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Total Synthesis of (−)-Nemorosone and (+)-Secohyperforin

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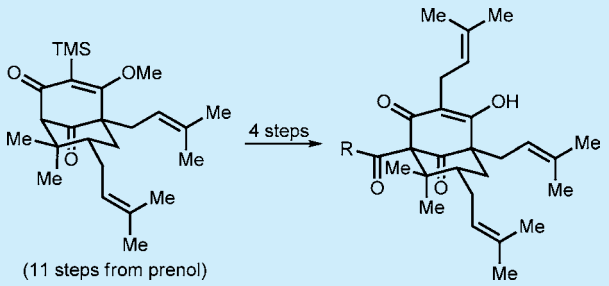
Supporting Information

ABSTRACT: A general strategy for the synthesis of polycyclic polyprenylated acylphloroglucinols is described in which a scalable, Lewis acid catalyzed epoxide-opening cascade cyclization is used to furnish common intermediate **4**. The utility of this approach is exemplified by the total syntheses of both *ent*-nemorosone and (+)-secohyperforin, which were each accomplished in four steps from this intermediate.



The polycyclic polyprenylated acylphloroglucinols (PPAPs) are a burgeoning class of phytochemical natural products, of which there are currently over 260 members.[1] PPAPs are isolated from medicinal plants used in many traditional and ethnopharmaceutical therapies and display antibacterial, antioxidant, anti-inflammatory, and antiproliferative effects as well as activity against neurological disorders. From a structural point of view, PPAPs contain a densely substituted, highly oxygenated bicyclo[3.3.1]nonane core. Owing to their wide ranging biological activity as well as their structural complexity, PPAPs have garnered significant attention from the chemical community leading to several total syntheses.[2]

Recently, we reported the enantioselective total synthesis of the PPAP hyperforin (**1**, Figure 1).[3] Hyperforin is considered

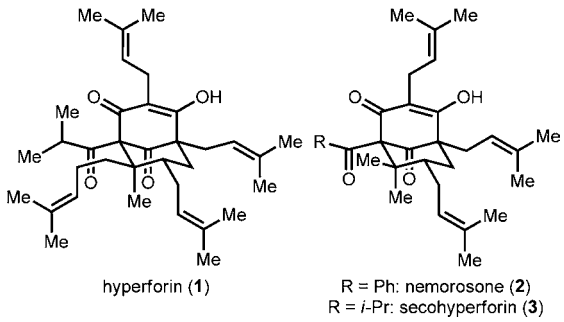


Figure 1. Structures of hyperforin, nemorosone, and seco-hyperforin.

to be the active component of St. John's wort (SJW), a medicinal herb widely used in the treatment of depression. While hyperforin-enriched SJW extracts have proven efficacy and tolerability in numerous clinical studies,[4] hyperforin potently activates pregnane X receptor (PXR), upregulating xenobiotic metabolism and subsequently causing significant drug−drug interactions, which has limited its utility as a depression therapeutic option.[5]

In order to obviate this unwanted side effect while maintaining potency, we have begun a program to probe the SAR of hyperforin. We deliberately incorporated elements of modularity into our hyperforin synthesis strategy to facilitate access to diverse hyperforin analogues. As part of this program, we targeted the total synthesis of several other naturally occurring PPAPs. While hyperforin has been extensively studied, no other PPAP has been probed for antidepressant activity.[6] Herein, we describe the first total synthesis of secohyperforin as well as the first enantioselective synthesis of nemorosone.[7]

Nemorosone (**2**) has been isolated from five species of *Clusia* throughout Brazil, Venezuela, and Cuba as well as from the propola of Cuban honeybees.[8] Several studies have demonstrated that nemorosone is cytotoxic toward a variety of cancer cell lines.[9] This activity may be in part due to epigenetic effects; nemorosone interacts with p300 histone acetyltransferase and alters cancer cell gene expression.[10] This PPAP also displayed mild antileishmanial, antitrypanosomal, and antiviral effects as well as dose-dependent activity against the molting of *Rhodnius prolixus*, an insect vector of Chagas disease.[11] Interestingly, nemorosone demonstrated activity against *Paenibacillus larvae* and *Paenibacillus alvei*, two honeybee pathogens.[8c] Antioxidant activity was observed in a DPPH assay.[8h]

