Tetrahedron 64 (2008) 5072–5078

Contents lists available at ScienceDirect

Tetrahedron

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

Photochemical synthesis of benz[*h*]isoquinolines

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ARTICLE INFO

Article history:
Received 18 December 2007
Received in revised form 5 March 2008
Accepted 19 March 2008
Available online 22 March 2008

Keywords:
Benz[*h*]isoquinoline
Photochemistry
Cyclisation

ABSTRACT

The synthesis of benz[*h*]isoquinolines has been achieved using a highly convergent photochemical method. The approach presented provides ready access to biologically active compounds and building blocks not readily available through other methods.

1. Introduction

In the last few years a significant amount of work has been reported on the synthesis of 5-HT3 receptor antagonists as a way to control and down-regulate cancer chemotherapy-induced emesis. 5-HT3 receptor antagonists have also been shown to be highly effective in the treatment of animal models of schizophrenia and anxiety.[1]

Benz[*h*]isoquinolines have recently been identified as a new class of potent 5-HT3 receptor antagonists. As such, a significant amount of work has been invested in the synthesis of novel benz[*h*]isoquinolines as potential new frameworks for drug design and biological chemistry.[2–4]

The most commonly used approach for the synthesis of benz[*h*]-isoquinolines utilises the process developed by Eloy and Deryckere, in which the pyridone core is generated through the Curtius rearrangement of the corresponding α,β-unsaturated cinnamoyl azide (or the equivalent α,β,γ,δ-dienoyl azide) followed by the thermally induced cyclisation of the isocyanate intermediate.[5]

A different route was reported by Koelsch and Lindquist in which benz[*c*]phthalic anhydride is converted to the *N*-substituted imide.[6] A base promoted rearrangement then converts the newly generated ethyl benz[*c*]phthalimidoacetate into the corresponding 3-carbethoxy-1,4-dihydroxybenz[*f*]isoquinoline, which is saponified and decarboxylated to generate the desired benz[*h*]isoquinoline.[6]

An alternative and interesting method was proposed by Oppolzer, in which the benz[*h*]isoquinoline framework is accessed through a thermal 4π electron disrotatory ring opening followed by a 6π electron conrotatory electrocyclisation.[7]

Unfortunately, the approaches developed thus far are not easily amenable for the efficient generation of highly functionalised benz[*h*]isoquinoline derivatives without significant synthetic effort.

We would now like to report our convergent method for the synthesis of polyfunctionalised benz[*h*]isoquinolines and related tricyclic derivatives.

2. Results and discussion

In our initial approach, it was envisioned that the benz[*h*]isoquinoline core unit **1** could originate from the photocyclisation of the bis-aromatic enol **2**. Analogous photocyclisations have been used in the synthesis of quinolines, isoquinolines and benzoquinolines.[8,2b]

The bis-aromatic enol **2**, in turn, could then be easily accessed through the condensation of the pyridine anion **3** with the aromatic ester **4** (Scheme 1).

Our synthesis began with 2-fluoro-4-methylpyridine **5**, which was deprotonated and the resulting anion was trapped with methyl 4-(trifluoromethyl)benzoate to generate the desired bis-aromatic ketone **6** in good yield (Scheme 2). Acid hydrolysis of the 2-fluoropyridine unit then afforded the desired pyridone **7** in high yield.

At this point, we hoped to be able to take advantage of the keto–enol equilibrium to generate the corresponding conjugated enol of ketone **7**, which was expected to cyclise to generate benz[*h*]isoquinoline **8**.

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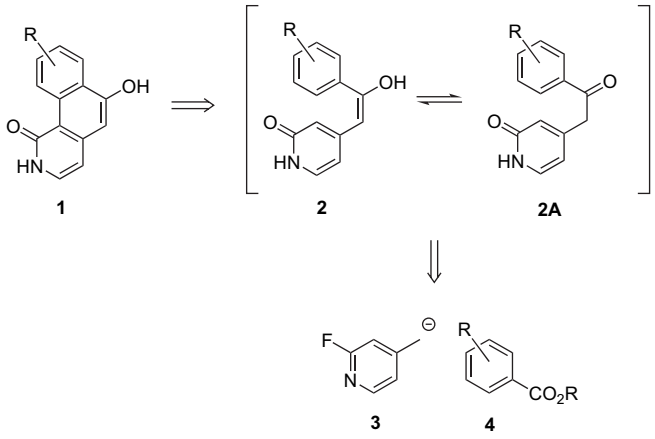
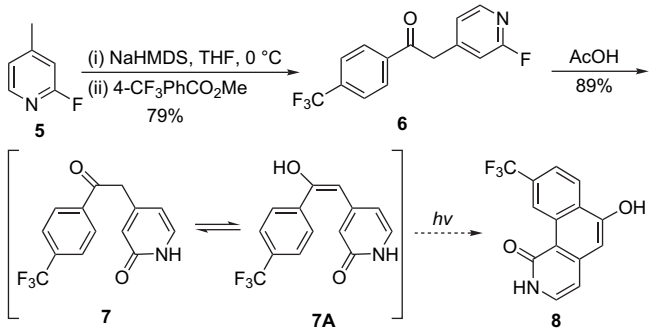
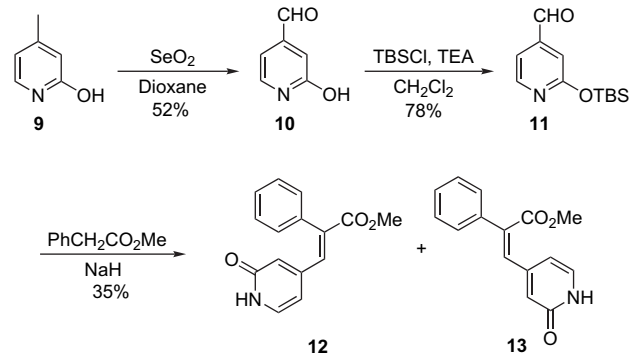
doi:10.1016/j.tet.2008.03.066



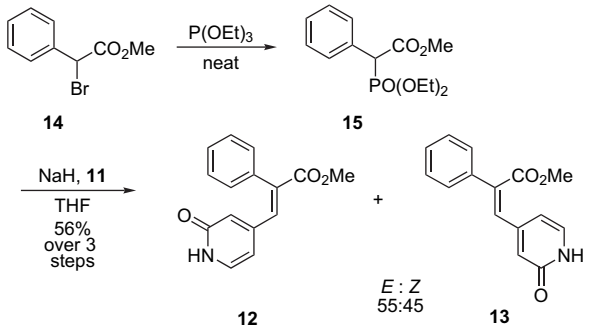
Scheme 1.



