Synthesis of Phenyl-substituted 2*H*,5*H*-Pyrano[4,3-*b*]pyran-5-ones and Related Heterocycles *via* a Domino Knoevenagel Condensation/ 6π-Electron Electrocyclization of 4-Hydroxy-6-phenyl-2*H*-pyran-2-one with Cyclic and Acyclic α,β-Unsaturated Aldehydes under Different Conditions

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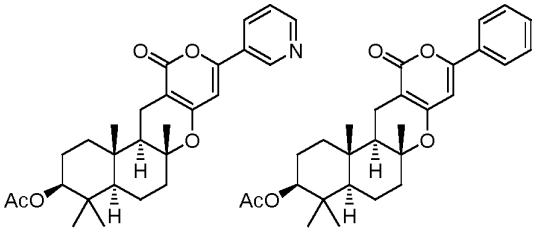
A range of new 7-phenyl-2*H*,5*H*-pyrano[4,3-*b*]pyran-5-ones and related tricyclic heterocycles was prepared in a single step by means of a domino Knoevenagel condensation/6π-electron electrocyclization under different reaction conditions, including thermal and microwave conditions. The influence of several ionic liquids as solvents was also studied.

Key words: Domino Reactions, Microwave Irradiation, Ionic Liquids, *O*-Heterocycles

Introduction

Microwave-assisted syntheses are a particularly attractive alternative to syntheses under thermal conditions since they often proceed much faster and deliver products with higher yields and higher purity [1]. Upon conventional heating using an external heat source like an oil bath or an electric heater the energy transfer depends on the thermal conductivity of the sample to be penetrated, which is relatively slow and inefficient. In contrast, the energy of the microwaves is directly transferred to the molecules of the reaction mixture *via* dielectric heating. The heating is largely caused by dipolar polarization and ionic conduction. Due to the transparency of the reaction vials normally used for microwave-assisted syntheses an inverted temperature gradient is established. Wall effects are minimized, and the reaction mixture is heated from inside. In addition to the purely thermal/kinetic effects and the "specific microwave effects" a number of scientists involved in microwave technology also consider "nonthermal microwave effects" which are supposedly based on a direct interaction between the electric field and specific molecules of the reaction mixture. It has been proposed that the electric field induces orientation effects of polar molecules/intermediates which affect the pre-exponential factor A or the activation energy (entropy term) in the Arrhenius equation. In a similar way, the activation energy of polar reactions – in which the polarity is increased on going from ground to transition state – is supposed to be decreased [1].

Over the last few years the use of ionic liquids as solvents/reaction media has received a substantial boost [2]. Ionic liquids are salts with a melting point below 100 °C. They have an ionic structure and generally consist of an organic cation and an inorganic or organic anion. This is why they have nearly no vapor pressure and thus offer a genuine alternative to organic solvents. When reactions were run in ionic liquids both a greatly increased reaction rate and a change in selectivities have been observed in several cases; these effects may be attributed to polar interactions between the ionic liquids and the substrates. Meanwhile a great number of reactions have been performed in ionic liquids [2], many of them from the field of heterocyclic chemistry [3]. Also, numerous other classical transformations like the Knoevenagel condensation can be successfully performed in ionic liquids [4]. In domino reactions starting with a Knoevenagel condensation ionic liquids have been employed less often [5]. The significance which ionic liquids have gained in organic synthesis is not only due to their solvent properties but to their catalytic effects as well [6]. The best known ionic liquids are the imidazolium salts which have been



Pyripyropene E (**1**) Phenylpyropene C (**2**)

successfully used as solvents or catalysts in numerous chemical transformations. In addition, there is a large number of other ionic liquids including guanidinium salts, which so far have been used in a small number of organic reactions [7], including Heck [7b] and aldol reactions [7c]. Also, guanidinium cations have several properties predisposing them for applications in dye-sensitized solar cells and as hydraulic fluids [8]. Due to their high polarity/high dielectricity constant ionic liquids can be efficiently heated up by microwave irradiation [9]. Hence, reactions in ionic liquids can benefit tremendously from microwave conditions.

Natural products with a decahydro-2*H*,11*H*-naphtho[2,1-*b*]pyrano[3,4-*e*]pyran-11-one skeleton exhibit interesting biologic activities. These include pyripyropenes like the pyripyropene E (**1**), which Omura *et al.* isolated from a cultural broth of *Aspergillus fumigatus* FO-1289-2501 [10]. These compounds are potent inhibitors of acyl-CoA:cholesterol acyltransferase (ACAT). Inhibition of this enzyme, which accounts for the intracellular esterification of cholesterol, is a promising approach to the prevention of atherosclerosis. The phenylpyropene C (**2**), which was isolated from *Penicillium griseofulvum* F1959, has the same skeleton and is also a well-known ACAT inhibitor [11a]. In addition, it has been demonstrated that phenylpyropene C (**2**) inhibits both the JAK/STAT signal cascade [11b] in various cell lines und the diacylglycerol acyltransferase [11c].

The underlying structural motif of all pyripyropenes and related natural products is the pyrano[4,3-*b*]pyran-5-one skeleton (Fig. 1). Several groups have shown that a number of *O*-heterocycles of this type exhibit cytotoxic properties against several cancer cell lines *in*

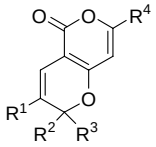
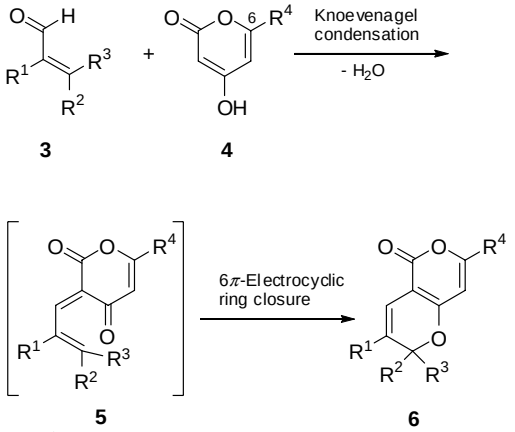


Fig. 1. The pyrano[4,3-*b*]pyran-5-one skeleton.



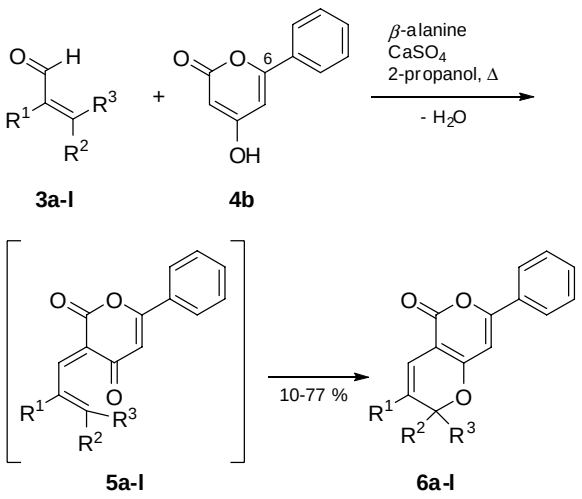
Scheme 1.

vitro [12]. Some tricyclic derivatives inhibit aldose reductase, a property which might prove useful in the prevention of diabetes [13]. In a series of papers Hua *et al.* also describe the *in vitro* and *in vivo* inhibition of the Alzheimer amyloid toxicity by tricyclic pyrones [14].

It has been demonstrated that pyrano[4,3-*b*]pyran-5-one and related structures can be efficiently formed *via* transformation of α,β-unsaturated aldehydes **3** with 6-substituted 4-hydroxy-2*H*-pyran-2-ones **4** under conventional reaction conditions [15]. It is assumed that in the presence of compounds like L-proline or piperidinium acetate a Knoevenagel condensation takes place initially. The resulting 1-oxatriene **5** usually cannot be isolated, but subsequently reacts in an electrocylic ring closure to form the 2*H*,5*H*-pyrano[4,3-*b*]pyran-5-one **6** (Scheme 1). In a previous paper we demonstrated that the reaction between the 6-methyl substituted 4-hydroxy-2*H*-pyran-2-one **4a** and the aldehydes **3** can considerably be accelerated by using microwave irradiation at higher reaction temperatures [16]. Based on these findings we will here describe the transformation of the 6-phenyl substituted 4-hydroxy-2*H*-pyran-2-one **4b** with the α,β-unsaturated aldehydes **3** under varying reaction conditions. The influence of reflux and microwave conditions as well as the impact of conventional solvents and ionic liquids on the outcome of the reactions will be addressed.

