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Total Synthesis of Hyperforin

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Supporting Information

ABSTRACT: A 10-step total synthesis of the polycyclic polyprenylated acylphloroglucinol (PPAP) natural product hyperforin from 2-methylcyclopent-2-en-1-one is reported. This route was enabled by a diketene annulation reaction and an oxidative ring expansion strategy designed to complement the presumed biosynthesis of this complex meroterpene. The described work enables the preparation of a highly substituted bicyclo[3.3.1]nonane-1,3,5-trione motif in only six steps and thus serves as a platform for the construction of easily synthesized, highly diverse PPAPs modifiable at every position.

The bicyclo[3.3.1]nonane-containing family of polycyclic polyprenylated acylphloroglucinols (PPAPs) have captivated synthetic chemists for decades because of their distinctive molecular structures and ability to induce an extraordinarily wide range of biological effects.[1] Well over 150 PPAPs have been isolated, with properties ranging from antiviral to anticancer, yet to date a general, global model correlating PPAP biological function with structural type or substitution pattern is lacking. In addition to their extensive and promising medicinal attributes, PPAPs have also served as an excellent inspiration for the development of new ring-forming reactions in organic synthesis, and numerous synthetic groups have documented creative strategies en route to the bicyclo[3.3.1]-nonane scaffold.[2] Moreover, a number of laboratories have completed innovative total syntheses of full PPAP natural products.[3]

In 1975, Bystrov and co-workers disclosed the structure of hyperforin (**1**),[4] which became perhaps the flagship polycyclic polyprenylated acylphloroglucinol, possessing some of the most medicinally relevant PPAP attributes as well as their most formidable synthetic obstacles (Figure 1a).[5] Hyperforin has noted antibiotic, anticancer, antidepressant, and procognitive effects, among others,[5] and as an active constituent of St. John's wort, **1** has seen centuries of documented use. Biochemically, hyperforin is a known activator of the transient receptor potential cation channel 6 (TRPC-6),[6] an inhibitor of human sirtuins (SIRT-1 and -2),[7] and a potent pregnane X receptor ligand (leading to increased xenobiotic metabolism).[8] Structurally, hyperforin belongs to the synthetically challenging type A subclass of PPAPs wherein the hindered acyl ketone side chain at C-1 resides next to the hallmark C-8 quaternary carbon. A number of biologically active PPAPs bear this pattern, including nemorosone (**2**) and garsubellin A (**3**), although these compounds lack the formidable all-carbon stereogenic center at C-8. Nearly three and a half decades after its isolation and following significant effort by a number of research groups,[2] in 2010 Shibasaki and co-workers documented the first synthetic route to hyperforin (~50 synthetic steps).[9] In the past several years, impressive efforts by the research groups of Nakada,[10] Shair,[11] and Barriault[12] have greatly reduced the number of transformations needed to access this important secondary metabolite (35, 18, and 17 steps, respectively). Herein we report a unique solution to **1** employing a diketene annulation reaction and an oxidative ring expansion strategy, both of which should find use in the synthesis of numerous PPAP natural products and designed congeners.

