Synthesis of Copolymers of Isocyanides Derived from Alanylserine and Alanylhistidine[1]

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Three optically active isocyanides were synthesized from the dipeptides L-Ala-L-Ser, L-Ala-D-Ser, and L-Ala-L-His by converting the amino group of these compounds into an isocyano function. These isocyanides, as well as *n*-dodecyl isocyanide, were mixed in various monomeric ratios and polymerized with catalytic amounts of nickel(II) chloride. The resulting optically active copolymers have left-handed helical configurations. Their molecular weights are in the $\bar{M}_v$ range 70000–250000. The number of imidazolyl, carboxyl, and hydroxymethyl functions in the copolymers were determined by potentiometric titration. Two types of imidazolyl functions are present in the copolymers: type A with pK_a (ImH^+) $\simeq 7$ and type B with pK_a (ImH^+) $\simeq 9.5$. The fraction of imidazole groups B increases with decreasing amounts of Ala-Ser residues in the copolymers.

In the preceding paper[2] we reported on the advantages of synthesizing polymers of isocyanides that combine imidazolyl, carboxyl, and hydroxymethyl groups in one molecule. In that paper the synthesis of three isocyanides derived from diastereomeric alanylhistidinylserine tripeptides is described. Homopolymerization afforded the corresponding polymers.

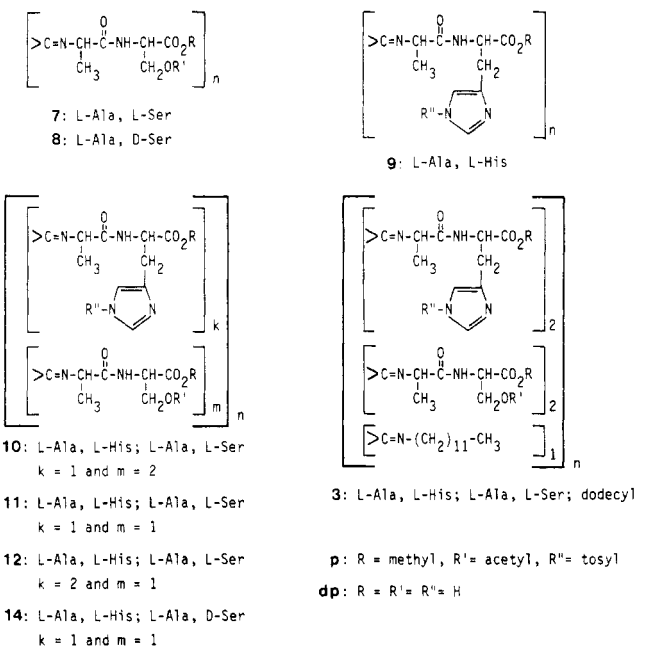
In the work described in the present paper, the desired combination of functional groups is obtained by copolymerization of isocyanides derived from dipeptides. The parts concerning the esterolytic activity and enantioselectivity will be published separately.[3] The surprising effect of surfactants on these properties has been described in preliminary communications.[4,5]

Results and Discussion

Two types of protected isocyanide monomers were synthesized, one containing a carboxylic acid and an imidazole residue, **5c**, the other containing a carboxylic acid and a hydroxymethyl residue. The latter monomer was prepared in two diastereomeric forms, **5a** and **5b**. The synthetic route is given in Scheme I.

Coupling of *N*-formyl-L-alanine, **1**, and compounds **2** by applying the dicyclohexylcarbodiimide method[6] afforded compound **3**. Group X of **3** had to be protected prior to the synthesis of **5**. The imidazolyl function of **3c** was protected by the tosyl group (Tos)[7] and the hydroxyl function of **3a** and **3b** by the easily removable acetyl group.[8] The isocyanides **5a** and **5b** were obtained by the phosphorus oxychloride/triethylamine procedure at low temperatures.[9] The synthesis of isocyanide **5c** has been described before by Van der Eijk.[10] We modified his procedure by using phosphorus oxychloride and triethylamine instead of trichloroformate and *N*-methylmorpholine as the dehydrating agent and base.

Chart I



The structures of the formamides **4** and the isocyanides **5** were confirmed by spectroscopic techniques. From ^1H NMR it appeared that no racemization had occurred within the limits of detection. The infrared absorption spectra of the various isocyanides showed characteristic isocyanide vibrations at 2145 cm^{-1} (**5a,5b**) and 2148 cm^{-1} (**5c**). *n*-Dodecyl isocyanide **6**[11] was prepared in order to study the effect of a hydrophobic moiety in the polymer.

Copolymerization was achieved by mixing appropriate amounts of various isocyanides **5** and dodecyl isocyanide **6**, dissolved in chloroform and subsequently adding 0.1 mol% of nickel(II) chloride dissolved in methanol. The molar ratios of the monomers in the starting mixtures are listed in Table I. For comparison, isocyanides **5** were also homopolymerized.

The polymerizations were followed by observing the disappearance of the isocyanides in TLC and in the infrared absorption spectra of the reaction mixtures. The isocyanide absorptions in the infrared spectra were suf-

