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Solid-phase synthesis of 4*H*-2-(3-hydroxy-4-methoxyphenyl)-naphtho[1,2-*b*]pyran-1-one☆

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Abstract—An effective solid-phase preparation of the pharmaceutically interesting 4*H*-2-(3-hydroxy-4-methoxyphenyl)-naphtho[1,2-*b*]pyran-1-one system from an anchored bisarylacetylene is described.

A Baeyer–Villiger[1] reaction is one of the key steps in the solid-phase synthesis of pentacyclic lamellarins,[2] as recently described by our group (Fig. 1).[3] This transformation allows the use of the formyl group of a substituted benzaldehyde **2** to mask the required phenol, which in turn allows the introduction of a second element of diversity in a putative library. Diversity is further increased by the use of an iodophenol, the first building block anchored to the starting resin to give **1**, and a dihydroisoquinoline. An intramolecular [3+2] cycloaddition then allows the formation on solid phase of the pentacyclic system that is characteristic of lamellarins.[4]

The Baeyer–Villiger oxidation–transposition, which has few precedents in solid phase, gave good results using MCPBA and base.[3] However, the number of commercially available substituted benzaldehydes is relatively small and their preparation is tedious. With the aim of reducing the number of steps in solid phase and transforming the synthetic strategy into a more convergent route, we tested a Pd(0) cross-coupling reaction between the anchored 5-iodo-2-methoxyphenol (**1**)[5] with a hydroxynaphthylacetylene protected with the *O*-methoxymethyl (MOM) group (**5**).[6]

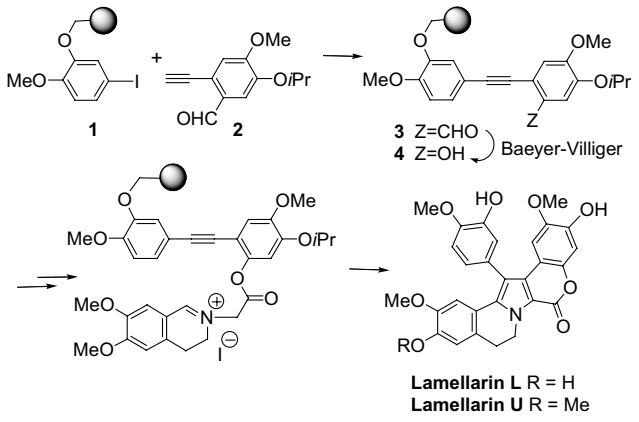

Figure 1. Solid phase synthesis of Lamellarins U and L.

The choice of MOM as a protecting group can be attributed to its facile removal under mild acidic conditions, which are compatible with Merrifield resin, as well as the fact that basic conditions can be avoided altogether. The latter is relevant because base promoted nucleophilic addition can lead to the formation of condensed polycyclic systems if one of the aryl rings linked to the triple bond is deactivated or a π-deficient system.[7]

Keywords: Solid-phase synthesis; Heterocycles; Naphthopyrones; Chromones.

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The coupling reaction between the resin **1** and acetylene **5** with $PdCl_2(PPh_3)_2$, CuI as catalyst, Et_3N as base, and THF as solvent cleanly afforded the resin **6** (Fig. 2).[8] Evidence for the formation of the anchored bisarylacetylene was provided by the absorption band of the triple bond at 2200 cm^{-1} in the IR spectrum as well as signals for the quaternary acetylenic carbons at 94.0 and 80.0 ppm and the CH_2 and CH_3 of the MOM at 95.6 and 56.4 ppm in the gel-phase ^{13}C NMR spectrum.[8]

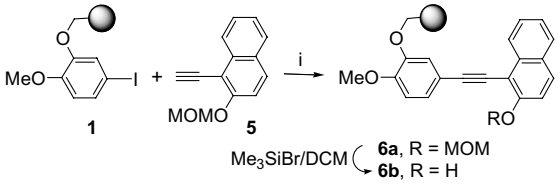

Figure 2. Cross-coupling reaction between **1** and **5**. Reagents: (i) $Pd(PPh_3)_2Cl_2$ (0.3 equiv), CuI (0.6 equiv), THF–Et_3N (3:1), N_2, 20 h, room temperature.

