Pergamon

Tetrahedron Vol. 51, No. 31, pp. 8459-8470, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4020/95 $9.50+0.00

0040-4020(95)00461-0

A Highly Efficient Synthesis of the Anthelmintic Cyclooctadepsipeptide PF1022A

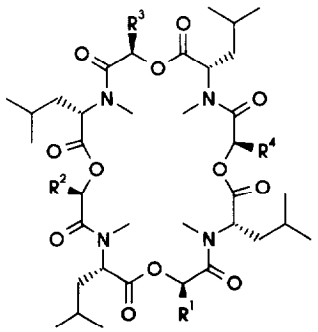
Jürgen Scherkenbeck[a*], Andrew Plant[a], Achim Harder[b], Norbert Mencke[b]

[a]Central Research
[b]Business Group Animal Health
Bayer AG, D-51368 Leverkusen (Germany)

Abstract: The potent anthelmintic cyclooctadepsipeptide PF1022A was synthesized by a series of fragment condensations starting from the known (*S*)-2-chloropropanoic acid and (*S*)-2-chloro-3-phenylpropanoic acid in eleven steps with a total yield of 13%. Noteworthy is the excellent yield of the BOP-Cl mediated lactamization reaction of the linear precursor **17** leading to the 24-membered macrocycle.

Introduction

Recently Sasaki et al.[1] reported the isolation and structure determination of the cyclooctadepsipeptide PF1022A, the most active member of a novel class of anthelmintic agents.[2] PF1022A was isolated from a mycelia cake of *Mycelia sterilia PF1022* belonging to the order Agonomycetales. The strain was recently isolated from the microflora found on the leaf of the plant *Camellia japonica*, collected at Ibaraga Prefecture in Japan.[3] *In vitro* motility of intestinal nematodes such as *Heterakis spumosa* was completely inhibited 2 hrs post treatment with 10^{-7} g/ml of PF1022A. Chickens infected with *Ascaridia galli* were treated orally with PF1022A at a dosage of 4 mg/kg, leading to rapid expulsion of worms within several hours after treatment. Oral application of the compound in dogs infected with *Toxocara canis* and *T. cati* at a dosage of 0.2 mg/kg was completely efficacious, and worms were expelled from the host on the first day after treatment.[3] Due to its potency and rapid



	R^1	R^2	R^3	R^4
PF1022A	Me	Bn	Me	Bn
PF1022B	Bn	Bn	Bn	Bn
PF1022C	Bn	Bn	Me	Bn
PF1022D	Me	Me	Me	Bn
PF1022E	Me	$CH_2C_6H_4OH$	Me	Bn
Bassianolide	^iPr	^iPr	^iPr	^iPr

Figure 1.

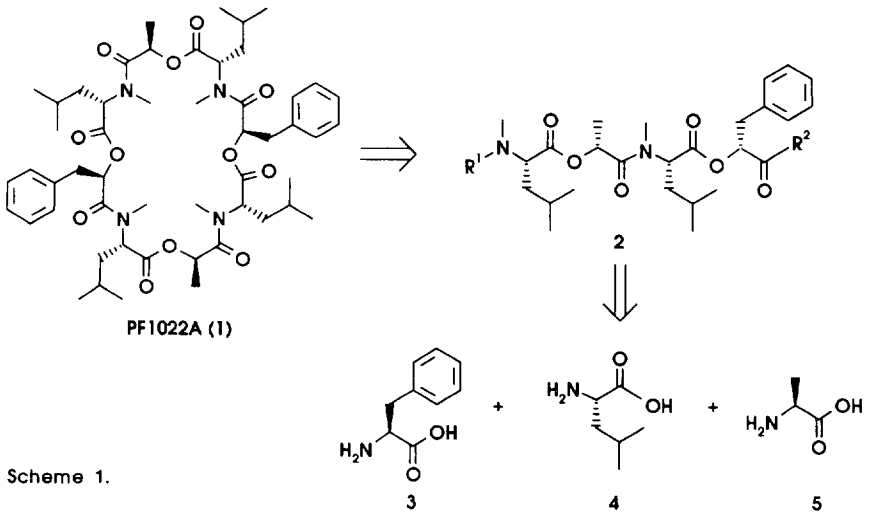
action[4] in combination with its extremely low toxicity, PF1022A is one of the most outstanding anthelmintics to emerge since the discovery of the avermectins and milbemycins.[5]

Structurally, the PF1022 anthelmintics belong to the group of cyclooctadepsipeptides. There are close similarities to bassianolide[6], an insecticidal compound isolated from the mycelia of *Beauveria bassiana*, and to the enniatins[7], a group of cyclic hexadepsipeptides with manifold biological activities. In contrast to the enniatins, only very few reports have focused on the synthesis, mode of action and structure-activity relationships of cyclooctadepsipeptides. To evaluate the anthelmintic properties of PF1022A and related compounds we have developed a general and highly efficient synthesis providing the desired depsipeptides on a gram scale.

Synthetic Strategy

PF1022A consists of four N-methyl-(*S*)-leucine (MeLeu) residues, two 3-phenyl-(*R*)-lactate (PheLac) units and two (*R*)-lactate (Lac) moieties linked together in a pattern giving the molecule a two-fold axis of symmetry. Thus the synthetic problem is reduced to the dimerization of two identical tetradepsipeptides, each composed of a MeLeu-Lac and MeLeu-PheLac didepsipeptide unit (scheme 1).

To date, two total syntheses of PF1022A have been reported. Both of them proceed via suitably protected lactic and phenyllactic acids. The expensive (*R*)-lactic acid and (*R*)-phenyllactic acids are used as starting materials in the Upjohn synthesis.[8] The Meiji route requires a Mitsunobo inversion to establish the (*R*)-configuration of the hydroxycarboxylic acid units and manipulation of two different protective groups for the lactic acid and phenyl lactic acid moieties.[9] Key features of our synthesis are: (i) the formation of **9** and **10** via enantiomerically pure (*S*)-2-chloro-propanoic acid and (*S*)-2-chloro-3-phenyl-propanoic acid respectively, (ii) the preparation of a defined linear octadepsipeptide which allows the ring closure to the target molecule by forming an amide bond between the nitrogen of MeLeu and the carboxy group of PheLac, and (iii) a highly efficient BOP-Cl mediated macrocyclization to afford PF1022A in excellent yield.



Scheme 1.

Synthesis of the linear precursors

(*R*)-α-hydroxycarboxylic acids are constitutive structural elements of many natural products and are usually obtained from (*R*)-amino acids via desamination procedures.[10] Due to their greater structural diversity, high optical purity and good availability we chose (*S*)-amino acids as starting materials for the synthesis of the (*R*)-Lac and (*R*)-PheLac containing didepsipeptides **9** and **10** (scheme 2).

