

58. Synthesis of Cyclic Depsipeptides and Peptides via Direct Amide Cyclization

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Dedicated to Professor Dr. Hans-Jürgen Hansen on the occasion of his 60th birthday

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The 2,2-disubstituted 2*H*-azirin-3-amines **7** (2,2-disubstituted 3-amino-2*H*-azirines) were used as amino-acid synthons in the preparation of medium-sized cyclic depsipeptides and peptides derived from salicylic acids **6** and anthranilic acid **19**, respectively (*Schemes 2–4* and *5*, resp.). The combination of the 'azirine/oxazolone method' for the synthesis of linear peptides containing α,α -disubstituted α -amino acids and the acid-catalyzed amide cyclization in DMF at 60° proved to be an excellent preparative route to ten-membered cyclic depsipeptides and peptides. In the case of the anthranilic-acid derivative, a transannular ring-closure reaction was observed (**24** $\rightarrow$ **25**). Larger rings proved to be extremely sensitive to hydrolysis.

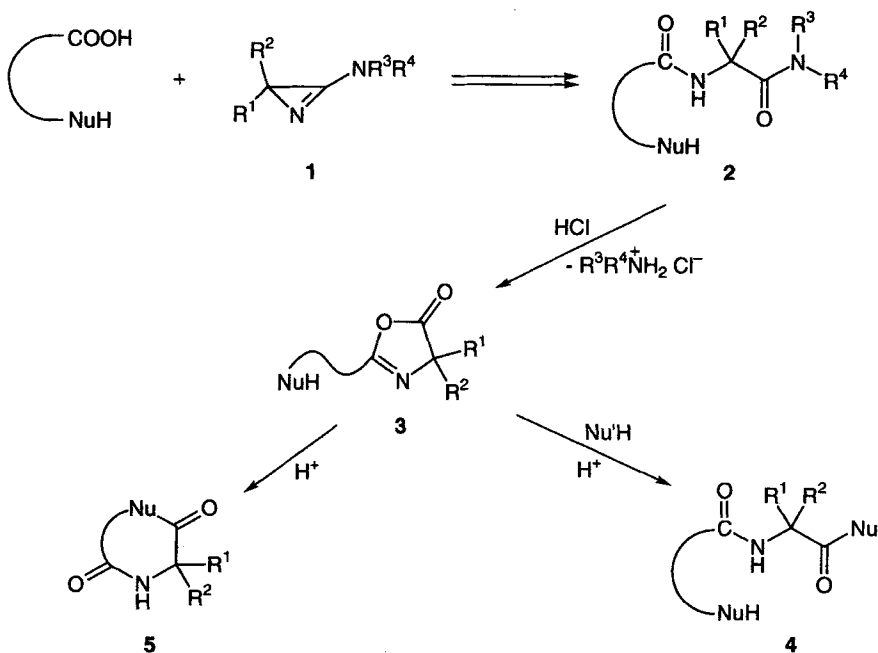
1. Introduction. – As already shown, 2,2-disubstituted 2*H*-azirin-3-amines (3-amino-2*H*-azirines) are useful synthons in peptide chemistry [1–7] as well as in heterocyclic chemistry [2] [8–12]. The so-called 'azirine/oxazolone method' [13] has been shown to be particularly useful in the synthesis of peptaibols (*cf.* [3] [7] [14]) and in the synthesis of conformationally restricted cyclic peptides [4] (*cf.* [2]). A further application is the synthesis of cyclic depsipeptides by the so-called 'direct amide cyclization' [15]. The concept of the latter is shown in *Scheme 1*: Condensation of a carboxylic acid, bearing a nucleophilic group, with a 2*H*-azirine-3-amine **1**, leads to the corresponding diamide of type **2** that, on treatment with dry HCl, affords the corresponding 1,3-oxazol-5(4*H*)-one **3**. Under the acidic conditions, this intermediate can be attacked by a nucleophile leading to **4** *via* ring opening. In the absence of an external nucleophile, suitable substrates are able to undergo an intramolecular nucleophilic attack yielding the ring-enlarged products of type **5**.

So far, ten-membered cyclodepsipeptides and cyclotriptides containing a β -hydroxy or β -amino acid have received little attention [16–18]. The synthesis of this class of compounds has been achieved either by the incorporation of a β -hydroxy- or β -amino-acid residue into piperidin-2-ones *via* ring enlargement [19] [20] (*cf.* also [21]) or by cyclization of the linear precursor *via* the 'active-ester method' [22–24]. Recently, the preparation of ten-membered cyclotriptides has also been reported by *Rothe* and coworkers [25].

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Scheme 1



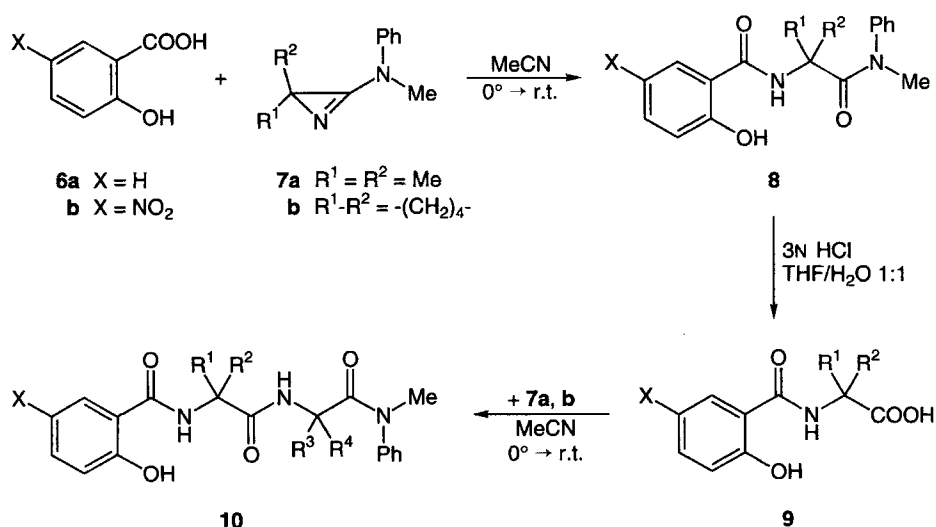
Based on these precedents, it was of interest to apply a combination of the 'azirine/oxazolone method' and the 'direct amide cyclization' procedure in order to obtain medium-sized cyclodepsipeptides and peptides, and to find suitable conditions for an efficient cyclization.

2. Results and Discussion. – The first β -hydroxy acids selected were salicylic acids **6** ($X = H, NO_2$; Scheme 2). The reaction with *N*-methyl-*N*-phenyl-2*H*-azirin-3-amines **7** in dry MeCN at 0° led to diamides **8**, isolated in very high yield after a simple filtration of the resulting solid. Hydrolysis under standard conditions with 3*N* HCl in THF/ H_2O at room temperature gave the corresponding carboxylic acids **9** in nearly quantitative yield. These acids were further condensed with a second 2*H*-azirin-3-amine **7** under the same conditions, yielding the corresponding salicyloyl-dipeptides of type **10** (80–85% overall yield; Table 1).

Table 1. Prepared Salicyloyl-peptides **8** and **10**

	R^1, R^2	R^3, R^4	X	Yield [%]
8a		Me, Me	–	H99
b	$-(CH_2)_4-$	–	H	94
c	Me, Me	–	NO_2	89
10a	Me, Me	Me, Me	H	91
b	Me, Me	$-(CH_2)_4-$	H	90
c	$-(CH_2)_4-$	$-(CH_2)_4-$	H	98
d	$-(CH_2)_4-$	Me, Me	H	98
e	Me, Me	Me, Me	NO_2	87

Scheme 2



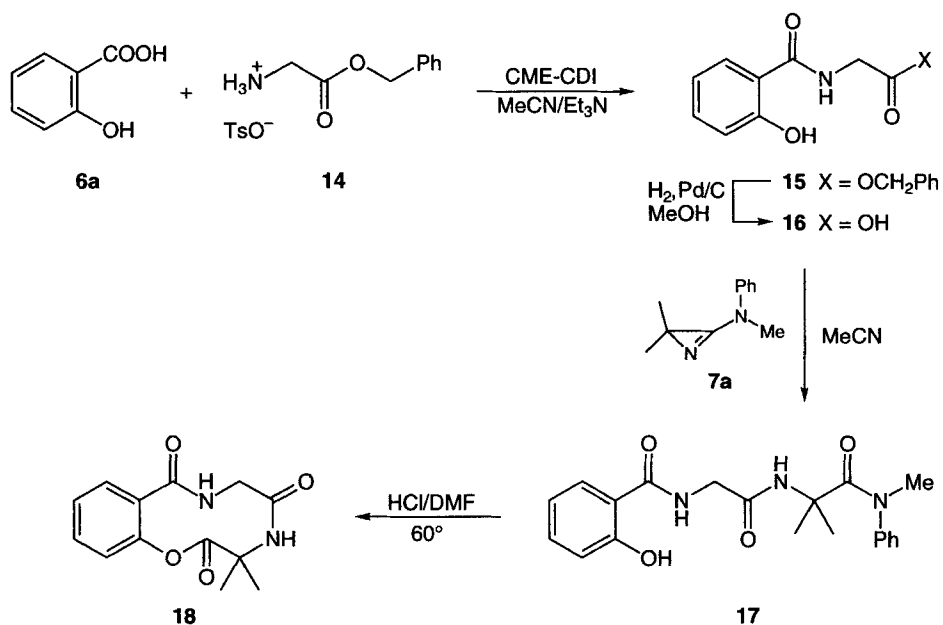
Treatment of solutions of **10** in dry DMF with dry HCl gas at 60° for 10–30 min and stirring for another hour under N₂ gave the corresponding 1,4,7-benzoxadiazecine-2,5,8-triones **11** in high yields (*Scheme 3, Table 2*). These compounds were isolated as colorless powders (except for **11e**, which was slightly yellow) after simple chromatographic workup and generally showed a strong tendency to be hydrolyzed to the corresponding open-chain carboxylic acids. Most likely, the formation of **11** occurred *via* the corresponding oxazol-5(4*H*)-ones **12** as reactive intermediates, followed by an intramolecular nucleophilic attack of the aromatic OH group onto C(5) of the oxazolone ring (*Scheme 3*).

Table 2. Prepared Cyclic Depsipeptides of Type **11**

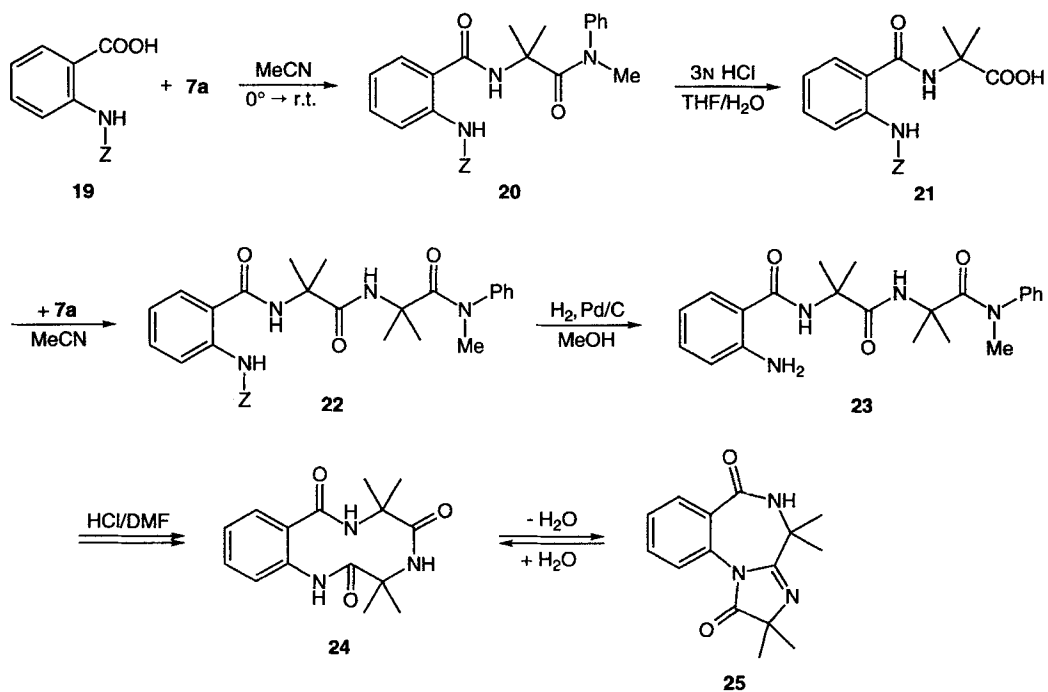
	R ¹	R ²	R ³	R ⁴	X	Yield [%]
11a		Me	Me	Me	Me	H92
b	Me	Me	-(CH ₂) ₄ -		H	96
c		-(CH ₂) ₄ -	-(CH ₂) ₄ -		H	93
d		-(CH ₂) ₄ -	Me	Me	H	95
e	Me	Me	Me	Me	NO ₂	88

It is worth mentioning that no C=O absorption for the lactone group could be observed in the IR spectra (KBr) of compounds **11a–e**. In addition to the strong bands at *ca.* 1630 and 1605 cm⁻¹ for the lactam groups, a strong and broad band appeared at 3400 cm⁻¹, indicating the presence of NH and/or OH groups. On the other hand, three C=O signals were present in the ¹³C-NMR spectra (CDCl₃; *ca.* 183, 176, and 169 ppm), and the ¹H-NMR spectra ((D₆)DMSO) showed two signals for NH. The two Me₂C groups of **11a** appeared in the ¹H-NMR spectrum as two *s* at 1.46 and 1.40 ppm and in

Scheme 4



Scheme 5



with another unit of **7a** to give the protected tripeptide **22**. Deprotection of the amino group by hydrogenolysis (Pd/C in MeOH) led to compound **23** that was cyclized on treatment with HCl gas in DMF at 60° yielding the heterobicyclic compound **25** (Scheme 5). The formation of **25** can be rationalized by a transannular ring closure of the initially formed **24** followed by elimination of H₂O. It is worth mentioning that the analogous cyclic peptide cyclo(-*N*-methylantraniloyl-L-phenylalanyl-L-prolyl-), whose structure has been established by X-ray crystallography, is stable as the ten-membered ring [29].

