A New Neighbouring-Group Reaction to Form Pyridopyrrolobenzoxazinediones

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Dedicated to Professor Christoph Rüchardt on the occasion of his 75th birthday

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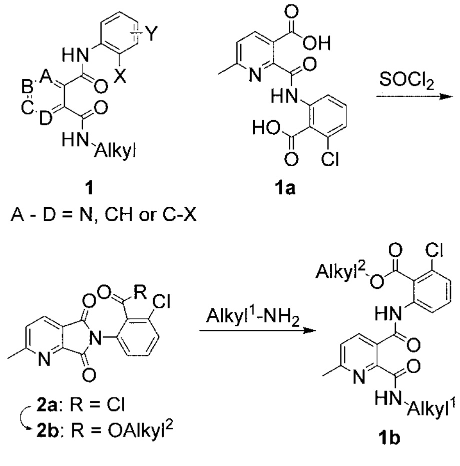
The azaphthalimide **2a** is the first phthalimide oxygen found to undergo a neighboring-group participation reaction with a vicinal *N*-phenyl carboxylic acid chloride upon nucleophilic addition with alcohols. Owing to the free rotation of the *N*-phenyl moiety, hetero-anellated benzoxazinedione isomers **3** and **4** are accessible, whereby **3** is preferred to **4** as the pyridine nitrogen in **2a** preferentially activates the *o*-carbonyl group. Yields of up to 92% were obtained when bases such as HCl acceptors were avoided by heating **2a** with alcohols. The reaction is restricted to primary and secondary alcohols, as **2a** is nonplanar in respect of the heterocyclic and benzene moiety, which prevents tertiary alcohols attacking the pyrrolidinedione carbonyl group.

Introduction

The aromatic heterocyclic dicarboxylic diamide derivatives **1** and **1b** are a new class of important herbicidal and insecticidal leads.[1] They are available by opening the ring of *N*-phenyl dicarboximides in the presence of aliphatic amines. The source of the herbicidal and insecticidal activity is two substituents in the phenyl moiety, one of which must be an alkyl, alkoxyalkyl, cyano or ester substituent in the *ortho* position (Scheme 1). For an economic variation of the ester group in herbicidal pyridine diamides **1b**, we were interested in first synthesizing cyclic imides **2b** with different ester groups in the phenyl moiety before opening the ring with different amines.[1b] Compound **2a** was selected as the starting material. It is made from **1a** by opening the ring of 6-methylpyridine-2,3-dicarboxylic anhydride with 2-amino-6-chlorobenzoic acid and subsequent reaction with thionyl chloride to yield **2a**. To our surprise, the addition of different alcohols revealed the occurrence of a neighboring group participation reaction, which gives rise to two different pyridopyrrolobenzoxazinediones.



Scheme 1. Herbicidal and insecticidal leads **1** and **1b**

Results and Discussion

Neighbouring group participation is well documented as far as the mechanism and scope of the reaction are concerned.[2] Neighbouring-group effects have been found to be responsible, for example, for the regioselective and diastereoselective alkylation of diketones[3a] and for the reaction of α-acetoxy carboxylic acid chlorides, or their corresponding gluconic acid chlorides, with hydroperoxides, yielding 2-alkylperoxy-1,3-dioxolan-4-ones instead of the expected esters.[3b,3c] Similarly, the reaction of γ-keto-acid chlorides and *o*-aroylbenzoyl chlorides with hydroperoxides delivered heterocyclic peroxides.[3d] Ribonucleoside phosphodichloridate, with a free *cis*-vicinal hydroxy group, shows a definite rate enhancement upon alcoholysis relative to the *cis* unsubstituted compounds.[3e][3f] Also, *N*-acyl functions have been shown to promote the conversion of nitriles into carboxamides under mild conditions by a neighbouring-group effect,[3g] and 2-carbamoylbenzoates readily release fragrance alcohols by neighbouring-group-

