The Total Synthesis of Hyperforin

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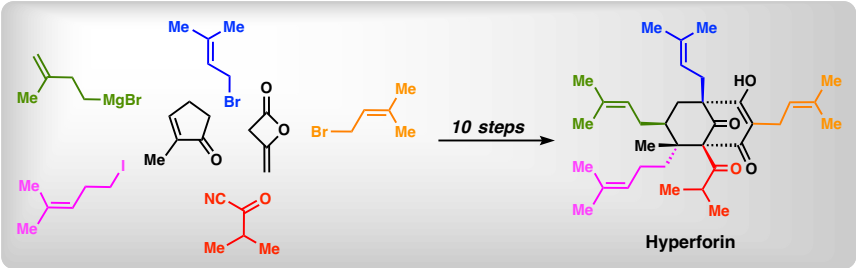


Received:
Accepted:
Published online:
DOI:

Abstract: Hyperforin has remained a popular and challenging synthetic target since its isolation over forty years ago. As a result, numerous synthetic strategies and ring-forming reactions have been developed to address its formidable molecular architecture. Herein we describe our contributions to this area resulting in a ten-step synthetic pathway enabled by a novel diketene annulation reaction and oxidative ring expansion strategy.

Key words: meroterpene, hypervalent iodine, ring expansion, total synthesis, natural products, annulation

The polycyclic polyprenylated acylphloroglucinols (PPAPs) have captivated the interest of chemists for decades owing to their diverse range of biological properties and formidable molecular structures.[1] Over 150 PPAP natural products have been isolated from the *Guttiferae* and related plant families, most of which contain the signature bicyclo [3,3,1] nonane 1,3,5-trione motif uniquely decorated with prenyl and geranyl groups as well as a variable ketone side chain. Further cyclization, often under oxidative conditions, serves to broaden the molecular diversity of this already large natural product family.[2] The existence of vicinal quaternary carbon centers (C-1 and C-8) in this class of natural products has posed a significant challenge to synthetic chemists, and the problem is only exacerbated in the case of hyperforin (**1**) where C-8 is an all-carbon quaternary stereocenter (Figure 1).[3,4]

In addition to their structural complexity, PPAPs possess myriad and diverse biological properties.[2] Hyperforin (**1**), the active constituent of St. John's Wort, has been utilized as an anti-depressant for centuries,[5] presumably by modulating neurotransmitter levels (serotonin, norepinephrine, dopamine, and others).[6] Hyperforin also has documented antibacterial and antimalarial activity, is an inhibitor of human Sirtuins, and activates the pregnane X receptor, leading to increased xenobiotic metabolism.[7,8] Other PPAPs such as nemorosone (**2**), garsubellin A (**3**), and clusianone (**4**) possess anticancer,[9] antineurodegenerative[10] and anti-HIV[11] properties respectively (Figure 1).

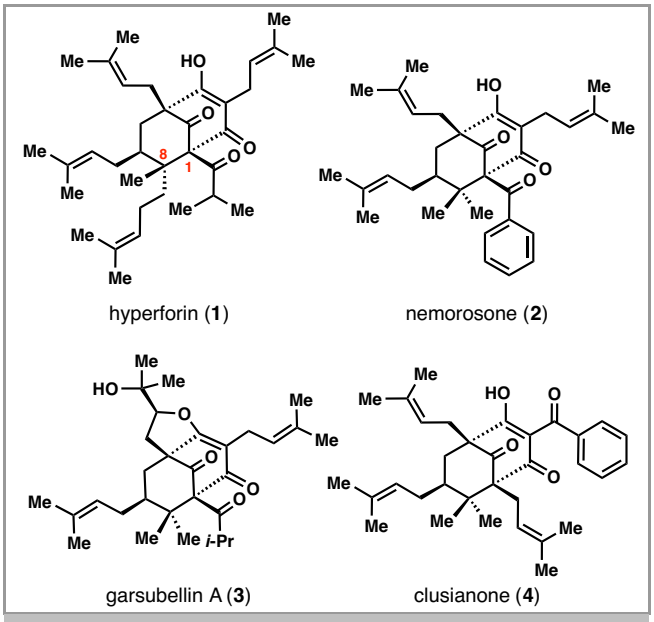


Figure 1 Representative Polycyclic Polyprenylated Acylphloroglucinols (PPAPs)

While many synthetic groups have reported total syntheses of PPAP natural products,[12] it was only recently that Shibasaki and co-workers disclosed the first total synthesis of hyperforin in 2010.[13] Since then, contributions by Nakada,[14] Shair[15] and Barriault[16] have each contributed heavily to advances in synthetic efficiency toward this complex target (Figure 2). As the bicyclo [3,3,1] nonane 1,3,5-trione is the defining feature of **1**, it is prudent to highlight the disconnections made by these groups en route to their eventual total syntheses.

