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Diels-Alder Reactions of Pyridine *o*-Quinodimethane Analogues Generated from Functionalised *o*-Bis(chloromethyl)pyridines.[1]

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Abstract: The polyfunctional 2,3- and 3,4-*o*-bis(chloromethyl)pyridines **3**, produced via cycloaddition of the oxazinones **2** with propargyl chloride and 1,4-dichloro-2-butyne, were used as precursors of various pyridine *o*-quinodimethane analogues. The 2,3- and 3,4-dimethylenepyridine systems were generated via reductive 1,4-elimination with iodide and trapped *in situ* with various dienophiles to form the tetrahydroquinoline and -isoquinoline type adducts. A regiospecific cycloaddition was observed for the 3,4-dimethylenepyridine system with electron-rich dienophiles, i.e. dihydrofuran and ethyl vinyl ether, in contrast to the reaction with methyl acrylate.

INTRODUCTION

Heteroaromatic analogues of *o*-quinodimethane **1** (*o*-QDM) constitute an important research field which has led to a number of novel *o*-dimethylene systems, i.e. those derived from furan, pyrrole, isoxazole, quinoline, etc. (figure 1). These reactive intermediates are used as diene components in various Diels-Alder reactions.[2] Despite the increasing interest in heteroaromatic *o*-QDM analogues, little attention has been paid to the corresponding pyridine system and, to our knowledge, only the groups of Ito and Kametani have described the application of *o*-dimethylenepyridines in Diels-Alder reactions.[3]

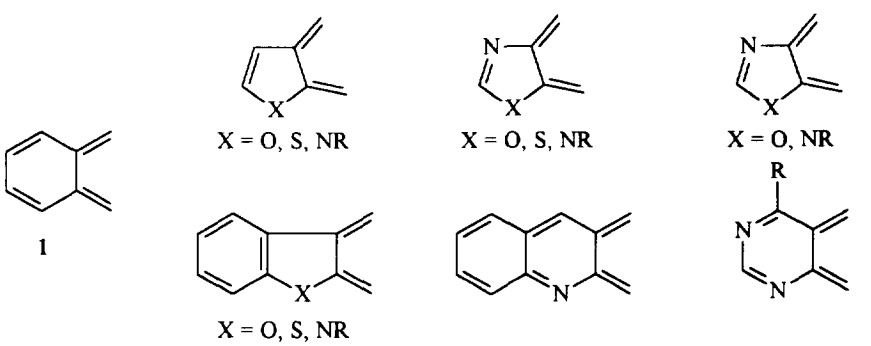
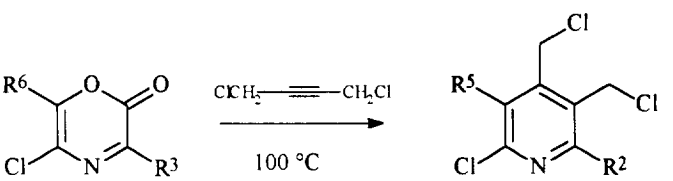


Figure 1. *o*-Quinodimethane and various heteroaromatic analogues.

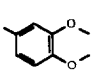
To generate the 2,3- and 3,4-dimethylenedihydropyridines we envisaged the reductive 1,4-elimination of the corresponding dihalogen precursors: 2,3- and 3,4-bis(chloromethyl)pyridines. These were prepared according to our general approach for the synthesis of polyfunctional pyridines using cycloaddition of the oxazinone azadiene system **2** and chloromethyl substituted alkynes.[4] Subsequent treatment with iodide afforded the expected pyridine *o*-QDM intermediates which were made to react *in situ* with various dienophiles. A similar reductive 1,4-elimination already has been applied to benzylic dihalogen precursors, e.g. 4,5-bis(chloromethyl)veratrole, to produce various benzenoid *o*-QDM systems.[5]

RESULTS AND DISCUSSION

The cycloaddition of the oxazinones **2** and alkyne compounds proceeds with concomitant expulsion of carbon dioxide to produce the polyfunctional bis(chloromethyl)pyridines **3**. As illustrated in schemes 1 to 3, several routes were explored to vary the substitution pattern of the pyridine compounds. In the first, most successful approach (scheme 1), the oxazinones **2a-f** were made to react with the symmetrical dienophile 1,4-dichloro-2-butyne. These reactions were carried out at 120 °C to afford the 3,4-bis(chloromethyl)-pyridines **3a-f** in excellent yields (80-95 %). The required oxazinone precursors were prepared either directly from the corresponding cyanohydrin compounds RCHOH-CN (3-chlorooxazinones **2a-c**) or through additional nucleophilic substitution of the imidoyl chloro atom of oxazinone **2b** (R^3-substituted compounds **2d-f**).[4]

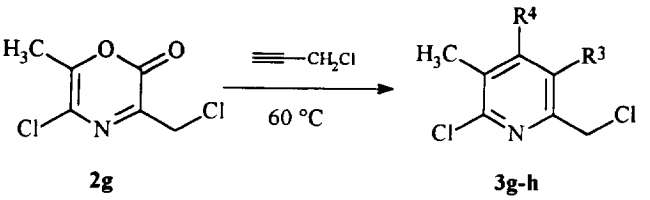


2a-f **3a-f**

2/3	a	b	c	d	e	f
R^6/R^5	H	CH_3	Ph	CH_3	CH_3	CH_3
R^3/R^2	Cl	Cl	Cl	OCH_3	Ph	
yield (%)	80	91	95	80	81	87

Scheme 1. Synthesis of 3,4-bis(chloromethyl)pyridines.

In our second approach (scheme 2), one of the chloromethyl groups was introduced at the oxazinone stage, and cycloaddition of the resulting 3-(chloromethyl)oxazinone **2g** with the non symmetric dienophile propargyl chloride was used to prepare the alternate 2,3-bis(chloromethyl)-pyridine **3g**. However, this route turned out to be less efficient since it produced a mixture of the 2,3- and 2,4-regioisomers **3g** and **3h** from which the desired compound **3g** was isolated as the major product by HPLC. Like the other R^3-substituted oxazinones **2d-f**, the starting 3-(chloromethyl)oxazinone **2g** was obtained through a nucleophilic displacement of the imidoyl chloro atom of **2b**. This was achieved *via* successive treatment with diazomethane and HCl.[6]

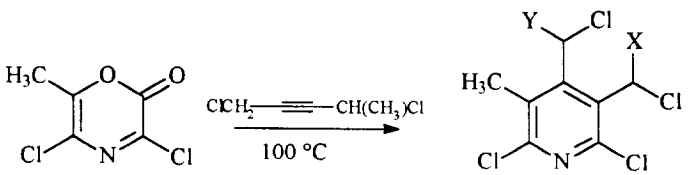


3	R^3	R^4	yield (%)
g	CH_2Cl	H	39
h	H	CH_2Cl	26

2g **3g-h**

Scheme 2. Synthesis of 2,3-bis(chloromethyl)pyridine **3g** and its 2,4-regioisomer **3h**.

To extend one of the pyridine side chains we tried the cycloaddition of the oxazinone **2b** with 1,4-dichloro-2-pentyne. Unfortunately, this reaction produced an inseparable mixture of the regioisomeric pyridines **3i** and **3j** (1:1; total yield 26 %).

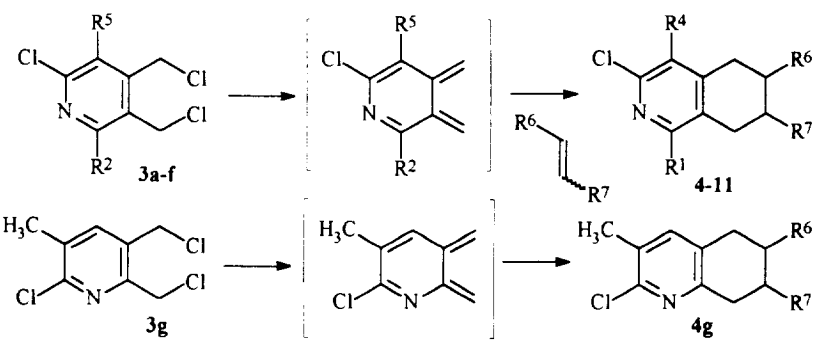


3	X	Y	yield (%)
i	CH_3	H	13
j	H	CH_3	13

2b **3i-j**

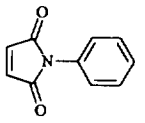
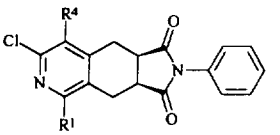
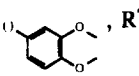
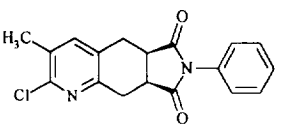
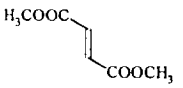
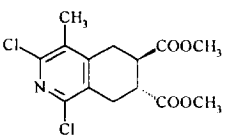
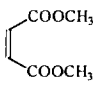
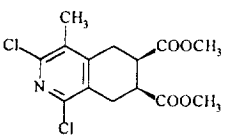
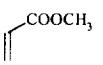
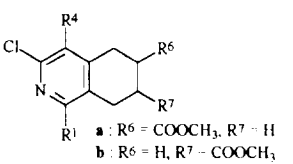
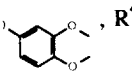
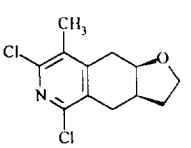
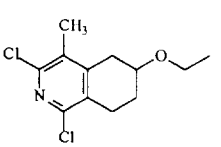
Scheme 3. Cycloaddition of the oxazinone **2b** with 1,4-dichloro-2-pentyne.

