Studies on Hybrid Peptides of Fragments from Fibrinogen

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Abstract. In the present paper the hybrid peptides of P6A and RGD, namely ARPAKRGDS **17**, ARPAKRGDV **19**, ARPAKRGDF **21**, QRPAKRGDS **18**, QRPAKRGDV **20** and QRPAKRGDF **22**, were synthesized *via* the solution method, segment condensation and TFA/TFMSA-catalyzed deprotection (in 93–96% yield). The bioassay indicated that all of the tetrapeptides, pentapeptides and nonapeptides showed vasodilating effect obviously. Coupling tetrapeptides with pentapeptides gave no significant advantageous to enhancing the vascular activity. Antiaggregation effect *in vitro* suggested the tetrapeptides and pentapeptides were more sensitive to ADP than PAF. The hybrid peptides, however, were sensitive to both of the two aggregators, suggested the antiaggregation effect may be enhanced by use of this hybrid strategy. Antithrombosis effect *in vivo* showed that coupling RGDS **14** and RGDV **15** with pentapeptides may improve the bioactivity. If RGDF **16** was used instead of RGDS and RGDV the coupling gave negative results. The bioactivity mentioned may be understood with the help of the energies of their stable conformations.

P6A(ARPAK), one of the products degraded from fibrinogen β-chain, was known to increase microvascular permeability and coronary blood flow and enhance thrombolysis significantly [1–3].

Platelet aggregation plays an essential role in normal homeostasis and is dependent on the interaction of the membrane glycoprotein IIb/IIIa (GP IIb/IIIa) complex with plasma adhesive glycoprotein, including fibrinogen, von Willebrand factor, and fibronectin [4]. The platelet fibrinogen receptor GP IIb/IIIa belongs to the integrin supergene family of cell-surface receptor, which is responsible for cellular binding to various adhesive proteins. Functional GP IIb/IIIa is only minimally present on unstimulated platelets, but the number of functional receptors increases when platelets are activated, which may either be due to a change in the conformation of the receptor, making it accessible for fibrinogen binding or due to reorganization of the platelet surface to expose more receptors.

Studies on fibrinogen binding to GP IIb/IIIa have identified two distinct amino acid sequences within the fibrinogen molecule that mediate its attachment to the GP IIb/IIIa receptor. Their sequences are RGDS, RGDV and RGDF.

In our opinion, the specific interaction of GP IIb/IIIa receptor and RGD may result in the targeting ability for RGD containing peptides [5]. In the design of targeting antithrombosis peptides, P6A and its analog QP6A (QRPAK) were linked with RGDS, RGDV and RGDF, respectively. This kind of the hybrid peptides may provide one possibility for the design of the lead compound of targeting antithrombus peptides.

Results and Discussion

Synthesis of Hybrid Peptides

The protective intermediates (**1**–**5**) were prepared *via* the solution method according to the route depicted in Scheme1. The stepwise synthesis(C→N, in 83–96% yield) was carried out starting with benzyl ester of *L*-Lys(*Z*), *L*-Ser(Bzl), *L*-Val and *L*-Phe as the C-terminal residue, respectively. After the removal of Boc group of protective pentapeptides and benzyl group of protective tetrapeptides the protective pentapeptide fragments with free carboxyl group and the protective tetrapeptide fragments with free amino group were coupled to provide protective nonapeptides (**6**–**11**, in 93–96% yield) which were deprotected in the presence of TFA/TFMSA at 0 °C for 2 h, then purified with Sephadex G 10 and HPLC to give the corresponding goal products (**17**–**22**, in 83–90% yield). The related data were listed in Table 1 and Table 2.

Vasodilating Effect in Vitro

Immediately after decapitation rat aortic strips were taken and put in a perfusion bath with 5 ml warmed (37 °C), oxygenated (95% O_2/5% CO_2) Kreb's solution (pH 7.4). The aortic strip was connected to a tension transducer, and the relaxation contraction curve of muscles was registered. Administration of 10^{-9} mol/l noradrenaline (NE) induced hypertonic contraction of the vessel strip. As the contraction reaches its maximum, NE was washed out, and the vessel strip was stabilized for 30 min. After renewal of the solution, NE (1×

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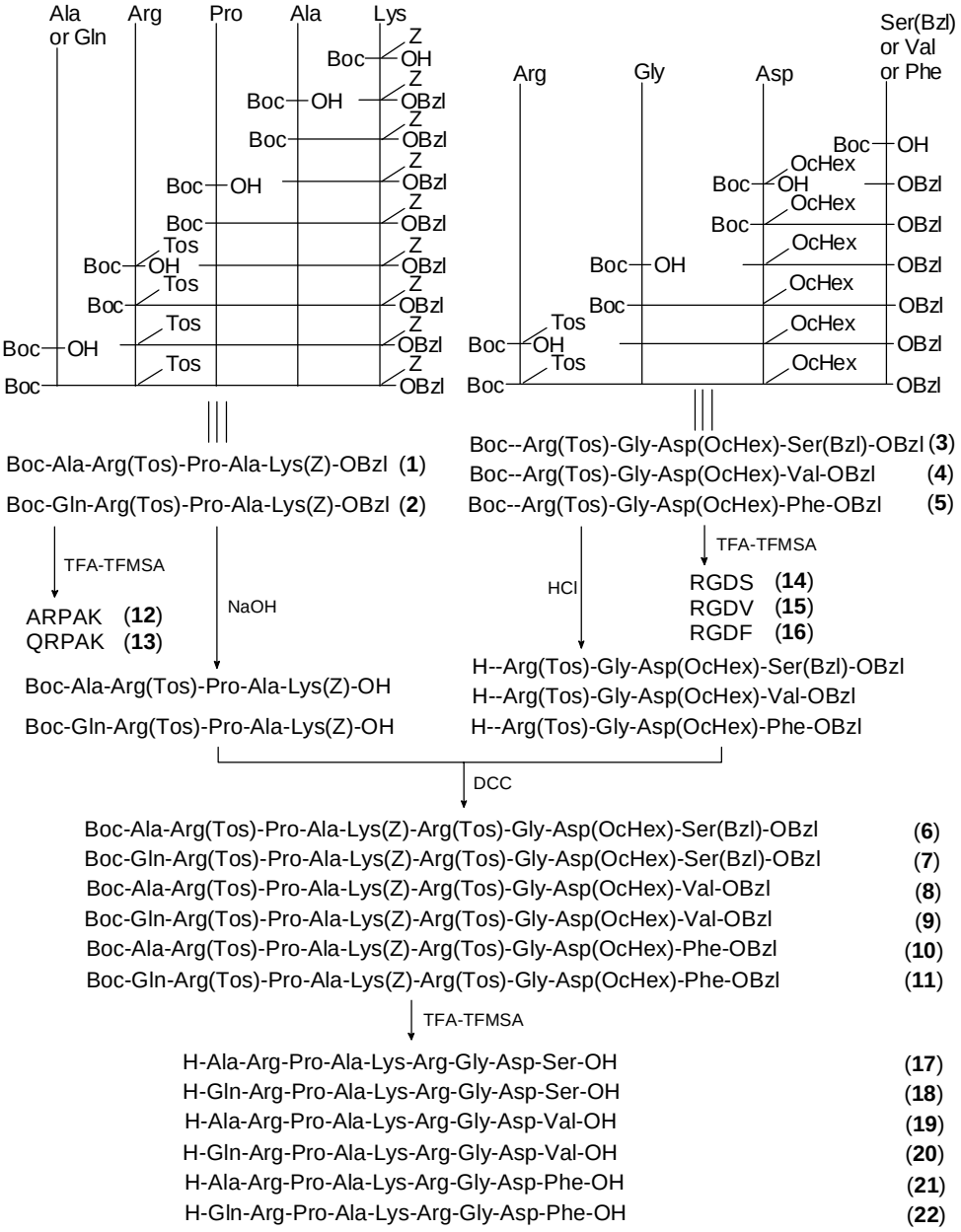