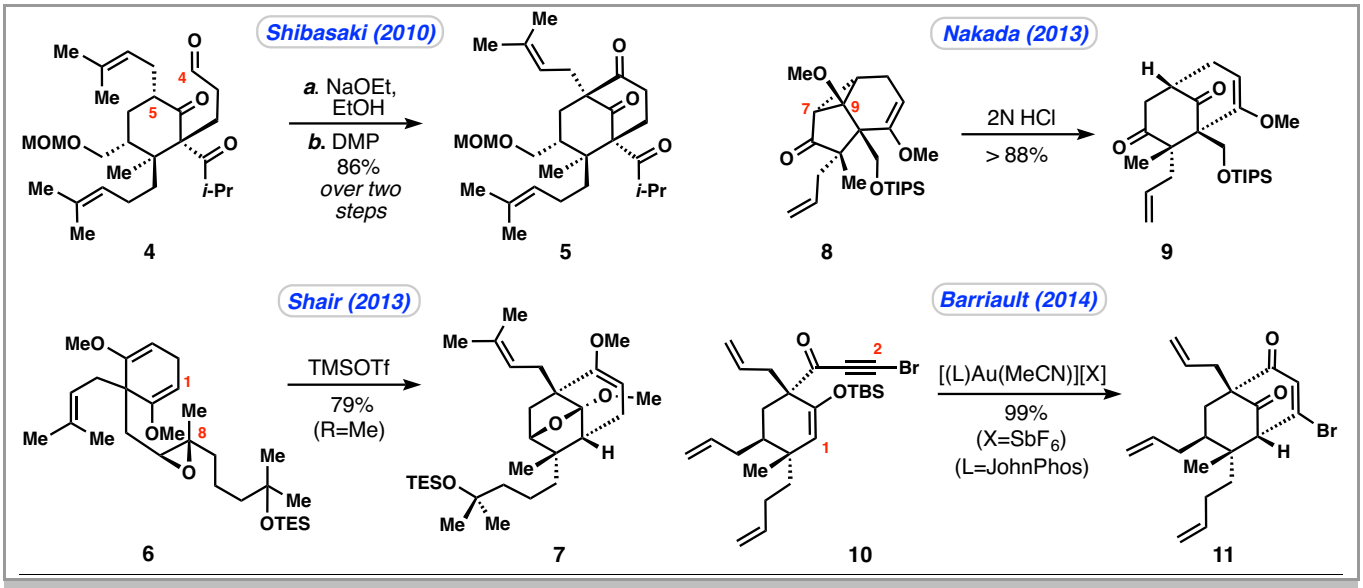


Figure 2 Key C–C bond-forming reactions utilized in past total syntheses of hyperforin

It is quite noteworthy that while each of these researchers disconnects the [3.3.1] bicycle in largely different manners, all of the key steps employed are highly efficient (yields ~80-99%).

In Shibasaki's inaugural 2010 synthesis, an aldol reaction was used to forge the C-4/C-5 bond and, following oxidation, bicycle **5** was formed in excellent yield from precursor **4** (Figure 2).[13] The Shair group's 2013 report detailed an impressive Lewis acid-mediated epoxide opening reaction of **6** to ketal **7** (C-1/C-8 bond formation). Notably, this transformation also forged hyperforin's challenging C-8 quaternary stereocenter.[15] As with much work in the PPAP synthetic field, including our own, this transformation took inspiration from the presumed biosynthesis of the PPAPs (Figure 3). Nakada and co-workers unveiled PPAP bicycle **9** via a creative, acid-mediated C–C cleavage reaction of cyclopropane **8** which itself is the product of an intramolecular cyclopropanation reaction.[14] Finally, in 2014 the group of Barriault disclosed an exceedingly efficient method to forge the PPAP bicycle utilizing a gold-catalyzed, *6-endo-dig* carbocyclization of silyl enol ether **10** (C-1/C-2 bond formation). Remarkably, bicycle **11** was formed in nearly quantitative yield (99%).[16]