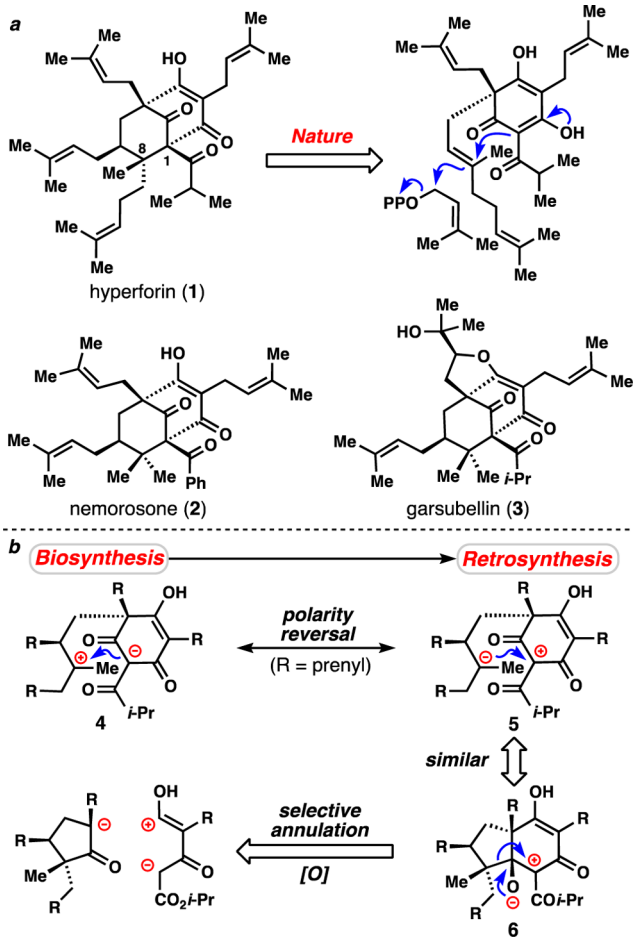

Figure 1. (a) Hyperforin (**1**), related PPAPs, and presumed biosynthesis. (b) Biosynthetic polarity reversal leads to new disconnections for PPAP construction.

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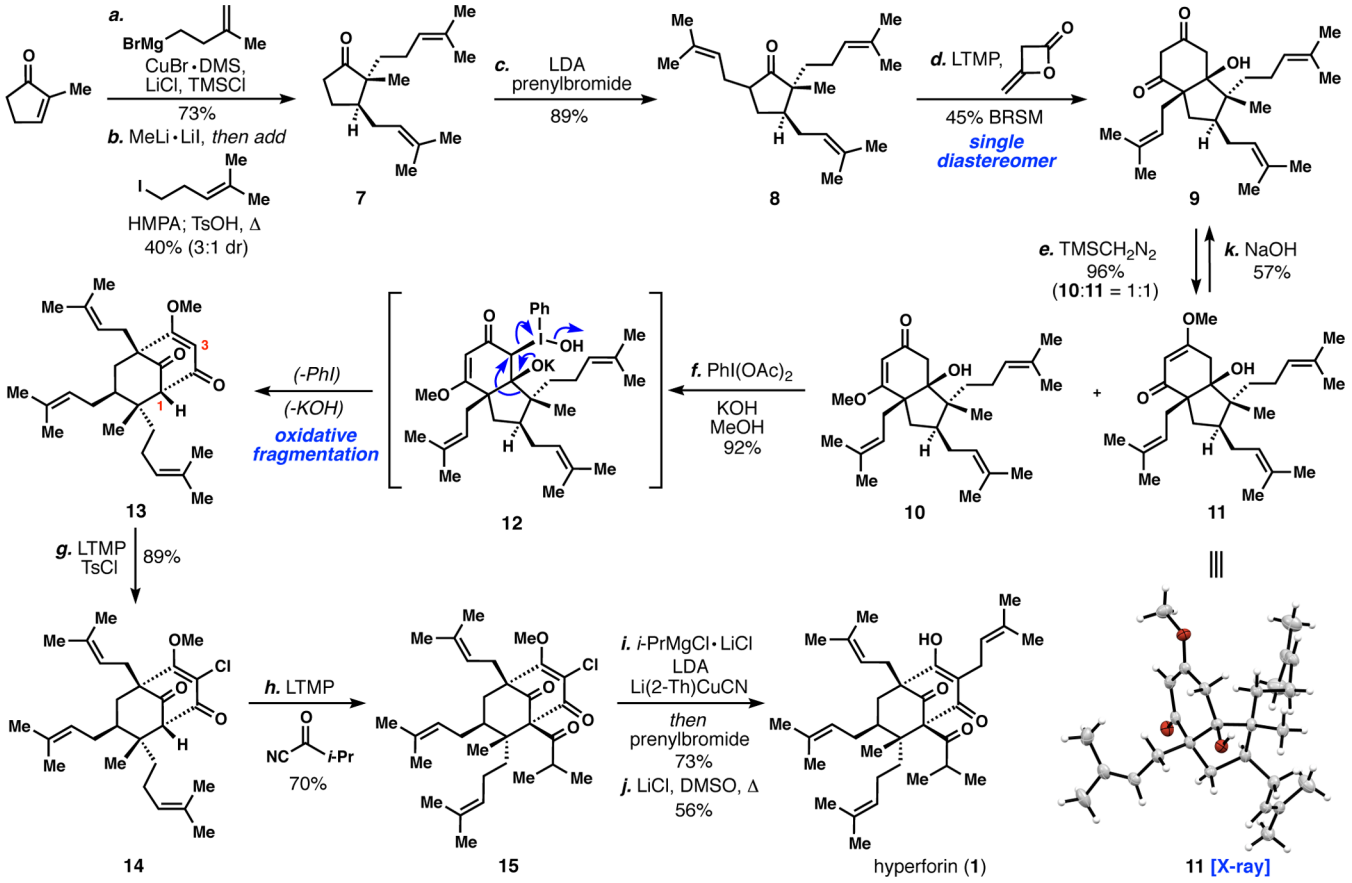
Scheme 1. Ten-Step Total Synthesis of Hyperforin (1)[a]



