α,β-Didehydroamino acid derivatives with an isoxazolyl or a pyrazolyl moiety: The effect of substituents and reaction conditions on their stereoselective formation from 2*H*-pyran-2-ones

Lidija Vraničar, Anton Meden, Slovenko Polanc and Marijan Kočevar *

Faculty of Chemistry and Chemical Technology, University of Ljubljana, Aškerčeva 5, P.O. Box 537, SI-1000 Ljubljana, Slovenia. E-mail: marijan.kocevar@uni-lj.si

Received (in Cambridge, UK) 22nd August 2001, Accepted 14th January 2002
First published as an Advance Article on the web 4th February 2002

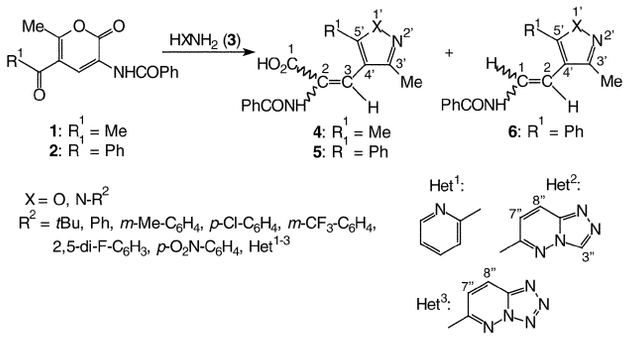
2*H*-Pyran-2-ones **1** and **2** and hydroxylamine or hydrazines are used as synthons for the synthesis of *E*- or *Z*-α,β-didehydroamino acid derivatives **4** and **5** containing an isoxazolyl or a pyrazolyl ring attached at the β-position. The emphasis of our study is on the effect of substituents on both reagents as well as on the reaction conditions (solvent, catalyst, and temperature) influencing the ratio between (*E*)- and (*Z*)-isomers and, in some cases, decarboxylated analogues **6**.

Introduction

Dehydroamino acids and their derivatives play an important role as constituents of various natural products and as synthetic intermediates for the preparation of optically pure amino acids.[1,2] A large number of amino acid derivatives containing a pyrazol-4-yl, isoxazol-4-yl or other heterocyclic moiety have been prepared for biological reasons, many of them as potential agonists or antagonists for central glutamate receptors in connection with (*R*,*S*)-2-amino-3-(3-hydroxy-5-methylisoxazol-4-yl)propanoic acid (AMPA), a bioisostere of (*S*)-glutamic acid.[3] β-Heteroaryl-α,β-didehydroalanines might be considered as conformationally constrained AMPA analogues or congeners and might be potential candidates for the synthesis of novel types of AMPA congeners *via* their hydrogenation. Recently, β-imidazolyl and β-triazolyl α,β-didehydroamino acid derivatives have been prepared,[4] while we have described a synthesis of β-pyrazolyl derivatives.[5] Although isoxazoles[6] and related pyrazoles[7] can, in general, be prepared by a variety of methods, dehydroamino acids containing an isoxazolyl moiety at the β-position are, to our knowledge, unknown so far.

Results and discussion

We report here a detailed study of the transformation of 2*H*-pyran-2-one derivatives **1**[8] and **2**[5b] with hydroxylamine (**3**, X = O) and various hydrazines (**3**, X = R^2N, R^2 = Bu^t, Ph, aryl, heteroaryl) in order to obtain novel types of isomerically pure α,β-didehydroamino acid derivatives **4** and **5**. Depending on the substrate and the reagent used, a decarboxylation to the corresponding enamines **6** also occurred during the course of the reaction (Scheme 1, Table 1). When starting from the 2*H*-pyran-2-one **1** and hydroxylamine as a nucleophile in a mixture of absolute ethanol and pyridine as solvent at room temperature, to our surprise we isolated isoxazoles containing dehydroamino acid derivative **4a** (R^1 = Me, X = O) as a mixture of the (*E*)- and (*Z*)-isomer in the ratio 33 : 67 (Table 1, run 1). With starting compound **2**, (*Z*)-isomer **5a** (R^1 = Ph, X = O) was again the main product in both cases, at room temperature and on heating (runs 2 and 3). Isomerically pure (*Z*)-**4a** and (*Z*)-**5a** were easily obtained from the reaction mixtures by crystallisation. These results were a complete contradiction of our previous observation.[5b] Namely, the structure around the C=C double bond was (*Z*) in the main products, and the structure of the isoxazole moiety seemed as if it had appeared after nucleophilic attack of the amino group at position 6 in the pyran-2-one ring. For this reason we decided to investigate this reaction starting from the 2*H*-pyran-2-one derivative **2** by applying a variety of hydrazines and thus trying to prepare a novel series of pyrazole derivatives. Starting from compound **2** and sterically hindered *tert*-butylhydrazine a mixture of (*E*)-**5b** (R^1 = Ph, X = Bu^{t}N) and the enamine (*E*)-**6a** (R^1 = Ph, X = Bu^{t}N) (run 4) was obtained. With various arylhydrazines containing different substituents the isomerically pure derivatives (*E*)-**5** were derived in high yields (runs 5–9), while with *p*-nitrophenylhydrazine (run 10) a mixture of compounds [(*E*)-**5h**, (*Z*)-**5h** and decarboxylated (*E*)-**6b**; R^1 = Ph, X = *p*-$O_2NC_6H_4N$] was isolated. It seemed that the strong electron-withdrawing effect of the *p*-nitro group was responsible for the formation of the mixture of products. To support this assumption we performed a series of reactions with heterocyclic hydrazines containing different numbers of ring nitrogen atoms and consequently different withdrawing effects on the adjacent hydrazine nitrogen atom. The reactions became much more complex and we obtained (*E*/*Z*) mixtures of dehydroamino acid derivatives **5** and enamines **6** (runs 11–18). To obtain some more information about the reaction pathways we carried out some of the reactions under different reaction conditions (basic, acidic and neutral). On the basis of the results obtained it was not clear whether the (*Z*)-**5** products and/or the enamines **6** were formed from (*E*)-**5** derivatives or from intermediates. In order to be able to confirm this we tried to carry out either isomerisation or decarboxylation of compounds (*E*)-**5j** and (*Z*)-**5j** (R^1 = Ph, X = Het^2N). Both