Results and Discussion

First, the reactions of 4-hydroxy-6-phenyl-2*H*-pyran-2-one (**4b**) with α,β-unsaturated aldehydes **3** were performed under reflux conditions. Best results with the domino Knoevenagel condensation/ 6π-electron electrocyclization were achieved when



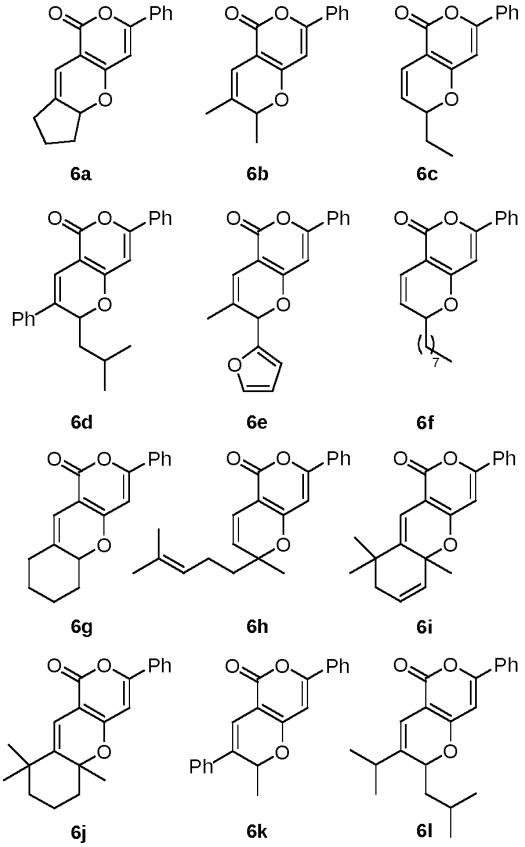
Scheme 2.

1.1 equivalents of 4-hydroxy-6-phenyl-2*H*-pyran-2-one (**4b**) were refluxed with 1.0 equivalent of **3** in the presence of 50 mol-% β-alanine and calcium sulfate as dehydrating reagent in 2-propanol as a solvent (Scheme 2, Table 1). 1-Cyclopentene-1-carboxaldehyde (**3a**), (*E*)-2-methyl-2-butenal (**3b**), (*E*)-2-pentenal (**3c**), 5-methyl-2-phenyl-2-hexenal (**3d**), 3-(2-furyl)-2-methyl-propenal (**3e**), 2-undecenal (**3f**), 1-cyclohexene-1-carboxaldehyde (**3g**), citral (**3h**), safranal (**3i**), β-cyclocitral (**3j**), 2-phenyl-2-butenal (**3k**) and 2-isopropyl-5-methyl-2-hexenal (**3l**) were selected as α,β-unsaturated aldehydes. By applying the experimental conditions described and with reaction times ranging from 30 min to 71 h the heterocycles **6a**–**l** were isolated with yields from 10 to 77 %.

Most of the reactions required only a few hours for completion and delivered the corresponding products in good to sufficient yields, except for the reactions with the aldehydes **3i** and **3j** which remained unsatisfactory (extremely long reaction times and very low product yields for **6i** and **6j**; Table 1, entries 9 and 10). A comparison of the reactions of safranal (**3i**) and β-cyclocitral (**3j**) with the transformation of 1-cyclohexene-1-carboxaldehyde (**3g**) (Table 1, entry 7) suggests that the long reaction times and the low yields associated with **3i** and **3j** are probably due to steric hindrance.

A comparison between the transformations of the 6-phenyl-substituted 4-hydroxy-2*H*-pyran-2-one **4b** and the 6-methyl-substituted 4-hydroxy-2*H*-pyran-2-one **4a** reveals that 1) all reactions of **4b** proceed faster than those of **4a** and that 2) the reactions of **4b** tend to provide lower yields than **4a** [16]. The first effect can be put down to a higher reactivity of **4b**. The second effect is due to a greater product loss upon chromatographic purification of **6a**–**l** which in turn can probably be attributed to a lower product stability. To summarize, it was established that the transformations of 4-hydroxy-6-phenyl-2*H*-pyran-2-one (**4b**) and the α,β-unsaturated aldehydes **3** can be performed under reflux conditions providing a reliable access to 7-phenyl-

Table 1. Domino reactions of **3a**–**l** with **4b** in 2-propanol under reflux conditions.



Entry	**3**	Time (h)	**6**	Yield (%)
1	**a**	4	**a**	72
2	**b**	2	**b**	68
3	**c**	0.67	**c**	38
4	**d**	16	**d**	66
5	**e**	17	**e**	31
6	**f**	2.75	**f**	42
7	**g**	2.5	**g**	77
8	**h**	0.5	**h**	75
9	**i**	49	**i**	10
10	**j**	71	**j**	15
11	**k**	1	**k**	34
12	**l**	23.5	**l**	53

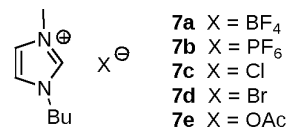
Table 2. Comparison of the reactions of **3j**–**l** and **4b** in 2-propanol under reflux and under microwave conditions.

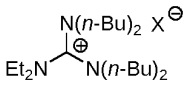
Entry	3	6	Reflux 82 °C, $CaSO_4$		MW 110 °C	
			Time (h)	Yield (%)	Time (h)	Yield (%)
1	**j**	**j**	71	15	3	9
2	**k**	**k**	1	34	0.75	31
3	**l**	**l**	23.5	53	1	63

2*H*,5*H*-pyrano[4,3-*b*]pyran-5-ones and related heterocycles **6**. The disadvantages include very long reaction times in combination with low yields that were observed in some cases.

From our experience a considerable reduction of the reaction times was to be expected from microwave-assisted reactions. This is why the aldehydes **3j**–**l** – as representative examples – were reacted with **4b** under microwave conditions (Table 2). The best results were obtained when the reactions were run in a sealed vial using a focused single-mode microwave reactor at 110 °C. Under these conditions it was unnecessary to add a dehydrating agent like calcium sulfate. As expected, applying microwaves as the energy source dramatically shortened the reaction times in some cases; the yields, however, could not be improved likewise. In detail, the reaction time needed for transforming **3j** and **4b** was decreased from 71 h to 3 h; however, the yield of 1*H*,7*H*-pyrano[4,3-*b*]chromen-1-one (**6j**) amounted to a mere 9 % (Table 1, entry 10 and Table 2, entry 1). The reaction time for the domino reaction of **3k** with **4b** under microwave conditions was only marginally reduced, and the yield of **6k** (31 %) was similar to that observed under reflux conditions (Table 1, entry 11 and Table 2, entry 2). Microwave irradiation only paid off with the transformation of **3l** and **4b** by reducing the reaction time from 23.5 h (reflux conditions) to 1 h (microwave conditions; 110 °C) and at the same time increasing the yield of the 2*H*,5*H*-pyrano[4,3-*b*]pyran-5-one (**6l**) from 53 % (reflux conditions) to 63 % (microwave conditions; 110 °C) (Table 1, entry 12 and Table 2, entry 3).

For direct comparison between thermal and microwave conditions **3l** and **4b** were heated in a sealed vial at 110 °C using a preheated oil bath. After 1 h **6l** could be isolated with 62 % yield – perfectly matching the yield of **6l** under microwave conditions (63 %). This control experiment clearly demonstrates that – at least in this case – the advantage of microwave reactions in a sealed vial does not rely on using microwave irradiation as the energy source but rather on the use of a sealed vial that allows the reaction to be run at a higher pressure and temperature.





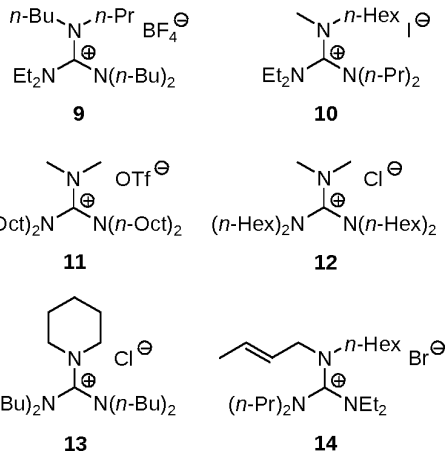


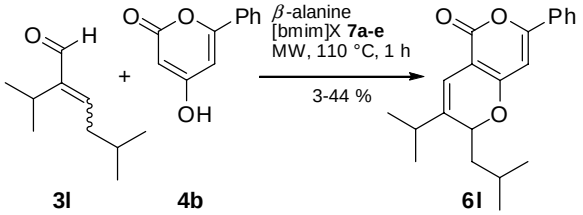
Fig. 2. The ionic liquids **7**–**14**.

Another objective of this study was to establish whether 1) traditional solvents like 2-propanol can be replaced by ionic liquids and 2) ionic liquids can be used as catalysts for the domino Knoevenagel condensation/6π-electron electrocyclization. For these studies the reaction of aldehyde **3l** with **4b** was selected as a model. First, **3l** and **4b** were reacted for 1 h at 110 °C in a sealed vial under microwave conditions in the presence of 50 mol-% β-alanine and several ionic liquids as the reaction media, namely each of the five 1-butyl-3-methyl-imidazolium salts **7a**–**e** and each of the eight guanidinium salts **8**–**14** (Fig. 2). In general, using ionic liquids as solvents requires roughly about one third of the microwave power that is necessary for heating the reaction mixture in 2-propanol. The results obtained with the imidazolium salts **7a**–**e** are presented in Scheme 3 and Table 3; details of the reactions with the guanidinium salts **8**–**14** are given in Scheme 4 and Table 4.

