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Synthetic Approach to Hypoxyxylerone, Novel Inhibitor of Topoisomerase I

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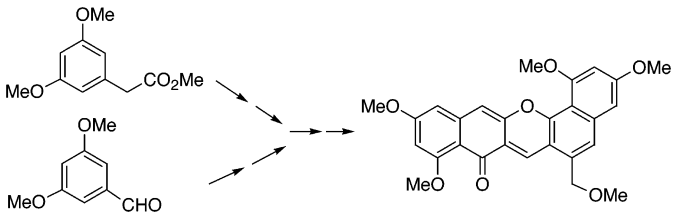
ABSTRACT



A potential route to the topoisomerase I inhibitor hypoxyxylerone is demonstrated by a highly convergent synthesis of the penta(*O*-methyl) derivative. The key step in the approach is an anionic homo-Fries rearrangement, little used to date in natural product synthesis and employed here for the first time with a dinaphthalenic substrate, to access the pentacyclic system of hypoxyxylerone.

DNA topoisomerases play a fundamental role in the replication, transcription, and recombination of DNA.[1] These ubiquitous enzymes, which create single- or double-strand breaks (topoisomerases I and II, respectively), are the cellular targets of important antibiotic and anticancer drugs.[2]

Over the past 10 years, the number of topoisomerase I inhibitors has grown considerably and now includes some 60 structurally diverse compounds obtained from a variety of sources.[3] Very few of these substances, however, demonstrate in vivo antitumor activity; except for camptothecin and related compounds,[4] only certain indolocarbazoles have to date provided encouraging results.[5] In this paper, a potential route to the novel in vitro topoisomerase I inhibitor hypoxyxylerone (**1**) is disclosed that should allow access not only to the natural product but also to derivatives with greater bioavailability (Figure 1).[6]

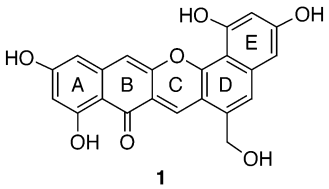


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Figure 1. Hypoxyxylerone.

Hypoxyxylerone was isolated by Edwards and co-workers from the fungus *Hypoxylon fragiforme* in 1991 and was shown to possess the dibenzo[*b*,*h*]xanthene ring system, previously unknown among natural products.[7] This substance, which is responsible for the green coloration in strains of

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(1) Froelich-Ammon, S. J.; Osheroff, N. *J. Biol. Chem.* **1995**, *270*, 21429−21432. Wang, J. C. *Annu. Rev. Biochem.* **1996**, *65*, 635−691.

(2) Wang, H.-K.; Morris-Natschke, S. L.; Lee, K.-H. *Med. Res. Rev.* **1997**, *17*, 367−425. Recently, another type has been identified: Hania, R.; Caron, P. R.; Wang, J. C. *Proc. Natl. Acad. Sci. U.S.A.* **1996**, *93*, 3653−3657. Goulaic, H.; Roulon, T.; Flamand, O.; Grondard, L.; Lavelle, F.; Riou, J.-F. *Nucleic Acids Res.* **1999**, *27*, 2443−2450.

(3) Bailly, C. *Curr. Med. Chem.* **2000**, *7*, 39−58. Long, B. H.; Balasubramanian, B. N. *Exp. Opin. Ther. Patents* **2000**, *10*, 635−666.

(4) Garcia-Carbonero, R.; Supko, J. G. *Clin. Cancer Res.* **2002**, *8*, 641−661. Kehrer, D. F.; Soepenberg, O.; Loos, W. J.; Verweij, J.; Sparreboom, A. *Anticancer Drugs* **2001**, *12*, 89−128.

(5) Gescher, A. *Biochem. Pharmacol.* **1998**, *31*, 721−728. Gescher, A. *Crit. Rev. Oncol. Hematol.* **2000**, *34*, 127−135.

(6) See: Gimbert, Y.; Chevenier, E.; Greene, A. E.; Massardier, C.; Piettre, A. EP 01 402 551 4, 2001.

