1,3-Oxazol-5(4*H*)-ones as Intermediates in the Formation of Macrolides, Cyclodepsipeptides and Cyclopeptides

Heinz Heimgartner*, Franziska S. Arnhold, Stephan P. Fritschi, Kristian N. Koch, J. E. Florian Magirius and Anthony Linden

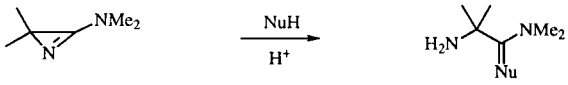
Organisch-chemisches Institut der Universität Zürich, Winterthurerstrasse 190, CH-8057 Zürich, Switzerland

J. Heterocyclic Chem., **36**, 1539 (1999).

Introduction.

During our ongoing studies into the use of 3-amino-2*H*-azirines **1** in organic synthesis [1] we have shown that these cyclic three-membered amidines are versatile building blocks for α,α-disubstituted glycines. *E.g.*, the acid-catalyzed ring opening of 3-dimethylamino-2,2-dimethyl-2*H*-azirine (**1a**) with nucleophiles yields derivatives of 2-aminoisobutyric acid (Aib) (**2**) (*cf.* [2], Scheme 1).

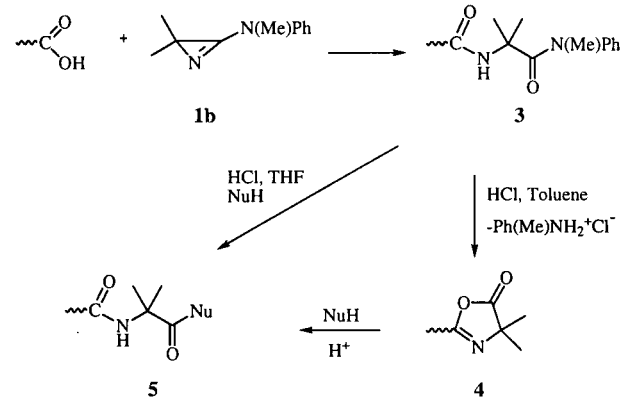
Scheme 1



1a **2**

Especially interesting is their potential in the preparation of peptides which contain α,α-disubstituted glycines [3-6]. The strategy for the addition of 2-aminoisobutyric acid to a peptide chain by using the 'azirine/oxazolone method' [7] is shown in Scheme 2: the coupling of a peptide acid with the 3-(*N*-methyl-*N*-phenylamino)-2*H*-azirine (**1b**) leads to the extended peptide amide **3**. Treatment of a suspension of **3** with dry hydrogen chloride gas yields 1,3-oxazol-5(4*H*)-one **4** (*cf.* [8]), which undergoes an acid-catalyzed nucleophilic ring opening to give the 2-aminoisobutyric acid peptide **5**. In principle, the nucleophile NuH can be a properly protected amino acid derivative or peptide segment, but for preparative purposes the direct hydrolysis of **3** to give the extended peptide acid **5** (Nu = OH) is most convenient. We propose that the observed selectivity of this hydrolysis is a result of the easy formation of an intermediate oxazolone of type **4**, which is assisted by the *gem*-dimethyl effect [9]. In the case of *N*-methyl-*N*-phenylamides **3**, the required conditions for the hydrolysis are astonishingly mild, *e.g.*, 3*N* hydrochloric acid in tetrahydrofuran/water at room temperature [7]. The peptide acid **5** is then submitted to segment condensations which, again, proceed *via* formation of a 1,3-oxazol-5(4*H*)-one as the reactive intermediate.

Scheme 2



1b **3** **5** **4**

The selectivity of the cleavage of a peptide chain containing an α,α-disubstituted amino acid is further used in a resolution of racemic α,α-disubstituted glycines [10,11]. After condensation of the racemic mixture with (*S*)-phenylalanine cyclohexylamide, chromatographic separation of the diastereoisomers followed by selective hydrolysis yields the enantiomerically pure (*R*)- and (*S*)-configured α,α-disubstituted α-amino acids and the unchanged chiral auxiliary.

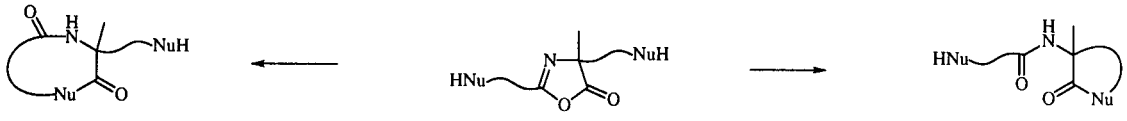
In all these intermolecular reactions with nucleophiles, the ring-opening of the intermediate 1,3-oxazol-5(4*H*)-one proceeds by cleavage of the O(1),C(5) bond, *i.e.*, the nucleophilic attack occurs at C(5). This is the 'normal' ring-opening observed in many reactions with water, alcohols, thioles, phenols, amines, hydrazines, and phosphates, as well as with some enzymes [12-17]. On the other hand, a few examples of the nucleophilic attack of water and hydrazoic acid at C(2) and subsequent cleavage of the O(1),C(2)-bond are also known [18,19].

A few years ago, we became interested in intramolecular nucleophilic ring opening reactions of 1,3-oxazol-5(4*H*)-ones which lead to the formation of new heterocyclic ring systems. We have elaborated protocols for the cyclization of hydroxy- and amino-substituted derivatives of type **3** *via* intermediate oxazolones **6** and formation of a lactone or lactam bond, respectively (Scheme 3). Depending on the position of the nucleophilic group (OH, NH_2), two different types of ring systems are formed. With NuH in the 'main chain' of **3**, *i.e.* at C(2) of the oxa-

zolone **6**, the ring enlargement to give products of type **7** has been used for the synthesis of cyclodepsipeptides and cyclopeptides, whereas with NuH in the 'side chain' of **3**, *i.e.* at C(4) of **6**, lactones and lactams of type **8** have been prepared.