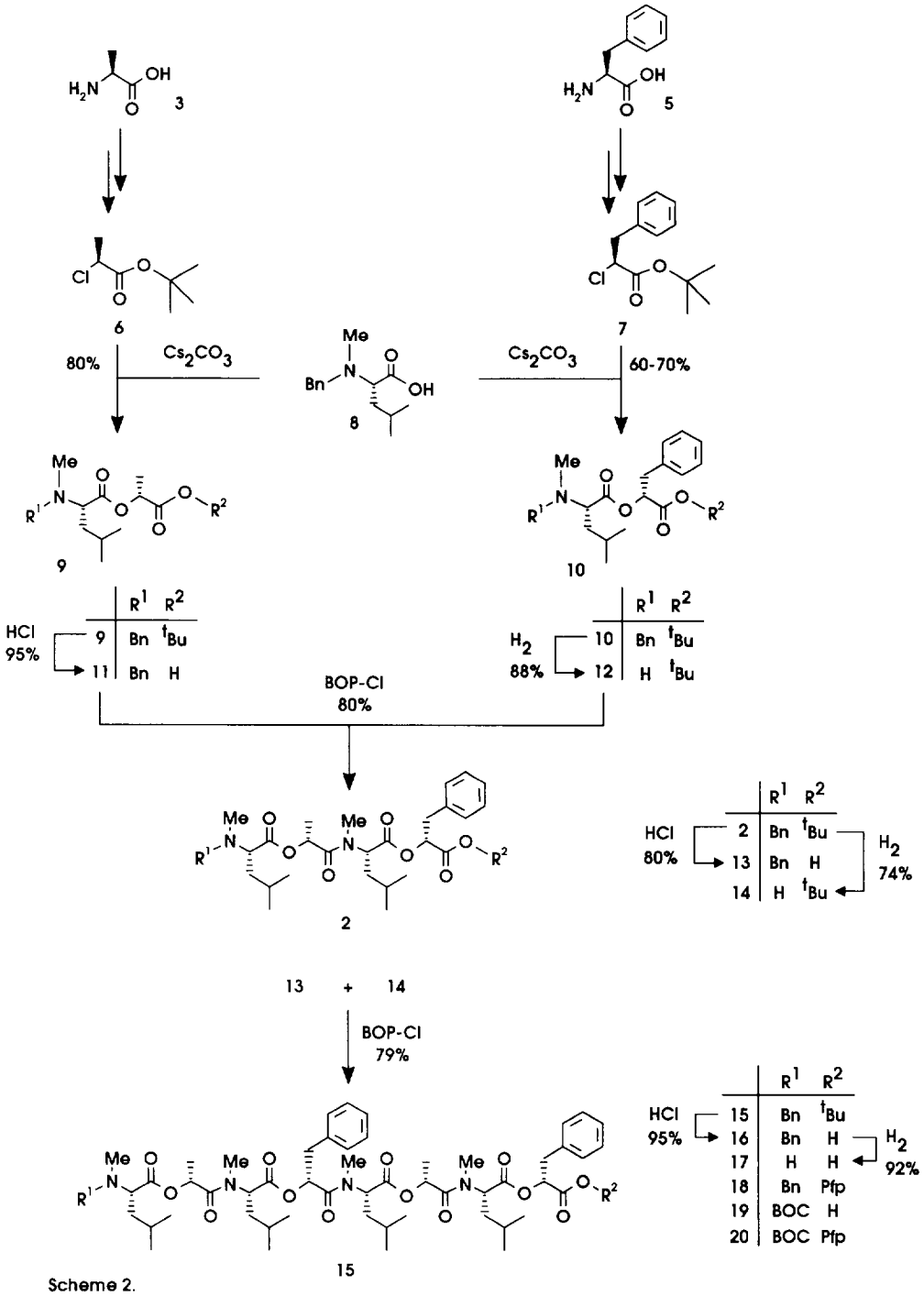
According to standard literature procedures[11] (*S*)-alanine and (*S*)-phenylalanine were transformed into the corresponding (*S*)-2-chlorocarboxylic acids with an e.e. > 98% (GC analysis of the corresponding menthyl esters) indicating a complete retention of configuration. After protection as their ^{t}butyl esters the chlorocarboxylic acids **6** and **7** were reacted with the cesium salt of N-benzyl-N-methyl-(*S*)-leucine (**8**). Utilization of the cesium effect accounts for the high coupling yields and a high degree of inversion even in sterically problematic cases (Val-HyVal).[12] Thus no diastereomeric side products (^{13}C-NMR) were found for **9**, while coupling of MeLeu with the ^{t}butyl (*S*)-2-chloro-3-phenyl-lactate **7** entails partial racemization (87% d.e.), the minor diastereomer being easily removed by flash chromatography. Cleavage of the ^{t}butyl group (**9** → **11**) with gaseous hydrogen chloride in methylene chloride and hydrogenolytic cleavage (**10** → **12**) of the N-benzyl group with the Pearlman catalyst[13] afforded the deprotected didepsipeptides in excellent yields.

Peptide bond formation involving N-methylated amino acids or peptides requires considerable activation of the corresponding carboxyl group. The possible and observed side reactions are numerous (formation of urethanes or piperazines, amidoacylation, etc.) even at low temperatures.[14] Thus using standard procedures[15] such as DCC/HOBt, DCC/N-hydroxysuccinimide or the mixed anhydride method, only insufficient yields were obtained, while DEPC, DPPA,[16] and the acid chloride method[15] produced higher yields (70-80%) of partially racemized coupling products. Encouraging results concerning coupling sterically congested N-methylated amino acid residues in solution have been reported using BOP-Cl[14,17] and PyBroP[18]. The reagent of choice proved to be BOP-Cl affording the tetradepsipeptide **2** in 85-90% yield with negligible racemization. A 3:1 mixture of trans and cis amide rotamers was observed for **2**, slowly interconverting on the NMR time scale. The linear octadepsipeptide **15** was prepared by repeating the protective group manipulations and condensation procedure described above.

Macrocyclization

Ring closure to form a peptolide ring can be achieved either by amide or by ester formation. The former procedure is more advantageous since an amide bond is formed more rapidly than an ester bond and also does not require such a high activation of the carbonyl group.[19] In such cyclizations, yields are influenced by certain structural key features of the linear depsipeptide precursors. The same absolute configuration of the amino acids, bulky side-chains, and the absence of N-alkyl substitution in the precursor, all diminish cyclization yields.[20] Despite numerous total syntheses of cyclic (depsi)peptides and systematic studies of factors influencing the success of the cyclization reaction[21], no general rules exist for the optimal connection point in a given linear sequence. Dramatic variation of the cyclization yields dependent upon the position of peptide bond formation were found in the 36 membered ionophores of the valinomycin group[20,22] as well as in the chlamydomycins[19,23], one of the rare families of naturally occurring cyclotetrapeptides.

