camune, G.S. Bates, J.W. Corcoran, *Angew. Chem.* **1977**, *89*, 602; *ibid. Int. Ed.* **1977**, *16*, 585;
cacs. M. Ohno, 'Recent Progress in the Chemical Synthesis of Antibiotics', Springer-Verlag, Heidel-
990.
bach, A.K. Beck, R. Breitschuh, K. Job, *Org. Synth.* **1992**, *71*, 39.
aga, K. Hirata, H. Saeki, T. Katsuka, M. Yamaguchi, *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989.
rown, C. Christodoulou, C.B. Reese, G. Sindona, *J. Chem. Soc., Perkin Trans. 1* **1984**, 1785; P. Sieber,
edron Lett. **1987**, *28*, 6147.
ert, T. Kelly, *J. Org. Chem.* **1988**, *53*, 449.
colajczyk, P. Kielbasinski, *Tetrahedron* **1981**, *37*, 233.
at, R.M. Utrilla, A. Olano, *An. Quim.* **1969**, *65*, 829; *Chem. Abstr.* **1970**, *72*, 54840.
es, W. Steglich, *Angew. Chem.* **1978**, *90*, 556; *ibid. Int. Ed.* **1978**, *17*, 522.
Voodword, F.E. Bader, H. Bickel, A.J. Frey, R.W. Kierstead, *Tetrahedron* **1958**, *2*, 1.
isner, V. Alexanian, *Tetrahedron Lett.* **1978**, 4475; G. Höfle, W. Steglich, H. Vorbrüggen, *Angew.*
1978, *90*, 602; *ibid. Int. Ed.* **1978**, *90*, 569.
ith, J.G. Moffatt, H.G. Khorana, *J. Am. Chem. Soc.* **1958**, *80*, 6204.
lironova, G.F. Dvorko, T.N. Skuratovskaya, *Ukr. Khim. Zh.* **1969**, *35*, 726.
ll, A. Rouvé, *Helv. Chim. Acta* **1934**, *17*, 1283.
bach, H.-M. Müller, H.-M. Bürger, D.A. Plattner, *Angew. Chem.* **1992**, *104*, 443; *ibid. Int. Ed.* **1992**, *31*,

ischer, J.J. Kabara, *Anal. Biochem.* **1964**, *9*, 303.
bach, U. Brändli, H.-M. Müller, M. Dobler, M. Egli, M. Przybylski, K. Schneider, *Helv. Chim. Acta*
2, 1704.
touchi, Y. Chatani, H. Tadokoro, K. Teranishi, H. Tani, *Polymer* **1973**, *14*, 267.
touchi, Y. Chatani, H. Tadokoro, H. Tani, *Polym. J.* **1974**, *6*, 248.
anitz, *Science* **1994**, *264*, 670.
effrey, W. Saenger, 'Hydrogen Bonding in Biological Structures', Springer Verlag, Berlin, 1991.
heldrick, 'SHELX-86, Program for the Solution of Crystal Structures', University of Göttingen, 1986.
Sheldrick, 'SHELX-76, Program for Crystal Structures Determination', University of Cambridge,

heldrick, 'SHELXL-93', *Current Contents (Physical, Chemical and Earth Sciences)* **1989**, *29*, 14.

177. Synthesis of Tri-, Penta-, and Heptapeptides Containing an (*R*)-2-Alkyl-2-amino-3-(methylamino)-propionic Acid Residue in the Central Position[1])

by **Dieter Seebach***, **Armido Studer**[2]), and **Elmar Pfammatter**[3])

