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Convergent and rapid assembly of benzonaphthopyranone cores of chartreusin, chrymutasins and hayumicins

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Dedicated to Professor Frank M. Hauser on the occasion of his 60th birthday

Abstract—A new methodology for the rapid regiospecific synthesis of benzonaphthopyranones has been developed, on the basis of a tactical extension of the Hauser–Kraus annulation. The prowess of the methodology has been illustrated by a short synthesis of chartarin (**22b**) and a facile entry to the chrymutasin scaffold (**26**).
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Chartreusins (e.g., **1**), chrymutasin (e.g., **2**), hayumicins (e.g., **3**) and gilvocarcins (e.g., **4**) are a distinct group of glycosidic polyketide antibiotics sharing a common benzonaphthopyranone nucleus (Fig. 1).[1] Chartreusin (**1**), the most studied member, shows promising antitumour activity against various human cancer cell lines. Due to its poor solubility in water and rapid biliary excretion in the case of intravenous injection, it could not find clinical applications.[2] However, IST-622, a semi-synthetic derivative of chartreusin is undergoing phase II clinical trials in Japan for the treatment of patients with breast cancer.[3] On the other hand, chrymutasins,[4] isolated and characterized in 1994 have not received any attention for further development as drugs, even though chrymutasin A (**2**) showed stronger antitumour activities than chartreusin (**1**). Nor has it been the subject of any synthetic research activity. In view of the sustained interest[2] in chartreusin (**1**) and its striking similarities with chrymutasins, we became interested in developing a diversity-oriented synthetic approach[5] for the title molecules. Furthermore, benzonaphthopyranones are embodied in many organic electroluminescent materials[6] as well as synthetic intermediates of axially chiral biaryl natural products.[7]

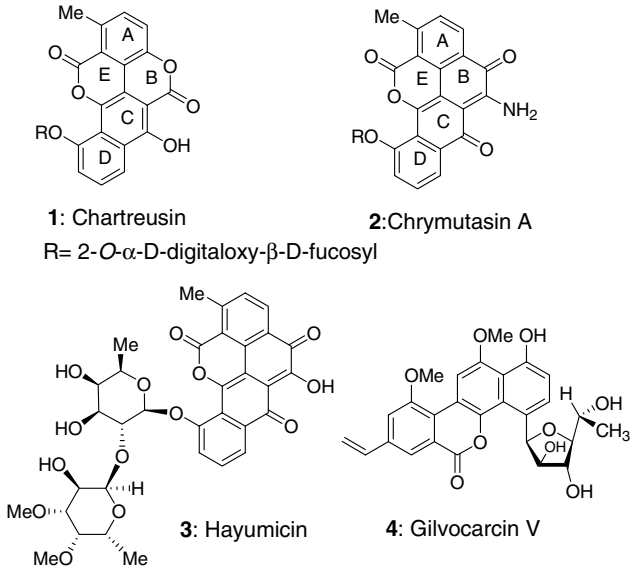

Figure 1. Structures of benzonaphthopyranone antibiotics.

Although chartreusin (**1**) and chrymutasin A (**2**) are markedly different in the constitution of the B-rings of their aglycones, they possess a similar bioactivity profile, implying freedom of structural modification/diversity in the B-ring part of the molecules. Hence, we focused our attention on the synthesis of B-ring analogs of these molecules, and formulated a strategy as shown in Scheme 1. We envisioned that the aryloxy anion of the intermediate **7**, generated in the Hauser–Kraus annulation[8] of **5** with **6** can be intramolecularly trapped via nucleophilic attack of the anion to a proximal suitably

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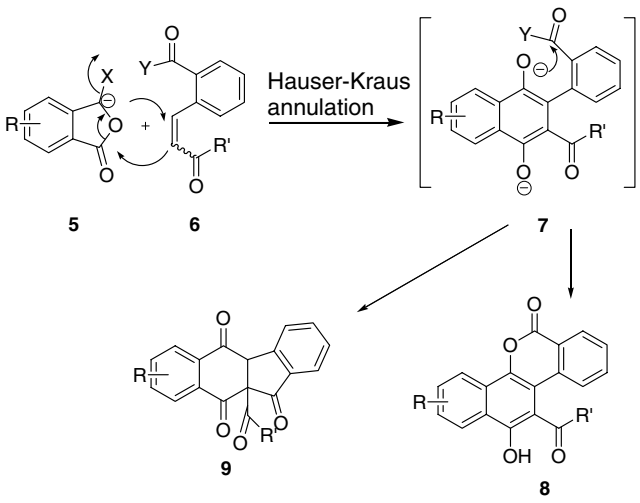
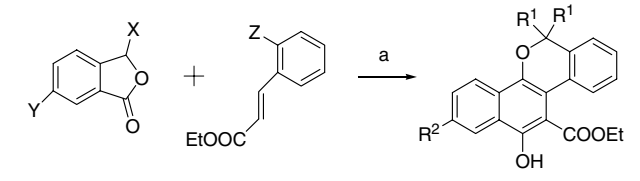


Scheme 1. Strategy for the synthesis of benzonapthopyranones.

placed ester in Michael acceptor **6**, resulting in the in situ formation of the lactone ring of the product **8**. This synthetic approach would prove to be highly convergent since, in a single step, it would form both the C and E rings of the natural products in a regiospecific manner while the A, B and D rings could be derived from the isobenzofuranone and a suitable Michael acceptor with a preset substitution pattern.