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Scheme I

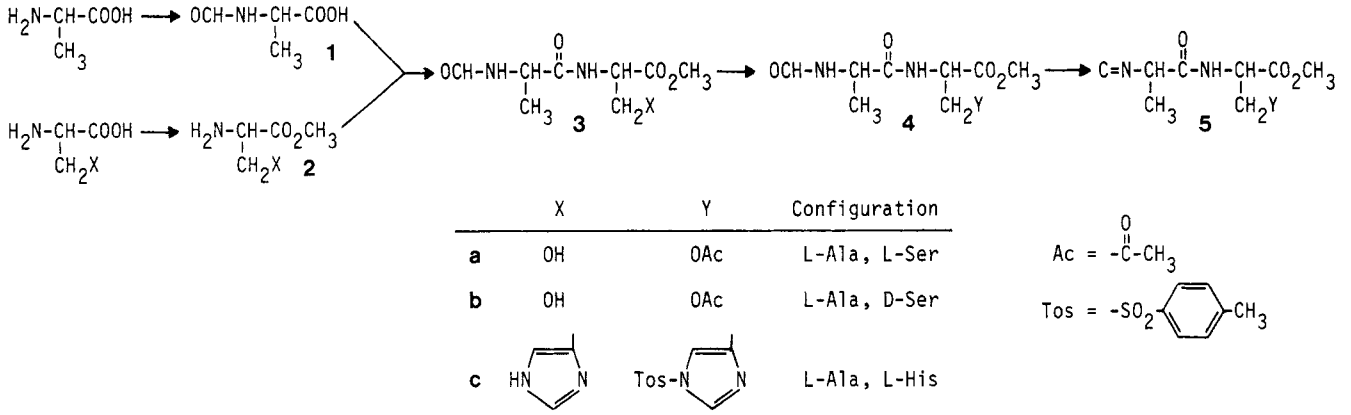

Table I. Homopolymerization and Copolymerization of Isocyanides 5 and 6[a]

monomer ratio in starting mixture							polymer composition[c]			
5a	5b	5c	6	reactn[b] time, h	product	yield %	5a	5b	5b	6
1				<0.5	**7**	87	1.00			
	1			<4	**8**	78		1.00		
		1[d]		~4	**9**	90			1.00	
2		1		<0.5	**10**	76	2		1.07	
1		1		<0.5	**11**	72	1		0.85	
1		2		<0.5	**12**	65	1		2.08	
2		2	1	1.5	**13**	53	2		2.15	1.05
	1	1		3	**14**	90		1	1.07	

[a] Reaction conditions: 0.1 mol % of $NiCl_2 \cdot 6H_2O$ in chloroform–methanol, 4.3:1 v/v, 25 °C. [b] Reaction time for complete conversion of isocyanide. [c] Ratio of repeating units derived from 5 and 6 in the deprotected polymers as determined by both elemental analysis and potentiometric titration. [d] See ref 10.

ficiently spaced apart to observe the diminution and eventual disappearance of the separate isocyanides. Polymerization of pure isocyanide **5a** to **7** was completed within 0.5 h (Table I); the formation of **8** took 4 h and **9** took somewhat less than 4 h.[10] The formations of **10**, **11**, and **12** had a complete isocyanide consumption within 0.5 h; **13** took 1.5 h and **14** 3 h. During the synthesis of **10**, **11**, and **12**, it was observed that the isocyanides disappeared almost simultaneously. This simultaneous consumption of the isocyanides in the mixture suggests that copolymers are formed indeed.

We found that it was not possible to copolymerize just any combination of isocyanides. For instance, in a 2:1 mixture of **5c** and **6** and a 2:2:1 mixture of **5b**, **5c**, and **6**, no polymerization occurred at all. After being kept for one month at room temperature, the isocyanides were still intact. Other attempts (heating, addition of trifluoroacetic acid or $ZnCl_2$[12]) to initiate these polymerizations were in vain. Apparently, restrictions seem to exist which are still not completely understood.

The polymerization reactions leading to **7**, **10**, **11**, and **12** are very fast, even when compared to the high rate of polymerization of certain aliphatic isocyanides.[13] The protected (**p**) polymers were isolated in good yields as solids varying in color from white to light-brown. The homopolymers **7p** **8p** and **9p** are soluble in chloroform, slightly soluble in methanol, and insoluble in water, ether, benzene, and the lower straight-chain hydrocarbons. The copolymers **10p**–**14p** are slightly soluble in chloroform and methanol, soluble in chloroform–methanol mixtures ranging from 10:1–5:2 v/v, and insoluble in water, ether, and the lower straight-chain hydrocarbons.

The *N*(Im)-tosyl group in compounds **9p**–**14p** was removed by treatment with acetic anhydride and pyridine.[7] In order to remove the remaining protective groups, these polymers as well as **7p** and **8p** were subsequently treated for 2 days with 0.5 M aqueous NaOH or KOH at 40 °C. During this reaction no hydrolysis of the polymer imino functions occurred, as we checked separately. After ultrafiltration and freeze-drying, polymers **7dp** and **8dp** (**dp** stands for deprotected) were obtained as sodium salts and polymers **11dp**–**14dp** as potassium salts. Polymers **9dp** and **10dp** were isolated as hydrochloric acid salts from their acidified aqueous solutions. Compounds **7dp**, **9dp**, and **11dp** are spongy solids, varying in color from light-brown to brown; the other compounds are dark-brown powdery solids. From elemental analyses and potentiometric titrations the ratios of the various repeating units in the copolymers were calculated. These ratios are presented in Table I. All deprotected polymers contained crystal water in varying amounts. In addition, **8dp** contained small amounts of acetyl groups. Polymers **7dp** and **8dp** are completely soluble in water at pH's >6. Below pH 6 precipitation occurs. In the pH range 3–11, homopolymer **9dp** and the copolymers **10dp**–**14dp** are soluble in water.

In Table II the intrinsic viscosities of the protected and deprotected polymers are given. The intrinsic viscosity is the intercept at $c = 0$ of the reduced viscosity vs. concentration plot. For all protected polymers except **11p** these plots are linear.