As the ring closure is usually performed as the last, or one of the last steps, poor yields in this critical reaction dramatically reduce the value of the total synthesis. With this in mind selected cyclization strategies were studied. First of all we tried the pentafluorophenyl ester cyclization, developed by Schmidt.[24] The superiority of this cyclization strategy over other cyclization methods has been demonstrated several times.[19,25]


3
5
6
7
80%
Cs_2CO_3
8
60-70%
9
10
HCl
95%
H_2
88%
BOP-Cl
80%
2
HCl
80%
H_2
74%
13 + 14
BOP-Cl
79%
HCl
95%
H_2
92%
15

Scheme 2.

Surprisingly, poor yields (20-30%) were obtained in the hydrogenolysis of the N-benzyl protected pentafluorophenyl ester **18** as well as in the two-phase cyclization of the Boc-protected Pfp-ester **20**. Performing the cyclization reaction with the fully deprotected precursor **17** under high dilution conditions using EDC/HOBt as the condensation reagent, PF1022A could be isolated in 59% yield. BOP-Cl has been used successfully in several other cyclization reactions giving generally higher yields than comparable carboxyl activating reagents. Here again BOP-Cl proved to be the reagent of choice, affording an 85-90% yield of PF1022A. This unusually high yield for a peptide bond forming macrocyclization may be attributed to the cis-amide rotamers in the linear precursor, resulting in a U-type conformation with the terminal amino and carboxyl groups spatially close together. The cyclization process is further facilitated by the coordination[14] of the amino group to the intermediate mixed anhydride, which is formed on reaction of the carboxyl group with BOP-Cl. The synthetic PF1022A was completely identical to the natural substance with respect to all spectroscopic data and biological activity.

In conclusion, the potent anthelmintic cyclooctadepsipeptide PF1022A has been prepared in eleven steps starting from the known (*S*)-2-chlorocarboxylic acid esters **6** and **7** in 13% overall yield. The results described above would appear to recommend further application of BOP-Cl as a peptide cyclization reagent.

EXPERIMENTAL

General

All reactions were performed in oven-dried glassware under a positive pressure of argon. Solvents were dried by filtration through basic alumina (ICN Alumina, Act. I). Standard work-up refers to partioning the reaction mixture between water and an organic solvent, drying the combined organic extracts over Na_2SO_4, and removal of the solvent by distillation in vacuo at 40°C, using a rotatory evaporator. The instrumentation used was as follows: ^{1}H NMR: XL 200 (Varian), AMX 500 (Bruker); ^{13}C NMR: AMX 500 (Bruker); FT-IR: FTS-60 (BIO-RAD); MS (Finnigan): CI-MS: MAT 8340, FAB-MS: MAT 900, EI-MS: MAT 212; LC: Preparative low pressure chromatography (LPLC) was performed using silica gel 60 µm (230-400 mesh, E. Merck), Ismatec pump, UV detector Uvicord SII (Pharmacia LKB). Abbreviations: BOP-Cl, N,N'-bis(2-oxo-3-oxazolidinyl)phosphinic chloride; DCC, N,N'-dicyclohexylcarbodiimide; DEPC, diethylphosphorocyanidate; DPPA, diphenylphosphoroazidate; EDCI, 1-ethyl-3-(3-dimethyl-aminopropyl)carbodiimide; HOBt, 1-hydroxybenzotriazole; Pfp, pentafluorophenyl; PyBroP, bromo tripyrrolidino phosphonium hexafluorophosphate.

N-Benzyl-N-methyl-(*S*)-leucine (8)

8 was prepared from (*S*)-leucine as previously described.[26]

(*S*)-2-Chloropropanoic acids[10a,12a]. General Procedure.

Sodium nitrite (0.94 mol) was added in small portions to a solution of the (*S*)-amino acid (0.56 mol) in 6N hydrochloric acid (500 ml), with the internal temperature not exceeding 5°C. Subsequently, the reaction mixture was allowed to warm to 20°C and was stirred at this temperature for 4 h. Standard work-up (extraction with ethyl acetate) and distillation in vacuo afforded the (*S*)-2-chloropropanoic acids.- (*S*)-2-Chloro-propanoic acid (56%) $[\alpha]_D^{21}$ = -17.5 (pure); Lit.[10a,12a] $[\alpha]_D^{22}$ = -17.9 (pure).- (*S*)-2-Chloro-3-phenylpropanoic acid (56%) $[\alpha]_D^{21}$ = +4.9 (c 1.4 in MeOH); Lit.[10a,12a] $[\alpha]_D^{22}$ = +4.0 (c 1.4 in MeOH).

***tert.*-Butyl (*S*)-2-chloropropanoates[10a,12a]. General Procedure.**

Isobutene (1.2 l) was introduced to a solution of the (*S*)-2-chlorocarboxylic acid (2.42 mol) and conc. H_2SO_4 (8 ml) in CH_2Cl_2 (200 ml) and stirred for 48 h at 20°C in an autoclave. After evaporation of the excessive isobutene, the solution was washed with 2M $KHCO_3$ solution until the pH was neutral, and then dried over Na_2SO_4. Distillation in vacuo afforded the *tert.*-butyl (*S*)-2-chloropropanoates.- **6** (73%): $[\alpha]_D^{24}$ = -16.4 (pure); Lit.[10a,12a] $[\alpha]_D^{22}$ = -16.6 (pure).- **7** (76%): $[\alpha]_D^{24}$ = +27.5 (c 2.0 in MeOH); Lit.[10a,12a] $[\alpha]_D^{22}$ = +26.5 (c 1.0 in MeOH).