Attempts at *O*-deprotection of **6a** using HCl (cat.) in a mixture of THF–MeOH (2:1) were unsuccessful.[9] Me_3SiBr[10] in DCM was tested for *O*-deprotection and was found to be successful after two treatments (30 equiv) for 3 h at 0 °C each. Deprotection was confirmed by the absence of the characteristic MOM signals in the gel-phase ^{13}C NMR spectrum of resin **6b**. However, it was also apparent that the acetylenic carbon signals were absent from the ^{13}C NMR spectrum and the triple and OH bond absorptions were not observed in the IR spectrum.[11] A weak signal at 178.1 ppm was also observed in the gel-phase ^{13}C NMR spectrum. Although the significance of these results remains unclear, the original strategy was followed as outlined in Figure 1. Thus, reaction of the anchored naphthol **6b** with iodoacetic acid using the standard conditions for ester formation was followed by reaction with 3,4-dihydro-6,7-dimethoxyisoquinoline and subsequent treatment with DIEA.[3] At this stage, the spectroscopic data of the resulting resin were the same as for **6b**. Cleavage of this resin with $AlCl_3$ in dry DCM gave a very clean crude product, which was analyzed by HPLC–MS. The HPLC shows only two compounds (**8** and **9**) in the ratio 5.4:1 with a UV peak shape different from that which is characteristic of lamellarins and with *m*/*z* values of 318 and 353, respectively.[12]

The ^1H NMR spectrum of **8**[13] shows three coupled systems and a singlet at 8.03 ppm in the aromatic region and only one methoxy group at 3.95 ppm. These signals provide evidence for the absence of the dimethoxyisoquinoline moiety. A bidimensional COSY experiment on **8** allowed the three coupled systems to be identified as belonging to the trisubstituted aryl group (Ar), the α,β-disubstituted ring of naphthalene (**Nth-A**), and the non-substituted naphthalene ring (**Nth-B**). A gHSQC experiment allowed the correlation of each proton with its supporting carbon (Fig. 3).

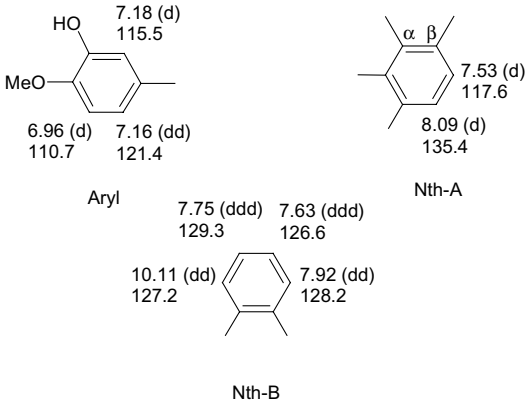

Figure 3. ^1H- and ^{13}C NMR chemical shifts of the three coupled aromatic systems of **8**.

The molecular formula corresponding to an *m*/*z* value of 318 and containing all of the aforementioned C and H units must be $C_{20}H_{14}O_4$. Two possible structures can be proposed for this formula: **8A** and **8B** (Fig. 4). The low field chemical shift (δ 10.11 ppm) of one α-H of naphthalene (**B**) can be explained by the anisotropic effect of the keto group in position 1 of structure **8A**. In contrast, structure **8B** is not consistent with these values, as the keto group is in position 3. Structure **8A** is also more consistent with the chemical shift of the keto group at 178.1 ppm, as envisaged in the anchored compound (**7** in Fig. 5) and also in the cleaved compound **8**. A NOESY experiment proved definitive for assigning the structure **8A**. A NOE effect was not observed between the naphthalene α-H10 at δ 10.11 ppm and the singlet at 8.03 ppm. A significant NOE effect was observed between the Ar 2′-H (at 7.17 ppm) or the Ar 6′-H (at 7.16 ppm) protons and the singlet at 8.03 ppm. Other NOE effects observed are shown in Figure 4.