Unlike nemorosone, very little is known about secohyperforin (**3**). This PPAP was isolated in small quantities from *Hypericum performatum* in Yerevan, Armenia and was characterized using flow techniques (i.e., LC−MS and LC−NMR).[12]

Our retrosynthesis strategy for nemorosone and secohyperforin is found in Scheme 1a. We postulated that both natural products could be accessed from a common intermediate, **4**. This intermediate would be the expected product generated from sequential allylic oxidation and Keck allylation of **5**, which

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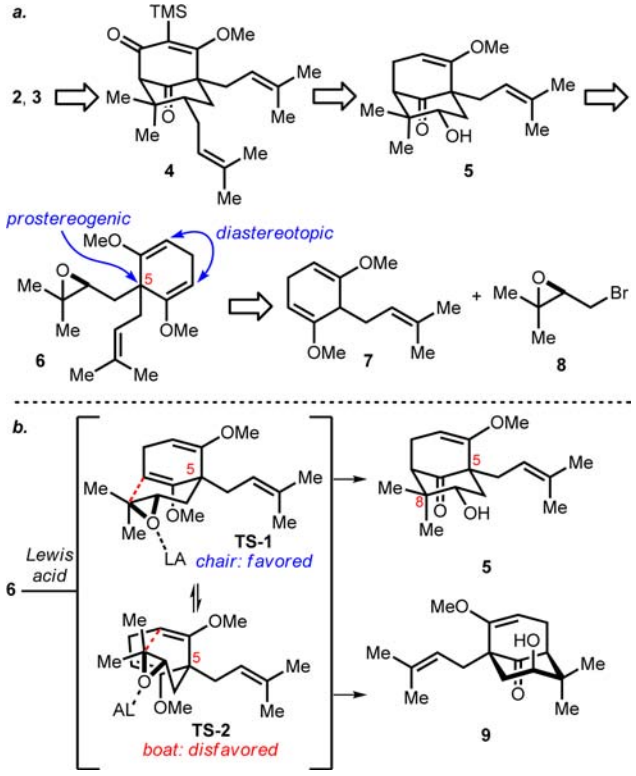
Scheme 1. (a) Retrosynthesis of Nemorosone (2) and Secohyperforin (3) and (b) Transition-State Analysis of the Key Cyclization

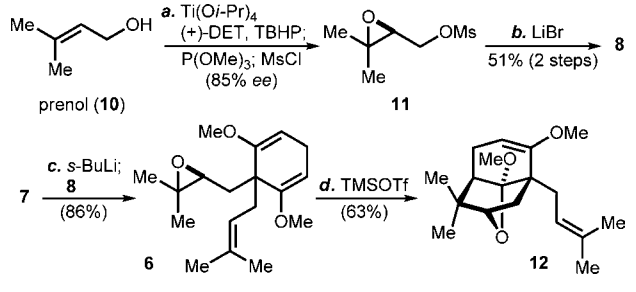


would be generated via a diastereoselective, Lewis acid-mediated epoxide-opening cyclization of **6**. Finally, this cyclohexadiene would be made from the regioselective alkylation of **7** with (bromomethyl)oxirane **8**.

In the key transformation, the two diastereotopic enol ethers flanking the prostereogenic C5 quaternary center of **6** would be differentiated through a preferred chairlike transition state **TS-1** over its diastereomeric transition state **TS-2**, which must adopt a boatlike conformation bearing two unfavorable eclipsing interactions (Scheme 1b). Therefore, **5** was predicted to be favored over **9**, and in a single operation, the shared bicyclic core of both **2** and **3** would be generated bearing three key stereocenters. A similar cyclization was implemented during our total synthesis of hyperforin.[3]

We began our studies by focusing on the synthesis of (*R*)-(bromomethyl)oxirane **8** from prenol (**10**, Scheme 2). The enantioselective Sharpless epoxidation of **10** was problematic owing to the significant water solubility of epoxyprenol. A

Scheme 2. Synthesis of (*R*)-(Bromomethyl)oxirane 8 and Formation of Ketal 12 from 6

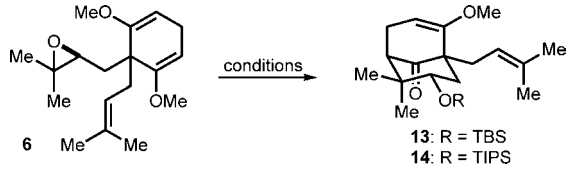


nonaqueous workup protocol developed by Sharpless[13] involving $P(OMe)_3$-facilitated in situ derivitization to the corresponding water-insoluble mesylate **11** in 85% ee.[14] Bromination of this unstable intermediate provided **8** in 51% yield over two steps.