Scheme 1

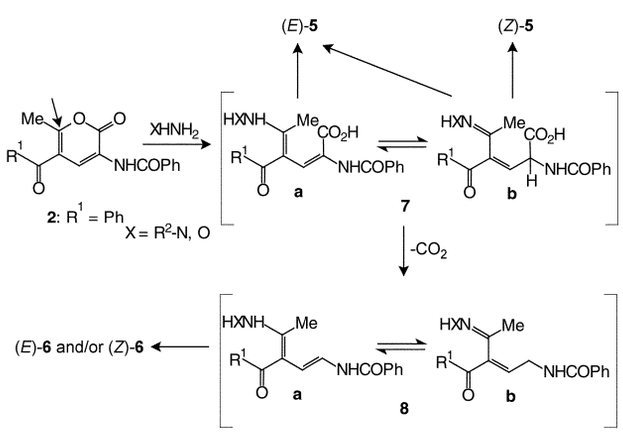
DOI: 10.1039/b107624h

Table 1 Reaction conditions and yields of products **4**, **5** and **6**

Run	Starting material	Reagent **3** (X =)	Conditions	Products	Yield (%)[a]
1	**1**	O[b]	EtOH–Py, 5 h, rt	(*E*)-**4a**/(*Z*)-**4a** 33/67[c]	76
2	**2**	O[b]	EtOH–Py, 3 h, rt	(*E*)-**5a**/(*Z*)-**5a** 9/91[c]	92
3	**2**	O[b]	EtOH–Py, 15 min, Δ	(*E*)-**5a**/(*Z*)-**5a** 17/83[c]	95
4	**2**	Bu^tN[b]	EtOH–Py, 7 h, Δ	(*E*)-**5b**/(*E*)-**6a** 61/39[c]	90
5	**2**	PhN	EtOH–Py, 4.5 h, rt	(*E*)-**5c**	96
6	**2**	*m*-MeC_6H_4N[b]	EtOH–Py, 6 h, Δ (65 °C)	(*E*)-**5d**	97
7	**2**	*p*-ClC_6H_4N[b]	EtOH–Py, 80 min, Δ	(*E*)-**5e**	95
8	**2**	*m*-$(CF_3)C_6H_4N$	EtOH–Py, 1.5 h, rt	(*E*)-**5f**	99
9	**2**	2,5-di-FC_6H_3N	EtOH–Py, 3.5 h, rt	(*E*)-**5g**	98
10	**2**	*p*-$O_2NC_6H_4N$	EtOH–Py, 3 h, rt	(*E*)-**5h**/(*Z*)-**5h**/(*E*)-**6b** 60/13/27[c]	91
11	**2**	Het^1-N	EtOH–Py, 160 min, rt	(*E*)-**5i**/(*Z*)-**5i**/(*E*)-**6c** 68/14/18[c]	96
12	**2**	Het^1-N	H_2O,[d] 1.5 h, Δ (110 °C)	(*E*)-**5i**/(*E*)-**6c** 79/21[c]	90
13	**2**	Het^2-N	EtOH–Py, 130 min, Δ	(*E*)-**5j**/(*Z*)-**5j**/(*E*)-**6d**/(*Z*)-**6d** 25/25/42/8[e]	93
14	**2**	Het^2-N	H_2O,[d] 3h, Δ	(*E*)-**5j**/(*Z*)-**5j**/(*E*)-**6d** 78/8/14[c]	92
15	**2**	Het^2-N	EtOH–AcOH,[f] 1.5 h, Δ	(*E*)-**5j**/(*Z*)-**5j**/(*E*)-**6d** 65/11/24[e]	73
16	**2**	Het^3-N	EtOH–Py, 4 h, Δ	(*Z*)-**5k**/(*E*)-**6e**/(*Z*)-**6e** 19/58/23[c]	93
17	**2**	Het^3-N	1,4-dioxane–Py, 2 h, Δ	(*Z*)-**5k**/(*E*)-**6e** 31/69[c]	90
18	**2**	Het^3-N	EtOH–DABCO,[g] 5 h, Δ	(*Z*)-**5k**/(*E*)-**6e**/(*Z*)-**6e** 14/43/43[c]	96

[a] Yields of isolated products are given. [b] Reagent was used as the hydrochloride. [c] Products ratio was determined on the basis of a ^{1}H NMR spectrum of the crude mixture of products. [d] H_2O (5 ml). [e] Products ratio was determined on the basis of a ^{1}H NMR spectrum of crude mixtures after the separation of didehydroamino acid derivatives **5** from enamines **6**. [f] EtOH (5 ml) and AcOH (0.1 ml). [g] EtOH (5 ml) and 123 mg (1.1 mmol) of DABCO.

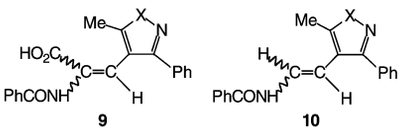
compounds remained unchanged under the reaction conditions used in the experiment given in Table 1 (run 13). On the basis of these results we can conclude that isomerisation as well as decarboxylation occurs in the intermediary step. The most likely mechanism for the formation of the product types **5** and **6** would include the tautomeric intermediate **7** (Scheme 2) resulting from the nucleophilic attack at position 6 in the 2*H*-pyran-2-one **2**. The intermediate **7** can be transformed into products (*E*)-**5** *via* the tautomeric form **7a** or eventually *via* **7b**, but (*Z*)-**5** can be formed only *via* intermediate **7b**, which possesses a single bond between C-2 and C-3 allowing rotation to occur. The formation of enamines **6** can be explained by decarboxylation of the intermediate **7** giving a new tautomeric intermediate **8**, which is then cyclised into a final (*E*)-**6** and/or (*Z*)-**6**. As shown in Table 1 (and also from some other unpublished experiments), the reaction tends toward the formation of decarboxylated products under more basic conditions. An explanation for this fact might be the formation of the anionic form of the carboxylic group, which is more likely to eliminate CO_2 than is a neutral carboxylic group. It is also evident that a stronger electron-withdrawing and/or sterically hindered group on the hydrazine nitrogen gives more (*Z*)-**5** and/or **6** products. The probable reason for this is the diminished nucleophilicity of the second nitrogen (or oxygen, where X = O) in the intermediate **7**, due to the group on it, and consequently to the longer life of the intermediate **7**, which is transformed to the form **7b** (yielding the product (*Z*)-**5**, probably a thermodynamically more stable isomer, and possibly also (*E*)-**5**), and into intermediate **8**, yielding the products (*E*)-**6** or (*Z*)-**6**. In hydroxylamine, the hydroxy group has a lower nucleophilicity than the amino group and the consequence of this is the formation of (*Z*)-**5a** (R^1 = Ph, X = O) (runs 2 and 3). Concerning the effect of solvents, water seems to be a useful solvent (runs 12 and 14), but unfortunately it did not work well in many other examples we tried. A mixture of ethanol and pyridine was (with a few exceptions) the best solvent for our purposes. Higher temperatures did not influence very much the *E*/*Z* ratio between the isomers (runs 2 and 3), but many reactions required heating for an efficient transformation. An expected consequence of such a reaction at higher temperatures might be less selective conversion.



Scheme 2

We would also like to mention that the proposed mechanism is based on the structure of products as determined by various techniques (see below). It is clear, of course, that the nucleophilic attack of the nitrogen-containing nucleophile at the exocyclic benzoyl moiety [attack (b) in ref. 5*b*] of the 2*H*-pyran-2-one derivative **2** would finally result in the formation of isomeric 5-methyl-3-phenylisoxazolyl or 5-methyl-3-phenylpyrazolyl derivatives of type **9** and **10** (X = O, R^2N). For the starting 2*H*-pyran-2-one **1** such a mechanism could not be

excluded, because it would give the same products as the attack at position 6 of the pyran-2-one ring. Since we had not found in the case of the starting compound **2** any firm evidence for the formation of products **9** or **10** we excluded such a reaction pathway. It might also be possible that, under the influence of the nucleophilic solvent (especially when water is present), before the reaction with hydroxylamine or a hydrazine derivative takes place the 2*H*-pyran-2-one ring is opened to give a benzoylacetone derivative as an intermediate. Even if this had happened, the nucleophilic attack of the nitrogen-containing nucleophile would have to be expected to occur at the more reactive acetyl group of the benzoylacetone derivative to give intermediates **7** and **8** and finally products **5** and **6**.



The structure around the C^2,C^3 double bond in (*E*)- or (*Z*)-α,β-didehydroamino acid derivatives **4** and **5** was easily determined on the basis of their NOESY spectra,[5] which were taken for compounds (*E*)-**5b** (R^1 = Ph, X = Bu^{t}N), (*E*)-**5c** (R^1 = Ph, X = PhN) and for the mixture of compounds (*E*/*Z*)-**5j** (R^1 = Ph, X = Het^2N). In the case of *E*-products we observed NOE between PhCON*H* and 3-H, while such an enhancement was not observed in the case of *Z*-products. 1D NOE spectroscopy was also used to determine the structure around the C^2,C^3 double bond of compounds (*Z*)-**5a** (R^1 = Ph, X = O), (*E*)-**5c** (R^1 = Ph, X = PhN), (*E*)-**5g** (R^1 = Ph, X = 2,5-di-FC_6H_3N), (*E*)-**5i** (R^1 = Ph, X = Het^1N) and (*Z*)-**5k** (R^1 = Ph, X = Het^3N). Furthermore, the chemical shifts for the 3-H of the *E*-didehydroamino acid derivatives are in the δ-range between 6.43 and 6.51, while the same signals for almost all the (*Z*)-didehydroamino acid derivatives can be found in the range between δ 6.81 and 6.95; the isoxazolyl derivatives (*E*)-**5a** (R^1 = Ph, X = O) (6.77), (*Z*)-**5a** (7.04) and *tert*-butylpyrazolyl derivative (*E*)-**5b** (R^1 = Ph, X = Bu^{t}N) (6.02) are exceptions to this rule. All *Z*-products show a downfield shift (0.27–0.49 ppm) with respect to their *E*-isomers. The determination of the structure around the C^1,C^2 double bond in *E*- or *Z*-enamine derivatives **6** is based on the magnitude of the ^{1}H coupling constants of vinylic enamine protons (15.1 Hz for (*E*)-**6** and 9.4 Hz for (*Z*)-**6**) and also on the chemical shifts of both vinylic protons. The chemical shifts for 2-H of the *E*-enamines **6** are in the δ-range 6.26–6.28 with the exception of 1-*tert*-butylpyrazolyl derivative (*E*)-**6a** (5.85), while in the *Z*-enamines the chemical shifts for 2-H are at about δ 5.5. Enamine protons 1-H show (in comparison with 2-H) a downfield shift of about 1.2 ppm for *E*-**6** isomers and even higher shift for (*Z*)-**6** isomers. The signals are doublets of doublets as shown for (*E*)-**6a** (R^1 = Ph, X = Bu^{t}N) and (*Z*)-**6d** (R^1 = Ph, X = Het^2N); in all other cases they are covered with the signals of aromatic protons, but their chemical shifts can be determined by HMBC and 1D NOE spectroscopy. The ^{13}C chemical shift of the carbon atom *via* which the group at position 4′ is bound to the pyrazolyl moiety (C-3 in (*E*/*Z*)-**5** or C-2 in (*E*/*Z*)-**6**) might also be distinctive as shown for pairs (*E*/*Z*)-**5j** (R^1 = Ph, X = Het^2N) (δ_C 114.4 *vs.* 121.7 ppm) and (*E*/*Z*)-**6d** (R^1 = Ph, X = Het^2N) (δ_C 103.1 *vs.* 100.8 ppm).