Compound **25** was isolated as a colorless solid, and its structure was deduced on the basis of the IR and mass spectra. An interesting effect was observed while recording the ¹H-NMR spectrum of **25**. Because of the partial insolubility in DMSO, the suspension was heated to 65–75°; at this temperature, a slightly cloudy solution was still present, but it was possible to record the ¹H-NMR spectrum. The latter indicated the presence of a 1:2 mixture of **24** and **25**. Obviously, **24** resulted from the addition of H₂O to **25**. Further heating to 100° led to a clear solution and to complete hydration of **25**. Under these conditions, the spectrum of **24** was obtained exclusively. The structure of **25** was established by X-ray crystallography (Fig. 1).

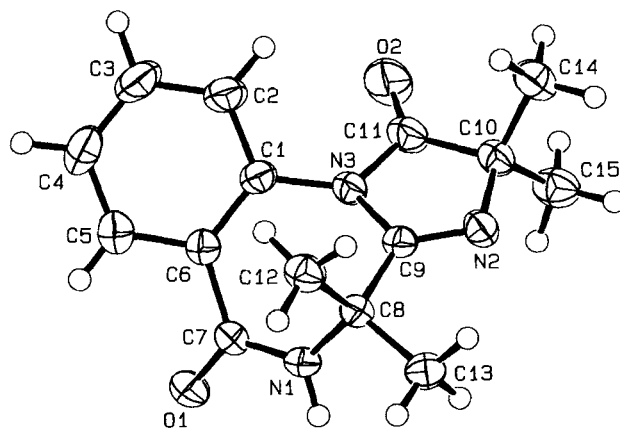
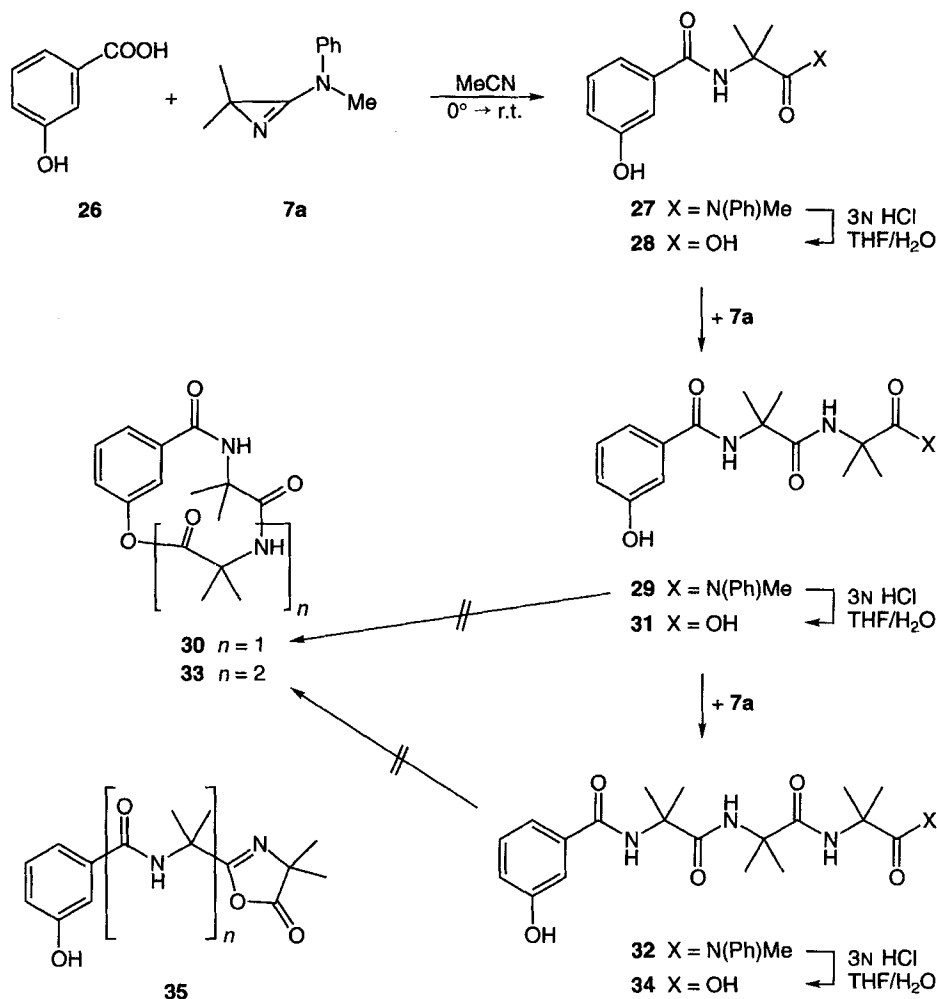


Fig. 1. ORTEP Plot [30] of the molecular structure of **25** (with 50% probability ellipsoids)

Another hydroxy acid selected for synthesizing cyclodepsipeptides was 3-hydroxybenzoic acid (**26**). Its reaction with aziramine **7a** yielded the diamide **27**, which was selectively transformed to the carboxylic acid **28** and further condensed with **7a** to give the hydroxy-tripeptide **29** (Scheme 6). All attempts to cyclize **29** under acidic conditions to the eleven-membered ring **30** failed. Only the corresponding carboxylic acid **31** was isolated.

Condensation of **31** with a third aziramine unit **7a** yielded tetrapeptide **32** that we tried to cyclize under standard conditions (DMF/HCl at 60°). However, after workup, the carboxylic acid **34** was obtained in 87% yield instead of the cyclic depsipeptide **33**. The structure of **34** was deduced from its spectroscopic data. As suitable crystals were

Scheme 6



obtained from MeOH by slow evaporation of the solvent, the structure was confirmed by X-ray crystallography (Fig. 2).

Based on the present results, two possible pathways for the formation of the carboxylic acids **31** and **34** instead of the expected cyclic depsipeptides **30** and **33**, respectively, can be proposed. In analogy to many other reactions studied, the primary formation of a terminal 1,3-oxazol-5(4*H*)-one intermediate of type **35** from **29** and **32** is most likely. In the case of **35** (n = 1), the intramolecular nucleophilic attack of the phenolic OH group onto the oxazolone C=O group is difficult for steric reasons. Therefore, a hydrolytic ring opening of **35** (n = 1) either by small amounts of H₂O present in the reaction mixture or during workup yields **31**. An analogous formation of **34** from **35** (n = 2) is also possible, but in this case, the cyclodepsipeptide **33** is possibly formed first. During workup, the

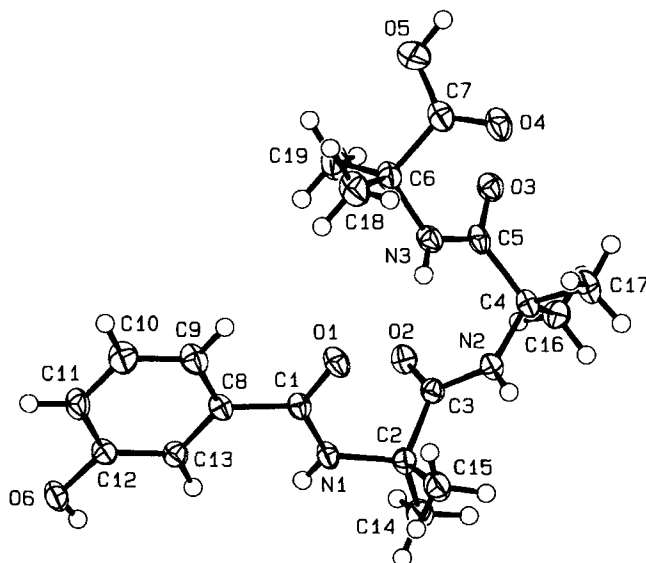


Fig. 2. ORTEP Plot [30] of the molecular structure of **34** (with 50% probability ellipsoids)

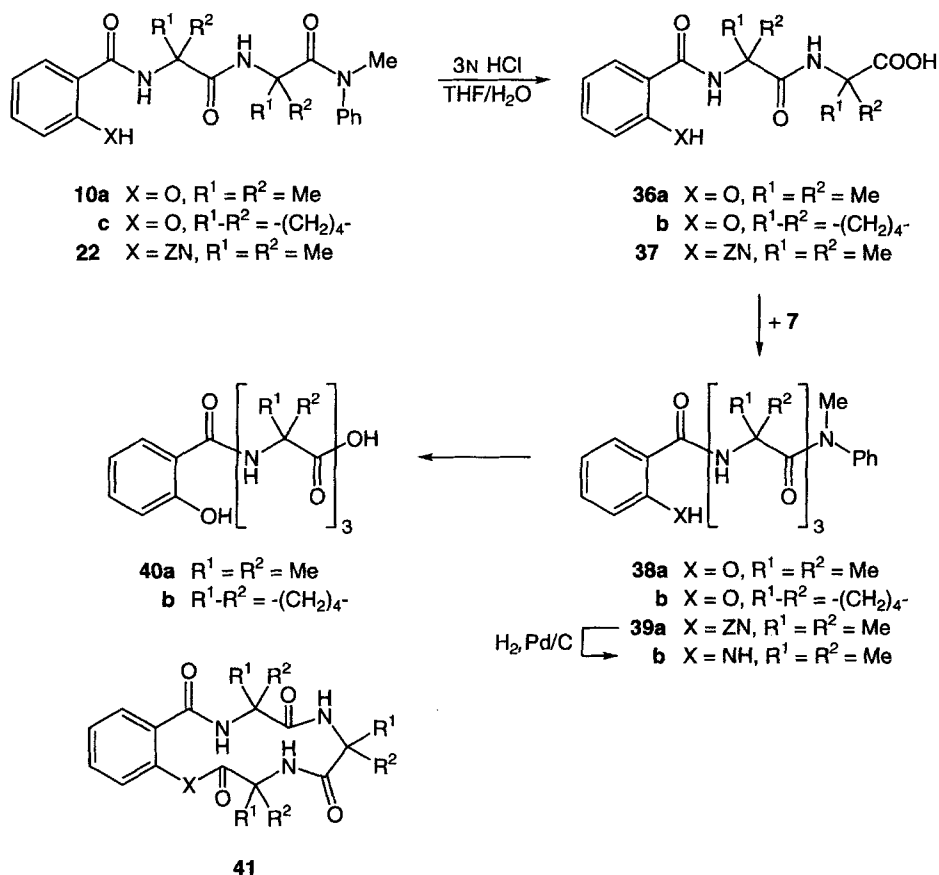
latter can be hydrolyzed to give **34**, as the phenolic lactone group of the strained, medium-sized ring **33** is labile towards hydrolysis.

Finally, tetrapeptide amides **38** and **39** were prepared from **10 a, c** and **22**, respectively, via selective hydrolysis of the terminal amide group and coupling of the peptide acids **36 a, b** and **37** with another azirine unit **7** (Scheme 7). Unfortunately, all attempts to cyclize these tetrapeptide derivatives by using the conditions already described (HCl in DMS at 60°) did not yield the expected cyclic products of type **41**, but the open-chain tetrapeptide acids **40** in the case of **38**, and an intractable mixture of compounds in the case of **39 b**.

In conclusion, we have shown that the combination of the 'azirine/oxazolone method' with the 'direct amide cyclization' proved to be a reasonable preparative route to ten-membered cyclic depsipeptides and peptides containing α,α -disubstituted α -amino acids. Unfortunately, the analogous synthesis of corresponding 13- and 14-membered cyclic depsipeptides has so far been unsuccessful. However, as compounds of type **41** are of interest as analogues of the so-called 'cycloaspeptides', recently isolated from the fungus *Aspergillus* sp NE-45 [31], further studies toward the synthesis of such cyclic peptide analogues using the strategy described above, are in progress.