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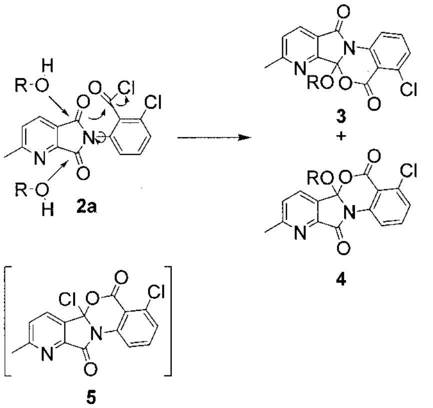
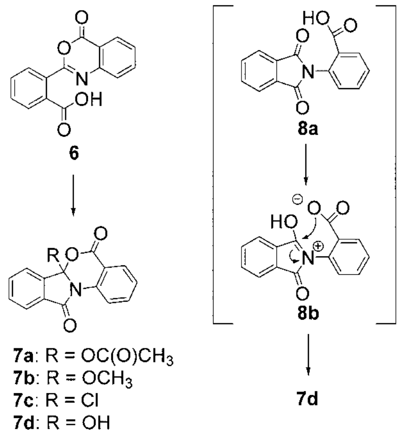
assisted alkaline hydrolysis.[3h] Apart from neighbouring-group effects of five- to seven-membered chelates ("chele-selectivity"),[3a] as far as isolable, direct S_N substitution products are concerned, five-membered rings are preferred to larger ring sizes.[2] To the best of our knowledge, the reaction described herein is the first example of the direct involvement of a phthalimide-type group in a neighbouring-group participation reaction with a carboxylic acid chloride, upon reaction with a nucleophile, leading to a six-membered ring. As shown in Scheme 2, the nucleophile does not attack the acid chloride function but adds to the pyrrolidinedione carbonyl group of **2a**, which, by lactonization via a six-membered ring, attacks the acid chloride with the subsequent elimination of the chloride. Owing to the free rotation of the *N*-phenyl moiety two isomers are formed, of which **3** is preferred to **4**.



Scheme 2. Synthesis of pyridopyrrolo[1,2-*a*][3,1]benzoxazine-5,11(6a*H*)-diones **3** and **4**

This new hetero-anellation does not occur via a preformed chlorobenzoxazinedione, such as **5**, since IR and ^{13}C NMR spectroscopic data confirm the involvement of the acid chloride **2a** (IR: ν[C(=O)Cl] 1798, ν[C(=O)N] 1733 cm^{-1}) rather than the benzoxazinedione **5**; for the sake of comparison, **4a** (R = Me) has ν[C(=O)O] 1758 and ν[C(=O)N] 1742 cm^{-1}. A related compound, **7b**, has been synthesised by Butula and Otting by a three-step condensation and addition reaction of anthranilic acid and phthalyl chloride to form benzoxazin-4-one **6** and subsequent reactions with acetic anhydride and methanol to yield **7a** and **7b**, respectively (Scheme 3).[4a] Later, 2-(2-carboxybenzamido)benzoic acid and the erroneously assigned 2-phthalimidobenzoic acid **8a** ("phthalanthranilic acid") were reacted with thionyl chloride to give the quadricycle **7c** and then with methanol to yield **7b**.[4b] Compound **8a**, however, has already been shown to possess the cyclic structure of **7d**, formed under the conditions for fusion of anthranilic acid and phthalic anhydride by nucleophilic attack of the carboxylate in **8b** on the protonated phthalimide moiety and yielding **7c** upon reaction with phosphorus pentachloride.[4c] Double cyclisation of phthalic anhydride with anthranilic acid to the lactonol **7d** and further reactions with acetic anhydride and methanolysis to give **7a** and **7b**, respectively, have been independently confirmed.[4d] For **7c**, unlike **2a**, ν(C=O) values of 1770 and 1730 cm^{-1}, in agreement with the angular chlorobenzoxazinedione, have been reported.[4b]

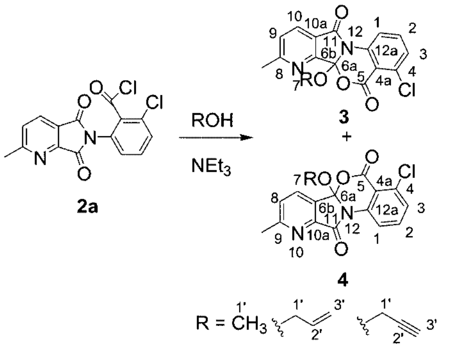


Scheme 3. Chemical structures of **6** and **7a−d** and the mechanism for the synthesis of **7d**

The formation of **2a** instead of **5** is apparently due to both the mesomeric and the inductive properties of the pyridine nitrogen, which stabilises the pyrrolidinedione ring, preventing further condensation, and creates the basis for the surprising neighboring-group participation during the subsequent nucleophilic step. Note that **2a** is not obtained as a hydrochloride after work up, demonstrating once more the interaction of the pyridine nitrogen with the pyrrolidinedione moiety.