The bis(chloromethyl)pyridines **3** were heated with sodium iodide in DMF at 65 °C and the resulting *o*-QDM analogues were trapped *in situ* with various dienophiles to afford the adducts shown in scheme 4 and table 1. Both electron-deficient (*N*-phenylmaleimide, dimethyl maleate and fumarate, and the non symmetrical methyl acrylate) and electron-rich dienophiles (dihydrofuran and ethyl vinyl ether) were used to trap the 3,4-dimethylenepyridine intermediates. For several adducts (**4b**, **4c**, **5**, **7**, **10**, **11** and **12**) we could improve the yield by using a slightly modified procedure, i.e. replacing DMF with acetone as the solvent and adding 4Å molecular sieves.[7] Upon omission of the trapping agent in the reaction of pyridine **3b** we isolated the analogous bis(iodomethyl)pyridine (**3k**), which presumably is a direct precursor in the 1,4-elimination of iodine producing the *o*-QDM analogues.[8]



Scheme 4. Conversion of *o*-bis(chloromethyl)pyridines into *o*-QDM systems and their cycloaddition with various dienophiles.

Table 1. Cycloaddition of Pyridine *o*-QDM Analogues with Various Dienophiles.

pyr	dienophile	adduct	adduct number and substituents	yield (%)[a]
3a			**4a**: R^1 = Cl, R^4 = H	48*
3b			**4b**: R^1 = Cl, R^4 = CH_3	65/82*
3c			**4c**: R^1 = Cl, R^4 = Ph	15[b]/47*
3d			**4d**: R^1 = OCH_3, R^4 = CH_3	60
3e			**4e**: R^1 = Ph, R^4 = CH_3	56
3f			**4f**: R^1 =  , R^4 = CH_3	75
3g			**4g**	90
3b			**5**	56/74*
3b			**6**	53
3b			**7a/7b** R^1 = Cl, R^4 = CH_3	23/49*
3c			**8a/8b** R^1 = Cl, R^4 = Ph	35
3d			**9a/9b** R^1 = OCH_3, R^4 = CH_3	58
3e			**10a/10b** R^1 =  , R^4 = CH_3	80
3b			**11**	35/48*
3b			**12**	25/55*

[a] these yields were obtained by using DMF or acetone (denoted by *) as the solvent.

[b] yield for crystallised product

Cycloaddition with *N*-phenylmaleimide (NPMA) afforded the adducts **4a-g** in good to moderate yields (table 1). The structures and the conformational behaviour of these NPMA and other adducts described below were determined from their proton NMR spectral data.

An equilibrium of two boat conformers, **A** and **B**, may be conceived for the *cis*-fused ring system of the NPMA adducts **4** (figure 2).[9] However, conformational calculations using a molecular mechanics program[10] indicated that the diaxial orientation of the maleimide ring in **A** is energetically preferred over the diequatorial one in **B**. In fact, form **A** was shown to be largely predominant over **B** by the NOESY spectrum and the coupling pattern of protons in the cyclohexene ring of adduct **4b**. To distinguish these cyclohexene protons, the ASIS technique (aromatic solvent shift induced by the addition of deuterobenzene) was utilised since most aliphatic protons absorbed in the same region (*ca.* 3.50 ppm) in the deuterochloroform spectrum.

The NOESY spectrum of **4b** revealed a single NOE interaction of the 8-methyl group with only one of the geminal H-9 protons: consequently, these H-9 protons can be differentiated into the adjacent H-9eq and the remote H-9ax. On basis of this unique NOE interaction we may conclude that a single or predominant conformer is present, i.e. either **A** or **B**, with H-9eq representing one or the other H-9 proton (figure 2). Clearcut evidence for **A** as the major form was provided by a further NOE observed between H-9ax and the angular proton H-9a: this interaction clearly shows the *cis*-ax,eq disposition of these protons and precludes the *trans*-diaxial orientation present in form **B**.

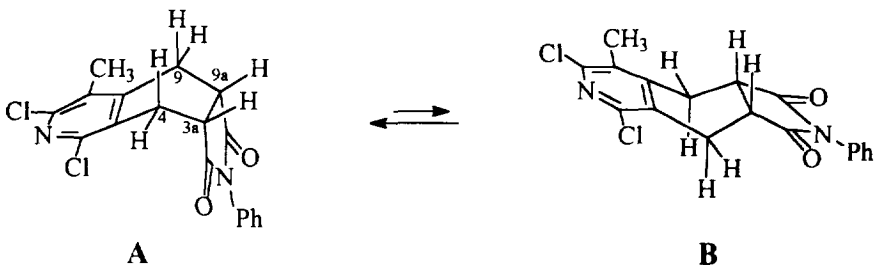
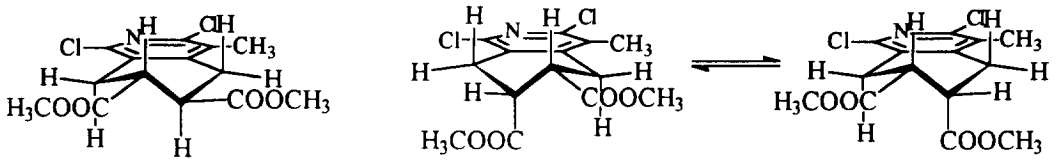


Figure 2. Alternative boat conformers **A** and **B** for the NPMA adduct **4b**.

The occurrence of the diaxial boat form **A** was confirmed by the ^3J values observed for the mutual coupling of the angular protons H-3a, H-9a (10 Hz) and for the further coupling of H-3a, H-9a with the axial and equatorial protons H-4 and H-9 ($^3J_{4ax,3a} = {}^3J_{9ax,9a}$ = 6 Hz, and $^3J_{4eq,3a} = {}^3J_{9eq,9a}$ = 4 Hz). The low ^3J values for the axial protons H-9ax and H-4ax again preclude the exclusive *trans*-diaxial orientation that would apply if **B** and not **A** is the only or predominant conformer present. The same boat conformation **A** also was inferred for the other NPMA adducts since their ^{1}H NMR spectra displayed very similar values for the $J_{3a,4}$ and the $J_{9a,9}$ coupling constants.

From the reaction with dimethyl fumarate and maleate, the expected *trans*- and *cis*-substituted cycloaddition compounds **5** and **6** were isolated. The diequatorial half-chair form **C** was assigned to the fumarate adduct **5** (figure 3). The ^{1}H NMR analysis started with the NOE-diff measurement on the methyl group of the pyridine ring, which allowed to assign the equatorial proton H-5eq as nearest neighbour of this methyl group. The *trans*-diaxial orientation of each pair of vicinal protons H-5ax, H-6 and H-8ax, H-7, and therefore the diequatorial orientation of the ester groups, was established by the coupling constant values $^3J_{5ax,6}$ = 9 Hz, and $^3J_{8ax,7}$ = 10 Hz ($^3J_{5eq,6} = {}^3J_{8eq,7}$ = 4 Hz). Protons H-6 and H-7 displayed coinciding signals at 2.74 ppm.

For the *cis*-fused maleate adduct **6** an equilibrium of the half-chair forms **D** and **E** was inferred from the average values ($^3J_{5,6}$ and $^3J_{7,8}$ = 6-8 Hz) observed for the coupling constants of the protons H-5, H-6 and H-7, H-8.



C **D** **E**

Figure 3. Conformational structures for the fumarate (**C**) and maleate (**D, E**) adducts **5** and **6**.

The addition of methyl acrylate on the *o*-QDM analogues derived from pyridines **3b-d,f** led to a mixture of the regiomeric adducts **7a,b** to **10a,b**, produced in an isomeric ratio of *ca.* 2:3 in favour of the 7-substituted compounds **7b** to **10b**. Following separation of each regiomeric pair by preparative T.L.C on alumina using the solvent system hexanes/chloroform (30/70), the regioisomers were structurally characterised by ^{1}H NMR spectrometry. For compounds **7a** and **7b** the complete analysis included a) NOE-diff. measurement on the 4-methyl group to identify the adjacent equatorial proton H-5eq and b) elucidation of the ^{1}H coupling pattern for H-5eq and the other protons on the cyclohexene ring to determine the position of the ester group. From the *triplet*,dd patterns observed for each of the axial protons H-6 in **7a** ($^3J_{6,5ax}$ = $^3J_{6,7ax}$ = 10 Hz, $^3J_{6,5eq}$ = 5 Hz, $^3J_{6,7eq}$ = 3 Hz), and H-7 in **7b** ($^3J_{7,8ax}$ = $^3J_{7,6ax}$ = 10 Hz, $^3J_{7,8eq}$ = 5 Hz, $^3J_{7,6eq}$ = 3 Hz), both regioisomers were shown to occur as the half chair conformers with the ester substituent mainly in the equatorial position (compare to the 6,7-diequatorial form **C** for diester **5**, figure 3).

In contrast to the reaction with methyl acrylate which slightly favoured (2:3) the 7-substituted ester adducts **7b** to **10b**, cycloaddition with the electron-rich dienophiles dihydrofuran and ethyl vinyl ether exclusively yielded the 6-*O*-substituted isoquinoline analogues **11** and **12**. Clearly, the inversed regioselectivities can not be explained on basis of the steric effect exerted by the 5-methyl group of the diene component but rather must be correlated with the energies and coefficients of the frontier molecular orbitals.[11,12] These were calculated using AM1 and HMO semi-empirical methods.[13] The energy levels derived from the AM1 calculations are shown in figure 4a. To account for the regiochemistry, this figure also displays the relative magnitude for the HOMO and LUMO coefficients calculated with the HMO method. From the energy diagram it appears that for electron-rich (X-substituted) olefins, the "inverse electron demand" interaction LUMO-diene, HOMO-dienophile is largely preferred (*ca.* 2.6-2.7 eV). The addition to X-substituted olefins therefore must proceed *via* the energetically favoured reaction pathway (1) shown in figure 4b. Consequently, to account for the production of the 6-X-substituted regioisomers, a larger relative contribution is to be expected for the LUMO-diene coefficient at the 3-methylene position as compared to the 4-methylene group. This was confirmed by the HMO calculations.