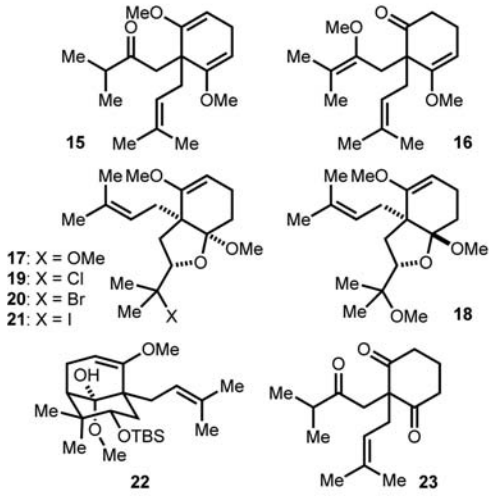
Coupling of epoxy bromide **8** with cyclohexadiene **7** afforded cyclization precursor **6**. While cyclization using TMSOTf accessed **12**, we wished to preclude the formation of a cyclic ketal. An analogous cyclic ketal utilized in our total synthesis of hyperforin required the use of Me_2BBr for cleavage; this pyrophoric reagent was difficult to implement on larger scale reactions and provided inconsistent yields.

The results of screening a panel of Lewis and Brønsted acids with **6** for the selective conversion to the bicyclo[3.3.1]nonane products **13** and **14** are shown in Table 1. A variety of products were obtained throughout these studies. Aside from ketal **12**, exposure of TMSOTf also produced a mixture of **15** and **16** (entry 1). The reaction of **6** with PPTS in MeOH selectively afforded tertiary methyl ether **17** (entry 2), the product of epoxide-opening methanolysis followed by ketalization of the

Table 1. Reactions of Various Acids with 6



entry	conditions	result
1	TMSOTf, 2,6-lutidine, CH_2Cl_2, –78 °C	**12** (63%), [**15**,**16**] (11%)
2	PPTS, MeOH, 0 °C to rt	**17** (62%)
3	HCl, MeOH, –78 °C to rt	1:1 mixture of **17**:**18**
4	Et_2AlCl, CH_2Cl_2, –78 °C	selectively afforded **19**
5	Me_2BBr, NEt_3, CH_2Cl_2, –78 °C	**20** (33%)
6	Et_2AlI, CH_2Cl_2, –78 °C	**21** (39%)
7	TESOTf, 2,6-lutidine, CH_2Cl_2, –78 °C	2:1 mixture of **12**:[**15**,**16**]
8	TBSOTf, 2,6-lutidine, CH_2Cl_2, –78 °C	**22** (46%)
9	TBSOTf, pyr, CH_2Cl_2, –78 °C to rt	**13** (48%), **23** (14%)
10	TIPSOTf, 2,6-lutidine, CH_2Cl_2, –78 °C to rt	**14** (95%)