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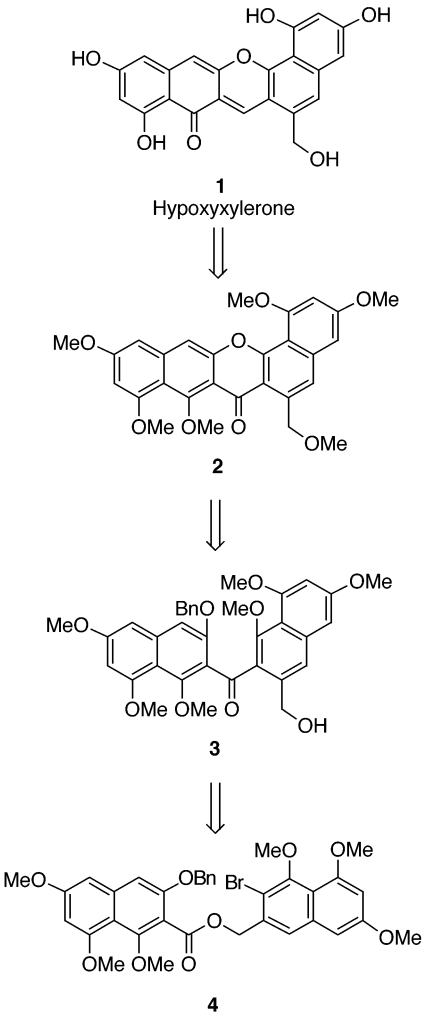
Hypoxylon, was later found to be an in vitro inhibitor of topoisomerase I.[6] It lacks in vivo solubility, however, and thus the preparation of more soluble derivatives, in addition to the novel pentacyclic compound itself, seemed a worthwhile pursuit. Scheme 1 summarizes retrosynthetically our envisioned approach to hypoxyxylerone.

Scheme 1. Retrosynthesis of Hypoxyxylerone



The key reaction in our planned approach was an anionic homo-Fries rearrangement to convert ester **4** into the dinaphthyl ketone **3**, which might then be transformed into xanthone **2** by debenzylation and cyclization. It was hoped that this xanthone could then be reduced to access hypoxyxylerone and derivatives. The anionic homo-Fries rearrangement,[8] like the anionic Fries rearrangement,[9] had been used in synthesis, but had never been applied to naphthyl-naphthyl partners, nor even phenyl-naphthyl ones. It appeared, though, to be ideally suited for use in this approach since a hydroxymethyl group was present in the final product.

A salient advantage of the homo-Fries rearrangement (and the Fries) is that it offers convergency. For the preparation of the homo-Fries substrate **4**, the similarly complex and similarly substituted naphthalene units **5** and **6** were necessary (Figure 2). While structures closely related to each had

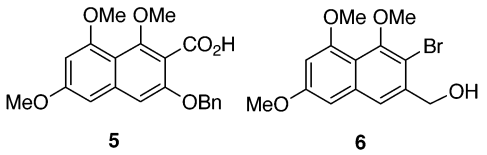
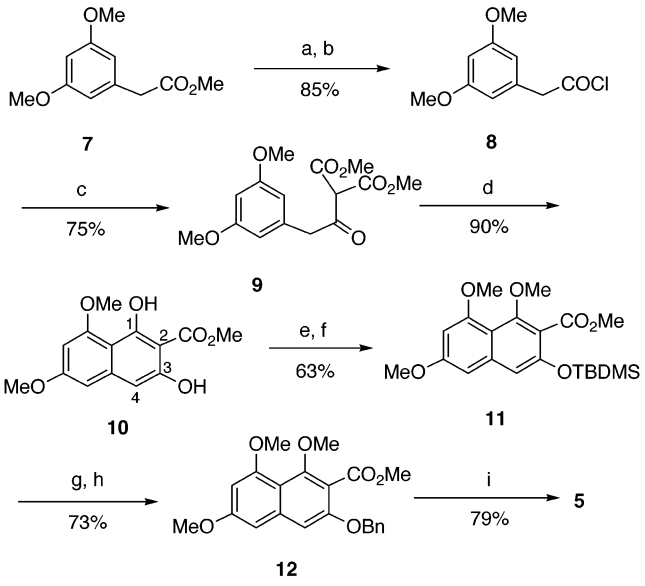


Figure 2. Naphthalene precursors.

previously been prepared,[10] the syntheses suffer from low yields and/or poor reproducibility, and thus a number of modifications have been introduced.

