Facile Synthesis of 1-Adamantyl Esters of L-α-Amino Acids, a New Class of Carboxy Protected Derivatives

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Received 27 March 1996; revised 4 June 1996

1-Adamantyl esters of several *N*-unprotected L-α-amino acids were directly prepared in good optical purity and yield by reaction of the corresponding amino acid 4-toluenesulfonate salts with 1-adamantanol (AdOH) and dimethyl sulfite in boiling toluene. The fully protected tripeptide Boc-Leu-Ala-Val-OAd, prepared from TsOH.H-Val-OAd (entry **2b**) was amino deprotected to H-Leu-Ala-Val-OAd by the action of 4N HCl in dioxane for 25 minutes at 20 °C, while the latter was carboxy deprotected to the free peptide by the action of trifluoroacetic acid for 60 minutes at 20 °C. The 1-adamantyl ether of threonine **(5)** was also prepared and the 1-adamantyl moiety was completely cleaved from Troc-Thr(OAd)-OH by the action of trifluoroacetic acid for 30 minutes at 20 °C.

Carboxylic acids are often converted to trialkylmethyl esters which are then employed as carboxy-protected derivatives, the carboxy function being eventually restored to the free state by acidolysis of the ester under mild conditions. The *tert*-butyl group typically represents this class of carboxy protecting groups and is much used in the field of peptide synthesis.[1]

The tricyclic tertiary alcohol 1-adamantanol (tricyclo-[3.3.1.1.^{3,7}]decan-1-ol) on the other hand is known[2] to generate at the bridgehead position a carbenium ion which contrary to its analogous *tert*-butyl carbenium ion is free of olefin producing side reactions and less stable[3] by a factor of approximately 10^3. The 1-adamantyl esters of α-amino acids would then be expected to be acid labile but more stable than their *tert*-butyl-analogues.

The 1-adamantyl esters of several common *N*-unprotected L-α-amino acids (Table 1, entries **2a–f, 3a–d,g,h**) were initially obtained (although in low yield) by direct acid catalyzed esterification of the acids with excess 1-adamantanol under water removal as the toluene azeotrope, but the products could not be easily freed from reactants with simple crystallization.[5]

Almost complete esterification of TsOH.H-Ile-OH (**2a**, Table 1) was achieved in the same solvent by employing the crystalline di-1-adamantyl sulfite **(4)** as the alkylating agent, easily prepared from the alcohol and thionyl chloride in the presence of triethylamine. The reaction proceeded smoothly under evolution of sulfur dioxide gas and 1-adamantanol was the major byproduct.[5]

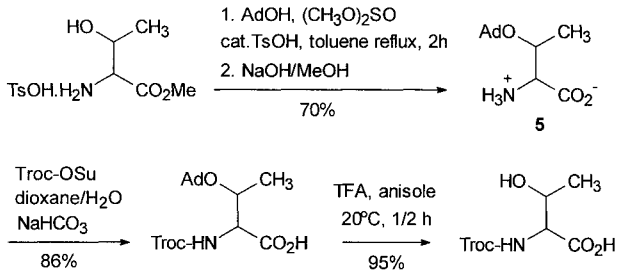
More efficient utilization of 1-adamantanol was achieved when the esterification reaction was performed in the presence of dimethyl sulfite (1.2 equivalents) in toluene solution, refluxing under a short air condenser allowing most of the methanol produced in the reaction to escape. Although dimethyl sulfite has been used to prepare methyl esters of α-amino acids[4] under vigorous acid catalysis, under the reaction conditions we employed such esters were not detected in the reaction mixture and the isolated 1-adamantyl esters (Table 1) were identical to those prepared in the absence of sulfite. In the case of aspartic and glutamic acids **(1g,h)** attempts to prepare the desirable monoesters by controlling the amounts of reagents were unsuccessful and consequently we used close to stoichiometric quantities to obtain directly the diesters **3g,h**, respectively.

The protonated α-amine function of the amino acids survives the esterification treatment intact but the β-hydroxy group of L-threonine easily reacts with dimethyl sulfite via an acid-catalyzed transesterification process towards unstable mixed sulfites which in the case of Z-Thr-OMe has been isolated as a diastereomeric mixture.[5]

Dimethyl sulfite probably reacts with the water produced in the reversible esterification process[6] thus displacing the equilibrium towards the ester product.

When the method was applied on the 4-toluenesulfonates of serine and threonine, simultaneous etherification and esterification of the hydroxy amino acid was observed chromatographically in a sluggish reaction along with considerable decomposition.