By applying the Mark–Houwink equation as determined for poly(1-methylheptyliminomethylene),[14] the molecular weights of the polymers are estimated to be in the range of 60 000–250 000 (Table II). It is noteworthy, that in the series of the protected compounds **7p**–**14p**, there seems to

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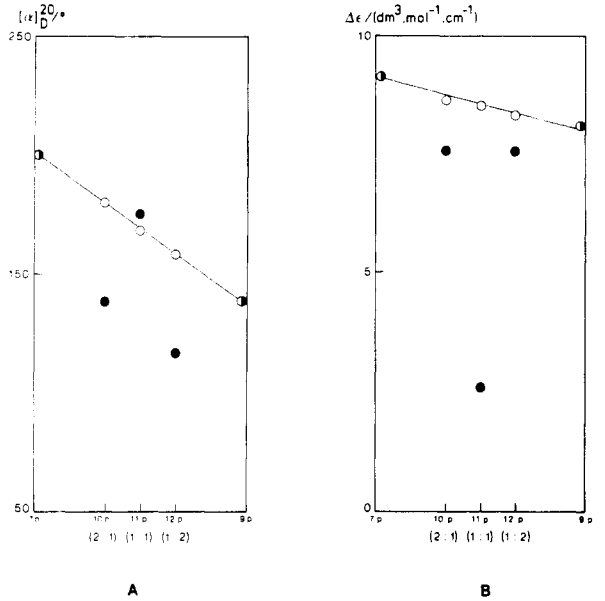
Table II. Viscosity and Optical Rotation Data of Polymers and Copolymers of Isocyanides 5 and 6

	$[\eta]$, dL/g[a]			$[\alpha]^{20}_D$,[a] deg		
no.	p	dp	$10^{-5}\ \bar{M}_v$[b]	p	dp	screw sense
7	4.1	0.15	2.5	+205	- 63	*M*
8	0.35		0.63	- 33	- 57	*M*
9	1.0	0.05	1.15	+139	+126	*M*
10	3.1	0.60	2.2	+134	- 43	*M*
11	3.9	0.42	2.5	+174	-130	*M*
12	3.1	0.55	2.2	+115	- 30	*M*
13	1.0	0.20	1.15	+ 59	- 87	*M*
14	0.45	0.08	0.73	+ 28	- 82	*M*

[a] Measured at 30.00 °C in $CHCl_3$–MeOH 5:2 v/v (*p*) or in 0.02 M Tris buffer pH 8.0 (d*p*). [b] Calculated from viscosity data of protected polymers.



A B

Figure 1. (A). Specific optical rotation of copolymers (●) and mixtures of homopolymers (○) as a function of polymer composition. (B). $\Delta\epsilon$ at 307 nm in the CD spectrum of copolymers (●) and mixtures of homopolymers (○) as a function of polymer composition.

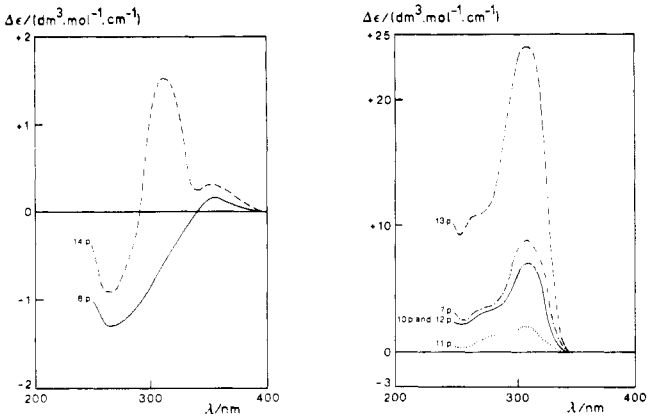
be a correlation between the intrinsic viscosity and the rate of polymerization. The most striking examples of this are **7p** and **8p** and **11p** and **14p**. Apparently, the side chains of the monomers leading to **7p** and **11p** fit more easily into the developing polymer helix than those leading to **8p** and **14p**.

The intrinsic viscosities of aqueous solutions of the unprotected polymers are considerably lower than those of the protected ones (Table II). Apparently, the viscosity behavior in water is quite different from that in chloroform–methanol, 5:2 v/v.

The optical rotation data (Table II) support the view that we are dealing with copolymers. With block polymers or a mixture of homopolymers a proportional behavior between specific rotation and molar ratio would be expected. The polymers **10p–12p** did not show such a behavior, whereas the corresponding mixtures of homopolymers did, as we separately checked (Figure 1, part A).

On deprotection, all polymers in Table II show a shift in their $[\alpha]^{20}_D$'s in a negative direction. Although sometimes optical rotation data can be used to answer the question which screw sense is in excess, it is more reliable to consider the circular dichroism (CD) spectra.

The ultraviolet (UV) spectra of each of the protected polymers **7p–14p** in chloroform–methanol 5:2 v/v showed a shoulder at about 310 nm on the onset of a much larger band in the far UV region. This shoulder can be attributed



A B

Figure 2. (A). CD spectra of homopolymer **8p** and copolymer **14p** in chloroform–methanol, 5:2 v/v. (B). CD spectra of homopolymer **7p** and copolymers **10p–13p** in chloroform–methanol, 5:2 v/v.

to the n–π^* transition of the N=C chromophore of the polymer main chain.[15] Except for **14dp** an n–π^* transition of the N=C chromophore is not clearly visible in the UV spectra of the unprotected polymers. The spectra of all the deprotected polymers, except for **14u**, look alike and do not show pronounced peaks or shoulders.

