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Synthesis of Pyrroles and a 1,2-Dihydropyrrolo[1,2-*a*]pyrazin-3(4*H*)-one Identified as Maillard Reaction Products

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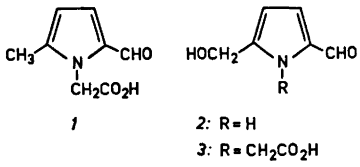
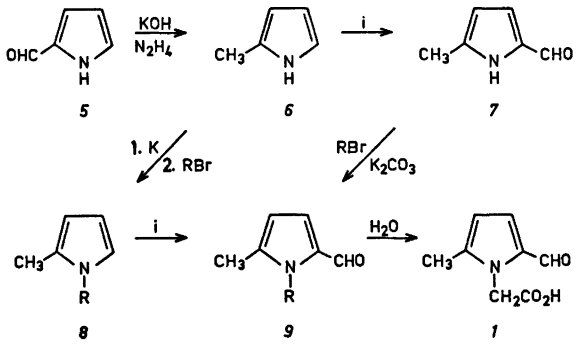
2-Formyl-5-methylpyrrole-1-acetic acid (*1*), 5-(hydroxymethyl)pyrrole-2-carboxaldehyde (*2*), 2-formyl-5-(hydroxymethyl)pyrrole-1-acetic acid (*3*) and 6-formyl-3,4-dihydro-3-oxopyrrolo[1,2-*a*]pyrazine-2(1*H*)-acetic acid (*4*) have been synthesized from pyrrole-2-carboxaldehyde (*5*) and shown to be identical with products recently obtained from D-glucose and glycine.



The so-called Maillard reaction between carbohydrates and amino compounds [1] is important in food chemistry and often yields pyrroles,[2] some of which have been synthesized.[3,4] This paper deals with the synthesis of compounds *1*—*4*, which were recently obtained from D-glucose and glycine along with several other products.[5] Compounds *1*—*4* had not been described previously, although similarly formed *3* had been identified as its methyl ester.[2] The closest analogues of *4* in the literature are probably 3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one, described in some patents,[6] and the lactone of *3*, identified (GLC—MS) among the products from glucose and glycine at 200 °C.[7] Owing to the aromatic character and natural abundance of the pyrrole nucleus, its chemistry has been studied extensively.[8] However, *1*—*4* and their analogues, known [4,9] or expected as products in the Maillard reaction of hexoses and amino acids, have apparently not been synthesized.

RESULTS AND DISCUSSION

Compound *1* was prepared from 2-methylpyrrole (*6*) [10] by two routes, as shown in Scheme 1. The route through the known [10,11]



Scheme 1. Synthesis of 2-formyl-5-methylpyrrole-1-acetic acid (*1*). R = CH_2CO_2Et and i = $POCl_3$, $HCONMe_2$.

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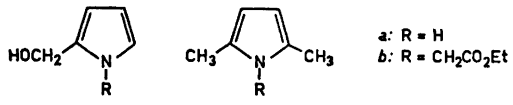
aldehyde *7* was preferred because of the smoother *N*-alkylation step.

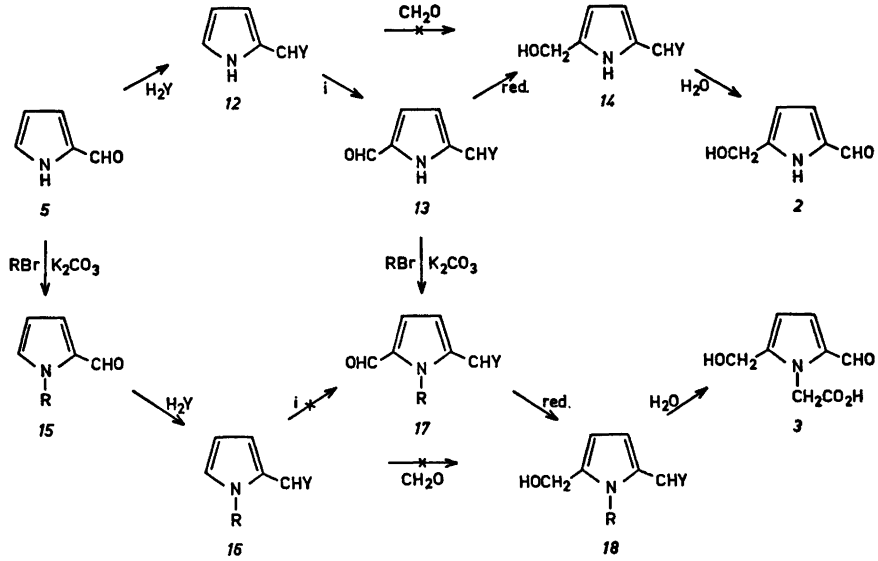
It was not possible to synthesize *2* and *3* in a similar straightforward manner. Thus, the direct hydroxymethylation of pyrrole-2-carboxaldehyde (*5*) and – as expected [3] – also the Vilsmeier formylation of 2-pyrrolemethanol (*10a*) [12] were unsuccessful. Also unsuccessful was an attempt to prepare *2* from *7* by bromination with copper(II) bromide,[13] followed by hydrolysis. Similar experiments were performed with 2,5-dimethylpyrrole (*11a*) and the related ester *11b*,[14] but neither *N*-bromosuccinimide [15] nor lead(IV) acetate [16] converted compounds *11* to any of *1*–*3* or to any of their precursors.