In developing a retrosynthesis of PPAPs, we were also captivated by the divergent nature of PPAP biosynthesis (Figure 3).[17] By constructing three different regioisomeric permutations of bicycle **12**, hundreds of PPAP structures are possible from a few simple building blocks. In type A structures, the acyl group resides on C-1, in type B PPAPs it is connected to C-3, and in the rare type C structures, on C-5. These three scaffolds in turn, arise from the cationic cyclization cascade of dearomatized phenol **13** with a prenyl or geranyl-based electrophile. Unsurprisingly, biomimetic syntheses of PPAPs have been extensively studied.[18] Despite significant efforts, only the type B PPAPs have succumbed to direct biomimetic synthesis as recently showcased by Porco's remarkable six-step route to clusianone (**4**).[19]

In developing a synthetic blueprint for PPAP construction we sought a strategy that would ultimately address the synthesis of all three PPAP sub-types, allow for diverse side-chain incorporation, and be capable of constructing PPAPs containing C-8 stereocenters (Scheme 1). We began by tracing full PPAPs (**14**) back to [3.3.1] bicycle **15** by excising the C-1 and C-3 side chains–a tactic common in the PPAP synthetic field. As our hallmark disconnection, we envisioned the bicyclo [3,3,1] nonane nucleus arising via a *[1,2]*-alkyl shift pathway of *5/6*-fused bicycle **16**. We viewed the *cis*-fused carbocyclic skeleton of **16** as the product of a formal [4+2] annulation reaction of enolate **17** and hypothetical acylium ion synthon **18**. It was hypothesized that the simple feedstock chemical diketene (**19**) could serve as suitable chemical precursor to the chemistry envisioned of **18**.[20] The highly substituted cyclopentanone ring in **17** could be traced back to **20,** which in turn could be assembled by the

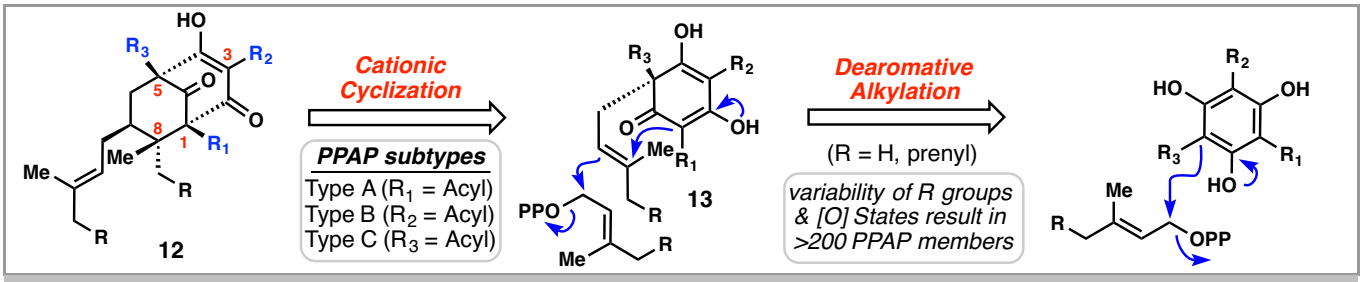
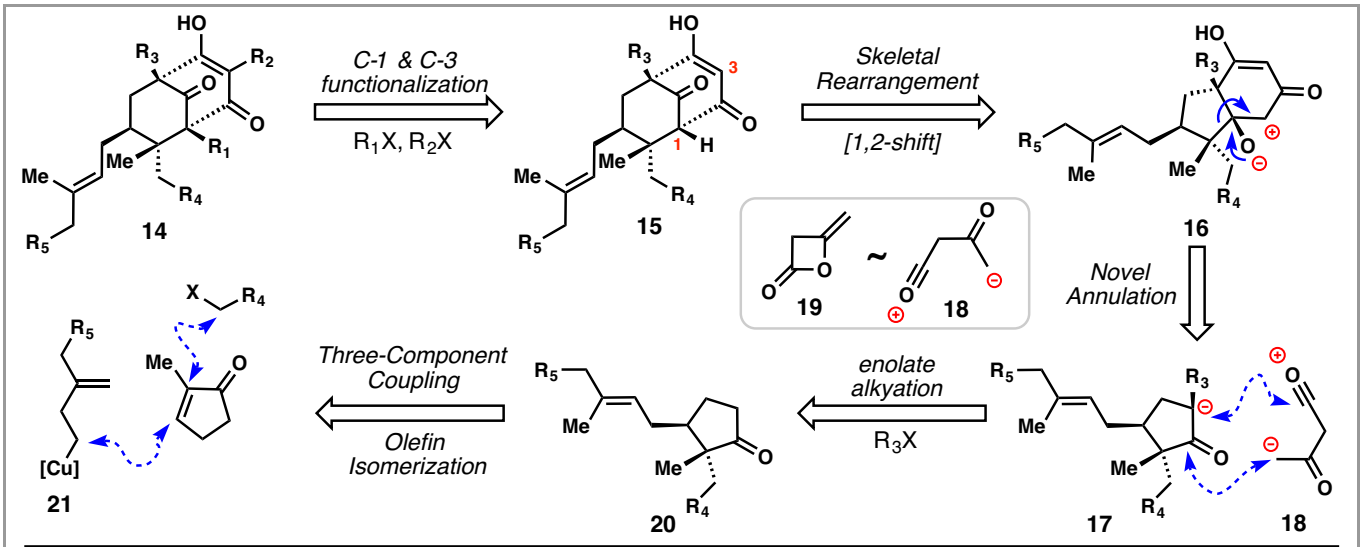


