Synthesis of 4-Arylsulfonylquinolines by Double Condensation of Allyl Aryl Sulfones with Nitroarenes

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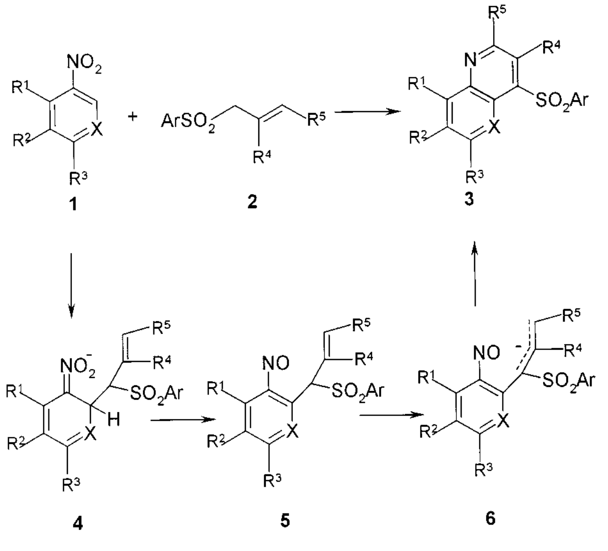
Allyl aryl sulfones **2** react with aryl nitrocompounds **1** in a DBU/MgCl2 system giving the 4-arylsulfonyl quinolines **3**. Some mechanistic aspects of the reaction are discussed. Application of this reaction to the formal total synthesis of the natural product (−)-*Eupolauramine* is described.

Introduction

The addition of a nucleophilic agent to an aromatic nitro compound leads to the σ^H adduct which can be stabilized in a variety of ways.[1] One of the stabilization pathways involves the reduction of a nitro to a nitroso compound which, being a very reactive intermediate, usually undergoes further transformations as reported for the reaction of nitroarenes with arylacetonitriles,[2–4] cyanide anion,[5] dimethyl phosphite[6,7] or Grignard reagents.[8] Recently we reported a new transformation from the reaction of nitroarenes and cinnamyl aryl sulfones under the influence of base and Lewis acid or a silylating agent leading to 2-aryl-4-arylsulfonylquinoline derivatives.[9,10] The reaction probably proceeds via the mechanistic pathway shown in Scheme1.



Scheme 1. Proposed mechanistic pathway for the reaction of nitroarenes with allyl aryl sulfones

Base-catalysed formation of the σ^H adduct **4**, followed by the loss of hydroxide anion (probably silane or Lewis acid mediated), leads to the nitroso compound **5** which undergoes an intramolecular cyclization and aromatization to give the product **3**. This procedure, which was successful for cinnamyl sulfones (**2**, R^5 = Ar), gave only very poor results in the case of allyl sulfones (**2**, R^5 = H, alkyl). Further investigations revealed that 1-nitronaphthalene **(1a)** reacts with allyl 4-tolyl sulfone **(2a)** in the presence of 10 equiv. of $MgCl_2$ and 5 equiv. of DBU in HMPA to give 4-tolylsulfonylbenzo[*h*]quinoline **(3a)** in 48% yield. The reaction is less effective in other solvents such as *N*-methylpyrrolidone, DMF, DMSO, pyridine or acetonitrile. It was also discovered that the amount of $MgCl_2$ can be reduced to 0.625 equiv. Addition of 1.25−5.0 equiv. of bis(trimethylsilyl)-acetamide (BIMSA) slightly increased the product yield to between 55 and 58%. The reaction did not proceed in the absence of $MgCl_2$. Other salts, such as LiCl, $ZnCl_2$, CuCl and $CaCl_2$, were found to be ineffective. Of the Lewis acids tested as catalysts only $Ti(i\text{OPr})_4$ exhibits similar activity to $MgCl_2$. Its role has however not been explained until now. There is a probability that chelation of the nitro group oxygens with $MgCl_2$ facilitates both formation of the σ^H adduct **4** and its further conversion into the nitroso intermediate **5**. This supposition was strongly supported in the reaction of **1a** with methyl phenyl acetate **(7)**, where the nitroso derivative **8** could be isolated as its oxime tautomer **9** (Scheme 2). Oximes similar to **9** (with a cyano instead of ester group) have been reported by Davis et al. to be formed in the reaction of aromatic nitro compounds with aryl acetonitriles in the presence of a base in a protic solvent.[3] The presence of a protic solvent was essential in the reaction process as it was assumed that it protonates the σ^H adduct before its conversion into the nitroso compound via the loss of a water molecule. In aprotic solvents the formation of other products was observed. Lewis acids in aprotic solvents can react in the same manner. In this case the nucleophilic agent enters exclusively at the *para* position in relation to the nitro group; hence amine **10** was isolated after the reduction with Zn in acetic acid without evidence for the formation of amide **11**.