10 *11*

Although oxidative routes to *2* and *3* appeared to be closed, these compounds might be obtained by partial reduction of, for example, the corresponding 2,5-diformyl derivatives. Such dialdehydes have been prepared by various indirect routes.[3,17] Moreover, 1-methyl-2-pyrrolemethanol has been formylated, though in modest yield, through condensation with phenylglyoxal, followed by oxidation with periodate.[3] The routes *5*→*10a*→*2* and *15*→*10b*→*3* may therefore also be possible; syntheses of ethyl 2-formylpyrrole-1-acetate (*15*) are shown in Schemes 2 and 3. We preferred however to investigate the hydroxymethylation of *5* and *15*, after protecting the formyl group through reaction with 1,2-ethanedithiol [18] or ethyl cyanoacetate.[19] Whereas direct hydroxymethylation invariably failed under acidic as well as basic conditions, Vilsmeier formylation followed by reduction provided routes to *2* and *3* (Scheme 2).

The aldehyde *5* was converted to its 1,3-dithiolane derivative (*12a*) and to the cyanoacrylate (*12b*) in the presence of anilinium chloride and diethylamine,[19] respectively. The well-known sensitivity of pyrroles to acids precluded the normal use of a strongly acidic catalyst in the former reaction, as already noted for derivatives of *5* without an additional electronegative substituent.[18] The Vilsmeier formylation of *12a* was accompanied by considerable resinification. The reaction of *12a* with triethyl orthoformate in trifluoroacetic acid [20] or with 1,3,5-triazine and hydrogen chloride [21] yielded still less aldehyde (*13a*). No *13a* was obtained from ethyl formate and the

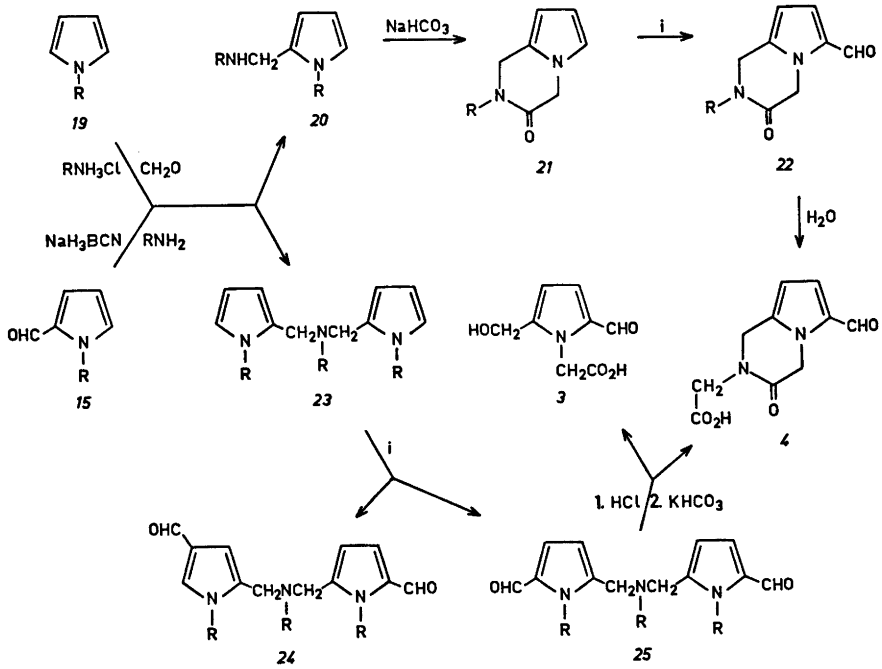


Scheme 2. Synthesis of pyrroles *2* and *3* through 1,3-dithiolanes (route *a*, Y = $-SCH_2CH_2S-$) or ethyl 2-cyanoacrylates (route *b*, Y = $=C(CN)CO_2Et$). R = CH_2CO_2Et and i = $POCl_3$, $HCONMe_2$.

Grignard reagent of *12a*.[22] The Vilsmeier formylation of *12b* presented no problems, probably because the deactivating substituent reduces the basicity of the pyrrole nucleus. The aldehydes (*13*) were reduced with potassium borohydride. While *13a* mainly yielded the expected alcohol (*14a*), the olefinic bond as well as the ester and formyl groups were attacked in *13b*. However, *13b* was mainly reduced to the desired alcohol (*14b*) by sodium cyanoborohydride in aqueous *p*-dioxane–formic acid. Without the formic acid, the olefinic bond reacted preferentially. Previous results of similar reductions[23] differ somewhat from ours. Compound *2* was obtained from *14a* by *S*-methylation and hydrolysis[24] and, in better yield (46 %), from *14b* by hydrolysis in hot strong alkali.[19]

In order to synthesize *3* by similar routes, *15* was prepared by *N*-alkylation of *5* (*cf.* the reaction *7*→*9* in Scheme 1). The conversion of *15* to the protected derivatives (*16*) parallelled that of *5*, but the formylation of both *16a* and *16b* failed. However, the desired products (*17*) were readily obtained by *N*-alkylation of the respective aldehydes *13* and reduced to the corresponding alcohols (*18*) as described for *13*. The yields of *18* were somewhat lower than those of *14*, partly owing to slight reduction of the extra ester group (in R). The alcohol *18a* was converted to *3* by the procedure[24] used to prepare *2* from *14a*, followed by hydrolysis of the ester group. Surprisingly, *18b* was hydrolysed directly to *3* even by potassium hydrogen carbonate in aqueous *p*-dioxane. *N*-Alkylation of *2*, followed by hydrolysis, resulted in a complex mixture, where *3* was identified (TLC) as a minor component.