CD spectra of poly(iminomethylenes) often reveal which screw sense is in excess.[14,15] In many cases, so-called exciton couplets can be detected which give information about the screw sense.[16] These exiton couplets are often partly or completely masked by bands due to the chiral side chains of the polymers. The CD spectra of polymers **8p** and **14p** are depicted in Figure 2, part A. In both spectra a positive couplet is visible, indicative of a predominantly left-handed (*M*) helical configuration.[16] In the CD spectrum of **14p** the couplet is partly masked by the band due to the side chain contribution to the n–π^* transition. The CD spectra of the polymers **7p**, **10p–13p** (Figure 2, part B) show a great similarity in shape. The couplet is not visible at all. On first sight, the high intensity in $\Delta\epsilon$ at approximately 310 nm might be ascribed to the tosyl group. However, this cannot be true since this peak is also present in the spectrum of **7p**. The latter compound does not have a tosyl group. We assume that the side chain contributions to the n–π^* transition of the C=N chromophore are responsible for the observed CD bands. Apparently, these side chain contributions are much larger than the contribution of the helical main chain. The $\Delta\epsilon$ values of copolymers **10p–12p** are lower than those of homopolymer **7p**. Noteworthy is the increase in $\Delta\epsilon$ of copolymer **13p** compared to the closely related **11p** from which it only differs by the presence of the dodecyl moiety. This phenomenon is not yet understood. In Figure 1, part B the $\Delta\epsilon$ values at 307 nm of the polymers **10p**, **11p**, and **12p** are compared with those of the homopolymers **7p** and **9p** and their mixtures. The figure clearly shows that the polymers are real copolymers.

The CD spectra of the deprotected polymers are given in Figure 3. There is a qualitative similarity regarding the CD spectral shape of the deprotected polymers **7dp**, **8dp**, **10dp–14dp**. This similarity suggests the same screw sense in these polymers, i.e., an *M* screw based on the presence of a positive couplet at ~300 nm. The CD

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Table III. pK_a and n Values of Carboxylic Acid and Imidazole Functions of Polymers 7dp–14dp

	COOH		A ImH$^+$		B ImH$^+$			fraction[b] L-Ala-L-Ser in	fraction[c] imidazole B in
no.	pK_a	n	pK_a	n	pK_a	n	I[a]	polymer	polymer
7dp	5.2	2.0							
8dp	4.9	1.0							
9dp	3.1	1.4			9.1	2.1	5.4	0.00	1.00
10dp	4.6	1.8	7.2	1.0	9.6	0.6	5.2	0.65	0.20
11dp	3.8	2.3	7.2	1.0	9.7	0.5	3.8	0.54	0.33
12dp	4.7	1.3	7.1	0.6	9.6	0.7	5.2	0.32	0.43
13dp	5.4	1.8	8.4	1.3			5.6		
14dp	5.3	1.7	8.4	1.2			5.6		

[a] Isoelectric point. [b] Calculated from elemental analysis and titration data. [c] Calculated from titration data.

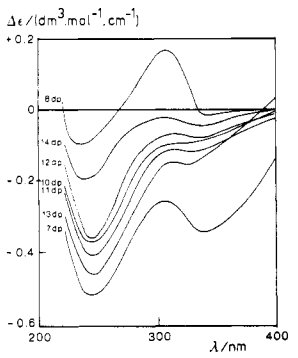


Figure 3. CD spectra of deprotected polymers **7dp**, **8dp**, and **10dp–14dp** in Tris buffer.

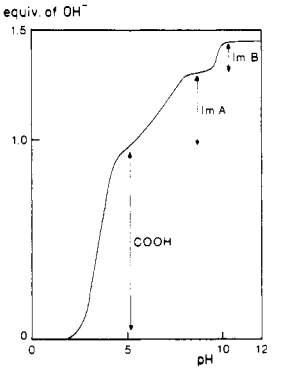
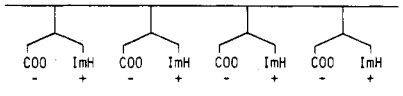


Figure 4. Titration curve of copolymer **11dp**.

spectra of **9p** and **9dp** have been discussed by van der Eijk.[10] From optical rotation data it was concluded that polymers **9** predominantly have an *M* helical configuration, i.e., the same configuration as the other polymers mentioned above.

The ionization state of polymers **7dp–14dp** as a function of pH was determined by potentiometric titration. These titration experiments revealed that the imino functions of the polymer main chain have a low basicity and remain unprotonated even at pH's <2. From the titration curves the fractions of unprotonated imidazole, α_{Im}, and of carboxylate ions, α_{COO^-}, were calculated by using the modified Henderson–Hasselbach equation:[17] $pH = pK_a - n \log ((1 - \alpha)/\alpha)$ The values calculated for n, $pK_a(ImH^+)$ and $pK_a(COOH)$ are presented in Table III. The titration curves give the impression that copolymers **10dp**, **11dp**, and **12dp** have two different imidazole groups, A and B. Imidazole groups A have a normal $pK_a(ImH^+)$ value of about 7; imidazole groups B have a $pK_a(ImH^+)$ of about 9.5. An example of such a titration is given in Figure 4.

The fraction of imidazole groups B increases with decreasing amounts of L-Ala-L-Ser residues in the polymers, as can be seen from Table III. The high value of $pK_a(ImH^+)$ of imidazole groups B suggests that these groups strongly interact with neighboring carboxylate ions, for instance along the stacks of the side chains, as indicated below. When L-Ala-L-Ser residues (Table III) are inserted



in these stacks the regular packing of imidazolyl and carboxylate functions is destroyed, giving rise to new sites of imidazole groups A with a lower $pK_a(ImH^+)$ value. In line with this theory, homopolymer **9dp** should only possess type B imidazole groups, which is indeed the case as can be concluded from Table III. The titration data for polymers **13dp** and **14dp** suggest that in these copolymers two types of imidazole groups are also present, which are, however, not clearly separated in the titration curves. Thus, apparent values of $pK_a(ImH^+)$ 8.4 are calculated from these curves, intermediate to those of imidazole groups A and B.

