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Citation	Sparling, Brian A., David C. Moebius, and Matthew D. Shair. 2013. Enantioselective Total Synthesis of Hyperforin. Journal of the American Chemical Society 135, no. 2: 644–647.
Published Version	doi:10.1021/ja312150d
Accessed	February 19, 2015 5:11:54 PM EST
Citable Link	http://nrs.harvard.edu/urn-3:HUL.InstRepos:12563735
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JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

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Communication

Enantioselective Total Synthesis of Hyperforin

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J. Am. Chem. Soc., **Just Accepted Manuscript** • DOI: 10.1021/ja312150d • Publication Date (Web): 28 Dec 2012

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Enantioselective Total Synthesis of Hyperforin

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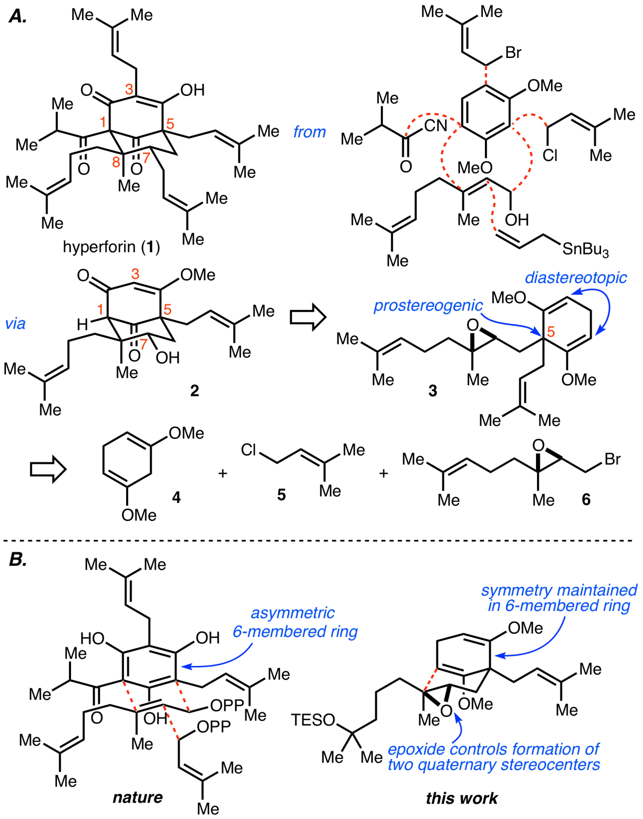
Supporting Information Placeholder

ABSTRACT: A modular, 18-step total synthesis of hyperforin is described. The natural product was quickly accessed using latent symmetry elements, whereby a group-selective, Lewis acid-catalyzed epoxide-opening cascade cyclization was used to furnish the bicyclo[3.3.1]nonane core and set two key quaternary stereocenters.

Hyperforin (**1**)[1,2] was first isolated in 1971 from St. John's Wort (*Hypericum perforatum* L.) and is now considered to be the constituent of the medicinal herb responsible for its antidepressant activity.[3,4] Hyperforin blocks the reuptake of a variety of neurotransmitters through a unique mechanism of action, possibly by selectively activating TRPC6 (classical transient receptor potential protein).[5] TRPC6 activation leads to a cellular influx of Na^+ and Ca^{2+}, diminishing membrane electrochemical gradient (thus indirectly inhibiting neuronal neurotransmitter reuptake) and triggering cell differentiation. As a selective activator of TRPC6, hyperforin is a powerful probe of TRPC6 biology, a critical lead for the treatment of depression and possibly other human diseases. However, the therapeutic potential of hyperforin is severely handicapped by its poor water solubility, facile oxidative degradation upon exposure to light and air,[6] and potent activation of pregnane X receptor,[7] leading to increased expression of many genes involved in xenobiotic metabolism. Access to a wide variety of hyperforin analogs is critical for mitigating these shortcomings while maintaining TRPC6 activation. While limited semisynthetic manipulation of isolated hyperforin is feasible,[8] total synthesis is the only possible means of obtaining diverse hyperforin analogs.

