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SYNTHESIS OF PEPTIDE DERIVATIVES WITH THREE PEPTIDE CHAINS CONNECTED BY A NITROGEN ATOM

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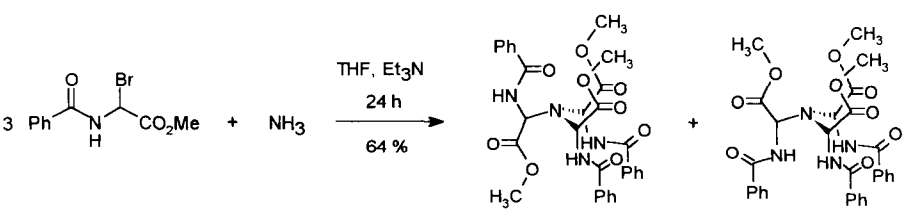
Summary: Reaction of methyl *N*-benzoyl-2-bromoglycinate with ammonia yields trimethyl 2,2',2''-nitrilotris[2-(benzoylamino)acetate] in form of two diastereomers **2a** and **2b**, which can be separated by recrystallization. The *RRR/SSS*-compound **2b** is used as a template for the synthesis of C_3-symmetric peptide derivatives in which three peptide chains are closely aligned in a parallel fashion. The stereochemistry of the new compounds has been determined by X-ray structure analyses.

The reaction of electrophilic glycine equivalents with nucleophiles is a versatile method for the synthesis of α-amino acids[1] and modified peptide derivatives.[2] In this communication we describe the application of this technique for the construction of novel peptide derivatives with C_3-point-group symmetry.

Reaction of methyl *N*-benzoyl-2-bromoglycinate (**1**)[3] with ammonia yields trimethyl 2,2',2''-nitrilotris[2-(benzoylamino)acetate][4] as a 6:1 mixture of the diastereomers **2a** and **2b**[5], which can be easily separated by fractional crystallization from methanol on a 30 g scale. Their stereochemistry follows from the X-ray crystal structures depicted in Fig. 1.[6] In the symmetrical isomer **2b**, the three α-substituted glycine residues are of the same absolute configuration and arranged parallel, whereas in **2a** one of the residues is of opposite configuration and aligned antiparallel to the others. Each conformation is stabilized by intramolecular hydrogen bonds between the benzoylamino groups.



1 **2a** (*RRS/SSR*) **2b** (*RRR/SSS*)

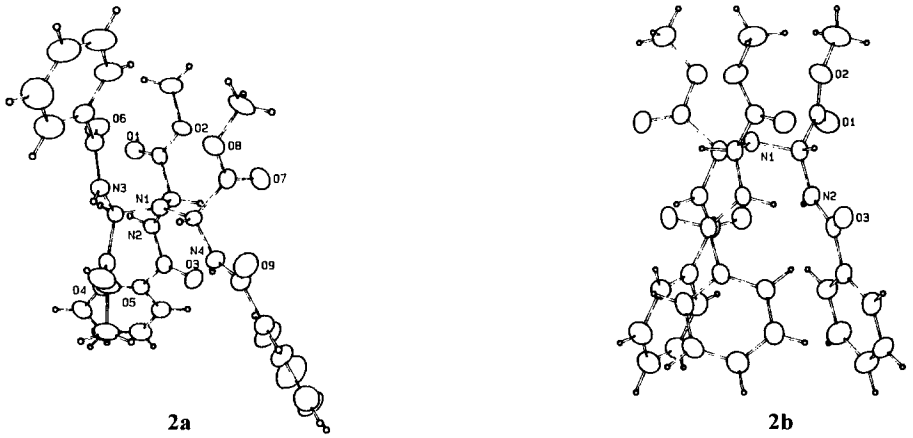
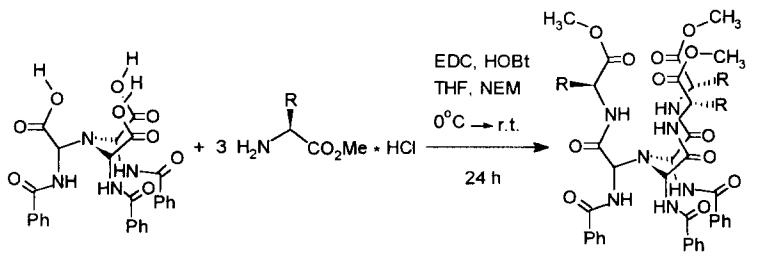


Fig. 1. X-ray crystal structures of stereoisomers **2a** and **2b**

On hydrolysis with lithium hydroxide in methanol-water[7] the symmetrical stereoisomer **2b** yields the corresponding tricarboxylic acid **3b**[8] in 92% yield, whereas isomer **2a** gives 66% of the unsymmetrical tricarboxylic acid **3a**[9] and 33% of **3b**. Since both acids can be readily separated by fractional crystallization, the symmetrical triacid **3b** is available in larger quantities.