[a]Reagents and conditions: (a) (3-methylbut-3-en-1-yl)magnesium bromide (1.0 equiv), CuBr·DMS (1.2 equiv), LiCl (1.2 equiv), TMSCl (1.2 equiv), THF, −78 °C, 1 h, 73%; (b) MeLi·LiI (1.2 equiv), THF, 0 °C, 1 h, then add 5-iodo-2-methylpent-2-ene (5 equiv), HMPA, −78 °C → 5 °C, 30 h, then *p*TsOH (0.1 equiv), PhH, 70 °C, 24 h, 40% (3:1 dr); (c) LDA (1.1 equiv), 1-bromo-3-methylbut-2-ene (1.1 equiv), THF/HMPA, −78 °C → 0 °C, 30 min, 89%; (d) LTMP (1.2 equiv), diketene (1.2 equiv), THF/Et_2O, −40 °C, 1.5 h, 35% **9** + 22% **8**; (e) $TMSCH_2N_2$ (1.5 equiv), PhMe/MeOH, 25 °C, 30 min, 48% **10** + 48% **11**; (f) $PhI(OAc)_2$ (2.6 equiv), KOH (1.8 M in MeOH), 25 °C, 2 h, 92%; (g) LTMP (2.1 equiv), TsCl (2.2 equiv), THF, −78 °C, 30 min, 89%; (h) LTMP (3.2 equiv), *i*-PrCOCN (5.0 equiv), THF, −78 °C → −35 °C, 30 min, 70%; (i) *i*-PrMgCl·LiCl (3.4 equiv), LDA (3.8 equiv), Li(2-Th)CuCN (7.0 equiv), THF, −78 °C, then add prenyl bromide (17 equiv), −78 °C → −30 °C, 1.5 h, 73%; (j) LiCl (10.0 equiv), DMSO, 120 °C, 30 min, 56%; (k) NaOH (21 equiv), dioxane/H_2O, 80 °C, 18 h, 57%. DMS = dimethyl sulfide, HMPA = hexamethylphosphoramide, LDA = lithium diisopropylamide, LTMP = lithium tetramethylpiperidide, TMS = trimethylsilyl, Th = thienyl.