Structurally, hyperforin is one of over 200 polycyclic polyprenylated acylphloroglucinol (PPAP) natural products.[9] Many PPAPs are characterized by a highly oxidized bicyclo[3.3.1]nonane core densely substituted with terpenoid side chains. Widespread interest in their bioactivity and structural complexity has culminated in the total syntheses of several PPAPs.[10] While these PPAPs contain a geminal dimethyl group at the C8 position (hyperforin numbering), differential substitution at the hyperforin C8 position renders these otherwise effective strategies inapplicable toward hyperforin total synthesis. Numerous approaches toward hyperforin[11] have only resulted in one total synthesis of *ent*-hyperforin, accomplished by the Shibasaki group in 2010.[12] Given the considerable length of this route (51 steps from propargyl bromide), we set out to devise a new enantioselective approach that would not only incorporate elements of modularity but also exploit latent symmetry. A practical total synthesis would enable the first full SAR study of hyperforin.

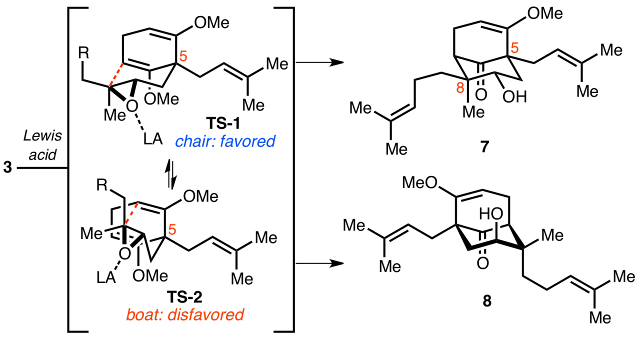
Scheme 1. (A) Synthesis Strategy for Hyperforin (1), (B) Comparison of This Work to Hyperforin Biosynthesis.


A.
hyperforin (1)
from
via
2
3
4
5
6
diastereotopic
prostereogenic
B.
asymmetric 6-membered ring
symmetry maintained in 6-membered ring
epoxide controls formation of two quaternary stereocenters
nature
this work

Our strategy for the construction of hyperforin is shown in Scheme 1. The synthesis can be deconstructed into the stepwise fusion of six easily obtainable chemicals (Scheme 1a). We postulated that **1** would be accessible from alcohol **2** through bridgehead acylation at C1 and prenylations at C3 and C7. We would access key intermediate **2** from cyclohexadiene **3** via a group-selective, Lewis acid-mediated epoxide-opening cyclization. Cyclohexadiene **3** would be synthesized in two steps through the regioselective coupling of 1,5-dimethoxy-1,4-cyclohexadiene **4** with prenyl chloride **5** and known epoxygeranyl bromide **6**.[13]

In developing our hyperforin synthesis, we drew inspiration from its proposed biosynthesis[14] (Scheme 1b). In nature, hyperforin is formed from alkylation of a nucleophilic, polyketide-derived acylphoroglucinol with geranyl pyrophosphate. Stereochemical fidelity over the course of this coupling in the biosynthesis is governed by enzyme catalysis.

Scheme 2. Transition-State Analysis of the Cyclization of 3.



OMe
R
5
Me
Me
OMe
Me
O
LA
TS-1
chair: favored
Lewis acid
3
R
OMe
Me
5
O
LA
OMe
Me
Me
TS-2
boat: disfavored
OMe
5
Me
Me
8
O
OH
Me
Me
Me
7
MeO
HO
Me
Me
Me
O
Me
Me
8

We envisioned utilizing a similar bond disconnection in the key cyclization of our synthesis, specifically one involving a geraniol-derived fragment. While unable to exploit enzyme-driven stereoselection, we postulated that an epoxide functionality strategically placed in the geraniol fragment would be an effective means of relaying stereochemical information to the C1, C5, and C8 carbon centers, when employed in concert with a truncated, symmetric cyclohexadiene ring.

