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The first total synthesis of toddaquinoline, an alkaloid from *Toddalia asiatica*

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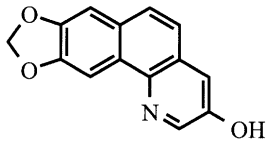
Abstract—The paper describes the first total synthesis of toddaquinoline, an alkaloid from the root bark of Formosan *Toddalia asiatica*. The key step is cobalt(I) mediated radial cyclisation to a pyridine. Cobalt appears to play a dual role in the reaction, firstly initialising homolysis of the carbon to halogen bond then acting as a Lewis acid to promote cyclisation to C-6. Other approaches examined are also outlined. These include a photocyclisation of an azastilbene; a cyclisation induced by halogen to metal exchange and a tin mediated radical cyclisation.

1. Background

In 1993, Chen et al. reported the isolation and characterisation of an unusual alkaloid found in the root bark of Formosan *Toddalia asiatica*,[1] a constituent of many Asian folk medicines.[2] Named toddaquinoline, its structure **1** was elucidated by a series of NMR and derivatisation experiments, and featured a unique tetracyclic skeleton. However, the low yield from natural sources coupled with the inevitable losses suffered during structural determination, left insufficient material to allow meaningful biological testing to be completed. Thus, toddaquinoline attracted our attention as a target for total synthesis.[3]



toddaquinoline **1**

2. A photocyclisation approach

The first strategy involved photocyclisation of an azastilbene, viz. **8**→**9**.[4] While this approach was convergent and did not require a specific alkene geometry for **8**, the mode of cyclisation was uncertain.[5] Our synthesis of azastilbene **8** was straightforward and began with 3,5-dibromopyridine **2**. Nucleophilic aromatic substitution of one of the aryl halides with methoxide gave **3** which,[6] on treatment with butyllithium and quenching with DMF, was readily transformed into aldehyde **4**.[6] A Wittig coupling with the ylid derived from **7** then gave a 1:1 mixture of *cis*- and *trans*-azastilbenes **8**. Unfortunately, when a cyclohexane solution of **8** was irradiated using a medium pressure lamp the major product given was benzo[*f*]isoquinoline **10** (54%), resulting from cyclisation between C-4 of the pyridine and C-6 of the benzo[1,3]dioxole.[5] Toddaquinoline methyl ether **9** was also isolated as a minor component in 20% yield together with 23% recovered azastilbenes **8** (Scheme 1).

3. Using an intramolecular addition of an aryllithium to a pyridine

Our second approach employed an intramolecular cyclisation induced by the addition of a polar organometallic species to the pyridine. In principle, this strategy would bias the reaction in favour of addition to the more electrophilic C-6 of the pyridine; the disadvantage being the need to control the alkene geometry.[7] To test its effectiveness we prepared the phosphonium salt **12** and coupled it with aldehyde **4** using standard Wittig chemistry.[8] Pleasingly, the resulting azastilbenes **13** and **14** were formed as a 2:5 mixture of diastereoisomers favouring the desired (*Z*)-alkene.

When a cooled THF solution of **14** was treated with *n*-BuLi two tetracyclic products were obtained. The major

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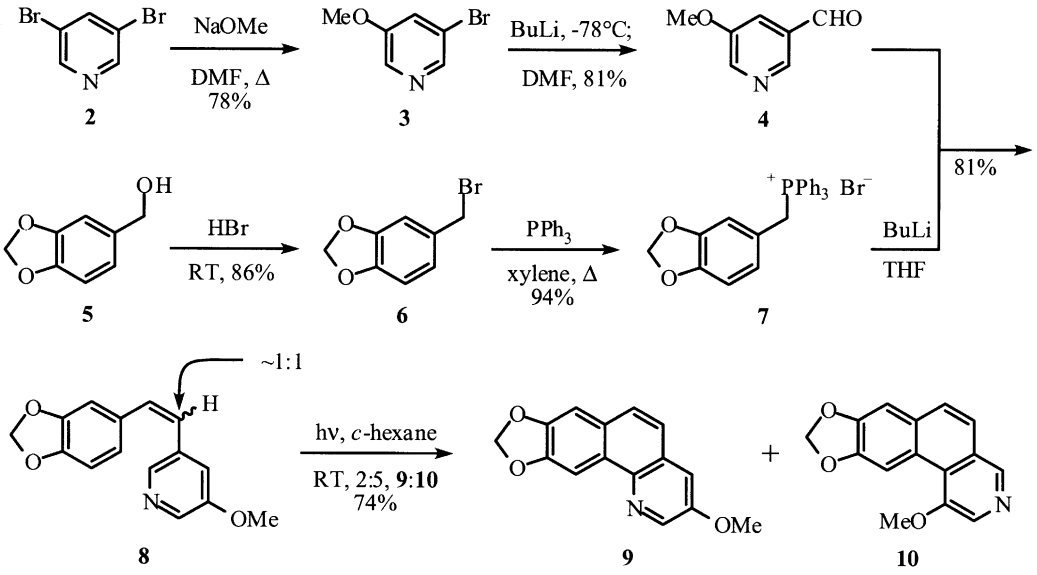


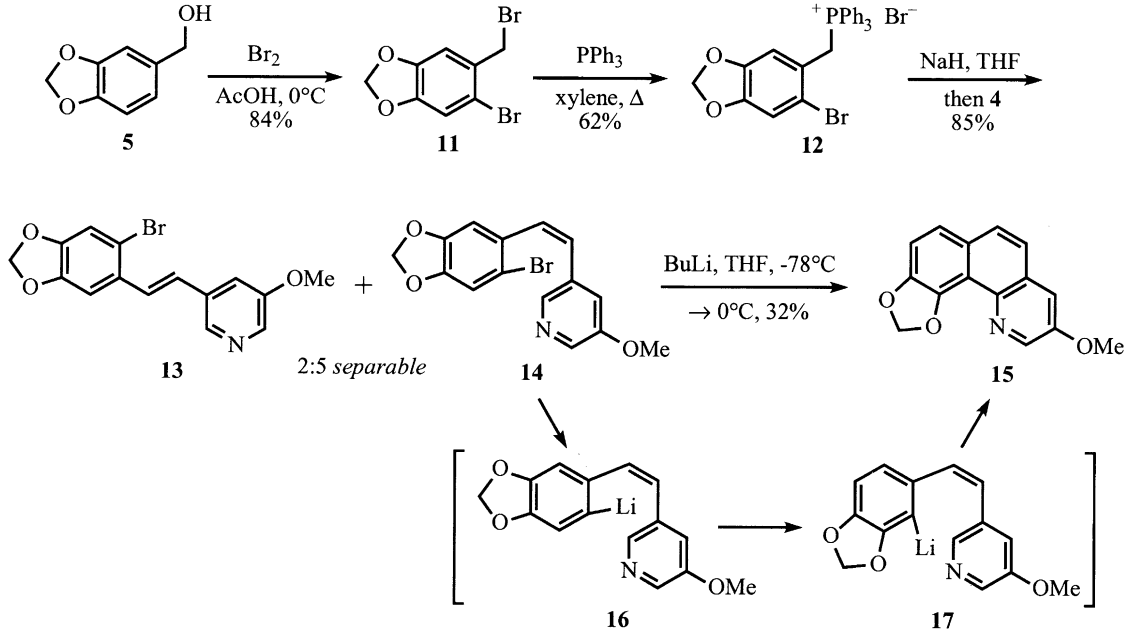
Scheme 1.

component proved to be rather unstable and, though this prevented full characterisation, it was clear that the reaction had followed an unexpected course. Indeed, analysis showed that a new carbon to carbon bond had been created between C-4 of the benzodioxole and C-6 of the pyridine moiety suggesting that the intermediate aryllithium **16** had equilibrated to the thermodynamically favoured aryllithium **17** (presumably via a dilithiated species) prior to cyclisation (Scheme 2).[9] The minor component, given in 11% yield, exhibited spectral characteristics identical to those reported for toddaquinoline methyl ether **9**.