For the synthesis of the naphthalene unit **5**, methyl 3,5-dimethoxyphenylacetate (**7**), easily obtained on a large scale as described by Gaudry and co-workers,[11] was used as the starting material (Scheme 2). Hydrolysis of **7**, followed by exposure of the resulting acid to oxalyl chloride, provided acid chloride **8**. Conversion of this substance into naphthalene **10** could be accomplished in 67% yield by successive

Scheme 2[a]



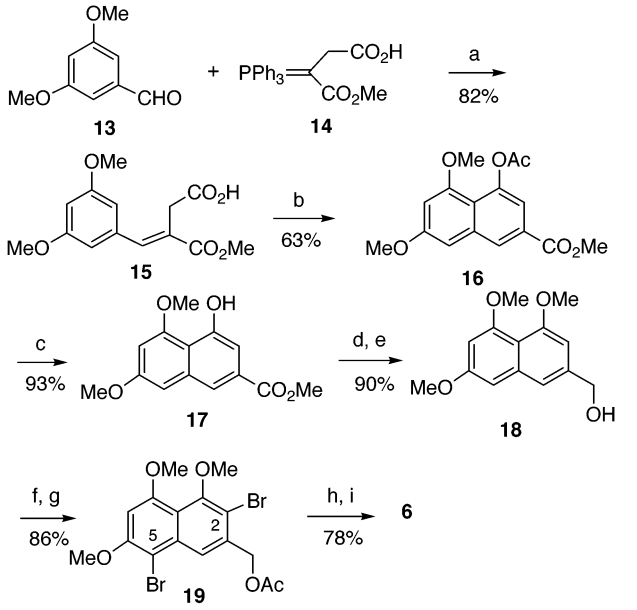
[a] (a) K_2CO_3, MeOH−H_2O, 20 °C, 16 h. (b) $(COCl)_2$, DMF (cat.), toluene, 0 → 20 °C, 2 h. (c) $(MeO_2C)_2CHNa$, THF, 60 °C, 16 h. (d) $MeSO_3H$, 20 °C, 4 h. (e) TBDMSCl, imidazole, DMF, 20 °C, 14 h. (f) DMS, K_2CO_3, acetone, reflux, 16 h. (g) KF, HBr (cat.), DMF, 20 °C, 45 min. (h) BnBr, K_2CO_3, DMF, 20 °C, 4 h. (i) 10% KOH, EtOH, reflux, 18 h.

(7) Edwards, R. L.; Fawcett, V.; Maitland, D. J.; Nettleton, R.; Shields, L.; Whalley, A. J. S. *J. Chem. Soc., Chem. Commun.* **1991**, 1009−1010.
(8) Horne, S.; Rodrigo, R. *J. Chem. Soc., Chem. Commun.* **1992**, 164−166. Nicolaou, K. C.; Bunnage, M. E.; Koide, K. *J. Am. Chem. Soc.* **1994**, *116*, 8402−8408. Lampe, P. F.; Hugues, C. K.; Biggers, C. K.; Smith, S. H.; Hu, H. *J. Org. Chem.* **1996**, *61*, 4572−4581. Couture, A.; Deniau, E.; Lebrun, S.; Grandclaudon, P. *J. Chem. Soc., Perkin Trans. 1* **1999**, *7*, 789−794.

treatment with sodium dimethyl malonate and methanesulfonic acid. The reported procedure (magnesium dimethyl malonate, phosphoric acid−phosphorus pentoxide) proceeded in only 36% yield.[12] This naphthalene was found to be highly susceptible to oxidation, and therefore it was best used directly. Selective *tert*-butyldimethylsilylation of the more accessible hydroxyl in **10**, followed by methylation of the one remaining, delivered the fully protected naphthalene **11** in 63% yield. After silyl → benzyl protecting group exchange to afford **12**,[13] saponification led to the desired acid **5**. The overall yield of **5** from ester **7** was 21% for the nine steps (84%/step).

The second unit, naphthalene **6**, was synthesized by substantially modifying the procedure described by Giles and collaborators[14] (Scheme 3). It was found that ester **16** could

Scheme 3[a]



