

Enhancing a Neat Microwave-Assisted Transformation. Diels–Alder Reaction of 2*H*-Pyran-2-ones toward Fused Bicyclo[2.2.2]octenes

Krištof Kranjc and Marijan Kočevar*

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

Received April 27, 2007; E-mail: marijan.kocevar@fkkt.uni-lj.si

An efficient, green access to polysubstituted and highly constrained bicyclo[2.2.2]octenes via a microwave-assisted cycloaddition reaction is described. The double Diels–Alder reaction of a series of 2*H*-pyran-2-ones with *N*-substituted maleimides was investigated under different reaction conditions: neat and in the presence of a minor amount of a liquid additive. A comparison of the different conditions showed the advantage of the presence of a minor amount of butan-1-ol in the otherwise neat reaction mixture.

Dehydroamino acids and their derivatives play an important role as the constituents of various natural products and biologically active compounds, as well as representing versatile intermediates in organic syntheses.[1] Among them, β-heteroaryl-α,β-didehydroamino acid derivatives and compounds containing amino acid moiety partly or completely incorporated in the heterocyclic ring are of current interest.[2]

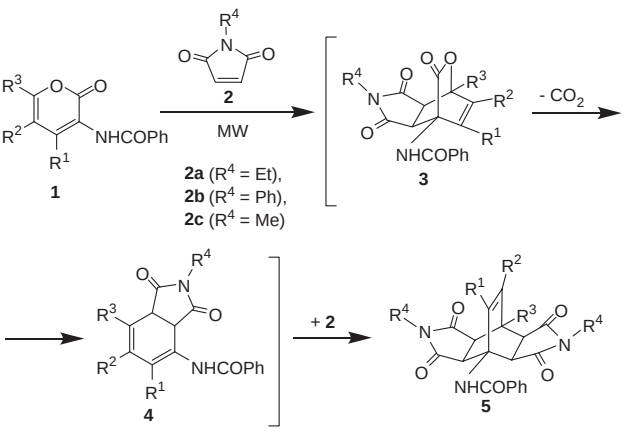
Bicyclo[2.2.2]octenes and their fused derivatives have also been shown to serve as useful building blocks in organic syntheses.[3] Among them, bicyclo[2.2.2]oct-7-enes (bicyclo[2.2.2]oct-2-enes when unsubstituted) containing a free or protected amino group at the bridgehead carbon atom are very rare compounds,[4a] although they can be found in the skeleton of naturally occurring *Kopsia* alkaloids.[4b] As part of our recent investigation of the transformations of 2*H*-pyran-2-ones and fused pyran-2-ones, containing a dehydroamino acid moiety in their structure, we have prepared a series of aminobicyclo[2.2.2]oct-7-enes bearing fused heterocyclic rings, such as a fused maleic anhydride moiety[5a] or a fused, substituted succinimide moiety.[5b–e]

Over the past few years, investigations in chemistry have been oriented toward adopting green methods and processes that use less-toxic chemicals, produce smaller amounts of by-products and consume less energy.[6] Microwave-assisted reactions have attracted considerable attention and many efficient, eco-friendly syntheses of a variety of organic products have been developed.[7] Of these reactions, neat reaction conditions[8] are very useful for investigating specific microwave effects.[7e,8e]

In our previous investigations of microwave-assisted reactions, we have used water as a green solvent or carried out various reactions in the absence of any solvent, i.e., as a neat reaction, without any support or catalyst.[5c–e,9] We have shown that reactions under microwave (MW) irradiation in a closed system can be enhanced by adding a small amount of butan-1-ol.[9c] Recently, we have also described an efficient, green synthesis of sterically constrained prochiral dehydroamino acid derivatives of type **5**,[5d] containing a bicyclo[2.2.2]oct-7-ene skeleton and two fused maleimide rings.

Diels–Alder reactions with 2*H*-pyran-2-ones can be conducted either with alkynes, yielding benzene derivatives, or with alkenes, producing different products, for example, bicyclo[2.2.2]octenes (via double cycloaddition and CO_2 elimination).[10] The synthesis of products **5**[5d] is based on such a double cycloaddition sequence of 2*H*-pyran-2-ones **1**[11] with maleimides **2** as dienophiles. Though most of the previously investigated transformations take place as microwave-assisted reactions in aqueous conditions, for a few examples, neat reaction conditions have been shown to be better. Here, we report a detailed study of this transformation under neat conditions in the presence of a minor amount of butan-1-ol, with the emphasis on showing the advantages of this method (See Scheme 1 and Table 1).

We decided to do a preliminary investigation on the effects of various reaction conditions on the above conversion. All test reactions were performed with 0.5 mmol of 2*H*-pyran-2-one **1** and 1.1 mmol of *N*-substituted maleimide **2** (the quantities of the additives discussed later in the text correspond to these amounts) (Table 2). First, we investigated the effect of the



Scheme 1. Synthesis of bicyclo[2.2.2]octene systems **5**.

Published on the web October 12, 2007; doi:10.1246/bcsj.80.2001

Table 1. Reaction Conditions and Yields for the Synthesis of **5**

Run	Starting **1**				Starting **2**		Product	*t*	Yield
	R^1	R^2	R^3		R^4		**5**	/min[a]	/%[b]
1	H	H	Me	**1a**	Et	**2a**	**5a**	15	93
2	H	H	Ph	**1b**	Et	**2a**	**5b**	45	85
3	H	H	Ph	**1b**	Ph	**2b**	**5c**	25	94
4	H	H	2-furyl	**1c**	Et	**2a**	**5d**	45	95
5	H	H	2-furyl	**1c**	Me	**2c**	**5e**	45	93
6	H	H	2-thienyl	**1d**	Ph	**2b**	**5f**	40	98
7	Me	H	Ph	**1e**	Et	**2a**	**5g**	90[c]	88
8	Me	H	Ph	**1e**	Ph	**2b**	**5h**	50	97
9	Me	H	2-thienyl	**1f**	Et	**2a**	**5i**	60	96
10	Me	H	2-thienyl	**1f**	Ph	**2b**	**5j**	90	98
11	H	4-$MeOC_6H_4$	Me	**1g**	Et	**2a**	**5k**	15	86
12	H	3,4-$(MeO)_2C_6H_3$	Me	**1h**	Et	**2a**	**5l**	10	92

a) Microwave irradiation in a closed vessel (10 mL) at 150 °C with the addition of 100 mg of butan-1-ol. b) Yield of isolated products. c) Temperature was set to 160 °C.