***tert.*-Butyl N-benzyl-N-methyl-(*S*)-leucyl-(*R*)-3-phenyllactate (10)**

A Cs_2CO_3 solution (0.127 mol in 200 ml water) was added to an ethanol (1000 ml) - water (500 ml) solution of **8** (50 g, 0.212 mol) and stirred at 20°C for 5 h. The solvents were removed by distillation. The crude cesium carboxylate was dried by codistillation with DMF (two times) and heating in vacuo for 12 h at 80°C. A solution of the cesium carboxylate and **7** (51.0 g, 0.212 mol) in DMSO (530 ml) was stirred at 20°C for 20 h. The reaction mixture was poured into brine followed by standard work-up (extraction with ethyl acetate). LPLC (cyclohexane-ethyl acetate 100:1) afforded pure **10** (26.6 g, 29%) and a further fraction contaminated with cinnamic acid ^{t}butyl ester (48.9 g, 53%).- $[\alpha]_D^{23}$ = -20.9 (c 0.22 in MeOH).- ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.79 (d, 3H, CH_3-Leu, $J_{\delta,\gamma}$ = 8 Hz), 0.82 (d, 3H, CH_3-Leu, $J_{\delta,\gamma}$ = 8 Hz), 1.45 (s, 9H, CH_3-^{t}butyl), 1.51-1.68 (m, 3H, C_βH-Leu, C_γH-Leu), 2.21 (s, 3H, NCH_3), 3.10 and 3.20 (AB part of an ABX system, 2H, C_βH-PheLac, $J_{\alpha,\beta}$ = 6 Hz, $J_{\alpha,\beta'}$ = 8 Hz, $|J_{\beta,\beta'}|$ = 16 Hz), 3.38 (dd, 1H, C_αH-Leu, $J_{\alpha,\beta}$ = 7 Hz, $J_{\alpha,\beta'}$ = 8 Hz) 3.52 and 3.75 (AB system, 2H, N-CH_2-Ph), 5.12 (X part of an ABX system, 1H, C_αH-PheLac), 7.2-7.4 (m, 10H, Ar-H).- ^{13}C NMR (125 MHz, $CDCl_3$, DEPT): δ = 21.93 (CH_3-Leu), 22.92 (CH_3-Leu), 24.43 (C_γH-Leu), 27.98 (CH_3-^{t}Bu), 37.48 (NCH_3), 37.55 ($C_\beta H_2$-PheLac), 38.71 ($C_\beta H_2$-Leu), 58.06 (N-CH_2-Ph), 63.33 (C_αH-Leu), 73.33 (C_αH-PheLac), 82.21 (C_q-^{t}Bu), 126.77, 126.91, 128.11, 128.38, 128.70, 129.40 (Ar-CH), 136.23 (Ar-C_q), 139.88 (Ar-C_q), 168.77 ($\underline{C}O_2{}^t$Bu), 172.42 ($\underline{C}O_2$Leu).- IR: 1738 cm^{-1} (C=O).- EI-MS: m/z (%) = 363 (1), 190 (100).- $C_{27}H_{37}NO_4$ (439), calc C 74.94, H 8.43, N 3.19; found C 74.27, H 8.38, N 3.14.

***tert.*-Butyl N-benzyl-N-methyl-(*S*)-leucyl-(*R*)-lactate (9)**

The cesium salt of leucine (77.7 g, 0.212 mol; prepared following the procedure described for compound **10**) and **6** (34.76 g, 0.212 mol) were stirred in DMSO (530 ml) for 20 h at 20°C. The reaction mixture was poured into brine and extracted with ethyl acetate. The organic layers were combined, washed with water, dried over Na_2SO_4, filtered and concentrated. The residue was chromatographed (cyclohexane-ethyl acetate 60:1) to give **9** (63.5 g, 82%).- $[\alpha]_D^{25}$ = -35.04 (c 2.09 in MeOH).- ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.85 (d, 3H, CH_3-Leu, $J_{\delta,\gamma}$ = 8 Hz), 0.92 (d, 3H, CH_3-Leu, $J_{\delta,\gamma}$ = 8 Hz), 1.50 (s and d, 12H, CH_3-^{t}butyl + CH_3-Lac), 1.52-1.80 (m, 3H, C_βH-Leu, C_γH-Leu), 2.32 (s, 3H, NCH_3), 3.44 (dd, 1H, C_αH-Leu, $J_{\alpha,\beta}$ = 8 Hz, $J_{\alpha,\beta'}$ = 9 Hz), 3.75 (AB-system, 2H, N-CH_2-Ph, J = 14 Hz), 4.97 (q, 1H, C_αH-Lac, $J_{\alpha,\beta}$ = 8 Hz), 7.20-7.38 (m, 5H, Ar-H).- ^{13}C NMR (125 MHz, $CDCl_3$, DEPT): δ = 17.18 (CH_3-Lac), 21.90 (CH_3-Leu), 23.07 (CH_3-Leu), 24.57 (C_γH-Leu), 28.02 (CH_3-^{t}butyl), 37.54 (NCH_3), 38.73 ($C_\beta H_2$-Leu), 58.23 (N-CH_2-Ph), 63.22 (C_αH-Leu), 69.10 (C_αH-Lac), 81.86 (C_q-^{t}butyl) 126.82, 128.16, 128.78 (Ar-CH), 139.89 (Ar-C_q), 169.97 ($\underline{C}O_2{}^t$Bu), 172.37 ($\underline{C}O_2$Leu).- IR: 1737cm^{-1} (C=O).- EI-MS: m/z (%) = 363 ($M^{+\cdot}$, 1), 250 (1), 190 (100).- $C_{21}H_{33}NO_4$ (363), calc C 69.42, H 9.09, N 3.86; found C 69.19, H 9.01, N 3.69.

N-Benzyl-N-methyl-(*S*)-leucyl-(*R*)-lactic acid (11)

Hydrogen chloride was bubbled through a solution of **9** (16.7 g, 46.0 mmol) in CH_2Cl_2 (470 ml) at 0°C for 2 h. The reaction mixture was then allowed to warm to 20°C and stirred for 12 h. The solvent was evaporated,

the residue dissolved in CH_2Cl_2 and concentrated again. This procedure was repeated and then the acid was dried under high vacuum to give **11** (13.5 g, 95%).- $[\alpha]_D^{22}$ = +16.6 (c 2.0 in MeOH).- ^{1}H NMR (500 MHz, MeOH-d_4): δ = 0.97 (2d, 6H, 2xCH_3-Leu), 1.58 (d, 3H, CH_3-Lac, $J_{\alpha,\beta}$ = 8 Hz), 1.74 (m, 1H,C_γH-Leu), 1.82 and 1.95 (m, 2H, C_βH-Leu), 2.29 (s, 3H, NCH_3), 4.10 (dd, 1H, C_αH-Leu, $J_{\alpha,\beta}$ = 5 Hz, $J_{\alpha,\beta'}$ = 12.5 Hz), 4.38 (AB system, 2H, N-CH_2-Ph), 5.23 (q, 1H, C_αH-Lac, $J_{\alpha,\beta}$ = 8 Hz), 7.47-7.53 (m, 5H, Ar-H).- ^{13}C NMR (125 MHz, MeOH-d_4, DEPT): δ = 17.23 (CH_3-Lac), 21.71 (CH_3-Leu), 23.41 (CH_3-Leu), 26.48 (C_γH-Leu), 37.60 ($C_\beta H_2$-Leu), 38.01 (NCH_3), 59.90 (N-CH_2-Ph), 65.56 (C_αH-Leu), 72.20 (C_αH-Lac), 130.19, 130.85, 132.07 (Ar-CH), 132.31 (Ar-C_q), 169.70 ($\underline{C}O_2{}^t$Bu), 178.30 ($\underline{C}O_2$Leu).- IR: 1746 (C=O), 2490-3420 cm^{-1} (OH).- EI-MS: m/z (%) = 307 ($M^{+\cdot}$, 0.5), 190 (72), 91 (100).- $C_{17}H_{25}NO_4$ (307 x HCl x 0.5 H_2O), calc C 57.95, H 7.67, N 3.98; found C 57.93, H 7.72, N 4.01.

