Oxidative Ring-Opening of *rel*-(2*R*,3*R*,5*S*)-5-Aryl-2-benzoylamino-6,7-bis(methoxycarbonyl)-2,3-dihydro-1-oxo-3-phenyl-1*H*,5*H*-pyrazolo[1,2-*a*]-pyrazoles. Synthesis of *rel*-(2*R*,3*R*)-3-Phenyl-3-[5-aryl-3,4-bis(methoxycarbonyl)pyrazolyl-1]alanine Esters

Andrej Prešeren, Jurij Svete*, and Branko Stanovnik*

Faculty of Chemistry and Chemical Technology, University of Ljubljana, Ljubljana, Slovenia

Received November 23, 1998

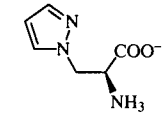
rel-(2*R*,3*R*)-*N*-Benzoylamino-6,7-bis(methoxycarbonyl)-2,3-dihydro-1-oxo-1*H*,5*H*-pyrazolo[1,2-*a*]-pyrazoles **5**, accesible by cycloaddition of dimethyl acetylenedicarboxylate (**3**) to (1*Z*)-*rel*-(4*R*,5*R*)-1-aryl-methylidene-4-benzoylamino-5-phenyl-3-pyrazolidinone-1-azomethine imines **4**, undergo oxidative ring cleavage with methanolic bromine giving *rel*-(2*R*,3*R*)-*N*-benzoyl-3-phenyl-3-[5-aryl-3,4-bis(methoxy-carbonyl)pyrazolyl-1]alanine methyl esters **6** as products.

J. Heterocyclic Chem., **36**, 799 (1999).

Due to their occurance in nature and biological activity, several synthetic approaches for the preparation of heteroaryl-alanines have been developed in last few decades [1]. Among them, considerable attention has been payed to the synthesis of 3-(pyrazolyl-1)alanine (**1**), which was isolated from the semen of *Citrullus vulgaris* and which is so far the only naturally occuring amino acid with a pyrazolyl residue [2-7]. 3-(Pyrazolyl-1)alanine (**1**) was also used as constituent of highly potent renine inhibitors **2a,b** [8, 9] (Figure 1).

Azomethine imines **4** and cycloadducts **5** were prepared according to the procedure described previously [10]. Treatment of **5** with methanolic bromine gave the corresponding *rel*-(2*R*,3*R*)-*N*-benzoyl-3-phenyl-3-[5-aryl-3,4-bis(methoxycarbonyl)pyrazolyl-1]alanine methyl esters **6**. Presumably, the reaction mechanism could procede *via* bromination of pyrazolo[1,2-*a*]pyrazole system, followed by ring opening and elimination of hydrogen bromide. The initial bromination can occur either at the allylic

Figure 1



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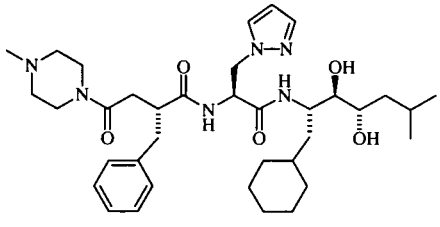
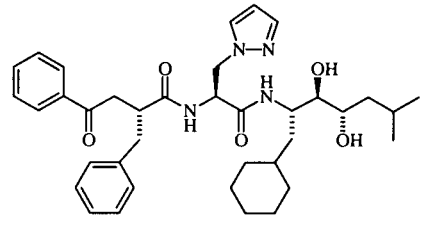


2a



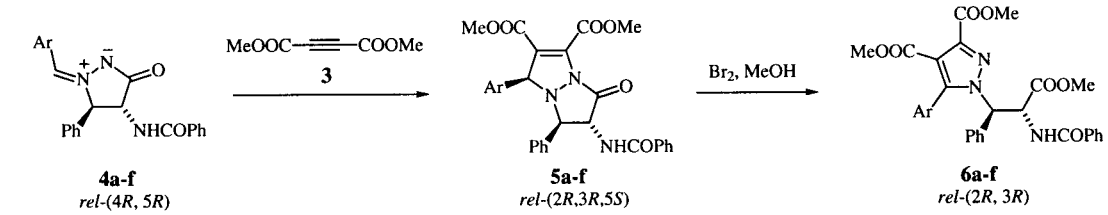
2b

Compound **2**	Enzyme, Conditions	IC_{50} (nM)	Lit
2a	Human plasma renin, pH 7.4	18	[8]
2b	Human plasma renin, pH 7.4	1.6	[9]

Previously, we have reported on the preparation of substituted *rel*-(2*R*,3*R*,5*S*)-5-aryl-6,7-bis(methoxycarbonyl)-2,3-dihydro-1-oxo-1*H*,5*H*-pyrazolo[1,2-*a*]pyrazoles **5** by stereoselective cycloadditions of dimethyl acetylenedicarboxylate (**3**) to (1*Z*)-*rel*-(4*R*,5*R*)-1-arylmethylidene-4-benzoylamino-5-phenyl-3-pyrazolidinone-1-azomethine imines **4** [10]. In this paper we report on the transformation of pyrazolo[1,2-*a*]pyrazoles **5** into *rel*-(2*R*,3*R*)-*N*-benzoyl-3-phenyl-3-[5-aryl-3,4-bis(methoxycarbonyl)pyrazolyl-1]-alanine methyl esters **6** by oxidative ring opening reaction. position to give intermediates **7**, or by the addition to C=C double bond giving adducts **8**. However, regardless of the site of bromination, nucleophilic attack of methanol and elimination of hydrogen bromide lead to the same type of products **6** (Scheme 1).

