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A novel approach to the synthesis of benzo[*b*]fluoren-11-ones

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Abstract—A novel intramolecular palladium-mediated arylation approach to benzo[*b*]fluoren-11-ones has been investigated. This approach involves the novel oxidation of the key starting 2-(2′-bromobenzyl)naphthols to 2-(2′-bromobenzyl)-1,4-naphthoquinones, followed by protection of the quinone moiety of the latter compounds and the final Pd-promoted bi-arylic cyclization of the resulting 2-(2′-bromobenzyl)-1,4-dimethoxynaphthalenes.

Quinones are compounds of perennial chemical interest on account of their widespread occurrence in nature and their wide ranging biological activity and industrial applications.[1] In fact, quinonoid systems have been extensively studied in the context of continued interest in the search for new antibiotics. For instance, benzo[*b*]fluorene based quinonoids kinobscurinone (**9a**),[2] kinafluorenone (**9b**),[3] stealthin A (**10a**)[4] (a potent radical scavenger), stealthin B (**10b**)[4] and stealthin C (**10c**)[5] are metabolites found in the extract of *Streptomyces murayamaensis* and prekinamycin (**9c**) has attracted considerable attention because it is present in the biosynthetic pathways leading to the kinamycin family of antibiotics, some of which display antibacterial and antitumoural activity.[6]

The biological activities as well as the unique structure of these compounds (**9** and **10**) prompted their synthesis by a biomimetic approach involving benzo[*b*]fluorenone **8c**,[7] which includes a naphthoquinone subunit masked as 1,4-dimethoxynaphthalene. Several approaches to this common precursor **8c** have been reported, most involving Friedel–Crafts closure[8] of acylbiphenyls (approach a) or Pd-mediated[9] or Ti-mediated[10] closure of diphenylketones (approach b). But both approaches involve complex preparation of aromatic ketones and the latter includes a low yielding bi-arylic cyclization. As a continuation of our work on tetracyclic naphthoquinones by condensation of 1-indanones with benzaldehydes,[11] we present here preliminary results of a novel synthesis of benzo[*b*]fluorenones **8** (Scheme 1). This new route is based on a strategy involving approach b that precludes the limitations outlined above.

The starting 2-(2-bromobenzyl)-1-naphthol **4a**[12] was easily and efficiently obtained by aldol condensation of 1-tetralone[13] with *o*-bromobenzaldehyde[13] followed by a spontaneous oxidation of the resulting 2-benzylidene-1-tetralone **3a** under the reaction conditions.[14] Subsequent oxidation with Fremy's salt[15] allowed us to carry out the first transformation of a 2-benzyl-1-naphthol (**4a**) into 2-benzyl-1,4-naphthoquinone (**5a**), a compound that has both the carbon skeleton and the quinone moiety required for the preparation of the target compound **8a**. Palladium-mediated bi-arylic cyclization of **5a** failed, but this desired ring closure was achieved after protection of the quinone system of **5a**. Thus reduction of **5a** with sodium dithionite followed by transformation of dinaphthol **6a**, which was directly converted into dimethoxynapahthalene **7a** by treatment with methyl iodide in a basic medium.[16] Finally, a mixture of **7a**, palladium acetate, triphenylphosphine and sodium bicarbonate in DMF was heated at 100 °C for seven hours,[9] to give the target benzo[*b*]fluorenone **8a**[17] directly in 55% yield, probably by cyclization and oxidation.[18]

The potential of this new synthetic route was confirmed by the successful preparation of benzo[*b*]fluorenone **8b** from 1-tetralone and 2-bromo-4,5-dimethoxybenzaldehyde,[19] via compounds **3b**, **4b**, **5b**, **6b** and **7b**.

