Syntheses of γ-Oxo Acids or γ-Oxo Esters by Photooxygenation of Furanic Compounds and Reduction Under Ultrasound: Application to the Synthesis of 5-Aminolevulinic Acid Hydrochloride

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Received 29 June 1994; revised 11 October 1994

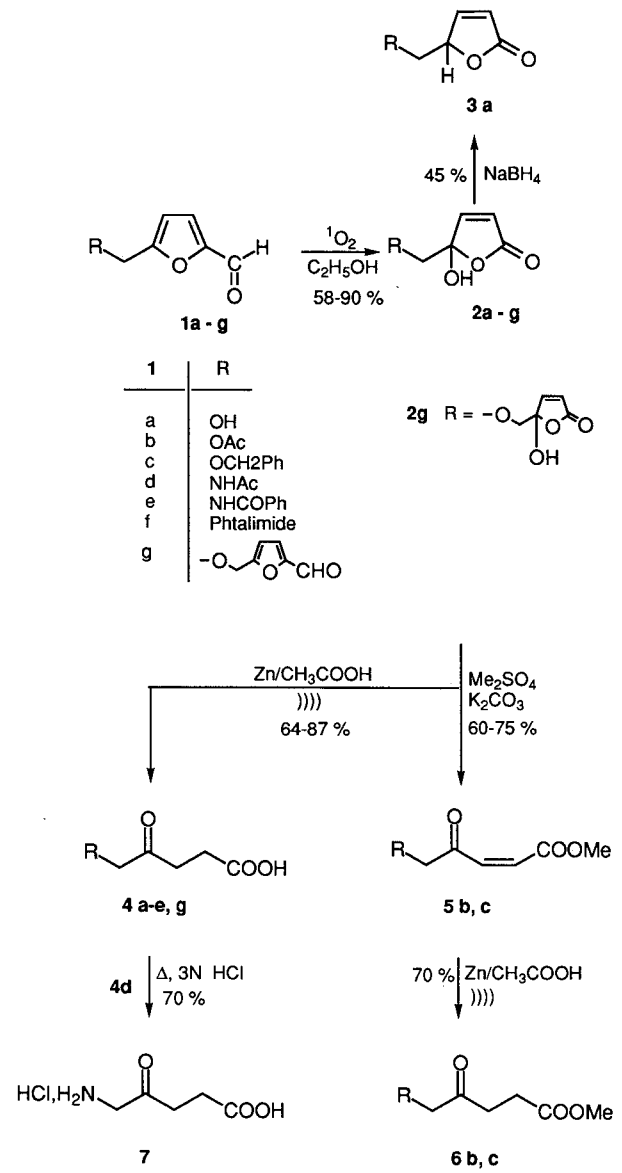
The photooxygenation of 5-hydroxymethyl-2-furfural **(1a)** or derivatives **1b–g** yields 4-hydroxy-Δ^2-butenolides **2** which are the percursors of butenolides **3** or α,β-unsaturated γ-oxo esters **5**. The selective reduction of olides **2** or oxo esters **5** with zinc in acetic acid under sonication leads to γ-oxo acids **4** or γ-oxo esters **6**. The photooxygenation of amino derivative **1d**, followed by selective reduction of corresponding lactone **2d**, gives 5-aminolevulinic acid hydrochloride **(7)** (ALA) after hydrolysis.

The photooxygenation of furfural derivatives yields 4-hydroxy-Δ^2-butenolides.[1–4] For instance, 5-hydroxymethyl-2-furfural (HMF) **(1a)**, obtained by acid-catalysed dehydration of saccharides,[5–8] reacts with singlet oxygen giving 5-hydroxy-5-(hydroxymethyl)furan-2(5*H*)-one **(2a)**.[9] The unsaturated lactone **2a** has been reduced to 5-(hydroxymethyl)furan-2(5*H*)-one **(3a)**[9] probably via the tautomeric linear ketonic form (Scheme 1). Such Δ^2-butenolides **2** are easily transformed into butanolides by hydrogenation over palladium[10] or platinum(IV) oxide.[11]