Reactions of **3l** with **4b** in the imidazolium salts **7a**–**e** delivered **6l** with yields ranging from 3 to 44 %. The best result (44 %) was obtained with [bmim]PF_6

Table 3. Reactions of **3l** with **4b** under microwave conditions (1 h, 110 °C) using imidazolium salts [bmim]X **7a – e** as solvents.

Entry	Ionic liquid	Yield of **6l** (%)
1	**7a**	34
2	**7b**	44
3	**7c**	18
4	**7d**	17
5	**7e**	3



Scheme 3.

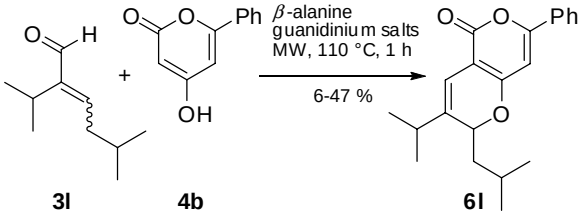
(**7b**) as the reaction medium (Table 3, entry 2). The yield of **6l** was much lower (34 %) when [bmim]BF_4 (**7a**) was used (Table 3, entry 1). The transformations with [bmim]Cl (**7c**), [bmim]Br (**7d**) and [bmim]OAc (**7e**) produced even lower yields: 18 %, 17 % and 3 %, respectively (Table 3, entries 3 – 5). In conclusion, the classic solvent can be replaced by an imidazolium salt, but the yields are disappointingly low. Quite obviously, the anions of the ionic liquids exert a large influence on the outcome.

We studied also whether the β-alanine which is necessary to bring about the initial Knoevenagel condensation of the domino process can be replaced by an ionic liquid. For this purpose aldehyde **3l** and 4-hydroxy-2*H*-pyran-2-one **4b** were heated for 5 h at 110 °C under microwave conditions in [bmim]BF_4 (**7a**) in the absence of β-alanine. **6l** was isolated with 5 % yield, which renders this approach impractical. The influence of the decomposition observed under these reaction conditions was not further investigated.

With the guanidinium salts **8 – 14** the transformations of **3l** with **4b** afforded **6l** with yields between 6 und 47 % (Scheme 4, Table 4). The highest yield (47 %) was obtained with the guanidinium triflate **11** (Table 4, entry 5). This single result cannot obscure the fact that the reactions in the remaining guanidinium salts (**8 – 10** and **12 – 14**) with yields of not more than 18 % were very unsatisfactory (Scheme 4, Table 4). And what is more, partial decomposition of the reaction mixtures occurred resulting in the formation of numerous unidentified side products. This seriously hampered the work-up of the reaction mixtures by column chromatography. To summarize, the organic solvent in the model reaction can be replaced with a guanidinium salt as well, but except for one all these transformations produced very low yields. Without any further detailed experiments it cannot be established whether the yields of the reactions in guanidinium salts largely depend on their anions as was the case with the imidazolium salts.

Table 4. Reactions of **3l** with **4b** under microwave conditions (1 h, 110 °C) using guanidinium salts **8 – 14** as solvents.

Entry	Ionic liquid	Yield of **6l** (%)
1	**8a**	14
2	**8b**	7
3	**9**	15
4	**10**	9
5	**11**	47
6	**12**	9
7	**13**	6
8	**14**	18



Scheme 4.

Conclusion

It has been demonstrated that 7-phenyl-2*H*,5*H*-pyrano[4,3-*b*]pyran-5-ones and related heterocycles **6** can be efficiently synthesized in a domino process by reacting an α,β-unsaturated aldehyde **3** with 4-hydroxy-6-phenyl-2*H*-pyran-2-one (**4b**) in the presence of β-alanine and calcium sulfate as a dehydrating agent under conventional reflux conditions using 2-propanol as a solvent. Some of the reactions have also been studied under microwave conditions in a sealed vial. It was found that the transformations under microwave conditions benefit from reduced reaction times. Using the reaction of **3l** with **4b** as an example it was demonstrated that the domino process can also be performed in imidazolium und guanidinium salts as the solvents; the yields, however, cannot compare to the yields in ordinary organic solvents. With the imidazolium salts [bmim]X **7**, a remarkable dependence of the yields on the nature of the anion was observed.

Experimental Section

General

Commercial reagents were used without further purification. 4-Hydroxy-6-phenyl-2*H*-pyran-2-one (**4b**) was synthesized according to ref. [17]. All solvents were distilled prior to use. 2-Propanol was distilled from sodium. All microwave-assisted reactions were performed with a Discover™ single mode cavity microwave synthesizer (CEM Corp.) producing continuous microwave irradiation at 2450 MHz. Thin-layer chromatography (TLC) was performed on silica gel SIL G/UV_{254} (Macherey-Nagel); compounds were visualized with UV light (λ = 254 nm) and/or immersion in $KMnO_4$ solution followed by heating. Flash chromatography was performed on silica gel 60 (0.040 – 0.063 mm) (Baker). Melting points were determined on a B-545 melting point apparatus (Büchi) and are uncorrected. UV/Vis spectra were measured using a CARY 4E spectrometer (Varian). IR (ATR) spectra were taken on a Spectrum One instrument (Perkin Elmer). NMR spectra were recorded on Varian ^{Unity}INOVA spectrometers (300/75 MHz and 500/125 MHz, respectively) in $CDCl_3$; the ^1H and ^{13}C chemical shifts were referenced to residual solvent signals at δ_H = 7.26 and δ_C = 77.0 relative to TMS. Mass spectra (EI) were recorded on a MAT 8200 instrument (Finnigan MAT) with 70 eV ionization energy. Elemental analyses were carried out by F. Hambloch, Institut für Organische und Biomolekulare Chemie der Universität Göttingen.

*Typical procedure for the synthesis of the 2H,5H-pyrano[4,3-b]pyran-5-ones (**6**) under reflux conditions using 2-propanol as a solvent*

0.655 g (4.3 mmol) of 2-isopropyl-5-methyl-2-hexenal (**3l**), 0.879 g (4.7 mmol) of 4-hydroxy-6-phenyl-2*H*-pyran-2-one (**4b**), 0.189 g (2.1 mmol) of β-alanine, and 0.506 g (3.7 mmol) of anhydrous calcium sulfate were heated in 40 mL of dry 2-propanol under reflux under argon until complete consumption of the aldehyde **3** (TLC control). After cooling to r. t., the reaction mixture was diluted with 60 mL of water and 40 mL of methylene chloride. The aqueous layer was extracted three times with 20 mL of methylene chloride, and the combined organic layers were washed with 20 mL of a saturated sodium bicarbonate solution and 15 mL of brine, dried over magnesium sulfate, and concentrated *in vacuo*. The crude product was purified by flash chromatography on 140 g of silica gel (diethyl ether/petroleum ether = 1 : 3) to give 0.753 g (53 %) of pure **6l** as a yellow oil.

*Typical procedure for the synthesis of the 2H,5H-pyrano[4,3-b]pyran-5-ones **6j – l** under microwave conditions using 2-propanol as a solvent*

A microwave glass vial (8 mL) with a magnetic stirring bar was heated to 150 °C for 8 h and cooled to room temperature under argon. The vial was charged with 43 mg (0.28 mmol) of 2-isopropyl-5-methyl-2-hexenal (**3l**), 60 mg (0.32 mmol) of 4-hydroxy-6-phenyl-2*H*-pyran-2-one (**4b**), 12 mg (0.13 mmol) of β-alanine, and 1 mL of 2-propanol, flushed with argon and sealed. The reaction mixture was heated to 110 °C until complete consumption of the aldehyde **3** (Table 2), starting with 100 W. After reaching the final temperature the average radiation power was approx. 15 W. After cooling to r. t., 2 mL of water was added, and the reaction mixture was extracted five times with 5 mL of *tert*-butyl methyl ether. The combined organic layers were washed with 2 mL of brine and concentrated *in vacuo*. The crude product was purified by flash chromatography on 12.5 g of silica gel (diethyl ether/petroleum ether = 1 : 3) to give 57 mg (63 %) of **6l**.

*Typical procedure for the synthesis of (2RS)-2-isobutyl-3-isopropyl-7-phenyl-2H,5H-pyrano[4,3-b]pyran-5-one (**6l**) under microwave conditions using ionic liquids*

A microwave glass vial (8 mL) with a magnetic stirring bar was heated to 150 °C for 8 h and cooled to r. t. under argon. The vial was charged with 43 mg (0.28 mmol) of 2-isopropyl-5-methyl-2-hexenal (**3l**), 60 mg (0.32 mmol) of 4-hydroxy-6-phenyl-2*H*-pyran-2-one (**4b**), 12 mg (0.13 mmol) of β-alanine, and 1 g of the ionic liquid, flushed with argon and sealed. The reaction mixture was heated to 110 °C for 1 h, starting with 10 W. After reaching the final temperature the average radiation power was approx. 1 – 5 W. After cooling to r. t., the reaction mixture was extracted five times with 5 mL of *tert*-butyl methyl ether and centrifuged for separation of the layers. With **7c – e**, **8b**, **13**, and **14**, 2 mL of water was added before extraction. The combined organic layers were concentrated *in vacuo*; if water had been added, washing with 2 mL of brine was necessary. The crude product was purified by flash chromatography on 12.5 g of silica gel, using a solvent gradient [petroleum ether/methylene chloride = 1 : 3 (50 mL) to methylene chloride (200 mL)] to give **6l** in yields ranging from 3 to 47 % (see Tables 3 and 4). For ionic liquids **7d**, **10**, and **14**, the product was further purified by a second flash chromatography on 5.5 g of silica gel using methylene chloride as an eluent. The reaction mixtures containing **11** and **12** were directly applied onto 50 g of silica gel and separated using pure methylene chloride.