Scheme 1 Preparing the tetrapeptides, pentapeptides and nonapeptides by use of stepwise synthesis (C→N), segment condensation and TFA/TFMSA-catalyzed deprotection

Tab. 1 Physical data and FAB–MS of **1–22**

No.	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**
m.p. (°C)	86–89	83–85	91–93	97–98	98–99	98–101	93–95	106–108	118–120	108–110	87–90
$[\alpha]_D$(°) [a]	–13(0.2)	–9(0.3)	–34(0.4)	–24(0.4)	–25(0.4)	–60(0.3)	–25(0.2)	–29(0.5)	–30(0.3)	–32(0.5)	–6.7(0.3)
MS[M+Na]$^+$	1042	1099	972	894	942	1783	1840	1705	1762	1753	1810
No.	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**
m.p. (°C)	126–129	143–146	110–111	120–121	125–126	140–142	137–139	147–149	131–134	150–153	142–145
$[\alpha]_D$(°) [a]	–40(0.1)	–35(0.4)	–20(0.2)	–20(0.3)	–40(0.2)	–50(0.3)	–38(0.2)	–40(0.2)	–53.3(0.3)	–70(0.2)	–39(0.2)
MS[M+H]$^+$	542	599	434	446	494	957	1014	969	1026	1017	1074

[a]) $[\alpha]_D$ of peptide **1–11** and **12–22** were determined in $CHCl_3$ and 6 mol/l HCl, respectively. c = 0.2 for compounds **1**, **7**, **14**, **16**, 1**8**, **19**, **21**, and **22**. c = 0.3 for compounds **2**, **6**, **9**, **11**, **15**, **17**, and **20**. c = 0.4 for compounds **3**, **4**, **5**, **13**. c = 0.5 for compounds **8** and **10**.

Tab. 2 Amino acid analyses of **12**–**22**

	Amino acid residue									
No.	Ala	Pro	Lys	Glu	Arg	Gly	Asp	Ser	Val	Phe
12	2.02	1.01	0.97	–	1.02	–	–	–	–	–
13	1.02	1.03	1.00	0.99	1.01	–	–	–	–	–
14	–	–	–	–	1.02	0.99	0.98	1.01	–	–
15	–	–	–	–	1.03	0.98	1.01	–	0.99	–
16	–	–	–	–	1.00	0.99	0.99	–	–	1.01
17	1.98	0.97	0.97	–	1.96	0.98	1.01	0.96	–	–
18	1.97	0.98	0.97	–	1.98	1.01	0.97	–	1.01	–
19	1.99	1.00	0.98	–	1.97	1.00	0.98	–	–	1.01
20	–	1.01	0.97	0.99	1.98	0.99	0.99	0.97	–	–
21	–	0.97	0.99	0.97	1.98	0.98	0.98	–	0.99	–
22	–	0.98	0.97	0.98	1.98	0.99	0.97	–	–	0.98

10^{-9} mol/l) was added. When the hypertonic contraction value of the aortic strip reached the peak, the tested peptides (**12**–**22**) were administrated to observe their vasodilations, and the results (Table 3) indicated that except peptide **22** all of the pentapeptides, tetrapeptides and nonapeptides showed vasodilating effect obviously (compare to control $p<0.05$ or $p<0.01$). The vasodilating effect of peptides **12**, **14**, **17**, **19**, **20** and **21** was dose dependent. On the other hand, however, their vasodilating potencies showed no significant differences, suggested that the hybrid peptides (**12**–**22**) were not significantly advantageous to improving the vasodilating effect of peptides **12**–**16**.

Tab. 3 Effect of **12**–**22** on rat aortic strips treated with NE [d])

		relaxing extent (X ± S%)		
No.	Control	10^{-7} (mol/l)	10^{-6} (mol/l)	10^{-5} (mol/l)
12 [c])	2.561 ± 0.301	3.175 ± 1.891	5.720 ± 0.420 [b])	22.571 ± 1.672 [b])
13	2.562 ± 0.297	5.212 ± 2.325 [a])	29.700 ± 4.160 [b])	33.105 ± 6.594 [b])
14 [c])	2.556 ± 0.295	2.505 ± 0.256	5.865 ± 3.005 [a])	20.672 ± 2.254 [b])
15	2.558 ± 0.289	3.411 ± 2.006	5.251 ± 2.950 [a])	18.155 ± 2.064 [b])
16	2.562 ± 0.292	2.841 ± 3.005	3.833 ± 1.503 [a])	16.263 ± 3.155 [b])
17 [c])	2.559 ± 0.313	2.705 ± 0.311	4.005 ± 1.711 [a])	7.495 ± 2.298 [b])
18	2.567 ± 0.310	3.589 ± 2.985	5.345 ± 3.065 [a])	14.991 ± 2.014 [b])
19 [c])	2.560 ± 0.305	2.612 ± 2.818	5.001 ± 3.101 [a])	8.501 ± 3.015 [b])
20 [c])	2.555 ± 0.287	3.121 ± 2.955	6.627 ± 2.701 [b])	20.676 ± 2.015 [b])
21 [c])	2.569 ± 0.315	2.676 ± 3.001	18.166 ± 2.560 [b])	25.677 ± 1.955 [b])
22	2.563 ± 0.304	–1.667 ± 2.423	–1.650 ± 2.732	–1.400 ± 2.179

[a]) compare to control $p < 0.05$; [b]) compare to control $p < 0.001$; [c]) The vasodilating effect was dose dependent; [d]) n = 10

