

Trapping enols of esters and lactones with diazomethane

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Received 11 November 2006; revised 1 February 2007; accepted 4 February 2007

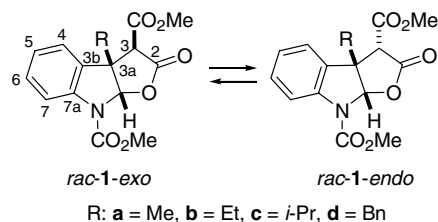
Available online 7 February 2007

Abstract—A series of regioisomeric ketene-*O,O*-dialkyl acetals were prepared from ambident β -dicarbonylfuroindoles by trapping the enol tautomers of esters and lactones with diazomethane. Definitive structural characterization was accomplished by X-ray crystal structure determination on a ketene-*O,O*-dimethyl acetal (R = Me).

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In recent years, extensive studies of enols of carboxylic acid derivatives¹ provided essential information on the relative importance of electron withdrawing β -substituents,² push–pull effects,³ steric effects,⁴ hydrogen-bonding,^{3,5} solvent effects,³ and the acid group derivatives that are responsible for the stability of these enol types.⁶ For instance, in recent theoretical studies, Rappoport and co-workers⁷ found that enols of anhydrides and amides have a better chance of being observed than enols of acids and esters. This finding supports previous suggestions about the relevant contribution of the heteroatom in stabilizing the acid tautomer by electron donation.^{1a} Consequently, only few reports dealing with the detection, preparation, and characterization of highly unstable enols of esters are available.⁸

As part of a synthetic program aimed to develop practical pathways for the synthesis of therapeutically promising *Flustra foliacea* constituents,⁹ we have recently reported a convenient method for the preparation of β -dicarbonylfuroindoles **1a–d**.¹⁰ It was found that, in solution and at room temperature, compounds **1a–d** show a dynamic stereochemistry governed by the steric preferences of the ester group at the C3 stereocenter (Scheme 1). In these epimeric mixtures, the methine proton bearing two electron-withdrawing groups rapidly



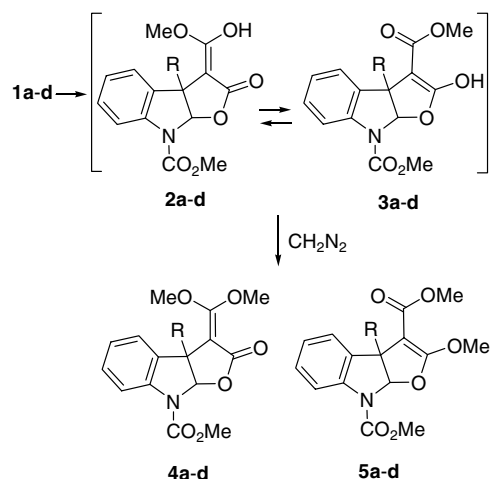
Scheme 1. Epimeric mixture of β -dicarbonylfuroindoles **1a–d** showing the relative stereochemistry.

exchanges with deuterium. Although, even in non-polar CD_2Cl_2 solvent, enol forms were not detected by NMR measurements in this series of compounds, it is well recognized¹¹ that the H–D exchange reaction in β -dicarbonyl acid derivatives occurs through the enol tautomer as the rate-limiting step. Thus, in the case of β -dicarbonylfuroindoles **1a–d** the possible mechanism of the H–D exchange process could involve enol tautomers as intermediates. Therefore, we became interested in trapping such very rare species. In this respect, one recent example of the reaction of enols of amides with diazomethane described the occurrence of a diversity of reactions, among them, O- and C-methylation.¹²

On the basis of the above considerations, the ambident β -dicarbonylfuroindoles **1a–d** could provide unique systems to study a competing enolization process between the ester and lactone groups by trapping the corresponding enol esters **2a–d** and enol lactones **3a–d** with

Keywords: Ketene-*O,O*-dialkyl acetals; β -Dicarbonylfuroindoles; Enols of esters; Enols of lactones; Diazomethane.