With the aim of exemplifying the usefulness of this cyclization method, we chose tetrapeptide **13** as another model compound (Scheme 5). This precursor had been prepared by coupling aminoazirine **1a** to *Z*-alanine, deprotection of the amino group *via* hydrolysis, and coupling

Scheme 3



7 **6** **8**

Preparation of Cyclodepsipeptides.

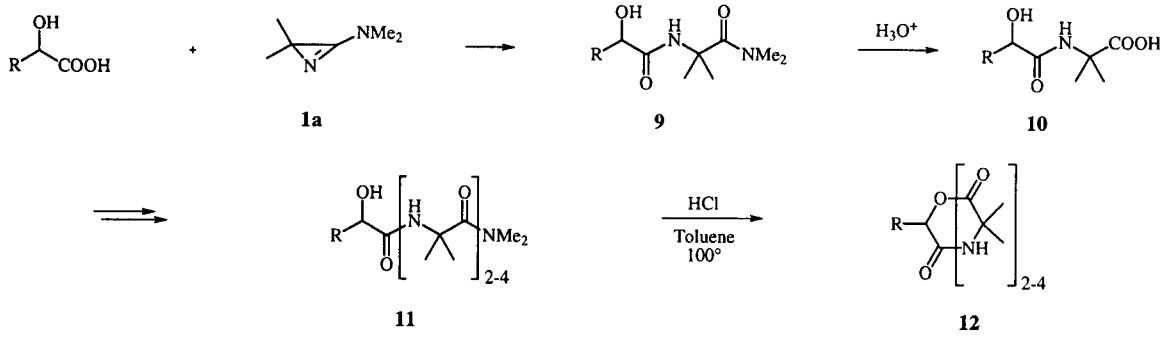
The reaction of α-hydroxy acids (R = Ph, $PhCH_2$) with aminoazirine **1a** and hydrolysis of the resulting **9** gave the acid **10** in high yield (Scheme 4). By repeating this sequence, the 'tri-, tetra-, and pentamers' **11** were obtained. Treatment of suspensions of them in dry toluene at 100° with hydrogen chloride gas led to the 9-, 12-, and 15-membered cyclodepsipeptides in 85, 90, and 86% yield, respectively [20]. The surprisingly high yield of this 'direct amide cyclization' can be rationalized by a smooth oxazolone formation with the C-terminal 2-aminoisobutyric acid and an intrinsic high dilution of the reactive intermediate as a result of the very low solubility of **11** in toluene.

with *N*-((*S*)-2-hydroxy-3-phenylpropanoyl)-L-proline. The cyclization of a suspension of **13** in toluene at 100° yielded cyclodepsipeptide **14** [21], which is an analogue of the cyclopeptide *Chlamydocin* [22].

The success of these early experiments encouraged us to investigate further examples starting with β-hydroxy acids. So far, the corresponding 10-membered cyclodepsipeptides have received little attention. The synthesis of this class of compounds has been achieved either by a ring enlargement of piperidin-2-ones by incorporation of a β-hydroxy acid [23] or by cyclization of the linear precursor *via* the 'active-ester method' [24].

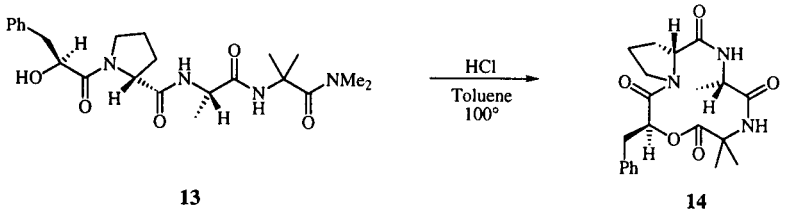
The linear 'trimers' **15** were prepared from salicylic acid either by a twofold coupling with 3-amino-2*H*-azirines **1**

Scheme 4



1a **9** **10** **11** **12**

Scheme 5

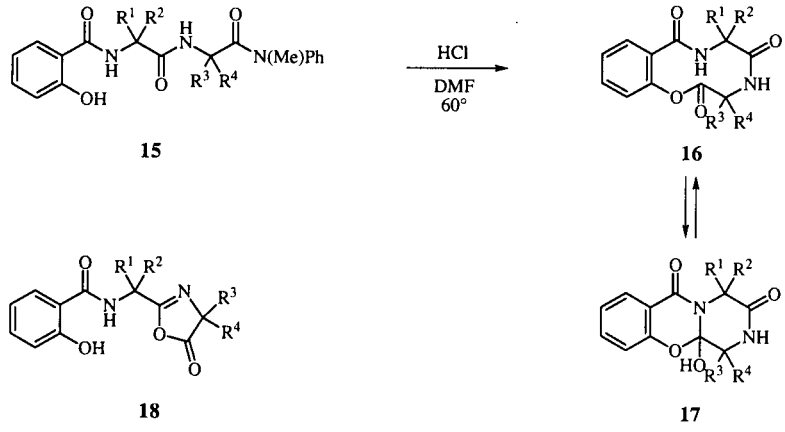


13 **14**

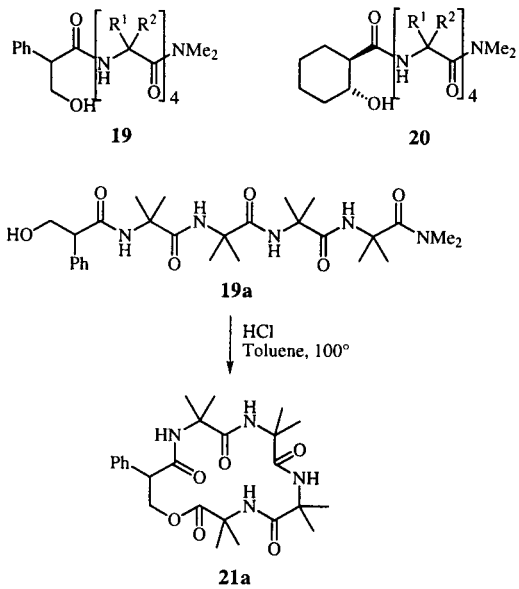
or by coupling with benzyl glycinate using a carbodiimide and, after deprotection, reaction with **1** (Scheme 6). The cyclization was performed with hydrogen chloride in dry dimethylformamide at 60° in 90-95% yield [25]. Spectroscopic studies revealed the existence of cyclodepsipeptides **16** in solution, but in the crystalline state, the corresponding 'oxacyclols' **17** are present. They are formed *via* a reversible transannular ring contraction (*cf.* [23,26,27]). Again, we believe that 1,3-oxazol-5(4*H*)-ones of type **18** are the reactive intermediates in the cyclizations of **15**. Unfortunately, all attempts to prepare larger analogous rings failed, and after workup, the corresponding acids were isolated as the only products.