Using threonine methyl ester 4-toluenesulfonate and controlling the amount of dimethyl sulfite we obtained cleanly the etherification product, which was converted to the potentially more useful threonine 1-adamantyl ether **(5)**.



A preliminary evaluation of the acid lability of such ethers was obtained by converting **5** to its amino protected derivative *N*-(2,2,2-trichloroethoxycarbonyl)threonine 1-adamantyl ether (Troc-Thr(OAd)-OH) by the action of 2,2,2-trichloroethyl succinimidyl carbonate (Troc-OSu)[12] and subjecting the latter to the action of TFA in the

presence of anisole as cation scavenger, at room temperature (20 °C). This treatment resulted in complete cleavage of the ether within 30 minutes to afford Troc-Thr-OH as a glassy solid, in good yield.

The amino acid esters, isolated and characterized as 4-toluenesulfonate salts (entries **2a–f**, Table 1) and/or hemioxalate salts (entries **3a–d,g,h**, Table 1), are crystalline nonhygroscopic solids, stable on long storage at ordinary temperature, decomposing slowly near their melting points or in warm aqueous solution. They can serve as amino components in peptide synthesis as exemplified by the preparation of the known tripeptide Leu-Ala-Val **(10)**. The dipeptide Z-Ala-Val-OAd **(6)** was obtained from TsOH.H-Val-OAd (entry **2b**) and Z-Ala-OH using DCC as the coupling agent. The amino protecting group of **6** was hydrogenolytically removed to give H-Ala-Val-OAd which was then condensed with the active ester Boc-Leu-OSu to give the fully protected tripeptide Boc-Leu-Ala-Val-OAd **(8)** found to be freely soluble in petroleum ether. We selectively removed the *tert*-butyloxycarbonyl group by the action on **8** of 4N HCl in anhydrous dioxane, at 20 °C, over 25 minutes and obtained the amino free tripeptide H-Leu-Ala-Val-OAd from which the 1-adamantyl ester was finally cleaved by anhydrous TFA at 20 °C, during 60 minutes to afford the free tripeptide H-Leu-Ala-Val-OH, $[\alpha]_D^{25}$ −31 ($c = 1$, H_2O) [lit.[7] $[\alpha]_D^{29}$ −31 ($c = 1$, H_2O)] thus showing that the 1-adamantyl carboxy protecting group for α-amino acids can be successfully employed in small peptide synthesis in solution.

Apart from the action of TFA as a solvent on **9**, a milder cleavage of the 1-adamantyl group was achieved in the case of Z-Ala-Val-OAd **(6)**, by the action of TFA/CH_2Cl_2 (1 : 2, V : V) over 15 hours, at room temperature. Under these conditions the benzyloxycarbonyl group remained unaffected.

Table 1. 1-Adamantyl Esters of L-α-Amino Acids (Isolated as 4-Toluenesulfonate and/or Hemioxalate Salts)

Product[a]	Reaction Time (h)	Yield (%)	mp[b] (°C) (Solvent)	$[\alpha]_D^{20}$	Molecular Formula[c]
2a	4	74	184–186 (MeCN)	+13.3 ($c = 2$, $CHCl_3$)	$C_{23}H_{35}NO_5S$ (437.6)
3a	4	65	145–147 (MeCN)	+19.5 ($c = 1.5$, 96% EtOH)	$C_{18}H_{29}NO_6$ (355.4)
2b	0.75	78	177–179 (EtOAc)	+7.8 ($c = 2$, $CHCl_3$)	$C_{22}H_{33}NO_5S$ (423.5)
3b	0.75	68	168–169 (MeOH/Et_2O)	+10.4 ($c = 1$, 96% EtOH)	$C_{17}H_{27}NO_6$ (341.4)
2c	3	80	141–145 (acetone)	+26.1 ($c = 1.5$, $CHCl_3$) +27.1 ($c = 1.5$, 96% EtOH)	$C_{26}H_{33}NO_5S$ (471.6)
3c	3	80	172–174 (MeOH/Et_2O)	+18.6 ($c = 1$, MeOH)	$C_{21}H_{27}NO_6$ (389.4)
2d	1	71	133–135 (EtOAc/P.E.)	+9.0 ($c = 3$, $CHCl_3$)	$C_{23}H_{35}NO_5S$ (437.6)
3d	1	61	143–145 (EtOAc)	+3.2 ($c = 1.5$, MeOH)	$C_{18}H_{29}NO_6$ (355.4)
2e[d]	0.5	71	181–183 (acetone)	−1.45 ($c = 1.5$, 96% EtOH)	$C_{20}H_{29}NO_5S$ (395.5)
2f[d]	1	70	181–183 (acetone)	–	$C_{19}H_{27}NO_5S$ (381.5)
3g[e]	1.5	71	105–107 (MeCN)	+6.3 ($c = 0.5$, 96% EtOH)	$C_{26}H_{37}NO_8$ (491.6)
3h[e]	1.5	72	89–91 (EtOAc/P.E.)	+11.7 ($c = 1.5$, $CHCl_3$)	$C_{27}H_{39}NO_8$ (505.6)

