Tetrahedron 67 (2011) 2269–2278

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Synthesis of 3-substituted benzo[*g*]isoquinoline-5,10-diones: a convenient one-pot Sonogashira coupling/iminoannulation procedure

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ARTICLE INFO

Article history:
Received 10 December 2010
Received in revised form 21 January 2011
Accepted 24 January 2011
Available online 1 February 2011

Keywords:
Benzo[*g*]isoquinoline-5,10-diones
Quinones
Sonogashira
Naphthalene
Iminoannulation

ABSTRACT

A series of 3-substituted 5,10-dimethoxybenzo[*g*]isoquinolines were prepared by coupling of terminal alkynes with the *tert*-butylimine of 3-bromo-1,4-dimethoxy-2-naphthaldehyde in the presence of a Pd-catalyst and subsequent Cu-catalyzed cyclization of the intermediate 3-alkynyl-2-naphthylcarbaldehyde. A CAN-mediated oxidative demethylation yielded the corresponding 2-azaanthraquinones in excellent yields. Since this methodology proved to be limited to alkynes bearing aromatic groups, an alternative and more general Pd-catalyzed coupling procedure was developed, starting from 3-bromo-1,4-dimethoxy-2-naphthaldehyde. For more acidic terminal alkynes, like phenylacetylene, a combination of $Pd(OAc)_2$/P(*t*-Bu)$_3$/CuI (2/6/1) with potassium carbonate in DMF gave a complete conversion within 24 h. For less acidic acetylenes, 2 equiv of alkyne and caesium carbonate as a base were required in order to obtain complete conversion of the starting material within 24 h. These altered Sonogashira conditions also allowed the isolation of a benzo[*f*]indenone as an interesting side product in case Bu_4NCl was added to the reaction mixture. The 3-alkynyl-1,4-dimethoxy-2-naphthaldehyde acquired after completion of the Pd-catalyzed coupling could be cyclized by adding a solution of ethanolic ammonia and an extra equivalent of potassium carbonate to the reaction mixture. As such, this consecutive one-pot coupling/iminoannulation procedure was a convenient alternative to the Larock isoquinoline procedure, enabling the isolation of a series of 3-substituted 5,10-dimethoxybenzo[*g*]isoquinolines.

1. Introduction

Nowadays 2-azaanthraquinones receive increasing attention as potential anticancer and antimicrobial antibiotics.[1] Their cytotoxicity is mainly based upon two mechanisms: first their DNA intercalating properties, where they have the potential to stabilize the topoisomerase II–DNA or gyrase–DNA complex and thereby effectively inhibiting the relaxation of supercoiled DNA[2] and second their ability to disrupt the cellular respiratory pathway by interaction with NADH or NADPH dehydrogenases and the subsequent generation of toxic super oxide anions.[3] In the past a number of synthetic routes have been developed to access this interesting class of compounds. Most of the documented routes make use of a Diels–Alder protocol, be it the formation of the heterocyclic ring by a cycloaddition of a polyoxygenated diene to a 2-azanaphthoquinone[4] or the formation of the terminal heterocyclic ring by cycloaddition of a heterodiene to a 1,4-naphthoquinone.[5] Alternatively, a number of direct lithiation protocols have also been reported.[4,6] These generally involve the condensation of a 3-lithiopyridine with a phthalic anhydride or a benzamide followed by the construction of the central 1,4-benzoquinone ring. All these procedures however suffer from low yields and a lack of regioselectivity. More recently, a facile entry to a series of naturally and non naturally occurring 3-substituted 2-azaanthraquinones has been established by reaction of 2-acylated-3-phenoxymethyl-1,4-naphthoquinones with aqueous ammonium hydroxide.[7]

We present a second, general and easy accessible synthetic route towards a number of 3-substituted 2-azaanthraquinones **1** involving the construction of a 3-substituted 5,10-dimethoxybenzo[*g*]isoquinoline **2**, followed by a cerium(IV) ammonium nitrate (CAN) mediated oxidative demethylation as the key steps (Scheme 1).

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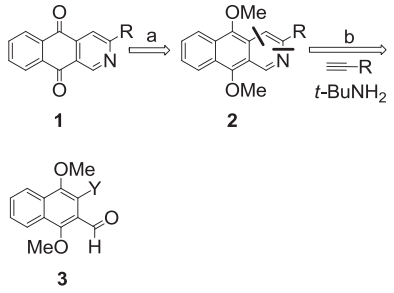
doi:10.1016/j.tet.2011.01.074

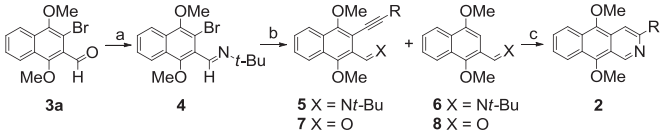


Scheme 1. Retrosynthetic analysis: (a) oxidative demethylation. (b) Sonogashira coupling and iminoannulation.

2. Results and discussion

2.1. Benzo[*g*]isoquinoline synthesis

Initially the Larock protocol[8] was considered to be a valuable tool for the construction of the 3-substituted 5,10-dimethoxybenzo[*g*]isoquinolines **2**. To use this versatile procedure a synthetic pathway was envisaged, starting from 2-bromonaphthylcarbaldehyde **3a** (Y = Br) (Scheme 2).[9] Condensation of **3a** with *tert*-butylamine in the presence of anhydrous magnesium sulfate afforded the aldimine **4** in quantitative yield. Next, a $PdCl_2(PPh_3)_2$/CuI catalyzed Sonogashira coupling was carried out with a number of terminal acetylenes in triethylamine at 70 °C. When this coupling was complete, as indicated by TLC, the solvent and precipitates were removed and DMF and CuI were added to the residue **5** in order to induce the cyclization of **5** at 100 °C. This protocol worked fine for alkynes bearing aromatic groups and 3-methoxyprop-1-yne (Table 1, entries 1–5) and increasingly less for aliphatic alkynes (Table 1, entries 6–8), where the conversion rates were significantly lower, with the formation of the debrominated compounds **6** and **8** as the main products. The observed yields for entries 1–5 are very satisfying in view of the fact that no efficient Larock isoquinoline synthesis has been described so far with completely substituted *ortho*-halobenzaldimines.[8,10]



Scheme 2. Reagents and conditions: (a) 3 equiv *t*-$BuNH_2$, CH_2Cl_2, $MgSO_4$, rt, 16 h, 100%; (b) 1.1 equiv HC≡CR, 4 mol % $PdCl_2(PPh_3)_2$, 4 mol % CuI, Et_3N, 70 °C, 24 h, Ar (Table 1); (c) 10 mol % CuI, DMF, 100 °C, 4 h (Table 1).

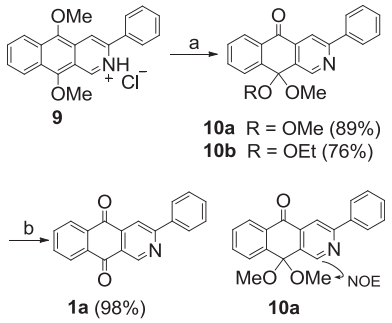
Table 1
Synthesis of benzo[*g*]isoquinolines by Pd-catalyzed coupling and Cu-catalyzed cyclization of terminal alkynes

Entry	Alkyne R–C≡CH (R)	Ratio[a] (%)			Product (**2**)	Yield[b] (%)
		3a+**4**	**5**+**7**	**6**+**8**		
1	C_6H_5	0	98	2	**2a**	80
2	3-$MeOC_6H_4$	0	86	14	**2b**	50
3	2-Me–4-$MeOC_6H_3$	0	100	0	**2c**	59
4	4-MeC_6H_4	0	91	9	**2d**	55
5	$MeOCH_2$	7	93	0	**2e**	91
6	*c*Hex	13	65	22	**2f**	31
7	$CH(OEt)_2$	82	6	12	**2g**	5
8	*n*-Bu	40	29	31	**2h**	19
9	CMe_2OMe	0	90	0	**2i**	0
10	CH_2NH_2	100	0	0	**2j**	0
11	CH_2OH	80	0	10	**2k**	0

[a] The ratio was determined by ^1H NMR analysis of the reaction mixture obtained after the alkynylation (step b, Scheme 2).
[b] Isolated yield (Scheme 2).

The reaction of **4** with sterically demanding acetylenes (Table 1, entry 9) resulted in coupling, but no ring closed product was observed. The presence of a free hydroxy group or a free amino group (Table 1, entries 10 and 11) in the alkyne was not tolerated at all. In the latter two cases only the debrominated starting material **6** was isolated afterwards. The latter three findings were in accordance with the earlier reported limitations of the Larock isoquinoline synthesis.[8a]

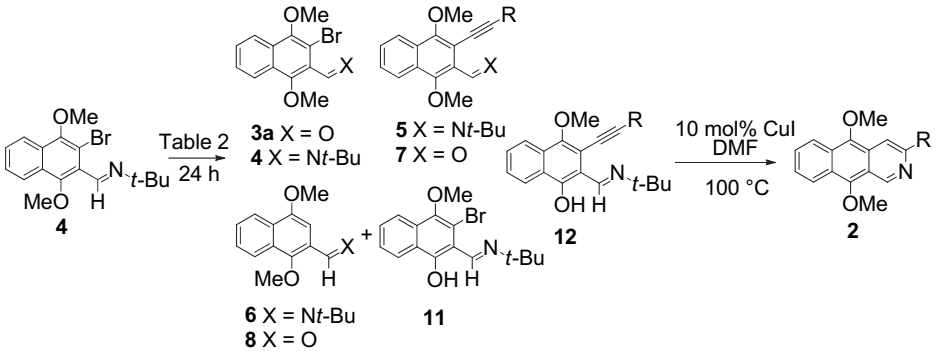
Due to the basicity of the isoquinoline nitrogen the 3-substituted 5,10-dimethoxybenzo[*g*]isoquinolines **2** were isolated as a mixture of protonated and non-protonated species after workup with aqueous ammonium chloride. In an attempt to completely neutralize this mixture it was stirred with 100 equiv NaOH in MeOH (0.1 M) under reflux. Surprisingly an unknown compound was isolated, which was identified afterwards as 10,10-dimethoxy-3-phenylbenzo[*g*]isoquinolin-5(10*H*)-one (**10a**) (Scheme 3). NOESY analysis established a proximity correlation between H-1 and the protons of the acetal thereby pinpointing its position at C-10. The quantity of NaOH was crucial, since the addition of only 20 equiv of NaOH and stirring for 20 h at room temperature left **9** unaltered. The reaction was repeated in EtOH, adding 100 equiv of NaOH and stirring it under reflux for 48 h. After workup only the mixed acetal **10b** was isolated. Both acetals could be easily converted into the corresponding quinone **1a** in almost quantitative yield. The conversion of these protonated 5,10-dimethoxybenzo[*g*]isoquinolines into the corresponding quinones by treatment with excess base and followed by an acidic workup is in fact a valuable metal-free alternative for the CAN-oxidative demethylation, which is the standard procedure (vide infra).



Scheme 3. Reagents and conditions: (a) 100 equiv NaOH, ROH, reflux, 48 h; (b) acetone/2 N HCl_{aq}, reflux, 3 h.