Scheme 2.



Scheme 3.



Scheme 4.

Unfortunately, the desired photocyclisation failed to take place even when acid or base catalysed isomerisation was attempted. We believe that the failure to obtain any of the desired benz[*h*]isoquinolines is likely due to lack of ketone enolisation, which then prevents the photocyclisation from taking place.

Therefore it was decided to generate and isolate the corresponding enol ether, which, it was believed, would be more likely to undergo a successful photocyclisation.

However, despite extensive experimentation, it was not possible to control the regiochemistry of enolisation. All attempts at converting keto pyridone **7** into the desired enol ether were unsuccessful, with various ratios of pyridone protection (both O and N protections) observed. Photocyclisation of the pyridone protected product was attempted without success.

This prompted us to re-consider our cyclisation strategy and to generate a cyclisation precursor in which the enol unit was replaced by a more stable alkene unit.

Our revised synthesis began with 2-hydroxy-4-methylpyridine **9**, which was selectively oxidised under Ren's conditions (Scheme 3).[9] An Aldol type condensation of the protected aldehyde **11** with methyl phenylacetate then proceeded to generate the *E* and *Z* conjugated esters **12** and **13** in moderate yield. The TBS group was cleanly cleaved under the reaction conditions.

In an attempt to improve the yield of this coupling, a Horner–Wadsworth–Emmons approach was then attempted. Hence, commercially available methyl bromo(phenyl)acetate **14** was subjected to an Arbuzov reaction with triethylphosphite to generate the desired phosphonate **15** (Scheme 4).

Gratifyingly, the Horner–Wadsworth–Emmons olefination of carbaldehyde **11** with phosphonate **15** proceeded to generate the desired *E* and *Z* conjugated esters **12** and **13** as a 55:45 mixture in good overall yield over the three steps. The double bond geometry of the two isomers was corroborated by X-ray crystallography (Figs. 1 and 2).[10]

Having obtained the desired acyclic precursor, the photochemical cyclisation studies were then undertaken. This included the use of different solvents (including acetonitrile, benzene, dichloromethane, diethyl ether and tetrahydrofuran) and different wavelengths (254, 350 and 420 nm).

After considerable experimentation, the mixture of *E* and *Z* conjugated esters **12** and **13** was successfully cyclised to the desired benz[*h*]isoquinoline **16** when exposed to a 254 nm light source in tetrahydrofuran (Scheme 5).[11] Only a small amount of photocyclisation was observed at the longer wavelengths.

Treatment of the pure *Z* isomer **13** under the same photochemical conditions cleanly isomerised the internal double bond

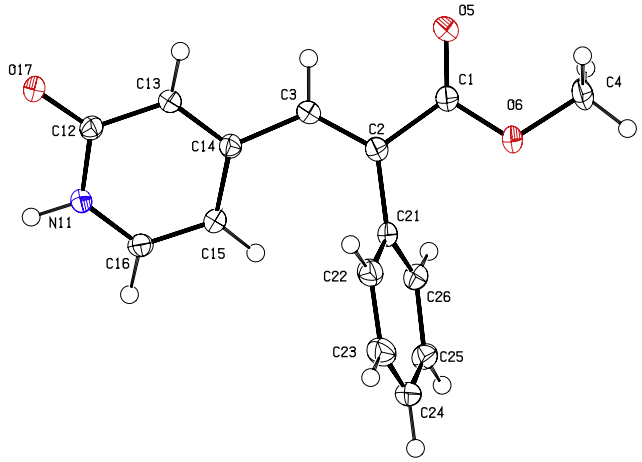


Figure 1. Crystal structure of *E* isomer **12**.

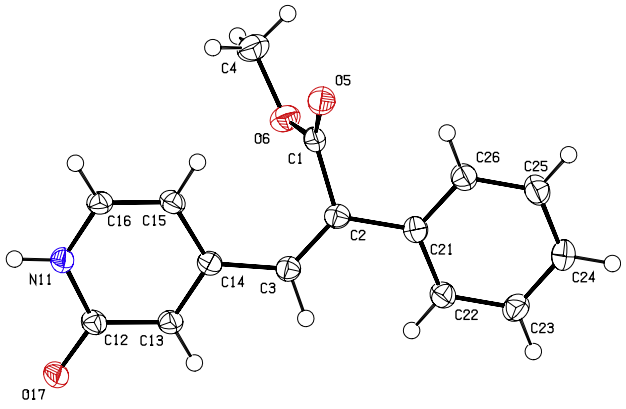
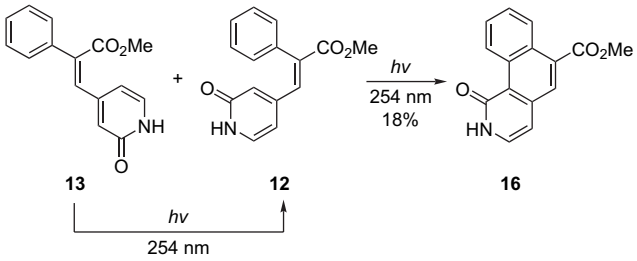


Figure 2. Crystal structure of *Z* isomer **13**.



Scheme 5.

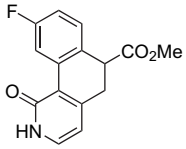
before undergoing the desired photocyclisation to also generate benz[*h*]isoquinoline **16**.

Having successfully demonstrated the potential of this procedure, the synthesis of the methoxy-, trifluoromethyl- and fluoro-substituted benz[*h*]isoquinolines was then undertaken.