Antiaggregation in Vitro

Platelet-rich plasma was prepared by centrifugation of normal rabbit blood anticoagulated using sodium citrate with a final concentration of 0.38%. The platelet counts were adjusted to 2×10^{-5}/μl by addition of autologous plasma. Platelet aggregation studies were conducted in an aggregometer using the standard turbidimetric technique. The agonists used were platelet activating factor (PAF) and adenosine diphosphate (ADP). The effects of the peptides **12**–**22** on PAF- or ADP-induced platelet aggregation were studied. The tested peptide, dissolved in normal saline (NS), was added to 300 μl of platelet-rich plasma, stirred at 37 °C in an aggregation cuvette. In control experiment, NS alone was added. The rate of platelet aggregation was represented by the peak height of the aggregation curve, and the plasma without platelet was defined as 100%. The results indicated that introducing RGD sequence into ARPAK or QRPAK sometimes may enhance the antiaggregation effect. The peptides showed different response to platelet aggregations induced by ADP and PAF. In general, peptides **12**–**16** were more sensitive to platelet aggregation induced by ADP than that induced by PAF. At most cases the hybrid peptides **17**–**22** were sensitive to platelet aggregation induced by both ADP and PAF.

Antithrombosis in Vivo

Wistar rats with 250–300 g of weight (purchased from Animal Center of Beijing Medical University) were used. The tested peptides (**12**–**22**) were dissolved in NS just before use and kept in an ice bath. The rats were anesthetized with pentobarbital sodium (30 mg/kg, ip), and 1 cm of segment bitateral carotid arteries were dissected free. The tested compound was administrated *via*

Tab. 4 Effect of **12**–**22** on the maximal rate of platelet aggregation induced by ADP [e])

		rate of maximal aggregation (X ± S%)		
No.	control	10^{-6} (mol/l)	10^{-5} (mol/l)	10^{-4} (mol/l)
12	11.19 ± 2.79	7.68 ± 1.12 [b])	7.38 ± 4.82 [a])	5.14 ± 2.15 [c])
13	11.19 ± 2.79	8.52 ± 5.88	6.48 ± 3.35 [c])	7.50 ± 4.96
14	21.74 ± 5.29	16.61 ± 3.02 [a])	14.80 ± 2.77 [b])	11.25 ± 1.93 [c])
15	13.50 ± 2.92	10.90 ± 3.04	7.53 ± 2.43 [c])	5.23 ± 0.80 [c])
16	38.11 ± 4.91	37.05 ± 3.18	33.64 ± 7.15	27.66 ± 3.97 [c])
17	29.75 ± 3.77	31.73 ± 2.44	27.01 ± 1.73	26.58 ± 1.67 [a])
18	19.90 ± 3.02	21.48 ± 2.57	20.78 ± 2.71	19.79 ± 3.24
19	31.44 ± 4.72	28.14 ± 7.87	29.58 ± 1.66	23.96 ± 3.24 [c])
20	26.14 ± 3.03	23.09 ± 6.91	21.27 ± 5.10 [a])	21.11 ± 3.92 [b])
21	28.05 ± 1.18	21.11 ± 3.93 [c])	27.30 ± 4.41	19.40 ± 3.71 [c])
22 [d])	37.24 ± 5.82	27.56 ± 3.07 [c])	23.24 ± 2.50 [c])	16.88 ± 1.03 [c])

[a]) Compare to control $P < 0.05$; [b]) Compare to control $P < 0.01$; [c]) Compare to control $P < 0.001$;
[d]) The antiaggregation effect was dose dependent; [e]) n = 10, and the dose of ADP was 5×10^{-6} mol/l

Tab. 5 Effect of **12**–**22** on the maximal rate of platelet aggregation induced by PAF [d])

		rate of maximal aggregation (X ± S%)		
No.	control	10^{-6} (mol/l)	10^{-5} (mol/l)	10^{-4} (mol/l)
12	28.69 ± 3.08	24.97 ± 2.15	26.14 ± 3.61	29.31 ± 5.45
13	28.69 ± 3.08	28.26 ± 3.25	29.74 ± 1.53	29.94 ± 4.86
14	34.86 ± 3.31	33.20 ± 3.62	15.91 ± 3.36 [c])	14.68 ± 5.82 [c])
15	29.76 ± 4.94	29.70 ± 5.04	28.50 ± 4.95	29.58 ± 5.41
16	29.76 ± 4.94	29.40 ± 5.12	29.34 ± 4.86	25.39 ± 2.97 [a])
17	42.68 ± 6.71	34.49 ± 3.86 [b])	32.99 ± 2.41 [c])	30.78 ± 3.18 [c])
18	22.25 ± 2.41	21.85 ± 5.90	20.67 ± 4.31	12.78 ± 1.58 [c])
19	22.79 ± 2.62	21.78 ± 3.83	16.12 ± 2.89 [c])	18.56 ± 2.41 [b])
20	29.81 ± 6.69	28.01 ± 4.66	19.33 ± 3.51 [c])	18.84 ± 4.86 [c])
21	26.05 ± 3.99	26.74 ± 2.24	30.69 ± 4.97	27.02 ± 2.14
22	26.58 ± 3.99	28.23 ± 3.45	27.28 ± 2.54	27.34 ± 4.52

[a]) compare to control $P < 0.05$; [b]) compare to control $P < 0.01$; [c]) compare to control $P < 0.001$
[d]) n = 10, the dose of PAF was 5×10^{-10} mol/l

the vena sublingualins, then thrombosis was triggered immediately by vessel wall damage according to the modified method of Kurz [6]. The artery was wrapped in gauze strip (0.5 cm in width and 3 cm in length), which was saturated by 25% ferric chloride solution for 10 min. The resulting thrombi in 0.5 cm of artery segment were excised, and the size of each thrombus was determined by measuring its weight after dried at 20 °C for 24 h. The mean weight of the thrombus for each animal was then calculated (Table 6).

The results indicated that though 5.0 µmol/kg of RGDS and RGDV exhibited no antithrombosis effect, the potency of 2.5 µmol/kg of ARPAKRGDS and ARPAKRGDV did show no significant difference to that of 5.0 µmol/kg of ARPAK. The phenomenon that the antithrombosis effect of RGDS and RGDV was enhanced in a sense, and this kind of enhancement of the activity may result from hybridization. The similar phenomena were also observed in QRPAK, QRPAKRGDS and QRPAKRGDV. On the other hand, however, coupling RGDF with ARPAK and QRPAK the antithrombosis effect of ARPAKRGDF and QRPAKRGDF were abolished. The observation suggested that introducing RGDF sequence into other sequences may be harmful to the antithrombosis effect.