A variety of nitroarenes were treated similarly with allyl aryl sulfones to give the corresponding quinolines in moderate yields (see Table 1). The reaction proceeds effectively with activated aromatic nitro compounds such as bicyclic and heterocyclic nitroarenes. Unfortunately, reaction with

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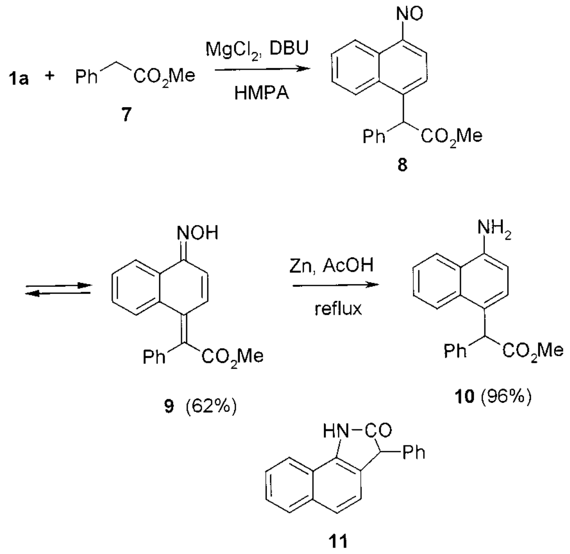
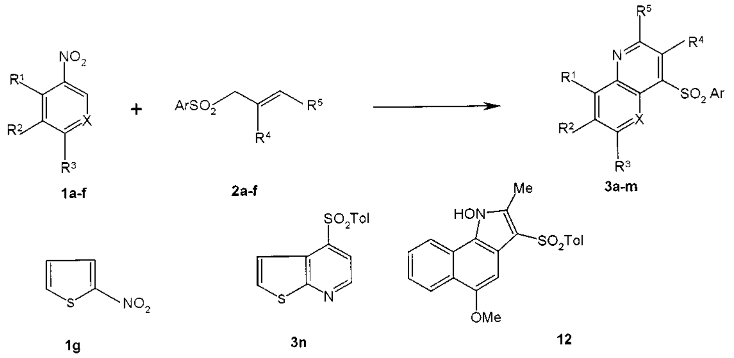


Scheme 2. Formation of the nitroso compound **8** in the reaction of 1-nitronaphthalene **1a** with methyl phenylacetate (**7**)

3-nitrobenzonitrile, which is supposed to be the most electrophilic of the series, was fast and led only to tars under the conditions A or B specified in Table 1. However, a reverse addition of the substrates and short time of the reaction resulted in formation of 7-cyano-4-(4-methylphenyl)sulfonylquinoline **(3m)**, albeit in low yield.

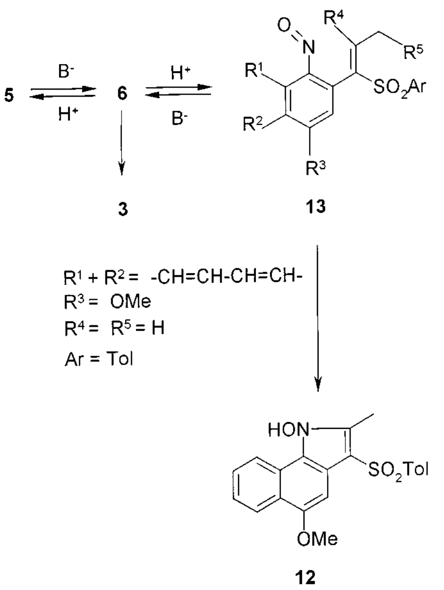
In the reaction of 4-methoxynitronaphthalene **(1b)** with **2a**, apart from the anticipated quinoline **3g** a considerable amount of 1-hydroxy-5-methoxy-2-methyl-3-tolylsulfonylbenzo[*g*]indole **(12)**, which resulted from five-membered ring closure, was obtained. This result can be explained on the base of Scheme 1. The nitroso intermediate **5**, with an unsaturated β,γ double bond, may exist in equilibrium with its α,β unsaturated isomer **13** via carbanion **6** (Scheme 3). Both **5** and **13** can give **6** (then **3**) when treated with a base, but an intramolecular cyclization to **12**, probably an electrocyclic reaction,[11] is possible only from the isomer **13**. The presence of an electron-donating OMe substituent weakens the electrophilic character of the nitroso group and lowers the acidity of the whole system thus directing the reaction towards **12**.

