1,4-Dipolar Cycloaddition Reactions in Ionic Liquids: A Facile Synthesis of 9a*H*,15*H*-[1]Benzopyrano[3′,2′:3,4]pyrido[2,1-*a*]isoquinolines (= 9a*H*,15*H*-Benzo[*a*][1]benzopyrano[2,3-*h*]quinolizines)

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Ionic liquids were found to be a suitable reaction medium for 1,4-dipolar cycloaddition reactions of an isoquinoline, an activated alkyne, and a 4-oxo-4*H*-1-benzopyran-3-carboxaldehyde at room temperature to afford [1]benzopyrano-pyrido-isoquinoline (= 9a*H*,15*H*-benzo[*a*][1]benzopyrano[2,3-*h*]quinolizine) derivatives selectively in good yields. The ionic liquid can be recovered and recycled in further runs without loss of activity.

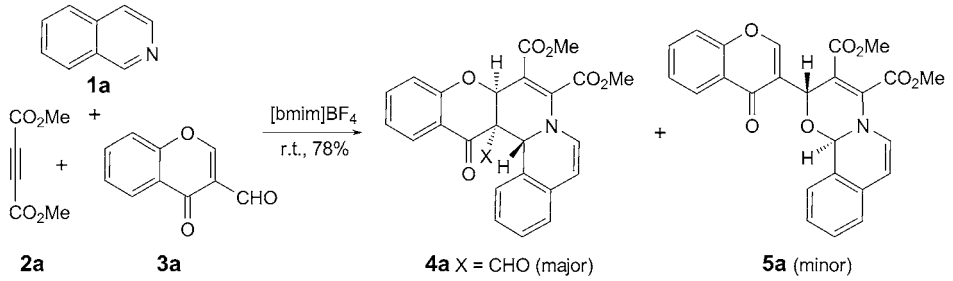
Introduction. – Multicomponent reactions (MCRs) are highly important because of their wide range of applications in pharmaceutical chemistry for the production of diversified structural scaffolds and combinatorial libraries for drug discovery [1]. This approach offers significant advantages over classical step-by-step approaches allowing the formation of several bonds and the construction of complex molecular architectures from simple precursors in a single step without the need for isolation of intermediates [2].

Huisgen [3] has reported the formation of 1,4-dipoles from isoquinoline and dimethyl acetylenedicarboxylate (= dimethyl but-2-ynedioate; DMAD) and their trapping by phenyl isocyanate, diethyl mesoxalate, and dimethyl azodicarboxylate to generate six-membered heterocycles. The dihydroisoquinoline motif is frequently found in many natural alkaloids [4]. Consequently, a large number of elegant approaches have been developed for the synthesis of 1,2-dihydroisoquinolines [5]. Of these, the *Reissert*-type reaction is one of the direct methods for the functionalization of activated isoquinolines [6], and recently, its asymmetric versions have also been investigated [7]. Furthermore, the reaction of 3-methylisoquinoline, acetylenedicarboxylates and 4-oxo-4*H*-1-benzopyran-3-carboxaldehyde in dimethoxyethane has recently been reported to yield 9a*H*,15*H*-[1]benzopyrano[3′,2′:3,4]pyrido[2,1-*g*]isoquinolines (= 9a*H*,15*H*-benzo[*a*][1]benzopyrano[2,3-*h*]quinolizines) [8]. Inspired by this methodology, we investigated this three-component reaction with various isoquinolines in an ionic liquid to study the effect on yield and selectivity. Knowing the power of multicomponent reactions of isoquinoline derivatives, the preparation of new analogs is of prime importance in both synthetic and medicinal chemistry. However, to the best of our knowledge, there have been no reports on the use of ionic liquids for 1,4-dipolar cycloaddition reactions. Furthermore, ionic liquids are known to

activate dipolar species in many dipolar cycloadditions to afford improved yields, enhanced reaction rates, and selectivity [9].

Results and Discussion. – Following our interest in the functionalization of activated aza-aromatic systems [10][11], we herein report a simple, convenient, and highly efficient approach for the synthesis of 9a*H*,15*H*-[1]benzopyrano[3′,2′:3,4]pyrido[2,1-*a*]isoquinoline derivatives by means of a three-component coupling of isoquinoline (**1**), dimethyl acetylenedicarboxylate (DMAD; **2**), 4-oxo-4*H*-1-benzopyran-3-carboxaldehyde (**3**) in [bmim]BF_4 (=1-*tert*-butyl-3-methyl-1*H*-imidazolium tetrafluoroborate(1)) media. The coupling reaction went to completion at room temperature and gave a mixture **4a**/**5a** (racemic) in a 4:1 ratio in 78% yield (*Scheme 1*; *Table, Entry a*). The products **4a** and **5a** were separated by column chromatography (SiO_2, AcOEt/hexane 1:9).

Scheme 1. *The Three-Component Coupling Reaction of Isoquinoline* (**1a**), *DMAD* (**2a**), *and 4-Oxo-4*H*-1-benzopyran-3-carboxaldehyde* (**3a**)



The structure and relative configuration of **4a** and **5a** were confirmed by NMR spectroscopy, HR-MS, and also by X-ray crystallography (*Figs. 1* and *2*). The configuration of product **4a** (crystallized as hemiacetal) was different from that of an analogous product obtained in dimethoxyethane by the use of 3-methylisoquinoline [8]. The products **4a** and **5a** were dissolved in a small amount of MeOH, then 2–3 drops of H_2O were added, and the resulting mixture was kept at room temperature for 3–4 d. The diester **4a** crystallized in its hemiacetal form with MeOH (*Fig. 1*), while **5a** crystallized as colorless crystals (*Fig. 2*). The structure of the hemiacetal derivative of **4a** was also confirmed by the ^{1}H-NMR spectrum ($CDCl_3$): The aldehyde H-atom of **4a** at δ(H) 9.98 (*s*, 1 H) was absent, and three new peaks at δ(H) 5.17 (*d*, J = 12.8 Hz, 1 H), 4.34 (*d*, J = 12.8 Hz, 1 H), and 3.31 (*s*, 3 H) were observed, which indicated the complete conversion of the aldehyde function to its hemiacetal derivative.