The complete ^{13}C NMR assignment of **8** was possible after a bidimensional long distance H–C correlation (HMBC). The most important correlations are shown in Figure 4 and all of the observed correlations are detailed in Table 1. The HMBC correlation between the H10 and the keto group and also the cross-ring correlations between H3–C1′ and H6′–C2 confirms the proposed structure.

Compound **9**[14] has a similar ^1H NMR spectrum to that of compound **8**, with the exception of the aryl group signals. The NMR spectrum of **9** shows two singlets for the aryl group at 6.98 and 7.01 ppm due to two protons that are not coupled, in contrast to the ABC coupling system observed for **8**. Furthermore, the MS clearly shows the presence of a chloro-substituent, which explains the ^1H NMR data. Electrophilic chlorination of electronically rich rings has been previously observed during the cleavage of similar resins with $AlCl_3$.[15]

A possible explanation for the formation of the benzochromone system present in **7** and the partial chlorination of **8** to give **9** is detailed in Figure 5. Thus, *O*-silylation of the MOM methoxy group with Me_3SiBr

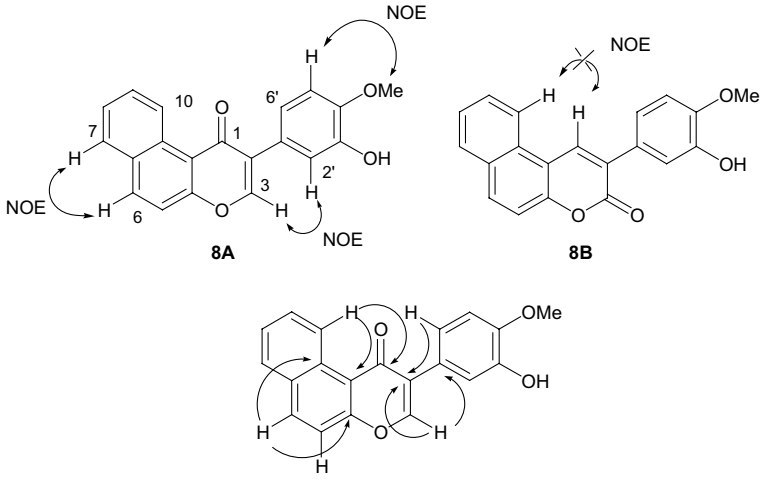

Figure 4. Structures of **8A** and **8B**. Observed NOEs. g-HMBC correlations of **8**.

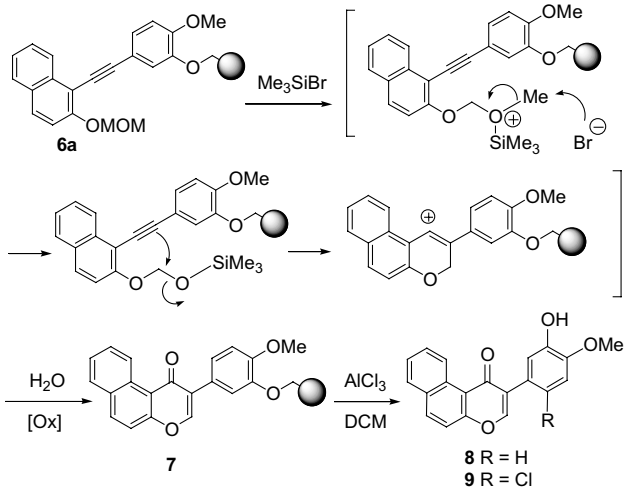

Figure 5. Suggested mechanism for the formation of compound **8**.