Tab. 6 Effect of **12**–**22** on the thrombosis (n = 10)

No.	Dose (µmol/kg)	weight of thrombus (mg)
NS	–	0.67 ± 0.12
12	5.0	0.34 ± 0.22[c)]
13	2.5	0.44 ± 0.08[c)]
14	5.0	0.61 ± 0.23
15	5.0	0.59 ± 0.16
16	2.5	0.41 ± 0.26 [a])
17	2.5	0.45 ± 0.28 [a])
18	2.5	0.48 ± 0.10 [a]), [d])
19	2.5	0.45 ± 0.15 [a]), [d])
20	2.5	0.41 ± 0.11 [b]), [d])
21	2.5	0.71 ± 0.17
22	2.5	0.44 ± 0.37

[a]) compare to NS, $P<0.05$; [b]) compare to NS, $P<0.01$
[c]) compare to NS, $P<0.001$; [d]) compare to RGDS, RGDV, $P<0.05$

Conformational Analysis

In order to search the effects of the conformations of the hybrid peptides **17**–**22** on the bioactivities, the energies (including bond energy, theta energy, phi energy, out of plane energy, nonbond energy, nonbond repulsion energy, nonbond dispersion energy, coulomb energy and total energy) for their beta structure, *L*-helix and *R*-helix conformations *in vacuo*, water and octanol were

Tab. 7 Total energy (kcal/mol) of **17**–**22** *in vacuo*, water and octanol

	in vacuo			in Water			in Octanol		
No.	*R*–helix	*L*–helix	Beta	*R*–helix	*L*–helix	Beta	*R*–helix	*L*–helix	Beta
17	–70.23670	–42.10924	–56.51387	85.99238	105.10438	86.38486	71.17535	92.84931	71.18735
18	–99.33916	–67.75318	–84.52022	92.12459	112.23668	88.37715	70.47351	92.96623	72.29632
19	–75.89726	–42.47290	–59.86140	91.48372	110.63236	88.61769	75.71206	97.12606	75.66746
20	–100.98672	–68.04735	–87.84562	97.61810	117.791063	93.63262	75.12507	97.29384	76.79340
21	–46.07630	–16.75062	–33.84021	124.51362	143.23169	121.96638	107.72936	129.11492	108.23431
22	–75.08343	–42.25922	–61.69285	130.77677	150.51822	127.13717	108.67115	130.35860	109.53881

calculated with the Discover Program from Biosym Company. The total energy is shown in Table 7.

In general, there are three possible conformations, i.e. *L*-helix, *R*-helix and beta structure. The calculation indicated that under stable conformations, the bond energy, theta energy, phi energy, out of plane energy, nonbond energy, nonbond repulsion energy, nonbond dispersion energy, coulomb energy and total energy were different from each other for the hybrid peptides **17**–**22**. Comparing the energy of the stable conformations of *L*-helix, *R*-helix and beta structure, the *R*-helix with the lowest total energy may lead to their real conformation in solution.

In water and octanol the total energies of **21** (ARPAKRGDF) and **22** (QRPAKRGDF) were significantly higher than those of the others. Perhaps, it could be difficult for the peptides with high-energy conformations to bind to GP IIb/IIIa resulting in antithrombosis effect. On the other hand, however, the lower energies of **17** (ARPAKRGDS), **18** (QRPAKRGDS), **19** (ARPAKRGDV) and **20** (QRPAKRGDV) resulted in their conformational stability. This made it easy to make them bind to GP IIb/IIIa. As the analogs of P6A they were obviously able to show antithrombosis effect.

Conclusion

a. By use of the solution method and coupling of the fragments the hybrid peptides can be prepared with excellent yield.
b. With the exception of **22** (QRPAKRGDF), at a dose of 10^{-5} mol/l, all of the peptides showed obvious relaxation *in vitro*, and the potencies of the hybrid peptides are comparable with those of the fragments coupled.
c. Even though the antiaggregation effect of most the hybrid peptides were not good, QRPAKRGDF and ARPAKRGDF significantly inhibited platelet aggregation induced by ADP at three doses and by PAF at low doses, respectively.
d. With the exception of RGDF-containing hybrid peptide, **21** (ARPAKRGDF) and **22** (QRPAKRGDF), all of the hybrid peptides showed desirable antithrombosis *in vivo*, suggesting the hybridization of fibrinogen fragments may provide lead compound.
e. All of the bioactivities were conformation-dependent.

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Experimental

The protected amino acids used were of *L*-configuration. The purity of the intermediates and the products was confirmed by TLC (Merck silica gel plates of type 60 F_{254}, 0.25 mm layer thickness) and HPLC (Waters, C_{18} column 4.6 × 150 mm). The amino acid sequences were determined by a Hitachi 835-50 instrument. FAB-MS were determined by a VG-ZAB-MS and a HP ES-5989x instrument. Optical rotations were determined at 20 °C on a Schmidt+Haensch Polartronic D instrument.

Boc-Ala-Lys(Z)-OBzl

473 mg (2.5 mmol) of Boc-Ala-OH was dissolved in 5 ml of anhydrous THF, and at 0 °C 338 mg (2.5 mmol) of HOBt and 515 mg (2.5 mmol) of DCC were added. The reaction mixture was stirred at 0 °C for 24 h. Precipitated DCU was removed by filtration. The filtrate was evaporated under reduced pressure, and the residue was triturated with petroleum ether to provide the corresponding active ester. 1.016 g (2.5 mmol) of Lys(Z)-OBzl · HCl, 297 mg (2.7 mmol) of *N*-methylmorpholine, and the active ester, as mentioned above, were mixed in 10 ml of anhydrous THF. The reaction mixture was stirred at room temperature for 24 h. After evaporation the residue was dissolved in 50 ml of ethyl acetate. The solution was washed successively with 5% sodium bicarbonate, 5% citric acid and saturated sodium chloride. The organic phase was dried over anhydrous sodium sulfate. After filtration and evaporation under reduced pressure and purification by chromatography ($CHCl_3$:CH_3OH, 30:1) the title compound was obtained in 1.298 g (96%) yield. FAB-MS (*m/e*): 542 $[M+H]^+$.

Ala-Lys(Z)-OBzl·HCl

1.353 g (2.5 mmol) of Boc-Ala-Lys(Z)-OBzl was dissolved in 10 ml of 6 mol/l hydrogen chloride-ethyl acetate and stirred at room temperature for 4 h. The reaction mixture was evaporated under reduced pressure with ethyl acetate repeatedly to remove hydrogen chloride. The residue obtained was triturated with ether to provide the title compound which was used for the next reaction directly.

Boc-Pro-Ala-Lys(Z)-OBzl

580 mg (2.7 mmol) of Boc-Pro-OH was dissolved in 5 ml of anhydrous THF, and at 0 °C 365 mg (2.7 mmol) of HOBt and 556 mg (2.7 mmol) of DCC were added. The reaction mixture was treated, as mentioned above, to provide the corresponding active ester. 1.194 g (2.5 mmol) of Ala-Lys(*Z*)-OBzl · HCl, 297 mg (2.7 mmol) of *N*-methylmorpholine, and the active ester, as mentioned above, were mixed in 10 ml of anhydrous THF. The reaction mixture was stirred at room temperature for 24 h and worked up, as mentioned above, to give the title compound in 1.436 g (90%) yield. FAB-MS (*m/e*): 639 $[M+H]^+$.