We thank the analytical units of our institute for spectra and analyses, especially Mr. H. Frohofer for elemental analyses and IR spectra, Mr. M. Vöhler, Dr. D. Nanz, and Mr. T. Plüss for NMR spectra, Mrs. Dr. A. Lorenzi-Riatsch for mass spectra, and Dr. A. Linden for the crystal-structure determinations. Financial support by the Swiss National Science Foundation, F. Hoffmann-La Roche AG, Basel, and the Prof. Dr. Hans E. Schmid-Stiftung is gratefully acknowledged.

Scheme 7



Experimental Part

General. See [8]. Unless otherwise stated, IR spectra in KBr and NMR spectra in (D₆)DMSO (¹H (300 MHz) and ¹³C (50.4 MHz)). EI-MS at 70 eV, CI-MS with 2-methylpropane or NH₃.

1. Reaction of N-Methyl-N-phenyl-2H-azirin-3-amines 7 with Salicylic Acids 6. 1.1. 2-(2-Hydroxybenzamido)-2,N-dimethyl-N-phenylpropanamide (**8a**). To a well stirred soln. of salicylic acid (2-hydroxybenzoic acid; **6a**; 1 g, 7.24 mmol) in dry MeCN (15 ml), a soln. of N,2,2-trimethyl-N-phenyl-2H-azirin-3-amine (**7a**; 1.25 g, 7.24 mmol) in MeCN (6 ml) was added at 0°. The mixture was stirred at r.t. overnight under N₂. Then, the precipitated solid was collected by filtration, washed with cold hexane/Et₂O, and dried under h.v.: 2.23 g (99%) of **8a**. Colorless powder. M.p. 198.4–199.2°. IR: 3340s, 3060w, 2980w, 2920w, 1640s, 1630s, 1625s, 1595s, 1550s, 1540s, 1495s, 1470w, 1460w, 1450m, 1400s, 1380s, 1370s, 1335m, 1305m, 1260s, 1230s, 1205m, 1170m, 1140m, 1110w, 1080m, 1040m, 1025w, 1005w, 830m, 775m, 755s, 715s, 675m, 620m. ¹H-NMR: 8.28 (br. s, NH); 7.62 (d, J = 7.2, 1 arom. H); 7.35–7.3 (m, 1 arom. H); 7.14 (br. s, 5 arom. H); 6.85–6.75 (m, 2 arom. H); 3.15 (s, MeN); 1.50 (s, Me₂C). ¹³C-NMR: 172.0, 168.0 (2s, 2 C=O); 159.4, 145.0 (2s, 2 arom. C); 133.7, 129.0, 128.7, 127.2, 126.9, 118.5, 117.1 (7d, 9 arom. CH); 115.9 (s, 1 arom. C); 57.2 (s, Me₂C); 40.1 (q, MeN); 26.8 (q, Me₂C). CI-MS: 313 (29, [M + 1]⁺), 248 (5), 207 (12), 206 (100), 108 (5), 107 (9). Anal. calc. for C₁₈H₂₀N₂O₃ (312.36): C 69.21, H 6.45, N 8.96; found: C 69.29, H 6.72, N 9.21.

1.2. 1-(2-Hydroxybenzamido)-N-methyl-N-phenylcyclopentanecarboxamide (**8b**). Analogously to 1.1, **6a** (1 g, 7.24 mmol) was reacted with N-methyl-N-phenyl-1-azaspiro[2.4]hept-1-en-2-amine (**7b**; 1.45 g, 7.24 mmol): 2.30 g

(94%) of **8b**. Colorless powder. M.p. 198.5–199.5°. IR: 3320s, 3060w, 2960m, 2930m, 1645s, 1630s, 1590s, 1545s, 1540s, 1495s, 1480m, 1445m, 1380s, 1345m, 1310s, 1260m, 1240m, 1170w, 1145m, 1135w, 1090m, 1070w, 1040w, 1025w, 835m, 760s, 710s, 620m. ¹H-NMR (CDCl₃): 12.22 (s, OH); 7.4–7.3 (m, 1 arom. H); 7.15–7.05 (m, 5 arom. H); 6.94 (d, *J* = 8.3, 1 arom. H); 6.7–6.55 (m, 2 arom. H); 5.48 (br. s, NH); 3.26 (s, MeN); 2.65–2.35 (m, 2H); 2.2–1.55 (m, 6H). ¹³C-NMR (CDCl₃): 172.0, 169.2 (2s, 2 C=O); 161.2, 144.2 (2s, 2 arom. C); 134.1, 129.2, 127.3, 126.9, 125.4, 118.2 (6d, 9 arom. CH); 114.1 (s, 1 arom. C); 67.3 (s, C(α)); 40.5 (q, MeN); 39.3, 24.6 (2t, 4 CH₂). CI-MS: 339 (40, [*M* + 1]⁺), 233 (9), 232 (100), 107 (11). Anal. calc. for C₂₀H₂₂N₂O₃ (338.40): C 70.98, H 6.55, N 8.27; found: C 70.77, H 6.81, N 8.32.

1.3. 2-(2-Hydroxy-5-nitrobenzamido)-2,N-dimethyl-N-phenylpropanamide (**8c**). Analogously to 1.1, 2-hydroxy-5-nitrobenzoic acid (**6b**; 1 g, 5.46 mmol) was reacted with **7a** (950 mg, 5.46 mmol): 1.73 g (89%) of **8c**. Yellow powder. M.p. 210.4°. IR: 3380s, 3000m, 1655s, 1620s, 1590s, 1520s, 1495s, 1430m, 1360m, 1345s, 1305s, 1250m, 1205m, 1195w, 1170w, 1120m, 1070m, 1020w, 1000w, 850m, 760m, 750m, 705m, 680m. ¹H-NMR: 8.65, 8.57 (2 br. s, 1 arom. H, NH); 8.22 (dd, *J* = 6.3, 2.6, 1 arom. H); 7.15–7.0 (m, 6 arom. H); 3.14 (s, MeN); 1.53 (s, Me₂C). ¹³C-NMR: 171.7, 165.9 (2s, 2 C=O); 164.8, 144.8, 139.2 (3s, 3 arom. C); 129.2, 128.8, 127.2, 127.1, 125.6, 118.3 (6d, 8 arom. CH); 116.5 (s, 1 arom. C); 57.6 (s, Me₂C); 41.5 (q, MeN); 26.9 (q, Me₂C). CI-MS: 358 (77, [*M* + 1]⁺), 108 (100). Anal. calc. for C₁₈H₁₉N₃O₅ (357.36): C 60.49, H 5.35, N 11.75; found: C 60.46, H 5.30, N 11.91.

2. Hydrolysis of (Salicyloylamino)amides **8**. 2.1. General Procedure. Peptide amides of type **8** were dissolved in THF/6*N* HCl 1:1 (v/v; ca. 5 ml/mmol) at 0° and stirred overnight at r.t. Then, the solvent was evaporated, CH₂Cl₂ and H₂O were added and the layers separated. The aq. layer was washed once with Et₂O and the combined org. layer dried (MgSO₄) and evaporated: salicyloyl-peptides **9** which were pure enough (up to 90%) to be used in the next step without further purification.

2.2. 2-(2-Hydroxybenzamido)-2-methylpropanoic Acid (**9a**). Recrystallized from EtOH. Colorless microcrystals. M.p. 182.1–183°. IR: 3420s, 3070w, 3010w, 3000w, 2880w, 1770s, 1650s, 1595s, 1535s, 1495s, 1475m, 1450s, 1420m, 1385s, 1375s, 1340m, 1315m, 1300s, 1250s, 1220m, 1185m, 1175m, 1150m, 1040w, 1020w, 925m, 880m, 820m, 815m, 780s, 755s, 700m, 615s. ¹H-NMR: 12.2 (br. s, COOH); 8.78 (s, NH); 7.95–7.9 (m, 1 arom. H); 7.4–7.35 (m, 1 arom. H); 6.9–6.85 (m, 2 arom. H); 1.50 (q, Me₂C). ¹³C-NMR: 175.3 (s, COOH); 167.8 (s, C=O); 159.3 (s, 1 arom. C); 133.7, 128.8, 118.5, 117.2 (4d, 4 arom. CH); 115.9 (s, 1 arom. C); 55.7 (s, Me₂C); 24.9 (q, Me₂C). CI-MS: 224 (100, [*M* + 1]⁺).

2.3. 1-(2-Hydroxybenzamido)cyclopentanecarboxylic Acid (**9b**). Recrystallized from MeCN. Colorless prisms. M.p. 205–206°. IR: 3430s, 3010m, 2970m, 2880m, 1705s, 1645s, 1595s, 1520s, 1495s, 1450m, 1415m, 1395w, 1370s, 1330s, 1300s, 1285s, 1255s, 1230s, 1205s, 1180m, 1145w, 1115w, 1050w, 1040w, 945m, 860m, 820m, 770m, 755s, 700m, 625m. ¹H-NMR: 8.82 (br. s, NH); 7.94 (dd, *J* = 6.5, 1.8, 1 arom. H); 7.5–7.35 (m, 1 arom. H); 6.95–6.85 (m, 2 arom. H); 2.25–1.95 (m, 2 CH₂); 1.8–1.65 (m, 2 CH₂). ¹³C-NMR: 175.1 (s, COOH); 168.8 (s, C=O); 159.7 (s, 1 arom. C); 133.8, 128.6, 118.4, 117.3 (4d, 4 arom. CH); 115.5 (s, 1 arom. C); 65.6 (s, C(α)); 36.6, 24.4 (2t, 4 CH₂). EI-MS: 249 (38, *M*⁺), 203 (20), 174 (11), 138 (14), 137 (23), 122 (12), 121 (93), 120 (40), 95 (11), 93 (24), 92 (13), 84 (100), 83 (55), 82 (15), 81 (13), 74 (16), 69 (16), 67 (24), 65 (37). Anal. calc. for C₁₃H₁₃N₂O₄ (249.26): C 62.64, H 6.06, N 5.62; found: C 62.85, H 5.80, N 5.62.

2.4. 2-(2-Hydroxy-5-nitrobenzamido)-2-methylpropanoic Acid (**9c**). Hydrolysis of **8c** according to 2.1 yielded **9c**, which was used directly in the next step without further purification.

3. Reaction of (Salicyloylamino) Acids **9** with N-Methyl-N-phenyl-2H-azirin-3-amines **7**. 3.1. General Procedure. To a well stirred soln. of **9** (2.5 mmol) in dry MeCN (7 ml), a soln. of **7** (2.5 mmol) in 0.5 ml of MeCN was added at 0°. The mixture was stirred under N₂ overnight while raising the temp. from 0° to r.t. Then, the precipitated **10** was collected by filtration, washed with cold hexane/Et₂O, and dried under h.v.

3.2. 2-[2-(2-Hydroxybenzamido)-2-methylpropanamido]-2,N-dimethyl-N-phenylpropanamide (**10a**). Yield 903 mg (91%). Colorless powder. M.p. 235.5–236.1°. IR: 3330s, 3310s, 3060w, 3000m, 2980m, 2940m, 1650s, 1540s, 1635s, 1595s, 1535s, 1490s, 1465s, 1445m, 1395s, 1370s, 1335m, 1305m, 1290w, 1260m, 1230s, 1210m, 1170m, 1140m, 1110w, 1090s, 1070w, 1040w, 1030w, 1005w, 850m, 815m, 755s, 710s. ¹H-NMR: 8.78 (s, NH); 7.9–7.85 (m, 1 arom. H); 7.78 (s, NH); 7.4–7.3 (m, 3 arom. H); 7.25–7.2 (m, 3 arom. H); 6.9–6.85 (m, 2 arom. H); 3.23 (s, MeN); 1.48, 1.36 (2s, 2 Me₂C). ¹³C-NMR: 173.1, 172.4, 166.9 (3s, 3 C=O); 158.5, 145.6 (2s, 2 arom. C); 133.2, 129.1, 128.7, 127.2, 126.4, 118.7 (6d, 8 arom. CH); 117.3 (s, 1 arom. C); 117.0 (d, 1 arom. CH); 56.8, 56.7 (2s, 2 Me₂C); 40.0 (q, MeN); 25.7, 24.6 (2q, 2 Me₂C). CI-MS: 398 (86, [*M* + 1]⁺), 292 (19), 291 (100), 290 (10), 206 (5), 108 (8), 107 (11). Anal. calc. for C₂₂H₂₇N₃O₄ (397.47): C 66.48, H 6.84, N 10.57; found: C 66.37, H 6.94, N 10.82.