The structures of 3-phenyl-3-pyrazolylalanine derivatives **6** were confirmed by nmr characterisation and elemental analyses. From a stereochemical point of view, one center of chirality is lost during this transformation. However, since the reaction does not take place at the other

Scheme 1



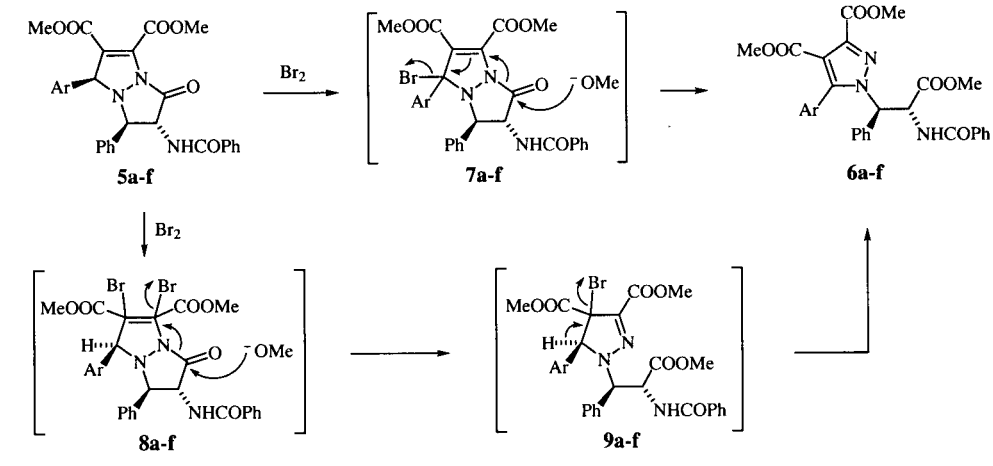
4a-f
rel-(4*R*, 5*R*)

5a-f
rel-(2*R*,3*R*,5*S*)

6a-f
rel-(2*R*, 3*R*)

Compounds **4-6** Ar

a	phenyl
b	4-methylphenyl
c	4-methoxyphenyl
d	3-nitrophenyl
e	4-nitrophenyl
f	2,6-dichlorophenyl



5a-f **7a-f** **6a-f**

8a-f **9a-f**

Table 1
Experimental and Analytical Data

Compound Analyses	yield (%)	mp °C	Molecular Formula
6a	87	91-92 (from cyclohexane)	$C_{30}H_{27}N_3O_7$ Calcd.: C, 66.54; H, 5.03; N, 7.76 Found: C, 66.43; H, 4.87; N, 8.04
6b	94	90-92 (from cyclohexane)	$C_{31}H_{29}N_3O_7$ Calcd.: C, 67.02; H, 5.26; N, 7.56 Found: C, 67.09; H, 5.10; N, 7.95
6c	93	88-90 (from cyclohexane)	$C_{31}H_{29}N_3O_8$ Calcd.: C, 65.14; H, 5.11; N, 7.35 Found: C, 65.08; H, 5.10; N, 7.61
6d	83	93-95 (from cyclohexane)	$C_{30}H_{26}N_4O_9$ Calcd.: C, 61.43; H, 4.47; N, 9.55 Found: C, 61.59; H, 4.08; N, 9.79
6e	86	99-101 (from cyclohexane)	$C_{30}H_{26}N_4O_9$ Calcd.: C, 61.43; H, 4.47; N, 9.55 Found: C, 61.58; H, 4.38; N, 9.69
6f	89	81-82 (from cyclohexane)	$C_{30}H_{25}N_3O_7Cl_2$ Calcd.: C, 59.03; H, 4.13; N, 6.88 Found: C, 58.90; H, 4.05; N, 7.11

two chiral centers at the positions 2 and 3, the reaction provides access to *rel*-(2*R*,3*R*)-3-phenyl-3-[5-aryl-3,4-bis(methoxycarbonyl)pyrazolyl-1]alanine esters **6** with known relative configuration.