The respective overall yields of *2* and *3* from *5* were 4 and 6 % by the dithiolane route (*a*), compared with 21 and 11 % by the cyanoacrylate route (*b*). The higher yields by route *b* arose essentially in the steps *12*→*13* and *14*→*2*. Hence, route *b* was superior to route *a*, particularly for synthesis of *2*. Easier control of most reactions also favoured route *b*. Finally, all intermediates along route *b* were readily crystallized and purified, whereas those along route *a* (except *13a*) formed oils or syrups, which were used without purification. A third



Scheme 3. Synthesis of 1,2-dihydropyrrolo[1,2-*a*]pyrazin-3(4*H*)-ones. R = CH_2CO_2Et and i = $POCl_3$, $HCONMe_2$.

route to *3* is described below (Scheme 3).

Compound *4* was synthesized through the amino ester *20* (Scheme 3), which was obtained from glycine ethyl ester by Mannich reaction [25] with the known [26] ester *19* or by reductive amination [27] of *15*. This was prepared by formylation of *19* or by *N*-alkylation of *5* (Scheme 2). The route *5*→*15*→*20* was preferred. The tertiary amine *23* accompanied *20*, no doubt because *20* competed with the glycine ester for the aldehyde. Accordingly, an excess of glycine ester was used. Sodium cyanoborohydride was used in the reductive amination, because in analogy with previous reports,[27] it was expected to reduce the intermediate aldimmonium ion without affecting any free *15*.

At pH 8, *20* cyclized to the lactam (*21*), which was readily formylated. Hydrolysis of the ester group in the resulting aldehyde (*22*) yielded *4*. The overall yield of *4* from either *15* or *19* was 16 %. It may be improved by utilizing the by-product *23*. Thus, diformylation of *23* yielded both the desired dialdehyde (*25*) and its isomer *24*. After separation from the isomer, *25* was treated with hydrochloric acid, followed by weak alkali (pH 8). In the acidified reaction mixture, *3* and *4* were identified (TLC and ^{1}H NMR) as the major products. Presumably, *25* was cleaved by the acid to *3* and a precursor, which cyclized to *4* at pH 8.

Compounds *1*–*4* were identical (TLC, MS and ^{1}H NMR) with the respective products from glucose and glycine.[5] As *3* failed to crystallize, its identity was confirmed through conversion to the lactone [7] by means of dicyclohexylcarbodiimide. The present syntheses of *1*, *3* and *4* should be easy to extend to analogous products from Maillard reactions of amino acids other than glycine.

EXPERIMENTAL

General

Formylations were carried out essentially as for pyrrole.[28] Phosphoryl chloride (1.68 g, 1.00 ml, 11.0 mmol) was added dropwise and with stirring to *N*,*N*-dimethylformamide (0.80 g, 0.85 ml, 11.0 mmol), kept at *ca.* 10 °C by cooling with ice-water. The mixture was diluted with cold 1,2-dichloroethane (10–15 ml) and kept for 10 min at *ca.* 10 °C. The stirring and cooling were then continued while the compound (10.0 mmol) to be formylated was added in small portions, dissolved or suspended in 1,2-dichloroethane (10–15 ml). In the synthesis of *13a*, the mixture was left without cooling for 10–15 min; otherwise it was refluxed for the same period. In either case, the mixture was then refluxed with aq. 20 % sodium acetate (20–25 ml) for 10–15 min. Unless the product began to crystallize (*15b*), the lower layer was separated, washed with a little water and evaporated.

Solvent mixtures are defined by volume ratios (v/v). All reactions were monitored by TLC on silica gel (Merck, HF_{254}). Chloroform–acetic acid, 3:2, was used as eluent for acids and their salts, and chloroform–acetic acid, 9:1, or chloroform–ethyl acetate, 4:1, for other compounds. After the plates had been inspected in UV light, ethanolic *p*-anisaldehyde–sulfuric acid and phloroglucinol–hydrochloric acid [29] were used as spray reagents. Solutions were dried with sodium sulfate before evaporation. Evaporations were performed at reduced pressure below 50 °C. CC was carried out on silica gel (Merck 60, 230–400 mesh) and monitored by TLC as described above but with the eluent indicated for CC.

Melting points are corrected. IR, ^{1}H NMR (100.0 MHz, *ca.* 30 °C) and mass spectra (70 eV and direct insertion unless otherwise stated) were recorded on Perkin-Elmer 337, Varian HA-100 D and Varian MAT CH 7 instruments, respectively. MS data are listed for M and the strongest peaks above *m/e* 42. Constants $|J|$ for spin–spin coupling between ethyl or pyrrole protons are not listed. They were within or very close to the normal ranges,[8,30] except for the fairly high $J_{3,4}$ values (4.0–4.6 Hz).

Materials

Unless otherwise stated, these were commercial samples of good grade. The solvents were freshly distilled before use. The light petroleum boiled at 40–60 °C. 2-Methylpyrrole (*6*),[21,10] 5-methylpyrrole-2-carboxaldehyde (*7*),[28,10,11] 2-pyrrolemethanol (*10a*),[12] ethyl 2,5-dimethylpyrrole-1-acetate (*11b*) [14] and ethyl pyrrole-1-acetate (*19*) [26] were obtained according to, or in analogy with, the respective references first cited; further references to physical data are given as required. A similar yield of *19* was obtained in shorter time, when 1-pyrrolylpotassium was not isolated. The following spectral data have apparently not been reported.