4-Methoxyphenylacetic acid **17**, 4-trifluoromethylphenylacetic acid **18** and 4-fluorophenylacetic acid **19** were esterified and then brominated to afford the benzyl bromides **23**–**25** (Scheme 6). The corresponding phosphonates **26**–**28** were then generated in situ, and coupled with the previously described carbaldehyde **11** to afford the desired bis-aryl olefins **29**–**34** in excellent yields over the entire sequence.

As expected, photolysis of *E*/*Z* mixtures of bis-aryl olefins **29**–**34** at 254 nm afforded the desired methoxy-, trifluoromethyl- and fluoro-substituted benz[*h*]isoquinolines **35**–**37**, respectively.

On a side note, the photocyclisation of alkenoate esters **33** and **34** also yielded a small amount of dihydrobenz[*h*]isoquinoline **38** (Scheme 7).



38

Scheme 7.

The structure of ester **38** was determined by NMR analysis and subsequently corroborated through X-ray crystallography (Fig. 3).[12] Compound **38** is consistent with the six electron photocyclisation of olefins **33** and **34**, which then fail to be oxidised to the desired benz[*h*]isoquinoline **37**. However, the mechanism for the formation of benz[*h*]isoquinoline **37** is not clear.

In conclusion, we have successfully developed a four-step synthesis for the generation of benz[*h*]isoquinolines core unit and related analogues. These results provide an efficient approach to the synthesis of these important building blocks, and significantly improve on existing methodologies.[2–7]

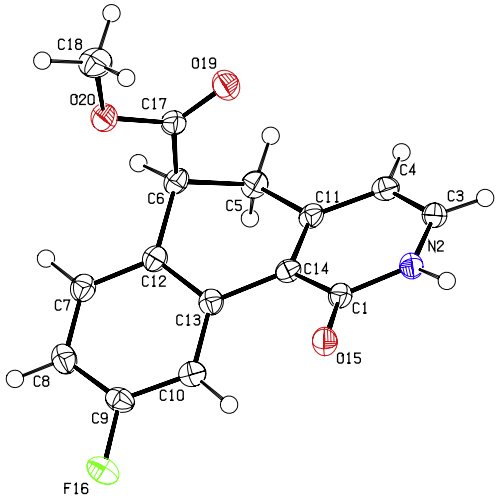
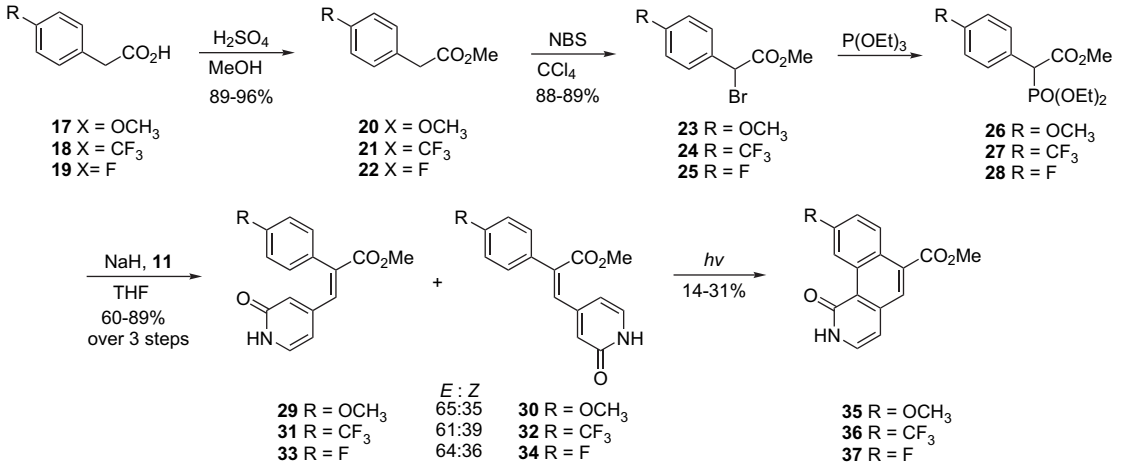


Figure 3. Crystal structure of reduced analogue **38**.



Scheme 6.

We are currently working on the expansion of the chemical diversity around the benz[*h*]isoquinoline core structure and the biological assessment of this series of compounds.

3. Experimental

3.1. General

All reactions were performed in oven-dried glassware under an inert argon atmosphere unless otherwise specified. Tetrahydrofuran, diethyl ether and dichloromethane were distilled before use. All other reagents were used as-received unless specified otherwise. ^{1}H NMR spectra were obtained at 300 or 500 MHz using Bruker DPX300 or Bruker Avance 500 instruments, respectively. Chemical shifts (δ) are reported in parts per million (ppm) and referenced to the residual solvent peak. The order in citation in parentheses is: (1) multiplicity (s=singlet, br s=broad singlet, d=doublet, t=triplet, q=quartet, m=multiplet, br=broad); (2) number of equivalent nuclei (by integration); (3) coupling constant (*J*) quoted in Hertz to the nearest 0.1 Hz. ^{13}C NMR spectra were recorded at 75.5 or 125.7 MHz using Bruker DPX300 or Bruker Avance 500 instruments. Chemical shifts (δ) are quoted in parts per million and referenced to the residual solvent peak. Mass Spectra (MS) were completed using a PerSeptive Biosystems Mariner ES1-TOF spectrometer. High-Resolution Mass Spectra (HRMS) were realised with a Bruker MicroTOF spectrometer by electrospray ionisation mass spectrometry operating at a resolution of 15,000 full widths at half height. Photochemical reactions were carried out using a LuzChem Photoreactor fitted with 10×8 W low-pressure germicidal lamps (UVC λ=254 nm). IR spectra were recorded on a JASCO FT/IR410 Fourier transform spectrometer. Only significant absorptions (ν_{max}) are reported in wavenumbers (cm^{-1}). Flash column chromatography was performed using Silica Gel 60 A C.C. 35–70 μm (SDS ref. 2000027). TLC was performed on aluminium sheets ore-coated with silica (Merck Silica Gel 60 F_{254}) and visualised by the quenching of UV fluorescence (λ_{max} 254 nm).