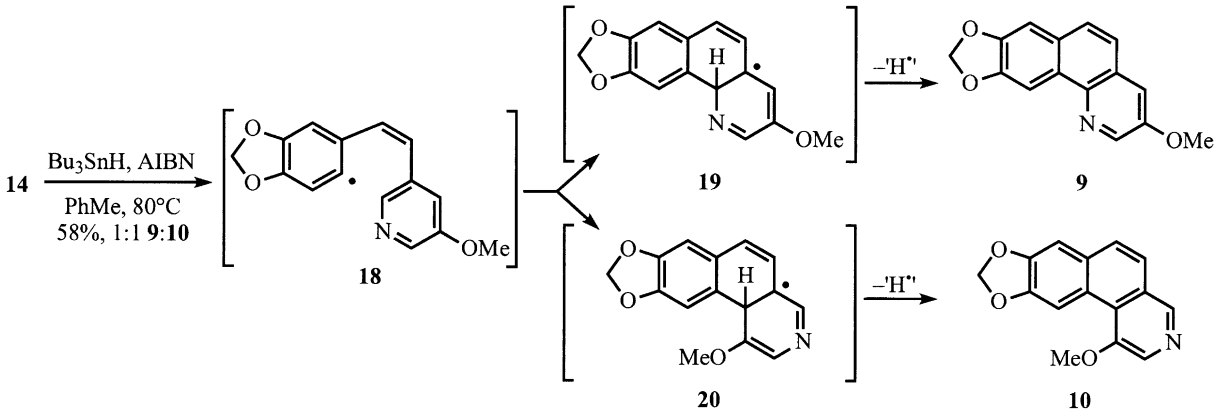
4. Radical approaches

We now sought a method of generating a reactive intermediate at C-6 of the benzodioxole that was not prone to rearrangement. Though intermolecular radical additions to pyridines were known to be inefficient,[10] the intramolecular variant had received scant attention.[11] It therefore seemed appropriate to examine this option. Gratifyingly, treatment of **14** under standard tin mediated radical cyclisation conditions led to a separable 1:1 mixture of benzo[*h*]-quinoline **9** and benzo[*f*]isoquinoline **10** in 58% yield. The less polar product was shown to be toddaquinoline methyl ether **9** through comparison of our spectral and physical data with those reported in the isolation paper.[1] Notably, though the reaction had been conducted under reducing conditions, no products derived from hydrogen atom transfer to the intermediates **19** or **20** were observed (Scheme 3).[12]

One disappointing feature of the aforementioned reaction was its lack of regiochemical control. In seeking to improve

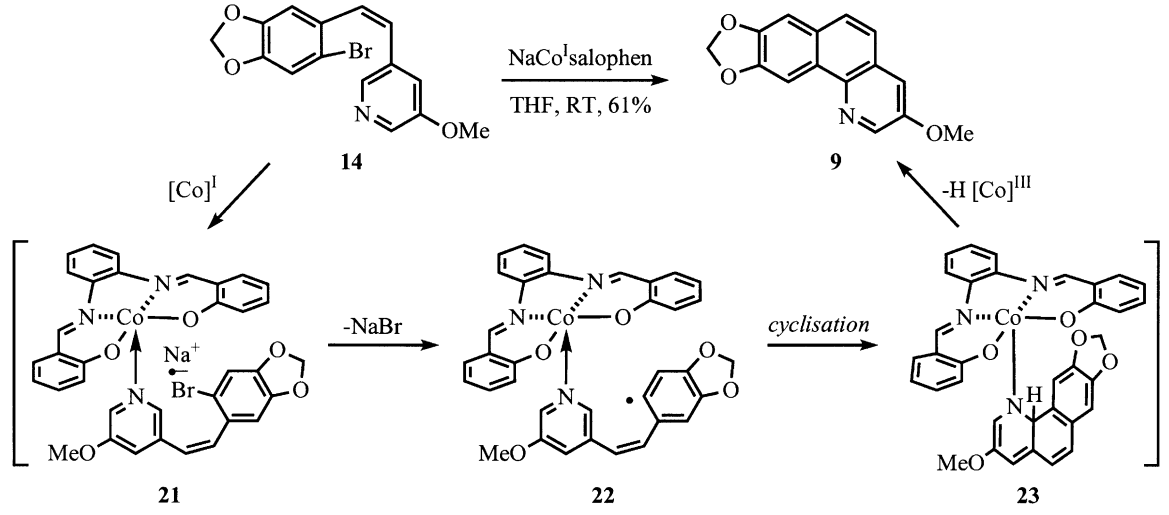


Scheme 2.

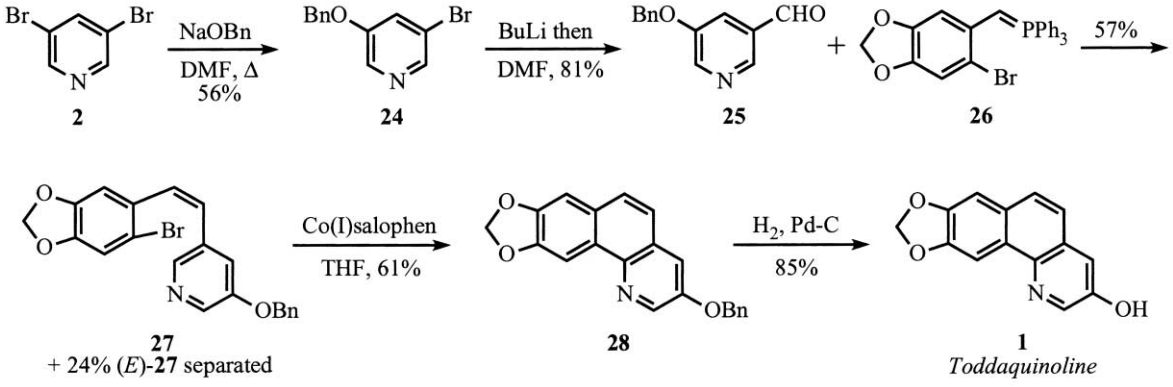


Scheme 3.

the efficiency of our key step, other methods of generating aryl radicals were investigated. These studies led us to discover an interesting dichotomy between tin and cobalt mediated radical cyclisations to pyridines.[13] Thus, when azastilbene **14** was exposed to sodium cobalt(I)salophen it underwent cyclisation to toddaquinoline methyl ether **9** exclusively. That the tin and cobalt(I) mediated radical cyclisations followed a different regiochemical course was quite unexpected and, by analogy with vitamin B_{12} chemistry, may be due to the Lewis acidic nature of cobalt.[14] It seems plausible that single electron transfer from cobalt(I)salophen first generates radical anion **21** in which Co(II)salophen is complexed to the pyridine. This Lewis acid–Lewis base interaction enhances electrophilicity at C-6 in the pyridine and, hence, accelerates addition of the nucleophilic aryl radical to that centre relative to C-4 (viz. **22→23**). A dehydrocobaltation then liberates toddaquinoline methyl ether (Scheme 4).



