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Synthesis of substituted naphthalenes from α-tetralones generated by a xanthate radical addition–cyclisation sequence

Alejandro Cordero-Vargas, Inés Pérez-Martín, Béatrice Quiclet-Sire and Samir Z. Zard*
Laboratoire de Synthèse Organique associé au CNRS, Ecole Polytechnique, 91128 Palaiseau, France. E-mail: zard@poly.polytechnique.fr

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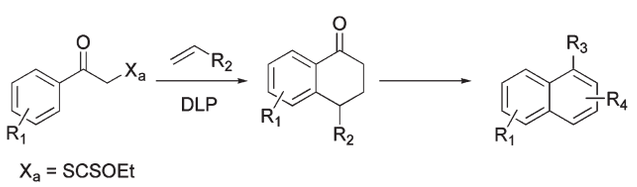
A simple, highly efficient and cheap synthesis of substituted naphthalenes is reported. These aromatic compounds can be easily prepared in acidic or basic conditions from α-tetralones, obtained by a xanthate-mediated addition–cyclisation sequence.

Introduction

Much attention has recently been focused on the regioselective synthesis of substituted naphthalene derivatives.[1] These compounds constitute the basic skeleton of many biologically important natural products and pharmaceuticals[2] and synthetic routes to the naphthalene moiety are highly desirable.

Due to their stability, these aromatic compounds react with difficulty under mild conditions and, on many occasions, the use of drastic methods results in non-regioselective reactions. In addition, when regioselectivity exists, it usually depends on the nature of the substituents already present in the aromatic ring (electron-withdrawing or electron-donating groups).

In order to circumvent these limitations, we have developed a simple methodology for the preparation of the naphthalene skeleton by using the functionalisation of an α-tetralone and its aromatisation under acidic or basic conditions, independently of the nature of the substituents in the ring (Scheme 1).

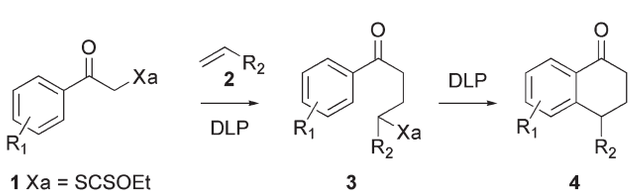


Scheme 1

It is known that tetralones can be transformed into their corresponding aromatic structures by different methods such as oxidation with DDQ or Pd/C at high temperatures. However, commercially available tetralones are limited, as well as general methods to obtain functionalised precursors for the desired aromatic systems.

Results and discussion

A few years ago, we reported a new method for the preparation of α-tetralones using xanthate free radical chemistry (Scheme 2).[3]



Scheme 2 Radical addition–cyclisation sequence.

We had shown that xanthates such as **1** undergo a radical chain reaction to a great variety of olefinic traps **2** to give adduct **3**, which can be used as a starting point for another radical sequence, in this case, to construct the six-membered ring of α-tetralone **4**. This methodology has important virtues such as simplicity, cheapness, absence of heavy metals, ease of scale-up and the possibility of operating under fairly concentrated conditions.

With the aim of accessing substituted naphthalenes, obtained from modified α-tetralones, we prepared different precursors through a two-step one-pot protocol using a range of xanthates and olefins (Table 1). This is in contrast to our earlier work where the intermediate adduct **3** was isolated.

The selection of vinyl pivalate **2a** as the radical trap was not arbitrary. It was anticipated that the OPiv group could serve as a leaving group for the aromatisation in acidic media in order to facilitate the last step of the route. Furthermore, the pivaloxy group is compatible with a number of useful transformations as shown below.

One important aspect that emerges from inspection of the examples in Table 1 is that in principle, practically all of the positions of the tetralone structure may be functionalised by the appropriate choice of the initial xanthate and olefin components or by subsequent modification of the product. Although the overall yields of tetralones **4a**–**4f** may seem moderate, it must be realised that they correspond to two difficult radical processes: an intermolecular addition to a non-activated olefin and a ring closure to an aromatic ring. Both of these steps would have been difficult to perform using other radical methods. As for substituents on the starting xanthate moiety, both electrodonating and electron-withdrawing groups are tolerated.

In the case of tetralones **4a**, **4b** and **4c**, we found that addition of camphorsulfonic acid (CSA) during the ring-closing step was beneficial and allowed up to 20% increase in yield. Protonation of the ketone oxygen presumably causes a speeding up of the radical addition to the aromatic ring.[4] In contrast, with **4d** and **4f**, which contain electron donating groups, the addition of CSA proved deleterious causing a rapid degradation and a dramatic lowering of the yield (to about 10%). The reason may be the premature elimination of the pivaloxy group. Such an elimination is facilitated by electron releasing substituents.

Preparation of the required naphthalenes was accomplished starting from these suitably substituted tetralones or by modification of the precursors followed by aromatisation under acidic or basic conditions as summarized in Table 2 and Scheme 3.

The initial experiments were carried out directly on the tetralones **4a**, **4e** and **4f** (entries 1, 2 and 3) employing *p*-toluenesulfonic acid (PTSA) in refluxing toluene. We obtained the corresponding naphthols in good yields, except in the case of tetralone **4f** (entry 3), where a complex mixture of products was observed.

Next, a simple, but important functionalisation was made prior to the aromatisation step. In this way, tetralones **4a**, **4c**, **4d** and **4f** were treated with pyridinium bromide perbromide, to give compounds **7**, **9**, **12** and **14** respectively, without affecting the pivalate group.[5] These compounds were then subjected directly to different aromatisation processes. Thus, in the case

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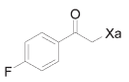
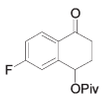
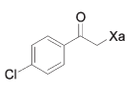
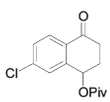
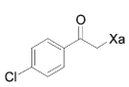
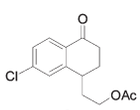
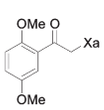
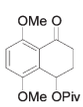
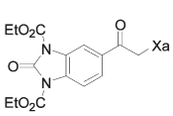
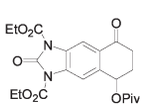
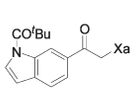
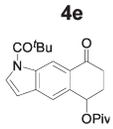
Table 1 Formation of α-tetralones employed like precursors[a]

Xanthate **1**	Olefin **2**	Product **4**	Yield[b] (%)
 **1a**	 **2a**	 **4a**	49[c]
 **1b**	**2a**	 **4b**	81[c]
 **1b**	 **2b**	 **4c**	50
 **1c**	**2a**	 **4d**	52[d]
 **1d**	**2a**	 **4e**	54
 **1e**	**2a**	 **4f**	41

[a] Reactions were performed with dilauroyl peroxide (DLP) in 1,2-dichloroethane at reflux. [b] Global yield of the xanthate radical addition–cyclisation processes. [c] Camphorsulfonic acid (CSA) was added (10 mmol%). [d] If CSA is added, a rapid degradation is observed.

of **7** and **9** the reaction was carried out under acidic conditions with PTSA and pyridinium bromide perbromide, respectively, and the corresponding α-bromonaphthols were produced in good yields (entries 4 and 5). These compounds are important in organic synthesis because they are substrates for various transition metal catalysed reactions and are appropriate precursors for the generation of benzynes which, although not isolable, act as dienophiles that can be trapped with dienes in Diels–Alder reactions to give more complex tricyclic compounds.[6] Alternatively, the treatment of tetralones **7** and **12** with Li_2CO_3 and LiBr in dimethylformamide gave regioselectively monoprotected naphthalenediols **11** and **13** in 57 and 64% yield respectively (entries 6 and 7), but unfortunately, in the case of the tetralone **14**, a complex mixture was obtained (entry 8).

Tetralone **15**, which possesses a xanthate group at the carbon in the α position to the carbonyl group, was obtained in 68% yield by nucleophilic displacement of the bromine atom in tetralone **7**. The aromatisation was carried out in the presence of PTSA, and the product **16** was obtained in excellent yield, resulting from the aromatisation process and nucleophilic addition of the resulting phenolic oxygen onto the thiocarbonyl group (entry 9).

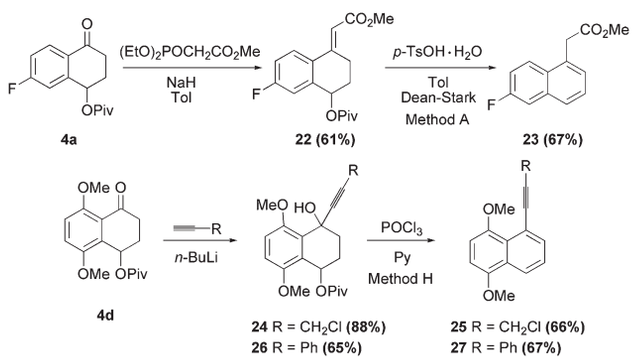
When α-bromotetralone **7** was treated with ethyl cyanoacetate and K_2CO_3, naphthalene **17** was produced in 51% yield after acidification with an aqueous citric acid solution (entry 10).[7]

In the formation of naphthol **18**, advantage was taken of the nucleophilic character of the α-carbon to the carbonyl group in the corresponding tetralone to carry out an aldol condensation with benzaldehyde. The isomerisation of the exocyclic double bond in the basic medium generates the corresponding naphthol **18** in moderate yield (entry 11).