3.3. 1-[2-(2-Hydroxybenzamido)-2-methylpropanamido]-N-methyl-N-phenylcyclopentanecarboxamide (**10b**). Yield 951 mg (90%). Colorless powder. M.p. 230–230.9°. IR: 3320s, 3060w, 2990m, 2960m, 1660s, 1635s, 1600s,

1540s, 1495s, 1470m, 1450s, 1385s, 1365s, 1340m, 1310m, 1280m, 1260m, 1230s, 1170m, 1145m, 1120w, 1100w, 1080w, 1040w, 1030w, 760s, 705m, 670m, 625m. ¹H-NMR: 11.91 (br. s, OH); 8.73 (s, NH); 7.86 (dd, *J* = 6.6, 1.1, 1 arom. H); 7.73 (br. s, NH); 7.4–7.15 (m, 6 arom. H); 6.9–6.85 (m, 2 arom. H); 3.20 (s, MeN); 2.25–2.15 (m, 2H); 1.9–1.65 (m, 2H); 1.55–1.35 (m, with s at 1.45, 10 H). ¹³C-NMR: 173.0, 172.3, 167.0 (3s, 3 C=O); 158.5, 145.5 (2s, 2 arom. C); 133.1, 129.1, 128.6, 126.8, 125.9, 118.6 (6d, 8 arom. CH); 117.2 (s, 1 arom. C); 116.9 (d, 1 arom. CH); 66.5, 56.7 (2s, 2 C(α)); 39.9 (q, MeN); 36.4, 24.6 (2t, 4 CH₂); 24.0 (q, Me₂C). CI-MS: 425 (74, [M + 1]⁺), 319 (20), 318 (100).

3.4. *1-[1-(2-Hydroxybenzamido)cyclopentanecarboxamido]-N-methyl-N-phenylcyclopentanecarboxamide (10c)*. Yield 1.092 g (98%). Colorless powder. M.p. 271.5–272°. IR: 3320s, 2970m, 2880m, 1660s, 1635s, 1600s, 1540s, 1525s, 1490m, 1455m, 1390m, 1340w, 1310m, 1260m, 1230m, 1145w, 1100w, 1040w, 755s, 700m. ¹H-NMR (CDCl₃): 8.48 (br. s, NH); 7.9–7.85 (m, 1 arom. H); 7.77 (br. s, NH); 7.45–7.15 (m, 6 arom. H); 6.95–6.85 (m, 2 arom. H); 3.21 (s, MeN); 2.55–2.5 (m, 4H); 2.2–1.85 (m, 8H); 1.70 (br. s, 4H); 1.48 (br. s, 2H). ¹³C-NMR ((D₆)DMSO/CF₃COOH): 175.9, 173.3, 169.0 (3s, 3 C=O); 160.0, 138.0 (2s, 2 arom. C); 133.6, 130.4, 129.3, 124.1, 122.6, 118.2, 117.4 (7d, 9 arom. CH); 117.2 (s, 1 arom. C); 67.0, 65.6 (2s, 2 C(α)); 36.7, 35.4, 24.6, 24.3 (4t, 8 CH₂); MeN could not be detected. CI-MS: 447 (4, [M + 1]⁺), 343 (37), 342 (10), 108 (11), 107 (27), 91 (14), 85 (14), 84 (100), 82 (11), 77 (10), 67 (18), 66 (15), 65 (13). Anal. calc. for C₂₆H₂₈N₃O₄ (446.52): C 69.93, H 6.32, N 9.41; found: C 70.12, H 6.52, N 9.30.

3.5. *2-[1-(2-Hydroxybenzamido)cyclopentanecarboxamido]-2,N-dimethyl-N-phenylpropanamide (10d)*. Yield 1.03 g (98%). Colorless powder. M.p. 244.5–245.2°. IR: 3220s, 2980m, 2960m, 2940m, 1650s, 1635s, 1595s, 1535s, 1490s, 1470m, 1450m, 1395m, 1365s, 1335m, 1310m, 1260m, 1230s, 1200m, 1170w, 1140w, 1090s, 1040w, 1000w, 770w, 750m, 705m. ¹H-NMR: 8.54 (br. s, NH); 7.9–7.85 (m, 1 arom. H); 7.80 (s, NH); 7.4–7.2 (m, 6 arom. H); 6.9–6.85 (m, 2 arom. H); 3.23 (s, MeN); 2.2–2.0 (m, 4H); 1.65–1.6 (m, 4H); 1.34 (s, Me₂C). ¹³C-NMR: 172.8, 172.5, 168.4 (3s, 3 C=O); 159.1, 145.9 (2s, 2 arom. C); 133.5, 129.2, 128.9, 127.4, 126.5, 118.8, 117.1 (7d, 9 arom. CH, 1 arom. C); 67.2, 56.8 (2s, 2 C(α)); 40.0 (q, MeN); 36.3 (t, 2 CH₂); 25.7 (q, Me₂C); 24.1 (t, 2 CH₂). CI-MS: 423 (100, [M + 1]⁺). Anal. calc. for C₂₄H₂₉N₃O₄ (423.51): C 68.06, H 6.90, N 9.92; found: C 67.98, H 7.11, N 9.82.

3.6. *2-[2-(2-Hydroxy-5-nitrobenzamido)-2-methylpropanamido]-2,N-dimethyl-N-phenylpropanamide (10e)*. Yield 961 mg (87%). Yellow microcrystals. M.p. 124–126° (dec.). IR: 3280m, 3060w, 2980w, 2940w, 1650s, 1630s, 1605s, 1595s, 1545m, 1520s, 1490s, 1390m, 1365m, 1340s, 1300s, 1220m, 1200m, 1170w, 1140m, 1115w, 1090w, 705m. ¹H-NMR: 9.20 (s, NH); 8.81 (d, *J* = 2.9, 1 arom. H); 8.24 (dd, *J* = 6.2, 2.9, 1 arom. H); 7.80 (s, NH); 7.4–7.0 (m, 6 arom. H); 3.23 (s, MeN); 1.50, 1.37 (2s, 2 Me₂C). ¹³C-NMR (CD₃OD): 175.7, 168.2, 166.1 (3s, 3 C=O); 146.8, 141.6 (2s, 2 arom. C); 130.6, 129.8, 128.9, 128.8, 127.0, 119.3 (6d, 8 arom. CH, 1 arom. C); 59.2 (s, Me₂C); 41.6 (q, MeN); 26.6, 25.5 (2q, 2 Me₂C); 1 Me₂C could not be detected. CI-MS: 443 (36, [M + 1]⁺), 337 (11), 336 (58), 306 (15), 193 (10), 108 (100), 107 (45).

4. *Reaction of Salicyloyl-dipeptides 10 with dry HCl: Cyclic Dipeptides 11*. 4.1. *General Procedure*. Through a well stirred soln. of the corresponding dipeptide **10** (150 mg, 0.5–0.15 mmol) in abs. DMF (50–62 ml, *c* = 0.008M), a stream of dry HCl gas was bubbled for ca. 30 min at 60°. After completion of the reaction (TLC), a stream of N₂ was passed through the soln. for another 2 h with good stirring at 60° to remove excess HCl. Then, the solvent was evaporated and the residue filtered through a short column of SiO₂ (CH₂Cl₂/MeOH 14:1) yielding **11**.

4.2. *3,4,6,7-Tetrahydro-3,3,6,6-tetramethyl-2H-1,4,7-benzoxadiazecine-2,5,8-trione (11a)*. Crystallized from i-PrOH/Et₂O/hexane: 133 mg (92%). Colorless powder. M.p. 239.7–244° (dec.). IR: 3400s (br.), 2980m, 2930m, 1630s, 1605s, 1500m, 1455s, 1415m, 1385m, 1365s, 1325m, 1220m, 1175w, 1100w, 1040w, 1020w, 755m. ¹H-NMR: 9.19 (br. s, NH); 7.9–7.8 (m, 1 arom. H, NH); 7.35–7.3 (m, 1 arom. H); 6.95–6.75 (m, 2 arom. H); 1.46, 1.40 (2s, 2 Me₂C). ¹³C-NMR (CD₃OD): 183.6, 175.9, 169.2 (3s, 3 C=O); 150.6 (s, 1 arom. C); 134.7, 130.7, 120.2 (3d, 3 arom. CH); 118.5 (s, 1 arom. C); 118.1 (d, 1 arom. CH); 58.6, 58.3 (2s, 2 Me₂C); 25.6, 25.1 (2q, 2 Me₂C). CI-MS: 291 (10, [M + 1]⁺), 206 (100), 178 (94).

4.3. *6,7-Dihydro-6,6-dimethylspiro[2H-1,4,7-benzoxadiazecine-3(4H),1-cyclopentane]-2,5,8-trione (11b)*. Crystallized from i-PrOH/Et₂O/hexane: 106 mg (96%). Colorless powder. M.p. 235.6–240° (dec.). IR: 3400s (br.), 2970m, 2870m, 1630s, 1605s, 1455m, 1415m, 1385m, 1370m, 1325w, 1305w, 1235w, 1100w, 1040w, 1020w, 655m. ¹H-NMR: 8.96 (s, NH); 7.88 (dd, *J* = 6.3, 1.3, 1 arom. H); 7.77 (s, NH); 7.4–7.3 (m, 1 arom. H); 6.95–6.8 (m, 2 arom. H); 2.0–1.85 (m, 4H); 1.75–1.6 (m, 4H); 1.47 (s, Me₂C). ¹³C-NMR (CD₃OD): 182.5, 177.0, 169.6 (3s, 3 C=O); 159.1 (s, 1 arom. C); 135.0, 131.1, 120.8 (3d, 3 arom. CH); 118.9 (s, 1 arom. C); 118.0 (d, 1 arom. CH); 68.8, 58.4 (2s, C(3), C(6)); 38.1 (t, 2 CH₂); 35.6, 25.9 (2q, Me₂C); 25.8 (t, 2 CH₂).

4.4. *Dispiro[cyclopentane-1,3'(4'H)-/2H-1,4,7-benzoxadiazecine-6'(7'H),1'-cyclopentane]-2',5',8'-trione (11c)*. Crystallized from i-PrOH/Et₂O/hexane: 47 mg (93%). Colorless powder. M.p. 245° (dec.). IR: 3400s (br.),

2960m, 2930m, 2860m, 1640s, 1610s, 1570s, 1550s, 1495m, 1455m, 1420m, 1385m, 1330m, 1235m, 1100w, 1040w, 755m. ¹H-NMR: 8.85 (s, NH); 7.9–7.8 (m, 1 arom. H); 7.71 (s, NH); 7.4–7.3 (m, 1 arom. H); 6.9–6.85 (m, 2 arom. H); 2.25–2.1 (m, 2H); 1.95–1.85 (m, 6H); 1.65–1.4 (m, 8H). ¹³C-NMR (CD₃OD): 182.4, 176.3, 169.5 (3s, 3 C=O); 158.7 (s, 1 arom. C); 134.7, 130.8, 120.6 (3d, 3 arom. CH); 118.9 (s, 1 arom. C); 117.7 (d, 1 arom. CH); 68.7, 68.8 (2s, C(3'), C(6')); 37.8, 37.5, 25.5, 24.9 (4t, 8 CH₂).

4.5. *3,4-Dihydro-3,3-dimethylspiro[2H-1,4,7-benzoxadiazecine-6(7H),1-cyclopentane]-2,5,8-trione (11d)*. Crystallized from i-PrOH/Et₂O/hexane: 106 mg (95%). Colorless powder. M.p. 280° (dec.). IR: 3400s (br.), 2970m, 2880w, 1630s, 1610s, 1550s, 1535s, 1495m, 1475m, 1455m, 1420m, 1385m, 1365m, 1330m, 1240m, 1220m, 1160w, 1110w, 1045w, 755m, 620m. ¹H-NMR (400 MHz): 9.23 (br. s, NH); 7.92 (dd, *J* = 6.7, 1.1, 1 arom. H); 7.90 (s, NH); 7.35–7.3 (m, 1 arom. H); 6.9–6.8 (m, 2 arom. H); 2.15–2.05 (m, 2H); 2.0–1.95 (m, 2H); 1.7–1.6 (m, 4H); 1.38 (s, Me₂C). ¹³C-NMR (CD₃OD): 182.3, 175.3, 169.3 (3s, 3 C=O); 158.8 (s, 1 arom. C); 134.7, 131.0, 120.6 (3d, 3 arom. CH); 118.7 (s, 1 arom. C); 117.8 (d, 1 arom. CH); 68.8, 58.6 (2s, C(3), C(6)); 37.6 (t, 2 CH₂); 25.3 (q, Me₂C); 24.8 (t, 2 CH₂). CI-MS: 317 (6, [*M* + 1]⁺), 233 (13), 232 (73), 204 (16), 120 (34), 102 (27), 91 (13), 86 (11), 85 (23), 73 (100), 72 (15).