3.1.1. 2-Hydroxypyridine-4-carbaldehyde **10**[9]

To a mixture of 2-hydroxy-4-methylpyridine (2.10 g, 19.2 mmol) and selenium dioxide (2.50 g, 22.5 mmol) was added anhydrous dioxane (35 mL). The heterogeneous solution was then refluxed under argon for 48 h before being cooled down to room temperature, treated with sodium hydrogen carbonate (1.5 g) and stirred for 3 h to neutralise acidic by-products. The resulting dark brown suspension was filtered through a pad of magnesium sulfate (2.5 g), Florisil (2.5 g) and Celite (2.5 g) to remove insoluble residues. The yellow filtrate was concentrated in vacuo to obtain the crude compound (1.40 g). Purification of the crude product was completed using silica column chromatography in ethyl acetate, followed by 9:1 ethyl acetate/methanol then 8:2 ethyl acetate/methanol to give the desired aldehyde **10** (1.23 g, 9.99 mmol, 52%) as a yellow solid. ^{1}H (500 MHz, DMSO-d_6) δ 11.93 (s, 1H, NH), 9.87 (s, 1H, CHO), 7.52 (d, 1H, *J*=7.0 Hz, Ar), 6.95 (s, 1H, Ar), 6.42 (d, 1H, *J*=6.5 Hz, Ar). ^{13}C (125 MHz, DMSO-d_6) δ 193.5, 162.8, 145.8, 137.0, 125.6, 99.7. Mp: 79–81 °C (lit. 83 °C).[8,2b]

3.1.2. 2-(tert-Butyldimethylsilanyloxy)-pyridine-4-carbaldehyde **11**[13]

A solution of 2-hydroxypyridine-4-carbaldehyde **10** (1.24 g, 10.1 mmol) in dry dichloromethane (40 mL) was treated with triethylamine (3.60 mL, 25.8 mmol) and *tert*-butyldimethylsilyl chloride (1.66 g, 11.0 mmol). The reaction mixture was stirred at room temperature overnight and then quenched with methanol (5 mL). The solvent was then removed in vacuo and the crude residue triturated with petroleum spirit. The solvent washings were then combined, dried over sodium sulfate and then concentrated in vacuo to afford the expected silyl ether **11** (1.88 g, 7.92 mmol, 78%) as an oil. ^{1}H (300 MHz, $CDCl_3$) δ 9.99 (s, 1H, CHO), 8.31 (d, 1H, *J*=5.1 Hz, Ar), 7.26 (d, 1H, *J*=5.2 Hz, Ar), 7.08 (s, 1H, Ar), 0.99 (s, 9H, 3×Me), 0.33 (s, 6H, 2×Me). ^{13}C (75 MHz, $CDCl_3$) δ 197.1, 169.6, 154.3, 150.6, 120.5, 119.7, 31.0, 1.6.

3.1.3. 3-(2-Hydroxypyridin-4-yl)-2-phenylacrylic acid methyl esters **12** and **13**

A suspension of washed and dried sodium hydride (31.5 mg, 0.79 mmol) in tetrahydrofuran (1 mL) was cooled to 0 °C and treated with a solution of phenylacetic acid methyl ester (118 mg, 113 μL, 0.79 mmol) in tetrahydrofuran (1 mL). The resulting mixture was then stirred at 0 °C for 15 min and then treated with 2-(*tert*-butyldimethylsilanyloxy)-pyridine-4-carbaldehyde **11** (170 mg, 0.72 mmol). The reaction mixture was allowed to warm up to room temperature overnight. The reaction mixture was quenched with brine (2 mL) and extracted with ethyl acetate (2×10 mL). The combined organic phases were dried over sodium sulfate and the solvent removed in vacuo. The crude residue was purified by flash column chromatography (silica gel, elution gradient: 100% petroleum ether to 100% ethyl acetate) to give the desired alkene as a pale yellow solid (70.0 mg, 0.27 mmol, 35%) as ca. 1:1 mixture of *E* and *Z* isomers.

Alternative procedure: Neat methyl α-bromophenylacetate (460 mg, 2.00 mmol) was stirred while triethylphosphite (415 mg, 2.50 mmol) was carefully added drop-wise at room temperature. The resulting mixture was then heated at 160 °C for 1 h before being cooled slightly and then treated with a second portion of triethylphosphite (415 mg, 2.5 mmol). The reaction mixture was then heated up to 160 °C for an extra 1 h and then cooled to room temperature. The excess triethylphosphite was then removed through vacuum distillation and the clean crude residue was dissolved in anhydrous THF (5 mL) under argon. The freshly generated solution was added drop-wise to a cooled (0 °C) suspension of sodium hydride (60% oil dispersion, 80.0 mg, 2.00 mmol) in anhydrous THF (2.5 mL). The suspension was stirred for 15 min before a solution of 2-(*tert*-butyldimethylsilanyloxy)-pyridine-4-carbaldehyde **11** (450 mg, 2.00 mmol) in anhydrous THF (2.5 mL) was added slowly. The resulting reaction mixture was then stirred overnight at room temperature, the solvent was concentrated under vacuum and the crude residue was partitioned between ethyl acetate and water (50 mL, 1:1). The organic layer was separated, dried over sodium sulfate and concentrated in vacuo. Purification of the crude residue was completed using flash column chromatography (silica gel, elution gradient: 100% petroleum spirit to 100% ethyl acetate). The desired alkenes were obtained in 56% (288 mg) yield as white amorphous solids and an overall ratio of 55:45 *E*/*Z* isomers.

3.1.3.1. (E)-3-(2-Hydroxypyridin-4-yl)-2-phenylacrylic acid methyl ester **12**

^{1}H (300 MHz, $CDCl_3$) δ 12.62 (br s, 1H, NH), 7.58 (s, 1H, Ar), 7.37–7.35 (m, 3H, Ar), 7.20–7.16 (m, 2H, Ar), 7.07 (d, 1H, *J*=6.9 Hz, Ar), 6.42 (s, 1H, =CH), 5.71 (d, 1H, *J*=6.8 Hz, Ar), 3.82 (s, 3H, Me). ^{13}C (75 MHz, $CDCl_3$) δ 167.4, 165.3, 148.4, 137.7, 137.0, 134.3, 133.9, 129.6, 128.6, 121.7, 107.5, 52.8. Mp: 191–194 °C. MS: *m*/*z*=256.1069 ([M+H]$^+$). HRMS: calcd for $C_{15}H_{13}NO_3$+H 256.0968, found 256.0958.