These last two examples illustrate the possibility of creating C–C bonds next to the carbonyl group in order to obtain more complex naphthalene structures. In recent times, the synthesis of such structures has relied heavily on transition metal catalysed processes.[8]

Naphthylamines can be obtained *via* the corresponding Schiff base. For example, when compound **4b** was treated with benzylamine followed by *in situ* aromatisation of the intermediate imine with $AlCl_3$, naphthalene **19a** was produced in good yield (entry 12). When a Fischer indole synthesis was carried out with the same tetralone **4b**, by treatment with phenylhydrazine in polyphosphoric acid,[9] the tetracyclic compound **20** was obtained in 56% yield (entry 13). These types of products have attracted a great deal of attention from synthetic as well as medicinal chemists because such structures are present in a number of natural products.[10]

Finally, examples of treatment of the α-tetralones with carbon nucleophiles and aromatisation are depicted in Scheme 3.



Scheme 3 Aromatisation of compounds derived from tetralones.[11]

In the first case, starting from the tetralone **4a** and applying a Horner–Emmons reaction, olefin **22** was obtained in good yield. The aromatisation process was carried out with *p*-toluenesulfonic acid to produce naphthalene **23** in 67% yield.

Lithium acetylides could also be added to the tetralone carbonyl without affecting the pivaloxy group as illustrated by the efficient synthesis of **24** and **26**. Subsequent aromatization with $POCl_3$/Py gave the corresponding naphthalenes. In these cases, the usual treatment with PTSA was not satisfactory. Compound **25** is especially interesting since it contains a reactive propargyl chloride and thus represents a springboard for numerous subsequent transformations.

In summary, we have described a convergent approach to naphthalene structures with a diverse pattern of substitution. The process involves cheap, readily available reagents and is based on radical chemistry that does not involve the use of heavy metals such as tin or mercury.

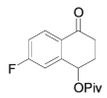
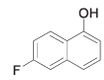
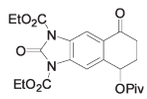
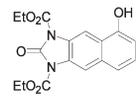
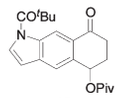
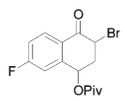
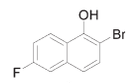
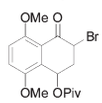
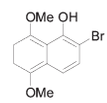
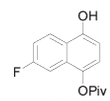
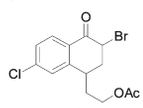
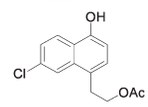
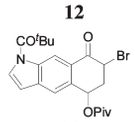
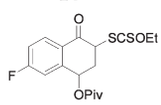
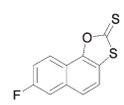
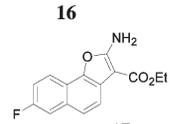
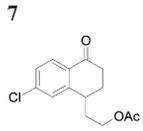
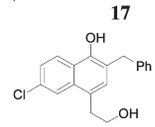
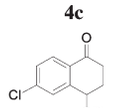
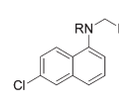
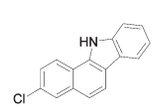
Experimental

All reactions were carried out under an inert atmosphere. Commercial reagents were used as received without further purification. All products were purified by using silica gel SDS 60 C. C. 40–63 or by crystallisation. NMR spectra were recorded in $CDCl_3$ with TMS as an internal standard at room temperature on a Bruker AMX400 operating at 400 MHz for ^1H and 100 MHz for ^{13}C. Infrared absorption spectra were recorded as a solution in CCl_4 with a Perkin-Elmer 1600 Fourier Transform Spectrophotometer. Some mass spectra were determined at 70 eV with an AutoSpec Micromass and the others were recorded with an HP 5989B mass spectrometer using ammonia as the reagent gas. Melting points were determined using a Reichert microscope apparatus and were uncorrected.

Dithiocarbonic acid [2-(2,5-dimethoxy-phenyl)-2-oxo-ethyl] ester ethyl ester (1c)

To a cold (0 °C) solution of 2,5-dimethoxy-2′-bromoacetophenone[12] (5 g, 19.29 mmol) in acetone (38.6 mL)

Table 2 Aromatisation of substituted α-tetralones

	Tetralone	Method[a]	Product	Yield (%)
1	 **4a**	A	 **5**	84
2	 **4e**	A	 **6**	74
3	 **4f**	A	—	—
4	 **7**	A	 **8**	69
5	 **9**	B	 **10**	75
6	**7**	C	 **11**	57
7	 **12**	C	 **13**	64
8	 **14**	C	—	—
9	 **15**	A	 **16**	90
10	**7**	D	 **17**	51
11	 **4c**	E	 **18**	32
12	 **4b**	F	 **19a** R=H **19b** R=Ac	75
13	**4b**	G	 **20**	56

[a] METHOD A: Tetralone derivative (1 mmol) in toluene (35 mL) containing *p*-toluenesulfonic acid (3 mmol) was refluxed using a Dean–Stark apparatus. METHOD B: Tetralone derivative (1 mmol) in acetic acid (10 mL) containing pyridinium bromide perbromide (1 mmol) was stirred at room temperature for 1 h. METHOD C: Tetralone derivative (1 mmol) in dry dimethylformamide (6 mL) containing Li_2CO_3 (2 mmol) and LiBr (2 mmol) was warmed at 140 °C. METHOD D: To a cold solution of ethyl cyanoacetate (12 mmol) in acetone (2 mL) was added K_2CO_3 (3 mmol) and the tetralone (1 mmol) was added at 0 °C. The mixture was stirred at room temperature and then acidified with an aqueous solution of citric acid. METHOD E: To the tetralone derivative (1 mmol) and benzaldehyde (1.5 mmol) in dry *tert*-butanol (10 mL) was added *t*-BuOK (2 mmol) and the mixture was heated under reflux conditions. METHOD F: Tetralone derivative (1 mmol) in dry toluene (10 mL) containing benzylamine (2 mmol) was heated under reflux for 3 h. Then, $AlCl_3$ (2 mmol) was added at room temperature and the solution was refluxed for 15 min. METHOD G: Fischer indole synthesis. The tetralone (1 mmol) was treated with phenylhydrazine (2 mmol) and polyphosphoric acid (2.5 mmol), and the mixture was heated at 100 °C for 15 min.

was added portionwise potassium *O*-ethylxanthate (3.4 g, 21.22 mmol). The reaction mixture was stirred at 0 °C for a further 1 h, the solvent was evaporated and the resulting mixture partitioned between water and CH_2Cl_2. The aqueous phase was extracted with CH_2Cl_2, the combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure. Recrystallization of the residue from CH_2Cl_2–petroleum ether gave xanthate **1c** (95% yield) as yellow crystals. mp = 71–72 °C; ν_{max}/cm^{-1} 1676 (C=O), 1223 (S–*C*=S), 1050 (*S*–*C*=S); δ_H (400 MHz) 7.31 (1H, d, *J* = 3.2 Hz, C*H* arom), 7.07 (2H, dd, *J* = 9.2, 3.2 Hz C*H* arom), 6.93 (1H, d, *J* = 9.2 Hz, C*H* arom), 4.59–4.64 (4H, m, OCH_2 and CH_2–S), 3.91 (3H, s, OCH_3), 3.78 (3H, s, OCH_3), 1.39 (3H, dd, *J* = 7.2, 7.2 Hz, CH_3); δ_C (100 MHz) 213.8 (C, *C*=S), 193.5 (C, *C*=O), 153.8 (C, *C*–OMe), 153.4 (C, *C*–OMe), 126.6 (C, *C*–CO), 121.3 (CH, *C*H arom), 114.4 (CH, *C*H arom), 113.2 (CH, *C*H arom), 70.3 (CH_2, O*C*H_2), 56.2 (CH_3, O*C*H_3), 55.9 (CH_3, O*C*H_3), 47.7 (CH_2, *C*H_2–S), 13.8 (CH_3); *m*/*z* (CI + NH_3) 318 (MH^+ + NH_3), 301 (MH^+).

General procedure for the preparation of tetralones 4a–4f

A solution of xanthate (1 mmol) and vinyl pivalate (2 mmol) in 1,2-dichloroethane (DCE) (1 mL) was refluxed for 15 min under argon. Lauroyl peroxide (DLP) (5 mol%) was then added to the refluxing solution, followed by additional portions (2.5 mol% every 90 min). When starting material was completely consumed the mixture was cooled to room temperature, concentrated under reduced pressure and the crude mixture, redissolved in 1,2-dichloroethane (10 mL) together with camphorsulfonic acid (0.1 mmol, when electron-withdrawing groups are present in the aromatic ring). DLP was then added to the refluxing solution (20 mol% every hour). When starting material was totally consumed, the mixture was cooled to room temperature, concentrated under reduced pressure and purified by flash column chromatography (silica gel, petroleum ether–ethyl acetate, a small layer of basic alumina was placed on the top of the silica to remove any lauric acid present) to give the final tetralone.