***tert.*-Butyl N-methyl-(*S*)-leucyl-(*R*)-3-phenyllactate (12)**

10 (26.5 g, 60.0 mmol) and 20% $Pd(OH)_2$/C (2.91 g) were stirred in ethanol (165 ml) for 6 h at 20°C under hydrogen (atmospheric pressure). After filtration of the catalyst and evaporation of the solvent the residue was chromatographed (cyclohexane ethyl acetate 3:1) to give pure **12** (18.39 g, 88%).- $[\alpha]_D^{27}$ = +27.74 (c 2.03 in MeOH).- ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.80 (2d, 6H, CH_3-Leu), 1.30 (m, 2H, C_βH-Leu), 1.50 (m, 1H, C_γH-Leu), 1.43 (s, 9H, CH_3-^{t}butyl), 2.28 (s, 3H, NCH_3), 3.05 (AB part of an ABX system, 1H, C_βH-PheLac, $J_{\alpha,\beta}$ = 12 Hz, $|J_{\beta,\beta'}|$ = 16 Hz), 3.20 (m, 3H, C_βH'-PheLac and C_αH-Leu), 5.12 (X part of an ABX system, 1H, C_αH-PheLac, $J_{\alpha,\beta'}$ = 5 Hz), 7.2-7.4 (m, 5H, Ar-H).- ^{13}C NMR (125 MHz, $CDCl_3$, DEPT): δ = 22.35 (CH_3-Leu), 22.60 (CH_3-Leu), 24.68 (C_γH-Leu), 27.90 (CH_3-^{t}Bu), 34.60 (NCH_3), 37.40 ($C_\beta H_2$-PheLac), 42.58 ($C_\beta H_2$-Leu), 61.53 (C_αH-Leu), 73.47 (C_αH-PheLac), 82.23 (C_q-^{t}Bu), 126.90, 128.40, 129.28 (Ar-CH), 136.22 (C-Ar), 168.57 ($\underline{C}O_2{}^t$Bu), 175.25 ($\underline{C}O_2$Leu).- IR: 1740 (C=O), 3300 cm^{-1} (NH).- EI-MS: m/z (%) = 349 ($M^{+\cdot}$, 1), 276 (2), 100 (100).- $C_{20}H_{31}NO_4$ (349), calc C 68.77, H 8.88, N 4.01; found C 68.63, H 8.99, N 4.17.

***tert.*-Butyl N-benzyl-N-methyl-(*S*)-leucyl-(*R*)-lactyl-N-methyl-(*S*)-leucyl-(*R*)-3-phenyllactate (2)**

12 (8.0 g, 22.9 mmol) and **11** (8.44 g, 27.5 mmol) were dissolved in CH_2Cl_2 (80 ml). Diisopropylethylamine (9.98 ml, 57.3 mmol) and BOP-Cl (7.59 g, 29.8 mmol) were then added at 0°C. The reaction mixture was stirred 1 h at 0°C and 1 h at 20°C. After filtration the solution was diluted with CH_2Cl_2, washed with water, dried over Na_2SO_4 and concentrated. LPLC (cyclohexane-ethyl acetate 15:1) furnished **2** (11.6 g, 80%).- $[\alpha]_D^{27}$ = -42.2 (c 1.05 in MeOH).- ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.83 (d, 3H, CH_3-Leu, J = 5.5 Hz), 0.85-1.00 (d, 9H, CH_3-Leu), 1.33-1.46 (m, 4H, C_βH-Leu), 1.38 (s, 9H, CH_3-^{t}butyl), 1.50 (d, 3H, CH_3-Lac, J = 6.5 Hz), 1.52-1.80 (m, 2H, C_γH-Leu), 2.30, 2.32 (s, 3H, NCH_3), 2.84, 3.00 (s, 3H, $CONCH_3$), 3.18 (d, 1H, C_βH-PheLac, $J_{\alpha,\beta}$ = 3 Hz), 3.02-3.23 (m, 1H, C_βH'-PheLac), 3.45 and 3.51 (2 dd, 1H, C_αH-Leu, $J_{\alpha,\beta}$ = 5 Hz, $J_{\alpha,\beta'}$ = 10 Hz), 3.78 (AB system, 2H, N-CH_2-Ph), 4.51 and 5.33 (2 dd, 1H, C_αH-Leu), 5.07 and 5.13 (2dd, 1H, C_αH-PheLac, $J_{\alpha,\beta}$ = 5 Hz, $J_{\alpha,\beta'}$ = 10 Hz), 5.50 (q, 1H, C_αH-Lac, J = 7 Hz), 7.2-7.5 (m, 10 H, Ar-H).- ^{13}C NMR (125 MHz, $CDCl_3$, DEPT): δ = 16.91 (CH_3-Lac), 21.20, 21.65, 23.02, 23.22, 24.43, 24.79 (CH_3-Leu, C_γH-Leu), 27.78 (CH_3-^{t}Bu), 31.29 (NCH_3), 36.97, 37.22, 38.61 ($C_\beta H_2$-Leu, $C_\beta H_2$-PheLac), 37.43 (NCH_3), 54.97 (C_αH-Leu), 58.28 (N-CH_2-Ph), 63.54 (C_αH-Leu), 67.02 (C_αH-Lac), 74.39 (C_αH-PheLac), 82.31 (C_q-^{t}Bu), 126.61, 126.80, 127.98, 128.22, 128.64, 129.62 (Ar-CH), 135.97, 139.83 (Ar-C_q), 168.11, 170.77, 171.10, 172.44 (C=O).- IR: 1670 (C=O, amide), 1738 cm^{-1} (C=O, ester). FAB-MS: m/z (%) = 639 $(M+H)^+$, 190 (100).- $C_{37}H_{54}N_2O_7$ (638), calc C 69.59, H 8.46, N 4.39; found C 69.38, H 8.40, N 4.18.

N-Benzyl-N-methyl-(*S*)-leucyl-(*R*)-lactyl-N-methyl-(*S*)-leucyl-(*R*)-3-phenyllactic acid (13)

Hydrogen chloride was bubbled through a solution of **2** (5.46 g, 8.56 mmol) in CH_2Cl_2 (150 ml) for 2 h at 0°C.