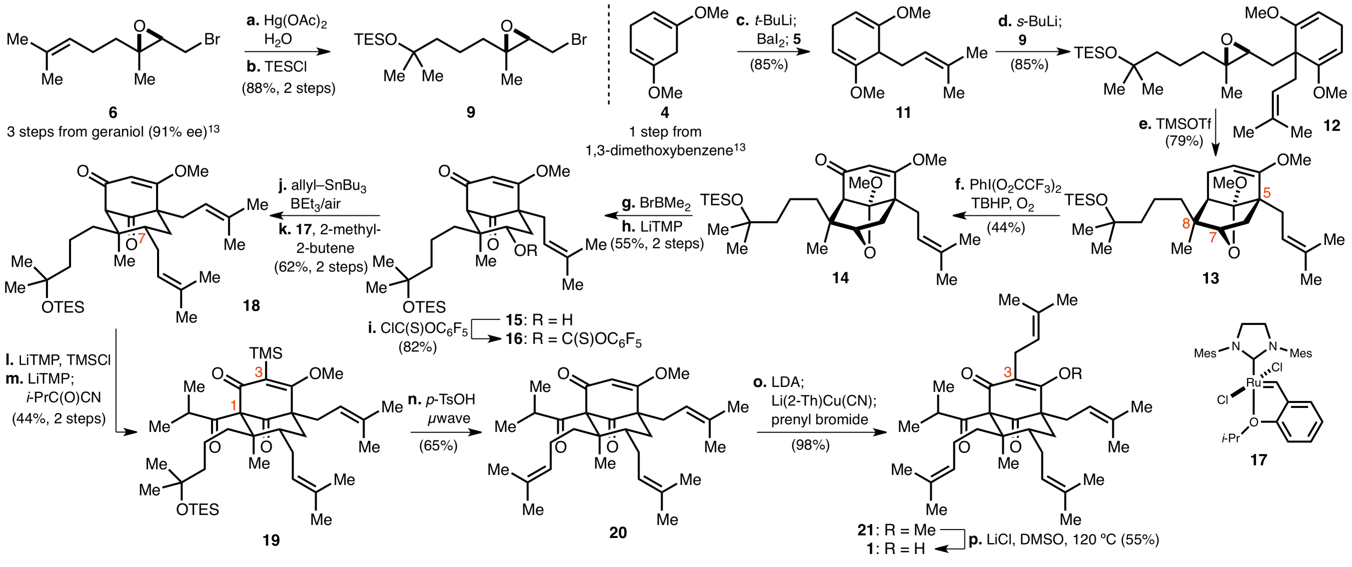
An analysis of the cyclization of **3** is depicted in Scheme 2. Owing to the symmetry of compound **3**, the quaternary carbon at C5 is prostereogenic, and the two methyl enol ethers are diastereotopic. Exposure of **3** to Lewis acid activates the epoxide for nucleophilic attack. While either methyl enol ether may engage this activated epoxide, transition state **TS-1** is favored to yield **7** over its diastereomeric transition state **TS-2**, which must adopt a boat-like conformation containing two severe eclipsing interactions in forming **8**. Additionally, a 6-(*enolendo*)-tet cyclization should be favored over a 5-(*enolendo*)-tet cyclization due to geometric constraints of the substrate.[15] The contributions of these factors culminate in: (1) the formation of the hyperforin bicyclo[3.3.1]nonane skeleton; (2) the introduction of stereochemistry at the C5 quaternary position; and (3) the creation of a stereogenic quaternary center at C8.

Our synthesis of hyperforin is depicted in Scheme 3. Oxymercuration followed by reductive workup of epoxygeranyl bromide **6** and subsequent TESCl-mediated silylation gave **9**. Over the course of the synthesis, it became apparent that formal silanolysis of the olefin present in **6** was indispensible. Deprotonation of cyclohexadiene **4** with *t*-BuLi, treatment with freshly prepared BaI_2,[16] and alkylation with prenyl chloride **7** yielded diene **11**. In the absence of BaI_2, non-regioselective prenylation across the pentadienyl anion took place. Coupling of **9** with the anion generated from diene **11** and *s*-BuLi gave cyclization precursor **12**.