Realization of the strategy hinges upon the success of the initial Hauser–Kraus annulation, especially with a sterically crowded Michael acceptor, and prevention of the unwanted intramolecular *C*-acylation leading to formation of a benzo[*b*] fluorenone skeleton (see **9**). In this paper it is shown that this reaction can indeed be terminated intramolecularly with participation of the aryloxy anion, thereby affording a one-pot synthesis of benzonaphthopyranones. The methodology has been successfully applied to the convergent synthesis of chartarin **22b** as well as the first entry to the pentacyclic carbocyclic scaffold **26b** of chrymutasins and hayumicins.

In order to evaluate this concept (Scheme 1), the known cinnamate **11**[9] containing a bromomethyl appendage was prepared in two steps from *o*-tolualdehyde and submitted to reaction with isobenzofuranone **10** in the presence of freshly prepared lithium *tert*-butoxide at −60 °C (Scheme 2). After 5–6 h, the reaction was quenched with a solution of ammonium chloride. The desired product



10 X = SPh, Y = H **11** Z = CH_2Br **12** R^1,R^1 = H, R^2 = H (65%)
13 X = CN, Y = H **14** Z = COOMe **15** R^1,R^1 = O, R^2 = H (81%)
16 X = SPh, Y = NO_2 **14** Z = COOMe **17** R^1,R^1 = O, R^2 = NO_2 (86%)

Scheme 2. Hauser–Kraus annulation with *ortho*-substituted cinnamates. Reagents and conditions: (a) LiO^{t}Bu, −60 °C → rt, THF.

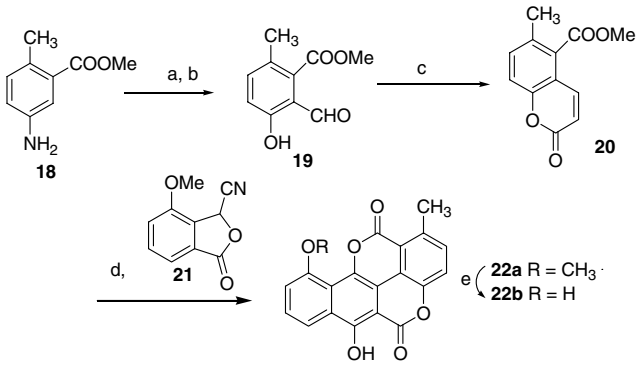
12 containing a pyran ring was obtained in an unoptimized yield of 65%, after chromatographic purification. There was no indication of the formation of any trace of the benzofluorene (cf. **9**).

Our primary objective to construct the benzonaphthopyranone skeleton was next achieved by reacting cyanophthalide **13** with ester appended cinnamate **14**[10] to give **15** in 81% resembling the gilvocarcin nucleus. Nitro substituted isobenzofuranone **16** similarly provided **17** in 86%, the nitro group of which would provide an avenue for structural diversity. The new benzopyranones **12**, **15** and **17** were fully characterized as their *O*-methyl derivatives.

The encouraging results obtained with cinnamates **11** and **14** as Michael acceptors prompted us to examine the suitability of 5-substituted coumarins towards Hauser–Kraus annulation with respect to the total synthesis of chartreusin (**1**). It is worth mentioning that the condensation of coumarin and its 6-methyl derivative with 3-substituted isobenzofuranones to give the corresponding benzo[*b*]naphtha[*d*]pyran-6-ones were previously reported by Hauser and Combs.[11] One of these products was carried forward in a circuitous manner to complete the synthesis of chartarin **22b**, the aglycone of chartreusin (**1**). Installation of the E-ring of chartreusin required several steps and rigorous experimentation. Interestingly, the annulation between a 5-methylcoumarin and 3-phenylsulfonylisobenzofuranone failed to give any condensation product, thus eluding direct entry to the chratreusin nucleus. While there was no explanation for this failure, we encountered similar problems during our work on chemistry of thiophthalides[12] and the synthesis of angucyclines,[13] and tentatively reasoned that the Hauser annulation is sensitive to steric effects caused by the bulky 3-phenylsulfonyl group. The effect becomes more prominent when a complementary bicyclic Michael acceptor is substituted with a group in the vicinity of the centre of incipient Michael addition.[14] We have recently shown that replacement of the phenylsulfonyl group with a phenylthio group can alleviate part of the steric problem, giving cleaner annulations.[15] We also anticipated less steric effects with a cyano group in place of the sulfone group.