In the reaction with methyl acrylate, the normal HOMO-diene, LUMO-dienophile interaction is slightly favoured over the inverse interaction (*ca.* 0.55 eV). This small difference suggests a competition between

pathways (2) and (3). In the inverse electron demand mode (3), the 6-regioisomer should be favoured as in the reaction with X-substituted olefins. Therefore, the 7-regioisomer can be formed as the major product only if reaction pathway (2) involving the LUMO-(Z-substituted olefin) is operating. The relative magnitude calculated for the HOMO-diene coefficients is in agreement with that expected for a predominant formation of the 7-regioisomer.

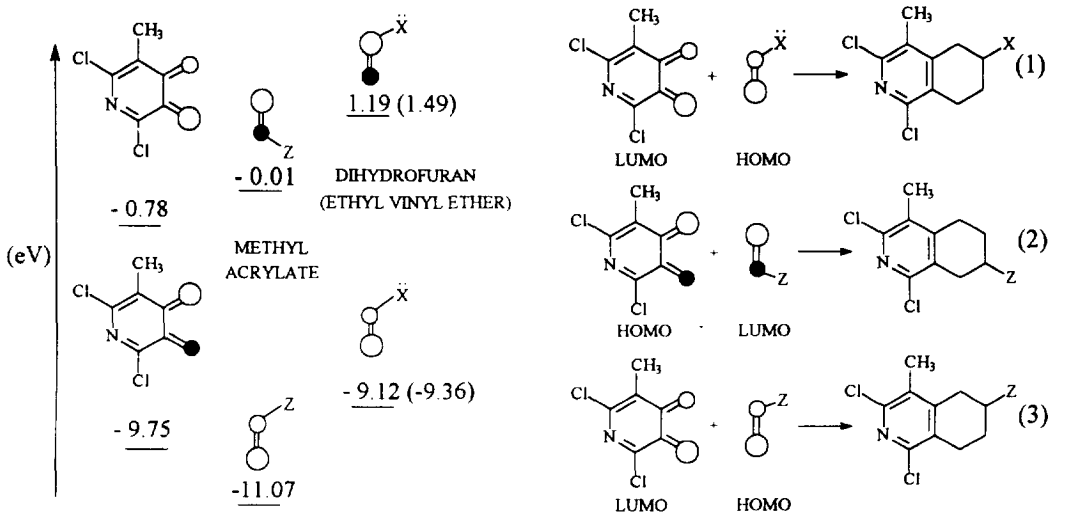
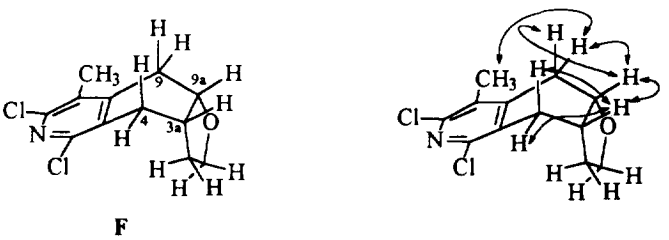


Figure 4. a) Energy levels calculated for the frontier molecular orbitals; b) cycloaddition modes of the 3,4-dimethylenepyridine with electron-rich and electron-deficient X- and Z-substituted olefins.

The structural characterisation of the adducts **11** and **12** was based on ^{1}H NMR analysis using the NOE-diff, COSY, and NOESY spectra. The diaxial boat structure **F** was attributed to the *cis*-fused DHF adduct (figure 5a). The ^{1}H NMR analysis again started with the identification of the equatorial proton H-9eq based on the NOE diff interaction with the 8-methyl group on the pyridine ring. In the subsequent COSY analysis this H-9eq served as a reference to identify the other protons and to assign the position of the ring *O*-atom.



F

Figure 5. a) Structure of DHF adduct: *cis*-fused ax,ax-boat form **F**; b) important NOE interactions.

The conformational structure was derived from NOESY analysis and from the coupling constant values for the angular protons H-3a and H-9a. A diequatorial orientation of these protons was inferred from the

nearly equal ^3J values observed for the coupling with the *cis* and *trans* disposed vicinal protons on the six-membered ring ($^3J_{3a,4ax}$ and $^3J_{3a,4eq}$ = 6 and 5.5 Hz, $^3J_{9a,9ax}$ = $^3J_{9a,9eq}$ = 4.5 Hz). These values are in accordance with the similar torsional angles (*cis*: 50°; *trans*: 65°) that were calculated for the energetically optimised ax,ax boat form **F**. This conformer has an axial orientation for both the *O*-atom and CH_2-group of the furan ring, in contrast to the energetically less favourable eq,eq boat and ax,eq half-chair forms.

The NOESY spectrum confirmed that the DHF adduct occurs mainly as the ax,ax boat conformer **F**. The most important interactions are shown in figure 5b. Each of the angular protons gave a strong NOE with both the *cis*- and *trans*-disposed vicinal protons on the six-membered ring: these interactions can be accommodated only if both H-3a and H-9a have an equatorial orientation.

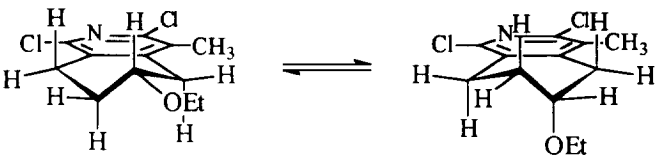


Figure 6. Compound **12**: conformational mixture of the 6-ax and 6-eq half chair forms.

The adduct formed with ethyl vinyl ether was characterised as the 6-ethoxy compound **12** (table 1) corresponding to the same mode of addition as the DHF adduct. The position of the ethoxy group was shown by decoupling of the low-field proton H-6 and the geminal H-5 protons both of which displayed a NOE with the 4-methyl group on the pyridine ring. From this result and from the ^3J values observed for H-5, H-6 (^3J = 5-6.5 Hz), we may conclude that, in contrast with the analogous 6-substituted ester compound **7a**, the 6-ethoxy compound **12** does not occur primarily as the 6-eq half chair conformer but rather as a mixture of the 6-ax and 6-eq half chair forms (figure 6).

Whereas the main focus of the present work centres around the development of synthetic methodology, the compounds synthesised may be of interest by themselves. Firstly, the substitution and hydrogenation pattern for the quinoline and isoquinoline structures reported herewith is different from those encountered frequently. Secondly, the 1*H*-pyrrolo[3,4-*g*]isoquinoline skeleton has been mentioned only in a few Russian papers.[14] Finally, a furo[2,3-*g*]isoquinoline structure was reported as a structural analogue of the pentacyclic natural product rotenone, functioning as an electron transport inhibitor.[15]

CONCLUSION

Cycloaddition of oxazinones and alkyne dienophiles provides a very useful route to various polyfunctional pyridines, due to the rich substitution pattern of the oxazinone azadiene system. In the present work this route was used to prepare 2,3- and 3,4-bis(chloromethyl)pyridines serving as precursors of the corresponding dimethylenepyridine *o*-QDM analogues. These were generated with iodide and trapped *in situ* with both electron-rich and electron-deficient dienophiles to produce the corresponding cycloadducts in good to moderate yields. The 3,4-dimethylenepyridine system was found to give a regiospecific cycloaddition with the electron-rich dienophiles dihydrofuran and ethyl vinyl ether, in contrast to the reaction with methyl acrylate. A disadvantage of the approach presented is the apparent lack of an easy pathway for substitution of one or both of the chloromethyl groups.

EXPERIMENTAL

General methods.

Infrared spectra were recorded on a Perkin-Elmer 297 grating IR spectrophotometer and a Perkin-Elmer 1720 Fourier transform spectrometer. ^{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 TLC and column chromatography analytical plates (Alugram Sil G/UV$_{254}$) and 70-230 mesh silica gel 60 (E.M. Merck) were used, respectively. Melting points were determined using a Reichert-Jung Thermovar apparatus and an Electrothermal IA 9000 digital melting point apparatus and are uncorrected. HPLC was performed on a Waters Associates configuration coupled to a 410 differential refractometer. Microanalyses were performed by Janssen Pharmaceutica on a Carlo Erba elemental analyser type 1106.

General procedure for the synthesis of pyridines 3a-3f

A solution of the oxazinone **2** (5.0 g) in 1,4-dichlorobutyne (10 ml) was subjected to three consecutive freeze-pump-thaw cycles, and then heated in a sealed glass tube at 120 °C for 5 days (4 hours for **2a**). The reaction mixture was subjected to a kugelrohr distillation to recover the excess of acetylene reagent and to isolate the higher boiling pyridine fraction. The latter was chromatographed on silica gel using a step gradient chloroform/ethyl acetate (100 % $CHCl_3$ to 85 $CHCl_3$ / 15 ethyl acetate). The pyridine compounds were crystallised from ethanol.

2,6-Dichloro-3,4-bis(chloromethyl)pyridine (3a)

Yield: 93 %; m.p.: 51.5-53 °C (ethanol); ^{1}H NMR ($CDCl_3$/TMS): δ = 7.41 (s, 1H, H-5), 4.81 (s, 2H; CH_2Cl), 4.66 (s, 2H; CH_2Cl); ^{13}C NMR: ($CDCl_3$) δ = 151.4 (C-2), 150.7 (C-6), 150.1 (C-4), 128.9 (C-3), 124.1 (C-5), 40.7 (4-CH_2), 38.0 (3-CH_2); MS [m/z (%)]: 243 (19) $M^{+\cdot}$, 208 (96), 173 (16), 172 (11), 136 (19); HRMS: calcd for $C_7H_5Cl_4N$: 242.9176, found: 242.9178.