Table 1. Reaction of nitroarenes **1** with allylic sulfones **2** in selected systems



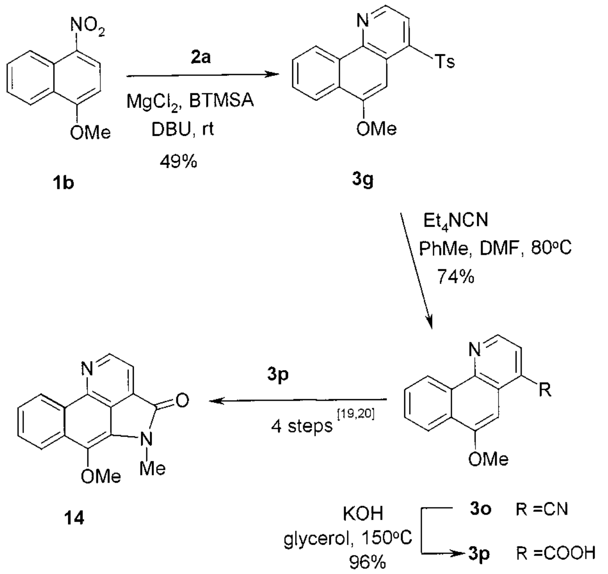
	Substrates	X	R1	R2	R3	R4	R5	Ar	System[a]	Time[b]	Prod.	Yield[%][c]
1	**1a+2a**	CH	CH=CH-CH=CH		H	H	H	4-Tol	A(B)	2d(6d)	**3a**	60 (48)
2	**1a+2b**	CH	CH=CH-CH=CH		H	H	H	Ph	B	6d	**3b**	52
3	**1a+2c**	CH	CH=CH-CH=CH		H	H	H	$4\text{-}FC_6H_4$	B	6d	**3c**	43
4	**1a+2d**	CH	CH=CH-CH=CH		H	Me	H	4-Tol	A	2d	**3d**	35
5	**1a+2e**	CH	CH=CH-CH=CH		H	H	Me	4-Tol	A(B)	2d(6d)	**3e**	53 (35)
6	**1a+2f**	CH	CH=CH-CH=CH		H	H	Ph	Ph	A	2d	**3f**	72
7	**1b+2a**	CH	CH=CH-CH=CH		OMe	H	H	4-Tol	A	2d	**3g**	35[d]
8	**1c+2a**	CH	H	H	Cl	H	Me	4-Tol	A	2d	**3h**	33
9	**1d+2a**	CH	CH=CH-CH=N		H	H	H	4-Tol	A	2d	**3i**	49
10	**1d+2e**	CH	CH=CH-CH=N		H	H	Me	4-Tol	A	2d	**3j**	27
11	**1e+2a**	N	H	H	OMe	H	H	4-Tol	A(B)	2d(6d)	**3k**	35 (27)
12	**1a+2e**	N	H	H	OMe	H	Me	4-Tol	A(B)	2d(6d)	**3l**	48 (41)
13	**1f+2a**	CH	H	CN	H	H	H	4-Tol	C	10min.	**3m**	13
14	**1g+2a**	See formula above				H	H	4-Tol	A	2d	**3n**	45

[a] A: **1** (1 mmol), **2** (1 mmol), $MgCl_2$ (0.625 mmol), BTMSA (2.5 mmol),DBU (5 mmol), HMPA (1.25 mL); B: **1** (1 mmol), **2** (1 mmol), $MgCl_2$ (10 mmol), DBU (5 mmol), HMPA (5 mL); C: like A but **1** + **2** added to other reagents. – [b] d = days. – [c] Isolated by column chromatography. – [d] Can be improved, see Scheme 4; 14% of **12** was isolated as a by-product.



Scheme 3. Intramolecular six- versus five-membered ring closure of the intermediate **6**

Bearing in mind that the yields of the present reaction are moderate, the process may be nevertheless useful in the chemistry of heterocycles because of its simplicity. To illustrate this, a formal total synthesis of the natural product *Eupolauramine*[12,13] **14** was performed (Scheme 4).



Scheme 4. Formal total synthesis of *Eupolauramine*

4-Methoxynitronaphthalene **(1b)** reacts with allyl 4-tolyl sulfone **(2a)** to give 6-methoxy-4-(4-methylphenyl)sulfonylbenzo[*h*]quinoline **(3g)** in 35% yield (which can be increased to 49% by the addition of two portions of **2a** in excess) together with 16% of 1-hydroxy-5-methoxy-2-(4-methylphenyl)sulfonylbenzo[*g*]indole **(12)** as a by-product. Replacement of the 4-tolyl-sulfonyl group by cyano (tetraethylammonium cyanide in a toluene/DMF solution at 80 °C) led to the 4-cyano-6-methoxybenzo[*h*]quinoline **(3o)** in 74% yield. The acid **3p** was obtained almost quantitatively by subjecting **3o** firstly to a basic hydrolysis at elevated temperature (following the procedure elaborated by Peng et al.[14]) and then to acidification. This compound has previously been described in the literature[12,13] and can be transformed into *Eupolauramine* **14** in four steps.