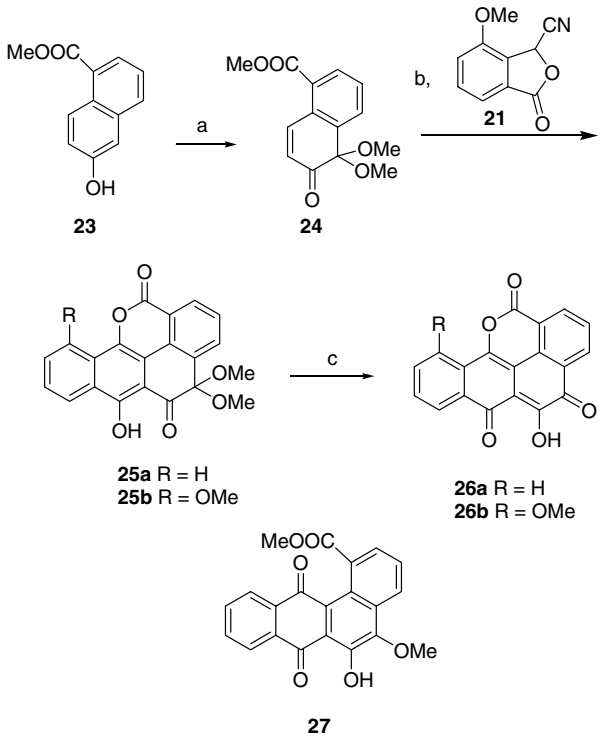
Accordingly, we prepared cyanophthalide **21**[8e] from methyl 3-hydroxybenzoate through regioselective Duff reaction as a key step. As shown in Scheme 3, the required coumarin **20** was prepared in three steps from aminotoluate **18**, which, in turn, was obtained from methyl *o*-toluate. Conversion of trisubstituted benzaldehyde **19** to compound **20** was achieved using the protocol of Harayama et al. for coumarin synthesis.[16] The crucial annulation of **21** with **20** was then performed to give **22a** in 86% yield. HBr-promoted demethylation of **22a** provided chartarin **22b**, identity of which was validated by comparison of its ^{1}H NMR data with those reported.[17]

Following the short synthesis of chartarin **22b**, we proceeded to extend the strategy to the chrymutasin nucleus **26**. Although it appears to be straightforward, we were



Scheme 3. Total synthesis of chartarin. Reagents and conditions: (a) i. 5.4 vol% H_2SO_4, $NaNO_2$, 0 °C, ii. Δ (66%); (b) $(CH_2)_6N_4$, PPA, Δ (30%); (c) $Ph_3P{=}CHCOOEt$, Et_2NPh, Δ (95%); (d) LiO^{t}Bu, −60 °C → rt (86%); (e) HBr, AcOH, Δ (81%).

quite apprehensive that the reaction between **13** and the required naphthoquinone monoketal **24**, prepared from methyl 6-hydroxynaphthoate **23** might lead to the formation of hydroxymethoxyanthraquinone **27**, in accordance with our reported results.[13] It may also be noted that in an earlier investigation of ours, the naphthoquinone monoketal **24** desisted from undergoing annulation with phthalide sulfone. Gratifyingly, cyanophthalide **13** underwent smooth annulation with Michael acceptor **24** giving the desired product **25a** in an excellent yield (Scheme 4). When methoxy substituted cyanophthalide **21** was submitted to annulation



Scheme 4. Synthesis of chrymutasin and hayumicin skeletons. Reagents and conditions: (a) PIDA (2 equiv), CH_3OH, 0 °C (68%); (b) LiO^{t}Bu, −60 °C → rt (87%); (c) aq HCl, MeOH (98%); PIDA = phenyliodonium diacetate.

with naphthoquinone monoketal **24**, the corresponding product **25b** was also obtained in excellent yield. Acid assisted deketalization of **25** correspondingly provided **26** having all the important structural components of the hayumicin[18] (**3**) aglycon.

In conclusion, a novel extension of the Hauser–Kraus annulation has been utilized for the one-pot regiospecific synthesis of three different categories (i.e., **12**, **22** and **26**) of benzonaphthopyranones from readily accessible starting materials. The methodology has been successfully applied to a concise total synthesis of chartarin **22b** and the first entry to the chrymutasin scaffold **26** through hitherto unknown and structurally unique benz[*a*]anthraquinone monoketals **25**. Work is in progress towards the completion of the total synthesis of aglycons of chrymutasins and gilvocarcins. It is foreseeable that the present methodology would be able to generate a large number of useful benzonaphthopyranones.

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