An Anionic Polycondensation Strategy for the Synthesis of Dibenzoxanthenones: Progress Toward the Synthesis of Hypoxyxylerone

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Abstract: An anionic polycondensation has been used as the key step in a highly convergent strategy for the preparation of hypoxyxylerone derivatives.

Key words: antitumor agents, condensation, heterocycles, natural products, total synthesis

Hypoxyxylerone (**1**), a dibenzoxanthenone isolated from the fungus *Hypoxylon fragiforme* in 1991 by Edwards and coworkers, has been shown to inhibit in vitro topoisomerase I.[1]

We have been interested in the synthesis of not only this scarce metabolite, but also diverse analogs that might provide insight into structure–activity relationships. We have already disclosed a first-generation approach to the structurally unique natural product, which culminated in the preparation of its penta(*O*-methyl) derivative **5** (Scheme 1).[2] This route, based on a novel anionic homo-Fries rearrangement of ester **2** to secure the key xanthone intermediate **4**, via **3**, was convergent, but the preparation of each of the naphthalene moieties in **2** was long, which made it ill-suited for the synthesis of analogs.

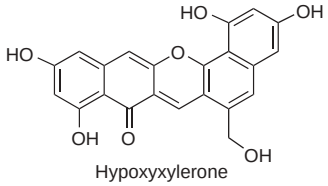

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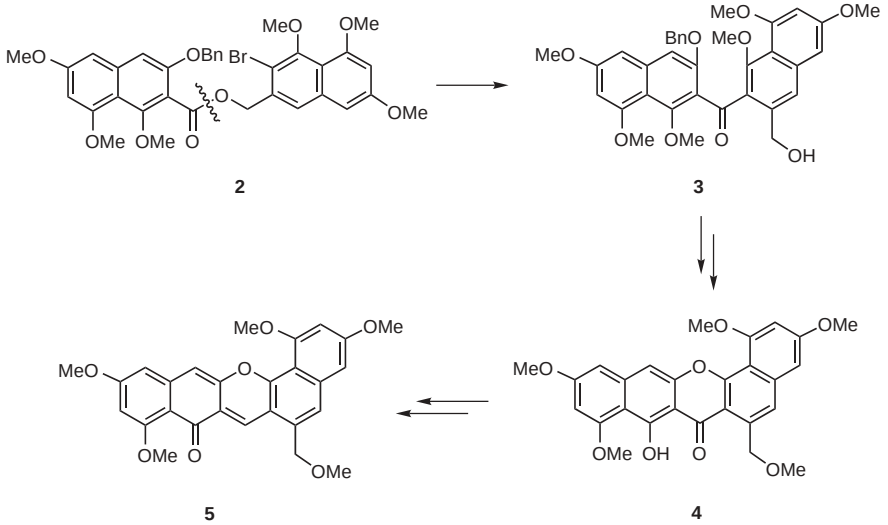
Figure 1

The anionic polycondensation reported over 20 years ago by Kjaer and coworkers,[3] although demonstrated only for acetophenones, appeared to offer an attractive alternative. This under-used methodology, if it could be successfully extrapolated to acetonaphthones, seemed capable of providing a short, highly convergent, and quite flexible approach to hypoxyxylerone and diverse derivatives.

The key step in the envisaged approach, outlined in Scheme 2, would be the formation of dibenzoxanthone **I** through anionic polycondensation of acetonaphthone **IV** with homophthalate **III**. Each of these components can be readily prepared with considerable structural and functional group variation.