Table 2. Effects of Different Additives on Conversions for the Reactions between **1** and **2**

Run	Starting		Heating	*t*	Additives	Prod.	Conv.
	1	**2**	method[a]	/min		**5**	/%[b]
1	**1a**	**2a**	MW	15	—	**5a**	95
2	**1a**	**2a**	MW	15	100-mg *n*-BuOH	**5a**	100
3	**1c**	**2a**	MW	60	—	**5d**	87
4	**1c**	**2a**	MW	45	100-mg *n*-BuOH	**5d**	100
5	**1c**	**2a**	MW	45	50-mg *n*-BuOH	**5d**	94
6	**1b**	**2b**	MW	15	100-mg *n*-BuOH	**5c**	80
7	**1b**	**2b**	MW	15	100-mg toluene	**5c**	80
8	**1f**	**2a**	MW	30	—	**5i**	80
9	**1f**	**2a**	MW	10	100-mg *n*-BuOH	**5i**	67
10	**1f**	**2a**	MW	20	100-mg *n*-BuOH	**5i**	90
11	**1f**	**2a**	MW	30	100-mg *n*-BuOH	**5i**	95
12	**1f**	**2a**	MW	30	100-mg toluene	**5i**	95
13	**1f**	**2a**	MW	30	100-mg H_2O	**5i**	78
14	**1f**	**2a**	MW	30	0.5-mL *n*-BuOH	**5i**	40
15	**1f**	**2a**	MW	30	1.5-mL *n*-BuOH	**5i**	30
16	**1f**	**2a**	MW	30	0.5-mL H_2O	**5i**	60
17	**1f**	**2a**	MW	30	1.5-mL H_2O	**5i**	51
18	**1f**	**2a**	CH	30	—	**5i**	60
19	**1f**	**2a**	CH	30	100-mg *n*-BuOH	**5i**	60
20	**1b**	**2a**	CH	20	100-mg *n*-BuOH	**5b**	70
21	**1b**	**2a**	MW	20	100-mg *n*-BuOH	**5b**	95
22	**1f**	**2a**	MW	30	100-mg IL[c]	**5i**	87

a) MW: microwave irradiation in closed 10 mL vessels at 150 °C with different additives; CH: conventional heating in a round-bottomed flask equipped with reflux condenser and immersed in an oil bath heated to 150 °C with different additives. b) Conversions estimated from ^{1}H NMR spectrum of crude mixtures. c) Ionic liquid: 1-butyl-3-methylimidazolium tetrafluoroborate.

addition of a minor amount of a liquid additive on the conversion rate. For this, we compared the reaction between **1a** and **2a** and found that under otherwise identical conditions, that is, 15 min of MW irradiation at 150 °C, the conversion starting from neat reagents was around 95% (estimated from the ^{1}H NMR spectrum of the crude reaction mixture) (Table 2, Run 1), whereas the reaction with 100 mg of butan-1-ol added was complete (Table 2, Run 2). Similar results were obtained for the reaction between **1c** and **2a**: the conversion after 1 h of MW irradiation at 150 °C without butan-1-ol was around 87% (Table 2, Run 3), whereas the reaction with the addition of 100 mg of butan-1-ol was complete after 45 min (Table 2, Run 4). When we decreased the amount of butan-1-ol to 50 mg the conversion was 94% (Table 2, Run 5).

We were curious to find out if other liquids could be employed instead of butan-1-ol. When we compared the conversion for the reaction between **1b** and **2b** (Table 2, Runs 6 and 7), we found that, after 15 min of MW irradiation at 150 °C, the conversion in the presence of 100 mg of butan-1-ol was nearly the same as when 100 mg of toluene was added.

A similar situation was observed for the case of the reaction between **1f** and **2a**: without any additives, the conversion after 30 min of MW irradiation at 150 °C was around 80% (Table 2, Run 8). However, when we added 100 mg of butan-1-ol, the conversion increased to 95% (Table 2, Run 11), and with the addition of 100 mg of toluene, it was nearly the same (Table 2, Run 12). With the shorter reaction time (when 100 mg of butan-1-ol was added), the conversion was also smaller (Table 2, Runs 9 and 10). On the other hand, with the addition of 100 mg of water (Table 2, Run 13), the conversion also decreased and was nearly the same as without any additives (around 78%). However, when we repeated the same reaction under the same conditions with the addition of 0.5 mL of butan-1-ol as a solvent, the result was dramatically different: the conversion was only about 40% (Table 2, Run 14). With the addition of a larger volume of butan-1-ol (1.5 mL) and with the other conditions being identical to those described above, the conversion was still lower (≈30%) (Table 2, Run 15). The conversion was around 60% when 0.5 mL of water was added, instead of butan-1-ol (Table 2, Run 16), which is somewhat higher than that in the presence of 0.5 mL of butan-1-ol, but still lower than that with just a minor amount of butan-1-ol. The same reaction was also repeated under previously used conditions[5d] (i.e., with 1.5 mL of water as a solvent), and the conversion was found to be only 51% (Table 2, Run 17), thus proving that neat reaction conditions (or with a minor amount of liquid additive) are superior to those when a solvent is used.

We also decided to elucidate the differences between the use of MW irradiation and heating using a traditional oil bath. For the reaction between **1f** and **2a** conducted in an open flask, equipped with a reflux condenser and heated in an oil bath at 150 °C for 30 min, the conversion was found to be around 60%, irrespective of the addition of butan-1-ol (Table 2, Runs 18 and 19). Conversions for the same reaction, under otherwise identical reaction conditions, carried out with MW irradiation were found to be 95 and 80%, with and without the addition of a minor amount of butan-1-ol, respectively (Table 2, Runs 11 and 8). Similar results were obtained in the case of the reaction between **1b** and **2a**, which had a conversion for the reaction conducted in an oil bath at 150 °C after 20 min was around 70% (with the addition of 100 mg of butan-1-ol) (Table 2, Run 20), whereas under MW irradiation conditions (with the other parameters unchanged), the conversion was around 95% (Table 2, Run 21).

We were also curious to find out what impact the addition of an ionic liquid would have on the reaction progress. Therefore, a mixture of **1f** and **2a**, as above, but with the addition of 100 mg of an ionic liquid (1-butyl-3-methylimidazolium tetrafluoroborate), instead of butan-1-ol, was irradiated with MW at 150 °C for 30 min. The conversion was found to be 87% (Table 2, Run 22), showing that the addition of a small amount of the ionic liquid facilitated the reaction; however, the conversion was lower than that when butan-1-ol was added. After considering the costs of ionic liquids and the additional problems associated with the isolation of products, we do not believe that the use of an ionic liquid in these cases would be appropriate.