Compound 10a. MS, *m/e* (rel. int.): 80 (100), 79 (87), 97 (87, M), 52 (80), 51 (40), 68 (39), 53 (38), 50 (31), 96 (19), 78 (12). ^{1}H NMR (CD_3OD): δ 4.49 (CH_2, s), 6.01 (3,4-H_2, d), 6.66 (5-H, t).

Compound 11b. MS, *m/e* (rel. int.): 108 (100), 94 (43), 181 (36, M), 67 (20), 152 (18), 107 (15), 92 (12), 109 (12), 65 (10), 106 (10). ^{1}H NMR ($CDCl_3$): δ 1.25 (CH_2CH_3, t), 2.15 (2- and

5-CH_3, s), 4.21 (OCH_2, q), 4.46 (NCH_2, s), 5.79 (3,4-H_2, s).

Compound 19. MS, *m/e* (rel. int.): 80 (100), 53 (28), 153 (25, M), 81 (16), 78 (9), 57 (9), 43 (8), 51 (7), 52 (6), 71 (5). ^{1}H NMR ($CDCl_3$): δ 1.24 (CH_3, t), 4.17 (OCH_2, q), 4.53 (NCH_2, s), 6.15 (3,4-H_2, t), 6.60 (2,5-H_2, t).

Compound 15. *A*. A solution of *5* (4.8 g, 50 mmol) and ethyl bromoacetate (25 g, 150 mmol) in *p*-dioxane (100 ml) was stirred and refluxed with potassium carbonate (25 g) for 3 h, diluted with toluene (250 ml), filtered and evaporated. Two additional evaporations with water yielded *15* as a brownish oil (7.9 g, 87 %), which crystallized after a few days, m.p. 29–30 °C. MS, *m/e* (rel. int.): 108 (100), 53 (55), 80 (50), 181 (39, M), 94 (26), 153 (25), 124 (16), 52 (16), 51 (15), 107 (14). IR (film), $\tilde{\nu}_{max}$: 1655 (s), 1750 (s) cm^{-1}. ^{1}H NMR (CD_3OD): δ 1.24 (CH_3, t), 4.16 (OCH_2, q), 5.06 (NCH_2, s), 6.27 (4-H, dd), 7.04 (3-H, dd), 7.11 (5-H, m), 9.42 (CHO, s).

B. Formylation of *19* (1.53 g, 10.0 mmol) yielded *15* (1.68 g, 93 %).

Syntheses according to Scheme 1

Compound 8. Potassium (1.45 g, 37 mmol) was added in small portions to a solution of *6* (3.0 g, 37 mmol) in dry benzene (50 ml), which was stirred and gently refluxed under nitrogen. One hour after the last addition, the heating was discontinued and ethyl bromoacetate (6.5 g, 39 mmol) added at such a rate that gentle reflux was maintained. The stirred mixture was refluxed for another 15 min, cooled and carefully diluted with ethanol, followed by water. The benzene layer was separated, washed with water, dried with sodium sulfate and distilled, yielding *8* (1.9 g, 34 %), b.p. 115–120 °C/12 mmHg. MS (mol. leak), *m/e* (rel. int.): 94 (100), 167 (31, M), 95 (16), 80 (13), 93 (13), 78 (12), 67 (11), 53 (10), 65 (8), 138 (7). IR (film), $\tilde{\nu}_{max}$: 1750 (s) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.24 (CH_2CH_3, t), 2.14 (2-CH_3, s), 4.17 (OCH_2, q), 4.48 (NCH_2, s), 5.86 (3-H, m), 6.03 (4-H, t), 6.50 (5-H, dd).

Compound 9 was prepared as *15* but from *7* or *8*.

A. Compound *7* (1.09 g, 10.0 mmol) yielded *9* as a brownish oil (1.61 g, 82 %). MS, *m/e* (rel. int.): 122 (100), 94 (86), 195 (71, M), 53 (67), 93 (51), 121 (46), 108 (42), 166 (42), 92 (31), 167 (30). IR (film), $\tilde{\nu}_{max}$: 1655 (s), 1750 (s) cm^{-1}. ^{1}H NMR (CD_3OD): δ 1.24 (CH_2CH_3, t), 2.22 (5-CH_3, s), 4.18 (OCH_2, q), 5.09 (NCH_2, s), 6.08 (4-H, d), 6.94 (3-H, d), 9.27 (CHO, s).

B. Compound *8* (1.67 g, 10.0 mmol) yielded crude *9* (*ca*. 1.75 g).

Compound 1. A solution of *9* (1.00 g, 5.1 mmol) in moist methanol (50 ml) was stirred and refluxed with potassium carbonate (5 g) for 45 min, diluted with water (100 ml), washed with ethyl acetate, carefully acidified with hydrochloric acid and extracted with ethyl acetate (3 × 25 ml). The extract was evaporated and the residue recrystallized from benzene or methanol–diisopropyl ether, yielding *1* (0.38 g, 45 %). Anal. $C_8H_9NO_3$: C, H, N, O. Physical data were given in Ref. 5. When *1* was prepared from *8 via* crude *9*, the yield of *1* was 39 % (calc. on *8*).

