X-Y-P'_1) replaces the central dipeptide in a short peptide chain (P_n---P'_n), are potent inhibitors of aspartic proteases.[1] Considering the crucial role played by enzymes belonging to this class in the propagation of several pathologies, such as acquired immunodeficiency syndrome (HIV-protease), hypertension (renin), malaria (plasmepsin) and Alzheimer's disease (cathepsin D), the development of new inhibitors, potentially useful in therapy, is becoming increasingly important.[2]

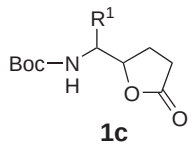
Hydroxyethylene dipeptide isosteres such as **1a** and its diamino derivative **1b** have proved particularly useful in the design of efficient peptidomimetic inhibitors. In particular, the 5-amino-4-hydroxyacid core (**1a**) has been incorporated in effective inhibitors of HIV-1 protease,[3–6] of renin[7,8] and of the protease from *Candida albicans*,[9] a yeast responsible for opportunistic infections in AIDS patients.



1a



1b



1c

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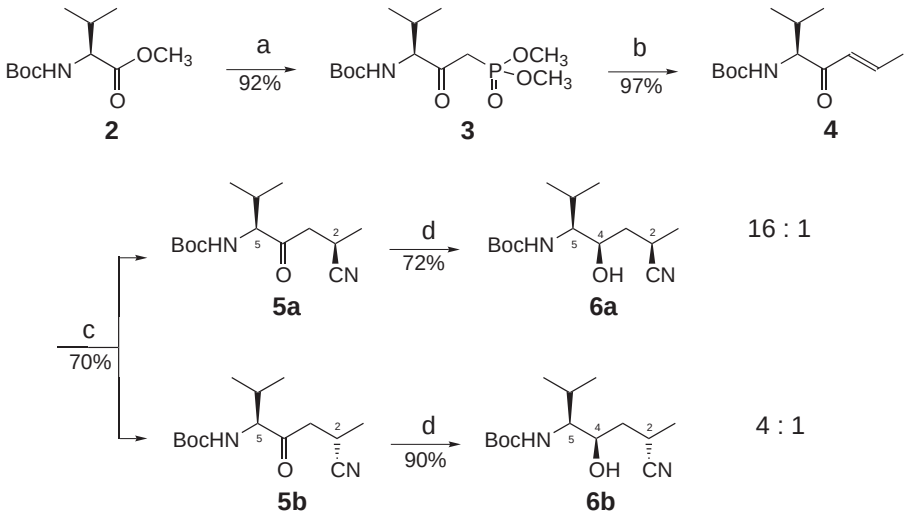
The most common approach to acids **1a** is based on the alkylation of lactones **1c**.[10,11] This route is generally efficient and stereoselective, but is somewhat limited by the range of R^2 substituents that can be introduced and by the relative stereochemistry of the OH and R^2 groups which is determined by the *trans* selectivity of the alkylation step.[11] This strategy therefore cannot be used for the synthesis of hydroxyaminoacids **1a** differing only at the configuration of C_2. In this communication we report on the synthesis of two diastereoisomeric isosteres of the Val-Ala dipeptide (**1a**, $R^1=CH(CH_3)_2$, $R^2=CH_3$) epimers at C_2, by a common route that is based on the hydrocyanation of an aminoacid-derived α,β-unsaturated ketone.