Pro-Ala-Lys(Z)-OBzl·HCl

1.595 g (2.5 mmol) of Boc-Pro-Ala-Lys(Z)-OBzl was dissolved in 10 ml of 6 mol/l hydrogen chloride-ethyl acetate and stirred at room temperature for 4 h. The reaction mixture was treated, as mentioned above. The residue obtained was triturated with petroleum ether to provide the title compound which was used for the next reaction directly.

Boc-Arg(Tos)-Pro-Ala-Lys(Z)-OBzl

1.156 g (2.7 mmol) of Boc-Arg(Tos)-OH was dissolved in 10 ml of anhydrous THF, and at 0 °C 365 mg (2.7 mmol) of HOBt and 556 mg (2.7 mmol) of DCC were added. The reaction mixture was treated, as mentioned above, to give the corresponding active ester. 1.436 g (2.5 mmol) of Pro-Ala-Lys(*Z*)-OBzl · HCl, 297 mg (2.7 mmol) of *N*-methylmorpholine, and the active ester, as mentioned above, were mixed in 10 ml of anhydrous THF and stirred at room temperature for 30 h. The reaction mixture was worked up, as mentioned above, to provide the title compound in 2.06 g (87%) yield. FAB-MS (*m/e*): 949 $[M+H]^+$.

Arg(Tos)-Pro-Ala-Lys(Z)-OBzl·HCl

2.37 g (2.5 mmol) of Boc-Arg(Tos)-Pro-Ala-Lys(*Z*)-OBzl was dissolved in 15 ml of 6 mol/l hydrogen chloride-ethyl acetate and stirred at room temperature for 6 h. The reaction mixture was treated, as mentioned above. The residue obtained was triturated with ether to provide the title compound which was used for the next reaction directly.

Boc-Ala-Arg(Tos)-Pro-Ala-Lys(Z)-OBzl (**1**)

510 mg (2.7 mmol) of Boc-Ala-OH was dissolved in 5 ml of anhydrous THF, and at 0 °C 365 mg (2.7 mmol) of HOBt and 556 mg (2.7 mmol) of DCC were added. The reaction mixture was treated, as mentioned above, to give the corresponding active ester. 2.21 g (2.5 mmol) of Arg(Tos)-Pro-Ala-Lys(*Z*)-OBzl · HCl, 297 mg (2.7 mmol) of *N*-methylmorpholine, and the active ester, as mentioned above, were mixed in 20 ml of anhydrous THF and stirred at room temperature for 48 h. The reaction mixture was worked up, as mentioned above, to provide the title compound in 2.114 g (83%) yield.

Boc-Gln-Arg(Tos)-Pro-Ala-Lys(Z)-OBzl (**2**)

664 mg (2.7 mmol) of Boc-Gln-OH was dissolved in 5 ml of anhydrous THF, and at 0 °C 365 mg (2.7 mmol) of HOBt and 556 mg (2.7 mmol) of DCC were added. The reaction mixture was treated, as mentioned above, to give the corresponding active ester. 2.21 g (2.5 mmol) of Arg(Tos)-Pro-Ala-Lys(*Z*)-OBzl · HCl, 297 mg (2.7 mmol) of *N*-methylmorpholine, and the active ester, as mentioned above, were mixed in 20 ml of anhydrous THF and stirred at room temperature for 48 h. The reaction mixture was worked up, as mentioned above, to provide the title compound in 2.34 g (87%) yield.

Boc-Asp(OcHex)-Ser(Bzl)-OBzl

788 mg (2.5 mmol) of Boc-Asp(OcHex)-OH was dissolved in 5 ml of anhydrous THF, and at 0 °C 338 mg (2.5 mmol) of HOBt and 515 mg (2.5 mmol) of DCC were added. The reaction mixture was treated, as mentioned above, to provide the corresponding active ester. 804 mg (2.5 mmol) of Ser(Bzl)-OBzl · HCl, 297 mg (2.7 mmol) of *N*-methylmorpholine, and the active ester, as mentioned above, were mixed in 10 ml of anhydrous THF. The reaction mixture was stirred at room temperature for 24 h. The reaction mixture was worked up, as mentioned above, to give the title compound in 1.31 g yield (90%). FAB-MS (*m/e*): 583 $[M+H]^+$.

Asp(OcHex)-Ser(Bzl)-OBzl·HCl

1.455 g (2.5 mmol) of Boc-Asp(OcHex)-Ser(Bzl)-OBzl was dissolved in 10 ml of 6 mol/l hydrogen chloride-ethyl acetate and stirred at room temperature for 4 h. The reaction mixture was treated, as mentioned above. The residue obtained was triturated with ether to provide the title compound which was used for the next reaction directly.

Boc-Gly-Asp(OcHex)-Ser(Bzl)-OBzl

472 mg (2.7 mmol) of Boc-Gly-OH was dissolved in 5 ml of anhydrous THF, and at 0 °C 365 mg (2.7 mmol) of HOBt and 556 mg (2.7 mmol) of DCC were added. The reaction mixture was treated, as mentioned above, to provide the corresponding active ester. 1.296 g (2.5 mmol) of Asp(OcHex)-Ser(Bzl)-OBzl · HCl, 297 mg (2.7 mmol) of *N*-methylmorpholine, and the active ester, as mentioned above, were mixed in 15 ml of anhydrous THF. The reaction mixture was stirred at room temperature for 24 h. The reaction mixture was worked up, as mentioned above, to give the title compound in 1.422 g (89%) yield. FAB-MS (*m/e*): 640 $[M+H]^+$.

Gly-Asp(OcHex)-Ser(Bzl)-OBzl·HCl

1.598 g (2.5 mmol) of Boc-Gly-Asp(OcHex)-Ser(Bzl)-OBzl was dissolved in 10 ml of 6 mol/l hydrogen chloride-ethyl acetate and stirred at room temperature for 4.5 h. The reaction mixture was treated, as mentioned above. The residue obtained was triturated with ether to provide the title compound which was used for the next reaction directly.

Boc-Arg(Tos)-Gly-Asp(OcHex)-Ser(Bzl)-OBzl (**3**)

1.156 g (2.7 mmol) of Boc-Arg(Tos)-OH was dissolved in 5 ml of anhydrous THF, and at 0 °C 365 mg (2.7 mmol) of HOBt and 556 mg (2.7 mmol) of DCC were added. The reaction mixture was treated, as mentioned above, to provide the corresponding active ester. 1.439 g (2.5 mmol) of Gly-Asp(OcHex)-Ser(Bzl)-OBzl · HCl, 297 mg (2.7 mmol) of *N*-methylmorpholine, and the active ester, as mentioned above, were mixed in 20 ml of anhydrous THF. The reaction mix-

ture was stirred at room temperature for 30 h. The reaction mixture was worked up, as mentioned above, to give the title compound in 1.969 g (83%) yield.

