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PAPER

A facile synthesis and crystallographic analysis of *N*-protected β-amino alcohols and short peptaibols†

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A facile, efficient and racemization-free method for the synthesis of *N*-protected β-amino alcohols and peptaibols using *N*-hydroxysuccinimide active esters is described. Using this method, dipeptide, tripeptide and pentapeptide alcohols were isolated in high yields. The conformations in crystals of β-amino alcohol, dipeptide and tripeptide alcohols were analysed, with a well-defined type III β-turn being observed in the tripeptide alcohol crystals. This method is found to be compatible with Fmoc-, Boc- and other side-chain protecting groups.

Introduction

β-Amino alcohols are an important C-terminal component of biologically active peptaibols.[1] They have been extensively used as chiral auxiliaries in asymmetric synthesis,[2] precursors for the synthesis of β-amino acids,[3] starting materials for the synthesis of optically active α-amino aldehydes,[4] diamines, triamines[5] and α-halo-β-amines.[6] Numerous methods have been reported for the synthesis of *N*-protected β-amino alcohols starting from the reduction of activated carboxylic group of *N*-protected amino acids. A variety of carboxylic-acid-activated derivatives of protected amino acids including mixed anhydrides,[7] acid fluorides,[8] acid chlorides,[9] 1-hydroxybezotriazole esters,[10] 1-succinimidyl esters,[11] pentafluorophenyl esters,[12] *N*-carboxyanhydrides (UNCAs)[13] and carboxy methyleniminium chlorides[14] have been used for reduction using mild $NaBH_4$. Other mild reducing agents, such as $NaBH_4$–I_2,[15] $ZnBH_4$[16] and $Ti(OiPr)_4$ and $(EtO)_3SiH$,[17] have also been reported with protected amino acid derivatives.

We have been interested in the synthesis of peptides containing γ- and functionalized γ-amino acids.[18] *N*-Protected β-amino alcohols are the starting materials for the synthesis of functionalized γ-amino acids. We followed the most widely used mixed anhydride protocol for the synthesis; however, in our hands yields were lower than the expected, and we found up to 15% of the isobutyl ester as a byproduct.[9] In our continuing search for mild, low-cost and high-yielding methods for the synthesis of *N*-protected β-amino alcohols, we envisioned that *N*-hydroxysuccinimide esters would be ideal reagents because of their easy accessibility, shelf-stability and cost-effectiveness.

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† Electronic supplementary information (ESI) available: Detailed experimental procedures; characterization data; crystallographic data; ^1H and ^{13}C NMR and mass spectra for all compounds. CCDC reference numbers 794215 (**3**), 805264 (**16**) and 794216 (**20**). For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c0ob01226b

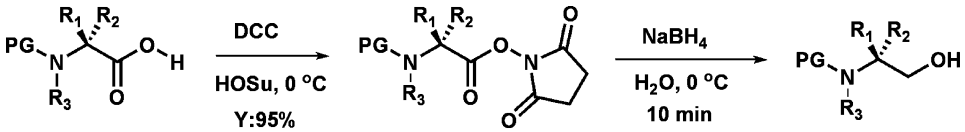
N-Hydroxysuccinimide (HOSu) has been widely used as an additive in carbodiimide-mediated peptide couplings to reduce racemization.[19] Recently, the use of *N*-hydroxysuccinimide esters in the synthesis of *N*-protected homoserines starting from aspartic and glutamic acids has been demonstrated.[20] Further, the combination of carbodiimide and HOSu has been used in the immobilization of proteins, peptides, antibodies on sensor surfaces.[21] Because of their shelf-stability and slow reactivity, *N*-hydroxysuccinimide esters have also been used in the single-step synthesis of dipeptide acids.[22]

Herein, we report the synthesis of *N*-protected-β-amino alcohols and peptide alcohols starting from *N*-hydroxysuccinimide esters of *N*-protected amino acids and peptides. This method is compatible with *N*-Fmoc, *N*-Boc and other carboxylic acid, alcohol, thiol and guanidine protecting groups. Using chiral HPLC, we demonstrated that this protocol is free from racemization. In addition, the crystal conformations of Fmoc-Valol, Boc-Ala-Valol and the tripeptide alcohol Boc-Aib-Ala-Leuol synthesized using this method were studied.

