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4,6-Dichloro-2-oxa-5-azabicyclo[2.2.2]oct-5-en-3-ones and their Use in the Synthesis of 1,6-Dihydro-6-oxo-2-pyridine- and 6-Oxo-2-piperidinecarboxylates.

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Abstract: 4,6-Dichloro-2-oxa-5-azabicyclo[2.2.2]oct-5-en-3-ones obtained from cycloaddition of 2*H*-1,4-oxazin-2-ones and alkene compounds, undergo lactone cleavage with alcohols to yield 1,4,5,6-tetrahydro-5-hydroxy-6-oxo-2-pyridinecarboxylates which can be dehydrated or reduced to afford 1,6-dihydro-6-oxo-2-pyridine- or 6-oxo-2-piperidinecarboxylates.

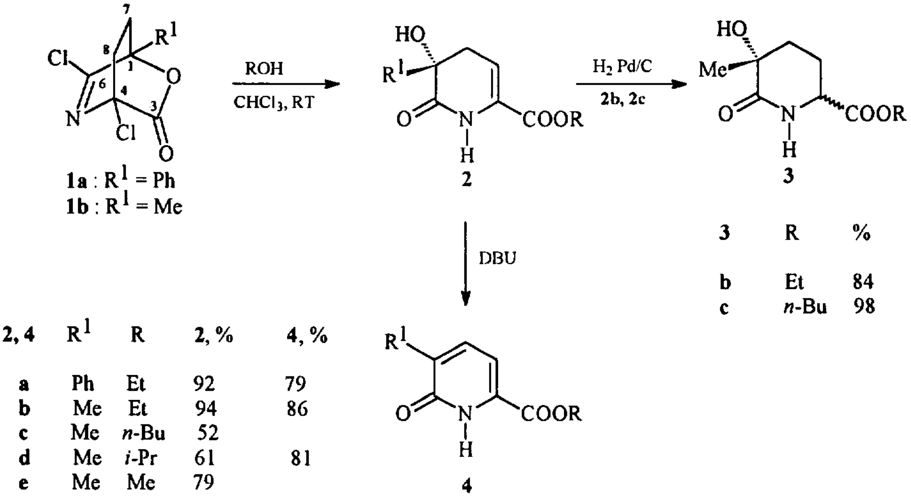
The cleavage of lactones by different nucleophiles[1] makes them useful synthetic intermediates for the preparation of ω-substituted carboxylic or carbocyclic acids and derivatives. We here report a general method for the generation of variably substituted 1,6-dihydro-6-oxo-2-pyridine- or 6-oxo-2-piperidinecarboxylates via the corresponding di- and tetrahydropyridines obtained via lactone cleavage of bicyclic adducts **1, 10** with alcohols. The latter are easily and variably accessible via Diels-Alder reaction of 2*H*-1,4-oxazin-2-ones with olefins.[2] Some 1,6-dihydro-6-oxo-[3] and 2-pyridinecarboxylic acid derivates are known to exhibit bio-activity[4] and can be important intermediates for the preparation of (phyto)pharmaca[5]. Futhermore some 5-hydroxy-6-oxo-2-piperidinecarboxylic acids have been mentioned as intermediates in the synthesis of analogues of camptothecin[6] and tabtoxin[7].

RESULTS AND DISCUSSION

The (±)-4,6-dichloro-2-oxa-5-azabicyclo[2.2.2]oct-5-en-3-ones **1a,b** were prepared from the reaction of the corresponding 3,5-dichloro-2*H*-1,4-oxazin-2-ones with ethene (20 atm) in toluene at 110 °C.[2] These cycloadducts of ethene have bielectrophilic characteristics, due to a lactone and a chlorimine function. On treatment of **1a** or **1b** with 4 equivalents of ethanol in chloroform for four hours (or one day) at room temperature the (±)-ethyl 1,4,5,6-tetrahydro-5-hydroxy-6-oxo-5-phenyl-2-pyridinecarboxylic ester **2a** or the corresponding 5-methyl analogue **2b** were obtained in 92 % and 94 % yield respectively (Scheme 1). Simple reaction of the chlorimine leading to an iminoether structure could be rejected. The products **2a** or **2b** have IR-absorptions corresponding with an ester group at 1720 cm^{-1} (**2a**) or at 1730 cm^{-1} (**2b**). The absorptions at

1690 cm^{-1} and 1660 cm^{-1} (**2a**) or 1700 cm^{-1} and 1665 cm^{-1} (**2b**), indicate a lactam function instead of a lactone. Furthermore the ^{1}H-NMR spectrum in $CDCl_3$ does not show the four multiplets expected for an ethylene bridge; two dd-absorptions at 2.94 ppm and 3.05 ppm (**2a**) or 2.58 ppm and 2.69 ppm (**2b**) are consistent with the protons in position 4 of the structures **2a,b**: both protons in **2b** are coupled with each other (^2J = 18.5 Hz) and with H-3 (^3J = 3.0, 6.5 Hz). In addition H-3 (ddd, ^4J = 2.0 Hz) is coupled with the amide proton and two broad singlets are observed for the alcohol and amide protons.

As expected, reaction of **1b** with *n*-butanol or 2-propanol at room temperature for one day yielded compound **2c** or **2d** respectively. In these cases the reaction was performed with the nucleophile as solvent, as the reaction ran too slowly in $CHCl_3$.

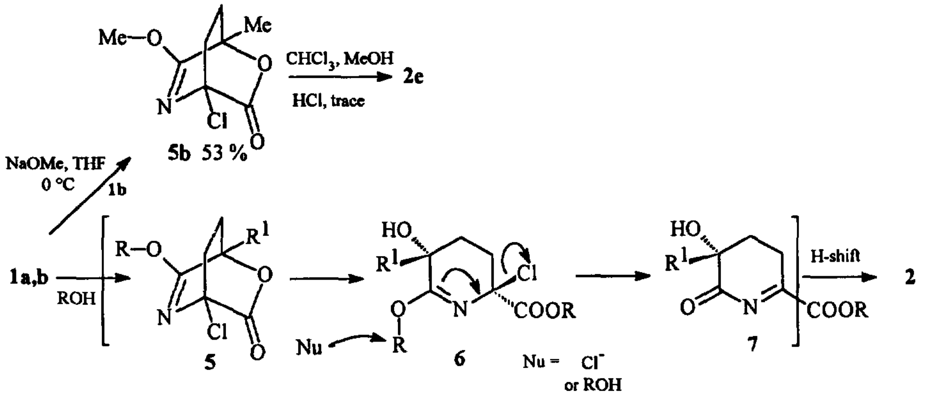


2, 4	R^1	R	2, %	4, %
a	Ph	Et	92	79
b	Me	Et	94	86
c	Me	*n*-Bu	52	
d	Me	*i*-Pr	61	81
e	Me	Me	79	

3	R	%
b	Et	84
c	*n*-Bu	98

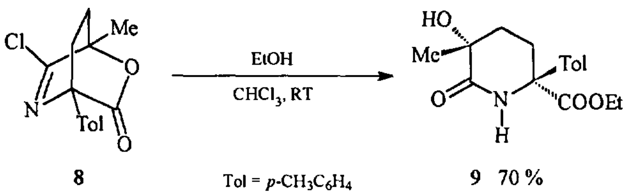
Scheme 1. Lactone cleavage of the adducts 2 with alcohols followed by dehydration or hydrogenation.