The decomposition of the starting material **4**, when alkynes bearing aliphatic groups were used, was an indication of an insufficiently fast transmetalation or deprotonation step. For this type of terminal alkynes an optimization of the reaction conditions was attempted (Table 2). Because of the moderate conversion of cyclohexylacetylene with **4** (Table 2, entry 1), this reaction was studied in more detail. With the formation of the copper acetylide being not so efficient, some obvious changes to the reaction conditions like increasing the quantity of CuI, raising the temperature or doubling the quantity of the acetylene were first investigated (Table 2, entries 2–4). Unfortunately, adding more CuI was not tolerated as the conversion rate decreased steeply, whereas changing the temperature did not lead to a significant improvement in yield. Using an excess of acetylene proved beneficial for the conversion, however the unreacted acetylene hampered the subsequent cyclization, lowering the isolated yield of **2f**. Changing the catalytic system to $Pd(OAc)_2$/P(*t*-Bu)$_3$ further deteriorated the conversion (Table 2, entry 5). As a last attempt a series of experiments were conducted with DMF as a solvent and $Pd(OAc)_2$ as a precatalyst. Reactions where PPh_3 was used as a ligand and

Table 2
Optimization of the Sonogashira coupling with *N*-[(3-bromo-1,4-dimethoxynaphthalen-2-yl)methylene]-2-methylpropan-2-amine **4**



Entry	R (equiv)	Catalyst (mol %)	CuI (mol %)	Ligand (mol %)	Solvent	Base (equiv)	T (°C)	Ratio (%)[a]			Yield[b] **2** (%)
								3+**4**	**5**+**7**	**6**+**8**	
1[c]	*c*Hex (1.1)	$PdCl_2(PPh_3)_2$ (4)	4	PPh_3	Et_3N	Et_3N	70	13	65	22	31
2	*c*Hex (1.1)	$PdCl_2(PPh_3)_2$ (4)	10	PPh_3	Et_3N	Et_3N	70	73	27	0	NA[d]
3	*c*Hex (1.1)	$PdCl_2(PPh_3)_2$ (4)	4	PPh_3	Et_3N	Et_3N	100	8	63	29	NA[d]
4	*c*Hex (2)	$PdCl_2(PPh_3)_2$ (4)	4	PPh_3	Et_3N	Et_3N	70	1	73	10	16
5	*c*Hex (1.1)	$Pd(OAc)_2$ (4)	4	P(*t*-Bu)$_3$ (12)	Et_3N	Et_3N	70	42	28	30	13
6[e]	*c*Hex (1.1)	$Pd(OAc)_2$ (4)	4	PPh_3 (12)	DMF	Cs_2CO_3 (2)	100	66	10	20	3
7	*c*Hex (1.1)	$Pd(OAc)_2$ (4)	4	PPh_3 (12)	DMF	DBU (2)	100	71	11	18	NA[d]
8	*c*Hex (1.1)	$Pd(OAc)_2$ (4)	4	P(*t*-Bu)$_3$ (12)	DMF	K_2CO_3 (1.1)	100	47	10	43	0
9	*c*Hex (1.1)	$Pd(OAc)_2$ (4)	4	P(*t*-Bu)$_3$ (12)	DMF	Cs_2CO_3 (1.1)	100	50	40	10	0
10	*c*Hex (1.1)	$Pd(OAc)_2$ (4)	4	P(*t*-Bu)$_3$ (12)	DMF	Na_2CO_3 (1.1)	100	36	35	29	0
11[f]	*c*Hex (1.1)	$PdCl_2(PPh_3)_2$ (4)	4	PPh_3	DMF	Cs_2CO_3 (2)	100	41	24	16	4
12	*c*Hex (1.1)	$Pd(OAc)_2$ (4)	4	PPh_3 (12)	DMF	DBU (10)	100	72	6	22	NA[d]
13[g]	*c*Hex (1.1)	$PdCl_2(PPh_3)_2$ (4)	4	PPh_3	Et_3N	Et_3N	70	0	78	22	58
14[g]	$CH(OEt)_2$ (1.1)	$PdCl_2(PPh_3)_2$ (4)	4	PPh_3	Et_3N	Et_3N	70	3	78	19	53
15[h]	$CH(OEt)_2$ (2)	$PdCl_2(PPh_3)_2$ (4)	4	PPh_3	Et_3N	Et_3N	70	76	12	12	0

[a] The ratio was determined by ^{1}H NMR analysis of the reaction mixture obtained after the alkynylation reaction (step b, Scheme 2).
[b] Isolated yield.
[c] Compound **12f** was observed additionally as a side product.
[d] NA: no cyclization was attempted.
[e] Compound **11** (1 mol %) was observed as a side product.
[f] Compound **11** (18 mol % of) was observed as a side product.
[g] After 24 h the reaction mixture was filtered over decalite, and the same amount of catalyst (Pd and Cu) and alkyne was added anew, after which the mixture was stirred at 70 °C for an additional 24 h.
[h] Other side products, that could not be identified, were present.

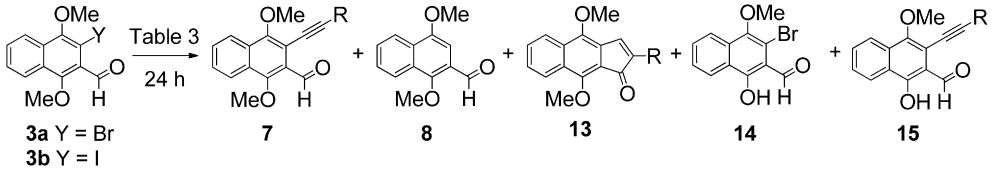
Cs_2CO_3 or DBU as a base performed poor (Table 2, entries 6 and 7). A slight improvement was observed when PPh_3 was replaced with P(*t*-Bu)$_3$. Of the three carbonate bases tested in combination with P(*t*-Bu)$_3$, Cs_2CO_3 gave the best result (Table 2, entries 8–10). However, when the ring closing step was carried out by filtering the reaction mixture over decalite, adding 10 mol % CuI and stirring for several days at 100 °C, no isoquinoline **2f** was isolated. Investigation by ^{1}H NMR revealed that the *N*-*tert*-butylaldimine **4** was still intact. Most likely the presence of P(*t*-Bu)$_3$ combined with the absence of an amine base plays a role in the inhibition of the CuI catalyzed iminoannulation. Surprisingly, almost complete conversion could be achieved when applying a double addition protocol that implied adding the indicated quantities of catalyst and alkyne, monitoring the reaction until it stalled, filtrating the reaction mixture over decalite and once more adding the same quantity of catalyst together with a slight excess of alkyne in comparison to the non reacted aldimine **4** (conversion was estimated via HPLC (λ=540 nm)) and following the reaction till completion (Table 2, entry 13). In this case, ring closure did proceed smoothly, enabling us to isolate the isoquinoline **2f** in a good overall yield. The intermediate filtration before adding additional alkyne and catalyst seemed vital, since omitting the filtration left the degree of coupling unchanged. Accumulation of triethylammonium bromide salts probably inhibits any further coupling. Removal of these salts by filtration made it possible to reinitiate the catalytic cycle by adding fresh catalyst and alkyne. The same double addition protocol was used successfully to boost the coupling with 3,3-diethoxyprop-1-yne (Table 2, entry 14).

Contrary to the coupling with cyclohexylacetylene (Table 2, entry 4), doubling the amount of 3,3-diethoxyprop-1-yne to 2 equiv did not result in a better coupling and no cyclization was observed either (Table 2, entry 15).

2.2. Sonogashira coupling/iminoannulation protocol

Since we were not completely pleased with the outcome of the iminoannulation protocol with cyclohexylacetylene and 3,3-diethoxyacetylene, an alternative approach was pursued. Instead of carrying out a Sonogashira coupling on the *tert*-butylimine **4**, the Pd-catalyzed coupling was directly performed on 2-bromonaphthylaldehyde **3a** (Table 3). First the coupling of **3a** with phenylacetylene was carried out under literature conditions.[8a] To our surprise no reaction at all was observed (Table 3, entry 1). Since no decomposition of the bromide **3a** occurred, the lack of reactivity was probably due to a sluggish oxidative addition step. This fact was further supported when the reaction was carried out with 2-iodo-1,4-dimethoxy-2-naphthaldehyde (**3b**) leading to the alkynylaldehyde **7a** in good yield (Table 3, entry 2). We preferred to optimize the reaction conditions for the bromide **3a** instead. The solvent was changed to DMF, while $Pd(OAc)_2$ was used as a Pd source and P(*t*-Bu)$_3$[11] as a ligand. K_2CO_3 was chosen arbitrarily as a base. Taking into account that the starting compound **3a** has two substituents in

Table 3
Optimization of the Sonogashira coupling with 3-bromo-1,4-dimethoxy-2-naphthaldehyde



3a Y = Br
3b Y = I
7 **8** **13** **14** **15**

Entry	Y	R (equiv)	Catalyst (mol %)	Ligand (mol %)	Base (equiv)	Ratio[a] (%)					Yield[c] **7** (%)
						3	**7**	**8**	**13**	**14**[b]	
1[d]	Br	C_6H_5 (1.1)	$PdCl_2(PPh_3)_2$ (2)	PPh_3 (4)	Et_3N	100	0	0	0	0	**7a** (0)
2[d]	I	C_6H_5 (1.1)	$PdCl_2(PPh_3)_2$ (2)	PPh_3 (4)	Et_3N	10	90	0	0	0	**7a** (69)
3[f]	Br	C_6H_5 (1.1)	$Pd(OAc)_2$ (4)	P(*t*-Bu)$_3$ (12)	K_2CO_3 (1.2)	9	91	0	0	0	**7a** (58)
4[e]	Br	C_6H_5 (1.1)	$Pd(OAc)_2$ (4)	P(*t*-Bu)$_3$ (12)	K_2CO_3 (1.2)	0	100	0	0	0	**7a** (81)
5[e]	Br	C_6H_5 (1.1)	$PdCl_2(PhCN)_2$ (4)	P(*t*-Bu)$_3$ (12)	K_2CO_3 (1.2)	53	10	18	19	0	**7a** (0)
6[e]	Br	C_6H_5 (1.1)	$PdCl_2(MeCN)_2$ (4)	P(*t*-Bu)$_3$ (12)	K_2CO_3 (1.2)	44	23	13	19	0	**7a** (1)
7[e]	Br	C_6H_5 (1.1)	$Pd(dba)_2$ (4)	P(*t*-Bu)$_3$ (12)	K_2CO_3 (1.2)	40	52	4	4	0	**7a** (36)
8[e]	Br	C_6H_5 (1.1)	$Pd(OAc)_2$ (4)	[(*t*-Bu)$_3$PH]BF_4 (12)	K_2CO_3 (1.2)	58	31	11	0	0	**7a** (ND)[g]
9[e]	Br	$CH(OEt)_2$ (1.1)	$Pd(OAc)_2$ (4)	P(*t*-Bu)$_3$ (12)	K_2CO_3 (1.2)	13	64	23	0	0	**7g** (31)
10[e]	Br	*c*Hex (1.1)	$Pd(OAc)_2$ (4)	P(*t*-Bu)$_3$ (12)	K_2CO_3 (1.2)	12	70	5	11	2	**7f** (51)
11[e]	Br	*c*Hex (1.1)	$Pd(OAc)_2$ (4)	P(*t*-Bu)$_3$ (12)	Cs_2CO_3 (1.2)	9	77	6	6	2	**7f** (67)
12[e]	Br	*c*Hex (1.1)	$Pd(OAc)_2$ (4)	P(*t*-Bu)$_3$ (12)	Na_2CO_3 (1.2)	80	8	0	5	7	**7f** (8)
13[e]	Br	*c*Hex (1.1)	$Pd(OAc)_2$ (4)	P(*t*-Bu)$_3$ (12)	Et(*i*-Pr)$_2$N (1.2)	96	4	0	0	0	**7f** (4)
14[e]	Br	*c*Hex (2)	$Pd(OAc)_2$ (4)	P(*t*-Bu)$_3$ (12)	Cs_2CO_3 (1.2)	0	91	0	9	0	**7f** (73)
15[h]	Br	*c*Hex (1.1)	$Pd(OAc)_2$ (4)	P(*t*-Bu)$_3$ (12)	Cs_2CO_3 (2)	7	82	7	3	1	**7f** (58)
16[e]	Br	*c*Hex (1.1)	$Pd(OAc)_2$ (4)	P(*t*-Bu)$_3$ (12)	Cs_2CO_3 (4)	6	74	15	4	2	**7f** (50)
17[i]	Br	*c*Hex (1.1)	$Pd(OAc)_2$ (4)	P(*t*-Bu)$_3$ (12)	K_2CO_3 (1.2)	11	66	6	5	5	**7f** (60)
18[j]	Br	*c*Hex (1.1)	$Pd(OAc)_2$ (4)	P(*t*-Bu)$_3$ (12)	K_2CO_3 (1.2)	19	24	12	37	0	**7f** (15)
19[e]	Br	C_6H_5 (2)	$Pd(OAc)_2$ (4)	P(*t*-Bu)$_3$ (12)	Cs_2CO_3 (1.2)	0	91	0	9	0	**7f** (63)