It is also important to mention that it is possible to conduct these reactions on larger scales. Namely, a mixture of **1f** (2 mmol) and **2a** (4.4 mmol) with 100 mg of butan-1-ol was irradiated with MW at 150 °C for 30 min, and the reaction basically went to completion (96%), yielding **5i** like in the case when only 0.5 mmol of **1f** was used. With this experiment, we have shown that there is no need to scale the amount of liquid additive; the amount appropriate for 0.5 mmol of **1** is sufficient on the 2 mmol scale as well.

Based on all these data, we propose a simple explanation as to why a minor amount of liquid additive can increase the conversions of MW-irradiated reactions in closed systems. Namely, when some of these reactions were tried without any liquid additives, a thin layer of sublimated material was observed on the upper (colder) parts of the reaction vessels, and for the reaction between **1g** and **2a**, we have proven using ^{1}H NMR spectroscopy that this sublimated material is indeed *N*-substituted maleimide **2a**. Since we do not employ a large excess of the dienophile **2** it is understandable that the reactions in this way cannot proceed to completion even after prolonged MW irradiation times. For example, for the reaction between **1f** and **2a**, the conversion without the addition of butan-1-ol after 30 or 120 min of MW irradiation at 150 °C was estimated to be around 80% in both cases (see above). In the presence of a minor amount of butan-1-ol, the reaction was complete within 1 h (Run 9).

The presented data shows that the small amount of butan-1-ol not only enhances the contact between the reactants as one might propose, but must have another, more important effect (see below). This is also supported by the fact that a larger amount of butan-1-ol (0.5 or 1.5 mL) tended to reduce the conversion rate (see above). It seems that the reaction conditions when 0.5 or 1.5 mL of butan-1-ol is added approach the conditions under which the reactions are taking place in solutions, where the concentrations in a homogeneous liquid phase are important. When water (0.5 or 1.5 mL) was added instead of butan-1-ol, the conversions were higher than with the same amounts of butan-1-ol. This fact might be explained in terms of different parameters: (i) the special characteristics of water, such as polarity, surface tension, cohesive pressure, etc.,[12] (ii) the low solubility of the reagents, which are, at least at room temperature, practically insoluble in water, and (iii) the possibility that the reactions take place in a separated melted phase as a neat reaction. These parameters are more or less pronounced in the individual cases, and as such, they control the reaction speed. However, the reactions, in the presence of a minor amount of liquid additive, most probably take place predominantly in a melted phase, and so the main role of the liquid additive is mostly just to rinse the sublimated reactants from the upper (colder) parts of the reaction vessels. This is evident from the fact that the conversion in the presence of 100 mg of butan-1-ol was greater than that in the presence of 100 mg of water (where it was nearly the same as without any additive). Because of high surface tension of water and because of the lower solubility of the reagents in it, water does not seem to be as efficient at rinsing as butan-1-ol is. Additionally, butan-1-ol might also better enhance the contact between the reactants than would water.

In conclusion, we presented a green method for the preparation of a variety of fused bicyclo[2.2.2]oct-7-enes. With the addition of a minor amount of butan-1-ol, we shortened the

reaction times, eliminated the need for large excesses of maleimides **2** (a 5% excess of maleimides was sufficient in all examples) and reduced the consumption of solvents to a minimal amount (100 mg). Very high conversions (above 98%) and in general very good yields of isolated products (85–98%) render this synthesis environmentally benign, and as such, we believe it can be applied to the preparation of other types of products as well. Moreover, it is important to mention that this method is more convenient (with significantly shortened reaction times) for the preparation of the above products than the procedure previously used for the synthesis of related compounds in aqueous conditions.[5d] It might also be used as an expedient way toward some structure directing agent molecules (SDAs) that could be applied to template the structure of zeolites, while compensating for all of the negative charges generated.[13] For the isolation, no extraction and/or chromatography is required; just the addition of a small amount of water and an alcohol followed by the filtration of the solid product.

Experimental

Instruments. Melting points were determined on a Kofler micro hot stage and are uncorrected. ^{1}H NMR spectra were recorded with a Bruker Avance DPX 300 spectrometer at 29 °C (unless otherwise stated) and 300 MHz, using TMS as an internal standard. ^{13}C NMR spectra were recorded on the same instrument at 75.5 MHz and are referenced against the central line of the solvent signal (DMSO-d_6 septet at $\delta = 39.5$ ppm or $CDCl_3$ triplet at $\delta = 77.0$ ppm). The coupling constants (J) are given in Hz. IR spectra were obtained with a Bio-Rad FTS 3000MX (KBr pellets for all products). MS spectra were recorded with a VG-Analytical AutoSpec Q instrument. Elemental analyses (C, H, N) were performed with a Perkin-Elmer 2400 Series II CHNS/O Analyzer. TLC was carried out on Fluka silica-gel TLC-cards. MW reactions were conducted in air using a focused MW unit (Discover by CEM Corporation, Matthews, NC). The machine consists of a continuous, focused-microwave power-delivery system with an operator-selectable power output from 0 to 300 W. Reactions were performed in glass vessels (capacity 10 mL) sealed with a septum. The pressure was controlled by a load cell connected to the vessel via the septum. The temperature of the contents of the vessel was monitored using a calibrated infrared temperature controller mounted under the reaction vessel. All of the mixtures were stirred with a Teflon-coated magnetic stir bar in the vessel. Temperature, pressure, and power profiles were recorded using commercially available software provided by the manufacturer of the MW unit.

Materials. Starting compounds **1** were prepared according to the published procedures: **1a–1d**,[11a] **1e** and **1f**,[11b] and **1g** and **1h**.[11c] All other reagents and solvents were used as received from commercial suppliers.

General Procedure for Microwave-Assisted Preparation of 5a–5l (Chart 1). A mixture of 2*H*-pyran-2-one derivative **1** (0.5 mmol or 1 mmol), appropriate *N*-substituted maleimide **2** (1.1 or 2.2 mmol) and 100 mg of butan-1-ol was irradiated in a closed vessel in the focused MW equipment. The power was set to 100 W, and the temperature was set to 150 °C (except for the synthesis of **5g**, where it was set to 160 °C). The ramp time was set to 5 min. Thereafter, the reaction mixture was cooled; for estimating the conversion values (Table 2), the crude mixture was analyzed by ^{1}H NMR, whereas for isolation, the solid was dispersed in 2 mL of a mixture of distilled water and methanol (1:1), filtered off and washed with the same mixture (3–5 mL). For typical temperature, pressure and power profiles, see Fig. 1.