Mechanistically, the conversion of **1** into **2** may proceed via an iminoether **5** and the hydrogen chloride formed then catalyses the lactone cleavage leading to intermediate **6** (Scheme 2). A nucleophilic attack (Cl^- or EtOH) on the iminoether function assisted by the leaving chloride and a subsequent proton shift in intermediate **7** eventually leads to compounds **2**. An indication for the possible intervention of an intermediate of type **5** is given by the reaction of **5b** - obtained from treatment of **1b** with NaOMe in THF at 0 °C - with four equivalents of methanol and a trace of HCl in $CHCl_3$ as the solvent. After reaction for one day at ambient temperature the (±)-methyl 1,4,5,6-tetrahydro-5-hydroxy-5-methyl-6-oxo-2-pyridinecarboxylic ester **2e** was obtained in 79 % yield (Scheme 1).



Scheme 2: Mechanistic pathway for the reaction of **1a,b** with alcohols.

In order to control the effect of the chlorine substituent in **5** and **6** we also studied the reaction of **8**.[2] When this adduct was treated with four equivalents of EtOH in $CHCl_3$ for two days, compound **9** was isolated in 70 % yield (Scheme 3). We presume that the ester **9** results from a nucleophilic attack on an intermediate of type **6** wherein loss of HCl is impossible due to the replacement of Cl by *p*-tolyl.

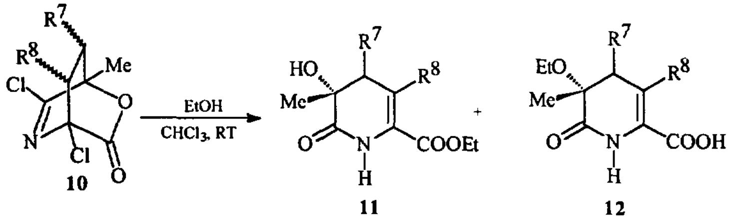


Scheme 3: Reaction of the 4-tolyl-substituted adduct **8** with ethanol.

The usefulness of this lactone cleavage is demonstrated in the preparation of 6-oxo-2-piperidinecarboxylates **3** and the corresponding 1,6-dihydro-6-oxo-2-pyridinecarboxylates **4**, obtained by reduction or dehydration of compounds **2** (Scheme 1). The reduction of **2b** and **2c** in ethanol with hydrogen on Pd/C (10 %) led to a high yield (84 % and 95 %) of two isomeric 6-oxo-2-piperidinecarboxylic esters **3b** or **c** in a ratio 2:1. They were not separated but the 400 MHz ^{1}H-NMR data allowed their structure identification. The two isomers of **3b** show a different coupling-pattern for H-2. For the major product $\Sigma\ ^3J$-values for the coupling of H-2 with the protons on C-3 are large (^3Jaa = 10 Hz, ^3Jae = 5 Hz) and refer to an axial-axial coupling. For the minor product H-2 takes an equatorial position (^3Jee = 6 Hz = ^3Jae). The stereochemical determination in the 5-position is based on the ^{1}H coupled ^{13}C-NMR spectrum. The two isomers show somewhat different absorptions for most of the carbon atoms. The Σ^3J-value (8.5 Hz) for the coupling of the methyl carbon atom on C-5 with the protons in 4-position lies in between the literature data[8] on the $\Sigma(^3J$ae + ^3Jee)- and $\Sigma(^3J$ae + ^3Jaa)-values. Considering the estimated angles and the lowering effect of an electron attracting group (OH)[8] on ^3J-values, a *cis* relationship between the 5-methyl group and the 2-ester function in the major product is assumed.

Treatment of **2a-b** or **2d** with triethylamine or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in refluxing chloroform or acetonitrile gave the corresponding 1,6-dihydro-6-oxo-2-pyridinecarboxylic esters **4a-b** or **4d** in high yield (Scheme 1). This elimination of H_2O proceeds probably by an E_1cb-mechanism. The ^{1}H-NMR spectra show a typical dd-absorption at ± 6.9 and 7.4 ppm (^3J = ± 7 Hz) for the protons on C-3 and C-4 (instead of the ABX pattern for these protons in **2**) and a broad singlet absorption for the amide proton (7.40 - 10.6 ppm). Also the specific absorptions in the ^{13}C-NMR spectrum correspond with those of a pyridinone structure.

In order to examine the scope of the reaction sequence of scheme 1, other cycloadducts (**10a-f**) with various substituents in positions 7 and 8 were used.[2] The ethanol cleavage of adduct **10a**, possessing an *endo*-group (substituent oriented towards the imine-system) in the 8-position yielded the ester **11a** and the acid **12a**, in a 1:1 ratio. Treatment of adducts **10b** or **10c** with ethanol gave only one product. In the case of **10b** with an *exo*-directed group in the 8-position, acid **12b** (37 %) was isolated. Cleavage of the other adduct **10c**, with an *endo*-directed group in the 7-position, led to the 4-phenoxymethyl-2-pyridinecarboxylate **11c**. Evidence for the *endo* structure in **10c** was given by the ^{1}H coupled ^{13}C-NMR spectrum showing specific ^3J-values for the coupling of the carbonyl atom (C3) and the imidoylcarbon atom (C6) with the protons H-7 and H-8: ($J_{C6\text{-}H7exo}$ = 8.5 Hz, $J_{C3\text{-}H8exo} \approx$ 1 Hz, $J_{C3\text{-}H8endo}$ = 7.5 Hz, $J_{C6\text{-}CH_3}$ = 4.5 Hz). From literature data[2,9] we know that the values of $J_{C3\text{-}H8endo}$ and $J_{C6\text{-}H7exo}$ are higher than those of $J_{C3\text{-}H8exo}$ and $J_{C6\text{-}H7endo}$ due to the trans- and gauche-configurations. The absorptions and coupling constants for C3 and C6 of adduct **10c** unequivocally prove the proposed 7-substituted *endo* structure and therefore the 4-phenoxymethyl group and the 5-Me substituent of compound **11c** should be *cis* oriented. Reaction of the *endo* disubstituted adduct **10d** gave exclusively the O-acyl cleaved product **11d** (76 %) (same reasoning could be made regarding the stereochemistry as for compound **11c**) which like compounds **3** could also be dehydrated with three equivalents of DBU in refluxing CH_3CN to yield (95 %) the ester **13d** (Scheme 4).