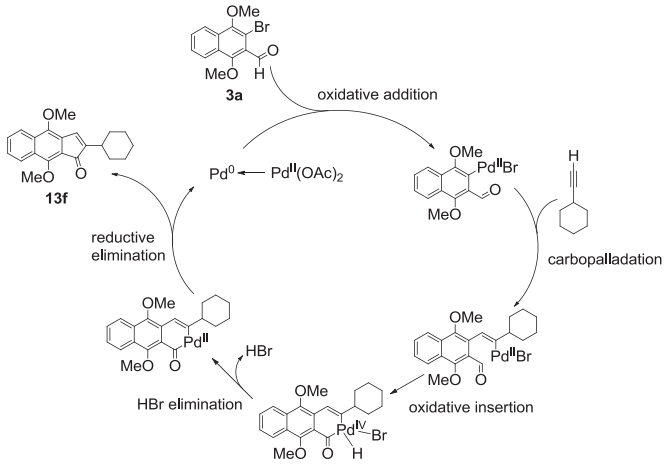
[a] The ratio was determined by ^{1}H NMR analysis of reaction mixture after a crude purification over a short silica column to remove all traces of salts, phosphine ligands and Pd catalyst.
[b] Tentative structure based on ^{1}H NMR.
[c] Isolated yield.
[d] +1 mol % CuI, Et_3N, 50 °C, 4 h.
[e] +2 mol % CuI, DMF, 100 °C, 24 h.
[f] +1 mol % CuI, DMF, 100 °C, 24 h.
[g] ND: not determined.
[h] +2 mol % CuI, DMF, 100 °C, 36 h.
[i] +2 mol % CuI, 10 mol % TBAB, DMF, 100 °C, 24 h; additionally 7 mol % of **15** was isolated as a side product.
[j] +2 mol % CuI, 10 mol % TBAB, DMF/H_2O (10/1), 100 °C, 24 h; additionally 8 mol % of **15** was isolated as a side product.

ortho position of the bromide and is further deactivated by two methoxy groups, the electron rich, monoligated $Pd^0P(t\text{-}Bu)_3$ would probably undergo an easier oxidative addition. This was confirmed by the experimental results (Table 3, entry 3). A further improvement of the conversion was established by adding 2 mol % CuI, giving an almost quantitative coupling and a good isolated yield (Table 3, entry 4). If the catalyst precursor was changed to bis(benzonitrile) palladium(II) dichloride ($PdCl_2(PhCN)_2$), bis(acetonitrile)palladium (II) dichloride ($PdCl_2(MeCN)_2$) or to bis(dibenzylideneacetone)palladium(0) ($Pd(dba)_2$) a steep deterioration of the conversion was observed (Table 3, entries 5–7) with most noticeably a partial decomposition of the naphthylbromide **3a** and the formation of a benzo[*f*]indenone side product **13f** (vide infra). When replacing the phosphine ligand with the air stable [(*t*-Bu)$_3$PH]BF_4 salt the degree of conversion was inferior in comparison to P(*t*-Bu)$_3$ (Table 3, entry 8).

The initial reaction conditions with $Pd(OAc)_2$/P(*t*-Bu)$_3$ as catalyst gave excellent results with phenylacetylene, but when introducing more demanding acetylenes, like 3,3-diethoxyprop-1-yne and cyclohexylacetylene (Table 3, entries 9 and 10) the degree of coupling dropped. To attain a more general and higher yielding procedure, a further optimization of the reaction conditions was attempted. The conversions with K_2CO_3, Cs_2CO_3, Na_2CO_3 and *i*-Pr_2NEt were compared (Table 3, entries 10–13), with Cs_2CO_3 giving the best results. Next, the amount of added alkyne (Table 3, entry 14) was doubled. This resulted in complete conversion. Further tests were performed with Cs_2CO_3 combined with 1.1 equiv of alkyne, like prolonging the reaction time and adding 2 or 4 equiv of base (Table 3, entries 15 and 16), but this did not lead to any significant improvement in coupling. Cs_2CO_3 probably gave better results in comparison with K_2CO_3 and Na_2CO_3 due to its superior solubility in organic solvents. A further enhancement of the reaction might be obtained by adding a phase transfer (PT) catalyst.[12] A first experiment conducted under PT conditions (Table 3, entry 17) consisted in adding 10 mol % tetrabutylammonium bromide (TBAB) to the reaction mixture. This did not result in any improvement in the degree of coupling. Since it was reported in literature[13] that an alkali metal base (K_2CO_3) requires the addition of 10 v/v% water to the solvent to perform optimally under PT conditions, the reaction was repeated with addition of 10 v/v% of water (Table 3, entry 18). Instead of an improved coupling, we noticed an increased formation of **13f**, which was observed in earlier experiments (Table 3, entries 5–17) but was only marginally present. Under the new PT conditions **13f** was the major product after workup. A structural elucidation was based on LC–MS, ^{1}H NMR, ^{13}C NMR and ATR-IR measurements. The compound had a molecular mass of 322, equal to the *o*-alkynylnaphthylaldehyde **7c**, but lacked an aldehyde proton (^{1}H NMR), although a carbonyl group was present according to IR (1684 cm^{-1}). ^{1}H NMR further revealed the presence of the cyclohexyl group and of a fifth aromatic proton (δ 7.43, d, J=1.3 Hz). IR absorption peaks at 2922 cm^{-1} and 2849 cm^{-1} indicated a double bond, corroborating that a benzo[*f*]indenone might be formed. The analytical data of compound **13f** were compared to those of indenones reported in literature thus further supporting the proposed structure.[14]

The observation that terminal alkynes were able to annulate with *o*-bromonaphthaldehydes was remarkable, since only the

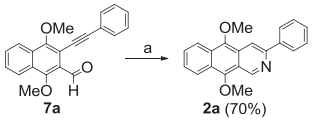
preparation of 2,3-disubstituted-1-indenones by a Pd catalyzed annulation of internal alkynes was reported in literature by Larock and Doty.[15] Since Larock employed conditions (5 mol % $Pd(OAc)_2$, 1 or 4 equiv of Na_2CO_3, 1 equiv of *n*-Bu_4NCl, *N*,*N*-dimethylacetamide, 100 °C) that were partially similar to our conditions, it was assumed that both annulation processes proceeded via an identical catalytic cycle with following steps: the oxidative addition of the in situ generated Pd^0 to the aryl bromide followed by arylpalladium π-complexation to the alkyne and a consecutive carbopalladation with formation of a *Z*-alkenylpalladium(II) intermediate. A second oxidative insertion into the formyl C–H bond would create a Pd^{IV} species. The regeneration of Pd^0 occurs by a HBr elimination and a reductive elimination generating the indenone **13f** (Scheme 4). For comparison, the optimal coupling conditions for cyclohexylacetylene (Table 3, entry 14) were repeated with phenylacetylene (Table 3, entry 19). The yield of **7a** was less compared to initial employed coupling procedure (Table 3, entry 1), but more remarkably 9 mol % (^{1}H NMR) of the corresponding benzo[*f*]indenone **13a** was formed as well, but could not be isolated.



Scheme 4. Plausible catalytic cycle for benzo[*f*]indenone formation (ligands have been omitted for clarity).

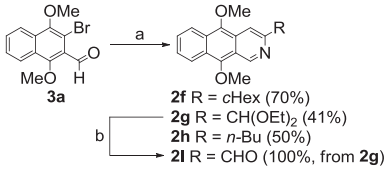
2.3. One-pot coupling/cyclization procedure

Ring closure of the acquired alkynylnaphthylaldehydes **7** could be accomplished by treating them with an aqueous ammonia solution.[16] This was demonstrated by refluxing **7a** in the presence of K_2CO_3 in an ethanol/aqueous ammonia solution for 2 h, where after the isoquinoline **2a** was isolated in good yield (Scheme 5).



Scheme 5. Reagents and conditions: (a) 1.5 equiv K_2CO_3, 27% NH_4OH_{aq}, EtOH, reflux, 2 h.

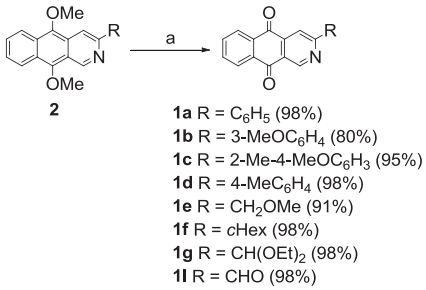
The similar polarities of the coupled product **7a**, the aldehyde **3a** and the other side products (**8**, **14**, **15**) made their purification by column chromatography a difficult task. The isoquinoline **2a** on the other hand exhibited a quite different retention time in comparison to the *o*-alkynylnaphthylaldehyde **7a**, which facilitated its isolation as a pure compound, despite the sometimes significant adsorption of the product **2a** on silica or on Al_2O_3. Further improvement to the synthetic procedure was made by directly adding an aqueous ammonia solution to the reaction mixture obtained after the coupling reaction and stirring it at 100 °C for 2 h (Scheme 6). This one-pot procedure went quite well, furnishing the isoquinolines **2** in moderate to good yields after chromatography.



Scheme 6. Reagents and conditions: (a) (1) 2 equiv HC≡CR, 4 mol % $Pd(OAc)_2$, 0.12 equiv P(*t*-Bu)$_3$, 2 mol % CuI, 1.2 equiv Cs_2CO_3, DMF, 100 °C, 24 h; (2) 1 equiv K_2CO_3, NH_4OH_{aq}, 100 °C, 2 h; (b) 2 N HCl_{aq}, Et_2O, rt, 2 h.

2.4. Oxidation

The acquired 3-substituted 5,10-dimethoxybenzo[*g*]isoquinolines **2** were oxidized with cerium(IV) ammonium nitrate (CAN)[17] and furnished the corresponding 3-substituted 2-azaanthraquinones **1** in almost quantitative yield (Scheme 7). Even mixtures of protonated and non-protonated 5,10-dimethoxybenzo[*g*]isoquinolines **2** could be oxidized. The 2-azaanthraquinones **1** were isolated solely as the non-protonated species after flash chromatography.



Scheme 7. Reagents and conditions: (a) 3 equiv CAN, CH_3CN/H_2O (2/1), 0 °C, 1 h.

3. Conclusions

In conclusion, a convenient procedure based on the Larock isoquinoline synthesis was developed to construct a series of 3-substituted benzo[*g*]isoquinoline-5,10-diones **1**. The protocol worked satisfactorily for terminal alkynes bearing aromatic groups and for 3-methoxypropyne. For alkynes, bearing aliphatic groups, an alternative procedure starting from an *ortho*-bromonaphthaldehyde **3a** and consisting of a consecutive one-pot Sonogashira coupling and an iminoannulation was pursued. As a key step the coupling of an *ortho*-bromonaphthaldehyde **3a** with cyclohexylacetylene was investigated thoroughly, revealing the formation of benzo[*f*]indenone **13** as an interesting side product in case Bu_4NCl was added to the reaction mixture. In all cases the 3-substituted 5,10-dimethoxybenzo[*g*]isoquinolines **2** were easily CAN oxidized into the desired 2-azaanthraquinones **1**.