Syntheses according to Scheme 2, route *a*

Compound 12a. 1,2-Ethanedithiol (4.0 g, 43 mmol), *5* (3.8 g, 40 mmol) and anilinium chloride (50–100 mg) were dissolved in methanol (50 ml). After 1 h, the solution was evaporated. The residue was extracted with toluene (50 ml). The extract was evaporated, yielding crude *12a* as a reddish oil (*ca*. 6.8 g) in nearly quantitative yield. MS, *m/e* (rel. int.): 45 (100), 110 (62), 52 (40), 111 (36), 67 (30), 59 (30), 51 (30), 60 (28), 143 (22), 83 (20,..., 171 (13, M). IR (film), $\tilde{\nu}_{max}$: 3380 (s, broad) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 3.35 (CH_2CH_2, m), 5.81 (2-CH, s), 6.08 (4-H, m), 6.18 (3-H, m), 6.74 (5-H, m), 8.59 (NH, broad m).

Compound 13a was prepared by formylation of crude *12a* (*ca*. 6.8 g). The crude product was extracted with boiling toluene. The hot extract was treated with Norite and filtered. Crystallization at −20 °C yielded *13a* (1.8 g, 26 % calc. on *5*), m.p. 107–108 °C. MS, *m/e* (rel. int.): 199 (100, M), 138 (73), 171 (72), 142 (60), 139 (53), 45 (32), 110 (22), 78 (18), 51 (16), 83 (15). IR (KBr), $\tilde{\nu}_{max}$: 1640 (s), 3225 (s) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 3.37 (CH_2CH_2, m), 5.70 (5-CH, s), 6.30 (4-H, d), 6.87 (3-H, d), 9.44 (CHO, s).

Compound 14a. A solution of *13a* (0.80 g, 4.0 mmol) in *p*-dioxane (40 ml) was stirred for 1 h with potassium borohydride (0.22 g, 4.0 mmol), dissolved in water (20 ml). The solution was diluted with water (100 ml) and extracted with ether (3 × 50 ml). The extract was evaporated, yielding crude *14a* as a reddish oil (*ca*. 0.8 g). MS, *m/e* (rel. int.): 124 (100), 183 (34), 173 (30), 80 (29), 45 (28), 79 (24), 201 (21, M), 122 (21), 51 (18), 52 (17). IR (film), $\tilde{\nu}_{max}$: 3340 (s, broad) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 2.34 (OH, broad s), 3.33 (CH_2CH_2, m), 4.52 (OCH_2, s), 5.74 (5-CH, s), 5.96 (3-H, t), 6.08 (4-H, t), 8.92 (NH, broad m).

Compound 2, *cf*. Ref. 24. A solution of crude *14a* (*ca*. 0.8 g) and iodomethane (2.3 g, 1.0 ml, 16 mmol) in acetone (20 ml) and water (5 ml) was stirred and gently refluxed with barium carbonate (0.8 g) for 16 h, diluted with acetone (25 ml) and chloroform (50 ml), filtered and evaporated. CC of the residue with chloroform – 95 % ethanol, 9:1, as eluent gave two fractions. The second one was evaporated and the residue recrystallized from benzene, yielding *2* (75 mg, 15 % calc. on *13a*).

Compound 16a was prepared as *12a* but from *15* (2.7 g, 15 mmol). The reaction time was extended to 90 min. Crude *16a* was obtained as a reddish oil. MS, *m/e* (rel. int.): 257 (100, M), 124 (50), 196 (48), 46 (19), 170 (17), 123 (17), 197 (15), 229 (14), 156 (13), 80 (13). IR (film), $\tilde{\nu}_{max}$: 1740 (s) cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.21 (CH_3, t), 3.27 (CH_2CH_2, m), 4.15 (OCH_2, q), 4.79 (NCH_2, s), 5.74 (2-CH, s), 6.00 (4-H, m), 6.22 (3-H, m), 6.60 (5-H, t).

Compound 17a was prepared as *15*, method *A*, but from *13a* (1.00 g, 5.0 mmol). Crude *17a* was obtained as a brownish syrup (*ca.* 1.4 g) in nearly quantitative yield. MS, *m/e* (rel. int.): 256 (100), 285 (48, M), 257 (17), 228 (15), 45 (11), 152 (11), 258 (10), 198 (5), 59 (5), 212 (4). IR (film), $\tilde{\nu}_{max}$: 1660 (s), 1750 (s) cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.26 (CH_3, t), 3.37 (CH_2CH_2, m), 4.22 (OCH_2, q), 5.27 (NCH_2, s), 5.60 (5-CH, s), 6.46 (4-H, d), 6.86 (3-H, d), 9.46 (CHO, s).

Compound 18a was prepared as *14a* but from crude *17a* (*ca.* 1.4 g). The crude *18a* was a brownish syrup (*ca.* 0.94 g). MS, *m/e* (rel. int.): 269 (100), 136 (94), 256 (53), 45 (47), 80 (46), 152 (36), 105 (32), 168 (30), 108 (27), 124 (27),..., 287 (8, M). IR (film), $\tilde{\nu}_{max}$: 1745 (s), 3400 (m, broad) cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.26 (CH_3, t), 2.34 (OH, s), 3.34 (CH_2CH_2, m), 4.21 (CH_3CH_2, q), 4.49 (2-CH_2, s), 4.97 (NCH_2, s), 5.77 (5-CH, s), 6.03 (3-H, d), 6.21 (4-H, d).