Laboratorium für Organische Chemie der Eidgenössischen Technischen Hochschule, ETH-Zentrum, Universitätstrasse 16, CH–8092 Zürich

and **Hans Widmer**

Präklinische Forschung, *Sandoz Pharma AG*, CH–4002 Basel

(4.V.94) HELVETICA CHIMICA ACTA
Vol 77 (1994) 2035-2050

By conventional peptide-coupling methods (C to N direction; mixed anhydride, bis(2-oxooxazolidin-3-yl)phosphinoyl chloride (Bop-Cl), or dicyclohexylcarbodiimide (DCC), 2-amino-2-methyl-3-(methylamino)-propionic acid and 2-amino-2-ethyl-3-(methylamino)propionic acid (= 2-amino-2-[(methylamino)methyl]butanoic acid) are incorporated in the central position of tri-, penta-, and heptapeptides (see **3**–**7**, **21**, and **22**). The fragment coupling of the β-amino group of the diamino-acid moiety in a tetrapeptide led to partial epimerization, and thus, two epimeric heptapeptide derivatives were actually obtained (**7** and epi-**7**). The final deprotection to the free heptapeptide (involving a Me_3SiI cleavage of BocNH and MeOCONH, a saponification with NaOH, and HPLC purification) gave both the desired product (isopeptide **21**), with the β-amino group inside the peptide backbone, and a product (peptide **22**) of transpeptidation, with the α-amino group of the diamino acid incorporated and a (methylamino)methyl group as the side chain. Peptide **22** is completely converted to the isopeptide **21** by prolonged treatment with base. The heptapeptide **21** was analyzed by elaborate 2QF-COSY and NOESY NMR measurements in H_2O/CD_3OD at −5° (*Table*, *Fig.*); there is no indication for β-sheet or helical structures, a fact which was also confirmed by CD measurements.

Introduction. – During the last twenty years, many new biologically active peptides were discovered. Structural analogues were synthesized for studying structure/activity correlations. Especially the relationship of conformation and activity is of great importance. Non-proteinogenic amino acids such as α-aminoisobutyric acid (Aib) [1], αβ-didehydrophenylalanine (ΔPhe) or other dehydroamino acids [2], dibenzofuran-based amino acids [3] and spiro-lactam systems [4] were introduced into the peptide chain, in order to stabilize a defined conformation.

A special amino acid, also occurring naturally [5], is 2,3-diaminopropionic acid (A_2pr). Normally, it is found to be a peptide residue with an aminomethyl side chain[4]) (see, *e.g.*, **A**). In a *Chemical Abstract* search, we found only one example, a family of cyclic peptides with antibiotic activity (capreomycin, viomycin, tuberactinomycin) in which A_2pr is incorporated with the β-amino group as part of the backbone [5b] (*Formula* **B**; containing a total of five β-amino acid units!).

[1]) This project was supported by the *Swiss National Science Foundation*, project No. 20-30770.91.
[2]) Part of the Diplomarbeit (1991) and of the projected Doktorarbeit of *A.S.*
[3]) Part of the Doktorarbeit of *E.P.*, Dissertation No. 9703, ETH-Zürich, 1992.
[4]) There are numerous peptides with this side chain ('aza-serine derivatives'). For two recently isolated fungizides containing A_2pr, see [5a].