The structure of the isoxazole moiety of the product (*Z*)-**5a** (R^1 = Ph, X = O) was determined with HMBC (^{1}H–^{13}C and ^{1}H–^{15}N correlation) spectra and supported by some data from the literature.[6b] Similarly, the structure of (*E*)-**5a** was identified by ^{1}H–^{15}N HMBC analysis of the crude (*E*/*Z*)-mixture of isomers. On the other hand, the pyrazole structure determination of the other didehydroamino acid derivatives **5** and their decarboxylated analogues **6** was not so evident. Previously mentioned NOESY spectra of *E*- and *Z*-α,β-didehydroamino acid derivatives **5** as well as NOESY spectra of enamines (*E*)-**6a** (X = Bu^{t}N) and (*E*)-**6e** (X = Het^3N) did not show NOE between protons of the methyl group and any protons of the group attached at position 1 of the pyrazolyl moiety. On this basis we ascribed the methyl group to position 3′ (and consequently the phenyl group to position 5′) of the pyrazolyl moiety. Besides such a 'negative' proof of the structure (absence of the signal) we also wanted to find an additional, positive proof. First we analysed the ^{1}H chemical shift of 3′-methyl groups and the positions of their carbon atoms in ^{13}C NMR spectra. It is evident that the chemical shifts for the protons of the methyl group for the didehydroamino acid derivatives *E*-**5** are in the narrow δ-range 2.20–2.27 with the exception of 1-*tert*-butylpyrazolyl derivative (*E*)-**5b** (2.09), while ^{13}C chemical shifts of the methyl group can be found at δ_C 12.9–13.0 ppm [for (*E*)-**5b** 13.4 ppm, for (*E*)-**5g** 12.4 ppm (at 70 °C)]. Chemical shifts for (*Z*)-**5** derivatives are also within a narrow δ-range 2.14–2.19 for protons and δ_C 13.3–13.5 ppm for ^{13}C of the methyl group. On the other side, chemical shifts in (*E*)-**6** for protons and ^{13}C of the methyl group are δ 2.45–2.53 for protons (δ_C 14.3–14.6 ppm for the carbon atom), while in (*Z*)-**6d** or (*Z*)-**6e** the position of methyl protons is at δ 2.28 or 2.30 and ^{13}C chemical shift for (*Z*)-**6d** is δ_C 12.7 ppm. These data show a spectroscopic analogy of the proposed types of products, though differences amongst individual classes are not large and therefore not completely distinctive [for (*E*/*Z*)-**5j** for example, difference in δ_H 0.09 ppm and in δ_C 0.4 ppm; for (*E*/*Z*)-**6d**: $\Delta\delta_H$ 0.2 ppm, $\Delta\delta_C$ 1.9 ppm]. The structure of the substituent at position 1′ (R^2) has a negligible influence on ^{1}H and ^{13}C chemical shifts of the methyl group within the same class of compounds (the same 4′-substituent), but the structure of the group at position 4′ has a more pronounced effect in compounds having the same R^2 group. We believe that chemical shifts for C-3′ and C-5′ in the ^{13}C spectrum and the correlation in the two-dimensional spectrum of these carbon atoms with protons of attached methyl and phenyl groups at positions 3′ and 5′ should be even more relevant for the elucidation of the structure of the pyrazolyl moieties. For some related pyrazole derivatives we could find literature data for chemical shifts of C-3′ in the range between δ_C 146.1 and 151.1 ppm and of C-5′ in the range between δ_C 135.6 and 145.0 ppm.[9] Since these two ranges are quite close together and since we found, for example, in the case of compounds (*E*)-**5b** (R^1 = Ph, X = Bu^{t}N) or (*E*)-**6a** (R^1 = Ph, X = Bu^{t}N) signals for C-3′ and C-5′ at δ_C 142.9 or 141.1 (C-3') and 141.5 or 139.9 ppm (C-5'), we could not exclude overlapping positions of these two signals for our compounds. For this reason the structures of compounds (*E*)-**5d**[10] (R^1 = Ph, X = *m*-MeC_6H_4N) and enamine (*Z*)-**6d** (R^1 = Ph, X = Het^2N) were assigned by an X-ray diffraction study [for (*Z*)-**6d** see Fig. 1].[11] We can see that the methyl group is attached at

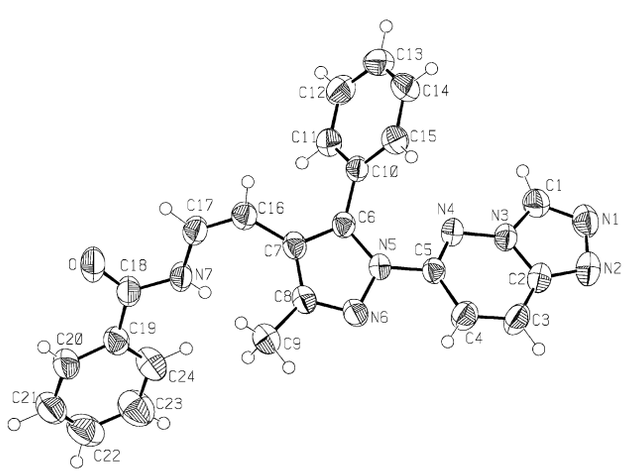


Fig. 1 ORTEP view of the compound (*Z*)-**6d**. The ellipsoids are plotted at 50% probability.

position 3′ and the phenyl group at position 5′ of the pyrazolyl moiety. In addition, the orientation around the double bond in the didehydroamino acid moiety is clearly evident (*E* in the case of **5d** and *Z* in the case of **6d**). On the basis of these two structures and by using the ^{1}H–^{13}C HMBC spectra we determined that the signal for C-3′ is shifted downfield with respect to the signal for C-5′. Consequently, the pyrazolyl structures of all compounds were assigned through HMBC spectra. Chemical shifts of C-3′ atoms in all investigated pyrazolyl compounds are in the range δ_C 146.4–151.0 ppm [for (*E*)-**5b** 142.9 ppm], and for all C-5′ atoms are at δ_C 139.7–143.3 ppm. Here the 4′-substituent has a less pronounced effect on changes in δ-values than does the group at position 1′ (R^2). Chemical shifts of both carbons are higher at the more electron-withdrawing R^2 group. The highest difference $\Delta\delta_C$ between individual related classes is shown for (*E*/*Z*)-**5j** (R^2 = Het^2) and amounts to 1.6 ppm for C-5′ [for (*Z*)-**5j** δ_C being higher than for (*E*)-isomer].

We were not able to isolate compounds (*Z*)-**5i** (R^1 = Ph, X = Het^{1}N) and (*Z*)-**6e** (R^1 = Ph, X = Het^{3}N). Here, ^1H chemical shifts for Me, 3-H [of (*Z*)-**5i**] and 2-H [of (*Z*)-**6e**] supported proposed structures, and the typical *cis*-coupling constant also supports the structure of (*Z*)-**6e**; for (*Z*)-**5i** we also determined the position of the Me group in the ^{13}C NMR spectrum (δ 13.5 ppm) and it also supported the proposed structure.