Compound 3, *cf.* Ref. 24. A solution of crude *18a* (*ca.* 0.94 g) and iodomethane (4.6 g, 2.0 ml, 32 mmol) in acetone (20 ml) and water (5 ml) was stirred and gently refluxed with barium carbonate (0.8 g) for 5 h and then evaporated. The residue was stirred with potassium carbonate (1.0 g), *p*-dioxane (25 ml) and water (25 ml) at 60 °C for 45 min. The mixture was diluted with water (100 ml), washed with ethyl acetate (3 × 50 ml), carefully acidified with 85 % phosphoric acid and extracted with ethyl acetate (4 × 50 ml). The extract was evaporated and the residue extracted with chloroform (100 ml). The new extract was evaporated, yielding fairly pure *3* as a yellow syrup (215 mg, 23 % calc. on *13a*).

Syntheses according to Scheme 2, route *b*

Compound 12b, *cf.* Ref. 19. A solution of *5* (9.5 g, 100 mmol), ethyl cyanoacetate (16 g, 140 mmol) and diethylamine (0.7 g, 1.0 ml, 10 mmol) in toluene (125 ml) was refluxed for 1 h, using a water separator. After cooling, the crystals were collected, washed with light petroleum and air-dried, yielding *12b* (18.1 g, 95 %), m.p. 135–138 °C. MS, *m/e* (rel. int.).: 190 (100, M), 144 (80), 118 (79), 145 (69), 117 (45), 63 (33), 90 (33), 116 (22), 162 (19), 91 (18). IR (KBr), $\tilde{\nu}_{max}$: 1585 (s), 1695 (s), 2190 (m), 3295 (s) cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.38 (CH_3, t), 4.34 (CH_2, q), 6.42 (4-H, m), 6.95 (5-H, m), 7.24 (3-H, m), 8.02 (2-CH, s), 9.88 (NH, broad m).

Compound 13b was prepared by formylation of *12b* (19.0 g, 100 mmol). Crystallization by cooling the reaction mixture overnight yielded *13b* (15.3 g, 70 %), m.p. 199–201 °C. MS, *m/e* (rel. int.): 144 (100), 118 (84), 218 (75, M), 190 (70), 145 (58), 90 (40), 117 (38), 173 (32), 63 (32), 116 (28). IR (KBr), $\tilde{\nu}_{max}$: 1610 (s), 1675 (s), 1690 (s), 2220 (w), 3310 (s) cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.39 (CH_3, t), 4.40 (CH_2, q), 7.04 (4-H, d), 7.20 (3-H, d), 8.14 (2-CH, s), 9.72 (CHO, s), 10.4 (NH, very broad).

Compound 14b. Sodium cyanoborohydride (1.26 g, 20.0 mmol) was added to a suspension of *13b* (4.36 g, 20.0 mmol) in water (10 ml), formic acid (10 ml) and *p*-dioxane (50 ml). The mixture was stirred for 40 min, diluted with water (200 ml), carefully neutralized to pH 8 and extracted with ethyl acetate (3 × 100 ml). The extract was evaporated and the residue recrystallized from toluene, yielding *14b* (3.10 g, 70 %), m.p. 144–148 °C. MS, *m/e* (rel. int.): 220 (100, M), 146 (82), 145 (74), 157 (64), 175 (54), 173 (50), 118 (39), 102 (36), 130 (34), 174 (31). IR (KBr), $\tilde{\nu}_{max}$: 1595 (s), 1690 (s), 2210 (m), 3290 (s), 3335 (s) cm^{-1}. ^1H NMR (CD_3OD): δ 1.33 (CH_3, t), 4.28 (CH_3CH_2, q), 4.64 (5-CH_2, s), 6.35 (4-H, d), 7.40 (3-H, d), 8.06 (2-CH, s).

Compound 2, *cf.* Ref. 19. The methanol was boiled off from a solution of potassium hydroxide (20 g) and *14b* (2.20 g, 10.0 mmol) in water (40 ml) and methanol (50 ml). The remaining aqueous solution was heated on a steam-bath for 2 h, diluted with water (150 ml) and extracted with ethyl acetate (3 × 75 ml). The extract was evaporated and the residue recrystallized from benzene, yielding *2* (0.58 g, 46 %). Anal. $C_6H_7NO_2$: C, H, N, O. Physical data were given in Ref. 5.

Compound 16b, *cf.* Ref. 19. A solution of *15* (1.81 g, 10.0 mmol), ethyl cyanoacetate (1.6 g, 14 mmol) and diethylamine (70 mg, 0.1 ml, 1 mmol) in toluene (12.5 ml) was refluxed for 3 h, using a water separator, cooled and diluted with light petroleum. Crystallization at −20 °C yielded *16b* (1.29 g, 47 %), m.p. 86–89 °C. MS, *m/e* (rel. int.): 146 (100), 129 (58), 131 (56), 104 (53), 276 (53, M), 130 (37), 51 (32), 78 (31), 159 (29), 145 (28). IR (KBr), $\tilde{\nu}_{max}$: 1595 (s), 1720 (s), 1740 (s), 2220 (m) cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.26 (CH_3, t), 1.34 (CH_3, t), 4.22 (OCH_2, q), 4.31 (OCH_2, q), 4.80 (NCH_2, s), 6.42 (4-H, dd), 7.06 (5-H, dd), 7.75 (3-H, dd), 7.92 (2-CH, s).