Table 2

^{1}H NMR Data

Compound	^{1}H NMR (δ - TMS)
6a	3.68 (3H, s, 4'-COOMe), 3.75 (3H, s, 1-COOMe), 4.00 (3H, s, 3'-COOMe), 5.52 (1H, t, 2-H), 6.00 (1H, d, 3-H), 6.82 (1H, d, NH), 7.08-7.70 (15H, m, 3Ph), $J_{H2H3} = J_{CHNH} = 7.0$ Hz
6b	2.36 (3H, s, CH_3-C_6H_4), 3.65 (3H, s, 4'-COOMe), 3.72 (3H, s, 1-COOMe), 3.97 (3H, s, 3'-COOMe), 5.47 (1H, t, 2-H), 5.98 (1H, d, 3-H), 6.80 (1H, d, NH), 7.08-7.70 (14H, m, 10H-Ph, C_6H_4), $J_{H2H3} = J_{CHNH} = 7.0$ Hz
6c	3.67 (3H, s, 4'-COOMe), 3.72 (3H, s, 1-COOMe), 3.83 (3H, s, CH_3O-C_6H_4), 3.98 (3H, s, 3'-COOMe), 5.49 (1H, t, 2-H), 6.00 (1H, d, 3-H), 6.86 (2H, d, 2H-C_6H_4), 6.95 (1H, d, NH), 7.11 (2H, d, 2H-C_6H_4), 7.30-7.54 (10H, m, 2Ph), $J_{H2H3} = J_{CHNH} = 6.8$ Hz, $J_{o,m\text{-}C6H4} = 8.4$ Hz
6d	3.70 (3H, s, 4'-COOMe), 3.76 (3H, s, 1-COOMe), 4.00 (3H, s, 3'-COOMe), 5.50 (1H, t, 2-H), 6.00 (1H, d, 3-H), 6.78 (1H, d, NH), 7.30-7.69 (12H, m, 10H-Ph, 2H-C_6H_4), 8.03-8.09 (1H, m, 1H-C_6H_4),), 8.24-8.47 (1H, m, 1H-C_6H_4), $J_{H2H3} = J_{CHNH} = 7.0$ Hz
6e	3.68 (3H, s, 4'-COOMe), 3.75 (3H, s, 1-COOMe), 4.00 (3H, s, 3'-COOMe), 5.48 (1H, t, 2-H), 6.00 (1H, d, 3-H), 6.75 (1H, d, NH), 7.30 (5H, s, Ph), 7.40 (2H, d, 2H-C_6H_4), 7.50 (5H, s, Ph), 8.27 (2H, d, 2H-C_6H_4), $J_{H2H3} = J_{CHNH} = 7.2$ Hz, $J_{o,m\text{-}C6H4} = 9.0$ Hz
6f	3.63 (3H, s, 4'-COOMe), 3.79 (3H, s, 1-COOMe), 4.01 (3H, s, 3'-COOMe), 5.46 (1H, dd, 2-H), 5.80 (1H, d, 3-H), 7.10 (1H, d, NH), 7.28-7.82 (13H, m, 10H-Ph, 3H-C_6H_3), $J_{H2H3} = 4.8$ Hz, $J_{CHNH} = 7.0$ Hz

EXPERIMENTAL

Melting points were taken on a Kofler micro hot stage. The ^{1}H nmr spectra were obtained on a Varian E-360 (60 MHz) spectrometer with deuteriochloroform as solvent and tetramethylsilane as internal standard. The microanalyses for C, H, and N were obtained on a Perkin-Elmer CHN Analyser 2400. *rel*-(2*R*,3*R*,5*S*)-5-Aryl-6,7-bis(methoxycarbonyl)-2,3-dihydro-1-oxo-1*H*,5*H*-pyrazolo[1,2-*a*]pyrazoles **5a-f** were prepared according to the procedures described in the literature [10]. Crude *rel*-(2*R*,3*R*)-*N*-benzoyl-3-[5-aryl-3,4-bis(methoxycarbonyl)pyrazolyl-1]-3-phenylalanine methyl esters **6a-f** were purified by crystallisation from cyclohexane.

rel-(2*R*,3*R*)-*N*-Benzoyl-3-[5-aryl-3,4-bis(methoxycarbonyl)pyrazolyl-1]-3-phenylalanine Methyl Esters **6a-f**. General Procedure.

A mixture of *rel*-(2*R*,3*R*,5*S*)-5-aryl-6,7-bis(methoxycarbonyl)-2,3-dihydro-1-oxo-1*H*,5*H*-pyrazolo[1,2-*a*]pyrazole (**5a-f**, 0.001 mole), methanol (4 ml), and bromine (0.06 ml, 0.00117 mole) was heated at reflux temperature for 30 minutes and volatile components evaporated *in vacuo*. Methanol (2 ml), triethylamine (0.28 ml, 0.002 mole), and water (10 ml) were added to the residue, and the precipitate collected by filtration to give **6a-f**, respectively. Experimental and analytical data for *rel*-(2*R*,3*R*)-*N*-benzoyl-3-[5-aryl-3,4-bis(methoxycarbonyl)-pyrazolyl-1]-3-phenylalanine methyl esters **6a-f** are given in Tables 1 and 2.

Acknowledgement.

The financial support by the Ministry of Science and Technology of Slovenia is gratefully acknowledged.

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