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Experimental Section

Melting points were determined on a Mettler FP5/FP51 photoelectric melting point apparatus. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. Infrared (IR) spectra were recorded on Perkin-Elmer 297 and 284 spectrophotometers. Ultraviolet spectra were recorded on a Perkin-Elmer 254 UV–vis spectrophotometer. ^1H NMR spectra were obtained on a Varian EM 390 instrument. Chemical shifts (δ) are given in ppm downfield from internal tetramethylsilane or sodium 2,2,3,3-tetradeuterio-3-(trimethylsilyl)propionate. Abbreviations used: s = singlet, d = doublet, q = quartet, m = multiplet, b = broad. Elemental analyses were carried out by the Elemental Analytical Section of the Institute of Chemistry TNO, Utrecht, The Netherlands. TLC was performed on silica (Schleicher and Schüll TLC Ready Plastic Foil FR-1500) and detection was effected by UV and/or iodide vapor. Column chromatography was performed on silica (Merck Kieselgel 60, 230–400 mesh). CD spectra were recorded on a home built apparatus. This instrument measures the differential absorbance (ΔA) with a sensitivity better than 1×10^{-6}. Solution visocisities were obtained with a Cannon-Ubbelohde viscometer. Intrinsic viscosities, optical rotation, and CD data for solutions of the deprotected polymers were obtained in 0.023 M Tris buffer, pH 8.0–8.1. Titrations were performed on Mettler automatic titrator devices types DV 10, DK 12, DK 14, and DK 25.

L-Histidine monohydrochloride, $[\alpha]^{20}_D$ +9.2° (*c* 5, 5 M HCl), was purchased from Fluka; L-alanine, $[\alpha]^{20}_D$ +9.7°, and D-alanine, $[\alpha]^{20}_D$ −9.4° (*c* 2, 1 M HCl) were purchased from BDH; L-serine, $[\alpha]^{20}_D$ −6.8°, and D-serine $[\alpha]^{20}_D$ +6.6° (*c* 2, water), were purchased from Aldrich.

***N*-Formyl-L-alanine** (1) was prepared by formylating L-alanine with a mixture of formic acid and acetic anhydride as described previously.[10]

L-Serine methyl ester hydrochloride (2a) and D-serine methyl ester hydrochloride (2b) were synthesized from L-serine and D-serine through esterification with thionyl chloride in

methanol.[2]

L-Histidine methyl ester dihydrochloride (2c) was obtained from L-histidine monohydrochloride by treatment with hydrogen chloride gas in methanol.[10] It was used without further purification for the synthesis of compound **3c**.

***N*-Formyl-L-alanyl-L-histidine Methyl Ester (3c).** The synthesis of this dipeptide was performed as described before.[10] Recrystallization of the crude product from methanol–ether gave white crystals: yield 80%; mp 127–128 °C (lit.[10] mp 127–128 °C); $[\alpha]^{20}_D$ −38.9° (*c* 1, methanol).

***N*-Formyl-L-alanyl-*O*-acetyl-L-serine Methyl Ester (4a).** An amount of 10 g (39.8 mmol) of **2a** was suspended in 150 mL of acetonitrile. After the reaction mixture was cooled to 0 °C, 4 g of triethylamine and 4.7 g (40.2 mmol) of **1** were added. After stirring this mixture at 0 °C for 15 min, coupling of **1** and **2a** was effected by adding 9 g (44 mmol) of dicyclohexylcarbodiimide (DCC). The reaction mixture was subsequently stirred for 3 h at 0 °C. After standing overnight at room temperature, the dicyclohexylurea was filtered off and the remaining solution concentrated in vacuum to yield a light-yellow oil (**3a**). To this oil an amount of 75 mL of acetic anhydride and 2 mL of pyridine was added. The mixture was stirred overnight at room temperature and concentrated at a temperature below 50 °C in an oil pump vacuum. The resulting oil was dissolved in 100 mL of chloroform and extracted three times with 50 mL of water. The organic layer was dried (Na_2SO_4) and concentrated in vacuum. Compound **4a** was obtained by crystallization from methanol–ether as a white crystalline product: yield 7.8 g (75%); mp 110–111 °C; $[\alpha]^{20}_D$ −33.1° (*c* 2, methanol); IR (KBr) 3320 (NH), 1740 ($COOCH_3$, $OCOCH_3$), 1650, 1680 cm^{-1} (NHCO); ^1H NMR ($CDCl_3$ + a trace of CD_3OD) δ 8.2 (s, 1 H, CHO), 4.9 (t, 1 H, C*H*CH_2), 4.8 (q, 1 H, C*H*CH_3), 4.4 (d, 2 H, CH_2CH), 3.8 (s, 3 H, OCH_3), 2.1 (s, 3 H, $COCH_3$), 1.3 ppm (d, 3 H, CH_3CH).

***N*-Formyl-L-alanyl-*O*-acetyl-D-serine methyl ester (4b)** was obtained from **1** and **2b** as described for **4a**: yield 3.4 g (64%). The product was obtained as a yellow oil, slightly contaminated with pyridine: $[\alpha]^{20}_D$ −8.9° (*c* 1, methanol); IR (neat) data as for **4a** within 10 cm^{-1}; ^1H NMR data are the same as for **4a** within 0.05 ppm.

***N*-Formyl-L-alanyl-*N*(Im)-tosyl-L-histidine Methyl Ester (4c).** The synthesis of this compound was performed as described previously.[10] Recrystallization from chloroform–ethyl acetate afforded white crystals of pure **4c**: yield 74%; mp 113–135 °C; $[\alpha]^{20}_D$ +7.4° (*c* 2, chloroform) (lit.[10] mp 133–134 °C; $[\alpha]^{20}_D$ +7.6° (*c* 2, chloroform)).