2,6-Dichloro-3,4-bis(chloromethyl)-5-methylpyridine (3b)

Yield: 91 %; m.p.: 53-54 °C (ethanol); ^{1}H NMR ($CDCl_3$/TMS): δ = 4.80 (s, 2H; CH_2Cl), 4.68 (s, 2H; CH_2Cl), 2.48 (s, 3H; CH_3); ^{13}C NMR: ($CDCl_3$) δ = 151.3 (C-6), 148.3 (C-4), 148.2 (C-2), 131.5 (C-5), 129.3 (C-3), 38.9 (4-CH_2), 38.1 (3-CH_2), 15.5 (CH_3); MS [m/z (%)]: 257 (21); $M^{+\cdot}$; 222 (100), 186 (37), 150 (10); HRMS: calcd for $C_8H_7Cl_4N$: 256.9332, found: 256.9329; Analysis calcd for $C_8H_7Cl_4N$: C 37.11, H 2.72, N 5.41, found: C 36.94, H 2.65, N 5.27.

2,6-Dichloro-3,4-bis(chloromethyl)-5-phenylpyridine (3c)

Yield: 93 %; m.p.: 99-101 °C ($CHCl_3$/hexanes); ^{1}H NMR ($CDCl_3$/TMS): δ = 7.53-7.23 (m, 5H; Ph), 4.90 (s, 2H; CH_2Cl), 4.37 (s, 2H; CH_2Cl); ^{13}C NMR ($CDCl_3$): δ = 150.5 (C-6), 150.3 (C-2), 148.3 (C-4), 136.7 (C-5), 133.4 (C-*ipso*), 129.8 (C-3, C-*p*), 129.1 (C-*o*), 128.7 (C-*m*), 38.8 (3-CH_2), 38.7 (4-CH_2); MS [m/z (%)]: 319 (50) $M^{+\cdot}$, 284 (43), 248 (100); HRMS: calcd for $C_{13}H_9Cl_4N$: 318.9489; found: 318.9504.

2-Chloro-4,5-bis(chloromethyl)-6-methoxy-3-methylpyridine (3d)

Yield: 80 %; m.p.: 35.5-37 °C ($CHCl_3$/ hexanes); ^{1}H NMR ($CDCl_3$/TMS): δ = 4.70 (s, 2H; CH_2), 4.64 (s, 2H; CH_2), 3.99 (s, 3H; OCH_3), 2.39 (s, 3H; CH_3); ^{13}C NMR ($CDCl_3$): δ = 159.3 (C-6), 149.2 (C-2), 147.8 (C-4), 123.5 (C-3), 117.5 (C-5), 54.5 (OCH_3), 38.0 (5-CH_2), 36.3 (4-CH_2), 14.8 (CH_3); MS [m/z

(%)]: 253 (19) $M^{+\cdot}$, 218 (100), 188 (24), 153 (13); HRMS: calcd for $C_9H_{10}Cl_3NO$: 252.9828, found: 252.9829.

2-Chloro-4,5-bis(chloromethyl)-3-methyl-6-phenylpyridine (3e)

Yield: 81%; m.p.: 119-121 °C ($CHCl_3$/ hexanes); ^1H NMR ($CDCl_3$/TMS): δ = 7.64 (m, 2H; Ph), 7.46 (m, 3H; Ph), 4.82 (s, 2H; CH_2Cl), 4.63 (s, 2H; CH_2Cl), 2.55 (s, 3H; CH_3); ^{13}C NMR ($CDCl_3$): 157.8 (C-6), 152.3 (C-2), 147.1 (C-4), 137.9 (C-*ipso*), 131.1 (C-5), 129.0 (C-*p*), 128.8 (C-*o*), 128.4 (C-*m*), 128.2 (C-3), 40.4 (5-CH_2), 38.3 (4-CH_2), 15.9 (CH_3); MS [m/z (%)]: 300 (49) MH^+, 264 (100), 229 (57), 192 (19); HRMS: calcd for $C_{14}H_{12}Cl_3N$: 299.0035, found: 299.0035.

2-Chloro-4,5-bis(chloromethyl)-6-(3,4-dimethoxyphenyl)-3-methylpyridine (3f)

Yield: 87 %; m.p.: 161 °C (CH_2Cl_2); ^1H NMR ($CDCl_3$/TMS): δ = 7.25 (dd, ^3J = 8 Hz, ^4J = 2 Hz, 1H; PhH-6'), 7.23 (d, ^4J = 2 Hz, 1H; PhH-2'), 6.97 (d, ^3J = 8 Hz, 1H; PhH-5'), 4.83 (s, 2H; CH_2Cl), 4.69 (s, 2H; CH_2Cl), 3.96 (s, 3H; OCH_3), 3.95 (s, 3H; OCH_3), 2.55 (s, 3H; CH_3); ^{13}C NMR ($CDCl_3$): δ = 157.5 (C-6), 152.2 (C-2), 149.7 (C-3'), 148.7 (C-4'), 147.1 (C-4), 130.7 (C-1'), 130.5 (C-5), 127.9 (C-3), 121.6 (C-6'), 112.1 (C-2'), 110.0 (C-5'), 55.9 (OCH_3), 40.8 (5-CH_2), 38.3 (4-CH_2); MS [m/z (%)]: 359 (100) $M^{+\cdot}$, 324 (65), 293 (39); HRMS: calcd for $C_{16}H_{16}Cl_3NO_2$: 359.0246, found: 359.0247.

2-Chloro-5,6-bis(chloromethyl)-3-methylpyridine (3g) and 2-chloro-4,6-bis(chloromethyl)-3-methylpyridine (3h)

A solution of the oxazinone **2g** in neat propargyl chloride was heated at 60 °C for 2 days. The reaction mixture was subjected to a kugelrohr distillation to recover the excess of acetylene reagent and to isolate the higher boiling pyridine fraction. The latter was chromatographed on silica gel using a step gradient chloroform/ethyl acetate (100 % $CHCl_3$ to 85 $CHCl_3$ / 15 ethyl acetate). The isomers **3g** and **3h** were separated by HPLC on a silicagel column using $CHCl_3$. The pyridine compound **3g** was crystallised from ethanol. **3g**: Yield: 39 %; m.p.: 55-56 °C; ^1H NMR ($CDCl_3$/TMS): δ = 7.61 (s, 1H; H-4), 4.72 (s, 2H; CH_2), 4.69 (s, 1H; CH_2), 2.39 (s, 1H; CH_3); ^{13}C NMR ($CDCl_3$): δ = 152.4 (C-6), 150.6 (C-2), 141.5 (C-4), 133.3 (C-3), 131.2 (C-5), 43.4 (CH_2), 41.0 (CH_2), 19.1 (CH_3); MS [m/z (%)]: 223 (26) $M^{+\cdot}$, 188 (100), 152 (19); HRMS: calcd for $C_8H_8Cl_4N$: 222.9722, found: 222.9726; **3h**: Yield: 26 %; ^1H NMR ($CDCl_3$/TMS): δ = 7.42 (s, 1H; H-5), 4.59 (s, 2H; CH_2), 4.55 (s, 1H; CH_2), 2.44 (s, 1H; CH_3); ^{13}C NMR ($CDCl_3$): δ = 154.5 (C-6), 151.8 (C-2), 147.4 (C-4), 130.5 (C-3), 122.0 (C-5), 45.4 (CH_2), 42.6 (CH_2), 15.1 (CH_3).

2,6-Dichloro-3-(1-chloroethyl)-4-chloromethyl-5-methylpyridine (3i) and 2,6-dichloro-4-(1-chloroethyl)-3-chloromethyl-5-methylpyridine (3j)

A solution of the oxazinone **2b** in 1,4-dichloro-2-pentyne was subjected to one freeze-pump-thaw cycle. The glass tube tube was sealed and heated at 120 °C for 5 days. The reaction mixture was subjected to a kugelrohr distillation to recover the acetylene from the pyridine fraction. The latter was chromatographed on silica gel using a step gradient of chloroform/ethyl acetate to give a mixture of the regiomeric pyridines **3i** and **3j**. The isomers could not be separated by HPLC. Yield: 26 %; ^1H NMR ($CDCl_3$/TMS): δ = 5.82 (br, 1H; CHCl), 5.57 (q, ^3J = 9 Hz, 1H; CHCl), 5.15 (br, 1H; CH_2Cl), 4.98 (br, 1H; CH_2Cl), 4.78 (d, ^3J = 9 Hz, 1H; CH_2Cl) 4.68 (d, ^3J = 9 Hz, 1H; CH_2Cl), 2.58 (s, 3H; CH_3), 2.49 (s, 3H; CH_3), 2.00 (d, ^3J = 9 Hz, 3H; CH_3), 1.95 (d, ^3J = 9 Hz, 3H; CH_3); ^{13}C NMR ($CDCl_3$): δ = 152.0, 150.6, 148.2, 132.8, 52.4 (CHCl), 51.8 (CHCl), 39.5 (CH_2Cl), 38.6 (CH_2Cl), 24.0 (CH_3), 23.3 (CH_3), 17.0 (CH_3), 15.4 (CH_3); MS [m/z (%)] 271 (21) $M^{+\cdot}$, 236 (54), 200 (100), 165 (54), 165 (54), 164 (42).

