# Conversion of Dipeptides and a Tetrapeptide to Macrocyclic Ionophores by means of Caesium Aided Ring Closure of the *N*-2-Chloroacetyl Derivatives

**Wim H. Kruizinga, Rob Kingma, Libbe Leegstra, Edward Rokaszewski, Gert Gruppen and Richard M. Kellogg***

*Department of Organic Chemistry, University of Groningen, Nijenborgh 16, 9747 AG Groningen, The Netherlands*

Three di-, $(Gly)_2$, $(Val)_2$ and $(Leu)_2$, and one tetra-peptide, $(Gly)_4$, have been acylated with 2-chloroacetyl chloride and the resulting products treated with $Cs_2CO_3$ in dimethylformamide (DMF) solution; $(Gly)_2$ and $(Leu)_4$ provided strained 9-membered rings whereas $(Val)_2$ dimerized to the 18-membered ring.

The structure of enniatin *A* or *B* (**1**, R = Bu$^s$ and/or Pr$^i$) exemplifies a strategy employed by Nature in the design of ionophores. The (*S*)-amino acid/(*R*)-α-hydroxy acid units are linked together through ester rather than amide bonds. General preparative methods for the synthesis of synthetic analogues of these natural 'crown ethers,' wherein amide and ester bonds are incorporated, could open the path to systematic investigation of cavity properties, variation of ring size and the effect of positioning of various amino acid substituents. Various syntheses of specific compounds have been reported.[1] We report here an approach that has proved its worth for the preparation of some relatively simple macrocycles containing one ester linkage and a peptide backbone. Ring-closure involves formation of a carboxylate–carbon bond.

Schotten–Baumann acylation with 2-chloroacetyl chloride followed by ring closure mediated by caesium carbonate as illustrated in Scheme 1 provides the macrocycles. We had explored the use of caesium salts in depth for other systems,[2] and had shown that in many cases pronounced improvement in yields of macrocyclizations can be obtained relative to other alkali cations. Parallel with this work *N*-acylation with optically active α-haloacids had been developed into a method for determination of enantiomeric purity of synthetically obtained amino acids.[3] The report of Fischer[4] that α-amino acids on reaction with chloroacetyl chloride followed by treatment with tertiary amines cyclize to 6-membered morpholine-2,4-diones provided the hint how to unify these observations.

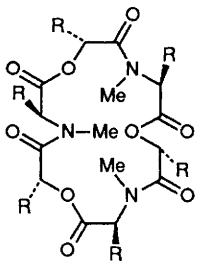
Treatment of $(Gly)_2$ **2** with 2-chloroacetyl chloride [NaOH (2 mol dm$^3$) solution, 5 °C] gave **3**, m.p. 178.7–179.1 °C, in 81% yield. Compound **3** (4 mmol) was dissolved in DMF (40 ml) and $H_2O$ (10 ml) to which an excess (2.5 mmol) of dry, powdered $Cs_2CO_3$ had been added. After 24 h at 80 °C the DMF was removed and the residue was dissolved in MeOH (40 ml) and then filtered over Dowex W50 acidic resin. The extremely strained 9-membered ring compound **4** was isolated in 85% yield (Scheme 2).† The 18-membered dimer of **3** (not illustrated), which we had expected, was not detected. With $Na_2CO_3$ or $K_2CO_3$ instead of $Cs_2CO_3$ much intractable

† *Spectroscopic data*: **4**: m.p. 129–130.6 °C, osmom. mol. wt. 178 in MeOH, calcd. 172; $^1$H NMR ($CD_3OD$): δ 3.92 (s, $CH_2$), 3.98 (s, $CH_2$), 4.03 (s, $CH_2$); $^{13}$C NMR: δ 41.42 (t), 42.67 (t), 62.63 (t), 171.66 (s), 171.89 (s), and 175.56 (s).

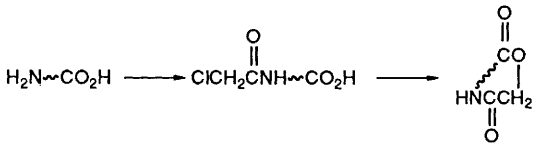
**6**: m.p. decomp.; $^1$H NMR ($D_2O$–$CD_3OD$): δ 4.13, 4.03, 3.99, 3.95, 3.73 (all singlets, 2H); $^{13}$C NMR ($D_2O$–$CD_3OD$): δ 176.52, 175.75, 172.21, 172.03, 171.09 (all singlets); δ 61.06, 43.29, 42.62, 42.47, 42.10 (all triplets), mass spectrum calcd. *m/z* 286 (parent), found *m/z* 286.