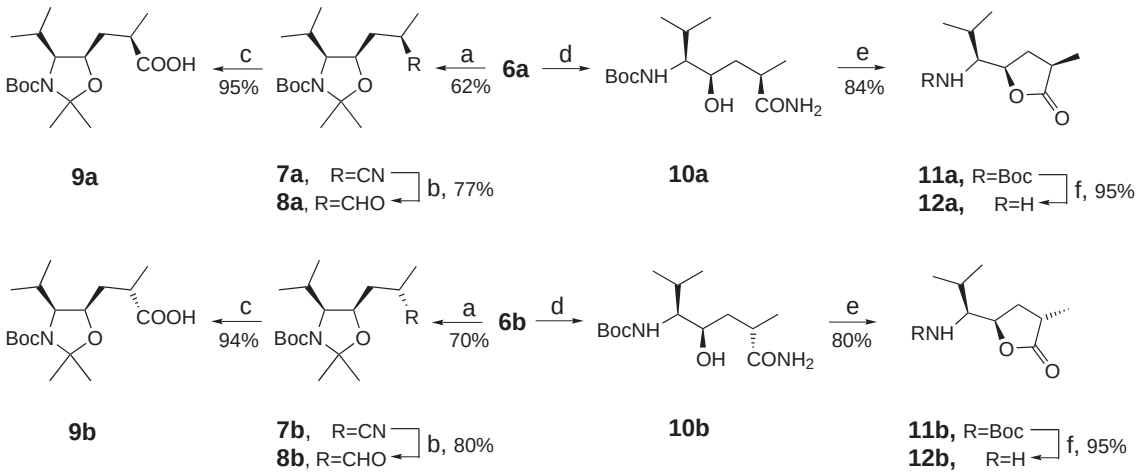
The α,β-unsaturated ketone **4** was obtained in two steps in 89% overall yield, as shown in Scheme 1. The methyl ester of L-valine (**2**) was first converted into the known phosphonate **3**[12] by reaction with lithiated methyldimethylphosphonate (−78 to −30°C). Horner–Emmons olefination of **3** with acetaldehyde and sodium carbonate in ethanol[13] gave the *trans* enone **4**. Having thus positioned the valine and alanine side chains along the skeleton, the carboxy terminal of the isostere was then installed by the conjugate addition of cyanide to this unsaturated ketone. To this end the enone **4** was treated with an excess diethylaluminium cyanide,[14] in toluene at room temperature, to give a 1:1 mixture of diastereoisomeric cyano ketones **5a** and **5b**.[15] A moderate stereoselectivity was observed at lower temperatures and a 2:1 mixture of **5a** and **5b** was obtained at −70°C. The stereochemical outcome of this reaction indicates an insufficient 1,4-induction from the existing stereocentre in the hydrocyanation of the enone **4** and/or an equilibration between the resulting diastereoisomeric aluminium enolates.[14]



Scheme 1. Reagents and conditions: (a) $(CH_3O)_2P(O)CH_3$, *n*BuLi, THF, −78°C; (b) CH_3CHO, Na_2CO_3, EtOH, 25°C; (c) Et_2AlCN, toluene, 25°C; (d) $NaBH_4$, MeOH, 0°C

The next step is the reduction of the ketones **5** with sodium borohydride in methanol, at 0°C, to give the 4-*R* alcohols **6a** and **6b**, together with minor amounts of the corresponding epimers at C_4.[15,16] The stereoselectivity is 16:1 and 4:1 in favour of **6a** and **6b**, respectively, in agreement with previous reports on the reduction of α-aminoketones.[12,17]

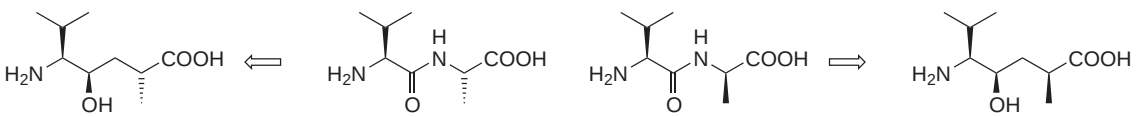
The aminoalcohols **6a**,**b** were then converted into the corresponding 2,2-dimethyl oxazolidines **7a**,**b** (Scheme 2) by treatment with 2,2-dimethoxypropane in the presence of *p*-toluenesulfonic acid. Basic hydrolysis of the nitriles **7** (30% KOH in refluxing methanol) resulted in epimeriza-



Scheme 2. Reagents and conditions: (a) 2,2-dimethoxypropane, cat. *p*TsOH; (b) DIBALH, toluene, 25°C, then H_3O^+; (c) $KMnO_4$, *t*BuOH, phosphate buffer, pH 7; (d) H_2O_2, K_2CO_3, DMSO; (e) 1N HCl, H_2O/dioxane, 25°C; (f) TFA, CH_2Cl_2

tion of the stereogenic centre on the side chain, leading to the formation of 1:1 mixtures of acids. Thus the nitriles were reduced with diisobutylaluminium hydride to aldehydes **8** and these were then oxidized with potassium permanganate in buffered aqueous *t*-butanol[18] to give the acids **9a** and **9b**[19] in 45 and 53% yield from the corresponding alcohols **6a** and **6b**. Alternatively, hydration of the nitriles **6** with hydrogen peroxide in dimethylsulfoxide[20] afforded the corresponding amides **10** which readily cyclize to lactones **11** in aqueous dioxane at pH 2 (Scheme 2). Removal of the *tert*-butoxycarbonyl protection under the usual conditions (TFA, dichloromethane) finally gave the aminolactones **12a**,**b**[21] in 80 and 77% overall yield from the cyano alcohols **6a** and **6b**, respectively.