Experimental Section

General: Melting points are uncorrected. ^1H NMR spectra were recorded with a Varian Gemini (200 M Hz) in [D_6]DMSO solutions. Chemical shifts are expressed in ppm with reference to TMS as an internal standard. Coupling constants are given in Hz. Mass spectra were obtained with a ADM-604 (ADM Intectra GmbH Germany). Column chromatography was performed on silica gel 240–400 mesh (Merck). Reagents were used in commercially available form. Solvents were purified and dried according to common procedures. Nitroarenes, allyl phenyl sulfone **2b** and methyl phenyl acetate **(7)** were commercially available. Sulfones **2a,**[15] **2c,**[16] **2d,**[17] **2e**[18] and **2g**[10] were prepared according to known procedures.

Reaction of 1-Nitronaphthalene (1a) with Methyl Phenyl Acetate (7): A mixture of 1-nitronaphthalene **(1a)** (173 mg, 1 mmol), methyl phenyl acetate **(7)** (165 mg, 1.1 mmol) and $MgCl_2$ (238 mg, 2.5 mmol) in HMPA (2.5 mL) was treated with DBU (746 µL, 5 mmol) and stirred for 3 days at room temperature. After pouring into dilute aqueous acetic acid, extraction with ethyl acetate and chromatography, oxime **9** was isolated as the main product (175 mg, 62%) as yellow crystals, m.p. 146–147°C. – ^1H NMR showed 2 isomers (2:3 ratio): major: δ = 3.74 (s, 1 H), 6.83–7.59 (sets of m, 10 H), 8.10–8.19 (m, 1 H), 11.98 (s, 1 H). – minor: δ = 3.79 (s, 1 H), 6.83–7.59 (sets of m, 10 H), 8.03–8.09 (m, 1 H), 12.01 (s, 1 H). – MS *m/z* (%): 306 (21.2), 305 (100.0), 389 (12.6), 274 (16.5), 256 (17.3), 246 (14.9), 245 (19.5), 230 (14.2), 229 (29.8). – HRMS $C_{19}H_{15}NO_3$: calcd. 305.1052; found 305.1044.

Oxime **9** (30 mg, 0.1 mmol) and Zn dust (65 mg, 1 mmol) were refluxed in glacial acetic acid (1 mL) for 20 min, then cooled, neutralized cautiously with aq. $NaHCO_3$, extracted with ethyl acetate and chromatographed to yield amino ester **10** (25 mg, 96%) as orange crystals, m.p. 126–127°C. – ^1H NMR: δ = 3.66 (s, 3 H), 5.71 (s, 1 H), 5.76 (broad s, 2 H), 6.63 (d, J = 7.9 Hz, 1 H), 6.98 (d, J = 7.9 Hz, 1 H), 7.18–7.46 (m, 7 H), 7.80–7.90 (m, 1 H), 8.05–8.15 (m, 1 H). – MS *m/z* (%): 292 (9.1), 291 (41.5), 233 (19.9), 232 (100.0), 230 (13.7), 215 (17.2). – HRMS $C_{19}H_{17}NO_2$: calcd. 291.1259; found 291.1259.

Reactions of Nitroarenes with Allyl Sulfones (Table 1). – Procedure A: A mixture of nitroarene (1 mmol), allyl sulfone (1.1 mmol), $MgCl_2$ (60 mg, 0.625 mmol) and BTMSA (642 µL, 2.5 mmol) in HMPA (1.25 mL) was stirred at room temperature for 20 min. then treated with DBU (746 µL, 5.0 mmol) and stirred at room temperature for two days. After completion (TLC control) the reaction mixture was placed on the top of chromatography column and separated with toluene (entry 1, 8, 9) or hexane/ethyl acetate mixtures as eluents.

Procedure B: A mixture of nitroarene (1 mmol), allyl aryl sulfone (1.1 mmol) and $MgCl_2$ (952 mg, 10 mmol) in HMPA (5 mL) was stirred at room temperature for 20 min. then treated with DBU (746 µL, 5 mmol) and stirred at room temperature for six days. After pouring onto saturated aq. NH_4Cl solution, extraction with ethyl acetate (5 × 20 mL), washing the extract with dil. NaCl solution and drying with $MgSO_4$ the product was isolated by column chromatography.