*(5aRS)-5a,6,7,8-Tetrahydro-3-phenyl-1H-cyclopenta[b]pyrano[3,4-e]pyran-1-one (**6a**)*

M. p. 129 °C. – R_f = 0.48 (SiO_2; PE/Et_2O = 1 : 1). – UV/Vis (CH_3CN): $\lambda_{max}(\lg\varepsilon_{max})$ = 257 (4.19), 381 nm (4.14). – IR (ATR): ν = 3055 (ar.-H), 2962 (C-H), 1705 (C=O), 1621, 1612 and 1538 (C=C), 1409 (C-H), 1171 and 1027 (C-O), 765 and 685 cm^{-1}(monosubst. ar.). – ^1H NMR (500 MHz, $CDCl_3$): δ = 1.70 – 1.92 (m, 2H, 7-H_2), 1.92 – 2.42 (m, 2H, 6-H_2), 2.42 – 2.62 (m, 2H, 8-H_2), 5.02 – 5.06

(m, 1H, 5a-H), 6.32 (q, $^4J_{9\text{-H},8\text{-H}2}$ = $^4J_{9\text{-H},5a\text{-H}}$ = 2.4 Hz, 1H, 9-H), 6.49 (s, 1H, 4-H), 7.42 – 7.46 (m, 3H, 3′-H, 5′-H and 4′-H), 7.78 – 7.82 (m, 2H, 2′-H and 6′-H). – ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.50 (C-7), 28.34 (C-8), 32.18 (C-6), 80.73 (C-5a), 97.61 (C-4), 103.53 (C-9a), 111.75 (C-9), 125.73 (C-2′ and C-6′), 129.13 (C-4′ or C-3′, C-5′), 131.00 (C-4′ or C-3′, C-5′), 131.52 (C-1′), 135.73 (C-8a), 159.48 (C-3), 162.20 (C-1), 164.25 (C-4a). – MS (EI, 70 eV): *m/z* (%) = 266 (100) $[M]^+$, 238 (96), 210 (9), 201 (18), 147 (7), 105 (47), 91 (22), 77 (45), 51 (16). – $C_{17}H_{14}O_3$ (266.29): calcd. C 76.68, H 5.30; found C 76.53, H 5.33.

*(2RS)-2,3-Dimethyl-7-phenyl-2H,5H-pyrano[4,3-b]pyran-5-one (**6b**)*

M. p. 110 °C. – R_f = 0.48 (SiO_2; PE/Et_2O = 1 : 1). – UV/Vis (CH_3CN): $\lambda_{max}(\lg\varepsilon_{max})$ = 256 (4.20), 291 (3.59), 377 nm (4.13). – IR (ATR): ν = 3066 (ar.-H), 2972 (C-H), 1688 (C=O), 1625 and 1553 (C=C), 1415 (C-H), 1184 and 1045 (C-O), 763 and 681 cm^{-1} (monosubst. ar.). – ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.45 (d, $^3J_{2\text{-CH3},2\text{-H}}$ = 6.6 Hz, 3H, 2-CH_3), 1.82 (s, 3H, 3-CH_3), 4.99 (q, $^3J_{2\text{-H},2\text{-CH3}}$ = 6.6 Hz, 1H, 2-H), 6.26 (s, 1H, 4-H), 6.45 (s, 1H, 8-H), 7.42 – 7.46 (m, 3H, 3′-H, 5′-H and 4′-H), 7.78 – 7.82 (m, 2H, 2′-H and 6′-H). – ^{13}C NMR (125 MHz, $CDCl_3$): δ = 19.22 (3-CH_3), 19.45 (2-CH_3), 76.76 (C-2), 97.55 (C-8), 100.47 (C-4a), 112.50 (C-4), 125.44 (C-2′ and C-6′), 128.84 (C-4′ or C-3′, C-5′), 130.63 (C-3), 130.70 (C-4′ or C-3′, C-5′), 131.28 (C-1′), 159.28 (C-7), 161.67 (C-5), 161.99 (C-8a). – MS (EI, 70 eV): *m/z* (%) = 254 (39) $[M]^+$, 239 (100) $[M–CH_3]^+$, 105 (33), 77 (28), 69 (6), 51 (10), 39 (4). – $C_{16}H_{14}O_3$ (254.28): calcd. C 75.57, H 5.55; found C 75.51, H 5.69.

*(2RS)-2-Ethyl-7-phenyl-2H,5H-pyrano[4,3-b]pyran-5-one (**6c**)*

R_f = 0.59 (SiO_2; PE/Et_2O = 3 : 7). – UV/Vis (CH_3CN): $\lambda_{max}(\lg\varepsilon_{max})$ = 202 (4.40), 253 (4.16), 292 (3.69), 311 (3.64), 376 nm (4.01). – IR (ATR): ν = 3061 (ar.-H), 2969 and 2935 (C-H), 1704 (C=O), 1621 and 1546 (C=C), 1453, 1426 and 1392 (C-H), 1185 and 1051 (C-O), 765 and 688 cm^{-1}(monosubst. ar.). – ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.05 (t, $^3J_{2'\text{-H3},1'\text{-H2}}$ = 7.5 Hz, 3H, 2′-H_3), 1.80 – 1.86 (m, 2H, 1′-H_2), 5.00 – 5.04 (m, 1H, 2-H), 5.48 (dd,$^3J_{3\text{-H},4\text{-H}}$ = $^3J_{3\text{-H},2\text{-H}}$ = 10.1 Hz, $^4J_{3\text{-H},1'\text{-H2}}$ = 3.3 Hz, 1H, 3-H), 6.45 (s, 1H, 8-H), 6.54 (d, $^3J_{4\text{-H},3\text{-H}}$ = 10.1 Hz, 1H, 4-H), 7.42 – 7.47 (m, 3H, 3″-H, 5″-H and 4″-H), 7.79 – 7.83 (m, 2H, 2″-H and 6″-H). – ^{13}C NMR (125 MHz, $CDCl_3$): δ = 8.88 (C-2′), 29.21 (C-1′), 79.16 (C-2), 97.72 (C-8), 100.13 (C-4a), 118.50 (C-4), 120.50 (C-3), 125.83 (C-2″ and C-6″), 129.13 (C-4″ or C-3″, C-5″), 131.18 (C-4″ or C-3″, C-5″), 131.44 (C-1″), 160.50 (C-7), 161.81 (C-5), 165.07 (C-8a). – MS (EI, 70 eV): *m/z* (%) = 254 (16) $[M]^+$, 225 (100) $[M–C_2H_5]^+$, 105 (32), 77 (26), 69 (6), 51 (8). – $C_{16}H_{14}O_3$ (254.28): calcd. C 75.57, H 5.55; found C 75.71, H 5.70.