As the interest in cyclodepsipeptides increases continuously [28], we extended our methodology to the synthesis of some 16-membered model compounds. Starting with 3-hydroxy-2-phenylpropanoic acid or *trans*-2-hydroxycyclohexanecarboxylic acid, the 'pentamers' **19** and **20**, respectively, were prepared by consecutive azirine coupling and selective hydrolysis [29] (Scheme 7). As expected, X-ray crystallography showed that these peptides adopt helical conformations (3_{10}-helices), which are characteristic of 2-aminoisobutyric acid-containing peptides (*cf.* [30-32]). The cyclizations were performed in toluene suspensions at 80-100° with hydrogen chloride gas and led to the 16-membered cyclodepsipeptides **21** in yields of 40-60%. The crystal structure of **21a** is shown in Figure 1. It is worth mentioning that two β-turns are characteristic elements of this structure, including two '10-membered rings' resulting from the formation of two intramolecular H-bonds.

Scheme 6



Scheme 7



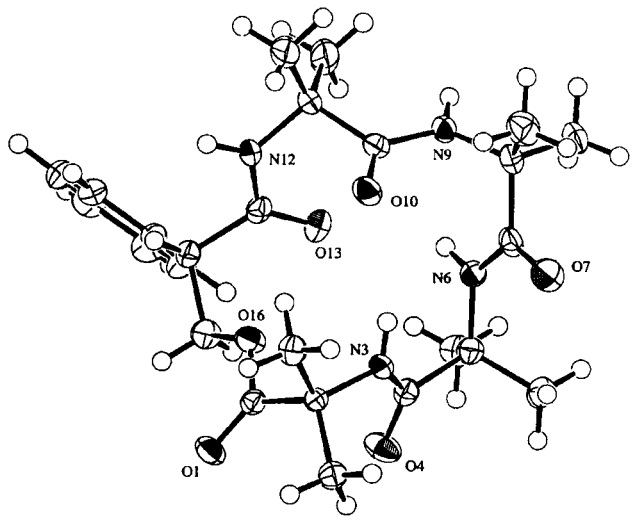


Figure 1.

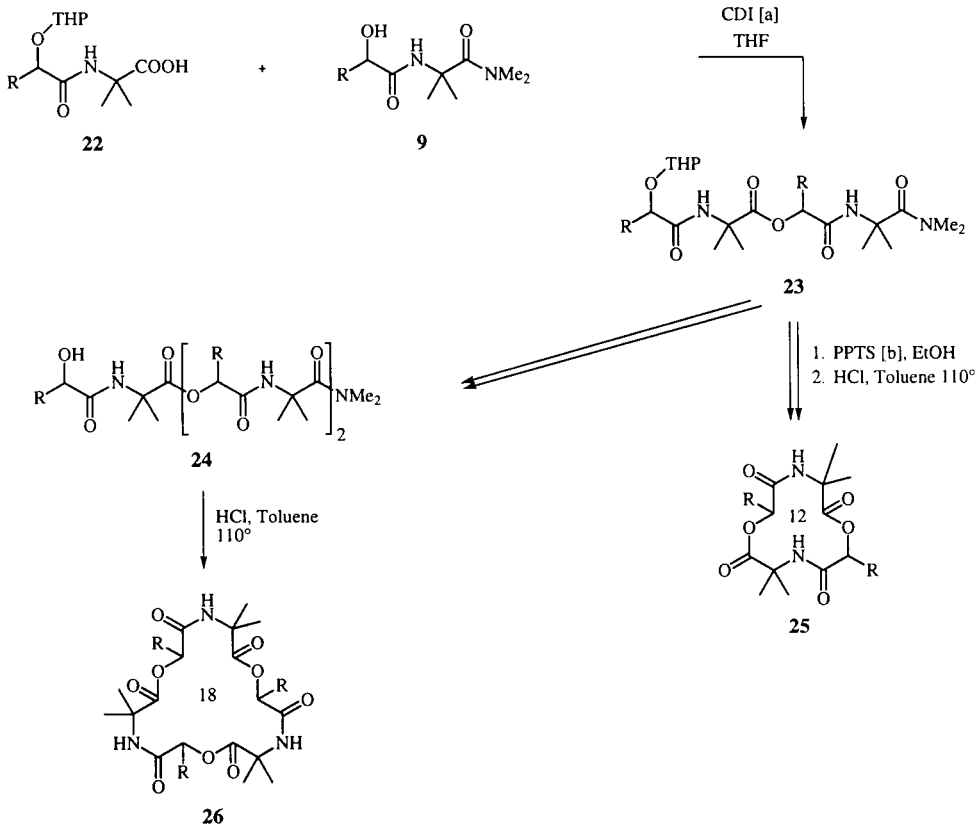
Preliminary experiments have shown that 19- and 22-membered cyclodepsipeptides with structures analogous to **21** can also be prepared by the same methodology. After selective hydrolysis of the terminal amide group of **19**, the peptide backbone was extended by one or two 2-aminoisobutyric acid units *via* the azirine coupling method. Cyclization under the usual conditions gave the desired compounds in 15-25% yield.