Val-Ala-L-Leu-Moc-(R)-Aib(NMe)-Val-Ala-OMe (7). M.p. 178–181°. $[\alpha]_D^{r.t.} = -30.9$ ($c = 0.68$, CD: $-6.74 \cdot 10^{-4}$ (195.0), $+1.70 \cdot 10^{-4}$ (213.5), $-5.14 \cdot 10^{-3}$ (234.5). IR ($CHCl_3$): 3670*w*, 3420*m*, 3320*s*, 30*s*, 2940*w*, 2870*m*, 1725*w*, 1665*s*, 1510*s*, 1470*w*, 1455*w*, 1420*m*, 1390*m*, 1370*m*, 1260*m*, 1240*m*, 1165*s*, 80*m*, 870*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 0.89–0.99 (*m*, Me(Val,Leu)); 1.32–1.39 (2 Me(Ala)); 1.44 (*s*, ·)); 1.47–1.65 (*m*, CH_2–C(2.7), CH_2–C(2.3), CH–C(3.7), CH–C(3.3)); 2.0–2.2 (*m*, CH(Val)); 2.2–2.4 (Val)); 3.10 (*s*, MeN); 3.54 (*d*, $J = 14.5$, H–C(3.4)); 3.61 (*s*, MeO); 3.72 (*s*, MeO); 3.99 (*d*, $J = 14.4$,), 3.9–4.1 (br. *s*, H–C(α)); 4.27–4.31 (*m*, H–C(α)); 4.52–4.62 (*m*, 2 H–C(α)); 4.64–4.69 (*m*, H–C(α)); (br. *s*, H–C(α)); 5.23 (*d*, $J = 7.6$, NHCOO); 6.87–6.88 (br. *s*, NH); 7.14–7.27 (br. *s*, 3 NH); 7.3–7.4 (br. ^{13}C-NMR (75 MHz, $CDCl_3$): 17.51 (Me); 17.68 (Me); 18.19 (Me); 19.29 (Me); 21.06 (Me); 21.76 (Me);); 22.80 (Me); 23.34 (Me); 24.75 (CH); 28.33 (Me); 30.50 (CH); 31.11 (CH); 38.13 (Me); 40.95 (CH_2); 2); 48.54 (CH); 48.90 (CH); 50.80 (CH); 52.10 (Me); 52.25 (Me); 56.19, 56.28 (CH_2, rotamers); 59.46 3 (CH); 62.48 (C); 79.96 (C); 155.92 (C); 156.09 (C); 171.13 (C); 171.53 (C); 172.03 (C); 172.35 (C); ; 173.25 (C); 175.61 (C). FAB-MS: 893.4 (21.81, $[M + Na]^+$), 871.4 (12.40, $[M + H]^+$), 771.4 (11.51), 56), 488.2 (49.18), 244.2 (14.58), 215.1 (14.82), 146.1 (12.34), 145.1 (36.55), 116.0 (10.30), 98.0 (10.67), 72.0 (42.94), 56.9 (40.90), 54.9 (13.29). Anal. calc. for $C_{41}H_{74}N_8O_{12}$ (871.09): C 56.53, H 8.56, N 12.86; 56.63, H 8.43, N 12.69.

Val-Ala-D-Leu-Moc-(R)Aib(NMe)-Val-Ala-OMe (epi-7). $[\alpha]_D^{r.t.} = +4.9$ ($c = 0.575$, MeOH). CD: $^{-4}$ (213.0). IR (KBr): 3670*w*, 3420*m*, 3320*m*, 3010*s*, 2960*s*, 2940*w*, 2870*m*, 1710*s*, 1670*s*, 1500*s*, 1470*w*, 20*m*, 1390*m*, 1370*s*, 1260*w*, 1240*m*, 1160*m*, 1080*m*, 870*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 0.8–1.0 (*m*, u)); 1.34 (*d*, $J = 7.1$, Me(Ala)); 1.39 (*d*, $J = 7.1$, Me(Ala)); 1.44, 1.45 (2*s*, Me–C(2.4), rotamers); (*m*, CH_2–C(2.7), CH_2–C(2.3), CH–C(3.7), CH–C(3.3)); 2.08–2.19 (*m*, CH(Val)); 2.22–2.31 (*m*, 2.89, 3.09, 3.12 (3*s*, MeN, rotamers); 3.59 (*d*, $J = 10.8$, H–C(3.4)); 3.63 (*s*, MeO); 3.65–3.70 (*m*, ; 3.72 (*s*, MeO); 3.8–4.0 (br. *m*, H–C(α)); 4.2–4.3 (*m*, H–C(α)); 4.45–4.65 (*m*, 3 H–C(α)); 4.8–4.9 (*m*, 5.1–5.2 (br. *s*, NHCOO); 6.8–6.9 (*m*, 2 NH); 6.9–7.0 (br. *s*, NH); 7.15–7.25 (br. *s*, NH); 7.25–7.30 (br. *s*, -7.40 (br. *s*, NH). ^{13}C-NMR (75 MHz, $CDCl_3$): 17.55 (Me); 17.55 (Me); 18.66 (Me); 19.33 (Me); 19.55 4 (Me); 21.47 (Me); 21.59 (Me); 21.84 (Me); 22.76 (Me); 23.30 (Me); 23.37 (Me); 24.72 (CH_2); 24.81 2 (Me); 30.24, 30.59 (CH, rotamers); 30.82, 31.04 (CH, rotamers); 36.42, 38.21 (MeN, rotamers); 40.82, 2, rotamers); 41.24 (CH_2); 47.99 (CH); 48.56, 48.62 (CH, rotamers); 48.84 (CH); 50.76, 50.84 (CH, 52.05 (Me); 52.22 (Me); 55.78 (Me); 59.08, 59.26, 59.37 (CH, rotamers); 59.82, 59.98 (CH, rotamers); 1 (C, rotamers); 80.02, 80.14 (C, rotamers); 155.93, 156.04 (C, rotamers); 156.48 (C); 170.88 (C); 171.34, rotamers); 171.93 (C); 172.18, 172.32 (C, rotamers); 172.81, 172.90 (C, rotamers); 173.02, 173.21 (C, 175.29, 175.57 (C, rotamers). FAB-MS: 894.4 (23.60), 893.4 (48.49, $[M + Na]^+$), 871.4 (15.59, , 771.4 (18.81), 489.2 (22.58), 488.2 (84.44), 343.1 (11.43), 244.2 (13.48), 215.1 (19.49), 147.1 (18.46), 9), 132.9 (14.48), 116.0 (11.79), 86.0 (100), 72.9 (45.80), 71.9 (45.89), 56.9 (58.84), 54.9 (17.13).