However, no example has been reported for the direct transformation of butenolides such as the compounds **2** into γ-oxo acids **4** (Scheme 1). As the reduction of the hydroxy compound **2a** into the unsaturated lactone **3a**[9] proceeds via an α,β-unsaturated γ-dicarbonyl chain, we have considered some of the reduction procedures that are used for the selective reduction of the C=C bond of α,β-unsaturated γ-dicarbonyl compounds. D'Auria et al.[12] noted that available procedures for the selective reduction of the C=C bond in unsaturated dicarbonyl compounds either require expensive reagents or afford only low yields. They reported a new method using sodium iodide and hydrochloric acid in acetone which, unfortunately, is not applicable to the reduction of butenedioic acids or their esters. More recently, Marchand and Reddy[13] published a new procedure with unactivated powdered zinc in acetic acid at room temperature under sonication. Ultrasound avoids using activated zinc[14] or heating at high temperature (180 °C).[15] This new method offers a general and highly efficient selective reduction of the C=C bond in α,β-unsaturated dicarbonyl compounds, including diacids and diesters.

We now report the selective reduction of different 4-hydroxy-Δ^2-butenolides **2** (Table 1) or α,β-unsaturated γ-oxo esters **5** using Marchand's method.

The hydroxymethyl-2-furfural derivatives **1** have been synthesized as described below. The acetate **1b** was prepared according Fenton's method.[16] The benzyl ether **1c** was obtained from **1a** by using benzyl bromide and silver oxide. The conversion of **1a** into 5-acetamido **1d**[17] or 5-benzamido derivative **1e**[17] was performed by using the Ritter reaction, while the Mitsunobu reaction led to 5-phthalimidomethyl-2-furfural **(1f)**. Finally, the ether **1g** was obtained by a condensation reaction as described by Nigay.[18]



Scheme 1

All these substrates were converted into 4-hydroxy-Δ^2-butenolides **2a–g** by a photooxygenation reaction under specific conditions. The transesterification of compounds **2b** and **2c** with dimethyl sulfate and potassium carbonate led to the *cis*-α,β-unsaturated γ-oxo esters **5b** and **5c**.

The results of the selective reduction of compounds **2a–g** and **5b,c** under sonication yielding mainly the saturated

Table 1. Reduction of Butenolides **2** or α,β-Unsaturated γ-Oxo-Esters **5**

Compound	Equiv Zn (mol)	Reaction time (h)	Conversion (%)	Products	Yield (%)
2a	15	3	100	**4a**	65
2b	9.7	1.5	90	**4b**	84
2c	15	5	100	**4c**	64
2d	9.5	1.5	100	**4d**	87
2d[a]	9.5	1.5	81	**4e**	45
2e	9.5	2	100	**4f**	85
2f	9.5	2	100	unidentified products	
2g	25	4	100	**4g**	70
5a	15	5	100	**6a**	70
5b	15	5	100	**6b**	70

[a] Without sonication.

γ-oxo acids **4** or esters **6** are summarized in Table 1. The conversion is quantitative except for the ester **2b** (conversion = 90%) after a time of sonication of 1.5–5 h. The yields of isolated products (between 64 and 87%) are higher with ester **2b** or amido derivatives **2d** or **2e** than with hydroxy- or benzylbutenolides **2a** or **2c**. Unfortunately, the phthalimido derivative **2f** is damaged leading to a mixture of several products. The selective reduction works also with the α,β-unsaturated γ-oxo esters **5b** and **5c** giving the corresponding saturated esters **6b** and **6c** with a yield of 70%. It should be pointed out that the selective reduction is easier if the butenolides **2** contain an ester or an acetamido group. As can be seen in Table 1, the compounds **2b,d** and **e** need less zinc and less time than the alcohol **2a** or its benzyl ether **2c**.

This method was applied to the ether **2g** having two butenolide moieties. A fair yield was obtained with only 12.5 equivalents of zinc for each ring. This amount of zinc was less important than that employed for the corresponding monobutenolide **2a**. During the reduction of **2g** we did not observe (chromatography or NMR) the formation of a product corresponding to the reduction of one double bond only.