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Scheme 2. Preparation of regioisomeric ketene-*O,O*-dialkyl acetals **4a–d** and **5a–d**.

diazomethane (Scheme 2). On the other hand, it is known¹³ that enols may be stabilized by introduction of bulky groups onto the β -carbon to the carbonyl groups. In this context, the influence of the bulkiness of β -alkyl groups on the relative stability of the expected regioisomeric ketene-*O,O*-dialkyl acetals **4a–d** and **5a–d** could be evaluated, without, at the same time, introducing electronic effects.

Thus, a reaction run of **1a** with an excess of freshly prepared diazomethane in ether, 2 h at room temperature, furnished a mixture of the regioisomeric pair **4a** and **5a** ($\Delta R_f = \text{ca. } 0.2$ hexane/AcOEt 9:1), which was easily separated into their individual components by routine flash chromatography on silica gel. The product ratio of **4a/5a** was 1:4 with a combined yield of 95% (Table 1, entry 1). It is pointed out that the sterically congested C-methylated products at the α -carbon to the carbonyl groups were not detected in the crude reaction mixture. To check the relationship between the chemoselectivity and the steric effect of the β -alkyl substituent present in dicarbonylfuroindoles **1a–d**, the reactions of **1b–d** with diazomethane were examined under the reaction conditions mentioned above. Interestingly, the formed products exhibited similar distribution and yields as those obtained from **1a**, although **4d** is isolated in lower yields due to its instability. Table 1 summarizes the results of the reaction of β -dicarbonylfuroindoles **1a–d** with diazomethane in ether. In all cases, compounds **4a–d** and **5a–d** cleanly return to the starting β -dicarbonylfuroindoles **1a–d** when treated with $\text{CCl}_3\text{CO}_2\text{H}$ at

Table 1. Regioselective O-methylation of ambident β -dicarbonylfuroindoles **1a–d** with CH_2N_2

Compound	R		4 (%)	5 (%)
1a	Me	a	18	77
1b	Et	b	17	75
1c	<i>i</i> -Pr	c	17	80
1d	Bn	d ^a	18	51

^a The **4/5** ratio of the crude reaction mixture is ca. 1:4, as determined by ¹H NMR.

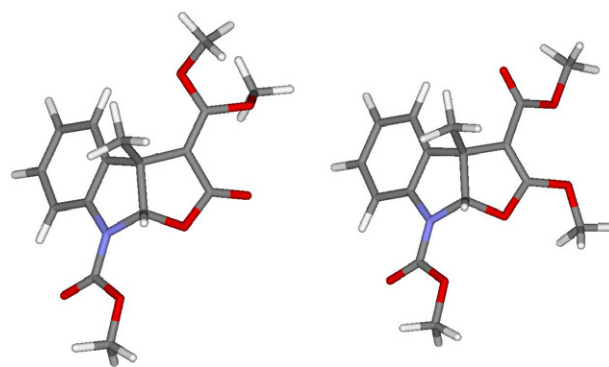


Figure 1. Global minima conformations of regioisomeric ketene-*O,O*-dialkyl acetals **4a** (left) and **5a** (right).

room temperature for 15 min, as determined by GC/MS.

The optimized geometry calculated (MMFF) for **4a–d** and **5a–d** was consistent with our experimental data, that is, the ketene-*O,O*-dialkyl acetals **5a–d** were lower in energy than their regioisomers **4a–d**, with relative values between the predominant **4a–d/5a–d** pairs of conformers ranging from 1.2 to 1.8 kcal/mol. Figure 1 shows the global minima conformations for **4a** and **5a** as examples. The diminished stability observed for **4a–d** with respect to **5a–d** can be explained based on the knowledge that the formation of endocyclic double bonds is preferred over exocyclic double bonds.¹⁴ In addition, the very low spanning range of 0.6 kcal/mol shows that the β -alkyl groups had no significant impact on the product ratio, once again in good agreement with experimental observations.