-3-[N-(Benzyloxycarbonyl)-N-methylamino]-2-[N-(methoxycarbonyl)amino]-2-methylpropanoyl}-thyl Ester (*Moc-(R)-Aib(N(Z)Me)-Ala-OMe*; **8**). Coupling and workup according to *G.P.2* with **2a** .63 mmol), Bop-Cl (687 mg, 2.65 mmol), Et(i-Pr)$_2$N (0.91 ml, 5.26 mmol), CH_2Cl_2 (11 ml), H-Ala- (510 mg, 2.7 mmol), Et(i-Pr)$_2$N (0.46 ml, 2.7 mmol), and CH_2Cl_2 (8 ml). The crude peptide was used for ng deprotecting procedure without further purification. ^{1}H-NMR (200 MHz, $CDCl_3$): 1.37 (*d*, $J = 7.0$, .50–1.51 (*m*, Me–C(2.1)); 2.92 (*s*, MeN); 3.52 (*d*, $J = 15.4$, H–C(3.1)); 3.65 (*s*, MeO); 3.71 (*s*, MeO); = 14.2, H–C(3.1)); 4.4–4.6 (*m*, H–C(2.2)); 5.16 (*s*, PhCH_2); 7.0–7.2 (*m*, 2 NH).

-2-[N-(Methoxycarbonyl)amino]-2-methyl-3-(methylamino)propanoyl]alanine Methyl Ester (*Moc-HMe)-Ala-OMe*; **9**). To a soln. of **8** (700 mg, 1.70 mmol) in EtOH (7 ml) under Ar, 10% Pd/C (70 mg) The Ar atmosphere was replaced by H_2. The suspension was stirred for 14 h, the catalyst removed by ver *Celite*, and the filtrate evaporated: **9** (462 mg, 99%). The slight green oil was used for the following ·ocedure without further purification. ^{1}H-NMR (200 MHz, $CDCl_3$): 1.40 (*d*, $J = 7.4$, Me–C(3.2)); 1.55 2.1)); 2.46 (*s*, MeN); 2.61 (*d*, $J = 12.4$, H–C(3.1)); 3.24 (*d*, $J = 12.2$, H–C(3.1)); 3.64 (*s*, MeO); 3.72 (*s*, 4.6 (*m*, H–C(2.2)); 6.20 (br. *s*, NH); 6.25 (*s*, NH).