In order to remove hydrogen chloride from the reaction mixture containing **2a** and the nucleophile, we initially used an excess of base at room temperature, which gave yields of **3** and **4** of only 19−32%. Table 1 shows the results of adding alcohol to **2a** under basic, neutral and acidic conditions at room temperature and at 90 °C. As the pyrrolidinedione moiety is cleaved under relatively mild conditions in the presence of base,[1b] reaction by-products prevail, which were removed during the basic work up. However, by reducing the excess of base from 2.2 to 1.1 equivalents in the reaction with allyl alcohol as a strong nucleophile, the total yield of **3** and **4** increased to 61% (Table 1, entry f). Although higher reaction temperatures required a change of solvent, the polarity of the solvent was roughly maintained. Use of 1,4-dioxane − a little less polar (E_T = 36.0) than dichloromethane (E_T = 41.0) − at 90 °C for 0.5 h in the absence of base provided the highest yields, with **3** clearly dominating (Table 1, entry a). Owing to the pyridine nitrogen, the *o*-carbonyl group is more reactive than the *m*-carbonyl group, which favours the formation of **3** rather than **4**. When chloroethanol (Table 1, entry i) was added in the absence of base, the highest amount of a single isomer, that is, **3**, was obtained in 45 and 80% yield in dichloromethane and 1,4-dioxane, respectively, which means that, from the

Table 1. Reactions of acid chloride **2a** with various alcohols



Entry	R	NEt$_3$ (equiv.)	Solvent[a]	*T* (°C)	*T* (h)	Yield of **3** (%)	Yield of **4** (%)
a	CH$_3$	–	I	22	6	24	18
		2.1	I	22	4	13	6
		–	II	90	0.5	60	30[b]
b	C$_2$H$_5$	2.1	I	22	12	13	14
		–	II	90	0.5	42	13
c	*n*-C$_3$H$_7$	–	II	90	0.5	60	30[b]
d	*i*-C$_3$H$_7$	–	I	22	12	33	24
		–	II	90	0.5	64	12[b]
e	*tert*-C$_4$H$_9$	–	II	90	8	–	–
f	CH$_2$=CH-CH$_2$	1.1	I	22	12	38	23
		2.2	I	22	12	14	8
g	HC≡C–CH$_2$	–	II	90	0.5	60	30[b]
h	CH$_3$OCH$_2$CH$_2$	2.1	I	22	12	17	15
i	ClCH$_2$CH$_2$	–	I	22	12	45	–
		–	II	90	0.5	80	12[b]

[a] I = dichloromethane, II = 1,4-dioxane. [b] Both yields were determined by NMR spectroscopy after work up of the obtained product mixture.

perspective of a push-pull-mechanism, the weaker nucleophile increases the proportion of **3** relative to **4**.

The acid chloride function was not attacked under acidic conditions, even after prolonged reaction times. This is clearly indicated by the reaction with *tert*-butyl alcohol, which has to add perpendicular to the pyrrolidinedione moiety, but comes into conflict with the phenyl ring. This steric inhibition effectively prohibits the attack of tertiary alcohols at the sterically most hindered position, while secondary and primary alcohols can penetrate without such hindrance. Conformational analysis of related *N*-aryl-3,4,5,6-tetrahydrophthalimides has shown that these molecules can undergo a range of rotations except for those conformations in which the heterocycle and the benzene ring are nearly coplanar.[5] The fact that at room temperature more **4** is formed than is expected seems to indicate a preferential orientation of the acid chloride with respect to the pyridine *m*-carbonyl group, which is more nucleophilic than its *ortho* counterpart. When the temperature was raised from 22 to 90 °C, however, the amount of the kinetically controlled isomer **4** decreased relative to **3**, apparently because of thermodynamically enhanced rotations, so that the pyridine nitrogen is the dominant factor determining the regiospecificity of the reaction.

