

2*H*-Pyran-2-ones as Synthons for (*E*)- α,β -Didehydroamino Acid Derivatives

Lidija Vraničar, Slovenko Polanc, and Marijan Kočever*^a

Faculty of Chemistry and Chemical Technology, University of Ljubljana, Aškerčeva 5, SI-1000 Ljubljana, Slovenia

Received 16 September 1998; revised 16 October 1998; accepted 29 October 1998

Abstract

2*H*-Pyran-2-ones with the defined (*E*)-structure of a α,β -didehydroamino acid unit were used as synthons for a series of configurationally stable (*E*)- α,β -didehydroamino acid derivatives containing a benzoyl protected amino function and a pyrazolyl residue. They were derived from 2*H*-pyran-2-ones and hydrazines under various reaction conditions. A possibility of the formation of (*Z*)-isomers from the above-mentioned precursors is also discussed. © 1998 Elsevier Science Ltd. All rights reserved.

Keywords: Amino acids and derivatives; Pyrazoles; Isomerisation; NMR

Dehydroamino acids and their derivatives play an important role as constituents of various natural products and as synthetic intermediates.¹ Amongst others, they are valuable synthons for the preparation of optically pure amino acids.² For this reason their isolation from natural sources¹ as well as their synthesis have attracted much attention.³ α,β -Didehydroamino acid derivatives in the defined pure isomeric form can be prepared by various methods, though some of them result in *E/Z* mixtures of isomers. The synthesis of pure (*Z*)-isomers can be performed easier and with higher yields than the synthesis of their (*E*)-analogs, most probably due to higher thermodynamic stability of the former.^{1,3} It is well-known that esters of (*E*)- α,β -didehydroamino acid derivatives can be transformed into the (*Z*)-esters under either acidic^{3a,h,i} or basic^{3g,h} conditions, by radical processes^{3h} or by illumination.^{3d,e,f} *E*→*Z* Isomerisation occurred even during homogeneous catalytic hydrogenation of (*E*)-2-(acylamino)propenoic acid derivatives with chiral rhodium-phosphine catalysts.^{2b,c} This can be avoided by the use of THF^{2b} or benzene^{2c} as solvents. However, (*Z*)-isomers seem to be better substrates for the synthesis of enantiomerically pure amino acids, but there are also efficient methods for their formation from (*E*)-isomers.^{2a-c} For this reason, (*E*)-didehydroamino acid derivatives are highly important compounds as well. The most frequently used method for their synthesis was the cleavage of (*E*)-aryl-methylene-5(4*H*)-oxazolones, but yields were higher for (*Z*)-isomers.^{1a,3b} Elimination of water from appropri-

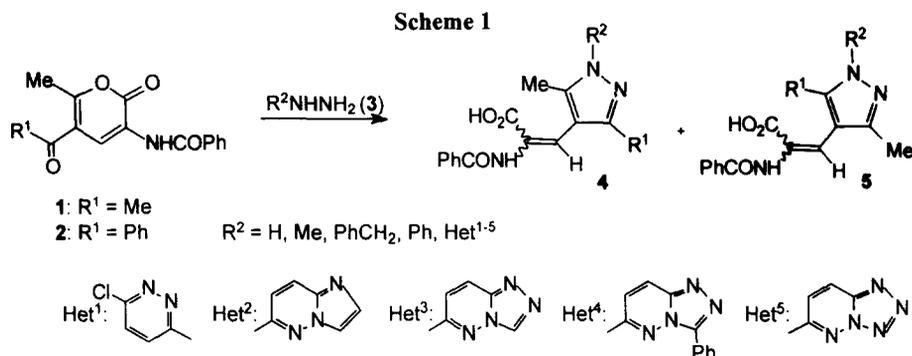
^a E-mail: marijan.kocevar@uni-lj.si

ately substituted β -hydroxy- α -amino acid derivatives is the second general method for the synthesis of pure (*E*)-isomers.^{1,3g,i} Recently, a conversion of *N*-(5-acetyl-6-methyl-2-oxo-2*H*-pyran-3-yl)benzamide (**1**) with a heterocyclic hydrazine under acidic conditions into (*E*)-*N*-[5-[1-[(imidazo[1,2-*b*]pyridazin-6-yl)hydrazono]ethyl]-6-methyl-2-oxo-2*H*-pyran-3-yl]benzamide and further into (*E*)-2-(benzoylamino)-3-[1-(imidazo[1,2-*b*]pyridazin-6-yl)-3,5-dimethyl-1*H*-pyrazol-4-yl]propenoic acid (*E*-**4e**) under basic conditions was described.⁴

