Total Synthesis

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Total Syntheses of Hyperforin and Papuaforins A–C, and Formal Synthesis of Nemorosone through a Gold(I)-Catalyzed Carbocyclization**

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Abstract: *The remarkable biological activities of polyprenylated polycyclic acylphloroglucinols (PPAPs) combined with their highly decorated bicyclo[3.3.1]nonane-2,4,9-trione frameworks have inspired synthetic organic chemists over the last decade. The concise total syntheses of four natural products PPAPs; hyperforin and papuaforins A–C, and the formal synthesis of nemorosone are reported. Key to the realization of this strategy is the short and scalable synthesis of densely substituted PPAP scaffolds through a gold(I)-catalyzed 6-endo-dig carbocyclization of cyclic enol ethers for late-stage functionalization.*

Polyprenylated polycyclic acylphloroglucinols (PPAPs) are a family of natural products isolated from *Guttiferae* plants, the therapeutic effects of which have been used for centuries.[1,2] These compounds are characterized by unique highly oxygenated and densely substituted bicyclo[3.3.1]nonane frameworks, which can be divided in three distinct groups; A, B, and C (Figure 1). In group A, the acyl moiety at C1 is contiguous to a quaternary center at C8, whereas in group C, the acyl group on C5 is positioned adjacent to a methylene unit. Group B is characterized by an acyl moiety located on C3. In the past two decades, more than 150 PPAPs have been isolated and they display a wide range of biological activities. Notably, hyperforin (**1**),[3] isolated from St. John's wort, displays antidepressant, antimalarial, and human histone deacetylase inhibitory activities to name but a few.[4] Other PPAPs, such as papuaforin A (**2**),[5] nemorosone (**3**),[6] and garsubellin A (**4**),[7] showed antibacterial, antitumor, and antineurodegenerative activities, respectively.

Owing to the intricate architectures of PPAPs and their impressive therapeutic profiles, considerable research efforts have been devoted to the synthesis of these natural products.[8] Recently, several of these approaches were successfully applied in the total syntheses of hyperforin (**1**),[9] nemorosone (**3**),[10] garsubellin A (**4**),[11] and other PPAPs.[12] Although important progress in the synthesis of PPAPs has been realized in recent years, the development of a general and flexible method for the synthesis of these intriguing natural products has yet to be described.

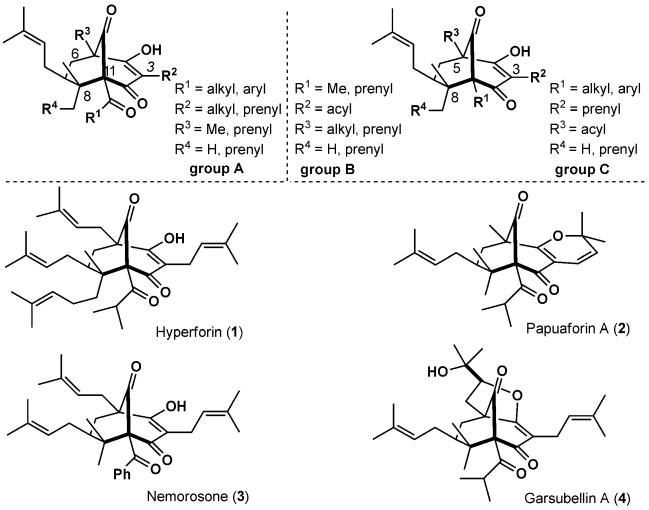
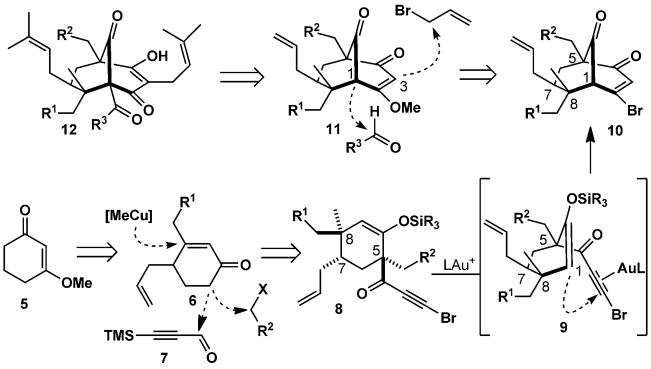


Figure 1. Structures of various PPAPs.