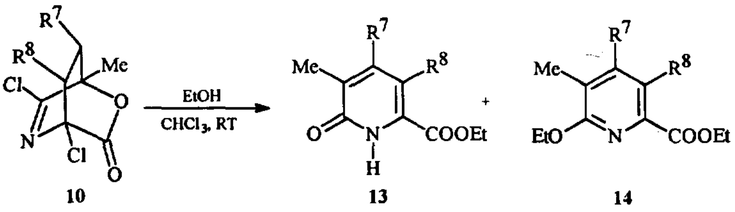


10	R7	R8	11, %	12, %
a	H	Ph *endo*	47	48
b	H	2-oxo-1-pyrrolidinyl *exo*	/	37
c	PhOCH$_2$ *endo*	H	70	/
d	-(CH$_2$)$_3$- *endo*		76	

↓ DBU

13d 95 %

Scheme 4: Reaction of the 7- or / and 8-substituted adducts **10a-d** with ethanol.



10	R^7	R^8	13, %	14, %
e	COOMe	COOMe *endo*	52	16
f	-CONHPhCO- *endo*		/	65

Scheme 5: Reaction of the 7,8-disubstituted adducts **10e,f** with ethanol.

The above mentioned results points to a competition between an O-acyl or O-alkyl cleavage. According to some authors the way of cleavage (O-acyl or O-alkyl) in esters and lactones depends on various factors.[1,10] The most important ones are the nature of the nucleophile and the degree of substitution on the ester or lactone. We suppose that the O-acyl cleavage is dominant in the case of the 7,8-unsubstituted adducts **1a,b** or the disubstituted adduct **10d** and certainly when the S_N2 attack on C-1 is disfavoured as in **10c**; the O-alkyl cleavage will come into competition with the O-acyl cleavage when the steric hindrance in 8-position is more pronounced as in **10a** and **10b**. The structure determination of the compounds **11a** and **11c,d** and of **12a,b** is mainly based on the NMR data, which are comparable to those of compounds **2**. The A_2X_3-pattern for the methylene protons of the ethyl group in the ^{1}H-NMR spectra of compounds **11a,c** is replaced by a ABX_3-pattern in the spectra of compounds **12** indicating the presence of an asymmetric center in the neighbourhood of the methylene protons. The two products can also be distinguished in the ^{13}C-NMR spectra: the ester carbonyl absorbs at 161.2 - 161.9 ppm and the acid carbonyl at 163.6 - 163.7 ppm.

The reaction sequence was also examined for adducts **10e,f** with electron withdrawing groups (*endo*) in the positions 7 and 8 of the adduct (Scheme 5). Treatment of **10e** (R^7 = R^8 = COOMe) with 4 equivalents ethanol in $CHCl_3$ at ambient temperature, gave 52 % of the 1,6-dihydro-6-oxo-2-pyridinecarboxylic ester **13e** along with 16 % of the 6-ethoxy-2-pyridinecarboxylic ester **14e**. In the case of **10f** only **14f** (65 %) and no product of type **13** was isolated. We presume that the normal conversion of an intermediate of type **6** into **7** is now competitive with the rapid loss of H_2O and HCl due to the electron withdrawing nature of the substituents R^7 and R^8. The ^{13}C absorptions of **13** and **14** correspond with the assigned structures. The ^{1}H-NMR spectra of **13** show a broad singlet at 10 - 11 ppm (amide proton) and absorptions consistent with one ethyl group. Two ethyl groups are observed in the ^{1}H-NMR spectra of products **14**.

Conclusion. We can state that reaction of the bicyclic adducts **1** and **10** with alcohols is an interesting pathway for the preparation of (3),(4),5-substituted 1,4,5,6-tetrahydro-5-hydroxy-6-oxo-2-pyridinecarboxylates **2, 11** which to our knowledge have scarcely been described.[11] By dehydration or hydrogenation compounds **2** have been converted into (3),(4),5-substituted 1,6-dihydro-6-oxo-2-pyridinecarboxylates **4, 13** and into 5-hydroxy-6-oxo-2-piperidinecarboxylates **3** respectively. Compounds of type **3** and **9** (obtained from adduct **8**) are related to 5-hydroxy-2-piperidinecarboxylic acids[12], which have been mentioned as intermediates in the synthesis of some natural products analogues.[6,7] Reaction of 7- or 8-substituted adducts **10** gave O-acyl and/or O-alkyl cleavage depending on the steric hindrance in the neighbourhood of C-1 or C-3.

EXPERIMENTAL

Infrared spectra were recorded as thin films between NaCl plates or as solids in KBr pellets on a Perkin-Elmer 297 grating IR spectrophotometer and a Perkin-Elmer 1720 Fourier transform spectrometer. The mentioned IR-absorptions were observed as strong bands. ^{1}H NMR spectra and ^{13}C NMR spectra were recorded on a Bruker WM 250 or on a Bruker AMX 400 instrument. The ^{1}H and ^{13}C chemical shifts are reported in ppm relative to tetramethylsilane or the deuterated solvent as an internal reference. Mass spectra were run by using a Kratos MS50TC instrument and a DS90 data system. For chromatography analytical TLC plates (Alugram Sil G/UV$_{254}$) and 70-230 mesh silica gel 60 (E.M. Merck) were used. Melting points were taken using a Reichert-Jung Thermovar apparatus and an Electrothermal IA 9000 digital melting point apparatus and are uncorrected. Microanalyses were performed by Janssen Pharmaceutica on a Carlo Erba elemental analyser type 1106. The preparation of all cycloadducts except **5b** and **10c** *endo* has been described in a preceeding paper[2].

I. Synthesis of the cycloadducts 5b and 10c endo.

(±)-4-chloro-6-methoxy-1-methyl-2-oxa-5-azabicyclo[2.2.2]oct-5-en-3-one 5b.