The influence of the ultrasound was checked with 4-acetamidomethyl-4-hydroxy-Δ^2-butenolides **(2d)**. Under the same conditions, but without sonication, a rapid degradation was detected by thin layer chromatography and the yield of **4d** was limited to 45%.

The structure of the acids **4** or the esters **6** was determined by NMR spectroscopy. The transformation was monitored in the ^{1}H NMR spectrum by the presence of two triplets ($\delta = 1.02$ and 2.64) corresponding to the two methylenic groups and was confirmed in the ^{13}C NMR spectrum by the chemical shift of the carbon C_1 of **4** or **6**.

Using this process we have synthesized 5-aminolevulinic acid hydrochloride **(7)** in only four steps from **1a**[17] with a total yield of 24%. The other reported syntheses from oxazolinone,[19–21] unsaturated nitroso compound,[22] phthalimido derivatives[23] or different furans or tetrahydrofurans[24–26] need at least five steps, and give yields of less than 25%.

In conclusion, the selective reduction of 4-hydroxybutenolides **2** or α,β-unsaturated γ-oxo esters **5** gives a good yield with unactivated zinc in acetic acid under sonication. This work compliments Marchand's method. This process associated with the photooxygenation of starting furanic compounds **1** leads to γ-oxo acid **4** or γ-oxo esters **5** and was applied to the synthesis of 5-aminolevulinic acid hydrochloride **(7)** (ALA).

Mps are uncorrected and were recorded on an Electrothermal 9100 melting point apparatus. Infrared spectra were recorded on a Perkin-Elmer spectrophotometer. ^{1}H NMR spectra were recorded on a Varian EM 360 (60 MHz) and a Bruker AC 200 or AM 300 instrument; chemical shifts are given in ppm relative to TMS. ^{13}C NMR spectra were recorded on a Bruker AC 200. Merck Kieselgel 60 (0.040–0.063 mm) or Amicon (60 A) was used for flash column chromatography; Merck Kieselgel 60 F_{254} on aluminium was used for TLC tests. The photooxygenations were performed according to the literature[9] procedure. The reactions under sonication were performed on ultrasonic cleaning-bath Branson (90 W, 47 KHz) or ultrasonic sonde Vibra-Cell (20 KHz, max 600 W).

Compounds **1b–e** and **5b,c** gave C, H (and N where appropriate) analysis ± 0.23%; also see Tables 2 and 3.

5-Acetoxymethyl-2-furfural (1b):
Ac_2O (20 mL, 2.5 equiv) was added dropwise to a stirred mixture of 5-hydroxymethyl-2-furfural **(1a)** (12 g, 95 mmol) and NaOAc (14.5 g, 198 mmol) maintained at 80 °C. The mixture was stirred for 2.5 h, then cooled to 20 °C and hydrolyzed with water (45 mL). The solution was evaporated under reduced pressure. The solid was collected on a filter and the filtrate was extracted with Et_2O (5 × 20 mL). After drying ($MgSO_4$), filtration, evaporation of the solvent, the crude product (14.3 g) was purified by distillation (bp 95 °C at 1 Torr) to give **1b** which slowly crystallized; yield: 12.9 g (81%); mp 33 °C.

IR (neat): $\nu = 1750$ (C=O ester), 1680 cm^{-1} (C=O aldehyde).

^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 9.63$ (s, 1 H, CHO), 7.21 (d, 1 H, $J = 3.6$ Hz, H3), 6.58 (d, 1 H, $J = 3.6$ Hz, H4), 5.12 (s, 2 H, CH_2), 2.1 (s, 3 H, CH_3).

5-Benzyloxymethyl-2-furfural (1c):
Benzyl bromide (4.3 g, 25.1 mmol) and silver oxide (2.9 g, 12.6 mmol) were successively added to a stirred solution of **1a** (2 g, 15.8 mmol) dissolved in DMF (20 mL). The mixture was stirred for 53 h at r.t. The solution was evaporated under reduced pressure. The residue was chromatographed (silica; hexane–EtOAc, 1:1) to give **1c**; yield: 2.47 g (72%).