Table 1. HMBC: bidimensional long distance H–C (5 Hz) correlations of **8**

H	C
3	1, 2, 1′, 4a
5	4a, 4b, 6a
6	4a, 6a, 7, 10a
7	6, 9, 10a
8	6a, 10
9	7, 10a
10	1, 8, 10a
5′	1′, 3′, 4′, 6′, 1′
6′	2, 2′, 3′, 5′
OMe	4′
OH	2′, 3′

followed by demethylation via nucleophilic attack of bromide could give the *O*-trimethylsilyl derivative. This compound is susceptible to further electrophilic addition by the triple bond and trapping of the resulting carbocation intermediate by atmospheric H_2O would then generate the keto group. Further oxidation would give the anchored compound **7**. Final cleavage with $AlCl_3$ renders **8** and **9**.

In conclusion, an effective solid-phase strategy for the preparation of the quite rare 2-(aryl)naphtho[1,2-*b*]pyran-1-one[16,17] is described. These compounds, like other polycondensed heterocyclic systems bearing electron-donating substituents, are of undoubted pharmaceutical interest.[18] The solid-phase synthetic strategy described here will facilitate the preparation of libraries with applications in drug discovery.

Acknowledgements

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References and notes

1. (a) Toda, F. *Kagaku* **1989**, *44*, 312–317; (b) Iyer, P.; Ghosh, S. K. *Tetrahedron Lett.* **2002**, *43*, 9437–9440.
2. Cironi, P.; Albericio, F.; Álvarez, M. In *Progress in Heterocyclic Chemistry*; Gribble, G. W., Joule, J. A., Eds.; Pergamon: Oxford, UK, 2004; Vol. 16, Chapter 1, pp 1–26.
3. Cironi, P.; Manzanares, I.; Albericio, F.; Álvarez, M. *Org. Lett.* **2003**, *5*, 2959–2962.
4. This strategy was first used in solution by: Banwell, M.; Flynn, B.; Hockless, D. *Chem. Commun.* **1997**, 2259–2260.
5. Merrifield-OH resin (loading 0.98 mmol g^{-1}, 100–200 mesh, 1% divinylbenzene) was used as a solid support. Conditions for the anchoring are those described in Ref. 3.
6. 1-Ethynyl-2-methoxymethoxynaphthalene **5** was obtained by cross-coupling reaction between 1-iodo-2-(methoxymethoxy) naphthalene and trimethyl(trimethylsilylethynyl)-stannane with $Pd(PPh_3)_4$ as a catalyst. The reaction was performed in dry toluene under reflux for 24 h followed by desilylation with K_2CO_3 in MeOH to give 95% yield. Compound **5**: ^1H NMR ($CDCl_3$, 400 MHz) 3.58 (s, 3H);

3.73 (s, 1H); 5.39 (s, 2H); 7.41–7.44 (m, 2H); 7.56 (dd, *J* 8.4, 7.6 and 1.4 Hz, 1H); 7.80 (dd, *J* 9.2 and 8.4 Hz, 1H); 8.29 (dd, *J* 8.4 and 0.8 Hz, 1H). ^{13}C NMR ($CDCl_3$, 400 MHz) 157.6, 134.6, 130.4, 129.0, 128.0, 127.4, 125.3, 124.7, 116.1, 107.0, 95.3, 86.4, 78.1, 56.3. MS (CI) 213 (M+1, 80). CI-HRMS calculated for $C_{14}H_{12}O_2$ 212.0837. Found $[M]^+$ 212.0840.