*(2RS)-2-Isobutyl-3,7-diphenyl-2H,5H-pyrano[4,3-b]pyran-5-one (**6d**)*

M. p. 126 °C. – R_f = 0.57 (SiO_2; PE/Et_2O = 1 : 1). – UV/Vis (CH_3CN): $\lambda_{max}(\lg\varepsilon_{max})$ = 251 (4.35), 402 nm (4.31). – IR (ATR): ν = 3090 (ar.-H), 2955 (C-H), 1715 (C=O), 1608, 1573 and 1543 (C=C), 1495, 1447 and 1419 (C-H), 1177 and 1042 (C-O), 747 and 680 cm^{-1} (monosubst. ar). – ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.94 (d, $^3J_{2'\text{-CH3(A)},2'\text{-H}}$ = 6.6 Hz, 3H, 2′-$CH_{3(A)}$), 1.05 (d, $^3J_{2'\text{-CH3(B)},2'\text{-H}}$ = 6.6 Hz, 3H, 2′-$CH_{3(B)}$), 1.34 (ddd, $^2J_{1'\text{-HA},1'\text{-HB}}$ = 14.7 Hz, $^3J_{1'\text{-HA},2'\text{-H}}$ = 9.3 Hz, $^3J_{1'\text{-HA},2\text{-H}}$ = 2.5 Hz, 1H, 1′-H_A), 1.90 – 1.97 (m, 1H, 2′-H), 1.97 – 2.05 (ddd, $^2J_{1'\text{-HB},1'\text{-HA}}$ = 14.8 Hz, $^3J_{1'\text{-HB},2\text{-H}}$ = 10.7 Hz, $^3J_{1'\text{-HB},2'\text{-H}}$ = 4.4 Hz, 1H, 1′-H_B), 5.64 (dd, $^3J_{2\text{-H},1'\text{-HB}}$ = 10.6 Hz, $^3J_{2\text{-H},1'\text{-HA}}$ = 2.6 Hz, 1H, 2-H), 6.56 (s, 1H, 8-H), 6.96 (s, 1H, 4-H), 7.31 (bt, $^3J_{4''\text{-H},3''\text{-H}}$ = $^3J_{4''\text{-H},5''\text{-H}}$ =7.3 Hz, 1H, 4″-H), 7.39 (bt, $^3J_{3''\text{-H},4''\text{-H}}$ = $^3J_{5''\text{-H},4''\text{-H}}$ = $^3J_{3''-\text{H},2''-\text{H}}$ = $^3J_{5''\text{-H},6''\text{-H}}$ = 7.3 Hz, 2H, 3″-H and 5″-H), 7.45 – 7.50 (m, 5H, 2″-H, 6″-H, 3‴-H, 5‴-H and 4‴-H), 7.84 – 7.88 (m, 2H, 2‴-H and 6‴-H). – ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.71 (2-$CH_{3(B)}$), 23.58 (2-$CH_{3(A)}$), 24.61 (C-2′), 42.33 (C-1′), 77.00 (C-2), 97.77 (C-8), 102.18 (C-4a), 113.46 (C-4), 125.18 (C-2″, C-6″, C-3‴, C-5‴ or C-4‴), 125.87 (C-2‴ and C-6‴), 128.29 (C-4″ and C-5″), 129.16 (C-3″and C-5″), 129.18 (C-2″, C-6″, C-3‴, C-5‴ or C-4‴), 131.25 (C-2″, C-6″, C-3‴, C-5‴or C-4‴), 131.41 (C-1″), 131.78 (C-1‴), 136.34 (C-3), 160.43 (C-7), 161.97 (C-5), 162.73 (C-8a). – MS (EI, 70 eV): *m/z* (%) = 358 (78) $[M]^+$, 301 (100) $[M–C_4H_9]^+$, 151 (12), 115 (14), 105 (78), 77 (54), 69 (6) 41 (8). – $C_{24}H_{22}O_3$ (358.43): calcd. C 80.42, H 6.19; found C 80.34, H 6.26.

*(2RS)-2-(Furan-2-yl)-3-methyl-7-phenyl-2H,5H-pyrano [4,3-b]pyran-5-one (**6e**)*

M. p. 141 °C. – R_f = 0.28 (SiO_2; PE/Et_2O = 1 : 1). – UV/Vis (CH_3CN): $\lambda_{max}(\lg\varepsilon_{max})$ = 203 (4.46), 256 (4.27), 376 nm (4.17). – IR (ATR): ν = 3133 (ar.-H), 2916 (C-H), 1689 (C=O), 1619 and 1552 (C=C), 1494 and 1411 (C-H), 1179 and 1027 (C-O), 755 and 684 cm^{-1} (monosubst. ar.). – ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.83 (s, 3H, 3-CH_3), 5.85 (s, 1H, 2-H), 6.36 – 6.38 (m, 1H, 4′-H), 6.42 (s,1H, 3′-H), 6.43 (s, 1H, 8-H), 6.54 (s, 1H, 4-H), 7.40 – 7.44 (m, 3H, 3″-H, 5″-H and 4″-H), 7.46 – 7.48 (m, 1H, 5′-H), 7.74 – 7.79 (m, 2H, 2″-H and 6″-H). – ^{13}C NMR (125 MHz, $CDCl_3$): δ = 19.73 (3-CH_3), 74.71 (C-2), 97.72 (C-8), 100.87 (C-4a), 110.84 (C-3′), 110.92 (C-4′), 115.08 (C-4), 125.71 (C-2″ and C-6″), 126.11 (C-3), 129.09 (C-4″ or C-3″, C-5″), 131.04 (C-4″ or C-3″, C-5″), 131.41 (C-1″), 144.33 (C-5′), 150.66 (C-2′), 159.76 (C-7), 161.76 (C-8a), 161.87 (C-5). – MS (EI, 70 eV): *m/z* (%) = 306 (100) $[M]^+$, 291 (21) $[M–CH_3]^+$, 277 (10), 263 (6), 225 (4), 201 (6), 147 (10), 132 (20), 105 (43), 77 (40), 69 (8), 51 (12). – HRMS (EI, 70 eV): *m/z* = 306.08916 (calcd. 306.08920 for $C_{19}H_{14}O_4$, $[M]^+$).

*(2RS)-2-Octyl-7-phenyl-2H,5H-pyrano[4,3-b]pyran-5-one (**6f**)*

M. p. 59 °C. – R_f = 0.57 (SiO_2; PE/Et_2O = 1 : 1). – UV/Vis (CH_3CN): $\lambda_{max}(\lg\varepsilon_{max})$ = 202 (4.37), 246 (4.11), 292 (3.66), 376 nm (3.96). – IR (ATR): ν = 3087 (ar.-H), 2922 and 2852 (C-H), 1687 (C=O), 1453 and 1424 (C-H), 1190 and 1014 (C-O), 765 and 682 cm^{-1} (monosubst. ar.). – ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.89 (t, $^3J_{8'\text{-H3},7'\text{-H2}}$ = 6.8 Hz, 3H, 8′-H_3), 1.20 – 1.56 (m, 12H, 7′-H_2, 6′-H_2, 5′-H_2, 4′-H_2, 3′-H_2, 2′-H_2), 1.70 – 1.88 (m, 2H, 1′-H_2), 5.04 – 5.06 (m, 1H, 2-H), 5.49 (dd, $^3J_{3\text{-H},4\text{-H}}$ = 10.2 Hz, $^3J_{3\text{-H},2\text{-H}}$ = 3.3 Hz, 1H, 3-H), 6.45 (s, 1H, 8-H), 6.51 (dd, $^3J_{4\text{-H},3\text{-H}}$ = 9.0 Hz, 1H, 4-H), 7.42 – 7.48 (m, 3H, 3″-H, 5″-H and 4″-H), 7.78 – 7.84 (m, 2H, 2″-H and 6″-H). – ^{13}C NMR (125 MHz, $CDCl_3$): δ = 15.50 (C-8′), 22.88, 24.55, 29.44, 29.61, 29.68, 32.07 (C-2′, C-3′, C-4′, C-5′, C-6′ or C-7′), 36.14 (C-1′), 78.12 (C-2), 97.77 (C-8), 100.18 (C-4a), 118.24 (C-4), 120.90 (C-3), 125.83 (C-2″ and C-6″), 129.12 (C-4″ or C-3″, C-5″), 131.18 (C-4″ or C-3″, C-5″), 131.45 (C-1″), 160.48 (C-7), 161.82 (C-5), 164.97 (C-8a). – MS (EI, 70 eV): *m/z* (%) = 338 (12) $[M]^+$, 225 (100) $[M–C_8H_{17}]^+$, 105 (21), 77 (11), 69 (7), 41 (5). – HRMS (EI, 70 eV): *m/z* = 338.18946 (calcd. 338.18820 for $C_{22}H_{26}O_3$, $[M]^+$).