4.6. *3,4,6,7-Tetrahydro-3,3,6,6-tetramethyl-10-nitro-2H-1,4,7-benzoxadiazecine-2,5,8-trione (11e)*. Crystallized from i-PrOH/hexane: 95 mg (88%). Yellow powder. M.p. 295° (dec.). IR: 3400s (br.), 2980w, 2930m, 1620s, 1590s, 1540s, 1475s, 1430m, 1385m, 1365m, 1310s, 1205m, 1195m, 1080m, 845m, 710m, 695m, 645m. ¹H-NMR: 11.50 (s, NH); 8.50 (d, *J* = 3.3, 1 arom. H); 7.87 (s, NH); 7.79 (dd, *J* = 6.2, 3.3, 1 arom. H); 6.25 (d, *J* = 6.5, 1 arom. H); 1.41, 1.39 (2s, 2 Me₂C).

5. *3,4,6,7-Tetrahydro-3,3-dimethyl-2H-1,4,7-benzoxadiazecine-2,5,8-trione (18)*. 5.1. *Benzyl N-(2-Hydroxybenzoyl)glycinate (15)*. To a well stirred soln. of **6a** (1 g, 7.24 mmol) in dry MeCN (25 ml) at 0°, CME-CDI (3.220 g, 1.05 equiv.) was added. The mixture was stirred for 30 min under N₂, then glycinium benzyl ester toluene-4-sulfonate (**14**; 2.687 g, 1.1 equiv.) was added followed by slow addition of Et₃N (1.2 equiv.). The mixture was stirred overnight, raising the temp. from 0° to r.t. Filtration of the formed urea and evaporation led to a residue that was dissolved in AcOEt. The soln. was washed with H₂O, 5% citric acid, H₂O, 10% NaHCO₃ soln., and again H₂O, dried (MgSO₄), and evaporated and the residue purified by flash chromatography (hexane/AcOEt 4:1): 1.487 g (72%) of **15**. Colorless powder. M.p. 109.4–105.4°. IR: 3420s, 3060w, 3040m, 2990w, 2960w, 1730s, 1645s, 1600s, 1545s, 1490m, 1450m, 1415m, 1395m, 1370m, 1335m, 1310m, 1275s, 1255m, 1235s, 1205s, 1150m, 1115w, 1045w, 1030w, 1005w, 990m, 820m, 750s, 730s, 695m. ¹H-NMR: 12.20 (br. s, OH); 9.22 (br. s, NH); 7.85 (dd, *J* = 6.3, 1.6, 1 arom. H); 7.45–7.35 (m, 6 arom. H); 6.95–6.85 (m, 2 arom. H); 5.16 (s, PhCH₂); 4.12 (d, *J* = 5.1, CH₂N). ¹³C-NMR: 169.6, 168.9 (2s, 2 C=O); 159.6 (s, 1 arom. C); 134.0, 128.5, 128.4, 128.2, 128.0, 119.0, 117.4 (7d, 9 arom. CH); 115.4 (s, 1 arom. C); 66.1 (t, PhCH₂); 40.1 (t, CH₂N). CI-MS: 286 (100, [*M* + 1]⁺). Anal. calc. for C₁₆H₁₅NO₄ (285.29): C 67.35, H 5.30, N 4.90; found: C 67.29, H 5.20, N 5.06.

5.2. *N-(2-Hydroxybenzoyl)glycine (16)*. To a soln. of **15** (1 g, 3.5 mmol) in MeOH (10 ml), 10% Pd/C (100 mg) was added at 0° and the mixture stirred overnight at r.t. under H₂. Then, the soln. was filtered over a *Celite* pad, the solvent evaporated, and the resulting residue purified by flash chromatography (CH₂Cl₂/MeOH 14:1): 627 mg (92%) of **16**. Colorless powder. M.p. 150.1–151.8°. IR: 3400s, 3350s, 1710s, 1610s, 1565s, 1550s, 1540s, 1500s, 1460s, 1445m, 1435m, 1345s, 1290m, 1260s, 1240s, 1210m, 1160m, 1095m, 1040w, 1000w, 760m, 640m, 620m. ¹H-NMR: 9.11 (br. s, NH); 7.86 (d, *J* = 7.6, 1 arom. H); 7.39 (t, *J* = 7.5, 1 arom. H); 6.95–6.85 (m, 2 arom. H); 3.98 (d, *J* = 5.2, CH₂N). ¹³C-NMR: 171.1, 168.7 (2s, 2 C=O); 159.6 (s, 1 arom. C); 133.9, 128.4, 118.9, 117.4 (4d, 4 arom. CH); 115.5 (s, 1 arom. C); 40.9 (t, CH₂N). CI-MS: 196 (100, [*M* + 1]⁺).

5.3. *2-[2-(2-Hydroxybenzamido)acetamido]-2,N-dimethyl-N-phenylpropanamide (17)*. To a soln. of **16** (500 mg, 2.56 mmol) in dry MeCN (6 ml), a soln. of **7a** (445 mg, 2.56 mmol) in MeCN (2 ml) was added at 0°. The mixture was stirred overnight, raising the temp. from 0° to r.t. The precipitate was collected by filtration, washed with cold hexane/Et₂O, and dried under h.v.: 869 mg (86%) of **17**. Colorless powder. M.p. 161–162.5°. IR: 3300s, 3060w, 2980w, 2940w, 1645s, 1600s, 1550s, 1540s, 1500s, 1450m, 1390s, 1365s, 1310m, 1260m, 1230m, 1150w, 1120w, 1095w, 1075w, 1040w, 1000w, 760m, 710m. ¹H-NMR: 8.94 (br. s, NH); 7.86 (dd, *J* = 6.3, 1.6, 2 arom. H); 7.4–7.15 (m, 5 arom. H, NH); 6.95–6.9 (m, 2 arom. H); 3.64 (br. s, CH₂N); 3.13 (s, MeN); 1.36 (s, Me₂C). CI-MS: 370 (10, [*M* + 1]⁺), 264 (15), 263 (100), 178 (31), 108 (25).

5.4. *Cyclization to 18*. According to 4.1 reaction of **17** (100 mg, 0.27 mmol) in dry DMF (34 ml, *c* = 0.008M) led to 66 mg (95%) of **18**. Colorless powder. M.p. 238–240° (dec.). IR (KBr): 3400s (br.), 3060m, 2980w, 2930w, 1645s (br.), 1600s, 1550s, 1490m, 1470m, 1455m, 1415m, 1385m, 1365m, 1250m, 1210w, 1155w, 1105w, 1040w, 755m. ¹H-NMR: 9.55 (br. s, NH); 7.96 (s, NH); 7.87 (dd, *J* = 6.6, 1.2, 1 arom. H); 7.35–7.2 (m, 1 arom. H); 6.95–6.75 (m, 2 arom. H); 3.86 (d, *J* = 4.6, CH₂N); 1.40 (s, Me₂C).

6. *Reactions with Anthranilic-Acid Derivatives*. 6.1. *N-[(Benzyloxy)carbonyl]anthranilic Acid (19)*. To a well stirred soln. of anthranilic acid (2.5 g, 18.24 mmol) in dioxane/1N NaOH 1:1 (60 ml) at 0°, benzylchloroformate

(= benzyl carbonochloridate; Z-Cl; 3 ml, 1.25 equiv.) was slowly added. The mixture was stirred overnight at r.t., the dioxane evaporated, 2N HCl added until pH 1–2 was reached, and the soln. washed twice with CH_2Cl_2 . The combined org. layer was dried (MgSO_4) and evaporated and the residue crystallized from MeCN. The solid was washed with hexane and dried under h.v.: 3.558 g (72%) of **19**. Colorless microcrystals. M.p. 135–137°. IR: 3220s, 3030w, 2960w, 2880w, 1735s, 1695s, 1605s, 1590s, 1535s, 1450s, 1410m, 1375s, 1300s, 1255s, 1240s, 1230s, 1195s, 1160s, 1140s, 1090m, 1085m, 1040s, 1000w, 980m, 805m, 780m, 755s, 695s, 670m, 650s, 625m. $^1\text{H-NMR}$: 13.67 (s, COOH); 10.80 (s, NH); 8.3–8.25 (m, 1 arom. H); 7.97 (dd, $J = 6.4, 1.5$, 1 arom. H); 7.65–7.55 (m, 1 arom. H); 7.45–7.3 (m, 5 arom. H); 7.15–7.05 (m, 1 arom. H); 5.18 (s, PhCH_2). $^{13}\text{C-NMR}$ (CD_3OD): 171.5, 155.1 (2s, 2 C=O); 143.1, 138.0 (2s, 2 arom. C); 135.6, 132.8, 129.8, 129.5, 129.4, 123.1, 119.8 (7d, 9 arom. CH); 116.8 (s, 1 arom. C); 68.1 (t, PhCH_2). CI-MS: 272 (12, $[M + 1]^+$), 181 (25), 164 (100), 91 (30).

6.2. 2-{2-[(Benzyloxy)carbonylamino]benzamido}-2,N-dimethyl-N-phenylpropanamide (**20**). To a well stirred soln. of **19** (1.5 g, 5.53 mmol) in dry MeCN (12 ml), a soln. of **7a** (962 mg, 5.53 mmol) in MeCN (4 ml) was added at 0°. The mixture was stirred overnight, raising the temp. from 0° to r.t. The precipitate was collected by filtration, washed with hexane, and dried under h.v.: 2.25 g (92%) of **20**. Recrystallization from EtOH: 2.116 g (86%). Colorless microcrystals. M.p. 168.3–168.6°. IR: 3320m, 3280s, 3060w, 3000w, 2990w, 1740s, 1645s, 1635s, 1595s, 1540s, 1530s, 1520s, 1495s, 1450s, 1395s, 1375s, 1365s, 1320s, 1285s, 1250m, 1240s, 1220s, 1210s, 1105m, 1090s, 1040s, 1030m, 1005w, 950m, 925m, 875m, 845m, 765m, 760s, 745s, 710s, 695s, 615m. $^1\text{H-NMR}$ (CDCl_3): 10.72 (s, NH); 8.35 (d, $J = 8.5$, 1 arom. H); 7.5–7.15 (m, 11 arom. H); 7.0–6.85 (m, 2 arom. H); 6.47 (s, NH); 5.21 (s, PhCH_2); 3.28 (s, MeN); 1.60 (s, Me_2C). $^{13}\text{C-NMR}$ (CDCl_3): 172.8, 167.7, 153.6 (3s, 3 C=O); 144.2, 144.0, 136.3 (3s, 3 arom. C); 132.4, 129.4, 128.4, 128.2, 128.0, 127.8, 127.6, 126.5, 121.4, 119.8 (10d, 14 arom. CH); 119.6 (s, 1 arom. C); 66.6 (t, PhCH_2); 58.4 (s, Me_2C); 41.3 (q, MeN); 26.4 (q, Me_2C). CI-MS: 446 (33, $[M + 1]^+$), 340 (18), 339 (100), 231 (43), 225 (35), 108 (28), 71 (13). Anal. calc. for $\text{C}_{26}\text{H}_{27}\text{N}_3\text{O}_4$ (445.51): C 70.09, H 6.10, N 9.43; found: C 70.10, H 6.04, N 9.52.

6.3. 2-{2-[(Benzyloxy)carbonylamino]benzamido}-2-methylpropanoic Acid (**21**). According to 2.1, hydrolysis of **20** (1 g, 2.24 mmol) led to 789 mg (99%) of **21**. Colorless flakes. M.p. 197–198.2°. IR: 3350m, 3320m, 3030w, 2995w, 2960w, 1715s (br.), 1650s, 1605s, 1590s, 1530s, 1520s, 1465m, 1450s, 1420m, 1380m, 1365w, 1325m, 1295s, 1285s, 1260m, 1240s, 1220s, 1185m, 1175m, 1165m, 1105w, 1075w, 1040s, 1005w, 985m, 945m, 920m, 875m, 845m, 770s, 755s, 705s, 680m, 615m. $^1\text{H-NMR}$: 12.30 (br. s, COOH); 10.64, 8.74 (2s, 2 NH); 8.18 (dd, $J = 7.4, 0.9$, 1 arom. H); 7.76 (dd, $J = 6.5, 1.4$, 1 arom. H); 7.55–7.3 (m, 6 arom. H); 7.15–7.1 (m, 1 arom. H); 5.15 (s, PhCH_2); 1.43 (s, Me_2C). $^{13}\text{C-NMR}$: 175.5, 168.3, 152.9 (3s, 3 C=O); 139.1, 136.6 (2s, 2 arom. C); 129.0, 128.7, 128.3, 121.9 (4d, 8 arom. CH); 120.0 (s, 1 arom. C); 118.7 (d, 1 arom. CH); 66.3 (t, PhCH_2); 56.0 (s, Me_2C); 25.0 (q, Me_2C). CI-MS: 357 (100, $[M + 1]^+$), 340 (13), 339 (54), 313 (22), 295 (19), 263 (11), 223 (17), 222 (13), 215 (24), 214 (25), 205 (67), 204 (29), 91 (18).