The structural characterization of trapped isomeric enols **4a–d** and **5a–d** was accomplished by one- and two-dimensional NMR parameters, IR and HRMS.¹⁵ The IR and ¹H NMR spectra of **4a–d** showed very similar patterns to those of **5a–d** except for the double bond absorption which appears around 1625 cm^{-1} for **4a–d** and around 1635 cm^{-1} for **5a–d** in the IR spectra. A common feature of regioisomeric compounds **4a–d** and **5a–d** is their π -conjugative push–pull nature, which is evidenced from the observed large ¹³C chemical shift differences between the two ethylenic carbon atoms (C3=C9 in **4a–d**, and C2=C3 in **5a–d**), which occur in the range 80–85 ppm (Table 2), reflecting a significant

Table 2. Selected ¹³C chemical shifts (δ , in ppm) of ketene-*O,O*-dialkyl acetals **4a–d** and **5a–d**

Compound	C3	C9	$\Delta\delta_{\text{C9-C3}}$
4a	90.3	168.7	78.4
4b	88.0	168.5	80.5
4c	89.1	168.0	78.9
4d	88.6	168.1	79.5
	C2	C3	$\Delta\delta_{\text{C2-C3}}$
5a	167.4	83.6	83.8
5b	167.6	81.5	86.1
5c	167.4	82.1	85.3
5d	167.9	82.1	85.8

zwitterionic character. Since there is no plane of symmetry through the C3–C9 axis in **4a–d**, the twisted methoxy groups show different carbon-13 NMR signals. The assignment of the *syn* *O*-methyl group at higher frequency (δ ca. 63 ppm) than the *anti* *O*-methyl group (δ ca. 54 ppm) in **4a–d** was made considering that the *syn* *O*-methyl group is under the deshielding field of the carbonyl lactone group, as was confirmed by NOESY experiments.

The crystal structure of **4a**¹⁶ is shown in Figure 2, with selected bond lengths given in the caption. A survey of the Cambridge Structural Database (version 5.27) reveals that this is the first structure having the ketene acetal C=C(OR)₂ moiety as part of a push–pull system. The X-ray structure of **4a** exhibits geometrical parameters and characteristic torsion angles which are strikingly close to values predicted by MMFF calculations for the lowest energy conformer. Furthermore, consistent with calculations, but in contrast to precedents, the interatomic distances within the atoms involved in the π -conjugative push–pull interaction do not show special effects on their bond lengths,¹⁷ for example, the C3=C9 distance of 1.333(3) Å is typical for sp²-hybridized carbons not involved in a zwitterionic form.¹⁸

In summary, we quite efficiently trapped enol esters and enol lactones as the corresponding ketene-*O,O*-dialkyl acetals by reaction of β -dicarbonylfuluroindoles with diazomethane. The reaction occurs rapidly at room temperature in the absence of a catalyst. Calculations support that the observed product selectivity depends on the thermodynamic stability of products. Although the β -alkyl substituents do not influence the **4a–d/5a–d** product ratio, they could impede the formation of the C-methyl-

ation products of tautomers **2a–d/3a–d**. The selective protection of one of the carbonyl groups in **1a–d** might further be of utility for synthetic purposes. The crystal structure of ketene-*O,O*-dimethyl acetal **4a** shows unexpected bond lengths for the compound involved in a π -conjugative push–pull interaction.

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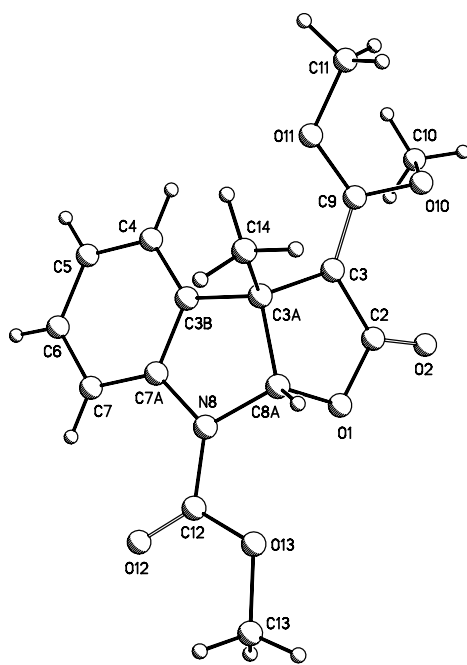