An important class of naturally occurring cyclodepsipeptides are the 18-membered *Enniatins* [33]. These ionophore antibiotics consisting of an alternating sequence of (*R*)-configured α-hydroxy and (*S*)-configured α-amino acids are related structurally to *Valinomycin*. Our goal was to prepare analogous model compounds containing α,α-disubstituted glycines by using the 'azirine/oxazolone method' in combination with the 'direct amide cyclization' [34,35]. The synthesis of 'tetramers' of type **23** was achieved in a straightforward manner by coupling **9** to O-protected 'dimers' **22**. Treatment of suspensions of **23** in dry toluene with hydrogen chloride gas yielded 12-membered cyclodepsipeptides of type **25** (Scheme 8). Deprotection of the hydroxy group of **23**, coupling with a third 'dimer' **22**, and acid catalyzed cyclization of the resulting **24** gave the expected 18-membered products **26** in 18-54% yield.

Synthesis of Cyclopeptides.

Since the elucidation of the cyclic structure of the antibiotic *Gramicidine S* in 1945 [36] and its first synthesis in 1957 [37], cyclic peptides continue to arouse great interest (*cf.* [38]). Other well known examples of homodetic cyclopeptides are the cycloundecapeptide *Cyclosporin A*, the cyclodecapeptide *Antamanide*, the cyclic octapeptide *Amatoxin*, the cycloheptapeptide *Phallotoxin*, and the cyclopentapeptides *Malformin*. As cyclopeptides containing α,α-disubstituted α-amino acids are almost unknown, we decided to prepare some model compounds using the methodology which has been successfully applied to the synthesis of cyclic depsipeptides. Unfortunately, the 'direct amide cyclization' *via* an intermediate 1,3-oxazol-5(4*H*)-one of type **6** and formation of a lactam bond (→ **7** (NuH = NH_2), Scheme 3) failed to give the corresponding cyclopeptides, because under the acidic conditions needed for this cyclization, the primary amino group of a peptide amide of type **6** is completely protonated. There is only one exception known so far (Scheme 9): starting with Z-protected anthranilic acid, the linear tripeptide **28** was prepared by repeated coupling with aminoazirine **1b** and deprotection of the amino group by

Scheme 8

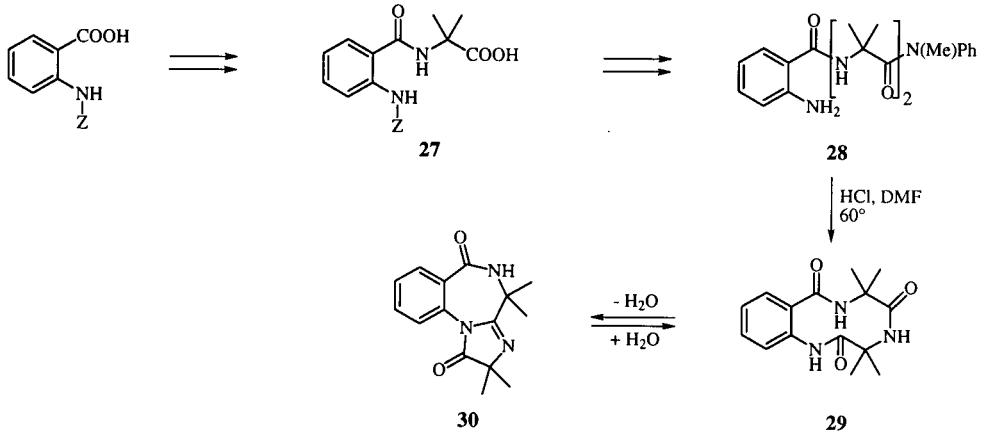


[a] CDI: *N,N'*-Carbonyldiimidazole; [b] PPTS: Pyridinium *p*-Toluenesulfonate.

hydrogenolysis. The cyclization was performed in dimethylformamide at 60° by treatment with hydrogen chloride gas. Under the conditions of its formation, the 10-membered cyclotripeptide **29** underwent a transannular ring contraction followed by elimination of water to yield the tricyclic product **30** [25]. The structure of the latter was established by X-ray crystallography. The nmr studies showed that in dimethyl sulfoxide solutions **29** and **30** are in an equilibrium which, at 100°, is strongly in favor of the 10-membered ring (for an analogous cyclotripeptide see [39]).

(Scheme 10). After deprotection, the cyclization of Gly-D,L-Phe(2Me)-Aib-Aib-Gly (**31** n = 2) with diphenyl phosphorazidate as the coupling reagent gave the best results (60% of **32**). The analogous cyclization of the corresponding hexapeptide **31** (n = 3) gave *cyclo*[Gly-D,L-Phe(2Me)-Aib-Aib-Aib-Gly] in 42% yield. On the other hand, the reaction with tetrapeptide **31** (n = 1) led to a 1:2 mixture of the expected *cyclo*[Gly-D,L-Phe(2Me)-Aib-Gly] and the corresponding dimer *cyclo*[Gly-D,L-Phe(2Me)-Aib-Gly-Gly-D,L-Phe(2Me)-Aib-Gly] in a total yield of 45%.

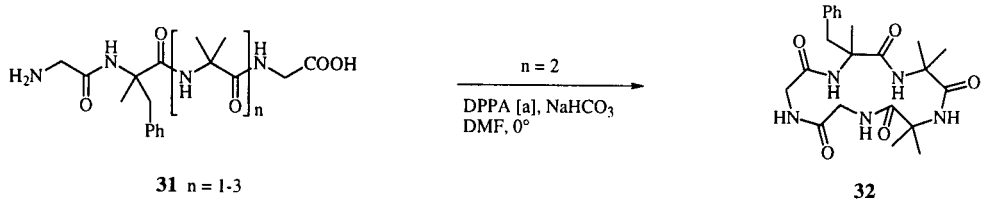
Scheme 9



For the general synthesis of 2-aminoisobutyric acid-containing cyclopeptides, a combination of the 'azirine/oxazolone method' and a classic cyclization is suitable. The linear tetra-, penta-, and hexapeptides **31** were prepared *via* subsequent coupling of *Z*-glycine with 2-benzyl-3-dimethylamino-2-methyl-2*H*-azirine (**1c**), 2,2-dimethyl-3-(*N*-methyl-*N*-phenylamino)-2*H*-azirine (**1b**), and methyl glycinate. The last coupling was performed with *N*,*N*-dicyclohexylcarbodiimide/zinc chloride and proceeded again *via* a 1,3-oxazole-5(4*H*)-one as the intermediate [40]