Procedure C: A solution of **1f** (148 mg, 1 mmol) and **2a** (216 mg, 1.1 mmol) in HMPA (2.5 mL) was added within 5 min to a solution of $MgCl_2$ (60 mg, 0.625 mmol), BTMSA (642 µL, 2.5 mmol) and DBU (746 µL, 5 mmol) in HMPA (2.5 mL) at room temperature. After 5 min. stirring the mixture was worked up as in procedure B.

4-(4-Methylphenyl)sulfonylbenzo[*h*]quinoline (3a): Yield 60%, procedure A; yellow powder, m.p. 160−163°C (1,2-dichloroethane/ethyl acetate). − ^{1}H NMR: δ = 2.35 (s, 3 H), 7.45 (app d, J ≈ 8.5 Hz, 2 H), 7.80−7.84 (m, 2 H), 7.97 (app d, J ≈ 8.5 Hz, 2 H), 8.05−8.08 (m, 1 H), 8.13 (d, J = 9.2 Hz, 1 H), 8.35 (d, J = 4.6 Hz, 1 H), 8.47 (d, J = 9.2 Hz, 1 H), 9.19−9.24 (m, 1 H), 9.32 (d, J = 4.6, 1 H). − MS *m*/*z* (%): 335 (7.3), 334 (22.8), 333 (100.0), 269 (28.0), 268 (38.8), 254 (33.4), 177 (15.0), 151 (21.9). − $C_{20}H_{15}NO_2S$ (333.41): calcd. C 72.05, H 4.53, N 4.20; found C 71.99, H 4.39, N 3.87.

4-Phenylsulfonylbenzo[*h*]quinoline (3b): Yield 52%, procedure B; fine yellow crystals, m.p. 153−156°C (1,2-dichloroethane/hexane). − ^{1}H NMR: δ = 7.61−7.88 (m, 5 H), 8.04−8.15 (m, 4 H), 8.39 (d, J = 4.6 Hz, 1 H), 8.47 (d, J = 9.3 Hz, 1 H), 9.17−9.26 (m, 1 H), 9.34 (d, J = 4.6 Hz, 1 H). − MS *m*/*z* (%): 321 (7.2), 320 (21.7), 319 (100.0), 256 (5.2), 255 (26.7), 254 (50.6), 178 (9.7), 166 (7.9), 151 (10.9). − HRMS $C_{19}H_{13}NO_2S$: calcd. 319.0667; found 319.0666.

4-(4-Fluorophenyl)sulfonylbenzo[*h*]quinoline (3c): Yield 43%, procedure B; fine yellow crystals, m.p. 154−155°C (ethyl acetate/hexane). − ^{1}H NMR: δ = 7.50 (app t, J ≈ 9.0 Hz, 2 H), 7.80−7.88 (m, 2 H), 8.06−8.14 (m, 1 H), 8.16−8.26 (m, 2 H), 8.37 (d, J = 4.6 Hz, 1 H), 8.47 (d, J = 9.3 Hz, 1 H), 9.18−9.26 (m, 1 H), 9.34 (d, J = 4.6 Hz, 1 H). − MS *m*/*z* (%): 339 (7.2), 338 (21.8), 337 (100.0), 273 (39.5), 272 (71.7), 178 (24.4), 166 (18.5), 151 (32.4), 150 (17.8). − HRMS $C_{19}H_{12}FNO_2S$: calcd. 337.073; found 337.0582.

3-Methyl-4-(4-methylphenyl)sulfonylbenzo[*h*]quinoline (3d): Yield 35%, procedure A; fine yellow crystals, m.p. 142−145°C. − ^{1}H NMR: δ = 2.34 (s, 3 H), 2.95 (s, 3 H), 7.42 (app d, J ≈ 8.5 Hz, 2 H), 7.75−7.84 (m, 2 H), 7.90 (app d, J ≈ 8.5 Hz, 2 H), 7.99−8.08 (m, 2 H), 8.75 (d, J = 9.6 Hz, 1 H), 9.13 (s, 1 H), 9.15−9.22 (m, 1 H). − MS *m*/*z* (%): 349 (7.5), 348 (23.8), 347 (100.0), 284 (12.8), 283 (58.9), 282 (82.1), 269 (21.3), 268 (95.0), 192 (21.3), 190 (19.5). − HRMS $C_{21}H_{17}NO_2S$: calcd. 347.0980; found 347.0976. − calcd. C 72.60, H 4.93, N 4.03; found 72.05, H 4.53, N 4.10.