Type-A PPAPs are presumably generated in nature via a cascade cyclization reaction wherein a nucleophilic enol engages a carbocationic intermediate in C−C bond formation (see Figure 1a and **4** in Figure 1b).[13] Not surprisingly, this reaction manifold has been extensively studied from the vantage point of biomimetic synthesis.[14,15] In developing a retrosynthesis of PPAP natural products, we were drawn to the alternative (and hypothetical) polarity-reversed intermediate **5** and its carbonyl addition product, alkoxide **6**. If an intermediate similar to **6** could be generated, it could in principle isomerize to the PPAP skeleton via a [1,2] alkyl shift pathway. This maneuver would reduce the complexity of PPAPs to that of simple 6/5-cis-fused bicycles, which in turn could be prepared by the hypothetical annulation reaction shown in Figure 1b.

We began our studies by preparing highly substituted cyclopentanone **7** (Scheme 1). Copper-mediated conjugate addition of (3-methylbut-3-en-1-yl)magnesium bromide followed by lithium enolate generation and alkylation with homoprenyl iodide furnished **7** after simple acid-catalyzed isomerization of the exocyclic olefin.[16] Notably, this sequence formally accomplishes a linear-selective conjugate addition of a prenyl nucleophile to a cyclopentenone. Cyclopentanone **7** could be further alkylated (LDA, prenyl bromide) to afford ketone **8**, setting the stage for a key annulation reaction. After much experimentation, it was found that the highly hindered lithium enolate of **8** (formed via LTMP-mediated deprotonation) engaged simple diketene in a formal C-acylation/ring annulation process leading to complex 5/6-fused bicycle **9** as a single diastereomer in 45% yield based on recovered starting material.[17] Diketone **9** then reacted smoothly with trimethylsilyldiazomethane (96%) to afford an easily separable 1:1 mixture of regioisomeric vinylogous esters **10** and **11**, the latter of which was amenable to single-crystal X-ray structure analysis. Regioisomer **10** was ultimately discovered to be crucial in completing the total synthesis of **1**, and from a practical perspective, **11** could be recycled to **9** via basic hydrolysis (Scheme 1).[18]

With compound **10** secured, we were in a position to test the key ring expansion strategy, and we sought to generate cationic intermediate **6** (Figure 1b) via the oxidation of an enolate or formal equivalent. A plethora of conditions were explored to elicit this process, yet few were highly successful (Table 1). Our initial attempts to realize this transformation relied on forming a dianionic intermediate via deprotonation with a strong base

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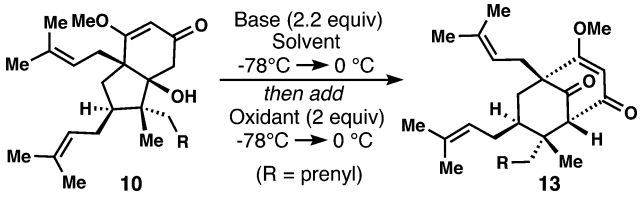
Table 1. Synthesis of Bicyclo[3.3.1]nonane 13 via Oxidative Rearrangement: Selected Optimization[a]



entry	base/solvent	oxidant	yield (%)[b]
1	**KOH/MeOH**	**$PhI(OAc)_2$**	**92**[c,d,e,f]
2	LDA/THF	$PhI(CN)_2$	40[c]
3	LDA/THF	$PhI(OTFA)_2$	23
4	LDA/THF	$PhI(OAc)_2$	11
5	LDA/THF	I_2	15
6	LDA/THF	NBS	9
7	LDA/THF	$Fe(acac)_3$	6
8	LDA/THF	Cu(2-ethylhexanoate)$_2$	0

[a]Reactions were performed on a 0.1 mmol scale. [b]Determined by ^{1}H NMR analysis. [c]Isolated yield. [d]T = 25 °C. [e][KOH] = 1.8 M. [f]Yield on 1 mmol scale = 82%.