Scheme 4.



Scheme 5.

5. Toddaquinoline total synthesis

Our attempts to remove the methyl ether in **9** using a host of deprotection methods either failed or provided toddaquinoline **1** in low yield.[15] Indeed, to complete a synthesis of toddaquinoline required us to change to a benzyl protecting group: the synthesis being summarised in Scheme 5.

In conclusion, we have completed the first total synthesis of toddaquinoline **1**. Notable features are the facile intramolecular addition of an aryl radical to a pyridine and the dual role played by cobalt in the cyclisation of **14** to **9**. We are presently examining further the dichotomy between the cobalt(I) and tin mediated radical cyclisation reactions and investigating other intramolecular radical additions to aromatic and heteroaromatic substrates.[16]

6. Experimental section

6.1. General remarks

Melting points were obtained using a Mel-Temp (II) apparatus and are uncorrected. UV spectra were recorded on a Pye Unicam SP800 spectrometer. IR spectra of oils and mulls were recorded on a Perkin Elmer 1600 series Fourier transform infrared spectrometer using NaCl cells. For most solids, IR spectra were recorded directly using a Bio-Rad FTS 135 Fourier transform infrared spectrometer equipped with a Golden Gate Single Reflection Diamond ATR. NMR spectra were recorded on a Bruker AC300 (operating at 300 MHz for ^{1}H and at 75 MHz for ^{13}C). Chemical shifts (δ_H) are reported as values in parts per million relative to tetramethylsilane (δ_H 0.00, δ_C 0.00), $CDCl_3$ (δ_C 77.2) or residual $CHCl_3$ (δ_H 7.27). Mass spectra were recorded on a variety of instruments either in house or at the EPSRC mass spectrometry centre, Swansea.

All reactions were magnetically stirred under an inert atmosphere. Photochemical reactions were performed in a quartz reaction vessel with irradiation from a 125 W medium pressure mercury lamp and were water cooled. Reactions were monitored by thin layer chromatography using Macherey-Nagel Alugram Sil G/UV$_{254}$ precoated aluminium foil plates of layer thickness 0.25 mm. Compounds were visualised firstly by UV irradiation, then by exposure to iodine vapour and finally by heating plates exposed to solutions of phosphomolybdic acid in ethanol or basified aqueous potassium permanganate. Column chromatography was performed on Sorbsil 60 silica (230–400 mesh), slurry packed and run under low pressure.

Ether refers to diethyl ether and petrol refers to the fraction of petroleum ether in the boiling point range 40–60°C. 5-Bromo-3-methoxypyridine **3**, mp 33–35°C (petrol) [lit. 34–35°C (hexanes)],[6] and 5-methoxy-3-pyridinecarboxaldehyde **4** were prepared by the methods of Comins and Killpack.[6] Piperonyl bromide **6**, mp 44–46°C (petrol) [lit. 46–48°C (petrol)],[17] was prepared by the method of Beard et al.[17] [(6-Bromo-1,3-benzodioxolo-5-yl)methyl]bromide **11**, mp 83–85°C (ethanol) [lit. 89–91°C (hexanes)[18] was prepared by the method of Padwa et al.[18]

6.1.1. [(1,3-Benzodioxol-5-yl)methyl]triphenylphosphonium bromide 7. A solution of piperonyl bromide **6** (5.70 g, 26.51 mmol) and triphenylphosphine (8.33 g, 31.81 mmol) in xylene (60 ml) was stirred at reflux for 3 h then cooled to RT. The resulting white precipitate was collected by filtration, washed with cold xylene (2×20 ml) and petrol (3×20 ml) then dried in vacuo to provide the title compound **7** (11.92 g, 24.99 mmol, 94%) as a white solid; mp 227–229°C (xylene) [lit. 236.5–238.5°C (toluene)];[8] IR (nujol, cm^{-1}) ν_{max} 1586 w, 1502 w, 1488 m, 1250 m, 1110 m, 1037 m; UV (MeOH, nm) λ_{max} (ϵ_{max}) 286 (6360), 272 (7160), 224 (38,560); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.79–7.58 (15H, m, 15×PhH), 6.60 (1H, ddd, J=8.1, 3.3, 1.8 Hz, ArH), 6.54–6.50 (2H, m, 2×ArH), 5.85 (2H, s, OCH_2O), 5.30 (2H, d, J_{P-H}=14.0 Hz, CH_2P); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 147.9 (2×*C* [Ar]), 135.2 (3×*C*H [Ph]), 134.5 (d, J_{P-C}=9.7 Hz, 6×*C*H [Ph]), 130.3 (d, J_{P-C}=12.5 Hz, 6×*C*H [Ph]), 125.6 (d, J_{P-C}=6.3 Hz, *C*H [Ar]), 120.2 (J_{P-C}=9.1 Hz, *C* [Ar]), 117.9 (d, J_{P-C}=85.4 Hz, 3×*C* [Ph]), 111.5 (*C*H [Ar]), 108.7 (*C*H [Ar]), 101.4 (O*C*H$_2$O), 30.7 (d, J_{P-C}=46.7 Hz, *C*H$_2$P); LRMS (ES+) 397 ([M−Br]$^+$, 100%).