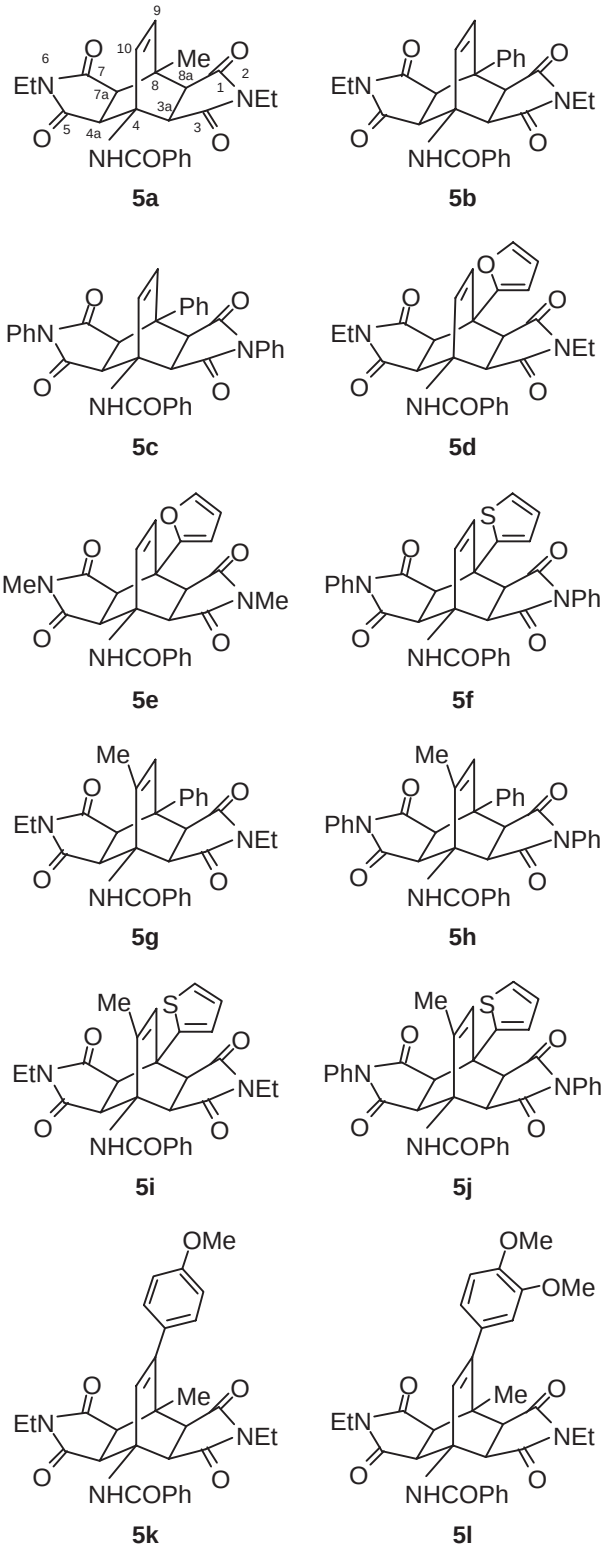


Chart 1.

General Procedure for Oil Bath Heating Experiments. A mixture of 2*H*-pyran-2-one derivative **1** (0.5 mmol), appropriate *N*-substituted maleimide **2** (1.1 mmol) and 100 mg of butan-1-ol (or alternatively without butan-1-ol) was stirred in a small round-

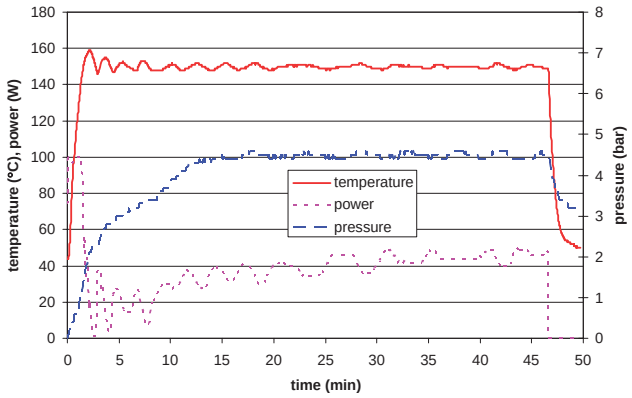


Fig. 1. Typical temperature (red), power (violet), and pressure (blue) profiles in the microwave irradiated synthesis of **5b**.

bottomed flask equipped with reflux condenser, which was immersed in an oil bath heated on 150 °C. Thereafter, the reaction mixture was cooled, and the crude mixture was analyzed by ^{1}H NMR.

Analytical and Spectroscopic Data of Products. ***N*-[2,6-Diethyl-2,3,3a,4a,5,6,7,7a,8,8a-decahydro-8-methyl-1,3,5,7-tetraoxo-4,8-ethenobenzo[1,2-*c*:4,5-*c*′]dipyrrol-4(1*H*)-yl]benzamide (5a):** Mp 255–257 °C (EtOH); IR (KBr) 1764, 1699 br, 1645, 1545 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.94 (t, J = 7.2 Hz, 6H, 2 × CH_2CH_3), 1.76 (s, 3H, Me), 3.02 (d, J = 8.2 Hz, 2H, 7a-H, 8a-H), 3.27 (q, J = 7.2 Hz, 4H, 2 × CH_2CH_3), 4.25 (d, J = 8.2 Hz, 2H, 3a-H, 4a-H), 5.86 (d, J = 8.7 Hz, 1H), 6.34 (d, J = 8.7 Hz, 1H, 9-H, 10-H), 7.53 (m, 3H, Ph), 7.88 (m, 2H, Ph), 8.69 (s, 1H, NH); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 12.9, 19.2, 33.6, 40.1, 43.5, 48.8, 57.6, 127.2, 128.6, 130.9, 131.6, 135.2, 135.3, 169.3, 174.5, 174.9; MS (m/z, %) 435 (M^+, 11), 105 (100). Anal. Calcd for $C_{24}H_{25}N_3O_5$: C, 66.19; H, 5.79; N, 9.65%. Found: C, 65.89; H, 5.92; N, 9.45%.

