A Concise Synthesis of Pleurotin Enabled by a Nontraditional C–H Epimerization

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ABSTRACT: An 8-step synthesis of a known pentacyclic intermediate towards the natural product pleurotin (**1**) is described. Pleurotin and related benzoquinone natural products are of great interest for their powerful anticancer and antibiotic activities. The route features a regio- and diastereoselective intermolecular Diels-Alder cycloaddition and an alkoxy-radical-induced HAT-mediated C–H epimerization to construct pleurotin's carbon framework with appropriate relative stereochemical relationships. The synthesis concludes with a ring-forming benzylic C–H oxidation to deliver oxepane **19.**

In 1947, Robbins, Kavanagh, and Hervey described the isolation of large amber-colored crystals from an extract of the culture fluid of the basidiomycete fungus, *Pleurotus griseus*.[1] A solution of these crystals inhibited the growth of *Staphylococcus aureus*, and the crystalline antibiotic was named pleurotin. The intricate polycyclic structure of this new antibiotic was revealed by a systematic study of its chemical transformations by Schelling and Arigoni[2] and confirmed by an X-ray crystallographic analysis by Dobler.[3] Two additional characterizations of pleurotin by the method of X-ray crystallography also described the isolation of this metabolite from the basidiomycetes, *Hohenbuehelia geogenius*[4] and *Nematoctonun robustus*.[5] While the sequence of reactions by which pleurotin arises in nature is still unknown, Arigoni proposed that its molecular skeleton may evolve from farnesylhydroquinone **2** by several cyclization, rearrangement, and oxidation steps.[6] Pleurotin, shown as **1** in Figure 1, comprises a benzoquinone, two heterocyclic rings, a tetrasubstituted *trans*-hydrindane framework, and eight contiguous stereocenters. The intriguing possibility that a bioreduction of the pleurotin quinone could give access to a bis-bioalkylation agent in the form of transient quinone methides was suggested by Moore.[7] In addition to its inhibitory activity against Gram-positive bacteria, pleurotin (**1**) displays antitumor activity against Erlich's ascites carcinoma, L-1210 lymphoid leukemia, and a slow-growing mammary tumor in mice.[8]

In the period of 1997–2006, there was a renewed interest in the therapeutic potential of pleurotin through the discovery that this natural product is a potent irreversible inhibitor of the thioredoxin-thioreductase system (IC_{50} = 170 nM).[9] By this action, pleurotin (**1**) significantly reduces the levels of HIF-1α in cancer cells and thereby inhibits the transcription of cancer-related genes that mediate cellular adaptations to hypoxia, angiogenesis (via VEGF production), and glucose transport and metabolism.[10]