6.1.2. (*E*)- and (*Z*)-3-[2″-(1′,3′-Benzodioxol-5′-yl)]-1″-ethenyl-5-methoxypyridine 8. Phosphonium bromide **7** (3.90 g, 8.18 mmol) was suspended in tetrahydrofuran (50 ml) and cooled to −78°C. *n*-Butyllithium (1.37 M in hexanes, 6.0 ml, 8.18 mmol) was added dropwise over 5 min and the resulting solution was stirred at −78°C for 10 min, warmed to RT over 30 min, then re-cooled to −78°C. A solution of 5-methoxy-3-pyridinecarboxaldehyde **4** (800 mg, 5.84 mmol) in tetrahydrofuran (5 ml) was added dropwise over 5 min, the mixture was stirred for 30 min then warmed to RT. After 6 h the reaction mixture was filtered through Celite® and concentrated in vacuo. Purification by column chromatography (silica gel, 30% ether in petrol) yielded firstly (*Z*)-**8** as a pale yellow oil (265 mg, 1.04 mmol, 18%); IR (neat, cm^{-1}) ν_{max} 3009 w, 1582 m, 1504 s, 1487 s, 1443 s, 1273 m, 1239 s, 1039 s, 935 m, 880 m, 804 m; UV (EtOH, nm) λ_{max} (ϵ_{max}) 317 (16500), 300 (15200), 235 (17,500); ^{1}H NMR (300 MHz, $CDCl_3$), δ_H 8.14 (1H, d, *J* 2.9 Hz, PyH), 8.10 (1H, d, *J* 1.7 Hz, PyH), 7.08 (1H, dd, *J* 2.9, 1.7 Hz, PyH), 6.73 (1H, s, ArH), 6.72 (1H, d, *J* 8.5 Hz, ArH), 6.71 (1H, d, *J* 8.5 Hz, ArH), 6.64 (1H, d, *J* 12.0 Hz, =C*H*), 6.44 (1H, d, *J* 12.0 Hz, =C*H*), 5.93 (2H, s, OCH_2O), 3.73 (3H, s, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 155.3 (*C* [Py]), 147.7 (*C* [Ar]), 147.2 (*C* [Ar]); 142.7 (*C*H [Py]), 136.2 (*C*H [Py]), 132.5 (*C*H [Py]), 133.7 (*C* [Py]), 130.5 (*C* [Ar]), 125.4 (=*C*H), 123.1 (=*C*H), 120.2 (*C*H [Ar]), 109.0 (*C*H [Ar]), 108.6 (*C*H [Ar]), 101.2 (O*C*H$_2$O), 55.5 (O*C*H$_3$); LRMS (CI) *m/z* 255 (M$^+$, 100%), 226 (8%), 196 (14%), 154 (28%), 127 (17%), 101 (6%); HRMS (CI) *m/z* Found MH$^+$: 256.0981, $C_{15}H_{14}NO_3$ requires 256.0974; then a mixture of (*Z*)-**8** and (*E*)-**8** (400 mg, 1.57 mmol, 27%), and finally (*E*)-**8** as a white solid (530 mg, 2.08 mmol, 36%); mp 100–102°C (ether/petrol); IR (nujol, cm^{-1}) ν_{max} 1582 m, 1503 s, 1488 s, 1444 s, 1253 s, 1193 m, 1038 s, 930 m, 704 m; UV (MeOH, nm) λ_{max} (ϵ_{max}) 348 (21,400), 304 (10,500), 268 (10500), 224 (18900); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 8.31 (1H, d, *J* 1.7 Hz, PyH), 8.19 (1H, d, *J*=2.8 Hz, PyH), 7.30 (1H, dd, *J*=2.8, 1.7 Hz, PyH), 7.09 (1H, d, *J*=1.7 Hz, ArH), 7.08 (1H, d, *J*=16.4 Hz, =C*H*), 6.97 (1H, dd, *J*=8.1, 1.7 Hz,

Ar*H*), 6.90 (1H, d, *J*=16.4 Hz, =C*H*), 6.83 (1H, d, *J*=8.1 Hz, Ar*H*), 5.99 (2H, s, OCH_2O), 3.94 (3H, s, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 155.9 (*C* [Py]), 148.4 (*C* [Ar]), 148.0 (*C* [Ar]), 141.2 (*C*H, [Py]), 137.7 (*C*H [Py]), 133.9 (*C* [Py]), 131.3 (*C* [Ar]), 130.8 (*C*H [Py]), 123.1 (=*C*H), 122.1 (=*C*H), 116.7 (*C*H [Ar]), 108.6 (*C*H [Ar]), 105.7 (*C*H [Ar]), 101.4 (O*C*H$_2$O), 55.7 (O*C*H$_3$); LRMS (CI) 255 (M^+, 100%), 226 (6%), 196 (14%), 154 (25%), 127 (18%), 98 (10%), 77 (12%); HRMS (EI) *m/z* Found M^+: 255.0886, $C_{15}H_{13}NO_3$ requires 255.0895.

6.1.3. 3-(Methoxy)[1,3]dioxolo-[4′,5′:4,5]benzo[*h*]quinoline (*toddaquinoline methyl ether*) 9 and 1-(methoxy)[1,3]-dioxolo-(4′,5′:4,5]benzo[*f*]isoquinoline 10 by photocyclisation of azastilbenes 8. A condensor jacketed Quartz photochemical cell was charged with a solution of azastilbenes **8** (1:1 mixture of (*E*)- and (*Z*)-isomers, 150 mg, 0.59 mmol) in cyclohexane (100 ml). After irradiation at RT with a medium pressure mercury lamp for 16 h the reaction mixture was concentrated in vacuo. Purification by column chromatography (silica gel, 40–100% ether/petrol) yielded firstly toddaquinoline methyl ether **9** (30 mg, 0.12 mmol, 20%) as an off-white solid; mp 151–153°C (ether/petrol) [lit. 145–148°C (MeOH/$CHCl_3$)];[1] IR (solid, cm^{-1}) ν_{max} 2932 w, 1604 m, 1498 s, 1406 m, 1382 m, 1255 s, 1169 s, 1036 s, 941 m, 874 m; UV (MeOH, nm) λ_{max} (ϵ_{max}) 341 (6070), 296 (4430), 233 (5440); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 8.70 (1H, d, *J*=2.0 Hz, Ar*H*), 8.55 (1H, s, Ar*H*), 7.68 (1H, d, *J*=8.8 Hz, Ar*H*), 7.55 (1H, d, *J*=8.8 Hz, Ar*H*), 7.50 (1H, d, *J*=2.0 Hz, Ar*H*), 7.21 (1H, s, Ar*H*), 6.10 (2H, s, OCH_2O), 3.99 (3H, s, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 154.6 (*C*), 148.6 (*C*), 148.2 (*C*), 141.2 (*C*H), 140.3 (*C*), 129.0 (*C*), 127.9 (*C*H), 127.0 (*C*), 123.4 (C), 123.4 (*C*H), 114.3 (*C*H), 105.0 (*C*H), 102.0 (*C*H), 101.5 (O*C*H$_2$O), 55.8 (O*C*H$_3$); LRMS (ES+) 254 (MH^+, 100%); HRMS (ES+) *m/z* Found MH^+:254.0817, $C_{15}H_{12}NO_3$ requires 254.0817 [these spectral and physical characteristics were consistent with literature values];[1] then a 1:1 mixture of (*Z*)-**8** and (*E*)-**8** (35 mg, 0.14 mmol, 23%) and finally benzoisoquinoline **10** (80 mg, 0.32 mmol, 54%) as an off-white solid; mp 140–141°C (ether/petrol); IR (solid, cm^{-1}) ν_{max} 2924 w, 1471 s, 1370 m, 1279 m, 1246 m, 1215 m, 1090 m, 1038 m, 934 m, 863 m; UV (EtOH, nm) λ_{max} (ϵ_{max}) 383 (380), 371 (300), 315 (250), 303 (354), 292 (420), 288 (630), 272 (1900), 217 (400); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 9.08 (1H, s, Ar*H*), 8.88 (1H, s, Ar*H*), 8.33 (1H, s, Ar*H*), 7.78 (1H, d, *J*=8.8 Hz, Ar*H*), 7.72 (1H, d, *J*=8.8 Hz, Ar*H*), 7.02 (1H, s, Ar*H*), 6.15 (2H, s, OCH_2O), 4.19 (3H, s, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 153.6 (*C*), 148.2 (*C*), 148.1 (*C*), 145.1 (*C*H), 131.4 (*C*), 128.9 (*C*H), 128.1 (*C*), 127.6 (*C*H), 125.7 (*C*), 124.5 (*C*), 123.3 (*C*H), 107.6 (*C*H), 105.8 (*C*H), 101.7 (O*C*H$_2$O), 56.4 (O*C*H$_3$); LRMS (CI) 254 (MH^+, 100%).