Taking advantage of the high affinity of phosphino gold(I) complexes for alkynes in the presence of other functional groups,[13] we envisioned a *6-endo-dig* gold(I)-catalyzed carbocyclization of cyclic enol ether **8** to produce bicyclo-[3.3.1]nonadione **10** (Scheme 1).[14] Recently, we reported that selective *5-exo-* and *6-endo-dig* carbocyclizations of silyl enol ethers to alkynes can be achieved by modulating the steric and electronics properties of the ancillary ligand on the cationic gold complex.[15] Starting from commercially available ketone **5**, we envisaged that a careful orchestration of stereospecific allylation, alkylation, and aldol reactions [**6**→**8**] would install the functional groups at C5, C7, and C8. The modular approach would provide a rapid and scalable syn-



Scheme 1. Retrosynthetic analysis.

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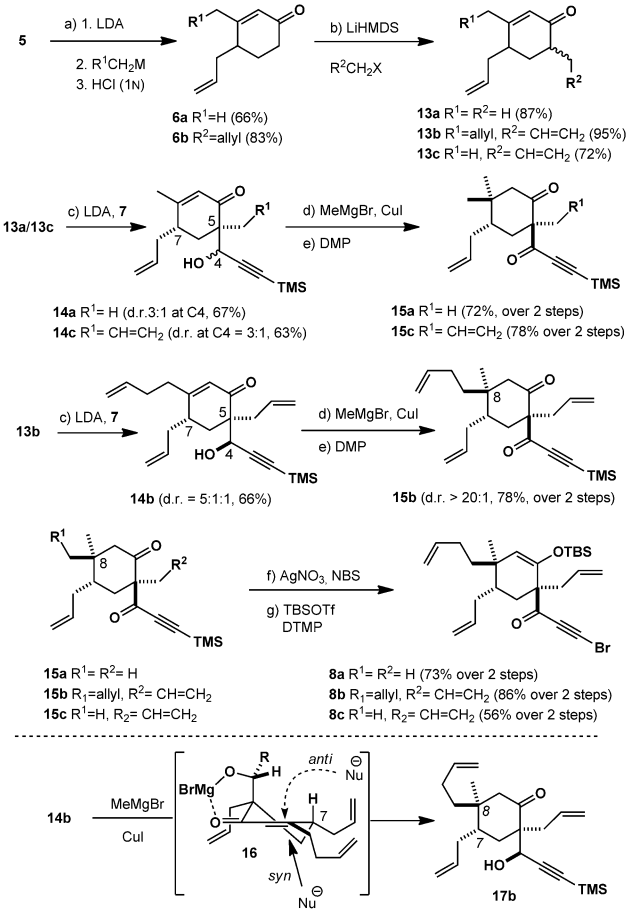
thesis of bicyclo[3.3.1]nonadione **10**, which could serve as a pivotal intermediate for the assembly of various PPAPs (**12**) through late-stage functionalization at C1 and C3 on intermediate **11**.

The synthesis began with a one-pot allylation/alkylation of ketone **5** by using LDA and allylbromide, followed by a 1,2-addition of the appropriate alkylating agent (H_2C=$CHCH_2CH_2MgBr$ or MeLi) and subsequent treatment with HCl 1N to give enones **6a** and **6b** in 66% and 83% yields, respectively (Scheme 2). A second alkylation with LDA and R^2CH_2–X provided enones **13a–c** in 87%, 95%, and 72% yields, respectively. Next, the installation of the propargyl unit was realized through the addition of 3-(trimethylsilyl)-2-propynal **7** to enones **13a–c** in the presence of LDA. The alcohols **14a** and **14c** were isolated as the major diastereomers at C5–C7 in 67% and 66% yields, respectively (d.r. 3:1 at C4).[16]