*(5aRS)-5a,6,8,9-Tetrahydro-3-phenyl-1H,7H-pyrano[4,3-b]chromen-1-one (**6g**)*

M. p. 135 °C. – R_f = 0.47 (SiO_2; PE/Et_2O = 1 : 1). – UV/Vis (CH_3CN): $\lambda_{max}(\lg\varepsilon_{max})$ = 204 (4.47), 257 (4.25), 289 (3.64), 386 nm (4.11). – IR (ATR): ν = 3002 (ar.-H), 2924 and 2861 (CH), 1706 (C=O), 1630 and 1552 (C=C), 1457 and 1422 (CH), 1197 and 1012 (C-O), 767 and 688 cm^{-1} (monosubst. ar.). – ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.37 (qt, $^2J_{8\text{-H(ax)},8\text{-H(eq)}}$ = $^3J_{8\text{-H(ax)},7\text{-H(ax)}}$ = $^3J_{8\text{-H(ax)},9\text{-H(ax)}}$ = 13.0 Hz, $^3J_{8\text{-H(ax)},9\text{-H(eq)}}$ = $^3J_{8\text{-H(ax)},7\text{-H(eq)}}$ = 3.7 Hz, 1H, 8-$H_{(ax)}$), 1.49 (qt, $^2J_{7\text{-H(ax)},7\text{-H(eq)}}$ = $^3J_{7\text{-H(ax)},6\text{-H(ax)}}$ = $^3J_{7\text{-H(ax)},8\text{-H(ax)}}$ = 13.3 Hz, $^3J_{7\text{-H(ax)},6\text{-H(eq)}}$ = $^3J_{7\text{-H(ax)},8\text{-H(eq)}}$ = 3.3 Hz, 1H, 7-$H_{(ax)}$), 1.80 (qd, $^2J_{6\text{-H(ax)},6\text{-H(eq)}}$ = $^3J_{6\text{-H(ax)},5a\text{-H(ax)}}$ = $^3J_{6\text{-H(ax)},7\text{-H(ax)}}$ = 12.8 Hz, $^3J_{6\text{-H(ax)},7\text{-H(eq)}}$ = 3.6 Hz, 1H, 6-$H_{(ax)}$), 1.80 (m, 1H, 8-$H_{(eq)}$), 1.90 – 1.96 (m, 1H, 7-$H_{(eq)}$), 2.03 (td, $^2J_{9\text{-H(ax)},9\text{-H(eq)}}$ = $^3J_{9\text{-H(ax)},8\text{-H(ax)}}$ = 13.6 Hz, $^3J_{9\text{-H(ax)},8\text{-H(eq)}}$ = 2.4 Hz, 1H, 9-$H_{(ax)}$), 2.16 – 2.22 (m, 1H, 6-$H_{(eq)}$), 2.46 (dt, $^2J_{9\text{-H(eq)},9\text{-H(ax)}}$ = 14.6 Hz, $^3J_{9\text{-H(eq)},8\text{-H(eq)}}$ = $^3J_{9\text{-H(eq)},8\text{-H(ax)}}$ = 1.7 Hz, 1H, 9-$H_{(eq)}$), 5.09 (dd, $^3J_{5a\text{-H(ax)},6\text{-H(ax)}}$ = 11.5 Hz, $^3J_{5a-\text{H(ax)},6\text{-H(eq)}}$ = 5.2 Hz, 1H, 5a-H), 6.15 (s, 1H, 10-H), 6.38 (s, 1H, 4-H), 7.40 – 7.46 (m, 3H, 3′-H, 5′-H and 4′-H), 7.76 – 7.81 (m, 2H, 2′-H and 6′-H). – ^{13}C NMR (125 MHz, $CDCl_3$): δ = 24.52 (C-7), 26.89 (C-8), 33.21 (C-9), 35.21 (C-6), 79.78 (C-5a), 97.32 (C-4), 98.89 (C-10a), 109.35 (C-10), 125.40 (C-2′ and C-6′), 128.83 (C-4′ or C-3′, C-5′), 130.65 (C-4′ or C-3′, C-5′), 131.31 (C-1′), 134.01 (C-9a), 159.14 (C-3), 161.78 (C-1), 163.04 (C-4a). – MS (EI, 70 eV): *m/z* (%) = 280 (100) $[M]^+$, 251 (93), 201 (12), 175 (4), 160 (10), 147 (9), 105 (55), 77 (40), 69 (8), 51 (10), 39 (6). – $C_{18}H_{16}O_3$ (280.32): calcd. C 77.12, H 5.75; found C 77.06, H 5.83.

*(2RS)-2-Methyl-2-(4-methyl-3-penten-1-yl)-7-phenyl-2H,5H-pyrano[4,3-b]pyran-5-one (**6h**)*

R_f = 0.56 (SiO_2; PE/Et_2O = 1 : 1). – UV/Vis (CH_3CN): $\lambda_{max}(\lg\varepsilon_{max})$ = 253 (4.12), 291 (3.59), 376 nm (3.95). – IR (ATR): ν = 3021 (ar.-H), 2969 and 2924 (C-H), 1707 (C=O), 1637, 1547 and 1496 (C=C), 1451 and 1422 (C-H), 1177 and 980 (C-O), 765 and 688 cm^{-1} (monosubst. ar.). – ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.47 (s, 3H, 2-CH_3), 1.60 (s, 3H, 4′-$CH_{3(A)}$), 1.67 (s, 3H, 4′-$CH_{3(B)}$), 1.78 – 1.87 (m, 2H, 1′-H_2), 2.12 (q, $^3J_{2'\text{-H2},1'\text{-H2}}$ = $^3J_{2'\text{-H2},3'\text{-H}}$ = 7.8 Hz, 2H, 2′-H_2), 5.09 (bt, $^3J_{3'\text{-H},2'\text{-H2}}$ = 7.2 Hz, 1H, 3′-H), 5.39 (d, $^3J_{3\text{-H},4\text{-H}}$ = 10.3 Hz, 1H, 3-H), 6.44 (s, 1H, 8-H), 6.52 (d, $^3J_{4\text{-H},3\text{-H}}$ = 10.3 Hz, 1H, 4-H), 7.43 – 7.47 (m, 3H, 3″-H, 5″-H and 4″-H), 7.80 – 7.84 (m, 2H, 2″-H and 6″-H). – ^{13}C NMR (125 MHz, $CDCl_3$): δ = 17.91 (4′-$CH_{3(A)}$), 22.86 (C-2′), 25.90 (4′-$CH_{3(B)}$), 27.84 (2-CH_3), 42.09 (C-1′), 83.09 (C-2), 97.96 (C-8), 99.27 (C-4a), 117.23 (C-4), 123.66 (C-3′), 124.61 (C-3), 125.81 (C-2″ and C-6″), 129.12 (C-4″ or C-3″, C-5″), 131.12 (C-4″ or C-3″, C-5″), 131.51 (C-1″), 132.50 (C-4′), 160.32 (C-7), 161.94 (C-5), 164.52 (C-8a). – MS (EI, 70 eV): *m/z* (%) = 322 (13) $[M]^+$, 307 (3) $[M–CH_3]^+$, 279 (4), 239 (100) $[M–C_6H_{11}]^+$, 201 (2), 147 (2), 105 (28), 77 (19), 69 (7), 41 (18). – $C_{21}H_{22}O_3$ (322.40): calcd. C 78.23, H 6.88; found C 78.15, H 7.05.

*(5aRS)-8,9-Dihydro-5a,9,9-trimethyl-3-phenyl-1H,5aH-pyrano[4,3-b]chromen-1-one (**6i**)*

R_f = 0.43 (SiO_2; PE/Et_2O = 1 : 1). – UV/Vis (CH_3CN): $\lambda_{max}(\lg\varepsilon_{max})$ = 203 (3.93), 256 (3.71), 290 (3.12), 377 nm (3.64). – IR (ATR): ν = 3033 (ar.-H), 2964 (C-H), 1704 (C=O), 1615, 1578 and 1549 (C=C), 1452, 1409 and 1366 (C-H), 1215 and 1046 (C-O), 765 and 700 cm^{-1} (monosubst. ar.). – ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.18 (s, 3H, 9-$CH_{3(A)}$), 1.31 (s, 3H, 9-$CH_{3(B)}$), 1.51 (s, 3H, 5a-CH_3), 1.99 (dd, $^2J_{8\text{-HA},8\text{-HB}}$ = 17.3 Hz, $^3J_{8\text{-HA},7\text{-H}}$ = 5.6 Hz, 1H, 8-H_A), 2.15 (d, $^2J_{8\text{-HB},8\text{-HA}}$ = 17.3 Hz, 1H, 8-H_B), 5.82 (bd, $^3J_{6\text{-H},7\text{-H}}$ = 10.0 Hz, 1H, 6-H), 5.95 – 6.00 (m, 1H, 7-H), 6.44 (s, 1H, 10-H), 6.52 (s, 1H, 4-H), 7.43 – 7.47 (m, 3H, 3′-H, 5′-H and 4′-H), 7.80 – 7.85 (m, 2H, 2′-H and 6′-H). – ^{13}C NMR (125 MHz, $CDCl_3$): δ = 24.84 (5a-CH_3), 28.55 (9- $CH_{3(A)}$), 28.72 (9- $CH_{3(B)}$), 36.08 (C-9), 40.03 (C-8), 79.42 (C-5a), 98.04 (C-4), 102.52 (C-10a), 111.19 (C-10), 125.77 (C-2′ and C-6′), 129.00 (C-3′, C-5′, C-4′ or C-6), 129.13 (C-3′, C-5′, C-4′ or C-6), 130.12 (C-7), 131.03 (C-4′ or C-3′, C-5′), 131.56 (C-1′), 140.61 (C-9a), 159.78 (C-3), 162.27 (C-1), 163.16 (C-4a). – MS (EI, 70 eV): *m/z* (%) = 320 (80) $[M]^+$, 305 (100) $[M–CH_3]^+$, 277 (24), 263 (5), 201 (22), 174 (17), 147 (31), 105 (78), 77 (54), 69 (21). –

HRMS (EI, 70 eV): *m/z* = 320.14199 (calcd. 320.14124 for $C_{21}H_{20}O_3$, $[M]^+$).