^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 9.61$ (s, 1 H, CHO), 7.35 (s, 5 H, arom), 7.21 (d, 1 H, $J = 3.5$ Hz, H3), 6.53 (d, 1 H, $J = 3.5$ Hz, H4), 4.64 (2 s, 4 H, CH_2OCH_2).

5-Acetamidomethyl-2-furfural (1d):
1a (0.302 g, 2.4 mmol) dissolved in CH_2Cl_2 (10 mL) was slowly added at r.t. to a mixture of trifluoromethanesulfonic acid (0.42 mL, 4.8 mmol), MeCN (0.25 mL, 4.8 mmol) and CH_2Cl_2 (2 mL). The mixture was stirred for 2.5 h, then poured into ice and neutralized with solid K_2CO_3 (0.34 g, 2.17 mmol). The aqueous solution was extracted with CH_2Cl_2 (3 × 50 mL). The combined extracts were dried ($MgSO_4$). The solvent was evaporated and the residue purified by column chromatography (silica gel; CH_2Cl_2–EtOAc, 1:1), to give **1d** as a solid; yield: 0.2 g (50%); mp 55 °C.

^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 9.5$ (s, 1 H, CHO), 7.17 (d, 1 H, $J = 3.5$ Hz, H3), 6.9 (m, 1 H, NH), 6.42 (d, 1 H, $J = 3.5$ Hz, H4), 4.44 (d, 2 H, $J = 5.9$ Hz, H6), 2.0 (s, 3 H, CH_3).

^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 200.6$ (C7), 193.7 (CHO), 181.8 (C5), 175.4 (C2), 146.8 (C3), 133.4 (C4), 59.8 (C6), 46.1 (CH_3).

5-Benzamidomethyl-2-furfural (1e):
To **1a** (5.99 g, 47.6 mmol) dissolved in benzonitrile (46.8 mL) was added a mixture of trifluoromethanesulfonic acid (12.8 mL, 145.7 mmol) and water (1.7 mL, 94 mmol). The mixture was stirred for 3 h at r.t., then poured into ice and neutralized with solid K_2CO_3 (10 g, 72.3 mmol). The aqueous solution was extracted with CH_2Cl_2 (3 × 500 mL). The combined extracts were dried ($MgSO_4$). After

Table 2. The Photooxygenation of Aldehydes **1**

Compound	Amount (g) (mmol)	EtOH (mL)	Resin (mg)	Eluent (ratio)	Product[a]	Yield (g) (%)	mp (°C)	^{1}H NMR (MHz, Solvent) δ, J (Hz)
1b	1.68 (10)	15	400	CH_2Cl_2–EtOAc (3 : 2)	**2b**	1.55 (90)	59	(200, CD_3COCD_3): 7.43 (d, 1H, J = 5.7, H-4), 6.25 (d, 1H, J = 5.7, H-3), 4.37 (d, 1H, J = 22, CH_2), 4.32 (d, 1H, J = 22, CH_2), 2.01 (s, 3H, CH_3)
1c	1.3 (6)	15	400	hexane–EtOAc (1 : 1)	**2c**	1.05 (80)	–	(200, $CDCl_3$): 7.32 (m, 5H, arom), 7.19 (d, 1H, J = 5.6, H-4), 6.16 (d, 1H, J = 5.6, H-3), 4.64 (s, 2H, CH_2Ph), 3.71 (s, 2H, CH_2O)
1d	1.76 (10.5)	15	326	CH_2Cl_2–EtOH (10 : 1)	**2d**	1.04 (58)	–	(60, CD_3COCD_3): 7.6 (m, 2H, OH and NH), 7.3 (d, 1H, J = 6, H-4), 6.05 (d, 1H, J = 6, H-3), 4.5 (m, 2H, CH_2), 1.8 (s, 3H, CH_3)
1e	1.42 (6.18)	21	391	not purified	**2e**	(61) (NMR)		(60, CD_3COCD_3): 7.9 (m, 3H, arom), 7.5 (m, 5H, arom H-4, NH, OH), 6.1 (d, 1H, J = 5, H-3), 3.9 (m, 2H, CH_2)
1f	0.24 (0.95)	10	100	Et_2O	**2f**	0.17 (71)	78[27]	(200, $CDCl_3$): 7.77 (m, 4H, arom), 7.28 (d, 1H, J = 5.6, H-4), 6.07 (d, 1H, J = 5.6, H-3), 5.28 (s, 1H, OH), 4.15 (2d, 2H, J_{gem} = 14.4, CH_2)
1g	0.4 (1.72)	10	93	CH_2Cl_2–EtOH (10 : 1)	**2g**[b]	0.28 (68)		(300, CD_3COCD_3): 7.42 (d, 1H, J = 5.8, H-4), 7.39 (d, 1H, J = 5.7, H-4'), 6.76 (m, 2H, OH), 6.21 (d, 1H, J = 5.8, H-3), 6.19 (d, 1H, J = 5.7, H-3'), 3.90 (d, 1H, J_{gem} = 11.2, CH_2), 3.88 (d, 1H, J_{gem} = 10.6, CH_2), 3.82 (d, 1H, J_{gem} = 10.6, CH_2), 3.81 (d, 1H, J_{gem} = 11.2, CH_2)