2,6-Dichloro-3,4-bis(iodomethyl)-5-methylpyridine (3k)

A solution of pyridine **3b** and NaI in DMF was heated at 65 °C for 3 hours. Water was added and de solution was decolorised by the addition of saturated aqueous sodium hydrogen sulfite. The pyridine compound was extracted with CH_2Cl_2 and purified by column chromatography. Yield: 39 %; m.p.: 103-105 °C ($CHCl_3$/hexanes); ^{1}H NMR ($CDCl_3$/TMS): δ = 4.52 (s, 2H; CH_2I), 4.40 (s, 2H; CH_2I), 2.34 (s, 3H; CH_3); ^{13}C NMR ($CDCl_3$): δ = 150.2 (C-6), 148.9 (C-2), 147.5 (C-4), 130.5 (C-5), 130.2 (C-3), 38.6 (3-CH_2), 37.8 (4-CH_2), 15.6 (CH_3); MS [m/z (%)]: 441 (1) $M^{+\cdot}$, 314 (83), 187 (100), 152 (18), 117 (8); HRMS: calcd for $C_8H_7Cl_2I_2N$: 440.8045, found: 440.8043.

General procedure for the generation of pyridine *o*-QDM analogues and their *in situ* reaction with dienophiles:

A solution of pyridine compound (**5a-c**, **6a**, 250 mg), dienophile (3 mol equiv.) and NaI (5 mol equiv.) was heated in DMF (2.5 ml) at 65 °C under argon atmosphere for 12-24 hours. After completion of the reaction, water (50 ml) was added and the solution was decolorised with aqueous sodium hydrogen sulfite. The mixture was extracted with chloroform and the organic phase was dried and evaporated. Chromatographic purification (silica/$CHCl_3$/EtOAc for compounds **4-6** or alumina/$CHCl_3$/hexanes for **7-11**) gave the adducts mentioned below. In some cases acetone was used as the solvent instead of DMF under the same reaction conditions.

5,7-Dichloro-3a,4,9,9a-tetrahydro-2-phenyl-1*H*-pyrrolo[3,4-*g*]isoquinoline-1,3(2*H*)-dione (4a)

Yield: 48 %; m.p.: 210-211.5 °C ($CHCl_3$/hexanes); IR (KBr): 1709 cm^{-1} (s); ^{1}H NMR ($CDCl_3$/TMS): δ = 7.38 (m, 3H; Ph), 7.14 (s, 1H; H-8), 7.02 (dd, ^3J = 6, ^4J = 2 Hz, 2H; Ph) , 3.59 (dd, ^2J = 15, ^3J = 3.5 Hz, 1H; H-4eq), 3.50 (m, 2H; H-3a, H-9a), 3.21 (dd, ^2J = 15 Hz, ^3J = 3.5 Hz, 1H; H-9eq), 2.96 (dd, ^2J = 15 Hz, ^3J = 6.5 Hz, 1H; H-4ax), 2.94 (dd, ^2J = 15 Hz, ^3J = 6 Hz, 1H; H-9ax); ^{13}C NMR ($CDCl_3$): δ = 176.8 (CO), 150.0, 148.8, 148.6, 131.2 (C-*ipso*), 129.1 (C-*m*), 128.8 (C-*p*), 128.5 , 126.3 , 126.0 (C-*o*), 122.5 (C-8), 39.1 (CH), 38.8 (CH), 29.6 (CH_2), 25.3 (CH_2); MS [m/z (%)]: 346 (85) $M^{+\cdot}$, 198 (100), 164 (47), 119 (66); HRMS: calcd for $C_{17}H_{12}Cl_2N_2O_2$: 346.0275, found: 346.0283.

5,7-Dichloro-3a,4,9,9a-tetrahydro-8-methyl-2-phenyl-1*H*-pyrrolo[3,4-*g*]isoquinoline-1,3(2*H*)-dione (4b)

Yield: 82 %; m.p.: 240-242 °C ($CHCl_3$/hexanes); IR (KBr): 1707 cm^{-1} (s); ^{1}H NMR ($CDCl_3$/TMS): δ = 7.38 (m, 3H; Ph), 6.98 (d, ^3J = 9 Hz, 2H; Ph), 3.66 (dd, ^2J = 15 Hz, ^3J = 4 Hz, 1H; H-4eq), 3.52 (m, 3H; H-3a, H-9a, H-9eq), 2.93 (dd, ^2J = 15 Hz, ^3J = 6 Hz, 1H; H-4ax), 2.85 (dd, ^2J = 15 Hz, ^3J = 6 Hz, 1H; H-9ax), 2.39 (s, 3H; CH_3); ^{1}H NMR (C_6D_6/C_6D_5H): δ = 3.25 (dd, ^2J = 15 Hz, ^3J = 4 Hz, 1H; H-4eq), 2.71 (dd, ^2J = 15 Hz, ^3J = 4 Hz, 1H; H-9eq), 2.43 (ddd, ^3J = 10 Hz, ^3J = 6 Hz, ^3J = 4 Hz, 1H; H-3a), 2.34 (ddd, ^3J = 10 Hz, ^3J = 6 Hz, ^3J = 4 Hz, 1H; H-9a), 2.15 (dd, ^2J = 15 Hz, ^3J = 6 Hz, 1H; H-4ax), 1.86 (s, 3H; CH_3), 1.77 (dd, ^2J = 15 Hz, ^3J = 6 Hz, 1H; H-9ax); ^{13}C NMR ($CDCl_3$): δ = 177.2 (CO), 177.0 (CO), 149.1 (C-7), 148.3 (C-8a), 145.8 (C-5), 131.3 (C-*ipso*), 129.3 (C-8), 129.2 (C-*m*), 128.9 (C-*p*), 128.4 (C-4a), 126.1 (C-*o*), 39.2 (CH), 38.9 (CH), 26.8 (CH_2), 26.1 (CH_2), 15.5 (CH_3); MS [m/z (%)]: 360 (44) $M^{+\cdot}$, 212 (86), 91 (100); HRMS: calcd for $C_{18}H_{14}Cl_2N_2O_2$: 360.04323, found: 360.0447.

5,7-Dichloro-3a,4,9,9a-tetrahydro-2,8-diphenyl-1*H*-pyrrolo[3,4-*g*]isoquinoline-1,3(2*H*)-dione (4c)

Yield: 47 % (after crystallisation); m.p.: 218-219 °C ($CHCl_3$/hexanes); IR (KBr): 1709 cm^{-1} (s); ^{1}H NMR ($CDCl_3$/TMS): δ = 7.43 (m, 6H; Ph), 7.15 (m, 2H; Ph), 7.04 (m, 2H; Ph), 3.70 (dd, ^2J = 15 Hz, ^3J = 4

Hz, 1H; H-4eq), 3.51 (ddd, ^3J = 10 Hz, ^3J = 7 Hz, ^3J = 4 Hz, 1H; H-3a), 3.36 (ddd, ^3J = 10 Hz, ^3J = 7 Hz, ^3J = 4 Hz, 1H; H-9a), 3.13 (dd, ^2J = 15 Hz, ^3J = 4 Hz, 1H; H-9eq), 2.99 (dd, ^2J = 15 Hz, ^3J = 7 Hz, 1H; H-4ax), 2.67 (dd, ^2J = 15 Hz, ^3J = 7 Hz, 1H; H-9ax); ^{13}C NMR ($CDCl_3$): δ = 177.0 (CO), 176.7 (CO), 148.5 , 148.2, 147.5, 135.1 (C-8), 134.5, 131.4 (C-*ipso*), 129.4, 129.3 (C-*m*), 129.0, 128.7 (C-*p*), 128.5 (C-4a), 126.1 (C-*o*), 39.0 (CH), 27.5 (CH_2), 26.0 (CH_2); MS [m/z (%)]: 422 (57) $M^{+\cdot}$, 387 (8), 274 (52), 238 (34), 204 (66), 119 (54), 91 (100); HRMS: calcd for $C_{23}H_{16}Cl_2N_2O_2$: 422.0588, found: 422.0582.

7-Chloro-3a,4,9,9a-tetrahydro-5-methoxy-8-methyl-2-phenyl-1*H*-pyrrolo[3,4-g]isoquinoline-1,3(2*H*)-dione (4d)

Yield: 60 %; m.p.: 175-176.5 °C ($CHCl_3$/hexanes); IR (KBr): 1711 cm^{-1} (s); ^{1}H NMR ($CDCl_3$/TMS): δ = 7.38 (m, 3H; Ph), 6.98 (d, ^3J = 8 Hz, 2H; Ph), 3.92 (s, 3H; OCH_3), 3.48 (dd, ^2J = 15 Hz, ^3J = 3 Hz, 1H; H-4eq), 3.44 (m, 3H; H-3a, H-9a, H-9eq), 2.76 (dd, ^2J = 15 Hz, ^3J = 7 Hz, 1H; H-4ax), 2.71 (dd, ^2J = 15 Hz, ^3J = 7 Hz, 1H; H-9ax), 2.30 (s, 3H; CH_3); ^{13}C NMR ($CDCl_3$): δ = 177.9 (CO), 177.8 (CO), 158.2 (C-5), 147.5 (C-8a), 146.2 (C-7), 131.5 (C-*ipso*), 129.1 (C-*m*), 128.7 (C-*p*), 126.2 (C-*o*), 121.6 (C-8), 115.9 (C-4a), 54.0 (OCH_3), 39.5 (CH), 38.9 (CH), 26.1 (CH_2), 21.9 (CH_2), 14.9 (CH_3); MS [m/z (%)]: 356 (57) $M^{+\cdot}$, 208 (100); HRMS: calcd for $C_{19}H_{17}ClN_2O_3$: 356.0927, found: 356.0926; Analysis calc for $C_{19}H_{17}ClN_2O_3$: C 63.96, H 4.80, N 7.85, found: C 64.06, H 4.73, N 7.83.