Results and discussion

A schematic representation of the synthesis of *N*-protected β-amino alcohols using *N*-hydroxysuccinimide is shown in Scheme 1. We synthesized a variety of *N*-hydroxysuccinimide esters of Fmoc-amino acids using DCC as a coupling agent in quantitative yield. In a typical reaction procedure, the succinimide esters were dissolved in distilled THF and then treated with a solution of $NaBH_4$ in ice-cold water. The course of the reaction was monitored by TLC. Intriguingly, it was found that within 5 min the active ester was completely converted to alcohol; however, we continued the reaction for another 5 min.

A list of Fmoc-protected β-amino alcohols synthesized using this method is given in Table 1. Except Fmoc-Ile-OH (entry 5), all Fmoc-β-amino alcohols were isolated in yields above 80%. For comparison, we synthesized the same Fmoc-β-amino alcohols



PG=Fmoc-, 1) R_1=H, R_2=CH_3 R_3=H

PG= Fmoc-, R_3=H, R_2=H R_1= 2) -CH_3, 3) -$CH(CH_3)_2$, 4) -$CH_2CH(CH_3)_2$, 5) -$CH(CH_3)$-CH_2CH_3, 6) -$CH(OBu^t)CH_3$, 7)-CH_2COOBu^t, 8) -$CH_2(CH_2)_3NHBoc$, 9) -$CH_2CONHTrt$ 10) $CH_2CH_2CONHTrt$

PG=Boc-,R_3=H, R_2=H, R_1= 11) -CH_3, 12)-$CH(CH_3)_2$,13)-$CH_2CH(CH_3)_2$, 14) -CH_2-indole and 15) R_3, R_1= -CH_2-CH_2-CH_2-

Scheme 1 Schematic representation of the synthesis of *N*-protected-β-amino alcohols using *N*-hydroxysuccinimide esters.

using mixed anhydride method ('IBC-Cl'), and these values are also given in Table 1.

A clear improvement of the yields can be observed for the *N*-hydroxysuccinimide method relative to the mixed anhydride method in the case of side-chain-protected amino acids (entries 6–10). The optical rotation and the melting points of Fmoc-β-amino alcohols derived from the *N*-hydroxysuccinimide esters are in agreement with the mixed anhydride method (Table 1).

To investigate the racemization during the synthesis of β-amino alcohols, we synthesized Fmoc-β-amino alcohols from D-, L- and DL-alanine. These amino alcohols were subjected to chiral HPLC separation using a chiralpack AD column. The HPLC profiles of Fmoc-protected D-, L- and DL-Alaol is shown in Fig. 1. Single peaks were obtained for Fmoc-L-Alaol and Fmoc-D-Alaol at t_R 6.24 min and 7.66 min, respectively. For the DL mixture two peaks with t_R at 6.26 and 7.70 min were observed, corresponding to the individual enantiomers. These results indicate that no racemization occurred during the syntheses of the β-amino alcohols.

Given these encouraging results, we extended the same methodology to the synthesis of Boc-β-amino alcohols. The *N*-hydroxysuccinimide esters of Boc-amino acids were prepared from the coupling reaction of Boc-amino acids and HOSu using DCC as a coupling agent (Scheme 1). A list of Boc-β-amino alcohols is given in Table 2 (entries 11–15). The yields and optical rotations of Boc-β-amino alcohols from the succinimide method are in agreement with the mixed anhydride method (data not shown). Except for **15**, all Boc-β-amino alcohols were isolated as oils.