[a] **a** Isoleucine, **b** Valine, **c** Phenylalanine, **d** Leucine, **e** Alanine, **f** Glycine, **g** Aspartic acid, **h** Glutamic acid.
[b] Uncorrected; P.E. petroleum ether bp 40–60 °C.
[c] Satisfactory microanalyses obtained: C ± 0.36, H ± 0.32, N ± 0.34.
[d] Microanalyses of the hemioxalate salts of alanine and glycine (**3e**, **f**) were not satisfactory.
[e] Diester.

Table 2. ^1H NMR Spectra (200 MHz) of Amino Acid 1-Adamantyl Esters **2a–f**, **3g**, **h**

Product	Solvent	δ
2a	$CDCl_3$	0.83 (t, 3H, CH_δIle), 0.95 (d, 3H, CH_γIle), 1.37 (m, 2H, CH_γIle), 1.60 (s, 6H, CH_δAd), 1.95 (m, 1H, CH_βIle), 2.02 (s, 6H, CH_βAd), 2.11 (s, 3H, CH_γAd), 2.35 (s, 3H, CH_3Ar), 3.83 (d, 1H, CH_αIle), 7.15 (d, 2H, Ar), 7.80 (d, 2H, Ar), 8.05 (broad, 3H, H_3N^+)
2b	$CDCl_3$	0.96 (2d, 6H, CH_γVal), 1.60 (s, 6H, CH_δAd), 2.06 (m, 9H, $CH_{\beta,\gamma}$Ad), 2.22 (m, 1H, CH_βVal), 2.34 (s, 3H, CH_3Ar), 3.75 (d, 1H, CH_αVal), 7.14 (d, 2H, Ar), 7.79 (d, 2H, Ar), 7.89 (broad, 3H, H_3N^+)
2c	$CDCl_3$	1.50 (s, 6H, CH_δAd), 1.80 (s, 6H, CH_βAd), 1.98 (s, 3H, CH_γAd), 2.30 (s, 3H, CH_3Ar), 3.00 (dd, 1H, CH_βPhe), 3.26 (dd, 1H, CH_βPhe), 4.13 (dd, 1H, CH_αPhe), 7.12 (m, 7H, Ph, Ar), 7.75 (d, 2H, Ar)
2d	$CDCl_3$	0.79 (2d, 6H, CH_δLeu), 1.63 (m, 9H, CH_δAd, $CH_{\beta,\gamma}$Leu), 1.98 (s, 6H, CH_βAd), 2.07 (s, 3H, CH_γAd), 2.32 (s, 3H, CH_3Ar), 3.77 (t, 1H, CH_αLeu), 7.12 (d, 2H, Ar), 7.77 (d, 2H, Ar), 8.03 (broad, 3H, H_3N^+)
2e	$CDCl_3/CD_3OD$ 5 : 1	1.51 (d, 3H, CH_βAla), 1.67 (s, 6H, CH_δAd), 2.10 (s, 6H, CH_βAd), 2.20 (s, 3H, CH_γAd), 2.38 (s, 3H, CH_3Ar), 3.89 (q, 1H, CH_αAla), 7.22 (d, 2H, Ar), 7.75 (d, 2H, Ar)
2f	CD_3OD/CCl_4 2 : 1	1.73 (s, 6H, CH_δAd), 2.18 (m, 9H, $CH_{\beta\gamma}$Ad), 2.41 (s, 3H, CH_3Ar), 3.68 (s, 2H, CH_αGly), 7.24 (d, 2H, Ar), 7.72 (d, 2H, Ar)
3g	CD_3OD	1.73 (s, 12H, CH_δAd), 2.18 (s, 18H, $CH_{\beta\gamma}$Ad), 2.95 (m, 2H, CH_βAsp), 4.20 (m, 1H, CH_αAsp)
3h	$CDCl_3$	1.68 (s, 12H, CH_δAd), 2.26 (m, 22H, $CH_{\beta\gamma}$Ad, $CH_{\beta\gamma}$Glu), 4.16 (m, 1H, CH_αGlu), 8.05 (broad, 4H, $(CO_2H)_2 \cdot H_2N$–)