To a stirred solution of 4,6-dichloro-1-methyl-2-oxa-5-azabicyclo[2.2.2]oct-5-en-3-one **1b** (0.5 g, 1.85 mmol) in dry THF (5 ml), NaOMe (0.49 g, 9.2 mmol) was added at 0 °C. After one hour the reaction mixture was centrifuged and the solution decanted to remove salts. The salts were washed with dry THF, centrifuged and decanted again. After evaporation of the combined filtrates the reaction mixture was purified by flash chromatography (silica gel, eluent: 5 % EtOAc/CH$_2$Cl$_2$). Yield: 53 %; unstable oil; IR (KBr) cm^{-1}: 1730, 1619; ^{1}H NMR (CDCl$_3$): 1.27 (s, 3H, 1-CH$_3$), 1.90 - 2.10 (m, 4H, CH$_2$CH$_2$), 3.86 (s, 3H, OCH$_3$); ^{13}C NMR (CDCl$_3$): 19.8 (1-CH$_3$), 27.5, 30.5 (C-7 and C-8), 53.4 (OCH$_3$), 92.2 (C-4), 82.4 (C-1), 161.2 (C-6), 167.8 (C-3); m/z (%): 204 (MH$^+$, 1), 176 (81), 140 (45), 43 (100); exact mass for $C_8H_{11}N_1O_3Cl_1$: 204.0427 [MH]$^+$; found 204.0420 (MH$^+$ due to bimolecular ion-molecule reaction)

(±)-*endo* 4,6-dichloro-1-methyl-7-phenoxymethyl-2-oxa-5-azabicyclo[2.2.2]oct-5-en-3-one 10c.

Allyl phenyl ether (0.017 mmol, 3 equiv) was added at once to a stirred solution of 3,5-dichloro-6-methyl-2*H*-1,4-oxazin-2-one (1.0 g, 5.6 mmol) in CHCl$_3$ (5 ml) at 70 °C. After reflux for 6 hours the solvent was evaporated and the mixture of the two regioisomers purified by chromatography (silica gel, eluent: 5 % EtOAc/CHCl$_3$). Yield of **10c**: 39 %; m.p.: 85 °C (CCl$_4$); IR (KBr) cm^{-1}: 1790, 1610; ^{1}H NMR (CDCl$_3$): 1.80 (s, 3H, CH$_3$), 2.00 - 2.80 (m, 3H, H-7*exo*, H-8*exo*, H-8*endo*), 3.95 and 4.28 (m, 2H, CH$_2$O), 6.81 - 7.52 (m, 5H, Ar-H); ^{13}C NMR (CDCl$_3$): 19.6 (CH$_3$), 36.0 (C-8), 43.6 (C-7), 64.8 (CH$_2$O), 83.2 (C-4), 86.2 (C-1), 114.4, 121.8, 129.7 (Ar-C), 157.8 (C-*ipso*), 164.4 (C-6), 165.4 (C-3); $J_{C6\text{-}CH_3}$ = 4.5 Hz, $J_{C6\text{-}H7exo}$ = 8.5 Hz, $J_{C3\text{-}H8exo}$ ≈ 1 Hz, $J_{C3\text{-}H8endo}$ = 7.5 Hz indicative for an 7-substituted *endo* structure[2,9]; m/z (%): 313 (M^+, 10), 176 (17), 107 (51), 94 (100); exact mass for $C_{14}H_{13}N_1O_3Cl_2$: 313.0271; found 313.0270

II. Reaction of the cycloadducts 1 with alcohols: synthesis of 1,4,5,6-tetrahydro-5-hydroxy-6-oxo-2-pyridinecarboxylates 2.

The alcohol (4 equiv) was added to the cycloadducts **1** (5 mmol) dissolved in $CHCl_3$ (10 ml) at room temperature. However in the cases **2c-d** and **2e** *n*-butanol, *i*-propanol and $CHCl_3$/HCl were used as solvent. The mixture was stirred for 15 min to two days at ambient temperarure. After evaporation of the solvent, purification was done by chromatography (silica gel, eluent: EtOAc/$CHCl_3$). Yields are given in scheme 1.

(±)-ethyl 1,4,5,6-tetrahydro-5-hydroxy-6-oxo-5-phenyl-2-pyridinecarboxylate 2a.
reaction time 12h. oil; IR (NaCl plates) cm^{-1}: 1720, 1690, 1660; ^1H NMR ($CDCl_3$) δ: 1.30 (t, 3H, ^3J = 7Hz, CH_3), 2.94 (dd, 1H,^2J = 18 Hz, ^3J = 3 Hz, H-4), 3.05 (dd, 1H,^2J = 18 Hz, ^3J = 6 Hz, H-4), 4.25 (q, 2H, ^3J = 7 Hz, OCH_2), 4.60 (br s, 1H, OH), 6.25 (dd, 1H, ^3J = 6, 3 Hz, H-3), 7.30 (m, 5H, Ar-H), 8.40 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$): 13.9 (CH_3), 35.5 (C-4), 62.0 (OCH_2), 85.2. (C-5), 113.9 (C-3), 125.1, 128.4, 128.7 (Ar-C), 128.5 (C-2), 137.3 (C-*ipso*), 162.5 (CO), 170.8 (C-6); m/z (%): 261 (M^+, 42), 235 (24), 215 (7), 187 (4), 161 (27), 105 (100); exact mass for $C_{14}H_{15}NO_4$: 261.1001; found: 261.1005

(±)-ethyl 1,4,5,6-tetrahydro-5-hydroxy-5-methyl-6-oxo-2-pyridinecarboxylate 2b.
reaction time 15 min. m.p.: 79 °C (CCl_4); IR (KBr) cm^{-1}: 1730, 1700, 1665; ^1H NMR ($CDCl_3$) δ: 1.35 (t, 3H, ^3J = 7 Hz, CH_3), 1.36 (s, 3H, 5-CH_3), 2.58 (dd, 1H, ^2J = 18.5 Hz, ^3J = 6.5 Hz, H-4), 2.69 (dd, 1H, ^2J = 18.5 Hz, ^3J = 3.0 Hz, H-4), 3.75 (br s, 1H, OH), 4.33 (q, 2H, ^3J = 7 Hz, OCH_2), 6.29 (ddd, 1H, ^3J = 6.5 Hz, ^3J = 3.0 Hz, ^4J = 2.0 Hz, H-3), 7.75 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$): 13.7 (CH_3), 25.2 (5-CH_3), 34.9 (C-4), 61.4 (OCH_2), 68.5 (C-5), 113.6 (C-3), 127.9 (C-2), 161.0 (CO), 173.6 (C-6); m/z (%): 199 (M^+, 2), 173 (66), 155 (14), 99 (100); exact mass for $C_9H_{13}NO_4$: 199.0845; found: 199.0840