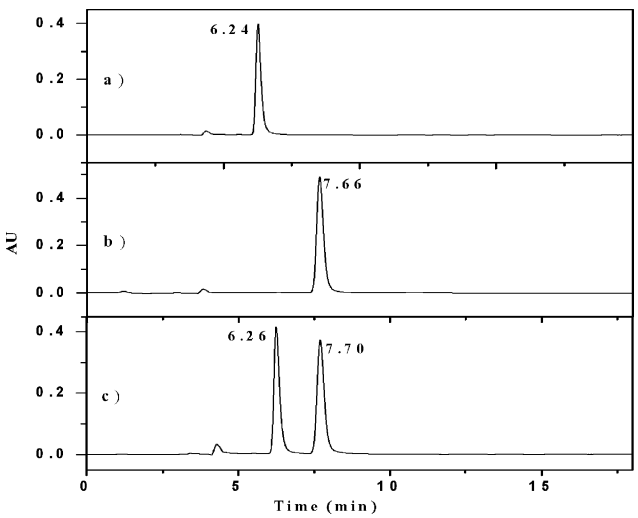


Fig. 1 Chiral HPLC of Fmoc-protected L-, D- and DL-Alaol. HPLC was performed on a chiralpack AD column using 90% isopropanol in n-hexane as the solvent system in the isocratic mode with a flow rate of 1 mL min^{-1}. HPLC profiles for: a) Fmoc-L-Alaol; b) Fmoc-D-Alaol; c) Fmoc-DL-Alaol.

We further explored the *N*-hydroxysuccinimide method to verify whether or not it can be used to reduce the peptide acids into the corresponding peptide alcohols. A variety of methods have been

Table 1 Comparison of Fmoc-protected β-amino alcohol obtained from HOSu and IBC-Cl method

		Yield (%)		mp (°C)		$[\alpha]_D^{25}$ (*c* 1, MeOH)	
Entry/Cpd no.	Fmoc-AA-OH	HOSu	IBC-Cl	HOSu	IBC-Cl	HOSu	IBC-Cl
1	Fmoc-Alaol	90	70	150–153	150–153	−2.0	−1.5
2	Fmoc-D-Alaol	85	NS[a]	148–151	—	+2.0	—
3	Fmoc-Valol	90	76	121–122	124–127	−13.0	−13.6
4	Fmoc-Leuol	81	68	133–135	135–136	−20.1	−17.0
5	Fmoc-Ileol	65	50	114–116	108–110	−11.7	−13.0
6	Fmoc-Thr(O*t*Bu)ol	85	55	Oil	Oil	+6.1	+6.4
7	Fmoc-Asp(O*t*Bu)ol	92	47	93–96	95–96	−7.4	−7.0
8	Fmoc-Lys(Boc)ol	75	64	136–138	114	−6.9	−6.0
9	Fmoc-Asn(Trt)ol	90	65	155–159	132–134	−12.3	−10.3
10	Fmoc-Gln(Trt)ol	85	72	74–77	73–77	−5.8	−6.7

[a] NS: Not synthesized.

Table 2 Boc-protected β-amino alcohols and di-, tri-, and pentapeptide alcohols synthesized using the *N*-hydroxysuccinimide method

Entry/Cpd no.	Alcohol	Yield (%)	$[\alpha]_D^{25}$ (*c* 1, MeOH)
11	Boc-Alaol	80	–8.5
12	Boc-Valol	70	–17.6
13	Boc-Leuol	85	–23.2
14	Boc-Prool	78	–45.7
15	Boc-Trpol	75	–22.2
16	Boc-Ala-Valol	86	–22.2
17	Boc-Val-Valol	82	–34.7
18	Boc-Val-Leuol	82	–35.9
19	Boc-Ala-Leu-Valol	76	–34.5
20	Boc-Aib-Ala-Leuol	79	–13.6
21	Boc-Val-Leu-Ala-Val-Leuol	65	ND[a]

[a] ND: Not determined.

reported in the literature for the synthesis of peptide alcohols, including the nucleophilic substitution of free amino alcohols in *N*-protected amino acid benzotriazoles,[23] *O*–*N* acyl transfer of peptide esters,[24] and the coupling reaction of *N*-protected amino acids and free amino alcohols using standard coupling reaction conditions.[25] To extend this methodology to peptide alcohols, we synthesized the following methyl esters of Boc-protected dipeptides using a DCC and HOBt protocol – Boc-Ala-Val-OMe, Boc-Val-Val-OMe and Boc-Val-Leu-OMe. The pure dipeptide acids were obtained after the saponification of methyl esters using 1 N NaOH. The conversion of dipeptide acid to its alcohol is shown in Scheme 2.