7-Chloro-3a,4,9,9a-tetrahydro-8-methyl-2,5-diphenyl-1*H*-pyrrolo[3,4-g]isoquinoline-1,3(2*H*)-dione (4e)

Yield: 56 %; m.p.: 162-164 °C ($CHCl_3$/hexanes); IR (KBr): 1710 cm^{-1} (s); ^{1}H NMR ($CDCl_3$/TMS): δ = 7.41 (m, 8H; Ph), 6.95 (d, ^3J = 8 Hz, 2H; Ph), 3.58 (dd, ^2J = 15 Hz, ^3J = 4 Hz, 1H; H-4eq), 3.51 (m, 2H; H-9a, H-9eq), 3.41 (ddd, ^3J = 10 Hz, ^3J = 6 Hz, ^3J = 4 Hz, 1H; H-3a), 2.86 (dd, ^2J = 15 Hz, ^3J = 7 Hz, 1H; H-4ax), 2.84 (dd, ^2J = 15 Hz, ^3J = 6 Hz, 1H; H-9ax), 2.48 (s, 3H; CH_3); ^{13}C NMR ($CDCl_3$): δ = 177.7 (CO), 177.5 (CO), 155.4 (C-5), 149.9 (C-7), 146.5 (C-8a), 137.9 (C-ipso), 131.4 (C-*ipso*), 129.3, 129.2 (C-*m*), 128.9 (C-*p*), 128.5, 128.5 (C-8), 128.4, 127.3 (C-4a), 126.2 (C-*o*), 39.4 (CH), 26.5 (CH_2), 26.0 (CH_2), 15.7 (CH_3); MS [m/z (%)]: 402 (36) $M^{+\cdot}$, 254 (100); HRMS: calcd for $C_{24}H_{19}ClN_2O_2$: 402.1135, found: 402.1141; Analysis calc for $C_{24}H_{19}ClN_2O_2$: C 71.55, H 4.75, N 6.95, found: C 71.17, H 4.61, N 6.74.

7-Chloro-3a,4,9,9a-tetrahydro-5-(3,4-dimethoxyphenyl)-8-methyl-2-phenyl-1*H*-pyrrolo[3,4-g]isoquinoline-1,3(2*H*)-dione (4f)

Yield: 75 %; m.p.: 139-141 °C ($CHCl_3$/hexanes); IR (KBr): 1711 cm^{-1} (s); ^{1}H NMR ($CDCl_3$/TMS): δ = 7.42-7.23 (m, 3H; Ph), 7.07-6.99 (m, 5H; Ph), 3.89 (s, 3H; OCH_3), 3.88 (s, 3H; OCH_3), 3.57 (dd, ^2J = 15 Hz, ^3J = 3 Hz, 2H; H-4eq, H-9eq), 3.48 (ddd, ^3J = 10 Hz, ^3J = 6 Hz, ^3J = 3 Hz, 1H), 3.40 (ddd, ^3J = 10 Hz, ^3J = 6 Hz, ^3J = 3 Hz, 1H), 2.78 (dd, ^2J = 15 Hz, ^3J = 6 Hz, 2H; H-9ax, H-4ax), 2.43 (s, 3H; CH_3); ^{13}C NMR ($CDCl_3$): δ = 177.5 (CO), 177.4 (CO), 155.0 (C-5), 149.6, 149.3, 148.8, 146.5, 131.4 (C-*ipso*), 130.6, 129.0 (C-*m*), 128.6 (C-*p*), 127.9, 127.0, 126.1 (C-*o*), 121.8, 112.5 (C-5'), 111.0 (C-2'), 55.9 (OCH_3), 55.8 (OCH_3), 39.3 (CH), 39.3 (CH), 26.3 (CH_2), 25.7 (CH_2), 15.5 (CH_3); MS [m/z (%)]: 462 (100) $M^{+\cdot}$, 314 (50); HRMS: calcd for $C_{26}H_{23}ClN_2O_4$: 462.1346, found: 462.1355.

6-Chloro-3a,4,9,9a-tetrahydro-7-methyl-2-phenyl-1*H*-pyrrolo[3,4-g]quinoline-1,3(2*H*)-dione (4g)

Yield: 90 %; m.p.: 203-205 °C ($CHCl_3$/Hexane); IR (KBr): 1706 cm^{-1} (s); ^{1}H NMR ($CDCl_3$/TMS): δ = 7.33 (m, 8H; ArH), 7.02 (dd, ^3J = 8 Hz, ^4J = 2 Hz, 2H; ArH), 3.52-3.33 (m, 3 H; H-3a, H-9a, H-4eq),

3.19 (dd, ^2J = 15, ^3J = 4 Hz, 1H; H-9eq), 3.10 (dd, ^2J = 15.5 Hz, ^3J = 7 Hz, 1H; H-4ax), 2.95 (dd, ^2J = 15 Hz, ^3J = 7 Hz, 1H; H-9ax), 2.31 (s, 3 H; CH_3); ^{1}H NMR (C_6D_6): δ = 3.36 (dd, ^2J = 15, ^3J = 3 Hz, 1H; H-4eq), 2.74 (dd, ^2J = 15 Hz, ^3J = 4 Hz, 1H; H-9eq), 2.52 (m, 3H; H-3a, H-9a, H-4ax), 2.12 (dd, ^2J = 15 Hz, ^3J = 7 Hz, 1H; H-9ax); ^{13}C NMR ($CDCl_3$): δ = 177.6 (CO), 177.2 (CO), 153.2 (C-4a), 149.5 (C-6), 138.8 (C-8), 131.5 (C-*ipso*), 131.0 (C-7), 129.0 (C-8a), 128.9 (C-*m*), 128.5 (C-*p*), 126.1 (C-*o*), 39.5 (CH), 31.4 (CH_2), 28.2 (CH_2), 19.1 (CH_3); MS [m/z (%)]: 326 (85) $M^{+\cdot}$, 178 (100); HRMS: calcd for $C_{18}H_{15}ClN_2O_2$: 326.0822, found: 326.0823.

Dimethyl 1,3-dichloro-5,6,7,8-tetrahydro-4-methyl-(*trans*)-6,7-isoquinolinedicarboxylate (5)

Yield: 74 %; m.p.: 130-131 °C ($CHCl_3$/hexanes); IR (KBr): 1741 cm^{-1} (s); ^{1}H NMR ($CDCl_3$/TMS): δ = 3.75 (s, 3H; OCH_3), 3.74 (s, 3H; OCH_3), 3.16 (dd, ^2J = 18 Hz, ^3J = 4 Hz, 1H), 3.06 (m, 3H), 2.83 (m, 2H), 2.27 (s, 3H; CH_3); ^{1}H NMR (C_6D_6/C_6D_5H): δ = 3.42 (s, 3H; OCH_3), 3.40 (s, 3H; OCH_3), 3.02 (dd, ^2J = 18 Hz, ^3J = 4 Hz, 1H; H-8eq), 2.74 (m, 2H; H-6, H-7), 2.52 (dd, ^2J = 18 Hz, ^2J = 10 Hz, 1H; H-8ax), 2.47 (dd, ^2J = 18 Hz, ^2J = 4 Hz, 1H; H-5eq), 2.16 (dd, ^3J = 18 Hz, ^2J = 9 Hz, 1H; H-5ax), 1.69 (s, 3H; CH_3); ^{13}C NMR ($CDCl_3$): δ = 173.7 (CO), 147.6 (C-4a), 147.1 (C-1, C-2), 129.3 (C-4), 127.5 (C-8a), 52.4 (OCH_3), 40.8 (CH), 40.6 (CH), 29.9 (CH_2), 28.6 (CH_2), 15.3 (CH_3); MS [m/z (%)]: 331 (12) $M^{+\cdot}$, 271 (70), 212 (100), 176 (22), 140 (28); HRMS: calcd for: 331.0378, found: 331.0384; Analysis calc for $C_{14}H_{15}Cl_2NO_4$: C 50.62, H 4.55, N 4.22, found: C 50.47, H 4.58, N 4.14.

Dimethyl 1,3-dichloro-5,6,7,8-tetrahydro-4-methyl-(*cis*)-6,7-isoquinolinedicarboxylate (6)

Yield: 53 %; m.p.: 136-137 °C ($CHCl_3$/hexanes); IR (KBr): 1742 cm^{-1} (s); ^{1}H NMR ($CDCl_3$/TMS): δ = 3.73 (s, 3H; OCH_3), 3.70 (s, 3H; OCH_3), 3.31 (td, ^3J = 6 Hz, ^3J = 3 Hz, 1H), 3.20 (m, 3H), 3.00 (dd, ^2J = 18 Hz, ^3J = 7 Hz, 1H), 2.76 (dd, ^2J = 17 Hz, ^3J = 8 Hz, 1H), 2.30 (s, 3H; CH_3); ^{1}H NMR (C_6D_6/C_6D_5H): δ = 3.34 (s, 3H; OCH_3), 3.27 (s, 3H; OCH_3), 3.20 (dd, ^2J = 18 Hz, ^3J = 6 Hz, 1H; H-8), 2.91 (dd, ^2J = 17 Hz, ^3J = 8 Hz, 1H; H-5), 2.89 (m, 1H; H-7), 2.61 (m, 1H; H-6), 2.59 (dd, ^2J = 18 Hz, ^3J = 7 Hz, 1H; H-8), 2.32 (dd, ^2J = 17 Hz, ^3J = 6 Hz, 1H; H-5), 1.76 (s, 3H; CH_3); ^{13}C NMR ($CDCl_3$): δ = 172.3 (CO), 147.5 (C-1), 147.4 (C-3), 147.3 (C-4a), 129.5 (C-8a), 127.5 (C-4), 52.3 (CH_3O), 52.2 (CH_3O), 39.5 (C-6), 39.1 (C-7), 28.2 (C-5), 27.4 (C-8), 15.2 (CH_3); MS [m/z (%)]: 331 (8) $M^{+\cdot}$, 300 (12), 271 (68), 212 (100), 176 (20), 140 (26); HRMS: calcd for $C_{14}H_{15}Cl_2NO_4$: 331.0378, found: 331.0384; Analysis calc for $C_{14}H_{15}Cl_2NO_4$: C 50.62, H 4.55, N 4.22, found: C 50.46, H 4.49, N 4.16.