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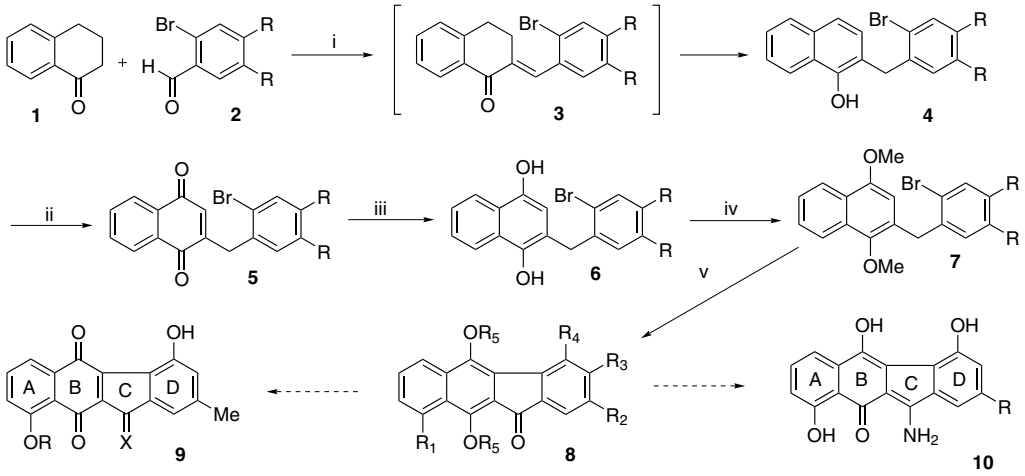

Scheme 1. Compounds **1**, **2**, **3**, **4**, **5**, **6**, **7**: (a) R = H; (b) R = OMe. Compound **8**: (a) $R_1 = R_2 = R_3 = R_4 = H$, $R_5 = OMe$; (b) $R_1 = R_4 = H$, $R_2 = R_3 = R_5 = OMe$; (c) $R_1 = R_4 = R_5 = OMe$, $R_2 = Me$, $R_3 = H$; (d) $R_1 = R_4 = R_5 = OH$, $R_2 = Me$, $R_3 = H$. Compound **9**: (a) X = O, R = OH; (b) X = O, R = OMe; (c) $X = N_2$, R = OH. Compound **10**: (a) $R = CH_2OH$; (b) R = CHO; (c) R = Me. Reagents and conditions: (i) *t*-BuOK/*t*-BuOH, reflux, 23 h (70–74% yield); (ii) (a) Fremy's salt, KH_2PO_4, acetone/H_2O, rt, 2.5 h (80–92% yield); (iii) $Na_2S_2O_4$, H_2O/dioxane, rt, 5 h; (iv) K_2CO_3, MeI, *t*-BuOK/THF, DMF, rt, 15 h (75–89% yield, two steps); (v) $Pd(OAc)_2$, PPh_3, $NaHCO_3$, DMF, 100 °C, 7 h (50–55% yield).

In summary, we have developed a general synthesis of benzo[*b*]fluorenones **8** that includes the novel oxidation of 2-benzylnaphth-1-ols (**4**) to 2-benzyl-1,4-naphthoquinones (**5**) and the novel cyclization of 2-benzyl-1,4-dimethoxynaphthalenes (**7**). This route is shorter and simpler than the previous ones, so may have great utility for an efficient preparation of stealthins A, B and C (**10a**–**c**) and their analogues. An additional milestone is the synthesis of kynamycin antibiotics, since they are benzo[*b*]fluorene derivatives **9c** that have a saturated and highly functionalized D ring. Work currently in progress in this area includes studies directed at improving the efficiency of the cyclization of compounds **7**.

