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Application of directed metallation in synthesis: total synthesis of model compounds related to semivioxanthin

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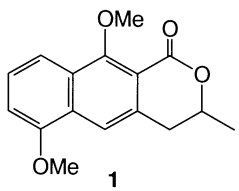
Abstract—Two model compounds related to the naturally occurring antifungal compound semivioxanthin were synthesized from readily available starting materials using a directed metallation–transmetallation–allylation–cyclization protocol.

The undiminished importance of heteroatom directed *ortho* metallation[1] as an effective tool in synthetic aromatic chemistry is corroborated by its continuing use in regioselective functionalisation of aromatic or heteroaromatic nuclei and the subsequent utilization of the introduced functionalities for annelation purposes. We report here the application of this methodology for the synthesis of two model compounds **1** and **2** related to the naturally occurring antifungal compound semivioxanthin[2] (**3**), from commercially available or easily accessible starting materials.



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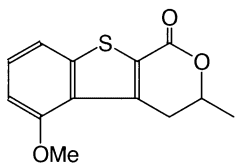

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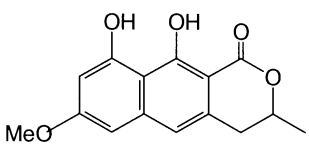

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Semivioxanthin was earlier synthesized via long routes[3] or using toxic chemicals.[4] The directed metallation–transmetallation–allylation–cyclization protocol utilised here is an attractive alternative because it involves only a few steps and can be equally adopted to synthesize the natural product or analogues.

The synthesis of 2,3-dihydro-2-methyl-5,9-dimethoxy naphtho[7,6-*c*]pyran 10-one (**1**) from commercially available 1,5-dihydroxynaphthalene is shown in Scheme 1.[5]

The two hydroxyl functions of **4** were converted sequentially into methoxy and *O*-carbamate groups and the resulting compound **6** was deprotonated in the position *ortho* to the *O*-carbamate under standard directed metallation conditions.[1] When kept at room temperature for 16 h, the deprotonated species underwent an anionic Fries rearrangement[6] and the resulting salicylamide was methylated without further purification to afford **7** in a 35% overall yield. Attempts to introduce an allyl group *ortho* to the $CONEt_2$ function via metallation–transmetallation[7] were unsuccessful. An examination of the NMR of the reaction product suggested that demethylation of the methoxy group *ortho* to $CONEt_2$ was followed by formation of the *O*-allylated product among others, leading to an intractable mixture. This problem was circumvented by introducing a $CONEt_2$ function *ortho* to the *O*-carbamate by deprotonation and quenching with *N*,*N*-diethyl carbamoyl chloride affording **8**. Allylation *ortho* to the $CONEt_2$ in **8** was achieved in high yield by lithiation, transmetallation with $CuBr–SMe_2$[8] and quenching with allyl bromide. The resulting compound **9** was cyclized by heating with 6N HCl for 36 h. The *O*-carbamate function was hydrolyzed during the cyclization as corroborated by the disappearance of the carbonyl peak at 1708 cm^{-1} in the IR of the cyclized product and the

Keywords: semivioxanthin; directed metallation; transmetallation.

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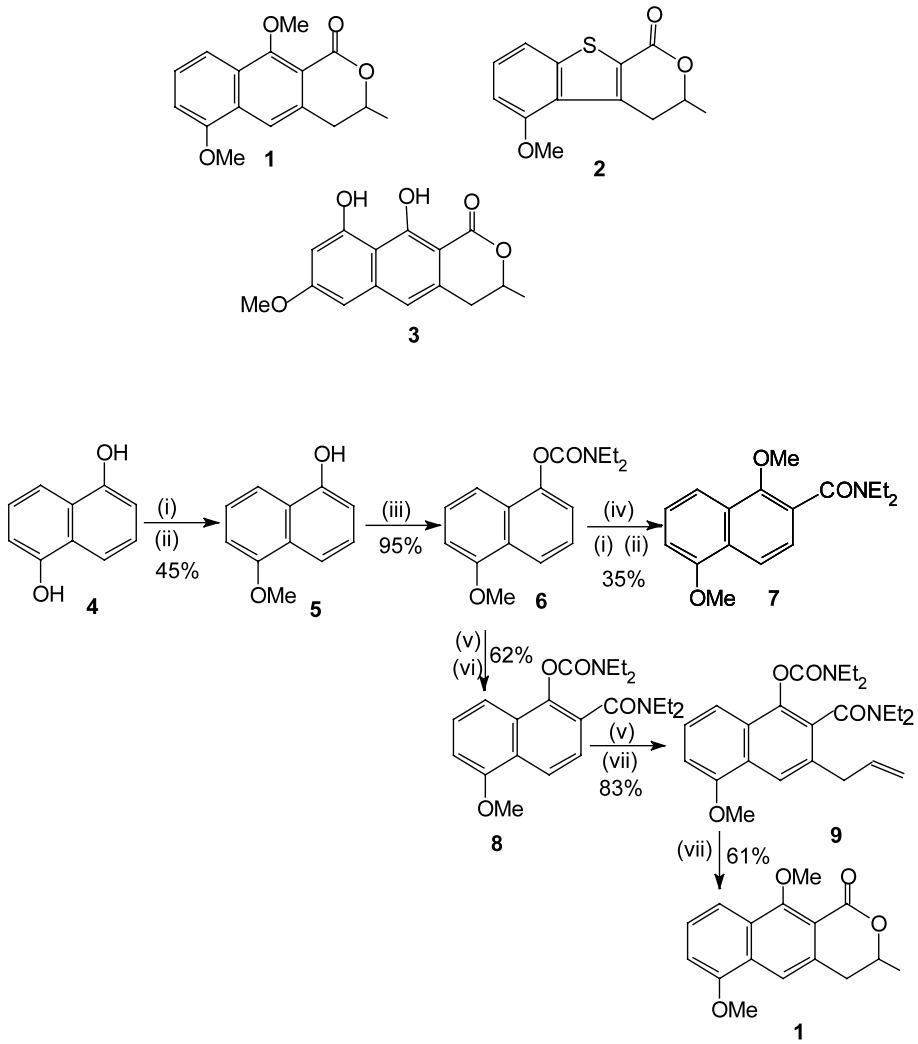
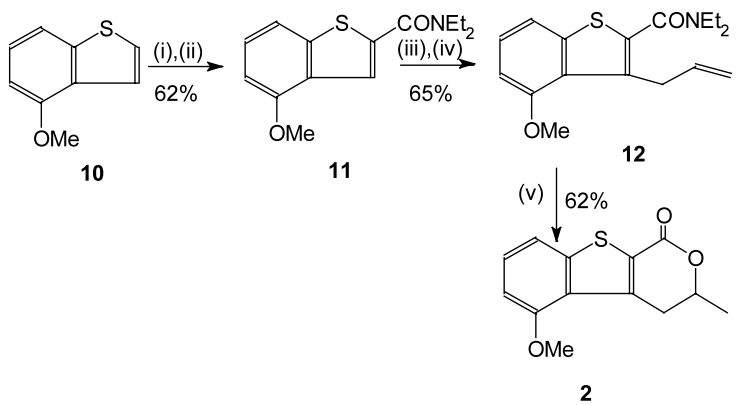