***N*-[2,6-Diethyl-2,3,3a,4a,5,6,7,7a,8,8a-decahydro-1,3,5,7-tetraoxo-8-phenyl-4,8-ethenobenzo[1,2-*c*:4,5-*c*′]dipyrrol-4(1*H*)-yl]benzamide (5b):** Mp 295–297 °C (EtOH); IR (KBr) 1770, 1699 br, 1638, 1549 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.88 (t, J = 7.1 Hz, 6H, 2 × CH_2CH_3), 3.17 (q, J = 7.1 Hz, 4H, 2 × CH_2CH_3), 3.77 (d, J = 8.3 Hz, 2H, 7a-H, 8a-H), 4.39 (d, J = 8.3 Hz, 2H, 3a-H, 4a-H), 6.54 (d, J = 9.0 Hz, 2H), 6.83 (d, J = 9.0 Hz, 2H, 9-H, 10-H), 7.28 (m, 2H), 7.40 (m, 2H), 7.53 (m, 3H), 7.79 (m, 1H), 7.91 (m, 2H, 2 × Ph), 8.78 (s, 1H, NH); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 12.6, 32.5, 43.4, 45.7, 48.8, 58.1, 126.2, 127.2, 127.37, 127.43, 127.6, 127.9, 128.0, 129.3, 130.9, 131.4, 135.8, 138.7, 168.0, 174.2, 174.3 (For 8-Ph 6 signals were observed); MS (m/z, %) 497 (M^+, 7), 105 (100). Anal. Calcd for $C_{29}H_{27}N_3O_5 \cdot H_2O$: C, 67.56; H, 5.67; N, 8.15%. Found: C, 67.67; H, 5.87; N, 8.14%.

***N*-[2,3,3a,4a,5,6,7,7a,8,8a-Decahydro-1,3,5,7-tetraoxo-2,6,8-triphenyl-4,8-ethenobenzo[1,2-*c*:4,5-*c*′]dipyrrol-4(1*H*)-yl]benzamide (5c):** Mp 289–291 °C (EtOH); IR (KBr) 1773, 1717, 1656, 1528, 1497 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 4.04 (d, J = 8.1 Hz, 2H, 7a-H, 8a-H), 4.64 (d, J = 8.1 Hz, 2H, 3a-H, 4a-H), 6.80 (d, J = 9.1 Hz, 1H, 9-H or 10-H), 7.07 (m, 4H of Ph), 7.14 (d, J = 9.1 Hz, 1H, 10-H or 9-H), 7.22–7.58 (m, 13H, 4 × Ph), 7.88 (m, 3H of Ph), 8.87 (s, 1H, NH); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 43.8, 46.2, 49.1, 58.4, 126.3, 126.8, 127.3, 127.5, 127.6, 127.9, 128.0, 128.3, 128.7, 129.9, 131.0, 131.8, 132.1, 135.7, 138.7, 168.2, 173.6, 173.8 (For 8-Ph 5 signals were observed); MS (m/z, %) 594 (($M+1$)$^+$, 55), 105 (86), 55 (100). Anal. Calcd for $C_{37}H_{27}N_3O_5$: C, 74.86; H, 4.58; N, 7.08%. Found: C, 74.79; H, 4.48; N, 6.73%.

***N*-[2,6-Diethyl-8-(2-furyl)-2,3,3a,4a,5,6,7,7a,8,8a-decahydro-1,3,5,7-tetraoxo-4,8-ethenobenzo[1,2-*c*:4,5-*c*′]dipyrrol-4(1*H*)-yl]benzamide (5d):** Mp 256–258 °C (EtOH); IR (KBr) 1768, 1703 br, 1647, 1551 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.91 (t, J = 7.0 Hz, 6H, 2 × CH_2CH_3), 3.22 (q, J = 7.2 Hz, 4H, 2 × CH_2CH_3), 3.61 (d, J = 8.3 Hz, 2H, 7a-H, 8a-H), 4.42 (d, J = 8.3 Hz, 2H, 3a-H, 4a-H), 6.42–6.57 (m, 4H), 7.56 (m, 3H), 7.68 (m, 1H), 7.92 (m, 2H, Ph, furyl, 9-H, 10-H), 8.79 (s, 1H, NH); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 12.6, 32.6, 42.5, 43.1, 47.6, 57.9, 107.8, 110.3, 127.6, 128.0, 128.9, 131.0, 131.8, 135.7, 142.0, 151.8, 168.0, 173.8, 174.3; MS (m/z, %) 487 (M^+, 3), 105 (100). Anal. Calcd for $C_{27}H_{25}N_3O_6 \cdot 1/4H_2O$: C, 65.91; H, 5.22; N, 8.54%. Found: C, 65.92; H, 5.36; N, 8.52%.

***N*-[8-(2-Furyl)-2,3,3a,4a,5,6,7,7a,8,8a-decahydro-2,6-dimethyl-1,3,5,7-tetraoxo-4,8-ethenobenzo[1,2-*c*:4,5-*c*′]dipyrrol-4(1*H*)-yl]benzamide (5e):** Mp 280–283 °C (EtOH); IR (KBr) 1772, 1703 br, 1656, 1537 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.65 (s, 6H, 2 × Me), 3.63 (d, J = 8.3 Hz, 2H, 7a-H, 8a-H), 4.43 (d, J = 8.3 Hz, 2H, 3a-H, 4a-H), 6.43 (m, 2H), 6.52 (m, 2H), 7.55 (m, 3H), 7.68 (m, 1H), 7.91 (m, 2H, Ph, 9-H, 10-H, furyl), 8.77 (s, 1H, NH); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 24.2, 42.5, 43.3, 47.8, 57.9, 107.8, 110.3, 127.6, 128.0, 129.3, 131.0, 132.1, 135.6, 142.0, 151.7, 167.9, 174.1, 174.6; MS (m/z, %) 459 (M^+, 3), 105 (100). Anal. Calcd for $C_{25}H_{21}N_3O_6$: C, 65.35; H, 4.61; N, 9.15%. Found: C, 65.06; H, 4.67; N, 9.22%.

***N*-[2,3,3a,4a,5,6,7,7a,8,8a-Decahydro-1,3,5,7-tetraoxo-2,6-diphenyl-8-(2-thienyl)-4,8-ethenobenzo[1,2-*c*:4,5-*c*′]dipyrrol-4(1*H*)-yl]benzamide (5f):** Mp 280–282 °C (EtOH); IR (KBr) 1775, 1716, 1661, 1528, 1495 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.87 (br, 2H, 7a-H, 8a-H), 4.65 (d, J = 8.3 Hz, 2H, 3a-H, 4a-H), 6.75–7.14 (m, 7H), 7.48 (m, 11H), 7.87 (m, 2H, 3 × Ph, thienyl, 9-H, 10-H), 8.86 (s, 1H, NH); ^{13}C NMR (75.5 MHz, DMSO-d_6, 69 °C) δ 43.7, 44.5, 50.7, 58.1, 124.1, 125.2, 126.2, 126.5, 127.2, 127.6, 127.9, 128.4, 130.6, 130.7, 131.9, 132.0, 135.6, 143.5, 167.9, 172.7, 172.9; MS (m/z, %) 599 (M^+, 5), 426 (100), 105 (100). Anal. Calcd for $C_{35}H_{25}N_3O_5S$: C, 70.10; H, 4.20; N, 7.01%. Found: C, 70.12; H, 4.10; N, 6.87%.