(±)-*n*-butyl 1,4,5,6-tetrahydro-5-hydroxy-5-methyl-6-oxo-2-pyridinecarboxylate 2c.
reaction time 24h. oil; IR (NaCl plates) cm^{-1}: 1725, 1695, 1660; ^1H NMR ($CDCl_3$) δ: 0.95 (t, 3H, ^3J = 7 Hz, CH_3), 1.40 (s, 3H, 5-CH_3), 1.45 (sext, 2H, ^3J = 7 Hz, $CH_3C\underline{H}_2CH_2CH_2$), 1.70 (pent, 2H, ^3J = 7 Hz, $CH_3CH_2C\underline{H}_2CH_2$), 2.60 (dd, 1H, ^2J = 18.5 Hz,^3J = 5.5 Hz, H-4), 2.70 (dd, 1H, ^2J = 18.5 Hz,^3J = 3 Hz, H-4), 4.21 (br. s, 1H, OH), 4.25 (t, 2H, ^3J = 7 Hz, $CH_3CH_2CH_2C\underline{H}_2O$), 6.30 (ddd, 1H, ^3J = 5.5, 3 Hz, ^4J ≈ 1 Hz, H-3), 8.25 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$): 13.4 (CH_3), 25.4 (5-CH_3), 18.8, 30.2, 35.0 (CH_2 and C-4), 65.5 (OCH_2), 68.6 (C-5), 113.7 (C-3), 127.9 (C-2), 161.1 (CO), 173.6 (C-6); m/z (%): 227 (M^+, 53), 171 (15), 153 (48), 125 (36), 100 (100); exact mass for $C_{11}H_{17}NO_4$: 227.1153; found: 227.1160

(±)-*i*-propyl 1,4,5,6-tetrahydro-5-hydroxy-5-methyl-6-oxo-2-pyridinecarboxylate 2d.
reaction time 24h. m.p.: 128 °C (CCl_4); IR (KBr) cm^{-1}: 1731, 1691, 1652; ^1H NMR ($CDCl_3$) δ: 1.31 (d, 3H, ^3J = 6 Hz, CH_3), 1.33 (d, 3H, ^3J = 6 Hz, CH_3), 1.36 (s, 3H, 5-CH_3), 2.56 (dd, 1H, ^2J = 18 Hz, ^3J = 6 Hz, H-4), 2.70 (dd, 1H, ^2J = 18 Hz, ^3J = 3.5 Hz, H-4), 4.20 (br. s, 1H, OH), 5.14 (sept, 1H, ^3J = 6 Hz, CH), 6.28 (ddd, 1H, ^3J = 3.5 Hz, ^3J = 6 Hz, ^4J = 1.5 Hz, H-3), 8.21 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$): 21.3 (CH_3),

25.3 (5-CH_3), 34.9 (C-4), 69.5 (OCH), 69.6 (C-5), 113.5 (C-3), 128.1 (C-2), 160.5 (CO), 173.7 (C-6); m/z (%): 213 (M^+, 62), 171 (48), 153 (41), 100 (100); exact mass for $C_{10}H_{15}NO_4$: 213.0997; found: 213.1005; anal cald for $C_{10}H_{15}NO_4$: C 56.33, H 7.09, N 6.57; found: C 56.01, H 7.12, N 6.44

(±)-methyl 1,4,5,6-tetrahydro-5-hydroxy-5-methyl-6-oxo-2-pyridinecarboxylate 2e.
reaction time 24h. m.p.: 106 °C (CCl_4); IR (KBr) cm^{-1}: 1736, 1697, 1656; ^1H NMR ($CDCl_3$) δ: 1.35 (s, 3H, 5-CH_3), 2.54 (dd, 1H, ^2J = 18.5 Hz, ^3J = 6.5 Hz, H-4), 2.67 (dd, 1H, ^2J = 18.5 Hz, ^3J = 3.5 Hz, H-4), 3.85 (s, 3H, OCH_3), 4.09 (br s, 1H, OH), 6.30 (m, 1H, H-3), 8.06 (br s, 1H, NH); 25.7 (5-CH_3), 35.2 (C-4), 52.7 (OCH_3), 68.9 (C-5), 114.3 (C-3), 127.9 (C-2), 161.8 (CO), 173.8 (C-6); m/z (%): 185 (M^+, 51), 153 (28), 114 (100); exact mass for $C_8H_{11}NO_4$: 185.0688; found: 185.0693

III. Synthesis of 5-hydroxy-6-oxo-2-piperidinecarboxylates 3.
To a solution of **2b** (0.3 g, 1.5 mmol) or **2c** (0.3 g, 1.3 mmol) in ethanol (5 ml), was added 50 % Pd/C (0.15 g) and one equiv $NaHCO_3$. The mixture was hydrogenated at 1 atm for 4 hours. The catalyst was removed by filtration through Celite and the filtrate evaporated. The 6-oxo-piperidinecarboxylates were purified by crystallisation from CCl_4. (yields are given in scheme 1)

(±)-ethyl 6-oxo-5-hydroxy-5-methyl-2-piperidinecarboxylate 3b (major product) and its isomer 3b'.
white solid; IR (KBr) cm^{-1}: 1738, 1657; ^1H NMR ($CDCl_3$) **3b** δ: 1.30 (t, 3H, CH_3), 1.45 (s, 3H, 5-CH_3), 1.83, 1.94, 2.29 (m, 4H, CH_2CH_2), 3.60 (br s, 1H, OH), 4.14 (ddd, 1H, ^3J = 10, 5, 1 Hz, H-2), 4.24 (q, 2H, ^3J = 7 Hz, $CH_3\underline{CH_2}O$), 6.40 (br s, 1H, NH); ^1H NMR ($CDCl_3$) **3b'** δ: 1.30 (t, 3H, CH_3), 1.45 (s, 3H, 5-CH_3), 1.83, 1.94, 2.11 (m, 4H, CH_2CH_2), 3.54 (br s, 1H, OH), 4.07 (td, 1H, ^3J = 6, 2Hz, H-2), 4.24 (q, 2H, ^3J = 7 Hz, $CH_3\underline{CH_2}O$), 6.48 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$) **3b**: 14.1 (CH_3), 27.4 (5-CH_3), 23.5, 33.6 (C-3 and C-4), 55.1 (C-2), 61.9 (OCH_2), 69.7 (C-5), 170.8 (CO), 175.7 (C-6); ^{13}C NMR ($CDCl_3$) **3b'**: 14.1 (CH_3), 27.4 (5-CH_3), 22.9, 32.9 (C-3 and C-4), 54.8 (C-2), 61.9 (OCH_2), 69.7 (C-5), 170.8 (CO), 175.7 (C-6); exact mass for $C_9H_{15}NO_4$: 201.0997; found: 201.0999; anal cald for $C_9H_{15}NO_4$: C 53.72, H 7.51, N 6.96; found: C 53.95, H 7.45, N 6.76