7-Fluoro-4-oxo-1,2,3,4-tetrahydro-1-naphthalenyl pivalate (4a)

Obtained from xanthate **1a**[13] as a yellow oil (49%) (silica gel, petroleum ether–ethyl acetate, 9 : 1); ν_{max}/cm^{-1} 1732 (O–*C*=*O*), 1694 (C=O), 1148 (*O*–*C*=O); δ_H (400 MHz) 7.97 (1H, dd, *J* = 8.8, 5.2 Hz, C*H* arom), 7.12 (2H, m, C*H* arom), 6.06 (1H, dd, *J* = 8.0, 4.0 Hz, 1-H), 2.89 (1H, ddd, *J* = 20.0, 8.0, 4.0 Hz, 3-H_a), 2.68 (1H, ddd, *J* = 16.8, 8.0, 4.0 Hz, 3-H_b), 2.42 (1H, m, 2-H_a), 2.24 (1H, m, 2-H_b), 1.25 (9H, s, 3 × Me); δ_C (100 MHz) 195.4 (C, C-4), 176.3 (C, O–*C*O), 166.0 (C, C-7, $^1J_{C-F}$ = 254.6 Hz), 144.5 (C, *C*–CO), 130.6 (CH, d, $^3J_{C-F}$ = 10.5 Hz, *C*H arom), 116.4 (CH, d, $^2J_{C-F}$ = 23.0 Hz, *C*H arom), 115.5 (C, *C*–CH), 114.4 (CH, d, $^2J_{C-F}$ = 23.0 Hz, *C*H arom), 68.6 (CH, C-1), 39.1 (C, ^{t}Bu), 34.7 (CH_2, C-3), 28.7 (CH_2, C-2), 27.1 (3 × CH_3, ^{t}Bu); *m*/*z* (CI + NH_3) 282 (MH^+ + NH_3), 265 (MH^+), 164 (MH^+ − OPiv); Anal. calcd. for $C_{15}H_{17}O_3F$: C, 68.17; H, 6.48. Found: C, 68.31; H, 6.65%.

7-Chloro-4-oxo-1,2,3,4-tetrahydro-1-naphthalenyl pivalate (4b)

Obtained from xanthate **1b**[13] as a yellow solid (81%), (silica gel, petroleum ether–ethyl acetate, 9 : 1), mp 76–80 °C (petroleum ether); ν_{max}/cm^{-1} 1733 (O–*C*=*O*), 1696 (C=O), 1143 (*O*–*C*=O); δ_H (400 MHz) 8.00 (1H, d, *J* = 8.0 Hz, C*H* arom), 7.42 (1H, d, *J* = 8.0 Hz, C*H* arom), 7.41 (1H, s, C*H* arom), 6.05 (1H, dd, *J* = 8.0, 4.0 Hz, 1-H), 2.90 (1H, ddd, *J* = 18.0, 10.0, 4.0 Hz, 3-H_a), 2.69 (1H, ddd, *J* = 20.0, 8.0, 4.0 Hz, 3-H_b), 2.41 (1H, m, 2-H_a), 2.26 (1H, m, 2-H_b), 1.25 (9H, s, 3 × Me); δ_C (100 MHz) 195.3 (C, C-4), 177.3 (C, O–*C*O), 142.5 (C, *C*–CO), 139.9 (C, C-7), 129.9 (C, *C*–CH), 128.9 (*C*H arom), 128.6 (*C*H arom), 127.4 (*C*H arom), 67.9 (CH, C-1), 38.6 (C, ^{t}Bu), 34.2 (CH_2, C-3), 28.1 (CH_2, C-2), 27.1 (3 × CH_3, ^{t}Bu); *m*/*z* (CI + NH_3) 299 (MH^+ + NH_3), 297 (MH^+ + NH_3), 283 (MH^+), 281 (MH^+), 182 (MH^+ − OPiv), 180 (MH^+ − OPiv); Anal. calcd. for $C_{15}H_{17}O_3Cl$: C, 64.17; H, 6.10. Found: C, 64.04; H, 6.25%.

2-(7-Chloro-4-oxo-1,2,3,4-tetrahydro-1-naphthalenyl)ethyl acetate (4c)

According to the typical procedure, a solution of xanthate **1b** (3.80 g, 13.8 mmol) and 3-butenyl acetate **2b** (3.15 g, 27.6 mmol) in DCE (14 mL) was treated with DLP. A refluxing solution of the crude adduct and CSA (0.32 g, 1.4 mmol) in DCE (140 mL) was then subjected to the described reaction conditions to afford tetralone **4c** as a yellow oil (50%) (silica gel, petroleum ether–ethyl acetate, 9 : 1). ν_{max}/cm^{-1} 1745 (O–*C*=*O*), 1691 (C=O); δ_H (400 MHz) 7.96 (1H, d, *J* = 8.0 Hz, C*H* arom), 7.26–7.30 (2H, m, 2 × C*H* arom), 4.15–4.23 (4H, m, CH_2–OAc and CH–CH_2), 3.06 (1H, m, 1-H), 2.74 (1H, ddd, *J* = 17.9, 11.6, 5.1 Hz, 3-H_a), 2.60 (1H, ddd, *J* = 18.0, 5.2, 5.2 Hz, 3-H_b), 2.28 (1H, m, 2-H_a), 2.01 (1H, m, 2-H_b), 2.07 (3H, s, CO–CH_3); δ_C (100 MHz) 196.6 (C, *C*=O), 171.0 (C, O–*C*O), 148.7 (C, C-7), 139.9 (C, *C*-CO), 130.2 (CH, *C*–CH), 129.3 (*C*H arom), 128.1 (*C*H arom), 127.5 (*C*H arom), 62.1 (CH_2, *C*H_2–OAc), 42.8 (CH, C-1), 34.9 (CH_3, OC(O)*C*H_3), 34.6 (CH_2, C-3), 33.1 (CH_2, CH–*C*H_2), 26.7 (C-2); *m*/*z* (CI + NH_3) 286 (MH^+ + NH_3), 284 (MH^+ + NH_3), 269 (MH^+), 267 (MH^+); Anal. calcd. for $C_{14}H_{15}ClO_3$: C, 63.04; H, 5.67. Found: C, 62.83; H, 5.73%.

5,8-Dimethoxy-4-oxo-1,2,3,4-tetrahydro-1-naphthalenyl pivalate (4d)

Obtained from xanthate **1c** as a yellow solid (52%) (silica gel, petroleum ether–ethyl acetate, 4 : 1). mp 102–103 °C (CH_2Cl_2–petroleum ether); ν_{max}/cm^{-1} 1728 (O–*C*=*O*), 1695 (C=O); δ_H (400 MHz) 7.06 (1H, d, *J* = 8.8 Hz, C*H* arom), 6.97 (1H, d, *J* = 9.2 Hz, C*H* arom), 6.31 (1H, br s, 1-H), 3.86 (3H, s, OCH_3), 3.77 (3H, s, OCH_3), 2.82 (1H, ddd, *J* = 15.2, 5.1, 5.1 Hz, 3-H_a), 2.53 (1H, ddd, *J* = 16.4, 16.4, 4.8 Hz, 3-H_b), 2.33 (1H, dddd, *J* = 14.4, 14.4, 2.3, 0.0 Hz, 2-H_a), 2.17 (1H, dddd, *J* = 14.2, 14.2, 3.6, 3.6 Hz, 2-H_b), 1.13 (9H, s, ^{t}Bu); δ_C (100 MHz) 197.2 (C, *C*=*O*), 177.6 (C, O–*C*O), 153.4 (C, *C*–OMe), 150.6 (C, *C*–OMe), 130.0 (C, *C*–CO), 122.6 (C, *C*–CH), 116.8 (*C*H arom), 113.5 (*C*H arom), 63.7 (C-1), 56.5 (CH_3, OMe), 56.2 (CH_3, OMe), 38.9 (C, ^{t}Bu), 34.9 (CH_2, C-3), 27.1 (3 × CH_3, ^{t}Bu), 26.9 (CH_2, C-2); *m*/*z* (CI + NH_3) 307 (MH^+), 205 (MH^+ − OPiv); Anal. calcd. for $C_{17}H_{22}O_5$: C, 66.65; H, 7.24. Found: C, 66.32; H, 7.25%.