It should also be mentioned that the above method of esterification seems to be applicable (as it might be expected) with other lower dialkyl sulfites as well, of which bis(2,2,2-trifluoroethyl) sulfite has already given good results with TsOH.H-Ile-OH (entry **2a**).[5]

The 4-toluenesulfonic acid salts of the amino acids were prepared according to the reported procedure[8] from amino acids purchased from Fluka. Reagent quality solvents were used without further purification. ^{1}H NMR spectra were recorded on a Bruker 200 MHz instrument. Optical rotation values were measured on a Perkin-Elmer 141 polarimeter. Melting points were measured on a Büchi instrument and are uncorrected. TsOH.H-Phe-OH prepared according to lit.[8] had $[\alpha]_D^{20}$ −8.2 (c = 2, H_2O). Dimethyl sulfite prepared according to lit.[6] was once more distilled (bp 125–127 °C) to ensure absence of chlorosulfite contamination. The esterification reactions were performed on a 4 mmol scale in a 25-mL round bottom flask, while the solvent refluxed ~ 3 cm below the air condenser outlet.

Amino Acid 1-Adamantyl Esters (2a–f, 3a–d,g,h, Table 1):

1. Isolated as 4-Toluenesulfonic Acid Salts **(2a–f)***; General Procedure:*

The amino acid 4-toluenesulfonic acid salt **1a–d** (4 mmol), AdOH (0.8 g, 5.2 mmol), $(CH_3O)_2SO$ (440 μL, 4.8 mmol) and a catalytic amount of anhyd TsOH (~ 20 mg, 0.12 mmol) were suspended in toluene (4 mL) and refluxed with magnetic stirring under a short air condenser for the indicated time (Table 1). The homogenous solution was diluted with $CHCl_3$ (30 mL), washed with H_2O (5 mL) and the organic layer was dried (Na_2SO_4) and evaporated in vacuo. Et_2O (petroleum ether bp 40–60 °C in the case of **1d**) (30 mL) was added to the residue and the crystalline precipitate was filtered, washed with Et_2O (2 × 20 mL) and recrystallized (Table 1).

1-Adamantyl Esters of Alanine and Glycine 4-Toluenesulfonic Acid Salts **(2e,f):**

The amino acid 4-toluenesulfonic acid salt **1e,f** (4 mmol) and AdOH (1.2 g, 8 mmol), were ground together and suspended in a mixture of toluene (1.2 mL) and 1,1,2,2-tetrachloroethane (2.4 mL). $(CH_3O)_2SO$ (540 μL, 5.8 mmol) and a catalytic amount of anhyd TsOH (~ 20 mg, 0.12 mmol) were added and the mixture refluxed with magnetic stirring under a short air condenser for the indicated time (Table 1, entries **2e,f**). The reaction mixture was then diluted with $CHCl_3$ (20 mL), washed with H_2O (4 mL), the aqueous layer was back extracted with $CHCl_3$ (8 mL) and the combined $CHCl_3$ extracts were filtered through a small layer of Na_2SO_4, concentrated in vacuo to about 10 mL and diluted with petroleum ether bp 40–60 °C (40 mL). The crystalline precipitate was filtered, washed with the same solvent mixture and recrystallized (Table 1, entries **2e,f**).

2. Isolated as Hemioxalate Salts **(3a–d,g,h):**

The reaction of the amino acid 4-toluenesulfonic acid salt **(1a–d,g,h)** with AdOH and $(CH_3O)_2SO$ was carried out according to the above described general procedure. In the case of **1g,h** AdOH (2.6 mmol) and $(CH_3O)_2SO$ (2.4 mmol) were employed per mmol of amino acid in order to prepare the diesters **3g,h**. After refluxing for the indicated time (Table 1) the reaction mixture was diluted with Et_2O (40 mL) washed with 10% aq Na_2CO_3 (2 × 20 mL) and H_2O (20 mL), dried (Na_2SO_4) and concentrated in vacuo to approximately 20 mL. A solution of oxalic acid (0.4 g, 4.4 mmol) in MeOH/Et_2O (1 : 6, 12 mL) was added and the precipitated product was filtered, washed with Et_2O and recrystallized (Table 1).