In spite of the strongly acidic conditions when working in the absence of base, **3** and **4** are remarkably stable and no open-chain esters could be observed; this is in contrast to the observation that, under acidic conditions, **7b** readily rearranges to the open-chain ester.[4b] To sum up these results: neighbouring-group participation increases on progression from basic to neutral and then to acidic conditions and also at higher temperatures.

NMR signals were assigned for compound **3f** as an example using standard 2D NMR methods. ^{1}H,^{15}N-gs-HMBC (t = 200 ms) spectroscopy shows two peaks at δ = −80.0 and −242.5 ppm (with nitromethane as reference) due to pyridine and amide nitrogen atoms, respectively. The aromatic protons H-9 and H-10 of the pyridine moiety could be assigned by correlation to the pyridine nitrogen. The carbon shifts of C-1, C-2, C-3, C-9 and C-10 (δ = 119.58, 135.18, 128.89, 126.04 and 132.89 ppm, respectively) were easily obtained by ^{1}H,^{13}C-gs-HSQC.

The quaternary carbon atoms were assigned by ^{1}H,^{13}C-gs-HMBC (t = 62.5 ms). ^{2-4}J correlations of H-9 and H-10 led directly to C-6a (δ = 105.59 ppm, weak correlation to 10-H), C-6b (δ = 158.38 ppm), C-8 (δ = 165.72 ppm), C-10a (δ = 122.04 ppm) and C-11 (δ = 161.80 ppm). The proton signals of 1-H, 2-H and 3-H show long-range correlations to C-4 (δ = 137.44 ppm, typical of an *ipso*-carbon with chlorine), C-4a (δ = 113.18 ppm), C-5 (δ = 157.04 ppm) and C-12a (δ = 137.06 ppm). Finally, the allylic protons show a ^3J correlation to C-6a, whose low-field shift can be explained by the fact that this carbon bridges the pyridine, the lactone and the lactam moiety.

Hetero-anellation is also accompanied by a characteristic shift in the IR and NMR signals. In accordance with the electron-withdrawing effect of the pyridine nitrogen, the protons of the alkoxy group of **3** are shifted downfield in the NMR spectrum, while the IR signal of the lactam of **4** in most cases shows a small shift to higher wavenumber.

Conclusion

While acetates and ketones are well known as participants in neighboring-group reactions, the above azaphthalimide is the first example of a phthalimide oxygen actively taking part in an efficient synthesis of pyridopyrrolobenzoxazinediones by neighboring-group participation. Attractive features of this procedure are the mild reaction conditions, high conversions and inexpensive starting materials. By virtue of the variations that are possible in the substrates, an interesting range of new heterocycles should be available for further biological and chemical studies.

Experimental Section

General Remarks: All commercially available products were purchased from Aldrich and used without further purification. Reactions were performed under a N_2 atmosphere. Liquid flash chromatography was performed using Macherey−Nagel silica gel 60 M (230−400 mesh), and analytical thin layer chromatography (TLC) was performed on fluorescent Macherey−Nagel POLYGRAM® SIL G/UV 254 precoated plastic sheets. For HPLC analysis a Merck−Hitachi apparatus with an L-6200A precision pump and an L-4000A UV detector were used: retention times in min; HPLC column: 250 × 4 mm RP 18 LiChrospher 100 (5 µm) Merck; mobile phase: acetonitrile/water 60:40 → 1 min → 80:20 → 7 min → 60:40, flow rate 1 mL·min^{-1}, UV 254 nm. IR spectra were recorded using a Bruker IFS 66 spectrometer (KBr). NMR spectra were recorded on a Bruker AC-400 (400.13 MHz for ^{1}H, 100.77 MHz for ^{13}C), DRX-500 (500.13 MHz for ^{1}H, 125.77 MHz for ^{13}C), Varian INOVA 500 (499.96 MHz for ^{1}H, 125.73 MHz for ^{13}C) and Varian INOVA 600 (599.92 MHz for ^{1}H, 150.86 MHz for ^{13}C) in $CDCl_3$ unless stated.