We report here a novel synthesis of isomerically pure (*E*)- α,β -didehydroamino acid derivatives **4**, accompanied in one case by isomeric product **5**, starting from 2*H*-pyran-2-one derivatives **1–2** and various hydrazines **3**. A brief investigation towards (*Z*)-analogs of the above-mentioned compounds is also discussed. 2*H*-Pyran-2-ones are known to react with nitrogen-containing nucleophiles either at a side chain or by opening of the pyran-2-one ring and the acyclic products may cyclize again to give the corresponding pyridin-2(1*H*)-ones, pyrazoles or other rings.⁵ In our case, pyran derivatives **1**⁶ and **2**,⁷ containing a masked (*E*)- α,β -didehydroamino acid unit, were transformed in high yields into (*E*)-products **4** and **5** (Scheme 1, Table 1). Reactions were performed under basic conditions in a mixture of ethanol and pyridine, which gave much higher yields of the desired products than the previously used mixture of ethanol, water and triethylamine for the transformation of a hydrazone precursor into product *E*-**4e**.⁴ For the synthesis of the pure product *E*-**4h** the employment of ethanol as a solvent is advantageous, since in the mixture of ethanol and pyridine we obtained products *E*-**4h** and *Z*-**4h** in the ratio 87:13. The application of a mixture of ethanol, water and triethylamine as a solvent resulted in a 1:1 mixture of both products. Similarly, in toluene and triethylamine as the solvent and under argon atmosphere (run 11) both products were obtained again. In the reaction between compound **2** and benzyl hydrazine two products were isolated, namely *E*-**4k** and *E*-**5**. Several attempts to prepare pure isomers **4k** or **5** failed (runs 15–18).

The structure of products was determined on the basis of NOESY spectra. In the case of (*E*)-products we observed NOE between PhCONH and 3-H, while this enhancement was not observed in the case of *Z*-**4h**. Furthermore, chemical shifts for 3-H of all (*E*)-products are in narrow δ ranges (6.53–6.71). Chemical shift for 3-H of product *Z*-**4h** shows a downfield shift of 0.45 ppm with respect to *E*-**4h**. This data is in disagreement with many previously described data for α,β -didehydroamino acids and esters containing alkyl moieties, but is in agreement with those for derivatives containing aryl or heterocyclic moieties.^{3b,d,g,4} The structure of the pyrazole moiety of products **4j**, **4k** and **5** was determined on the basis of the NOE between substituents at positions 1 and 5 in the pyrazole ring.⁸

Based on the results obtained, the following reaction pathways can be postulated. In the starting material (**1** or **2**) three nucleophilic attacks might occur, namely (a), (b) or (c) (Scheme 2). Since we did not obtain pyridinones of types **7** or **8**, the attack of the hydrazine reagent at position 2 in the pyran-2-one ring is excluded. Attack (b) would result in the formation of the intermediate **9**, which would further give exclusively *E*-**4** if pyran-2-one ring was not opened to give intermediate **11**. The latter could be transformed into *E*-**4**, but also to *Z*-**4** via **11b**. However, the formation of product **5** cannot be explained by intermediate **11**. Further-