Figure 2. Crystal structure of **4a** showing a non-planar *gauche-gauche* conformation. Selected bond lengths (Å): C(9)–O(11) 1.323(3), C(9)–O(10) 1.343(3), C(3)–C(9) 1.333(3), C(2)–C(3) 1.449(3), C(2)–O(2) 1.201(3).

15. General procedure for reaction with diazomethane: To a solution of the corresponding β -dicarbonylfuroindole **1** (0.075–0.085 mmol) in ether (10 mL) was added an excess of freshly prepared ethereal solution of diazomethane¹⁹ (15 mL, ca. 13.6 mg CH₂N₂/mL, 4.8 mmol). The reaction mixture was stirred at room temperature for 2 h and evaporated at room temperature under atmospheric pressure with a stream of nitrogen which was bubbled into a solution containing 5% acetic acid in ethanol. ¹H NMR spectroscopic analysis of the crude products indicated a pair of regioisomers in a ca. 4:1 ratio. Separation of the regioisomers was achieved by purification of the resultant residue by flash chromatography (2:3 EtOAc/hexane) to yield first **5** as the major component, followed by **4**. Data for **4a**: colorless crystals (18%); mp 165–166 °C (from EtOAc/hexane); *R*_f = 0.21 (EtOAc/hexane 3:2); IR (CH₂Cl₂) ν_{\max} 3024, 1731, 1624, 1070 cm⁻¹; ¹H NMR (CD₂Cl₂) δ 7.74 (1H, br s, H7), 7.49 (1H, dd, *J* = 7.6, 0.9 Hz, H4), 7.23 (1H, td, *J* = 7.5, 1.4 Hz, H6), 7.03 (1H, td, *J* = 7.6, 1.1 Hz, H5), 5.97 (1H, s, H8a), 4.05 (3H, s, OMe *syn*), 3.90 (3H, s, OMe *anti*), 3.89 (3H, s, CO₂Me), 1.63 (3H, s, Me); ¹³C NMR (CD₂Cl₂) δ 168.7 (s, C9), 168.1 (s, C2), 153.4 (s, CO₂Me), 140.0 (s, C7a), 136.8 (s, C3b), 128.9 (d, C6), 124.7 (d, C4), 124.2 (d, C5), 115.1 (d, C7), 95.6 (s, C8a), 90.3 (s, C3), 63.5 (q, OMe *syn*), 54.9 (q, OMe *anti*), 53.5 (q, CO₂Me), 51.0 (s, C3a), 23.8 (q, Me); EIMS *m/z* 319 (M⁺, 90), 290 (100), 262 (60), 216 (32), 200 (34); accurate EIMS: calculated for C₁₆H₁₇NO₆ 319.1056, found 319.1060. Data for **4b**: colorless oil (17%); *R*_f = 0.28 (EtOAc/hexane 3:2); IR (CH₂Cl₂) ν_{\max} 3024, 1735, 1625, 1076 cm⁻¹; ¹H NMR (CD₂Cl₂) δ 7.78 (1H, br s, H7), 7.44 (1H, dd, *J* = 7.6, 1.4 Hz, H4), 7.24 (1H, td, *J* = 7.5, 1.3 Hz, H6), 7.03 (1H, td, *J* = 7.5, 1.1 Hz, H5), 