In a systematic study of the cyclization step, a series of 2-aminoisobutyric acid- and Phe(2Me)-containing linear pentapeptides were prepared either in a linear or in a convergent synthesis (segment coupling) using the 'azirine/oxazolone method' for introducing the α,α-disubstituted glycines, *e.g.*, *Z*-Gly-Aib-L-Phe(2Me)-Aib-Gly-OMe **35a**, *Z*-Gly-D-Phe(2Me)-Pro-Aib-Phe-OMe **35b**, and *Z*-Gly-D-Phe(2Me)-Pro-Aib-Aib-N(Me)Ph **35c**. X-Ray crystal structure determinations proved that, in general, these pentapeptides adopt a helical conformation, *e.g.*, **35a**

Scheme 10



31 n = 1-3

32

[a] DPPA: Diphenyl Phosphorazidate.

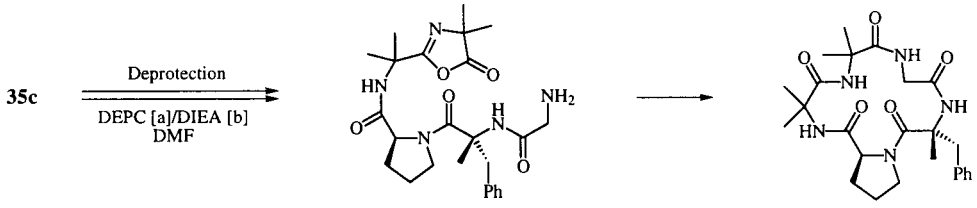
forms a left-handed 3_{10}-helix, *i.e.* three consecutive β-turns of type III' [41].

Out of several protocols for the cyclization process, the treatment of a solution of the deprotected pentapeptide in dimethylformamide at 0° with diethyl phosphorocyanidate and diisopropyl(ethyl)amine proved to be the method of choice. In summary, the best yields of cyclopentapeptides were obtained in those cases where a C-terminal 2-aminoisobutyric acid was present. This is in accordance with the proposal of an activation of the carboxyl group by formation of a 1,3-oxazole-5(4*H*)-one intermediate **36**, which then led to the cyclopentapeptide **37** *via* an intramolecular nucleophilic attack at C(5) of **36** and cleavage of the O(1),C(5)-bond (Scheme 11). Even the *cyclo*[Aib-Aib-Aib-Aib-Aib] could be prepared, although the yield dropped to 12% [42]. The crystal structure of *cyclo*[Gly-Aib-D-Phe(2Me)-Aib-Gly] is shown in Figure 2. Again, an intramolecular H-bond forming a β-turn stabilizes the structure.

Formation of Lactones and Lactams.

In all intramolecular reactions with intermediate 1,3-oxazol-5(4*H*)-ones of type **6** described so far, the nucleophilic group was located in the 'main chain' attached to C(2). Therefore, the newly formed heterocycles **7** contained all of the ring atoms from the oxazolone (Scheme 3). In the last section, some reactions with a nucleophilic group in the 'side chain', *i.e.* attached to C(4) of the oxazolone will be discussed. In these cases, only C(4) and C(5) of the oxazolone are included in the new lactone or lactam ring **8**. The acylation of 1,3-oxazol-5(4*H*)-ones **38** by means of the *Dakin-West* reaction can be performed with acid anhydrides or acid chlorides [43]; the mechanism of this reaction has been established by *Steglich* and *Höfle* [44]. A novel approach to 4-acylated oxazolones **39** described in 1989, uses carboxylic acids and *N,N*-dicyclohexylcarbodiimide in the presence of 4-dimethylaminopyridine as the coupling reagent [45]. With the latter method, we prepared a series of 4-acyl-1,3-oxazol-5(4*H*)-ones **39** [46]

Scheme 11



[a] DEPC: Diethyl Phosphorocyanidate; [b] DIEA: *N,N*-Diisopropyl(ethyl)amine.

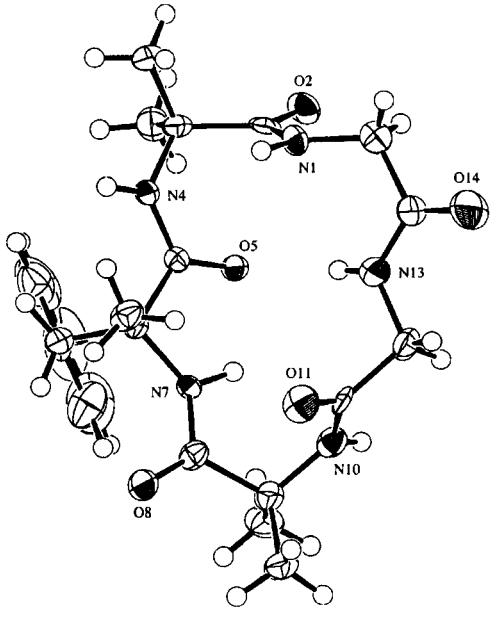
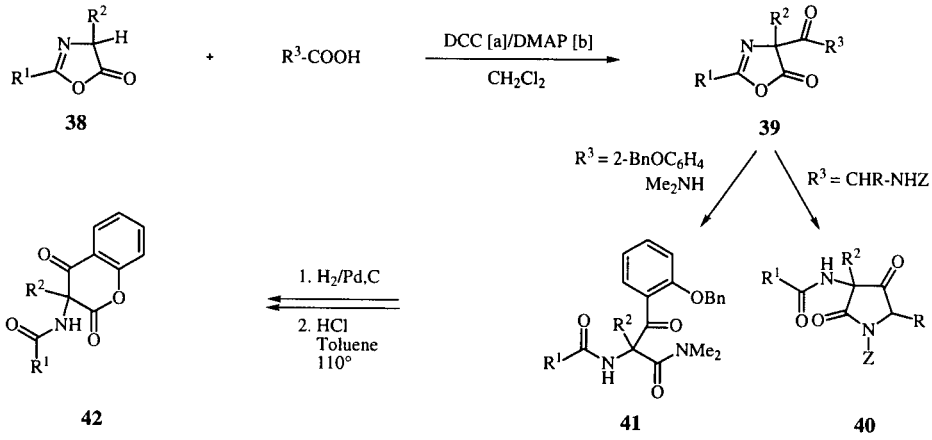


Figure 2.