The racemic triacid **3b** is an interesting template for the synthesis of compounds in which three parallel peptide chains are closely aligned together.[10] Thus, the pseudo-hexapeptides **4a-d** were obtained by coupling *rac*-**3b** with L-α-amino acid methyl esters by the EDC-HOBt method [EDC = *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide].[11] The resulting peptides **4a-4d** are 1:1 mixtures of stereoisomers varying in their configuration at the template unit.



3b (*RRR/SSS*) **4a-d**

	R	yield (%)*
4a	H	81
4b	CH_3	75
4c	$CH(CH_3)_2$	80
4d	CH_2OH	72

*1:1 mixture of diastereomers

In all cases the (2*S*,2'*S*,2"*S*) and (2*R*,2'*R*,2"*R*)-compounds can be separated by fractional crystallization from methanol. Interestingly, the glycyl derivative **4a** crystallizes as a conglomerate which allows the optical resolution of this compound by sorting out the enantiomorphic crystals. Due to the interaction of the three helically arranged benzoylamino groups, these enantiomers exhibit characteristic couplets in their CD spectra (Fig. 2).[12] The result of the X-ray structure determination of the *RRR*-enantiomer of **4a** is depicted in Fig. 3.[13]

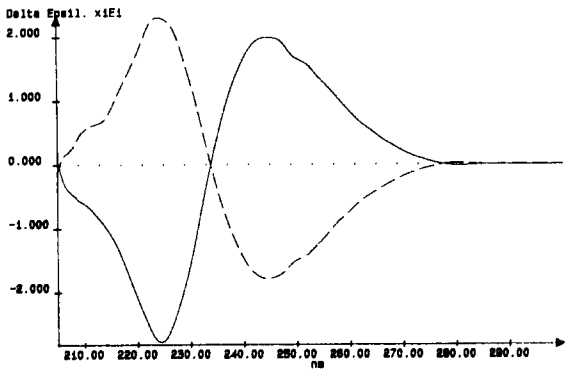


Fig. 2. CD spectra of the *RRR*- (—)and *SSS*- (- - -) enantiomers of pseudo-hexapeptide **4a** in CH_3CN

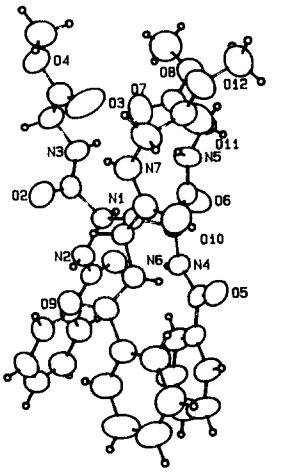
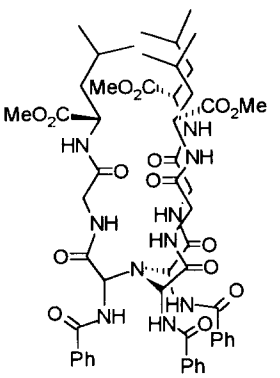


Fig. 3. X-ray crystal structure of (*RRR*)-**4a**

The absolute configuration of this compound follows from the close correspondence of its CD spectrum with that of pseudo-nonapeptide **5** (Fig. 4). Since the *RRR*-configuration of the 2,2',2"-nitrilotris[2-(benzoylamino)acetyl] unit in **5** is known from the X-ray crystal structure given in Fig. 4,[14] the glycine derivative depicted in Fig. 3 must have the same absolute configuration. Peptide **5** was obtained in 75% yield by EDC-HOBt coupling of **3b** with H-Gly-Leu-OMe followed by separation of the diastereomers by fractional crystallization.[15] According to the X-ray structure determination, the three peptide chains in **5** adopt a C_3-symmetrical right-handed helical structure stabilized by six interstrand hydrogen bonds.



5

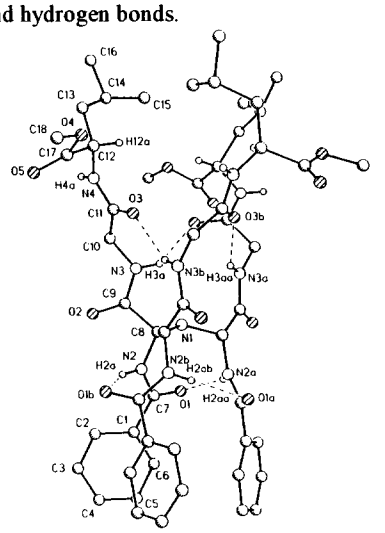


Fig. 4. X-ray crystal structure of pseudo-nonapeptide **5**

The synthesis of longer peptides of this type and their conversion into capped compounds and metal complexes is under active investigation.