Figure 3 Presumed biosynthesis of the polycyclic polyprenylated acylphloroglucinols (PP = pyrophosphate)

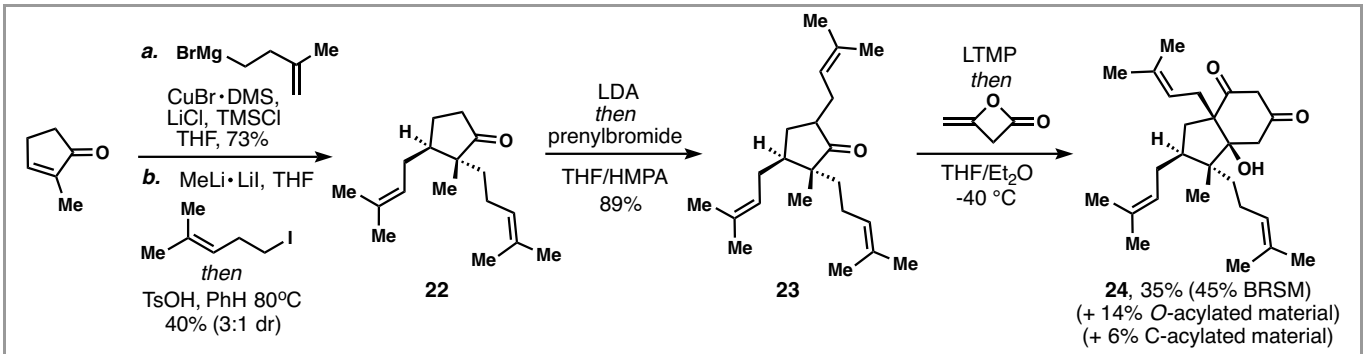


PPAP Type	Target	R_1	R_2	R_3	R_4	R_5
A	hyperforin (**1**)	isobutyryl	prenyl	prenyl	prenyl	H
	nemorosone (**2**)	benzoyl	prenyl	prenyl	H	H
	garsubellin A (**3**)	isobutyryl	prenyl	*[O]* prenyl	H	H
	hyperevolutin A	isobutyryl	H	prenyl	prenyl	H
	chamone I	benzoyl	prenyl	isogeranyl	H	H
B	clusianone (**4**)	prenyl	benzoyl	prenyl	H	H
	guttiferone G	prenyl	3,4-hydroxybenzoyl	prenyl	prenyl	geranyl
C	garcinielliptone M	prenyl	*[O]* prenyl	isobutyryl	H	H
	garcinielliptone L	prenyl	*[O]* prenyl	isobutyryl	H	H