2-Methyl-4-(4-methylphenyl)sulfonylbenzo[*h*]quinoline (3e): Yield 53%, procedure A; m.p. 178−181°C (ethyl acetate/hexane). − ^{1}H NMR: δ = 2.34 (s, 3 H), 2.92 (s, 3 H), 7.42 (app. d, J ≈ 8.5 Hz, 2 H), 7.70−7.84 (m, 2 H), 7.94−8.08 (m, 4 H), 8.30 (s, 1 H), 8.41 (d, J = 9.3 Hz, 1 H), 9.15−9.22 (m, 1 H). − MS *m*/*z* (%): 349 (7.7), 348 (25.3), 347 (100.0). 283 (16.1), 282 (21.9), 269 (7.4), 268 (31.6), 192 (17.3), 191 (11.1), 180 (10.6), 151 (23.3). − $C_{21}H_{17}NO_2S$ (347.10): calcd. C 72.60, H 4.93, N 4.03; found C 72.66, H 4.75, N 3.91.

2-Phenyl-4-phenylsulfonylbenzo[*h*]quinoline (3f): Yield 72%, procedure A; fine yellow crystals, m.p. 226−228°C (1,2-dichloroethane), ref.[10] m.p. 227−228°C.

6-Methoxy-4-(4-methylphenyl)sulfonylbenzo[*h*]quinoline (3g): Yield 35%, procedure A; m.p. 206−208°C (ethyl acetate/hexane). − ^{1}H NMR: δ = 2.35 (s, 3 H), 4.07 (s, 3 H), 7.34−7.49 (m, 2 H), 7.63 (s,1 H), 7.79−7.89 (m. 2 H), 7.94−8.01 (m, 2 H), 8.20−8.30 (m, 1 H), 8.33 (d, J = 4.7 Hz, 1 H), 9.13 (d, J = 4.7 Hz, 1 H), 9.14−9.22 (m, 1 H). − MS *m*/*z* (%): 365 (8.1), 364 (24.2), 363 (100.0), 299 (12.3), 284 (16.7), 283 (5.1), 269 (28.3), 268 (74.8), 267 (8.5), 241 (5.2). − $C_{21}H_{17}NO_3S$ (363.10): calcd. C 69.40, H 4.71, N 3.85; found C 69.34, H 4.54, N 3.81.

6-Chloro-2-methyl-4-(4-methylphenyl)sulfonylquinoline (3h): Yield 33%, procedure A; fine light brownish crystals, m.p. 188−189°C (ethyl acetate). − ^{1}H NMR: δ = 2.37 (s, 3 H), 2.80 (s, 3 H), 7.44−7.49 (m, 2 H), 7.84 (dd, J = 9.0, 2.3 Hz, 1 H), 8.09 (d, J = 9.0 Hz, 1 H), 8.21 (s, 1 H), 8.42 (d, J = 2.3 Hz, 1 H). − MS *m*/*z* (%): 333 (12.5), 332 (6.7), 331 (32.9), 233 (19.3), 232 (100.0), 231 (6.7), 176 (6.4). − $C_{17}H_{14}ClNO_2S$ (331.82): calcd. C 61.53, H 4.25, N 4.22; found C 61.34, H 4.11, N 3.77.

4-(4-Methylphenyl)sulfonylpyrido[3,2-*h*]quinoline (3i): Yield 49%, procedure A; off white crystals, m.p. 239−241°C (1,2-dichloroethane/ethyl acetate). − ^{1}H NMR: δ = 2.36 (s, 3 H), 7.47 (app d, J ≈ 8.5 Hz, 2 H), 7.85 (dd, J = 8.4, 4.4 Hz, 1 H), 8.00 (app d, J ≈ 8.5 Hz, 2 H), 8.22 (dd, J = 9.6, 0.6 Hz, 1 H), 8.40 (d, J = 4.6 Hz, 1 H), 8.75 (d, J = 9.6 Hz, 1 H), 9.13 (dd, J = 4.4, 1.7 Hz, 1 H), 9.38 (d, J = 4.6 Hz, 1 H), 9.50 (ddd, J = 8.4, 1.7, 0.7 Hz, 1 H). − MS *m*/*z* (%): 336 (7.5), 335 (22.9), 334 (100.0), 333 (6.8), 271 (7.4), 270 (40.7), 269 (83.5), 268 (6.5), 256 (16.8), 255 (82.1), 179 (15.4), 152 (34.3). − $C_{19}H_{14}N_2O_2S$ (334.39): calcd. C 68.24, H 4.22, N 8.31; found C 68.08, H 4.04, N 8.43.