Methyl 1,3-dichloro-5,6,7,8-tetrahydro-4-methyl-6-isoquinolinecarboxylate (7a)

Yield: 19 %; m.p.: 100-101 °C ($CHCl_3$/hexanes); IR (KBr): 1740 cm^{-1} (s); ^{1}H NMR ($CDCl_3$/TMS): δ = 3.75 (s, 3H; OCH_3), 2.96 (dd, ^2J = 18 Hz, ^3J = 5 Hz, 1H; H-5eq), 2.93-2.80 (m, 2H; H-5ax, H-8eq), 2.74 (tdd, ^3J = 10 Hz, ^3J = 5 Hz, ^3J = 3 Hz, 1H; H-6), 2.68 (ddd, ^2J = 17 Hz, ^3J = 10 Hz, ^3J = 6 Hz, 1H; H-8ax), 2.30 (s, 3H; CH_3), 2.25 (m, 1H; H-7eq), 1.84 (dtd, ^2J = 13 Hz, ^3J = 10 Hz, ^3J = 5 Hz, 1H; H-7ax); ^{1}H NMR (C_6D_6/C_6D_5H): δ = 3.41 (s, 3H; OCH_3), 2.55 (dt, ^2J = 17 Hz, ^3J = 5 Hz, 1H; H-8eq), 2.36 (m, 2H; H-5ax, H-5eq), 2.20 (m, 2H; H8-ax, H-6), 1.83 (m, 1H; H-7eq), 1.81 (s, 3H; CH_3), 1.41 (dtd, ^2J = 13 Hz, ^3J = 10 Hz, ^3J = 5 Hz, H-7ax); ^{13}C NMR ($CDCl_3$): δ =174.6 (CO), 148.3 (C-4a), 147.2 (C-3), 147.1 (C-1), 129.5 (C-4), 129.1 (C-8a), 52.1 (OCH_3), 38.7 (C-6), 30.1 (C-5), 25.9 (C-8), 24.4 (C-7), 15.2 (CH_3); MS [m/z (%)]:273 (23) $M^{+\cdot}$; 241 (17), 213 (100), 178 (86), 142 (18); HRMS: calcd for $C_{12}H_{13}Cl_2NO_2$: 273.0323, found: 273.0326.

Methyl 1,3-dichloro -5,6,7,8-tetrahydro-4-methyl-7-isoquinolinecarboxylate (7b)

Yield: 30 %; m.p.: 89-91.0 °C ($CHCl_3$/hexanes); IR (KBr): 1734 cm^{-1} (s); ^1H NMR ($CDCl_3$/TMS): δ = 3.74 (s, 3H; OCH_3), 3.06 (dd, ^2J = 17 Hz, ^3J = 5 Hz, 1H; H-8eq), 2.83 (m, 2H; H-5eq, H-8ax), 2.72 (tdd, ^3J = 10 Hz, ^3J = 5 Hz, ^3J = 3 Hz, 1H; H-7), 2.67 (ddd, ^2J = 17 Hz, ^3J = 10 Hz, ^3J = 6 Hz, 1H; H-5ax), 2.25 (s, 3H; CH_3), 2.22 (m, 1H; H-6eq), 1.87 (dtd, ^2J = 15 Hz, ^3J = 10.5 Hz, ^3J = 6 Hz, 1H; H-6ax); ^1H NMR (C_6D_6/TMS): δ = 3.37 (s, 3H; OCH_3), 2.81 (dd, ^2J = 17 Hz, ^3J = 5 Hz, 1H; H-8eq), 2.64 (dd, ^2J = 17 Hz, ^3J = 10 Hz, 1H; H-8ax), 2.19 (tdd, ^3J = 10 Hz, ^3J = 5 Hz, ^3J = 3 Hz, 1H; H-7), 2.03 (ddd, ^2J = 17 Hz, ^3J = 6 Hz, ^3J = 4 Hz, 1H; H-5eq), 1.75 (m, 2H; H5-ax, H-6eq), 1.38 (dtd, ^2J = 15 Hz, ^3J = 10 Hz, ^3J = 4 Hz, 1H; H-6ax); ^{13}C NMR ($CDCl_3$): 174.5 (CO), 149.1 (C-4a), 147.3 (C-3), 147.1 (C-1), 129.2 (C-4), 128.5 (C-8a), 52.0 (OCH_3), 38.3 (C-7), 28.8 (C-5), 27.2 (C-8), 24.4 (C-6), 15.1 (CH_3); MS [m/z (%)]: 273 (11) $M^{+\cdot}$, 241 (4), 213 (100), 178 (78), 142 (25); HRMS: calcd for $C_{12}H_{13}Cl_2NO_2$: 273.0323, found: 273.0316.

Methyl 1,3-dichloro-5,6,7,8-tetrahydro-4-phenyl-6-isoquinolinecarboxylate (8a)

Yield: 12 %; m.p.: 105-107 °C ($CHCl_3$/hexanes); IR (KBr): 1732 cm^{-1} (s); ^1H NMR ($CDCl_3$/TMS): δ = 7.47 (m, 3H; Ph), 7.18 (m, 2H; Ph), 3.66 (s, 3H; OCH_3), 2.95 (dt, ^2J = 17 Hz, ^3J = 5 Hz, 1 H; H-8eq), 2.76 (ddd, ^2J = 17 Hz, ^3J = 10 Hz, ^3J = 6 Hz, 1H; H-8ax), 2.64 (m, 3 H; H-6, H-5ax, H-5eq), 2.20 (m, 1 H; H-7eq), 1.92 (dtd, ^2J = 14 Hz, ^3J = 10 Hz, ^3J = 5 Hz, 1 H; H-7ax); ^{13}C NMR ($CDCl_3$): δ = 174.5 (CO), 149.1, 148.7, 146.5, 135.5, 135.4, 129.5, 129.1, 129.0, 128.9, 128.7, 128.4, 52.0 (OCH_3), 38.6 (C-5), 31.1 (C-8), 28.8 (C-6), 24.7 (C-7); MS [m/z (%)]: 335 (65) $M^{+\cdot}$, 275 (100), 240 (52), 204 (62); HRMS: calcd for $C_{17}H_{15}Cl_2NO_2$: 335.0479, found 335.0492.

Methyl 1,3-dichloro-5,6,7,8-tetrahydro-4-phenyl-7-isoquinolinecarboxylate (8b)

Yield: 23 %; m.p.: 130-132 °C ($CHCl_3$/hexanes); IR (KBr): 1727 cm^{-1} (s); ^1H NMR ($CDCl_3$/TMS): δ = 7.46 (m, 3H; Ph), 7.15 (m, 2H; Ph), 3.73 (s, 3 H; OCH_3), 3.14 (dd, ^2J = 16 Hz, ^3J = 6 Hz, 1 H; H-8eq), 2.95 (dd, ^2J = 16 Hz, ^3J = 9 Hz, 1H; H-8ax), 2.75 (tdd, ^3J = 9 Hz, ^3J = 6 Hz, ^3J = 3 Hz, 1H; H-7ax), 2.48 (m, 2H; H-5ax, H-5eq), 2.07 (m, 1 H; H-6eq), 1.74 (dtd, ^2J = 14 Hz, ^3J = 9 Hz, ^3J = 6 Hz, 1H; H-6ax); ^{13}C NMR ($CDCl_3$): δ =174.6 (CO), 149.5, 149.2, 146.4, 135.6, 135.1, 128.9, 128.9, 128.9, 128.3, 52.1 (OCH_3), 38.6 (C-5), 28.9 (C-7), 28.3 (C-8), 24.5 (C-6); MS [m/z (%)]: 335 (41) $M^{+\cdot}$, 275 (100), 239 (47), 204 (58); HRMS: calcd for $C_{17}H_{15}Cl_2NO_2$: 335.0479, found: 335.0503.

Methyl 3-chloro-5,6,7,8-tetrahydro-1-methoxy-4-methyl-6-isoquinolinecarboxylate (9a)

Yield: 22 %; m.p.: 67-68.5 °C ($CHCl_3$/hexanes); IR (KBr): 1731 cm^{-1} (s); ^1H NMR ($CDCl_3$/TMS): δ = 3.91 (s, 3H; OCH_3), 3.74 (s, 3H; OCH_3), 2.96-2.62 (m, 4H), 2.49 (ddd, ^2J = 16 Hz, ^3J = 11 Hz, ^3J = 6 Hz, 1H), 2.21 (s, 3H; CH_3), 2.19 (m, 1H; H-7), 1.73 (dtd, ^2J = 14 Hz, ^3J = 10 Hz, ^3J = 6 Hz, 1H; H-7); ^{13}C NMR ($CDCl_3$): δ = 175.3 (CO), 158.9 (C-1), 146.7, 144.4, 121.8, 117.4, 53.6 (OCH_3), 51.9 (OCH_3), 39.2, 29.7, 24.3, 22.2, 14.6 (CH_3); MS [m/z (%)]: 269 (100) $M^{+\cdot}$, 254 (28), 209 (85), 194 (41); HRMS: calcd for $C_{13}H_{16}ClNO_3$: 269.0818, found: 268.0818.