[a] Satisfactory microanalysis obtained: C ± 0.21; H ± 0.08.
[b] **2g**: ^{13}C NMR (75 MHz, CD_3COCD_3): δ = 171.2 (C-2, C-2'), 154.5 (C-4, C-4'), 124.6 (C-3, C-3'), 107.2 (C-5, C-5'), 74.3 and 74.2 (CH_2).

evaporation of CH_2Cl_2, and distillation of excess benzonitrile, the residue was purified by column chromatography (silica gel; CH_2Cl_2 then CH_2Cl_2–EtOAc, 1:1) to give **1e**; yield: 5.2 g (48%); mp 62–63°C.

^{1}H NMR (60 MHz, CD_3COCD_3): δ = 9.6 (s, 1H, CHO), 8.5 (m, 1H, NH), 8.0 (m, 2H, arom), 7.5 (m, 4H, arom, H3), 6.7 (d, 1H, J = 4 Hz, H4), 5.7 (d, 2H, J = 6 Hz, CH_2).

5-Phthalimidomethyl-2-furfural (1f):
To 5-hydroxymethyl-2-(2-dioxolanyl)furan[18] (1.1 g, 6.5 mmol), triphenylphosphine (2.6 g, 10 mmol) and phthalimide (1.5 g, 10 mmol) dissolved in THF (20 mL) and cooled at 0°C was added dropwise the diethyl azodicarboxylate (1.58 mL, 10 mmol). The mixture was stirred overnight at r.t. After evaporation under vacuum, the residue was chromatographed (silica, CH_2Cl_2 – EtOAc, 4:1) to give the 5-phthalimidomethyl-2-(2-dioxolanyl)furan, yield 1.06 g (55%). To this product (0.38 g, 1.29 mmol), dissolved in acetone (8 mL), were added pyridinium hydrochloride (0.076 g, 0.65 mmol) and water (0.4 mL, 22.2 mmol). The mixture was refluxed for 15 min. After concentration the residue was chromatographed (silica, CH_2Cl_2) to give **1f**[27] as a solid; yield: 0.284 g (86%); mp 115°C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 9.59 (s, 1H, CHO), 7.8 (m, 4H, arom), 7.18 (d, 1H, J = 3.5 Hz, H3), 6.53 (d, 1H, J = 3.5 Hz, H4), 4.95 (s, 2H, CH_2).

Bis(5-formyl-2-furfuryl) Ether (1 g):
1a (12.6 g, 0.1 mol), ion exchange resin IR 120 (H^+) (3 g) in benzene (150 mL) were refluxed in a Dean-Stark apparatus for 5 h. After filtration, the solvent was evaporated. The residue was mixed with Et_2O (100 mL) and filtered. The solid was recrystallized from acetone–petroleum ether to give **1g**, yield: 4.4 g (38%); mp 108°C (Lit.[28] mp 100–110°C).