Boc-Asp(OcHex)-Val-OBzl

788 mg (2.5 mmol) of Boc-Asp(OcHex)-OH was dissolved in 5 ml of anhydrous THF, and at 0 °C 338 mg (2.5 mmol) of HOBt and 515 mg (2.5 mmol) of DCC were added. The reaction mixture was treated, as mentioned above, to provide the corresponding active ester. 609 mg (2.5 mmol) of Val-OBzl·HCl, 297 mg (2.7 mmol) of *N*-methylmorpholine, and the active ester, as mentioned above, were mixed in 10 ml of anhydrous THF. The reaction mixture was stirred at room temperature for 24 h. The reaction mixture was worked up, as mentioned above, to give the title compound in 1.210 g (96%) yield. FAB-MS (*m/e*): 505 $[M+H]^+$.

Asp(OcHex)-Val-OBzl·HCl

1.260 g (2.5 mmol) of Boc-Asp(OcHex)-Val-OBzl was dissolved in 10 ml of 6 mol/l hydrogen chloride-ethyl acetate and stirred at room temperature for 4 h. The reaction mixture was treated, as mentioned above. The residue obtained was triturated with ether to provide the title compound which was used for the next reaction directly.

Boc-Gly-Asp(OcHex)-Val-OBzl

472 mg (2.7 mmol) of Boc-Gly-OH was dissolved in 5 ml of anhydrous THF, and at 0 °C 365 mg (2.7 mmol) of HOBt and 556 mg (2.7 mmol) of DCC were added. The reaction mixture was treated, as mentioned above, to provide the corresponding active ester. 1.101 g (2.5 mmol) of Asp(OcHex)-Val-OBzl·HCl, 297 mg (2.7 mmol) of *N*-methylmorpholine, and the active ester, as mentioned above, were mixed in 15 ml of anhydrous THF. The reaction mixture was stirred at room temperature for 24 h. The reaction mixture was worked up, as mentioned above, to give the title compound in 1.290 g (92%) yield. FAB-MS (*m/e*): 562 $[M+H]^+$.

Gly-Asp(OcHex)-Val-OBzl·HCl

1.402 g (2.5 mmol) of Boc-Gly-Asp(OcHex)-Val-OBzl was dissolved in 10 ml of 6 mol/l hydrogen chloride-ethyl acetate and stirred at room temperature for 4.5 h. The reaction mixture was treated, as mentioned above. The residue obtained was triturated with ether to provide the title compound which was used for the next reaction directly.

Boc-Arg(Tos)-Gly-Asp(OcHex)-Val-OBzl (**4**)

1.156 g (2.7 mmol) of Boc-Arg(Tos)-OH was dissolved in 5 ml of anhydrous THF, and at 0 °C 365 mg (2.7 mmol) of HOBt and 556 mg (2.7 mmol) of DCC were added. The reaction mixture was treated, as mentioned above, to provide the corresponding active ester. 1.244 g (2.5 mmol) of Gly-Asp(OcHex)-Val-OBzl·HCl, 297 mg (2.7 mmol) of *N*-methylmorpholine, and the active ester, as mentioned above, were mixed in 20 ml of anhydrous THF. The reaction mixture was stirred at room temperature for 30 h. The reaction mixture was worked up, as mentioned above, to give the title compound in 1.873 g (86%) yield.

Boc-Asp(OcHex)-Phe-OBzl

788 mg (2.5 mmol) of Boc-Asp(OcHex)-OH was dissolved in 5 ml of anhydrous THF, and at 0 °C 338 mg (2.5 mmol) of HOBt and 515 mg (2.5 mmol) of DCC were added. The reaction mixture was treated, as mentioned above, to provide the corresponding active ester. 729 mg (2.5 mmol) of Phe-OBzl·HCl, 297 mg (2.7 mmol) of *N*-methylmorpholine, and the active ester, as mentioned above, were mixed in 10 ml of anhydrous THF. The reaction mixture was stirred at room temperature for 24 h. The reaction mixture was worked up, as mentioned above, to give the title compound in 1.297 g (94%) yield. FAB-MS (*m/e*): 553 $[M+H]^+$.

Asp(OcHex)-Phe-OBzl·HCl

1.382 mg (2.5 mmol) of Boc-Asp(OcHex)-Phe-OBzl was dissolved in 10 ml of 6mol/l hydrogen chloride-ethyl acetate and stirred at room temperature for 4 h. The reaction mixture was treated, as mentioned above. The residue obtained was triturated with ether to provide the title compound which was used for the next reaction directly.

Boc-Gly-Asp(OcHex)-Phe-OBzl

472 mg (2.7 mmol) of Boc-Gly-OH was dissolved in 5 ml of anhydrous THF, and at 0 °C 365 mg (2.7 mmol) of HOBt and 556 mg (2.7 mmol) of DCC were added. The reaction mixture was treated, as mentioned above, to provide the corresponding active ester. 1.221 g (2.5 mmol) of Asp(OcHex)-Phe-OBzl·HCl, 297 mg (2.7 mmol) of *N*-methylmorpholine, and the active ester, as mentioned above, were mixed in 15 ml of anhydrous THF. The reaction mixture was stirred at room temperature for 24 h. The reaction mixture was worked up, as mentioned above, to give the title compound in 1.385 g (91%) yield. FAB-MS (*m/e*): 610 $[M+H]^+$.

Gly-Asp(OcHex)-Phe-OBzl·HCl

1.522 g (2.5 mmol) of Boc-Gly-Asp(OcHex)-Phe-OBzl was dissolved in 10 ml of 6 mol/l hydrogen chloride-ethyl acetate and stirred at room temperature for 4.5 h. The reaction mixture was treated, as mentioned above. The residue obtained was triturated with ether to provide the title compound which was used for the next reaction directly.

Boc-Arg(Tos)-Gly-Asp(OcHex)-Phe-OBzl (**5**)

1.156 g (2.7 mmol) of Boc-Arg(Tos)-OH was dissolved in 10 ml of anhydrous THF, and at 0 °C 365 mg (2.7 mmol) of HOBt and 556 mg (2.7 mmol) of DCC were added. The reaction mixture was treated, as mentioned above, to provide the corresponding active ester. 1.364 g (2.5 mmol) of Gly-Asp(OcHex)-Phe-OBzl·HCl, 297 mg (2.7 mmol) of *N*-methylmorpholine, and the active ester, as mentioned above, were mixed in 20 ml of anhydrous THF. The reaction mixture was stirred at room temperature for 30 h. The reaction mixture was worked up, as mentioned above, to give the title compound in 2 g (87%) yield.