6.4. 2-{2-[2-[(Benzyloxy)carbonylamino]benzamido]-2-methylpropanamido}-2,N-dimethyl-N-phenylpropanamide (**22**). Analogously to 6.2, reaction of **21** (560 mg, 1.57 mmol) with **7a** (273 mg, 1.56 mmol) led to **22**: 707 mg (85%; recrystallized from EtOH). Colorless powder. IR: 3320s (br.), 3060w, 3040w, 2980w, 2940w, 1735s, 1660s, 1640s (br.), 1590s, 1530s, 1520s, 1495m, 1470m, 1450s, 1435s, 1395m, 1370m, 1325s, 1325m, 1300w, 1280m, 1250s, 1215s, 1175w, 1165w, 1100m, 1090s, 1045s, 1030m, 1000w, 760s, 745m, 710s, 700m. $^1\text{H-NMR}$: 10.43, 8.35 (2s, 2 NH); 8.11 (dd, $J = 7.4, 0.9$, 1 arom. H); 7.80 (dd, $J = 6.5, 1.4$, 1 arom. H); 7.72 (s, NH); 7.55–7.1 (m, 12 arom. H); 5.10 (s, PhCH_2); 3.21 (s, MeN); 1.44, 1.31 (2s, 2 Me_2C). $^{13}\text{C-NMR}$: 172.4, 172.0, 167.4, 152.3 (4s, 4 C=O); 145.1, 138.0, 135.7 (3s, 3 arom. C); 131.1, 128.1, 127.8, 127.5, 127.4, 127.3, 126.6, 125.7 (8d, 12 arom. CH); 121.3 (s, 1 arom. C); 120.9, 118.4 (2d, 2 arom. CH); 65.5 (t, PhCH_2); 56.4, 56.1 (2s, 2 Me_2C); 39.8 (q, MeN); 24.9, 24.3 (2q, 2 Me_2C). CI-MS: 531 (2, $[M + 1]^+$), 424 (13), 387 (13), 386 (49), 339 (15), 321 (21), 283 (31), 281 (12), 231 (14), 198 (25), 197 (10), 194 (29), 193 (100), 148 (11), 147 (26), 108 (74), 107 (19), 91 (53). Anal. calc. for $\text{C}_{30}\text{H}_{34}\text{N}_4\text{O}_5$ (530.62): C 67.90, H 6.45, N 10.55; found: C 67.98, H 6.65, N 10.80.

6.5. 2-[2-(2-Aminobenzamido)-2-methylpropanamido]-2,N-dimethyl-N-phenylpropanamide (**23**). Analogously to 5.2, hydrogenolysis of **22** (500 mg, 0.94 mmol) yielded 343 mg (92%) of **23**. Colorless powder. M.p. 183.5–185°. IR: 3460s, 3340s, 2980w, 2940w, 1660s, 1635s, 1590m, 1580m, 1525s, 1490s, 1395m, 1365m, 1325w, 1265m, 1215w, 1200w, 1170w, 1155w, 1090m, 1070w, 1025w, 1000w, 750m, 710m. $^1\text{H-NMR}$: 7.87 (s, NH); 7.7–7.55 (m, 2 arom. H, NH); 7.4–7.1 (m, 5 arom. H); 6.7–6.55 (m, 2 arom. H); 6.22 (s, NH_2); 3.26 (s, MeN); 1.44, 1.36 (2s, 2 Me_2C). $^{13}\text{C-NMR}$: 173.4, 172.5, 168.5 (3s, 3 C=O); 149.3, 145.6 (2s, 2 arom. C); 131.5, 128.7, 128.6, 127.2, 126.3, 116.1 (6d, 8 arom. CH); 115.4 (s, 1 arom. C); 114.5 (d, 1 arom. CH); 56.5, 56.3 (2s, 2 Me_2C); 39.0 (q, MeN); 25.5, 24.9 (2q, 2 Me_2C). CI-MS: 397 (49, $[M + 1]^+$), 304 (15), 295 (21), 291 (17), 290 (100).

6.6. 4,5-Dihydro-2,2,4,4-tetramethyl-1H-imidazo[1,2-a][1,4]benzodiazepine-1,6(2H)-dione (**25**) and 3,4,6,7-Tetrahydro-3,3,6,6-tetramethyl-1,4,7-benzotriazecine-2,5,8(1H)-trione (**24**). Through a well stirred soln. of **23** (120 mg, 0.30 mmol) in dry DMF (38 ml, $c = 0.008\text{M}$), a stream of dry HCl gas was passed during 30 min at 60°,

followed by a stream of N_2 for additional 2 h. The solvent was evaporated and the residue partitioned between H_2O and CH_2Cl_2 . The org. layer was dried ($MgSO_4$) and evaporated: 34 mg (42 %) of **25**, which was recrystallized from MeOH.

25: Colorless prisms. M.p. 239.5–240.7°. IR: 3180m, 3060m, 2990m, 2940w, 1745s, 1660s, 1640s, 1600m, 1490m, 1460s, 1400m, 1380m, 1345m, 1310m, 1270w, 1200m, 1160m, 1130w, 1085w, 760m, 740m. 1H -NMR (65–75°; from the mixture with **24**): 8.67 (s, NH); 7.8–7.75 (m, 1 arom. H); 7.65–7.6 (m, 2 arom. H); 7.5–7.4 (m, 1 arom. H); 1.33, 1.28 (2s, 2 Me_2C). CI-MS: 272 (100, $[M + 1]^+$). EI-MS: 271 (92, M^+), 243 (15), 229 (16), 228 (100), 186 (22), 146 (18), 118 (22), 117 (53), 106 (12), 90 (17), 77 (15).

24: 1H -NMR (100°): 11.15 (s, NH); 8.26 (d, $J = 8.1$, 1 arom. H); 8.18 (s, NH); 7.94 (d, $J = 7.2$, 1 arom. H); 7.65 (s, NH); 7.5–7.4 (m, 1 arom. H); 7.15–7.05 (m, 1 arom. H); 1.39, 1.35 (2s, 2 Me_2C).

Recrystallization from MeOH yielded crystals of **25** suitable for an X-ray crystal-structure determination.

7. Reactions with 3-Hydroxybenzoic Acid (**16**). 7.1. 2-(3-Hydroxybenzamido)-2,N-dimethyl-N-phenylpropanamide (**27**). Analogously to 1.1, reaction of **26** (650 mg, 4.71 mmol) with **7a** (819 mg, 47 mmol) led to **27**: 1.353 g (92 %). Colorless powder. M.p. 180.3–180.4°. IR: 3300s, 3060m, 3015w, 2940w, 1635s, 1625s, 1595s, 1585s, 1580s, 1495s, 1485s, 1455m, 1430w, 1390s, 1370m, 1320s, 1310s, 1290m, 1270w, 1240m, 1210m, 1170w, 1120m, 1095w, 1075w, 1025w, 1000w, 760m, 710s, 690m. 1H -NMR: 9.58 (s, CH); 8.04 (br. s, NH); 7.25–7.1 (m, 8 arom. H); 6.9–6.85 (m, 1 arom. H); 3.15 (s, MeN); 1.45 (s, Me_2C). ^{13}C -NMR: 172.6, 166.2 (2s, 2 C=O); 157.2, 145.6, 136.0 (3s, 3 arom. C); 129.1, 129.0, 127.4, 118.3, 114.7 (5d, 9 arom. CH); 57.1 (s, Me_2C); 39.7 (q, MeN); 26.7 (q, Me_2C). CI-MS: 313 (100, $[M + 1]^+$), 205 (67).

7.2. 2-(Hydroxybenzamido)-2-methylpropanoic Acid (**28**). Hydrolysis of **27** (976 mg, 3.1 mmol) according to 2.1 yielded 691 mg (100 %) of **28**. Colorless powder. M.p. 145.6–149.5°. IR: 3385s, 3100m, 3070m, 2985m, 1645s, 1630s, 1595s, 1585s, 1550s, 1540s, 1485s, 1475s, 1460s, 1410m, 1385m, 1310m, 1250m, 1210m, 1180m, 1125w, 1080w, 1040w, 1020w, 1000w, 755m, 695m, 625m. 1H -NMR: 8.29 (s, NH); 7.25–7.15 (m, 3 arom. H); 6.9–6.85 (m, 1 arom. H); 1.49 (s, Me_2C). ^{13}C -NMR: 178.5, 165.4 (2s, 2 C=O); 157.9, 137.1 (2s, 2 arom. C); 129.6, 118.3, 117.6, 114.3 (4d, 4 arom. CH); 56.9 (s, Me_2C); 24.8 (q, Me_2C). CI-MS: 224 (100, $[M + 1]^+$).

7.3. 2-[2-(3-Hydroxybenzamido)-2-methylpropanamido]-2,N-dimethyl-N-phenylpropanamide (**29**). Reaction of **28** (564 mg, 2.52 mmol) with **7a** (438 mg, 2.5 mmol) according to 1.1 gave 860 mg (86 %) of **29**. Colorless powder. M.p. 197.6–198°. IR: 3350s, 3190s, 3060m, 3020m, 2990m, 2940m, 1660s, 1630s, 1590s, 1575s, 1530s, 1495s, 1480s, 1440s, 1390s, 1370s, 1320s, 1280m, 1240s, 1220s, 1205s, 1180s, 1125m, 1090s, 1025w, 1000m, 865m, 820m, 770s, 710s, 695s, 620s. 1H -NMR: 9.63 (s, OH); 8.00, 7.71 (2s, 2 NH); 7.4–7.2 (m, 8 arom. H); 6.96–6.9 (m, 1 arom. H); 3.24 (s, MeN); 1.45, 1.35 (2s, 2 Me_2C). ^{13}C -NMR: 173.3, 172.5, 166.0 (3s, 3 C=O); 157.2, 145.6, 136.4 (3s, 3 arom. C); 129.1, 128.7, 127.3, 126.4, 118.0, 117.9, 114.3 (7d, 9 arom. CH); 56.7, 56.6 (2s, 2 Me_2C); 40.0 (q, MeN); 25.6, 24.8 (2q, 2 Me_2C). CI-MS: 398 (100, $[M + 1]^+$). Anal. calc. for $C_{22}H_{27}N_3O_4$ (397.47): C 66.48, H 6.85, N 10.57; found: C 66.68, H 7.05, N 10.49.

7.4. 2-[2-(3-Hydroxybenzamido)-3-methylpropanamido]-2-methylpropanoic Acid (**31**). Hydrolysis of **29** (300 mg, 0.75 mmol) according to 2.1 yielded 219 mg (95 %) of **31**. Colorless plates. M.p. 184–185°. IR: 3280s, 3060m, 2990s, 2940m, 1740s, 1665s, 1640s, 1570s, 1550s, 1495s, 1485m, 1460m, 1390s, 1365m, 1315s, 1255m, 1230s, 1170m, 1150m, 1085w, 1020w, 1000w, 760m, 690m, 650m. 1H -NMR: 12.20 (br. s, COOH); 9.62 (s, OH); 8.12, 7.58 (2s, 2 NH); 7.25–7.15 (m, 3 arom. H); 6.95–6.85 (m, 1 arom. H); 1.44, 1.34 (2s, 2 Me_2C). ^{13}C -NMR: 175.8, 173.4, 166.0 (3s, 3 C=O); 157.2, 136.3 (2s, 2 arom. C); 129.2, 118.0, 117.9, 114.2 (4d, 4 arom. CH); 56.4, 55.2 (2s, 2 Me_2C); 24.7, 24.5 (2q, 2 Me_2C). CI-MS: 309 (100, $[M + 1]^+$), 224 (28), 206 (62), 104 (36).

7.5. 2-[2-(3-Hydroxybenzamido)-2-methylpropanamido]-2-methylpropanamide (**32**). Reaction of **31** (150 mg, 0.48 mmol) with **7a** (83 mg, 0.48 mmol) according to 1.1 gave 220 mg (95 %) of **32**. Colorless powder. M.p. 241–242°. IR: 3420s, 3250s, 3060m, 2990m, 2940m, 1690s, 1640s, 1585s, 1550s, 1535s, 1495s, 1465s, 1395s, 1370s, 1330s, 1265m, 1240m, 1225s, 1210s, 1175m, 1165m, 1125w, 1115w, 1095s, 1070w, 1020w, 1000w, 770m, 745m, 710s, 620m. 1H -NMR: 9.68 (br. s, OH); 8.38 (s, NH); 7.6–7.55 (m, 1 arom. H, NH); 7.4–7.15 (m, 7 arom. H, NH); 6.95–6.9 (m, 1 arom. H); 3.25 (s, MeN); 1.44, 1.40, 1.30 (3s, 3 Me_2C). ^{13}C -NMR: 173.9, 172.9, 172.6, 166.9 (4s, 4 C=O); 157.2, 146.0, 135.7 (3s, 3 arom. C); 129.1, 128.6, 126.8, 125.9, 118.3, 118.1, 114.5 (7d, 9 arom. CH); 56.5, 56.3, 56.0 (3s, 3 Me_2C); 39.9 (q, MeN); 25.7, 25.1, 24.7 (3q, 3 Me_2C). CI-MS: 376 (100, $[M - Ph(Me)N]^+$), 291 (21), 108 (93), 58 (19). Anal. calc. for $C_{26}H_{34}N_4O_5$ (482.57): C 64.71, H 7.10, N 11.61; found: C 64.61, H 6.96, N 11.62.