Conclusions

We have presented an efficient method for the synthesis and structure determination of novel types of *Z*- and *E*-α,β-didehydroamino acid derivatives containing β-isoxazolyl or pyrazolyl moieties. We have also clarified the reaction pathway and have shown that the formation of the product can be controlled by appropriate selection of the starting compounds and/or reaction conditions. Hydroxylamine yields predominantly *Z*-products. In contrast to the previously described reaction of compound **2** with methylhydrazine and benzylhydrazine,[5b] phenylhydrazines containing electron-donating groups or weak to moderate electron-withdrawing groups (Me, Br,[10] Cl, F, CF_3, CO_2H,[10] *etc.*) give almost exclusively *E*-**5** products, while those having strong electron-withdrawing groups as well as heterocyclic hydrazines yield also *Z*-**5** and/or decarboxylated products **6**. In the case of a very strong electron-withdrawing tetrazolo[1,5-*b*]pyridazine product(s) **6** became even predominant. In the reactions, where more than one product was obtained, the separation of almost all main products can be achieved by various procedures as shown in the Experimental section. In some cases the amount of individual isomers was small and isolation with crystallisation or isolation with any kind of chromatography was, due to close R_f factors, impossible. We would also like to note that decarboxylation of didehydroamino acid derivatives to the corresponding enamines has been previously described,[12] but decarboxylation *via* an intermediate as described by us is, to our knowledge, unprecedented. The NMR data collected and combining the described methods can be used as a helpful tool for the structure determination of related types of products.

Experimental

Melting points were determined on a Kofler micro hot stage and are uncorrected. ^1H (300 MHz) and ^{13}C (75 MHz) NMR spectra, reported in ppm, were obtained on a Bruker Avance DPX 300 spectrometer for solutions in DMSO-d_6 with TMS as internal standard. *J*-Values are given in Hz. ^{13}C Spectra were referenced to a chemical shift of DMSO-d_6 (δ_C 39.5 ppm). ^{15}N NMR spectra, reported in ppm, were obtained on a Varian/Nova 600 spectrometer for solutions in DMSO-d_6 and referenced to a chemical shift of benzamide in DMF-d_7 (δ_C −279.3 ppm). IR spectra, reported in cm^{-1}, were recorded with a Perkin-Elmer 1310 spectrophotometer. Mass spectra, reported in units of *m*/*z*, were measured with a VG-Analytical AutospecQ instrument. Elemental analyses were performed with a Perkin-Elmer 2400 CHN Analyzer. X-Ray data were collected with a Nonius Kappa CCD. Thin-layer chromatography was carried out on FLUKA silica gel plates (F_{254}). Column chromatography: Silica gel 60 (220–240 mesh). Preparative chromatography: 2 mm plates Fluka Kieselgel 60 F_{254}. Radial chromatography: Merck Kieselgel PF_{254}. The 2*H*-pyran-2-one derivatives **1**[8] and **2**,[5b] 6-hydrazino-1,2,4-triazolo-[4,3-*b*]pyridazine[13] and 6-hydrazinotetrazolo[1,5-*b*]pyridazine[13] were prepared as described in the literature. MeOH and 1,4-dioxane were distilled and dried (MeOH over molecular sieves, 1,4-dioxane over sodium) prior to use. All other solvents and reagents were used as received from commercial sources. Petroleum ether refers to the fraction with distillation range 40–60 °C.

General procedure for the transformation of pyran-2-one derivatives (1, 2) into didehydroamino acid derivatives (4a, 5a–k) and their corresponding decarboxylated enamines (6a–e)

A mixture of the 2*H*-pyran-2-one derivative (**1** or **2**, 1 mmol) and hydroxylamine (**3**, X = O, 1.1 mmol) or a hydrazine (**3**, X = NR^2, 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. In all cases (except when water was used as solvent) the solvent was removed *in vacuo* and water (4 ml) was added to the residue. If not otherwise stated, the separation proceeded in the following way: the pH-value of the resulting aqueous 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.

(*E*/*Z*)-2-(Benzoylamino)-3-(3,5-dimethylisoxazol-4-yl)propenoic acid 4a. The (*Z*)-isomer was obtained after crystallisation of the crude (*E*/*Z*)-mixture from EtOAc–EtOH; mp 218–222 °C; IR (KBr) ν_{max}/cm^{-1} 1716, 1643, 1614; ^1H NMR δ 2.13 (s, 3H, Me), 2.21 (s, 3H, Me), 6.95 (s, 1H, 3-H), 7.49 (m, 2H, Ph), 7.58 (m, 1H, Ph), 7.90 (m, 2H, Ph), 9.80 (s 1H, NH), 12.75 (br s, 1H, OH); ^{13}C NMR δ 10.3, 11.9, 110.6, 119.5, 127.6, 128.4, 130.3, 131.9, 133.2, 158.7, 165.5, 165.7, 166.8; EIMS *m*/*z* 286 (M^+, 10%), 105 (100). HRMS Calc. for $C_{15}H_{14}N_2O_4$: *M*, 286.0953. Found: M^+, 286.0962. Anal. Calc. for $C_{15}H_{14}N_3O_4$: C, 62.93; H, 4.93; N, 9.79. Found: C, 63.28; H, 5.01; N, 9.72%. ^1H NMR data of the (*E*)-isomer were obtained from the spectrum of the crude (*E*/*Z*)-mixture: δ 2.06 (s, 3H, Me), 2.27 (s, 3H, Me), 6.46 (s, 1H, 3-H), 7.55 (m, 3H, Ph), 7.92 (m, 2H, Ph), 10.31 (s 1H, NH), 12.8 (br s, 1H, OH).

(*E*/*Z*)-2-(Benzoylamino)-3-(3-methyl-5-phenylisoxazol-4-yl)-propenoic acid 5a. The (*Z*)-isomer was obtained after crystallisation of the crude (*E*/*Z*)-mixture from aq. EtOH; mp 90–93 °C; IR (KBr) ν_{max}/cm^{-1} 1715, 1658, 1601; ^1H NMR δ 2.16 (s, 3H, Me), 7.04 (s, 1H, 3-H), 7.49 (m, 6H, Ph, COPh), 7.66 (m, 4H, Ph, COPh), 10.33 (s 1H, NH), 12.97 (br s, 1H, OH); ^{13}C NMR δ 10.4 (Me), 109.9 (C-4′), 118.4 (C-3), 126.6, 127.3, 127.5, 128.2, 128.9, 130.2, 131.7, 131.9, 133.1, 159.4 (C-3′), 165.1, 165.3, 165.4 (last three signals belong to C-5′, CONH, C-1); ^{15}N NMR δ −14 (N-2′), 40 (NHCO); EIMS *m*/*z* 348 (M^+, 3%), 105 (100). Anal. Calc. for $C_{20}H_{16}N_2O_4$: C, 68.96; H, 4.63; N, 8.04. Found: C, 68.74; H, 4.62; N, 8.04%. ^1H and ^{15}N NMR data of the (*E*)-isomer were obtained from the spectra of the crude (*E*/*Z*)-mixture: δ 2.21 (s, 3H, Me), 6.77 (s, 1H, 3-H), 7.49 (m, 6H, Ph, COPh), 7.66 (m, 4H, Ph, COPh), 9.75 (s 1H, NH), 12.97 (br s, 1H, OH); ^{15}N NMR δ −16 (N-2′).

Run 4 (Table 1). The mixture of compounds (*E*)-**5b** and (*E*)-**6a** was separated by column chromatography (chloroform–methanol 25 : 1 to 5 : 1). Yield: 175 mg (43%) of *E*-**5b** and 110 mg (31%) of *E*-**6a**.

(*E*)-2-(Benzoylamino)-3-(1-*tert*-butyl-3-methyl-5-phenyl-1*H*-pyrazol-4-yl)propenoic acid 5b. Mp 207–210 °C (from EtOAc); IR (KBr) ν_{max}/cm^{-1} 1699, 1667br, 1602; ^{1}H NMR δ 1.35 (s, 9H, Bu^t), 2.09 (s, 3H, Me), 6.02 (s, 1H, 3-H), 7.32 (m, 2H, Ph), 7.49 (m, 6H, Ph and PhCO), 7.82 (m, 2H, PhCO), 9.97 (s, 1H, NH), 12.52 (br s, 1H, OH); ^{13}C NMR δ 13.4 (Me), 30.7 (Bu^t), 60.4 (Bu^t-*C*), 115.5 (C-4′), 117.2 (C-3), 127.5 (C-2 and C-6 of PhCO), 128.2, 128.3, 128.7, 128.8, 130.6, 131.7 (C-4 of PhCO), 132.9, 133.2, 141.5 (C-5′), 142.9 (C-3′), 164.8 (CONH), 166.0 (C-1); EIMS *m*/*z* 403 (M$^+$, 33%), 105 (100). Anal. Calc. for $C_{24}H_{25}N_3O_3$: C, 71.44; H, 6.25; N, 10.41. Found: C, 71.38; H, 6.21; N, 10.61%.