^{1}H NMR (60 MHz, CD_3COCD_3): δ = 9.7 (s, 1H, CHO), 7.4 (d, 1H, J = 4 Hz, H3), 6.7 (d, 1H, J = 4 Hz, H4), 4.6 (s, 2H, CH_2).

Photooxygenation of Furanic Compounds 1; Typical Procedure:
A mixture of **1** and rose bengal/Sephadex resin[9] in EtOH was irradiated under oxygen at 20°C with a halogen lamp (150 W) as previously described for **1a**.[9] When the stoichiometric amount of oxygen was absorbed (ca. 4 h), the irradiation was switched off. The reaction mixture was stored at r.t. for 12 h. After filtration and evaporation of EtOH, the residue was chromatographed on silica to obtain the pure butenolide **2**. The amounts of products and solvent, chromatography eluents, yields, properties and ^{1}H NMR data are presented in Table 2.

Reduction of Unsaturated Compounds 2 and 5; Typical Procedure:
For Amounts of **2** *or* **5** *Less Than 1g:*
A reaction flask, containing the unsaturated compounds **2** or **5** dissolved in AcOH, was partially immersed in a sonication water bath. Zinc dust was then added in portions over 1 h. The mixture was allowed to react for 1.5–5 h (Table 1), as monitored by TLC. After filtration through Celite, the filtrate was evaporated under vacuum. The residue was dissolved in toluene (30 mL) and evaporated again. The raw product was purified by chromatography on silica to give the acid **4** or the ester **6**. The amounts of product and solvent, chromatography eluents, and yields are presented in Table 3 as well as the physical properties and ^{1}H NMR data.

For Amounts of **2** *or* **5** *Larger Than 1g:*
A sonic horn with an electric power of 300 W was partially immersed in an AcOH solution (100 mL) of **2b** (2.8 g, 16.28 mmol). The temperature was maintained at 50°C by external cooling and the use of pulsed waves of 30 s. Zinc dust (10.4 g) was added in portions over 3 h. The reaction mixture was sonicated over 5 h and worked up as described above; yield: 2.49 g (87.9%).

Methyl (*Z*)-5-Acetoxy-4-oxo-2-pentenoate (5b):
To **2b** (0.757 g, 4.4 mmol) dissolved in dry acetone (27 mL) was added dimethyl sulfate (1.1 mL, 11.6 mmol) and K_2CO_3 (0.92 g, 6.6 mmol). The mixture was stirred for 2 h at r.t., then filtered. After evaporation of acetone, the residue was chromatographed (silica, CH_2Cl_2–EtOAc, 1:1) to give **5b** as a colorless oil; yield: 0.49 g (60%).

^{1}H NMR (60 MHz, $CDCl_3$): δ = 6.55 (d, 1H, J = 12 Hz, H2), 6.15 (d, 1H, J = 12 Hz, H3), 4.9 (s, 2H, H5), 3.7 (s, 3H, OCH_3), 2.1 (s, 3H, CH_3).

Methyl (*Z*)-5-Benzyloxy-4-oxo-2-pentenoate (5c):
To **2c** (1.299 g, 5.9 mmol) dissolved in dry acetone (30 mL) was added dimethyl sulfate (1.44 mL, 15.2 mmol) and K_2CO_3 (1.2 g, 8.7 mmol). The mixture was stirred for 2 h at r.t., then filtered.

Table 3. The Reduction of Compounds **2** and **5** and Physical Data for γ-Oxo Acids **4** and γ-Oxo Esters **6**