Interestingly, various substituted isoquinolines such as 4-bromo-, 3-methyl-, 5-nitro-, and 5-bromo derivatives, treated with DMAD, also underwent smooth cycloaddition with 4-oxo-4*H*-1-benzopyran-3-carboxaldehyde to produce the corresponding pentacyclic compounds in good to excellent yields (*Table*, *Entries c* and *k*, *d*, *f*, and *g* and *l*, resp.). Diethyl acetylenedicarboxylate (=diethyl but-2-ynedioate; DEAD) was also found to be equally effective for this conversion (*Entries e* and *h*). Next, we successfully performed the three-component reactions with 6-methyl- and 6-isopropyl-substituted

Table. *Systhesis of [1]Benzopyrano-pyrido-isoquinoline Derivative* via *a Three Component Reaction in [bmim]BF_4*

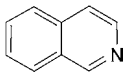
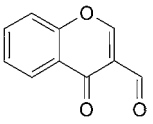
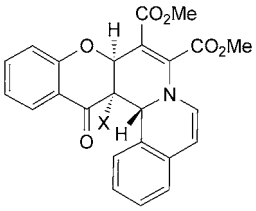
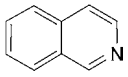
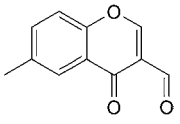
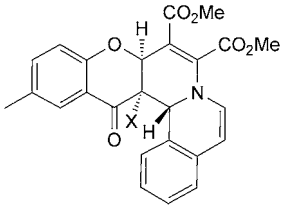
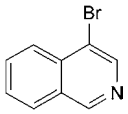
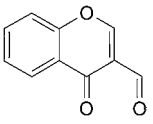
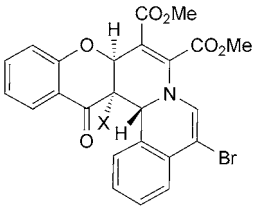
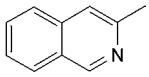
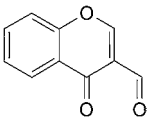
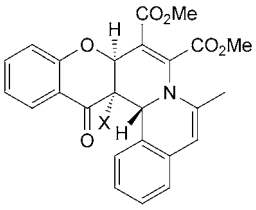
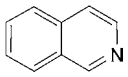
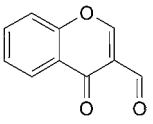
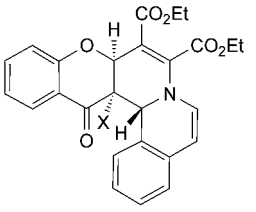
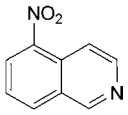
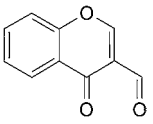
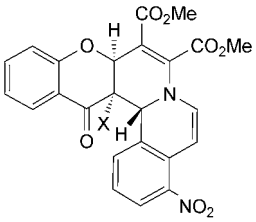
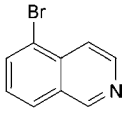
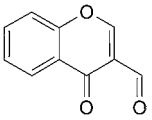
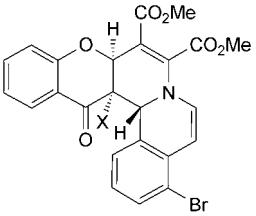
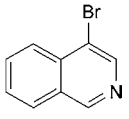
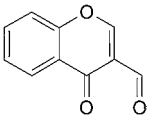
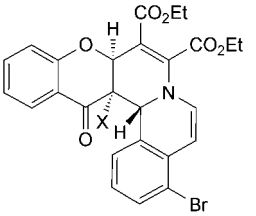
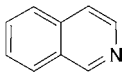
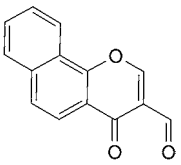
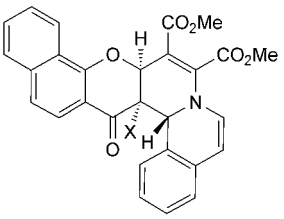
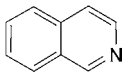
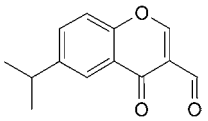
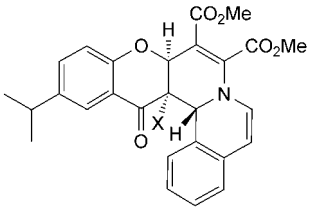
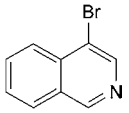
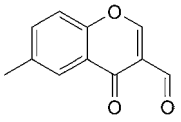
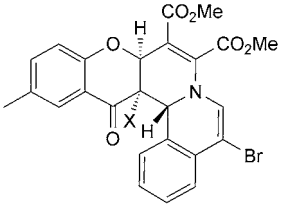
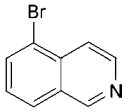
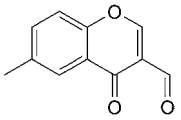
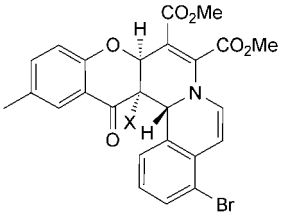
Entry	Isoquinoline **1**	**2**	**3**	Product **4**[a])	Time [h]	Yield of **4**/**5** [%][b])	Ratio **4**/**5**
a					10.0	78	8 : 2
b					8.0	83	8 : 2
c					8.0	72	9 : 1
d					10	68	9 : 1
e					14.0	76	8 : 2
f					15.0	71	8 : 2

Table (cont.)

Entry	Isoquinoline **1**	**2**	**3**	Product **4**[a])	Time [h]	Yield of **4/5** [%][b])	Ratio **4/5**
g					10.0	74	8 : 2
h					11	73	8 : 2
i					8.0	72	8 : 2
j					12.0	77	8 : 2
k					10.0	68	9 : 1
l					13	71	8 : 2

[a]) The *Entry* label corresponds to the products label, *e.g.*, *Entry a* → **4a**/**5a**; the products were characterized by NMR, IR, and mass spectrometry; X = CHO. [b]) Yield of pure product after chromatography.