Alcohols **14a** and **14c** underwent a sequence of conjugated addition/oxidation reactions to afford ketones **15a** and **15c** in 72% and 78% yields, respectively, over 2 steps. On the other hand, enone **13b** was subjected to the above aldol reaction conditions and propargyl alcohol **14b** was isolated in 63% yield along with a mixture of three other minor diastereomers (ca. 25% combined yield). At the outset, we had concerns about the diastereoselectivity of the organocuprate addition. Indeed, the addition of organocopper reagents to δ-substituted cyclohexenones[17] such as **14b** gives mainly the *trans* isomer through an attack *anti* to the adjacent substituent.[18] In our case, the addition must proceed through a *syn* pathway in order to obtain the required stereochemistry at C8. To our delight, treating **14b** with MeMgBr in the presence of CuI followed by an oxidation gave **15b** as the sole diastereomer in 73% yield over two steps (d.r. > 20:1). The unusual diastereoselectivity can be rationalized through the formation of a Mg-chelated intermediate such as **16**. The latter can adopt a conformation in which the axial substituent shields the top face, thus favoring *syn* addition of the organocopper reagent to provide **17b** as the major diastereomer.[19] Next, the replacement of the TMS group by a bromide was achieved without incident by using $AgNO_3$ and NBS (**15**→**8**). The resulting bromoethynyl compounds were transformed into the corresponding silylenol ethers **8a–c** in readiness for a gold(I)-catalyzed *6-endo-dig* carbocyclization.

With [(JohnPhos)Au(NCMe)][SbF_6] as the catalyst (5 mol%), the silylenol ethers **8a–c** were converted into the desired bicyclic ketones **10a–c** in high yields (Scheme 3). Remarkably, the gold(I)-catalyzed cyclization proceeded in a sterically crowded environment and was amenable to large-scale synthesis (> 10 g). Treating **10a–c** with MeONa in MeOH followed by silylation at C3 produced the bridgehead ketones **18a–c**. The latter compounds represent key intermediates that can be transformed into a wide range of naturally occurring PPAPs. For instance, compound **18c** was converted into ketone **19** through a high-yielding cross-metathesis reaction by using isobutene and Grubbs II as the catalyst.[10c] Simpkins and co-workers reported the synthesis of nemorosone (**3**) in five steps from intermediate **19**.[10b] The synthesis of intermediate **19** thus completes a formal total synthesis of the natural product.

The preparation of hyperforin (**1**) and papuaforin A (**2**) from intermediates **18b** and **18a**, respectively, was then examined (Scheme 4). Initial attempts at direct acylation at the sterically congested C1 position by using a lithium amide base and an acyl chloride, acyl cyanide, or aldehyde have thus far been unproductive. In light of the previous work of Danishefsky[10a,11b] and Simpkins,[10b,11c] we envisaged the installation of the acyl group via a bridgehead iodo intermediate. After considerable experimentation, we found that deprotonation with LDA (3.5 equiv) in the presence of TMSCl (5 equiv) followed by the addition of iodine gave the corresponding iodoketones **20a** and **20b** in 29% and 18% yields, respectively, along with significant amounts of reduced by-products **21a**,**b** (41–42%) and recovered starting materials **18a**,**b** (24–35%). Although a competitive LDA-mediated reduction was operative,[20] the formation of the bridgehead iodo intermediates **20** proved to be highly reproducible and amenable to gram-scale synthesis.[21] Iodo-lithium exchange/alkylation followed by oxidation and treatment with TBAF



Scheme 2. Syntheses of enol ethers **8a–c**. Reagents and conditions. a) 1. LDA, allyl bromide, THF, −78 °C, 2 h; 2. MeLi or H_2C=$CHCH_2CH_2MgBr$, −78 °C then 3. HCl (1 N); b) LiHMDS, R^2CH_2X, THF; c) LDA, **7**, THF, −78 °C; d) MeMgBr, CuI, DMS, THF, −78 °C; e) DMP, dichloromethane, RT; f) $AgNO_3$, NBS, RT; g) TBSOTf, DTMP, dichloromethane. LDA = lithium diisopropylamide, THF = tetrahydrofuran, DMS = dimethyl sulfide, DMP = Dess–Martin periodinane, NBS = *N*-bromosuccinimide, TBSOTf = *tert*-butyldimethylsilyl triflate, DTMP = 2,6-di-*tert*-butyl-4-methylpyridine.