Di-1-adamantyl Sulfite [$(AdO)_2SO$, 4]:

A solution of $SOCl_2$ (160 μL, 2.2 mmol) in anhyd Et_2O (6 mL) was added dropwise to a cooled (0 °C), magnetically stirred mixture of AdOH (0.60 g, 4 mmol) and Et_3N (670 μL, 4.8 mmol), in anhyd Et_2O (25 mL) and stirring was continued for 5 h at r.t. The reaction mixture was then filtered, the filter cake washed with Et_2O and the combined filtrates were concentrated in vacuo to a small volume and diluted with petroleum ether, bp 40–60 °C (10 mL). Filtration of the precipitated crystals afforded $(AdO)_2SO$ (0.5 g). Concentration of the filtrates under reduced pressure and addition of petroleum ether afforded a second crop of product (0.08 g) with the same mp (total yield 82%); mp 229 °C.

Anal calcd for $C_{20}H_{30}O_3S$ C 68.53; H 8.63; found C 68.11; H 8.71.

^{1}H NMR ($CDCl_3$/TMS): δ = 1.64 (m, 12 H, CH_δAd), 2.06 (m, 12 H, CH_βAd), 2.18 (broad, 6 H, CH_γAd).

Benzyloxycarbonyl-alanyl-valine 1-Adamantyl Ester (Z-Ala-Val-OAd, 6):

To a cool (ice) stirred solution of **2b** (1.0 g, 2.3 mmol), benzyloxycarbonyl-alanine (0.54 g, 2.4 mmol) and Et_3N (320 μL, 2.3 mmol), in CH_2Cl_2 (4 mL), was added a solution of DCC (0.52 g, 2.5 mmol) in CH_2Cl_2 2 mL) and cooling was maintained for 30 min. After stirring for another 2 h at r.t., the solvent was evaporated under reduced pressure, the residue was taken up with EtOAc (25 mL) was washed succesively with 1 N aq citric acid (20 mL), 10% aq Na_2CO_3 (20 mL), H_2O (10 mL) and the organic layer was dried (Na_2SO_4), concentrated under reduced pressure to about 10 mL and frozen for 1 h. The precipitated dicyclohexylurea was filtered, washed with a small volume of EtOAc and with Et_2O and the combined filtrates were evaporated to a glassy solid, which after treatment with petroleum ether bp 40–60 °C crystallized. Recrystallization from a Et_2O/petroleum ether bp 40–60 °C mixture gave 0.92 g (87%) of **6**; mp 68–70 °C; $[\alpha]_D^{25}$ −26.8 (c = 2, dioxane); $[\alpha]_D^{25}$ −12.6 (c = 2, CH_2Cl_2).

Anal calcd for $C_{26}H_{36}N_2O_5$ C 68.39; H 7.95; N 6.14; found C 68.07; H 7.46; N 6.13.

^{1}H NMR ($CDCl_3$/TMS): δ = 0.86 (2 d, 6 H, CH_γVal), 1.38 (d, 3 H, CH_βAla), 1.65 (s, 7 H, CH_δAd, CH_βVal), 2.11 (m, 9 H, $CH_{\beta,\gamma}$Ad), 4.27 (m, 1 H, CH_αAla), 4.40 (dd, 1 H, CH_αVal), 5.10 (s, 2 H, CH_2Ph), 5.40 (d, 1 H, NH Ala), 6.45 (d, 1 H, NH Val), 7.32 (s, 5 H, Ph).

Alanyl-valine 1-Adamantyl Ester Hemioxalate Salt [$(CO_2H)_2$.H-Ala-Val-OAd, 7]:

Compound **6** (0.69 g, 1.5 mmol) was dissolved in MeOH (5 mL) containing HOAc (180 μL, 3 mmol). 5% Pd/C (0.1 g) was added and the mixture was hydrogenated (1 atm, r.t.) for 3 h. After filtration of the catalyst, the filtrate was evaporated in vacuo and the residue was dissolved in Et_2O (20 mL). The solution was washed with 10% aq Na_2CO_3 (20 mL) and H_2O (10 mL) and dried (Na_2SO_4). Addition of a solution of $(CO_2H)_2$ (0.15 g, 1.7 mmol) in a MeOH/Et_2O mixture (1 : 6, 6 mL) caused the precipitation of **7** which after filtration was recrystallized from MeCN to give 0.59 g (93%) of **7**; $[\alpha]_D^{25}$ −26.8 (c = 2, 96% EtOH).