3.1.3.2. (Z)-3-(2-Hydroxypyridin-4-yl)-2-phenylacrylic acid methyl ester **13**

^{1}H (300 MHz, $CDCl_3$) δ 12.70 (br s, 1H, NH), 7.47–7.36 (m, 6H, Ar), 6.80 (s, 1H, Ar), 6.55 (s, 1H, =CH), 6.28 (d, 1H, *J*=6.7 Hz, Ar), 3.83 (s, 3H, Me). ^{13}C (75 MHz, $CDCl_3$) δ 168.9, 165.6, 149.2, 139.5, 135.7, 134.5, 129.4, 129.0, 128.0, 126.7, 118.9, 106.6, 52.7. Mp: 182–184 °C. MS: *m*/*z*=256.1095 ([M+H]$^+$). HRMS: calcd for $C_{15}H_{13}NO_3$+H 256.0968, found 256.0962.

*3.1.4. 1-Hydroxy-benz[h]isoquinoline-6-carboxylic methyl ester **16***

A solution of methyl esters **12** and **13** (100 mg, 0.39 mmol) in THF (100 mL) was placed in a in a quartz vessel and stirred inside the UV photoreactor for 75 min. The solvent was concentrated in vacuo to obtain the crude residue, which was purified using flash column chromatography (silica gel, elution gradient 100% dichloromethane to 99:1 dichloromethane/methanol). The semi-crude product obtained (27.7 mg) was then recrystallised from methanol to obtain 17.4 mg (18%) of analytically pure benz[*h*]isoquinoline **16** as a pale solid. ^{1}H (300 MHz, DMSO-d_6) δ 11.90 (br s, 1H, NH), 10.29 (d, 1H, J=8.5 Hz, Ar), 8.54 (d, 1H, J=8.3 Hz, Ar), 8.23 (s, 1H, Ar), 7.80–7.68 (m, 2H, Ar), 7.52 (d, 1H, J=6.5 Hz, Ar), 6.88 (d, 1H, J=6.8 Hz, Ar), 4.00 (s, 3H, Me). ^{13}C (75 MHz, DMSO-d_6) δ 166.9, 161.8, 138.0, 132.3, 131.6, 131.2, 127.8, 127.6, 126.5, 126.2, 125.1, 120.2, 105.3, 52.4. ν_{max} (film)/cm^{-1} 3271, 3124, 2877, 2793, 1720, 1631, 1600, 1539, 1500, 1253. Mp: 226–228 °C. MS: m/z=254.1007 ([M+H]$^+$). HRMS: calcd for $C_{15}H_{11}NO_3$+H 254.0812, found 254.0818.

*3.1.5. 4-Methoxyphenylacetic acid methyl ester **20**[14]*

A solution of 4-methoxyphenylacetic acid (4.15 g, 25.0 mmol) in methanol (10 mL) was treated by the careful addition of concentrated sulfuric acid (0.5 mL). The resulting mixture was heated to reflux overnight, then cooled to room temperature and concentrated in vacuo. The crude residue was dissolved in diethyl ether (100 mL) to which water (50 mL) was added. The phases were separated, and the organic layer was washed with satd aq sodium hydrogen carbonate (50 mL), dried over sodium sulfate and concentrated under vacuum to yield 4.02 g of the required ester **20** as a pale yellow oil (22.3 mmol, 89%), which was used without any further purification. ^{1}H (300 MHz, $CDCl_3$) δ 7.28 (d, 2H, J=9.0 Hz, Ar), 6.94 (d, 2H, J=9.0 Hz, Ar), 3.86 (s, 3H, OMe), 3.76 (s, 3H, OMe), 3.64 (s, 2H, CH_2). ^{13}C (75 MHz, $CDCl_3$) δ 172.4, 158.8, 130.3, 126.1, 114.1, 55.3, 52.0, 40.3.

*3.1.6. α-Bromo-(4-methoxyphenyl) acetic acid methyl ester **23**[15]*

A solution of 4-methoxyphenylacetic acid methyl ester **20** (1.00 g, 5.55 mmol) in carbon tetrachloride (20 mL) was treated with *N*-bromosuccinimide (1.06 g, 5.95 mmol) and benzoyl peroxide (24.0 mg, 0.100 mmol). The reaction mixture was refluxed under UV light for 4 h before being cooled down to room temperature and filtered through Celite. The filtrate was concentrated under vacuum to obtain 1.26 g of the desired bromide **23** (88%) as a yellow oil. ^{1}H (300 MHz, $CDCl_3$) δ 7.49 (d, 2H, J=9.0 Hz, Ar), 6.88 (d, 2H, J=9.0 Hz, Ar), 5.36 (s, 1H, CH), 3.80 (s, 3H, OMe), 3.78 (s, 3H, OMe). ^{13}C (75 MHz, $CDCl_3$) δ 169.0, 160.4, 130.2, 127.8, 114.3, 55.4, 53.4, 46.6.

*3.1.7. 3-(2-Hydroxypyridin-4-yl)-2-(4-methoxyphenyl)-acrylic acid methyl ester **29** and **30***

α-Bromo-(4-methoxyphenyl)-acetic acid methyl ester **23** (617 mg, 2.38 mmol) was stirred while triethylphosphite (495 mg, 2.98 mmol) was added carefully. The reaction mixture was heated to 160 °C for 1 h, before being cooled slightly and treated with a further portion of triethylphosphite (495 mg, 2.98 mmol). The reaction mixture was then heated again for 1 h at 160 °C, cooled down to room temperature and the excess triethylphosphite was removed under vacuum. The residue, essentially constituting the phosphonyl ester **26**, was dissolved in anhydrous THF (5 mL) under argon. This solution was then added drop-wise to a cooled (0 °C) suspension of sodium hydride (60% oil dispersion, 95 mg, 2.38 mmol) in anhydrous THF (4 mL). The suspension was stirred for 15 min before being treated with a solution of 2-(*tert*-butyldimethylsilanyloxy)-pyridine-4-carbaldehyde **11** (565 mg, 2.38 mmol) in anhydrous THF (4 mL) at 0 °C. The reaction mixture was then stirred overnight at room temperature. Solvent was concentrated under vacuum and the crude residue partitioned between ethyl acetate and water (30 mL, 1:1). The organic layer was washed with water (15 mL), dried over sodium sulfate and concentrated under vacuum. Flash column chromatography (silica gel, elution gradient 100% petroleum spirit to 100% ethyl acetate) generated 405 mg of the expected methyl esters **29** and **30** (1.42 mmol, 60%) as a white solid containing a mixture of *E* and *Z* isomers (65:35).