***N*-[(*E*)-2-(1-*tert*-Butyl-3-methyl-5-phenyl-1*H*-pyrazol-4-yl)-ethenyl]benzamide 6a.** Mp 207–210 °C (from EtOAc); IR (KBr) ν_{max}/cm^{-1} 1634, 1603; ^{1}H NMR δ 1.33 (s, 9H, Bu^t), 2.30 (s, 3H, Me), 5.85 (d, 1H, *J* 15.1, 2-H), 7.03 (dd, 1H, J_1 15.1, J_2 9.8, 1-H), 7.34 (m, 2H, Ph), 7.48 (m, 6H, Ph), 7.86 (m, 2H, Ph), 10.22 (d, 1H, *J* 9.8, NH); ^{13}C NMR δ 14.1 (Me), 30.6 (Bu^t), 60.2 (Bu^t-*C*), 104.7 (C-2), 115.9 (C-4′), 121.8 (C-1), 127.4 (C-2 and C-6 of PhCO), 128.2, 128.3, 128.7, 130.9, 131.5 (C-4 of PhCO), 133.1, 133.4, 139.9 (C-5′), 141.1 (C-3′), 163.1 (CONH); EIMS *m*/*z* 359 (M$^+$, 57%), 105 (100). Anal. Calc. for $C_{23}H_{25}N_3O$: C, 76.85; H, 7.01; N, 11.69. Found: C, 77.11; H, 6.95; N, 11.94%.

(*E*)-2-(Benzoylamino)-3-(3-methyl-1,5-diphenyl-1*H*-pyrazol-4-yl)propenoic acid 5c. Mp 222–225 °C (from EtOH); IR (KBr) ν_{max}/cm^{-1} 1700, 1678, 1627; ^{1}H NMR δ 2.21 (s, 3H, Me), 6.44 (s, 1H, 3-H), 7.19 (m, 4H, Ph), 7.32 (m, 6H, Ph), 7.49 (m, 2H, Ph), 7.57 (m, 1H, Ph), 7.90 (m, 2H, Ph), 10.13 (s, 1H, NH), 12.71 (br s, 1H, OH); ^{13}C NMR δ 13.0 (Me), 115.5 (C-4′), 116.3 (C-3), 124.5, 127.2, 127.7, 128.5, 128.66, 128.71, 129.0, 129.7, 129.8, 131.0 (C-2), 132.0, 133.3, 139.5, 140.8 (C-5′), 147.5 (C-3′), 165.2 (CONH), 165.8 (C-1); EIMS *m*/*z* 423 (M$^+$, 13%), 105 (100). Anal. Calc. for $C_{26}H_{21}N_3O_3$: C, 73.74; H, 5.00; N, 9.92. Found: C, 73.70; H, 5.01; N, 9.95%.

(*E*)-2-(Benzoylamino)-3-[3-methyl-1-(3-methylphenyl)-5-phenyl-1*H*-pyrazol-4-yl]propenoic acid 5d. Mp 125–127 °C (from EtOAc); IR (KBr) ν_{max}/cm^{-1} 1706, 1673, 1662, 1608; ^{1}H NMR δ 2.20 (s, 3H, Me), 2.25 (s, 3H, *Me*C$_6$H$_4$), 6.44 (s, 1H, 3-H), 6.87 (m, 1H, Ph or C$_6$H$_4$), 7.14 (m, 5H, Ph and C$_6$H$_4$), 7.38 (m, 3H, Ph and C$_6$H$_4$), 7.54 (m, 3H, PhCO), 7.89 (m, 2H, PhCO), 10.13 (s, 1H, NH), 12.69 (br s, 1H, OH); ^{13}C NMR δ 12.9 (Me), 20.8 (*Me*C$_6$H$_4$), 115.3 (C-4′), 116.1 (C-3), 121.4, 124.9, 127.6 (C-2 and C-6 of PhCO), 128.2, 128.4, 128.46, 128.52, 128.8, 129.5, 129.7, 130.9 (C-2), 131.8 (C-4 of PhCO), 133.2 (C-1 of PhCO), 138.4, 139.3, 140.5 (C-5′), 147.2 (C-3′), 164.9 (CONH), 165.7 (C-1); EIMS *m*/*z* 437 (M$^+$, 43%), 105 (100). Anal. Calc. for $C_{27}H_{23}N_3O_3$: C, 74.13; H, 5.30; N, 9.60. Found: C, 74.33; H, 5.22; N, 9.60%.

(*E*)-2-(Benzoylamino)-3-[1-(4-chlorophenyl)-3-methyl-5-phenyl-1*H*-pyrazol-4-yl]propenoic acid 5e. Mp 119–122 °C (from EtOH); IR (KBr) ν_{max}/cm^{-1} 1704br, 1669br, 1601; ^{1}H NMR δ 2.21 (s, 3H, Me), 6.44 (s, 1H, 3-H), 7.01 (m, 4H, Ph and C$_6$H$_4$), 7.40 (m, 5H, Ph and C$_6$H$_4$), 7.54 (m, 3H, PhCO), 7.91 (m, 2H, PhCO), 10.14 (s, 1H, NH), 12.73 (br s, 1H, OH); ^{13}C NMR δ 12.9 (Me), 115.7 and 115.8 (C-3 and C-4′), 125.8, 127.6 (C-2 and C-6 of PhCO), 128.4 (C-3 and C-5 of PhCO), 128.7, 128.9, 129.4, 129.6, 131.20, 131.25 (C-2), 131.8 (C-4 of PhCO), 133.2 (C-1 of PhCO), 138.2, 140.6 (C-5′), 147.8 (C-3′), 165.0 (CONH), 165.6 (C-1); EIMS *m*/*z* 457 (M$^+$, 9%), 105 (100). Anal. Calc. for $C_{26}H_{20}ClN_3O_3$: C, 68.20; H, 4.40; N, 9.18. Found: C, 68.30; H, 4.29; N, 9.46%.

(*E*)-2-(Benzoylamino)-3-{3-methyl-5-phenyl-1-[3-(trifluoromethyl)phenyl]-1*H*-pyrazol-4-yl}propenoic acid 5f. Mp 212–214 °C (from EtOAc); IR (KBr) ν_{max}/cm^{-1} 1710, 1662, 1617, 1600; ^{1}H NMR δ 2.24 (s, 3H, Me), 6.46 (s, 1H, 3-H), 7.25 (m, 2H, Ph), 7.53 (m, 10H, Ph, PhCO and C$_6$H$_4$), 7.90 (m, 2H, PhCO), 10.16 (s, 1H, NH), 12.76 (br s, 1H, OH); ^{13}C NMR δ 12.9 (Me), 115.4 (C-3), 116.4 (C-4′), 120.3 (q, *J* 4), 123.3 (q, *J* 3.7), 123.5 (q, *J* 272.5), 127.60, 127.64, 128.4, 128.8, 128.9, 129.4, 129.6 (q, *J* 32.3), 129.7, 130.2, 131.5 (C-2), 131.9, 133.2, 139.8, 140.8 (C-5′), 148.4 (C-3′), 165.1 (CONH), 165.7 (C-1); EIMS *m*/*z* 491 (M$^+$, 26%), 105 (100). Anal. Calc. for $C_{27}H_{20}F_3N_3O_3$: C, 65.99; H, 4.10; N, 8.55. Found: C, 65.89; H, 3.82; N, 8.36%.