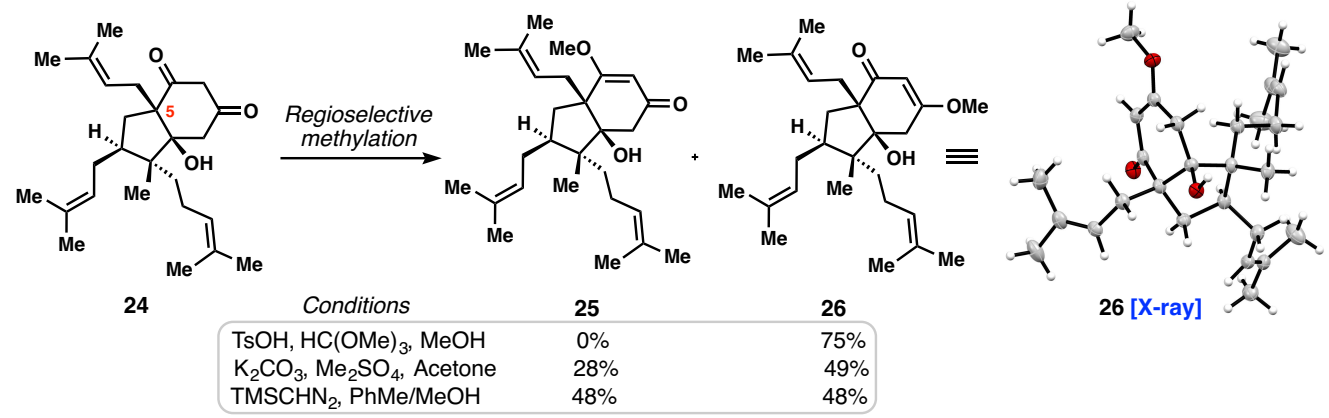
Scheme 1 Synthetic blueprint to access myriad PPAP members.

3-component coupling reaction shown, along with isomerization of the 1,1-disubstituted olefin into its more stable configuration (see **21** to **20**). The coupling of **21** combined with olefin isomerization serves as a prenyl nucleophile surrogate and avoids issues of regioselectivity during addition (α vs. γ attack). Through variations in the input building blocks, as well as their order of incorporation, a wide range of type A, B, and C PPAPs could in principle be generated in short order (Scheme 1). Moreover this route uses reliable conjugate addition chemistry to construct the core cyclopentane ring–a reaction we viewed as being susceptible to asymmetric synthesis.[21]

Our synthesis commenced with the copper-mediated conjugate addition of 3-methyl-3-butenylmagnesium bromide to 2-methylcyclopentenone utilizing conditions reported by Lipshutz (Scheme 2).[22] The resulting trimethylsilyl enol ether was then treated with methyllithium/lithium iodide, generating a lithium enolate that could be alkylated with homoprenyl iodide in the presence of HMPA. Attempts to engage magnesium enolates in this alkylation reaction were largely unsuccessful. Following acid-catalyzed isomerization of the 1,1-disubstituted alkene with *para*-toluenesulfonic acid in hot benzene, ketone **22** could be isolated as a 3:1 mixture of diastereomers. Deprotonation of **22** with LDA and alkylation with prenylbromide resulted in the formation of highly substituted cyclopentanone **23** in 89% yield. With this compound in hand, we were poised to develop the aforementioned [4+2] annulation reaction. After careful experimentation, we found that LTMP-mediated deprotonation of **23**, followed by the addition of freshly distilled diketene in a THF/Et_2O mixture at -40 °C, produced ring annulated bicycle



Scheme 2 Synthesis of 5/6-fused bicycle **24** via an annulation reaction with diketene.