*3.1.7.1. (E)-3-(2-Hydroxypyridin-4-yl)-2-(4-methoxyphenyl)-acrylic acid methyl ester **29**.* ^{1}H (300 MHz, $CDCl_3$) δ 12.62 (br s, 1H, NH), 7.52 (s, 1H, Ar), 7.11 (d, 2H, J=8.4 Hz, Ar), 7.04 (d, 1H, J=6.6 Hz, Ar), 6.87 (d, 2H, J=8.4 Hz, Ar), 6.43 (s, 1H, =CH), 5.72 (d, 1H, J=6.9 Hz, Ar), 3.87 (s, 6H, OMe). ^{13}C (75 MHz, $CDCl_3$) δ 167.8, 165.3, 159.9, 148.8, 137.4, 136.4, 133.7, 131.2, 126.4, 121.7, 114.1, 107.6, 55.3, 52.8. Mp: 168–170 °C. MS: m/z=286.1172 ([M+H]$^+$). HRMS: calcd for $C_{16}H_{15}NO_4$+H 286.1074, found 286.1067.

*3.1.7.2. (Z)-3-(2-Hydroxypyridin-4-yl)-2-(4-methoxyphenyl)-acrylic acid methyl ester **30**.* ^{1}H (300 MHz, $CDCl_3$) δ 12.69 (br s, 1H, NH), 7.39 (d, 2H, J=8.7 Hz, Ar), 7.31 (d, 1H, J=6.9 Hz, Ar), 6.92 (d, 2H, J=9.0 Hz, Ar), 6.71 (s, 1H, Ar), 6.52 (s, 1H, =CH), 6.24 (d, 1H, J=6.8 Hz, Ar), 3.84 (s, 6H, OMe). ^{13}C (75 MHz, $CDCl_3$) δ 168.2, 164.5, 159.7, 148.4, 133.3, 130.2, 127.1, 124.8, 117.7, 113.4, 113.2, 105.7, 54.5, 51.7. Mp: 208–211 °C. MS: m/z=286.1082 ([M+H]$^+$). HRMS: calcd for $C_{16}H_{15}NO_4$+H 286.1074, found 286.1083.

*3.1.8. 1-Hydroxy-9-methoxy-benz[h]isoquinoline-6-carboxylic acid methyl ester **35***

A solution of the methyl esters **29** and **30** (353 mg, 1.24 mmol) in THF (100 mL) was stirred in the photoreactor for 1 h in a quartz container and placed in the UV photoreactor. The solvent was then concentrated in vacuo to obtain a crude residue, which was purified through flash column chromatography (silica gel, elution gradient: 100% dichloromethane to 99:1 dichloromethane/methanol) to produce 80 mg of the desired cyclisation product **35** as a white solid (0.282 mmol, 23%). ^{1}H (300 MHz, DMSO-d_6) δ 11.80 (br s, 1H, NH), 9.88 (d, 1H, J=2.7 Hz, Ar), 8.49 (d, 1H, J=9.3 Hz, Ar), 8.06 (s, 1H, Ar), 7.48 (t, 1H, J=6.3 Hz, Ar), 7.37 (dd, 1H, J=9.3, 2.7 Hz, Ar), 6.83 (d, 1H, J=6.8 Hz, Ar), 3.98 (s, 3H, OMe), 3.93 (s, 3H, OMe). ^{13}C (75 MHz, DMSO-d_6) δ 167.7, 162.7, 159.2, 139.2, 134.3, 132.7, 131.8, 127.2, 125.8, 123.3, 120.2, 117.9, 107.5, 106.1, 55.5, 53.0. ν_{max} (film)/cm^{-1} 3117, 2855, 2835, 1728, 1639, 1597, 1516, 1438, 1253. Mp: 259–260 °C. MS: m/z=284.1123 ([M+H]$^+$). HRMS: calcd for $C_{16}H_{13}NO_4$+H 284.0917, found 284.0922.

*3.1.9. 4-Trifluoromethylphenylacetic acid methyl ester **21**[16]*

4-Trifluorophenylacetic acid (1.00 g, 4.89 mmol) was treated under the same conditions as 4-methoxyphenylacetic acid to yield 941 mg of the desired methyl ester **21** (4.31 mmol, 90%) as a clear oil. ^{1}H (300 MHz, $CDCl_3$) δ 7.59 (d, 2H, J=8.1 Hz, Ar), 7.41 (d, 2H, J=8.1 Hz, Ar), 3.72 (s, 3H, OMe), 3.70 (s, 2H, CH_2). ^{13}C (75 MHz, $CDCl_3$) δ 171.3, 138.1, 129.8, 129.3, 126.0, 125.6, 125.5, 122.5, 118.9, 52.2, 40.9.

*3.1.10. α-Bromo-(4-trifluoromethylphenyl)-acetic acid methyl ester **24**[17]*

4-Trifluoromethylphenylacetic acid methyl ester **21** (520 mg, 2.83 mmol) was reacted with *N*-bromosuccinimide (424 mg, 2.83 mmol) under the same conditions as methyl ester **20** to obtain 748 mg of bromide **24** (2.52 mmol, 89%) as a yellow oil. ^{1}H (300 MHz, $CDCl_3$) δ 7.68 (d, 2H, J=8.4 Hz, Ar), 7.63 (d, 2H, J=8.4 Hz, Ar), 5.38 (s, 1H, CH), 3.80 (s, 3H, OMe). ^{13}C (75 MHz, $CDCl_3$) δ 168.4, 139.7, 134.4, 126.0, 125.9, 53.7, 45.1.