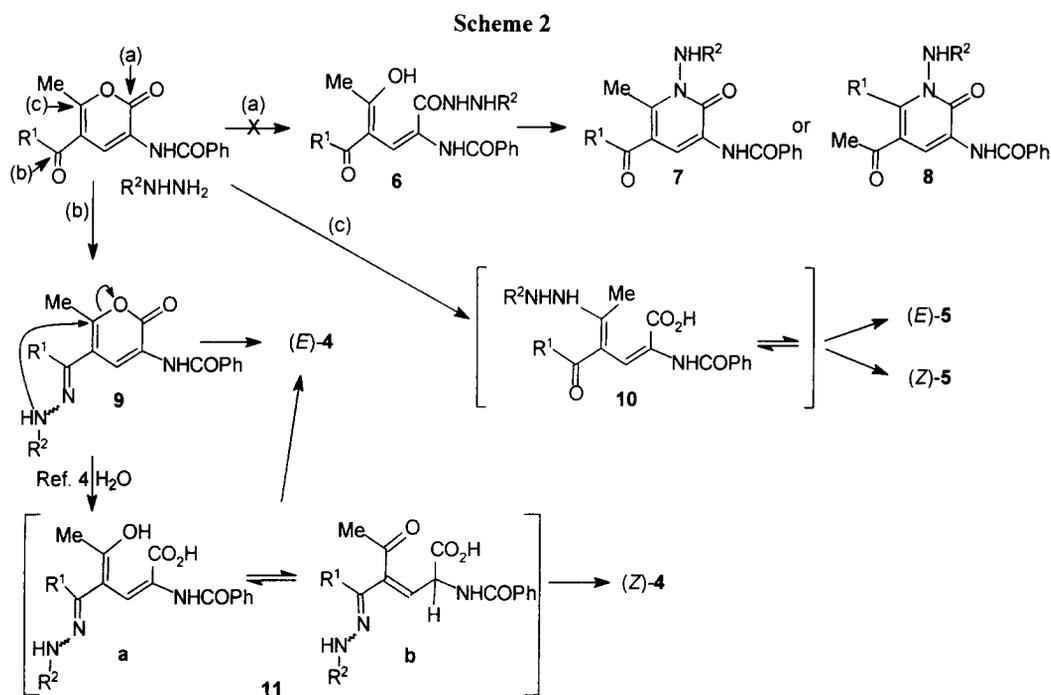
**Table 1**

Reaction Conditions and Yields of Products 4 and 5

Run	SM	Substrate 3 (R ² =)	Conditions	Product (yield, %) ^a
1	1	H	EtOH/Py, 70 min, rt	<i>E-4a</i> (96)
2	1	PhCH ₂ ^b	EtOH/Py, 7 h, Δ	<i>E-4b</i> (96)
3	1	Ph	EtOH/Py, 2 h, Δ	<i>E-4c</i> (97)
4	1	Het ¹	EtOH/Py, 1 h, rt	<i>E-4d</i> (99)
5	1	Het ²	EtOH/Py, 1 h, Δ	<i>E-4e</i> (92)
6	1	Het ³	EtOH/Py, 2.5 h, Δ	<i>E-4f</i> (93)
7	1	Het ⁴	EtOH/Py, 0.5 h, Δ	<i>E-4g</i> (86)
8	1	Het ⁵	EtOH, 6 h, Δ	<i>E-4h</i> (97)
9	1	Het ⁵	EtOH/Py, 190 min, Δ	4h (93); <i>E/Z</i> 87/13 ^c
10	1	Het ⁵	EtOH/H ₂ O/Et ₃ N, ^d 6 h, Δ	4h (98); <i>E/Z</i> 1/1 ^c
11	1	Het ⁵	Ph-Me/Et ₃ N, ^e 6h, Δ	4h (79); <i>E/Z</i> 77/23 ^c
12	2	H	EtOH/Py, 100 min, rt	<i>E-4i</i> (78)
13	2	Me	EtOH/Py, 15 min, rt	<i>E-4j</i> (94)
14	2	PhCH ₂ ^b	EtOH/Py, 7 h, Δ	<i>E-4k/E-5</i> 56/44 (96) ^{c,f}
15	2	PhCH ₂ ^b	EtOH/DABCO, ^g 8 h, rt	<i>E-4k/E-5</i> 59/41 (87) ^c
16	2	PhCH ₂ ^b	EtOH/1 M NaOH, ^h 5 h, rt	<i>E-4k/E-5</i> 63/37 (82) ^c
17	2	PhCH ₂ ^b	CH ₂ Cl ₂ /DABCO, ⁱ 5.5 h, Δ	<i>E-4k/E-5</i> 77/23 (96) ^c
18	2	PhCH ₂ ^b	CH ₂ Cl ₂ /Py, ^j 14.5 h, Δ	<i>E-4k/E-5</i> 66/34 (93) ^c

^aYields of isolated products are given. ^bBenzylhydrazine dihydrochloride was used. ^c*E/Z* ratio was determined on the basis of ¹H NMR spectrum of the crude mixture of products. ^dEtOH (2 mL), H₂O (2 mL) and Et₃N (1 mL). ^ePh-Me (4 mL) and Et₃N (1 mL); under argon atmosphere. ^fProducts were separated by column chromatography (CHCl₃/MeOH 10:1 as eluent). ^gEtOH (4 mL) and 269 mg (2.4 mmol) of 1,4-diazabicyclo[2.2.2]octane. ^hEtOH (4 mL) and 1 M NaOH (3 mL). ⁱCH₂Cl₂ (4 mL) and 269 mg (2.4 mmol) of DABCO. ^jCH₂Cl₂ (4 mL) and pyridine (1 mL).