Anal calcd for $C_{20}H_{32}N_2O_7 \cdot 1/2\,H_2O$ C 56.99; H 7.89; N 6.14; found C 56.80; H 7.53; N 6.76.

To obtain the ^{1}H NMR spectrum of the free amine H-Ala-Val-OAd, **7** was shaken with 10% aq Na_2CO_3 and Et_2O, the ether layer was dried (Na_2SO_4) and the solvent was removed in vacuo.

^{1}H NMR ($CDCl_3$/TMS): δ = 0.86 (2 d, 6 H, CH_γVal), 1.28 (d, 3 H, CH_βAla), 1.59 (s, 7 H, CH_δAd, CH_βVal), 2.08 (m, 11 H, $CH_{\beta,\gamma}$Ad, NH_2Ala), 3.49 (q, 1 H, CH_αAla), 4.36 (dd, 1 H, CH_αVal), 7.72 (d, 1 H, NH Val).

***tert*-Butyloxycarbonyl-leucyl-alanyl-valine 1-Adamantyl Ester (Boc-Leu-Ala-Val-OAd, 8):**

Compound **7** (0.43 g, 1 mmol) was partitioned between Et_2O and 10% aq Na_2CO_3 and the organic layer was dried (Na_2SO_4) and concentrated in vacuo. The residue was dissolved in anhyd THF (5 mL), cooled (0 °C) and Boc-Leu-OSu (0.33 g, 1 mmol) was added. The solution was allowed to reach r.t. and after 5 h the solvent was removed under reduced pressure. The residue was taken up with Et_2O (20 mL) washed with 1 N aq citric acid (10 mL), 5% aq Na_2CO_3 (10 mL) and H_2O (10 mL). The organic layer was dried (Na_2SO_4) and Et_2O was removed in vacuo to leave 0.43 g (80%) of **8** as a glassy solid, soluble in petroleum ether bp 40–60 °C; $[\alpha]_D^{25}$ −44.4 (c = 3, CH_2Cl_2).

^{1}H NMR ($CDCl_3$/TMS): δ = 0.88 (m, 12 H, CH_γVal, CH_δLeu), 1.36 (d, 3 H, CH_βAla), 1,42 (s, 10 H, $(CH_3)_3$C-, CH_γLeu), 1.63 (m, 9 H, CH_δAd, CH_βLeu, CH_βVal), 2.12 (m, 9 H, $CH_{\beta,\gamma}$Ad), 4.11 (m, 1 H, CH_αLeu), 4.38 (dd, 1 H, CH_αVal), 4.48 (m, 1 H, CH_αAla), 4.91 (d, 1 H, NH Leu), 6.56, 6.66 (d, d, 1 H, 1 H, NH Ala, Val).

Leucyl-alanyl-valine 1-Adamantyl Ester Hemioxalate Salt [$(CO_2H)_2$.H-Leu-Ala-Val-OAd, 9]:
A solution of **8** (0.27 g, 0.5 mmol) in 4 N HCl/dioxane (2.5 mL) was left at r.t. for 25 min and then evaporated under reduced pressure. The residue was dissolved in Et_2O (15 mL) and the solution was washed with 10% aq Na_2CO_3 (20 mL), H_2O (10 mL) and dried (Na_2SO_4). A solution of $(CO_2H)_2$ (45 mg, 0.5 mmol) in MeOH/Et_2O (1 : 6, 2 mL) was then added and the precipitated solid was filtered and recrystallized from a MeOH/Et_2O mixture to give **9** (0.21 g, 80%); mp 148–150°C; $[\alpha]_D^{25}$ −32.2 (c = 2, 96% EtOH).

Anal calcd for $C_{26}H_{43}N_3O_8$ C 59.41; H 8.24; N 7.99; found C 59.74; H 8.16; N 7.82.

Leucyl-Alanyl-Valine (H-Leu-Ala-Val-OH.2 H_2O, 10):
Compound **9** (0.13 g, 0.25 mmol) was partitioned between Et_2O and 10% aq Na_2CO_3 and the organic layer was dried (Na_2SO_4) and evaporated to dryness. TFA (580 μL, 7.5 mmol) and anisole (55 μL, 0.5 mmol) were added to the residue and the solution was left at r.t. for 1 h. The solvent was removed under reduced pressure and the residue was partitioned between Et_2O and H_2O. The aqueous layer was washed again with Et_2O and then concentrated to dryness. The solid residue was dissolved in acetone (5 mL) and a solution of Et_3N in acetone was added dropwise until the solution appeared slightly acidic on moist indicator paper. The precipitated solid was filtered and washed well with acetone; 0.06 g (70%) of **10** were obtained; $[\alpha]_D^{25}$ −29.1 (c = 2, H_2O) or $[\alpha]_D^{25}$ 31.0 (c = 2, H_2O) for the anhydrous tripeptide [Lit.[7] $[\alpha]_D^{29}$ −31 (c = 1, H_2O)].