Diethyl 5-[(2,2-dimethylpropanoyl)oxy]-2,8-dioxo-5,6,7,8-tetrahydro-1*H*-naphtho[2,3-*d*]imidazole-1,3(2*H*)-dicarboxylate (4e)

Obtained from xanthate **1d**[14] as a white solid (54%) (silica gel, petroleum ether–ethyl acetate, 8 : 2), mp 120–123 °C (AcOEt); ν_{max}/cm^{-1} 1791 (O–*C*=*O*), 1752 (O–*C*=*O*), 1731 (O–*C*=*O*), 1694 (C=O); δ_H (400 MHz) 8.10 (2H, s, 2 × C*H* arom), 6.36 (1H, dd, *J* = 7.2, 4.0 Hz, 5-H), 4.46–4.55 (4H, m, 2 × COOCH_2CH$_3$), 2.81 (1H, m, 7-H_a), 2.70 (1H, m, 7-H_b), 2.50 (1H, m, 6-H_a), 2.14 (1H, m, 6-H_b), 1.47 (6H, dd, *J* = 15.2, 6.8 Hz, 2 × COOCH$_2$CH_3), 1.14 (9H, s, ^{t}Bu); δ_C (100 MHz) 195.4 (C, *C*=O), 177.3 (C), 149.6 (2 × C), 147.7 (C), 131.4 (C, *C*–N), 129.5 (C, *C*–N), 126.6 (C, *C*–CO), 125.1 (*C*H arom), 123.6 (C, *C*–CH), 114.5 (*C*H arom), 66.8 (CH, C-5), 65.6 (CH_3), 64.6 (CH_3), 39.0 (C, ^{t}Bu), 33.6 (CH_2, C-7), 27.4 (CH_2, C-6), 26.9 (3 × CH_3, ^{t}Bu), 14.1 (2 × CH_3, 2 × CO_2Et); *m*/*z* (CI + NH_3) 464 (MH^+ + NH_3), 447 (MH^+).

1-(2,2-Dimethylpropanoyl)-8-oxo-5,6,7,8-tetrahydro-1*H*-benzo[*f*]indol-5-yl pivalate (4f)

Obtained from xanthate **1e**[13] as a white solid (41%) (silica gel, petroleum ether–ethyl acetate, 95 : 5), mp 149–151 °C (petroleum ether); ν_{max}/cm^{-1} 1724 (O–*C*=*O*), 1682 (C=O); δ_H (400 MHz) 8.06 (1H, d, *J* = 8.0 Hz, C*H* arom), 7.75 (1H, d, *J* = 3.6 Hz, C*H* arom), 7.63 (1H, d, *J* = 8.4 Hz, C*H* arom), 6.63 (1H, d, *J* = 3.6 Hz, C*H* arom), 6.44 (br s, 5-H), 2.98 (1H, ddd, *J* = 18.4, 12.6, 6.0 Hz, 7-H_a), 2.70 (1H, m, 7-H_b), 2.35–2.49 (2H, m, 6-H_2), 1.58 (9H, s, ^{t}Bu), 1.06 (9H, s, ^{t}Bu); δ_C (100 MHz) 197.9 (C, *C*=*O*), 180.1 (C, N–*C*O), 177.5 (C, O–*C*O), 136.0 (C, *C*–N–Piv), 133.6 (C, *C*–CO), 130.2 (C, *C*–C–N), 130.0 (*C*H arom), 129.3

(C, *C*–CH), 123.1 (*C*H arom), 121.7 (*C*H arom), 107.1 (*C*H arom), 65.8 (CH, C-5), 42.1 (C, N–CO–*C*$(CH_3)_3$), 38.8 (C, O–CO–*C*$(CH_3)_3$), 32.6 (CH_2, C-7), 29.0 (3 × CH_3, N–CO–C(*C*$H_3)_3$), 27.5 (CH_2, C-6), 27.1 (3 × CH_3, O–CO–C(*C*$H_3)_3$); *m*/*z* (CI + NH_3) 387 ($MH^+ + NH_3$), 370 (MH^+), 268 ($MH^+ - OPiv$).

Aromatisation of substituted α-tetralones

Method A. ***6-Fluoro-1-naphthol (5).*** A solution of tetralone **4a** (0.1 g, 0.378 mmol) and of PTSA·H_2O (0.21 g, 1.13 mmol) in 12.5 mL of toluene was refluxed for 3 h with a Dean–Stark apparatus. When the starting material was totally consumed, the reaction mixture was allowed to cool to room temperature, neutralised with saturated aqueous Na_2CO_3, extracted with CH_2Cl_2, dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified by flash column chromatography (silica gel, petroleum ether–ethyl acetate, 9 : 1) to give naphthol **5** (84%) as a pale brown solid. mp 112–113 °C (petroleum ether); ν_{max}/cm^{-1} 3605 (OH); δ_H (400 MHz) 8.21 (1H, dd, *J* = 10.0, 6.0 Hz, C*H* arom), 7.42 (1H, dd, *J* = 14.0, 6.0 Hz, C*H* arom), 7.22–7.38 (3H, m, 3 × C*H* arom), 6.75 (1H, d, *J* = 4.0 Hz, C*H* arom); δ_C (100 MHz) 161.3 (C, d, $^1J_{CF}$ = 244.6 Hz, *C*–F), 151.8 (C, C-1), 135.9 (C, d, $^3J_{CF}$ = 9.3 Hz, *C*–CH), 127.3 (*C*H arom), 124.7 (CH, d, $^3J_{CF}$ = 9.2 Hz, *C*H arom), 121.6 (C, *C*–C–OH), 120.1 (CH, d, $^4J_{CF}$ = 5.1 Hz, *C*H arom), 115.5 (CH, d, $^2J_{CF}$ = 25.1 Hz, *C*H arom), 110.7 (CH, d, $^2J_{CF}$ = 20.3 Hz, *C*H arom), 107.9 (CH, d, $^5J_{CF}$ = 2.2 Hz, *C*H arom); *m*/*z* (CI + NH_3) 163 (MH^+); *m*/*z* (rel intensity) 162 (M^+, 100); HRMS calcd for $C_{15}H_{13}ClO_2$: 162.048093; found 162.047009.

Diethyl 5-hydroxy-2-oxo-1H-naphtho[2,3-d]imidazole-1,3(2H)-dicarboxylate (6). A solution of tetralone **4e** (40 mg, 0.09 mmol) and PTSA·H_2O (44 mg, 0.23 mmol) in toluene (3 ml) was stirred at reflux for 2.5 h using a Dean–Stark apparatus. The reaction mixture was allowed to cool to room temperature, diluted with a saturated sodium bicarbonate solution, and extracted with dichloromethane. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The residue was purified by column chromatography (silica gel, petroleum ether–ethyl acetate, 75 : 25) to afford compound **6** (23 mg, 74%) as an amorphous solid; ν_{max}/cm^{-1} 3608 (OH), 1797 (*C*=O), 1748(*C*=O), 1714 (*C*=O); δ_H (400 MHz) 8.22 (1H, d, *J* = 9.2 Hz), 8.14 (1H, d, *J* = 9.2 Hz), 7.35–7.37 (2H, m), 6.84 (1H, m), 6.84 (1H, m), 5.90 (1H, br s, OH), 4.55–4.63 (4H, m, 2 × C*H*$_2$CH$_3$), 1.51–1.52 (6H, m, 2 × CH$_2$C*H*$_3$); δ_C (100 MHz) 203.9 (C, N–*C*O$_2$Et), 200.3 (C, N–*C*O$_2$Et), 190.6 (C, N–*C*O–N), 152.1 (C), 150.0 (C), 148.6 (C), 126.8 (*C*H arom), 122.4 (C), 121.5 (C), 120.0 (*C*H arom), 114.5 (*C*H arom), 112.6 (*C*H arom), 107.9 (*C*H arom), 65.2 (CH_2, *C*H$_2$CH$_3$), 64.2 (CH_2, *C*H$_2$CH$_3$), 14.1 (2 × CH_3, 2 × CH$_2$*C*H$_3$); *m*/*z* (CI + NH_3) 345 (MH^+), 362 ($M^+ + NH_3$); *m*/*z* (rel intensity) 344 (M^+, 79), 272 ($M^+ - 1 - C_3H_5O_2$, 30), 200 (100); HRMS calcd for $C_{17}H_{16}N_2O_6$: 344.100836; found 344.101677.

2-Bromo-6-fluoro-1-naphthol (8). Pyridinium bromide perbromide (52 mg, 0.16 mmol) was added to a solution of tetralone **4a** (43 mg, 0.16 mmol) in acetic acid (1.6 ml) and the mixture was then stirred for 2 h at room temperature. It was diluted with a saturated sodium carbonate solution, and extracted with ethyl acetate. The combined organic layers were dried, filtered and concentrated. The residue was dissolved in toluene (5.6 ml) and PTSA·H_2O (91 mg, 0.48 mmol) was added. The solution was stirred at reflux for 3.5 h using a Dean–Stark apparatus. The reaction mixture was allowed to cool to room temperature, diluted with a saturated sodium bicarbonate solution, and extracted with dichloromethane. The combined organic layers were dried, filtered and concentrated. The residue was purified by column chromatography (silica gel, petroleum ether–ethyl acetate, 95 : 5) to afford compound **8** (26 mg, 69%) as a white solid. mp 60–65 °C (CH_2Cl_2); ν_{max}/cm^{-1} 3517 (OH); δ_H (400 MHz) 8.24 (1H, dd, *J* = 9.2, 5.6 Hz), 7.49 (1H, d, *J* = 8.8 Hz), 7.39 (1H, dd, *J* = 9.6, 2.4 Hz), 7.29 (1H, ddd, *J* = 9.2, 9.2, 2.8 Hz), 7.24 (1H, d, *J* = 8.8 Hz), 6.01 (1H, br s, OH); δ_C (100 MHz) 162.5 (C), 160.1 (C), 148.4 (C), 134.8 (2 × C), 129.7 (CH), 125.2 (CH, $^3J_{CF}$ = 9.2 Hz), 120.6 (CH, $^4J_{CF}$ = 5.1 Hz), 116.1 (CH, $^2J_{CF}$ = 16.4 Hz), 110.8 (CH, $^2J_{CF}$ = 20.7 Hz); *m*/*z* (CI + NH_3) 240 ($M^+ - 1$), 257 ($M^+ - 1 + NH_3$); *m*/*z* (rel intensity) 242 (M^+, 11), 240 (M^+, 100); HRMS calcd for $C_{10}H_6FBrO$: 241.956558; found 241.953297. Anal. Calcd. for $C_{10}H_6FBrO$: C, 49.83; H, 2.51. Found: C, 50.26; H, 3.02%.