Figure 1a: benzoquinone natural products

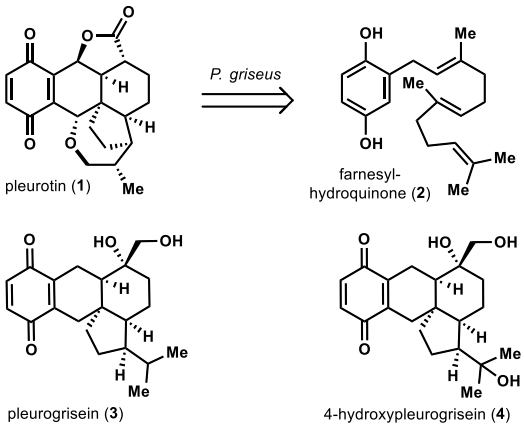
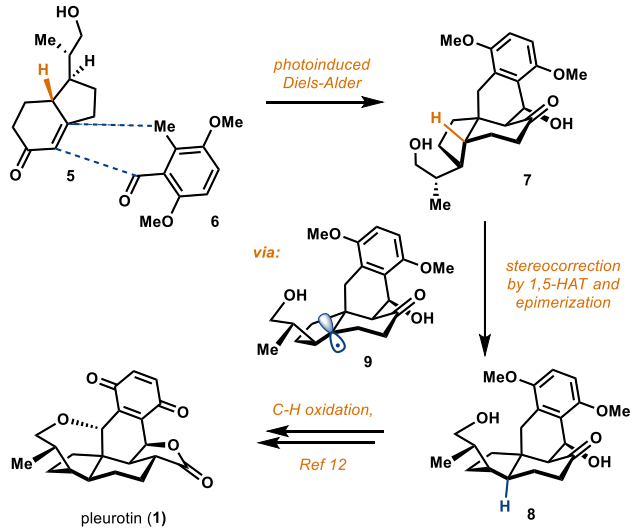
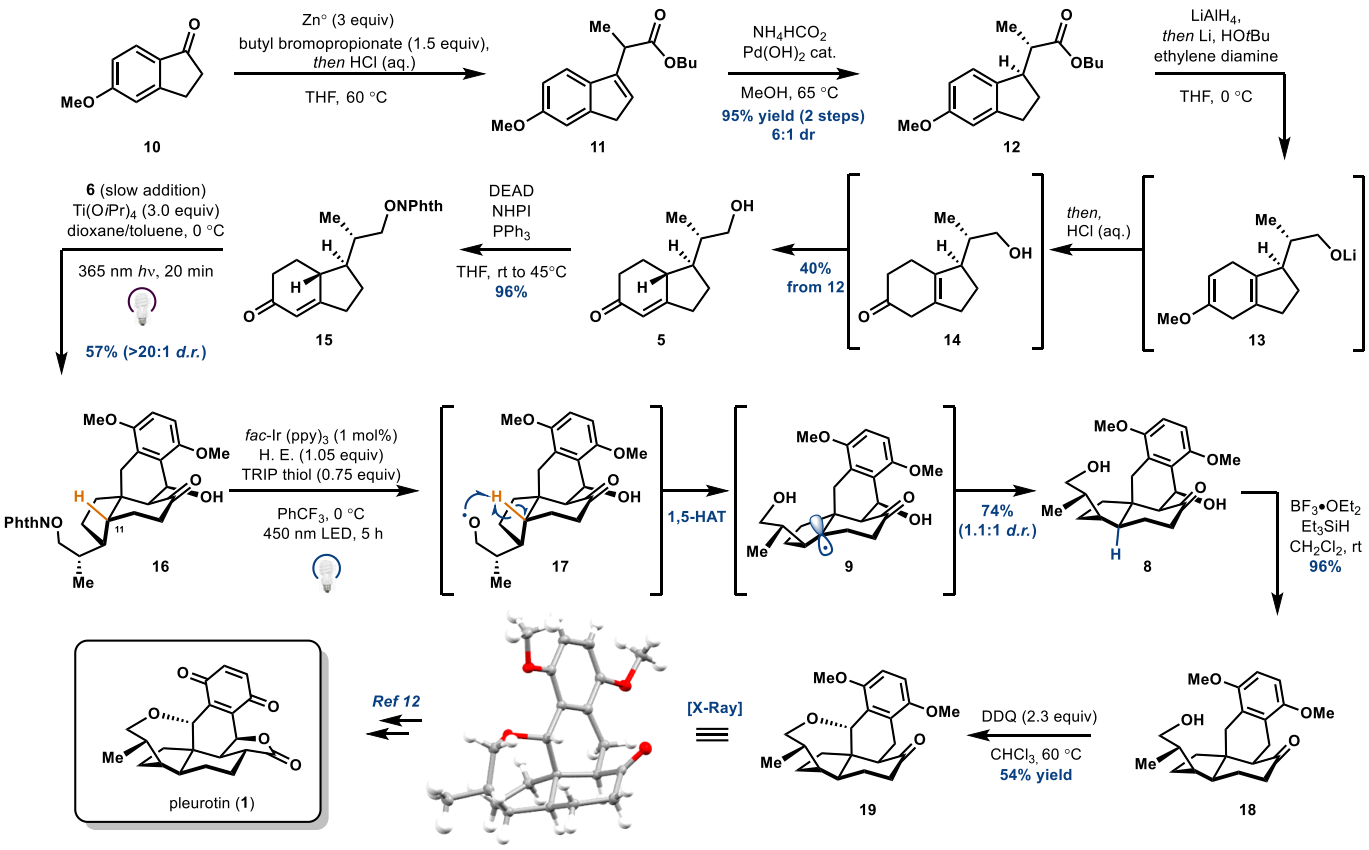