L-Carbylalanyl-*O*-acetyl-L-serine Methyl Ester (5a). In a round-bottomed flask, equipped with a magnetic stirrer and CO_2–acetone reflux condensor (kept at −50 °C), 2.6 g (10 mmol) of **4a** was dissolved in 75 mL of dichloromethane, brought under a nitrogen atmosphere, and cooled to −40 °C. After stirring for 15 min, 3.6 mL of triethylamine was added. An amount of 3.0 g (20 mmol) of phosphorus oxychloride in 25 mL of dichloromethane was introduced into the stirred reaction mixture over a period of 1.5 h. The reaction was followed by TLC ($CHCl_3$–acetone, 4:1 v/v, R_f **5a** 0.45, R_f **4a** 0.10). The temperature was allowed to rise to −10 °C and the reaction mixture was stirred for an additional hour. Subsequently, 50 mL of 10% aqueous sodium bicarbonate (0 °C) was introduced at once. After stirring for 10 min the organic layer was separated and extracted twice with 25 mL of water. The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure at 40 °C. A yellowish-brown oil was obtained which was slightly contaminated with **4a**. The product was subjected to column chromatography (eluent $CHCl_3$–acetone, 4:1 v/v). Compound **5a** was obtained as a slightly yellow oil: yield 1.55 g (63%); $[\alpha]^{20}_D$ −58.1° (*c* 2, chloroform); IR (neat) 3320 (NH), 2145 (N=C), 1740 ($COOCH_3$, $OCOCH_3$), 1660 cm^{-1} (NHCO); ^1H NMR ($CDCl_3$ + a trace of CD_3OD) δ 4.9 (t, 1 H, C*H*CH_2), 4.2 (q, 1 H, C*H*CH_3), 4.4 (d, 2 H, CH_2CH), 3.8 (s, 3 H, OCH_3), 2.1 (s, 3 H, $COCH_3$), 1.5 (d, 3 H, CH_3CH). Isocyanide **5a** is a labile compound. When kept at room temperature it decomposed within a week. However, when stored in a refrigerator under nitrogen it could be kept for about a week without appreciable decomposition.

L-Carbylalanyl-*O*-acetyl-D-serine Methyl Ester (5b). This isocyanide was synthesized from 3.4 g (13.1 mmol) of **4b** as described for **5a**. The product was obtained as a light yellow oil: yield 2.3 g (75%); TLC ($CHCl_3$–acetone, 4:1 v/v) R_f **5b** 0.48, R_f **4b** 0.13; $[\alpha]^{20}_D$ −12.0° (*c* 1, chloroform); IR (neat) 2145 cm^{-1} (N=C) other peaks as described for **5a** within 10 cm^{-1}; ^1H NMR δ 4.3 (q, 1 H, C*H*CH_3), 1.5 (d, 3 H, CH_3CH), other signals as described for **5a** within 0.1 ppm. In contrast to **5a**, **5b** was stable.

L-Carbylalanyl-*N*(Im)-tosyl-L-histidine Methyl Ester (5c).[10] This isocyanide was synthesized from 3.9 g (10.8 mmol) of **4c** as described for **5a**. Compound **5c** was obtained as a crystalline white solid: yield 2.6 g (70%); TLC ($CHCl_3$–acetone, 4:1 v/v) R_f **5c** 0.48, R_f **4c** 0.10; mp 137–137.5 °C; $[\alpha]^{20}_D$ −41.8° (*c* 1, chloroform) (lit.[10] mp 137.0–137.2 °C; $[\alpha]^{20}_D$ +40.6° (*c* 2, chloroform)).

***n*-Dodecyl isocyanide (6)** was synthesized from *n*-dodecylamine as described in the literature.[11]

Polymerization. The following stock solutions were prepared: A, 0.5 M of **5a** in chloroform; B, 0.5 M of **5b** in chloroform; C, 0.5 M of **5c** in chloroform–methanol (9:1 v/v); D, 0.5 M of **6** in chloroform; E, 2×10^{-3} M of $NiCl_2 \cdot 6H_2O$ in methanol.

Homopolymer 7p. Isocyanide **5a** was polymerized by adding 0.7 mL of stock solution E to 3 mL of stock solution A. The reaction was completed within 0.5 h. The solvent was removed in vacuum and the dark-yellow residue dissolved in 5 mL of hot chloroform. While stirring, this solution was added dropwise to a 50-fold excess of methanol–water 1:3 v/v. The precipitate was filtered off, washed with ether and water and dried in vacuum to yield 320 mg (87%) of **7p** as a pale yellow solid: $[\alpha]^{20}_D$ +205° (*c* 0.2, chloroform–methanol, 5:2 v/v); [η] 4.1 dL/g (chloroform–methanol, 5:2 v/v, 30.00 °C); IR (KBr) 3260 (NH), 1740 ($OCOCH_3$, $COOCH_3$), 1660 cm^{-1} (NHCO).

Homopolymer 8p. This polymer was synthesized as described for **7p** by using 0.7 mL of stock solution E and 3 mL of stock solution B. The polymerization took 4 h and yielded 285 mg (78%) of **8p** as a light-brown powder: $[\alpha]^{20}_D$ −33° (*c* 0.2, chloroform–methanol, 5:2 v/v); [η] 0.35 dL/g (chloroform–methanol, 5:2 v/v, 30.00 °C); IR (KBr) 3260 (NH), 1740 ($OCOCH_3$, $COOCH_3$), 1660 cm^{-1} (NHCO).

Homopolymer 9p. The synthesis of this polymer was performed as described before.[10]

Copolymer 10p. This polymer was obtained by mixing 2 mL of stock solution A and 1 mL of stock solution C, followed by the addition of 0.7 mL of stock solution E. The reaction was completed within 0.5 h. Isolation of the product was achieved as described for **7p**: yield 340 mg (76%) of **10p** as a light-yellow powder: $[\alpha]^{20}_D$ +134° (*c* 0.2, chloroform–methanol, 5:2 v/v); [η] 3.1 dL/g (chloroform–methanol, 5:2 v/v, 30.00 °C); IR (KBr) 3270 (NH), 1740 ($COCH_3$, $OCOCH_3$), 1660 (NHCO), 1600, 1375 and 1180 cm^{-1} (tosyl).