2-Methyl-4-(4-methylphenyl)sulfonylpyrido[3,2-*h*]quinoline (3j): Yield 27%, procedure A; off white crystals, m.p. 216−218°C (ethyl acetate). − ^{1}H NMR: δ = 2.35 (s, 3 H), 2.94 (s, 3 H), 7.46 (app d, J ≈ 8.5 Hz, 2 H), 7.80 (dd, J = 8.4, 4.4 Hz, 1 H), 7.99 (app d, J ≈ 8.5 Hz, 2 H), 8.12 (d, J = 9.6 Hz, 1 H), 8.35 (s, 1 H), 8.68 (d, J = 9.6 Hz, 1 H), 9.09 (dd, J = 4.4, 1.7 Hz,1 H), 9.47 (ddd, J = 8.4, 1.7, 0.7 Hz, 1 H). − MS *m*/*z* (%): 350 (6.9), 349 (21.3), 348 (81.3), 284 (28.7), 283 (46.2), 270 (21.7), 269 (100.0), 243 (9.9), 193 (19.9), 192 (20.9). − HRMS $C_{20}H_{16}N_2O_2S$: calcd. 348.0933; found 348.0930.

6-Methoxy-4-(4-methylphenyl)sulfonylpyrido[3,2-*b*]pyridine (3k): Yield 35%, procedure A; off white crystals, m.p. 181−183°C. − ^{1}H NMR: δ = 2.37 (s,3 H), 3.92 (s, 3 H), 7.36 (d, J = 9.2 Hz, 1 H), 7.41 (app d, J ≈ 8.3 Hz, 2 H), 7.88 (app d, J ≈ 8.3 Hz, 2 H), 8.38 (d, J = 9.2 Hz, 1 H), 8.42 (d, J = 4.5 Hz, 1 H), 9.11 (d, J = 4.1 Hz, 1 H). − MS *m*/*z* (%): 313 (1.4), 251 (6.3), 250 (40.4), 249 (100.0), 235 (50.1). − $C_{16}H_{14}N_2O_3S$ (314.36): calcd. C 61.13, H 4.49, N 8.91; found C 61.15, H 4.51, N 8.73.

6-Methoxy-2-methyl-4-(4-methylphenyl)sulfonylpyrido[3,2-*b*]pyridine (3l): Yield 48%, procedure A; off white crystals, m.p. 191−196°C (ethyl acetate/hexane). − ^{1}H NMR: δ = 2.37 (s, 3 H), 2.79 (s, 3 H), 2.89 (s, 3 H), 7.25 (d, J = 9.1 Hz, 1 H), 7.42 (app d, J ≈ 8.5 Hz, 2 H), 7.95 (app d, J ≈ 8.5 Hz, 2 H), 8.26 (d, J = 9.1 Hz, 1 H), 8.31 (s,1 H). − MS *m*/*z* (%): 328 (1.1), 327 (1.8), 265 (7.7), 264 (46.4), 263 (100.0), 250 (8.5), 249 (48.3). − $C_{17}H_{16}N_2O_3S$ (328.39): calcd. C 62.18, H 4.91, N 8.53; found C 62.17, H 4.89, N 8.61.

7-Cyano-4-(4-methylphenyl)sulfonylquinoline (3m): Yield 13%, procedure A; fine pale-pink crystals, m.p. 208−210°C (ethyl acetate/hexane). − ^{1}H NMR: δ = 2.37 (s, 3 H), 7.46 (app d, J ≈ 8.5 Hz, 2 H), 7.98 (app d, J ≈ 8.5 Hz, 2 H), 8.08 (dd, J = 8.9, 1.7 Hz, 1 H), 8.38 (d, J = 4.4 Hz, 1 H), 8.71 (d, J = 8.9 Hz, 1 H), 8.78 (d, J = 1.7 Hz, 1 H), 9.36 (d, J = 4.4 Hz, 1 H). − MS *m*/*z* (%): 310 (7.1), 309 (21.3), 308 (100.0), 307 (19.9), 245 (13.1), 244 (73.9), 243 (89.2), 230 (17.6), 229 (94.3), 155 (10.3), 153 (18.7), 139 (43.9). − HRMS $C_{17}H_{12}N_2O_2S$: calcd. 308.0620; found 308.0627. − calcd. C 66.22, H 3.92, N 9.08; found C 65.80, H 3.54, N 8.94.

4-(4-Methylphenyl)sulfonylthieno[2,3-*b*]pyridine (3n): Yield 45%, procedure A; fine off-white crystals, m.p. 102−106°C (ethyl acetate/tetrachloromethane). − ^{1}H NMR: δ = 2.36 (s, 3 H), 7.42 (app d,

$J \approx 8.4$ Hz, 2 H), 7.83 (d, $J = 6.1$ Hz, 1 H), 7.88 (app d, $J \approx 8.4$ Hz, 2 H), 8.03 (d, $J = 4.9$ Hz, 1 H), 8.23 (d, $J = 6.1$ Hz, 1 H), 8.86 (d, $J = 4.9$ Hz, 1 H). − MS *m*/*z* (%): 291 (11.2), 290 (17.7), 289 (100.0), 225 (12.2), 224 (15.8), 210 (17.8), 139 (87.5). − HRMS $C_{14}H_{11}NO_2S_2$: calcd. 289.0231; found 289.0239.