Methyl 3-chloro-5,6,7,8-tetrahydro-1-methoxy-4-methyl-7-isoquinolinecarboxylate (9b)

Yield: 36 %; m.p.: 83.5-85.5 °C ($CHCl_3$/hexanes); IR (KBr): 1732 cm^{-1} (s); ^1H NMR ($CDCl_3$/TMS): δ = 3.91 (s, 3H; OCH_3), 3.72 (s, 3H; OCH_3), 2.95 (m, 1H), 2.78 (dt, ^2J = 17 Hz, ^3J = 5 Hz, 1H), 2.70-2.49 (m, 3H), 2.20 (m, 1H; H-6), 2.18 (s, 3H; CH_3), 1.83 (m, 1H; H-6); ^{13}C NMR ($CDCl_3$): δ =175.3 (CO), 159.0 (C-1), 147.5, 144.5, 121.7, 116.6, 53.7 (OCH_3), 51.8 (OCH_3), 36.3, 26.8, 25.3, 24.8, 14.6 (CH_3);

MS [m/z (%)]: 269 (84) $M^{+\cdot}$, 210 (100), 194 (24); HRMS: calcd for $C_{13}H_{13}ClNO_3$: 269.0818, found: 269.0818.

Methyl 3-chloro-1-(3,4-dimethoxyphenyl)-4-methyl-6-isoquinolinecarboxylate (10a)

Yield: 32 %; m.p.: 172-174 °C ($CHCl_3$/hexanes); IR (KBr): 1737 cm^{-1} (s); ^1H NMR ($CDCl_3$/TMS): δ = 7.36 (d,^4J = 2 Hz, 1H; ArH), 6.99 (dd, ^3J = 8 Hz, ^4J = 2 Hz, 1H; ArH), 6.89 (d,^3J = 8 Hz, 1H; ArH), 3.91 (s, 3H; OCH_3), 3.90 (s, 3H; OCH_3), 3.76 (s, 3H; $COOCH_3$), 3.04 (dd, ^2J = 16 Hz, ^3J = 6 Hz, 1H), 2.95-2.70 (m, 4H), 2.36 (s, 3H; CH_3), 2.13 (m, 1H; H-7eq), 1.68 (ddt, ^2J = 13 Hz, ^3J = 10 Hz ^3J = 8 Hz, 1H; H-7ax); ^{13}C NMR ($CDCl_3$): δ = 175.1 (CO), 155.8 (C-1), 149.1 (C-3'), 148.7 (C-4'), 148.3, 146.1, 131.9 (C-1'), 128.5, 128.4, 121.6 (C-6'), 110.7 (C-5'), 55.9 (OCH_3), 51.9 (OCH_3), 39.1 (C-6), 30.0, 27.1, 25.1, 15.4 (CH_3); MS [m/z (%)]: 375 (100) $M^{+\cdot}$, 316 (91); HRMS: calcd for $C_{20}H_{22}ClNO_4$: 375.1237, found: 375.1248.

Methyl 3-chloro-1-(3,4-dimethoxyphenyl)-4-methyl-7-isoquinolinecarboxylate (10b)

Yield: 48%; m.p.: 93-95 °C ($CHCl_3$/hexanes); IR (KBr): 1734 cm^{-1} (s); ^1H NMR ($CDCl_3$/TMS): δ = 7.02 (d,^4J = 2 Hz, 1H; ArH), 7.00 (dd, ^3J = 9 Hz, ^4J = 2 Hz, 1H; ArH), 6.91 (d, ^3J = 9 Hz, 1H; ArH), 3.92 (s, 3 H; OCH_3), 3.91 (s, 3H; OCH_3), 3.68 (s, 3 H; $COOCH_3$), 3.01-2.80 (m, 3H; H-8eq, H-8ax, H-5eq), 2.70 (ddd, ^2J = 17 Hz, ^3J = 10 Hz, ^3J = 6 Hz, 1H; H-5ax), 2.57 (tdd^3J = 10 Hz, ^3J = 6 Hz, ^3J = 3 Hz, 1H; H-7), 2.34 (s, 3 H; CH_3), 2.28 (m, 1H; H-6eq), 1.93 (dtd, ^2J = 14 Hz, ^3J = 10 Hz ^3J = 6 Hz 1H; H-6ax); ^{13}C NMR ($CDCl_3$): δ = 175.0 (CO), 156.0 (C-1), 149.1 (C-3'), 148.7 (C-4'), 148.3, 146.7, 131.8, 128.2, 127.6, 121.5, 112.4, 110.6, 55.7, 51.7, 38.9, 30.1, 27.2, 25.0, 15.3 (CH_3); MS [m/z (%)]: 375 (37) $M^{+\cdot}$, 316 (100); HRMS: calcd for $C_{20}H_{22}ClNO_4$: 375.1237, found: 375.1243.

5,7-Dichloro-2,3,3a,4,9,9a-hexahydro-8-methylfuro[2,3-*g*]isoquinoline (11)

Yield: 48 %; m.p.: 64-66 °C ($CHCl_3$/hexanes); ^1H NMR ($CDCl_3$/TMS): δ = 4.30 (dt, ^3J = 8 Hz, ^3J = 4.5 Hz, 1H; H-9a), 3.71 (ddd, ^2J = 8.5 Hz, ^3J = 8 Hz, ^3J = 4 Hz, 1H; H-2A), 3.54 (td, $^{2,3}J$ = 8.5 Hz, ^3J = 7 Hz, 1H; H-2B), 3.04 (dd, ^2J = 15.5 Hz, ^3J = 4.5 Hz, 1H; H-9eq), 2.77 (dd, ^2J = 15.5 Hz, ^3J = 5.5 Hz, 1H; H-4eq), 2.73 (dd, ^2J = 15.5 Hz, ^3J = 6 Hz, 1H; H-4ax), 2.71 (dd, ^2J = 15.5 Hz, ^3J = 4.5 Hz, 1H; H-9ax), 2.62 (ddddd, ^3J = 8.5 Hz, ^3J = 8 Hz, ^3J = 6.5 Hz, ^3J = 6 Hz, ^3J = 5.5 Hz, 1H; H-3a), 2.36 (s, 3 H; CH_3), 2.16 (dddd, ^2J = 12 Hz, ^3J = 8.5 Hz, ^3J = 6.5 Hz, ^3J = 4 Hz, 1H; H-3A), 1.44 (dddd, ^2J = 12 Hz, ^3J = 8.5 Hz, ^3J = 8 Hz, ^3J = 7 Hz, 1H; H-3B); ^{13}C NMR ($CDCl_3$): δ = 149.7 (C-5), 147.8 (C-7), 145.7 (C-8a), 130.4 (C-8), 129.4 (C-4a), 76.5 (C-9a), 66.8 (C-2), 36.0 (C-3a), 32.9 (C-9), 31.7 (C-4), 28.9 (C-3), 15.4 (CH_3); MS [m/z (%)]: 257 (69) $M^{+\cdot}$, 239 (41), 226 (52), 213 (51), 211 (43), 204 (55), 187 (100), 152 (37); HRMS: calcd for $C_{12}H_{13}Cl_2NO$: 257.0374, found: 257.0351.

1,3-Dichloro-6-ethoxy-4-methyl-5,6,7,8-tetrahydroisoquinoline (12)

Yield: 55 %; m.p.: 78-79 °C (ethanol); IR (KBr): 1112 cm^{-1} (s); ^1H NMR ($CDCl_3$/TMS): δ = 3.80 (m, 1H; H-6eq), 3.63 (dq, ^2J = 9 Hz, ^3J = 7 Hz, 1H; OCH_2), 3.59 (dq, ^2J = 9 Hz, ^3J = 7 Hz, 1H; OCH_2), 2.92 (dd, ^2J = 17 Hz, ^3J = 5.5 Hz, 1H; H-5A), 2.88 (dt, ^2J = 17 Hz, ^3J = 6.5 Hz, 1H; H-8A), 2.69 (dd, ^2J = 17 Hz, ^3J = 6.5 Hz 1H; H-5B), 2.67 (dt, ^2J = 17 Hz, ^3J = 5.5 Hz, 1H; H-8B), 2.26 (s, 3 H; CH_3), 1.94 (m, 2H; H-7), 1.23 (t, ^3J = 7 Hz, 3H; CH_3); ^1H NMR (C_6D_6): δ = 3.26 (dq, ^2J = 9 Hz, ^3J = 7 Hz,1H; OCH_2), 3.24 (m, 1H; H-6), 3.17 (dq, ^2J = 9 Hz, ^3J = 7 Hz, 1H; OCH_2), 2.62 (dt, ^2J = 17 Hz, ^3J = 6.5 Hz, 1H; H-8A), 2.30 (dt, ^2J = 17 Hz, ^3J = 5.5 Hz, 1H; H-8B), 2.22 (dd, ^2J = 17 Hz, ^3J = 5.5 Hz 1H; H-5A), 2.14 (dd, ^2J = 17 Hz, ^3J = 6.5 Hz, 1H; H-5B), 1.73 (s, 3 H; CH_3), 1.46 (m, 2H; H-7), 1.07

(t, ^3J = 7 Hz, 3H; CH_3); ^{13}C NMR ($CDCl_3$): δ = 152.1 (C-1), 149.5 (C-3), 147.8 (C-4a), 130.7 (C-4), 129.2 (C-8a), 72.1 (C-6), 63.6 (OCH_2), 34.5 (C-5), 26.1 (C-7), 23.8 (C-8), 15.5 (CH_3), 15.2 (CH_3); MS [m/z (%)]: 259 (31) $M^{+\cdot}$, 213 (85), 178 (100); HRMS: calcd for $C_{12}H_{15}Cl_2NO$: 259.0531, found: 259.0537.

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