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3. Kober, R.; Steglich, W. *Liebigs Ann. Chem.* **1983**, 599-609.
4. For an unsuccessful attempt to obtain compounds **2a/2b**, see Easton, C. J.; Peters, S. C. *Aust. J. Chem.* **1990**, *43*, 87-97.
5. Preparation of compounds **2a** and **2b**: To a stirred solution of 84.8 g methyl *N*-benzoyl-2-bromoglycinate (**1**) (0.31 mol, 5.0 equiv) in dry THF (700 ml) at 20 °C was added triethylamine (52 ml, 0.37 mol) and ammonia (155 ml, 0.4 M solution in THF, 1 equiv). Stirring was continued for 24 h at 20 °C. Ethyl acetate (350ml) was added, and the solution was washed with 1 N HCl, satd. aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, filtered, and then evaporated under reduced pressure. After the addition of methanol (300 ml), the unsymmetrical isomer **2a** (20 g, 55%) crystallized immediately and was filtered off. The symmetrical isomer **2b** (3.3 g, 9.2%) was obtained from the mother liquor on standing overnight. *rac*-**2a**: m.p. 200 °C , ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.41 (s, 3H) , 3.74 (s, 6H), 5.70-5.78 (m, 3H), 7.44-7.66 (m, 10H), 7.88 (d, J = 6.8 Hz, 2H), 8.04 (d, J = 6.8 Hz, 4H), 8.86 (d, J = 5.5 Hz, 2H); *rac*-**2b**: m.p. 204 °C, ^{1}H NMR: δ = 3.89 (s, 9H), 6.05 (d, J = 9.6 Hz, 3H), 7.13-7.23 (m, 6H), 7.30-7.42 (m, 9H), 8.37 (d, J = 9.6 Hz, 3H). Both compounds gave correct elemental analyses.
6. Crystallographic data for **2a**: $C_{30}H_{30}N_4O_9$, M = 590.6, space group $P\bar{1}$ (N° 2), triclinic with a = 7.236(2), b = 12.869(3), c = 17.073(5) Å, α = 111.03(2), β = 92.69(2), γ = 102.63(2), V = 1434.2 Å^3, Z = 2, d_c = 1.367 g/cm^3; Mo-K_α radiation (23 °C); reflections collected 3643, unique reflections 3498, observed reflections 2799, R-index 0.0743 [I > 3 σ (I_o)]. **2b**: $C_{30}H_{30}N_4O_9 \cdot 0.642H_2O$, M = 602.15, space group $R\bar{3}$ (N° 148), rhombohedral with a = 11.786(3), α = 77.43(2), V = 1534.5 Å^3, Z = 2, d_c = 1.397 g/cm^3; Mo-K_α radiation (23 °C); reflections collected 3891, unique reflections 1423, observed reflections 1163, R-index 0.0343 [I > 3 σ (I_o)]. The full data for all X-ray crystal structures have been deposited at the Cambridge Crystallographic Data Centre.
7. Corey, E. J.; Székely, I.; Shiner, C. S. *Tetrahedron Lett.* **1977**, *40*, 3529-3532.
8. *rac*-**3b**: m.p. 110 °C; ^{1}H NMR (300 MHz, [D_6]DMSO): δ = 5.90 (d, J = 9.0 Hz, 3H), 7.16-7.27 (m, 6H), 7.35-7.51 (m, 9H), 8.55 (d, J = 9.0 Hz, 3H); FAB-MS: 549 (MH^+); correct elemental analysis.
9. Formula corresponds to that of **2a** with carboxy instead of ester groups.
10. For the use of templates in the synthesis of compounds with multiple peptide chains see e. g. Mutter, M.; Tuchscherer, G. G.; Miller, C.; Altmann, K.-H.; Carey, R. I.; Wyss, D. F. ; Labhardt, A. M.; Rivier, J. E. *J. Am. Chem. Soc.* **1992**, *114*, 1463-1470; Nowick, J. S.; Abdi, M. A.; Bellamo, K. A.; Love, J. A.; Martinez, E. J.; Noronha, G.; Smith, E. M.; Ziller, J. W. *J. Am. Chem. Soc.* **1994**, in press, and references given therein.
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12. Harada, N.; Nakanishi, K. *Circular Dichroic Spectroscopy - Exciton Coupling in Organic Chemistry*; University Science Books: Mill Valley, CA., 1983.
13. Crystallographic data for (*RRR*)-**4a**: $C_{36}H_{39}N_7O_{12}$, M = 761.8, space group $P2_1$ (N° 5), monoclinic with a = 11.276(3), b = 10.655(3), c = 16.169(6) Å, β = 102.56(2), V = 1896.2 Å^3, Z = 2, d_c = 1.334 g/cm^3; Mo-K_α radiation (23 °C); reflections collected 5239, unique reflections 5227, observed reflections 4544, R-index 0.0375 [I > 3 σ (I_o)].
14. Crystallographic data for **5**: $C_{54}H_{72}N_{10}O_{15}$, M = 1101.2, space group $R3$ (N° 146), hexagonal with a = 15.004(2), c = 23.890(9) Å, V = 4657.6 Å^3, Z = 3, d_c = 1.178 g/cm^3; Mo-K_α radiation (-70 °C); reflections collected 2982, unique reflections 2982, observed reflections 2195, structure refined against F^2, R_1: 0.0785 [F > 4.0 σ (F_o)], wR2: 0.2014, SHELXR93.
15. Recrystallization by slow diffusion of pentane into a solution of **5** in acetone; m.p. 221 °C, $[\alpha]^{23}_D$ = -9 (c = 1, MeOH).

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