more, for the formation of product **4h**, we performed several experiments under conditions where water was excluded from the reaction mixture and obtained again product *Z*-**4h** together with *E*-**4h**. On the other hand, starting from **1** and 6-hydrazinotetrazolo[1,5-*b*]pyridazine we prepared a product of type **9** under acidic conditions,⁴ which remained unchanged under conditions used for the synthesis of **4h** from **1** and the hydrazine derivative (runs 8 and 9). An attempt to transform compound *E*-**4h** into *Z*-**4h** under the same conditions as required for their synthesis (run 10) resulted in the recovery of the starting *E*-**4h** in 84% yield. On the basis of the described experiments, pathway (c) and intermediate **10** should be postulated for the formation of product **5** and possibly also for the formation of at least some of products **4** from starting compound **1**. The fact that we did not observe the formation of (*Z*)-isomers in other cases might be explained by the assumption that intermediates **10** and **11** have not been transformed into the tautomer possessing a single bond between C-2 and C-3, where the rotation could occur (like in **11b**), as the formation of (*E*)-product seems to be faster process.



In conclusion, we have developed a novel and very efficient method for the synthesis of (*E*)- α,β -didehydroamino acid derivatives and have shown its limitation for the synthesis of (*Z*)-isomers.

EXPERIMENTAL

Melting points were determined on a Kofler micro hot stage and are uncorrected. Proton and carbon NMR spectra, reported in ppm, were obtained on a Bruker Avance DPX 300 spectrometer in DMSO- d_6 with TMS as an internal standard. IR spectra, reported in cm^{-1} , were recorded with a Perkin Elmer 1310 spectrophotometer. Mass spectra, reported in units of m/z , were obtained with a VG-Analytical AutospecQ instrument. Elemental analysis (C, H, N) were performed with a Perkin Elmer 2400 CHN Analyzer. TLC was carried out on FLUKA silica gel plates (F₂₅₄). Column chromatography was performed using Silica gel 60 (220–240 mesh). Toluene and triethylamine were distilled from P₄O₁₀ and stored over molecular sieves (toluene) or KOH (triethylamine). 2*H*-Pyran-2-one derivative **1**,⁶ 3-chloro-6-hydrazinopyridazine,^{9a} 6-hydrazino-1,2,4-triazolo[4,3-*b*]pyridazine,^{9b} 6-hydrazinotetrazolo[1,5-*b*]pyridazine^{9b} and 6-hydrazino-3-phenyl-1,2,4-triazolo[4,3-*b*]pyridazine^{9c} were prepared as described in the literature. 2*H*-Pyran-2-one **2** was prepared by a known method.⁷ Other solvents and reagents were used as received from commercial sources.

General Procedure. A mixture of the pyran-2-one derivative (**1** or **2**, 1 mmol) and a hydrazine **3** (1.1 mmol) in a mixture of absolute ethanol (4 mL) and pyridine (1 mL) or other solvent was stirred at room temperature or heated under reflux. The solvent was removed *in vacuo* and water (4 mL) was added to the residue. The pH value of the resulting mixture was adjusted to 2 by 9% hydrochloric acid. Upon cooling the products were separated by filtration and washed with a small amount of water. Reaction conditions and yields are given in Table 1. Products **4d**, **4f** and **4g** were obtained as light yellow solids, **4c** was light pink. All other products were isolated as white solids.

Analytical and Spectroscopic Data of Compounds 4 and 5:

(*E*)-2-(Benzoylamino)-3-(3,5-dimethyl-1*H*-pyrazol-4-yl)propenoic acid (*E*-4a): mp 132–135 °C (EtOAc/EtOH); ¹H NMR δ 2.08 (s, 6H, two Me), 6.53 (s, 1H, 3-H), 7.55 (m, 3H, Ph), 7.93 (m, 2H, Ph), 10.12 (s, 1H, NH), 12.35 (br s, 1H, OH); ¹³C δ 11.6, 111.2, 118.5, 127.6, 128.0, 128.5, 131.8, 133.5, 142.0, 165.2, 166.3; IR 1680 br, 1650, 1610; MS 285 (M⁺, 20), 105 (100). Anal. Calcd for C₁₅H₁₅N₃O₃ · 0.5 H₂O: C, 61.22; H, 5.48; N, 14.28. Found: C, 61.59; H, 5.83; N, 14.52.