*(5aRS)-5a,6,8,9-Tetrahydro-5a,9,9-trimethyl-3-phenyl-1H,7H-pyrano[4,3-b]chromen-1-one (**6j**)*

M. p. 154 °C. – R_f = 0.63 (SiO_2; PE/Et_2O = 1 : 1). – UV/Vis (CH_3CN): $\lambda_{max}(\lg\varepsilon_{max})$ = 204 (4.42), 256 (4.19), 380 nm (4.13). – IR (ATR): ν = 2937 (C-H), 1706 (C=O), 1617 and 1556 (C=C), 1456 and 1383 (C-H), 1231 and 1050 (C-O), 758 and 685 cm^{-1} (monosubst. ar.). – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.17 (s, 3H, 9-$CH_{3(ax)}$), 1.26 (s, 3H, 9-$CH_{3(eq)}$), 1.42 (td, $^2J_{8\text{-H(ax)},8\text{-H(eq)}}$ = $^3J_{8\text{-H(ax)},7\text{-H(ax)}}$ = 12.9 Hz, $^3J_{8\text{-H(ax)},7\text{-H(eq)}}$ = 4.6 Hz, 1H, 8-$H_{(ax)}$), 1.48 – 1.54 (m, 1H, 8-$H_{(eq)}$), 1.52 (s, 3H, 5a-$CH_{3(ax)}$), 1.67 (qt, $^2J_{7\text{-H(ax)},7\text{-H(eq)}}$ = $^3J_{7\text{-H(ax)},6\text{-H(ax)}}$ = $^3J_{7\text{-H(ax)},8\text{-H(ax)}}$ = 13.8 Hz, $^3J_{7\text{-H(ax)},6\text{-H(eq)}}$ = $^3J_{7\text{-H(ax)},8\text{-H(eq)}}$ = 3.4 Hz, 1H, 7-$H_{(ax)}$), 1.70 – 1.76 (m, 1H, 7-$H_{(eq)}$), 1.90 (td, $^2J_{6\text{-H(ax)},6\text{-H(eq)}}$ = $^3J_{6\text{-H(ax)},7\text{-H(ax)}}$ = 13.1 Hz, $^3J_{6\text{-H(ax)},7\text{-H(eq)}}$ = 4.8 Hz, 1H, 6-$H_{(ax)}$), 2.05 – 2.16 (m, 1H, 6-$H_{(eq)}$), 6.41 (s, 1H, 10-H), 6.46 (s, 1H, 4-H), 7.42 – 7.45 (m, 3H, 3′-H, 5′-H and 4′-H), 7.79 – 7.83 (m, 2H, 2′-H and 6′-H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.93 (C-7), 26.03 (5a-$CH_{3(ax)}$), 30.49 (9-$CH_{3(ax)}$), 30.73 (9-$CH_{3(eq)}$), 35.97 (C-9), 39.25 (C-8), 39.62 (C-6), 82.13 (C-5a), 97.68 (C-4), 101.49 (C-10a), 110.84 (C-10), 125.44 (C-2′ and C-6′), 128.83, 130.68 (C-3′, C-4′, C-5′), 131.35 (C-1′), 143.49 (C-9a), 159.39 (C-3), 161.99 (C-1), 162.44 (C-4a). – MS (EI, 70 eV): *m/z* (%) = 322 (28) $[M]^+$, 307 (100) $[M–CH_3]^+$, 265 (4), 201 (10), 147 (5), 105 (25), 77 (12), 69 (4). – $C_{21}H_{22}O_3$ (322.40): calcd. C 78.23, H 6.88; found C 77.98, H 6.63.

*(2RS)-2-Methyl-3,7-diphenyl-2H,5H-pyrano[4,3-b]pyran-5-one (**6k**)*

M. p. 133 °C. – R_f = 0.55 (SiO_2; PE/Et_2O = 1 : 1). – UV/Vis (CH_3CN): $\lambda_{max}(\lg\varepsilon_{max})$ = 250 (4.34), 401 nm (4.32). – IR (ATR): ν = 3100 (ar.-H), 2960 (C-H), 1713 (C=O), 1626, 1607 and 1542 (C=C), 1446 and 1419 (C-H), 1180 and 1023 (C-O), 751 and 685 cm^{-1} (monosubst. ar.). – ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.51 (d, $^3J_{2\text{-CH3},2\text{-H}}$ = 6.6 Hz, 3H, 2-CH_3), 5.70 (q, $^3J_{2\text{-H},2\text{-CH3}}$ = 6.6 Hz, 1H, 2-H), 6.56 (s, 1H, 8-H), 6.97 (s, 1H, 4-H), 7.31 (t, $^3J_{4'\text{-H},3'\text{-H}}$ = $^3J_{4'\text{-H},5'\text{-H}}$ = 7.3 Hz, 1H, 4′-H), 7.39 (t, $^3J_{3'\text{-H},2'\text{-H}}$ = $^3J_{3'\text{-H},4'\text{-H}}$ = $^3J_{5'\text{-H},4'\text{-H}}$ = $^3J_{5'\text{-H},6'\text{-H}}$ = 7.6 Hz, 2H, 3′-H, 5′-H), 7.45 – 7.50 (m, 5H, 2′-H, 6′-H, 3″-H, 5″-H and 4″-H), 7.83 – 7.87 (m, 2H, 2″-H and 6″-H). – ^{13}C NMR (125 MHz, $CDCl_3$): δ = 20.05 (2-CH_3), 75.02 (C-2), 97.56 (C-8), 101.37 (C-4a), 112.85 (C-4), 124.95 (C-2′, C-6′, C-3″, C-5″ or C-4″), 125.59 (C-2″ and C-6″), 128.07 (C-2′, C-6′, C-3″, C-5″ or C-4″), 128.87 (C-3′ and C-5′), 128.92 (C-4′ and C-6′), 130.98 (C-2′, C-6′, C-3″, C-5″ or C-4″), 131.13 (C-1″), 131.86 (C-3), 135.88 (C-1′), 160.09 (C-7), 161.72 (C-5), 162.46 (C-8a). – MS (EI, 70 eV): *m/z* (%) = 316 (53) $[M]^+$, 301 (100) $[M–CH_3]^+$, 239 (5), 141 (11), 105 (42), 77 (30), 69 (7), 51 (7). – HRMS (EI, 70 eV): *m/z* = 316.10936 (calcd. 316.10995 for $C_{21}H_{16}O_3$, $[M]^+$).

*(2RS)-2-Isobutyl-3-isopropyl-7-phenyl-2H,5H-pyrano[4,3-b]pyran-5-one (**6l**)*

R_f = 0.53 (SiO_2; PE/Et_2O = 1 : 1). – UV/Vis (CH_3CN): $\lambda_{max}(\lg\varepsilon_{max})$ = 204 (4.32), 257 (4.10), 290 (3.54), 379 nm (4.03). – IR (ATR): ν = 3069 (ar.-H), 2958 (C-H), 1710 (C=O), 1622 and 1551 (C=C), 1452 and 1384 (C-H), 1189 and 1038 (C-O), 760 and 690 cm^{-1} (monosubst. ar.). – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.91 (d, $^3J_{2'\text{-CH3(A)},2'\text{-H}}$ = 6.4 Hz, 3H, 2′-$CH_{3(A)}$), 1.00 (d, $^3J_{2'\text{-CH3(B)},2'-\text{H}}$ = 6.4 Hz, 3H, 2′-$CH_{3(B)}$), 1.12 (d, $^3J_{1''\text{-CH3(A)},1''\text{-H}}$ = 6.9 Hz, 3H, 1″-$CH_{3(A)}$), 1.18 (d, $^3J_{1''\text{-CH3(B)},1''\text{-H}}$ = 6.9 Hz, 3H, 1″-$CH_{3(B)}$), 1.19 – 1.28 (m, 1H, 1′-H_{AorB}), 1.82 – 1.96 (m, 2H, 1′-H_{BorA} and 2′-H), 2.22 (sept, $^3J_{1''\text{-H},1''\text{-(CH3)2}}$ = 6.7 Hz, 1H, 1″-H), 4.93 (dd, $^3J_{2\text{-H},1'\text{-HA}}$ = 10.3 Hz, $^3J_{2\text{-H},1'\text{-HB}}$ = 2.1 Hz, 1H, 2-H), 6.29 (s, 1H, 4-H), 6.47 (s, 1H, 8-H), 7.40 – 7.48 (m, 3H, 2‴-H, 6‴-H or 3‴-H, 5‴-H; 4‴-H), 7.77 – 7.85 (m, 2H, 2‴-H, 6‴-H or 3‴-H, 5‴-H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.93 (1″-$CH_{3(B)}$), 21.75 (2′-$CH_{3(B)}$), 22.62 (1″-$CH_{3(A)}$), 23.74 (2′-$CH_{3(A)}$) 24.60 (C-2′), 31.10 (C-1″), 42.34 (C-1′), 77.63 (C-2), 97.91 (C-8), 101.88 (C-4a), 110.06 (C-4), 125.75, 129.11, 130.99 (C-2‴, C-3‴, C-4‴, C-5‴, C-6‴), 131.56 (C-1‴), 141.05 (C-3), 159.71 (C-7), 162.05 (C-5 or C-8a), 162.22 (C-5 or C-8a). – MS (EI, 70 eV): *m/z* (%) = 324 (23) $[M]^+$, 281 (5) $[M–C_3H_7]^+$, 267 (100) $[M–C_4H_9]^+$, 225 (2), 147 (1), 126 (5), 105 (31), 77 (16), 43 (6). – HRMS (EI, 70 eV): *m/z* = 324.17255 (calcd. 324.17313 for $C_{21}H_{24}O_3$, $[M]^+$).

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[1] a) C. O. Kappe, A. Stadler, *Microwaves in Organic and Medicinal Chemistry*, Wiley-VCH, Weinheim, **2005**; b) B. L. Hayes, *Microwave Synthesis: Chemistry at the Speed of Light*, CEM Publishing, Matthews, NC, **2002**; c) A. Loupy (Ed.), *Microwaves in Organic Synthesis*, Wiley-VCH, Weinheim, **2002**.

[2] P. Wasserscheid, W. Keim, *Angew. Chem*. **2000**, *112*, 3926 – 3945; *Angew. Chem. Int. Ed.* **2000**, *39*, 3772 – 3789.

