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Total Synthesis of Euplectin, a Natural Product with a Chromone Fused Indenone

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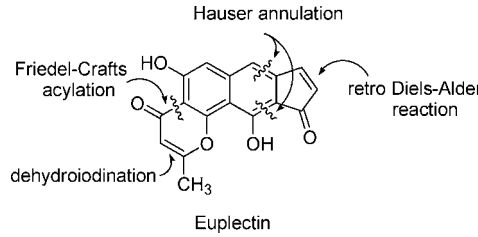
ABSTRACT



Euplectin

The first total synthesis of euplectin, a rare metabolite with a chromone annulated indenone motif, has been accomplished in 17 steps. This has been possible through interplay among three key reactions: a Hauser sulfoxide annulation, a new chromone formation and a late-stage retro-Diels−Alder reaction. The entire regiochemical integrity of the successful route is established by an iodine-catalyzed aromatization of a cyclohexane-1,3-dione and the Hauser annulation.

The natural products with annulated chromone nuclei are an emerging class of metabolites. In recent years, members like 6-methoxycomapavin **1**,[1] isonigerone **2**,[2] and pluramycin **3**[3] (Figure 1) have gained enormous attention due to their antitumor, antibacterial, and enzyme inhibitory activities. Their synthetic chemistry has duly been advanced by many research groups: namely, Dallavalle,[4] Danishefsky,[5] Hauser,[6] Hecht,[7] Kozlowski,[8] Krohn,[9] McDonald,[10] Suzuki,[11] Tietze,[12] and Uno[13] groups. More specifically, 5-hydroxychromones, annu-

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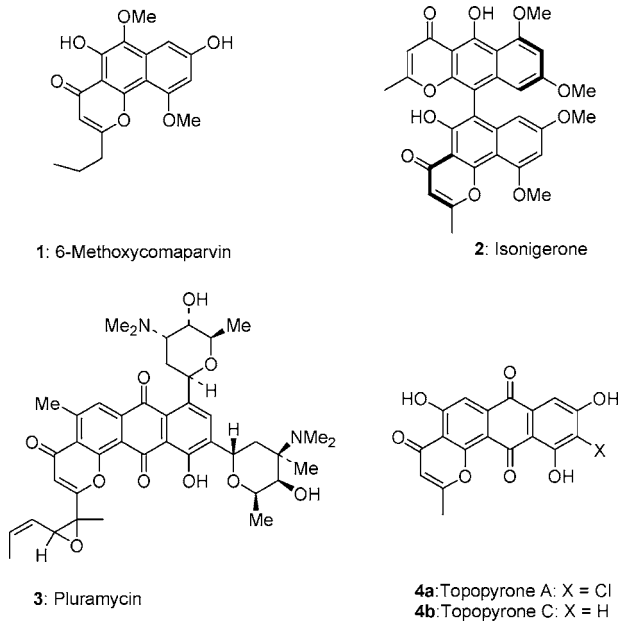


Figure 1. Representative structures of naturally occurring annulated chromones.

lated to a quinone represented by topopyrones **4** have begun to receive attention due to their promising topoisomerase inhibitory activity.[14] Euplectin (**5a**), one of the five related but rare natural products[15] (Figure 2), with an indenone