Boc-Ala-Arg(Tos)-Pro-Ala-Lys(Z)-OH

1.528 g (1.5 mmol) of Boc-Ala-Arg(Tos)-Pro-Ala-Lys(*Z*)-OBzl was dissolved in 5 ml of 1 mol/l sodium hydroxide in water/methanol and stirred at 0 °C for 2 h. The reaction mix-

ture was neutralized with 2 mol/l hydrochloric acid to pH 7. The reaction mixture was evaporated to remove methanol. The residue was then acidified with 2 mol/l hydrochloric acid to pH 2 and evaporated to dryness. The residue was triturated with ether to provide the title compound which was used for the next reaction directly.

Boc-Gln-Arg(Tos)-Pro-Ala-Lys(Z)-OH

1.614 g (1.5 mmol) of Boc-Gln-Arg(Tos)-Pro-Ala-Lys(*Z*)-OBzl was dissolved in 5 ml of 1 mol/l sodium hydroxide in water/methanol and stirred at 0 °C for 2 h. The reaction mixture was neutralized with 2 mol/l hydrochloric acid to pH 7. The reaction mixture was evaporated to remove methanol. The residue was then acidified with 2 mol/l hydrochloric acid to pH 2 and evaporated to dryness. The residue was triturated with ether to provide the title compound which was used for the next reaction directly.

Arg(Tos)-Gly-Asp(OcHex)-Ser(Bzl)-OBzl·HCl

1.424 g (1.5 mmol) of Boc-Arg(Tos)-Gly-Asp(OcHex)-Ser(Bzl)-OBzl was dissolved in 10 ml of 6 mol/l hydrogen chloride-ethyl acetate and stirred at room temperature for 4.5 h. The reaction mixture was treated, as mentioned above. The residue obtained was triturated with ether to provide the title compound which was used for the next reaction directly.

Arg(Tos)-Gly-Asp(OcHex)-Val-OBzl·HCl

1.306 g (1.5 mmol) of Boc-Arg(Tos)-Gly-Asp(OcHex)-Val-OBzl was dissolved in 10 ml of 6 mol/l hydrogen chloride-ethyl acetate and stirred at room temperature for 4.5 h. The reaction mixture was treated, as mentioned above. The residue obtained was triturated with ether to provide the title compound which was used for the next reaction directly.

Arg(Tos)-Gly-Asp(OcHex)-Phe-OBzl·HCl

1.378 g (1.5 mmol) of Boc-Arg(Tos)-Gly-Asp(OcHex)-Phe-OBzl was dissolved in 10 ml of 6 mol/l hydrogen chloride-ethyl acetate and stirred at room temperature for 4.5 h. The reaction mixture was treated, as mentioned above. The residue obtained was triturated with ether to provide the title compound which was used for the next reaction directly.

Boc-Ala-Arg(Tos)-Pro-Ala-Lys(Z)-Arg(Tos)-Gly-Asp-(OcHex)-Ser(Bzl)-OBzl (**6**)

232 mg (0.25 mmol) of Boc-Ala-Arg(Tos)-Pro-Ala-Lys(*Z*)-OH was dissolved in 15 ml of anhydrous THF, then 34 mg (0.25 mmol) of HOBt and 52 mg (0.25 mmol) of DCC were added at 0 °C. The reaction mixture was treated, as mentioned above, to provide the corresponding active ester which was used for the next reaction directly. 221 mg (0.25 mmol) of Arg(Tos)-Gly-Asp(OcHex)-Ser(Bzl)-OBzl·HCl, 29.7 mg (0.27 mmol) of *N*-methylmorpholine, and 261.5 mg (0.25 mmol) of the corresponding active ester, as mentioned above, were mixed in 10 ml of anhydrous THF. The reaction mixture was stirred at room temperature for 30 h. The reaction mixture was worked up as mentioned above to give the title compound in 418 mg (95%) yield.

Boc-Gln-Arg(Tos)-Pro-Ala-Lys(Z)-Arg(Tos)-Gly-Asp-(OcHex)-Ser(Bzl)-OBzl (**7**)

246.5 mg (0.25 mmol) of Boc-Gln-Arg(Tos)-Pro-Ala-Lys(*Z*)-OH was dissolved in 15 ml of anhydrous THF, then 34 mg (0.25 mmol) of HOBt and 52 mg (0.25 mmol) of DCC were added at 0 °C. The reaction mixture was treated, as mentioned above, to provide the corresponding active ester which was used for the next reaction directly. 221 mg (0.25 mmol) of Arg(Tos)-Gly-Asp(OcHex)-Ser(Bzl)-OBzl·HCl, 29.7 mg (0.27 mmol) of *N*-methylmorpholine, and 275.8 mg (0.25 mmol) of the corresponding active ester, as mentioned above, were mixed in 10 ml of anhydrous THF. The reaction mixture was stirred at room temperature for 30 h. The reaction mixture was worked up, as mentioned above, to give the title compound in 422 mg (93%) yield.

Boc-Ala-Arg(Tos)-Pro-Ala-Lys(Z)-Arg(Tos)-Gly-Asp-(OcHex)-Val-OBzl (**8**)

232 mg (0.25 mmol) of Boc-Ala-Arg(Tos)-Pro-Ala-Lys(*Z*)-OH was dissolved in 15 ml of anhydrous THF, then 34 mg (0.25 mmol) of HOBt and 52 mg (0.25 mmol) of DCC were added at 0 °C. The reaction mixture was treated, as mentioned above, to provide the corresponding active ester which was used for the next reaction directly. 202 mg (0.25 mmol) of Arg(Tos)-Gly-Asp(OcHex)-Val-OBzl·HCl, 29.7 mg (0.27 mmol) of *N*-methylmorpholine, and 261.5 mg

(0.25 mmol) of the corresponding active ester, as mentioned above, were mixed in 10 ml of anhydrous THF. The reaction mixture was stirred at room temperature for 30 h. The reaction mixture was worked up, as mentioned above, to give the title compound in 404 mg (96%) yield.

Boc-Gln-Arg(Tos)-Pro-Ala-Lys(Z)-Arg(Tos)-Gly-Asp-(OcHex)-Val-OBzl (**9**)

246.5 mg (0.25 mmol) of Boc-Gln-Arg(Tos)-Pro-Ala-Lys(Z)-OH was dissolved in 15 ml of anhydrous THF, then 34 mg (0.25 mmol) of HOBt and 52 mg (0.25 mmol) of DCC were added at 0 °C. The reaction mixture was treated, as mentioned above, to provide the corresponding active ester which was used for the next reaction directly. 202 mg (0.25 mmol) of Arg(Tos)-Gly-Asp(OcHex)-Val-OBzl·HCl, 29.7 mg (0.27 mmol) of *N*-methylmorpholine, and 275.8 mg (0.25 mmol) of the corresponding active ester, as mentioned above, were mixed in 10 ml of anhydrous THF. The reaction mixture was stirred at room temperature for 30 h. The reaction mixture was worked up, as mentioned above, to give the title compound in 409 mg (94%) yield.