*3.1.11. 3-(2-Hydroxypyridin-4-yl)-2-(4-trifluoromethylphenyl)-acrylic acid methyl esters **31** and **32***

α-Bromo methyl ester **24** (619 mg, 2.08 mmol) was reacted with triethylphosphite (2×433 mg, 2.60 mmol) under the same

conditions as bromide **23** to produce phosphonyl ester **27**. Phosphonyl ester **27** was reacted with carbaldehyde **11** (565 mg, 2.38 mmol) under identical conditions as phosphonyl ester **26** to generate 305 mg of alkenes **31** and **32** (0.945 mmol, 45%) as a white solid containing a mixture of both *E* and *Z* isomers (61:39).

*3.1.11.1. (E)-3-(2-Hydroxypyridin-4-yl)-2-(4-trifluoromethylphenyl)-acrylic acid methyl ester **31**.* ^{1}H (300 MHz, $CDCl_3$) δ 12.93 (br s, 1H, NH), 7.75 (s, 1H, Ar), 7.68 (d, 2H, *J*=8.1 Hz, Ar), 7.42 (d, 2H, *J*=6.8 Hz, Ar), 7.21 (d, 1H, *J*=6.8 Hz, Ar), 6.34 (s, 1H, =CH), 5.88 (d, 1H, *J*=6.9 Hz, Ar), 3.81 (s, 3H, OMe). ^{13}C (75 MHz, $CDCl_3$) δ 166.7, 165.1, 147.9, 138.2, 137.8, 136.7, 136.3, 134.3, 130.6, 130.3, 128.6, 125.7, 125.6, 122.2, 121.9, 121.8, 107.3, 53.0. Mp: 167–172 °C. MS: *m*/*z*=324.1006 ($[M+H]^+$). HRMS: calcd for $C_{16}H_{12}F_3NO_3$+Na 346.0661, found 346.0653.

*3.1.11.2. (Z)-3-(2-Hydroxypyridin-4-yl)-2-(4-trifluoromethylphenyl)-acrylic acid methyl ester **32**.* ^{1}H (300 MHz, $CDCl_3$) δ 13.15 (br s, 1H, NH), 7.68–7.56 (m, 4H, Ar), 7.39 (d, 1H, *J*=6.9 Hz, Ar), 6.86 (s, 1H, Ar), 6.57 (s, 1H, =CH), 6.29 (d, 1H, *J*=6.6 Hz, Ar), 3.84 (s, 3H, OMe). ^{13}C (75 MHz, MeOD) δ 170.1, 166.0, 151.3, 136.3, 135.9, 131.9, 131.5, 131.1, 128.8, 127.7, 126.9, 119.8, 118.3, 108.3, 107.7, 76.4, 53.6. Mp: 224–226 °C. MS: *m*/*z*=324.0881 ($[M+H]^+$). HRMS: calcd for $C_{16}H_{12}F_3NO_3$+H 324.0842, found 324.0833.

*3.1.12. 1-Hydroxy-9-trifluoromethyl-benz[h]isoquinoline-6-carboxylic acid methyl ester **36***

Methyl esters **31** and **32** (80 mg, 0.25 mmol) were cyclised under the same conditions and wavelength as esters **29** and **30** to yield 11.2 mg of the desired cyclic product **36** as a white solid (0.035 mmol, 14%). ^{1}H (300 MHz, DMSO-d_6) δ 12.13 (br s, 1H, NH), 10.72 (s, 1H, Ar), 8.81 (d, 1H, *J*=8.7 Hz, Ar), 8.45 (s, 1H, Ar), 7.99 (d, 1H, *J*=8.9 Hz, Ar), 7.61 (t, 1H, *J*=6.3 Hz, Ar), 6.96 (d, 1H, *J*=6.7 Hz, Ar), 4.01 (s, 3H, OMe). ^{13}C (75 MHz, DMSO-d_6) δ 166.6, 162.0, 139.2, 132.7, 131.9, 131.3, 131.1, 129.9, 128.5, 128.1, 127.7, 127.3, 126.3, 123.9, 123.8, 122.7, 122.3, 119.1, 106.2, 52.9. ν_{max} (film)/cm^{-1} 3155, 3109, 2839, 1724, 1647, 1635, 1604, 1546, 1516, 1311, 1253. Mp: 262–264 °C. MS: *m*/*z*=322.0968 ($[M+H]^+$). HRMS: calcd for $C_{16}H_{10}F_3NO_3$+H 322.0686, found 322.0676.

*3.1.13. 4-Fluorophenylacetic acid methyl ester **22**[14]*

4-Fluorophenylacetic acid (2.50 g, 16.2 mmol) was esterified under the same conditions as 4-methoxyphenylacetic acid to yield 2.61 g of methyl ester **22** (15.5 mmol, 96%) as a pale yellow oil. ^{1}H (300 MHz, $CDCl_3$) δ 7.15–7.13 (m, 2H, Ar), 6.92 (t, 2H, *J*=8.7 Hz, Ar), 3.60 (s, 3H, OMe), 3.51 (s, 2H, CH_2). ^{13}C (75 MHz, $CDCl_3$) δ 172.0, 163.7, 160.5, 131.0, 130.9, 129.8, 115.6, 115.4, 52.1, 40.3.

*3.1.14. α-Bromo-(4-fluorophenyl)-acetic acid methyl ester **25**[14]*

Methyl ester **22** (4.10 g, 24.4 mol) was brominated with *N*-bromosuccinimide (4.34 g, 24.4 mmol) and benzoyl peroxide (24.6 mg, 0.106 mmol) under the same conditions as ester **20** to afford 5.39 g of the brominated methyl ester **25** (89%) as a yellow oil. ^{1}H (300 MHz, $CDCl_3$) δ 7.54 (dd, 2H, *J*=8.8, 5.2 Hz, Ar), 7.05 (t, 2H, *J*=8.6 Hz, Ar), 5.34 (s, 1H, CH), 3.79 (s, 3H, OMe). ^{13}C (75 MHz, $CDCl_3$) δ 168.8, 164.8, 161.5, 131.8, 130.9, 116.1, 115.8, 53.5, 45.5.