The dipeptide acids were converted to *N*-hydroxysuccinimide active esters using DCC and HOSu in ice-cold THF. The separated DCU was filtered, and the filtrate containing Boc-dipeptide active ester was reduced *in situ* using $NaBH_4$ in water. As anticipated, all peptide alcohols were isolated in pure form without column purification in high yields (Table 2, entries 16, 17 and 18). The ^1H, ^{13}C NMR and HPLC profiles are given in the ESI†. The results from both ^1H-NMR and HPLC reveal single enantiomers as the products, indicating that the synthesis is free from racemization.

We further extended this methodology to the synthesis of Boc-protected tripeptide alcohols, Boc-Ala-Leu-Valol (**19**), Boc-Aib-Ala-Leuol (**20**) and a pentapeptide alcohol, Boc-Val-Leu-Ala-Val-Leuol (**21**). Most peptaibols are Aib (α,α-dimethyl glycine)-rich peptides,[1,26] so we included Aib in peptaibol **20** to mimic the C-terminal sequences of peptaibols. The tri- and pentapeptide acids were obtained after the saponification of the C-terminal methyl esters. These peptide acids were converted to active esters as described for the dipeptide acids and subjected to *in situ* reduction. The tripeptide alcohols (**19** and **20**) were isolated in pure form without column purification in good yields, while the peptaibol (**21**) was purified by reverse-phase HPLC using a C_{18} column. The ^1H, ^{13}C NMR and HPLC profiles are given in the ESI†. Out of all the peptides, we were able to obtain single crystals for Boc-Ala-Valol (**16**) and Boc-Aib-Ala-Leuol (**20**). The conformation of these peptide alcohols is described below.

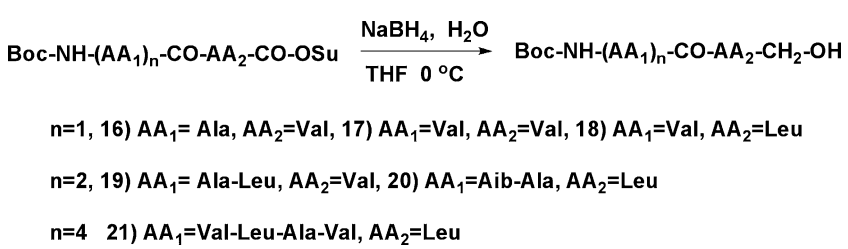
Crystal structures of β-amino alcohol and dipeptide and tripeptide alcohols

Crystals of Fmoc-Valol were obtained after slow evaporation of ethyl acetate, and the crystal structure is shown in Fig. 2A. The molecule adopted an extended-sheet type of assembly by the intermolecular H-bonding of NH and OH groups with the urethane carbonyl of the neighboring molecule (see ESI†). Crystals of the dipeptide alcohol **16** obtained in methanol solution yield the structure shown in Fig. 2B. Two molecules appear in the asymmetric unit, with significant variation in the torsional values (given in the ESI†). The dipeptide alcohol adopted an irregular structure in the crystal packing. Notably, an energetically unfavorable *cis*-Boc–urethane bond is observed in the molecule B (Fig. 2B).