Figure 1b: synthetic strategy



While the lack of available pleurotin hampered its continued advance as an anticancer lead compound, Shipley, Newman, and coworkers developed an improved

Scheme 1. Formal Synthesis of Pleurotin



[a]DEAD = diethyl azodicarboxylate, NHPI = *N*-hydroxyphthalimide, Phth = phthalimidoyl, PPh_3 = triphenylphosphine, H.E. = Hantzsch ester, TRIP thiol = 2,4,6-triisopropylbenzenethiol, DDQ = 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone

process for producing this natural product via the fermentation of *Hohenbuehelia atrocaerulea*.[11] Pleurotin is also accessible by the concepts and methods of organic synthesis and was synthesized for the first time in 1988 by the laboratory of Hart, a milestone achievement featuring an impressive diastereoselective radical cyclization and requiring 26 steps.[12] Our laboratory was drawn to the considerable challenge of synthesizing pleurotin in few steps via a flexible design that would also permit short syntheses of an expanded family of pleurotin-like anticancer screening candidates, as well as the related natural products pleurogrisein (**3**)[6] and the potent hepatitis C virus inhibitor 4-hydroxypleurogrisein (**4**).[13] Herein, we describe an 8-step formal synthesis of pleurotin (**1**) that intersects the pioneering synthesis by Hart at the stage of compound **19**.

Our initial approach to the molecular skeleton of **1** was based on an intramolecular Diels-Alder addition of a transient *o*-quinodimethide to a tethered hydrindenone (not shown). Despite promising early studies by the Kraus laboratory[14] and extensive efforts in our group,[15] this strategy proved untenable (see Supporting Information). Instead, we turned to an intermolecular light-mediated Diels-Alder coupling of the known aryl aldehyde **6** and readily accessible enone **5** to rapidly generate the carbon framework of **1.** This powerful concept for ring annulation, discovered by Yang,[16] pioneered in synthesis by Nicolaou,[17] and improved by Gao,[18] has been shown to be exceptionally tolerant of steric crowding in the dienophilic partner and specifically to engage β,β-disubstituted cyclohexenones efficiently. However, in order to obtain the correct facial selectivity in the pivotal merger of enone **5** with an *o*-quinodimethide derived from **6**, it would be necessary to maintain the unnatural configuration at the indane ring junction (Fig. 1b, C–H highlighted in orange in **5**). If **7** could be formed in a regio- and stereocontrolled fashion, we would approach the challenging problem of converting the *cis*-fused hydrindane in **7** to the desired *trans*-fused diastereoisomer **8** on the foundation of a tried and true tactic in organic synthesis: a reactive oxygen-centered radical, to be generated from the primary alcohol in **7** (or a derivative thereof), would effect a downhill 1,5-hydrogen atom transfer (HAT) reaction to give tertiary carbon radical **9**.[19] An exogenous HAT reagent could then transfer a hydrogen atom to the underside of radical **9** in a kinetically-controlled step to complete the needed epimerization and formation of *trans*-fused isomer **8**. From *trans*-hydrindane **8**, a C–H oxidation to close the oxepane ring generating **19** would intercept Hart's synthesis of pleurotin.

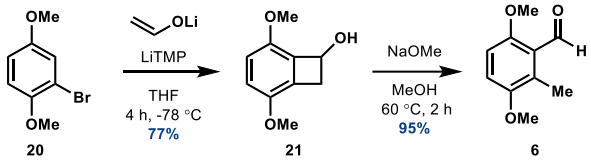
Our synthesis commenced with a scalable Reformatsky reaction between *n*-butyl bromopropionate and methoxyindanone **10** to form indenyl ester **11** (Scheme 1).[20] The butyl ester of bromopropionate was selected as it yielded superior diastereoselectivity to simpler alkane congeners in the subsequent hydrogenation. Butyl ester **11** was subjected to heterogeneous hydrogenation (with *in situ* H_2 generation from ammonium formate) in the presence of