(Scheme 12). In the case of Z-protected amino acids as acylating reagents, a spontaneous ring transformation of the intermediates **39** led to pyrrolidine-2,4-dione derivatives **40** in 65-98% yield. Treatment of the salicyloyl derivative **39** (R^1 = Ph, R^2 = $PhCH_2$, R^3 = 2-$PhCH_2OC_6H_4$) with dimethylamine in dichloromethane yielded the diamide **41**. After deprotection of the phenolic OH group, the acid catalyzed cyclization with hydrogen chloride in refluxing toluene gave the benzopyrane-2,4-dione **42** in 70% yield.

Despite many attempts to introduce alkyl groups at C(4) of 1,3-oxazol-5(4*H*)-ones by alkylation, satisfying results were obtained only with the most reactive alkylation reagents (allyl, benzyl, and methyl groups) [47]. Improved results have been described for alkylations under phase transfer conditions [48] or by variation of the solvent and the base [49]. Using lithium diisopropylamide in a mixture of tetrahydrofuran/hexamethylphosphoric triamide, the alkylation of oxazolones **38** with alkyl iodides bearing a protected nucleophilic group in the ω-position to give **43** was achieved with fair-to-good yields (typically 25-60%,

Scheme 12



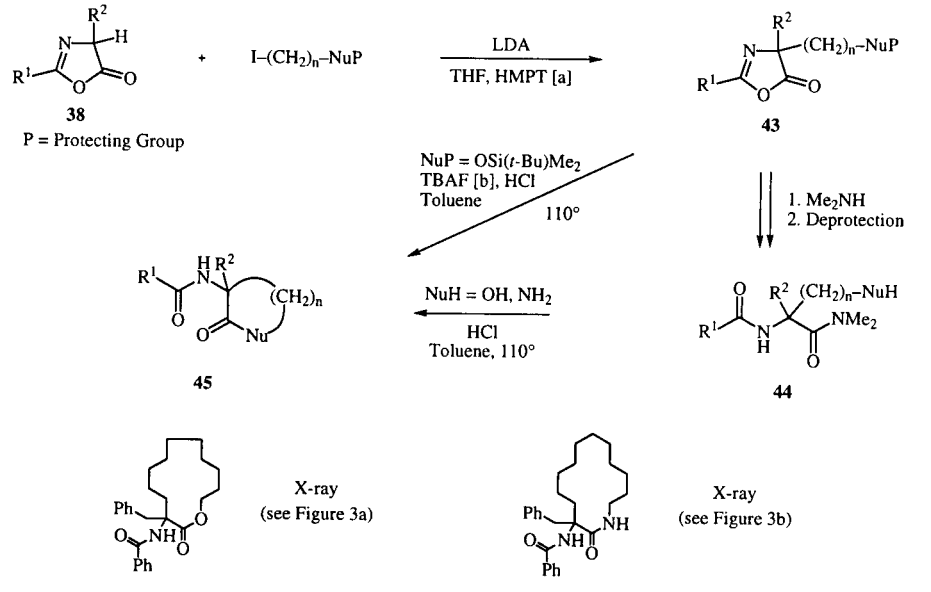
[a] *N,N*-Dicyclohexylcarbodiimide; [b] 4-Dimethylaminopyridine.

ratio of *C*- and *O*-alkylation 10:1 to 4:1) [46] (Scheme 13). In the case of tetrahydropyranyl-protected hydroxy groups (NuP = oxytetrahydropyran), successive treatment of **43** with dimethylamine and pyridinium tosylate in ethanol gave the diamides **44** (NuH=OH) which were again cyclized with hydrogen chloride in boiling toluene to yield the lactones of type **45**.

the expected trend: high yields were obtained for 5- and 6-membered rings (100 and 86%, respectively), the yields decreased for medium sized rings (9- to 11-membered: 51, 20, and 10%, respectively), and large rings were formed in good yields again (13- to 15-membered: 51-69%).

An analogous procedure was used for the formation of lactams, but the yields of the cyclizations were only modest.

Scheme 13



[a] HMPT: Hexamethylphosphoric Triamide; [b] TBAF: Tetrabutylammonium Fluoride.

Even better results were obtained by following a different protocol: oxazolones **43** (NuP = OSi(*t*-Bu)Me_2) were transformed directly into **45** by treatment with tetrabutylammonium fluoride and hydrogen chloride gas in boiling toluene [46]. The yields of the formed lactones **45** show

The alkylation of **38** was performed with ω-azidoiodoalkanes, and, after ring opening of **43** with dimethylamine, the azido group was reduced to the amino group *via* a *Staudinger* reaction with triethylphosphine and water (*cf.* [50]). Cyclization of **44** (NuH = NH_2) with

hydrogen chloride gas in refluxing toluene gave the 13- to 15-membered lactams of type **45** in 11-27% yield [46] (Scheme 13). The structures of the prepared lactones and lactams have been established by X-ray crystallography. The crystal structures of a 13-membered lactone and a 14-membered lactam are shown in Figure 3.