**8**: m.p. decomp.; $^1$H NMR ($CDCl_3$): δ 0.90–1.05 (m, 12H, Me), 1.60–1.80 (m, 6H, 2CH + $2CH_2$), 4.10 (s, 2H, $CH_2O$), 4.12 (m, 1H, CH), 4.50 (m, 1H, CH), 8.60 (s, 1H, NH); $^{13}$C NMR ($CDCl_3$): δ 175.0 (s), 173.7 (s), 170.3 (s), 62.6 (t), 55.1 (d), 53.0 (d), 43.2 (t), 42.1 (t), 26.1 (d), 26.0 (d), 23.7 (q), 23.5 (q), 22.4 (q), 21.6 (q); $[\alpha]_D^{20}$ −19.4° [*c* 1, NaOH (1 mol dm$^{-3}$)]. Owing to extremely poor solubility accurate osmometric weights could not be determined; mass spectrum calcd. *m/z* 284 (parent), found *m/z* 284. Attempts to obtain high resolution or chemical ionization mass spectra were unsuccessful owing to the low volatility.

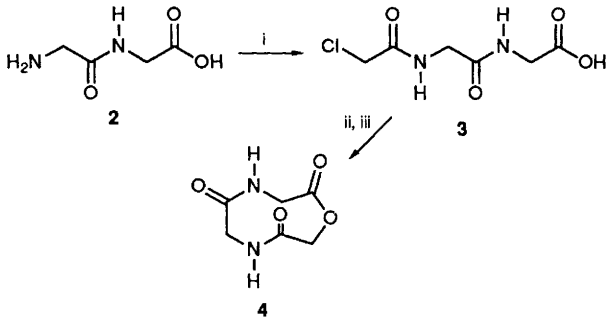
**9**: m.p. >255 °C decomp.; $^1$H NMR [$^2H_6$]dimethyl sulphoxide (DMSO), δ 0.78–0.97 (m, 24H, Me), 2.04 (m, 2H, CH), 2.25 (m, 2H, CH), 3.66 (m, 2H, CH), 4.20 (m, 2H, CH), 4.25 and 4.82 (AB, each 2H, $CH_2$), 7.95 (m, 2H, NH), 8.98 (d, 2H, NH); $^{13}$C NMR [$^2H_6$]-DMSO, δ 169.70 (s), 166.56 (s), 62.39 (t), 57.94 (d), 57.78 (d), 29.49 (d), 29.34 (d), 20.15 (q), 19.05 (q), 18.68 (q), 18.23 (q); $[\alpha]_D^{20}$ −225.6° (*c* 0.25, MeOH); mass spectrum (chem. ionization) *m/z* 512.286, calcd. 512.285, no monomer (*m/z* 256) observed.



1



Scheme 1



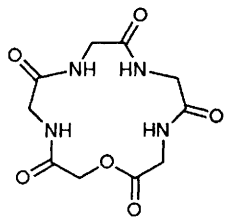
**Scheme 2** *Reagents and conditions*: i, NaOH, $H_2O$, $ClCH_2COCl$, 5 °C; ii, $Cs_2CO_3$ in $H_2O$–DMF; iii, Dowex

material, apparently oligomeric, was formed. Pure **4** could not be isolated from these reaction mixtures. Attempts to obtain a crystal structure for **4** and related compounds have failed so far.

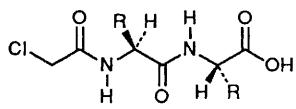
Tetraglycine (**5**, not illustrated) on similar treatment provided in 81% yield the chloroacetylated derivative, which was cyclized at $6 \times 10^{-3}$ mol $dm^{-3}$ in DMF containing 1% $H_2O$. The fifteen-membered macrocycle **6** was obtained in 50% yield on work-up as described for **4**. Identification of **6** was analogous to that for **4**.† No characterizable product was obtained when either $K_2CO_3$ or $Na_2CO_3$ was used for the cyclizations.

Extensions of this procedure to optically active amino acids have been made, although not without complications with regard to solubility and purification of cyclized materials. Chloroacetylation of $(Leu)_2$ and $(Val)_2$ to provide, respectively **7a** and **7b** proceeded in 85–90% yield. Cyclization under conditions analogous to those already described led to formation of **8** and **9**.† Isolated yields were 88 and 90%, respectively. Although not proved, it seems likely that **8** should be accompanied by a minor amount of dimer and **9** by some monomer. These minor products are presumably lost on purification.

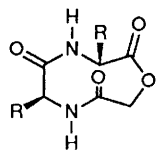
The formation of 9-membered rings like **4** and **8** is unusual. Clearly the balance between kinetic (9-membered and *cis*-amide bonds) and thermodynamic (18-membered) control is delicate as witnessed by the formation of **8** or **9** dependent on amino acid substituent. We believe that the synthetic methodology described here can provide access to still more



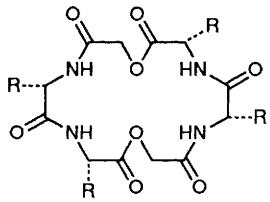
6



7
**a**; R = $Bu^i$
**b**; R = $Pr^i$



8
R = $Bu^i$



9
R = $Pr^i$

macrocycles with structural characteristics closely allied to those of natural ionophores. Studies of the complexing properties are being undertaken.

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