(*E*)-2-(Benzoylamino)-3-[1-(2,5-difluorophenyl)-3-methyl-5-phenyl-1*H*-pyrazol-4-yl]propenoic acid 5g. Mp 206–209 °C (from EtOAc); IR (KBr) ν_{max}/cm^{-1} 1710, 1680, 1668, 1623, 1602; ^{1}H NMR δ 2.22 (s, 3H, Me), 6.51 (s, 1H, 3-H), 7.21 (m, 2H, Ph), 7.33 (m, 5H, Ph and C$_6$H$_3$), 7.55 (m, 4H, PhCO, Ph or C$_6$H$_3$), 7.92 (m, 2H, PhCO), 10.16 (s, 1H, NH), 12.75 (br s, 1H, OH); ^{13}C NMR (70 °C) δ 12.4, 114.6, 115.6 (dd, J_1 13, J_2 13), 116.5 (dd, J_1 24, J_2 8), 117.3 (dd, J_1 23, J_2 9), 127.2, 128.0, 128.0 (dd, J_1 25, J_2 11), 128.1, 128.2, 128.5, 128.90, 128.92, 131.1, 131.4, 133.3, 142.2, 148.2, 152.0 (dd, J_1 247, J_2 3), 157.3 (dd, J_1 243, J_2 2.5), 164.9, 165.0; ^{13}C NMR (29 °C) δ 12.9 (Me), 115.5 (C-3), 142.5 (C-5′), 148.4 (C-3′); EIMS *m*/*z* 459 (M$^+$, 26%), 105 (100). Anal. Calc. for $C_{26}H_{19}F_2N_3O_3$: C, 67.97; H, 4.17; N, 9.15. Found: C, 68.20; H, 4.15; N, 9.11%.

Run 10. The mixture of compounds (*E*/*Z*)-**5h** and (*E*)-**6b** was separated by preparative chromatography (chloroform–methanol 25 : 1).

(*E*/*Z*)-2-(Benzoylamino)-3-[3-methyl-1-(4-nitrophenyl)-5-phenyl-1*H*-pyrazol-4-yl]propenoic acid 5h. (*E*)-Isomer—^{1}H NMR δ 2.24 (s, 3H, Me), 6.46 (s, 1H, 3-H), 7.27 (m, 2H), 7.49 (m, 8H), 7.90 (m, 2H) and 8.20 (m, 2H) (Ph, COPh, C$_6$H$_4$), 10.17 (s, 1H, NH), 12.7 (br s, 1H, OH). (*Z*)-Isomer—^{1}H NMR δ 2.16 (s, 3H, Me), 6.84 (s, 1H, 3-H), 7.27 (m, 2H), 7.49 (m, 8H), 7.90 (m, 2H), 8.20 (m, 2H) (Ph, COPh, C$_6$H$_4$), 9.77 (s, 1H, NH), 12.7 (br s, 1H, OH). These data were obtained from the ^{1}H NMR spectrum of the mixture of compounds (*E*)-**5h** and (*Z*)-**5h**. The mixture of compounds was separated by transformation into the methyl esters (with CH_2N_2/Et_2O in MeOH) and as such separated by HPLC (Preparative column Alltech Econosil Silica 10U, petroleum ether–EtOAc 2 : 1) to give isomerically pure (*E*)-ester and an *E*/*Z*-mixture of esters. The structure of the pyrazolyl moiety of the methyl ester of (*E*)-**5h** was determined by using the ^{1}H–^{13}C HMBC spectrum; ^{13}C NMR δ 12.5 (Me), 141.1 (C-5′) and 149.0 (C-3′).[10]

***N*-{(*E*)-2-[3-Methyl-1-(4-nitrophenyl)-5-phenyl-1*H*-pyrazol-4-yl]ethenyl}benzamide 6b.** Mp 179–182 °C; IR (KBr) ν_{max}/cm^{-1} 1661, 1638; ^{1}H NMR δ 2.47 (s, 3H, Me), 6.28 (d, 1H, *J* 15.1, 2-H), 7.45 (m, 11H, 1-H, 8H of Ph and PhCO, 2H of C$_6$H$_4$), 7.92 (m, 2H, PhCO), 8.17 (m, 2H, C$_6$H$_4$), 10.48 (d, 1H, *J* 9.8, NH); ^{13}C NMR δ 14.3 (Me), 103.1 (C-2), 117.9, 123.7, 124.3, 124.4, 127.4, 128.4, 129.1, 129.5, 130.2, 131.8, 133.2, 139.7 (C-5′), 144.2, 144.8, 147.7 (C-3′), 163.5 (CONH) (one signal is hidden); EIMS *m*/*z* 424 (M$^+$, 59%), 105 (100). HRMS Calc. for $C_{25}H_{20}N_4O_3$: *M*, 424.1535. Found: M$^+$, 424.1544.

Run 11. The mixture of compounds (*E*/*Z*)-**5i** and (*E*)-**6c** was separated by column chromatography (chloroform–methanol 25 : 1).

(*E*/*Z*)-2-(Benzoylamino)-3-[3-methyl-5-phenyl-1-(pyridin-2-yl)-1*H*-pyrazol-4-yl]propenoic acid 5i. The (*E*)-isomer was obtained by crystallisation of the mixture of compounds (*E*)-**5i** and (*Z*)-**5i** from EtOAc–EtOH; mp 202–204 °C; IR (KBr) ν_{max}/cm^{-1} 1701, 1679br; ^{1}H NMR δ 2.22 (s, 3H, Me), 6.43 (s, 1H, 3-H), 7.18 (m, 2H, Ph), 7.32 (m, 4H, 3H of Ph, 1H of Py), 7.57 (m, 4H, 3H of PhCO, 1H of Py), 7.93 (m, 3H, 2H of PhCO, 1H

of Py), 8.20 (ddd, 1H, J_1 4.9, J_2 2.1, J_3 0.8, 6″-H of Py), 10.14 (s, 1H, NH), 12.76 (br s, 1H, OH); ^{13}C NMR δ 12.9 (Me), 115.8 (C-3), 116.4 (C-4′), 118.2 (Py), 122.5 (Py), 127.6 (C-2 and C-6 of PhCO), 128.0 (Ph), 128.1 (Ph), 128.4 (C-3 and C-5 of PhCO), 129.3 (Ph), 130.4 (Ph), 131.4 (C-2), 131.8 (C-4 of PhCO), 133.2 (C-1 of PhCO), 138.8 (Py), 140.9 (C-5′), 147.7 (Py), 148.0 (C-3′), 151.9 (Py), 164.9 (CONH), 165.6 (C-1); MS FAB *m*/*z* 425 (M^+ + 1, 70%), 105 (100). Anal. Calc. for $C_{25}H_{20}N_4O_3$: C, 70.74; H, 4.75; N, 13.20. Found: C, 70.78; H, 4.69; N, 13.04%. ^{1}H and ^{13}C NMR data of the (*Z*)-isomer were obtained from spectra of the crude (*E*/*Z*)-mixture: ^{1}H NMR δ 2.14 (s, 3H, Me), 6.87 (s, 1H, 3-H), 7.43 (m, 10H, Ph, PhCO and Py), 7.93 (m, 3H, 2H of PhCO, 1H of Py), 8.20 (deg ddd, 1H, Py), 9.82 (s, 1H, NH), 12.76 (br s, 1H, OH); ^{13}C NMR δ 13.5 (Me).

***N*-{(*E*)-2-[3-Methyl-5-phenyl-1-(pyridin-2-yl)-1*H*-pyrazol-4-yl]ethenyl}benzamide 6c.** Mp 182–184 °C (from EtOH); IR (KBr) ν_{max}/cm^{-1} 1668, 1631; ^{1}H NMR δ 2.45 (s, 3H, Me), 6.27 (d, 1H, *J* 15.1, 2-H), 7.42 (m, 11H, 1-H, Ph, PhCO and Py), 7.90 (m, 3H, 2H of PhCO, 1H of Py), 8.15 (ddd, 1H, J_1 4.9, J_2 1.9, J_3 0.85, 6″-H of Py), 10.45 (d, 1H, *J* 9.8, NH); ^{13}C NMR δ 14.3 (Me), 103.6 (C-2), 116.8 (C-4′), 117.9 (Py), 122.1 (Py), 123.8 (C-1), 127.4 (C-2 and C-6 of PhCO), 127.9, 128.2, 128.3, 129.7, 130.7, 131.7 (C-4 of PhCO), 133.3, 138.6 (Py), 139.8 (C-5′), 146.4 (C-3′), 147.6 (Py), 151.8, 163.4 (CONH); EIMS *m*/*z* 380 (M^+, 100%), 105 (83). Anal. Calc. for $C_{24}H_{20}N_4O$: C, 75.77; H, 5.30; N, 14.73. Found: C, 76.03; H, 5.19; N, 14.44%.

Run 13. After the addition of water (4 ml), the pH-value of the resulting mixture was adjusted to 12 by 1 M NaOH. The undissolved mixture of products (*E*)-**6d** and (*Z*)-**6d** was separated by filtration and washed with a small amount of water. The pH-value of the filtrate was then adjusted to 2 by 9% hydrochloric acid. Upon cooling the *E*/*Z*-mixture of products **5j** was separated by filtration and washed with a small amount of water.