Scheme 1

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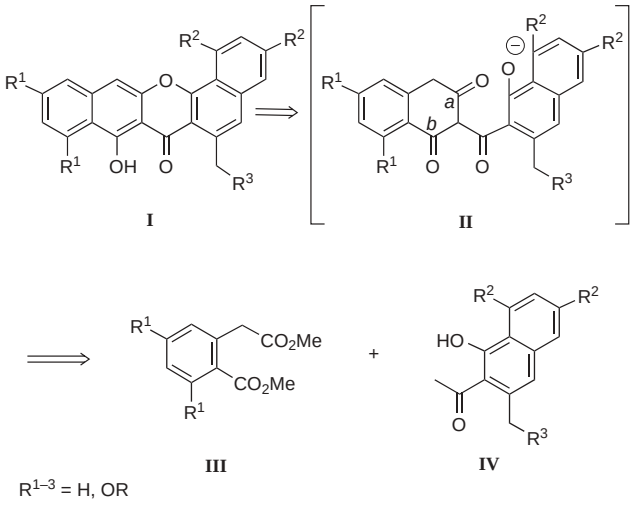
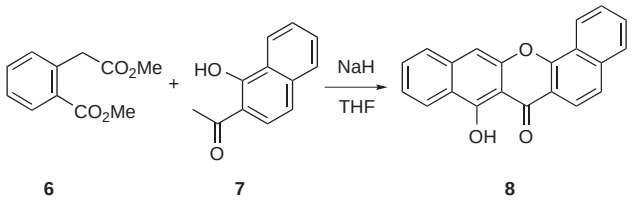


Scheme 2

For the purpose of rapidly ascertaining whether the acetonaphthone condensation would in fact be feasible and, if so, whether it would produce primarily the desired L-shaped product **I** through selective cyclization at carbonyl *a* in the likely intermediate **II** (as opposed to the U-shaped product through cyclization at *b*), the reaction of commercially available 1′-hydroxy-2′-acetonaphthone with dimethyl homophthalate was first examined (Scheme 3).

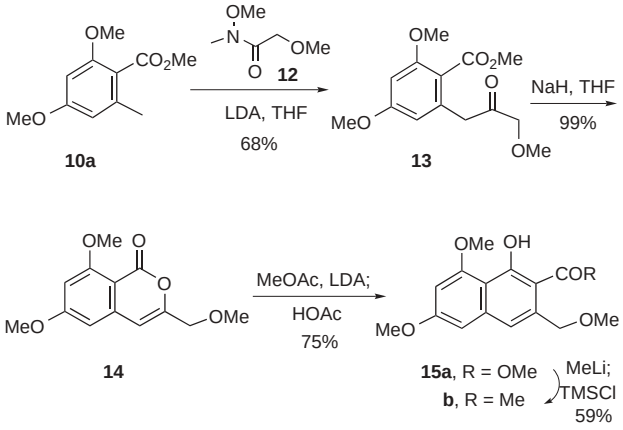


Scheme 3

Under the conditions described by Kjaer and coworkers,[3] a unique xanthone **8** was formed in 46% yield, which was shown to have the desired L-shape geometry, as from acetophenones, by X-ray analysis.[4] Extensive optimization of the reactions conditions (separate dianion formation over 1 h, 1.7 equiv of diester, 22 h reaction time) led to the formation of the pentacyclic xanthone in a much improved 69% yield.

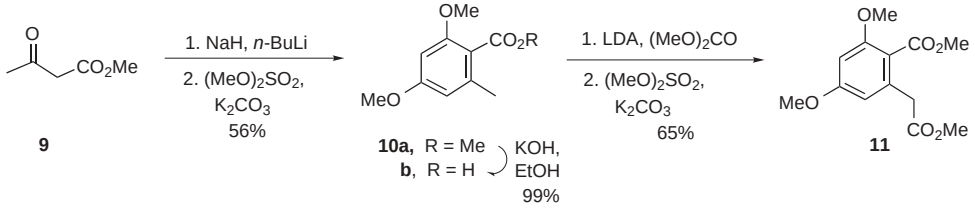
This encouraging result prompted efforts to prepare more complex derivatives of hypoxyxylerone through the use of this approach. For comparison with the previous approach, the penta(*O*-methyl) derivative **4** was first targeted. The requisite, known[3] homophthalate diester **11** could be easily prepared on a large scale as shown in Scheme 4. Methyl acetoacetate was autocondensed[5] to give methyl orsellinate which was converted to diether **10a** with dimethyl sulfate and potassium carbonate in refluxing acetone (56%, 2 steps). Carbomethoxylation at the benzylic position of **10a** was best accomplished indirectly by carboxylation of the corresponding acid **10b** to yield the diacid derivative,[6] followed by methylation to afford diester **11** (65%, 2 steps).