6.05 (1H, s, H8a), 4.06 (3H, s, OMe *syn*), 3.89 (3H, s, OMe *anti*), 3.89 (3H, s, CO₂Me), 2.15 and 1.89 (2H, 2dq, *J* = 14.2, 7.5 Hz, CH₂), 0.83 (3H, t, *J* = 7.5 Hz, Me); ¹³C NMR (CD₂Cl₂) δ 168.5 (s, C9), 168.5 (s, C2), 153.4 (s, CO₂Me), 140.6 (s, C7a), 136.0 (s, C3b), 128.9 (d, C6), 124.6 (d, C4), 124.4 (d, C5), 115.1 (d, C7), 92.9 (s, C8a), 88.0 (s, C3), 63.6 (q, OMe *syn*), 55.5 (s, C3a), 54.8 (q, OMe *anti*), 53.5 (q, CO₂Me), 28.1 (t, CH₂), 8.8 (t, Me); EIMS *m/z* 333 (M⁺, 96), 304 (74), 276 (100), 216 (22); accurate EIMS: calculated for C₁₇H₁₉NO₆ 333.1223, found 333.1223. Data for **4c**: colorless oil (17%); *R*_f = 0.32 (EtOAc/hexane 3:2); IR (CH₂Cl₂) ν_{\max} 3026, 1728, 1624, 1062 cm⁻¹; ¹H NMR (CD₂Cl₂) δ 7.74 (1H, br s, H7), 7.45 (1H, dd, *J* = 7.6, 1.4 Hz, H4), 7.26 (1H, td, *J* = 7.4, 1.4 Hz, H6), 7.05 (1H, td, *J* = 7.6, 1.1 Hz, H5), 6.12 (1H, s, H8a), 4.04 (3H, s, OMe *syn*), 3.91 (3H, s, OMe *anti*), 3.90 (3H, s, CO₂Me), 2.78 (1H, h, *J* = 6.9 Hz, CH), 1.02 and 0.60 (6H, 2d, *J* = 6.9 Hz, 2Me); ¹³C NMR (CD₂Cl₂) δ 168.5 (s, C2), 168.0 (s, C9), 153.3 (s, CO₂Me), 140.9 (s, C7a), 135.7 (s, C3b), 128.9 (d, C6), 124.3 (d, C4), 124.2 (d, C5), 115.0 (d, C7), 89.8 (s, C8a), 89.1 (s, C3), 63.4 (q, OMe *syn*), 59.1 (s, C3a), 54.6 (q, OMe *anti*), 53.5 (q, CO₂Me), 31.2 (d, CH), 18.0 and 16.7 (2q, 2Me); EIMS *m/z* 347 (M⁺, 32), 304 (72), 276 (100), 232 (23), 218 (27); accurate EIMS: calculated for C₁₈H₂₁NO₆ 347.1369, found 347.1373. Data for **4d**: colorless crystals (18%); mp 175–176 °C (from EtOAc/hexane); *R*_f = 0.27 (EtOAc/hexane 3:2); IR (CH₂Cl₂) ν_{\max} 3016, 1730, 1623, 1076 cm⁻¹; ¹H NMR (CD₂Cl₂) δ 7.70 (1H, br s, H7), 7.64 (1H, dd, *J* = 7.4, 1.7 Hz, H4), 7.26 (1H, td, *J* = 7.7, 1.4 Hz, H6), 7.23–6.97 (5H, m, Ph), 7.09 (1H, td, *J* = 7.6, 1.1 Hz, H5), 6.19 (1H, s, H8a), 4.01 (3H, s, OMe *syn*), 3.99 (3H, s, OMe *anti*), 3.79 (3H, s, CO₂Me), 3.41 and 3.34 (2H, d, *J* = 14.3 Hz, CH₂); ¹³C NMR (CD₂Cl₂) δ 168.7 (s, C2), 168.1 (s, C9), 153.3 (s, CO₂Me), 140.6 (s, C7a), 136.5 (s, C3b), 135.8 (s, Ci), 130.1 (d, Co), 129.1 (d, C6), 128.6 (d, Cm), 127.4 (d, Cp), 125.0 (d, C4), 