(*E*/*Z*)-2-(Benzoylamino)-3-[3-methyl-5-phenyl-1-(1,2,4-triazolo[4,3-*b*]pyridazin-6-yl)-1*H*-pyrazol-4-yl]propenoic acid 5j. The (*Z*)-isomer was obtained by crystallisation of the mixture of compounds (*E*)-**5j** and (*Z*)-**5j** from DMF–EtOH; mp 260–263 °C; IR (KBr) ν_{max}/cm^{-1} 1718br, 1666, 1620; ^{1}H NMR δ 2.18 (s, 3H, Me), 6.85 (s, 1H, 3-H), 7.41 (m, 5H, Ph), 7.48 (m, 2H, PhCO), 7.57 (m, 1H, PhCO), 7.68 (d, 1H, *J* 10.0, 7″-H), 7.90 (m, 2H, PhCO), 8.47 (dd, 1H, J_1 10.0, J_2 1, 8″-H), 9.24 (d, 1H, *J* 1, 3″-H), 9.84 (s 1H, NH), 12.78 (br s, 1H, OH); ^{13}C NMR δ 13.3 (Me), 117.6 (C-4′), 118.8, 121.7 (C-3), 126.3, 127.7 (C-2 and C-6 of PhCO), 128.3 (C-3 and C-5 of PhCO), 128.4, 128.9, 129.0, 129.5, 129.8, 131.8 (C-4 of PhCO), 133.3 (C-1 of PhCO), 139.1, 142.5 (C-8a″), 143.1 (C-5′), 149.1 (C-6″), 150.0 (C-3′), 165.4 (CONH), 165.6 (C-1); EIMS *m*/*z* 465 (M^+, 3%), 105 (100). Anal. Calc. for $C_{25}H_{19}N_7O_3$: C, 64.51; H, 4.11; N, 21.06. Found: C, 64.89; H, 3.94; N, 20.93%.

The filtrate after crystallisation was evaporated and the (*E*)-isomer was obtained after recrystallisation of the residue from aq. EtOH; mp 215–217 °C; IR (KBr) ν_{max}/cm^{-1} 1700br, 1671, 1623; ^{1}H NMR δ 2.27 (s, 3H, Me), 6.48 (s, 1H, 3-H), 7.38 (m, 5H, Ph), 7.54 (m, 3H, PhCO), 7.73 (d, 1H, *J* 10.0, 7″-H), 7.90 (m, 2H, PhCO), 8.44 (dd, 1H, J_1 10.0, J_2 1, 8″-H), 9.23 (d, 1H, *J* 1, 3″-H), 10.20 (s 1H, NH), 12.80 (br s, 1H, OH); ^{13}C NMR δ 12.9 (Me), 114.4 (C-3), 118.2 (C-4′), 118.8 (C-7″), 126.2 (C-8″), 127.6 (C-2 and C-6 of PhCO), 128.38, 128.43, 128.7, 129.2, 129.4, 131.9 (C-4 of PhCO), 132.6 (C-2), 133.1 (C-1 of PhCO), 139.1 (C-3″), 141.5 (C-5′), 142.5 (C-8a″), 149.2 (C-6″), 150.5 (C-3′), 165.0 (CONH), 165.4 (C-1); EIMS *m*/*z* 465 (M^+, 17%), 105 (100). Anal. Calc. for $C_{25}H_{19}N_7O_3$: C, 64.51; H, 4.11; N, 21.06. Found: C, 64.84; H, 3.92; N, 21.36%.

***N*-{(*E*/*Z*)-2-[3-Methyl-5-phenyl-1-(1,2,4-triazolo[4,3-*b*]pyridazin-6-yl)-1*H*-pyrazol-4-yl]ethenyl}benzamide 6d.** The (*E*)-isomer was obtained by crystallisation of the mixture of compounds (*E*)-**6d** and (*Z*)-**6d** from DMF–EtOH; mp 230–232 °C; IR (KBr) ν_{max}/cm^{-1} 1664, 1639, 1601; ^{1}H NMR δ 2.48 (s, 3H, Me), 6.27 (d, 1H, *J* 15.1, 2-H), 7.42 (m, 8H, 1-H, Ph and PhCO), 7.56 (m, 1H, PhCO), 7.71 (d, 1H, *J* 10.0, 7″-H), 7.90 (m, 2H, PhCO), 8.39 (dd, 1H, J_1 10.0, J_2 1, 8″-H), 9.11 (d, 1H, *J* 1, 3″-H), 10.53 (d, 1H, *J* 10.0, NH); ^{13}C NMR δ 14.6 (Me), 103.1 (C-2), 119.0 and 119.1 (C-4′ and C-7″), 125.2 (C-1), 126.2 (C-8″), 127.8 (C-2 and C-6 of PhCO), 128.8, 128.9, 129.1, 129.8, 130.1, 132.2 (C-4 of PhCO), 133.3, 139.3 (C-3″), 140.6 (C-5′), 142.7 (C-8a″), 149.4 (C-6″), 149.5 (C-3′), 164.1 (CONH); EIMS *m*/*z* 421 (M^+, 47%), 105 (100). Anal. Calc. for $C_{24}H_{19}N_7O$: C, 68.40; H, 4.54; N, 23.26. Found: C, 68.24; H, 4.59; N, 23.14%.

The filtrate after crystallisation was left at rt for a few days and crystals of the (*Z*)-isomer precipitated; mp 206–208 °C; IR (KBr) ν_{max}/cm^{-1} 1667, 1657, 1621, 1603; ^{1}H NMR δ 2.28 (s, 3H, Me), 5.55 (d, 1H, *J* 9.4, 2-H), 6.98 (dd, 1H, J_1 9.4, J_2 10.2, 1-H), 7.36 (m, 7H, Ph and PhCO), 7.52 (m, 1H, PhCO), 7.66 (m, 2H, PhCO), 7.68 (d, 1H, *J* 10, 7″-H), 8.47 (dd, 1H, J_1 10, J_2 1, 8″-H), 9.24 (d, 1H, *J* 1, 3″-H), 9.48 (d, 1H, *J* 10.2, NH); ^{13}C NMR δ 12.7 (Me), 100.8 (C-2), 118.0 (C-4′), 119.0 (C-7″), 125.2 (C-1), 126.1 (C-8″), 127.7 (C-2 and C-6 of PhCO), 128.0, 128.2, 128.5, 129.2, 129.6, 131.7 (C-4 of PhCO), 133.0, 139.1 (C-3″), 141.1 (C-5′), 142.4 (C-8a″), 149.4 (C-6″), 150.7 (C-3′), 164.7 (CONH); EIMS *m*/*z* 421 (M^+, 36%), 105 (100). Anal. Calc. for $C_{24}H_{19}N_7O$: C, 68.40; H, 4.54; N, 23.26. Found: C, 68.66; H, 4.57; N, 22.98%.

Run 16. The mixture of compounds (*Z*)-**5k** and (*E*/*Z*)-**6e** was separated by radial chromatography (EtOAc).

(*Z*)-2-(Benzoylamino)-3-[3-methyl-5-phenyl-1-(tetrazolo[1,5-*b*]pyridazin-6-yl)-1*H*-pyrazol-4-yl]propenoic acid 5k. Mp 233–235 °C (from EtOH); IR (KBr) ν_{max}/cm^{-1} 1715, 1654; ^{1}H NMR δ 2.19 (s, 3H, Me), 6.81 (s, 1H, 3-H), 7.45 (m, 7H, Ph and PhCO), 7.57 (m, 1H, PhCO), 7.89 (m, 2H, PhCO), 8.23 (d, 1H, *J* 9.6, 7″-H), 8.84 (d, 1H, *J* 9.6, 8″-H), 9.86 (s, 1H, NH), 12.80 (br s, 1H, OH); ^{13}C NMR δ 13.5 (Me), 119.1 (C-4′), 121.6 (C-3), 122.7 (C-7″), 126.8 (C-8″), 127.7 (C-2 and C-6 of PhCO), 128.4, 128.5, 129.1, 129.2, 129.7, 130.4, 132.0 (C-4 of PhCO), 133.4, 142.3 (C-8a″), 143.3 (C-5′), 150.3 (C-6″), 151.0 (C-3′), 165.4 (CONH), 165.7 (C-1); EIMS *m*/*z* 466 (M^+, 2%), 105 (100). Anal. Calc. for $C_{24}H_{18}N_8O_3$: C, 61.80; H, 3.89; N, 24.02. Found: C, 61.75; H, 3.99; N, 24.26%.