TFA Cleavage of Peptide Ester 6:
To a solution of **6** (0.15 g, 0.33 mmol) in CH_2Cl_2 (0,5 mL) was added anisole (70 μL, 0.66 mmol) and TFA (0.25 mL, 3.3 mmol). After 15 h at r.t. the solvents were evaporated in vacuo and the residue was treated with Et_2O (10 mL) and extracted with 10% aq Na_2CO_3 (5 mL). The aqueous layer was acidified with 1 N aq HCl (down to pH 2) and extracted with EtOAc (2 × 5 mL). The organic layer was dried (Na_2SO_4), concentrated in vacuo (to ~ 1 mL) and diluted with petroleum ether bp 40–60°C (5 mL). The precipitated solid was filtered and recrystallized from a EtOAc/petroleum ether bp 40–60°C mixture to give crystalline benzyloxycarbonyl-alanyl-valine (0.10 g, 95%); mp 145–148°C; $[\alpha]_D^{20}$ −22.5 (c = 1.5, MeOH); $[\alpha]_D^{20}$ −13.7 (c = 2, EtOH) [Lit.[9] $[\alpha]_D^{22}$ −12.8 (c = 3.6, EtOH)]. For the D-D-dipeptide:[10] mp 149–150°C; $[\alpha]_D$ +23 (c = 2, MeOH).

The ether layer from the above procedure was evaporated in vacuo and the residue was chromatographed on silica gel, using EtOAc/petroleum ether bp 40–60°C (1 : 99) as eluent; 0.05 g (60%) of crystalline 4-(1-adamantyl) anisole was obtained: mp 80–82°C (Lit.[11] mp 76–77°C).

^{1}H NMR (CCl_4/$CDCl_3$ 3 : 1/TMS): δ = 1.75 (s, 6 H, CH_δAd), 1.86 (s, 6 H, CH_βAd), 2.08 (s, 3 H, CH_γAd), 3.75 (s, 3 H, CH_3OAr), 6.78 (d, 2 H, Ar), 7.20 (d, 2 H, Ar).

Threonine 1-Adamantyl Ether [H-Thr(OAd)-OH, 5];
To a mixture of TsOH.H-Thr-OMe (0.61 g, 2 mmol), AdOH (0.60 g, 4 mmol), anhyd TsOH (30 mg, 0.18 mmol) and toluene (3 mL), refluxing under a short air condenser, $(MeO)_2SO$ (190 μL, 2 mmol) was added in four portions over a period of 1.5 h and refluxing continued for a total of 2 h. The resulting clear yellow solution was diluted with diethyl ether, extracted with 10% aq Na_2CO_3 (5 mL) and concentrated in vacuo. The concentrate was diluted with MeOH (5 mL), 1 N aq NaOH (3 mL) was added and the mixture was refluxed for 30 min, then concentrated again under reduced pressure. The semisolid residue of evaporation was diluted with H_2O (4 mL), extracted with Et_2O (10 mL) and the pH of the aqueous phase was brought to approximately 6, by dropwise addition of HOAc. After cooling in ice the precipitated solid was filtered with suction, washed with ice cold water (1 mL) and dried, to afford 0.38 g (70%) of **5**; mp 179–182°C (dec); the mp was raised to 211–213°C after drying over P_2O_5 in vacuo; $[\alpha]_D^{25}$ −28.6 (c = 1, MeOH).

Anal calcd for $C_{14}H_{23}NO_3.1/2\ H_2O$ C 64.09; H 9.22; N 5.34; found C 64.65; H 9.24; N 5.36.

^{1}H NMR (CD_3SOCD_3/CD_3OD 3 : 1); δ = 1.13 (d, 3 H, CH_3), 1.52 (m, 12 H, $CH_{\beta,\delta}$Ad), 1.98 (s, 3 H, CH_γAd), 3.14 (d, 1 H, CH_αThr), 4.21 (m, 1 H, CH_βThr), 4,55 (broad singlet, H_2O).