The 4-step preparation of the second moiety, acetonaphthone **15b**, was based on chemistry that had previously been applied for the synthesis of molecules similar to naphthoate **15a**, but required considerable modification to obtain serviceable results (Scheme 5).[7] The anion formed from the methyl orsellinate derivative **10a** was treated with Weinreb amide **12**[8] to provide in 68% yield α-methoxy ketone **13**[3,9,10] which was smoothly converted into isocoumarin **14**[11] with sodium hydride in THF.[9]

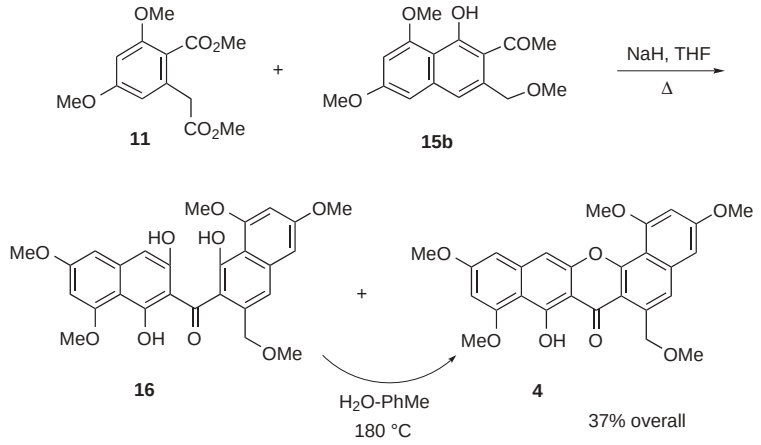


Scheme 5

This isocoumarin was next transformed in 75% yield into methyl naphthoate **15a** by using a procedure similar to that developed by Roush and Murphy for their synthesis of olivine.[12] Treatment of this ester with methyllithium and trimethylsilyl chloride[13] then provided acetonaphthone **15b** (59%; 30% overall from **10a**).



Scheme 4



Scheme 6

The polycondensation of the 2 fragments, diester **11** and ketone **15b**, was effected under the optimized model-system conditions to give a mixture of naphthonaphthone **16** and the desired xanthone **4** (Scheme 6); the mixture, by heating in water–toluene at 180 °C in a closed vessel, could be transformed completely into xanthone **4** (37% overall yield).[14,15]

Although the present convergent route to **4** is only slightly higher yielding overall than the previous (11% vs 10%), it is considerably more reproducible and rapid (7 steps vs 13 steps, longest linear sequence) and, furthermore, lends itself more readily to analog preparation.

To demonstrate the flexibility inherent in this approach, a family of hypoxyxylerone analogs with OMe's in lieu of OH's and a Me in place of the CH_2OH group has been prepared. The polycondensations were carried out with the homophthalates **6** and **11** and the acetonaphthones **17a**,**b** (Scheme 7).[16] The resulting pentacyclic xanthones (**18a**–**d**), obtained in quite acceptable yields in view of the conciseness of the approach, were all assigned the L-shape geometry based on the structures of derivatives **4** and **8** and X-ray analysis of **18d**.[17]

The *o*-quinone methide substructure found in hypoxyxylerone (**1**) could be generated in **18a**–**d** through lithium aluminum hydride reduction, followed by in situ hydrolytic rearrangement of the intermediate xanthols, which gave derivatives **19a**–**d**.[18,19] The hypoxyxylerone analogues **19b**,**d** were found to inhibit topoisomerase I in vitro, albeit less so than the natural product.

In summary, the anionic polycondensation developed by Kjaer and coworkers for acetophenones has been successfully extended to acetonaphthones for a new, flexible approach to hypoxyxylerone derivatives. Current efforts are focused on the use of this convergent strategy to access other analogs as well as the natural product itself.