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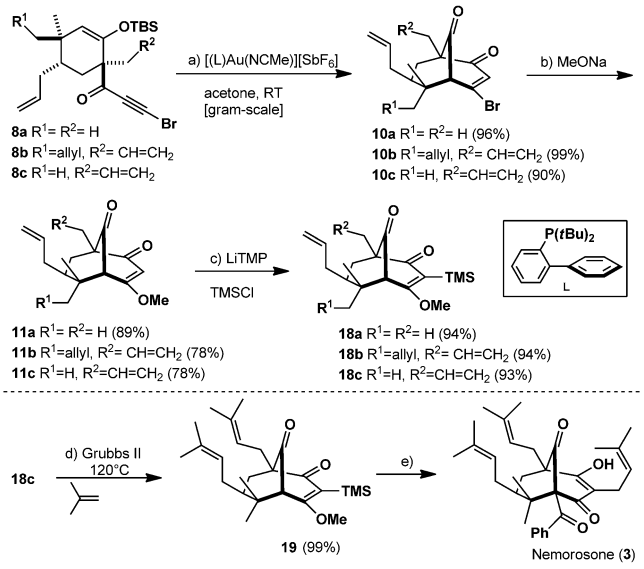


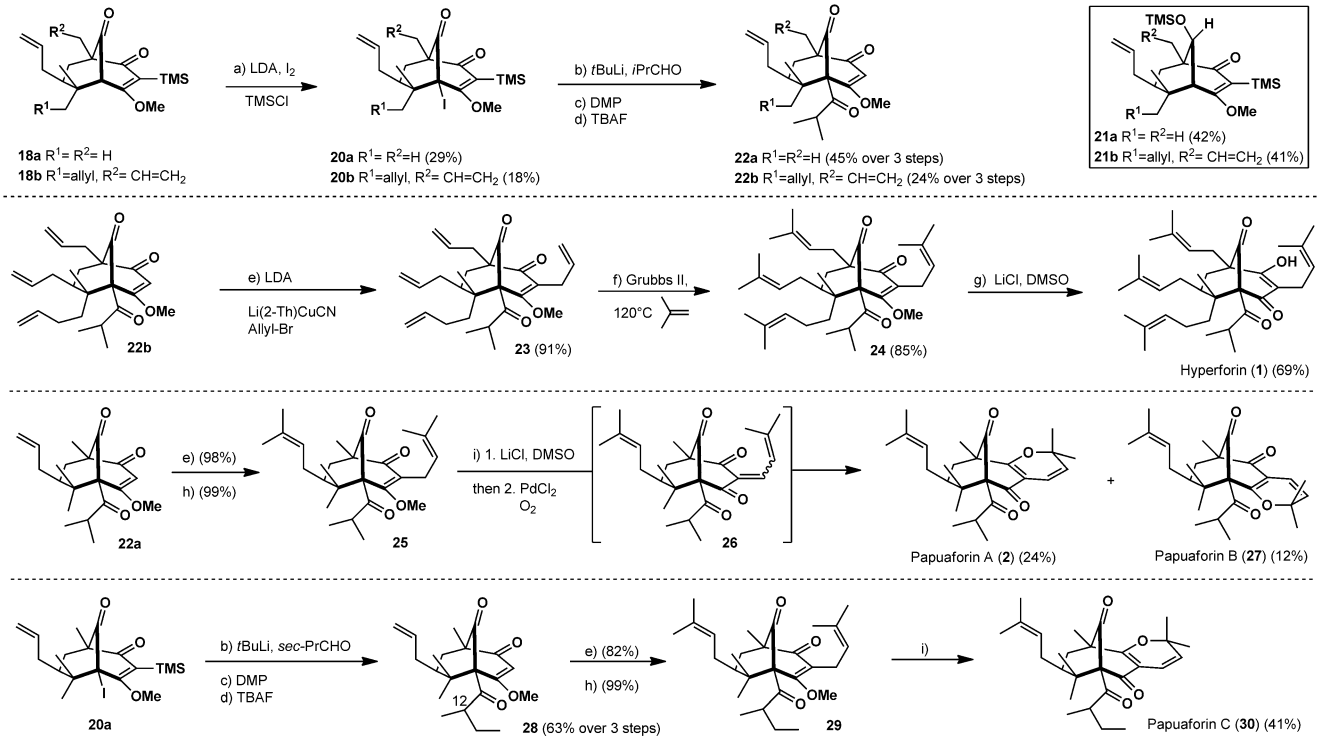
Scheme 3. Syntheses of intermediates **18a–c** and formal synthesis of nemorosone (**3**). Reagents and conditions. a) [(JohnPhos)Au(NCMe)][SbF_6] (5 mol%), acetone, RT; b) Na, MeOH, RT; c) LiHMDS, TMSCl, THF, −78°C; d) Grubbs II (5 mol%), isobutylene, 120°C; e) see Ref. [10b] (five steps). LiHMDS = lithium hexamethyldisilazide, TMSCl = trimethylchlorosilane, Grubbs II = Grubbs second-generation catalyst.