Copolymer 11p. This polymer was synthesized as described for **7p** and **10p** by mixing the following stock solutions: 1.5 mL of A, 1.5 mL of C, and 0.7 mL of E. The reaction was completed within 0.5 h and yielded 349 mg (72%) of **11p** as a white solid: $[\alpha]^{20}_D$ +174° (*c* 0.2, chloroform–methanol, 5:2 v/v); [η] 3.9 dL/g (chloroform–methanol, 5:2 v/v, 30.00 °C); IR (KBr) 3260 (NH), ($OCOCH_3$, $COOCH_3$), 1660 (NHCO), 1600, 1375 and 1180 cm^{-1} (tosyl).

Copolymer 12p. This polymer was synthesized as described for **7p** and **10p** by using 1 mL of stock solution A, 2 mL of C, and 0.7 mL of E. The reaction was completed within 0.5 h and yielded 340 mg (65%) of **12p** as a white solid: $[\alpha]^{20}_D$ +115° (*c* 0.2, chloroform–methanol, 5:2 v/v); [η] 3.1 dL/g (chloroform–methanol, 5:2 v/v, 30.00 °C); IR (KBr) 3260 (NH), 1740 ($OCOCH_3$, $COOCH_3$), 1660 (NHCO), 1500, 1375 and 1180 cm^{-1} (tosyl).

Copolymer 13p. This polymer was synthesized as described for **7p** and **10p** by using 2 mL of solution A, 2 mL of C, 1 mL of D, and 1.2 mL of E. The polymerization took 1.5 h and yielded 380 mg (53%) of **13p** as a white solid: $[\alpha]^{20}_D$ +59° (*c* 0.2, chloroform–methanol, 5:2 v/v); [η] 1.02 dL/g (chloroform–methanol, 5:2 v/v, 30.00 °C); IR (KBr) 3260 (NH), 2950 (CH), 1740 ($OCOCH_3$, $COOCH_3$), 1660 (NHCO), 1600, 1375 and 1180 cm^{-1} (tosyl).

Copolymer 14p. This polymer was synthesized as described for **7p** and **10p** by using 1.5 mL of stock solution B, 1.5 mL of C, and 0.7 mL of E. The polymerization took 3 h and yielded 340 mg (90%) of **14p**: $[\alpha]^{20}_D$ +28° (*c* 0.2, chloroform–methanol, 5:2 v/v); [η] 0.45 dL/g (chloroform–methanol, 5:2 v/v, 30.00 °C); IR (KBr) 3260 (NH), 1740 ($OCOCH_3$, $COOCH_3$), 1660 (NHCO),

1600, 1375 and 1180 cm^{-1} (tosyl).

Homopolymer 7dp. **7p** (290 mg) was treated with 20 mL of 0.5 M aqueous NaOH for two days at 40 °C. The reddish-brown solution was submitted to ultrafiltration (Diaflo-Ultrafilter UM-2) and freeze-dried. The polymer was obtained as a brown spongy solid: yield 164 mg (60%) of **7dp**; $[\alpha]^{20}_D$ −63° (*c* 0.2, Tris buffer); $[\eta]$ 0.15 dL/g (Tris buffer, 30.00 °C). Anal. Calcd for $C_7H_9N_2O_4Na(H_2O)_{0.72}$: C, 37.8; H, 5.0; N, 12.7; O, 34.1; Na, 10.4. Found: C, 37.8; H, 5.0; N, 12.7; O, 34.2; Na, 10.3. IR (KBr) 3700–3200 (NH, OH, and H_2O), 1650 cm^{-1} (NHCO). The vibration of the azomethine (C=N) group is masked by NHCO and COO^- vibrations. This is also the case for the other deprotected polymers. Variations in the deprotection reaction time gave polymer samples with identical physical properties.

Homopolymer 8dp. **8p** (250 mg) was deprotected as described for **7dp**. The polymer was obtained as a dark-brown powder: yield 243 mg (100%) of **8dp**; $[\alpha]^{20}_D$ −57° (*c* 0.2 Tris buffer). Anal. Calcd for $C_7H_9N_2O_4Na(H_2O)_{1.5}(C_2H_2O)_{0.15}$: C, 36.3; H, 5.2; N, 11.7; O, 37.4; Na, 9.5. Found: C, 36.4; H, 5.4; N, 11.9; O, 36.8; Na, 9.5. Ir (KBr) data as for **7dp** within 5 cm^{-1} and in addition 1720 cm^{-1} ($COOCH_3$).

Homopolymer 9dp. This polymer was deprotected as described previously.[10]

Copolymer 10dp. **10p** (580 mg) was detosylated by dissolving this polymer in 30 mL of acetic anhydride–pyridine, 1:1 v/v, and keeping this solution overnight at room temperature. After removal of the solvent in vacuum the residue was treated for two days with 20 mL of 0.5 M aqueous NaOH at 40 °C. The reddish-brown solution was acidified (pH 2.5), submitted to ultrafiltration (Diaflo Ultra-Filter UM-2), and freeze-dried. Polymer **10dp** was obtained as a reddish-brown powder: yield 412 mg (100%); $[\alpha]^{20}_D$ −43° (*c* 0.2 Tris buffer); $[\eta]$ 0.60 (Tris buffer, 30.00 °C). Anal. Calcd for $C_{24.7}H_{32.8}N_{8.3}O_{11.2}(HCl)_{0.3}(H_2O)_{0.5}$: C, 46.5; H, 5.2; N, 18.2; O, 28.1; Cl, 1.9. Found: C, 46.8; H, 5.4; N, 18.1; O, 27.9; Cl, 1.8 IR (KBr) data as for **8dp** within 5 cm^{-1} and in addition 2800–2200 cm^{-1} (HCl).