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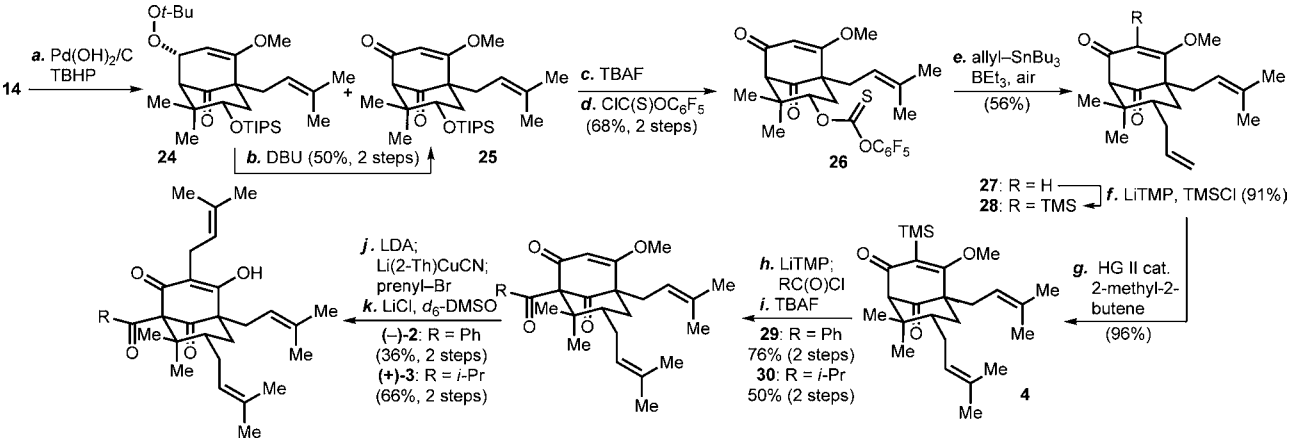
Scheme 3. Synthesis of Common Intermediate 4 from 14 and Conversion to (−)-Nemorosone (2) and (+)-Secohyperforin (3)



resulting secondary carbinol with one of the methyl enol ethers. Exposure to HCl in MeOH afforded a mixture of **17** and ketal epimer **18** (entry 3). We observed chloride **19** selectively when Et_2AlCl was employed (entry 4). The reaction of **6** to Me_2BBr or Et_2AlI afforded bromide **20** and iodide **21**, respectively (entries 5 and 6).

We also investigated the use of other trialkylsilyl triflates. TESOTf produced a mixture of **12**, **15**, and **16** (entry 7), very similar to TMSOTf. In contrast, hemiketal **22** was isolated upon exposure of **6** to TBSOTf (entry 8). If pyridine was used instead of 2,6-lutidine, no reaction was observed at −78 °C, but upon warming to rt, we isolated both ketone **13** and triketone **23** (entry 9). While this was an extremely promising result that would allow us to circumvent Me_2BBr-mediated ketal hydrolysis, the yield was mediocre. Gratifyingly, warming a solution of **6**, TIPSOTf, and 2,6-lutidine from −78 °C to rt afforded a very high yield of **14** as a single product. This reaction was both reproducible and scalable. We hypothesized that the increased steric demand of larger trialkylsilyl groups prevented cyclic ketal formation.

Allylic oxidation of **14** was a very challenging transformation given the steric environment around the desired site of reactivity and the presence of other, more accessible allylic sites (Scheme 3). Exposure of **14** to Pearlman's catalyst and TBHP[15] afforded a mixture of unstable allylic peroxide **24** and the desired β-methoxyenone **25**. DBU facilitated the isohypsic fragmentation of peroxide **24** to **25**. Stepwise desilylation and thionocarbonylation of **25** produced radical cyclization precursor **26**, and Keck allylation afforded **27**. After vinyl silylation to give **28**, olefin cross-metathesis with 2-methyl-2-butene mediated by Hoveyda−Grubbs second-generation catalyst[16] yielded **4**.

Both nemorosone and secohyperforin were synthesized in four steps from **4**. First, bridgehead acylation with benzoyl and isobutyryl chlorides followed by desilylation afforded **29** and **30**, respectively. Unsurprisingly, the bridgehead acylation reaction with benzoyl chloride was much cleaner and higher yielding than with isobutyryl chloride, since the former does not contain an acidic proton that would facilitate unintended proton exchange, as found in the latter. Vinyl prenylation[17] via lithiation, transmetalation, and alkylation afforded the *O*-methyl ethers of each natural product, and demethylation under Krapcho conditions afforded both natural products nemorosone (**2**) and secohyperforin (**3**).

Nemorosone synthesized herein was found to be opposite in optical rotation sign compared to naturally isolated material.[18] This was further confirmed through optical rotation analysis of nemorosone *O*-methyl ether.[19] No optical rotation data has been published for secohyperforin.

In summary, we have rapidly implemented our hyperforin synthesis strategy toward two other PPAP natural products, secohyperforin and nemorosone. Continued efforts in our laboratory will allow us to access many other hyperforin mimetics using this chemistry, and we will begin testing these analogues for antidepressant activity as well as other bioactivity.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, spectroscopic data, and ^1H and ^{13}C NMR spectra. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01121.

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Notes

The authors declare no competing financial interest.

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