Compound	Amount (mg) (mmol)	Zn (g)	AcOH (mL)	Eluent (ratio)	Product	Yield (mg) (%)	mp (°C)	^{1}H NMR (200 MHz, Solvent) δ, J (Hz)
2a	183 (1.4)	1.4	10	CH_2Cl_2–AcOH (10 : 3)	**4a**	120 (65)	99 100[29]	(CD_3COCD_3): 6.2 (m, 2H, OH and CO_2H), 4.21 (s, 2H, H-5), 2.72 (t, 2H, J = 5.9, H-3), 2.62 (t, 2H, J = 5.9, H-2)
2b	166 (0.96)	0.6	10	CH_2Cl_2–EtOH (20 : 1)	**4b**[a]	140 (84)	88	($CDCl_3$): 9.41 (m, 1H, CO_2H), 4.68 (s, 2H, H-5), 2.69 (m, 4H, H-2 and H-3), 2.15 (s, 3H, CH_3)
2c	211 (0.95)	0.95	10	CH_2Cl_2–EtOAc (4 : 1)	**4c**[a]	137 (64)	74	($CDCl_3$): 7.86 (m, 1H, CO_2H), 7.35 (m, 5H, arom), 4.59 (s, 2H, CH_2Ph), 4.08 (s, 2H, H-5), 2.7 (m, 4H, H-2 and H-3)[b]
2d	265 (2.42)	0.97	10	CH_2Cl_2–AcOH (10 : 3)	**4d**	234 (87)	96 96[31]	(DMSO-d_6): 8.17 (t, 1H, J = 5.2, NH), 3.94 (d, 2H, J = 5.5, H-5), 2.64 (t, 2H, J = 6.2, H-3), 2.62 (t, 2H, J = 6.2, H-2), 1.87 (s, 3H, CH_3)
2e	874 (3.75)	2.33	40	CH_2Cl_2–AcOH (10 : 3)	**4e**	749 (85)	118	(DMSO-d_6): 8.84 (t, 1H, J = 5.6, NH), 7.88 (m, 2H, arom), 7.52 (m, 3H, arom), 4.12 (d, 2H, J = 5.7, H-5), 2.71 (t, 2H, J = 6.4, H-3), 2.43 (t, 2H, J = 6.4, H-2)
2g	536 (2.2)	3.63	45	CH_2Cl_2–AcOH (10 : 3)	**4g**[a]	398 (70)	134	(DMSO-d_6): 4.20 (s, 4H, H-5), 2.61 (t, 4H, J = 6, H-3), 2.43 (t, 4H, J = 6.2, H-2)
5b	180 (0.97)	0.95	10	CH_2Cl_2–EtOH (20 : 1)	**6b**[a]	127 (70)	oil	($CDCl_3$): 4.71 (s, 2H, H-5), 3.68 (s, 3H, OCH_3), 2.7 (m, 4H, H-2 and H-3), 2.17 (s, 3H, CH_3)
5c	200 (0.85)	0.83	10	hexane–EtOAc (1 : 1)	**6c**[a]	140 (70)	oil	($CDCl_3$): 7.35 (s, 5H, arom), 4.6 (s, 2H, CH_2Ph), 4.11 (s, 2H, H-5), 3.67 (s, 3H, OCH_3), 2.8 (t, 2H, J = 6, H-3), 2.62 (t, 2H, J = 6, H-2)

[a] C, H analysis ±0.17%.

[b] Similar with data reported in literature.[30]

After evaporation of acetone, the residue was chromatographed (silica, hexane–EtOAc, 1 : 1) to give **5c** as a colorless oil; yield: 1.03 g (75%).

^{1}H NMR (60 MHz, $CDCl_3$): δ = 7.4 (s, 5H, arom), 6.6 (1H, J = 12 Hz, H2), 6.2 (d, 1H, J = 12 Hz, H3), 4.6 (s, 2H, CH_2Ph), 4.3 (s, 2H, H5), 3.7 (s, 3H, CH_3).

5-Aminolevulinic Acid Hydrochloride (7):

A solution of **4d** (0.173 g, 1 mmol) and 3 N HCl (7 mL) was refluxed for 1 h and then was evaporated to dryness under vacuum. The solid residue was recrystallized from EtOH/EtOAc to give pure **7**; yield: 0.117 g (70%); mp 144–146°C (Lit.[24] 145–148°C). IR and ^{1}H NMR spectrum of **7** were identical with data reported in literature.[24]

We thank Südzucker AG (Mannheim, Germany) for providing 5-hydroxymethyl-2-furfural.

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