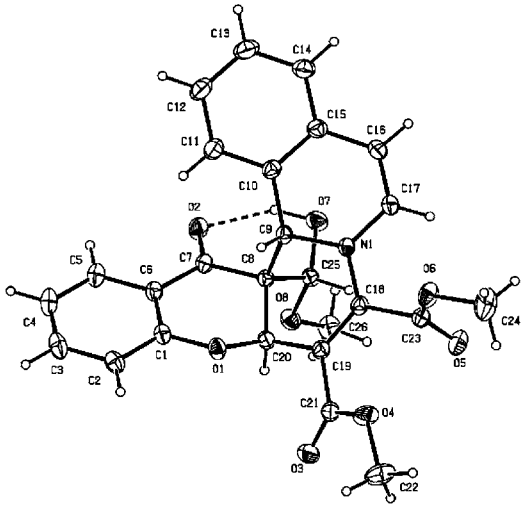


Fig. 1. *ORTEP Diagram of the hemiacetal of* **4a**. Arbitary atom numbering

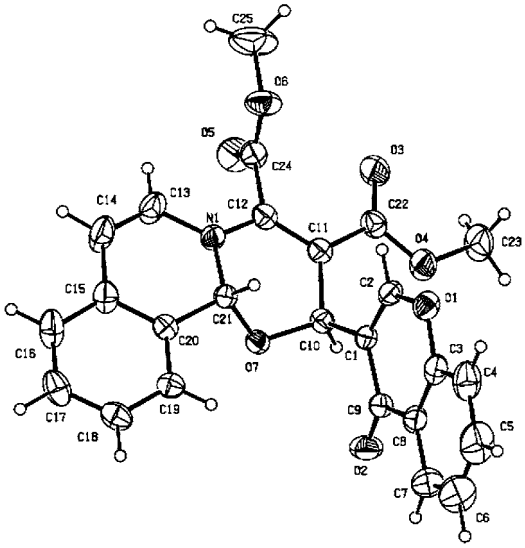
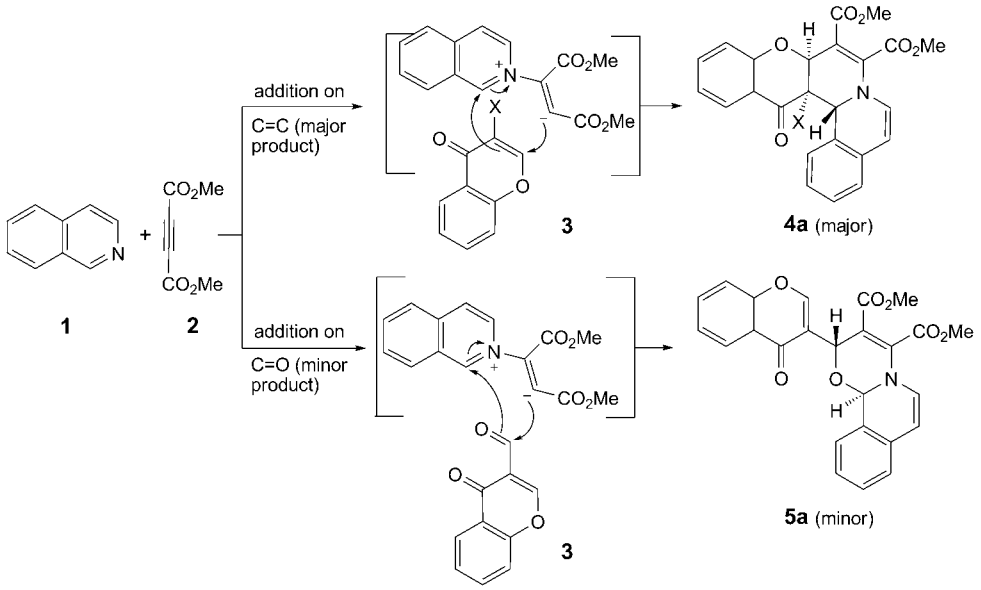


Fig. 2. *ORTEP Diagram of* **5a**. Arbitary atom numbering

4-oxo-4*H*-1-benzopyran-3-carboxaldehydes (*Entries b*, *k*, and *l*, and *j*, resp.). However, the reaction of quinoline (instead of isoquinoline), DMAD, and **3a** gave the products as inseparable mixtures under identical conditions.

The reaction likely proceeds *via* the initial formation of a zwitterionic intermediate [3][12] from isoquinoline and DMAD. The thus formed zwitterion may undergo 1,4-dipolar cycloaddition with 4-oxo-4*H*-1-benzopyran-3-carboxaldehyde either by addition on the activated C=C bond (major product) or on the C=O bond of the α,β-

Scheme 2. *A Plausible Reaction Mechanism for the formation of* **4a** *and* **5a**



unsaturated aldehyde (minor product) to furnish the isolated products as shown in *Scheme 2*.

This method worked well with both electron-rich and electron-deficient isoquinolines. Various groups such as nitro and halogeno substituents were well tolerated under the reaction conditions (*Table*). No additives or catalysts were required to effect this reaction. The cycloaddition was carried out in both hydrophilic ([bmim]BF_4) and hydrophobic ([bmim]PF_6) ionic liquids. Among these ionic liquids, [bmim]BF_4 was superior in terms of conversion and selectivity. The ionic solvents could easily be recovered during workup and be recycled in subsequent runs. As the products were partially soluble in the ionic phase, they were easily isolated by simple extraction with Et_2O. The remaining viscous ionic liquid was thoroughly washed with Et_2O (4×10 ml) and dried at 80° under reduced pressure. The thus activated ionic liquid was reused in five runs without any loss of activity, the products being obtained in the same purity and in the same yield as in the first run. For instance, treatment of isoquinoline (**1a**) with **2a** and **3a** in [bmim]BF_4 gave the mixture **4a**/**5a** in 78, 76, 75, 77, and 78% yields over five runs without any change in the ratio.

The use of ionic liquid offers some advantages such as reusability of the solvent and slightly improved yields and reaction rates when compared to dimethoxyethane. For example, treatment of 3-methylisoquinoline (**1d**) with **2a** and **3a** in [bmim]BF_4 gave the corresponding products **4d** and **5d** in 68% yield in a 9:1 ratio within 10 h (*Table*, *Entry d*), whereas the same reaction in DME gave product **4d** in 51% yield in 12 h. In summary, we demonstrated the novel use of a ionic liquid as a convient and recyclable reaction medium for the one-pot cycloaddition of 4-oxo-4*H*-1-benzopyran-3-carboxaldehydes with zwitterionic adducts of isoquinolines and dimethyl or diethyl

acetylenedicarboxylate to produce 9a*H*,15*H*-[1]benzopyrano[3′,2′:3,4]pyrido[2,1-*a*]isoquinoline derivatives as major products along with oxazino-isoquinolines as minor products in good yields.

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Experimental Part

General. Column chromatography (CC): silica gel (SiO_2; 100–200 mesh; *Merck*). M.p.: *Büchi-R-535* apparatus; uncorrected. IR Spectra: *Perkin-Elmer-FT-IR-240-c* spectrophotometer; in KBr; $\tilde{\nu}$ in cm^{-1}. ^1H- and ^{13}C-NMR Spectra: *Bruker-300* or *Varian-Unity 400* spectrometers; at 400 (^1H) and 75 Mhz (^{13}C) in $CDCl_3$; δ in ppm rel. to Me_4Si as internal standard, J in Hz. MS: *Finnigan-MAT-1020* mass spectrometer; at 70 eV; in m/z.

General Procedure. To a stirred soln. of isoquinoline (1 mmol) and 4-oxo-4*H*-1-benzopyran-3-carboxaldehyde **3** (1.1 mmol) in [bmim]BF_4 (2 ml) at 25° was added dimethyl or diethyl acetylenedicarboxylate **2** (1.2 mmol). The mixture was stirred at r.t. for the appropriate time (*Table*). After complete conversion (TLC monitoring, the mixture was extracted with Et_2O (6 × 10 ml), the combined extract dried (Na_2SO_4) and concentrated, and the resulting crude product seperated by CC (silica gel, AcOEt/hexane 1:9): pure **4** and **5** (*Table*).

X-Ray Crystal-Structure Determination. The crystal of the hemiacetal derivative of **4a** belongs to the triclinic crystal system, space group $P\bar{1}$ with $a = 8.8491(13)$ Å, $b = 10.8402(16)$Å, $c = 13.129(2)$Å, $\alpha = 79.009(2)°$, $\beta = 75.332(2)°$, $\gamma = 69.511(2)°$, $V = 1134.0(3)$ Å^3, $\rho_{calc} = 1.398$ mg m^{-3}, λ 0.71073Å, (MoK_α) = 0.105 mm^{-1}, $F(000) = 500$, and T 294(2) K. Data collection yielded 7224 reflections resulting in 3793 unique, averaged reflections, 3597 with $I > 2\sigma(I)$, θ range 2.44–25.00°. Full-matrix least-squares refinement led to a final $R = 0.0384$, $wR = 0.1062$, and g.o.f. = 1.018. Intensity data were measured with a *Bruker Smart Apex* and CCD area detector. CCDC-771095 contains the supplementary crystallographic data for the structure of the hemiacetal derivative of **4a** (*Fig. 1*)[1]).