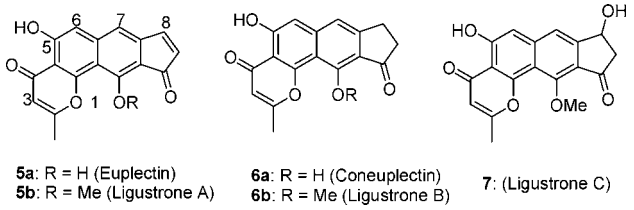


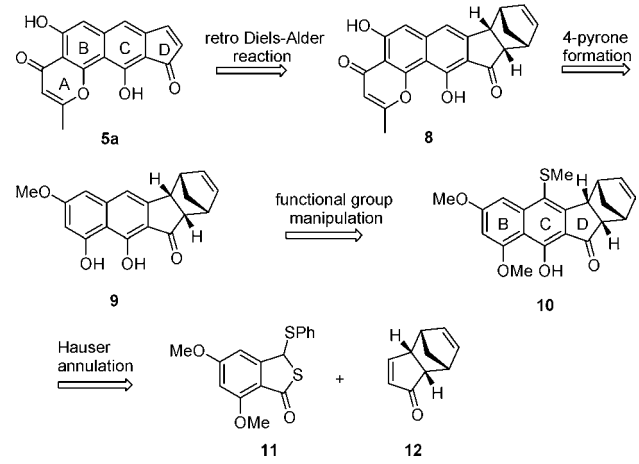
Figure 2. Structures of naturally occurring hydroxychromone[*f*]indenones.

moiety fused to a 5-hydroxychromone, was isolated in 2000 and reported to exhibit cytotoxicity against the growth of murine P-815 mastocytoma cells.[16] The bioactivity of the congener, coneuplectin (**6a**) could not be evaluated due to the paucity of the material obtained from the natural source. Our interest in these molecules stemmed from the intriguing fact that a 2,3-unsubstituted indenone like **5a** survives the harsh processes of a scheme of isolation, while the simplest indenone easily polymerizes at ordinary temperatures even in diffuse light.[17]

In part, the interest was reinforced owing to our conjecture that euplectin (**5a**) could be an artifact of 8-hydroxyconeuplectin. Herein, we disclose the first successful route leading to the total synthesis of euplectin (**5a**).

Inspection of the structure of euplectin (**5a**) revealed fusion of two prominent motifs: a hydroxychromone and a hydroxyindenone (Scheme 1). Hence, the formulation of the retrosynthesis was focused on three stages: (i) formation of indenone skeleton with free OH groups, (ii) formation of

Scheme 1. Retrosynthesis of Euplectin (**5a**)



pyrone moiety, and (iii) construction of naphthol unit. Since 2,3-unsubstituted indenones are known to dimerize in both acidic and basic conditions,[18] the creation of the indenone double bond was considered the last step. It was expected to be achieved by the retro-Diels−Alder reaction of hexacycle **8**, construction of which was planned from **9** via a chromone synthesis, which, in turn, should be obtainable from **10** through functional group interconversion. The BCD ring, i.e., benz[*f*]indan scaffold of **10** was envisaged to be assembled by annulation[19] of thiophthalide **11** with masked cyclopentadienone **12**. Among the various methods[20] known in the literature for naphthol annulation, the reaction between **11** and **12** was chosen because such a reaction allows introduction of the 9-hydroxy group of benz[*f*]indenones, concomitant with the benzannulation.[21] Moreover, the commonly conceived 1,4-dipolar synthons like *ortho* toluate

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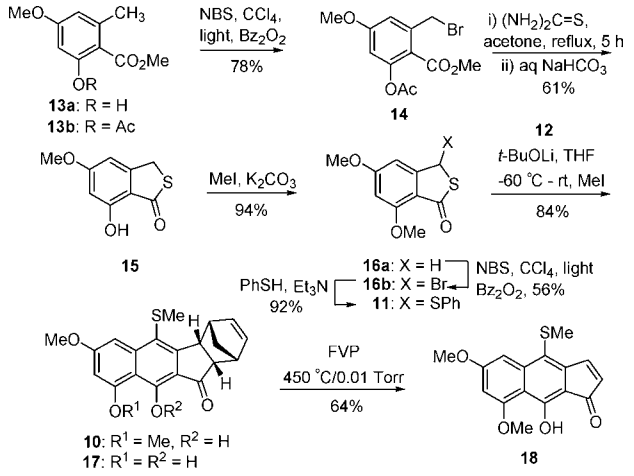
sulfoxides and homophthalic anhydrides do not undergo anionic cycloaddition with the tricyclic enone **12**.[19,22]