Acknowledgment

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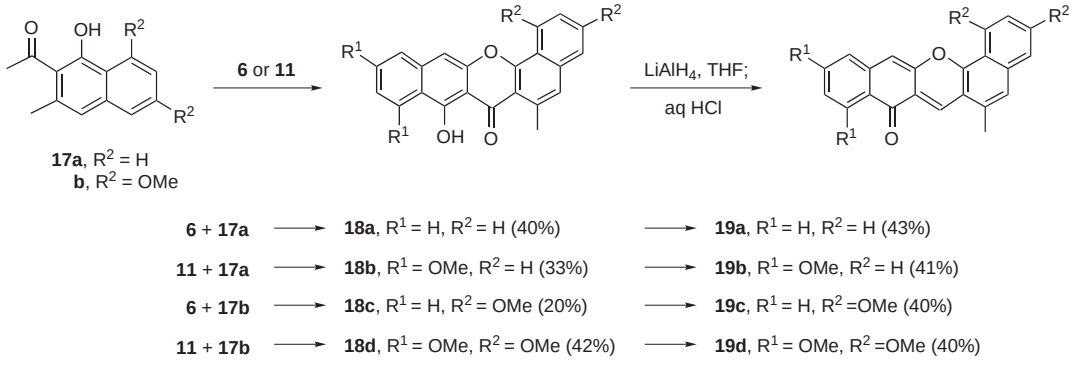

6 + **17a** → **18a**, R^1 = H, R^2 = H (40%) → **19a**, R^1 = H, R^2 = H (43%)

11 + **17a** → **18b**, R^1 = OMe, R^2 = H (33%) → **19b**, R^1 = OMe, R^2 = H (41%)

6 + **17b** → **18c**, R^1 = H, R^2 = OMe (20%) → **19c**, R^1 = H, R^2 =OMe (40%)

11 + **17b** → **18d**, R^1 = OMe, R^2 = OMe (42%) → **19d**, R^1 = OMe, R^2 =OMe (40%)

Scheme 7

References

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(4) Crystal data for **8**: $C_{21}H_{12}O_3$ monoclinic. $P2_1/n$; a = 7.729 (1) Å, b = 8.127 (3) Å, c = 23.067 (3) Å; β = 95.95 (1)°; V = 1441.1 (5) Å^3; D = 1.44 gcm^{-3}; μ = 0.96 cm^{-1}; λ = 0.71073 Å. $2c_{max}$ = 48°. 2501 measured reflections, 2440 independent reflections; 220 parameters. Reflections/parameters ratio: 6.8; R [$I>1.1\sigma(I)$] = 5.8%; wR [all data] = 5.8%. G. O. F. (all data) = 1.54. Full lists of fractional atomic co-ordinates, bond lengths and angles, and thermal parameters have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-247512.