-2-{[N-(Benzyloxycarbonyl)-N-methylamino]methyl}-2-[N-(methoxycarbonyl)amino]butanoyl}ala-l Ester (*Moc-(R)-Abu(CH$_2$N(Z)Me)-Ala-OMe*; **10**). Coupling and workup according to *G.P.2* with 3.5 mmol), Bop-Cl (917 mg, 3.6 mmol), Et(i-Pr)$_2$N (1.24 ml, 7.0 mmol), CH_2Cl_2 (15 ml), H-Ala- (750 mg, 4.0 mmol), Et(i-Pr)$_2$N (0.71 ml, 3.5 mmol) and CH_2Cl_2 (15 ml). The crude **10** was used for the leprotecting procedure without further purification. ^{1}H-NMR (200 MHz, $CDCl_3$): 0.70–0.95 (*m*, .32 (*d*, $J = 7.2$, Me(3.2)); 1.60–2.40 (*m*, CH_2(3.1)); 2.94 (*s*, MeN); 3.8–4.3 (*m*, 1 H, MeNCH_2–C(2.1)); 7.34 (*s*, PhCH_2).

{(2R)-2-[N-(Methoxycarbonylamino]-2-[(methylamino)methyl]butanoyl}alanine Methyl Ester (*Moc-(R)-Abu(CH$_2$NHMe)-Ala-OMe*; **11**). As described for **9**, with **10** (1.3 g, 3.8 mmol), EtOH (13 ml), and 10% Pd/C (130 mg): 874 mg (99%) of **11**. The slight green oil was used for the following coupling procedure without further purification. ^{1}H-NMR (200 MHz, $CDCl_3$): 0.70–0.90 (*m*, Me(4.1)); 1.2–1.4 (*m*, Me–C(3.2)); 1.7–2.4 (*m*, CH_2(3.1)); 2.6–2.9 (*m*, ^{1}H, MeNCH_2–C(2.1)); 2.9–3.0 (2*s*, MeN, rotamers); 3.3–3.5 (*m*, 1 H, MeNCH_2–C(2.1)); 3.63 (*s*, MeO); 3.72 (*s*, MeO); 4.4–4.5 (*m*, H–C(2.2)); 6.27 (br. *s*, NH); 6.25 (*s*, NH); 8.75 (br. *s*, NH).

{(2R)-3-[N-(Benzyloxycarbonyl)-N-methylamino]-2-[N-(methoxycarbonyl)amino]-2-methylpropanoyl}-phenylalanyl-phenylalanin Methyl Ester (*Moc-(R)-Aib(N(Z)Me)-Phe-Phe-OMe*; **12**). Coupling and workup according to *G.P.2*, with **2a** (404 mg, 1.50 mmol), Bop-Cl (380 mg, 1.50 mmol), Et(i-Pr)$_2$N (0.52 ml, 3.10 mmol), CH_2Cl_2 (8 ml), H-Phe-Phe-OMe·HCl (640 mg, 1.76 mmol), Et(i-Pr)$_2$N (0.30 ml, 1.80 mmol), and CH_2Cl_2 (5.2 ml): **12** (800 mg, 85%). Colorless foam. $[\alpha]_D^{r.t.} = +36.5$ ($c = 1.00$, CH_2Cl_2). ^{1}H-NMR (300 MHz, $CDCl_3$): 1.23–1.64 (3*s*, Me–C(2.1), rotamers); 2.82 (*s*, MeN); 2.92–3.08 (*m*, CH_2–C(2.3), CH_2–C(2.2)); 3.46–3.72 (*m*, 2 MeO, 2 H–C(3.1)); 4.55–4.58 (*m*, H–C(2.3) or H–C(2.2)); 4.70–4.72 (*m*, H–C(2.3) or H–C(2.2)); 5.13–5.18 (br. *s*, PhCH_2); 6.40–6.50 (*s*, NH); 6.96–7.05 (*m*, 2 NH); 7.17–7.36 (*m*, arom. H). ^{13}C-NMR (75 MHz, $CDCl_3$); 20.28 (Me); 37.48 (Me); 37.56 (CH_2); 37.74 (CH_2); 52.21 (2 Me); 54.80 (CH); 56.84 (CH); 57.13 (CH_2); 62.24 (C); 67.97 (CH_2); 126.98 (CH); 127.91 (CH); 128.05 (CH); 128.22 (CH); 128.52 (CH); 128.63 (CH); 129.12 (CH); 135.35 (C); 136.15 (C); 136.66 (C); 156.22 (C); 158.90 (C); 170.19 (C); 171.40 (C); 172.37 (C). FAB-MS: 633.3 (25.1, $[M + H]^+$), 454.2 (14.7), 307.1 (24.6), 180.1 (11.1), 154.0 (12.1), 136.0 (11.8), 134.1 (17.7), 120.0 (33.5), 92.0 (100.0).

