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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 Ca2+, 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 progesterone 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 polypropenylated 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 hyperforin11 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.

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 biosynthesis14 (Scheme 1b). In nature, hyperforin is formed from alkylolation of a nucleophile, polykete-derived acylphloroglucinol with geranyl pyrophosphate. Stereochemical fidelity over the course of this coupling in the biosynthesis is governed by enzyme catalysis.
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 epoxy-aryl bromide 6 and subsequent TESCl-mediated silylation gave 9. Over the course of the synthesis, it became apparent that formal silylation of the olefin present in 6 was indispensable. Deprotonation of cyclohexadiene 4 with t-BuLi, treatment with freshly prepared BaI₂, and alkylation with prenyl chloride 7 yielded diene 11. In the absence of BaI₂, 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 ketone was an unexpected yet fortuitous outcome to this reaction, safeguarding the C7 carbon 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(O₂CCF₃)₂, and O₃ to afford vinylogous ester 14. 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).

Conditions: (a) Hg(OAc)₂, Me₂CO/H₂O; NaOH, 0 °C; NaBH₄, 0 °C, 91% (b) TESCI, imid, DMF, 97%; (c) t-BuLi, THF, −78 °C; BaI₂, −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, CH₂Cl₂, −78 °C, 79%; (f) PhI(O₂CCF₃)₂, TBHP, Cs₂CO₃, 4Å MS, EtOAc, O₂, −78 to 0 °C, 44%; (g) BrBMe₂, NEt₃, CH₂Cl₂, −95 °C; NEt₃, sat. aq. NaHCO₃, 57%; (h) LiTMP, THF, −78 to 0 °C, 97%; (i) CIC(S)(O)CF₃, N-hydroxysuccinimide, pyr, PhMe, 80 °C, 82%; (j) allyl–SnBu₃, B₂Et₃, PhH, air, 72%; (k) 17, 2-methyl-2-butenyl, CH₂Cl₂, 40 °C, 86%; (l) LiTMP, TMSCI, 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-H₂O, PhMe, HOAc, 2-methyl-2-butenyl, 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%.

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

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 proterogenic, and the two methyl enol ethers are diastereotropic. 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. The contributions of these factors culminate in the proper diastereoselection, with the formation of the hyperforin bicyclo[3.3.1]nonane framework.
oxidation site. Hydrolysis of the ketal present in 14 to yield alcohol 15 was performed in two steps: treatment of 14 with BrBMe₂ followed by LiTMP-mediated methanol extrusion from the intermediate hemiketal. It was crucial to maintain the temperature of the BrBMe₂-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 Heck alkylation approach. A radical precursor, thionocarbonated 16, was generated from the reaction of alcohol 15 with ClC(S)OC₂F₅. Using B/Et₃/air as an initiator, radical alkylation of 16 with allyl-SnBu₃ 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-butenyl catalyzed by Hoveyda–Grubbs 2nd generation catalyst 17 afforded 18 containing the requisite C7 prenyl moiety.

After silylation at the C3 position, sequential bridgehead deprotonation-acetylation using LiTMP and i-PrC(O)CN(CH₃)₂ yielded ketone 19. This direct, one-step bridgehead alkylation is noteworthy given that previously reported instances of PPAP bridgehead alkylation at the C1 position require multiple steps involving a bridgehead iodo intermediate. One-pot desilylation and elimination to give 20 was accomplished through microwave irradiation of 19 with p-TsOH·H₂O. The final C3 prenyl group was installed utilizing a precedent sequence to afford hyperforin methyl ether 21. (4) Deprotection of 20 with LDA, (2) transmetalation with Li(2-Th)CuCN, 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 efficient, requiring 18 steps at its longest sequence, starting from geraniol. This approach is also highly efficient, requiring 24 h for the temperature of the BrBMe₂ bridgehead acyl group.

REFERENCES

ASSOCIATED CONTENT

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

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(18) For other examples of allylic oxidation to form the C2–C4 vinyllogous ester, see ref. 10p and Takagi, R.; Inoue, Y.; Obkata, K. J. Org. Chem. 2008, 73, 9320-9325.


(23) For other examples of C3 metation-alkylation, see ref. 10d,h,l,p and Ahmad, N. M.; Rodeschini, V.; Simpkins, N. S.; Ward, S. E.; Wilson, C. Org. Biomol. Chem. 2007, 5, 1924-1934.

(24) The NMR data for this compound is consistent with that of 21 generated from treatment of isolated hyperforin with diazomethane (ref. 8a). See Supporting Information for more details.

18 steps from geraniol

hyperforin