The reaction mixture was allowed to warm to 20°C and stirred for 12 h. After concentrating the solution, the material was taken up again in CH_2Cl_2 and evaporated. This procedure was repeated twice. The residue was dissolved in methanol and stirred with basic ion exchanger (15 g DOWEX 1-X4) for 4 h and filtered. The filtrate was concentrated and dried under high vacuum affording **13** (4.1 g, 80%).- $[\alpha]_D^{27}$ = +56.78 (c 2.02 in MeOH).- ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.80-1.00 (m, 12H, CH_3-Leu), 1.35-1.80 (m, 6H, C_βH-Leu, C_γH-Leu), 1.32 and 1.47 (d, 3H, CH_3-Lac, J = 8 Hz), 2.49 (s, 3H, NCH_3), 2.72 and 2.92 (s, 3H, $CONCH_3$), 3.08 and 3.30 (AB part of an ABX system, 2H, C_βH-PheLac, C_βH'-PheLac, $J_{\alpha,\beta}$ = 5 Hz, $J_{\alpha,\beta'}$ = 9 Hz), 3.75 and 3.86 (dd, 1H, C_αH-Leu, J = 5 Hz), 4.15 (AB system, N-CH_2-Ph), 4.48 and 5.22 (m, 2H, C_αH-Leu, C_αH-PheLac), 5.35 and 5.49 (q, C_αH-Lac, J = 8 Hz), 7.15-7.45 (m, 10 H, Ar-H).- ^{13}C NMR (125 MHz, $CDCl_3$): δ = 16.49 (CH_3-Lac), 21.52, 21.88, 22.68, 23.13, 24.93, 25.13 (CH_3-Leu, C_γH-Leu), 31.39 (NCH_3), 36.58 (NCH_3), 36.87, 37.16, 37.37 ($C_\beta H_2$-Leu, $C_\beta H_2$-PheLac), 55.03 (C_αH-Leu), 57.83 (N-CH_2-Ph), 62.53 (C_αH-Leu), 68.08 (C_αH-Lac), 74.31 (C_αH-PheLac), 126.70, 128.32, 128.38, 128.44, 128.49, 128.63, 129.30, 129.54, 130.42 (Ar-CH, Ar-C_q), 137.03 (Ar-C_q), 170.39, 170.48, 172.21 (C=O).- IR: 1662 (C=O, amide), 1748 (C=O, acid), 2600-3400 cm^{-1} (OH). FAB-MS: m/z (%) = 583 $(M+H)^+$, 539, 493, 435, 190.- $C_{33}H_{46}N_2O_7$ (582).

***tert.*-Butyl N-methyl-(*S*)-leucyl-(*R*)-lactyl-N-methyl-(*S*)-leucyl-(*R*)-3-phenyllactate (14)**

2 (6.08 g, 9.53 mmol) was dissolved in ethanol (37 ml), 20% $Pd(OH)_2$/C (0.6 g) was added and the mixture hydrogenated at 20°C until the hydrogen uptake ceased. The reaction mixture was filtered and concentrated. The residue was purified by chromatography (^{t}BuOMe-cyclohexane-ethanol 1:1:0.05), furnishing **14** (3.87 g, 74%).- $[\alpha]_D^{23}$ = +7.6 (c 1.99 in MeOH).- ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.75-1.08 (m, 12H, CH_3-Leu), 1.30-1.85 (m, 6H, C_βH-Leu, C_γH-Leu), 1.41 (s, 9H, CH_3-^{t}butyl), 1.45 (d, 3H, CH_3-Lac, J = 7 Hz), 2.39 (s, 3H, NCH_3), 2.81 and 2.95 (s, 3H, $CONCH_3$), 3.12 (d, 2H, C_βH-PheLac, J = 8 Hz), 3.30 (m, 1H, C_αH-Leu), 5.08 (dd, 1H, C_αH-PheLac, J = 6 Hz), 5.33 (m, 1H, C_αH-Leu), 5.50 (q, 1H, C_αH-Lac, J = 8 Hz), 7.2-7.4 (m, 5H, Ar-H).- ^{13}C NMR (125 MHz, $CDCl_3$, DEPT): δ = 16.79 (CH_3-Lac), 21.27, 22.31, 22.73, 23.32, 24.87, 24.95 (CH_3-Leu, C_γH-Leu), 27.91 (CH_3-^{t}Bu), 31.19 (NCH_3), 34.72 (NCH_3), 37.01, 37.31, 42.53 ($C_\beta H_2$-Leu, $C_\beta H_2$-PheLac), 54.58 (C_αH-Leu), 61.34 (C_αH-Leu), 67.18 (C_αH-Lac), 74.10 (C_αH-PheLac), 82.38 (C_q-^{t}Bu), 126.94, 128.33, 129.71 (Ar-CH), 136.08 (Ar-C_q), 168.22, 170.84, 170.96, 175.32 (C=O).- IR: 1658 (C=O, amide), 1738 (C=O, ester), 3340-3440 cm^{-1} (NH). FAB-MS: m/z (%) = 549 $(M+H)^+$, 493.- $C_{30}H_{48}N_2O_7$ (548 x EtOH), calc C 64.65, H 9.09, N 4.71; found C 64.70, H 8.89, N 4.67.

***tert.*-Butyl N-benzyl-N-methyl-(*S*)-leucyl-(*R*)-lactyl-N-methyl-(*S*)-leucyl-(*R*)-3-phenyllactyl-N-methyl-(*S*)-leucyl-(*R*)-lactyl-N-methyl-(*S*)-leucyl-(*R*)-3-phenyllactate (15)**

14 (1.38 g, 2.52 mmol) and **13** (1.46 g, 2.52 mmol) were dissolved in CH_2Cl_2 (15 ml), diisopropylethylamine (0. 159 ml, 0.912 mmol) and BOP-Cl (111.5 mg, 0.438 mmol) were added at 0°C and the reaction mixture was stirred for 1.5 h at 0°C. The solution was diluted with CH_2Cl_2, washed with water, dried over Na_2SO_4 and concentrated. Chromatography (cyclohexane-^{t}BuOMe 2:1) of the crude material gave **15** (2.18 g, 79%).- $[\alpha]_D^{27}$ = -62.67 (c 1.01 in MeOH).- ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.80-1.03 (m, 24H, CH_3-Leu), 1.30-1.50 (m, 15H, CH_3-Lac, CH_3-^{t}butyl), 1.52-1.76 (m, 12H, C_βH-Leu, C_γH-Leu), 2.30 (s, 3H, NCH_3), 2.80-3.22 (m, 13H, C_βH-PheLac, $CONCH_3$), 3.42-3.53 (m, 1-H, C_αH-Leu), 3.76 (AB system, 2H, N-CH_2-Ph), 5.05-5.57 (m, 7H, C_αH-Leu, C_αH-Lac, C_αH-PheLac), 7.16-7.38 (m, 15H, Ar-H).- ^{13}C NMR (125 MHz, $CDCl_3$, DEPT): δ = 16.53, 16.98 (CH_3-Lac), 21.30, 21.35, 21.37, 21.78, 23.15, 23.20, 23.31, 23.38, 24.52, 24.56, 24.92 (CH_3-Leu, C_γH-Leu), 27.94 (CH_3-^{t}Bu), 31.13, 31.66, 31.72 (NCH_3), 37.09, 37.12, 37.17, 37.21, 37.78, 38.74 ($C_\beta H_2$-Leu, $C_\beta H_2$-PheLac), 37.59 (NCH_3), 54.43, 54.98 (C_αH-Leu), 58.02 (N-CH_2-Ph), 63.33 (C_αH-Leu), 66.91, 67.97 (C_αH-Lac), 72.21, 74.22 (C_αH-PheLac), 82.32 (C_q-^{t}Bu), 126.73, 126.89, 127.07, 128.11, 128.29, 128.57,

128.73, 128.77, 128.90, 129.29, 129.61, 129.81 (Ar-CH), 135.81, 136.27, 140.00 (Ar-C_q), 170.38, 170.59, 170.74, 170.95, 171.27, 172,54 (C=O).- IR: 1667 (C=O, amide), 1739 cm^{-1} (C=O, ester).- FAB-MS: m/z (%) = 1113 $(M+H)^+$, 1023, 909, 710.- $C_{63}H_{92}N_4O_{13}$ (1112), calc C 67.98, H 8.27, N 5.03; found C 67.95, H 8.50, N 5.00.