7.6. Attempted Cyclization of **32**. Analogously to 4.1, a soln. of **32** (125 mg, 0.25 mmol) in DMF (32 ml, $c = 0.008M$) was treated with HCl gas. After the usual workup, 2-[2-(3-hydroxybenzamido)-2-methylpropanamido]-2-methylpropanamide (**34**) was isolated: 85 mg (87 %). Colorless powder. M.p. 155–157°. IR: 3340s, 2990s, 2940m, 1715s, 1650s, 1595s, 1540s, 1450s, 1390m, 1370m, 1305s, 1260m, 1230s, 1195m, 1180m, 1075w, 1030m, 1000w, 760m, 690m, 610m. 1H -NMR: 9.77 (br. s, OH); 8.33, 7.59, 7.52 (3s, 3 NH);

7.35–7.25 (*m*, 3 arom. H); 6.95 (*d*, *J* = 7.8, 1 arom. H); 1.39, 1.36, 1.26 (3*s*, 3 Me₂C). ¹³C-NMR: 175.8, 173.4, 173.2, 166.8 (4*s*, 4 C=O); 157.3, 135.7 (2*s*, 2 arom. C); 129.0, 118.3, 118.1, 114.6 (4*d*, 4 arom. CH); 56.5, 55.7, 54.9 (3*s*, 3 Me₂C); 24.9, 24.7, 24.6 (3*t*, 3 Me₂C). CI-MS: 394 (100, [*M* + 1]⁺).

Recrystallization of **34** from MeOH yielded crystals suitable for an X-ray crystal-structure determination.

8. *Tripeptide Derivatives of Type 36 and 37*. Reaction of 1 mmol of **10** or **22** with 5 ml of 3*N* HCl (THF/H₂O 1:1) and workup according to 2.1 led to the corresponding carboxylic acids **36** and **37**, resp., in almost quantitative yields.

8.1. 2-[2-(2-Hydroxybenzamido)-2-methylpropanamido]-2-methylpropanoic Acid (**36a**): Colorless microcrystals. M.p. 195–196.3°. IR: 3350*m*, 3320*m*, 3060*m*, 3040*m*, 2990*m*, 1710*s*, 1650*s*, 1630*s*, 1605*s*, 1550*s*, 1500*w*, 1460*m*, 1440*w*, 1420*w*, 1385*m*, 1320*m*, 1285*w*, 1250*w*, 1225*w*, 1185*w*, 1095*m*, 1040*m*, 1020*w*, 940*s*, 890*s*, 870*m*, 785*m*, 755*s*, 615*s*. ¹H-NMR: 12.14 (*s*, COOH); 11.82 (*s*, OH); 8.81 (*s*, NH); 7.9–7.85 (*m*, 1 arom. H); 7.71 (*s*, NH); 7.4–7.3 (*m*, 1 arom. H); 6.9–6.85 (*m*, 2 arom. H); 1.50, 1.34 (2*s*, 2 Me₂C). ¹³C-NMR: 175.6, 173.1, 166.9 (3*s*, 3 C=O); 158.4 (*s*, 1 arom. C); 133.1, 129.1, 118.6, 117.6 (4*d*, 4 arom. CH); 116.9 (*s*, 1 arom. C); 56.6, 55.2 (2*s*, 2 Me₂C); 29.7, 29.6 (2*q*, 2 Me₂C). CI-MS: 309 (100, [*M* + 1]⁺).

8.2. 1-[1-(2-Hydroxybenzamido)cyclopentanecarboxamido]cyclopentanecarboxylic Acid (**36b**): Colorless microcrystals. M.p. 218–219°. IR: 3400*s*, 3340*s*, 2960*m*, 2880*m*, 1700*s*, 1655*s*, 1640*s*, 1600*s*, 1530*s*, 1515*s*, 1490*s*, 1470*w*, 1450*s*, 1410*w*, 1370*s*, 1340*s*, 1305*s*, 1260*m*, 1230*s*, 1210*m*, 1170*w*, 1150*w*, 1120*w*, 1040*w*, 790*m*, 760*s*. ¹H-NMR: 11.90 (*s*, COOH); 8.49 (*s*, NH); 7.87 (*dd*, *J* = 6.6, 1.3, 1 arom. H); 7.65 (*s*, NH); 7.4–7.3 (*m*, 1 arom. H); 6.9–6.85 (*m*, 2 arom. H); 2.25–2.1 (*m*, 2H); 1.95–1.8 (*m*, 6H); 1.65–1.45 (*m*, 8H). ¹³C-NMR: 175.7, 172.9, 168.6 (3*s*, 3 C=O); 159.3 (*s*, 1 arom. C); 133.5, 129.1, 118.7, 117.1 (4*d*, 4 arom. CH); 117.0 (*s*, 1 arom. C); 66.6, 65.2 (2*s*, 2 C(α)); 36.2, 36.1, 24.5, 24.0 (4*t*, 8 CH₂). EI-MS: 360 (9, *M*⁺), 231 (25), 205 (17), 204 (68), 203 (20), 121 (62), 85 (15), 84 (100), 83 (24), 67 (12), 65 (13).

8.3. 2-{2-[2-[(Benzyloxy)carbonyl]amino]benzamido}-2-methylpropanamido}-2-methylpropanoic Acid (**37**). Colorless powder. M.p. 150.2–151°. IR: 3350*s* (br.), 3300*s* (br.), 3040*w*, 2980*w*, 2940*w*, 1730*s*, 1710*s*, 1660*s*, 1590*s*, 1540*s*, 1515*s*, 1450*s*, 1400*w*, 1380*w*, 1365*w*, 1305*m*, 1280*m*, 1240*m*, 1215*s*, 1185*w*, 1170*w*, 1100*w*, 1045*m*, 1030*w*, 760*m*, 695*m*. ¹H-NMR: 12.20 (br. *s*, COOH); 10.37, 8.44 (2*s*, 2 NH); 8.09 (*d*, *J* = 8, 1 arom. H); 7.76 (*d*, *J* = 8, 1 arom. H); 7.58 (*s*, NH); 7.55–7.3 (*m*, 6 arom. H); 7.15–7.1 (*m*, 1 arom. H); 5.13 (*s*, PhCH₂); 1.41, 1.28 (2*s*, 2 Me₂C). ¹³C-NMR: 175.8, 172.8, 167.9, 152.8 (4*s*, 4 C=O); 138.3, 136.4 (2*s*, 2 arom. C); 131.8, 128.6, 128.4, 128.0, 127.9, 121.9 (6*d*, 8 arom. CH); 121.6 (*s*, 1 arom. C); 119.0 (*d*, 1 arom. CH); 66.0 (*t*, PhCH₂); 56.6, 55.0 (2*s*, 2 Me₂C); 24.7, 24.4 (2*q*, 2 Me₂C). CI-MS: 424 (9, [*M* – H₂O]⁺), 339 (100), 104 (26).

9. *Tetrapeptide Derivatives of Type 38 and 39*. 9.1. *General Procedure*. To well stirred suspensions of **36** and **37** in 4 ml of dry MeCN and *i*-PrOH, resp., a soln. of 1 mmol of the corresponding 2*H*-azirin-3-amine **7** in 1 ml of MeCN or *i*-PrOH was added at r.t. The mixture was stirred overnight, and the formed solid was collected by filtration, washed with hexane, and dried under h.v.

9.2. 2-[2-[2-(2-Hydroxybenzamido)-2-methylpropanamido]-2-methylpropanamido]-2, *N*-dimethyl-*N*-phenylpropanamide (**38a**). Yield 428 mg (89%). Colorless powder. M.p. 224° (dec.). IR: 3340*s*, 3310*s*, 3060*w*, 2980*m*, 2930*m*, 1680*s*, 1660*s*, 1630*s*, 1595*s*, 1530*s*, 1500*s*, 1495*s*, 1470*s*, 1440*m*, 1415*w*, 1390*s*, 1365*s*, 1340*s*, 1305*s*, 1260*s*, 1230*s*, 1210*s*, 1170*s*, 1140*w*, 1110*w*, 1090*w*, 1040*w*, 1025*w*, 1000*w*, 780*m*, 750*s*, 710*s*. ¹H-NMR: 11.64 (br. *s*, OH); 8.74 (*s*, NH); 7.9–7.85 (*m*, 1 arom. H); 7.62 (*s*, NH); 7.45–7.3 (*m*, 4 arom. H); 7.2–7.15 (*m*, 2 arom. H, NH); 6.95–6.9 (*m*, 2 arom. H); 3.23 (*s*, MeN); 1.44, 1.41, 1.30 (3*s*, 3 Me₂C). CI-MS: 483 (21, [*M* + 1]⁺), 376 (100).

9.3. 1-[1-[1-(2-Hydroxybenzamido)cyclopentanecarboxamido]cyclopentanecarboxamido]-*N*-methyl-*N*-phenylcyclopentanecarboxamide (**38b**). Yield 537 mg (96%). Colorless powder. M.p. 285–285.3°. IR: 3340*s*, 3070*w*, 2960*m*, 2880*m*, 1680*s*, 1645*s*, 1600*s*, 1545*s*, 1540*s*, 1525*s*, 1500*s*, 1445*m*, 1375*m*, 1340*m*, 1330*m*, 1310*m*, 1260*m*, 1235*m*, 1210*m*, 1175*w*, 1145*w*, 1125*w*, 1040*w*, 1030*w*, 775*m*, 705*m*, 610*m*. ¹H-NMR: 8.91 (br. *s*, NH); 7.82 (*d*, *J* = 7.1, 1 arom. H); 7.65–7.05 (*m*, 6 arom. H, 2 NH); 7.0–6.85 (*m*, 2 arom. H); 3.20 (*s*, MeN); 2.25–1.8 (*m*, 12 H); 1.65–1.55 (*m*, 12 H). ¹³C-NMR ((D₆)DMSO/CF₃COOH): 176.0, 174.2, 173.6, 169.1 (4*s*, 4 C=O); 158.8, 138.2 (2*s*, 2 arom. C); 133.9, 130.6, 130.5, 129.6, 122.8, 119.4, 117.5 (7*d*, 9 arom. CH); 112.9 (*s*, 1 arom. C); 67.3, 66.6, 65.7 (3*s*, 3 C(α)); 39.8 (*q*, MeN); 39.7, 37.0, 36.0, 25.0, 24.8, 24.5 (6*t*, 12 CH₂). CI-MS: 454 (83, [*M* – Ph(Me)N]⁺), 453 (15), 343 (42), 319 (2), 138 (43), 108 (100), 107 (44).

9.4. 2-[2-[2-[2-[(Benzyloxy)carbonyl]amino]benzamido]-2-methylpropanamido]-2-methylpropanamido]-2, *N*-dimethyl-*N*-phenylpropanamide (**39a**). Yield 565 mg (92%). Colorless powder. M.p. 237.3–238.7°. IR: 3320*s*, 3270*m*, 3060*w*, 3030*w*, 2990*w*, 2940*w*, 1740*s*, 1660*s*, 1630*s*, 1595*s*, 1545*m*, 1525*s*, 1515*s*, 1495*s*, 1450*s*, 1390*m*, 1360*m*, 1330*m*, 1300*m*, 1280*m*, 1210*s*, 1170*m*, 1090*m*, 1040*m*, 1000*w*, 760*m*, 705*m*. ¹H-NMR: 10.36, 8.73 (2*s*, 2 NH); 8.11 (*d*, *J* = 7.5, 1 arom. H); 7.85 (*d*, *J* = 6.5, 1.4, 1 arom. H); 7.70 (*s*, NH); 7.55–7.5 (*m*, 1 arom. H); 7.4–7.25 (*m*, 7 arom. H, NH); 7.15–7.05 (*m*, 4 arom. H); 5.13 (*s*, PhCH₂); 3.14 (*s*, MeN); 1.40, 1.30, 1.29 (3*s*, 3 Me₂C). ¹³C-NMR (CD₃OD): 176.4, 175.3, 171.0, 154.8 (4*s*, 5 C=O); 146.5, 140.3, 137.5 (3*s*, 3 arom. C); 133.6,

130.1, 129.9, 129.6, 129.5, 129.4, 128.2, 128.0, 123.4 (9d, 13 arom. CH); 121.6 (s, 1 arom. C); 120.5 (d, 1 arom. CH); 67.9 (t, PhCH₂); 58.5, 58.4, 58.0 (3s, 3 Me₂C); 41.0 (q, MeN); 26.5, 25.6, 25.2 (3q, 3 Me₂C). CI-MS: 509 (40, [M – Ph(Me)N]⁺), 403 (18), 402 (100), 279 (14).