[3] a) E. S. H. El Ashry, A. A. Kassem, E. Ramadan in *Advances in Heterocyclic Chemistry*, Vol. 90 (Ed.: A. R. Katritzky), Elsevier, Amsterdam, **2006**, pp. 1 – 123; b) E. S. H. El Ashry, E. Ramadan, A. A. Kassem, M. Hagar in *Advances in Heterocyclic Chemistry*, Vol. 88 (Ed.: A. R. Katritzky), Elsevier, Amsterdam, **2005**, pp. 1 – 110.

[4] a) H. Valizadeh, A. Shockravi, H. Gholipur, *J. Heterocycl. Chem.* **2007**, *44*, 867 – 870; b) B. C. Ranu, R. Jana, *Eur. J. Org. Chem.* **2006**, 3767 – 3770; c) D. C. Forbes, A. M. Law, D. W. Morrison, *Tetrahedron Lett.* **2006**, *47*, 1699 – 1703; d) Y. Hu, P. Wei, H. Huang, Z.-G. Le, Z.-C. Chen, *Synth. Commun.* **2005**, *35*, 2955 – 2960; e) Y. Hu, J. Chen, Z.-G. Le, Q.-G. Zheng, *Synth. Commun.* **2005**, *35*, 739 – 744; f) Y. Hu, Z.-C. Chen, Z.-G. Le, Q.-G. Zheng, *Synth. Commun.* **2004**, *34*, 4521 – 4529; g) Z.-C. Chen, Q.-G. Zheng, *Synthesis* **2003**, 555 – 559; h) R. V. Hangarge, D. V. Jarikote, M. S. Shingare, *Green Chem.* **2002**, *4*, 266 – 268.

[5] a) M. Kidwai, K. Singhal, S. Kukreja, *Can. J. Chem.* **2008**, *86*, 799 – 802; b) M. Baidossi, A. V. Joshi, S. Mukhopadhyay, Y. Sasson, *Tetrahedron Lett.* **2005**, *46*, 1885 – 1887; c) J. S. Yadav, B. V. S. Reddy, V. Naveenkumar, R. Srinivasa Rao, K. Nagaiah, *Synthesis* **2004**, 1783 – 1788.

[6] a) M. A. P. Martins, C. P. Frizzo, D. N. Moreira, N. Zanatta, H. G. Bonacorso, *Chem. Rev.* **2008**, *108*, 2015 – 2050; b) J.-C. Plaquevent, J. Levillain, F. Guillen, C. Malhiac, A.-C. Gaumont, *Chem. Rev.* **2008**, *108*, 5035 – 5060; c) P. Domínguez de María, *Angew. Chem*. **2008**, *120*, 7066 – 7075; *Angew. Chem. Int. Ed.* **2008**, *47*, 6960 – 6968; d) K. Bica, P. Gaertner, *Eur. J. Org. Chem.* **2008**, 3235 – 3250.

[7] a) J. Shah, J. Liebscher, *Synthesis* **2008**, 917 – 920; b) S. Li, Y. Lin, H. Xie, S. Zhang, J. Xu, *Org. Lett.* **2006**, *8*, 391 – 394; c) A. Zhu, T. Jiang, B. Han, J. Huang, J. Zhang, X. Ma, *New J. Chem.* **2006**, *30*, 736 – 740; d) L. C. Branco, P. M. P. Gois, N. M. T. Lourenço, V. B. Kurteva, C. A. M. Afonso, *Chem. Commun.* **2006**, 2371 – 2372; e) T. Isobe, K. Fukuda, T. Ishikawa, *J. Org. Chem.* **2000**, *65*, 7770 – 7773.

[8] a) P. Wang, S. M. Zakeeruddin, M. Grätzel, W. Kantlehner, J. Mezger, E. V. Stoyanov, O. Scherr, *Appl. Phys. A* **2004**, *79*, 73 – 77; b) A. Boesmann, T. J. S. Schubert, *Ger. Offen.*, DE 102004033021 A1 20060202, **2006**.

[9] a) V. Polshettiwar, R. S. Varma, *Acc. Chem. Res.* **2008**, *41*, 629 – 639; b) J. Habermann, S. Ponzi, S. V. Ley, *Mini-Rev. Org. Chem.* **2005**, *2*, 125 – 137; c) N. E. Leadbeater, H. M. Torenius, H. Tye, *Comb. Chem. High Throughput Screening* **2004**, *7*, 511 – 528.

[10] a) K. Shiomi, H. Tomoda, K. Otoguro, S. Omura, *Pure Appl. Chem.* **1999**, *71*, 1059 – 1064; b) H. Tomoda, N. Tabata, D.-J. Yang, H. Takayanagi, H. Nishida, S. Omura, *J. Antibiot.* **1995**, *48*, 495 – 503.

[11] a) M.-C. Rho, H. S. Lee, K.-T. Chang, H. Y. Song, O. E. Kwon, S. W. Lee, J. S. Ko, S. G. Hong, Y.-K. Kim, *J. Antibiot.* **2002**, *55*, 211 – 214; b) G. Erkel, J. Rether, T. Anke, O. Sterner, *J. Antibiot.* **2003**, *56*, 337 – 343; c) S. W. Lee, M.-C. Rho, J.-H. Choi, K. Kim, Y. S. Choi, H. S. Lee, Y. K. Kim, *J. Microbiol. Biotechnol.* **2008**, *18*, 1785 – 1788;

[12] a) H. Leutbecher, L. A. D. Williams, H. Rösner, U. Beifuss, *Bioorg. Med. Chem. Lett.* **2007**, *17*, 978 – 982; b) E. M. Perchellet, J. B. Ladesich, M. J. Magill, Y. Chen, D. H. Hua, J.-P. Perchellet, *Anti-Cancer Drugs* **1999**, *10*, 489 – 504; c) S. W. Newell, E. M. Perchellet, J. B. Ladesich, J. A. Freeman, Y. Chen, L. Liu, D. H. Hua, S. L. Kraft, R. J. Basaraba, J.-P. Perchellet, *Int. J. Oncol.* **1998**, *12*, 433 –442.

[13] S. Lewis, J. Karrer, S. Saleh, Y. Chen, Z. Tan, D. Hua, J. McGill, Y.-P. Pang, B. Fenwick, A. Brightman, D. Takemoto, *Mol. Vis.* **2001**, *7*, 164 – 171.

[14] a) S. Rana, H.-S. Hong, L. Barrigan, L.-W. Jin, D. H. Hua, *Bioorg. Med. Chem. Lett.* **2009**, *19*, 670 – 674; b) H.-S. Hong, S. Rana, L. Barrigan, A. Shi, Y. Zhang, F. Zhou, L.-W. Jin, D. H. Hua, *J. Neurochem.* **2009**, *108*, 1097 – 1108; c) I. Maezawa, H.-S. Hong, H.-C. Wu, S. K. Battina, S. Rana, T. Iwamoto, G. A. Radke, E. Pettersson, G. M. Martin, D. H. Hua, L.-W. Jin, *J. Neurochem.* **2006**, *98*, 57 – 67; d) D. H. Hua, X. Huang, M. Tamura, Y. Chen, M. Woltkamp, L.-W. Jin, E. M. Perchellet, J.-P. Perchellet, P. K. Chiang, I. Namatame, H. Tomoda, *Tetrahedron* **2003**, *59*, 4795 – 4803.

[15] a) H. C. Shen, J. Wang, K. P. Cole, M. J. McLaughlin, C. D. Morgan, C. J. Douglas, R. P. Hsung, H. A. Coverdale, A. I. Gerasyuto, J. M. Hahn, J. Liu, H. M. Sklenicka, L.-L. Wei, L. R. Zehnder, C. A. Zificsak, *J. Org. Chem.* **2003**, *68*, 1729 – 1735; b) R. P. Hsung, L.-L. Wei, H. M. Sklenicka, H. C. Shen, M. J. McLaughlin, L. R. Zehnder in *Trends in Heterocycl. Chem.*, Vol. 7 (Eds.: R. A. Abramovitch, A. Brossi, J. P. Kutney, S. Oae, S. W. Pelletier, C. Szantay, M. Tisler), Research Trends, Trivandrum, India, **2001**, pp. 1 – 24; c) D. H. Hua, Y. Chen, H.-S. Sin, M. J. Maroto, P. D. Robinson, S. W. Newell, E. M. Perchellet, J. B. Ladesich, J. A. Freeman, J.-P. Perchellet, P. K. Chiang, *J. Org. Chem.* **1997**, *62*, 6888 – 6896.

[16] H. Leutbecher, J. Conrad, I. Klaiber, U. Beifuss, *QSAR Comb. Sci.* **2004**, *23*, 895 – 898.

[17] J. V. N. Vara Prasad, K. S. Para, P. J. Tummino, D. Ferguson, T. J. McQuade, E. A. Lunney, S. T. Rapundalo, B. L. Batley, G. Hingorani, J. M. Domagala, S. J. Gracheck, T. N. Bhat, B. Liu, E. T. Baldwin, J. W. Erickson, T. K. Sawyer, *J. Med. Chem.* **1995**, *38*, 898 – 905.