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On-site Modification of Oligopeptides: Conversion of Seryl into (*exo*)-2-Azabicyclo[2.2.1]hept-5-ene-3-carbonyl Residues

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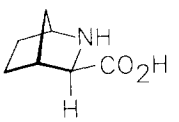
Summary: Diels-Alder addition of cyclopentadiene to Z-valyl-dehydroglycine methyl ester and similar peptides affords conformationally constrained (*exo*)-2-azabicyclo[2.2.1]hept-5-ene-3-carbonyl derivates **4** with high stereoselectivity. The stereochemistry of the cycloadducts follows from NMR evidence and an X-ray structure analysis of dioxopiperazine **8**. The double bond in the 2-azabicyclo-[2.2.1]hept-5-ene residues is used for further modifications.

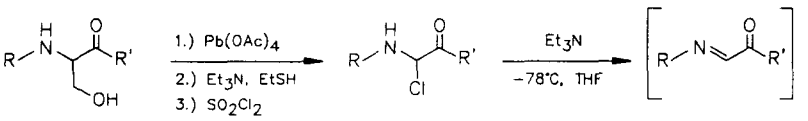
(*exo*)-2-Azabicyclo[2.2.1]heptane-3-carboxylic acid (**1**) has received attention as a conformationally more rigid substitute for proline in biologically active peptides.[1] Derivatives of this amino acid have been obtained by Diels-Alder addition of cyclopentadiene to *N*-protected dehydroglycine esters[2,3] followed by catalytic hydrogenation of the resulting 2-azabicyclo[2.2.1]hept-5-ene intermediates.[3] To our knowledge, derivatives of **1** have not been resolved, and only peptides containing this amino acid in *N*-terminal position have been prepared so far.



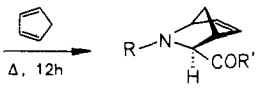
1

In this communication we report on the stereoselective synthesis of (*exo*)-2-azabicyclo[2.2.1]hept-5-ene-3-carbonyl peptides **5** from dehydroglycyl peptides **4**. The latter can be easily prepared from Z-seryl peptide esters **2** *via* the corresponding α-chloroglycyl peptides **3** according to Scheme 1.[4] Heating of the dehydroglycyl peptides **4** with cyclopentadiene in refluxing tetrahydrofuran affords the cycloadducts **5**[5] in fair yields. Their NMR spectra and HPLC analyses indicate the presence of two diastereomers in a ratio of 9:1 (d.e. 80%). The major isomers **5a-c** can be obtained by column chromatography on silica gel. The stereochemistry of **5a-c** follows from the close agreement of their ^{1}H NMR data with those of the known *exo*-isomers **6**[2,3] and **7**[6]. In all

cases the signals for 5-H and 6-H appear around δ 6.4, whereas *endo*-isomers like **8**[6] experience a downfield shift of 5-H to δ 6.15 due to deshielding by the neighbouring ester group.



2 **3** **4**

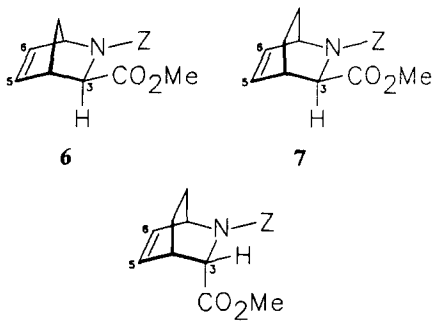


5

	R	R'	yield
5a	Z-L-Val	OMe	67 %
5b	Z-L-Phe	OMe	60 %
5c	Z-L-Val	L-Val-OBn	41 %

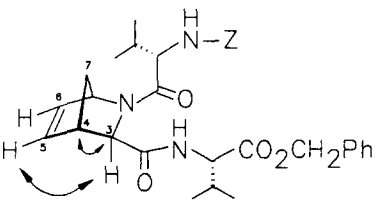
Scheme 1

The *exo*-stereochemistry of the major cycloadducts was confirmed by NOESY experiments carried out with the tripeptide derivative **5c**. Its proton at C-3 exhibits only cross peaks with 4-H and 5-H, whereas for the *endo*-isomer a correlation between 3-H and one of the protons at C-7 would be expected. Furthermore, the lack of vicinal coupling between 3-H and 4-H in the COSY spectrum is in accord with the assigned configuration.



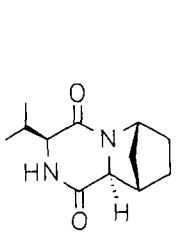
6 **7**

8



5c

Proof for the (3*S*)-configuration of the newly formed amino acid in the major diastereomers was gained by an X-ray structure analysis of dioxopiperazine **9** (Fig. 1)[7], obtained in 80% overall yield from **5a** by hydrogenation on Pd/C and heating of the resulting dihydrodipeptide ester in ethyl acetate.