(±)-*n*-butyl 6-oxo-5-hydroxy-5-methyl-2-piperidinecarboxylate 3c and its isomer 3c'.
white solid; IR (KBr) cm^{-1}: 1740, 1660; ^1H NMR ($CDCl_3$) **3c, 3c'** δ: 0.95 (t, 3H, CH_3), 1.43 (s, 3H, 5-CH_3), 1.1-2.5 (m, 8H, CH_2CH_2 + $CH_3\underline{CH_2}\underline{CH_2}CH_2O$), 4.15 (br s, 1H, OH), 4.20 (t, 2H, $CH_3CH_2\underline{CH_2}CH_2O$), 6.95 (br s, 1H ,NH); m/z (%): 229 (M^+, 1), 128 (84), 100 (100); exact mass for $C_{11}H_{19}NO_4$: 229.1309; found: 229.1301

IV. Synthesis of 1,6-dihydro-6-oxo-2-pyridinecarboxylates 4.
A mixture of **2** (5 mmol) with 3 equiv Et_3N (or DBU) in $CHCl_3$ or CH_3CN (15 ml) was stirred at reflux temperature for one day. After evaporation of the solvent, purification was done by chromatography (silica gel, eluent: EtOAc/$CHCl_3$). Yields of the products are given in scheme 1.

ethyl 1,6-dihydro-6-oxo-5-phenyl-2-pyridinecarboxylate 4a.

solvent: $CHCl_3$, reaction time 72h. m.p.: 118 °C (CCl_4); IR (KBr) cm^{-1}: 1730, 1640, 1615; ^1H NMR ($CDCl_3$) δ: 1.38 (t, 3H, ^3J = 7 Hz, CH_3), 4.42 (q, 2H, ^3J = 7 Hz, OCH_2), 7.07 (d, 1H, ^3J = 7 Hz, H-3), 7.42 (m, 3H, Ar-H), 7.61 (d, 1H, ^3J = 7 Hz, H-4), 7.29 (m, 2H, Ar-H), 7.42 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$): 14.1 (CH_3), 62.6 (OCH_2), 109.8 (C-3), 128.3, 128.5, 128.7 (Ar-C), 132.5 (C-5), 135.4 (C-2), 137.3 (C-4), 137.4 (C-*ipso*), 160.6, 160.8 (CO and C-6); m/z (%): 243 (M^+, 100), 215 (10), 196 (8), 171 (45); exact mass for $C_{14}H_{13}NO_3$: 243.0892; found: 243.0890

ethyl 1,6-dihydro-5-methyl-6-oxo-2-pyridinecarboxylate 4b.

solvent: CH_3CN, reaction time 48h. m.p.: 105 °C (CCl_4); IR (KBr) cm^{-1}: 1725, 1650, 1615; ^1H NMR ($CDCl_3$) δ: 1.27 (t, 3H, ^3J = 7.5 Hz, CH_3), 2.10 (s, 3H, 5-CH_3), 4.28 (q, 2H, ^3J = 7.5 Hz, CH_2), 6.80 (d, 1H, ^3J = 7.5 Hz, H-3), 7.19 (m, 1H, ^3J = 7.5 Hz, H-4), 10.60 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$): 13.9 (CH_3), 16.8 (5-CH_3), 62.1 (OCH_2), 109.5 (C-3), 131.6 (C-2), 136.4 (C-4), 136.6 (C-5), 160.9, 162.7 (CO and C-6); m/z (%): 181 (M^+, 48), 135 (100), 107 (83), 79 (19); exact mass for $C_9H_{11}NO_3$: 181.0736; found: 181.0738

***i*-propyl 1,6-dihydro-5-methyl-6-oxo-2-pyridinecarboxylate 4d.**

solvent: $CHCl_3$, reaction time 24h. m.p.: 91 °C (*n*-Hex); IR (KBr) cm^{-1}: 1732, 1656, 1615; ^1H NMR ($CDCl_3$) δ: 1.37 (d, 6H, ^3J = 6 Hz, CH_3), 2.22 (s, 3H, 5-CH_3), 5.25 (sept, 1H, ^3J = 6 Hz, OCH), 6.93 (d, 1H, ^3J = 6 Hz, H-3), 7.32 (d, 1H, ^3J = 6 Hz, H-4), 10.50 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$): 16.9 (5-CH_3), 21.6 (CH_3), 70.3 (CH), 109.4 (C-3), 132.0 (C-2), 136.6 (C-4), 136.7 (C-5), 160.5 (CO), 162.8 (C-6); m/z (%): 195 (M^+, 37), 153 (35), 135 (100), 107 (51); exact mass for $C_{10}H_{13}NO_3$: 195.0892; found: 195.0899; anal cald for $C_{10}H_{13}NO_3$: C 61.53, H 6.83, N 7.18; found: C 61.55, H 6.69, N 7.10

V. **(±)-ethyl 6-oxo-5α-hydroxy-5β-methyl-2β-(4-methylphenyl)-2α-piperidinecarboxylate 9.**

Using the procedure for the preparation of compounds **2**, the title compound was obtained as a white solid (reaction time 24h). m.p.: 124 °C (CH_2Cl_2/Et_2O); IR (KBr) cm^{-1}: 1740, 1665; ^1H NMR ($CDCl_3$) δ: 1.25 (t, 3H, ^3J = 7 Hz, CH_3), 1.40 (s, 3H, 5-CH_3), 1.74 - 2.70 (m, 4H, CH_2CH_2), 2.35 (s, 3H, Ar-CH_3), 3.90 (br s, 1H, OH), 4.21 (q, 2H, ^3J = 7 Hz, OCH_2), 6.92 (br s, 1H ,NH), 7.24 (m, 4H, Ar-H); ^{13}C NMR ($CDCl_3$): 13.8 (CH_3), 20.8 (5-CH_3), 27.1 (Ar-CH_3), 30.6 (C-4), 31.9 (C-3), 62.3 (OCH_2), 65.8 (C-2), 69.4 (C-5), 171.1 (C-6), 176.0 (CO); m/z (%): 276 (M^+-CH_3, 1), 218 (100), 200 (20), 190 (31); exact mass for $C_{16}H_{21}NO_4$ -CH_3: 276.1231; found: 276.1225; anal cald for $C_{16}H_{21}NO_4$: C 65.96, H 7.27, N 4.81; found: C 66.00, H 7.33, N 4.85

*VI. Reaction of 7- and/or 8-substituted adducts **10** with ethanol: generation of compounds **11-14**.*

The same procedure as for adducts **2** was applied (except for **13d** where the procedure for compounds **4** was used).