4. Experimental section

4.1. General experimental methods

^{1}H NMR spectra were recorded on a Bruker Avance DRX 250 spectrometer at 250 MHz, Bruker Avance II 500 spectrometer at 500 MHz with an internal standard TMS. *J* values are given in hertz. ^{13}C NMR spectra were recorded on a Bruker Avance DRX 250 spectrometer at 63 MHz, Bruker Avance II 500 spectrometer at 125 MHz with internal standard $CDCl_3$ (δ=77). ^{13}C NMR

assignments were made using DEPT spectra. Melting points were determined on a Büchi melting point apparatus B-540 and are uncorrected. GC–MS analyses were performed using an Interscience GC 8000 series gas chromatograph with a EC™-5 column (length: 30 m, internal diameter: 0.32 mm, film thickness: 0.25 μm). Products were injected in a split injector (250 °C); the inert carrier gas is helium. The mass spectrometer was a Fisons Instruments MD 800 using electron impact (70 eV) as ionization method. HRMS was measured with a VGQuattro II mass spectrometer. Infrared spectra were recorded with an Avatar 370 FT-IR apparatus (Thermo Nicolet), using the attenuated total reflection technology (ATR). Column chromatography was performed using Merck silica (diameter 40–63 μm). Preparative HPLC was carried out with an Agilent 1100 series equipped with a Discovery BIO wide Pore® RP C18 column (25 cm×4.6 mm×5 μm) using a MeCN/H_2O gradient containing 0.1% TFA. TLC-analysis was performed on glass backed plates (Merck) coated with 0.2 mm silica 60 F_{254}.

4.2. Preparation of *N*-[(3-bromo-1,4-dimethoxynaphthalen-2-yl)methylene]-2-methyl-propan-2-amine (4)

3-Bromo-1,4-dimethoxy-2-naphthaldehyde (**3a**)[9] (2.28 g, 7.7 mmol) was dissolved in dry CH_2Cl_2 (20 mL). *tert*-Butylamine (1.69 g, 23.2 mmol) and anhydrous $MgSO_4$ (3 g) were added and the reaction mixture was stirred for 20 h at room temperature. After completion, the reaction mixture was filtrated and afterwards concentrated in vacuo. The imine was isolated as a yellowish-white solid (0.8 g, 100%). No further purification was required. Mp 67–68 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ_H 1.41 (9H, s, $C(CH_3)_3$), 3.93 (3H, s, OCH_3), 3.98 (3H, s, OCH_3), 7.56 (1H, dd, *J* 2.5 and 7.2, CH_{ar}), 7.56 (1H, dd, *J* 3.9 and 5.8, CH_{ar}), 8.07–8.16 (2H, m, CH_{ar}), 8.51 (1H, s, CH=N). ^{13}C NMR (63 MHz, $CDCl_3$): δ_C 29.5 ($C(CH_3)_3$), 58.7 ($C(CH_3)_3$), 61.4 (OCH_3), 63.4 (OCH_3), 100.2 (C_q), 113.0 (C_q), 122.5 (CH_{ar}), 123.1 (CH_{ar}), 126.8 (CH_{ar}), 127.5 (CH_{ar}), 128.5 (C_q), 129.1 (C_q), 150.0 (C–OMe), 151.5 (C–OMe), 153.3 (C=N). IR (ATR): ν_{max} 763, 1007, 1079, 1347, 1454, 2966 cm^{-1}. MS (70 eV, *m*/*z* (%)): 351 (17), 349 (17), 294 (82), 292 (79), 279 (82), 277 (85), 240 (51), 198 (100), 113 (47). HRMS (ESI): calcd for $C_{17}H_{20}BrNO_2$+H^+: 350.0750; found 350.0731.

4.3. Palladium/copper catalyzed formation of 3-substituted 5,10-dimethoxybenzo[*g*]isoquinolines from terminal acetylenes

The synthesis of 5,10-dimethoxy-3-phenylbenzo[*g*]isoquinoline (**2a**) is representative.

The imine **4** (0.8 g, 2.29 mmol), phenylacetylene (0.256 g, 2.51 mmol), $Pd(PPh_3)_2Cl_2$ (0.064 g, 0.09 mmol) and CuI (0.017 g 0.09 mmol) were placed in a pressure tube and dissolved in Et_3N (11 mL). The vial was flushed with argon, closed with a screw-top and heated in an oil bath to 70 °C for 24 h. After completion, the precipitate was filtered over decalite and rinsed with Et_2O. The filtrate was subsequently concentrated in vacuo. The residue was redissolved in DMF (11 mL) and CuI (0.044 g, 0.23 mmol) was added. The reaction mixture (poured in an argon flushed pressure tube) was heated to 100 °C for 4 h. After completion the mixture was cooled, diluted with Et_2O, washed with aqueous NH_4Cl, dried over $MgSO_4$ and filtered. The solvent was removed in vacuo and the crude residue was purified by column chromatography (PE/EtOAc, 9/1). The isolated solid was either treated with NaOH in MeOH (50 equiv NaOH, 0.1 M solution, 24 h) or further purified via preparative RP-HPLC.

*4.3.1. 5,10-Dimethoxy-3-phenylbenzo[g]isoquinoline (**2a**) (HCl salt).* Purified over a silica column (*c*Hexane/EtOAc, 9/1) or Al_2O_3 (*c*Hexane/EtOAc, 12/1) and obtained in 80% yield as a yellow powder. An analytically pure sample was obtained by purification via preparative RP-HPLC. Mp 107.7–108.4 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ_H 4.17 (3H, s, C_5–OCH_3), 4.32 (3H, s, C_{10}–OCH_3), 7.53–7.64 (3H, m, H-3′, H-4′, H-5′), 7.68 (1H, ddd, *J* 1.3, 6.6 and 8.6, H-7), 7.77 (1H, ddd, *J* 1.3, 6.6 and 8.6, H-8), 8.03 (2H, d, *J* 6.8, H-2′, H-6′), 8.36 (1H, d, *J* 8.5, H-6), 8.41 (1H, d, *J* 8.4, H-9), 8.50 (1H, s, H-4), 10.27 (1H, s, H-1), 16.07 (1H, s, NH). ^{13}C NMR (63 MHz, $CDCl_3$): δ_C 63.9 (C_5–OCH_3), 65.9 (C_{10}–OCH_3), 115.1 (C-4), 117.3 (C-4a), 122.9 (C-6), 123.8 (C-9), 125.5 (C-10a), 126.9 (C-5a), 127.5 (C-7), 127.6 (C-2′, C-6′), 129.5 (C-3′, C-4′), 130.1 (C-8), 130.2 (C-4′), 131.2 (C-9a), 134.0 (C-1′), 143.2 (C-3), 148.1 (C-5), 148.7 (C-1), 154 (C-10). IR (ATR): ν_{max} 670, 775, 966, 1071, 1297, 1367, 1456, 1605 cm^{-1}. MS (ES^+) *m*/*z* (%): 316 ($M+H^+$, 100). HRMS (ESI): calcd for $C_{21}H_{17}NO_2$+H^+: 316.3726; found 316.3712.

*4.3.2. 5,10-Dimethoxy-3-(3-methoxyphenyl)benzo[g]isoquinoline (**2b**).* Purified over a silica column (*c*Hexane/EtOAc, 9/1) and afterwards stirred in a MeOH/NaOH solution for 24 h, affording **2b** in 50% yield as a yellow powder. Mp 149.7–150.1 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ_H 3.95 (3H, s, $C_{3'}$–OCH_3), 4.15 (3H, s, C_5–OCH_3), 4.23 (3H, s, C_{10}–OCH_3), 6.99 (1H, dd, *J* 1.9 and 8.1, H-4′), 7.44 (1H, t, *J* 7.9, H-5′), 7.54 (1H, dd, *J* 6.7 and 8.5, H-7), 7.60 (1H, dd, *J* 7.0 and 7.9, H-8), 7.79 (1H, d, *J* 7.7, H-6′), 7.85 (1H, s, CH_{ar}), 8.31 (1H, d, *J* 8.7, H-6), 8.35 (1H, d, *J* 8.6, H-9), 8.40 (1H, s, H-2′), 9.88 (1H, s, H-1). ^{13}C NMR (126 MHz, $CDCl_3$): δ_C 54.4 (OCH_3), 62.4 (OCH_3), 63.6 (OCH_3), 109.2 (CH_{ar}), 111.3 (CH_{ar}), 113.5 (CH_{ar}), 117.8 (C_q), 118.4 (CH_{ar}), 121.5 (CH_{ar}), 122.1 (CH_{ar}), 124.8 (C_q), 124.9 (CH_{ar}), 125.1 (C_q), 126.4 (CH_{ar}), 127.3 (C_q), 128.8 (CH_{ar}), 140.2 (C_q), 146.9 (C_q), 147.7 (C_q), 148.9 (CH_{ar}), 149.9 (C_q), 159.2 (C_q). IR (ATR): ν_{max} 699, 765, 865, 966, 1070, 1367, 1453, 1595 cm^{-1}. MS (ES^+) *m*/*z* (%): 346 ($M+H^+$, 100). HRMS (ESI): calcd for $C_{22}H_{19}NO_3$+H^+: 346.3986; found 346.3971.

*4.3.3. 5,10-Dimethoxy-3-(4-methoxy-2-methylphenyl)benzo[g]isoquinoline (**2c**).* Purified over a silica column (*c*Hexane/EtOAc, 9/1) and afterwards stirred in MeOH/NaOH solution for 24 h, affording **2c** in 59% yield as a yellow powder. Mp 155.8–157.3 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ_H 2.50 (3H, s, CH_3), 3.86 (3H, s, $C_{4'}$–OCH_3), 4.10 (3H, s, C_5–OCH_3), 4.24 (3H, s, C_{10}–OCH_3), 6.88–6.89 (2H, m, H-5′, H-6′), 7.25–7.60 (3H, m, H-7, H-8, H-3′), 8.04 (1H, s, H-4), 8.30 (1H, d, *J* 4.3, H-6), 8.35 (1H, d, *J* 4.3, H-9), 9.85 (1H, s, H-1). ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 21.0 (CH_3), 55.3 (OCH_3), 63.4 (OCH_3), 64.6 (OCH_3), 111.4 (CH_{ar}), 113.5 (CH_{ar}), 116.3 (CH_{ar}), 118.3 (C_q), 122.5 (CH_{ar}), 123.1 (CH_{ar}), 125.6 (C_q), 125.8 (CH_{ar}), 125.9 (C_q), 127.4 (CH_{ar}), 128.2 (C_q), 131.5 (CH_{ar}), 133.5 (C_q), 137.8 (C_q), 147.5 (C_q), 149.2 (CH_{ar}), 147.5 (C_q), 149.2 (CH_{ar}), 150.9 (C_q), 151.0 (C_q), 159.5 (C_q). IR (ATR): ν_{max} 689, 772, 811, 860, 965, 1070, 1254, 1286, 1286, 1367, 1607 cm^{-1}. MS (ES^+) *m*/*z* (%): 360 ($M+H^+$, 100). HRMS (ESI): calcd for $C_{23}H_{21}NO_3$+H^+: 360.4251; found 360.4268.