2,2-Dimethyl-propionic acid 3-ethoxythiocarbonylsulfanyl-7-fluoro-4-oxo-1,2,3,4-tetrahydro-naphthalen-1-yl ester (15). To a solution of tetralone **4a** (0.2 g, 0.75 mmol) in acetic acid (7.5 mL) at room temperature was slowly added pyridinium bromide perbromide (0.29 g, 0.91 mmol). The reaction was stirred at room temperature for 4 h, neutralised with saturated aqueous Na_2CO_3, extracted with dichloromethane, dried (Na_2SO_4) and evaporated. To a cold solution (0 °C) of the residue in acetone (1.5 mL) was then slowly added potassium *O*-ethyl xanthate (0.13 g, 0.83 mmol). The reaction mixture was stirred at 0 °C for a further 1 h, the solvent was evaporated and the resulting mixture partitioned between water and CH_2Cl_2. The aqueous phase was extracted with CH_2Cl_2, the combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure. Flash chromatography of the residue (silica gel, petroleum ether–ethyl acetate, 99 : 1 to 95 : 5), gave xanthate **15** (68% overall yield) as a yellow oil and an inseparable mixture of diastereoisomers (ratio 2 : 1). ν_{max}/cm^{-1} 1734 (O–*C*=*O*), 1695 (C=O), 1235 (S–*C*=*S*), 1052 (*S*–*C*=S); δ_H (400 MHz) 8.10–8.16 (1H, m, C*H* arom), 7.12–7.20 (2H, m, 2 × C*H* arom), 6.23 (1H, dd, *J* = 10.4, 4.4 Hz, C*Hb*–OPiv), 6.08 (1H, dd, *J* = 2.8, 2.8 Hz, C*Ha*–OPiv), 5.16 (1H, dd, *J* = 12.4, 4.8 Hz, C*Ha*–S), 4.87 (1H, dd, *J* = 13.2, 4.8 Hz, C*Hb*–S), 4.61–4.67 (2H, m, O–C*Ha* and O–C*Hb*), 2.94 (1H, ddd, *J* = 12.0, 4.8, 4.8 Hz, CH_2b), 2.84 (1H, ddd, *J* = 14.0, 4.0, 4.0 Hz, CH_2a), 2.64 (1H, ddd, *J* = 13.2, 13.2, 2.8 Hz, CH'_2a), 2.41 (1H, q, *J* = 11.5 Hz, CH'_2b), 1.38 (3H, dd, *J* = 7.2, 7.2 Hz, CH_2–CH_3a and CH_2–CH_3b), 1.30 (3H, s, (CH_3b)$_3$), 1.22 (6H, s, (CH_3a)$_3$); δ_C (100 MHz) 212.5 (*Ca*=S), 212.0 (*Cb*=S), 190.6 (*Ca*=O), 189.9 (*Cb*=O), 177.7 (O–*Ca*O and O–*Cb*O), 166.4 (C, d, *Cb*–F, $^1J_{CF}$ = 256 Hz), 166.1 (C, d, *Ca*–F, $^1J_{CF}$ = 255 Hz), 142.4 (*Cb*–CO), 142.3 (*Ca*–CO), 131.4 (3 × *C*H arom), 128.4 (*Ca*–CH and *Cb*–CH), 117.4 (CH, d, $^2J_{CF}$ = 21.8 Hz, *C*H arom), 116.4 (CH, d, $^2J_{CF}$ = 22.1 Hz, *C*H arom), 112.9 (CH, d, $^2J_{CF}$ = 22.9 Hz, *C*H arom), 70.8 (O–*C*H$_2a$ and O–*C*H$_2b$), 67.9 (*C*H*a*–OPiv), 67.8 (*C*H*b*–OPiv), 54.0 (*C*H*a*–S), 52.6 (*C*H*b*–S), 38.8 (*Ca*(CH$_3$)$_3$ and *Cb*(CH$_3$)$_3$), 36.0 (*C*H$_2b$), 35.2 (*C*H$_2a$), 27.2 ((*C*H$_3a$)$_3$ and (*C*H$_3b$)$_3$), 13.8 (CH_2–*C*H$_2a$ and CH_2–*C*H$_3b$); *m*/*z* (CI + NH_3) 385 (MH^+), 283 ($MH^+ - OPiv$).

7-Fluoronaphtho[2,1-d][1,3]oxathiole-2-thione (16). According to the general method A, this compound was prepared from tetralone derivative **15** to give compound **16** (89%) as an orange solid. mp 157–159 °C (CH_2Cl_2–petroleum ether); ν_{max}/cm^{-1} 1189 (C=S); δ_H (400 MHz) 8.25 (1H, dd, *J* = 8.8, 5.6 Hz, C*H* arom), 7.76 (1H, d, *J* = 8.4 Hz, C*H* arom), 7.54 (1H, d, *J* = 9.6 Hz, C*H* arom), 7.47 (1H, d, *J* = 8.4 Hz, C*H* arom), 7.43 (1H, d, *J* = 8.0 Hz, C*H* arom); δ_C (100 MHz) 201.5 (C, *C*=S), 161.3 (C, d, $^1J_{CF}$ = 247.0 Hz, *C*–F), 150.5 (C, *C*–O), 133.9 (C, d, $^3J_{CF}$ = 9.6 Hz, CH–*C*–CH), 125.8 (*C*H arom), 123.9 (CH, d, $^3J_{CF}$ = 9.0 Hz, *C*H arom), 120.4 (C, *C*–C–O), 118.8 (*C*H arom), 118.5 (CH, d, $^2J_{CF}$ = 25.9 Hz, *C*H arom), 117.3 (C, *C*–S), 111.9 (CH, d, $^2J_{CF}$ = 26.0 Hz, *C*H arom); *m*/*z* (CI + NH_3) 237 (MH^+); *m*/*z* (rel intensity) 236 (M^+, 12), 176 ($M^+ - COS$, 100); HRMS calcd for $C_{11}H_5FOS_2$: 235.973215; found 235.973385.

7-Fluoro-4-(2-methoxy-2-oxoethylidene)-1,2,3,4-tetrahydro-1-naphthalenyl pivalate (22). Methyl (diethoxyphosphoryl)-acetate (0.36 mL, 1.96 mmol) was added dropwise to a cooled suspension of NaH (80% dispersion in mineral oil, 60 mg, 1.98 mmol) in anhydrous toluene (1.2 mL). The mixture was then stirred for 1 h at 60 °C to ensure the formation of the ylide.

The formed solution was cooled, and a solution of tetralone **4a** (368 mg, 1.39 mmol) in anhydrous toluene (1.2 ml) was added dropwise. The mixture was refluxed for 3 h, cooled to room temperature, and then washed with cold water and extracted with dichloromethane. The separated organic layer was dried over $MgSO_4$, and the solvent was evaporated under reduced pressure. The crude residue was chromatographed (petroleum ether–ethyl acetate, 95 : 5) to yield **22** (272 mg, 61%) as a colourless oil. ν_{max}/cm^{-1} 1728 (C=O), 1605 (C=O); δ_H (400 MHz) complex mixture of isomers; δ_C (100 MHz) complex mixture of isomers; *m*/*z* (CI + NH_3) 291 ($MH^+ - 2CH_3$), 308 ($MH^+ + NH_3 - 2CH_3$), 323 ($MH^+ + NH_3 - CH_3$), 338 ($MH^+ + NH_3$).