6.1.4. [(6-Bromo-1,3-dioxol-5-yl)methyl]triphenylphosphonium bromide 12. A solution of bromide **11** (8.00 g, 27.2 mmol) and triphenylphosphine (9.50 g, 36.4 mmol) in xylene (50 ml) was heated at 80°C for 4 h then cooled to RT. The resulting white precipitate was collected by filtration, washed with cold xylene (2×20 ml) and petrol (3×20 ml) then dried in vacuo to provide the title compound **12** (9.40 g, 16.9 mmol, 62%) as a white solid; mp >250°C (EtOH); [lit. 278–280°C (ether /MeOH)];[8] IR (nujol, cm^{-1}) ν_{max} 1503 m, 1476 s, 1437 s, 1243 m, 1111 s, 1032 m, 923 m, 732 s; UV (MeOH, nm) λ_{max} (ϵ_{max}) 302 (3890), 271 (5000), 218 (28,910); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.90–7.55 (15H, m, 3×C_6H_5), 7.02 (1H, d, J_{P-H}=2.0 Hz, Ar*H*), 6.80 (1H, s, Ar*H*), 5.95 (2H, s, OCH_2O), 5.52 (2H, d, J_{P-H}=12.9 Hz, CH_2P); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 149.1 (*C* [Ar]), 148.1 (*C* [Ar]), 135.4 (3×*C*H [Ph]), 134.5 (d, J_{P-C}=10.0 Hz, 6×*C*H [Ph]), 130.4 (d, J_{P-C}=12.5 Hz, 6×*C*H [Ph]), 120.1 (d, J_{P-C}=8.8 Hz, 3×*C* [Ph]), 117.6 (d, J_{P-C}=85.6 Hz, *C* [Ar]), 117.0 (*C* [Ar]), 112.7 (*C*H [Ar]), 112.3 (*C*H [Ar]), 102.4 (O*C*H$_2$O), 31.2 (d, J_{P-C}=48.3 Hz, *C*H$_2$P); LRMS (ES+) 477 ([M−Br{^{81}Br}]$^+$, 100%), 475 ([M−Br{^{79}Br}]$^+$, 90%); Anal. Found: C, 55.96; H, 3.77; $C_{26}H_{21}Br_2O_2P$ requires C, 56.14; H, 3.81.

6.1.5. (*E*)-3-[2-(6-Bromo-1,3-benzodioxol-5-yl)-1-ethenyl]-5-(methoxy)pyridine 13 and (*Z*)-3-[2-(6-bromo-1,3-benzodioxol-5-yl)-1-ethenyl]5-(methoxy)pyridine 14. Sodium hydride (60% in mineral oil, 132 mg, 3.30 mmol), pre-washed with tetrahydrofuran (10 ml), was suspended in tetrahydrofuran (30 ml) and cooled to 0°C. Phosphonium bromide **12** (1.67 g, 3.00 mmol) was added in one portion and the mixture stirred at RT for 2 h then cooled to 0°C. Aldehyde **4** (340 mg, 2.48 mmol) was added as a solution in tetrahydrofuran (10 ml) and the mixture stirred at RT for 2 h then filtered through Celite® and concentrated in vacuo. Purification by column chromatography (silica gel, 40% ether/petrol) provided firstly azastilbene **14** (495 mg, 1.48 mmol, 60%) as a pale yellow solid; mp 106–109°C (ether/petrol); IR (solid, cm^{-1}) ν_{max} 2922 w, 1583 m, 1501 m, 1476 s, 1283 m, 1229 m, 1037 s, 878 m; UV (MeOH, nm) λ_{max} (ϵ_{max}) 336 (6350), 302 (8680), 214 (16,530); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 8.12 (1H, d, *J*=1.9 Hz, Py*H*), 8.05 (1H, d, *J*=1.2 Hz, Py*H*), 7.06 (1H, s, Ar*H*), 6.98 (1H, app. t, *J*=1.6 Hz, Py*H*), 6.67 (1H, d, *J*=11.8 Hz, =C*H*), 6.59 (1H, s, Ar*H*), 6.54 (1H, d, *J*=11.8 Hz, =C*H*), 5.93 (2H, OCH_2O), 3.72 (3H, s, OCH_3), ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 155.3 (*C* [Py]), 148.2 (*C* [Ar]), 147.4 (*C* [Ar]), 142.8 (*C*H [Py]), 136.3 (*C*H [Py]), 132.8 (*C* [Py]), 132.1 (*C*H [Py]), 130.3 (*C* [Ar]), 127.2 (=*C*H), 120.0 (=*C*H), 114.9 (*C* [Ar]), 112.9 (*C*H [Ar]), 110.1 (*C*H [Ar]), 102.0 (O*C*H$_2$O), 55.5 (O*C*H$_3$); LRMS (ES+) 336 ([MH{^{81}Br}]$^+$, 100%), 334 ([MH{^{79}Br}]$^+$, 95% HRMS (EI) *m/z* Found M^+: 332.9995, $C_{15}H_{12}{}^{79}BrNO_3$ requires 333.0001; then azastilbene **13** (210 mg, 25%) as an off-white solid; mp 112–114°C (ether/petrol); IR (solid, cm^{-1}) ν_{max} 2902 w, 1582 m, 1503 m, 1475 s, 1411 m, 1245 m, 1170 m, 1037 s, 955 m, 932 m, 859 m, 843 m; UV (MeOH, nm) λ_{max} (ϵ_{max}) 342 (13,550), 304 (9920), 258 (9730), 220 (16,410); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 8.33 (1H, d, *J*=1.9 Hz, Py*H*), 8.22 (1H, d, *J*=2.6 Hz, Py*H*), 7.43 (1H, d, *J*=16.2 Hz, =C*H*), 7.31 (1H, app. t, *J*=2.2 Hz, Py*H*), 7.12 (1H, s, Ar*H*), 7.03 (1H, s, Ar*H*), 6.84 (1H, d, *J*=16.2 Hz, =C*H*), 6.00 (2H, s, OCH_2O), 3.90 (3H, s, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 156.0 (*C* [Py]), 148.6 (*C* [Ar]), 148.0 (*C* [Ar]), 141.4 (*C*H [Py]), 136.8 (*C*H [Py]), 129.9 (*C* [Py]), 129.7 (*C*H [Py]), 125.9 (=*C*H), 122.9 (*C* [Ar]), 117.0 (=*C*H), 115.8 (*C* [Ar]), 113.0 (*C*H [Ar]), 106.0 (*C*H [Ar]), 102.1 (O*C*H$_2$O), 55.8 (O*C*H$_3$); LRMS (ES+) 336 (MH{^{81}Br}$^+$, 100%), 334 (MH{^{79}Br}$^+$, 95%); HRMS (EI) *m/z* Found M^+: 333.0001, $C_{15}H_{12}{}^{79}BrNO_3$ requires 333.0001.