Colourless crystals of peptaibol **20** were obtained after slow evaporation of $CHCl_3$, and the X-ray diffraction analysis is described below. Interestingly, a well-folded structure of the tripeptide alcohol is observed in the crystals, as shown in the ORTEP diagram (Fig. 2C). The crystallographic asymmetric unit contains four molecules of tripeptide alcohol and four solvent $CHCl_3$ molecules. Intriguingly, two peptaibols are connected by intermolecular hydrogen bonding, while the other two are independent (Fig. 2D). Two intramolecular hydrogen bonds correspond to Boc C═O···NH Leuol(3), and Ala(2) C═O···OH Leu(3)ol observed in the crystal structure (Fig. 2C). As a consequence of the two intramolecular C10 hydrogen bonds, two types of β-bends are observed. The relevant torsional angles and hydrogen bond parameters are tabulated in Tables 3 and 4, respectively. A ten-membered H-bond between the urethane carbonyl and the Leu NH (1→4) leading to the formation of a type III β-turn with torsional angles $\phi_1 = -60°$, $\psi_1 = -30°$, $\phi_2 = -61°$ and $\psi_2 = -25°$.[27] Interestingly, the type III β-turn was further stabilized by another C10 H-bond between the Ala2 carbonyl and the terminal OH (Fig. 2C).[28] The solvent $CHCl_3$ interacted with the peptaibol

Table 3 Torsion angles (°) in **20**

Residue	ϕ	ψ	ω	χ_1	χ_2	χ_3
Aib1	–60	–30	179	—	—	—
Ala2	–61	–25	172	175	—	—
Leuol3	–110	58	—	–55	–179	–53



Scheme 2 Schematic representation of the synthesis of peptide alcohols using *N*-hydroxysuccinimide active esters.