N-Benzyl-N-methyl-(*S*)-leucyl-(*R*)-lactyl-N-methyl-(*S*)-leucyl-(*R*)-3-phenyllactyl-N-methyl-(*S*)-leucyl-(*R*)-lactyl-N-methyl-(*S*)-leucyl-(*R*)-3-phenyllactic acid (16)

Applying the procedure described for the compounds **11** and **13** afforded crude **16** which was dissolved in water-methanol 1:1 and stirred for 3 h at 20°C with basic ion exchanger (1.0 g Dowex 1-X4). The solution was filtered, concentrated and dried under high vacuum to give **16** (1.65 g, 95%).- FAB-MS: m/z (%) = 1057 ($M^{+\cdot}$), 967, 909.- $C_{59}H_{84}N_4O_{13}$ (1057).

N-Methyl-(*S*)-leucyl-(*R*)-lactyl-N-methyl-(*S*)-leucyl-(*R*)-3-phenyllactyl-N-methyl-(*S*)-leucyl-(*R*)-lactyl-N-methyl-(*S*)-leucyl-(*R*)-3-phenyllactic acid (17)

A solution of **16** (1.29 g, 1.222 mmol) in ethanol (50 ml) was hydrogenated in the presence of 20% $Pd(OH_2)$/C (200 mg) at 20°C until the hydrogen uptake stopped (2 h). Filtration of the catalyst and evaporation of the solvent afforded crude **17** (1.09 g, 92%) which was used without further purification.- $[\alpha]_D^{27}$ = -32.00 (c 1.06 in MeOH).- ^1H NMR (500 MHz, $CDCl_3$): δ = 0.78-1.05 (m, 24H, CH_3-Leu), 1.30-1.85 (m, 12H, $C_\beta H$-Leu, $C_\gamma H$-Leu), 1.47, 1.52 (2 d, 6H, CH_3-Lac, J = 8 Hz), 2.58-3.40 (m, 16H, $C_\beta H$-PheLac, NCH_3), 3.32 (2 dd, $C_\alpha H$-Leu), 3.71 (q, 1H, $C_\alpha H$-Lac), 3.91 (m, 1H, $C_\alpha H$-Leu), 4.95-5.53 (m, 6H, $C_\alpha H$-Leu, $C_\alpha H$-Lac, $C_\alpha H$-PheLac), 7.18-7.35 (m, 10H, Ar-H).- ^{13}C NMR (125 MHz, $CDCl_3$, DEPT): δ = 16.10, 16.18 (CH_3-Lac), 21.33, 21.39, 21.42, 21.65, 22.93, 23.02, 24.69, 24.75, 25.05, 25.12 (CH_3-Leu, $C_\gamma H$-Leu), 31.07, 32.99 (NCH_3), 36.11, 36.99, 37.24, 37.26, 37.31, 38.78 ($C_\beta H_2$-Leu, $C_\beta H_2$-PheLac), 54.19, 55.08 ($C_\alpha H$-Leu), 60.35 ($C_\alpha H$-Leu), 67.93, 69.34 ($C_\alpha H$-Lac), 72.53, 72.94 ($C_\alpha H$-PheLac), 126.79, 127.21, 128.34, 128.53, 128.61, 129.33, 129.41, 129.61 (Ar-CH), 135.49, 136.66 (Ar-C_q), 169.44, 179.22, 170.27, 170.52, 170.99, 171.28, 171.32 (C=O).- IR: 1665 (C=O, amide), 1745 (C=O, ester), 3300-3500 cm^{-1} (OH).- FAB-MS: m/z (%) = 967 $(M+H)^+$, 923.- $C_{52}H_{78}N_4O_{13}$ (966).

Pentafluorophenyl N-benzyl-N-methyl-(*S*)-leucyl-(*R*)-lactyl-N-methyl-(*S*)-leucyl-(*R*)-3-phenyllactyl-N-methyl-(*S*)-leucyl-(*R*)-lactyl-N-methyl-(*S*)-leucyl-(*R*)-3-phenyllactate (18)

To a solution of **16** (500 mg, 0.473 mmol) in pyridine (5 ml) was added pentafluorophenol trifluoracetate[27] (97.6 µl, 0.568 mmol) at 0°C. The reaction mixture was allowed to warm to 20°C, stirred for 3 h at this temperature and then concentrated. The residue was codistilled with toluene (3x) and taken up in CH_2Cl_2. This solution was washed with 5% aq. $NaHCO_3$ solution. The crude product **18** (576 mg, 98%) was used without further purification.- FAB-MS: m/z (%) = 1057 $(M\text{-}Pfp)^+$, 967, 909, 864, 819.- IR: 1666 (C=O, amide), 1743 (C=O, ester), 1801 cm^{-1} (C=O, Pfp-ester).- $C_{65}H_{83}F_5N_4O_{13}$ (1222).

N-*tert.*-Butoxycarbonyl-N-methyl-(*S*)-leucyl-(*R*)-lactyl-N-methyl-(*S*)-leucyl-(*R*)-3-phenyllactyl-N-methyl-(*S*)-leucyl-(*R*)-lactyl-N-methyl-(*S*)-leucyl-(*R*)-3-phenyllactic acid (19)

BOC_2O (200 µl, 0.869 mmol) was added at 0°C to a solution of **17** (700 mg, 0.725 mmol) in dioxane (2 ml), water (1 ml) and 1N NaOH (1 ml). The reaction mixture was stirred for 5 min at 0°C and then at 20°C for 5 h. An additional amount of BOC_2O (50 µl) and 1N NaOH were added and stirring was continued for 30 min. Ethyl acetate was added and the solution was acidified to pH 2-3 with aq. $KHSO_4$. The layers were separated and the aqueous layer extracted with ethyl acetate. The combined organic layers were dried and concentrated

to give the crude product **19** (770 mg, 99%), which was used without further purification.- FAB-MS: m/z (%) = 1065 $(M-H)^-$, 967 $(M-Boc)^+$.- $C_{57}H_{86}N_4O_{15}$ (1066).