Total Synthesis of Eupolauramine (14). Improved synthesis of 6-methoxy-4-(4-methylphenyl)sulfonylbenzo[*h*]quinoline (3g): A mixture of 4-methoxynitronaphthalene (**1b**) (4.06 g, 20 mmol), sulfone **2a** (3.92 g, 20 mmol) and $MgCl_2$ (1.19 g, 12.5 mmol) was stirred in HMPA (25 mL) and bis(trimethylsilyl)acetamide (12.8 mL, 50 mmol) for 20 min. and then DBU (14.9 mL, 100 mmol) was added in one portion. The reaction flask was stoppered and the mixture stirred at room temperature. After 24 h the second portion of solid sulfone **2a** (1.96 g, 10 mmol) was added and the stirring continued for 24 h. After pouring into aqueous NH_4Cl solution (150 mL), extraction with ethyl acetate (5 × 50 mL), washing the extracts with dil. NaCl solution (2 × 50 mL), drying with $MgSO_4$ and evaporation of the solvent the residue was treated with hot toluene (20 mL). After cooling 1.80 g of **3g** was filtered off. The mother liquor was concentrated and chromatographed with toluene as an eluent to give a further 1.73 g of **3g** (total amount 3.53 g, 49%) and **13a** (1.21 g, 16%).

1-Hydroxy-5-methoxy-2-methyl-3-(4-methylphenyl)sulfonylbenzo-[*g*]indole (13a): (16%), light brownish powder, m.p. 205−205°C, dec. (ethyl acetate). − ^{1}H NMR: $\delta = 2.32$ (s, 3 H), 2.71 (s, 3 H), 4.01 (s, 3 H), 7.35 (app. d, $J \approx 8.2$ Hz, 2 H), 7.37 (s, 1 H), 7.42−7.49 (m, 1 H), 7.57−7.65 (m, 1 H), 7.85 (app. d, $J \approx 8.2$ Hz, 2 H), 8.16−8.28 (m, 2 H), 12.63 (s, 1 H). − MS *m*/*z* (%): 367 (8.0), 366 (24.3), 365 (100.0), 286 (6.8), 285 (14.2), 271 (12.3). − HRMS $C_{21}H_{19}NO_3S_2$: calcd. 365.1086; found 365.1044. − calcd. C 66.12, H 5.02, N3.67; found 65.72, H 5.04, N 3.48.

6-Methoxybenzo[*h*]quinoline-4-carbonitrile (3o): A solution of sulfone **3g** (910 mg, 2,5 mmol) and tetraethylammonium cyanide (1.56 g, 10 mmol) in dry toluene (10 mL) and DMF (5 mL) was stirred and heated to 80°C in a sealed tube for 48 h. After cooling the reaction mixture was diluted with ethyl acetate (50 mL), washed with dil. NaCl solution, dried ($MgSO_4$), the solvent evaporated and product separated by column chromatography to give 435 mg of **3o** (74%) as fine pale-yellow crystals, m.p. 168−169°C (ethyl acetate). − ^{1}H NMR: $\delta = 4.14$ (s, 3 H), 7.06 (s, 1 H), 7.81−7.91 (m, 2 H), 8.09 (d, $J = 4.6$ Hz, 1 H), 8.23−8.32 (m, 1 H), 8.96 (d, $J = 4.6$ Hz, 1 H), 9.06−9.15 (m, 1 H). − MS *m*/*z* (%): 235 (17.3), 234 (100.0), 233 (16.3), 192 (11.4), 191 (74.9), 165 (5.4), 164 (15.2). − HRMS $C_{15}H_{10}N_2O$: calcd. 234.0792; found 234.0785. − calcd. C 76.91, H 4.30, N 11.96; found C 76.80, H 3.86, N 11.87.

6-Methoxybenzo[*h*]quinoline-4-carboxylic Acid (3p): Following the procedure described by Peng et al.[14] nitrile **3o** (500 mg, 2.136 mmol) was added to a solution of KOH (560 mg, 10 mmol) in glycerine (4 mL) and heated with stirring at 150°C for 8 h. After cooling the mixture was diluted with water (5 mL), filtered, the filtrate acidified with glacial acetic acid (3 mL) and the precipitate filtered off and dried over P_2O_5 under vacuum to give acid **3p** (516 mg, 96%): m.p. 262−265°C (acetic acid) ref.[12] m.p. 266−267°C (acetic acid). − ^{1}H NMR and MS spectra were in agreement with ref.[12]

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