***N*-{(*E*/*Z*)-2-[3-Methyl-5-phenyl-1-(tetrazolo[1,5-*b*]pyridazin-6-yl)-1*H*-pyrazol-4-yl}ethenyl]benzamide 6e.** The (*E*)-isomer was obtained by crystallisation of the mixture of compounds (*E*)-**6e** and (*Z*)-**6e** from DMF–EtOH; mp 252–255 °C; IR (KBr) ν_{max}/cm^{-1} 1664, 1640, 1618; ^{1}H NMR δ 2.53 (s, 3H, Me), 6.26 (d, 1H, *J* 15.1, 2-H), 7.45 (m, 8H, 1-H, Ph and PhCO), 7.58 (m, 1H, PhCO), 7.92 (m, 2H, PhCO), 8.29 (d, 1H, *J* 9.8, 7″-H), 8.80 (d, 1H, *J* 9.8, 8″-H), 10.55 (d, 1H, *J* 10.2, NH); ^{13}C NMR δ 14.5 (C–Me), 102.4 (C-2), 120.1 (C-4′), 122.4 (C-7″), 125.5 (C-1), 126.3 (C-8″), 127.5 (C-2 and C-6 of PhCO), 128.4, 128.5, 128.8, 129.7, 129.9, 131.9, 133.1 (C-4 of PhCO), 140.2 (C-5′), 141.9 (C-8a″), 150.0 (C-3′), 150.3 (C-6″), 163.6 (CONH); EIMS *m*/*z* 422 (M^+, 13%), 105 (100). Anal. Calc. for $C_{23}H_{18}N_8O$: C, 65.39; H, 4.29; N, 26.52. Found: C, 65.19; H, 4.38; N, 26.51%.

^{1}H NMR data of the (*Z*)-isomer were obtained from the spectrum of the crude (*E*/*Z*)-mixture: δ 2.30 (s, 3H, Me), 5.53 (d, 1H, *J* 9.4, 2-H), 7.32–7.93 (m, 11H, 1-H, Ph and PhCO), 8.25 (d, 1H, *J* 9.8, 7″-H), 8.84 (d, 1H, *J* 9.8, 8″-H), 9.55 (d, 1H, *J* 9.6, NH).

Acknowledgements

We thank the Ministry of Education, Science and Sport of the Republic of Slovenia for financial support (P0-0503-103). Dr B. Kralj and Dr D. Žigon (Center for Mass Spectroscopy, 'Jožef Stefan' Institute, Ljubljana, Slovenia) are gratefully acknowledged for the mass measurements.

References

1 (*a*) U. Schmidt, A. Lieberknecht and J. Wild, *Synthesis*, 1988, 159; (*b*) R. O. Duthaler, *Tetrahedron*, 1994, **50**, 1539.

2 (*a*) R. Williams, *Synthesis of Optically Active α-Amino Acids*, Pergamon Press, Oxford, 1989, pp. 230–256; (*b*) R. Noyori, *Asymmetric Catalysis in Organic Synthesis*, Wiley, New York, 1994, pp. 16–94; (*c*) M. Nógrádi, *Stereoselective Synthesis*, VCH, Weinheim, 2nd edn., 1995, pp. 45–65; (*d*) U. Nagel and J. Albrecht, *Top. Catal.*, 1998, **5**, 3; (*e*) M. J. Burk, *Acc. Chem. Res.*, 2000, **33**, 363; (*f*) A. V. Komarov and A. Börner, *Angew. Chem., Int. Ed.*, 2001, **40**, 1197.

3 (*a*) A. N. Bowler, A. Dinsmore, P. M. Doyle and D. W. Young, *J. Chem. Soc., Perkin Trans. 1*, 1997, 1297; (*b*) T. N. Johansen, B. Ebert, H. Bräuner-Osborne, M. Didriksen, I. T. Christensen, K. K. Søby, U. Madsen, P. Krogsgaard-Larsen and L. Brehm, *J. Med. Chem.*, 1998, **41**, 930; (*c*) E. Falch, L. Brehm, I. Mikkelsen, T. N. Johansen, N. Skjærbæk, B. Nielsen, T. B. Stensbøl, B. Ebert and P. Krogsgaard-Larsen, *J. Med. Chem.*, 1998, **41**, 2513; (*d*) R. M. Adlington, J. E. Baldwin, D. Catterick, G. J. Pritchard and L. T. Tang, *J. Chem. Soc., Perkin Trans. 1*, 2000, 2311; (*e*) S. B. Vogensen, H. S. Jensen, T. B. Stensbøl, K. Frydenvang, B. Bang-Andersen, T. N. Johansen, J. Egebjerg and P. Krogsgaard-Larsen, *Chirality*, 2000, **12**, 705; (*f*) U. Madsen, H. Bräuner-Osborne, K. Frydenvang, L. Hvene, T. N. Johansen, B. Nielsen, C. Sanchez, T. B. Stensbøl, F. Bischoff and P. Krogsgaard-Larsen, *J. Med. Chem.*, 2001, **44**, 1051.

4 P. M. T. Ferreira, H. L. S. Maia, L. S. Monteiro and J. Sacramento, *Tetrahedron Lett.*, 2000, **41**, 7437.

5 (*a*) P. Trebše, S. Polanc, M. Kočevar, T. Šolmajer and S. Golič Grdadolnik, *Tetrahedron*, 1997, **53**, 1383; (*b*) L. Vraničar, S. Polanc and M. Kočevar, *Tetrahedron*, 1999, **55**, 271.

6 (*a*) S. A. Lang, Jr. and Y.-i. Lin, in *Comprehensive Heterocyclic Chemistry*, ed. A. R. Katritzky and C. W. Rees, Pergamon Press, Oxford, 1984, vol. 6, pp. 1–130; (*b*) M. Sutharchanadevi and R. Murugan, in *Comprehensive Heterocyclic Chemistry II*, ed. A. R. Katritzky, C. W. Rees and E. F. V. Scriven, Pergamon Press, Oxford, 1996, vol. 3, pp. 221–260.

7 (*a*) J. Elguero, in *Comprehensive Heterocyclic Chemistry*, ed. A. R. Katritzky and C. W. Rees, Pergamon Press, Oxford, 1984, vol. 5, pp. 167–343; (*b*) J. Elguero, in *Comprehensive Heterocyclic Chemistry II*, ed. A. R. Katritzky, C. W. Rees and E. F. V. Scriven, Pergamon Press, Oxford, 1996, vol. 3, pp. 1–75; (*c*) K. Makino, H. S. Kim and Y. Kurasawa, *J Heterocycl. Chem.*, 1999, **36**, 321.

8 V. Kepe, M. Kočevar, S. Polanc, B. Verček and M. Tišler, *Tetrahedron*, 1990, **46**, 2081.

9 M. Begtrup, G. Boyer, P. Cabildo, C. Cativiela, R. M. Claramunt, J. Elguero, J. I. García, C. Toiron and P. Vedsø, *Magn. Reson. Chem.*, 1993, **31**, 107.

10 Unpublished results.

11 Single crystals of compound (*Z*)-**6d** were crystallised from DMF–EtOH. A suitable crystal was selected, glued onto a glass fibre and mounted on the diffractometer. Data collection was performed at room temperature. Crystal data: $C_{24}H_{19}N_7O$, M = 421.46, monoclinic, a = 24.8950(10), b = 16.4810(10), c = 10.2980(10) Å, β = 93.967(9)°, V = 4215.1(5) Å^3, T = 293 K, space group $C2/c$ (no. 15), Z = 8, μ(Mo-K$_\alpha$) = 0.087 mm^{-1}, 12461 reflections measured, 4253 unique, 2722 'observed' with $F > 3\sigma(F)$. The latter were used for all calculations. The final $wR(F)$ was 0.045 for 'observed' reflections and 0.052 for all reflections. CCDC reference number 165720. See http://www.rsc.org/suppdata/p1/b1/b107624h/ for crystallographic files in .cif or other electronic format.

12 U. Schmidt and A. Lieberknecht, *Angew. Chem.*, 1983, **95**, 575.

13 N. Takahayashi, *J. Pharm. Soc. Jpn.*, 1956, **76**, 765 (*Chem. Abstr.*, 1957, **51**, 1192d).