(LDA) followed by the addition of a suitable oxidant. A variety of oxidants were surveyed for their ability to promote this rearrangement. Metal oxidants based on Fe(III) and Cu(II) were largely ineffective (entries 7 and 8). While NBS (entry 6) and simple molecular iodine showed promise (entry 5), we focused our attention on the hypervalent iodine(III) series because of their electronic tunability (entries 2−4). While $PhI(CN)_2$ (prepared in situ from TMSCN and $PhI(OTFA)_2$)[19] proved to be optimal, the yield of **13** still remained low. Ultimately it was discovered that simply stirring **10** with $PhI(OAc)_2$ in basic methanol at room temperature effected a very clean (92%) rearrangement to give **13**, presumably via an intermediate similar to **12** (Scheme 1). These final optimized conditions, which took inspiration from classic Favorskii-type rearrangements of steroid frameworks,[20] presumably maintain a lower concentration of enolate, which is then rapidly trapped by the hypervalent iodine reagent. Under such conditions, side-product formation is minimized, the transformation is scalable, and importantly, simple $PhI(OAc)_2$ can be utilized.

With bicyclo[3.3.1]nonane **13** in hand, a significant hurdle in PPAP chemistry needed to be addressed, namely, functionalization of the bridgehead (C-1) position. Deprotonation of the type A PPAP skeleton at this position and subsequent functionalization of the resulting bridgehead anion has been extensively studied and is often a low-yielding and substrate-dependent transformation.[3b,d,f,h,11,12,21] After examination of a number of reaction conditions on various substrates, a suitable process emerged. The C-3 position of **13** was first chlorinated (LTMP, TsCl), thus blocking this site from competitive deprotonation as well as installing a handle for downstream functionalization. Subjecting chloride **14** to Shair's bridgehead functionalization protocol (LTMP as the base, *i*-PrCOCN as the electrophile)[11] afforded **15** in 70% yield. This is the highest yield reported to date for this crucial transformation, and it appears that the presence of the inductively electron-withdrawing chlorine atom actually improves this process. With chloride **15** in hand, all that remained was the attachment of the final prenyl group, a task which proved challenging with Pd-catalyzed cross-coupling. While vinyl chlorides are not typically effective substrates for metal−halogen exchange processes, we found that **15** reacted with excess isopropylmagnesium chloride,[22] and following transmetalation onto copper, the C-3 position could be readily functionalized with prenyl bromide.[11,12] Demethylation (LiCl, DMSO, Δ) afforded hyperforin.[23]

In conclusion, a short synthesis of the complex PPAP natural product hyperforin has been developed in which two-thirds of the steps forge or rearrange C−C bonds.[24] Nature appears to subtly modulate PPAP function by varying the groups around the conserved bicyclo[3.3.1]nonane core, and our synthetic approach is particularly well-suited for varying such residues in a straightforward and systematic manner. Moreover, we expect that the reported diketene annulation will find more widespread use in C−C bond-forming processes, as it represents a higher-oxidation-state variant of the venerable Robinson annulation reaction.[25] Further exploration of this transformation and the synthesis of other PPAP members are underway and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b06939.

X-ray crystallographic data for **11** (CIF)
Experimental procedures and spectroscopic data for all compounds (PDF)

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Notes

The authors declare no competing financial interest.

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(17) O-Acylated material (~15%) and noncyclized C-acylated material (~5–10%) are also formed in this reaction.

(18) Isomer **11** is thermodynamically favored and forms exclusively when **9** is treated with $HC(OMe)_3$ and TsOH.

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(22) The *i*-PrCl formed likely consumed some of the C-2 magnesiate via an E2 elimination pathway. The yield was improved by the addition of LDA.

(23) While our exploratory work was conducted with racemic material, we have found that the asymmetric Cu-catalyzed conjugate addition recently disclosed by Minnaard and co-workers (see: Calvo, B. C.; Madduri, A. V. R.; Harutyunyan, S. R.; Minnaard, A. J. *Adv. Synth. Catal.* **2014**, *356*, 2061.) can be employed using (3-methylbut-3-en-1-yl)magnesium bromide (see the Supporting Information).

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