Compound 17b. A solution of *13b* (4.36 g, 20.0 mmol) in ethyl bromoacetate (25 ml) was stirred with potassium carbonate (5 g) at 100 °C for 1 h, diluted with toluene (50 ml), filtered, and evaporated as far as possible. The residual oil was diluted with toluene (5 ml), followed by light petroleum (25 ml). Crystallization at −20 °C yielded *17b* (4.85 g, 80 %), m.p. 102–103 °C after recrystallization from 95 % ethanol. MS, *m/e* (rel. int.): 304 (100, M), 219 (78), 276 (65), 174 (65), 203 (58),

247 (57), 159 (57), 158 (55), 231 (54), 186 (49). IR (KBr), $\tilde{\nu}_{max}$: 1590 (s), 1665 (s), 1720 (s), 1730 (sh), 2225 (w) cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.30 (CH_3, t), 1.38 (CH_3, t), 4.24 (OCH_2, q), 4.37 (OCH_2, q), 5.31 (NCH_2, s), 7.12 (4-H, d), 7.71 (3-H, d), 7.98 (2-CH, s), 9.71 (CHO, s).

Compound 18b was prepared as *14b* but from *17b* (6.08 g, 20.0 mmol). Recrystallization from toluene yielded *18b* (3.07 g, 50 %), m.p. 120–122 °C. MS, *m/e* (rel. int.): 231 (100), 306 (86, M), 260 (79), 143 (72), 203 (71), 173 (59), 153 (58), 261 (55), 175 (55), 131 (54). IR (KBr), $\tilde{\nu}_{max}$: 1590 (s), 1690 (s), 1730 (s), 2215 (m), 3440 (s, broad) cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.29 (CH_3, t), 1.36 (CH_3, t), 2.27 (OH, broad s), 4.24 (CH_3CH_2, q), 4.33 (CH_3CH_2, q), 4.64 (5-CH_2, s), 4.92 (NCH_2, s), 6.38 (4-H, d), 7.69 (3-H, d), 7.91 (2-CH, s).

Compound 3. A mixture of *18b* (2.45 g, 8.0 mmol), potassium hydrogen carbonate (10 g), water (100 ml) and *p*-dioxane (100 ml) was stirred and refluxed for 1 h, washed with ethyl acetate (100 ml), carefully acidified to pH 3.5 with 85 % phosphoric acid, washed with light petroleum (100 ml) and extracted with ethyl acetate (3 × 100 ml). The extract was evaporated. CC of the residue with butanone, saturated with water, as eluent yielded *3* as a pale yellow syrup (0.63 g, 43 %). Physical data were given in Ref. 5.

Lactone. The preceding experiment was repeated, but dicyclohexylcarbodiimide (3.3 g, 16 mmol) was dissolved in the dried ethyl acetate extract. This was evaporated after 24 h. The residue was extracted with warm (50 °C) toluene (100 ml). The new extract was evaporated and the residue crystallized from abs. ethanol, yielding the lactone (185 mg, 14 % calc. on *18b*), m.p. 149–151 °C after sublimation at *ca.* 125 °C and 0.5 mmHg. Anal. $C_8H_7NO_3$: C, H, N. The mass spectrum agreed with the published one.[7] IR ($CHCl_3$), $\tilde{\nu}_{max}$: 1660 (s), 1760 (s) cm^{-1}. ^1H NMR (CD_3OD): δ 5.25 (NCH_2, s), 5.49 (OCH_2, s), 6.28 (4-H, d), 7.08 (3-H, d), 9.47 (CHO, s).

Syntheses according to Scheme 3

Compound 20. *A.* Glycine ethyl ester hydrochloride (10.5 g, 75 mmol) and *19* (2.30 g, 15.0 mmol) were dissolved in methanol (20 ml) and water (4 ml). Aq. 35 % formaldehyde (1.41 g, 1.30 ml, 16.0 mmol) was added to the stirred solution over 30 min. After stirring for 24 h, the crude reaction mixture was diluted with water (25 ml), carefully saturated with sodium hydrogen carbonate and immediately extracted with dichloromethane. The extract was evaporated. CC of the residue with dichloromethane–ethyl acetate, 4:1, as eluent yielded *20* and *23* as brownish oils. Only the purest fractions were saved for spectral analysis. The following data were obtained for *20*. MS, *m/e* (rel. int.): 166 (100), 181 (46), 80 (45), 93 (36), 94 (27), 83 (26), 138 (20), 85 (18). 268 (12, M), 167 (12). IR (film), $\tilde{\nu}_{max}$: 1740 (s), 1755 (sh), 3340 (w) cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.25 (2 CH_3, t), 1.74 (NH, s), 3.30 ($NHCH_2CO$, s), 3.74 (2-CH_2, s), 4.16 (OCH_2, q), 4.18 (OCH_2, q), 4.76 (1-CH_2, s), 6.05 (3,4-H_2, m), 6.60 (5-H, t).

B. A solution of glycine ethyl ester hydrochloride (10.5 g, 75 mmol) in water (15 ml) was neutralized to pH 7.0 with dipotassium hydrogen phosphate trihydrate. Sodium cyanoborohydride (0.63 g, 10.0 mmol) was added, followed by *15* (1.81 g, 10.0 mmol), dissolved in methanol (30 ml). After stirring for 24 h, the crude reaction mixture was processed as in method *A* with similar result.