9

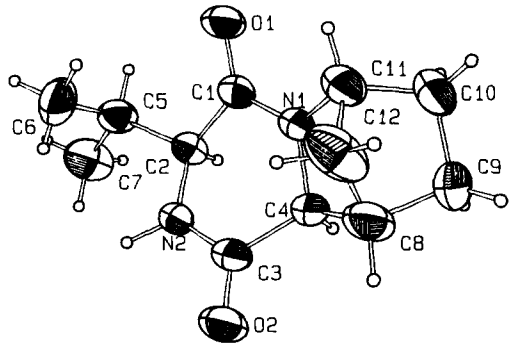
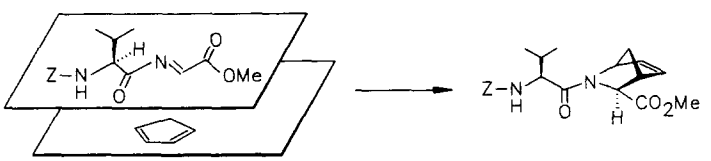


Figure 1: X-ray crystal structure of dioxopiperazine **9** (with unsystematical atom numbering scheme)

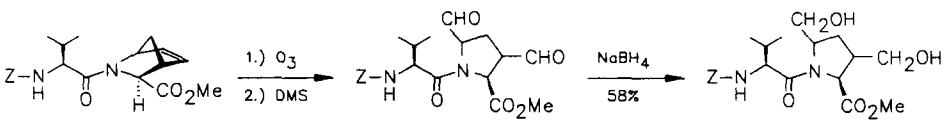
The (3*S*)-*exo*-stereochemistry of the major diastereomers **5a-c**[8] can be explained by the *N*-acyliminoester **4a** adopting the *E*-configuration[2,9] and the diene approaching from the less hindered α-face, opposite to the sterically demanding alkyl group of the (*S*)-valine residue[10] and *endo* to the *N*-acyl group of the dehydroglycine moiety (Scheme 2).[11] The stronger *endo*-directing ability of an *N*-acyl relative to a competing *C*-acyl group is known from similar imino dienophiles.[6,9]



5a

Scheme 2

The double bond in the cyclopentene unit of cycloadducts **5** allows further on-site peptide modifications. Thus, ozonolysis of **5a** and reductive work-up with dimethyl sulfide yielded the dialdehyde **10**, which was characterized as its bis-2,4-dinitrophenylhydrazone and transformed into the more polar bis-hydroxymethyl derivative **11**[12] by reduction with sodium borohydride.



5a **10** **11**

In conclusion, we have developed a stereoselective on-site method for the introduction of conformationally constrained 'proline-like' amino acids into preformed peptide chains, which compares favorably with classical

stepwise procedures.[13] Cycloaddition reactions of dehydroglycyl peptides with other dienes are under active investigation.