(±)-ethyl 1,4,5,6-tetrahydro-5-hydroxy-5-methyl-6-oxo-3-phenyl-2-pyridinecarboxylate 11a.

reaction time: 24h. m.p.: 165 °C (CCl_4); IR (KBr) cm^{-1}: 1745, 1710, 1640, 1600; ^1H NMR ($CDCl_3$) δ: 0.99 (t, 3H,^3J = 6.5 Hz CH_3), 1.56 (s, 3H, 5-CH_3), 2.76 (d, 1H, ^2J = 18.5 Hz, H-4), 3.15 (d, 1H, ^2J = 18.5 Hz, H-4), 3.89 (br s, 1H, OH), 4.11 (q, 2H, ^3J = 6.5 Hz, OCH_2), 7.21 (m, 2H, Ar-H), 7.44 (m, 3H, Ar-H), 8.01 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$): 13.3 (CH_3), 25.0 (5-CH_3), 44.1 (C-4), 61.7 (OCH_2), 68.5 (C-5), 122.9 (C-2), 127.6, 127.7, 128.0, 128.6, 128.8 (Ar-C), 129.4 (C-*ipso*), 139.1 (C-3), 161.9 (CO), 173.1 (C-6); m/z (%): 275 (M^+, 87), 230 (44), 212 (48), 202 (100), 184 (50); exact mass for $C_{15}H_{17}NO_4$: 275.1153; found: 275.1159; anal cald for $C_{15}H_{17}NO_4$: C 65.44, H 6.22, N 5.09; found: C 65.15, H 6.14, N 4.96

(±)-ethyl 1,4,5,6-tetrahydro-5α-hydroxy-5β-methyl-6-oxo-4β-phenoxymethyl-2-pyridinecarboxylate 11c. reaction time: 48h. m.p.: 118 °C (*n*-Hex/Et_2O); IR (KBr) cm^{-1}: 1730, 1670, 1600; ^{1}H NMR ($CDCl_3$) δ: 1.30 (s, 3H, 5-CH_3), 1.35 (t, 3H,^3J = 7.5 Hz CH_3), 3.22 (m, 1H, H-4), 4.20 (br s, 1H, OH), 4.25 (m, 2H, OCH_2), 4.30 (q, 2H, ^3J = 7.5 Hz, $OOCH_2$), 6.50 (br s, 1H, H-3), 6.95 (m, 3H, Ar-$H_{o,p}$), 7.30 (m, 2H, Ar-H_m), 8.15 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$): 13.9 (CH_3), 20.1 (5-CH_3), 43.1 (C-4), 62.0 and 64.8 ($OOCH_2$ and CH_2O), 70.1 (C-5), 114.6 (C-3), 127.7 (C-2), 116.5, 121.0, 129.4, (Ar-C), 158.3 (C-*ipso*), 161.2 (CO), 173.7 (C-6); m/z (%): 305 (M^+, 43), 259 (19), 211 (58), 43 (100); exact mass for $C_{16}H_{19}NO_5$: 305.1258; found: 305.1250; anal cald for $C_{16}H_{19}NO_5$: C 62.94, H 6.27, N 4.59; found: C 62.88, H 6.28, N 4.43

(±)-ethyl 2,3,4,4aα,6,7-hexahydro-4α-hydroxy-4β-methyl-3-oxo-5*H*-1-pyrindinecarboxylate 11d. reaction time: 24h. m.p.: 87 °C (*n*-Hex/Et_2O); IR (KBr) cm^{-1}: 1700, 1670; ^{1}H NMR ($CDCl_3$) δ: 1.15 (s, 3H, 4-CH_3), 1.35 (t, 3H, ^3J = 7.5 Hz, CH_3), 1.70 (m, 2H, $CH_2C\underline{H}_2CH_2$), 2.05, 3.00 (m, 4H, $C\underline{H}_2CH_2C\underline{H}_2$), 2.65 (m, 1H, H-4a), 3.70 (br s, 1H, OH), 4.30 (q, 2H, ^3J = 7.5 Hz, OCH_2), 7.60 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$): 13.9 (CH_3), 18.9 (4-CH_3), 25.3, 31.3 (CH_2), 50.5 (C-4a), 61.2 (OCH_2), 70.5 (C-4), 140.6 (C-7a), 118.9 (C-1), 161.4 (CO), 174.3 (C-3); m/z (%): 239 (M^+, 45), 193 (100), 168 (60); exact mass for $C_{12}H_{17}NO_4$: 239.1153; found: 239.1160; anal cald for $C_{12}H_{17}NO_4$: C 60.24, H 7.16, N 5.85; found: C 60.25, H 7.23, N 5.77

(±)-5-ethoxy-1,4,5,6-tetrahydro-5-methyl-6-oxo-3-phenyl-2-pyridinecarboxylic acid 12a. reaction time: 24h. m.p.: 118 °C (CCl_4); IR (KBr) cm^{-1}: 3330, 1690; ^{1}H NMR ($CDCl_3$) δ: 1.32 (t, 3H,^3J = 7.0 Hz, CH_3), 1.74 (s, 3H, 5-CH_3), 3.03 (d, 1H, ^2J = 17.5 Hz, H-4), 3.15 (d, 1H, ^2J = 17.5 Hz, H-4), 4.05 (br s, 2H, NH and COOH), 4.25 (2 × qd, 2H, ^2J = 18.0 Hz, ^3J = 7.0 Hz, OCH_2), 7.47 (m, 5H, Ar-H); ^{13}C NMR ($CDCl_3$): 14.1 (CH_3), 24.2 (5-CH_3), 37.4 (C-4), 62.2 (OCH_2), 81.6 (C-5), 115.4 (C-2), 127.1, 127.7, 127.8 (Ar-C), 128.9 (C-*ipso*), 137.4 (C-3), 163.6 (CO), 172.2 (C-6); m/z (%): 275 (M^+, 100), 229 (12), 204 (55); exact mass for $C_{15}H_{17}NO_4$: 275.1153; found: 275.1157; anal cald for $C_{15}H_{17}NO_4$: C 65.44, H 6.22, N 5.09; found: C 65.34, H 6.25, N 5.04