9.5. 2-{2-[2-(2-Aminobenzamido)-2-methylpropanamido]-2-methylpropanamido}-2,N-dimethyl-N-phenylpropanamide (**39b**). Reaction of 420 mg (0.68 mmol) of **39a** with H₂ (Pd/C) according to 5.2 led to 289 mg (88%) of **39b**. Colorless microcrystals. M.p. 247–248°. IR: 3430s, 3340m, 3270s, 3040w, 2990m, 2940w, 1680s, 1665s, 1630s, 1590s, 1570m, 1540s, 1490s, 1465m, 1450m, 1440m, 1395m, 1380m, 1360m, 1310m, 1265m, 1220m, 1170m, 1090m, 1070w, 1040w, 1020w, 755m, 710m, 665m, 615m. ¹H-NMR: 8.20 (s, NH); 7.65 (d, *J* = 6.9, 1 arom. H); 7.59, 7.53 (2s, 2 NH); 7.35–7.15 (m, 6 arom. H); 6.70 (d, *J* = 7.9, 1 arom. H); 6.6–6.55 (m, 1 arom. H); 6.27 (s, NH₂); 3.23 (s, MeN); 1.40, 1.30 (2s, 3 Me₂C). ¹³C-NMR: 174.0, 173.1, 172.5, 169.4 (4s, 4 C=O); 149.4, 145.9 (2s, 2 arom. C); 131.9, 129.1, 128.6, 126.9, 126.0, 116.2 (6d, 8 arom. CH); 115.1 (s, 1 arom. C); 114.7 (d, 1 arom. CH); 56.3, 56.0 (2s, 3 Me₂C); 38.2 (q, MeN); 25.7, 24.9, 24.8 (3q, 3 Me₂C). CI-MS: 482 (15, [M + 1]⁺), 375 (100).

10. Attempted Cyclization of **38**. Analogously to 4.1, **38** (0.25 mmol) in DMF (32 ml, *c* = 0.008M) was reacted with dry HCl gas. Only the hydrolyzed products of type **40** were obtained.

10.1. 2-{2-[2-(2-Hydroxybenzamido)-2-methylpropanamido]-2-methylpropanamido}-2-methylpropanoic Acid (**40a**): Yield 81 mg (87%). Colorless powder. M.p. 237–238.5°. IR: 3340s (br.), 2980m, 2940m, 1730s, 1640s, 1600s, 1550s, 1530s, 1455m, 1390m, 1370m, 1310m, 1230s, 1170m, 1095w, 1040w, 760m, 705w. ¹H-NMR: 11.86 (br. s, COOH); 8.78 (s, NH); 7.9–7.85 (m, 1 arom. H); 7.69 (s, NH); 7.4–7.35 (m, 1 arom. H, NH); 6.95–6.9 (m, 2 arom. H); 1.44, 1.36, 1.28 (3s, 3 Me₂C). ¹³C-NMR: 175.6, 173.4, 172.8, 167.4 (4s, 4 C=O); 158.4 (s, 1 arom. C); 133.3, 129.3, 118.7, 117.2 (4d, 4 arom. CH); 117.0 (s, 1 arom. C); 56.5, 55.8, 54.8 (3s, 3 Me₂C); 24.9, 24.8, 24.6 (3q, 3 Me₂C). CI-MS: 376 (100, [M + 1]⁺).

10.2. 1-{1-[1-(2-Hydroxybenzamido)cyclopentanecarboxamido]cyclopentanecarboxamido}cyclopentanecarboxylic Acid (**40b**): Yield 99 mg (84%). Colorless powder. M.p. 263.4–264.1°. IR: 3380s, 3340s, 2970m, 2880m, 1730s, 1685s, 1640s, 1600s, 1590s, 1550s, 1540s, 1520s, 1500s, 1445m, 1370m, 1345m, 1315m, 1220m, 1205m, 1160w, 1115w, 1050w, 760m, 610m. ¹H-NMR: 8.77 (s, NH); 7.89 (d, *J* = 8.4, 1 arom. H); 7.70 (s, NH); 7.45–7.35 (m, 1 arom. H, NH); 6.95–6.9 (m, 2 arom. H); 2.25–1.5 (m, 12 CH₂). ¹³C-NMR: 175.5, 173.0, 172.9, 168.3 (4s, 4 C=O); 158.2 (s, 1 arom. C); 133.4, 129.6, 119.0 (3d, 3 arom. CH); 117.9 (s, 1 arom. C); 117.1 (d, 1 arom. CH); 66.7, 66.0, 65.1 (3s, 3C(α)); 36.6, 36.3, 24.6, 24.4, 24.1 (5t, 12 CH₂). CI-MS: 472 (54, [M + 1]⁺), 455 (12), 454 (40), 343 (47), 337 (52), 319 (13), 232 (34), 231 (11), 226 (13), 208 (34), 204 (26), 180 (18), 138 (100), 137 (17), 130 (29).

11. X-Ray Crystal-Structure Determination of Compounds **25** and **34**³⁾. For **25**, all measurements were made on a Nicolet-R3 diffractometer, while for **34**, a Rigaku-AF5CR diffractometer fitted to a 12-kW rotating anode generator was employed. MoK_α radiation (*λ* = 0.71069 Å) was used in both cases. The intensities were corrected for Lorentz and polarization effects but not for absorption. The structures were solved by direct methods using SHELXS86 [32] which revealed the positions of all non-H-atoms. The non-H-atoms were refined anisotropically. For **25**, all H-atoms were located in a difference electron density map, and their positions were allowed to refine together with individual isotropic displacement parameters. For **34**, all H-atoms were initially located in a difference electron density map, but the positions of the Me and Ph H-atoms were subsequently fixed in geometrically idealized positions with a C–H distance of 0.95 Å, the orientations of the Me groups being based on the difference map positions. The positions of the remaining H-atoms (NH and OH) were allowed to refine, and individual isotropic displacement parameters were refined for all H-atoms. All refinements were carried out on *F* using full-matrix least-squares procedures which minimized the function $\sum w(|F_o| - |F_c|)^2$, where $1/w = [\sigma^2(F_o) + (pF_o)^2]$. Data collection and refinement parameters are listed in Table 3, and views of the molecules are shown in Figs. 1 and 2. Neutral-atom scattering factors for non-H-atoms were taken from [33a] and the scattering factors for H-atoms from [34]. Anomalous dispersion effects were included in *F*_{calc} [35]; the values of *f*' and *f*'' were those of [33b]. All calculations were performed using the TEXSAN [36] crystallographic software package.

For **25**, intermolecular H-bonds between N(1)–H and O(1') (*d*(N···O) = 2.915(2), *d*(H···O) = 2.03(2) Å, N–H···O angle = 175(2)°) link the molecules into centrosymmetric dimers. The crystal lattice of **34** contains

³⁾ Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication No. CCDC-10/47. Copies of the data can be obtained, free of charge, on application to the Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: + 44(0)1223 336033, or email: teched@chemcrs.cam.ac.uk).

Table 3. Crystallographic Data for Compounds **25** and **34**

	25	34
Crystallized from	MeOH	MeOH
Empirical formula	C ₁₅ H ₁₇ N ₃ O ₂	C ₁₉ H ₂₇ N ₃ O ₆ · CH ₃ OH
Formula weight	271.32	425.48
Crystal color, habit	colorless, prism	colorless, plate
Temp. [K]	295(1)	173(1)
Crystal dimensions [mm]	0.21 × 0.28 × 0.55	0.15 × 0.40 × 0.50
Crystal system	triclinic	monoclinic
Lattice parameters:		
Reflections for unit cell determination	25	18
2 θ range [°]	28–32	35–39
<i>a</i> [Å]	5.8265(6)	18.689(3)
<i>b</i> [Å]	8.663(1)	9.479(3)
<i>c</i> [Å]	13.718(2)	13.472(2)
α [°]	94.38(1)	90
β [°]	94.22(1)	105.67(1)
γ [°]	89.82(1)	90
<i>V</i> [Å ³]	688.5(2)	2298.0(8)
Space group	<i>P</i> $\bar{1}$	<i>Cc</i>
<i>Z</i>	2	4
<i>D</i> _x [g cm ^{−3}]	1.309	1.230
Absorp. coefficient μ (MoK α) [mm ^{−1}]	0.0891	0.0931
Scan type	Wyckoff- ω	ω -2 θ
2 $\theta_{\max}$ [°]	55	60
Total reflections measured	3492	3632
Symmetry-independent reflections	3178	3441
Reflections observed (<i>I</i> > 2 σ (<i>I</i>))	2444	2907
Variables	250	318
<i>R</i>	0.0443	0.0454
<i>R</i> _w	0.0487	0.0449
Goodness of fit <i>s</i>	2.367	2.158
Weighting scheme	0.01	0.0075
<i>p</i> for $w = [\sigma^2(F_o) + (pF_o)^2]^{-1}$		
Final $\Delta_{\max}/\sigma$	0.0003	0.002
$\Delta\rho_{(\max; \min)}$ [eÅ ^{−3}]	0.24, −0.24	0.44, −0.27

one molecule of MeOH for every molecule of **34**. The peptide and the solvent molecules are linked into an infinite 3-dimensional network by a complex pattern of intermolecular H-bonds (Fig. 3). There are two weak intramolecular H-bonds between N(3)–H and O(1) ($d(\text{N} \cdots \text{O}) = 3.070(3)$, $d(\text{H} \cdots \text{O}) = 2.40(3)$ Å, N–H $\cdots$ O angle = 143(3)°), and N(3)–H and N(2) ($d(\text{N} \cdots \text{N}) = 2.762(4)$, $d(\text{H} \cdots \text{N}) = 2.35(3)$ Å, N–H $\cdots$ N angle = 113(3)°) thus forming the β -turn-like conformation of the peptide backbone. Intermolecular H-bonds exist between N(1)–H and O(4') of a neighboring peptide molecule ($d(\text{N} \cdots \text{O}) = 2.974(3)$, $d(\text{H} \cdots \text{O}) = 2.20(3)$ Å, N–H $\cdots$ O angle = 163(3)°), as well as between O(6)–H and O(3') of the same neighboring molecule ($d(\text{O} \cdots \text{O}) = 2.628(3)$, $d(\text{H} \cdots \text{O}) = 1.94(5)$ Å, O–H $\cdots$ O angle = 160(6)°), and between N(2)–H and O(6'') of a third peptide molecule ($d(\text{N} \cdots \text{O}) = 3.313(4)$, $d(\text{H} \cdots \text{O}) = 2.53(3)$ Å, N–H $\cdots$ O angle = 153(3)°). MeOH acts as an H-acceptor for O(5)–H ($d(\text{O} \cdots \text{O}) = 2.580(4)$, $d(\text{H} \cdots \text{O}) = 1.66(4)$ Å, O–H $\cdots$ O angle = 169(4)°) and as a donor to O(2) of a fourth peptide molecule ($d(\text{O} \cdots \text{O}) = 2.694(4)$, $d(\text{H} \cdots \text{O}) = 1.96(5)$ Å, O–H $\cdots$ O angle = 162(5)°).

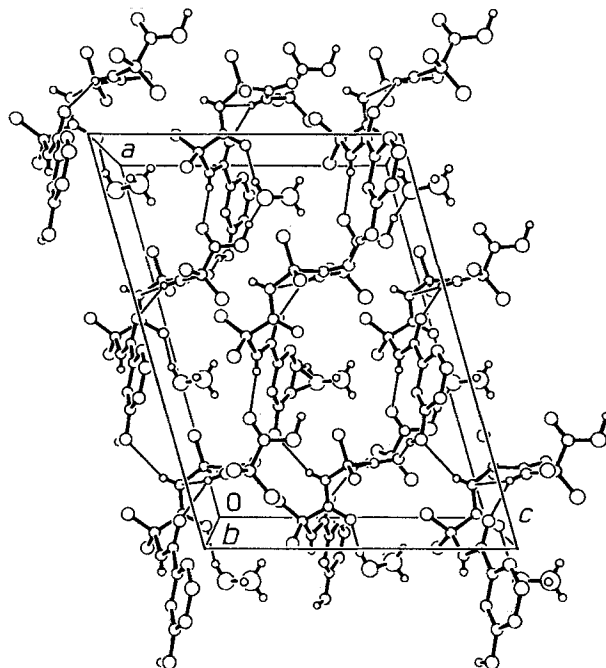


Fig. 3. Packing diagram of compound **34**, showing the hydrogen bonding

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