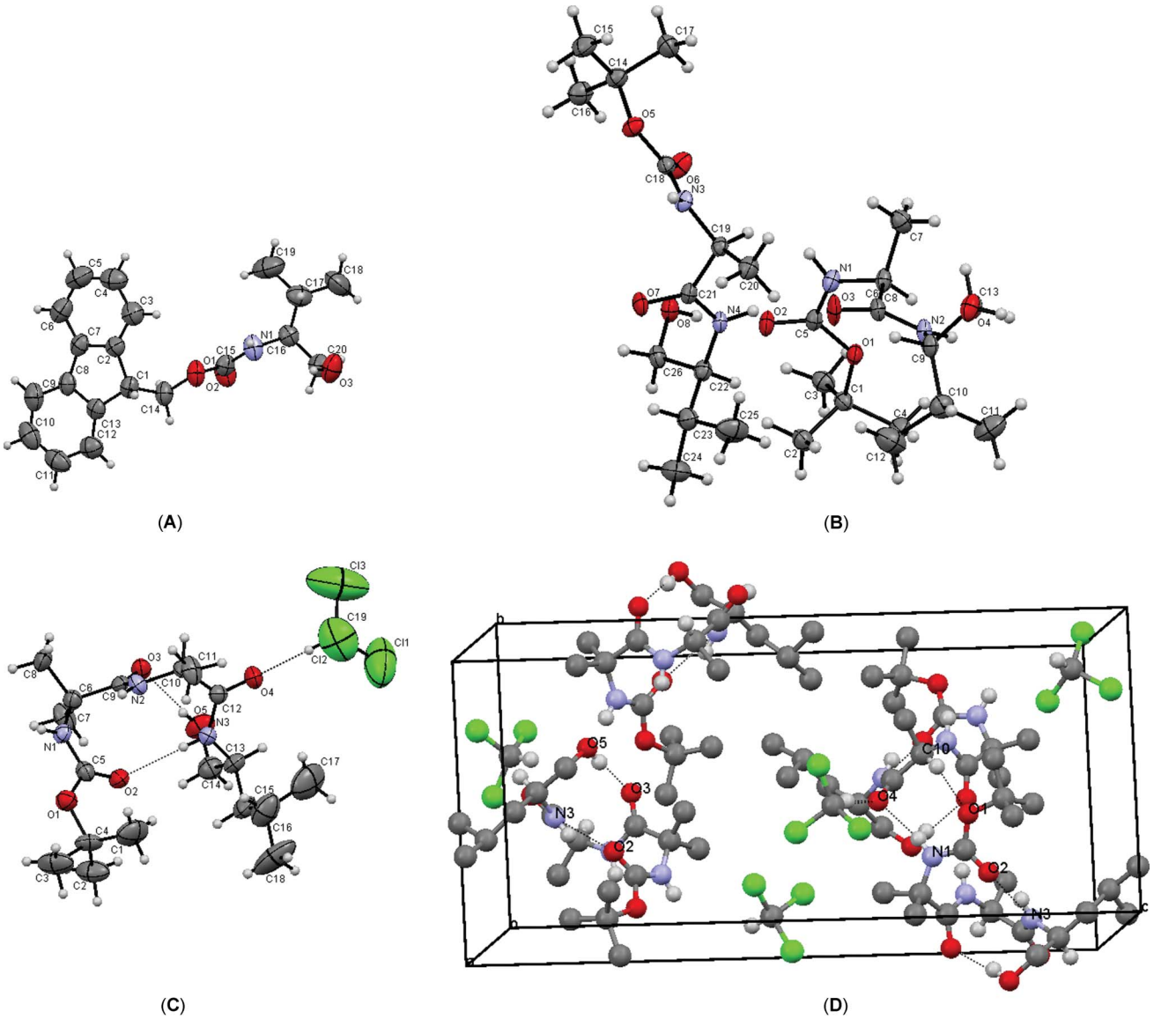


Fig. 2 Crystal structures of Fmoc-Valol (**3**), Boc-Ala-Valol (**16**) and Boc-Aib-Ala-Leuol (**20**). The H-atoms are not labeled for clarity. **A**: The crystal structure of Fmoc-Valol. **B**: ORTEP diagram showing the two molecules of **16** (A and B) in the asymmetric unit. **C**: ORTEP diagram showing the conformation of the tripeptide alcohol in crystals. Two intramolecular H-bonds are shown by dotted lines. The interaction of solvent molecule ($CHCl_3$) with peptide through a CH···O hydrogen bond is also shown. **D**: The unit cell showing four molecules of tripeptide alcohol and four molecules of $CHCl_3$ in the asymmetric unit. All side-chain H-atoms are omitted for clarity.

Table 4 Intra- and intermolecular H-bonding in crystals of the tripeptide **20**

Donor (D)	Acceptor (A)	Type	A···H (Å)	D···A (Å)	D–H···A (°)
N1	O4	Intermolecular (NH···O=C)	2.142	2.994	171
N3	O2	Intramolecular (NH···O=C)	2.203	2.974	149
O5	O3	Intramolecular (O–H···O=C)	2.188	2.914	148
C10	O1	Intermolecular (C–H···O)	2.548	3.505	165
C19[a]	O4	Intermolecular (C–H···O=C)	2.126	3.102	171

[a] Solvent $CHCl_3$.

through a CH···O hydrogen bond having an H···O distance of 2.126 Å and a C–H···O angle of 171°. However, interaction between the $CHCl_3$ molecules is not observed in the structure (the Cl···Cl distance is 3.9 Å). It appears that the solvent is stabilizing the crystal packing by filling the vacant space. The two folded conformers of the tripeptide alcohol are held together by two intermolecular hydrogen bonds between Aib(1)NH and Ala(2)CO and between the Boc-urethane oxygen O1 and Ala2C_αH in the crystals (Fig. 2D). Overall, we observed an irregular structure in the dipeptide alcohol and a well-defined type III β-turn in the tripeptide alcohol. The type III β-turn in the tripeptide alcohol may be induced by the presence of the conformationally restricted dialkyl amino acid residue (Aib) at the N-terminus of the tripeptide. Toniolo *et al.* and others have also shown the formation of type III and III′ β-turns by di- and tripeptides containing dialkyl amino acids.[27,29]

Conclusion

In conclusion, we have developed a facile, efficient and racemization-free protocol for the synthesis of *N*-protected β-amino alcohols and peptaibols. This method was found to be compatible with Fmoc, Boc, and other side-chain protecting groups. Further, the crystal conformations of the β-amino alcohol, di- and tripeptide alcohols were analyzed, and the tripeptide alcohol found to adopt a type III β-turn. This β-turn was further stabilized by a C10 hydrogen bond with the terminal alcohol and carbonyl of Ala2.