7. Cironi, P.; Tulla-Puche, J.; Barany, G.; Albericio, F.; Álvarez, M. *Org. Lett.* **2004**, *6*, 1405–1408.
8. Compound **6**: IR (KBr, cm^{-1}) *v* 2200; gel-phase ^{13}C NMR (300 MHz, $CDCl_3$) 56.0, 56.4, 70.9, 80.0, 94.0, 95.6, 111.4, 116.7, 148.0, 149.9.
9. Similar reaction conditions gave good results in solution: Droz, A. S.; Neidlein, U.; Anderson, S.; Seiler, P.; Diederich, F. *Helv. Chim. Acta* **2001**, *84*, 2243–2289.
10. Huffman, J. W.; Zhang, X.; Wu, M.-J.; Joyner, H. H.; Pennington, W. T. *J. Org. Chem.* **1991**, *56*, 1481–1489.
11. The absence of these absorptions was not considered significant because they are frequently not observed in bisarylacetylenes.
12. Cleavage of 80 mg of **7** gave a crude product, which was purified by HPLC to afford **8** (6 mg, 43% overall yield) and **9** (1 mg, 7% overall yield).
13. Compound **8**: ^{1}H NMR ($CDCl_3$, 400 MHz) 3.95 (s, 3H); 6.96 (d, *J* 8.8 Hz, 1H, H5′); 7.16 (dd, *J* 8.8 and 2.4 Hz, 1H, H6′); 7.18 (d, *J* 2.4 Hz, 1H, H2′); 7.53 (d, *J* 8.8 Hz, 1H, H5); 7.63 (ddd, *J* 7.4, 7.2 and 1.2 Hz, 1H, H8); 7.75 (ddd, *J* 8.4, 7.2 and 1.6 Hz, 1H, H9); 7.92 (dd, *J* 7.4 and 1.6 Hz, 1H, H7); 8.03 (s, 1H, H3); 8.09 (d, *J* 8.8 Hz, 1H, H6); 10.11 (dd, *J* 8.4 and 1.2 Hz, 1H, H10). ^{13}C NMR ($CDCl_3$, 400 MHz) 178.1 (C1); 157.4 (C4a); 150.3 (C3); 146.7 (C4′); 145.6 (C3′); 135.4 (C6); 130.9 (C6a); 130.7 (C10a); 129.3 (C9); 128.2 (C7); 127.6 (C2); 127.2 (C10); 126.6 (C8); 125.2 (C1′); 121.4 (C6′); 117.8 (C10b); 117.6 (C5); 115.5 (C2′); 110.7 (C5′); 56.1 (OMe); CI-HRMS *m*/*z* 318.0895 calcd for $C_{20}H_{14}O_4$ $[M]^+$ found 318.0892.
14. Compound **9**: ^{1}H NMR ($CDCl_3$, 400 MHz) 3.94 (s, 3H); 6.98 (s, 1H, H5′); 7.01 (s, 1H, H2′); 7.55 (d, *J* 8. 8 Hz, 1H, H5); 7.63 (ddd, *J* 8.0, 8.0 and 1.2 Hz, 1H, H8); 7.74 (ddd, *J* 8.0 and 1.2 Hz, 1H, H8); 7.92 (dd, *J* 7.4, 7.2 and 1.2 Hz, 1H, H8); 7.98 (s, H3); 8.12 (d, *J* 8.8 Hz, 1H, H6); 10.11 (dd, *J* 8.4 and 1.2 Hz, 1H, H10); CI-HRMS *m*/*z* 353.0581 calcd for $C_{20}H_{14}Cl^{35}O_4$ $[M+H]^+$ found 353.0575.
15. A precedent for the chlorination of a similar aromatic ring was previously described by: Cironi, P.; Cuevas, C.; Albericio, F.; Álvarez, M. *Tetrahedron*, **2004**, *60*, in press. doi:10.1016/j.tet.2004.05.119.
16. A SciFinder search showed just 11 references containing the 2-(aryl)naphtho[1,2-*b*]pyran-1-one.
17. Also known as 3-(aryl)benzo[*f*]chromone.
18. Chromones have been described as inhibitors of phosphatidylinositol 3′-kinase in human colon cancer cells by: Sembra, S.; Itoh, M.; Harada, M.; Yamakawa, M. *Clin. Cancer Res.* **2002**, *8*, 1957–1963; , as hypoglycemic agents by: Reddy, R. R.; Reddy, V. M. *Indian Drugs* **1997**, *34*, 258–263; for preventing asthmatic symptoms by: Kllutchko, S.; Brown, R. E.; Von Strandtmann, M. (Warner-Lambert CO., USA) US 74-504628 19740909.