produced ketones **22a** and **22b** in 45% and 24% yields, respectively, over 3 steps. At this point, the completion of the hyperforin (**1**) and papuaforin A (**2**) syntheses were within reach.

In the case of hyperforin (**1**), the installation of the prenyl moiety at C3 is not without precedent.[22] Treating **22b** with LDA in the presence of Li(2-Th)CuCN and allyl bromide produced tetraallyl **23** in 91% yield. A global cross-metathesis of **23** gave the penultimate polyprenylated intermediate **24** in 85% yield, which upon treatment with LiCl in hot DMSO delivered **1** in 69% yield and matching the reported spectroscopic data.[9]

The completion of the papuaforin A (**2**) synthesis was contingent upon the installation of the 2,2-dimethyl-2*H*-pyran ring unit. To this end, allyl **22a** was converted into prenyl **25**. The latter was subjected to a one-pot demethylation/oxidation/electrocyclization with LiCl in DMSO followed the addition $PdCl_2$ and O_2[23] to produce papuaforin A (**2**) in 24% yield and papuaforin B (**27**) in 12% yield, presumably via intermediate **26**.[24] Building on the success of these syntheses, we exploited a similar synthetic approach to prepare papuaforin C (**30**). An efficient three-step sequence of alkylation with *sec*-butyraldehyde followed by oxidation and desilylation provided intermediate **28** in 63% yield over three steps. It is important to note that after oxidation with the Dess–Martin periodinane, a single diastereomer was obtained, presumably through thermodynamic epimerization at C12. Although the relative stereochemistry of the acyl group remained elusive, ketone **28** carried through to the final sequence provided synthetic papuaforin C (**30**), which was spectroscopically identical to the natural product.[5]

In summary, concise total syntheses of hyperforin (**1**) and papuaforins A (**2**), B (**27**), and C (**30**) were accomplished in 17 steps, along with a formal synthesis of nemorosone (**3**) in 11



Scheme 4. Total syntheses of hyperforin (**1**) and papuaforins A (**2**), B (**27**), and C (**30**). Reagents and conditions. a) LDA, TMSCl, I_2, −78°C; b) *t*BuLi, *i*PrCHO, or *s*PrCHO, THF, −78°C; c) DMP, dichloromethane, RT; d) TBAF, THF, RT; e) LDA, Li(2-Th)CuCN, allyl bromide, −78°C; f) Grubbs II (5 mol%), isobutylene, 120°C, g) LiCl, DMSO, 120°C; h) Grubbs II (10 mol%), 2-methyl-2-butene, dichloromethane, 40°C; i) 1. LiCl, DMSO, 120°C then 2. $PdCl_2$, H_2O, O_2, RT. TBAF = tetrabutylammonium fluoride, DMSO = dimethylsulfoxide.

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steps from commercially available starting materials. The salient features of our synthetic method include 1) a multigram-scale synthesis of the bicyclo[3.3.1]nonanones **10** in 8 steps through an efficient gold(I)-catalyzed carbocyclization 2) the synthesis of pivotal intermediates that allow late-stage functionalization for unified access to a wide variety of PPAPs. This modular approach serves as a platform to quickly assemble PPAPs for further synthetic and biological studies.[25]

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[25] Experimental procedures and spectroscopic data for all new compounds can be found in the Supporting Information. CCDC 993657 (TMS-**14b**), 993658 (**18b**), and 993659 (**20a**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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