Boc-Ala-Arg(Tos)-Pro-Ala-Lys(Z)-Arg(Tos)-Gly-Asp-(OcHex)-Phe-OBzl (**10**)

232 mg (0.25 mmol) of Boc-Ala-Arg(Tos)-Pro-Ala-Lys(*Z*)-OH was dissolved in 15 ml of anhydrous THF, then 34 mg (0.25 mmol) of HOBt and 52 mg (0.25 mmol) of DCC were added at 0 °C. The reaction mixture was treated, as mentioned above, to provide the corresponding active ester which was used for the next reaction directly. 214 mg (0.25 mmol) of Arg(Tos)-Gly-Asp(OcHex)-Phe-OBzl·HCl, 29.7 mg

(0.27 mmol) of *N*-methylmorpholine, and 261.5 mg (0.25 mmol) of the corresponding active ester, as mentioned above, were mixed in 10 ml of anhydrous THF. The reaction mixture was stirred at room temperature for 30 h. The reaction mixture was worked up as mentioned above to give the title compound in 411 mg (95%) yield.

Boc-Gln-Arg(Tos)-Pro-Ala-Lys(Z)-Arg(Tos)-Gly-Asp-(OcHex)-Phe-OBzl (**11**)

246.5 mg (0.25 mmol) of Boc-Gln-Arg(Tos)-Pro-Ala-Lys(*Z*)-OH was dissolved in 15 ml of anhydrous THF, then 34 mg (0.25 mmol) of HOBt and 52 mg (0.25 mmol) of DCC were added at 0 °C. The reaction mixture was treated, as mentioned above, to provide the corresponding active ester which was used for the next reaction directly. 214 mg (0.25 mmol) of Arg(Tos)-Gly-Asp(OcHex)-Phe-OBzl · HCl, 29.7 mg (0.27 mmol) of *N*-methylmorpholine, and 275.8 mg (0.25 mmol) of the corresponding active ester, as mentioned above, were mixed in 10 ml of anhydrous THF. The reaction mixture was stirred at room temperature for 30 h. The reaction mixture was worked up, as mentioned above, to give the title compound in 415 mg (93%) yield.

H-Ala-Arg-Pro-Ala-Lys-OH (ARPAK, **12***)*

153 mg (0.15 mmol) of Boc-Ala-Arg(Tos)-Pro-Ala-Lys(*Z*)-OBzl was mixed with 1 ml of dimethyl sulfide, 1 ml of phenyl methyl ether, and 5 ml of CF_3COOH-CF_3SO_3H (4:1). The mixture was stirred at 0 °C for 2 h. After removal of CF_3COOH-CF_3SO_3H the residue was triturated with ether, and the residue was purified on Sephadex G 10 and HPLC to provide the title compound in 69 mg (85%) yield.

H-Gln-Arg-Pro-Ala-Lys-OH *(*QRPAK, **13***)*

161 mg (0.15 mmol) of Boc-Gln-Arg(Tos)-Pro-Ala-Lys(*Z*)-OBzl was treated, as mentioned above, to provide the title compound in 74 mg (82%) yield.

H-Arg-Gly-Asp-Ser-OH (RGDS, **14***)*

142 mg (0.15 mmol) of Boc-Arg(Tos)-Gly-Asp(OcHex)-Ser(Bzl)-OBzl was treated, as mentioned above, to provide the title compound in 55 mg (85%) yield.

H-Arg-Gly-Asp-Val-OH (RGDV, **15***)*

131 mg (0.15 mmol) of Boc-Arg(Tos)-Gly-Asp(OcHex)-Val-OBzl was treated, as mentioned above, to provide the title compound in 58 mg (87%) yield.

H-Arg-Gly-Asp-Phe-OH (RGDF, **16***)*

138 mg (0.15 mmol) of Boc-Arg(Tos)-Gly-Asp(OcHex)-Phe-OBzl was treated, as mentioned above, to provide the title compound in 61 mg (83%) yield.

H-Ala-Arg-Pro-Ala-Lys-Arg-Gly-Asp-Ser-OH (ARPA-KRGDS, **17***)*

264 mg (0.15 mmol) of Boc-Ala-Arg(Tos)-Pro-Ala-Lys(*Z*)-Arg(Tos)-Gly-Asp(OcHex)-Ser(Bzl)-OBzl was treated, as mentioned above, to provide the title compound in 125 mg (87%) yield.

H-Gln-Arg-Pro-Ala-Lys-Arg-Gly-Asp-Ser-OH (QRPA-KRGDS, **18***)*

273 mg (0.15 mmol) of Boc-Gln-Arg(Tos)-Pro-Ala-Lys(*Z*)-Arg(Tos)-Gly-Asp(OcHex)-Ser(Bzl)-OBzl was treated, as mentioned above, to provide the title compound in 131 mg (86%) yield.

H-Ala-Arg-Pro-Ala-Lys-Arg-Gly-Asp-Val-OH (ARPA-KRGDV, **19***)*

252 mg (0.15 mmol) of Boc-Ala-Arg(Tos)-Pro-Ala-Lys(*Z*)-Arg(Tos)-Gly-Asp(OcHex)-Val-OBzl was treated, as mentioned above, to provide the title compound in 123 mg (85%) yield.

H-Gln-Arg-Pro-Ala-Lys-Arg-Gly-Asp-Val-OH (QRPA-KRGDV, **20***)*

261 mg (0.15 mmol) of Boc-Gln-Arg(Tos)-Pro-Ala-Lys(*Z*)-Arg(Tos)-Gly-Asp(OcHex)-Val-OBzl was treated as mentioned above to provide the title compound in 135 mg (88%) yield.

H-Ala-Arg-Pro-Ala-Lys-Arg-Gly-Asp-Phe-OH (ARPA-KRGDF, **21***)*

260 mg (0.15 mmol) of Boc-Ala-Arg(Tos)-Pro-Ala-Lys(*Z*)-Arg(Tos)-Gly-Asp(OcHex)-Phe-OBzl was treated, as mentioned above, to provide the title compound in 126 mg (83%) yield.

H-Gln-Arg-Pro-Ala-Lys-Arg-Gly-Asp-Phe-OH (QRPA-KRGDF, **22***)*

268 mg (0.15 mmol) of Boc-Gln-Arg(Tos)-Pro-Ala-Lys(*Z*)-Arg(Tos)-Gly-Asp(OcHex)-Phe-OBzl was treated, as mentioned above, to provide the title compound in 145 mg (90%) yield.

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