***N*-[2,6-Diethyl-2,3,3a,4a,5,6,7,7a,8,8a-decahydro-10-methyl-1,3,5,7-tetraoxo-8-phenyl-4,8-ethenobenzo[1,2-*c*:4,5-*c*′]dipyrrol-4(1*H*)-yl]benzamide (5g):** Mp 286–288 °C (EtOH); IR (KBr) 1767, 1703, 1644, 1528 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.87 (t, J = 7.1 Hz, 6H, 2 × CH_2CH_3), 1.93 (s, 3H, Me), 3.17 (q, J = 7.1 Hz, 4H, 2 × CH_2CH_3), 3.74 (d, J = 8.1 Hz, 2H, 7a-H, 8a-H), 4.47 (d, J = 8.1 Hz, 2H, 3a-H, 4a-H), 6.54 (s, 1H, 9-H), 7.33 (m, 4H), 7.55 (m, 4H), 7.80 (m, 1H), 7.87 (m, 2H, 2 × Ph, NH); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 12.6, 18.0, 32.5, 43.2, 45.8, 48.9, 59.8, 123.2, 126.2, 127.2, 127.3, 127.5, 127.7, 127.8, 128.2, 131.3, 135.7, 138.0, 138.8, 168.0, 174.3, 174.4 (For 8-Ph 6 signals were observed); MS (m/z, %) 511 (M^+, 4), 105 (100). Anal. Calcd for $C_{30}H_{29}N_3O_5$: C, 70.44; H, 5.71; N, 8.21%. Found: C, 70.49; H, 5.87; N, 8.03%.

***N*-[2,3,3a,4a,5,6,7,7a,8,8a-Decahydro-10-methyl-1,3,5,7-tetraoxo-2,6,8-triphenyl-4,8-ethenobenzo[1,2-*c*:4,5-*c*′]dipyrrol-4(1*H*)-yl]benzamide (5h):** Mp 288–289 °C (EtOH); IR (KBr) 1773, 1716, 1663, 1525, 1501 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.13 (s, 3H, Me), 4.02 (d, J = 8.2 Hz, 2H, 7a-H, 8a-H), 4.73 (d, J = 8.2 Hz, 2H, 3a-H, 4a-H), 6.84 (s, 1H, 9-H), 7.05 (m, 4H), 7.24 (m, 2H), 7.32–7.62 (m, 11H), 7.68 (s, 1H), 7.86 (m, 3H) (4 × Ph, NH); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 18.1, 43.6, 46.2,

49.2, 60.1, 123.7, 126.2, 126.8, 127.2, 127.3, 127.6, 127.7, 127.9, 128.2, 128.3, 128.8, 131.3, 132.0, 135.6, 138.6, 138.7, 168.2, 173.79, 173.82 (For 8-Ph 6 signals were observed); MS (*m/z*, %) 607 (M^+, 2), 105 (100). Anal. Calcd for $C_{38}H_{29}N_3O_5$: C, 75.11; H, 4.81; N, 6.92%. Found: C, 75.33; H, 4.73; N, 6.70%.

***N*-[2,6-Diethyl-2,3,3a,4a,5,6,7,7a,8,8a-decahydro-10-methyl-1,3,5,7-tetraoxo-8-(2-thienyl)-4,8-ethenobenzo[1,2-*c*:4,5-*c*′]dipyrrol-4(1*H*)-yl]benzamide (5i):** Mp 273–275 °C (EtOH); IR (KBr) 1768, 1703, 1646, 1526 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6, 70 °C) δ 0.93 (t, $J = 6.8$ Hz, 6H, 2 × CH_2CH_3), 1.92 (s, 3H, Me), 3.24 (q, $J = 6.8$ Hz, 4H, 2 × CH_2CH_3), 3.59 (d, $J = 8.1$ Hz, 2H, 7a-H, 8a-H), 4.51 (d, $J = 8.1$ Hz, 2H, 3a-H, 4a-H), 6.28 (s, 1H, 9-H), 7.03 (m, 1H), 7.17 (m, 1H), 7.32 (m, 1H), 7.45 (m, 1H), 7.56 (m, 3H), 7.90 (m, 2H, Ph, thienyl, NH); ^{13}C NMR (75.5 MHz, DMSO-d_6, 60 °C) δ 12.1, 17.2, 32.3, 43.1, 44.2, 50.4, 59.4, 123.8, 124.1, 124.8, 126.1, 127.1, 128.0, 130.9, 135.4, 138.1, 143.6, 167.5, 173.2, 173.8; MS (*m/z*, %) 517 (M^+, 5), 105 (100). Anal. Calcd for $C_{28}H_{27}N_3O_5S$: C, 64.97; H, 5.26; N, 8.12%. Found: C, 65.05; H, 5.45; N, 7.92%.

***N*-[2,3,3a,4a,5,6,7,7a,8,8a-Decahydro-10-methyl-1,3,5,7-tetraoxo-2,6-diphenyl-8-(2-thienyl)-4,8-ethenobenzo[1,2-*c*:4,5-*c*′]dipyrrol-4(1*H*)-yl]benzamide (5j):** Mp 284–287 °C (EtOH); IR (KBr) 1773, 1715, 1666, 1532, 1497 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6, 70 °C) δ 2.09 (s, 3H, Me), 3.85 (d, $J = 7.9$ Hz, 2H, 7a-H, 8a-H), 4.75 (d, $J = 7.9$ Hz, 2H, 3a-H, 4a-H), 6.57 (m, 1H), 6.99 (m, 1H), 7.08 (m, 4H), 7.24 (m, 1H), 7.42 (m, 11H), 7.86 (m, 2H, 3 × Ph, thienyl, 9-H, NH); ^{13}C NMR (75.5 MHz, DMSO-d_6, 80 °C) δ 17.2, 43.5, 44.6, 50.7, 59.6, 123.9, 124.6, 125.0, 126.1, 126.3, 127.0, 127.9, 128.3, 130.8, 131.8, 135.3, 138.8, 143.4, 167.7, 172.5, 173.1 (1 signal hidden); MS (*m/z*, %) 613 (M^+, 1), 105 (100). Anal. Calcd for $C_{36}H_{27}N_3O_5S$: C, 70.46; H, 4.43; N, 6.85%. Found: C, 70.29; H, 4.64; N, 6.81%.