The crystal of **5a** belongs to the orthorhombic crystal system, space group *Pbca*, with $a = 10.0339(9)$ Å, $b = 15.7959(14)$ Å, $c = 26.722(2)$ Å, $V = 4235.2(7)$ Å^3, $\rho_{calc} = 1.397$ mg m^{-3}, λ 0.71073Å, (MoK_α) = 0.103 mm^{-1}, $F(000) = 1856$, and T 294(2) K. Data collection yielded 5057 reflections resulting in 3725 unique, averaged reflections, 3232 with $I > 2\sigma$ (I), θ range 2.52–25.00. Full-matrix least-squares refinement led to a final $R = 0.0547$, $wR = 0.1465$, and g.o.f. = 1.067. Intensity data were measured with a *Bruker Smart Apex* and CCD area detector. CCDC-771096 contains the supplementary crystallographic data for the structure **5a** (*Fig. 2*)[1]).

Dimethyl rel-*(9a*R*,15a*R*,15b*R*)-15a-Formyl-15a,15b-dihydro-15-oxo-9a*H*,15*H*-benzo[*a*][1]benzopyrano[2,3-*h*]quinolizine-8,9-dicarboxylate* (**4a**): Yellow solid. M.p. 183–184°. IR (KBr): 2951, 1743, 1709, 1670, 1601, 1569, 1463, 1301, 1264, 1231, 1140, 1109, 990, 776, 732, 528. ^1H-NMR (300 MHz): 9.98 (*s*, 1 H); 7.78 (*dd*, $J = 8.3, 1.5$, 1 H); 7.54–7.61 (*m*, 1 H); 7.21 (*d*, $J = 8.3$, 1 H); 7.12 (*t*, $J = 7.5$, 2 H); 7.03 (*t*, $J = 7.5$, 2 H); 6.46 (*d*, $J = 8.3$, 1 H); 6.13 (*d*, $J = 7.5$, 1 H); 5.66 (*d*, $J = 7.5$, 1 H); 5.62 (*s*, 1 H); 5.48 (*s*, 1 H); 3.92 (*s*, Me); 3.85 (*s*, Me). ^{13}C-NMR (H-decoupled, 75 MHz): 197.0; 187.7; 165.1; 163.6; 160.1; 145.1; 137.1; 129.4; 129.0; 128.6; 126.7; 126.4; 126.0; 125.4; 124.1; 122.4; 120.5; 118.2; 106.3; 104.5; 71.0; 65.1; 55.5; 53.3; 52.0. ESI-MS: 446 ($[M+H]^+$), 416, 290. HR-MS: 446.1219 ($[M+H]^+$, $C_{25}H_{20}NO_7^+$; calc. 446.1239).

Dimethyl rel-*(9a*R*,15a*R*,15b*R*)-15a,15b-Dihydro-15a-[hydroxy(methoxy)methyl]-15-oxo-9a*H*,15*H*-benzo[*a*][1]benzopyrano[2,3-*h*]quinolizine-8,9-dicarboxylate* (hemiacetal of **4a**): ^1H-NMR (300 MHz): 7.93 (*dd*, $J = 7.5, 1.5$, 1 H); 7.51–7.59 (*m*, 1 H); 6.88–7.17 (*m*, 5 H); 6.24 (*d*, $J = 7.5$, 1 H); 6.18 (*d*, $J = 7.5$, 1 H); 5.73 (*d*, $J = 7.5$, 1 H); 5.54 (*s*, 1 H); 5.48 (*s*, 1 H); 5.17 (*d*, $J = 12.8$, 1 H); 4.34 (*d*, $J = 12.8$, 1 H); 3.96 (*s*, Me); 3.82 (*s*, Me); 3.31 (*s*, Me).

Dimethyl rel-*(9a*R*,15a*R*,15b*R*)-15a-Formyl-15a,15b-dihydro-13-methyl-15-oxo-9a*H*,15*H*-benzo[*a*][1]benzopyrano[2,3-*h*]quinolizine-8,9-dicarboxylate* (**4b**): Yellow solid. M.p. 186–187°. IR (KBr):

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[1]) These data can be obtained free of charge from the *Cambridge Crystallographic Data Centre via* http://www.ccdc.cam.ac.uk/data_request/cif.

2920, 2855, 1709, 1670, 1596, 1572, 1488, 1443, 1380, 1267, 1229, 1101, 984, 774, 733, 676, 606, 532. ^{1}H-NMR (300 MHz): 9.98 (*s*, 1 H); 7.65 (*s*, 1 H); 7.37 (*dd*, *J* = 8.3, 2.2, 1 H); 7.21 (*d*, *J* = 7.5, 1 H); 7.04 (*q*, *J* = 7.5, 2 H); 6.97 (*d*, *J* = 8.3, 1 H); 6.47 (*d*, *J* = 8.3, 1 H); 6.12 (*d*, *J* = 7.5, 1 H); 5.66 (*d*, *J* = 7.5, 1 H); 5.57 (*s*, 1 H); 5.47 (*s*, 1 H); 3.91 (*s*, Me); 3.84 (*s*, Me); 2.38 (*s*, Me). ^{13}C-NMR (H-decoupled, 75 MHz): 197.3; 188.0; 165.3; 163.8; 158.5; 145.2; 138.3; 132.2; 129.7; 129.1; 128.9; 126.6; 126.3; 125.5; 124.4; 120.4; 118.2; 106.5; 105.0; 71.2; 65.4; 55.8; 53.4; 52.2; 20.5. ESI-MS: 460 ($[M+H]^+$), 297, 290. HR-MS: 460.1381 ($[M+H]^+$, $C_{26}H_{22}NO_7^+$; calc. 460.1396).

Dimethyl rel-*(9a*R*,15a*R*,15b*R*)-5-Bromo-15a-formyl-15a,15b-dihydro-15-oxo-9a*H*,15*H*-benzo[*a*][1]benzopyrano[2,3-*h*]quinolizine-8,9-dicarboxylate* (**4c**): Dark yellow semi-solid. IR (KBr): 3080, 2946, 1747, 1705, 1667, 1601, 1461, 1402, 1303, 1263, 1231, 1180, 1116, 1033, 992, 757, 488. ^{1}H-NMR (400 MHz): 9.99 (*s*, 1 H); 7.87 (*dd*, *J* = 8.0, 1.4, 1 H); 7.55–7.62 (*m*, 1 H); 7.50 (*d*, *J* = 8.0, 1 H); 7.34 (*t*, *J* = 7.3, 1 H); 7.12 (*q*, *J* = 7.3, 2 H); 7.07 (*d*, *J* = 8.0, 1 H); 6.45 (*d*, *J* = 8.0, 1 H); 6.43 (*s*, 1 H); 5.61 (*s*, 1 H); 5.47 (*s*, 1 H); 3.95 (*s*, Me); 3.86 (*s*, Me). ^{13}C-NMR (H-decoupled, 75 MHz): 196.7; 187.4; 165.0; 160.3; 163.4; 144.1; 137.3; 129.6; 128.9; 128.7; 127.8; 127.1; 125.6; 124.4; 122.8; 120.7; 118.4; 106.3; 101.7; 71.1; 56.2; 53.7; 52.4. ESI-MS: 546 ($[M+Na]^+$), 496, 494, 251, 149. HR-MS: 546.0178 ($[M+Na]^+$, $C_{25}H_{18}BrNNaO_7^+$; calc. 546.0164).