(*E*)-2-(Benzoylamino)-3-(1-benzyl-3,5-dimethyl-1*H*-pyrazol-4-yl)propenoic acid (*E*-4b): mp 198–200 °C (EtOAc/petroleum ether); ¹H NMR δ 2.07 (s, 3H, Me), 2.10 (s, 3H, Me), 5.23 (s, 2H, CH₂), 6.56 (s, 1H, 3-H), 7.10 (m, 2H, Ph), 7.30 (m, 3H, Ph), 7.55 (m, 3H, Ph), 7.93 (m, 2H, Ph), 10.13 (s, 1H, NH), 12.52 (br s, 1H, OH); ¹³C NMR δ 10.5, 12.7, 51.9, 112.8, 118.3, 126.9, 127.4, 127.7, 128.6, 128.7, 128.9, 131.9, 133.5, 137.58, 137.62, 145.6, 165.4, 166.2; IR 1685 br, 1660, 1640; MS 375 (M⁺, 21), 105 (100). Anal. Calcd for C₂₂H₂₁N₃O₃ · 0.5 H₂O: C, 68.74; H, 5.77; N, 10.93. Found: C, 68.98; H, 6.05; N, 10.82.

(*E*)-2-(Benzoylamino)-3-(3,5-dimethyl-1-phenyl-1*H*-pyrazol-4-yl)propenoic acid (*E*-4c): mp 168–170 °C (EtOAc); ¹H NMR δ 2.15 (s, 3H, Me), 2.22 (s, 3H, Me), 6.63 (s, 1H, 3-H), 7.40 (m, 1H, Ph), 7.54

(m, 7H, Ph), 7.95 (m, 2H, Ph), 10.22 (s, 1H, NH), 12.65 (br s, 1H, OH); ^{13}C NMR δ 12.1, 12.8, 114.6, 117.3, 124.2, 127.4, 127.8, 128.6, 129.3, 129.8, 132.0, 133.5, 137.5, 139.4, 147.3, 165.5, 166.1; IR 1705, 1647; MS 361 (M^+ , 13), 105 (100). Anal. Calcd for $\text{C}_{21}\text{H}_{19}\text{N}_3\text{O}_3$: C, 69.79; H, 5.30; N, 11.63. Found: C, 69.81; H, 5.51; N, 11.59.

(E)-2-(Benzoylamino)-3-[1-(6-chloro-3-pyridazin-6-yl)-3,5-dimethyl-1H-pyrazol-4-yl]propenoic acid (E-4d): mp 187–189 °C (EtOH/DMF); ^1H NMR δ 2.20 (s, 3H, Me), 2.55 (s, 3H, Me), 6.63 (s, 1H, 3-H), 7.57 (m, 3H, Ph), 7.96 (m, 2H, Ph), 8.04 (d, 1H, $J = 9.4$ Hz, 4'-H), 8.19 (d, 1H, $J = 9.4$ Hz, 5'-H), 10.28 (s 1H, NH), 12.80 (br s, 1H, OH); IR 1705, 1634; MS 397 (M^+ , 2), 105 (100). Anal. Calcd for $\text{C}_{19}\text{H}_{16}\text{ClN}_5\text{O}_3$: C, 57.36; H, 4.05; N, 17.60. Found: C, 57.19; H, 4.00; N, 17.49.

(E)-2-(Benzoylamino)-3-[1-(imidazo[1,2-b]pyridazin-6-yl)-3,5-dimethyl-1H-pyrazol-4-yl]propenoic acid (E-4e): mp 242–244 °C (DMF/EtOH), mp lit.⁴ 241–243 °C.

(E)-2-(Benzoylamino)-3-[3,5-dimethyl-1-(1,2,4-triazolo[4,3-b]pyridazin-6-yl)-1H-pyrazol-4-yl]propenoic acid (E-4f): mp 253–255 °C (EtOH/DMF); ^1H NMR δ 2.21 (s, 3H, Me), 2.57 (s, 3H, CH₃), 6.63 (s, 1H, 3-H), 7.57 (m, 3H, Ph), 7.92 (d, $J = 10.0$ Hz, 1H, 7'-H), 7.96 (m, 2H, Ph), 8.46 (dd, 1H, $J = 10.0$ and 1 Hz, 8'-H), 9.62 (d, 1H, $J = 1$ Hz, 3'-H), 10.30 (s 1H, NH), 12.82 (br s, 1H, OH); ^{13}C NMR δ 12.7, 13.6, 114.8, 117.6, 117.8, 126.2, 127.7, 128.6, 132.0, 132.1, 133.3, 139.3, 139.5, 142.5, 150.1, 150.3, 165.4, 165.6; IR 1710 br, 1660, 1620; MS 403 (M^+ , 16), 105 (100). Anal. Calcd for $\text{C}_{20}\text{H}_{17}\text{N}_7\text{O}_3$: C, 59.55; H, 4.25; N, 24.31. Found: C, 59.32; H, 4.18; N, 24.48.