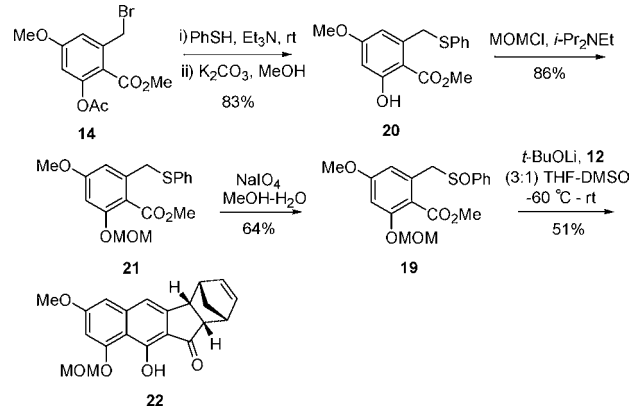
Synthesis of the required thiophthalide **11** commenced with the reported regioselective preparation[23] of **13a** from methyl acetoacetate and methyl crotonate (Scheme 2). The corresponding acetate **13b** was brominated with NBS to give bromide **14** in 78% yield. This was treated with thiourea followed by aq $NaHCO_3$ solution to afford thiophthalide **15** in 61% yield. For further elaboration, the free OH of **15** was protected as methyl ether with $CH_3I-K_2CO_3$ affording **16a**. NBS bromination of **16a** to **16b** followed by reaction with $PhSH-Et_3N$ yielded the desired thiophthalide **11** in 92% yield. This was then annulated with the tricyclic enone **12** in the presence of *t*-BuOLi in THF to furnish benzo[*b*]fluorenone **10** in good yield. To construct the pyrone ring on **10**, selective demethylation of **10** to phenol **17** was examined. Unfortunately, all attempts (BBr_3, $AlCl_3$, HBr−AcOH, TMSI, $Ph_2S_2-CaH_2$, etc.) failed to furnish the desired phenol **17**. Flash vacuum pyrolysis of **10** provided benz[*f*]indenone **18**, but it was not amenable to further elaboration due to its instability to acidic conditions.

Scheme 2. Synthesis and Annulation of Thiophthalide **11**



Next, we resorted to the Hauser sulfoxide annulation[24a] which furnishes α-naphthols. Although its compatibility with cycloalkenone acceptors or unsaturated lactones[24f] is unpredictable, we demonstrated that such a reaction is achievable with the base-stable cyclic enone acceptor **12** and a furan-derived sulfoxide donor.[22] We also showed that the annulation of **12** does not work with *ortho* toluate derived sulfoxide donors.[25] However, the recent report[26] on the remarkable effect [yield: 0% (THF)[26] and 5% (THF);[25] 31% (THF−DMSO)[26]] of DMSO on such annulations prompted us to examine the reactivity of the toluate sulfoxide **19** toward enone **12**. Benzyl bromide **14** was reacted with $PhSH-Et_3N$ followed by K_2CO_3−MeOH to furnish phenyl sulfide **20** in 83% yield. Phenyl sulfide **20** was reacted with MOMCl−*i*-Pr_2NEt to give MOM ether **21** in 86% yield. Oxidation of the SPh group in **21** with $NaIO_4$ afforded the requisite sulfoxide **19** in 64% yield. An initial cursory attempt at condensation of the sulfoxide **19** with enone **12** in THF under commonly employed conditions (*t*-BuOLi, THF, −60 to 0 °C) failed to produce the desired product **22**. When carried out in the mixed solvent, i.e., 3:1 THF−DMSO, the same reaction afforded the product **22** in 51% yield (Scheme 3).

Scheme 3. Model Studies with the Hauser Sulfoxide Annulation



Frustratingly, all standard attempts ($BF_3{\cdot}OEt_2$, PPTS, or dilute HCl) to remove MOM ether in **22** caused severe decomposition of the pentacycle **22**. This compound slowly decomposed even upon storage at rt under ambient conditions. Although further work on utilization of the MOM ether **22** was discontinued, this study established the viability of the Hauser sulfoxide annulation in fabrication of the euplectin core.

Lessons learned from the preceding schemes led us to examine the chromanone sulfoxide **23** route (Scheme 4). The sulfoxide was prepared from toluate sulfide **20** via (i) chromanone formation (**20** → **24**), (ii) oxidation of sulfide to sulfoxide (**24** → **25**), and (iii) protection of keto carbonyl group as a 1,3-dithiane (**25** → **23**).