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12. All new compounds gave satisfactory analytical and spectroscopic data. Selected physical and spectroscopic data follow. Compound **4a**. Mp 85–87 °C (AcOEt/hexane). ^{1}H NMR (δ, ppm, $CDCl_3$): 4.22 (s, 2H, $-CH_2-$), 5.26 (s, 1H, OH), 7.01–7.26 (m, 4H, 4 × Ar–H), 7.38–7.53 (m, 3H, 3 × Ar–H), 7.59 (d, 1H, $J = 7.3$ Hz, Ar–H), 7.75–7.84 (m, 1H, Ar–H), 8.08–8.16 (m, 1H, Ar–H). ^{13}C NMR (δ, ppm, $CDCl_3$): 36.3 (CH_2), 118.5 (C), 120.7 (CH), 121.0 (CH), 124.6 (C), 124.7 (C), 125.4 (CH), 125.8 (CH), 127.7 (2 × CH), 128.1 (CH), 128.6 (CH), 130.3 (CH), 132.8 (CH), 133.7 (C), 138.6 (C), 148.8 (C). MS (*m*/*z*, %): 314 (M^+, 16), 312 (M^+, 15), 156 (100). Compound **4b**. Mp 105–107 °C (AcOEt/hexane). ^{1}H NMR (δ, ppm, $CDCl_3$): 3.60 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 4.13 (s, 2H, CH_2), 5.59 (s, 1H, OH), 6.60 (s, 1H, Ar–H), 7.01 (s, 1H, Ar–H), 7.17 (d, 1H, $J = 8.3$ Hz, Ar–H), 7.35–7.46 (m, 3H, 3 × Ar–H), 7.71–7.79 (m, 1H, Ar–H), 8.06–8.15 (m, 1H, Ar–H). ^{13}C NMR (δ, ppm, $CDCl_3$): 35.7 (CH_2), 55.8 (OCH_3), 56.0 (OCH_3), 113.0 (CH), 114.2 (C), 115.3 (CH), 119.1 (C), 120.4 (CH), 121.0 (CH), 124.6 (C), 125.3 (CH), 125.7 (CH), 127.5 (CH), 128.2 (CH), 130.7 (C), 133.5 (C), 148.1 (C), 148.5 (C), 148.7 (C). MS (*m*/*z*, %): 374 (M^++2, 14), 372 (M^+, 15), 218 (100). Compound **5a**. Mp 121–123 °C (MeOH). ^{1}H NMR (δ, ppm, $CDCl_3$): 4.06 (d, 2H, $J = 1.8$ Hz, CH_2), 6.41 (t, 1H, $J = 1.8$ Hz, Ar–H), 7.12–7.22 (m, 1H, Ar–H), 7.27–7.34 (m, 2H, 2 × Ar–H), 7.57–7.64 (m, 1H, Ar–H), 7.71–7.79 (m, 2H, 2 × Ar–H), 8.02–8.08 (m, 1H, Ar–H), 8.12–8.17 (m, 1H, Ar–H). ^{13}C NMR (δ, ppm): 35.8 (CH_2), 125.0 (C), 126.1 (CH), 126.6 (CH), 127.8 (CH), 128.9 (CH), 131.8 (CH), 132.0 (C), 132.1 (C), 133.2 (CH), 133.7 (CH), 133.8 (CH), 135.5 (CH), 136.2 (C), 149.1 (C), 184.7 (C=O), 184.9 (C=O). MS (*m*/*z*, %): 328 (M^++2, 14), 326 (M^+, 15), 247 (100). Compound **5b**.