(E)-2-(Benzoylamino)-3-[3,5-dimethyl-1-(3-phenyl-1,2,4-triazolo[4,3-b]pyridazin-6-yl)-1H-pyrazol-4-yl]propenoic acid (E-4g): mp 285–288 °C (EtOH/DMF); ^1H NMR δ 2.23 (s, 3H, Me), 2.60 (s, 3H, Me), 6.65 (s, 1H, 3-H), 7.60 (m, 6H, Ph), 7.96 (m, 2H, Ph), 8.00 (d, 1H, $J = 10.0$ Hz, 7'-H), 8.31 (m, 2H, Ph), 8.52 (d, 1H, $J = 10.0$ Hz, 8'-H), 10.33 (s 1H, NH), 12.85 (br s, 1H, OH); IR 1665 br, 1625; MS 479 (M^+ , 7), 105 (100). Anal. Calcd for $\text{C}_{26}\text{H}_{21}\text{N}_7\text{O}_3$: C, 65.13; H, 4.41; N, 20.45. Found: C, 65.04; H, 4.50; N, 20.49.

(E)-2-(Benzoylamino)-3-[3,5-dimethyl-1-(tetrazolo[1,5-b]pyridazin-6-yl)-1H-pyrazol-4-yl]propenoic acid (E-4h): mp 246–248 °C (EtOH/DMF); ^1H NMR δ 2.24 (s, 3H, Me), 2.63 (s, 3H, Me), 6.66 (s, 1H, 3-H), 7.58 (m, 3H, Ph), 7.96 (m, 2H, Ph), 8.36 (d, 1H, $J = 9.8$ Hz, 7'-H), 8.83 (d, 1H, $J = 9.8$ Hz, 8'-H), 10.32 (s 1H, NH), 12.89 (br s, 1H, OH); ^{13}C NMR δ 12.7, 13.8, 114.2, 118.6, 121.7, 126.5, 127.7, 128.5, 132.0, 132.5, 133.2, 139.6, 142.0, 151.3, 151.4, 165.3, 165.5; IR 1703, 1630 br; MS 404 (M^+ , 4), 105 (100). Anal. Calcd for $\text{C}_{19}\text{H}_{16}\text{N}_8\text{O}_3$: C, 56.43; H, 3.99; N, 27.71. Found: C, 56.17; H, 4.10; N, 27.62.

(Z)-2-(Benzoylamino)-3-[3,5-dimethyl-1-(tetrazolo[1,5-b]pyridazin-6-yl)-1H-pyrazol-4-yl]propenoic acid (Z-4h): ^1H NMR δ 2.21 (s, 3H, Me), 2.53 (s, 3H, Me), 7.11 (s, 1H, 3-H), 7.54 (m, 3H, Ph), 7.93 (m, 2H, Ph), 8.32 (d, 1H, $J = 9.8$ Hz, 7'-H), 8.82 (d, 1H, $J = 9.8$ Hz, 8'-H), 9.84 (s 1H, NH), 12.8 (br s, 1H, OH). These data were obtained from ^1H NMR spectrum of the mixture of compounds **E-4h** and **Z-4h**.

(E)-2-(Benzoylamino)-3-(5-methyl-3-phenyl-1H-pyrazol-4-yl)propenoic acid (E-4i): mp 219–222 °C ($\text{CHCl}_3/\text{MeCN}$); ^1H NMR δ 2.13 (s, 3H, Me), 6.64 (s, 1H, 3-H), 7.30 (m, 1H, Ph), 7.41 (m, 2H, Ph), 7.57 (m,

5H, Ph), 7.93 (m, 2H, Ph), 10.14 (s, 1H, NH), 12.5 (br s, 1H, OH); ^{13}C δ 11.2, 110.6, 118.1, 126.9, 127.5, 127.6, 128.4, 128.5, 129.9, 131.8, 132.8, 133.4, 141.0, 145.9, 165.1, 165.8; IR 1660 br; MS FAB 348 (MH^+). Anal. Calcd for $\text{C}_{20}\text{H}_{17}\text{N}_3\text{O}_3$: C, 69.15; H, 4.93; N, 12.10. Found: C, 69.15; H, 4.96; N, 12.20.