***N*-[2,6-Diethyl-2,3,3a,4a,5,6,7,7a,8,8a-decahydro-9-(4-methoxyphenyl)-8-methyl-1,3,5,7-tetraoxo-4,8-ethenobenzo[1,2-*c*:4,5-*c*′]dipyrrol-4(1*H*)-yl]benzamide (5k):** Mp 335–337 °C (EtOH); IR (KBr) 1766, 1699, 1641, 1606, 1553, 1510 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 0.95 (t, $J = 7.2$ Hz, 6H, 2 × CH_2CH_3), 1.74 (s, 3H, Me), 3.17 (d, $J = 8.3$ Hz, 2H, 7a-H, 8a-H), 3.30 (m, 4H, 2 × CH_2CH_3), 3.73 (s, 3H, OMe), 4.30 (d, $J = 8.3$ Hz, 2H, 3a-H, 4a-H), 6.20 (s, 1H, 10-H), 6.78 and 6.89 (AA′XX′, $J = 9.0$ Hz, 4H, C_6H_4), 7.53 (m, 3H, Ph), 7.89 (m, 2H, Ph), 8.67 (s, 1H, NH); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 12.9, 18.7, 32.8, 42.3, 43.4, 48.9, 55.0, 58.0, 113.6, 126.9, 127.6, 128.0, 128.7, 129.6, 130.9, 135.8, 144.9, 158.8, 167.9, 174.5, 176.1; MS (*m/z*, %) 541 (M^+, 13), 105 (100). Anal. Calcd for $C_{31}H_{31}N_3O_6$: C, 68.75; H, 5.77; N, 7.76%. Found: C, 68.92; H, 6.03; N, 7.62%.

***N*-[2,6-Diethyl-2,3,3a,4a,5,6,7,7a,8,8a-decahydro-9-(3,4-dimethoxyphenyl)-8-methyl-1,3,5,7-tetraoxo-4,8-ethenobenzo-[1,2-*c*:4,5-*c*′]dipyrrol-4(1*H*)-yl]benzamide (5l):** Mp 264–266 °C (MeOH/H_2O); IR (KBr) 1765, 1699, 1668, 1537, 1515 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 0.96 (t, $J = 7.2$ Hz, 6H, 2 × CH_2CH_3), 1.77 (s, 3H, Me), 3.18 (d, $J = 8.3$ Hz, 2H, 7a-H, 8a-H), 3.30 (q, $J = 7.2$ Hz, 4H, 2 × CH_2CH_3), 3.68 (s, 3H, OMe), 3.74 (s, 3H, OMe), 4.31 (d, $J = 8.3$ Hz, 2H, 3a-H, 4a-H), 6.22 (s, 1H, 10-H), 6.41 (m, 2H, C_6H_3), 6.91 (m, 1H, C_6H_3), 7.52 (m, 3H, Ph), 7.89 (m, 2H, Ph), 8.67 (s, 1H, NH); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 12.9, 18.8, 32.8, 42.3, 43.4, 48.9, 55.3, 55.4, 58.0, 111.2, 111.5, 120.0, 126.8, 127.6, 128.0, 129.8, 131.0, 135.8, 145.0, 147.9, 148.4, 167.9, 174.5, 176.2; MS (*m/z*, %) 571 (M^+, 26), 105 (100). Anal. Calcd for $C_{32}H_{33}N_3O_7 \cdot 1/2H_2O$: C, 66.19; H, 5.90; N, 7.24%. Found: C, 66.49; H, 5.93; N, 7.13%.

We thank the Ministry of Higher Education, Science and Technology of the Republic of Slovenia and the Slovenian Research Agency for financial support (No. P1-0230-0103 and J1-6693-0103). 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, J. Wild, *Synthesis* **1988**, 159. b) C. Bonauer, T. Walenzyk, B. König, *Synthesis* **2006**, 1.

2 For selected recent examples of different types of heterocyclic dehydroamino acid derivatives, see: a) L. Vraničar, S. Polanc, M. Kočevar, *Tetrahedron* **1999**, *55*, 271. b) T. Trček, A. Meden, B. Verček, *Synlett* **2000**, 1458. c) L. Vraničar, A. Meden, S. Polanc, M. Kočevar, *J. Chem. Soc., Perkin Trans. 1* **2002**, 675. d) L. Vraničar, F. Požgan, S. Polanc, M. Kočevar, *Amino Acids* **2003**, *24*, 273. e) P. M. T. Ferreira, H. L. S. Maia, L. S. Monteiro, *Eur. J. Org. Chem.* **2003**, 2635. f) T. Trček, B. Verček, *ARKIVOC* **2003**, 246. g) T. Trček, B. Verček, *ARKIVOC* **2005**, 96. h) T. Trček, B. Verček, *Acta Chim. Slov.* **2005**, *52*, 171. i) T. Trček, B. Verček, *Synthesis* **2006**, 3437. j) F. Požgan, S. Polanc, M. Kočevar, *Tetrahedron* **2006**, *62*, 9718. k) F. Požgan, M. Krejan, S. Polanc, M. Kočevar, *Heterocycles* **2006**, *69*, 123. l) F. Požgan, S. Kafka, S. Polanc, M. Kočevar, *Heterocycles* **2006**, *70*, 235.

3 For selected recent examples, see: a) K. Komatsu, T. Nishinaga, *Synlett* **2005**, 187. b) A. Friberg, T. Johanson, J. Franzén, M. F. Gorwa-Grauslund, T. Frejd, *Org. Biomol. Chem.* **2006**, *4*, 2304. c) V. Singh, S. Pal, S. M. Mobin, *J. Org. Chem.* **2006**, *71*, 3014. d) Y. Endo, T. Yoshimi, K. Ohta, T. Suzuki, S. Ohta, *J. Med. Chem.* **2005**, *48*, 3941. e) T.-C. Chou, C.-L. Hwa, J.-J. Lin, K.-C. Liao, J.-C. Tseng, *J. Org. Chem.* **2005**, *70*, 9717. f) D. Yamazaki, T. Nishinaga, K. Komatsu, *Org. Lett.* **2004**, *6*, 4179. g) T.-C. Chou, G.-H. Lin, *Tetrahedron* **2004**, *60*, 7907. h) M.-S. Yang, S.-S. Lu, C.-P. Rao, Y.-F. Tsai, C.-C. Liao, *J. Org. Chem.* **2003**, *68*, 6543.