catalytic Pearlman's catalyst, yielding alkylindane **12** in nearly quantitative yield as a 6:1 ratio of diastereomers. Indane **12** could be carried forward without chromatographic purification into a reduction-hydrolysis sequence, wherein **12** was first reduced to the alkoxide with lithium aluminum hydride, immediately followed by an ammonia-free Koide-Birch reduction.[21] The reaction was quenched and acidified with 6 M aqueous HCl, which induced hydrolysis of the intermediate enol ether in **13** and isomerization to the α,β-unsaturated cyclohexenone **5** (**13** → **14** → **5**). This one-pot procedure afforded **5** in 40% yield, representing an average yield of 80% for each of the four discrete transformations.

With an eye toward the eventual generation of a reactive alkoxy radical to drive an epimerization of an unactivated stereocenter (*vide supra*), we elected to install an *N*-alkoxyphthalimidoyl moiety via a high-yielding Mitsunobu reaction with *N*-hydroxypthalimide. Among several options,[22] this radical progenitor was selected for its ease of installation and well-established behavior under reductive conditions for the generation of alkoxy radicals.[23] Additionally, its installation at this stage served a dual purpose as a hydroxyl protecting group in the subsequent Diels-Alder reaction.

To set the stage for the key intermolecular Diels-Alder cycloaddition, known aryl aldehyde **6** was prepared in two straightforward steps (Scheme 2). Dimethoxybenzyne derived from dimethoxybromobenzene **20** was subjected to a [2+2] cycloaddition with the enolate of acetaldehyde (generated *in situ* from the decomposition of lithiated THF) by the method of Dong,[24] affording benzocyclobutanol **21**; this compound was smoothly incised under basic conditions to form **6** in high yield.[25]

Scheme 2. Synthesis of Aldehyde 6

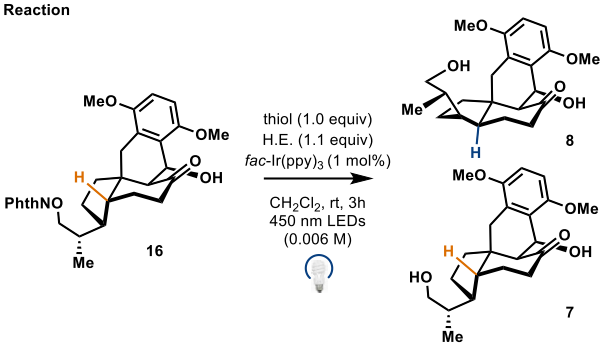


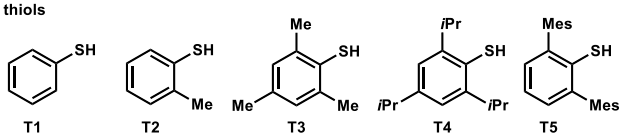
[a]LiTMP = lithium tetramethylpiperidide, THF = tetrahydrofuran

With both partners of the pivotal Diels-Alder coupling in hand, their exposure to the modified conditions of Gao and coworkers[18] resulted in the formation of tetracycle **16** as a single isolated regio- and *endo*-diastereomer in 57% yield. By adding aldehyde **6** dropwise to enone **15** at 0 °C under 365 nm irradiation, the relative concentration of *in situ* generated photoenol was kept low, minimizing undesired reactivity (particularly the dimerization of **6**). Cooling was required to curtail the facile dehydration of **16** to its corresponding chalcone. Presumably the superb diastereoselectivity of this transformation arises from a lower transition state energy leading to a *cis*-indane rather than the isomeric *trans*-indane.

Compound **16**, with its reducible *N*-alkoxyphthalimide group ($E^{o}_{1/2}{}^{red}$ ~ -1.35 V vs. SCE in MeCN),[23b] would be useful to us only if it were capable of undergoing the needed epimerization at C-11 (pleurotin numbering). Our hopes were buoyed by creative methodological examples of radical epimerizations in the recent literature,[26] but we were wary of several concerns inherent in this transformation: (1) a premature HAT to the ephemeral alkoxy radical would simply generate compound **7** (Fig. 1b); (2) a competing and unavoidable 1,5-HAT involving the equidistant methylene group in the 5-membered ring, also leading to **7**; and/or (3) a redox fragmentation leading to an aldehyde[27] or β-scission leading to a secondary alkyl radical could all undermine the desired pathway and reduce its efficiency.