{(2R)-2-[N-(Methoxycarbonyl)amino]-2-methyl-3-(methylamino)propanoyl}-phenylalanyl-phenylalanin Methyl Ester (*Moc-(R)-Aib(NHMe)-Phe-Phe-OMe*; **13**). As described for **9**, with **12** (780 mg, 1.24 mmol), EtOH (5 ml), and 10% Pd/C (50 mg): 615 mg (99%) of **13**. The oil was used for the following coupling procedure without further purification. ^{1}H-NMR (200 MHz, $CDCl_3$): 1.54 (*s*, Me–C(2.1)); 2.22 (*s*, MeN); 2.90–3.14 (*m*, CH_2–C(2.3), CH_2–C(2.2)); 3.59–3.70 (2*s*, 2 MeO); 4.61–4.82 (*m*, H–C(2.3), H–C(2.2)); 5.95 (*s*, NH); 6.61–6.64 (*d*, $J = 7.0$, NH); 6.94–7.18 (*m*, NH); 7.20–7.37 (*m*, arom. H); 8.07–8.10 (*m*, NH).

N-(tert-Butoxycarbonyl)-alanyl-leucine Methyl Ester (*Boc-Ala-Leu-OMe*; **14**). Coupling and workup according to *G.P.1*, with Boc-Ala-OH (3 g, 15.9 mmol), NMM (1.55 ml, 16.5 mmol), THF (80 ml), isobutyl chloroformate (2.07 ml, 15.9 mmol), H-Leu-OMe·HCl (3 g, 16.5 mmol), NMM (1.55 ml, 16.5 mmol), and DMF (30 ml). The resulting oil was purified by FC (AcOEt/hexane 1:1): **14** (4.25 g, 85%). Colorless solid. M.p. 66°. $[\alpha]_D^{r.t.} = -54.4$ ($c = 1.1$, MeOH). IR (KBr): 3320*s*, 2980*m*, 2960*m*, 2940*m*, 2870*w*, 1760*s*, 1750*s*, 1630*s*, 1610*s*, 1535*s*, 1510*s*, 1455*m*, 1390*m*, 1370*s*, 1340*w*, 1310*w*, 1285*m*, 1275*m*, 1255*m*, 1220*m*, 1200*m*, 1160*s*, 1070*w*, 1005*m*, 855*w*, 790*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 0.95 (*d*, $J = 5.7$, 2 Me–C(4.2)); 1.36 (*d*, $J = 6.9$, Me(3.1)); 1.45 (*s*, *t*-Bu); 1.5–1.7 (*m*, CH_2(3.2), CH(4.2)); 3.73 (*s*, MeO); 4.18 (*m*, CH(2.2)); 4.59 (*m*, CH(2.1)); 5.05 (*d*, $J = 6.9$, NHCOO); 6.59 (*d*, $J = 6.6$, NH). ^{13}C-NMR (75 MHz, $CDCl_3$): 17.92 (Me); 21.82 (Me); 22.85 (Me); 24.76 (CH); 28.29 (Me); 41.53 (CH_2); 49.92 (CH); 50.68 (CH); 52.28 (Me); 80.14 (C); 155.55 (C); 172.43 (C); 173.25 (C). FAB-MS: 318.1 (12.24), 317.1 (53.73, $[M + H]^+$), 262.1 (22.56), 261.1 (100), 229.1 (12.81), 218.1 (11.96), 217.1 (65.38), 201.1 (17.16), 146.1 (45.74), 144.1 (14.18), 87.9 (24.86), 86.0 (72.79), 56.9 (60.98).