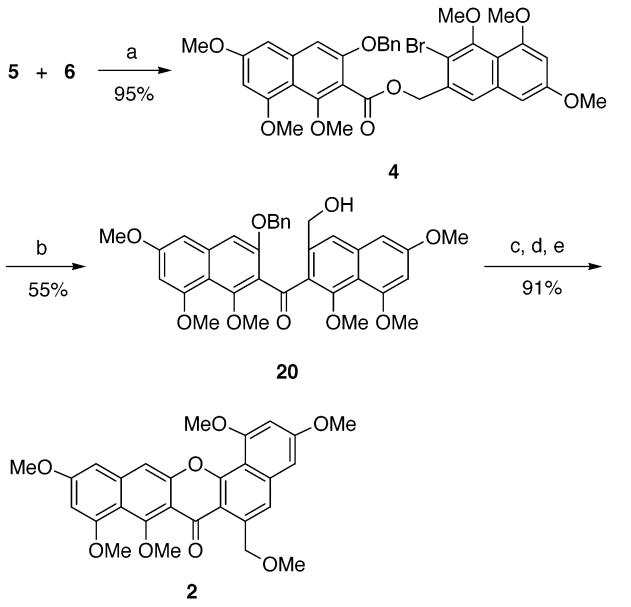
[a] (a) Benzene, 20 °C, 12 d. (b) Ac_2O, AcOK, reflux, 15 min. (c) MeOH−acetone, K_2CO_3, 35 °C, 3 h. (d) DMS, K_2CO_3, acetone, reflux, 16 h. (e) $LiAlH_4$, THF, 20 °C, 1 h. (f) Ac_2O, pyr., 50 °C, 1.5 h. (g) Br_2, AcOH, 20 °C, 20 min. (h) CF_3CO_2H, 1,2,4-TMB, CH_2Cl_2, reflux, 12 h. (i) 1% KOH, MeOH, 20 °C, 30 min.

be better obtained from 3,5-dimethoxybenzaldehyde (**13**) by reaction with ylide **14**[15] followed by cyclization of the resultant acid **15** with potassium acetate in acetic anhydride, according to the procedure outlined by Rizzacasa and collaborators,[16] than through the Giles approach that involved Stobbe condensation with dimethyl succinate and cyclization with sodium acetate in acetic anhydride (51% versus 30% overall yield). Compound **16** so obtained was next converted, as described by Lown and co-workers,[17] with methanol and potassium carbonate in acetone into naphthol **17**, which was methylated (rather than isopropylated[14]) and then reduced to provide alcohol **18** in excellent yield.

The acetate of **18**, obtained conventionally, was dibrominated to provide the highly substituted naphthalene **19**. Mono-debromination of **19** was effected by exposure to trifluoroacetic acid and 1,2,4-trimethoxybenzene (TMB) in refluxing dichloromethane[14] to give a difficult to separate mixture of the desired product[18] together with TMB and 5-bromo-TMB. Fortunately, purification of the mono bromide could be easily accomplished after saponification to naphthol **6**. This esterification partner of acid **5** was thus obtained in nine steps from aldehyde **13** with an overall yield of 29% (87%/step).

The anionic homo-Fries substrate, ester **4**, could readily be formed by Mitsunobu coupling of the naphthalene units **5** and **6** (Scheme 4). The key acyl transfer proceeded

Scheme 4[a]



[a] (a) DEAD, PPh_3, THF, 20 °C, 4 h. (b) *n*-BuLi, THF, −55 → −45 °C, 1.5 h. (c) Ag_2O, MeI, CH_2Cl_2, 20 °C, 7 d. (d) H_2, $Pd(OH)_2$/C, EtOH−CH_2Cl_2, 16 h. (e) KOH, MeOH, reflux, 12 h.

smoothly, following optimization, to afford naphthonaphthone **20** in a reproducible 50−60% yield. In view of the steric encumbrance at the carbonyl site in **4**, the efficiency

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(10) See, for example: Yamaguchi, M.; Okuma, S.; Nakamura, S.; Minami, T. *J. Chem. Soc., Perkin Trans. 1* **1990**, 183−190. Harris, T. M.; Wittek, J. *J. Am. Chem. Soc.* **1975**, *11*, 3270−3277. Dodd, J. H.; Weinreb, S. M. *Tetrahedron Lett.* **1979**, *38*, 3593−3596. Carpenter, T. A.; Evans, G. E.; Leeper, F. J.; Stauton, J.; Wilkinson, M. R. *J. Chem. Soc., Perkin Trans. 1* **1984**, 1043−1050. Cameron, D. W.; Feutrill, G. I.; Pannan, L. J. H. *Aust. J. Chem.* **1987**, *40*, 1737−1745.