Compounds **9a**, **12a** and **9b**, **12b** are internally protected equivalents of [2*R*,4*R*,5*S*]- and [2*S*,4*R*,5*S*]-5-amino-4-hydroxy-2,6-dimethylheptanoic acid (**13a** and **13b**) and can be used as building blocks for the synthesis of pseudopeptide inhibitors containing this hydroxyethylene isostere. However, the methodology described here for the synthesis of isosteres of the L-Val-L-Ala and L-Val-D-Ala dipeptides is quite general and can be applied to the synthesis of other hydroxyethylene dipeptide isosteres.



Acknowledgements

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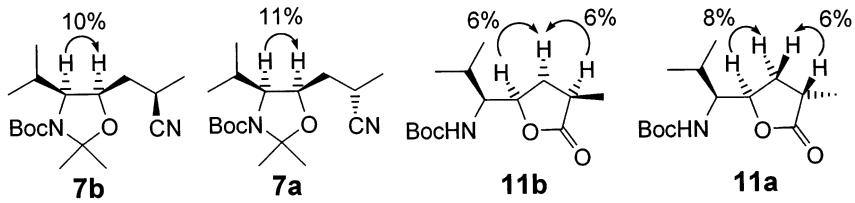
15. The configuration of the newly formed stereocentres was assigned from an analysis of NOE in the NMR spectra of oxazolidines **7** and lactones **11**:



16. The optical purity of alcohols **6** ($\geq$96%) was determined from the NMR spectra of the corresponding Mosher esters.
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19. **9a**: $[\alpha]_D^{25}=+17$ (MeOH, $c=0.20$)—^{1}H NMR (δ) two rotamers: 0.97 (m, 6H, CH_3), 1.24 (m, 3H, CH_3), 1.48 (s, 9H, ^{t}Bu), 1.50 (m, 6H, CH_3), 1.67–2.10 (m, 2H, CH_2), 1.91 (m, 1H, CH), 2.68 (m, 1H, CHCOOH), 3.63 (m, 0.5H, CHN), 3.80 (m, 0.5H, CHN), 4.06 (m, 1H, CHO), 11–12 (broad, 1H, COOH)—^{13}C NMR (δ) two rotamers: 16.1–16.2, 19.1–19.5, 21.8–22.2, 23.3–24.9, 26.2–26.8, 28.4, 28.5–28.6, 32.2–32.3, 36.7–36.8, 63.9–64.0, 74.1–74.3, 79.6–79.8, 92.3–92.8, 152.7–153.4, 182.2–182.3. **9b**: $[\alpha]_D^{25}=-7.4$ (MeOH, $c=0.27$)—^{1}H NMR (δ) two rotamers: 0.96 (m, 6H, CH_3), 1.28 (m, 3H, CH_3), 1.47 (s, 9H, ^{t}Bu), 1.50 (m, 6H, CH_3), 1.67–2.05 (m, 2H, CH_2), 1.90 (m, 1H, CH), 2.76 (m, 1H, CHCOOH), 3.63 (m, 0.5H, CHN), 3.79 (m, 0.5H, CHN), 4.06 (m, 1H, CHO), 11–12 (broad, 1H, COOH)—^{13}C NMR (δ) two rotamers: 18.0–18.2, 19.1–19.5, 21.8–22.2, 23.3–24.9, 26.2–26.8, 28.4, 28.5, 33.1, 37.0, 63.9–64.0, 74.9–75.3, 79.6–79.8, 92.3–92.8, 152.7–153.4, 182.1–182.3.
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21. **12a**: ^{1}H NMR (δ): 0.96 (m, 6H, CH_3), 1.29 (d, 3H, CH_3, $J=7.0$ Hz), 1.37 (bs, 2H, NH_2), 1.81 (m, 2H, CH_2+CH), 2.39 (ddd, 1H, CH_2, $J=5.5$, 8.7, 12.6 Hz), 2.69 (m, 1H, CHCO), 2.84 (m, 1H, CHN), 4.36 (m, 1H, CHO)—^{13}C NMR (δ): 15.0, 17.5, 19.6, 29.5, 32.1, 35.6, 58.4, 79.4, 179.5. **12b**: ^{1}H NMR (δ): 0.95 (m, 6H, CH_3), 1.24 (bs, 2H, NH_2), 1.29 (d, 3H, CH_3, $J=7.5$ Hz), 1.80 (m, 1H, CH_2), 2.44 (ddd, 1H, CH_2, $J=5.6$, 9.5, 12.9 Hz), 1.90 (m, 1H, CH), 2.77 (m, 2H, CHN, CHO), 4.46 (m, 1H, CHO)—^{13}C NMR (δ): 16.4, 17.0, 19.6, 29.3, 31.0, 34.4, 58.4, 79.5, 180.3.