Methyl (6-fluoro-1-naphthyl)acetate (23). According to the general method A, this compound was prepared from derivative **22** to give compound **23** (67%) as a solid amorphous. ν_{max}/cm^{-1} 1738 (C=O), 1634 (C=O); δ_H (400 MHz) 8.01 (1H, dd, *J* = 5.2, 9.2 Hz, C*H* arom), 7.74 (1H, d, *J* = 8.4 Hz, C*H* arom), 7.44–7.50 (2H, m, 2 × C*H* arom), 7.38 (1H, d, *J* = 6.8 Hz, C*H* arom), 7.32 (1H, m, C*H* arom), 4.17 (1H, d, *J* = 14.4 Hz, CH_2), 4.15 (1H, d, *J* = 14.4 Hz, CH_2), 4.06 (3H, s, CH_3); δ_C (100 MHz) 161.6 (*C*), 134.8 (*C*), 130.9 (*C*), 129.1 (*C*), 127.8 (*C*), 126.6 (2 × *C*H arom), 118.7 (2 × *C*H arom), 116.6 (2 × *C*H arom), 61.1 (*C*H_3), 39.4 (*C*H_2); *m*/*z* (CI + NH_3) 218 (M^+), 233 (M^+ + NH). *m*/*z* (CI + NH_3) 218 (M^+), 233 (M^+ + NH); *m*/*z* (rel intensity) 218 (M^+, 15), 159 ($M^+ - C_2H_3O_2$, 100); HRMS calcd for $C_{13}H_{11}FO_2$: 218.074308; found 218.073933.

Method B. ***2-Bromo-5,8-dimethoxy-1-naphthol (10).*** To a stirred solution of tetralone **9** (0.2 g, 0.65 mmol) in acetic acid (6.5 mL) at room temperature was added slowly pyridinium bromide perbromide (0.21 g, 0.65 mmol). The mixture was stirred at room temperature for 1 h, neutralised with saturated aqueous Na_2CO_3, extracted with CH_2Cl_2, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, petroleum ether–ethyl acetate, 8 : 2) to give directly the naphthol **10** (75%) as a brown-green solid. mp 137–138 °C (CH_2Cl_2–petroleum ether) (lit.,[15] 134 °C).

Method C. ***7-Fluoro-4-hydroxy-1-naphthyl pivalate (11).*** A mixture of residue **7** (29 mg), LiBr (15 mg, 0.17 mmol), and Li_2CO_3 (12.5 mg, 0.17 mmol) in dry DMF (0.5 mL) was stirred at 140 °C for 2 h under nitrogen. The reaction mixture was cooled to room temperature, poured into dilute HCl and extracted with ether. The combined organic layers were washed with water, dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography (silica gel, petroleum ether–ethyl acetate, 95 : 5) to afford compound **11** (13 mg, 60%) as a yellow solid. mp 136–142 °C (AcOEt); ν_{max}/cm^{-1} 3605 (OH); δ_H (400 MHz) 8.08 (1H, dd, *J* = 9.2, 5.6 Hz, C*H* arom), 7.31 (1H, dd, *J* = 10.4, 2.8 Hz, C*H* arom), 7.21 (1H, ddd, *J* = 8.4, 8.4, 2.4 Hz, C*H* arom), 6.96 (1H, d, *J* = 8.0 Hz, C*H* arom), 6.53 (1H, d, *J* = 8.4 Hz, C*H* arom), 5.82 (1H, br s, OH), 1.50 (9H, s, ^{t}Bu); δ_C (100 MHz) 178.1 (C, O–*C*O), 162.7 (C, *C*–OH), 160.3 (C, *C*–OPiv), 149.7 (C, *C*–F), 128.8 (2 × *C*), 125.5 (CH, $^3J_{CF}$ = 9.0 Hz, *C*H arom), 119.1 (*C*H arom), 115.6 (CH, $^2J_{CF}$ = 25.1 Hz, *C*H arom), 107.1 (*C*H arom), 104.8 (CH, $^2J_{CF}$ = 23.0 Hz, *C*H arom), 77.2 (C, ^{t}Bu), 27.4 (3 × CH_3, ^{t}Bu); *m*/*z* (CI + NH_3) 263 (MH^+), 280 ($MH^+ + NH_3$); *m*/*z* (rel intensity) 262 (M^+, 15), 178 ($M^+ - 1 - C_5H_9O$, 100); HRMS calcd for $C_{15}H_{15}FO_3$: 262.100523; found 262.101006. Anal. calcd. for $C_{15}H_{15}FO_3$: C, 68.69; H, 5.76. Found: C, 68.71; H, 6.05%.

2-(7-Chloro-4-hydroxy-1-naphthyl)ethyl acetate (13). To a stirred solution of **4c** (0.2 g, 0.75 mmol) in acetic acid (7 mL) at room temperature was added slowly pyridinium bromide perbromide (0.24 g, 0.75 mmol). The mixture was stirred at room temperature for 15 min, neutralised with saturated aqueous Na_2CO_3, extracted with ethyl acetate, dried and concentrated. The residue was then dissolved in DMF (4 mL). Li_2CO_3 (0.11 g, 1.5 mmol) and LiBr (0.13 g, 1.5 mmol) were added and the solution was heated for 30 minutes at 140 °C, cooled to room temperature, neutralised with saturated aqueous citric acid, extracted with diethyl ether and the combined organic extracts were dried and concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel, petroleum ether–ethyl acetate, 8 : 2) to give naphthol **13** (64%) as a brown-green solid. mp 101–104 °C (CH_2Cl_2–petroleum ether); ν_{max}/cm^{-1} 3358 (OH), 1743 (O–*C*=*O*); δ_H (400 MHz) 8.23 (1H, d, *J* = 8.8 Hz, C*H* arom), 8.00 (1H, d, *J* = 1.2 Hz, C*H* arom), 7.44 (1H, dd, *J* = 8.8, 1.6 Hz, C*H* arom), 7.19 (1H, d, *J* = 7.6 Hz, C*H* arom), 6.75 (1H, d, *J* = 7.6 Hz, C*H* arom), 6.55 (1H, s, O*H*), 4.41 (2H, dd, *J* = 7.4, 7.4 Hz, CH_2–OAc), 3.29 (2H, dd, *J* = 7.2, 7.2 Hz, Ar–CH_2), 2.13 (3H, s, OC(O)CH_3); δ_C (100 MHz) 172.2 (O–*C*O), 151.2 (*C*–OH), 133.9 (*C*–Cl), 132.9 (*C*–CH_2), 128.2 (*C*H arom), 125.7 (*C*H arom), 123.2 (*C*–C–OH), 124.6 (*C*H arom), 122.7 (*C*–C–CH_2), 122.6 (*C*H arom), 108.4 (*C*H arom), 64.9 (*C*H_2–OAc), 31.5 (Ar–*C*H_2), 21.1 (CH_3, OC(O)*C*H_3); *m*/*z* (CI + NH_3) 284 ($MH^+ + NH_3$), 282 ($MH^+ + NH_3$). Anal. calcd. for $C_{14}H_{13}ClO_3$: C, 63.52; H, 4.95. Found: C, 63.48; H, 4.92%.

Method D. ***Ethyl 2-amino-7-chloronaphtho[1,2-b]furan-3-carboxylate (17).*** To a stirred solution of tetralone **4b** (0.1 g, 0.35 mmol) in acetic acid (3.5 mL) was added pyridinium bromide perbromide (0.11 g, 0.35 mmol). The mixture was stirred at room temperature for 15 min, neutralised with saturated aqueous Na_2CO_3, extracted with ethyl acetate, dried and concentrated. A solution of the residue in acetone (0.7 mL) was then added to a stirred mixture of ethyl cyanoacetate (0.07 mL, 0.08 g, 0.71 mmol) and K_2CO_3 (0.15 g, 1.07 mmol) in acetone (0.7 mL) at 0 °C. The resulting mixture was stirred at room temperature for a further 4 h and then acidified with saturated aqueous citric acid, extracted with dichloromethane and the combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel, petroleum ether–ethyl acetate, 9 : 1) to give furan **17** (51%) as a brown–green solid. mp 192–195 °C (CH_2Cl_2–petroleum ether); ν_{max}/cm^{-1} 3486 (NH_2), 3365 (NH_2), 1682 (O–C=O); δ_H (400 MHz) 7.98 (1H, d, *J* = 8.0 Hz, C*H* arom), 7.97 (1H, s, C*H* arom), 7.91 (1H, d, *J* = 8.4 Hz, C*H* arom), 7.70 (1H, d, *J* = 8.4 Hz, C*H* arom), 7.49 (1H, dd, *J* = 8.8, 1.6 Hz, C*H* arom), 7.30 (2H, s, NH_2), 4.36 (2H, ddd, *J* = 7.1, 7.1, 7.1 Hz, O–CH_2), 1.40 (3H, dd, *J* = 7.0, 7.0 Hz, CH_3); δ_C (100 MHz) 167.0 (C, O–*C*O), 166.7 (C, *C*–CO_2Et), 144.0 (C, *C*–OH), 132.2 (C, *C*–Cl), 130.4 (C, *C*–C–CO_2Et), 128.9 (*C*H arom), 128.8 (*C*H arom), 125.7 (C, *C*–C–OH), 125.1 (*C*H arom), 122.2 (*C*H arom), 122.0 (*C*H arom), 120.0 (C, *C*–CH), 86.2 (C, *C*–NH_2), 61.0 (CH_2, O–*C*H_2), 15.9 (CH_3); *m*/*z* (CI + NH_3) 292 (MH^+), 290 (MH^+); *m*/*z* (rel intensity) 289 (M^+, 63), 243 ($M^+ - C_2H_6O$, 100); HRMS calcd for $C_{15}H_{12}ClNO_3$: 289.050571; found 289.046883.