Compound 21. Either synthesis of *20* was repeated, but the crude reaction mixture was diluted with methanol (200 ml) and water (200 ml). After careful addition of sodium hydrogen carbonate (12 g), the stirring was continued for 48 h. The mixture was carefully acidified with concentrated hydrochloric acid and extracted with dichloromethane (2 × 100 ml). The extract was washed with water and evaporated. CC of the residue with chloroform–ethyl acetate, 4:1, as eluent yielded *21* as a brownish syrup (*A.* 1.38 g, 41 % calc. on *19*; *B.* 0.87 g, 39 % calc. on *15*), distinguished by a characteristic orange colour formed with the *p*-anisaldehyde spray reagent. MS, *m/e* (rel. int.): 135 (100), 107 (38), 80 (33), 43 (24), 93 (22), 222 (22, M), 149 (15), 83 (14), 120 (12), 66 (12). IR (film), $\tilde{\nu}_{max}$: 1665 (s), 1745 (s) cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.27 (CH_3, t), 4.20 (OCH_2, q), 4.22 (2-CH_2, s), 4.59 (1-H_2, s), 4.62 (4-H_2, s), 5.95 (8-H, m), 6.19 (7-H, t), 6.57 (6-H, dd).

Compound 22. Formylation of *21* (0.67 g, 3.0 mmol) yielded crude *22* as a brownish syrup (*ca.* 0.7 g). MS, *m/e* (rel. int.): 163 (100), 250 (71, M), 135 (60), 108 (32), 93 (20), 148 (19), 193 (18), 149 (18), 147 (16), 177 (15). IR(film), $\tilde{\nu}_{max}$: 1660 (s), 1745 (s) cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.29 (CH_3, t) 4.22 (OCH_2, q), 4.25 (2-CH_2, s), 4.69 (1-H_2, broad s), 5.10 (4-H_2, broad s), 6.13 (8-H, d), 6.96 (7-H, d), 9.48 (CHO, s).

Compound 4. A solution of crude *22* (*ca.* 0.7 g) in moist methanol (25 ml) was stirred and refluxed with potassium carbonate (2.0 g) for 1 h, processed as described for *1* but recrystallized from 95 % ethanol, yielding *4* (0.27 g, 40 % calc. on *21*). Anal. $C_{10}H_{10}N_2O_4$: C, H, N. Physical data were given in Ref. 5.

Compound 23 was formed as a by-product in the syntheses of *20*. It yielded the following data. MS, *m/e* (rel. int.): 166 (100), 94 (23), 80 (23), 167 (18), 267 (18), 138 (15), 93 (12), 110 (9), 280 (7), 59 (7),..., 433 (0.5, M). IR (film), $\tilde{\nu}_{max}$: 1750 (s) cm^{-1}. ^1H NMR (CCl_4): δ 1.21 (CH_3, t), 1.24 (2 CH_3, t), 3.04 (CH_2CO, s), 3.48 (2- and 2'-CH_2, s), 4.03 (OCH_2, q), 4.10 (2 OCH_2, q), 4.66 (2 CH_2CO, s), 5.89 (3,4,3',4'-H_4, m), 6.43 (5,5'-H_2, t).

Compounds 24 *and* 25 were prepared by diformylation of *23* (1.09 g, 2.5 mmol). CC of the

crude product with dichloromethane – ethyl acetate, 4:1, as eluent yielded *24* (60 mg, 5 %) and *25* (270 mg, 22 %) as yellow syrups. The following data were obtained for *24*. MS (IP 30 eV), *m/e* (rel. int.): 194 (100), 295 (31), 195 (15), 108 (14), 122 (13), 59 (12), 166 (12), 138 (6), 121 (4), 416 (4),..., 489 (2, M). IR (film), $\tilde{\nu}_{max}$: 1660 (s), 1740 (s) cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.23 (CH_3, t), 1.27 (CH_3, t), 1.29 (CH_3, t), 3.16 (aliph. NCH_2CO, s), 3.62 (2-CH_2, s), 3.64 (2′-CH_2, s), 4.10 (OCH_2, q), 4.18 (OCH_2, q), 4.20 (OCH_2, q), 4.87 (1-CH_2, s), 5.16 (1′-CH_2, s), 6.21 (3′-H, d), 6.54 (3-H, d), 6.88 (4′-H, d), 7.28 (5-H, d), 9.47 (5′-CHO, s), 9.70 (4-CHO, s). The following data were obtained for *25*. MS, *m/e* (rel. int.): 194 (100), 295 (67), 59 (44), 108 (38), 122 (31), 166 (26), 93 (20), 249 (19), 195 (15), 80 (12),..., 489 (4, M). IR (film), $\tilde{\nu}_{max}$: 1655 (s), 1740 (s) cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.24 (CH_3, t), 1.30 (2 CH_3, t), 3.17 (CH_2CO, s), 3.71 (2- and 2′-CH_2, s), 4.13 (OCH_2, q), 4.20 (2 OCH_2, q), 5.19 (2 CH_2CO, s), 6.20 (3,3′-H_2, d), 6.89 (4,4′-H_2, d), 9.48 (2 CHO, s).

Acid-catalysed cleavage of 25. A solution of *25* (30 mg) in 1 M hydrochloric acid (1.1 ml) and *p*-dioxane (1.0 ml) was kept at 75 °C for 6 h, cooled and carefully neutralized to pH 8 with potassium hydrogen carbonate. After stirring for 24 h, the mixture was diluted with water, carefully acidified with 85 % phosphoric acid and extracted with ethyl acetate. In the extract, *3* and *4* were identified (TLC and ^1H NMR) as the major products.

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