(±)-5-ethoxy-1,4,5,6-tetrahydro-5-methyl-6-oxo-3-(2-oxo-1-pyrrolidinyl)-2-pyridinecarboxylic acid 12b. reaction time: 24h. m.p.: 149 °C (EtOAc); IR (KBr) cm^{-1}: 3400-3300, 1740, 1725, 1675, 1600; ^{1}H NMR ($CDCl_3$) δ: 1.27 (t, 3H,^3J = 7.0 Hz, CH_3), 1.65 (s, 3H, 5-CH_3), 2.20 (pent, 2H, ^3J = 7 Hz, $NCH_2C\underline{H}_2CH_2$), 2.51 (m, 2H, CH_2CO), 2.75 (d, 1H, ^2J = 16.8 Hz, H-4), 2.98 (d, 1H, ^2J = 16.8 Hz, H-4), 3.62 (m, 2H, CH_2N), 4.10 (br s, 2H, NH and COOH), 4.25 (2 × dq, 2H,^2J = 22.4 Hz, ^3J = 7 Hz, OCH_2); ^{13}C NMR ($CDCl_3$): 14.0 (CH_3), 24.2 (5-CH_3), 19.0, 31.2, 47.3 (CH_2), 34.1 (C-4), 62.4 (OCH_2), 76.9 (C-5), 117.0, 124.8 (C-2 and C-3), 163.7, 171.9 (CO), 172.9 (C-6); m/z (%): 282 (M^+, 46), 265 (9), 237 (6), 237 (8), 112 (100); exact mass for $C_{13}H_{18}N_2O_5$: 282.1211; found: 282.1203; anal cald for $C_{13}H_{18}N_2O_5$: C 55.31, H 6.43, N 9.92; found: C 55.14, H 6.51, N 9.87

ethyl 6,7-dihydro-4-methyl-3-oxo-5*H*-1-pyrindinecarboxylate 13d.
solvent: $CHCl_3$, reaction time: 24h. m.p.: 155 °C (*n*-Hex/Et_2O); IR (KBr) cm^{-1}: 1723, 1651, 1613; ^1H NMR ($CDCl_3$) δ: 1.41 (t, 3H, $^3J = 7$ Hz, CH_3), 2.08 (pent, 2H, $^3J = 6$ Hz, $CH_2\underline{H_2}CH_2$), 2.12 (s, 3H, 4-CH_3), 2.79 and 3.19 (t, 4H, $^3J = 6$ Hz, $C\underline{H_2}CH_2C\underline{H_2}$), 4.42 (q, 2H, $^3J = 7$ Hz, OCH_2), 10.12 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$): 13.1 (CH_3), 13.9 (C-6), 24.5 (4-CH_3), 30.9, 31.0 (CH_2), 61.7 (OCH_2), 123.7 (C-7a), 129.1 (C-4), 129.2 (C-1), 156.0 (C-4a), 161.4, 162.3 (CO and C-3); m/z (%): 221 (M^+, 91), 192 (84), 175 (71), 147 (100), 119 (40); exact mass for $C_{12}H_{15}NO_3$: 221.1048; found: 221.1049; anal cald for $C_{12}H_{15}NO_3$: C 65.14, H 6.83, N 6.33; found: C 65.15, H 6.85, N 6.29

2-ethyl 3,4-dimethyl 1,6-dihydro-5-methyl-6-oxo-2,3,4-pyridinetricarboxylate 13e.
reaction time: 48h. m.p.: 166 °C (CCl_4); IR (KBr) cm^{-1}: 1745, 1660; ^1H NMR ($CDCl_3$) δ: 1.40 (t, 3H, $^3J = 7$ Hz, CH_3), 2.20 (s, 3H, 5-CH_3), 3.85 (s, 3H, CH_3O), 3.90 (s, 3H, CH_3O), 4.40 (q, 2H, $^3J = 7$ Hz, OCH_2), 11.00 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$): 13.6 (5-CH_3, CH_3), 52.6 (2 × CH_3O), 63.0 (OCH_2), 112.1 (C-3), 132.1 (C-2), 134.4 (C-5), 140.2 (C-4), 160.2, 162.6, 164.7 (CO), 165.7 (C-6); m/z (%): 297 (M^+, 39), 265 (100), 205 (11); exact mass for $C_{13}H_{15}NO_7$: 297.0844; found: 297.0848; anal cald for $C_{13}H_{15}NO_7$: C 52.53, H 5.09, N 4.71; found: C 52.50, H 5.02, N 4.62

2-ethyl 3,4-dimethyl 6-ethoxy-5-methyl-2,3,4-pyridinetricarboxylate 14e.
reaction time: 48h. m.p.: 54 °C (*n*-Hex/Et_2O); IR (KBr) cm^{-1}: 1740, 1585; ^1H NMR ($CDCl_3$) δ: 1.38 (t, 3H, $^3J = 7$ Hz, CH_3), 1.40 (t, 3H, $^3J = 7$ Hz, CH_3), 2.20 (s, 3H, 5-CH_3), 3.85 (s, 3H, CH_3O), 3.92 (s, 3H, CH_3O), 4.40 (q, 2H, $^3J = 7$ Hz, OCH_2), 4.50 (q, 2H, $^3J = 7$ Hz, OCH_2); ^{13}C NMR ($CDCl_3$): 12.6 (5-CH_3), 13.9, 14.2 (CH_3), 52.5, 52.6 (CH_3O), 61.8, 63.3 (OCH_2), 117.1 (C-3), 120.6 (C-5), 142.9 (C-2), 146.8 (C-4), 163.0, 165.4, 165.7, 166.7 (CO and C-6); m/z (%): 325 (M^+, 50), 310 (54), 293 (72), 280 (55), 265 (74), 78 (100); exact mass for $C_{15}H_{19}NO_7$: 325.1156; found: 325.1157; anal cald for $C_{15}H_{19}NO_7$: C 55.38, H 5.89, N 4.31; found: C 55.41, H 5.93, N 4.23

ethyl -2,3-dihydro-1,3-dioxo-6-ethoxy-7-methyl-2-phenyl-1*H*-pyrrolo[3,4-*c*]pyridine-4-carboxylate 14f.
reaction time: 48h. m.p.: 131 °C (*n*-Hex); IR (KBr) cm^{-1}: 3480, 3350, 1725; ^1H NMR ($CDCl_3$) δ: 1.27 (t, 3H, $^3J = 7$ Hz, CH_3), 1.33 (t, 3H, $^3J = 7$ Hz, CH_3), 2.46 (s, 3H, 7-CH_3), 4.34 (q, 2H, $^3J = 7$ Hz, OCH_2), 4.42 (q, 2H, $^3J = 7$ Hz, OCH_2), 7.30 (m, 5H, Ar-H); ^{13}C NMR ($CDCl_3$): 10.4 (7-CH_3), 13.7, 14.0 (CH_3), 62.1, 64.1 (OCH_2), 115.8 (C-3a), 123.3 (C-7), 126.5, 128.1, 128.9, (Ar-C), 131.4 (C-*ipso*), 137.5 (C-7a), 143.1 (C-4), 163.4, 164.0, 165.4, 165.7 (CO and C-6); m/z (%): 354 (M^+, 100), 308 (34), 280 (26); exact mass for $C_{19}H_{18}N_2O_5$: 354.1211; found: 354.1214; anal cald for $C_{19}H_{18}N_2O_5$: C 64.30, H 5.12, N 7.91; found: C 64.21, H 5.01, N 7.80

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