Dimethyl rel-*(9a*R*,15a*R*,15b*R*)-15a-Formyl-15a,15b-dihydro-6-methyl-15-oxo-9a*H*,15*H*-benzo[*a*][1]benzopyrano[2,3-*h*]quinolizine-8,9-dicarboxylate* (**4d**): Pale yellow solid. M.p. 206–207°. IR (KBr): 3073, 3002, 2949, 1713, 1670, 1598, 1459, 1392, 1303, 1226, 1184, 1111, 1023, 990, 751, 674, 616, 541. ^{1}H-NMR (300 MHz): 9.92 (*s*, 1 H); 7.77–7.85 (*m*, 1 H); 7.49–7.58 (*m*, 1 H); 7.22 (*d*, *J* = 7.5, 1 H); 6.95–7.14 (*m*, 4 H); 6.48 (*d*, *J* = 7.5, 1 H); 5.67 (*s*, 1 H); 5.50 (*s*, 1 H); 5.10 (*s*, 1 H); 3.88 (*s*, Me); 3.83 (*s*, Me); 1.80 (*s*, Me). ^{13}C-NMR (H-decoupled, 100 MHz): 197.2; 185.9; 166.0; 164.7; 160.3; 141.8; 137.3; 136.9; 131.0; 129.1; 128.3; 127.1; 125.6; 124.7; 123.9; 122.6; 121.0; 118.3; 108.6; 72.2; 68.4; 61.3; 53.2; 52.5; 20.6. ESI-MS: 460 ($[M+H]^+$), 432, 144. HR-MS: 460.1388 ($[M+H]^+$, $C_{26}H_{22}NO_7^+$; calc. 460.1396).

Diethyl rel-*(9a*R*,15a*R*,15b*R*)-15a-Formyl-15a,15b-dihydro-15-oxo-9a*H*,15*H*-benzo[*a*][1]benzopyrano[2,3-*h*]quinolizine-8,9-dicarboxylate* (**4e**): Yellow solid. M.p. 173–174°. IR (KBr): 2981, 2744, 1738, 1701, 1670, 1600, 1463, 1403, 1302, 1266, 1238, 1148, 1107, 1025, 985, 774, 633. ^{1}H-NMR (300 MHz): 9.99 (*s*, 1 H); 7.87 (*dd*, *J* = 7.9, 1.5, 1 H); 7.51–7.61 (*m*, 1 H); 7.21 (*d*, *J* = 7.5, 1 H); 6.97–7.16 (*m*, 4 H); 6.46 (*d*, *J* = 7.9, 1 H); 6.14 (*d*, *J* = 7.9, 1 H); 5.66 (*d*, *J* = 7.9, 1 H); 5.63 (*s*, 1 H); 5.47 (*s*, 1 H); 4.17–4.44 (*m*, 4 H); 1.30–1.45 (*m*, 6 H). ^{13}C-NMR (H-decoupled, 75 MHz): 197.2; 187.9; 164.7; 163.3; 160.5; 145.3; 137.2; 129.8; 129.2; 128.9; 127.0; 126.6; 126.3; 125.4; 124.4; 122.5; 120.8; 118.3; 106.3; 105.2; 71.4; 65.7; 62.8; 61.0; 55.9; 14.2; 13.8. ESI-MS: 474 ($[M+H]^+$), 444, 442, 360. HR-MS: 474.1531 ($[M+H]^+$, $C_{25}H_{24}NO_4^+$; calc. 474.1552).

Dimethyl rel-*(9a*R*,15a*R*,15b*R*)-15a-Formyl-15a,15b-dihydro-4-nitro-15-oxo-9a*H*,15*H*-benzo[*a*][1]benzopyrano[2,3-*h*]quinolizine-8,9-dicarboxylate* (**4f**; *Table*): Dark yellow semi-solid. IR (KBr): 3072, 2953, 2852, 1746, 1712, 1665, 1600, 1523, 1462, 1295, 1254, 1224, 1182, 771, 527. ^{1}H-NMR (300 MHz): 10.01 (*s*, 1 H); 7.93 (*d*, *J* = 7.5, 1 H); 7.90 (*dd*, *J* = 8.3, 1.5, 1 H); 7.61 (*m*, 1 H); 7.04–7.20 (*m*, 3 H); 6.64 (*d*, *J* = 7.5, 1 H); 6.51 (*d*, *J* = 8.3, 1 H); 6.32 (*d*, *J* = 8.3, 1 H); 5.61 (*s*, 1 H); 5.48 (*s*, 1 H); 3.93 (*s*, Me); 3.87 (*s*, Me). ^{13}C-NMR (H-decoupled, 75 MHz): 196.1; 186.9; 164.8; 163.1; 160.4; 144.5; 144.0; 137.6; 133.8; 130.8; 127.1; 126.8; 126.0; 125.8; 125.3; 123.0; 120.6; 118.5; 107.5; 99.8; 70.8; 66.1; 55.8; 53.6; 52.5. ESI-MS: 491 ($[M+H]^+$), 461, 437. HR-MS: 513.0890 ($[M+Na]^+$, $C_{25}H_{18}N_2NaO_9^+$; calc. 513.0910).

Dimethyl rel-*(9a*R*,15a*R*,15b*R*)-4-Bromo-15a-formyl-15a,15b-dihydro-15-oxo-9a*H*,15*H*-benzo[*a*][1]benzopyrano[2,3-*h*]quinolizine-8,9-dicarboxylate* (**4g**): Orange solid. M.p. 204–205°. IR (KBr): 2949, 2834, 1744, 1704, 1670, 1598, 1554, 1458, 1311, 1251, 1135, 1100, 950, 769, 517. ^{1}H-NMR (400 MHz): 10.0 (*s*, 1 H); 7.87 (*dd*, *J* = 8.3, 1.5, 1 H); 7.53–7.62 (*m*, 1 H); 7.46 (*d*, *J* = 7.5, 1 H); 7.03–7.17 (*m*, 2 H); 6.88 (*t*, *J* = 7.5, 1 H); 6.38 (*d*, *J* = 7.5, 1 H); 6.20 (*d*, *J* = 8.3, 1 H); 6.08 (*d*, *J* = 8.3, 1 H); 5.60 (*s*, 1 H); 5.43 (*s*, 1 H); 3.92 (*s*, Me); 3.85 (*s*, Me). ESI-MS: 546 ($[M+Na]^+$), 524, 396, 215. HR-MS: 546.0155 ($[M+Na]^+$, $C_{29}H_{32}NNaO_6^+$; calc. 546.0164).