Method E. ***6-Chloro-2-[3-(2-hydroxyethyl)benzyl]-1-naphthol (18).*** To a stirred solution of tetralone **4c** (0.1 g, 0.37 mmol) and benzaldehyde (0.06 mL, 0.56 mmol) in *tert*-butanol (3.7 mL) was added potassium *tert*-butoxide (0.08 g, 0.75 mmol). The resulting suspension was then refluxed for 8 h, cooled to room temperature and acidified with saturated aqueous citric acid. The reaction mixture was extracted with ethyl acetate and the combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel, petroleum ether–ethyl acetate, 9 : 1) to give **18** (32%) as a yellow solid. mp 140–141 °C (CH_2Cl_2–petroleum ether); ν_{max}/cm^{-1} 3601 (OH), 3530 (OH); δ_H (400 MHz) 8.13 (1H, d, *J* = 8.8 Hz, C*H* arom), 7.94 (1H, d, *J* = 1.6 Hz, C*H* arom), 7.41 (1H, dd, *J* = 9.0, 1.8 Hz, C*H* arom), 7.25–7.34 (6H, m, 6 × C*H* arom), 4.12 (2H, s, CH_2–Ph), 3.95 (2H, dd, *J* = 6.8, 6.8 Hz, CH_2–O*H*), 3.21 (2H, dd, *J* = 6.6, 6.6 Hz, CH_2–CH_2–OH); δ_C (100 MHz) 148.5 (C, *C*–OH), 138.8 (C, *C*–Cl), 133.0 (C, *C*–C–OH), 132.3 (C, *C*–CH_2–Ph), 131.5 (*C*H arom), 129.2 (2 × *C*H arom), 128.5 (2 × *C*H arom), 127.1 (*C*H arom), 126.0 (*C*H arom), 125.9 (C, *C*–C–CH_2), 124.3 (*C*H arom), 123.9 (C, *C*–CH_2–C), 122.7 (*C*H

arom), 119.7 (C, *C*–CH_2), 63.1 (CH_2, *C*H_2–Ph), 36.8 (CH_2, *C*H_2–OH), 35.6 (CH_2, *C*H_2–CH_2–OH); *m*/*z* (CI + NH_3) 332 ($MH^+ + NH_3$), 330 ($MH^+ + NH_3$), 315 (MH^+), 313 (MH^+).

Method F. ***N-Benzyl-6-chloro-1-naphthalenamine (19a).*** A solution of tetralone **4b** (0.1 g, 0.35 mmol) and benzylamine (0.08 mL, 0.71 mmol) in toluene (3.5 mL) was refluxed in a system equipped with a Dean–Stark apparatus. The reaction was monitored by ^{1}H NMR and after 3 h the starting material was completely consumed. At this point, the reaction mixture was cooled to room temperature and $AlCl_3$ (0.95 g, 0.71 mmol) was added to the imine solution. The reaction was refluxed for a further 15 min, neutralised with saturated aqueous $NaHCO_3$ and extracted with dichloromethane. The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure. Flash chromatography of the residue (silica gel, petroleum ether–ethyl acetate, 98 : 2), gave naphthylamine **19a** (75%) as a green–yellow oil. ν_{max}/cm^{-1} 3428 (NH); δ_H (400 MHz) 7.80 (1H, d, *J* = 2.0 Hz, C*H* arom), 7.75 (1H, d, *J* = 8.8 Hz, C*H* arom), 7.36–7.48 (7H, m, C*H* arom), 7.18 (1H, d, *J* = 8.0 Hz, C*H* arom), 6.64 (1H, d, *J* = 7.6 Hz, C*H* arom), 4.68 (1H, br s, N*H*), 4.50 (2H, s, CH_2–Ph); δ_C (100 MHz) 143.4 (C, *C*–NH), 138.8 (C, *C*–Cl), 135.2 (C, *C*–C–NH), 131.7 (C, *C*–CH_2), 128.8 (2 × *C*H arom), 128.0 (*C*H arom), 127.8 (*C*H arom), 127.6 (*C*H arom), 127.3 (*C*H arom), 125.4 (*C*H arom), 121.9 (*C*H arom), 121.6 (C, *C*–CH), 116.8 (2 × *C*H arom), 105.1 (*C*H arom), 48.6 (CH_2, *C*H_2–Ph); *m*/*z* (CI + NH_3) 270 ($MH^+ + NH_3$), 268 ($MH^+ + NH_3$).

Methyl benzyl(6-chloro-1-naphthyl)carbamate (19b). Acetic anhydride (0.03 mL, 0.03 g, 0.30 mmol) was added to a solution of 0.027 g (0.10 mmol) of naphthylamine **19a** and DMAP (0.025 g, 0.20 mmol) in CH_2Cl_2 (1 mL) at 0 °C. The mixture was stirred for 10 h at room temperature and then partitioned between water and dichloromethane. The aqueous phase was extracted with dichloromethane, the combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure. Flash chromatography of the residue (silica gel, petroleum ether–ethyl acetate, 9 : 1) gave acetamide **19b** (97%) as a yellow oil. ν_{max}/cm^{-1} 1667 (N–*C*=O); δ_H (400 MHz) 7.88 (1H, d, *J* = 2.0 Hz, C*H* arom), 7.74 (1H, d, *J* = 8.0 Hz, C*H* arom), 7.66 (1H, d, *J* = 8.8 Hz, C*H* arom), 7.44 (1H, dd, *J* = 9.0, 1.8 Hz, C*H* arom), 7.38 (1H, dd, *J* = 7.8, 7.8 Hz, C*H* arom), 7.22–7.23 (3H, m, 3 × C*H* arom), 7.16–7.17 (2H, m, 2 × C*H* arom), 6.96 (1H, d, *J* = 7.2 Hz, C*H* arom), 5.55 (1H, d, *J* = 14.0 Hz, CH_2–Ph), 4.32 (1H, d, *J* = 14.0 Hz, CH_2–Ph), 1.76 (3H, s, CH_3); δ_C (100 MHz) 171.0 (C, N–*C*O), 139.0 (C, *C*–N), 137.5 (C, *C*–Cl), 135.4 (C, *C*–C–N), 132.8 (C, *C*–CH_2), 129.4 (2 × *C*H arom), 128.8 (C, *C*–CH), 128.4 (2 × *C*H arom), 128.4 (*C*H arom), 127.9 (*C*H arom), 127.6 (*C*H arom), 127.4 (*C*H arom), 127.1 (*C*H arom), 126.9 (*C*H arom), 124.3 (*C*H arom), 52.6 (CH_2, *C*H_2–Ph), 22.3 (CH_3); *m*/*z* (CI + NH_3) 329 ($MH^+ + NH_3$), 327 ($MH^+ + NH_3$), 312 (MH^+), 310 (MH^+); *m*/*z* (rel intensity) 309 (M^+, 13), 267 ($M^+ - 1 - C_2H_3O$, 14), 91 (100); HRMS calcd for $C_{19}H_{16}ClNO$: 309.092042; found 309.089706.

Method G. ***3-Chloro-11H-benzo[a]carbazole (20).*** A mixture of tetralone **4b** (0.2 g, 0.71 mmol), phenylhydrazine (0.14 mL, 1.4 mmol) and 0.5 g of polyphosphoric acid (PPA) was heated at 100 °C for 15 min. The mixture was allowed to cool to room temperature and then partitioned between water and CH_2Cl_2. The aqueous phase was extracted with dichloromethane, the combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure. Flash chromatography of the residue (silica gel, petroleum ether–ethyl acetate, 98 : 2) gave compound **21** (56%) as an orange–brown solid. mp 212–214 °C (acetone–petroleum ether): ν_{max}/cm^{-1} 3604 (NH), 3478 (NH); δ_H (400 MHz) 11.35 (1H, s, NH), 8.49 (1H, d, *J* = 8.8 Hz, C*H* arom), 8.27 (1H, d, *J* = 8.4 Hz, C*H* arom), 8.18 (1H, d, *J* = 7.6 Hz, C*H* arom), 8.08 (1H, s, C*H* arom), 7.66 (1H, d, *J* = 5.6 Hz, C*H* arom), 7.64 (1H, d, *J* = 6.4 Hz, C*H* arom), 7.69 (1H, d, *J* = 8.4 Hz, C*H* arom), 7.44 (1H, dd, *J* = 7.6, 7.6 Hz, C*H* arom), 7.28 (1H, dd, *J* = 7.4, 7.4 Hz, C*H* arom); δ_C (100 MHz) 141.0 (*C*), 137.0 (*C*), 135.1 (*C*), 132.1 (*C*), 129.3 (*C*H arom), 127.6 (*C*H arom), 126.8 (*C*H arom), 125.5 (*C*), 125.3 (*C*H arom), 122.6 (*C*H arom), 121.6 (*C*H arom), 121.5 (*C*H arom), 120.5 (*C*H arom), 120.3 (*C*), 113.2 (*C*H arom); *m*/*z* (CI + NH_3) 254 (MH^+), 252 (MH^+); Anal. calcd. for $C_{16}H_{10}NCl$: C, 76.35; H, 4.00. Found: C, 76.54; H, 3.98%.