6.1.6. 9-(Methoxy)[1,3]dioxolo-[4′,5′:3,4]benzo[*h*]quinoline 15 and 3-(methoxy)[1,3]dioxolo-[4′,5′:4,5]benzo[*h*]quinoline (*toddaquinoline methyl ether*) 9. To a cooled (−78°C) solution of azastilbene **14** (374 mg, 1.12 mmol) in tetrahydrofuran (20 ml) was added dropwise via syringe over 5 min *n*-BuLi (1.16 M in hexanes, 1.1 ml, 1.28 mmol). After 30 min the reaction was warmed to 0°C, maintained at that temperature for 30 min then partitioned between ether (20 ml) and brine (20 ml). The aqueous phase was extracted with ether (2×20 ml) and the combined organic phases dried (K_2CO_3) and concentrated in vacuo. Purification by column chromatography gave firstly toddaquinoline methyl ether **9** (30 mg, 0.12 mmol, 11%, data as previously stated) then benzo[*h*]quinoline **15** (90 mg, 0.36 mmol, 32%) as an *unstable* off-white solid; mp decomposed; IR (solid, cm^{-1}) ν_{max} 2932 w, 1577 m, 1477 m, 1433 s, 1408 m, 1313 s, 1276 s, 1215 m, 1089 m, 945 m; ^1H NMR (300 MHz, d_6-acetone) δ_H 8.78 (1H, s, Ar*H*), 8.42 (1H, s, Ar*H*), 7.77 (1H, d, *J*=10.0 Hz, Ar*H*), 7.62 (1H, d, *J*=10.0 Hz, Ar*H*), 7.55 (1H, d, *J*=10.0 Hz, Ar*H*), 7.37 (1H, d, *J*=10.0 Hz, Ar*H*), 6.21 (2H, s, OCH_2O), 4.12 (3H, s, OCH_3); ^{13}C NMR (75 MHz, d_6-acetone) δ_C 152.3 (*C* [Ar]), 147.0 (*C* [Ar]), 144.8 (*C* [Ar]), 143.1 (*C*H [Ar]), 130.3 (*C* [Ar]), 130.1 (*C*H [Ar]), 129.6 (*C*H [Ar]), 128.9 (*C* [Ar]), 122.7 (*C*H [Ar]), 122.3 (*C* [Ar]), 121.7 (*C*H [Ar]), 112.4 (*C* [Ar]), 110.7 (*C*H [Ar]), 100.8 (O*C*H$_2$O), 56.1 (O*C*H$_3$); LRMS (ES+) 254 (MH^+, 100%). Note: the product deteriorated on standing and satisfactory Anal. or HRMS could not be obtained.

6.1.7. 3-(Methoxy)[1,3]dioxolo-[4′,5′:4,5]benzo[*h*]quinoline (*toddaquinoline methyl ether*) 9 and 1-(methoxy)[1,3]-dioxolo-[4′,5′:4,5]benzo[*f*]isoquinoline 10 by tin mediated radical cyclisation of 14. Azastilbene **14** (220 mg, 0.66 mmol), tri-*n*-butyltin hydride (200 μl, 220 mg, 0.76 mmol) and azobisisobutyronitrile (16 mg, 0.10 mmol) were stirred in toluene (25 ml) at 80°C for 4 h then the reaction mixture was cooled to RT. Aqueous potassium fluoride solution (10% w/v, 20 ml) was added and the reaction vigorously stirred for 36 h. The mixture was diluted with ether (50 ml) and the organic phase washed with water (2×50 ml), dried ($MgSO_4$), concentrated in vacuo and purified by column chromatography (silica gel, 40% ether/petrol) to yield firstly toddaquinoline methyl ether **9** (47 mg, 0.19 mmol, 28%) as a white solid [data as previously stated]; then recovered **14** (35 mg, 0.10 mmol, 16%) and finally benzo[*f*]isoquinoline **10** (50 mg, 0.20 mmol, 30%) as a white solid [data as previously stated].

6.1.8. 3-(Methoxy)[1,3]dioxolo-[4′,5′:4,5]benzo[*h*]quinoline (*toddaquinoline methyl ether*) 9 by cobalt(I) mediated radical cyclisation of 14. Sodium (100 mg, 4.35 g atom) was added portionwise to mercury (10 g, 49.5 g atom) WITH CARE: EXOTHERMIC. Tetrahydrofuran (30 ml) and cobalt(II)salophen (380 mg, 1.56 mmol) were added and the reaction mixture vigorously stirred at RT under an argon atmosphere for 3 h. The resulting dark green solution was transferred to a second flask via cannula and cooled to −78°C. Azastilbene **14** (130 mg, 0.39 mmol) as a solution in tetrahydrofuran (5 ml) was added dropwise over 2 min and the solution stirred at −78°C for 2 h, at 0°C for 1 h and at RT for 16 h. The mixture was filtered through a pad of silica (eluting with ether) then concentrated in vacuo. Purification by column chromatography (silica gel, 40% ether/petrol) provided toddaquinoline methyl ether **9** (60 mg, 0.24 mmol, 61%) as an off-white solid [data as previously stated].

6.1.9. 3-(Benzyloxy)-5-bromopyridine 24. Sodium (160 mg, 6.96 g atom) was added portionwise to benzyl alcohol (10 ml) and upon complete dissolution (ca. 5 h) the excess alcohol was removed by distillation under reduced pressure. The resulting pale brown solid was dissolved in *N*,*N*-dimethylformamide (20 ml) and 3,5-dibromopyridine **2** (1.0 g. 4.22 mmol) added. The reaction mixture was stirred at 65°C for 90 min then cooled to RT. Water (20 ml) was added and the mixture extracted with ether (3×20 ml). The combined organic phases were washed with water (15 ml) and brine (15 ml) then dried ($MgSO_4$), concentrated in vacuo and purified by column chromatography (silica gel, 20% ether/petrol) to yield the title compound **24** (625 mg, 2.37 mmol, 56%) as a white solid; mp 64–65°C (ether/petrol); IR (solid, cm^{-1}) ν_{max} 3034 w, 1574 s, 1553 m, 1446 m, 1429 s, 1380 m, 1310 s, 1262 s, 1220 m, 1184 m, 1008 s, 887 m, 856 m, 736 m, 694 s; UV (MeOH, nm) λ_{max} (ϵ_{max}) 290 (5120), 212 (24,920); ^1H NMR (300 MHz, $CDCl_3$) δ_H 8.34–8.30 (2H, m, 2×Py*H*), 7.46–7.33 (6H, m, Py*H*+C_6H_5), 5.10 (2H, s, OCH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 155.4 (*C* [Py]), 143.3 (*C*H [Py]), 136.8 (*C*H [Py]), 135.6 (*C* [Ph]), 129.0 (2×*C*H [Ph]), 128.7 (*C*H [Ph]), 127.7 (2×*C*H [Ph]), 124.6 (*C*H [Py]), 120.6 (*C* [Py]), 70.8 (O*C*H$_2$); LRMS (ES+) 307 ([MH+MeCN{^{81}Br}]$^+$, 42%), 305 ([MH+MeCN{^{79}Br}]$^+$, 40%), 266 ([MH{^{81}Br}]$^+$, 27%), 264 ([MH{^{79}Br}]$^+$, 28%), 140 (38%), 138 (43%), 127 (100%); Anal. Found: C, 54.69; H, 3.80; N, 5.23; $C_{12}H_{10}BrNO$ requires C, 54.57; H, 3.82; N, 5.30.