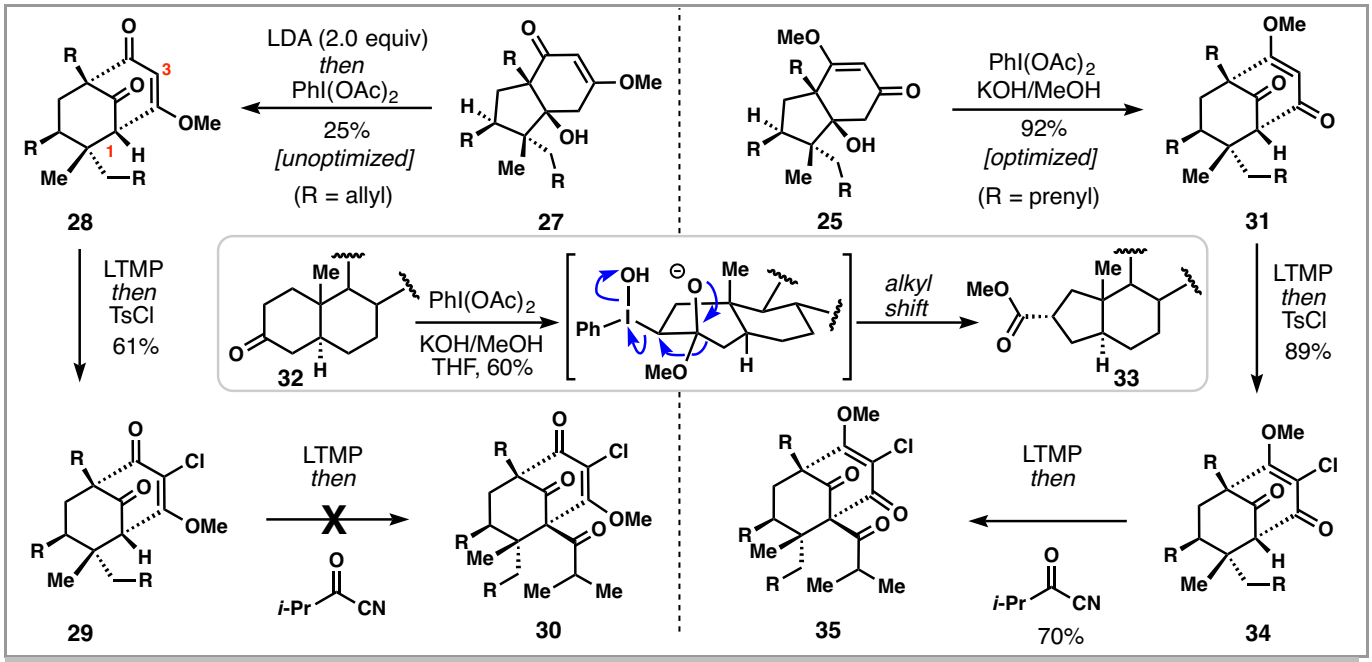


Scheme 3 Regioselective methylation studies of 1,3-diketone 24

24 in 35% isolated yield (45% BRSM). Isolable byproducts also included *O*-acylated (14%) and C-acylated (6%) material. It is noteworthy that the product of this reaction is formed as a single diastereomer, with reagent approach occurring opposite to the β-disposed methyl and prenyl chains. It's also worth noting that the desired product was only obtained in ethereal solvents, and as previously noted in enolate acylation chemistry,[23] increasing the polarity of the reaction medium (i.e. adding HMPA for example) strongly favors the formation of the *O*-acylated product. While the yield of this transformation is modest on this substrate, we have prepared multi-gram quantities of bicycle **24** using this chemistry.

With 1,3-diketone **24** secured, we proceeded to convert this material into its corresponding vinylogous ester in preparation for the key alkyl shift reaction (Scheme 3). A variety of conditions were found to efficiently methylate **24** leading to two chromatographically separable isomers (**25** and **26**). Utilizing acidic methanol (TsOH, $HC(OMe)_3$, MeOH) the thermodynamically more stable isomer (**26**) could be prepared selectively in 75% yield (Scheme 3). In this regioisomer, the newly installed methyl group resides away from the all-carbon quaternary stereocenter on C-5. The stereochemistry of this product was secured by single crystal X-ray diffraction. Under basic methylation conditions (MeI, K_2CO_3, acetone) a 1:1.8 mixture of **25**:**26** was observed in good yield (77%). Finally, using the highly reactive electrophile $TMSCHN_2$ a statistical 1:1 mixture of products was formed in nearly quantitative yield (97% total). As we will see, isomer **25** was crucial in completing the total synthesis of **1**. Fortunately, undesired isomer **26** could be hydrolyzed back to **24** via saponification (NaOH, H_2O/dioxane, 80 °C) in 57% yield .