Annulation of the sulfoxide **23** with the enone **12** under the conditions *t*-BuOLi, THF−DMSO, −60 to 0 °C, yielded the expected product **26** in 25−28% yield. Remarkable improvement in the yield (88%) of the process was met by heating the reaction mixture at reflux for 2 h before quenching. The dithiane group of **26** was smoothly removed under the standard protocol[27] ($HgCl_2$, aq CH_3CN) to give

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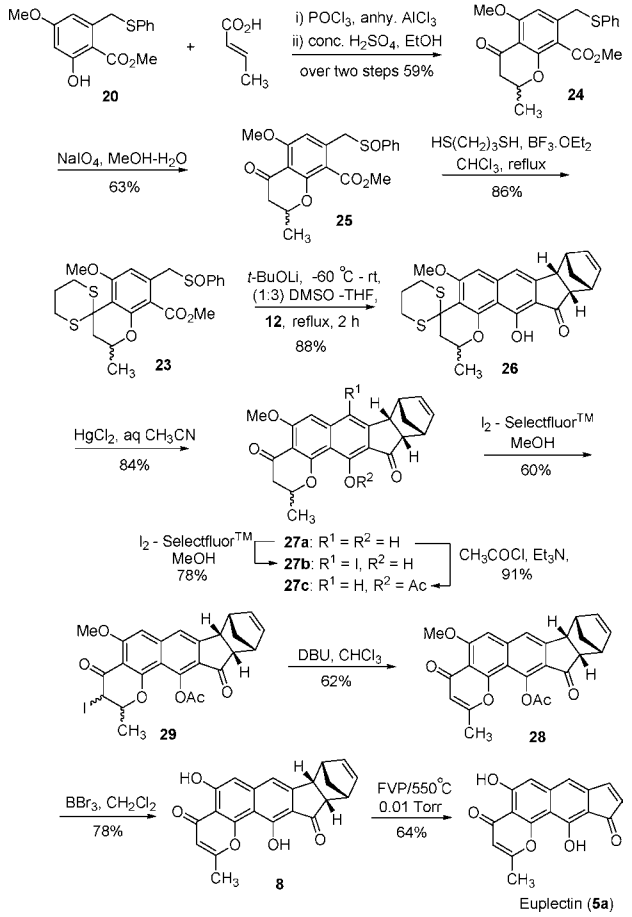
Scheme 4. Total Synthesis of Euplectin (**5a**)



annulated chromanone **27a** in 84% yield. Transformation of chromanone **27a** to chromone **28** was not a trivial problem. Attempts at dehydrogenation using DDQ were not feasible. This failure was anticipated based upon the literature background and the well-known sensitivity of naphthol moieties. Alternatively, selective iodination at the α-position to the pyrone carbonyl group followed by dehydroiodination was considered for introduction of the chromone double bond. But this strategy also posed serious problems. Attempted α-iodination of **27a** by I_2-Selectfluor[28] resulted in the nuclear iodination product **27b** rather than the desired product. At last, hexacycle **27a** was derivatized to the acetate **27c**, controlled reaction of which with I_2-Selectfluor afforded the requisite product **29** in moderate yield (60%). This was treated with DBU to give annulated chromone **28** (62%) along with a small amount of the corresponding deacetylated product. *O*-Demethylation of **28** was possible after rigorous and controlled experimentation. Treatment of **28** with BBr_3 furnished **8** in respectable yield (78%). Flash vacuum pyrolysis (FVP) of **8**, though daunting, could be effected at 550 °C and 0.01 Torr to furnish euplectin (**5a**) in 64% yield. Both ^1H and ^{13}C NMR spectral data of the synthetic **5a** were in complete agreement with the original[16] data.

In conclusion, we have accomplished the first total synthesis of euplectin (**5a**) in 17 steps from commercially available chemicals. The synthesis thus confirms the originally assigned structure of euplectin. The crucial steps include an optimized Hauser sulfoxide annulation and a new chromone formation via selective α-iodination of ketone. Further application of this strategy to the other members of euplectin-type natural products is under investigation.

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Supporting Information Available: General experimental methods, experimental procedures, and ^1H, ^{13}C, and DEPT-135 NMR spectra of the new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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