Synthesis of 2-[(2-Carboxy-3-chloroanilino)carbonyl]-6-methyl-3-pyridinecarboxylic Acid (1a): A mixture of 6-methylpyridine-2,3-dicarboxylic acid anhydride (25 g, 0.153 mol), and 2-amino-6-chlorobenzoic acid (26.3 g, 0.153 mol) in 1,2-dichloroethane (750 mL) was refluxed for 2 h. After cooling to room temp., diethyl ether (500 mL) was added and the crystalline product was filtered and washed to yield **1a** (44.4 g, 78%). M.p. 193 °C (decomp.). IR (KBr): $\tilde{\nu}$ = 1751, 1682, 1592, 1577, 1537, 1450 cm^{-1}. ^{1}H NMR (400.13 MHz, [D$_6$]DMSO): δ = 10.91 (s, OH), 8.21 (d, J = 10 Hz, H-4), 8.00 (d, J = 10 Hz, H-6′), 7.60 (d, J = 10 Hz, H-5), 7.54 (t, J = 10.5 Hz, H-5′), 7.37 (d, J = 9.5 Hz, H-4′), 2.62 (Me) ppm. ^{13}C NMR (100.73 MHz, [D$_6$]DMSO): δ = 168.22 (3-COOH), 166.38 (2′-COOH), 162.38 (CONH), 158.54 (C-6), 146.24 (C-2), 137.10 (C-4), 136.47 (C-1′), 131.34 (C-5′), 130.74 (C-3′), 127.57 (C-3), 125.89 (C-4′), 125.59 (C-5), 124.99 (C-2′), 120.44 (C-6′), 23.71 (Me) ppm.

Synthesis of 2-Chloro-6-(2-methyl-5,7-dioxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)benzoyl Chloride (2a): Thionyl chloride (37.5 g, 0.316 mol) was added to the above intermediate (**1a**) (35.2 g, 0.105 mol) in 1,2-dichloroethane (600 mL) at 60 °C over 25 min and refluxed for 2 h. The solvent was removed under reduced pressure, and the crude product was purified by crushing in a mortar, refluxing it with diethyl ether, then filtering and washing the product to obtain **2a** (32.1 g, 91%). M.p. 169−172 °C. IR(KBr): $\tilde{\nu}$ = 1798, 1733, 1589, 1458, 1371, 1197 cm^{-1}; the typical broad hydrochloride absorption bands between 2000−2900 cm^{-1} were completely absent, indicating the presence of the free pyridine. ^{1}H NMR (499.96 MHz, $CDCl_3$): δ = 8.17 (d, J = 8.0 Hz, H-4′), 7.60 (m, H-3, H-4, H-5), 7.37 (m, H-3′) ppm. ^{13}C NMR (125.73 MHz, $CDCl_3$): δ = 167.42 (C-2′), 164.63 (C-5′), 164.55 (C-7′), 164.18 (COCl), 150.89 (C-7a′), 135.37 (C-2), 132.59 (C-4), 132.16 (C-4′), 131.66 (C-6), 131.29 (C-3), 129.40 (C-1), 128.15 (C-5), 127.96 (C-3′), 124.52 (C-4a′), 25.14 (Me) ppm; the carbon NMR spectrum is in agreement with the free pyridine base, as C-2′ of the acid chloride has approximately the same chemical shift (δ = 167.42 ppm) as the corresponding C atoms in the neutral compounds **3a** (C-8: δ = 165.80 ppm) and **4a** (C-9: δ = 164.05 ppm).

General Procedure for the Preparation of Pyridopyrrolobenzoxazinediones 3a−i and 4a−i: A mixture of **2a** (2.5 g, 7.46 mmol) and alcohol (8.125 mmol) in dichloromethane (75 mL) was stirred under nitrogen at room temp. for 5 h. To complete the reaction (HPLC) more alcohol (2.19 mmol) was added and the reaction mixture was stirred for a further 1 h. For the work up, dichloromethane (50 mL) was added and the mixture was extracted with 3% aqueous sodium hydrogencarbonate and saturated aqueous sodium chloride solutions. After drying over magnesium sulfate, most of the solvent was evaporated and the reaction mixture was purified by column chromatography on silica gel with cyclohexane/ethyl acetate (1:1) to yield **3** and **4** as separated isomers. The reaction conditions and yields are given in Table 1, HPLC and m.p. data in Table 2, and IR data in Table 3.