124.2 (d, C5), 115.3 (d, C7), 92.4 (s, C8a), 88.6 (s, C3), 63.5 (q, OMe *syn*), 55.9 (s, C3a), 54.7 (q, OMe *anti*), 53.5 (q, CO₂Me), 41.5 (t, CH₂); EIMS *m/z* 395 (M⁺, 10), 336 (18), 304 (100), 276 (30); accurate EIMS: calculated for C₂₂H₂₁NO₆ 395.1369, found 395.1377. Data for **5a**: colorless oil (77%); *R*_f = 0.45 (EtOAc/hexane 3:2); IR (CH₂Cl₂) ν_{\max} 3016, 1732, 1638, 1085 cm⁻¹; ¹H NMR (CD₂Cl₂) δ 7.74 (1H, br s, H7), 7.66 (1H, dd, *J* = 7.7, 0.8 Hz, H4), 7.21 (1H, td, *J* = 7.4, 1.4 Hz, H6), 7.02 (1H, td, *J* = 7.7, 1.1 Hz, H5), 6.20 (1H, s, H8a), 3.90 (3H, s, OMe), 3.90 (3H, s, NCO₂Me), 3.69 (3H, s, CO₂Me), 1.71 (3H, s, Me); ¹³C NMR (CD₂Cl₂) δ 167.4 (s, C2), 165.3 (s, CO₂Me), 153.6 (s, NCO₂Me), 140.1 (s, C7a), 137.4 (s, C3b), 128.4 (d, C6), 125.1 (d, C4), 124.2 (d, C5), 114.9 (d, C7), 99.9 (s, C8a), 83.6 (s, C3), 57.5 (q, OMe), 54.2 (s, C3a), 53.8 (q, NCO₂Me), 50.6 (q, CO₂Me), 24.7 (q, Me); EIMS *m/z* 319 (M⁺, 13), 287 (48), 260 (100), 229 (27), 217 (18); accurate EIMS: calculated for C₁₆H₁₇NO₆ 319.1056, found 319.1053. Data for **5b**: colorless oil (75%); *R*_f = 0.49 (EtOAc/hexane 3:2); IR (CH₂Cl₂) ν_{\max} 3016, 1730, 1638, 1090 cm⁻¹; ¹H NMR (CD₂Cl₂) δ 7.73 (1H, br s, H7), 7.63 (1H, dd, *J* = 7.6, 1.5 Hz, H4), 7.21 (1H, td, *J* = 7.4, 1.5 Hz, H6), 7.02 (1H, td, *J* = 7.6, 1.1 Hz, H5), 6.29 (1H, s, H8a), 3.90 (3H, s, OMe), 3.90 (3H, s, NCO₂Me), 3.68 (3H, s, CO₂Me), 2.31 and 1.92 (2H, 2dq, *J* = 14.5, 7.5 Hz, CH₂), 0.83 (3H, t, *J* = 7.5 Hz, Me); ¹³C NMR (CD₂Cl₂) δ 167.6 (s, C2), 165.3 (s, CO₂Me), 154.0 (s, NCO₂Me), 140.4 (s, C7a), 136.6 (s, C3b), 128.4 (d, C6), 125.1 (d, C4), 124.2 (d, C5), 114.9 (d, C7), 97.2 (s, C8a), 81.5 (s, C3), 59.1 (s, C3a), 57.5 (q, OMe), 53.5 (q, NCO₂Me), 50.6 (q, CO₂Me), 28.9 (t, CH₂), 9.0 (q, Me); EIMS *m/z* 333 (M⁺, 6), 301 (27), 274 (100), 269 (77), 216 (30); accurate EIMS: calculated for C₁₇H₁₉NO₆ 333.1212, found 333.1223. Data for **5c**: colorless oil (80%); *R*_f = 0.53 (EtOAc/hexane 3:2); IR (CH₂Cl₂) ν_{\max} 3022, 1729, 1638, 1095 cm⁻¹; ¹H NMR (CD₂Cl₂) δ 7.74 (1H, br s, H7), 7.63 (1H, dd, *J* = 7.6, 1.5 Hz, H4), 7.21 (1H, td, *J* = 