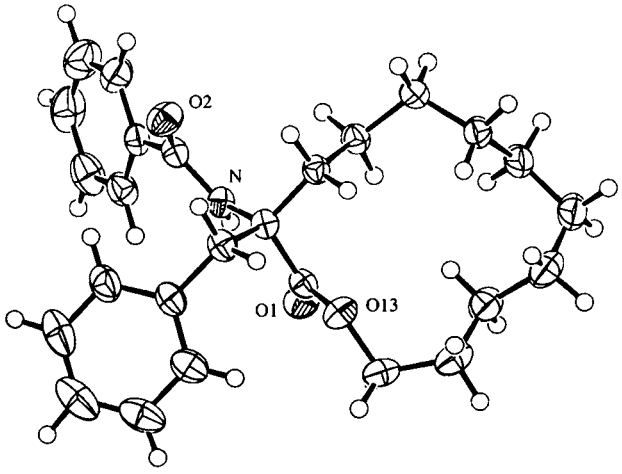


Figure 3a.

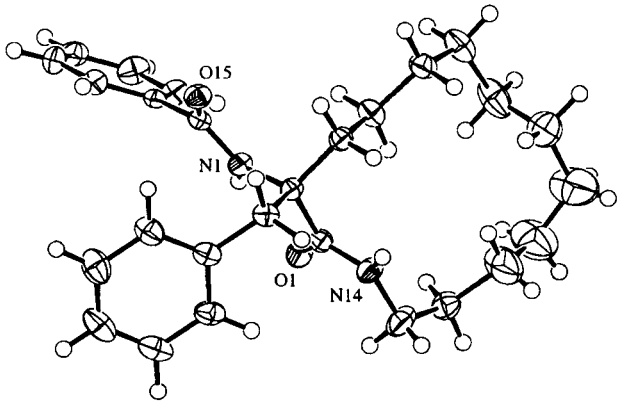


Figure 3b.

Conclusion.

The results presented here have shown that 1,3-oxazol-5(4*H*)-ones are suitable intermediates for ring formation *via* intramolecular nucleophilic addition to C(5) of the oxazolone and subsequent ring opening. With this methodology, lactones and cyclodepsipeptides have been synthesized, as well as lactams and cyclopeptides.

Acknowledgements.

We gratefully acknowledge financial support of this work by the *Swiss National Science Foundation*, *F. Hoffmann-La Roche AG*, Basel, the *Stiftung für wissenschaftliche Forschung an der Universität Zürich*, the *Stipendienfonds für Studierende auf dem Gebiete der Chemie und Biochemie*, Basel, and the *Dr. Helmuth Legerlotz-Foundation*, Zürich.

REFERENCES AND NOTES

[*] E-mail: heimgart@oci.unizh.ch; Fax: 01/635 68 12; Telephone: 01/635 42 82.

[1] H. Heimgartner, *Angew. Chem., Int. Ed. Engl.*, **30**, 238 (1991).

[2] P. Hoet, Ph.D. thesis, Université Catholique de Louvain, 1975.

[3] C. B. Bucher, A. Linden and H. Heimgartner, *Helv. Chim. Acta*, **78**, 935 (1995); C. B. Bucher and H. Heimgartner, *Helv. Chim. Acta*, **79**, 1903 (1996).

[4] R. Luykx, C. B. Bucher, A. Linden and H. Heimgartner, *Helv. Chim. Acta*, **79**, 527 (1996).

[5] C. Strässler, A. Linden and H. Heimgartner, *Helv. Chim. Acta*, **80**, 1528 (1997).

[6] J. Lehmann, A. Linden and H. Heimgartner, *Tetrahedron*, **54**, 8721 (1998); *Tetrahedron*, **55**, 5359 (1999); *Helv. Chim. Acta*, **82**, 888 (1999).

[7] P. Wipf and H. Heimgartner, *Helv. Chim. Acta*, **69**, 1153 (1986); *Helv. Chim. Acta*, **70**, 354 (1987).

[8] D. Obrecht and H. Heimgartner, *Chimia*, **36**, 78 (1982).

[9] C. Galli, G. Giovanelli, G. Illuminati and L. Mandolini, *J. Org. Chem.*, **44**, 1258 (1979); D. F. DeTar and N. P. Luthra, *J. Am. Chem. Soc.*, **102**, 4505 (1980); J.-W. Drijfhout, A. Wagenaar and J. B. F. N. Engberts, *Tetrahedron Letters*, **27**, 2423 (1986).

[10] F. Stierli, D. Obrecht and H. Heimgartner, *Chimia*, **38**, 432 (1984).

[11] D. Obrecht, C. Spiegler, P. Schönholzer, K. Müller, H. Heimgartner and F. Stierli, *Helv. Chim. Acta*, **75**, 1666 (1992).

[12] J. W. Cornforth, The Chemistry of Penicillins, H. T. Clarke, J. R. Johnson and R. Robinson, eds, Princeton University Press, 1949, p 1410.

[13] J. W. Cornforth, Heterocyclic Compounds, Vol. 5, R. C. Elderfield, ed, J. Wiley & Sons, New York, 1957, p 298.

[14] R. Filler, *Adv. Heterocyclic Chem.*, **4**, 75 (1965).

[15] W. Steglich, *Fortschr. Chem. Forsch.*, **12**, 77 (1969).

[16] R. Filler and Y. S. Rao, *Adv. Heterocyclic Chem.*, **21**, 175 (1977).

[17] A. W. D. Avison, *J. Chem. Soc.*, 732 (1955).

[18] W. Steglich, V. Anstel and A. Prox, *Angew. Chem., Int. Ed. Engl.*, **7**, 726 (1968).

[19] H. Behringer and W. Grimme, *Chem. Ber.*, **92**, 2967 (1959).

[20] D. Obrecht and H. Heimgartner, *Helv. Chim. Acta*, **70**, 329 (1987).

[21] D. Obrecht and H. Heimgartner, *Helv. Chim. Acta*, **67**, 526 (1984).

[22] A. Closse and R. Huguenin, *Helv. Chim. Acta*, **57**, 533 (1974).

[23] M. M. Shemyakin, V. K. Antonov, A. M. Shkrob, V. I. Shchelokov and Z. E. Agadzhanyan, *Tetrahedron*, **21**, 3537 (1965); L. Andreeva, T. M. Ivanova, E. S. Efremov, V. K. Antonov and M. M. Shemyakin, *Zh. Obshch. Khim.*, **40**, 475 (1970).