NMR Data of Selected Products 3 and 4

4-Chloro-6a-methoxy-8-methyl-5*H*-pyrido[2′,3′:3,4]pyrrolo[1,2-*a*]-[3,1]benzoxazine-5,11(6a*H*)-dione (3a) (Table 1, entry a): ^{1}H NMR

Table 2. HPLC and m.p. data of **3** and **4**

Entry	R	HPLC (min)		M.p. (°C)	
		3	**4**	**3**	**4**
a	CH_3	5.06	4.64	234−237	196−198
b	C_2H_5	5.82	5.28	202−204	200−203
c	*n*-C_3H_7	6.61	5.98	−	−
d	*i*-C_3H_7	6.64	5.80	160−165	148−160
e	*tert*-C_4H_9	−	−	−	−
f	$CH_2{=}CH{-}CH_2$	6.04	5.51	144−145	118−120
g	$HC{\equiv}C{-}CH_2$	5.30	4.82	−	168−171
h	$CH_3OCH_2CH_2$	4.99	4.68	188−190	149−152
i	$ClCH_2CH_2$	5.58	5.06	156−160	−

Table 3. IR data of **3** and **4**

Entry	R	$\tilde{\nu}$ (cm^{-1}) **3**			$\tilde{\nu}$ (cm^{-1}) **4**		
		C(=O)O	C(=O)N	C=O	C(=O)O	C(=O)N	C=O
a	CH_3	1754	1730	–	1758	1742	–
b	C_2H_5	–	–	1739	–	–	1744
c	*n*-C_3H_7	–	–	–	–	–	–
d	*i*-C_3H_7	–	–	1742	–	–	1746
e	*tert*-C_4H_9	–	–	–	–	–	–
f	$CH_2{=}CH{-}CH_2$	1760	1743	–	1759	1740	–
g	$HC{\equiv}C{-}CH_2$	–	–	–	–	–	–
h	$CH_3OCH_2CH_2$	1759	1733	–	–	–	1746
i	$ClCH_2CH_2$	–	–	1742	–	–	–

(500.13 MHz, [D$_6$]DMSO): δ = 8.32 (d, *J* = 7.9 Hz, H-10), 8.04 (dd, *J* = 8.2 and 1.0 Hz, H-1), 7.87 (t, *J* = 8.2 Hz, H-2), 7.71 (d, *J* = 8.1 Hz, H-9), 7.59 (dd, *J* = 8.1 and 1.0 Hz, H-3), 3.18 (s, H-1′), 2.73 (s, Me) ppm. ^{13}C NMR (125.77 MHz, [D$_6$]DMSO): δ = 165.38 (C-8), 161.44 (C-11), 156.63 (C-5), 156.53 (C-6b), 136.61 (C-12a), 136.06 (C-2), 135.44 (C-4), 133.17 (C-10), 128.60 (C-3), 126.56 (C-9), 122.27 (C-10a), 119.94 (C-1), 112.41 (C-4a), 105.93 (C-6a), 52.37 (C-1′), 24.49 (Me) ppm.

4-Chloro-6a-isopropoxy-8-methyl-5*H*-pyrido[2′,3′:3,4]pyrrolo[1,2-*a*]-[3,1]benzoxazine-5,11(6a*H*)-dione (3d) (Table 1, entry d): ^{1}H NMR (500.13 MHz, [D$_6$]DMSO): δ = 8.30 (d, *J* = 7.5 Hz, H-10), 8.02 (dd, *J* = 8.0 and 0.5 Hz, H-1), 7.86 (t, *J* = 8.0 Hz, H-2), 7.71 (d, *J* = 8.0 Hz, H-9), 7.58 (dd, *J* = 8.0 and 0.5 Hz, H-3), 4.12 (quint, *J* = 6.0 Hz, H-1′), 2.72 (s, Me), 0.99 (d, *J* = 6.0 Hz, H-2′^{a}), 0.80 (d, *J* = 6.0 Hz, H-2′^{b}) ppm.

6a-Allyloxy-4-chloro-8-methyl-5*H*-pyrido[2′,3′:3,4]pyrrolo[1,2-*a*]-[3,1]benzoxazine-5,11(6a*H*)-dione (3f) (Table 1, entry f): ^{1}H NMR (599.92 MHz, CDCl$_3$): δ = 8.12 (d, *J* = 8.0 Hz, H-10), 8.06 (d, *J* = 8.0 Hz, H-1), 7.64 (t, *J* = 8.2 Hz, H-2), 7.48 (d, *J* = 8.2 Hz, H-9), 7.43 (d, *J* = 8.2 Hz, H-3), 5.72 (m, H-2′), 5.09 (m, H-3′), 4.42 (m, H-1′), 2.78 (s, Me) ppm.