Gratifyingly, exposure of **12** to TMSOTf and 2,6-lutidine gave the ketal **13** in 79% yield as the only isolated product. As previously mentioned, the stereochemistry of two key quaternary centers were established as a result of this transformation: at the previously prostereogenic C5 carbon, and at the C8 position. Aside from the construction of the bicyclo[3.3.1]nonane framework, the formation of a cyclic methyl ketal was an unexpected yet fortuitous outcome to this reaction, safeguarding the C7 carbinol during the subsequent allylic oxidation step. The efficiency of this approach was demonstrated by our ability to easily prepare 60 grams of **13**.

After extensive optimization, allylic oxidation of **13** was accomplished using TBHP, $PhI(O_2CCF_3)_2$, and O_2[17] to afford vinylogous ester **14**.[18] This was an exceptionally challenging transformation given the four allylic sites present in **13** and the steric environment surrounding the desired

Scheme 3. Total Synthesis of Hyperforin (1).[a]



Me
O
Br
Me
Me
6
3 steps from geraniol (91% ee)13
a. Hg(OAc)2
H2O
b. TESCl
(88%, 2 steps)
TESO
Me Me
O
Br
Me
9
OMe
OMe
4
1 step from 1,3-dimethoxybenzene13
c. t-BuLi;
BaI2; 5
(85%)
OMe
Me
OMe
Me
11
d. s-BuLi;
9
(85%)
TESO
Me Me
O
Me
MeO
OMe
Me
Me
12
e. TMSOTf
(79%)
OMe
MeO
5
TESO
Me
Me
8
7
Me
O
Me
Me
13
f. PhI(O2CCF3)2
TBHP, O2
(44%)
O
OMe
MeO
TESO
Me
Me
Me
O
Me
Me
14
g. BrBMe2
h. LiTMP (55%, 2 steps)
O
OMe
O
Me
OR
Me
Me
Me
Me
OTES
i. ClC(S)OC6F5 (82%)
15: R = H
16: R = C(S)OC6F5
j. allyl–SnBu3
BEt3/air
k. 17, 2-methyl-2-butene
(62%, 2 steps)
O
OMe
O
7
Me
Me
Me
Me
Me
Me
Me
OTES
18
l. LiTMP, TMSCl
m. LiTMP;
i-PrC(O)CN
(44%, 2 steps)
TMS
3
O
OMe
1
Me
Me
O
O
Me
Me
Me
Me
Me
Me
Me
OTES
19
n. p-TsOH
μwave
(65%)
O
OMe
Me
Me
O
O
Me
Me
Me
Me
Me
Me
Me
20
o. LDA;
Li(2-Th)Cu(CN);
prenyl bromide
(98%)
Me
Me
3
O
OR
Me
Me
O
O
Me
Me
Me
Me
Me
Me
Me
21: R = Me
1: R = H
p. LiCl, DMSO, 120 °C (55%)
Mes
N
N
Mes
Cl
Ru
Cl
O
i-Pr
17

[a] Conditions: (a) $Hg(OAc)_2$, Me_2CO/H_2O; NaOH, 0 °C; $NaBH_4$, 0 °C, 91% (b) TESCl, imid, DMF, 97%; (c) *t*-BuLi, THF, –78 °C; BaI_2, –78 °C; **5**, –78 to –5 °C, 85%; (d) **11**, *s*-BuLi, THF, –78 to –30 °C; **9**, –78 to –40 °C, 85%; (e) TMSOTf, 2,6-lut, CH_2Cl_2, –78 °C, 79%; (f) $PhI(O_2CCF_3)_2$, TBHP, Cs_2CO_3, 4Å MS, EtOAc, O_2, –78 to 0 °C, 44%; (g) $BrBMe_2$, NEt_3, CH_2Cl_2, –95 °C; NEt_3; sat. aq. $NaHCO_3$, 57%; (h) LiTMP, THF, –78 to 0 °C, 97%; (i) $ClC(S)OC_6F_5$, *N*-hydroxysuccinimide, pyr, PhMe, 80 °C, 82%; (j) allyl–$SnBu_3$, BEt_3, PhH, air, 72%; (k) **17**, 2-methyl-2-butene, CH_2Cl_2, 40 °C, 86%; (l) LiTMP, TMSCl, THF, –78 to 0 °C, 90%; (m) LiTMP, THF, –78 to 0 °C; *i*-PrC(O)CN, –78 to –30 °C, 49%; (n) *p*-TsOH·H_2O, PhMe, HOAc, 2-methyl-2-butene, μwave, 100 °C, 65%; (o) LDA, THF, –78 °C; Li(2-Th)CuCN, –78 to –40 °C; prenyl bromide, –78 to –30 °C, 98%; (p) LiCl, DMSO, 120 °C, 55%.