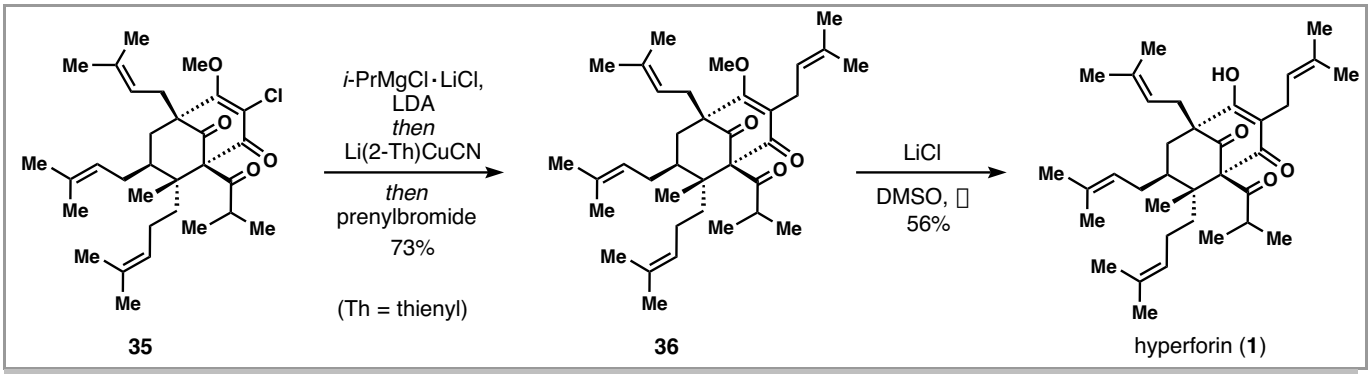
We began our studies towards the synthesis of the bicyclo [3,3,1] nonane 1,3,5-trione motif utilizing regioisomerically pure model substrate **27** since it was the



Scheme 4 Successful oxidative rearrangement and disparate reactivity of regioisomeric vinylogous esters.

most easily prepared (Scheme 4). Our initial attempts to elicit the requisite ring shift reaction focused on utilizing enolate oxidation chemistry to access hypothetical intermediate **16** (Scheme 1).[24] In this regard, vinylogous ester **27** was treated with excess lithium diisopropylamide (2.0 equiv.) presumably forming a dianionic species which was then reacted with the hypervalent iodine (III) oxidant $PhI(OAc)_2$. Much to our delight, bicycle **28** was formed in 25% yield (unoptimized). In an attempt to advance this compound into the full hyperforin skeleton, we were aware of the need to functionalize the bridgehead (C-1) position, a challenging operation in the PPAP synthetic field.[11,15,16] As previously noted,[25] the C-3 vinyl proton is more acidic than the C-1 bridgehead proton and this observation allowed us to cleanly prepare vinyl chloride **29** via LTMP-mediated deprotonation and quenching with TsCl. At this junction, vinyl chloride **29** was subjected to Shair's one-pot bridgehead acylation protocol (LTMP as base, *i*-PrCOCN as electrophile),[15] which unfortunately only resulted in trace quantities of **30** (<<5%) with substantial recovered starting material. Barriault and co-workers have reported similar difficulties when attempting to utilize this vinylogous ester regioisomer in bridgehead functionalization chemistry.[16] In their case, C-1 iodination was possible utilizing the LDA/TMSCl base system developed by Danishefsky,[11b,11c] however the overall net yield for attaching the acyl sidechain via this route is low. These results prompted us to begin working with regioisomer **25**. After surveying a variety of conditions to improve the yield of the key oxidative rearrangement, we discovered that stirring **25** and $PhI(OAc)_2$ in basic methanol forged bicycle **31** in high yield (92%). These conditions took inspiration from the oxidative rearrangement of cholestanone (see **32**→**33**, Scheme 4) wherein a mechanistically related C–C migration is proposed to occur.[26] Bicycle **31** underwent clean C-3 chlorination (in analogy to **28**) affording vinylchloride **34** in 89% yield. In contrast to **29**, regioisomer **34** participated in an efficient bridgehead acylation reaction utilizing Shair's aforementioned conditions. Yields of 70% could be obtained in this reaction representing the highest yields reported for this transformation to date. We hypothesize that the inductively-withdrawing chlorine atom facilitates this challenging deprotonation. It should be noted that bromine and iodine atoms at the C-3 position do not survive this deprotonation reaction. With a route to **35** developed, only one C–C bond remained to be constructed en route to the total synthesis of **1** (Scheme 5). We encountered significant difficulties in appending the final prenyl group to this intermediate. Specifically, prenyl Suzuki coupling methodology only afforded modest amounts of product (10-20%) along with substantial quantities of dechlorinated material.[27] Ultimately a workable solution emerged wherein **35** was treated with excess *i*-PrMgCl•LiCl and LDA, generating an anionic intermediate which could be transmetallated onto copper using lithium 2-thienylcyanocuprate, and ultimately alkylated with prenylbromide.[11c,11e,25] The addition of LDA following treatment with *i*-PrMgCl•LiCl was crucial as we believe it deprotonated any material which was quenched via an E-2 elimination reaction with the formed isopropyl chloride. Finally, demethylation of **36** (LiCl, DMSO, Δ) afforded hyperforin in ten steps overall from methyl cyclopentenone.[28]