4-Chloro-6a-propargyloxy-8-methyl-5*H*-pyrido[2′,3′:3,4]pyrrolo[1,2-*a*][3,1]benzoxazine-5,11(6a*H*)-dione (3g) (Table 1, entry g): ^{1}H-NMR (500.13 MHz, CDCl$_3$): δ = 8.14 (d, *J* = 7.9 Hz, H-10), 8.06 (d, *J* = 8.2 Hz, H-1), 7.66 (t, *J* = 8.2 Hz, H-2), 7.52 (d, *J* = 8.0 Hz, H-9), 7.44 (d, *J* = 8.1 Hz, H-3), 4.76 (dd, *J* = 16.0 and 2.1 Hz, H-1′^{a}), 4.57 (dd, *J* = 16.0 and 2.1 Hz, H-1′^{b}), 2.78 (s, Me), 2.46 (s, H-3′) ppm.

4-Chloro-6a-methoxy-9-methyl-5*H*-pyrido[3′,2′:3,4]pyrrolo[1,2-*a*]-[3,1]benzoxazine-5,11(6a*H*)-dione (4a) (Table 1, entry a): ^{1}H NMR (500.13 MHz, [D$_6$]DMSO): δ = 8.35 (d, *J* = 8.0 Hz, H-7), 8.10 (d, *J* = 8.0 Hz, H-1), 7.88 (t, *J* = 8.5 Hz, H-2), 7.77 (d, *J* = 8.0 Hz, H-8), 7.59 (d, *J* = 8.0 Hz, H-3), 3.09 (s, H-1′), 2.71 (s, Me) ppm.

4-Chloro-6a-isopropoxy-9-methyl-5*H*-pyrido[3′,2′:3,4]pyrrolo[1,2-*a*][3,1]benzoxazine-5,11(6a*H*)-dione (4d) (Table 1, entry d): ^{1}H NMR (500.13 MHz, [D$_6$]DMSO): δ = 8.38 (d, *J* = 8.0 Hz, H-7), 8.06 (dd, *J* = 8.0 and 1.0 Hz, H-1), 7.88 (t, *J* = 8.5 Hz, H-2), 7.75 (d, *J* = 8.0 Hz, H-8), 7.59 (dd, *J* = 8.5 and 1.0 Hz, H-3), 3.70 (m, H-1′), 2.70 (s, Me), 0.95 (d, *J* = 6.5 Hz, H-2′^{a}), 0.73 (d, *J* = 6.0 Hz, H-2′^{b}) ppm.

6a-Allyloxy-4-chloro-9-methyl-5*H*-pyrido[3′,2′:3,4]pyrrolo[1,2-*a*]-[3,1]benzoxazine-5,11(6a*H*)-dione (4f) (Table 1, entry f): ^{1}H NMR (499.96 MHz, CDCl$_3$): δ = 8.16 (d, *J* = 8.5 Hz, H-7), 8.05 (d, *J* = 8.0 Hz, H-1), 7.66 (t, *J* = 8.5 Hz, H-2), 7.53 (d, *J* = 8.0 Hz, H-8), 7.45 (dd, *J* = 8.0 and 0.5 Hz, H-3), 5.59 (m, H-2′), 5.05 (m, H-3′), 3.81 (m, H-1′), 2.79 (s, Me) ppm.

4-Chloro-6a-propargyloxy-9-methyl-5*H*-pyrido[3′,2′:3,4]pyrrolo[1,2-*a*][3,1]benzoxazine-5,11(6a*H*)-dione (4g) (Table 1, entry g): ^{1}H NMR (500.13 MHz, CDCl$_3$): δ = 8.17 (d, *J* = 8.2 Hz, H-7), 8.09 (d, *J* = 8.2 Hz, H-1), 7.67 (t, *J* = 8.3 Hz, H-2), 7.54 (d, *J* = 7.9 Hz, H-8), 7.46 (d, *J* = 8.2 Hz, H-3), 4.06 (dd, *J* = 16.1 and 2.4 Hz, H-1′^{a}), 3.97 (dd, *J* = 16.1 and 2.4 Hz, H-1′^{b}), 2.80 (s, Me), 2.31 (t, *J* = 2.5 Hz, H-3′) ppm.

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