Mp 151–153 °C (MeOH). ^{1}H NMR (δ, ppm, $CDCl_3$): 3.86 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 3.97 (d, 2H, $J = 1.6$ Hz, CH_2), 6.44 (t, 1H, $J = 1.6$ Hz, Ar–H), 6.80 (s, 1H, Ar–H), 7.06 (s, 1H, Ar–H), 7.67–7.78 (m, 2H, $2 \times$ Ar–H), 7.99–8.16 (m, 2H, $2 \times$ Ar–H). ^{13}C NMR (δ, ppm, $CDCl_3$): 35.4 (CH_2), 56.0 (OCH_3), 56.1 (OCH_3), 114.0 (CH), 115.0 (C), 115.7 (CH), 126.1 (CH), 126.6 (CH), 127.8 (C), 132.0 (C), 132.1 (C), 133.6 (CH), 133.7 (CH), 135.3 (CH), 148.6 (C), 148.7 (C), 149.3 (C), 184.9 (C=O), 185.0 (C=O). MS (*m*/*z*, %): 388 (M^++2, 5), 386 (M^+, 6), 307 (100). Compound **7a**. Mp 77–79 °C (Et_2O). ^{1}H NMR (δ, ppm, $CDCl_3$): 3.81 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 4.28 (s, 2H, CH_2), 6.48 (s, 1H, Ar–H), 6.96–7.15 (m, 3H, $3 \times$ Ar–H), 7.38–7.60 (m, 3H, $3 \times$ Ar–H), 8.05 (d, 1H, $J = 8.4$ Hz, Ar–H), 8.22 (d, 1H, $J = 7.9$ Hz, Ar–H). ^{13}C NMR (δ, ppm, $CDCl_3$): 35.9 (CH_2), 55.4 (OCH_3), 61.9 (OCH_3), 105.7 (CH), 121.8 (CH), 122.3 (CH), 124.8 (C), 125.0 (CH), 125.7 (C), 126.5 (CH), 127.0 (C), 127.4 (CH), 127.7 (CH), 128.5 (C), 130.5 (CH), 132.5 (CH), 140.2 (C), 147.3 (C–OCH_3), 151.8 (C–OCH_3). MS (*m*/*z*, %): 358 (M^+, 97), 356 (M^+, 100). Compound **7b**. Mp 83–85 °C (Et_2O). ^{1}H NMR (δ, ppm, $CDCl_3$): 3.67 (s, 3H, OCH_3), 3.86 (s, 6H, $2 \times OCH_3$), 3.89 (s, 3H, OCH_3), 4.24 (s, 2H, CH_2), 6.51 (s, 1H, Ar–H), 6.64 (s, 1H, Ar–H), 7.07 (s, 1H, Ar–H), 7.40–7.58 (m, 2H, $2 \times$ Ar–H), 8.07 (d, 1H, $J = 8.0$ Hz, Ar–H), 8.21 (d, 1H, $J = 7.8$ Hz, Ar–H). ^{13}C NMR (δ, ppm, $CDCl_3$): 35.2 (CH_2), 55.6 (OCH_3), 55.9 (OCH_3), 56.1 (OCH_3), 62.0 (OCH_3), 105.4 (CH), 113.4 (CH), 114.5 (C), 115.3 (CH), 121.8 (CH), 122.3 (CH), 125.0 (CH), 125.7 (C), 126.6 (CH), 127.6 (C), 128.5 (C), 132.2 (C), 147.1 (C–OCH_3), 148.0 (C–OCH_3), 148.4 (C–OCH_3), 151.9 (C–OCH_3). MS (*m*/*z*, %): 419 (MH^+, 26), 417 (MH^+, 34), 201 (100). Compound **8b**. Mp 215–217 °C ($CHCl_3$). ^{1}H NMR (δ, ppm, $CDCl_3$): 3.97 (s, 3H, OCH_3), 4.02 (s, 3H, OCH_3), 4.07 (s, 3H, OCH_3), 4.28 (s, 3H, OCH_3), 7.26 (s, 1H, Ar–H), 7.45–7.54 (m, 2H, $2 \times$ Ar–H), 7.61 (t, 1H, $J = 8.2$ Hz, Ar–H), 8.00 (d, 1H, $J = 8.2$ Hz, Ar–H), 8.27 (d, 1H, $J = 8.2$ Hz, Ar–H). ^{13}C NMR (δ, ppm, $CDCl_3$): 56.2 (OCH_3), 56.3 (OCH_3), 61.3 (OCH_3), 63.1 (OCH_3), 106.0 (CH), 106.4 (CH), 120.2 (C), 122.2 (CH), 125.6 (CH), 126.7 (CH), 127.3 (C), 129.4 (C), 129.5 (CH), 131.0 (C), 133.5 (C), 137.6 (C), 145.7 (C–OCH_3), 149.9 (C–OCH_3), 153.2 (C–OCH_3), 154.7 (C–OCH_3), 189.5 (C=O). MS (*m*/*z*, %): 350 (M^+, 92), 150 (100).

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