In conclusion, a short total synthesis of hyperforin has been achieved. In essence, the described route to **1** relied on two powerful reactions to parlay simple conjugate addition chemistry to that of complex [3.3.1] bicyclic ring systems. Nevertheless this route is certainly not without flaw as several steps proceed in low yields and with low selectivity. Some of these shortcomings reflect general deficiencies in basic synthetic organic methodology, for example the alkylation of cyclopentanone-derived enolates with unactivated alkyl electrophiles. Efforts to render this synthesis enantioselective, extend the chemistry to other PPAP family members, and explore the annulative capabilities of diketene are underway and will be reported in due course.



Scheme 5 Final side chain attachment and completion of the total synthesis of hyperforin

Acknowledgment

Financial support for this work was provided by UC-Berkeley, the UC-Berkeley Hellman Fellows Fund, The Alfred P. Sloan Foundation, and the NSF (CAREER award to TJM (1554544) and pre-doctoral fellowship to CPT (DGE-1106400)). Dr. Antonio DiPasquale is acknowledged for X-ray crystallographic analysis and support from NIH Shared Instrument Grant (S10-RR027172)

Supporting Information

NO

Primary Data

NO

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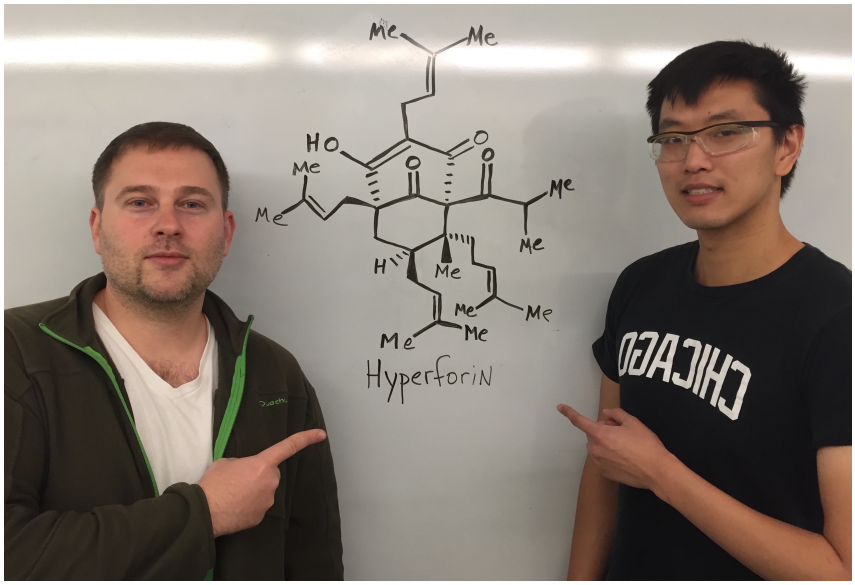
Biosketches



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