Table 1. Effect of Thiol HAT Additives on the Photoredox Epimerization Reaction





entry	thiol	conversion	yield **8**[a]	yield **7**[a]	*d. r.* [a]
1	**T1**	96%	18%	36%	1 : 2.0
2	**T2**	95%	22%	31%	1 : 1.4
3	**T3**	96%	29%	33%	1 : 1.1
4	**T4**	95%	31%	31%	1 : 1.0
5	**T5**	99%	2%	24%	1 : 12

increasing steric bulk

[a] Reactions performed on a 0.026 mmol scale and yields determined by ^{1}H NMR using CH_2Br_2 as internal standard.

During initial optimization studies (See SI), we observed that irradiation of **16** with 450 nm light in the presence of stoichiometric Hantzsch ester (H.E.), a catalytic amount of the reducing iridium photocatalyst *fac*-Ir(ppy)$_3$ ($E^{o}_{1/2}{}^{III/II}$= -2.19 V vs. SCE in MeCN)[28] and thiol additive, the desired reduction occurs, generating a mixture of diasteromeric tetracycles (Table 1). The diastereomeric ratio of these products is strongly influenced by the steric crowdedness of the thiol. Unhindered thiols **T1** and **T2** preferentially generated undesired isomer **7**, while bulkier thiols produced both **7** and **8** in equal amounts. 2,6-Dimesitylbenzenethiol **T5** was found to be excessively crowded and overwhelmingly led to undesired byproduct formation. Thiols **T3** and **T4** were found to have the optimal substitution in proximity to the sulfur atom, yielding the best product ratios. Both electron-rich and electron-poor sterically unencumbered thiols were found to give poor diastereomeric ratios and low yields (See SI).

After extensive optimization, we were able to achieve modest stereocontrol (74%, 1.1:1 *d.r*) using 75 mol% TRIP thiol (**T4**) as HAT reagent in trifluorotoluene as solvent. Lower concentrations of thiol led to a variety of undesired products. Since it was possible to chromatographically resolve the 1.1:1 mixture of **8** and **7** and difficult to imagine an alternative chemical process that could invert the configuration at C-11 in compound **7**, we moved forward and were delighted that we could access the pleurotin-like *trans*-locked hydrindane from a compound that required only 5-steps to prepare. We envision that the reductive epimerization of **16** to **8** passes through the intermediacy of radicals **17** and **9** and features sequential intramolecular and intermolecular HAT reactions.

With the entire core architecture in place, a high-yielding ionic deoxygenation ($BF_3{\cdot}OEt_2/Et_3SiH$) selectively excised the reactive benzylic hydroxyl group in **8** and afforded tetracyclic alcohol **18** in 96% yield. Finally, on exposure to DDQ in hot chloroform, alcohol **18** underwent oxidative cyclization to give the desired oxepane heterocycle. This etherification step completes the synthesis of pentacycle **19**, and it was possible to confirm the constitution and relative stereochemistry of this compound by an X-ray crystallographic analysis.

Hart and coworkers previously synthesized pentacycle **19** in 21 steps and completed the first synthesis of pleurotin in five additional steps. A 13-step synthesis of pleurotin thus arises from the combination of the reactions described herein and Hart's efficient end-game sequence. Our efforts to leverage this concise sequence of reactions in syntheses of novel structural relatives of pleurotin, including compounds that would be inaccessible by structural modifications of naturally occurring pleurotin have started and will be reported in due course.

ASSOCIATED CONTENT

The Supporting Information is available free of charge via the Internet at http://pubs.acs.org.

Experimental procedures and analytical data (^1H, ^{13}C, NMR, IR, MS) for all new compounds (PDF)

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Both authors have given approval to the final version of the manuscript.

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