6.1.10. 5-(Benzyloxy)nicotinaldehyde 25. 3-(Benzyloxy)-5-bromopyridine **24** (1.09 g, 4.11 mmol) was dissolved in tetrahydrofuran (50 ml) and cooled to −100°C. *n*-Butyllithium (1.37 M in hexanes, 3.6 ml, 4.93 mmol) was added dropwise over 10 min and the mixture stirred at −100°C for 1 h. *N*,*N*-Dimethylformamide (1.2 ml, 1.16 g, 15.92 mmol) was added dropwise over 5 min, the reaction mixture was allowed to warm to −60°C over 30 min then quenched with brine (25 ml) and extracted with diethyl ether (3×20 ml). The combined organic phases were dried (K_2CO_3), concentrated under reduced pressure and purified by column chromatography (silica gel, 30% ether/petrol) to yield the title aldehyde **25** (704 mg, 3.31 mmol, 81%) as a white solid; mp 62–64°C (ether/petrol); IR (solid, cm^{-1}) ν_{max} 1698 s, 1584 m, 1454 m, 1380 m, 1318 s, 1280 s, 1249 m, 1172 m, 741 m; UV (MeOH, nm) λ_{max} (ϵ_{max}) 310 (910), 286 (4260), 220 (19,470); ^1H NMR (300 MHz, $CDCl_3$) δ_H 10.08 (1H, s, C*H*O), 8.68 (1H, d, *J*=1.5 Hz, Py*H*), 8.63 (1H, d, *J*=2.9 Hz, Py*H*), 7.69 (1H, dd, *J*=2.9, 1.5 Hz, Py*H*), 7.46–7.35 (5H, m, C_6H_5), 5.17 (2H, s, OCH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 190.8 (*C*HO), 155.5 (*C* [Py]), 145.6 (*C*H [Py]), 145.4 (*C*H [Py]), 135.5 (*C* [Ph]), 132.2 (*C* [Py]), 129.0 (2×*C*H [Ph]), 128.7 (*C*H [Ph]), 127.8 (2×*C*H [Ph]), 117.8 (*C*H [Py]), 70.7 (O*C*H$_2$); LRMS (ES+) 255 ([MH+MeCN]$^+$, 55%), 214 (MH^+, 43%), 186 ([MH−CO]$^+$, 60%), 140 (46%), 127 (100%); Anal. Found: C, 73.18; H, 5.20; N, 6.52; $C_{13}H_{11}NO_2$ requires C, 73.22; H, 5.20; N, 6.57.

6.1.11. (*Z*)-3-(Benzyloxy)-5-[2′-(6″-bromo-1,3-benzodioxol-5″-yl)-1′-ethenyl]pyridine 27 and (*E*)-3-(benzyloxy)-5-[2′-(6″-bromo-1,3-benzodioxol-5″-yl)-1′-ethenyl]pyridine (*E*)-27. Sodium hydride (60% in mineral oil), (180 mg, 4.50 mmol) was pre-washed with petrol (10 ml) then suspended in tetrahydrofuran (30 ml) and cooled to 0°C. Phosphonium bromide **12** (1.79 g, 3.22 mmol) was added and the reaction mixture stirred at RT for 2 h then cooled to 0°C and 5-(benzyloxy)nicotinaldehyde **25** (527 mg, 2.47 mmol) in tetrahydrofuran (5 ml) was added. After a further 2 h the reaction mixture was filtered through Celite® (eluting through with ether) and the organic filtrate concentrated in vacuo. Purification by column chromatography (silica gel, 40% ether/petrol) gave firstly (*Z*)-azastilbene **27** (473 mg, 1.15 mmol, 47%) as a colourless oil; IR (neat, cm^{-1}) ν_{max} 3031 m, 2899 w, 1574 m, 1500 m, 1475 s, 1432 m, 1271 m, 1230 s, 1037 m, 697 m; UV (MeOH, nm) λ_{max} (ϵ_{max}) 296 (8920), 282 (8920), 228 (20,300); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 8.20 (1H, d, *J*=2.9 Hz, Py*H*), 8.05 (1H, d, *J*=1.8 Hz, Py*H*), 7.44–7.33 (5H, m, C_6H_5), 7.06 (1H, s, Ar*H*), 7.04 (1H, app. t, *J*=2.2 Hz, Py*H*), 6.67 (1H, d, *J*=12.1 Hz, =C*H*), 6.58 (1H, s, Ar*H*), 6.54 (1H, d, *J*=12.1 Hz, =C*H*), 5.92 (2H, s, OCH_2O), 4.96 (2H, s, OCH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 154.6 (*C* [Py]), 148.3 (*C* [Ar]), 147.4 (*C* [Ar]), 143.0 (*C*H [Py]), 137.2 (*C*H [Py]), 136.2 (*C* [Ph]), 132.8 (*C*H [Py]), 132.1 (*C* [Ar]), 130.2 (*C* [Py]), 128.9 (2×*C*H [Ph]), 128.4 (*C*H [Ph]), 127.6 (2×*C*H [Ph]), 127.1 (=*C*H), 121.3 (*C*H [Ar]), 114.9 (*C* [Ar]), 113.0 (=*C*H), 110.1 (*C*H [Ar]), 102.0 (OCH_2O), 70.5 (OCH_2); LRMS (ES+) 412 ($MH\{^{81}Br\}^+$, 100%); 410 ($MH\{^{79}Br\}^+$, 98%; HRMS (EI) *m/z* Found M^+: 409.0317, $C_{21}H_{16}{}^{79}BrNO_3$ requires 409.0314; then a mixture of (*Z*)-**27** and (*E*)-**27** (~2:1, 140 mg, 0.38 mmol, 15%) and finally (*E*)-azastilbene (*E*)-**27** (193 mg, 0.47 mmol, 19%) as a pale yellow solid; mp 146–147°C (ether/petrol); IR (solid, cm^{-1}) ν_{max} 2900 w, 1580 m, 1502 m, 1474 s, 1410 m, 1292 m, 1244 m, 1173 m, 1037 s, 698 m; UV (MeOH, nm) λ_{max} (ϵ_{max}) 334 (15,500), 297 (11,100), 253 (12,000), 226 (21,100); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 8.35 (1H, d, *J*=1.5 Hz, Py*H*), 8.28 (1H, d, *J*=2.9 Hz, Py*H*), 7.55–7.30 (7H, m, Py*H*, =C*H* and C_6H_5), 7.17 (1H, s, Ar*H*), 7.09 (1H, s, Ar*H*), 6.83 (1H, d, *J*=16.2 Hz, =C*H*), 6.02 (2H, s, OCH_2O), 5.17 (2H, s, OCH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 155.2 (*C* [Py]), 148.6 (*C* [Ar]), 148.1 (*C* [Ar]), 141.8 (*C*H [Py]), 137.1 (*C*H [Py]), 136.2 (*C* [Ph]), 133.7 (*C* [Ar]), 130.0 (*C* [Py]), 129.8 (*C*H [Py]), 128.9 (2×*C*H [Ph]), 128.5 (*C*H [Ph]), 127.8 (2×*C*H [Ph]), 125.8 (=*C*H), 118.1 (*C*H [Ar]), 115.9 (*C* [Ar]), 113.1 (=*C*H), 106.0 (*C*H [Ar]), 102.1 (OCH_2O), 70.7 (OCH_2); LRMS (ES+) 412 ($[MH\{^{81}Br\}]^+$, 100%), 410 ($[MH\{^{79}Br\}]^+$, 98%); Anal. Found: C, 61.27; H, 3.96; N, 3.35; $C_{21}H_{16}BrNO_3$ requires C, 61.48; H, 3.93; N, 3.41.