Pentafluorophenyl N-*tert.*-butoxycarbonyl-N-methyl-(*S*)-leucyl-(*R*)-lactyl-N-methyl-(*S*)-leucyl-(*R*)-3-phenyl-lactyl-N-methyl-(*S*)-leucyl-(*R*)-lactyl-N-methyl-(*S*)-leucyl-(*R*)-3-phenyllactate (20)

Trifluoroacetic acid (85.7 µl, 0.499 mmol) was added at 0°C to a solution of **19** (442.8 mg, 0.416 mmol) in pyridine (4 ml). The reaction mixture was stirred at 0°C for 30 min and 1 h at 20°C, after which time additional trifluoroacetic acid (85 µl) was added and the solution stirred for a further 30 min. After evaporation of the solvent, the residue was codistilled with toluene (3x) and dried under high vacuum. LPLC (silica gel dried by heating to 250°C and cooling under argon) with the eluent cyclohexane-ethyl acetate 3:1 afforded pure **20** (162.2 mg, 32%) and several decomposition products. FAB-MS: m/z (%): 1233 $(M+H)^+$, 1133 $(M-BOC)^+$, 1065 $(M-Pfp)^+$, 967 $(M-BOC-PfP)^+$, 917.- $C_{63}H_{85}F_5N_4O_{15}$ (1232).

Cyclooctadepsipeptide PF1022A

1. Schmidt cyclization, hydrogenation variant

Pd/C (10%, 1.0 g) was suspended in a solution of pyrrolidinopyridine (67.3 mg, 0.454 mmol) in dioxane (550 ml) and ethanol (1.1 ml). To this suspension was injected within 6 h a solution of **18** (554.8 mg, 0.454 mmol) in dioxane (37 ml) at 90-100°C. During the addition hydrogen was passed through the reaction mixture under vigorous stirring. After cooling to 20°C the solution was filtered, the catalyst washed with dioxane (3x), and the solvent evaporated. LPLC (cyclohexane-^{t}BuOMe 1:1) of the residue afforded slightly impure PF1022A (197 mg, 46%), which was chromatographed again with the eluent toluene-isopropanol 10:1 to give pure PF1022A (121.7 mg, 28%) and a second fraction (45.3 mg) contaminated with unidentified byproducts.

2. Schmidt cyclization, two-phase variant

A solution of **20** (160.0 mg, 0.129 mmol) in CH_2Cl_2 (5 ml) and trifluoroacetic acid (2 ml) were stirred for 1 h at 0°C. The reaction mixture was concentrated, the residue dried under high vacuum, and dissolved in CH_2Cl_2 (3 ml). This solution was injected into a vigorously stirred mixture of chloroform (3 ml) and 1N aq. K_2CO_3 (3 ml) and stirred at 20°C. After 12 h, TLC showed the formation of a small amount of PF1022A accompanied by decomposition products. Consequently, no product isolation was performed.

3. EDC/HOBt - Cyclization

EDC (39.7 mg, 0.207 mmol) and HOBt (56.0 mg, 0.414 mmol) were dissolved in CH_2Cl_2 (100 ml), **17** (100.0 mg, 0.104 mmol) was added at 0°C and the reaction mixture was stirred for 48 h at 20°C. The solution was washed with saturated aq. $NaHCO_3$, dried (Na_2SO_4) and concentrated. LPLC of the residue (toluene-isopropanol 10:1) afforded PF1022A (57.7 mg, 59%).

4. BOP-Cl - Cyclization

BOP-Cl (31.6 mg, 0.124 mmol) was added at 0°C to a solution of **17** (100.0 mg, 0.104 mmol) and diisopropylethylamine (45.0 µl, 0.258 mmol) in CH_2Cl_2 (100 ml). After stirring for 24 h at 20°C more BOP-Cl (31.6 mg, 0.124 mmol) and diisopropylethylamine (45 µl, 0.258 mmol) were added and stirring was continued for another 24 h. The solution was then washed with saturated aq. $NaHCO_3$, dried (Na_2SO_4), and concentrated producing a white foam. LPLC of this material (toluene-isopropanol 10:1) afforded pure PF1022A (85.0 mg, 87%). The ^1H and ^{13}C NMR spectra were identical with the published spectra.- $[\alpha]_D^{23}$ = -99.2 (c 2.02 in MeOH).-

^{1}H NMR (500 MHz, DMSO): δ = 0.68-0.95 (m, 15H, CH_3-Leu, CH_3-Lac), 1.15-1.75 (m, 12H, C_βH-Leu, C_γH-Leu), 1.28 (d, 3H, CH_3-Lac, J = 10 Hz), 2.68, 2.77, 2.80, 2.85, 2.91 (s, 12H, NCH_3), 3.05 (m, 2H C_βH-Phe-Lac), 4.41, 5.11, 5.22 (dd, m, dd, 4H, C_αH-Leu), 5.01, 5.32, 5.42 (3q, 2H, C_αH-Lac), 5.52, 5.68, 5.71 (dd, t, t, 2H, C_αH-PheLac), 7.20-7.35 (m, 5H, Ar-H).- ^{13}C NMR (125 MHz, DMSO, DEPT): δ = 15.51, 16.34, 16.84 (CH_3-Lac), 20.37, 20.59, 20.77, 20.80, 20.87, 20.99, 22.99, 23.07, 23.18, 23.22, 23.35, 23.87, 24.16, 24.27, 24.33, 24.41, 28.88, 30.07, 30.14, 30.22, 30.28, 30.57 (CH_3-Leu, NCH_3, C_γH-Leu), 35.66, 36.28, 36.51, 36.55, 36.69, 36.72, 36.83, 37.14, 37.29 ($C_\beta H_2$-Leu, $C_\beta H_2$-PheLac), 53.03, 53.21, 53.29, 56.36 (C_αH-Leu), 66.71, 67.47, 67.72 (C_αH-PheLac), 70.11, 70.85, 71.04 (C_αH-Lac), 126.66, 126.72, 126.78, 128.11, 128.17, 128.19, 129.45 (Ar-CH), 135.14, 135.23, 135.92 (Ar-C_q), 168.96, 169.05, 169.27, 169.53, 169.69, 170.21, 170.29, 170.65, 170.86 (C=O).- IR: 1658 (C=O, amide), 1754 cm^{-1} (C=O, ester). FAB-MS: m/z (%) = 949 $(M+H)^+$, 921, 903, 835, 819.- $C_{52}H_{76}N_4O_{12}$ (948), calc C 65.82, H 8.02, N 5.91; found C 65.29, H 8.10, N 5.78.

Acknowledgements: We thank Meiji Seika Kaisha Ltd. for providing us with an authentic sample of PF1022A and Dr. D. Gondol for his help in interpreting the NMR spectra.

REFERENCES AND NOTES

Dedicated to Professor H.-D. Scharf on the occasion of his 65th birthday

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(*Received in Germany* 27 *April* 1995; *accepted* 9 *June* 1995)