*4.3.4. 5,10-Dimethoxy-3-p-tolylbenzo[g]isoquinoline (**2d**).* Purified over a silica column (*c*Hexane/EtOAc, 9/1) and isolated with 55% yield as an orange powder. Mp 135–137 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ_H 2.44 (3H, s, CH_3), 4.15 (3H, s, C_5–OCH_3), 4.23 (3H, s, C_{10}–OCH_3), 7.53 (1H, ddd, *J* 1.4, 6.6 and 8.2, H-7), 7.60 (1H, ddd, *J* 1.4, 6.6 and 8.3, H-8), 7.35 (2H, d, *J* 7.5, H-3′, H-5′), 8.12 (2H, d, *J* 8.2, H-2′, H-6′), 8.31 (1H, dd, *J* 1.7 and 5.7, H-6), 8.34 (1H, dd, *J* 1.7, and 8.0, H-9), 8.37 (1H, d, *J* 1, H-4), 9.87 (1H, d, *J* 1, H-1). ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 21.33 (CH_3), 63.4 (C_5–OCH_3), 64.7 (C_{10}–OCH_3), 109.4 (C-4), 118.7 (C-4a), 122.5 (C-6), 123.1 (C-9), 125.6 (C_q-10a), 125.8 (C-7), 126.2 (C-5a), 126.9 (C-3′, C-5′), 127.4 (C-8), 128.2 (C-4′), 129.6 (C-2′, C-6′), 136.8 (C-9a), 138.5 (C-1′), 147.7 (C-3), 149.0 (C-5), 149.9 (C-1), 150.9 (C-10). IR (ATR): ν_{max} 757, 769, 827, 1072, 1369, 1605 cm^{-1}. MS (ES^+) *m*/*z* (%): 330 ($M+H^+$, 100). HRMS (ESI): calcd for $C_{22}H_{19}NO_2$+H^+: 330.3992; found 330.3979.

*4.3.5. 5,10-Dimethoxy-3-(methoxymethyl)benzo[g]isoquinoline (**2e**).* This compound was isolated as an orange powder in 91% yield

after purification over a silica gel column (gradient: *c*Hexane/EtOAc, 9/1 over *c*Hexane/EtOAc, 4/1 to EtOAc). Mp 102.0–103.5 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 3.60 (3H, s, CH_2OCH_3), 4.12 (3H, s, C_5–OCH_3), 4.20 (3H, s, C_{10}–OCH_3), 4.79 (2H, s, CH_2), 7.55 (1H, dt, *J* 1.0 and 7.5, H-7), 7.61 (1H, dt, *J* 1.0 and 7.6, H-8), 8.04 (1H, s, H-4), 8.22 (1H, d, *J* 9.0, H-6), 8.35 (1H, d, *J* 8.5, H-9), 9.76 (1H, s, H-1). ^{13}C NMR (63 MHz, $CDCl_3$): δ_C 58.9 (CH_2OCH_3), 63.4 (OCH_3), 64.6 (OCH_3), 75.7 (CH_2), 111.4 (CH_{ar}), 119.0 (C_q), 119.0 (C_q), 122.6 (CH_{ar}), 123.1 (CH_{ar}), 125.6 (C_q), 125.9 (CH_{ar}), 127.4 (CH_{ar}), 128.2 (C_q), 131.9 (C_q), 149.0 (C_q), 149.9 (CH_{ar}), 150.9 (C_q). IR (ATR): ν_{max} 741, 769, 968, 1065, 1364, 1621, 2981 cm^{-1}. MS (ES$^+$) *m*/*z* (%): 284 (M+H$^+$, 100). HRMS (ESI): calcd for $C_{17}H_{17}NO_3$+H$^+$: 284.3292; found 284.3304.

*4.3.6. 3-Cyclohexyl-5,10-dimethoxybenzo[g]isoquinoline (**2f**).* Purified over a silica column (*c*Hexane/EtOAc, 9/1) and afterwards stirred in MeOH/NaOH solution for 24 h, affording **2f** in 31% yield as a yellow powder. Mp 124–125 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 1.34–1.41 (1H, m, CH), 1.47–1.55 (2H, m, CH_2), 1.64–1.72 (2H, m, CH_2), 1.78–1.82 (1H, m, CH), 1.92–1.94 (2H, m, CH_2), 2.12–2.15 (2H, m, CH_2), 2.88–2.93 (1H, m, H-1′), 4.10 (3H, s, C_5–OCH_3), 4.20 (3H, s, C_{10}–OCH_3), 7.50 (1H, dd, *J* 7.3 and 7.3, H-7), 7.57 (1H, dd, *J* 7.3 and 7.3, H-8), 7.77 (1H, s, H-4), 8.27 (1H, d, *J* 8.5, H-6), 8.32 (1H, d, *J* 8.5, H-9), 9.75 (1H, s, H-1). ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 26.25 (CH_2), 26.74 (2×CH_2), 33.03 (2×CH_2), 46.26 (C-1′), 63.06 (C_5–OCH_3), 64.49 (C_{10}–OCH_3), 109.3 (C-4′), 118.7 (C-4a), 122.4 (C-6), 123.1 (C-9), 125.1 (C-10a), 125.4 (C-7), 126.2 (C-5a), 127.1 (C-8), 128.0 (C-9a), 147.0 (C-3), 149.4 (C-1), 150.8 (C-5), 157.9 (C-10). IR (ATR): ν_{max} 703, 772, 969, 1063, 1294, 1367, 1450, 1613, 2847, 2923 cm^{-1}. MS (ES$^+$) *m*/*z* (%): 322 (M+H$^+$, 100). HRMS (ESI): calcd for $C_{21}H_{23}NO_2$+H$^+$: 322.4202; found 322.4218.

*4.3.7. 3-(Diethoxymethyl)-5,10-dimethoxybenzo[g]isoquinoline (**2g**).* Isolated after purification over a short Al_2O_3 column (Petroleum ether/EtOAc, 9/1) as a red powder in 5% yield. Mp 108.3–109.2 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ_H 1.33 (6H, d, *J* 7.1, 2×CH_3), 3.77 (4H, qd *J* 7.0 and 9.2, 2×CH_2), 4.13 (3H, s, C_5–OCH_3), 4.20 (3H, s, C_{10}–OCH_3), 5.72 (1H, s, H-1′), 7.49–7.67 (2H, m, H-7, H-8), 8.26 (1H, d, *J* 0.4, H-4), 8.32 (1H, d, *J* 8.9, H-6), 8.35 (1H, d, *J* 8.6, H-9), 9.79 (1H, s, H-1). ^{13}C NMR (63 MHz, $CDCl_3$): δ_C 15.3 (2×CH_3), 62.4 (2×CH_2), 63.5 (C_5–OCH_3), 64.6 (C_{10}–OCH_3), 102.7 (C-1′), 111.5 (C-4), 119.4 (C-4a), 122.6 (C-6), 123.1 (C-9), 125.4 (C-10a), 125.9 (C-9a), 126.1 (C-7), 127.4 (C-8), 128.2 (C-4a), 148.1 (C-3), 149.0 (C-5), 149.9 (C-1), 150.1 (C-10). IR (ATR): ν_{max} 770, 968, 1059, 1369, 1439, 1452, 1610 cm^{-1}. MS (ES$^+$) *m*/*z* (%): 342 (M+H$^+$, 100). HRMS (ESI): calcd for $C_{20}H_{23}NO_4$+H$^+$: 342.4083; found 342.4068.

*4.3.8. 3-Butyl-5,10-dimethoxybenzo[g]isoquinoline (**2h**).* Isolated as an equimolar mixture of the isoquinoline **2h** and the isoquinolinium chloride **2h**·HCl after Al_2O_3 flash chromatography (gradient: Petroleum ether/EtOAc, 20/1 over Petroleum ether/EtOAc, 12/1 to Petroleum ether/EtOAc, 9/1). The compounds were treated with a solution of NaOH (50 equiv) in MeOH and the mixture was stirred for 24 h, affording **2h** with 50% yield (still 15% present as the hydrochloride). Mp 54–58 °C. Yellow powder. Spectral data for **2h** were obtained from an equimolar mixture of **2h** and **2h**·HCl. ^{1}H NMR (250 MHz, $CDCl_3$): δ_H 0.99 (3H, t, *J* 7.3, H-4′), 1.47 (2H, pseudo sextet, *J* 7.4, H-3′), 1.80 (2H, pseudo quintet, *J* 7.6, H-2′), 3.00 (2H, t, *J* 7.7, H-1′), 4.11 (3H, s, OCH_3), 4.20 (3H, s, OCH_3), 7.51 (1H, dd, *J* 1.4 and 7.6, H-7), 7.58 (1H, dd, *J* 1.4 and 7.8, H-8), 7.79 (1H, s, H-4), 8.26–8.43 (2H, m, H-6, H-9), 9.74 (1H, s, H-1). ^{13}C NMR (63 MHz, $CDCl_3$): δ_C 14.02 (CH_3), 22.55 (CH_2), 31.96 (CH_2), 38.05 (CH_2), 63.13 (OCH_3), 64.55 (OCH_3), 101.5 (C_q), 111.1 (C_q), 122.4 (CH_{ar}), 123.1 (CH_{ar}), 125.1 (CH_{ar}), 125.5 (CH_{ar}), 127.2 (CH_{ar}), 128.1 (CH_{ar}), 136.7 (C_q), 138.8 (C_q), 146.8 (*C*–OMe), 150.8 (*C*–OMe). IR (ATR): ν_{max} 771, 870, 977, 1068, 1368, 1453, 1614, 2855, 2953 cm^{-1}. MS (ES$^+$) *m*/*z* (%): 296 (M+H$^+$, 100), 328 (73). HRMS (ESI): calcd for $C_{19}H_{21}NO_2$+H$^+$: 296.1645; found 296.1659.

*4.3.9. 5,10-Dimethoxybenzo[g]isoquinoline-3-carbaldehyde (**2l**) (HCl salt).* This compound was prepared by stirring **2g** in a biphasic Et_2O/2 N HCl_{aq} solution at ambient temperature for 2 h. Neutralization of the aqueous phase with 2 N NaOH, extraction with Et_2O and combination of the organic phases gave after drying over $MgSO_4$ and removal of the volatiles **2l** as a yellow powder. An analytically pure sample was obtained by preparative RP-HPLC. Mp 167.5–167.7 °C. Yellow powder. ^{1}H NMR (250 MHz, $CDCl_3$): δ_H 4.18 (3H, s, C_5–OCH_3), 4.23 (3H, s, C_{10}–OCH_3), 7.63–7.73 (2H, m, H-7, H-8), 8.35–8.43 (2H, m, H-6, H-9), 8.73 (1H, d, *J* 0.9, H-4), 9.86 (1H, d, *J* 0.8, H-1), 10.31 (1H, s, CHO). ^{13}C NMR (63 MHz, $CDCl_3$): δ_C 64.3 (C_5–OCH_3), 64.8 (C_{10}–OCH_3), 118.3 (C-4), 120.2 (C-4a), 123 (C-6), 123.3 (C-9), 124.3 (C-10a), 127.6 (C-7), 128.0 (C-5a), 128.1 (C-8), 128.7 (C-9a), 144.8 (C-3), 150.5 (C-5), 150.9 (C-1), 151.1 (C-10), 193.0 (CHO). IR (ATR): ν_{max} 690, 741, 965, 1067, 1364, 1694, 2828 cm^{-1}. MS (ES$^+$) *m*/*z* (%): 268 (M+H$^+$, 100). HRMS (ESI): calcd for $C_{16}H_{13}NO_3$+H$^+$: 268.2867; found 268.2881.