6.1.12. 3-(Benzyloxy)[1,3]dioxolo[4′,5′:4,5]benzo[*h*]quinoline 28 (*toddaquinoline benzyl ether*). Sodium (60 mg, 2.64 g atom) was added portionwise to mercury (6 g, 29.7 g atom) WITH CARE: EXOTHERMIC. The resulting amalgam was covered with tetrahydrofuran (30 ml), cobalt(II)salophen was added and the mixture stirred at RT for 2 h. The resulting dark green solution was transferred to a second flask via cannula and cooled to −78°C. Azastilbene **27** (62 mg, 0.15 mmol) as a solution in tetrahydrofuran (5 ml) was added dropwise over 2 min and the solution stirred at −78°C for 2 h, at 0°C for 1 h and at RT for 1 h. The mixture was left to stand in air for 16 h then filtered through Celite® (eluting with ether) and concentrated in vacuo. Purification by column chromatography (silica gel, 20% ether/petrol) yielded toddaquinoline benzyl ether **28** (30 mg, 0.09 mmol, 61%) as a pale yellow solid; mp 129–131°C (ether/petrol); IR (solid, cm^{-1}) ν_{max} 1603 m, 1462 s, 1379 m, 1254 s, 1171 s, 1038 m, 874 m; UV (MeOH, nm) λ_{max} (ϵ_{max}) 360 (1320), 340 (2630), 292 (27,640), 241 (47,380); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 8.78 (1H, d, *J*=2.9 Hz, Ar*H*), 8.52 (1H, s, Ar*H*), 7.65 (1H, d, *J*=2.9 Hz, Ar*H*), 7.58–7.50 (6H, m, Ar*H* and C_6H_5), 7.43 (1H, d, *J*=8.8 Hz, Ar*H*), 7.21 (1H, s, Ar*H*), 6.12 (2H, s, OCH_2O), 5.24 (2H, s, OCH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 152.7 (*C* [Ar]), 148.4 (*C* [Ar]), 148.2 (*C* [Ar]), 141.2 (*C*H [Ar]), 136.2 (*C* [Ph]), 128.9 (*C* [Ar]), 128.8 (2×*C*H [Ph]), 128.7 (*C* [Ar]), 128.3 (*C*H [Ph]), 127.7 (*C*H [Ar]), 127.6 (*C* [Ar]), 127.6 (2×*C*H [Ph]), 126.2 (*C* [Ar]), 123.3 (*C*H [Ar]), 115.8 (*C*H [Ar]), 104.9 (*C*H [Ar]), 101.9 (*C*H [Ar]), 101.3 (OCH_2O), 70.5 (OCH_2); LRMS (ES+) 330 (MH^+, 40%); HRMS (EI) *m/z* Found M^+: 329.1055, $C_{21}H_{15}NO_3$ requires 329.1052.

6.1.13. [1,3]Dioxolo[4′,5′:4,5]benzo[*h*]quinolin-3-ol (*toddaquinoline*) 1. Benzyl ether **28** (52 mg, 0.16 mmol) was dissolved in acetic acid (5 ml). 5% Palladium on carbon (65 mg, 0.03 g atom Pd) was added and the reaction mixture stirred at RT under an atmosphere of hydrogen for 16 h with an additional portion of catalyst (2×25 mg) added after 4 and 8 h. Water (1 ml) and diethyl ether (5 ml) were added and the mixture neutralised to pH 7 with sodium hydrogen carbonate. The organic phases were washed with saturated sodium hydrogen carbonate solution (2×5 ml), dried ($MgSO_4$) and concentrated in vacuo. Purification by column chromatography (silica gel, 1% MeOH/$CHCl_3$) yielded toddaquinoline **1** (32 mg, 0.13 mmol, 85%) as a white solid; mp 229–231°C ($CHCl_3$/MeOH) [lit. 235–237°C (MeOH/ether)];[1] IR (solid, cm^{-1}) ν_{max} 3416 br m, 2916 m, 1463 m, 1256 m, 1113 m, 1054 s, 1028 s, 1008 m, 910 m, 740 s; UV (MeOH, nm) λ_{max} (ϵ_{max}) 288 (1070), 236 (2550); ^{1}H NMR (300 MHz, $CDCl_3$+d_6-DMSO) δ_H 9.42 (1H, s, O*H*), 8.55 (1H, d, *J*=2.9 Hz, Ar*H*), 8.38 (1H, s, Ar*H*), 7.50 (1H, d, *J*=8.8 Hz, Ar*H*), 7.38 (1H, d, *J*=2.9 Hz, Ar*H*), 7.35 (1H, d, *J*=8.8 Hz, Ar*H*), 7.08 (1H, s, Ar*H*), 5.99 (2H, s, OCH_2O); ^{13}C NMR (75 MHz, $CDCl_3$+d_6-DMSO) δ_C 151.4 (*C* [Ar]), 148.2 (*C* [Ar]), 147.7 (*C* [Ar]), 140.7 (*C*H [Ar]), 139.7 (*C* [Ar]), 128.4 (*C* [Ar]), 128.3 (*C* [Ar]), 127.3 (*C*H [Ar]), 126.7 (*C* [Ar]), 123.2 (*C*H [Ar]), 117.8 (*C*H [Ar]), 104.9 (*C*H [Ar]), 101.6 (*C*H [Ar]), 101.2 (OCH_2O); LRMS (ES+) 240 (MH^+, 100%); HRMS (EI) *m/z* Found M^+: 239.0584, $C_{14}H_9NO_3$ requires 239.0582. These data were consistent with those reported in the isolation paper.[1]

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