Experimental section

1. General procedure for the synthesis of *N*-protected β-amino alcohols from *N*-hydroxysuccinimide

To a solution of Fmoc- or Boc-protected amino acid (2 mmol) and *N*-hydroxysuccinimide (0.345 g, 3 mmol) at 0 °C in THF (5 mL), was added DCC (0.413 g, 2 mmol), and reaction was stirred at this temperature for 1h. Precipitated DCU was filtered and washed with THF (3 × 2 mL), combined organic layer was cooled to ice temperature and the solution of $NaBH_4$ (0.152 g, 4 mmol) in water (1 mL) was added in one portion which leads to the vigorous evolution of gas. After 10 min. 5 mL of 0.5 *N* HCl was added to quench unreacted $NaBH_4$. Reaction mixture was extracted in EtOAc (3 × 10 mL), and combined organic layer was washed with 5% Na_2CO_3 (3 × 10 mL), brine (3 × 10 mL), dried over Na_2SO_4, and concentrated in *vacuo*. After aqueous work up, *N*-protected β-amino alcohols were obtained as pure product over 80–90% yield.

2. General procedure for the synthesis of Boc-protected dipeptide alcohol and tripeptide alcohol (peptaibol)

The previous procedure was utilized to synthesize Boc-protected dipeptide, tripeptide and pentapeptide alcohols. Products were obtained in pure form after work-up, and were obtained with over 70–85% yield for the di- and tripeptide alcohols. The pure pentapeptide alcohol was isolated after HPLC purification using a C_{18} column in a MeOH–water solvent system.

3. Synthesis of peptides

Dipeptide, tripeptide and pentapeptides were synthesized by conventional solution-phase methods using a fragment-condensation strategy. The *tert*-butyloxycarbonyl group was used for N-terminus protection, and the C-terminus was protected as a methyl ester. Deprotections were performed with trifluoroacetic acid and saponification for the N- and C-termini, respectively. Couplings were mediated by dicyclohexylcarbodiimide (DCC) and 1-hydroxybenzotriazole (HOBt). The tripeptide Boc-Aib-Ala-Leu-OMe was prepared by [2 + 1] condensation involving N-terminal dipeptide acid Boc-Aib-Alaol and H-Leu-OMe. The tripeptide Boc-Ala-Leu-Val-OMe was prepared by [2 + 1] condensation involving N-terminal dipeptide acid Boc-Ala-Leuol and H-Val-OMe. The pentapeptide Boc-Val-Leu-Ala-Val-Leu-OMe was prepared by [3 + 2] condensation involving N-terminal tripeptide acid Boc-Val-Leu-Alaol and H-Val-Leu-OMe.

Crystal structure of Boc-Aib-Ala-Leuol (20)

A colourless crystal with approximate dimensions 1.2 × 0.55 × 0.15 mm had the following characteristics: formula $C_{18}H_{35}N_3O_5{\cdot}CHCl_3$; crystal class orthorhombic; space group $P2_12_12_1$; a = 10.578(4); b = 11.206(4); c = 23.306(8) Å; $\alpha = \beta = \gamma = 90°$; V = 2762.7(17) Å^3; T = 296(2) K; Z = 4; ρ_{calc} = 1.185 Mg m^{-3}; $2\theta_{max}$ = 56.56°; Mo-Kα λ = 0.71073 Å. A fine-focus sealed tube source with a graphite monochromator was used. Treatment of H atoms was mixed-type. R = 0.0673 (for 1573 reflection $I > 2\sigma(I)$), wR = 0.1608, which was refined against $|F^2|$ and S = 0.715 for 280 parameters and 6526 unique reflections. The structure was obtained by direct methods using SHELXS-97.[30] All non-hydrogen atoms were refined anisotropically. The hydrogen atoms were fixed geometrically in the idealized position and refined in the final cycle of refinement as riding over the atoms to which they are bonded; μ = 0.361 mm^{-1}; minimum/maximum residual electron density –0.233/0.444 e Å^{-3}.

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