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5. Preparation of compounds **5**: To a solution of α-chloroglycyl peptide **3** (1 mmol) in dry THF (30 ml) was added Et_3N (0.14 ml, 1 mmol) with stirring at -78°C under an argon atmosphere. After 30 min freshly destilled cyclopentadiene (0.20 g, 3 mmol) in 5 ml dry THF was added and the mixture was refluxed for 15 h. After cooling to room temperature and addition of 20 ml dilute aqueous citric acid the solution was extracted with EtOAc. The organic layer was washed with water and dried. The pure major diastereomers were obtained as colourless oils by flash column chromatography on silica gel using EtOAc/petroleum ether (40/60) 1:2. **5a**: $[\alpha]^{25}_D$ = -376 (c = 0.5 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ= 0.97, 1.05 (2d, *J* = 6.7 Hz, 6H), 1.62-1.64 (m, 1H), 2.04-2.07 (m, 2H), 3.33 (s, 1H), 3.63-3.83 (m, 1H), 3.73 (s, 3H), 4.37 (dd, *J* = 9.2 and 6.4 Hz, 1H), 4.83 (s, 1H), 5.03-5.11 (AB-system, 2H), 5.40 (d, *J* = 9.1 Hz, NH), 6.31-6.44 (m, 2H), 7.29-7.34 (m, 5H); $C_{21}H_{26}N_2O_5$ (386.45). **5b**: $[\alpha]^{25}_D$ = -129 (c = 0.5 in $CHCl_3$); ^1H NMR: δ= 1.40 (d, *J* = 8.7 Hz, 1H), 1.78 (d, *J* = 9.0 Hz, 1H), 3.09 (d, *J* = 6.7 Hz, 2H), 3.26 (s, 1H), 3.68 (s, 1H), 3.79 (s, 3H), 4.18 (s, 1H), 4.69 (q, *J* = 6.7 Hz, 1H), 5.04-5.12 (AB-system, 2H), 5.58 (d, *J* = 8.0 Hz, NH), 6.32-6.36 (m, 2H), 7.20-7.36 (m, 10H); $C_{25}H_{26}N_2O_5$ (434.49). **5c**: $[\alpha]^{25}_D$ = -52 (c = 0.5 in $CHCl_3$); ^1H NMR: δ= 0.84, 0.87 (2d, *J* = 6.9 Hz, 6H), 0.96, 1.04 (2d, *J* = 6.8 Hz, 6H), 1.70 (d, *J* = 8.7 Hz, 1H), 1.96 (d, *J* = 8.7 Hz, 1H), 2.01-2.09 (m, 1H), 2.12-2.20 (m, 1H), 3.58 (s, 1H), 3.73 (s, 1H), 4.48 (dd, *J* = 6.3 and 9.3 Hz, 1H), 4.52 (dd, *J* = 8.3 and 4.8 Hz, 1H), 4.74 (s, 1H), 5.05-5.21 (m, 4H), 5.48 (d, *J* = 9.5 Hz, NH), 6.37-6.39 (m, 1H), 6.47-6.49 (m, 1H), 7.31-7.36 (m, 10H), 7.80 (d, *J* = 8.3 Hz, NH); $C_{32}H_{39}N_3O_6$ (561.68).
6. Krow, G. R.; Johnson, C.; Boyle, M. *Tetrahedron Lett.* **1978**, *43*, 1971-1974.
7. **9**: m.p. 221-222 °C; $[\alpha]^{25}_D$ = 4 (c = 0.4 in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ = 0.94, 1.06 (2d, *J* = 7.0 Hz, 6H), 1.36 (br.s, 2H), 1.44-1.53 (m, 1H), 1.62-1.84 (m, 3H), 2.43-2.54 (dsept, *J* = 7.0 und 3.3 Hz, 1H), 3.13 (br.s, 1H), 3.57 (s, 1H), 3.74 (d, *J* = 3.3 Hz, 1H), 4.68 (br.s, 1H), 6.25 (br.s, NH); $C_{12}H_{18}N_2O_2$ (222.29). Crystallographic data: space group $P2_1$ (N° 4), monoclinic with a = 582.5(1), b = 2053.8(4), c = 990.2(1) pm, β = 92.748(9)°, V = 1.1833 nm^3, Z = 4, d_c = 1.248 g/cm^3; Mo-K_α radiation (23°C); reflections collected 3669, unique reflections 3289, observed reflections 2952 [$I > 3\sigma(I_o)$], R = 0.0315, R_w= 0.0411, SIR, MolEN. The full data for the X-ray crystal structure have been deposited at the Cambridge Crystallographic Data Centre.
8. The ^1H NMR spectra of the crude cycloadducts indicate the (3*R*)-*exo*-stereochemistry for the minor diastereomers.
9. Nader, B.; Bailey, T. R.; Franck, R. W.; Weinreb, S. M. *J. Am. Chem. Soc.* **1981**, *103*, 7573-7580.
10. For directing effects of chiral α-amino acyl residues on reactions at attached dehydroglycine centres, see ref. 4.
11. *Exo*-addition of cyclopentadiene to the (*Z*)-*N*-acyldehydroglycine unit from the α-face should afford the (3*R*)-*exo*-isomer and can therefore be excluded for **5a-c**. For the formation of the minor diastereomers, however, *endo*-addition of cyclopentadiene to the (*E*)-acylimine from the sterically more hindered β-face appears more likely.
12. **11**: ^1H NMR (300 MHz, $CDCl_3$): δ = 0.88-1.07 (m, 6H), 1.54-1.73 (br.m, 2H), 1.91-2.05 (m, 1H), 2.94-3.00 (br.m, 1H), 3.34-3.38 (m, 1H), 3.61-3.79 (m, 5H), 4.00-4.05 (t, *J* = 6.7 Hz, 1H), 4.27 (dd, *J* = 9.2 und 7.2 Hz, 1H), 4.55 (br.s, 1H), 5.02-5.15 (m, 3H), 5.37 (br.d, *J* = 9.5 Hz, 1H), 7.23-7.35 (m, 5H) ; $C_{21}H_{30}N_2O_7$ (422.48). Partial epimerisation at the aldehyde stage **10** can not be excluded.
13. For a discussion of the advantages of on-site peptide modifications vs. stepwise approaches, see Bossler, H. G.; Seebach, D. *Helv. Chim Acta.* **1994**, *77*, 1124-1165.

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