*4.3.10. 1,4-Dimethoxy-3-(3-methoxy-3-methylbut-1-ynyl)-2-naphthaldehyde (**7i**).* An analytically pure sample was obtained via preparative RP-HPLC, isolating **7i** as a black viscous liquid. ^{1}H NMR (250 MHz, $CDCl_3$): δ_H 1.65 (6H, s, CH_3), 3.54 (3H, s, OCH_3), 4.05 (3H, s, OCH_3), 4.10 (3H, s, OCH_3), 7.61 (1H, ddd, *J* 1.4, 6.8 and 8.2, CH_{ar}), 7.68 (1H, ddd, *J* 1.4, 6.8 and 8.3, CH_{ar}), 8.16 (1H, d, *J* 8.4, CH_{ar}), 8.25 (1H, d, *J* 8.4, CH_{ar}), 10.7 (1H, s, CHO). ^{13}C NMR (63 MHz, $CDCl_3$): δ_C 28.23 (2×CH_3), 52.08 (OCH_3), 61.70 (OCH_3), 64.53 (OCH_3), 71.35 (C_q), 102.2 (C_q), 111.1 (C_q), 122.9 (CH_{ar}), 124.0 (CH_{ar}), 128.0 (CH_{ar}), 128.8 (C_q), 129.7 (CH_{ar}), 131.6 (C_q), 156.0 (*C*–OMe), 156.6 (*C*–OMe), 195.1 (CHO). IR (ATR): ν_{max} 775, 965, 1061, 1350, 1690, 2934, 2982 cm^{-1}. MS (ES$^+$) *m*/*z* (%): 299 (M+H$^+$, 100), 281 (41), 281 (100). HRMS (ESI): calcd for $C_{19}H_{20}O_4$+H$^+$: 313.1434; found 313.1452.

4.4. 2-[(*tert*-Butylimino)methyl]-3-(cyclohexylethynyl)-4-methoxynaphthalen-1-ol (12f)

This compound was isolated impure via flash chromatography on silica gel of the reaction mixture from entry 1 in Table 2 (gradient: PE/EtOAc, 12/1 to 9/1). ^{1}H NMR (250 MHz, $CDCl_3$): δ_H 1.49 (9H, s, $C(CH_3)_3$), 1.92–2.00 (2H, m, CH_2), 2.72–2.85 (1H, m, CH), 3.96 (3H, s, OCH_3), 7.44 (1H, ddd, *J* 1.2, 7.1 and 8.0, CH_{ar}), 7.60 (1H, ddd, *J* 1.4, 6.4 and 8.8, CH_{ar}), 7.89 (1H, d, *J*=8.1, CH_{ar}), 8.42 (1H, d, *J*=8.9, CH_{ar}), 8.46 (1H, br s, HC=N), 13.5 (1H, br s, OH). The other cyclohexyl protons could not be discerned due to other impurities. MS (ES$^+$) *m*/*z* (%): 365 (22), 364 (M+H$^+$, 100), 363 (19).

4.5. 3-Bromo-2-[(*tert*-butylimino)methyl]-4-methoxynaphthalen-1-ol (11)

This compound was isolated via flash chromatography on silica gel of the reaction mixture from entry 11 in Table 2 (gradient: PE/EtOAc, 12/1 to 9/1). Mp 73.0–73.5 °C, yellow powder. ^{1}H NMR (250 MHz, $CDCl_3$): δ_H 1.50 (9H, s, $C(CH_3)_3$), 3.88 (6H, s, OCH_3), 7.41 (1H, ddd, *J* 1.3, 7.0 and 8.1, CH_{ar}), 7.62 (1H, ddd, *J* 1.3, 7.0 and 8.2, CH_{ar}), 7.85 (1H, dd, *J* 0.6 and 8.2, CH_{ar}), 8.42 (1H, s, HC=N), 8.46 (1H, d, *J* 5.2, CH_{ar}), 13.8 (1H, s, OH). ^{13}C NMR (63 MHz, $CDCl_3$): δ_C 29.83 (C(CH_3)$_3$), 54.58 (*C*(CH_3)$_3$), 60.83 (OCH_3), 105.9 (C_q), 113.4 (C_q), 122.1 (CH_{ar}), 126.0 (CH_{ar}), 126.4 (CH_{ar}), 130.8 (C_q), 131.2 (CH_{ar}), 132.6 (C_q), 141.7 (C_q), 156.8 (CH), 177.5 (HC=N). IR (ATR): ν_{max} 701, 769, 1228, 1324, 1599, 1624 cm^{-1}. MS (ES$^+$) *m*/*z* (%): 338 (M+H$^+$, 100), 336 (M+H$^+$, 100), 282 (30), 280 (30). HRMS (ESI): calcd for $C_{16}H_{18}BrNO_2$+H$^+$: 337.2310; found 337.2294.

4.6. Synthesis of 3-substituted 5,10-dimethoxybenzo[*g*]-isoquinolines 2 via the double addition protocol

*4.6.1. 3-(Diethoxymethyl)-5,10-dimethoxybenzo[g]isoquinoline (**2g**).* The imine **4** (0.8 g, 2.29 mmol), 3,3-diethoxy-1-propyne (0.324 g, 2.51 mmol), $PdCl_2(PPh_3)_2$ (0.064 g, 0.09 mmol) and CuI (0.017 g, 0.09 mmol) were placed in a pressure tube and dissolved in Et_3N (11 mL). The vial was flushed with argon, closed with a screw-top and heated in an oil bath to 70 °C. The reaction mixture was stirred and monitored with HPLC until the conversion stalled (after approximately 8 h). The reaction mixture was subsequently filtered over decalite and rinsed with Et_3N. The collected filtrate was placed in a pressure tube, $PdCl_2(PPh_3)_2$ (0.032 g), CuI (0.08 g) and 3,3-diethoxypropyne (0.162 g) were added anew in quantities depending on the earlier degree of conversion (estimated via HPLC at ~50%), the reaction vessel was flushed with argon, closed and heated at 70 °C for another 8 h. After completion, the reaction mixture was filtered over decalite and rinsed with Et_2O. The filtrate was subsequently concentrated in vacuo. The residue was dissolved in DMF (11 mL) and CuI (0.044 g, 0.23 mmol) was added. The reaction mixture (poured in an argon flushed pressure tube) was heated to 100 °C for 4 h. After completion the mixture was cooled, diluted with Et_2O, washed with aqueous NH_4Cl, dried over $MgSO_4$ and filtered. The solvent was removed in vacuo and the crude residue was purified by Al_2O_3 gel column chromatography (PE/EtOAc, 9/1), isolating **2g** (0.414 g, 53%) as a red powder.

*4.6.2. 3-Cyclohexyl-5,10-dimethoxybenzo[g]isoquinoline (**2f**).* The procedure to synthesize **2f** was identical to that of **2g** (vide supra). **2f** was isolated as a yellow powder after flash chromatography (PE/EtOAc, 9/1) in 58% yield.

4.7. Sonogashira coupling of aldehyde 3a with alkynes

The synthesis of 1,4-dimethoxy-3-(phenylethynyl)-2-naphthaldehyde (**7a**) is representative.

The aldehyde **3a** (0.148 g, 0.5 mmol) was dissolved in DMF (3 mL) in a pressure tube. $Pd(OAc)_2$ (0.005 g, 0.02 mmol), CuI (0.004 g, 0.02 mmol), K_2CO_3 (0.083 g, 0.6 mmol), P(*t*-Bu)$_3$ (0.012 g, 0.06 mmol) and phenylacetylene (0.061 g, 0.6 mmol) were added subsequently, after which the pressure tube was purged with argon, closed with a screw top and placed in a 100 °C oil bath for 24 h while being stirred. Afterwards, the reaction mixture was cooled to room temperature and quenched with 10 mL of aqueous NH_4Cl. Extraction with Et_2O (3×10 mL), drying ($MgSO_4$) of the combined organic phases and in vacuo concentration resulted in a brown residue that was further purified by silica column chromatography (PE/EtOAc, 9/1). Compound **7a** was isolated as a red powder (0.128 g, 81%).

*4.7.1. 1,4-Dimethoxy-3-(phenylethynyl)-2-naphthaldehyde (**7a**).* Mp 96–97 °C. Red solid. ^{1}H NMR (250 MHz, $CDCl_3$): δ_H 4.08 (1H, s, OCH_3), 4.19 (1H, s, OCH_3), 7.35–7.45 (2H, m, CH_{ar}), 7.73–7.45 (5H, m, CH_{ar}), 8.19–8.29 (2H, m, CH_{ar}), 10.8 (1H, s, CHO). ^{13}C NMR (63 MHz, $CDCl_3$): δ_C 61.9 (OCH_3), 64.6 (OCH_3), 83.1 (C_q), 100.2 (C_q), 111.4 (C_q), 122.9 (CH_{ar}), 123.2 (C_q), 124.0 (CH_{ar}), 128.0 (CH_{ar}), 128.5 (2×CH_{ar}), 128.8 (CH_{ar}), 128.9 (C_q), 129.7 (CH_{ar}), 131.6 (2×CH_{ar}), 156.0 (*C*–OMe), 156.7 (*C*–OMe), 190.2 (CHO). IR (ATR): ν_{max} 2935, 1694, 1348, 1023, 778, 756, 692 cm^{-1}. MS (ES$^+$) *m*/*z* (%): 317 (M+H$^+$, 100). HRMS (ESI): calcd for $C_{21}H_{16}O_3$+H$^+$: 317.3573; found 317.3562.

*4.7.2. 3-(3,3-Diethoxyprop-1-ynyl)-1,4-dimethoxynaphthalene-2-carbaldehyde (**7g**).* Compound **7g** was purified via Al_2O_3 gel column chromatography (*c*Hexane/EtOAc, 9/1) and isolated as a yellow, viscous liquid with a yield of 31%. ^{1}H NMR (250 MHz, $CDCl_3$): δ_H 1.31 (6H, t, *J* 7.1, 2×CH_3), 3.77 (2H, q, *J* 7.1, CH_2), 3.90 (2H, q, *J* 7.1, CH_2), 5.64 (1H, s, CH), 7.60–7.73 (2H, m, CH_{ar}), 8.17 (1H, d, *J* 8.4, CH_{ar}), 8.26 (1H, *J* 8.5, CH_{ar}). ^{13}C NMR (63 MHz, $CDCl_3$): δ_C 15.18 (2×CH_3), 61.16 (2×CH_2), 62.04 (OCH_3), 64.59 (OCH_3), 78.46 (C_q), 92.02 (CH), 95.31 (C_q), 110.1 (C_q), 123.0 (CH_{ar}), 124.0 (CH_{ar}), 128.2 (CH_{ar}), 129.1 (C_q), 129.8 (CH_{ar}), 131.5 (C_q), 156.7 (*C*–OCH_3), 156.8 (*C*–OCH_3), 189.9 (CHO). IR (ATR): ν_{max} 720, 775, 979, 1061, 1339, 1351, 1687, 2936, 2971 cm^{-1}. MS (ES$^+$) *m*/*z* (%): 343 (M+H$^+$, 20), 315 (100), 297 (35). HRMS (ESI): calcd for $C_{20}H_{22}O_5$+H$^+$: 343.3931; found 343.3945.