(E)-2-(Benzoylamino)-3-(1,5-dimethyl-3-phenyl-1H-pyrazol-4-yl)propenoic acid (E-4j): mp 238–240 °C (EtOH); ^1H NMR δ 2.17 (s, 3H, Me), 3.79 (s, 3H, Me), 6.66 (s, 1H, 3-H), 7.29 (m, 1H, Ph), 7.40 (m, 2H, Ph), 7.59 (m, 5H, Ph), 7.95 (m, 2H, Ph), 10.17 (s 1H, NH), 12.56 (br s, 1H, OH); ^{13}C δ 10.5, 36.4, 111.3, 118.1, 126.9, 127.2, 127.6, 128.4, 128.5, 130.1, 131.9, 133.4, 133.8, 138.2, 146.9, 165.1, 165.7; IR 1685 br, 1658; MS 361 (M^+ , 10), 105 (100). Anal. Calcd for $\text{C}_{21}\text{H}_{19}\text{N}_3\text{O}_3$: C, 69.79; H, 5.30; N, 11.63. Found: C, 69.68; H, 5.33; N, 11.79.

(E)-2-(Benzoylamino)-3-(1-benzyl-5-methyl-3-phenyl-1H-pyrazol-4-yl)propenoic acid (E-4k): mp 197–200 °C (CH_3CN); ^1H NMR δ 2.15 (s, 3H, Me), 5.39 (s, 2H, CH_2), 6.71 (s, 1H, 3-H), 7.16 (m, 2H, Ph), 7.35 (m, 6H, Ph), 7.56 (m, 3H, Ph), 7.71 (m, 2H, Ph), 7.95 (m, 2H, Ph), 10.17 (s, 1H, NH), 12.62 (br s, 1H, OH); ^{13}C δ 10.5, 52.4, 111.8, 117.9, 126.7, 126.9, 127.3 (two signals), 127.6, 128.41, 128.44, 128.6, 130.6, 131.8, 133.4, 133.7, 137.3, 138.4, 147.4, 165.2, 165.7; IR 1688, 1640; MS 437 (M^+ , 21), 105 (100). Anal. Calcd for $\text{C}_{27}\text{H}_{23}\text{N}_3\text{O}_3$: C, 74.13; H, 5.30; N, 9.60. Found: C, 74.28; H, 5.20; N, 9.71.

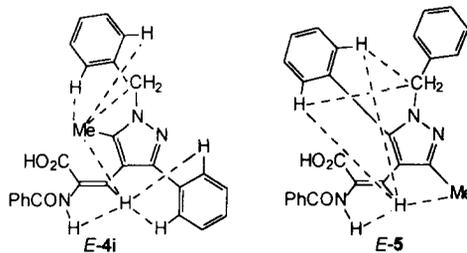
(E)-2-(Benzoylamino)-3-(1-benzyl-3-methyl-5-phenyl-1H-pyrazol-4-yl)propenoic acid (E-5): mp 101–104 °C; ^1H NMR δ 2.13 (s, 3H, Me), 5.19 (s, 2H, CH_2), 6.63 (s, 1H, 3-H), 6.99 (m, 2H, Ph), 7.40 (m, 11H, Ph), 7.86 (m, 2H, Ph), 10.05 (s, 1H, NH), 12.5 (br s, 1H, OH); ^{13}C δ 13.0, 52.1, 114.2, 115.1, 126.6, 127.2, 127.4, 128.4, 128.5, 128.6, 128.7, 129.4, 129.8, 131.1, 131.7, 133.7, 137.9, 141.5, 146.1, 164.7, 166.0; IR 1660 br; MS 437 (M^+ , 45), 105 (100). HRMS Calcd. for $\text{C}_{27}\text{H}_{23}\text{N}_3\text{O}_3$: 437.1739. Found: 437.1743.

Acknowledgements. We thank the Ministry of Science and Technology for the financial support. Dr. B. Kralj and Dr. D. Žigon (Center for Mass Spectroscopy, "Jožef Stefan" Institute, Ljubljana, Slovenia) are gratefully acknowledged for mass measurements.

REFERENCES AND NOTES

- (a) Schmidt, U.; Lieberknecht, A.; Wild, J. *Synthesis* **1988**, 159–172. (b) Duthaler, R. O. *Tetrahedron* **1994**, *50*, 1539–1650.
- (a) Williams, R. *Synthesis of Optically Active α -Amino Acids*; Pergamon Press: Oxford, **1989**; Chapter 6. (b) Noyori, R. *Asymmetric Catalysis In Organic Synthesis*; Wiley & Sons: New York, **1994**; Chapter 2. (c) Nógrádi, M. *Stereoselective Synthesis*; VCH: Weinheim, 2nd ed. **1995**; pp. 45–65. (d) Imamoto, T.; Watanabe, J.; Wada, Y.; Masuda, H.; Yamada, H.; Tsuruta, H.; Matsukawa, S.; Yamaguchi, K. *J. Am. Chem. Soc.* **1998**, *120*, 1635–1636.
- (a) Poisel, H.; Schmidt, U. *Chem. Ber.* **1975**, *108*, 2547–2553. (b) Cativiela, C.; Diaz de Villegas, M. D.; Mayoral, J. A.; Melendez, E. *Synthesis* **1983**, 899–902. (c) Ciattini, P. G.; Morera, E.; Ortar, G. *Synthesis* **1988**, 140–142. (d) Horenstein, B. A.; Nakanishi, K. *J. Am. Chem. Soc.* **1989**, *111*, 6242–6246. (e) Schmidt, U.; Meyer, R.; Leitenberger, V.; Lieberknecht, A.