Method H. ***4-(3-Chloro-1-propynyl)-4-hydroxy-5,8-dimethoxy-1,2,3,4-tetrahydro-1-naphthalenyl pivalate (24).*** *n*-Butyllithium (0.42 mL, 1.1 M solution in hexanes) was added to 3-chloro-1-propyne (39 mL, 0.52 mmol) in THF (2 mL), which had been previously cooled to −78 °C under a nitrogen atmosphere. After 30 min, tetralone **4d** (145 mg, 0.47 mmol) dissolved in dry THF (1 ml) was added dropwise. The reaction was allowed to warm to room temperature over 3 h. Saturated ammonium chloride was slowly added to the reaction followed by distilled water, and the resulting solution was extracted with ether. The organic fractions were combined, dried over $MgSO_4$, filtered and concentrated. The residue was purified by column chromatography (silica gel, petroleum ether–ethyl acetate, 85 : 15) to afford compound **24** (159 mg, 88%) as a white solid. mp 135–138 °C (AcOEt); ν_{max}/cm^{-1} 3537 (OH), 1725 (O–*C*=O); δ_H (400 MHz) 6.93 (1H, d, *J* = 8.9 Hz, C*H* arom), 6.77 (1H, d, *J* = 9.0 Hz, C*H* arom), 6.07 (1H, m, 1-H), 5.33 (1H, s, O*H*), 4.13 (2H, s, CH_2Cl), 3.94 (3H, s, OCH_3), 3.73 (3H, s, OCH_3), 2.19–2.21 (2H, m), 2.07–2.10 (2H, m), 1.15 (9H, s, ^{t}Bu); δ_C (100 MHz) 177.6 (C, *C*O), 152.4 (*C*), 151.0 (*C*), 130.3 (*C*), 123.0 (*C*), 112.7 (*C*H arom), 109.8 (*C*H arom), 89.4 (C, *C*≡C), 77.3 (C, C≡*C*), 67.1 (C, C-4), 63.7 (C, C-1), 56.7 (CH_3, O*C*H_3), 55.5 (CH_3, O*C*H_3), 38.7 (C, ^{t}Bu), 32.0 (*C*H_2), 30.6 (*C*H_2), 27.0 (3 × CH_3, ^{t}Bu), 25.7 (*C*H_2); *m*/*z* (CI + NH_3) 397 ($M^+ + NH_3$), 395 ($M^+ + NH$).

5-(3-Chloro-1-propynyl)-1,4-dimethoxynaphthalene (25). To a cold (0 °C) solution of **24** (0.044 g, 0.11 mmol) in pyridine (0.1 mL) was added phosphorous oxychloride (0.14 mL, 1.54 mmol) over a 30 min period. The reaction was allowed to warm to room temperature and stirred for 40 h. The mixture was poured into ice-water and was extracted with diethyl ether. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The residue was purified by column chromatography (silica gel, petroleum ether–ethyl acetate, 9 : 1) to afford compound **25** (20 mg, 66%) as an amorphous solid. ν_{max}/cm^{-1} 3070, 2931, 1622, 1590, 1462, 1408, 1267, 1238, 1074; δ_H (400 MHz) 8.26 (1H, d, *J* = 8.0 Hz, C*H* arom), 7.46–7.53 (2H, m, 2 × C*H* arom), 6.72–6.81 (2H, m, 2 × C*H* arom), 4.45 (2H, s, CH_2Cl), 3.97 (3H, s, OCH_3), 3.85 (3H, s, OCH_3); δ_C (100 MHz) 149.8 (C, *C*–OMe), 148.0 (C, *C*–OMe), 129.8 (C, *C*–C≡C), 129.0 (*C*H arom), 125.9 (*C*), 125.0 (*C*H arom), 122.4 (*C*H arom), 117.1 (*C*), 106.5 (*C*H arom), 103.5 (*C*H arom), 94.9 (C, *C*≡C), 94.7 (C, C≡*C*), 56.5 (O*C*H_3), 55.7 (CH_3, O*C*H_3), 29.6 (CH_2, *C*H_2Cl); *m*/*z* (CI + NH_3) 261 (MH^+), 279 ($MH^+ + NH_3$); *m*/*z* (rel intensity) 261 ($M^+ + 1$, 50), 260 (M^+, 28), 246 (100); HRMS calcd. for $C_{15}H_{13}ClO_2$: 260.060408; found 260.065285.

4-Hydroxy-5,8-dimethoxy-4-(phenylethynyl)-1,2,3,4-tetrahydro-1-naphthalenyl pivalate (26). *n*-Butyllithium (0.52 mL, 1.1 M hexanes) was added to ethynylbenzene (0.07 mL, 0.64 mmol) in THF (2.5 mL), which had been previously cooled to −78 °C under a nitrogen atmosphere. After 30 min, tetralone **4d** (178 mg, 0.58 mmol) dissolved in dry THF (1 mL) was added dropwise. The reaction was allowed to warm to room temperature and stirred for 3.5 h. Saturated ammonium chloride was slowly added to the reaction followed by distilled water, and the resulting solution, extracted with diethyl ether. The organic fractions were combined, dried over $MgSO_4$, filtered and concentrated. The residue was purified by column chromatography (silica gel, petroleum ether–ethyl acetate, 95 : 5) to afford compound **26** (151 mg, 65%) as a white solid. mp 50–53 °C (AcOEt); ν_{max}/cm^{-1} 3540 (OH), 1724 (C=O); δ_H (400 MHz) 7.36–7.38 (2H, m, 2 × C*H* arom), 7.26–7.27 (3H, m, 3 × C*H* arom), 6.94 (1H, d,

J = 9.2 Hz, C*H* arom), 6.78 (1H, d, J = 8.8 Hz, C*H* arom), 6.12 (1H, br s, 1-H), 5.44 (1H, s, O*H*), 3.96 (3H, s, OCH_3), 3.74 (3H, s, OCH_3), 2.15–2.31 (4H, m, 2-H_2, 3-H_2), 1.18 (9H, s, ^{t}Bu); δ_C (100 MHz) 177.6 (C, *C*O), 152.5 (*C*), 151.1 (*C*), 131.6 (2 × *C*H arom), 131.1 (*C*), 128.1 (3 × *C*H arom), 122.9 (*C*), 122.8 (*C*), 112.9 (*C*H arom), 109.6 (*C*H arom), 92.2 (C, C-4), 82.9 (C, *C*≡C), 67.6 (C, C≡*C*), 63.9 (CH, C-1), 56.7 (CH_3, O*C*H_3), 55.4 (CH_3, O*C*H_3), 38.7 (C, ^{t}Bu), 32.4 (*C*H_2), 27.0 (3 × CH_3, ^{t}Bu), 25.9 (*C*H_2); *m*/*z* (CI + NH_3), 409 (MH^+), 305 (M^+ − OPiv).

1,4-Dimethoxy-5-(phenylethynyl)naphthalene (27). To a cold (0 °C) solution of **26** (31 mg, 0.08 mmol) in pyridine (0.07 mL) was added phosphorous oxychloride (0.029 ml, 0.31 mmol) over a 30 min period. The reaction was allowed to warm to room temperature and stirred for 36 h. The mixture was poured into ice-water and was extracted with diethyl ether. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The residue was purified by column chromatography (silica gel, petroleum ether–ethyl acetate, 9 : 1) to afford compound **27** (15 mg, 67%) as an amorphous solid. ν_{max}/cm^{-1} 2934, 1462, 1407, 1261, 884; δ_H (400 MHz) 8.26 (1H, d, J = 8.4 Hz), 7.80 (1H, d, J = 7.2 Hz), 7.60–7.62 (2H, m), 7.45 (1H, dd, J = 7.2, 7.2 Hz), 7.32–7.38 (3H, m), 6.85 (1H, d, J = 8.4 Hz), 6.76 (1H, d, J = 8.4 Hz), 4.01 (3H, s), 3.98 (3H, s); δ_C (100 MHz) 159.2 (*C*), 149.8 (*C*), 133.8 (*C*H), 131.4 (*C*H), 128.2 (3 × *C*H), 127.7 (*C*H), 127.0 (*C*), 126.5 (*C*), 125.8 (*C*), 124.9 (*C*H), 122.6 (*C*H), 117.6 (*C*), 103.9 (*C*H), 91.6 (2 × *C*), 56.9 (*C*H_3), 55.7 (*C*H_3); *m*/*z* (CI + NH_3) 306 (MH^+ + NH_3), 289 (MH^+), 274 (MH^+ + NH); *m*/*z* (rel intensity) 288 (M^+, 100), 273 (M^+ − CH_3, 58), 258 (M^+ − 2 × CH_3, 19); HRMS calcd for $C_{20}H_{16}O_2$: 288.115030; found 288.113342.

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11 METHOD A: like Method A, Table 2. METHOD G: To a cold solution of substrate (1 mmol) in pyridine (1 ml) was added $POCl_3$ (15.5 mmol) and the reaction was stirred at room temperature.

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