Diethyl rel-*(9a*R*,15a*R*,15b*R*)-15a-Formyl-15a,15b-dihydro-15-oxo-9a*H*,15*H*-benzo[*a*][1]benzopyrano[2,3-*h*]quinolizine-8,9-dicarboxylate* (**4h**): Dark yellow solid. M.p. 205–206°. IR (KBr): 2981, 2904, 1740, 1708, 1664, 1602, 1467, 1308, 1252, 1141, 1021, 949, 748, 519. ^{1}H-NMR (300 MHz): 10.0 (*s*, 1 H); 7.87 (*dd*, *J* = 7.5, 1.5, 1 H); 7.53–7.61 (*m*, 1 H); 7.46 (*d*, *J* = 8.3, 1 H); 7.12 (*t*, *J* = 7.5, 1 H); 7.05 (*d*, *J* = 8.3, 1 H); 6.88 (*t*, *J* = 7.5, 1 H); 6.39 (*d*, *J* = 7.5, 1 H); 6.22 (*d*, *J* = 8.3, 1 H); 6.08 (*d*, *J* = 8.3, 1 H); 5.61 (*s*, 1 H); 5.42 (*s*,

1 H); 4.22–4.44 (*m*, 4 H); 1.4 (*t*, *J* = 6.7 Me); 1.35 (*t*, *J* = 6.7, Me). ^{13}C-NMR (H-decoupled, 75 MHz): 196.8; 187.5; 164.5; 162.9; 160.4; 144.6; 137.3; 133.3; 129.6; 128.3; 128.2; 127.2; 127.0; 126.3; 122.7; 120.7; 118.3; 106.5; 104.5; 71.2; 66.0; 62.9; 61.1; 55.9; 13.8; 14.1. ESI-MS: 552 ($[M+H]^+$), 398, 352.

Dimethyl rel-*(9a*R*,17a*R*,17b*R*)-17a-Formyl-17a,17b-dihydro-17-oxo-9a*H*,17*H*-benzo[*a*]naphtho[2′,1′:5,6]pyrano[2,3-*h*]quinolizine-8,9-dicarboxylate* (**4i**): Yellow solid. M.p. 190–191°. IR (KBr): 2923, 2852, 1743, 1704, 1655, 1595, 1437, 1387, 1307, 1234, 1142, 768, 567. ^{1}H-NMR (300 MHz): 10.5 (*s*, 1 H); 8.29 (*d*, *J* = 8.3, 1 H); 7.81 (*d*, *J* = 9.0, 2 H); 7.43–7.71 (*m*, 3 H); 7.21 (*d*, *J* = 7.5, 1 H); 6.96–7.07 (*m*, 2 H); 6.47 (*d*, *J* = 7.5, 1 H); 6.15 (*d*, *J* = 8.3, 1 H); 5.79 (*s*, 1 H); 5.68 (*d*, *J* = 7.5, 1 H); 5.51 (*s*, 1 H); 3.95 (*s*, Me); 3.90 (*s*, Me). ^{13}C-NMR (H-decoupled, 75 MHz): 197.4; 187.2; 165.4; 163.8; 159.1; 145.7; 137.7; 130.5; 129.6; 129.2; 129.0; 127.9; 126.8; 126.7; 126.0; 125.5; 124.5; 124.2; 123.6; 122.3; 120.8; 115.5; 106.7; 104.3; 72.1; 64.8; 55.9; 53.5; 52.2. ESI-MS: 496 ($[M+H]^+$), 472, 466.

Dimethyl rel-*(9a*R*,15a*R*,15b*R*)-15a-Formyl-15a,15b-dihydro-13-(Methylethyl)-15-oxo-9a*H*,15*H-*benzo[*a*][1]benzopyrano[2,3-*h*]quinolizine-8,9-dicarboxylate* (**4j**): Pale yellow solid. M.p. 174–175°. IR (KBr): 2955, 1743, 1669, 1602, 1488, 1432, 1265, 1230, 1138, 1107, 990, 770, 677. ^{1}H-NMR (300 MHz): 9.99 (*s*, 1 H); 7.68 (*d*, *J* = 2.2, 1 H); 7.44 (*dd*, *J* = 9.0, 2.2, 1 H); 7.21 (*d*, *J* = 7.5, 1 H); 6.98–7.10 (*m*, 3 H); 6.49 (*d*, *J* = 7.5, 1 H); 6.12 (*d*, *J* = 7.5, 1 H); 5.66 (*d*, *J* = 8.3, 1 H); 5.56 (*s*, 1 H); 5.46 (*s*, 1 H); 3.91 (*s*, Me); 3.83 (*s*, Me); 2.84–3.10 (*m*, 1 H); 1.28 (*d*, *J* = 6.7, 6 H). ^{13}C-NMR (H-decoupled, 75 MHz): 197.2; 188.0; 165.2; 163.7; 158.7; 145.1; 143.1; 135.9; 129.6; 129.0; 128.8; 126.5; 126.2; 125.4; 124.3; 123.6; 120.4; 118.2; 106.4; 104.8; 71.0; 65.4; 55.7; 53.3; 52.0; 33.1; 23.7; 23.6. ESI-MS: 488 ($[M+H]^+$), 436, 359.

Dimethyl rel-*(9a*R*,15a*R*,15b*R*)-5-Bromo-15a-formyl-15a,15b-dihydro-13-methyl-15-oxo-9a*H*,15*H-*benzo[*a*][1]benzopyrano[2,3-*h*]quinolizine-8,9-dicarboxylate* (**4k**): Orange semi-solid. ^{1}H-NMR (300 MHz): 9.98 (*s*, 1 H); 7.64 (*s*, 1 H); 7.50 (*d*, *J* = 7.5, 1 H); 7.29–7.42 (*m*, 2 H); 7.13 (*t*, *J* = 7.5, 1 H); 6.97 (*d*, *J* = 8.3, 1 H); 6.46 (*d*, *J* = 7.5, 1 H); 6.42 (*s*, 1 H); 5.56 (*s*, 1 H); 5.45 (*s*, 1 H); 3.95 (*s*, 3 H); 3.85 (*s*, Me); 2.38 (*s*, Me). ^{13}C-NMR (H-decoupled, 75 MHz): 196.8; 187.4; 164.9; 163.3; 158.3; 143.9; 138.4; 132.3; 129.4; 128.8; 128.6; 127.7; 126.9; 126.3; 125.4; 124.3; 120.2; 118.1; 106.3; 101.5; 70.9; 65.2; 56.0; 53.5; 52.2; 20.4. ESI-MS: 539 ($[M+H]^+$), 508, 506, 332, 304.

Dimethyl rel-*(9a*R*,15a*R*,15b*R*)-4-Bromo-15a-formyl-15a,15b-dihydro-13-methyl-15-oxo-9a*H*,15*H-*benzo[*a*][1]benzopyrano[2,3-*h*]quinolizine-8,9-dicarboxylate* (**4l**): Light yellow solid. M.p. 219–220°. IR (KBr): 2923, 2850, 1740, 1718, 1665, 1599, 1487, 1291, 1250, 1142, 1000, 937, 775, 536. ^{1}H-NMR (300 MHz): 9.98 (*s*, 1 H); 7.63 (*s*, 1 H); 7.46 (*d*, *J* = 7.8, 1 H); 7.37 (*dd*, *J* = 2.9, 8.7, 1 H); 6.97 (*d*, *J* = 8.7, 1 H); 6.90 (*t*, *J* = 7.8, 1 H); 6.39 (*d*, *J* = 7.8, 1 H); 6.19 (*d*, *J* = 8.7, 1 H); 6.07 (*d*, *J* = 7.8, 1 H); 5.55 (*s*, 1 H); 5.42 (*s*, 1 H); 3.91 (*s*, Me); 3.84 (*s*, Me); 2.38 (*s*, Me). ^{13}C-NMR (H-decoupled, 75 MHz): 196.8; 187.5; 165.0; 163.4; 158.4; 144.5; 138.4; 133.2; 132.3; 128.1; 127.2; 126.3; 126.2; 120.7; 120.2; 118.1; 106.1; 104.5; 70.9; 65.6; 55.7; 53.4; 52.2; 20.3. ESI-MS: 539 ($[M+H]^+$).