oxidation site. Hydrolysis of the ketal present in **14** to yield alcohol **15** was performed in two steps: treatment of **14** with $BrBMe_2$[19] followed by LiTMP-mediated methanol extrusion from the intermediate hemiketal. It was crucial to maintain the temperature of the $BrBMe_2$-mediated hydrolysis below −90 °C; above this temperature, elimination of the triethylsilyl ether was observed.

After surveying a variety of methods to install the C7 prenyl group from **15**, we pursued a radical Keck allylation approach.[20] A radical precursor, thionocarbonate **16**, was generated from the reaction of alcohol **15** with $ClC(S)OC_6F_5$.[21] Using BEt_3/air as an initiator, radical allylation of **16** with allyl–$SnBu_3$ afforded a product containing a C7 allyl group as a single diastereomer. Employing more reactive radical precursor functionality or either photochemical or thermal radical generation conditions gave inferior results for this coupling reaction. An ensuing cross-metathesis with 2-methyl-2-butene catalyzed by Hoveyda–Grubbs 2nd generation catalyst **17**[22] afforded **18** containing the requisite C7 prenyl moiety.

After silylation at the C3 position, sequential bridgehead deprotonation-acylation using LiTMP and *i*-PrC(O)CN[10n] yielded ketone **19**. This direct, one-step bridgehead acylation is noteworthy given that previously reported instances of PPAP bridgehead acylation at the C1 position require multiple steps involving a bridgehead iodide intermediate.[10b,d,l] One-pot desilylation and elimination to give **20** was accomplished through microwave irradiation of **19** with *p*-$TsOH{\cdot}H_2O$. The final C3 prenyl group was installed utilizing a precedented sequence[23] to afford hyperforin methyl ether **21**:[24] (1) deprotonation of **20** with LDA, (2) transmetalation with Li(2-Th)CuCN,[25] and (3) trapping with prenyl bromide. Finally, hyperforin (**1**) was revealed by heating a DMSO solution of **21** with LiCl.

In summary, we report an enantioselective total synthesis of hyperforin. The synthesis is 18 steps at its longest sequence, starting from geraniol. This approach is also highly scalable; to date, we have prepared over 40 mg of hyperforin. Latent symmetry elements were utilized to quickly access the hyperforin bicyclo[3.3.1]nonane core and to set two key quaternary stereocenters, specifically in the conversion of epoxide **12** to ketal **13**. This practical and modular route is already being exploited to create diverse hyperforin analogs, which we are using to further understand the SAR and underlying mechanisms of hyperforin biological and medicinal activity. Results from these studies will be reported in due course.

ASSOCIATED CONTENT

Supporting Information. Experimental procedures, spectroscopic data, and ^1H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Funding Sources

No competing financial interests have been declared. We acknowledge financial support from Chemiderm, Inc. B.A.S. acknowledges a NSF Predoctoral Fellowship.

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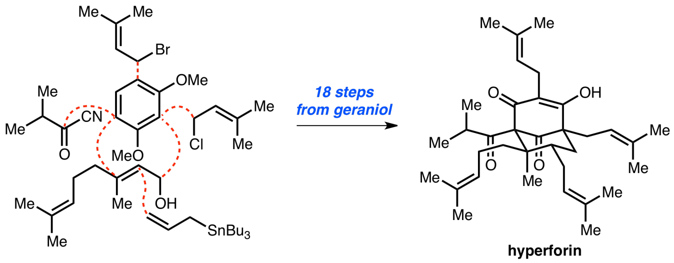
18 steps
from geraniol

hyperforin