- Angew. Chem.* **1989**, *101*, 946–948. (f) Kim, D.; Li, Y.; Horenstein, B. A.; Nakanishi, K. *Tetrahedron Lett.* **1990**, *31*, 7119–7122. (g) Balsamini, C.; Duranti, E.; Mariani, L.; Salvatori, A.; Spadoni, G. *Synthesis* **1990**, 779–781. (h) Schmidt, U.; Griesser, H.; Leitenberger, V.; Lieberknecht, A.; Mangold, R.; Meyer, R.; Riedl, B. *Synthesis* **1992**, 487–490. (i) Cativiela, C.; Diaz de Villegas, M. D. *Tetrahedron*, **1993**, *49*, 497–506. (j) Trost, B. M.; Dake, G. R. *J. Am. Chem. Soc.* **1997**, *119*, 7595–7596. (k) Groundwater, P. W.; Sharif, T.; Arany, A.; Hibbs, D. E.; Hursthouse, M. B.; Nyerges, M. *Tetrahedron Lett.* **1998**, *39*, 1433–1436. (l) Moglioni, A. G.; Garcia-Expósito, E.; Moltrasio, G. Y.; Ortuño, R. M. *Tetrahedron Lett.* **1998**, *39*, 3593–3596.
4. Trebše, P.; Polanc, S.; Kočevar, M.; Šolmajer, T.; Golič Grdadolnik, S. *Tetrahedron* **1997**, *53*, 1383–1390.
5. (a) Ellis, G. P. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R.; Rees, C. W., Eds.; Pergamon Press: Oxford, **1984**, Vol. 3, pp. 647–736. (b) Elguero, J. In ref. 5a, Vol. 5, pp. 167–343. (c) Roedig, A.; Hilberth, J.; Renk, H. A. *Liebigs Ann. Chem.* **1975**, 2251–2260. (d) Ram, V. J.; Verma, M.; Hussaini, F. A.; Shoeb, A. *Liebigs Ann. Chem.* **1991**, 1229–1231. (e) Rachedi, Y.; Hamdi, M.; Sakellariou, R.; Spéziale, V. *Synth. Commun.* **1991**, *21*, 1189–1199.
6. Kepe, V.; Kočevar, M.; Polanc, S.; Verček, B.; Tišler, M. *Tetrahedron* **1990**, *46*, 2081–2088.
7. Compound **2** was prepared from benzoylacetone (16.5 g, 0.1 mol) and 4-ethoxymethylene-2-phenyl-5(4*H*)-oxazolone (21.8 g, 0.1 mol) in methylene chloride (50 mL) in 2 days at room temperature (Method: Behringer, H.; Falkenberg, K. *Chem. Ber.* **1963**, *96*, 1428–1435). After evaporation, to the remaining crude product ethanol (200 mL) was added and, upon cooling and filtering off, the resulting product was crystallized from a large amount of ethanol to give pure product **2**; mp 154–156 °C, mp lit. 158–160 °C (Svete, J.; Čadež, Z.; Stanovnik, B.; Tišler, M. *Synthesis* **1990**, 70–72).
8. The following cross-peaks observed in the NOESY spectrum of compound **4k** and of the mixture of compounds **4k** and **5** (in DMSO-*d*₆ solution at 29 °C, mixing time 300 or 400 ms) were determining parameters for the elucidation of the structure of both products.



9. (a) Takahayashi, N. *J. Pharm. Soc. Japan* **1955**, *75*, 778–781; *Chem. Abstr.* **1956**, *50*, 4970c. (b) Takahayashi, N. *J. Pharm. Soc. Japan* **1956**, *76*, 765–767; *Chem. Abstr.* **1957**, *51*, 1192d. (c) Pollak, A.; Tišler, M. *Tetrahedron* **1966**, *22*, 2073–2079.