Copolymer 11dp. **11p** (315 mg) was treated as described for **10dp** except that for the hydrolysis 0.5 M aqueous KOH was used. Polymer **11dp** was obtained as a voluminous, spongy, yellowish-brown solid: yield 190 mg (85%); $[\alpha]^{20}_D$ −130° (*c* 0.2, Tris buffer); $[\eta]$ 0.42 dL/g (Tris buffer 30.00 °C). Anal. Calcd for $C_{15.4}H_{20.1}N_{5.2}O_{6.5}K_{0.2}(H_2O)_{1.3}$: C, 44.4; H, 5.4; N, 18.0; O, 30.0; K, 2.2. Found: C, 44.6; H, 5.2; N, 18.0; O, 30.1; K, 2.1. IR (KBr) data as for **8dp** within 5 cm^{-1}.

Copolymer 12dp. **12p** (256 mg) was treated as described for **11dp**. Polymer **12dp** was obtained as a reddish-brown powdery solid: yield 92 mg (50%); $[\alpha]^{20}_D$ −30° (*c* 0.2, Tris buffer); $[\eta]$ 0.55 dL/g (Tris buffer, 30.00 °C). Anal. Calcd for $C_{27.8}H_{34.1}N_{10.3}O_{10.2}K_{0.9}(H_2O)_{4.2}$: C, 42.5; H, 5.4; N, 18.3; O, 29.3; K, 4.5. Found: C, 42.7; H, 5.2; N, 18.2; O, 29.6; K, 4.3. IR (KBr) data as for **8dp** within 5 cm^{-1}.

Copolymer 13dp. **13p** (350 mg) was treated as described for **11dp**. Polymer **13dp** was obtained as a dark-brown powdery solid: yield 194 mg (66%); $[\alpha]^{20}_D$ −87° (*c* 0.2, Tris buffer); $[\eta]$ 0.20 dL/g (Tris buffer, 30.00 °C). Anal. Calcd for $C_{49.2}H_{72.1}N_{13.7}O_{14.5}K_{4.1}(H_2O)_{2.8}$: C, 45.5; H, 5.7; N, 13.9; O, 22.5; K, 12.4. Found: C, 45.3; H, 5.6; N, 13.8; O, 22.8; K, 12.5. IR (KBr) data as for **8dp** within 5 cm^{-1} and in addition 2920 cm^{-1} (CH).

Copolymer 14dp. **14p** (316 mg) was treated as described for **11dp**. Polymer **14dp** was obtained as a dark-brown powdery solid: yield 192 mg (99%); $[\alpha]^{20}_D$ −82° (*c* 0.2, Tris buffer); $[\eta]$ 0.08 dL/g (Tris buffer, 30.00 °C). Anal. Calcd for $C_{17.7}H_{22.1}N_{6.3}O_{3.2}K_{0.7}(H_2O)_{0.75}$: C, 44.2; H, 5.3; N, 18.3; O, 26.5; K, 5.7. Found: C, 44.3; H, 5.1; N, 18.3; O, 26.4; K, 5.9. IR (KBr) data as for **7dp** and **8dp** within 5 cm^{-1}.

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Registry No. **1**, 10512-86-4; **2a**, 5680-80-8; **2b**, 5874-57-7; **4a**, 97171-35-2; **4b**, 97171-36-3; **4c**, 75382-89-7; **5a**, 97171-40-9; **5b**, 97171-37-4; **5c**, 75345-20-9; **7p**, 97190-26-6; **8p**, 97171-38-5; **10p**, 97171-41-0; **13p**, 97233-23-3; **14p**, 97233-24-4; $NiCl_2$, 7718-54-9; acetic anhydride, 108-24-7.

Manganese(III) γ-Lactone Annulation with Substituted Acids

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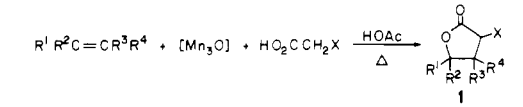
Manganese(III) acetate oxidation of several $HOOCCH_2X$, X = electron withdrawing group, in the presence of alkenes led to the formation of α-substituted γ-lactones. Chloroacetic acid gave α-chloro γ-lactones, which were converted in two steps to the corresponding α,β-unsaturated γ-lactones. 3-Chloropropanoic acid led to the α-methylene γ-lactone after base induced elimination of HCl. Cyanoacetic acid produced α-cyano γ-lactones which could be hydrolytically decyanated or converted to the α-methylene γ-lactones in two steps. Potassium methyl malonate was oxidized and annulated onto alkenes to give α-carbomethoxy γ-lactones in reasonable yields. The method demonstrates a general route into several useful types of substituted γ-lactones.

The annulation of a γ-lactone ring onto an alkene by manganese(III) acetate, $[Mn_3O(OAc)_6(OAc)(HOAc)]\cdot 5H_2O$ = $[Mn_3O]$, according to eq 1 has been examined by us[2] and others.[3-6] In addition, limited studies of substituted acetic acid, XCH_2COOH, X = Me,[3a,b,7] CN,[3a] have been reported including the use of malonic acid to generate spiro dilactones.[8,9] Our interest in furthering the use of Mn(III) in organic synthesis, and the desirability of a simple, one-step route to α-substituted γ-lactones led us to investigate the Mn(III) oxidation of a number of acids. This paper outlines our results with chloroacetic, 3-chloropropanoic, cyanoacetic, and monomethyl malonic acid.



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