Dimethyl rel-*(2*R*,11b*R*)-2-(4-Oxo-4*H*-1-benzopyran-3-yl)-2*H*,11b*H*-[1,3]oxazino[2,3-*a*]isoquinoline-3,4-dicarboxylate* (**5a**): White solid. IR (KBr): 2950, 1741, 1697, 1646, 1589, 1568, 1462, 1344, 1238, 1141, 1046, 913, 769, 534. ^{1}H-NMR (400 MHz): 8.33 (*dd*, *J* = 8.6, 1.5, 1 H); 7.83 (*s*, 1 H); 7.65–7.71 (*m*, 1 H); 7.42–7.47 (*m*, 2 H); 7.07–7.22 (*m*, 3 H); 6.97 (*d*, *J* = 7.8, 1 H); 6.24 (*d*, *J* = 7.8, 1 H); 6.10 (*s*, 1 H); 6.08 (*s*, 1 H); 5.67 (*d*, *J* = 7.8, 1 H); 3.98 (*s*, Me); 3.64 (*s*, Me). ^{13}C-NMR (H-decoupled, 75 MHz): 175.5; 164.6; 163.3; 157.1; 156.0; 143.7; 133.9; 129.5; 129.1; 127.7; 127.0; 126.8; 126.3; 126.1; 125.4; 124.7; 124.1; 123.2; 118.1; 105.0; 100.7; 77.8; 66.3; 53.3; 51.7. ESI-MS: 446 ($[M+H]^+$).

Dimethyl rel-*(2*R*,11b*R*)-2-(6-Methyl-4-oxo-4*H*-1-benzopyran-3-yl)-2*H*,11b*H*-[1,3]oxazino[2,3-*a*]isoquinoline-3,4-dicarboxylate* (**5b**): Yellow semi-solid. ^{1}H-NMR (300 MHz): 8.10 (*s*, 1 H); 7.80 (*s*, 1 H); 7.48 (*dd*, *J* = 8.4, 2.0, 1 H); 7.34 (*d*, *J* = 8.4, 1 H); 7.07–7.23 (*m*, 3 H); 6.97 (*d*, *J* = 7.3, 1 H); 6.23 (*d*, *J* = 7.7, 1 H); 6.09 (*s*, 2 H); 5.66 (*d*, *J* = 7.7, 1 H); 3.98 (*s*, Me); 3.64 (*s*, Me); 2.51 (*s*, Me). ESI-MS: 460 ($[M+H]^+$).

Dimethyl rel-*(2*R*,11b*R*)-7-Bromo-2-(4-oxo-4*H*-1-benzopyran-3-yl)-2*H*,11b*H*-[1,3]oxazino[2,3-*a*]isoquinoline-3,4-dicarboxylate* (**5c**): Pale yellow semi-solid. ^{1}H-NMR (400 MHz): 8.32 (*dd*, *J* = 8.0, 1.6, 1 H); 7.82 (*s*, 1 H); 7.66–7.71 (*m*, 1 H); 7.13–7.50 (*m*, 6 H); 6.57 (*s*, 1 H); 6.13 (*s*, 1 H); 6.07 (*s*, 1 H); 4.01 (*s*, Me); 3.66 (*s*, Me). ESI-MS: 524 ($[M+H]^+$), HR-MS: 546.0144 ($C_{25}H_{18}NNaO_7Br^+$; calc. 546.0164).

Dimethyl rel-*(2*R*,11b*R*)-6-Methyl-2-(4-oxo-4*H*-1-benzopyran-3-yl)-2*H*,11b*H*-[1,3]oxazino[2,3-*a*]isoquinoline-3,4-dicarboxylate* (**5d**): Orange semi-solid. ^{1}H-NMR (400 MHz): 8.25 (*m*, 1 H); 8.0 (*s*,

1 H); 7.85–7.95 (*m*, 1 H); 7.37–7.77 (*m*, 3 H); 6.80–7.20 (*m*, 3 H); 6.11 (*s*, 1 H); 6.01 (*s*, 1 H); 5.08 (*s*, 1 H); 3.97 (*s*, Me); 3.64 (*s*, Me); 1.79 (*s*, Me). ESI-MS: 460 ($[M+H]^+$).

Diethyl rel-*(2*R*,11b*R*)-2-(4-Oxo-4*H*-1-benzopyran-3-yl)-2*H*,11b*H*-[1,3]oxazino[2,3-*a*]isoquinoline-3,4-dicarboxylate* (**5e**): Orange semi-solid. ^{1}H-NMR (300 MHz): 8.3 (*dd*, *J* = 8.3, 1.5, 1 H); 7.86 (*s*, 1 H); 7.58–7.72 (*m*, 2 H); 7.40–7.49 (*m*, 2 H); 7.09–7.23 (*m*, 2 H); 6.96 (*d*, *J* = 7.5, 1 H); 6.26 (*d*, *J* = 7.5, 1 H); 6.09 (*s*, 2 H); 5.67 (*d*, *J* = 7.5, 1 H); 4.43 (*q*, *J* = 14.3, 6.7, 2 H); 4.10 (*q*, *J* = 14.3, 6.7, 2 H); 1.43 (*t*, *J* = 6.7, Me); 1.14 (*t*, *J* = 6.7, Me). ESI-MS: 474 ($[M+H]^+$).

Dimethyl rel-*(2*R*,11b*R*)-8-Nitro-2-(4-oxo-4*H*-1-benzopyran-3-yl)-2*H*,11b*H*-[1,3]oxazino[2,3-*a*]isoquinoline-3,4-dicarboxylate* (**5f**): Yellow semi-solid. ^{1}H-NMR (300 MHz): 8.32 (*dd*, *J* = 8.3, 1.5, 1 H); 7.91 (*d*, *J* = 8.3, 1 H); 7.84 (*s*, 1 H); 7.67–7.74 (*m*, 1 H); 7.41–7.50 (*m*, 3 H); 7.17–7.24 (*m*, 1 H); 6.52 (*d*, *J* = 8.3, 1 H); 6.45 (*d*, *J* = 8.3, 1 H); 6.07 (*s*, 1 H); 3.99 (*s*, Me); 3.67 (*s*, Me). ^{13}C-NMR (H-decoupled, 75 MHz): 175.6; 164.3; 163.1; 157.3; 156.2; 143.9; 142.5; 134.2; 132.1; 128.9; 127.6; 126.5; 126.2; 125.8; 125.7; 125.2; 124.3; 123.5; 118.2; 98.7; 77.1; 66.8; 53.6; 52.1. ESI-MS: 491 ($[M+H]^+$).