4 a) A. S. Kende, J. Lan, D. Arad, *Tetrahedron Lett.* **2002**, *43*, 5237, and references cited therein. b) P. Magnus, L. Gazzard, L. Hobson, A. H. Payne, T. J. Rainey, N. Westlund, V. Lynch, *Tetrahedron* **2002**, *58*, 3423.

5 a) K. Kranjc, I. Leban, S. Polanc, M. Kočevar, *Heterocycles* **2002**, *58*, 183. b) K. Kranjc, S. Polanc, M. Kočevar, *Org. Lett.* **2003**, *5*, 2833. c) M. Martelanc, K. Kranjc, S. Polanc, M. Kočevar, *Green Chem.* **2005**, *7*, 737. d) K. Kranjc, M. Kočevar, F. Iosif, S. M. Coman, V. I. Parvulescu, E. Genin, J.-P. Genêt, V. Michelet, *Synlett* **2006**, 1075. e) J. Hren, K. Kranjc, S. Polanc, M. Kočevar, *Heterocycles* **2007**, *72*, 399.

6 a) R. A. Sheldon, *Green Chem.* **2005**, *7*, 267. b) A. Matlack, *Green Chem.* **2003**, *5*, G7. c) B. M. Trost, *Acc. Chem. Res.* **2002**, *35*, 695. d) P. N. Anastas, M. M. Kirchhoff, *Acc. Chem. Res.* **2002**, *35*, 686. e) B. M. Trost, D. F. Toste, A. B. Pinkerton, *Chem. Rev.* **2001**, *101*, 2067.

7 a) *Microwaves in Organic Synthesis*, ed. by A. Loupy, Wiley-VCH, Weinheim, **2002**. b) B. L. Hayes, *Microwave Synthesis: Chemistry at the Speed of Light*, CEM Publishing, Matthews NC, **2002**. c) P. Lidström, J. Tierney, B. Wathey, J. Westman, *Tetrahedron* **2001**, *57*, 9225. d) R. S. Varma, *Green Chem.* **1999**, *1*, 43. e) C. O. Kappe, *Angew. Chem., Int. Ed.* **2004**, *43*, 6250. f) A. de la Hoz, A. Díaz-Ortiz, A. Moreno, *Chem. Soc. Rev.* **2005**, *34*, 164. g) E. S. H. El Ashry, A. A. Kassem, *ARKIVOC* **2006**, 1.

8 For recent selected microwave assisted neat reactions, see: a) J. Pospíšil, M. Potáček, *Tetrahedron* **2007**, *63*, 337. b) A. de la Hoz, A. Díaz, J. Elguero, A. Jiménez, A. Moreno, A. Ruiz, A. Sánchez-Migallón, *Tetrahedron* **2007**, *63*, 748. c) H. Koizumi, Y. Itoh, T. Ichikawa, *Chem. Lett.* **2006**, *35*, 1350. d) Raunak, V. Kumar, S. Mukherjee, Poonam, A. K. Prasad, C. E. Olsen, S. J. C. Schäffer, S. K. Sharma, A. C. Watterson, W. Errington, V. S. Parmar, *Tetrahedron* **2005**, *61*, 5687. e) D. C. G. A. Pinto, A. M. S. Silva, C. M. Brito, A. Sandulache, J. R. Carrillo, P. Prieto, A. Díaz-Ortiz, A. de la Hoz, J. A. S. Cavaleiro, *Eur. J. Org. Chem.* **2005**, 2973. f) A. Loupy, *C. R. Chim.* **2004**, *7*, 103. g) A. Dandia, K. Arya, M. Sati, S. Gautam, *Tetrahedron* **2004**, *60*, 5253. h) A. Loupy, F. Maurel, A. Sabatié-Gogová, *Tetrahedron* **2004**, *60*, 1683.

9 a) M. Ješelnik, R. S. Varma, S. Polanc, M. Kočevar, *Chem. Commun.* **2001**, 1716. b) M. Ješelnik, R. S. Varma, S. Polanc, M. Kočevar, *Green Chem.* **2002**, *4*, 35. c) K. Kranjc, M. Kočevar, *Collect. Czech. Chem. Commun.* **2006**, *71*, 667.

10 a) K. Afarinkia, V. Vinader, T. D. Nelson, G. H. Posner, *Tetrahedron* **1992**, *48*, 9111. b) B. T. Woodard, G. H. Posner, in *Advances in Cycloaddition*, ed. by M. Harmata, JAI Press Inc., Greenwich, **1999**, Vol. 5, pp. 47–83. c) N. P. Shusherina, *Russ. Chem. Rev.* **1974**, *43*, 851. d) K. Kranjc, B. Štefane, S. Polanc, M. Kočevar, *J. Org. Chem.* **2004**, *69*, 3190. e) K. Kranjc, M. Kočevar, *New J. Chem.* **2005**, *29*, 1027. f) N. A. Tolmachova, I. I. Gerus, S. I. Vdovenko, M. Essers, R. Fröhlich, G. Haufe, *Eur. J. Org. Chem.* **2006**, 4704.

11 For the synthesis of **1a**–**1h**, see: a) V. Kepe, M. Kočevar, S. Polanc, *J. Heterocycl. Chem.* **1996**, *33*, 1707. b) V. Kepe, S. Polanc, M. Kočevar, *Heterocycles* **1998**, *48*, 671. c) F. Požgan, K. Kranjc, V. Kepe, S. Polanc, M. Kočevar, *ARKIVOC* **2007**, 97.

12 a) M. C. Pirrung, *Chem. Eur. J.* **2006**, *12*, 1312. b) A. P. Brogan, T. J. Dickerson, K. D. Janda, *Angew. Chem., Int. Ed.* **2006**, *45*, 8100. c) Y. Hayashi, *Angew. Chem., Int. Ed.* **2006**, *45*, 8103. d) S. Narayan, J. Muldoon, M. G. Finn, V. V. Fokin, H. C. Kolb, K. B. Sharpless, *Angew. Chem., Int. Ed.* **2005**, *44*, 3275.

13 A. Cantín, A. Corma, M. J. Diaz-Cabanas, J. L. Jordá, M. Moliner, *J. Am. Chem. Soc.* **2006**, *128*, 4216.