*4.7.3. 3-(Cyclohexylethynyl)-1,4-dimethoxy-2-naphthaldehyde (**7f**).* The aldehyde **3a** (0.077 g, 0.26 mmol) was dissolved in DMF (1 mL) in a pressure tube. $Pd(OAc)_2$ (0.0023 g, 0.01 mmol), CuI (0.001 g, 0.005 mmol), Cs_2CO_3 (0.102 g, 0.31 mmol), P(*t*-Bu)$_3$ (0.012 g, 0.03 mmol) and cyclohexylacetylene (0.056 g, 0.52 mmol) were added subsequently. The reaction vessel was purged with argon, closed with a screw top and placed in a 100 °C oil bath while the reaction mixture was stirred for 24 h. Afterwards, the reaction mixture was cooled to room temperature and quenched with 10 mL of aqueous NH_4Cl. Extraction with Et_2O (3×10 mL), drying of the combined organic phases and in vacuo concentration resulted in a brown residue that was further purified by column chromatography on silica gel (PE/EtOAc, 9/1). Compound **7f** was isolated as a red viscous liquid (0.062 g, 73%). ^{1}H NMR (250 MHz, $CDCl_3$): δ_H 1.37–2.00 (10H, m, $(CH_2)_5$), 2.79 (1H, ddd, *J* 3.8, 8.9 and 12.7, C*H*(CH_2)), 4.03 (3H, s, OCH_3), 4.09 (3H, s, OCH_3), 7.58 (1H, ddd, *J* 1.4, 6.8 and 8.2, CH_{ar}), 7.66 (1H, ddd, *J* 1.5, 6.8 and 8.2, CH_{ar}), 8.15 (1H, dd, *J* 1.3 and 8.3, CH_{ar}), 8.25 (1H, dd, *J* 1.4 and 8.4, CH_{ar}), 10.7 (1H, s, CHO). ^{13}C NMR (63 MHz, $CDCl_3$): δ_C 24.87 (2×CH_2), 25.91 (CH_2), 30.24 (CH), 32.47 (2×CH_2), 61.51 (OCH_3), 64.21 (OCH_3), 73.54 (C_q), 106.3 (C_q), 112.9 (C_q), 122.6 (CH_{ar}), 124.1 (C_q), 124.1 (CH_{ar}), 127.5 (CH_{ar}), 128.5 (C_q), 129.5 (CH_{ar}), 131.6 (C_q), 155.5 (*C*–OMe), 155.8 (*C*–OMe), 191.1 (CHO). IR (ATR): ν_{max} 728, 776, 908, 1076, 1283, 1350, 1449, 1565, 1694, 2852, 2929 cm^{-1}. MS (ES$^+$) *m*/*z* (%): 323 (M+H$^+$, 100). HRMS (ESI): calcd for $C_{21}H_{22}O_3$+H$^+$: 323.4050; found 323.4033.

*4.7.4. 2-Cyclohexyl-4,9-dimethoxy-1H-cyclopenta[b]naphthalen-1-one (**13f**).* This compound was isolated from the reaction mixture obtained in entry 18 in Table 3.

Yellow viscous liquid. ^{1}H NMR (250 MHz, $CDCl_3$): δ_H 1.25–2.27 (10H, m, $(CH_2)_5$), 2.38–2.47 (1H, m, CH), 4.02 (3H, s, OCH_3), 4.27 (3H, s, OCH_3), 7.43 (1H, d, *J* 1.3, CH), 7.43 (1H, dt, *J* 1.3 and 7.6, CH_{ar}), 7.54 (1H, dt, *J* 1.3 and 7.6, CH_{ar}), 7.96 (1H, dd, *J* 1.0 and 8.3, CH_{ar}), 8.21 (1H, dd, *J* 0.9 and 8.1, CH_{ar}). ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 24.78 (CH_2), 25.75 (CH_2), 26.36 (CH_2), 29.50 (CH), 32.15 (CH_2), 32.29 (CH_2), 62.71 (OCH_3), 62.84 (OCH_3), 119.3 (C_q), 122.8 (CH_{ar}), 125.6 (CH_{ar}), 126.8 (CH_{ar}), 131.0 (C_q), 132.8 (C_q), 137.2 (CH_{ar}), 144.3 (C_q), 145.9 (C_q), 148.7 (*C*–OMe), 151.9 (*C*–OMe), 193.2 (C=O). IR (ATR): ν_{max} 770, 1034, 1341, 1448, 1685, 2849, 2922 cm^{-1}. MS (ES$^+$) *m*/*z* (%): 323 (M+H$^+$, 100). HRMS (ESI): calcd for $C_{21}H_{22}O_3$+H$^+$: 323.1642; found 323.1629.

4.8. A sequential one-pot cyclization and ammonia annulation procedure

The synthesis of 3-cyclohexyl-5,10-dimethoxybenzo[*g*]isoquinoline (**2f**) is representative.

The aldehyde **3a** (0.077 g, 0.26 mmol) was dissolved in DMF (1 mL) in a pressure tube. $Pd(OAc)_2$ (0.0023 g, 0.01 mmol), CuI (0.001 g, 0.005 mmol), Cs_2CO_3 (0.102 g, 0.31 mmol), P(*t*-Bu)$_3$ (0.012 g, 0.03 mmol) and cyclohexylacetylene (0.056 g, 0.52 mmol) were added subsequently. The reaction vessel was purged with argon, closed with a screw cap and placed in a 100 °C oil bath while the reaction mixture was stirred for 24 h. Afterwards 1 mL of a 28% aqueous NH_4OH solution was added together with K_2CO_3 (0.036 g, 0.26 mmol) and the mixture was heated to 100 °C for 2 h. Upon completion the reaction mixture was diluted with water (20 mL)

and extracted with Et_2O (3×10 mL). The combined organic phases were dried over $MgSO_4$, concentrated in vacuo and purified via silica gel column chromatography (PE/EtOAc, 9/1), resulting in a yellow powder **2f** (0.058 g, 70%).

Compounds **2g** (0.036 g, 41%) and **2h** (0.036 g, 50%) were constructed according to the above described procedure. After purification by Al_2O_3 flash chromatography (gradient PE/EtOAc, 20/1 over PE/EtOAc, 12/1 to PE/EtOAc, 9/1) **2h** was treated with a NaOH (50 equiv) solution in MeOH (0.02 M) and stirred for 24 h at room temperature prior to NMR analysis. Compound **2g** was purified by Al_2O_3 flash chromatography (PE/EtOAc, 9/1).

*4.8.1. Synthesis of 10,10-dimethoxy-3-phenylbenzo[g]isoquinolin-5(10H)-one (**10a**).* To a solution of **9** (0.07 g, 0.2 mmol) in MeOH (4 mL), NaOH (0.48 g, 16 mmol) was added. The reaction mixture was stirred at 80 °C for 30 h, where after it was diluted with water (20 mL) and extracted with Et_2O (2×10 mL). The organic phases were combined, dried over $MgSO_4$ and the volatiles were removed in vacuo. The isolated residue was purified over a short silica column (PE/EtOAc, 12/1 to PE/EtOAc, 9/1) to give a yellow powder (58 mg, 89%). Mp 92.5–93.7 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ_H 3.06 (6H, s, 2×OCH_3), 7.52–7.56 (3H, m, H-3′, H-4′, H-5′), 7.63 (1H, ddd, *J* 7.5, 7.5 and 1.2, H-8), 7.82 (1H, ddd, *J* 7.5, 7.5 and 1.2, H-7), 7.92 (1H, dd, *J* 0.9 and 7.9, H-9), 8.14–8.23 (2H, m, H-2′, H-6′), 8.33 (1H, dd, *J* 1.0 and 7.8, H-6), 8.5 (1H, s, H-4), 9.2 (1H, s, H-1). ^{13}C NMR (63 MHz, $CDCl_3$): δ_C 52.1 (2×OCH_3), 97.0 (C-10), 115.5 (C-4), 127.1 (C-2′,C-6′,C-9), 127.5 (C-6), 129.0 (C-3′, C-5′), 129.8 (C-4′), 129.9 (C-8), 130.9 (C-4a), 132.8 (C-9a), 135.0 (C-7), 138.1 (C-1′), 182.4 (C=O), 139.4 (C-10a), 139.6 (C-5a), 150.3 (C-1), 158.8 (C-3). IR (ATR): ν_{max} 693, 710, 1064, 1291, 1383, 1596, 1676 cm^{-1}. MS (ES$^+$) *m*/*z* (%): 332 (M+H$^+$, 100). HRMS (ESI): calcd for $C_{21}H_{17}NO_3$+H$^+$: 332.3720; found 332.3738.

*4.8.2. Synthesis of 10-ethoxy-10-methoxy-3-phenylbenzo[g]isoquinolin-5(10H)-one (**10b**).* To a solution of **9** (0.035 g, 0.1 mmol) in EtOH (4 mL), NaOH (0.48 g, 16 mmol) was added. The reaction mixture was stirred at 80 °C for 30 h, where after it was diluted with water and extracted with Et_2O. The combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo. The isolated residue was purified over a short silica column (PE/EtOAc, 9/1) to give a yellow powder (26 mg, 76%). Mp 117.9–120.9 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ_H 1.66 (3H, t, *J* 7.0, CH_3), 4.16 (3H, s, OCH_3), 4.38 (2H, q, *J* 7.0, CH_2), 7.43–7.64 (5H, m, CH_{ar}), 8.19–8.24 (2H, m, CH_{ar}), 8.29–8.37 (2H, m, CH_{ar}), 8.41 (1H, d, *J* 1.1, H-4), 9.88 (1H, d, *J* 1.1, H-1). ^{13}C NMR (63 MHz, $CDCl_3$): δ_C 16.01 (CH_3), 63.43 (OCH_3), 73.34 (OCH_2CH_3), 109.9 (CH_{ar}), 119.1 (C_q), 122.5 (CH_{ar}), 123.4 (CH_{ar}), 125.8 (CH_{ar}), 126.1 (CH_{ar}), 127.0 (2×CH_{ar}), 127.2 (C_q), 127.4 (CH_{ar}), 128.2 (C_q), 128.5 (CH_{ar}), 128.8 (2×CH_{ar}), 139.7 (C_q), 147.6 (C_q), 148.9 (C_q), 150.1 (C_q), 150.2 (C_q), C=O was not visible. IR (ATR): ν_{max} 700, 768, 1070, 1354, 1375, 1608 cm^{-1}. MS (ES$^+$) *m*/*z* (%): 346 (M+H$^+$). HRMS (ESI): calcd for $C_{22}H_{19}NO_3$+H$^+$: 346.1438; found 346.1419.

4.9. Oxidative demethylation of 5,10-dimethoxybenzo[g]-isoquinolines with CAN

The synthesis of 3-phenylbenzo[g]isoquinoline-5,10-dione (**1a**) is representative.

To a solution of **1a** (0.1 g, 0.32 mmol) in a mixture of CH_3CN/H_2O (2/1) (3 mL) was added CAN (0.53 g, 0.96 mmol) at 0 °C. The mixture was stirred for 1 h at 0 °C and the solution was quenched with water (20 mL) and extracted with EtOAc (3×10 mL). The combined organic phases were dried over $MgSO_4$, and the residue collected after removal of the volatiles was further purified by means of silica gel column chromatography (gradient: PE/EtOAc, 9/1 to PE/EtOAc 4/1). Compound **1a** was isolated as a yellow powder (0.088 g, 98%).

*4.9.1. 3-Phenylbenzo[g]isoquinoline-5,10-dione (**1a**).* Mp 203.7–204.0 °C (lit.,[7] 199.7–201.6 °C). Yellow powder. The spectral data are, within the experimental error, in accordance with the literature.[7] ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 7.50–7.57 (3H, m, CH_{ar}), 7.85 (1H, d×pseudo t, *J* 1.5 and 7.5, CH_{ar}), 7.88 (1H, d×pseudo t, *J* 1.5 and 7.5, CH_{ar}), 8.21 (2H, d, *J* 7.0, CH_{ar}), 8.34 (1H, dd, *J* 1.5 and 6.8, CH_{ar}), 8.36 (1H, dd, *J* 1.0 and 6.0, CH_{ar}), 8.50 (1H, s, CH_{ar}), 9.61 (1H, s, CH_{ar}). ^{13}C NMR (126 MHz, $CDCl_3$): δ_C 115.3 (C-4), 124.6 (C_q), 127.3 (CH_{ar}), 127.4 (CH_{ar}), 127.6 (2×CH_{ar}), 129.0 (CH_{ar}), 129.2 (CH_{ar}), 130.7 (CH_{ar}), 133.2 (C_q), 133.4 (C_q), 134.4 (CH_{ar}), 135.0 (CH_{ar}), 137.7 (C_q), 139.3 (C_q), 150.1 (C-1), 162.9 (C-3), 182.3 (C=O), 182.8 (C=O). IR (ATR): ν_{max} 711, 925, 1285, 1580, 1674 cm^{-1}. MS (ES$^+$) *m*/*z* (%): 286 (M+H$^+$, 100).