Scheme 1. *Reagents and conditions*: (i) K_2CO_3/acetone; (ii) MeI; (iii) $ClCONEt_2$/NaH/THF; (iv) *sec*-BuLi (2.5 equiv.)/TMEDA/–78°C to rt, 12 h; (v) *sec*-BuLi (2.5 equiv.) TMEDA/THF/–78°C; (vi) $ClCONEt_2$; (vii) CuBr–Me_2S, allyl bromide; (viii) 6N HCl/Δ/36 h.

appearance of a peak due to the hydroxyl function at 3323 cm^{-1}. The crude product was methylated (K_2CO_3–acetone–MeI) to afford **1** in a 61% overall yield.

The model compound 2,3-dihydro-2-methyl-4-methoxy-[1]benzothieno[2,3-*c*]pyran 9-one (**2**) was synthesized from 4-methoxy benzo[*b*]thiophene(**10**)[9] (Scheme 2).



Scheme 2. *Reagents and conditions*: (i) *n*-BuLi (1.2 equiv.)/THF/–78°C/THF, rt, 16 h; (ii) *n*-BuLi (1.1 equiv.)/THF/–78°C/$ClCONEt_2$/–78°C–rt/16 h; (iii) *sec*-BuLi (2.5 equiv.)/THF/CuBr-Me_2S/–78 to –30°C; (iv) allyl bromide/–78°C; (v) 6N HCl reflux for 60 h.

Introduction of the $CONEt_2$ functionality at the 2-position in **10** was achieved by deprotonation with *n*-BuLi followed by quenching with *N*,*N*-diethyl carbamoyl chloride. Introduction of the allyl function *ortho* to the $CONEt_2$ and cyclization was carried out by the usual metallation–transmetallation process.

The construction of the linear tricyclic skeleton carrying oxygenated functions present in semivioxanthin in reasonably good yields is thus achievable by this methodology. Work is in progress on the total synthesis of the natural product and other analogues which will be reported later.

Acknowledgements

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5. All the new compounds reported in this paper have correct elemental analyses and spectral data.
   Compound 1: Low melting white solid. Yield: 61%. IR (neat) $\nu_{c=o}$1714 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.8 (d, H-8, $J=8.4$ Hz), 7.75 (s, H-4), 7.36 (dd, H-7, $J=8.1$ and 7.5 Hz), 6.87 (d, H-6, $J=7.5$ Hz), 4.62 (m, H-2), 4.1 (s, -OMe, 3H), 4.00 (s, -OMe, 3H), 3.06 (m, $-CH_2$, 2H), 1.51 (d, $-CH_3$, 3H). ^{13}C NMR: 155.36 (C-10), 134–107 (aromatic carbons), 63.72 and 56.11 (two -OMe), 37.06 ($-CH_2$), 21.14 ($-CH_3$).
   Compound 2: Mp 136–140°C. IR ($CHCl_3$) $\nu_{c=o}$ 1708 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.71 (d, H-7, $J=8.7$ Hz), 7.13 (dd, H-6, $J=6$ Hz), 7.08 (d, H-5, $J=5$ Hz) 4.91 (m, H-2, 1H), 3.9 (s, -OMe, 3H), 3.04 (m, $-CH_2$, 2H) 1.63 (d, $-CH_3$, 3H). ^{13}C NMR: 157.88 (carbonyl), 124.63, 119.26, 105.11 (three aromatic protonated carbons), 76.95 (aliphatic -CH), 55.66 (-OMe), 30.51 ($-CH_2$), 20.9 ($-CH_3$)
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