Alanyl-leucine Methyl Ester Hydrochloride (*H-Ala-Leu-OMe·HCl*; **15**·HCl). A soln. of **14** (3.75 g, 11.86 mmol) in 3 ml of an Et_2O soln. sat. with HCl was stirred at r.t. for 2 h and then evaporated: 2.95 g (99%) of **15**·HCl. Colorless powder. M.p. 62°. $[\alpha]_D^{r.t.} = -25.8$ ($c = 1.0$, MeOH). IR (KBr): 3500–2500 (br.), 1740*s*, 1680*s*, 1555*s*, 1500*m*, 1470*m*, 1440*m*, 1390*w*, 1370*w*, 1160*m*, 1125*m*. ^{1}H-NMR (300 MHz, CD_3OD): 0.9–1.0 (*m*, 2 Me–C(4.2)); 1.53 (*d*, $J = 6.9$, Me(3.1)); 1.6–1.8 (*m*, CH_2(3.2), CH(4.2)); 3.71 (*s*, MeO); 3.96 (*m*, CH(2.1)); 4.48 (*t*, $J = 7.2$, CH(2.2)). ^{13}C-NMR (75 MHz, CD_3OD): 17.64 (Me); 21.72 (Me); 23.29 (Me); 25.96 (CH); 41.24 (CH_2); 50.11 (CH); 52.31 (CH); 52.80 (Me); 171.27 (C); 174.19 (C). FAB-MS: 649.2 (13.55, $[3(M - HCl) + H]^+$), 434.1 (15.27), 433.1 (48.83, $[2(M - HCl) + H]^+$), 218.1 (23.30), 217.1 (100, $[(M - HCl) + H]^+$), 146.1 (44.70), 85.9 (25.21).

N-(tert-Butoxycarbonyl)-valyl-alanyl-leucine Methyl Ester (*Boc-Val-Ala-Leu-OMe*; **16**). Coupling and workup according to *G.P.3* with Boc-Val-OH (1.736 g, 8 mmol), H-Ala-Leu-OMe·HCl (2.016 g, 8 mmol), HOBt (1.224 g, 8 mmol), NMM (0.76 ml, 8 mmol), THF (10 ml), and DCC (1.691 g). The crude peptide was purified by FC (AcOEt/hexane 1:1): **16** (2.79 g, 84%). Colorless solid. M.p. 157°. $[\alpha]_D^{r.t.} = -68.1$ ($c = 1.1$, MeOH). IR (KBr): 3310*s*, 2970*m*, 2930*w*, 2870*w*, 1745*s*, 1700*s*, 1675*s*, 1640*s*, 1530*s*, 1450*m*, 1430*w*, 1390*m*, 1365*m*, 1335*w*, 1285*m*, 1245*s*, 1220*s*, 1170*s*, 1090*w*, 1040*w*, 1015*w*, 680*m*. ^{1}H-NMR (300 MHz, CD_3OD): 0.9–1.0 (*m*, 2 Me–C(4.3), 2 Me–C(3.1)); 1.35 (*d*, $J = 7.2$, Me(3.2)); 1.44 (*s*, *t*-Bu); 1.5–1.8 (*m*, CH_2(3.3), CH(4.3)); 1.8–2.2 (*m*, CH(3.1)); 3.69 (*s*, MeO); 3.7–3.9 (*m*, CH(2.3)); 4.38–4.46 (*m*, CH(2.2), CH(2.1)). ^{13}C-NMR (75 MHz, CD_3OD): 18.22 (Me); 18.34