*3.1.15. 2-(4-Fluorophenyl)-3-(2-hydroxypyridin-4-yl)-acrylic acid methyl esters **33** and **34***

α-Bromo ester **25** (513 mg, 2.08 mmol) reacted with triethylphosphite (2×431 mg, 2.605 mmol) to produce phosphonyl ester **28**. Phosphonyl ester **28** was then coupled with carbaldehyde **11** (493 mg, 2.08 mmol) under the same conditions as phosphonyl ester **26** to afford 503 mg of alkenes **33** and **34** (1.84 mmol, 89%) as a white solid and a mixture of the *E* and *Z* isomers (64:36).

*3.1.15.1. (E)-2-(4-Fluorophenyl)-3-(2-hydroxypyridin-4-yl)-acrylic acid methyl ester **33**.* ^{1}H (300 MHz, $CDCl_3$) δ 12.61 (br s, 1H, NH), 7.58 (s, 1H, Ar), 7.19–7.01 (m, 5H, Ar), 6.40 (s, 1H, =CH), 5.72 (d, 1H, *J*=6.8 Hz, Ar), 3.82 (s, 3H, OMe). ^{13}C (75 MHz, $CDCl_3$) δ 167.2, 165.3, 164.5, 161.2, 148.3, 137.4, 136.6, 134.1, 131.6, 130.2, 121.7, 115.8, 115.7, 107.5, 52.9. Mp: 190–193 °C. MS: *m*/*z*=274.1003 ($[M+H]^+$). HRMS: calcd for $C_{15}H_{12}FNO_3$+H 274.0874, found 274.0872.

*3.1.15.2. (Z)-2-(4-Fluorophenyl)-3-(2-hydroxypyridin-4-yl)-acrylic acid methyl ester **34**.* ^{1}H (300 MHz, $CDCl_3$) δ 12.91 (br s, 1H, NH), 7.46–7.41 (m, 2H, Ar), 7.37 (d, 1H, *J*=6.8 Hz, Ar), 7.10 (t, 2H, *J*=8.6 Hz, Ar), 6.75 (s, 1H, Ar), 6.54 (s, 1H, =CH), 6.26 (dd, 1H, *J*=6.8, 1.5 Hz, Ar), 3.83 (s, 3H, OMe). ^{13}C (75 MHz, MeOD) δ 168.7, 165.2, 165.1, 161.8, 149.2, 138.5, 134.4, 131.7, 128.8, 128.7, 128.1, 119.0, 116.3, 116.0, 106.8, 52.9. Mp: 238–240 °C. MS: *m*/*z*=274.1045 ($[M+H]^+$). HRMS: calcd for $C_{15}H_{12}FNO_3$+H 274.0874, found 274.0874.

*3.1.16. 9-Fluoro-1-hydroxy-benz[h]isoquinoline-6-carboxylic methyl ester **37***

Methyl esters **33** and **34** (300 mg, 1.10 mmol) were cyclised under the same conditions as esters **29** and **30** to produce 92.9 of the desired cyclic ester **37** as a white solid (0.34 mmol, 31%). ^{1}H (300 MHz, DMSO-d_6) δ 11.99 (br s, 1H, NH), 10.02 (d, 1H, *J*=13.4 Hz, Ar), 8.65 (t, 1H, *J*=7.8 Hz, Ar), 8.20 (s, 1H, Ar), 7.60 (t, 1H, *J*=8.1 Hz, Ar), 7.55 (d, 1H, *J*=6.5 Hz, Ar), 6.87 (d, 1H, *J*=6.5 Hz, Ar), 3.99 (s, 3H, OMe). ^{13}C (75 MHz, DMSO-d_6) δ 166.9, 162.9, 162.1, 159.7, 139.2, 133.6, 133.4, 132.2, 132.1, 128.2, 128.1, 127.9, 125.1, 120.0, 119.9, 116.2, 115.9, 111.1, 110.7, 105.7, 52.8. ν_{max} (film)/cm^{-1} 3128, 3105, 2835, 2812, 1724, 1658, 1632, 1604, 1550, 1512, 1415, 1249, 1269, 1192. Mp: 280–281 °C. MS: *m*/*z*=272.0899 ($[M+H]^+$). HRMS: calcd for $C_{15}H_{10}FNO_3$+H 272.0717, found 272.0726.

A side product was also isolated as a white solid (108 mg, 39.5 mmol) and identified as tetrahydro-benz[*h*]isoquinoline **38**.

*3.1.17. 9-Fluoro-1-oxo-1,2,5,6-tetrahydro-benz[h]isoquinoline-6-carboxylic acid methyl ester **38***

^{1}H (300 MHz, $CDCl_3$) δ 13.29 (br s, 1H, NH), 8.71 (d, 1H, *J*=11.1 Hz, Ar), 7.41 (d, 1H, *J*=5.8 Hz, Ar), 7.26 (d, 1H, *J*=7.5 Hz, Ar), 6.99 (s, 1H, Ar), 6.37 (d, 1H, *J*=5.7 Hz, Ar), 4.02 (s, 1H, CH), 3.63 (s, 3H, OMe), 3.04–2.97 (m, 2H, CH_2). ^{13}C (75 MHz, $CDCl_3$) δ 172.7, 163.9, 163.0, 160.7, 150.0, 133.9, 133.1, 132.9, 129.6, 129.5, 128.4, 121.1, 114.6, 114.3, 114.2, 114.0, 108.9, 52.4, 42.9, 31.8. ^{13}C DEPT (75 MHz, $CDCl_3$) δ 134.1, 129.9, 129.8, 114.9, 114.7, 114.6, 114.4, 109.3, 52.7, 43.2, 32.1. ν_{max} (film)/cm^{-1} 3405, 2950, 2839, 1646, 1450, 1411, 1111. Mp: 171–173 °C. MS: *m*/*z*=296.0739 ($[M+Na]^+$). HRMS: calcd for $C_{15}H_{13}FNO_3$+H 274.0874, found 274.0886.

Acknowledgements

The financial support for this work was provided by the Medical Research Council Technology Gap Fund and the University of Dundee. R.M. is grateful to Dr. Ian Sword and the University of Glasgow for financial support. We would also like to thank Dr. Richard Hartley for very helpful discussions.

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