*4.9.2. 3-(3-Methoxyphenyl)benzo[g]isoquinoline-5,10-dione (**1b**).* Isolated with 80% yield after purification over a short silica column (PE/EtOAc, 4/1) to remove traces of CAN. Mp 191.4–192.1 °C. Yellow powder. ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 3.94 (3H, s, OCH_3), 7.07 (1H, dd, *J* 1.5 and 8.0, CH_{ar}), 7.46 (1H, pseudo t, *J* 8.0, CH_{ar}), 7.77–7.79 (2H, m, CH_{ar}), 7.86 (1H, d×pseudo t, *J* 1.5 and 7.3, H-7), 7.89 (1H, d×pseudo t, *J* 1.3 and 7.4 Hz, H-8), 8.35 (1H, dd, *J* 1.0 and 7.0, H-6), 8.37 (1H, dd, *J* 1.5 and 6.8, H-9), 8.50 (1H, s, H-4), 9.62 (1H, s, H-1). ^{13}C NMR (63 MHz, $CDCl_3$): δ_C 53.21 (OCH_3), 110.1 (CH_{ar}), 113.2 (CH_{ar}), 114.7 (CH_{ar}), 117.7 (CH_{ar}), 122.4 (C_q), 125.0 (CH_{ar}), 125.2 (CH_{ar}), 127.8 (CH_{ar}), 130.9 (C_q), 131.0 (C_q), 132.2 (CH_{ar}),133.7 (CH_{ar}), 136.7 (C_q), 136.9 (C_q), 147.6 (CH_{ar}), 158.0 (C_q), 160.2 (C_q), 180.0 (C=O), 180.5 (C=O). IR (ATR): ν_{max} 679, 712, 1294, 1322, 1582, 1673 cm^{-1}. MS (ES$^+$) *m*/*z* (%): 316 (M+H$^+$, 100). HRMS (ESI): calcd for $C_{20}H_{13}NO_3$+H$^+$: 316.3295; found 316.3287.

*4.9.3. 3-(4-Methoxy-2-methylphenyl)benzo[g]isoquinoline-5,10-dione (**1c**).* Isolated with 95% yield after purification over a short silica column (PE/EtOAc, 4/1) to remove traces of CAN. Mp 197.5–198.5 °C. Yellow powder. ^{1}H NMR (250 MHz, $CDCl_3$): δ_H 2.49 (3H, s, CH_3), 3.87 (3H, s, OCH_3), 6.86 (1H, s, H-3), 7.84–7.89 (2H, m, H-7, H-8), 8.18 (1H, s, H-4), 8.27–8.38 (2H, m, H-6, H-9), 9.61 (1H, s, H-1). ^{13}C NMR (63 MHz, $CDCl_3$): δ_C 21.1 (CH_3), 29.7 (C-2′), 55.3 (OCH_3), 111.7 (C-3′), 116.8 (C-5′), 127.3 (C-7), 127.4 (C-8), 131.6 (C-4, C-6), 133.2 (C_q), 133.3 (C_q), 134.4 (C-6), 135.0 (C-9), 138.3 (C_q), 138.6 (C_q), 149.4 (C-1), 160.6 (2×C_q), 165.7 (C-4′), 182.4 (C=O), 182.9 (C=O). IR (ATR): ν_{max} 711, 923, 1117, 1249, 1293, 1328, 1578, 1671 cm^{-1}. MS (ES$^+$) *m*/*z* (%): 330 (M+H$^+$, 40), 238 (40), 200 (65). HRMS (ESI): calcd for $C_{21}H_{15}NO_3$+H$^+$: 330.3561; found 330.3555.

*4.9.4. 3-p-Tolylbenzo[g]isoquinoline-5,10-dione (**1d**).* Isolated with 98% yield after purification over a short silica column (PE/EtOAc, 4/1) to remove traces of CAN. Mp 190.8–191.2 °C (lit.,[7] 192–193 °C). Yellow powder. The spectral data are, within the experimental error, in accordance with the literature.[7] ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 2.36 (3H, s, CH_3), 7.26 (2H, d, *J* 7.8, H-2′, H-6′), 7.76 (1H, pseudo t, *J* 7.7, H-7), 7.80 (1H, pseudo t, *J* 7.7, H-8), 8.01 (2H, d, *J* 8.0, H-3′, H-5′), 8.24 (1H, d, *J* 7.5, H-6), 8.26 (1H, d, *J* 7.3, H-9), 8.38 (1H, s, H-4), 9.50 (1H, s, H-1). ^{13}C NMR (126 MHz, $CDCl_3$): δ_C 20.5 (CH_3), 114.1 (CH_{ar}), 123.4 (C_q), 126.3 (CH_{ar}), 126.4 (CH_{ar}), 126.5 (CH_{ar}), 126.5 (CH_{ar}), 128.9 (2×CH_{ar}), 132.2 (C_q), 132.3 (C_q), 133.4 (CH_{ar}), 133.8 (C_q), 134.0 (CH_{ar}), 138.2 (C_q), 140.3 (C_q), 148.9 (CH_{ar}), 161.7 (CH_{ar}), 181.2 (CO), 181.8 (CO). IR (ATR): ν_{max} 704, 717, 742, 820, 924, 1298, 1584, 1668 cm^{-1}. MS (ES$^+$) *m*/*z* (%): 300 (M+H$^+$, 100).

*4.9.5. 3-(Methoxymethyl)benzo[g]isoquinoline-5,10-dione (**1e**).* Isolated with 98% yield after purification over a short silica

column (PE/EtOAc, 4/1) to remove traces of CAN. Mp 114.6–116.6 °C. Yellow powder. ^{1}H NMR (250 MHz, $CDCl_3$): δ_H 3.57 (3H, s, OCH_3), 4.76 (2H, s, CH_2) 7.84–7.91 (2H, m, H-7, H-8), 8.21 (1H, s, H-4), 8.30–8.36 (2H, m, H-6, H-9), 9.50 (1H, s, H-1). ^{13}C NMR (63 MHz, $CDCl_3$): δ_C 59.2 (OCH_3), 75.1 (CH_2), 116.3 (CH_{ar}), 125.3 (CH_{ar}), 127.3 (CH_{ar}), 127.4 (CH_{ar}), 133.1 (C_q), 133.2 (C_q), 134.5 (2×CH_{ar}), 135.0 (2×CH_{ar}), 139.1 (C_q), 149.4 (CH_{ar}), 165.8 (C_q), 182.4 (C=O), 182.6 (C=O). IR (ATR): ν_{max} 707, 927, 1106, 1121, 1295, 1586, 1677 cm^{-1}. MS (ES$^+$) m/z (%): 254 (M+H$^+$, 100). HRMS (ESI): calcd for $C_{15}H_{11}NO_3$+H$^+$: 254.2601; found 254.2620.

*4.9.6. 3-Cyclohexylbenzo[g]isoquinoline-5,10-dione (**1f**).* Isolated with 98% yield after purification over a short silica column (PE/EtOAc, 4/1) to remove traces of CAN. Mp 157.6–159.2 °C. Yellow powder. ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 1.26–1.81 (6H, m, $(CH_2)_3$), 1.90–1.93 (2H, m, CH_2), 2.02–2.04 (2H, m, CH_2), 2.92–2.99 (1H, m, H-1′), 7.84 (1H, d×pseudo t, J 1.1 and 5.9, H-7), 7.86 (1H, d×pseudo t, J 1.3 and 7.6, H-8) 7.93 (1H, s, H-4), 8.32 (1H, dd, J 1.2 and 8.6, H-6), 8.32 (1H, dd, J 1.2 and 8.6, H-9), 9.48 (1H, s, H-1). ^{13}C NMR (63 MHz, $CDCl_3$): δ_C 25.9 (C-4′), 26.3 (C-3′ and C-5′), 32.6 (C-2′ and C-6′), 47.3 (C-1′), 116.3 (C-4), 124.4 (C_q), 127.3 (2×CH_{ar}), 133.2 (2×C_q), 134.4 (CH_{ar}), 134.9 (CH_{ar}), 138.9 (C_q), 149.4 (C-1), 173.7 (C-3), 182.5 (C=O), 183.1 (C=O). IR (ATR): ν_{max} 712, 928, 1309, 1327, 1584, 1679, 2920 cm^{-1}. MS (ES$^+$) m/z (%): 292 (M+H$^+$, 100). HRMS (ESI): calcd for $C_{19}H_{17}NO_2$+H$^+$: 292.3512; found 292.3498.

*4.9.7. 3-(Diethoxymethyl)benzo[g]isoquinoline-5,10-dione (**1g**).* Isolated with 98% yield after purification over a short Al_2O_3 column (PE/EtOAc, 9/1) to remove traces of CAN. Mp 118.8–119.8 °C. Brown powder. ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 1.29 (6H, t, J 7.0, 2×CH_3), 3.66–3.78 (4H, m, 2×CH_2), 5.62 (1H, s, CH), 7.87 (1H, d pseudo t, J 1.5 and 7.0, H-7), 7.88 (1H, d×pseudo t, J 1.5 and 7.0, H-8), 8.33 (1H, dd, J 2.0 and 5.0, H-6), 8.35 (1H, dd, J 2.0 and 5.0, H-9), 8.37 (1H, s, H-4), 9.54 (1H, s, H-1). ^{13}C NMR (63 MHz, $CDCl_3$): δ_C 15.2 (2×CH_3), 62.5 (2×CH_2), 101.8 (CH), 116.9 (CH_{ar}), 126.0 (C_q), 127.3 (CH_{ar}), 127.5 (CH_{ar}), 133.1 (C_q), 133.2 (C_q), 134.6 (CH_{ar}), 135.0 (CH_{ar}), 139.2 (C_q), 149.3 (CH_{ar}), 164.7 (C_q), 182.3 (C=O), 182.5 (C=O). IR (ATR): ν_{max} 706, 924, 1288, 1584, 1676 cm^{-1}. MS (ES$^+$) m/z (%): 312 (M+H$^+$, 100), 307 (45), 266 (38), 238 (37). HRMS (ESI): calcd for $C_{18}H_{17}NO_4$+H$^+$: 312.3393; found 312.3379.

*4.9.8. 5,10-Dioxobenzo[g]isoquinoline-3-carbaldehyde (**1l**).* Isolated with 98% yield after purification over a short silica column (PE/EtOAc, 4/1) to remove traces of CAN. Mp 173.0–173.8 °C. Brown powder. ^{1}H NMR (250 MHz, $CDCl_3$): δ_H 7.90–7.94 (2H, m, H-7, H-8), 8.36–8.40 (2H, m, H-6, H-9), 8.71 (1H, s, H-4), 9.72 (1H, s, H-1), 10.3 (1H, s, CHO). ^{13}C NMR (63 MHz, $CDCl_3$): δ_C 117.7 (C-4), 127.6 (CH_{ar}), 127.7 (CH_{ar}), 133.0 (C_q), 135.1 (CH_{ar}), 135.5 (CH_{ar}), 150.4 (C-1), 181.5 (C=O), 181.9 (C=O), 191.9 (CHO). IR (ATR): ν_{max} 708, 764, 927, 1196, 1286, 1581, 1676, 1719 cm^{-1}. MS (ES$^+$) m/z (%): 238 (M+H$^+$, 100). HRMS (ESI): calcd for $C_{14}H_7NO_3$+H$^+$: 238.0499; found 238.0514.

Acknowledgements

We gratefully acknowledge the Research Foundation—Flanders (FWO-Vlaanderen) and the IWT for financial support of this research.

Supplementary data

Copies of ^{1}H NMR and ^{13}C NMR spectra for compounds **1a**–**g**, **1l**, **2a**–**h**, **2l**, **4**, **7a**, **7f**, **7g**, **7i**, **10a**, **10b**, **11** and **13f** are included in the Supplementary data. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2011.01.074. These data include MOL files and InChiKeys of the most important compounds described in this article.

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