To obtain the ^{1}H-NMR spectrum of the 4-toluenesulfonate of threonine 1-adamantyl ether, **5** was dissolved in MeOH, the calculated amount of anhyd TsOH was added and the solvent was removed under vacuum.

^{1}H NMR ($CDCl_3$): δ = 1.19 (d, 3 H, CH_3Thr), 1.50 (m, 12 H, $CH_{\beta,\delta}$Ad), 1.97 (s, 3 H, CH_γAd), 2.32 (s, 3 H, CH_3Ar), 3.93 (m, 1 H, CH_βThr), 4.32 (d, 1 H, CH_αThr), 7.12 (d, 2 H, Ar), 7.69 (m, 5 H, H_3N^+, Ar).

***N*-(2,2,2-Trichloroethoxycarbonyl)threonine 1-Adamantyl Ether (Troc-Thr(OAd)-OH):**
H-Thr(OAd)-OH **(5)**, (0.35 g, 1.3 mmol) was dissolved in 1 N aq NaOH (1.3 mL) and 1 N aq $NaHCO_3$ (2.6 mL) was added. To the ice cold, stirred solution was added in one portion a solution of Troc-OSu (0.40 g, 1.4 mmol) in dioxane (2.6 mL) and stirring was continued at r.t. for 10 min. The mixture was then concentrated under vacuum to a small volume, diluted with H_2O (20 mL) and washed with Et_2O (10 mL). The ether layer was back extracted with 5% aq. Na_2CO_3 (2 × 10 mL) and H_2O (10 mL) and the united aqueous phases were acidified with 1 N aq HCl to pH 2 and extracted with EtOAc (2 × 25 mL). The organic phase was washed with water (15 mL), dried (Na_2SO_4) and evaporated under reduced pressure to a viscous oil, which crystallized on treatment with petroleum ether bp 40–60°C (25 mL). The white precipitate was isolated with suction filtration and was recrystallized from a EtOAc/petroleum ether bp 40–60°C mixture to give Troc-Thr(OAc)-OH (0.48 g, 86%); mp 146–148°C; $[\alpha]_D^{25}$ +31.6 (c = 2, $CHCl_3$).

^{1}H NMR ($CDCl_3$): δ = 1.14 (d, 3 H, CH_3), 1.72 (m, 12 H, $CH_{\beta,\delta}$Ad), 2.17 (s, 3 H, CH_γAd), 4.28 (dd, 1 H, CH_αThr), 4.50 (octuplet, 1 H, CH_βThr), 4.73 (s, 2 H, CH_2CCl_3), 5.95 (d, 1 H, NH).

TFA Cleavage of Amino Acid Ether Troc-Thr(OAd)-OH:
Troc-Thr(OAd)-OH (0.46 g, 1.07 mmol) was dissolved in TFA (2 mL, 26 mmol) and anisole (200 μL, 1.8 mmol) was added. After 30 min at r.t. the solvent was evaporated in vacuo and the residue was partitioned between 10% aq Na_2CO_3 (5 mL) and Et_2O (10 mL). The aqueous phase was separated, acidified with conc HCl to pH 2 and extracted with EtOAc (2 × 10 mL). The organic extract was dried (Na_2SO_4) and evaporated under reduced pressure to give Troc-Thr-OH as a glassy solid (0.30 g, 95%).

^{1}H NMR ($CDCl_3$): δ = 1.32 (d, 3 H, CH_3), 4.41 (d, 1 H, CH_αThr), 4.53 (m, 1 H, CH_βThr), 4.69 (d, 1 H, CH_2CCl_3), 4.90 (d, 1 H, CH_2CCl_3), 6.01 (broad singlet, 2 H, OH, CO_2H), 6.41 (d, 1 H, NH).

The *tert*-butyl ammonium salt of Troc-Thr-OH (Troc-Thr-OH.$H_2NC(CH_3)_3$)[12] had; $[\alpha]_D^{25}$ +5.5 (c = 7, MeOH).

^{1}H NMR ($CDCl_3$): δ = 1.23 (d, 3 H, CH_3Thr), 1.38 (s, 9 H, $(CH_3)_3C$), 4.10 (d, 1 H, CH_αThr), 4.36 (m, 1 H, CH_βThr), 4.68 (d, 1 H, CH_2CCl_3), 4.82 (d, 1 H, CH_2CCl_3), 6.25 (d, 1 H, NH), 6.40 (very broad, H_3N^+).

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