7.7, 1.3 Hz, H6), 7.02 (1H, td, *J* = 7.5, 1.1 Hz, H5), 6.32 (1H, s, H8a), 3.90 (3H, s, NCO₂Me), 3.89 (3H, s, OMe), 3.67 (3H, s, CO₂Me), 2.97 (1H, h, *J* = 6.9 Hz, CH), 1.00 and 0.56 (6H, 2d, *J* = 6.9 Hz, 2Me); ¹³C NMR (CD₂Cl₂) δ 167.4 (s, C2), 165.2 (s, CO₂Me), 153.3 (s, NCO₂Me), 140.7 (s, C7a), 136.5 (s, C3b), 128.3 (d, C6), 124.8 (d, C4), 124.2 (d, C5), 114.8 (d, C7), 94.1 (s, C8a), 82.1 (s, C3), 62.9 (s, C3a), 57.5 (q, OMe), 53.5 (q, NCO₂Me), 50.6 (q, CO₂Me), 30.9 (d, CH), 18.3 and 16.6 (2q, 2Me); EIMS *m/z* 347 (M⁺, 12), 315 (43), 304 (100), 288 (53), 283 (86), 276 (42); accurate EIMS: calculated for C₁₈H₂₁NO₆ 347.1368, found 347.1358. Data for **5d**: colorless oil (51%); *R*_f = 0.49 (EtOAc/hexane 3:2); IR (CH₂Cl₂) ν_{\max} 3018, 1734, 1635, 1094 cm⁻¹; ¹H NMR (CD₂Cl₂) δ 7.83 (1H, dd, *J* = 7.7, 1.6 Hz, H4), 7.63 (1H, br s, H7), 7.26–7.00 (5H, m, Ph), 7.22 (1H, overlapped, H6), 7.08 (1H, td, *J* = 7.5, 1.1 Hz, H5), 6.36 (1H, s, H8a), 3.83 (3H, s, NCO₂Me), 3.78 (3H, s, OMe), 3.76 (3H, s, CO₂Me), 3.68 and 3.19 (2H, 2d, *J* = 13.8 Hz, CH₂); ¹³C NMR (CD₂Cl₂) δ 167.9 (s, C2), 165.6 (s, CO₂Me), 153.2 (s, NCO₂Me), 140.5 (s, C7a), 136.9 (s, C3b), 136.8 (s, Ci), 130.4 (d, Co), 128.6 (d, C6), 128.5 (d, Cm), 125.3 (d, C4), 124.3 (d, C5), 115.1 (d, C7), 96.5 (s, C8a), 82.1 (s, C3), 59.3 (s, C3a), 57.5 (q, OMe), 53.6 (q, NCO₂Me), 50.8 (q, CO₂Me), 41.7 (t, CH₂); EIMS *m/z* 395 (M⁺, 10), 336 (18), 304 (100), 276 (30); accurate EIMS: calculated for C₂₂H₂₁NO₆ 395.1369, found 395.1374.
16. Crystal data for **4a**: C₁₆H₁₇O₆N₁, colorless, crystal size 0.42 × 0.38 × 0.20 mm, monoclinic, space group *P*2₁/*c*, *a* = 11.396(3) Å, *b* = 8.837(1) Å, *c* = 15.840(2) Å, $\alpha = \gamma = 90^\circ$, $\beta = 100.13(2)^\circ$, *V* = 1570.4(5) Å³, *Z* = 4,

$D_c = 1.35 \text{ mg/mm}^3$, $\lambda = 1.54184 \text{ \AA}$, $\mu(\text{Cu K}\alpha) = 0.878 \text{ mm}^{-1}$, $F(000) = 672$, $3.94 < \theta < 59.95^\circ$, $R = 4.7\%$, $wR_2 = 13.5\%$, largest difference in peak and hole: 0.255 and -0.163 e/\AA^3 . The CCDC deposition number is 635173.

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