Dimethyl rel-*(2*R*,11b*R*)-8-Bromo-2-(4-oxo-4*H*-1-benzopyran-3-yl)-2*H*,11b*H*-[1,3]oxazino[2,3-*a*]isoquinoline-3,4-dicarboxylate* (**5g**): Pale yellow semi-solid. ^{1}H-NMR (300 MHz): 8.32 (*dd*, *J* = 8.4, 1.5, 1 H); 7.82 (*s*, 1 H); 7.63–7.74 (*m*, 1 H); 7.36–7.51 (*m*, 3 H); 7.10 (*d*, *J* = 7.7, 1 H); 6.96 (*t*, *J* = 7.9, 1 H); 6.32 (*d*, *J* = 8.3, 1 H); 6.09 (*s*, 1 H); 6.08 (*d*, *J* = 8.3, 1 H); 6.07 (*s*, 1 H); 3.98 (*s*, Me); 3.65 (*s*, Me). ^{13}C-NMR (H-decoupled, 75 MHz): 175.6; 164.6; 163.5; 157.2; 156.2; 143.3; 134.1; 133.2; 129.5; 128.5; 127.9; 126.3; 125.5; 125.0; 124.4; 124.0; 119.9; 118.2; 103.4; 102.0; 77.7; 66.7; 53.5; 52.0. ESI-MS: 524 ($[M+H]^+$). HR-MS: 546.0155 ($C_{25}H_{18}Br^+NNaO_7$; calc. 546.0164).

Diethyl rel-*(2*R*,11b*R*)-8-Bromo-2-(4-oxo-4*H*-1-benzopyran-3-yl)-2*H*,11b*H*-[1,3]oxazino[2,3-*a*]isoquinoline-3,4-dicarboxylate* (**5h**): Orange semi-solid. ^{1}H-NMR (300 MHz): 8.32 (*dd*, *J* = 8.3, 1.5, 1 H); 7.84 (*s*, 1 H); 7.65–7.72 (*m*, 1 H); 7.40–7.49 (*m*, 3 H); 7.10 (*d*, *J* = 7.5, 1 H); 6.95 (*t*, *J* = 7.5, 1 H); 6.35 (*d*, *J* = 7.5, 1 H); 6.08 (*s*, 1 H); 6.07 (*d*, *J* = 7.5, 1 H); 6.06 (*s*, 1 H); 4.43 (*q*, *J* = 14.3, 7.5, 2 H); 4.11 (*q*, *J* = 13.5, 6.7, 2 H); 1.44 (*t*, *J* = 6.7, Me); 1.15 (*t*, *J* = 7.5, Me). ESI-MS: 552 ($[M+H]^+$).

Dimethyl rel-*(2*R*,11b*R*)-2-(4-Oxo-4*H*-naphtho[1,2-*b*]pyran-3-yl)-2*H*,11b*H*-[1,3]oxazino[2,3-*a*]isoquinoline-3,4-dicarboxylate* (**5i**): Light yellow semi-solid. IR (KBr): 2924, 2855, 1744, 1641, 1593, 1452, 1385, 1234, 764. ^{1}H-NMR (400 MHz): 8.42 (*d*, *J* = 8.7, 1 H); 8.27 (*d*, *J* = 8.0, 1 H); 8.06 (*s*, 1 H); 7.92 (*d*, *J* = 7.3, 1 H); 7.81 (*d*, *J* = 8.7, 1 H); 7.55–7.74 (*m*, 3 H); 7.06–7.20 (*m*, 2 H); 6.96 (*d*, *J* = 7.3, 1 H); 6.25 (*d*, *J* = 8.0, 1 H); 6.16 (*s*, 1 H); 6.15 (*s*, 1 H); 5.68 (*d*, *J* = 8.0, 1 H); 3.99 (*s*, Me); 3.65 (*s*, Me). ESI-MS: 496 ($[M+H]^+$).

Dimethyl rel-*(2*R*,11b*R*)-2-[6-(1-Methylethyl)-4-oxo-4*H*-1-benzopyran-3-yl]-2*H*,11b*H*-[1,3]oxazino[2,3-*a*]isoquinoline-3,4-dicarboxylate* (**5j**): Yellow semi-solid. ^{1}H-NMR (300 MHz): 8.15 (*d*, *J* = 1.5, 1 H); 7.81 (*s*, 1 H); 7.54 (*dd*, *J* = 9.0, 2.2, 1 H); 7.37 (*d*, *J* = 9.0, 1 H); 7.06–7.23 (*m*, 3 H); 6.96 (*d*, *J* = 7.5, 1 H); 6.23 (*d*, *J* = 8.3, 1 H); 6.10 (*s*, 1 H); 6.08 (*s*, 1 H); 5.67 (*d*, *J* = 7.5, 1 H); 3.98 (*s*, Me); 3.64 (*s*, Me); 2.98 (*m*, 1 H); 1.33 (*d*, *J* = 6.7, 6 H). ^{13}C-NMR (H-decoupled, 75 MHz): 175.8; 164.8; 163.8; 157.0; 154.6; 146.4; 143.7; 132.9; 129.6; 129.1; 127.1; 126.9; 126.5; 124.7; 124.1; 124.0; 123.4; 122.9; 118.0; 105.1; 101.1; 77.9; 66.5; 53.3; 51.8; 33.7; 23.9; 23.8; ESI-MS: 488 ($[M+H]^+$).

Dimethyl rel-*(2*R*,11b*R*)-7-Bromo-2-(6-methyl-4-oxo-4*H*-1-benzopyran-3-yl)-2*H*,11b*H*-[1,3]oxazino[2,3-*a*]isoquinoline-3,4-dicarboxylate* (**5k**): Pale yellow semi-solid. ^{1}H-NMR (300 MHz): 8.06–8.13 (*m*, 1 H); 7.79 (*s*, 1 H); 7.09–7.53 (*m*, 6 H); 6.56 (*s*, 1 H); 6.11 (*s*, 1 H); 6.06 (*s*, 1 H); 4.0 (*s*, Me); 3.65 (*s*, Me); 2.49 (*s*, Me). ESI-MS: 539 ($[M+H]^+$).

Dimethyl rel-*(2*R*,11b*R*)-8-Bromo-2-(6-methyl-4-oxo-4*H*-1-benzopyran-3-yl)-2*H*,11b*H*-[1,3]oxazino[2,3-*a*]isoquinoline-3,4-dicarboxylate* (**5l**): Orange semi-solid. ^{1}H-NMR (300 MHz): 8.06–8.11 (*m*, 1 H); 7.79 (*s*, 1 H); 7.39–7.52 (*m*, 2 H); 7.33 (*d*, *J* = 8.3, 1 H); 7.09 (*d*, *J* = 8.3, 1 H); 6.95 (*t*, *J* = 7.5, 1 H); 6.32 (*d*, *J* = 7.5, 1 H); 6.08 (*s*, 1 H); 6.07 (*s*, 1 H); 6.06 (*d*, *J* = 7.5, 1 H); 3.97 (*s*, Me); 3.65 (*s*, Me); 2.50 (*s*, Me). ESI-MS: 539 ($[M+H]^+$).

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