[24] M. Rothe, K. Reichert and M. Rosenbauer, Peptides 1992, C. H. Schneider and A. N. Eberle, eds, ESCOM, Leiden, 1993, p 391.

[25] J. M. Villalgordo and H. Heimgartner, *Helv. Chim. Acta*, **80**, 748 (1997).

[26] R. C. Sheppard, *Experientia*, **19**, 125 (1963); R. K. A. Giger, H. R. Loosli, M. D. Walkinshaw, B. J. Clark and J. M. Vigouret, *Experientia*, **43**, 1125 (1987).

[27] M. Schläpfer-Dähler and H. Heimgartner, *Helv. Chim. Acta*, **76**, 2321 (1993).

[28] K. Hamano, M. Kinoshita, K. Furuya, M. Miyamoto, Y. Takamatsu, A. Hemmi and K. Tanzawa, *J. Antibiot.*, **45**, 899 (1992); M. T. Reese, N. K. Gulavita, Y. Nakao, M. T. Hamann, W. Y. Yoshida, S. J. Coval and P. J. Scheurer, *J. Am. Chem. Soc.*, **118**, 11081 (1996); M. Murakami, S. Kodani, K. Ishida, H. Matsuda and K. Yamaguchi, *Tetrahedron Letters*, **38**, 3035 (1997); G. N. Belofsky, P. R. Jensen and W. Fenical, *Tetrahedron Letters*, **40**, 2913 (1999).

[29] K. N. Koch, planned Ph.D. thesis, University of Zürich.

[30] B. Di Blasio, V. Pavone, A. Lombardi, C. Pedone and E. Benedetti, *Biopolymers*, **33**, 1037 (1993); C. Toniolo, M. Crisma, F. Formaggio, G. Valle, G. Cavicchioni and G. Précigoux, *Biopolymers*, **33**, 1061 (1993).

[31] E. Benedetti, *Biopolymers*, **40**, 3 (1996).

[32] H. Balaram, M. Sukumar and P. Balaram, *Biopolymers*, **25**, 2209 (1986).

[33] Y. A. Ovchinnikov, *FEBS Letters*, **44**, 1 (1974); G. N. Tishchenko, Molecular Structure and Biological Activity, J. F. Griffin and W. L. Duax, eds, Elsevier Science Publishers, Amsterdam, 1982, p 229; G. N. Tishchenko, Z. Karimov, B. K. Vainshtein, A. V. Evstratov, V. T. Ivanov and Y. A. Ovchinnikov, *FEBS Letters*, **65**, 315 (1976).

[34] D. Obrecht and H. Heimgartner, *Helv. Chim. Acta*, **73**, 221 (1990).

[35] J. E. F. Magirius, Ph.D. thesis, University of Zürich, 1995; J. E. F. Magirius, A. Linden and H. Heimgartner, in preparation.

[36] R. L. M. Synge, *Biochem. J.*, **39**, 363 (1945).

[37] R. Schwyzer and P. Sieber, *Helv. Chim. Acta*, **40**, 624 (1957).

[38] T. Wieland and C. Birr, International Review of Science, Organic Chemistry, Vol. **6**, D. H. Hey, ed, Butterworth, London, 1976, p 183; G. Schmidt, *Topics Curr. Chem.*, **136**, 109 (1986); U. Schmidt, *Nachr. Chem. Techn. Lab.*, **37**, 1034 (1989); H. A. Nagarajaram and C. Ramakrishnan, *J. Biosci.*, **20**, 591 (1995).

[39] S. Cerrini, E. Gavuzzo, G. Lucente and F. Pinnen, *Int. J. Pept. Protein Res.*, **31**, 477 (1988).

[40] I. Dannecker-Dörig, Ph.D. thesis, University of Zürich, 1995; I. Dannecker-Dörig and H. Heimgartner, Peptides 1990, E. Giralt and D. Andreu, eds, ESCOM, Leiden, 1991, p 460.

[41] F. S. Arnhold, Ph.D. thesis, University of Zürich, 1997.

[42] F. S. Arnhold and H. Heimgartner, unpublished results.

[43] H. D. Dakin and R. West, *J. Biol. Chem.*, **78**, 745 (1928).

[44] W. Steglich and G. Höfle, *Chem. Ber.*, **102**, 883 (1969); *Chem. Ber.*, **102**, 1129 (1969); *Chem. Ber.*, **104**, 3644 (1971); G. Höfle and W. Steglich, *Chem. Ber.*, **104**, 1408 (1971).

[45] P. K. Misra, S. A. N. Hashami, W. Haq and S. B. Katti, *Tetrahedron Letters*, **30**, 3569 (1989).

[46] S. P. Fritschi, Ph.D. thesis, University of Zürich, 1995.

[47] S. Götze, B. Kübel and W. Steglich, *Chem. Ber.*, **109**, 2331 (1976); B. Kübel, P. Gruber, R. Hurnaus and W. Steglich, *Chem. Ber.*, **112**, 128 (1979); R. Lohmar and W. Steglich, *Chem. Ber.*, **113**, 3706 (1980); H. Wegmann, G. Schulz and W. Steglich, *Chem. Ber.*, **113**, 1736 (1980); H. Wegmann and W. Steglich, *Chem. Ber.*, **114**, 2580 (1981).

[48] M. L. Gelmi, D. Pocar and L. M. Rossi, *Synthesis*, 763 (1984).

[49] D. Obrecht and H. Heimgartner, *Tetrahedron Letters*, **25**, 1712 (1984); D. Obrecht, U. Bohdal, R. Ruffieux and K. Müller, *Helv. Chim. Acta*, **77**, 1423 (1994).

[50] H. Staudinger and J. Meyer, *Helv. Chim. Acta*, **2**, 635 (1919); S. Nagarajan and B. Ganem, *J. Org. Chem.*, **52**, 5044 (1987); N. Knouzi, M. Vaultier and R. Carrié, *Bull. Soc. Chim. France*, 815 (1985).