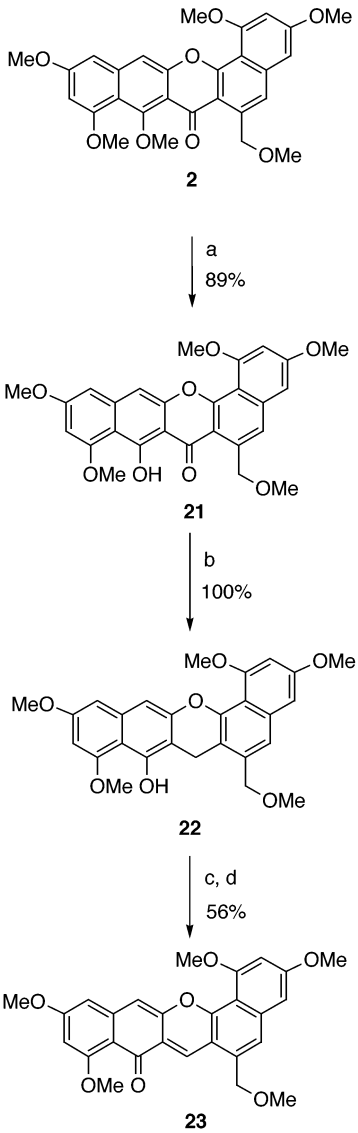
(11) Viviani, F.; Gaudry, M.; Marquet, A. *J. Chem. Soc., Perkin Trans. 1* **1990**, 1255−1261.

(12) Birch, A. J.; Donovan, F. W. *Aust. J. Chem.* **1955**, *8*, 529−534.

(13) The benzyl group could not be directly introduced in **10** because of the unavoidable occurrence of C-4 benzylation.

(14) Giles, R. G. F.; Green, I. V.; Knight, L. S.; Lee Son, V. R.; Mitchell, P. R. K.; Yorke, S. C. *J. Chem. Soc., Perkin Trans. 1* **1994**, 853−866.

Scheme 5[a]



[a] (a) LiCl, DMF, 110 °C, 13 h. (b) BH_3·Me_2S, CH_2Cl_2, reflux, 48 h. (c) TMSOTf, CH_2Cl_2, 2,6-lutidine, 0 °C, 2.5 h. (d) $Pd(OAc)_2$, MeCN, reflux, 12 h.

of this first reported naphthonaphthone preparation through an anionic homo-Fries reaction was particularly satisfying.

Conversion of **20** into xanthone **2** was effected without purification of intermediates by methylation (Ag_2O, CH_3I) of the free hydroxyl group, followed by hydrogenolysis of the benzyl group in the presence of Pearlman's catalyst and cyclization in methanolic KOH. Xanthone **2** could be obtained pure by simple trituration in 91% overall yield. It is worth pointing out that this B-ring O^- attack on the pro D-ring is essential in order to achieve the desired regiochemical outcome in the cyclization; pro D-ring O^- attack on the B-ring results in the formation of the regioisomeric xanthone.

Because exposure of the xanthol derived from **2** to solvolytic conditions failed to generate the dienone ether motif of hypoxyxlerone, a reduction−oxidation strategy was pursued (Scheme 5). Thus, the B-ring methoxyl in xanthone **2** was selectively demethylated (possible because of carbonyl adjacency) with lithium chloride in DMF,[19] and the carbonyl was reduced with excess borane in dichloromethane. Silylation of the free OH in **22** set the stage for Saegusa−Ito dehydrosilylation[20] with palladium(II) acetate, which gave penta(*O*-methyl**)** hypoxyxylerone **23** in 50% overall yield.[21]

This highly convergent first approach to hypoxyxylerone and congeners, which features a novel naphthyl-naphthyl anionic homo-Fries reaction, is reasonably short and efficient: 18 linear steps with an overall yield of 5% (85%/step). Further developments will be publish in due course.

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Supporting Information Available: Experimental procedures and full characterization for the preparation of compound **23** from **5** and **6** and biological test protocol for **23**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) Rizzacasa, M. A.; Sargent, M. V. *Aust. J. Chem.* **1987**, *40*, 1737−1743.

(17) Liu, J.; Diwu, Z.; Lown, J. W. *Synthesis* **1995**, 914−916.

(18) Despite considerable effort, we were unable to realize direct, selective monobromination at C-2. Bromination reagents reacted selectively at the more electron-rich C-5 center, and *ortho*-metalation reactions were nonselective.

(19) Nakanishi, T.; Suzuki, M. *Org. Lett.* **1999**, *7*, 985−989. The correct solvent is DMF and not DMSO.

(20) Ito, Y.; Hirao, T.; Saegusa, T. *J. Org. Chem.* **1978**, *49*, 3671−3675.

(21) This fully OH-protected hypoxyxylerone was found to be an inhibitor of topoisomerase I in vitro, albeit less active than the natural product. For the test protocol, see Supporting Information.