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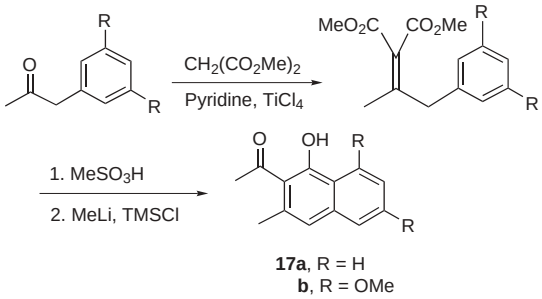
(15) **Procedure for the Preparation of 4 – Polycondensation of 11 and 15b:** To a stirred suspension of pentane-washed NaH (79 mg, 3.29 mmol, from a 60% dispersion in mineral oil) in anhyd THF (2.5 mL) under argon at 0 °C was added dropwise a solution of **15b** (130 mg, 0.45 mmol) in THF (5.0 mL). The mixture was stirred at 25 °C for 1 h before the addition of a solution of homophthalate **11** (204 mg, 0.76 mmol) in THF (3.5 mL). The resultant mixture was stirred at 25 °C for 2 h and then heated at 80 °C for 20 h (pressure tube). The solution was cooled and aq HCl (6 N) was added, and the resultant mixture was extracted with $CHCl_3$. After the usual workup, the product was flash chromatographed (SiO_2, EtOAc in pentane, 30–50%) to give a mixture of **4** and **16** (12% and 25%, respectively, NMR), which was heated in H_2O–toluene 5:1 (12 mL) at 180 °C for 16 h (pressure tube). The cooled solution was worked up in the usual way with $CHCl_3$ to afford a solid product, which was triturated with Et_2O and filtered to give **4** (79 mg, 37%) as an orange solid. Mp 268–269 °C ($CHCl_3$). IR (neat): 3411, 1649, 1620, 1602 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.62 (s, 3 H), 3.89 (s, 3 H), 3.90 (s, 3 H), 3.98 (s, 3 H), 4.04 (s, 3 H), 5.16 (s, 2 H), 6.32 (d, J = 2.2 Hz, 1 H), 6.52 (d, J = 2.2 Hz, 1 H), 6.57 (d, J = 2.2 Hz, 1 H), 6.70 (d, J = 2.2 Hz, 1 H), 6.98 (s, 1 H), 7.65 (s, 1 H). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 55.5 (CH_3), 55.6 (CH_3), 56.3 (CH_3), 56.4 (CH_3), 59.1 (CH_3), 73.6 (CH_2), 96.9 (CH), 97.9 (CH), 99.6 (CH), 99.8 (CH), 100.8 (CH), 104.4 (C), 108.2 (C), 109.7 (C), 112.4 (C), 119.7 (CH), 137.5 (C), 140.4 (C), 141.8 (C), 152.0 (C), 157.2 (C), 159.8 (C), 161.0 (C), 161.7 (C), 161.8 (C), 163.9 (C), 183.8 (C). MS (DCI, NH_3 + *iso*butane): *m/z* (%) = 477 (100) [MH$^+$]. HRMS: *m/z* calcd for $C_{27}H_{24}O_8$: 476.1471. Found: 476.1479 (M$^+$). Xanthone **4** was identical in all respects with the material prepared earlier[2] through the homo-Fries route.

(16) (a) Although acetonaphthone **17a** was known,[16b] the reported yield was only 3.5%. Therefore, a new route was developed (Scheme 8, R = H; 30% overall yield). Acetonaphthone **17b**[16c] could be prepared through a route analogous to that used for the preparation of acetonaphthone **15b** (Scheme 5, *N*-methoxy-*N*-methylacetamide replaces **12**); however, a route analogous to that used for **17a** proved superior (Scheme 8, R = OMe; 52% overall yield). (b) Yang, N. C.; Lin, L. C.; Shani, S.; Yang, S. S. *J. Org. Chem.* **1969**, *34*, 1845. (c) Dodd, J. H.; Garigipati, R. S.; Weinreb, S. M. *J. Org. Chem.* **1982**, *47*, 4045.



Scheme 8

(17) Crystal data for **18d**: $C_{26}H_{22}O_7$ triclinic. P-1; a = 10.404 (3) Å, b = 11.124 (3) Å, c = 15.392 (6) Å; α = 67.91 (2)°, β = 77.29 (2)°, γ = 66.97 (2)°. V = 1513.5 (9) Å^3; D = 1.49 gcm^{-3}; μ = 1.97 cm^{-1}, λ = 0.56083 Å; $2c_{max}$ = 35.7°. 3863 measured reflections, 3863 independent reflections. 424 parameters. Reflections/parameters ratio: 5; R [$I>2\sigma(I)$] = 9.7%; wR [all data] = 9.9%. G. O. F. = 2.22. The poor resolution is due to problems associated with severely disordered $CHCl_3$ molecules in the asymmetric cell and desolvation (capillary tube). Full lists of fractional atomic co-ordinates, bond lengths and angles, and thermal parameters have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-247513.

(18) This procedure for accessing the *o*-quinone methides was found to be more convenient than that previously used[2] based on Saegusa dehydrosilylation.

(19) The corresponding unprotected derivatives **19b–d** (R^1, R^2 = H, OH) could also be secured in moderate yield through treatment of the xanthones **18b–d** with boron tribromide prior to reduction–hydrolysis.